Dose Escalation with High Dose Rate Brachytherapy or Protons in Curative Radiotherapy of Prostate Cancer

LENNART ÅSTRÖM
The aim of the thesis was to study the outcome and side effects after dose-escalated radiotherapy with high dose rate brachytherapy (HDR-BT) or proton beam therapy (PBT) boost in prostate cancer.

The first cohorts of men in Sweden treated with either HDR-BT or PBT in combination with conventional photon beam therapy (2 Gray (Gy) fractions to 50 Gy) were analysed. The HDR-BT was given with two 10 Gy fractions, and the PBT with four fractions of 5 Gy. The analyses included 823 men in two HDR-BT cohorts, and 265 men in the PBT cohort. A large proportion of the cohorts, from 38% to 53%, were classified as high risk. After a follow-up between four and eleven years, both combinations showed low risks for relapse. The overall 5-year risk for PSA relapse was 0% for men with low risk. After PBT, the 5-year PSA relapse risk for intermediate and high risk were 5% and 26% respectively. After HDR-BT the 10-year risks for PSA relapse were 0%, 21% and 33% for low, intermediate, and high risk, respectively.

The risk for early and late toxicity was low. Genitourinary (GU) toxicity was more frequent than gastrointestinal (GI) toxicity. GU toxicity may have a late onset and progress slowly with time after HDR-BT. The 5- and 10-year actuarial incidences of urethral stricture were 6% and 10% respectively after HDR-BT. With applied dose constraints to the urethra the 10-year risk was 5%. The actuarial prevalence of GI toxicity declined slowly with time after HDR-BT as well as after PBT.

A PSA bounce after HDR-BT was seen in 26% of the patients, more frequent with younger age and lower Gleason score, and followed by a low risk for relapse.

For dose-escalated radiotherapy with HDR-BT or PBT:

- long-term tumour control was achieved, not only for low- and intermediate risk, but also for the majority of high risk patients,
- a PSA bounce after HDR-BT was followed by a good prognosis,
- levels of late toxicity were low,
- genitourinary toxicity was more frequent than gastrointestinal toxicity,
- dose constraints to risk organs must be applied to minimise risks for late toxicity.

Keywords: Prostate cancer, radiotherapy, brachytherapy, high dose rate, protons, PSA bounce

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Hippokrates (460-370 f.Kr.)

To Sara, Johanna, Jonatan, Emma, and Jakob
List of Papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.


IV Åström L, Sandin F., Holmberg L. Good Prognosis following a PSA bounce after high dose rate brachytherapy with external radiotherapy in prostate cancer. *Submitted to Radiother Oncol.*

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<tr>
<td>3D</td>
<td>3-Dimensional</td>
</tr>
<tr>
<td>3-T</td>
<td>3-Tesla</td>
</tr>
<tr>
<td>ADT</td>
<td>Androgen Deprivation Therapy</td>
</tr>
<tr>
<td>ASTRO</td>
<td>American Society for Radiation Oncology</td>
</tr>
<tr>
<td>BF</td>
<td>Biochemical Failure</td>
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<tr>
<td>BT</td>
<td>Brachytherapy</td>
</tr>
<tr>
<td>CT</td>
<td>Computed Tomography</td>
</tr>
<tr>
<td>CTV</td>
<td>Clinical Target Volume</td>
</tr>
<tr>
<td>D90</td>
<td>Minimum dose covering 90% of the PTV</td>
</tr>
<tr>
<td>DRE</td>
<td>Digital Rectal Examination</td>
</tr>
<tr>
<td>EBRT</td>
<td>External Beam Radiotherapy</td>
</tr>
<tr>
<td>EORTC</td>
<td>European Organisation for Research and Treatment for Cancer</td>
</tr>
<tr>
<td>EQD2</td>
<td>Equivalent dose in 2 Gray fractions</td>
</tr>
<tr>
<td>GI</td>
<td>Gastro-Intestinal</td>
</tr>
<tr>
<td>GnRH</td>
<td>Gonadotropine Releasing Hormone</td>
</tr>
<tr>
<td>GU</td>
<td>Genito-Urinary</td>
</tr>
<tr>
<td>Gy</td>
<td>Gray</td>
</tr>
<tr>
<td>HDR-BT</td>
<td>High Dose Rate Brachytherapy</td>
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<tr>
<td>IMRT</td>
<td>Intensity Modulated Radiotherapy</td>
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<tr>
<td>iPSA</td>
<td>initial (pretreatment) PSA</td>
</tr>
<tr>
<td>LDR-BT</td>
<td>Low Dose Rate Brachytherapy</td>
</tr>
<tr>
<td>LQ</td>
<td>Linear Quadratic (Model)</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic Resonance Imaging</td>
</tr>
<tr>
<td>MRSI</td>
<td>Magnetic Resonance Spectroscopy Imaging</td>
</tr>
<tr>
<td>NCCN</td>
<td>National Comprehensive Cancer Network</td>
</tr>
<tr>
<td>OAR</td>
<td>Organs at Risk</td>
</tr>
<tr>
<td>OS</td>
<td>Overall Survival</td>
</tr>
<tr>
<td>PBT</td>
<td>Proton Beam Therapy</td>
</tr>
<tr>
<td>PC</td>
<td>Prostate Cancer</td>
</tr>
<tr>
<td>ac-PET</td>
<td>$^{11}$C-Acetate Positron Emission Tomography</td>
</tr>
<tr>
<td>PSA</td>
<td>Prostate Specific Antigen</td>
</tr>
<tr>
<td>iPSA</td>
<td>initial (pretreatment) PSA</td>
</tr>
<tr>
<td>PTV</td>
<td>Planning Target Volume</td>
</tr>
<tr>
<td>QOL</td>
<td>Quality of Life</td>
</tr>
<tr>
<td>RBE</td>
<td>Relative Biologic Effectiveness</td>
</tr>
<tr>
<td>RTOG</td>
<td>Radiation Therapy Oncology Group</td>
</tr>
<tr>
<td>Acronym</td>
<td>Description</td>
</tr>
<tr>
<td>---------</td>
<td>-------------</td>
</tr>
<tr>
<td>RT</td>
<td>Radiotherapy</td>
</tr>
<tr>
<td>SPCG</td>
<td>Scandinavian Prostate Cancer Study Group</td>
</tr>
<tr>
<td>SV</td>
<td>Seminal Vesicles</td>
</tr>
<tr>
<td>TRUS</td>
<td>Transrectal Ultrasound</td>
</tr>
<tr>
<td>TURP</td>
<td>Transurethral resection of the prostate</td>
</tr>
<tr>
<td>V100</td>
<td>Percentage of the volume receiving 100% of the prescribed dose (at HDR-BT)</td>
</tr>
<tr>
<td>V150</td>
<td>Percentage of volume receiving 150% of the prescribed dose</td>
</tr>
<tr>
<td>V200</td>
<td>Percentage of volume receiving 200% of the prescribed dose</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organisation</td>
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</table>
Introduction

Prostate cancer presents several challenges for patients, clinicians and researchers.

- First, a large number of men die of the disease, in Sweden almost 2,500 each year.
- Second, the patients and clinicians must face the coexisting risks for over- as well as undertreatment. An even higher number of men are diagnosed each year with prostate cancer that would never give rise to clinical symptoms. If treated, their risk for side effects will be higher than their risk for disease progression.
- Third, the researcher must take the long natural history of the disease into account. Relapses after curatively intended treatments may appear first after many years. Studies on prostate cancer outcome need a long follow-up.
- Fourth, when studying the effects of radiotherapy, a long observation period is necessary. Complications may appear late.
- Fifth, randomised trials in the curative setting are not as frequent as for other common cancers, with less available level 1 evidence.

All these aspects have to be taken into account when studying a local therapy for prostate cancer with a curative intent. Is it possible to achieve long-term cure with local therapy for a malignant disease? Which factors are relevant for the treatment outcome and what are the potential risks for toxicity?

Two randomised studies from the Scandinavian Prostate Cancer Study Group (SPCG) have investigated the role of local treatment in prostate cancer. The surgical approach with radical prostatectomy was analysed in the SPCG-4 trial. Men with localised PC were randomised between radical prostatectomy (RP), and watchful waiting [1]. After eight years of follow-up the RP arm showed lower mortality, both overall and disease-specific, lower incidence of local progression and distant metastases compared to watchful waiting. The absolute mortality risk reduction was low, 5%, but statistically significant. In patients with locally advanced prostate cancer, the SPCG-7 trial [2] investigated the addition of external beam radiotherapy (EBRT) to endocrine treatment with antiandrogens compared to endocrine treatment alone. The risk for biochemical relapse was considerably lower for the
combination arm with EBRT, 26% vs 75% at 10 years. After a median follow-up of 12 years there was a 10% absolute survival benefit at 10 years for the combination arm [3]. The clinical failure rates have not been reported.

The SPCG-7 trial demonstrated a survival benefit for local RT in combination with systemic ADT. However, the total dose in the RT arm was only 70 Gy. One of the questions put forward by the investigators was if a higher radiation dose would result in a better outcome. What could be achieved with local dose escalation?

Radiotherapy of Prostate Cancer

History

In 1904 Imbert and Imbert [4] used X-rays as one of the first attempts to treat prostate cancer with radiation. A number of French urologists began to use radium in the early 20th century with different applicators to treat prostate hypertrophy and tuberculosis. When the first brachytherapy of prostate cancer was performed has not been exactly documented. Pasteau [5] inserted radium capsules in the urethra with a special catheter. Paschkis in Vienna [6] reported a successful treatment of a malignant prostate tumor with radium inserted in a cystostomy tube in 1910.

Modern curative external beam radiotherapy of prostate cancer with linear accelerators began in the early 1960s after studies by Bagshaw [7] and others. Proton therapy of prostate cancer started at the Massachusetts General Hospital in Boston in the late 1970s, where Shipley [8] reported results with a transperineal beam approach. The radiotherapy modalities have later developed considerably with time and organ-confined disease as well as locally advanced prostate tumours [3] may now be treated successfully.

Radiobiology

The effect of radiation on living cells is supposed to be due to induction of single- and double-strand breaks in the cell DNA. The breaks may be induced directly or indirectly via formation of free radicals by the ionising radiation. Cells have varying capabilities to repair these DNA damages, and will consequently show a different sensitivity to radiation. As tumour cells often have deficient DNA repair mechanisms, they will generally be more sensitive to radiation than normal tissues [9]. This tumour cell susceptibility forms the cornerstone of curative radiotherapy. A radiation dose with a high probability of tumour control may still have a low risk for normal tissue damage. The assumed sigmoid dose-response curves are demonstrated in figure 1.
In the generally accepted Linear Quadratic (LQ) model [10] for calculations of radiation effects, the effect (E) for a certain radiation dose (D) is estimated according to the linear quadratic formula:

\[ E = \alpha D + \beta D^2 \quad (1) \]

where \( \alpha \) is the linear and \( \beta \) the quadratic component. To some extent simplified, the linear component (\( \alpha \)) represent the double strand breaks causing irreversible damage, whereas the quadratic component (\( \beta \)) the reversible single strand break damages. As the effect on cell population survival is Poisson distributed, the effect on the surviving cell fraction (SF) will be:

\[ SF = e^{-\alpha D - \beta D^2} \quad (2) \]

Neutrons or alpha particles with densely ionising radiation will cause mainly irreversible damage, i.e. the surviving fraction will be an exponential function of the dose:

\[ SF = e^{-\alpha D} \quad (3) \]

SF is typically measured in cell culture experiments, and from these values for \( \alpha \) and \( \beta \) may be estimated. The \( \alpha/\beta \) ratio is used to compare the radiation effects on different tissues. A schematic diagram of survival curves after photon irradiation for two cell lines with different values for \( \alpha/\beta \) are demonstrated in figure 2, together with a curve after neutron radiation. The neutron curve is
linear in the logarithmic graph, while the survival curves for photons will have a “shoulder”, more prominent with lower values for α/β. Tissues or organs with a lower α/β ratio will have a higher sensitivity for fraction size.

![Log Cell Survival](image)

**Figure 2.** Dose-response curves for α/β values of 3 Gy (red), 10 Gy (blue) and for neutrons (green).

The LQ model has been corroborated in cell line experiments and clinical studies within normal fraction ranges (2-10 Gy) [11], but considered less appropriate at higher fraction doses (>17-18 Gy) [12]. The equivalent dose in 2 Gy fractions (EQD2) for a fractionation schedule with n fractions with a dose d will be:

\[
EQD2 = nd \frac{1+d/(\alpha/\beta)}{1+2/(\alpha/\beta)}
\]

(4)

When calculating EQD2 for different RT fractionation schedules, larger fraction sizes will have a relatively higher biological effect in tissues with a lower α/β ratio. Tissues with high capacity of DNA repair or slow proliferation tend to have a lower α/β ratio [13].

The Relative Biologic Effectiveness (RBE) has also to be taken into account when comparing particle therapy with photon therapy. Heavy particles have a linear energy transfer (LET) different from photons. A radiation source with high capacity of linear damage, e.g. neutrons, will have a negligible quadratic component, as shown in figure 2.
Radiobiology of Prostate Cancer

A paper by Brenner & Hall in 1999 [3] suggested that prostate cancer might have a higher sensitivity for hypofractionation, i.e. having a low $\alpha/\beta$ ratio. Estimations of the $\alpha/\beta$ ratio for prostate carcinoma suggested a low value, 1.5-3 Gy compared to other tumour types [14-18], where the $\alpha/\beta$ ratio were estimated to be 10 Gy or higher. Thus, the use of higher doses per fraction could increase the tumour control rate in prostate cancer without increasing the normal tissue toxicity. The authors suggested that “(HDR) brachytherapy would be a highly appropriate modality for treating prostate cancer”. Their paper inspired a wide range of hypofractionation studies in prostate cancer radiotherapy. Several randomised studies with conventional EBRT and moderate hypofractionation schemes (up to 3 Gy/fraction) followed. However, the first studies did not demonstrate superiority for the moderately hypofractionated regimens [19]. Later, large randomised noninferiority trials [20-22] showed moderate hypofractionation to be non-inferior to conventional EBRT for low- and intermediate risk cancers. Extreme hypofractionation (>5 Gy per fraction) has been investigated in a Swedish randomised trial comparing 6.1 Gy in 7 fractions to conventional 2 Gy in 39 fractions. The toxicity has been reported after a 2-year follow-up [23], but results on clinical outcome are pending.

Dose escalation

Prostate cancer was historically treated with external beam radiotherapy (EBRT) to a total dose of up to 70 Gy, given in 2 Gy fractions. The persistent challenge is to deliver an adequately high radiation dose to the prostate to achieve tumour control, and at the same time avoid unnecessary toxicity in the adjacent normal tissues. An early observation by Hanks et al. showed increased local failure rates for doses below 60 Gy [24]. A randomised study by Pollack et al. [25] showed an increased rate of biochemical control with conventional external beam radiotherapy when increasing the total dose from 70 to 78 Gy. However, the dose escalation also led to a doubled risk for rectal toxicity.

Dose escalation can be achieved by using EBRT techniques with Intensity Modulated Radiotherapy (IMRT), protons or brachytherapy. The randomised dose escalation trials with either EBRT [25, 26], HDR-BT[27], LDR-BT[28], or protons [29], have all shown that a higher dose is associated with a significant reduction in biochemical failure [30]. However, these radiotherapy modalities are not equal. The dose distributions to the tumour and the normal tissues are different [31], and the subsequent pattern of complications are diverse. High dose rate brachytherapy and proton beams are the subject of this thesis, and are discussed in more detail below.
External Beam Radiotherapy (EBRT)
Several recent randomised trials have investigated dose escalation to doses above 70 Gy [29, 32, 33]. For EBRT, doses of at least 74 Gy is recommended for low-risk patients [34]. Higher dose levels for EBRT in randomised trials have been 79.2 Gy [33], up to 95 Gy in 2.7 Gy fractions for a simultaneous integrated focal boost, recently reported in the FLAME trial [35].

Intensity Modulated Radiation Therapy (IMRT)
IMRT is a refined conformal radiotherapy technique that produces individualised dose distributions, tailored to the anatomy of the specific patient. A further development of the technique is Volumetric Arc Therapy (VMAT) or RapidArc® Radiotherapy Technology that delivers a precisely-sculpted 3D dose distribution with a 360° rotation of the gantry in a single or multi-arc treatment. The clinical applications include conformal avoidance strategies aimed at reducing the radiation dose to organs at risk (rectum, small bowel and bladder). The goal is to reduce normal tissue radiation toxicity in order to achieve dose escalation to tumours and achieve increased tumour control. The use of IMRT instead of conformal EBRT for pelvic irradiation in PC reduces normal tissue doses adjacent to the target, improves target coverage, and has a promising toxicity profile [36, 37]. IMRT/VMAT will however inevitably give low doses to large parts of the peripheral surrounding normal tissue, with a potential increased risk for secondary malignancies [38].

Brachytherapy

![Figure 3. The inverse square law.](image)

Brachytherapy means delivery of the radiation within, or from a very short distance to the tumour (greek \( \beta \rho \alpha \chi \zeta = \text{short} \)). The technique has several
advantages in curative radiotherapy of prostate cancer. The steep dose gradient, according to the inverse square law (figure 3), gives a possibility to deliver a high intraprostatic dose with sparing of surrounding normal tissues. The positioning of the radiation source in the target eliminates the problem with target movement during radiotherapy, but requires a minor surgical procedure under regional or general anaesthesia.

Brachytherapy can be effectuated with low dose rate (LDR) or high dose rate (HDR). High dose rate means delivery of the radiation with >12 Gy/hour where LDR means delivering treatment with <2 Gy/hour. The different characteristics of LDR and HDR are shown in table 1.

History
The first brachytherapy treatment of prostate cancer was made in the early 20th century [5, 6]. The modern era of BT of prostate cancer started in Denmark, where Hans Henrik Holm developed the technique of transperineal applicator insertion under transrectal ultrasound guidance [39]. All further development of both the low dose rate (LDR-BT) technique with permanent seed implantation, and HDR-BT with a temporary application of a Ir-192 source were based on this innovation. LDR-BT was further improved by Haakon Ragde and Steve Blasko at the Swedish Institute in Seattle [40, 41] while HDR-BT was primarily implemented in Kiel [42] and Gothenburg [43]. In Uppsala the addition of a HDR-BT boost to EBRT was initiated in 1995.

High Dose Rate Brachytherapy (HDR-BT)
Where conventional EBRT or proton therapy often give a homogeneous dose to the target volume, the BT dose distribution is heterogeneous. Manipulation of source dwell times and dwell positions give possibilities specific for HDR-BT. It is possible to lower the dose to risk organs inside the target, the urethra, and at the same time increase the dose in other areas of the target. An intraprostatic tumour boost could be defined, or an increase of the margin where there is capsular extension. Moreover, the high dose rate allows giving high doses per fraction which could be of radiobiological advantage.
Table 1. Selected characteristics of HDR and LDR.

<table>
<thead>
<tr>
<th>Method</th>
<th>High dose rate (HDR)</th>
<th>Low dose rate (LDR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Implant</td>
<td>temporary</td>
<td>permanent</td>
</tr>
<tr>
<td>Isotopes used</td>
<td>Iridium-192</td>
<td>Iodine-125</td>
</tr>
<tr>
<td></td>
<td>Palladium-103</td>
<td></td>
</tr>
<tr>
<td>Number of treatments</td>
<td>two or more</td>
<td>one</td>
</tr>
<tr>
<td>Radiation duration</td>
<td>minutes</td>
<td>months</td>
</tr>
<tr>
<td>Live dose plan optimisation</td>
<td>almost unlimited</td>
<td>limited</td>
</tr>
<tr>
<td>Radiation exposure to staff</td>
<td>none</td>
<td>minor</td>
</tr>
<tr>
<td>Radiation precautions after</td>
<td>none</td>
<td>patient restrictions</td>
</tr>
<tr>
<td>treatment</td>
<td></td>
<td>[44, 45]</td>
</tr>
</tbody>
</table>

**Clinical results**

Dose escalation with HDR-BT in PC was introduced more than 30 years ago, with a few large dose fractions mainly for logistical reasons. Today the increasing evidence for advantages of hypo-fractionation in PC supports the use of high doses per fraction as in HDR-BT. Retrospective and randomised trials have shown excellent results with HDR-BT and tolerable side effects [27, 46-48]. Where dose escalation with conventional EBRT resulted in increased rectal complications, a randomised trial exploring dose escalation with HDR-BT did not show any increase in rectal toxicity [27]. The number of HDR-BT fractions and prescribed dose for each fraction varies between different institutions [49]. In Sweden 2 fractions of 10 Gy HDR-BT have been used with EBRT 50 Gy in 2 Gy fractions ever since the schedule originally was set up in Gothenburg 1988 [43, 47]. Assuming a value of α/β = 3 Gy the EQD2 for the schedule will be 102 Gy according to the Linear Quadratic Model(LQ).
Proton beam therapy (PBT)

Figure 4. Proton beams with Bragg peaks, native and modified (spread-out), compared to a photon beam [50].

The physical characteristics of the proton beam therapy (particle therapy) differ from the photon beam. Proton beam therapy (PBT) will characteristically give a peak (the Bragg peak, figure 4) in the dose distribution at a particular depth close to the maximum range of the protons. Beyond the maximum range the dose drops to zero. Proton beams have reduced lateral scatter at small depth. At larger depths the side scatter increases resulting in penumbras of the same magnitude as for high-energy photons. The characteristics of the proton beam can be used to give a high dose to the tumour target and at the same time keep the dose to surrounding tissues low. Proton beam therapy therefore offers an opportunity to increase the radiation dose without increasing treatment toxicity, as each proton beam can be made conformal to the target.

History
Uppsala was the first proton facility in the world to treat patients with cancer in 1957 [51, 52] at the Gustaf Werner Institute of Nuclear Chemistry, later the The Svedberg Laboratory. Prostate cancer has been treated with PBT for almost thirty years [8, 53-56]. Clinical trials and retrospective studies have shown excellent results with PBT[57-59]. However, Uppsala was among the first to report results from hypofractionated proton therapy (paper II). It has only recently been reported from three other centers [60-62], where one ongoing randomised trial will compare 38 Gy (RBE) in 5 fractions with 79.2 Gy in 44 fractions [62].
Side effects of Prostate Radiotherapy

**Acute toxicity**

When exposed to radiation, tissues and tumours react differently and with a different time pattern. Tissues with a higher proliferation rate, such as skin mucosa, or intestinal epithelium will react with inflammation within days or weeks. In the bladder, an acute inflammatory reaction will appear, resulting in dysuria and urgency [63]. Correspondingly, in the rectal mucosa the inflammatory reaction leads to increased mucus production, and stimulated intestinal motility, with subsequent risk for urgency and diarrhoea [64]. The acute reactions are most often reversible and will subside with time.

**Late toxicity**

Late effects, more than 3 months after radiotherapy, typically occur in more slowly proliferating tissues. They may consist of vascular changes with telangiectasia, fibrosis, strictures, or atrophy. The effects may progress with time and become irreversible. They are therefore considered as dose-limiting. Fibrosis may develop in the bladder wall with reduced bladder capacity [63], and similarly in the rectum with reduced storage capacity and subsequent frequent bowel movements [64].

**Androgen Deprivation Therapy (ADT) in Conjunction with Radiotherapy**

ADT may be given before, during, and/or after curative radiotherapy.

**Neoadjuvant and Concomitant**

The use of neoadjuvant and concomitant androgen deprivation with radiotherapy in patients with PC has been shown to delay disease progression and to improve overall survival in both intermediate and high-risk patients [65-68].

One rationale for giving ADT prior to radiation is to decrease the volume of the tumour and the prostate. The relation between tumour volume, or number of clonogenic cells, and the probability of tumour control by radiotherapy is well-known. The larger the tumour, the larger the risk for inadequate tumour control [69, 70]. The larger the irradiated volume, the larger also the risk for side effects [71]. Reducing the target volume will also reduce the total irradiated volume lowering the risk for normal tissue toxicity. A second rationale for giving concomitant ADT and radiation is a potential synergistic effect [67].
**Adjuvant**

Adjuvant ADT after radiotherapy has been shown to improve both disease-free and overall survival [72-77]. The subgroup of high-risk patients appeared to have the most benefit. The ADT duration was between 6 months and 3 years. However, the radiotherapy given in these studies was 70 Gy or lower, which is suboptimal for adequate tumour control. A more recent study comparing 4 months vs 2 years of adjuvant ADT demonstrated a benefit for longer ADT with better OS and BFS, particularly for high-risk patients [78]. The minimum dose in the study was 76 Gy but included fewer patients and had a shorter follow-up than the EORTC and RTOG trials. A multiinstitutional prospective study of dose-escalated radiotherapy with HDR-BT could not demonstrate a benefit of ADT [79]. A study of men treated with the higher dose in the dose escalation trial RTOG 94-06 could not demonstrate an improvement in BFS or DFS with ADT for intermediate risk patients [80]. They questioned the need for ADT in patients with intermediate risk undergoing dose-escalated RT.

**Side effects**

The side effects of ADT are well-known. With short-term use the dominating toxicities are hot flushes, weight gain, decreased libido and erectile dysfunction. With long-term use the risk increases for osteoporosis, reduced muscle mass, increase in abdominal fat, fatigue, cognitive defects, depression, and metabolic disturbances (hyperglycemia, altered lipoprotein profile, decreased insulin sensitivity) [81]. Reports on increased cardiovascular toxicity exist [82]. However, a recent population-based study could not find an increased risk for cardiovascular mortality in the nonmetastatic setting [83]. The randomised studies by Bolla [74] and Roach [66] investigating the addition of ADT to radiotherapy, did not see an increase in cardiovascular toxicity. An analysis of cardiovascular mortality in RTOG 92-02 could not see an increase with longer duration of ADT [84].
Aims

In prostate cancer patients undergoing dose-escalated radiotherapy with HDR-BT (paper I & III) or proton beam (paper II):

- Evaluate clinical and biochemical outcome in relation to prognostic factors and risk groups;
- Describe late complications from adjacent normal tissues – the urethra, bladder, and rectum – and investigate possible risk factors for toxicity;
and
- Investigate the PSA bounce phenomenon after HDR-BT in relation to outcome, risk groups and concurrent symptoms (paper IV).
Patients and methods

Patients
The papers in this thesis analyse the first cohorts of men in Sweden with prostate cancer treated with HDR-BT or proton therapy. Men with localised, or locally advanced PC, treated with curatively intended dose-escalated radiotherapy, were analysed. The RT was given with a combination of EBRT and either HDR-BT or protons. HDR-BT was set up in Gothenburg in 1988, as one of the first centers in the world, and in Uppsala in 1995 as the second center in Sweden. The proton beam therapy for prostate cancer was set up at the The Svedberg laboratory in Uppsala in 2002. The retrospective studies in Uppsala have been approved by the local Ethics Committee (EC).

Paper I
The analysed cohort in Gothenburg included the first 214 men treated between 1988 and 2001 with a minimum follow-up period of 12 months. Two men with distant metastases diagnosed before treatment were excluded from the analysis.

Paper II
The PBT cohort consisted of the first 278 men in Sweden treated with proton therapy from 2002 to 2008. Thirteen patients were lost in follow-up, and 265 were analysed in the study.

Paper III and IV
In these papers the first 878 men treated with HDR-BT in Uppsala between 1995 and 2008 were examined. Patients treated with EBRT at other hospitals (n = 221), were not included in the study. Among them were 81 patients from Stockholm, who were mostly diagnosed by fine needle biopsies without Gleason grading. Seventeen patients were lost in follow-up, of whom 5 had moved abroad. Men with distant metastases or other malignant disease diagnosed before or during treatment (n=17), were also excluded. A total of 623 men were included in the analysis.
Diagnosis

**T-classification**
was based on patient records and the digital rectal examination performed by the diagnosing urologist.

**N-classification**
Surgical pelvic lymph node staging was performed in patients with negative prognostic factors such as elevated PSA (above 20 ng/ml), aggressive Gleason (>=8) or a T3-classification.

**M-classification**
Patients with a PSA above 20 ng/ml were examined with a bone scintigraphy.

Histopathological grading
The Gleason grading system [85] was gradually introduced in Sweden during the 1990s. In paper I, 54% of the patients had biopsies graded according to Gleason, and 46% according to the WHO classification [86]. In paper II-IV 100% resp. 99% had Gleason graded biopsies, classified or revised by the university uropathologists. The general trend towards recording of higher Gleason patterns in the later years of the study periods is an observandum. The biopsies in the studies have not been regraded according to the current revisions of the Gleason grading system [87, 88].

Risk group definitions
In paper I Gleason score >7, PSA >10 ng/ml, and T-classification >T2b (UICC 2002) were considered as negative prognostic factors, table 2.

Table 2. Risk stratification in paper I.

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Risk level</th>
<th>Risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSA (ng/ml)</td>
<td>Low risk</td>
<td>no</td>
</tr>
<tr>
<td>Gleason score</td>
<td>Intermediate risk</td>
<td>one</td>
</tr>
<tr>
<td>T classification</td>
<td>High riska</td>
<td>two or more</td>
</tr>
</tbody>
</table>

*High risk* refers to the combination of any two or more of the risk factors mentioned.
Patients were divided into three risk groups according to prognostic factors. No negative prognostic factors implicated *low* risk disease. One negative factor *intermediate-*-, and two or more factors *high* risk disease [89].

Table 3. Risk stratification according to the NCCN criteria.

<table>
<thead>
<tr>
<th>Risk level</th>
<th>PSA (ng/ml)</th>
<th>Gleason score</th>
<th>Clinical stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk</td>
<td>&lt; 10</td>
<td>≤ 6</td>
<td>and T1–T2a</td>
</tr>
<tr>
<td>Intermediate risk</td>
<td>10–20</td>
<td>7</td>
<td>or T2b-T2c</td>
</tr>
<tr>
<td>High risk</td>
<td>&gt; 20</td>
<td>8–10</td>
<td>or T3a</td>
</tr>
<tr>
<td>Very high risk</td>
<td>&gt; 20</td>
<td>8–10</td>
<td>and T3a</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Primary Gleason pattern 5</td>
<td>T3b-T4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt; 4 biopsies with Gleason 8-10</td>
<td></td>
</tr>
</tbody>
</table>

The definition of risk groups in paper II-IV was according to the National Comprehensive Cancer Network (NCCN) practice guidelines [90, 91] shown in table 3. The very high-risk group definition was not used in paper II.

**Radiotherapy**

**HDR-BT**

The HDR-BT was administered in two separate 10 Gy fractions in a pause half-way in the EBRT treatment. The BT was performed under spinal anaesthesia with the patient in lithotomy position. The patients remain in situ from applicator insertion to treatment delivery. From 10 to 20 applicators were inserted transperineally guided by transrectal ultrasound. The necessary number of needle applicators and their positions were defined in such a way that the PTV was covered by the 10 Gy isodose line. After 2006, the dose plan was constructed based on real-time ultrasound images, with the applicator needles in place. The ultrasound transducer had a water-standoff, which was deflated after needle insertion. The anterior part of the rectal wall was thereby retracted from the prostate and applicators during treatment. A remote afterloading technique with an HDR Ir-192 source was used for treatment delivery.

EBRT was given with 2 Gy fractions to 50 Gy and the HDR-BT consisted of two 10 Gy fractions. The equivalent dose in 2 Gy fractions (EQD2) for the
combined treatment was 102 Gy calculated with the linear quadratic model with an α/β ratio of 3 Gy.

**Proton Beam Therapy**

Boost to the prostate with protons was administered at the Svedberg Laboratory in Uppsala with a single, fixed, horizontal beam with 180 MeV energy, produced by a synchrocyclotron. To localise the prostate and accurately position the patient for the proton treatment, four radiopaque fiducial markers were inserted into the prostate in local anaesthesia using a transperineal applicator. In 147 of the 265 patients a cylindrical rod of Perspex [92] was inserted in the rectum to retract it from the prostate both at the dose planning CT and during proton treatment. The prostate as well as the rectal retractor had 3-4 radiopaque markers for position verification on the dose plan CT and at the proton treatment. Hypofractionation of the proton therapy was expected to improve the therapeutic ratio. However, with the use of a few, larger fractions, the accuracy of treatment dose delivery becomes more influenced by the physical uncertainties resulting from inter- and intrafractional motion [93]. The insertion of a rectal rod was expected to minimise the intrafraction prostate movement due to rectal and intestinal motility.

The schedule was 20 Gy in 4 fractions with PBT followed by 50 Gy in 2 Gy fractions delivered by EBRT. With a relative biological effectiveness (RBE) of 1.1 for protons, the 5 Gy proton fraction is equivalent to 5.5 Gy with photons. The EQD2 for the combined treatment was 87 Gy calculated with the linear quadratic model with an α/β ratio of 3 Gy.

**Target Volumes**

The definitions of target volumes were generally based on the International Commission on Radiological Units and Measurements (ICRU) Report #50 [94], prescribing, recording and reporting Photon Beam Therapy.

To summarise, the gross tumour volume (GTV) is the volume of known tumour. As the exact tumour volume in the prostate has not been possible to visualise, the GTV definition has historically not been used in radiotherapy of prostate cancer. The clinical target volume (CTV) includes the GTV and the volumes of suspected microscopic spread. Two margins allowing for uncertainties in position are then applied. The internal margin (IM) allows for physiological uncertainties caused by filling and movements of the rectum and bladder. The volume formed by adding the IM to the CTV is the internal target volume (ITV). The ITV concept was introduced in ICRU 62 (1999). The setup margin (SM) considers uncertainties in fixation of the patient and inaccuracies in the technical delivery of the radiation treatment. Adding the SM to the ITV forms the planning target volume (PTV). The net effect of all possible
geometrical variations and inaccuracies should be considered in the PTV to ensure that the prescribed dose is actually absorbed in the CTV.

In the present cohorts the ITV was not defined *per se* (following general practice in Sweden). The older ICRU 50 definition prevailed where a margin was added directly to the CTV to form the PTV. The PTV has also inconsistently been modified according to risk group definitions and considerations of risk organs.

**EBRT**

In Gothenburg the CTV was defined as the prostate. Seminal vesicles were included only in high risk pts. The PTV was defined as the CTV with 2 cm margin except dorsally to the rectum where it was 1.5 cm.

In Uppsala the prostate and basal part of the seminal vesicles were included in the CTV. The PTV was defined as the CTV with a 1.5 cm margin. In later years the seminal vesicles were not included for low risk patients and the margin dorsally was reduced to 1 cm.

**HDR-BT:**
The HDR-BT PTV was defined as equal to the CTV and consisted of the prostate with a 2 mm margin.

**Proton therapy**
The CTV was defined as the prostate. The PTV was defined as the CTV with 3 mm margin and 2 mm dorsally to the rectum and cranially to the bladder. For high risk pts the margin was increased to 5 mm but preserving the 2 mm margin to the rectum and bladder.

**Organs at Risk (OAR)**
The urinary bladder and rectum have historically been defined and considered as risk organs at EBRT. At HDR-BT the rectum was defined from start in paper I and from 2000 in paper III. The urethra was defined from 1995 and onwards in paper I and from 2002 in paper III. In paper II the penile bulb was defined at PBT in addition to the bladder and rectum. The neurovascular bundles, femoral heads or symphysis pubis have not been considered as risk organs in these retrospective cohorts.

**Treatment Verifications**
The absorbed dose was determined according to current standard procedures (IAEA, TRS 398, 2004). The dose given to each patient was verified separately where possible. For proton treatments the dose for each individual beam was verified before treatment start. In HDR-BT dosimetry was done at setup and calibration but not for individual patient treatments.
Follow-up

In paper I, III, and IV the follow-up time was calculated from the end of radiotherapy, whereas in paper II it was calculated from the start of radiotherapy. Events during follow-up were registered directly from medical records. For paper III and IV representative samples of the registrations were independently validated by a study nurse from the clinical research unit in Uppsala.

Biochemical failure

The first ASTRO consensus definition [95] of biochemical failure was having three consecutive PSA rises after a nadir with the date of failure as the point halfway between the nadir date and the first rise. Any rise great enough to provoke initiation of therapy would also constitute a failure. This definition was used in paper I.

The current standard definition for biochemical failure after radiotherapy is according to the recommendations of the RTOG-ASTRO Phoenix consensus conference [96]. A failure is defined as a rise by 2 ng/ml or more above the nadir PSA, and the date of failure is to be determined “at call” and not backdated. A PSA bounce (temporary elevation of PSA) is not considered as a failure. This definition was used in paper II-IV.

Local failure

A local recurrence documented by any radiological method (investigations such as acPET, 3T-MRI), preferably verified by biopsy or autopsy. The date of the investigation was considered as the date for local failure. A local recurrence suspected on DRE examination only, had to be histologically confirmed.

Regional failure

Recurrent disease in regional lymph nodes, documented by any radiological method. The date of the investigation was considered as the date for locoregional recurrence.

Distant failure

Metastatic disease outside the regional pelvic lymph nodes documented by any radiological method, prompted by symptoms or biochemical progression. The date when the investigation was done was considered as the date for distant recurrence.

PSA bounce

A PSA bounce was defined as a temporary rise in PSA of at least 0.2 ng/ml from the prebounce nadir PSA. Other bounce definitions are shown in figure 5.
Toxicity

The grading of late toxicities was performed with regard to symptom severity and type of required treatment [97] in paper I. Grade 1 toxicities were symptoms that did not require treatment, grade 2 were symptoms requiring medication, grade 3 were symptoms requiring surgical intervention, and a grade 4 toxicity was when an operative intervention requiring organ resection was indicated. This corresponded to the modified NCI CTCAE (v3.0) [98] toxicity score that was used in paper III and IV. In paper II the grading followed the patient questionnaires adapted after the SOMA-LENT scale (Subjective, Objective, Management and Analytical evaluation of injury – Late Effects on Normal Tissue) [99, 100], with subsequent conversion to a RTOG toxicity grading [101].

Acute complication

A side effect of radiotherapy occurring during treatment or within three months after end of RT treatment.

Late complication

A side effect of radiotherapy observed three months or later after end of radiotherapy.
**Patient-reported outcome**

Patient questionnaires were used in paper II to record smoking habits and contribute to the assessment of baseline symptoms and late toxicity grades. In the Gothenburg cohort (paper I) patient questionnaires were not in use during the study period. For the HDR-BT cohort in Uppsala (paper III-IV) questionnaires were in use from 2003. As patient reported baseline data were not available for the entire cohort, these were not used in the analyses.

**Statistical methods**

Actuarial estimates of overall survival, disease specific survival, clinical failure-free survival (FFS, defined as no local progression and no distant metastases), biochemical failure, and complication risks were calculated according to the Kaplan Meier method [102]. Levels of significance were calculated with the log-rank test. A p-value $\leq 0.05$ was considered statistically significant.

The multivariate analyses were performed using Cox proportional hazards model with results presented as hazard ratios with 95 percent confidence intervals. For the analysis of the PSA bounce phenomenon, PSA bounce was included as a time-varying covariate in the model for the outcome PSA relapse. The follow-up time of a patient experiencing PSA bounce was split into two parts, representing the time before and after PSA bounce, and the covariate for PSA bounce was set to different values in the two follow-up intervals.

The risks for late toxicity were calculated with actuarial estimates. In paper I complication risks were estimated according to the Kaplan Meier method. Actuarial estimates of the prevalence of persistent toxicities were calculated using the method proposed by Pepe et al. [103] in paper II. In paper III the actuarial analyses included incidence as estimated by the net probability and prevalence using the Aalen-Johansen estimator [104]. A case-control of concurrent genitourinary toxicity at the time of PSA bounce was performed in paper IV.

In paper I the analyses were performed with Statview (SAS Institute Inc., Cary, NC, USA). In paper II-IV the statistical analyses were performed using the R Statistical Software Package (R Core Team (2017), Vienna, Austria. https://www.R-project.org/).
Results

Paper I

Risk group reclassification
To allow a comparison with more recent cohorts, the patients in the study were here reclassified according to the NCCN criteria [91] (table 4)

Table 4. Reclassification of the cohort in paper I according to NCCN risk groups.

<table>
<thead>
<tr>
<th>NCCN Risk group</th>
<th>Original</th>
<th>Low</th>
<th>Intermediate</th>
<th>High</th>
<th>Very High</th>
<th>No</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>25</td>
<td>55</td>
<td>0</td>
<td>0</td>
<td>80</td>
<td>37</td>
<td></td>
</tr>
<tr>
<td>Intermediate</td>
<td>0</td>
<td>45</td>
<td>41</td>
<td>1</td>
<td>87</td>
<td>41</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>0</td>
<td>7</td>
<td>37</td>
<td>3</td>
<td>47</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>25</td>
<td>107</td>
<td>78</td>
<td>4</td>
<td>214</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percent</td>
<td>12</td>
<td>50</td>
<td>36</td>
<td>2</td>
<td>100</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Disease outcome
The 5-year actuarial estimates of overall survival, prostate cancer specific survival, and clinical failure-free survival were recalculated for the NCCN risk groups. Table 5 here corresponds to table 2 in paper I.

Table 5. Actuarial 5-year survival estimates in percent according to the NCCN risk groups.

<table>
<thead>
<tr>
<th>NCCN Risk group</th>
<th>Low</th>
<th>Intermediate</th>
<th>High</th>
<th>Very High</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSA relapse-free</td>
<td>100</td>
<td>91</td>
<td>67</td>
<td>38</td>
<td>82</td>
</tr>
<tr>
<td>Clinical failure-free</td>
<td>100</td>
<td>96</td>
<td>84</td>
<td>67</td>
<td>91</td>
</tr>
<tr>
<td>Disease specific</td>
<td>100</td>
<td>100</td>
<td>92</td>
<td>100</td>
<td>97</td>
</tr>
<tr>
<td>Overall</td>
<td>96</td>
<td>90</td>
<td>84</td>
<td>100</td>
<td>89</td>
</tr>
</tbody>
</table>

Risk for PSA relapse
The dates for PSA relapse were adjusted to the Phoenix definition [96] (nadir + 2 ng/ml). The 5-year estimates of risk for PSA relapse then were 0%, 9%, 33%, and 62% for the NCCN low-, intermediate-, high-, and very high-risk patients respectively. The risk for PSA relapse according to the reclassified risk groups is shown in figure 6.
Figure 6. Actuarial estimates of risk for PSA relapse according to NCCN risk group.

Toxicity

The most frequent grade 3 late GU toxicity was urethral stricture with a 5-year actuarial incidence of 7% and a median latency of three years. The incidence of GI toxicities were low, and no Grade 3 or higher toxicity was found.

In a subset of 30 representative patients from the early and late part of the cohort, HDR-BT dose plans were reconstructed, and the maximum dose to the urethra and rectum were calculated (figure 7) [105]. The maximum total dose (EQD2) to the urethra was higher in the first part of the cohort, with a median EQD2 of 199 Gy compared to 148 Gy in the later part. The occurrence of grade 3 GU toxicity was evaluated and found to be higher for patients in the first part of the cohort with a higher EQD2 to the urethra. (17% vs 4%, data not shown). The maximum total dose (EQD2) to the anterior rectal wall was
considerably lower, with a median of 62 Gy (54-78 Gy). No Grade 3 GI toxicity was found.

Figure 7. Above: Estimated total dose (EQD2) to the urethra in a subset of 30 representative patients. To the right the maximum total EQD2 for present-day treatments as a comparison. Below. Estimated total dose (EQD2) to the rectum for the same patients.
The actuarial risk for erectile dysfunction according to endocrine treatment or not, is shown in fig 8. The difference was significant (p=0.02).

In the study we found that dose escalated radiotherapy with HDR-BT was feasible, achieving long-term cure even in men with locally advanced prostate cancer. The risk for late GI toxicity was low with no grade 3 rectal complications. GU toxicity was more frequent than GI toxicity with urethral stricture as the most common grade 3 late complication. The strictures appeared after a long latency period.
A total of 265 men were analysed after a median follow-up of 57 months (range 6-109 months) from the start of radiotherapy with proton boost.

Outcome
The 5-year actuarial PSA relapse was 0%, 5%, and 26%, for the low-, intermediate- and high-risk groups, respectively. The 5-year probability of distant metastases was 0%, 4%, and 20%, for low-, intermediate-, and high-risk patients. In the multivariate analysis for PSA relapse and distant metastases, a T3 classification and higher Gleason score were statistically significant factors in both analyses.

The 5-year overall survival for the whole cohort was 89%. The figures for low, intermediate-, and high-risk groups at 5 years were 90%, 90%, and 87%, respectively. Only 8 patients, all being at high-risk, died of PC during the observation period. The 5-year prostate cancer-specific mortality was 0% for the low and intermediate risk groups compared to 7% for the high-risk group. A PSA bounce was observed in 21% of the patients.

Toxicity
The cohort with mild genitourinary symptoms at baseline showed a significantly higher degree of toxicity compared to the cohort without symptoms. Multivariate analysis of the group with pre-treatment symptoms showed that TUR-P before radiotherapy and the treatment volume for the PBT were significant predictive factors in developing GU side effects.

The study concluded that a hypofractionated proton boost combined with EBRT was associated with an excellent clinical outcome and low rates of treatment toxicities. A longer follow up is needed to evaluate potential late sequelae. Dose escalated radiotherapy with protons is feasible with a minimal failure risk for low risk patients. Late complications were predominantly from the urinary bladder.
Paper III

A total of 623 men were analysed after a median follow-up of 121 months (range 2-266 months) from the end of radiotherapy.

Figure 9. Overall survival (above) and prostate cancer specific survival (below).
Outcome
The overall and prostate cancer specific survival in relation to risk groups are shown in figure 9. The 10-year probability of PSA relapse was 0%, 21%, 33%, and 65% for low-, intermediate-, high- and very high-risk patients respectively.

Toxicity
The 10-year actuarial prevalence for ≥ grade 2 GU- and GI-toxicities were 28% and 12% respectively. There were no dose constraints set for risk organs the first treatment years, and men treated in these years had a higher risk for GU complications. Reconstructed data in a subset of patients in the Uppsala cohort showed high values for V150 and V200, indicating a risk for high doses to the urethra.

The study showed that the combination of EBRT and HDR-BT – with adequate dose constraints to risk organs – provides satisfactory long-term tumour control. GI toxicity stabilised but GU toxicity progressed slowly during the 10-year follow up.

Genitourinary toxicity in paper II and III
We observed that having a larger prostate volume indicated a risk for increased GU toxicity after a proton boost as well as after HDR-BT (paper II, III). Although the median volume did not differ between the cohorts, a proportion of the proton patients were selected for the PBT and not HDR-BT due to a large prostate volume. Baseline GU toxicity was important in the PBT cohort but was not significant in the partly parallel HDR-BT cohort. The HDR-BT EQD2 dose was higher than the proton dose, and the higher dose could have more importance for the late toxicity than the level of symptoms at baseline.
A temporary PSA bounce may occur after prostate brachytherapy, and may be difficult to discriminate from a PSA failure, figure 10. The phenomenon was analysed in paper IV after combined HDR-BT and EBRT, in the same cohort of 623 patients as in paper III. A temporary PSA bounce (> 0.2 ng/ml) was seen in 159 patients (26%), of which 31 (5%) had multiple bounces. The median time to bounce was 15 months. Only 20 of the patients with bounce developed a biochemical failure. The net probability for PSA relapse 5 years after an early PSA bounce (<15 months after treatment) was 4%, compared to 12% after a late bounce (>15 months). The PSA bounces appeared earlier than biochemical failures, with 75% of the bounces occurring within the first 2 years. In a multivariate analysis of the of PSA bounce in relation to age, T-classification, iPSA, Gleason score, proportion of positive biopsies, and endocrine therapy, only younger age and lower Gleason score were significantly associated with higher occurrence of a PSA bounce. There was no clear association between prostate volume and PSA bounce. The bounce was followed by a long time to PSA nadir and associated with a lower relapse risk in a multivariate analysis for PSA relapse. In the analysis, time to PSA bounce was entered as a time-varying covariate, thus reducing the risk for immortal time bias. We found no correlation to contemporary genitourinary toxicity in a case control study, where patients with a PSA bounce were matched to controls without bounce at the time of the bounce peak.

To conclude, a PSA bounce is a relatively common observation after dose-escalated radiotherapy with HDR-BT, and followed by a good prognosis.
Discussion

Strengths and weaknesses

The patient cohorts have been analysed in retrospective studies. This method has obvious disadvantages with potential missing baseline data, lack of monitored follow-up, and data depending on the accuracy of the available patient records. Retrospectively collected toxicity data may underestimate as well as overestimate toxicity. A prospective study protocol would have handled these problems [106] and give a basis for later reporting [107]. This was unfortunately not strictly implemented in the actual locations at the treatment setup. Furthermore, in a retrospective review of medical records, blinding with regard to outcome is difficult and resource-demanding. However, in the largest study (paper III & IV) a representative sample of medical records were validated by an independent study nurse.

A retrospective study has however the advantage of allowing analysis of data from a previous follow-up period long before data would be available in a future prospective study.

Patient selection

The men in the HDR-BT studies were selected both positively and negatively in regard to comorbidity. Patients unfit for surgery would to a larger extent be selected for radiotherapy. One minor exception were the few patients included in the randomised study comparing the HDR-BT combination with prostatectomy in the late 90s. On the other hand patients not suitable for the brachytherapy procedure were excluded.

The proton cohort was partly selected among patients unfit for brachytherapy, Thus, patients with a larger prostate volume or comorbidity could be selected for protons.

Dose distributions

In the HDR-BT studies, physical dose distribution data for the brachytherapy were unavailable for most of the patients in the early parts of the cohorts. It was therefore not possible to analyse e.g. maximum dose to the urethra as a potential factor for late GU toxicity. Nonetheless, if all data were available, these would only be from the preplan and from the reconstructed applicator positions. During insertion of the needles, the prostate and urethra will change form and position slightly. The actual delivered dose distribution within the
prostate may therefore differ considerably from the preplan. This issue was addressed in 2006 with new dose planning software [108] (Oncentra Prostate, Elekta, Stockholm). The dose plan was then based on the actual position of applicators and live images of the prostate and urethra.

Prostate cancer outcome

Low risk patients had excellent outcomes, with no biochemical failures observed in 5, respective 10 years of follow-up. These patients are today mostly followed with active treatment deferred until signs of disease progression. Hamdy et al. found an overall low risk for death of prostate cancer in the ProtecT trial [109] with a large proportion of low-risk cancers followed in active monitoring. A recent report from the National Prostate Cancer Registry (NPCR) in Sweden [110] found only small differences in prostate cancer mortality after primary treatment with surgery compared to radiotherapy.

The intermediate risk patients also had excellent outcomes. In contrast to the low risk group, they had an ongoing, albeit low, rate of PSA relapses during the study period, continuing beyond 10 years of follow-up. The relapse risks did not show a “plateau”. This demonstrates the importance of reporting not only 5-year relapse risks but continue until 10 years – or longer, when possible. Yaxley reported a 5 and 10-year PSA relapse free survival probability of 93% and 87% respectively for intermediate risk patients after a HDR-BT combination [111]. Galalae reported 71% and 64% correspondingly for intermediate risk in a smaller cohort [112]. in the Uppsala HDR-BT cohort the 5-year PSA relapse risk was 12% while the 10-year probability was 21% for intermediate risk. The increase in PSA relapse risk with longer follow-up is reported also after prostatectomy. In a contemporary cohort from Denmark, Kurbegovic reported 5- and 10-year relapse risks of 22% versus 32% for intermediate risk according to the d’Amico criteria [113].

The HDR-BT cohort was separated into a high- and very high-risk (VHR) group according to the NCCN criteria [91], showing a worse outcome for the VHR group. Seminal vesicle engagement is classified as VHR, and is more difficult to treat adequately with BT. The comparatively short period of ADT used here could also contribute to the difference in outcome. Ishiyama reported a 5-year PSA relapse-free probability of 82% for VHR patients in a HDR-BT combination with hypofractionated EBRT and 42 months of ADT [114]. Although in retrospect, paper III supports the relevance in using the VHR criteria. A VHR classification could draw more attention to the men in the subgroup, and the possible need for additional systemic treatment. At present this subdivision is not in clinical use in Sweden.
Dose escalation

A recent randomised study by Michalski et al., RTOG 0126, compared dose escalated EBRT to 79.2 Gy in 44 fractions with 70.2 Gy in 39 fractions [33] in intermediate risk PC. With 1499 men in the study and a median follow-up over 8 years, they found a lower risk for BF, local recurrences and distant metastasis after dose escalation, but no difference in overall survival. However, one may note that the EQD2 (calculated with $\alpha/\beta=3$ Gy) in the dose-escalated arm and control arm were relatively low, 76 Gy and 67.4 Gy respectively. The recent ASCENDE-RT randomised trial compared adding a LDR BT boost to 46 Gy EBRT compared to dose-escalated EBRT to 78 Gy. The risk for local recurrences and biochemical failure was lower for the LDR-BT boost arm but no difference was seen for OS [115]. The total dose in the control arm in the ASCENDE-RT study, 78 Gy was higher than in the dose-escalated arm of the RTOG study. The reported actuarial 5-year risk for BF was 16% compared to 20% in the RTOG study.

A similar observation has been made by Bartelink et al. after adjuvant radiotherapy of early breast cancer. Local dose escalation with a boost of 16 Gy compared to no boost resulted in a lower risk for ipsilateral recurrence and significantly fewer salvage mastectomies, but no difference in overall survival [116].

According to the linear quadratic formalism [4] the $\alpha/\beta$ ratio is used to assess response after radiotherapy in different tissues. A lower $\alpha/\beta$ ratio for PC would imply a higher sensitivity for fraction size [6]. For the HDR-BT combination, the EQD2 would be 33 Gy for the HDR-BT and 83 Gy totally with an $\alpha/\beta$ ratio of 10 Gy. With a lower $\alpha/\beta$ ratio, e.g. of 3 Gy, the EQD2 for the BT would be 52 Gy and the total EQD2 102 Gy. Hence, the addition of two large fractions of HDR-BT to the EBRT would result in a biological dose escalation, potentially larger if the $\alpha/\beta$ ratio for PC is lower. Such a high dose cannot be delivered to the prostate gland by EBRT alone and might be an explanation of the good results found in our studies. With few local recurrences observed these studies do not contradict the hypothesised low $\alpha/\beta$ ratio of prostate cancer.

Late complications

A learning curve is inevitable when setting up a new technique. Issues or complications, unknown at setup, will emerge. This is particularly the case in radiotherapy, as late complications may develop first many years after treatment. As in the HDR-BT cohort from Stockholm [117], the urethra was not delineated in the first treatment years of HDR-BT. In parallel, the incidence of grade 3 late urethral toxicities reported here were higher in the early part of the cohorts. In the absence of exact information on dose
distributions for each case, the available samples showed high doses to the urethra (figure 7). The grade 4 complications seen in the early part were rare in the latter part. After visualisation of the urethra and dose restrictions to the urethra were applied, lower GU complication rates were seen in the latter part of the HDR-BT cohorts, compatible with a learning curve effect. Yaxley reported falling urethral stricture rates in a similar cohort after applying measures to better define the urethra and prostate apex, and define limits for V200 [111].

Severe rectal complications were not seen in these studies, neither after HDR-BT, nor after protons. This might be explained by the techniques used. The patient was not moved during the BT procedure, eliminating the risk for applicator movement [118]. Probably more important was the deflation of the probe water-standoff before treatment. With the probe still in place this resulted in a retraction of the anterior rectal wall from the prostate. With a steep BT dose gradient this would result in lower doses to the anterior rectal wall, and consequently a lower risk for rectal complications. Galalae reports 4% frequency of proctitis at 5 years with a similar technique [48]. After dose escalation with EBRT alone from 70 to 78 Gy, Pollack reported an increase in grade 2 rectal toxicity from 12% to 26% at 5 years [119]. A recent Cochrane review investigating measures to reduce toxicity in pelvic radiotherapy found conformal RT to be an improvement over conventional RT, with moderate level of evidence[120].

A rectal retractor rod was used in 147 patients (56%) during the proton treatment, which at minimum would lower the dose to the dorsal rectal wall. However, the use of the rectal rod was not shown to lower the risk for GI toxicity. The sharp penumbra of the transperineal proton beam, and a tight PTV margin towards the anterior rectal wall, contribute to a lower total rectal dose for the PBT combination compared to conventional EBRT. The observed low risk for late GI toxicity after the PBT combination is consistent with the lower rectal dose achieved with this treatment setup. Colaco reported a 0.9% risk for grade 3 GI toxicity three years after proton therapy to a median dose of 78 Gy with lateral beams, rectal balloon, and small PTV margins [121]. Zietman found no associated increase in late rectal toxicity in a randomised trial comparing a proton boost to 79.2 Gy with 70.2 Gy with photons [29].

The PSA bounce phenomenon
Temporary PSA elevations after radiotherapy, PSA bounces, have been observed and reported ever since the first study by Critz et al. in 2000 [122]. Several efforts have been made to discern the bounce from a PSA relapse [123]. PSA bounces appear earlier than PSA relapses [124], and reported to be more frequent with higher fractional doses in HDR-BT monotherapy[125]. There are statistical pitfalls, as the phenomenon can only be analysed retrospectively, when the long-term prognosis is known. A direct, unadjusted
A comparison of prognosis after PSA bounce versus no bounce is inherently flawed, as patients with an immediate PSA relapse never experience a bounce. In paper IV we tried to correct for the intrinsic time bias by including PSA bounce as a time-varying covariate in the multivariate analysis for PSA relapse. This would strengthen our conclusion that a PSA bounce is followed by a good prognosis.
Summary and Conclusions

The studies in this thesis demonstrate the feasibility of HDR-BT or protons in combination with photon beam radiotherapy as treatment options in localised and locally advanced PC. After a follow-up between four and eleven years, both combinations show low risks for relapse. A PSA bounce is common and followed by a good prognosis after HDR-BT. The treatments were initially given without adjustment for risk factors and without dose constraints to risk organs. A learning curve effect was observed for HDR-BT with a lower risk for late toxicity after adequate dose restrictions were applied.

**Dose escalated radiotherapy with HDR-BT or protons**

- Showed excellent long-term tumour control for the low- and intermediate risk group,
- Long term tumour control is achieved for the majority of high risk patients,
- A PSA bounce after HDR-BT was followed by a good prognosis,
- The risk for late toxicity was low,
- Showed a higher risk for genitourinary than gastrointestinal toxicity,
- Genitourinary toxicity may have a late onset and progress slowly with time after HDR-BT,
- Dose constraints to risk organs must be applied to minimise late toxicity.

The HDR-BT combination is currently a standard curative treatment in Sweden, while proton beam therapy is still under investigation.
Future perspectives

The HDR-BT technique has developed considerably from the start in 1988. The BT procedure has been technically refined with better ultrasound imaging, more accurate positioning of the applicators, and live dose planning based on the actual applicator position within the prostate. Dose constraints to risk organs are regularly applied. Almost all university hospitals in Sweden treat prostate cancer with HDR-BT. Dose plans are based on live imaging with the applicators in situ, and within a near future treatment plans will be MRI-based. The extra- and intraprostatic extension of the tumour is now taken into consideration, and the possibilities exist for giving an intraprostatic boost to the tumour. Monotherapy with HDR-BT has been in use for over a decade, and a national study protocol for monotherapy with HDR-BT is in preparation.

The proton facility at the Svedberg laboratory is no longer in use. A national protocol for treating prostate cancer with protons at the new Skandion clinic in Uppsala is in the final planning stage. The study is based on the findings from paper II in this thesis, with modifications due to the specific configuration of the Skandion facility. The same fractionation scheme and technique with a rectal retraction rod will be used.

To conclude, dose escalation with HDR-BT or PBT in these retrospective studies, demonstrate an excellent outcome with low long-term relapse risks. HDR-BT is currently a standard treatment option for prostate cancer in Sweden, while the use of PBT boost still needs to be defined. Which patients could be considered for PBT? How should dose escalation be performed in the high- and very high risk group? How should very high risk patients be treated optimally? Are there high risk patients who could avoid the long period with adjuvant ADT? With the knowledge that HDR-BT has lower late rectal complication risks than EBRT, could the use of HDR-BT as monotherapy be justified? The answers to these questions could only come from future prospective randomised trials.

Syftet med avhandlingen var att studera sjukdomsutfall och biverkningar efter doseskaladerad strålbehandling med hög dosrat brachyterapi (HDR-BT) eller protonstrålbehandling (PBT) vid prostatacancer. De första patientkohorterna i Sverige som behandlats med antingen HDR-BT eller PBT ingick i studien. HDR-BT gavs med två 10 Gray (Gy) fraktioner, PBT med fyra fraktioner på vardera 5 Gy och konventionell fotonstrålbehandling gavs med 2 Gy fraktioner till 50 Gy. Analyserna inkluderade 823 män i två HDR-BT-kohorter och 265 män i PBT-kohorten. En stor del av kohorterna, från 38% till 53%, klassificerades som högrisk. Efter en medianuppföljning mellan fyra och elva år visade båda kombinationerna låga risker för återfall. Risken för PSA relaps vid 5 år var 0% för män med låg risk. Efter PBT var 5-års PSA-återfallsrisken för mellan- och högrisk 5% respektive 26%. Efter HDR-BT var den 10-åriga PSA-återfallsrisken 0%, 21% och 33% för låg, intermediär och hög risk.

Tidig och sen toxicitet var låg. Urinvägstoxicitet var mer frekvent än gastrointestinal (GI) toxicitet. Urinvägstoxicitet kan ha en sen debut och progrediera med tiden efter HDR-BT. Den 5- och 10-åriga risken för urethrastriktur var 6% respektive 10% efter HDR-BT. Med införda dosbegränsningar till urethra var 10-årsrisken 5%. Den aktuella prevalensen av GI-toxicitet minskade långsamt med tiden efter både HDR-BT och PBT.

En PSA”bounce” (tillfällig stegning av PSAvärdet) efter HDR-BT sågs hos 26% av patienterna. Den var vanligare hos yngre och vid lägre Gleason score. Det var en låg risk för PSA återfall efter bounce.

Med 5 respektive 10 års uppföljning efter doseskaladerad strålbehandling med PBT eller HDR-BT sågs
• Inga återfall i lågriskgruppen,
• Låg återfallsrisk för intermediärrisk,
• Majoriteten av högriskpatienterna var fria från återfall 10 år efter HDR-BT,
• PSA bounce efter HDR-BT innebar en god prognos.
• Risken för sen toxicitet var låg,
• urinvägstoxicitet var vanligare än gastrointestinal toxicitet,
• dosbegränsningar till riskorgan är nödvändiga för att minimera risken för senbiverkningar.

HDR-BT-kombinationen är idag en standardbehandling i Sverige, medan protonstrålbehandling fortfarande är under utprövning.
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References


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A doctoral dissertation from the Faculty of Medicine, Uppsala University, is usually a summary of a number of papers. A few copies of the complete dissertation are kept at major Swedish research libraries, while the summary alone is distributed internationally through the series Digital Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine. (Prior to January, 2005, the series was published under the title “Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine”.)