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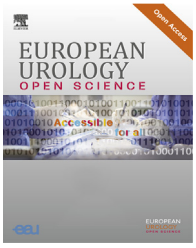

European Association of Urology

Open to Debate: For

How To Manage T3b Prostate Cancer in the Contemporary Era: Is Radiotherapy the Standard of Care?

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Patients with prostate cancer (PCa) who undergo surgery for locally advanced disease have a significant risk of biochemical relapse. For instance, for patients with seminal vesicle involvement (SVI) at final pathology the 5-yr and 10-yr biochemical progression–free survival (bPFS) rates are 36% and 12%, respectively, in the absence of adjuvant treatment [1]. Surgery is seldom enough to cure these patients and the need for further treatment is the foundation for the multimodal treatment concept. However, it is far from clear that this approach is suited to the needs of patients with high-risk (HR) PCa.

First, the optimal sequence for different treatments is not obvious. Historically, radiotherapy (RT) was proposed as an adjuvant treatment for men with adverse features after radical prostatectomy (RP) following results from three randomized controlled trials (RCTs): SWOG S8794 [2], EORTC 22911 [3], and ARO 96-02 [4]. These three RCTs showed a progression-free survival (PFS) benefit, and an overall survival (OS) benefit in the SWOG trial [5], with the use of adjuvant radiotherapy (ART) over observation in this population. Recently, three more RCTs (RADICALS RT [6], RAVES [7], and GETUG-AFU-17 [8]) and a meta-analysis using individual-patient data from these trials (ARTISTIC [9]) compared ART versus early salvage RT (eSRT) in terms of oncological outcomes and toxicity. ART was not superior to eSRT in term of PFS, with higher rates of genitourinary (GU) toxicity in the ART arm, suggesting less frequent use of ART. However, abandoning ART as an appropriate management strategy would be premature given the under-representation of patients with HR features in these trials (only 9–17% with Gleason score $\geq$8 and $\sim$20% with SVI). In a retrospective propensity score–matched analysis of 26 118 patients with PCa with adverse pathology, ART in comparison to eSRT was associated with lower all-cause mortality risk [10]. These contradictory results underline the fact that the decision-making process on whether to add ART to RP for patients with PCa with adverse features is a complex one and that the best treatment sequence in a multimodal treatment approach is not straightforward.

Moreover, assuming that postoperative RT is recommended, the long-term toxicity of a multimodal treatment solution requires focused attention. On the one hand, the surgical procedure has its own toxicity. In the ProtecT trial, 20% of men required at least 1 pad/d at 6 yr after RP [11]; in the more recent PACE A trial, this rate was 46.8% at 2 yr after RP [12]. Although GU toxicity data are scare for patients with HR PCa, it may be assumed that the incontinence rate would be higher than in the ProtecT and PACE A studies, which mainly included patients with low- or intermediate-risk PCa. In addition, and according to the European Association of Urology PCa guidelines [13], a patient with advanced disease for whom the first approach is surgery should undergo extended pelvic lymph-node

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dissection (PLND). However, it has been shown that PLND is a risk factor for the occurrence of early postoperative complications [14]. On the other hand, postoperative RT results in higher rates of grade ≥2 GU or gastrointestinal (GI) toxicities in comparison to observation [2–4,6–8]. Finally, following results from the RTOG 0534 SPPORT trial that showed a benefit of adding pelvic lymph-node RT to prostate-bed RT in the salvage setting [15], pelvic irradiation will become increasingly used, which after PLND could increase the risk of lower-limb lymphedema [16].

The question of systemic spread of PCa and therefore the need for systemic treatment is thus very relevant in the context of locally advanced disease. Patients harboring HR features will die from metastases and need hormonal treatment to reduce this risk of spread. Abdollah and colleagues [17] showed that high pathological stage predicted lymph node invasion among 5274 patients treated with RP and PLND. Similarly, Park et al [18] found that preoperative T stage on magnetic resonance imaging in a cohort of 101 patients with PCa who underwent RP with PLND was predictive of micrometastases to pelvic lymph nodes. On the basis of recommendations [13], in the context of multimodal treatment, patients who would benefit from a systemic treatment would not be able to receive one. For now, studies addressing the role of systemic therapy in combination with RP, except for pN+ disease, do not allow reliable conclusions owing to low patient numbers, lack of a standard of care (SOC) as a control, and short follow-up [19]. Moreover, the three RCTs evaluating addition of ART to RP for patients with PCa with adverse features did not combine androgen deprivation therapy (ADT) with RT and did not show a clear benefit in term of metastasis-free survival (MFS). Therefore, even if hormonal treatment is key for patients with HR PCa, hormonoradiotherapy is not an SOC in the adjuvant setting. On the contrary, among cases receiving RT as the primary treatment, all patients with HR features would benefit from a systemic treatment. First, several RCTs have demonstrated an OS benefit from addition of ADT to RT [20–24]. Second, recent evaluation of addition of an androgen receptor signaling inhibitor (ARSI) to ADT ± RT in patients with HR nonmetastatic PCa revealed a significant improvement in 6-yr MFS on ARSI addition (82%, 95% confidence interval [CI] 79–85% vs 69%, 95% CI 66–72%) [25]. These results represent the highest level of evidence in this population.

Local relapse after RT is a frequently identified concern among urologists, with salvage RP associated with higher rates of GU and GI toxicities than primary RP [26]. However, salvage RP is not the only treatment modality, and reirradiation with stereotactic body RT or high-dose rate or low-dose rate brachytherapy appears to result in less severe GU toxicity than RP, with acceptable oncological outcomes [27]. Moreover, patterns of clinical progression for radiorecurrent HR PCa revealed that 25% of patients with radiorecurrent PCa developed distant metastases within 1 yr of biochemical relapse [28], relegating salvage local treatment to a secondary role. Finally, increasing the dose to the prostate could be a way to decrease local relapse events [29]. Two RCTs have assessed the effect of increasing the dose to the whole prostate gland [30] or the intraprostatic tumor [31] in HR PCa population with less than 3% of purely local relapse. The trials both showed a bPFS benefit of dose escalation, with no additional toxicity when the boost was restricted to the intraprostatic tumor [31]. Dose escalation to the primary tumor, in combination with hormonal treatment, is therefore a recommended treatment strategy for patients with HR PCa.

To conclude, in the absence of level 1 evidence favoring RP over hormonoradiotherapy in the context of a multimodal approach, factors such as treatment complexity, toxicity, and ability to eradicate the micrometastatic disease load should be considered. When making a decision, in light of what has been discussed above, RT-based treatment may represent the best approach for patients with localized HR PCa.

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

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