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Current Insights in the Management of High-risk Prostate Cancer: Still More Questions than Answers

Valerie Fonteyne *, ***Piet Ost***

Department of Radiation Oncology, Ghent University Hospital, Ghent, Belgium

High-risk prostate cancer (PC) is considered to be a curable disease, but ultimately one out of three PC patients with high-risk features will have progression and develop a lethal metastatic disease. For many years an aggressive local therapy, either by external beam radiotherapy (EBRT) or surgery, was offered as principal or sole therapy for high-risk PC patients. Whether adding systemic therapies to local therapy improves outcome has been the subject of different published and ongoing studies. So far, no consensus regarding the optimal approach has been reached.

In this month's issue of *European Urology*, Tosco and colleagues [1] present a systematic review summarising current evidence and future perspectives about multimodal treatment for high-risk PC. Their conclusions are in line with the recent publication of Pignot et al. [2]. Both groups confirm that nowadays the only irrefutable positive effect of combining therapies in high-risk PC has been proved in the setting of EBRT combined with androgen deprivation therapy (ADT) [1,2]. Although phase 3 trials suggest a beneficial effect of adding docetaxel to ADT, whether or not combined with EBRT, in nonmetastatic high-risk PC, only improvement in failure-free survival has been demonstrated so far without any significant impact on overall survival. Longer follow-up is thus required to define whether docetaxel prolongs metastasis-free survival and overall survival in these patients. In the meanwhile, potential benefits of adding chemotherapy must be weighed against a substantial risk of increasing severe grade 3–5 toxicity, described in 52% of the patients receiving docetaxel [3].

It is hypothesised that residual androgen receptor (AR) signalling supports DNA repair and provides a survival signal for PC cells otherwise receiving a lethal dose of radiation. Next-generation AR pathway inhibitors enhance AR signalling blockade and might result in improved survival when added to EBRT [4,5]. This is currently investigated in several randomised trials. Again either studies are still ongoing or results are regarded as being preliminary for overall survival.

Moreover, in the postoperative setting, several studies are actually recruiting patients to evaluate the potential benefit of adding ADT or chemotherapy to surgery, and no results are available yet. Consequently, in the absence of more mature data demonstrating a survival benefit for combining local therapy and systemic therapies, it is unlikely that this systematic review will currently alter clinical practice.

If studies confirm that the addition of docetaxel and next-generation AR pathway inhibitors improve survival in the nonmetastatic high-risk setting, as is the case for metastatic PC, the question remains which agent to use upfront. Recently, Sydes et al. [6] performed a comparative analysis of both treatments based on survival data of patients included in the STAMPEDE trial. The patients included in this analysis received either standard of care (SOC) + docetaxel and prednisolone versus SOC + abiraterone acetate + prednisolone. The authors concluded that there was no difference in overall survival or PC-specific survival between both therapies. Similarly, no statistically significant difference in overall survival was found between ADT + docetaxel and prednisolone and ADT + abiraterone acetate + prednisolone for patients with high-risk nonmetastatic or metastatic hormone-naïve PC in a recently published meta-analysis [7].

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* Corresponding author. Department of Radiation Oncology, Ghent University Hospital, C. Heymanslaan 10, Ghent 9000, Belgium. Tel. +3293325972; Fax: +3293323040.
E-mail address: Valerie.fonteyne@uzgent.be (V. Fonteyne).

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As recognised by the authors, interpretation of current studies is also hampered by the multiplicity of definitions for high-risk PC that have been used in different trials. As such, the title of the systematic review by Tosco et al. [1], indicating that it concerns an evaluation of combined therapies for localised high-risk PC, is somewhat misleading. For patients with localised high-risk PC defined as prostate-specific antigen (PSA) >20 ng/ml or Gleason >7 or *c*T2c PC, excellent long-term survival has been reported after either radical prostatectomy or EBRT combined with long-term ADT. It is therefore doubtful whether the association of other potentially toxic drugs will further improve this outcome. In contrast, a large proportion of patients who were included in the trials evaluating upfront docetaxel or abiraterone acetate in a nonmetastatic setting presented with more advanced tumour stage or more aggressive tumour characteristics. Nonmetastatic high-risk PC was defined as having at least one risk factor: T3–T4, Gleason ≥8, PSA >20 ng/ml, or node-positive disease (with 67% of patients presenting with T3–T4 disease at diagnosis), or presenting with ≥2 features: T3–T4, Gleason 8–10, PSA >40 ng/ml, or node-negative/positive disease (with 37% of patients presenting with node-positive disease) in the GETUG and STAMPEDE trials, respectively [3,8]. For patients presenting with locally advanced PC, the impact of adding therapies might be more beneficial, but still has to be confirmed.

Better insights into tumour biology and evolution sustain the assumption that clinical variables alone do not reflect tumour aggressiveness. Prognostic biomarkers are useful to distinguish aggressive from indolent tumours. Recently, it has been shown that evaluation of subclonality also results in improved prediction of tumour aggressiveness [9]. Patients whose tumour harbour multiple subclones showed significantly inferior outcome compared with those whose tumours were monoclonal. Clonality characterises tumours more likely to relapse after definitive local therapy as well as those more likely to metastasise [9]. Integrating subclonal architecture and biomarker features can result in improved selection of aggressive tumours most probably benefiting of adjuvant systemic treatments. Incorporating biomarker stratification in further trials is crucial to improve cure rates through personalised therapy and is currently under investigation in the STAMPEDE trial [10].

Conflicts of interest: The authors have nothing to disclose.

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