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European Association of Urology

Letter to the Editor

Re: Marco Moschini, Emanuele Zaffuto, Pierre I. Karakiewicz, et al. External Beam Radiotherapy Increases the Risk of Bladder Cancer When Compared with Radical Prostatectomy in Patients Affected by Prostate Cancer: A Population-based Analysis. Eur Urol 2019;75:319–28

We read with interest the analysis by Moschini et al. [1] regarding the proposed increased risk of bladder cancer after radiotherapy for prostate cancer (PCa). The authors analyzed the Surveillance, Epidemiology, and End Results (SEER) Medicare insurance program-linked database to include PCa patients, who were aged >65 yr and treated with radical prostatectomy (RP) or external beam radiation therapy (RT) between 1988 and 2009. They used multivariable competing-risk regression analyses to assess the risk of developing a second bladder or rectal cancer. The authors concluded that patients treated with RT are at an increased risk of developing a second primary bladder cancer compared with those treated with RP. We believe that the current analysis has innate forms of bias present that ultimately invalidate the authors' conclusions.

There have been heavily publicized inconsistencies with the RT variable in SEER [2–7]. Due to such inconsistencies, in 2016, the National Cancer Institute removed the RT variable from the SEER database [8]. Thus, it is unclear which patients actually received RT in the work by Moschini et al. [1]. Additionally, SEER does not provide granular details on performance status or risk factors for secondary cancers, including exposure and/or duration of exposure (eg, smoking, schistosoma infection, exposure to aniline dyes), and RT dose, volume treated, technique, and treatment intent.

Due to differences in patients who undergo RT or RP for PCa, it has previously been shown that RT patients are more likely to die from many causes (eg, pneumonia, chronic obstructive pulmonary disorder) [9]. If Moschini et al. [1] had explored the risk of death from other causes, as

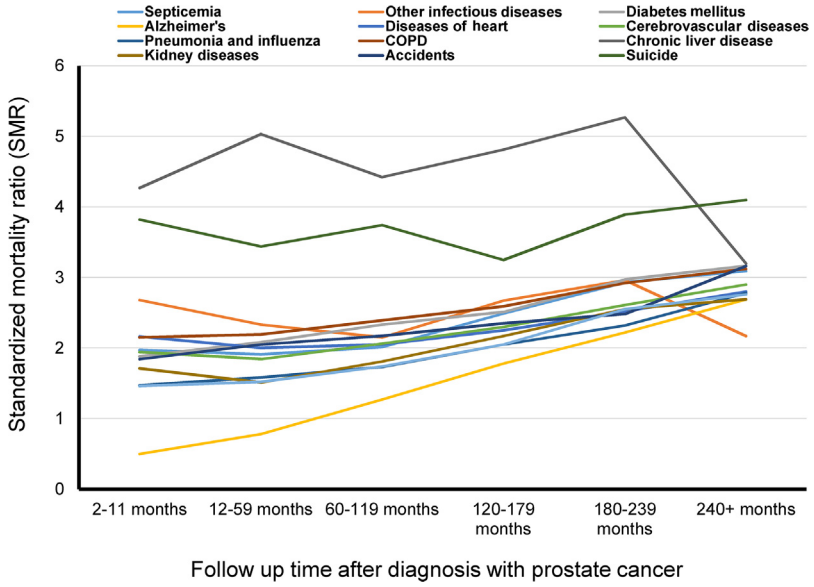

Fig. 1 – Standardized mortality ratio (SMR) versus follow-up time after diagnosis with prostate cancer. SMRs for the leading causes of non-cancer death were characterized after diagnosis with prostate cancer, binned by time periods. An SMR above 1 represents a higher relative risk of death for a particular cause when compared with the general population. Prostate cancer patients are at a risk of death from all causes after diagnosis, including the risk of secondary cancers and non-cancer deaths.

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previously done with SEER [10], they then would have found that these patients are at risk to die from many causes, as shown in Fig. 1. Would the authors have concluded that RT puts patients at risk to die of pneumonia and liver disease?

Randomized controlled trials (RCTs) and pooled meta-analyses have not demonstrated a measurable increased risk of secondary cancers; many actually show numerically lower rates even without an identifiable "trend." In a meta-analysis [11] of 6884 PCa patients from 12 RCTs with enrollment started after 1990, there were almost no patients reported to have died from secondary cancers. In the ProtecT [12] RCT that randomized 1643 patients with localized PCa to active monitoring, RP, or RT, less than 5% of patients in each group died from a neoplasm other than PCa (22, 25, and 23 patients, respectively). In the EORTC trial [13], which randomized 1005 men to observation or adjuvant RT, second cancers occurred in 69 patients in the observation arm (13.7%) and 68 in the adjuvant RT arm (13.5%). Finally, Wiltink et al. [14] pooled three RCTs of rectal and endometrial cancer patients (n = 2,554 total) treated with surgery with or without RT and showed no significant difference in the development of secondary cancers in RT-treated patients.

In summary, population registries are unable to answer the question at hand. The only reliable method to estimate the risk of secondary cancers "caused" by RT for men with PCa is to use RCT data which allow one to reduce and remove unavoidable forms of bias present in retrospective research. This is paramount when studying PCa given the innumerable differences between populations that undergo RP and RT. RT does have a theoretical risk of secondary malignancies in adults (which should be discussed with patients), but the absolute risk is under 1% and has yet to be even accurately identified or quantified.

Conflicts of interest: The authors have nothing to disclose.

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