available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Hormone Therapy for Prostate Cancer: Exploring Current Controversies

Francesco Montorsi [a,*], *Richard Berges* [b], *Jacques Irani* [c], *Claude C. Schulman* [d]

[a] *Department of Urology, Milan, Italy*
[b] *PAN-Klinik am Neumarkt, Cologne, Germany*
[c] *Service d'Urologie, Poitiers, France*
[d] *Department of Urology, Clinic E. Cavell and University of Brussels, Brussels, Belgium*

Article info

Keywords:
Androgen deprivation therapy
Hormone therapy
Intermittent hormone therapy
Luteinising hormone-releasing hormone agonist
Neoadjuvant therapy
Adjuvant therapy
Prostate cancer
Quality of life
Radical prostatectomy
Radiotherapy
Testosterone

Abstract

Context: Although there is increasing interest in the use of neoadjuvant or adjuvant hormone therapy with local treatment for patients with prostate cancer (PCa), the survival benefit of hormone therapy is still debated. In addition, hormone therapy is associated with adverse events, which can have negative effects on a patient's quality of life (QoL). Intermittent hormone therapy is being investigated as an alternative to continuous hormone therapy for advanced PCa with the aims of delaying progression to hormone-refractory PCa and minimising adverse events.
Objective: To summarise current controversies on hormone therapy for PCa.
Evidence acquisition: This manuscript is based on presentations given at a satellite symposium held at the 2nd World Congress on Controversies in Urology (CURy) in Lisbon, Portugal. Recent English-language reports were identified through a search of Medline and abstracts of scientific congresses on hormone therapy for PCa. Data from review papers, original papers, and abstracts were compiled and interpreted.
Evidence synthesis: Neoadjuvant hormone therapy with radical prostatectomy (RP) does not seem to offer a survival advantage over RP alone in patients with localised and locally advanced PCa. Neoadjuvant hormone therapy with radiotherapy (RT) appears to improve treatment outcomes over RT alone in patients with locally advanced PCa, but the impact on overall survival is still unclear. Adjuvant hormone therapy with RT seems to increase overall survival in high-risk localised and locally advanced PCa. Final results of a phase 3 trial suggest that intermittent hormone therapy improves QoL without a negative effect on overall survival compared with continuous hormone therapy. Furthermore, the patient–physician dialogue should be enhanced and patients' preferences should be taken into consideration in the decision-making process.
Conclusions: Neoadjuvant or adjuvant hormone therapy with radical treatment may improve survival in carefully selected patients with PCa. Intermittent hormone therapy seems to reduce adverse events and improve QoL without a negative effect on survival. The availability of different formulations of a luteinising hormone-releasing hormone agonist offers patients an individualised treatment approach.

* Corresponding author. Università Vita Salute San Raffaele, Department of Urology, Via Olgettina 60, 20132 Milan, Italy. Tel. +39 02 26437423; Fax: +39 02 26437298.
E-mail address: montorsi.francesco@hsr.it (F. Montorsi).

1569-9056/$ – see front matter doi:10.1016/j.eursup.2009.05.001

1. Introduction

Prostate cancer (PCa) is the most commonly diagnosed male cancer in Europe, accounting for 20.3% of new cancer cases in 2006 [1]. The incidence of PCa is increasing, partly as a result of improved detection and screening methods in the ageing population [1,2]. Overall, PCa is responsible for approximately 9% of cancer deaths, with only lung cancer and colorectal cancer associated with more deaths in men [1]. The management of PCa depends to a large extent on the stage of the disease at the time of diagnosis. Watchful waiting represents a treatment option for patients with well- and moderately differentiated PCa and a life expectancy of <10 yr. Radical prostatectomy (RP) or radiotherapy (RT) have become the most appropriate treatments for patients with T1b-T2b PCa, particularly in younger patients with a life expectancy of >10 yr who are willing to accept treatment-related complications. Selected patients with clinical stage T3 disease may be candidates for curative treatments as well. In symptomatic patients with extensive T3-T4 PCa or in patients with more advanced PCa (N+, M+), hormone therapy is the recommended treatment option. Chemotherapy has emerged as the reference treatment for metastatic hormone-refractory PCa [3].

Since Huggins and Hodges established the hormone responsiveness of PCa [4], androgen deprivation therapy (ADT) has been the mainstay of treatment for metastatic PCa. In addition, multimodal approaches of ADT with curative treatments to improve clinical outcomes have garnered interest. Different types of hormone therapy are presently available, including surgical castration (ie, bilateral orchidectomy) or medical castration (eg, luteinising hormone-releasing hormone [LHRH] agonists, LHRH antagonists, oestrogens), antiandrogens, and combination therapies (eg, maximal androgen blockade [MAB], minimal androgen blockade, intermittent ADT, continuous ADT) [3]. However, the added value of neoadjuvant or adjuvant hormone therapy with curative treatments is still a matter of debate. Moreover, patients on hormone therapy frequently complain of impaired quality of life (QoL) and of certain adverse events including hot flushes, loss of libido, impotence, and fatigue. Other adverse events such as bone demineralisation, anaemia, decreased muscle mass, lipid disorders, obesity, mood changes, neurocognitive decline, increased risk of cardiovascular complications, and the development of hormone-refractory PCa have been reported to be associated with long-term use of hormone therapy [3,5,6]. The potential of intermittent hormone therapy to delay progression to hormone-refractory PCa and reduce morbidity is currently under investigation. Furthermore, appropriate management of adverse events and integration of the patient's expectations into treatment decisions may improve QoL for patients on hormone therapy.

2. Evidence acquisition

This paper was based on presentations given at a satellite symposium on hormone therapy for PCa that was held during the 2nd World Congress on Controversies in Urology (CURy) on 6 February 2009 in Lisbon, Portugal. Recent English-language reports were identified through a search of Medline and abstracts of scientific congresses on hormone therapy for PCa. Data from review papers, original papers, and abstracts were compiled and interpreted.

3. Evidence synthesis

3.1. What is the added value of neoadjuvant or adjuvant hormone therapy with radical prostatectomy?

According to a systematic review and meta-analysis of randomised controlled trials of neoadjuvant hormone therapy with primary therapy (RP or RT) for localised and locally advanced PCa, neoadjuvant hormone therapy with RP did not provide a statistically significant survival benefit but did significantly reduce positive surgical margin rates ($p < 0.00001$), organ confinement ($p < 0.0001$), and lymph node invasion ($p < 0.02$) over RP alone [7]. The randomised studies were heterogeneous for the type of hormone therapy. Three of the 10 studies of neoadjuvant hormone therapy with RP included either an antiandrogen or an LHRH agonist. The remaining studies used combination therapy.

Adjuvant ADT with RT has been shown to improve outcomes in patients with high-risk PCa; however, the benefit of ADT during salvage RT after RP has not been established. At the American Society for Therapeutic Radiology and Oncology (ASTRO) 2008 annual meeting, Jang et al. [8] demonstrated that initiation of ADT during salvage RT after RP may lead to longer biochemical failure–free survival compared to salvage RT alone. Nevertheless, a prospective, randomised study is necessary to determine whether ADT should be used in combination with salvage RT in patients who received RP. Furthermore, the optimal timing to initiate hormone therapy, the optimal duration of hormone therapy, and which patients may benefit remain questions. A recently published retrospective matched-cohort study reported that adjuvant ADT modestly improved PCa-specific survival but not overall survival after RP in patients with localised PCa [9]. The survival advantage was lost when ADT was delivered at the time of prostate-specific antigen (PSA) recurrence or systemic progression. Walz et al. [10] developed a nomogram predicting the probability of early biochemical recurrence for patients who underwent RP for localised PCa. From the data cited above, we may conclude that patients at high risk of biochemical recurrence might benefit the most from adjuvant hormone therapy.

3.2. What is the added value of neoadjuvant or adjuvant hormone therapy with radiotherapy?

Following the European Organisation for Research and Treatment of Cancer (EORTC) 22863 trial, long-term (3 yr) adjuvant hormone therapy with RT has been considered standard treatment for patients with locally advanced PCa

[11]. At the ASTRO 2008 annual meeting, the 10-yr follow-up results of this phase 3 EORTC trial were presented [12]. The beneficial effect on overall survival of long-term adjuvant ADT with RT was maintained without increasing cardiovascular mortality. Widmark et al. [13] recently published the results of the first open randomised phase 3 trial comparing combination therapy (antiandrogen plus RT) with hormone therapy (antiandrogen alone) in patients with locally advanced or high-risk localised PCa. Addition of RT to antiandrogen therapy halved the 10-yr PCa-specific mortality (11.9% vs 23.9%; $p = 0.00003$), with a fully acceptable risk profile of adverse events compared to antiandrogen therapy alone. In line with these data, D'Amico et al. [14] reported that the addition of 6 mo of ADT to RT increased overall survival at a median follow-up of 7.6 yr in men with unfavourable-risk PCa. These results provide evidence that adjuvant hormone therapy with RT is the standard treatment for patients with high-risk localised or locally advanced PCa.

Better methods of stratifying PCa patients may help select patients who benefit most from adjuvant hormone therapy with RT. In this respect, D'Amico et al. [14] demonstrated that the overall survival benefit with adjuvant ADT plus RT in localised high-risk PCa may pertain only to men without moderate or severe comorbidity. Another study showed that patients with intermediate-risk PCa and $\geq$50% positive biopsy cores seem to have the highest risk for biochemical failure and might be more likely to benefit from hormone therapy in the setting of dose-escalated RT [15]. Furthermore, the addition of ADT to RT seems to improve biochemical failure but not overall survival in high-risk PCa patients >70 yr old [16]. In the setting of neoadjuvant ADT, Malik et al. [17] found that a shorter PSA halving time during neoadjuvant ADT and prior to RT was associated with better biochemical control. Moreover, Jones et al. [18] suggested that ADT should be continued at least until PSA drops to <0.1 ng/ml before initiation of RT rather than for a fixed duration. Based on these findings, comorbidity, percentage of positive biopsy cores, age, PSA halving time, and PSA response may be considered major determinants of patient outcome with combined treatment.

3.3. What is the optimal duration of neoadjuvant or adjuvant hormone therapy with radiotherapy?

The updated 10-yr follow-up findings of the Radiation Therapy Oncology Group (RTOG) 8610 trial suggest that patients with high-risk locally advanced PCa who decline or who are not considered candidates for long-term ADT should be offered short-term neoadjuvant (2 mo) and concomitant (2 mo) ADT with RT [19]. The addition of 4 mo of ADT to RT had a profound effect on clinically meaningful end points (except overall survival) in men with high-risk locally advanced PCa, with no statistically significant impact on the risk of fatal cardiac events. A Canadian phase 3 trial evaluated the effect of 3 mo versus 8 mo of neoadjuvant ADT with RT for localised PCa [20]. A longer duration of neoadjuvant ADT with RT did not alter patterns of survival in patients with low- or intermediate-risk PCa. In patients with high-risk PCa, 8 mo of neoadjuvant ADT significantly improved 7-yr disease-free survival versus 3 mo of neoadjuvant ADT with RT (Fig. 1). An update of the randomised phase 3 EORTC 22961 trial failed to prove noninferiority in terms of survival with 6 mo versus 3 yr of concomitant and adjuvant hormone therapy with RT in patients with locally advanced PCa [21]. In accordance with these findings, the 10-yr follow-up results of the RTOG 92-02 trial demonstrated statistically significant improvements for several end points with long-term (2 yr) hormone therapy with RT over short-term (4 mo) hormone therapy with RT in locally advanced PCa (Fig. 2) [22]. Only in a subgroup of patients with Gleason score 8–10, a significant overall survival difference was observed in favour of long-term versus short-term hormone therapy (31.9% vs 45.1%; $p = 0.0061$).

Although there is still no consensus regarding the optimal duration of ADT, the long-term results from several phase 3 trials support the recommendation that long-term ADT is superior to short-term ADT with RT for patients with locally advanced PCa. However, we have to keep in mind that androgen suppression is associated with certain adverse events (eg, hot flushes, loss of libido, general fatigue, metabolic syndrome, cardiovascular mortality/morbidity, osteoporosis) and with impaired QoL [23,24].

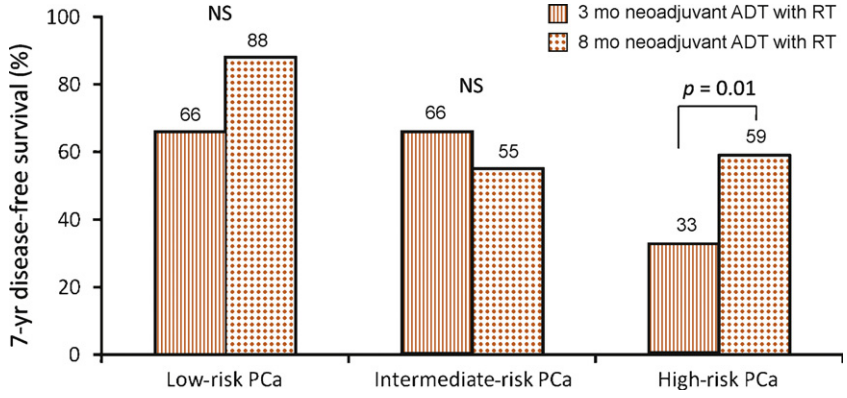

Fig. 1 – The effect of 3 mo versus 8 mo of neoadjuvant androgen deprivation therapy (ADT) prior to conventional-dose radiotherapy (RT) on disease-free survival for low-risk, intermediate-risk, or high-risk localised prostate cancer (PCa) in a Canadian phase 3 trial [20].
NS = not significant.

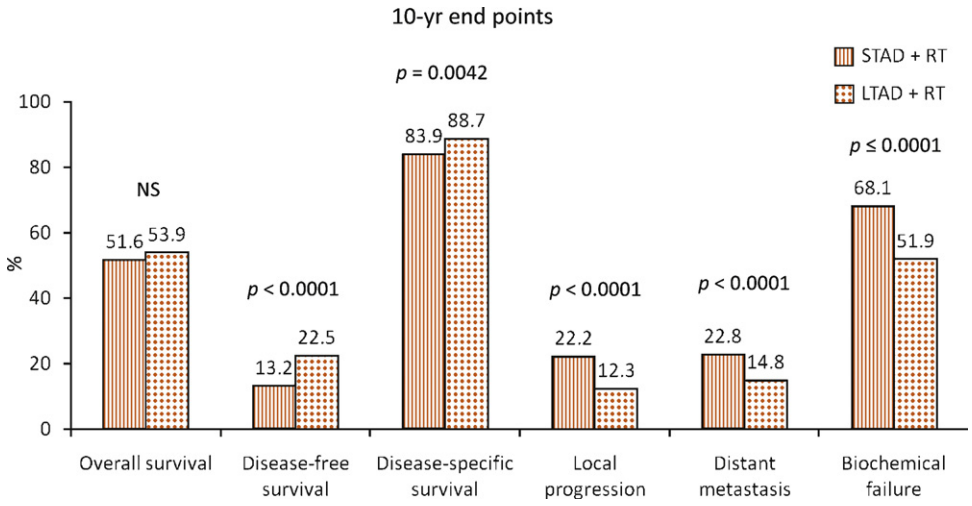

Fig. 2 – Ten-year follow-up results of the Radiation Therapy Oncology Group (RTOG) 92-02 trial evaluating long-term (2 yr) adjuvant hormone therapy (LTAD) over short-term (4 mo) adjuvant hormone therapy (STAD) with radiotherapy (RT) in locally advanced prostate cancer [22].
NS = not significant.

Clear understanding of the timing and extent of testosterone recovery after discontinuation of ADT will provide better insight into how long the adverse events of ADT may persist. In a recent prospective trial, Yoon et al. [25] observed that testosterone recovery is prolonged after prolonged ADT (>2 yr) in patients with pT3N0M0 PCa. Older age and longer duration of ADT resulted in significantly longer recovery times to baseline or normal testosterone levels. These longer recovery times have several clinical implications.

3.4. Continuous or intermittent hormone therapy in advanced prostate cancer?

The use of hormone therapy is typically continuous and is maintained until the disease progresses or the patient dies. Many patients will receive hormone therapy for a long time, making them increasingly vulnerable to related adverse events. Intermittent hormone therapy might be an alternative treatment option for advanced PCa, with the aims of delaying progression to hormone-refractory PCa and minimising the adverse events and costs of care while maximising the clinical benefits and the patient's QoL [26,27].

Intermittent hormone therapy is a cyclic therapy consisting of on-treatment periods followed by off-treatment (ie, observation) periods. Clinically, intermittent therapy can only be achieved by using reversible hormone therapies such as an LHRH agonist and/or an antiandrogen. Response to therapy and potential disease progression are usually monitored by measuring the patient's PSA level at 3-mo intervals; logically, monitoring should also include testosterone measurement. The on-treatment period is generally fixed, lasting for 6–9 mo or in some protocols until a PSA nadir <4 ng/ml is reached. In contrast, the off-treatment period is variable and depends on the initial stage of the disease and on disease progression. If there is evidence of a significant rise in PSA, a new treatment cycle is initiated [26,28]. Intermittent hormone therapy can be considered for patients who respond to hormone therapy with a decline in PSA levels to normal values. A normal value is considered to be <4 ng/ml in previously untreated patients and <0.5 ng/ml for patients who relapsed after local treatment.

Several small phase 2 trials of intermittent hormone therapy have been published over the last decade. Most studies involved the use of an LHRH agonist plus an antiandrogen (MAB) [29]. According to a meta-analysis including 1446 men from 10 phase 2 trials, patients spent a mean of 39% of the time off treatment [30]. Overall, the phase 2 studies demonstrated that intermittent hormone therapy seems to be feasible and safe in localised biochemically recurrent or metastatic PCa. Patients experienced improved QoL during the off-treatment period, and treatment-related toxicity was reduced. In addition, intermittent hormone therapy did not appear to negatively affect time to progression or survival [28].

Further investigations of intermittent hormone therapy are ongoing or have been recently completed in randomised controlled phase 3 trials (Table 1). The largest, the Southwest Oncology Group (SWOG) 9346 trial, enrolled 1345 men with newly diagnosed metastatic PCa and a baseline PSA ≥5 ng/ml [31]. Patients with a PSA reduction to ≤4 ng/ml after 7 mo of induction hormone therapy (MAB; an LHRH agonist plus an antiandrogen) received intermittent versus continuous hormone therapy. An interim analysis demonstrated that a PSA reduction to ≤4 ng/ml after 7 mo of induction therapy was a strong and specific predictor of risk of death. Patients with a PSA ≤0.2 ng/ml had the greatest survival advantage. In two European studies, intermittent hormone therapy was compared with continuous hormone therapy in patients with locally advanced or metastatic PCa. The final South European Uroncological Group (SEUG) 9401 trial included 766 patients with cT3-T4 M0-1 PCa who did

Table 1 – Overview of phase 3 trials evaluating intermittent hormone therapy

Trials	Study population	No. of patients randomised	Final/preliminary data
SWOG 9346 [31]	M+ PCa (PSA ≥5 ng/ml)	1345	PSA normalisation rates (open)
SEUG 9401 [32]	Locally advanced or M+ PCa	626	No difference in overall survival and time to progression between intermittent and continuous HT. Intermittent HT is associated with fewer adverse events and better sexual activity than continuous HT (closed).
Europe [33]	Locally advanced or M+ PCa	914	Intermittent HT is associated with better sexual activity and fewer adverse events than continuous HT (open).
EC507 [34]	PSA relapse after RP	201	No difference in time to progression between intermittent and continuous HT. Intermittent HT is associated with an improved quality of life and lower incidence of adverse events than continuous HT (closed).

SWOG = Southwest Oncology Group; SEUG = South European Uroncological Group; PCa = prostate cancer; PSA = prostate-specific antigen; M+ = metastatic; RP = radical prostatectomy; HT = hormone therapy.

not receive previous treatment [32]. After an induction therapy of 3 mo, 626 patients whose PSA decreased to <4 ng/ml or to 80% less than initial PSA were randomised to intermittent or continuous hormone therapy (MAB). Among the 314 patients on intermittent therapy, 50% of patients were off treatment for ≥13 mo; 29% of patients were off treatment for ≥36 mo. After a median follow-up of 51 mo, 54.2% of patients died. There were no significant differences in overall survival (hazard ratio [HR]: 0.99; 95% confidence interval [CI]: 0.80–1.23; $p = 0.96$) (Fig. 3) and time to any progression (HR: 0.81; 95% CI: 0.63–1.05; $p = 0.11$) between the different treatment regimens. Furthermore, intermittent hormone therapy was associated with fewer adverse events and better sexual activity than continuous hormone therapy. The early results from the second European trial are promising and in line with other studies on intermittent therapy. Intermittent monotherapy resulted in fewer adverse events and better QoL than continuous combined androgen deprivation [33].

Another European randomised prospective phase 3 study (EC507) investigated the differences between intermittent and continuous hormone therapy in PCa patients with PSA relapse after RP over a 2-yr period. All patients received a 6-mo induction therapy with a 3-mo depot of leuprorelin acetate and a flare-up prophylaxis with cyproterone acetate. Patients were randomised to intermittent or continuous hormone therapy when PSA dropped to <0.5 ng/ml. The on-treatment period consisted of 6 mo of therapy, and treatment was discontinued if PSA decreased to <0.5 ng/ml. The treatment was resumed when PSA increased to >3 ng/ml. Intermittent hormone therapy was associated with better QoL and lower incidence of adverse events and was equally as effective as continuous hormone therapy in terms of time to androgen-independent progression [34]. At present, intermittent hormone therapy is widely offered to patients with PCa in various clinical settings, and its status should no longer be regarded as investigational [3].

3.5. *Quality of life of prostate cancer patients on hormone therapy: Do we care enough?*

According to the European Association of Urology (EAU) guidelines, hormone therapy for advanced PCa delays disease progression, prevents the risk of complications, and palliates symptoms effectively [3]. Hormone therapy, however, is associated with deleterious adverse events which can have a detrimental effect on QoL. Many young patients receiving long-term hormone therapy for PCa are still physically and sexually active, so QoL is an issue of

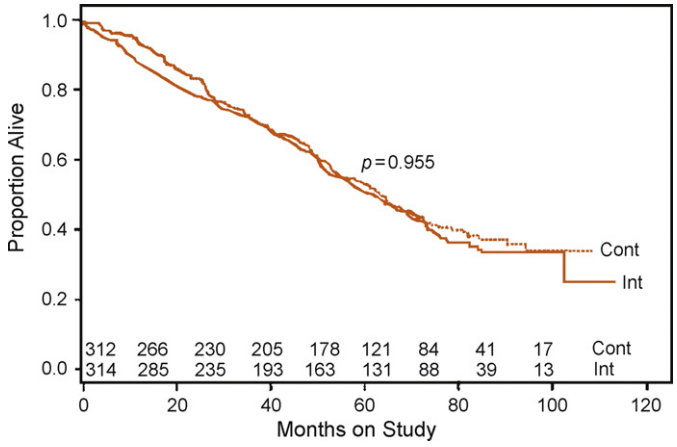

Fig. 3 – Overall survival data of the South European Uroncological Group (SEUG) trial comparing intermittent (Int; *n* = 314) with continuous (Cont; *n* = 312) maximal androgen blockade in patients with T3-T4 M0-1 prostate cancer who did not receive previous treatment [32]. Reprinted with permission from Elsevier.

paramount importance. Consequently, the physician as well as the patient are desperately needed to play roles in reducing adverse events and promoting better QoL.

Before initiation and during hormone therapy, physicians should assess the general risk of potential consequences of hormone therapy (eg, diabetes, cardiovascular disease, low-density lipoprotein cholesterol, osteoporosis) and provide better awareness of the adverse events. In addition, it is the role of the physician to educate the patient and provide him with tips to prevent adverse events [35]. A variety of lifestyle changes (eg, diet, physical activity) may have an enormous impact on a patient's health during hormone therapy. Physical activity can have a profound positive effect on fatigue, mental health, muscle mass, and bone mineral density, while lifestyle changes may reduce obesity, increase insulin sensitivity, and improve cardiovascular health [35]. Furthermore, new treatment modalities may help to relieve adverse events. According to an interim analysis, toremifene, a second-generation selective oestrogen-receptor modulator (SERM), appears to increase bone mineral density [36] and improve lipid profiles [37] in men receiving ADT.

It has become widely accepted that health care is changing fast and that patients' experiences and expectations are also changing. Patients no longer see themselves as passive recipients of care. They expect to be involved in all decisions that affect them [38]. Therefore, the patient–physician dialogue should be enhanced and patients' preferences should also be taken into consideration in the decision-making process. Providing patients with balanced information will further contribute to a well-considered decision, which in turn can minimise future regret [39]. A survey conducted among 200 patients with PCa from five European countries investigated patients' needs and expectations during hormone therapy and treatment decision making. The majority of patients (83%) considered maintaining lifestyle during hormone therapy to be very important. In addition, 69% of patients emphasised the importance of being involved in the decision-making process and 67% of patients noted that the physician should consider their lifestyles during treatment decisions [40]. To put this feedback into practice, therapies should be tailored to the patient's stage of disease and individual needs. If LHRH agonists are available in different formulations that have the same efficacy in decreasing and maintaining appropriate testosterone levels as seen with bilateral orchidectomy, patients have the option to choose the treatment that best fits his lifestyle. However, it seems that the majority of patients, independent of age, would prefer injections every 6 mo over injections every 1 mo or 3 mo (Fig. 4) [40]. The advantages of fewer injections as perceived by patients appear to be improved QoL, fewer reminders of the disease, fewer restrictions in activity, and less pain or discomfort [40].

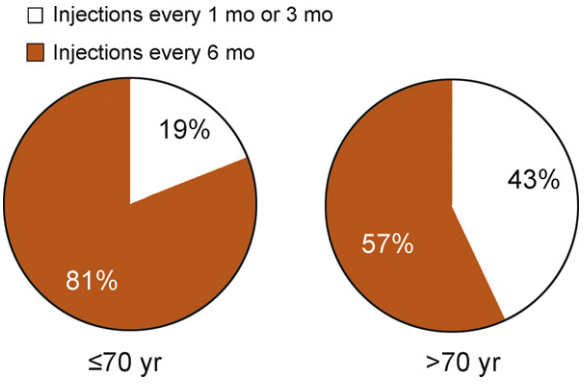

Fig. 4 – Preferred frequency of injections for patients aged ≤70 yr (n = 89) or >70 yr (n = 111) [40].

4. Conclusions

Neoadjuvant hormone therapy with RP does not seem to offer a survival benefit over RP alone in patients with localised and locally advanced PCa. Immediate hormone therapy after RP may be beneficial in high-risk patients with PCa, but randomised controlled trials are needed to provide more convincing evidence. Neoadjuvant hormone therapy with RT appears to improve treatment outcomes over RT alone in patients with locally advanced PCa, but the impact on overall survival is still unclear. In contrast, adjuvant HT (at least 6 mo) with RT seems to improve survival over RT alone in high-risk localised and locally advanced PCa. Recent final results from phase 3 studies suggest that intermittent hormone therapy and continuous hormone therapy are equally effective in terms of overall and progression-free survival. Caution, however, is warranted in patients with a high pretreatment PSA level, high clinical stage, or high metastatic stage. If these patients do not show adequate biochemical PSA response to hormone therapy, intermittent hormone therapy is not recommended. Furthermore, the treatment of PCa is more and more oriented towards the individual patient. Most patients want to be involved in the decision-making process of the treatment. Therefore, the possibility of having different formulations of an LHRH agonist offers more flexibility for an individually tailored treatment approach.

Conflicts of interest

Francesco Montorsi has nothing to disclose. Richard Berges is a speaker/consultant for Astellas. Jacques Irani is speaker/consultant for Astellas, Sanofi Pasteur, Takeda, GenProbe, Ferring, and Steba. Claude C. Schulman is speaker/consultant for Astellas, Novartis, Pierre Fabre Medicament, OM PHARMA, and Eli Lilly.

Funding support

None.

Acknowledgements

The authors are grateful to Ismar Healthcare NV for assistance in writing of the manuscript.

References

[1] Ferlay J, Autier P, Boniol M, Heanue M, Colombet M, Boyle P. Estimates of the cancer incidence and mortality in Europe in 2006. Ann Oncol 2007;18:581–92.

[2] Quinn M, Babb P. Patterns and trends in prostate cancer incidence, survival, prevalence and mortality. Part II: individual countries. BJU Int 2002;90:174–84.

[3] Heidenreich A, Bolla M, Joniau S, et al. Guidelines on prostate cancer. Arnhem, Netherlands: European Association of Urology; 2009. http://www.uroweb.org/fileadmin/tx_eauguidelines/2009/Full/Prostate_Cancer.pdf. Accessed May 2009.

[4] Huggins C, Hodges CV. Studies on prostatic cancer. I. The effect of castration, of estrogen and of androgen injection on serum phosphatases in metastatic carcinoma of the prostate. Cancer Res 1941;1:293–7.

[5] Mottet N, Prayer-Galetti T, Hammerer P, Kattan MW, Tunn U. Optimizing outcomes and quality of life in the hormonal treatment of prostate cancer. BJU Int 2006;98:20–7.

[6] Higano CS. Side effects of androgen deprivation therapy: monitoring and minimizing toxicity. Urology 2003;61(Suppl 1):32–8.

[7] Shelley MD, Kumar S, Wilt T, Staffurth J, Coles B, Mason MD. A systematic review and meta-analysis of randomised trials of neoadjuvant hormone therapy for localised and locally advanced prostate carcinoma. Cancer Treat Rev 2009;35:9–17.

[8] Jang JW, Jones ND, Malkowicz S, Vapiwala N. Use of up-front androgen deprivation therapy with salvage radiation in the post-prostatectomy setting may improve biochemical outcomes. Int J Radiat Oncol Biol Phys 2008;72:S309, abstract 2313.

[9] Siddiqui SA, Boorjian SA, Inman B, Bagniewski S, Bergstralh EJ, Blute ML. Timing of androgen deprivation therapy and its impact on survival after radical prostatectomy: a matched cohort study. J Urol 2008;179:1830–7.

[10] Walz J, Chun FK, Klein EA, et al. Nomogram predicting the probability of early recurrence after radical prostatectomy for prostate cancer. J Urol 2009;181:601–8.

[11] Bolla M, Gonzalez D, Warde P, et al. Improved survival in patients with locally advanced prostate cancer treated with radiotherapy and goserelin. N Engl J Med 1997;337:295–300.

[12] Bolla M, Colette L, Van Tienhoven G, et al. Ten year results of long term adjuvant androgen deprivation with goserelin in patients with locally advanced prostate cancer treated with radiotherapy: a phase III EORTC study. Int J Radiat Oncol Biol Phys 2008;72:S30–1, abstract 65.

[13] Widmark A, Klepp O, Solberg A, et al. Endocrine treatment, with or without radiotherapy, in locally advanced prostate cancer (SPCG-7/SFUO-3): an open randomised phase III trial. Lancet 2009;373:301–8.

[14] D'Amico AV, Chen MH, Renshaw AA, Loffredo M, Kantoff PW. Androgen suppression and radiation vs radiation alone for prostate cancer: a randomized trial. JAMA 2008;299:289–95.

[15] Liauw SL, Correa D, Jani AB. Intermediate-risk prostate cancer and dose escalated radiation therapy: selection of patients for androgen deprivation therapy using percent positive cores. Int J Radiat Oncol Biol Phys 2008;72:S89–90, abstract 2269.

[16] Silverman JS, Ruth K, Horwitz EM, Pollack A, Chen DYT, Buyyounouski MK. Radiation therapy for high risk prostate cancer: do patients 70 years or older benefit from combined androgen deprivation therapy? Int J Radiat Oncol Biol Phys 2008;72:S75–6, abstract 166.

[17] Malik R, Jani AB, Liauw SL. PSA "halving-time" during neoadjuvant androgen deprivation therapy and prior to radiotherapy is associated with biochemical control. Int J Radiat Oncol Biol Phys 2008;72:S56, abstract 122.

[18] Jones SO, Alexander A, Crook J, Lesperance M, Ludgate C. Biochemical response is more critical than total duration of neo-adjuvant hormone therapy (NAHT) prior to radiotherapy for localized prostate cancer: analysis of the 3 vs 8 month data. Int J Radiat Oncol Biol Phys 2008;72:S74, abstract 163.

[19] Roach III M, Bae K, Speight J, et al. Short-term neoadjuvant androgen deprivation therapy and external-beam radiotherapy for locally advanced prostate cancer: long-term results of RTOG 8610. J Clin Oncol 2008;26:585–91.

[20] Crook JM, Ludgate C, Malone S, et al. Final report of a Canadian phase III trial of 3 vs. 8 months neoadjuvant androgen deprivation prior to 66 Gray external beam radiotherapy for clinically localized prostate cancer. Int J Radiat Oncol Biol Phys 2008;72:S75, abstract 165.

[21] Bolla M, De Reijke ThM, Van Tienhoven GJ, et al. Six-month concomitant and adjuvant hormonal treatment with external beam irradiation is inferior to 3-years hormonal treatment for locally advanced prostate cancer: results of the EORTC randomised phase III trial 22961. Eur Urol Suppl 2008;7:117, abstract 186.

[22] Horwitz EM, Bae K, Hanks GE, et al. Ten-year follow-up of radiation therapy oncology group protocol 92-02: a phase III trial of the duration of elective androgen deprivation in locally advanced prostate cancer. J Clin Oncol 2008;26:2497–504.

[23] Keating NL, O'Malley AJ, Smith MR. Diabetes and cardiovascular disease during androgen deprivation therapy for prostate cancer. J Clin Oncol 2006;24:4448–56.

[24] Saigal CS, Gore JL, Krupski TL, Hanley J, Schonlau M, Litwin MS. Androgen deprivation therapy increases cardiovascular morbidity in men with prostate cancer. Cancer 2007;110:1493–500.

[25] Yoon FH, Gardner SL, Danjoux C, Morton G, Cheung P, Choo R. Testosterone recovery after prolonged androgen suppression in patients with prostate cancer. J Urol 2008;180:1438–43.

[26] Tunn U. The current status of intermittent androgen deprivation (IAD) therapy for prostate cancer: putting IAD under the spotlight. BJU Int 2007;99(Suppl 1):19–22.

[27] Gleave M, Klotz L, Taneja SS. The continued debate: Intermittent vs. continuous hormonal ablation for metastatic prostate cancer. Urol Oncol 2009;27:81–6.

[28] Tunn U. Can intermittent hormone therapy fulfil its promise? Eur Urol Suppl 2008;7:752–7.

[29] Boccon-Gibod L, Hammerer P, Madersbacher S, Mottet N, Prayer-Galetti T, Tunn U. The role of intermittent androgen deprivation in prostate cancer. BJU Int 2007;100:738–43.

[30] Shaw GL, Wilson P, Cuzick J, et al. International study into the use of intermittent hormone therapy in the treatment of carcinoma of the prostate: a meta-analysis of 1446 patients. BJU Int 2007;99:1056–65.

[31] Hussain M, Tangen CM, Higano C, et al. Absolute prostate-specific antigen value after androgen deprivation is a strong independent predictor of survival in new metastatic prostate cancer: data from Southwest Oncology Group Trial 9346 (INT-0162). J Clin Oncol 2006;24:3984–90.

[32] Calais da Silva FEC, Bono AV, Whelan P, et al. Intermittent androgen deprivation for locally advanced and metastatic prostate cancer: results from a randomised phase 3 study of the South European Uroncological Group. Eur Urol 2009;55:1269–77.

[33] Calais Da Silva FE, Goncalves F, Santos A, et al. Evaluation of quality of life, side effects and duration of therapy in a phase 3 study of intermittent monotherapy versus continuous combined androgen deprivation. Eur Urol Suppl 2008;7:205, abstract 540.

[34] Tunn UW, Canepa G, Hillger H, Fuchs W. Intermittent androgen deprivation in patients with PSA-relapse after radical prostatectomy—final results of a European randomized prospective phase-III clinical trial AUO study AP 06/95, EC 507. J Urol 2007;177:201, abstract 600.

[35] Moyad MA. Promoting general health during androgen deprivation therapy (ADT): a rapid 10-step review for your patients. Urol Oncol 2005;23:56–64.
[36] Smith MR, Malkowicz SB, Chu F, et al. Toremifene increases bone mineral density in men receiving androgen deprivation therapy for prostate cancer: interim analysis of a multicenter phase 3 clinical study. J Urol 2008;179:152–5.
[37] Smith MR, Malkowicz SB, Chu F, et al. Toremifene improves lipid profiles in men receiving androgen-deprivation therapy for prostate cancer: interim analysis of a multicenter phase III study. J Clin Oncol 2008;26:1824–9.
[38] Coulter A, Magee H. The European patient of the future (state of health). Maidenhead, UK: Open University Press; 2003.
[39] Sartor O. Counselling the prostate cancer patient. Eur Urol Suppl 2008;7:765–71.
[40] Schulman C. Assessing the attitudes to prostate cancer treatment among European male patients. BJU Int 2007;100(Suppl 1): 6–11.