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

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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. 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 the use of ADT in the treatment of low-risk localised prostate cancer. There appears to be an increased risk of cardiovascular morbidity and mortality associated with luteinizing hormone-releasing hormone 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 *versus* surgery in the management of localised and locally advanced prostate cancer, particularly with regards to men with pre-existing comorbidities.

Keywords

Adverse effects, androgen deprivation, cardiovascular disease, co-morbidities, localised prostate cancer, locally advanced prostate cancer, prostate cancer, radiotherapy, review, survival

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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 gonadotrophin-releasing hormone (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

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and clinicians alike, and is much more commonly used. For most of the last 30 years, all forms of ADT were assumed to be equivalent in effect and adverse effects; but more recently, doubt has been cast over this assumption.[5]

The role (or indeed lack of it) of ADT in the 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 comorbidities, 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.

In a 2015 publication, Mason et al.[9] randomised 1205 patients to lifelong ADT alone *versus* RT and lifelong ADT. At a median follow-up of 8 years, their overall survival was greater by 6% in the combination group, with deaths from prostate cancer reduced 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 (three of four) either specifically excluded men with node positive disease or did not document their nodal status at initiation (PRO7), raising the question whether men with nodal involvement stand to benefit from ADT. The 2009 study by Bolla et al.[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, their numbers were relatively small.

Most trials report a combination of a luteinizing hormone-releasing hormone (LHRH) agonist and an antiandrogen, although doses and regimes vary. The Early Prostate Cancer (EPC) trial shows improved progression-free survival in men with locally advanced disease when bicalutamide monotherapy was added to the standard care[11]; however, as a monotherapy, LHRH agonists were shown to be oncologically superior to antiandrogens,[12] although 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 60–70 Gy. Dose escalation studies suggest that RT doses in excess of 70 Gy might improve outcomes. One study[13] shows that patients with high-risk locally advanced prostate cancer (T3/4 and/or Gleason $\geqslant$ 8 and/or PSA $\geqslant$ 20 μg/l) treated with 80 Gy 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. In 2014, Lu-Yao et al.[15] looked at 66,717 patients diagnosed with localised prostate cancer in whom no definitive local therapy was commenced within 180 days of diagnosis and who had 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]

In a study published in 2011, Jones et al.[18] treated men with localised prostate cancer with a combination of RT and 4 months of maximal androgen blockade in the form of flutamide and a 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 < 10 ng/mL and a Gleason score of < 6. At a median follow-up of 9.1 years, there was a 5% difference in overall survival (the 10-year rate of overall survival was 57% in the RT-alone group and

Table 1. Trials comparing ADT and RT in men with locally advanced prostate cancer.

Study	Patients (*n*)	Type of ADT	RT dose	Pelvic node irradiated	Comparison	Patient characteristics	Stage	Outcome
Bolla et al., 2009 EORTC	970	LHRH agonist	70 Gy	Yes	RT + 6/12 ADT *versus* RT + 3 yrs ADT	ECOG 0-2, Hb > 10 g/dL, WCC > $2x10^9$	T1c-T2bN1-2M0 or T2c-T4N0-2M0	Reduced overall mortality with 3-yr treatment (difference 3.8% at 5 yrs, 15.2% *versus* 19%)
Widmark et al., 2009 SPCG-7/ SFUO-3	875	LHRH agonist 3/12 plus flutamide	70 Gy	No	Lifelong ADT *versus* lifelong ADT + RT	Good performance status, life expectancy > 10 yr	T3N0M0	Reduced overall mortality with combined treatment (difference 9.8% at 10 yrs, 39.4% *versus* 29.6%)
Denham et al., 2011 TROG 96.01	818	LHRH agonist 3/12 or 6/12 plus flutamide	66 Gy	No	RT alone *versus* RT + 3/12 ADT *versus* RT + 6/12 ADT	No significant comorbidities	T2b-4N0M0	No benefit with 3/12 ADT *versus* RT alone, reduced overall mortality with 6/12 ADT (difference 13.3% at 10 yrs, 42.5% RT alone *versus* 29.2%)
Mason et al., 2015 NCIC CTG PR3/MRC PR07	1205	Orchidectomy or LHRH agonist	65–69 Gy	Yes	Lifelong ADT *versus* lifelong ADT + RT	ECOG 0–2, age < 80 yrs	T1-4N0M0	Reduced overall mortality (difference 6% at 10 yrs, 51% *versus* 45%)

ADT: androgen deprivation therapy; ECOG: Eastern Cooperative Oncology Group; Gy: Gray; LHRH: luteinizing hormone-releasing hormone; NCIC GTC: National Cancer Institute of Canada Clinical Trials Group; RT: radiation therapy; SFUO: Scandinavian Prostate Cancer Group; SPCG: Scandinavian Prostate Cancer Group; TROG: Trans Tasman Radiation Oncology Group; yrs: years.

Table 2. Risk stratification for men with localised prostate cancer.

Risk level	PSA		Gleason score		Clinical stage
Low risk	< 10 ng/mL	and	⩽ 6	and	T1–T2a
Intermediate risk	10–20 ng/mL	or	7	or	T2b
High risk[a]	> 20 ng/mL	or	8–10	or	⩾ T2c

[a]High-risk prostate cancer is also included in the definition of locally advanced prostate cancer.
mL: millilitre; PSA: prostate-specific antigen.

62% in the combined-therapy group) and a 4% difference in disease-specific survival (10-year disease-specific mortality of 8% in the RT-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, it is 3 years (36 months), although questions have been raised regarding the possibility of reducing this to 18 months.

A 2009 publication by Bolla et al.[6] provided a recommendation of 3 years ADT in combination with RT over 6 months ADT, with RT for the treatment of any locally advanced disease, based on their findings of a reduced 5-year overall mortality with longer treatment (19% *versus* 15.2%). In their study, the side effects of ADT persisted for the duration of androgen suppression, but improved after the 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 a 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 that suggests 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 4141 patients in eight 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 with therapy by GNrH agonists and orchidectomy) and of coronary heart disease, myocardial infarction and sudden cardiac death (in therapy with 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 CV events seemed to be most at risk.

Albertsen et al.[28] observed a > 50% reduction in the risk of CV events among men with pre-existing CV disease, when treated with a GnRH antagonist, as compared with a GnRH agonist[28]; however, CV risk was not increased in men without pre-existing CV disease. To date, despite the large body of epidemiological and retrospective data supporting that there is an increased risk of CV events in some men, there is little understanding of which men might be at an 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?

In 2004, D'Amico et al.[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 a median follow-up of 4.5 years suggested higher survival rates in the combination group; however, the updated results of the same trial published in 2015 show 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 RT alone (94% mortality at median 16.62 years *versus* 70%). Moreover, analysis of the cause

Table 3. Trials comparing ADT and RT in men with localised prostate cancer.

Trial	Number of pts	Type of ADT	Comparison	Stage	Outcome
D'Amico 2008	206	Flutamide + LHRH agonist	RT *versus* RT + 6/12 ADT	T1b-T2b,N0,M0	Increase in overall mortality with RT alone at 7.6 yrs (42.3% *versus* 29.4%)
D'Amico et al., 2015[a]	206	Flutamide + LHRH agonist	RT *versus* RT + 6/12 ADT	T1b-T2b, N0, M0	No benefit from combination therapy at 15 yrs, reduced survival with combined therapy in men with moderate/severe comorbidity (8.3% *versus* 20%)
Jones et al., 2011 RTOG	1979	Flutamide + LHRH agonist	RT *versus* RT + 4/12 ADT	T1b-T2b, N0, M0	Increase in 10-yr overall survival with ADT (5% increase, 62% *versus* 57%), benefit in men with intermediate-risk disease

[a]Long-term update of previously published study results (D'Amico 2008).
ADT: androgen deprivation therapy; LHRH: luteinizing hormone-releasing hormone; RT: radiation therapy; yrs: years.

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 had 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 their 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 (with or without ADT)[31]; however, the greatest benefit was seen in younger men with fewer comorbidities and a 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.

Conclusions

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 the 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 co-morbidities.

Conflicting interests

The authors declare that there is no conflict of interest.

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CG, AG and DR researched the literature and wrote the manuscript, reviewed and edited the manuscript, and approved the final version of the manuscript.

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