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Should we expand the carbon ion footprint of prostate cancer?

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Ionising radiation is a known carcinogen, and radiation-related second malignant neoplasia is a complication of radiotherapy with a latency period potentially extending to decades after treatment.[1] Radiation-related second malignant neoplasia might be associated with a worse prognosis compared with sporadic malignancies because of a more aggressive biology of these tumours and the risks imposed by the cumulative toxicities of previous and subsequent treatments.[2,3]

As evidenced by a recent meta-analysis of 21 studies,[4] radiation-related second malignant neoplasia is an uncommon complication in patients with localised prostate cancer after photon radiotherapy; however, the widespread use of this modality in combination with improved overall survival in this setting, early diagnosis, and younger age at treatment will probably increase the prevalence of radiation-related second malignant neoplasia in this population. Understanding the magnitude of the risk and possible ways to mitigate it is, therefore, crucial to an informed discussion with a patient considering radiotherapy or other options for potentially curable prostate cancer.

Unfortunately, reliable data about the relative and absolute risk of radiation-related second malignant neoplasia following radiotherapy in patients with prostate cancer are difficult to obtain. The challenges and pitfalls faced in data collection and interpretation from retrospective databases were previously well described by Wang and colleagues.[5] In addition to large patient cohorts and adequate follow-up (ideally at least 10–20 years) required to identify uncommon events occurring after an appropriate latency period, they recommended that competing risks, including all-cause mortality and non-treatment-related malignancies, be accounted for. With this approach, they identified an increased 10-year incidence of 1% for solid tumours and 0·5% for haematopoietic malignancies following external beam radiotherapy (EBRT) or brachytherapy compared with surgery in patients with prostate cancer. The adjusted hazard ratios for subsequent solid tumour after EBRT (1·931; p<0·001) and brachytherapy (2·072; p<0·001) were significantly increased compared with surgery. Similarly, the adjusted hazard ratios for subsequent haematopoetic malignancies after EBRT (1·504; p<0·001) and brachytherapy (1·214; p=0·012) were also significantly increased compared with surgery. Notably, Krasnow and colleagues[6] reported that the risk of radiation-related second malignant neoplasia in patients with prostate cancer after radiotherapy is largely borne by patients who received treatment at a young age. The incidence ratio of subsequent tumours in those patients who received radiotherapy compared with those who did not was 1·98 [95% CI 1·63–2·41] for patients younger than 55 years, 1·71 [1·60–1·84] for those aged 55–64 years, 1·55 [1·47–1·63] for those aged 65–74 years, and 1·26 [1·09–1·46] for those aged 75 years or older.

Carbon ion radiotherapy was first implemented in Japan 25 years ago and, although its clinical use otherwise remains limited to a few centres in Germany, Italy, and China, additional facilities are under construction worldwide. Treatment volumes with carbon ions are highly conformed to the intended target and allow very little scattered radiation into adjacent normal tissue. The radiation dose distribution of carbon ion radiotherapy is similar to that of proton beam therapy, although carbon ions have a higher relative biological effect than protons or photons.

Mohamad et and colleagues[7] provide data, published in *The Lancet Oncology*, supporting the hypothesis that improved surrounding normal tissue protection during prostate cancer treatment with carbon ion radiotherapy reduces the relative risk of radiation-related second malignant neoplasia compared with photon radiotherapy and surgery in patients with localised prostate cancer. The authors used retrospective cancer registry data for the photon radiotherapy and surgery groups and encountered the analysis challenges previously outlined in this Comment, including, but not limited to, relatively short follow-up, incomplete or no data on important confounding factors (such as alcohol or tobacco use), relevant comorbidities, and specific details about radiotherapy dose, volume, and radiation technique. Propensity score matching was used to minimise the effect of known confounding factors when comparing the carbon ion radiotherapy cohort with the photon radiotherapy and surgery groups, but this analysis further reduced the already modest numbers of patients for this type of analysis and power to identify differences between cohorts. In fact, their calculated hazard ratio of 1·18 (95% CI 1·02–1·36) for photon radiotherapy compared with surgery is actually more favourable than that reported by either Wang and colleagues[5] or Krasnow and colleagues,[6] and possibly reflects the shorter median follow-up. Notwithstanding these concerns, Mohamad and colleagues' study is noteworthy as one of the very few investigations that exceeds studies of dose modelling to support the use of particle beam therapy to decrease the risk of radiation-related second malignant neoplasia.

The most important contribution of this paper is probably an increasing awareness of radiation-related second malignant neoplasia following prostate radiotherapy. The published literature confirms that the overall risk of photon radiotherapy is small but not inconsequential for patients younger than 65 years. Carbon ion radiotherapy appears to reduce this risk, but limited access to these facilities makes it impractical for most patients. Although Mohamed and colleagues did not address it, scarce data suggests that more widely available proton therapy might provide the same advantage as carbon ions for radiation-related second malignant neoplasia and should be investigated further.[8,9] Moreover, their report should not encourage a general move from photon radiotherapy for those who choose radiotherapy for their prostate cancer. Ready access, favourable economics, and abundant level 1 evidence of safety and efficacy weigh heavily in its favour. Nonetheless, the risk of radiation-related second malignant neoplasia should be a part of patient discussion, especially for younger patients with treatment options beyond photon radiotherapy.

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We declare no competing interests.

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Importance of early treatment in metastatic prostate cancer: a question of life or death

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Patients diagnosed with metastatic prostate cancer have become less common with the widespread use of prostate-specific antigen tests and improved awareness of prostate cancer. Although screening remains controversial, patients who walk into our clinics with newly diagnosed metastatic castration-sensitive prostate cancer (mCSPC) remain the most challenging to treat group of patients with prostate cancer. These patients generally have a poor prognosis and overall survival times are still only around 3 years, despite substantial