Key considerations when reviewing subsequent primary cancers following radiotherapy

Authors' reply

We thank Amar Kishan and colleagues for their interest in and comments on our research.[1] We agree that our study has several limitations, which were extensively discussed in the Article. We also acknowledge the concern about the biological plausibility of the increased risk of subsequent primary cancers in the surgery versus carbon ion radiotherapy comparison. Theoretically, unmeasured confounders can be adjusted for, but they are difficult to completely eliminate in the real world, which can be done in randomised trials. Therefore, we agree with the need for prospective studies in this field.

Additionally, we agree that the crude and cumulative incidences reported in our Article are higher than those in the referenced studies. However, we caution that comparing the incidence of subsequent primary cancers across studies might be inappropriate. Different studies have different populations with different ethnicities, age distributions, comorbidities, exposures, follow-up routines, treatment eras, competing risks, and subsequent primary cancers definitions, which all heavily affect subsequent primary cancer incidence. The referenced US Surveillance, Epidemiology, and End Results study,[2] for example, excluded patients with a time interval to second malignancy of less than 5 years for solid cancers or 2 years for haematological malignancies, which was not done in our study. Comparing subsequent primary cancer incidence across studies might be misleading. For example, patients who received whole pelvic radiotherapy for localised prostate cancer in RTOG 9413[3] have a 13·2% incidence of death from a secondary cancer (median follow-up 8·8 years, IQR 5·07–13·84), which is higher than the incidence of death reported in EORTC 22863,[4] which treated a similar cohort of patients with similar follow-up. Thus, we believe that not much could be gained from such comparisons. Notably, the 10-year cumulative incidence of cancer (excluding prostate cancer) is estimated to be 16·4% in 70-year-old men according to the Japanese National Cancer Center data.[5] The cumulative incidence of subsequent primary cancers reported for the surgical and carbon ion radiotherapy cohorts in our study did not largely differ from this value.

Nonetheless, we feel the data remain unique and valuable for guiding prospective studies comparing carbon ion radiotherapy to photon radiotherapy and surgery.

We declare no competing interests.

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