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Impact of Surgical and Medical Castration on Serum Testosterone Level in Prostate Cancer Patients

Key Words

Prostatic neoplasms • Testosterone • GnRH agonist • LHRH agonist

Abstract

Introduction: The paper aims at evaluating the role of testosterone levels and their cut-off points in the treatment of prostate cancer with androgen deprivation therapy. **Materials and Methods:** We performed a non-systematic review of the literature, searching Medline using the following key words: 'Prostatic neoplasms/therapy' [MeSH], 'Buserelin' [MeSH], 'Goserelin' [MeSH], 'Leuprolide' [MeSH], 'Triptorelin' [MeSH], 'prostate cancer*' [tiab], and 'testoster*' [tiab]. **Results:** The most commonly used cut-off point of testosterone to define castration was 50 ng/dl. In this respect, GnRH agonists allowed castration in a very high percentage of patients (87.5–100%). Specifically, triptorelin was reported to yield castration level of testosterone in 98.8%, the classical formulation of leuprolide in 95–98.8% of the cases, and Eligard®, a novel formulation of leuprolide, in 99–100%. With regard to the 20-ng/dl breakpoint, available data suggest that goserelin yields castration level of testosterone in 96%, the classical formulation of leuprolide in 87–92% of the patients, and the novel formulation in 88–97.5%. **Conclusions:** The clinical significance of different levels of testosterone

yielded during androgen deprivation therapy is still unknown. Considering the standard cut-off point of 50 ng/dl, GnRH agonists allowed castration in a very high percentage of patients.

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Introduction

Prostate cancer is a major healthcare problem in the Western world. Epidemiological data suggested that 186,320 cases would be diagnosed in the USA during 2008 and cause 28,660 deaths. Such figures make prostate neoplasm the cancer with the highest incidence and the second most common oncological cause of death in the Western world [1]. Despite the diffusion of PSA test and the subsequent increase in the percentage of clinically-localized prostate cancer at the moment of the initial diagnosis suitable for radical treatments, androgen deprivation therapy is a very common treatment. Specifically, according to both the European Association of Urology (EAU) and the National Comprehensive Cancer Network (NCCN) clinical practice guidelines, indications for androgen deprivation therapy includes locally-advanced or metastatic cancers, adjuvant therapy after surgery for those patients harboring lymph node metastases, neoad-

juvant and adjuvant therapies associated with external beam radiotherapy or brachytherapy, and biochemical and clinical relapses after primary radical treatments [2, 3].

Following the data of several randomized, controlled clinical trials and formal meta-analyses showing the equivalence of gonadotropin-releasing hormone (GnRH) agonists and orchiectomy with regard to overall survival [4], bilateral orchiectomy has been almost completely abandoned. Recent data from the Surveillance, Epidemiology and End Results (SEER) database suggest that GnRH agonists are the most commonly used form of androgen deprivation and that the use of GnRH agonists is consistently increasing for all patient ages, and tumor stages and grades [5].

Several GnRH agonists are currently available, namely buserelin (Suprefact®), goserelin (Zoladex®), leuprolide (Enantone®), triptorelin (Decapeptyl®) as well as different extended-release formulations of these drugs. A single GnRH antagonist, abarelix (Plenaxis®), is currently on the market.

Eligard®, a new formulation of extended-release leuprolide whose novel delivery system (Atrigel®) has been supposed to be responsible for improving the pharmacodynamic profile [6, 7], has recently been put on the market [8–10]. Specifically Atrigel consists of a biodegradable polymer dissolved in a biocompatible solvent which, once injected into the body, forms a single large implant where leuprolide is encapsulated. Because of the large size of the sphere compared to the microsphere of the classical formulation, Atrigel can contain a greater amount of leuprolide, delivering a twofold higher dose. The novel formulation was shown to reduce testosterone levels <20 ng/dl in 94–98% of the patients [6, 8–10]. However, to date, the clinical relevance of the level of testosterone reached during androgen deprivation therapy by GnRH agonists is not clearly known.

The purpose of the present study is to evaluate the available pieces of evidence on the role of testosterone level in the treatments of prostate cancer by androgen deprivation therapy.

Search Strategy

We performed a non-systematic review of the literature in February 2007. Data were identified by searching the Medline database, using both MeSH and free text searches. Specifically, the MeSH search was conducted using the terms ‘Prostatic neoplasms/therapy’, ‘Busere-

lin’, ‘Goserelin’, ‘Leuprolide’, ‘Triptorelin’, retrieved from the MeSH browser provided by Medline. The free text search employed the following terms through the field ‘title and abstract’ of the records: ‘prostate cancer*’, ‘testosterone*’. The Medline searches were pooled and the following search limits were used: ‘Humans’, gender (Male), and languages (‘English’).

352 records were identified, whose full texts were reviewed by the authors to select the studies to be considered most relevant for the purposes of this review. In addition, other significant texts cited in the reference lists of the selected papers were considered, as well as Cochrane Database of Systematic Reviews.

All the papers were ranked according to the grade of evidence as stated by Phillips et al. [11]. Meta-analyses of randomized controlled trials (RCTs) constitutes the highest evidence (level 1a), followed by an adequately sampled single RCT (level 1b); low-quality RCTs, prospective cohort studies, and high-quality case-control studies give level 2 of evidence, as well as extrapolations from level 1 studies. A lower grade of evidence is provided by systematic review of case-control studies or individual case-control studies (level 3), while case series provide level 4 of evidence [11].

Definition of Castration

Various levels of testosterone have been reported to define castration [12]. The most commonly used value is 50 ng/dl or less, but values up to 100 ng/dl have been reported [13]. The castration testosterone cut-off point of 50 ng/dl or less derives from assay methods developed in the late 1960s and early 1970s [12]. These early methods used the double-isotope-derivative dilution technique, which had 50 ng/dl as the lower detection limit. These methods of measuring serum testosterone have been abandoned for the more rapid and accurate radioimmunoassay technique and, more recently, the chemiluminescence technique. Despite these advances in methodology with more accurate lower limits of detection however, the definition of testosterone levels after bilateral orchiectomy has not been updated.

Testosterone Levels after Bilateral Orchiectomy

Table 1 summarizes the median levels of serum testosterone after bilateral orchiectomy in patients with prostate cancer. Our Medline search identified 7 studies re-

Table 1. Median testosterone levels in patients undergoing bilateral orchiectomy for prostate cancer

Group (first author)	Study design	Cases	Dosage technique	Testosterone level, ng/dl	Level of evidence
Parmar, 1987 [14]	RCT	49	RIA	41.6	II
Kaisary, 1991 [15]	RCT	144	NR	26.3	II
Soloway, 1991 [16]	RCT	83	NR	<50.0	II
Rohl, 1992 [17]	Case series	40	RIA	21	IV
Lin, 1994 [18]	Case series	13	RIA	<20	IV
Vogelzang, 1995 [19]	RCT	145	NR	20.0	II
Oefelein, 2000 [12]	Case series	35	CL	15	IV

RIA = Radioimmunoassay; CL = chemiluminescence; NR = not reported.

porting data on testosterone level after surgical castration. Specifically, we found data in 4 RCTs [14–16, 19] and in 3 prospective case series [12, 17, 18].

Rohl and Beuke [17] were the first to report on the testosterone level of 40 patients with prostate cancer who had undergone bilateral orchiectomy, using a radioimmunoassay technique. The authors found median total serum testosterone values of 21 and 16 ng/dl, 1 month and 1 year after orchiectomy, respectively. More recently, Oefelein et al. [12] reported on 35 prostate cancer patients undergoing orchiectomy where chemiluminescence methods were used to dose median testosterone level. Specifically, the authors found that the median value of testosterone 33 months after surgery was 15 ng/dl (interquartile range 10–20 ng/dl), being 30 ng/dl the highest recorded value. Following these data, 20 ng/dl has been advocated as a new possible cut-off point to define castration but, considering that 25% of the patients who had undergone bilateral orchiectomy in Oefelein's series stay beyond this value, this cut-off point has probably to be regarded as too strict.

Testosterone Levels during Androgen Deprivation Therapy with GnRH Agonists

Our Medline search identified 16 studies reporting data on testosterone level after medical castration with GnRH agonists. We found data from 4 RCTs [15, 20–22] and 12 case series [23, 32]. Specifically, a single paper assessed the efficacy of buserelin, 4 of goserelin, 9 of leuprolide (including 4 studies evaluating the novel formulation), and 3 of triptorelin.

Table 2 summarizes the mean levels of serum testosterone during androgen deprivation therapy with GnRH

agonists. Only 4 studies, 3 from the group of the University Hospital of Cleveland [23–25] and a 1 from Vall d'Hebron University Hospital, Barcelona, Spain [31], used the chemiluminescence technique to dose serum testosterone, while in 7 studies radioimmunoassay was the technique of choice [8, 22, 28–32]; in all the other papers, the technique to dose testosterone was not specified.

The most common cut-off point to define castration was 50 ng/dl, although some authors provided separate analysis for both 50- and 20-ng/dl breakpoints. Considering 50 ng/dl as cut-off point, GnRH agonists allowed castration in a very high percentage of patients, ranging from 87.5 to 100%. Specifically, the classical formulation of leuprolide was reported to yield a castration level of testosterone in 95–98.8% of the cases [25, 26], while the novel formulation achieved a castration testosterone level in 99–100% of the patients [8, 9, 28, 30]; finally, triptorelin reached a castration level in 98.8% [21].

With regard to the 20-ng/dl breakpoint, the available data suggest that the classical 3-month depot formulation of leuprolide yields a castration level of testosterone in 87–92% of the patients [23, 25], the novel formulation leuprolide in 88–97.5% [8, 9, 28, 30], and goserelin in 96% [27].

The recorded mean levels of serum testosterone were quite variable, depending on drug, formulation, and testosterone dosage methods, ranging from 5 ng/dl for the buserelin 3-month depot [29] to 36.3 ng/dl for the goserelin 1-month depot [15].

Discussion

The data from the available literature suggest that all the GnRH agonists yield overlapping levels of serum testosterone, with minimal differences between the different

Table 2. Testosterone levels during androgen deprivation therapy with GnRH agonists

Group (first author)	Study design	Drug	Formulation	Cases	Dosage technique	Cut-off point to define castration, ng/dl	Mean testosterone level, ng/dl	% of patients below the cut-off point	Level of evidence
Kaisary 1991 [15]	RCT	Goserelin	1-month depot	148	NR	NR	36.3	NR	II
Fernandez del Moral 1996 [20]	RCT	Goserelin	1-month depot	83	NR	69	20.8	100	II
Fernandez del Moral 1996 [20]	RCT	Goserelin	3-month depot	77	NR	69	25.3	98.8	II
Oefelein 1998 [23]	Prospective case series	Leuprolide	3-month depot	13	CL	20	10* (month 3)	92	IV
Oefelein 1999 [24]	Prospective case series	Leuprolide	3-month depot	32	CL	20	20* (month 3)	NR	IV
Oefelein 2000 [25]	Prospective case series	Leuprolide	3-month depot	38	CL	50 20	NR	95 87	IV
Fowler 2000 [26]	Prospective case series	Leuprolide	1-year depot	80	NR	50	9.3 (week 52)	98.8	IV
Chu 2002 [9]	Prospective case series	Leuprolide	Eligard 3-month depot	117	NR	50 20	10.1	100 94	IV
Perez-Marreno 2002 [8]	Prospective case series	Leuprolide	Eligard 1-month depot	120	RIA	50 20	6.3	100 97.5	IV
Fontana 2003 [27]	Prospective case series	Goserelin	3-month depot	120	NR	20	NR	96	IV
Sartor 2003 [28]	Prospective case series	Leuprolide	Eligard 4-month depot	82	RIA	50 20	12.4	100 89	IV
Heyns 2003 [21]	RCT	Triptorelin	1-month depot	137	NR	50	NR	98.8	II
Heyns 2003 [21]	RCT	Leuprolide	1-month depot	140	NR	50	NR	97.3	II
Teillac 2004 [22]	RCT	Triptorelin	1-month depot	68	RIA	NR	24.7	NR	II
Teillac 2004 [22]	RCT	Triptorelin	3-month depot	63	RIA	NR	25.0	NR	II
Pettersson 2006 [29]	Prospective case series	Buserelin	3-month depot	21	RIA	58	5.0	NR	IV
Crawford 2006 [30]	Prospective case series	Leuprolide	Eligard 12-month depot	103	RIA	50 20	12.3	99 88	IV
Morote 2006 [31]	Cross-sectional study	Unspecified	3-month depot	48	CL	50 20	29.5	87.5 62.5	IV
Yri 2006 [32]	Retrospective series	Leuprolide	3-month depot	40	RIA	81	17.3	90	IV
Yri 2006 [32]	Retrospective series	Goserelin	3-month depot	25	RIA	81	26.0	100	IV

NR = Not reported; CL = chemiluminescence; RIA = radioimmunoassay. * Median value.

drugs and formulations regardless of the applied cut-off and the used assay. Androgen deprivation therapy is a mainstay in the treatment of prostate cancer. It aims at reducing testosterone levels, which acts by promoting programmed cell death in cancer cells. Bilateral orchiectomy was the only way to achieve castration before the

development of GnRH agonists, which has been shown to obtain clinical results in terms of cancer-specific survival similar to those of surgical castration in several RCTs and meta-analyses [4]. Consequently, it has been postulated that GnRH analogs should suppress testosterone to obtain at least the same level as bilateral orchiectomy [33].

The FDA has established serum testosterone levels of ≤ 50 ng/dl as being consistent with levels obtained after surgical castration. This level of testosterone has been used as the standard reference for approval of new hormonal therapies in the USA since the advent of GnRH agonists. This traditionally accepted testosterone castrate level of <50 ng/dl is, however, under debate because based on the double-isotope derivative dilution technique, introduced in the late 1960s and not currently used in the clinical practice due to the availability of more reliable technique, such as radioimmunoassay and chemiluminescence, which allowed to hypothesize that the real testosterone level of patients undergoing surgical castration might be lower than 20 ng/dl [12]. On this basis, in the 2001 version of the prostate cancer guidelines, the NCCN recommended that orchiectomy or the addition of an oral antiandrogen should be considered if a patient's serum testosterone level was >20 ng/dl during GnRH agonist monotherapy [34]. This threshold is not based on solid pieces of evidence, because no controlled trials have shown that the cancer-specific survival probabilities of the patients achieving testosterone level <20 ng/dl were more favorable compared to those having testosterone level between 20 and 50 ng/dl. In fact, this cut-off point was not recommended in the subsequent versions of the NCCN guidelines, including the last one released in 2007.

Using a cut-off point of 50 ng/dl as definition of castration, current studies demonstrate that only about 5% of patients being treated with GnRH agonist therapy fail to achieve castration [25], without any clear prognostic factor useful for identifying such patients. However, the clinical relevance of this relative lack of suppression in terms of unfavorable cancer-related outcome is far from being understood. When using a castrate testosterone level of <20 ng/dl rather than 50 ng/dl, some patients treated with conventional GnRH agonist formulations have been considered as being treatment failures. Consequently, some authors advocated the importance of proper testosterone monitoring in order to evaluate treatment response, suggesting the need for a pharmacological agent that adequately suppresses testosterone to castrate levels, equaling those seen with orchiectomy [35]. However, these theoretical considerations are not supported by clinical studies suggesting better prognosis in case of further hormonal manipulations. Indeed, indirect evidence deriving from the available RCTs and meta-analyses comparing the clinical efficacy of orchiectomy and GnRH agonists discourage such an approach. Specifically, a meta-analysis of 10 RCTs evaluating $>1,900$ patients

treated by bilateral orchiectomy or GnRH agonists failed to show any statistically significant survival difference between the two treatments [4], allowing to hypothesize that the slightly lower testosterone levels after bilateral orchiectomy were not clinically significant. However, most of the trials seem to have an inadequate follow-up duration to assess the long-term effect on the development of hormone refractory prostate cancer, and the differences in cancer-specific survival and, despite of the number of patients included in the meta-analysis, the power of the study might be regarded as insufficient to detect very small survival differences.

On the other hand, further indirect considerations on the prognostic role of testosterone level after GnRH agonist therapy might be drawn analyzing the comparative studies evaluating GnRH agonist monotherapy and their association with antiandrogens, the so-called combined androgen blockade. If GnRH agonists would be insufficient to yield castration levels of testosterone, it might be easy to hypothesize that concomitant antiandrogen therapy might improve the cancer-related outcome. Two formal meta-analyses, one of the Cochrane Collaboration, reporting on 20 randomized controlled trials and 6,320 patients [36] and one from the Prostate Cancer Trialists' Collaborative Group (PCTCG) including 27 trials and 8,275 patients [37], showed only a modest advantage in the 5-year cancer-specific survival probabilities in favor of those patients randomized to maximum androgen blockade. Specifically, Cochrane meta-analysis suggests a 5% improvement in the 5-year cancer-specific survival probabilities, while the larger PCTCG identified a 5-year cancer-specific survival advantage as low as 1.8% [36, 37]. However, in the PCTCG meta-analysis the results were independent of the kind of castration used (surgical or medical), suggesting similar efficacy for antiandrogens following bilateral orchiectomy and GnRH agonists [38]. Moreover, with regard to the different antiandrogens, the PCTCG meta-analysis suggested a 2.9% increase in the 5-year cancer-specific survival for those patients randomized to maximum androgen blockade including flutamide or nilutamide, compared to the GnRH agonist monotherapy, while the use of combination therapy with cyproterone acetate caused a significant decrease in the cancer-related survival, compared to the GnRH agonist monotherapy [38]. Based on the available clinical data and the indirect evidence deriving from the available randomized clinical trials, we do believe that randomized controlled clinical trials should be designed to assess whether the use of antiandrogens or surgical castration might be of benefit for those patients who do not achieve

castration levels of testosterone during GnRH agonist monotherapy, i.e. testosterone levels higher than both 20 and 50 ng/dl. Indeed, considering the natural history of prostate cancer, such trials would require a very large cohort of patients to avoid being underpowered and a very long follow-up duration, which makes these studies very difficult to perform.

Conclusion

Androgen deprivation therapy is a mainstay in the treatment of prostate cancer. 50 ng/dl is the cut-off point of testosterone level established by the FDA as the standard reference for approval of new hormonal therapies. Few studies using the chemiluminescence technique to dose testosterone suggest that lower testosterone levels are achieved by surgical castration, leading to consider these levels also for monitoring GnRH agonists. However, the clinical significance of the different levels of tes-

tosterone yielded during androgen deprivation therapy is still unknown and long-term data on the occurrence of androgen-independent prostate cancer and cancer-specific survival are not available.

Although some authors advocated the importance of proper testosterone monitoring in order to evaluate treatment response, suggesting the need for pharmacological agents that adequately suppress testosterone to castrate levels, high-quality evidence is not available in the field, while the figures of the available RCTs and meta-analyses question such proposals. RCTs assessing the impact of further hormonal manipulation in patients with testosterone levels in the range of 20–50 ng/dl as well as in those patients failing to reach the standard castration level during GnRH agonist monotherapy would be desirable. However, such studies are very hard to conduct, due to the large number of patients needed to achieve a sufficient statistical power and the required long-term follow-up.

References

- Jemal A, Siegel R, Ward E, Hao Y, Xu J, Murray T, Thun MJ: Cancer statistics, 2008. *CA Cancer J Clin* 2008;58:71–96.
- Heidenreich A, Aus G, Abbou CC, Bolla M, Joniau S, Matveev V, Schmid HP, Zattoni F: EAU guidelines on prostate cancer. Downloaded at http://www.uroweb.org/fileadmin/user_upload/Guidelines/07_Prostate_Cancer_2007.pdf.
- NCCN Clinical practice guidelines in oncology. Prostate cancer v. 1.2008. Downloaded at http://www.nccn.org/professionals/physician_gls/PDF/prostate.pdf.
- Seidenfeld J, Samson DJ, Hasselblad V, Aronson N, Albertsen PC, Bennett CL, Wilt TJ: Single-therapy androgen suppression in men with advanced prostate cancer: a systematic review and meta-analysis. *Ann Intern Med* 2000;132:566–577.
- Shahinian VB, Kuo YF, Freeman JL, Orihuela E, Goodwin JS: Increasing use of gonadotropin-releasing hormone agonists for the treatment of localized prostate carcinoma. *Cancer* 2005;103:1615–1624.
- Berges R, Bello U: Effect of a new leuporelin formulation on testosterone levels in patients with advanced prostate cancer. *Curr Med Res Opin* 2006;22:649–655.
- Sartor O: Eligard: a new form of treatment for prostate cancer. *Eur Urol Suppl* 2006;5:905–910.
- Perez-Marreno R, Chu FM, Gleason D, Loizides E, Wachs B, Tyler RC: A six-month, open-label study assessing a new formulation of leuprolide 7.5 mg for suppression of testosterone in patients with prostate cancer. *Clin Ther* 2002;24:1902–1914.
- Chu FM, Jayson M, Dineen MK, Perez R, Harkaway R, Tyler RC: A clinical study of 22.5 mg La-2550: a new subcutaneous depot delivery system for leuprolide acetate for the treatment of prostate cancer. *J Urol* 2002;168:1199–1203.
- Berges R: Eligard: pharmacokinetics, effect on testosterone and PSA levels and tolerability. *Eur Urol Suppl* 2005;4:20–25.
- Phillips B, Ball C, Sackett D, et al: Levels of evidence and grades of recommendation. Oxford Centre for Evidence-Based Medicine. Downloaded at http://www.cebm.net/levels_of_evidence.asp#levels.
- Oefelein MG, Feng A, Scolieri MJ, Ricchiutti D, Resnick MI: Reassessment of the definition of castrate levels of testosterone: implications for clinical decision making. *Urology* 2000;56:1021–1024.
- Isurugi K, Kondo Y, Hirasawa K, et al: Testicular endocrine function in patients with prostatic cancer receiving medical castration by long-term administration of LH-RH agonists. *Nippon Hinyokika Gakkai Zasshi* 1989;80:1466–1470.
- Parmar H, Edwards L, Phillips RH, Allen L, Lightman SL: Orchiectomy versus long-acting D-Trp-6-LHRH in advanced prostatic cancer. *Br J Urol* 1987;59:248–254.
- Kaisary AV, Tyrrell CJ, Peeling WB, Griffiths K: Comparison of LHRH analogue (Zoladex) with orchiectomy in patients with metastatic prostatic carcinoma. *Br J Urol* 1991;67:502–508.
- Soloway MS, Chodak G, Vogelzang NJ, Block NL, Schellhammer PF, Smith JA Jr, Scott M, Kennealey G, Gau TC: Zoladex versus orchiectomy in treatment of advanced prostate cancer: a randomized trial. *Zoladex Prostate Study Group. Urology* 1991;37:46–51.
- Rohl HF, Beuke HP: Effect of orchidectomy on serum concentrations of testosterone and dihydrotestosterone in patients with prostatic cancer. *Scand J Urol Nephrol* 1992;26:11–14.
- Lin BJ, Chen KK, Chen MT, Chang LS: The time for serum testosterone to reach castrate level after bilateral orchiectomy or oral estrogen in the management of metastatic prostatic cancer. *Urology* 1994;43:834–837.
- Vogelzang NJ, Chodak GW, Soloway MS, Block NL, Schellhammer PE, Smith JA, Caplan RJ, Kennealey GT, for the Zoladex prostate study group: Goserelin versus orchiectomy in the treatment of advanced prostate cancer: final results of a randomized trial. *Urology* 1995;46:220–226.

- 20 Fernandez del Moral P, Dijkman GH, Debruyne FMJ, Witjes WPJ, Kolvenbag GJCM, for the Dutch South East Cooperative Urological Group: Three-month depot of Goserelin acetate: clinical efficacy and endocrine profile. *Urology* 1996;48:894–900.
- 21 Heyns CF, Simonin MP, Groscurin P, Schall R, Porchet HC, for the South African Triptorelin Study Group: Comparative efficacy of triptorelin pamoate and leuprolide acetate in men with advanced prostate cancer. *BJU Int* 2003;92:226–231.
- 22 Teillac P, Heyns CF, Kaisary AV, Bouchot O, Blumberg J: Pharmacodynamic equivalence of a decapeptyl 3-month SR formulation with the 28-day SR formulation in patients with advanced prostate cancer. *Horm Res* 2004;62:252–258.
- 23 Oefelein MG: Time to normalization of serum testosterone after 3-month luteinizing hormone-releasing hormone agonist administered in the neoadjuvant setting: implications for dosing schedule and neoadjuvant study consideration. *J Urol* 1998;160:1685–1688.
- 24 Oefelein MG: Serum testosterone-based luteinizing hormone-releasing hormone agonist redosing schedule for chronic androgen ablation: a phase I assessment. *Urology* 1999;54:694–699.
- 25 Oefelein MG, Cornum R: Failure to achieve castrate levels of testosterone during luteinizing hormone-releasing hormone agonist therapy: the case for monitoring serum testosterone and a treatment decision algorithm. *J Urol* 2000;164:726–729.
- 26 Fowler JE, Flanagan M, Gleason DM, Klimberg IW, Gottesman JE, Sharifi R, for the VIADUR Study Group: Evaluation of an implant that delivers leuprolide for 1 year for the palliative treatment of prostate cancer. *Urology* 2000;55:639–642.
- 27 Fontana D, Mari M, Martinelli A, Boccafocchi C, Magno C, Turriziani M, Maymone SS, Cosciani Cunico S, Zanollo A, Montagna G, Frongia M, Jacobellis U: Three-month formulation of goserelin acetate (Zoladex 10.8-mg depot) in advanced prostate cancer: results from an Italian open multicenter trial. *Urol Int* 2003;70:316–320.
- 28 Sartor O, Dineen MK, Perez-Marreno R, Chu FM, Carron GJ, Tyler RC: An eight-month clinical study of LA-2575 30.0 mg: a new 4-month, subcutaneous delivery system for leuprolide acetate in the treatment of prostate cancer. *Urology* 2003;62:319–323.
- 29 Pettersson B, Varenhorst E, Petas A, Sandow J: Duration of testosterone suppression after a 9.45-mg implant of the GnRH-analogue Buserelin in patients with localised carcinoma of the prostate. A 12-month follow-up study. *Eur Urol* 2006;50:483–489.
- 30 Crawford ED, Sartor O, Chu F, Perez R, Karlin G, Garrett JS: A 12-month clinical study of LA-2585 (45.0 mg): a new 6-month subcutaneous delivery system for leuprolide acetate for the treatment of prostate cancer. *J Urol* 2006;175:533–536.
- 31 Morote J, Esquena S, Abascal JM, Trilla E, Cecchini L, Raventos CX, Catalan R, Reventos J: Failure to maintain a suppressed level of serum testosterone during long-acting depot luteinizing hormone-releasing hormone agonist therapy in patients with advanced prostate cancer. *Urol Int* 2006;77:135–138.
- 32 Yri OE, Bjoro T, Fossa SD: Failure to achieve castration levels in patients using leuprolide acetate in locally advanced prostate cancer. *Eur Urol* 2006;49:54–58.
- 33 Tombal B, Berges R: Eligard: advantages for optimal testosterone control. *Eur Urol Suppl* 2006;5:900–904.
- 34 National Comprehensive Cancer Network: Prostate cancer. Treatment guidelines for patients. Version II. Last update: 2001.
- 35 Tombal B, Berges R: How good do current LhRH agonists control testosterone? Can this be improved with Eligard? *Eur Urol Suppl* 2005;4:30–36.
- 36 Schmitt B, Bennett C, Seidenfeld J, Samson D, Wilt T: Maximal androgen blockade for advanced prostate cancer. *Cochrane Database Syst Rev* 2000;2:CD001526.
- 37 Prostate Cancer Trialists' Collaborative Group: Maximum androgen blockade in advanced prostate cancer: an overview of the randomised trials. *Lancet* 2000;355:1491–1498.
- 38 Klotz L: Combined androgen blockade: an update. *Urol Clin North Am* 2006;33:161–166.