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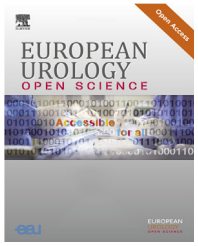

European Association of Urology

Open to Debate: Con

How To Manage T3b Prostate Cancer in the Contemporary Era: The Benefits of Surgery

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High-risk and locally advanced prostate cancer (PCa) are heterogeneous entities. Prognosis is based on various parameters, depending on the classification of interest: clinical local extent (T stage on digital rectal examination, prostate-specific antigen [PSA], International Society of Urological Pathology grade group [GG] at biopsy, number of positive cores, percentage tumor in biopsy samples, and lesion characteristics on multiparametric magnetic resonance imaging [mpMRI]) [1]. These criteria allow classification of patients for determining the most appropriate treatment. Recent studies have shown that mpMRI leads to upstaging in approximately one-third of patients in comparison to digital rectal examination, mainly because of superior detection of T3 disease [2]. Extracapsular extension (ECE) and seminal vesicle invasion (SVI) are key prognostic factors for biochemical recurrence following treatment [3]. Thus, an increasing number of patients are considered with non–organ-confined disease (ie, locally advanced PCa) and their management is a challenge.

For high-risk or locally advanced PCa, surgery appears to be an adequate strategy for several reasons. The European Association of Urology guidelines recommend offering radical prostatectomy (RP) for locally advanced PCa as a potential first step in a multimodal strategy [1]. Although RP for T3 PCa is associated with a higher risk of positive surgical margins (R1) and positive lymph nodes, current strategies allow good long-term outcomes [1]. Joniau et al. [4] demonstrated that these patients had 10-yr cancer-specific survival of 80–95% and 10-yr overall survival of 59–84%, depending on the number of risk factors (GG >3, >cT2, or PSA >20 ng/ml). Hence, selected patients with non–organ-confined PCa as a unique risk factor are the best candidates for surgery.

Second, PCa with SVI is considered at high risk of recurrence [3]. A multimodal approach is therefore often advocated, for which surgery is the cornerstone. If complementary treatments are indicated, studies have shown that salvage external beam radiotherapy (EBRT) is not inferior to adjuvant EBRT [5]. Salvage EBRT should be discussed before PSA exceeds 0.5 ng/ml and theoretically at the earliest timing of approximately 0.2 ng/ml [1]. For patients with pathological specimen characteristics associated with a high risk of relapse (R1, pT3, or GG 4/5) but with undetectable PSA after surgery, no immediate adjuvant treatment is recommended, but can be discussed for young patients with more than one adverse feature [1]. More than half of patients with only one adverse feature on pathology could avoid irradiation and subsequent toxicities with this strategy [5].

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Third, there is frequent downstaging and downgrading between preoperative mpMRI and pathology assessment of the RP specimen [2]. Although some studies have described better prediction of oncological outcomes with mpMRI than with digital rectal examination [6], mpMRI can overdiagnose ECE and especially SVI, and thus overclassify patients as having locally advanced disease [7]. Approximately 20% of patients initially considered to have SVI on MRI might be reclassified postoperatively as having pT3a and even sometimes organ-confined disease [2,7]. Not offering a surgical approach in a decision based solely on local extension deprives these patients of one valid treatment option.

Besides the advantages of surgery, radiotherapy (RT) for treatment of PCa with local extension has some limitations. The first pitfall of EBRT is the choice of salvage treatment if biochemical recurrence occurs. Whereas salvage therapies after surgery are codified, management of local failures after definitive EBRT is controversial [1]. The risks of genitourinary and gastrointestinal toxicities associated with local salvage treatments following RT failure (eg, local reirradiation or salvage RP) are significant [8]. Moreover, comparisons of RP and EBRT as salvage modalities showed more failures in the EBRT group [9].

Second, EBRT with curative intent for patients with SVI must cover the whole gland as well as the seminal vesicles [1]. Dose escalation has shown better treatment outcomes and hypofractionation is noninferior to conventional fractionation schemes in low- and intermediate-risk PCa [10]. Owing to their motion, the seminal vesicles require a relatively large margin for the planning target volume [10]. Thus, a high-fraction dose results in higher doses to the bladder and the rectum and consequently higher toxicities. In addition, local recurrences after EBRT for PCa involve the seminal vesicles in approximately 40% of cases [11]. Local recurrences are significantly associated with PCa-specific and overall survival [12]. Patients with SVI at diagnosis might then be at even higher risk of seminal vesicle recurrence and mortality when treated with EBRT.

Furthermore, current enhanced imaging strategies are better at stratifying patients according to their micrometastatic status, with more "true" N0M0 high-risk cases identified. Avoidance of systemic therapy in this context is even more reasonable.

Finally, patients with locally advanced PCa without nodal invasion and only one "very high risk" factor (ie, T3) according to the STAMPEDE M0 trial are ineligible for treatment intensification with abiraterone [13]. These patients have poor prognosis and an aggressive approach is beneficial. Multimodal therapy appears to be an adequate strategy, potentially justifying the place for surgery.

In conclusion, PCa with ECE and, especially, SVI is a widespread pathology with an aggressive course. Radiohormonotherapy is one valid option, especially for patients with very high risk according to the STAMPEDE criteria. However, surgery is still of major interest when considered in a multimodal approach for patients with only one adverse feature. The place of perioperative intensification is still under debate and ongoing randomized trials will dictate the future of surgery for this scenario (PROTEUS trial, NCT03767244).

To date, there are no evidence-based studies comparing RP with EBRT plus androgen deprivation therapy (ADT) for locally advanced disease. Several nonrandomized studies showed better survival outcomes after RP in comparison to EBRT plus ADT among well-selected patients [14]. However, results from retrospective cohorts are inconsistent and biased. Both approaches are currently used, and surgery with pelvic lymph node dissection (PLND) is a strategy recommended for non–organ-confined PCa [1]. It is noteworthy that the template for PLND is still under debate. Extended PLND provides better pathological staging without demonstrating differences in oncological outcomes in comparison to a limited template [15]. However, extended PLND for PCa with aggressive pathological features on biopsy (GG 3–5) may yield a biochemical recurrence–free survival benefit [16].

Results from SPCG-15, a Scandinavian prospective, multicenter, phase 3, randomized clinical trial comparing RP with radiohormonotherapy for this scenario, are eagerly awaited.

Conflicts of interest: The authors have nothing to disclose.

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