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Hypofractionation of radiation dose to the prostate does not necessarily imply a greater risk of acute radiation proctitis

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Dear Sir,

We read with great interest the recent article by Sinzabakira et al. who conducted an exhaustive systematic review and meta-analysis of prospective studies on acute and late toxicities among localized prostate cancer patients submitted to moderate hypofractionated radical radiotherapy [1]. Overall, the authors pooled the data from 17 studies, 10 of which have also a parallel arm treated with standard fractionation of 2 Gy/day. Their conclusions deal with an increased risk of 6,3% of acute gastrointestinal (GI) toxicity when using moderate hypofractionation of radiation dose rather than standard fractionation. Conversely, no significant differences regarding genitourinary and late GI toxicities were reported. We commend the authors for their painstaking work, which is highly valuable and well-conducted. However, we would share some considerations with them. Since the intention of their meta-analysis was to include only prostate or prostate plus seminal vesicles-directed radiotherapy studies (third from last column from the right of table 1), it would be natural to assume that the investigated GI toxicities are those involving the rectum, namely the radiation proctitis (RP). The authors' paper is focused on the dose prescribed to the prostate (±seminal vesicles) rather than on the dose to which the rectum was exposed, as if the former may work as a surrogate for the latter. We understand that collecting dosimetric data on the rectum from the included studies was practically impossible. Indeed, as recently highlighted by our review, the risk of RP depends not only on the dose prescribed to the prostate but also on several more factors [2]. Among these, the use of image-guided radiotherapy (IGRT) plays a key role in reducing the risk of RP by allowing the contouring of narrower planning target volume margins compared to non-IGRT treatments [3]. Less rectal exposure to harmful radiation is a consequence. Only 6 out of the 17 studies included in the meta-analysis used IGRT [4–9]. Moreover, IGRT protocols are not equivalent to each other: the risk of RP decreases by switching from a bone- or fiducial marker-based setup verification (by electronic portal imaging) to a soft tissue-based one (by cone beam computed tomography, CBCT, or magnetic resonance imaging guidance, MRI), as the latter provides information on the relationship of the rectum with the prostate, enabling appropriate corrections before radiotherapy fraction delivery [10].

Additionally, the two trials listed by the authors as proof of a significantly greater risk of acute $\geq$ G2 GI toxicity for hypofractionation over standard fractionation used portal imaging- and fiducial marker-based setup verification protocols [11,12].

The frequency of the setup verification also has a relevant impact on the rate of RP, as demonstrated by de Crevoisier et al. who reported a significantly reduced risk of RP by adopting a daily schedule compared to a weekly one [13]. Of the six IGRT studies mentioned above [4–9], only that by Krupa et al. used a reliable IGRT protocol based on daily CBCT [7], since the other five were biased by the non-exclusive use of soft tissue-based setup verification or by the extent of radiotherapy fields to include also the pelvic nodes, thus conditioning the overall GI toxicity rate. Therefore, contrary to what one could infer from the pooled results [1], hypofractionation of radiation dose to the prostate does not necessarily imply a greater risk of acute RP [14]. We invite the authors to discuss these observations as well as our summary on RP [2] and the original findings about the use of topical supportive therapy for the prevention of such toxicity [15,16].

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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