



European Association of Urology



## Platinum Priority – Editorial and Reply from Authors

Referring to the article published on pp. 966–972 of this issue

# Who Should Receive Androgen Deprivation Therapy?

**Karim Fizazi\***

Department of Cancer Medicine, Institut Gustave Roussy, University of Paris Sud, 39 rue Camille Desmoulins, 94800 Villejuif, France

Because an increased prostate-specific antigen (PSA) level arouses fear in patients, many physicians have been tempted to use androgen-deprivation therapy (ADT) in a wide variety of prostate cancer (PCa) situations where its benefit is unproven and where it may even be harmful. A typical example is that of elderly patients with good-risk localized disease. As the gene for PSA, kallikrein-related peptidase 3, is downstream of the androgen receptor, ADT is indeed capable of inducing dramatic declines in serum PSA in these patients (and, hopefully, capable of allaying patient fears), albeit with no proven clinical benefit.

In this issue of the journal, Lu-Yao and colleagues report on a large survey of US Medicare patients aged  $\geq 66$  yr, with localized PCa, and who had received ADT without a local treatment [1]. In a subgroup of this elderly population (median age: 78 yr) with low-risk localized PCa, slightly more patients who had initially been treated with ADT had subsequently required chemotherapy for their PCa (0.9 vs 0.7 per 100 patients per year for patients who had not initially received ADT).

There are obvious inherent potential biases in this nonrandomized retrospective study, one of the main ones being that the use of ADT in a given patient may well have been driven by reasons not captured in the Surveillance Epidemiology and End Results–Medicare files. Not unexpectedly, clear imbalances were found between the two groups of patients (with and without ADT) regarding stage (T1: 30% vs 49%), prognostic groups (good risk: 59% vs 85%), and age (median: 80 vs 77 yr). The authors tried to circumvent these imbalances by conducting their analysis among risk groups. However, a major potential bias derives from the fact that baseline PSA level was also imbalanced between groups. As serum PSA level is a recognized prognostic factor in localized disease, independent of the T stage and the Gleason score, one would assume that it may well have played a major role in the decision to prescribe

ADT. For example, a 78-yr-old patient with a T2 Gleason 7 PCa would have been more likely to receive ADT if his serum PSA level were 100 ng/ml than if it were 6 ng/ml. If so, it is no wonder that the probability of clinical progression and, thus the need for subsequent therapies, was found to be higher in the first case, with likely no relationship with the use of ADT but rather with cancer bulk and aggressiveness.

Moreover, the definition of risk-group distribution is unclear. In the low-risk group, the reported mean PSA level for patients who had received ADT was 11.2 ng/ml, which indicates that the majority of patients had a baseline PSA level  $>10$  ng/ml, although this is the usual cut-off threshold for the definition of a low risk. A classic bias is found in multiple analysis, and it is noteworthy that among at least eight analyses examining patient outcomes and the need for subsequent treatments, only the one that focused on the use of chemotherapy reported an apparent significant difference.

Finally, when one considers the curves reported in Figure 1 in the article, the actual apparent differences in the incidence of subsequent treatments (eg, chemotherapy) between the two treatment groups (ADT or no ADT) was minimal (0.2% per person/year), making this result even less robust and more sensitive to potential biases. Such a tiny difference would have been challenged as borderline clinically relevant if the results had been obtained in a well-conducted, randomized, phase 3 trial. That they were, in fact, obtained in a nonrandomized retrospective study with potential issues about prognostic assessment and major imbalances between groups indicates that the level of evidence is quite low.

Nevertheless, even if the authors' analysis has flaws and potential biases, their main message may, at least, be partially valid: The use of ADT in elderly patients does not eliminate the risk of subsequent recourse to more aggressive therapy when PCa progresses from local to advanced disease.

DOI of original article: <http://dx.doi.org/10.1016/j.eururo.2012.05.003>

\* Tel. +33 1 42 11 43 17.

E-mail address: [fizazi@igr.fr](mailto:fizazi@igr.fr).

In the literature, the subgroups of patients identified with evidence-based, proven, clinical benefit from ADT are simply those who fulfilled the following two conditions: (1) a PCa that is aggressive enough to be potentially lethal and (2) a likelihood of a life expectancy that encompasses the time it would take for PCa to induce death, or at least symptomatic metastases. The following data obtained in randomized trials support this statement:

- In patients with high-risk localized PCa treated with radiotherapy, ADT increased overall survival [2], and prolonged ADT was superior to short-term ADT [3]. Insufficient data are available from phase 3 trials testing ADT in patients with high-risk disease when a prostatectomy is the local treatment.
- In patients with localized disease “not suitable for [definitive] local treatment” (>80% had  $\geq$ T2-T3 stage), immediate ADT resulted in a more modest 25% reduction in the relative risk of death over deferred ADT [4].
- In patients with positive nodal disease on pathology, evidence supports early versus deferred ADT, although trials were not sufficiently powered to firmly demonstrate this and with the caveat that in patients with an undetectable serum PSA level postprostatectomy, early salvage ADT may result in a similar outcome [5,6].
- In patients with newly diagnosed metastatic PCa, early ADT was better than delayed ADT both in terms of overall survival and local symptom control [7]. In these patients with metastatic disease, continuous ADT was better than intermittent ADT [8].

Recent surveys indicate that in the United States, approximately 15% of patients who receive ADT do not fit into a subgroup of patients with a recognized indication according to guidelines [9]. The paper by Lu-Yao and colleagues reminds us that more efforts should be expended to better adhere to indications for the use of ADT.

Finally, in patients with high-risk disease in whom ADT is being considered, it is also of major importance to remind physicians of the recently demonstrated role of local treatment in overall survival, among other outcomes [10].

**Conflicts of interest:** The author has nothing to disclose.

## References

- [1] Lu-Yao GL, Albertsen PC, Li H, et al. Does primary androgen-deprivation therapy delay the receipt of secondary cancer therapy for localized prostate cancer? *Eur Urol* 2012;62:966–72.
- [2] Bolla M, Collette L, Blank L, et al. Long-term results with immediate androgen suppression and external irradiation in patients with locally advanced prostate cancer (an EORTC study): a phase III randomised trial. *Lancet* 2002;360:103–6.
- [3] Bolla M, de Reijke TM, Van Tienhoven G, et al. Duration of androgen suppression in the treatment of prostate cancer. *N Engl J Med* 2009;360:2516–27.
- [4] Studer UE, Whelan P, Albrecht W, et al. Immediate or deferred androgen deprivation for patients with prostate cancer not suitable for local treatment with curative intent: European Organisation for Research and Treatment of Cancer (EORTC) Trial 30891. *J Clin Oncol* 2006;20:1868–76.
- [5] Schröder FH, Kurth K-H, Fossa SD, et al. Early versus delayed endocrine treatment of T2-T3 pN1-3 M0 prostate cancer without local treatment of the primary tumour: final results of European Organisation for the Research and Treatment of Cancer protocol 30846 after 13 years of follow-up (a randomised controlled trial). *Eur Urol* 2009;55:14–22.
- [6] Messing EM, Manola J, Yao J, et al. Immediate versus deferred androgen deprivation treatment in patients with node-positive prostate cancer after radical prostatectomy and pelvic lymphadenectomy. *Lancet Oncol* 2006;7:472–9.
- [7] Medical Research Council Prostate Cancer Working Party Investigators Group. Immediate versus deferred treatment for advanced prostatic cancer: initial results of the Medical Research Council Trial. *Br J Urol* 1997;79:235–46.
- [8] Hussain M, Tangen CM, Higano CS, et al. Intermittent (IAD) versus continuous (CAD) androgen deprivation in hormone sensitive metastatic prostate cancer (HSM1PC) patients (pts): results of S9346 (INT 0162) an international phase III trial. *J Clin Oncol* 2012;30(Suppl), abstract 4.
- [9] Kuykendal AR, Hendrix LR, Salloum RG, et al. Guideline discordant androgen deprivation therapy (ADT) use in localized prostate cancer (CaP) and cost implications: a population-based study. *J Clin Oncol* 2012;30(Suppl), abstract 4647.
- [10] Mason MD, Parulekar W, Sydes MR, et al. Final analysis of intergroup randomized phase III study of androgen deprivation therapy (ADT) plus radiation therapy (RT) in locally advanced prostate cancer (CaP) (NCIC-CTG, SWOG, MRC-UK, INT: 094-0110). *J Clin Oncol* 2012;30(Suppl), abstract 4509.

<http://dx.doi.org/10.1016/j.eururo.2012.06.046>

## Platinum Priority

**Reply from Authors re: Karim Fizazi. Who Should Receive Androgen Deprivation Therapy? *Eur Urol* 2012;62:973–4**

### **Overcoming Patient Selection Bias in Observational Studies**

Grace Lu-Yao \*, Siu-Long Yao, Peter Albertsen

Cancer Institute of New Jersey, Robert Wood Johnson Medical School, New Brunswick, NJ, USA

DOIs of original articles: <http://dx.doi.org/10.1016/j.eururo.2012.05.003>, <http://dx.doi.org/10.1016/j.eururo.2012.06.046>

We thank Dr. Fizazi for his thoughtful comments [1]. As noted by Dr. Fizazi, bias can be common in nonrandomized studies and, in many instances, can markedly limit the ability to derive scientifically correct conclusions upon which to base patient care. Many statistical approaches have been devised to account for potential biases, but in general most of these methods require that a bias be recognized and data on

\* Corresponding author. Cancer Institute of New Jersey, Robert Wood Johnson Medical School, Medicine, 195 Little Albany Street, New Brunswick, NJ 08901, USA. Tel. +1 732 235 8830; Fax: +1 732 235 8808. E-mail address: luyaogr@umdnj.edu (G. Lu-Yao).