Radiation therapy combined with hormone treatment for primary prostate cancer

Effects of radiation dose escalations and assessment of side effects

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In the memory
of my father

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Abbrevations

ADT	Androgen deprivation therapy
AJCC	American joint committee on cancer
ASTRO	The American Society for Therapeutic Radiology and Oncology
bNED	No evidence of disease activity measured biochemically, i.e. PSA normal or not detectable
C-ion	Carbon ion
CRT	Conformal radiotherapy
CSS	Cancer specific survival
CT	Computer tomography
CTC	Common toxicity criteria
CTV	Clinical target volume
DRE	Digital rectal examination
DVH	Dose volume histogram
EBRT	External beam radiation therapy
FDA	Food and drug administration
GI	Gastrointestinal
GTV	Gross tumor volume

GU	Genitourinary
HDR	High dose rate brachytherapy
HRPC	Hormone refractory prostate cancer
HT	Hormone therapy
ICRU	International commission on radiation units and measurements
IMRT	Intensity- modulated radiotherapy
ITV	Internal target volume
LDR	Low dose rate brachytherapy
LHRH	Luteinising hormone releasing hormone
MAB	Maximal androgen blockade
MLC	Multileaf collimator
MRI	Magnetic resonance imaging
NCCN	National comprehensive cancer network
NUCG	Norwegian Urological Cancer Group
OR	Organ at risk
OS	Overall survival
PC	Prostate cancer
PET	Positron-emission tomography
PSA	Prostate specific antigen

PTV	Planning target volume
QoL	Quality of life
RP	Radical prostatectomy
RT	Radiation therapy
RTOG	Radiation Therapy Oncology Group
SIB	Simultaneous integrated boost
SPECT	Single-photon emission CT
TNM	Tumour node metastasis system, UICC classification
TURP	Transurethral resection of prostate
UICC	International union against cancer
WHO	World Health Organisation
WW	Watchful waiting

List of papers and presentations

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

I Karlsdóttir Á, Muren LP, Wentzel-Larsen T, Johannessen DC, Bakke A, Ørgreid P, Halvorsen OJ, Dahl O. Radiation dose escalation combined with hormone therapy improves outcome in localised prostate cancer. Acta Oncologica 2006; 45: 454-462

II Karlsdóttir Á, Muren LP, Wentzel-Larsen T, Johannessen DC, Haukaas SA, Halvorsen OJ, Dahl O. Outcome in intermediate or high risk prostate cancer patients receiving radiation dose and hormone therapy. Accepted, Acta Oncologica 15.4.2009.

III Karlsdóttir Á, Johannessen DC, Muren LP, Wentzel-Larsen T, Dahl O. Acute morbidity related to treatment volume during 3D- conformal radiation therapy for prostate cancer. Radiother Oncol 2004; 71: 43-53

IV Karlsdóttir Á, Muren LP, Wentzel-Larsen T, Dahl O. Late gastrointestinal morbidity after 3D- conformal radiation therapy for prostate cancer fades with time in contrast to genitourinary morbidity. Int J Radiat Oncol Biol Phys 2008; 70: 1478-1486

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- The 21th ESTRO Meeting in Prague, Czech Republic, September 17-21, 2002 Abstract # 922
- The 23th ESTRO Meeting in Amsterdam, The Netherlands, October 24-28, 2004 Abstract # 891
- The 9th Biennial ESTRO Meeting on physics and radiation technology for clinical radiotherapy in Barcelona, Spain, September 8-13, 2007 Abstract # 349

Contents

1. General introduction

1.1 Epidemiology

Prostate cancer (PC) is the most common cancer in men in Europe, North America, and some parts of Africa [1], and is a large and growing public health problem. Incidence of PC is steadily increasing in almost all countries, yet we know little about what causes this disease. In Norway, with a total population of 4.7 million people, 3817 new cases of PC were diagnosed in 2006 (95.3 per 100,000), making it the most common cancer in Norway [2]. The mortality in 2004 was 1074 (20.5 per 100,000). The natural ageing of the population, combined with the continued and widespread use of improved diagnostic tests such as serum prostate specific antigen (PSA), contributes to the increase in the numbers of men diagnosed with localised PC.

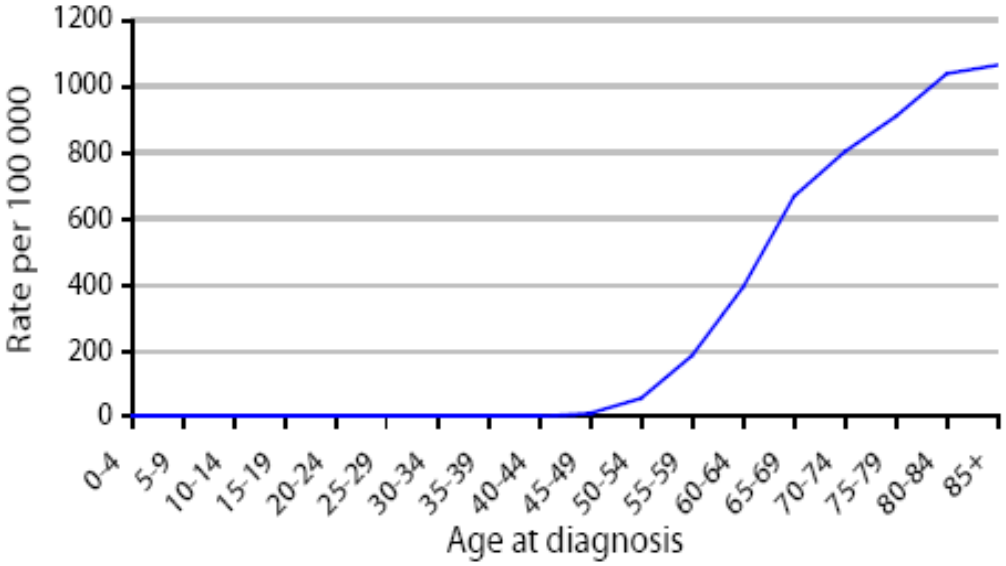


Figure 1: Age-specific incidence of prostate cancer in Norway 2000-2004 [3]

PC is rare before age 50 years, thereafter the incidence increases steeply with age (Figure 1).

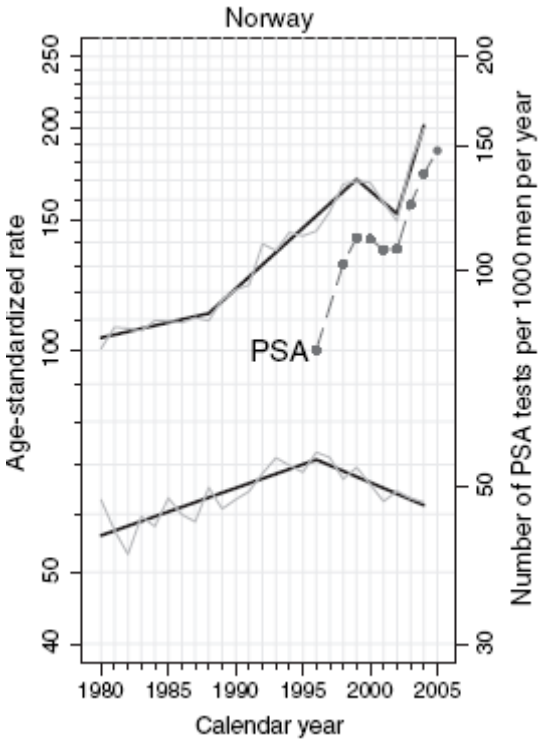


Figure 2. Time trend in incidence and mortality of prostate cancer in Norway, in relation to use of PSA testing [4].

PC is a disease of the elderly; around the world, three-quarters of cases occur in men aged ≥ 65 years [5]. The incidence of PC has been increasing the last 20 years, but mortality is now decreasing also in Norway (Figure 2). PC mortality rate in Norway are among the highest in the world [5]. From 1996 to 2004 mean annual decline in PC mortality rates in Norway was 1.8% [4].

The rapid increase in incidence during the early 1990s coincided with the introduction of the PSA test and conveys little information about the occurrence of potentially lethal disease. Mortality rates, however, have recently stabilized or declined in countries where PSA testing and curative treatment have been commonly practiced since the late 1980s [4]. PSA became available in the Nordic countries around 1990 [6]; rapid increases in PSA testing were associated with sharp increases in PC incidence (Figure 2).

Several reviews of the evidence on the causes and risk factors for PC have been published but the causes remain essentially unknown [1, 7]. The strongest risk factor

for PC is age, but hereditary factors (genes), race, dietary factors, and lifestyle-related factors contribute to the development of PC [8]. Finasteride, a selective inhibitor of 5α-reductase, inhibits the conversion of testosterone to dihydrotestosteron, taken for 7 years in the Prostate Cancer Prevention Trial reduced the prevalence of PC by 24.8 % versus placebo in 18882 men randomized to treatment with that agent [9]. Despite this definitive evidence of risk reduction, finasteride has generally not been accepted clinically because the first analyses showed increased risk of high-grade PC in the finasteride group. The results from radical prostatectomy (RP) have recently been reported and suggest that grading artefacts in biopsy Gleason scoring may have occurred [10-12].

With the more widespread use of screening, the prevalence of latent PC has decreased 3-fold (USA) [13]. In the period 1955-1960 vs. 1991-2001, the prevalence of latent PC detected only at autopsy in men older than 40 years was 4.8% compared to 1.2%, respectively. It appears that there is a shift toward lower stage and grade among the latent PC diagnosed at autopsy in the more recent period. However, a similar decrease in the prevalence of autopsy detected cancer was observed in Norway between 1957 and 1991, when there was no coordinated screening [14]. The proportion of PC reported to the Norwegian Cancer Registry as having been detected at autopsy between 1957 and 1961, 1977 and 1981, and 1987 and 1991 was 2.3%, 2.8% and 1.6%, respectively. A potential explanation for this finding is sampling error since the autopsy rate in Norway decreased significantly during this period. The median age at diagnosis in Norway in the period 1987-1991 was 75.1 years.

About one third of all patients in Norway under the age of 75 years with recently diagnosed PC were treated with curative intention in 1998 and 2001 (1998:28%, 2001:33%), but in Western- Norway it was 39% and 41% [15]. Data from the Norwegian Cancer Registry show that five years relative survival in Norway 1995-1999 was 74.9% and in Western-Norway 79.9%, probably reflecting a more active attitude for curative treatment, offering both surgery and radiation as treatment. Curative radiotherapy has increased in Haukeland University Hospital in the study

period (Figure 3), and in addition Stavanger University Hospital has offered curative radiation therapy since 1999.

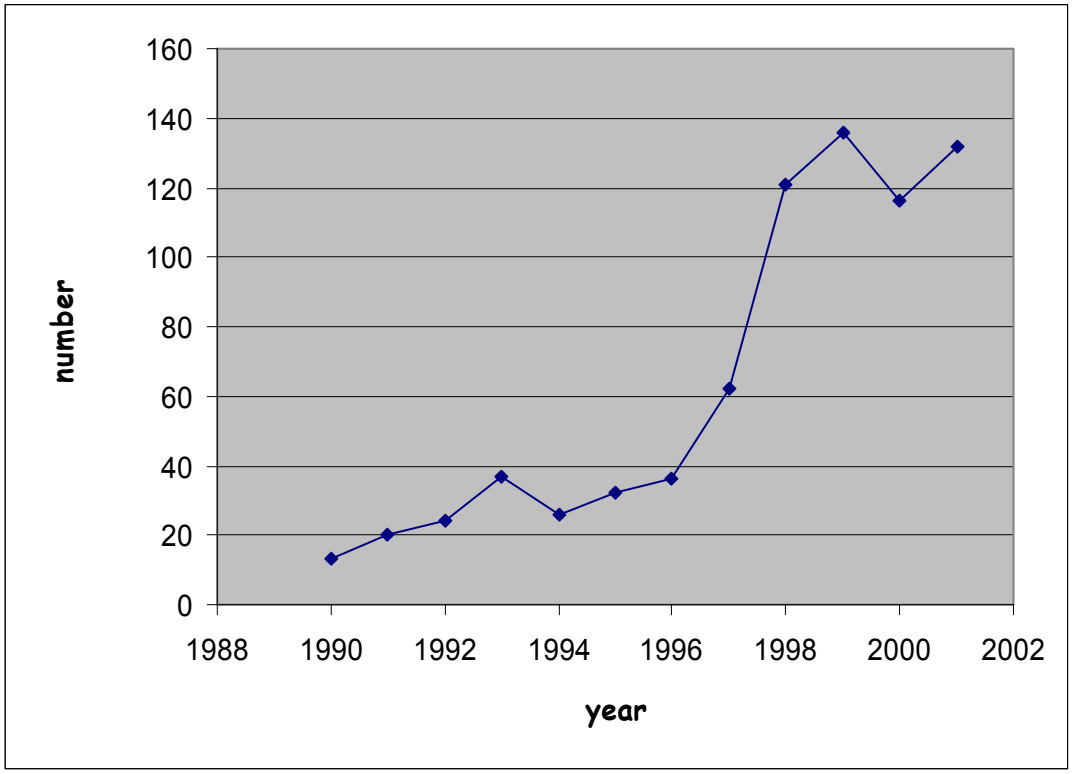


Figure 3. Number of prostate cancer patients having curative radiation treatment at Haukeland University Hospital in the period 1990 – 2001.

1.2 TNM categorisation of prostate cancer

The Tumour Node Metastases (TNM) classification system is the internationally accepted system for staging malignant tumour. The first uniform staging system for PC was published by the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC) in 1992, after earlier versions dating back to 1978 [16, 17]. The TNM staging system is used for treatment planning, prognosis estimation and evaluation of treatment results.

Two classifications are described for PC, clinical classified TNM (or cTNM) is based on evidence acquired before treatment. Such data arises from physical examination (digital rectal examination (DRE)), ultrasound, chest radiography, bone scan, PSA

and biopsy. For pathological classification, pTNM, histologic examination of the resected specimen is required after RP and lymph node sampling. The TNM system is used to numerically describe the anatomical extent of cancer and is based on three components: T, extent of the primary tumour; N, absence or presence of the disease in the regional lymph nodes; M, absence or presence of distant metastases [18]. The addition of number to these components indicates the extent of malignant disease. The M category is examined by chest X-ray and bone scan.

The TNM system thus incorporates a clinical and a pathological evaluation and has been revised in 2002 [19]. The present study applies the 1992 [20] and 1997 version [21]. The clinical stage is essential to select and evaluate therapy, while the pathological stage provides the most precise data to estimate prognosis and calculate end results [19].

In practice we have included patients in the following categories: stage T1c (often denoted T1), T2, T3 and T4.

Table 1. **UICC-TNM staging system (1992)**

T	**Primary tumour**
Tx	Primary tumour cannot be assessed
T0	No evidence of primary tumour
T1	Clinically unapparent tumour not palpable or visible by imaging
T1a	Tumour, an incidental histological finding in 5% or less of tissue resected
T1b	Tumour, an incidental histological finding in more than 5% of tissue resected
T1c	Tumour identified by needle biopsy
T2	Tumour confined within prostate
T2a	Tumour involves half a lobe or less
T2b	Tumour involves more than half a lobe but not both lobes
T2c	Tumor involves both lobes
T3	Tumour extends through prostate capsule
T3a	Unilateral extracapsular extension
T3b	Bilateral extracapsular extension
T3c	Tumour invades seminal vesicle(s)
T4	Tumour is fixed or invades adjacent structures other than seminal vesicles
T4a	Fixed or invades adjacent structures; bladder neck, external sphincter, rectum
T4b	Tumor invades levator muscles, fixed to pelvic wall
N	**Regional lymph node(s)**
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single regional lymph node < 2 cm
N2	Metastasis in a single regional lymph node > 2 cm but not > 5 cm
N3	Metastasis in regional lymph node > 5 cm in greatest dimension
M	**Distant metastasis**
Mx	Presence of distant metastasis cannot be assessed
M0	No distant metastasis
M1a	Non-regional lymph node(s)
M1b	Bone(s)
M1c	Other sites

Table 2. **UICC-TNM staging system (1997)**

T	**Primary tumour**	
Tx	Primary tumour cannot be assessed	
T0	No evidence of primary tumour	
T1	Clinically apparent tumour not palpable or visible by imaging	
	T1a	Tumour incidental finding in 5% or less of tissue resected
	T1b	Tumour incidental finding in more than 5% of tissue resected
	T1c	Tumour identified by needle biopsy (e.g. because of elevated PSA)
T2	Tumour confined within prostate	
	T2a	Tumour involves one lobe
	T2b	Tumour involves both lobes
T3	Tumour extends through prostate capsule	
	T3a	Extracapsular extension (unilateral or bilateral)
	T3b	Tumour invades seminal vesicle
T4	Tumour is fixed or invades adjacent structures other than seminal vesicles: bladder neck, external sphincter, rectum, levator muscles and/or pelvic wall	
N	**Regional lymph nodes**	
Nx	Regional lymph nodes cannot be assessed	
N0	No regional lymph node metastasis	
N1	Regional lymph node metastasis	
M	**Distant metastasis**	
Mx	Presence of distant metastasis cannot be assessed	
M0	No distant metastasis	
M1a	Non-regional lymph node(s)	
M1b	Bone(s)	
M1c	Other site(s)	

1.3 Histology

In Norway up to 2001, grading of PC was commonly performed according to the World Health Organisation (WHO) system. The WHO grading system takes into account the degree of nuclear anaplasia (nuclear grades) and the pattern of glandular differentiation (histologic grades) [22].

A widely acknowledged method of grading the aggressiveness of PC was developed by Donald F Gleason between 1969 and 1974, based solely on the architectural pattern of the tumour (Figure 4). Now the Gleason score is the most frequently used grading system for PC [23, 24].

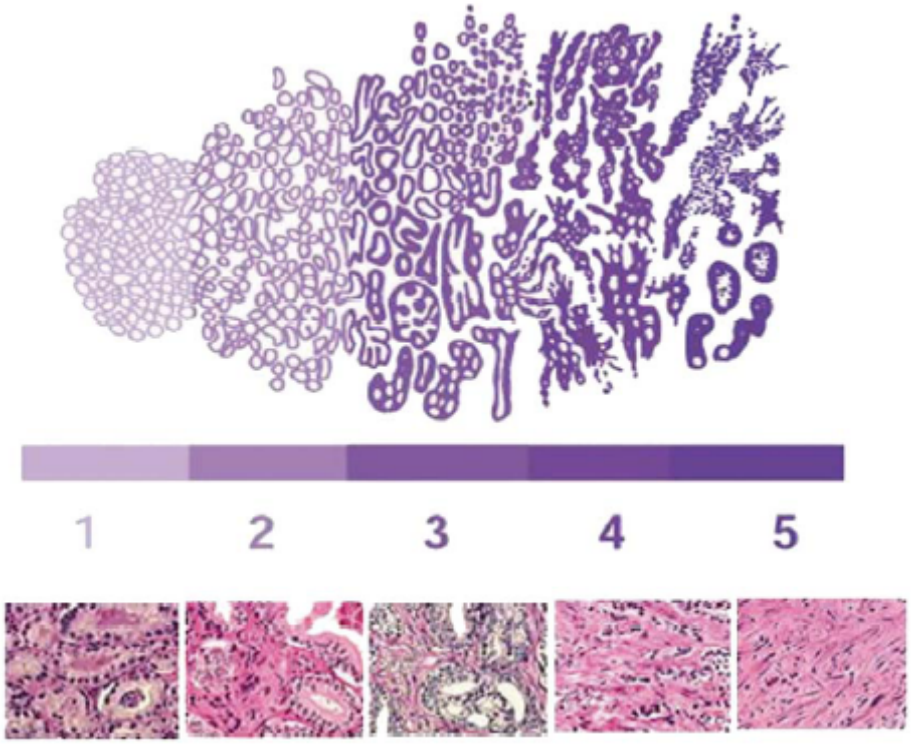


Figure 4. Schematic diagram of Gleason grading system [24]

Grade 1 (well differentiated), circumscribed mass of evenly spaced, closely packed, uniform shaped glands, with no evidence of infiltration of the stroma.

Grade 2 (well differentiated), some infiltration into the surrounding stroma and more variation in gland size and spacing, although this is limited.

Grad 3 (moderately differentiated), most common grade with more variation in size, shape, and separation of the glands, less defined boundaries, and less intervening stroma.

Grad 4 (poorly differentiated), fusion of the glands forming a solid anastamosing network with a ragged invasive edge.

Grad 5 (undifferentiated), characterised by a complete absence of gland formation with sheets or clusters of cells.

Because of the histological variation within each tumour, two grades, the predominant or primary grade, and the less extensive, or secondary grade, were recorded in each case, and then summed. For consistency, if only one grade was present, this was doubled. Then the outcome was reported as the Gleason score (score 2 – 10) [24]. Weaknesses in the Gleason grading system is that growth patterns that do not constitute the primary or secondary patterns (i.e., the tertiary growth patterns) are not reflected in the total score [23]. To deal with this issue, the International Society of Urological Pathology held in 2005 a consensus conference to address controversial issues surrounding the Gleason grading system [25]. Their recommendation regarding tertiary Gleason grade depended on the source of the specimen. For needle biopsy specimens, both the primary patterns and the highest grade should be recorded. For RP one assigns the Gleason score based on the primary and secondary patterns with a comment as to the tertiary pattern.

The Gleason score is routinely categorised into a three-tiered Gleason scoring system, scores 2-6, score 7 and score 8-10 [26]. Gleason score 7 tumours have been shown to behave significantly worse than Gleason score 5-6 tumours [27], but have a better prognosis than Gleason score 8-9 tumours [28]. Gleason score 7 tumours are heterogeneous in their biologic behaviour. The major prognostic shift is between 6 and 7, with further sub classification of score 7 to 3+4 or 4+3 with worse prognosis

associated with 4+3 [26]. The differences in prognosis for patients with Gleason scores 3+4 and 4+3 tumours at radical prostatectomy are significant [29-33]. A study by Patel and co workers [34], showed that men with PC having biopsy Gleason score 7 and tertiary grade 5 had a higher risk of PSA-failure when compared with men with Gleason score 7 without tertiary grade 5 and had a comparable risk with men with Gleason score 8 to 10.

The Gleason grading on prostate biopsy is a poor predictor of pathological outcome after RP, both undergrading and overgrading are considerable as only 29.2 % had identical grading in a reported study [35]. When grouped into more meaningful categories, Gleason 2-4, 5-6, 7 and 8-10, the correlation improved, with 48.5 % of patients remaining in the same group after RP [35]. There are also inter-observer variation in the reporting of Gleason scores for diagnostic biopsies, low grade tumours are often upgraded when reviewed by experts in urological pathology [36, 37].

It is now considered unacceptable to score Gleason sum 2-4 on diagnostic biopsies [36], because low-grade cancer are mostly located anteriorly in the prostate within the transition zone and tend to be small [38].

1.4 PSA

PSA is a single-chain glycoprotein produced almost exclusively by the epithelial component of the prostate gland [39], with a molecular weight of 33 kD and is about 7% carbohydrate. This antigen was initially identified and purified by Wang and associates [40] in 1979 from prostatic tissue, and detected in sera obtained from PC patients in 1980 [41]. Since the late 1980s PSA has been used widely in the clinical setting and has emerged as the most important tumour marker for PC [6, 42].

PSA is organ specific for the prostate gland, but not cancer specific. The specificity of the PSA test is suboptimal; a critical challenge is discriminating benign prostatic

hyperplasia from PC [39]. Many approaches have been proposed to make this task easier, age specific PSA, PSA-density, PSA-velocity and free/total PSA radio [43, 44]. The serum PSA levels can be temporarily altered by various pharmacological therapies, prostatic diseases and urological manipulations [45].

In clinical practise measurement of serum PSA supports the diagnosis of PC, monitors the efficacy of treatment and may serve as a prognostic tool.

After RP the majority of men have a rapid decline in serum PSA to undetectable levels. As a corollary the failure of PSA to become undetectable is highly suggestive of persistent disease after surgery [45]. PSA has been used as a surrogate end point to monitor disease activity following prostatic irradiation and this has been a major advance in recent years [46-48]. However, response of PSA to irradiation is more unpredictable; after radiation therapy PSA level decline more slowly and may not reach undetectable levels due to persistence of normal prostate tissue [45].

There are various guidelines for the interpretation of post radiation PSA profile and determination of biochemical failure (i.e. rising PSA). The most widely used guidelines are the **American Society for Therapeutic Radiology and Oncology (ASTRO**) [49] **guidelines**:

1. Biochemical failure is not justification per se to initiate additional treatment. It is not equivalent to clinical failure. It is, however, an appropriate early end point for clinical trials.

2. Three consecutive increases in PSA is a reasonable definition of biochemical failure after radiation therapy (RT). For clinical trials, the date of failure should be the midpoint between the post irradiation nadir PSA and the first of the three consecutive rises.

3. No definition of PSA failure had, as yet, been shown to be a surrogate for clinical progression or survival.

4. Nadir PSA is a strong prognostic factor, but no absolute level is a valid cut point for separating successful and unsuccessful treatments. Nadir PSA is similar in prognostic value to pre-treatment prognostic variable.

The ASTRO definition has been criticized because of its dependence on backdating and the erroneous conclusion that may be drawn if the follow-up is inadequate [50-52]. Also it lacks specificity when androgen deprivation therapy is used, leading to biochemical failure misclassification because the PSA level can rise transiently after the release of androgen deprivation [53].There is also a potential for false positives secondary to "benign PSA bounces" [54, 55]. It has also been shown to have a lower sensitivity and specificity for clinical outcomes than several alternative definitions [52].

In the thesis we used the "**Houston criteria**", which specify that relapse is scored when the PSA level is 2 ng/ml greater than the nadir (defined as the lowest no rising value) [52, 56-58]. Relapse was scores at the time when the "2 ng/ml over nadir" was first observed.

Because of the many shortcomings in the ASTRO definition, in 2006 a second Consensus Conference was sponsored by ASTRO and the Radiation Therapy Oncology Group (RTOG) in Phoenix, to revise the ASTRO definition.

Recommendations of the **RTOG-ASTRO Phoenix consensus** conference [59], suggested the following guidelines for the use of PSA as a parameter of prognosis and efficacy of radiotherapy:

1. A rise by 2 ng/ml or more above the nadir PSA be considered the standard definition for biochemical failure after external beam radiotherapy (EBRT) with or without hormone therapy (HT)

2. The date of failure be determined "at call" (not backdated)

Thus the definition we have used is the current recommended method to define biochemical failure after radiation treatment for PC.

Screening:

The PSA test detects PC at an early stage in many cases. At present, data are not yet available from large, well-designed, randomizes trials to determine whether early detection is beneficial or harmful or has no effects. As a result, the optimal strategy for early detection with PSA testing remains unknown [39]. PSA screening is recommended by the American Urological Association and the American Cancer Society annually for all men 50 years or older. For men with a family history of PC or of African-American descent PSA testing should begin at age 40 years [45]. The Norwegian Urological Cancer Group (NUCG) and Health Authorities do not recommend PSA screening at the present point [60, 61]. However, a revision of the statement awaits the results from the ongoing screening trials and taking into consideration that it has now been documented that surgery is better than observation [62]. The guideline is based on the presumption that no therapy is effective in prostate cancer.

The value of screening for PC in terms of lowering PC mortality is at present unproven. Two large studies [63, 64] address the issue and results are expected within the next few years. The decline in mortality observed in several countries the last years (Figure 2) may be related to “wildscreening” with PSA testing, better local therapy, or both.

2. Treatment of prostate cancer

The selection of optimal treatment for men with localised PC is controversial. As there is still no randomised trial with sufficient power comparing the main treatment alternatives, there is little solid evidence showing one management strategy to be superior to another. The choice of treatment often depends on the personal conviction of the physician in charge of the patients [65].

Partin tables are constructed for general patient risk evaluation, and the tables have recently been updated. They represent risk estimation using the baseline PSA, clinical stage and Gleason score, based on the pathologic evaluation of 5079 surgically managed patients [66, 67]. The Kattan nomogram was developed to predict the 5-years probability of treatment failure, defined as rising PSA level, among men with clinically localized PC treated with RP [68] or EBRT [69]. The RP nomograms was developed using clinical data and disease follow-up for 983 men with clinically localized PC, treated with RP. The clinical data included pre-treatment PSA, stage and biopsy Gleason score [68]. The nomograms for EBRT was based on clinical parameters of 1042 PC patients treated with three-dimensional conformal radiotherapy (3D-CRT), including stage, biopsy Gleason score, pre-treatment PSA, and whether neoadjuvant androgen deprivation therapy was administered, and the radiation dose delivered [69].

2.1 Radical Prostatectomy

The surgical treatment of PC consists of RP, meaning the removal of the entire prostate gland between the urethra and the bladder, with resection of both seminal vesicles. Current surgical techniques include an open retropubic or perineal incision, and quite a number of centres are now gaining experience with laparoscopic radical prostatectomy [70]. Pelvic lymphadenectomy can be performed concurrently with

radical prostatectomy and is generally reserved for patients with higher risk of nodal involvement [71].

RP is widely used in the treatment of low to medium risk PC; the patients need to have a life expectancy of at least 10 years and absence of comorbidity. Survival is remarkable with 10 year's cancer specific survival of 94-98 % [72, 73]. Long-term side effects may include erectile dysfunction (14-71%) and urinary incontinence (7 - 14%) [74-76]. The effect of surgery on potency seems to be age dependent [74]. Surgical experience has decreased the complication rates and improved cancer cure [77, 78].

RP is the only treatment for localized PC that has shown a cancer specific survival benefit when compared to watchful waiting (WW) in a prospective, randomized trial [62].

2.2 External beam radiation therapy

EBRT was introduced for PC as early as in the 1930s when Wiedmann reported palliation with low-energy orthovoltage treatment in patients with this disease [79]. This treatment was superseded in the early 1940s by introduction of hormone deprivation by Huggins and Hodges [79]. In the mid 1950s definitive external radiation of PC was introduced by Bagshaw who applied the linear accelerator technology and by George and Del Regato who used cobalt units [79]. Since then, the technological development in RT has been enormous. Besides, also the treatment techniques and the treated volumes have changes considerably over the years. Bagshaw [79] introduced large fields to encompass the pelvic lymph nodes (up to 50 Gy) before completing treatment using smaller fields up to full dose.

Early use of definitive EBRT for PC involved so-called two-dimensional (2D) radiotherapy, usually consisting of a single beam from one to four directions. Beam setups were usually quite simple; plans frequently consisted of opposing AP/PA or lateral fields or four field "boxes". The introduction of 3D, or CT-based, planning

represented a major step forward because it became possible to take into account axial anatomy and complex tissue contours. While 3D planning allowed for accurate dose calculations, 3D-CRT first became available in the mid 1980s, and by the early 1990s reports from several institutions supported the notion that compared with conventional therapy, rectal toxicity was lower than expected despite higher doses [80, 81].

Radiation target volumes are defined according to the International Commission on Radiation Units and Measurements (ICRU) report 50 [82]. The Gross Tumor Volume (GTV) is defined as all known disease indicated by the planning CT or any other information. The Clinical Target Volume (CTV) is defined as the GTV and subclinical microscopic malignant disease. In PC, the entire prostate is usually considered the CTV. Finally, the Planning Target Volume (PTV) is the CTV plus a surrounding margin to account for the variability of treatment setup and the internal organ motion. The ICRU 62 report [83] provided guidelines and a framework for studies on internal motion and set-up variability for determination of treatment margins.

EBRT remains a mainstay in the treatment of patients with PC. High radiation dose is important to eradicate all tumour cells. The improved technologies have improved the ability to dose-escalation to the prostate while sparing the volume of normal tissue (rectum and bladder) that receives clinically significant doses, resulting in a reduction in complication rates [84].

A Scandinavian randomized phase III trial [85] has demonstrated a 10 % absolute survival benefit after a median follow up of 7.5 years, from addition of EBRT to HT, in patients with locally advanced PC . Absolute difference in cumulative incidence of PSA recurrence at 7 years was 53.5 %, indicating that with longer follow-up the survival benefit will further increase.

2.2.1 Intensity modulated radiation therapy (IMRT)

IMRT is a refined CRT technique that produces highly individualised dose distributions, tailored to the anatomy of the specific patient. The clinical applications include conformal avoidance strategies aimed at reducing the radiation dose to organ at risk (OR) (rectum, small bowel and bladder) and hence normal tissue radiation toxicity, or radiation dose escalation to tumours with the goal of increased tumour control [86]. This is accomplished by using computer-controlled movement of the multileaf collimator (MLC), either by continuous movement during beam delivery (dynamic IMRT) or by step-wise leaf movement between the beam segments (segmental IMRT). The third conventional IMRT approach called intensity-modulated arc therapy (IMAT) [87] or volumetric modulated arc therapy (VMAT), uses multiple irregular fields shaped with a conventional MLC during gantry rotation, in the latter also the dose rate is modulated during beam delivery [88-90].

Use of IMRT for pelvic irradiation in PC reduces normal tissue doses, improves target coverage, and has a promising toxicity profile [91].

The use of IMRT is opening the way for concomitant delivery of different doses to different target volumes, e.g., combining two-phase treatment using integrated boost as well as local dose escalation, resulting in a shorter duration for the overall treatment time [92]. In October 2006 our institution moved into a Phase II IMRT study of a simultaneous integrated boost (SIB) for locally advanced PC patients, where we simultaneously treat both pelvic lymph nodes (with conventional fractionation, i.e., 2 Gy per fraction) combined with hypofractionated doses (2.4-2.7 Gy per fraction) to the prostate and seminal vesicle, in a total of 25 fractions [93, 94].

IMRT and inverse treatment planning have provided new methods to deliver nonuniform or shaped dose distribution. There is an increasing interest in integrating biological information into IMRT. New types of image can provide biological and mechanistic data, for example, MRI spectroscopy, single-photon emission CT (SPECT) and positron-emission tomography (PET), allowing for identification of the

cancer within the prostate gland, enabling “dose painting” to the tumour areas [95-97]. Dose painting strives to tailor the dose inside the tumor to deliver the exact amount of radiation needed for eradication and challenges the dogma of dose homogeneity to the target [98].

2.2.2 Image-guided radiation therapy

Organ motion is a challenge facing RT, recent studies have shown a significant organ motion of the prostate, both inter- and intrafraction [99]. Implanting three fiducial gold seed markers in the posterior and apical prostate gland is well tolerated and no significant seed migration occurs [100]. Daily electronic portal imaging of intraprostatic markers has been established as a reliable standard for online verification of treatment [101]. This allows for reduction of the PTV margins because of improved setup accuracy and reproducibility, and a corresponding lower dose to the ORs [102], it can also monitor volume change in the prostate that can occur over time due to hormone or RT [100].

Helical Tomotherapy is another approach to image-guided radiotherapy. In the last years there has been a transition in radiation oncology from standard treatment planning and targeting methods to more advanced approaches based on significant improvements in imaging and treatment delivery [103]. The helical delivery permit to obtain highly tailored dose distribution with excellent coverage and homogeneity within different targets, especially in the case of concomitant boost delivery [104, 105]. Dose delivery is performed by translating the patients in a continuously rotating fan beam modulated by a binary MLC [106]. A clinical study with Helical Tomotherapy in 35 patients with PC, pelvic lymph node where simultaneously treated combined with hypofractionated doses to the prostate and seminal vesicle or the prostatic bed only, in a total of 28 fractions, showed very low incidence of acute Grade 2 and no acute Grade 3 toxicity [106]. However, longer follow up is necessary for final evaluation of this approach.

2.2.3 Acute and late toxicities after EBRT

Along with improvement in cancer survival, the importance of toxicity measurements for cancer treatment is becoming increasingly important. In PC, there is a variety of different treatment options with the same outcome in terms of cure, but with different late toxicities.

The therapeutic use of ionizing radiation is predicated on sparing normal tissue effects while attempting to achieve lethal effects on tumour cells.

Early normal-tissue response: Treatment related morbidity that occurs within 90 days after the start of radiotherapy (Cox 1995). Early reaction is usually transient. The development of early effects in rapidly renewing tissue such as skin, gastrointestinal tract and the heamopoietic system is generally due to damage to parenchymal cells, and α/β ratios tends to be high [107].

Late normal-tissue response: Treatment related toxicity that occur or are persistent 90 days or more from the start of radiotherapy. Late effects manifest months to years after acute effects heal, and often progress with time. Late effects can be expected in slowly proliferating tissues, such as lung, kidney, heart, liver and central nervous system, generally due to damage to connective-tissue cells, and α/β ratios tends to be low [107].

Several authors have indicated a direct relationship between acute and late GI morbidity, independent of dose [108, 109]. This phenomenon, known as consequential late effect, is defined as a direct consequence of acute radiation response causing tissue damage, which eventually leads to late effects after a latent symptom-free interval [110, 111].
The RTOG developed the late RTOG toxicity criteria in 1981 and in 1985 the acute RTOG criteria as a complimentary scheme [112]. The National Cancer Institute developed standard toxicity criteria in 1990, but late effects were not considered. In 1995 the LENT SOMA scoring system was introduced, with the acronym LENT referring to Late Effects in Normal Tissue and SOMA referring to Subjective,

Objective, Management and Analytic [113]. The Common Toxicity Criteria version 1.0 (CTC v1.0) of 1983 was developed for chemotherapy-related adverse effects. It was upgraded and expanded in 1998, but CTC v2.0 was still focused on acute effects, including early radiation effects [114]. In 2003 a new version, CTCAE v3.0 (Common Terminology Criteria for Adverse Events v3.0) was published which represents the first comprehensive multimodal grading system to include both acute and late effects of cancer treatment [115]. It is considered as a "dynamic" document and will be updated regularly as necessary. Overall, this large activity underlines the importance of standardisation to improve the recording of toxicity. A therapeutic gain cannot be achieved without carefully balancing tumour cure and survival rates against morbidity. Development of standardized common toxicity criteria and a widespread adoption of these in clinical trials would be a major step forward for clinical cancer research [116].

2.3 Brachytherapy

There are two major methods of prostate brachytherapy, low dose rate (LDR) permanent seed implantation using iodine 125 (^{125}I) or palladium 103 (^{103}Pd) and high dose rate (HDR) temporary brachytherapy using iridium 192 (^{192}Ir). The dose prescribed is usually 145 Gy for ^{125}I and 125 Gy for ^{103}Pd at the periphery of the target volume. The prescribed dose for HDR temporal brachytherapy is usually 10-15 Gy/2 fractions in addition to 40-50 Gy delivered using EBRT [117-119] and maximal androgen blockade (MAB) [120].

The American Brachytherapy Society has recommended brachytherapy monotherapy for patients with clinical stage T1c-T2a, serum PSA level of $\leq$ 10 ng/ml, and a Gleason score of $\leq$ 6, with the addition of supplemental EBRT for all those with higher risk feature [121]. The prostate volume should be less than 50cm^3, the patients should have a low urinary symptom score and a life expectancy of at least 5 years [118].

Factors that predict higher complication rates include prostate size at the time of treatment (larger than 50-60 cm^3). The patient's urinary symptom score before treatment (this is the most sensitive predictor of urinary morbidity), as well as recent transurethral resection of prostate (TURP) (being associated with a higher than usual risk of incontinence [117, 122]). Long term side effects are urethral stricture in 1.7-12 %, proctitis in 2-11 % and approximately 30-53 % may become impotent [118, 123, 124].

2.4 "Active surveillance" or "watchful waiting"

In early PC, the choice of therapy is complex. The majority of newly diagnosed PC patients now have low risk T1c disease. Pathology studies have suggested that 16-19 % of T1c cancers are insignificant [125, 126]. Patients with PC who fall into this category include men with a Gleason score $\leq$ 6, a PSA of $\leq$ 10 ng/ml and stage T1c or T2a disease [127]. As a result of stage migration because of PSA screening, the proportions of newly diagnosed patients who fall into the "favourable-risk" category has increased and now constitute 50 % to 60 % of patients [128]. Although patients with these characteristics have a much more favourable natural history and progression rate than those with a higher Gleason score or PSA, some of them still progress to advanced, incurable PC and death [129]. The main challenge in these patients is to identify the minority of patients with aggressive PC, and offer them curative treatment, while sparing the remainder the morbidity of unnecessary treatment [130]. A new promising option is **active surveillance**, which aims at individualised therapy by selecting only those men with progression and therefore significant cancer for curative therapy [131, 132]. However, this policy depends on active monitoring using PSA and repeated prostate biopsies and about one third will sooner or later need treatment [133]. Klotz reported on a cohort of 299 patients, in which 80 % was defined as low risk. At 8 years, the overall survival was 85 % and disease specific survival was 99 %. However, he concluded that **WW** is clearly appropriate for elderly PC patients with high rate of comorbidities. For low risk,

young, healthy patients, this study supports the feasibility of long-term, close monitoring with early intervention for those who exhibit rising PSA [131].

Active surveillance for screening-detected, low volume cancer is based on the following 5 postulates [134]:

1. PC screening results in the detection of PC that is not clinically significant in many patients (i.e. untreated, would not pose a threat to health).
2. The patients who fall into this category can be identified with reasonable accuracy.
3. There is no treatment that is minimal in terms of side effects and cost.
4. Patients who are initially classified as low risk who reclassify over time as higher risk and are treated radically are still cured in most cases.
5. The psychological burden of living with untreated cancer has less impact on quality of life than unnecessary but curative therapy.

It is important to distinguished active surveillance from WW. WW involves observation with late treatment for those who develop symptoms of progressive disease [133]. It is appropriate for elderly PC patients with co morbidities or limited life expectancy. In the PSA era, few patients are willing to be managed with WW until metastatic disease develops [135].

At present, there is no reliable individual clinical or pathologic factor that can differentiate an indolent tumour from an aggressive one [136].

2.5 Future prospects of radiation therapy

During the last 20 years, the primary focus for technologic advancement in radiation oncology had been on improving the methods of dose delivery, for both maximum tumor control and minimum normal tissue toxicity [101]. The fast development of EBRT modalities is very promising, and more patients are now cured with RT. In the early to mid 2000s, functional and anatomic imaging began to be used to better define

the extent of disease for men with clinically localized PC. During the next 5 to 10 years, better understanding of biology combined with functional and anatomic imaging will likely drive future advantage in radiotherapy for PC [101].

Proton therapy has been in clinical use since the 1970, the main rationale had been poor local disease control with conventional therapy, and the proximity of critical dose-limiting normal tissue, which is a bar to safe dose escalation using conventional photon RT [137]. A single proton beam has a low entrance dose, a maximal dose at a user-defined depth (the “Bragg peak”), and no exit dose. These characteristics make possible a substantial reduction in integral dose (i.e dose delivered to normal tissue), and a favourable dose-distribution over conformal therapy [138]. However the role of proton RT in the treatment of PC remain unclear because similar treatment results have been reported for modern photon techniques such as IMRT or stereotactic photon RT [139].

Carbon ion (C-ion) beam offer advantageous biological and physical properties in RT (inverse dose profile, Bragg peak) [140, 141] both improved dose distribution and probability of normal tissue complication will be minimized. They have a high relative biological effectiveness resulting from high linear energy transfer [142], the relative biological effectiveness value for C-ion is estimated to be about 3 times those of photons [143]. Clinical phase II studies of hypofractionated C-ion RT for PC have confirmed the effectiveness and safety of the treatment [143-145]. At the present time no conclusion can be draw concerning the utility of C-ions in the treatment of PC [146].

2.6 Hormone therapy and chemotherapy

Primary androgen deprivation therapy (ADT) may be employed with the goal of providing symptomatic control of PC for patients in whom definitive treatment with surgery or radiation is not possible or acceptable [71].

One rational for combining adjuvant hormones with definitive radiation is to decrease the volume of the prostate, which decreases the size of the treatment fields, which in turn potentially decreases toxicity to adjacent normal tissues. A second rationale for combining hormones and radiation is to improve the effectiveness of radiation [147]. The use of early ADT in combination with radiotherapy in patients with localized and locally advanced disease, has shown to delay disease progression and to improve overall survival (OS) [148-152]. The National Comprehensive Cancer Network (NCCN) recommends HT plus RT for patients with high-risk disease [153].

Neoadjuvant ADT before RP is not indicated today and should not be utilized outside a clinical research setting [154]. Timing of the institution of ADT for PC remains controversial, but there is a growing consensus that men with nodal disease at the time of RP have a survival benefit from immediate ADT [154-156].

ADT is the mainstay of treatment for recurrent metastatic PC (chemical or surgical castration). The response to treatment last for a median duration of 18-24 months. Most men become resistant to therapy and develop hormone refractory PC (HRPC) [157]. ADT provides important quality of life benefits, including reduction of bone pain, pathological fracture, spinal cord compression and ureteral obstruction. However, it is not clear whether there is an improvement in long-term survival [158]. Although no clear-cut guidelines have been established, there is a growing tendency to treat patients with recurrent PC with ADT at some point when PSA is rising, prior to symptom development [154]. Once all hormonal options have been exhausted, advanced disease can be considered to be truly hormone refractory, although luteinising hormone releasing hormone (LHRH) agonist therapy should be continued to avoid testosterone-induced accelerated progression [159].

Until recently, few options were available for men with HRPC. The aim of the chemotherapy is to prolong survival and improve well-being. In the late 90s two studies comparing mitoxantrone plus corticosteroids or corticosteroids alone for symptomatic HRPC, showed pain relive and improve quality of life more frequently with the combination arm than corticosteroids alone, but neither demonstrated an

improvement in survival [160, 161]. Consequently the Food and Drug Administration (FDA) approved the combination of mitoxantrone and corticosteroids for the treatment of symptomatic patients with HRPC [157].

Combination of vinorelbine and hydrocortisone versus hydrocortisone alone in randomised phase 3 study [162], showed an advance in the combination arm, in terms of six-month progression-free survival, PSA response and clinical benefit, but no improvement in survival. In a phase 3 trial comparing vinblastin with vinblastin plus estramustine, a statistically significant advantage in terms of time to progression and PSA response was found in favour of the combination arm, but not significant improvement in OS [163].

Vinorelbine and hydrocortisone represents a valid alternative therapeutic option for the treatment of patients with HRPC, especially those who are not suitable for treatment with taxanes and/or mitoxantrone, or after taxane failure [162].

A phase 2 study with weekly docetaxel and prednisolone versus prednisolone (best supportive care) alone in HRPC patients was conducted in Norway [164], the study confirms the activity of weekly docetaxel in HRPC patients and indicated superiority in pain relief and quality of life assessment.

In 2004, two large randomized phase 3 trials SWOG 99-16 [165] and TAX327 [166], where published. The SWOG 99-16 trial compared docetaxel plus estramustine with mitoxantrone plus prednisone. It showed advances in median OS and median time to progression in the docetaxel arm. The TAX327 trial had two schedules of docetaxel administered with prednisone were compared with mitoxantrone plus prednisone, the standard chemotherapy for HRPC. It showed a significant improvement in median OS for the group that received docetaxel every three weeks than for the mitoxantrone group, but not for the group that received weekly docetaxel. Overall, as compared with the mitoxantrone group, the docetaxel group had better pain control, better quality of life and more frequent PSA response, but at the cost of higher incidence of adverse effects.

In May 2004 the FDA approved docetaxel 75mg/m^2 every 3 weeks plus prednisone, as front line therapy of HRPC [167]. It is reasonable to conclude that treatment with docetaxel plus prednisone administered every 3 week can be considered the treatment of choice in the first line in HRPC in fit patients. If the goal of treatment is palliation, weekly docetaxel therapy is justified. Mitoxantrone plus prednisone has become the de facto second-line regiment [157].

Even though HRPC remains incurable, it is not untreatable, today there are many phase 2 study ongoing focusing on antiangiogenic drugs in combination with chemotherapy [168].

3. Aims of the study

The aims of the present thesis were:

1. To analyse the effect of radiation **dose escalation** (cohorts of 64 Gy, 66 Gy and 70 Gy) on PSA failure, cancer specific survival (CSS) and OS in patients with prostate cancer (Papers I and II).

2. To analyse the impact of radiation dose escalation and hormone treatment on PSA failure free survival (bNED), CSS and OS in prostate cancer patients according to **risk group** (Paper II).

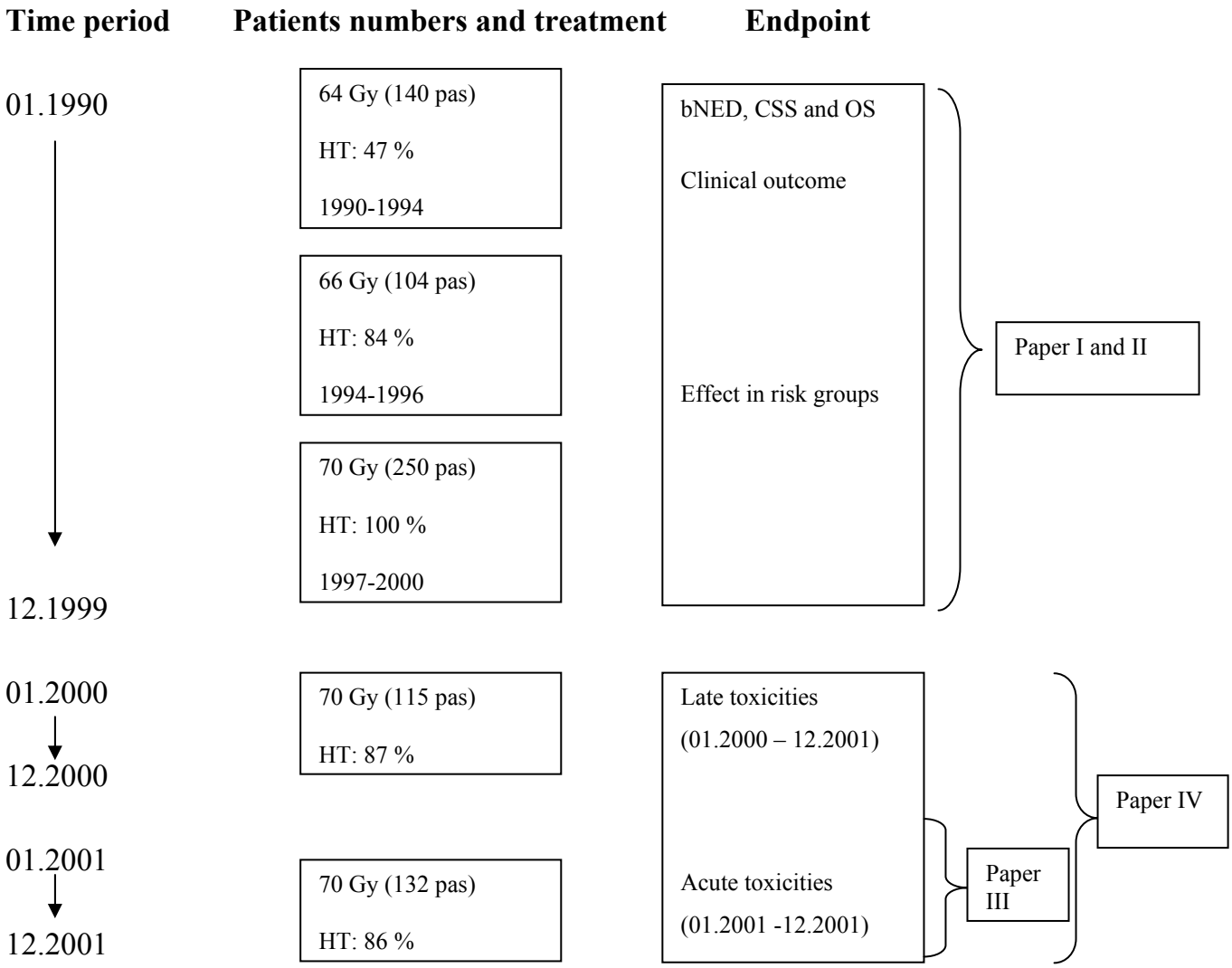
3. To investigate frequency of **acute toxicity** (gastrointestinal and genitourinary), the relation between **acute toxicity** and irradiated volume in the organs at risk (rectum and bladder) during three-dimensional conformal radiation therapy for prostate cancer (Paper III).

4. To investigate the incidence, time course and relation to irradiated volumes of **late toxicity** after three-dimensional conformal radiation therapy for prostate cancer (Paper IV).

4. Patients and methods

This chapter gives an overview of the patients series included and the methods applied to fulfil the aims of the study. More specific details can be found in the corresponding papers (Papers I-IV).

4.1 Patients materials



This study included patients with localised and locally advanced prostate cancer (T1-T4NxM0) that were offered EBRT, with or without androgen deprivation, between January 1990 and December 2001 at Haukeland University Hospital.

In paper I-II, the study population (494 patients) included patients treated between January 1990 and December 1999. In this period the tumour dose was stepwise escalated from 64 Gy via 66 Gy to 70 Gy. After radiotherapy the patients were scheduled to be followed at the department of urology at the local hospital, or with the patient's general practitioner. Annual reports were sent to the Department of Oncology, Haukeland University Hospital, reporting on clinical progression, adverse effects and death. All patients were followed to death or to May 5, 2004.

PSA level was used as a surrogate endpoint for disease activity. We used the Houston method which specify that a relapse is scored when PSA is 2 ng/ml greater than the nadir PSA [56-59]. All patients with a rising PSA above this level were considered as having biochemical failures.

In paper II we defined three risk groups, with patients in the low risk group having stage T_{1c} disease, a pretreatment PSA level ≤ 10 ng/ml and a WHO Grade 1. In the intermediate risk group, patients had one or more of the following adverse factors: stage T_2 disease, PSA > 10 ng/ml and ≤ 20 ng/ml and biopsy WHO Grade 2. Patients in the high-risk group had one or more of the following factors: stage T_3 disease, PSA > 20 ng/ml and biopsy WHO Grade 3.

In paper III, the study population (132 patients) included all patients treated from January to December 2001. In paper IV, the study population (247 patients) included all patients treated from January 2000 to December 2001. All these patients were prescribed a total dose of 70 Gy. Patients were stratified into three treatment groups according to T-stage, PSA and Gleason score:

Group P: In patients with clinically organ-confined disease of stage T1c, PSA ≤ 10 and Gleason score ≤ 7 (3+4 but not 4+3), the CTV encompassed the prostate only.

The patients received radiation to the prostate med wide margin to 50 Gy, followed by a 20 Gy boost to the prostate with narrow margin.

Group PSV: Patients with clinically organ-confined disease of stage T1c with PSA > 10 but ≤ 30 or Gleason score ≥ 7 (4+3 but not 3+4), as well as all patients with T2 disease, received radiation to the prostate and seminal vesicles to 50 Gy, followed by a 20 Gy boost to the prostate only.

Group MPF: In patients with stage T3 or N+ a larger volume was treated with modified pelvic fields to 50 Gy, followed by a reduced volume, which encompassed the prostate and seminal vesicle [148].

In paper III, 26 patients (20 %) were in Group P, 86 patients (65 %) in Group PSV and 20 (15 %) in Group MPF. In paper IV, 48 patients (20 %) were in Group P, 154 patients (62 %) in Group PSV and 45 (18 %) in Group MPF. All patients were seen for follow-up every 6 months during the first year and then annually thereafter. At each follow-up visit, late gastrointestinal (GI) and genitourinary (GU) morbidity was scored.

Pre-radiotherapy diagnostic work up: The patients were staged by physical examination, PSA testing and isotope bone scan. For most patients a diagnostic transrectal ultrasound and computer tomography (CT) scan was also performed. Surgical lymph node staging and magnetic resonance imaging (MRI) were not routinely performed. In Papers I and II the primary tumour was clinically staged according to the 1992 TNM classification for PC [20] and in Papers III and IV according to the 1997 TNM classification for PC [18], but without grouping into subcategories (a, b, c). Histology was in the first part of the study based on WHO histological grading (302 patients) [22], later according to the Gleason scoring system (192 patients) [169]. As the treatment decision were based on the original WHO grading, we have used the original grading in the analyses. But in the uni-and multivariate analysis in Paper I and II, we converted Gleason score into WHO

grading: Gleason score 4-6 to well differentiated, Gleason score 7 to moderately differentiate and Gleason score 8-10 to poorly differentiated [170].

4.2 Radiotherapy and hormonal therapy

All patients underwent EBRT with individualised treatment planning, using high energy photons to a total tumour dose of 64 - 70 Gy, in 2 Gy fractions five days a week, over 6 - 7 weeks. Before 1995 the treatment plan was based on a diagnostic CT with adaptation to the patients contour at simulation, later all treatment plans were based on images from our dedicated CT scanner. Until 1995 we applied a four-field box technique (opposing anterior-posterior fields and two opposing lateral fields) with 2 cm uniform margins to 50 Gy before a boost with smaller margins were delivered using four fields or two lateral fields to a total dose of 64 Gy (Figure 5).

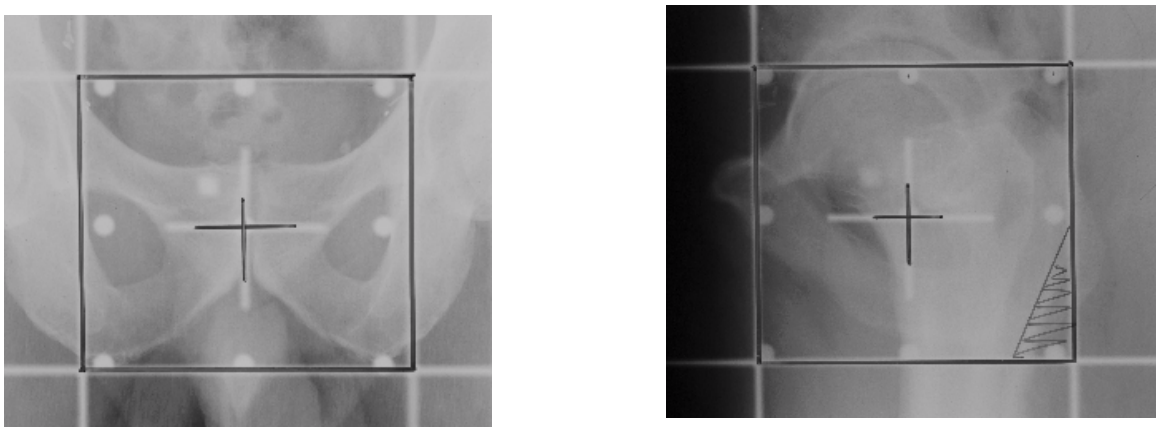


Figure 5. Typical conventional definitive radiotherapy of prostate cancer using two opposing AP-PA fields (a), and two opposing lateral fields (b), as used 1990 - 1995.

Field shaping with individually customised blocks was used occasionally in the first part of the study period, and routinely from 1994. In 1996, the use of customised blocks was substituted by MLC. In addition, the dose was increased, first to a total dose of 66 Gy, and then further increased to 70 Gy in 1997 (Figure 6). A dose of 50 Gy was given during a five-week period to a large volume, while an additional 20 Gy was given over the last two weeks to a smaller target volume (the boost volume). The dose was prescribed as the mean dose to the internal target volume (ITV).

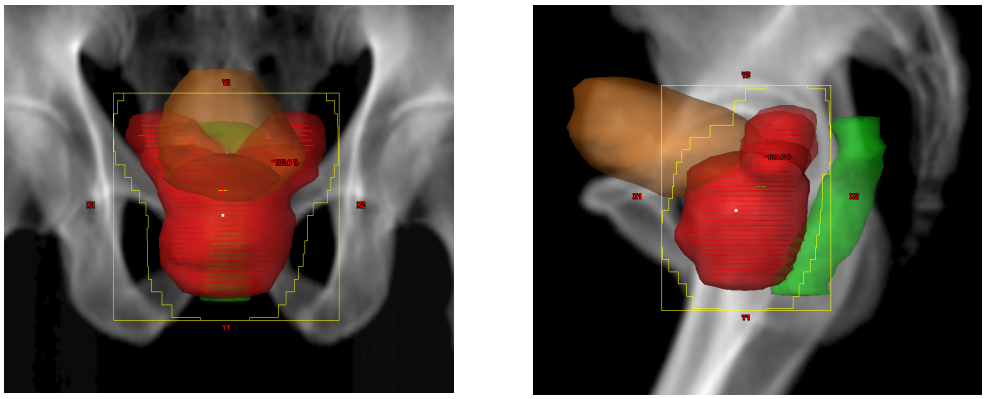


Figure 6. Conformal radiotherapy (CRT) of prostate cancer, AP-PA field with vesicular seminalis included (a) and lateral field (b), used 1996 – 2001.

Neoadjuvant and adjuvant HT was used in many patients. In the first part of the study period LHRH agonist was used to downstage tumours before RT for an average of 4-6 months. Later patients presenting with more advanced tumours in the prostate (stage ≥ T2a, PSA > 10 or Gleason score ≥ 7 [4+3 but not 3+4]) were candidates for a 6-months course of LHRH agonist and antiandrogen (MAB). The endocrine treatments started 3-4 months before CRT and were administered to reduce the prostate volume and thereby reduce the dose of radiation delivered to the rectum and bladder [171-178]. The HT continued during and at least one month after the start of RT, to exploit the possible synergy between HT and radiation [179].

4.3 Scoring of acute and late side effects

In Paper III symptoms of acute GI, anal and GU toxicity induced by the radiotherapy was recorded. The RTOG acute toxicity scoring system was used to grade GI and GU toxicity during the course of treatment [112]. Anal symptoms were scored according to the modified scoring system of Koper et al. [180] (Table 3). In general, GI or GU symptoms that needed medical prescriptions were scored at least as Grade 2 toxicity. Patients were seen before and at least two times during treatment (week two and six), or more frequently if required.

In Paper IV symptoms of late GI and GU toxicity induced by the RT was recorded. The RTOG scoring system [112] was used to grade late GI and GU toxicity from 3 months after treatment and up to 5 years after treatment. Late complications were defined as side effects developing more than 90 days after the completion of irradiation or those that started prior to and persisted for longer than 90 days after completion of treatment. For each symptom, the maximum recorded grade was defined as the grade of late toxicity, even when the side effect later declined. When patients were diagnosed with a locoregional recurrence, further assessment of complications was omitted from that moment on, as distinction between treatment-related or recurrence-related symptoms can be difficult. Patients with biochemical relapse or distant metastases only were not censored from the analysis.

Table 3. The modified RTOG acute scoring system

Grade	Lower GI including rectum	Genitourinary	Anal*
0	No change	No change	No change
1	Increased frequency or change in quality of bowel habits not requring medication/rectal discomfort not requiring analgesics.	Frequency of urination or nocturia twice pre-treatment habit/dysuria, urgency not requiring medication	Discomfort or pain not requiring analgesics
2	Diarrhea requiring parasympatholytic drugs/mucoous discharge not necessitating sanitary pads/rectal or abdominal pain requiring analgesics.	Frequency of urination or nocturia that is less frequent than every hour. Dysuria, urgency, bladder spasm requiring local anesthetic	Discomfort or pain requiring analgesics
3	Diarrhea requiring parental support/serve mucous or blood discharge necessitating sanitary pads/abdominal distention	Frequency with urgency and nocturia hourly or more frequently/dysuria, pelvis pain or bladder spasm requiring regular, frequent narcotic/gross hematuria	Discomfort or pain requiring narcotics
4	Acute or subacute obstruction, fistula or perforation; GI bleeding requiring transfusion; abdominal pain or tenesmus requiring tube decompression or bowel diversion	Hematuria requiring transfusion/acute bladder obstruction not secondary to clot passage, ulceration or necrosis	

*ad modum Koper et al. [180] and RTOG [112]

4.4 Dose-Volume Histograms (DVH)

In Papers III and IV the DVHs were calculated for the total treatment plan (to 70 Gy) for both ORs, e.g. the bladder and rectum, to investigate a possible correlation with observed toxicity (acute and late toxicity). Since both the rectum and bladder were defined as solid organs, the DVHs contained the dose to the whole of this volume (i.e., including contents). From the DVHs of each patient, the mean dose and the

volume fraction above dose levels from 0 to 75 Gy in steps of 1 Gy were derived [181].

4.5 Statistics

In Paper I, the primary endpoint was CSS, with OS and biochemical failure (BF) being secondary endpoints. The time to the relevant events was measured from the start of RT, analysed by Kaplan-Meier plots and assessed by the log-rank test [182]. Differences between groups were analysed by Kaplan-Meier plots and tested for statistical significance, initially using the log-rank test while Cox regression was used for univariate analyses of continuous covariates. Multivariate analysis was conducted using the Cox proportional hazard regression model. The statistical significance of the variables entered into the multivariate analysis was assessed using likelihood ratio tests.
In Paper II, the primary endpoint was CSS, with OS and bNED being secondary endpoints. The time to the relevant events was measured from the start of radiation therapy, analysed by the Kaplan-Meier method and assessed by the log-rank test as well as the multivariate Cox regression models.

In Paper III, we evaluated the differences between treatments groups, testing the effect of co-morbidity on toxicity and effect of volume on acute toxicity with the Jonckheere-Terpstra test. To evaluate the differences between groups for the median DVH, one-way ANOVA with Scheffé post hoc analysis was used (the non-parametic version were seen to give the same results). A permutation test (using StatXact 5) was performed to evaluate the difference in relative DVH parameters between patients with Grade 0+1 vs. Grade 2 or higher morbidity. The effect of various treatment and background variables on acute toxicity was tested by logistic regression. In the DVH analyses, the significance of differences between the groups was tested by ANOVA and the Kruskal-Wallis-test. The effects of including each DVH variable in our logistic regression models were evaluated using the crude correlation measure of

predictive power introduced by Zheng and Agresti [183] and their *p*-values based on the likelihood ratio test [181].

In Paper IV, comparison of patient characteristics between treatment groups was done using exact chi-square tests and one-way analysis of variance (ANOVA) for categorical and continuous variables, respectively. Changes of ≥ Grade 2 GI and GU morbidity during follow-up were analysed by population average logistic regression models adjusted for treatment groups. Time-adjusted actuarial incidence of ≥ Grade 2 GI and GU morbidity were compared using Kaplan–Meier analysis with log-rank tests, with confidence intervals based on the log-log transformation. A multivariate analysis was performed using the Cox proportional hazard model.

To evaluate the differences in relative DVH parameter between patients and the effect of various treatment and background variables on late toxicity, we used the same methods as in Paper III.

Finally in Paper IV, complication atlases [184] were constructed. These atlases are summaries of both the DVH and clinical complication data for all patients, in the form of a 2D map with the same axes as the DVH. Each grid point in the map contains both the number of patients with complication whose integral DVH passes above this specific grid point and the total number of patients in the study who also have an integral DVH passing above this point [184]. Grid point (0,0) thus contains the total number of complications and the total numbers of patients whereas in the grid points corresponding to the higher dose and volume combinations, progressively less patients are eligible for assessment of side effects. In this part of the analysis we applied the GU morbidity at least Grade 2 at 5 years, whereas for GI we used the maximum morbidity at least Grade 2 throughout the 5 years, because of only 3 events at 5 years follow-up.

All referred p-values were derived from two-side test when appropriate. A p-level of 0.05 was regarded as statically significant. We used the statistical software SPSS (versions 11, 12, 13 and 14, SPSS Inc., Chicago, USA) (in Papers I-IV), R (The R

Foundation for Statistical Computing, Vienna, Austria) [185] (in Papers II-IV) and StatXact (version 5 and 7, Cytel Software, Cambridge, MA, USA) (in Paper III and IV).

5. Summary of the results

5.1 Paper I

Radiation dose escalation combined with hormone therapy improves outcome in localised prostate cancer.

In this first paper we presented the impact of systematic radiation dose escalation – from 64 Gy via 66 Gy to 70 Gy, on the outcome after radiation therapy alone or combined with HT in a series of 494 patients with T1-3NxM0 prostate cancer treated during 1990-1999.

Of the 494 patients, 175 (35 %) had PSA failure at a median interval of 29 months, the 5 years OS and CSS rates were 85 % and 92 %, respectively. After a median of 68 months 360 patients were alive, 340 of these patients without signs of progression.

Prognostic factors for PSA failure, OS and CSS were investigated using multivariate analysis. T stage, pre-treatment PSA, grade, radiation dose and HT were found to be independent predictors of PSA failure. T stage, grade and HT were also independent predictors of both OS and CSS, while radiation dose was a significant predictor for OS and indicated a trend (p=0.07) for CSS.

A dose of 70 Gy combined with hormonal treatment improves PSA failure free survival and OS in localised prostate cancer compared with doses of 64-66 Gy.

5.2 Paper II

Outcome in intermediate or high risk prostate cancer patients receiving radiation dose and hormone therapy.

In this paper we analysed the impact of radiation dose escalation and HT according to risk groups, in the same series as in Paper I. The patients were divided into three risk groups, where the low risk group (stage T_{1c}, pretreatment PSA level ≤ 10 ng/ml, WHO Grade 1) included 26 patients, the intermediate risk group (either stage T_2, PSA 10.1 - 20 ng/ml or WHO Grade 2) comprised 149 patients whereas the high-risk group (either stage T_3, PSA > 20 ng/ml or WHO Grade 3) included 319 patients.

In the intermediate risk group, the 5-years bNED rate was 92 %, 69 % and 61 % after a radiation dose of 70 Gy, 66 Gy or 64 Gy, respectively ($p<0.001$). In the high-risk group, the 5-year bNED rate was 79 %, 69 % and 34 % for the same dose levels ($p<0.001$). The 5-years CSS rates were not significantly different between the dose levels in the intermediate risk group while for the high-risk group it was 93 %, 92 % and 80 % for the three dose levels ($p<0.001$). Risk group and radiation doses were independent predictors of bNED, CSS and OS, for bNED also hormone treatment was independent predictors.

From these findings we concluded that radiation dose is important for the outcome in intermediate and high risk prostate cancer patients.

5.3 Paper III

Acute morbidity related to treatment volume during 3D- conformal radiation therapy for prostate cancer.

In this paper we investigated the acute toxicity after radiotherapy for prostate cancer. From January to December 2001, 132 prostate cancer patients received a target dose of 70 Gy using 3-D CRT. Twenty-six patients (20 %) received irradiation to the prostate only (Group P), 86 patients (65 %) had field arrangements encompassing the prostate and seminal vesicles (Group PSV) while 20 (15 %) received modified pelvic fields (Group MPF). Acute toxicity according to the RTOG scoring system was prospectively recorded throughout the course of treatment.

Overall, radiation was well tolerated with 11 %, 16 % and 35 % Grade 2 GI toxicity and 19 %, 34 % and 35 % Grade 2 or higher GU toxicity in Groups P, PSV and MPF, respectively. In univariate and multivariate analyses treatment group was a significant predictor for Grade 2 or higher acute toxicity. In multivariate logistic regression, the rectum DVH parameters were correlated to the incidence of acute Grade 2 GI toxicity, with the fractional volumes receiving more than 37-40 Gy and above 70 Gy showing the statistically strongest correlation. The fractional bladder volume receiving more than 14-27 Gy showed the statistically strongest correlation with acute GU toxicity.

5.4 Paper IV

Late gastrointestinal morbidity after 3D- conformal radiation therapy for prostate cancer fades with time in contrast to genitourinary morbidity.

In this paper we investigated the late toxicity after radiotherapy for prostate cancer. From January 2000 to December 2001, 247 prostate cancer patients received a target dose of 70 Gy using 3-D CRT. Forty-eight patients (20 %) received irradiation to the prostate only (Group P), 154 patients (62 %) to the prostate and seminal vesicles (Group PSV) while 45 (18 %) received modified pelvic fields (Group MPF). Androgen deprivation was given to 86 % of the patients. The median follow-up time was 62 months. Late GI and GU toxicity were recorded according to the RTOG scoring system.

We observed 9 %, 7 % and 25 % Grade ≥ 2 GI toxicity and 36 %, 30 % and 21 % ≥ 2 GU toxicity in Groups P, PSV and MPF, respectively. In multivariate analyses age and treatment groups were independent predictors for the incidence of late Grade ≥ 2 GI toxicity, whereas age and urinary symptom before treatment were independent predictors for late Grade ≥ 2 GU toxicity. Acute side effects predicted for late effects. The rectum DVH parameters correlated to the incidence of late Grade ≥ 2 GI toxicity, especially the fractional volume receiving more than 40–43 Gy. The side effects tended to decrease with time. At 5 years follow-up, the rate of Grade 2 late GI toxicity was only 1 % and Grade ≥ 2 GU toxicity 11 %.

6. General discussion

6.1 Survival analyses (Papers I and II)

In the time period (1990-1999) we systematically increased the radiation dose - in accordance with other centres - from 64 Gy [186] via 66 Gy [187] to 70 Gy. Our results confirm that the two lowest doses yielded suboptimal tumour control [188]. Higher radiation doses can be used safely and particularly for localised tumours in the high-risk group have doses in the range of 74 – 81 Gy improved the tumour control rate [189, 190].

In the literature PC patients are often divided into three risk groups [127] - low, intermediate and high risk - in accordance to T stage, PSA and Gleason score. In our material we used this classification with modification because in our institution T stage was classified T1c, T2 and T3 and we only had grade but not Gleason score for the patients included in the first part of the study.

Biochemical PSA failure is widely used as a surrogate endpoint for disease activity in PC, with various definitions being applied. Some authors have, however, not found an association [46] or questioned its relationship with increasing mortality [191]. The ASCO definition [49] was the most widely used definition of PSA failure but it had some problematic aspects; it performed poorly in patients undergoing hormone therapy and backdating biased the Kaplan-Meier estimates of event-free survival. We therefore used the "Houston criteria" were PSA relapse is scored when PSA is 2 ng/ml greater than nadir [192], this definition is probably not affected by the use of hormones or follow-up length [58]. This method is the current recommended method to define biochemical failure after RT for PC [59].

In a previous study [193-195], the effect of radiation dose on relapse-free survival and overall mortality disappeared when year of treatment was included in the model. This finding indicates a more favourable presentation of localized PC in current years

that is not necessarily reflected in the patients PSA level or Gleason score. This phenomenon is probably related to a combination of many factors, such as PSA screening, possibly also to changing cancer biology, but more likely to increased physician and patients' awareness leading to more aggressive biopsies detecting of earlier presentation of the cancer [194, 195]. In our cohorts, on the other hand, year of treatment was not a significant factor for survival, while radiation dose remained a significant factor in the Cox model. The improved outcome after higher radiation dose can therefore hardly only reflect a better case mix alone. We have also analysed the data by consecutive time periods, excluding dose as this also reflects the time period. Unfortunately we can not present a randomized study where period of treatment can be separately analysed in a model containing also the dose. We can therefore not exclude that stage migration contribute to our findings as there is several significant differences between the groups. However, as multivariate Cox regression represents a scientific approach to weight for the unbalanced factors, the results indicate that dose is an important factor for outcome for patients treated by radiation therapy combined with hormone suppression.

In our cohort 81 % of the patients had adjuvant/neoadjuvant hormone treatment (mostly short-term). The addition of HT improved the effect of the lowest dose, 64 Gy, but we unfortunately cannot assess its role at the highest dose level as most patients had started with hormones at the time of referral. There is now general acceptance for addition of long-term (3 years) hormonal suppression for locally advanced and high risk prostate cancer [149, 151, 196-198], but short-term ($\leq$ 6 months) HT can not substitute for radiation dose in high risk patients [199]. Short-term hormone therapy was given to most patients in the current series in order to maximise the effect of radiation. It is of interest that the dose used in D'Amico's study [151] in T1b-2b patients with PSA >10 ng/ml or Gleason score at least 7 (range 7-10) was 70 Gy with 6 months HT was the same as used in our study. Our current data seems therefore to confirm the excellent results in the combined arm by the American study.

6.2 Acute and late side effects of radiotherapy (Paper III and IV)

In the recent years there has been an increased focus on acute and late toxicity after radiotherapy for PC. As PC patients have a potentially long survival, assessment of late toxicity is of major importance. The basis of CRT is that there is a dose response relationship for tumor control and that there are dose/volume response relationships for the involved normal tissues. The dose and volume response of normal tissue in general is such that irradiating a smaller volume to a higher dose is possible within generally accepted limits of complications [200, 201]. The most important dose-limiting ORs in RT of PC are the rectum and the bladder.

In Paper III we presented acute radiation toxicity and in Paper IV late radiation toxicity data after CRT for PC, treating different volumes according to the tumour stage and documented risk factors. Overall the acute GI toxicity remained very favourable for Groups P and PSV, with 11 % and 16 % Grade 2 toxicity respectively, but there was only a trend towards higher Grade 2 toxicity (35 %) observed in Group MPF (p=0.06). We had no late Grade 3 GI or higher toxicity. The rectum dose in the three groups were clearly different, e.g. the median dose was 43 Gy and 46 Gy in Group P and PSV vs. 62 Gy in MPF, being a likely explanation for the difference in toxicity. However, it should be mentioned that the RTOG acute GI toxicity scoring system does not strictly discriminate between small bowel and rectal toxicity. And according to Koper et al. [180], anal toxicity also contribute to the GI toxicity. The low anal toxicity being reported in our study indicates a low anal radiation dose with our treatment technique.

Most patients in our series had no or only Grade 1 late GI toxicity; Grade 2 late GI toxicity was observed in 10 % of the patients. We had no Grade 3 GI toxicity and only one Grade 4 GI and GU toxicity was observed in a patient in group PSV who had hemochromatosis. The GI toxicity remained very favourable for Groups P and PSV, with only 8 % Grade 2 toxicity or higher observed in both groups. There was,

however, significantly higher Grade 2 toxicity (25 %) observed in Group MPF (p = 0.001).

It is generally believed that late toxicity is permanent and may be progressive in severity. In contrast, our data show that most of the late Grade 2 GI toxicity was reversible. At 5 years, only 3 patients had still Grade 2 late GI toxicity (1 %). The 5-year actuarial incidence of developing late Grade ≥ 2 GI toxicity was 10 %. The median time to presentation was 13 months, with a further increase in incidence during the first 3 years after which the incidence stabilised. Others have reported that symptom levels may improve or resolve after Grade 2, but worse symptom levels after longer follow-up periods have also been reported [202-204]. Of interest is that Denham and co workers [205] indicated that patients who experienced little or no acute proctitis developed late symptoms that almost entirely resolved within 3 years of therapy. However, patients who experienced moderate or severe acute proctitis endured more prolonged late symptoms.

In our institution we now use IMRT to tread locally advanced PC patients (group MPF). A recent study on this regimen showed 28 % acute Grade 2 GI toxicity and only 5 % late Grade 2 GI toxicity with a 12 months median follow-up [91].

It has been suggested that urethral mucositis and oedema within the prostate cause most of the urinary symptoms. This assumption is supported by the nature of the symptoms (frequency, urgency) as well as the particularly low incidence of acute GU toxicity in patients treated with 3D-CRT after radical prostatectomy [206]. The finding that use of IMRT for prostate cancer reduces rectal toxicity but not bladder toxicity despite reduced dose to the bladder [207] further supports the notion that most of the acute GU toxicity is caused by RT effects on the urethra within the prostate rather than in the bladder. According to this view, it seems unlikely that GU symptoms can be avoided when irradiating the whole prostate and thus including a segment of the urethra. In agreement with this, the differences in acute GU toxicity between the treatment groups in this series were less pronounced than the differences

in acute GI toxicity, despite considerable differences in the DVH and the DVH parameters also for the bladder.

Bladder doses with our technique were relatively high, but there was still only 2 % acute Grade 3 GU toxicity rate in our material, in accordance with previous 3D-CRT series for prostate cancer, showing a 0-3 % incidence of acute grade 3 and 4 GU toxicity [180, 208-210]. We found a statistically significant difference between patients with Grade 0-1 vs Grade 2-3 acute GU toxicity for low doses only, but Valicenti et al. [211] found that the fraction of the bladder (≤ 30 % vs. > 30 %) receiving more than the prescription dose (68.4 Gy to 79.2Gy) were a significant predictor for acute GU toxicity. They also showed that men with poor baseline urinary function who were given HT had a significantly increased risk of acute GU toxicity.

In our data analysis, late GU toxicity ≥ Grade 2 was not significantly different between the three treatments groups (p = 0, 95), despite differences in irradiated volume. This finding agrees with the study of Dearnaley [212].

As reported in other studies, the rate of late GU toxicity for these patients continued to increase with time for at least five years [213, 214]. In our cohort the 5-year actuarial incidence of developing late Grade ≥ 2 GU toxicity was 29 % and median time 14.5 months. Furthermore two-third of late Grade 2 GU toxicity is reversible: at 5 years only 23 (10.6 %) patients had late Grade ≥ 2 GU toxicity. De Meerleer and colleagues similarly showed that 81 % of late Grade 2 GU toxicity was transient, except for incontinence, from which only 1 patient recovered [204].

With regard to reliable DVH data, rectum and bladder present special problems because they are both hollow and tend to have temporal variations in size, shape and position due to difference in filling [215-217]. The rectum and bladder DVHs based on the planning scan only may therefore not be fully representative for all of the daily treatment sessions, confounding the correlation between DVH parameters and toxicity. Still, it seems reasonable to assume that DVHs of the organ with content are

less sensitive to organ motion than DVHs of the wall or surface only [217-219]. Several investigators have reported that the volume of normal tissue exposed to higher radiation dose levels may represent the most significant factor affecting the development of late Grade 2 toxicity [220, 221].

Jackson et al. [181] found that late rectal bleeding correlates with the volume receiving doses above 70 Gy, but reported also a correlation between bleeding and the volume exposed to intermediate doses (40-50 Gy). This possibly indicates that when high-dose region are surrounded by extensive volumes receiving intermediate doses, the ability of this surrounding tissue to aid in the repair of a central injury may be impaired. Paper III confirms these findings, with a similar correlation between acute Grade 2 GI toxicity and the relative rectal volume receiving high (above 70 Gy) and intermediate doses (37-44 Gy). We found a similar correlation between late Grade $\geq$ 2 GI toxicity and the relative rectal volume receiving intermediate (40 – 43 Gy) and low doses (7 – 8 Gy). At highest dose levels (71 – 74 Gy) the correlation approached but did not reach statistical significance. Al-Albany and co workers [222] found that the risk of fecal leakage and urgency correlated with volumes of rectum receiving doses in the interval 25-42 Gy, but no association with blood and mucus in stools.

The correlation between bladder DVH parameters and bladder toxicity (Grade 0+1 vs. Grade 2+3) found for doses in the range 14-27 Gy and the difference found for fractional bladder volumes receiving more than 20 Gy were in general also slightly weaker than the corresponding correlations found for the rectum. Its biological explanation is uncertain, but it probably reflects a RT side effect linked to the whole (or most) of the bladder, e.g. reduced elasticity.

Several authors have indicated a direct relationship between acute and late GI toxicity, independent of dose [109]. This phenomenon, known as a consequential late effect, is a direct consequence of acute radiation response causing tissue damage, which eventually leads to late toxicity after a latent symptom-free interval [110, 111, 205]. In our study Cox multivariate analysis revealed acute toxicity to be an

independent factor when compared with late toxicity ≥ Grade 1 GI and GU. Acute rectal toxicity ($p = 0.001$) was the only independent predictor for the incidence of late Grade ≥ 1 GI toxicity and acute GU toxicity ($p = 0.003$) was the only independent predictor for the incidence of late Grade ≥ 1 GU toxicity. Others have also shown that both acute GI and GU toxicity were significantly related to their corresponding late injuries [84, 213, 223]. As late toxicity is partly a direct result of acute toxicity, it may be possible to limit late toxicity by limiting acute toxicity.

6.3 Ongoing and future research

The appropriate dose to cure early PC is still under investigation as 3D-CRT and IMRT dose escalation studies have provided strong evidence for radical treatment of early PC with doses > 72 Gy. These doses can be safely delivered with no increase in GI toxicities.

From September 2005 we have used IMRT to treat high risk patients (Group MPF), with the RT course consisting of a initial IMRT plan delivering 50 Gy to PTV1 (prostate, seminal vesicles, and lymph nodes with margin) (Figure 7) followed by a four-field CRT plan delivering 20 Gy to PTV2 (prostate and seminal vesicle with margin). Our early experiences suggest that IMRT reduces the dose to important ORs such as the intestine, bladder, and rectum when treating pelvic lymph nodes, while also improving target coverage. Clinical outcomes observed thus far are also promising, with a very low GI toxicity [91].

In October 2006 we moved into a Phase II IMRT study of a SIB for locally advanced PC patients, where we simultaneously treated pelvic lymph nodes (with conventional fractionation, i.e., 2 Gy per fraction) combined with hypofractionated doses (2.4-2.7 Gy per fraction) to the prostate and seminal vesicle, in a total of 25 fractions. Gold fiducials inserted into the prostate are used for daily on-line target localisation, allowing for a considerable margin reduction. All patients start with endocrine therapy 3 months pre-RT with LHRH agonist and minimum 4 weeks with

antiandrogen, to exploit the reduction of the prostate volume, and continued with LHRH agonist 24 months after the start of RT. The aim is to include 100 patients into this study – currently 85 patients are included - with the primary endpoint being clinical and biochemical control after 5 years. Secondary aims are late GU and GI side effects and local control after 5 years.

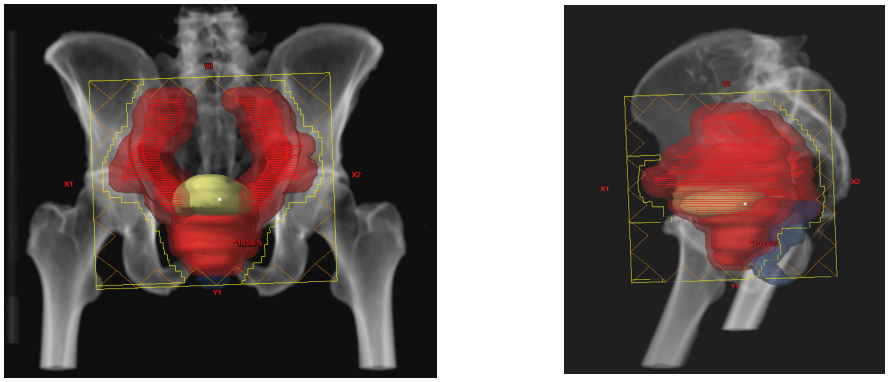


Figure 7. Intensity modulated radiation therapy (IMRT) plan for prostate cancer, anterior view (a) and lateral view (b), current standard

Treatment of prostate cancer using radiotherapy can induce disturbance in a patient's quality of life (QoL) and urinary and intestinal function. We intend to compare the difference between the treatment group and changes over time.

From January 2000 to December 2001, a total of 247 patients with prostate cancer were treated with curative intent by using conformal radiation therapy to 70 Gy. Forty-eight patients (20 %) received irradiation to the prostate only (Group P), 154 patients (62 %) received irradiation to the prostate and seminal vesicles (Group PSV), and 45 patients (18 %) received modified pelvic fields (Group MPF).

Cancer specific QoL was evaluated with European Organization for Research and Treatment of Cancer's QLQ-C30 formula, it is a questionnaire developed for the measurement of quality of life in cancer patients in clinical trial [224]. PC specific

QoL (urinary, intestinal and sexual function) was evaluated with a validated symptom specific self-assessment questionnaire, QUFW94/99© [225].

The patients answered the first questionnaire before treatment and then under treatment (132 patients treated in 2001). All the patients answered the questionnaire 6, 12, 24, 36, 42 and 60 months after the completion of treatment.

This project will be evaluated when the thesis is completed.

7. Conclusions

The current thesis consists of four papers addressing different aspect of RT for PC. In Paper I and II, dose response is analysed for all patients together and in subgroups according to risk assessment. In Paper III and IV, acute and late side effects, respectively, were prospectively assessed in patients treated at the same dose level as the highest dose level in Paper I and II.

For the whole group receiving external beam radiotherapy (64 Gy, 66 Gy and 70 Gy) with or without hormonal treatment, 35 % has PSA failure at a median interval of 29 months, with the 5 years OS and CSS rates being 85 % and 92 %, respectively. A dose of 70 Gy combined with hormonal treatment improved PSA failure free survival and OS in localised PC compared with doses of 64-66 Gy, while only a trend for CSS, probably due to low actual deaths from PC.

When analysed in risk groups (low risk, intermediate risk and high risk group), higher radiation dose was found to be important for PSA failure and CSS in high risk PC patients, however, in the intermediate risk group the effect was only demonstrated on bNED.

3D-CRT radiation therapy for PC to 70 Gy was well tolerated. Only two of the 132 patients in the cohort experienced acute bladder toxicity Grade 3, none had Grade 3 rectal toxicity. Uni- and multivariate analyses indicated that the volume treated was a significant factor for the incidence of Grade 2 or higher acute morbidity.

Late GI morbidity was low and faded with time, with only 1 % late Grade 2 GI morbidity at 5 years. GU morbidity was stable with time, with 11 % late Grade ≥ 2 GU morbidity at 5 years. GU morbidity did not vary with treatment groups which probably reflected the fact that the urethra was included in all fields. Acute side effects predicted for late effects.

8. References

[1] Gronberg H. Prostate cancer epidemiology. The Lancet 2003; 361: 859-64.

[2] Cancer Registry of Norway. Cancer in Norway 2006. Oslo, Norway, 2007.

[3] Cancer Registry of Norway. Cancer in Norway 2004. Oslo, Norway, 2004.

[4] Kvale R, Auvinen A, Adami HO, et al. Interpreting trends in prostate cancer incidence and mortality in the five Nordic countries. J Natl Cancer Inst 2007; 99: 1881-7.

[5] Quinn M and Babb P. Patterns and trends in prostate cancer incidence, survival, prevalence and mortality. Part I: international comparisons. BJU Int 2002; 90: 162-73.

[6] Haukaas S, Skaarland E, Halvorsen OJ, et al. [Prostate-specific antigen. A new biological serum marker for prostatic adenocarcinoma]. Tidsskr Nor Laegeforen 1990; 110: 2990-3.

[7] Lichtenstein P, Holm NV, Verkasalo PK, et al. Environmental and heritable factors in the causation of cancer--analyses of cohorts of twins from Sweden, Denmark, and Finland. N Engl J Med 2000; 343: 78-85.

[8] Nelson WG, De Marzo AM, and Isaacs WB. Prostate Cancer. N Engl J Med 2003; 349: 366-81.

[9] Thompson IM, Goodman PJ, Tangen CM, et al. The Influence of Finasteride on the Development of Prostate Cancer. N Engl J Med 2003; 349: 215-24.

[10] Pinsky P, Parnes H, and Ford L. Estimatin rate of true high-grade disease in the prostate cancer prevention trial. Cancer Prevention Research 2008; 1: 182-6.

[11] Logothetis C and Schellhammer P. High-grade prostate cancer and the prostate cancer prevention trial. Cancer Prevention Research 2008; 1: 151-2.

[12] Redman MW, Tangen CM, Godman PJ, et al. Finasterid dose not increase the risk of high-grade prostate cancer: A bias-adjusted modeling approach. Cancer Prevention Research 2008; 1: 174-81

[13] Konety BR, Bird VY, Deorah S, et al. Comparison of the incidence of latent prostate cancer detected at autopsy before and after the prostate specific antigen era. J Urol 2005; 174: 1785-8; discussion 1788.

[14] Harvei S, Tretli S, and Langmark F. Cancer of the prostate in Norway 1957-1991--a descriptive study. Eur J Cancer 1996; 32A: 111-7.

[15] Kvale R, Skarre E, Tonne A, et al. [Curative treatment of prostatic cancer in Norway in 1998 and 2001]. Tidsskr Nor Laegeforen 2006; 126: 912-6.

[16] Schroder FH, Hermanek P, Denis L, et al. The TNM classification of prostate cancer. Prostate Suppl 1992; 4: 129-38.

[17] van der Kwast TH. Substaging pathologically organ confined (pT2) prostate cancer: an exercise in futility? Eur Urol 2006; 49: 209-11.

[18] Hermanek P, Hutter RVP, Sobin LH, et al., TNM Atlas. Illustrated Guide to the TNM/pTNM Classification of Malignant Tumours. 1997, Heidelberg: Springer-Verlag Berlin Heidelberg.

[19] Sobin LH and Wittekind C, TNM classification of malignant tumours. 6th ed. ed. International Union Against Cancer (UICC). 2002, New York: Wiley-Liss.

[20] Hermanek P and Sobin LH, TNM classification of malignant tumours. 4th ed. ed. International Union Against Cancer (UICC). 1992, Berlin, Heidelberg, New York Springer Verlag.

[21] Sobin LH and Wittekind C, TNM classification of malignant tumours. Fifth edition ed. International Union Against Cancer (UICC). 1997, New York: Wiley-Liss.

[22] Mostofi FK, Sesterhenn IA, and Sobin LH, Histological typing of prostate tumours. 1980, Geneva: World Health Organization.

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

[24] Harnden P, Shelley MD, Coles B, et al. Should the Gleason grading system for prostate cancer be modified to account for high-grade tertiary components? A systematic review and meta-analysis. Lancet Oncol 2007; 8: 411-9.

[25] Epstein JI, Allsbrook WC, Jr., Amin MB, et al. The 2005 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason Grading of Prostatic Carcinoma. Am J Surg Pathol 2005; 29: 1228-42.

[26] Lilleby W, Torlakovic G, Torlakovic E, et al. Prognostic significance of histologic grading in patients with prostate carcinoma who are assessed by the Gleason and World Health Organization grading systems in needle biopsies obtained prior to radiotherapy. Cancer 2001; 92: 311-9.

[27] Green GA, Hanlon AL, Al-Saleem T, et al. A Gleason score of 7 predicts a worse outcome for prostate carcinoma patients treated with radiotherapy. Cancer 1998; 83: 971-6.

[28] Tefilli MV, Gheiler EL, Tiguert R, et al. Should Gleason score 7 prostate cancer be considered a unique grade category? Urology 1999; 53: 372-7.

[29] Chan TY, Partin AW, Walsh PC, et al. Prognostic significance of Gleason score 3+4 versus Gleason score 4+3 tumor at radical prostatectomy. Urology 2000; 56: 823-7.

[30] Han M, Snow PB, Epstein JI, et al. A neural network predicts progression for men with gleason score 3+4 versus 4+3 tumors after radical prostatectomy. Urology 2000; 56: 994-9.

[31] Khoddami SM, Shariat SF, Lotan Y, et al. Predictive value of primary Gleason pattern 4 in patients with Gleason score 7 tumours treated with radical prostatectomy. BJU Int 2004; 94: 42-6.

[32] Sakr WA, Tefilli MV, Grignon DJ, et al. Gleason score 7 prostate cancer: a heterogeneous entity? Correlation with pathologic parameters and disease-free survival. Urology 2000; 56: 730-4.

[33] Rasiah KK, Stricker PD, Haynes AM, et al. Prognostic significance of Gleason pattern in patients with Gleason score 7 prostate carcinoma. Cancer 2003; 98: 2560-5.

[34] Patel AA, Chen MH, Renshaw AA, et al. PSA failure following definitive treatment of prostate cancer having biopsy Gleason score 7 with tertiary grade 5. JAMA 2007; 298: 1533-8.

[35] Lattouf JB and Saas F. Gleason score on biopsy: is it reliable for predicting the final grade on pathology? BJU Int 2002; 90: 694-9.

[36] Epstein JI. Gleason score 2-4 adenocarcinoma of the prostate on needle biopsy: a diagnosis that should not be made. Am J Surg Pathol 2000; 24: 477-8.

[37] Sooriakumaran P, Lovell DP, Henderson A, et al. Gleason scoring varies among pathologists and this affects clinical risk in patients with prostate cancer. Clin Oncol (R Coll Radiol) 2005; 17: 655-8.

[38] DeMarzo AM, Nelson WG, Isaacs WB, et al. Pathological and molecular aspects of prostate cancer. Lancet 2003; 361: 955-64.

[39] Barry MJ. Clinical practice. Prostate-specific-antigen testing for early diagnosis of prostate cancer. N Engl J Med 2001; 344: 1373-7.

[40] Wang MC, Valenzuela LA, Murphy GP, et al. Purification of a human prostate specific antigen. Invest Urol 1979; 17: 159-63.

[41] Papsidero LD, Wang MC, Valenzuela LA, et al. A prostate antigen in sera of prostatic cancer patients. Cancer Res 1980; 40: 2428-32.

[42] Partin AW and Oesterling JE. The clinical usefulness of prostate specific antigen: update 1994. J Urol 1994; 152: 1358-68.

[43] Vis AN, Roemeling S, Kranse R, et al. Should we replace the Gleason score with the amount of high-grade prostate cancer? Eur Urol 2007; 51: 931-9.

[44] Miller K, Abrahamsson PA, Akakura K, et al. The continuing role of PSA in detection adn management of prostate cancer. European Urology Supplements 2007; 6: 327-33.

[45] Polascik TJ, Oesterling JE, and Partin AW. Prostate specific antigen: a decade of discovery--what we have learned and where we are going. J Urol 1999; 162: 293-306.

[46] Kupelian PA, Buchsbaum JC, Patel C, et al. Impact of biochemical failure on overall survival after radiation therapy for localized prostate cancer in the PSA era. Int J Radiat Oncol Biol Phys 2002; 52: 704-11.

[47] D'Amico AV, Moul JW, Carroll PR, et al. Surrogate end point for prostate cancer-specific mortality after radical prostatectomy or radiation therapy. J Natl Cancer Inst 2003; 95: 1376-83.

[48] D'Amico AV, Kantoff P, Loffredo M, et al. Predictors of mortality after prostate-specific antigen failure. Int J Radiat Oncol Biol Phys 2006; 65: 656-60.

[49] Consensus statement: guidelines for PSA following radiation therapy. American Society for Therapeutic Radiology and Oncology Consensus Panel. Int J Radiat Oncol Biol Phys 1997; 37: 1035-41.

[50] Vicini FA, Kestin LL, and Martinez AA. The importance of adequate follow-up in defining treatment success after external beam irradiation for prostate cancer. Int J Radiat Oncol Biol Phys 1999; 45: 553-61.

[51] Coen JJ, Chung CS, Shipley WU, et al. Influence of follow-up bias on PSA failure after external beam radiotherapy for localized prostate cancer: Results from a 10-year cohort analysis. Int J Radiat Oncol Biol Phys 2003; 57: 621-8.

[52] Thames H, Kuban D, Levy L, et al. Comparison of alternative biochemical failure definitions based on clinical outcome in 4839 prostate cancer patients treated by external beam radiotherapy between 1986 and 1995. Int J Radiat Oncol Biol Phys 2003; 57: 929-43.

[53] Buyyounouski MK, Hanlon AL, Horwitz EM, et al. Biochemical failure and the temporal kinetics of prostate-specific antigen after radiation therapy with androgen deprivation. Int J Radiat Oncol Biol Phys 2005; 61: 1291-8.

[54] Zietman AL, Christodouleas JP, and Shipley WU. PSA bounces after neoadjuvant androgen deprivation and external beam radiation: impact on definitions of failure. Int J Radiat Oncol Biol Phys 2005; 62: 714-8.

[55] Horwitz EM, Levy LB, Thames HD, et al. Biochemical and clinical significance of the posttreatment prostate-specific antigen bounce for prostate cancer patients treated with external beam radiation therapy alone: a multiinstitutional pooled analysis. Cancer 2006; 107: 1496-502.

[56] Kestin LL, Vicini FA, and Martinez AA. Practical application of biochemical failure definitions: what to do and when to do it. Int J Radiat Oncol Biol Phys 2002; 53: 304-15.

[57] Pickles T, Kim-Sing C, Morris WJ, et al. Evaluation of the Houston biochemical relapse definition in men treated with prolonged neoadjuvant and adjuvant androgen ablation and assessment of follow-up lead-time bias. Int J Radiat Oncol Biol Phys 2003; 57: 11-8.

[58] Buyyounouski MK, Hanlon AL, Eisenberg DF, et al. Defining biochemical failure after radiotherapy with and without androgen deprivation for prostate cancer. Int J Radiat Oncol Biol Phys 2005; 63: 1455-62.

[59] Roach III M, Hanks G, Thames J, Howard, et al. Defining biochemical failure following radiotherapy with or without hormonal therapy in men with clinically localized prostate cancer: Recommendations of the RTOG-ASTRO Phoenix Consensus Conference. Int J Radiat Oncol Biol Phys 2006; 65: 965-74.

[60] Fossa SD, Eri LM, Skovlund E, et al. No randomised trial of prostate-cancer screening in Norway. Lancet Oncol 2001; 2: 741-5; discussion 746-9.

[61] Fossa S, Høiseter PÅ, Bjerklund Johansen B, et al. Dokumentasjonsgrunnlaget for den helsemessige effekten ved rutinemessig screening. Senter for medisinsk metodevurdering, SINTEF Unimed, SMM-rapport 1999.

[62] Bill-Axelson A, Holmberg L, Ruutu M, et al. Radical Prostatectomy versus Watchful Waiting in Early Prostate Cancer. N Engl J Med 2005; 352: 1977-84.

[63] Roobol MJ and Schroder FH. European Randomized Study of Screening for Prostate Cancer: achievements and presentation. BJU Int 2003; 92 Suppl 2: 117-22.

[64] Gohagan JK, Prorok PC, Hayes RB, et al. The Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial of the National Cancer Institute: history, organization, and status. Control Clin Trials 2000; 21: 251S-272S.

[65] Fowler FJ, Jr., McNaughton Collins M, Albertsen PC, et al. Comparison of recommendations by urologists and radiation oncologists for treatment of clinically localized prostate cancer. JAMA 2000; 283: 3217-22.

[66] Partin AW, Mangold LA, Lamm DM, et al. Contemporary update of prostate cancer staging nomograms (Partin Tables) for the new millennium. Urology 2001; 58: 843-8.

[67] Khan MA and Partin AW. Partin tables: past and present. BJU Int 2003; 92: 7-11.

[68] Kattan MW, Eastham JA, Stapleton AM, et al. A preoperative nomogram for disease recurrence following radical prostatectomy for prostate cancer. J Natl Cancer Inst 1998; 90: 766-71.

[69] Kattan MW, Zelefsky MJ, Kupelian PA, et al. Pretreatment nomogram for predicting the outcome of three-dimensional conformal radiotherapy in prostate cancer. J Clin Oncol 2000; 18: 3352-9.

[70] Rassweiler J, Stolzenburg J, Sulser T, et al. Laparoscopic radical prostatectomy--the experience of the German Laparoscopic Working Group. Eur Urol 2006; 49: 113-9.

[71] Thompson I, Thrasher JB, Aus G, et al. Guideline for the management of clinically localized prostate cancer: 2007 update. J Urol 2007; 177: 2106-31.

[72] Pound CR, Partin AW, Eisenberger MA, et al. Natural history of progression after PSA elevation following radical prostatectomy. JAMA 1999; 281: 1591-7.

[73] Hull GW, Rabbani F, Abbas F, et al. Cancer control with radical prostatectomy alone in 1,000 consecutive patients. J Urol 2002; 167: 528-34.

[74] Kundu SD, Roehl KA, Eggener SE, et al. Potency, continence and complications in 3,477 consecutive radical retropubic prostatectomies. J Urol 2004; 172: 2227-31.

[75] Penson DF, McLerran D, Feng Z, et al. 5-year urinary and sexual outcomes after radical prostatectomy: results from the prostate cancer outcomes study. J Urol 2005; 173: 1701-5.

[76] Walsh PC, Marschke P, Ricker D, et al. Patient-reported urinary continence and sexual function after anatomic radical prostatectomy. Urology 2000; 55: 58-61.

[77] Yao SL and Lu-Yao G. Population-based study of relationships between hospital volume of prostatectomies, patient outcomes, and length of hospital stay. J Natl Cancer Inst 1999; 91: 1950-6.

[78] Vickers AJ, Bianco FJ, Serio AM, et al. The surgical learning curve for prostate cancer control after radical prostatectomy. J Natl Cancer Inst 2007; 99: 1171-7.

[79] Bagshaw MA. External radiation therapy of carcinoma of the prostate. Cancer 1980; 45: 1912-21.

[80] Bucci MK, Bevan A, and Roach M, 3rd. Advances in radiation therapy: conventional to 3D, to IMRT, to 4D, and beyond. CA Cancer J Clin 2005; 55: 117-34.

[81] Dahl O, Kardamakis D, Lind B, et al. Current status of conformal radiotherapy. Acta Oncol 1996; 35: 41-57.

[82] ICRU, Report 50: Prescribing, recording, and reporting photon beam therapy. 1993, International Commission on Radiation Units and Measurements: Bethesda.

[83] ICRU, Report 62: Prescribing, recording and reporting photon beam therapy (supplement to ICRU repotr 50). 1999, International Commission on Radiation Units and Measurements: Bethesda.

[84] Schultheiss TE, Lee WR, Hunt MA, et al. Late GI and GU complications in the treatment of prostate cancer. Int J Radiat Oncol Biol Phys 1997; 37: 3-11.

[85] Widmark A, Klepp O, Fransson P, et al. A randomized trial comparing antiandrogen with or without radiotherapy in the treatment of locally advanced prostate cancer: Survival and Qol outcome. Late breaker abstract. ASTRO, 2008.

[86] Guerrero Urbano MT and Nutting CM. Clinical use of intensity-modulated radiotherapy: part II. Br J Radiol 2004; 77: 177-82.

[87] Shepard DM, Cao D, Afghan MK, et al. An arc-sequencing algorithm for intensity modulated arc therapy. Med Phys 2007; 34: 464-70.

[88] Intensity-modulated radiotherapy: current status and issues of interest. Int J Radiat Oncol Biol Phys 2001; 51: 880-914.

[89] Otto K. Volumetric modulated arc therapy: IMRT in a single gantry arc. Med Phys 2008; 35: 310-7.

[90] Palma D, Vollans E, James K, et al. Volumetric Modulated Arc Therapy for Delivery of Prostate Radiotherapy: Comparison with Intensity-Modulated Radiotherapy and Three-Dimensional Conformal Radiotherapy. Int J Radiat Oncol Biol Phys 2008; 72: 996-1001.

[91] Muren LP, Wasbø E, Helle SI, et al. Intensity-modulated radiotherapy of pelvic lymph nodes in locally advanced prostate cancer: planning procedures and early experience. Int J Radiat Oncol Biol Phys 2008; 71: 1034-41.

[92] Mott JH, Livsey JE, and Logue JP. Development of a simultaneous boost IMRT class solution for a hypofractionated prostate cancer protocol. Br J Radiol 2004; 77: 377-86.

[93] Li XA, Wang JZ, Jursinic PA, et al. Dosimetric advantages of IMRT simultaneous integrated boost for high-risk prostate cancer. Int J Radiat Oncol Biol Phys 2005; 61: 1251-7.

[94] Hong TS, Tome WA, Jaradat H, et al. Pelvic nodal dose escalation with prostate hypofractionation using conformal avoidance defined (H-CAD) intensity modulated radiation therapy. Acta Oncol 2006; 45: 717-27.

[95] Ling CC, Humm J, Larson S, et al. Towards multidimensional radiotherapy (MD-CRT): biological imaging and biological conformality. Int J Radiat Oncol Biol Phys 2000; 47: 551-60.

[96] Bentzen SM. Theragnostic imaging for radiation oncology: dose-painting by numbers. Lancet Oncol 2005; 6: 112-7.

[97] Bentzen SM. Dose painting and theragnostic imaging: towards the prescription, planning and delivery of biologically targeted dose distributions in external beam radiation oncology. Cancer Treat Res 2008; 139: 41-62.

[98] Galvin JM and De Neve W. Intensity modulating and other radiation therapy devices for dose painting. J Clin Oncol 2007; 25: 924-30.

[99] Landoni V, Saracino B, Marzi S, et al. A study of the effect of setup errors and organ motion on prostate cancer treatment with IMRT. Int J Radiat Oncol Biol Phys 2006; 65: 587-94.

[100] Pouliot J, Aubin M, Langen KM, et al. (Non)-migration of radiopaque markers used for on-line localization of the prostate with an electronic portal imaging device. Int J Radiat Oncol Biol Phys 2003; 56: 862-6.

[101] Speight JL and Roach M, 3rd. Advances in the treatment of localized prostate cancer: the role of anatomic and functional imaging in men managed with radiotherapy. J Clin Oncol 2007; 25: 987-95.

[102] Chung HT, Xia P, Chan DW, et al. Dose image-guided radiotherapy improve toxicity profile in whole pelvic-treated high-risk prostate cancer ? comparison between IG-IMRT and IMRT. Int J Radiat Oncol Biol Phys 2008; Article in press.

[103] Mackie TR, Kapatoes J, Ruchala K, et al. Image guidance for precise conformal radiotherapy. Int J Radiat Oncol Biol Phys 2003; 56: 89-105.

[104] Fiorino C, Alongi F, Broggi S, et al. Physics aspects of prostate tomotherapy: planning optimization and image-guidance issues. Acta Oncol 2008; 47: 1309-16.

[105] Beavis AW. Is tomotherapy the future of IMRT? Br J Radiol 2004; 77: 285-95.

[106] Cozzarini C, Fiorino C, Di Muzio N, et al. Significant reduction of acute toxicity following pelvic irradiation with helical tomotherapy in patients with localized prostate cancer. Radiother Oncol 2007; 84: 164-70.

[107] Basic clinical radiobiology. 3rd ed, ed. Steel G G. 2002, London: Arnold: London

[108] Dahl O, Horn A, and Mella O. Do acute side-effects during radiotherapy predict tumour response in rectal carcinoma? Acta Oncol 1994; 33: 409-13.

[109] Dorr W and Hendry JH. Consequential late effects in normal tissues. Radiother Oncol 2001; 61: 223-31.

[110] Heemsbergen WD, Peeters ST, Koper PC, et al. Acute and late gastrointestinal toxicity after radiotherapy in prostate cancer patients: consequential late damage. Int J Radiat Oncol Biol Phys 2006; 66: 3-10.

[111] Vargas C, Martinez A, Kestin LL, et al. Dose-volume analysis of predictors for chronic rectal toxicity after treatment of prostate cancer with adaptive image-guided radiotherapy. Int J Radiat Oncol Biol Phys 2005; 62: 1297-308.

[112] Cox JD, Stetz J, and Pajak TF. Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). Int J Radiat Oncol Biol Phys 1995; 31: 1341-6.

[113] LENT SOMA tables. Radiother Oncol 1995; 35: 17-60.

[114] Trotti A, Byhardt R, Stetz J, et al. Common toxicity criteria: version 2.0. an improved reference for grading the acute effects of cancer treatment: impact on radiotherapy. Int J Radiat Oncol Biol Phys 2000; 47: 13-47.

[115] Trotti A, Colevas AD, Setser A, et al. CTCAE v3.0: development of a comprehensive grading system for the adverse effects of cancer treatment. Semin Radiat Oncol 2003; 13: 176-81.

[116] Bentzen SM, Dorr W, Anscher MS, et al. Normal tissue effects: reporting and analysis. Semin Radiat Oncol 2003; 13: 189-202.

[117] Ash D, Flynn A, Battermann J, et al. ESTRO/EAU/EORTC recommendations on permanent seed implantation for localized prostate cancer. Radiother Oncol 2000; 57: 315-21.

[118] The GEC ESTRO handbook of brachytherapy, ed. Gerbaulet A, Potter R, Mazeron J, et al. 2002, Leuven, Belgium: ACCO.

[119] Salembier C, Lavagnini P, Nickers P, et al. Tumour and target volumes in permanent prostate brachytherapy: a supplement to the ESTRO/EAU/EORTC recommendations on prostate brachytherapy. Radiother Oncol 2007; 83: 3-10.

[120] Kalkner KM, Wahlgren T, Ryberg M, et al. Clinical outcome in patients with prostate cancer treated with external beam radiotherapy and high dose-rate iridium 192 brachytherapy boost: a 6-year follow-up. Acta Oncol 2007; 46: 909-17.

[121] Nag S, Beyer D, Friedland J, et al. American Brachytherapy Society (ABS) recommendations for transperineal permanent brachytherapy of prostate cancer. Int J Radiat Oncol Biol Phys 1999; 44: 789-99.

[122] Peschel RE and Colberg JW. Surgery, brachytherapy, and external-beam radiotherapy for early prostate cancer. The Lancet Oncology 2003; 4: 233-41.

[123] Crook J, Fleshner N, Roberts C, et al. Long-term urinary sequelae following 125iodine prostate brachytherapy. J Urol 2008; 179: 141-5; discussion 146.

[124] Norderhaug I, Dahl O, Hoisaeter PA, et al. Brachytherapy for prostate cancer: a systematic review of clinical and cost effectiveness. Eur Urol 2003; 44: 40-6.

[125] Epstein JI, Walsh PC, Carmichael M, et al. Pathologic and clinical findings to predict tumor extent of nonpalpable (stage T1c) prostate cancer. JAMA 1994; 271: 368-74.

[126] Lerner SE, Seay TM, Blute ML, et al. Prostate specific antigen detected prostate cancer (clinical stage T1c): an interim analysis. J Urol 1996; 155: 821-6.

[127] D'Amico AV, Whittington R, Malkowicz SB, et al. Biochemical Outcome After Radical Prostatectomy, External Beam Radiation Therapy, or Interstitial Radiation Therapy for Clinically Localized Prostate Cancer. JAMA 1998; 280: 969-74.

[128] Jemal A, Siegel R, Ward E, et al. Cancer statistics, 2007. CA Cancer J Clin 2007; 57: 43-66.

[129] Klotz L. Active surveillance for favorable risk prostate cancer: What are the results, and how safe is it? Semin Radiat Oncol 2008; 18: 2-6.

[130] Parker C. Active surveillance: towards a new paradigm in the management of early prostate cancer. Lancet Oncol 2004; 5: 101-6.

[131] Klotz LH. Active surveillance for good risk prostate cancer: rationale, method, and results. Can J Urol 2005; 12 Suppl 2: 21-4.

[132] Warlick C, Trock BJ, Landis P, et al. Delayed versus immediate surgical intervention and prostate cancer outcome. J Natl Cancer Inst 2006; 98: 355-7.

[133] Choo R, Klotz L, Danjoux C, et al. Feasibility study: watchful waiting for localized low to intermediate grade prostate carcinoma with selective delayed intervention based on prostate specific antigen, histological and/or clinical progression. J Urol 2002; 167: 1664-9.

[134] Klotz L. Active surveillance with selective delayed intervention for favorable risk prostate cancer. Urol Oncol 2006; 24: 46-50.

[135] Klotz L. Active surveillance for prostate cancer: for whom? J Clin Oncol 2005; 23: 8165-9.

[136] Choo R, DeBoer G, Klotz L, et al. PSA doubling time of prostate carcinoma managed with watchful observation alone. Int J Radiat Oncol Biol Phys 2001; 50: 615-20.

[137] Brada M, Pijls-Johannesma M, and De Ruysscher D. Proton therapy in clinical practice: current clinical evidence. J Clin Oncol 2007; 25: 965-70.

[138] Slater JD, Rossi CJ, Jr., Yonemoto LT, et al. Proton therapy for prostate cancer: the initial Loma Linda University experience. Int J Radiat Oncol Biol Phys 2004; 59: 348-52.

[139] Schulz-Ertner D and Tsujii H. Particle radiation therapy using proton and heavier ion beams. J Clin Oncol 2007; 25: 953-64.

[140] Nikoghosyan A, Schulz-Ertner D, Didinger B, et al. Evaluation of therapeutic potential of heavy ion therapy for patients with locally advanced prostate cancer. Int J Radiat Oncol Biol Phys 2004; 58: 89-97.

[141] Brahme A. Recent advances in light ion radiation therapy. Int J Radiat Oncol Biol Phys 2004; 58: 603-16.

[142] Suzuki M, Kase Y, Yamaguchi H, et al. Relative biological effectiveness for cell-killing effect on various human cell lines irradiated with heavy-ion medical accelerator in Chiba (HIMAC) carbon-ion beams. Int J Radiat Oncol Biol Phys 2000; 48: 241-50.

[143] Tsuji H, Yanagi T, Ishikawa H, et al. Hypofractionated radiotherapy with carbon ion beams for prostate cancer. Int J Radiat Oncol Biol Phys 2005; 63: 1153-60.

[144] Ishikawa H, Tsuji H, Kamada T, et al. Carbon ion radiation therapy for prostate cancer: results of a prospective phase II study. Radiother Oncol 2006; 81: 57-64.

[145] Ishikawa H, Tsuji H, Kamada T, et al. Risk factors of late rectal bleeding after carbon ion therapy for prostate cancer. Int J Radiat Oncol Biol Phys 2006; 66: 1084-91.

[146] Lodge M, Pijls-Johannesma M, Stirk L, et al. A systematic literature review of the clinical and cost-effectiveness of hadron therapy in cancer. Radiother Oncol 2007; 83: 110-22.

[147] Horwitz EM and Hanks GE. External beam radiation therapy for prostate cancer. CA Cancer J Clin 2000; 50: 349-75; quiz 376-9.

[148] Bolla M, Gonzalez D, Warde P, et al. Improved survival in patients with locally advanced prostate cancer treated with radiotherapy and goserelin. N Engl J Med 1997; 337: 295-300.

[149] Bolla M, Collette L, Blank L, et al. Long-term results with immediate androgen suppression and external irradiation in patients with locally advanced prostate cancer (an EORTC study): a phase lll randomised trial. The Lancet 2002; 360: 103-8.

[150] Pilepich MV, Winter K, Lawton CA, et al. Androgen suppression adjuvant to definitive radiotherapy in prostate carcinoma--long-term results of phase III RTOG 85-31. Int J Radiat Oncol Biol Phys 2005; 61: 1285-90.

[151] D'Amico AV, Manola J, Loffredo M, et al. 6-Month Androgen Suppression Plus Radiation Therapy vs Radiation Therapy Alone for Patients With Clinically Localized Prostate Cancer: A Randomized Controlled Trial. JAMA 2004; 292: 821-7.

[152] Denham JW, Steigler A, Lamb DS, et al. Short-term androgen deprivation and radiotherapy for locally advanced prostate cancer: results from the Trans-Tasman Radiation Oncology Group 96.01 randomised controlled trial. Lancet Oncol 2005; 6: 841-50.

[153] Mohler J, Bahnson RR, Boston B, et al. National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines In Oncology. Prostate Cancer version 2.2008. http://www.nccn.org/professionals/physician_gls/PDF/prostate.pdf.

[154] Hellerstedt BA and Pienta KJ. The Current State of Hormonal Therapy for Prostate Cancer. CA Cancer J Clin 2002; 52: 154-79.

[155] Messing EM, Manola J, Sarosdy M, et al. Immediate hormonal therapy compared with observation after radical prostatectomy and pelvic lymphadenectomy in men with node-positive prostate cancer. N Engl J Med 1999; 341: 1781-8.

[156] Messing EM, Manola J, Yao J, et al. Immediate versus deferred androgen deprivation treatment in patients with node-positive prostate cancer after radical prostatectomy and pelvic lymphadenectomy. Lancet Oncol 2006; 7: 472-9.

[157] Calabro F and Sternberg CN. Current indications for chemotherapy in prostate cancer patients. Eur Urol 2007; 51: 17-26.

[158] Sharifi N, Gulley JL, and Dahut WL. Androgen Deprivation Therapy for Prostate Cancer. JAMA 2005; 294: 238-44.

[159] Klotz L, Akakura K, Gillatt D, et al. Advanced Prostate Cancer: Hormones and Beyond. European Urology Supplements 2007; 6: 354-64.

[160] Kantoff PW, Halabi S, Conaway M, et al. Hydrocortisone with or without mitoxantrone in men with hormone-refractory prostate cancer: results of the cancer and leukemia group B 9182 study. J Clin Oncol 1999; 17: 2506-13.

[161] Tannock IF, Osoba D, Stockler MR, et al. Chemotherapy with mitoxantrone plus prednisone or prednisone alone for symptomatic hormone-resistant prostate cancer: a Canadian randomized trial with palliative end points. J Clin Oncol 1996; 14: 1756-64.

[162] Abratt RP, Brune D, Dimopoulos MA, et al. Randomised phase III study of intravenous vinorelbine plus hormone therapy versus hormone therapy alone in hormone-refractory prostate cancer. Ann Oncol 2004; 15: 1613-21.

[163] Hudes G, Einhorn L, Ross E, et al. Vinblastine versus vinblastine plus oral estramustine phosphate for patients with hormone-refractory prostate cancer: A Hoosier Oncology Group and Fox Chase Network phase III trial. J Clin Oncol 1999; 17: 3160-6.

[164] Fossa SD, Jacobsen AB, Ginman C, et al. Weekly docetaxel and prednisolone versus prednisolone alone in androgen-independent prostate cancer: a randomized phase II study. Eur Urol 2007; 52: 1691-8.

[165] Petrylak DP, Tangen CM, Hussain MH, et al. Docetaxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer. N Engl J Med 2004; 351: 1513-20.

[166] Tannock IF, de Wit R, Berry WR, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. N Engl J Med 2004; 351: 1502-12.

[167] Dagher R, Li N, Abraham S, et al. Approval summary: Docetaxel in combination with prednisone for the treatment of androgen-independent hormone-refractory prostate cancer. Clin Cancer Res 2004; 10: 8147-51.

[168] Hadaschik BA and Gleave ME. Therapeutic options for hormone-refractory prostate cancer in 2007. Urol Oncol 2007; 25: 413-9.

[169] Mellinger GT, Gleason, D., Bailar J. The histology and prognosis of prostatic cancer. J Urology 1967; 97: 331-8.

[170] Van der Kwast TH, Roobol MJ, Wildhagen MF, et al. Consistency of prostate cancer grading results in screened populations across Europe. BJU Int 2003; 92 Suppl 2: 88-91.

[171] Forman JD, Kumar R, Haas G, et al. Neoadjuvant hormonal downsizing of localized carcinoma of the prostate: effects on the volume of normal tissue irradiation. Cancer Invest 1995; 13: 8-15.

[172] Horwich A, Wynne C, Nahum A, et al. Conformal radiotherapy at the Royal Marsden Hospital (UK). Int J Radiat Biol 1994; 65: 117-22.

[173] Lilleby W, Fossa SD, Knutsen BH, et al. Computed tomography/magnetic resonance based volume changes of the primary tumour in patients with prostate cancer with or without androgen deprivation. Radiotherapy and Oncology 2000; 57: 195-200.

[174] Lilleby W, Dale E, Olsen DR, et al. Changes in treatment volume of hormonally treated and untreated cancerous prostate and its impact on rectal dose. Acta Oncol 2003; 42: 10-4.

[175] Shearer RJ, Davies JH, Gelister JS, et al. Hormonal cytoreduction and radiotherapy for carcinoma of the prostate. Br J Urol 1992; 69: 521-4.

[176] Yang FE, Chen GT, Ray P, et al. The potential for normal tissue dose reduction with neoadjuvant hormonal therapy in conformal treatment planning for stage C prostate cancer. Int J Radiat Oncol Biol Phys 1995; 33: 1009-17.

[177] Zelefsky MJ, Leibel SA, Burman CM, et al. Neoadjuvant hormonal therapy improves the therapeutic ratio in patients with bulky prostatic cancer treated with three-dimensional conformal radiation therapy. Int J Radiat Oncol Biol Phys 1994; 29: 755-61.

[178] Zelefsky MJ and Harrison A. Neoadjuvant androgen ablation prior to radiotherapy for prostate cancer: reducing the potential morbidity of therapy. Urology 1997; 49: 38-45.

[179] Akakura K, Bruchovsky N, Goldenberg SL, et al. Effects of intermittent androgen suppression on androgen-dependent tumors. Apoptosis and serum prostate-specific antigen. Cancer 1993; 71: 2782-90.

[180] Koper PC, Stroom JC, van Putten WL, et al. Acute morbidity reduction using 3DCRT for prostate carcinoma: a randomized study. Int J Radiat Oncol Biol Phys 1999; 43: 727-34.

[181] Jackson A, Skwarchuk MW, Zelefsky MJ, et al. Late rectal bleeding after conformal radiotherapy of prostate cancer. II. Volume effects and dose-volume histograms. Int J Radiat Oncol Biol Phys 2001; 49: 685-98.

[182] Altman D, Practical statistics for medical research. 1991: Chapman and Hall (London and New York). 611.

[183] Zheng B and Agresti A. Summarizing the predictive power of a generalized linear model. Stat Med 2000; 19: 1771-81.

[184] Jackson A, Yorke ED, and Rosenzweig KE. The atlas of complication incidence: a proposal for a new standard for reporting the results of radiotherapy protocols. Semin Radiat Oncol 2006; 16: 260-8.

[185] Ihaka R and Gentleman R. A Language for Data Analysis and Graphics. Journal of Computational and Graphical Statistics 1996; 5: 299-314.

[186] Duchesne GM. Radiation for prostate cancer. The Lancet Oncology 2001; 2: 73-81.

[187] Fossa SD, Lilleby W, Waehre H, et al. Definitive radiotherapy of prostate cancer: the possible role of staging lymphadenectomy. Int J Radiat Oncol Biol Phys 2003; 57: 33-41.

[188] Zagars GK, Pollack A, and Smith LG. Conventional external-beam radiation therapy alone or with androgen ablation for clinical stage III (T3, NX/N0, M0) adenocarcinoma of the prostate. Int J Radiat Oncol Biol Phys 1999; 44: 809-19.

[189] Vicini FA, Abner A, Baglan KL, et al. Defining a dose-response relationship with radiotherapy for prostate cancer: is more really better? Int J Radiat Oncol Biol Phys 2001; 51: 1200-8.

[190] Kupelian PA, Potters L, Khuntia D, et al. Radical prostatectomy, external beam radiotherapy =72 Gy, permanent seed implantation, or combined seeds/external beam radiotherapy for stage T1-T2 prostate cancer. Int J Radiat Oncol Biol Phys 2004; 58: 25-33.

[191] Sandler HM, Dunn RL, McLaughlin PW, et al. Overall survival after prostate-specific-antigen-detected recurrence following conformal radiation therapy. Int J Radiat Oncol Biol Phys 2000; 48: 629-33.

[192] Roach M, 3rd, Hanks G, Thames H, Jr., et al. Defining biochemical failure following radiotherapy with or without hormonal therapy in men with clinically localized prostate cancer: recommendations of the RTOG-ASTRO Phoenix Consensus Conference. Int J Radiat Oncol Biol Phys 2006; 65: 965-74.

[193] J acob R, Hanlon AL, Horwitz EM, et al. The relationship of increasing radiotherapy dose to reduced distant metastases and mortality in men with prostate cancer. Cancer 2004; 100: 538-43.

[194] Kupelian PA, Buchsbaum JC, Elshaikh MA, et al. Improvement in relapse-free survival throughout the PSA era in patients with localized prostate cancer treated with definitive radiotherapy: Year of treatment an independent predictor of outcome. Int J Radiat Oncol Biol Phys 2003; 57: 629-34.

[195] Kupelian P, Thames H, Levy L, et al. Year of treatment as independent predictor of relapse-free survival in patients with localized prostate cancer treated with definitive radiotherapy in the PSA era. Int J Radiat Oncol Biol Phys 2005; 63: 795-9.

[196] Maximum androgen blockade in advanced prostate cancer: an overview of 22 randomised trials with 3283 deaths in 5710 patients. Prostate Cancer Trialists' Collaborative Group. Lancet 1995; 346: 265-9.

[197] Kupelian P. External beam radiation therapy: role of androgen deprivation. World J Urol 2003; 21: 190-9.

[198] Gottschalk AR and Roach M, 3rd. The use of hormonal therapy with radiotherapy for prostate cancer: analysis of prospective randomised trials. Br J Cancer 2004; 90: 950-4.

[199] Nguyen KH, Horwitz EM, Hanlon AL, et al. Does short-term androgen deprivation substitute for radiation dose in the treatment of high-risk prostate cancer? Int J Radiat Oncol Biol Phys 2003; 57: 377-83.

[200] Hanks GE, Schultheiss TE, Hunt MA, et al. Factors influencing incidence of acute grade 2 morbidity in conformal and standard radiation treatment of prostate cancer. Int J Radiat Oncol Biol Phys 1995; 31: 25-9.

[201] Kutcher GJ and Burman C. Calculation of complication probability factors for non-uniform normal tissue irradiation: the effective volume method. Int J Radiat Oncol Biol Phys 1989; 16: 1623-30.

[202] Christie D, Denham J, Steigler A, et al. Delayed rectal and urinary symptomatology in patients treated for prostate cancer by radiotherapy with or without short term neo-adjuvant androgen deprivation. Radiother Oncol 2005; 77: 117-25.

[203] O'Brien PC, Hamilton CS, Denham JW, et al. Spontaneous improvement in late rectal mucosal changes after radiotherapy for prostate cancer. Int J Radiat Oncol Biol Phys 2004; 58: 75-80.

[204] De Meerleer GO, Fonteyne VH, Vakaet L, et al. Intensity-modulated radiation therapy for prostate cancer: Late morbidity and results on biochemical control. Radiother Oncol 2007; 82: 160-6.

[205] Denham JW, O'Brien PC, Dunstan RH, et al. Is there more than one late radiation proctitis syndrome? Radiother Oncol 1999; 51: 43-53.

[206] Zelefsky MJ, Aschkenasy E, Kelsen S, et al. Tolerance and early outcome results of postprostatectomy three- dimensional conformal radiotherapy. Int J Radiat Oncol Biol Phys 1997; 39: 327-33.

[207] Teh BS, Mai WY, Uhl BM, et al. Intensity-modulated radiation therapy (IMRT) for prostate cancer with the use of a rectal balloon for prostate immobilization: acute toxicity and dose-volume analysis. Int J Radiat Oncol Biol Phys 2001; 49: 705-12.

[208] Chou RH, Wilder RB, Ji M, et al. Acute toxicity of three-dimensional conformal radiotherapy in prostate cancer patients eligible for implant monotherapy. Int J Radiat Oncol Biol Phys 2000; 47: 115-9.

[209] Pollack A, Zagars GK, Starkschall G, et al. Conventional vs. conformal radiotherapy for prostate cancer: preliminary results of dosimetry and acute toxicity. Int J Radiat Oncol Biol Phys 1996; 34: 555-64.

[210] Zelefsky MJ, Leibel SA, Gaudin PB, et al. Dose escalation with three-dimensional conformal radiation therapy affects the outcome in prostate cancer. Int J Radiat Oncol Biol Phys 1998; 41: 491-500.

[211] Valicenti RK, Winter K, Cox JD, et al. RTOG 94-06: Is the addition of neoadjuvant hormonal therapy to dose-escalated 3D conformal radiation therapy for prostate cancer associated with treatment toxicity? Int J Radiat Oncol Biol Phys 2003; 57: 614-20.

[212] Dearnaley DP, Khoo VS, Norman AR, et al. Comparison of radiation side-effects of conformal and conventional radiotherapy in prostate cancer: a randomised trial. Lancet 1999; 353: 267-72.

[213] Zelefsky MJ, Cowen D, Fuks Z, et al. Long term tolerance of high dose three-dimensional conformal radiotherapy in patients with localized prostate carcinoma. Cancer 1999; 85: 2460-8.

[214] Cheung MR, Tucker SL, Dong L, et al. Investigation of bladder dose and volume factors influencing late urinary toxicity after external beam radiotherapy for prostate cancer. Int J Radiat Oncol Biol Phys 2007; 67: 1059-65.

[215] Hoogeman MS, van Herk M, Yan D, et al. A model to simulate day-to-day variations in rectum shape. Int J Radiat Oncol Biol Phys 2002; 54: 615-25.

[216] Jackson A. Partial irradiation of the rectum. Semin Radiat Oncol 2001; 11: 215-23.

[217] Muren LP, Ekerold R, Kvinnsland Y, et al. On the use of margins for geometrical uncertainties around the rectum in radiotherapy planning. Radiother Oncol 2004; 70: 11-9.

[218] Muren LP, Hafslund R, Gustafsson A, et al. Partially wedged beams improve radiotherapy treatment of urinary bladder cancer. Radiotherapy and Oncology 2001; 59: 21-30.

[219] Muren LP, Jebsen N, Gustafsson A, et al. Can dose-response models predict reliable normal tissue complication probabilities in radical radiotherapy of urinary bladder cancer? The impact of alternative radiation tolerance models and parameters. Int J Radiat Oncol Biol Phys 2001; 50: 627-37.

[220] Huang EH, Pollack A, Levy L, et al. Late rectal toxicity: dose-volume effects of conformal radiotherapy for prostate cancer. Int J Radiat Oncol Biol Phys 2002; 54: 1314-21.

[221] Boersma LJ, van den Brink M, Bruce AM, et al. Estimation of the incidence of late bladder and rectum complications after high-dose (70-78 GY) conformal radiotherapy for prostate cancer, using dose-volume histograms. Int J Radiat Oncol Biol Phys 1998; 41: 83-92.

[222] al-Abany M, Helgason AR, Cronqvist AK, et al. Toward a definition of a threshold for harmless doses to the anal-sphincter region and the rectum. Int J Radiat Oncol Biol Phys 2005; 61: 1035-44.

[223] Zelefsky MJ, Levin EJ, Hunt M, et al. Incidence of late rectal and urinary toxicities after three-dimensional conformal radiotherapy and intensity-modulated radiotherapy for localized prostate cancer. Int J Radiat Oncol Biol Phys 2008; 70: 1124-9.

[224] Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 1993; 85: 365-76.

[225] Fransson P, Damber JE, Tomic R, et al. Quality of life and symptoms in a randomized trial of radiotherapy versus deferred treatment of localized prostate carcinoma. Cancer 2001; 92: 3111-9.

9. Errata

Paper I, page 456, Table I: overhead, “Group 2 (6 Gy)” should be: “Group 2 (66 Gy)”

Paper III, page 45, second last sentence: it should be reference 19 but not 21

Paper III, page 46, Table 2: it should be reference 24 and 6 but not 19 and 18

Paper III, page 47, sixth paragraph: “… fractional volumes between 21-224 Gy.”

Should be: “….fractional volumes between 21-24 Gy.”

Appendices

Pasient no: _____

REGISTRERINGSSKJEMA FOR AKUTTE EFFEKTER ETTER STRÅLEBEHANDLING AV PROSTATAKREFT.

NAVN:_____ FØDT:_____

HENVISNINGSDATO:_____ DIAGNOSEDATO:_____

TIDLIGERE SYKDOMMER (0 - 7):_____
(0 ingen, 1 DM, 2 hypertensjon, 3 hjerte sykdom, 4 tarm sykdom, 5 claudicatio(gen. art. scl. sykdom), 6 blære kreft, 7 annet)

Bruker statiner (JA/NEI): _____

KLINISK UTREDNING:

SYMPTOMER : _____
PROSTATA BIOPSI (JA / NEI): _____ DATO: _____
TUR-P (JA / NEI): _____ HVIS JA, HVILKEN ÅR: _____
CT / MR (JA / NEI): _____ ULTRALYD (JA / NEI): _____
STAGING LAPAROTOMI (JA / NEI): _____
SCINTIGRAFI (JA / NEI): _____
PSA(dato): _____ TNM: _____ GLEASON: _____
PSA(før start av behandling/dato): _____

BEHANDLING:

HORMON BEHANDLING (JA / NEI): _____
TAB (start): _____ TAB (slutt): _____
TYPE ANTIANDROGEN: _____
TYPE LHRH ANALOGE: _____

STRÅLING:
FELT: _____ DAGS DOSE: _____ TOTAL DOSE: _____
BEHANDLINGS START: _____ BEHANDLINGS SLUTT: _____

DATO: _____
DOSE: _____

AKUTTE BIVIRKNINGER

Skjema for akutte bivirkninger etter RTOG-gradering og Koper et. al., skal nyttast ved kontroll under pågående strålebehandling.

TARM:

0 ingen symptomer

1 øket tarm tømming eller forandringer i avførings mønster, trenger ikke medikamenter

2 diare, trenger medikamenter, ikke inkontinens, abdominal smerter trenger smertestillende.

3 diare, trenger parenteral ernæring, slim/blod i avføring, trenger pads, utblåst abdomen (røntgen abdomen viser oppblåste tarmslynger)

4 akutt eller subakutt obstruksjon/perforasjon, gastrointestinal blødning trenger blodtransfusion, abdominal smerter/tenesmus trenger tube decompression or bowel diversion

ANAL:

0 ingen symptomer

1 ubehag/smerter, trenger ikke smertestillende

2 ubehag/smerter, trenger smertestillende

3 ubehag/ smerter, trenger opioider

4 avlastande colostomi

URINVEIER:

0 ingen symptomer

1 vannlatning/nocturi > 2x utgangspunkt, dysuri og urgency, trenger ikke medikamenter

2 vannlatning/nocturi mindre en hver time, dysuri, urgency og blære spasmer trenger medikamenter

3 vannlatning/nocturi > hver time, dysuri, smerter i bekkenregionen og blære spasmer, trenger opioider regelmessig, hematuri

4 hematuri trenger blodtransfusjon, akutt blære tamponade (ikke sekundært til "clot"), ulcerasjon eller necrose

HUD:

0 ingen forandringer

1 rubor, tørr epitelitt

2 mindre epitelitt (til dels våt), moderat ødem

3 uttalt epitelitt (våt), pitting ødem

4 sår, nekrose, hemorrhage

BEHANDLING AV BIVIRKNINGER:

REGISTRERINGSSKJEMA FOR SEIN-EFFEKTAR ETTER STRÅLEBEHANDLING AV PROSTATAKREFT.

Pasientnamn: _____ Fødselsnummer: _____

Kontroll(mnd): _____ Dato for konsultasjon: _____ Utført av: _____

Generell status:

Karnofsky-status: _____ Vekt(kg):_____ PSA:_____

Skjema for status for normalvev på dei påfølgjande sider har 4 klassifiseringar: RTOG-gradering samt S, O og M-kategorisering i frå LENT/SOMA. Skjemaet skal nyttast ved kontrollar etter 6, 12, 24 og 60 mnd, etter utført strålebehandling.

Blære og urethra :

	0	Grad 1	Grad 2	Grad 3	Grad 4	5
RTOG	ingen	Slight epithelial atrophy; minor telangiectasia (microscopic hematuria)	Moderate frequency; generalized telangiectasia; intermittent macroscopic hematuria	Severe frequency & dysuria; severe generalized telangiectasia (often with petechiae); frequent hematuria; reduction in bladder capacity (< 150cc)	Necrosis/Contracted bladder (capacity < 100 cc) Severe hemorrhagic cystitis	Mors
Subjektiv	ingen					Mors
Dysuri		Sjelden	Vekslende	Vedvarende	Betydelig	
Miksjonsfrekvens		3-4 timer	2-3 timer	1-2 timer	Hver time	
Hematuri		Sjelden	Vekslende	Vedvarende	Betydelig	
Inkontinens		< 1 / uke	< 1 / dag	< 2 truser / dag	Betydelig	
Strålefylde		Av og til nedsatt	Nedsatt	Delvis stopp	Total stopp	
Objektiv	ingen					Mors
Hematuri		Mikroskopisk	Sjelden makroskopisk	Makroskopisk	Makroskopisk med koagler	
Endoscopi		Flekket atrofi / teleangiektasier uten blødning	Stor atrofi / teleangiektasier med blødning	Ulcerasjon i muskulatur	Perforasjon eller fistel	
Maksimalt volum		>300-400 cm3	>200-300 cm3	>100-200 cm3	< 100 cm3	
Residualvolum		<25 cm3	> 25-100 cm3	> 100 cm3	Urinretensjon	
Tiltak	ingen					Mors
Dysuri		Sjelden perifert virkende analgetika	Jevnlig perifert virkende analgetika	Jevnlig sentralt virkende analgetika	Kirurgisk behandling	
Miksjonsfrekvens		Alkalisering av urinen	Sjelden spasmolytika	Jevnlig sentralt virkende analgetika	Cystektomi	
Hematuri		Jernmedikasjon	En transfusjon eller kauteriser	Jevnlig transfusjon eller koaguler	Kirurgisk intervensjon	
Inkontinens		Sjelden bleier	Hyppig bleier	Alltid bleier eller ren intermitterende kateterisering	Permanent kateter	
Urinstråle		Redusert kraft på urinstrålen	Ren intermitterende kateterisering < 1/dag	Dilatasjon eller ren intermitterende katetrisering > 1/dag	Foleykateter eller kirurgi	

Rektum-status:

	0	Grad 1	Grad 2	Grad 3	Grad 4	5
RTOG	None	Mild diarrhea; mild cramping; bowel movement 5 times daily; slight rectal discharge or bleeding	Moderate diarrhea and colic; bowel movement > 5 times daily; excessive rectal mucus or intermittent bleeding	Obstruction or bleeding, requiring surgery	Necrosis/perforation fistula	Death
Subjektiv	ingen					Mors
Tenesmer		Sjelden	Vekslende	Vedvarende	Uttalt	
Slim i avføring		Sjelden	Vekslende	Vedvarende	Uttalt	
Sphincter kontroll		Sjelden	Vekslende	Vedvarende	Uttalt	
Avføringsfrekvens		2-4 / døgn	4-8 / døgn	> 8 / døgn	Ukontrollert diare	
Smerter		Sjelden	Vekslende	Vedvarende	Uttalt	
Objektiv	ingen					Mors
Blødning		Kjemisk påvist	> 2 / uke	Vedvarende eller daglig	Større blødning	
Ulcerasjon		Overflatisk < 1 cm2	Overflatisk > 1 cm2	Dyp ulcerasjon	Perforasjon eller fistle	
Striktur		> 2/3 av normal diameter med dilatasjon	1/3 - 2/3 av normal diameter med dilatasjon	< 1/3 av normal diameter	Total obstruksjon	
Tiltak	ingen					Mors
Tenesmer og tømmefrekvens		≤ 2 / uke med antidiaremiddel	> 2 / uke med antidiaremiddel	➢ 2 / dag med antidiaremiddel	Kirurgisk terapi, eventuell kolostomi	
Smerter		Sjelden perifert virkende analgetika	Regelmessig perifert virkende analgetika	Jevnlig sentralt virkende analgetika	Kirurgisk terapi, eventuell kolostomi	
Blødning		Stool softener, iron therapy	Sjelden transfusjon	Jevnlig transfusjon	Kirurgisk terapi, eventuell kolostomi	
Ulcerasjon		Diett eller laksantia	Periodevis steroider	Steroidklyster, Hyperbar O2	Kirurgisk terapi, eventuell kolostomi	
Striktur		Diett	Sjelden dilatasjon	Regelmessig dilatasjon	Kirurgisk terapi, eventuell kolostomoi	
Sphincter kontroll		Sjelden bleier	Hyppig bleier	Alltid bleier	Kirurgisk terapi, eventuell kolostomi	

Tarmstatus:

	0	Grad 1	Grad 2	Grad 3	Grad 4	5
RTOG	None	Mild diarrhea; mild cramping; bowel movement 5 times daily; slight rectal discharge or bleeding	Moderate diarrhea and colic; bowel movement > 5 times daily; excessive rectal mucus or intermittent bleeding	Obstruction or bleeding, requiring surgery	Necrosis/perforation fistula	Death
Subjektive	ingen					Mors
Avføringsfrekvens		2-4 / døgn	5-8 / døgn	> 8 / døgn	Ukontrollert diare	
Avføringskonsistent		Bulky	Løs	Slim, mørk, vann		
Smerter		Sjelden	Vekslende	Vedvarende	Uttalt	
Obstipation		3-4 / uke	2 / uke	1 / uke	> 10 døgn	
Objektive	ingen					Mors
Melena		Sjelden	Vekslende, normal hemoglobin	Vedvarende, 10-20% ned i hemoglobin	Uttalt, > 20% ned i hemoglobin	
Vekttap fra oppstart av behandling		≥ 5-10%	➢ 10-20%	> 20-30%	> 20-30%	
Striktur		> 2/3 av normal diameter med dilatasjon	1/3 - 2/3 av normal diameter med dilatasjon	< 1/3 av normal diameter	Total obstruksjon	
Ulcerasjon		Overflatisk ≤ 1 cm2	Overflatisk > 1 cm2	Dyp ulcerasjon	Perforasjon eller fistle	
Tiltak	ingen					Mors
Smerter		Sjelden perifert virkende analgetika	Regelmessig perifert virkende analgetika	Jevnlig sentralt virkende analgetika	Kirurgisk terapi, eventuell kolostomi	
Tømmefrekvens / konsistent		Diet modifikasjon	Regelmessig perifert virkende analgetika, antidiaremiddel	Jevnlig sentral virkende analgetika, antidiaremiddel		
Blødning		Jern behandling	Periodevis transfusion	Jevnlig transfusion	Kirurgisk terapi	
Striktur		Sjelden diet modifikasjon	Diet modifikasjon nødvendig	Medical intervention, NG suction	Kirurgisk terapi	
Ulcerasjon				Medical intervention	Kirurgisk terapi	

Hoftebein-status:

	0	Grad 1	Grad 2	Grad 3	Grad 4	5
RTOG		Asymptomatic; no growth retardation; reduced bone density	Moderate pain or tenderness; growth retardation; irregular bone sclerosis	Sever pain or tenderness; complete arrest of bone growth; dense bone sclerosis	Necrosis/Spontaneous fracture	Death
Subjektiv	Ingen					Mors
Smerter		Sjelden	Vekslende	Vedvarende	Betydelig	
Funksjon		Interferes with athletic recreation	Interferes with work	Interferes with daily activity	Complete lack of function	
Ledd bevegelse		Stiffness interfering with athletic recreation	Stiffness interfering with work	Stiffness interfering with daily activity	Complete fixation, necrosis	
Objektiv	Ingen					Mors
Brudd				Partial thickness	Full thickness	
Mucosa soft tissue				Sequestration		
Hud over bone		Erythema	Sår	Sinus	Fistula	
Ledd bevegelse		< 10% mindre	< 10 - 30% mindre	< 30 - 80% mindre	> 80% mindre	
Tiltak	Ingen					Mors
Smerter		Sjelden perifert virkende analgetika	Regelmessig perifert virkende analgetika	Jevnlig sentralt virkende analgetika	Kirurgisk terapi	
Funksjon		Sjelden fysioterapi	Periodevis fysioterapi	Regelmessig fysioterapi eller medisinsk terapi	Kirurgisk terapi	
Ledd bevegelse		Sjelden fysioterapi	Intensive fysioterapi	Kirurgisk terapi		

SEKSUELL DYSFUNKSJON:

	0	Grad 1	Grad 2	Grad 3	Grad 4
Subjektive	Ingen				
Erectile function for vaginal penetration		Occasionally insufficient	Intermittently insufficient	Not sufficient	Impotent
Dryness		Occcasional	Intermittent	Persistent	Refractory
Desire		Occasional	Intermittent	Seldom	Never
Satisfaction		Occasional	Intermittent	Seldom	Never
Objektive	Ingen				
Frequency			Decreased form normal	Rare	Never
Orgasm		Occasional	Intermittent	Seldom	Never
Tiltak	Ingen				
Impotence			Medikal terapi	Kirurgisk terapi	

BEHANDLING PGA. SEIN-EFFEKTAR (JA / NEI):

HVIS JA; HVILKEN BEHANDLING:

RESIDIV (JA / NEI / USIKKER): hvis ja, dato:

STIGENDE PSA (3 siste PSA med dato):

LOKALT:

DISTALT (bein, visceral, lymph node,annet):

STARTET BEHANDLING PGA. RESIDIV (JA / NEI):

DATO:

HVILKEN BEHANDLING:

STATUS (%)	*KARNOFSKY PERFORMANCE STATUS SCORE*
100%	*Normal; no complain*
90%	*Able to carry on normal activities; minor signs or symptom of disease*
80%	*Normal activity with effort*
70%	*Cares for selv; unable to carry on normal activity or to do active work*
60%	*Requires occasional assistance but able to care for most of his needs*
50%	*Requires considerable assistance and frequent medical care*
40%	*Disabled; requires special care and assistance*
30%	*Severely disabled; hospitalization indicated though death is not imminent*
20%	*Very sick; hospitalization necessary; active supportive treatment necessary*
10%	*Moribund*
0%	*Dead*