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The modern role of androgen deprivation therapy in the management of localised and locally advanced prostate cancer

Keywords

prostate cancer, androgen deprivation, localised, locally advanced, radiotherapy, adverse effects

Abstract

Introduction: Approximately 50% of men diagnosed with prostate cancer will be exposed to androgen deprivation therapy (ADT) at some stage. The role of ADT in the management of metastatic disease has long been recognised and its place in the management of localised and locally advanced disease has become clearer in the past few years. Nevertheless concerns remain that some men might not benefit from ADT in earlier stage disease.

Aim: The purpose of the current article is to provide a brief narrative review of the role of ADT as part of a strategy of treatment with curative intent, concentrating mainly on key recent developments in the area.

Methods: Narrative literature review of key publications in the English language relating to ADT in the management of localised and locally advanced prostate cancer.

Results: In locally advanced and high risk localised prostate cancer the use of ADT in combination with radiotherapy improves disease-specific and overall survival. There is no evidence to support use of ADT in the treatment of low risk localised prostate cancer. There appears to be an increased risk of cardiovascular morbidity/ mortality associated with LHrH agonists, particularly in men with pre-existing cardiovascular disease, but the relevance of this in the adjuvant/neoadjuvant setting is currently unclear.

Conclusions: Future studies should focus on identification of men who are at risk from cardiovascular complications associated with ADT and on the comparison of radiotherapy with ADT vs surgery in the management of localised and locally advanced prostate cancer, particularly with regards to men with pre-existing comorbidities.

Key points

- In locally advanced and high risk localised prostate cancer the use of ADT in combination with radiotherapy improves disease-specific and overall survival
- There is no evidence to support use of ADT in the treatment of low risk localised prostate cancer
- There appears to be an increased risk of cardiovascular morbidity/ mortality associated with LHrH agonists, but the relevance of this when used in such an adjuvant/ neoadjuvant setting is currently unclear.
- Future studies should focus on comparison of radiotherapy with ADT vs surgery in the management of localised and locally advanced prostate cancer, particularly with regards to men with pre-existing co-morbidities.

Introduction

Approximately 50% of men diagnosed with prostate cancer will be exposed to androgen deprivation therapy (ADT) at some stage(1). ADT has a clear role in the management of metastatic prostate cancer, for which there is good evidence for reduction in complications and variable evidence for improved survival. In such a setting, ADT reduces the burden of metastatic disease and improves patient quality of life (2, 3).

ADT is most commonly administered in the form of GnRH agonists. The GnRH antagonist, Degarelix, is less widely used but avoids the testosterone surge associated with GnRH agonists and has a more rapid onset of action (4). Medical castration is regarded as more acceptable than traditional orchidectomy by patients and clinicians alike, and is much more commonly used. For most of the last thirty years, all forms of ADT were assumed to be equivalent in effect and adverse effects – more recently, doubt has been cast over this assumption (5).

The role (or indeed lack of it) of ADT in earlier stages of prostate cancer has become clearer in the past decade, particularly for locally advanced and localised prostate cancer. The purpose of the current article is to review the role of ADT as part of a strategy of treatment with curative intent, concentrating particularly on key recent developments in the area.

Locally advanced prostate cancer

There is strong evidence to support the use of ADT in combination with radiotherapy (RT) for men with locally advanced prostate cancer (T3/4 N+/- M0). The results of four major trials are summarised in table 1. (6-9). The radiosensitising effect of ADT is the generally accepted mechanism for improved outcomes with combination therapy (10). Most of these studies excluded patients with multiple co-morbidities, a poor performance status (>2) or older age. This leaves a question over whether the results that apply to fitter, younger patients can be extrapolated to the old and infirm, particularly with respect to overall survival.

Mason et al (2015)(9) randomised 1205 patients to lifelong ADT alone vs RT and lifelong ADT. At a median follow up of 8 years, overall survival was greater by 6% in the combination group, with deaths from prostate cancer reduced by from 52% to 32% with the addition of RT to ADT.

While the evidence is conclusive as to the benefits of combining RT with ADT for locally advanced (T3/4) prostate cancer, the benefit to men with node positive disease is uncertain. Most of the studies above (3 of 4) either specifically excluded men with node positive disease or did not document nodal status at initiation (PRO7), raising the question whether men with nodal involvement stand to benefit from ADT. The study by Bolla et al (2009)(6) which did include patients with node positive disease did not specifically analyse for benefit in node positive patients and, although the distribution of these patients between trial arms was equal, the numbers were relatively small.

Most trials have reported a combination of a LHRH agonist and an antiandrogen, although doses and regimes vary. The Early Prostate Cancer (EPC) trial showed improved progression-free survival in men with locally advanced disease when bicalutamide monotherapy was added to standard care (11). However, as monotherapy, LHRH agonists have been shown to be oncologically superior to antiandrogens (12), but the side effects are notably worse. Given the recognised adverse events of ADT, particularly on sexual function, a reduction in the duration might improve quality of life. This benefit must be balanced against the known improvement in mortality with a longer course of ADT (6).

The dose of RT varied between studies but was usually in the range of 60-70Gy. Dose escalation studies suggest that RT doses in excess of 70Gy might improve outcomes. One study (13) showed that patients with high risk locally advanced prostate cancer (T3/4 and/or Gleason ≥8 and/or PSA ≥20µg/l) treated with 80Gy RT had a biochemical progression free rate of 79% at 5 years.

There is no evidence that adjuvant ADT with radical prostatectomy for locally advanced prostate cancer improves survival, even in patients with margin-positive disease. Indeed, the 2014 NICE Guidelines (14)recommend against the use of ADT in these patients. The optimal treatment for locally advanced disease is not certain although multimodality therapy is generally required. Whether the best strategy is radical prostatectomy and extended lymphadenectomy, followed by adjuvant RT in those who require it or ADT with RT in all has yet to be determined.

Localised prostate cancer

Localised prostate cancer can be classified according to risk at the time of diagnosis using the D'Amico risk stratification tool, as shown in table 2.

There is little evidence to support the use of ADT alone in localised prostate cancer. Lu-Yao et al (2014)(15) looked at 66,717 patients diagnosed with localised prostate cancer in whom no definitive local therapy was commenced within 180 days of diagnosis, who received varying amounts of ADT. The data strongly confirmed that the use of primary ADT in localised prostate cancer does not improve long-term overall or disease-specific survival.

High risk localised prostate cancer is most commonly combined with locally advanced prostate cancer in clinical trials, thus in interpreting the results of most studies, it is difficult to draw a distinction between high risk localised disease and early locally advanced disease. With this in mind, it still remains evident that the use of ADT is of benefit in the treatment of high risk localised prostate cancer only when combined with radiotherapy (10, 16), with demonstrable improved survival when compared with ADT alone (7, 17).

Jones et al (2011)(18) treated men with localised prostate cancer with a combination of RT and four months of maximal androgen blockade in the form of Flutamide and an LHRH agonist. RT consisted of 46.8 Gy delivered to the pelvis (prostate and regional lymph nodes) in daily 1.8 Gy fractions followed by 19.8 Gy to the prostate, for a total dose of 66.6 Gy. Treatment of the regional lymph nodes was omitted in patients with negative lymph-node dissections or with a PSA level of less than 10 ng per millilitre and a Gleason score of less than 6. At a median follow-up of 9.1 years, there was a 5% difference in overall survival (10-year rate of overall survival 57% in the radiotherapy-alone group and 62% in the combined-therapy group) and a 4% difference in disease-specific survival (10-year disease-specific mortality 8% in the radiotherapy-alone group and 4% in the combined-therapy group). Sub-group analysis suggested the benefit lay in those men with intermediate-risk disease rather than those with low-risk disease.

Duration of adjuvant/ neoadjuvant ADT

The current standard treatment with ADT for high-risk localised disease is 6 months and for men with T3 disease is 3 years, although questions have been raised regarding possibility of reducing this to 18 months.

Bolla et al (2009)(6) provided recommendation of 3 years ADT in combination with RT over 6 months ADT with RT for the treatment of locally advanced disease, based on their findings of reduced 5 year overall mortality with longer treatment (19% vs 15.2%). In their study side effects of ADT persisted for the duration of androgen suppression but improved after cessation of treatment, while overall quality of life measures were no different between the 6 month and 3 year ADT groups.

In contrast, one trial reported no difference in cancer-specific outcomes between 18 and 36 months of ADT, with improved quality of life associated with shorter duration of ADT, although it was underpowered and not designed as a non-inferiority study (19).

Adverse effects of ADT

The adverse effects of ADT are well documented (20) and have a deleterious effect on quality of life (21). ADT has also been linked to a metabolic type syndrome of insulin insensitivity, increased central obesity and decreased muscle mass (20, 22). The adverse events associated with ADT might be reduced by limiting the duration of exposure (19) or by the use of non-steroidal anti-androgens such as bicalutamide (11).

There is evidence accumulating suggesting an association between cardiovascular (CV) risk and ADT, in particular with the use of GnRH agonists. This remains a highly controversial topic, with a meta-analysis of 4,141 patients in 8 randomised trials failing to show a clear association between ADT and CV death (23). The methodological flaws of this meta-analysis, including contamination bias, have already been highlighted (24). A large US observational study found that men on ADT had a significantly increased risk of diabetes (both GNrH agonists and orchidectomy) and of coronary heart disease, myocardial infarction and sudden cardiac death (GNrH agonists only) (25). The findings of a Danish registry study on 31,571 men reported a 31% increased risk of myocardial infarction and a 16% risk of stroke in men on GnRH ADT compared with orchidectomy (26). Conversely, the Swedish

registry study showed equivalent increases in CV risk with both orchidectomy and GNrH agonists, but not with anti-androgens (27). In this study, men with a previous history of cardiovascular events seemed to be most at risk. Albertsen et al observed a greater than 50% reduction in the risk of cardiovascular events among men with pre-existing cardiovascular disease when treated with a GnRH antagonist when compared with a GnRH agonist (28). CV risk was not increased, however, in men without pre-existing CV disease. To date, despite the large body of epidemiological and retrospective data supporting an increased risk of CV events in some, there is little understanding of which men might be at increased risk, how these men could be identified and what should be done about attempting to reduce this risk.

Does every man with high-risk localised cancer benefit from ADT?

D'Amico et al in 2004 (29)published early results of their trial comparing RT alone with RT and ADT in combination for the treatment of localised prostate cancer (table 3). Initial results at median follow up 4.5 years suggested higher survival rates in the combination group, however the updated results of the same trial published in 2015 showed that the initial perceived benefit of combination therapy was not sustained (29, 30). Most interestingly, when the survival data were examined by sub-group, separating men according to their co-morbidity status pre-treatment, there was a suggestion that men with moderate or severe co-morbidity might actually fare worse with combination therapy than with radiotherapy alone (94% mortality at median 16.62 years vs 70%). Moreover, analysis of cause of death showed a significant increase in CV mortality, as defined by lethal myocardial infarction, in the same comorbid subgroup. How then do we explain this?

If indeed, the treatment directed towards reducing cancer mortality actually has the effect of increasing CV risk, it remains a plausible hypothesis that there exists a significant sub-group of men at risk of a subsequent cardiac event, for whom ADT in combination will reduce overall survival, particularly if their a priori risk of dying of prostate cancer (e.g. low-risk prostate cancer) was not particularly high. Most prospective trials comparing RT with and without ADT have excluded patients with significant comorbidity or advanced age (6-9) and in any case, have not been designed to show a difference in significant adverse events.

Controversies and future work

Clearly, there is a need for subsequent randomised trials examining ADT to stratify patients according to CV risk to prospectively look for an association. If certain men are more vulnerable, and this appears to be the case, then the ability to identify and stratify them at the time of treatment planning is key to minimising risk.

Given the potential negative effects of ADT, there remains a question as to the role of surgery in the management of these men, particularly in those with pre-existing comorbidity. An observational study of 34,515 men with locally advanced/localised prostate cancer over a 15-year period reported a cancer specific survival benefit of surgery when compared with RT (+/- ADT) (31). However the greatest benefit was seen in younger men with fewer comorbidities and higher risk disease. As an observational study, care should be taken when drawing conclusions, however there appears to be sufficient evidence to warrant a direct comparison between RT (+/- ADT) and surgery in a future randomised trial.

Conclusion

In localised and locally advanced prostate cancer ADT alone confers no survival benefit and in some cases might be detrimental. ADT in combination with RT improves overall and cancer specific survival in locally advanced and high-risk localised prostate cancer. ADT does not benefit patients with low risk localised prostate cancer. Further research is required to clarify which patients are at greatest risk of CV mortality associated with ADT. The optimisation of medical therapy, including lifestyle factors, to reduce CV risk is likely to play a significant role in the future. Further research is also required to identify the true role of surgery in the management of prostate cancer, particularly in men with comorbidity.

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