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 concerning 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


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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<td>DSB</td>
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<tr>
<td>EBRT</td>
<td>External Beam Radiation Therapy</td>
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<td>EORTC</td>
<td>European Organization for Research and Treatment of Cancer</td>
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<td>ESMO</td>
<td>European Society for Medical Oncology</td>
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<td>FFF</td>
<td>Freedom From Failure</td>
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<td>FSH</td>
<td>Follicular Stimulating Hormone</td>
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<td>GnRH</td>
<td>Gonadotropin Releasing Hormone</td>
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<td>HDR</td>
<td>High Dose Rate</td>
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Male Reproductive Tract

Bladder
Prostate
Penis
Urethra
Rectum
Seminal Vesicles
Anus
Vas Deferens
Epididymis
Testis
Tunica Vaginalis
Scrotum

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% for 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 correlation with overall PCa risk found. In subgroup analyses, however, a low-penetrant 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; Rohrman 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 naïve 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 usually 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 urethelial 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 become 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).
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 metastasis\(^4\)

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 patients 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 specialized 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 (Peteriet 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 103Paladium or 125Iodine 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 125Iodine source, a dose of 145 Gy achieved whereas with 103Paladium, 125 Gy achieved. For both isotopes, the prescribed dose reduced when combined with external-beam radiation (Beyer, 2001). High dose rate brachytherapy (HDR-BT): 192Iridium 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 steroidal 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 concomitant 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 effects 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 al., 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 dysfunction 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:

\[
\text{BED} = nd \times \left(1 + \frac{d}{\alpha/\beta}\right)
\]

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-naive 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, pamidronate 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 (Alemoazzafar 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-Axelson 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 comparaion 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

<table>
<thead>
<tr>
<th>Author</th>
<th>Journal/Year</th>
<th>Study design and purpose</th>
<th>Number of patients</th>
<th>RP/RT and ADT</th>
<th>Instrument Assessment point after therapy</th>
<th>Results</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basaria et al.</td>
<td>Clin Endocrin 2002</td>
<td>Cross-sectional</td>
<td>n=58</td>
<td>n=20 (ADT 12 months)</td>
<td>Watts sexual function questionnaire and other measures to examine bone and fat mass</td>
<td>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</td>
<td>Osteoporosis, unfavorable body composition, sexual dysfunction and reduced HRQoL were found in ADT after 12 months. More studies were warranted</td>
</tr>
<tr>
<td>Drummond et al.</td>
<td>J Cancer Surviv 2015</td>
<td>Cross-sectional</td>
<td>n=6559</td>
<td>EBRT 34%, RP 28%, EBRT + ADT 18%, ADT 9%, Observation 5%, BT 4%</td>
<td>EORTC C-30, EORTC-PR25 Once at three time points after diagnosis: &lt;5 yrs; 5-10 yrs; &gt;10 yrs</td>
<td>Response rate 54%, HRQoL was better in RP than EBRT or ADT alone; but were similar compared to other groups</td>
<td>Long-term HRQoL varied in survivors depending on the treatment given</td>
</tr>
<tr>
<td>Lubeck et al.</td>
<td>Urol 2001</td>
<td>Cohort study</td>
<td>n=699</td>
<td>n=106 (surveillance)</td>
<td>UCLA-PCI SF-36 Baseline and every 3 months up to 9 months</td>
<td>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.</td>
<td>Longer follow-up needed after ADT start to know the impact on HRQoL.</td>
</tr>
<tr>
<td>Potosky et al.</td>
<td>J Natl Cancer Inst 2002</td>
<td>Population based cohort study</td>
<td>n=661</td>
<td>n=245 (ADT) n=416 (no therapy)</td>
<td>SF-36 Base line and 1 year after therapy</td>
<td>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.</td>
<td>Physical wellbeing and sexual function should be considered in the first year following treatment with ADT</td>
</tr>
<tr>
<td>Alibhai et al.</td>
<td>JCO 2010</td>
<td>Prospective longitudinal study</td>
<td>n=259</td>
<td>n=87 (ADT) n=86 (PC controls) n=86 (Healthy controls)</td>
<td>SF-36 Baseline, 3, 6, 12 months</td>
<td>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</td>
<td>Components of QoL are affected within 3 months of starting ADT. Up-front exercise interventions are warranted.</td>
</tr>
</tbody>
</table>

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. Surprisingly, 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 (emotional 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**

<table>
<thead>
<tr>
<th>Method</th>
<th>STUDY I</th>
<th>STUDY II</th>
<th>STUDY III</th>
<th>STUDY IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paired t-test</td>
<td></td>
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<td></td>
<td>X</td>
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<tr>
<td>ANOVA repeated measurements</td>
<td>X</td>
<td></td>
<td></td>
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<tr>
<td>Kaplan-Meier analysis</td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
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<tr>
<td>Log rank test</td>
<td></td>
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<td>X</td>
<td></td>
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<tr>
<td>Linear regression model</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Wald test</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Fishers-exact test</td>
<td></td>
<td>X</td>
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</tbody>
</table>
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<0.001), 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 prospective 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). Surprisingly, ≥10% PV increase was found in four AA-patients and in one TAB-patient. This might be explained by inter-physician variability 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 tiresome 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 intended 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 referred 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


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).


Syfte, patienter, metod och resultat

Delarbete 1: Undersöker PC patienters uppfattning av information inför, under och efter kurativt syftande strålbehandling, samt deras tillfredsställelse 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 tillfredsställelse 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 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 följes 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.


**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 för tid, 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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