Androgen deprivation therapy (ADT) has been a mainstay in the treatment of advanced prostate cancer since its establishment by Huggins and Hodges in 1941.\(^1\)

Androgen deprivation was classically accomplished surgically by bilateral orchiectomy. The discovery of luteinizing hormone-releasing hormone (LHRH) allowed medical castration through suppression of the hypothalamic-pituitary-gonadal axis without the thromboembolic effects of estrogens.\(^3\) Medical ADT is presently often favoured over orchiectomy because of the potential for intermittent androgen deprivation, the lack of procedural complications and possible psychologic benefits.

**TESTOSTERONE MEASUREMENT IN CASTRATION- RESPONSIVE PROSTATE CANCER**

Testosterone elevated above the castrate range during ADT is referred to as testosterone escape.\(^2\) There are two types of testosterone elevations during ADT – acute-on-chronic responses and breakthrough responses. Acute-on-chronic responses are testosterone elevations that occur shortly after LHRH agonist administration, excluding the initial LHRH administration, and resultant testosterone flare. These responses arise because of direct action of the LHRH agonist on the LHRH receptor and have an uncertain clinical significance.\(^2\)

Breakthrough elevations occur when testosterone production recommences in the setting of continued LHRH agonist or antagonist administration due to incomplete drug effect.\(^4\) Study of breakthrough elevations has been difficult because, prior to 1995, testosterone was measured with double-isotope-derivative dilution techniques, which were inaccurate below 1.7 nmol/L. Consequently, 1.7 nmol/L has traditionally been used as the threshold defining adequate medical castration,\(^5,6\) even though several studies have documented that testosterone levels are usually 0.7 nmol/L or less after surgical castration.\(^5,7\)

The advent of a chemiluminescent assay in 1995 has significantly improved the accuracy of testosterone measurement in the castrate range (<1.7 nmol/L).\(^8\)

These advances in analytic techniques have translated into widely available commercial assays that may be used in research and clinical practice.\(^5,8,10\) Accordingly, we have recently gained more insight into the significance of testosterone kinetics below 1.7 nmol/L. This is relevant as a significant proportion of patients undergoing ADT will not achieve testosterone levels equivalent to surgical castration. In a recent review, up to 12.5% of study patients do not achieve levels below 1.7 nmol/L and up to 37.5% remain above 0.7 nmol/L.\(^4\)

Our group has recently evaluated the clinical significance of this large proportion of patients who do not achieve testosterone levels equivalent to orchiectomy.\(^11\) Specifically, we looked at whether a lack of testosterone breakthroughs above 0.7 nmol/L and 1.1 nmol/L in the first year of ADT affected time to progression to castrate-resistant prostate cancer (CRPC). We measured serum testosterone every 3 months in our prospective cohort series of patients undergoing ADT with LHRH agonists or antagonists. Patients with a 1-year average testosterone of 1.7 nmol/L or greater were excluded as this is already known to be insufficient castration. For analysis, patients were stratified into groups based on those achieving testosterone levels of 0.7 nmol/L or less and 1.1 nmol/L or less at 6 months, 9 months and for an average across 12 months. A total of 32 patients were included in this study, with a mean patient followup of 25.7 months. Patients with 1-year average testosterone levels under 1.1 nmol/L had a significantly increased time to CRPC (p=0.05), and a median progression-free survival (PFS) of 33.1 months vs 12.5 months for those with a 1-year average testosterone of 1.1–1.7 nmol/L. Patients with a 9-month absolute testosterone less than 1.1 nmol/L had a significantly increased time to CRPC (p=0.001, median PFS 33.1 months [<1.1 nmol/L] vs 12.5 months [>1.1 nmol/L]). Patients with a 6-month absolute testosterone less than 1.1 nmol/L had an increased time...
to CRPC, which was not statistically significant (p=0.085, median PFS 33.1 months [<1.1 nmol/L] vs 14.6 months [>1.1 nmol/L]). A testosterone threshold of 0.7 nmol/L at 6 months, 9 months or a 1-year average did not correlate with time to progression to CRPC. Our study thus supports a lower threshold of adequate castration testosterone levels (T<1.1 nmol/L) than the accepted standard (1.7 nmol/L).11

Similar findings have been previously reported by Morote et al10 in their study of 73 patients with non-metastatic prostate cancer receiving 3-month depots of LHRH agonist. Serum testosterone was determined 3 times in 6 months and patients were stratified to breakthrough groups of 1.7 nmol/L, 1.1 nmol/L and 0.7 nmol/L. After a median followup of 51 months, 41 patients had progressed to CRPC. These authors found testosterone breakthroughs above 1.7 nmol/L and 1.1 nmol/L to predict progression to CRPC. These data are also interesting because patients with a breakthrough testosterone above 1.7 nmol/L had a significantly improved freedom from CRPC if treated with bicalutamide. As in our study, breakthroughs above 0.7 nmol/L did not predict progression to CRPC.

Perachino and colleagues have also published an important series on this topic.9 Their retrospective series included 129 previously untreated bone-only metastatic prostate cancer patients who received 3-month depots of goserelin. PSA and testosterone were determined every 3 months. After a mean followup of 47.5 months, 58 (45%) patients were alive. Median testosterone at 6 months was 1.01 nmol/L (range 0.62–1.77 nmol/L). Using multivariate Cox regression analysis, cancer-specific mortality was predicted by Gleason score, 6-month PSA level and 6-month serum testosterone level (HR 1.32, p<0.05).

These studies suggest that 1.7 nmol/L may not be a sufficient level of castration for patients undergoing ADT as those patients achieving lower levels of testosterone have significantly increased time to progression to CRPC. A threshold of 1.1 nmol/L may be more appropriate — but this is not achieved by a significant percentage of men undergoing ADT. The optimal approach in these cases is unknown but consideration should be given to switching ADT agent and/or adding an antiandrogen.

TESTOSTERONE MEASUREMENT TO DIAGNOSE CASTRATE-RESISTANT PROSTATE CANCER
CRPC — the inevitable result of ADT-treated prostate cancer — involves a rising PSA despite adequate castration. Testosterone measurement is essential in the diagnosis of CRPC. Accordingly, both National Comprehensive Cancer Network (NCCN) and European Association of Urology (EAU) guidelines state that testosterone evaluation is mandatory in the face of rising PSA or clinical progression during ADT.12,13

To illustrate why this recommendation exists, Casey et al have recently presented baseline prospective testosterone data in men progressing to CRPC on gonadotropin-releasing hormone (GnRH) agonist therapy.14 CRPC was defined as a 50% or greater increase in PSA on two determinations made at least a week apart. Of their 44 enrolled patients, testosterone levels above 1.7 nmol/L, 1.1 nmol/L and 0.7 nmol/L were observed in 3 (6.5%), 5 (11.4%) and 11 (25.0%) patients, respectively. The results of Casey, Morales and Siemens corroborate the results of other authors who find that, during ADT, 12% and 37% of patients fail to achieve testosterone levels below 1.7 nmol/L and 0.7 nmol/L, respectively.4,6 The diagnosis of inadequate castration during disease progression provides an obvious therapeutic target — attempts should be made to lower testosterone by pharmacologic or surgical means.12

Despite these mounting indications for testosterone measurement, it remains a controversial issue. To illustrate this point, Dalla Nora and Shayeeghan have recently presented survey data from 15 industri-sponsored discussion groups held across Canada in 2011.15 Prior to the discussion group, only 24% indicated that they measured testosterone routinely
and 53% felt 1.7 nmol/L was an adequate castrate testosterone. In a 2005 survey of 400 attendants at a forum on testosterone control in prostate cancer, 29% stated that they knew the testosterone levels of none of their patients and 49% reported that they knew the levels of only a few patients. Respondents who felt that castrate levels should be 1.7 nmol/L and 0.7 nmol/L were 31% and 64%, respectively.

Clinical practice guidelines are vague on the question of testosterone measurement during ADT. The latest guidelines from the National Comprehensive Cancer Network suggest further hormonal manipulation if testosterone levels exceed 1.7 nmol/L but make no recommendations on when or if testosterone should be measured. Although European Association of Urology guidelines provide more details as to when testosterone should be measured, no direct evidence supports these recommendations. They suggest the measurement of testosterone levels 1 month after initiating ADT to check the testosterone nadir, as well as at 6 months to ensure that castrate levels are being maintained. Should appropriate castration not be achieved, these guidelines recommend switching ADT agent or surgical orchectomy. These guidelines, however, make no clear recommendation on an appropriate castrate level of testosterone. Both guidelines do clearly state that it is necessary to measure testosterone during ADT when the PSA is rising, to confirm progression to CRPC.

In our practice, we measure testosterone at baseline as well as routinely during ADT, as mounting evidence suggests a poorer prognosis with inadequate castration levels in patients with prostate cancer. Should acceptable castration (1.1 nmol/L) not be achieved, we attempt to change the LHRH modulator and also think it reasonable to add an antiandrogen. Prospective trials are needed to determine the best method of dealing with inadequate castration during ADT.

We also measure testosterone in the setting of a rising PSA during ADT to confirm the diagnosis of CRPC. Early recognition of CRPC is becoming more important given a recent interim analysis of abiraterone in the pre-chemotherapy setting that demonstrated improvements in PFS, overall survival and quality-of-life outcomes. Studies are ongoing as to whether enzalutamide has a similar benefit (PREVAIL, NCT01212991). Early recognition of CRPC in patients with known bone metastases may also allow for the early initiation of denosumab or zoledronic acid to prevent skeletal-related events.

References