Androgen-Deprivation Therapy—It’s All a Matter of Timing

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Although it is now 68 years since Charles Huggins first recognised the hormonal dependence of prostate cancer, androgen-deprivation therapy (ADT) still remains the only therapeutic option that can influence the course of this disease once it is too advanced for local treatment.

The case for immediate ADT in patients with symptomatic metastatic prostate cancer remains compelling [1], but the lack of certainty about the correct time to initiate ADT in men with locally advanced nonmetastatic cancer is highlighted in the 2007 European Association of Urology Prostate Cancer Guidelines.

“It remains unclear whether immediate ADT for locally advanced and asymptomatic metastatic disease favourably influences survival and quality of life as compared to deferred ADT at the time of symptomatic progression” [2].

With such uncertainty it would seem unlikely that the exact timing of treatment exerts a dramatic effect on survival. So what does guide us in our decision to initiate ADT in patients with prostate cancer who are not suitable for local treatment?

1. Trends in ADT

When surgical castration was the only practical means to achieve androgen deprivation, any decision to initiate treatment was achieved by balancing the degree of reluctance on the part of the patient, who did not want to lose his testicles if it was not absolutely necessary, against the degree of certainty on the part of the urologist that treatment was going to be of benefit for him.

Two unrelated developments in the management of prostate cancer have disrupted this balance. First, the introduction of luteinising hormone-releasing hormone (LHRH) analogues provided a medical, reversible alternative to surgical castration. The rapid adoption by the medical profession of this more acceptable form of treatment has probably resulted in doctors being less discerning about when and for whom they recommend ADT. Second, the discovery of prostate-specific antigen (PSA) and its widespread uptake in clinical practice has meant that patients are now diagnosed with prostate cancer at earlier stages of the disease and followed up more closely. We know that PSA commonly serves only to “produce stress and anxiety” for patients and a rising level will often prompt them to seek active treatment in the form of LHRH analogue injections where previously their desire for surgical castration would have been less than enthusiastic.

These two factors, driven by both the urologist and his patients, have combined to result in ADT being used at earlier and earlier stages of the disease.

2. The evidence base for early ADT

What is the evidence to justify earlier commencement of ADT in patients with prostate cancer that is
not suitable for local therapy? It is not as robust as we might like to think.

1. Analysis of the original American Veterans studies only showed a slight survival advantage in favour of immediate ADT for men with high-grade tumours although the high death rates from cardiovascular disease in patients treated with oestrogen made the results from these studies difficult to interpret [3].

2. Although the Medical Research Council (MRC)-sponsored immediate versus deferred treatment trial initially showed a survival advantage for the 256 MO patients receiving immediate ADT, among the 54 additional men who died in the deferred treatment arm, 29 never even received endocrine therapy [1]. This survival advantage disappeared with longer follow-up, but the reduction in major complications for those in the immediate treatment arm is often cited as the most important result from this study [4].

3. A Cochrane systematic review of 2167 patients confirmed that early use of ADT in advanced prostate cancer reduces disease progression compared to deferred treatment but there was no evidence for any improvement in survival [5].

4. The European Organization for Research and Treatment of Cancer (EORTC) study 30891 randomised 985 men with advanced prostate cancer to either immediate or deferred ADT. Although it showed a small but statistically significant improvement in overall survival for those on immediate treatment, there was no difference in cancer-specific or symptom-free survival. The average time lag between study entry and treatment in the deferred arm of the study was 7 yr and many men died from other causes without ever needing treatment [6].

It is worth stressing that the bulk of the evidence derived from these studies comes from the pre-PSA era. Whilst it does provide some support for the earlier use of ADT, particularly from the viewpoint of delaying disease progression and preventing related complications, it is also clear that the survival advantages are not great and that with regular PSA monitoring of patients on deferred therapy, many can be spared inappropriate ADT.

3. **Toxicity**

The first commandment for us as doctors is “Primum non nocere” — “First do no harm.” Part of our decision-making on the relative merits of immediate or deferred ADT should therefore acknowledge that the adverse effects of ADT can have a profound effect on a patient’s quality of life.

Loss of libido, erectile dysfunction, hot flushes, gynaecomastia, anaemia, weight gain, increased body fat and metabolic syndrome, loss of bone mineral density with potential osteoporotic fracture, and altered cognitive function make for a litany of potential side-effects that should make the urologist and the patient question whether the benefits of early ADT for locally advanced nonmetastatic prostate cancer outweigh this daunting list [7].

Whilst there may not be major advantages to immediate ADT in terms of survival, it is clear that the real benefit from deferred ADT might come from limitation of the unwanted side-effects, and an elderly patient may die from unrelated causes before he ever develops symptoms that justify such treatment.

4. **Further analysis of EORTC 30891**

Whatever the relative advantages and disadvantages of ADT for patients with advanced prostate cancer we have now already moved to a position where ADT is being started at earlier and earlier stages of the disease when claims for benefit are unproven or limited and the consequences of unnecessary treatment are clear for us all to see. Can we really say which patients will benefit from ADT and when that treatment should start?

Urs Studer and his collaborators in the EORTC have provided us with timely information to answer this important question in this issue of *European Urology* [8]. They have further analysed the results from EORTC trial 30891 and used PSA data to inform us in a very clear and practical way to guide us in our clinical practice.

EORTC 30891 demonstrated a small overall survival advantage for immediate ADT in 985 patients with locally advanced prostate cancer but without overt metastatic disease. This difference was due to increased non-prostate cancer-related mortality. After a median follow up of 7 yr, only 20% of patients in the entire study have died from progressive prostate cancer. Furthermore, only 50% of men in the deferred ADT arm ever started treatment including 25% who had died of unrelated causes without ever requiring ADT.

The following points from this important paper should be considered by urologists and discussed with our patients whenever we are considering ADT for men with locally advanced prostate cancer.
1. Patients with a PSA at diagnosis of >50 ng/ml are likely to eventually die of prostate cancer and are therefore appropriate candidates for immediate ADT to prevent or delay complications from progressive disease.

2. Patients with a baseline PSA of ≤8 ng/ml are at very low risk of dying from prostate cancer within 7 yr of diagnosis and may never require ADT.

3. For those patients with a serum PSA between 8 and 50 ng/ml, ADT should be initiated as soon as a PSA doubling time of <12 mo is identified.

Despite the improvement in overall survival seen with early ADT in this study, immediate treatment is clearly not necessary for the majority of patients. Rather than using our current blunderbuss approach to ADT, we can now accurately target those who may derive benefit from immediate ADT and stop all other patients from feeling that they need to start treatment as soon as possible. Through discussion and explanation with our patients we can now make clear recommendations about the need for ADT and also how it can be safely deferred until its use becomes necessary.

Although these facts are clearly supported by this large randomised trial, we know that the logic of patients in their decision-making processes will often fly in the face of such evidence. We nonetheless have a responsibility, both as surgeons and educators, to help our patients make better decisions.

**Conflicts of interest**

The author has nothing to disclose.

**References**


