Peer Review File

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**Reviewer A**

*Comment 1:* I read this article with interest. It suffers from a lack of detail on a numerical or statistical level. No hazard ratios, numbers in cohorts, or tables summarizing results. It would benefit from tables summarizing key studies.

*Reply 1:* Thank you for your feedback and for your interest in our article. We appreciate your suggestion regarding the inclusion of numerical and statistical details, such as hazard ratios, cohort numbers, and summary tables of key studies. While our review paper is not a systematic review, we acknowledge the importance of clarity and have therefore incorporated a table summarizing the key findings regarding SBC after EBRT for PCa.

*Changes in text:*
*Table 1.* Studies examining SBC risk in PCa patients receiving EBRT.

| **Study** | **Type of data** | **Comparison group** | **No. patients receiving EBRT** | **Median follow-up** | **Risk of SBC** | **Magnitude of SBC risk** |
|---|---|---|---|---|---|---|
| Wu (2020) (20) | SEER Registry | Non-irradiated patients | 97,799 | 10.5 years | Increased | HR: 1.60 (1.50-1.70), p<0.01 |
| Davis (2014) (21) | SEER Registry | General population | 525,569 | Not specified | Increased | SIR: 1.42 (1.28-1.58) |
| Guo (2019) (22) | SEER Registry | Non-irradiated patients | 143,679 | 6.1 years | Increased | HR: 1.41 (1.33-1.51), p<0.01 |
| Abern (2013) (23) | SEER Registry | General population | 495,132 | 5.4 years | Increased | SIR: 1.14 (1.08-1.20) |
| Aksnessaether (2020) (25) | Randomized controlled trial | PCa patients receiving androgen deprivation therapy | 429 | 12.2 years | Increased | HR: 2.54 (1.14-5.60), p=0.023 |
| Jahreiß (2021) (27) | Netherlands Cancer Registry | Radical prostatectomy | 42,069 | 5.2 years | Increased | sHR: 1.83 (1.63-2.05), p<0.01 |
| Jahreiß (2021) (27) | Netherlands Cancer Registry | General Population | 42,069 | 5.2 years | Increased | SIR: 1.33 (1.26-1.44) |

HR = hazard ratio; SIR = standardized incidence ratio; sHR = subhazard ratio

**Reviewer B**

After treatment for prostate cancer, the development of secondary cancer is an interesting topic due to the relatively long survival rate compared to other solid tumors. The authors have compiled a detailed review on the above topic.

*Comment 1:* Considering the latency period and risk factors between the occurrence of SBC after radiation therapy, most of the previously reported results are retrospective or case reports. Before the conclusion paragraph, an additional paragraph describing a recently published retrospective analysis or even case report related to SBC could add value to this review.

*Reply 1:* In the Discussion section, we have included supplementary text to underscore the significance of considering more recent findings. We agree that recent research outcomes better capture the realistic risks associated with present-day treatment protocols, contrasting with older studies that may encompass data from survivors subjected to outdated therapeutic regimens.

*Changes in text - page 12 , lines 293-296:* As treatment modalities evolve, more recent research findings provide important insight into the changing landscape of second cancer risks, offering more accurate reflection of the current treatment protocols. However, the long latency period of second cancers complicates the assessment of newer treatment protocols.

**Reviewer C**

*Comment 1*: The authors are to be commended for their efforts to bring clarity to a topic of growing importance as more men pursue definitive radiotherapy as a choice for curing their prostate cancer. Unfortunately, the topic is a bit more complicated than the authors seem to be aware of. Their discussion of radiation types is a bit too long and detailed.

*Reply 1:* We thank the reviewer for his/her thorough review. We did indeed include a detailed description of radiation types, because we believe that the readers of TAU have different background, for some this information will be obsolete and for some this will be useful.

*Comment 2:* The first issue is using surgically treated (RP) patients as the control group to estimate the risk of second cancers is problematic. This point is made clear in J Urology Eifler et al. 2012 (shown below). They showed that the risk of second cancers in men who undergo RP is <1/2 that of the general population (not irradiated patients). Thus, SEER data are essentially worthless, as are other studies using RP patients as the control group.
Overall:
All causes 1,419/3,033.8 0.47. (0.44–0.49)
Malignancy* 425/954.2 0.45 (0.40–0.49)

Heart disease 217/798.2 0.27 (0.24–0.31)
Chronic lower respiratory disease 22/182.9 0.12 (0.07–0.17)
Cerebrovascular disease 43/134.1 0.32 (0.23–0.42)
Diabetes 12/107.7 0.11 (0.05–0.17)
Accident 40/98.7 0.40 (0.28–0.53)

The best data to use to estimate the risk of second cancers comes from randomized comparing the long term outcomes of patients treated with ADT +/- RT such as the report by Aksnessaether et al. IJROBP 2020 entitled" Second Cancers in Patients With Locally Advanced Prostate Cancer Randomized to Lifelong Endocrine Treatment With or Without Radical Radiation Therapy: Long-Term Follow-up of the Scandinavian Prostate Cancer Group-7 Trial" (as attached). Of note, the incidence of second cancers were increased at 10 years and beyond similar for lung cancer and bladder cancer but not increased for colon and rectum. This finding suggest that this phenomena is not simply a dose and volume effect but also possibly due the immunosuppressive impact of pelvic RT especially in smokers.

*Reply 2:* The reviewer points out a topical discussion about comparing radiotherapy patients with prostatectomy patients. The main goal of our review is to summarize relevant literature. Due to the feedback from another reviewer, in the revised paper we now have incorporated a table presenting the findings of several studies exploring SPC risk after EBRT. This table clearly specifies the comparison group (general population or radical prostatectomy). Furthermore, we have added a paragraph to the Discussion section of the paper to discuss this matter, and here we included the references of the reviewer (Eifler et al and Akssnessaether et al). In the study of Akssnesaether et al, a significant excess risk for secondary bladder cancer is reported with an estimated HR of 2.54 (95% CI of 1.1-5.7), which we compare in our added discussion paragraph with estimations from the large retrospective epidemiological studies, comparing with prostatectomy and general populations.

*Changes in text - page 7, lines 150-169:* It has been argued that a prostatectomy cohort is not a valid comparison group for EBRT because it concerns healthier patients with less comorbidity and less smokers, which are both risk factors for various cancers including bladder cancer. In a study by Eifler et al. (2012) (24) they observed that the risk of dying from cancer after radical prostatectomy was significantly lower compared to the general population with a standardized mortality ratio (SMR) of 0.45 for cancer in general and 0.47 for bladder cancer. In a study conducted by our research group (27) we calculated relative risks for SBC for EBRT patients compared to both the general population and prostatectomy patients, and we found a relative risk of 1.33 and 1.81 respectively (*Table 1*), which also suggests that the risk is overestimated using a prostatectomy comparison group. It is also noteworthy that in our comparison with a prostatectomy group, there was a significant increase in the risk of second lung cancer, likely attributed to poorer comorbidity/smoking profiles. This was not the case for the general population comparison. In the study of Eifler et al, the risk of dying from lung cancer risks was largely reduced (SMR of 0.31). In a randomized control trial by Akssnessaether et al. (25), PCa patients receiving androgen deprivation therapy (ADT) were compared to patients receiving ADT + EBRT. An increased risk of SBC among patients receiving EBRT was found, with a

relative risk point estimate of 2.54 and a confidence interval of 1.1-5.6. These findings, when considered alongside those from retrospective cohort studies, underscore the consistent elevation in risk associated with pelvic radiotherapy. The findings of the main studies exploring SBC risk after EBRT are summarized in *Table 1*.

*Comment 3:* The issue of age is also problematic. Although it is true that the risk of second cancers is higher in the young who are irradiated, the time horizon for developing second cancers maybe shortened for those at higher risk of developing that cancer "naturally", i.e., older smokers.

*Reply 3*: You rightly point out the nuanced relationship between age and the risk of second cancers post-irradiation. While younger patients face a prolonged risk window, older patients with pre-existing risk factors, such as smoking, may experience an accelerated onset of second cancers. This underscores the complexity of assessing the risk-benefit ratio across different age groups and risk profiles. We will clarify this point in the revised manuscript.

*Changes in text - page 10, lines 253-262:* However, despite the observed trend of reduced risk of radiation-induced cancers with increasing age, it is important to consider the interplay of specific relative risks alongside the potential acceleration of second cancers in older patients with pre-existing risk factors such as smoking. While younger patients face a prolonged risk window, older patients may experience an accelerated onset of second cancers due to these factors. This underscores the complexity of assessing the risk-benefit ratio across different age groups and risk profiles. Given that the majority of the PCa population is aged 65 and above, it is crucial to note that while advanced age itself may not elevate the risk, the presence of other risk factors like smoking could contribute to an increased likelihood of second cancers during the post-radiotherapy follow-up period.