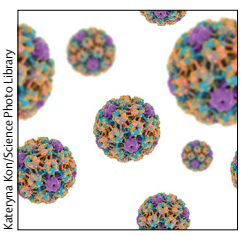
New directions in penile cancer



Kateryna Kon/Science Photo Library

Published Online
December 17, 2018
http://dx.doi.org/10.1016/S1470-2045(18)30695-8

See Articles page 145

Penile cancer is a rare disease, but offers insight into aspects of viral carcinogenesis and potential for personalised radiotherapy. The study by Tina Olesen and colleagues in *The Lancet Oncology*[1] is a well performed viral epidemiology analysis by an accomplished Danish team. The investigators screened the published literature for cases of penile cancer and penile intraepithelial neoplasia and collated their findings with reports of human papillomavirus (HPV) DNA and $p16^{INK4a}$ positivity. The authors report a pooled HPV prevalence of 50·8% in penile cancer (which was especially high in basaloid squamous cell carcinomas and warty-basaloid carcinoma), with HPV16 being the predominant oncogenic HPV type, and a pooled HPV prevalence in penile intraepithelial neoplasia of 79·8%. The pooled $p16^{INK4a}$ percent positivity was 41·6% in penile cancer and 49·5% in penile intraepithelial neoplasia.

Although the data presented in this study add to the body of knowledge and understanding of HPV prevalence in penile cancer and pre-neoplastic lesions, we have a slight concern about this Article,[1] related to biases inherent to the meta-analysis technique. In biomarker reviews such as this, the available data are affected by several underlying limitations. First and foremost is the fact that the search was restricted to reports or presentations published in the English language; second, the articles included must have been published in a peer-reviewed journal; and finally, the journal must have been searchable using a conventional medical search engine. Although we appreciate some intriguing new findings (eg, those relating to penile intraepithelial neoplasia and $p16^{INK4a}$), the subset analyses by histological subtype and geographical differences are less robust. There was no central pathology review across the included studies, which varied by geographical location; therefore, to make broad associations is challenging. Such data should be optimally drawn from a prospective multicentre study in which patient identification and tissue processing is completed using uniform methods. Overall, we consider the histological differences to be hypothesis generating, and the geographical distinctions spurious at best.

Despite our concerns, these data are still extremely valuable in that they confirm that opportunities exist for two broad campaigns of clinical intervention in penile cancer: first, increasing vaccination against HPV as a mechanism of decreasing future HPV-related cases, and second, personalised targeting based on genomic characteristics.

In the only HPV vaccine trial done in men to assess clinical efficacy of the vaccine, the four-valent HPV vaccine showed robust efficacy against external genital HPV infection persistence and condylomata.[2,3] Although penile intraepithelial neoplasia was only observed in men randomly assigned to the placebo group of the trial, the low total penile intraepithelial neoplasia case count prohibited a formal evaluation of efficacy, and as such no indication exists for vaccination for the prevention of penile cancer. Despite this situtation, the consistent observation that HPV-related penile cancer and penile intraepithelial neoplasia are primarily caused by HPV types against which available HPV vaccines protect[4–6] suggests that prevention of HPV-related penile cancer in men might be possible if boys and men were vaccinated. These data strongly support the need for gender-neutral HPV vaccine policies globally to fully realise the cancer prevention benefit of HPV vaccination in men as well as women.

In another arena, we now understand that clinical correlates of HPV association vary widely between sites of cancer. In squamous cell carcinoma of the oropharynx, treatment intensity might be decreased for HPV-associated carcinomas,[7] yet no equivalent clinical strategy exists for HPV-related penile cancer. Squamous cell carcinoma of the penis is a radioresistant epithelial lesion, rather like melanoma, and is quite different to squamous cell carcinoma of the head and neck (unpublished data). Our work in this area is based on a ten-gene signature panel, the radiosensitivity index,[8] which is disease-agnostic and specific for lesions treated with radiotherapy.[9] Last year in *The Lancet Oncology*, we discussed this tool and proposed a corollary, the genomic-adjusted radiation dose (GARD).[10] Our GARD model predicts that improved outcomes in cancer might require adjusting the radiation dose delivered according to the genomics of the lesion.[10] Our increasing understanding of the genomics of penile cancer does not suggest any of the benefit of HPV association in this type of cancer, unlike that which exists in oropharyngeal cancer.

Well performed epidemiological studies inform clinical innovation in cancer prevention and control. The study by Oleson and colleagues[1] supports the clinical association of HPV with penile carcinogenesis and adds evidence supporting rational gender-neutral HPV vaccination policies worldwide. In an entirely different direction, the results of their study also add information to potential personalised approaches to the disease—which is revealing itself to be a different clinical entity to similar lesions in other locations such as the oropharynx.

Peter A S Johnstone, Philippe E Spiess, Anna R Giuliano
Center for Immunization and Infection Research in Cancer, Moffitt Cancer Center, Tampa, FL 33612, USA
peter.johnstone@moffitt.org

ARG is a member of Merck & Co advisory boards, and her institution has received funds to conduct investigator-initiated studies. PASJ and PES declare no competing interests.

1 Olesen TB, Sand FL, Rasmussen CL, et al. Prevalence of human papillomavirus DNA and p16^{INK4a} in penile cancer and penile intraepithelial neoplasia: a systematic review and meta-analysis. *Lancet Oncol* 2018; published online Dec 17. http://dx.doi.org/10.1016/S1470-2045(18)30682-X.
2 Giuliano AR, Palefsky JM, Goldstone S, et al. Efficacy of quadrivalent HPV vaccine against HPV Infection and disease in males. *N Engl J Med* 2011; **364:** 401–11.
3 Castellsagué X, Giuliano AR, Goldstone S, et al. Immunogenicity and safety of the 9-valent HPV vaccine in men. *Vaccine* 2015; **33:** 6892–901.
4 Ingles DJ, Pierce Campbell CM, Messina JA, et al. Human papillomavirus virus (HPV) genotype- and age-specific analyses of external genital lesions among men in the HPV infection in men (HIM) study. *J Infect Dis* 2014; **211:** 1060–67.
5 Sudenga S, Ingles DJ, Pierce Campbell CM, et al. Genital human papillomavirus infection progression to external genital lesions: the HIM study. *Eur Urol* 2016; **69:** 166–73.
6 Sudenga SL, Torres BN, Fulp WJ, et al. Country-specific HPV-related genital disease among men residing in Brazil, Mexico, and the United States: the HIM study. *Int J Cancer* 2017; **140:** 337–45.
7 Sturgis EM, Ang KK. The epidemic of HPV-associated oropharyngeal cancer is here: is it time to change our treatment paradigms? *J Natl Compr Canc Netw* 2011; **9:** 665–73.
8 Eschrich S, Zhang H, Zhao H, et al. Systems biology modeling of the radiation sensitivity network: a biomarker discovery platform. *Int J Radiat Oncol Biol Phys* 2009; **75:** 497–505.
9 Torres Roca JF. A molecular assay of tumor radiosensitivity: a roadmap towards biology-based personalized medicine. *Pers Med* 2012; **9:** 547–57.
10 Scott JG, Berglund A, Schell M, et al. A genome-based model for adjusting radiotherapy dose (GARD): a retrospective, cohort-based study. *Lancet Oncol* 2017; **18:** 202–11.

Radiosurgery and risk of intracranial malignancies: more research needed

Radiotherapy is a mainstay of cancer treatment, but it is less frequently used in the management of non-oncological conditions.[1] Benign brain lesions can cause adverse consequences (eg, neurological deficits, seizures, bleeding, and pain), which can be prevented, delayed, or reversed by radiotherapy. Stereotactic radiosurgery capitalises on modern radiotherapy advances, delivering high doses of radiation, typically in one session, with extraordinary precision and spatial accuracy. Mounting evidence has shown excellent disease control and toxicity outcomes after stereotactic radiosurgery treatment for various benign pathologies.[2]

Clinical applications of ionising radiation capitalise on its favourable therapeutic index underpinned by the capacity to physically concentrate dose on targets, together with the surrounding normal tissues' ability to more proficiently overcome the effects of radiotherapy. Despite physical and biological targeting, the potential of radiotherapy to induce cancer is well established, and multiple elements have been shown to modulate this risk, including age, tissue type exposed, dose, irradiated volume, environmental factors, genetic predisposition, immunological, and hormonal factors.[3] A defining feature of radiotherapy-induced malignancies is the long latency between exposure and cancer occurrence: cohort studies have shown increasing incidence of cancer extending beyond 30 years.[4] Consequently, the risk of radiotherapy-induced cancer requires careful consideration, especially in young patients with long life expectancy.

In *The Lancet Oncology*, Amparo Wolf and colleagues[5] report on the incidence of malignancies after stereotactic radiosurgery with Gamma Knife (Elekta AB, Stockholm, Sweden) in a subgroup of 4905 patients, predominantly (ie, 97%) from three institutions. Radiotherapy-induced tumours were defined as those emerging within the 2 Gy dose region (although lower doses have also been linked to occurrence of secondary cancers).[6] Their conclusion is that the 10-year risk of malignant intracranial tumours is low (<1%), similar to the risk of spontaneous development of similar tumours in the general population. The results are consistent with those


APHM-GARO/Phanie/Science Photo Library

Published Online
November 22, 2018
http://dx.doi.org/10.1016/S1470-2045(18)30711-3

See Articles page 159