

Well performed epidemiological studies inform clinical innovation in cancer prevention and control. The study by Oleson and colleagues¹ 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.

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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 colleagues⁵ 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



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reported by researchers from Sheffield,⁷ benchmarked against their national mortality and cancer registries. Wolf and colleagues should be congratulated for bringing attention to this important topic; however, some limitations are worth consideration to ensure appropriate clinical interpretation.

The emergence of tumours after radiotherapy is a delayed phenomenon, with low but non-zero risk during the first decade, and increasing incidence thereafter.⁸ Indeed, the first descriptions of radiotherapy-induced cancers were in patients treated for benign conditions, in whom the increased risk was not initially apparent.⁹ Consequently, the study of radiotherapy-induced cancers requires reliable long-term follow-up, generally for at least two decades. The authors⁵ attempt to address this by stipulating a 5-year minimum follow-up for all patients (median follow-up 8.1 years); however, only 25.6% of patients had follow-up of 10–15 years and 8.5% had a follow-up of longer than 15 years. Hence, the low 10-year estimate is reassuring but not surprising. The data cannot address what the 20-year and 30-year incidence will be. Notably, two of the three observed malignant tumours occurred with latencies greater than 10 years.

Follow-up protocols determine the observed incidence of secondary cancers, thus thoroughly describing the surveillance methods (eg, modality and frequency of brain imaging) is key for assessing whether results accurately reflect the true incidence in the overall population and whether comparison with population-based estimates is valid. For example, treated patients might have cancer incidences that are subject to biased overestimation (eg, routine imaging not done in the general population) or underestimation (eg, clinic-based follow-up is necessary for outcome occurrence identification). Little information is provided to the reader to ascertain these matters. A related issue is the absence of a formal statistical estimate of the standardised incidence ratio or absolute excess risk compared with the general population. Instead, the researchers did separate calculations of the incidence per 100 000 person-years in the cohort and age-adjusted incidence derived from population-based registries, noting that the incidences appear to be similar. Ideally, not only age but also sex (a recognised risk factor in brain tumours), follow-up interval, attained age, and other treatment characteristics would

be adjusted for.¹⁰ Again, substantially longer follow-up would be required to create robust multivariable models and to better adjust for confounders.

We agree with Wolf and colleagues that the overall risk of secondary cancers appears reassuringly low at 10 years, and this concern alone should not preclude stereotactic radiosurgery when warranted. With an expected long survival of patients with benign conditions, it is prudent to advocate for properly quantified longer-term outcomes (>15–20 years) to guide judicious decision making and surveillance strategies. The authors appropriately state that “prospective cohort studies with longer follow-up are warranted to support the results of this study”. Secondary cancers can be a devastating consequence of treatment and collaborative efforts to create high-quality data to better elucidate this long-term risk after radiotherapy are needed.

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