Testosterone suppression in the treatment of recurrent or metastatic prostate cancer — A Canadian consensus statement

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Abstract

Testosterone suppression, achieved through orchiectomy or medically-induced androgen deprivation therapy (ADT), is a standard treatment for men with recurrent and metastatic prostate cancer. Current assay methods demonstrate the capacity for testosterone suppression to <0.7 nmol/l, and clinical data support improved outcomes from ADT when lower levels are achieved. Practical clinical guidelines are warranted to facilitate adoption of 0.7 nmol/l as the new standard castrate testosterone level.

A pan-Canadian group of experts, representing diverse clinical specialties, identified key clinical issues, searched and reviewed relevant literature, and developed consensus statements on testosterone suppression for the treatment of prostate cancer. The expert panel found that current evidence supports the clinical benefit of achieving low testosterone levels during ADT, and encourage adoption of ≤0.7 nmol/l as a new castrate level threshold. The panel recommends

regular monitoring of testosterone (e.g., every 3–6 months) and PSA levels as clinically appropriate (e.g., every 3–6 months) during ADT, with reassessment of therapeutic strategy if testosterone is not suppressed or if PSA rises regardless of adequate testosterone suppression. The panel also emphasizes the need for greater awareness and education regarding testosterone assay specifications, and strongly promote the use of mass spectrometry-based assays to ensure accurate measurement of testosterone at castrate levels.

Introduction

Prostate cancer remains the most common cancer diagnosis in men in Canada and is still among the top 3 leading causes of cancer death [1]. Men with early disease generally have a good prognosis; however, disease recurrence after initial treatment remains significant [2-5]. Androgen deprivation therapy (ADT) is the standard first-line treatment for men with recurrent or metastatic prostate cancer [6]. The goal of ADT is suppression of testosterone, an androgenic hormone associated with growth and progression of prostate cancer [7]. There is mounting evidence that suppression of patients' testosterone levels below the historical castrate standard of 1.7 nmol/l (e.g., ≤0.7–1.1 nmol/l), is associated with improved treatment outcomes versus patients with higher levels [8-13]. Although data support a relationship between lower testosterone levels and clinical benefit, many questions remain on how to translate this knowledge to practice [13]. This Canadian Consensus summarizes evidence and provides guidance developed by a multi-disciplinary panel of experts to assist practicing clinicians in implementing a lower castrate testosterone threshold during ADT for prostate cancer.

Methods

A Steering Committee of 4 clinical experts surveyed clinical issues among participants who represented multiple clinical specialties (academic/community urology, radiation oncology, and clinical biochemistry) and provided a pan-Canadian perspective. The Steering Committee conducted a topic-directed literature search, and developed proposed consensus statements that addressed clinical issues. All statements were graded by level of supporting evidence and level of consensus according to National Comprehensive Cancer Network (NCCN) consensus methodology (Table 1) [14, 15]. Between September 5–October 11, 2017, experts virtually reviewed and voted on proposed consensus statements. Statements not approved via ≥85% consensus were revised and confirmed at >85% in a second round of review and voting.

Consensus statements

1. Clinical benefit of low testosterone during ADT

Studies of the association of testosterone suppression level during ADT and outcomes of therapy have consistently demonstrated clinical benefit and importance of greater testosterone suppression during ADT [8-12, 16]. Prospective studies of ADT for the treatment of prostate

cancer have assessed a range of testosterone level thresholds below the historical castrate level standard, including ≤0.7, ≤0.9, ≤1.0, or ≤1.1 nmol/l, and demonstrated that patients achieving these low levels had longer time to castration resistant prostate cancer (CRPC) or death than their counterparts with respectively higher levels (Table 2) [8-12]. The largest prospective trial enrolled 626 patients with localized or locally advanced prostate cancer with treatment via orchiectomy, or LHRH agonist (LHRHa) therapy plus a non-steroidal anti-androgen for at least 4 weeks [8, 16]. Assessment of serum testosterone levels was completed every 2 months and results indicated that lower testosterone level was associated with longer time to CRPC. Analysis of testosterone levels during the first year of ADT demonstrated that time to CRPC was significantly improved for patients with nadir testosterone levels ≤0.7 nmol/l, compared with those with levels between >0.7 nmol/l and <1.7 nmol/l or ≥1.7 nmol/l (p=0.015). Median times to CRPC were 10.0, 7.21 and 3.62 years, respectively. Additionally, median testosterone level >0.7 nmol/l was associated with a higher risk of developing CRPC compared with lower levels (p=0.02; Table 2) [8, 16].

In retrospective analyses of ADT outcomes, including rates of testosterone breakthrough, progression-free survival (PFS), cause-specific survival (CSS), or overall survival (OS), relative to testosterone suppression level, 4 out of 6 studies demonstrated improved outcomes among patients with testosterone levels of ≤0.7 nmol/l or ≤1.1 nmol/l versus respectively higher levels [17-20].

Of the thresholds examined, ranging from ≤0.7 to ≤1.1 nmol/l, the greatest number of studies supported a testosterone suppression threshold of 0.7 nmol/l. There was a clinical benefit associated with concentrations at or below this cut-off [8, 9, 12, 16-18]. These data suggest that 0.7 nmol/l is an appropriate target testosterone level during ADT [16]. Based on the available evidence, we offer the following consensus statements.

CONSENSUS STATEMENT 1

In men receiving ADT for prostate cancer:

1a. There appears to be a clinical benefit associated with achieving a serum testosterone level of ≤0.7 nmol/l (Category 2A)

1b. Testosterone suppression to ≤ 0.7 nmol/l is a reasonable clinical goal (Category 2A)

Although current evidence supports adoption of a new castrate level threshold of ≤0.7 nmol/l during ADT, additional prospective studies are necessary to determine and validate the optimal threshold associated with the greatest therapeutic benefit [16].

2. Application

2a. Frequency of testosterone and PSA testing

Given the benefit of achieving a target testosterone level of ≤0.7 nmol/l, testosterone assay timing is important. Current guidelines support the goal of achieving castrate testosterone levels within the first year of ADT [8, 21, 22]. Although new dissolvable implants and gel-based depots permit more flexible dosing frequencies, physicians should consider monitoring testosterone every 3–6 months, or as appropriate, during the first year to ensure target levels are achieved [8, 21-23]. Once the target threshold has been reached, lengthening the monitoring frequency as appropriate for a patient's risk of relapse would be acceptable.

As a marker of testosterone signaling and disease control or potential progression, regular monitoring of prostate-specific antigen (PSA) level is also recommended every 3–6 months, or as clinically appropriate [13, 16, 21, 22].

CONSENSUS STATEMENT 2a

Prescribers of ADT should perform regular monitoring of testosterone and PSA levels throughout the first year of treatment (Category 2A)

2b. Accuracy of testing and collaboration with clinical labs

The first hormone assays were developed decades ago, and their limited sensitivity had a significant influence in setting the historical castrate testosterone level standard of 1.7 nmol/l [24-27]. More recent technological advances in assay methodology include improved immunoassays (IA) and the development of mass spectrometry (MS), allowing greater sensitivity and accuracy of detection [25, 26, 28, 29]. IA has long been the standard method for testosterone measurement and is most commonly used [30]. However, there are significant limitations in specificity, and therefore accuracy of IAs, particularly at the new target testosterone threshold of ≤0.7 nmol/l [31-38] (Figure 1A). A recent study by Morote et al. demonstrated the lack of reliability of IAs in the context of ADT for prostate cancer [38]. This prospective study, enrolling 249 patients, compared two commercially available IAs and reported that the methods showed different behaviors, with modest correlation between them. One method showed only 24.9% of patients with levels below the threshold of 0.7 nmol/l, and the other indicated that over 77.5% of patients had testosterone levels below 0.7 nmol/l. These data suggest that IA methods could compromise the monitoring of castrate testosterone levels and therefore evaluation of ADT.

In contrast, several studies have demonstrated that the variability of results obtained with different MS based assays is substantially less than those obtained by IA methods (especially at low testosterone concentrations) and confirmed that the threshold of sensitivity of MS is sufficient for monitoring testosterone in the context of ADT (Figure 1B) [31, 33, 39-41]. As an example, an externally validated LC-MS/MS method [40, 42] was used to assess testosterone levels in men on ADT [40]. A total of 34 men underwent surgical castration and 32 men received an LHRHa. Serum samples were collected and analyzed by LC-MS/MS ≥3 months from the date of surgery or initiation of medical ADT. Results showed that men on LHRHa had significantly lower testosterone levels (median 4.0 ng/dl [0.14 nmol/l], range <2.9 to 20.2 ng/dl [<0.1 to 0.7 nmol/l]) compared to those surgically castrated (median 9.2 ng/dl [0.32 nmol/l], range <2.9 to 28.8 ng/dl [<0.1 to1.0 nmol/l], p <0.001), demonstrating the ability of this method to accurately differentiate testosterone levels in the castrate range [40].

Use of LC-MS/MS is becoming more prevalent in clinical labs, while also accessible through out-sourcing of sample analysis to validated LC-MS/MS reference laboratories [31, 39, 40]. Average turnaround times for outsourced samples range from 7 to 10 days. LC-MS/MS should be considered the gold standard for testosterone assay at levels ≤ 0.7 nmol/l and sought out as a preferred method of testing over IA. Indeed, the American Endocrine Society recommends use of only MS for the measurement of testosterone at low levels [33, 39, 41]. If regular use of LC-MS/MS for low level testosterone assay is either unavailable or not feasible through on-site analysis or out-sourcing, IA methods validated against MS may be considered. An important aspect in establishing assays for testosterone measurement in local clinical laboratories is participation in accuracy-based external quality assessment (EQA) and standardization programs for both MS and IA. EQA programs ensure assay reliability over time and allow standardization of testosterone measures across laboratories (see Appendix for details on measures of accuracy) [41, 43-48]. These assessments are essential to ensuring ongoing reliability of results at low testosterone concentrations.

Given the potential variability in testing methods available at clinical labs, clinicians should clearly express their assay needs by requesting low/castrate testosterone levels for patients on ADT. They may also consider adding notation to the requisition form or including an accompanying note or additional material (e.g., information presented in Appendix) to reinforce the need for use of an assay method that is accurate at low testosterone levels.

CONSENSUS STATEMENTS 2b-1 and 2b-2

2b-1. For men with recurrent or metastatic prostate cancer receiving ADT

- Immunoassay (IA) may not be sufficiently specific, sensitive, accurate or reproducible in the detection of castrate level serum testosterone unless the method is externally validated against MS
- Validated liquid chromatography tandem mass spectrometry (LC-MS/MS) methods are the gold standard for castrate level testosterone assays, with adequate specificity, sensitivity, and accuracy at low concentrations (≤ 0.7 nmol/l)
  (Category 2A)

2b-2. Clinicians treating men with recurrent or metastatic prostate cancer receiving ADT

- Should consider encouraging access to validated testosterone assays, preferably by LC-MS/MS, either at their center or through collaboration with other centers
- Should consider ways to communicate the need for testosterone assay in the castrate range and consider providing additional notation with the requisition to promote reliable and accurate testosterone assessment at low levels
  (Category 2A)

3. Management

Clinical management strategies are necessary to address cases in which testosterone and/or PSA thresholds are not achieved. Testosterone levels during ADT reflect the efficacy of treatment, while the serum PSA concentrations are a reflection of disease control. Preferably, both testosterone and PSA levels remain low (≤0.7 nmol/l and ≤2 ng/ml, respectively), but if either begin to rise, reassessment and a change in therapeutic strategy may be warranted. There are two general scenarios defined by testosterone level (i.e., inadequate vs adequate testosterone suppression) that can be used to guide treatment strategy, with further differentiation according to relative PSA levels (Figures 2 and 3).

3a. Inadequately suppressed testosterone

The first scenario applies to patients receiving ADT and demonstrating consistently inadequate testosterone suppression, as assessed via testosterone measurements taken during continuous ADT or the on-therapy intervals of intermittent ADT within the first year [8, 16]. These patients may have either stable or rising PSA levels. For those with stable PSA (non-metastatic or metastatic), a testosterone level above 0.7 nmol/l may indicate treatment failure and alternate

medical or surgical treatments should be considered [8, 16] (Figure 2). For those with rising PSA, inadequate testosterone suppression may also indicate treatment failure. For non-metastatic or metastatic disease, alternate medical or surgical treatments should be considered [16]. In either case, combined androgen blockade with a non-steroidal anti-androgen may provide protection against the effects of failure to suppress serum testosterone below 0.7 nmol/l [18]. However, for those with metastatic disease, testosterone level <1.7 nmol/l and PSA >2 ng/ml, treatment for CRPC following CUA-CUOG guidelines should be implemented [49].

CONSENSUS STATEMENT 3a

For men with recurrent or metastatic prostate cancer receiving ADT, a testosterone level consistently above the target threshold of 0.7 nmol/l may indicate treatment failure and alternate medical or surgical therapy should be considered (Category 2A)

3b. Adequately suppressed testosterone

The second scenario applies to patients receiving ADT with adequately suppressed testosterone. In this case, stable PSA indicates effective disease control and patients should continue their current ADT (Figure 3). Rising PSA in the context of suppressed testosterone may indicate CRPC [16]. For non-metastatic patients, addition or withdrawal of an anti-androgen may be considered, while treatment for the management of CRPC [49] is recommended for patients with metastatic disease. For patients receiving intermittent ADT, rising PSA levels during the off-treatment interval occur normally, prompting re-initiation of therapy, usually when the PSA reaches a level of 10–20 ng/ml [16].

CONSENSUS STATEMENT 3b

For men with recurrent or metastatic prostate cancer receiving ADT with adequate testosterone suppression, rising PSA levels require consideration of alternate therapy, including treatment for CRPC (Category 2A)

The current recommendations for management of recurrent or metastatic prostate cancer are based on available evidence and expert consensus regarding standards of current practice. The described approaches may also apply in the treatment of locally advanced/high risk disease with or without local therapy. During ADT, a castrate testosterone level of ≤0.7 nmol/l is a reasonable and practical goal. Understanding the implications of testosterone levels relative to PSA levels during treatment guides therapeutic strategy. While low testosterone correlates with

an improved outcome, explicit clinical evidence for the benefit of reducing testosterone in men whose levels are not fully suppressed is limited. Further prospective research is necessary to confirm that adjusting therapy in inadequately suppressed patients to achieve testosterone suppression ≤ 0.7 nmol/l will result in improved treatment outcomes [16].

4. Knowledge translation

Identification, clinical assessment and documentation of the link between achieving lower testosterone levels during ADT and improved outcomes for prostate cancer patients are essential first steps in improving patient care. However, distribution of knowledge and translation to clinical application are necessary to ensure a real clinical impact. A recent survey of Canadian clinicians treating prostate cancer suggests a fundamental knowledge gap regarding the practical steps needed to ensure maximal testosterone suppression during ADT [13]. Among surveyed Canadian urologists, uro-oncologists, and radiation oncologists treating prostate cancer, including community urologists, approximately one-third were unaware of the lower limit of detection of the castrate testosterone assays used. Approximately 40% were monitoring testosterone regularly (e.g., every 3–6 months, or prior to each LHRHa injection), and the majority were unaware of the testosterone assay method used in their centre/laboratory [13]. There is a need for increased awareness regarding the importance and implications of testosterone suppression during ADT, as well as a baseline level of technical knowledge for proper selection and interpretation of testosterone assay data to guide assay selection and ensure detectability at or below 0.7 nmol/l.

Summary and Conclusions

Optimal care for men receiving ADT for prostate cancer includes the testosterone suppression goal of ≤0.7 nmol/l, regular monitoring of testosterone and PSA levels, and reassessment of therapeutic strategy if (1) serum testosterone is not suppressed or (2) PSA rises regardless of adequate testosterone suppression. We encourage clinicians to be aware of the assays used to assess testosterone level in samples from patients on ADT, and to ensure that the laboratories selected provide LC-MS/MS analysis calibrated for low testosterone levels, whether it is achieved in-house or via outsourcing.

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Figures and Tables

Fig. 1A. Limitations of IAs at low testosterone levels. Due to a lack of specificity, interference by serum or plasma components, particularly when testosterone levels are low (1-2), may result in inaccurate measurements. Immunoassays tend to overestimate steroid levels at low concentrations (3).

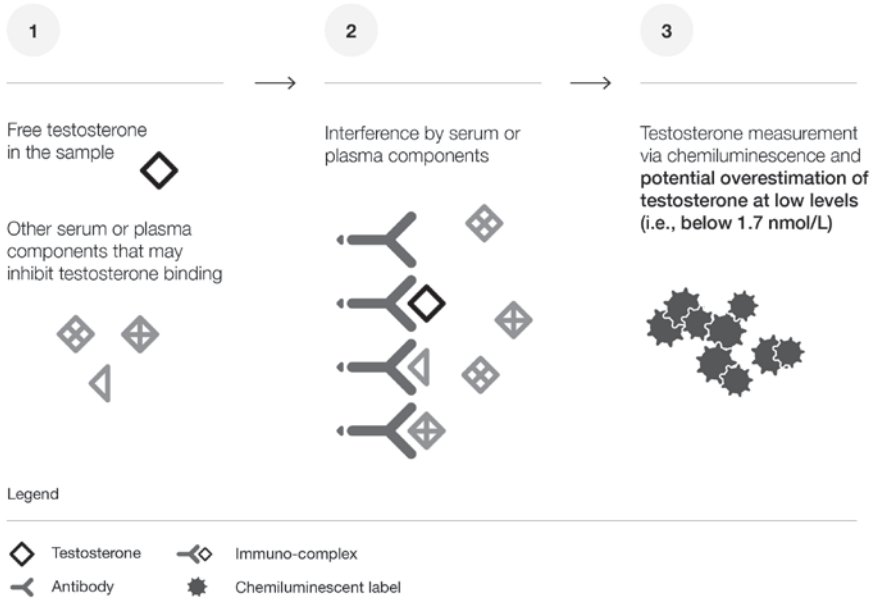

Fig. 1B. High specificity and greater accuracy by LC-MS/MS at low testosterone levels. Non-target serum components are eliminated via sample preparation and liquid chromatography (1); specificity and quantification are ensured by detection of ions (or mass-to-charge ratios) selected by the MS (2); two levels of mass separation further eliminate non-target compounds (MS/MS) (2), ensuring high specificity (3).

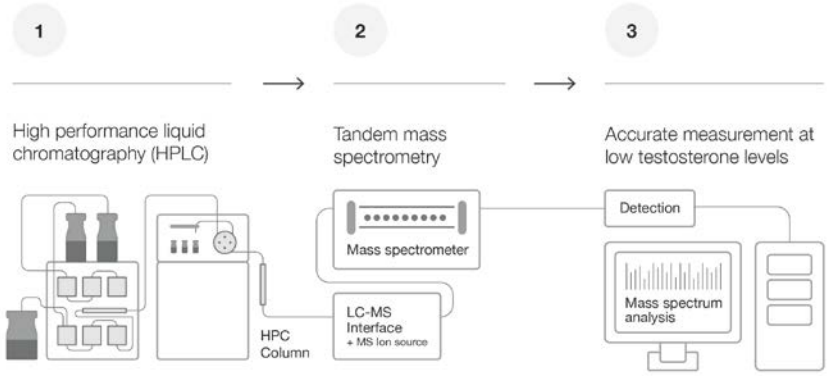

Fig 2. Management of patients on ADT with testosterone levels above target threshold of 0.7 nmol/l. * Follow CUA-CUOG guidelines [49] for management of CRPC; ADT: androgen deprivation therapy; CRPC: castration-resistant prostate cancer; PSA: prostate-specific antigen; T: testosterone.

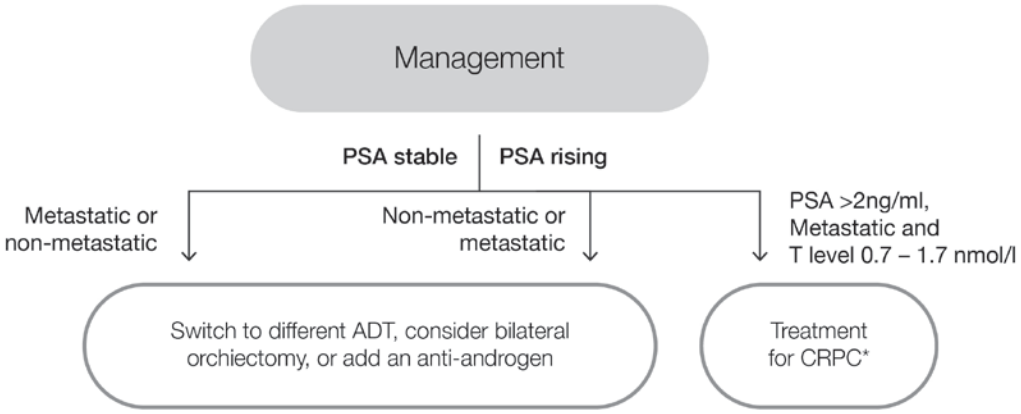

Fig. 3. Management of patients on ADT with testosterone levels at or below target threshold of 0.7 nmol/l. * Follow CUA-CUOG guidelines [49] for management of CRPC; ADT:, androgen deprivation therapy; CRPC: castration-resistant prostate cancer; PSA: prostate-specific antigen.

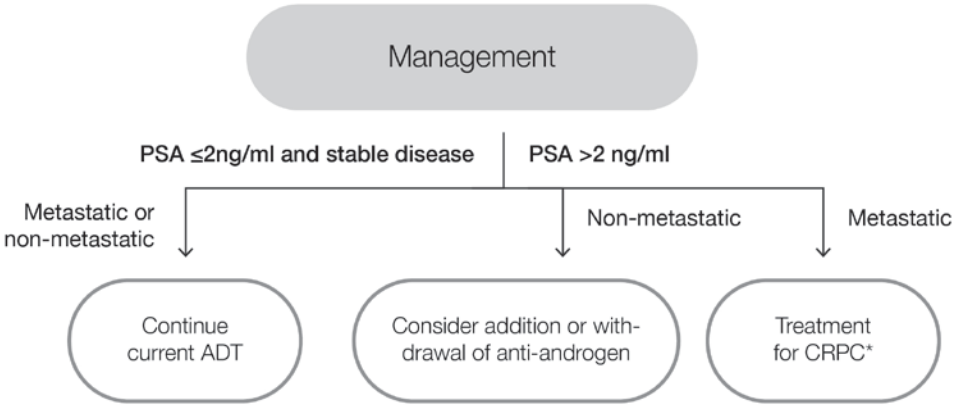

Table 1. NCCN consensus methodology [14, 15]

Description	**Level of consensus**
Category 1 – Based upon high-level evidence, there is uniform consensus that the intervention is appropriate	Uniform consensus: ≥85% agreement
Category 2A – Based upon lower-level evidence, there is uniform consensus that the intervention is appropriate	Uniform consensus: ≥85% agreement
Category 2B – Based upon lower-level evidence, there is consensus that the intervention is appropriate	Non-uniform consensus: 50-84% agreement
Category 3 – Based upon any level of evidence, there is major disagreement that the intervention is appropriate	No consensus: <50% agreement

Table 2: Prospective studies of androgen deprivation therapy outcomes by testosterone level. Adapted from Klotz et al. Maximal testosterone suppression in the management of recurrent and metastatic prostate cancer. Can Urol Assoc J 2017;11:16-23. Copyright 2017 by CUAJ. Adapted with permission.

Study type/ n/ setting	**ADT regimen(s)**	**T level**	**Time to CRPC (months) HR (95% CI)**	**PFS (months) HR (95% CI)**	**OS (months) HR (95% CI) or (range)**
Klotz 2015 [8] RCT, Multi-center 626 Recurrent	Orchiectomy or LHRHa plus nonsteroidal antiandrogen for minimum of 4 weeks	≤0.7 nmol/l (NT year 1; n=489)	10.0[a] (yrs) (*p*=0.015[b])	NR	Not reached[a] (CSS; *p*=0.02[b])
		>0.7 to <1.7 nmol/l (NT year 1; n=129)	7.21[a] (yrs) 1.62 [1.20-2.18]		10.07[a] (yrs) (CSS) 2.08 [1.28-3.38]
		≥1.7 nmol/l (NT year 1; n=8)	3.62[a] (yrs) 1.90 [0.98-4.70]		Not reached[a] (CSS) 2.93 [0.70-12.30]
Wang 2016 [12] Single-center 206 Met	LHRHa every mo. or long-acting LHRHa every 3 mo. Bicalutamide 50 mg/day Secondary HT of LHRHa and flutamide 250 mg 3 times a day after bicalutamide withdrawal for 6 weeks	≤0.9 nmol/l (n=98)	19.1[c] (*p*=0.0004)	NR	NR
		>0.9 nmol/l (n=108)	14.6[c]		
Bertaglia 2013 [9]	LHRHa (long-acting formulation) every 3	<0.7 nmol/l (n=25) vs	NR	NR 0.58	NR 0.19 [0.04-0.76]

Study type/ n/ setting	**ADT regimen(s)**	**T level**	**Time to CRPC (months) HR (95% CI)**	**PFS (months) HR (95% CI)**	**OS (months) HR (95% CI) or (range)**
Single-center 153 L, LA & Met	mo. Bicalutamide 50 mg daily during the first 4 weeks	≥0.7 nmol/l (n=128)		[0.30-1.15] (TTP; *p*=0.12)	(*p*=0.020)[d]
		≤1.0 nmol/l (n=56) vs >1.0 nmol/l (n=97)		NR 0.76 [0.46-1.26] (TTP; *p*=0.30)	NR 0.45 [0.22-0.94] (*p*=0.034)
		<1.7 nmol/l (n=94) vs ≥1.7 nmol/l (n=59)		NR 0.84 [0.52-1.37] (TTP; *p*=0.51)	NR 0.74 [0.42-1.33] (*p*=0.32)
Kawakami 2013 [11] Single-center 69 Met	LHRHa (goserelin, leuprolide or buserelin)	≤0.7 nmol/l (n=56)	NR	**Other results:** PSA minimum, maximum, median and mean were all higher for the cohort of patients with levels of T > 0.7 nmol/l. PSA correlated with total T (correlation 0.42; p = 0.003). T levels >0.7 nmol/l were found in 17% (7/41), 19% (4/21) and 28% (2/7) of patients on goserelin, leuprolide and buserelin, respectively. No statistical difference	
		>0.7 nmol/l (n=13)			

Study type/ n/ setting	**ADT regimen(s)**	**T level**	**Time to CRPC (months) HR (95% CI)**	**PFS (months) HR (95% CI)**	**OS (months) HR (95% CI) or (range)**
				among the 3 LHRH agonists in proportion of patients not achieving optimal levels of T.	
Dason 2013 [10] Cohort series 32 L, LA & Met	LHRHa (goserelin, leuprolide or triptorelin), 3-month depots and a 1-month course of bicalutamide on ADT initiation OR LHRH antagonist (degarelix), 1-month depots	<1.1 nmol/l[c] (1 yr; n=28)	33.1[a] (*p*=0.05)	**Other results:** Patients with a 9-month absolute T measurement <1.1 nmol/l had increased time to CRPC (p=0.001, median: 33.1 months [<1.1 nmol/l] vs. 12.5 months [>1.1 nmol/l]). Patients with a 6-month absolute T <1.1 nmol/l had an increased time to CRPC, which was not statistically significant (p=0.085, median: 33.1 months [<1.1 nmol/l] vs. 14.6 months [>1.1 nmol/l]). Mean T level <0.7 nmol/l compared to 0.7 to 1.7 nmol/l at 6, 9 or 12 months did not significantly predict time to CRPC.	
		1.1-1.7 nmol/l[c] (1 yr; n=4)	12.5[a]		

[a]Median; [b]adjusted for multiple test based on the Hochberg method (Hochberg et al. Biometrics 1988; 75:800-802). [c]mean; [d]serum T level <0.7 nmol/l significantly associated with lower risk of death. ADT: androgen deprivation therapy; CI: confidence interval; CRPC: castration-resistant prostate cancer; CSS: cause (cancer)-specific survival; HR: hazard ratio; HT: hormonal therapy; L: localized; LA: locally advanced; LHRH(a): luteinizing hormone-releasing hormone (agonist); Met: metastatic; mo: month(s); NR: not reported; NT: nadir testosterone; OS: overall survival.;

PFS: progression-free survival; PSA: prostate-specific antigen; RCT: randomized controlled trial; T: testosterone; TTP: time to progression; yr(s): year(s).