Testosterone and prostate cancer: Friend or foe? A survey of uro-oncologists in the UK

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Disclosures

None.

Summary

Aim: To explore the practice and attitudes of uro-oncologists in the UK regarding monitoring testosterone levels and the use of testosterone replacement therapy (TRT) in their prostate cancer patients treated with androgen deprivation therapy (ADT).

Methods: An expert-devised online questionnaire was completed by members of the British Uro-oncology Group (BUG).

Results: Of 160 uro-oncologists invited, 84 completed the questionnaire. Before initiating ADT in patients with non-metastatic prostate cancer, only 45% of respondents measured testosterone levels and 61% did not measure testosterone at all during ADT in the adjuvant or neoadjuvant setting. However, in men with metastatic prostate cancer, 71% of the uro-oncologists measured testosterone before starting ADT and the majority continued testing during treatment. Approximately two-thirds of respondents did not prescribe TRT for their patients who were in remission following neo(adjuvant) ADT and who had castration levels of testosterone.

Discussion: Among UK uro-oncologists, measurement of testosterone levels before and during ADT was not typically part of routine practice in the management of patients with prostate cancer. However, testosterone levels were checked more frequently for patients with metastatic disease than disease at an earlier stage. Testing could be conducted in parallel with PSA measurement as testosterone levels are linked to biochemical failure. The majority of specialists participating in the survey did not prescribe TRT for their patients in remission following ADT.

Conclusion: Uro-oncologists in the UK do not generally measure testosterone as part of their patient management and they remain cautious about the possible benefits of TRT in men with prostate cancer.

What's known?

Androgen deprivation therapy (ADT) is widely used in men with localised or metastatic prostate cancer. However, castration levels of testosterone may be associated with adverse effects on bone, muscle, metabolism and sexual function. Testosterone replacement therapy (TRT) has been used successfully in men with hypogonadism due to other causes. However, its use in patients with prostate cancer remains controversial, even though studies have shown its benefits and acceptable safety.

What's new?

The results of this survey suggest that many uro-oncologists in the UK do not measure testosterone levels routinely, before, during or after ADT in their patients with prostate cancer, in either the metastatic or non-metastatic disease setting. Prescribing of TRT remains infrequent even for prostate cancer patients in remission with castration levels of testosterone following ADT.

1 INTRODUCTION

The value of testosterone in maintaining wellbeing in men is often underestimated. Indeed, clinically significant testosterone deficiency (hypogonadism) can be associated with erectile dysfunction (ED), decreased lean mass and muscle strength, abnormal bone mineralisation, deleterious metabolic changes, atherosclerosis, cognitive impairment and mood changes.[1-6] In some men the nature and severity of symptoms requires consideration of testosterone replacement therapy (TRT),[7] and this treatment can have positive benefits on symptoms such as ED,[8] body composition,[9] and mood.[10] It has also been proposed that TRT can improve quality of life in men with hypogonadism.[10, 11]

Testosterone depletion with androgen deprivation therapy (ADT) is the mainstay of therapy in men with metastatic prostate cancer and is widely used in the neo(adjuvant) setting in combination with radiotherapy.[12, 13] The most commonly used types of ADT include luteinising hormone releasing hormone (LHRH) agonists, gonadotropin releasing hormone (GnRH) agonists and GnRH antagonists. Antiandrogens (e.g. bicalutamide) may be necessary to manage the tumour flare associated with the initial testosterone surge caused by LHRH and GnRH agonist therapy; GnRH antagonist therapy is not associated with this phenomenon.[13-15]

Achievement of castration levels of testosterone during androgen deprivation therapy (ADT) is associated with clinical outcomes. Indeed, a study of patients with non-metastatic prostate cancer who had rising prostate specific antigen (PSA) levels after completion of definitive radiotherapy evaluated the effect of testosterone levels on outcomes.[16] Results showed that those patients achieving a testosterone level ≤0.7 nmol/L (<20 ng/dL) had a significantly reduced risk of developing castration-resistance prostate cancer relative to those not achieving this level during ADT. Cancer-specific survival was also associated with

testosterone levels during treatment. In a separate study of men with metastatic prostate cancer or biochemical failure after radiotherapy, when a threshold value of <50 ng/dL testosterone was considered as adequate suppression with 6 months of LHRH agonist therapy, there was no correlation with mortality.[17] However, when the lower threshold of <20 ng/dL was used there was a significant reduction in risk of mortality. Notably, only a small proportion of patients (16%) achieved a testosterone nadir of <20 ng/dL. Breakthrough rises in testosterone can also occur during ADT following initial achievement of castration levels and this has been linked to disease progression.[18]

Routine and frequent measurement of testosterone levels during ADT should therefore be considered in order to ensure that a castration threshold has been met and maintained. However, there is little evidence to suggest that this occurs in oncologists' clinical practice. In a single-centre retrospective review of patients with early disease receiving LHRH agonists, at a median follow-up of 4.7 years, the median number of testosterone measurements was only 6 per patient.[19] However, for each course of treatment there was a significant minority of patients who experienced a rise in testosterone to above castration levels. In a previous UK-based survey regarding guidelines for the management of men with ED following ADT, 28 specialists were asked about measurement of testosterone. A total of 8 stated that they measured testosterone before and after ADT, with another 11 stating that they sometimes did this.[20]

Following ADT, by its very nature, testosterone levels are depleted. Studies have shown that after cycles of intermittent ADT, achievement of pre-treatment levels can take between 3 months to 2 years or even longer, depending on the type and duration of ADT and on-treatment testosterone levels.[21-23] Numerous systematic reviews and meta-analyses of

observational studies have therefore suggested that men who have received this treatment are at risk of the complications of testosterone deficiency. These are comparable to men with hypogonadism due to other causes and include ED,[24] depression,[25] type 2 diabetes,[26] adverse changes in body composition,[27] increased risk of fractures and decreased bone mineral density,[28, 29] and cardiovascular disease.[30] There are numerous interventions available to manage these adverse effects of ADT. For example, resistance and weight training has been shown to increase lean muscle mass and reduce fat mass,[31] reduced bone mineral density and risk of fractures can be improved with bisphosphonates and denosumab,[32, 33] and ED managed with phosphodiesterase-5 inhibitors.[20, 24] Lifestyle interventions such as physical exercise may also be beneficial for ameliorating ADT-related fatigue.[31]

In theory, TRT would seem logical to compensate for the testosterone deficiency following adjuvant ADT in non-metastatic prostate cancer. However, concerns remain among healthcare professionals regarding cancer recurrence or rapid progression with the use of TRT in men with prostate cancer following completion of ADT. A recent meta-analysis and a large registry study have shown that there is no direct causal effect between TRT and the incidence of prostate cancer or changes in PSA.[34, 35] Moreover, a small number of retrospective studies in men with localised disease have shown minimal increased risk of disease recurrence or cancer-specific mortality with TRT.[36-41]

This report presents the results of a survey of uro-oncologists in the UK conducted by the British Uro-oncology Group (BUG) to understand their views on testosterone measurement and TRT in men with prostate cancer.

2 METHODS

Members of the British Uro-oncology Group (BUG) were contacted via email, and provided with a link to the questionnaire, which was conducted online, using SurveyMonkey. The questionnaire was constructed by the Executive Committee of BUG.

No formal statistical testing was performed on the data collected; number of respondents and percentages are presented.

3 RESULTS

The questionnaire was distributed to 160 uro-oncologist members of BUG. A total of 84 (52.5%) members completed the survey, with the majority (76%) being consultant clinical uro-oncologists.

Non-metastatic prostate cancer

When asked to consider their definition of castration levels of testosterone, 54% stated that they regarded <20 ng/dL as the threshold, while another 40% used <50 ng/dL as their cut-off value.

A total of 75 respondents (92%) stated that they manage patients with non-metastatic prostate cancer, and that measuring testosterone levels was not routine practice for men in this setting. Indeed, 55% of the sample said that they did not typically measure testosterone at baseline prior to initiation of treatment for this group of patients, while another 20% stated that they sometimes conducted these tests.

Regarding patients undergoing management with ADT in the (neo)adjuvant setting, 61% of the uro-oncologists never measured testosterone levels, while only one-quarter performed these tests in both settings. Around 5% of respondents questioned why they needed to do it. When asked how often they measured testosterone levels during neoadjuvant or adjuvant treatment, a total of just 10.4% stated that tests were performed either every month, every 3 months or every 6 months (Figure 1). Once ADT has been stopped in these patients, 51% of the uro-oncologists did not measure testosterone, although 42% did at this stage of management. A total of 19.7%, 7.9% and 1.3% of respondents stated that they measured testosterone monthly, every 3 months, and every 6 months, respectively; 29% never tested after completion of ADT.

Almost three-quarters of the uro-oncologists did not recommend regular testosterone measurement in primary care. However, this was mostly due to the fact that most of these specialists did not recommend the monitoring of patients in primary care.

Metastatic prostate cancer

A total of 94% of the uro-oncologists managed men with metastatic prostate cancer. Before initiation of ADT in these patients, 71% of respondents measured testosterone levels. However, during ADT, none of the uro-oncologists conducted monthly testing, and only 17.5% tested on a 3- or 6-monthly basis; 15% stated that they never measured testosterone levels, and 12.5% tested every time that PSA levels were tested (Figure 2). Perhaps surprisingly, around 70% of respondents stated that they would measure testosterone levels once the patients had progressed to castration-resistant prostate cancer.

When comparing treatment with LHRH agonists and GnRH antagonists, around one-third felt that there was a difference between types of treatment in terms of the speed at which testosterone control is achieved; another 37% felt that this was not the case. However, 24% of respondents had used only an LHRH agonist. Additionally, only 11% of the uro-oncologists stated that they had noticed a difference between these types of treatments for maintenance of testosterone suppression; 56% felt that there was no difference. Again, these results are impacted by the small but significant proportion of uro-oncologists who only prescribed LHRH agonists.

Similar to patients with non-metastatic prostate cancer, 83% of the uro-oncologists would not recommend that primary care professionals monitor testosterone regularly. This was mainly because they did not believe that patients with metastatic disease should be managed in primary care.

Prescribing TRT

The specialists were asked for their views on prescribing TRT for their prostate cancer patients. For men with non-metastatic prostate cancer who have completed (neo)adjuvant ADT and were in remission with castration levels of testosterone, approximately two-thirds stated that they had not prescribed TRT. If they were to prescribe TRT, the uro-oncologists would mostly recommended initiation at 2 years after ADT cessation. Thirty-three (56%) of the specialists who were not already prescribing TRT felt that they would consider prescribing it for men is this setting in the future, whereas 21 (36%) would not consider it.

If prescribing TRT, the majority of respondents (71%) favoured a transdermal gel formulation. Once a patient had started on TRT, 58% of the uro-oncologists would monitor testosterone levels on a 3-monthly basis (Figure 3). Approximately two-thirds would also measure PSA at this frequency.

4 DISCUSSION

The importance of measuring testosterone levels in the context of prostate cancer is unequivocal. In the present survey, however, more than one-half of respondents stated that they do not measure testosterone in non-metastatic disease, and only 10% monitored testosterone during (neo)adjuvant ADT. At the completion of ADT, almost one-third never tested testosterone, even though they offer routine follow-up, and it has been shown that testosterone recovery following intermittent ADT is associated with rises in PSA[42] (the Phoenix definition of biochemical failure following radiotherapy without hormonal therapy is PSA ≥2 ng/ml[43]). Knowledge of a patient's testosterone levels may therefore help to interpret PSA findings. Notably, there are no recommendations in current guidelines regarding testosterone measurement in patients with localised prostate cancer.[12, 44]

However, European guidelines make clear recommendations regarding the measurement of testosterone during ADT in men with advanced prostate cancer.[13] In the advanced disease setting, after initiation of ADT testosterone should be measured every 3–6 months, at the same time as PSA measurement (which would be the most convenient schedule); in patients receiving intermittent ADT, testosterone should be measured at 3-month intervals. In patients with stage M1 prostate cancer and a good response to treatment, it is recommended that testosterone is measured as part of routine follow-up, every 3–6 months. Finally, castration-resistant prostate cancer should be confirmed by a testosterone level <50 ng/dL and suspected

progression.[13] Although 71% of the respondents in the current survey measure testosterone at baseline in patients with metastatic prostate cancer, only 30% continue to monitor testosterone during ADT. Current European guidelines define castration levels of testosterone as <50 ng/dL (<1.7 mmol/L); therefore, almost all respondents to this survey aimed for this target or lower (<20 ng/dL or <0.7 mmol/L).[13]

Concerning the different types of ADT, it is difficult to arrive at definite conclusions, as almost one-quarter of the uro-oncologists participating in this survey have experience with LHRH agonists alone. However, numerous studies have reported that significant proportions of patients may not achieve castration levels with LHRH agonist therapy;[14, 17, 19] only a small number of patients fail to achieve castration testosterone levels with GnRH antagonist treatment.[15]

There remains a reluctance to prescribe TRT to patents with non-metastatic disease, although the results indicate that this may change in the future. This is despite the fact that numerous retrospective studies in men with treated localised prostate cancer (radiotherapy or prostatectomy) have shown minimal increased risk of biochemical or clinical cancer recurrence or prostate cancer-specific mortality with TRT.[36-40] Additionally, a single-centre study of men with localised disease treated with ADT reported no association between TRT and biochemical recurrence of prostate cancer.[41]

In conclusion, uro-oncologists in the UK do not typically measure testosterone as part of their prostate cancer patient management, either in the early or advanced disease settings. However, this could be easily conducted at the same time as PSA measurements. Specialists

remain cautious about the possible benefits of TRT in men with prostate cancer, even though recent studies to date indicate no increased risk of recurrence.

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Author contributions

Heather Payne and Rhona McMenemin (Trustees of BUG) led the design of the questionnaire, which was approved by the BUG Executive Committee; Right Angle (BUG Secretariat) collated the data for analysis by Heather Payne. All authors reviewed and commented on the manuscript.

Conflict of interests

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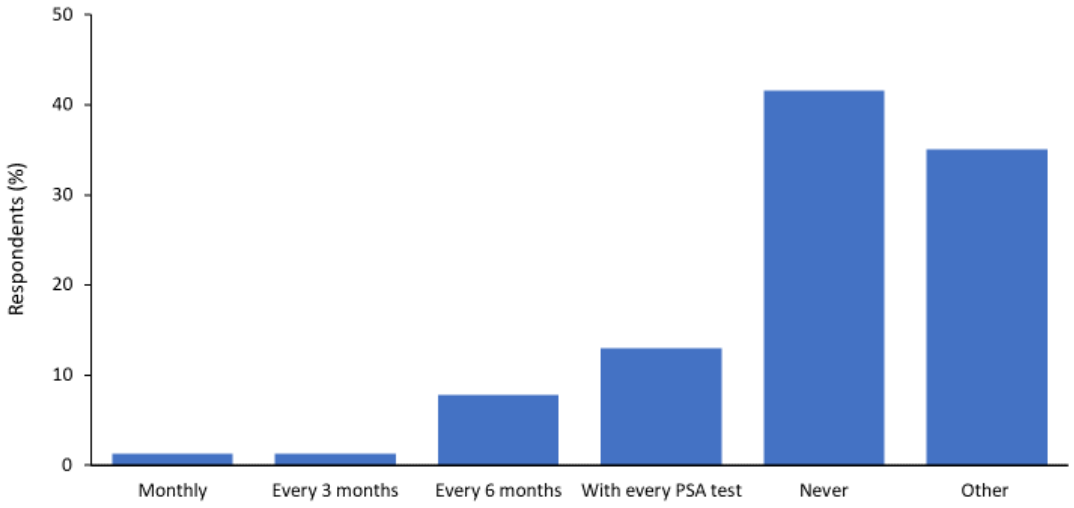
FIGURES

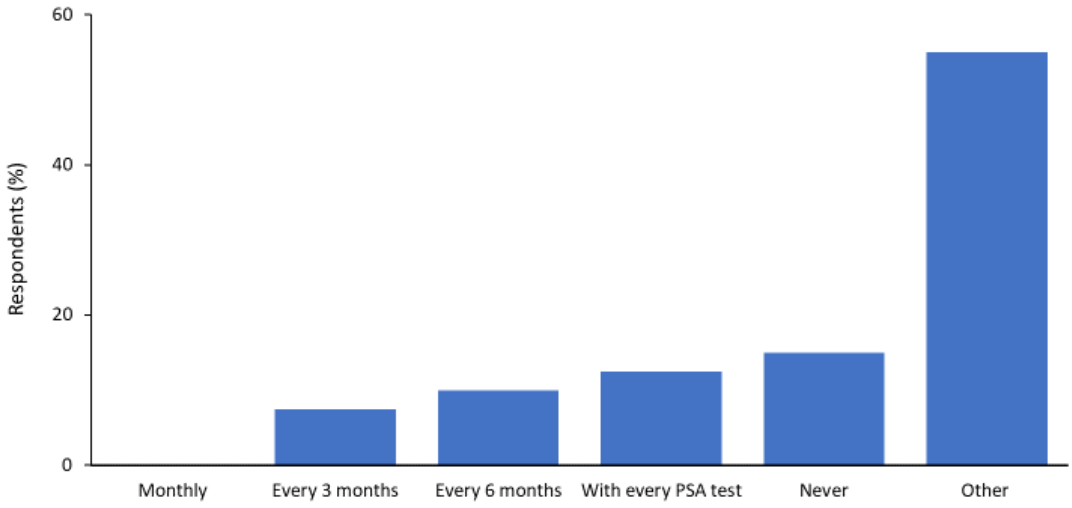
FIGURE 1 Frequency of testosterone measurement during neoadjuvant or adjuvant ADT in patients with non-metastatic prostate cancer (N=77)



'Other' category included: whenever PSA rises; progression; inadequate response to ADT; if symptoms detected.

ADT: androgen deprivation therapy; PSA: prostate-specific antigen

FIGURE 2 Frequency of testosterone measurement during ADT in patients with metastatic prostate cancer (N=80)



'Other' category included: whenever PSA rises; biochemical failure; progression; inadequate response to ADT; if it would alter management; to check castration levels had been reached. Note: such responses could also be within any of the other positive categories.

ADT: androgen deprivation therapy; PSA: prostate-specific antigen

FIGURE 3 Frequency of testosterone and PSA measurement following initiation of TRT in men with non-metastatic prostate cancer (N=62)