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Managing Prostate Cancer Recurrence After Local Treatment: Balancing Benefits Against Risks in a Rapidly Changing Environment

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Management of prostate cancer recurrence after radical treatment is far from being standardized, as the disease at this stage is extremely heterogeneous. For years, the questions were simple: is there a role for salvage local treatment and when should systemic treatment be started? Androgen deprivation therapy (ADT), via continuous or intermittent administration and, to a lesser extent, bicalutamide monotherapy, was the sole treatment available. Hundreds of reviews have been devoted to the topic but strong consensus is still lacking. The topic would have sunk into oblivion if not for the recent enthusiasm for "intensified" ADT, revisiting the old concept of maximal androgen blockade with modern AR-targeted agents (ARTAs).

In this issue of *European Urology Oncology*, Weiner et al [1] present a systemic review of first-line systemic treatments for recurrent hormone-naïve prostate cancer (HNPC). Their review highlights the well-conducted randomized controlled trials (RCTs) comparing ADT versus ADT + an ARTA in metastatic HNPC, focusing on the group with metachronous/recurrent disease. The authors conclude that the ARTAs apalutamide, darolutamide, and enzalutamide significantly delay progression-free survival (PFS) and prolong OS, while the benefit of docetaxel is clearly restricted to patients with high-volume disease. ADT combined with one of these three ARTAs is thus seen as the new standard of care for recurrent mHNPC. As for patients with recurrent nonmetastatic cancer, until results from the EMBARK trial (NCT02319837) become available, the authors simply acknowledge that we have made no significant progress since publication of the CAN-NCIC-PR7 trial on intermittent ADT [2].

So, the genie is out of the bottle, but at what risk and at what cost?

The first risk is generalization. Conventional medical wisdom, and often guidelines, traditionally worships RCTs to the point that it is forgotten that they carry own limitations. The main one relevant here is the fact that patients were enrolled into the trials because the investigator estimated that they required ADT. This is especially true for the subgroup of patients with recurrent or metachronous low-volume disease. On the basis of two phase 2 trials, many contemporary patients are offered metastatic-directed therapy (MDT) for oligometastatic lesions instead of, or together with, intensified ADT [3,4]. The potential selection bias, whereby the investigator selected "favorable" cases for MTD and "unfavorable" cases for the clinical trial, is not known. A meta-analysis of individual participant data from large trials recently presented by the STOPCAP M1 group clearly highlighted the good prognosis for these patients, so there is an urgent need to obtain more information on the risk-benefit ratio for continuous lifelong intensified ADT in this heterogeneous subgroup [5].

The second risk is the widespread use of modern imaging technologies in the biochemical recurrence setting and the stage shift it induces. Patients with nonmetastatic disease may be reclassified as having oligometastatic cancer. During the 2021 Advanced Prostate Cancer Consensus Conference (APCCC), 64% of panelists voted for MDT plus systemic therapy for the treatment of metachronous, low volume mHSPC, 26% voted for systemic therapy alone (including ADT), and 10% voted for MDT alone (without systemic therapy) [6]. Strikingly, for metachronous mHSPC that is low volume according to next-generation imaging (NGI) and nonmetastatic according to conventional imaging, among the panelists who voted for systemic treatment alone, 90% voted for ADT plus an ARTA (abiraterone, apalutamide, or

DOI of original article: https://doi.org/10.1016/j.euo.2021.10.005
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https://doi.org/10.1016/j.euo.2022.06.004

Please cite this article as: B. Tombal, Managing Prostate Cancer Recurrence After Local Treatment: Balancing Benefits Against Risks in a Rapidly Changing Environment, Eur Urol Oncol (2022), https://doi.org/10.1016/j.euo.2022.06.004

enzalutamide) and 10% voted for ADT alone. Thus, it is clear that stage migration is occurring and treatment practices have shifted. Similarly, low-volume recurrence may be upgraded to high-volume disease on NGI and these patients may be offered triplet ADT with docetaxel for a disease that looks more aggressive than it is. As highlighted by the STOPCAP meta-analysis only patients with high-risk disease defined on standard imaging derived benefit from docetaxel. Clearly, there is a risk.

The cost is somewhat easy to evaluate. Patients will receive intensified treatment for months, even years, with an increase in the risk of cardiovascular disease and fractures.

A recent meta-analysis of studies conducted in nonmetastatic castration-resistant prostate cancer concluded that addition of novel hormonal agents to ADT is associated with a significant increase in the risk of cardiovascular events (risk ratio [RR] 1.71, 95% confidence interval [CI] 1.29–2.27) and grade 3–4 hypertension (RR 1.53, 95% CI 1.19–1.97) [7]. In another recent review, ARTA use was associated with increases in the risk of falls and fractures: the RR was 1.8 (95% CI 1.42–2.24; $p < 0.001$) all-grade falls, 1.6 (95% CI 1.27–2.08; $p < 0.001$) for grade $\geq$3 falls, 1.59 (95% CI 1.35–1.89; $p < 0.001$) for all-grade fracture, and 1.71 (95% CI 1.12–2.63; $p = 0.01$) for likely grade $\geq$3 fractures [8]. It is important that physicians are aware of these risks and ensure that patients on ARTA are also treated for comorbidities including cardiovascular disease and bone heath and given proper advice on diet adjustments and suitable exercise routines [9].

There is thus an urgent need to investigate whether a shorter treatment duration could be used for patients with low-volume disease on conventional imaging or NGI and for those with a deep prostate-specific antigen response after 6–12 mo of treatment. As a reminder, intermittent ADT was noninferior to continuous therapy with respect to overall survival in the biochemical recurrence setting, while quality of life improved [2]. Remarkably, among the APCCC 2021 panelists who voted for systemic treatment plus MDT for metachronous, low-volume mHSPC, 78% voted for intermittent (temporary) systemic therapy and 22% voted for continuous/lifelong systemic therapy [6]. To some extent, the panelists recognized that the concept of treating to progression, which is required for registration trials, should not be automatically transferred to real-life practice. This concept of treatment optimization is not specific to intensified ADT in prostate cancer and is common to many cancers for which long-lasting chronic treatments such as immunotherapy are now the standard of care. Identification of the optimized dosage and duration for treatment is high on the European agenda, as highlighted by the launch of the Cancer Medicines Forum by the European Medicines Agency, together with representatives from academic organizations including European Organization for Research and Treatment of Cancer with the aim of advancing research into optimized cancer treatments. It is hoped that this will help in reconciling the benefits of new treatments with the risks of excessive exposure.

Conflicts of interest: The author has received honoraria from Amgen, Astellas Pharma, Bayer, Ferring, Sanofi, Janssen, Pfizer, and Myovant Sciences; has received fees for a consulting or advisory role from Astellas Pharma, Bayer, Ferring, Janssen, Takeda, Steba Biotech, Sanofi, Myovant Sciences, and Pfizer/Astellas; has received speaker bureau fees from Amgen, Janssen, and Astellas Pharma; has received institutional research funding from Ferring; has provided expert testimony for Steba Biotech; and has received travel and accommodation expenses from Amgen, Astellas Pharma, Bayer, Ferring, Janssen, and Sanofi.

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Please cite this article as: B. Tombal, Managing Prostate Cancer Recurrence After Local Treatment: Balancing Benefits Against Risks in a Rapidly Changing Environment, Eur Urol Oncol (2022), https://doi.org/10.1016/j.euo.2022.06.004