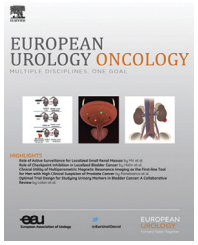
EUROPEAN UROLOGY ONCOLOGY XXX (2019) XXX–XXX

available at www.sciencedirect.com
journal homepage: euoncology.europeanurology.com



European Association of Urology

Management of Prostate Cancer Patients with Clinically Positive Lymph Nodes

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Patients with prostate cancer (PC) with clinically positive lymph nodes detectable via conventional imaging have always been perceived as a challenge, especially with regard to the value of applying local treatment. Over the years, many of these patients have been treated with androgen deprivation therapy (ADT) only. Studies in this specific setting are scarce and mostly retrospective. This issue of *European Urology Oncology* contains a systematic review of the role of local treatments in this patient population by Ventimiglia et al. [1]. On the basis of the five papers that they included in the meta-analysis, the authors conclude that local treatment was consistently associated with a benefit in overall survival (OS) and cancer-specific survival (CSS) in cN+ PC patients. Interestingly, however, they recommend performing more randomised control trials (RTCs) designed to answer the question of the value of local treatment for cN+ patients. We do not completely agree with this conclusion and would argue that different questions that are likely to be beneficial for the majority of patients may be more important than the role of local treatment in these patients.

Patients with clinically positive pelvic lymph nodes fall in between locally advanced and metastatic disease according to conventional imaging (computed tomography [CT] and bone scintigraphy). It has been robustly demonstrated that men with locally advanced PC should receive local treatment on the basis of results from two large RCTs comparing ADT alone to ADT + external beam radiotherapy (RT) [2,3]. More recently, one large RCT and one meta-analysis have concluded that patients with limited metastatic burden also benefit from radiotherapy of the primary tumour [4,5]. Thus, it is very likely that cN+ patients would benefit from local treatment as well. Designing a specific trial for these patients would require a large effort and enormous resources that could be useful elsewhere.

We believe that the true challenges lie elsewhere, and in our opinion the three most urgent issues that need to be addressed promptly in properly designed clinical trials are as follows. The first issue is diagnostic. Bone and CT scans have very low diagnostic accuracy in detecting low-volume metastatic disease. They will be progressively replaced by newer imaging technologies (NITs) such as positron emission tomography/CT scans targeting tracers such as prostate-specific antigen membrane and/or whole-body magnetic resonance imaging. NITs have much better sensitivity and specificity [6] than conventional imaging. A consequence is that patients are reclassified, usually towards more advanced disease. This generates several questions and more importantly creates the challenge of evaluating whether complementing treatment of the primary tumour by targeted treatment of all NIT-visible metastatic lesions, surgically or with RT, improves outcomes. Many trials on this topic are under way.

The second challenge is to address the role of radical prostatectomy in this setting. Four of the five studies included in this systematic review and all the aforementioned RCTs used RT to treat the primary tumour. Surgery is clearly feasible in this setting, but should we consider it equivalent without further studies? The biggest caveat to the Stampede arm testing RT of the primary tumour is that we do not understand precisely why this treatment extended OS for patients with a low burden metastatic disease. One of the hypotheses is that it prevents reseeding from the primary tumour, in which case surgery and RT would be equivalent. However, another hypothesis is that RT induced a profound immunomodulatory effect, also known as the abscopal effect, that induces additional systemic activity [7]. If this is the case, surgery would be less efficient since there is little evidence that surgery provokes

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https://doi.org/10.1016/j.euo.2019.04.010

Please cite this article in press as: Gillessen S, Tombal B. Management of Prostate Cancer Patients with Clinically Positive Lymph Nodes. Eur Urol Oncol (2019), https://doi.org/10.1016/j.euo.2019.04.010

an immune response [8]. In addition, besides OS and CSS, there are many other endpoints, including side effects and quality of life, that could distinguish surgery from RT.

Third, there are two questions related to systemic treatment. The first one is the duration of ADT. In the Stampede trial, the duration of ADT was limited to approximately 2 yr for patients with cN + M0 disease and in that setting the combination of ADT and abiraterone for 2 yr significantly increased failure-free survival (FFS), with an impressive hazard ratio of 0.21; FFS was >90% at 4 yr for the patients with nonmetastatic disease included in this arm [9]. Similarly, the systematic analysis by Vale et al. [10] demonstrated a consistent progression-free survival benefit from docetaxel for patients with nonmetastatic PC.

In conclusion, we would recommend that further trials in this setting should be prospective and focus on studying the optimal combination and duration of systemic treatment. Until such results become available, men should be made aware that there is a potential benefit of docetaxel and abiraterone for some patients with nonmetastatic PC. Ultimately these trials should help us to find or validate molecular markers for selecting patients who could benefit from a specific additional treatment and patients for whom treatment could be less intensive.

Conflicts of interest: Silke Gillessen acts in an advisory role and as a speaker for AAA International, Active Biotech, Amgen, Astellas Pharma, Bayer, Bristol-Myers Squibb, CellSearch, Clovis, CureVac, Dendreon, ESSA Pharmaceuticals, Ferring, Innocrin Pharmaceuticals, Janssen Cilag, MaxiVAX SA, Millenium, Nectar, Novartis, Orion, Pfizer, ProteoMediX, Roche, and Sanofi; is co-inventor of a patented method for biomarker discovery (WO 2009138392 A1; granted in China, Europe, Japan, and the USA); is deputy chair of the ESMO guidelines committee for GU cancers, a member of the EAU guideline panel for prostate cancer, and past chair of the EORTC GU group; and is a member of the STAMPEDE trial management group. Bertrand Tombal has received consulting fees or honoraria from Astellas, Medivation, Amgen, Ferring, Sanofi-Aventis, and Bayer; serves as a board member for Amgen, Ferring, Sanofi-Aventis, and Bayer; and is paid for speaker bureau activities by Amgen, Ferring, Sanofi-Aventis, and Bayer.

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Please cite this article in press as: Gillessen S, Tombal B. Management of Prostate Cancer Patients with Clinically Positive Lymph Nodes. Eur Urol Oncol (2019), https://doi.org/10.1016/j.euo.2019.04.010