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Hanne Tøndel

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Image-Guided Radiotherapy for Prostate Cancer and Side Effects after Treatment

Thesis for the degree of Philosophiae Doctor

Trondheim, February 2019

Norwegian University of Science and Technology
Faculty of Medicine and Health Sciences
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Bivirkninger etter moderne bildestyrt kurativ strålebehandling for prostatakreft

Strålebehandling er en viktig behandlingsmetode for pasienter med prostatakreft. Vanlige akutte strålebivirkninger er hyppig og smertefull vannlatning, løs avføring og luftplager. Noen pasienter får plager med senbivirkninger som kan komme måneder og år etter strålebehandling og som ofte er en videreføring av de akutte bivirkningene. Tidligere forskning viser at graden av akutte bivirkninger kan forutsi senbivirkninger hos denne pasientgruppen.

Ved hjelp av ny teknologi kan vi kontrollere at stråledosen blir gitt mer presist. Dette gjøres ved at en CT-undersøkelse av pasienten blir gjort i behandlingsleie før strålebehandlingen gis. Dette gir større presisjon og strålebehandlingen kan gis med reduserte sikkerhetsmarginer rundt målvolumet. I teorien kan dette redusere bivirkninger. Det er ikke gjort store randomiserte studier som sammenligner denne typen moderne bildestyrt strålebehandling mot standard behandling for denne pasientgruppen.

St. Olavs Hospital og Ålesund sykehus gjennomførte en randomisert studie med 260 menn som fikk åtte ukers kurativ strålebehandling for prostatakreft. Pasientene ble randomisert i to grupper. Én gruppe fikk strålebehandling med ukentlig kontroll av behandlingsleie og standard sikkerhetsmarginer. Den andre gruppen fikk strålebehandling med daglig CT-kontroll og reduserte sikkerhetsmarginer. Den totale stråledosen var lik i begge armer. Vårt primære endepunktet var akutte bivirkninger fra endetarmen etter åtte ukers strålebehandling. Vi fant ingen signifikante forskjeller mellom gruppene hverken relatert til generell livskvalitet eller spesifikke mål relatert til mage/tarm og urinveissymptomer. Vi har også analysert seksualfunksjon 18 måneder etter avsluttet strålebehandling og fant ingen forskjeller mellom de to gruppene på dette tidspunktet. I tillegg har vi analysert hvordan endetarmsvolumet endres gjennom strålebehandlingsperioden i et utvalg pasienter fra gruppen som fikk daglig bildestyrt strålebehandling. Vi fant at volumet ble signifikant redusert etter åtte ukers behandling, men at den reelle stråledosen til endetarmen holdt seg stabil.

Vår studie understreker at ny teknologi innenfor strålebehandling bør evalueres nøye med tanke på klinisk nytteverdi for pasienter. Våre pasienter vil bli fulgt i ti år med tanke på sykdomskontroll og utvikling av sene bivirkninger.

Name of candidate:	Hanne Tøndel
Department:	Department of Clinical and Molecular Medicine Cancer Clinic, St. Olavs hospital, Trondheim University Hospital
Main supervisor:	Jo-Åsmund Lund
Co-Supervisors:	Arne Solberg and Stein Kaasa
Funding:	The Norwegian Cancer Society
Date of defence:	26th. of February 2019

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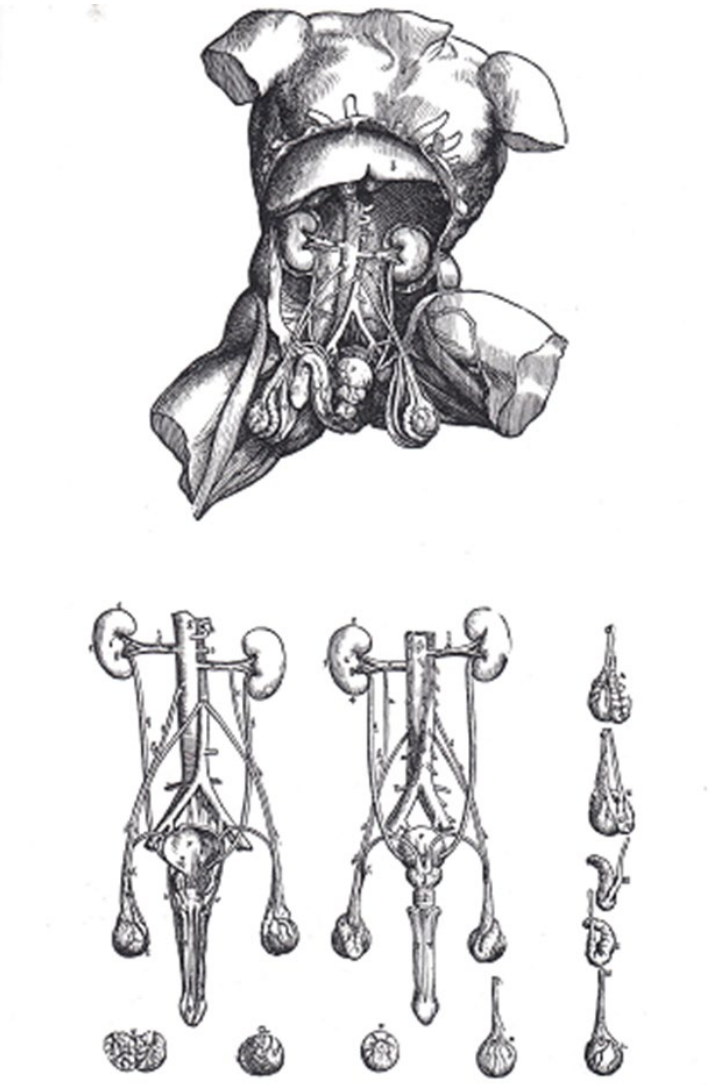

J.B. de C. M. Daunders and Charles D. O`Malley: The Illustrations from the Works of Andreas Vesalius of Brussels. Cleveland and New York 1950, page 168/169, plate 59.
With permission form Deutsches Museum.

"They are called wise who put things in their right order and govern them well"

St. Thomas Aquinas
(1225-74)

"*Prostate cancer is like golf. You need to play it as it lies. Because the disease is variable, each treatment solution requires a unique strategy*."

Dr. Charles "Snuffy" Myers

Avalanche in Grasdalen 1975.
Photo by Ingvar Tøndel, printed with permission

Acknowledgements

The work of this thesis was carried out at the Department of Clinical and Molecular Medicine, Norwegian University of Science and Technology (NTNU), Trondheim and at the Cancer Clinic, St. Olavs Hospital, Trondheim University Hospital. The work was funded by the Norwegian Cancer Society.

First, I want to thank all the patients who participated in the RIC study. Without your willingness and eagerness, this project would have been impossible. I have very much enjoyed talking to all of you, and your recruitment to the study usually went very smoothly, often before I had finished informing you!

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I want to thank Arne Solberg for his northern Norwegian enthusiasm and hard work in this project. Arne, in addition of having unparalleled clinical skills, you are a brilliant writer and a tip-top statistician! Without you, this thesis would not have been made.

Professor Stein Kaasa has contributed to making this thesis more solid, valid and with a better foundation. Your research skills are indisputable and have undoubtedly raised the quality of the project. It has been a pleasure working with you all, and I hope our collaboration will continue in the future.

I am grateful for the contribution of the co-authors of my articles. Professor Stian Lydersen deserves special thanks, keeping up with my challenges in statistical understanding and always answering my questions pedagogically and patiently (although sometimes with some blushing when discussing the primary outcome question in Paper III). Christer Jensen also deserves special thanks. Your clear brain and good memory both made my work easier, and I appreciate this a lot. Bjørg Y. Aksnessæther and Anne D Wanderås: you helped increase the quality of this work, and I will always be grateful for your participation.

The RIC study was a two-center study, and the cooperation with Ålesund was a pleasure.

Big thanks to all of the staff at the Department of Oncology in Ålesund and in particular the radiation team.

The help I received from NTNU and the European Palliative Care Research Centre (PRC) made my days easier. I want to thank Ragnhild Green Helgås for being the oracle answering all my administrative questions and all of the other good colleagues and neighbors, both in my office and down the corridors. Special thanks to Trude Camilla Frøseth: your well-ordered head in addition to your nice smile and personality made my days better, and I am sure, raised the response rate from the patients!

I am grateful for having had the opportunity to work part-time at the Cancer Clinic during this period and I want to thank all my colleagues there and at the Department of Ear, Nose and Throat, Head and Neck Surgery for making this a good and interesting place for me to be. Special thanks to Heidi Knobel and Torgrim Tandstad at the uro-oncology section for their contribution in both including patients and answering my questions. Always wise, always nice and encouraging! To my working colleagues at the radiation therapy section, Monika, Mirjam, Boris, and Tora: Your support has been important to me, both in good times and on less bright days. In addition, thanks to everyone else in the basement: physicists, radiation therapists, and Bente: I love working on the bottom floor with you all! I never had a boring day at work! Last, but very important to me, I want to thank my best friend at work, Morten. Without our moments of “Hanne-and-Morten-time”, the days spent at work and in this project would have been of lower quality, and that goes for my life as well. I love you a lot!

I would like to thank my loving parents for always being supportive, encouraging, and very helpful with day-to-day life, which can be critically busy sometimes. The same goes for my friends and neighbors for all the support and help you have given me and my family. Special thanks to my knitting club: You are my yoga!

At last, I want to thank the four most important people in my life, my dear Sverre and our wonderful children Selma, Felix, and Clara. I love you all so much!

Sverre: I wish others could experience your kind of support, which can be hysterically amusing sometimes but also sensible and intelligent. Selma, Felix and Clara: You always remind me of what is truly important in life besides work and a PhD. I know you are proud of me being a researcher in cancer, although your grandfather’s degree in avalanches still ranks higher.

Abbreviations

AC	adenocarcinoma
ADT	androgen deprivation therapy
ALAT	alanin aminotransferase
ALP	alkaline phosphatase
ASCO	American Society of Clinical Oncology
ASTRO	American Society for Radiation Oncology
BT	brachytherapy
CBCT	cone beam computed tomography
CSA	cross-sectional area
CT	computed tomography
CTCAE	common toxicity criteria for adverse events
CTV	clinical target volume
CVD	cardiovascular disease
DM	diabetes mellitus
DNA	deoxyribonucleic acid
DSS	disease-specific survival
DVH	dose-volume histogram
EAU	European Association of Urology
EBRT	external beam radiotherapy
ED	erectile dysfunction
EORTC	European Organization for Research and Treatment of Cancer
ePLND	extended pelvic lymph node extension
ET	endocrine therapy
FFBF	freedom from biochemical failure
FFCF	freedom from clinical failure
FSH	follicle-stimulating hormone
GnRH	gonadotrophin-releasing hormone
GS	Gleason score
GT	gammaglutamyltransferase
GU	genitourinary
HDR	high dose-rate
HRQoL	health-related quality of life
ICRP	International Commission on Radiological Protection
ICRU	International Commission on Radiation Units & Measurements
IGRT	image-guided radiotherapy
IMRT	intensity modulated radiation therapy
ISUP	International Society of Urological Pathology
KV	kilovoltage

LDR	low dose-rate
LH	luteinizing hormone
LHRH	luteinizing hormone-releasing hormone
LINAC	linear accelerator
LUTS	lower urinary tract symptoms
MLC	multi-leaf collimators
MRI	magnetic resonance imaging
MV	megavoltage
NOK	Norwegian kroner
NRPA	Norwegian Radiation Protection Authority
OARs	organs at risk
OS	overall survival
PB	penile bulb
PC	prostate cancer
PET	positron emission tomography
PROMs	patient-reported outcome measure
PSA	prostate-specific antigen
PTV	planning target volume
QA	Quality assurance
QLQ C30	quality of life core questionnaire
QoL	quality of life
QUALY	quality of life-adjusted gain in life years
QUANTEC	Quantitative Analyses of Normal Tissue Effects in the Clinic
QUFW	Questionnaire Umeå Fransson Widmark
RALP	robot-assisted laparoscopic prostatectomy
RARP	robot-assisted radical prostatectomy
RCT	randomized controlled trial
RT	radiotherapy
RTOG	Radiation Therapy Oncology Group
RV	rectal volume
RVV	rectal volume variation
SBRT	stereotactic body radiation therapy
SIB	simultaneously integrated boost
SPCG	Scandinavian Prostate Cancer Group
SV	seminal vesicles
TAB	total androgen blockage
TURP	transurethral resection of the prostate
VMAT	volumetric modulated arc therapy

Summary in English

Prostate cancer (PC) is the most common cancer among Norwegian men, with nearly 5,000 new cases in 2016. The prognosis of localized disease is good, and the 5-year overall survival rate is above 90%. Radical radiotherapy (RT) is one of the most important modalities in the treatment of PC and can last for approximately 8 weeks. RT is generally well tolerated; however some patients may experience both acute and late side effects. The most common acute side effects are increased urinary frequency, painful urination, loose stools, flatulence, and skin soreness. Late side effects can be a continuation of the acute side effects and can also include urinary obstruction, impotence, and rectal bleeding. Late side effects may occur months and years after RT. Previous studies have shown that acute side effects after RT might predict late side effects in PC patients.

Modern external beam radiotherapy (EBRT) is delivered with linear accelerators and often involves image-guided radiotherapy (IGRT). IGRT can be defined as organ imaging in the treatment room with positional adjustments for geometrical deviations prior to RT. This measures the patient's position more accurately, so the radiation dose can be aimed more precisely at the target volume. The most common modality of IGRT is computed tomography (CT). In theory, modern IGRT can improve the treatment and reduce side effects. By reducing safety margins around the target volume, the dose to the normal tissue is also reduced and theoretically, so are the side effects. In hypofractionated treatment, the daily dose is larger, and the total treatment time is reduced. Shorter treatment time is an advantage for the patient and requires fewer resources from the healthcare system. In clinical practice, modern IGRT is consider as standard when using new techniques such as intensity-modulated radiation treatment (IMRT), volumetric-modulated arc therapy (VMAT), stereotactic body radiation therapy (SBRT), and particle therapy (protons and carbon ions). Large randomized studies comparing the use of modern IGRT to standard two-dimensional (2D) imaging in EBRT have not been conducted in this group of patients, and the evidence level for clinical outcomes is debatable.

In collaboration with Kreftavdelinga at Ålesund Hospital, the Cancer Clinic at St. Olavs Hospital conducted a randomized study, the RIC study, that included 260 patients with PC suitable for radical EBRT. We compared daily cone beam computed tomography (CBCT) IGRT

with reduced safety margins around the target volume against weekly 2D-based image verification with standard safety margins around the target volume. We found no significant differences in acute gastrointestinal (GI) or genito-urinary (GU) side effects between the groups. In addition, no differences occurred in health-related quality of life between groups (Paper I).

Paper II reports our analysis of rectal volume variation (RVV) in 30 patients from the experimental arm who received daily IGRT and reduced safety margins. We found a significant reduction in rectal volume (RV) throughout the course of treatment. However, the percentage of irradiated RV remained stable and within the recommended dose level. The use of daily IGRT and reduced safety margins around the target volume ensured good precision without giving excessive doses to the rectum and may explain these findings.

Paper III reports our analysis of sexual function 18 months after initiation of radiation therapy in the two study arms. We found no differences between the groups, despite the fact that the radiation dose to the penile bulb was significantly larger in the group being treated with large safety margins around the target volume. The rate of erectile dysfunction (ED) is generally high in this proportion of the population. The reasons for this are multifactorial: high age, comorbidity, hormone treatment, and radiation therapy. The frequency of ED is probably not affected to any great extent by the radiation dose in this group of PC patients.

The results of this thesis underline the need for technical medical innovations to be thoroughly evaluated in controlled clinical trials with long-term follow-up.

Norsk sammendrag

Prostatakreft er den vanligste kreftsykdommen blant norske menn med nesten 5000 nye tilfeller diagnostisert i 2016. Prognosen ved lokalisert sykdom er god og samlet 5-års overlevelse er nå godt over 90%. Kurativ strålebehandling med varighet på ca. 8 uker er en av de viktigste modalitetene i behandling av prostatakreft. Som regel tolereres strålebehandlingen godt, men pasienter kan få både akutte og sene bivirkninger. De vanligste akutte bivirkningene er hyppig og smertefull vannlatning, løs og hyppig avføring, luftplager og sårhet i hud. Sene bivirkninger kan være en videreføring av de akutte samt urinobstruksjon, impotens og blødning fra rektum (stråleproktitt). Sene bivirkninger kan komme måneder og år etter avsluttet strålebehandling. Tidligere studier har vist at akutte bivirkninger kan predikere sene bivirkninger etter strålebehandling for prostatakreft.

Moderne stråleterapi gis med lineær akseleratorer. De fleste sentra inkluderer bruk av bildestyrt stråleterapi (image-guided radiotherapy, IGRT). IGRT kan defineres som hyppig eller daglig billedtaking av pasienten i behandlingsrommet med registrering av avvik i forhold til tumor (eller surrogater) og korrigering før behandling på bakgrunn av dette bildeopptaket. Dette gjør at plasseringen av pasienten i forhold til lineær akseleratoren blir mer nøyaktig og stråledosen kan gis mer presist i målvolumet. Den den vanligste modaliteten for bildeopptak er computer tomografi (CT).

Moderne IGRT kan teoretisk gi flere muligheter til forbedret behandling og reduserte bivirkninger. Ved å redusere sikkerhetsmarginer rundt målvolumet blir dosen også redusert til normalvevet rundt. Dette kan gi mindre bivirkninger. Moderne IGRT muliggjør også hypofraksjonert behandling med større daglig dose. Dermed kan den totale behandlingstiden reduseres og det blir mulig å gi høyere doser i målvolumet. Kortere behandlingstid er en fordel for pasienten og gir mindre ressursbruk for helsevesenet. I klinisk hverdag anser mange moderne IGRT som standard ved bruk av nye teknikker innen stråleterapi som for eksempel Intensitet modulert strålebehandling (IMRT), Volumetrisk modulert bue behandling (VMAT), Stereotaktisk strålebehandling (SBRT) og behandling med partikkelstråling (protoner og karbonioner). Det er ikke gjort store randomiserte studier som sammenligner bruk av moderne IGRT mot standard to-dimensjonal (2D) billedtaking i

strålebehandling for pasienter med prostatakreft. Evidensnivået er derfor diskutabelt for kliniske utfall.

I samarbeid med Kreftavdelinga ved Ålesund sykehus har Kreftklinikken ved St. Olavs hospital gjennomført en randomisert studie som inkluderte totalt 260 pasienter med prostatakreft som fikk kurativ strålebehandling (" RIC studien"). Vi har sammenlignet strålebehandling med daglig CT- basert bildeverifikasjon og reduserte sikkerhetsmarginer rundt målvolumet versus ukentlig 2D-basert bildeverifikasjon og standard sikkerhetsmarginer rundt målvolumet. Vi fant ingen signifikante forskjeller i akutte gastro-intestinale eller genito-urinale bivirkninger mellom gruppene. Det ble heller ikke funnet forskjeller i generell livskvalitet (artikkel I).

I artikkel II har vi analysert endringer i rektumvolumet gjennom strålebehandlingsperioden for 30 av pasientene i den eksperimentelle armen hvor det ble gjennomført daglig CT verifikasjon. Vi fant en signifikant reduksjon av rektumvolumet gjennom behandlingsforløpet. Den prosentvise bestrålingen av tarmen holdt seg imidlertid stabil og innenfor anbefalte dosenivå. Dette skyldes trolig daglig IGRT og mindre marginer til planleggingsvolumet (PTV) som sikrer god presisjon fra dag til dag uten å gi for store doser til rektum.

I artikkel III har vi analysert seksualfunksjon 18 måneder etter oppstart strålebehandling i de to studie-armene. Vi fant ingen forskjeller mellom gruppene i opplevde ereksjonsproblemer til tross for at stråledosen til penil bulb var signifikant større i gruppen som fikk store marginer rundt målvolumet. Frekvensen av erektil dysfunksjon er generelt høy i denne andelen av populasjonen. Årsakene til dette er multifaktoriell; høy alder, komorbiditet, bruk av hormonbehandling og strålebehandling. Sannsynligvis vil ikke frekvensen av erektil dysfunksjon påvirkes i så stor grad av stråledosen i denne selekterte gruppen av prostatakreftpasienter.

Arbeidet presentert i denne avhandlingen understreker at innføring av nye teknikker innenfor strålebehandling bør evalueres med tanke på klinisk nytteverdi for pasientene.

List of Papers

Paper I

Tøndel H, Lund JÅ, Lydersen S, Wanderås AD, Aksnessæther B, Jensen CA, Kaasa S, Solberg A.

Radiotherapy for prostate cancer- Does daily image guidance with tighter margins improve patient reported outcomes compared to weekly orthogonal verified irradiation? Results from a randomized controlled trial.

Radiother Oncol. 126 (2018) 229-235

Paper II

Tøndel H, Jensen CA, Solberg A, Lydersen S, Kaasa S, Lund JÅ.

Rectal volume variations and estimated rectal dose during 8 weeks of image-guided radical 3D conformal external beam radiotherapy for prostate cancer.

Accepted for publication in Clinical and Translational Radiation Oncology (Jan 2019)

Paper III

Tøndel H, Lund JÅ, Lydersen S, Wanderås AD, Aksnessæther BY, Jensen CA, Kaasa S, Solberg A.

Dose to penile bulb is not associated with erectile dysfunction 18 months post radiotherapy: a secondary analysis of a randomized trial.

Clinical and Translational Radiation Oncology 13 (2018) 50-56

1. Introduction

Prostate cancer (PC) is the most common cancer in Norwegian men, with 4889 new cases in 2016. The 5-year relative survival rate has increased substantially, from 56.5% in 1977-1981 to 93.6% in 2012-2016 (1) (Fig. 1). This is also reflected in the 15-year relative survival rate (74.6% in 2012-2016) (1). The mean age at time of diagnosis is 69 years, and the mean age of patients dying of PC is 83 years (2). The increase in prevalence has also been considerable, from 23,704 men in 2006 to 47,088 in 2016 (1). This has led to a stronger focus on late side effects, as a substantial proportion of these patients will live long and hopefully good-quality lives after finishing their cancer treatment.

Late side effects after cancer treatment is usually defined as side effects or complications that last for more than one year after the cancer treatment has finished or side effects that start more than one year after the treatment has finished and are related to the main cancer treatment (3).

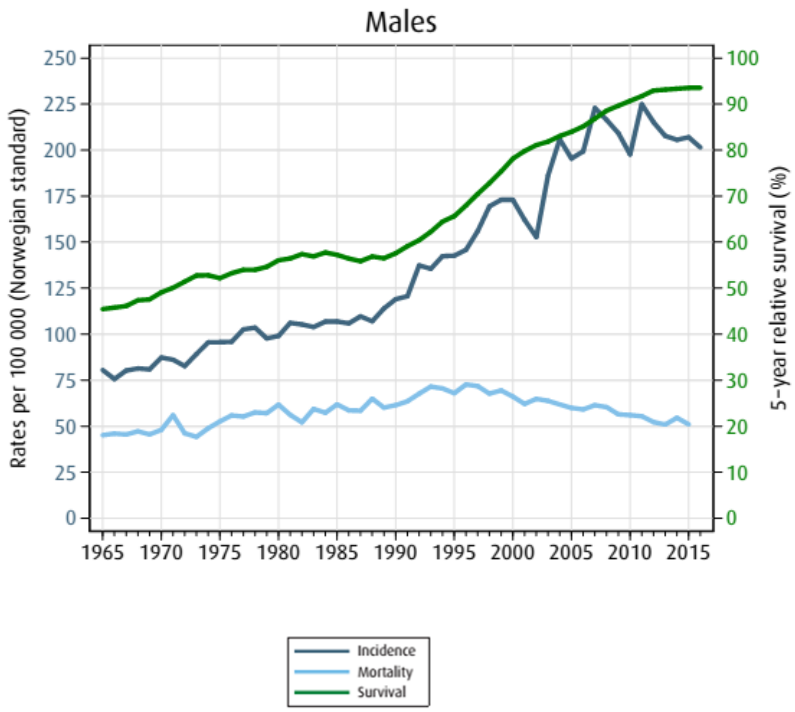

Fig. 1. Trends in incidence and mortality rates and 5-year relative survival rates in Norway.
With permission from Cancer Registry of Norway. Cancer in Norway 2016 - Cancer incidence, mortality, survival and prevalence in Norway. Oslo: Cancer Registry of Norway, 2017 (1).

Radical treatment in PC includes surgery and/or radiotherapy (RT) often combined with endocrine treatment (ET). All treatment modalities have potential acute and late side effects. The most common side effects after surgery are urinary obstruction, urinary incontinence, impotence, and urinary leakage (4). RT can cause side effects such as rectal bleeding, increased urinary frequency, and loss of erection (5, 6). Patients may also experience side effects from endocrine therapy (ET) such as fatigue, osteoporosis, anemia, reduced libido, and gynecomastia (5, 7). Although prostate-cancer-specific mortality is low and similar for surgery, RT, and active surveillance, both surgery and RT are associated with lower incidences of disease progression and metastases (8).

External beam radiotherapy (EBRT) by means of image guided RT (IGRT) is defined as organ imaging of the patient in the treatment room, with positional adjustments of geometric deviations prior to irradiation (9). Until the 1990s, megavoltage (MV) x-ray was used to image the patient and to control the treatment positioning, often by imaging of bony landmarks. These images were often of low quality and resulted in low geometrical accuracy. Computed tomography (CT) images is now the most common method for image capturing in IGRT worldwide and provides a substantially better insight into the position and motion of internal organs. Theoretically, modern IGRT may improve treatment in several ways:

- Optimized safety margins with reduced normal-tissue irradiation
- Reduced side effects, both acute and late
- Increased total tumor dose without corresponding increase in dose to normal tissues
- Increased daily dose (hypofractionation)
- Decreased treatment costs, improved efficiency, and increased patient throughput at the clinic

Although IGRT has several potential advantages, the level of evidence regarding clinical outcomes and benefits is low.

St. Olavs Hospital and Ålesund Hospital performed a randomized controlled trial, the RIC study (A **R**andomized, two-center trial on daily cone-beam **I**GRT vs standard weekly orthogonal IGRT in **C**urative radiotherapy for prostate cancer) in order to investigate the possible clinical advantages of cone beam CT (CBCT) IGRT regarding acute and late side

effects. This thesis is based on the RIC study. In total, the study included 260 men with PC suitable for radical EBRT combined with ET. Previous studies have demonstrated that acute urinary and rectal side effects can independently predict corresponding late radiotherapy-induced toxicity (10-12). The primary outcome in our study was acute rectal toxicity at end of EBRT (Paper I). In addition, we analyzed acute genitourinary (GU) toxicity and health-related quality of life (HRQoL) at end of EBRT (Paper I), rectal volume variation (RVV) during EBRT (Paper II), and erectile function at 18 months after EBRT (Paper III).

2. Background

2.1 Historical background

The earliest known information about PC comes from the mummy of a human male who lived in Egypt about 285-30 BC. (13). Scientists used multi-detector CT (MDCT) to generate detailed images showing multiple sclerotic bone metastasis in the man, who died aged 51-60 years old of an extensive and aggressive prostate cancer (Fig. 2). The prostate gland was first described in 1536 by the Italian anatomist Niccolò Massa (1485-1569), and the first to illustrate it was the Flemish anatomist Andreas Vesalius (1514-1564) in 1538 (frontpage). PC was not identified until 1853, when J. Adams, a surgeon at the London Hospital, described the first case (14).

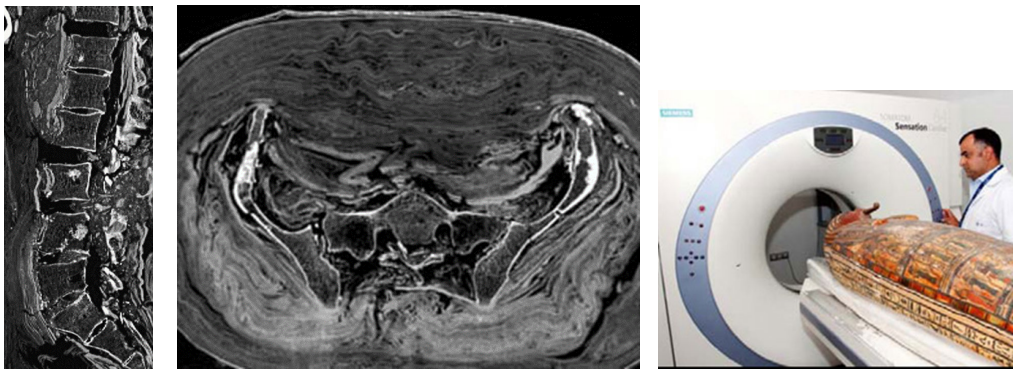

Fig. 2. MDCT imaging of Egyptian mummy with sclerotic vertebra and pelvic bone.
Reprinted from Internal Journal of Paleopathology, Prates et al., Prostate metastatic bone cancer in an Egyptian Ptolemaic mummy, a proposed radiologic diagnosis, Vol 1(2011) 98-103.
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Throughout the years, several different approaches have been applied to remove the prostate gland. Sriprasad et al. describes the history of PC treatment, including an evaluation of nine surgical methods used between 1834 and the early part of the 20th century (15). The first operations were performed to relieve urinary outlet obstruction. However, these procedures were only partial prostatectomies. In 1904, Hugh H. Young performed the first radical perineal prostatectomy for prostate cancer with a technique that remained standard for over 40 years. In the 1920s, transurethral resection of the prostate (TURP) was introduced to relieve obstruction, and it is still frequently used in patients with benign prostatic hyperplasia and PC. Schuessler et al. reported on the first nine patients who

underwent a transperitoneal laparoscopic technique to remove the prostate radically in 1997 (16). This was followed by the introduction of the robot-assisted laparoscopic radical prostatectomy (RALP), first performed in France in 2000 by Abbou et al. (17).

Two Nobel Prizes in Physiology and Medicine have been awarded to scientists for their efforts in developing ET for PC. In 1941, Charles Brenton Huggins published studies evaluating the effect of estrogen in reducing testosterone production (chemical castration) in men with metastatic PC (18). He won the Nobel Prize for this work in 1966. In 1977, Roger Guillemin and Andrew V. Schally were awarded the Nobel Prize for their discoveries of the peptide hormone production of the brain. They determined the role of gonadotropin-releasing hormone (GnRH) in reproduction, which led to the development of GnRH agonists such as leuprolide and gosereline, which still constitute the cornerstone of ET in PC treatment (19).

In 1895, Wilhelm Conrad Röntgen, a German mechanical engineer and physicist, discovered a new form of radiation while experimenting with electricity. Röntgen called this invention X-rays and received the first Nobel Prize in physics for his discovery in 1901 (20). The medical use of X-rays in treatment of malignant tumors developed quickly and was described as early as 1896, when Emil H. Grubbe treated a patient with recurrent inoperable breast cancer, resulting in good local response. In the beginning, types of skin cancer were the most frequent diagnoses treated with X-rays due to low penetration of the irradiation. During the 1910s, the development of X-rays with higher energies began. In addition, understanding of fractionated radiation therapy improved, leading to better clinical responses and reduced RT side effects. In 1930-1950, brachytherapy (BT), cobalt therapy, and linear accelerators were introduced, which made multi-field plans feasible (21).

2.2 Prostate cancer

The prostate gland (from Ancient Greek *prostates*, literally “one who stands before”, “protector”) is a fibromuscular and glandular organ of the male reproductive system lying inferior to the bladder and surrounding the urethra (Fig. 3). The prostate has a peripheral zone, a central zone, and a transitional zone. Approximately 75% of tumors arise in the peripheral zone, 20% in the transitional zone, and 5% in the central zone (4).

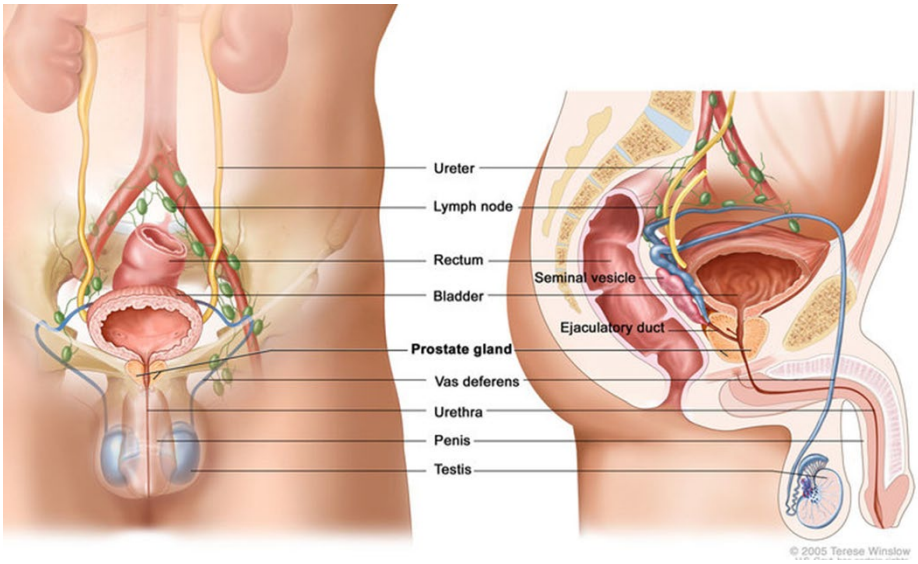

Fig. 3. Male Genitourinary Anatomy.
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The overwhelming majority of PC's (>95%) are acinar adenocarcinomas (ACs) (22). The remaining cases are unusual histologic variants such as mucinous AC, ductal AC, signet ring cell carcinoma, neuroendocrine carcinoma, and adenosquamous carcinoma (23). Due to the variation in response between the different subtypes to both ET and RT, it is crucial to make the correct histopathologic diagnosis before treatment starts.

2.3 Histopathology

The Gleason score (GS) is a histological grading system for PC developed by Donald Gleason between 1966 and 1974 (24). A high GS is associated with poor prognosis. GS is calculated from a total score based on the most dominant occurring cell differentiation (grade 1-5) and the non-dominant pattern with the highest grade (grad 1-5) in each core biopsy. Lower grades are associated with small, closely packed glands. Cells spread out and lose glandular architecture as grade increases (Fig. 4). The assigning of Gleason pattern/grade 1 and 2 has virtually disappeared in modern surgical pathology, making the lowest possible Gleason score being 3+3=6. A new grading system (i.e. Grade Group 1-5), based on the modified

Gleason system) has then been approved by both International Society of Urological Pathology and WHO (25).

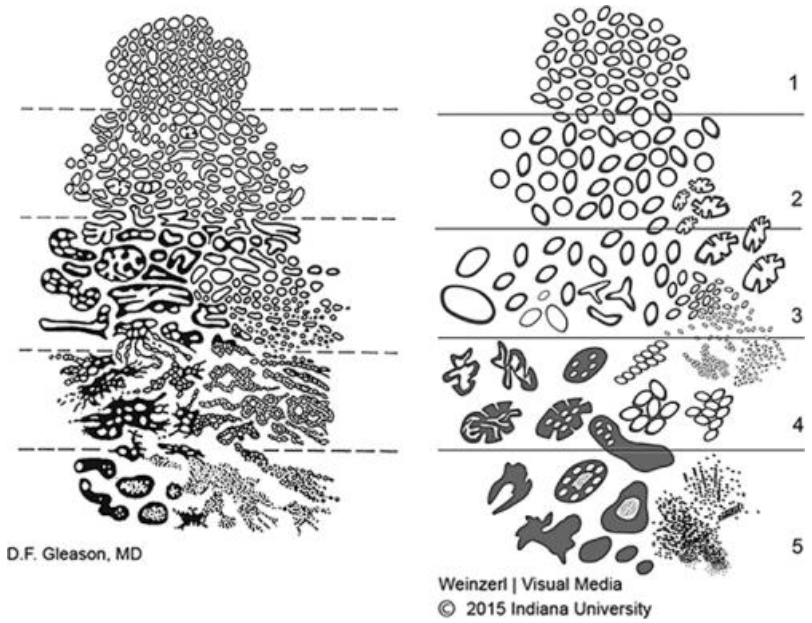

Fig. 4 Prostatic adenocarcinoma (histologic patterns):
Original (left) and 2015 Modified ISUP Gleason schematic diagrams.
Printed with permission by Epstein et al., Prostatic Carcinoma: Definition of Grading Patterns and Proposal for a New Grading System, American Journal of Surgical Pathology, 2016 Feb; 40 (2):244-52 (25).

PC can metastasize both locoregionally and distantly. Infiltration to the seminal vesicles (SVs) is most common, but spread to other adjacent organs such as bladder and rectum is also observed. According to the European Association of Urology (EAU) guidelines, the risk of pelvic and retroperitoneal lymph node metastasis is 20-45% if any biopsy core has a predominantly Gleason 4 pattern, or >3 cores contain Gleason 4 patterns (26, 27). Distant metastases are most frequently seen in the skeleton, appearing as sclerotic lesions primarily in the red hematopoietic bone marrow (columna, pelvic bones, rib, sternum and proximal femora/humeri). In 30% of all patients, pain or neurological symptoms from bone metastasis is the first symptom of cancer (28). The 5-year relative survival rate in patients with distant metastasis is 36.8% (1).

2.4 Diagnostic workups and risk stratification

Although the majority of prostate cancer cases are asymptomatic, symptoms of PC include lower urinary tract symptoms (LUTS) with urinary tract obstruction (70%) and acute urinary retention (25%). Other symptoms are back pain (15%), hematuria (5%), uremia (5%), fatigue, and weight loss in advanced disease (28). Early-stage PC is often asymptomatic. The most common indications for prostate biopsy are elevated serum-prostate-specific antigen (s-PSA), LUTS, and suspect findings at digital rectal exploration (4). PSA is a glycoprotein enzyme secreted by the epithelial cells of the prostate gland and was first detected in human blood in 1980 (29). It is organ-specific but not cancer-specific and may be elevated, for example, in benign prostatic hypertrophy and prostatitis. The incidence of PC rises with increased levels of s-PSA. There is no consensus regarding the cut-off value of s-PSA in relation to the risk of PC, although > 4.0 ng/ml is frequently used (30).

Malignant tumors are most often located in the peripheral zone of the gland, and a trans-rectal approach with the guide of ultrasound is the most common procedure for biopsy. A 10-core biopsy is recommended to establish the diagnosis (4, 31). In patients with negative biopsies and elevated s-PSA, MRI is recommended to help find the area of the prostate most suitable for biopsy (32). A recently published study suggests that risk assessment with MRI before biopsy and MRI-targeted biopsy is superior to standard transrectal ultrasonography-guided biopsy in men at clinical risk for PC who have not previously undergone biopsy (33). Patients with high-risk and locally advanced PC should undergo MRI scans of the prostate and pelvic area to detect metastatic disease before treatment is decided.

Positron emission tomography (PET) uses radioactive tracers to detect rapidly growing cells such as cancer cells, which consume more glucose than normal cells due to the rapid cell division. This appears as a signal on the PET images. PET has not yet proven to be superior to MRI in the primary diagnosis of prostate cancer (34, 35). PET is recommended in situations of relapse or recurrence after radical treatment, especially if the s-PSA velocity (ng/ml/year) is more than >2ng/ml per year (36).

Gleason score, s-PSA level, and clinical T stage (Table 2) are of major importance for prognosis and outcome in PC. In 1998, D'Amico et al. suggested a risk stratification system based on these three factors to predict post-treatment biochemical failure after radical prostatectomy or EBRT (Table 1) (37). This risk stratification has three categories (low, intermediate and high risk) and was used to categorize patients in the RIC study into risk groups. Various risk stratification systems have been described and used since the study by D'Amico et al; these include new risk groups (very low risk and extra high risk).

Risk group	**s-PSA**	**Gleason Score**	**Clinical Stage**
Low-risk	< 10 mg/dL	≤ 6	≤ T2a
Intermediate risk	≥ 10 < 20 mg/dL	= 7	T2b
High-risk	>20	8-10	≥ T2c

Table 1. Risk stratification according to D'Amico et al.
For low risk, all three criteria must be met. For intermediate and high risk, only one criterion must be met.

Clinical (cT)	
T category	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	**Clinically inapparent tumor that is not palpable**
T1a	Tumor incidental histologic finding in 5% or less of tissue resected
T1b	Tumor incidental histologic finding in more than 5% of tissue resected
T1c	Tumor identified by needle biopsy found in one or both sides, but not palpable
T2	**Tumor is palpable and confined within prostate**
T2a	Tumor involves one-half of one side or less
T2b	Tumor involves more than one-half of one side but not both sides
T2c	Tumor involves both sides
T3	**Extraprostatic tumor that is not fixed or does not invade adjacent structures**
T3a	Extraprostatic extension (unilateral or bilateral)
T3b	Tumor invades seminal vesicle(s)
T4	**Tumor is fixed or invades adjacent structures** other than seminal vesicles, such as external sphincter, rectum, bladder, levator muscles, and/or pelvic wall
Pathologic (pT)	
T category	
T2	Organ confined
T3	Extraprostatic extension
T3a	Extraprostatic extension (unilateral or bilateral) or microscopic invasion of bladder neck
T3b	Tumor invades seminal vesicle(s)
T4	Tumor is fixed or invades adjacent structures other than seminal vesicles, such as external sphincter, rectum, bladder, levator muscles, and/or pelvic wall
N category	
NX	Regional lymph nodes were not assessed
N0	No positive regional lymph nodes
N1	Metastases in regional lymph node(s)
M category	M criteria
M0	No distant metastasis
M1	Distant metastasis
M1a	Nonregional lymph node(s)
M1b	Bone(s)
M1c	Other site(s) with or without bone disease

Table 2. TNM classification of adenocarcinomas of the prostate gland.
AJCC (American Joint Committee on Cancer) (38).

3. Treatments other than RT in non-metastatic prostate cancer

PC may exhibit a range of clinical presentations, from indolent and slowly growing to an aggressive and rapidly developing disease with a heavy symptom burden and short life expectancy. Several treatment options are available in non-metastatic PC patients, including external-beam radiotherapy (EBRT), BT, radical prostatectomy (robot-assisted or open), and observation. The choice of treatment should be discussed with the patient and based on tumor stage, age, comorbidity, and the risk of acute and late side effects (4, 26).

3.1 Active surveillance and watchful waiting

Patients with low-risk PC and indolent disease without symptoms, often detected from s-PSA screening, will not benefit from radical and aggressive treatment (39). To avoid unnecessary treatment and possible acute and late side effects, the best option for these patients can be either active surveillance or watchful waiting. Active surveillance keeps the patients under close monitoring, and treatment is offered to patients whose life expectancy is >10 years. Watchful waiting refers to conservative management until symptoms are present due to disease progression in patients whose life expectancy is <10 years. Threshold levels are still being evaluated for both active surveillance and watchful waiting against treatment (40, 41).

3.2 Surgical treatment

Modern surgery in PC involves removal of the entire prostate gland or resection of the SVs and surrounding tissue to obtain negative margins with either open or laparoscopic technique. Robot-assisted laparoscopic prostatectomy (RALP) is replacing radical retro-pubic prostatectomy as the most common surgical approach in the western world (42, 43). One meta-analysis demonstrated better early functional outcomes (e.g. erectile function and urinary continence recovery) for RALP than for radical open prostatectomy (43, 44). Other studies have not been able to reproduce the same results, suggesting the need of longer follow-up time (45, 46). The mean age of patients operated with radical prostatectomy in Norway is 63 years, while patients treated with EBRT have a mean age of 69 years (2). In patients with clinical localized disease (T1-T2), studies have shown a lower risk of metastasis

and death from PC for prostatectomy than for watchful waiting, especially in patients < 65 years (47).

Patients with a clinical-stage T3 tumor represent a heterogeneous group, and some patients can be suitable for surgical treatment, especially when life expectancy is >10 years. However, the risk of positive margins after surgery is high, often leading to adjuvant treatment with EBRT or ET with the risk of excessive side effects. No randomized controlled trials have yet compared radical treatment with EBRT against radical surgery with or without EBRT in patients with T3 disease, but an ongoing Scandinavian trial will address this (Scandinavian Prostate Cancer Group (SPCG)-15, clinicaltrials.gov Identifier NCT 0212477). The choice of treatment in high-risk patients should be carefully discussed at both doctors' and patients' discretion.

Pelvic lymph node dissection is considered the most accurate staging procedure. Lymph nodal metastasis occurs in 3-42% of patients with localized disease and has a strong negative impact on survival (48, 49). However, the therapeutic role of pelvic lymph node dissection is controversial. A recent review published by Fossati et al. found worse intraoperative and perioperative outcomes in patients receiving node dissection; these authors suggests more robust and powered clinical trials (50). EAU guidelines recommend extended pelvic lymph node dissection (obturator and external and internal iliac nodes) in high-risk or intermediate-risk patients when the risk of positive lymph nodes estimated by the use of preoperative nomograms exceeds 5% (26). Medical nomograms are widely used with both PC and other cancer patients. Medical nomograms use biological and clinical variables, such as tumor grade and age, to determine a statistical prognostic model that generates a probability of a clinical event, such as cancer recurrence or death, for a particular individual (51).

3.3 Endocrine treatment

Testosterone production is regulated by luteinizing hormone-releasing hormone (LHRH) and luteinizing hormone (LH) (Fig. 5). The hypothalamus releases LHRH, which stimulates the release of LH from the pituitary gland. Testosterone is secreted by the Leydig cells in the testicles in response to LH, and follicle-stimulating hormone (FSH), also released from the pituitary gland, stimulates the Sertoli cells, which nourish the sperm cells.

Small amounts of additional testosterone are produced in the adrenal glands. The biological effects of androgens are exerted on target organs that contain a specific androgen receptor protein. Testosterone is taken up by prostate cells, where it either binds to the androgen receptor directly or is converted to the more potent dihydro-testosterone which has a greater binding affinity for the androgen receptor than testosterone. The dihydro-testosteron-androgen receptor complex then migrates to the nucleus, where it binds with a nuclear protein and induces the DNA-RNA transcription process that is essential for the formation and functioning of the prostate gland (52).

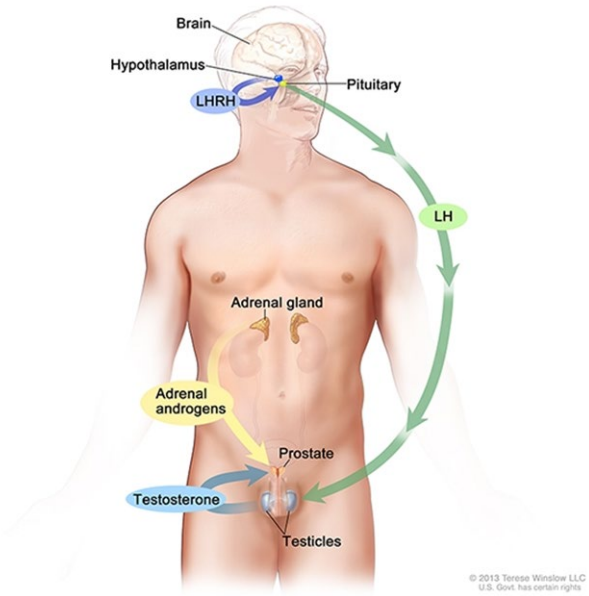

Fig. 5. Androgen production in men.
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Androgen deprivation is achieved by either suppressing the secretion of testicular androgens (LHRH agonists) or inhibiting the action of circulating androgens at their receptors (antiandrogens). A combination of these techniques is known as total androgen blockage (TAB). Androgens stimulate the growth of both normal and cancerous prostatic cells, and the proliferation of cancer cells decreases when the level of androgens is reduced (Fig. 6).

The castration level of testosterone was defined more than 40 years ago as s-testosterone < 1.7 nmol/l, although the mean value after surgical castration is lower (0.5 nmol/l) (53). LHRH

agonists are administered as subcutaneous depot injections every 1, 2, 3, or 6 months or yearly, and the castration level of testosterone is usually achieved within 2-4 weeks. Anti-androgens are oral medications that compete with androgens at receptors and are classified according to their chemical structure as steroidal or non-steroidal. In Norway, Bicalutamide (non-steroidal) is the most widely used antiandrogen.

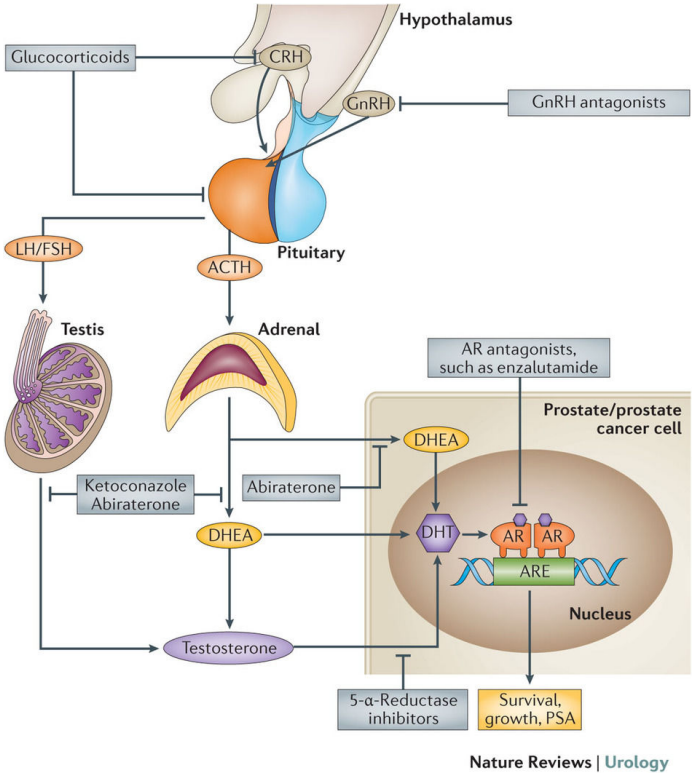


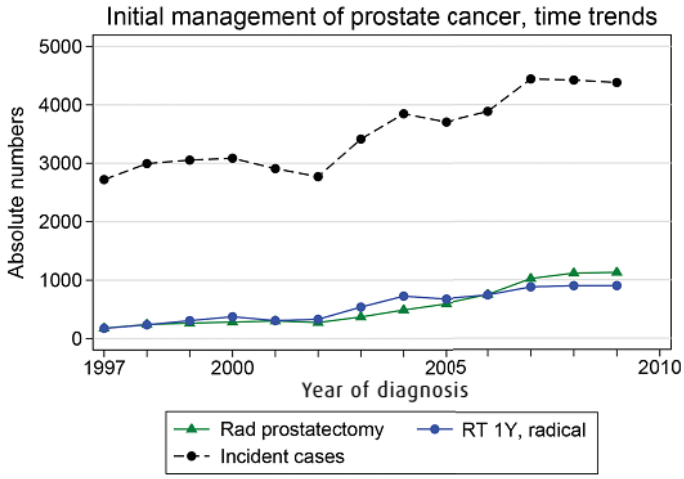
Fig. 6. Androgen synthesis and signaling pathways:
Drugs used for androgen deprivation therapy and to block androgen action**.** Printed by permission from Nature Reviews Urology volume 13, pages 47–60 (2016), Androgen-glucocorticoid interactions in the era of novel prostate cancer therapy. (54).

EBRT and ET are often combined in radical PC treatment (55, 56). ET can be administered as a neo-adjuvant, concomitant, and adjuvant treatment depending on clinical stage and risk group. If the treatment is given neo-adjuvantly, its main purpose is to reduce the volume of the prostate gland before EBRT starts (55, 57). LHRH agonist given alone or in combination with an antiandrogen is the most commonly used regime (58, 59). In combination with EBRT, ET has improved survival in PC patients significantly, although at the cost of increased acute and late side effects (60, 61). Side effects from antiandrogens chiefly include gynecomastia, breast pain, and reduced sexual function. LHRH agonists can cause more severe symptoms of fatigue, impotence, muscle weakness, osteoporosis, and cardiovascular disease. However this might diminish when the patient's levels of testosterone return to normal after finishing ET. Some patients, often the elderly, experience prolonged testosterone suppression, which can affect their QoL (62).

4. Radiotherapy

4.1 Background

Estimates show that 50-60% of new cancer patients will require RT during their lifetime (63). In PC, the proportion of patients in Norway receiving RT within 1 year after diagnosis more than doubled from 8.6% in 1997 to 22.6% in 2009. This is also illustrated with absolute numbers in Fig. 7 (64).



Supplementary fig. 5.
Numbers of incident cancer cases and initial treatment management of invasive prostate cancer in Norway (1997-2009). Abbreviations: Rad = radical; RT 1Y = radical radiotherapy received within 1 year of diagnosis.

Fig. 7. International Journal of Radiation Oncology*Biology*Physics, Vol 90, Issue 3, Asli et al, Utilization of Radiation Therapy in Norway after the Implementation of The National Cancer Plan—A National, Population-Based Study, Copyright (2014), with permission from Elsevier (64).

In RT, the deoxyribonucleic acid (DNA) strands are damaged and cause double or single strand breaks. If the DNA damage cannot be repaired, cell division stops, leading to cell death. Normal cells surrounding the tumor are also affected by the irradiation but often have a higher tolerance, since the DNA repair system works better (65). Nevertheless, the tolerance of normal tissue is the most important dose-limiting factor in radical RT.

The unit of ionizing radiation dose is the Gray (Gy), defined as the absorption of radiation energy per kilogram of matter (1 Gy = 1 joule/kg).

Cell survival as a function of dose can be described by a linear quadratic (LQ) model (65):

$$S = e^{-\alpha D - \beta D2},$$

where α is the average probability per unit dose that a single-particle event will occur, and β is the mean probability per unit square of the dose that two separate ionizing particles events will occur. The shape of the cell survival curve is determined by the ratio α/β, which differs between different tissues. The LQ model provides a quantitative relationship between dose per fraction and the isoeffective total dose. Late-responding tissues with slow proliferation have a low α/β ratio (< 3-5Gy). In such tissues, the cells' cycle is prolonged, and the cells will have more time to repair DNA damage. Late-responding tissues will be particularly sensitive to hypofractionated RT. Early-responding tissues, typically rapidly proliferating tumors with poorer repairing abilities, have a high α/β ratio (>10Gy), and will not be as sensitive to hypofractionated RT as late-responding tissues. Most malignant tumors are rapidly growing, with a high α/β ratio, resulting in lower sensitivity to the fractionation dose than tumors with low α/β ratio. However, new evidence suggests that the α/β ratio in PC is lower than previously assumed (66-68). This has led to stronger focus on hypofractionated RT treatment in PC. Nonetheless, it is important to remember that PC is a heterogeneous disease, both clinically and histologically. Areas with both poor and well differentiation can be seen in a tumor as described in the Gleason scoring system, leading to varying α/β ratios within the same tumor.

4.2 Modern radical radiotherapy in prostate cancer

Several RT modalities and techniques are available, including 3D-conformal photon therapy, IMRT, VMAT, BT, and proton beam therapy. Although curative PC irradiation has been used for decades, the SPCG-7 study published in 2009 was the first randomized controlled trial (RCT) to demonstrate that the survival of patients undergoing EBRT combined with ET was superior to that of patients undergoing ET alone in locally advanced and/or aggressive PC (59, 69).

Randomized trials have compared doses of 64-70Gy to dose-escalated EBRT with 74-80Gy and demonstrated improved disease-free survival with escalated dose but with increased acute and late side effects (70-78). A meta-analysis reported by Ohri et al. showed rates of grade ≥ 2 and grade ≥ 3 late GI toxicity of 15% and 2% respectively in randomized dose escalation trials (79). A large randomized study (n=1643) reported by Hamdy et al. (ProtecT study) compared active monitoring, radical prostatectomy, and 3D conformal EBRT for clinically localized PC, in which cancer is confined to the prostate gland, and found a low PC-specific mortality (1%) with no difference among groups at 10 years (8). Surgery and EBRT were associated with lower incidence of disease progression and metastasis than active monitoring. The study only included tumor stages T1-T2, and 56% of the patients in the active monitoring group received radical treatment within 10 years. When comparing patient-reported outcomes (PROs) among the three groups, they found that prostatectomy had the greatest negative impact on sexual function and urinary continence while EBRT had the worst effect on bowel function (80). No level I evidence has yet compared RP and EBRT in high-risk PC patients.

Intensity-modulated radiation therapy (IMRT) was introduced in the late 1990s as a consequence of improvements in planning software. Although it showed advantages in dosimetry over 3D-conformal EBRT, most of the published data on clinical outcomes are retrospective and not based on RCTs (81-84). A meta-analysis reported by Yu et al. included 23 studies (n=9556) comparing clinical outcomes, including GI toxicity, GU toxicity, and OS between IMRT and 3D conformal EBRT (85). IMRT significantly decreased grades 2-4 acute and late GI toxicity and late rectal bleeding and achieved improved biochemical control in comparison with 3DCRT. The occurrence of acute rectal toxicity, late GU toxicity, and OS remained the same while IMRT slightly increased grades 2–4 acute GU toxicity (85). IMRT/VMAT has been widely adopted and is considered the standard treatment for PC in by most RT centers in the western world (84).

National guidelines recommend elective irradiation of pelvic lymph nodes in patients with high risk of nodal metastases, based on retrospective studies showing improved survival and disease control in node-positive PC patients, although at the cost of increased acute and late side effects (86-88). No level 1 evidence supports elective pelvic EBRT in node-negative PC (89). A review reported by Dirix et al. included three randomized trials comparing elective

pelvic RT with prostate-only RT in clinically node-negative PC patients (89). All three were negative with respect to both biochemical disease-free survival and overall survival (OS). The use of IMRT/VMAT has resulted in dose reduction to organs at risk (OARs) such as the rectum, urinary bladder, and small intestine (90-92).

The target volumes and OARs are usually delineated using CT- or MRI-based dose-planning systems. MRI is considered superior to CT in defining the prostate gland and surrounding tissue (93, 94). Based on histopathological studies and consensus guidelines, the clinical target volume (CTV) should include the prostate gland and basal 1.4-2.2 cm of the SVs in intermediate- and high-risk patients (95-97). A boost volume often includes the prostate gland; however, the SVs should also be included in the high dose volume if infiltrated (stage T3b). The recommended dose to the target volume has until recently been 74-78Gy (98). Several attempts have been made to shorten the treatment period by using hypofractionated regimes. Moderate (2.2- 4Gy per fraction) hypofractionation leads to comparable acute and late side effects and similar cancer control in intermediate-risk PC patients in randomized controlled trials, but results with high-risk patients are not consistent (66, 71, 78, 83, 99-111). Hypofractionated EBRT is also appealing from a socioeconomic perspective as it potentially decreases treatment costs and reduces the patients' time away from daily life.

Brachytherapy for PC involves placing the radiation source inside the prostate gland. Low dose-rate BT (LDR-BT) utilizes radioactive seeds (Iodine 125-I or Palladium 103-Pd) implanted in the prostate gland with trans-rectal ultrasound guidance. LDR-BT is given either as monotherapy or as a BT boost in patients with low-and intermediate-risk PC (112). LDR-BT is currently not available in Norway. In high dose-rate BT (HDR-BT), a radioactive source (Iridium 192-Ir) is temporarily implanted in the prostate. The treatment is often delivered in combination with EBRT and enables dose escalation combined with high precision and acute and late toxicity comparable to EBRT (113-115). In 2017, only 31 patients were given this treatment in Norway (Sverre Levernes, Norwegian Radiation Protection Authority, personal communication).

In theory, proton therapy has several advantages over photon therapy due to the favorable dose distribution (Bragg Peak) (116). The sharp fall-off of the proton beams can effectively reduce the dose to the surrounding normal tissue. Proton therapy is frequently applied in

pediatric cancer patients who undergo radical RT and have long life expectancies (117, 118). Several studies have compared the radiation plans of proton beam therapy with IMRT/VMAT plans for PC and found proton therapy to provide a better dose distribution (78). However, clinical studies have not yet proven the superiority of proton beam therapy regarding toxicity in PC patients (119-122). PC patients in Norway are not offered proton therapy.

4.3 Image guided radiotherapy

Substantial target movement can occur during the RT period. The positioning of the patient must be very exact to deliver the prescribed radiation dose to the target volume very accurately. Various patient fixation methods have been applied to reduce changes in relative position during irradiation, such as rectal balloons, plastic masks, and body frames with abdominal compression.

The patient is usually placed in the supine position. Lasers that are installed in the treatment room are aimed at marks made on the patient's skin (or fixation mask) to ensure correct positioning.

IGRT can be defined as organ imaging in the treatment room with positional adjustments for geometrical deviations prior to EBRT (9). Until the 1990s, MV x-ray imaging of bony landmarks was used to control the treatment position. MV images were often of low quality and resulted in low geometrical accuracy in regard to internal organs (Fig. 8). The introduction of 3D imaging such as ultrasound, CT, and MRI have provided considerably better insight into the position and motion of internal organs (Fig. 8) (123).

Several image guidance techniques are available including CT, MRI, ultrasound, fiducial markers, and continuous electromagnetic monitors (124). In-room CT-based image guidance consists of various systems. Kilo voltage (KV) imaging is superior to MV imaging with enhanced soft-tissue image contrast (93). CBCT is a compact and faster version of common diagnostic CT. Through the use of a cone shaped X-ray beam, the size of the scanner, radiation dose, and time needed for scanning are all significantly lower than that required for diagnostic CT (125). CBCT is frequently used and is often attached to the linear accelerator (Fig. 9). IGRT offers several advantages, including more exact positioning of the patient and a better visualization of the target volume(123). Reduced normal tissue doses by

minimizing safety margins around the target volumes might enable dose escalation to the target volume with the possibility of improved tumor control. The number of fractions can be reduced by giving hypofractionated RT, and the treatment costs can be reduced. In addition, IGRT is important when optimizing the treatment plan during the treatment period, for instance if the patient experiences a significant weight loss or if tumor shrinkage leads to a substantial change in anatomy.

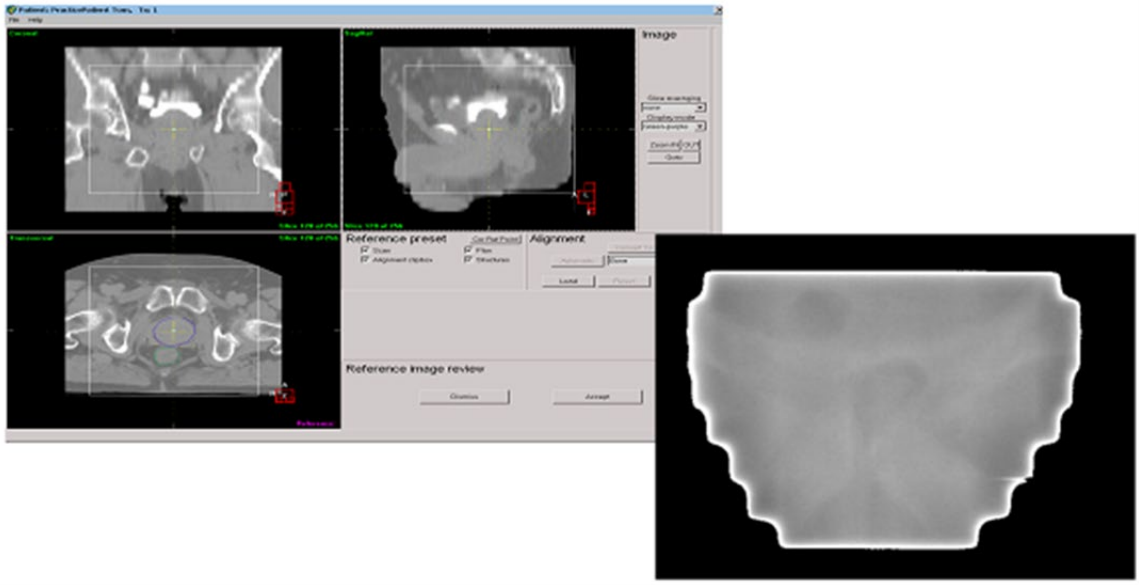


Fig. 8. To the left: IGRT: CBCT image of the pelvic area. To the right: IGRT: MV x-ray image of the pelvic area. These images illustrate the difference in image quality.

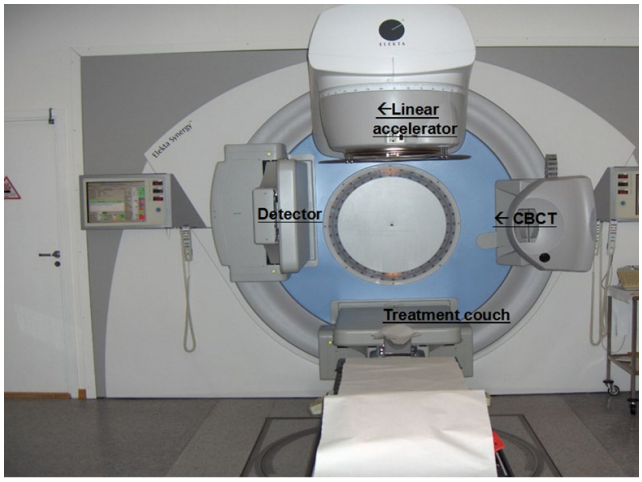


Fig. 9. Linear Accelerator at St. Olav's Hospital.
Illustrating the Cone Beam CT (CBCT) and the linear accelerator mounted in the treatment room.

4.4 Image guided radiotherapy in prostate cancer

The size of the rectum and urinary bladder and their positions relative to the prostate gland will vary during the 8-week treatment period (126-131). Interfraction displacement of the prostate gland during EBRT is often observed in response to variations in rectum and bladder filling and can range from 0 to 20 mm (132). Several IGRT modalities are available including CT-based imaging, radiopaque intraprostatic markers, transabdominal ultrasound, electromagnetic transponders, and MRI (93).

CT imaging can be used for daily visualization of the prostate before each RT fraction. Changes such as prostate deformation, rectal distention, and bladder filling can be detected and can give useful information for replanning and adaptive EBRT (93). Disadvantages are the limited image quality and the additional dose contribution.

Fiducial markers and continuous electromagnetic monitors have improved the accuracy of EBRT (93, 133-135). Fiducial markers are low cost and easy to use and constitute a surrogate marker for the prostate position. The markers can be visualized with either 2D or 3D imaging. The implantation of fiducial markers is an invasive procedure with possible risk of bleeding, infection, and discomfort for the patient similar to a prostate biopsy. Electromagnetic nonradioactive transponders (e.g. Calypso®System, Seattle, Wash., USA), are implanted in the prostate prior to the treatment. A tracking console in the treatment

room communicates with the transponders and allows both pretreatment localization and evaluation of the intrafraction motion (136). Patients with obesity, pacemakers, hip prostheses or other large metal implants are ineligible. In addition to its invasiveness, this limitation is considered to be a disadvantage of the procedure.

Transabdominal ultrasound uses suprapubic transducers for imaging of patients in the treatment position. The procedure is operator dependent, but comes with low cost and without ionizing radiation. Studies have shown uncertainties in image quality, inter-observer variability, and reproducibility, and the authors suggest using the technique with caution (93, 137).

MRI has potential advantages in both target delineation and target localization over CT (138). Patients with pacemakers or metallic implants are not suitable for MRI. In addition, multiple technical challenges with motion artefacts and magnetic fields complicate EBRT delivery. The developing MRI–linear accelerator (LINAC) systems are of great interest in this context.

Several authors have reviewed the evidence base for IGRT and found promising results concerning quality assurance (QA) and setup uncertainties, both in PC and in general cancer treatment (9, 93, 123, 139-141). Although modern IGRT reduces the frequency of systematic errors effectively, random errors, such as day-to-day variations in positioning of the patient, are not affected (141).

Several studies have compared clinical outcomes for IG-IMRT and 3D conformal EBRT (142-148). Three recently published review articles address possible clinical benefits from IGRT, such as improved toxicity profiles (78, 83, 93). A recently published phase III trial reported by de Crevoisier et al. compared the safety and efficacy of daily and weekly IGRT (149). To our knowledge, the RIC study is the first randomized controlled trial (RCT) comparing clinical outcomes following CBCT-IGRT with standard orthogonal portal imaging in PC patients.

5. Patient-reported outcome measures (PROMs)

A PROM is defined as any outcome reported directly by the patient with a subjective evaluation about disease and treatment without interpretation by clinicians or relatives (150). The aim of PROMs is to measure subjective experience by gathering patients' responses to validated questionnaires. The use of PROMs can have several benefits for cancer patients in general.

- Increased patient satisfaction (151)
- Improved patient–physician communication (152)
- Increased symptom discussion and intensified symptom management (153)
- Improved symptom control (154)
- Improved QoL (155)

Historically, side effects have been reported by professional healthcare providers applying common toxicity criteria for adverse events (CTCAE) or similar toxicity scoring systems. Several studies have shown only a modest correlation between PROMs and CTCAE scoring (156-160). A review by Atkinson et al. showed moderate agreement between CTCAE and PROMs in cancer patients in general and recommended integrating PROMs into the clinical reporting of adverse effects (160). A review by Holch et al. demonstrated an underrepresentation of PROMs in RCTs on acute and late adverse effects after RT for PC. The review recommends that PROMs be used to evaluate RT throughout the whole time course of RT (161).

PC was the first cancer for which a therapy was approved based on improvement measured by PROMs alone. In a study published in 1999, Osoba et al. randomized 161 patients with castrate-resistant PC in two groups receiving either mitoxantrone intravenously plus prednisolone or prednisolone alone (162). They observed no difference in OS, but the group receiving mitoxantrone had superior global QoL and pain control. This introduced a new era in the use of PROMs in clinical studies. PROMs are continuously being developed, modified, and adapted to new treatments. Technical advancements such as the use of computer-based systems and smartphone applications for completing the questionnaires have recently been

introduced. These can simplify daily clinical work, be easier for patients, and reduce paperwork (163).

6. Aims of the project

The overall aim of the project was to improve treatment of PC and to increase the knowledge of side effects after EBRT by investigating the potential benefits of CBCT-IGRT in reducing side effects after radical EBRT in PC patients.

The following research questions were hypothesized:

- Does daily image guidance with CBCT and tighter PTV-margins improve patient-reported acute rectal side effects at the end of EBRT as compared to weekly orthogonally verified irradiation with wider PTV margins in patients receiving 3D-conformal EBRT for intermediate- and high-risk prostate cancer?

- Are rectal volumes reduced or increased, and are rectal doses consequently reduced or increased during 8 weeks of radical EBRT in patients with intermediate- and high-risk prostate cancer?

- Does daily image guidance with CBCT and tighter PTV-margins improve erectile function 18 months after radical EBRT as compared to wider PTV margins and weekly verification in intermediate- and high-risk prostate cancer patients?

7. Material and methods

7.1 Introduction

This thesis is based on a phase III **r**andomized two-center trial on standard weekly orthogonal IGRT vs. daily cone-beam **I**GRT in **c**urative radiotherapy for prostate cancer (the RIC study). The study was conducted at St. Olavs hospital, Trondheim University Hospital, and Ålesund Hospital. Patients with intermediate and high-risk PC were randomized to receive 78Gy in 39 fractions guided by either weekly offline orthogonal portal imaging (arm A, 15 mm margins from CTV to PTV) or by daily online CBCT-IGRT (arm B, 7 mm margins from CTV to PTV). Patient reported outcomes were used to assess side effects after treatment. The study was registered at ClinicalTrials.gov with ID NCT01550237.

In **Paper I,** the primary endpoint in the RIC study was acute rectal toxicity at the end of EBRT as measured by PROMs, the Questionnaire Umeå Fransson Widmark (QUFW94). Secondary endpoints in the RIC study were freedom from biochemical progression at three years from randomization according to the ASTRO definition (nadir s-PSA value + 2ng/ml) (164), acute genitourinary side effects at end of EBRT, overall survival, prostate-cancer-specific survival, and late genitourinary and rectal side effects at 5 and 10 years as measured by the European Organization for Research and Treatment of Cancer Quality of Life Core Questionnaire (EORTC QLQ-C30) and QUFW94. Acute genitourinary side effects and QoL at end of EBRT was analyzed and are reported in Paper I.

In **Paper II**, we analyzed rectal volume variation (cm^3). Based on previous studies, we chose to analyze 30 consecutive patients randomized to arm B of the RIC trial during 8 weeks of IGRT with daily CBCT (165-168). The percentage of RV irradiated in the same period was estimated and its implications were analyzed for delivered dose during 8 weeks of EBRT.

In **Paper III**, we compared patient-reported sexual function in the two groups 18 months after EBRT using the QUFW94 questionnaire single item “can you get an erection?” as primary outcome. This item is graded on an 11-point scale, where 10 represents the highest degree of erectile dysfunction.

Secondary outcomes were the additional eight questions in the questionnaire regarding sexual function and the impact of radiation dose to penile bulb (PB) on sexual function as measured by the QUFW94.
Volumes (cm^3) and dose-volume histograms (DVHs) were estimated for the PB.
The PhD candidate was involved in the study by including patients, performing follow-up controls, collecting, organizing, and analyzing data for all parts of this thesis, and by playing a lead role in preparing the manuscripts and presenting results.

7.2 The RIC study

7.2.1 Inclusion of patients

Inclusion criteria for the RIC study were biopsy-confirmed AC of the prostate, no evidence of nodal or distant metastases, age between 18 and 80 years, informed consent and intermediate- or high-risk disease based on the D'Amico risk stratification (T stage, PSA level and Gleason score)(37).

Exclusion criteria were previous treatment for cancer in last 5 years (except basal cell carcinoma of skin), any previous radiotherapy (except KV or electron treatment of skin tumor outside the pelvis), metallic hip joint replacement, pre-existing intestinal or GU disease with increased risk of side effects, any pre-existing condition making the patient unsuitable for EBRT, any pre-existing condition making the patient unsuitable for ET, any pre-existing condition making the patient unsuitable for MRI, alanine aminotransferase (ALAT), gamma-glutamyltransferase (GT), alkaline phosphatase (ALP), and creatinine > 1.5 x upper normal limit.

Patients had a clinical examination before inclusion with medical history and screening of blood samples (hemoglobin, leukocytes, platelets, creatinine, ALAT, GT, ALP, PSA, s-testosterone). All patients underwent a bone scan and pelvic MRI and had fiducial gold markers implanted in the prostate gland prior to EBRT. The TNM stage was established by clinical examination and diagnostic imaging.

Randomization and data collection were performed using a web-based randomization and data collection system developed and administered by the Unit of Applied Clinical Research,

The Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology, Trondheim, Norway: webCRF (https://webcrf.medisin.ntnu.no).

The patients were randomly assigned to one of two study arms:

> Arm A (2D-IGRT) received RT with weekly orthogonal verification by fiducial markers and standard PTV margins (15 mm).
>
> Arm B (3D-IGRT) received RT with daily CBCT verification by fiducial markers and reduced PTV margins (7 mm).

Randomization was stratified by center and risk group. Data was registered prospectively from medical journals and the dose-planning system. Questionnaires were either handed out at the first consultation or sent to the patient and returned by mail. Completed questionnaires were scanned into SPSS® for further management.

7.2.2 Endocrine treatment

Recommendations for ET were in accordance with national guidelines (4). All patients received at least 3 months of neo-adjuvant treatment with total androgen blockage (TAB) (goserelin acetate 10.8 mg as one subcutaneous injection every third month and bicalutamide 50 mg ×1). TAB was continued for a total of 6 months. In addition, patients with high-risk PC received bicalutamide 150 mg x 1 over a total treatment period of 3 years.

7.2.3 RT planning and treatment in the RIC study

The procedure for patients' positioning and bladder filling were equal for dose-planning CT and MRI scans, which were performed at intervals of no more than 24 hours. The patients were asked to urinate one hour ahead, and then to drink two glasses of water during the next hour. Patients were encouraged not to urinate again until after the CT or MRI scan had been taken. The dose-planning CTs were performed with the patient in the supine position. No rectal emptying was performed prior to examination. CT slices were no more than 3 mm in thickness. MRI images with high resolution, 3-dimension, T1- and T2-weighted were preferred and included imaging of the entire pelvis from the iliac crest to the ischial tuberosity.

The definition of volumes was according to the recommendations given by the Norwegian Radiation Protection Authority (169). These recommendations are based on the International Commission on Radiation Units & Measurements (ICRU) recommendations reports 50 and 62 (170).

The clinical target volume (CTV) prostate was defined as the prostate gland including any suspected extracapsular tumor growth or infiltration into the SVs as described by clinical findings, transrectal ultrasound and/or MRI. The CTV prostate and vesicles included the prostate gland and basal (proximal) 1 cm or 2 cm of the vesicles in intermediate- and high-risk patients, respectively.

The internal target volume was included in the planning target volume (PTV) and was not defined as a separate volume. The PTV included the CTV with margins to account for delineation uncertainties, internal movement, and setup uncertainties. In Arm A, the PTV (0-70Gy) was the CTV prostate and vesicles with a 15 mm margin in all directions. The PTV (70-78Gy) was the CTV prostate with a 3 mm margins. In arm B, the PTV (0-70Gy) was the CTV prostate and vesicles with a 7 mm margin in all directions. The PTV (70-78Gy) was the CTV prostate with a 3 mm margin (Fig. 10).

The following OARs were delineated: RV, rectal mucosa, anal canal, urinary bladder, femoral heads, penile bulb, and testes.

The RV was outlined as the outer contour of the rectum including the rectal wall from the recto-sigmoid junction to the anus. The rectal mucosa was outlined with the same cranio-caudal limits as the rectum, with a 2 mm thickness and limited by air on the inside.

The anal canal was outlined as a separate volume from the external sphincter of the anus and 4 cm in the cranio-caudal direction.

The volume of the bladder was outlined as the outer contour of the bladder, including the muscle wall.

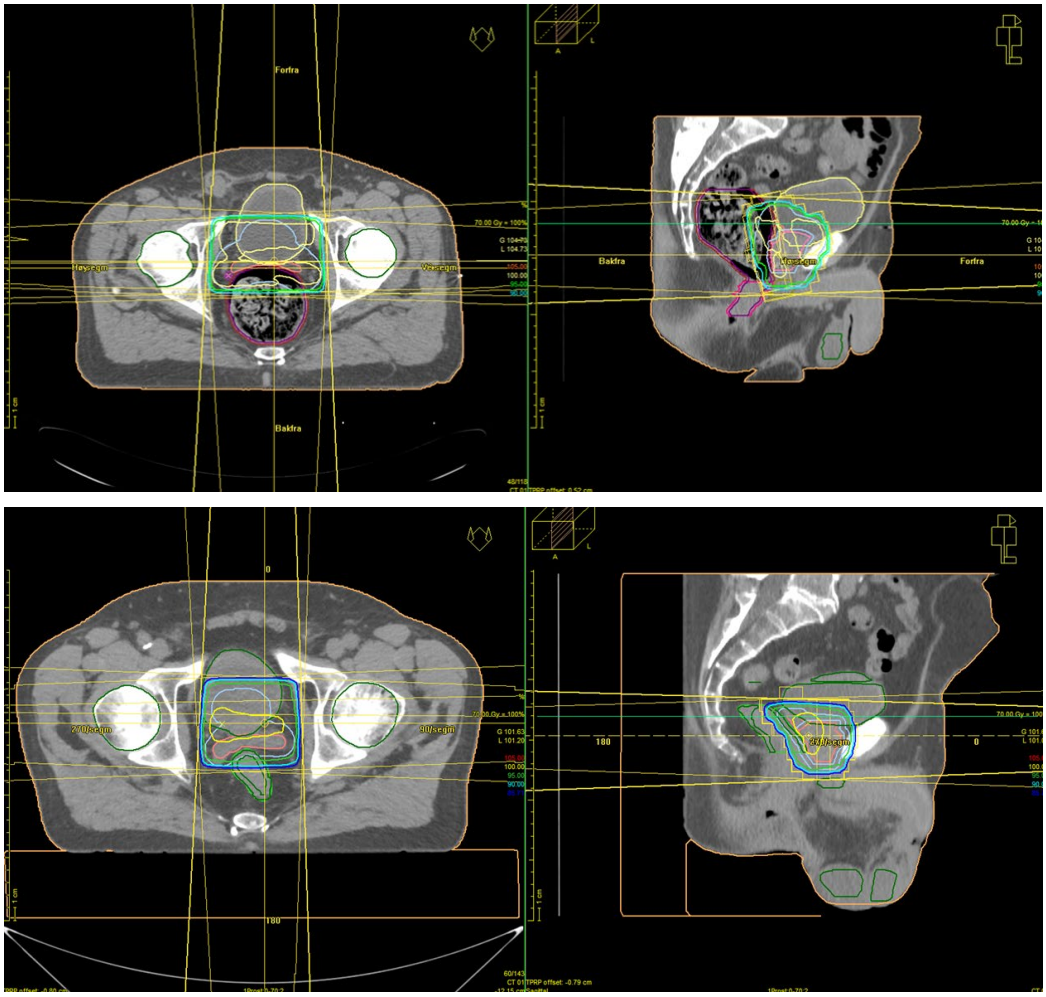


Fig. 10. Examples from the dose-planning system.
Upper: Patient in arm A with wider PTV margins
Lower: Patient in arm B with tighter PTV margins

The outer bony contour of both femoral heads was outlined without including the collum femoris.

The penile bulb was defined as the posterior thick part of the spongious body of the penis. Both testes were defined as separate volumes. The cranial border was the cranial border of the testicle, and no part of the spermatic cord was included.

CT based, 3D conformal dose planning was mandatory, as were multileaf collimators. The dose-planning principles were equal in both study arms. The patients were treated with 15

MV photon beams, applying a four-field box technique with supplemental segments as necessary from 0 to 70Gy. For doses 70-78Gy, a five-field technique (1 anterior, 2 oblique anterior and 2 lateral portals) was applied. Doses within target volumes were held within the limits of 95-107% of the prescribed dose, and the isocenter was placed in the gold marker located closest to the base of the prostate. The dose limit for the rectum was defined as 60Gy to half of the rectal circumference.

In arm A (2D-IGRT), the positioning of the patient was controlled with skin markers and 2D MV portal imaging of fiducial markers on the first three treatment days. Errors smaller than five mm were not corrected until treatment day 4, when a summed vector calculation of the errors recorded on days 1-3 was used to guide correction. Thereafter, position was controlled by a two-plan MV imaging of fiducial markers once weekly until the patient had received a total dose of 70Gy. Only errors larger than ten mm were corrected. The full treatment of one field could be given prior to position control of the next field. Daily treatment positioning and correction by orthogonal MV imaging of fiducial markers was performed prior to the four last fractions (70-78Gy).

In arm B (3D-IGRT), the treatment position was controlled by skin markers initially. For each treatment, 3D KV imaging of fiducial markers was performed and all errors were corrected prior to treatment each day.

7.2.4 Patient-reporting assessment tools in Papers I and III

7.2.4.1 EORTC QLQ-C30

(Appendix 1)

The European Organization for Research and Treatment of Cancer Quality of Life Core Questionnaire (EORTC QLQ-C30) was developed to assess the quality of life of cancer patients (171). It has been translated into over 100 languages and is frequently used in studies worldwide (172). It consists of 30 items that enquire about nine symptoms (fatigue, nausea/vomiting, pain, dyspnea, insomnia, appetite loss, constipation, and diarrhea) and six functional domains (global health status, physical function, role function, emotional function, cognitive function, and social function). The patient is asked to evaluate symptoms experienced during the previous week. The first 28 questions are scored on a four-level scale from “not at all” to “very much,” and the last two questions are scored on a seven-level scale

from “very poor” to “excellent”. A high score represents a higher response level. Thus, a high score on a functional scale represents a high level of functioning, a high score for the global health status/QoL represents a high QoL, but a high score for a symptom item represents a high level of symptoms. All of the scales and single-item measures are linearly transformed to a value between 0 and 100 according to the EORTC QLQ-C30 scoring manual (173). The questionnaire was handed out to the patients by the clinical oncologist at their inclusion in the study and sent by post during follow-up. The RIC study participants were asked to complete EORTC QLQ-C30 version 3.0. The results are reported in Paper I.

7.2.4.2 QUFW94

(Appendix 2)

The Questionnaire Umeå Fransson Widmark (QUFW94), also referred to as the Prostate Cancer Symptom Scale, is a self-assessment tool designed to evaluate the side effects experienced by PC patients following pelvic EBRT. It is divided into four main categories: general function, urinary problems, intestinal problems, and sexual problems, and it has been tested in several studies (174-177). The patient is asked to evaluate symptoms experienced during the previous week. The questionnaire utilizes a modified linear analog scale with response boxes containing numerical values between 0 and 10, where 0= “no problem/very good function” and 10= “many problems/very bad function”. Five items regarding intestinal problems represent the rectal bother scale (overall bother from all bowel symptoms, stool frequency, stool leakage, planning of toilet visits, and limitations in daily activity caused by bowel symptoms) (178). The average estimate of each item is summarized and then divided by five to calculate a mean estimate for the rectal bother scale (range 0-10). This is the primary outcome in the study; the remaining items in QUFW94 were secondary outcomes in Paper I. In Paper III, nine out of eleven questions regarding sexual function 18 months after radical EBRT were analyzed and reported. The remaining two items excluded from consideration were “If you have any problem(s) with your sex life, which problem is the greatest?” and “Have you had sexual intercourse/contact in the last… week/month/year/not in the last year”. These were not analyzed due to written answer from the patient and low response rate respectively. The questionnaire was handed out to

the patients by the clinical oncologist at their inclusion and mailed to the patients' homes during follow-up.

7.2.5 Follow-up and trial plan

Months	-3 to 0	0	2	5	12	18	24	36	48	60	120
	Start TAB	Start RT	End RT	Follow up	Follow up	Follow up	Follow up	Follow up	Follow up	Follow up	Follow up
Implantation of gold markers	X										
QOL (EORTC QLQ-C30 and QUFW 94)	X		X	X	X	X	X	X	X	X	X
CTCAE v4.0	X		X	X	X	X	X	X	X	X	X
Lab tests	X		X	X	X	X	X	X	X	X	X
Pelvic MRI	X										
Bone scan	X										
Clinical exam	X		X	X	X	X	X	X	X	X	X
CT + MRI for dose planning	X										

Abbreviations: TAB: total androgen blockage, RT: radiotherapy, QoL: quality of life, EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire, QUFW94: Questionnaire Umeå Fransson Widmark 1994, MRI: Magnetic Resonance Imaging, CT: Computer tomography.

Table 3: Trial plan. Month 0 representing time of inclusion.

7.2.6. Calculation of volumes and doses in CBCT in Paper II

For the analyses in Paper II, the RV included the anus and rectum to the recto-sigmoid junction. The RV was manually outlined by the PhD candidate on the dose-planning CT (CT1) scan and on the eight weekly CBCT scans obtained at fraction numbers 1, 6, 11, 16, 21, 26, 31, and 36 (CBCT1-8) in 30 consecutive patients in arm B. This resulted in 9 rectum contours for each patient and 270 for all 30 patients. The eight rectum contours obtained from each patient were imported and merged with CT1 using the prostatic fiducial gold markers as geometrical reference points. The rectal dose was recalculated for each CBCT1-8 using the original planning CT and setup beams. DVHs for RVs receiving 50, 60, 65, and 70Gy (V50Gy, V60Gy, V65Gy and V70Gy) were estimated, both in cm^3 and in percentage of irradiated RV.

7.2.7 Statistics

All analyses reported in Papers I-III were preplanned with predefined primary and secondary outcomes. To evaluate the efficacy of IGRT in reducing rectal side effects in Paper I, a minor clinical difference was anticipated between groups of 0.75 reduction in mean score of the bother scale in QUFW94 in favor of the patients in study arm B (178). Based on this, a mean symptom score on single item frequency of 3.5 with a standard deviation of 2.0 was anticipated at the end of EBRT in arm A. To detect a difference of 0.75 in symptom score with 80% power (α=0.05), 113 patients in each arm would need to be included. Approximately 15%, 34 patients, were estimated not to be evaluable; hence a sample of 260 patients was estimated. With 2×130 patients, 84 months biochemical progression-free survival 0.85 and 0.70 (hazard rate per month 0.0019 and 0.0042), and a dropout rate 0.0040 per month gave 72% power with α= 0.05. The dropout rate 0.0040 per month was the mortality per month for men in Norway in 2008, age 75-79. Hence, the planned inclusion of 260 patients would result in 72% power in detecting a difference between groups in biochemical free survival of 0.70% vs. 0.85%.

The analyses of the primary and secondary outcomes in Paper I were performed by regression analysis with the mean rectal bother scale at end of EBRT as dependent variable and treatment group, pretreatment rectal bother scale, site (Ålesund Hospital versus St. Olavs hospital), and dichotomized risk group as covariates. For the primary outcome, significance level was set at 0.05. For secondary outcomes, the significance level was set at 0.01 due to multiple comparisons.

In Paper II, the time trend in RV was analyzed by applying a three-level mixed model with percentage of irradiated RV as dependent variable, patient as random effect, time point as random effect nested within patient, dose as a four-level categorical covariate, week number (0 to 8) as continuous covariate, and interaction between dose and week number, with a possible deviating volume at initial planning CT scan (time 0).

As for all scale outcome variables in Paper III, the effect of treatment group on the QUFW94 questionnaire item “can you get an erection?” was estimated using linear regression analysis. The analysis was adjusted for site (Ålesund Hospital versus St Olavs Hospital) and risk group (high versus intermediate), since randomization was stratified on these. We also adjusted for age, which is an important prognostic factor for erectile dysfunction. In addition, regression analysis was carried out for the primary outcome with mean dose to PB as covariate instead of treatment group. We also performed the analysis with testosterone level at 18 months as covariate. Otherwise, the analysis was a logistic regression for dichotomous outcome variables and ordinal logistic regression for the question with three ordered alternatives.

7.2.8 Ethics and financial support

The RIC study was approved by the Regional Ethics Committee of Central Norway (REK midt) and funded by the Norwegian Cancer Society and St Olavs Hospital, Trondheim University Hospital.

8. Results and summary of papers

8.1 Paper I

- ***RQ1:*** Does daily image guidance with CBCT and tighter PTV margins improve patient reported acute rectal side effects at end of EBRT as compared to weekly orthogonal verified irradiation with wider PTV margins in patients receiving 3D-conformal EBRT for intermediate- and high-risk prostate cancer?

8.1.1 Patients

Between October 2012 and June 2015, a total of 257 men with histologically proven intermediate- or high-risk prostate cancer were included in the RIC study (Fig. 11). Two patients were included erroneously, and one patient withdrew from the study before randomization. Additionally, seven patients did not complete EBRT and did not report side effects at the end of EBRT. The reasons for interrupting EBRT were pancreatic cancer, acute myocardial infarction, patients' withdrawal, and clinical decisions (1, 1, 2, 3 patients, respectively). The clinical decisions were: 1) converting a dose plan from 3D-conformal EBRT to VMAT in a patient in arm A due to a significant volume of intestine in the irradiation field, 2) deciding to perform frequent IGRT in a patient in arm A due to large rectal variation, and 3) a patient failing to complete MRI in arm A.

Treatment arms were balanced for the baseline characteristics: height, weight, comorbidities (cardiovascular disease, diabetes mellitus, gastrointestinal and kidney disease) and CTCAE as graded by the physician (Table 4).

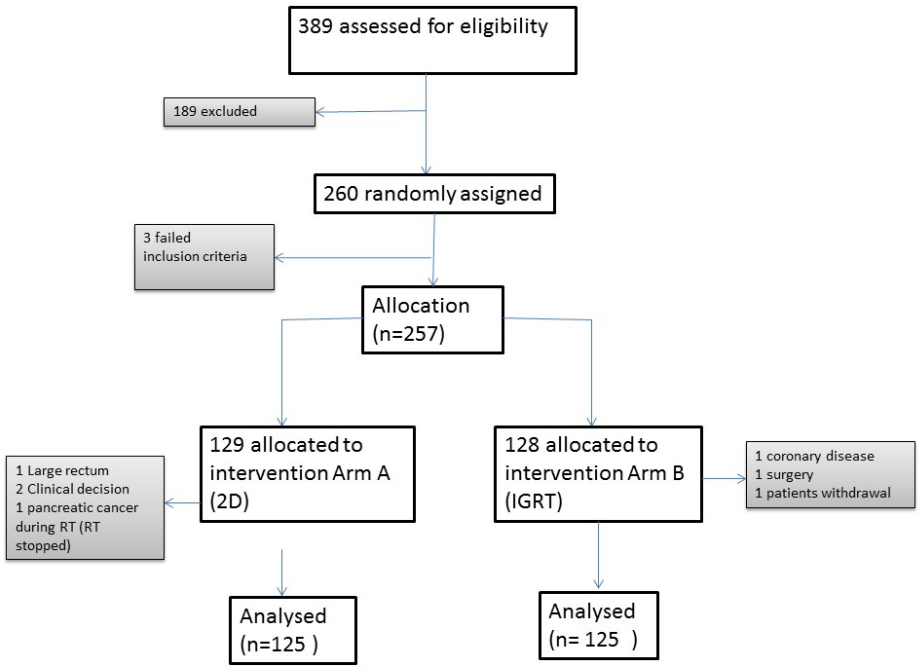


Fig. 11. Consort diagram.

	2D-IGRT (n=125)	3D-IGRT (n=125)
Age (years)	72.4	71.9
Aalesund Hospital (n)	63	60
St Olavs Hospital (n)	62	65
PSA mean (nmol/L)	16.57	16.09
Tumor stage		
T1 (n)	21	27
T2 (n)	47	40
T3 (n)	57	57
T4 (n)	0	1
Gleason score (mean)		
Gleason 6 (n)	9	11
Gleason 7 (n)	69	77
Gleason 8 (n)	25	17
Gleason 9 (n)	19	17
Gleason 10 (n)	3	3
High Risk (n)	77	75
Intermediate Risk (n)	48	50
Diabetes Mellitus (n)	14	21
Cardiovascular disease (n)	81	77
Gastrointestinal disease (n)	4	5
Kidney disease (n)	5	4
Height (cm)	177	175.7
Weight (kg)	86.9	86.9
CTC-score (mean)	0.49	0.43

CTC: Common Toxicity Criteria.

Table 4. Baseline characteristics in 250 eligible patients at time of inclusion.

8.1.2 Response and toxicity

Of 250 evaluable patients, 239 (96%) returned the QUFW94 and EORTC-QLQ-C30 at baseline, and 241 (97%) returned these at end of EBRT. Ålesund Hospital included 123 patients and St. Olavs Hospital 127. The stratification data on sites and risk groups showed greater numbers of patients with intermediate-risk disease at Ålesund Hospital (n=59) than at St. Olavs Hospital (n=38) and correspondingly higher numbers of patients with high-risk disease included at St. Olavs Hospital (n=89) than at Ålesund Hospital (n=64) (Table 5).

Center	Intermediate risk group	High risk group	Total
St Olavs Hospital	38	89	127
Ålesund Hospital	59	64	123
Total	97	153	250

Table 5. Number and stratification data on 250 evaluable RIC-patients according to center and risk group.

The patients reported a low degree of side effects for both GI and GU symptoms at the end of EBRT. There was no significant difference between groups for the primary outcome (bother scale 1.871 vs. 1.884, p=0.804) (Table 6). Although there was a trend towards more frequent nocturia in arm B (mean 3.73 in arm A vs mean 4.37 in arm B, p=0.02), and hematuria in arm A (mean 0.36 in arm A vs mean 0.10 in arm B, (p=0.04), the difference did not reach the level of statistical significance ($p<0.01$) set for multiple comparisons. In addition, no differences were found between groups for any other urinary or GI symptoms as measured by the QUFW94. HRQoL analyses demonstrated no differences between groups (Table 7).

	2D-IGRT (arm A)		3D-IGRT (arm B)		Difference between treatment arms A and B*	
	Mean	95% CI	Mean	95% CI	Estimate (95% CI)	p *
URINARY SYMPTOMS						
Overall bother from all urinary symptoms	4.17	3.55-4.78	4.25	3.69-4.81	-0.16 (-0.94 to 0.63)	0.698
Nocturia	3.73	3.35-4.11	4.37	3.89-4.84	-0.68 (-1.25 to -0.11)	0.020
Urinary frequency per day	9.09	8.22-9.95	9.21	8.32-10.09	-0.17 (-1.24 to 0.90)	0,758
Pain while urinating	2.73	2.15-3.32	3.04	2.45-3.63	-0.52 (-1.29 to 0.25)	0.188
Starting problem	2.66	2.13-3.18	2.89	2.38-3.40	-0.30 (-1.02 to 0.42)	0.415
Urinary leakage	0.98	0.66-1.31	1.10	0.70-1.49	-0.10 (-0.55 to 0.35)	0.658
Urgency	2.83	2.33-3.34	3.11	2.58-3.64	-0.36 (-1.05 to 0.34)	0.314
Blood in urine	0.36	0.08-0.63	0.10	0.03-0.18	0.29 (0.01 to 0.56)	0.040
Limitation in daily activity caused by urinary symptoms	2.38	1.89-2.87	2.58	2.09-3.06	-0.11 (-0.74 to 0.51)	0.722
BOWEL SYMPTOMS						
Overall bother from all bowel symptoms	2.26	1.77-2.74	2.22	1.73-2.72	0.15 (-0.53 to 0.83)	0.660
Stool frequency	3.20	2.82-3.58	3.27	2.78-3.75	0.12 (-0.58 to 0.61)	0.968
Stool leakage	0.76	0.49-1.02	0.63	0.39-0.87	-0.13 (-0.35 to 0.33)	0.942
Planning of toilet visits	1.68	1.22-2.14	1.78	1.28-2.28	-0.02 (-0.68 to 0.64)	0.954
Flatulence	3.74	3.24-4.24	3.94	3.40-4.48	-0.12 (-0.78 to 0.54)	0.714
Bowel cramp	1.60	1.17-2.04	1.28	0.84-1.71	0.33 (-0.28 to 0.94)	0.283
Mucus	2.09	1.64-2.54	1.78	1.32-2.23	0.19 (-0.45 to 0.82)	0.558
Blood in stools	0.42	0.22-0.62	0.45	0.21-0.68	-0.06 (-0.35 to 0.24)	0.696
Limitation in daily activity caused by bowel symptoms	1.52	1.14-1.90	1.61	1.14-2.07	0.28 (-0.27 to 0.84)	0.314
Bother scale	1.871	1.557-2.186	1.884	1.540-2.230	0.06 (-0.39 to 0.50)	0.804

* P-value for treatment, from linear regression with baseline value, treatment, site, and risk group as covariates.

Table 6. Urinary and bowel symptoms at end of radiotherapy.

	2D-IGRT (arm A)		3D-IGRT (arm B)		
	Mean	(95% CI)	Mean	95% CI	P *
FUNCTIONING SCALES					
Physical function	85.3	83.8-86.8	83.6	82.0-85.3	0.335
Role function	80.1	77.9-82.2	78.1	75.8-80.4	0.449
Emotional function	88.8	87.3-90.2	87.7	86.4-89.1	0.492
Cognitive function	86.9	85.4-88.4	86.9	85.4-88.4	0.742
Social function	81.4	79.5-83.3	82.0	80.3-83.8	0.899
Global health/QoL	74.8	73.0-76.6	76.2	74.4-77.9	0.319
SINGLE SYMPTOMS					
Fatigue	29.4	27.4-31.4	30.2	28.4-32.1	0.496
Nausea/Vomiting	1.9	1.2-2.6	1.7	1.2-2.2	0.149
Pain	14.1	12.1-16.1	12.2	10.4-14.0	0.553
Dyspnea	24.0	21.7-26.2	20.7	18.3-23.1	0.738
Insomnia	23.0	20.5-25.4	22.4	20.1-24.7	0.997
Appetite loss	4.2	3.0-5.4	4.2	3.1-5.2	0.466
Constipation	17.1	14.9-19.3	17.0	15.0-19.0	1.000
Diarrhea	20.4	18.1-22.7	20.6	18.6-22.6	0.523
Financial difficulties	3.7	2.6-4.9	4.1	2.8-5.5	0.494

* P-value for treatment, from linear regression with baseline value, treatment, site, and risk group as covariates

Table 7. Health-related quality of life scores (EORTC QLQ-C30) at end of radiotherapy.

8.1.3 Radiation doses to target volumes and organs at risk

The irradiated CTV volumes did not differ between the treatment groups. Analyses of DVHs demonstrated that the PTV2 (0-70Gy) was, as expected, significantly larger in patients in arm A, who received wider PTV margins (mean PTV2 270.1 cm^3 in arm A vs mean PTV2 131.0 cm^3 in arm B, ($p< 0.001$), (Table 8). Due to rectal dose constraint of no more than 60Gy to no more than half of the rectal circumference, posterior shielding with multileaf collimators (MLC) was frequently applied in arm A. Nonetheless, the rectal V50Gy, V60Gy, V70Gy, and V66.5Gy to the PTV2 (0-70Gy) remained significantly larger in arm A. The mean doses to the PTV 2 in arms A and B were 74.5 and 76.2Gy, respectively ($p< 0.001$).

	2D- IGRT (arm A) Mean (95% CI)	3D-IGRT (arm B) Mean (95% CI)	p*
Rectum			
V50 (cm^3)	44.9 (40.8-49.0)	29.8 (26.9-32.6)	<0.001
V60 (cm^3)	36.2 (32.7-39.7)	22.6 (20.4-24.8)	<0.001
V70 (cm^3)	18.5 (16.3-20.62)	11.5 (10.3-12.7)	<0.001
Bladder			
V50(cm^3)	83.6 (78.6-88.5)	53.8 (50.0-57.7)	<0.001
V60 (cm^3)	74.0 (69.5-78.6)	45.1 (41.6-48.5)	<0.001
V70 (cm^3)	46.3 (42.5-50.0)	30.4 (27.5-33.3)	<0.001
CTV2 (0-70)			
Total volume (cm^3)	49.2 (45.5-52.9)	49.2 (45.8-52.6)	0.687
Mean dose (Gy) #)	77.59 (77.21-77.78)	77.65 (77.58-77.72)	0.449
PTV2 (0-70)			
Total volume (cm^3)	279.7 (269.1-290.3)	131.9 (125.7-138.2)	<0.001
V66.5 (cm^3)	270.1 (259.8-280.3)	131.0 (124.8-137.1)	<0.001
Mean dose (Gy)	74.5 (74.1-74.8)	76.2 (76.1-76.4)	<0.001

*Student's t-test assuming unequal variances

[¤]Due to non-normally distributed data, p-values are from Mann-Whitney's test, and confidence intervals are bias corrected and accelerated (BCa) Bootstrap confidence intervals with B=10000 bootstrap samples.

Table 8. Irradiated volumes

8.2 Paper II

8.2.1 Patients

- ***RQ2:*** Are rectal volumes reduced or increased, and are rectal doses consequently reduced or increased during 8 weeks of radical EBRT in patients with intermediate- and high-risk prostate cancer?
-

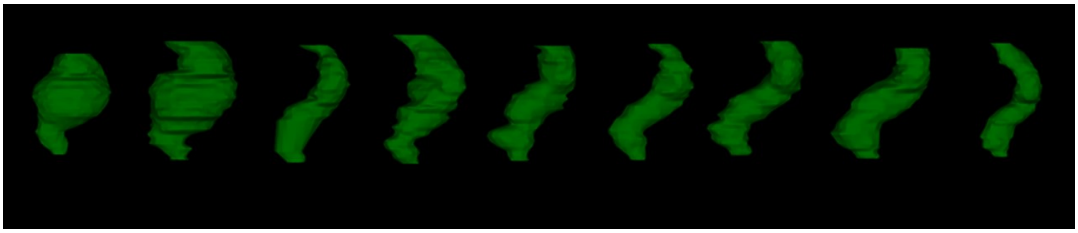
This spin-off study from the RIC study included the first 30 consecutive patients in arm B receiving daily CBCT-IGRT (Table 9).

Age (years) (SD)	**71.0 (5.3)**
Aalesund Hospital	9
St. Olavs hospital	21
PSA mean (nmol/l) (SD)	17.7 (13.2)
Clinical stage	
T1	6
T2	10
T3	14
Gleason score	
6	3
7	16
8	6
9	5
High risk	18
Intermediate risk	12
CTCAE grade at inclusion	
0	23
1	5
2	2
CTCAE grade at end of RT	
0	6
1	21
2	3

Table 9. Patient characteristics in 30 consecutive patients in arm B receiving daily IGRT.

8.2.2 Results

The mean RV of the planning CT (CT 1) was 114.6 (43.9-259.1) cm³. For all 240 CBCT scans, the mean volume was 94.3 (41.9-278.3) cm³ (Table 10). The individual rectal volume variation (RVV) during the treatment course (including CT1) was considerable, with an estimated mean of 95.6 cm³; six out of 30 patients had a RVV >150 cm³ (Fig. 12). In the two patients with the largest (202.1 cm³) and smallest (20.3 cm³) RVVs, the volumes ranged from 61.8 to 263.9 cm³ and 67.4 to 87.7cm³, respectively (Fig. 14).



CT 1 CBCT 1 CBCT 2 CBCT 3 CBCT 4 CBCT 5 CBCT 6 CBCT 7 CBCT 8

Fig. 12. Example of rectal volume variation during treatment for one patient.

Maximal volume on CT 1 = 259.1 cm³, minimal volume on CBCT 2 = 87.6 cm³. Range 171.5 cm³.

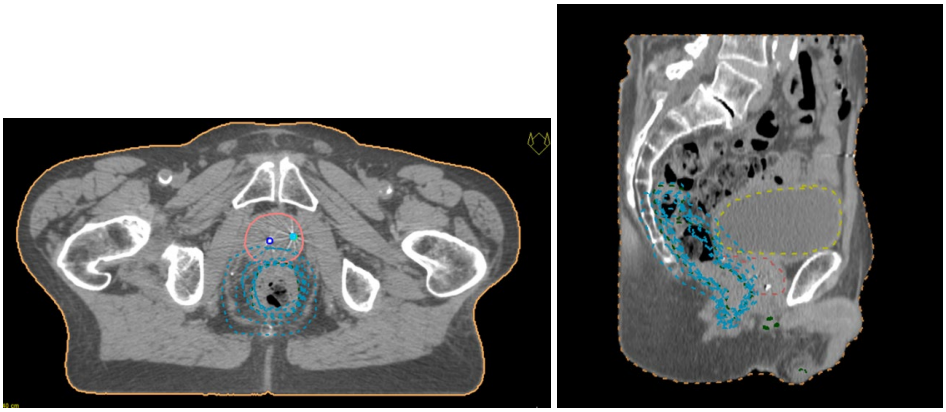


Fig. 13. Example of fusion of rectal volumes from the treatment period into the dose-planning system (blue dotted lines).

	Initial planning CT-scan	CBCT 1	CBCT 2	CBCT 3	CBCT 4	CBCT 5	CBCT 6	CBCT 7	CBCT 8
Mean (cm^3)	114.6	119.2	94.9	91.6	85.1	99.1	90.2	91.3	82.8
SD	55.3	56.6	38.2	27.5	37.2	53.0	37.7	44.8	22.5

Table 12: Mean and SD for rectal volumes for the n=30 patients at initial planning CT scan, and then weekly during treatment.

The RVs of all patients decreased significantly during the treatment period, with an estimated reduction of 3.55 cm^3 per week. The mean proportion of RVs irradiated to 50Gy (V50Gy) on the planning CT scan and CBCT1-8 were 34.1% (Table 13). The corresponding estimates for V60, V65, and V70Gy were 26.9, 22.3, and 15.6%, respectively. The estimated increase for the V70Gy was 0.18% (CI -0.182 to 0.550, p=0.30) per week, corresponding to an absolute increase of 1.47% over 8 weeks. The absolute increase over 8 weeks for volumes irradiated to 50, 60, and 65Gy was 1.14, 1.12, and 1.20%, respectively; these were not statistically significant (p=0.42, 0.43, and 0.39, respectively).

The grade of CTCAE in this side study corresponded well to the overall grade of CTCAE reported in arm B. However, we found no grade 3 toxicity in these 30 patients compared to 1 out of 125 patient in arm B.

	CT 1	CBCT 1	CBCT 2	CBCT 3	CBCT 4	CBCT 5	CBCT 6	CBCT 7	CBCT 8
V50Gy	33.0% (50.4 -21.6)	35.7% (49.8-17.9)	33.8% (57.5-12.1)	33.5% (54.4-18.7)	32.7% (54.8-15.5)	33.5% (56.8-21.6)	34.6% (51.5-22.2)	33.9% (50.6-21.6)	36.1% (59.9-18.3)
V60Gy	25.6% (42-16.3)	28.7% (39.8-12.7)	26.5% (47.3-8.6)	26.3% (44.6-13)	25.7% (46.1-10.3)	26.5% (48.1-17.1)	27.3% (43.7-15.8)	26.6% (42.4-15.4)	28.8% (49.5-14.3)
V65Gy	20.9% (36.3-12.8)	24.1% (34.1-9.9)	21.8% (41.3-6.5)	21.9% (39.3-10.0)	21.2% (41.1-7.6)	22.1% (43.5-13.5)	22.8% (38.8-11.5)	22.0% (38.1-11.5)	24.2% (43.7-11.3)
V70Gy	14.0% (24.4-8.0)	16.8% (25.4-6.4)	15.1% (29.2-4.2)	15.2% (28.3-5.9)	14.9% (31.9-4.2)	15.7% (33.0-3.3)	16.2% (28.5-7.5)	15.1% (29.1-7.1)	17.4% (31.6-7.9)

Table 13. Mean percentage of irradiated rectal volumes for V50Gy, V60Gy, V65Gy, and V70Gy, range (%) in parentheses.

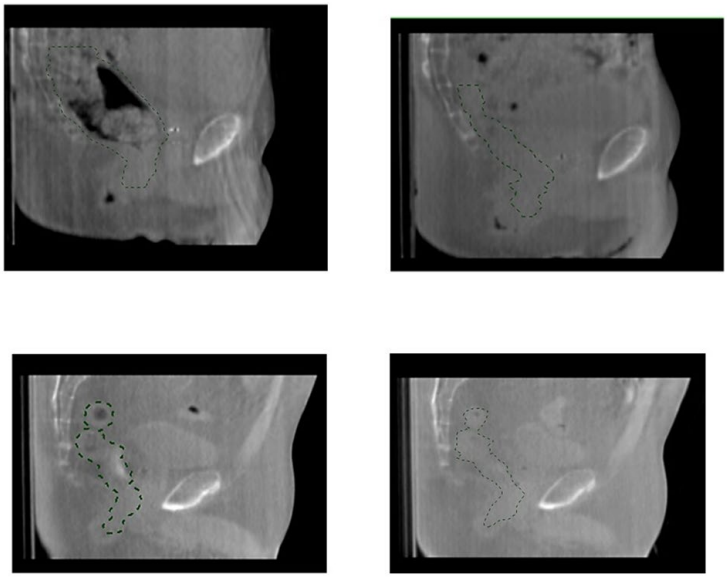


Fig 14. Images for the patients with the largest (above line) and smallest (below line) range on CBCT 1-8 (range 202.1 cm³ and 20.3 cm³, respectively).
Green line represents outlined rectal volume. Left images represent CBCT 1 (volumes 263.9 cm³ and 87.7 cm³, respectively), right images represent CBCT 6 (61.8 cm³) and CBCT 3 (67.4 cm³), respectively.

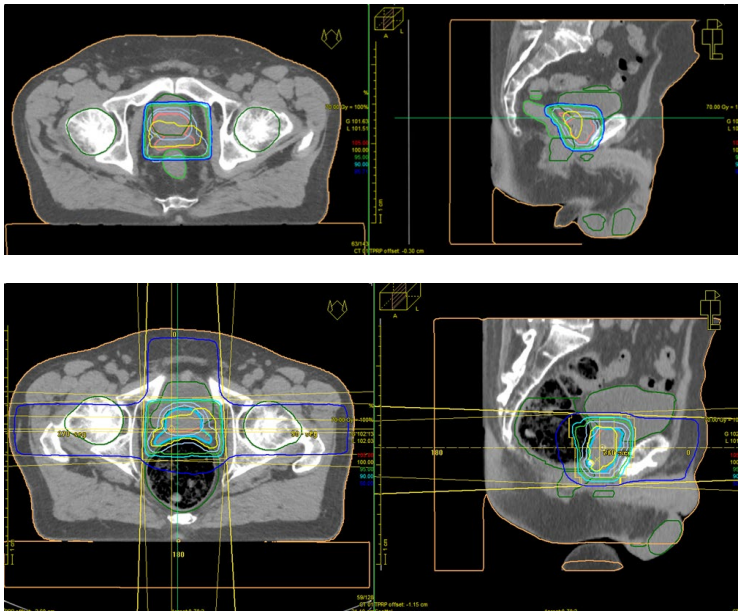


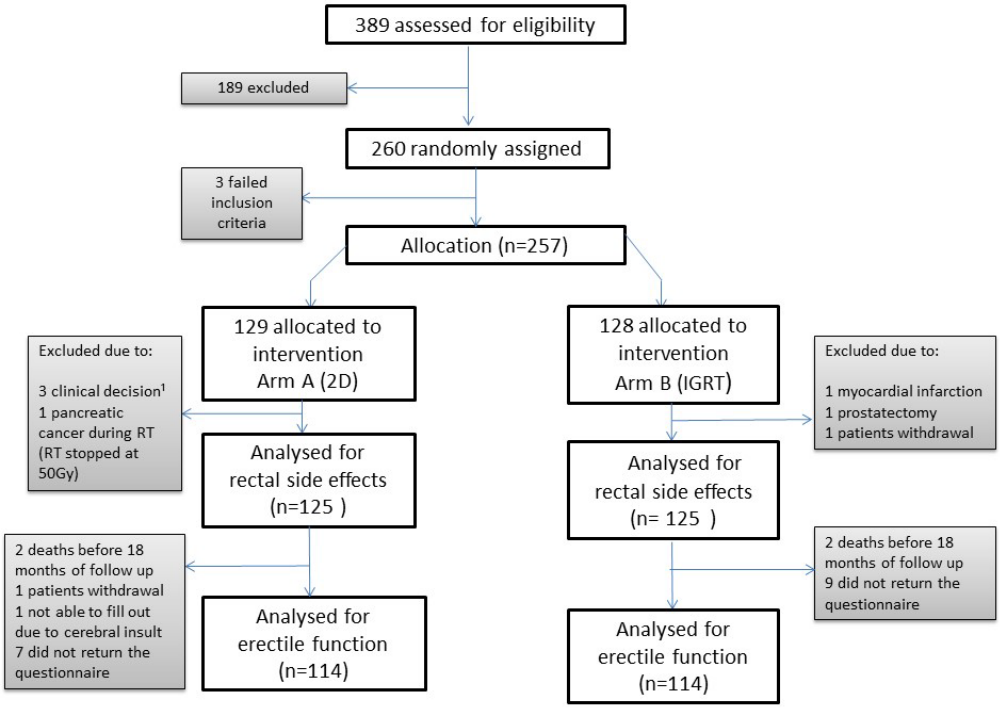
Fig. 15. Images from two patients illustrating different rectal volumes at the time of the dose planning.
Patient with small volume in upper line, patient with large volume in bottom line.

8.3 Paper III

- ***RQ3:*** Does daily image guidance with CBCT and tighter PTV margins improve erectile function 18 months after radical EBRT as compared to wider PTV margins and weekly verification in intermediate- and high-risk prostate cancer patients?

8.3.1 Patients

This study included the 228 (91% out of 250) RIC study patients who returned the EORTC QLQ-C30 and QUFW94 questionnaires 18 months after EBRT (Fig. 16). Of these, 119 patients were included at St. Olavs Hospital and 109 at Ålesund Hospital. A total of 22 patients did not return the questionnaires; 3 patients died before the 18-month follow-up due to other causes than prostate cancer (pancreatic cancer, lung cancer and malignant melanoma diagnosed after end of prostatic irradiation), and one patient died for an unknown reason. One patient withdrew from the study, one patient was not able to fill out the questionnaire due to a cerebral insult, and 16 patients (7 in arm A and 9 in arm B) did not give any reason for not returning the questionnaire.



[1]Two patients ineligible for study therapy, one patient unable to complete magnetic resonance imaging

Fig. 16 Consort diagram.

	2D-IGRT (n=114) (SD)	3D-IGRT (n=114) (SD)
Age (years) at inclusion, mean (SD)	72.2 (4.3)	71.4 (4.6)
Risk group		
High, n (%)	70 (61.4)	69 (60.5)
Intermediate, n (%)	44 (38.6)	45 (39.5)
PSA[1] at treatment start, mean (SD)	16.5 (15.1)	16.2 (12.1)
Tumor stage, n (%)		
T1	20 (17.6)	25 (21.9)
T2	42 (36.8)	36 (31.6)
T3	52 (45.6)	52 (45.6)
T4	0 (0)	1 (0.9)
Gleason score, n (%)		
Gleason score 6	8 (7.0)	11 (9.7)
Gleason score 7	64 (56.1)	67 (58.8)
Gleason score 8	24 (21.1)	17 (14.9)
Gleason score 9	15 (13.2)	16 (14.0)
Gleason score 10	3 (2.6)	3 (2.6)
Diabetes Mellitus, n (%)	18 (15.8)	13 (11.4)
Cardiovascular disease and risk factors[2], n (%)	69 (60.5)	74 (64.9)
Other disease[3], n (%)	9 (7.9)	6 (5.3)
PB volume[4,5], mean (SD)	3.5 (1.8)	3.9 (2.1)
PB dose[5,6], mean (SD)	59.8 (14.8)	35.0 (21.4)
Testosterone level at 18 months[1,6], mean (SD)	8.9 (6.1)	9.4 (6.6)
Median time to testosterone normalization, months (IQR)	18.00 (6)	18.00 (6)

Abbreviations: EORTC QLQ-C30: European Organization for Research and Treatment of Cancer questionnaire regarding health-related quality of life, QUFW94: Questionnaire Umeå Fransson Widmark 1994, 2D: Two-dimensional, IGRT: image-guided radiotherapy, 3D: three-dimensional, SD: standard deviation, PSA: prostate specific antigen, PB: penile bulb, IQR: interquartile range.

[1]nmol/l, [2]according to WHO (World Health Organization) definition including risk factors (hypertension and hypercholesterolemia), [3]include gastrointestinal and kidney disease, [4]cm^3, [5]Evaluable in 219 patients,[5]Gy, [6]evaluable in 190 patients.

Table 14: Baseline characteristics in 228 RIC study patients who returned the EORTC QLQ-C30 and QUFW94 questionnaires at 18 months.

8.3.2 Results

Baseline characteristics were balanced between treatment arms (Table 14). The mean age at inclusion was 71.8 years. A total of 143 (63%) patients had cardiovascular disease (CVD) according to the World Health Organization (WHO) definition or associated risk factors such as hypertension and hypercholesterolemia, and 31 (13.5%) had diabetes mellitus (DM). Seven patients in arm A and six patients in arm B still had castrate levels (<1.7 nmol/l) of testosterone at 18 months, most often caused by prolonged LHRH-agonist treatment.

The primary-outcome single-item question “Can you get an erection?” in QUFW94, had a mean score of 7.44 in arm A and 7.39 in arm B (p=0.93) (Table 15). Only 16% of the patients (n=15 in arm A and n=16 in arm B) reported an erection sufficient to perform sexual intercourse at 18 months; the baseline characteristics for these patients are reported in Table 17. Five patients in each study arm reported a need for assistance (alprostadil, sildenafil, apomorphine or others) to perform sexual intercourse. The patients reported a high degree of sexually related problems, with mean scores > 6.5 for all relevant single items scaled from 0-10 (means ranged from 6.52 to 8.04).

The volume of the PB (cm^3) did not differ significantly between the treatment groups (Table 14). The PB dose was significantly larger in arm A due to larger PTV margins (mean 59.8Gy vs mean 35.1Gy, p<0.001). We found no effect of mean PB dose on the primary outcome in linear regression analysis adjusted for site, risk group, or age (Regression coefficient -0.01 Gy^{-1}, CI 0.03 to 0.01, p=0.34). When adjusting for testosterone level at 18 months, the effect of mean dose to PB remained statistically insignificant (regression coefficient -0.006 Gy^{-1}, CI -0.03 to 0.02, p=0.61).

	2D-IGRT (n=114)		3D-IGRT (n=114)		Coefficient (β) 2D-IGRT versus 3D-IGRT	
Question Scale: 0-10	**Number of respondents**	**Mean (SD)**	**Number of respondents**	**Mean (SD)**	**Estimate [2] (95% CI)**	**p-value**
[1]Can you get an erection?	108	7.44 (3.3)	113	7.39 (3.1)	0.04 (-0.81 to 0.89)	0.93
Do you have a problem with your sex life?	98	7.00 (3.8)	101	6.67 (3.6)	0.35 (-0.70 to 1.40)	0.51
Do you feel like sexual activity?	109	6.74 (3.1)	111	6.52 (3.1)	0.19 (-0.62 to 1.0)	0.65
Are you able to have an erection without medication?	103	7.75 (3.2)	108	7.55 (3.2)	0.18 (-0.68 to 1.04)	0.68
Can you get an erection (with assistance)?	32	7.22 (3.6)	25	8.04 (2.9)	-1.03 (-2.87 to 0.80)	0.26

Abbreviations: QUFW94: Questionnaire Umeå Fransson Widmark 1994, 2D:Two-dimensional, IGRT: image-guided radiotherapy, 3D: three-dimensional, SD: standard deviation. CI: confidence interval.

[1] Primary outcome, [2] Coefficient for 2D-IGRT versus 3D-IGRT in linear regression, adjusted for site, risk group, and age.

Table 15. Response to selected single items from QUFW94 questionnaire graded on an 11-point (0-10) scale. Ten denotes the worst outcome.

	2D-IGRT (n=114)		3D-IGRT (n=114)			
Question Scale: Yes / no	**Number of respondents**		**Number of respondents**		**Odds Ratio (95%CI)[1]**	**p**
Is the erection sufficient to carry out sexual intercourse?	95	yes: 15.8%	100	yes: 16.0%	1.06 (0.48 to 2.32)	0.89
Is the erection sufficient (without assistance) to carry out sexual intercourse?	91	yes: 13.2%	94	yes: 16%	0.87 (0.375 to 2.03)	0.75
Is the erection sufficient (with assistance) to carry out sexual intercourse?	37	yes: 24.3%	23	yes: 17.4%	1.69 (0.432 to 6.56)	0.45
Question Scale: always/ seldom/not at all	**Number of respondents**		**Number of respondents**		**Odds Ratio (95% CI)[2]**	**p**
Have you used assistance to carry out sexual intercourse?	89	always: 5.6% seldom: 9.0% not at all: 85.4%	101	always: 5% seldom: 5.9% not at all: 89.1%	0.71 (0.30 to 1.68)	0.43

Abbreviations: QUFW94: Questionnaire Umeå Fransson Widmark 1994, 2D: Two-dimensional, IGRT: image-guided radiotherapy, 3D: three-dimensional, CI: confidence interval.

[1]Odds ratio (OR) for 2D-IGRT versus 3D-IGRT in logistic regression, adjusted for site, risk group, and age.
[2]Odds ratio (OR) for arm B (versus A) in ordinal logistic regression, adjusted for site, risk group, and age.

Table 16: Response to the QUFW94 questionnaire with dichotomous or categorical responses.

	ARM A (2D-IGRT) (n=15)	ARM B (3D-IGRT) (n=16)
Age (years) at inclusion, mean (SD)	72.9 (3.6)	68.3 (5.1)
St.Olavs Hospital (n)	10	9
Ålesund Hospital (n)	5	7
Risk group		
High-risk (n)	8	7
Intermediate-risk (n)	7	9
PSA[1] (nmol/l) at treatment start, mean (SD)	20.3 (SD 17.6)	15.9 (SD 10.4)
Tumor stage (n)		
T1	1	5
T2	10	5
T3	4	6
Gleason score (n)		
Gleason score 6	0	1
Gleason score 7	12	13
Gleason score 8	2	1
Gleason score 10	1	1
PB volume[2], mean (SD)	3.4 (SD 2.0)	4.2 (SD1.7)
PB dose[3], mean (SD)	63.8 (SD 8.0)	33.0 (SD 25)
Cardiovascular disease and risk factors[4] (n)	10	11
Gastrointestinal disease	1	0
Testosterone recovery[5] at 18 mnd (n)		
Yes	12	15
No	3	1

[1] nmol/l, [2]cm[3], [3]Gy, [4]according to World Health Organization (WHO) definition including risk factors (hypertension and hypercholesterolemia), [5] within normal range: 6,73-31,8 nmol/l (St. Olavs Hospital) and 4.5-26.6 nmol/l (Ålesund Hospital)

Table 17. Baseline characteristics in 31 potent RIC study patients at 18 months.

9. Discussion

9.1 Discussion of main findings

9.1.1 IGRT in radical radiotherapy for prostate cancer

To our knowledge, the RIC study is the first published randomized controlled trial that compares side effects following radical 3D conformal EBRT for PC with either daily CBCT or weekly orthogonal portal imaging. The results presented in Paper I demonstrated that significantly larger rectal, urinary bladder, and planning target volumes were irradiated in patients in arm A than in those in arm B. Due to the rectal dose constraint of 60Gy to half of the rectum circumference specified in the study protocol, posterior blocking of the PTV2 (0-70Gy) was performed frequently in arm A but rarely in arm B. This decreased the actual PTV irradiated in arm A and may have reduced the patient-reported rectal toxicity. Nevertheless, analysis of the DVHs clearly demonstrated that the V50Gy, V60Gy, and V70Gy delivered to the rectum were significantly smaller in arm B (daily IGRT) than in arm A. Contrary to our hypotheses, this did not translate into a difference in primary outcomes, patient-reported acute rectal side effects at end of EBRT, or secondary outcomes, GU side effects and HRQoL scores at end of EBRT. Although extended use of IGRT and reduced PTV margins are commonly recommended in international clinical guidelines, we were unable to demonstrate a clinical benefit regarding acute rectal toxicity from following these recommendations.

Radical RT in PC is generally well tolerated (5, 6, 179). However, the impact on QoL can be severe in those experiencing side effects (70, 180). Several studies have shown an association between the grade of acute side effects and the development of late side effects (10-12, 181, 182). In a study conducted by Wortel et al., acute toxicity, age >70 years, and baseline complaints were found to be strong independent predictors of grade ≥2 late toxicity (181). A study reported by Maebayashi et al. showed that age >75 years was a predictor for late rectal toxicity in addition to patients given anticoagulation/antiplatelet agents and those with severe internal iliac artery calcification (182). One might argue that anticoagulation and artery calcification are merely indicators of comorbidity, as anticoagulation is used in patients with CVD, and artery calcification is a generally CVD symptom and not a local problem; such an argument would support the findings in Paper III of this thesis. A review by

Peach et al. analyzed the relationship between acute and late GI toxicity after RT for PC (12). The authors suggest evaluating acute GI toxicity as a surrogate endpoint for late effects in prospective trials and using acute GI toxicity to identify at-risk patients who may benefit from closer follow-up to prevent late toxicity (12). However, whether our findings of no difference in acute side effects (Paper I) eventually translate into similar late side effects is likely to remain unresolved for some years: until we have sufficient long-term follow-up of the men randomized in the RIC trial.

Nonrandomized trials have compared modern IGRT using fiducial markers and/or CT imaging with previously used IGRT regimes using 2D orthogonal verification and found reduced side effects (143-145, 147, 148, 181, 183). Gill et al. found a significant improvement in acute treatment-related toxicity according to CTCAE when comparing patients given IGRT (with fiducial markers and daily orthogonal imaging) and dose escalation to 78Gy (n=249) with patients treated with weekly orthogonal imaging and no fiducial markers to 74Gy (n=26) (143). A study reported by Singh et al. showed a significant reduction in bowel dysfunction in a group receiving IGRT (n=154) compared to a group without IGRT (n=128) (183). Engels et al. reported on 238 patients treated with conventionally verified EBRT and 25 patients treated with advanced IGRT in a non-randomized prospective trial (148). A 3–4 millimetres CTV to PTV margin was applied. Although few patients experienced acute side effects, the risk of biochemical (s-PSA) progression after 5 years was higher in patients receiving IGRT with a 3-4 millimetres PTV margin. A study reported by Wortel et al. demonstrated a significant reduction in patient-reported GI and GU symptoms following IG-IMRT both at the end of RT and at 5-year follow-up (145, 181). Zelefsky et al. compared clinical outcomes in 186 patients treated with IGRT to 86.4Gy and patients given the same dose without IGRT (144). These authors found a significant reduction in toxicity profiles and improved biochemical control in the IGRT arm. However, other studies have not been able to confirm such differences in side effects (144, 184). Although the discrepancy between these results and our findings may be due to the addition of IMRT, different PTV margins, radiation dose or different measures of side effects, we cannot rule out bias caused by the non-randomized comparison in these trials as the cause of this discrepancy.

A recently published phase III trial reported by de Crevoisier et al. compared the safety and efficacy of daily IGRT with that of weekly IGRT (149). The study included 470 men from 21

centers with node negative localized prostate cancer suitable for 3D-conformal EBRT or IMRT. The patients were randomized in two arms and received daily (CBCT or ultrasound) or weekly (orthogonal electronic portal imaging) control. The primary outcome was recurrence-free survival defined as the time from randomization to biochemical PSA recurrence, clinical recurrence, or death by any cause, whichever occurred first, or to the date of last follow-up. Secondary outcomes were OS and safety (acute and late toxicity). In addition, several post-hoc analyses were performed. For the primary outcome, there was no statistically significant difference between the groups after a median follow-up of 4.1 years. Acute rectal bleeding and late rectal toxicity was significantly lower in the daily group than in the weekly group. OS was worse in the daily group. This study included more patients at several centers than the RIC study did, and it used a longer follow-up time. The irradiation dose was 70-80Gy, and both 3D-conformal EBRT and IMRT was allowed, giving a more heterogeneous group of study patients than the RIC study. In addition, the study used CTCAE reported by clinicians to define toxicity, rather than PROMs. All of these might explain the differences between the RIC trial and the study by de Crevoisier et al.

In the RIC study, CTV delineation was based on clinical findings, transrectal ultrasound and/or pelvic MRI in addition to the planning CT scan. The CT scans were fused with T1+T2 MRI scans at the doctor's discretion. Other studies comparing delineation on MRI and CT scans have shown that the CTV decreases by up to 35% when delineation is performed in MRI (185-187). We have not compared delineation on MRI and CT scans, but we assume the distribution was balanced between treatment arms due to the randomized design of the trial.

The risk of second malignancies following RT has been an issue for decades. A study reported by Brenner et al. estimated that one out of 70 PC patients treated with RT who are alive >10 years after being diagnosed will develop a radiation-induced cancer (188). Modern EBRT technology (e.g. IMRT and VMAT) can theoretically increase the risk of second malignancy because larger volumes of normal tissue are exposed to low doses of irradiation (a higher integral dose) (189). Secondary malignancies after irradiation for PC predominantly occur in the rectum, sigmoid, urinary bladder, and pelvis. Although irradiated PC patients have a higher risk of a second malignancy than unexposed patients, the absolute risk remains low (190, 191). The extra irradiation dose from the CBCT is of concern. Kan et al. reported an

increase of 2-4% in the risk of second malignancy when daily CBCT verification was used (192). In the phase III trial reported by de Crevoisier et al. on daily versus weekly PC IGRT, an increased risk of second malignancy was reported in the daily IGRT arm (149) . The second malignancies were predominantly in the abdomen (33%) and pelvis (18%). Median follow-up was 4.1 years, which is considered short in this context. Although the incidence of second malignancies was not a secondary end point in the RIC study, a post hoc analysis of this important late side effect is to be considered.

In IGRT, several methods are available to reduce the irradiation dose to the normal tissue, and the As Low As Reasonably Achievable (ALARA) principle for dose should always be followed. Imaging doses, field of view, and the resolution of the images can all be reduced (149, 193). In the RIC study, the estimated dose from the 3D-KV pelvic IGRT was 0.03Gy per uptake, in total 1.17Gy over all 39 fractions. This was added to the prescribed dose of 78Gy in 2Gy fractions, leading to a higher dose in arm B (3D-IGRT), although still within the limits of the prescribed dose (95-107%). House data from our QA protocols show that the current estimated dose from the CBCT is lower, approximately 0.003Gy per uptake. However, if the image quality of CBCT is reduced, the option of better imaging with an increased estimated dose of 0.011Gy might be applied. The extra dose contribution from the CBCT should be considered and used with caution, especially in younger individuals who are more susceptible to secondary cancer (193). We do not believe that the minor increase in total dose when applying daily CBCT affected the results of the RIC trial (rectal side effects at end of EBRT), as the dose is within commonly accepted dose variations.

Several authors claim that the PTV margins should be at least 5-8 mm when using daily imaging and fiducial markers (124, 194-196). Other uncertainties such as variation in delineation, positioning of the patient, and quality of the linear accelerator should also be taken into account. Although reduced PTV margins can theoretically reduce side effects, it is important to avoid insufficient target volume coverage by excessive margin reduction. This applies especially in patients with rectal distention at the time of the planning CT and/or if modern IGRT is not applied (140, 148, 197, 198). Whether distention of the rectum at planning of EBRT for the men included in the RIC trial resulted in any change in biochemical control can only be explored after long-term follow-up.

9.1.2 Rectal volume variation

The main findings in Paper II were that the RV decreased significantly during 8 weeks of conformal radical IGRT for PC. The RVV did not influence the percentage of irradiated RV receiving 50, 60, 65, or 70Gy, all of which were almost constant during the 8-week treatment period. Most of the RV reduction occurred early in the treatment period, and the inter-individual RVV was considerable.

The volume of rectum receiving ≥ 60Gy is associated with a risk of grade ≥ 2 late rectal toxicity and rectal bleeding and may be a limiting factor for dose escalation (5, 11, 199-202). Internal organs move due, for instance, to respiration and organ filling and emptying (129, 132, 203). The relative position of the prostate gland is known to shift substantially, mainly in anteroposterior and superior-inferior directions ("the dancing prostate") (204). This shift in relative position can affect the dose delivered to both the target volume and the OARs.

A range of strategies have been applied, such as rectal emptying before dose planning and each treatment, implantation of rectal balloon catheters, BeamCath® urethral catheter with radio-opaque fiducial markers, and recently the use of injected hydrogel in the perirectal space, to minimize the movement of the prostate gland (129, 205). Although these interventions are generally well tolerated, some patients may experience side effects such as bleeding, infection, and pain (206).

Several authors recommend rectal emptying before dose planning and before each treatment, or at least the first days of treatment (126, 198, 207). Nevertheless, the optimal regime and effectiveness of rectal emptying is still unknown. A review by McNair et al. compared dietary interventions, oral and intravenous laxatives, enemas, and combinations of these (208). No strategy was identified as superior. Hosni et al. investigated the tolerability and impact of milk of magnesia upon interfraction rectal filling during PC EBRT (78Gy) in a retrospective study (209). Forty patients were given an anti-flatulence diet with milk of magnesia starting 3 days prior to the EBRT, and 40 patients followed the same anti-flatulence diet without milk of magnesia. Milk of magnesia caused diarrhea in a substantial portion of patients, who then discontinued its use, but led to no reduction in interfraction variation in rectal filling. Moreover, no significant difference in RV was observed in another cohort of 80 PC patients receiving EBRT at one of the RIC study centers, 40 of whom were

given laxatives regularly during the 8-week treatment period (210). No rectal emptying was performed prior to the dose-planning CT or the subsequent radiotherapy fractions in the RIC study. Given that the IGRT technique applied in the RIC study ensures adequate safety margins regarding the CTV, in our opinion, emptying of the rectum might be omitted.

In accordance with previous studies, the main reduction in RV reported in Paper II occurred early in the treatment period (165-167). Radiation-induced proctitis can lead to reduced RV due to rectal muscle contraction, especially towards the end of the RT period. Other reasons might be stress and anxiety prior to the treatment, but the clinical relevance of these is uncertain (211, 212). Although the shrinkage in RV was significant, the percentage of irradiated RV in our study remained unchanged. These findings indicate that, in addition to reduced margins from CTV to PTV, the IGRT technique applied in the RIC study might eliminate the risk of increased dose to the rectum caused by volume shrinkage.

Previous studies have indicated that RVV during radiotherapy may increase the risk of geographical miss and thus hamper local control. In a retrospective analysis, de Crevoiser et al. reported a decreased 5-year biochemical control in patients with distended rectum (CSA > 11.2 cm^2) at the planning of EBRT (140). The Dutch PC dose-escalation trial reported by Heemsbergen et al. (78Gy vs. 68Gy) analyzed 549 patients (213). The study showed a significant reduction of freedom from clinical failure (FFCF) in patients with anorectal volumes ≥ 90 cm^3 on the planning CT scan. Engels et al. analyzed freedom from biochemical failure (FFBF) in 238 patients given conformal EBRT to a total dose of 70-78Gy and found that an average rectal CSA of ≥ 16 cm^2 was associated with worse FFBF (148). In another study reported by Engels et al., 50 patients were treated with IGRT and daily positioning using fiducial gold markers (197). This study demonstrated a reduced 5-year FFBF in patients with a rectal distention on the planning CT scan compared to those with limited rectal distention (75% vs 89%). Other authors claim that the adverse effects of rectal distention upon local control can be compensated by the use of modern IGRT. A retrospective study showed no that rectal distention was not a predictor of biochemical failure or rectal or urinary toxicity in PC patients treated with daily ultrasound-based IGRT and a 4-mm PTV margin (214).

Park et al. measured CSA on the planning CT scans in 962 PC patients receiving adaptive EBRT with a median prescribed dose of 75.6Gy (215). The authors found that initial rectal distention was not significantly associated with decreased 5-year biochemical control or grade ≥2 GU and GI toxicity; they concluded that adaptive IGRT reduces the risk of geographical miss. Silverman et al. examined 172 prostate cancer patients receiving conformal EBRT to a total dose of 74Gy at a median of 72 months follow-up (216). A large (>4.5 cm) rectal diameter on the planning CT scan was not associated with increased risk of PSA relapse. However, the PTV margins applied in Park et al.'s study were larger than those reported by Engels et al. (10 vs 3-5 mm) (148).

The dose constraint to the rectum in the RIC study was 60Gy to no more than 50% of the rectum circumference on the planning CT scan, and accordingly, the limit of 60Gy to 50% of the estimated RV was not exceeded in any of the 30 patients included in this study. Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC) recommends keeping the following rectal dose constraints in RT for PC with a dose up to 79.2Gy in 1.8-2Gy fractions: V50Gy to < 50%, V60Gy <35%, V65Gy < 25% and V70Gy < 20% (202). This is supposed to limit Grade ≥2 late toxicity to < 15% and the probability of Grade ≥3 late rectal toxicity to < 10%. Despite reduced margins from CTV to PTV, the QUANTEC constraints were exceeded in several patients in our study (one patient exceeded the mean V50Gy recommendation (52.9%), five had a mean V60Gy > 35%, seven a mean V65Gy > 25%, and five a mean V70Gy > 20%). Whether this affected the toxicity is as yet uncertain.

The increasing use of hypofractionated regimes and stereotactic body radiation therapy (SBRT) in PC with dose delivery times as high as 10-20 minutes will have to take both the intrafraction and interfraction organ motion into account. In this case, rectal peristalsis can result in a substantial RVV and displacement of the prostate gland during treatment (93). Our study results imply that modern IGRT and reduced PTV margins ensure a stable dose to the rectum in PC patients treated with reduced margins and daily CBCT-IGRT. We believe rectal emptying and other more invasive and expensive methods for limiting the movement of internal organs can be omitted if fiducial markers and daily CBCT are used.

9.1.3 Erectile function 18 months after radical radiotherapy

The key finding in this study was that the ability to have an erection 18 months after 78Gy EBRT for prostate cancer was not different in patients treated with a reduced PTV margin and daily CBCT from those who received the same treatment with wider margins and weekly verification. Moreover, no association was identified between radiation dose to the PB and erectile function. We found a high degree of sexual-related problems in all patients 18 months after EBRT.

The estimated prevalence of erectile dysfunction (ED) increases with age and range between 50 and 100% in men older than 70 years in the general population (217). Shiri et al. reported a prevalence of 89% in Finnish men aged 75 and 76.5% in men aged 50-75 years (218). However, other studies have reported lower prevalences (20-40% in men aged 60-69 and 50% in men > 70 years) (219). The discrepancy may be due to differences in questionnaires and diagnostic criteria. In the RIC study, more than 60% of the patients reported CVD or associated risk factors according to WHO definitions, and 14% reported DM. ED may be the first sign of DM type 2 and is strongly associated with other conditions such as CVD, sleep disorders, pulmonary disease, smoking, alcohol abuse, and a sedentary lifestyle (217, 218). In the RIC study, the exact distribution of cardiovascular disease, hypertension, hyperlipidemia, and other diseases such as neurological, endocrine or pulmonary conditions, medication, smoking, and alcohol abuse is unknown. Nevertheless, we expect an even distribution of these ED risk factors due to the randomized design of the study.

RT has been considered to result in lower frequency of ED than radical prostatectomy (220). The degree of ED increases gradually after RT, and there is some evidence that the functional decline stabilizes after approximately 2 years. Thereafter, few patients with ED will regain their sexual function (221-223). In the ProtecT-trial (prostate testing for cancer and treatment), 67% of the patients (mean age 62 years) reported erection firm enough for intercourse prior to treatment for PC. By 6 months, the proportion fell to 22% in patients given EBRT, increasing to 37% at 12 months and thereafter declining to 34% at 24 months and 27% at 6 years (Fig. 16) (80). The corresponding figures following prostatectomy at 6 months and 6 years were 12% and 17%, respectively. The active monitoring group scored best with 52% after 6 months and 30% after 6 years, demonstrating that factors other than cancer therapy (e.g. age and comorbidity) are involved in ED development (80). There is a

lack of long-term follow-up studies on ED after RT. Fransson et al. analyzed sexual function 15 years after EBRT for prostate cancer (224) and found that 78% of irradiated patients and 38% of age-matched controls were sexually inactive. However, QoL was similar. The authors suggest prospective longitudinal studies with PROMs of sexual function and assessment of pretreatment potency (224). Although the results from the RIC study correspond well with the findings in the ProtecT- trial, longer follow-up is needed to confirm the results from our study.

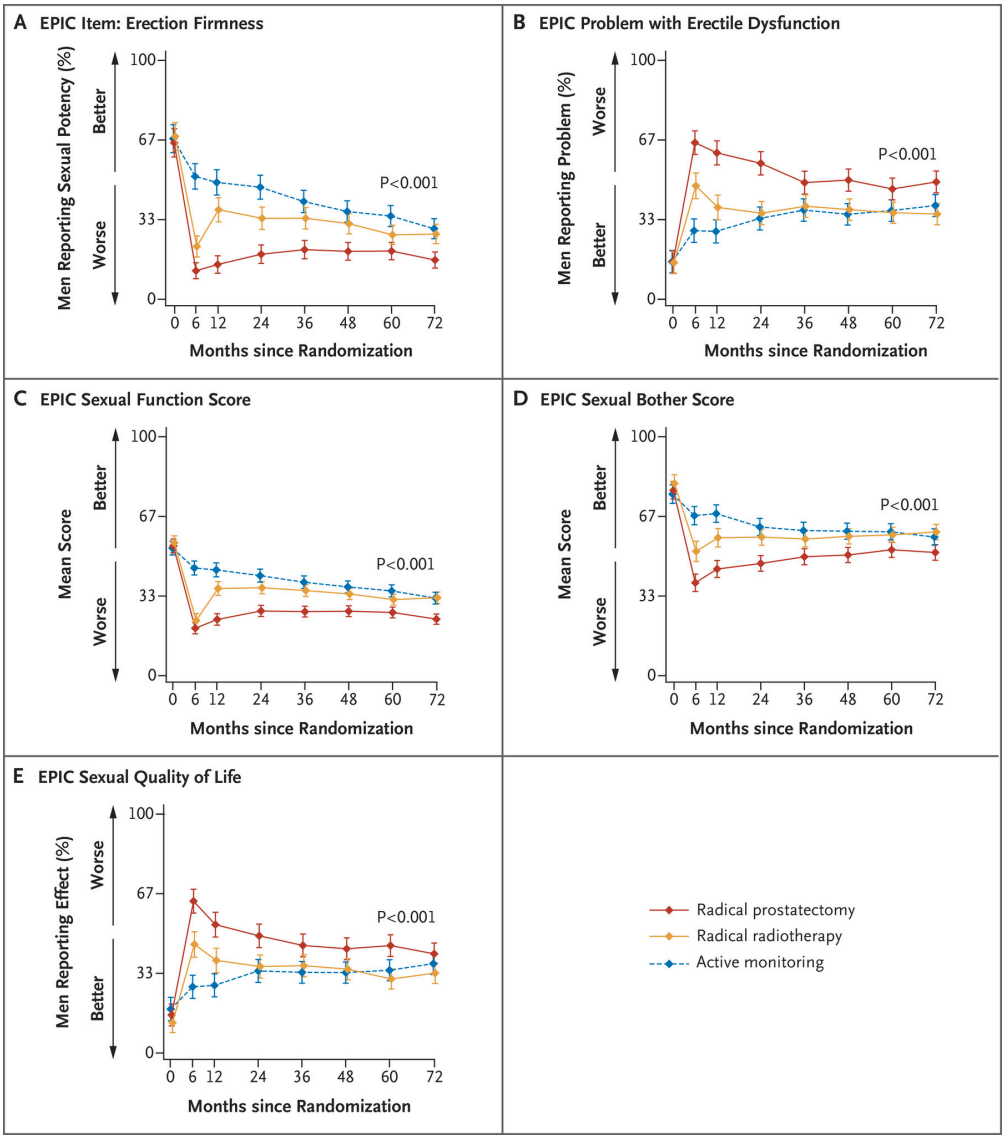


Fig. 16. **Outcomes for Sexual Function and Effect on Quality of Life.**
Reproduced with permission, Copyright Massachusetts Medical Society (80).

QUANTEC recommend keeping the mean dose to 95% of the PB volume to < 50Gy (220). Damage to small vessels, nerves, and tissue fibrosis are considered to be of major importance in the development of ED (225). Rivin del Campo et al. evaluated erectile function 2 years or more after EBRT in PC patients in a review that included 8 studies

examining the relationship between PB dose and erectile function (226). An association was found in four of these studies. A reliability score was constructed with five items: potency before EBRT, questionnaire used for potency evaluation, dose range to PTV, threshold effect, and PB definition. The studies with the highest scores support the PB dose–volume constraint recommended by QUANTEC. In addition to the PB, other structures may be critical in ED development. In a phase II trial reported by Spratt et al., vessel-sparing EBRT was given to 135 men with localized PC to preserve erectile function (227). MRI and MRI angiograms were used to delineate and avoid the erectile vasculature, and patients were treated with IMRT to a total dose of 45.6-79.2Gy. The patients had a mean age of 63 years and had to score >16 on the internal index of erectile function (IIEF-5) (mild to moderate ED). The study showed that almost 90% of these patients remained sexually active 5 years after IMRT. Given the high reported proportion with preserved sexual function after 5 years, vessel-sparing IMRT appears to be more effective than both nerve-sparing radical prostatectomy and conventional EBRT (228).

In our study, the mean PB dose was significantly higher in arm A due to larger PTV margins (59.8Gy vs. 35.1Gy), and exceeded the levels recommended by QUANTEC. ED was common in both study arms, and few patients (16%) were able to complete sexual intercourse 18 months after EBRT (Table 16). The dose to PB and the frequency of comorbidity corresponded to the main findings for patients (n=228) in both arms. The majority of the potent patients (27 out of 31, 87%) had a normal level of testosterone 18 months after EBRT.

At 18 months, nearly 60% of patients with high-risk PC still used bicalutamide. Although this drug does not reduce the testosterone level, it is likely that its use contributed to the low potency rate in the total study population. Our study did not provide evidence that a radiation dose to the PB higher than the levels recommended by QUANTEC increased ED. It is still possible that the younger patients with lower comorbidity (who are currently usually selected for surgical treatment) might benefit from a reduced PB dose if treated with radical EBRT. This is important to bear in mind, since the evidence in support of selecting younger men for surgery is poor.

In conclusion, although the patients in arm B received a significantly lower PB dose, the RIC study did not reveal any effect of the reduced dose of IGRT with reduced margins on erectile

and sexual function 18 months after start of radical EBRT in combination with ET. Our study suggests that the development of ED is multifactorial and caused by age, ET, EBRT, and comorbidity. Dose to penile structures is not necessarily the critical cause of ED in this group of elderly PC patients.

9.2 Strengths and limitations

9.2.1 Internal and external validity

Internal validity is defined as the degree to which a study establishes the cause-and-effect relationship between the treatment and the observed outcome (229). The key question in internal validity is whether observed changes can be attributed to the intervention (i.e., the cause) and not to other possible causes. Randomized controlled trials are considered the gold standard for clinical investigations into the safety and efficacy of new treatment methods because of their potential to reduce selection bias. The randomized design in the RIC study ensures high internal validity. In addition, an adequate estimated sample size and very low rates of drop-outs, both at end of EBRT and 18 months after EBRT, strengthen the internal validity.

External validity is defined as causal relationships that can be generalized to different measures, persons, settings, and times (230). In contrast to internal validity, the external validity of RCTs is generally low, most often due to strict inclusion criteria. In addition, RCTs can be both expensive and time-consuming, and the relevance of the data can be limited when published as the technology develops further. Thus, the relevance of results from a clinical trial planned several years earlier may be of minor interest by the time they are published. In the RIC study, wide inclusion criteria such as an age limit of 80 years, comorbidity allowed, and no prespecified level of performance status ensures high external validity. This also applies for the implementation and conduct of the study which to a large extent reflects daily practice.

The mean age of patients undergoing radical prostatectomy in Norway is 63 years, while patients treated with EBRT have a mean age of 69 years (2). The RIC study patients were even older, with a mean age of 71.8 years. This selection bias towards the general PC

population has to be considered when interpreting the results from our studies. Nevertheless, we believe the results are valid for patients currently selected for curative EBRT in Norway due to the randomized study design. Thus, when current clinical practice in Norway is considered, we believe that the external validity of the RIC study is high. Should, however, the SPCG 15 study or other trials demonstrate that younger patients should be referred to EBRT, the external validity of the RIC trial would be reduced.

In the RIC study, 389 patients were assessed for eligibility in the inclusion period and 260 were included. The excluded group included patients with hip prostheses and contraindications to MRI. In addition, some of the patients were probably not considered for inclusion due to lack of awareness of the trial amongst professional care givers.

Place of residence might have affected the choice of treatment. Of the patients included at Ålesund Hospital, 48% had intermediate-risk PC. At St. Olavs Hospital, the equivalent figure was 30%. (Table 5). Some of the intermediate-risk patients from Ålesund may well have been suitable for surgical treatment. Patients from Ålesund are referred to St. Olavs Hospital for surgical treatment. The travelling distance between the two hospitals (300 km) could be one reason for selecting patients otherwise fit for radical surgery to EBRT at the local hospital. Baseline characteristics were balanced between treatment groups regarding risk group and center. In addition, center and risk group were included as covariates in the regression analysis in Paper I. Thus, we do not believe the high number of intermediate-risk patients included at Ålesund Hospital influenced the results reported in Paper I.

Uncertainties in delineation can be an important source of systematic errors. Dummy runs prior to EBRT are recommended in addition to the use of MRI for dose planning (231). Three dummy runs were performed prior to the start of the study, and these revealed some variance between the participating clinical oncologists and centers. In the RIC study, CT-MRI fusion was used at the physician's discretion to delineate the prostate gland. Given that the CTV volumes were similar in both arms A and B, we have no reason to believe that a difference in the use of MRI between arms introduced a bias that influenced the study results. Nevertheless, the differences in use of MRI in delineation and its impact on CTV and PTV volumes were not analyzed, which decreases the external validity of our study. However, the prostate gland and OARs were delineated by several clinical oncologists at the

two participating centers. We believe this reflects daily practice both at our center and in others with a large group of patients. In our opinion, this strengthens the external validity of the study.

In patients with localized PC, a major issue is the lack of studies demonstrating superiority of one treatment modality over another. The treatment decision is strongly associated with the specialty of the counselling clinician (232-235). A study reported by Sommers el al. showed that actual treatment choice had little correlation with the patient's preferences and instead demonstrated a strong association with clinician's specialty (233). Ideally, the patients are well informed about the risks and benefits of each treatment option, and multidisciplinary meetings are recommended prior to the final treatment decision in each case (234). The RIC study patients met an urologist at initial clinical examination, at biopsy, and at start of ET, but not all patients were discussed in a multidisciplinary team prior to treatment decision. Usually, the oncologist was consulted immediately prior to the start of EBRT. The lack of multidisciplinary meetings could have influenced the group of patients included in the RIC study if the urologist referred patients suitable for EBRT to surgical treatment.

9.2.2 Patient-reported outcome measures (PROMs)

A PROM is defined as any outcome reported directly by the patient with a subjective evaluation about disease and treatment without interpretation by clinicians or relatives (150). The aim of PROMs is to measure subjective experience gathering the patients' responses to validated questionnaires. The use of PROMs can have several benefits for cancer patients in general.

- Increased patient satisfaction (151)
- Improved patient–physician communication (152)
- Increased symptom discussion and intensified symptom management (153)
- Improved symptom control (154)
- Improved QoL (155)

Historically, side effects have been reported by professional healthcare providers applying CTCAE or similar toxicity scoring systems. Several studies have shown only a modest

correlation between PROMs and CTCAE scoring (156-160). A review by Atkinson et al. showed moderate agreement between CTCAE and PROMs in cancer patients in general and recommended integrating PROMs into the clinical reporting of adverse effects (160). A review by Holch et al. demonstrated an underrepresentation of PROMs in RCTs on acute and late adverse effects after RT for PC. The review recommends that PROMs be used to evaluate RT throughout the whole time course of RT (161).

PC was the first cancer for which a therapy was approved based on improvement measured by PROMs alone. In a study published in 1999, Osoba et al. randomized 161 patients with castrate-resistant PC into a group that received mitoxantrone intravenously plus prednisolone and a control group that received prednisolone alone (162). They observed no difference in OS, but the group receiving mitoxantrone had superior global QoL and pain control. This introduced a new era in the use of PROMs in clinical studies. PROMs are continuously being developed, modified, and adapted to new treatments. Technical advancements such as the use of computer-based systems and smartphone applications for completing the questionnaires have recently been introduced. These can simplify daily clinical work, be easier for patients, and reduce paperwork (163).

The EORTC QLQ-C30 is a frequently used measure for self-reported HRQoL in cancer patients worldwide (171, 172). The QUFW-94 questionnaires used in our study were developed to assess the HRQoL of cancer patients in general and to evaluate side effects experienced by PC patients following pelvic RT. The SPCG research group (including members of our local research group) have used the QUFW-94 previously in large randomized trials and in validity trials (5, 178). Thus, the questionnaire is well known in our research group and chosen for the RIC study.

We consider the use of PROMs with high response rates to the questionnaires as one of the major strengths of our study. Unfortunately, we do not have data on GI symptoms, GU symptoms, sexual function, or QoL before the start of neoadjuvant ET. These data might have given additional information that would have been useful in interpreting the results. Some previous studies have tried to investigate the pre-RT status of symptoms by scoring them retrospectively (236). However, collecting data retrospectively was considered unreliable and was not performed in this study.

9.2.3 Relevance of endpoints

Late toxicity and OS may be considered to be the most important outcomes in PC studies. However, these outcomes demand at least 5-10 years of follow-up and/or large study samples. Although radical RT in PC is well tolerated in general, several studies report a high correlation between acute and late rectal side effects (10-12, 181, 237). In a review reported by Peach et al., 13 of 19 studies demonstrated an association between acute and late complications (12). The studies showing no such association tended to have smaller sample sizes. The authors conclude that the overwhelming majority of published studies supports an association between acute and late GI toxicity after RT for localized PC. The authors also suggest that acute toxicity may be considered a surrogate for late GI toxicity and that scoring of acute toxicity can be used to identify patients at high risk of late GI toxicity (12). Given these assumptions, the primary endpoint in the RIC study, acute rectal side effects at the end of RT as measured by QUFW94, may be a valid proxy outcome for late rectal side effects after radical RT in PC patients. To conclude, however, we have to await the analysis of the late toxicity data from the RIC trial. These analyses might affect the conclusions presented in this thesis.

Tight margins may have potential for reduced disease control through lack of target volume coverage and increased risk of geographical miss, especially in patients with distended rectum at the time of the dose-planning CT (140, 148, 197, 198). In the RIC study, the CTV to PTV margins were 7 mm, which corresponds well with the recommended margins when daily imaging and fiducial markers are applied (124, 194-196). Due to the low symptom burden and high tolerability reported at the end of EBRT in both arms of the RIC study, the need for further reduction in PTV margins could be unnecessary, especially as it may affect disease control.

Secondary endpoints in the RIC study were freedom from biochemical progression at 3 years from randomization, according to the ASTRO definition (nadir + 2ng/ml) (164), acute GU side effects at end of EBRT, OS, PC-specific survival, and late GU and rectal side effects at 5 and 10 years as measured by EORTC QLQ-C30 and QUFW94. All these endpoints are frequently used in RCTs involving PC patients and are considered relevant (238). Longer follow-up is needed to confirm the results of the RIC study.

In Paper II, we analyzed RVV during 8 weeks of radical EBRT to observe whether the percentage of irradiated RV was reduced or increased compared to the initial rectal dose on the planning CT. In 30 consecutive patients, eight CBCT scans (slice thickness 2 mm) obtained at fraction numbers 1, 6, 11, 16, 21, 26, 31 and 36 (CBCT1-8) were analyzed. The merging of the planning CT and the eight CBCTs was based on the fiducial markers, which might have differed to some extent from the applied clinical shift. Still, we believe the estimated dose in the CBCT is close to the actual delivered dose and representative for irradiated RV. Similar studies have been performed using one to eight CBCTs during EBRT, and we believe our choice to use 1 CBCT scan obtained each treatment week and to compare them with the dose-planning CT scan gave a representative and realistic sample with which to estimate the true RVV during EBRT in PC patients (126, 165, 167).

Previous studies on RVV have included few patients (n=10-24) and have not reported on toxicity (165-168). In this side-study to the RIC trial, analysis of toxicity and side effects were not preplanned due to the small sample size and thus not carried out.

In Paper III, we analyzed erectile function 18 months after start of EBRT. As QUFW94 is analyzed as single-item results in most studies, we chose one single item as primary outcome (178, 239) . This single item was the question “Can you get an erection?” which is closest to the EAU’s definition of ED, the persistent inability to attain and maintain an erection sufficient to permit satisfactory sexual performance, and was considered a relevant outcome (240). Secondary outcomes were eight additional questions regarding sexual activity from the QUFW94 questionnaire and the impact of dose to PB on sexual function.

The addition of ET to RT has improved survival in PC patients significantly, although at a cost of acute and late side effects such as ED (59-61). The reported median time to normalization of testosterone level after medical castration range between 18.3 and 25 months, depending on duration and substance used (241, 242). We evaluated erectile function 18 months after inclusion, when 71% of the study population had regained testosterone levels within normal range. Even though recovery of normal testosterone levels is achieved in the majority following medical castration, a large proportion still report impotence (243). Most likely, the proportion of patients with normal testosterone levels was higher at 24 months, with a possible favorable effect on potency. In addition, nearly 60% of the patients still used

bicalutamide 18 months after EBRT. Although bicalutamide does not reduce testosterone levels, a well-known side effect is reduced sexual function. If analyzed at 24 months, the grade of ED might have been lower. On the other hand, the gradual decline of erectile function is often caused by increasing age and onset of late radiation side effects, thus causing an opposing tendency (80). In conclusion, we believe that the possible difference between ED figures at 24 months and those obtained at 18 months in this study will be marginal.

The estimated prevalence of ED in the general population ranges between 50 and 100% in men older than 70 years (217). It is reasonable to assume that elderly and comorbid patients cured from cancer, such as the RIC study patients, are less concerned about reduced sexual function than younger patients with active sexual lives. Accordingly, concern about ED is important when a treatment option is decided and contributes to the current tendency to select younger PC patients for surgery.

In 2010, QUANTEC published a special edition with a collection of reviews focusing on summaries of dose, volume, and outcome information for different OARs, replacing the previous publication of 1991 by Emami (244, 245). Roach et al. reported radiation dose–volume effects and clinical outcomes regarding PB (220). They identified ten studies assessing the correlation between EBRT dose, irradiated PB volume, clinical factors such as age, ET and comorbidity, and ED. Most studies showed an association between impotence and dosimetric parameters. The authors suggest the mean dose should be restricted to 95% of the PB volume < 50Gy, and the D70 and D90 should be limited to 70Gy and 50Gy respectively (220). Although not all studies show a correlation between PB dose and ED, we considered dose to PB to be a well-known surrogate marker for RT-induced damage to structures critical for erectile function (220). The dose to PB was significantly higher in arm A than in arm B (mean 59·8Gy vs mean 35·1Gy). However, there was no association between radiation dose to the PB and erectile function in the RIC study population. In this group of elderly and comorbid men treated with RT and ET, we suggest that dose to PB has limited impact on the development of ED.

The main limitation of Paper III is the missing data on sexual function prior to start of ET. Collecting data on erectile function retrospectively was considered unreliable. Presumably,

due to high age and comorbidity, a large portion of the patients in our study had reduced sexual function before the start of ET, and the impact of EBRT on developing ED would be smaller. To determine whether dose to penile bulb is related to ED, a more optimal study design might have been only to randomly assign patients without ED prior to EBRT to study therapy.

9.3 Discussion of the thesis

Radical RT in PC is in generally well tolerated (5, 6, 179). Our results from the RIC study reported in Paper I support this and demonstrate a low grade of side effects independently of the size of the PTV margin. Furthermore, the results indicate that further reduction in PTV margins should be avoided due to tolerable side effects and the risk of decreased disease control.

Results reported in Paper II suggest that dose to the RV is stable throughout the treatment period. These findings support the results reported in Paper I demonstrating minimal rectal side effects in patients treated with daily CBCT-IGRT. In addition, the results reported in Paper III emphasize that there were no detectable difference in side effects between groups at 18 months as the frequency of ED was similar in both study arms.

The level of evidence supporting improved clinical outcomes when comparing modern IGRT to standard EBRT is low. Whether the scientific evidence is yet sufficient to change clinical practice is questionable (9, 147, 148). Nevertheless, IGRT has been included in daily routine practice at a number of centers (139, 198). Several reasons might support introducing new technology into daily clinical routine despite limited scientific evidence. Compared to EBRT, modern radiation techniques (IMRT, SBRT and VMAT) have increased the need for improved imaging and QA due to a more complex, detailed, and geometrically more precise dose distribution. Without image guidance, these techniques may result in unintended irradiation of OARs, leading to unnecessary toxicity, insufficient target dose, and reduced disease control. In addition, the increasing use of IGRT in routine RT is probably based on the subjective opinions of professional healthcare givers rather than strict scientific evidence. A survey conducted among physician members of the American Society for Radiation Oncology (ASTRO) revealed a high prevalence of IGRT and frequent use of daily CBCT (246). However,

there was no association between IGRT frequency and Planning Target Volume (PTV) margins. The conclusion was that consensus guidelines and further evidence-based approaches for PTV margin selection are needed to ensure safe and cost-effective use of IGRT. We believe the results of the RIC trial are an important contribution to the evidence base called for by this ASTRO publication.

Participation in clinical trials including RT often demands application of modern IGRT even though the scientific evidence supporting improved patient outcome is almost absent. Even though such clinical trials might explore relevant research questions, demanding IGRT will increase the likelihood of implementing IGRT into routine clinical practice.

Implementing IGRT into clinical practice results in additional costs (247). A randomized cost analysis reported by Perrier et al. showed a mean cost per treatment course of € 679 when daily CBCT was performed versus € 187 for weekly CBCT for EBRT in PC patients (248).
At the start of the RIC study, the estimated time spent on daily CBCT was discussed, as it prolonged the daily treatment by several minutes. However, thanks to rapid technological development, this is now of minor concern, as both the treatment time and time spent on CBCT has decreased significantly. This is also an argument in the cost debate, as less time spent in the treatment room for each patient allows the treatment of more patients in total. The argument of reduced costs is also emphasized with the increasing use of hypofractionated EBRT, which potentially decreases treatment costs and reduces the patients' time away from daily life. Nevertheless, the cost of CBCT equipment investment will surpass the investments attached to orthogonal verification by far. In addition, the cost of training and education of RT personnel support the findings of Perrier et al. (248).

In general, modern technology in healthcare is an important driver of health-care costs. Novel cancer drugs are subject to strict scientific evaluation of safety and efficacy and usually undergo a cost effectiveness analysis before approval for use in clinical practice. This scientific evaluation is often not performed for new techniques in RT. Compared to such other medical cancer treatments as immunotherapy, the costs in RT are low.

The lack of evidence-based research in RT has been referred to as the "Catch-22" of RT. This relates to the rapid development and performance of valid clinical research, which can be

both expensive and time consuming. Even though a clinical trial in RT may be well planned and highly relevant at patient inclusion, the technology develops further, and the relevance of results from a clinical trial planned several years earlier may be of minor interest by the time they are published, especially for trials with long term follow-ups. Thus, the cycle of implementing new methods into clinical practice without sufficient scientific evidence of improved patient outcome starts again. It is noteworthy that we have not been able to demonstrate any clinical benefit from extended use of IGRT and reduced PTV margins for the RIC study patients so far. Whether this fact will be relevant for late side effects after PC RT remains to be seen. Even though one might argue that the results of this thesis only apply to "old fashioned RT" and the relevance of the results from the RIC study can be debated, they underline the need for technical medical innovations to be thoroughly evaluated in controlled clinical trials with long-term follow-up.

10. Conclusion

In a study population representative of Norwegian men who currently receive curative EBRT for PC, CBCT-IGRT did not add important clinical improvements beyond those of weekly orthogonal verification. Furthermore:

- There was no difference in patient-reported rectal toxicity, GU toxicity, or HRQoL at the end of EBRT between PC patients treated to 78Gy with daily CBCT-IGRT and tighter PTV margins and patients treated with weekly orthogonal verified EBRT and wider PTV margins.

- The rectal volume decreased significantly during the EBRT period in 30 patients receiving EBRT for PC with tight PTV margins and daily CBCT-IGRT. The percentage of irradiated rectal volume was close to constant during the 8 weeks of treatment

- Erectile function was similar in PC patients 18 months after the start of radical EBRT with either daily CBCT-IGRT and tight PTV margins or weekly orthogonal verified EBRT with wider PTV margins. There was no association between mean dose to the PB and erectile function at 18 months.

11. Future perspective

Since the completion of the RIC study, several changes in PC treatment have been implemented at our clinic. Several of the implementations are state-of-the-art recommendations, and some are local adjustments.

ET: High-risk patients receive 6 months of TAB and additional 18 months of bicalutamide, reducing the total ET time from 36 to 24 months. This is based on a study reported by Nabid et al., which demonstrated that 18 months of ET gave fewer side effects with the same OS and disease-specific survival as 36 months of ET (249). Local adjustments have been made in the ET treatment at our clinic.

EBRT: Intermediate-risk patients receive hypofractionated EBRT with 3Gy × 20 to the prostate gland, based on a publication by Catton et al. (108). Their study included 1206 patients with intermediate-risk PC who were randomized in two arms and received either 60Gy in 20 fractions or 78Gy in 39 fractions. Median follow-up was 6.0 years and the 5-year BCF disease-free survival rate was 85% in both arms with no difference in grade ≥3 toxicity. High-risk patients are treated with moderate hypofractionation and SIB with 2.2Gy x 35 to the prostate/extra prostatic extension and 2Gy x 35 to seminal vesicles as a local adjustment according to the SPSC 15 protocol. If the risk of lymph node metastasis is > 20% according to the Memorial Sloan Kettering Cancer Center (MSKCC) nomogram (https://www.mskcc.org/nomograms/prostate/pre_op), the patient is offered adjuvant pelvic EBRT with 1.6Gy × 35, even though this is not recommended by the EAU (250).

EBRT is given with VMAT with daily imaging and fiducial gold markers. The margins from CTV to PTV are 5 mm (left-right) and 7 mm (anterior-posterior and superior-inferior).

Several new medical and technological innovations have been introduced into RT. In 2015, Mariados et al. published a study evaluating the use of a hydrogel spacer (SpaceOAR system) in a blinded prospective multicenter randomized trial including patients with stages T1 and T2 PC (Fig. 18) (205). The study showed that the hydrogel was well tolerated and the perirectal space increased, leading to reduced rectal toxicity and increased QoL. Follow-up studies have shown a sustained benefit regarding toxicity (251, 252).

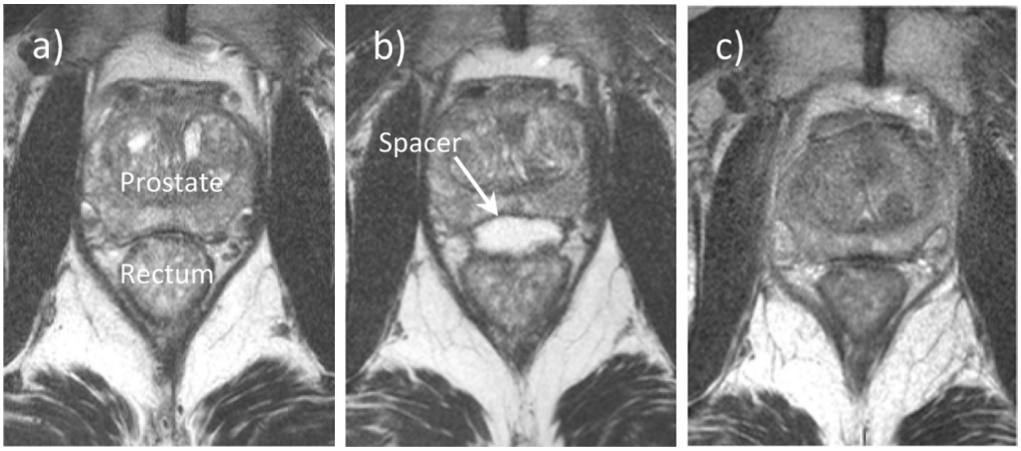


Fig. 18. T2-weighted magnetic resonance images of a spacer patient at baseline (a), post-application (b), and 12 months after spacer application (c). Printed with permission (205)

PET using prostate-specific membrane antigen (PSMA) as a tracer has been shown to be superior to standard routine imaging in lymph node staging (253-257). Adaptive treatment with fast online replanning can be utilized to eliminate daily variation (258). MRI linear accelerators enables biological planning dose distribution, adaptive planning, and intrafraction verification and suggests a safe reduction of the CTV–PTV margin to 3 mm (259). Furthermore, SBRT can also increase the therapeutic ratio (111, 260, 261).

The need for modern IGRT increases with hypofractionated EBRT and reduced safety margins. In 2013, Jaffray et al. published a study on safety considerations for the use of IGRT (Table 17) (262). As those authors state: “Failure to properly apply IGRT methods or to coordinate their use with an appropriate PTV margin can result in a treatment that is ‘precisely wrong’” (262). These considerations should be implemented in every RT department. Although IGRT systems are now excellent and precise, other uncertainties such as variation in tumor, OAR delineation, and patient positioning should not be forgotten.

Recommendation
1. Establish a multi-professional team responsible for IGRT activities.
2. Establish and monitor a program of daily, monthly, and annual QA for all new or existing IGRT sub-systems.
3. Provide device- and process-specific training for all staff operating IGRT systems or responsible for IGRT delivery.
4. Perform 'end-to-end' testing for all new IGRT procedures (from simulation to dose delivery) and document performance prior to clinical release.
5. Establish process-specific documentation and procedures for IGRT.
6. Clearly identify who is responsible for approval of IGRT correction decision and the process whereby this decision is made and documented.
7. Establish and document site-specific planning procedures; specifically, the procedure for defining PTV margins. Link these planning procedures to IGRT procedures.
8. Multi-professional peer-review of PTV volumes. Peer-review of GTV/CTV volumes by ROs.
9. Verify proper creation and transfer of IGRT reference data (PTV, OARs, DRRs, etc) to IGRT system.
10. Establish a reporting mechanism for IGRT-related variances in the radiation treatment process.

GTV/CTV, gross tumor volume/clinical target volume; IGRT, image guided radiation therapy; PTV, planning target volume; OARs, organs at risk; QA, quality assurance; ROs, radiation oncologists.

Table 17. Recommendations to establish a foundation for safe and effective IGRT practices. Reprinted from Practical Radiation Oncology, Vol 3, Jaffray et al., Safety considerations for IGRT: Executive summary, 167-170, Copyright (2013), with permission from Elsevier (262).

The prevalence of cancer patients in Norway has increased dramatically. In 2016, >260,000 patients lived with a previous cancer diagnosis, compared to just 178,000 in 2006 (1). The total costs of cancer care in Norway (excluding the value of lost years), were estimated to be almost 40 billion Norwegian Kroner (NOK) in 2014 (> 4 billion Euro) (263). New and prolonged treatment options for the patients can result in a need for closer follow-up and increased pressure on both outpatient clinics and oncology wards. It is noteworthy that the differences in availability of RT equipment worldwide are substantial, and many cancer patients will never benefit from modern RT treatment. A survey by ESTRO Health Economics in Radiation Oncology (ESTRO-HERO) found that 12 out of the 27 countries used cobalt machines (264). In Norway, the use of cobalt machines was discontinued in 2000 (Sverre Levernes, Norwegian Radiation Protection Authority, personal communication). In the future, the distribution of resources will be challenging, as both the PC patient population

and the medical and technical innovations available will increase and thus increase costs. Tools and systems will be needed to select individuals in need of extra follow-up after cancer treatment. A review by Peach et al. suggests that acute GI toxicity may be used to identify PC patients in need of medical intervention and closer follow-up to prevent late toxicity (12).

Several questions remain unanswered in our study. Whether there will be a difference in late side effects, OS, freedom from biochemical progression, and HRQoL remains to be seen; the patients will be followed for ten years. In addition, the RIC study still seeks to answer several other interesting research questions.

- Will there be a difference in secondary cancer between groups?
- Is there a difference in CTV between patients delineated in MRI and those delineated in CT?
- Will a difference in delineated volume between MRI and CT lead to a difference in toxicity score in PC patients?
- What is the association between PROMs and clinician-based CTCAE?

The optimal way of treating PC patients is still being debated in 2018. In the ProtecT study, the authors compared active monitoring, radical prostatectomy, and 3D conformal EBRT for clinically localized PC and found a low PC-specific mortality (1%) with no difference among groups at 10 years (8). As previously mentioned, there is no level I evidence comparing RP and EBRT in high-risk patients, but an ongoing trial by the SPCG (SPCG 15, ClinicalTrials.gov identifier: NCT02102477) will address this. Whether hypofractionated EBRT with a BT boost could provide an additional advantage for side effects and disease control is also of interest. Randomized trials including high-risk PC patients that compare hypofractionated EBRT with a BT boost to VMAT and integrated boost are feasible and appealing. In addition, new trials randomizing node-negative patients to pelvic irradiation or not could be of interest in the new era of hypofractionated EBRT, especially when combined with VMAT and IGRT methods. Studies of target volume delineation in MRI and the use of the SpaceOAR system could also be of interest and feasible at our institution. OS is high in non-metastatic PC patients, and late side effects after treatment could be addressed as research questions in future studies.

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13. Appendix

EORTC QLQ C30

QUFW94

EORTC QLQ-C30

EORTC QLQ-C30

(Versjon 3.0)

Mnd [ ][ ][0] [1][0][0][5]

Dato: [ ][ ].[ ][ ].[ ][ ][ ][ ]

Pasientens initialer: [ ][ ][ ]

Vi er interessert i forhold vedrørende deg og din helse. Vær så vennlig å besvare hvert spørsmål ved å sette et kryss x i den boksen som best beskriver din tilstand. Det er ingen «riktige» eller «gale» svar. Alle opplysningene vil bli behandlet konfidensielt.

	Ikke i det hele tatt	Litt	En del	Svært mye
1. Har du vanskeligheter med å utføre anstrengende aktiviteter, slik som å bære en tung handlekurv eller en koffert?	☐	☐	☐	☐
2. Har du vanskeligheter med å gå en lang tur?	☐	☐	☐	☐
3. Har du vanskeligheter med å gå en kort tur utendørs?	☐	☐	☐	☐
4. Er du nødt til å ligge til sengs eller sitte i en stol i løpet av dagen?	☐	☐	☐	☐
5. Trenger du hjelp til å spise, kle på deg, vaske deg eller gå på toalettet?	☐	☐	☐	☐

I løpet av den siste uka:	Ikke i det hele tatt	Litt	En del	Svært mye
6. Har du hatt redusert evne til å arbeide eller utføre andre daglige aktiviteter?	☐	☐	☐	☐
7. Har du hatt redusert evne til å utføre dine hobbyer eller andre fritidsaktiviteter?	☐	☐	☐	☐
8. Har du vært tung i pusten?	☐	☐	☐	☐
9. Har du hatt smerter?	☐	☐	☐	☐
10. Har du hatt behov for å hvile?	☐	☐	☐	☐
11. Har du hatt søvnproblemer?	☐	☐	☐	☐
12. Har du følt deg slapp?	☐	☐	☐	☐
13. Har du hatt dårlig matlyst?	☐	☐	☐	☐
14. Har du vært kvalm?	☐	☐	☐	☐

Bla om til neste side

Mnd | | 0 | 1 | 0 | 0 | 5 |

I løpet av den siste uka:	Ikke i det hele tatt	Litt	En del	Svært mye
15. Har du kastet opp?	☐	☐	☐	☐
16. Har du hatt treg mage?	☐	☐	☐	☐
17. Har du hatt løs mage?	☐	☐	☐	☐
18. Har du følt deg trett?	☐	☐	☐	☐
19. Har smerter påvirket dine daglige aktiviteter?	☐	☐	☐	☐
20. Har du hatt problemer med å konsentrere deg, f.eks. med å lese en avis eller se på TV?	☐	☐	☐	☐
21. Har du følt deg anspent?	☐	☐	☐	☐
22. Har du vært engstelig?	☐	☐	☐	☐
23. Har du følt deg irritabel?	☐	☐	☐	☐
24. Har du følt deg deprimert?	☐	☐	☐	☐
25. Har du hatt problemer med å huske ting?	☐	☐	☐	☐
26. Har din fysiske tilstand eller medisinske behandling påvirket ditt familieliv?	☐	☐	☐	☐
27. Har din fysiske tilstand eller medisinske behandling påvirket dine sosiale aktiviteter?	☐	☐	☐	☐
28. Har din fysiske tilstand eller medisinske behandling gitt deg økonomiske problemer?	☐	☐	☐	☐

Som svar på de neste spørsmålene, sett et kryss i den boksen fra 1 til 7 som best beskriver din tilstand.

29. Hvordan har din helse vært i løpet av den siste uka?

☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7

Svært dårlig — Helt utmerket

30. Hvordan har livskvaliteten din vært i løpet av den siste uka?

☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7

Svært dårlig — Helt utmerket

QUFW94

Dato for utfylling ☐☐.☐☐.20☐☐ Mnd ☐☐ 10 2005

Besvares ved å markere med "X" i den boksen som best beskriver din situasjon DEN SISTE UKEN

31. Begrenser din prostatakreft deg i dine daglige gjøremål?

Ikke noe	0	1	2	3	4	5	6	7	8	9	10	Svært mye
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	

32. Har du andre sykdommer som begrenser din daglige aktivitet?

☐ Ja ☐ Nei

Hvis ja, hvilke sykdommer .....

33. Har du brukt medisiner for å regulere avføringen?

☐ Ja ☐ Nei

Hvis ja, hvilke medisiner, styrke og hvor mange pr dag .....

34. Hvordan har din evne til å ta initiativ vært?

Meget bra	0	1	2	3	4	5	6	7	8	9	10	Meget dårlig
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	

35. Har du hatt plager med urinveiene?

Ikke noe	0	1	2	3	4	5	6	7	8	9	10	Svært mye
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	

36. Hvor mange ganger har du på det meste måttet late vannet pr DAG? ☐☐

37. Hvor mange ganger må du opp om natten for å late vannet? ☐☐

38. Har du hatt svie eller smerte når du måtte late vannet?

Ikke noe	0	1	2	3	4	5	6	7	8	9	10	Svært mye
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	

39. Måtte du vente lenge før vannlatingen kom i gang?

Ikke noe	0	1	2	3	4	5	6	7	8	9	10	Svært mye
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	

Mnd | | 0 | 1 | 0 | 0 | 5 |

40. Har du hatt urinlekkasje (inkontinens)?

Ikke noe	0	1	2	3	4	5	6	7	8	9	10	Svært mye
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	

41. Har du brukt bleier (pga urinlekkasje)?

☐ Ja ☐ Nei Antall pr dag: | |

42. Opplevde du mer eller mindre kontinuerlig vannlatingstrang?

Ikke noe	0	1	2	3	4	5	6	7	8	9	10	Svært mye
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	

43. Har du hatt blod i urinen?

Ikke noe	0	1	2	3	4	5	6	7	8	9	10	Svært mye
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	

44. Har du brukt kateter?

☐ Ja ☐ Nei

45. Hvor mye har dine eventuelle urinveisproblemer påvirket din daglige aktivitet?

Ikke noe	0	1	2	3	4	5	6	7	8	9	10	Svært mye
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	

46. Dersom du har hatt plager med urinveiene, hva har plaget deg mest?

.....

47. Har du hatt problemer med avføringen?

Ikke noe	0	1	2	3	4	5	6	7	8	9	10	Svært mye
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	

48. Hvor mange ganger måtte du på det meste gå på do (avføring) pr døgn? | |

49. Hvordan var konsistensen på avføringen?

Meget løs	0	1	2	3	4	5	6	7	8	9	10	Meget hard
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	

Mnd | | 0 | 1 | 0 | 0 | 5 |

50. Hadde du avføringslekkasje?

Ikke noe	0	1	2	3	4	5	6	7	8	9	10	Svært mye
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	

51. Medførte ditt avføringsproblem at du måtte planlegge dine toalettbesøk?

Ikke noe	0	1	2	3	4	5	6	7	8	9	10	Svært mye
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	

52. Har du hatt problemer med mye luft i magen?

Ikke noe	0	1	2	3	4	5	6	7	8	9	10	Svært mye
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	

53. Har du brukt bleie (pga avføringslekkasje)?

☐ Ja ☐ Nei Antall/dag | |

54. Har du hatt smerter ved avføring?

Ikke noe	0	1	2	3	4	5	6	7	8	9	10	Svært mye
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	

55. Har du hatt slim i avføringen?

Ikke noe	0	1	2	3	4	5	6	7	8	9	10	Svært mye
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	

56. Har du hatt blod i avføringen?

Ikke noe	0	1	2	3	4	5	6	7	8	9	10	Svært mye
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	

57. Har du spist spesiell mat for å regulere avføringen?

☐ Ja ☐ Nei Hvis ja: ☐ Fettfattig
☐ Fiberrik kost
☐ Mat uten melk
☐ Annet

Mnd | | 0 | 1 | 0 | 0 | 5 |

58. Hvor mye har ditt avføringsproblem påvirket din daglige aktivitet?

Ikke noe	0	1	2	3	4	5	6	7	8	9	10	Svært mye
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	

59. Dersom du har vært plaget med avføringen, hva har plaget deg mest?

.....

.....

60. Har du opplevd problemer med ditt seksualliv?

Ikke noe	0	1	2	3	4	5	6	7	8	9	10	Svært mye
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	

61. Har du hatt noen partner (gift, samboer)?

☐ Ja ☐ Nei

62. Har du følt lyst til seksuell aktivitet?

Svært mye	0	1	2	3	4	5	6	7	8	9	10	Ikke noe
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	

63a. Har du hatt ereksjon (reisning)?

Svært mye	0	1	2	3	4	5	6	7	8	9	10	Ikke noe
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	

63b. Har du fått ereksjon (reisning) uten hjelpemiddel?

Svært mye	0	1	2	3	4	5	6	7	8	9	10	Ikke noe
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	

64a. Var ereksjonen (reisningen) tilstrekkelig til å gjennomføre samleie?

☐ Ja ☐ Nei

64b. Var ereksjonen tilstrekkelig uten hjelpemiddel til å gjennomføre samleie?

☐ Ja ☐ Nei

Mnd [ ][ ]0 1 [0][0][5]

64c. Har du brukt noe hjelpemiddel for å gjennomføre samleie?

☐ Alltid ☐ Sjelden ☐ Ikke i det hele tatt

☐ Ja ☐ Caverject ☐ Nei, gå til spørsmål 65
☐ Bondil
☐ Viagra (tablett)
☐ Uprima (tablett)
☐ Annet _____

64d. Kan du få ereksjon (reisning) med hjelpemiddel?

Svært mye	0	1	2	3	4	5	6	7	8	9	10	Ikke noe
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	

64e. Er ereksjonen tilstrekkelig (med hjelpemiddel) til å gjennomføre samleie?

☐ Ja ☐ Nei

65. Hvor mange ganger har du hatt samleie den siste ..

Uken [ ][ ] Måneden [ ][ ] Året [ ][ ] Mer enn et år siden ☐

66. Dersom du har opplevd problemer med seksuallivet, hva plager deg mest?

.....

.....

67. Har du hatt ømme bryst/brystvorter?

Ikke noe	0	1	2	3	4	5	6	7	8	9	10	Svært mye
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	

68. Har du lagt merke til om brystene dine er blitt større?

Ikke noe	0	1	2	3	4	5	6	7	8	9	10	Svært mye
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	

69. Synes du noen av spørsmålene er vanskelige å svare på?

Hvis ja, hvilke: .....

.....

12864

Takk for at du tok deg tid til å svare på spørsmålene!

Paper I

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Phase III randomised trial

Radiotherapy for prostate cancer – Does daily image guidance with tighter margins improve patient reported outcomes compared to weekly orthogonal verified irradiation? Results from a randomized controlled trial

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ABSTRACT

Background: Novel cancer drugs are subject to strict scientific evaluation of safety and efficacy and usually undergo a cost effectiveness analysis before approval for use in clinical practice. For new techniques in radiotherapy (RT) such as image-guided radiotherapy (IGRT), this is often not the case. We performed a randomized controlled trial to compare daily cone beam computer tomography (CBCT) IGRT with reduced planning target volume (PTV) margins vs weekly orthogonal portal imaging with conventional PTV margins. The primary aim of the study was to investigate the effect of two different image guidance techniques on patient reported outcome (PRO) using early side effects as proxy outcome of late rectal side effects in patients receiving curative RT for prostate cancer.

Methods: This open label, phase 3 trial conducted at two RT centers in Norway enrolled men aged 18 years or older with previously untreated histologically proven intermediate or high-risk adenocarcinoma of the prostate. Patients eligible for radical RT received it after 3 months of total androgen blockage and were randomly assigned to 78 Gy in 39 fractions guided either by weekly offline orthogonal portal imaging (15 mm margins to PTV) or by daily online CBCT IGRT (7 mm margins to PTV). Based on previous results indicating that acute rectal side effects are a valid proxy outcome for late rectal side effects, the primary outcome was acute rectal toxicity at end of RT as evaluated by rectal bother scale (five of the items from PRO's QUFW94). The RIC-trial is registered with ClinicalTrials.gov, number NCT01550237.

Findings: Between October 2012 and June 2015, 257 patients were randomly assigned to weekly offline portal imaging ($n = 129$) or daily online CBCT IGRT ($n = 128$). Out of 250 evaluable patients, 96% completed PROs at baseline and 97% at end of RT. Baseline analyses demonstrated balance between groups for baseline characteristics as well as for PROs. In general, patients reported a small degree of side effects at end of RT, and there was no difference between groups for primary outcome (rectal bother scale of QUFW94 1.871 vs 1.884, $p = 0.804$). In addition, there were no significant differences between groups for any other gastrointestinal or urinary symptom as reported by QUFW94. Health related quality of life analyses (EORTC QLQ 30) demonstrated no differences between groups.

Interpretation: In radical RT for prostate cancer, daily CBCT IGRT with reduced PTV margins demonstrated no advantage with respect to patient reported side effects at end of RT as compared to weekly orthogonal offline portal imaging with standard PTV margins.

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Rectal bleeding, increased urinary frequency and loss of erection constitute common side effects of curative external beam radiotherapy (EBRT) for prostate cancer [1,2]. Previous studies have demonstrated that acute urinary and rectal side effects independently predict corresponding late radiotherapy-induced

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toxicity [3,4]. Stereotactic-Body-Radiation-Therapy (SBRT), Intensity-Modulated Radiation-Therapy (IMRT) and Volumetric-Modulated Arc-Therapy (VMAT) are examples of new techniques implemented in radiotherapy (RT) presumably to reduce such unwanted effects. However, such technological progress is rarely subjected to empirical prospective testing in well-designed clinical trials. IMRT/VMAT is now considered standard therapy for prostate cancer according to guidelines from the European Association of Urology (EAU) even though there is a lack of scientific reports providing level one evidence of clinical benefits in patients [5].

The introduction of 3-dimensional imaging techniques such as ultrasound, Computer Tomography (CT) and Magnetic Resonance Imaging (MRI) has increased understanding of internal organs motion during RT planning and delivery [6]. Moreover, IGRT using fiducial gold markers implanted in the prostate gland and 3-dimensional Cone Beam CT (CBCT) as well as the use of continuous electromagnetic monitors (e.g. Calypso®System, Seattle, Wash., USA) improves accuracy [7].

Such modern prostatic IGRT reduces the magnitude of systematic errors effectively but not random errors such as day-to-day variations in set-up positioning [8].

More exact patient positioning combined with daily CBCT of the target volume, enables safety margin reductions, radiation dose escalation and enhanced local tumor control, although at a higher cost compared to weekly CBCT-verification [9].

Several non-randomized studies have reported that modern IGRT may reduce radiation-induced toxicity in prostate cancer patients [10,11]. However, to our knowledge no randomized controlled trials (RCTs) have compared clinical outcomes following daily IGRT online vs weekly offline orthogonal portal imaging [12–15].

A survey conducted among physician members of the American Society for Radiation Oncology (ASTRO) has recently called for consensus guidelines and further evidence-based approaches for planning target volume (PTV) margin selection to ensure safe and cost-effective use of IGRT [16].

To explore the effect of different image guidance techniques on acute rectal side effects in curative EBRT for prostate cancer, we have performed a RCT comparing daily online CBCT-IGRT with reduced (PTV) margins vs weekly offline orthogonal portal imaging with conventional PTV-margins. Herein we report the results of the first analysis of patient reported outcomes (PRO) on acute gastrointestinal (GI) side effects. The RIC-trial is registered with ClinicalTrials.gov, number NCT01550237.

Methods and patients

The RIC-trial included men younger than 80 years with histologically proven intermediate or high risk non-metastatic prostate cancer [17]. Patients with metallic hip joint replacements, previous cancer treatment the last 5 years, previous RT except for kilovolt (kV) treatment outside the pelvis, patients unable to perform a magnetic resonance imaging (MRI) or patients with abnormal kidney or liver function were excluded. Patients were enrolled at two centers in Mid-Norway; Department of Oncology, Ålesund Hospital, and The Cancer Clinic, St. Olav's Hospital, Trondheim University Hospital. Randomization was computer based, stratified by center and risk (high vs intermediate) group. All patients received 6 months of total androgen blockage (TAB) with Gosereline acetate and Bicalutamide started 3 months neo-adjuvant prior to prostatic irradiation with 78 Gy in 2 Gy's fractions. High-risk patients received Bicalutamide for an additional 2.5 years. Four prostatic gold fiducial markers were implanted during the neo-adjuvant period. Approximately one week before radiotherapy, patients giving their written informed consent were randomly assigned to receive 0–70 Gy RT in which position control was done by weekly offline orthogonal portal imaging (standard treatment, arm A) or with daily CBCT verification (experimental treatment, arm B). An IGRT boost from 70 to 78 Gy with daily verification was applied in both arms. Elective pelvic nodal irradiation was not applied.

Radiotherapy planning

CT and MRI for dose planning was performed no more than 24 h apart and less than one week prior to start of RT with the same instructions for rectal and bladder filling. There were no routinely rectal emptying and participant were encouraged to urinate one hour prior to examination and drink 300 ml of water during the last hour before examination. Prescription and reporting of RT-volumes and doses were based on International Commission on Radiation Units & Measurements (ICRU) recommendations [18]. Target volume delineation was based on clinical findings; CT-scans eventually fused with T1 + T2 MRI-scans at the doctor's discretion. The following target volumes were defined:

Clinical target volume (CTV) prostate: the prostate including any suspected extra capsular tumor growth or infiltration into the seminal vesicles (SV) as described by clinical findings, transrectal ultrasound and/or pelvic MRI. The CTV-prostate/SV included the basal 1 or 2 cm of the SV in intermediate and high-risk patients, respectively.

In patients receiving standard treatment (arm A), the planning target volume (PTV2) receiving 0–70 Gy included the CTV-prostate/SV with an additional 15 mm margin in all directions. In arm B the corresponding PTV2 (0–70 Gy) included the CTV-prostate/SV with an additional 7 mm margin in all directions.

The PTV 1 (70–78 Gy) was equal to the CTV-prostate with an additional 3 mm margin in both study arms. The following organs at risk (OARs) were delineated: Rectum, defined as the outer contour of the rectal wall from the recto-sigmoid junction to the anal canal, the corresponding rectal mucosa, defined as a 2 mm thick layer limited by air on the inside. Additionally, the urinary bladder, testicles, femoral heads, anal canal and penile bulb were delineated.

CT-based, 3-D conformal treatment planning was mandatory, as were multi- leaf collimators (MLC). Using a four-field box technique with necessary supplemental field segments, 15 megavolt (MV) photon beams from 0 to 70 Gy were applied. For the 70–78 Gy boost, a 5 field (1 anterior, 2 oblique anterior and 2 lateral) technique was applied. Isocenter was placed in the fiducial gold marker located closest to the base of the prostate. The target volume doses should be within 95–107% of the prescribed dose. However, the rectal dose constraint was defined as 60 Gy to no more than half of the circumference in both study arms. If necessary, posterior blocking with MLC was accepted.

Dose–volume histograms were retrieved from the treatment planning system for rectal volumes receiving 50 Gy or more (V50 Gy) and 60 Gy or more (V60 Gy). Treatment planning was performed in Oncentra v4.3 (Elekta AB, Sweden) and patients were treated on Elekta Synergy® or Elekta Precise platforms.

Verification procedures

Study arm A: After alignment by skin markers, position was controlled by 2-D MV portal imaging of fiducial markers on treatment days 1–3. Errors smaller than 10 mm were not corrected until treatment day 4, when a summed vector calculation of the errors on days 1–3 guided total correction. After correction, position was controlled by orthogonal MV-imaging of fiducial markers once weekly and only errors exceeding 10 mm were corrected. On treatments 36–39, daily online corrections of position were performed

based on orthogonal MV-imaging of fiducial markers, as only the CTV with a small margin was treated from 70 to 78 Gy.

Study arm B: After alignment by skin markers, 3D kV imaging with CBCT of prostate with fiducial markers were performed and all localization errors corrected prior to each fraction.

Measures

Bowel symptoms (primary endpoint) and urinary symptoms (secondary endpoint) were measured using the validated self-assessment questionnaire QUFW94, aka Prostate Cancer Symptom Scale [19,20] The questionnaire utilizes a modified linear analog scale with response boxes containing numerical values between 0 and 10, where 0 = "no problem/very good function" and 10 = " many problems/very bad function". Five items from the questionnaire represent the rectal bother scale (overall bother from all bowel symptoms, stool frequency, stool leakage, planning of toilet visits and limitations in daily activity caused by bowel symptoms). The average estimate of each item is added and then divided by five. The resulting score constitutes the primary outcome measure in the present study.

The European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaire was used to evaluate health-related quality of life (HRQOL) [21]. This questionnaire consists of five functional scales: physical, role, emotional, cognitive, and social functioning. It also includes a global health status/QOL scale. Higher score on the functional scales means higher function/higher HRQOL. Three symptom scales and six symptom single items are also included. Higher score on the symptom scales/items means worse symptoms/reduced HRQOL. All calculations based on the EORTC QLQ-C30 were performed according to the EORTC guidelines [21]. The patients were asked to evaluate their symptoms during the previous week.

Statistics

The primary endpoint was acute gastrointestinal side effects at end of radiotherapy as measured by the rectal bother scale from the QUFW94 questionnaire [1,22]. Secondary endpoints included freedom from biochemical progression at 3 years from randomization defined according to ASTRO guidelines (nadir + 2 ng/ml) [23], cancer specific- and overall survival at 5 and 10 years, acute genitourinary side effects as well as late (5 + 10 years) genitourinary and rectal side effects as measured by QUFW94 and CTCv4.0.

For evaluation of the efficacy of IGRT in reducing rectal side effects, a minor clinical absolute difference between groups of 0.75 reduction in mean score of the rectal bother scale in QUFW94 in favor of study arm B patients was anticipated. Based on previous results, a mean symptom score on single item "frequency" of 3.5 with a standard deviation of 2.0 were anticipated at end of radiotherapy in the standard arm [19]. In order to detect a difference of 0.75 in symptom score with 80% power ($\alpha = 0.05$), 113 patients in each arm would need to be included. As approximately 15% (34 patients) were assumed non-evaluable, the study aimed to include 260 patients.

The statistical analysis was performed according to a pre-planned strategy:

The main analysis was regression analysis with the mean rectal bother scale at end of RT as dependent variable, and treatment group, pre-treatment mean rectal bother scale, site (Ålesund Hospital vs St. Olav's Hospital), and dichotomized risk group as covariates. [24,25]. Site and risk group were included because they were used as stratification variables in the randomization [25].

Normality of residuals was checked by visual inspection of Q-Q plots. For some of the single item measures, the residuals were slightly skewed. Hence, alternative analyses with log-transformed data were carried out.

Missing data on the five rectal bother items were singly imputed using the Expectation-Maximation algorithm with the scores on these items as predictors. Analyses were carried out blinded to treatment group. For single-item measures in QUFW94 and for health related quality of life measures (EORTC QLQ C-30) the regression analysis was performed on available cases, data not imputed.

For primary outcome (rectal bother scale), significance level was set at 0.05, for all other HRQOL scales and symptoms, the level was 0.01 due to multiple outcomes measuring similar constructs.

Irradiated volumes (V50 Gy and V60 Gy) were compared between treatment groups using Student's t-test assuming unequal variances.

Results

From October 2012 to June 2015, 260 (St. Olavs Hospital 131 and Ålesund Hospital 129) patients were included. Three erroneously included patients not fulfilling the inclusion criteria were not randomized and seven additional patients who did not finish RT for reasons other than side effects were excluded from the final analyses (Fig. 1, consort diagram). Baseline characteristics were balanced between treatment arms (Table 1). The patients were balanced regarding height, weight, and comorbidities (diabetes mellitus, gastrointestinal, kidney and liver disease), data not shown. Out of 250 evaluable patients, 239 (96%) and 241 (97%) returned the QUFW94 and EORTC-QLQ C30 at baseline and at end of RT, respectively. The patients reported low degree of gastrointestinal side effects. There was no significant difference between groups for primary outcome (rectal bother scale 1.871 vs 1.884, $p = 0.804$) (Table 2). Although there was a trend toward increased nocturia in arm B (mean 3.73 in arm A vs mean 4.37 in arm B, $p = 0.020$), and hematuria in arm A (mean 0.36 in arm A vs mean 0.10 in arm B, ($p = 0.040$), the differenced did not reach the pre specified level of statistical significance ($p < 0.01$). In addition, there were no differences between groups for any other urinary or gastrointestinal symptoms as measured by QUFW94.

HRQOL analyses demonstrated no differences between groups (Table 3).

Secondary analysis with log transformed data were carried out for the single-item measures with slightly skewed residuals. These secondary analyses gave essentially the same results as for untransformed data (data not shown).

The volume (cm^3) of CTV2 (0–70 Gy) did not differ between the two treatment groups (Table 4).

Analyses of dose volume histograms (DVHs) demonstrated that the volume (cm^3) of PTV2 (0–70 Gy) was, as expected, significantly larger in patients in arm A receiving EBRT with standard PTV2 margins of 15 mm in all directions compared to patients in arm B with reduced PTV2 margins (7 mm in all directions) (Table 4). Posterior shielding with MLC because of the 60 Gy rectal dose constraint to no more than half of the rectal circumference was applied frequently in arm A. Still, V50 Gy. V60 Gy and V70 Gy to the rectal volume and V66.5 Gy to PTV2 (0–70 Gy) were significantly larger in arm A (mean PTV2 270.1 cm^3 in arm A vs mean PTV2 131.0 cm^3 in arm B, $p < 0.001$, Table 4). The mean doses to the PTV 2 in arms A and B were 74.5 and 76.2 Gy, respectively ($p < 0.001$).

Discussion

As compared to weekly orthogonal portal imaging in patients with intermediate and high-risk prostate cancer, IGRT with daily CBCT verification and reduced margins from CTV to PTV significantly reduced the volume receiving 70 Gy (PTV 2) and rectal

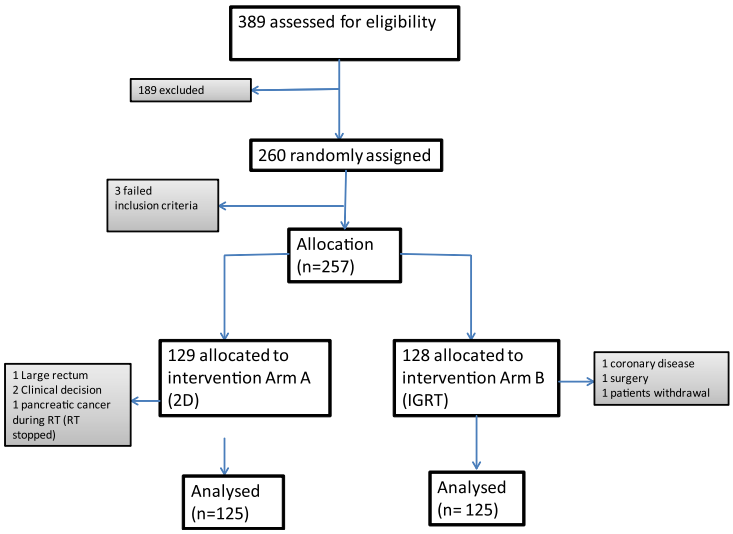

Fig. 1. Consort diagram.

Table 1
Baseline characteristics.

	2D-IGRT (n = 125)	3D-IGRT (n = 125)
Age (years)	72.4	71.9
Aalesund Hospital (n)	63	60
St Olavs Hospital (n)	62	65
PSA mean (nmol/L)	16.57	16.09
T1 (n)	21	27
T2 (n)	47	40
T3 (n)	57	57
T4 (n)	0	1
Gleason 6 (n)	9	11
Gleason 7 (n)	69	77
Gleason 8 (n)	25	17
Gleason 9 (n)	19	17
Gleason 10 (n)	3	3
High Risk (n)	77	75
Intermediate Risk (n)	48	50

volumes receiving 50, 60 and 70 Gy. Contrary to what was hypothesized in the trial, this did not translate into a reduction of patient reported acute side effects from the gastrointestinal tract or higher HRQOL scores at end of RT. For blood in urine, we found very low symptom burden in both study arms and the trend toward a difference did not reach the pre-specified level of statistical significance (p = 0.01). Given the very low symptom burden in both arms, we consider the possible difference clinically insignificant. For nocturia the mean score was lower in arm A than in arm B (3.73 vs 4.37, p = 0.020) neither is this of any statistical significance nor of clinical significance.

There is evidence that patient reported acute side effects predict urinary as well as rectal long term RT-toxicity and such constitute a clinically important proxy outcome [3,4].

The RIC-study is to our knowledge the first RCT that compares side effects following curative EBRT for prostate with either daily IGRT or verification by weekly orthogonal portal imaging. However, several non-randomized studies have previously compared IGRT to non-IGRT. While Chung et al. found reduced acute rectal and urinary side effects when comparing image guided IMRT (IG-IMRT) to IMRT without image guiding for high risk prostate cancer in a small patient series (n = 25), Zhong et al. found no such benefit [12,26]. Engels et al. reported increased biochemical failure in a group of patients with distended rectum receiving IGRT with reduced safety margins [13]. Several other non-randomized trials have compared IG-IMRT to IMRT in prostate cancer treatment [11,15]. In accordance with the RIC-study, none of these studies demonstrated that IGRT reduce acute toxicity.

Wortel and co-workers compared two cohorts of prostate cancer patients given 78 Gy in 2 Gy's fractions in two separate RCT's [14,27]. Patients who received IG-IMRT (5–8 mm margins from CTV to PTV) in the standard arm of a hypofractionation trial performed during 2007–2011 were compared with patients treated with 3-field 3D conformal radiotherapy (10 mm margins from CTV to PTV) in the high dose arm of a dose escalation trial performed during 1997–2003. Acute toxicity score based on the RTOG scoring system were derived directly from patient reported outcome measures. Even though the margin differences from CTV to PTV in these two cohorts were smaller than the margin differences between the two arms in our trial, the patients in Wortel's study reported significant reductions of both acute patient reported gastrointestinal and urinary symptoms following IG-IMRT. The GI symptoms were significantly reduced also at 5 years follow up, whereas urinary symptoms diminished with time. Although the discrepancy between these results and our findings may be due to the addition of IMRT or to different measures of side effects, a bias caused by the non-randomized comparison in the Wortel trial cannot be ruled out.

One might speculate that the additional irradiation derived from kV imaging may have contributed to acute side effects in the IGRT arm and thus diminish the potential difference. However, the total dose derived from daily 3-D kV pelvic imaging during 39 treatment days is less than 1 Gy, i.e. far less than the variation of 95–107% dose coverage that is commonly accepted in modern RT and considered negligible.

There is a well-known relationship between side effects and irradiated volume [28]. The RIC-study patients did not receive prophylactic pelvic lymph node irradiation, a procedure that is controversial but frequently applied in high-risk patients. Notwithstanding our findings, the daily prostatic IGRT with tight

Table 2
Urinary and bowel symptoms at end of radiotherapy.

	2D-IGRT		3D-IGRT		Difference between treatment arms A and B*	
	Mean	95% CI	Mean	95% CI	Estimate (95% CI)	p*
Urinary symptom						
Overall bother from all urinary symptoms	4.17	3.55–4.78	4.25	3.69–4.81	−0.16 (−0.94 to 0.63)	0.698
Nocturia	3.73	3.35–4.11	4.37	3.89–4.84	−0.68 (−1.25 to −0.11)	0.020
Urinary frequency per day	9.09	8.22–9.95	9.21	8.32–10.09	−0.17 (−1.24 to 0.90)	0.758
Pain while urinating	2.73	2.15–3.32	3.04	2.45–3.63	−0.52 (−1.29 to 0.25)	0.188
Starting problem	2.66	2.13–3.18	2.89	2.38–3..40	−0.30 (−1.02 to 0.42)	0.415
Urinary leakage	0.98	0.66–1.31	1.10	0.70–1.49	−0.10 (−0.55 to 0.35)	0.658
Urgency	2.83	2.33–3.34	3.11	2.58–3.64	−0.36 (−1.05 to 0.34)	0.314
Blood in urine	0.36	0.08–0.63	0.10	0.03–0.18	0.29 (0.01 to 0.56)	0.040
Limitation in daily activity caused by urinary symptoms	2.38	1.89–2.87	2.58	2.09–3.06	−0.11 (−0.74 to 0.51)	0.722
Bowel symptom						
Overall bother from all bowel symptoms	2.26	1.77–2.74	2.22	1.73–2.72	0.15 (−0.53 to 0.83)	0.660
Stool frequency	3.20	2.82–3.58	3.27	2.78–3.75	0.12 (−0.58 to 0.61)	0.968
Stool leakage	0.76	0.49–1.02	0.63	0.39–0.87	−0.13 (−0.35 to 0.33)	0.942
Planning of toilet visits	1.68	1.22–2.14	1.78	1.28–2.28	−0.02 (−0.68 to 0.64)	0.954
Flatulence	3.74	3.24–4.24	3.94	3.40–4.48	−0.12 (−0.78 to 0.54)	0.714
Bowel cramp	1.60	1.17–2.04	1.28	0.84–1.71	0.33 (−0.28 to 0.94)	0.283
Mucus	2.09	1.64–2.54	1.78	1.32–2.23	0.19 (−0.45 to 0.82)	0.558
Blood in stools	0.42	0.22–0.62	0.45	0.21–0.68	−0.06 (−0.35 to 0.24)	0.696
Limitation in daily activity caused by bowel symptoms	1.52	1.14–1.90	1.61	1.14–2.07	0.28 (−0.27 to 0.84)	0.314
Bother scale	1.871	1.557–2.186	1.884	1.540–2.230	0.06 (−0.39 to 0.50)	0.804

* *p*-Value for treatment, from linear regression with baseline value, treatment, site and risk group as covariates.

Table 3
Health related quality of life scores (EORTC QLQ-C30) at end of radiotherapy.

	2D-IGRT		3D-IGRT		p*
	Mean	(95% CI)	Mean	95% CI	
Functioning scale					
Physical function	85.3	83.8-86.8	83.6	82.0-85.3	0.335
Role function	80.1	77.9-82.2	78.1	75.8-80.4	0.449
Emotional function	88.8	87.3-90.2	87.7	86.4-89.1	0.492
Cognitive function	86.9	85.4-88.4	86.9	85.4-88.4	0.742
Social function	81.4	79.5-83.3	82.0	80.3-83.8	0.899
Global health/QOL	74.8	73.0-76.6	76.2	74.4-77.9	0.319
Single symptom					
Fatigue	29.4	27.4-31.4	30.2	28.4-32.1	0.496
Nausea/Vomiting	1.9	1.2-2.6	1.7	1.2-2.2	0.149
Pain	14.1	12.1-16.1	12.2	10.4-14.0	0.553
Dyspnea	24.0	21.7-26.2	20.7	18.3-23.1	0.738
Insomnia	23.0	20.5-25.4	22.4	20.1-24.7	0.997
Appetite loss	4.2	3.0-5.4	4.2	3.1-5.2	0.466
Constipation	17.1	14.9-19.3	17.0	15.0-19.0	1.000
Diarrhea	20.4	18.1-22.7	20.6	18.6-22.6	0.523
Financial difficulties	3.7	2.6-4.9	4.1	2.8-5.5	0.494

* *p*-Value for treatment, from linear regression with baseline value, treatment, site and risk group as covariates.

CTV-PTV margins applied in arm B of the RIC-study may still be beneficial for patients also receiving adjuvant irradiation of the pelvic lymph nodes.

Reduced CTV-PTV safety margins have the potential of less side effects, but it is of major importance not to reduce the margins excessively due to the risk of geographical miss and lack of target volume coverage. This applies especially for patients with rectal distension at the time of the planning CT [13,29,30].

Moreover, the RIC study evaluated the effect of reduced irradiated volume in arm B, and in our opinion, sufficient precision with such tight margins cannot be achieved without daily image guiding.

The rectal dose constraint was 60 Gy to no more than half of the circumference in both study arms which frequently resulted in some degree of posterior blocking of the PTV2 (0–70 Gy) in patients given EBRT with weekly verification (arm A). The reduction of irradiated rectal volume introduced by this blocking of the PTV2 may have reduced patient reported rectal toxicity in arm A. On the other hand, the analyses of the DVHs demonstrate clearly that the V50 Gy, V60 Gy and V70 Gy delivered to the rectum were significantly smaller in arm B (IGRT arm) as compared to arm A (Table 4). Thus, although IGRT with daily CBCT verification significantly reduced normal tissue irradiation it still failed to decrease acute side effects.

Although within the 95–107% requirement, the mean PTV-dose was significantly lower in arm A as could be expected due to the posterior blocking (Table 4). The mean CTV-dose was however identical in both arms, and, in our opinion, the probability of local control should be equal in both treatment groups.

The ideal study design is a blinded randomized trial. This study was open and one could expect that the open label design would result in more rather than less patient reported side effects in arm A due to patient's expectations. CT-MRI fusion was used at the physician's discretion. Given that the CTV volumes were similar in arm A and B, it is not reason to believe that any difference MRI-use between arms have influenced on the study results. Additionally, the OARs were outlined on the CT-scans only. Modern

Table 4
Irradiated volumes.

	2D-IGRT (arm A) Mean (95% CI)	3D-IGRT (arm B) Mean (95% CI)	p^*
Rectum			
V50 (cm^3)	44.9 (40.8–49.0)	29.8 (26.9–32.6)	<0.001
V60 (cm^3)	36.2 (32.7–39.7)	22.6 (20.4–24.8)	<0.001
V70 (cm^3)	18.5 (16.3–20.62)	11.5 (10.3–12.7)	<0.001
Bladder			
V50 (cm^3)	83.6 (78.6–88.5)	53.8 (50.0–57.7)	<0.001
V60 (cm^3)	74.0 (69.5–78.6)	45.1 (41.6–48.5)	<0.001
V70 (cm^3)	46.3 (42.5–50.0)	30.4 (27.5–33.3)	<0.001
CTV2 (0–70)			
Total volume (cm^3)	49.2 (45.5–52.9)	49.2 (45.8–52.6)	0.687
Mean dose (Gy) [#]	77.59 (77.21–77.78)	77.65 (77.58–77.72)	0.449
PTV2 (0–70)			
Total volume (cm^3)	279.7 (269.1–290.3)	131.9 (125.7–138.2)	<0.001
V66.5 (cm^3)	270.1 (259.8–280.3)	131.0 (124.8–137.1)	<0.001
Mean dose (Gy)	74.5 (74.1–74.8)	76.2 (76.1–76.4)	<0.001

[#] Due to non-normally distributed data, *p*-values are from Mann-Whitney's test, and confidence intervals are Bias corrected and accelerated (BCa) Bootstrap confidence intervals with B = 10,000 bootstrap samples.
[*] Student's *t*-test assuming unequal variances.

technology in health care is an important driver of health care costs. IGRT increases costs because of the investments necessary as well as increased personnel time spent [9]. Although commonly recommended in international clinical guidelines, it is noteworthy that we have not been able to demonstrate any clinical benefit from extended use of IGRT and reduced PTV margins for the RIC-study patients so far. Our patients will be followed up for at least 10 years from inclusion, and it remains to see whether the daily CBCT-IGRT applied in arm B will result in reduced late effects without adversely affecting disease control. In our opinion, the present results underline the need for technical medical innovations to be thoroughly evaluated in controlled clinical trials with long-term follow up.

Contributors

JÅL, AS, BA, ADW, CAJ, SK and SL planned the study initially and amended the protocol together with HT in 2012. JÅL, AS, BA and HT enrolled patients and collected data at the study centers. SL was responsible for statistical planning and data analysis in collaboration with the first and last authors. JÅL, HT and AS were responsible for data collection and drafted the manuscript. JÅL and HT has contributed equally as first authors. All authors were involved in revision and have approved the final manuscript.

Declaration of interests

Dr. Kaasa reports a patent Eir Solution AS licensed.
All other authors declare no conflicts of interests.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.radonc.2017.10.029.

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Paper II

Rectal volume variations and estimated rectal dose during 8 weeks of image-guided radical 3D conformal external beam radiotherapy for prostate cancer.

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Keywords: Prostate cancer, IGRT, 3D conformal radiotherapy, rectal dose, rectal volume.

Abstract:

Purpose:

Rectal volume variation (RVV) during external beam radiotherapy (EBRT) may increase the risk of geographical miss and hamper local control in the treatment of prostate cancer (PC). Image guided radiotherapy (IGRT) with daily Cone-beam computed tomography (CBCT) is now considered part of standard EBRT in an increasingly number of cancer patients. This study aims to analyze RVVs during 8 weeks of radical three-dimensional (3D) conformal EBRT with daily CBCT-IGRT in PC patients and its implications on delivered rectal dose.

Methods and materials:

Thirty patients receiving 78Gy in 2Gys fractions with daily CBCT-IGRT were included. Rectal volume was outlined on the planning computed tomography (CT) and on eight weekly CBCT-scans during the treatment period. The outlined rectal volumes from the CBCT-scans were imported and merged with the planning CT using prostatic fiducial gold markers as reference before recalculating doses in the original RT plan. Dose-volume histograms (DVHs) were calculated for rectal volumes and percentage of irradiated rectal volumes were estimated.

Results:

Mean rectal volume was 114.6 (range 43.9 to 259.1) cm^3 in the planning CT. Mean rectal volume of all CBCT's was 94.2 (range 41.9 to 278.3) cm^3. Estimated weekly reduction in rectal volume was 3.55 cm^3. The percentage of irradiated rectal volume increased but was not statistically significant. The estimated absolute increase over 8 weeks for volumes irradiated to 50, 60, 65 and 70Gy was 1.1, 1.1, 1.2 and 1.5 %, respectively. The individual variation in rectal volume over the treatment course was large (range 20.3-202.1 cm^3).

Conclusions:

Rectal volumes were significantly reduced in this population of PC patients during the treatment period. The percentage of irradiated rectal volume did not change statistically significant. When reduced margins are applied, our study shows that daily CBCT ensures a close to stable dose to the rectum despite a significant variation in rectal volume.

Introduction:

The introduction of modern image guided radiotherapy (IGRT) has given new insight regarding organ motion in RT, both in general and in treatment for PC (1). Interfraction displacement of the prostate gland during radiotherapy (RT) is often observed in response to the variations in rectum and bladder filling, and can range from 0-20 mm (1-7). Accordingly, rectal volume variation (RVV) during RT may increase the risk of biochemical and local failure if modern IGRT and adequate safety margins are not applied (8-13). Moreover, the volume of rectum receiving ≥ 60Gy is associated with increased risk of grade ≥ 2 late rectal toxicity or rectal bleeding and can be a limiting factor for dose escalation (14-19).
Some small sample-size studies have reported variable rectal dose distribution due to RVV during RT (2, 20, 21). In order to minimize RVV, some authors advocate rectum emptying using an enema eventually combined with laxatives and dietary measures at the time of the initial planning computed tomography (CT) and during the treatment period, especially if daily IGRT is not applied (22, 23). Consequently, studies on radiation dose distribution and variations in Organs at Risk (OARs) during the total treatment period are essential to gain knowledge about the accuracy of dose delivery to the tumor and the surrounding normal tissue.

The aim of this study was to answer the following research question: Are rectal volumes reduced or increased, and are rectal doses consequently reduced or increased during eight weeks of radical 3D conformal CBCT-IGRT in patients treated for PC?

Material and Methods:

Patient selection and RT treatment:

Between October 2012 and June 2013, 30 consecutively treated patients with high risk or intermediate risk PC (according to D'Amico's risk stratification) at two Norwegian hospitals (St. Olavs Hospital and Ålesund Hospital) were included in this study (24). All patients received 70Gy to a planning target volume (PTV) which included a clinical target volume (CTV) consisting of the prostate and basal 10 mm (intermediate risk PC) or 20 mm (high risk PC) of the seminal vesicles with an additional 7 mm margin in all directions, followed by an

8Gy boost to a PTV consisting of the prostate with a 3 mm margin. Elective lymph node irradiation was not performed. CT-based, 3D-conformal treatment planning was mandatory, as were multi- leaf collimators (MLC). A four-field box technique with necessary supplemental field segments was applied with 15 megavoltage photon beams from 0 to 70Gy. For the 8Gy boost, a 5 field (1 anterior, 2 oblique anterior and 2 lateral) technique was applied. All patients had 4 prostatic fiducial gold markers implanted prior to the RT and the isocenter was placed in the fiducial gold marker located closest to the base of the prostate. The target volume doses were within 95-107% of the prescribed dose. The rectal dose constraint was defined as 60Gy to no more than half of the rectal circumference. If necessary, posterior blocking of the rectum with MLC was accepted even if this resulted in reduced dose to the PTV. Patients were treated in supine position without rigid immobilization. After alignment by skin markers, 3D kilovoltage imaging with CBCT (XVI, Elekta AB©, Stockholm, Sweden), of prostate with fiducial markers were performed and all localization errors corrected prior to each fraction (treatment 1-39). One hour before the initial planning CT-scan (CT1) patients were asked to empty the bladder and drink two glasses of water. Emptying of the rectum was not mandatory before the dose planning CT or the subsequent RT fractions.

The present study was a side study to a previous published phase III randomized controlled trial (a **R**andomized, two centre trial on daily cone-beam **I**GRT vs standard weekly orthogonal IGRT in **C**urative radiotherapy for prostate cancer, the RIC-study) which included 257 PC patients (25).

Calculation of volume and doses on CBCT:

In each patient, eight CBCT-scans (slice thickness 2 mm) obtained at fraction number 1, 6, 11, 16, 21, 26, 31 and 36 (CBCT1-8) were transferred to the Oncentra© (Elekta AB, Stockholm, Sweden) treatment planning system. The rectal volume was manually outlined on CT1 and CBCT1-8, resulting in 9 rectum contours for each patient (270 for all 30 patients). One Clinical Oncologist (HT) outlined the rectal volumes including the outer wall from the recto-sigmoid transition to the caudal part of the anus on all CBCTs, and the rectal volumes (cm^3) were calculated automatically. The eight rectum contours obtained from each patient were imported and merged with CT1 using the prostatic fiducial gold markers as reference.

Recalculation of rectal dose was done for each CBCT1-8 using the original CT and set up beams. Dose-volume histograms (DVHs) for rectal volumes receiving 50, 60, 65, and 70Gy (V50Gy, V60Gy, V65Gy and V70Gy) were estimated, both in cm^3 and in percentage of irradiated rectal volume.

Statistics:

Descriptive statistics for volumes are reported as mean and standard deviation (SD), and illustrated with box plots displaying the mean, quartiles, and minimum and maximum values. A time trend in rectal volume was analyzed using a two-level mixed model with volume as dependent variable, patient as random effect and week number (0 to 8) as continuous covariate, with a possible deviating volume at initial planning CT-scan (time 0). A time trend in percent irradiated volume was analyzed using a three-level mixed model with irradiated percent as dependent variable, patient as random effect, time point as random effect nested within patient, dose as a four-level categorical covariate, week number (0 to 8) as continuous covariate, and interaction between dose and week number, with a possible deviating volume at initial planning CT-scan (time 0). Normality of residuals was checked by visual inspection of Q-Q plots. The residuals for rectal volume were slightly skewed. Hence, alternative analyses with log transformed rectal volume as dependent variable was carried out. Ninety-five percent confidence intervals (CI) are reported where relevant.
Analyses were carried out in SPSS® ver. 22.

Results:

Baseline characteristics are described in Table 1. Mean age was 71 years and 60% of the patients had high risk PC.
The mean rectal volume in the planning CT (CT 1) was 114.6 (43.9-259.1) cm^3 whereas the mean rectal volume in all 240 CBCT scans was 94.3 (41.9-278.3) cm^3. (Table 2, Figure 1). In the two patients with the largest (202.1 cm^3) and smallest (20.3 cm^3) RVV, the volumes ranged from 61.8 to 263.9 cm^3 and 67.4 to 87.7cm^3, respectively (Figure 2). The individual RVV over the treatment course (including CT1) was considerable with an estimated mean of

95.6 cm^3. Six out of 30 patients had a RVV of >150 cm^3. Figure 3 shows the rectal volumes as outlined on CT1 and CBCT1-8 in one randomly selected patient with a RVV of 171.5 cm^3, ranging from 87.6 cm^3 (CBCT2) to 259.1 cm^3 (CBCT1).
When applying a linear mixed regression model, the mean volume was estimated as 110.1 – 3.55*t cm^3, where t is week number (set to 0 at the initial planning). That is, the mean volume was reduced by an estimated 3.55 cm^3 (CI 1.90 to 5.21) per week. Adding an extra term for the initial planning (time 0) did not change the estimates notably. The distribution was slightly skewed at each time point, and the mean volumes and variance tended to be higher at the time of dose planning and in the first week of RT (Figure 1). Secondary analysis with log transformed volumes gave symmetric distributions with equal variances, and gave essentially the same reduction in volume over time as for untransformed volumes.

The mean proportion of rectal volumes irradiated to 50Gy (V50Gy) on the planning CT-scan and CBCT1-8 was 34.1%. The corresponding figures for V60, V65, and V70Gy were 26.9, 22.3, and 15.6 %, respectively (Figure 4).
Applying a linear mixed regression model, the volume irradiated to 70Gy was estimated to an absolute increase with an average of 0.18 % (CI -0.182 to 0.550, p=0.30) per week, corresponding to an absolute increase of 1.47 % over 8 weeks. The absolute increase over 8 weeks for volumes irradiated to 50, 60, and 65Gy (1.14, 1.12, and 1.20 %, respectively) was not statistically significant (p=0.42, 0.43, and 0.39, respectively). Adding an extra term for the initial planning (time 0) gave essentially the same results.
Table 3 shows the distribution of percentage of rectal volumes receiving 50, 60, 65, and 70Gy (V50Gy, V60Gy, V65Gy and V70Gy).

Discussion:

The principal finding in this study was that although the rectal volume decreased significantly in this cohort of PC patients, the RVV did not influence on the percentage of planned irradiated rectal volume receiving 50, 60, 65 and 70Gy, which were close to constant during the eight weeks of RT. Most of the rectal volume reduction occurred early in the treatment period and mainly between the initial planning CT and CBCT2. Moreover,

the inter-individual RVV was considerable and ranged from 20.3 cm^3 to 202.1 cm^3 during the treatment period.

One major limitation in previous studies on RVV in prostatic RT have been few (24 or less) included patients (20, 21, 26, 27). Our study included 30 consecutive PC patients from the experimental arm of a RCT (the RIC-study). It is possible that rarely occurring extreme variations in rectal volume may have been missed also in our study due to a limited sample size of 30 patients. On the other hand, a total of 270 CT-scans were included, and our estimates are most likely representative of rectal volume variations amongst patients receiving RT for PC.

Several authors have found a decrease in rectal volume during EBRT for PC and in accordance with our findings, the main reduction in rectal volume occurs early in the treatment period (21, 26, 27). Sripadam et al. found a significant decrease in rectal cross-sectional area (CSA) in CBCT-scans obtained immediately after the daily treatment in 13 of 15 PC patients receiving RT (50Gy in 16 fractions) (21). Zellars et al. reported a significant decrease in rectal volume in 18 of 24 patients when comparing the planning CT-scan with a single CT-scan 4-5 weeks after prostatic irradiation (27). Antolak et al. compared the planning CT-scan with three CT-scans obtained during the 8 weeks treatment period and also found a significant decrease in rectal volume in 17 patients receiving prostatic irradiation (26). Other authors have reported significant variations, but no systematic changes (2, 20).

Previous studies have indicated that RVV during RT may increase the risk of geographical miss and thus hamper local control, especially in patients with a distended rectum on the planning CT-scan (8-11). Heemsbergen et al. analysed 549 patients included in the Dutch prostate cancer dose-escalation trial (78Gy vs. 68Gy), and found a significantly reduced freedom from clinical failure (FFCF) in patients with anorectal volumes ≥ 90 cm^3 on the planning CT-scan (10). Engels et al. analysed freedom from biochemical failure (FFBF) in 238 patients given conformal RT to a total dose 70-78Gy (9) and found that an average rectal CSA of ≥ 16 cm^2 was associated with worse FFBF. In another study reported by Engels et al., 50 patients treated with IGRT and daily positioning using fiducial gold markers were analysed (11). This study demonstrated a reduced 5-year FFBF in patients with a rectal distention on the planning CT-scan compared to those with limited rectal distention (75 % vs 89 %). Other authors claim that the adverse effects of rectal distention on local control can be compensated by the use of modern IGRT (12, 28). Park et al. measured CSA on the planning

CT-scans in 962 prostate cancer patients receiving adaptive RT with a median prescribed dose of 75.6Gy (28). The authors found that initial rectal distention was not significantly associated with reduced 5-years biochemical cancer control or grade ≥2 genitourinary (GU) and gastrointestinal (GI) toxicity, and concluded that adaptive IGRT reduces the risk of geographical miss. Silverman et al. examined 172 prostate cancer patients receiving conformal RT to a total dose of 74 Gy at a median of 72 months follow up (12). The rectal diameter was measured at the midpoint of the PTV on the planning CT-scan. A large (>4.5 cm) rectal diameter on the planning CT-scan was not associated with increased risk of PSA-relapse. The PTV margins applied in Park and Silvermans studies were, however, larger than the studies reported by Engels et al. (3-5 mm), (9).

A reduced CTV-PTV safety margin also has the potential to lower side effects. Thus, since the irradiated rectal volume remained unchanged in this study, we believe that the use of daily IGRT with sufficient PTV-margins also has the potential to counteract adverse effects of RVV and initial distention on rectal toxicity.

Emptying of the rectum was not routine before the planning CT-scan or the subsequent RT fractions in our study. Several authors recommend use of laxatives and/or rectal emptying before dose planning/ each fraction, especially if daily IGRT is not applied (2, 22, 23). Chen et al. advocate that prostatic IMRT should be planned with an empty rectum in order to increase the accuracy of the dose distribution (2). Engels et al. aimed to predict which PC patients may benefit from daily rectal emptying by analysing 18 patients receiving RT to the prostate and iliac nodes with daily IGRT (23). Before the planning CT-scan all patients had an enema. Two typical groups were observed; one with a limited and stable rectal diameter and one with a large RVV. The authors suggest that a CSA cut-off value estimated using data from the first 3-5 fractions may be helpful in deciding which patients would benefit from an enema. A review regarding effectiveness of rectal emptying reported by McNair et al. compared dietary interventions, oral and intravenous laxatives, enemas, or combinations (29). No evidence in support of a superior strategy was found. Moreover, no significant difference in rectal volume was observed in another cohort of 80 PC patients given EBRT at one of the RIC-study centers, of whom 40 were given laxatives regularly during the eight weeks treatment period (30). Thus the optimal regime and effectiveness of rectal emptying is still unknown. Although the shrinkage in total rectal volume in our study was significant, the percentage of irradiated rectal volume remained unchanged. These findings indicate that

the IGRT-technique applied in the RIC-study eliminates the risk of increased dose to the rectum caused by volume shrinkage. Based on our results, we believe rectal emptying and other more invasive and expensive methods for limiting the movement of internal organs can be omitted if fiducial markers and daily CBCT are used.

The volume of rectum receiving ≥ 60Gy is associated with the risk of grade ≥ 2 late rectal toxicity or rectal bleeding and may be a limiting factor for dose escalation (14-19). The grade of CTCAE in this side study corresponded well to the overall grade of CTCAE reported in the main study (Table 1). However, we found no grade 3 toxicity in these 30 patients compared to 1 out of 125 patient in the corresponding arm in the RIC-study.

The dose constraint to the rectum in the RIC-study was 60Gy to no more than 50 % of the rectum circumference on the planning CT-scan. If exceeded, a posterior shielding of the PTV with multi leaf collimators was accepted. Accordingly, the limit of 60Gy to 50 % of the estimated rectal volume was not exceeded in any of the included patients in this subset of 30 patients. However, Quantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC) recommends a V50Gy to < 50 % of the rectal volume, V60Gy <35 %, V65Gy < 25 % and V70Gy < 20 % as rectal dose constraints in RT for PC with a dose up to 79.2Gy in 1.8-2Gy fractions (19). This will limit Grade ≥2 late toxicity to < 15 % and the probability of Grade ≥3 late rectal toxicity to < 10 %. In our study, one patient exceeded the mean V50Gy recommendation (52.9 %), five had a mean V60Gy > 35 %, seven a mean V65Gy > 25 % and five a mean V70Gy > 20 % despite the small margins from CTV to PTV (7 mm).

In conclusion, the rectal volume decreased significantly by an estimated 3.55 cm^3 per week during 8 weeks of radical, 3D conformal RT in 30 prostate cancer patients. The majority of the reduction occurred during the initial 2-3 weeks. However, the irradiated rectum volumes during the treatment period remained unchanged. Consequently, the use of frequent IGRT with CBCT and fiducial gold markers seems to eliminate possible adverse effects of RVV ensuring an acceptable and stable radiation dose to the rectum which corresponds with the initial planned rectal dose and within the recommended dose levels.

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Age (years) (SD)	**71.0 (5.3)**
Aalesund Hospital	9
St. Olavs hospital	21
PSA mean (nmol/l) (SD)	17.7 (13.2)
Clinical stage	
T1	6
T2	10
T3	14
Gleason score	
6	3
7	16
8	6
9	5
High risk	18
Intermediate risk	12
CTCAE grade at inclusion	
0	23
1	5
2	2
CTCAE grade at end of RT	
0	6
1	21
2	3

Table 1. Patient characteristics in 30 consecutive patients in arm B receiving daily IGRT. SD: Standard deviation, CTCAE: Common toxicity criteria for adverse effects version 4.0.

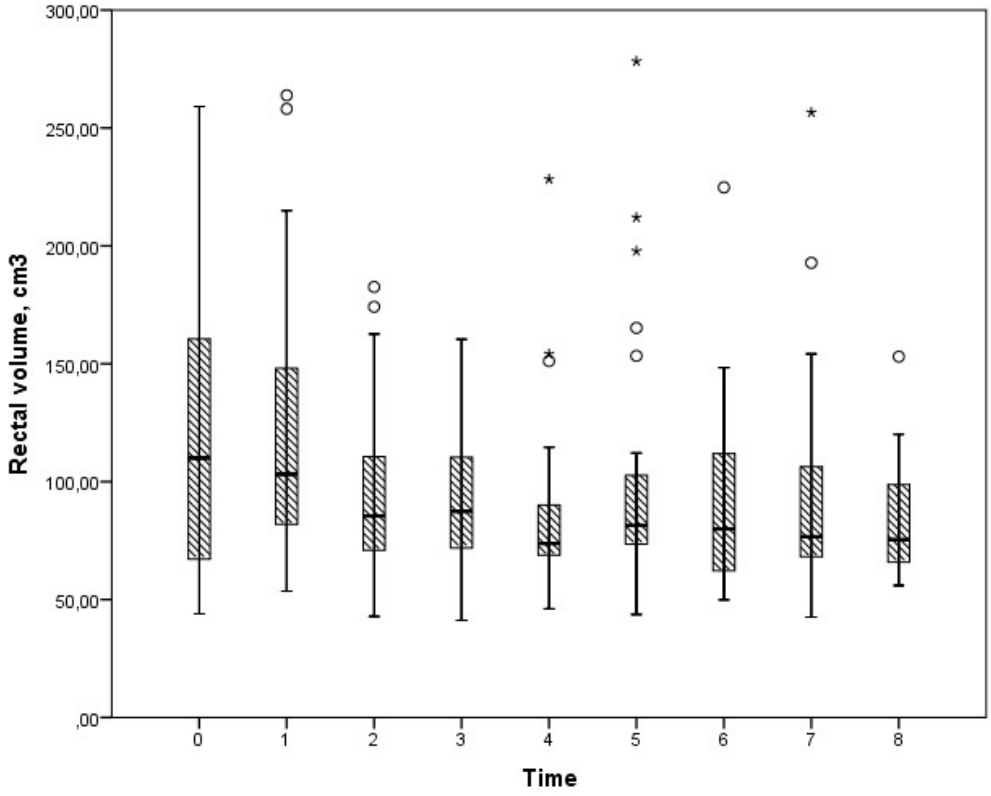


Fig. 1. Boxplot of rectal volumes at initial planning CT-scan (0) and during treatment (week 1 to 8). The horizontal line represents the median, and the box covers the inter-quartile range. The ends of the whiskers show the range of observations less than 1.5 inter-quartile range from the box, and circles and asterisks show the more distant observations, more than 1.5 box-lengths and more than 3 box-lengths away from the box, respectively.

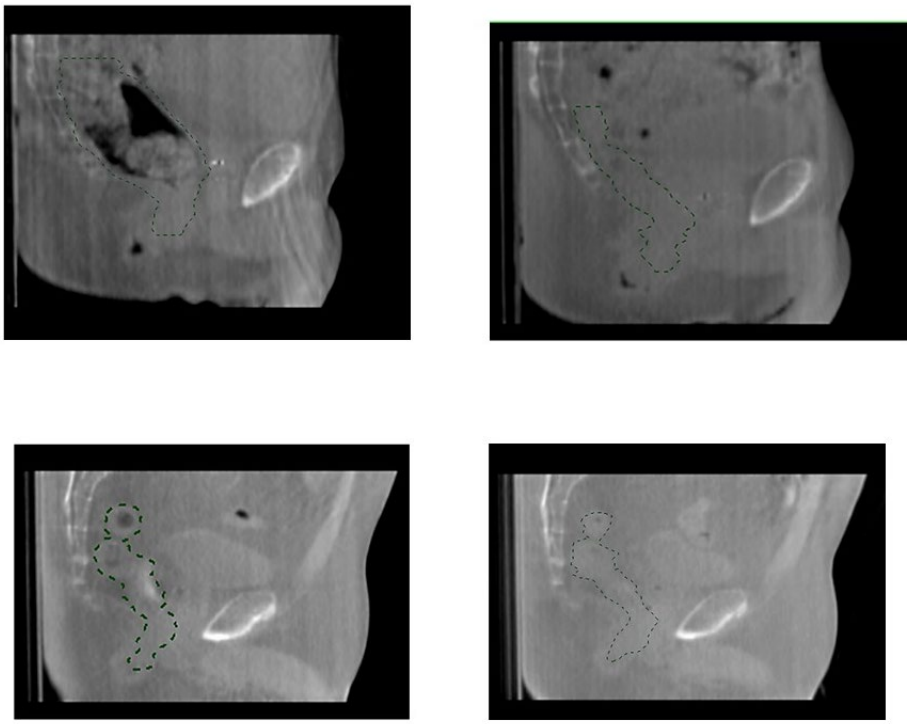
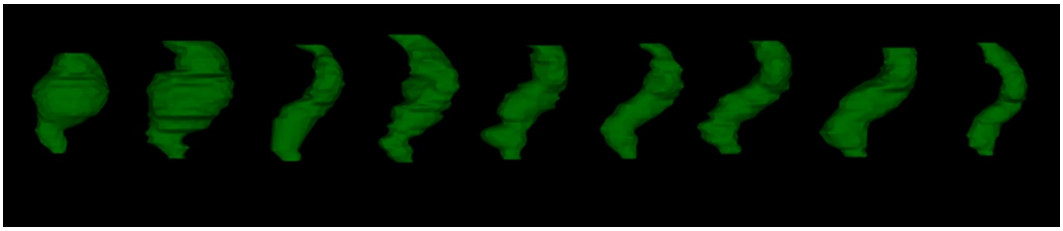


Fig. 2. Images for the patients with the largest (above line) and smallest (below line) range on CBCT 1-8 (range 202.1 cm^3 and 20.3 cm^3, respectively).
Green line representing outlined rectal volume. Left images represents CBCT 1 (volumes 263.9 cm^3 and 87.7 cm^3, respectively), right images represents CBCT 6 (61.8 cm^3) and CBCT 3 (67.4 cm^3), respectively.



CT 1 CBCT 1 CBCT 2 CBCT 3 CBCT 4 CBCT 5 CBCT 6 CBCT 7 CBCT8

Fig. 3. Example of rectal volume variation during treatment for one patient. Maximal volume on CT 1 = 259.1 cm³, minimal volume on CBCT 2 = 87.6 cm³. Range 171.5 cm³.

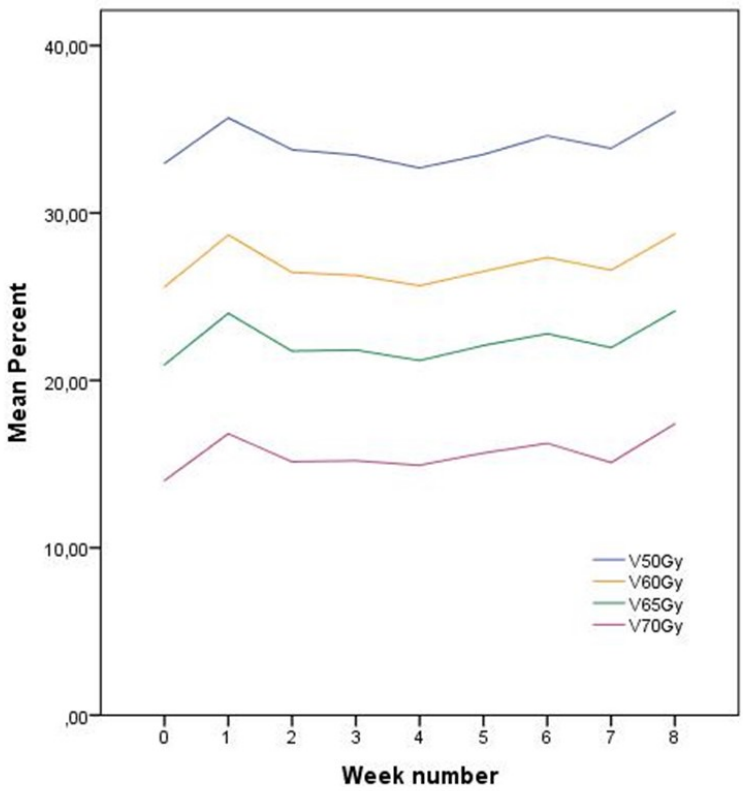


Fig. 4. Mean value of percentage of irradiated rectal volume at time 1-9 for V50 Gy (blue line), V60 Gy (green line), V65 Gy (red line) and V70 Gy (purple line).

	Initial planning CT-scan	CBCT 1	CBCT 2	CBCT 3	CBCT 4	CBCT 5	CBCT 6	CBCT 7	CBCT 8
Mean (cm^3)	114.6	119.2	94.9	91.6	85.1	99.1	90.2	91.3	82.8
SD	55.3	56.6	38.2	27.5	37.2	53.0	37.7	44.8	22.5

Table 2: Mean and SD for rectal volumes for the n=30 patients at initial planning CT-scan, and then weekly during treatment.

	CT 1	CBCT 1	CBCT 2	CBCT 3	CBCT 4	CBCT 5	CBCT 6	CBCT 7	CBCT 8
V50 Gy	33.0 % (50.4 -21.6)	35.7 % (49.8-17.9)	33.8 % (57.5-12.1)	33.5 % (54.4-18.7)	32.7 % (54.8-15.5)	33.5 % (56.8-21.6)	34.6 % (51.5-22.2)	33.9 % (50.6-21.6)	36.1 % (59.9-18.3)
V60 Gy	25.6 % (42-16.3)	28.7 % (39.8-12.7)	26.5 % (47.3-8.6)	26.3 % (44.6-13)	25.7 % (46.1-10.3)	26.5 % (48.1-17.1)	27.3 % (43.7-15.8)	26.6 % (42.4-15.4)	28.8 % (49.5-14.3)
V65 Gy	20.9 % (36.3-12.8)	24.1 % (34.1-9.9)	21.8 % (41.3-6.5)	21.9 % (39.3-10.0)	21.2 % (41.1-7.6)	22.1 % (43.5-13.5)	22.8 % (38.8-11.5)	22.0 % (38.1-11.5)	24.2 % (43.7-11.3)
V70 Gy	14.0 % (24.4-8.0)	16.8 % (25.4-6.4)	15.1 % (29.2-4.2)	15.2 % (28.3-5.9)	14.9 % (31.9-4.2)	15.7 % (33.0-3.3)	16.2 % (28.5-7.5)	15.1 % (29.1-7.1)	17.4 % (31.6-7.9)

Table 3. Mean percentage of irradiated rectal volumes for V50Gy, V60Gy, V65Gy and V70Gy, range (%) in parenthesis.

Paper III

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Original Research Article

Dose to penile bulb is not associated with erectile dysfunction 18 months post radiotherapy: A secondary analysis of a randomized trial

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ABSTRACT

Background: Erectile dysfunction is a common side effect of prostate cancer (PC) therapy. In this randomized study (The RIC-study) we used patient reported outcomes to evaluate sexual function 18 months after combined endocrine therapy and radical radiotherapy (RT) given with either wide or tight planning target volume (PTV) margins. We also analyzed the impact of radiation dose to penile bulb on sexual function.

Methods: The RIC-study included 257 men with intermediate and high-risk PC. All patients received 6 months of total androgen blockage started 3 months prior to randomization. In high-risk patients, an oral anti-androgen (Bicalutamide) was administered for an additional 2.5 years. Patients were randomized to receive 78 Gy in 39 fractions guided either by weekly offline orthogonal portal imaging or by daily online cone beam computed tomography image-guided RT. Sexual function was evaluated at 18 months after start of RT using the Questionnaire Umeå Fransson Widmark 1994. Ability to have an erection was assessed on an 11-point scale numerical rating scale (0 = no and 10 = very much) as the primary outcome. In addition, the association between penile bulb (PB) radiation dose and erectile function was analyzed.

Findings: Of 250 evaluable patients, 228 (mean age 71.8 years) returned the questionnaires. The patients reported a high degree of sexual related problems with mean scores to the primary outcome question (221 respondents) of 7.44 and 7.39 in the 2D weekly IGRT-arm and 3D daily IGRT-arm ($p = 0.93$) respectively. For four additional questions (scale 0–10) regarding sexual function resulted in mean scores >6.5 with no difference between study arms. The mean dose to PB was substantially larger in the 2D weekly IGRT-arm vs the 3D daily IGRT-arm (mean 59.8 Gy vs mean 35.1 Gy).

We found no effect of mean PB-dose on the primary outcome adjusted for study-site, risk-group and age. When adjusting for serum-testosterone level at 18 months in addition, the effect of mean PB-dose remained insignificant.

Interpretation: IGRT protocol or PB dose had no effect on ED 18 months after RT in this study population. The low potency rates can partly be explained by the prolonged use of anti-androgen in high risk patients. Longer follow-up is needed to confirm the results from the RIC-study.

1. Introduction

The prevalence of prostate cancer (PC) in Norway is doubled from 2005 to 2015, leading to an increased focus on late side effects after cancer treatment [1]. This includes reduced sexual

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function among both younger individuals and still sexually active elderly men in good health.

The European Association of Urology (EAU) guidelines define erectile dysfunction (ED) as "the persistent inability to attain and maintain an erection sufficient to permit satisfactory sexual performance" [2]. ED increases with age with a reported prevalence of >70% in men by the age of 70 [3]. Furthermore, ED may be the first sign of Diabetes Mellitus (DM) type 2 and is strongly associated with other conditions such as cardiovascular disease (CVD), sleep disorders, pulmonary disease and smoking, as well as alcohol abuse and a sedentary lifestyle [3,4].

ED is common after PC treatment including prostatectomy, endocrine therapy (ET) and radiotherapy (RT). The risk is increased when ET is given in addition to RT [5–8]. Furthermore, several studies have reported that the ED risk increases with radiation dose to the erectile apparatus such as the corpora cavernosa including the penile bulb (PB) [9–12].

We have previously reported acute rectal and genitourinary side effects after radical RT for PC in patients randomized to either weekly orthogonal portal imaging with conventional PTV margins or daily cone beam computed tomography (CBCT) image-guided radiotherapy (IGRT) and reduced planning target volume (PTV) margins (the RIC-study) [13]. In the present analysis, we compared patient reported sexual function in the two groups 18 months after RT using the Questionnaire Umeå Fransson Widmark 1994 (QUFW94) questionnaire single item "can you get an erection?" as primary outcome. In addition, we evaluated the impact of radiation dose to the PB on sexual function.

2. Methods

The RIC-study has been described in detail previously [13]. In short, the study included 257 men younger than 80 years treated at two Norwegian Hospitals (Ålesund Hospital and St. Olavs Hospital) with histologically proven intermediate- or high risk PC suitable for radical external beam radiotherapy (EBRT) to a total dose of 78 Gy. All patients received ET with 6 months of total androgen blockage (TAB) with a luteinizing hormone-releasing hormone (LHRH)-agonist (Gosereline acetate 10·8 mg, two injections with three months interval) and an antiandrogen (Bicalutamide 50 mg/day orally). The ET started 3 months prior to prostatic irradiation. Whereas all ET was discontinued after six months (three months after start of RT) in the intermediate risk patients, all high-risk patients received Bicalutamide (150 mg/day) for an additional 2·5 years. At start of RT, patients were randomized in two arms receiving 0–70 Gy RT in 2 Gy fractions in which position control was done by weekly offline orthogonal portal imaging (2D weekly IGRT-arm) or with daily CBCT-verification (3D daily IGRT-arm). Randomization was computer based and stratified by center and risk group. All patients received a 2 Gy × 4 boost to 78 Gy with daily CBCT-verification.

A CT-based dose-planning system was applied, and the clinical target volume (CTV) 1 included the prostate and any suspected extra capsular tumor growth or infiltration into the seminal vesicles (SV) as described by clinical findings, trans-rectal ultrasound and/or pelvic MRI. The CTV2 included the prostate and basal 1 or 2 cm of the SV in intermediate and high-risk patients, respectively. In patients given standard treatment (2D weekly IGRT-arm), the planning target volume (PTV) 2 receiving 70 Gy included the CTV2 with an additional 15 mm margin in all directions. In the 3D daily IGRT-arm the corresponding PTV2 included the CTV2 with an additional 7 mm margin in all directions. The 4 Gy boost volume (PTV1) included the CTV1 with an additional 3 mm margin in both study arms.

The PB was outlined as an organ at risk (OAR) on the planning CT-scan according to the study protocol and defined as the posterior thick part of the spongious body of the penis. No dose constraint regarding the penile structures was defined. Treatment planning was performed in Oncentra v4·3 (Elekta AB, Sweden) and patients were treated on Elekta Synergy® or Elekta Precise® platforms. Volumes (cm^3) and mean dose (Gy) for the PB were estimated.

Patients met a clinical oncologist at inclusion, at end of RT and every 6 months thereafter. At inclusion, the end of RT, and at 5, 12 and 18 months follow up, the patients returned the European Organization for Research and Treatment of Cancer questionnaire regarding health-related quality of life (EORTC QLQ-C30) and organ specific questions (urinary, bowel and sexual symptoms) by use of the Questionnaire Umeå Fransson Widmark 1994 (QUFW94), also called Prostate Cancer Symptom Scale [14]. Both questionnaires evaluate symptoms during the previous week and have been developed to assess the quality of life in cancer patients and to evaluate side effects experienced by PC patients following pelvic RT [14,15].

The following items in the QUFW94 questionnaire regarding sexual function were graded on an 11-point scale: Ability to have an erection, ability to have an erection with and without assistance (0 = normal and 10 = not at all), problems with sex life (0 = no and 10 = very much), sexual desire (0 = very much and 10 = not at all). Moreover, the patients were requested to record whether the erection was sufficient to carry out sexual intercourse and if the erection was sufficient with and without medication (yes/no). The use (always/seldom/not at all) as well as type of medication (alprostadil, sildenafil, apomorphine or others) to carry out sexual intercourse was recorded.

2.1. Statistics

The statistical analysis was performed according to a preplanned strategy using the QUFW94 questionnaire item "can you get an erection?" as primary outcome. The main analysis were linear regression for scale outcome variables, logistic regression for dichotomous outcome variables, and ordinal logistic regression for the question with three ordered alternatives. Treatment group was the covariate of primary interest, and was adjusted for site (Ålesund Hospital versus St Olavs Hospital) and risk group (high versus intermediate), since randomization was stratified on these. We also adjusted for age which is an important prognostic factor as recommended by Vittinghoff et al. 2012, page 417 [16].

We used available case analysis. That is, each analysis included the patients with complete data on the relevant variable(s). In addition, regression analysis with mean dose to PB as covariate instead of treatment group was carried out for the primary outcome. We also performed the analysis with testosterone level at 18 months as covariate.

3. Results

In total, 250 out of 257 included patients were analyzed in the previous published RIC-study [13]. At 18 months after start of RT, 228 (91%) out of 250 patients returned the questionnaires (Fig. 1). Out of these, 119 patients were included at St. Olavs Hospital and 109 at Ålesund Hospital. Three patients died before 18 months of follow-up due to other causes than PC (pancreatic cancer, lung cancer and malignant melanoma) diagnosed after finishing prostatic irradiation. One patient died of unknown reason, one patient withdrew from the study, one patient was unable to fill out the questionnaire due to a cerebral insult, and 16 patients did not give any reason for not returning the questionnaires.

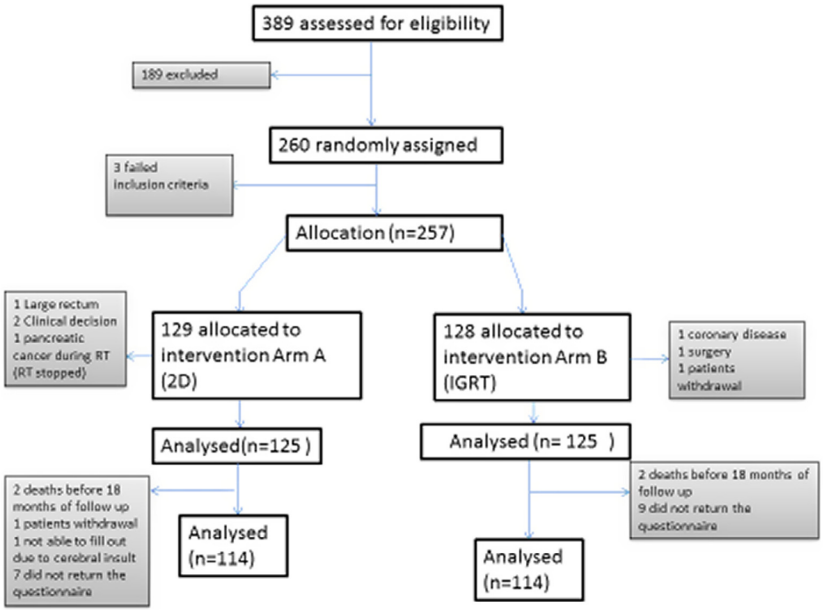

Fig. 1. Consort diagram.

Baseline characteristics were balanced between treatment arms (Table 1). The mean age was 71·8 years. A total of 143 (63%) patients had cardiovascular disease (CVD) according to WHO (World Health Organization) definition or associated risk factors such as hypertension and hypercholesterolemia and 31 (13·5%) had diabetes mellitus.

Data on testosterone level (normal range 6·73–31·8 nmol/l at St. Olavs Hospital and 4·5–26·6 nmol/l at Ålesund Hospital, respectively) were obtained in 190 (83%) of the 228 study patients. Of these, 135 (71%) had testosterone level within normal range at 18 months, with mean levels (SD) of 8·9 (6·1) and 9·4 (6·6) nmol/l in the 2D weekly IGRT-arm and 3D daily IGRT-arm, respectively ($p = 0.496$). Seven patients in the 2D weekly IGRT-arm and six patients in the 3D daily IGRT-arm who were given prolonged LHRH-agonist treatment due to side effects from Bicalutamide or metastatic disease, still had castrate levels (<1·7 nmol/l) of testosterone at 18 months.

Of the 228 patients who returned the questionnaires 18 months after start of RT, 221 (97%) responded to the primary outcome question, "Can you get an erection". We found no difference between the arms for this outcome at 18 months follow up: The mean score was 7·44 in 2D weekly IGRT-arm and 7·39 in the 3D daily IGRT-arm, regression coefficient 0·04 (CI −0·81 to 0·89, $p = 0.93$) when adjusting for site, risk group and age, see Table 2. Only 16% (n = 15 in the 2D weekly IGRT-arm and n = 16 in the 3D daily IGRT-arm) of the patients reported a sufficient erection to carry out sexual intercourse at 18 months (Table 3). Baseline characteristics in the 31 potent patients are described in table 4. The majority of potent patients had CVD (10 in the 2D weekly IGRT-arm and 11 in the 3D daily IGRT-arm). Five patients in each study arm reported need of medication to carry out sexual intercourse. Patients reported a high degree of sexual related problems for all five questions scaled from 0 to 10 with mean scores from 6·52 to 8·04 (Table 2).

Table 1
Baseline characteristics in 228 RIC-study patients who returned the EORTC QLQ-C30 and QUFW94 questionnaires at 18 months.

	2D weekly IGRT (n = 114) (SD)	3D daily IGRT (n = 114) (SD)
Age (years) at inclusion, mean (SD)	72·2 (4·3)	71·4 (4·6)
Risk group		
High, n (%)	70 (61·4)	69 (60·5)
Intermediate, n (%)	44 (38·6)	45 (39·5)
PSA[1] at treatment start, mean (SD)	16·5 (15·1)	16·2 (12·1)
Tumor stage, n (%)		
T1	20 (17·6)	25 (21·9)
T2	42 (36·8)	36 (31·6)
T3	52 (45·6)	52 (45·6)
T4	0 (0)	1 (0·9)
Gleason score, n (%)		
Gleason score 6	8 (7·0)	11 (9·7)
Gleason score 7	64 (56·1)	67 (58·8)
Gleason score 8	24 (21·1)	17 (14·9)
Gleason score 9	15 (13·2)	16 (14·0)
Gleason score 10	3 (2·6)	3 (2·6)
Diabetes Mellitus, n (%)	18 (15·8)	13 (11·4)
Cardiovascular disease and risk factors[2], n (%)	69 (60·5)	74 (64·9)
Other disease[3], n (%)	9 (7·9)	6 (5·3)
PB volume[4,5], mean (SD)	3·5 (1·8)	3·9 (2·1)
PB dose[5,6], mean (SD)	59·8 (14·8)	35·0 (21·4)

Abbreviations: EORTC QLQ-C30: European Organization for Research and Treatment of Cancer questionnaire regarding health-related quality of life, QUFW94: Questionnaire Umeå Fransson Widmark 1994, 2D: Two-dimensional, IGRT: image-guided radiotherapy, 3D: three-dimensional, SD: standard deviation, PSA: prostate specific antigen, PB: penile bulb.

[1] nmol/l.
[2] According to WHO (World Health Organization) definition including risk factors (hypertension and hypercholesterolemia).
[3] Include gastrointestinal and kidney disease.
[4] cm^3.
[5] Evaluable in 219 patients.
[6] Gy.

Table 2
Response to the QUFW94 questionnaire graded on an 11-point (0–10) scale. Ten denotes the worst outcome.

	2D weekly IGRT (n = 114)		3D daily IGRT (n = 114)		Coefficient (β) 2D weekly IGRT versus 3D daily IGRT	
Question Scale: 0–10	Number of respondents	Mean (SD)	Number of respondents	Mean (SD)	Estimate [2] (95% CI)	p-value
[1]Can you get an erection?	108	7·44 (3·3)	113	7·39 (3·1)	0·04 (−0·81 to 0·89)	0·93
Do you have a problem with your sex life?	98	7·00 (3·8)	101	6·67 (3·6)	0·35 (−0·70 to 1·40)	0·51
Do you feel like sexual activity?	109	6·74 (3·1)	111	6·52 (3·1)	0·19 (−0·62 to 1·0)	0·65
Are you able to have an erection without medication?	103	7·75 (3·2)	108	7·55 (3·2)	0·18 (−0·68 to 1·04)	0·68
Can you get an erection (with assistance)?	32	7·22 (3·6)	25	8·04 (2·9)	−1·03 (−2·87 to 0·80)	0·26

Abbreviations: QUFW94: Questionnaire Umeå Fransson Widmark 1994, 2D:Two-dimensional, IGRT: image-guided radiotherapy, 3D: three-dimensional, SD: standard deviation. CI: confidence interval.
[1] Primary outcome.
[2] Coefficient for 2D weekly IGRT versus 3D daily IGRT in linear regression, adjusted for site, risk group, and age.

Table 3
Response to the QUFW94 questionnaire with scale yes/no and always/seldom/often.

	2D weekly IGRT (n = 114)		3D daily IGRT (n = 114)			
Question Scale: Yes/no	Number of respondents		Number of respondents		Odds Ratio (95%CI)[1]	p
Is the erection sufficient to carry out sexual intercourse?	95	yes: 15·8%	100	yes: 16·0%	1·06 (0·48 to 2·32)	0·89
Is the erection sufficient (without assistance) to carry out sexual intercourse?	91	yes: 13·2%	94	yes: 16%	0·87 (0·375 to 2·03)	0·75
Is the erection sufficient (with assistance) to carry out sexual intercourse?	37	yes: 24·3%	23	yes: 17·4%	1·69 (0·432 to 6·56)	0·45
Question Scale: always/seldom/not at all	Number of respondents		Number of respondents		Odds Ratio (95% CI)[2]	p
Have you used assistance to carry out sexual intercourse?	89	always: 5·6% seldom: 9·0% not at all: 85·4%	101	always: 5% seldom: 5·9% not at all: 89·1%	0·71 (0·30 to 1·68)	0·43

Abbreviations: QUFW94: Questionnaire Umeå Fransson Widmark 1994, 2D: Two-dimensional, IGRT: image-guided radiotherapy, 3D: three-dimensional, CI: confidence interval.
[1] Odds ratio (OR) for 2D weekly IGRT versus 3D daily IGRT in logistic regression, adjusted for site, risk group, and age.
[2] Odds ratio (OR) for the 3D daily IGRT arm (versus the 2D weekly IGRT arm) in ordinal logistic regression, adjusted for site, risk group, and age.

The mean PB volumes (SD) were 3·5 (1·8) and 3·9 (2·1) cm^3 in 2D weekly IGRT-arm (108 evaluable patients) and the 3D daily IGRT-arm (111 evaluable patients), respectively (Table 1). The mean dose to PB was substantially larger in the 2D weekly IGRT-arm vs the 3D daily IGRT-arm (mean 59·8 Gy vs mean 35·1 Gy). We found no effect of mean dose to PB in regression analysis for the primary outcome ("can you get an erection?") adjusted for site, risk group and age (Regression coefficient −0·01 Gy^{-1}, CI −0·03 to 0·01, $p = 0·34$). When adjusting for testosterone level at 18 months in addition, the effect of mean dose to PB remained insignificant (regression coefficient −0·006 Gy^{-1}, CI −0·03 to 0·02, $p = 0·61$).

4. Discussion

The key finding in this study was that the ability to have an erection 18 months after local 78 Gy EBRT for prostate cancer was not different in patients treated with a reduced PTV margin and daily CBCT as compared to those who received the same treatment with wider margins and weekly verification. Moreover, there was no identified association between radiation dose to the PB and erectile function.

Although controversial, RT has been considered to yield less ED than radical prostatectomy [11]. The degree of ED increases gradually after RT, and there is some evidence that the functional decline is stabilized after approximately 2 years. Thereafter few patients with ED will regain their sexual function [17–19]. In the ProtecT-trial (Prostate Testing for Cancer and treatment), 67% of the patients (mean age 62 years) reported erection firm enough for intercourse prior to treatment for PC. By 6 months, the proportion fell to 22% in patients given RT, increasing to 37% at 12 months and thereafter declining to 34% at 24 months and 27% at 6 years. The corresponding figures following prostatectomy at 6 months and 6 years were 12% and 17%, respectively. The active monitoring group scored best with 52% after 6 months and 30% at year 6, demonstrating that other factors than cancer therapy, such as aging and comorbidity, are involved in ED development [20].

The estimated prevalence of ED in the general population range between 50 and 100% in men older than 70 years [3]. Shiri et al. reported a prevalence of 89% in Finnish men aged 75, and 76·5% in men aged 50–75 years [4]. However, other studies report lower prevalence (20–40% in men aged 60–69 and 50% in men >70 years) [21]. The discrepancy may be due to different questionnaires and diagnostic criteria. Moreover, CVD and DM are strongly associated with ED [3]. The mean age in our study population was 71·8 years. More than 60% of the patients reported CVD or associated risk factors according to WHO and 14% reported DM (Table 1). The mean age of patients operated with radical prostatectomy in Norway is

Table 4
Baseline characteristics in 31 potent RIC-study patients at 18 months.

	2D weekly IGRT (n = 15)	3D daily IGRT (n = 15)
Age (years) at inclusion, mean (SD)	72.9 (3.6)	68.3 (5.1)
St. Olavs hospital (n)	10	9
Ålesund hospital (n)	5	7
Risk group		
High-risk (n)	8	7
Intermediate risk (n)	7	9
PSA[1] (nmol/l) at treatment start, mean (SD)	20.3 (SD 17.6)	15.9 (SD 10.4)
Tumor stage (n)		
T1	1	5
T2	10	5
T3	4	6
Gleason score (n)		
Gleason score 6	0	1
Gleason score 7	12	13
Gleason score 8	2	1
Gleason score 10	1	1
PB volume[2], mean (SD)	3.4 (SD 2.0)	4.2 (SD1.7)
PB dose[3], mean (SD)	63.8 (SD 8.0)	33.0 (SD 25)
Cardiovascular disease and risk factors[4] (n)	10	11
Gastrointestinal disease	1	0
Testosterone recovery[5] at 18 mnd (n)		
Yes	12	15
No	3	1

[1] nmol/l.
[2] cm^3.
[3] Gy.
[4] According to WHO (World Health Organization) definition including risk factors (hypertension and hypercholesterolemia).
[5] Within normal range: 6.73–31.8 nmol/l (St. Olavs hospital) and 4.5–26.6 nmol/l (Ålesund hospital).

63 years, while patients treated with RT are older with a mean age of 69 years [22]. The RIC study patients were even older. It is thus still possible that the younger patients with lesser comorbidity (who are currently selected for surgical treatment) could have benefited from a reduced PB-dose if treated with radical RT. This is important to bear in mind since the evidence in support of selecting younger men for surgery is poor.

The addition of ET to RT has improved survival in PC patients significantly although at cost of increased acute and late side effects, especially ED [8,23,24]. The reported median time to normalization of testosterone level after medical castration range between 18·3 and 25 months dependent on duration and substance used [25,26]. In our study, 71% of the patients had testosterone recovery 18 months after the last Gosereline acetate injection. In potent patients, 87% had testosterone recovery at 18 months. Even though recovery of a normal testosterone level is achieved in the majority following medical castration, a large proportion still report impotency. Wilke et al. found that only 10% regained potency after 2 years of ET treatment combined with RT, despite the return to supracastrate levels [27]. We evaluated erectile function 18 months after inclusion when 71% of the study population had regained testosterone level within normal range. Most likely, the proportion was higher at 24 months with a possible favorable effect on potency. On the other hand, the gradual decline of erectile function caused by irradiation and age contribute in the opposite direction [20]. We believe that the possible difference between ED figures at 24 months and those obtained at 18 months in this study would be marginal.

Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC) recommends to keep the mean dose to 95% of the PB volume to <50 Gy [11]. Damage to small vessels, nerves and tissue fibrosis are considered to be of major importance in ED development [28]. A review by Rivin del Campo et al. on ED 2 years or more after RT in PC included 8 studies which examined the relationship between PB dose and ED [29]. An association was found in 4 of these studies. A reliability score with five items (potency before RT, questionnaire used for potency evaluation, dose range to PTV, threshold effect and PB definition) was used. The studies with the highest scores, support the PB dose-volume constraint recommended by QUANTEC. Evidence from randomized studies of a favorable effect on erectile function from modern RT-techniques with reduced PB-dose has, however, been missing. In our study, the dose to PB was significantly higher in the 2D weekly IGRT-arm due to larger PTV-margins (mean 59·8 Gy vs mean 35·1 Gy). Notably, the percentage of ED was high in both study arms, and few patients (16%) were able to complete sexual intercourse 18 months after RT. The mean dose to PB in potent patients was 63.8 Gy in the 2D weekly IGRT-arm and 33.0 Gy in the 3D daily IGRT-arm. Our study did not provide evidence that a radiation dose to the PB higher than the levels recommended by QUANTEC increased ED.

This study has some limitations. The RIC-study patients were included after 3 months neo-adjuvant TAB at a time when erectile dysfunction is expected to be total. We do not have data on sexual function at the start of neo-adjuvant ET. It is, however likely that a high proportion of these elderly and relatively comorbid men already had ED at treatment start, although evenly distributed in the two treatment groups due to the randomized study design. Moreover, 60% of the patients still used Bicalutamide at 18 months due to high-risk disease. It is thus highly likely that Bicalutamide in addition to high age, comorbidity and incomplete testosterone recovery in 29% contributed to the high incidence of ED found in this study. The exact distribution of cardiovascular disease, hypertension, hyperlipidemia and other diseases such as neurological, endocrine or pulmonary conditions, medication, smoking or alcohol abuse in the RIC study population is unknown. Notwithstanding the adverse effect on erectile function, we expect that these ED risk-factors were evenly distributed with similar effects in both groups in this randomized study.

The Radiation Therapy Oncology Group (RTOG) defines PB as the part of the bulbus spongiosum immediately inferior to the genitourinary diaphragm with rounded shape, best identified with Magnetic Resonance Imaging (MRI) (T2) or Computed Tomography (CT)-scan with urethra contrast [30]. In the RIC-study, the PB was defined as the posterior thick part of the spongious body of the penis and was delineated on CT-scans without intravenous or urethral contrast. This anatomic definition differs to some extend from the definition by RTOG in the study reported by Gay et al. [30]. Even though MRI is superior to CT imaging of pelvic soft tissue, and the penile bulb appears best on T2-weighted MR images [31], CT-based dose-planning with narrow slice thickness such as the 2 mm applied in this study is still commonly used in daily practice.

Modern RT applying different IGRT-techniques has led to less random errors associated with set-up and also better control with organ motion during treatment. Nevertheless, systematic errors may still be introduced due to uncertainties in delineating of different target volumes and OARs prior to the treatment. Perna et al. performed a dummy run in which 15 physicians from different institutes delineated the PB on CT-images [32]. Due to large inter-observer variation, the authors recommend MRI for RT dose-planning as well as dummy-runs prior to studies and fewer physicians involved in the target contouring. Prior to the start of the RIC-study, three dummy-runs were performed revealing some variability in the contouring of the PB from center to center. All the oncologists involved in the daily routine at the two participating RT-centers contoured the PB in our study. Arguably, adherence to

the recommendations by Perna et al. may have reduced the variability in PB contouring. On the other hand, the RIC-study reflects daily practice ensuring a higher external validity. Another strength of the study was the high compliance (97%) to the primary outcome question.

In conclusion, although the patients in the 3D daily IGRT-arm received a significantly lower PB dose, the RIC-study did not reveal an effect of IGRT with reduced margins on erectile and sexual function 18 months after radical EBRT in combination with ET in men with PC. The RIC-study results must, however, be interpreted with care. The reduction of irradiated volume may protect against a variety of late side effects, and shielding of the corpora cavernosa and the PB in particular may still be justified, especially in younger sexually active men with less comorbidity. More so since modern RT and daily imaging gives the opportunity to reduce OAR-dose including the PB without compromising dose to the tumor. Longer follow-up is needed to confirm the results from the RIC-study.

Research in context

Evidence before this study

The prevalence of prostate cancer is increasing worldwide, leading to enlarged focus on late side effects after cancer treatment, including reduced sexual function. Erectile dysfunction is a common side effect of all treatment modalities for prostate cancer (surgery, endocrine therapy and radiotherapy). Modern IGRT such as Cone Beam CT (CBCT) was introduced in the late 1990s and gave a new insight to the internal organs motion during RT planning and delivery. Theoretically, this opened doors to several clinical improvements, especially dose escalation. Results from previous non-randomized studies suggest that modern IGRT and tighter PTV margins reduce radiation-induced toxicity in radical RT treatment for prostate cancer patients. There is, however, a lack of scientific evidence from randomized studies that IGRT provides such benefits.

Added value of this study

To our knowledge, the RIC-study is the first randomized trial that compares patient reported outcomes of modern IGRT and reduced margins versus weekly portal imaging and standard margins in radical RT in prostate cancer patients.

We performed a randomized phase 3-trial including patients suitable for radical external beam prostatic irradiation (total dose 78 Gy) in two arms, either with 7 mm PTV margins and daily CBCT IGRT or 15 mm PTV margins and weekly orthogonal portal imaging. The primary aim of the study was acute rectal side effects and the results are reported previously. In the present analysis, we compared patient reported sexual function in the two groups 18 months after RT using the Questionnaire Umeå Fransson Widmark 1994 (QUFW94) questionnaire single item "can you get an erection?" as primary outcome. In addition, we evaluated the impact of radiation dose to the PB on sexual function. We found no difference between groups for these outcomes in this elderly patient population with a high degree of comorbidity.

Implications of all the available evidence

Studies have shown that the degree of erectile dysfunction gradually increases after radiotherapy, and some evidence suggest stabilization after 2 years. Increasing age, comorbidity, the use of endocrine therapy as well as radiation dose to erectile structures are risk factors for erectile dysfunction.

Results from previous non-randomized studies suggest that modern IGRT and tighter PTV margins reduce radiation-induced toxicity in radical RT treatment for prostate cancer. This randomized phase 3-trial study demonstrated, however, no benefit of daily IGRT regarding erectile function in patients receiving radical external beam RT for prostate cancer. Undoubtedly, new RT techniques are often implemented in standard clinical practice with limited evidence of benefits to patients. So far, this randomized study has not provided such evidence. The patients will, however, be followed for at least ten years regarding late side effects and cancer control. Longer follow-up is needed to confirm the results from the RIC-study.

6. Contributors

JÅL, AS, BA, ADW, CAJ, SK and SL planned the study initially and amended the protocol together with HT in 2012. JÅL, AS, BA and HT enrolled patients and collected data at the study centres. SL was responsible for statistical planning and data analysis in collaboration with the first and last author. HT and AS were responsible for data collection and drafted the manuscript. All authors were involved in revision and have approved the final manuscript.

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