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COMMENTARY

Cite as: Morgan SC, Corkum MT. Second primary cancers following radiotherapy for prostate cancer: How many are actually due to the radiotherapy? *Can Urol Assoc J* 2024;18(4):129-30. http://dx.doi.org/10.5489/cuaj.8760

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Second primary cancers following radiotherapy for prostate cancer: How many are actually due to the radiotherapy?

External beam radiotherapy (EBRT) is carcinogenic and associated with a small but definite increased risk of second primary cancers, particularly among younger patients treated with large-volume EBRT.[1] Quantifying this risk for patients with prostate cancer, however, has proved to be more elusive. Estimates of the rates of second cancers thought to be induced by prostate EBRT vary considerably in the literature from small fractions of a percent to a few percent.[2] Defining this risk is especially relevant in younger men with localized prostate cancer, where a late-appearing risk that rises non-linearly over time might influence choice of primary local therapy.

In this issue of *CUAJ*, Huynh et al report an analysis of the SEER database for men diagnosed with localized, node-negative prostate cancer from 1995–2011 and treated with radical prostatectomy (RP) or EBRT.[3] In separate multivariable models, compared to RP, receipt of EBRT was associated with a 2.12-fold increased risk of second bladder cancer and a 1.94-fold increased risk of second rectal cancer. Only second cancers with a lag time of at least five years were included. In absolute terms, the cumulative incidence at 10 years of secondary bladder cancer was 1.71% and 3.7%, and secondary rectal cancer was 0.52% and 0.99% for the groups receiving RP and EBRT, respectively.

Some caution is required in the interpretation of these findings, particularly when counselling patients. Almost 40% of men treated with RP may receive EBRT as salvage treatment for biochemical failure[4] and this is not recorded in the SEER database unless delivered within a year of RP. More importantly, while registries such as SEER have ample power for identifying rare events, they do not capture all the known relevant factors influencing the background risk of subsequent primary cancers, to say nothing of unknown factors. Attempts to control for covariates in the registry will inevitably be subject to residual confounding.

Compared to patients that undergo RP, those receiving EBRT are older and have greater body mass index (BMI),[5] both of which increase the risk of rectal cancer. Smokers are more likely to receive EBRT than non-smokers, which increases the baseline risk of bladder cancer.[6] BMI, smoking status, and measures of performance status and frailty are among the covariates lacking in the SEER database. Further, prostate EBRT has been associated in a prior SEER analysis with implausible risks of second cancers well outside the regions at risk following pelvic EBRT — lung, brain, stomach, melanoma, and transverse colon — that almost certainly reflect differences in baseline risks for these malignancies.[7] Selection bias for RP is so strong that men treated with RP have greater overall survival than men without a prostate cancer diagnosis in the SEER-Medicare-linked database, even after matching covariates.[8] In the analysis of Huynh et al, it is uncertain how much of the observed increased risk of second bladder and rectal cancers is due to baseline differences in the risk of developing these cancers and how much is due to EBRT itself.

Datasets from randomized controlled trials ensure balance in baseline characteristics but are generally too small and have insufficient followup to capture differences in events as rare and late-occurring as second cancers. Long-term outcome data from ProtecT, the largest randomized trial to compare RP, EBRT, and active monitoring in localized prostate cancer, are nonetheless informative.[9] At a median followup of 15 years, crude rates of death from other cancers were similar across the three groups: 9.4% in the RP group (52/553 patients randomized to RP), 9.9% (54/545) in the EBRT group, and 10.6% (58/545) in the active monitoring group. Rectal and bladder cancers were not reported separately.

Huynh et al are to be congratulated on this study and the additional insights it provides. Ultimately, an adequately powered dataset that can be interrogated to analyze the true risk of second cancer induction following prostate radiotherapy is lacking and we are left in some darkness on this subject.

COMPETING INTERESTS: The authors do not report any competing personal or financial interests related to this work.

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