Key considerations when reviewing subsequent primary cancers following radiotherapy

We read, with great interest, the manuscript by Osama Mohamad and colleagues[1] examining the risk of subsequent primary cancers following carbon ion radiotherapy, photon radiotherapy, or radical prostatectomy for localised prostate cancer. The investigators retrospectively analysed patients in the National Institute of Radiological Sciences (NIRS) database who received carbon ion radiotherapy and, as a comparator cohort, analysed patients in the Osaka Cancer Registry who received photon radiotherapy of surgery. They reported that carbon ion radiotherapy was associated with a lower risk of subsequent malignancy than photon radiotherapy (hazard ratio [HR] 0·81 [95% CI 0·66–0·99], p=0·038) or surgery (HR 0·80 [0·68–0·95], p=0·0088).

The investigators should be commended for a thorough analysis, but some issues warrant further discussion. One issue is that multiple carcinogenic exposures (eg, smoking and alcohol consumption) were not accounted for in this study. For instance, smoking history was a powerful predictor for subsequent primary cancers after carbon ion radiotherapy (HR 1·64 [1·24–2·16], p<0·0005) in the NIRS database; however, these data were not available in the Osaka registry. Although the authors argued that the equal incidence of subsequent head and neck cancers between the NIRS and Osaka cohorts suggests no difference of smoking history on cancer development, numerous other environmental drivers of head and neck cancers exist. Notably, the lower HR for subsequent primary cancers after carbon ion radiotherapy versus surgery is biologically implausible, which suggests the presence of unappreciated confounders.

Another issue is that the crude and cumulative incidences of subsequent primary cancers across all cohorts in this study are high when compared with data from randomised trials and the US Surveillance, Epidemiology, and End Results (SEER) population-based registry. In the European Organisation for Research and Treatment of Cancer (EORTC) 22683 trial (median follow-up 9·1 years), incidence of crude subsequent primary cancers ranged from 7% to 9% after photon radiotherapy[2] and in the EORTC 22911 trial (median follow-up 10·6 years) crude incidence of subsequent primary cancers after upfront radical prostatectomy was 13·5% with upfront prostatectomy and 13·7% without adjuvant photon radiotherapy.[3] In the SEER registry study, crude subsequent primary cancer incidence in patients who received radiotherapy (median follow-up 11·4 years) was 13·4% and in those who received prostatectomy (median follow-up 11·6 years) was 13·0%.[4] By contrast, in the Osaka cohort the crude subsequent primary cancer incidence in patients who received photon radiotherapy (median follow-up 5·7 years) was 15·3% and in those who received radical prostatectomy (median follow-up 6·4 years) was 14·1%. When the Osaka data are compared directly against the SEER data with a cumulative incidence estimation of subsequent primary cancers incidence, a similar discord can be appreciated. Specifically, the cumulative incidence of all subsequent primary cancers in the Osaka photon radiotherapy cohort was 24·0% and in the radical prostatectomy cohort was 18·7% at 9·9 years. In comparison, cumulative subsequent primary cancers incidence at 9·9 years among 386 456 patients in the SEER registry was 15·6% (35·0% less) after radiotherapy and 10·0% (47·0% less) after radical prostatectomy. The elevated subsequent primary cancers incidence in the Osaka registry questions the generalisability of the findings reported by Mohamad and colleagues, particularly when considering that, based on global epidemiologic data, the incidence of cancer in general in a Japanese cohort would be expected to be lower than that seen in European or US cohorts.[5] We look forward to randomised trials evaluating the exciting potential benefit of carbon ion radiotherapy.

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