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Open to Debate – Referee

Primary Tumour Treatment in Oligometastatic Prostate Cancer: Radiotherapy Versus Radical Prostatectomy

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The utilisation of positron emission tomography imaging based on prostate-specific membrane antigen has led to an increase in the detection of patients with prostate cancer (PC) with low metastatic burden. Although definitions vary, in general, oligometastatic PC (OMPC) refers to those with five or fewer bone or lymph node metastases [1].

There is a survival benefit with local radical treatment in addition to systemic therapy in de novo OMPC, as shown by data for arm H of the STAMPEDE trial. Patients who received radiotherapy (RT) to the prostate in addition to systemic treatment had better overall survival (OS), with 3-yr OS of 81% compared to 72% for the group who received systemic treatment only. There are no randomised data comparing treatment of OMPC with radical prostatectomy (RP) versus RT, and thus the choice of primary local treatment for these patients remains an ongoing controversy in urological practice.

Here we synthesise a balanced viewpoint on RT versus RP in the primary treatment of OMPC on the basis of the

two points presented by Knipper and Graefen [2] and van Moorselaar et al [3].

Knipper and Graefen [2] rightly comment that RP and RT have equivalent oncological outcomes for localised PC and thus it is not unreasonable to extrapolate and expect similar outcomes in the oligometastatic setting.

There are some data regarding RP in OMPC; however, these data are retrospective in nature and limited by lack of quality-of-life data and administration of adjuvant RT, which makes interpretation of oncological outcomes difficult. While retrospective studies have shown the safety and technical feasibility of RP in OMPC with good preliminary oncological outcomes [4], these cases were highly selected and TRoMbone is examining these parameters, as well as quality of life, in a randomised setting to avoid such selection biases [5]. Other similar randomised trials such as g-RAMPP closed early because of changes in the standard of care for these patients as a result of STAMPEDE, and SWOG 18-02 includes patients with a higher metastatic burden and offers a nonrandomised treatment choice between RP and RT [6].

Case selection is paramount, in that the tumour must be resectable and those at high risk of local symptoms from progression may potentially derive more benefit from RP, especially as there are high levels of genitourinary toxicity from RT in advanced PC, even after transurethral resection of the prostate. RP also has the advantage of yielding tissue for molecular analysis, which would further our biological understanding of OMPC as a transitory disease state between localised/locally advanced cancer and fully disseminated disease [7]. It is also true that trials have shown no significant difference in oncological outcome between RP

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and RT for localised PC [8], and thus there is no reason to expect a significant difference between modalities for OMPC. The data regarding the abscopal effect of RT are preliminary and mostly limited to animal studies.

van Moorselaar et al [3] quote results from the two randomised prospective trials (STAMPEDE and HORRAD) looking at RT to the primary tumour in de novo OMPC. As expected, a meta-analysis of both these trials by the STOPCAP M1 Radiotherapy collaborators showed a 7% improvement in 3-yr OS among men with fewer than five bone metastases [9–11].

One rationale for treating the primary tumour in de novo OMPC is the abscopal effect, whereby RT to the primary tumour leads to an immunomodulatory response with an effect on metastatic lesions, as explained by the authors. In addition, patients with OMPC are living longer with new systemic therapies, and local symptoms are problematic in the late stages if left untreated. Furthermore, PC can persist in the primary site after systemic treatment and it is hypothesised that this can drive disease by seeding further metastases.

There is a strong recommendation in the 2021 European Association of Urology guidelines to offer androgen deprivation therapy combined with RT to patients who first present with low-volume metastatic disease [12]. Until mature data from randomised controlled trials are released, it is difficult to make any strong recommendations about the role of RP in de novo OMPC. However, there is a strong recommendation to offer RP to highly selected patients with N1 disease, but only as part of multimodal therapy.

The strength of the available evidence lies in favour of RT in OMPC. Although retrospective data assessing the efficacy of RP in the context of oligometastatic disease appear promising, the lack of data from prospective randomised trials means that this cannot be considered the current standard of care, whereas there is clear evidence of a survival benefit associated with RT delivered to patients with OMPC.

Hence, the role of RP in de novo OMPC should be restricted to clinical trials. While trials are in accrual, none are examining a direct comparison between RP and RT in OMPC specifically; such a trial (once feasibility within a randomised setting is confirmed from TRoMbone) is being planned by the TRoMbone authors.

Conflicts of interest: The authors have nothing to disclose.

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