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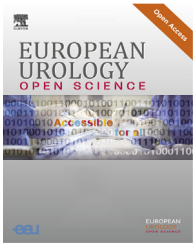

Open to Debate – Referee

How To Manage T3b Prostate Cancer in the Contemporary Era: Referee Position

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For the management of high-risk to very high-risk prostate cancer, all contemporary guidelines merely report a list of the treatment options available, with very scarce details on the relative merits of each of them [1,2]. The general picture is disappointing and there are few clear indications to help clinicians in daily routine when counselling a specific patient and his family. Furthermore, there is no evidence from randomised trials directly comparing the different treatment strategies. We should also not forget that, regardless of the classification used, aggressive prostate cancer is a very heterogeneous disease, with interplay among different known prognosticators that translate to extremely different prognoses [3].

Prostate cancer with seminal vesicle invasion (SVI; stage T3b) is not a common entity and is generally identified via diagnostic imaging (multiparametric magnetic resonance imaging) and seldom confirmed by pathology, as seminal vesicles are not routinely biopsied by urologists. Against this background, we know that standard imaging is not perfect, and even metabolic imaging may lead to misclassification of the disease. It is not uncommon to find an intraprostatic cancer in a prostatectomy specimen when SVI was the preoperative clinical diagnosis. However, the opposite is not rare, with clinical intraprostatic disease often diagnosed as locally advanced (pT3a or/and pT3b) at final pathology [4,5]. Thus, when present, SVI is recognised as one of the most powerful prognosticators of metastatic disease and this has several implications. First, local control of T3b cancer is of paramount importance and several randomised trials have clearly shown that a systemic treatment alone (with androgen deprivation therapy) is unsatisfactory in comparison to local irradiation [6,7], but the prognosis for these patients probably depends more on control of the risk of metastatic disease. Second, the pattern of relapse for pT3b disease after primary treatment is rarely only local, so a local salvage treatment (with associated toxicity) is seldom indicated. Finally, it appears that systemic treatment for a patient diagnosed with T3b cancer is at least as important as local control of the disease. In this respect, the STAMPEDE group has been instrumental in defining a new standard of care for very high-risk prostate cancer [8].

A multimodal approach is essential to optimise the chance of cure for patients diagnosed with T3b cancer, which holds true regardless of which first-line treatment is chosen. A body of data indicates that addition of long-term androgen deprivation therapy improves overall survival in comparison to irradiation alone [9,10], but a rate of biochemical relapse of 50% at 5 yr after surgery alone clearly indicates that some form of adjuvant or salvage therapy is also needed for patients with T3b disease managed surgically [11]. Recent publication of meta-analysis data for the ARTISTIC cohort seems to have definitively closed

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the debate on postprostatectomy adjuvant radiotherapy (RT) versus a salvage RT approach, but it is not clear whether the results may also apply to the pT3b subgroup of patients, as only approximately one-fifth of the ARTISTIC cohort had SVI at definitive pathology [12,13]. In any case, patients and their families should be informed about the need for treatment intensification and the related toxicities, which are far from being trivial. Regarding multimodal RT approaches, external beam RT with a brachytherapy boost (with either a low or high dose rate) for high-risk cancer may also represent a very promising option, with large multi-institutional series showing a benefit of this strategy over radical prostatectomy or external beam RT alone [14,15].

Where do we stand in 2023 regarding the management of patients diagnosed with cT3b prostate cancer? Is it possible to make any firm recommendation in terms of the "best" treatment available? The Scandinavian SPCG-15 trial has almost completed recruitment of patients with locally advanced prostate cancer. SPCG-15 is the only phase 3 trial randomising patients to a surgery- versus radiotherapy-based approach; the recently published characteristics for the first 600 patients in the study indicate that one-third overall will have T3b disease [16] and this means that the debate will certainly not be closed even when definitive results become available. The best strategy is probably a patient-centred approach: patients and their families should be directly involved in the decision-making process, with acknowledgment of any treatment that has shown superiority for a hard endpoint, but in terms of impact on quality of life, the patient himself should have the last word. Professionals and care providers should ensure that the best technology for surgery and for radiotherapy is available in their centre, and that the best and most up-to-date systemic treatments are delivered.

Conflicts of interest: The authors have nothing to disclose.

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