DISSERTATIONS IN
HEALTH
SCIENCES

Arto J. Salonen

Intermittent versus Continuous Androgen Deprivation in Patients with Advanced Prostate Cancer

The FinnProstate Study VII

Publications of the University of Eastern Finland
Dissertations in Health Sciences

UNIVERSITY OF
EASTERN FINLAND

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Publications of the University of Eastern Finland
Dissertations in Health Sciences
Number 168

Department of Urology, Kuopio University Hospital
School of Medicine, Faculty of Health Sciences
University of Eastern Finland
Kuopio
2013

Kopijyvä Oy
Kuopio, 2013

Distributor:
University of Eastern Finland
Kuopio Campus Library
P.O.Box 1627
FI-70211 Kuopio, Finland
http://www.uef.fi/kirjasto

ISBN (print): 978-952-61-1115-5
ISBN (pdf): 978-952-61-1116-2
ISSN (print): 1798-5706
ISSN (pdf): 1798-5714
ISSN-L: 1798-5706

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Salonen, Arto J.
Intermittent versus Continuous Androgen Deprivation in Patients with Advanced Prostate Cancer. The FinnProstate Study VII. University of Eastern Finland, Faculty of Health Sciences
Publications of the University of Eastern Finland. Dissertations in Health Sciences 168. 2013. 69 p.

ISBN (print): 978-952-61-1115-5
ISBN (pdf): 978-952-61-1116-2
ISSN (print): 1798-5706
ISSN (pdf): 1798-5714
ISSN-L: 1798-5706

ABSTRACT

Androgen deprivation therapy (ADT) has been the standard treatment for advanced prostate cancer (PC) since the 1940s. However, ADT use is associated with adverse effects which have an impact on the patient's quality of life (QoL). Furthermore, the duration of response of PC to ADT is limited, leading to disease progression with time.

The FinnProstate Study VII (FPVII) was planned as a randomised, controlled, multicenter clinical trial to compare the efficacy of intermittent androgen deprivation (IAD) with continuous androgen deprivation (CAD) in treatment of advanced PC with time to progression as the primary endpoint. Secondary objectives were to compare treatment arms in terms of overall survival (OS), PC-specific survival (PCS), time to treatment failure (TTF), and QoL. Between May 1997 and February 2003, 852 patients were prospectively enrolled to receive ADT for 24 weeks. Of these, 554 patients (65%) whose prostate-specific antigen (PSA) decreased to <10 ng/ml or at least by 50% (when baseline <20 ng/ml) were randomised in a 1:1 manner to either IAD or CAD. In the IAD arm, ADT was withdrawn and resumed again for at least 24 weeks whenever PSA increased >20 ng/ml or above the baseline level.

Patients with the most aggressive and the most advanced PC who had a high PSA and metastatic disease with more than five skeletal hot spots did not show an adequate response to ADT and were not candidates for IAD. IAD was equal with CAD both in locally advanced disease (M0) and in metastatic disease (M1) in terms of time to progression, to death, to PC-specific death, and to treatment failure. No significant delay in the onset of castrate resistance or any improvement in survival was seen with IAD. However, QoL was better with IAD than CAD, especially in the domains of activity limitation, physical capacity, and sexual functioning. The incidence of adverse events was not significantly lower with IAD. Except in the domain of sexual functioning, ADT improved QoL to some extent in M1 patients, with IAD conferring some extra benefit.

IAD is a feasible, efficient, safe and optional method in treatment of locally advanced and metastatic PC when compared with CAD. The QoL was better to some extent with IAD. In patients with metastatic disease, ADT improved QoL in most domains.

National Library of Medicine Classification: WB 340, WJ 762, WJ 875
Medical Subject Headings: Androgen Antagonists/therapeutic use; Drug Administration Schedule; Prognosis; Prostatic Neoplasms/drug therapy; Quality of Life; Survival

Salonen, Arto J.
Jaksoittainen ja jatkuva kastraatiohoito edennyttä eturauhassyöpää sairastavilla potilailla. FinnProstata VII. Itä-Suomen yliopisto, terveystieteiden tiedekunta
Publications of the University of Eastern Finland. Dissertations in Health Sciences 168. 2013. 69 s.

ISBN (print): 978-952-61-1115-5
ISBN (pdf): 978-952-61-1116-2
ISSN (print): 1798-5706
ISSN (pdf): 1798-5714
ISSN-L: 1798-5706

TIIVISTELMÄ

Androgeenideprivaatio- eli kastraatiohoito (AD-hoito) on ollut 1940-luvulta lähtien edenneen eturauhassyövän vakiintunut hoitomuoto. Hoitoon liittyy kuitenkin sivuvaikutuksia, jotka vaikuttavat potilaiden elämänlaatuun. Tämän lisäksi hoitovasteen kesto on rajallinen, mikä ajan kuluessa johtaa sairauden progressioon eli hoitovasteen menettämiseen.

Satunnaistettu ja kontrolloitu FinnProstata VII -monikeskustutkimus suunniteltiin vertaamaan jaksoittaisen AD-hoidon tehokkuutta jatkuvaan AD-hoitoon. Ensisijaisena päätetapahtumana oli aika eturauhassyövän progression kehittymiseen. Toissijaisina päätetapahtumina olivat kokonais- ja eturauhassyöpäspesifinen kuolleisuus, aika tutkimuksen päättymiseen kunkin potilaan kohdalla ja elämänlaadun muutokset. Toukokuun 1997 ja helmikuun 2003 välisenä aikana tutkimukseen rekisteröitiin 852 potilasta. Ne 554 potilasta (65%), joiden eturauhassyöpäspesifinen antigeeni (PSA) laski alle arvon 10 μg/l tai vähintään 50%, mikäli alkuvaiheen PSA oli alle 20 μg/l, satunnaistettiin suhteessa 1:1 jaksoittaiseen tai jatkuvaan AD-hoitoryhmään. Jaksoittaista hoitoa saaneiden hormonihoito aloitettiin uudelleen vähintään 24 viikon ajaksi, mikäli PSA-arvo nousi hoitotauon aikana yli lähtötason tai yli arvon 20 μg/l.

Potilaat, joilla oli huonosti erilaistunut tai laajalle levinnyt eturauhassyöpä (korkea PSA ja enemmän kuin viisi luustoetäpesäkettä) eivät reagoineet riittävästi hormonihoitoon eivätkä näin soveltuneet jaksoittaiseen kastraatiohoitoon. Jaksoittainen hoito oli teholtaan samanveroinen jatkuvaan hoitoon verrattuna progression kehittymisen, kuolleisuuden ja tutkimushoidon keston suhteen niin paikallisesti levinneessä (M0) kuin etäpesäkkeisessäkin (M1) eturauhassyövässä. Jaksoittainen hoito ei kuitenkaan pidentänyt hoitovastetta eikä eloonjäämisaikaa. Elämänlaatu oli parempi aktiivisuuden rajoittumisen, fyysisen suorituskyvyn ja seksuaalisten toimintojen osa-alueilla jaksoittaisella hoidolla. Haittatapahtumien esiintyvyydessä ei kuitenkaan ollut merkittävää eroa. Kastraatiohoito paransi etäpesäkkeistä eturauhassyöpää sairastavien potilaiden elämänlaatua useimmilla osa-alueilla paitsi seksuaalisten toimintojen kohdalla. Jaksoittainen annostelu lisäsi AD-hoidon suotuisaa vaikutusta.

Jaksoittainen hormonihoito on jatkuvaan hormonihoitoon verrattuna tehokas, turvallinen ja vaihtoehtoinen hoitomuoto edenneessä ja etäpesäkkeisessä eturauhassyövässä. Jaksoittainen hormonihoito parantaa elämänlaatua tietyin osin. Androgeenideprivaatiohoito parantaa etäpesäkkeistä eturauhassyöpää sairastavien potilaiden elämänlaatua useimmilla osa-alueilla.

Yleinen suomalainen asiasanasto: elämänlaatu; eturauhassyöpä – lääkehoito; kastraatio – jaksotus; selviytyminen

to Kati

Acknowledgements

The present study was conducted as a multicenter trial in 27 urological clinics in Finland during 1997–2010 with support from AstraZeneca. I wish to acknowledge all the urologists and nurses in trial centers. I would also like to thank AstraZeneca and Kirsi Nikkola for monitoring the data.

I want to express my gratitude to Professor Heikki Kröger, M.D., Ph.D., Docent Markku Härmä, M.d., Ph.D., Chief of Clinical Services, and Leena Setälä, M.D., Ph.D., Chief of the Surgical Department in Kuopio University Hospital, for providing me with the facilities for this research work and thesis.

I wish to express my utmost and sincere gratitude to my principal supervisor, Professor Teuvo L. J. Tammela, M.D., Ph.D., Chairman of the Department of Surgery in Tampere University Hospital, for proposing the topic of this study. His experience, advice, and guidance were essential during the study and in completing this thesis.

I express my warmest thaks to my supervisor Docent Martti Ala-Opas, M.D., Ph.D., the former Chief of the Department of Urology in Kuopio University Hospital and Helsinki University Hospital, for his enthusiastic support and help in the beginning of and during this study.

I am greatly indebted to Professor Kimmo Taari, M.D., Ph.D., Chief of the Department of Urology in Helsinki University Hospital, for his guidance, advice and support in drafting the original manuscripts and for his encouragement during these years.

I am grateful to Docent Sirpa Aaltomaa, M.D., Ph.D., Chief of the Department of Urology in Kuopio University Hospital, for her enthusiastic support and encouragement during the last few years and for providing the facilities to accomplish this work.

I would like to thank Jyrki Ollikainen, M.Sc., Research Manager, and Hanna L. Koskinen, M.Sc., in the University of Tampere for their valuable help and guidance regarding the statistical analysis of this study.

I am grateful to Docent Peter Boström, M.D., Ph.D. and Docent Mika Raitanen, M.D., Ph.D. for their valuable expertise and constructive criticism as official reviewers of this thesis.

I acknowledge Docent Carolyn Norris, Ph.D., for revising the language of the original manuscripts, and Ewen Mac Donald, D. Pharm., for revising the English of this thesis.

I want to thank my relatives, friends, and colleagues for their encouragement during this study. Especially, I want to thank Tuula and Matti Huttunen for their friendship, support and prayers during all these years. I want to honour the memory of my parents, Eila and Veikko Salonen, for their love and for providing me with the possibilities to receive my medical education.

Finally, I send my loving thaks to my dear and wonderful wife Kati for her love, support and patience.

This study has been financially supported by Kuopio University Hospital (EVO fund), AstraZeneca, and the Finnish Urological Association.

Kuopio, May 2013

Arto Salonen

List of the original publications

This dissertation is based on the following original publications:

I **Arto J. Salonen**, Jouko Viitanen, Seppo Lundstedt, Martti Ala-Opas, Kimmo Taari, Teuvo L.J. Tammela and the FinnProstate Group: Finnish Multicenter Study Comparing Intermittent to Continuous Androgen Deprivation for Advanced Prostate Cancer: Interim Analysis of Prognostic Markers Affecting Initial Response to Androgen Deprivation. *J Urol 2008; 180:915-920.*

II **Arto J. Salonen**, Kimmo Taari, Martti Ala-Opas, Jouko Viitanen, Seppo Lundstedt, Teuvo L.J. Tammela and the FinnProstate Group: The FinnProstate Study VII: Intermittent versus Continuous Androgen Deprivation in Patients with Advanced Prostate Cancer. *J Urol 2012; 187: 2074-2081.*

III **A.J. Salonen**, K. Taari, M. Ala-Opas, J. Viitanen, S. Lundstedt, T.L.J. Tammela, the FinnProstate Group: Advanced prostate cancer treated with intermittent or continuous androgen deprivation in the randomised FinnProstate Study VII: quality of life and adverse effects. *Eur Urol 2012; 63:111-120.*

IV **Arto J. Salonen**, Kimmo Taari, Martti Ala-Opas, Anna Sankila, Jouko Viitanen, Seppo Lundstedt, Teuvo L. J. Tammela and the FinnProstate Group: Comparison of Intermittent and Continuous Androgen Deprivation and Quality of Life between Patients with a Locally Advanced and Patients with a Metastatic Prostate Cancer: a Post-hoc Analysis of the Randomised FinnProstate Study VII. *(submitted)*

Contents

Abbreviations

AA	Androgen receptor antagonist/ Antiandrogen
ADR	Adverse drug reaction
ADT	Androgen deprivation therapy
AE	Adverse effect
AEV	Adverse event
ALP	Alkaline phosphatase
AR	Androgen receptor
CAD	Continuous androgen deprivation
CRPC	Castration-resistant prostate cancer
CV	Cardiovascular
DRE	Digital rectal examination
IAD	Intermittent androgen deprivation
LHRHa	Luteinizing hormone-releasing hormone analogue/ agonist
MAB	Maximal androgen blockade
OS	Overall survival
PFS	Progression-free survival
PC	Prostate cancer
PSA	Prostate-specific antigen
PSADT	PSA doubling time
PSPA	Performance status, prostate cancer pain, analgesics use score
QLQ-C30	The European Organisation for Research and Treatment of Cancer (EORTC) quality of life questionnaire
QoL	Quality of life
SAE	Serious adverse event
TTF	Time to treatment failure
TFS	Treatment failure survival
TOFF	Treatment-off period/phase
TON	Treatment-on period/phase
TRUS	Transrectal ultrasonography
TURP	Transurethral resection of prostate

1 Introduction

Prostate cancer (PC) is the most common cause of cancer and the second leading cause of cancer death among Finnish males.[1] Androgen deprivation therapy (ADT) has been the standard treatment for metastatic or advanced PC since the 1940s. However, ADT use is associated with acute and long-term adverse effects (AE), which have an impact on the patient's quality of life (QoL). Prostate-specific antigen (PSA) testing and screening during the last decades have led to a stage shifting from distant to local-regional stage at the time of diagnosis.[2] This has led to identification of an increasing number of men with asymptomatic locally advanced or locally recurrent PC after curative-intended treatment, having life expectancies of years but who carry a risk of significant AEs and declining QoL from ADT. Furthermore, the duration of response of PC to ADT is limited, leading to disease progression in time.

These observations have led to the search for alternative treatment strategies and to the concept of intermittent androgen deprivation (IAD) or cyclic therapy administered in pulses. The two objectives of IAD were to defer hormone resistance for which there was some theoretical basis with the potential for prolonging life, and secondly, to improve QoL by the intermittent restoration of normal androgen levels and thereby reducing ADT-related AEs.[3, 4] Early trials indicated that IAD could be a promising, feasible, and safe treatment modality in the treatment of PC with hormonal therapy. The background to this thesis was the attempt to answer three essential questions. Does IAD delay the onset of castrate resistance? Can IAD improve the overall survival?[5] Does IAD offer better QoL than CAD?

The FinnProstate Study VII (FPVII) was planned in the 1990s as an open-label, randomised, controlled, multicenter clinical trial to compare the efficacy of IAD with continuous androgen deprivation (CAD) in the treatment of advanced PC in terms of time to progression as the primary endpoint. Secondary objectives were overall survival (OS), PC-specific survival (PCS), time to treatment failure (TTF), and QoL. The trial was registered with ClinicalTrials.gov, identifier NCT00293670.

2 Review of the Literature

2.1 EPIDEMIOLOGY

Prostate cancer (PC) has been the most common cancer among Finnish males since 1993, with 4697 new detected PCs (32% of all new male cancers) in 2010, and the second leading cause of cancer death since the middle of the 1980s, with 845 PC deaths (14% of all male cancer deaths) in 2010 (Fig. 1).[1] Incidence has remained stable during the most recent years but mortality has decreased by 3.1% per year since 2000.[6, 7]

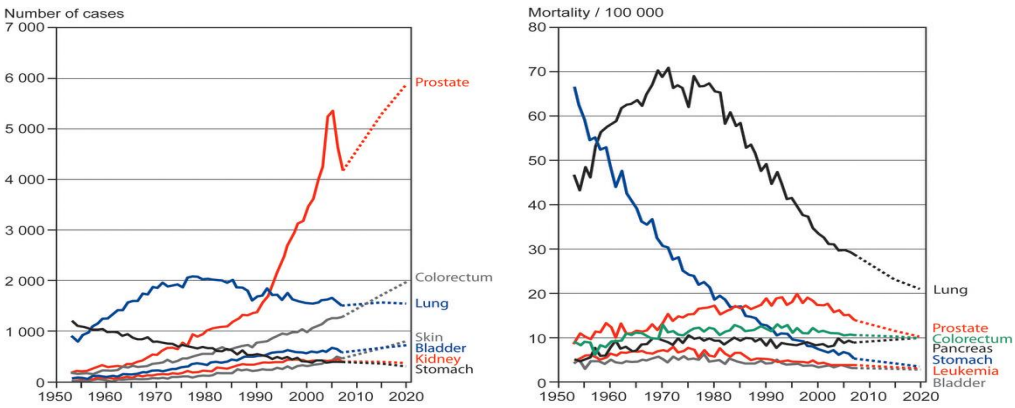

Figure 1. Number of new cancer cases and age-adjusted mortality trends of common sites with prediction among Finnish males (Finnish Cancer Registry).[1]

In global terms, PC is the second most common cause of cancer and the sixth leading cause of cancer death among men, with almost 899 000 new PC cases and 258 000 PC deaths recorded in 2008.[6] Incidence rates are among the highest in the United States, although they have stabilised during the last 10 years; mortality rates are intermediate, declining by 4.3% over the last decade.[6] In most countries of western and northern Europe, overall mortality rates from PC have levelled off since the 1990s, with a peak of 15.0 PC deaths per 100 000 men in the EU in 1995 but declining to 12.5 per 100 000 in 2006, i.e. a reduction of 3.8% in recent years.[8]

PSA testing, introduced in the 1980s and early 1990s in many high-income countries, and increasing rates of transurethral resection of prostate (TURP) have been shown to increase the PC incidence.[7, 9-11] PSA testing and screening have led to a stage shifting from the distant to the local-regional stage at diagnosis.[2] Not only early detection and increased detection rates of PC, but also primary treatment changes and advances in therapeutics for recurrent and progressive disease, are thought to account for the declining mortality rates.[6, 12, 13]

2.2 HISTOLOGY

Almost all PCs, approximately 95%, are adenocarcinomas.[14] Isolated or primary urothelial carcinoma represents up to 4% of all prostatic neoplasms.[15] The incidence of other primary prostate malignancies is much more rare: the proportion of pure squamous cell carcinomas is 0.6–1%; sarcomas, originating from nonepithelial mesenchymal components of the

prostate, account for less than 0.1%; primary prostatic lymphoma is rare, as well, and much less common than secondary infiltration of the prostate.[16-18]

High-grade prostatic intraepithelial neoplasia (HGPIN), referring to architecturally benign prostatic acini and ducts lined by atypical cells, is found in 5–8% of needle biopsies; a diagnosis of atypical glands suspicious for carcinoma is reported in an average of 5% of needle biopsies.[19] The average risk of cancer following an atypical diagnosis is approximately 40%, whereas the median risk for cancer following the diagnosis of HGPIN is 24%.

Neuroendocrine (NE) differentiation in prostate carcinoma has been hypothesised to be involved in progression to castrate-resistant condition and metastatic disease.[20]. NE differentiation arises in three different forms: carcinoid or carcinoid-like tumor, small cell (oat cell) carcinoma, and foci of NE neoplastic cells in prostatic adenocarcinoma. NE tumor cells are androgen-insensitive, have a mitogenic effect on adjacent tumor cells (exocrine), and are resistant to irradiation or chemotherapy.[14]

2.2.1 Gleason scores

The Gleason score is a standard grading system for PC and has replaced the worldwide used World Health Organisation (WHO) differentiation grading system which is commonly used to grade other malignancies. The Gleason scoring protocol was published in 1966 and was based on the architectural pattern of the tumor, using a 5-point differentiation scale. The grade was defined as the sum of the two most common patterns, yielding a sum ranging between 2 and 10, with 2 being the least aggressive form and 10 the most aggressive.[21] The current standard for grading PC is based on the International Society of Urologic Pathology (ISUP, UICC) consensus conference held in 2005. According to this guideline, the modified Gleason score of PC detected in a prostate biopsy consists of the Gleason grade of the most extensive pattern plus the highest grade.[22, 23] The Gleason grading system is a quintessential prognostic factor of PC.[24, 25] In practise, PCs are often divided into low-risk (Gleason ≤6), intermediate-risk (Gleason 7) and high-risk cancers (Gleason 8–10).

2.3 STAGING, TNM CLASSIFICATION

The TNM classification of PC is based on the local advancement of the primary tumor, the involvement of the regional lymph nodes, and the presence of distant metastasis (Table 1).[26, 27] TNM classification can be used as a prognostic tool in conjunction with the Gleason score and PSA.

2.4 DIAGNOSIS

Digital rectal examination (DRE), serum prostate-specific antigen (PSA), and transrectal ultrasound (TRUS) -guided biopsies are the main tools in use to detect PC and to undertake the PC diagnosis.[28]

2.4.1 Digital rectal examination

DRE was virtually the only tool for early detection of PC before PSA assay. A positive DRE has been shown to have positive predictive value in the detection of PC, especially in conjunction with increasing PSA.[29, 30] In addition, DRE seems to detect more selectively high-grade cancers.[31, 32]

Table 1. TNM classification according to Union Internationale Contre le Cancer (UICC). [27]

T - Primary tumor	
TX	Primary tumor can not be assessed
T0	No evidence of primary tumor
T1	Clinically inapparent tumor not palpable or visible by imaging
T1a	Tumor incidental histological finding in 5% or less of resected tissue
T1b	Tumor incidental histological finding in more than 5% of resected tissue
T1c	Tumor identified by needle biopsy
T2	Tumor confined within the prostate
T2a	Tumor involves one half of one lobe or less
T2b	Tumor involves more than one half of one lobe but not both lobes
T2c	Tumor involves both lobes
T3	Tumor extends through the prostatic capsule
T3a	Extracapsular extension (unilateral or bilateral)
T3b	Tumor invades seminal vesicle(s)
T4	Tumor is fixed or invades adjacent structures other than seminal vesicles; external sphincter, rectum levator muscles, and/or pelvic wall
N – Regional lymph nodes	
NX	Regional lymph nodes not assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
M – Distant metastasis	
(MX	Distant metastasis not assessed, deleted from the latest version)
M0	No distant metastasis
M1	Distant metastasis
M1a	Non-regional lymph node(s)
M1b	Bone(s)
M1c	Other site(s)

2.4.2 Prostate-specific antigen

PSA, a 33 kilodalton glycoprotein product of the human kallikrein gene family, was purified and characterised in 1979.[33] PSA has been recognised as an important tumor marker for PC since the late 1980s. It is practically organ but not cancer-specific to the prostate gland, although PSA and its gene expression have been detected at low concentrations in other tissues and also in female serum.[34-42] Not only PC, but also other conditions, such as benign prostatic hyperplasia, acute or subclinical prostatitis, urinary retention, ejaculation, vigorous prostatic massage, prostate needle biopsy, and TURP, may elevate the serum levels of PSA.[43-50]

Originally, the standard cut-off of 4 ng/ml was considered as the upper limit of normal PSA. Age adjusted PSA reference ranges and the use of percent free-to-total PSA (below 15% defined as abnormal ratio) have improved PC detection sensitivity in younger men and the specificity in older men.[42, 51-55] Several modifications of serum PSA value, including PSA velocity, PSA doubling time (PSADT), and PSA density, have been described in attempts to improve the specificity of PSA in the early detection of PC. However, prospective trials have not confirmed the usefulness of these measurements in clinical practise.[28, 56]

2.4.3 Transrectal ultrasound (TRUS) and TRUS-guided biopsies

The TRUS probe was introduced four decades ago by Watanabe et al.[57] The clinical application of the gray scale TRUS in the search for PC was outlined in the late 1980s.[58, 59] However, TRUS alone is not very accurate in detecting or staging early PC.[60-63] Although hypoechoic areas on TRUS have been reported to contain cancer more than twice as likely as isoechoic areas, a notable proportion of cancers are detected in isoechoic and even in hyperechoic sectors of the prostate gland.[61, 64, 65] Ellis et al could not detect any differences in the pathological staging of hypoechoic and isoechoic cancers but Spajic et al observed higher Gleason scores in cancers of hyperechoic areas when compared with isoechoic and hypoechoic cancers.[65, 66]

TRUS has been reported to have clinical application in the staging of more advanced PC (T3) either by itself or in combination with DRE.[67, 68] Three-dimensional TRUS with power doppler further improves the accuracy of echographic imaging in the detection and staging of local or locally advanced PCs.[69-71] TRUS-guided random systematic biopsy protocol has been a standard procedure for years to help the surgeon to obtain tissue samples and to verify PC diagnosis. In the late 1980s, the systematic sextant biopsy protocol with six random ultrasound guided biopsy cores was proposed as a way to increase the accuracy of PC diagnosis.[72] Later, the extended prostate biopsy scheme consisting of 12 cores has become the standard procedure, with increased PC detection rate but without any significant increase in adverse events.[73] A transperineal approach instead of the transrectal counterpart may increase the sensitivity, especially in cases with "gray zone " PSA (4.1−10.0 ng/ml) and in transition zone cores.[74]

2.4.4 Imaging

Computed tomography (CT) and magnetic resonance imaging (MRI) can be used to evaluate the local extent of PC and the possibility of nodal involvement, although the sensitivity and specificity of MRI vary considerably and the sensitivity of CT is low (<30%) in local staging of PC. These modalities have low sensitivities in their abilities to detect lymph node involvement.[75-79]

The radionuclide bone scan (bone scintigraphy) has been the mainstay for detecting skeletal metastases since the 1970s, especially in high-risk PC patients (PSA >20 ng/ml, Gleason score >7, tumor stage of T3 or higher, peri-neural tumor invasion), although its specificity is limited.[80] False positives may occur from degenerative change, inflammation, Paget's disease, and trauma. Other imaging modalities such as plain radiography, CT, MRI, and positrone emission tomography (PET) can be used in combination with a bone scan in attempts to increase sensitivity and specificity.[79, 81]

2.5 TREATMENT MODALITIES WITH CURATIVE INTENT

Curative treatment aims to remove the cancer with the entire prostate gland or to eradicate PC cells from the prostate tissue. There are only a few randomised controlled trials comparing the curative-intended treatment modalities with each other. A recent comprehensive literature review indicated that a single treatment modality was efficient in low-risk (PSA <10 ng/ml, Gleason score ≤6, and cT1c−T2a) and intermediate-risk PC (PSA 10.1−20 ng/ml, Gleason score 7, or cT2b−c) but a multimodal approach may be needed for high-risk PC (PSA >20 ng/ml, Gleason 8−10, or cT3a−4).[82]

2.5.1 Radical prostatectomy (RP)

Radical prostatectomy, using a perineal approach, was applied already in the early years of the 20th century by Hugh H. Young.[83] The first retropubic RP was described in the late 1940s.[84] The standardisation of the anatomic retropubic RP was described by Walsh and Donker in 1982.[85] Since then, many authors have described applications attempting to

improve both cancer-specific (biochemical PSA failure-free, progression-free, and PC-specific survival) and functional outcomes (urinary continence, erectile function), as well as striving to reduce short-term and long-term morbidity.[86, 87] Bearing these aims in mind, since the late 1990s an increasing number of authors focused their interest on development of the technique of laparoscopic RP (LRP).[87, 88] A further development of laparoscopic technique led to a robot-assisted procedure (RALP) at the beginning of the 2000s.[89-92] Both LRP and RALP seem to achieve a better perioperative outcome than traditional RP: lower blood loss and decreased transfusion rates. The superiority of these treatment modalities over traditional RP has not yet been demonstrated in terms of oncological outcomes.[93] However, recent meta-analyses have pointed to better functional outcomes in favor of RALP in comparison with traditional RP and LPR.[94, 95]

Scandinavian randomised SPCG-4 trial demonstrated the survival benefit of RP in comparison with watchful waiting, with a nearly 40% decrease in the risk of death from PC among men <65 years of age.[96] RP has been associated with excellent long-term cancer control, with the risk of PC death after surgery in modern series between 5 and 10%.[86] RP is the most common treatment for newly diagnosed clinically localised PC in US.[97] Selected patients with high-risk PC and with more advanced disease (PSA ≥20 ng/ml, Gleason score 8−10, tumor stage of T3−4) are also likely to obtain benefits from RP.[28, 98-102]

2.5.2 External beam radiation therapy (EBRT)

Three-dimensional conformal radiotherapy (3D-CRT) is the gold standard for delivery of EBRT to the prostate gland. Intensity-modulated radiotherapy (IMRT) is an optimised form of 3D-CRT to better conform to the shape of the prostate.[28, 103] A large meta-analysis of seven randomised controlled studies with 2812 patients stated that the biochemical PSA control rate (BCR) in a 5-year regression analysis was essentially linear for the total dose of EBRT ranging from 64 to 79.2 Gy. Furthermore, between the doses of 70 and 80 Gy, there was a significant increase in 5-year BCR of 14, 17.8, and 19.2% in low-, intermediate-, and high-risk patients.[104] A minimum dose of at least 74 Gy is recommended in the EAU guidelines for low-risk PC.[28] For intermediate- and high-risk PC, an increase of the radiation dose up to 80 Gy seems to have a significant impact on 5-year BCR but not necessarily on the overall or PC-specific survival (PCS).[104-107] On the other hand, the risk for adverse effects increases with increasing doses of RT. Gastrointestinal complications and rectal bleeding are the most frequently reported side-effects with high-dose EBRT. Similarly, mild acute irritative urinary symptoms have been reported but no significant difference in the extent of late-onset genitourinary toxicity.[103, 104, 106, 107]

New techniques, such as intensity-modulated arc therapy or volumetric-modulated arc therapy and the CyberKnife® system, allow real-time tracking of the target and more precise EBRT delivery to the prostate. This, in turn, enables doses even higher than 80 Gy and better cancer control rates with similar or fewer side-effects than traditional EBRT.[108-112]

Neoadjuvant, concomitant, and adjuvant androgen deprivation therapy (ADT), from a few months up to 3 years in length, in combination with EBRT have been reported to improve BCR, overall survival (OS), and PCS in intermediate and high-risk PC and in locally advanced PC.[113-119]

The post-treatment PSA nadir has been reported to be significantly associated with the risk of PC-specific and all cause mortality after RT.[120-122] After biochemical PSA recurrence post RT, selected patients with confirmed local cancer recurrence and without any evidence of metastasis may be candidates for salvage RP, even though the procedure is technically demanding and carries high risk of surgical complications.[123]

2.5.3 Brachytherapy (BT)

Low-dose rate brachytherapy (LDR-BT) refers to low-energy radioactive sources (iodine-125 or palladium-103) inserted permanently into the prostate gland which emit radiation at a rate of <2 Gy/h. High-dose rate brachytherapy (HDR-BT) uses a high-energy emitting

radiation source (iridium-192) with a rate of ≥12 Gy/h which is implanted temporarily into the prostate gland.[124, 125] Both approaches are transperineal under TRUS guidance. HDR-BT tends to be used for more aggressive or more advanced PC and is usually combined with EBRT.[125]

LDR-BT is warranted for use in patients with low-risk PC.[28] Good long-term oncological and functional outcomes have been reported,[126-129] even in patients <60 years of age.[130, 131] However, there is a lack of randomised trials which would have compared BT with other treatment modalities.[124] Recently, a consensus meeting published guidance on patient selection and the optimal technique for focal LDR-BT.[132]

2.5.4 Focal therapy

As a result of screening, today there are increasing number of patients with an intracapsular small focus of PC, eligible for local treatment, such as cryosurgical ablation (i.e. freezing of the prostate), high-intensity focused ultrasound therapy (HIFU), laser-induced interstitial thermotherapy (LIIT, photothermal ablation), and vascular-targeted photodynamic therapy. However, there is a lack of high-quality comparative trials and long-term efficacy results.[28, 97, 133-135]

2.5.5 Active surveillance

Active surveillance (AS) is an option for immediate treatment intended to be curative. The aim is to avoid overtreatment and side-effects from therapy in highly selected patients with a life-expectancy of >10 years and with a low-risk PC. The commonly used inclusion criteria for AS are PSA ≤10 ng/ml, tumor stage ≤T2a, Gleason score ≤6 (3+3), and PSA density <0.2 ng/ml per milliliter.[136-141] The number of positive biopsy cores and the proportion of positivity in a single core are also defined. In some trials, the inclusion criteria have been expanded to include patients >70 years of age, PSA ≤15 ng/ml, and Gleason score ≤3+4.[139, 142, 143] The patients are followed up with close surveillance (PSA testing every 3 to 6 months, DRE, repeat biopsy at regular intervals) and treated if and when pre-defined thresholds are reached (upgrading of Gleason score, increasing proportion of positivity in biopsy cores, PSADT <2−4 years).

The published data is not yet sufficient to permit drawing any definitive recommendations. However, AS seems to produce a very modest decline in PCS among men with low-risk PC but does offer a significant benefit in terms of QoL.[28, 144-147] The recently published results of the PIVOT trial showed no significant difference in all-cause and PC-specific mortality during a 12-years of follow-up between RP and observation in patients with localised PC and who were randomly assigned to either treatment arm.[148]

2.6 HORMONAL TREATMENT

The positive effect of androgen deprivation on advanced PC was first described by Huggins and Hodges in 1941.[149, 150] Subsequently, the standard treatment approach for metastatic or advanced PC has been hormonal ablation either by surgical castration or by using luteinising hormone-releasing hormone (LHRH) agonists (with or without antiandrogens) and, recently, by using LHRH antagonists. Androgen withdrawal results in apoptosis, the cellular death of androgen-sensitive PC cells. During apoptosis, a subset of cells undergo genetic and biochemical changes leading to fragmentation of the nuclear DNA, followed by fragmentation of the cell and the removal of the cellular debris. This process results in tumor shrinkage and decreased production of prostate-specific proteins.[151] In addition to apoptosis, ADT seems to induce characteristics consistent with cellular senescence in a subset of androgen-sensitive PC cells.[152] Hormonal ablation therapy is not curative but simply palliative.

2.6.1 Androgen receptor signalling pathways, development of castration resistance

Testosterone and its metabolite dihydrotestosterone (DHT) are the two major growth factors of prostate cells. Testosterone and the other steroid hormones are primarily synthesised from cholesterol. Androgens act through the androgen receptor (AR), a steroid-hormone binding protein, encoded by the AR gene located on the X-chromosome, with DHT mainly regulating intraprostatic androgen-mediated processes.[153] AR signalling is critical to the proliferation and differentiation of epithelial and stromal prostate cells, to the development of the normal prostate gland, and it is fundamentally involved in the progression from primary PC to metastatic disease.[154, 155] After androgens bind to AR, the androgen−AR complex dissociates from AR-inactivating proteins (heat shock proteins) in the cytoplasm and enters the nucleus, stimulating the transcription of androgen-regulated genes which are involved in cell proliferation and PSA production.[156, 157] AR coregulators are proteins that interact with AR and regulate the AR-signalling pathway either by enhancing (coactivators) or by reducing (corepressors) transcriptional activity.[158]

Testosterone synthesis in Leydig cells of testes is regulated by the luteinising hormone (LH) released from the pituitary gland which, in turn, is regulated by LHRH from the hypothalamus. In prostate cells, testosterone is converted by 5-α-dehydrogenase into DHT, the most powerful intraprostatic intracellular androgen (Fig. 2). Prostate cells can produce testosterone also from adrenal steroids.[153] DHT can also be formed from progesterone by a so-called "backdoor pathway".[159] There is evidence that PC cells express all the necessary enzymes for, and are capable of, de novo androgen synthesis from available precursors instead of blood derived androgens.[160-162] It is apparent that prostate cells use the standard steroidogenic pathway in the normal androgenic environment, but they develop alternative pathways to continue AR-mediated functions in the androgen-deprived environment. Thus, PC cell growth becomes independent of the plasma testosterone level after an initial response to ADT.[153]

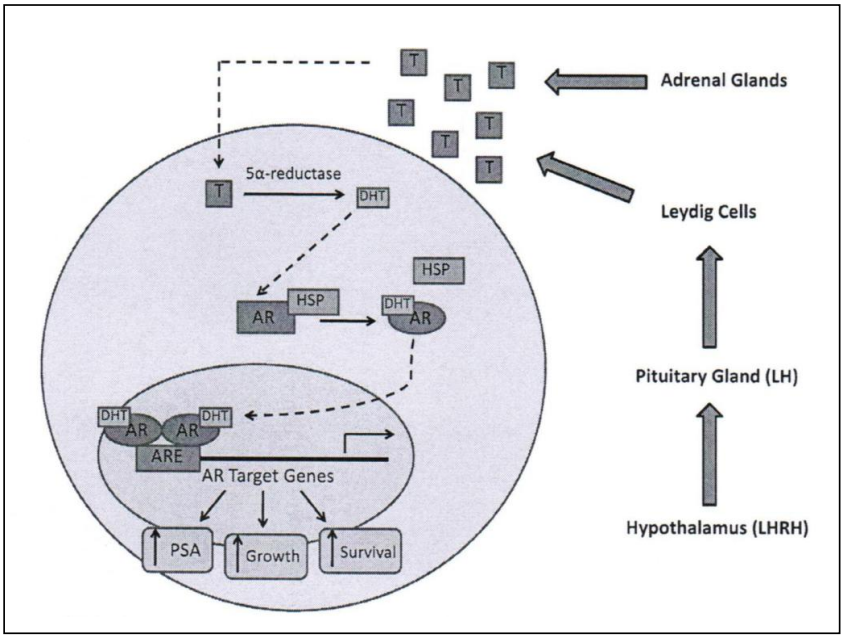

Figure 2. Mechanisms of the androgen action and androgen receptor signalling in prostate cells.[157] T=testosterone, DHT=dihydrotestosterone, HSP=heat-shock protein, AR=androgen receptor, ARE=androgen-responsive element, LH=luteinising hormone, LHRH=luteinising hormone-releasing hormone. Reprinted with the permission of the copyright owner.

Although the majority of patients with advanced PC have a good initial response, with up to 80–90% responding to ADT, unfortunately, nearly all patients will eventually progress to a castration-resistant state. The definition of castration resistant PC (CRPC) includes rising levels of PSA, radiographic progression and/or worsening of symptoms even with castrate levels of serum testosterone (<50 ng/dl or <1.7 nmol/l).[163] The development of CRPC involves the activation and re-expression of the AR program following primary ADT.[154] Thus, CRPC continues to be largely dependent on AR and AR-responsive pathways. The mean survival time of patients with metastatic disease used to be only 36 months, and the median survival time with CRPC used to be approximately 12-18 months before the most recent primary treatment changes and advances in treatment for progressive PC.[164, 165]

There are several mechanisms by which PC cells can develop from being androgen-dependent into a castration resistant state, independent of plasma testosterone concentrations (Fig. 3). Amplification of the AR gene and up-regulation or overexpression of the AR protein have been detected in CRPC cells.[166-168] These changes, as well as increased stability of AR proteins, sensitise tumor cells to survive and proliferate even under conditions with minimal androgen concentrations.[169, 170] AR gene mutations have been demonstrated at increasing rates in metastatic or CRPC.[171, 172] The mutations in the ligand-binding domain lead to decreased ligand specificity, such that the AR may be activated also by other steroid hormones, non-steroid hormones, and even by antiandrogens.[157, 173-175] AR isoforms lacking the ligand-binding domain, called AR splice variants, have been identified as being overexpressed in CRPC cells, leading to androgen independent cell growth.[154, 176] Mutations in coregulator genes or alterations in coregulator concentrations may modify the AR activity and promote PC cell growth.[153, 157] Furthermore, intracellular de novo androgen synthesis can enable CRPC cells to survive despite low serum testosterone levels.[160, 169] There is evidence for many other cellular and molecular mechanisms, called outlaw and bypass pathways, that can activate AR in a ligand-independent way or can use routes other than androgen–AR pathway to regulate PC growth and to circumvent androgen deprivation-induced apoptosis. These include growth factors, cytokines, kinases, and other proteins.[153, 157] Furthermore, epigenetic alterations and miRNA regulation have been speculated to have an impact on the progression of androgen-independent PC.[157] According to clonal selection hypotheses, an androgen insensitive (AI) cell population already exists in the benign prostatic epithelium and it is an outgrowth of these AI cells which occurs in CRPC under androgen-deprived circumstances.[177]

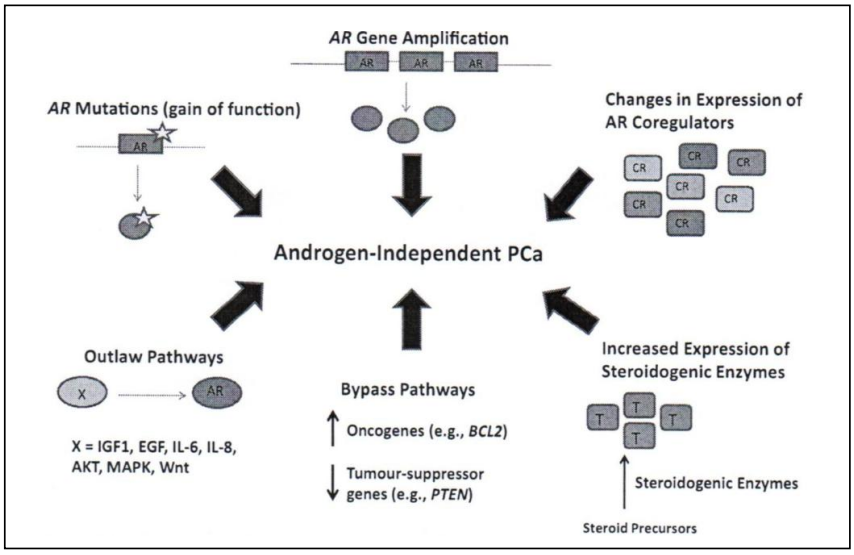

Figure 3. Mechanisms of androgen independence in prostate cancers.[157] AR=androgen receptor, CR=coregulator, T=testosterone. Reprinted with the permission of the copyright owner.

2.6.2 Androgen deprivation therapy

In treatment of PC, the hypothalamic–pituitary–testosterone–AR pathway can be targeted at different points, in order to eliminate androgenic action and to try to tackle the underlying mechanisms of PC cell proliferation.

2.6.2.1 Surgical castration, LHRH agonists, and LHRH antagonists

Surgical castration by bilateral orchiectomy eliminates testosterone production from testes, causes rapid and sustained suppression of testicular androgens, leading to declines in serum testosterone levels to <20 ng/dl (0.7 nmol/l) in most patients.[178] LHRH agonists (analogues, LHRHa), such as goserelin, leuprorelin, buserelin, and triptorelin, evoke a castration effect through negative feedback.[179] In fact, continuous stimulation of the pituitary by LHRHa induces regulatory changes, possibly down regulation of LHRH receptors, receptor desensitisation, and inhibition of LH release.[180] The equivalence of LHRHas and orchiectomy has been demonstrated, only about 5% of patients treated with LHRHas fail to achieve serum testosterone <50 ng/dl (<1.735 nmol/l).[181] However, the agonistic effect causes an initial stimulation of LHRH receptors with a serum testosterone surge during the first week which is associated with clinical flare symptoms in patients with advanced disease. The castrate levels of testosterone are achieved in 2–4 weeks.[182, 183] Short-term antiandrogen treatment can ameliorate flare symptoms at the beginning of LHRHa treatment.[184]

LHRH antagonists, such as abarelix and degarelix, bind directly to and are competitive inhibitors of LHRH receptors, leading to a rapid and reversible reduction in serum testosterone levels, without causing any testosterone surge and flare symptoms.[185-187] Thus, no antiandrogen treatment at the beginning of LHRH antagonist treatment is necessary. LHRH antagonists offer a rapid and effective non-surgical castration with symptomatic relief in patients with symptomatic metastatic PC.[188]

2.6.2.2 Androgen receptor antagonists, monotherapy, and maximal androgen blockade

AR antagonists (antiandrogens, AA) block the intracellular testosterone–AR pathway through a competitive inhibition of AR binding with testosterone and DHT. First-generation AR antagonists are nonsteroidal, such as bicalutamide, flutamide, and nilutamide, or steroidal agents, cyproterone acetate. Cyproterone acetate has both an androgenic and a progesteronic action, i.e. it binds also to progesterone receptors in the pituitary and inhibits the release of LH.[189] Bicalutamide can be used as an adjuvant treatment after curative-intended treatment with locally advanced disease, as a monotherapy in biochemical PSA failure after curative-intended treatment, or as a primary treatment in locally advanced disease without metastasis but not in patients with metastatic disease.[188, 190-192]

In maximal androgen blockade (MAB), AAs are combined with surgical castration, LHRH agonists, or LHRH antagonist. Some trials have shown that MAB can improve oncological outcome in metastatic or locally advanced PC,[193, 194] some trials have not found success.[195, 196] Two large meta-analyses showed no clear survival benefit with MAB in primary treatment of PC when compared with surgical or chemical castration alone.[197, 198] AAs can be added to castration monotherapy after biochemical PSA relapse to eliminate the stimulating effect of small concentrations of adrenal androgens on AR. About one third of patients seem to enjoy at least a short-lasting response.[199, 200]

Novel inhibitors of steroidogenesis and androgen synthesis and blockers of the AR-mediated pathway seem to confer a survival advantage in CRPC. The second-generation AR signalling inhibitors, enzalutamide (MDV3100) and RD162, have a high affinity to AR without any agonist activity.[201, 202] Abiraterone and orteronel (TAK-700) are androgen synthesis blockers which inhibit the enzymes needed in steroidogenesis in adrenal glands, testes, and prostate.[203, 204]

2.6.2.3 Watchful waiting and deferred therapy

Watchful waiting refers to delayed symptomatic noncurative treatment in patients who are not candidates for a curative-intended aggressive local treatment.[28] EORTC 30981 trial showed immediate ADT to offer a modest OS benefit but no significant difference in PC-specific or symptom-free survival in patients without metastasis. The median time to the start of deferred ADT was seven years.[205] Subsequently, the authors reported that patients with a baseline PSA >50 ng/ml and/or PSADT <12 months were at an increased risk to die from PC and might obtain benefit from early ADT whereas patients with a baseline PSA <50 ng/ml and/or PSADT >12 months were likely to die of causes unrelated to PC. Patients with a baseline PSA ≤8 ng/ml had a very low risk of dying from PC within seven years.[206] The tumor grade has a significant impact on survival with low survival rates for poorly differentiated PC.[207] Watchful waiting is an option for low−intermediate risk localised PC in patients >65 years of age and with two or more comorbidities that would increase the risk of their deaths from causes other than PC within 10 years.[208]

2.7 ADVERSE EFFECTS

ADT use is associated with short and long-term adverse effects (AE) which have an impact on QoL and may also compromise patient survival. Well-known side-effects of low testosterone levels are hot flushes (flashes), sweating during nighttime, erectile dysfunction, libido reduction, fatigue, depression, and gynaecomastia. In addition, decreased hemoglobin levels, changes in fat and lean body mass, changes in plasma lipoproteins, increased insulin levels, osteoporosis, and possibly impaired cognitive functions have been reported.[209-211] AA monotherapy does not lower testosterone levels and it is associated with less side-effects than castration therapy. However, gynaecomastia is more common with bicalutamide monotherapy.[191, 212]

2.7.1 Cardiovascular morbidity

Several factors which interact with the traditional cardiovascular (CV) risk, such as body fat and lean body mass, serum lipoproteins, insulin sensitivity, and obesity, have been demonstrated to be associated with ADT.[213-217] These have been evaluated to increase the odds of serious CV morbidity by as much as 20%, especially during the first 12 months.[218] Many population-based cohort studies have demonstrated the association of ADT with increased risk of thromboembolic events, peripheral arterial disease, myocardial infarction, and stroke.[219-222] Pretreatment CV morbidity seems to further elevate the risk of CV events during ADT.[223, 224] On the other hand, many reports have shown no evidence of increased CV mortality associated with ADT.[225, 225-228] Currently, the association between ADT and CV mortality remains controversial.[211, 229]

2.7.2 Osteoporosis and fracture risk

There is a positive relationship between free testosterone levels and bone mineral density (BMD) in elderly men.[230] Several studies have demonstrated the association of ADT with progressive osteoporosis and with even 5- to 10-fold increased loss of BMD compared with healthy controls or men with PC but not on ADT.[231, 232] The loss of BMD is progressive in conjunction with the duration of ADT but it is most significant during the first years after initiation of ADT.[232-234] Large population based cohort studies have revealed ADT to be associated with an excess risk of fractures or hospitalisation as a consequence of a fracture.[235-238] However, AA monotherapy does not seem to be associated with an increased risk of fractures.[238, 239]

2.7.3 Other adverse effects

There are conflicting reports on the impact of ADT on cognitive functions (CF), such as verbal memory, visuospatial abilities, executive functioning, and language. The trials have been relatively small, with reduced power, and CF assessments have vaned from study to study. Some trials have demonstrated impaired, other trials have reported improved CFs with ADT.[240, 241] Finally, one trial demonstrated no effect of ADT on CFs.[242]

2.7.4 Quality of life

The adverse effects from ADT impact on QoL. Thus, QoL is an important issue in patients receiving ADT. However, QoL should be assessed systematically using validated and formulated questionnaires addressing different kinds of functions and domains. One of the most commonly used validated questionnaires is The European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaire.[243] QLQ-C30 incorporates nine multi-item scales: five functional scales (physical, role, cognitive, emotional, and social); three symptom scales (fatigue, pain, and nausea and vomiting); and a global health and a QoL scale. Several single-item (symptom) measures are also included: dyspnoea, sleep disturbance, appetite loss, constipation, diarrhoea, and financial impact.

In 1995, Cleary et al devised a formulated and validated 30-item questionnaire for multinational use to explore the value of ADT for advanced PC.[244] The questionnaire consisted of ten domains: pain (four items), social functioning (two items), emotional well-being (five items), vitality (three items), activity limitation (one item), bed disability (one item), overall health (one item), physical capacity (six items), sexual functioning (four items), and sexuality (three items).

The interpretation of the significance of changes in QoL scores is challenging. Small numerical differences in mean scores derived from QoL assessment instruments may provide statistically significant results when large sample of subjects are involved, but the clinical significance of such small numerical differences is far from clear. To signify the importance of a change, Osoba et al (1998) devised the term “subjective significance” when referring to the changes in QoL scores that the subjects themselves considered to be important.[245] They developed a subjective significance questionnaire (SSQ) to determine the numerical changes in the QLQ-C30 scores that were present when the subjects indicated a change on the SSQ: no change; a slight change, worse or better; moderate change; very great change. In addition, evidence-based guidelines have been published for the determination of sample sizes in clinical trials and for interpretation of differences in QLQ-C30 scores.[246]

2.7.5 Testosterone recovery

Testosterone recovery is considered essential for relief from ADT-induced AEs and for achieving an improvement in QoL when concerning IAD.[164] The testosterone recovery rate has been demonstrated to be dependent on the baseline pretreatment testosterone prior to ADT, the duration of ADT, and on the age of patient.[247-250] In theory, time off therapy should be long enough to permit recovery of testosterone which is necessary for testosterone-induced tumour cell differentiation to defer hormone resistance, reduced side effects, recovery of sexual function, and normal sense of well-being.[164]

Early studies regarding IAD indicated that testosterone level normalisation occurred within 2 to 6 months.[4, 251-257] However, Irani et al showed that a predetermined off-treatment period (TOFF) of 6 months was not long enough to regain normal testosterone values or to achieve any difference in QoL between IAD and CAD after receiving six months in one year of MAB intermittently.[258] Another trial demonstrated that a median time of seven months was needed for normalisation of testosterone after withdrawal of ADT.[247]

In phase III trials, the proportion of patients showing normalisation of serum testosterone during TOFFs varied from 35 to 93%, and the time to serum testosterone normalisation ranged from 100 days up to 12 months. The percentage of patients experiencing

testosterone recovery and the levels of serum testosterone reached during TOFFs decreased in consecutive cycles.[250, 259-261] It has to be stated that not all phase III trials have reported testosterone recovery rates.

2.8 INTERMITTENT ANDROGEN DEPRIVATION

PSA testing and screening have resulted in an earlier diagnosis of PC, i.e. patients of younger ages and at earlier stages of disease.[2] This, in turn, has led to increasing number of men with asymptomatic locally advanced or locally recurrent PC, who by virtue of the natural history of the disease have life expectancies of years and are at risk of experiencing significant AEs and declining QoL from ADT. Therefore, the clinicians have to try to balance the potential benefits of early ADT with the risks of long-term complications from ADT.[164] Furthermore, hormonal ablation therapy is not curative but simply palliative with a limited time of response.

These observations triggered the search for alternative treatment strategies in the 1980s and 1990s to optimise the effectiveness of ADT while minimising AEs. The widespread use of potentially reversible medical castration and the possibility of monitoring the course of PC via the PSA assay led to the concept and development of intermittent androgen deprivation (IAD) or cyclic therapy, a form of ablative therapy administered in pulses.

Bruchovsky et al (1990) indicated that the development of androgen-independent cells within the Shionogi carcinoma was greatly increased in an androgen-depleted environment. This appeared to be linked to cessation of androgen-induced differentiation of tumorigenic stem cells and may have been a result from the ability of small number of initially androgen-dependent stem cells to adapt to the altered hormonal environment.[262] The rationale behind IAD was based on the hypothesis that if tumor cells surviving androgen withdrawal were forced along a normal pathway of differentiation by androgen replacement, then apoptotic potential might be restored and in that way progression to androgen independence delayed. Thus, it should be possible to maintain the apoptotic potential and to defer hormone resistance by achieving repeated cycles of androgen-stimulated growth, differentiation and androgen-withdrawal regression of tumor.[164, 255] The objectives of IAD were, at least on a theoretical basis, to defer hormone resistance with the potential for prolonging the life, and, secondly, to improve the QoL by the intermittent restoration of normal androgen levels and reducing AEs related to ADT.[3, 4]

2.8.1 Animal studies

The concept of treating cancer with intermittent endocrine therapy derives from studies by Noble (1977) regarding tumor biology in hormone-dependent tumors in various organs of the Nb strain of rats.[263] The first studies in animal models were conducted to determine whether intermittent hormonal therapy could delay the onset of hormone-independent growth of cancer. Several different methods were used but the results were conflicting. Russo et al (1987) determined the effect of intermittent diethylstilbestrol diphosphate (DES) on the Dunning R3327 rat PC and Trachtenberg (1987) examined the effect of intermittent testosterone implants on the Dunning R3327 PC in castrated male rats. No survival or any growth-retarding advantages were demonstrated with IAD when compared to castration or continuous androgen deprivation (CAD). Both studies indicated that IAD was clearly inferior to CAD in this respect.[264, 265] However, it was speculated later that the Dunning R3327 tumor model was androgen-sensitive but not androgen-dependent, which could have explained the results.[5, 164, 266]

In other studies either the androgen-dependent Shionogi carcinoma was transplanted into a succession of male mice prior to castration[267] or castrated mice bearing LNCaP tumours were intermittently subjected to hormonal stimulation via testosterone implants.[268, 269] Akakura et al (1993) demonstrated that IAD could induce multiple apoptotic regressions of the Shionogi tumor.[267] Furthermore, Buhler et al (2000) could not detect any significant

difference in survival between these two treatment models and proposed that IAD was not associated with any decrease in survival.[268] Gleave et al (1996) reported that IAD could prolong the time to androgen-independent PSA production by 3-fold with serum PSA levels increasing 9-fold faster with CAD.[270]

2.8.2 Pilot studies and phase II trials

The first clinical studies were performed to assess the feasibility of IAD in the treatment of PC. The concept of IAD for PC was first clinically examined by Klotz et al (1986) who reported results of intermittent DES therapy in 19 patients with advanced PC and of intermittent flutamide in one patient with the overall conclusion that IAD was not harmful to the patients. The authors reported recovery of potency after discontinuation of therapy during the period off treatment (TOFF), thus suggesting a beneficial effect on patient-rated QoL.[271] The early clinical studies were rather heterogeneous in terms of the patient population (metastatic disease, localised disease or biochemical failure after definitive local therapy) and the proposed treatment guidelines. For example, the methods and length of the initial ADT and the criteria for withdrawal and resumption of ADT varied from study to study.[3, 4, 249, 251-257, 266, 272-284] In most trials, the PSA cut-off level was 4 ng/ml for withdrawal of ADT and 10 to 20 ng/ml for resumption of ADT, this being guided mainly by the importance of tumor burden. The duration of the treatment-on phase (TON) ranged from 3 to 12 months but was usually 6 to 9 months before withdrawal of ADT. Mean and median duration of TOFFs showed a tendency with time to decrease from cycle to cycle. Median times to progression varied extensively according to advancement of PC.

A few studies have reported a median follow-up for more than five years, demonstrating the feasibility of IAD in long-term treatment of PC.[282-286] Prapotnich et al (2009) reported their 16-year clinical experience with a median follow-up of 81 months and with one patient even reaching his 13th cycle. Cycle duration decreased progressively from 23.7 months in the first cycle to 10.1 months in the 12th one, with a mean of 14 months off therapy. It seemed that patient's age, Gleason score, and initial PSA level were significant prognostic factors.[286] Furthermore, the PSA nadir during the first TON and the duration of the first TOFF have been proposed to be predictors of the time to clinical progression and CRPC.[287-289]

QoL was not assessed systematically via questionnaires in many of the early nonrandomised trials. In spite of the lack of any formulated questionnaire, many of these trials not only highlighted the feasibility of IAD but described an improvement of QoL during TOFF.[251, 252, 274, 279] However, some of the phase II trials did utilise some kind of questionnaire to assess QoL.[249, 255, 256, 266, 277, 284] Most of these have revealed an improvement of QoL, at least to some extent, during TOFF. In order to evaluate QoL, Albrect et al (2003) designed a 14-item ad-hoc questionnaire addressing symptoms and level of pain, overall QoL and the inconvience related to monthly blood tests. Overall QoL seemed to be slightly better during TOFF, but no definitive conlusions could be drawn. The proportion of potent men at the entry was only 17.8%, and thus, potency preservation seemed to be of minor importance.[266] Sato et al (2004) assessed QoL by a self-administered FACT-G questionnaire and by the IIEF-5-questionnaire. There seemed to be a remarkable and significant improvement of QoL in the categories of potency and social/family well-being during TOFF. Testosterone levels recovered to the normal range in 87% of patients within a median of 13 weeks. They detected an association between testosterone recovery and improvements in QoL scores and concluded that IAD offered major advantages over CAD with respect to QoL.[255] Bruchovsky et al (2008) assessed QoL using Southwest Oncology Group 9346 QoL questionnaire and the American Urological Association (AUA) symptom scores questionnaire. QoL improved in several categories of physiologic and psychologic function when ADT was stopped.[284]

The QLQ-C30 questionnaire was used in some of the early pilot and phase II trials. Bouchot et al (2000) could not observe any modifications in social activities, occupational

activities, emotional status, and sexual functions between pre-treatment, on-treatment, and off-treatment periods. Only the direct hormonal side-effect of hot flushes was reported to be improved during TOFF.[277] Cury et al (2006) reported IAD to limit hormone-related AEs but, generally, no significant change of QoL between off-treatment and on-treatment periods.[256] Spry et al (2006) demonstrated a trend for a progressive improvement of QoL that paralleled the testosterone recovery. The improvement reached its maximum by months 9−12; recovery was slower than the rate of deterioration of QoL during TON which lasted nine months.[249]

2.8.3 Phase III trials

The first randomised study comparing IAD with CAD was reported by de Leval et al in 2002.[290] Since then, a few more randomised trials with locally advanced, metastatic or recurrent PC have been published (Table 2). In most of the trials, the treatment regimen has consisted of MAB. The duration of the initial treatment-on phase has varied between three and eight months, but commonly was six months. The PSA cut-off level was usually 4 ng/ml for withdrawal of ADT and 10 to 20 ng/ml for resumption of ADT, as in the phase II trials. The PSA nadir during the first TON and the duration of the first TOFF have been demonstrated to be predictors of the time to clinical progression and to death.[259, 291, 292]

The SEUG trial 9401 used MAB for only 3 months before randomisation, without any demonstrated impact on survival. Gleason score and metastatic status were predictors of PSA response at randomisation, metastatic status and PSA level at randomisation (<2 vs 2−4 vs >4 ng/ml) were predictors of progression and PC death. No difference in OS between treatment arms was demonstrable (p=0.84), but a slightly higher risk for progression and cancer death emerged in the IAD arm. Of the IAD patients, 50% were off therapy for at least 52 weeks following randomisation, and 29% off therapy for >36 months.[292]

De Leval et al reported a mean delay of seven months to androgen-independence with IAD when compared with CAD. Progression rates were significantly lower with IAD than with CAD in patients without bone metastasis (p<0.001) and in patients with a high Gleason score >6 (p=0.018). No significant difference in progression rates was observed in patients with bone metastasis (p=0.32) or with Gleason score ≤6 (p=0.082). In the IAD arm, mean percentages of time off therapy ranged from 52.1% to 61.0% across eight successive cycles. The average duration of TOFF decreased almost linearly by approximately 20 days or 0.9% with each additional completed cycle.[290]

Langenhuijsen et al evaluated maximal androgen blockade given intermittently or continuously in 173 patients with metastatic (N+M0 or M1) PC. High baseline PSA (<50 vs ≥50 to <500 vs ≥500 ng/ml), pain, and high PSA nadir (≤0.2 vs >0.2 to ≤4 vs >4 ng/ml) were strong predictors for progression with ADT. Overall, patients on IAD showed a trend towards higher progression rates and seemed to fare worse than those receiving CAD, especially in patients with PSA nadir ≤0.2 ng/ml (2-year risk of progression 53% vs 31%, p=0.03). In the IAD arm, the mean duration of the 1st TOFF was 19 months, with the percentage time off-therapy decreasing with successive cycles.[259] Mottet et al reported no significant differences in PFS or OS among 173 patients with M1 disease randomised to IAD or CAD. The number and percentage of days off-therapy decreased from a mean of 126 days (54.6%) in the 1st cycle to 85 days (49.2%) in the 7th cycle.[293]

Recently published data of the large trial (JPR7) comparing IAD and CAD among patients with recurrent PC after definitive radiotherapy revealed no significant difference in OS between the treatment arms (8.8 vs 9.1 years in IAD vs CAD).[250] However, a few more PC deaths were reported in the IAD than CAD arm, with 7-year cumulative disease-related death rates of 18% and 15% (p=0.24). The median duration of TOFFs decreased progressively, with 20.1 months in the 1st, 13.2 months in the 2nd, and 9.1 months in the 3rd cycle, and it declined to approximately 4 to 5 months in subsequent cycles.

Table 2. Randomised phase III trials comparing intermittent and continuous androgen deprivation in treatment of prostate cancer.

Author	n	Diagnosis	Regimen	Duration of TON	PSA cut-offs (ng/ml) for withdrawal/ resumption	Follow-up	Outcome	Quality of life
De Leval et al (2002)[290]	68	Locally advanced, metastatic, or recurrent	LHRHa +AA	3-6 mo	≤4/ ≥10	30.8 mo (mean)	Estimated 3-year progression rate lower with IAD than CAD (7.0 vs 38.9%, p=0.0052)	Not assessed
Tunn et al (2004)[261]	184	Recurrent	LHRHa +AA*	6 mo	<0.5/ >3 or progression	28.4 mo (mean)	No difference in PFS	QLQ-C30: Slightly better QoL with IAD
Miller et al (2007)[298]	335	Locally advanced (N+M0) or metastatic (M1)	LHRHa +AA	6 mo	<4 or by at least 90% of baseline/ ≥10 or clinical symptomatic progression	3.9 yr (mean)	No difference in OS or time to progression	Self-assessment: better overall health and sexual activity with IAD
Verhagen et al (2008)[295]	366	Metastatic	AA**	3-6 mo	-	-	-	QLQ-C30: better physical and emotional functions but reduced cognitive functions with IAD than CAD (p<0.05)
Calais da Silva et al (2009)[292] (SEUG 9401)	626	Locally advanced or metastatic	LHRHa +AA	3 mo	<4 or by at least 80% of baseline/ ≥10 (symptomatic) or ≥20 (asympomatic) or ≥20% above nadir	51 mo (median)	No difference in OS; time to progression and PC death lower with IAD (NS)	QLQ-C30: better sexual function with IAD, other functions slightly lower with IAD
Langenhuijsen et al (2011)[259] (TULP)	193	Metastatic (N+M0 or M1)	LHRHa +AA	6 mo	<4/ ≥10 (N+M0 at baseline) or ≥20 (M1 at baseline)	31 mo (median)	Higher progression rates with IAD	QLQ C30 and PR24: no clinically significant difference; a trend towards more side effects with CAD
Mottet et al (2012)[293]	173	Metastatic (M1)	LHRHa +AA	6 mo	<4 / ≥10 or clinical progression	3.9 yr (mean)	No difference in OS or PFS	QLQ-C30 and Lukacs`Q: no clinically relevant difference; less side effects with IAD
Crook et al (2012)[250] (JPR7)	1386	Recurrent (M0)	LHRHa +AA***	8 mo	<4/ ≥10	6.9 yr (median)	No difference in OS; estimated 7-yr cumulative rates of PC-related deaths 18% vs 15 % in favour of CAD (p=0.24)	QLQ-C30: no significant difference for functional domains; significantly better scores for symptoms (hot flashes, sexual activity, and urinary symptoms) with IAD
Hussain et al (2006; 2013)[291, 294] (SWOG 9346, INT-0162)	1535	Metastatic	LHRHa +AA	7 mo	≤4/ ≥20 or ≥baseline (at the discretion of the investigator: ≥10 or symptoms)	9.8 yr (median)	No significant difference in OS (5.1 vs 5.8 yr); better OS with minimally invasive disease and CAD (p=0.035)	SWOG questionnaire: Improved sexual function and mental health with IAD at month 3 after randomisation but not thereafter

*flare prophylaxis with cyproterone acetate (CPA); **CPA 300mg/d; ***at least for 4 weeks; TON=treatment on; PFS=progression-free survival; OS=overall survival; QLQ-C30=EORTC quality of life questionnaire

The most recent results of the vast S9346 (INT-0162) trial with 3040 enrolled and 1535 randomised patients with metastatic PC showed a median survival of 5.1 and 5.8 years years for IAD and CAD, with a 10% relative increase in the risk of death with IAD (HR 1.10, 90% CI 0.95−1.23).[294] IAD was inferior to CAD in patients with minimally extensive disease (5.4 vs 6.9 years; HR 1.19, 95% CI 0.98−1.43) but not in those with extensive disease (4.9 vs 4.4 years; HR 1.02, 95% CI 0.85−1.22). PSA nadir (≤0.2 vs >0.2 to ≤4 vs >4 ng/ml) was a strong predictor for risk of death. Higher PSA, Gleason score ≥8, worse performance status (SWOG 0−1 vs 2−3), younger age, and presence of bone pain were independent predictors for failure to achieve PSA ≤4 ng/ml after seven months of ADT.[291]

Most of the phase 3 trials have used a validated questionnaire to evaluate QoL changes. Three of these trials could detect no clinically relevant difference in QoL between IAD and CAD but less side-effects were reported with IAD.[250, 259, 293, 294] Verhagen et al reported better physical and emotional functions but worse cognitive functions with IAD than CAD (p<0.05).[295] In the SEUG trial 9401, side-effects of hot flushes, gynaecomastia, headaches, and skin complaints were more frequent in the CAD arm. Surprisingly, QoL was reported to be slightly lower with IAD in the other domains, except sexual quality.[292] Hussain et al found better erectile function and mental health with IAD when compared with CAD at month three but not thereafter. [294]

Testosterone recovery rates have been reported in many but not all of the phase III trials. The data from the TULP study revealed that the median testosterone level started to rise above 0.2 ng/ml at 10 months and it was restored to normal levels at 12 months after cessation of the induction ADT (6 months) in the IAD arm. A median of four months was needed for testosterone to rise above the castrate level, with 92% of patients having a normalised serum testosterone at the end of the 1st cycle and 54% at the end of the 2nd cycle.[259] In the JPR 7 trial, only 35% of patients experienced a return to pretreatment levels of serum testosterone during the first TOFF.[250] Calais da Silva et al reported significantly higher geometric mean testosterone at fixed points at 3-monthly-intervals in the subgroup of IAD (192 patients at entry) compared with CAD (178 patients).[292] In the trial of Mottet et al, testosterone was found to increase to a mean value of 4.83 ng/ml during 1st TOFF within three months after cessation of ADT compared with the mean level of 0.29 ng/ml during 1st TON.[293] Tunn et al (2012) reported testosterone normalisation in 79.3% and 64.9% of patients during the 1st and 2nd TOFF, with a median time of 100 and 115 days to normalisation.[260] Previously, Tunn et al (2004) reported testosterone normalisation rates of 93% and 79.4% during the 1st and 2nd TOFF, with mean durations of TOFFs of 10.32, 5.97, and 3.60 months in the 1st, 2nd, and 3rd cycle, respectively.[261]

3 Aims of the Study

Androgen deprivation therapy (ADT) has been the standard treatment for advanced PC for seven decades. Despite an initial response rate of up to 80–90%, many patients experience a relapse within a few years. Furthermore, many patients are likely to experience significant AEs with a deterioration of QoL from ADT. These observations triggered the search for alternative treatment strategies, such as intermittent dosing, to optimise ADT efficacy while minimising AEs.

The general aim of this study was to compare intermittent and continuous androgen deprivation in patients with locally advanced or metastatic PC in terms of time to progression, to death, to PC-specific death, and to treatment failure, and to compare the effect of these treatment modalities on the quality of life. When the FPVII trial was planned in the middle of the 1990s, there were no published randomised, controlled trials regarding IAD.

The specific aims of the study were:

1. To identify what kinds of patients with advanced PC are appropriate for IAD.

2. To compare IAD and CAD on progression-free survival (PFS), overall survival (OS), PC-specific survival (PCS), and treatment failure survival (TFS).

3. To compare the effects of IAD and CAD on the quality of life (QoL) and on the prevalence of adverse effects from ADT.

4. To compare the effect of IAD and CAD on PFS, OS, PCS, TFS, and QoL separately in the subgroups of patients with nonmetastatic (M0) and metastatic (M1) disease.

4 Patients and Study Design

4.1 PATIENTS

4.1.1 Inclusion criteria

The FinnProstate Study VII (FPVII) was conducted as an open-label, randomised, controlled, parallel-group, multicenter clinical trial in 27 clinics in Finland between May 1997 and January 2010 (appendix 1). The trial was designed to compare IAD and CAD in patients with histologically confirmed metastatic PC (M1) at any PSA level. In an attempt to increase recruitment, the inclusion criteria were widened in June 1998 to include patients with locally advanced or recurrent PC without metastases (M0). M1 patients at any PSA level, M0 patients at PSA level ≥60 ng/ml, or T3−4M0 PC at PSA level ≥20 ng/ml, or previously surgically or radiotherapy-treated local PC and PSA recurrence ≥20 ng/ml; no previous hormonal or medical treatment for PC; and performance status WHO 0−2 with a life expectancy of at least 12 months, represented the inclusion criteria. The trial protocol and amendments were approved by Ethics committees in each center. All patients gave a signed informed consent.

4.1.2 Hormone sensitivity of the prostate cancer

In order to establish hormone sensitivity of PC, all patients recruited received LHRHa treatment goserelin depot 3.6 mg (Zoladex®, AstraZeneca) subcutaneously every 28 days for 24 weeks (run-in period). The antiandrogen (AA), cyproterone acetate (CPA), was administered 100 mg bid during the first 12.5 days in order to minimise the flare reaction. The hormone sensitivity was defined as a PSA decrease to <10 ng/ml or by at least 50% in patients with the baseline value <20 ng/ml.

4.1.3 Exclusion criteria

The exclusion criteria for the run-in period were as follows: any previous hormonal or medical treatment of PC; previous history or presence of any malignancy other than basal or squamous cell carcinoma of the skin within the last 5 years; any medication or treatment affecting sex hormone status; patient receiving any other investigational drug within 3 months prior to entering the trial; any physical or mental condition which could interfere with the patient's ability to comply with scheduled visits.

4.2 STUDY DESIGN

4.2.1 Visit 1 and 2

At visit 1, the eligibility of the patient was checked. The patient's demographic details (age, sex, race, weight, height), previous significant medical history and concomitant medication usage were recorded. A physical examination was performed at each visit. Any abnormalities, which may have been related to trial drugs but were not related to PC, were recorded. Any worsening of patient's physical condition compared with baseline, which may have been related to trial drugs, was reported on the suspected adverse drug reaction (ADR) form. An isotopic bone scan or a skeletal x-ray or both assessments were performed at visit 1 for every patient, at visit 3 for patients with bone metastases (M1), and thereafter when clinically indicated. Any other clinically measurable non-skeletal metastases were assessed by clinical examination at each visit, except at visit 2. Chest-x-ray was performed at visit 1 and thereafter when clinically indicated. Ultrasound, X-ray, CT-scan etc. were optional. DRE was done at each visit, except visit 2, for assessment of prostate dimensions (two largest diameters). TRUS was an optional method. Laboratory tests for testosterone,

alkaline phosphatase (ALP), creatinine (crea), blood count (haemoglobin, haematocrit, total white blood cells, erythrocytes, MCV, MCH, MCHC), as well as urinalysis (pH, proteins, glucose, ketone bodies and sediment), were measured at each visit except at visit 2. PSA was measured at each scheduled visit every 12 weeks and more frequently during TOFF in the IAD arm when necessary.

The aim of visit 2 was to evaluate the safety and efficacy of LHRHa treatment and to check the patient's initial response to the trial treatment. The visit included PSA assay, physical examination, and assessment for any ADR or any changes in concomitant medication usage.

4.2.2 Randomisation (visit 3) and follow-up visits

Patients who fulfilled all inclusion criteria, who completed the 24-week run-in period, and whose PC showed hormone sensitivity, were randomised at visit 3. In order to meet the randomisation criteria, PSA level had to decrease to <10 ng/ml or by at least 50% if the baseline value was <20 ng/ml. Patients with a hormone sensitive PC who were eligible for randomisation were allocated in a 1:1 manner to IAD or CAD by using the rand-function of Excel program. Patients not eligible (Group A) and patients eligible for randomisation (Group B) were evaluated in the interim analysis for prognostic markers affecting the initial response to ADT.

In the CAD arm, patients continued with goserelin depot 3.6 mg every 28 days or 10.8 mg every 12 weeks or they underwent bilateral orchiectomy. In the IAD arm, LHRHa was withheld immediately after randomisation and resumed, including flare protection with CPA, for at least 24 weeks whenever PSA increased above 20.0 ng/ml or above the baseline value, and withheld again by the same criteria as for randomisation. LHRHa was continued if PSA did not decrease to <10.0 ng/ml or decreased by <50% of the baseline. Patients in the IAD arm and patients with metastases were examined every 12 weeks. Patients in the CAD arm and without any metastases were monitored every 24 weeks, but laboratory tests were assayed at 12-weekly intervals (Fig. 4). From the randomisation forwards, the treatment cycle (duration in weeks) was defined as time off treatment (TOFF) plus time on treatment (TON).

4.2.3 Treatment failure, progression, and death

Treatment failure (TF) was defined as withdrawal from the protocol for any reason. Criteria for TF and disease progression are listed in table 3. Any progression criterion encountered during TOFF was considered as a real progression if initiation of ADT failed to relieve the symptoms. After withdrawal, patients were treated according to the investigator's decision (e.g. MAB, chemotherapy etc.). Patients were followed up every 12 weeks until progression, thereafter, every 24 weeks until death. Time to treatment failure (TTF), progression, and death were calculated from the date of randomisation.

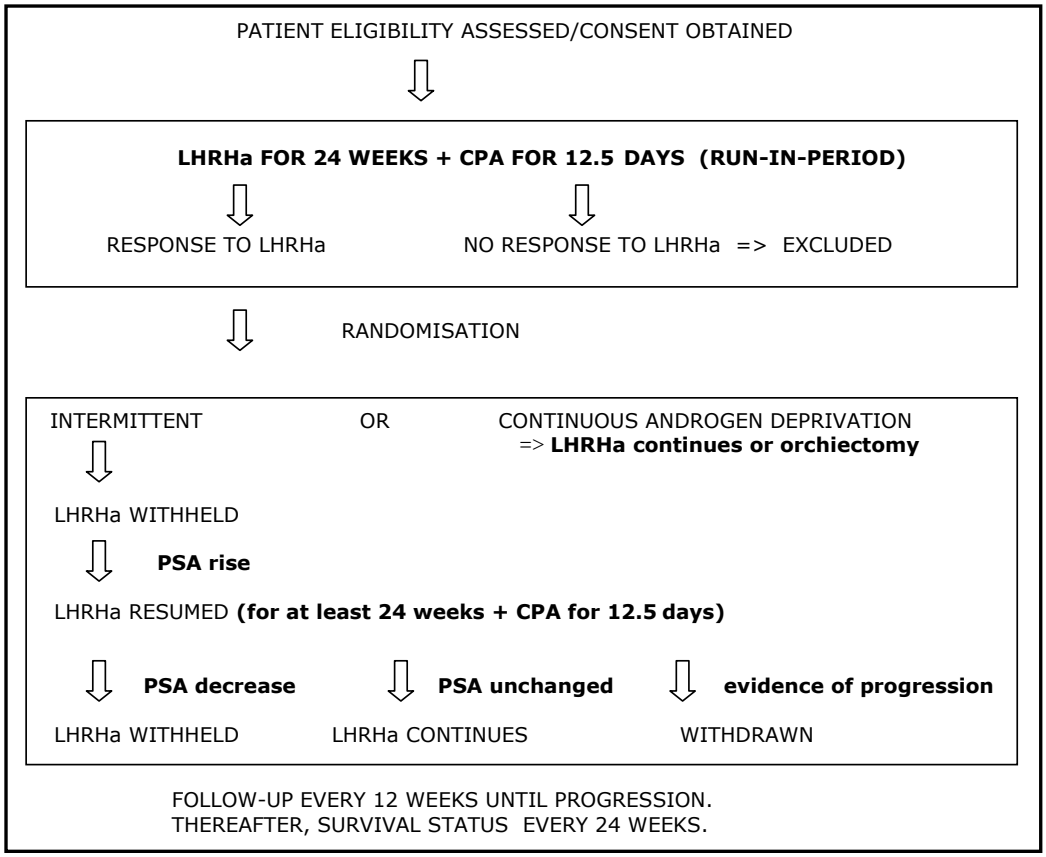

Figure 4. Trial plan. LHRHa=Luteinising hormone-releasing hormone analogue; CPA=Antiandrogen cyproterone acetate; PSA=Prostate-specific antigen

Table 3. Criteria for treatment failure and progression.

Treatment failure	death; adverse drug reaction requiring cessation of the randomised treatment; cancer progression; patient unwilling or unable to continue according to the protocol; patient refused the randomised treatment; administration of any additional systemic therapy or radiotherapy for prostate cancer; patient lost to follow-up; investigator's decision that it was in the patient's best interest to stop the randomised therapy
Progression	appearance of any new or worsening of existing bone metastases; increase in dimensions (by 25% or more) of any existing or appearance of any new extraskeletal metastases; ureteric obstruction either by primary tumour or pelvic nodal disease; lymphoedema of lower extremities due to pelvic nodal involvement; recurrent vesical obstruction, bleeding (macroscopic hematuria) or pain due to growth of primary tumor; PSA >100 ng/ml or PSA progressively elevated in two successive 12 weekly measurements during endocrine treatment (PSA should be >20 ng/ml for patients with baseline PSA ≥20 ng/ml, or PSA >visit 1 value with baseline PSA <20 ng/ml); death before evidence of objective progression

4.2.4 Quality of life analysis

QoL was monitored at each visit except at visit 2 by a formulated, validated, and self-administered 30-item Cleary questionnaire addressing ten domains: pain (questions 1−4), social functioning (5−6), emotional well-being (7−11), vitality (12−14), activity limitation (15), bed disability (16), overall health (17), physical capacity (18−23), sexual functioning (24−27), and sexuality (28−30) (appendix 2 and 3).[244] Patients continued to the last domain if they answered "yes" to the question 27. The sum of the numerical values of answers in each domain was recorded. In the statistical analysis, answers for questions 8, 10, 13, and 27 were renumbered in reverse. In summary, lower scores indicated better health in the domains of pain, activity limitation, bed disability, physical capacity, and sexuality. Higher scores indicated a favourable outcome in the domains of social functioning, emotional well-being, vitality, overall health, and sexual functioning.

4.2.5 PSPA-score

In addition to the QoL questionnaire, patient well-being was assessed by the PSPA-score, which represents the sum of the WHO performance status score, cancer-related pain score, and analgesics use score (appendix 4). PSPA and QoL questionnaire scores, PSA, and serum testosterone were analysed and summarised at the end of each TOFF and TON in the IAD arm and at approximately the same time point in the CAD arm. The approximate time point was defined by calculating the mean durations of previous cycles and the mean duration of the present TOFF or cycle. Patients in the CAD arm were selected by taking into account the visit closest to this point.

4.2.6 Adverse drug reactions (ADR), adverse events (AEV), and serious adverse events (SAE)

Any ADR, AEV, or SAE were inquired about at each visit, monitored, and summarised by the COSTART preferred term (PT; e.g. fracture) and primary body system (system of organ classes, SOC), according to the Medical Dictionary for Regulatory Activities (MedDRA).[296] The following SOCs were included: cardiac; vascular; metabolism and nutrition; musculoskeletal and connective tissue disorders; injury, poisoning, and procedural complications. A description of any event, the intensity, duration, any action, and outcome were recorded, and the relationship to the trial treatment were evaluated. Any ADR was also inquired 28 days after cessation of the trial treatment (treatment failure) or after 84 days for patients in the CAD arm with 10.8 mg depot.

4.2.7 Statistical analysis

The study was originally designed to enrol patients with metastatic PC. In conjunction with the widened inclusion criteria and with this more heterogeneous patient population, fewer events were expected to occur in the follow-up time previously specified as 36 months. Thus, the primary analysis was meant to be completed 14 months later, specified as 50 months. Median time to progression (primary objective) was estimated as 20.5 months, with a total of 600 patients (300:300) required to detect a hazard ratio of 1.345 with 90% power for CAD vs IAD. In comparing the patient characteristics between the treatment arms, Student`s t-test, the median test or chi-square ($\chi 2$) test were used. PFS, OS, PCS, and TFS were analysed using a univariate unadjusted Cox model; these were graphically displayed by the Kaplan-Meier method. Hazard ratios were estimated together with the associated 95% confidence interval and *p*-value. Differences in means of the QoL questionnaire were assessed by the Mann-Whitney U-test (MWU), the 0.5 standard deviation (SD) rule,[297] and repeated measures analysis of variance. PSPA-scores were analysed by using summary statistics only, differences in prevalences of ADRs and (S)AEs by the Chi-square test ($\chi 2$). All statistical tests were two-sided at a 5% significance level.

5 Results

Between May 1997 and February 2003, 852 patients were prospectively enrolled in 27 clinics to receive ADT. After the run-in period, 298 (35%) failed to meet the randomisation criteria and were excluded (group A). Of these, 259 (87%) did not meet the randomisation criteria, showed disease progression, or died. The remaining 554 subjects (65%) were randomised (group B): 274 (49.5%) to the IAD and 280 (50.5%) to the CAD arm. No patient with recurrent PC after prostatectomy or radiotherapy was enrolled.

5.1 COMPARISON BETWEEN PATIENTS ELIGIBLE AND NOT ELIGIBLE FOR RANDOMISATION

The characteristics of the non-randomised (group A) and randomised patients (group B) are presented in table 4.

Table 4. Patient characteristics at entry in non-randomised (A) and randomised (B) patient groups.

		Non-randomised (group A) n=298, (35%)	**Randomised (group B) n=554, (65%)**	**Total n=852, (100%)**	***p***
Age	Mean (range)	69.9 (46-90)	71.5 (47-94)	70.9 (46-94)	
	Median	70	72	71	0.007**
T-category	T1-2	23 (8%)	67 (12)	90 (10)	
	T3	162 (54)	354 (64)	516 (61)	<0.001*
	T4	113 (38)	133 (24)	246 (29)	
M-Category	M0	55 (18)	277 (50)	332 (39)	<0.001*
	M1	243 (82)	277 (50)	520 (61)	
	Hot spots ≤5	67 (28)	163 (59)		<0.001*
	Hot spots >5	176 (72)	114 (41)		
WHO grade	I	21 (7)	75 (14)	96 (11)	
	II	159 (53)	339 (61)	498 (58)	<0.001*
	III	117 (39)	140 (25)	257 (30)	
	X	1 (<1)	0 (0)	1 (<1)	
PSA (ng/ml)	Mean (range)	820.0 (0.9-12000.0)	151.5 (4.4-5123.0)		
	Median	261.3	67.6		<0.001**
	(n)	(297)	(554)		
ALP (IU/l)	Mean (range)	812 (72-9518)	277 (73-4341)		
	Median	303	173		<0.001**
	(n)	(291)	(545)		
Testosterone (nmol/l)	Mean (range)	14.1 (1.0-38.7)	15.1 (0.7-41.7)		
	Median	13.5	14.5		0.033**
	(n)	(279)	(528)		

*χ^2-test ; **t-test; T=tumour stage (local advancement); M=metastatic status; WHO=World Health Organisation; PSA=prostate-specific antigen; ALP=alkaline phosphatase.

The mean and median age of the enrolled patients was 71 years (range from 46 to 94 years), with 60% of patients 70 years or older. PSA ranged between 0.9 and 12000 ng/ml at entry. Only 4% of patients had PSA <20.0 ng/ml, 31% between 20.0–60.0 ng/ml, and 65% >60.0 ng/ml. ALP ranged from 72 to 9518 U/l, serum testosterone from 0.7 to 41.7 nmol/l. Sixty-

one percent of the patients had T3 and 29% T4 tumors. According to the WHO classification, 58% had intermediate, 30% poorly, and 11% well differentiated cancer. Sixty-one percent of patients had a metastatic disease. Mean and median PSA, mean and median ALP, proportion of T4 tumors, proportion of poorly differentiated cancers, proportion of metastatic disease, and the number of skeletal hot spots were significantly higher in the group A than group B (Table 5). Mean and median serum testosterone levels were slightly lower in the group A at entry. The value of the baseline testosterone was not significant in the logistic regression multivariate analysis (p=0.180).

Table 5. PSA, ALP, T-category, M-category and hot spots in logistic regression (multivariate) analysis.

	B	*p*	OR	95% CI
PSA	-0.001	<0.001	0.999	0.998–0.999
ALP	-0.000	0.007	1.000	0.999–1.000
T-category(T1-2)		0.013		
T-category(T3)	-0.424	0.141	0.654	0.372–1.151
T-category(T4)	-0.820	0.007	0.441	0.243–0.799
M-category	-0.696	0.001	0.499	0.329–0.755
Hot spots	-0.456	0.039	0.634	0.411–0.977
Constant	2.280	<0.001	9.775	

B=regression coefficient; OR=odds of risk ratio; CI=confidence interval. Testosterone dropped out because in previous logistic regression analysis p-value was non-significant (p=0.180).

5.2 COMPARISON OF INTERMITTENT AND CONTINUOUS ANDROGEN DEPRIVATION

Of the enrolled 852 patients, 274 were randomised to receive IAD (49.5%) and 280 CAD (50.5%). One patient refused to be entered to the randomised IAD. Median follow-up time from randomisation was 65 months, with a maximum of 11.6 years; 53% of the patients were followed up for longer than 5 years, with no patient lost to follow-up. 110 patients (19.9%) continued >5 years in the trial before TF: 52 (19.0%) in the IAD and 58 (20.7%) in the CAD arm (p=0.50).

5.2.1 Patient characteristics

The characteristics of the IAD and CAD patients are presented in table 6. Mean age was 71.5 years, with no difference in the distributions of patients in the different age groups (<50, 50–59, 60–69, 70–79, ≥80 years). Treatment arms were comparable with respect to advancement of PC, differentiation grade, PSA, ALP, testosterone, performance status, concurrent diseases, PSPA-score, and QoL. At entry, 40% and 38% of patients in the IAD and CAD arm had PSA <20 ng/ml, 60% and 62% had PSA ≥20 ng/ml (p=0.64). Of the randomised patients, 79% achieved PSA nadir ≤4 ng/ml.

Table 6. Patient characteristics at entry and at randomisation in intermittent and continuous treatment arms.

		Intermittent n=274, (%)	**Continuous n=280, (%)**	**Total n=554, (%)**	***p***
Age	<70 years	102 (37.2)	102 (36.4)	204 (36.8)	
	≥70 years	172 (62.8)	178 (63.6)	350 (63.2)	0.85*
				mean 71.5 yr	
M-Category	M0	140 (51.1)	137 (48.9)	277 (50.0)	0.61*
	M1	134 (48.9)	143 (51.1)	277 (50.0)	
TM-Category	T1-2M0	7 (2.5)	12 (4.3)	19 (3.4)	0.22*
	T1-2M1	20 (7.3)	28 (10.0)	48 (8.7)	0.31
	T3M0	101 (36.9)	99 (35.3)	200 (36.1)	0.71
	T3M1	81 (29.6)	73 (26.1)	154 (27.8)	0.36
	T4M0	32 (11.7)	26 (9.3)	58 (10.5)	0.43
	T4M1	33 (12.0)	42 (15.0)	75 (13.5)	0.37
WHO Grade	GI	32 (11.7)	43 (15.4)	75 (13.5)	
	GII	175 (63.9)	164 (58.6)	339 (61.2)	
	GIII	67 (24.5)	73 (26.1)	140 (25.3)	0.34*
Gleason†	≤6	13 (5.3)	15 (6.1)	28 (5.7)	
	3+4	32 (13.1)	33 (13.4)	65 (13.2)	
	4+3	57 (23.4)	55 (22.3)	112 (22.8)	0.98*
	8-10	142 (58.2)	144 (58.3)	286 (58.2)	
	Total	244 (100.0)	247 (100.0)	491 (100.0)	
PSA at baseline (ng/ml)	mean (SD)	116.0 (173.4)	186.3 (454.4)	151.5 (n=554)	
	median	64.0	70.3	67.6	0.31**
	95% CI	95.29-136.61	132.75-239.85		
PSA at 6 mos (randomisation) (ng/ml)	mean (SD)	2.37 (2.43)	2.45 (2.48)		
	median	1.40	1.60		0.71***
	95% CI	2.08-2.66	2.16-2.74		
Testosterone at baseline (nmol/l)	mean (SD)	15.25 (5.87)	14.94 (6.30)	15.1 (n=528)	
	median	14.58	14.30	14.5	0.56***
	95% CI	14.53-15.97 (n=261)	14.18-15.70 (n=267)		
Testosterone at 6 mos (nmol/l)	mean (SD)	0.84 (0.44)	1.05 (2.18)		
	median	0.80	0.78		
	95% CI	0.79-0.90 (n=261)	0.79-1.32 (n=267)		0.27**
ALP (IU/l)	mean (SD)	256.1 (354.9)	297.9 (443.1)	277 (n=545)	
	median	176.5	171.0	173	0.22***
	95% CI	213.38-298.90 (n=268)	245.38-350.39 (n=277)		

*χ^2-test ; **median test; ***t-test; †defined by two pathologists for 491 patients; M=metastatic status; T=tumour stage (local advancement); WHO=World Health Organisation; PSA=prostate-specific antigen; SD=standard deviation; CI=confidence interval; ALP=alkaline phosphatase.

5.2.2 Intermittent androgen deprivation treatment

In the IAD arm, the median number of cycles was 3 (0–14) with one patient reaching the 14th cycle. TOFF duration decreased from cycle to cycle, from a mean of 33.5 weeks in the 1st cycle to 14.7 weeks in the 10th cycle, with the longest duration being 312.0 weeks in the 1st cycle (Fig. 5). Plasma testosterone showed a recovery at the end of each TOFF, but without reaching the level at the end of the previous TOFF. Thus, mean and median testosterone at the end of TOFFs decreased from cycle to cycle. At entry, 81.2% of patients in the IAD arm

had testosterone ≥10 nmol/l, decreasing to 47.4% at the end of the 10th TOFF (Fig. 6). During the 12 first TONs, 81.6–100% of IAD patients reached a serum testosterone level <1.5 nmol/l, for the rest of them, testosterone levels were between 1.5 and <7 nmol/l.

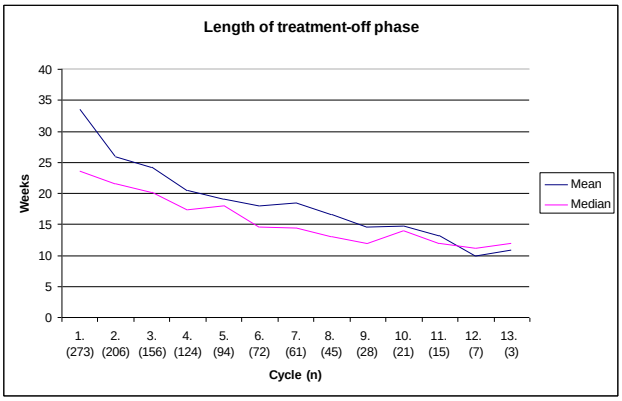

Figure 5. Mean and median duration of the treatment-off phase of each cycle in the intermittent arm.

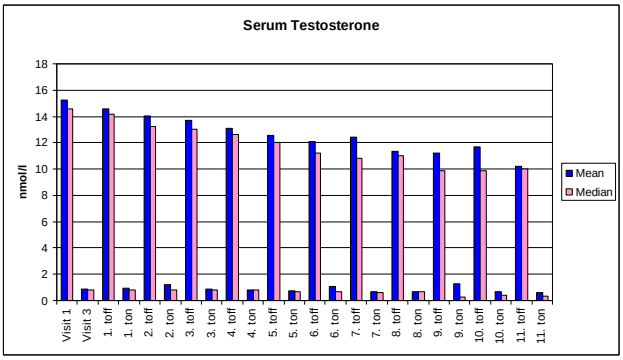

Figure 6. Mean and median testosterone at the end of each treatment-off and treatment-on phase in the intermittent arm; toff=treatment-off phase; ton=treatment-on phase.

5.2.3 Progression-free, overall, prostate cancer-specific, and treatment failure survival

During the trial, 492 patients (88.8%) were withdrawn. For 372, this was due to death or disease progression: 177 (64.6%) in the IAD and 195 (69.6%) in the CAD arm (p=0.76). At the end of the study, 392 patients of 554 (71%) had died: 186 (68%) in the IAD and 206 (74%) in the CAD arm (p=0.12). There were 248 (45%) PC deaths (63% of all deaths): 117 (43%) in the IAD and 131 (47%) in the CAD arm (p=0.29). Among patients with endpoints, median times from randomisation to progression in the IAD and CAD arms were 34.5 and 30.2 months, to death (all-cause) 45.2 and 45.7 months, to PC death 45.2 and 44.3 months, and to TF 29.9 and 30.5 months. No statistically significant differences were apparent in PFS, OS, PCS, or TFS between the treatment arms (Fig. 7), but the risk analysis showed a hazard ratio of 1.08–1.17 for CAD (Table 7). PSA level at randomisation (PSA <1.0; 1.0–4.0; >4.0 ng/ml) was associated with PFS (p=0.002), PCS (p=0.006), and TFS (p<0.001), but not with OS (p=0.290) in the whole study population (Fig. 8). The differentiation grade according to the Gleason scores also had an impact on PFS, OS, PCS, and TFS (p<0.001) (Fig. 9).

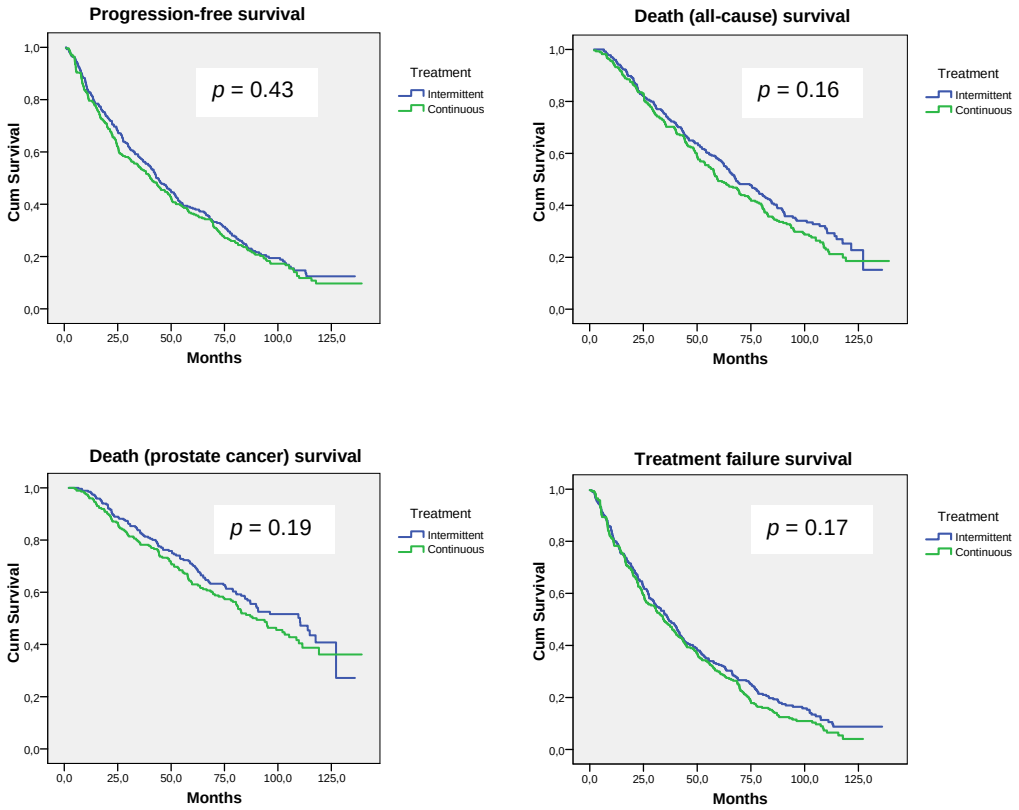

Figure 7. Kaplan-Meier curves for progression-free, overall, prostate cancer-specific, and treatment failure survival in intermittent and continuous treatment arms; *p*-values for log-rank tests.

Table 7. Hazard ratios and 95% confidence intervals (univariate unadjusted cox regression model) between intermittent and continuous treatment arms.

	HR	**95% CI**	***p*-value**
Progression			
IAD	**1**		
CAD	**1.08**	0.90-1.29	0.43
Death (all-cause)			
IAD	**1**		
CAD	**1.15**	0.94-1.40	0.17
Prostate cancer death			
IAD	**1**		
CAD	**1.17**	0.91-1.51	0.21
Treatment failure			
IAD	**1**		
CAD	**1.13**	0.95-1.35	0.17

HR=hazard ratio; CI=confidence interval; IAD=intermittent treatment arm; CAD=continuous treatment arm.

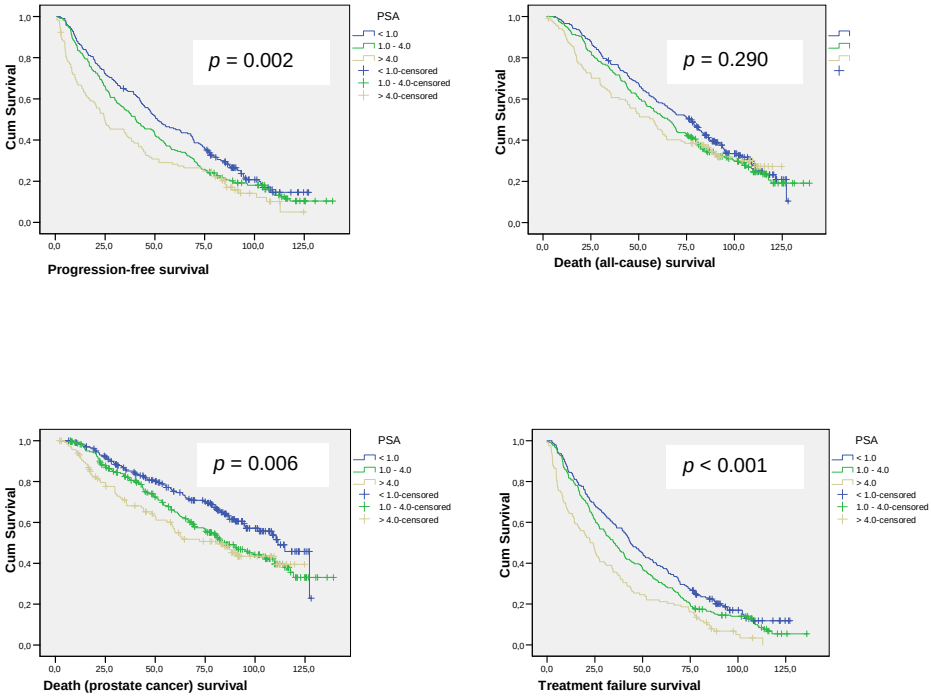

Figure 8. Kaplan-Meier curves for progression-free, overall, prostate cancer-specific, and treatment failure survival by prostate-specific antigen (PSA) at randomisation in the trial population. PSA <1.0 (n=206), 1.0–4.0 (n=229), >4.0 ng/ml (n=118); *p*-values for log-rank tests. One patient refused the intermittent trial therapy (n=553).

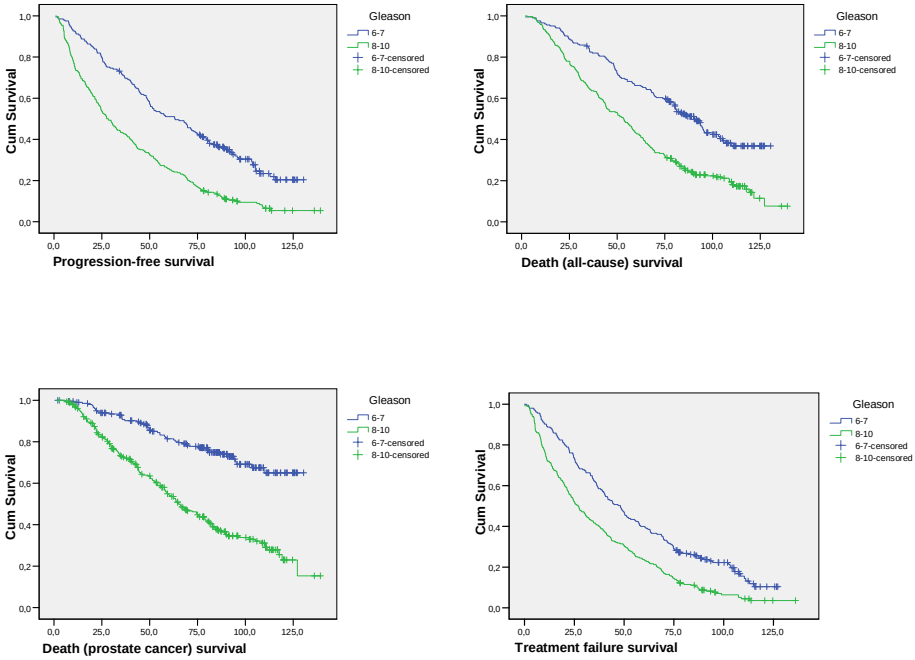

Figure 9. Kaplan-Meier curves for progression-free, overall, prostate cancer-specific, and treatment failure survival by differentiation grade of Gleason scores 6−7 (n=205) and 8−10 (n=286). The *p*-values are <0.001 (the log-rank test).

5.2.4 Quality of life, adverse events, adverse drug reactions, and PSPA-score

Treatment arms were comparable as regards QoL at entry and at randomisation (Mann-Whitney U-test, MWU). They were also balanced with respect to concurrent diseases that might predispose towards cardiac and vascular (CV) events or fractures. Eight patients in the IAD arm (2.9%) and 11 in the CAD arm (3.9%) used some form of bone-specific treatment during the trial (p=0.51). The response rates to the QoL questionnaire domains 1–9 were 86–92 % at entry and at randomisation, it was at lowest 73% and 69% in the IAD and CAD arm during the first five cycles.

According to MWU and 0.5 SD rule, the most-frequently detected significant differences in QoL between treatment arms were related to activity limitation, physical capacity, and sexual functioning, favouring IAD (Fig. 10). This was also confirmed by the repeated measures analysis of variance. A non-significant trend in favour of IAD was seen also in other domains, except sexuality. The response rate for the last domain (sexuality) was low. The proportion of respondents in the domain 9 (sexual functioning), who continued to the last domain 10 and reported any sexual activity during the past month, was 48.8% in the IAD and 40.1% in the CAD arm at entry, but decreased in both arms thereafter. In the IAD arm, the proportion of respondents was clearly higher at the end than in the beginning of each TOFF. In the CAD arm, the response rate was approximately 20%.

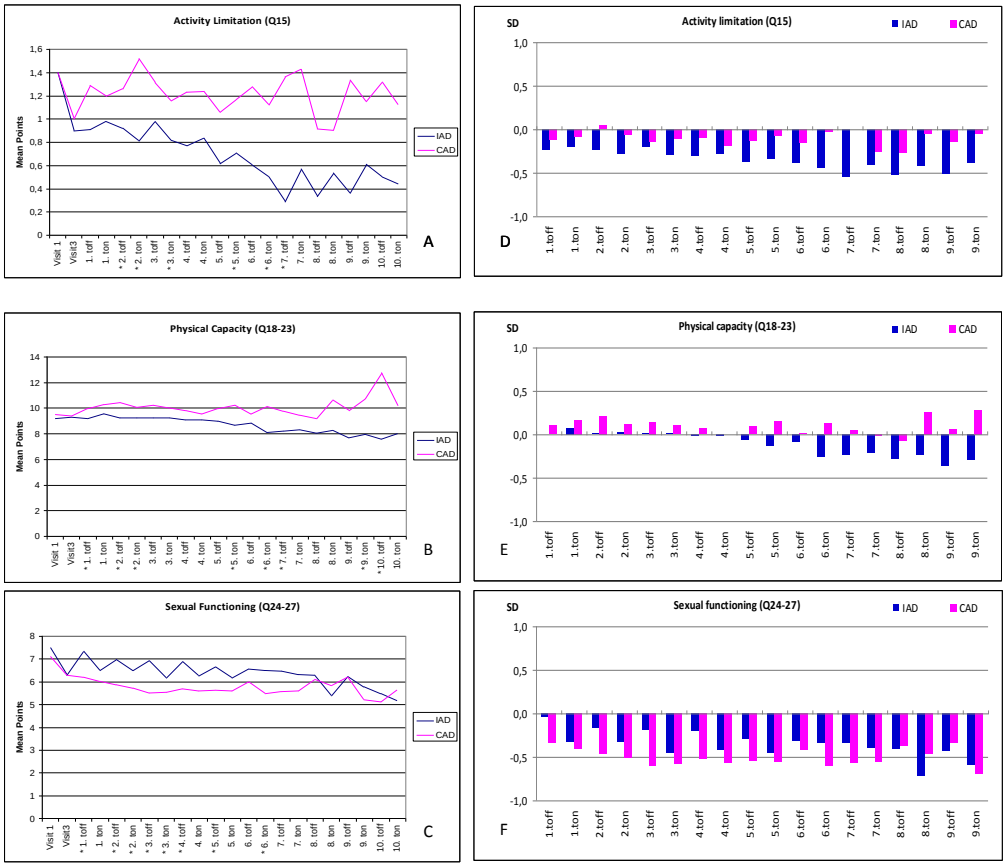

Figure 10. Differences in quality of life between treatment arms according to the Mann-Whitney U-test (A-C; *p<0.05) and the 0.5 standard deviation rule (D-F) in the domains of activity limitation, physical capacity, and sexual functioning. Lower scores indicate better health in activity limitation and physical capacity, higher scores in sexual functioning. SD=standard deviation; toff=treatment-off phase; ton=treatment-on phase.

The treatment arms did not differ from each other in the prevalence of adverse events. Cardiac and vascular (CV) events were the most prevalent AEVs, with 154 in the IAD and 162 in the CAD arm. Table 8. shows the number of patients suffering from any cardiovascular SAE or bone fracture, those withdrawn from the trial or who died because of SAE. In the final survival analysis, 78 patients of 554 (14.1%) died from any CV cause (20% of all 392 deaths): 35 in the IAD (12.8%) and 43 in the CAD arm (15.4%) (p=0.38).

Hot flushes or sweating during nighttime were the most commonly reported ADRs during the trial: 129 patients (47.1%) in the IAD and 141 (50.4%) in the CAD arm (p=0.44). Erectile dysfunction (ED) and depressed mood were reported more often in the IAD than CAD arm: 15.7 vs 7.9% (p=0.0042) and 2.2 vs 0% (p=0.038). Mean PSPA-scores at entry were 1.00 in the IAD and 1.01 in the CAD arm (p=0.94). No significant differences between treatment arms emerged during the trial, with the exception of the 6th TON (0.73 vs. 1.33, p=0.01), the 7th TOFF (0.82 vs. 1.44, p=0.02), and the 8th TON (0.84 vs. 1.56, p=0.04), in favour of IAD.

Table 8. Number of patients experiencing serious adverse events or adverse drug reactions, withdrawing from the trial, or dying because of an adverse event.

Patients	IAD (n=274) n (%)	CAD (n=280) n (%)	Total (n=554) n(%)	*p*
with cardiovascular SAEs	87 (31.8)	95 (33.9)	182 (32.9)	0.59
with bone fractures	19 (6.9)	15 (5.4)	34 (6.1)	0.44
withdrawn because of any SAE or ADR	57 (20.8)	62 (22.1)	119 (21.5)	0.70
withdrawn because of cardiovascular SAE	25 (9.1)	29 (10.4)	54 (9.7)	0.62
died because of any SAE	45 (16.4)	50 (17.9)	95 (17.1)	0.65
died because of cardiovascular SAE	21 (7.7)	24 (8.6)	45 (8.1)	0.70

SAE=serious adverse event; ADR=adverse drug reaction; IAD=intermittent treatment arm; CAD=continuous treatment arm.

5.3 COMPARISON OF INTERMITTENT AND CONTINUOUS ANDROGEN DEPRIVATION, AND QUALITY OF LIFE BETWEEN PATIENTS WITHOUT (M0) AND WITH METASTASIS (M1)

5.3.1 Patient characteristics

IAD and CAD treatment arms were comparable with each other in the subgroups of patients with M0 and M1 disease (Table 9).

5.3.2 Intermittent androgen deprivation treatment

Mean TOFF duration in the IAD arm decreased almost linearly from cycle to cycle in M0 and M1 groups from 37.6 and 29.1 weeks in the 1st cycle to 10.4 and 9.1 weeks in the 12th cycle (Fig. 11).

5.3.3 Progression-free, overall, cancer-specific, and treatment failure survival

Of our 554 patients, 492 (88.8%) had to withdraw from the trial (TF), 231 from the M0 and 261 from the M1 group. Cumulative percentages of TF in the M0 vs M1 group were first year: 9.0 vs 31.8%; second year: 19.8 vs 53.8%; and third year: 36.0 vs 63.9% (p<0.001). The main reasons for TF were either death or disease progression in 372 patients: 166 (59.9%) in the M0, and 206 (74.4%) in the M1 group (p=0.004). At the end of the study, 392 patients (71%) had died: 161 (58%) in the M0, and 231 (83%) in the M1 group (p<0.001), with 82 PC deaths (30%) in the M0, and 166 (60%) in the M1 (p<0.001). Mean and median times from randomisation to progression, death (overall), PC death, and TF are shown in table 10. Differences in PFS, OS, PCS, and TFS between IAD and CAD and between the subgroups of M0 and M1 are described in Figure 12. Risk analysis showed significant differences between the M0 and M1 subgroup but not between IAD and CAD, although a minor advantage was seen from IAD (Table 11).

Table 9. Patient characteristics at entry and at randomisation in intermittent and continuous treatment arms in the subgroups of patients without and with metastasis.

	M0 - IAD n=140 (25.3%)	**M0 - CAD n=137 (24.7)**	***p* (M0)**	**M1 - IAD n=134 (24.2)**	**M1 - CAD n=143 (25.8)**	***p* (M1)**
Age						
< 70 years	41 (29.3)	51 (37.2)		61 (45.5)	51 (35.7)	
≥ 70 years	99 (70.7)	86 (62.8)	0.162*	73 (54.5)	92 (64.3)	0.095*
mean	72.9	72.1		70.6	72.4	
TM-Category						
T1-2	7 (5.0)	12 (8.7)		20 (14.9)	28 (19.6)	
T3	101 (72.1)	99 (72.3)	0.382*	81 (60.5)	73 (51.0)	0.281*
T4	32 (22.9)	26 (19.0)		33 (24.6)	42 (29.4)	
WHO Grade						
GI	17 (12.1)	23 (16.8)		15 (11.2)	20 (14.0)	
GII	95 (67.9)	86 (62.8)	0.518*	80 (59.7)	78 (54.5)	0.645*
GIII	28 (20.0)	28 (20.4)		39 (29.1)	45 (31.5)	
Gleason†						
≤6	10 (8.1)	9 (7.5)		3 (2.5)	6 (4.7)	
3+4	20 (16.1)	21 (17.5)		12 (10.0)	12 (9.5)	
4+3	35 (28.2)	33 (27.5)	0.991*	22 (18.3)	22 (17.3)	0.826*
8-10	59 (47.6)	57 (47.5)		83 (69.2)	87 (68.5)	
	(n=124)	(n=120)		(n=120)	(n=127)	
PSA at baseline (ng/ml)						
mean (SD)	67.4 (58.7)	74.0 (58.2)		166.7 (230.3)	293.3 (615.3)	
median	52.2	54	0.674**	82.4	106.0	0.104**
95% CI	57.5-77.2	64.1-83.8		127.37-206.1	192.2-395.6	
PSA at 6 mos (ng/ml)						
mean (SD)	2.21 (2.25)	2.32 (2.45)		2.53 (2.61)	2.55 (2.50)	
median	1.3	1.51	0.697***	1.45	1.7	0.953***
95% CI	1.83-2.59	1.91-2.74		2.09-2.98	2.14-2.97	
Testosterone at baseline (nmol/l)						
mean (SD)	15.38 (5.95)	16.09 (6.14)		15.11 (5.81)	13.80 (6.28)	
median	14.85	15.2	0.342***	14.0	13.00	0.081***
95% CI	14.37-16.40	15.03-17.14		14.09-16.13	12.73-14.87	
	(n=134)	(n=133)		(n=127)	(n=134)	
Testosterone at 6 mos (nmol/l)						
mean (SD)	0.84 (0.56)	0.96 (1.55)		0.89 (0.44)	1.18 (2.69)	
median	0.80	0.80	0.843**	0.80	0.76	0.171**
95% CI	0.74-0.93	0.70-1.23		0.81-0.96	0.72-1.64	
	(n=133)	(n=132)		(n=128)	(n=135)	
ALP (IU/l)						
mean (SD)	162.3 (46.7)	163.7 (48.0)		352.8 (485.6)	425.5 (590.3)	
median	151.0	159.0	0.820***	205.5	209.5	0.269***
95% CI	154.4-170.3	155.5-171.8		269.2-436.4	327.6-523.4	
	(n=136)	(n=135)		(n=132)	(n=142)	

*χ^2-test ; **median test; ***t-test; †defined by two pathologists for 491 patients; T=tumour stage (local advancement); WHO=World Health Organisation; PSA=prostate-specific antigen; SD=standard deviation; CI=confidence interval; ALP=alkaline phosphatase; IAD=intermittent treatment arm; CAD=continuous treatment arm; M0=non-metastatic patient subgroup; M1=metastatic patient subgroup.

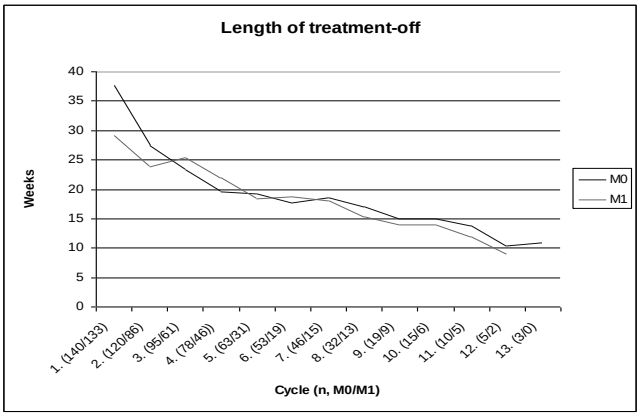

Figure 11. Mean duration of the treatment-off phase and the number of patients without (M0) and with (M1) metastasis in the intermittent arm.

Table 10. Time (months) to progression, death (all-cause), prostate cancer death, and treatment failure in patients with non-metastatic (M0) and metastatic (M1) prostate cancer.

Patient groups	**Time to progression**	**Time to death**	**Time to prostate cancer death**	**Time to treatment failure**
(n)	Mean ±SD (range)/ median (n)	Mean ±SD (range)/ median (n)	Mean ±SD (range)/ median (n)	Mean ±SD (range)/ median (n)
M0 (277)	49.4 ±28.8 (1.2-117.8)/ 46.8 (208)	57.1±29.9 (2.0-121.7)/ 57.6 (161)	57.5±29.9 (7.9-113.9)/ 59.5 (82)	45.9±27.7 (1.2-117.8)/ 41.9 (231)
M1 (277)	31.0±27.5 (0.7-115.7)/ 21.4 (253)	44.6±27.5 (2.9-127.2)/ 40.3 (231)	44.3±27.5 (4.7-127.2)/ 40.7 (166)	29.1±26.4 (0.0-115.7)/ 20.0 (261)
M0 – IAD (140)	49.2±28.4 (1.2-113.3)/ 46.6 (103)	57.6±30.2 (6.6-121.7)/ 62.2 (76)	61.4±29.1 (14.5-113.9)/ 63.9 (37)	45.4±28.3 (1.2-113.3)/ 40.4 (113)
M0 – CAD (137)	49.6±29.2 (2.0-117.8)/ 46.9 (105)	56.8±29.7 (2.0-117.8)/ 53.7 (85)	54.3±30.4 (7.9-111.4)/ 53.6 (45)	46.4±27.2 (2.0-117.8)/ 43.6 (118)
M1 –IAD (134)	32.0±27.0 (0.9-112.9)/ 23.2 (122)	45.1±27.4 (6.6-127.2)/ 42.0 (110)	45.0±27.8 (6.6-127.2)/ 40.7 (80)	29.3±26.5 (0.0-112.9)/ 20.7 (124)
M1 – CAD (143)	30.1±28.0 (0.7-115.7)/ 20.0 (131)	44.1±27.8 (2.9-119.2)/ 40.1 (121)	43.7±27.4 (4.7-119.2)/ 41.9 (86)	29.0±26.5 (0.0-115.7)/ 19.9 (137)

IAD=intermittent androgen deprivation; CAD=continuous androgen deprivation; SD=standard deviation.

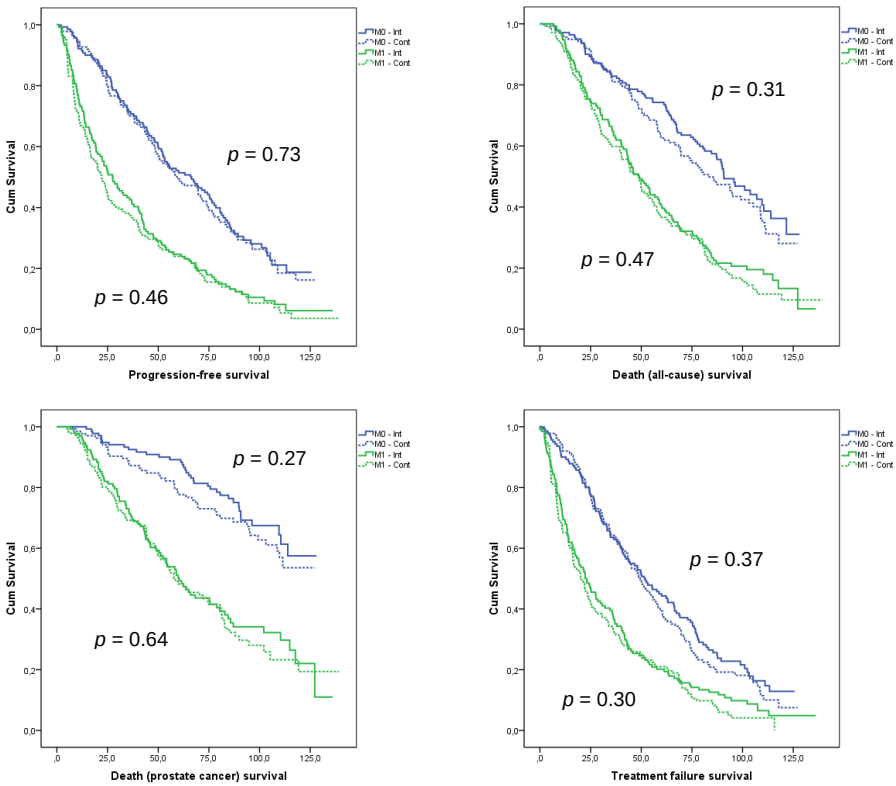

Figure 12. Kaplan-Meier curves for progression-free, overall, prostate cancer-specific, and treatment failure survival in patients with non-metastatic (M0) and metastatic (M1) prostate cancer in intermittent (Int) and continuous (Cont) treatment arms.; *p*-values for log-rank tests.

Table 11. Risk analysis with a univariate unadjusted Cox regression model.

	HR	95% CI	*p*-value*
Progression			
M0 -IAD (n=103)	**1**		
-CAD (105)	**1.05**	0.80-1.37	0.74
M1 -IAD (122)	**2.05**	1.58-2.67	<0.001
-CAD (131)	**2.26**	1.75-2.93	<0.001
Death (all-cause)			
M0 -IAD (76)	**1**		
-CAD (85)	**1.18**	0.87-1.61	0.29
M1 -IAD (110)	**2.25**	1.68-3.01	<0.001
-CAD (121)	**2.50**	1.87-3.33	<0.001
Prostate cancer death			
M0 -IAD (37)	**1**		
-CAD (45)	**1.29**	0.84-1.99	0.25
M1 -IAD (80)	**3.34**	2.26-4.94	<0.001
-CAD (86)	**3.63**	2.46-5.34	<0.001
Treatment failure			
M0 -IAD (113)	**1**		
-CAD (118)	**1.10**	0.86-1.44	0.43
M1 -IAD (124)	**1.88**	1.46-2.43	<0.001
-CAD (137)	**2.17**	1.69-2.79	<0.001

HR=hazard ratio; CI=confidence interval; M0=non-metastatic disease; M1=metastatic disease; IAD=intermittent treatment arm; CAD=continuous treatment arm; *p-values for comparison with a reference of M0-IAD.

5.3.4 Quality of life, adverse events, and adverse drug reactions

Response rates for the QoL questionnaire domains 1–9 were 84–92 % at entry and at randomisation in both subgroups, 24–48% of patients reported some type of sexual activity (domain 10) at entry. According to MWU, QoL was significantly worse among M1 than M0 patients at entry in all other domains, except overall health (p=0.08), sexual functioning (p=0.70), and sexuality (p=0.61). The differences disappeared during the trial. Sexual functioning was significantly worse in the CAD than IAD arm among M1 patients at entry (p=0.03). According to the 0.5 SD rule, ADT (IAD or CAD) had a beneficial effect on QoL in the M1 group in the domains of pain, activity limitation, and social functioning; and in both groups in emotional well-being (Fig. 13). IAD offered some extra benefit in terms of activity limitation and social functioning. Similarly, a mild beneficial effect of ADT was evident on bed disability in M1 patients, without any clear difference between IAD and CAD. A deleterious effect of ADT on QoL occurred in physical capacity in the M0 group, especially with CAD; and in sexual functioning in both groups, with IAD offering some recovery during TOFFs (Fig. 14).

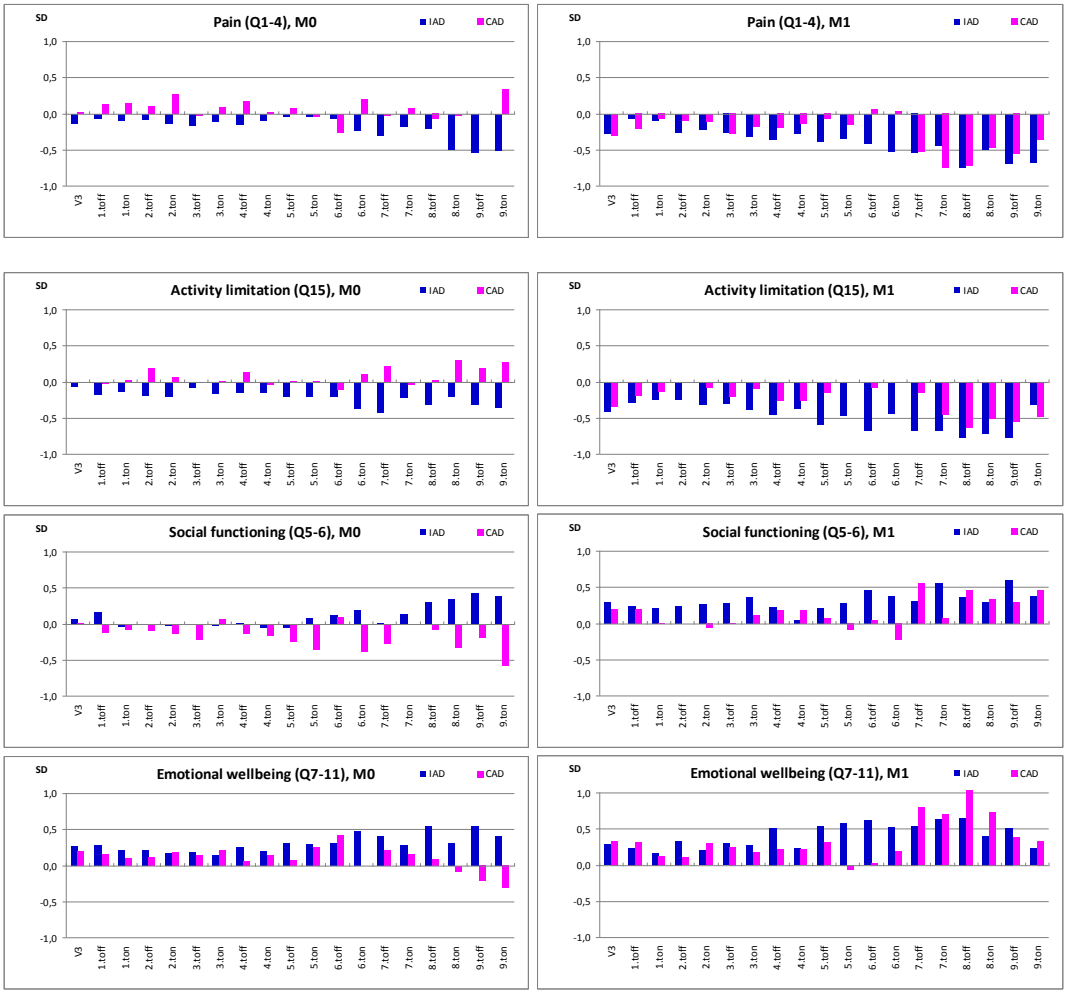

Figure 13. Changes in quality of life in the groups of locally advanced (M0) and metastatic (M1) prostate cancer patients on intermittent (IAD) or continuous (CAD) androgen deprivation according to the 0.5 standard deviation (SD) rule. Lower scores indicate better health in the domains of pain and activity limitation; higher scores indicate better health in social functioning and emotional well-being.

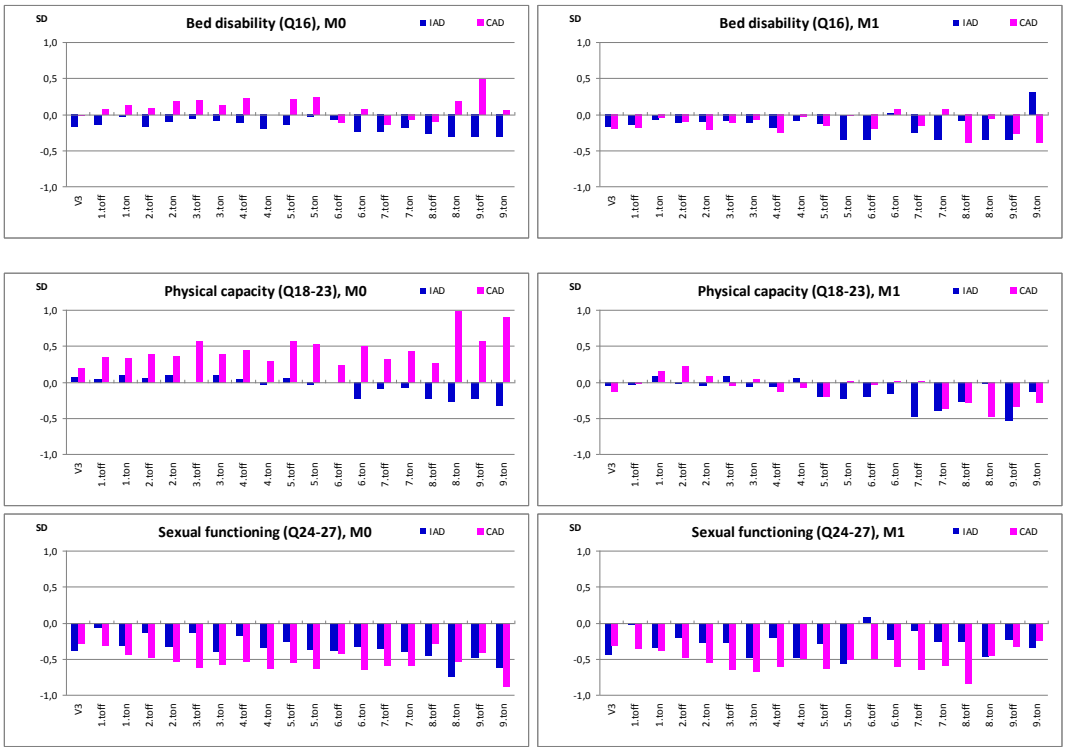

Figure 14. Changes in quality of life in the groups of locally advanced (M0) and metastatic (M1) prostate cancer patients on intermittent (IAD) or continuous (CAD) androgen deprivation according to the 0.5 standard deviation (SD) rule. Lower scores indicate better health in the domains of bed disability and physical capacity; higher scores indicate better health in sexual functioning.

In the M0 and M1 groups, 317 and 236 SAEs were recorded during the trial, overall, with CV events and pneumonia being the most prevalent. As a whole, 101 (36.5%) in the M0 group and 81 (29.2%) in the M1 had CV AEVs (p=0.07). Of the 78 patients dying from any CV cause (20% of all 392 deaths), 40 died in the M0 (14.4%) and 38 in the M1 group (13.7%) (p=0.81). Bone fractures occurred in 16 (5.8%) and 18 (6.5%) patients (p=0.72). Hot flushes or night sweats in 152 (54.9%) vs 120 patients (43.3%) (p=0.007) and erectile dysfunction (ED) in 39 (14.1%) vs 26 patients (9.4%) (p=0.086) were reported more often in the M0 group. No statistically significant difference emerged in the number of patients reporting other ADRs, such as depression, gynaecomastia, decreased libido, or fatigue. As a consequence, 119 patients had to withdraw from the trial because of SAE or ADR, 68 (24.5%) from the M0 and 51 (18.4%) from the M1 group (p=0.08).

6 Discussion

6.1 STUDY SAMPLE AND DESIGN

6.1.1 Study sample

The FinnProstate Study VII (FPVII) was planned to be conducted as a randomised multicenter clinical trial including patients with metastatic PC (M1). Based on the previous trial (Zeneca study 1166301/1509), the median time to progression for patients with metastatic PC (PSA >60 ng/ml), treated with continuous goserelin and who did not progress during the first 6 months, was 14.5 months. The primary analysis was estimated to be completed 36 months after the cessation of recruitment. In order to detect a difference of five months in the median time to progression with 90% power, it was calculated that a total of 600 patients (300:300) would be required. However, because of the slow recruitment rate, the inclusion criteria were widened in June 1998 to include patients with locally advanced or recurrent PC. In the Zeneca study 176334/0307, the median time to progression for patients with PSA >20 ng/ml and receiving continuous ADT was 35 months. With this more heterogeneous patient population, fewer events were expected to occur in the follow-up time previously specified as 36 months. In order to estimate the likely event rate in this new population, the median time to progression was calculated to be 20.5 months. Thus, to detect a hazard ratio of 1.345 with 90% power with 600 patients, the primary analysis was estimated to be completed 50 months after completion of recruitment (after a minimum follow-up of 50 months), with a difference of seven months in the median time to progression being capable of being detected. Thus, the widened inclusion criteria meant a more heterogeneous patient population and a longer follow-up than expected, although no patient with biochemical PSA relapse after curative intended treatment was enrolled. Ultimately, 852 patients were enrolled and 554 patients could be randomised, only slightly less than calculated for the desired statistical power. It is outstanding that none of our patients was lost to follow-up during the trial.

Many of the previous pilot and phase II trials had more heterogeneous patient populations with recurrent, localised, locally advanced, and metastatic PC, which complicates the comparison with previous trials and results. However, some trials included only patients with locally advanced and/or metastatic PC, making the patient population less heterogeneous.[3, 255, 266, 271, 277] Most of the phase III trials have included only patients with locally advanced and/or metastatic PC, as in the present study.[259, 292-295, 298]

The randomisation process succeeded well. Patients were evenly distributed and treatment arms were equivalent with each other. No stratification was done. For some unknown reason, PSA levels were somewhat higher at entry in the CAD arm and in the M1-CAD arm but no longer at the time of randomisation.

6.1.2 Study design

The concept of treating cancer with intermittent hormonal therapy arouse in the 1970s.[263] Planning of the FPVII trial was started in the early 1990s. By then, only a few trials in experimental animals and a couple of clinical pilot studies had been completed and no randomised trials had been published.

6.1.2.1 Treatment regimen

A well-documented LHRH analogue, goserelin acetate (Zoladex®, AstraZeneca), was chosen to be used for 24 weeks as induction treatment and during TONs. The steroidal antiandrogen, cyproterone acetate (CPA), was used only temporarily for 12.5 days in connection with the first LHRHa implant to minimise the flare reaction. CPA was chosen

because of its short half-life ($T_{½}$) which meant that it quickly established a steady state. In most of the other clinical trials, MAB was used during initial and later TONs. However, the benefit of MAB in comparison with surgical or chemical castration alone has not been proved.[197, 198] A few trials have used the LHRH analogue alone[256, 276] or antiandrogen monotherapy,[283, 295] mostly with recurrent PC after curative-intended teatment. In three trials, the use of AA with LHRHa was optional.[277, 281, 287, 288] In two of the randomised trials, only a short-term AA was used with an LHRHa to avoid flare reaction, as in this present study.[250, 261] Hence, the treatment regimen varied from study to study, complicating the comparison of trials with each other.

6.1.2.2 The initial treatment-on phase, the cut-offs for ADT withdrawal and resumption

The duration of the induction ADT is a matter of debate. There is controversy about the criteria for withdrawal and for reintroduction of therapy. The initial TON was chosen as 24 weeks, PSA cut-off for withdrawal of ADT <10 ng/ml or ≤50% of the baseline (when <20ng/ml), and for resumption >20.0 ng/ml or above baseline. However, most of the randomised patients, that is 79%, reached PSA level <4 ng/ml during the run-in period, which has been the cut-off level in many other trials.

In other trials, the duration of the initial TON has ranged from 3 to 12 months, although it has commonly been between 6 and 9 months. The most often used PSA cut-off for ADT withdrawal is 4 ng/ml and for resumption 10 to 20 ng/ml, depending on the baseline PSA and the nature of patient's PC (recurrent biochemical failure, previously untreated, localised, locally advanced, or metastatic). In some series, either biochemical failure or PSA velocity has been considered as the trigger point, whereas in others, clinical recurrence or recurrence of symptoms has been required prior to the reintroduction of ADT. When the present trial was started in 1997, there were no evidence based values for PSA cut-off levels or the duration of the induction ADT, especially with advanced PC and high baseline PSA levels. At that time, only a few phase 2 trials had been published, the first randomised study did not appear until 2002.[290] So, the cut-off levels of PSA and the duration of induction phase were only empirical.

Nevertheless, Gleave et al stated that androgen ablation should be continued until maximal castration-induced apoptosis and tumor regression had been induced, but halted before constitutive development of the androgen-independent phenotype.[164] Later, Grossfeld et al (2001) proposed that the first nadir PSA should be achieved within an average of 6 months,[278] whereas Albrecht et al (2003) stated it should occur within a median of 19 weeks.[266] Thus, the present treatment regimen of 24 weeks seemed appropriate. On the other hand, Calais da Silva et al (2009) reported a short-term MAB of only three months as having no demonstrated impact on survival.[292]

6.1.2.3 Quality of life assessment, PSPA-score, adverse drug reactions, and testosterone

There were no well-documented tools for assessment of QoL in the early 1990s when this trial was being planned. It was decided to utilise the Cleary 30-item validated questionnaire which was introduced in 1995, shortly before the final study protocol was completed in 1996. The Cleary instrument was based on two clinical international trials conducted in six countries with a total of 550 patients. It was designed for multinational use to explore the value of ADT for advanced PC.[244] It appears that there are no definitions (minimum) for clinically important differences when interpreting the results of the Cleary questionnaire. The QCQ-C30 questionnaire was developed at the same time.[243] Most trials concerning IAD and QoL have used QCQ-C30. Of the randomised trials, de Leval et al (2002) did not use any assessment of QoL.[290] The PSPA-score was included in the present trial protocol in order to have an extra tool for assessment of any differences in QoL between treatment arms. However, it is not a validated instrument.

PSPA and QoL questionnaire scores were analysed and summarised at the end of each TOFF and TON in the IAD arm and at approximately the same time point in the CAD arm.

The basis for the time point was as follows: at the end of the TOFF, patients had had the maximal duration of time without ADT and a maximal time for recovery of serum testosterone before the initiation of a new treatment-on period of at least 24 weeks. The duration of TOFF varied from patient to patient and was naturally dependent on cancer control and the velocity of PSA increase. The approximate point of time was defined by calculating the mean durations of previous cycles and the mean duration of the present TOFF or cycle. Patients in the CAD arm were selected by taking into account the visit closest to this time point. In the CAD arm, patients without metastases were examined only every 24 weeks (when QoL questionnaire was self-administered), although laboratory tests were monitored every 12 weeks. For these reasons, the number of patients analysed in the CAD arm at each time point varied quite extensively and may have caused some bias. In other randomised trials, QoL has been assessed at regular intervals or at fixed points regardless of the treatment phase, thus including patients both on treatment and off treatment in the IAD arm. This is likely to obscure possible differences between treatment arms perhaps masking the benefit of IAD.

The QoL questionnaire was self-administered by patients themselves without any help of co-investigators or staff. The questionnaires were monitored in the database and not analysed until the trial was closed. Thus, the investigators could not have any exerted influence on the answers or on the response rates. This is probably the explanation for the fact that response rates for all the items in the QoL questionnaire were not 100%.

The Mann-Whitney U-test was used to compare the sum of the scores in each domain between treatment arms at a certain time point. The 0.5 SD rule was used to find any minimally important changes and differences within the treatment arm by comparing the magnitude of the change with the baseline SD. The threshold of an important change is approximately one half of the baseline SD, a criterion which has been empirically derived.[297]

ADRs were assessed at each visit by their response to the question: "Has anything bothered you since your last visit?" No attempt was made to analyse the relief of ADRs during TOFF but relied on the QoL analysis in this respect. Thus, only the numbers of patients with any ADR in each treatment arm during the trial were estimated, but were unable to determine whether IAD offered any relief of an ADR during TOFF.

Serum testosterone was measured systematically every 12 weeks in this trial. Mean and median testosterone was analysed at the end of each TOFF, which means after a maximal time without ADT and maximal time for testosterone recovery, and at the end of each TON, which means after at least 24 weeks' exposure for ADT. Mean and median recovery times for testosterone were not analysed. In order to report mean and median delay for testosterone recovery, testosterone should have been measured at one month or shorter intervals. Many of the nonrandomised trials have included testosterone measurement and recovery rate analysis. However, not all randomised trials have reported testosterone determinations or recovery rates. Calais da Silva et al (2009) measured serum testosterone levels only in the subgroups of 192 (IAD) and 178 patients (CAD) at a fixed 3-monthly-interval.[292]

6.2 THE ELIGIBILITY OF PATIENTS FOR RANDOMISATION AND IAD

The interim analysis conducted during the run-in period showed that patients with advanced PC having a high PSA, ALP and metastatic disease with more than five skeletal hot spots did not show an adequate response to ADT. In other words, the patients with the most aggressive and the most advanced PC were not candidates for IAD. A PSA response for induction-ADT was essential to determine the patient's eligibility for IAD. This is in accordance with other reports.[4, 206, 259, 266, 281] Albrect et al (2003) proposed the exclusion of patients with more than five hot spots on the bone scan and/or visceral metastases from IAD, as only one third of these patients could start three or more treatment cycles in their nonrandomised trial.[266] Prapotnich et al (2003) showed that patients with bulky tumors,

with numerous lymph nodes or bone metastases and initial PSA >100 ng/ml or severe pain seemed to achieve only a partial or short-term response and were poor candidates for IAD.[4] Later, they suggested differentiation grade and patient age as being prognostic factors in addition to these parameters.[286]

In the present population of enrolled patients, 35% were not eligible for randomisation, mainly because they did not exhibit a sufficient PSA response, showed disease progression, or died during the run-in phase. In two other randomised trials with only metastatic PC, the percentage of patients not eligible for randomisation (with PSA cut-off of 4 ng/ml) was 33% and 49%.[259, 293] Instead, these figures were much better (82% and 99% eligible) in two other phase III trials which examined either more heterogeneous patient populations or patients with only nonmetastatic recurrent PC.[250, 292]

6.3 TREATMENT CYCLES IN THE INTERMITTENT ARM

The present median follow-up time was 65 months, with no patient lost to follow-up and one patient reaching the 14th cycle during 11.6 years' follow-up. Less than 50% of the IAD patients entered the 4th cycle. In other phase III trials, the mean or median follow-up time has ranged between 28 months and 9.2 years. The duration of TOFFs and percentage off-treatment during the cycle decreased in successive cycles throughout the trials. De Leval et al (2002) reported the length and percentage of time spent off therapy decreasing by a mean of 20 days (0.9%) with each consecutive cycle.[290] The mean TOFF in the present trial was 33.5 weeks (57% of cycle duration) in the first cycle but decreased to 10.0 weeks (27%) in the 12th cycle; in M0 and M1 subgroups from 37.6 and 29.1 weeks in the 1st cycle to 10.4 and 9.1 weeks in the 12th cycle. However, the treatment failure rate was much higher in the M1 than in the M0 group. These figures are comparable with those in the literature. Crook et al (2012) reported longer durations of TOFFs but they enrolled patients with minimally extensive recurrent and nonmetastatic PC.[250] In summary, the shortening TOFF seems to predict future disease progression.

6.4 PROGRESSION-FREE, OVERALL, PROSTATE CANCER-SPECIFIC, AND TREATMENT FAILURE SURVIVAL

PFS, OS, PCS, and TFS were equivalent in the two treatment arms. Though it was not possible to detect any significant differences between IAD and CAD, a slight advantage from IAD was seen in the risk analysis (HR 1.08−1.17, 95% CI 0.90−1.51, p=0.17−0.43). Survival rates were much lower with metastatic than non-metastatic disease, which is not surprising, but there was no difference apparent between IAD and CAD. Risk analysis revealed again a slight and statistically nonsignificant advantage from IAD in both subgroups of M1 and M0. The SEUG trial 9401 detected no difference in OS between IAD and CAD but a slightly higher risk for progression and death in the IAD arm. In the detailed risk analysis, there was a slight advantage in OS from CAD among 425 M0 patients (0.86; 95% CI: 0.65−1.14) but a small disadvantage among 191 M1 patients (1.26; 95% CI: 0.90−1.78), favouring IAD.[292] In the TULP trial, M1 patients on IAD showed a trend towards higher progression rates and seemed to fare worse than those with CAD.[259] Recently, Mottet et al reported no significant differences in PFS or OS between IAD and CAD among 173 patients with M1 disease.[293] The most recent results of the large SWOG 9346 trial of 1535 randomised M1 patients showed a trend favouring CAD for PCS and OS with a minimally extensive disease but could not show the inferiority of IAD, however.[294] In summary, no significant differences have appeared between IAD and CAD in the treatment of PC.

In the present trial, the differentiation grade of PC (Gleason scores ≤7 vs 8−10) had a significant impact on PFS, PCS, OS, and on TFS. PSA nadir at randomisation (<1.0; 1.0−4.0; >4.0 ng/ml) was also associated with prognosis. These results are in accordance with the results of the SEUG trial 9401 and the SWOG 9436 trial.[291, 292] PSA nadir and the duration of

the first TOFF have been demonstrated to be predictors of the time to clinical progression also in other trials.[287-289]

6.5 QUALITY OF LIFE AND PSPA-SCORE

The present trial showed that IAD did offer some benefits in QoL when compared with CAD, especially in the domains of activity limitation, physical capacity, and sexual functioning. QoL was significantly worse in most domains in the subgroup of M1 than M0 at trial entry, evidently due to advancement of PC. The differences disappeared with time. On the other hand, the trial treatment showed a beneficial effect on QoL of M1 patients in the domains of pain, activity limitation, and social functioning; and of both subgroups in emotional well-being. This is probably due to the cancer's response to ADT, resulting in relief of emotional and physical distress. In contrast, ADT showed a deleterious effect on QoL in terms of physical capacity in M0 patients and for sexual functioning in both groups. The advantage of IAD was evident in sexual functioning in both groups, in physical capacity in M0 group, and in activity limitation and social functioning in M1 group.

These results comparing QoL between M0 and M1 patients are in accordance with previous reports. Herr and O`Sullivan (2000) reported that ADT, especially MAB, caused fatigue, decreased physical activity, evoked emotional distress, and decreased general health in patients with asymptomatic nonmetastatic PC, thus significantly impairing QoL.[299] Kato et al (2007) claimed that ADT improved QoL significantly in the domains of pain, vitality, role-emotional health, and mental health in Japanese men with metastatic disease. In contrast, vitality declined in patients with localised PC.[300]

Many of the phase III trials have not been able to demonstrate any clear difference in QoL between IAD and CAD. Langenhuijsen et al (2011) reported a trend towards more side effects, like hot flushes, nausea, constipation, dyspnoea, and depression, from CAD but could not detect a consistently significant difference for any single QoL parameter between IAD and CAD.[259] Likewise, Mottet et al (2012) could identify no clinically relevant differences and no general trend in QoL scores between IAD and CAD. However, significantly fewer treatment-related AEs occurred in the IAD arm (p=0.042).[293] Furthermore, the results of the JPR7 trial showed only slightly better scores for functional domains of physical role and global health with IAD, but the differences were not statistically significant. However, IAD was associated with significantly better scores for items pertaining to symptoms: hot flashes (p<0.001), desire for sexual activity (p<0.001), urinary symptoms (p=0.006), and with a trend towards improvement in the level of fatigue (p=0.07).[250] Calais da Silva et al (2009) reported fewer major side-effects of hot flushes and gynaecomastia in the IAD arm of the SEUG trial 9401. Surprisingly, QoL figures, except for sexual quality, were slightly lower with IAD.[292] This may be due to the different kinds of questionnaires used or cultural differences between the Nordic countries and the Mediterranean area. Patients in the Mediterranean area may have experienced more anxiety during TOFF when without treatment. Instead, Verhagen et al reported better physical and emotional functions but worse cognitive functions with IAD than encountered with CAD (p<0.05).[295] A recent review of the literature summarised only some safety, tolerability, and QoL benefits associated with IAD over CAD.[301] Hussain et al (2013) found better erectile function and mental health with IAD when compared with CAD at month three but not thereafter.[294] However, the limitation of these trials is that QoL was assessed at regular intervals or at fixed points regardless the treatment phase, thus including patients both on treatment and off treatment in the IAD arm. This may have blurred the differences between the treatment arms. In the present trial, QoL was analysed at the end of each TOFF and TON in the IAD arm and defined approximately the same time point in the CAD arm in an attempt to compare the results between IAD and CAD. In addition, the rather low number of randomised patients in the trials of Langenhuijsen et al. and Mottet et al. may explain the modest impact of IAD on QoL.

According to the MWU-test, the significant differences in QoL between IAD and CAD did not emerge constantly during TOFFs but also sometimes during TONs, favouring IAD. This may suggest that even a short interruption of ADT compared with CAD might have a beneficial effect on QoL over the long term. On the other hand, this may suggest that the differences in QoL parameters are not dependent merely on the variations in the testosterone level. This is supported by the fact that approximately 20% of the present CAD patients reported sexual activity during the past month despite continuous castration. In summary, IAD seems to confer some beneficial effects on QoL.

In practical terms, no statistically significant differences could be detected in PSPA-scores between IAD and CAD. This is probably due to the narrow scale of PSPA-scores. On the other hand, the PSA cut-off 20 ng/ml for resumption of ADT was rather low to provoke any worsening of symptoms from PC. The value of the PSPA-score was very limited.

6.6 ADVERSE DRUG REACTIONS, ADVERSE EVENTS, AND TESTOSTERONE RECOVERY

In the present trial, the number of patients reporting ED and mood depression was higher in the IAD arm, which differs from other trials and was unexpected. This may be due to the way ADRs were assessed through the question: "Has anything bothered you since your last visit?" At entry, 48.8% of patients reported some level of sexual activity in the IAD arm compared with 40.1% in the CAD. Patients may have grown accustomed to their symptoms and no longer felt bothered, especially those receiving CAD. No attempt was made to analyse the relief of ADRs during TOFF, instead relying on QoL analysis in this respect. One would have expected the mood to be less depressed at the end of the TOFF with the recovery of the testosterone levels. On the other hand, patients may have experienced some anxiety during TOFFs being concerned that they were not receiving any specific treatment for their PC. In this respect, the anxiety and co-operation of patients have to be taken into account when considering IAD. In the present trial, one patient refused to be randomised to IAD. No significant differences were detected in the number of other ADT-related symptoms.

Although the number of adverse events was higher in the CAD arm, there were no significant differences between treatment arms in the present trial. No statistically significant differences emerged in the prevalence of AEVs or in the number of patients suffering from cardiovascular SAEs, nor in the incidence of deaths caused by any SAE or CV event. Furthermore, the incidence of bone fractures was practically the same in both treatment arms. Calais da Silva et al (2009) reported a trend towards more CV deaths in the CAD than IAD arm, with an HR of 1.27 (95% CI: 0.84–1.99).[292] In the study of Mottet et al (2012), SAEs were reported as often in the CAD as in the IAD arm (29.8% vs 31.3%).[293] Although several factors which have an adverse effect on CV risk have been associated with ADT, the association between ADT and CV mortality is still controversial.[211, 229] Nontheless, large population based cohort studies have shown ADT to be associated with an excess risk of fractures.[235-238]

In the present study, testosterone levels showed recovery at the end of each TOFF, but did not reach the same level as at the end of the previous TOFF. The proportion of patients with normalised testosterone levels ≥10 nmol/l during TOFF decreased from cycle to cycle. This has been shown also in other trials.[259, 260, 293] Crook et al (2012) reported only 35% of patients as returning to the pretreatment testosterone level during TOFF, and only 29 % of patients who were potent at entry as having recovery of potency.[250] As the TOFF duration declines from cycle to cycle, patients return to ADT sooner and sooner repeatedly and have less time to allow testosterone levels to recover. It seems that testosterone levels are restored more slowly than the corresponding PSA increases to the cut-off for resumption of ADT. This, probably, explains why no statistically significant differences were found in the incidence

of (S)AEs or their consequences between treatment arms despite intermittent dosing and shorter exposure time for ADT in the IAD arm.

6.7 COSTS OF THE ANDROGEN DEPRIVATION THERAPY

Orchiectomy has been shown to be the most cost-efficient method of castration over LHRH agonists, LHRH antagonist, or maximal androgen blockade, especially when life expectancy is more than two years.[302-304] However, the use of medical castration is increasing. Leuprorelin has been proposed to be the most cost-effective treatment in preference to other depot formulation LHRH agonists.[305] The LHRH antagonist, degarelix, is unlikely to be cost-effective compared to LHRH agonists plus a short-term course with an antiandrogen in the treatment of advanced hormone-dependent PC.[306]

Cost-effectiveness analysis was not one of the objectives of the present trial. However, IAD is likely to be cost-effective when compared to medical CAD. One-month depot therapy with LHRH agonists, as used in Finland, costs approximately 167 €, 3-month depots 415 €, and 6-month depots 745 €. The only available LHRH antagonist, degarelix, costs 702 € as a starting dose and thereafter 179 € every month. The mean duration of TOFF decreased from 33.5 weeks (approximately eight months) in the first cycle to 14.7 weeks (3.5 months) in the 10th cycle. Thus, the costs saved during these TOFFs would vary from a mean of 1336 € to 585 € with LHRH agonists, and from a mean of 1432 € to 627 € with the LHRH antagonist. Furthermore, the time of the nursing staff is freed up when no injections or implantation of the drug are needed during TOFF which is another factor which should be taken into account. However, patients on IAD need closer follow-up at shorter intervals during TOFFs. Apparently, the additional PSA tests every 3 months during TOFFs would not exceed these savings.

6.8 LIMITATIONS OF THE FINNPROSTATE STUDY VII

A total of 600 patients (300 and 300 in each treatment arm) was calculated to be required for statistically powerful analysis and to detect a hazard ratio of 1.345 with 90% power. Ultimately, 554 patients were randomised, somewhat less than originally estimated. The FPVII study was planned to include patients with metastatic PC (M1). However, because of the slow recruitment rate, the inclusion criteria were widened to enroll patients with locally advanced PC which led to a more heterogeneous patient population and longer follow-up time. The number of patients in each treatment arm (IAD vs CAD) of the subgroups of M0 and M1 (140:137 and 134:143) was rather small, reducing the statistical power in the subgroup analysis.

The PSA cut-off <10 ng/ml for withdrawal of ADT was different from and higher than in many other trials. This allows patients with higher tumour burden to be recruited and makes the patient population more heterogeneous than with the cut-off ≤4 ng/ml. However, nearly 80% of the randomised patients achieved PSA nadir ≤4 ng/ml.

In order to compare QoL between treatment arms at the end of TOFFs and TONs, the approximate time point was calculated for the CAD arm. The technique to define the time point was somewhat arbitrary and may have caused some bias. Furthermore, there are no definitions for clinically important differences in the Cleary questionnaire which complicated the analysis of the results. The relief of ADRs during TOFFs was not separately analysed but relied on the QoL analysis in this respect.

Finally, serum testosterone levels were measured at 3-monthly interval which meant that it was not possible to assess mean and median recovery times for testosterone. This would have required that testosterone concentrations should have been measured at one-monthly or even shorter intervals.

6.9 FUTURE PERSPECTIVES

Recently published review papers claim that the use of IAD for treatment of PC can no longer be considered experimental but represents an appropriate option for many patients requiring ADT for advanced or recurrent PC after biochemical PSA failure after curative-intended treatment, and for selected patients with metastatic disease.[307, 308] Nonetheless, further investigations are needed to define in detail the selection of patients who are appropriate for IAD, the criteria for withdrawal and resumption of ADT, and the optimal type of ADT.

Most of the trials have been conducted using LHRH analogues with or without antiandrogens. LHRH antagonists could represent a viable alternative since they do not provoke the serum testosterone surge and flare phenomenon and by reaching castrate testosterone levels more rapidly. Furthermore, other methods of hormonal therapy could be examined in intermittent treatment of PC. Antiandrogen monotherapy could be considered in treatment of recurrent PC after curative-intended treatment or with minimally extensive disease. Estrogens could be a possible option with advanced or even castrate-resistant PC,[309] as well as could the novel second-generation AR antagonists.

IAD can confer economic benefits due to the reduction of pharmaceutical costs during TOFF. On the other hand, IAD patients need more careful follow-up during TOFF, which means extra costs to the health care system. It would be interesting to conduct a thorough cost-effectiveness analysis between IAD and CAD.

Finally, there is a need for high-quality QoL evaluation between IAD and CAD, because it seems that the main advantage of IAD is not the survival benefit but the positive impact on QoL.

7 Summary and Conclusions

The purpose of the FinnProstate Study VII was to compare intermittent and continuous androgen deprivation in patients with advanced or metastatic PC in terms of times to progression, to death, to PC-specific death, and to treatment failure, as well as comparing the effect of these treatment modalities on the quality of life. The aim was to identify the kinds of patients most appropriate for IAD, whether IAD could delay the development of cancer progression to the castration-resistant status or could prolong survival, and whether IAD could offer any benefit for QoL.

Based on the present study, the following conclusions can be drawn:

1. Patients with the most aggressive and the most advanced PC having a high PSA, ALP and metastatic disease with more than five skeletal hot spots did not show an adequate response to ADT and were not candidates for IAD. A PSA response for induction ADT is essential to determine the patient's eligibility for IAD.

2. The long-term results of IAD were equal with CAD in terms of time to progression, to death, to PC-specific death, and to treatment failure. It was not possible to detect any significant delay in the onset of hormone resistance or improvement in survival with IAD.

3. IAD offered benefit in QoL when compared with CAD, especially in the domains of activity limitation, physical capacity, and sexual functioning. However, it is worth mentioning that the incidence of adverse events was not significantly lower with IAD.

4. IAD was as efficient as CAD in treatment of advanced PC in both locally advanced disease (M0) and metastatic disease (M1), in terms of PFS, OS, PCS, and TFS. ADT improved QoL, with the exception of sexual functioning, to some extent in M1 patients, with IAD conferring some extra benefits.

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APPENDICES 1-4

APPENDIX 1. The FinnProstate Group and Trial Centers.

Etelä-Karjala Central Hospital, Lappeenranta: Jaakko Permi, Veli-Matti Puolakka; Etelä-Pohjanmaa Central Hospital, Seinäjoki: Mikael Leppilahti, Markku Leskinen, Timo Marttila; Etelä-Savo Central Hospital, Mikkeli: Niilo Hendolin, Tapani Liukkonen; Hatanpää hospital, Tampere: Jukka Häkkinen; Helsinki University Hospital: Martti Ala-Opas, Jussi Aro, Eero Kaasinen, Kari Lampisjärvi, Ilkka Perttilä, Erkki Rintala, Mirja Ruutu, Kimmo Taari; Kainuu Central Hospital, Kajaani: Pentti Kemppainen; Keski-Pohjanmaa Central Hospital, Kokkola: Pekka Pellinen; Keski-Suomi Central Hospital, Jyväskylä: Susanna Laaksovirta, Seppo Lundstedt; Kuopio University Hospital: Sirpa Aaltomaa, Antero Heino, Arto Salonen; Kuusankoski District Hospital: Markku Multanen, Markku Onali; Lappi Central Hospital, Rovaniemi: Patrik Ehnström, Risto Kauppinen, Matti Rauvala; Länsi-Pohja Central Hospital, Kemi: Juhani Ottelin; Oulu University Hospital: Pekka Hellström, Jani Kuisma, Olavi Lukkarinen, Aare Mehik, Erkki Ollikkala, Ilkka Paananen, Teija Parpala-Spårman, Panu Tonttila; Pietarsaari District Hospital: Christian Palmberg; Pohjois-Karjala Central Hospital, Joensuu: Jouko Viitanen; Päijät-Häme Central Hospital, Lahti: Kalmer Innos, Taina Isotalo, Kari Lehtoranta, Martti Talja; Satakunta Central Hospital, Pori: Heikki Korhonen, Pekka Salminen; Savonlinna Central Hospital: Raino Terho; Tampere University Hospital: Martti Aho, Juha Koskimäki, Timo Kylmälä, Mika Matikainen, Teuvo Tammela; Turku University Hospital: Kimmo Kuusisto, Matti Laato, Martti Nurmi; Vaasa Central Hospital: Erkki Hansson, Susanna Hirsimäki, Peter Nylund; Valkeakoski District Hospital: Rauno Kulmala; Ähtäri District Hospital: Juha Ervasti.

APPENDIX 2. Summary of health-related Quality of Life Questionnaire: Domains and Scores. (Gleary et al. Qual Life Res 1995; 4: 207-220)

Assessment of pain (domain 1):
Q1. How much pain have you had on average since yesterday? (1-10; 1=no pain; 10=the worst pain you can imagine)
Q2. Which number best describes your worst pain during the past 7 days? (1-10;1=no pain; 10=the worst pain)
Q3. Which number best describes your least pain during the past 7 days? (1-10; 1=no pain; 10=the worst pain)
Q4. How much did your pain interfere with your activities during the past 7 days? (1-10; 1=not at all; 10=extremely)
Assessment of social functioning (domain 2):
How much of the time, during the past month, has your health limited
Q5. your ability to visit with close friends or relatives? (1-6; 1=all of the time; 6=none of the time)
Q6. your ability to participate in other social activities? (1-6; 1=all of the time; 6=none of the time)
Assessment of emotional well-being (domain 3):
How much of the time, during the past month,
Q7. have you been a very nervous person? (1-6; 1=all of the time; 6=none of the time)
Q8. have you felt calm and peaceful? (1-6; 1=all of the time; 6=none of the time)
Q9. have you felt downhearted and blue? (1-6; 1=all of the time; 6=none of the time)
Q10. have you been a happy person? (1-6; 1=all of the time; 6=none of the time)
Q11. have you felt so down in the dumps that nothing could cheer you up? (1-6; 1=all of the time; 6=none of the time)
Assessment of vitality (domain 4):
How much of the time, during the past month,
Q12. did you feel dull or sluggish? (1-6; 1=all of the time; 6=none of the time)
Q13. did you have or feel energy, pep, or vitality? (1-6; 1=all of the time; 6=none of the time)
Q14. have you felt tired, worn out, used up, or exhausted? (1-6; 1=all of the time; 6=none of the time)
Assessment of activity limitations (domain 5):
Q15. For how many days during the past 7 days did you cut down on the things that you usually do because of your health? (0-7)
Assessment of bed disability (domain 6):
Q16. For how many days during the past 7 days did you stay in bed for all or most of the day because of your health? (0-7)
Assessment of overall health (domain 7):
Q17. Which number best describes your overall health during the past month? (0-10; 0=worst; 10=perfect)
Assessment of physical capacity (domain 8):
How much difficulty have you had because of your health during the past month in doing each of the following activities?
Q18. Vigorous activities, like lifting heavy objects, running, or participating in sports (1-5; 1=no difficulty; 5=unable to do)
Q19. Moderate activities, like moving a table, carrying shopping or bowling (1-5;1=no difficulty; 5=unable to do)
Q20. Walking uphill or climbing a few flights of stairs (1-5;1=no difficulty; 5=unable to do)
Q21. Bending, lifting, or stooping (1-5;1=no difficulty; 5=unable to do)
Q22. Going for a short walk outdoors (1-5;1=no difficulty; 5=unable to do)
Q23. Shaving, dressing, bathing or showering. (1-5;1=no difficulty; 5=unable to do)
Assessment of sexual functioning (domain 9):
How much did the following statement apply to you during the past month?
Q24. I was interested in having sex. (1-5; 1=not at all; 5=a great deal)
Q25. I thought others found me sexually attractive. (1-5; 1=not at all; 5=a great deal)
Q26. I felt sexually attractive. (1-5; 1=not at all; 5=a great deal)
Q27. Have you tried to engage in any type of sexual activity including masturbation or intercourse during the past month? (1=yes; 2=no)
-if you circled the answer "NO", please skip to the end
Assessment of sexuality (domain 10):
How much did the following statement apply to you during the past month?
Q28. "I had difficulty becoming sexually aroused." (1-5; 1=not at all; 5=a great deal)
Q29. "I had difficulty getting or maintaining an erection." (1-5; 1=not at all; 5=a great deal)
Q30. "I had difficulty reaching orgasm." (1-5; 1=not at all; 5=a great deal)

APPENDIX 3. Kyselykaavake potilaan elämänlaadusta.

Kivun arviointi (osa-alue 1):
Ympyröikää se numero, joka parhaiten kuvaa
1. miten paljon kipua Teillä on keskimäärin ollut eilisen jälkeen. (1-10; 1=ei kipua; 10=pahin kipu, jota voitte kuvitella)
2. suurinta kipua viimeisen 7 päivän aikana. (1-10; 1=ei kipua; 10=pahin kipu, jota voitte kuvitella)
3. pienintä kipua viimeisen 7 päivän aikana. (1-10; 1=ei kipua; 10=pahin kipu, jota voitte kuvitella)
4. miten paljon kipunne häiritsi toimintaanne viimeisen 7 päivän aikana. (1-10; 1=ei häirinnyt; 10=häiritsi voimakkaasti)

Sosiaalisten toimintojen arviointi (osa-alue 2):
Kuinka paljon viimeisen kuukauden aikana on sairautenne rajoittanut
5. vierailujanne läheisten ystävien tai sukulaisten luona? (1-6; 1=kaiken aikaa; 6=ei lainkaan)
6. osallistumistanne muuhun sosiaaliseen kanssakäymiseen? (1-6; 1=kaiken aikaa; 6=ei lainkaan)

Tunne-elämän arviointi (osa-alue 3):
Kuinka usein viimeisen kuukauden aikana
7. olette ollut hyvin hermostunut? (1-6; 1=kaiken aikaa; 6=ei lainkaan)
8. olette tuntenut itsenne tyyneksi ja rauhalliseksi? (1-6; 1=kaiken aikaa; 6=ei lainkaan)
9. olette tuntenut itsenne masentuneeksi ja alakuloiseksi? (1-6; 1=kaiken aikaa; 6=ei lainkaan)
10. olette ollut onnellinen? (1-6; 1=kaiken aikaa; 6=ei lainkaan)
11. olette tuntenut itsenne niin masentuneeksi, ettei mikään piristäisi? (1-6; 1=kaiken aikaa; 6=ei lainkaan)

Elinvoimaisuuden arviointi (osa-alue 4):
Kuinka usein viimeisen kuukauden aikana
12. olette tuntenut itsenne laiskaksi ja saamattomaksi? (1-6; 1=kaiken aikaa; 6=ei lainkaan)
13. olette tuntenut itsenne energiseksi, aikaansaavaksi tai elinvoimaiseksi? (1-6; 1=kaiken aikaa; 6=ei lainkaan)
14. olette tuntenut väsymystä, liikarasittuneisuutta, uupumista tai loppuun kulumista? (1-6; 1=kaiken aikaa; 6=ei lainkaan)

Aktiivisuuden rajoittumisen arviointi (osa-alue 5):
15. Ympyröikää niiden päivien lukumäärä viimeisten 7 päivän aikana, jolloin teidän täytyi sairautenne vuoksi vähentää niiden asioiden tekemistä, joita tavallisesti teette. (0-7)

Vuoteeseen rajoittumisen arviointi (osa-alue 6):
16. Ympyröikää niiden päivien lukumäärä viimeisten 7 päivän aikana, jolloin olitte vuoteen omana koko tai suurimman osan päivästä sairautenne vuoksi. (0-7)

Yleisen terveydentilan arviointi (osa-alue 7):
17. Ympyröikää se numero, joka parhaiten kuvaa terveyttänne yleensä viimeisen kuukauden aikana. (0-10; 0=huonoin, jonka voi kuvitella; 10=täysin terve)

Fyysisen suorituskyvyn arviointi (osa-alue 8):
Ympyröikää se numero, joka parhaiten kuvaa sitä, miten vaikeaa teidän on viimeisen kuukauden aikana sairautenne vuoksi ollut
18. tehdä voimaa vaativia tehtäviä, kuten nostaa painavia esineitä, juosta tai urheilla. (1-5; 1=ei vaikeuksia; 5=mahdotonta)
19. liikkua ja toimia kohtuullisesti, kuten siirtää pöytää tai kantaa ostoksia. (1-5; 1=ei vaikeuksia; 5=mahdotonta)
20. kävellä ylämäkeä tai nousta muutama kerros portaita. (1-5; 1=ei vaikeuksia; 5=mahdotonta)
21. nostaa tai kumartua. (1-5; 1=ei vaikeuksia; 5=mahdotonta)
22. tehdä pieni kävelylenkki ulkona. (1-5; 1=ei vaikeuksia; 5=mahdotonta)
23. ajaa partaa, pukeutua, kylpeä tai käydä suihkussa. (1-5; 1=ei vaikeuksia; 5=mahdotonta)

Seksuaalisten toimintojen arviointi (osa-alue 9):
Ympyröikää se numero, joka parhaiten kuvaa, kuinka hyvin seuraava lause sopii teihin viimeisen kuukauden aikana:
24. "Olen ollut kiinnostunut seksistä." (1-5; 1=ei ollenkaan; 5=paljon)
25. "Luulen, että toiset pitävät minua seksuaalisesti puoleensa vetävänä." (1-5; 1=ei ollenkaan; 5=paljon)
26. "Olen tuntenut itseni seksuaalisesti puoleensa vetäväksi." (1-5; 1=ei ollenkaan; 5=paljon)
27. Oletteko yrittänyt harjoittaa seksuaalista toimintaa, mukaan lukien itsetyydytys ja sukupuoliyhdyntä, viimeisen kuukauden aikana? (1=kyllä; 2=ei)
    - jos vastasitte "EI", siirtykää kyselykaavakkeen loppuun.

Seksuaalisuuden arviointi (osa-alue 10):
Ympyröikää se numero, joka parhaiten kuvaa, kuinka hyvin seuraava lause sopii teihin viimeisen kuukauden aikana:
28. "Minun on ollut vaikea kiihottua seksuaalisesti." (1-5; 1=ei ollenkaan; 5=erittäin hyvin)
29. "Minun oli vaikea saada tai ylläpitää erektiota." (1-5; 1=ei ollenkaan; 5=erittäin hyvin)
30. "Minun oli vaikea saada orgasmi." (1-5; 1=ei ollenkaan; 5=erittäin hyvin)

APPENDIX 4. PSPA-score.

Performance status:
Able to carry out normal activity: 0 point
Restricted in physically strenuous activity but ambulatory and able to carry out light work: 1 point
Ambulatory and capable of all self-care but unable to carry out any work; up about more than 50 % of waking hours: 2 points
Capable only of limited self-care; confined to bed or chair more than 50% of waking hours: 3 points
Completely disabled, cannot carry out any self-care; totally confined to bed or chair: 4 points

Pain score:
None: 0 point
Mild: 1 point
Moderately severe: 2 points
Severe: 3 points
Intolerable: 4 points

Use of analgesics:
None: 0 point
Non-opioids occasionally: 1 point
Non-opioids regularly: 2 points
Opioids occasionally: 3 points
Opioids regularly: 4 points
> 100% increase in dose of opioids or epidural administration: 5 points

Arto J. Salonen

Intermittent versus Continuous Androgen Deprivation in Patients with Advanced Prostate Cancer

The FinnProstate Study VII

Androgen deprivation therapy (ADT) has been the standard treatment approach for advanced prostate cancer for decades. Despite a good initial response rate, many patients are likely to experience a disease relapse within a few years and to experience significant adverse effects with a deterioration of quality of life (QoL) from ADT.

The FinnProstate Study VII (FPVII) was conducted as a randomised, controlled, multicenter clinical trial to compare intermittent (IAD) and continuous androgen deprivation (CAD) in patients with advanced prostate cancer in terms of time to progression, overall survival, cancer-specific survival, time to treatment failure, and quality of life.

No difference emerged in progression or survival rates between IAD and CAD among the randomised 554 patients. However, QoL seemed to be better with IAD than CAD, especially in the domains of activity limitation, physical capacity, and sexual functioning.

UNIVERSITY OF
EASTERN FINLAND

Publications of the University of Eastern Finland
Dissertations in Health Sciences

ISBN 978-952-61-1115-5