COMMENT

Young men with penile cancer fare as poorly as elder patients: clinical implications

K. Vandermaesen [1] and M. Albersen [1]✉

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The study conducted by Pang et al. provides valuable insights into the long-term oncological outcomes of penile squamous cell carcinoma (pSCC) in both younger (age <50 years) and older (age >50 years) male populations [1]. They show comparable disease-specific survival (DSS), recurrence-free survival (RFS), and metastatic-free survical (MFS) in these two patient groups. However, a significant difference was reported in overall survival (OS), which likely stems from the higher comorbidities and generally less favorable health condition within the older patient group.

Patients in the older group were intentionally matched to their younger counterparts based on clinical stage, nodal stage, and the type of surgery for the primary tumor. While this matching methodology ensures the comparability of survival rates between age groups, it's imperative to acknowledge that such a study design inherently restricts the exploration of potential differences in the clinical presentation and tumor characteristics of penile cancer among patients of varying ages. Therefore, histological features and tumor grades were similar between men aged ≤50 y and those aged >50 y. The study implies based on these findings that tumor characteristics are similar in both age groups. However, given that recent studies show correlation between tumor grade and penile cancer stage [2], these conclusions may be based on an already preselected subgroup of patients with similar tumor characteristics and thus mortality rate. An examination of unmatched samples, on the contrary, would offer a broader and richer understanding of the nuanced clinical profiles across different age demographics and could unveil previously overlooked variations in disease presentation and progression. Therefore, while Pang et al. study undoubtedly contributes significant advancements to our understanding of pSCC outcomes, it's crucial to recognize the inherent limitations imposed by the chosen study design. Moving forward, future research endeavors in this field could benefit from adopting a different approach that explores the complexities and heterogeneity of penile cancer presentations across different age groups.

Another critical aspect addressed by Pang et al.'s study is the evolving landscape of penile cancer incidence. They demonstrate a rise in new diagnoses among patients aged <50 years old [1]. Existing literature confirms these findings, indicating a notable increase in penile cancer diagnoses in men under 64 years old in Norway, with an average annual percent change (AAPC) of +1.47% [3]. This rise of pSCC in younger patients is potentially attributed to an increased exposure to Human Papillomavirus (HPV) and shifts in sexual behavior.

Apart from age, penile cancer incidence in general is on the rise. Although the highest incidence rates of penile cancer are still seen in developing countries, the penile cancer incidence is rising in most European countries [4]. Especially HPV-associated penile cancers are experiencing an upward trend (AAPC of +2.36%) [5]. In 2016, the World Health Organization (WHO) has classified penile cancer into HPV-associated pSCC and HPV-independent pSCC, recognizing their distinct carcinogenesis [6]. About 30–50% of invasive pSCCs are HPV-driven, with HPV 16 as the most important carcinogenetic pathogen [7]. Annually, around 13,000 new penile cancer diagnoses related to HPV are made worldwide [8]. A meta-analysis by Sand et al. demonstrated that men with HPV-related penile cancer have a better DSS than men with HPV-unrelated disease [9]. In addition, HPV-positive patients seem to exhibit a lower burden of inguinal lymph node metastases compared to HPV-negative pSCC, resulting in a less aggressive disease progression [10].

HPV-related subtypes of penile squamous cell carcinoma (SCC) typically manifest at younger ages compared to their non-HPV-related counterparts [11]. Consequently, the observed rise in the incidence of penile SCC among relatively younger men aligns with an increasing proportion of HPV-related tumors. These same patterns are seen in HPV-related carcinomas of the vulva and oropharynx [12, 13], where histological types associated with HPV exhibit an onset at lower ages. A higher prevalence of HPV infection in the younger age group, although not significant, was also observed in the study by Pang et al. (12% vs 5%, $p = 0.08$) [1], however, these percentages are quite low compared to previous literature and meta-analyses [3, 9] indicating possibly a high rate of missing data and/or insufficient adoption of the WHO and EAU recommendation for pSCC classification in HPV-associated and HPV-independent carcinomas.

HPV vaccination in young girls resulted in a spectacular decrease of HPV 16 and HPV 18 prevalence 5–8 years following vaccination [14]. The implementation of the quadrivalent HPV vaccine for males has only been approved by the Food and Drug Administration (FDA) in 2009. While the spectacular results of the vaccine in girls seem promising for HPV-driven cancers in men, a noticeable decrease in HPV-positive pSCC rates may require patience, as the effects of vaccination might take decades to manifest due to the high age peak of the disease. Moreover, even if gender-neutral vaccination proves to be as effective as in girls, HPV-independent penile cancer will still persist, representing a more aggressive subtype of the disease. Additionally, as

[1]Department of Urology, University Hospitals Leuven, Leuven, Belgium. ✉email: maarten.albersen@uzleuven.be

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HPV-positive pSCC appears to be more prevalent in younger patients, the median age peak of penile cancer patients might increase due to vaccination programs in boys and decline of HPV-positive cases. This underscores the continuing need for sustained efforts in preventive strategies, the importance of comprehensive research, and tailored strategies for both HPV-driven and non-HPV-driven forms of penile cancer.

In conclusion, the study conducted by Pang et al. not only provides a comprehensive analysis of long-term outcomes in penile squamous cell carcinoma across age groups but also raises crucial questions about the evolving landscape of penile cancer, particularly in younger individuals. The under-studied nature of pSCC in individuals below the age of 50, coupled with the observed rising incidence, points to the importance of expanding research efforts in this demographic. A more comprehensive understanding of the disease in younger populations, preferably in an unmatched cohort, is critical for improved diagnosis and treatment strategies. While pSCC in younger cohorts are mainly HPV-driven, the full effect of HPV vaccination may take decades to manifest. Moreover, the persistence of HPV-independent penile cancer, which presents a more aggressive tumor phenotype, underscores the ongoing need for sustained efforts in comprehensive research on penile cancer.

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COMPETING INTERESTS

Maarten Albersen is a research mandate holder of the Belgian Foundation against Cancer.

ADDITIONAL INFORMATION

Correspondence and requests for materials should be addressed to M. Albersen.