Re: Sharma PK, Panaiyadiyan S, Kurra S, Kumar R, Nayak B, Singh P, *et al*. Association of human papillomavirus in penile cancer: A single-center analysis. Indian J Urol 2022;38(3): 210-15.

We read the recent article by Singh *et al*. with a great interest.[1] In their single-center prospective observational study of the association of human papillomavirus (HPV) in penile cancer (PeCa), they concluded that PeCa was commonly related to HPV infection, with HPV-16 being the most common subtype. They also demonstrated that

the relative E7 oncoprotein mRNA expression for HPV-18 and the relative telomerase activity were higher in PeCa patients, potentiating their role as surrogate markers of viral activity. An association of high-risk HPV types with increasing TNM stages of PeCa was not noted. Furthermore, there was no significant association of lymph node metastasis with high-risk HPV-positive or HPV-negative status.

The authors compared telomerase activity among PeCa cases and controls and found it to be increased in the PeCa group. However, there was no difference between the HPV-infected cases and HPV-negative cases. It would be interesting to know if there was any difference in the telomerase activity in the control group between high-risk HPV-infected and uninfected controls.

The authors provide some explanation for the results in their discussion, including small sample size, not evaluating the extensive panel of HPV subtypes for the estimation of HPV prevalence, unavailability of follow-up data, and survival analysis, albeit the primary aim was to study the association of HPV in PeCa at the molecular biological level. The authors conclude by suggesting the role of relative E7 mRNA expression for HPV-18 as potential surrogate markers of viral activity. However, HPV 16 was the most common virus seen in the cases, but its E6/7 expression though higher, was not statistically significant from that of controls.

A recent study stated that expression of programmed death-ligand 1 was found to be higher in non high-risk HPV penile tumors, with low levels associated with absent lymph node metastases and better prognosis.[2] Another systematic review concluded that vaccine effectiveness was low in individuals who are already infected with the corresponding HPV type.[3] In the same study, high-risk subtypes of HPV have been found in up to 40% of cases; the highest detection rates are in the warty and basaloid subtypes of squamous cell carcinoma. Lastly, the E7 oncoprotein has been observed to have a higher affinity for retinoblastoma-1 tumor suppressor protein in high-risk HPV than in the low-risk subtypes.[3]

We wonder if, for a better understanding of whether the HPV status of tumors has real therapeutic implications in affecting the clinical outcome, studies be performed after adequate selection and classification of the different subtypes of PeCa. It would also be interesting if, in addition to the genomic alterations, further insight on epigenetic alterations that induce oncogenesis could be studied as this may predict survival more accurately.

This study could provide the pathway for future research.

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