

## Prognostic Significance of HPV Associated Head and Neck Carcinomas

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### ABSTRACT

Human papilloma virus associated head and neck cancers represent a distinct clinic-pathological group of Head and Neck cancers. These tumors have special predilection for lingual & palatine tonsils, present at young age, are associated with high risk sexual behavior. HPV positive tumors responds better to cancer directed therapy and have favorable prognosis, long-term survival is as high as 80%. In this subset of patients there is 55% reduction in mortality when compared with the traditional head and neck carcinomas associated with smoking and alcohol consumption. Optimal therapy for these carcinomas remains unclear and undefined, although growing evidence supports the theory that this subset of patients should be treated differently with the aim of decreasing treatment related morbidity. In the present article, we summarize the prognostic significance HPV tumor status within large retrospective series, prospective phase III trials and meta-analysis.

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**Key words:** Human papilloma virus; Head and neck cancers; Prognosis

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### INTRODUCTION

HPV is epitheliotropic oncogenic DNA virus belonging to the Papillomaviridae family. The first clue to existence of viral etiology in head and neck cancers was suggested in 1983 by Stina Syrjänen (1) which was later confirmed in various studies<sup>[2-5]</sup>. A single subtype, HPV16 is associated with more than 90% of HNSCC<sup>[5]</sup>. HPV associated HNSCC have special predilection for the lingual and palatine tonsils, have prominent basaloid morphology, are poorly differentiated, lack keratinization and predominantly affect male population<sup>[1-6]</sup>. Clinically HPV-positive tumors present in loco-regionally advanced disease usually with early T stage and advanced nodal stage. The nodal metastases are usually cystic and multilevel regional involvement is common<sup>[7]</sup>.

In head and neck cancers unlike the typical malignant transformation observed after longstanding exposure to tobacco and alcohol, HPV induced carcinogenesis is induced by expression of viral oncoproteins (E6 and E7) that deregulate the tumor suppressor function of p53 and pRb proteins resulting in defective apoptosis, DNA repair and loss of cell cycle control<sup>[8-10]</sup>. The apparent clinical and molecular difference between HPV positive and HPV negative tumors have been highlighted in table No 1. We have elsewhere reviewed pathways of carcinogenesis, clinical & biology behavior HPV associated HNSCC<sup>[11]</sup>, in the present article we limit ourselves to address the impact of HPV status on treatment outcome of head and neck carcinomas as seen within large retrospective series, phase III trials and meta-analysis.

### METHODS-SEARCH STRATEGY

A systematic review of the literature was conducted using the NIH PubMed search engine and the following Mesh words: papillomavirus, and head and neck cancers. A hierarchical literature search in PubMed: 'Head and Neck cancers'; 'Papillomavirus,

**Table 1 Clinical And Molecular Difference Between Hpv Positive And Hpv Negative Head And Neck Cancers.**

S.No.	Associated factors	HPV positive	HPV negative
1	Tobacco use	Seldom	Heavy
2	Sexual behaviour	Associated	Not associated
3	Alcohol abuse	Mild	Heavy
4	Co-factors	Marijuana, Immunosuppression?	Diet, hygiene
5	Incidence	Increasing	Decreasing
6	Site	Oropharyngeal	Any
7	Age	Young	Old
8	T-classification	T1-2	Any
9	N-classification	Advanced	Any
10	Performance status	Good	Fair/Poor
11	Differentiation	Poorly differentiated/ Basaloid	Any
12	Stage	III-IV	Any
13	Survival	Better	Worse
14	pRb	Loss of expression.	Overexpression
15	Cyclin D 1	Loss of expression.	Overexpression
16	p 16	Over-expression.	Loss Of Expression
17	p 53	Inactivation.	Frequent Mutation

Human’; ‘survival’; ‘prospective, ‘retrospective’ and ‘meta-analysis’ was conducted. The additional keywords oral, tonsil, oropharynx, hypopharynx and cancer/carcinoma were also used. Search was limited between years 2000-2013; studies published in English were included. Only large retrospective studies with sixty or more patients were included in the study. The present review comprises of 17 studies (8 retrospective studies, 6 prospective phase III trials and 3 meta-analyses).

**(1) Impact of HPV status on treatment outcome within retrospective Series**

Causal association between HPV and head and neck cancer goes back to 1980s<sup>[1]</sup>, since then intensive laboratory and clinical investigations have recognized tumor HPV status as strong and consistent determinant of improved survival<sup>[3,17-28]</sup>. One of the first study<sup>[3]</sup> testing HPV status in 253 patients reported significantly improved overall survival (OS) compared to HPV-negative tumors, hazard ratio (HR) 0.57; 95% CI 0.34-1.0. HPV-positive tumors had 40% reduction in risk of death from all causes (HR 0.60; 95% CI 0.35-1.0) after adjustment for lymph node status, age, and alcohol consumption. In the year 2001 another large retrospective study<sup>[19]</sup> revealed that HPV 16 positive tumors had significantly reduced all-cause mortality (HR 0.34, 95% CI 0.14-0.83) and disease-specific mortality (HR 0.17, 95% CI 0.04-0.76). Similar over the next decade findings from other prominent retrospective studies (highlighted in table 2) confirmed superior outcomes of HPV associated head and neck cancers<sup>[3,17-23]</sup>. Results from these series suggest that HPV associated HNSCC are associated with markedly favorable treatment outcome with 5year OS for HPV positive HNSCC ranged from 54%-79% which was superior to survival for HPV-negative cancer (5 year OS 20%-49%)<sup>[3,17-23]</sup>.

As with retrospective series results within prospective series

demonstrated favorable survival for HPV associated HNSCC we briefly highlight pertinent data from prospective phase II and phase III trials.

**The Eastern Cooperative Oncology Group (ECOG) 2399**

**Phase II study:** Patients enrolled in the trial received two cycles of induction chemotherapy with intravenous paclitaxel and carboplatin followed by concomitant weekly intravenous paclitaxel and standard fractionation radiation therapy. Prospective evaluation of association of HPV status<sup>[24]</sup> with treatment outcome within ECOG 2399 trial revealed that HPV-positive tumors showed better response to induction chemotherapy (82% vs 55%,  $P=0.01$ ) and chemoradiotherapy (84% vs 57%,  $P=0.007$ ). HPV-positive tumors had improved OS (2-year OS 95% vs 62%  $P=0.005$ ). After adjustment for age, tumor stage, and ECOG performance status HPV tumors had lower risks of disease progression (HR 0.27, 95% CI 0.10-0.75) and death from any cause (HR 0.36, 95% CI 0.15-0.85). When analysis was restricted to patients with OPC, HPV-positive tumors had 61% lower risk of death (HR 0.39, 95% CI 0.15-1.05) and 62% lower risk of progression (HR 0.38, 95% CI 0.12-1.15) than patients with HPV-negative tumors.

**(2) Studies on Prospective Phase III randomized Trials**

**DAHANCA 5 TRIAL:** Study evaluating prognostic significance of p16INK4A<sup>[25]</sup> in the Danish Head and Neck Cancer Group (DAHANCA) 5 trial confirmed that tumor-positivity for p16INK4A significantly correlated with better loco-regional tumor control (5-year actuarial values 58% vs 28%;  $P=0.0005$ ), disease-specific survival (72% vs 34%;  $P=0.0006$ ), and improved overall survival (62% vs 26%;  $P=0.0003$ ). On multivariate analysis, p16INK4A remained a strong independent prognostic factor for locoregional failure (HR 0.35; 95% CI:0.19-0.64), disease-specific death (HR 0.36; 95% CI:0.20-0.64), and overall death (HR 0.44; 95% CI:0.28-0.68).

**DAHANCA 6 and 7 TRIALS:** HPV-associated p16-expression was evaluated in 794 patients enrolled in the DAHANCA 6 and 7 trial<sup>[26]</sup>, the aim was to evaluate influence of tumor p16-status on loco-regional tumor control and survival as a function of fractionation schedule (5 Fractions/week vs 6 Fractions/week). P16-positivity emerged out as independent prognostic factor for loco-regional control (adjusted HR 0.58; 95% CI 0.43-0.7), disease-specific survival (HR 0.47 95% CI 0.33-0.67) and OS (HR 0.54, 95% CI 0.42-0.68). Accelerated radiotherapy improved loco-regional control rate both in p16-positive as well as in p16-negative tumors. For HPV associated HNSCC, disease-specific survival significantly improved with the 6 Fx/week regimen (85% vs 70%,  $p=0.02$ ). In p16-negative group neither disease-specific survival nor overall survival improved by accelerated radiotherapy. Using risk of cancer specific death as endpoint, accelerated regimen was found to be independently associated with good prognosis in the total cohort and in p16-positive group, but no independent benefit was found in the p16-negative

**Table 2 studies favoring better prognosis for hpv associated hnscc.**

S.No.	Study	N	Evidence	DFS/FFS/PFS HR 95% CI	Overall survival
1	Gillison <i>et al</i> <sup>[3]</sup> 2000	252	Retrospective		Improved survival (HR=0.57 95% CI 0.34-1.0)
2	Mellin <i>et al</i> <sup>[18]</sup> 2002	60	Retrospective	0.4 (0.19-0.84)	5year OS: 54% vs 32% ( $p=0.023$ , cox multivariate)
3	Schwartz <i>et al</i> <sup>[19]</sup> 2001	254	Retrospective		All cause mortality HR 0.34, 95% CI 0.14-0.83
4	Lindel <i>et al</i> <sup>[20]</sup> 2001	99	Retrospective	0.5 (NR)	Better OS ( $p=0.046$ , log rank)
5	Ritchie <i>et al</i> <sup>[21]</sup> 2003	128	Retrospective	0.17 (0.04-0.76)	5 year OS: 71% vs 49% ( $p=0.07$ )
6	Weinberger <i>et al</i> <sup>[17]</sup> 2006	107	Retrospective	0.31 (0.09-0.9)	5 year OS: 79% vs 18-20% ( $p=0.0095$ , log rank)
7	Licitra <i>et al</i> <sup>[22]</sup> 2006	90	Retrospective	0.5 (0.2-1.6)	5 year OS: 79% vs 46% ( $P=0.0018$ , cox multivariate)
8	Sedaghat <i>et al</i> <sup>[23]</sup> 2009	75	Retrospective	0.2 (0.1-0.6)	88% lower risk of death (adjusted HR 0.12 95 CI (0.02-0.68)

group.

**Radiation Therapy Oncology Group (RTOG)-0129study<sup>[27]</sup>:**

In this study locally advanced HNSCC were randomized to either accelerated fractionation radiotherapy with concomitant boost consisting of 72 Gy delivered in 42 fractions over 6 weeks with 2 cycles of concurrent cisplatin, or the standard fractionation radiotherapy consisting of 70 Gy delivered in 35 fractions over 7 weeks with 3 cycles of concurrent cisplatin. Analysis of HPV status<sup>[27]</sup> (restricted to 323 OPC patients), revealed that HPV-positive cancer had better OS (3 year OS 82% vs 57%,  $P<0.001$ ) and better progression-free survival (3 year PFS 74% vs 43%,  $P<0.001$ ) than patients with HPV-negative cancer. Three year loco-regional failure was significantly lower for patients with HPV-positive tumors than for those with HPV-negative tumors (13.6% vs 35.1%,  $P<0.001$ ). HPV-positive tumors had 58% reduction in the risk of death as compared to HPV-negative tumors (HR 0.42 95% CI:0.27-0.66), similarly there was 51% reduction in risk of relapse or death (HR 0.49 95% CI:0.33-0.74) favoring HPV associated OPC group. Tobacco smoking was independently associated with inferior survival (OS and PFS) both in the subgroup of patients with oropharyngeal squamous-cell carcinoma and in the entire study population. Risk of death and cancer relapse or death significantly increased by 1% for each additional pack-year of tobacco smoking, and magnitude of tobacco effect was similar for patients with HPV-positive cancer (HR 1.01 95% CI:1.00-1.02) and those with HPV-negative cancer (hazard ratio, 1.01 95% CI:1.00-1.03).

Recursive-partitioning analysis revealed that HPV status was major determinant of OS, followed by number of pack-years of tobacco smoking ( $\leq 10$  vs  $>10$ ) and then nodal stage for HPV-positive tumors or tumor stage for HPV-negative tumors. With respect to risk of death patients enrolled in the study were stratified into three categories. HPV-positive tumors were considered to be at low risk, with the exception of smokers with a high nodal stage (i.e., N2b to N3), who were considered in intermediate risk; HPV-negative tumors were considered to be at high risk, with exception of nonsmokers with tumors of stage T2 or T3, who were considered in intermediate risk. Low risk category had most favorable survival (3 year OS 93.0%) followed by intermediate risk (3 year OS 70.8%) whereas patients in high risk experienced worse treatment outcomes (3 year OS 46.2%). The study laid emphasis on the fact that extent of tobacco smoking detracts favorable outcome of HPV positive HNSCC.

**TAX 324:** TAX 324 compared survival between two different sequential chemotherapy regimens comprising of docetaxel, cisplatin,

and 5-fluorouracil and cisplatin and 5- fluorouracil in previously untreated patients with locally advanced HNSCC. Of the 501 patients entered on TAX 324, 264 (53%) were identified as having OPC, of these 42% of OPC cases were evaluated for HPV16 status<sup>[28]</sup>, OS was significantly better of HPV positive cancers as compared to HPV negative tumors(79% vs 31%,  $P<0.0001$  ).Similarly PFS was better in HPV associated cancers (73% vs 29%,  $P<0.0001$ , MS was reached for HPV positive cancers whereas MS for HPV negative cancers was 21 months (95% CI 13-49 months). There was 80% reduction in mortality in HPV cancers as compared with HPV negative tumors (HR 0.2, 95% CI 0.10-0.38) and significant reduction in local-regional failure (13% vs 42%,  $P=0.0006$ ).(Discussion modifies and cut short).

**Trans Tasman Radiation Oncology Group (TROG) 02.02:**

In TROG 02.02 study locally advanced head and neck squamous cell cancer were randomly assigned to concurrent radiotherapy and cisplatin with or without tirapazamine. In total, 861 patients randomly assigned in the trial, 465 (54%) had OPC out of which P16 analysis<sup>[29]</sup> was restricted to in 206 patients. HPV positive tumors had outcome, 2 year OS 91% versus 74% for p16-negative cancers (HR 0.36; 95% CI:0.17-0.74), 2 year failure-free survival rates of 87% and 72%, (HR 0.39; 95% CI:0.20-0.74). Loco-regional control was better in p-16 positive patients, 2-year time to locoregional-failure rates were 93% in p16-positive patients and 86% in p16-negative patients (HR, 0.43; 95% CI:0.17-1.1). (Discussion cut short) Loco-regional failure and death without failure were lower in the p16-positive population, whereas rates of distant failure were similar in both arms. Cox regression analysis of overall survival demonstrated that p16 status was the only significant factor in multivariable analysis. There was a trend for improved locoregional control with the tirapazamine regimen in the p16-negative patients, 2-year time-to-locoregional-failure rate 92% in cisplatin and tirapazamine arm versus 81% in cisplatin arm (HR, 0.33; 95% CI:0.09-1.24;  $P=0.13$ ). Results from prospective studies evaluating treatment outcomes in HPV positive tumors have been briefly summarized in table 3.

**(3) Meta-analysis confirming Better outcomes for HPV+ HNSCC**

**CC Ragin *et al* Review and meta-analysis 2007:** One of the first meta-analysis that included 37 studies<sup>[30]</sup> reported significantly improved OS (meta HR: 0.85, 95% CI: 0.7-1.0) and DFS (meta HR: 0.62, 95% CI: 0.5-0.8) for patients with HPV-positive tumors. Patients with HPV-positive head and neck tumors had an 18% lower risk of dying (combined HR: 0.85, 95% CI:0.7-1.0) and 38% lower risk of disease-failure (combined HR: 0.62, 95% CI:0.5-0.8). Site-

**Table 3 Treatment Outcome by Tumor HPV Status From Patients Enrolled in Prospective randomised Trials.**

S.No.	Author	Study conducted on trial	N	Loco-regional control	End point HR 95% CI
1	Fakhry <i>et al</i> <sup>[24]</sup> 2008	ECOG 2399 Phase II trial	96	Lower risks of progression (HR = 0.27, 95% CI = 0.10-0.75)	2-year OS (95% vs 62%, $p=0.005$ ) Lower risk of death (HR = 0.36, 95% CI = 0.15 to 0.85)
2	Lassen <i>et al</i> <sup>[25]</sup> 2009	DHANCA5 Phase III trial	156	Loco-regional control 28% vs 58%; (OR, 0.26;95% CI, 0.12-0.57; $p=0.0005$ )	Disease-specific survival (72% vs 34%; $p=0.0006$ ), Overall survival (62% vs 26%; $p=0.0003$ )
3	Lassen <i>et al</i> <sup>[26]</sup> 2009	DHANCA 6 and 7 Phase III trial	794	Loco-regional control HR 0.58 (0.43-0.78)	Disease-specific survival; HR 0.47 (0.33-0.67) Overall survival; HR 0.54 (0.42-0.68)
4	Ang <i>et al</i> <sup>[27]</sup> 2010	RTOG 0129 Phase III trial	323	3 year loco-regional relapse (13.6% vs 39.1%, $p<0.001$ )	3-year OS (82.4%, vs 57.1% $P<0.001$ ) 3 year Progression-free survival (73.7% vs 43.4% $p<0.001$ )
5	Posner <i>et al</i> <sup>[28]</sup> 2011	TAX 324 Phase III trial	111	Local-regional failure (13% vs 42%, $p=0.0006$ )	Overall survival (79% vs 31%, $p<0.0001$ ) Progression free survival (73% vs 29%, $p<0.0001$ ).
6	Rischin <i>et al</i> <sup>[29]</sup> 2010	TROG 02.02 Phase III trial	185	Lower rates of locoregional failure. a trend favoring the tirapazamine arm for improved locoregional control in p16-negative patients (HR, 0.33; 95% CI, 0.09-1.24; $p=0.13$ ).	Failure-free survival; HR 0.39 (0.20-0.74, $p=0.003$ ) Overall survival; HR 0.36 (0.17-0.74, $p=0.004$ )

specific evaluation revealed that HPV-positive oropharyngeal tumors had a 28% reduced risk of death (meta HR:0.72, 95% CI:0.5-1.0) and have a 49% significantly lower risk of disease- failure than the patients with HPV-negative oropharyngeal tumors (meta HR: 0.51, 95% CI:0.4-0.7). There was no significant difference in the risk of death for patients with HPV-positive non-oropharyngeal tumors compared to patients with HPV-negative non-oropharyngeal tumors (meta HR: 0.79, 95% CI:0.5-1.3). The risk of failure for HPV-positive patients with tumors from the larynx was in fact more than 2 times greater than that of patients with HPV-negative tumors (unadjusted HR: 2.45, 95% CI: 0.3-23.6). The meta-analysis suggested that there may not only be an improved overall and DFS for patients with HPV-positive tumors, but that this effect might be site specific as well.

**Farshid Dayyani *et al.*: Meta -analysis of HPV on overall survival 2010:** A total of 5681 patients in 34 studies<sup>[31]</sup> were included in the analysis. HPV positive HNSCC demonstrated a better response to radiotherapy as compared to HPV negative HNSCC (non-adjusted OR=4.07; 95% CI:1.48-11.18, *p*=0.006). Similarly, HPV positive patients had improved response to concurrent chemo-radiation (non-adjusted OR:2.87; 95% CI:1.29-6.41, *p*=0.01). Impact

on overall survival showed better outcome for HPV positive patients compared to HPV negative patients (HR=0.42; 95% CI:0.27-0.56, *p*<0.0001). Improved survival in HPV positive patients was even more pronounced in the subgroup of oropharyngeal cancers (adjusted HR=0.40; CI:0.18-0.61, *p*< 0.0001), with a 60% lower risk of death.

**O Rorke *et al* systematic review and meta-analysis 2012:** The analysis<sup>[32]</sup> evaluated disease-specific (death from HNSCC), overall (all-cause mortality), progression-free and disease-free (recurrence free) survival outcomes in HPV-positive vs HPVnegative HNSCCs. Data extracted from 52 studies revealed that HPV-positive HNSCC had 54% better overall survival compared to HPV-negative patients HR 0.46 (95% CI:0.37-0.57); the pooled HR for tonsillar cancer and OPSCC was 0.50 (95% CI:0.33-0.77) and HR 0.47 (95% CI:0.35-0.62) respectively. Pooled HR for disease specific survival was 0.28 (95% CI:0.19-0.40). Both progression-free survival and disease-free survival were significantly improved in HPV-positive HNSCCs. HPV-positive HNSCCs and OPSCCs patients have a significantly lower disease specific mortality and were less likely to experience progression or recurrence of their cancer than HPV-negative patients. Results from meta-analysis addressing prognostic significance of HPV tumors status have been briefly summarized in table 4.

Table 4 Prognostic significance of HPV Status within meta-analysis.

S.No.	Study	N	Loco-regional control/any recurrence/response to treatment	Survival
1	C.C. Ragin <i>et al</i> [30] 2007	23studies included	lower risk of recurrence (meta HR: 0.62, 95% CI: 0.5-0.8)	HPV-positive HNSCC had 18% lower risk of dying (meta HR 0.85, 95% CI: 0.7-1.0) <b>Site-specific analyses</b> HPV-positive OPC had 28% reduced risk of death (meta HR: 0.72, 95%CI: 0.5-1.0) and better DFS (metaHR: 0.51, 95% CI: 0.4-0.7). There was no difference in OS between HPV-positive and negative non-oropharyngeal patients.
2	F Dayyani <i>et al</i> [31] 2010	34studies included	HPV positive HNSCC better response to radiotherapy (adjusted OR=4.07; 95% CI=1.48-11.18, <i>p</i> =0.006) and Concurrent chemo-radiation (nonadjusted OR=2.87; 95% CI 1.29-6.41, <i>p</i> = 0.01).	OS HNSCC 58% reduction in mortality (HR = 0.42; 95% CI 0.27-0.56, <i>p</i> <0.0001). HPV positive OPC more pronounced benefit in survival adjusted HR=0.40; CI=0.18-0.61, <i>p</i> <0.0001). Overall Survival HPV-positive HNSCC had a 54% better overall survival HR 0.46 (95% CI 0.37-0.57) HR for OPC 0.47 (95% CI 0.35-0.62) Disease specific survival Pooled HR 0.28 (95% CI 0.19-0.40) Progression free Survival. Pooled HR 0.40 (95% CI 0.29-0.56)
3	O Roreke <i>et al</i> [32] 2012	42 studies included		

## DISCUSSION

Favorable outcome for oropharyngeal carcinomas based by the HPV tumor status is not entirely understood at present, but is most likely caused by a combination of several factors. A part of the survival benefit may be ascribed to patient-related factors that include younger age at presentation, limited exposure to tobacco and alcohol, less co-morbidity and a better general condition. Better prognosis with HPV+HNSCC can also be explained partially by absence of "field cancerization". Favorable outcome of HPV positive HNSCC is also due to inherent sensitivity of these carcinomas to chemotherapy and radiotherapy. Presence of intact p53 is implicated as one of the potential mechanisms whereby removal of HPV E6 and E7 expression leads to the restoration of apoptotic pathways rendering the tumor more sensitive to chemo-radiation treatment. Another possible explanation could be that HPV positive HNSCC are less hypoxic and potentially respond with less pronounced accelerated repopulation when irradiated, but the precise mechanisms are yet to be elucidated.

### Impact on future perspectives

HPV tumor status may provide insight into the tumor biology and help to individualize cancer directed therapies. Clinically relevant hypoxia may be more pronounced in p16-negative tumors as compared to p16-positive tumors. The characteristic genotype and molecular biological profile of the HPV-associated HNSCC has been implicated to cause a differential response to hypoxic modification during radiotherapy suggesting that hypoxic radio-resistance may differ by tumor HPV status. Recently improved treatment outcomes for HPV negative tumors when subjected to hypoxic modification along with radiation therapy has been reported<sup>[29,33]</sup>. Given the dismal outcome for HPV negative HNSCC, treatment intensification might be more relevant in this subset of tumors whereas de-intensification of treatment to reduce treatment morbidity seems a viable option for HPV+HNSCC.

The demonstration of HPV as an etiological agent for a subset of head and neck squamous cell carcinoma and their precursor lesions has paved the way for the development of preventive and therapeutic

HPV vaccines that may lead to the control of HPV-associated malignancies and their potentially lethal consequences. HPV-associated cancers constantly express E6 and E7 viral oncogenes, even in the late stages of the disease and repression of viral oncogene expression by drugs that interfere with the expression or function of viral proteins can induce senescence and apoptosis of the malignant cells.

## CONCLUSIONS

The HPV tumor status is a strong, consistent & independent factor for improved survival, regardless of treatment strategy.

Retrospective series demonstrate five year overall survival of 54%-80% for HPV associated HNSCC as compared to 20%-50% for HPV negative tumors.

Studies on Prospective phase III trials demonstrate 58%-64% decrease in mortality in favor of HPV positive HNSCC.

Data from meta-analysis is in congruence with other studies and indicate that HPV associated HNSCC have a 55% lower risk of death.

Delivery of modest accelerated radiotherapy may be beneficial for these tumors. Tobacco smoking can determent the favorable treatment outcome for HPV associated HNSCC.

Ongoing clinical studies will better help to define the role of de-escalating cancer directed therapy, role of HPV vaccination & individualizing treatment decisions.

## CONFLICT OF INTERESTS

There are no conflicts of interest with regard to the present study.

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