Karolinska Institutet, Stockholm, Sweden

RADIOTHERAPY IN PROSTATE CANCER:
INFORMATION, QUALITY OF LIFE AND PROSTATE VOLUME

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Radiotherapy in Prostate Cancer: Information, Quality of Life and Prostate Volume

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My beloved wife *Rulu* and

Our beautiful daughters *Anisha* & *Tamali*

ABSTRACT

Prostate cancer (PC) is the most widespread form of cancer among men in Sweden, with an annual incidence of approximately 10,000 new cases. Treatment of localized prostate cancer is controversial. Curative intended treatments for localized disease include radical prostatectomy (RP) and radiotherapy (RT). These treatments considered to be equally effective, but have different side effects. ADT commonly used as neo-adjuvant therapy in curative intended radiotherapy. The various regimens of ADT have different side effect profiles. Thus, patients need information about how the different side effects might influence their health-related quality of life (HRQoL), both concering primary treatment (RP and RT) and about ADT.

Providing adequate information to cancer patients facilitate their adjustment to the cancer experience by increasing perceptions of control, reducing feelings of threat and anxiety, and in improving HRQoL.Thus, it is of importance to investigate satisfaction with information in prostate cancer patients treated with curative intention.

The aims of Paper 1, were to compare information perception and satisfaction with that and influence on HRQoL in patients primarily treated with RT alone or with salvage RT after failure of RP. Using the EORTC QLQ C-30 and EORTC INFO 25 questionnaires in 660 patients prospectively. Higher levels of satisfaction with information and more favorable HRQoL were found in patients treated with RT primarily compared to surgery + salvage RT.

In Paper 2, the aims were to compare HRQoL of RT and RP in a randomized trial of 89 patients in curative setting. EORTC QLQ C-33 questionnaire and 20 specific questions were asked by mailed questionnaires. No differences between the two treatments were found. It was not possible to draw any conclusion about efficacy of the treatments due to insufficient power of the study.

In Paper 3, the aims were to compare differences in HRQoL after randomizing anti-androgen versus total androgen blockade in 110 curative intent RT patients. EORTC QLQ C-30 and EORTC QLQ PR25 were used. Statistically significant differences in sexual interest and function were noted, in favour of anti-androgen treated patients. In addition, higher levels of overall quality of life and sexual interest as well as lower levels of fatigue, and urinary problems were found at the three-months assessment in the anti-androgen group compared to the total androgen blockade group. The difference in sexual interest remained to the 18-months assessment. At that point of time, significant difference favoring the anti-androgen group found in cognitive functioning.

In Paper 4, the aims were to compare differences in changes of prostate volume and in target volume in patients included in Paper 3. Ultrasound technique was used to investigate differences in PV after neo-adjuvant hormonal therapy according to randomization arm. Total androgen blockade was more effective in decreasing PV. This effect was translated to target volume. PV increased during treatment in a few patients in both groups.

Conclusion: Information is important for PC patients´ HRQoL and there is room for improvement, especially for men who are about to receive salvage radiotherapy. No differences in HRQoL were found between PC patients treated with RP or RT. The study was, however, underpowered. Anti-androgen treatment resulted in better HRQoL in the short run as compared to total androgen blockade. Largest effects were noted in the sexual area. Total androgen blockade had a better effect on decreasing prostate volume.

LIST OF SCIENTIFIC PAPERS

I. **Khairul Majumder**, Yvonne Brandberg, Hemming Johansson, Sten Nilsson, Mia Bergenmar. Less satisfaction with information in prostate cancer patients treated with surgery and salvage radiotherapy compared to patients with curative radiotherapy alone, despite similar health related quality of life. Clinical Genitourinary Cancer, 2014; 12: 71-82.

II. Bo Lennernäs, **Khairul Majumder**, Jan-Erik Damber, Per Albertsson, Erik Holmberg, Yvonne Brandberg, Ulf Isacsson, Gunilla Ljung, Ole Damm, Sten Nilsson. Radical prostatectomy versus high-dose irradiation in localized/locally advanced prostate cancer: A Swedish multicenter randomized trial with patient-reported outcomes. Acta Oncologica, 2015; 54: 875-881.

III. **Khairul Majumder**, Sten Nilsson, Hemming Johansson, Anders Ullen, Mia Bergenmar, Yvonne Brandberg. Better sexual functioning with anti-androgen than with total androgen blockade in prostate cancer patients treated with curative radiotherapy: A randomized prospective 18-month follow-up study (Revision submitted to EJC, April 2016).

IV. **Khairul Majumder,** Yvonne Brandberg, Hemming Johansson, Enrique Castellanos, Anders Ullen, Sten Nilsson. The effect on prostate volume of anti-androgen versus total androgen blockade in prostate cancer patients-a randomized study (manuscript).

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LIST OF ABBREVIATIONS

AA	Anti-androgen
ADT	Androgen Deprivation Therapy
ANOVA	Analysis Of Variance
ASR	Age standardised ratio
BED	Biologically Effective Dose
BMI	Basal Metabolic Index
BPH	Benign Prostatic Hyperplasia
BT	Brachytherapy
BRFS	Biochemical Recurrence-Free Survival
CI	Confidence Interval
CRF	Case Report Form
CRPC	Castration resistant prostate cancer
CTCAE	Common Terminology Criteria for Adverse Events
CTO	Clinical Trial Office
CTV	Clinical Target Volume
3D-CRT	Three-dimensional Conformal Radiation Therapy
DNA	Deoxyribonucleicacid
DFS	Disease Free Survival
DSB	Double Strand Break
EBRT	External Beam Radiation Therapy
EORTC	European Organization for Research and Treatment of Cancer
ESMO	European Society for Medical Oncology
FFF	Freedom From Failure
FSH	Follicular Stimulating Hormone
GI	Gastro-Intestinal
GU	Gastro-Urinary
GnRH	Gonadotropin Releasing Hormone
HDR	High Dose Rate
hK2	Human Kallikrein 2

HR	Hazard Ratio
HRQoL	Health Related Quality of Life
IGRT	Image Guided Radiation Therapy
LDR	Low Dose Rate
LHRH	Luteinizing Hormone Releasing Hormone
OS	Overall Survival
PC	Prostate Cancer
PFS	Progression Free Survival
PSA	Prostate Specific Antigen
PSMA	Prostate Specific Membrane Antigen
PTV	Planning Target Volume
PV	Prostate volume
QoL	Quality of Life
QLQ	Quality of Life Questionnaire
RCT	Randomized Controlled Trial
RP	Radical Prostatectomy
RT	Radiation Therapy
SPCG	Scandinavian Prostate Cancer Group
TAB	Total Androgen Blockade
TCD	Tumor Cell Death
TNM	Tumour Node Metastasis
TRUS	Transrectal Ultrasound
TTP	Time To Progression
UICC	Union Internationale Contre Cancer
VMAT	Volumetric Arc Therapy
WW	Watchful Waiting
WHO	World Health Organization

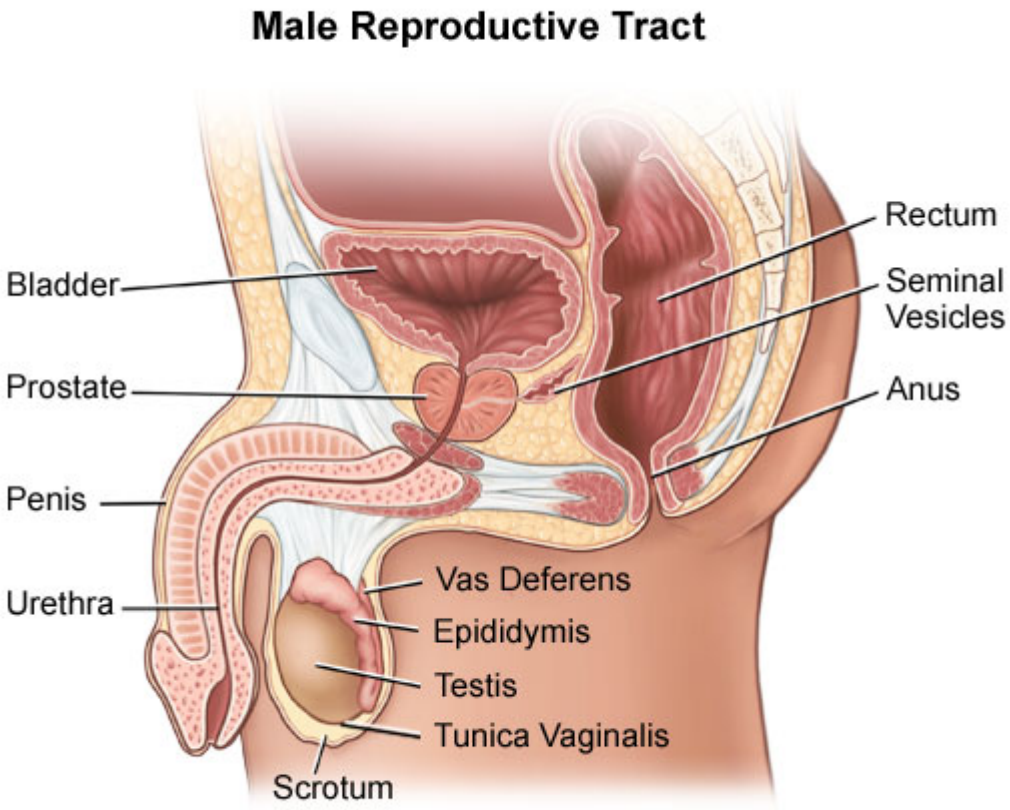


Figure 1. Source: Health Library, Johns Hopkins Medicine, 2016.

1 INTRODUCTION

Prostate cancer (PC) is the most common cancer among Swedish men (Socialstyrelsen, 2015). The incidence has increased over the last decades in the western world (Nilsson et al., 2004). The introduction of PSA testing has led to an increasing proportion of patients presenting with localised disease (Dearnaley et al., 2007). PC commonly affects men with high age. Other concurrent illnesses play role in treatment modalities chosen and for survival. The disease is for some patients aggressive at diagnosis, but for the majority, the expected survival time is long. The optimal treatment today for localized PC is a matter of debate (Nilsson et al., 2004; Dearnaley et al., 2007). Radical prostatectomy (RP) and radiotherapy (RT) are the most commonly used curative options at this stage. Both treatments are associated with side effects influencing health-related quality of life (HRQoL). Active surveillance and watchful waiting are other options for selected patients. Information regarding HRQoL is of utmost importance, as these modalities have different profiles of side effects and may affect the choice of treatment option.

In this thesis, patient reported outcomes regarding HRQoL, genitourinary, gastrointestinal and sexual problems highlighted in the context of curative intent RT in localized PC patients. In addition, patients' evaluation of information given during PC treatment been studied. Focus has also been on hormonal influence on prostate volume in the neo-adjuvant setting, and to side effects after radiotherapy with curative intent. Patient reported outcomes are the mainstay in our work, by using different EORTC (European Organization for Research and Treatment of Cancer)-questionnaires. The results of our studies may be supportive in PC-treatment decision-making consultations.

2 PROSTATE CANCER, TREATMENT AND HEALTH-RELATED QUALITY OF LIFE

2.1 EPIDEMIOLOGY

According to WHO there were 14.1 million new cancer cases, 8.2 million cancer deaths and 32.6 million people living with cancer (within 5 years of diagnosis) worldwide in 2012 (WHO, GLOBOCAN, 2012). PC is the second most common cancer in men. An estimated 1.1 million men worldwide were diagnosed with PC in 2012, accounting for 15% of the cancers diagnosed in men, with almost 70% of the cases (759 000) occurring in more developed regions. PC incidence varies more than 25-fold worldwide. The rates are highest in Australia/New Zealand and Northern America together with Western and Northern Europe, because of prostate specific antigen (PSA) testing and subsequent biopsy has become widespread in those regions. Age Standardised Ratio (ASR) varies between 97 -226/100,000. Incidence rates are also relatively high in certain less developed regions such as the Caribbean (80), Southern Africa (62) and South America (60), but remain low in Asian populations with estimated rates of 10.5 and 4.5 in Eastern and South-Central Asia respectively.

With an estimated 307,000 deaths in 2012, PC is the fifth leading cause of death from cancer in men (6.6% of total men deaths). Because PSA testing has a much greater effect on incidence than on mortality, there is less variation in mortality rates worldwide (ten-fold from approximately 3 to 30 per 100,000) than observed for incidence, with the number of deaths from PC larger in less developed regions than in more developed ones (165,000 compared to 142,000, respectively). Mortality rates are generally high in predominantly black populations (Caribbean, 29 per 100,000 and sub-Saharan Africa, ASRs 19-24 per 100,000), very low in Asia (2.9 per 100,000 in South-Central Asia for example) and intermediate in the Americas and Oceania (Australia/South East Asia/Malay Archipelago/parts of USA).

In Sweden, PC accounts for around 10,000 new cases in each year (Socialstyrelsen, 2015). PC constitutes over 30% of all malignancy in men in Sweden. Median age at diagnosis is >70 years. The average annual increase is 1.4 % over the last 20 years. The introduction of PSA testing partly explains the large increase in the late 1990s' and early 2000s', but the incidence appears to decrease during the last few years (Socialstyrelsen, 2015). There is an 80% risk of dying of PC if diagnosed before 60 years of age, 63% if diagnosed between 60 and 69 years, 53% för ages 70 and 79 years, and a 49% risk for ages 80 and over (Grönberg, 1997).

2.2 ETIOLOGY

The actual cause of PC is still unknown, but several factors associated with the risk of PC development, have been identified:

Age: Aging is the most significant risk factor for PC (Abate-Shen & Shen, 2000). The mean age at diagnosis in Sweden is 72–74 years, and about 85% of patients are diagnosed after 65 years of age (Grönberg, 2003).

Race and ethnicity: Afro-Americans have the highest recorded incidence, almost double the risk that of white Americans. Race and age of onset contribute independently to hereditary PC (Mydlo & Godec, 2003) and similar findings been observed in men in the Caribbean (Mallick et al., 2005). Higher incidence rates also observed in Uganda (Wabinga et al., 2000) and in Nigeria (Ogunbiyi & Shittu., 1999). In contrast, the incidence appears to be lower among Chinese and Japanese men. Japanese migrants to US, however, shown to have a higher incidence compared to men still living in Japan (Shimizu et al., 1991). These variations suggest that the risk for PC has a genetic component, and that lifestyle factors may play an important role. One study showed remarkable improvements in pathologic stages in Afro-American men after retropubic RP where pT3 disease minimized from 100% to 35%, whereas it decreased from 57% to 43% in white Americans (Paquette et al., 2001). Positive margins decreased from 100% to 26%, and 41% to 27% respectively. The authors concluded that equal availability of screening and PSA testing between both races made those differences.

Family history: Familial PC is commonly defined as a family in which there are two first-degree relatives (father, brother, son), or one first-degree and at least two second-degree relatives (grandfather, uncle, nephew, half brother) with PC (Stanford & Ostrander et al., 2001). A subset of familial PC is considered to be hereditary, defined by at least one of following criteria: 1) three or more first-degree relatives with PC; 2) three successive generations with PC, either through paternal or maternal lineage; or 3) two siblings with PC diagnosed at a relatively young age (e.g., <55 years). It estimated that hereditary PC might account for 5-10% of all cases of PC in the general population (Stanford & Ostrander et al., 2001; Karayi et al., 2004).

Gene changes: Several inherited genes that seem to raise PC risk have identified. In a meta-analysis of RNASEL (Ribonuclease L) polymorphisms, no corelation with overall PCa risk found. In subgroup analyses, however, a low-penetrent risk gene for sporadic PCa found (Wei et al., 2012). Tumour suppressor genes BRCA 1 and BRCA 2 are active in DNA repair. Inherited mutations in these genes more commonly cause breast and ovarian cancer in women, but also account for a very small number of PCs (Thompson et al., 2001; 2002). Inherited mutations in DNA mismatch repair genes MSH2 and MLH1 give rise to Lynch syndrome, and individuals´ cumulative lifetime risk of PC with this syndrome are two-fold higher than for the general population (Raymond et al., 2011). A case-control study showed a strong link between loss of the Y-chromosome and male carcinogenesis like coloncancer and PC (Noveski et al., 2016).

Diet: The exact role of diet in PC is not clear, although a number of factors had been studied. Dietary intake of tomatoes and tomato products, containing lycopene and carotenoids, has shown to be inversely associated with the risk of PC (Basu et al., 2007). A high intake of protein or calcium from dairy products suggested increasing the risk for PC (Allen et al., 2008). Several studies have reported associations between fat consumption and PC mortality, supporting the hypothesis of an increased risk in men who consume larger total calories as fat (Boyle et al., 1995). Other studies have shown an increased risk with saturated fat, specifically with high intake of processed red meat (Rodriguez et al., 2006; Rohrmann et al., 2007).

Obesity: Obesity appears be linked to aggressive PC (Allot et al., 2013). Excess adipose tissue generates a state of systemic inflammation and mediates steroid hormone metabolism, insulin sensitivity and cytokine release (Fowke et al., 2015). Other studies have suggested that a higher BMI is associated with PC mortality (Andersson et al., 1997; Kane et al., 2005), biochemical failure after treatment (Strom et al., 2005; Bassett

et al., 2005) and diagnosis of advanced PC (MacInnis et al., 2006; Gong et al., 2006).

Smoking and alcohol: A positive association between moderate alcohol consumption and the risk of PC has been demonstrated (Sesso et al., 2001). Liquor, but not wine or beer, consumption, was associated with increased PC risk. In a retrospective study of 8,190 men, current smokers were more likely to have acute prostatic inflammation than former and never smokers (Moreira et al., 2015). In another, prospective trial of more than 16,000 men, a decreased risk of diagnosed with PC found in current and former smokers, but current smokers were at an increased risk of dying from PC (Watters et al., 2009).

Environmental and occupational factors: A large Swedish study has shown an increased risk of PC in pesticide workers (Dich & Wiklund, 1998). In addition, men exposed to cadmium and those working in the nuclear power industry have found to have an increased risk of PC (Kirby & Brawer, 2004).

2.3 HORMONAL REGULATION

The prostate is regulated by androgens, and thereby dependent on androgens for development, growth, and maintenance of size and function (Hayward & Cunha, 2000). Testosterone is the main androgen in males and produced by leydig cells in the testes. Production of testosterone stimulated by the hypothalamus through luteinising hormone releasing hormone (LHRH) that activates the pituitary gland in anterior hypophysis to produce luteinising hormone (LH), which in turn stimulates the leydig cells. There is also a negative feedback loop where testosterone inhibits the release of LHRH. Testosterone converted in the prostate by 5-alfa-reductase to dihydrotestosterone, which is a more potent androgen (Krieg et al., 1995). Androgens are important in the development and maintenance of sexual function, and androgen stimulation plays a central role in the development of PC (Wu & Gu, 1991). Three distinct phenotypes in PC have postulated: *androgen-dependent, androgen-sensitive, and androgen-independent.* Androgen-dependent cancer cells require androgenic stimulation for their growth, without which they die (Isaacs et al., 1992). In contrast, androgen-sensitive cancer cells do not die, even if no androgen is present. Growth rate however decreases following androgen ablation. Androgen-independent cancer cells are completely autonomous to androgenic effects (DeVita et al., 1997).

2.4 DIAGNOSIS

Triple diagnostics, including prostate-specific antigen (PSA)-test, core biopsy, and digital rectal examination (DRE), is the recommended way to diagnose PC.

2.4.1 Prostate-specific antigen (PSA)

Prostate-specific antigen is an enzyme found in men without disease. PSA is a protease that keeps semen liquid (Neal et al., 1992; Nickel, 1999). The PSA level in prostatic fluid is approximately one million fold higher than that found in the serum. An

epithelial layer, a basal cell layer, and a basement membrane separate the intraductal PSA from the capillary and lymphatic drainage of the prostate (Brawer, 2008). Malignancy or inflammation in prostate interferes with this natural barrier; it believed the leakage of PSA into the serum causing an elevated PSA (Brawer, 2008). PSA is considered the best tumour maker for PC in serum analysis, but the specificity of serum PSA is low (Sardana et al, 2008). On the other hand, however, tissue expression of PSA is highly specific for prostate tissue (Sardana et al., 2008). There is a decreased PSA immunoreactivity in adenocarcinomas with higher Gleason scores, whereas all with a Gleason score six or seven were reactive for PSA (Goldstein, 2002). Selection of PSA cutoffs depends on the physicians' view of sensitivity-specificity tradeoffs. For PSA of >4 ng/ml, there is a 1 in 3 chances of finding cancer, regardless of patient age (Catalona et al., 1996). Biopsy detected PC including high-grade cancers is not rare with a PSA upto 4.0 ng/ml, level usually considered as normal (Thompson et al., 2004). PSA tends to rise with age, might be due to BPH-growth in transitional zone or deterioration of glandular structure in elderly prostate, facilitating more PSA to leak back into the circulation (Berry et al., 1984). Due to these above reasons, a cut-off 4.0 ng/ml, to some extent not logical (Shaida & Malone, 2008).

2.4.2 Digital rectal examination (DRE)

DRE is the standard way to define texture, shape, size and tenderness of the prostate gland. It is simple and virtually complication-free, but dependent on the examiner and therefore subjective (Varenhorst et al., 1993). DRE is less effective than PSA in finding PC but cancers in men with normal PSA levels sometimes found (American Cancer Society, 2015). DRE is limited because the procedure only allows palpating the posterior surface of the gland. Men with abnormal DRE should therefore proceed to core biopsy regardless of PSA value (Dunn & Kazer, 2011).

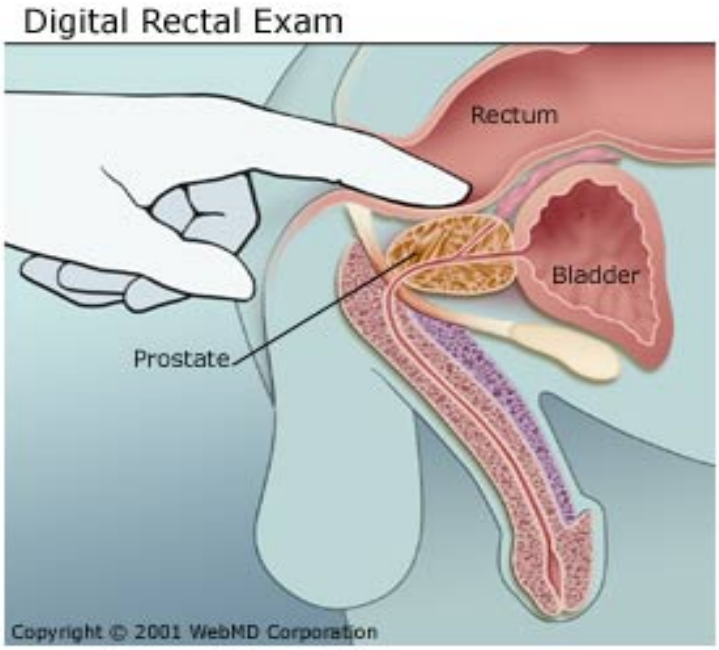


Figure 2: Digital Rectal Examination

(Reprinted with permission from WebMD Corporation).

2.4.3 Core biopsy

The clinical judgement and recommendation to proceed with a prostate biopsy depends on risk factors, such as PSA, DRE, a positive family history of PC, age, previous prostate biopsy, as well as the patient's life expectancy (Foley et al., 2016). EAU guidelines (2011) recommended 10 cores as a minimum. Saturation biopsy protocols (at least 20 cores) are occasionally used and regarded as a valuable tool by some authors (Ravery et al, 2008; Pal et al., 2012), but others claim that there is little increase in detection rate (Eichler et al, 2006). However, the probability of missing a cancer with prostate biopsy under TRUS guidance estimated at 25 %, even with saturation biopsies (Aganovic et al, 2011; Shariat, 2011). Transperineal Template Prostate Biopsy (TPTPB) is a technique that has gained more popularity over the last decade. A study assessed TPTPB in the initial and repeated biopsy setting, and found high rates of cancer detection (80%) in biopsy naı¨ve men, and with a rate of 46.9 % as a repeat biopsy (Taira et al. 2010). This partly been attributed to the fact that TPTPB detects, in particular, tumours located in the apical and anterior zones of the prostate, often poorly sampled by TRUS biopsy (Mabjeesh et al 2012; Dimmen et al, 2012).

2.4.4 Transrectal ultrasound (TRUS)

TRUS with rectal probe is being used to define prostate gland and for assistance during core biopsy. Low echogenicity usully give rise to the suspicion of cancer, confirmed by core biopsy. Today, Magnetic Resonance Imaging (MRI) is widely used to improve the diagnostic sensitivity of prostate biopsy (Toner et al., 2015). Prostate volume can be assessed by various methods, of which the most commonly used in TRUS is the ellipsoid formula (height*width*length*π/6) (Terris & Stamey, 1991; Bangma et al., 1996; Kälkner et al., 2006).

Histopathology

PC can be divided into tumors derived from the epithelial component and the nonepithelial/stromal component. The epithelial derived tumors further subdivided into the most common morphologic appearance to *acinar***,** comprising 90% of tumors and have variants such as microacinar, atrophic, pseudohyperplastic, and signet ring (Glaessgen, 2008). The *non-acinar* group includes ductal, sarcomatoid, and small cell carcinoma, as well as urothelial carcinoma. The rarer nonepithelial/stromal tumors occurring in the prostate include leiomyosarcomas and solitary fibrous tumors (Humphrey, 2012).

A prospective diagnostic study, aimed to increase the specificity compared to PSA in Swedish men aged between 50 and 69 years, was recently published (Grönberg et al., 2015). A predefined STHLM3 model bloodtest was used, consisting of a combination of plasma protein biomarkers as PSA, free PSA, intact PSA, hK2, MSMB, MIC1, genetic polymorphisms [232 SNPs], and also including clinical variables such as age, family history, previous prostate biopsy and prostate examination. The STHLM3 model performed significantly better than PSA alone for detection of cancers with a Gleason score of at least 7. PSA test using a cutoff of ≥3 ng/mL to diagnose high-risk prostate

cancer and the use of the STHLM3 model is estimated to reduce the number of biopsies by 32% and would avoid 44% of benign biopsies.

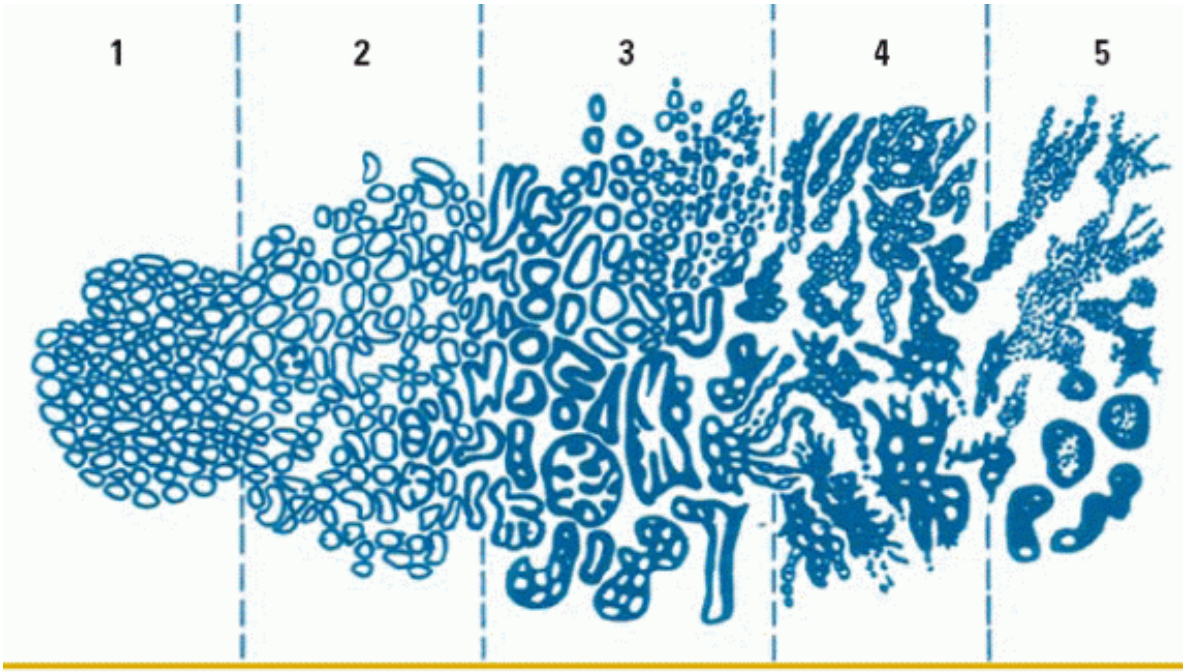
The WHO grading system (WHO, 1980) was previously the standard for grading prostate adenocarcinoma histopathologically. The Gleason grading system, using core biopsy-results, has becoming more and more popular since the 1990´s (Gleason & Mellinger, 1974; Gleason 1992).

The WHO grading system

The WHO grading system is a cytological grading system, where PC tumours are divided into three grades (G1-3 = well, moderately or poorly differentiated), based on glandular differentiation and nuclear pattern (WHO. Geneva 1980).

The Gleason grading system

WHO recommends the Gleason score (GS) as the official grading system in PC with core biopsy, where one can expect more prognostic information than from cytological grading (Eble, 2004; Roach et al., 1999). The Gleason grading system was developed between 1960 and 1974 by reviewing an accumulated number of around 5000 PC patients in randomized clinical trials (Bailar et al., 1966; Gleason 1966; Gleason & Mellinger, 1974; Gleason, 1992). Extent of glandular differentiation and growth patterns are analysed microscopically resulting into 1-5 patterns. The primary and secondary pattern, i.e the most prevalent and second most prevalent pattern are added to get a GS or sum (GS=Gleason pattern 1 + Gleason pattern 2). The score can range from 2-10. If the tumour has only one pattern, the GS obtained by doubling that pattern. In daily practice a cut-off at 5% often used for inclusion in the GS (Glaessgen, 2008). Numerous studies shown that GS is an independent and very powerful prognostic factor for prediction of natural history of PC (Albertsen et al., 1995; Egevad et al., 2002a; 2002b; Andren et al., 2006; Berney et al., 2007). GS used for assessment of risk for recurrence after RP (Epstein et al., 1996; Han et al., 2001; Hull et al., 2002; Han et al., 2003) or radiotherapy (Zagars et al., 1995; Green et al., 1998).



Source: Gleason DF. Histologic grading and clinical staging of prostatic carcinoma. In: Tannenbaum M, ed. *Urologic Pathology: The Prostate*. Philadelphia: Lea & Febiger, 1977;171.

Figure 3. Gleason Grading differentiation.

2.4.5 TNM classification

TNM classification is used for staging of PC according to The International Union Against Cancer (Leslie et al., 2009), Table 1.

Table 1. Tumour Node Metastasis (TNM) classification according to UICC (Leslie et al., 2009).

T-primary tumour

TX Primary tumour cannot be assessed.

T0 No evidence of primary tumour.

T1 Clinically unapparent tumour not palpable or visible by imaging.

T1a - Tumour incidental histological finding in 5% or less of tissue resected.

T1b-Tumour incidental histological finding in more than 5% of tissue resected

T1c – Tumour identified by needle biopsy (e.g. because of elevated prostate specific antigen, PSA level)

T2 Tumour confined within the prostate[1].

T2a – Tumour involves one half of one lobe or less.

T2b – Tumour involves more than half of one lobe, but not both lobes.

T2c - Tumour involves both lobes

T3 Tumour extends through the prostate capsule[2].

T3a – Extracapsular extension (unilateral or bilateral) including microscopic bladder neck involvement.

T3b –Tumour invades seminal vesicle(s)

T4 Tumour is fixed or invades adjacent structures other than seminal vesicles: external sphincter, rectum, levator muscles, and/or pelvic wall

N – Regional lymph nodes[3]

NX - Regional lymph nodes cannot be assessed

N0 - No regional lymph node metastasis

N1 – Regional lymph node metastasis

M – Distant meatastsis[4]

MX - Distant metastasis cannot be assessed

M0 – No distant metastasis

M1 – Distant metastasis

M1a - Non-regional lymph node(s)

M1b – Bone(s)

M1c – Other site(s)

[1] Tumour found in one or both lobes by needle biopsy, but not palpable or visible by imaging, is classified as T1c.

[2] Invasion into the prostate apex, or into (but not beyond) the prostate capsule, is not classified as pT3, but as pT2.

[3] Metastasis no larger than 0, 2 cm can be designated pN1 mi.

[4] When more than one site of metastasis is present, the most advanced category should be used.

2.5 PROGNOSIS

Prognosis prediction in tumour pathology is one of the greatest challenges (Burke et al., 2005). Despite attempts to introduce new biomarkers, histopathological grading remains the most important tissue-based predictor of prognosis for PC (Albertsen et al., 1995; Glaessgen, 2008). The clinical course of PC is highly variable. Prognosis and survival is largely dependent on stage, PSA and histological grading (Mikuz 1997; Oesterling 1991; Partin et al., 1997). In many men cancer will remain clinically insignificant and asymptomatic several years after diagnosis (Chodak et al., 1994; Johansson et al., 1997). Although the prognostic value of PSA is limited, measurement of the proportion of free PSA has improved the identification of patients with aggressive disease (Stenman et al., 2005). Furthermore, the rate of increase in serum PSA reflects tumour growth rate and prognosis (Stenman et al., 2005). Algorithms based on the combined use of free and total PSA and prostate volume in logistic regression can improve the diagnostic accuracy for prostate cancer, and other new markers may provide additional prognostic information (Stenman et al., 2005). Nomograms often used to predict biochemical recurrence-free survival (BRFS) for the different treatment modalities available and to aid in treatment selection (Zelefsky et al., 2007; Stephenson et al., 2006; Potters et al., 2010). However, as the definitions of BRFS differ across the various treatments, the ability of these nomograms to correlate BRFS appropriately with the more important endpoint of PC-specific mortality among different treatments remains unclear (Simon et al., 2015).

2.6 TREATMENT OF PROSTATE CANCER

Curative intended treatments for PC are surgery and radiotherapy. Other strategies, like Active Surveillance or Watchful Waiting are appropriate for some patients.

2.6.1 Surgery

There are four main types of radical prostatectomy (RP): Open retropubic prostatectomy, open perineal prostatectomy, laparoscopic prostatectomy, and robot-assisted laparoscopic prostatectomy. Salvage RP is an option for highly selected ptients with local recurrence after EBRT or Brachytherapy (BT) in absence of metastasis.

Open radical prostatectomy: This has been the most common surgical procedure with retropubic approach, but however, since 2005 it has been estimated that >75% of RPs performed using the *da Vinci* platform (Mottrie & Ficarra 2010; Mottrie et al., 2011).

Open perineal prostatectomy: This method used less frequently than the retropubic approach. This is because the nerves can't be spared easily, nor lymph-nodes be removed by using this surgical technique. However, this procedure takes less time and may be an option if nerve-sparing approach or lymph-node dissection aren't needed. In cosmetic point of view, the retropubic approach is better with a smaller incision.

Laparoscopic radical prostatectomy. Several small cuts needed to make to place the tools and a laparoscope placed inside through one of the cuts. This helps to gain a wider perspective inside.

Robotic-assisted radical prostatectomy. Laparoscopic surgery in this method uses a robotic system. It allows a more precise response and can be performed routinely with a relatively small risk of complications. Surgical experience, clinical patient characteristics, and cancer characteristics may affect the risk of complications. Blood loss and transfusion rates are usually significantly lower with this procedure than with laparoscopic method (Novara et al., 2012).

Nerve-sparing procedures represent the approach of choice in all men with normal erectile function and organ-confined disease. Robot-assisted laparoscopic technique is the gold standard surgical approach for clinically localized PCa in the United States and increasingly used in Europe (Novara et al., 2012). High BMI, large prostate volume, prior abdominal surgery, prior BPH (Benign Prostate Hyperplasia) surgery, or presence of median lobe may make the surgical procedure more difficult, possibly increasing operative time, blood loss, or catheterization time (Novara et al., 2012).

2.6.2 Radiotherapy

Three-dimensional conformal RT (3D-CRT) remains the gold standard in external-beam RT (EBRT) in many countries and institutions. However, image-guided RT (IGRT) and intensity-modulated RT (IMRT), which is an optimized form of 3D-CRT using implanted markers in the prostate, should become the standard treatment of choice (Bauman et al., 2012). 3D-CRT is a technique where the beams of radiation used in treatment shaped to match the tumour. 3D dose planning systems and treatment accelerators equipped with multi-leaf collimators have made 3D-CRT possible (Lennernäs et al., 1995). Compared to EBRT, this method uses 40-50% lesser volume of normal tissue in high-dose region during treatment of PC and feasibility study showed greater reduction in gastro-intestinal (GI) toxicity compared to those of EBRT (Dearnaley et al., 1999).

RT and androgen suppression: The rationale in combining androgen suppression with RT are to decrease prostate volume, reducing local relapse-risk within irradiated area, decreasing risk of distant metastases, improving the effectiveness of radiation (Bolla et al., 2012). Animal studies have shown that neoadjuvant ADT provides the greatest effect according to TCD 50, an apoptotic response and result in prolonged suppression of tumor growth (Zietman et al., 1997; Kaminski et al., 2003, Bolla et al., 2012).

Dose-escalated EBRT: Radiation doses of 64-70 Gy, not as effective as previously believed in the treatment of localized PC (Peeters et al., 2006). Dose-escalation has been possible with 3D-CRT. Studies showed improved freedom from failure (FFF) at the expense of increased overall GI-toxicity (Pollack et al., 2002; Zietman et al., 2005). However, in another randomized study, authors found a significant improved FFF using higher radiation dose of 78 Gy (Peeters et al., 2006). Higher cure rates seen with increasing doses and patients with high risk features seem to benefit most from dose escalation (Nilsson et al., 2004). Dose escalation did not result in significant deterioration of quality of life (Al-Mamgani et al., 2011). Hypofractionated RT, with high biologic effective dose using CRT, found to be well tolerated with minimal severe acute toxicity, compared with conventional RT (Viani et al., 2013).

Intensity modulated radiation therapy (IMRT) is a method of radiation technique where little beamlets of varying intensity occur after division of the beam. This method allows delivering required doses to target volumes while sparing normal structures. The introduction of IMRT or later developments volumetric modulated arc therapy (VMAT) or Rapid Arc, made it possible to treat targets like lymph node volumes, prostate with seminal vesicles (Lennernäs et al., 2011). Use of IMRT compared to CRT associated with less GI-morbidity and fewer hip-fractures but more erectile dysfunction; IMRT compared to proton therapy associated with less GI-morbidity (Sheets et al., 2012).

Brachytherapy (BT) is a specilized form of RT that entails the placement of an emitting radiation source (most commonly a radioactive isotope) in immediate proximity to macroscopic tumour. BT considered the ultimate form of conformal RT because it is unparalleled in its ability to direct a large dose of radiation to the tumour while minimizing exposure to surrounding sensitive normal structures (Petereit et al., 2015). BT offered using low-dose-rate (LDR) or high-dose-rate (HDR) techniques. Palladium-103 or Iodine-125 are radioactive sources used in LDR. These sources permanently placed in the prostate, whereas Iridium-192 used in HDR technique is temporary. BT usually performed using spinal or general anesthesia, where LDR delivered as a one-day procedure and HDR with overnight stay at the hospital with a urinary catheter. External beam radiotherapy combined with brachytherapy is used depending on stage of PC.

Permanent brachytherapy (seeds): In this LDR-BT, radioisotope placed in the prostate permanently where ^{103}Paladium or ^{125}Iodine usually used as source. This treatment offered alone or in combination with EBRT. Since the energy of the implanted sources is low, the radiation exposure surrounding the patient is low. With ^{125} Iodine source, a dose of 145 Gy achieved whereas with ^{103}Paladium, 125 Gy achieved. For both isotopes, the prescribed dose reduced when combined with external-beam radiation (Beyer, 2001). High dose rate brachytherapy (HDR-BT): ^{192}Iridium is a radioactive isotope of Iridium, usually used as radiation source in this HDR-BT. Temporarily placed sources in prostate emit radiation to kill cancercells. This can be used as monotherapy or in combination with EBRT. TRUS guided target definition used to position the implants. A minimum of 100 Gy achieved within the prostate when used in combination with EBRT. This afterloading technique was developed in Kiel in the 80ies (Bertermann 1986) and then distributed that technique to Swedish hospital where it was modified and first introduced in 1988 (Borghede et al., 1997).

2.6.3 High-intensity focused ultrasound

This may be a treatment option in low-risk PC. However, evidence on efficacy is limited and there is a concern as PC is commonly multifocal. Therefore, this procedure should only be used with special arrangements for clinical governance or research (NICE guidelines, 2012). This offered as salvage therapy to patients with recurrent PC after EBRT, brachytherapy or proton therapy (Uchida et al., 2011).

2.6.4 Cryotherapy

This is an intervention that involves freezing of the prostate gland. It may be a treatment of choice for men with localized disease where radical prostatectomy is contraindicated, and is usually restricted to men with stage T1-2 N0M0 PC (Mouraviev & Polascik, 2006). During cryotherapy, a cryoprobe inserted into the prostate under ultrasound

guidance and the prostate frozen to a temperature of −100° to −200° for approximately 10 minutes (Mouraviev & Polascik, 2006). Complications arising may be erectile dysfunction, urinary incontinence and urinary retention, rectal pain, and fistula.

2.6.5 Endocrine treatment

Use of androgen deprivation therapy in different settings depends on the intention for the individual patient. *Orchiectomy:* Testicular ablation or orchiectomy performed in acute situations, where spinal cord compression is an alarming sign (Damber & Peeker, 2012). This is a very cost effective method and easy to perform, and an immediate castration level of testosterone will be achieved.

Luteinizing hormone releasing hormone (LHRH) agonist/antagonist: LHRH agonists or antagonists are as effective as surgical castration (Damber & Peeker, 2012). It takes, however, two-four weeks to achieve castrate levels of testosterone with LHRH-agonist but very quick effect achieves with LHRH-antagonist as surgical castration (Damber & Peeker, 2012). These drugs used sub-cutaneously every month, or every three to six months' interval. They act on anterior pituitary gland to subsequent decrease the testosterone production by testes. Initial rise in testosterone noted in LHRH-agonist use, which usually prevented by adding anti-androgen.

Antiandrogens*:* These drugs are acting by blocking androgen receptors, resulting in growth-inhibition of PC cells (Iversen et al., 2001; Berges & Tombal, 2008). They may be steriodal or non-steroidal. The testosterone levels in blood remain unchanged or increased. Neo-adjuvant anti-androgens, not advised in RP, but used as neo-adjuvant and concomittant treatment during curative radiotherapy, combined with LHRH-agonist, and as adjuvant monotherapy in high risk PC.

Estrogens: Estrogens used in advanced PC (Damber & Peeker, 2012). Risk for gynecomastia and cardiovascular morbidity increased with this treatment (Damber & Peeker, 2012). Parenteral adminstration have shown to diminish the cardiovascular morbidity (Henriksson et al., 1991).

Total androgen blockade (TAB): The combination of antiandrogen and surgical or medical castration called total or maximum androgen blockade (TAB). This strategy used to minimize the testosterone to castration level (Prostate Cancer Collaborative Group, 2000; Klotz, 2008). This used in localized or metastatic settings.

2.6.6 Deferred treatment:

Active surveillance (AS) or watchful waiting may be the options used to different risk categories of PC depending on life expectancy and co-morbidities. AS may be an option suggested to men with longer life expectancy to maintain a follow-up schedule with PSA, DRE and core biopsy at regular intervals. AS is likely to produce a very modest decline in PC specific survival among men diagnosed with low-risk PC but could lead to significant benefits in terms of quality of life (Xia et al., 2012). The lack of clinical trials that directly compare various treatment modalities or identify the best management, especially for men with low-risk PC, makes the decision-making process difficult for both patients and physicians. Although general agreement exists on definition of candidates for

AS, men with low-volume and low-grade disease thought to be at low risk for rapid progression. Several key issues, such as optimal timing and appropriate triggers for active treatment remain to be established. The decision to initially pursue AS rather than active treatment after PC diagnosis is complex and involves factors, including estimation of life expectancy, consideration of quality of life, and assessment of ultimate oncologic outcome (Fung-Kee-Fung et al., 2013). Authors in a randomized trial comparing RP and watchful waiting showed reduction of disease specific mortality, overall mortality, risk of metastasis and local progression in RP compared to watchful waiting (SPCG-4) (Bill-Axelson et al., 2005). In men with locally advanced PCa for whom local therapy may not be mandatory, watchful waiting is a treatment alternative rather than ADT, with equivalent oncologic efficacy (Mottet et al, 2015).

2.6.7 Vaccine in prostate cancer

Quite a number of clinical trials been conducted in PC with vaccination. Unique proteins expressed by PC cells are PSA, prostate-specific membrane antigen (PSMA) and prostatic acid phosphatase (PAP), which can be specifically, targeted making this disease suitable for vaccine-based approach (Kokhaei, 2006). Specific immune responses to vaccine, seen in trials, have a significantly longer median progression-free survival in responders (Small et al., 2000). In a placebo controlled randomized trial, an improvement in clinical outcome in patients with Gleason score maximum 7 found (Schellhammer et al., 2005).

2.7 URINARY, SEXUAL AND BOWEL SYMPTOMS OF CURATIVE TREATMENTS

Patients with locally advanced PC, randomized to RT + endocrine therapy vs. endocrine therapy alone in the SPCG-7 trial (Fransson et al., 2009). After 4 years, moderate to severe urinary bother were reported by 18% in the combination arm, vs. 12% in the endocrine arm. Corresponding figures for overall bowel problems were 11% vs. 7%, whereas 85% vs. 72% expressed having erectile dysfunction, respectively. Social function decreased in the combination arm. After 5 years, urinary, rectal, and sexual problems were slightly more frequent in the combination arm (Widmark et al., 2009).

Dose escalation done with a 4-to 8 Gy-boost using the Beam-Cath technology (Beam Point AB, Umeå, Sweden) in 195 localized PC patients with 70-Gy conventional EBRT compared to another cohort of 168-patients treated with conventional way without increase in GI or GU late side effecs at 1 or 3 years' post-therapy (Fransson et al., 2002).

In a 5-year follow-up study in PC patients treated with RP, external beam RT and brachytherapy without hormonal treatment, urinary irritative-obstructive adverse effects and some sexual dysfunction in EBRT and brachytherapy group observed (Pardo et al., 2010). In addition, EBRT caused bowel bother. RP caused urinary incontinence and

sexual dysfunction, but improved pre-existing urinary irritative-obstructive symptoms. Relevant differences between treatment groups persisted for up to three years of follow-up, although the difference in sexual adverse effects between brachytherapy and prostatectomy tended to decline over long-term follow-up (Pardo et al., 2010).

Primary PC treatment often results in suboptimal urinary, bowel and/or sexual function. After treatment, the patients typically report high HRQoL scores. This discrepancy between disease-specific and generic results raises the question which meaning side effects actually have to patients. In a qualitative study with semi-structured interviews, the authors found two possible mechanisms, which could explain this discrepancy: insensitivity of generic HRQoL measures to these specific symptoms and adaptation to response shift (Korfage et a.l, 2006). Patients trivialized sexual (dys) function referring to old age and, did not view these dysfunctions as aspects of health. Many patients accepted the side effects as inevitable consequences of having being treated for PC, a condition they perceived as life threatening (Korfage IJ et al 2006).

Volumetric modulated arc therapy/Intensity modulated RT are common techniques used to minimize side effects from surrounding normal tissues. In a Swedish study, mild GU-symptoms were noted one year after RT compared to baseline; sexual symptoms deteriorated both during and after RT. Moreover, ADT-use was associated with worse sexual symptoms (Sveistrup et al., 2015).

In a meta-analysis, authors found the predicted probability of maintaining erectile function after brachytherapy was 0.76, after brachytherapy plus EBRT 0.60, after EBRT 0.55, after nerve-sparing RP 0.34, after standard RP 0.25 and after Cryotherapy 0.13 (Robinson et al., 2002).

Of the quality-of-life outcomes measured, erectile dysfunction is one of the most difficult outcomes to evaluate, as there is always a baseline variation. Moreover, the psychological impact associated with cancer diagnosis and treatment morbidity makes it difficult to estimate erectile dysfuntion caused by the treatment (Garcia et al., 2015). The aggressiveness of the nerve preservation at the time of surgery, is a balance between oncological control and future functional outcomes (Tewari et al, 2008). RP is associated with urinary incontinence and sexual dysfunction (Steineck et al 2002).

2.7.1 Radiotherapy-induced side effects

The prostate gland is surrounded by urinary bladder, rectum and urethra. These organs are at risk for receiving radiation when the PC is irradiated. To plan a curative intent radiotherapy, it has to be considered that the prostate gland is very movable organ. Radiotherapy always has to be planned with margins in order not to miss the cancer. This in turn gives rise to radiation side effects, classified as acute or late.

Acute side effects: Urethritis is the most common problem and variable. Most patients notice frequency, urgency and mild dysuria. Loose stool or diarrhoea may be another acute side effect, due to proctitis. In LDR, brachytherapy symptoms usually start after 4-5 days and may persist in several months. Urinary retention develops in 10% of patients. In contrast, after HDR brachytherapy, urethritis develops within two weeks and rapidly resolves within 6 weeks (Whelan et al., 2014). Proctitis is more common after EBRT.

Late side effects: Chronic cystitis/urethritis, urethral stricture, rectal bleeding, erectile

dysfunction may be debilitating late side effects of radiation for PC patients. Hypovascularity, decreased perfusion and fibrosis in irradiated areas seem to causing these symptoms.

Radiobiological aspects: Radiation is a form of energy transport. Becquerel discovered the radioactivity in 1896 and extraction of radium by Marie Curie in 1898. The Linear-Quadratic (LQ) model, which first proposed by Douglas and Fowler (Douglas & Fowler, 1976), considers a model, which describes cell killing, both for tumor control and for normal tissue complications. Most common underlying biological rationale is that radiation produces a double strand DNA break (DSB) using a single radiation track. Individual DSB be repaired, but if more than one unrepaired DSB is present in the cell at the same time (arising from two separate radiation tracks), can produce a lethal lesion. A single radiation track can also give rise to a lethal lesion by itself (e.g. point mutation in vital gene, eliminating vital gene, induced apoptosis, etc.) (Brenner et al., 1998). PC has a low growth fraction and has slow proliferation (Khoo et al., 1999; Haustermans et al., 1997). These characteristics are more typical of normal tissues exhibiting late reactions to irradiation (Duchesne et al., 1999). Late-reacting tissues have broad shoulder and steep falloff in cell survival curves, which have been characterized as having a low α/β ratio (α and β describe the linear and quadratic components of the cell survival curve). A majority of studies have estimated the α/β ratio for PC to be low, at approximately 1.5 Gy (Miralbell et al, 2012; Dasu et al., 2012), whereas that for the surrounding normal tissues has been estimated to be >3 Gy. A low α/β ratio indicates greater sensitivity to higher radiation doses per fraction. The biologically effective dose (BED) formula depends on *n* fractions of *d* grays each modified by a factor 1+d/ α/β, the relative effect:

$$BED = nd*(1+d/\ \alpha/\beta)$$

This allows for alterations of dose-per-fraction or dose rate without changing the effective dose.

2.8 TREATMENT IN ADVANCED PROSTATE CANCER

ADT has been the backbone of treatment for metastatic PC since the 1940s (Sweeney et al., 2015). ADT induces remission in 80 to 90% of men with advanced PC. Within two and a half years, however, an androgen-independent phenotype usually emerges (Hellerstedt & Pienta, 2002). Castration resistant PC (CRPC) arises when castration treatment fails (Pienta & Bradley, 2006). Three phase III trials in recent years compared ADT versus ADT plus Docetaxel: In CHAARTED trial docetaxel improved OS (HR 0.61, 95% CI 0.47-0.80) (Sweeney et al., 2014). In GETUG-15 trial, similar progression-free survival (PFS) found but no survival difference (HR 1.01; 95% CI 0.76-1.25) (Gravis et al., 2013). The STAMPEDE trial confirmed both PFS and OS benefit for adding docetaxel to ADT (James et al., 2016). Based on trials ADT recommended, as first-line treatment in metastatic hormone naïve disease, and docetaxel should be offered in men, fit enough for chemotherapy in this situation. Men treated with ADT have to be informed that regular exercise reduces fatigue and improves quality of life (Parker et al., 2015). Cabazitaxel, which is a semi-synthetic derivative of a natural taxoid plus prednisolone used to increase overall survival in second-line chemotherapy (de Bono et al., 2010). Immunotherapy with Sipuleucel-T, using activated autologous dendritic cells shown death reduction by 22% compared to placebo in men with asymptomatic or minimally symptomatic metastatic CRPC in pre-chemo

era (Kantoff et al., 2010), permitted in USA, but not in Europe. Corticosteroids minimize adrenal production of androgens and lead to favorable biochemical and clinical responses. Dexamethasone appears to be more active than prednisolone (Venkitaraman et al. 2015). Abiraterone acetate, CYP17 inhibitor, acts by inhibiting the synthesis of both estrogenic and androgenic steroids in CRPC (Reid et al., 2010; Danila et al., 2010; Ryan et al., 2010) shown to improve PFS significantly compared to placebo. Another androgen receptor antagonist, Enzalutamide, showed a 4.8-month advantage in median OS compared to placebo (Niraula et al., 2012). Abiraterone or Enzalutamide recommended for symptomatic men with chemotherapy-naïve metastatic CRPC (Parker et al., 2015). In the post-docetaxel setting, both drugs improved OS (de Bono et al., 2011; Scher et al., 2012). Palliation with EBRT against painful bone metastasis is frequently used. In situation with bone metastasis without visceral engagement, Alpharadin (Radium-223) is an alternative (Nilsson et al., 2013). Alpharadin is an alpha emitting nuclide that has shown improved OS and delay the time to first symptomatic skeletal event. Both bone metastases and fragility fractures due to bone loss result in considerable morbidity affecting QoL. Several bisphosphonates including alendronate, pamindronate and zoledronic acid, have shown to prevent bone mineral density loss in advanced PC patients (Michaelson et al., 2007). The biologic agent denosumab is more effective than zoledronic acid in preventing skeletal-related events in CRPC but not shown improvements in PFS or OS (Fizazi et al., 2011).

2.9 HEALTH RELATED QUALITY OF LIFE AND PROSTATE CANCER

2.9.1 Health related quality of life

The term quality of life (QoL) can be found in different disciplines. Philosophers have since antiquity referred to QoL as “the good life”, while in psychology QoL refers to the mental state, in sociology to welfare, and in economics to the gross domestic product (Brulde, 2003; Cella, 1993a). In 1948, the World Health Organisation (WHO) introduced a concept of health by defining it as “a state of complete physical, mental and social well-being, and not merely the absence of disease” (WHO, 1948). During the last decades, the interest has increased in patient-reported outcomes (PRO’s), defined as any report coming directly from the patient about a health condition and its treatment without the intervention of an observer (Cella, 1993a; Osoba, 2007). Health related quality of life (HRQoL) is one example of PRO’s.

HRQoL is one of the important aspects of this thesis. Most definitions of HRQoL agree that the “concept is a multidimensional construct which includes patients’ perceptions of both negative and positive aspects of at least four dimensions of quality of life: physical, emotional, social functions as well as disease and treatment related symptoms” (Fayers, 2007). HRQoL includes the subjective perception of symptoms and functions that only be understood from the patient´s point of view. Symptoms differ from signs. Signs are more objective such as body temperature, while symptoms are the patients’ subjective perception of disease and their expression of it, such as having pain (Rhodes, 1998). The concept of HRQoL emerged from the broader concept QoL, and is, by definition, more focused on aspects of life that influenced by or that can influence one´s health directly (Bergner, 1989). HRQoL in the present thesis, defined by the subscales, constituted with the responses to the items, in each scale.

2.9.2 Assessment of health related quality of life

Increasing interest in the systematic assessment of HRQoL in cancer patients using standardized, self-administered measures has emerged over the past two decades (Cella et al., 2007). HRQoL is a patient-centered variable, measured using questionnaire also known as instruments. The questionnaires developed using principle of psychometric test theory and are evaluated rigorously before use to ensure that collected data are valid and reliable (Penson & Litwin, 2003). Instruments are best while using self-assessment and thus the patient is best suited to assess his/her HRQoL (Aronsson 1989; Cella 1994). The items in the questionnaires most often constructed in scales. Each scale measures a different aspect or domain of HRQoL. HRQoL- instruments should fulfill requirements such as reliability, validity, responsiveness, interpretability, practicality and applicability:

Reliability: Refers to how reproducible an instrument or scale is. *Test-retest reliability* is a measure of response stability over time. *Internal consistency reliability* measures the similarity of an individual`s responses across several items, indicating the homogeneity of a scale. Multi-item measures considered more reliable as they are composed of several items allowing for more variation.

Validity: Refers to how perfect a scale or instrument measures the attribute it intended to measure. *Content validity* refers to qualitative assessment of a proposed scale whereas *criterion validity* refers to a quantitative approach. *Construct validity* refers to measure how well the scale or survey instrument performs in a multitude of settings and populations over a number of years.

Responsiveness: Refers to how sensitive the scales are to changes over time or in stages of illness (Fayers et al., 2005).

Interpretability: Refers to the degree to which meaning to the scores obtained by a measure, for instance presence of meaningful reference groups. In longitudinal studies, patients may serve as their own controls. Clinically relevant mean score differences have been suggested for some of the cancer specific HRQoL questionnaires (King 1996; Osoba et al., 1998).

Practicality: Refers to ensuring data quality by minimizing the bias. A questionnaire should be short and easily completed, and the procedures should be standardized and clearly described in the study protocol.

Applicability: Refers to the usefulness in a given population with respect to cultural and linguistic characteristics. This adaptation process follows a strict order and questionnaires used been tested in the appropriate cultural setting.

2.9.3 HRQoL instruments

A number of instruments been developed for the assessment of HRQoL. Irrespective of illness or the condition of the patient, instruments like Short Form-36 (SF-36) (Ware et al., 1992) and the Nottingham Health Profile (NHP) (Hunt, 1981) measure HRQoL. Cancer-specific instruments, developed in international collaboration, include the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 (EORTC QLQ-C30) (Aronsson et al., 1993), which been used in the present thesis. Another questionnaire originally validated for cancer patients is a general quality of life instrument intended for use with variety of chronic illnesses called Functional Assessment of Cancer Therapy-General (FACT-G) (Cella et al., 1993).

For evaluation of disease-specific HRQoL in PC, there are several questionnaires, such as the Expanded Prostate Cancer Index (EPIC) (Wei et al, 2002), Patient-Oriented Prostate Utility Scale (PORPUS) (Krahn et al, 2000), Prostate Cancer Quality of Life Instrument (PC-QoL) (Schmidt et al., 2014), The University of California Los Angeles Prostate Cancer Index (UCLA-PCI) (Litwin et al., 1999) and the prostate FACT (FACT-P) (Esper et al., 1997). The EORTC Quality of Life Questionnaire Prostate-25 (EORTC QLQ-PR25), developed by the EORTC Quality of Life Group (Borghede et al., 1996). It is a PC specific questionnaire, validated in an international study (Van Andel et al., 2008), and used in the present thesis. The Prostate Cancer Symptom Scale (PCSS) (Fransson et al., 2001) and the questionnaire used in the SPCG-4 study developed in Sweden for the assessment of HRQoL in PC patients (Steineck et al., 2002). Questionnaires used in this thesis presented in Table 8.

2.9.4 Health related quality of life in prostate cancer

2.9.5 HRQoL and PC surgery

Surgical intervention is associated with erectile dysfunction (ED) and urinary incontinence (Alemozaffar et al., 2011; Resnik et al, 2013). Nerve sparing RP in one study did not show any difference in sexual function compared to men who underwent non-nerve sparing technique (Talcott et al., 1997). In another study, however, significantly better sexual function reported in men who underwent nerve-sparing surgery (Litwin et al, 1999). Similar conclusions drawn from in a study in which nerve-sparing procedures were associated with better recovery of sexual QoL than procedures that were not nerve-sparing (Sanda et al, 2008). Incontinence and impotency rates of 66% and 88%, respectively, were reported in another study of 1 069 patients during post-prostatectomy period of six months (Kao et al., 2000). A complete impotency rate of 75% and incontinence rate of 35% at 12 months after RP observed (Talcott et al, 2001). In a longitudinal study, >90% of the patients recovered to baseline in all domains at 12 months. By this time 56% recovered their urinary function. Mean recovery time for sexual function from baseline was eleven months (Litwin et al., 2001). In one study, 8 % of PC patients remained continent after >18 months' post-surgery, whereas 60 % reported being impotent (Stanford et al, 2000). A multi-institutional longitudinal study revealed delayed recovery of urinary and sexual function in patients who underwent laparoscopic-RP, which appeared to affect their general HRQoL (Namiki et al., 2005). Taking age-related changes into account, general HRQoL-scores seemed to remain stable after RP, where the authors found no significant differences in any of the eight domains of the physical composite score at eight years' follow-up. About 15% reported urinary leakage at the one-year assessment, which remained at five years' follow-up. About 85% considered their ability to have an erection as "poor" or "very poor" beyond five years (Namiki et al., 2014).

In a large Swedish prospective, randomized controlled trial, HRQoL were compared between men receiving RP and men on watchful waiting (Bill-Axelsson et al., 2011). Five year outcomes revealed more erectile dysfunction (80% vs. 45%) and urinary leakage (49% vs. 21%), but less urinary obstruction (28% vs. 44%) in men who had undergone prostatectomy (Steineck et al., 2002). Bowel function, anxiety, depression, well-being, and overall HRQoL were similar in the two groups after five years, but at six to eight years, anxiety and depression deteriorated significantly for those who chose watchful waiting (Johansson et al., 2009).

In summary, RP influences HRQoL by decreasing functions in sexuality and urination. Controversy remains about method of choice to minimize sexual problems, but the nerve-sparing technique is to be preferred in order to retain sexual function. Urinary incontinence after RP is a common problem, which gradually diminishes in longer follow-ups. Bowel function appears not a problem after RP.

HRQoL and PC radiation therapy (RT)

RT regimens are formulated based on PC risk-level, where radiation with or without ADT can be chosen. Recovery of sexual function was worse among patients who received EBRT and androgen-suppression therapy combined with RT than in those who received RT alone in a randomized study (Sanda et al., 2008). Urinary symptoms improved over baseline after 24 months. Patients in the brachytherapy group reported significant detriments in urinary irritation or obstruction and incontinence, compared to baseline. Erectile dysfunction been reported to have a maximum drop at 3 months' post-RT, with a recovery at one year, been found to remain stable at two and three years' follow-up (Budäus et al., 2012; Incrocci & Jensen, 2013). In a Swedish study, generally high levels of HRQoL were noted in patients treated with combined EBRT + HDR BT + ADT, in spite of persistent urinary urgency, increased stool frequency and erectile problems five years' post-treatment (Wahlgren et al., 2005). In a randomized study with

conventional versus hypofractionated regimens in intermediate-risk localized PC, authors found low incidence of patient-reported bowel symptoms and were similar in compariaon to randomized groups (Wilkins et al., 2015).

In short, RT influences HRQoL by increasing urinary irritative/obstructive symptoms in the acute phase, mainly after brachytherapy, whereas bowel function deteriorates after EBRT. RT negatively influences both sexual- and urinary functions, and sexual functions more influenced by the addition av ADT. Hypofractionated regimens might be used in intermediate-risk PC without compromising HRQoL.

HRQoL and comparison between radiation therapy and radical prostatectomy

Treatment modalities for localized PC have shown treatment-related side effects such as incontinence, bowel disturbances, and impact on sexual activity (Wei et al., 2002; Frank et al., 2007). In a cross sectional study, comparing HRQoL between RP and a combined EBRT & HDR-brachytherapy, compared with normative data; high levels of overall QoL found in both groups, comparable with normative data (Hjälm-Eriksson et al, 2015). Statistically significant differences in bowel and urinary problems noted favoring RP-group, however clinical significance rated there small. No differences in sexual functions noted between the groups. Older men in a population-based study, observed to have urinary incontinence (15%) or decreased bowel functions (6%) (Litwin, 1999). HRQoL-studies in 3D-CRT-treated PC patients revealed urinary incontinence in 13-23% (Hanlon et al., 2001; Shrader-Bogen et al., 1997; Litwin et al., 1995), whereas for a combined EBRT-BT, 12-24% indicated daily urine-leakage (Joly et al., 1998; Talcott et al., 2001). In RP-treated patients, urinary leakage reported by 40-46% of the patients (Litwin et al., 1995; Shrader-Bogen et al., 1997; Yarbro et al., 1998). Comparing HRQoL-variables between RP or LDR-brachytherapy treated men, significantly lower scores in physical, social and role functioning in the RP-group noted during the first three months, but these returned to baseline at six months. In the LDR-group, no significant decrease in HRQoL-scores noted during the first 12 months' post-treatment (Namiki et al., 2006).

In summary, overall HRQoL in patients treated by RP or RT (combined technique with EBRT + Brachytherapy) is comparable with that of normative data. Level of urinary incontinence in men lies around 25% treated by RT, irrespective of techniques, compared to >40% in RP-treated men. Erectile dysfunction seems problematic in all modalities.

HRQoL and androgen deprivation therapy

An overview of HRQoL studies related to ADT treatments shown in table 2.
There are relatively few papers reporting on the effects of ADT on HRQoL. An 18-years follow-up study reported better HRQoL in RP than in EBRT or ADT alone group (Drummond et al., 2015). Poorer urinary-and sexual function in PC patients treated by RP, RT, or ADT compare to surveillance found in a cohort study of 699 patients. HRQoL scores improved in RP group compared to ADT and surveillance after 12 months (Lubeck et al., 2001). Another cohort study reported 80% impotency in ADT users after one year compared to 30% impotency in patients without ADT (Potosky et al., 2002). In a prospective longitudinal study gradual decreased physical functioning, role functioning and vitality were found in ADT users, compared to those with PC-controls and healthy-controls after one year (Alibhai et al., 2010).

In summary, ADT decreases sexual quality of life. In long-term follow-up, RP patients improve and appear to have better sexual functioning compared to patients treated with EBRT or ADT alone.

Table 2: Overview of HRQoL studies and ADT

Author	Journal/ Year	Study design and purpose	Number of patients	RP/RT and ADT	Instrument	Assessment point after therapy	Results	Conclusions
Basaria et al.	Clin Endocrin 2002	Cross sectional	n=58	n=20 (ADT 12 months) n=18 (nonmetastatic RP/RT) n=20 (age-matched controls)	Watts sexual function questionnaire and other measures to examine bone and fat mass	Baseline and 12 months	BMD significantly lower in ADT than in comparison groups; lower scores in overall sexual function-and QoL scores noted in ADT; ADT patients were more limited in physical-and role functioning	Osteoporosis, unfavorable body composition, sexual dysfunction and reduced HRQoL were found in ADT after 12 months. More studies were warranted
Drummond et al.	J Cancer Surviv 2015	Cross-sectional HRQoL up to 18 years	n=6559	EBRT 34%, RP 28%, EBRT + ADT 18%, ADT 9%, Observation 5%, BT 4%	EORTC C-30, EORTC-PR25	Once at three time points after diagnosis: <5 yrs; 5-10 yrs; >10 yrs	Response rate 54%, HRQoL was better in RP than EBRT or ADT alone; but were similar compared to other groups	Long-term HRQoL varied in survivors depending on the treatment given
Lubeck et al.	Urol 2001	Cohort study	n=699	n=106 (surveillance) n=167 (ADT) n=351 (RP) n=75(RT)	UCLA-PCI SF-36	Baseline and every 3 months up to 9 months	ADT had poorer urinary and sexual function, higher urinary-and sexual bother, as in RP-and RT groups compared to surveillance. In ADT-and surveillance groups, HRQoL scores remained low at 12 months, but RP group showed improvement.	Longer follow-up needed after ADT start to know the impact on HRQoL
Potosky et al.	J Natl Cancer Inst 2002	Population based cohort study	n=661	n=245 (ADT) n=416 (no therapy)	SF-36	Base line and 1 year after therapy	88 patients potent before ADT, 80% became impotent at 1 year and had more physical discomfort, statistically significant decline in vitality, but more satisfied with treatment decision 56% compared to controls (45%). 223 controls (no therapy) were potent, but 30% became impotent after 1 year.	Physical wellbeing and sexual function should be considered in the first year following treatment with ADT
Alibhai et al.	JCO 2010	Prospective longitudinal study	n=259	n=87 (ADT) n=86 (PC controls) n=86 (Healthy controls)	SF-36	Baseline, 3, 6, 12 months	Six minutes walk test was stable in ADT-group, but improved in both controls. Physical function decreased in ADT users especially at 12 month, even role function and vitality decreased gradually compared to controls	Components of QoL are affected within 3 months of starting ADT. Up-front exercise interventions are warranted.

N=number, BMD= Bone mineral density, BT=Brachytherapy, RP=Radical prostatectomy, RT=Radiotherapy, ADT=Androgen deprivation therapy, HRQoL=Health related quality of life, QoL=Quality of life, EBRT=External beam radiation therapy, EORTC=European organization for research and treatment of cancer, C30=Core 30, PR25=Prostate cancer module 25, UCLA-PCI= University of California and Los Angeles Prostate Cancer Index. SF-36= Short Form 36.

HRQoL and active surveillance (AS)

In a Finnish study, no short-term quality-of-life disturbances noted in patients who had adopted AS. None of the patients changed treatment due to anxiety. Surprisinglyly, PC patients on AS, had significantly better mental-and physical HRQoL compared to a general age-stratified Finnish male population (Vasarainen et al., 2012).

2.9.6 Information and Health Related Quality of Life

Shared treatment decision making is a process of interaction between a physician and a patient in which information exchanged about treatment options, personal preferences of the patient, the most relevant choices are deliberated and a decision jointly made about the treatment to be implemented (Charles et al., 1999). Shared decision-making considered an essential component of delivering patient-centered care (Carter et al., 2013). In light of evidence that survival and clinical outcomes may be similar across treatments for many conditions, HRQoL considerations may be the critical factor in medical decision-making (Bergman & Litwin, 2012). Providing adequate information to cancer patients facilitate their adjustment to the cancer experience by increasing perceptions of control, reducing feelings of threat and anxiety, and in improving HRQoL (Lerman et al, 1993; Meredith et al., 1996; Thomas et al., 1999). Satisfaction with information has shown to contribute to physical and social well-being (Davies et al., 2008). Adequate information enhances patients´participation in their treatment decision-making consultations, follow-ups, and at the same time coping with side effects (Bergenmar et al., 2014). Unmet information needs about the disease and its progression linked to negative psychological outcomes such as anxiety and depression (Mesters et al., 2001). Information provision is a key component of supportive care throughout the cancer trajectory and the prevalence of unmet needs do not seem to diminish in patients at follow-up (Harrison et al., 2009).

3 AIMS

Paper 1: to study how PC patients perceive information given at their visits before, during and after completion of curative intented radiation therapy, adopted either primarily or as salvage-radiotherapy after post-surgical PSA relapse. Another aim was to examine the relationship between health related quality of life and information needs.

Paper 2: to prospectively study differences in health related quality of life and side-effects between patients randomized to radical prostatectomy or combined external radiotherapy and high dose rate brachytherapy.

Paper 3: to prospectively study differences in quality of life in PC patients randomized to anti-androgen versus total androgen blockade in curative intended radiotherapy.

Paper 4: to study differences in prostate volume in curative intended PC patients randomized to anti-androgen versus total androgen blockade in curative intended radiotherapy.

4 PATIENTS AND METHODS

4.1 PATIENTS

Paper 1: Questionnaires sent to 660 consecutive patients with PC, who had undergone or planned to undergo radiotherapy (RT) with curative intent between December 2006 and March 2010 at the Department of Oncology, Karolinska University Hospital, Sweden. Eligible patients were identified in the computerized system for patients' medical files. Patients with metastatic disease or PSA relapse after curative intended RT during the study period were excluded (n=4), leaving 656 patients in the final sample.

Paper 2: A total of 89 men with localized/locally advanced PC, clinical stage T1b–T3a, N0, M0 (UICC, TNM, 1992), and a PSA value ≤ 50 ng/ml were randomized between RP versus combined external radiotherapy (EBRT) and high-dose-rate (HDR) brachytherapy in 1996–2001 in Gothenburg, Uppsala, Linköping, Eskilstuna, and Stockholm. Prior to inclusion, the patients given full oral and written information about the study and the respective treatment modality, and provided written informed consent. All included patients underwent total androgen blockade during six months.

Paper 3 and 4: 110 patients with localized/locally advanced PC, referred to the Oncology Department at Radiumhemmet, Karolinska University Hospital, Sweden for curative intended radiotherapy, were included between 2005 and 2011 and randomized between anti-androgen (AA) or total androgen blockade (TAB). Eligible patients screened at the Clinical Trials Unit at the Department of Oncology for inclusion in the study. Randomization was done after informed consent, with a ratio 1:1.

4.2 PROCEDURE

Paper 1: In April 2010, questionnaires, together with an information letter about the study, and a prepaid return envelope sent to the patients from the Unit for Outcome and Quality Assessment at the Oncology Department, Karolinska University Hospital. One reminder sent, together with a new questionnaire and return envelope after three weeks to those who did not return questionnaires.

Paper 2: HRQoL was assessed at three occasions: before randomization, and 12 and 24 months after randomization. The physician or study nurse handed the first questionnaire to each patient, which completed before randomization. At the subsequent assessment points, the questionnaires and pre-paid return envelopes sent to the patients' home address from the Department of Oncology, Sahlgrenska University Hospital, Gothenburg.

Paper 3: After informed consent, the patient responded to the questionnaires before randomization, the first point of assessment. HRQoL then assessed at additional five points: before start of RT (3 months), and subsequently 9, 12, 15 and 18 months after randomization. Questionnaires were sent with a return envelope at these assessments. The patients could choose to return questionnaires by post or during visits at the oncology clinic.

Paper 4: The patients' PV's were assessed before start of endocrine neo-adjuvant treatment (Volume 1) and before start of radiation therapy (RT) (Volume 2). The PV assessment was

performed by transrectal ultrasound before giving definitive recommendation of treatment with curative intention. The second PV assessment was conducted after three to six months of neo-adjuvant hormonal therapy before start of combined RT. Two oncologists measured the volumes at archive pictures taken during ultrasound to confirm the volumes.

4.3 INSTRUMENTS

The European Organization for Research and Treatment of Cancer Quality of Life Core Questionnaire (EORTC QLQ-C30) was used to assess HRQoL in Paper 1, 2 and 3 (Aaronson et al., 1993). In Paper 2, an earlier version, consisting of 33 items was used. The EORTC QLQ-C30 version 3 including 30-items was used in Papers 1 and 3. The questionnaire consists of functional and symptoms scales together with individual items. The five functional subscales are physical, role, social, emotional and cognitive. Fatigue, nausea/vomiting and pain are three symptoms scales. Six individual items are also included: dyspnoea, appetite loss, insomnia, diarrhoea, constipation, and financial difficulties. All items are scored in four point-scales (1=not at all, 4=very much). Moreover, there are two items addressing global health/QoL, scored on a seven-point scale (1= Very poor; 7= Excellent). The Swedish version of the questionnaire has been validated (Sigurdardottir et al., 1996).

The European Organization for Research and Treatment of Cancer Quality of Life Prostate Cancer Questionnaire (EORTC QLQ PR25) used to assess PC specific HRQoL in Papers 2 and 3. The initial version of this questionnaire, consisting of 20 items, used in Study 2 (Borghede et al., 1996). This was the first version of the questionnaire, developed in Gothenburg, Sweden, to gather information on side effects experienced by PC patients regarding bowel, urinary tract, and sexual functions. EORTC-PR25 includes four subscales. The four subscales aim at assessing urinary symptoms (9 items), bowel symptoms (4 items), treatment-related symptoms (6 items) and sexual functioning (6 items). The response format is similar to most items in the core questionnaire (1= not at all, 4= very much). EORTC QLQ PR25 has been validated in an international study (van Andel et al., 2008).

The European Organization for Research and Treatment of Cancer Quality of Life Information Questionnaire (EORTC QLQ INFO 25) was used in Paper 1 to gather information about patients' perception of information given and their satisfaction with that (Arraras et al., 2010). Total 25 items, divided into 4 multi-item categories including disease (4 items), medical tests (3 items), treatment (6 items), other services (4 items) and 8 single-item scales (information about different places of care, things you can do to help yourself get well, written information, information on CD and tape/video, satisfaction with information received, wish for more or less information, and if the overall information had been helpful). Response format for 21-items is a 4-point scale from 1 ("Not at all") to 4 ("Very much") and for 4 items "yes" or "no." The questionnaire has been validated in an international study (Arraras et al., 2011).

5 STATISTICAL ANALYSES

Paper 1: Item scores for EORTC QLQ-C30 and EORTC QLQ INFO25 were transformed into 0-100 scales. Higher scores in functional subscales and overall quality of life indicate higher function and QoL, but denote more problems in symptom scales. Five selected items from QLQ C30 (emotinal functioning, cognitive functioning, global QoL, fatigue & pain) were selected for this study. A linear regression model was used to study the association

between clinical and demographic variables with HRQoL and EORTC-INFO25 scales, both in the univariate and multivariate analyses.

Paper 2: Item scores for EORTC QLQ-C33 and EORTC QLQ-PR25 were transformed into 0-100 scales. A 20 symptom-questionnaire was used (the earlier version of PR25). ANOVA repeated measurements were performed to evaluate differences between randomization groups, time and group-by-time interactions. Survival analysis done by Kaplan-Meier technique. The Swedish Death Registry was used to identify the number of deaths at follow-up.

Paper 3: Item scores for EORTC QLQ C30 and EORTC QLQ-PR25 were transformed into 0-100 scales. Survival was estimated using the Kaplan-Meier technique. Linear regression model was used to analyse between-group-differences and variations over time.

Paper 4: Linear regression model was used to study groups at baseline and at follow-up. At follow-up visits, differences were studied both with univariate and multivariate analyses. P-values from these models refer to Wald-test. Paired t-test was used to study changes over time in each group between baseline and follow-up. Unpaired t-tests were performed to compare changes in PV and in planning target volumes between the randomization-groups.

Table 3: Overview of statistical methods used in studies I-IV

	STUDY I	STUDY II	STUDY III	STUDY IV
Paired t-test				**X**
ANOVA repeated measurements		**X**		
Kaplan-Meier analysis		**X**	**X**	
Log rank test			**X**	
Linear regression model	**X**	**X**	**X**	**X**
Wald test	**X**		**X**	**X**
Fishers-exact test		**X**		

6 RESULTS

Paper 1: A total of 92% (n=603) responded to the questionnaires in this cross-sectional study. For the item about satisfaction with information, 159 (27%) patients indicated "very much," 248 (42%) "Quite a bit," 143 (25%) "a little," and 35 (6%) "not at all". Younger patients reported having received more information about "other services" than older patients did ($p<0.001$). Patients who's first visit to the oncology clinic had occurred ≥ 1 year before completion of the questionnaires, reported having received more information about disease ($p<0.001$) and medical tests ($p=0.002$) than those who visited during the last year. We found statistically significant differences for "satisfaction with information" ($p=0.002$), and the "amount of information received" ($p<0.001$ for all differences), favoring the RT alone group in comparison to surgery + salvage RT. No interactions between treatments and time found for any of the subscales. There were statistically significant associations found between the EORTC QLQ-C30 variables analysed in this study, and "satisfaction with information" ($P<0.001$). Higher satisfaction was associated with better functioning and lower levels of symptoms.

Paper 2: A total of 89 patients were randomized between RP and RT in this curative intended multi-center study. A total of 66% completed questionnaires at all three assessment points. No statistically significant differences in HRQoL or treatment related symptoms and problems were found between the groups. A statistically significant improvement in emotional functioning over time was noted in both groups ($p<0.001$), although social functioning decreased ($p<0.01$) with time and financial difficulties increased ($p=0.001$). There were no statistically significant group-by-time interactions found. The study was underpowered, as it was closed before the intended number of patients could be recruited. Therefore, it was not possible to draw any conclusion about differences in efficacy between the treatments.

Paper 3: A total of 110 men were included in this randomized trial. Statistically significant differences between the groups at the 3-months assessment, favoring the AA group were found for overall quality of life ($p=0.006$), fatigue ($p=0.023$), sexual interest ($p<.001$), and urinary problems ($p=.036$). The difference in sexual interest was clinically "large", and for sexual functioning "moderate". At the 18- months assessment, statistically significant differences, favoring the AA group, were found for cognitive functioning ($p=0.040$) and sexual interest ($p=0.011$), the latter denoted as a "moderate" clinical difference. Statistically significant interactions over time were found for overall quality of life, cognitive functioning, fatigue and sexual interest, indicating that HRQoL scores developed differently between the randomization groups. At the median follow-up of 6.9 years, twelve PSA progressions (AA=8, TAB=4) and eight deaths (AA=5, TAB=3) were observed. Among these, one in each group denoted as PC-specific death. No statistically significant differences in OS or PSA-progression-free survival were found between the groups.

Paper 4: A total of 110 patients were included in the neo-adjuvant study, but 22 patients were not included in the final analysis (no PV information at baseline, n=11, 10%; treated with EBRT alone, n=11, 10%), leaving 88 patients (80%) to be analyzed in the final sample; 45 patients (51%) in the AA group and 43 patients (49%) in the TAB group.

TAB was more effective in PV reduction as compared to AA ($p<0.001$). Mean PV reduction was 16 % in the AA group compared to 29% in the TAB group. In the AA group, PV was reduced by ≥20% in 23 patients (51%). Corresponding figure for the TAB group was 34 patients (79%). PV was increased by ≥10% in 4 patients (8%) in the AA group and in 1

patient (2%) in the TAB group. The time between the assessments was similar in both groups, median 13 weeks. There was no statistically significant difference in duration of neo-adjuvant treatment or in clinical and demographic variables between the two groups.

7 DISCUSSION

Paper 1: The results of the study indicates substantial options for improvement regarding the information provided to PC patients undergoing RT. Younger, as compared to older patients reported having received more information about "other services", which is in concordance with previous studies, conducted in heterogenous groups of cancer patients (Arraras et al., 2011; Pinquart et al., 2004). Younger patients might be more prone to seek information themselves, e.g. through Internet. A positive association between HRQoL and satisfaction with information found, higher levels of HRQoL among satisfied patients. There are several explanations for this finding. One possible explanation is that, those who have better HRQoL provided with more adequate information, have been less anxious and able to comprehend the information. Another explanation is that adequate information affects patients' HRQoL in a positive way. Our result supported by a review of associations between information provision and HRQoL (Husson et al., 2011). Patients who had curative RT alone indicated higher levels of information than those who had RP + salvage RT. This finding might be explained by the fact that those who had RT alone mostly treated with neo-adjuvant ADT, implying multiple contacts with nurses, and thus, a possibility to get more information and to ask questions. Another possible explanation is that those who had RT after surgery due to PSA-relapse were disappointed and more worried. Our results indicate that it is of utmost importance to thoroughly inform patients who are about to receive RT in a salvage setting, and not rely on that they have been previously informed about.

Patients who responded to the questionnaires ≥ 1 year after their first visits at the oncology clinic reported having received more information about the disease and medical tests, which expected as they had more time to get information. There was no difference, however, in satisfaction with information between these two groups.

Paper 2: Our study represents the first report of a prospective randomized controlled trial comparing RP versus combination RT with EBRT & HDR-brachytherapy. This multicenter Swedish study intended to include 360 patients, but due to initiation of concurrent studies (SPCG-4 & SPCG-7), it was impossible to include patients as planned. Moreover, another study showed no differences in PFS in RP by adding neo-adjuvant endocrine therapy (Aus et al., 1998). The study closed in 2002 after including 89 patients. No statistically significant differences found for HRQoL and complications between the randomization groups, possibly due to the low sample size. The levels found were comparable with those found in a previous Swedish study, and similar to normative data from Swedish men (Wahlgren et al., 2004). Sexual problems were common in both groups at two years' post-treatment, probably as side effects of given treatments and due to aging. No conclusions drawn regarding survival or efficacy of treatment modalities, as the study was underpowered.

Paper 3: To our knowledge, this is the first prostpective trial randomizing anti-androgen versus total androgen blockade in curative intent RT in PC patients. At the three months'

assessment, statistically significant higher levels of overall quality of life and sexual interest, together with lower levels of fatigue and urinary problems reported in AA-group compared to TAB-group. Patients with higher sexual interest also showed significantly better sexual functioning. Our findings are similar to those reported by Iversen et al in locally advanced PC patients after 6.3 years of follow-up (Iversen et al, 2000). Sexual interest and physical functioning were better in the AA-group compared to castration-group. The mortality rate in that study (56%) was higher than in our study, which explained by patient categories (T3-T4), compared to our study where mostly an intermediate-riskgroup was included. In addition, the follow-up was longer, compared to our study. One patient in each group got PSA relapse around 11 months after randomization in our study. The patient in the AA arm (treated with EBRT only) missed 7 weeks of anti-androgen treatment at neo-adjuvant setting due to misunderstanding whereas the patient in TAB arm (treated with combination of HDR-BT and EBRT) found to have a more advanced tumor stage than anticipated at baseline. Deaths due to other causes were four (7%) in AA group compared to two (4%) in TAB group. This study is the first study, randomizing AA versus TAB in an intermediate-risk group of prostate cancer patients.

Paper 4: Prostate volume (PV) plays an important role in radiation planning with curative intention in PC patients, since large target volumes may affect organs at-risk causing subsequent radiation-related side effects and thus influence HRQoL negatively. Greatest falls in the radiation dose needed to kill 50% of cell population occur when maximum reduction in tumour volume occurs before EBRT, showed in an in-vivo study (Zietman et al., 1997). Neo-adjuvant ADT minimizes PV (Zelefsky et al, 1994; Henderson et al., 2003). In the present, prospective study, TAB significantly decreased PV more than AA treatment. Our results are comparable with other studies in this field (Lee 2002; Merrick et al., 2006; Petit et al., 2008). Suprisingly, ≥10% PV increase was found in four AA-patients and in one TAB-patient. This might be explained by inter-physician variablitity in PV assessment.

Overall quality of life, sexual interest, fatigue and urinary problems significantly differed in the present study at 3-months assessment, favouring men in AA-group compared to those in TAB-group (Paper 3). In addition, at the 18-months assessment, men in AA-group reported higher levels of sexual interest and cognitive functioning, and there were no differences in urinary or bowel symptoms. This was surprising as better HRQoL in the TAB-group expected as these patients received RT using smaller target volumes, and correspondingly lesser surrounding normal tissues. We assume that, as combined EBRT BT was the treatment modality in both groups, some positive effects in symptoms outweighed by brachytherapy side effects.

8 ETHICAL CONSIDERATIONS

Paper 1: The patients in this study generated from medical files at Radiumhemmet, Karolinska University Hospital where patients visited at least once, all got curative intent RT against localized prostate cancer. Patients may find the questionnaires sent home as integrity hampering as they reminded of their cancer diagnosis. We have, however, previous experience of this method and most patients do not seem to have any problems with the procedure. Patients may find this is an opportunity to consider their need for information, and might take some actions to gain more information. It may be tiredsome to fill-in the questionnaires with a total of 55 questions, but considering the high response rate, we do not believe that the length of the questionnaire was a problem for the patients. It is shown in studies that patients feel comfortable with health care but not always satisfied with information they have received, and thus, appreciate that this topic is being studied.

Paper 2: The patients in this study were included in a randomized study between 1996 and 2001 in five centre. Patients randomized to receive treatments with curative intention, RP or RT of combination technique. Patients who randomized to prostatectomy went through a laparoscopic operation first if they had high-risk of metastatic disease according to pre-defined criteria, in order to explore if there was any spread to the regional lymph nodes. This procedure could result in proceeding to RP or not. Thus, high-risk patients had to go through an operation with some anxiety. On the other hand, they were prepared thoroughly. In addition, TAB was given to all patients including those randomized to RP, although this was not a routine procedure in clinical practice. Patients castrated temporarily with this treatment which might have caused negative impact on their HRQoL. On the other hand, patients included in clinical studies might have easier access to medical care compared to those who are not. The patients were requested to complete HRQoL questionnaires, which might have caused anxiety or worries. We got, however, no indications about problems caused by the questionnaire-part of the study and our previous experiences with collecting HRQoL questionnaires in connection with cancer clinical trials are positive. Most patients appreciate, that these important aspects are studied in addition to the clinical problems.

Paper 3 & 4: The experimental arm, AA, was considered safe according to previous studies. In the original protocol, a substantially larger sample size was calculated in order to make an analysis of OS and TTP. In second amendment, anti-estrogen was allowed to use whenever needed if side effects of antiandrogen are bothersome. By this time thirteen patients were included who did not have that availability of anti-estrogen. But as we know that only twelve patients used anti-estrogen in total, eleven in antiandrogen group and one in TAB group, it was not a big ethical problem in this age group. Due to low accrual rate, a new calculation of sample size was performed based on HRQoL. It may be considered as an ethical problem that OS and TTP analyses cannot be performed in this group of low risk PC. Our follow-up figures suggest, however, that there are no differences with regards to these aspects between the treatment arms. Thus, HRQoL becomes even more important.

9 METHODOLOGICAL CONSIDERATIONS

Paper 1: A total of 660 patients were identified via medical files at Radiumhemmet, Karolinska. In addition, the patients' files reviewed in order to exclude patients who relapsed or who had died during the time since treatment. Thus, we consider the recruitment procedure to be thorough. The response rate was high, indicating that we obtained a representative sample. Validated questionnaires used. A cross sectional study procedure was, however used, asking about information received during a long period. The results are therefore subjected to possible recall bias. In addition, the study-design does not allow the exploration of the direction of the associations found between satisfaction with information and HRQoL.

Paper 2: This randomized study included PC patients in curative intented treatments of RP or RT. The study was performed at five centre, and there is a possibility that the treatments differed between centre. As the study was randomized, this was not considered a problem, as both arms were expected to be affected by this bias to the same extent. On the contrary, multicentre including patients, improves generalization of the results, as compared to single center studies. Validated questionnaires were used, making comparisons with other studies possible. The sample size was, however, a large methodological problem. The accrual rate was low, and the study was closed before the estimated sample size was reached. The results of the study must therefore be interpreted with caution.

Paper 3 & 4: The main methodological problem in this randomized study, as in Paper 3, is the sample size. An amendement, introducing a new sample calculation based on HRQoL, was introduced. The new sample size was estimated to 110 patients. It is therefore not possible to calculate OS and TTP in the study. The sample size was, however, sufficient to show differences in HRQoL between the two-randomization arms. Validated questionnaires were used, and the completion rates for the questionnaires at the assessment points were high.

Another methodological problem was the measurement of PV by different physicians, making a bias due to inter-individual variations possible. Two physicians, however, went through all estimations in order to minimize this risk of bias.

10 CLINICAL IMPLICATIONS

Paper 1: Information gained by this study may have great impact in future how we work in giving information to our patients with localized prostate cancer. This is because curative intent treatments have diverse side effects on urinary, bowel and sexual functions. We have found many areas of improvement to discuss at our clinic. Significant differences between oncology-and surgery clinic about patient satisfaction with information given at consultations found. This indicates that it is important to pay attention to information also to patients who have previously gone through RP, although these can be expected to have received thorough information earlier. They are, however, in a new situation when they are reffered to RT after treatment failure.

Paper 2: Conclusions about the efficacy of the two treatments in terms of OS and DFS could not be obtained due to low power in this study. No discernible differences between the groups in HRQoL or complications of treatments were found. The levels of problems reported by the

men in both randomization arms at different time points can, however, be conveyed to the patients when informing about treatment options. This information about what to expect in terms of HRQoL during and after treatment may help men coping with their disease and treatment.

Paper 3 & 4: The results suggest that AA is to be preferred compared to TAB in patients with low risk PC in the neoadjuvant setting. The effect on PV of TAB was better, but this effect did not appear to affect HRQoL. Thus, the rationale for decreasing the target volume in order not to hamper HRQoL not found in this study, further supporting the use of AA. It should be kept in mind, however, that OS and DFS could not be evaluated in this mostly intermediate-risk group, probably due to a small sample size. Our figures do not, however, indicate any negative effect on these parameters during follow-up.

11 GENERAL CONCLUSIONS

Based on all four studies included in this thesis, the conclusions made as follows:

- Patients treated with both prostatectomy and salvage RT reported significantly lower levels of satisfaction with information received, and of having received significantly less information than did patients treated with RT alone in curative setting. The majority reported being satisfied with the information received, despite room for improvement regarding information about disease, other services, different places of care and things you can do to help yourself.

- Open radical prostatectomy and the combined high-dose rate brachytherapy with external beam radiation therapy appeared to be comparable in the measured outcomes, as no statistically significant differences between the two randomization groups were found for any of the HRQoL variables or side effects of treatments. Emotional functioning improved over time, social functioning decreased and financial difficulties increased.

- Antiandrogen in the neoadjuvant setting is possible to be preferred compared to total androgen blockade, as higher levels of HRQoL, especially in the sexual domain found. There were no between-group differences in PC-specific deaths, PSA progression-free survival, or OS.

- Significantly larger reduction of prostate volume achieved following neoadjuvant total androgen blockade compared to antiandrogen. This reduction, however, did not appear to translate into a more favourable HRQoL profile of the subsequently given radiation therapy.

12 POPULÄRVETENSKAPLIG SAMMANFATTNING

Prostata cancer (PC) är den vanligaste cancerformen hos män i västvärlden. I Sverige drabbades 10,985 män under 2014, och den åldersstandardiserade incidensen var 226/100, 000 (Socialstyrelsen, 2015). Medelåldern är hög vid diagnos, cirka 70 år. Behandling av lokaliserad PC är kontroversiell. Radikal prostatektomi (kirurgi) och strålbehandling tillhör behandlingsalternativen med botande syfte. Få randomiserade studier har jämfört dessa alternativ (Grimm et al, 2012). Det finns också studier som visat att man kan leva länge även utan behandling (Albertsen et al, 2005). Det är viktigt att man vid behandlingsval diskuterar eventuella biverkningar av de olika behandlingarna med patienter, eftersom behandlingarna har biverkningsprofiler. Dessa biverkningsprofiler påverkar också den hälso-relaterade livskvaliteten på olika sätt (Ellett et al., 2013).

Studier har visat att många cancerpatienter kan hantera sin sjukdom väl om de får tillräcklig och god information. Dessutom minskar deras rädsla, och oro, samtidigt som den hälso-relaterade livskvaliteten förbättras (Lerman et al., 1993; Meredith et al., 1996; Thomas et al., 1999). Om man är nöjd med information mår man bättre, både fysiskt och socialt (Davies et al., 2008). Behovet av information kvarstår under hela cancerförloppet och är ett viktigt stöd för patienterna (Harrison et al., 2009). De flesta önskar mer information kring sin sjukdom, behandlingsalternativ, rehabiliterings möjligheter och uppföljning (Jenkins et al, 2001).

Hormonbehandling tillsammans med strålbehandling minskar risken för både återfall och död i lokalt-avancerad PC (Bria et al, 2009). Neo-adjuvant hormonbehandling används vanligen vid intermediär och hög-risk PC inför den kurativt syftande strålbehandlingen. Den vanligaste kombinationen är så kallat TAB (Total androgen blockad), vilken är en kombinaion av GnRH (Gonadotropin releasing hormone)-analog och en anti-androgen. Användning av enbart anti-androgen i monoterapi vid lokalt avancerad PC ger ingen signifikant skillnad i sjukdomsprogress eller överlevnad jämfört med kastrationsbehandling (Iversen et al, 2000). Dessutom, hade patienterna på monoterapi gruppen bättre fysisk- och sexuell förmåga jämfört med en kastrationsgrupp som led av svettningar, vallningar, trötthet. Bröstsvullnad och ömhet i brösten var dock dominerande i antiandrogen gruppen.

De flesta PC patienter botas idag och förväntas återgå till ett normalt liv. Det saknas evidens vilken av behandlingarna (kirurgi eller strålbehandling) som har den bästa kurativa effekten. Hälso-relaterade livskvalitet (HRQoL) är därför en viktig aspekt att beakta vid behandlingsval. Eftersom båda behandlingar har biverkningar bör man informera det vid möte inför patienten´s behandlingsval. Denna avhandling fokuserar att ta reda på hur nöjda PC-patienter är med information dem får och hur denna information påverkar deras HRQoL. Vidare studeras HRQoL i samband med kurativt syfte behandling (neoadjuvant hormonell behandling, kirurgi och strålbehandling). Slutligen undersöks effekterna på prostatavolym och strålbehandlingsfält av två olika neo-adjuvanta hormonbehandlingar.

Syfte, patienter, metod och resultat

Delarbete 1: Undersöker PC patienters uppfattning av information inför, under och efter kurativt syftande strålbehandling, samt deras tillfredställelse med information och kopplingen till hälso-relaterade livskvalitet. År 2010 skickades två validerade frågeformulär, EORTC QLQ C30 (livskvalitetsfrågor) + EORTC QLQ INFO25 (informationsfrågor) till 660 patienter med frankerat svarskuvert och information om studien. Svarsfrekvensen var 92 %.

Vi fann ett starkt samband mellan livskvalitet och tillfredställelse med informationen. Överraskande hade patienter som opererades och därefter strålbehandlades (salvage RT) pga PSA-återfall fått mindre information än de som fick strålbehandling som första behandlingsalternativ. Det finns ett utrymme för förbättring när det gäller vissa informationsområden.

Delarbete 2: Skillnader mellan kirurgi (RP) och strålbehandling (RT) vid kurativt syftande behandling studerades hos 89 patienter vid tre mätningstillfällen, vid randomisering, samt 12 månader och 24 månader efter behandling. Två frågeformulär användes, EORTC-QLQ C33 (livskvalitetsfrågor) och EORTC QLQ PR25 (symtomfrågor). Ingen signifikant skillnad noterades mellan behandlingarna avseende livskvalitet. Emotionell funktion förbättrades över tid i båda grupperna, medan social funktion minskade och ekonomiska svårigheter pga sjukdom och behandling ökade. Urininkontinens ökade i den grupp som genomgått kirurgi. Den strålbehandlade gruppen hade mer besvär med avföringsinkontinens efter två år. Impotens var ett vanligt problem i båda grupperna vid denna tidpunkt. Eftersom studiegruppen var liten kunde inga slutsatser avseende behandlingarnas kliniska effekter dras.

Delarbete 3: Studerade primärt livskvalitet hos PC-patienter med framför allt intermediär-risk, randomiserades mellan total androgen blockad och anti-androgen behandling. Totalt 110 patienter deltog (55 i vardera gruppen). Livskvalitet mättes vid sex tillfällen med EORTC QLQ-C30 och EORTC-PR25 (före randomisering och 3, 9, 12, 15, 18 månader efter). De som behandlats med anti-androgen hade större sexuellt intresse, bättre livskvalitet, och mindre vattenkastningsproblem och fatigue efter tre månader. Vid 18-månadersmätningen kvarstod endast skillnaden i sexuellt intresse. Patienter i anti-androgengruppen hade också bättre kognitiv funktion vid detta mättillfälle. I genomsnitt följdes patienterna upp i 6,9 år. Under den tiden avled två patienter av PC, en i vardera gruppen. Återfall i PC noterades hos totalt tolv patienter (åtta i antiandrogen; fyra i TAB. Sex patienter avled av andra orsaker (fyra i anti-androgen; två i TAB). Inga statistiskt signifikanta skillnader uppmättes mellan behandlingarna avseende total överlevnad eller PSA progression-fri överlevnad.

Delarbete 4: Patienterna var de samma som i delarbete 3. Syftet med studien var att jämföra förändringar i prostatavolym i de båda randomiseringsgrupperna, samt också att undersöka skillnader i storleken på planerade strålfält. Elva patienter som behandlades med enbart extern strålterapi kunde inte analyseras, eftersom volym före behandling inte mätts på dem. Det saknades också information om prostatavolym för ytterligare elva patienter vid studiestart. Totalt analyserades 88-patienters prostatavolym. I TAB gruppen minskade prostatavolymen mer än i anti-androgengruppen. Överraskande nog ökade volymen hos fem patienter (fyra i anti-androgen-grupp och en i TAB-grupp). Strålfälten blev mindre i TAB gruppen jämfört med anti-androgengruppen .

Slutsatser

Även om patienterna huvudsakligen var nöjda med den information de fått finns utrymme för förbättring. Patienter som var missnöjda med informationen hade sämre livskvalitet. De som genomgick strålbehandling på grund av PSA-återfall efter kirurgi, var inte lika nöjda med informationen jämfört med de som fick strålbehandling som första alternativ.

I den randomiserade studien där kirurgi och strålbehandling jämfördes fann vi inga skillnader i livskvalitet mellan behandlingarna. Eftersom studien avbröts i förtid, var studiegruppen för liten för att kunna utvärdera de kliniska effekter av behandlingarna.

Antiandrogen tycktes bättre än totalt androgen blockad avseende sexuellt intresse- och funktion, fatigue, vattenkastningsproblem och livskvalitet före start av strålbehandling.

Effekten på sexuellt intresse kvarstod vid 18-månaders mätning, då vi också fann en bättre kognitiv funktion i anti-androgengruppen. Ytterligare studier behövs dock för att avgöra om total androgen blockad är bättre avseende minskad risk för mikrometastaser jämfört med anti-androgen. Total androgen blockad minskade prostata-volym mer än anti-androgen behandling, vilket också påverkade storleken på strålfälten. Detta översattes dock inte i bättre livskvalitet i den grupp som behandlats med total androgen blockad.

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14 REFERENCES

Aaronson NK. Quality of life assessment in clinical trials: methodologic issues. Control Clin Trials. 1989; 10:195S-208S.

Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: A quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 1993; 85:365–376.

Abate-Shen C, Shen MM. Molecular genetics of prostate cancer. Genes Dev 2000; 14:2410-2434.

Aganovic D, Prcic A, Kulovac B, Hadziosmanovic O. Prostate cancer detection rate and the importance of premalignant lesion in rebiopsy. Med Arh 2011; 65:109–112.

Albertsen PC, Hanley JA, Fine J. 20-year outcomes following conservative management of clinically localized prostate cancer. JAMA 2005; 293:2095-2101.

Albertsen, PC, Fryback DG, Storer BE, et al. Long term survival among men with conservatively treated localized prostate cancer. JAMA 1995; 274:626-631.

Alemozaffar M, Regan MM, Cooperberg MR, et al. Prediction of erectile function following treatment for prostate cancer. JAMA 2011; 306:1205-1214.

Alibhai SMH, Breunis H, Timilshina N, et al. Impact of androgen-deprivation therapy on physical function and quality of life in men with nonmetastatic prostate cancer. J Clin Oncol 2010; 28:5038-5045.

Allen NE, Key TJ, Appleby PN, et al. Animal foods, protein, calcium and prostate cancer risk: The European Prospective Investigation into Cancer and Nutrition. Br J Cancer 2008; 98:1574–1581.

Allott EH, Masko EM, and Freedland SJ. Obesity and prostate cancer: Weighing the evidence. Eur Urol. 2013; 63:800–809.

Al-Mamgani A, van Putten W, van der Wielen GJ, Incrocci L. Dose escalation and quality of life in patients with localized prostate cancer treated with radiotherapy: Long-term results of the Dutch Randomized Dose-Escalation Trial (CKTO 96-10 Trial). Int J Radiat Oncol Biol Phys 2011; 79:1004-1012.

American Cancer Society. Prostate Cancer. Cancer Information Database, 2015.

Andersson S-O, Wolk A, Bergström R, et al. Body size and prostate cancer: A 20 year follow up study among 135006 Swedish contrctions workers. J Natl Cancer Inst 1997;89:385-389.

Andren O, Fall K, Franzen L, et al. How well does the Gleason score predict prostate cancer death? A 20-year follow-up of a population based cohort in Sweden. J Urol 2006; 175:1337-1340.

Arraras JL, Greimel E, Sezer O, et al. An international validation study of the EORTC QLQ INFO25 questionnaire: an instrument to assess the information given to cancer patients. Eur J Cancer 2010; 46:2726-2738.

Arraras JL, Manterola A, Hernandez B et al. The EORTC information questionnaire, EORTC QLQ INFO 25. Validation study for Spanish patients. Clin Transl Oncol 2011;13: 401-410.

Aus G, Abrahamsson PA, Ahlgren G, et al. Hormonal treatment before radical prostatectomy: A 3-year follow-up. J Urol 1998 ;159 :2013-2016; discussion 2016-2017.

Bailar JC[3rd], Mellinger JT, Gleason DF. Survival rates of patients with prostate cancer, tumour stage and differentiation-preliminary report. Cancer Chemother Rep 1966; 50:129-136.

Bangma CH, Neimer AQ, Grobbee DE, Schroder FH. Transrectal ultrasonic volumetry of the prostate: in vivo comparison of different methods. Prostate 1996; 28:107-110.

Basaria S, Lieb J[2nd], Tang AM, et al. Long-term effects of androgen deprivation therapy in prostate cancer patients. Clin Endocrin 2002; 56:779-786.

Bassett WW, Cooperberg MR, Sadetsky N, et al. Impact of obesity on prostate cancer recurrence after radical prostatectomy: data from CaPSURE. Urology. 2005; 66:1060–1065.

Basu A, Imrhan V. Tomatoes versus lycopene in oxidative stress and carcinogenesis: conclusions from clinical trials. Eur J Clin Nutr 2007; 61:295-303.

Bauman G, Rumble RB, Chen J, et al. Intensity-modulated radiotherapy in the treatment of prostate cancer. Clin Oncol (R Coll Radiol) 2012; 24:461–473.

Bergenmar M, Johansson H, Sharp L. Patients´perception of information after completion of adjuvant radiotherapy for breast cancer. Eur J of Oncol Nurs 2014; 18:305-309.

Berges R, Tombal B. Androgens and prostate cancer. Ismar Healthcare publishing, Duwijckstraat, Belgium 2009.

Bergman J and Litwin MS. Quality of Life in Men Undergoing Active Surveillance for Localized Prostate Cancer. J Natl Cancer Inst Monogr (2012) 2012 (45): 242-249.

Bergner M. Quality of life, health status, and clinical research. Med Care 1989;27: S148-156.

Berney DM, Fisher G, Kattan MW, et al. Major shifts in the treatment and prognosis of prostate cancer due to changes in pathological diagnosis and grading. BJU Int 2007;100: 1240-1244. J Urol 1984; 132: 474.

Berry SJ, Coffey DS, Walsh PC, Ewing LL. The development of human benign prostatic hyperplasia with age. J Urology, 1984; 132 (3): 474-479.

Bertermann HaB, F. Technik der perinealen interstitiellen Iridium-192-Betstrahlung des Prostatakarzinoms. Verh Dtsch Ges Urol. 1986:256-258.

Beyer DC. The evolving role of prostate brachytherapy. Cancer control, 2001;8:163-170.

Bill-Axelson A, Holmberg L, Ruutu M, et al. Radical prostatectomy versus watchful waiting in early prostate cancer. N Engl J Med. 2005; 352: 1977-84.

Bill-Axelson A, Holmberg L, Ruutu M, Garmo H, et al. Radical prostatectomy versus watchful waiting in early prostate cancer. N Engl J Med. 2011; 364:1708-1719.

Bolla M, Laramas M, on behalf of AROME (Association of Radiotherapy and Oncology of the Mediterranean area). Combined hormone therapy and radiation therapy for locally advanced prostate cancer. Critical Reviews in Oncology/Hematology 2012; 84: e30-e34.

Borghede G, Sullivan M. Measurement of quality of life in localized prostatic cancer patients treated with radiotherapy. Development ofa prostate cancer-specific module supplementing the EORTC QLQ-C30. Qual Life Res. 1996; 5:212-222.

Borghede G, Hedelin H, Holmang S, et al. Combined treatment with temporary short-term high-dose rate iridium-192 brachytherapy and external beam radiotherapy for irradiation of localized prostatic carcinoma. Radiother Oncol 1997; 44:237-244.

Boyle P, Alexander FE, Luchini L, Bishop T. Aetiology of prostate cancer. In: Garraway MG ed. Epidemiology of Prostate Disease. Springer, New York,1995.

Brawer MK. Prostate specific antigen: some observations. International Handbook of Prostate Cancer, 3rd edition, 2008. Published by Euromed Communications Ltd, London, UK.

Bria E, Cuppone F, Giannarelli D, et al. Does hormone treatment added to radiotherapy improve outcome in locally advanced prostate cancer? Cancer 2009; 115: 3446-3456.

Brenner DJ, Hlatky LR, Hahnfeldt PJ, et al. The linear-quadratic model and most other common radiobiological models result in similar predictions of time-dose relationships. Radiat Res 1998; 150:83-91.

Brulde B. Teorier om livskvalitet (Theories on quality of life). Lund, Studentlitteratur, 2003.

Budäus L, Bolla M, Bossi A, et al. Functional outcomes and complications following radiation therapy for prostate cancer: a critical analysis of the literature. Eur Urol 2012; 61:112-127.

Burke, HB, Bostwick DG, Meiers I, Montironi R. Prostate cancer outcome: epidemiology and biostatistics. Anal Quant Cytol Histol 2005; 27:211-217.

Carter HB, Albertsen PC, Barry MJ, et al. Early detection of prostate cancer: AUA guideline. J Urol 2013; 190:419-426.

Catalona WJ, Hudson MA, Scardino PT, Richie JP, Ahmann FR, Flanigan RC, et al. In Reply: Re: Selection of optimal prostate specific antigen cutoffs for early detection of prostate cancer: Receiver operating characteristic curves. J Urol 1996; 155:1396.

Cella DF, Tulsky DS. Quality of life in cancer: definition, purpose, and method of measurement. Cancer Invest 1993a; 11:327-336.

Cella DF, Tulsky DS, Gray G, et al. The Functional Assessment of Cancer Therapy scale: development and validation of the general measure. J Clin Oncol. 1993; 11:570-579.

Cella DF. Quality of life: concepts and definitions. J Pain Symptom Manage. 1994; 9:186-192.

Cella D, Wagner L, Cashy J, et al. Should health-related quality of life be measured in cancer symptom management clinical trials? Lessons learned using the functional assessment of cancer therapy. J Natl Inst Monogr 2007; 53-70.

Charles C, Gafni A, Whelan T. Decision-making in the physician-patient encounter: revisiting the shared treatment decision-making model. Soc Sci Med. 1999; 49:651-661.

Chodak GW, Thisted RA, Gerber GS, et al. Results of conservative management of clinically localized prostate cancer. NEJM 1994; 330:242-248.

Damber JE, Peeker R. Studentlitteratur AB Lund, Sweden, Werner Schmidt 2012; Vol 2:1: page 334.

Danila DC, Morris MJ, de Bono JS, et al. Phase II multicenter studyof abiraterone acetate plus, prednisolone therapy in patients with docetaxel-treated castration-resistant prostate cancer. J Clin Oncol 2010; 28:1496-1501.

Dasu A, Toma-Dasu I. Prostate alpha/beta revisited: An analysis of clinical results from 14,168 patients. Acta Oncol 2012; 51: 963-974.

Davies NJ, Kinman G, Thomas RJ, Bailey T. Information satisfaction in breast and prostate cancer patients: implications for quality of life. Psycho-oncology 2008; 17: 1048-1052.

Dearnaley DP, Khoo VS, Norman AR, et al. Comparison of radiation side-effects of conformal and conventional radiotherapy in prostate cancer: a randomized trial. Lancet. 1999; 353: 267-272.

Dearnaley DP, Sydes MR, Graham JD, Aird EG, Bottomley D, Cowan RA, et al on behalf of RT01 collaborators. Escalated-dose versus standard-dose conformal radiotherapy in prostate cancer: first results from the MRC RT01 randomised controlled trial. Lancet Oncol 2007; 8: 475-87.

de Bono JS, Oudard S, Ozguroglu M, et al. Prednisolone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. The Lancet 2010; 376:1147-1154.

de Bono JS, Logothetis CJ, Molina A et al. Abiraterone and increased survival in metastatic prostate cancer. N Engl J Med 2011; 364:1995-2005.

DeVita VT Jr., Hellman R, Rosenberg SA. Cancer, Principles & Practice of Oncology, 5th Edition, 1997; 1330-1331.Lippincott-Raven publishers, Philadelphia. New York.

Dich J, Wiklund K. Prostate cancer in pesticide applicators in Swedish agriculture. Prostate 1998; 34:100-112.

Dimmen M, Vlatkovic L, Hole KH, et al. Transperineal prostate biopsy detects significant cancer in patients with elevated prostate-specific antigen (PSA) levels and previous negative transrectal biopsies. BJU Int 2012;110: E69–E75.

Douglas BG, Fowler JF. The effect of multiple small doses of x rays on skin reactions in the mouse and a basic interpretation. Radiat Res 1976; 66:401-426.

Drummond FJ, Kinnear H, Donnelly OE, et al. Long-term health-related quality of life of prostate cancer survivors varies by primary treatment. Results from the picture (prostate cancer treatment, your experience) study. J Cancer Surviv 2015; 9:361-372.

Duchesne GM, Peters LJ. What is the alpha/beta ratio for prostate cancer? Rationale for hypofractionated high-dose-rate brachytherapy. Int J Radiat Oncol Biol Phys 1999; 44:747-748.

Dunn MW, Kazer MW. Prostate cancer overview. Semin Oncol Nurs 2011; 27:241-250.

Eble JN, S. G., Epstein JI, Sesterhenn IA. WHO classification of tumours. Pathology and genetics of tumours of the urinary system and male genital organs, Lyon, IARC press 2004.

Egevad L, Granfors T, Karlberg L, Bergh A, Stattin P. Percent Gleason grade 4/5 as prognostic factor in prostate cancer diagnosed at transurethral resection. J Urol 2002a; 168:509-513.

Egevad L, T Granfors, Karlberg et al. Prognostic value of the Gleason score in prostate cancer. BJU Int 2002b; 89:538-542.

Eichler K, Hempel S, Wilby J, et al. Diagnostic Value of Systematic Biopsy Methods in the investigation of Prostate Cancer: A Systematic Review. J Urol 2006; 175:1605-1612.

Ellett JD, Rosoff JS and Prasad SM. Long-term differences in urinary, bowel and sexual function among men treated with surgery versus radiation for prostate cancer. Asian J Androl 2013; 15: 443-444.

Epstein JI, Partin AW, Sauvageot J, Walsh PC. Prediction of progression following radical prostatectomy. A multivariate analysis of 721 men with long-term follow-up. Am J Surg Pathol 1996; 20: 286-292.

Esper P, Mo F, Chodak G, et al. Measuring quality of life in men with prostate cancer using the functional assessment of cancer therapy-prostate instrument. Urology 1997; 50: 920-928.

European Association of Urology (EAU) Guidelines on prostate cancer, presented at the 25th EAU Annual Congress, Barcelona 2010. Arnhem, The Netherlands: EAU Guidelines Office, Arnhem, The Netherlands, 2011.

Fayers P, Hays R. Assessing quality of life in clinical trials, 2nd ed: Oxford University Press, Oxford, UK, 2005.

Fizazi K, Carducci M, Smith M, Damiao R, Brown J, Karsh L, et al. Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: a randomized, double –blind study. Lancet 2011; 377(9768):813-22.

Foley RW, Gorman L, Sharifi N, et al. Improving multivariable prostate cancer risk assessment using the Prostate Health Index. BJU International 2016;117:409-417.

Fowke JH, McLerran DF, Gupta PC, et al. Associations of body mass index, smoking, and alcohol consumption with prostate cancer mortality in the Asia Cohort Consortium. Am J Epidemiol 2015; 182:381-389.

Frank SJ, Pisters LL, Davis J et al. An assessment of quality of life following radical prostatectomy, high dose external beam radiation therapy and brachytherapy iodine implantation as monotherapies for localized prostate cancer. J Urol 2007; 177:2151-2156.

Fransson P, Tavelin B, Widmark A. Reliability and responsiveness of a prostate cancer questionnaire for radiotherapy-induced side-effects. Support Care Cancer 2001; 9:187-198.

Fransson P, Bergström P, Löfroth PO, Widmark A. Prospective evaluation of urinary and intestinal side effects after BeamCath stereotactic dose-escalated radiotherapy of prostate cancer. Radiother Oncol 2002; 63:239-248

Fransson P, Lund JÅ, Damber JE, et al. Quality of life in patients with locally advanced prostate cancer given endocrine treatment with or without radiotherapy: 4-year follow-up of SPCG-7/SFUO-3, an open-label, randomised, phase III trial. Lancet Oncol 2009; 10:370-380.

Fung-kee-Fung SD, Porten SP, Meng MV, Kuettel M. The role of active surveillance in the management of prostate cancer. J Natl Compr Canc Netw 2013; 11:183-187.

Frank SJ, Pisters LL, Davis J et al. An assessment of qulity of life following radical prostatectomy, high dose external beam radiation therapy and brachytherapy iodine implantation as monotherapies for localized prostate cancer. J Urol 2007;178:2151-2156

Garcia FJ, Violette PD, Brock GB, Pautler SE. Predictive factors for return of erectile function in robotic radical prostatectomy: case series from a single centre. Int Impot Res, 2015; 27:29–32.

Glaessgen A: Markers of differentiation and prognosis in prostate cancer, 2008, Thesis; Karolinska Institutet, Stockholm, Sweden.

Gleason DF. Classification of prostatic carcinomas. Cancer Chemother Rep. 1966; 50:125-128.

Gleason DF, Mellinger GT. Prediction of prognosis for prostatic adenocarcinoma by combined histological grading and clinical staging. J Urol. 1974; 111: 58-64.

Gleason DF. Histological grading of prostate cancer: A perspective. Hum Pathol 1992; 23: 273-279.

Goldstein NS: Immunophenotypic characterization of 225 prostate adenocarcinomas with intermediate or high Gleason scores. Am J Clin Pathol 2002; 117: 471-477.

Gong Z, Neuhouser ML, Goodman PJ, et al. Obesity, diabetes, and risk of prostate cancer: results from the Prostate Cancer Prevention Trial. Cancer Epidemiol Biomarkers Prev. 2006; 15: 1977-1983.

Gravis G, Fizazi K, Joly F, et al. Androgen-deprivation therapy alone or with docetaxel in non-castrate metastatic prostate cancer (GETUG-AFU 15): a randomized, open-label, phase 3 trial. Lancet Oncol 2013; 14: 149-158.

Green GA, Hanlon AL, Al-Saleem T, Hanks GE. A Gleason score of 7 predicts a worse outcome for prostatic carcinoma patients treated with radiotherapy. Cancer 1998; 83: 971-976

Grimm P, Billiet I, Bostwick D, et al. Comparative analysis of prostate-specific antigen free survival outcomes for patients with low, intermediate and high risk prostate cancer treatment by radical therapy. Results from the Prostate Cancer Results Study Group. BJU Int 2012; 109 (Supp. 1): 22-29.

Grönberg H. Prostate Cancer Epidemiology. Lancet, 2003; 361: 859-864.

Grönberg H, Adolfsson J, Aly M, et al. Prostate cancer screening in men aged 50-69 years (STHLM3): a prospective population-based diagnostic study. Lancet Oncol 2015; 16:1667-1676.

Grönberg H, Damber L, Damber JE, Iselius L: Segregation analysis of prostate cancer in Sweden: Support for dominant inheritance. Am J Epidemiol 1997; 146:552-557.

Han M, Partin AW, Pound CR, et al. Long-term biochemical disease-free and cancer specific survival following anatomic radical retropubic prostatectomy. The 15-year Johns Hopkins experience. Urol Clin North Am 2001; 28:555-565.

Han M, Partin AW, Zahurak M, et al. Biochemical (prostate specific antigen) recurrence probability following radical prostatectomy for clinically localized prostate cancer. J Urol 2003; 169:517-523.

Hanlon AL, Watkins Bruner D, Peter R, Hanks GE. Quality of life study in prostate cancer patients treated with three-dimensional conformal radiation therapy: comparing late bowel and bladder quality of life symptoms to that of the normal population. Int J Radiat Oncol Biol Phys 2001; 49:51-59.

Harrison JD, Young JM, Price MA, et al. What are the unmet supportive care needs of people with cancer? A systematic review. Support Care Cancer 2009; 17:1117-1128.

Haustermans K, Hofland I, Poppel H, et al. Cell kinetic measurements in prostate cancer. Int J Radiat Oncol Biol Phys 1997; 37:1067-1070.

Hayward SW, Cunha GR. The prostate: development and physiology. Radio Clin North Am 2000; 38:1-14.

Hellerstedt BA, Pienta KJ. The current state of hormonal therapy for prostate cancer. CA Cancer J Clin 2002; 52:154-179

Henderson A, Langley SE, Laing RW. Is bicalutamide equivalent to goserelin for prostate volume reduction before radiation therapy? A prospective, observational study. Clin Oncol 2003; 15:318-321.

Henriksson P, Stege R. Cost comparison of parenteral estrogen and conventional hormonal treatment in patients with prostate cancer. Int J Technol Assess Health Care. 1991; 7:220-5.

Hjälm-Eriksson M, Lennernäs B, Ullen A, et al. Long-term health-related quality of life after curative treatment for prostate cancer: A regional cross-sectional comparison of two standard treatment modalities. Int J of Oncol 2015; 46:381-388.

Hull GW, Rabbani F, Abbas F, Wheeler TM, et al. Cancer control with radical prostatectomy alone in 1,000 consecutive patients. J Urol 2002; 167:528-534.

Humphrey PA. Histological variants of prostatic carcinoma and their significance. Histopathology 2012; 60:59-74.

Hunt SM, McKenna SP, McEwen J, et al. The Nottingham health profile: Subjective health status and medical consultations. Soc Sci Med 1981;15:221-229.

Husson O, Mols F, Van de Poll-Franse LV. The relation between information provision and health-related quality of life, anxiety and depression among cancer survivors: a systematic review. Ann Oncol 2011; 22:761-772.

Incrocci L, Jensen PT. Pelvic radiotherapy and sexual function in men and women. J Sex Med 2013;10 (Suppl 1):53-64.

Isaacs JT, Lundmo PI, Berges R, et al. Androgen regulation of programmed cell death of normal and malignant prostatic cells. J Androl 1992;13: 457-464.

Iversen P, Melezinek I, Schmidt A. Nonsteroidal antiandrogens: a therapeutic option for patients with advanced prostate cancer who wish to retain sexual interest and function. BJU International 2001;87:47-56

Iversen P, Tyrrell CJ, Kaisary AV, et al. Bicalutamide monotherapy compared with castration in patients with nonmetastatic locally advanced prostate cancer: 6.3 years of follow up. J Urol. 2000; 164:1579-158.

James ND, Sydes MR, Mason MD, et al. Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): survival results from an adaptive, multiarm, multistage, platform randomised controlled trial. Lancet 2016; 387:1163-1177.

Jenkins V, Fallowfield L, Saul J. Information needs of patients with cancer: results from a large study in UK Cancer Centre. Br J Cancer 2001; 84:48-51.

Johansson JE, Holmberg L, Johansson S, et al. Fifteen-year survival in prostate cancer. A prospective, population-based study in Sweden. JAMA 1997; 277:467-471.

Johansson E, Bill-Axelson A, Holmberg L, et al. Time, symptom burden, androgen deprivation, and self-assessed quality of life after radical prostatectomy or watchful waiting: The Randomized Scandinavian Prostate Cancer Group study number 4 (SPCG-4) clinical trial. Eur Urol. 2009; 55:422–430.

Joly F, Brune D, Couette J, et al. Health-related quality of life and sequelae in patients treated with brachytherapy and external beam irradiation for localized prostate cancer. Ann Oncol 1998;9:751-757.

Kaminski JM, Hanlon AL, Joon DL, Meistrich M, Hachem P, Pollack A. Effect of sequencing of androgen deprivation and radiotherapy on prostate cancer growth. Int J Radiat Oncol Biol Phys 2003;57(1):24-28.

Kane CJ, Bassett WW, Sadetsky N, et al. Obesity and prostate cancer clinical risk factors at presentation: data from CaPSURE. J Urol 2005; 173:732–736.

Kantoff PW, Higano CS, Shore ND, et al. Sipuleucel-T immunotherapy for castration resistant prostate cancer. N Engl J Med 2010;363:411-422

Kao T, Cruess D, Garner D, et al. Multicenter patient self-reporting questionnaire on impotence, incontinence and stricture after radical prostatectomy. J Urol 2000; 163:858-864.

Karayi MK, Markham AF. Molecular biology of prostate cancer. Prostate Cancer Prostatic Dis; 2004; 7:6-20.

Khoo V, Pollack A, Cowen D, et al. Relationship of Ki-67 labelingindex to DNA-ploidy, S-phase fraction, and outcome in prostate cancertreated with radiotherapy. Prostate 1999; 41:166-172.

King MT. The interpretation of scores from the EORTC quality of life questionnaire QLQ-C30. Qual Life Res 1996; 5:555-567.

Kirby RS, Brawer MK. Prostate Cancer, 2004, fourth edition, 10-13. Health Press Limited, Oxford, UK.

Klotz L. Maximal androgen blockade for advanced prostate cancer. Best Pract Res Clin Endocrinol Metab 2008; 22:331-340.

Kokhaei P. Preclinical therapeutic vaccination strategies in malignancies with focus on B-cell chronic lymphocytic leukemia. Thesis 2006, Karolinska Institutet.

Korfage IJ, Hak T, de Koning HJ, Essink-Bot ML. Patients' perceptions of the side-effects of prostate cancer treatment-A qualitative interview study. Soc Sci Med 2006; 63:911-919.

Krieg M, Weisser H, Tunn S. Potential activities of androgen metabolizing enzymes in human prostate. J Steroid Biochem Mol Biol 1995;53:395-400.

Kälkner KM, Kubicek G, Nilsson J, et al. Prostate volume determination: differential volume measurements comparing CT and TRUS. Radiother Oncol 2006; 81:179-183.

Lee WR. The role of androgen deprivation therapy combined with prostate brachytherapy. Urology 2002; 60:39-44.

Lennernäs B, Rikner G, Letocha H, Nilsson S. External beam radiotherapy of localized prostatic adenocarcinoma. Evaluation of conformal therapy, field number and target margins. Acta Oncol 1995; 34:953-958.

Lennernäs B, Castellanos E, Nilsson S, Levitt S. Four and five dimensional radiotherapies with reference to prostate cancer-definitions, state of the art and further directions-an overview. Acta Oncol 2011;50 (Suppl 1):104-110.

Lerman C, Daly M, Walsh WP, et al. Communication between patients with breast cancer and health care providers. Determinants and implications. Cancer 1993; 72:2612-2620.

Leslie H. Sobin, Mary K. Gospodarowicz, Christian Wittekind. The TNM Classification of Malignant Tumours 7th Edition, UICC, Nov 2009.

Litwin M, Hays R, Fink A, et al. Quality-of-life outcomes in men treated for localized prostate cancer. JAMA 1995; 273:129-135.

Litwin MS, Flanders SC, Pasta DJ, et al. Sexual function and bother after radical prostatectomy or radiation for prostate cancer: multivariate quality-of-life analysis from CaSURE. Cancer of the Prostate Strategic Urologic Research Endeavor. Urology 1999; 54:503-508.

Litwin MS, Melmed GY, Nakazon T. Life after radical prostatectomy: a longitudinal study. J Urol 2001; 166:587-592.

Lubeck DP, Grossfeld GD, Carroll PR. The effect of androgen deprivation therapy on health-related quality of life in men with prostate cancer. Urology 2001;58(Suppl 1):94-100.

Mabjeesh NJ, Lidawi G, Chen J, et al. High detection rate of significant prostate tumours in anterior zones using transperineal ultrasound-guided template saturation biopsy. BJU Int 2012; 110:993–997.

MacInnis RJ, English DR. Body size and composition and prostate cancer risk: systematic review and meta-regression analysis. Cancer Causes Control. 2006; 17:989–1003.

Mallick S, Blanchet P, Multigner L. Prostate cancer incidence in Guadeloupe, a French Caribbean Archipelago. Eur Urol 2005; 47:769-772.

Meredith C, Symonds P, Webster L, et al. Information needs of patients in west Scotland: cross sectional survey of patients' views. BMJ 1996,313:724-726.

Merrick GS, Butler WM, Wallner KE, et al. Efficacy of neoadjuvant bicalutamide and dutasteride as a cytoreductive regimen before prostatebrachytherapy. Urology 2006; 68:116-120.

Mesters I, van den Borne B, De Boer M, Pruyn J. Measuring information needs among cancer patients. Patient Educ Couns 2001; 43:253–262.

Michaelson et al. Randomized controlled trial of annual zoledronic acid to prevent gonadotropin-releasing hormone agonist-induced bone loss in men with prostate cancer. J Clin Oncol.2007; 25: 1038-1042

Mikuz G. Pathology of prostate cancer. Old problems and new facts. Adv Clin Path. 1997; 1:21-34.

Miralbell R, Roberts SA, Zubizarreta E, et al. Dose-fractionation sensitivity of prostate cancer deduced from radiotherapy outcomes of 5,969 patients in seven international institutional datasets: α/β =1.4(0.9-2.2) Gy. Int J Radiat Oncol Biol Phys 2012;82: e17-e24.

Moreira DM, Nickel JC, Gerber L, et al. Smoking is associated with acute and chronic prostatic inflammation: Results from the REDUCE Study. Cancer Prev Res 2015;8:312-317.

Mottet N, Bellmunt J, Briers E, et al. GUIDELINES ON PROSTATE CANCER, EAU, 2015. https://uroweb.org/guideline/prostate-cancer/

Mottrie A, Ficarra V. Can robot-assisted radical prostatectomy still be considered a new technology pushed by marketers? The IDEAL evaluation. Eur Urol 2010; 58:525-527.

Mottrie A, De Naeyer G, Novara G, Ficarra V. Robotic radical prostatectomy: a critical analysis of the impact on cancer control. Curr Opin Urol. 2011; 21:179-184.

Mouraviev V, Polascik TJ. Update on cryotherapy for prostate cancer in 2006. Curr Opin Urol, 2006; 16:152–156.

Mydlo JH, Godec CJ. Prostate Cancer: Science and Clinical practice 2003. Academic press, London, UK

Namiki S, Egawa S, Baba S et al. Recovery of quality of life in year after laparoscopic or retropubic radical prostatectomy: a multi-institutionl longitudinal study. Urology 2005; 65:517-523.

Namiki S, Satoh T, Baba S, Ishiyama H, Hayakawa K, Saito S, Arai Y. Quality of life after brachytherapy or radical prostatectomy for localized prostate cancer: a prospective longitudinal study. Urology 2006; 68:1230-1236.

Namiki S, Kaiho Y, Mitsuzuka K, Saito H, Yamada S, Nakagawa H, Ito A, Arai Y. Long-term quality of life after radical prostatectomy: 8-year longitudinal study in Japan. Int J Urol 2014; 21:1220-1226.

Neal DE Jr, Moon TD, Clejan S, Sarma D. Prostate specific antigen and prostatitis. Effect of prostatitis on serum PSA in the human and non-human primate. Prostate 1992; 20:105-111.

NICE (National Institute for Health and Care Excellence) guidelines. Treating localised prostate cancer using high-intensity ultrasound in a targeted area of the prostate, 2012.https:// www.nice.org.uk/guidance /CG175/chapter/1 -Recommendations#ftn.footnote_3

Nickel J Ed. (1999). Textbook of prostatitis, Isis Medical Media Limited, Oxford, UK.

Nilsson S, Norlen BJ, Widmark A. A systematic overview of radiation therapy effects in prostate cancer. Acta Oncol. 2004; 43:316-81.

Niraula S, Chi K, Joshua AM. Beyond Castration-Defining future directions in the hormonal treatment of prostate cancer. Horm Canc 2012; 3:3-13.

Nilsson S, Franzén L, Parker C, et al. Two-year survival follow-up of the randomized, double-blind, placebo-controlled phase II study of radium-223 chloride in patients with castration-resistant prostate cancer and bone metastases. Clin Genitourin Cancer. 2013; 11:20-6.

Novara G, Ficarra V, Rosen RC, et al. Systematic review and meta-analysis of perioperative outcomes and complications after robot-assisted radical prostatectomy. Eur Urol, 2012;62:431–452.

Noveski P, Madjunkova S, Stefanovska ES, et al. Loss of Y chromosome in peripheral blood of colorectal and prostate cancer patients. PLOS ONE. Jan 2016. DOI: 10.1371

Ogunbiyi JO, Shittu OB. Increased incidence of prostate cancer in Nigerians. J Natl Med Assoc 1999; 91:159-164.

Osoba D, Rodrigues G, Myles J, et al. Interpreting the significance of changes in health-related quality-of-life scores. J Clin Oncol. 1998; 16:139-144.

Osoba D: Translating the science of patient-reported outcomes assessment into clinical practice. J Natl Cancer Inst Monogr2007:5-11.

Oesterling JE. Prostate specific antigen: a critical assessment of the most useful tumor marker for adenocarcinoma of the prostate. J Urol. 1991; 145:907-923.

Pal RP, Elmussareh M, Chanawani M, Khan MA: The role of a standardized 36-core template assisted transperineal prostate biopby technique in patients with previously negative transrectal ultrasonography-guided prostate biosies. BJU Int 2012; 109:367-371.

Pardo Y, F Guedea F, Aguiló F, et al. Quality-of-life impact of primary treatments for localized prostate cancer in patients without hormonal treatment. J Clin Oncol 2010; 28:4687-4696.

Parker C, Gillessen S, Heidenreich A, Horwich A, on behalf of the ESMO Guidelines Committee. Cancer of the prostate: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann of Oncol 2015;26(Supplement 5): v69-v77.

Paquette EL, Connelly RR, Sesterhenn IA, et al. Improvements in pathologic staging for African-American men undergoing radical retropubic prostatectomy during the prostate specific antigen era. Cancer 2001; 92:2673-2679.

Partin AW, Kattan MW, Subong EN, et al. Combination of prostate-specific antigen, clinical stage, and Gleason score to predict pathological stage of localized prostate cancer. A multi-institutional update. JAMA 1997; 277:1445-1451.

Peeters ST, Heemsbergen WD, Koper PC, et al. Dose-response in radiotherapy for localized prostate cancer: results of Dutch multicenter randomized phase III trial comparing 68 Gy of radiotherapy with 78 Gy. J Clin Oncol 2006; 24:1990-1996.

Penson DF, Litwin MS. Quality of life after treatment for prostate cancer. Curr Urol Rep 2003;4: 185-195.

Petereit DG, Frank SJ, Viswanathan AN, et al. Brachytherapy: Where has it gone? J Clin Oncol 2015; 33:980-982.

Petit JH, Gluck C, Kiger WS 3rd, et al. Bicalutamide alone prior to brachytherapy achieves cytoreduction that is similar to luteinizing hormone-releasing hormone analogues with less patient-reported morbidity. Urol Oncol 2008; 26:372-377.

Pienta KJ, Bradley D. Mechanisms Underlying the development of androgen-independent prostate cancer. Clin Cancer Res 2006; 12:1665-1671.

Pinquart M, Duberstein PR. Information needs and decision-making processes in older cancer patients. Crit Rev Oncol Hematol 2004; 51:69-80.

Pollack A, Zagars GK, Starkschall G, et al. Prostate cancer radiation dose response: Results of the M.D. Anderson phase III randomized trial. Int J Radiat Oncol Biol Phys 2002; 53:1097-1105.

Potosky AL, Reeve BB, Clegg LX, et al. Quality of life following localized prostate cancer treated initially with androgen deprivation therapy or no therapy. J Natl Cancer Inst 2002; 94:430-437.

Potters L, Roach M3rd, Davis BJ, et al. Postoperative nomogram predicting the 9-year probability of prostate cancer recurrence after permanent prostate brachytherapy using radiation dose as a prognostic variable. Int J Radiat Oncol Biol Phys 2010; 76:1061-1065.

Prostate Cancer Trialists´Collaborative Group. Maximum androgen blockade in advanced prostate cancer: an overview of the randomised trials. Lancet 2000; 355:1491-1498.

Ravery V, Dominique S, Panhard X, et al. The 20-core prostate biopsy protocol -- a new gold standard? JUrol 2008; 179:504-507.

Raymond VM. Makherjee B, Wang F, et al. Elevated risk of prostate cancer among men with Lynch Syndrome. JCO 2013; 31:1713-1718.

Reid AH, Attard G, Danilla DC, et al. Significant and sustained antitumor activity in post-docetaxel castration-resistant prostate cancer with the CYP17 inhibitor abiraterone acetate. J Clin Oncol 2010; 28:1489-1495.

Resnick MJ, Koyama T, Fan KH, et al. Long-term functional outcomes after treatment for localized prostate cancer. N Engl J Med 2013; 368:436-45.

Rhodes VA, McDaniel RW, Matthews CA. Hospice patients' and nurses´ perceptions of self-care deficits based on symptom experience. Cancer Nurs 1998; 21:312-319.

Roach M, Lu J, Pilepich MV, et al. Long-term survival after radiotherapy alone: radiation therapy oncology group prostate cancer trials. J Urol. 1999; 161:864-868.

Robinson JW, Moritz S, Fung T. Meta-analysis of rates of erectile function after treatment of localized prostate carcinoma. Int J Radiat Oncol Biol Phys 2002; 54: 1063-8.

Rodriguez C, McCullough ML, Mondul AM, et al. Meat consumption among black and white men and risk of prostate cancer in the Cancer Prevention Study II Nutrition Cohort. Cancer Epidemiol Biomarkers Prev 2006; 15:211-216.

Rohrmann S, Platz EA, Kavanaugh CJ, et al. Meat and dairy consumption and subsequent risk of prostate cancer in a US cohort study. Cancer Causes Control 2007; 18:41-50.

Ryan CJ, Smith MR, Fong L, et al. Phase I clinical trial of the CYP17 inhibitor abiraterone acetate demonstrating clinical activity in patients with castration-resistant prostate cancer who received prior ketoconazole therapy. J Clin Oncol 2010; 28:1481-1488.

Sanda MG, Dunn RL, Michalski J, et al. Quality of life and satisfaction with outcome among prostate cancer survivors. N Engl J Med 2008; 358:1250-126.

Sardana G, Dowell B, Diamandis EP: Emerging biomarkers for the diagnosis and prognosis of prostate cancer. Clin Chem 2008; 54:1951-1960.

Scher HI, Fizazi K, Saad F, Mary-Ellen T, Sternberg CN, Miller K, et al. Increased survival with enzalutamide in prostate cancer after chemotherapy. N Engl J Med 2012; 367:1187-1197.

Schellhammer PF, Hershberg RM. Immunotherapy with autologous antigen presenting cells for the treatment of androgen independent prostate cancer. World J Urol 2005; 23:47-49.

Schmidt S, Garin O, Pardo Y, et al. Assessing quality of life in patients with prostate cancer: a systematic and standardized comparison of available instruments. Qual Life Res. 2014; 23:2169-2181.

Sesso HD, Paffenbarger RS Jr, Lee IM. Alcohol consumption and risk of prostate cancer: The Harvard Alumni Health Study. Int. J. Epidemiol. 2001; 30:749-755.

Shaida N and Malone PR. Diagnosis of early prostate cancer. International Handbook of Prostate Cancer, 3rd edition, 2008. Published by Euromed Communications Ltd, London, UK.

Shariat SF, Semjonow A, Lilja H, et al. Tumour markers in prostate cancer: blood-based markers. Acta Oncol 2011;50(Suppl1):61-75.

Sheets NC, Goldin GH, Meyer AM, et al. Intensity-modulated radiation therapy, proton therapy, or conformal radiation therapy and morbidity and disease control in localized prostate cancer. JAMA 2012; 307:1611-1620.

Shimizu H, Ross RK, Bernstein L, et al. Cancer of the prostate and breast among Japanese and white immigrants in Los Angeles County. Br J Cancer 1991; 63:963-966.

Shrader-Bogen C, Kjellberg JL, McPherson C, Murray CL. Quality of life and treatment outcomes: Prostate carcinoma patients`perspectives after prostatectomy or radiation therapy. Cancer 1997; 79:1977-1986.

Sigurdardóttir V, Brandberg Y, Sullivan M. Criterion-based validation of the EORTC QLQ-C36 in advanced melanoma: the CIPS questionnaire and proxy raters. Qual Life Res 1996; 5:375-386.

Simon RM, Salama JK, Freedland SJ. Radical prostatectomy versus radiation therapy: can pretreatment nomograms be used to select the appropriate prostate cancer treatment? Eur Urol 2015; 67:210-211.

Small EJ, Fratesi P, Reese DM, Strang G, Laus R, Peshwa MV, et al. Immunotherapy of hormone refractory prostate cancer with antigen-loaded dendritic cells. J Clin Oncol 2000; 18:3894-903.

Stanford JL, Feng Z, Hamilton AS, et al. Urinary and sexual function after radical prostatectomy for clinically localized prostate cancer: The Prostate Cancer Outcomes Study. JAMA 2000; 283:354-360.

Stanford J, Ostrander EA. Familial Prostate Cancer. Epidemiologic Reviews. 2001; 23:19-23.

Stenman UH, Abrahamsson PA, Aus G, et al. Prognostic value of serum markers for prostate cancer. Scand J Urol Nephrol Suppl, 2005;39:64-81.

Socialstyrelsen, 2015. Official Statistics of Sweden, Statistics-Health and Medical Care, CancerincidenceinSweden2014.http://www.socialstyrelsen.se/Lists/Artikelkatalog/Attachments/20008/2015-12-26.pdf

Socialstyrelsen. Statistikdatabasen 2015 http//www.socialstyrelsen.se/statistik/statistikdatabas/dodsorsaker2015

Steineck G, Helgesen F, Adolfsson J, et al. Quality of life after radical prostatectomy or watchful waiting. N Engl J Med 2002; 347:790–796.

Stephenson AJ, Scardino PT, Eastham JA, et al. Preoperative nomogram predicting the 10-year probability of prostate cancer recurrence after radical prostatectomy. J Natl Cancer Inst 2006; 98:715-717.

Strom SS, Wang X, Pettaway CA, et al. Obesity, weight gain, and risk of biochemical failure among prostate cancer patients following prostatectomy. Clin Cancer Res. 2005;11: 6889–6894.

Sveistrup J, Widmark A, Fransson P, et al. Prospective assessment of urinary, gastrointestinal and sexual symptoms before, during and after image-guided volumetric modulated arc therapy for prostate cancer. Scand Urol 2015; 49:58-69.

Sweeney C, Chen YH, Carducci M, et al. Impact on overall survival (OS) with chemo-hormonal therapy for hormone-sensitive newly metastatic prostate cancer (mPrCa): an ECOG-led phase III randomized trial. J Clin Oncol (ASCO Meeting Abstract) 2014;32 (Suppl 18): LBA2.

Sweeney CJ, Chen YH, Carducci M, Liu G, Jarrard DF, Eisenberger M, et al. Chemo-hormonal Therapy in Metastatic Hormone-sensitive prostate cancer. N Engl J Med 2015; 373(8):737-746.

Taira AV, Merrick GS, Galbreath RW, et al. Performance of transperineal template-guided mapping biopsy in detecting prostate cancer in the initial and repeat biopsy setting. Prostate Cancer Prostatic Dis 2010; 13:71–77.

Talcott JA, Reiker P, Propert KJ, et al. Patient reported impotence and incontinence after nerve-sparing radical prostatectomy. J Natl Cancer Inst 1997; 89:1117-1123.

Talcott J, Clark J, Stark P, et al. Long-term treatment related complications of brachytherapy for early prostate cancer: a survey of prevously treated patients. J Urol 2001; 166:494-499.

Terris MK, Stamey TA: Determination of prostate volume by transrectal ultrasound. J Urol 1991; 145:984-987.

Tewari A, Rao S, Martinez-Salamanca JI, et al. Cancer control and the preservation of neurovascular tissue: how to meet competing goals during robotic radical prostatectomy. BJU Int 2008;101:1013-1018.

Toner L, Weerakoon M, Bolton DM, et al. Magnetic resonance imaging for prostate cancer: Comparative studies including radical prostatectomy specimens and template transperineal biopsy. Prostate Int. 2015; 3:107-114.

Terris MK, Stamey TA: Determination of prostate volume by transrectal ultrasound. J Urol 1991;145: 984-987.

Thomas R, Deary A, Kaminski E, et al. Patients' preferences for videocassette recorded information: effect of age, sex and ethnic group. Eur J Cancer Care 1999; 8:83-86.

Thompson D, Easton D. Variation in cancer risks, by mutation position, in BRCA2 mutation carriers. Am J Hum Genet 2001; 68:410-419.

Thompson D, Easton DF. Cancer Incidence in BRCA 1 Mutation Carriers. J Nat Cancer Inst 2002; 94:1358-1365.

Thompson IM. Pauler DK, Goodman PJ, et al. Prevalence of prostate cancer among men with a prostate-specific antigen level < or = 4.0 ng per milliliter. The N Engl j Med 2004; 350:2239-2246.

Uchida T. Editorial Comment to Health-related quality of life after salvage high-intensity focused ultrasound (HIFU) treatment for locally radiorecurrent prostate cancer. Int J Urol 2011;18:651-652.

Van Andel G, Bottomley A, Fosså SD, et al. An international field study of the EORTC QLQ-PR25: a questionnaire for assessing the health-related quality of life of patients with prostate cancer. Eur J Cancer 2008; 44:2418-2424.

Vasarainen H, Lokman U, Ruutu M, et al. Prostate cancer active surveillance and health-related quality of life: results of the Finnish arm of the prospective trial. BJU Int 2012; 109:1614-1619.

Varenhorst E, Berglund K, Lofman O, Pedersen K. Inter-observer variation in assessment of the prostate by digital rectal examination. Br J Urol 1993; 72:173-176.

Venkitaraman R, Lorente D, Murthy V et al. A randomized phase 2 trial of dexamethasone versus prednisolone in castration-resistant prostate cancer. Eur Urol 2015; 67: 673-679.

Viani GA, da Silva LBG, da Silva BB, et al. Acute toxicity profile in prostate cancer with conventional and hypofractionated treatment. Radiat Oncol. 2013; 8:94.

Wabinga HR, Parkin DM, Wabwire-Mangen F, Nambooze S. Trends in cancer incidence in Kyadondo County, Uganda, 1960-1997. Br J Cancer 2000;82:1585-1592.

Wahlgren T, Brandberg Y, Häggarth L, et al. Health-related quality of life in men after treatment of localized prostate cancer with external beam radiotherapy combined with (192)

ir brachytherapy: a prospective study of 93 cases using the EORTC questionnaires QLQ-C30 and QLQ-PR25. Int J Radiat Oncol Biol Phys 2004; 60:51-59.

Wahlgren T, Nilsson S, Ryberg M, et al. Combined curative radiotherapy including HDR brachytherapy and androgen deprivation in localized prostate cancer: A prospective assessment of acute and late treatment toxicity. Acta Oncol 2005; 44:633-43.

Ware JE, Jr., Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care 1992; 30:473-483.

Watters JL, Park Y, Hollenbeck A, et al. Cigarette smoking and prostate cancer in a prospective US Cohort Study. Cancer Epidemiol Biomarkers Prev 2009; 18:2427-2435.

Wei B, Xu Z, Ruan J, et al. RNASEL Asp541Glu and Arg462Gln polymorphisms in prostate cancer risk: evidences from a meta-analysis. Mol Biol Rep 2012;39:2347–2353.

Wei Jt, Dunn RL, Sandler HM, et al. Comprehensive comparison of health related quality of life after contemporary therapies for localized prostate cancer. J Clin Oncol 2002; 20:557-566.

Whelan P, Tewari AK, Graham JD. Prostate cancer diagnosis and clinical management: Diagnosis and clinical management, 2014. John Wiley and sons, Ltd. West Sussex, UK.

Widmark A, Klepp O, Solberg A, Damberg JE, Angelsen A, Fransson P, Lund JÅ, Tasdemir I, Hoyer M, Wiklund F, Fosså S for the Scandinavian Prostate Cancer Group Study 7, the Swedish Association for Urological Oncology 3. Endocrine treatment, with or without radiotherapy, in locally advanced prostate cancer (SPCG-7/SFUO-3): an open randomized phase III trial. The Lancet 2009; 373(9660): 301-308.

Wilkins A, Mossop H, Syndikus I, Khoo V, Bloomfield D, Parker C, et al. Hypofractionated radiotherapy versus conventionally fractionated radiotherapy for patients with intermediate-risk localised prostate cancer: 2-year patient-reported outcomes of the randomised, non-inferiority, phase 3 CHHiP trial. The Lancet Oncology 2015; 16(16): 1605-1616.

World Health Organization. Constitution of the World Health Organization, Basic Documents. Geneva, Switzerland: World Health Organization; 1948.

World Health Organization. International histological classification of tumors. Histological typing of prostate tumors. Geneva: World Health Organization 1980.

World Health Organization. Histological typing of prostate tumors. Fathollah Keshvar Mostofi I Sesterhenn; L. H Sobin; Geneva 1980.

World Health Organization. International Agency for Research on Cancer. GLOBOCAN 2012: Estimated Cancer Incidence, Mortality and Prevalence in 2012.

Wu CP, Gu FL The prostate in eunuchs. Prog Clin Biol 1991; 370:249-255.

Xia J, Trock BJ, Cooperberg MR et al. Prostate cancer mortality following active surveillance versus immediate radical prostatectomy. Clin Cancer Res 2012:18;54715478.

Yarbro C, Ferrans C. Quality of life of patients with prostate cancer treated with surgery or radiation therapy. Oncol Nurs Forum 1998; 25:685-693.

Zagars GK, Ayala AG, von Eschenbach AC, Pollack A. The prognostic importance of Gleason grade in prostatic adenocarcinoma: a long-term follow-up study of 648 patients treated with radiation therapy. Int J Radiol Oncol Biol Phys 1995; 31:237-245.

Zelefsky MJ, Leibel SA, Burman CM, et al. Neoadjuvant hormonal therapy improves the therapeutic ratio in patients with bulky prostate cancer treated with three-dimensional conformal radiation therapy. Int J Radiat Oncol Biol Phys 1994; 29:755-761.

Zelefsky MJ, M.W. Kattan, P. Fearn, et al. Pretreatment nomogram predicting ten-year biochemical outcome of three-dimensional conformal radiotherapy and intensity-modulated radiotherapy for prostate cancer. Urology 2007; 70:283-287.

Zietman AL, Prince EA, Nakfoor BM, Park JJ. Androgen deprivation and radiation therapy: sequencing studies using the Shionogi in vivo tumor system. Int J Radiat Oncol Biol Phys 1997;38(5):1067–70.

Zietman AL, Nakfoor BM, Prince EA. The effect of androgen deprivation and radiation therapy on an androgen-sensitive murine tumour: an in vitro and in vivo study. Cancer J Sci AM 1997; 3:31-36.

Zietman AL, DeSilvo ML, Slater JD, et al. Comparison of conventional-dose vs high-dose conformal radiation therapy in clinically localized adenocarcinoma of the prostate. A randomized controlled trial. JAMA,2005;294:1233-1239.