


Stereotactic Radiotherapy for Localised Prostate Cancer: Time to Clarify the Possible Impact of Concurrent Androgen Deprivation Therapy

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Introduction

Surgical treatment and prostate irradiation are the primary methods used to treat localised prostate cancer (PCa). The results of the ProtecT trial [1] have demonstrated that surgery and radiotherapy (RT) have comparable oncological outcomes in terms of prostate cancer-specific survival and biochemical disease free survival (bDFS). Urinary incontinence and erectile dysfunction are more frequent after surgery, whereas gastrointestinal (GI) toxicity and urethral stricture are associated with increased risk after RT [2].

RT is delivered either with external beam RT (EBRT) or via implanted radioactive seeds (brachytherapy). Traditional EBRT exploits high-energy X-ray photons, and standard schedules consist of conventional fractionation (e.g. 74–78 Gy in 37–39 fractions; 1.8–2 Gy fraction) or moderate hypofractionated RT (e.g. 60–70 Gy in 20–28 fractions; 2.5–3.1 Gy fraction) [3].

“Unfavourable intermediate risk” or “high risk” localised PCa, is managed with the concurrent administration of androgen deprivation therapy (ADT) for 4–6 months (short term) or 18–36 months (long term), respectively. This combination reduces the risk of local failure and metastasis and increases bDFS and overall survival [4].

At least five mechanisms explain the biological synergy of RT and ADT. First, RT grants local disease control, and ADT eliminates undetected micro-metastases, establishing a “spatial cooperation” [5].

Androgen receptor signalling increases the expression of DNA repair genes (classical non-homologous end joining) and promotes the proliferation of prostate cancer by accelerating the repair of RT-induced DNA damage. Thus, ADT can prevent these radio-resistance mechanisms through cytotoxic enhancement [6].

Additionally, ADT enhances oxygenation in androgen-deprived tumour microenvironments, thus facilitating the perfusion of gland tissues and increasing the sensitivity of PCa to RT [7].

Lastly, ADT-related prostate and tumor cytorreduction, if managed within a neoadjuvant period before RT, enhances the coverage of the tumour target while reducing the dose to the rectum and bladder and thus results in temporal modulation and normal tissue protection [8].

Biologic Rationale of SRT-ADT Therapy

Stereotactic radiotherapy (SRT) is an advanced form of hypofractionation delivering high effective doses in a short time (usually delivered in 4–8 fractions; Fraction size ≥ 500 cGy). SRT is comparable to traditional EBRT in terms of oncological and clinical outcomes, such as bDFS, patient-reported outcomes (PRO), and quality of life (QoL). However, SRT slightly increases acute and reversible toxicity. SRT is revolutionising PCa management also thanks to a shorter overall treatment time that guarantees a logistical and economical advantage compared to traditional RT [9].

Understanding the potential biological interaction of ADT and SRT and comparing it to the classic context is crucial because of the effects of ADT on toxicity and QoL.

SRT may have some of the benefits of combining RT and ADT.

Spatial cooperation is a valid reason for ADT administration in the context of SRT. However, the subsistency of the spatial cooperation concept is strictly related to micrometastatic spreading, which cannot be detected by conventional imaging methods. Whether spatial cooperation remains a clinical need in the era of accurate molecular imaging remains an issue. Prostate specific membrane antigen positron emission tomography computed tomography (PSMA PET CT) now plays a major role in the identification of patients with real localised diseases, thus limiting the need for concurrent systemic therapies, such as ADT, and therefore limiting the validity of the spatial cooperation rationale [10].

Despite such a theoretical basis, this hypothesis remains an area of open debate. Temporal modulation can be

exploited with SRT. The biological cooperation and the cytotoxic enhancement that enables synergistic effects of RT and ADT in the classic RT context do not completely affect SRT. In fact, the ablative effect of SRT in comparison to normo-moderate hypofractionated RT is mainly related to different mechanisms, such as direct vascular damage, endothelial cell death and double-strand breaks.

With regard to normal tissue protection, genitourinary and GI toxicity considerably increases when ADT and SRT are combined. The underlying biological mechanisms are currently unknown but may be related to increased radiosensitivity of normal tissues subjected to ADT [11–13].

Clinical Data Supporting Combination of SRT-ADT

Scientific evidence supporting the use of SRT-ADT is limited. In prospective and retrospective cohorts, few patients are treated with SRT combined with ADT.

In the SHARP series, which prospectively evaluated 344 high-risk patients, 72% of patients received ADT concurrently with SRT (investigator's choice) for a median duration of 9 months. Univariate analysis results showed that the 4-year bDFS considerably increased in patients treated with concurrent ADT, in contrast to 4-year distant metastasis free survival. However, selection bias may have affected these results.

However, Jackson *et al.* [13] reported that ADT did not affect the bDFS of more than 6000 patients.

These findings share the same limitation. Pre-specification in ADT prescription is lacking, and accurate staging methods, such as PSMA PET CT, are rarely used [14].

Ongoing Trials Testing SRT-ADT

At least two randomised, phase III studies evaluate the effectiveness of SRT with or without ADT. The first trial (n° NCT03056638) compares SRT (40 Gy delivered in five fractions) on the prostate and the same SRT schedule combined with 6 months of Degarelix treatment. The primary endpoint is 2-year biopsy positivity rate.

The second trial (SPA-Trial, n° NCT05019846) includes unfavourable intermediate risk and a subgroup of high-risk patients treated with SRT (36.25 Gy in five fractions) and randomised to receive 6 months of triptoreline (22.5 mg) treatment [15]. The primary endpoint is 5-year bDFS. PRO, QoL and clinician-reported outcomes are considered secondary endpoints. Moreover, SPA is designed to detect increase in toxicity in patients treated with the ADT arm. This effect was previously attributed to radio-induced damage.

We are confident that the ongoing randomised controlled trials will provide reliable evidence to support treatment decisions in the exciting yet complex setting of SRT for PCa.

Availability of Data and Materials

Not applicable.

Author Contributions

MLB, LT and AG—developed the editorial topic and wrote the text; EM, AD, LG and VM—managed literature research; NN, AM, CT, LG, DA and MB—checked the manuscript's accuracy and revised the manuscript. All authors read and approved the final manuscript.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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