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High dose rate brachytherapy boost for localized prostate cancer
Clinical and patient-reported outcomes

Thomas Wahlgren

Stockholm 2006
To the ladies in my life

EWA
JULIA
CLARA

*Amor vincit omnia (Vergilius)*...
Curative treatment of prostate cancer is controversial. The therapeutic effects of surgery and radiotherapy (RT) have hitherto proved to be similar, why other endpoints such as health related quality of life (HRQoL) stay important in decision-making. The aims of this thesis were to evaluate clinical and patient-reported outcomes after combined external beam RT and high dose rate (HDR) brachytherapy boost including neoadjuvant androgen deprivation therapy (ADT).

Longitudinal studies of HRQoL after combined RT are scarce. Using the EORTC QLQ-C30 and PR25 questionnaires, short-term HRQoL was prospectively assessed twice in 80 patients at an 18 month interval 0-18 months after RT. Analysis included 2 subgroups of relapse-free patients in order to detect differences in acute and late reactions. The levels of HRQoL were generally high, did not change over time and were in large comparable to normative data. Urinary, bowel and sexual HRQoL outcomes corresponded to known acute and late effects of radical RT and ADT. Effects of ADT seemed to be substantial but mostly transitory.

Self-reported urinary, bowel and sexual side effects were investigated prospectively at the outpatient clinic, Radiumhemmet, at multiple assessment points before and 2-34 months after combined RT by means of a prostate-specific questionnaire. 525 patients responded to at least one questionnaire. Baseline sexual function was statistically significantly worse in patients receiving ADT. Urinary, bowel and sexual problems increased after RT and persisted at higher levels compared to baseline. Though there were signs of hormonal restitution, erectile dysfunction persisted. Side effects seemed comparable with those of other RT series.

Late HRQoL more than 5 years after RT was evaluated in 158 patients, using the EORTC QLQ-C30 and PR25 questionnaires. In comparison with normative data, minor differences in general HRQoL were demonstrated, possibly suggesting “response shift” effects. Longitudinal analysis of disease-specific HRQoL showed that urinary urgency, increased stool frequency and erectile problems persisted five years after treatment. Few signs of hormonal disturbances were noted. The frequency of late rectal bleeding was low. Fecal incontinence was reported by 25% of patients of which 80% considered it to be a minor problem.

A survival analysis included 154 patients. The 5-year relapse-free survival was 84%, comparable to other published series. No local recurrence was seen. Median PSA was non-measurable. 68% of patients staged T3 were relapse-free. In multivariate Cox regression, WHO grade statistically significantly influenced outcome (HR 2.46 95% CI 1.44-4.18). Using nomograms, predicted 5-year relapse-free survival rates for surgery and RT were 54% and 70 % respectively. Late RTOG grade 3 toxicity developed in 1% (bowel) and 4% (urinary) of patients.

In conclusion, combined RT provides high cure rates, but entails a risk of side effects of which most seem to be of limited duration.

Key words: Localized prostate cancer; radiotherapy; HDR brachytherapy; health related quality of life; questionnaires; side effects

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ABSTRACT

Curative treatment of prostate cancer is controversial. The therapeutic effects of surgery and radiotherapy (RT) have hitherto proved to be similar, why other endpoints such as health related quality of life (HRQoL) stay important in decision-making. The aims of this thesis were to evaluate clinical and patient-reported outcomes after combined external beam RT and high dose rate (HDR) brachytherapy boost including neoadjuvant androgen deprivation therapy (ADT).

Four samples from a cohort of 870 consecutive patients treated 1998-2003 at the Department of Oncology, Karolinska University Hospital, were studied.

Longitudinal studies of HRQoL after combined RT are scarce. Using the EORTC QLQ-C30 and PR25 questionnaires, short-term HRQoL was prospectively assessed twice in 80 patients at an 18 month interval 0-18 months after RT. Analysis included 2 subgroups of relapse-free patients in order to detect differences in acute and late reactions. The levels of HRQoL were generally high, did not change over time and were in large comparable to normative data. Urinary, bowel and sexual HRQoL outcomes corresponded to known acute and late effects of radical RT and ADT. Effects of ADT seemed to be substantial but mostly transitory.

Self-reported urinary, bowel and sexual side effects were investigated prospectively at the outpatient clinic, Radiumhemmet, at multiple assessment points before and 2-34 months after combined RT by means of a prostate-specific questionnaire. 525 patients responded to at least one questionnaire. Baseline sexual function was statistically significantly worse in patients receiving ADT. Urinary, bowel and sexual problems increased after RT and persisted at higher levels compared to baseline. Though there were signs of hormonal restitution, erectile dysfunction persisted. Side effects seemed comparable with those of other RT series.

Late HRQoL more than 5 years after RT was evaluated in 158 patients, using the EORTC QLQ-C30 and PR25 questionnaires. In comparison with normative data, minor differences in general HRQoL were demonstrated, possibly suggesting “response shift” effects. Longitudinal analysis of disease-specific HRQoL showed that urinary urgency, increased stool frequency and erectile problems persisted five years after treatment. Few signs of hormonal disturbances were noted. The frequency of late rectal bleeding was low. Fecal incontinence was reported by 25% of patients of which 80% considered it to be a minor problem.

A survival analysis included 154 patients. The 5-year relapse-free survival was 84%, comparable to other published series. No local recurrence was seen. Median PSA was non-measurable. 68% of patients staged T3 were relapse-free. In multivariate Cox regression, WHO grade statistically significantly influenced outcome (HR 2.46 95% CI 1.44-4.18). Using nomograms, predicted 5-year relapse-free survival rates for surgery and RT were 54% and 70 % respectively. Late RTOG grade 3 toxicity developed in 1% (bowel) and 4% (urinary) of patients.

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<th>Description</th>
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<tbody>
<tr>
<td>3D-CRT</td>
<td>Three-dimensional conformal radiotherapy</td>
</tr>
<tr>
<td>ACTH</td>
<td>Adrenocorticotropic hormone</td>
</tr>
<tr>
<td>ADT</td>
<td>Androgen deprivation therapy</td>
</tr>
<tr>
<td>ANOVA</td>
<td>Analyses of variance</td>
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<tr>
<td>BED</td>
<td>Biologically effective dose</td>
</tr>
<tr>
<td>bNED</td>
<td>Biochemical non-evidence of disease</td>
</tr>
<tr>
<td>DHEA</td>
<td>Dehydroepiandrosterone</td>
</tr>
<tr>
<td>DHT</td>
<td>Dihydrotestosterone</td>
</tr>
<tr>
<td>DRE</td>
<td>Digital rectal examination</td>
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<tr>
<td>EBRT</td>
<td>External beam radiotherapy</td>
</tr>
<tr>
<td>ED</td>
<td>Erectile dysfunction</td>
</tr>
<tr>
<td>EORTC</td>
<td>European Organization for Research and Treatment of Cancer</td>
</tr>
<tr>
<td>FNAC</td>
<td>Fine needle aspiration cytology</td>
</tr>
<tr>
<td>GI</td>
<td>Gastrointestinal</td>
</tr>
<tr>
<td>GU</td>
<td>Genitourinary</td>
</tr>
<tr>
<td>Gy</td>
<td>Gray</td>
</tr>
<tr>
<td>HDR</td>
<td>High dose rate</td>
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<tr>
<td>HRQoL</td>
<td>Health related quality of life</td>
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<tr>
<td>IMRT</td>
<td>Intensity modulated radiotherapy</td>
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<tr>
<td>LDR</td>
<td>Low dose rate</td>
</tr>
<tr>
<td>LH</td>
<td>Luteinizing hormone</td>
</tr>
<tr>
<td>LHRH</td>
<td>Luteinizing hormone releasing hormone</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
</tr>
<tr>
<td>NTD</td>
<td>Normalized total dose</td>
</tr>
<tr>
<td>PSA</td>
<td>Prostate-specific antigen</td>
</tr>
<tr>
<td>PTV</td>
<td>Planning target volume</td>
</tr>
<tr>
<td>QLQ-C30</td>
<td>Quality of Life Questionnaire - Core 30</td>
</tr>
<tr>
<td>QLQ-PR25</td>
<td>Quality of Life Questionnaire - Prostate 25</td>
</tr>
<tr>
<td>RP</td>
<td>Radical prostatectomy</td>
</tr>
<tr>
<td>RT</td>
<td>Radiotherapy</td>
</tr>
<tr>
<td>RTOG</td>
<td>Radiation Therapy Oncology Group</td>
</tr>
<tr>
<td>SPCG</td>
<td>Scandinavian Prostate Cancer Group</td>
</tr>
<tr>
<td>TAB</td>
<td>Total androgen blockade</td>
</tr>
<tr>
<td>TNM</td>
<td>Tumour, Nodes and Metastasis</td>
</tr>
<tr>
<td>TRUS</td>
<td>Transrectal ultrasound</td>
</tr>
<tr>
<td>TUR-P</td>
<td>Trans-urethral resection of the prostate</td>
</tr>
<tr>
<td>UICC</td>
<td>International Union Against Cancer</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
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</table>
INTRODUCTION

Prostate cancer is an increasing health problem, being the most common malignancy among males in the Western world. Its incidence has rapidly increased over the past few years, not at least in Sweden. The mean age at diagnosis is high, why patients in general have a limited expected survival and often suffer from other illnesses. Tumour growth is generally slow, implying that a majority of patients will not live long enough to develop symptoms or disability from their prostate cancer. Nevertheless, if localized, prostate cancer is a highly curable disease.

Active treatment includes surgery and radiotherapy (RT). All established curative measures can cause serious and long-lasting complications, whereas little definitive evidence supports the belief that they differ importantly in efficacy for most patients. Watchful waiting could also be considered a reasonable option for some patients, with no risk of treatment-related complications. However, which patients to treat and how to treat them remains a controversy.

Although coexisting medical problems influence treatment decisions to some extent, quality of life issues will be of vital importance and patients are often compelled to make implicit judgments about the relative value of maintaining their quality of life versus maximizing their survival. This often proves to be difficult due to the vast number of evolving treatment options available, where information regarding treatment-related quality of life factors quite often is lacking.

In this thesis, focus is set to patient-reported outcomes in terms of health related quality of life (HRQoL), genitourinary (GU), gastrointestinal (GI) and sexual problems after combined RT, including androgen deprivation therapy (ADT), external beam RT (EBRT) and high dose rate (HDR) brachytherapy (BT) boost. This evaluation is done prospectively, including both acute and late side effects, in order to enhance the understanding of this high dose treatment. Treatment efficacy in terms of 5-year relapse-free survival in relation to tumour characteristics is also assessed.

The results from this work will provide information to both physicians and patients in the decision-making process regarding treatment options for localized prostate cancer.
GENERAL BACKGROUND

1 PROSTATE CANCER

1.1 Epidemiology

Prostate cancer is the most common malignancy in Swedish males, accounting for 37% of all new cancer cases in 2004 (Socialstyrelsen 2005). The median age at diagnosis is 70 years. The age standardized incidence in the population has risen dramatically over the past few years (Figure 1), reaching 209/100000 in 2004 as compared to 124/100000 in 1994 (Socialstyrelsen 2005).

The Stockholm County accounted for 1924 new cases in 2004, having the highest age standardized incidence in the country (239/100000) (Socialstyrelsen 2005). This trend is probably explained by increased public awareness and use of opportunistic PSA screening, as well as a general increase in the mean age of the male population. Prostate cancer mortality has remained stable during the last 20 years, about 2500 men per year (age standardized incidence 47/100000).

The disease is highly prevalent, counting 54059 prevalent cases 2004 of which 34676 were diagnosed between year 2000-2004 (Socialstyrelsen 2006).

![Figure 1. Age standardized prostate cancer incidence per 100000 men in Sweden 1970-2004. Adapted from the National board of Health and Welfare.](image)

1.2 Etiology

Surprisingly little is known about the causes of prostate cancer. Age, geographical, racial and hereditary factors are the only established risk factors. No true association to smoking or alcohol has been shown (Pienta et al. 1993).

During recent years, much attention has been drawn to nutritional factors, such as high dietary fat intake, lycopenes, selenium and pomegranate, but the true implications of these findings have to be established (Wolk 2005).
1.3 Hormonal regulation

The importance of androgen stimulation in the development of prostate cancer has been known for over 60 years (Huggins et al. 1941). Testosterone is the principal circulating androgen in man, responsible for prostate gland formation in the embryo and for normal function throughout adulthood, including the production of PSA. Approximately 90% of the androgens produced by the Leydig cells in the testes are secreted as testosterone and the remainder by the adrenal cortex as dehydroepiandrosterone (DHEA), which can be converted to testosterone in other tissues. The production of testosterone by the testes is regulated by a negative feedback mechanism, involving the luteinizing hormone (LH) and the luteinizing hormone releasing hormone (LHRH) via the gonadal-hypothalamic-pituitary axis. Adrenal production is likewise stimulated by adrenocorticotropic hormone (ACTH). Testosterone may be converted to more potent forms, such as the androgen dihydrotestosterone (DHT) by the enzyme 5α-reductase, which is present in many androgen target tissues such as the prostate. Androgens in the prostate will be attached predominantly to an androgen receptor and the activated steroid-receptor complex will promote cellular growth (So et al. 2003).

![Diagram of the gonadal-hypothalamic-pituitary axis](image)

**Figure 2.** The gonadal-hypothalamic-pituitary axis. Pathways and feedback loops that regulate the production of androgens in males including procedures and agents used for blocking androgen activity. Adapted from So et al, 2003.
1.4 Diagnosis

The diagnostic procedures for prostate cancer are generally carried out by urologists after referral from general practitioners, either in patients with symptoms from the genitourinary sphere or nowadays commonly in symptom-free patients. The investigation is carried out as a triple diagnostics procedure:

1.4.1 Prostate-specific antigen (PSA)

PSA is a tissue-specific protein, formed in the cells of the glandular epithelium of the prostate and was first described in 1970 (Ablin et al. 1970). Immunohistochemical analysis of serum PSA has been commercially available since 1986 and is today the most important diagnostic method for prostate cancer, but is also highly useful for follow-up purposes. In Sweden, an arbitrary PSA normal upper limit of 4 ng/ml is normally recommended for diagnostic purposes.

In comparison with the earlier used acid phosphatase, PSA exhibits a higher sensitivity and better reflects disease development after treatment (Oesterling 1991). However, due to limited specificity of the PSA test, efforts have been made to propose additional assessment methods, such as the PSA ratio (Abrahamsson et al. 1997). The PSA ratio is mostly used to discriminate between hyperplasia and suspect tumours when assessing a slightly elevated PSA (4-10 ng/ml).

1.4.2 Digital rectal examination (DRE)

DRE is the standard way of manually assessing the prostate structures, capsular engagement in particular. The procedure is cheap and relatively easily performed, but highly subjective (Varenhorst et al. 1993). The positive predictive value for DRE is only about 30%, but combined with PSA and TRUS the diagnostic certainty improves. Tumour stage is classified according to the 2002 UICC TNM system, presented in Table 1 (International Union Against Cancer (UICC) 2002).

1.4.3 Transrectal ultrasound (TRUS)

TRUS permits, by means of a rectal probe, detailed imaging of the prostate gland, its contour and inner architecture as well as imaging of adjacent structures, such as the seminal vesicles and bowel wall. The method allows detection of lesions with different echogeneity and determination of glandular volume, but is most useful in combination with core biopsies (Hoisaeter et al. 1994), normally 6-10 biopsies evenly distributed throughout the prostate gland. As for DRE and PSA, this method alone has a low positive predictive value, which improves when combining methods. Additional staging by magnetic resonance imaging (MRI) is not routinely done in Sweden.
Table 1. T-stage according to UICC, 2002

<table>
<thead>
<tr>
<th>T-stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
<td>Primary tumour cannot be assessed.</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumour.</td>
</tr>
<tr>
<td>T1</td>
<td>Clinically unapparent tumour not palpable or visible by imaging.</td>
</tr>
<tr>
<td>T1a</td>
<td>Tumour incidental histological finding in 5% or less of tissue resected.</td>
</tr>
<tr>
<td>T1b</td>
<td>Tumour incidental histological finding in more than 5% of tissue resected.</td>
</tr>
<tr>
<td>T1c</td>
<td>Tumour identified by needle biopsy (e.g. because of elevated PSA).</td>
</tr>
<tr>
<td>T2</td>
<td>Tumour confined within the prostate.</td>
</tr>
<tr>
<td>T2a</td>
<td>Tumour involves one lobe.</td>
</tr>
<tr>
<td>T2b</td>
<td>Tumour involves both lobes.</td>
</tr>
<tr>
<td>T3</td>
<td>Tumour extends through the prostatic capsule.</td>
</tr>
<tr>
<td>T3a</td>
<td>Extracapsular extension (unilateral or bilateral).</td>
</tr>
<tr>
<td>T3b</td>
<td>Tumour invades seminal vesicle(s).</td>
</tr>
<tr>
<td>T4</td>
<td>Tumour is fixed or invades adjacent structures other than seminal vesicles: bladder neck, external sphincter, rectum, levator muscles, and/or pelvic wall.</td>
</tr>
</tbody>
</table>

Notes:
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 prostatic apex or into (but not beyond) the prostatic capsule is not classified as T3 but as T2.

1.5 Histopathology

Adenocarcinoma is the predominant type of cancer of the prostate and constitutes more than 95% of all tumours. Other tumour types of the prostate are distinctly rare, and include squamous cell carcinoma, transitional cell carcinoma, mesenchymal neoplasms and metastatic tumours.

There are currently many different systems in use for the histopathological grading of prostatic adenocarcinoma. The WHO grading system (WHO 1980), was the gold standard in Sweden for many years, used as long as the diagnosis of prostate cancer relied mainly on fine needle aspiration cytology (FNAC). TRUS and core needle biopsies for histologic diagnosis of prostate cancer are now predominant and therefore the Gleason scoring system (Gleason et al. 1974; Gleason 1992) has gained in popularity.

There is currently no consensus regarding the correlation between WHO grade and Gleason score, although methods for conversion have been proposed and evaluated (Jacobs et al. 1989; Maksem et al. 1988).

1.5.1 The WHO grading system

This cytological grading system, based on glandular differentiation and nuclear pattern, divides tumours mainly into 3 grades (G1-3) of well, moderately or poorly differentiated type.

1.5.2 The Gleason grading system

This system uses low-power architectural findings of core biopsies to define the pattern of the tumour. A 5-step grading system is used, and the two most prominent
grades are added together to yield the so called "Gleason score", which ranges from 2–10. The Gleason grading system offers valuable prognostic information (Chodak et al. 1994). The Gleason histologic grades are presented in Figure 3.

![Figure 3. Schematic diagram of the Gleason grading system. Adapted from Gleason et al., 1974.](image)

### 1.6 Prognosis

A majority of prostate cancers never progress to clinically significant disease, while a minor portion remains confined to the prostate for many years and other carcinomas progress rapidly to a life threatening disease. The dilemma for clinicians and pathologists dealing with this tumour is how to distinguish these three biologically different types from each other, and there is a call for better prognostic tools.

Today, prognosis and survival in prostate cancer is largely dependent on stage, PSA and histologic grading of the disease (Mikuz 1997; Oesterling 1991; Partin et al. 1997). Few biological markers besides PSA have yet proved to be practically applicable in the clinical setting (Hessels et al. 2004). Although there is yet no consensus concerning the most appropriate definition of risk features, many centres have adopted pretreatment PSA $\geq 10$, Gleason score $\geq 7$ and tumour stage $\geq T2b$ as poor risk features.

Results from conservative management of the disease have shown that well to moderately differentiated small carcinomas frequently run an indolent course and seldom cause death, especially in patients with an expected survival of less than 10 years (Chodak et al. 1994; Johansson et al. 1997). However, for patients with an expected survival of more than 15 years or having poorly differentiated tumours (Gleason score 7–10), disease progression is inevitable and treatment seems more beneficial (Adolfsson et al. 1993; Albertsen et al. 1995; Johansson et al. 2004; Lu-Yao et al. 1997).

Prognostic methods to predict treatment outcome in localized prostate cancer have been developed, combining prognostic variables from large patient cohorts to generate risk stratification groups, based on initial clinical stage, Gleason score, and
pretreatment serum PSA levels (Stephenson et al. 2006). Kattan and co-workers have presented so called nomograms for individual prediction of outcome after surgery and RT (Graefen et al. 2002; Graefen et al. 2002; Kattan et al. 1998; Kattan et al. 2000).

1.7 Treatment

In general, treatment with curative intent for prostate cancer should be considered if the tumour is localized to the prostate gland (T1-T3aN0M0) and the patient has an expected survival of more than 10 years. Palliative treatment will be the choice if the tumour is very locally advanced (T4) or metastasis is present. However, treatment of localized prostate cancer remains one of the most controversial topics of modern oncology, in large due to the uncertainty regarding which patients really benefit from active intervention and the risk of possibly harmful treatment-related side effects.

Treatment options include surgery, RT, hormonal (endocrine) and deferred treatment. There is currently no solid proof that active treatment can prolong survival as compared to symptomatic treatment, although recently published results from the Scandinavian Prostate Cancer Group (SPCG-4 study), comparing prostatectomy and watchful waiting, suggest slightly reduced overall mortality after 10 years ((Bill-Axelson et al. 2005). Neither have convincing differences regarding disease-free survival between surgery and RT been established (D'Amico et al. 1997), but solid randomized data is lacking.

1.7.1 Surgery

Radical prostatectomy (RP) is the surgical removal of the prostate and often seminal vesicles with re-implantation of the urethra. The surgical procedure is rather extensive with risk of bleeding and damage to nerves essential for erection. It is performed either as open surgery retropubically or perianally, or laparoscopically. Technical development includes a nerve-sparing technique, introduced already in the 1980ies (Walsh et al. 1983) in order to reduce complications, and during recent years robot-assisted laparoscopic surgery has evolved (Abbou et al. 2001).

Disease-specific survival for clinically localized tumours 10-15 years after surgery exceeds 90% (Adolfsson et al. 1993; Catalona et al. 1998; Zincke et al. 1994), but is highly dependent on tumour differentiation (Gerber et al. 1996).

The procedure should preferably be reserved for patients with smaller tumours (T1-T2) and good health, under the age of 70 years. However, in 40-50% of cases tumour growth extends beyond the prostatic capsule (Catalona et al. 1990). The surgeon’s first priority will be the removal of cancerous tissue and secondarily to preserve as much as possible of the patient’s ability to maintain urinary control and to retain erection. Complications of the procedure include urinary incontinence, urethral stricture and impotence besides the risk of morbidity related to the surgery.

After surgery, about 10-20% of patients will suffer from urinary leakage (stress incontinence), 40-80% from erectile disturbance and 5-10% from urethral stricture (Fowler et al. 1993). Nerve-sparing procedures and skilled surgeons report lower frequencies of complications (Catalona et al. 1998).
1.7.2 Radiotherapy

RT is an established method in the cure of prostate cancer since the 1950ies (Bagshaw 1985). Treatment options are still evolving and today include external beam radiotherapy (EBRT), brachytherapy (BT) or a combination of both.

EBRT is delivered with 3-dimensional conformal technique (3D-CRT) using conventional doses or dose-escalation. Intensity modulated radiotherapy (IMRT) may permit higher doses and better dose distribution.

BT is given using low dose rate (LDR) or high dose rate (HDR) technique. LDR BT uses permanent radioactive implants of iodine-125 or palladium-103, while HDR BT employs temporary iridium-192 implants.

RT is also important in the palliative setting, offering pain relief from bone metastasis and reduction of local symptoms (McQuay et al. 1997), and in the cure of residual tumour after surgery (Bolla et al. 2005).

1.7.3 Deferred treatment

Due to the generally rather indolent course of the disease and high mortality due to intercurrent disease, deferred treatment or watchful waiting would be an appropriate option for patients with an expected survival of less than 10 years, with substantial co-morbidity or having low-grade (G1-2) or early-stage tumours (Adolfsson et al. 1997; Albertsen et al. 1995; Chodak et al. 1994; Johansson et al. 1997).

However, in younger patients active treatment should be preferred, since local tumour progression and aggressive metastatic disease may develop in the long-term, notably among patients with an estimated life expectancy exceeding 15 years (Johansson et al. 2004).

Randomized data from the SPCG-4 study (Bill-Axelson et al. 2005), comparing prostatectomy and watchful waiting in patients with low grade tumours, showed that active treatment significantly reduced disease-specific mortality, overall mortality, and the risks of metastasis and local progression. However, the absolute reduction in the risk of death after 10 years was small. Active treatment entailed higher risks of side effects, but did not have any substantial effect on long-term wellbeing and subjective quality of life (Steineck et al. 2002).

Deferred treatment is not to be considered a passive process. Careful monitoring of symptoms should be carried out by the physician and hormonal therapy should be initiated on symptom progression. Methods for monitoring have been proposed (Klotz 2005).

1.7.4 Endocrine treatment (Hormone therapy)

Huggins and Hodges already in 1941 showed that castration therapy induced tumour regression in metastatic prostate cancer (Huggins et al. 1941). 70-80% of prostate tumours are dependent on androgens in order to proliferate, but this dependence is related to tumour differentiation. Primary androgen sensitivity is normally limited to about 12-24 months, after which a hormone-refractory disease develops (Schroder 1993).

Side effects from endocrine treatment are common, and include loss of libido, impotence, weight gain, sweating, hot flushes and psychological reactions. In the long run, osteoporosis, anemia and loss of muscular tissue are seen. Recently it has been
shown that hormone therapy can alter energy metabolism and increase the risk of developing diabetes or cardiovascular morbidity (Keating et al. 2006).

The timing of hormone therapy in patients without symptoms is controversial. In a recent Cochrane database systematic review, it is concluded that early androgen suppression reduces disease progression and complications due to progression. It may provide a small but statistically significant improvement in overall survival at 10 years (Nair et al. 2002).

The concept of intermittent androgen deprivation, aiming at increasing the hormonal sensitivity and reducing side effects, evolved in the mid 90ies. The implications for this treatment are currently being investigated (Wright et al. 2006).

Hormone therapy can be used for curative purposes as a neoadjuvant treatment, but is usually used in the palliative treatment of prostate cancer. It can be given as surgical orchiectomy or as medical therapy using LHRH agonists, estrogens or antiandrogens:

1.7.4.1 Orchiectomy

Orchiectomy, or testicular ablation, is a cheap and relatively easily performed surgical procedure, which ensures immediate castration levels of testosterone. Though not reversible, this method should be preferred when acute therapy effects are desired, such as in case of imminent spinal compression in previously non-treated patients.

1.7.4.2 LHRH agonists

These long acting drugs are given as subcutaneous injections every 4-12 weeks. They affect and desensitize the normal gonadotropin release of the pituitary gland, resulting in lowered levels of LH and castrate levels of testosterone in 2-4 weeks. However, initially a rise in the testosterone level is seen, why initial combination with antiandrogens is recommended. The effects of LHRH agonist treatment are reversible but are otherwise similar to orchiectomy.

1.7.4.3 Antiandrogens

Antiandrogens are drugs that act as blockers of the androgen receptor. They can be steroidal or non-steroidal. They result in inhibition of normal growth signals of the prostate cancer cells, while blood levels of testosterone remain unchanged or slightly increased. Known side effects include diarrhoea and liver toxicity. Sexual potency and libido are normally preserved, but there is a risk of gynecomastia with monotherapy. The effects of antiandrogen therapy seem similar to castration in patients without metastatic disease (Iversen et al. 1998), but are inferior in terms of survival in patients with metastasis (Tyrrell et al. 1998).

Due to a probable mutation in the androgen receptor, positive effects on PSA levels when withdrawing antiandrogen therapy due to progressive disease (androgen withdrawal response) can be seen in 30-60% of cases (Scher et al. 1993).

1.7.4.4 Estrogens

Estrogen therapy acts as an inhibitor of LH through a negative feed-back mechanism, resulting in castrate levels of testosterone. Though the risk of sweating and hot flushes is small, this treatment is since long associated with an increased risk of gynecomastia.
and cardiovascular morbidity. However, parenteral administration seems to reduce the risk of cardiovascular effects (Henriksson et al. 1991).

In a Scandinavian randomized study (SPCG-5), parental estrogen therapy and TAB was compared. Disease-specific as well as overall survival was almost identical, however, a slightly increased risk of cardiovascular mortality was seen in patients receiving estrogen therapy (Hedlund et al. 2000).

1.7.4.5 Total androgen blockade (TAB)

Total or maximal androgen blockade is a combination of surgical or medical castration and antiandrogen therapy. The rationale is to reduce the effects of all circulating androgens, including those produced in the adrenals. Many studies have compared the effects of regular castration therapy and TAB, and there was evidence for an increase in the time to progression and death using TAB, especially in men with limited metastatic burden (Crawford et al. 1989).

In a meta-analysis from 2000, a non-significant difference of 2-3% in overall survival was shown in favour of TAB (Prostate Cancer Trialists' Collaborative Group 2000). The current opinion is that there is no clinically important difference between TAB and regular castration therapy used in the palliative setting.

TAB is also used as a neoadjuvant treatment, in order to shrink the tumour before active therapy. Studies on TAB and RP have shown a lower prevalence of positive surgical margins, but no difference in the number of PSA recurrences or survival rates could be established. Neoadjuvant TAB before RP is therefore not practised in Sweden.

However, during the last decade increased attention has been brought to TAB in combination with RT of curative intent. One rationale for treatment would be a decrease in prostate volume, thus reducing the size of treatment fields. A second rationale would be to obtain increased lethal effect of the ionizing radiation on tumour cells, a phenomenon observed in experimental systems (Zietman et al. 1997).

The efficacy of ADT before and during RT has been investigated in randomized studies, where in a RTOG (Radiation Therapy Oncology Group) study significantly higher local progression rates were noted in the group not receiving TAB, but no difference in overall survival (Pilepich et al. 1995). D’Amico et al (D’Amico et al. 2004) found a significantly higher survival, lower prostate cancer-specific mortality and higher survival free of salvage therapy in favour of a 6 month course of TAB. Most studies included patients receiving a conventional dose of about 70 Gy. Criticism of the use of TAB with more dose-intense RT techniques has been put forward (Galalae et al. 2004; Martinez et al. 2005)
2 RADIOTHERAPY FOR PROSTATE CANCER

Since the early twentieth century, RT has been used in the treatment of prostate cancer, from early experiments with radium needles to the sophisticated computer-assisted high voltage accelerators of the 21st century. Today, a variety of treatment techniques can be offered to the patient. Improved positioning and planning has made possible the use of higher doses without increasing side effects, resulting in high cure rates.

2.1 Doses and EBRT techniques

In the effort to cure prostate cancer the radiation dose to the prostate should exceed 70 Gy (Nilsson et al. 2004). The importance of dose escalation in RT of localized prostate cancer has been thoroughly discussed over the last years, since there are indications of a high percentage of residual tumours using doses below 70 Gy (Ljung et al. 1995) or of increasing PSA and disease progression after therapy (Stamey et al. 1993). The use of conformal techniques has made it possible to increase the dose far above 70 Gy (Hanks et al. 1998), without increasing the rate of side effects from the rectum or bladder. Furthermore, interstitial brachytherapy provides the option of decreasing the dose to the rectum while delivering an even higher NTD (normalized total dose) to the prostate. The various techniques available are presented below:

2.1.1 External beam radiotherapy (EBRT)

2.1.1.1 Conventional EBRT

Before the advent of modern 3D-CRT techniques, conventional EBRT for prostate cancer was generally used. Doses used were in the range of 60-68 Gy. Treatment volume encompassed the prostate gland and a margin of surrounding tissues with or without the seminal vesicles. To ensure coverage of the target volume and to compensate for glandular mobility and day-to-day variations in positioning, rectangular field dimensions in the order of 8-12 cm were normally used, encompassing an unnecessarily large volume of normal tissues such as larger or lesser portions of rectum and urinary bladder neck. The tolerance of the normal tissues limits the total dose that can be delivered with conventional EBRT and, thus, also the likelihood of eradicating the malignancy.

Nevertheless, long-term local control has been achieved over the years with conventional EBRT in patients with low risk tumours. The local control has been good for patients with stage T1 cancers, but has been less secure with increasing T-stage. Typical conventional EBRT fields are presented in Figure 4.

2.1.1.2 3D-CRT

The development of reliable methods for reducing the volume of irradiated normal tissue has been the key focus over the past decade. 3D dose planning systems and treatment accelerators equipped with multi-leaf collimators have made 3D-CRT possible (Lennernas et al. 1995). The volume of normal tissue included in the high-dose region in the treatment of prostate cancer is reduced by 40-50 % with 3D-CRT compared with conventional EBRT. The feasibility of 3D-CRT has been studied, showing a marked reduction of GI toxicity in comparison with conventional EBRT.
(Dearmaley et al. 1999; Koper et al. 1999). These results have provided further support for the dose-escalation programmes that are currently being pursued with EBRT. 3D-CRT is today a standard technique at the vast majority of treatment centres. Typical 3D-CRT fields are presented in Figure 4.

Figure 4. Different RT treatment techniques. Adapted from Atlas of the prostate, Edited by Peter T. Scardino, Kevin M. Slawin. ©2006 Current Medicine LLC
2.1.2 Dose-escalated EBRT

Dose escalation can be carried using conventional 3D-CRT technique, but a steep increase in GI/GU toxicity after approximately 76 Gy has been reported (Hanks et al. 1998; Zelefsky et al. 1999). Therefore, IMRT techniques (see below) or techniques optimizing positioning of the prostate using catheters or gold markers (Bergstrom et al. 1998; Shimizu et al. 2000), have been developed, permitting smaller fields to be used. In summary, higher cure rates are seen with increasing doses and patients with poor risk features seem to benefit most from dose escalation (Nilsson et al. 2004). A dose-escalation trial using optimized catheter positioning and hypofractionation (6.1 Gy x 7) is currently ongoing in Sweden (Widmark et al: A phase III study of HYPO-fractionated dose-escalated radiotherapy (HYPO-RT) of intermediate risk prostate cancer, study protocol).

2.1.3 IMRT

With this technique, the beam is divided into a multitude of little beamlets of varying intensity, adapted to deliver required doses to target volumes while sparing normal structures even within the target volume. Theoretically, this results in further optimization and minimization of treatment volumes. The obvious obstacle is that the technique raises extremely high demands on patient and organ positioning during therapy to avoid geographic misses for the tumour and hits for more vulnerable normal tissues. A typical IMRT dose distribution is presented in Figure 4.

The evolving experience of IMRT has resulted in several reports. Acceptable toxicity and high cure rates are noted. Cause specific 8-year survival outcomes for favourable, intermediate and unfavourable risk cases after 81 Gy are reported to be 100%, 96% and 84%, respectively (Zelefsky et al. 2006). Results from hypofractionated RT using IMRT technique have been reported (Kupelian et al. 2005; Pollack et al. 2006).

2.2 Brachytherapy

Brachytherapy, meaning short-range RT or placement of radioactive sources in close proximity to the tumour, has been in use worldwide since shortly after the introduction of radioactive materials. It takes advantage of the simplest physical properties of radiation, where the highest doses of radiation are present in the vicinity of the radioactive source and where the radiation describes a rapid drop in dose with increasing distance from the source. Intra-cavitary or surface applications are used in some human tumour types, such as gynaecological, skin, and bronchial tumours, while interstitial insertions are useful for head and neck and prostate treatments.

2.2.1 Permanent brachytherapy (seeds)

The use of seed implantation with radioactive sources into the prostate was introduced already in the 1950s. Today, the two most commonly used radionuclides for permanent BT are Iodine-125 (I-125) and Palladium-103 (Pd-103). Both radionuclides have a very low energy and are not very penetrating, resulting in delivery of low dose rate (LDR) irradiation, and are normally used for treatment on an out-patient basis.
Treatment with I-125 and Pd-103 has most commonly been performed as monotherapy. However, BT may be also combined with EBRT and/or ADT. The choice of radionuclide has been the subject of debate for many years. The predicted radiation dose delivered with I-125 and Pd-103 in more recent treatment series has been in the range of 160 Gy and 120 Gy, respectively. These doses correspond largely to a dose of 70-72 Gy using EBRT with conventional dose fractionation (Beyer 2001).

Results from early techniques, advocating implantation during open laparotomy, were disappointing. This has mainly been due to lack of TRUS technology for guided implantation and/or the lack of dedicated dose planning systems. The main technical difference from modern BT series, which commonly use 3D BT dose planning systems, is that the seed implantations were performed rather empirically with approximate estimations of the number of seeds needed for the prostate gland and without precise information on the actual dose delivered to the tumour areas and to the risk organs.

Long-term (>5 years) treatment outcome with TRUS-guided permanent seed implantation BT seems to be indistinguishable to that from RP and, 3D-CRT in patients with favourable risk. However, most reports indicate that this treatment is less effective than the combination of HDR BT with EBRT and the 3D-CRT technique with doses ≥ 74 Gy in patients with unfavourable risk. The role of combination therapy with EBRT and neoadjuvant hormone therapy in this category of patients remains to be determined. Outcome data indicates no major differences in efficacy between I-125 and Pd-103 permanent seed implantation BT (Nilsson et al. 2004).

Figure 5. HDR Brachytherapy needles in position for therapy. Photograph by dr Kälkner, Radiumhemmet.

2.2.2 High dose rate brachytherapy (HDR BT)

Combined treatment with EBRT and temporary HDR BT boost to the prostate has attracted increased attention over the past years. TRUS is used for target definition and to guide the insertion of the implant needles under direct control of their positions. Afterloading systems make it possible to use high dose rate techniques and protect the working staff from irradiation. The isotope Iridium-192 (Ir-192) has a greater range than radionuclides such as I-125 and Pd-103 and is therefore more suitable for treating
patients with bulky tumours. The physical characteristics of Ir-192 also allow hypofractionated treatment to be given whilst protecting the rectum with a rapid dose fall-off. Depending on the $\alpha/\beta$ ratio assumed, a minimum dose of approximately 100 Gy is obtained within the prostate when this combination regimen is used, a dose well above levels so far reached in dose escalation protocols with 3D-CRT techniques using EBRT only or with BT using permanent I-125 or Pd-103 seed implantation.

This afterloading treatment technique was developed in Kiel in the 1980ies (Bertermann 1986), modified and first introduced in Sweden at Sahlgrenska University Hospital, Gothenburg, in 1988 (Borghede et al. 1997; Borghede et al. 1997). The technique has been in use at the Department of Oncology, Karolinska University Hospital, since 1998. This treatment experience currently includes more than 1500 patients.

Long-term clinical outcome and toxicity according to RTOG for various combined regimens have been presented in several studies (Astrom et al. 2005; Deger et al. 2002; Galalae et al. 2002; Galalae et al. 2004; Hiratsuka et al. 2004; Martin et al. 2004; Martinez et al. 2003; Mate et al. 1998; Pellizzon et al. 2003; Stevens et al. 2003), reporting 5-year bNED (biochemical non-evidence of disease) survival in the range of 67-93%. Toxicity is considered acceptable. A summary of the results is presented in Table 2.

Studies on HDR BT boost and HRQoL are few (Egawa et al. 2001; Galalae et al. 2004; Jo et al. 2005; Joly et al. 1998; Vordermark et al. 2006).

2.3 Radiotherapy-induced side effects

The anatomical localization of the prostate, in proximity to mucosal tissue of the urinary bladder, urethra and rectum, as well as the mobility of the gland, requiring the use of often extensive treatment field margins, predisposes to the development of radiation induced side effects. These effects are related to reactions to the ionizing radiation of normal tissue. Side effects are defined either as acute or late.

**Acute side effects** of pelvic RT occur during treatment and usually resolve within 2-3 months following completion of therapy. They are attributed to the effects of radiation on rapidly dividing cells, mostly mucosal, and include radiation induced cystitis and proctitis causing increased urinary frequency, dysuria and diarrhoea.

**Late side effects** of pelvic RT are not generally manifested until several months, mostly more than six months, after therapy and are more mediated by damage to the vasculo-connective tissue, resulting in hypovascularity, decreased perfusion and fibrosis. This results in rectal bleeding, chronic cystitis/urethritis and erectile dysfunction (ED), which can lead to chronic and debilitating morbidity. In the literature, mostly late effects have been studied by means of the RTOG scoring system.

2.3.1 Urinary symptoms

EBRT have since long been associated with urinary morbidity, including cystitis, urethritis and fibrosis of the bladder. Shipley (Shipley et al. 1994), reported in a retrospective analysis late urinary morbidity in 5.4% of patients, persisting in 1.2%. Acute morbidity was mostly mild.
Differences between conventional EBRT and 3D-CRT have been shown to be less pronounced for GU morbidity as compared to GI morbidity (Koper et al. 1999). Few patients require pads for urinary incontinence after 3D-CRT (Nguyen et al. 1998). Dose-escalation using 3D-CRT have shown that late bladder toxicity increases if the volume of the bladder receiving >65 Gy exceeds 30% (Michalski et al. 2000). An increase in GU toxicity has also been reported after androgen deprivation (Schultheiss et al. 1997). Previous trans-urethral resection (TUR-P) does not seem to influence late GU morbidity (Sandhu et al. 2000).

**Table 2.** Summary of earlier published studies combining EBRT and HDR BT boost and reporting long-term clinical outcome.

<table>
<thead>
<tr>
<th>Centres</th>
<th>Number of patients</th>
<th>3D EBRT Dose (Gy)</th>
<th>HDR dose NTD $\alpha/\beta=3$ (Gy)</th>
<th>Median Follow-up (months)</th>
<th>Outcome 5 years</th>
<th>RTOG Uro Grade 3</th>
<th>RTOG GI Grade 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Royal Oak US (Martinez et al. 2003)</td>
<td>207</td>
<td>46</td>
<td>5.5-11.5 Gy x 3</td>
<td>74-146</td>
<td>56</td>
<td>74%</td>
<td>8%</td>
</tr>
<tr>
<td>Seattle US (Mate et al. 1998)</td>
<td>104</td>
<td>50</td>
<td>3-4 Gy x 4</td>
<td>64-72</td>
<td>45</td>
<td>86%</td>
<td>10%</td>
</tr>
<tr>
<td>Kiel Germany (Galalae et al. 2004)</td>
<td>189</td>
<td>40</td>
<td>15 Gy x 2</td>
<td>148</td>
<td>78</td>
<td>78%</td>
<td>-</td>
</tr>
<tr>
<td>Together (Galalae et al. 2004)</td>
<td>611</td>
<td></td>
<td></td>
<td></td>
<td>60</td>
<td>67%</td>
<td>-</td>
</tr>
<tr>
<td>Sao Paulo Brasil (Pellizzon et al. 2003)</td>
<td>119</td>
<td>45</td>
<td>4-5 Gy x 4</td>
<td>66-76</td>
<td>41</td>
<td>75%</td>
<td>0%</td>
</tr>
<tr>
<td>Kurashiki Japan (Hiratsuka et al. 2004)</td>
<td>71</td>
<td>42-45</td>
<td>5.5 Gy x 3-4</td>
<td>70-81</td>
<td>44</td>
<td>93%</td>
<td>6%</td>
</tr>
<tr>
<td>Sydney Australia (Stevens et al. 2003)</td>
<td>82</td>
<td>45</td>
<td>5.5 Gy x 3</td>
<td>72</td>
<td>36</td>
<td>92%</td>
<td>6%</td>
</tr>
<tr>
<td>Berlin Germany (Deger et al. 2002)</td>
<td>230</td>
<td>40-50</td>
<td>9-10 Gy x 2</td>
<td>83-102</td>
<td>40</td>
<td>82%</td>
<td>10%</td>
</tr>
<tr>
<td>Offenbach am Main Germany (Martin et al. 2004)</td>
<td>102</td>
<td>40-45</td>
<td>5-7 Gy x 4</td>
<td>72-100</td>
<td>31</td>
<td>82%</td>
<td>5%</td>
</tr>
<tr>
<td>Gothenburg Sweden (Astrom et al. 2005)</td>
<td>214</td>
<td>50</td>
<td>10 Gy x 2</td>
<td>102</td>
<td>48</td>
<td>82%</td>
<td>10%</td>
</tr>
</tbody>
</table>
Borghede et al concluded that the risk of posttreatment complications was strongly correlated to pretreatment presence of symptoms from the organs at risk and that posttreatment complications arising more than 3 years after RT were rare (Borghede et al. 1997).

Late urinary morbidity after conventional EBRT was investigated by means of self-assessment questionnaires (Fransson et al. 1999; Widmark et al. 1994) and compared to an age-matched control population. Urgency, starting problems and leakage was reported by 32-42% of patients, less commonly by the controls. Late side effects remained unchanged 4-8 years after treatment. In a prospective evaluation of a dose-escalated RT technique using identical questionnaires, the same authors found decreasing urgency and starting problems after 3-5 years compared to baseline (Fransson et al. 2002; Fransson et al. 2006).

Urinary morbidity after permanent brachytherapy is not negligible, and sometimes persisting (Miller et al. 2005; Wei et al. 2002). After combined EBRT and HDR BT boost, late GU morbidity corresponding to RTOG grade 3 has been reported to be in the range of 0-10% (Table 2). Few RTOG grade 4 side effects have been reported.

2.3.2 Bowel symptoms

Bowel problems after RT include acute irritative problems, such as diarrhoea and increased stool frequency, and late chronic problems such as increased mucus excretion, fecal leakage and proctitis.

Proctitis or rectal bleeding is probably one of the most studied late side effects after RT for prostate cancer, constituting a treatment specific toxicity (Fowler et al. 1996). The frequency of bleeding has been reported to be 5-20% in various series, with less than 5 % severe or persisting problems (Shipley et al. 1994).

The use of 3D-CRT as compared to conventional shielding, markedly reduces the incidence of radiation-induced proctitis and bleeding after conventional doses (Dearnaley et al. 1999; Koper et al. 1999). However, increasing the dose above certain thresholds (76-78 Gy) results in higher incidence of rectal bleeding (Boersma et al. 1998; Zelefsky et al. 1999). A correlation between the percentage of rectum irradiated to more than 70 Gy and the likelihood of developing late rectal complications has also been shown (Nguyen et al. 1998). Sandler and co-workers (Sandler et al. 1995) reported the risk for developing chronic rectal morbidity to be low (3 % at 3 and 5 years). Similar data has been reported from additional studies (Borghede et al. 1997; Fransson et al. 2002; Schultheiss et al. 1997; Widmark et al. 1994), but unexpectedly GI and GU morbidity was found to be more frequent in patients treated with hormone manipulation prior to RT (Schultheiss et al. 1997).

Anorectal symptoms following RT are common (Yeoh et al. 2000). It has been proposed that the dose to the anal sphincter accounts for this side effect (al-Abany et al. 2004), but several factors including the reservoir capacity of the rectum could be responsible for fecal leakage (Berndtsson et al. 2002). Mucus and fecal leakage has been evaluated for conventional EBRT in two studies from Sweden. Widmark et al (Widmark et al. 1994) found 2-4 years after treatment that 38 % of treated patients complained of mucus in the stools, 27 % of fecal leakage. 90 % of the problems were minor. Al-Abany (al-Abany et al. 2002; al-Abany et al. 2004) concluded that among bowel symptoms, the strongest association with GI distress was found for fecal leakage.
After combined EBRT and HDR BT boost, GI morbidity corresponding to RTOG grade 2-4 has been reported to be in the range of 2-11% (Borghede et al. 1997; Dinges et al. 1998; Martin et al. 2000; Mate et al. 1998). GI toxicity after permanent brachytherapy with seeds has been found to be mild (Gelblum et al. 2000).

2.3.3 Sexual symptoms

Evaluating sexual symptom outcome in prostate cancer RT is difficult, since sexual problems are multifactorial in origin. Age, the prostate tumour itself, co-morbidity, endocrine treatment, and the RT all contribute to these common problems in the elderly male population. Radiation-induced damage to nerves and blood vessels are thought to be responsible for the effects attributed to RT, but doses to the penile bulb may also have an impact on sexual problems (Fisch et al. 2001; Merrick et al. 2002). Assessment of sexual problems normally includes erectile dysfunction (ED), sometimes together with sexual desire, satisfaction and ejaculatory disturbance.

In a review of ED after prostate cancer RT, Incrocci et al (Incrocci et al. 2002) concluded that the majority of studies lacked a clear definition of sexual potency; the analyses were retrospective and lacked co-morbidity information. Furthermore, there was commonly no information on the percentage of patients potent before treatment and often non-validated instruments were used. However, the review indicated higher ED rates for combined therapy (25-89%) than for EBRT (7-72%) or permanent BT (2-51%) alone. The better scores for BT monotherapy could be explained by less damage to the neurovascular bundles. The chance for preserving erectile function seemed better if the patient was younger and had a good erectile function before treatment.

The probability of maintaining erectile function after RT is reported to be higher than after surgery, 0.69 versus 0.42 (Robinson et al. 1997). Similar conclusions have been reached in previous studies (Fowler et al. 1996; Potosky et al. 2000; Shrader-Bogen et al. 1997), though no randomized data is available. However, erectile function clearly declines as late as 12-24 months after RT (Beard et al. 1997; Turner et al. 1999), why such comparisons could be misleading.

Fransson et al (Fransson et al. 1996), evaluating RT combined with castration, concluded that hormone therapy tends to increase sexual problems, especially in men < 70 years of age. In men > 74 years, decreased sexual function was not perceived as such a significant problem. ED rates remained unchanged between 4 and 8 years after RT (Fransson et al. 1999).

Neoadjuvant androgen deprivation does not seem to convincingly impact the risk of sexual dysfunction 1 year after completion of 3D-CRT (Chen et al. 2001). Helgason et al (Helgason et al. 1995) found that sexual desire diminishes among 77% of treated patients after conventional EBRT. Of those men retaining orgasm after treatment, 47% reported a decreased orgasmic pleasure.
2.4 Radiobiological considerations

While there has been considerable interest in optimizing the treatment dose through dose escalation studies, rather less attention has been paid to optimizing the fractionation pattern for EBRT or the dose rate for BT.

According to the linear quadratic model (LQ-model), $\alpha/\beta$ is the ratio of the radiosensitivity and the repair capacity of tumour cells, and varies with different tumour types. When the normal cell cycle is long such as for most prostate cancers, there is more time for repair (and mis-repair), making the $\alpha/\beta$ ratio smaller. Most tumours have an $\alpha/\beta$ ratio of 10 for acute effects, for prostate cancer the ratio has been considered to be 3. There is now indications for a ratio of as low as 1.5 (Brenner et al. 1999).

Normally, 2 Gy fractions are used for curative purposes. But changing the fractionation can actually improve effects. The biologically effective dose (BED) formula depends on $n$ fractions of $d$ grays each modified by a factor $1+ d/ \alpha/\beta$, the relative effect:

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

This allows for alterations of dose-per-fraction or dose rate without changing the effective dose. With low $\alpha/\beta$ ratios, high fractions or high dose rate therapy will be more effective, provided that the $\alpha/\beta$ ratio is less than for the late complications (<3 Gy). Another advantage would be a reduction in acute tissue reactions. This would support the use of hypofractionation and HDR BT for prostate cancer treatment and not favour low dose rate therapy, such as permanent BT. However, if there are concurrent, more rapidly proliferating clones, high fraction treatment would be less beneficial.

Applying the BED formula on the combined EBRT/HDR BT concept, where 10 Gy fractions of high dose rate radiation are used, the NTD of the total treatment translated into 2 Gy fractions would be 102 Gy for $\alpha/\beta = 3$ and 116 Gy for $\alpha/\beta = 1.5$. The rectal dose, where it is possible to reduce the dose contribution from HDR brachytherapy to 60% of the prescribed dose in the prostate, will likewise be equal to 72 Gy in 2 Gy per fractions for $\alpha/\beta = 3$.

This by far exceeds tumour doses used in dose escalation programmes while keeping rectal dose to a minimum.
3 HEALTH RELATED QUALITY OF LIFE

3.1 Definitions

The concept “Quality of life” has currently no generally accepted definition. The WHO definition of health as “a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity” in 1946 (WHO 1946), generated a broader concept of health that included not only physical and mental dimensions but also social dimensions. “Quality of life” is considered to be a broader concept than the health concept. It is multidimensional, covering a variety of aspects, such as functional, physical, emotional and social well-being. It is also subjective, as it can only be understood from the patient’s own point of view (Cella 1994; WHOQOL Group 1995).

The WHO definition of quality of life, competing with that of others and provided by their quality of life group (WHOQOL), encompasses “individuals’ perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns” (WHOQOL Group 1995).

Health related quality of life (HRQoL) has been distinguished from quality of life in its wider concept, as more specifically referring to quality of life in relation to disease and treatment. It is an appropriate term for clinical research and practice, as it focuses on aspects of life that are affected by health care interventions (Velikova et al. 1999). HRQoL is typically divided into general or generic HRQoL, addressing aspects of overall well-being, and disease-specific HRQoL focusing on the impact of particular organic dysfunctions that affect HRQoL (Patrick et al. 1989). In this thesis, the term HRQoL is used when describing quality of life.

3.2 Methodology

3.2.1 Measurement of HRQoL

Quantitative methods are generally used for clinical research purposes, being detailed, simple to perform and cost-effective. Therefore, in HRQoL research, data is preferably collected with HRQoL questionnaires or instruments, containing items organized into scales. Each scale measures an aspect of HRQoL. Some scales include several items, whereas others may include only one or two. Instruments are best when they use self-assessment, due to the subjectivity of HRQoL. The patient is thus the person best suited to assess his/her HRQoL and should preferably be the one completing the questionnaire (Aaronson 1989; Cella 1994; Velikova et al. 1999). In case of cognitive impairment, communication deficits or severe distress, information given by proxies could be valuable (Addington-Hall et al. 2001). It should be kept in mind, however, that such estimates of a patient’s HRQoL might differ from the patient’s own evaluation.

Structured interviews utilizing fixed response options can also be used, enabling the researcher to reduce misunderstanding and the amount of missing responses to individual items. However, they are time-consuming and in the absence of very professional interviewers they have the disadvantage of making the patients adapt to the perspective of a researcher or clinician (Litwin et al. 1998). Therefore, interviews are preferably used in instrument development, in order to obtain areas relevant for the patients in focus.
HRQoL instrument must adhere to certain requirements, such as reliability, validity, responsiveness, interpretability, practicality and applicability.

3.2.1.1 Reliability

This term refers to how reproducible an instrument or scale is. Test-retest reliability is a measure of response stability over time. It is assessed by administering scales to subjects at two time points, with the time interval short enough to preclude the possibility that the domains being assessed will have been affected by the disease or its treatment during the intervening period.

Internal consistency reliability measures the similarity of an individual's responses across several items, indicating the homogeneity of a scale. The statistic used to quantify the internal consistency or unidimensionality of a scale is called Cronbach's coefficient alpha. According to generally accepted standards, reliability statistics measured by these two methods should exceed 0.7 for group comparisons (Nunnally 1978). When used at the level of individual patients, a reliability coefficient of at least 0.9 is preferred. Multi-item measures are considered more reliable, due to the fact that they are composed of several items allowing for more variation.

3.2.1.2 Validity

Validity refers to how well the scale or instrument measures the attribute it is intended to measure. Content validity, sometimes referred to as “face validity”, involves qualitative assessments of the scope, completeness, and relevance of a proposed scale. Criterion validity is a more quantitative approach to assessing the performance of scales and instruments. It requires the correlation of a scale's score with results from established tests. Generally accepted standards also dictate that validity statistics should exceed 0.7. Construct validity, perhaps the most valuable assessment of a survey instrument, is a measure of how meaningful the scale or survey instrument performs in a multitude of settings and populations over a number of years.

3.2.1.3 Responsiveness

Responsiveness of a HRQoL instrument refers to how sensitive the scales are to changes over time. A questionnaire may be reliable and valid when used at a single point in time, but in some circumstances it must also be able to detect meaningful changes in quality of life in longitudinal studies, where HRQoL changes over time (Fayers et al. 2005). Different domains may become more or less prominent over time as the course of disease and recovery evolves. In addition, patients may experience a “response shift” as they learn to adapt to the effects of disease and treatment (Schwartz et al. 1999; Sprangers 1996).

3.2.1.4 Interpretability

Interpretability refers to the presence of meaningful reference groups, such as HRQoL data derived from patient populations or samples from the normal population, so called normative values. In longitudinal studies, patients may serve as their own controls. Of particular importance for the evaluation of HRQoL as an effect measure, is the interpretation of clinically relevant differences (King 1996; Osoba et al. 1998).
3.2.1.5 **Practicality**

This term refers to how to ensure data quality by minimizing bias. The feasibility of the questionnaire is important. It should be short and easily completed. As a guideline, a maximum of 15 minutes is acceptable (Cull 1997). The administration procedures should be standardized and clearly described in the study protocol.

3.2.1.6 **Applicability**

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 must have been tested in the appropriate cultural setting.

3.2.2 **Instruments**

Several well constructed and psychometrically valid HRQoL questionnaires have been developed. Examples of generic HRQoL instruments that measure the broadest aspects of HRQoL, irrespective of illness or the condition of the patient, include the Short form-36 (SF-36) (Ware et al. 1992) and the Nottingham health profile (NHP) (McDowell et al. 1978). Generic cancer-specific HRQoL instruments, developed in international collaboration, include the European Organization for Research and Treatment of Cancer quality of life questionnaire core-30 (EORTC QLQ-C30) (Aaronson et al. 1993) and the Functional Assessment of Cancer Therapy - General (FACT-G) (Cella et al. 1993).

For evaluation of disease-specific HRQoL in prostate cancer, the Los Angeles Prostate Cancer Index (PCI) (Litwin et al. 1998) or the prostate FACT (FACT-P) (Esper et al. 1997) are commonly used in the USA. The EORTC quality of life questionnaire prostate-25 (QLQ-PR25), developed by the EORTC Quality of Life Group (Borghede et al. 1996), is a prostate-specific questionnaire, currently being tested for psychometric properties in an international collaboration (Aaronson et al. 2002). The PCSS (Prostate Cancer Symptom Scale, earlier named QUFW94) (Fransson et al. 2001), the Radiumhemmets Scale of Sexual Function (Helgason et al. 1995) and the questionnaire used in the SPCG-4 study (Steineck et al. 2002) are disease-specific questionnaires developed in Sweden for use among prostate cancer patients.

3.2.3 **Study design**

In the effort to study HRQoL, the choice of study design is crucial. It includes how data is collected and how to compare the results. Randomized studies are superior by their ability to avoid confounding, however most HRQoL studies are still made non-randomized.

Prospective, longitudinal data collection is always best, because this approach may reveal time-dependent evolution of HRQoL, and patients can be used as their own controls through baseline assessment.

Cross-sectional methodology can also be used, assessing HRQoL once during an interval of time. In cross-sectional surveys, however, patients cannot serve as their own temporal controls, since it is well established that patients’ recall of pretreatment HRQoL is inaccurate, so called recall bias (Herrmann 1995). Hence, studies must rely
on appropriate control groups that have to be well defined, in order to permit interpretation in a valid context.

3.2.4 Analysis and interpretation

Quality of life data from questionnaires are often in the form of ordinal category variables and can be handled in different ways. Converted to numbers, they can be used summated in multi-item scales or as single-item measures, both descriptively and in longitudinal analysis. For event-driven longitudinal designs, multiple univariate analyses are used in a repeated measures design such as multiple t-tests, ANOVA or Wilcoxon rank sum tests. Both non-parametric and parametric approaches can be used.

Possible drawbacks include the Type I error and bias due to missing data. Missing data is a concern because of the potentially biased estimates of HRQoL when the reasons for missing data are related to factors that affect the patient’s HRQoL. Several imputation methods exist, and all studies must include a statement of how missing data was handled.

A well designed study, using a validated instrument and well defined comparison groups, facilitates interpretation and generalization of HRQoL results. The ongoing discussion of meaningful differences (King 1996; Neymark et al. 1998; Osoba et al. 1998) must be taken into consideration as well as problems related to multiple comparisons and cautious interpretation of statistically significant differences. The implication of a positive finding can also differ depending on the perspective of the interpreter. Finally there is a possibility of adaptation or “response shift” over time (Schwartz et al. 1999; Sprangers et al. 1993; Sprangers 1996).

3.3 Relevance in prostate cancer patients

3.3.1 General comments

Because of the long natural history of prostate cancer and the fact that an increasing number of men will be long-term survivors after treatment, there is a need for information about treatment-related HRQoL. Prostate cancer progresses slowly and usually occurs in older men during a time in their lives when other potentially lethal illnesses are increasingly likely to arise. The disease is in many cases successfully treated using a variety of equally efficient therapies with different risks of possibly permanent complications affecting HRQoL.

During the last 15 years the literature on quality of life in men treated for early and late-stage prostate cancer has expanded rapidly. Despite the absence of randomized controlled trials for curative treatment and the fact that the assessment of HRQoL is many times hampered by poor methodology (Efficace et al. 2003), a variety of well-conducted studies have revealed several important lessons.

3.3.2 Previous HRQoL studies and findings

No qualitative randomized studies have yet been performed for EBRT versus surgery and thus no detailed information is available regarding differences in HRQoL. However, well-designed non-randomized comparative studies have been reported (Fowler et al. 1996; Shradler-Bogen et al. 1997; Yarbro et al. 1998). The conclusion of the central findings reported, is that the domains of general quality of life, such as physical, emotional, and social functioning, do not differ substantially
across treatment groups. However, the domains of disease-specific quality of life, such as sexual, urinary, and bowel dysfunction, vary markedly across treatment groups. Generally, more urinary problems are reported in surgery groups, while more bowel problems are reported after RT. Over time, patients seem to accommodate at least partially to any dysfunction they may experience and differences in disease-specific HRQoL between groups undergoing surgery or RT diminish significantly over time.

Corresponding comparisons have been made between permanent brachytherapy, EBRT and surgery with similar conclusions (Bacon et al. 2001; Brandeis et al. 2000; Miller et al. 2005; Soderdahl et al. 2005; Wei et al. 2002). General HRQoL does not substantially differ and BT patients report less urinary and sexual problems than patients after surgery. Irritative urinary symptoms, however, can be persisting in patients treated with BT and negatively affect the HRQoL in the long run. Bowel problems after BT were generally mild and transient.

Published studies of HRQoL after combined therapy using EBRT and HDR BT boost are limited to 5 reports (Egawa et al. 2001; Galalae et al. 2004; Jo et al. 2005; Joly et al. 1998; Vordermark et al. 2006). Different combinations of EBRT and HDR BT are used as well as different BT techniques.

Galalae et al (Galalae et al. 2004), using a cross-sectional design, assessed long-term HRQoL (median 6.5 years) after treatment. General HRQoL was considered to be good, but detailed information regarding disease-specific HRQoL was lacking.

Joly et al (Joly et al. 1998) reported in a case-control study 4-8 years after treatment persisting urinary and sexual problems compared with the control group.

Egawa et al ((Egawa et al. 2001) performed a prospective survey including 6 points of assessment until 18 months after RT and reported substantial acute problems shortly after therapy, but marked recovery 12-18 months after treatment.

Using a comparative design, Jo et al (Jo et al. 2005) concluded that combined RT resulted in less urinary and sexual problems than nerve-sparing surgery more than 2 years after treatment.

Vordermark et al (Vordermark et al. 2006), comparing in a non-randomized fashion combined EBRT + HDR BT with dose-escalated 3D-CRT, found, despite completely different biologically effective doses, similar HRQoL profiles.

An overview of HRQoL studies after EBRT + HDR BT boost is given in Table 3.
Table 3. Overview of HRQoL studies after EBRT + HDR BT boost

<table>
<thead>
<tr>
<th>Author</th>
<th>Journal/ year</th>
<th>Study design</th>
<th>Purpose</th>
<th>Number of patients</th>
<th>RT technique</th>
<th>Instrument</th>
<th>Assessment point after therapy</th>
<th>Results</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Joly et al</td>
<td>Annals of Oncology 1998</td>
<td>Case-control</td>
<td>HRQoL late effects</td>
<td>71</td>
<td>2,4 Gy x 18 15 Gy EDR BT</td>
<td>NHP EORTC QLQ-C30 QLQ-PR25</td>
<td>4-8 years</td>
<td>No difference in general HRQoL. More urinary and sexual problems than in the control group</td>
<td>BT boost an alternative to EBRT</td>
</tr>
<tr>
<td>Egawa et al</td>
<td>Jpn J Clin Oncol 2001</td>
<td>Longitudinal</td>
<td>HRQoL treatment evaluation</td>
<td>58</td>
<td>3Gy x 10 4-5 Gy x 5 HDR BT during 3 days</td>
<td>SF-36 RTOG International prostate symptom score (IPSS)</td>
<td>Baseline 1,3,6,12,18 months</td>
<td>General HRQoL low and urinary problems increased after 1 month, restored after 12 months. Significant bowel problems after 12 months.</td>
<td>HRQoL worse after AD therapy and higher postRT PSA. No disease-specific HRQoL reported</td>
</tr>
<tr>
<td>Galalae et al</td>
<td>Strahlentherapie und Onkologie 2004</td>
<td>Cross-sectional + Multivariate and survival analysis</td>
<td>HRQoL late effects Survival analysis Instrument validation</td>
<td>189</td>
<td>2Gy x 20 15 Gy x 2 HDR BT during 2 weeks 45% ADT</td>
<td>EORTC QLQ-C30 PSM-G (German instrument)</td>
<td>Mean 6,5 years</td>
<td>78 % bNED</td>
<td>Well tolerated treatment with curative potential</td>
</tr>
<tr>
<td>Jo et al</td>
<td>BJU 2005</td>
<td>Cross-sectional Comparative</td>
<td>HRQoL after different treatment modalities</td>
<td>182</td>
<td>2,3 Gy x 16 6Gy x 4 HDR during 30 hours</td>
<td>SF-36 PCI</td>
<td>6-64 months</td>
<td>No difference in general HRQoL After &gt;2 years more sexual and urinary problems in the RP group, more bowel problems in the RT HDR group</td>
<td>HDR BT boost superior to RP regarding urinary and sexual problems</td>
</tr>
<tr>
<td>Vordermark et al</td>
<td>Acta Oncol 2006</td>
<td>Cross-sectional Comparative</td>
<td>HRQoL after different RT regimens</td>
<td>84</td>
<td>2Gy x 37 vs 2Gy x 23 +9Gy x 2 HDR</td>
<td>EORTC QLQ-C30 QLQ-PR25</td>
<td>3-32 months</td>
<td>No difference in general or disease-specific HRQoL. Diarrhoea and insomnia increased in relation to normative values</td>
<td>Despite different BED comparable HRQoL between groups</td>
</tr>
</tbody>
</table>
AIMS OF THE THESIS

In the present thesis the aim was to investigate clinical and patient-reported outcomes after combined RT for localized prostate cancer, including ADT, EBRT and HDR brachytherapy.

More specific aims included:

- Longitudinal short and long-term prospective descriptions of HRQoL and therapy-induced side effects, using self-administered questionnaires

- A comparison of reported HRQoL with baseline data and normative data from a sample of the Swedish normal population.

- An assessment of treatment outcome in terms of survival and recurrence rates compared to predicted efficacy from nomograms.

- An increased knowledge on treatment effects to facilitate decision-making regarding the appropriate approach to treatment.
PATIENTS AND METHODS

4 PATIENT COHORT

Four partly identical samples from a cohort of consecutive patients treated between 1998 and 2003 with ADT followed by combined RT including HDR BT at the Department of Oncology, Radiumhemmet or Söder hospital, were studied. The study samples are outlined in Figure 6 and their characteristics are summarized in Table 4. Participation rates were generally high. Reasons for non-participation included death, loss to follow-up/no answer or non-standardized treatment.

Figure 6. Study samples, treated patients. *treated or accepted for treatment

In Study I, the first 111 patients treated with combined RT between June 1998 and October 1999 were included in October 1999 and asked by mail for participation.

In Study II, the entire cohort, including 740 patients treated between June 1998 and June 2003 and 130 patients accepted for treatment later during 2003, was studied as part of a quality assurance project at the outpatient ward at the Department of Oncology, Radiumhemmet. Patients were asked for participation between April 2000 and June 2003 as part of their follow-up visits.
In Study III, the first 234 patients treated between June 1998 and August 2000 were included in September 2005 and asked by mail for participation. This sample included all patients in Study I and IV.

In Study IV, the first 154 patients treated between June 1998 and December 1999 were included as part of the clinical follow-up programme. Final analysis for 6-year outcome was carried out during spring 2006. This sample included all patients in Study I.

Table 4. Patient numbers and participants’ characteristics at time of RT

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>Study I</th>
<th>Study II</th>
<th>Study III</th>
<th>Study IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>---total in cohort</td>
<td>111</td>
<td>870</td>
<td>234</td>
<td>154</td>
</tr>
<tr>
<td>---total excluded in analysis</td>
<td>18</td>
<td>345</td>
<td>56</td>
<td>1</td>
</tr>
<tr>
<td>---death</td>
<td>8</td>
<td>?</td>
<td>35</td>
<td></td>
</tr>
<tr>
<td>---lost to follow-up/no answer</td>
<td>8</td>
<td>?</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>---other cause</td>
<td>2</td>
<td>4</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>---total participating</td>
<td>93</td>
<td>525</td>
<td>178</td>
<td>153</td>
</tr>
<tr>
<td>---participation rate</td>
<td>84%</td>
<td>60%</td>
<td>76%</td>
<td>99%</td>
</tr>
</tbody>
</table>

Participants

Age, in years

-Median: 68 69 67 68
-Range: 46-79 51-84 46-79 46-79

Stage (UICC, %)

-T1: 10 27 16 13
-T2: 35 35 36 34
-T2-T3: 11 10 11
-T3: 44 27 37 52
-TX: 0 1 0 1

Grade (WHO, %)

- 1: 32 18 31 29
- 2: 52 57 53 53
- 3: 16 25 16 18

PSA (ng/ml)

-Median: 14.0 14.0 14.0
-Range: 2-214 1.7-110 2-214 2-116

Length of TAB (months)

-Mean: 7 7
-Range: 3-13 2-14
4.1 Eligibility and pretreatment investigation

Only patients with localized prostate cancer (T1-T3aN0M0) after adequate pretreatment investigation were accepted for the treatment programme and thus considered eligible for the studies.

Pretreatment investigation included a serum PSA and TRUS with FNAC (before year 2000) or core biopsies (after year 2000). T-stage was determined by DRE and classified according to the UICC (International Union Against Cancer (UICC) 2002). Patients having a PSA < 20 (before June 2000 <10) and a WHO grade 1 or 2 or a Gleason score max 3 + 4 = 7 were considered to have localized disease with reference to the Partin tables (Partin et al. 1997; Partin et al. 2001). Patients with high risk WHO grade 3 (Gleason score 4+3=7 or higher) tumours or a PSA > 20 (before June 2000 >10) had to undergo an iliac lymph node dissection and a bone scan in order to exclude metastasis.

PSA relapse were defined according to the American Society of Therapeutic Radiology and Oncology (ASTRO) (ASTRO 1997) in Study I-III, and bNED as PSA levels < 2 ng/ml in Study IV.

4.2 Radiotherapy treatment programme

Only patients treated according to the description below were considered eligible for the studies:

4.2.1 Neoadjuvant androgen deprivation

All patients received neoadjuvant/concurrent ADT during at least 3 months before RT followed by 2 months during therapy using TAB including a LHRH agonist and an antiandrogen. The ADT was stopped at the end of RT, no adjuvant treatment was accepted.

4.2.2 External beam radiotherapy

A computed tomography-based dose plan was established, allowing a three-dimensional simulation of the RT. The planning target volume (PTV) of the EBRT included the prostate and the seminal vesicles with a 2 cm margin in all directions except posteriorly, where the margin was reduced to 1.5 cm.

High voltage accelerators equipped with multi-leaf collimators were used to give 3D-CRT. At Radiumhemmet, a four-field box technique was used, with all fields being equally weighted. At Söder hospital, a three-field box-technique was used, with one anterior and two lateral fields. The lateral fields were weighted 50% compared to the anterior field.

The target dose was 50 Gy in 2 Gy daily fractions, 5 days a week. The BT was delivered twice after an external dose of 24 or 26 Gy, with a two-week interval between fractions, after which the external treatment was continued.

4.2.3 Brachytherapy

A dose plan was established using TRUS images taken every 5 mm along the prostate gland. The BT PTV included the prostate and the base of the seminal vesicles plus a 3 mm margin, comprising an approximated mean volume of 39 cubic centimetres. The prescribed dose to the PTV was 10 Gy (x 2 fractions). The HDR boost dose to the
inner surface of the rectal wall was always kept below 60% of the prescribed dose of 10 Gy. The urethra was thought, during these first years of treatment, to be centrally located and needles were placed so as to avoid the geometrical centre of the prostate. The BT portion of the treatment was performed under spinal anaesthesia. In general 12-18 needles were used, and the duration of the procedure was usually 2 hours in total.

5 DATA COLLECTION

In studies I, II and III, data was collected using self-administered questionnaires. In Study IV, data was obtained from patient files and physician-based assessment of side effects. The procedures of data collection are described in detail below:

In Study I, patients treated with combined RT were mailed an invitation to participate in October 1999. They were asked to complete two questionnaires (EORTC QLQ-C30 and PR-25, Swedish translation). The forms were returned by mail in a prepaid envelope. Patients not responding in 4 weeks received a reminder including a questionnaire and a return envelope. The second assessment was performed in May 2001, using the same procedure and including all patients from the first assessment still alive.

In Study II, consecutive patients accepted for or treated with combined RT were asked between April 2000 and June 2003 to complete a prostate-specific questionnaire. This was done in conjunction to their regular outpatient visits at the Department of Oncology. Points of assessment were before treatment and after completion of therapy at follow-up at 2 months, 4 months and every 6 months thereafter until three years. Patients were given the questionnaire by a nurse or a physician and asked to leave it to a nurse after completion. Baseline questionnaires were filled in by patients on the first visit at the clinic or after treatment for a couple of months on ADT at an appointment with a nurse for further information regarding the treatment.

In Study III, patients treated with combined RT more than five years ago were mailed questionnaires (EORTC QLQ-C30 and PR-25, Swedish translation) and an invitation letter to participate in the study in September 2005. The forms were returned by mail in a prepaid envelope. Patients not responding in four weeks received a reminder including the questionnaires and a return envelope.

In Study IV, patients treated with combined RT were assessed by a physician as part of the regular follow-up procedure. Physician’s assessment of patient side effects was made using the RTOG toxicity criteria (see below), in part retrospectively at 6 weeks and 6 months after completion of therapy using recorded information, but also in a prospective manner when meeting the patient about 5 and a half years after treatment. Patient-related information such as serum PSA values was obtained from the patient files.

5.1 Questionnaires

The questionnaires used are listed in Table 5.
Table 5. Overview of questionnaires used in studies I-IV

<table>
<thead>
<tr>
<th>Questionnaire</th>
<th>Study I</th>
<th>Study II</th>
<th>Study III</th>
<th>Study IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>EORTC QLQ-C30</td>
<td>X</td>
<td>(X)</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>EORTC QLQ-PR25</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Prostate-specific questionnaire of Radiumhemmet</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Fecal incontinence questionnaire</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

5.1.1  **EORTC QLQ-C30**

The first version of this core questionnaire was developed by the EORTC in 1987 and initially comprised 36 questions (Aaronson et al. 1988). The questionnaire was designed to be cancer-specific, multi-dimensional in structure, appropriate for self-administration and applicable across a range of cultural settings (Aaronson et al. 1993; Fayers et al. 2002). Over the years, the questionnaire has been continuously developed and tested for validity and reliability. The present version EORTC QLQ-C30 (version 3.0) contains 30 questions (Aaronson et al. 1993) and has been shown to be more reliable than previous versions (Bjordal et al. 2000). Each item is scored in four categories from (1) “Not at all”, (2) “A little”, (3) “Quite a bit”, (4) “Very much” with the exception of two items in “global health status” which range from (1) “Very poor” to (7) “Excellent”. The time frame covered in the questionnaire is the past week.

The questionnaire items constitute scales that explore the following functional areas: physical, role, emotional, cognitive and social functioning as well as global health status. It also includes a number of multi-item scales and single items that assess a range of physical symptoms common among cancer patients (fatigue, nausea and vomiting, pain, dyspnoea, sleep disturbance (insomnia), loss of appetite, constipation and diarrhoea) as well as a question addressing the perceived financial impact of the disease. Scaling of the items is described in the EORTC Scoring Manual (Fayers et al. 1997).

5.1.2  **EORTC QLQ-PR25**

The prostate-specific module EORTC QLQ-PR25, developed by the EORTC Genito-Urinary Tract Cancer Cooperative Group, is a 25-item questionnaire, designed for use among patients with localized and metastatic prostate cancer. It was developed within the framework of the EORTC Quality of Life Group according to the rigorous guidelines for module development (Sprangers et al. 1993) and initially tested in Sweden by Borghede et al (Borghede et al. 1996).

It includes subscales assessing urinary symptoms (9 items), bowel symptoms (4 items), treatment-related symptoms (6 items) and sexual functioning (6 items). The response format is the same as for the EORTC QLQ-C30. This questionnaire is presently being validated in an international study (Aaronson et al. 2002).
5.1.3 Prostate-specific questionnaire of Radiumhemmet

In order to obtain individual self-assessed information regarding treatment-related side effects and their management for use in Study II, a questionnaire based on the principles of the EORTC LENT/SOMA (Pavy et al. 1995; Rubin et al. 1995) scale was developed at Radiumhemmet (Appendix). The questionnaire items assess in each area symptom severity and management. In total, the questionnaire includes 26 items in three sections. Each section begins with the question (named A1, B1 and C1 respectively): “Do you have urinary/bowel/sexual problems?” (Response categories: “Yes” or “No”). If the answer is “No”, the patient is asked to move on to the next section, leaving the items dealing with the problem in question more specifically:

Part A -- urinary tract problems:
Includes 12 items (A2-13), consisting of 8 category questions and 4 yes/no questions with supplementary textual answers.

Part B -- bowel problems:
Includes 8 items (B2-9), consisting of 5 category questions and 3 yes/no questions with supplementary textual answers.

Part C -- sexual problems:
Includes 6 items (C2-7), consisting of 5 category questions and 1 yes/no question with a supplementary textual answer.

A supplementary questionnaire with six items, evaluating the prostate-specific questionnaire in terms of comprehensiveness, relevance and upsetting potential, was enclosed to the first 100 patients. A majority found the questionnaire items both easy to answer, relevant and not upsetting.

5.1.4 Fecal incontinence questionnaire

In order to focus more on fecal leakage, a long-term problem after RT for prostate cancer recently brought to attention (al-Abany et al. 2004), an additional questionnaire including 7 items was created for Study III. The new questionnaire items were tested for feasibility in interviews with 20 patients.

5.2 Toxicity scoring

The toxicity criteria of the American Radiation Therapy Oncology Group (RTOG) (Cox et al. 1995), is a widely adapted way of assessing side effects after RT. The criteria include 5 grades, where grade 0 corresponds to no symptoms, and grade 5 implies that the effects were fatal. For prostate cancer RT, grade 1-2 denotes increased amount of diarrhoea or frequency of voiding, grade 3 corresponds to severe symptoms in terms of frequency, bleeding and need of sanitary pads or requirement of surgery. Grade 4 is equivalent to severe symptoms with requirement of blood transfusion or development of necrosis. Grades 3 - 5 refer to “major toxicities”.

Though commonly used by physicians after RT for prostate cancer, the criteria do not sufficiently differentiate between different aspects of radiation induced GU or GI side effects, nor between their severity and management. There is also a growing
knowledge that physicians tend to underestimate side effects, where self-administered questionnaires are more reliable (Egawa et al. 2001; Litwin et al. 1998; Slevin et al. 1988).

5.3 Nomograms

There are many models that predict treatment outcome in localized prostate cancer combining prognostic variables to generate risk stratification groups, based on initial clinical stage, Gleason score, and pretreatment serum PSA levels (Stephenson et al. 2006). However, inhomogeneous risk groups tend to have a limited predictive accuracy. In an effort to improve this accuracy, Kattan and co-workers have developed nomograms to predict individual 5-year recurrence probabilities in prostate cancer patients after RT (Kattan et al. 2000), with respect to actual delivered dose and hormonal therapy, and after surgery (Graefen et al. 2002; Kattan et al. 1998). The nomograms are presented in Figure 7a and b.

![Figure 7a](image1.png)

**Figure 7a.** Three-dimensional conformal radiation therapy (3D-CRT) nomogram. Adapted from Kattan et al 2000.

![Figure 7b](image2.png)

**Figure 7b.** Preoperative nomogram for definitive therapy with radical prostatectomy. Adapted from Kattan et al 1998.
6 ANALYSIS AND STATISTICAL METHODS

In the EORTC scoring manual (Fayers et al. 1997), linear transformation of quality of life data is suggested. This denotes transformation of response categories into numbers that are converted into a 0 to 100 scale with assumed linearity, either as single items or as summated mean scores of items representing a functional or symptom scale. This procedure allows parametric methods to be applied, which is done in the studies included in this thesis.

In order to highlight the magnitude of certain symptoms, some of the mean scores were supplemented with calculated category percentages.

Statistical tests were performed using the Statview™ for Windows software version 5.0.1 (SAS Institute Inc.) (Studies I-III) and the Statistica™ Release 4.1 software for Macintosh (Study IV). A p-value less than 0.05 was considered to be statistically significant.

6.1 EORTC QLQ scoring

The raw scores of the questionnaires QLQ-C30 and PR25 were linearly transformed into a 100-point scale according to the guidelines in the EORTC scoring manual (Fayers et al. 1997). A high mean score for functional scales and global health status reflected a better level of functioning, whereas a high mean symptom score reflected more problems. Mean scores with standard deviations or 95% confidence intervals were calculated on the summated scales. We beforehand chose not to include cognitive functioning, nausea and vomiting, dyspnoea, loss of appetite and financial difficulties in the analyses, areas not considered to be of particular relevance in this group of patients.

Since the EORTC QLQ-PR25 is still being validated (Phase IV), items were selected to represent symptoms as follows: Urinary urgency (item #33), urinary incontinence (item #36), nocturia (item #32), fecal incontinence (item #41), fecal blood (item #42), hot flushes (item #44), breast tenderness (item #45), erectile problems (item #53) and sexual interest (item #50). The provisional scale structure, suggested by the EORTC Quality of Life Group, was not used in order to enhance clinical interpretability.

6.1.1 Missing data

Missing data was not imputed, since every decision (including missing answers) in the self-assessment procedure was considered to be of equal importance and relevance to the individual patient. Therefore, it did not seem justified to replace any values in the analysis. However, imputation techniques are described in the EORTC scoring manual (Fayers et al. 1997)

6.1.2 Clinical relevance

A difference in EORTC mean scores of 10 or more has been proposed as clinically relevant (Osoba et al. 1998). In their study, mean score changes of 5 to 10 were perceived as small by patients, mean score changes of 10 to 20 as moderate and changes greater than 20 as large.
Though applied in many studies, there is no consensus regarding this clinically relevant difference (Neymark et al. 1998), thus it has not been applied in our studies.

6.2 Statistical methods

The statistical methods applied in the different studies are presented in Table 6.

<table>
<thead>
<tr>
<th>Table 6. Overview of statistical methods used in studies I-IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study I</td>
</tr>
<tr>
<td>Two sample t-test</td>
</tr>
<tr>
<td>Paired t-test</td>
</tr>
<tr>
<td>Chi-square test</td>
</tr>
<tr>
<td>ANOVA, repeated measurements</td>
</tr>
<tr>
<td>Kaplan-Meier analysis</td>
</tr>
<tr>
<td>Cox proportional hazards model</td>
</tr>
<tr>
<td>Log-rank test</td>
</tr>
</tbody>
</table>

In Study I, analyses of variance (ANOVA), repeated measurements, were used to evaluate the impact of time and between group differences, as well as interaction between these variables. A paired t-test was used to test differences between assessed scores and reference scores. No adjustments for multiple comparisons were made.

In Study II, data is mainly presented descriptively. Chi-square tests were performed at baseline to test for differences regarding prevalence of reported urinary, bowel and sexual side effects and specific sexual problems.

In Study III, two-sample t-tests were used for continuous variables and chi-square tests for category variables to test for differences between groups. Paired t-tests were used to test differences between assessed scores and reference scores. ANOVA, repeated measurements, were used to evaluate the impact of time in the longitudinal assessment. No adjustments for multiple comparisons were deemed necessary.

In Study IV, the survival analyses were calculated according to Kaplan-Meier, and the Log-rank test was used to demonstrate differences between the curves. The Cox proportional hazards model was used in order to quantify the relationships between PSA, WHO, T-stage and PSA relapse-free survival. Two-sample t-tests were used to compare means. Analyses of count and frequency data were performed with the chi-square test.
RESULTS

Summaries of the results of studies I-IV are presented below:

7 STUDY I

In this study, patients were assessed twice regarding HRQoL, in October 1999 (Assessment 1 – 0-18 months after RT) and in May 2001 (Assessment 2 - 18-36 months after RT).

Response rates for eligible, alive patients were 94 % (100/106) for Assessment 1 and 92% (93/101) for Assessment 2. Thirteen out of 93 responding patients had signs of recurrent disease and were not included in the main analysis.

Due to expected differences in the prevalence of problems, the study sample was divided in two groups. Group 1 included patients having finished RT during the 6 months preceding Assessment 1 (0-6 months). Group 2 comprised those treated 6-18 months before Assessment 1. For non-recurrent patients, patient characteristics are presented in Table 7. No statistically significant differences between groups, with respect to patient characteristics and known risk factors, were found.

### Table 7. Patient characteristics at time of radiation therapy, non-recurrent patients

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Group 1</th>
<th>Group 2</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of patients</strong></td>
<td>80</td>
<td>38</td>
<td>42</td>
<td></td>
</tr>
<tr>
<td><strong>Age, in years</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-Median</td>
<td>68</td>
<td>68</td>
<td>68</td>
<td>0.98</td>
</tr>
<tr>
<td>-Range</td>
<td>46-79</td>
<td>52-79</td>
<td>46-77</td>
<td></td>
</tr>
<tr>
<td><strong>Stage (UICC, %)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-T1</td>
<td>10</td>
<td>11</td>
<td>10</td>
<td>0.96</td>
</tr>
<tr>
<td>-T2</td>
<td>40</td>
<td>37</td>
<td>43</td>
<td></td>
</tr>
<tr>
<td>-T2-T3</td>
<td>10</td>
<td>10</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>-T3</td>
<td>40</td>
<td>42</td>
<td>38</td>
<td></td>
</tr>
<tr>
<td><strong>Grade (WHO,%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- 1</td>
<td>36</td>
<td>45</td>
<td>29</td>
<td>0.20</td>
</tr>
<tr>
<td>- 2</td>
<td>50</td>
<td>39</td>
<td>59</td>
<td></td>
</tr>
<tr>
<td>- 3</td>
<td>14</td>
<td>16</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td><strong>PSA (ng/ml)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-Median</td>
<td>12.8</td>
<td>14.0</td>
<td>11.3</td>
<td>0.71</td>
</tr>
<tr>
<td>-Range</td>
<td>2-214</td>
<td>2-53</td>
<td>2-214</td>
<td></td>
</tr>
<tr>
<td><strong>Length of TAB (months)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-Mean</td>
<td>7</td>
<td>7</td>
<td>7</td>
<td>0.51</td>
</tr>
<tr>
<td>-Range</td>
<td>3-13</td>
<td>4-13</td>
<td>3-11</td>
<td></td>
</tr>
</tbody>
</table>

* Differences between group 1 and 2 tested with Mann-Whitney U-test (continuous variables) or Chi-square test (category variables)
Using the EORTC QLQ-C30 results, the following comparisons were made:

1. **Changes over time** (Between Assessment 1 and 2)
   There were no statistically significant changes in the five functional areas over time.
   As for physical symptoms, pain (PA; p<0.01), sleep disturbance (SL; p<0.001) and diarrhoea (DI; p<0.01) significantly decreased from the first to the second assessment. This is presented graphically in Figure 8a+b.

2. **Group differences** (Between Group 1 and 2)
   Diarrhoea (DI) was the only variable statistically significantly differing between the two groups, with higher levels of problems generally reported among patients in group 2 (p=0.03).

3. **Group differences over time** (Group 1 trends versus Group 2 trends)
   Statistically significant interactions were obtained for several functional areas (PF; p=0.02; RF; p=0.01; SF; p=0.04), with increasing functioning in group 1, decreasing in group 2.
   The opposite statistically significant trend was seen for fatigue (FA; p=0.02), with decreasing values in group 1, whereas the value for group 2 remained at the same level.

4. **Between study sample and reference group** (Assessment 2 / normative values)
   Long-term HRQoL 18-36 months after RT was in large part comparable to normative values.
   Few statistically significant differences relative to normative values were seen. However, physical functioning (PF) was statistically significantly better among patients (p=0.01), than in the normative sample. The opposite was found for social functioning (SF) (p<0.01).
   Among physical problems, pain (PA) was statistically significantly less pronounced among the patients (p<0.001), while diarrhoea (DI) was statistically significantly more pronounced (p<0.001). This is presented graphically in Figure 8a + b.
Figure 8a. EORTC scores for EORTC QLQ-C30 functional areas assessed over time and in relation to normative data. GH=Global health status, PH=Physical functioning, RF=Role functioning, EF=Emotional functioning, SF=Social functioning.

Figure 8b. EORTC scores for EORTC QLQ-C30 physical symptoms assessed over time and in relation to normative data. FA=Fatigue, PA=Pain, SL=Sleep disturbance or Insomnia, CO=Constipation, DI=Diarrhoea

Using linearly transformed mean scores for EORTC QLQ-PR25 items, statistically significant changes between assessments were found regarding urinary incontinence (increasing, \( p=0.04 \)), nocturia (decreasing, \( p<0.001 \)), hot flushes (decreasing, \( p=0.001 \)) and sexual interest (increasing, \( p<0.001 \)). Pie chart graphs describing this are presented in Figure 9.

There were statistically significant group differences concerning rectal bleeding, more frequent in group 2 (\( p=0.02 \)), and hot flushes, significantly less frequent (\( p=0.02 \)) in group 2. Pie chart graphs are presented in Figure 10.

As for sexual interest, a statistically significant interaction was evident (increasing over time in group 1, mainly stable over time in group 2, \( p=0.007 \)).

No normative values were available for comparison.
Figure 9. Time-dependent changes in symptom severity frequencies.
In this descriptive study we assessed patient-reported urinary, bowel and sexual problems in different groups of treated patients at seven points of assessment. The assessment period encompassed a period of 34 months after combined treatment including a baseline assessment before treatment.

525 participating patients contributed at least one questionnaire of a total amount of 963. Number of questionnaires and response rates in relation to assessment points are presented in Table 8.

Table 8. Number of questionnaires and response rates in relation to assessment points

<table>
<thead>
<tr>
<th>Assessment point</th>
<th>Number of questionnaires</th>
<th>Response rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>161</td>
<td>24 %</td>
</tr>
<tr>
<td>2 months</td>
<td>173</td>
<td>51 %</td>
</tr>
<tr>
<td>4 months</td>
<td>178</td>
<td>53 %</td>
</tr>
<tr>
<td>10 months</td>
<td>126</td>
<td>41 %</td>
</tr>
<tr>
<td>16 months</td>
<td>120</td>
<td>43 %</td>
</tr>
<tr>
<td>22 months</td>
<td>88</td>
<td>36 %</td>
</tr>
<tr>
<td>28 months</td>
<td>69</td>
<td>35 %</td>
</tr>
<tr>
<td>34 months</td>
<td>48</td>
<td>31 %</td>
</tr>
</tbody>
</table>
The prevalence of reported urinary, bowel or sexual side effects with proportions of patients responding “Yes” to the question: “Do you have urinary/bowel/sexual problems?” is presented in Figure 11.

At baseline, 19% of the patients not yet on ADT (n=43) reported urinary tract problems, 14% bowel problems and 35% sexual problems. Corresponding figures for patients on ADT (n=118) were 27%, 13% and 59%, respectively. The difference in reported sexual side effects between groups was statistically significant (p<0.01).

More specifically, before ADT 95% of the patients reported a sexual desire (a little or more) and 82% sexual satisfaction (often/always) while only 48% had a durable erection for sexual intercourse often or always. Having started ADT, patients reported a sexual desire of 65% (p=0.001) and a sexual satisfaction of 40% (p=0.002), while only 13% (p<0.001) of the patients had a durable erection for sexual intercourse.

Thus ADT highly statistically significantly affected sexual outcome.

Other specific baseline problems reported include urinary frequency >1/h (3%), hematuria (3%), dysuria often/always (1%), daily urinary incontinence (1%), bowel urgency often/always (4%), bowel frequency >5/day (3%), rectal pain often/always (1%) and rectal bleeding >2/week (1%).

Symptom severity of urinary and bowel symptoms increased 2 months after completion of RT, with the exception of rectal bleeding. A late reaction with increased dysuria and rectal bleeding was seen (10-16 months), as well as an apparent increase in hematuria after 16 months. A higher level than before of urinary incontinence was observed after RT.

Sexually, a waning erectile function and sexual satisfaction 2 months after RT was observed, while sexual desire remained unchanged. In the late reaction phase, sexual desire slowly returned to baseline values, while erectile function and sexual satisfaction persisted at lower levels than before treatment.

---

**Months after RT**

Figure 11. Prevalence of side effects – proportion of patients responding “yes”.

<table>
<thead>
<tr>
<th>Baseline</th>
<th>2 months</th>
<th>4 months</th>
<th>10 months</th>
<th>16 months</th>
<th>22 months</th>
<th>28 months</th>
<th>34 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>Baseline</td>
<td>ADT</td>
<td>ADT</td>
<td>ADT</td>
<td>ADT</td>
<td>ADT</td>
<td>ADT</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Baseline</th>
<th>ADT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary</td>
<td>Bowel</td>
</tr>
<tr>
<td>%</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td>30</td>
<td>40</td>
</tr>
<tr>
<td>60</td>
<td>70</td>
</tr>
</tbody>
</table>

Symptom severity of urinary and bowel symptoms increased 2 months after completion of RT, with the exception of rectal bleeding. A late reaction with increased dysuria and rectal bleeding was seen (10-16 months), as well as an apparent increase in hematuria after 16 months. A higher level than before of urinary incontinence was observed after RT.

Sexually, a waning erectile function and sexual satisfaction 2 months after RT was observed, while sexual desire remained unchanged. In the late reaction phase, sexual desire slowly returned to baseline values, while erectile function and sexual satisfaction persisted at lower levels than before treatment.
Percentages of patients on medication for urinary frequency, bowel irregularity and ED at the various assessment points are listed in Table 9. The use of medication principally follows symptom development. This information was not included in the paper.

**Table 9.** Percentages of patients admitting use of medication at various assessment points, total number of respondents in brackets.

<table>
<thead>
<tr>
<th>Assessment point</th>
<th>Medication for urinary frequency</th>
<th>Medication for bowel irregularity</th>
<th>Medication for erectile dysfunction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>8 % (143)</td>
<td>8 % (147)</td>
<td>5 % (143)</td>
</tr>
<tr>
<td>2 months</td>
<td>8 % (150)</td>
<td>20 % (148)</td>
<td>5 % (145)</td>
</tr>
<tr>
<td>4 months</td>
<td>6 % (161)</td>
<td>17 % (153)</td>
<td>12 % (152)</td>
</tr>
<tr>
<td>10 months</td>
<td>7 % (114)</td>
<td>13 % (115)</td>
<td>12 % (106)</td>
</tr>
<tr>
<td>16 months</td>
<td>10 % (112)</td>
<td>25 % (106)</td>
<td>22 % (110)</td>
</tr>
<tr>
<td>22 months</td>
<td>10 % (81)</td>
<td>20 % (76)</td>
<td>19 % (78)</td>
</tr>
<tr>
<td>28 months</td>
<td>16 % (63)</td>
<td>15 % (61)</td>
<td>26 % (58)</td>
</tr>
<tr>
<td>34 months</td>
<td>16 % (45)</td>
<td>4 % (45)</td>
<td>21 % (43)</td>
</tr>
</tbody>
</table>

The EORTC QLQ-C30 questionnaire was completed in conjunction with the prostate-specific questionnaire, although the results have not been previously published. Short-term HRQoL (0-10 months after RT) for the different assessment groups is presented graphically in Figure 12 a + b.

There is a marked deterioration in most EORTC scores after 2 months, after which scores are gradually restored to baseline levels. However, after 10 months diarrhoea and pain seem to remain more pronounced than before treatment.

**Figure 12a.** EORTC scores for EORTC QLQ-C30 functional areas assessed over time. GH=Global health status, PF=Physical functioning, RF=Role functioning, EF=Emotional functioning, SF=Social functioning.
Figure 12b. EORTC scores for EORTC QLQ-C30 physical symptoms assessed over time. FA=Fatigue, PA=Pain, SL=Sleep disturbance or Insomnia, CO=Constipation, DI=Diarrhoea

9 STUDY III

In this study, HRQoL in a later phase of prostate cancer survivorship more than five years after combined RT was explored. HRQoL was compared with age-matched normative data for the Swedish male population and with reported outcomes from Study I in a longitudinal fashion, in order to characterize further changes over time. Patients were assessed once, with special attention given to fecal leakage. The response rate among living, eligible patients was 93% (182/196).

In the longitudinal study, 64 responding non-recurrent patients, being former participants of Study I and having a complete follow-up (3 assessment points), were included. A comparison of characteristics between patients belonging to this group and those with non-complete follow-up did not yield any statistically significant differences.

Comparisons of long-term HRQoL made with normative data showed that physical (p<0.001) and role functioning (p<0.01) were scored statistically significantly better than in Swedish men of the same age. Social functioning was scored statistically significantly worse (p<0.01). Physical symptom assessment revealed statistically significant differences for pain (less pronounced, p<0.001), sleep disturbance (more pronounced, p<0.001) and diarrhoea (more pronounced, p<0.001). 15 men aged 80 years or more on assessment were excluded from analysis, since no normative data for comparison was available. Long-term HRQoL is presented graphically in Figure 13 a + b.
Figure 13a. EORTC scores for EORTC QLQ-C30 functional areas assessed in relation to normative data. GH=Global health status, PH=Physical functioning, RF=Role functioning, EF=Emotional functioning, SF=Social functioning.

Figure 13b. EORTC scores for EORTC QLQ-C30 physical symptoms assessed in relation to normative data. FA=Fatigue, PA=Pain, SL=Sleep disturbance or Insomnia, CO=Constipation, DI=Diarrhoea

Data from the specific fecal leakage questionnaire revealed that 26.5% of patients recognized a rectal leakage problem. In this group, 80% was not or little bothered. Mucus leaking was somewhat more common than fecal matter. Less than 10% complained of extensive leakage. Sixty-five percent did not use pads. Considering the entire treated cohort, this indicates that about 2% of patients developed a serious fecal leakage problem after combined RT.

In the EORTC QLQ-C30 assessment, there was a negative trend over time regarding physical functioning (p=0.03), while social functioning demonstrated a positive trend (p=0.03). As for physical symptoms, sleeping problems seemed to increase (p=0.04) while there was a statistically significant decrease (p<0.01) in diarrhoea.
Analysis of disease-specific HRQoL scores over time showed that nocturia decreased statistically significantly (p=0.01), as well as hot flushes (p=0.04) and breast tenderness (p<0.01). A statistically significant increase in sexual desire (p<0.001) was seen as well, however, no corresponding decrease in ED was found.

10 STUDY IV

In this study, clinical outcome after combined RT in terms of 5-year relapse-free survival and 6-year bNED in relation to tumour characteristics and known risk factors was assessed. During the same period of time a three point assessment of RTOG scores for GI/GU side effects was performed. A comparison of survival rates was made with calculated results from accepted nomograms for RP and dose-escalated 3D-CRT EBRT.

Living patients were followed-up for a median of 6.1 years (range 2.8-7.9). Study sample fractions are outlined in Table 10.

### Table 10. Study sample fractions after completed follow-up

<table>
<thead>
<tr>
<th>Study sample fraction</th>
<th>Number of patients</th>
<th>% of total</th>
<th>Study sample fraction</th>
<th>Number of patients</th>
<th>% of total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of patients</td>
<td>153</td>
<td>100 %</td>
<td>Total number of patients</td>
<td>153</td>
<td>100 %</td>
</tr>
<tr>
<td>Patients alive after follow-up</td>
<td>129</td>
<td>84 %</td>
<td>Patients with PSA relapse</td>
<td>34</td>
<td>22 %</td>
</tr>
<tr>
<td>Deaths after follow-up</td>
<td>24</td>
<td>16 %</td>
<td>Non-recurrent patients</td>
<td>119</td>
<td>78 %</td>
</tr>
<tr>
<td>Deaths from prostate cancer after follow-up</td>
<td>9</td>
<td>6 %</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The majority of patients had at least one unfavourable prognostic factor, defined as a PSA ≥ 10 ng/ml, a T3 tumour or a poorly differentiated tumour (WHO grade III). 5-year relapse-free survival and 6-year bNED in relation to tumour characteristics or number of risk factors are presented in Table 11.

Statistically significant differences in 6-year bNED were found for stage T1-2 versus T3 tumours and for grade G1-2 versus G3 tumours, but not for PSA<10 ng/ml versus PSA≥10 ng/ml (Table 11).
Table 11. 5-year relapse-free survival and 6-year bNED in relation to tumour characteristics or number of risk factors.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>% of patients</th>
<th>5-year relapse-free survival</th>
<th>6-year bNED</th>
<th>Log rank p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Entire cohort</td>
<td>100 %</td>
<td>0.84</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 risk factors</td>
<td>21 %</td>
<td>0.97</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 risk factor</td>
<td>36 %</td>
<td>0.83</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 risk factors</td>
<td>34 %</td>
<td>0.83</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 risk factors</td>
<td>9 %</td>
<td>0.51</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PSA &lt; 10 bg/L</td>
<td>36 %</td>
<td></td>
<td>85 %</td>
<td></td>
</tr>
<tr>
<td>PSA ≥10 ng/ml</td>
<td>64 %</td>
<td></td>
<td>74 %</td>
<td>0.11</td>
</tr>
<tr>
<td>Stage T1/T2</td>
<td>47 %</td>
<td></td>
<td>88 %</td>
<td></td>
</tr>
<tr>
<td>Stage T3</td>
<td>53 %</td>
<td></td>
<td>69 %</td>
<td>0.003</td>
</tr>
<tr>
<td>Grade G1/G2</td>
<td>82 %</td>
<td></td>
<td>72 %</td>
<td></td>
</tr>
<tr>
<td>Grade G3</td>
<td>18 %</td>
<td></td>
<td>61 %</td>
<td>0.005</td>
</tr>
</tbody>
</table>

In a Cox regression univariate analysis, clinical features (PSA levels; <10, 10-20, >20 ng/ml and T-stage) and histopathologic parameters (WHO grade) yielded statistically significant prognostic information regarding PSA relapse-free survival. In multivariate analysis, however, only WHO grade remained independently statistically significant (Hazard ratio 2.46, 95% confidence interval 1.44-4.18).

GI and GU side effects using the RTOG toxicity criteria were assessed in relapse-free patients at 6 weeks (139 patients), 6 months (142 patients) and 6 years (131 patients) after completion of RT. Symptoms decreased over time and symptoms from the lower intestinal tract were seemingly less frequent than symptoms from the urinary tract. Results are presented in Figure 14 a + b.

Figure 14a. Proportions of patients with GI side effects 6 weeks, 6 months and 6 years after RT according to RTOG
The actual 5-year PSA relapse-free survival of the entire study sample was 84%. The predicted probability of a 5-year PSA relapse-free survival was calculated using the pretreatment data for each patient and the Kattan nomogram for RT (Kattan et al. 2000), assuming a total dose of 86.4 Gy and the use of neoadjuvant endocrine treatment. The average probability estimated for a 5-year PSA relapse-free survival following dose-escalated RT was 70%.

Similarly, the probability of a 5-year PSA relapse-free survival following surgery was calculated from the Kattan nomogram for RP (Graefen et al. 2002; Kattan et al. 1998). The average probability for a 5-year PSA relapse-free survival following surgery was predicted to be 54%. Calculated probabilities in relation to different numbers of risk factors indicated that, regardless of number of risk factors, RT was superior to RP in terms of 5-year relapse-free survival.

The actual 5-year relapse-free survival in this study surpasses all predicted probabilities using standard RP or dose-escalated RT.

**Figure 14b**: Proportions of patients with GU side effects 6 weeks, 6 months and 6 years after RT according to RTOG
DISCUSSION

11 FINDINGS, INTERPRETATIONS AND IMPLICATIONS

In the absence of convincing evidence for the best approach to curative treatment of prostate cancer, further study of HRQoL in relation to treatment has been highly warranted. This thesis contributes to increased knowledge of various outcomes following high dose RT for localized prostate cancer. Study findings are discussed in a comprehensive way according to outcome.

11.1 General HRQoL

11.1.1 Short-term HRQoL

General HRQoL 0-36 months after treatment was addressed in Study I and partly in Study II. In agreement with earlier studies on prostate BT (Brandeis et al. 2000; Jo et al. 2005; Lee et al. 2000; Wei et al. 2002; Vordermark et al. 2006), the levels of HRQoL were high in disease free patients on the functioning subscales, did not change significantly over time and were comparable to normative data. However, there were two exceptions. The patients scored higher on physical functioning but lower on social functioning. A possible explanation for the superiority in physical functioning could be ongoing effects of newly regained testosterone levels, however, effects of patient selection can not completely be ruled out. Prostate cancer patients eligible for RT could be physically healthier than the average man of the same age. This question will be addressed in future studies regarding co-morbidity. A low social functioning score is most probably related to changes of bowel and urinary habits as well as sexual function, reducing male self-esteem.

In order to detect differences related to acute irradiation effects and persisting testosterone castrate levels, the study sample of Study I was analyzed in subgroups, where assessment 1 was done <6 months from treatment (Group 1) or 6-18 months from treatment (Group 2). More acute effects from the RT and ADT were expected in Group 1, as well as more pronounced changes in HRQoL between assessments. As expected, statistically significant improvement was seen over time for physical, role and social functioning in Group 1, implying that there might be a marked deterioration in HRQoL shortly after completed combined therapy, as suggested by Egawa and co-workers (Egawa et al. 2001). They found that general HRQoL worsened significantly during the first month but recovered at 12 months. Such a fall in HRQoL levels during the first month after therapy is supported by not published HRQoL data from Study II, where a fall in functioning subscale scores 2 months after therapy is noted.

Interestingly, at Assessment point 2, it appears as if Group 1 constantly exhibits better HRQoL than Group 2, which, though assessed at a later stage in relation to the completion of RT, tends more to approach normative values. This could in fact be effects of a dose-planning and BT-delivery learning curve.

Among EORTC QLQ-C30 physical symptoms, initial problems with pain, sleep disturbance and diarrhoea decreased significantly between assessments. However, diarrhoea was statistically more pronounced when compared with normative data,
which was interpreted as a classic radiation effect. Pain, on the other hand, was significantly reduced in comparison with normative data, a fact speaking in favour of adaptation. Sleep disturbance seems to be influenced by treatment-related anxiety and nocturnal voiding. Fatigue notably improved over time only in Group 1, probably related to hormonal restitution.

11.1.2 Long-term HRQoL

General HRQoL more than 5 years after treatment was addressed in Study III. In comparison with age-matched normative data, statistically significantly better scores were found for physical and role functioning, as well as for pain. Patients still scored statistically significantly worse regarding social functioning. However, longitudinally there was a negative trend over time regarding physical functioning, while social functioning demonstrated a positive trend. Taken together, these findings are in accordance with those of Study I and other studies dealing with long-term HRQoL after combined RT using the EORTC QLQ-C30 questionnaire (Galalae et al. 2004; Joly et al. 1998), and support the impression that general long-term HRQoL is not substantially affected by combined RT. The positive development of role and social functioning could partly be explained by subsiding radiation induced effects, but adaptation or the more scientific term “response shift” cannot be ruled out as an explanation. This concept was elaborated by Sprangers and co-workers (Schwartz et al. 1999; Sprangers 1996), indicating changes in internal standards in the conceptualization of QoL which are catalyzed by health state changes. The age factor probably contributes to the reduction in physical functioning seen, but patients still function at a statistically significantly higher level than Swedish men of the same age.

The statistically significantly increased frequency of diarrhoea, however decreasing over time, could be explained by bowel disturbance induced by late radiation effects, while the increase in sleeping problems could be due to ageing, where increased susceptibility to nocturnal voiding could be considered.

11.2 Disease-specific HRQoL

11.2.1 Urinary problems

Urinary problems were evaluated as disease-specific self-reported HRQoL using the EORTC QLQ-PR25 questionnaire (Study I+III) and the prostate-specific questionnaire of Radiumhemmet (Study II), and as physician-assessed RTOG scores (Study IV).

Baseline urinary HRQoL for the PR-25 questionnaire was lacking throughout the studies, but was provided from a limited number of patients in Study II, using the prostate-specific questionnaire of Radiumhemmet. A fifth of the patients stated urinary problems before combined RT, most probably related to their malignancy. Regardless of hormone therapy, frequency and hematuria were predominant while dysuria and incontinence were more uncommon. Adding ADT yielded no statistically significant difference in urinary tract function.

After completion of RT, short-term problems included an increase in dysuria and frequency as part of the acute radiation effect. The incidence of gross hematuria was reported more frequently than expected in Study II. In the majority of hematuria cases, “a little” hematuria was admitted, which for instance could include
concentrated urine. This symptom rarely requires active investigation in the acute setting, but should perhaps be asked for more actively. Urinary incontinence increased shortly after RT and persisted at a higher level, probably related to a frequency-related bladder over-activity. This increase was statistically proven in Study I and has earlier been showed after combined RT by Joly and co-workers (Joly et al. 1998). The finding by Miller (Miller et al. 2005 76) of longitudinally increased urinary incontinence after EBRT was not supported by our study or by the study of Fransson et al (Fransson et al. 1999). Nocturia decreased statistically significantly over time probably related to tumour shrinkage (Study I and III), but scores remain high after 5 years.

Late urinary effects involving a mucosal reaction seemed to peak about two years after RT, consistent with the mean 22.7 months found by Schultheiss (Schultheiss et al. 1997). They included dysuria, hematuria and frequency. For comparative purposes, urinary frequency ≥1/hour corresponds to a RTOG ≥ grade 3 GU late effect, and was reported by 1-5% of patients in Study II more than 4 months after completion of RT. After 4-24 months, other HDR BT (>100 Gy) papers reported 2-8% grade 3-4 late GU toxicity (Galalae et al. 2002; Lennernas et al. 2002; Syed et al. 2001; Vicini et al. 2000), while papers reporting toxicity after conformal EBRT dose escalation (74-79 Gy) (Boersma et al. 1998; Michalski et al. 2000; Ryu et al. 2002) indicated 1-9% grade 3-4 toxicity. This suggests urinary side effects after combined RT to an extent consistent with earlier findings, which also is concluded using RTOG scores in Study IV. The frequency of long-term urinary morbidity is found to be higher than for bowel morbidity both for RTOG scores (Study IV) and PR-25 HRQoL (Study III).

Detailed longitudinal self-assessment studies of prostate-specific HRQoL after RT are uncommon. Fransson and co-workers (Fransson et al. 2002; Fransson et al. 2006) evaluated urinary side effects after dose-escalated RT, and found decreasing urgency and starting problems and slightly increased incontinence in comparison to pretreatment 3-5 years after RT. Litwin et al (Litwin et al. 2000) confirmed this decrease in urgency after RT, but used doubtful baseline criteria. Despite noted increased incontinence after RT, RP patients are still much more bothered by this complication (Potosky et al. 2000). The persistent urgency, however seemingly reduced over time, seen in our studies is probably related to chronic urethritis induced by the initial BT technique. No serious side effects requiring surgery were seen after combined RT.

In summary, the general findings regarding urinary morbidity after combined RT were consistent with those of earlier RT series; however, irritative urinary symptoms remain high 5 years after treatment. Based on technical improvement in BT delivery, a reduction in urinary irritative symptoms is expected in the future due to adjusted urethral doses.

11.2.2 Bowel problems

RT of the prostate is specifically associated with bowel problems, which were evaluated as disease-specific self-reported HRQoL using the EORTC QLQ-PR25 questionnaire (Study I+III) and the prostate-specific questionnaire of Radiumhemmet (Study II), and as physician-assessed RTOG scores (Study IV). Moreover, fecal
leakage was descriptively assessed using the fecal incontinence questionnaire (Study III).

As for urinary morbidity, baseline bowel HRQoL for the PR-25 questionnaire was lacking throughout the studies, but was provided from a limited number of patients in Study II, using the prostate-specific questionnaire of Radiumhemmet. 14 % of patients recognized a bowel problem before treatment. At baseline, there were very moderate complaints of bowel urgency and stool frequency >5/day, classic effects of bowel irradiation but here probably related to co-morbidity such as chronic bowel disease. Rectal pain and bleeding were uncommon. Adding ADT yielded no statistically significant difference in bowel function.

After completion of RT, short-term problems included increased bowel urgency, stool frequency and rectal pain as part of the acute radiation effect. In Study I, stool frequency or diarrhoea decreased statistically significantly over time but was found to be more pronounced in the first patients treated, possibly an effect of the learning curve. Pain also statistically significantly diminished between assessments. In comparison with normative data more than 18 months after treatment, scores for diarrhoea were more pronounced and for pain less pronounced. A “response shift” in the perception of pain is not unlikely.

Late bowel effects include mucosal changes leading to irritation and bleeding. As indicated above, both rectal urgency and stool frequency persist in the late setting. However, rectal bleeding seems to be one of the most studied late side effects after prostate cancer RT, constituting a dose limiting effect that can be detrimental to the patient. Its relation to irradiated rectal volume is evident (Boersma et al. 1998; Fiorino et al. 2002). In Study II, rectal bleeding was seemingly most pronounced between 10-16 months, consistent with the findings of Schultheiss et al (Schultheiss et al. 1997) that late GI toxicity appears earlier (median 13.7 months) than GU toxicity. For comparative purposes, rectal bleeding >2/week corresponds to a RTOG ≥ grade 2 GI late effect, and was reported by 1-7 % of patients in Study II after more than 4 months. After 4-24 months, other HDR BT (>100 Gy) papers reported 2-11% grade 2-4 late GI toxicity (Borghede et al. 1997; Dinges et al. 1998; Martin et al. 2000; Mate et al. 1998), while papers reporting toxicity after conformal EBRT dose escalation (74-79 Gy) (Boersma et al. 1998; Fransson et al. 2003; Michalski et al. 2000; Nguyen et al. 1998) indicated 6-14% grade 2-4 toxicity and papers concerning conventional/conformal EBRT (64-70 Gy) (Dearnaley et al. 1999; Sandler et al. 1995; Schultheiss et al. 1997; Teshima et al. 1997) reported 5-15%.

After more than 5 years, RTOG scores in Study IV support the findings of Study II. No RTOG grade 4 bowel side effects requiring surgery were reported. Longitudinally in Study III, a statistically non-significant decrease in rectal bleeding problems was observed over time.

Fecal leakage or incontinence after RT was recently brought to attention by Al-Abany and co workers (al-Abany et al. 2004). They concluded that about 25% of men having gone through external beam irradiation for prostate cancer suffered from this condition and found fecal leakage to be the strongest predictor of distress from the GI tract. This issue was specifically addressed descriptively in Study III since HDR BT boost is a means to avoid high doses to the rectum. We likewise found this problem in a fourth of patients; however, this leakage was seen as a minor problem in a majority (80%) of cases. Mucus leaking was somewhat more common than fecal matter but 65% never used pads.
The longitudinally persisting minor bowel problems after RT are confirmed in the study by Fransson and co-workers (Fransson et al. 2002; Fransson et al. 2006), comparing baseline and 3-5 year self-reported HRQoL data.

In summary, these findings suggest that combined RT, though entailing a risk of persistent increased stool frequency, seems to be associated with a low risk of severe long-term rectal complications, much due to low EBRT doses and the advantage of rectal sparing using HDR boost technique.

1.2.3 Sexual problems

Sexual problems were evaluated as disease-specific self-reported HRQoL using the EORTC QLQ-PR25 questionnaire (Study I+III) and the prostate-specific questionnaire of Radiumhemmet (Study II).

Baseline sexual HRQoL for the PR-25 questionnaire was lacking throughout the studies, but was provided from a limited number of patients in Study II, using the prostate-specific questionnaire of Radiumhemmet. About a third of patients reported having sexual problems before treatment. At baseline, sexual desire and satisfaction percentages were high while satisfactory erectile function was reported by half of the patients. Adding ADT worsened all sexual symptoms statistically significantly, which confirms the hormonal side effects affecting sexuality generally known to physicians using ADT.

Shortly after completion of RT, an increasing proportion of patients reported sexual discomfort in terms of sexual satisfaction and ability, probably a combination of castration effects and the bothersome situation in the GU sphere. From 4 months after RT sexual problems partly seemed to improve, however, erectile function and sexual satisfaction not as much as sexual desire. Furthermore, problems did not return to baseline levels, thus creating a pronounced gap between sexual desire and ability. The increase in sexual desire between assessments was statistically significantly proven in Study I, while improvement of erectile function was not found. This altogether pinpoints the fact shown by others (Chen et al. 2001), that RT effects are more responsible for sexual development than hormonally related factors in the long run. The inclusion of the penile bulb in the irradiated volume seems critical for this endpoint (Merrick et al. 2002). However, in Study I, where the median ADT treatment duration was 7 months, there are signs of prolonged hormonal effects known in the literature (Padula et al. 2002). The impact of this prolonged castration on long-term ED is difficult to tell, but younger men seem more susceptible to hormonal manipulation in terms of sexual dysfunction (Fransson et al. 1996).

Higher ED rates (25-89%) have been noted for combined RT than for EBRT or BT alone (Incrocci et al. 2002). In Study II, the prevalence of ED, defined as non-satisfactory erection, was 52% before any kind of treatment, 87% for patients on ADT and 80-89% 4-34 months after treatment.

Long-term sexual function was assessed in Study III. Sexual problems were still commonly seen five years after treatment, especially ED. The median age among assessed patients was 74 years, and whether this was part of a normal development associated with ageing is hard to establish. Notably, despite pronounced erectile problems, high levels of general HRQoL were reported, suggesting that many patients were not sexually active anymore. This is supported by the low response rates seen, since patients not sexually active were informed to leave the sexual part of the QLQ-
PR25. However, the reason for not being sexually active remains somewhat unclear, but impaired sexual function has been shown to matter less to patients older than 74 years (Fransson et al. 1996). Lennernäs et al (Lennernas et al. 2002), interviewing the first 41 HDR patients treated at their centre about 7 years after treatment, found ED in 75% of patients. The marked learning curve of combined RT was thought to influence the results. In Study, less than 10% of sexually active patients reported not having any erectile problems. Persisting long-term sexual problems have been reported in several other studies (Fransson et al. 1999; Joly et al. 1998; Miller et al. 2005)

In summary, sexual bother remains a concern after combined RT for prostate cancer, but long-term data is difficult to correctly assess due to the relatively high median age of participating patients. It is though obvious that combining EBRT with an implantation technique might affect both the neurovascular bundle and the penile bulb, thus increasing the risk of ED. However, whether such a risk should be emphasized has to be determined in future studies.

11.3 Outcomes related to neoadjuvant ADT

Loss of libido, impotence, weight gain, sweating, hot flushes and psychological reactions are common after ADT. Normally, the effects of short courses of the long-acting drugs used subside within 6 months from discontinuation, but longer ADT treatment predisposes to prolonged effects (Padula et al. 2002). ADT seems to affect the patients negatively in Study I-III, in Study I generally more evident in Group 1, where RT ended < 6 months before the first assessment. Between assessments, statistically significant improvement in physical functioning, fatigue, hot flushes and sexual desire was noted, most probably related to normalization of testosterone levels. However, even in Group 2 a substantial decrease is noted between assessments, suggesting the presence in some patients of castration effects as late as 6-18 months after treatment. Regardless of group, hot flushes and sexual desire scores improved, while no improvement of ED was found.

In Study II, statistically significant differences were found for baseline sexual symptoms before RT after initiation of ADT. Already 4 months after RT and discontinuation of the ADT, an improvement in sexual desire was noted but was not matched by an improvement in sexual ability.

In Study III, long-term hormonally dependent symptoms were scarce and only reported by 15% of patients, implying that in a majority of patients, normal testosterone levels prevailed on assessment and few effects related to the hormone deprivation therapy remained.

In summary, in the studies included in this thesis ADT most certainly substantially affects both general and disease-specific short-term HRQoL after combined RT, but there is low evidence of any marked long-term effects. An impact of ADT on GU toxicity, as suggested by Schultheiss and co-workers (Schultheiss et al. 1997), is unlikely but can not totally be ruled out. Any survival benefit related to ADT can not be determined.

11.4 Survival

Long-term clinical outcomes for combined RT using transperineal TRUS guided HDR technique have been published in reports from 9 centres (Astrom et al. 2005; Deger et al. 2002; Galalae et al. 2002; Hiratsuka et al. 2004; Martin et al. 2004;
Martinez et al. 2003; Mate et al. 1998; Pellizzon et al. 2003; Stevens et al. 2003). Three of these centres have recently reported on the treatment results in more than 600 patients (Galalae et al. 2004). In addition, centres have reported their experience using the Syed free-style template technique (Egawa et al. 2001; Syed et al. 1992). 5-year bNED survival has been reported to be in the range of 67-93%. These are encouraging results and the findings of Study IV are in agreement with earlier reports. There are surprisingly small differences in results despite different HDR techniques and NTD delivered to the prostate. However, comparison of results is hampered by different patient selection criteria, bNED definitions and PSA relapse criteria. No randomized studies have been conducted. This would complicate any effort to interpret differences in results.

In an attempt to compare the 5-year relapse-free survival rates found in Study IV with a defined control group, the widely accepted nomograms according to Kattan et al (Graefen et al. 2002; Kattan et al. 1998; Kattan et al. 2003) were used, based on patient pretreatment data from Study IV. Results indicated that the predicted outcome after surgery in this group of patients would be inferior to the predicted outcome after combined RT. This is explained by the inclusion of a high proportion of patients with intermediate and high-risk tumours. These patients are usually not candidates for surgery due to the high risk of extracapsular extension. The predicted differences between the results from the nomogram regarding dose-escalated EBRT and the present study were small, and since no confidence intervals were available it was not possible to draw any statistically significant conclusions. Furthermore a majority of patients included in Study IV was diagnosed with FNAC instead of core biopsies. This introduced an uncertainty regarding the tumour grading, since Gleason score is used in the nomograms. However, methods for conversion have been described (Jacobs et al. 1989; Maksem et al. 1988), thus WHO grades were converted into the lesser Gleason score of the Gleason score interval as proposed in the conversion method. For example, WHO Grade III was converted into Gleason score 8 and not 9 or 10 using the nomogram. This would make an overestimation of the results less probable.

Alternatively, core needle biopsy proven relapse as an end point could be used to report clinical outcome. This has been done in only two studies (Borghede et al. 1997; Dinges et al. 1998), probably because there is a risk of developing fistulae and rectal complications when performing transrectal biopsies of irradiated tissue. In Study IV, patients with PSA relapse were examined with DRE and suspected pathological findings were investigated using FNAC. No local recurrence was found.

11.5 Implications of irradiation technique and dose

Interstitial brachytherapy provides the option of decreasing the dose to the rectum while delivering an even higher NTD-equivalent dose to the prostate. A combination of external 3D-CRT and HDR BT delivers a tumour NTD exceeding 100 Gy in 2 Gy fractions to the prostate gland (assuming an alpha/beta ratio of 3) while the dose to the anterior wall of the rectum, due to the moderate EBRT dose, is kept below 72 Gy provided that during the HDR boost the rectal dose is below 6.0 Gy for each brachytherapy tumour-prescribed dose of 10 Gy application. This high dose to the tumour will provide excellent tumour response results with theoretically few side effects. The high rate of local control and non-measurable serum PSA levels after
therapy would seem to indicate that extracapsular growth is manageable using the combined EBRT and HDR BT approach.

However, volumes irradiated and the technical aspects of BT dose delivery are crucial in this context. A correct BT needle placement in accordance with established plans could be difficult, and HRQoL results suggest learning curve effects. Notably, all patients in Study I, II and IV were treated according to a modified Kiel protocol (Bertermann 1986), where a horseshoe placement of relatively few needles is applied, allowing for a dosimetric fall in the central and superior parts of the gland. This was done in order to theoretically spare the urethra, but the urethra was actually not identified. Instead, a surrogate urethra was used under the assumption that the urethra was centrally located. This practice did not ensure proper dose coverage of the gland. The urethra is considered to be rather resistant to irradiation. However, urethral strictures and urethral necrosis have been reported (Dinges et al. 1998; Galalae et al. 2002; Martinez et al. 2000). A TUR-P less than 6 months before irradiation has been proposed as a risk factor (Galalae et al. 2002). Still, the number of patients with severe symptoms in each report is limited and caution about the dose delivered to the urethra should be emphasized.

Theoretically, the number of needles used during HDR could impact results. A higher number of needles would facilitate a homogenous dose distribution within the prostate, but would make the implantation more complex and it would thereby be necessary to identify the urethra throughout the whole length of the prostate. Furthermore, the size of the EBRT fields affects the irradiated volume and consequently RT side effects. Volumes at risk include the rectal mucosa, the bladder floor, the urethra and the penile bulb. A reduction of the initially applied margins by 0.5 centimetres is currently practised. This will most certainly affect the development of late side effects, mainly by reducing irradiated rectal volumes.

However, using a combined technique could also have drawbacks. The increased ED rates reported for combined EBRT + BT (Incrocci et al. 2002) as well as the sexual dysfunction reported in Study I-III, could be associated with combined mechanical and radiation induced damage to neurovascular bundles concurrently with dose to the penile bulb and crura. This calls for elucidation in further studies.

Today, after more than 1500 treated patients, combined RT is a well-established and respected treatment for localized prostate cancer at the Karolinska University Hospital. Brachytherapists are more skilled, dose planning systems are modern, the number of needles used is close to 20, rectal doses are precise and the urethra is safely located by means of a urinary catheter during pre-planning. Hopefully, these adjustments will lead to better tumour control and better HRQoL for future patients.

### 11.6 Future research

Future research will have to deal with co-morbidity and dose-volume effects on HRQoL and further evaluate causes and development of sexual dysfunction after combined RT until ten years after treatment. The impact of treatment technique modifications on HRQoL have to be established. Randomized interventional studies are suggested in order to prevent poor HRQoL outcome. Elucidation of genetic patterns that predispose to increased radiosensitivity and consequently low HRQoL could be another field of interest.
12 METHODOLOGICAL CONSIDERATIONS

Some methodological aspects of the studies described in this thesis deserve particular attention.

12.1 Internal validity - systematic errors

Internal validity is defined as the absence of systematic errors within studies, roughly divided into bias (distortion of studied associations) and confounding.

12.1.1 Selection bias

This term refers to problems related to selection and participation. Non-participation is a potential source of selection bias, affecting the generalizability of the results. High participation rates and response rates normally preclude severe selection bias, which is the fact in most studies presented in this thesis. No patient was missed in the registration and few patients were lost at follow-up. However, in Study II, participation and response rates are low, much due to administrative problems particularly regarding questionnaire distribution and baseline assessment. These “drop-outs” are believed to be completely at random, and the study sample was though to well represent the patient population referred to the clinic.

The reason for this assumption of no systematic bias was that practically no patient declined to participate when asked and patient characteristics including risk factors were equally distributed over time. The influence of selection bias related to any deliberate non-participation should be limited in view of the high number of participating patients, possibly with the exception of sexually related questions where response rates were lower than expected. Selection bias can therefore not totally be ruled out, but is probably not a major concern in these studies.

12.1.2 Information bias

This term refers to problems related to misclassification. All of the present studies rely on information from questionnaires and patient records.

The staging and investigation procedures for prostate cancer are not optimal and prone to misclassification. The DRE is still a highly subjective way to determine tumour stage (Varenhorst et al. 1993). The histopathologic grading is less subjective but inter-observer differences exist. Since there is currently no consensus regarding the correlation between WHO grade and Gleason score, the translations made in all studies, such as converting Gleason 3+4 = 7 into G2 for comparative purposes, probably underestimate the risk profile of this tumour type. The specificity of a lymph node dissection is poor and bone scans often fail to detect early metastasis. In this material, most recurrences are probably in fact misclassification due to early metastasis, since signs of local disease after FNAC have not been found in PSA relapsing patients. The PSA value is more reliable, especially in the follow-up situation, to detect tumour recurrences. Using consensus guidelines regarding the definition of a PSA relapse, such as the ASTRO criteria (1997), will ensure correct classification of recurrences.

In summary, misclassification with respect to T-stage, metastasis and possibly histopathologic grade is likely in the study samples, but in case of understaging this
would rather make clinical outcomes even more impressive. The implications for equality testing between groups are probably negligible.

The use of psychometrically well validated self-administered questionnaires in clinical research on HRQoL will minimize information bias. The EORTC questionnaires have been found to be practical, easy to fill in with a time to completion of 10 to 15 minutes. The core questionnaire QLQ-C30 is thoroughly validated (Aaronson et al. 1993), while the prostate-specific questionnaire QLQ-PR25 is in phase IV validation (Aaronson et al. 2002). This validation procedure ensures cultural- and language-specifically valid responses. The self-assessment procedure prevents making the patients adapt to the perspective of a researcher or clinician (Litwin et al. 1998), which could be the fact using interviews, and permits completion in privacy whenever there is time.

However, there are methodological risks using questionnaires that are filled in at home, especially repeatedly. The influence of saved previous assessments can not be neglected, making the results too homogenous and thus affecting the responsiveness of the questionnaire. This was considered when Study II was designed, where patients were supposed to fill in the questionnaire on their follow-up visits, just before meeting their physician. However, the fact that the patients handed the questionnaires to the nurse, and that the treating physician had access to the questionnaires could have biased the responses. The questionnaires were completed before the medical examination, thus limiting the effects on HRQoL of information during the medical consultation. In addition, it can be assumed that many patients are distressed before the medical consultation, thus responses on affective items might differ in this context compared to when questionnaires are completed at home. However, all patients in Study II completed the questionnaires at the clinic, thus the possible biases described above are supposed to have the same effect across all assessment points, thus not hampering the comparison over time.

Using a non-validated questionnaire, such as the prostate-specific questionnaire of Radiumhemmet in Study II, is more crucial. However, it was used restrictively in a descriptive setting to collect disease-specific single item HRQoL. Comparison between groups was not made longitudinally.

Any remaining misclassification should be non-differential and bias any positive findings against the null hypothesis, thus diluting found associations.

12.1.3 Recall bias

Recall bias refers to the problem of retrospectively relating information regarding the period before treatment, where effects related to the treatment may influence answers. The prospective approach of studies I-III, where collected information refers to the actual time period, circumvents this problem. In Study I, however, the primary intention was to retrospectively collect baseline HRQoL data, but apparent recall bias made the data derived impossible to use.

12.1.4 Confounding

A confounder is a factor associated both with the exposure and the outcome under study, and is not in the causal pathway. Age is a common confounding factor in clinical studies. Confounding is best dealt with in randomized studies, where possible known and unknown confounders are supposed to be equally distributed between
arms, or in case-control studies using logistic regression models allowing for adjustment. In comparative studies, however, potential confounding factors can influence comparison between groups. Assuring equal distribution of known risk factors and characteristics between groups is a means of preventing apparent confounding, but this will not exclude possible effects from unknown confounders. Tests of equality between groups are performed successfully in Study I and III. Co-morbidity, irradiated volumes and current medication are important confounding factors, where information is lacking in the present studies. Likewise, individual radiosensitivity was unknown. There is no reason, however, to suspect great differences in this respect between groups compared.

To avoid confounding by tumour recurrence-related symptoms, only relapse-free patients were included in the analyses. However, as the present studies are not randomized, there is a possibility that other factors than those accounted for such as treatment and stage of disease, are responsible for differences between groups and changes over time.

12.2 Precision - random errors
Random error, the influence of chance, leads to uncertainty of the estimates found in a study. Assuming that the sample under study is a random sample of the true prostate cancer population eligible for curative therapy (internal validity), a 95% confidence interval around the point estimate, standard in most clinical research, includes the true population value in 19 out of 20 times. This interval is highly dependent on sample size and theoretically, chance can never be entirely ruled out as an explanation to observed findings.

In the present studies, most comparisons were made between groups of at least 40 individuals. This precision has to be considered as acceptable for these kinds of studies. However, as stated earlier, fewer respondents and thus less precision were noted for sexually related questions.

The risk of type I errors, denoting the occurrence of false positive findings reaching the level of statistical significance due to multiple testing, was considered to be low in the studies included in this thesis. No adjustments for multiple comparisons were thus made.

12.3 External validity
External validity refers to the possibility to generalize the findings to other populations than the one under study. Provided that there are internal validity and enough precision and treatment is given in a similar fashion, these results would be highly representative of the general localized prostate cancer population subjected to combined RT.

12.4 Interpretation of HRQoL findings

12.4.1 Reference groups
Interpretability is an essential attribute of any HRQoL instrument. It assumes valid and meaningful reference groups for comparison of HRQoL data. In longitudinal studies, pretreatment, baseline or internally-referenced comparison is of great value, where patients serve as their own controls either at an individual or group level. This way,
changes in HRQoL are easily detected. One of the major concerns in the studies included in this thesis refers to the lack of baseline HRQoL, especially regarding disease-specific HRQoL, which is often multi-factorial in origin. This partly hampers interpretation of direct treatment-related HRQoL effects.

Instead, an externally-referenced approach was used, namely the EORTC QLQ-C30 version 3 normative values established for a large sample of the Swedish population (Michelson et al. 2000). This random sample consisted of 3919 persons aged 18-79 years, and the normative values were based on 3069 questionnaires (78%). A reliability analysis was made. In Studies I and III, age-specific male values were used for comparison. A major drawback using this normative data is the absence of reference values concerning men older than 79 years. This age group constituted about 9% of assessed patients in Study III, patients which did not contribute to the group mean in the analysis. Most likely, these elderly men would have reduced normative HRQoL means to some extent, since substantial reduction in all functional area scores was seen between age group 60-69 and 70-79 years. The magnitude of this effect is, however, impossible to tell but score changes were minor in the actually assessed group.

12.4.2 Quality of life data

The EORTC quality of life questionnaires have to be considered well-established and psychometrically valid instruments in HRQoL research. However, further improvement is nevertheless warranted, especially for the disease-specific modules.

The questionnaires have been found easy to fill in, which is generally supported by patients and physicians. Response alternatives include category ordinal data, mostly summated to multiple-item scales, which improve reliability and allow random errors of measurement to average out.

In the present studies, the EORTC Scoring manual (Fayers et al. 1997) was followed in all parts of the linear transformation of the category data into numerical continuous data ranging from 0 to 100. However, contrary to the recommendations, no imputation of values was made in cases where less than half of the items from the scale were missing. This was not done with reference to patient integrity and respect for the individual standpoint not to respond to specific items, and was thought to have a limited impact on the generalizability of results.

The interpretation of a linearly transformed score might be difficult both in terms of actual score and differences between scores. If the sample size is large, small differences in mean scores can prove to be statistically significant. In quality of life research, clinical relevance might be more important than statistical significance. A difference in mean scores of 10 or more has been proposed as clinically relevant (Osoba et al. 1998), but there is no consensus regarding this clinically relevant difference (Neymark et al. 1998), and interpretations may be hazardous. In the context of completed RT with adjacent side effects, also small differences may be perceived by the patient as clinically relevant. In view of this and fairly small sample sizes, this clinically relevant minimum difference was not applied in our studies.
GENERAL CONCLUSIONS

Based on the findings in the studies included in this thesis, the following conclusions are made:

After combined RT, including EBRT, HDR BT boost and neoadjuvant ADT,

- Short-term general HRQoL seems to be negatively affected by a combination of acute radiation-induced effects and ADT. After 18 months general HRQoL was in large comparable to normative data.

- Long-term general HRQoL appears not to be substantially affected by combined RT. Possible “response shift” effects were noted.

- General findings regarding urinary morbidity were mainly consistent with those of earlier RT series. The long-term persisting irritative symptoms could be an effect of radiation-induced urethritis related to the BT technique.

- Despite evidence of persistent increased stool frequency, the risk of severe long-term rectal complications seems to be low. Fecal leakage does not seem to be a substantial patient problem.

- Short-and long-term sexual bother remain concerns, but competing risk factors have to be established.

- Effects of ADT on HRQoL seem to be substantial but generally transitory.

- The 5-year relapse-free survival is encouraging and in agreement with earlier studies.

- Patients have received a radical high dose treatment, providing high local cure rates even with extracapsular extension, but entailing a risk of side effects of which most are of limited duration.
POPULÄRVETENSKAPLIG SAMMANFATTNING

BAKGRUND
Prostatacancer är den vanligaste cancerformen hos män i västvärlden. Medelåldern vid diagnos är hög, cirka 70 år. En kraftig incidensökning har på senare år noterats, sannolikt beroende på ökad diagnostisk användning av tumörmarkören prostataspecifikt antigen (PSA) och ökad medellivslängd i befolkningen.

Ett kliniskt problem är att prostatacancer uppvisar stor variabilitet gällande förlopp och aggressivitet, där ingen entydig strategi för handläggning finns. Tumören kan behandlas aktivt med kirurgi eller strålbehandling eller lämnas utan åtgärd.

Naturalförloppet vid prostatacancer utan behandling är långsamt vid beskedliga tumörtyper, där endast 10-20 % av patienterna avlider av sin cancer. Patienter med snabbväxande tumörtyper och personer under 60 års ålder gynnas dock av aktiv behandling. Behandlingsresultaten vid aktiv terapi är goda och skiljer sig inte mellan terapialternativen, vilket det ibland påtagliga biverkningspanoramat gör. Kirurgi har förknippats med risk för impotens och urinläckage, medan strålbehandling förknippats med tarmsymptom.


PATIENTER OCH METOD

Formulär Avföringsinkontinens innehåller 7 tilläggsfrågor till QLQ-PR25, vilka är utarbetade på Radiumhemmet för att samlia detaljerad information kring avförings- och slemläckage efter strålbehandling.


RESULTAT


Delstudie II: Jämfört med före behandlingen ökade såväl tarmproblem, urinvägsbesvär som sexuella problem under strålbehandlingen och föreföll hålla i sig fram till 34 månader efter strålbehandling, även om en tendens till avklingande tarm- och urinvägsproblematik noterades över tid. Tillägg av total androgenblockad försämrade den sexuella problematiken. Inga biverkningar som krävde kirurgi noterades dock. Klassiska senneffekter såsom tarmblödning sågs under det andra året efter strålbehandling, men verkade vid jämförelse med dosökad extern strålbehandling möjligen mindre uttalade. Slutsatsen var att trots en mycket hög stråldos var biverkningarna begränsade.

Delstudie IV: 5-årsöverlevnaden utan PSA recidiv efter kombinationsbehandlingen var 84 % vilket överensstämmer med tidigare studier. Ingen patient uppvisade vid recidivutredning ett lokalrecidiv. Medianvärdet för PSA hos recidivfriska patienter efter 5 år var 0.05 µg/L. Det beräknade värdet för den studerade gruppen från Kattans nomogram för 5-årsöverlevnad utgående från tumöregenskaper var 54 % för radikal prostatektomi samt 70 % för extern strålbehandling motsvarande 86,4 Gy. Sen strålreaktion motsvarande RTOG grad 3 sågs från tarm hos 1 % av patienterna samt från urinvägar hos 4 % av patienterna.

KONKLUSION
ACKNOWLEDGEMENTS

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REFERENCES


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APPENDIX

Personnummer: _ _ _ _ _ _ - _ _ _ _

Namn....................................

Datum för ifyllande _ _ _ _

Välkommen till urologmottagningen på Radiumhemmet.
Vi ber Dig besvara nedanstående frågor i väntan på doktorn. Detta underlättar vid besöket och ger Dig mer tid att diskutera Dina frågor och bekymmer med doktorn. De flesta frågorna besvaras med ett kryss för det svarsalternativ som passar bäst för Dig.

A. Frågor om vattenkastning

1. Har Du några besvär från urinblåsan?
   o Nej (fortsätt till avsnitt B)
   o Ja

2. Hur ofta har Du smärta vid vattenkastning?
   o Aldrig
   o Vid enstaka tillfällen
   o Ibland
   o Ofta
   o Alltid

3. I vilken utsträckning har Du smärta vid vattenkastning?
   o Inte alls
   o Minimal
   o Uthärdlig
   o Intensiv
   o Outhärdlig

4. Tar Du någon medicin mot smärtan?
   o Nej
   o Ja  Vilken medicin?.................................................................

   Hur ofta tar Du medicinen?..............................................................

5. Ungefär hur ofta behöver Du kasta vatten?
   o Varje timme
   o 1 - 2 timmar emellan
   o 2 - 3 timmar emellan
   o 3 - 4 timmar emellan
   o Var femte timme eller mer sällan
6. Tar Du någon medicin för att minska behovet av att kasta vatten ofta?
   o Nej
   o Ja  Vilken medicin?.............................................................................

   Hur ofta tar Du medicinen?......................................................................

7. Har Du opererats för att minska behovet av att kasta vatten ofta?
   o Nej
   o Ja  Vilken typ av operation?...............................................................

8. Hur ofta har Du besvär med blod i urinen?
   o Aldrig
   o Vid enstaka tillfällen
   o Ibland
   o Ofta
   o Alltid

   a. Järnmedicin  o Nej  o Ja
   b. Enstaka blodtransfusion  o Nej  o Ja
   c. Regelbundna blodtransfusioner  o Nej  o Ja
   d. Blåsan har "etsats" en gång  o Nej  o Ja
   e. Blåsan har "etsats" flera gånger  o Nej  o Ja
   f. Annan operation  o Nej  o Ja

10. Hur ofta har Du svårt att "hålla tätt"?
    o Aldrig
    o Vid enstaka tillfällen
    o Ibland men inte varje dag
    o Flera gånger varje dag
    o Hela tiden (helt inkontinent)

11. Hur ofta använder Du inkontinensskydd ("droppskydd")?
    o Aldrig
    o Vid enstaka tillfällen
    o Flera gånger i veckan
    o Varje dag
12. Hur ofta använder Du kateter/kateteriserar Dig själv?
   - Aldrig
   - Vid enstaka tillfällen
   - Flera gånger i veckan
   - Varje dag
   - Har kateter hela tiden (”kvarkateter”)

13. Hur är Din stråle?
   - Normal
   - Vid enstaka tillfällen svag
   - Ibland svag
   - Alltid svag, men ej stopp
   - Helt stopp

**B. Frågor om tarmbesvär**

1. Har Du några besvär från tarmen?
   - Nej (fortsätt till avsnitt C)
   - Ja

2. Hur ofta har Du besvär med trängningar?
   - Aldrig
   - Vid enstaka tillfällen
   - Ibland
   - Ofta
   - Alltid

3. Hur ofta tömmer Du tarmen per dygn?
   - 1 gång
   - 2-4 gånger
   - 5-8 gånger
   - Mer än 8 gånger
   - Vattentunn diarré hela tiden

4. Tar Du någon medicin för att stabilisera tarmen?
   - Nej
   - Ja
     Vilken medicin? .................................................................
     Hur ofta tar Du medicinen? ................................................

5. Hur ofta har Du smärta i ändtarmen?
   - Aldrig
   - Vid enstaka tillfällen
   - Ibland
   - Ofta
   - Alltid
6. I vilken utsträckning har Du smärta i ändtarmen?
   - Inte alls
   - Minimal
   - Uthärdlig
   - Intensiv
   - Outhärdlig

7. Tar Du någon medicin för att lindra smärtan i tarmen?
   - Nej
   - Ja  Vilken medicin? .................................................................

   Hur ofta tar Du medicinen?..............................................................

8. Hur ofta har Du blödningar från tarmen?
   - Aldrig
   - Då och då
   - Mer än två gånger i veckan
   - Dagligen
   - Mycket stora blödningar varje dag

9. Tar Du någon medicin för att lindra besvären med blödningar i tarmen?
   - Nej
   - Ja  Vilken medicin? .................................................................

   Hur ofta tar Du medicinen?..............................................................

9. Har Du genomgått någon operation för att lindra besvären med blödningar i tarmen?
   - Nej
   - Ja  Vilken operation? .................................................................

   Datum för operation? ………………….

C. Frågor om sexualitet

1. Har Du några sexuella problem som hänger samman med Din sjukdom?
   - Nej (Fortsätt till avsnitt D)
   - Ja

2. I vilken utsträckning har Du sexuell lust?
   - Inte alls
   - Lite
   - En hel del
   - Mycket
   - Väldigt mycket

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3. I vilken utsträckning kan Du få erektion för att genomföra ett samlag?
   - Inte alls
   - Sällan
   - Ibland
   - Oftast
   - Varje gång

4. I vilken utsträckning kan Du få orgasm?
   - Inte alls
   - Sällan
   - Ibland
   - Oftast
   - Varje gång

5. Hur ofta har Du ejakulationsproblem (torrhetskänsla)?
   - Inte alls
   - Sällan
   - Ibland
   - Oftast
   - Varje gång

6. Hur ofta känner Du dig sexuellt tillfredsställd?
   - Inte alls
   - Sällan
   - Ibland
   - Oftast
   - Varje gång

7. Tar Du någon medicin för potensen?
   - Nej
   - Ja
      Vilken medicin? .................................................................

      Hur ofta tar Du medicinen? .............................................

D. Beskriv nedan om Du har andra besvär i samband med sjukdomen och behandlingen som Du vill diskutera vid läkarbesöket.

........................................................................................................
........................................................................................................
........................................................................................................
........................................................................................................
........................................................................................................

82
HEALTH-RELATED QUALITY OF LIFE IN MEN AFTER TREATMENT OF LOCALIZED PROSTATE CANCER WITH EXTERNAL BEAM RADIOTHERAPY COMBINED WITH $^{192}$Ir BRACHYTHERAPY: A PROSPECTIVE STUDY OF 93 CASES USING THE EORTC QUESTIONNAIRES QLQ-C30 AND QLQ-PR25

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Purpose: To describe prospectively the long-term health-related quality of life (HRQOL) and treatment-related symptoms in patients with localized prostate cancer treated with neoadjuvant androgen deprivation therapy and radical radiotherapy (RT), including external beam RT and iridium high-dose-rate brachytherapy, and to compare them with age-matched normative data.

Methods and Materials: A total of 93 patients with T1-T3a tumors consecutively treated with definitive RT at our institution completed the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (QLQ)-C30 and QLQ-prostate specific 25-item (PR25) module twice at an 18-month interval 0–18 months after RT. Subgroups were analyzed regarding acute and late effects on symptoms and quality of life.

Results: The main analysis included 80 patients who were disease free at the final assessment. The levels of HRQOL were generally high, did not change over time, and were comparable to the normative data. Symptom development (urinary, bowel, and sexual) correlated well with the known acute and late effects of radical RT and neoadjuvant androgen deprivation therapy.

Conclusion: Combining external beam RT and HDR brachytherapy when treating prostate cancer did not appear to impair HRQOL and was comparable to that of other brachytherapy methods. The negative contribution from late neoadjuvant androgen deprivation therapy on symptom development seemed to be substantial but mostly transitory. Additional research is needed to determine the long-term HRQOL (3–5 years), and interventional randomized studies are suggested. © 2004 Elsevier Inc.

Localized prostate cancer, HDR brachytherapy, Health-related quality of life, Side effects.

INTRODUCTION

Prostate cancer is a very prevalent malignancy in elderly men in Sweden, and the incidence has increased rapidly during the past few years, most probably as a result of the extended use of prostate-specific antigen (PSA) testing and the increase in the mean age of the population (1). The mortality rate, however, has not increased as substantially (2). Because the natural history of the disease exhibits great variation and an increasing number of patients are diagnosed with localized disease, the most crucial question remaining to be answered is which patients should be treated to benefit most from the remaining years of their life?

Much controversy exists concerning the most suitable treatment for localized disease. Currently under debate is the question of whether presumptively curative and aggressive treatments such as radical prostatectomy or radiotherapy (RT) are superior to watchful waiting. In a recently published randomized study from the Scandinavian Prostate Cancer Group (3), radical prostatectomy was shown to reduce disease-specific mortality significantly, but no statistically significant difference was found between surgery and watchful waiting in terms of overall survival. Several comparative treatment studies have also found no convincing difference in terms of overall survival between surgery and RT (4).

Therefore, because no statistically significant differences between the curative effects of radical prostatectomy and RT have been demonstrated and the curative rates for both treatment modalities remain high, the quality-of-life aspects...
have become increasingly important in the determination of the best approach to treatment. However, in terms of treatment-related side effects known differences exist. Prostatectomy has been associated with high rates of erectile dysfunction, urinary incontinence, and urethral stricture development (5). Steineck et al. (6), as part of the Scandinavian Prostate Cancer Group study (3), presented a detailed analysis of the effects of treatment. No statistically significant difference in global health status was found between the two arms, although the surgical approach entailed a greater risk of erectile dysfunction and urinary leakage. External beam RT, however, is known to cause more bowel symptoms, such as proctitis and rectal ulcers, as well as radiation-induced late effects to the bladder and urethra (7).

To reduce the side effects induced by RT, brachytherapy as a boost after external beam RT (EBRT) has been widely practiced, as has the use of brachytherapy alone. With this technique, theoretically, a smaller radiation dose is delivered to critical tissue such as the rectum. Various techniques, such as implants with radioactive iodine or palladium (6) delivering low-dose-rate (LDR) brachytherapy, have been used. In Sweden, however, high-dose-rate (HDR) brachytherapy combined with EBRT is practiced in many institutions. This technique, using $^{192}$Ir sources temporarily implanted through needles by an afterloading device, was developed in Kiel in the 1980s (9) and was modified and first introduced in Sweden by Borghede et al. (10) in 1988. The short-term toxicity was minimal (11).

Since 1998, >700 patients have been treated at our department at Radiumhemmet, Karolinska Hospital, with combined EBRT and HDR brachytherapy for localized prostate cancer (T1-T3aN0M0). All patients fulfilling the criteria for localized disease (see "Methods and Materials," "Pretreatment investigation and primary treatment techniques") and having an expected survival of at least 10 years were offered this treatment. The estimated disease-specific 10-year survival rate reported for combination iridium brachytherapy is 70–90%, depending on the risk factors, with few recurrences reported after 5 years (12–14).

Thus far, few studies have described patient-reported perceived side effects and health-related quality of life (HRQOL) after brachytherapy (15–19). In most studies, permanent source techniques have been used (15–17), with or without the addition of EBRT. They have unanimously reported good global health status after treatment. However, in terms of long-term disease-specific quality of life, the reports have varied. Only two studies (18, 19) have described HRQOL after combined transperineal $^{192}$Ir brachytherapy.

The main purpose of the present study was to describe prospectively the long-term HRQOL, as well as disease- and treatment-related problems, in patients diagnosed with localized prostate cancer treated with combination RT, including EBRT and iridium HDR brachytherapy. In addition, long-term HRQOL data, corresponding to assessment 2 (19–36 months after therapy), were compared with age-matched normative data.

The HRQOL data of patients who finished brachytherapy $>$6 months before assessment 1 (October/November 1999) were also compared with the data of those treated within 6 months to investigate differences in symptom presentation that could presumably be related to acute effects of RT or late effects of neoadjuvant hormonal treatment.

METHODS AND MATERIALS

Patients

The first 111 patients with localized prostate cancer (T1-T3aN0M0), consecutively treated with a combination of EBRT and iridium HDR brachytherapy between June 1998 and October 1999 at Radiumhemmet, Karolinska Hospital, Stockholm, were offered participation in this study in October 1999.

A total of 100 patients participated. The reasons for nonparticipation of the other 11 patients (10%) were death ($n = 3$), no answer/lost ($n = 6$), and noneligibility because of uncompleted RT ($n = 2$). By the end of the follow-up period (assessment 2) in May 2001, a total of 93 patients (84%) were eligible for analysis; 5 patients had died and 2 were lost to follow-up. Of these 93 patients, 13 (14%) had treatment failure: 5 (5%) were diagnosed with bone metastasis and 8 (9%) had PSA failure according to the American Society for Therapeutic Radiology Oncology criteria (20). Thus, 80 patients were free of recurrence at the end of the follow-up period (assessment 2).

Pretreatment investigation and primary treatment techniques

Patients with World Health Organization Grade 1 or 2 (maximal Gleason score 3 + 4) tumors and a PSA level $<$10 ng/mL were considered to be nonmetastatic with localized disease and, with reference to the Partin tables (21, 22), no additional measures were taken. Patients with World Health Organization Grade 3 (Gleason score 4 + 3 and greater) tumors or PSA level $>$10 ng/mL underwent iliac lymph node dissection and bone scanning to exclude disease spread. All patients received neoadjuvant androgen deprivation (NAAD) for at least 3 months before RT (mean total treatment period 7 months, range 3–13) with total androgen blockade, including a luteinizing hormone-releasing hormone agonist and an antiandrogen to reduce the tumor volume and increase radiosensitivity (23). Hormonal deprivation therapy was stopped at the end of RT.

The patients were treated with pelvic EBRT using three-dimensional conformal RT and a four-field technique to deliver a total of 50 Gy in 2-Gy fractions to the prostate and seminal vesicles. A margin of 2 cm was used to create the EBRT planning target volume, with the exception of the posterior (rectal) margin, which was limited to 1.5 cm. This treatment was split in half and combined with brachytherapy using an iridium source delivering HDR RT, 20 Gy in two fractions with a 10-day interval between treatments. Pretreatment dosimetry was performed using an ultrasound-based treatment planning system. The brachytherapy clini-
cal target volume included the entire prostate gland, excluding the seminal vesicles. A margin of 3 mm was used to create the brachytherapy planning target volume. The HDR source was temporarily implanted using 10–20 needles inserted transperineally by a remote afterloading device with transrectal ultrasound guidance. The entire prostate gland was included in the clinical target volume.

The expected acute (1–3 months) radiation effects included urinary symptoms such as frequency, nocturia, and dysuria and rectal symptoms such as diarrhea. The expected long-term (6–12 months) radiation effects included bowel urgency and bleeding and irritative urinary symptoms.

Data collection
The data collection procedure is presented in Fig. 1. In October 1999, all patients were mailed an invitation to participate in the study (assessment 1). They were asked to complete two HRQOL questionnaires, the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ) C30 and prostate-specific 25-item questionnaire (PR25) (Swedish translation). The forms were returned by mail in a prepaid envelope. Patients not responding within 4 weeks received a reminder.

This procedure was repeated in May 2001 with all patients (assessment 2). In summary, the time from RT completion to assessment 1 varied between 1 and 18 months and the interval between assessments was 18 months. Because of the expected differences in symptom profiles, the study sample was divided into two groups. Group 1 included patients who finished RT during the 6 months preceding assessment 1 (0–6 months). Group 2 comprised those treated 6–18 months before assessment 1. These groups were almost equal in size. The reasons for choosing 6 months as the division point were the clinically expected subsidence of acute radiation effects (11, 24) and late hormonal effects caused by neoadjuvant treatment (25).

Instruments
To investigate and evaluate the material, the EORTC questionnaires QLQ-C30 and PR25 were used to for comparison with a normative sample of the Swedish population established by Michelson et al. (26).

The EORTC QLQ-C30 is a questionnaire developed by the EORTC (Quality of Life Study Group) for the measurement of quality of life in cancer patients in clinical trials (27, 28). It explores the following functional areas: physical, role, emotional, cognitive, and social function, as well as global health status. It also includes a number of multi-item scales and single items that assess a range of physical symptoms (fatigue, nausea and vomiting, pain, dyspnea, sleep disturbance, loss of appetite, constipation, and diarrhea), as well as financial difficulties. Each item is scored from 1 to 4 (1, “Not at all”; 2 “A little”; 3, “Quite a bit”; and 4, “Very much”), with the exception of items in the global quality-of-life scale, which range from 1 (“Very poor”) to 7 (“Excellent”). The prostate-specific module EORTC QLQ-PR25, developed by the EORTC Genito-Urinary Tract Cancer Cooperative Group, is a 25-item questionnaire designed for use among patients with localized and metastatic prostate cancer. It was developed within the framework of the EORTC Quality of Life Group according to the rigorous guidelines for module development (29). It includes subscales assessing urinary symptoms (nine items), bowel symptoms (four items), treatment-related symptoms (six items), and sexual function (six items). This questionnaire is presently being validated in an international study (30).

Normative sample
Michelson et al. (26) investigated about 3000 people from a random sample of the Swedish population aged
The aims of their study were to provide normative data on the questionnaire and to investigate differences in HRQOL with respect to age, gender, sociodemographic characteristics, and reported chronic health problems. In the present study, the male normative data were used.

**Statistical analysis**

The raw scores of the QLQ-C30 and PR25 were transformed into a 100-point scale. For the functional scales, the computed scores ranged from 0 to 100, with the higher scores representing a higher level of functioning. For the item scales relative to physical symptoms and financial impact, higher scores represent a higher level of symptoms or problems.

Analyses of variance and repeated measurements were used to evaluate the impact of time and between group differences, as well as interactions between these variables. The analyses were performed as follows: (1) between groups (Group 1 vs. Group 2, regardless of assessment); (2) between assessments (entire study sample compared over time); (3) regarding interaction (Group 1 vs. Group 2 trends compared over time); and (4) between assessment 2 and normative data (entire study sample).

*p* < 0.05 was considered to be statistically significant. Comparisons between the treatment group and normative data were made using the *t* test.

To answer prostate symptom-specific questions, items from the EORTC PR25 were selected to represent symptoms as follows: urinary urgency (question 33), urinary...

---

### Table 1. Patient characteristics at radiotherapy

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Free of recurrence</th>
<th>Treatment failure</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (n)</td>
<td>80</td>
<td>13</td>
<td>93</td>
</tr>
<tr>
<td>Age (y)</td>
<td>Median</td>
<td>68</td>
<td>67</td>
</tr>
<tr>
<td>Range</td>
<td>46–79</td>
<td>58–74</td>
<td>46–79</td>
</tr>
<tr>
<td>Clinical stage* (%)</td>
<td>T1</td>
<td>10</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>T2</td>
<td>40</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>T2–T3</td>
<td>10</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>T3</td>
<td>40</td>
<td>69</td>
</tr>
<tr>
<td>WHO grade (%)</td>
<td>1</td>
<td>36</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>50</td>
<td>61</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>14</td>
<td>31</td>
</tr>
<tr>
<td>PSA (ng/mL)</td>
<td>Median</td>
<td>12.8</td>
<td>18.9</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>2–214</td>
<td>6.5–54</td>
</tr>
<tr>
<td>Patients with PSA</td>
<td>Level (%)</td>
<td>&lt;4 ng/mL</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>4–10 ng/mL</td>
<td>31</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td>11–20 ng/mL</td>
<td>34</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td>20–50 ng/mL</td>
<td>25</td>
<td>38</td>
</tr>
<tr>
<td></td>
<td>&gt;50 ng/mL</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>Neoadjuvant hormonal</td>
<td>therapy (mo)</td>
<td>Mean</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>3–13</td>
<td>5–10</td>
</tr>
</tbody>
</table>

**Abbreviations:** WHO = World Health Organization; PSA = prostate-specific antigen.

* International Union Against Cancer.

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### Table 2. HRQOL (EORTC QLQ-C30) in patients free of recurrence (n = 80)

<table>
<thead>
<tr>
<th>Item</th>
<th>Patients* (n)</th>
<th>Group 1†</th>
<th>Group 2‡</th>
<th>Normal data</th>
</tr>
</thead>
<tbody>
<tr>
<td>GH</td>
<td>37–38/41–42</td>
<td>72.4 (19.3)</td>
<td>77.7 (15.5)</td>
<td>67.5 (21.1)</td>
</tr>
<tr>
<td>PF</td>
<td>38–38/39–41</td>
<td>87.7 (16.3)</td>
<td>91.6 (12.5)</td>
<td>91.8 (12.6)</td>
</tr>
<tr>
<td>RT</td>
<td>38–38/40–41</td>
<td>82.5 (24.2)</td>
<td>92.1 (14.4)</td>
<td>87.1 (19.8)</td>
</tr>
<tr>
<td>EF</td>
<td>36–38/39–39</td>
<td>85.5 (17.0)</td>
<td>90.5 (13.7)</td>
<td>82.7 (23.2)</td>
</tr>
<tr>
<td>SF</td>
<td>37–38/39–41</td>
<td>74.1 (24.1)</td>
<td>82.9 (21.7)</td>
<td>79.6 (22.5)</td>
</tr>
<tr>
<td>FA</td>
<td>37–38/39–41</td>
<td>25.7 (20.2)</td>
<td>16.8 (16.7)</td>
<td>19.9 (19.6)</td>
</tr>
<tr>
<td>PA</td>
<td>37–38/39–41</td>
<td>16.7 (23.6)</td>
<td>9.0 (16.5)</td>
<td>17.1 (25.5)</td>
</tr>
<tr>
<td>SL</td>
<td>37–38/39–41</td>
<td>27.2 (26.7)</td>
<td>13.5 (21.5)</td>
<td>27.6 (27.8)</td>
</tr>
<tr>
<td>CO</td>
<td>37–38/39–41</td>
<td>14.9 (27.6)</td>
<td>7.2 (16.0)</td>
<td>5.7 (14.7)</td>
</tr>
<tr>
<td>DI</td>
<td>37–38/40–41</td>
<td>18.4 (26.5)</td>
<td>9.0 (15.0)</td>
<td>27.5 (27.1)</td>
</tr>
</tbody>
</table>

Abbreviations: HRQOL = health-related quality of life; EORTC = European Organization for Research and Treatment of Cancer; QLQ-C30 = Quality of Life Questionnaire-C30; AP = assessment point (1, October/November 1999; 2, May/June 2001); GH = global health; PF = physical function; RF = role function; EF = emotional function; SF = social function; FA = fatigue; PA = pain; SD = sleep disorder; CO = constipation; DI = diarrhea; RT = radiotherapy.

Data presented as mean value, with standard deviation in parentheses, unless otherwise noted.

Significance assessment: All calculations based on HRQOL EORTC QLQ-C30 scoring.

* Patients responding to item, group 1 (AP 1–AP 2)/2 (AP 1–AP 2).
† Patients who finished RT < 6 mo before assessment 1.
‡ Patients who finished RT ≥ 6 mo before assessment 1.
§ Statistically significant difference regarding interaction (p < 0.05).
¶ Statistically significant difference between AP 2 and normative data (p < 0.05).
# Statistically significant difference between APs (p < 0.05).
* Statistically significant difference between groups (p < 0.05).
incontinence (question 36), nocturia (question 32), fecal incontinence (question 41), fecal blood (question 42), hot flushes (question 44), breast tenderness (question 45), erectile problems (question 53), sexual interest (question 50).

Scores were computed and statistical analyses performed in the same way as described above. To highlight the magnitude of the problems, the percentage of patients responding in each of the response categories to these items were calculated (see Tables 3 and 5).

**RESULTS**

**Patient characteristics**

The main clinical patient characteristics (without or with recurrent disease) are listed in Table 1. The median patient age was 68 years (range, 46–79 years). Of the 93 patients, 45% presented with clinical Stage T1-T2 and 84% with World Health Organization Grade 1-2 tumors (Gleason score 1–7). The median pretreatment PSA level was 14.0 ng/mL (range, 2.0–214), with 36% of patients having <10 ng/mL and 68% <20 ng/mL. The mean length of neoadjuvant hormonal treatment was 7 months (range, 3–13 months).

**HRQOL questionnaire results**

The results for patients free of recurrence are presented in Tables 2 and 3. The data for patients with recurrent disease are shown in Tables 4 and 5. Statistical analyses were only performed for the data from disease-free patients (n = 80), because the patients with treatment failure constituted such a small fraction (n = 13). Thus, unless otherwise specified, the analyses concern the disease-free patient cohort.

The HRQOL EORTC QLQ-C30 comparison between assessment 1 and 2 (Table 2) revealed no statistically significant changes in the five functional areas over time. In the physical symptoms, pain (p = 0.009), sleep disturbance (p = 0.0006), and diarrhea (p = 0.006) decreased significantly from the first to the second assessment.

The HRQOL EORTC QLQ-C30 comparisons between

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Patients* (n)</th>
<th>Group 1 (%)</th>
<th>Group 2 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urgency</td>
<td>37–37/37–40</td>
<td>30 35 19 16</td>
<td>46 19 27 8</td>
</tr>
<tr>
<td>Urinary incontinence</td>
<td>38–38/38–41</td>
<td>87 8 5 0</td>
<td>66 31 3 0</td>
</tr>
<tr>
<td>Nocturia</td>
<td>37–38/39–40</td>
<td>11 43 41 5</td>
<td>34 48 13 5</td>
</tr>
<tr>
<td>Fecal incontinence</td>
<td>17–27/26–28</td>
<td>71 29 0 0</td>
<td>81 15 4 0</td>
</tr>
<tr>
<td>Fecal blood</td>
<td>17–28/26–30</td>
<td>94 6 0 0</td>
<td>75 21 4 0</td>
</tr>
<tr>
<td>Hot flushes</td>
<td>17–28/26–30</td>
<td>41 24 23 12</td>
<td>82 7 11 0</td>
</tr>
<tr>
<td>Breast tenderness</td>
<td>17–27/26–30</td>
<td>65 18 17 0</td>
<td>74 15 11 0</td>
</tr>
<tr>
<td>Erectile problems</td>
<td>13–19/16–22</td>
<td>8 31 23 38</td>
<td>16 37 21 26</td>
</tr>
<tr>
<td>Sexual interest</td>
<td>36–37/37–37</td>
<td>57 27 11 5</td>
<td>19 47 20 14</td>
</tr>
</tbody>
</table>

Abbreviations as in Table 2.

* Symptom severity scored from 1 to 4, with 1 = “Not at all”; 2 = “A little”; 3 = “Quite a bit”; 4 = “Very much.”

1 Patients responding to item, group 1 (AP 1-AP 2)/2 (AP 1-AP 2).

2 Patients who finished RT < 6 mo before AP 1.

3 Patients who finished RT ≥ 6 mo before AP 1.

![Table 3. Frequency of symptom severity* (EORTC QLQ-PR25) in patients free of recurrence (n = 80)](data:image/png;base64,iVBORw0KGgoAAAANSUhEUgAAAgAAAAAHCAYAAABOqaHbAAAABGdBTUEAAK/INw5oaAAACmUlEQVR42mP8X1IAwIRAwQ8AfA+W5gAAAABJRU5ErkJggg==)

<table>
<thead>
<tr>
<th>Item</th>
<th>Patients*</th>
<th>AP 1</th>
<th>AP 2</th>
<th>Normative data</th>
</tr>
</thead>
<tbody>
<tr>
<td>GH</td>
<td>12/13</td>
<td>73.1 (21.0)</td>
<td>76.9 (23.9)</td>
<td>77.1 (0.5)</td>
</tr>
<tr>
<td>PF</td>
<td>12/13</td>
<td>88.7 (17.1)</td>
<td>89.7 (16.2)</td>
<td>87.6 (3.1)</td>
</tr>
<tr>
<td>RF</td>
<td>12/13</td>
<td>88.9 (22.8)</td>
<td>91.0 (17.5)</td>
<td>86.3 (1.7)</td>
</tr>
<tr>
<td>EF</td>
<td>12/13</td>
<td>74.4 (27.7)</td>
<td>77.6 (25.1)</td>
<td>86.1 (1.2)</td>
</tr>
<tr>
<td>SF</td>
<td>12/13</td>
<td>76.9 (25.0)</td>
<td>78.2 (30.0)</td>
<td>90.3 (0.6)</td>
</tr>
<tr>
<td>FA</td>
<td>13/13</td>
<td>23.1 (21.5)</td>
<td>15.4 (17.3)</td>
<td>19.4 (1.5)</td>
</tr>
<tr>
<td>PA</td>
<td>13/13</td>
<td>23.1 (30.8)</td>
<td>12.8 (20.6)</td>
<td>18.2 (0.5)</td>
</tr>
<tr>
<td>SL</td>
<td>13/13</td>
<td>28.2 (32.9)</td>
<td>25.6 (30.9)</td>
<td>15.4 (1.8)</td>
</tr>
<tr>
<td>CO</td>
<td>13/13</td>
<td>10.3 (21.0)</td>
<td>10.3 (16.0)</td>
<td>4.1 (1.3)</td>
</tr>
<tr>
<td>DI</td>
<td>13/13</td>
<td>10.3 (16.0)</td>
<td>10.3 (16.0)</td>
<td>4.7 (0.4)</td>
</tr>
</tbody>
</table>

Abbreviations as in Table 2.

Data presented as mean value, with standard deviation in parentheses.

4 Patients responding to item, AP 1/AP 2.
treatment Groups 1 and 2 (Table 2) revealed diarrhea as the only variable showing differences between the two groups, with greater levels of problems reported among patients in Group 2, who had received RT 6–18 months before the first assessment. When assessing the group differences over time, statistically significant interactions were obtained for several functional areas (physical function, \( p < 0.02 \); role function, \( p < 0.01 \); and social function, \( p < 0.04 \)), with increasing function in Group 1 and decreasing in Group 2. The opposite statistically significant trend was seen for fatigue (\( p < 0.02 \)), with decreasing values in Group 1 and the value remaining the same for Group 2.

The HRQOL EORTC QLQ-C30 comparisons between assessment 2 and the normative values (Table 2) revealed that the long-term HRQOL in patients with prostate cancer was in large part comparable to the normative values. Few statistically significant differences relative to normative values were seen. However, physical function was significantly better statistically among patients (\( p < 0.01 \)) than in the normative sample. The opposite was found for social function (\( p < 0.005 \)). Among physical symptoms, pain was significantly less pronounced statistically among the patients (\( p = 0.0008 \)), and diarrhea was significantly more pronounced statistically (\( p = 0.0002 \)).

The results of the HRQOL EORTC QLQ-C30 comparison concerning disease- and treatment-related problems including the frequencies of single item symptom severity are presented in Table 3. Statistically significant changes between assessments in the mean scores (not presented) were seen regarding urinary incontinence (increasing, \( p = 0.04 \)), nocturia (decreasing, \( p = 0.0005 \)), hot flushes (decreasing, \( p = 0.001 \)), and sexual interest (increasing, \( p = 0.0001 \)).

Statistically significant group differences were observed for rectal bleeding, which was more frequent in Group 2 (\( p = 0.02 \)), and hot flushes, which were less frequent in Group 2 (\( p = 0.02 \)). A statistically significant interaction for sexual interest was evident (increasing with time in Group 1 and mainly stable in Group 2, \( p = 0.007 \)). No normative values were available for comparison.

**HRQOL (EORTC QLQ-C30 and PR25) in patients with treatment failure**

Data concerning the 13 patients with treatment failure are presented in Tables 4 and 5 to give a picture of the problems perceived by the patients with treatment failure.

**DISCUSSION**

In this prospective study, we sought to describe the long-term HRQOL outcome and disease- and treatment-related problems over time in patients diagnosed with localized prostate cancer and treated with NAAD and combination RT, including EBRT and iridium HDR brachytherapy. In addition, this information was compared with normative age-matched HRQOL data for the male Swedish population.

We obtained a fairly high response rate to the questionnaires. However, the response rate of the erectile dysfunction part was lower, possibly because some patients did not feel comfortable discussing this matter.

The reasons for removing the 13 patients with recurrent disease from the main analysis and considering them separately were several. First, they could have been informed of their recurrence and thus might have been reacting negatively in terms of HRQOL. Furthermore, the tumor burden and salvage hormonal therapy could have given them tumor- and treatment-related symptoms different from the symptoms found in the relapse-free men. Because of the low numbers, no statistical analysis was performed in this group. However, taking the small number of patients into account, several interesting, although nonstatistically significant, trends were noted. The levels of emotional function seemed to be lower and pain and sleep disorder scores greater in this group compared with those from the disease-free patients. Diarrhea and rectal bleeding seemed to be less pronounced and hot flushes to be persisting. Sexual problems appeared

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Table 5. Frequency of symptom severity* (EORTC QLQ-PR25) in patients with treatment failure (n = 13)

<table>
<thead>
<tr>
<th>Symptom</th>
<th>AP 1 (%)</th>
<th>AP 2 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 2 3 4</td>
<td>1 2 3 4</td>
</tr>
<tr>
<td>Urgency</td>
<td>12/12</td>
<td>17 67 16 0</td>
</tr>
<tr>
<td>Urinary incontinence</td>
<td>13/13</td>
<td>69 23 8 0</td>
</tr>
<tr>
<td>Nocturia</td>
<td>12/12</td>
<td>17 50 33 0</td>
</tr>
<tr>
<td>Fecal incontinence</td>
<td>7/11</td>
<td>71 29 0 0</td>
</tr>
<tr>
<td>Rectal bleeding</td>
<td>7/11</td>
<td>100 0 0 0</td>
</tr>
<tr>
<td>Hot flushes</td>
<td>7/11</td>
<td>57 43 0 0</td>
</tr>
<tr>
<td>Breast tenderness</td>
<td>7/12</td>
<td>57 29 14 0</td>
</tr>
<tr>
<td>Erectile dysfunction</td>
<td>6/8</td>
<td>18 67 0 17</td>
</tr>
<tr>
<td>Sexual interest</td>
<td>11/13</td>
<td>25 33 33 9</td>
</tr>
</tbody>
</table>

Abbreviations as in Table 2.  
* Symptom severity scored from 1 to 4, with 1 = “Not at all”; 2 = “A little”; 3 = “Quite a bit”; 4 = “Very much.”  
† Patients responding to item, AP 1/AP 2.
to increase with time. Many of these differences could probably be referred to the effects of salvage hormonal therapy and also to the emotional burden of having recurrent disease.

The choice of assessments requires comment. Our aim was to assess the HRQOL in all patients treated with combination RT, including brachytherapy, from the very start of this therapy modality at Radiumhemmet in 1998. Because the time from treatment ranged from 0 to 18 months, we asked the patients to respond to both questionnaires twice at assessment 1, first to recall their HRQOL at the start of treatment and the second to determine their HRQOL in the (then) present situation. Analysis of the first questionnaire (the estimated HRQOL before treatment), however, showed statistically significant differences between groups and appeared to be dependent on memory factors and affected by recall bias. Furthermore, judging from the answers, we also suspected a misinterpretation of the statement “before treatment” to include the NAAD period, resulting in false baseline symptom information. We, therefore, decided to refrain from using these data and, instead, to perform comparisons against normative data.

Assessment 2, 18 months after assessment 1, was chosen to evaluate patients’ HRQOL after the effects of acute RT and hormonal therapy had ceased and seemed appropriate with respect to effective data collection.

To detect differences related to acute radiation effects and persisting testosterone castrate levels, we analyzed the material in subgroups (assessment 1: Group 1, <6 months after treatment and Group 2, 6–18 months after treatment). In Group 1, for several functioning areas, statistically significant improvement was seen over time (physical function, role function, and social function). Symptoms such as fatigue, hot flushes, and sexual interest exhibited the same pattern; however, diarrhea and rectal bleeding were consistently significantly more severe in Group 2. Our interpretation of these differences was that patients in Group 1 at assessment 1 were still suffering from acute radiation effects and, in addition, most certainly, late hormonal effects. The changes in Group 2 over time were generally less marked, indicating that the acute radiation and hormonal treatment effects could have subsided. Speaking against this was the substantial decrease in hot flushes that occurred in Group 2, possibly indicating the known presence in some patients of hormonal castration effects even in the 6–18 months after treatment. The late bowel problems described mainly by patients in Group 2 corresponded well with late radiation effects. Why this phenomenon was not observed after 18 months in Group 1 is unknown. It could have been a result of the learning curve, such as improved dose planning and increased knowledge of the implantation technique after having treated the Group 2 patients, which would presumably affect late radiation toxicity.

We found, in agreement with earlier studies (15–18), that the levels of HRQOL were high in disease-free patients on the functioning subscales, did not change significantly with time, and were comparable with the normative data. However, two exceptions were found: patients scored greater on physical function but lower on social function.

Symptom development in urinary, bowel, and sexual function has been reported differently in earlier patient-reported HRQOL brachytherapy studies for localized prostate cancer. In cross-sectional surveys with permanent implant techniques with or without EBRT and NAAD and in comparison with prostatectomy patients, Brandeis et al. (15) found diminishing symptoms with time (3–17 months) solely in the brachytherapy patients. In contrast, Wei et al. (16) found that long-term symptoms (1–4 years) proved to be significantly worse than those in prostatectomy patients. Both studies concluded that adding EBRT seemed to impair disease-specific HRQOL compared with brachytherapy alone, although Wei et al. (16) found adverse HRQOL domain outcomes in pure brachytherapy patients as well (160 Gy 125I implants). However, that dose was far greater than the 144 Gy 125I or 115 Gy 103Pd implants given in the study by Brandeis et al. (15), which could explain the difference in HRQOL outcome. Furthermore, the studies reported results from different periods after therapy, making the interpretation more difficult. HRQOL restitution after 3 months was reported by Lee et al. (17). Their study, however, was small and the follow-up short.

The two published studies covering HRQOL in patients treated with combination RT and transperineal iridium brachytherapy also reported different findings. Joly et al. (18) assessed long-term HRQOL in patients treated mainly with an iridium LDR technique combined with EBRT. EBRT was delivered at 43.2 Gy to the pelvis in 4.5 weeks and 18 fractions, and the brachytherapy boost delivered 15 Gy to the prostate volume using four temporary iridium implants, mainly with a LDR technique (6–12 Gy within 12 h). Major problems that persisted ≥4 years after treatment included sexual disorders, urinary incontinence, and cystitis. Short-term toxicity and HRQOL (<1 year) was described prospectively by Egawa et al. (19). They treated 38 patients with a HDR technique and EBRT, starting with 4 Gy × five (20 Gy in 5 fractions) Ir HDR to the prostate during 3 days followed by EBRT at 30 Gy in 10 fractions to the prostate and seminal vesicles with a margin of 0.5 cm to create the planning target volume. General HRQOL and urinary symptoms worsened significantly during the first month but had recovered at 12 months. Physician-assessed Radiation Therapy Oncology Group scores failed to detect these changes, underlining the importance of patient-reported quality-of-life investigations. The study by Joly et al. (18) described a very different treatment technique with larger EBRT fields, a different fractionation schedule, and a LDR brachytherapy technique, making it difficult to compare their results with ours. The substantial short-term adverse HRQOL described by Egawa et al. (19) could very well have been related to the expected high level of acute toxicity with 3-Gy fractions.

In our study, problems with pain, sleep disorders, and diarrhea, as well as nocturia and hot flushes, decreased over time, and urinary incontinence and sexual interest increased.
At assessment 2, >18 months after treatment, the patients had fewer problems with pain but more problems with diarrhea than the male population in general. The difference in physical function seen over time could very well have been associated with regained testosterone levels, and the problems with social function were probably related to persisting side effects of treatment (i.e., loss of urine and bowel control, as well as sexual dysfunction, reducing male self-esteem).

The symptom reduction observed over time correlated well with the diminishing side effects of the treatment, with pain, diarrhea, and nocturia presumably dependent on radiation effects, sleep disorder on treatment-related anxiety, and hot flushes on regained hormonal function. Likewise, the increase in urinary incontinence was probably related to radiation effects and the improvement in sexual interest to hormonal effects. Improvement in erectile dysfunction, however, did not occur with increased testosterone levels. One explanation could be that few patients responded to this item; however, this symptom is frequently associated with late radiation effects, especially when the penile bulb has been included in the treatment field (31). Thus, this is an area in which pharmaceutical intervention or radiation techniques with different dose distribution could be tested.

The comparison with normative data showed, not surprisingly, that, except for social function and diarrhea, patients do well after HDR brachytherapy—sometimes even better than the normal male population. At assessment 2, it appeared as if Group 1 constantly exhibited better HRQOL than Group 2, which tended to approach the normative values. It might be that a plateau of maximal HRQOL is reached 18 months after therapy and thereafter equals to normative values. This could be an effect of the more bothersome HRQOL just after therapy and that HRQOL after 18 months is characterized by symptom relief and confidence in the future.

CONCLUSION

The results of the present study showed that HRQOL and symptom development in the disease-free cohort after combination RT, including iridium HDR brachytherapy, corresponds well with the known physiologic and psychological side effects of RT and NAAD and appears to be comparable with normative values after 18–36 months. We found indications of persisting castrate levels of testosterone >6 months after completion of RT and NAAD. This phenomenon has also been reported in the literature (25). Thus, combination RT does not appear to impair long-term HRQOL and, in this respect, comparable to other brachytherapy methods for localized prostate cancer. Information concerning very short-term HRQOL was not available in this study.

Additional research must determine long-term HRQOL status (3–5 years) and relate it to normative data. The optimal length and use of NAAD according to risk factors must also be established. To reduce the effects of RT, interventional randomized studies should be performed. Such studies could, in a randomized fashion, test the use of adjuvant medical or mechanical treatment for erectile dysfunction or protective medical measures to spare the urethral or rectal mucosa during NAAD and RT. With the support of techniques and planning improvements and the development of methods for estimating individual radiosensitivity in the clinical setting, this would most certainly affect the HRQOL outcome after RT for prostate cancer.

REFERENCES


Combined curative radiotherapy including HDR brachytherapy and androgen deprivation in localized prostate cancer: A prospective assessment of acute and late treatment toxicity

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1Department of Oncology/Pathology, Karolinska University Hospital and Institute, Stockholm, Sweden, 2Department of Oncology, Sahlgrenska Hospital and Academy, University of Gothenburg, Sweden

Abstract
Self-reported symptoms including urinary, bowel and sexual side effects were investigated prospectively at multiple assessment points before and after combined radiotherapy of prostate cancer including HDR brachytherapy and neoadjuvant androgen deprivation therapy. Between April 2000 and June 2003, patients with predominantly advanced localized prostate tumours subjected to this treatment were asked before treatment and on follow-up visits to complete a questionnaire covering urinary, bowel and sexual problems. The mainly descriptive analyses included 525 patients, responding to at least one questionnaire before or during the period 2–34 months after radiotherapy. Adding androgen deprivation before radiotherapy significantly worsened sexual function. During radiotherapy, urinary, bowel and sexual problems increased and were reported at higher levels up to 34 months, although there seemed to be a general tendency to less pronounced irritative bowel and urinary tract symptoms over time. No side effects requiring surgery were reported. Classic late irradiation effects such as mucosal bleeding were demonstrated mainly during the second year after therapy, but appear less pronounced in comparison with dose escalated EBRT series. In conclusion, despite the high radiation dose given, the toxicity seemed comparable with that of other series but long term (5–10 years) symptom outcome has to be determined.

Introduction
Prostate adenocarcinoma, with an annual incidence of 8000 cases, is a rapidly increasing malignancy in Sweden. This is probably due to earlier detection leading to an increasing number of small localized tumours. The question of best treatment for localized disease is debated. In many cases watchful waiting will be the most appropriate measure, but a recent study from Sweden advocates for more aggressive therapy to patients below the age of sixty years [1].

The curative potential of radiotherapy in prostate cancer is generally accepted, and no convincing difference to surgery, regarding disease free survival, has been shown [2,3]. Thus, quality of life factors play an important role in treatment decisions. Radical prostatectomy has been associated with high rates of erectile dysfunction, urinary incontinence and urethral strictures [4,5]. External radiotherapy, on the other hand, causes more bowel symptoms, such as proctitis and rectal ulcers, and radiation induced late effects to the bladder and urethra are also seen (6).

Adding high dose rate (HDR) brachytherapy (BT) as a boost to external beam radiotherapy (EBRT) has been widely practised [7–14], delivering a limited irradiation dose to critical tissues such as the rectum. In Sweden, a technique using temporary transperineally implanted iridium 192 sources was introduced at University Hospital Sahlgrenska, Gothenburg, in 1988, and this treatment has encouraging long term results [15]. At the department of Oncology, Radiumhemmet, Karolinska University Hospital, we have been treating patients since 1998 with EBRT + HDR BT boost for localized prostate cancer. The absence of nationwide PSA screening programmes in Sweden and
the possibility to treat more advanced stages (i.e. stage T3-tumours not involving the seminal vesicles) using this technique, has led to a predominance of stage T2–T3 tumours in the treated material as opposed to American materials where less advanced stages are more common [12,16–18].

Acute and long-term toxicity data on treatment with EBRT combined with HDR BT boost have been presented in several studies [10,12,13,15,19–22], mostly using the RTOG/EORTC scoring scheme [23], where the assessment has been made by the physician. Generally, low levels of acute and long-term toxicities have been reported, which has been considered to be acceptable. However, no prospective self-reported data is available.

In this descriptive study we present patient-reported urinary, bowel and sexual problems at seven points of assessment during a period from before radiotherapy until 34 months after combined treatment with EBRT, HDR BT and neoadjuvant androgen deprivation (AD) therapy for localized prostate cancer. In order to assess the symptomatic impact of irradiation and hormonal treatment, results at baseline (before treatment) with or without AD are described separately.

Material and methods

Patients

Between April 2000 and June 2003, consecutive patients with localized prostate cancer (T1–T3aN0M0), treated or in line for treatment at the department of Oncology, Radiumhemmet, with a combination of EBRT and HDR BT boost including neoadjuvant/concurrent AD therapy, were asked to complete questionnaires. Points of assessment were before treatment and at follow-up visits after completion of therapy at 2 months, 4 months and every 6 months thereafter up to three years. Baseline questionnaires were filled in by patients on the first visit at the clinic or after treatment for a couple of months with AD therapy when seeing a nurse for further treatment information. The total number of patients subjected to combined radiotherapy at our department from June 1998 to June 2003 was 740 [another 130 were in June 2003 accepted for treatment later during 2003]. Of these patients 264 were followed up at other institutions. This group contributed a few questionnaires before therapy but was not offered participation after completion of therapy. Treatment and follow-up related information is presented in detail in Table I.

Pretreatment investigation and primary treatment techniques

Pretreatment investigation included a prostate specific antigen (PSA) and transrectal ultrasound with fine needle aspiration cytology (before year 2000) or core biopsies (after year 2000). T-stage was determined by digital rectal examination and classified according to the UICC (International union against cancer). Patients having a PSA <20 and a WHO (World Health Organization) grade 1 or 2 or Gleason score 3 + 4 = 7 tumour were considered to be non-metastatic with localized disease [24]. Patients with high risk WHO grade 3 (Gleason score 4 + 3 = 7 and higher) tumours or a PSA value of more than 20 underwent iliac lymph node dissection and a bone scan in order to exclude spread of the disease. All patients received neoadjuvant/concurrent AD treatment during 3–9 months before radiotherapy with a total androgen blockade (TAB) including a LHRH agonist and an antiandrogen in order to reduce the tumour volume and increase the radiosensitivity [25]. The AD therapy was stopped at the end of radiotherapy.

The irradiation technique used has been described earlier, brachytherapy by Bertermann & Brix [7] and EBRT by Borghede and Lennernäs [8,26]. Treatment is given according to Figure 1, combining EBRT and HDR BT. The external beam pelvic irradiation is given using 3D conformal radiotherapy and a 4-field technique, delivering a total of 50 Gy in 2 Gy fractions to the prostate and seminal vesicles. A margin of 2 cm is used to create the external beam PTV, with the exception of the posterior (rectal) margin, which is limited to 1.5 cm. This treatment is boosted with brachytherapy using an iridium 192 source delivering high dose rate irradiation, 20 Gy in 2 fractions with a 2-week interval between treatments. Pretreatment dosimetry is performed using an ultrasound based treatment planning system. The brachytherapy CTV includes the entire prostate gland, excluding the seminal vesicles. A margin of 3 mm is used to create the brachytherapy PTV. Through ten to twenty needles inserted transperineally and guided by transrectal ultrasound, the HDR source is temporarily implanted by a remote afterloading device. The total dose converted to standard 2 Gy fractions of the combined treatment, assuming an α/β ratio of 1.5 according to the data of Brenner & Hall [27], will reach 116 Gy.

Instruments

The purpose of the present study was to prospectively collect data on urinary tract, bowel and sexual problems. When the study was launched, no standardized validated and reliability tested self-report...
A questionnaire with six items evaluating our questionnaire was given to the first 100 patients. They were asked to assess the following: Should an item be deleted or added? Was any item difficult to understand? Was it difficult or bothersome to complete the questionnaire? What is your opinion of this kind of questions? A majority found the questionnaire items both easy to answer and relevant.

**Statistical methods**

Data is mainly presented descriptively. Since some patients filled in several questionnaires, each assessment point represents a mixture of dependent and independent observations. Therefore it was impossible to reliably test for differences between observations after radiotherapy. However, at baseline a chi-square ($\chi^2$) assessment was performed regarding prevalence of reported urinary, bowel and sexual side effects and specific sexual problems. This analysis compares the distribution of response categories in patients receiving or not yet receiving AD therapy (independent observations).

For statistical purposes, when analyzing the specific questions in each part not completed by patients having stated “no problems” for the part in question, values corresponding to this response were inserted, i.e. “never” or “always”.

The category “months after radiotherapy” was calculated as the difference in months between the date of questionnaire completion and the last day of EBRT/\(\{2\}) weeks at 2 months, \(+/-\) 4 weeks at 4 months and \(+/-\) 2 months at 10 months and every 6 months thereafter.

**Results**

**Patient characteristics**

A total of 529 out of 870 patients participated in the study, each completing one or more questionnaires
on their visits at the clinic. Four patients were excluded from analysis due to multiple malignancies and another 26 patients had treatment failure during the study period. In order to avoid symptom bias associated with a recurrence, questionnaires completed after diagnosis of the recurrence were withdrawn from analysis. Thus 525 patients contributed at least one questionnaire and were included in the analyses, yielding a participation rate of 60%. The total amount of questionnaires analyzed was 963.

<table>
<thead>
<tr>
<th>Table II. Categories for symptoms analyzed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptom item (no)</td>
</tr>
<tr>
<td>-------------------</td>
</tr>
<tr>
<td>Dysuria (A2)</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Urinary frequency (A5)</td>
</tr>
<tr>
<td>Micturition interval?</td>
</tr>
<tr>
<td>Hematuria (A8)</td>
</tr>
<tr>
<td>Blood in the urine?</td>
</tr>
<tr>
<td>Urinary incontinence (A10)</td>
</tr>
<tr>
<td>Bowel urgency (B2)</td>
</tr>
<tr>
<td>How often?</td>
</tr>
<tr>
<td>Stool frequency (B3)</td>
</tr>
<tr>
<td>How many times/day?</td>
</tr>
<tr>
<td>Rectal pain (B5)</td>
</tr>
<tr>
<td>How often?</td>
</tr>
<tr>
<td>Rectal bleeding (B8)</td>
</tr>
<tr>
<td>Sexual desire (C2)</td>
</tr>
<tr>
<td>How much?</td>
</tr>
<tr>
<td>Erectile function (C3)</td>
</tr>
<tr>
<td>Sexual satisfaction (C6)</td>
</tr>
<tr>
<td>How often?</td>
</tr>
</tbody>
</table>

"Do you have urinary/bowel/sexual symptoms?" is presented in Table V. At baseline 19% of the patients not yet on AD reported urinary tract problems, 14% bowel problems and 35% sexual problems. Corresponding figures for patients on AD were 27% ($\chi^2=0.33$, $p=0.57$), 13% ($\chi^2=0.15$, $p=0.69$), and 59% ($\chi^2=8.2$, $p=0.004$), respectively.

**Urinary tract symptoms**

Urinary tract symptoms are shown in Table VI. At baseline 3% of the patients reported frequency (>1/h) and hematuria (occasionally or more often), while 1% reported dysuria (often/always) and daily incontinence. No differences were found between those who had AD and those who had not.

Giving radiotherapy increased all symptoms after 2 months. A late reaction with increased dysuria was seen, as well as an apparent increase of hematuria after 16 months. The degree of incontinence was stabilized on a higher level after radiotherapy.

**Bowel symptoms**

Bowel symptoms are shown in Table VII. Baseline problems include urgency (often/always) in 4% of the patients and frequency (>5/day) in 3% of the patients, while pain (often/always) and bleeding (>2 episodes/week) were reported by 1% of the
Table III. Eligible patients and response rates in relation to assessment points

<table>
<thead>
<tr>
<th>Year</th>
<th>Study period</th>
<th>Patients treated at Radiumhemmet</th>
<th>Patients followed up at Radiumhemmet</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1998 1999 2000 2001 2002 2003</td>
<td>31 123 144 166 170 106</td>
</tr>
<tr>
<td></td>
<td></td>
<td>April 2000</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>June 2003</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Assessment point</th>
<th>Eligible patients</th>
<th>April 2000</th>
<th>June 2003</th>
<th>Total</th>
<th>Questionnaires obtained</th>
<th>Response rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before RT</td>
<td>130 patients accepted June 2003 +</td>
<td>680</td>
<td>161</td>
<td>24%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 months</td>
<td>341</td>
<td>173</td>
<td>51%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 months</td>
<td>334</td>
<td>178</td>
<td>53%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 months</td>
<td>310</td>
<td>126</td>
<td>41%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16 months</td>
<td>281</td>
<td>120</td>
<td>43%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>22 months</td>
<td>247</td>
<td>88</td>
<td>36%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>28 months</td>
<td>195</td>
<td>69</td>
<td>35%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>34 months</td>
<td>153</td>
<td>48</td>
<td>31%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: RT = radiotherapy.
patients. No differences were found between those who had AD and those who had not.

Giving radiotherapy increased all symptoms after 2 months with the exception of rectal bleeding, but already after 4 months symptom relief was noted while bleeding problems escalated and were most pronounced in the beginning of year two after treatment.

Sexual symptoms

Sexual symptoms are shown in Table VIII. At baseline before AD therapy 95% of the patients reported a sexual desire (a little or more) and 82% sexual satisfaction (often/always) while only 48% had a durable erection for sexual intercourse often or always. When adding AD, the patients reported a sexual desire of 65% ($\chi^2 = 18.55, p = 0.001$) and a sexual satisfaction of 40% ($\chi^2 = 17.46, p = 0.002$), while only 13% ($\chi^2 = 19.435, p = 0.0006$) of the patients had a durable erection for sexual intercourse.

Two months after therapy a waning erectile function and sexual satisfaction was seen, while the sexual desire remained unchanged. In the late reaction phase, sexual desire slowly returned to baseline values, while erectile function and sexual satisfaction persisted at lower levels than before treatment.

Discussion

In this prospective and descriptive study we investigated self-reported urinary, bowel and sexual side effects in consecutive patients diagnosed with localized prostate cancer and treated with neoadjuvant AD therapy and combined radiotherapy including EBRT and HDR BT boost. In addition, this information was compared with symptoms before radiotherapy with or without AD and with symptom presentation in other radiotherapy series.

In this paper we tried to describe acute and late radiation toxicity for HDR brachytherapy prospectively at multiple assessment points in a way not done before. All patients analyzed were identically treated with respect to tumour size and according to the description above (see Materials and Methods).

Table IV. Patient characteristics at time of radiation therapy

<table>
<thead>
<tr>
<th></th>
<th>Number</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total number</strong></td>
<td>525</td>
<td>100</td>
</tr>
<tr>
<td><strong>Clinical stage (UICC)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>141</td>
<td>27</td>
</tr>
<tr>
<td>T2</td>
<td>182</td>
<td>35</td>
</tr>
<tr>
<td>T2-T3</td>
<td>144</td>
<td>10</td>
</tr>
<tr>
<td>T3</td>
<td>52</td>
<td>27</td>
</tr>
<tr>
<td>TX</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td><strong>Grade (WHO)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>97</td>
<td>18</td>
</tr>
<tr>
<td>2</td>
<td>299</td>
<td>57</td>
</tr>
<tr>
<td>3</td>
<td>129</td>
<td>25</td>
</tr>
<tr>
<td><strong>PSA (ng/ml)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;10</td>
<td>198</td>
<td>38</td>
</tr>
<tr>
<td>10–20</td>
<td>183</td>
<td>35</td>
</tr>
<tr>
<td>21–50</td>
<td>117</td>
<td>22</td>
</tr>
<tr>
<td>&gt;50</td>
<td>25</td>
<td>5</td>
</tr>
<tr>
<td>Not known</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>

Abbreviations: UICC = Union Internationale Contre le Cancer, WHO = World Health Organization.

Figure 2. Distribution of completed questionnaires at different assessment points. TAB = total androgen blockade.
The data was self-reported and not subjected to the physician's arbitrariness.

Well aware of the limitations of this descriptive material when interpreting symptom fluctuations over time, we decided to compare our findings with those of previously reported radiotherapy series, including treatment with conformal EBRT, dose escalated EBRT and HDR BT boost.

The study was planned to include all consecutive patients admitted for treatment or scheduled for follow-up visits at Radiumhemmet after completion of treatment. However, due to administrative problems at the clinic such as new doctors and no study nurse assigned for the project, all patients did not receive the questionnaires as intended. This was particularly true for baseline questionnaires (response rate 24%), where we had great problems to establish a proper distribution procedure. Distributing the questionnaires by mail was discussed, but would have allowed patients to save copies, which could have influenced future answers. Despite this methodological weakness we achieved response rates in the acute reaction phase of more than 50%, however slowly decreasing over time (31% at 34 months). We had no reason to believe that the random “drop-outs” would lead to any selection bias and assumed that the study sample well represented the patient population referred to our clinic. The reason for our assumption was that practically no patient declined to participate when asked and patient characteristics, including risk factors, were equally distributed over time. Thus, there seemed to be no systematic bias and the number of questionnaires at many assessment points was fairly high despite the somewhat moderate response rates. The low participation rate (60% of the patients) was assumed to a large extent reflect the lack of baseline questionnaires, since 264 patients of the 870 included were supposed to only contribute a baseline questionnaire, after which they were to be excluded and continue to follow-up at other institutions. We also initially aimed at having consecutive questionnaires from individual patients so as to be able to assess the same patient group over time. However, although we obtained a fairly high number of questionnaires, the majority came from individual patients (on an average two questionnaires for every participating patient).

Assessment before start of treatment was made in order to investigate the symptomatic impact of radiotherapy, since prostate tumours themselves quite often contribute substantial urinary, sexual and sometimes even bowel problems.

Only 43 questionnaires were obtained from patients who were not on hormonal therapy. However, statistically significant differences were found for the sexual symptoms before radiotherapy after initiation of AD therapy, confirming the hormonal side effects affecting sexuality generally known to physicians using AD.

A fifth of the patients stated urinary problems before combined radiotherapy, most probably

<table>
<thead>
<tr>
<th>Months after RT</th>
<th>Number of patients</th>
<th>Urinary</th>
<th>Bowel</th>
<th>Sexual</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before RT no TAB</td>
<td>43</td>
<td>19</td>
<td>14</td>
<td>35</td>
</tr>
<tr>
<td>Before RT with TAB</td>
<td>118</td>
<td>27</td>
<td>13</td>
<td>59</td>
</tr>
<tr>
<td>2 months</td>
<td>173</td>
<td>49</td>
<td>45</td>
<td>77</td>
</tr>
<tr>
<td>4 months</td>
<td>178</td>
<td>42</td>
<td>38</td>
<td>74</td>
</tr>
<tr>
<td>10 months</td>
<td>126</td>
<td>38</td>
<td>52</td>
<td>65</td>
</tr>
<tr>
<td>16 months</td>
<td>120</td>
<td>42</td>
<td>42</td>
<td>72</td>
</tr>
<tr>
<td>22 months</td>
<td>88</td>
<td>36</td>
<td>34</td>
<td>65</td>
</tr>
<tr>
<td>28 months</td>
<td>69</td>
<td>33</td>
<td>45</td>
<td>68</td>
</tr>
<tr>
<td>34 months</td>
<td>48</td>
<td>25</td>
<td>31</td>
<td>69</td>
</tr>
</tbody>
</table>

Abbreviations: RT = radiotherapy, TAB = total androgen blockade.

Table VI. Prevalence of side effects – do you have urinary/bowel/sexual problems?

<table>
<thead>
<tr>
<th>Months after RT</th>
<th>% of patients responding yes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of patients</td>
</tr>
<tr>
<td>Before RT no TAB</td>
<td>43</td>
</tr>
<tr>
<td>Before RT with TAB</td>
<td>118</td>
</tr>
<tr>
<td>2 months</td>
<td>173</td>
</tr>
<tr>
<td>4 months</td>
<td>178</td>
</tr>
<tr>
<td>10 months</td>
<td>126</td>
</tr>
<tr>
<td>16 months</td>
<td>120</td>
</tr>
<tr>
<td>22 months</td>
<td>88</td>
</tr>
<tr>
<td>28 months</td>
<td>69</td>
</tr>
<tr>
<td>34 months</td>
<td>48</td>
</tr>
</tbody>
</table>
related to their malignancy, and about a third sexual problems which could be multifactorial, i.e. tumour-induced or co-morbidity related (vascular, diabetes etc). Adding AD yielded no statistically significant difference in urinary tract or bowel function. However, after radiotherapy an increase of urinary and bowel problems was reported, probably due to the known irritative acute effects, while an increasing proportion of patients reported sexual discomfort, probably a combination of hormonal effects and the bothersome situation in the genito-urinary sphere. The proportion of reported problems persisted throughout the studied period (34 months).

Assessing urinary tract symptoms resulted in valuable information. At baseline, regardless of hormonal treatment, frequency and hematuria dominated while dysuria and incontinence were more uncommon. Dysuria, a well known pronounced acute radiation effect [6], initially increased as expected but there were indications of a late mucosal effect of the irradiation as well. Urinary frequency is a common side effect of radiotherapy for prostate cancer, both in the acute and late setting, which was also the case in this study.

The incidence of gross hematuria was reported more frequently than expected in these patients. They reported whether they had noticed blood in the urine or not. Such hematuria was reported to increase shortly after completion of therapy and tended to be more pronounced after 16–28 months, which is expected for a late urinary mucosal effect [30]. It is evident that in the majority of hematuria cases the category “a little” was stated, which could for instance indicate that concentrated urine was mistaken for blood. However, to our experience, this symptom rarely requires active investigation in the acute setting, but should perhaps be asked for more actively.

Urinary incontinence, a clinical problem in prostate tumour surgery [4], increased shortly after radiotherapy and persisted at a higher level throughout the studied period, probably related to the bladder over-activity, also responsible for the increased frequency.

Radiotherapy of the prostate is specifically associated with bowel problems; we assessed urgency, stool frequency, rectal pain and bleeding. The incidence of fecal leakage, a symptom after rectal irradiation that has attracted attention in a recent paper by al-Abany [31], was not assessed in our study. At baseline, there were complaints of bowel urgency (4%) and stool frequency >5/day (3%),

Table VII. Bowel symptoms

<table>
<thead>
<tr>
<th>Months after RT</th>
<th>Urgency (O/A)</th>
<th>Frequency (&gt;5/day)</th>
<th>Rectal pain (O/A)</th>
<th>Rectal bleeding (&gt;2/week)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before RT</td>
<td>4% (147)</td>
<td>3% (150)</td>
<td>1% (150)</td>
<td>1% (150)</td>
</tr>
<tr>
<td>2 months</td>
<td>12% (150)</td>
<td>7% (155)</td>
<td>4% (151)</td>
<td>1% (151)</td>
</tr>
<tr>
<td>4 months</td>
<td>6% (155)</td>
<td>6% (159)</td>
<td>2% (162)</td>
<td>3% (163)</td>
</tr>
<tr>
<td>10 months</td>
<td>7% (112)</td>
<td>4% (118)</td>
<td>3% (118)</td>
<td>5% (116)</td>
</tr>
<tr>
<td>16 months</td>
<td>9% (109)</td>
<td>7% (112)</td>
<td>3% (114)</td>
<td>6% (113)</td>
</tr>
<tr>
<td>22 months</td>
<td>5% (79)</td>
<td>4% (84)</td>
<td>0% (85)</td>
<td>1% (83)</td>
</tr>
<tr>
<td>28 months</td>
<td>3% (63)</td>
<td>3% (64)</td>
<td>2% (65)</td>
<td>3% (65)</td>
</tr>
<tr>
<td>34 months</td>
<td>4% (46)</td>
<td>4% (47)</td>
<td>2% (47)</td>
<td>7% (46)</td>
</tr>
</tbody>
</table>

Abbreviations: RT = radiotherapy, O/A = often/always.

Table VIII. Sexual symptoms

<table>
<thead>
<tr>
<th>Months after RT</th>
<th>Desire (yes)</th>
<th>Durable erection (O/A)</th>
<th>Satisfaction (O/A)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before RT no TAB</td>
<td>95% (37)</td>
<td>48% (37)</td>
<td>82% (37)</td>
</tr>
<tr>
<td>Before RT with TAB</td>
<td>65% (110)</td>
<td>13% (83)</td>
<td>40% (97)</td>
</tr>
<tr>
<td>2 months</td>
<td>50% (150)</td>
<td>4% (140)</td>
<td>12% (120)</td>
</tr>
<tr>
<td>4 months</td>
<td>71% (161)</td>
<td>11% (156)</td>
<td>26% (137)</td>
</tr>
<tr>
<td>10 months</td>
<td>78% (109)</td>
<td>17% (75)</td>
<td>40% (102)</td>
</tr>
<tr>
<td>16 months</td>
<td>83% (113)</td>
<td>17% (100)</td>
<td>40% (106)</td>
</tr>
<tr>
<td>22 months</td>
<td>80% (84)</td>
<td>15% (72)</td>
<td>45% (77)</td>
</tr>
<tr>
<td>28 months</td>
<td>77% (61)</td>
<td>20% (56)</td>
<td>36% (56)</td>
</tr>
<tr>
<td>34 months</td>
<td>89% (45)</td>
<td>14% (37)</td>
<td>41% (41)</td>
</tr>
</tbody>
</table>

Abbreviations: RT = radiotherapy, O/A = often/always, TAB = total androgen blockade.
classic effects of bowel irradiation but here probably related to other co-morbidity such as chronic bowel disease. Both of these symptoms undulated over time, indicating both acute and late mucosal radiation effects. Rectal pain increased after therapy and then slowly decreased, probably as an acute mucosal effect.

Rectal bleeding is a well studied side effect of prostate cancer radiotherapy [9,12,13,16,17,19,30,32–35], constituting a dose limiting late effect that can be detrimental to the patient. In our material it was pronounced between 10–16 months, consistent to the findings of Schultheiss et al. [30] that late GI toxicity appears earlier (median 13,7 months) than GU toxicity.

Evaluating sexual symptom outcome in prostate cancer radiotherapy is difficult since sexual problems depend on several factors: the prostate tumour itself, co-morbidity, AD treatment, and the radiotherapy.

At baseline without AD treatment sexual desire and satisfaction percentages were high while erectile function was reported by half of the patients. Adding AD worsened all sexual symptoms ($\chi^2$-p = 0.002).

Two months after therapy a nadir was reached, where sexual ability and satisfaction declined probably due to a combination of AD therapy and radiotherapy side effects. In addition, sexual desire initially declined due to hormonal effects, but was gradually restored from 4 months. A similar development was seen for erectile function and satisfaction which increased but never reached baseline levels, thus creating a pronounced gap between sexual desire and ability. This could in part be explained by regained hormonal levels in combination with late irradiation effects, affecting nerves and vascular tissue in the irradiated area. These are effects that could increase with time, which implies further studies on long term sexual outcome and randomized interventional studies.

The RTOG scoring scheme [23], though doctor dependent and not symptom-specific, is the most commonly used instrument to describe radiation toxicity in prostate cancer. Translating the results from the questionnaires used in our study into RTOG scores makes it possible to compare them with the results from other radiotherapy series. The relevance of doing so, despite moderate response rates in our study, lies in the fact that most series use different assessment points when describing radiation effects and often intervals. What is called a ‘late effect’ can mean anything from 4 months or later after therapy, mostly assessed at one occasion only. Since our data is more specific, we can use practically all our questionnaires from 4 months on (>500) for comparison of late effects, thus increasing the validity of the results.

Urinary frequency $\geq$1/h corresponds to a RTOG $\geq$grade 3 genito-urinary (GU) late effect. Other HDR BT (>100 Gy) papers report 2–8% grade 3–4 late GU toxicity [10,15,21,36], while papers reporting toxicity after conformal EBRT dose escalation (74–79 Gy) [16,18,32] indicate 1–9% grade 3–4 toxicity. The definition of the assessment point for late effects varies from 4 months to 24 months or more in these studies. In our material 1–5% reported RTOG grade 3 urinary frequency in the period 4–34 months with the highest values reported at 22–28 months, corresponding well to the findings of Schultheiss et al. [30].

Rectal bleeding $>2$/week corresponds to a RTOG $>2$ GI late effect. Other HDR BT (>100 Gy) papers report 2–11% grade 2–4 late GI toxicity [9,12,13,19], while papers reporting toxicity after conformal EBRT dose escalation (74–79 Gy) [16,32–34] indicate 6–14% grade 2–4 toxicity and papers concerning conventional/conformal EBRT (64–70 Gy) [17,30,35,37] report 5–15%. The definition of the assessment point for late effects varies from 4 months to 24 months or more in these studies as well. In our material 1–7% of patients reported RTOG grade 2–3 rectal bleeding in the period 4–34 months, or possibly more accurate 1–6% in the period 4–28 months after therapy. Furthermore, no grade 4 bowel side effects requiring surgery were reported in this study, and thus HDR BT boost seems to be associated with low/very low risk of severe rectal complications.

Erectile dysfunction (ED) is the most commonly assessed sexual symptom, but assessing sexual potency can be difficult for several reasons. In a review of erectile dysfunction after prostate cancer radiotherapy, Incrocci et al. [38] conclude that the majority of studies lacked a clear definition of sexual potency, the analyses were retrospective and lacked co-morbidity information. Furthermore there was commonly no information on the percentage of patients potent before treatment and often unvalidated instruments were used. However, the review indicated higher ED rates for combined therapy (25–89%) than for EBRT (7–72%) or permanent BT (2–51%) alone. The chance for preserving erectile function seemed better if the patient was younger and had a good erectile function before treatment.

In our material the prevalence of ED was 52% before any kind of treatment, 87% for patients on AD and 80–89% 4–34 months after, corresponding well with the findings in other studies [38].

In an earlier conformal EBRT study from Stockholm (Radiumhemmet, Söder hospital) [39], patients were treated during 1993–1996 using a three or four-field technique with a prescribed dose.

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Treatment toxicity after HDR brachytherapy for prostate cancer 641
ranging from 68–70.2 Gy in 1.8–2 Gy fractions. Margins applied were 2 cm except for the apex where 2.5 cm were used. Patients were assessed regarding late radiation effects by means of a questionnaire 29–59 months after therapy. 19/143 (13%) reported urination at least every hour and 26/145 (18%) reported blood or phlegm in stools twice a week or more. Erectile dysfunction was reported by 89% of previously potent patients (17/19). This assessment was performed later after the radiotherapy than ours (29–59 months), and the questions asked were sometimes wider. The results are therefore difficult to interpret and compare with ours. However, there are reasons to believe that the high radiation dose delivered to the rectum and bladder and the wide margins used contribute to the late toxicity seen. In our study, using smaller margins though delivering about 150% of the dose, less than 50% of the late toxicity noted in the EBRT study is seen, even in an early late period (10–30 months) where late toxicity is expected to peak. Thus, with a more modern radiotherapy approach such as the combined radiotherapy with HDR brachytherapy, the toxicity profile seems more acceptable.

In summary, this is the first study, prospectively reporting side effects after combined radiotherapy including EBRT + HDR BT boost with neoadjuvant AD, using self-reported data. All patients analyzed were identically treated with respect to tumour size. Despite an advanced tumour material (72% of patients with stage T2–T3 disease) and a high dose (>100 Gy) delivered, the side effects were comparable to other curative radiotherapy methods, and possibly superior to dose escalated EBRT regarding the risk for rectal bleeding. No RTOG grade 4 bowel complications were reported. Information regarding fecal leakage is lacking but will be assessed in a future study. The effects of neoadjuvant AD on sexual functions were statistically significant but were transitory. There was no indication of increased GI/GU symptoms as suggested by Schultheiss et al. [30].

A possible drawback with this method could be a long term increase of erectile dysfunction. However, in order to completely evaluate the side effects of this treatment modality for prostate cancer, real long term (5–10 years) symptom outcome has to be determined. This will have to be done using a different study design in order to increase patient compliance.

Acknowledgements
This work was supported by grants from the Swedish Association for Cancer and Traffic victims, the Swedish Cancer Society and the Cancer Society in Stockholm.

References

Treatment toxicity after HDR brachytherapy for prostate cancer


Promising long term health related quality of life after high dose rate brachytherapy boost for localized prostate cancer

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Supported by grants from the Swedish Cancer Society and the Cancer Society in Stockholm.

Running head: Late HRQoL after HDR BT boost for PC
ABSTRACT

**Purpose**: We sought to explore long term general and disease-specific health related quality of life (HRQoL) more than five years after combined radiotherapy for localized prostate cancer (PC) including high dose rate (HDR) brachytherapy boost and hormonal deprivation therapy.

**Patients and methods**: 182 (93%) out of 196 eligible patients with localized PC (T1-T3a) consecutively treated with curative radiotherapy at our institution between June 1998 and August 2000 completed the EORTC questionnaires QLQ-C30 and QLQ-PR25 including specific questions on fecal incontinence more than five years after treatment in September 2005. Comparison with age-matched normative data was made as well as a longitudinal analysis using HRQoL data from a previous study.

**Results**: The analysis included 158 non-recurrent patients. Comparisons made with normative data showed that physical and role functioning were scored statistically significantly better, and social functioning significantly worse. Diarrhoea and sleep disturbance were more pronounced and pain less pronounced than in a normal male population. Longitudinal analysis of disease-specific HRQoL showed that urinary urgency and erectile problems persisted five years after treatment, while nocturia and hormonally dependent symptoms declined statistically significantly over time. Fecal incontinence was recognized by 25% of patients of which 80% thought it to be a minor problem.

**Conclusion**: More than five years after combined radiotherapy, irritative urinary problems and erectile dysfunction remain concerns, while severe bowel disturbance including fecal incontinence seems to be a minor problem. Longitudinally, a decline mainly in hormonally dependent symptoms is seen. Minor differences in general HRQoL compared to normative data is observed, possibly including “response shift” effects.

**Key words**: Localized prostate cancer; radiotherapy; HDR brachytherapy; health related quality of life; questionnaires; side effects
INTRODUCTION

Health related quality of life (HRQoL) is an increasingly important endpoint in prostate cancer (PC) treatment, in large due to a lack of convincing evidence of a difference in efficacy between treatment modalities. In PC, this is certainly true in the light of increased PSA screening activity, leading to early detection of tumours confined to the prostate gland, where various approaches to treatment could be considered. The often indolent and prolonged course of this disease is another issue, where HRQoL aspects will be important. Therefore, studies on long-term HRQoL in PC survivors are of greatest importance, in particular when all active treatment modalities have known side effects\(^1,2\) and most patients are expected to return to normal life. The assessment of HRQoL, however, is many times hampered by poor methodology\(^3\), and therefore has to be carried out with precision.

High dose rate (HDR) brachytherapy as a boost to 3D conformal external beam radiotherapy is a modern radiotherapy approach delivering a high dose to the tumour while normal tissue to a large extent is spared. This technique has been widely practised in Sweden since the early nineties\(^4\), with our centre at the Radiotherapy unit at the Karolinska University Hospital being one of the most active single centres in the world, currently treating about 300 patients with localized PC per year and in total more than 1500 since the start in 1998.

We earlier reported HRQoL development 0-36 months after combined curative radiotherapy including external beam therapy, HDR brachytherapy and neoadjuvant androgen deprivation therapy (NAAD)\(^5,6\). There are few studies dealing with long term HRQoL results from this modern combination therapy\(^7,8\), and we are not aware of any study using a prospective longitudinal design.

In this study, we explore HRQoL in a later phase of PC survivorship more than five years after combined radiotherapy. Comparison is made with age-matched normative data for the Swedish male population and with earlier reported outcomes in a longitudinal fashion, in order to characterize changes over time. Special attention is given to fecal leakage, a symptom described after external beam rectal irradiation and presumably depending on the dose to the anal sphincter.
PATIENTS AND METHODS

Patients
Between June 1998 and August 2000 a total of 234 patients diagnosed with localized PC (T1-T3aN0M0) were consecutively treated with a combination of external beam irradiation and HDR brachytherapy at Radiumhemmet, Karolinska University Hospital, Stockholm. Some patients received their external beam treatment at Söder hospital, Stockholm. In August 2005, 196 patients were offered participation in the present study. A total of 35 patients had died (10 with PC as cause of death), 2 patients were excluded due to non-standardized brachytherapy treatment and 1 patient was impossible to locate.

A total of 182 answers were retrieved, yielding a response rate of 93%. Another 4 patients were then excluded due to multiple malignancies. Among the remaining 178 patients, 20 (11%) were found to have failed treatment, 4 (2%) of which were diagnosed with bone metastasis, the other 16 (9%) were considered PSA failures according to the ASTRO criteria. Thus in 158 patients (89%) there were no signs of recurrent disease.

In the group of patients not included in the final analysis, that is 14 non-responders and 4 excluded due to multiple malignancies, 9 (50%) were treatment failures, of which 4 (22%) with PSA failure and 5 (28%) with metastasis.

We earlier presented HRQoL results 0-36 months after treatment regarding 80 non-relapsing patients of the first 111 treated at our institution. 64 of them were found to be alive, non-relapsing and participating in the present study allowing a longitudinal analysis for time trends to be made.

Pretreatment investigation and primary treatment techniques
The investigation procedure and primary treatment technique were previously described in detail. In summary, staging was made using prostate specific antigen (PSA), a digital rectal examination (DRE) and either cytology (1998-99) or core biopsies (2000). A bone scan and a lymph node dissection were performed in patients presenting with poorly differentiated tumours (Gleason score 4+3 or higher) or a PSA value higher than 10 ng/L. All patients received neoadjuvant androgen deprivation (NAAD) treatment for at least 3 months before radiotherapy (mean total treatment period 7 months, range 3-12 months) with a total androgen blockade (TAB) including a LHRH agonist and an antiandrogen. The hormonal deprivation therapy was stopped at the end of radiotherapy.
3D conformal external beam radiotherapy, using a 4-field (Radiumhemmet) or 3-field (Söder hospital) technique, delivered a total of 50 Gy in 2 Gy fractions to the prostate and seminal vesicles. A margin of 2 cm was used to create the external beam PTV, with the exception of the posterior (rectal) margin, which was limited to 1.5 cm. After 13 fractions the external beam treatment was stopped and a boost of HDR brachytherapy 20 Gy in 2 fractions with a 10-day interval between treatments was given. Following this, external beam treatment was resumed. Brachytherapy pretreatment dosimetry was performed using an ultrasound based treatment planning system. The brachytherapy CTV included the entire prostate gland, excluding the seminal vesicles. A margin of 3 mm was used to create the brachytherapy PTV. Using ten to twenty needles inserted transperineally guided by transrectal ultrasound, the iridium-192 HDR source was temporarily implanted using a remote afterloading device. The entire prostate gland was included in the clinical target volume.

Data collection
In September 2005 all patients were mailed questionnaires and an invitation letter to participate in the study. The forms were returned by mail in a prepaid envelope. Patients not responding in four weeks received a reminder.

Instruments
The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30) is a questionnaire developed by the EORTC (Quality of Life Study Group) for the measurement of HRQoL in cancer patients in clinical trials. It explores the following functional areas: physical, role, emotional, cognitive and social functioning as well as global health status. It also includes a number of multi-item scales and single items that assess a range of physical symptoms (fatigue, nausea and vomiting, pain, dyspnoea, sleep disturbance or insomnia, loss of appetite, constipation, diarrhoea) as well as financial difficulties. Each item is scored in four categories from (1) “Not at all”, (2) “A little”, (3) “Quite a bit”, (4) “Very much” with the exception of items in “Global QoL”scale which range from (1) “Very poor” to (7) “Excellent”.

The prostate specific module EORTC QLQ-PR25, developed by the EORTC Genito-Urinary Tract Cancer Cooperative Group, is a 25-item questionnaire, designed for use among patients with localized and metastatic PC. It was developed within the framework of the EORTC Quality of Life Group and includes subscales assessing urinary symptoms (9 items), bowel symptoms (4 items), treatment-related symptoms (6 items) and sexual functioning (6...
items). This questionnaire is presently being validated in an international study\textsuperscript{11}. Items from the EORTC QLQ-PR25 were selected to represent symptoms as follows: Urinary urgency (item #33), urinary incontinence (item #36), nocturia (item #32), fecal incontinence (item #41), fecal blood (item #42), hot flushes (item #44), breast tenderness (item #45), erectile problems (item #53) and sexual interest (item #50).

In order to focus more on the problem of fecal leakage an additional questionnaire was created by the authors, adding 7 questions presented in Table 4. The new questionnaire items were tested for feasibility in interviews with 20 patients.

The normative sample
Michelson et al\textsuperscript{12} investigated about 3000 people in a random sample of the Swedish population aged 18-79 using the EORTC QLQ-C30 questionnaire. The aims of the study were to provide normative data on the questionnaire and to investigate differences in HRQoL with respect to age, gender, sociodemographic characteristics and reported chronic health problems. In the present paper the male normative data is used.

Statistical methods
The raw scores of the questionnaires QLQ-C30 and PR25 were linearly transformed into a 100-point scale according to the guidelines in the EORTC scoring manual\textsuperscript{13}. A higher mean score for functional scales and general health reflects a better level of functioning, while a higher mean score for symptoms reflects more problems. Mean scores with 95 \% confidence intervals were calculated on the summated scales. We beforehand chose not to include cognitive function, nausea and vomiting, dyspnoea, loss of appetite and financial difficulties in the analysis, areas not considered to be of particular relevance in this group.

For PR25 items, in order to highlight the magnitude of the problems, scores were supplemented with calculated percentages responding in each of the response categories to these items (Table 3).

To explore differences between groups in Table 1, a two-sample t-test was used for continuous variables and chi-square test for category variables. Paired t-test was used to test differences between assessed scores and reference scores. Analyses of variance (ANOVA), repeated measurements, were used to evaluate the impact of time in the longitudinal assessment. The fecal leakage questions were analyzed descriptively, and response categories presented as percentages.

Tests were performed using the Statview for Windows software version 5.0.1 (SAS
Ethical considerations
This study was approved by the local ethics committee at the Karolinska Institutet in January 2005 (Dnr 04-1025/3)

RESULTS

Patient characteristics
Main clinical characteristics of patients with non-recurrent disease are listed in Table 1. A comparison of characteristics between non-recurrent patients having participated in our first study with complete follow-up, i.e. three assessment points, and those with non complete follow-up did not yield any statistically significant differences.

HRQoL questionnaire results – long-term data
The results for non-recurrent patients more than five years after treatment are presented in Table 2 (QLQ-C30) and Table 3 (QLQ-PR25), the latter supplemented with frequencies of symptom severity besides standard linearly transformed means.

Fecal leakage questions
The specified questions and category frequencies for non-recurrent patients as percentages are presented in Table 4. Frequencies from questions 2-7 pertain to those patients having recognized a rectal leakage problem (26.5%).

The longitudinal assessment
The results from the longitudinal assessment, where 64 patients from our first study having a complete follow-up with three assessment points participated, are presented in Table 5 (QLQC30) and Table 6 (PR-25).
DISCUSSION

In this study, long term HRQoL more than five years after combined radiotherapy including HDR brachytherapy was explored. The assessment was made during a later phase of PC survivorship where treatment effects observed in non-recurrent patients are thought to be mainly stable. Study design included a comparison with an age-matched normative sample, descriptive analysis and a longitudinal comparison in order to study changes over time.

Ninety-three percent of the eligible patients responded, which has to be considered a high response rate. Further analyses were made only with respect to the non-recurrent cohort in order to avoid bias associated with salvage therapy and negative stress and focus in the present study was thus on the disease-free survivors.

In the comparison with an age-matched normative sample from the male Swedish population, statistically significantly better scores for physical and role function areas of the QLQ-C30 were found, as well as for pain. These findings could be explained by adaptation or by the more scientific term “response shift”, a concept elaborated by Sprangers and coworkers\(^1\), indicating changes in internal standards in the conceptualization of QoL which are catalyzed by health state changes. Selection bias could be considered as another explanation, but seems less probable since most patients referred to our clinic were accepted for therapy and few exclusion criteria existed. Social functioning, however, was statistically significantly scored worse, possibly implying an impact of prolonged urinary and sexual morbidity.

In the two other studies\(^7,8\) dealing with long term HRQoL after combined radiotherapy using the QLQ-C30 questionnaire, this phenomenon was not found, neither by Galalae and coworkers\(^7\) in a cross-sectional study using a reference population, nor by Joly et al in a case-control study\(^8\).

The statistically significantly increased frequency of diarrhoea could easily be explained by late radiotherapy effects, while the increase in sleeping problems could be due to ageing, where an increasing sensibility to nocturnal voiding could be considered.

The analysis of the PR-25 results was hampered by the fact that there was no normative or baseline data available for comparison. However, looking at the frequencies of symptom severity, urinary symptoms were more common than bowel problems after five years. This could be explained by the fact that before 2001, no effort was made to locate the urethra during therapy, which was assumed to be centrally located. This has resulted in high doses to the urethra possibly leading to chronic urethritis. We have reasons to believe that these side effects are less pronounced in patients treated from 2001, but this has to be further studied.
Long term hormonally dependent symptoms were scarce, implying that normal testosterone levels prevailed on assessment and few effects related to hormone deprivation remained. Sexual bother, however, was still commonly seen five years after treatment, especially erectile problems. Whether this was part of a normal development associated with ageing is hard to establish. However, response rates for sexual items were low, which could be explained by the fact that patients not sexually active were informed to leave the sexual assessment. The reason for not being sexually active was however somewhat unclear, pure disinterest or non-ability? A possible relation to the low scores for social functioning can not be ruled out as an explanation, but impaired sexual function has been shown to matter less to patients older than 74 years \(^\text{15}\).

In the study by Galalae et al\(^\text{7}\), long term disease-specific HRQoL results are not clearly demonstrated. Joly et al\(^\text{8}\) found 4-8 years after treatment significant differences between cases and controls regarding sexual activity, interest in sex, urinary incontinence, cystitis, rectal bleeding and diarrhoea. However, they used a different treatment technique with larger external beam fields, 3 Gy fractions and a LDR brachytherapy technique which could in part be responsible for the persistent long term toxicity seen. Lennernäs et al\(^\text{16}\), interviewing the first 41 patients treated at their centre about 7 years after treatment, found erectile dysfunction in 75% of patients, mild diarrhoea in 25% and interestingly enough few urinary symptoms. The marked learning curve of combined radiotherapy was thought to influence the results. In the present study, less than 10% of patients reported not having any erectile problems.

The problem of fecal incontinence was recently brought to attention by Al-Abany and co workers\(^\text{17}\). They concluded that about 25% of men having gone through external beam irradiation for PC suffered from this condition and found fecal leakage to be the strongest predictor of distress from the gastrointestinal tract. This issue was specifically addressed descriptively in our study since HDR brachytherapy boost is a means to avoid high doses to the rectum. Before using our complementary questions regarding fecal incontinence, they were tested for feasibility in 20 patients. We likewise found this problem in a fourth of patients; however, this leakage was seen as a minor problem in a majority (80%) of cases. Mucus leaking was somewhat more common than fecal matter and 65% never used pads.

The longitudinal assessment comprised 64 of the participants also having taken part in our first study\(^\text{5}\). There were three points of assessment (median time from radiotherapy 7, 24 and 77 months respectively) covering early and late effects. This approach provided insight into HRQoL development over time, where most studies use a cross-sectional design. Test for differences between this group and patients with incomplete follow-up proved to be
statistically non-significant, indicating that the results might be generalized to the entire non-recurrent study cohort. There are, however, possible drawbacks in the interpretation of results. First, the patients were the first to be treated at our institution, implying that the physicians’ learning curve could affect the outcome. Furthermore, when normative data is lacking, which is the case with items concerning PC specific HRQoL, no baseline information was available since retrospective assessment would have introduced bias. This is particularly crucial for symptoms with known multifactorial origin, such as sexual problems.

Longitudinally, there was a negative trend over time regarding physical functioning, while social functioning demonstrated a positive trend. Taken together, these findings are in accordance with earlier results \(^5,7,8\) and support the impression that general long-term HRQoL is not substantially affected by combined RT. Furthermore, we expected to see decreasing urinary and bowel problems, a marked decrease in hormonally related symptoms but persisting erectile dysfunction over time. Due to few responses and thus lack in precision, especially in the early assessment, statistically significant changes were only found for nocturia (decreasing) and hormonally related symptoms (decreasing). In fact, there was a clear decreasing but not statistically significant trend regarding urinary urgency and rectal bleeding.

We were not aware of any longitudinal long term study involving external beam radiotherapy and HDR brachytherapy boost. However, Miller et al\(^{18}\) recently reported results from 709 men participating in a longitudinal study comparing surgery, external beam therapy, permanent brachytherapy (seeds) and controls. No significant changes in general HRQoL were seen over time. Between assessments at a median of 2.4 and 6.2 years after external beam radiotherapy (55-80 Gy) they reported a significant increase in urinary incontinence and sexual problems. Only the external beam group noted significant deterioration of sexual function over time, but baseline data was lacking and this decline was mirrored by the control sample, suggesting a possible effect of ageing. The finding of increasing urinary incontinence was not supported by our study, nor by the study of Fransson et al\(^{19}\), who found no significant change in either urinary incontinence or overall urinary function between 4 and 8 years of follow-up after conventional external beam radiotherapy (median 65.3 Gy). Notably, these studies did evaluate old irradiation techniques including wider treatment fields and lower total doses, why conclusions regarding external beam side effects will have to be considered with caution.

In summary, more than five years after active treatment, we found in comparison with normative data and over time promising results regarding general and disease-specific
HRQoL. Irritative urinary problems and erectile problems seemed to persist, while severe bowel disturbances including fecal incontinence and hormonally depending symptoms constituted a minor problem.

We conclude that this treatment is associated with a risk of side effects, but many of them decline over time or are considered minor problems after more than five years. For erectile dysfunction, however, scores remain high but the implication of this is somewhat unclear in terms of patient wellbeing. It is obvious though that radiotherapy is but one cause accountable for this common state in the elderly male population, a fact that must be elucidated in further studies.
REFERENCES


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UICC= International Union Against Cancer, WHO= World Health Organization, PSA=prostate-specific antigen

†Any 1 or 2 questionnaires of the above mentioned
‡Differences between groups tested with two-sample t-test (continuous variables) or Chi-square test (category variables)
Table 2

HRQoL (EORTC QLQ-C30) >5 years after radiotherapy in non-recurrent patients <80 years (N=143)

Score mean with 95% confidence intervals in brackets

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<tr>
<td>CO</td>
<td>142</td>
<td>7.7 (4.8-10.7)</td>
<td>5.8 (5.6-6.0)</td>
</tr>
<tr>
<td>DI</td>
<td>142</td>
<td>10.8 (7.5-14.1)</td>
<td>4.4 (4.3-4.4)</td>
</tr>
</tbody>
</table>

HRQoL=health related quality of life, GH=global health status, PF=physical functioning, RF=role functioning,
EF=emotional functioning, SF=social functioning, FA=fatigue, PA=pain. SL=sleep disturbance,
CO=constipation, DI=diarrhoea

N=number of respondents, NS=non significant

* paired t-test
Table 3

Disease-specific HRQoL (EORTC PR-25) >5 years after radiotherapy in non-recurrent patients (N=158)

Score mean with 95% confidence intervals in brackets and frequency of symptom severity (%)

<table>
<thead>
<tr>
<th>Assessment point</th>
<th>September 2005</th>
<th>Frequency of symptom severity <em>(%)</em></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Item</td>
<td>N</td>
</tr>
<tr>
<td></td>
<td>Urinary</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Urgency</td>
<td>156</td>
</tr>
<tr>
<td></td>
<td>Incontinence</td>
<td>156</td>
</tr>
<tr>
<td></td>
<td>Nocturia</td>
<td>156</td>
</tr>
<tr>
<td></td>
<td>Bowel</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Incontinence</td>
<td>149</td>
</tr>
<tr>
<td></td>
<td>Blood</td>
<td>148</td>
</tr>
<tr>
<td></td>
<td>General</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hot flushes</td>
<td>149</td>
</tr>
<tr>
<td></td>
<td>Breast tenderness</td>
<td>147</td>
</tr>
<tr>
<td></td>
<td>Sexual</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Erectile problems</td>
<td>87</td>
</tr>
<tr>
<td></td>
<td>Sexual interest</td>
<td>155</td>
</tr>
</tbody>
</table>

HRQoL=health related quality of life, N=number of patients

* 1 = “Not at all” 2=”A little” 3=”Quite a bit” 4=”Very much”
Table 4

Fecal leakage, specified questions

Category frequencies (%) in patients having leakage problems (question 1)

<table>
<thead>
<tr>
<th>Question (N)</th>
<th>Categories</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Do you have a rectal leakage problem? (N=151)</td>
<td>Yes</td>
<td>No</td>
<td>26.5 %</td>
<td>73.5 %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. To what extent does your leakage bother you? (N=40)</td>
<td>Not at all</td>
<td>A little</td>
<td>Quite a lot</td>
<td>Much</td>
<td>Very much</td>
<td>10 %</td>
<td>70 %</td>
</tr>
<tr>
<td>3. How often have you had mucus in your stools? (N=40)</td>
<td>Never</td>
<td>Seldom</td>
<td>Occasionally</td>
<td>&gt;2/week</td>
<td>Daily</td>
<td>&gt;1/day</td>
<td>22.5 %</td>
</tr>
<tr>
<td>4. How much mucus have you had in your stools? (N=40)</td>
<td>Not at all</td>
<td>A little</td>
<td>Quite a lot</td>
<td>Much</td>
<td>Very much</td>
<td>23 %</td>
<td>64 %</td>
</tr>
<tr>
<td>5. How often do you leak fecal matter? (N=40)</td>
<td>Never</td>
<td>Seldom</td>
<td>Occasionally</td>
<td>&gt;2/week</td>
<td>Daily</td>
<td>&gt;1/day</td>
<td>10 %</td>
</tr>
<tr>
<td>6. How much fecal matter do you leak? (N=40)</td>
<td>Not at all</td>
<td>A little</td>
<td>Quite a lot</td>
<td>Much</td>
<td>Very much</td>
<td>17.5 %</td>
<td>70 %</td>
</tr>
<tr>
<td>7. How often do you use pads due to rectal leakage? (N=40)</td>
<td>Never</td>
<td>Seldom</td>
<td>Occasionally</td>
<td>&gt;2/week</td>
<td>Daily</td>
<td>&gt;1/day</td>
<td>65 %</td>
</tr>
</tbody>
</table>
Table 5

General HRQoL (EORTC QLQ-C30) score over time in non-recurrent patients (N=64)

Score mean with 95% confidence intervals in brackets

<table>
<thead>
<tr>
<th>Assessment point</th>
<th>October 1999</th>
<th>May 2001</th>
<th>September 2005</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Item</td>
<td>N</td>
<td>GH</td>
<td>PF</td>
<td>RF</td>
</tr>
<tr>
<td>GH</td>
<td>62-64</td>
<td>71.7 (67.1-76.3)</td>
<td>75.8 (71.4-80.3)</td>
<td>73.8 (69.2-78.5)</td>
</tr>
<tr>
<td>PF</td>
<td>62-64</td>
<td>92.0 (89.1-95.0)</td>
<td>92.4 (89.0-95.8)</td>
<td>87.6 (83.7-91.5)</td>
</tr>
<tr>
<td>RF</td>
<td>62-64</td>
<td>86.2 (81.3-91.2)</td>
<td>89.5 (84.7-94.3)</td>
<td>87.5 (82.4-92.6)</td>
</tr>
<tr>
<td>EF</td>
<td>61-63</td>
<td>85.2 (80.3-90.1)</td>
<td>85.4 (79.9-90.9)</td>
<td>84.7 (79.8-89.6)</td>
</tr>
<tr>
<td>SF</td>
<td>62-63</td>
<td>79.6 (74.1-85.0)</td>
<td>83.9 (78.7-89.0)</td>
<td>84.7 (79.1-90.2)</td>
</tr>
<tr>
<td>FA</td>
<td>62-64</td>
<td>20.8 (16.7-24.9)</td>
<td>17.9 (13.1-22.8)</td>
<td>21.4 (16.9-25.8)</td>
</tr>
<tr>
<td>PA</td>
<td>62-64</td>
<td>14.6 (9.5-19.6)</td>
<td>9.9 (5.0-14.9)</td>
<td>9.9 (5.4-14.4)</td>
</tr>
<tr>
<td>SL</td>
<td>62-64</td>
<td>28.6 (21.9-35.4)</td>
<td>19.9 (13.3-26.5)</td>
<td>25.0 (17.7-32.3)</td>
</tr>
<tr>
<td>CO</td>
<td>62-64</td>
<td>8.9 (3.3-14.5)</td>
<td>6.5 (2.4-10.5)</td>
<td>6.2 (2.4-10.1)</td>
</tr>
<tr>
<td>DI</td>
<td>62-64</td>
<td>21.7 (15.1-28.3)</td>
<td>15.6 (9.3-21.9)</td>
<td>11.5 (6.5-16.4)</td>
</tr>
</tbody>
</table>

HRQoL=health related quality of life, GH=global health status, PF=physical functioning, RF=role functioning, EF=emotional functioning, SF=social functioning, FA=fatigue, PA=pain, SL=sleep disturbance, CO=constipation, DI=diarrhoea

N=number of patients. NS=non significant

* ANOVA repeated measurements
Table 6

*Disease specific HRQoL (EORTC QLQ-PR25) score over time in non-recurrent patients (N=64)*

*Score mean with 95% confidence intervals in brackets*

<table>
<thead>
<tr>
<th>Assessment point</th>
<th>October 1999</th>
<th>May 2001</th>
<th>September 2005</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Item</strong></td>
<td>N</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Urinary</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urgency</td>
<td>60-64</td>
<td>41.5 (33.0-50.0)</td>
<td>35.0 (25.7-44.3)</td>
<td>32.3 (24.0-40.5)</td>
</tr>
<tr>
<td>Incontinence</td>
<td>62-64</td>
<td>7.0 (2.9-11.1)</td>
<td>12.4 (8.0-16.8)</td>
<td>10.9 (5.8-16.1)</td>
</tr>
<tr>
<td>Nocturia</td>
<td>62-64</td>
<td>44.6 (38.1-51.1)</td>
<td>34.9 (27.7-42.2)</td>
<td>34.9 (28.4-41.4)</td>
</tr>
<tr>
<td><strong>Bowel</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incontinence</td>
<td>34-60</td>
<td>11.8 (5.4-18.1)</td>
<td>9.8 (3.9-15.6)</td>
<td>12.8 (8.0-17.6)</td>
</tr>
<tr>
<td>Blood</td>
<td>34-60</td>
<td>12.7 (5.7-19.8)</td>
<td>15.9 (8.5-23.2)</td>
<td>3.9 (1.1-6.7)</td>
</tr>
<tr>
<td><strong>General</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hot flushes</td>
<td>34-60</td>
<td>25.5 (13.0-38.0)</td>
<td>5.6 (0.5-10.6)</td>
<td>6.1 (2.4-9.8)</td>
</tr>
<tr>
<td>Breast tenderness</td>
<td>34-60</td>
<td>24.5 (14.1-35.0)</td>
<td>8.7 (3.6-13.9)</td>
<td>5.0 (1.9-8.1)</td>
</tr>
<tr>
<td><strong>Sexual</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erectile problems</td>
<td>26-32</td>
<td>62.8 (47.9-77.7)</td>
<td>45.8 (33.3-58.3)</td>
<td>62.2 (51.0-73.4)</td>
</tr>
<tr>
<td>Desire</td>
<td>57-64</td>
<td>27.1 (10.3-34.9)</td>
<td>39.2 (31.0-47.4)</td>
<td>39.6 (32.5-46.7)</td>
</tr>
</tbody>
</table>

HRQoL=health related quality of life, N=number of patients, NS=non significant

* ANOVA repeated measurements
Clinical outcome in patients with prostate cancer treated with external beam radiotherapy and high dose-rate 192-Iridium brachytherapy boost: A 6-year follow-up

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ABSTRACT

**Purpose**: To report the long-term results for treatment of localized carcinoma of the prostate using high dose rate (HDR) brachytherapy, conformal external beam radiotherapy (3D EBRT) and neo-adjuvant hormonal therapy (TAB).

**Material and Methods**: From 1998 through 1999, 154 patients with localized prostate cancer were entered in the trial. Biologically no evidence of disease (bNED) was defined at PSA levels <2 µg/L. In order to compare the results of this treatment with other treatment modalities, the patient’s pre-treatment data were used to calculate the estimated 5-year PSA relapse free survival using Kattan’s nomograms for radical prostatectomy (RP) and 3D EBRT.

**Results**: After 6 years of follow-up, 129 patients remain alive. The actual 5-year relapse-free survival is 84%. None of the patients demonstrated clinical signs of local recurrence. The median PSA at follow-up among the relapse-free patients was 0.05 µg/L. Among the 80 patients who presented with clinical stage T3 tumours, 55 (68%) were relapse-free. The expected 5-year relapse-free survival using nomograms for RP and 3D EBRT was 54% and 70 %, respectively. Late rectal toxicity RTOG grade 3 occurred in 1% of the patients. Late urinary tract toxicity RTOG grade 3 developed in 4% of the patients.

**Conclusion**: Combined treatment, utilizing HDR, 3D EBRT and TAB, produces good clinical results. Rectal toxicity is acceptable. Urinary tract toxicity, most likely can be explained by the fact that during the first years of this treatment, no effort was made to localize the urethra, which was assumed to be in the middle of the prostate.

**Key words**: Prostate cancer; high dose rate brachytherapy; combined radiotherapy; clinical outcome; side effects.
INTRODUCTION

In Sweden, prostatic adenocarcinoma is the most common male cancer, with an annual incidence of 168/100 000 [1]. The optimal method of treatment for patients with localized prostate cancer remains to be defined, since there are several approaches to treatment such as radical prostatectomy, radiotherapy with curative intention or watchful waiting. Furthermore, the optimal method of radiation therapy, external beam radiotherapy, brachytherapy (low dose rate or high dose rate), or a combination, remains in question. The currently accepted standard is that the curative dose of irradiation should be 70 Gy or greater, and several dose-escalating projects are currently investigating the optimal dose for cure and minimal side effects.

Known side effects when using external beam radiotherapy include symptoms from the rectum and/or the urinary bladder caused by the dose of irradiation to these organs which are in close proximity to the prostate.

The advantage of brachytherapy is the short range of its irradiation, leading to reduced doses of irradiation to the rectum and bladder. However, this short range may also produce the problem of inhomogeneous dose-distributions and the risk of insufficient dose to parts of the target. Another problem is that the source must be accurately placed in the target or in very close proximity.

Since 1998, we have utilized a treatment method, which combines neo-adjuvant hormonal therapy, conformal external beam radiotherapy (EBRT), and two sessions of high dose rate (HDR) 192-Iridium source brachytherapy for patients with localized prostate cancer. The principle of this treatment has been reported previously [2]. This combination delivers a normalized dose equivalent of 2 Gy per fraction (NTD) of more than 104 Gy (assuming a conservative tumour alpha/beta ratio = 3 Gy). Presently, the patient-reported toxicity and quality of life up to 3 years after treatment seem acceptable [3, 4].

In this article, clinical outcome and side effects at a median follow-up of 6 years will be reported and compared with the calculated results using accepted nomograms for radical prostatectomy and dose escalated conformal external beam radiotherapy.
MATERIAL AND METHODS

Patients
From May 1998 through Dec 1999, 154 patients with localized prostate cancer entered this trial. The patients had a biopsy proven prostatic adenocarcinoma. The Karolinska has a long tradition of fine needle aspiration cytology (FNAC). Ultrasound guided core needle biopsies in the diagnosis of prostate cancer was introduced relatively late at the hospital. Briefly, with FNAC dispersions of isolated or groups of cells are assessed according to the morphology of nuclei and cytoplasm whereas core biopsies provide tissue pieces suitable for histopathological examination. Consequently, in the Initial period of the protocol most patients were diagnosed only with FNAC. The biopsies were reported according to the WHO grading system and later the Gleason system. The Gleason score was transformed to WHO high, middle or poor differentiation defining Gleason score ≤5 as denoting low grade cancer and Gleason score ≥7 (4+3) denoting high grade cancer. The T-stage was defined according to the 1997 TNM classification system.

A lymph node dissection was performed if the tumour was high grade or the prostate-specific antigen in serum (PSA) exceeded 20 µg/L. Only patients with negative lymph node sampling were included. In this report, 103 patients were surgically staged with negative biopsies of lymph nodes. A bone-scan was routinely performed if the PSA exceeded 10 µg/L, in order to exclude bone metastasis. All patients received neo-adjuvant hormonal (TAB) treatment for 6-9 months, consisting of anti testosterone (orally Bicalutamide 50mg x1 or Flutamide 250 mg x3) combined with subcutaneous implants of a gonadotropin releasing hormone analogue.

Patient characteristics at diagnosis are listed in Table 1. Pre-treatment PSA was missing in one patient and T-stage was not assessed in one patient. Poor prognostic risk factors were defined as follows: PSA >10 µg/L, T-stage 3 (TNM), and poorly differentiated prostate cancer (WHO grade III). 32 patients had no risk factors, 54 patients had one risk factor, 52 patients had two risk factors and 14 patients had all three risk factors.

All patients have been identified for follow-up and 24 have died, however, four patients have moved abroad, resulting in a follow-up period of 2.8 – 4.0 years for these patients. Routinely the follow-up consists of clinical visits every third month during the first year,
every sixth month during the second year and annually, beginning the third year. The clinical visits included physical examination with digital rectal examination and blood studies including PSA.

Biologically no evidence of disease (bNEd) was defined as PSA levels <2 µg/L, in order to exclude PSA-bounce. Time to PSA relapse was defined as the time from radiotherapy to the third raised PSA level that was above 2 µg/L. In 1998 when this study began there had been a recent consensus meeting of ASTRO defining PSA relapse as three consecutive increased PSA measurements [5]. This definition was not totally implemented in this trial since one of our laboratories did not titrate levels of PSA lower than 2 µg/L until 2000.

The side effects were assessed and recorded by the physicians according to the toxicity criteria of the USA Radiation Therapy Oncology Group (RTOG). Briefly, grade 0 corresponds to no symptoms, and grade 5 implies that the effects led to death. Grade 1-2 denotes increased amount of diarrhoea or frequency of voiding, grade 3 corresponds to severe symptoms in terms of frequency, bleeding, need of sanitary pads or requirement of surgery, grade 4 is equivalent to severe symptoms with requirement of blood transfusion or development of necrosis [6]. Grades 3 to 5 refer to “major toxicities”.

The study has been approved by the ethical committee at the Karolinska Institute in Stockholm.

Treatment
In total 153 of 154 patients received neo-adjuvant hormonal therapy and external beam radiotherapy combined with 2 fractions of trans-perineal-approach HDR brachytherapy with transrectal ultrasound guidance. One patient received only two sessions of brachytherapy due to personal preferences, and developed a PSA relapse after 2.0 years. Prostate cancer cells were verified with cytology from the prostate. Since the patient violated the treatment protocol, this patient was excluded from the outcome analysis.

External beam radiotherapy
Patients received their external beam radiotherapy (EBRT) at Södersjukhuset or Radiumhemmet, Karolinska University Hospital, Stockholm. For EBRT, a computed
A tomography-based dose plan was established allowing a three-dimensional simulation of the radiotherapy. The planning target volume (PTV) of the EBRT included the prostate and the seminal vesicles with a 2 cm margin in all directions except posterior where the margin was reduced to 1.5 cm. The treatment units consisted of high voltage accelerators equipped with multi-leaf collimators (MLC) making the treatment a true 3D conformal therapy treatment. The patients were placed in a supine position. At Radiumhemmet the EBRT was performed with a four-field box technique. All fields were equally weighted. The dose planning system was TMS-Radix 3D® (Nucletron). At Södersjukhuset the EBRT was performed with a three-field technique, one anterior and two lateral fields. The lateral fields were weighted 50% compared to the anterior field and for the dose plans Pinnacle v. 6.2 (Philips) were used.

The target dose was 50 Gy in 2 Gy daily fractions 5 days a week. The brachytherapy was delivered after an external dose of 24 or 26 Gy, during a gap of two weeks. The remainder of the EBRT was delivered after the second brachytherapy session.

**Brachytherapy**

All patients received their brachytherapy at Radiumhemmet, Karolinska University Hospital, Stockholm. The dose-planning system (Nucletron Planning System®, Nucletron, The Netherlands) used images from transrectal ultrasound (TRUS), with images taken every 5 mm of the prostate gland. The PTV of brachytherapy included the prostate and the base of the seminal vesicles plus a 3 mm margin. The prescribed dose to the PTV was 10 Gy (x 2 fractions). The HDR boost dose to the inner surface of the rectal wall was always kept below 60% of the prescribed dose of 10 Gy. The urethra was thought, during those years of treatment, to be centrally located and needles were placed so as to avoid the geometrical centre of the prostate.

The brachytherapy portion of the treatment was performed under spinal anaesthesia. The technique has previously been described in detail [2]. In general 10 -18 needles were used, and the duration of the procedure was usually 2 hours in total.

**Statistics**

The survival analyses were calculated according to Kaplan-Meyer, and the Log Rank Test
was used to demonstrate differences. The Cox proportional hazards model was used in order to quantify the relationships between PSA, WHO, T-stage and PSA relapse-free survival. Student T-test was used to compare means. Analyses of count and frequency data were performed with the chi-square test. The tests were performed with the Statistica™ Release 4.1 software for Macintosh. P-values equal to or less than 0.05 were considered statistically significant.

**Using the nomograms**

The patients’ pre-treatment data were used in the nomogram for radiotherapy according to Kattan et al [7] and in the nomogram for surgery [8]. In the nomogram for radiotherapy the highest dose-escalated total dose of 86.4 Gy was chosen for comparison.

In cases where only cytology was available, a conversion to a Gleason score was performed as follows: Cytologically well differentiated tumours (WHO grade I) = Gleason score 4, cytologically moderately differentiated tumours (WHO grad II) = Gleason score 6, and poorly differentiated tumours (WHO grade III) = Gleason score 8.

The 5-year probability of PSA-free survival was defined for each patient and treatment modality. An average of the predicted 5-year probabilities was then calculated for all 154 patients using the nomograms, one set for radiotherapy and another set for surgery, to produce the third and fourth columns in Table 3.

**RESULTS**

**Clinical outcome**

In 129 living patients the median follow-up was 6.1 years (range 2.8-7.9 years). Death occurred in twenty-four (16%) patients, 9 (6%) of the deaths were caused by prostate cancer. The remaining 15 patients died from other causes (cardiac infarction, pancreatic neoplasm, cerebral infarction, accident) without any evidence of recurrence. Thirty-four (22%) patients developed a PSA relapse after a median follow-up time of 3.1 years (range 0.4-7.3 years). In 119 patients without a PSA relapse the median PSA value was 0.05 µg/L (range 0.02-1.9 µg/L) and 58% of the patients had a PSA value ≤0.05 µg/L at the latest follow-up. The majority of patients had at least one unfavourable prognostic factor. According to the number of risk factors, the observed 5-year PSA relapse-free survival was
0.97, 0.83, 0.83 and 0.51 for 0, 1, 2 and 3 risk factors, respectively. The PSA relapse-free survival according to number of risk factors is demonstrated in Figure 1. Forty-seven (85%) of 55 patients with PSA <10 µg/L at diagnosis were bNED and 72 (74%) of 97 patients with PSA ≥10 µg/L at diagnosis were bNED. The difference is not statistically significant using the Log Rank Test (p=0.11). Fifty-five (69%) of the 80 patients presenting with a stage T3 tumour were bNED at their last follow-up. The relapse-free survival for patients with stage T3 tumour is demonstrated in figure 2. Taking stage T1 and T2 together, 63 (88%) of the 72 patients were bNED. When patients with stage T3 were compared with patients with stage T1-2 a statistically significant difference in relapse free survival was found (Log Rank Test p=0.003) in favour of the lower stage patients. Seventeen (61%) of 28 patients with high grade tumours (WHO grade III) were bNED at their latest follow-up. Among the 125 patients with well or moderately differentiated tumours (WHO grade I-II), 102 (72%) were bNED. Using the Log-Rank test there was a statistically significantly difference between the patients with WHO grades I-II and grade III (p=0.005).

In a Cox regression univariate analysis, clinical features (PSA levels; <10, 10-20, >20 µg/L and T-stage) and histopathologic parameters (WHO grade) yielded statistically significant prognostic information regarding bNED. In multivariate analysis only the WHO grade remained independently statistically significant (Table 2).

**Side Effects**
Urinary tract symptoms – In 139, 142 and 131 patients with no relapse at 6 weeks, 6 months and last follow-up, respectively, the RTOG score for urinary tract symptoms was assessed. There was a decrease of symptoms over time and the proportion of different RTOG scores at 6 weeks, 6 months and last follow-up are summarised in Figure 3.
Rectal symptoms – In 139, 142 and 130 patients with no relapse at 6 weeks, 6 months and last follow-up, respectively, the RTOG score for symptoms from the lower intestinal tract were assessed. There was a decrease of symptoms over time and the proportion of different RTOG scores at 6 weeks, 6 months and last follow-up are summarised in Figure 4. Symptoms from the lower intestinal tract were less frequent than symptoms from the urinary tract.
Comparison with nomograms
The 153 patients, of whom 80 were T3, had an actual 5-year bNED survival of 84%. The predicted probability of a 5-year bNED survival was calculated using the pre-treatment data for each patient and the Kattan’s nomogram for radiotherapy [7] assuming the total dose of 86.4 Gy and the use of neoadjuvant hormonal treatment. The average probability estimated for a 5-year bNED survival following dose-escalated radiotherapy was 70%.

Regarding surgery, the probability of a 5-year bNED survival was calculated using the pre-treatment data for each patient and the nomogram for radical prostatectomy [8]. The average probability for a 5-year bNED survival following surgery was predicted to be 54%. The calculated values for patients with 0-3 risk factors are demonstrated in Table 3 together with the numbers from the present study.

Radiobiological consideration
Using the linear-quadratic formula and assuming that $\alpha/\beta$ is a conservative 3 Gy, the tumour effect is predicted to be equivalent to 102 Gy in 2 Gy fractions. The rectal dose, where it is possible to reduce the dose contribution from HDR brachytherapy to 60% of the prescribed dose in the prostate, will be equal to 72 Gy in 2 Gy per fractions (table 4).

Regardless of the $\alpha/\beta$ ratio, a comparison with a multi-centre prostate tumour dose response curves passing through the 50% 5 year relapse-free rate produced by 66 Gy with a gamma-50 slope of 2.1 brings the apparent "Intermediate Risk" result here of 88% fitting that curve at 81 Gy NTD in 2 Gy fractions, instead of at 102 Gy NTD [9]. But this top end of the dose-response curve is very sensitive to uncertainties in the gamma-50 slope. If the slope were 1.4 as suggested if the "nadir + 2 µg/L” criterion [10] instead of ASTRO's criterion [5] was assumed, the matching dose would be close to 102 Gy NTD.

DISCUSSION
Clinical outcome
In the effort to cure prostate cancer the radiation dose to the prostate should be equal to or exceed 70 Gy [11]. When doses below 70 Gy have been used, a lower percentage of a histopathologically tumour free state has been reported [12]. The use of the conformal
EBRT technique has made it possible to increase the dose to 78-88 Gy [13, 14], without increasing the rate of side effects in the rectum or bladder. Interstitial brachytherapy provides the option of decreasing the dose to the rectum while delivering an even higher NTD-equivalent dose to the prostate. A combination of external beam conformal radiotherapy and HDR brachytherapy delivers a tumour NTD exceeding 100 Gy in 2 Gy fractions to the prostate gland (assuming the alpha/beta ratio = 3) while the dose to the anterior wall of the rectum is kept below 72 Gy provided that during the HDR boost the rectal dose is below 6.0 Gy for each brachytherapy tumour-prescribed dose of 10 Gy application (table 4). This high dose to the tumour will provide excellent tumour response results with acceptable side effects.

Long term clinical outcomes utilizing this trans-perineal transrectal ultrasound guided technique have been published in reports from 9 centres [15-23]. Three of these centres have recently reported on the treatment results in more than 600 patients [24]. The results are summarized in Table 5. In addition, centres have reported their experience using the Syed free-style template technique [25, 26]. There has been increasing experience with the use of HDR brachytherapy as a boost to external beam radiotherapy, and this has been evidenced in reports from a number of institutions of 5 years bNED survival in the range of 67-93%. These are encouraging results and our data is consistent with these earlier reports. There are surprisingly small differences in results despite the different NTD delivered to the prostate. However, no randomized trial has been conducted regarding the different fractionation schema. In addition, different selection criteria for recruiting patients, makes it difficult to compare the results.

All centres have reported the outcome data as bNED survival, however, different definitions of PSA relapse have been used, which complicates the interpretation. In an attempt to compare our results with outcome from conventional radiotherapy or surgery, we used the widely accepted nomograms according to Kattan et al and the patient pre-treatment data from the present study. The results indicated that the outcome from surgery in this group of patients would be inferior to the outcome from combined radiotherapy. This is explained by the inclusion of a high proportion of patients with intermediate and high-risk tumours. These patients are usually not candidates for surgery due to the high risk of extra capsular extension of disease. The high rate of local control and PSA <0.05 µg/L in
58\% of the patients treated by radiotherapy, would seem to indicate that extra capsular growth is manageable using the combined external beam and HDR brachytherapy radiotherapy. The predicted differences between the results from the nomogram regarding dose escalated external beam radiotherapy and the present study were small. Since no confidence interval was presented using the nomogram, it was not possible to make any statistically significant conclusions. Furthermore, in the present study, a majority of the patients had a diagnostic fine-needle aspiration cytology performed instead of core biopsies. This introduced an uncertainty regarding the tumour grading [27, 28]. However, the WHO grading from cytology was converted to the lesser Gleason score in the respective interval when placed in the nomogram. For example, WHO Grade III was converted to Gleason score 8 and not 9 or 10 during calculation in the nomogram. This makes an overestimation of our results less probable.

One alternative way to report outcome is to use core needle biopsy proven relapse as an end point. This has been reported in only two studies, probably because there is a risk of developing fistulae and rectal complications when performing trans-rectal biopsies of irradiated tissue. Borghede et al reported that biopsy proven local control was found in 48 of 50 patients and only 4 patients demonstrated a PSA above 2 µg/L with a median follow-up of 45 months [29]. Dinges et al reported the results from 82 evaluable patients, treated with external beam radiotherapy (45 Gy in 25 fractions) combined with two sessions of brachytherapy (9 Gy a week). Of these patients, 73\% had negative biopsies at 2 years follow-up and 43 patients had a PSA <1.0 µg/L after 24 months [30]. In our present study, patients with PSA relapse were examined with digital rectal examination and suspected pathological findings were investigated using fine-needle aspiration cytology. No local recurrence was found.

Side effects
Different methods for the evaluation of side-effects in patients with prostate cancer have been proposed using patients' self-assessed questionnaires covering local symptoms and disease specific quality of life [31] or criteria emanating from the Radiotherapy Oncology Group consensus meeting [32]. There is growing knowledge that self-assessed questionnaires are more sensitive when describing the presence of side effects compared to
different methods where physician report the side effects [26, 33, 34]. However, the RTOG scores for acute and late radiation reactions have reached a consensus and a widespread use, which makes it practical when comparing different radiotherapy methods.

Differences in the rate of side effects between different centres should not in general be a result of patient selection, however, age and long-term diabetes are well-known risk factors for developing late rectal bleeding. Furthermore, there are differences in the actual delivered dose to the prostate according to the NTD. Some institutions have performed dose-escalation trials and it appears that NTD exceeding 100 Gy can be safely delivered with HDR brachytherapy boost but not using EBRT alone using delivered daily doses of 1.8 or 2 Gy fractions.

In accordance with previous studies the present trial reports a higher frequency of RTOG grade 3 symptoms from the urinary tract compared to the lower intestinal tract. The urethra is considered to be rather resistant to irradiation. However, urethral strictures, urethral necrosis, urinary incontinence have been reported [30, 35, 36]. Galalae et al have identified trans-urethral resection of the prostate (TUR-P) less then 6 months before irradiation as a risk factor, and they reduced the urinary tract toxicity by excluding patients with previous history of TUR-P [36]. Still, the number of patients with severe symptoms in each report is limited and caution about the dose delivered to the urethra should be emphasized. One can speculate if different numbers of needles used during HDR could impact results. A higher number of needles would facilitate a homogenous dose distribution within the prostate, but would make the implantation more complex and it would thereby be necessary to identify the urethra throughout the whole length of the prostate. In the present study no effort was made to identify the urethra in the pre-planning situation, but a surrogate urethra was used making the assumption that the urethra was centrally located. Since 2001 we have identified the urethra with the use of a urinary catheter during the pre-planning process. Preliminary outcome data evaluation has demonstrated a reduction of urinary complications. Further studies will be performed to elucidate the maximum tolerable dose to the urethra.

**Conclusion**

In conclusion, this present report is the experience in treatment of localized prostate cancer
in a single institution with long term follow up. We conclude that HDR boost to the prostate combined with external beam radiotherapy and neo-adjuvant hormonal blockade, delivering an NTD over 100 Gy, can be safely given provided that precautions are taken regarding the dose to the urethra and floor of the urinary bladder. The 5-year PSA relapse-free survival rate is encouraging especially in the group of patients with intermediate risk tumours where surgery appears to produce less favourable results.

ACKNOWLEDGEMENTS

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REFERENCES


LEGENDS TO FIGURES

Figure 1
PSA relapse-free survival related to the number of risk factors. The risk factors are defined as PSA >10 µg/L, T-stage = 3 and high grade prostate cancer WHO = 3.

Figure 2
PSA relapse-free survival in stage T3 patients. The number of patients at risk each year is noted in the diagram.

Figure 3
Side effects from the urinary tract according to RTOG score and reported as proportion of patients at 6 weeks, 6 months and 6 years follow-up.

Figure 4
Side effects from the lower intestinal tract according to RTOG score and reported as proportion of patients at 6 weeks, 6 months and 6 years follow-up.
HEADINGS TO TABLES

Table 1
Patient characteristics covering age at diagnosis, PSA levels, differentiation grade according to WHO, T-stage and N-stage.

Table 2
Prognostic value of WHO grade, T-stage and PSA in PSA relapse-free survival. Tested with Cox regression multivariate analysis.

Table 3
The calculated values for the probability of 5-year PSA relapse-free survival using nomograms for surgery and dose-escalated radiotherapy are demonstrated. The patient characteristics in this study are used. The result is divided into the number of risk factors in terms of PSA, T-stage and WHO grade. The actual result from the present study is also demonstrated.

Table 4
Radiobiological calculations for tumour tissue and the rectum: F= fractions, BED= biologically effective dose, Gy3= assuming $a/\beta = 3$, NTD = normalized dose to 2 Gy per fraction.

Table 5
Review of the literature. Abbreviations: 3D EBRT = Three dimensional conformal external beam radiotherapy, HDR = high dose rate brachytherapy, NTD ($a/\beta = 3$) = Normalized dose to 2 Gy per fraction and alfa/beta ratio equal to 3, RFS = relapse free survival, RTOG GU = symptoms from the urogenital tract according to the Radiation Therapy Oncology Group, RTOG GI = lower intestinal symptoms according to RTOG.
Table 1

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* PSA at diagnose was missing in one patient
† Denoting a 71 years old man with PSA 8 µg/L who violated the protocol and was excluded in the outcome analyses.
### Table 2

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### Table 3

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