**Management of men with PSA failure after prostate radiotherapy: The case against early androgen deprivation**

Douglas Brand[1,2], Chris Parker[1,2]

1) The Royal Marsden NHS Foundation Trust, London, UK
2) The Institute of Cancer Research, London, UK

Men with prostate specific antigen (PSA) failure after radical radiotherapy for localised prostate cancer are often managed with early androgen deprivation therapy (ADT). However, the optimum timing of starting ADT is uncertain. Debate about the timing of ADT is not new [1], but has been revived by the results of the Timing Of Androgen Deprivation (TOAD) trial [2], [3]. Here we describe the rationale for delaying ADT in men with PSA-only failure after radiotherapy.

***1. Curative treatment options should be considered before starting ADT***

Before embarking on early ADT, which is not a curative treatment strategy, it is important to consider whether men with PSA failure might be curable with local salvage treatment. Men who are fit enough to be potential candidates for local salvage should be investigated with the best available imaging techniques +/- repeat prostate biopsy in order to identify those with local-only recurrence. Management of local recurrence is outside the scope of this piece, but salvage high dose rate brachytherapy, prostatectomy, high-intensity focussed ultrasound and cryotherapy are potentially curative options. Although the role of local salvage treatment has not been tested in good quality randomised controlled trials, it should not be forgotten. Tran and colleagues found only 2% of eligible patients in their Canadian cohort were offered local salvage treatment [4].

Curative treatment may also be an option not just for those men with local recurrence, but also those with oligometastatic recurrence. Once again, the role of salvage treatment for oligometastatic disease has not yet been tested in mature randomised controlled trials. However, early ADT for PSA failure, before the site of recurrent disease is known, denies men the opportunity to have such treatment, either within ongoing trials (such as CORE, NCT02759783) or as part of standard management. It should be made clear to patients, before starting early ADT, that by doing so they are missing a possible opportunity for curative treatment. Men may well prefer to continue on observation, avoiding ADT until the pattern of recurrence is known, in order to find out whether the location of their disease is amenable to a curative treatment strategy.

***2. Early ADT impairs quality of life***

The adverse effects of ADT are well known and include loss of sexual function, weight gain, hot flushes, and fatigue, as well as adverse effects on glucose tolerance, lipid profiles and

bone density. It is therefore not surprising that the TOAD trial found that early ADT had an adverse effect on quality of life [3]. These adverse effects on quality of life could only be justified if early ADT had a clear benefit in terms of overall survival.

***3. There is no clear survival benefit for early ADT***

To our knowledge, TOAD is the only published randomised controlled trial comparing early versus deferred ADT for men with PSA failure after radiotherapy [2]. It failed to reach its accrual target and included just 261 men with PSA failure, either after radical radiotherapy (n=165) or after prostatectomy +/- salvage radiotherapy (n=96). Median follow-up was just 5 years and only 40 deaths were available for analysis, 26 in men randomised to deferred ADT, and 14 in those randomised to early ADT. This difference was not statistically significant (HR 0.59, 95% CI: 0.26-1.30, p=0.19). Furthermore, only 18 of the 40 deaths were from prostate cancer, and there was an imbalance between the two trial arms in non-prostate cancer deaths. In the early ADT arm there were 8 deaths from other causes, compared with 14 such deaths in the deferred arm. It is counter-intuitive for early ADT to have a beneficial impact on non-prostate cancer mortality; if anything, one would expect the opposite. Taken together with the lack of statistical significance, it is clear that the overall survival results are consistent with the null hypothesis and the play of chance.

Other trials have compared early versus deferred ADT, but only in previously untreated men, and so their results should not be extrapolated to men with PSA failure after radiotherapy. For what it is worth, the EORTC 30891 trial of 985 patients found no significant difference in prostate cancer mortality (HR 1.05; 95% CI: 0.83-1.33, p=0.70), with 10-year rates of 25% versus 23% for deferred and early ADT, respectively [5]. Similarly, the EORTC 30846 trial of 234 men found no difference in long-term outcome, with 10-year prostate cancer mortality of 56% versus 52% for deferred and early ADT, respectively [6].

***4. Delaying ADT may enable earlier access to abiraterone and docetaxel***

Both abiraterone [7], [8] and docetaxel [9], [10] are substantially more effective when used in hormone naïve, rather than in castrate-refractory, disease. The use of these drugs for men with hormone naïve metastatic disease confers an improvement in median survival of around two years. This is now an important new consideration when it comes to the timing of starting ADT in men with PSA failure after radiotherapy. If ADT is started early, men develop castrate refractory disease before they develop metastases. They are not currently eligible for abiraterone or docetaxel until they subsequently develop castrate refractory metastatic disease. Conversely, if ADT is delayed until the site of recurrence is known, those men who recur with distant metastases are eligible to receive abiraterone or docetaxel together with ADT in the hormone naïve setting with the known, substantial, benefit in overall survival.

**Conclusions**

There is no proven survival benefit for early ADT in men with PSA failure after radical radiotherapy. However, there are at least three good reasons why ADT should be delayed until the site of recurrence is known. First, this allows consideration of curative treatment options; Second, it delays the morbidity associated with ADT; Third, this enables some patients to get earlier access to abiraterone and docetaxel with a resulting improvement in overall survival.

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