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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. In press. <https://doi.org/10.1016/j.eururo.2018.09.034>**

### ***Radiation Therapy Versus Radical Prostatectomy: No Way Out Without a Randomized Trial***

We read with interest the paper by Moschini and colleagues [1], who tried to investigate the risk of a second pelvic tumor according to the primary treatment for prostate cancer (PC), including prostatectomy (RP) and radiotherapy (RT). The authors conclude that patients with PC treated with RT have a significantly higher risk (by 72%) of developing a second primary bladder cancer within 5 yr when compared to RP. In our opinion, the interpretation deserves several considerations focused on undervalued criticisms.

#### **Type of analysis**

As reported, the Surveillance, Epidemiology and End Results database, covering 28% of the US population, and the retrospective nature of the analysis are the main limitations of the study. Considering the absolute number of second primary tumors (1.8% for RP, 2.1% for RT), a larger sample size and a more balanced distribution could reduce the differences. These results can be interpreted only as hypothesis-generating and not as definitive data.

#### **Inclusion criteria**

The analysis was conducted for a cohort of elderly patients, for whom the incidence of other primary tumors is high because of factors that include life span, lifestyle, comorbidities, and type/job exposure. It is noted that survivors of pediatric malignancies are at higher risk of RT-induced malignancy (RIM) with respect to elderly people [2]. All these parameters are lacking.

Among the inclusion criteria, the time between PC and another pelvic tumor was >6 mo. All the published data for

this setting assumed that the median time for RIM development was 10 yr (range 5–20). Thus, some doubts about staging and the correlation between second tumor and RT within 5 yr are legitimate.

#### **RT evaluation**

The study period (1988–2009) is too wide, and the analysis this includes very heterogeneous patients in terms of RT treatment plan because of the improvements in techniques and technologies. Thus, the RT limitations are as follows:

The total dose and fractionation and the photon energies [2];

- In terms of technique, intensity-modulated RT can reduce the dose to organs at risk (OARs) and is estimated to generate one-third less RIM with respect to a three-dimensional technique [2,3];
- In terms of the target, RIM is defined as any healthy region irradiated, so patients treated using wide RT fields are at higher risk. In the past, whole-pelvis irradiation was largely used, but this is not the case nowadays [2];
- Image-guided RT is useful in evaluating movements of the prostate, bladder, and rectum to achieve dose and target conformity, sparing OARs. Image-guided RT was not used in the past and is missing from this evaluation;
- In terms of OAR evaluation, OAR dose constraints have been more strictly defined after the publication of QUANTEC in 2010 [4]; and
- The clinical protocol during RT (empty or full bladder/rectum) should be described in detail.

#### **Overall survival**

The randomized trial published by Hamdy et al. [5] reported the same 10-yr overall survival for RP and RT for PC, despite the presumed difference in terms of second primary pelvic tumors. This issue was simply missed in the paper by Moschini et al.

Finally, the emphatic conclusion from the analysis should be mitigated. These data could be strongly affected by several substantial biases, most of them underestimated

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or omitted, and are not suitable as a basis for changes in decision-making strategies for PC patients.

**Conflicts of interest:** The authors have nothing to disclose.

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