Prostate Cancer without Distant Metastases

Treatment and Mortality in Norway 2001-2016

Kirsti Aas, MD

Vestre Viken Hospital Trust, Bærum Hospital, Department of Urology

&

Oslo University Hospital, Division of Cancer, Surgery and Transplantation,

Department of Oncology/Department of Urology

&

Cancer Registry of Norway

&

University of Oslo, Faculty of Medicine

Thesis for the degree of Philosophiae Doctor (PhD)

Oslo 2020

© Kirsti Aas, 2021

Series of dissertations submitted to the
Faculty of Medicine, University of Oslo

ISBN 978-82-8377-781-9

All rights reserved. No part of this publication may be
reproduced or transmitted, in any form or by any means, without permission.

Cover: Hanne Baadsgaard Utigard.
Print production: Reprosentralen, University of Oslo.

Acknowledgements

This work was conducted as a medical doctor in the Department of Urology at Bærum Hospital 2015-20 and as a research fellow attending the PhD program at the Faculty of Medicine, University of Oslo 2018-20.

First of all, thank you to the Cancer Registry of Norway for providing data and scientific support and the Vestre Viken Hospital Trust, Norwegian Cancer Association and the Radium Hospital Foundation for funding this project and bringing it to life. I feel privileged to have had the opportunity to combine clinical research and practice within a field of great personal interest.

Above all, I am sincerely grateful to my supervisors, Viktor Berge and Sophie D. Fosså, for their commitment and professional support throughout this project. Dr Berge´s expertise within urology and clinical research, combined with excellent supervision, has been greatly appreciated. Professor emerita Fosså is a pioneer and a mentor second to none within this field of research. The personal relationship and scientific discussions are deeply valued.

Thank you to my all co-authors for providing valuable feed-back along the way. A special thank you to Bjørn Møller at the Cancer Registry and Tor Åge Myklebust for providing excellent statistical support and for translating advanced statistics into clinically relevant analyses. I would also like to thank Karol Axcrona for his valuable contributions in the initial phases of this project.

My parents and Inger deserve my deepest gratitude, always supporting me and facilitating the pursuance of my academic career. Last, but not least, I am deeply grateful to my children Edvard (3), Ella (5) and Herman (7) for bringing color and balance to life, and to my husband for his continuous love and support.

Kirsti Aas
Oslo 2020

Table of Contents

Abbreviations

ADT	Androgen deprivation therapy
AS	Active surveillance
BCR	Biochemical recurrence
CPP	Cancer patient pathway
CRN	Cancer Registry of Norway
CT	Computed tomography
DRE	Digital rectal examination
EAU	European Association of Urology
ECOG	Eastern Cooperative Oncology Group
GGG	Gleason grade group
ISUP	International Society of Urological Pathology
NoPCR	Norwegian Prostate Cancer Registry
NPR	Norwegian Patient Registry
MRI	Magnetic resonance imaging
OM	Overall mortality
PCa	Prostate cancer
PCSM	Prostate cancer-specific mortality
PET	Positron emission tomography
PIVOT	Prostate Cancer Intervention Versus Observation Trial
PLND	Pelvic lymph node dissection
ProtecT	Prostate Testing for Cancer and Treatment (trial)
PSA	Prostate-specific antigen
PSMA	Prostate-specific membrane antigen
RAD	Radiotherapy
RP	Radical prostatectomy
SIOG	International Society of Geriatric Oncology
SPCG	Scandinavian Prostate Cancer Group
TNM	Tumour Node Metastasis
UICC	Union of International Cancer Control
WHO	World Health Organization
WW	Watchful waiting

“For a patient with prostate cancer, if treatment for cure is necessary,

is it possible? If possible, is it necessary?”

Willet F. Whitmore M.D. (1917-1995)
Professor of Urology, Memorial Hospital, New York

Thesis summary

The public health burden of prostate cancer (PCa) is a major challenge. PCa has evolved from being an infrequent disease with poor prognosis, to a widely common condition with high probability of survival when discovered in early phases. The greatly disproportionate incidence and mortality rates cause concerns about overdiagnosis and overtreatment of PCa. Still, a vast number of men continue to die from this disease. Patients, researchers, clinicians and policy makers are therefore seeking answers to the question: How to reduce PCa-related morbidity and mortality without compromising the health of a large number of men who would otherwise not suffer from this disease?

The majority of men with PCa have no distant metastases at the time of diagnosis. These men have overall good prognosis, and long-term follow-up is often necessary for any treatment-related survival benefits to become evident. Not previously documented in a population-based cohort of men with PCa in Norway, we present in paper one in this thesis, ten-year PCa-specific mortality (PCSM) in men stratified according to risk group and primary treatment. Patients with aggressive tumours and high-risk disease benefitted the most from curative treatment, and findings support the ongoing shift in patient selection for radical treatment.

The timing of radical prostatectomy (RP) has been debated since the Cancer Patient Pathway for PCa was implemented by the Norwegian Health Authorities in 2015. The second paper in this thesis investigates the impact of time from diagnosis to RP on prognosis, demonstrating that increase in such time interval up to six months does not worsen survival in any risk group. These findings are important for patient counselling and treatment planning.

Patterns of PCa care have evolved with better understanding of PCa biology and observed outcomes after treatment. The final paper in this thesis demonstrates that senior adults with high-risk PCa increasingly receive curative treatment with similar survival benefits to younger men, suggesting that these senior men should be considered for curatively intended treatment, assuming adequate health screening and in-depth patient counselling.

The research questions presented in this thesis arise from everyday clinical practice, and findings may aid clinicians when making treatment-decisions in men with early-stage PCa.

Articles in the thesis

Paper I

Aas, K., K. Axcrona, R. Kvåle, B. Møller, T. A. Myklebust, U. Axcrona, V. Berge, and S. D. Fosså. 2017. "**Ten-year Mortality in Men With Nonmetastatic Prostate Cancer in Norway."** *Urology*. 2017; 110: 140-147 (1).

Paper II

Aas, K., S. D. Fosså, R. Kvåle, B. Møller, T. A. Myklebust, L. Vlatkovic, S. Müller, and V. Berge. 2018. "**Is time from diagnosis to radical prostatectomy associated with oncological outcomes?**" *World J Urol.* 2019; 37(8): 1571-80 (2).

Paper III

Aas, K., S. D. Fosså, T. A. Myklebust, B. Møller, R. Kvåle, L. Vlatkovic, and V. Berge. "**Increased Curative Treatment is Associated with Decreased Prostate Cancer-specific and Overall Mortality in Senior Adults with High-risk Prostate Cancer; Results from a National Registry-based Cohort Study**" *Cancer Med. 2020.*

1. Introduction

1.1. Epidemiology

With estimated 1.3 million new cases in 2018, prostate cancer (PCa) is the second most common cancer in males worldwide and the most common male cancer in developed countries (3). The highest incidence rates of PCa are found in North America, Caribbean, Brazil, Oceania and Europe (4). The remarkable differences in geographical distribution of PCa may reflect international differences in underlying risk and diagnostic practices. With ageing of the population and increased life expectancy (LE), a significant increase in PCa incidence and prevalence is expected worldwide, particularly in senior men (5).

In 2018, 4848 men were diagnosed with PCa in Norway, accounting for 27.9% of all new cancers in males (6). The introduction of the prostate-specific antigen (PSA) test in the 1990s resulted in a steep increase in the incidence of PCa (Figure 1,2) (6-9), and increased diagnostic efforts have resulted in a decrease in the median age at PCa diagnosis, from 74 years in 1994-98 to 69 years in 2013-2017 (6). Although the absolute number of new PCa cases in Norway has slightly increased in the last decade (4391 in 2009), the incidence rate has gone down (6). The cumulative risk of being diagnosed with PCa by the age of 75 is 12.8 % in Norwegian males (8, 9). Disproportionate incidence and mortality rates have resulted in an almost doubling in PCa prevalence in the last decade (6). By the end of 2018, 52 061 men lived with a diagnosis of PCa in Norway (6).

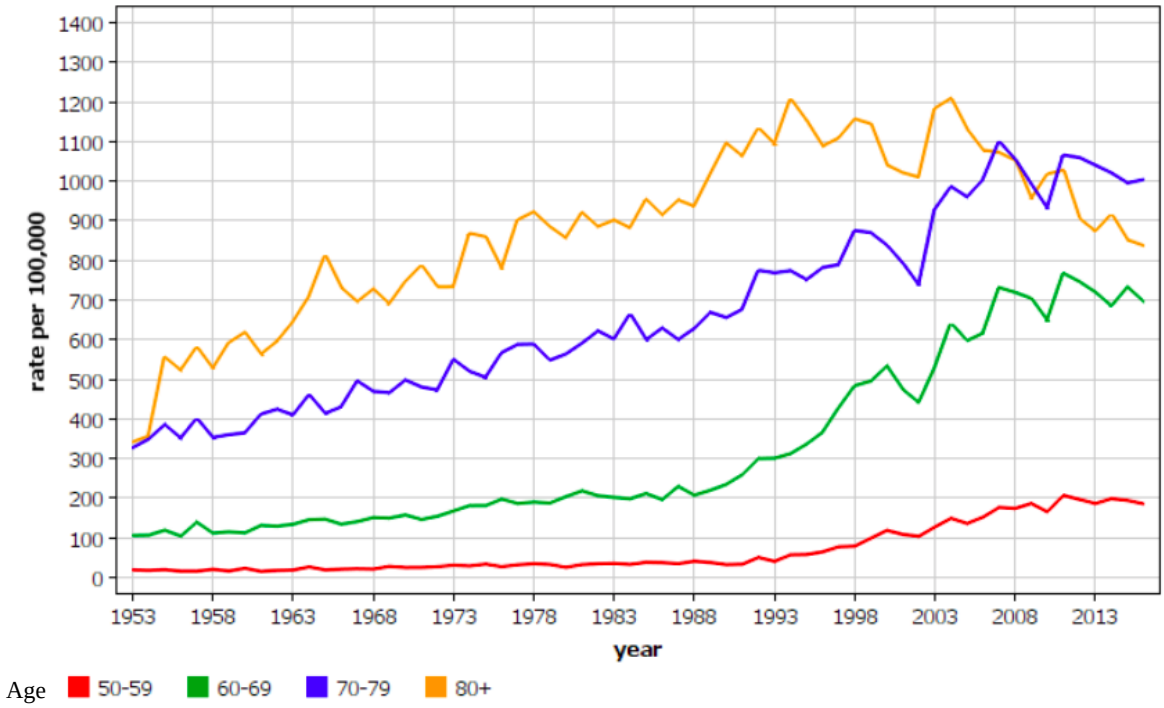


Figure 1. The incidence rates of PCa according to age in Norway 1953-2016 (8, 9). Copyright has been obtained.

Incidence and detection of PCa are strongly correlated with age (Figure 1) (7). Having a first-degree relative (father or brother) with PCa at any age doubles the risk of being diagnosed with PCa, and the risk further increases with several affected first-degree relatives (10). There is growing evidence that dietary habits and lifestyle factors are associated with PCa, however, results are conflicting (4, 11). Obesity has been linked to high-grade PCa (12, 13).

PCa is the fifth leading cause of cancer deaths in men worldwide (3). Age-standardized mortality rates are highest in regions with predominantly Black populations and Northern Europe and lowest in the South-East Asia, Northern Africa and the Middle-East (4, 14). Worldwide, the absolute number of PCa deaths increased from 260 000 in 2008 to 359 000 in 2018 (3), but the morality rates have declined in most developed countries (14).

In Norway, PCa is the second leading cause of cancer death among men, constituting 16% of all cancer deaths (6). The absolute number of PCa deaths per year (921 PCa deaths in 2017 compared to 1026 deaths in 2004) and the mortality rate have slightly declined in Norway over the past decades (Figure 2) (6, 15). The cumulative risk of dying from PCa before age 75 is 1% in Norwegian males (8, 9).

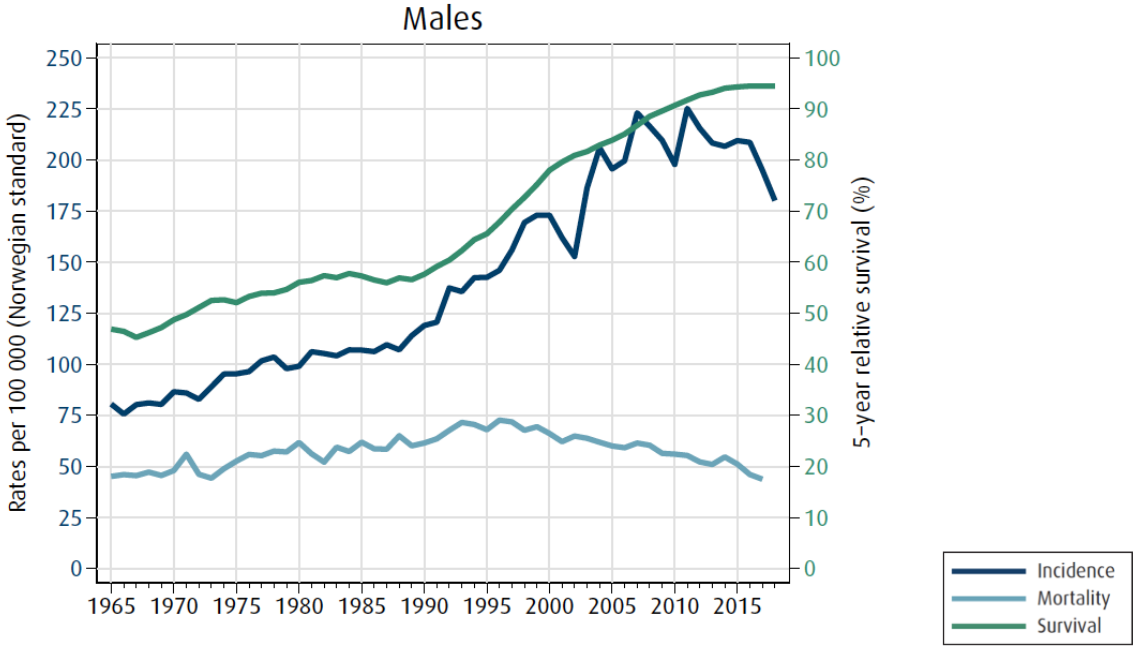


Figure 2. Trends in incidence and mortality rates and 5-year relative survival proportions – Prostate cancer (6). Copyright has been obtained.

1.2. Diagnosis

PCa is suspected on the basis of an abnormal digital rectal examination (DRE) and/or elevated or rising PSA in men with or without lower urinary tract symptoms, or in rare cases in men with symptoms of metastatic disease. The definitive diagnosis is based on histopathological confirmation of prostatic cancer cells.

1.2.1. Digital rectal examination

DRE is performed as part of a routine health check or when PCa is suspected. An abnormal DRE is an indicator of PCa (16). The positive predictive value of an abnormal DRE ranges from 6–33% and is associated with the PSA level (17). With increased use of magnetic resonance imaging (MRI) of the prostate, the diagnostic value of DRE has less relevance in determining the need for biopsies. Interchangeably, when PCa is confirmed, DRE still forms the basis for local staging, in part because of poor specificity of MRI (18, 19).

1.2.2. Prostate-specific antigen

PSA is an enzyme in the kallikrein family, produced by the secretory cells in the ducts and acini of the prostate gland and responsible for liquification of semen. PSA is an organ-specific, but not cancer-specific, serum marker. Benign conditions of the prostate (benign hyperplasia, prostatitis) may result in an elevated PSA, and in cancer-free men, values are influenced by the age of the patient and size of the prostate gland. Increasing PSA levels are associated with higher likelihood of PCa, although a considerable number of men harbor significant PCa in the presence of low PSA levels (20). When used as single measure, PSA has low specificity and low positive predictive value for PCa (21). PSA density, PSA velocity and PSA isoforms may add value to the absolute PSA value as a diagnostic test (22, 23). A PSA level >100 ng/ml has been used as an indicator of metastatic disease, even in patients without any evidence of metastatic lesions (24, 25). The PSA level at the time of diagnosis is prognostic for death from PCa and is incorporated into all risk classifications and nomograms predicting outcomes in PCa patients (26, 27).

Initially investigated as a forensic marker, PSA was discovered in the 1970s and became available as a serum marker for PCa in the 1980s (28). In 1994, PSA was approved by the Food and Drug Administration (FDA) in testing for PCa as a complement to DRE in asymptomatic men. The introduction of PSA in Norway in the early 1990s was followed by a rapid increase in PSA testing and PCa incidence (29). As a result, tumours were detected earlier in the course of the disease. Opportunistic screening, inconsistently practiced around the country, has been a debated practice in Norway since PSA became available (30). Since the initial registration of PSA in the Norwegian Prostate Cancer Registry (NoPCR), the median PSA level at the time of diagnosis has decreased, indicating widespread opportunistic testing (15). At the same time, the PSA level at the time of PCa diagnosis increases with age, suggesting less PSA testing in asymptomatic older men compared to younger men in Norway, similar to findings in Swedish cohorts (15, 31).

1.2.3. Tissue sampling and grading

Before introduction of the core needle biopsy technique, histopathological diagnosis of PCa was based on fine-needle aspiration cytology of the prostate or incidental detection by transurethral resections of the prostate (TURP). Core needle biopsies were initially obtained by digital guidance, until transrectal ultrasound (TRUS) guided biopsies were regarded as superior (32). Routine use of prebiopsy MRI has in recent years allowed for targeted biopsies of suspicious lesions in the prostate, either by cognitive or in-bore guidance, or more commonly, by fusion of MRI images with real-time TRUS. Targeted biopsies are currently recommended in combination with systematic biopsies in the initial work-up of PCa (33). To improve precision and reduce infection rates, transperineal biopsies are gradually becoming standard of care in Norway.

Adenocarcinomas are the most common morphological type of malignant tumours of the prostate, and the majority of tumours are located in the peripheral zones of the gland (4). Of all prostate cancers, 85-90% are multifocal, with an average of 2-3 tumour foci per gland (4). Based on the architectural pattern in malignant tissue, the Gleason grading system, developed by Donald Gleason and colleagues in 1966-74, designates a Gleason score (2-10) based on the

sum of the two most common grade patterns (1-5) in each individual prostate biopsy (4, 34, 35). The original study by Gleason demonstrated a progressive increase in mortality from PCa with increasing Gleason score, and today the system still remains one of the most powerful prognostic factors in PCa patients (4).

The initially rather subjective Gleason grading system has since its origin undergone major revisions. At the International Society of Urological Pathology (ISUP) grading conference in 2005, stringent criteria were applied to the grade 3 pattern, resulting in a grade migration from pattern 3 to 4 and an increase in the prevalence of higher recorded Gleason scores, referred to as the ´Gleason shift´ (36). At the ISUP grading consensus conference in 2014, further modifications in the assignment of Gleason grade pattern 3 and 4 were agreed on (37). Consensus was made that Gleason grade 1 and 2 should not be assigned on biopsy because of poor reproducibility and poor correlation with prostatectomy-based grading.

Recognizing the heterogeneity within the Gleason score 7 group, consensus was achieved in the 2014 conference to adopt a new simplified grading system consisting of five (1-5) distinct Grade groups (also referred to as Gleason grade groups (GGGs) or ISUP grade groups in this thesis) to be used in conjunction with the Gleason score. Originally based on the histopathological examination of RP specimens, and later validated for prostate biopsies, the Grade groups allow accurate prognostic stratification by predicting biochemical recurrence rates (BCR) in patients following RP or radiotherapy (RAD) with or without androgen deprivation therapy (ADT) (38, 39). The Grade groups have further been validated for prediction of metastatic progression and prostate cancer-specific mortality (PCSM) in PCa patients treated with curative and non-curative intent (Figure 3) (40, 41). The Grade groups were incorporated into the 2016 Edition of the World Health Organization (WHO) Classification of the Urinary System and Male Genital Organs (42).

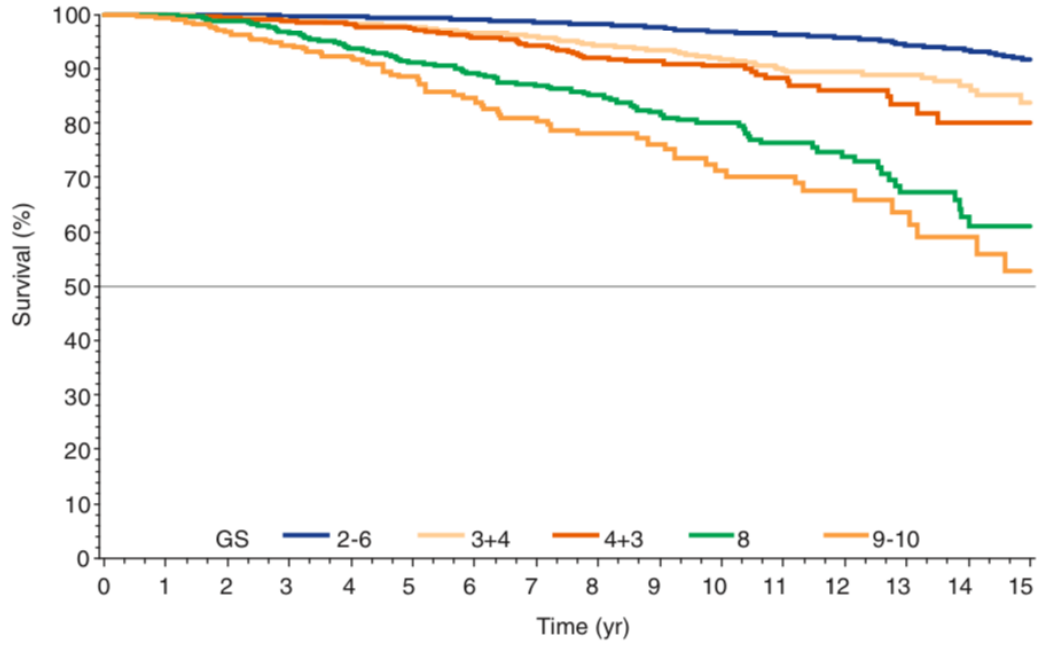


Figure 3: Prostate cancer-specific survival according to Gleason grade groups in biopsies; 1 (Gleason score (GS) 2-6), 2 (GS 3+4), 3 (GS 4+3), 4 (GS 8), 5 (GS 9-10) (41). Copyright has been obtained.

In Norway in 2018, 28%, 45% and 27% of patients featured ISUP grade groups 1, 2-3 and 4-5 in the first cancer-positive biopsy, respectively (15). Higher Gleason scores with increasing age at diagnosis have been documented in international literature (31, 43, 44). Little, however, is known about the prognostic value of ISUP grade groups according to age. When comparing ISUP grade groups in the first positive biopsies to findings in the RP specimens in Norwegian men, approximately 19% are under- and 23% are over-graded, the regional rates depending on the number of RP-specimens examined at the pathology units (6, 45).

1.2.4. Staging

Stage refers to the extent of cancer and is a major component of prognostic classification. Staging can be performed at several time points in the course of the disease. The Tumour Node Metastasis (TNM) system is the globally accepted method for PCa staging and is released by two separate organizations; the Union of International Cancer Control (UICC) and the American Joint Committee on Cancer (AJCC) (46, 47). The Cancer Registry of Norway (CRN) and the European Association of Urology (EAU) refer to the TNM classification provided by the UICC (Table 1). In the TNM-systems, each anatomical component (T, N, M) is assigned a category, which together form a stage group.

According to the 8th Editions of the UICC Classification of Malignant Tumours and the AJCC Staging Manual released in 2017, the clinical (c)T-category describes the local extent of the tumour and refers to DRE findings only (46, 47). Although imaging can add staging information, issues regarding patient selection, inter-observed reproducibility and contradictory results have been raised. At present, radiology findings should be presented in a descriptive text format. To evaluate diagnostic accuracy, pathological (p)T-category in the RP specimen can be compared with cT-category. In patients undergoing RP in Norway, 44% of tumours were found to be under-staged and 5% over-staged in 2018 (15). In recent years, the increased use of MRI for cT-categorization in clinical practice is likely to have impacted recordings compared to earlier time periods when cT was mainly based on DRE.

The clinical (c)N-category refers to the presence or absence of metastases in the regional lymph nodes (that is lymph nodes of the true pelvis below the bifurcation of the common iliac arteries). Traditionally, evaluation of N-status was achieved by pelvic lymph node dissection (PLND). This invasive method, although still considered the most accurate staging method, has largely been replaced by imaging. Computed tomography (CT) and MRI indirectly assess lymph node invasion by determining the morphological characteristics and diameters of the lymph nodes. Both modalities have low sensitivity for detection of N1-disease (48). Prostate-specific membrane antigen (PSMA) Positron emission tomography (PET)/CT shows higher sensitivity and similar specificity compared to multiparametric MRI and is currently being evaluated for routine use in staging of high-risk PCa (49). Predictive nomograms, correlated with findings from extended PLND (ePLND), provide probabilities of lymph node involvement and can aid planning of curative treatment (50, 51).

The clinical M-category refers to the presence or absence of metastases to non-regional lymph nodes and/or distant sites. According to contemporary EAU guidelines, all patients with ISUP grade group ≥3 tumours or high-risk disease (later described) should undergo metastatic screening with at least cross-sectional abdominopelvic imaging and bone scan (33). MRI and PET scans are, however, increasingly applied for M-categorization in clinical practice, often resulting in upstaging compared with traditional staging methods.

Little is known about stage distribution according to age at diagnosis in Norway. International literature shows that higher age is associated with more advanced disease (31, 43). Independent of primary treatment, the cT-category has been shown to be an independent prognostic factor for PCSM in patients with non-metastatic PCa (27).

Table 1: The TNM classification for prostate cancer adapted from the UICC 8th Edition (47)

T-category	**Criteria**
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
T1	*Clinically inapparant tumour that is not palpable*
T1a	Tumour incidental histologic finding in 5% or less of tissue resected
T1b	Tumour incidental histologic finding in more than 5% of tissue resected
T1c	Tumour identified by needle biopsy (e.g. because of elevated PSA)
T2	*Tumour that is palpable and confined within prostate*
T2a	Tumour involves one half of one lobe or less
T2b	Tumour involves more than one half of one lobe, but not both lobes
T2c	Tumour involves both lobes
T3	*Tumour extends through the prostatic capsule*
T3a	Extracapsular extension (unilateral or bilateral) including microscopic bladder neck involvement
T3b	Tumour invades seminal vesicle(s)
T4	Tumour is fixed or invades adjacent structures other than seminal vesicles: external sphincter, rectum, levator muscle, and/or pelvic wall
Invasion into the prostatic apex or into (but not beyond) the prostatic capsule is not classified as T3, but as T2.	
N-category	**Criteria**
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastases
N1	Regional lymph node metastases
Metastases no larger than 0.2 cm can be designated pNmi.	
M-category	**Criteria**
M0	No distant metastases
M1	Distant metastases
M1a	Non-regional lymph node(s)
M1b	Bone(s)
M1c	Other site(s)
When more than one site of metastases is present, the most advanced category is used.	

1.2.5. Risk stratification

PCa is a highly heterogenous disease, ranging from indolent tumours to rapidly progressive and lethal cancers. To aid treatment planning and prediction of oncological outcomes, including BCR after radical treatment and PCSM, PCa patients are categorized into risk groups based on similar disease characteristics at the time of diagnosis. Several risk stratification systems are available for classification of PCa patients without distant metastases (33, 52-56). The majority of risk classifications are based on the three-tiered D´Amico system (discussed later), all incorporating PSA (ng/ml), Gleason score/ISUP grade group and cT-category (57). These variables, however, allow multiple combinations and heterogeneity within the same risk group and between classifications systems. Several models have therefore been modified to include risk categories beyond the traditional three-tiered system, some of which include information on percentage of positive cores, percentage of cancer length per core, PSA-density and cN-category (52, 54-56).

In 1998, D´Amico and colleagues proposed a risk stratification system to predict BCR after PCa treatment with RP and external beam radiation therapy (EBRT), dividing patients into low-, intermediate- and high-risk groups based on initial PSA, cT-category and Gleason score (Table 2) (57). This group system has been validated for prediction of survival in RP-patients (58). Based on the D´Amico system, the EAU risk groups presented in 2011, included cT2c-tumours in the intermediate risk group until 2015, when these tumours were re-classified as high-risk localised, and cT3-tumours were categorized as locally advanced together with cT4-tumours and N1-disease (Table 3) (56, 59). Based on histology only, Gleason score 7 tumours are currently classified as intermediate-risk, although it is well recognized that ISUP grade group 2 (Gleason score 7a) and 3 (Gleason score 7b) tumours have different prognostic properties (38). Thus, the EAU intermediate-risk group may be further separated into a favorable and an unfavorable group based on the ISUP grade group.

Table 2: D´Amico risk groups (57)

Risk group	Low-risk	Intermediate-risk	High-risk
D´Amico	PSA ≤10 ng/ml and GS <7 and cT1-2a	PSA 10-20 ng/ml or GS 7 or cT2b	PSA >20 ng/ml or GS >7 or cT2c-3a

Table 3: EAU risk groups

Risk group	Low-risk	Intermediate-risk	High-risk	
EAU 2011-2014 (59, 60)	PSA <10 ng/ml and GS 6 and cT1-2a	PSA 10.1-20 ng/ml or GS 7 or cT2b-2c	PSA >20 ng/ml or GS 8-10 or ≥cT3a	
EAU 2015- (33, 56)	PSA <10 ng/ml and GS <7 (ISUP grade 1) and cT1-2a	PSA 10-20 ng/ml or GS 7 (ISUP grade 2/3) or cT2b	PSA > 20 ng/ml or GS >7 (ISUP grade 4/5) or cT2c	any PSA, any GS (any ISUP grade), cT3-4 or cN+
	Localised			**Locally advanced**

Several nomograms are available to predict oncological outcomes in PCa patients, demonstrating high prognostic performance for PCa mortality (61). The Cancer of the Prostate Risk Assessment (CAPRA) score (0-10) incorporates age, PSA category, Gleason score, cT-category and percentage of biopsy cores involved with cancer, to calculate the likelihood of recurrence, metastases and PCa death in patients treated for PCa (62).

Ultimately, diagnostic methods are rapidly evolving, and incorporation of findings from imaging, genetic profiling and biomarkers is expected to improve future individualized risk stratification and decision-making (63, 64).

1.3. Life expectancy

Long-term survival in PCa patients is influenced by PCa-related factors and risks associated with death from competing causes. Based on the available literature, a life expectancy (LE) of minimum 5-10 years is generally considered mandatory in men with localised PCa to benefit from any life-prolonging effect from curative treatment (52, 56). Accordingly, individual LE estimation, along with risk stratification, is essential to make treatment recommendations in PCa patients without distant metastases.

Age

Increasing age is strongly associated with increased likelihood of death from other causes than PCa (24, 65). In a study with long-term follow-up of 223 Swedish men with localised intermediate and highly differentiated PCa who received no curative treatment, the majority of men died from competing causes (65). In another Swedish landmark study, evaluating more than 75 000 non-curatively treated PCa patients of all ages, increasing age was strongly associated with increased likelihood of death from other causes within all risk groups (24). Assessment of biological age rather than chronological age for prediction of LE has been emphasized in the last decade (66, 67).

Comorbidity

Comorbidity is another major predictor of non-PCa death (24, 68-71), although the clinicians´ assessment of the impact of comorbidity on LE is highly subjective (72). The Charlson Comorbidity Index (CCI) is a feasible clinical assessment tool validated for prediction of non-cancer-specific death in patients with clinically localised PCa (71, 73-75). Albertsen and colleagues showed that men with significant comorbidities had a 2-fold greater chance of all-cause death compared to men without significant illnesses (69). Independent of risk group, Rider et al demonstrated a strong association between CCI score and cumulative ten-year mortality from other causes than PCa, especially in men <65 years (24). Though, rarely used in Norway, diagnostic codes needed for estimation of CCI in PCa patients can be extracted from electronic patient journals and the Norwegian Patient Registry (NPR). Each comorbidity category is assigned a number and the sum of all categories gives the comorbidity score. Satisfactory treatment for the listed conditions, however, is not accounted for.

Functional status

Assessment of physical functioning can be done by evaluating the patients´ performance status (PS) by use of standardized assessment tools. The Eastern Cooperative Oncology Group (ECOG) PS, also referred to as the WHO PS, was originally published by Oken in 1982 (Table 4) (76). This simple scoring system divides patients into five categories based on activity level and capability of selfcare. The ECOG score has been shown to correlate with response to treatment and survival in cancer patients, but is limited by interobserver variability (77). In a study by Fosså et al, ECOG PS was an independent prognostic covariate of 5-year PCSM and OM in patients with non-metastatic PCa (78).

Table 4. ECOG/WHO performance status (76)

Category	Description
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature e.g. light house work, office work.
2	Ambulatory and capable of all selfcare, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on selfcare. Totally confined to bed or chair.
5	Dead.

Estimation of life expectancy

The overall LE of a Norwegian male is currently 81.19 years (79). The expected remaining years to live decrease with increasing age, however, the higher age reached, the older one is likely to become. LE according to sex, chronological age, country of residence and time of entry can be extracted from population-based life tables (Table 5) (79, 80).

Table 5: Life expectancy in Norwegian males 2019 adapted from Statistics Norway (79)

Age (years)	Life expectancy (years)*
50	32.78
60	23.73
65	19.53
70	15.55
75	11.90
80	8.65
85	5.95

*Remaining years to live

For individual prediction in PCa patients, LE calculated from life tables must be adjusted for the patient´s health status, assessed by comorbidity, nutritional status, cognitive and physical functioning (81). According to the National Comprehensive Cancer Network (NCCN) principles, LE achieved from life tables can be adjusted according to the clinician´s assessment of overall health; 50% LE is added to the best quartile health, no adjustments for the middle two quartiles and 50% is subtracted from the worst quartile health (82).

Following recommendations by the International Society of Geriatric Oncology (SIOG) and the EAU, geriatric screening should be routinely performed in all patients ≥70 years at diagnosis, and abnormal screening results should warrant a comprehensive geriatric assessment (33, 67). Based on the assessments, patients are classified into one of three categories; fit, vulnerable or frail. Fit patients, and vulnerable patients with reversible impairments, should receive standard treatment as for younger patients (67).

1.4. Primary treatment

Treatment of PCa can be defined as primary or secondary. This thesis deals with outcomes after primary treatment of PCa. Although not legally binding, treatment of PCa is regulated by guidelines that are regularly updated based on available results from randomized controlled trials (RCTs) and observational studies from population-based PCa registries (83). The EAU guidelines on PCa have been the main references for clinical practice in Norway since their first release in 2001 (33, 84). National guidelines on PCa became available in Norway in 2009 (85).

Primary treatment for PCa without distant metastases can be broadly divided into curative and non-curative. Risk group allocation and LE form the basis for national and international treatment recommendations, and final decisions are further influenced by preferences of the patient and the treating physician. Online tools can aid decision-making by predicting outcomes based on individual patient- and disease characteristics (86, 87). Today, treatment recommendations for individual patients are routinely made by multidisciplinary teams.

Although the principal primary treatment categories for patients without distant metastases have been more or less unchanged in the last decades, treatments techniques have been modernized and refined, and treatment strategies have greatly evolved with increased knowledge about outcomes in subgroups of PCa patients.

1.4.1. Curative treatment

Patients without distant metastases are potential candidates for curative treatment comprising radical prostatectomy (RP) or definitive radiotherapy (RAD), in some cases preceded by a period of active surveillance (explained later) (33). The goal of curative treatment is to gain oncological control of the cancer while inflicting minimal adverse treatment-related effects. There is no upper age limit for curative treatment of PCa, but potential complications and side-effects from treatment must in the individual patient be carefully weighed against the expected clinical benefits in terms of reduced PCa morbidity and mortality.

Early diagnosis and increased lead time (time from diagnosis until patients develop symptoms) has altered the natural course of confirmed PCa and raised concerns of overtreatment (treatment of cancers that will not become symptomatic in the patient´s life-time), particularly in men with low-risk disease. The greatest benefits from curative treatment are observed in patients with intermediate- and high-risk disease (78, 88, 89). In patients with unfavorable disease, particularly in fit senior men, concerns about undertreatment have been brought to attention (31, 90, 91).

Radical prostatectomy

Radical prostatectomy is a curative treatment modality involving complete surgical removal of the prostate gland and the seminal vesicles, either by open or minimally invasive technique. According to the contemporary EAU guidelines, patients with PCa without distant metastases and a LE >10 years can be managed with RP, as part of multimodal treatment in patients with locally advanced disease (33). An ESMO consensus meeting and the NCCN Guidelines state that curative treatment with RP should be discussed with patients with high-risk disease and LE > 5 years (52, 92).

The prostatectomy technique has greatly evolved in the last 150 years, from the initial perineal partial prostatectomy performed by T. Billroth in 1866 to the first perineal extracapsular prostatectomy by H. Young in 1904 and the retropubic approach by T. Millin in 1945 (93-95). The first laparoscopic RP was performed in the early 1990s, followed by the introduction of the robot-assisted radical prostatectomy technique using the da Vinci Surgical System in 2002 (96). In Norway, the robot-assisted laparoscopic prostatectomy was introduced in 2004 and has become standard of care (97). The robotic technique allows 3D-vision, improved ergonomics and surgical techniques. There is no clear evidence that any open or minimally invasive technique is superior, although the latter method may result in reduced blood loss and shorter hospital stays compared with open procedures (98).

To improve post-operative functional outcomes, particularly preserving erectile function in pre-operatively potent men, dissection of the prostate can be performed with various degrees of nerve-sparing (NS), preserving the neurovascular bundle on one or both sides of the gland (99-101). Performing ePLND in patients with increased risk of lymph nodes metastases allows pathological assessment of the pelvic lymph nodes, although a therapeutic effect has

not been proven (102). Examination of the RP specimen permits pathological staging, grading and evaluation of surgical margins for prediction of further PCa outcomes (103).

RP has been compared with observation in four RCTs. In the first trial, no survival difference was demonstrated after 23 years follow-up of 142 patients with localised PCa randomized to radical prostatectomy or expectant management (104). In the second SPCG-4 trial, 695 patients <75 years diagnosed with clinically localised PCa were randomized to RP or watchful waiting (WW) (later explained) (105-107). Only 5% of patients had Gleason score ≥8 tumours. The ten-year absolute differences in PCSM and OM significantly favored RP, and the RP group had reduced risk of local progression and metastases compared to the WW group (107). The benefits of RP increased with longer follow-up and was largest in men aged <65 years for all outcomes. In men ≥65 years, a survival benefit from RP was not evident until more than twenty years follow-up (106), however, a reduction in the risk of metastases and need for palliative treatment was evident after thirteen years follow-up (105). In the third PIVOT trial, 731 patients ≤75 years diagnosed with localised PCa were randomized to RP or observation (108, 109). One in five patients had high-risk disease, but only 7% of patients had Gleason score ≥8. After almost thirteen years follow-up, PCa mortality was not significantly reduced in the RP group, although an improvement in overall survival was seen for intermediate-risk patients treated with RP. Treatment for disease progression was more frequent in the observation group compared to the RP group. Finally, in the most recent ProtecT study, 1643 patients <70 years with screening-detected localised PCa were randomized to active monitoring, RP or RAD (25). Only 2% had Gleason score ≥8 tumours. No difference in PCSM emerged in the treatment groups after ten years follow-up, although patients in the active monitoring group had significantly higher risk of disease progression. Population-based studies have demonstrated a survival benefit with RP compared to observation in patients with non-metastatic PCa, with varying effects according to disease characteristics (110-112).

The proportion of patients in the low- and intermediate-risk groups treated with RP in Norway has decreased in the past decade (15). In high-risk patients the use of RP has increased, particularly in men with locally advanced disease, although this finding may be influenced by the increased use of MRI for local staging. In 2018, approximately 1600 RPs were performed in Norway, of which half of the patients had high-risk disease (15). Not visualized by the

CRN data, it is estimated that approximately 100 Norwegian men are annually operated with RP abroad, but the exact number is unknown (113). Recognizing the association between prostatectomy volumes and post-RP outcomes, performance of RP has increasingly been centralized in Norway, from 19 operating public hospitals in 2012 to 12 public and one private hospital in 2018 (15, 114, 115). Until a decade ago, PCa patients aged >70 years were rarely considered for prostatectomy (15).

Radiotherapy

Radiotherapy has a place in the treatment of patients with PCa as curative local treatment (*definitive* or *adjuvant* RAD in the primary setting or *salvage* RAD in the secondary setting), as palliative RAD or as prophylactic means to prevent gynecomastia. This thesis deals with curative radiotherapy.

Definitive radiotherapy

According to the contemporary EAU guidelines, patients with localised and locally advanced PCa without distant metastases are potential candidates for RAD (33). (Neo-) adjuvant ADT has been shown to increase ten-year disease-free and overall survival in high-risk patients treated with definitive RAD, and ADT is generally given for six months in intermediate-risk and two-three years in high-risk patients (81, 116).

In Norway, definitive RAD for PCa was introduced in 1974 (117). In the past decades, definitive RAD techniques have undergone major modifications. Use of 3D-conformation has set the ground for high-precision techniques and is now considered the gold standard. Modern technical methods allow modifications of the shape and intensity of radiotherapy beams during the treatment (Intensity-Modulated Radiotherapy (IMRT), Volumetric-Modulated Arc Therapy (VMAT)) and application of escalated-dose RAD while sparing the surrounding tissue to reduce toxicity. These developments, together with increasing LE, have resulted in a gradual increase in the number of senior adults who are offered definitive RAD. Implantation of gold markers and image-guided radiation therapy (IGRT), visualizing the target prior to each treatment, has further improved precision. Hypo-fractionation and introduction of high-dose rate brachytherapy, mostly in combination with EBRT, are other developments in the curative radiotherapeutic management of PCa. Dose escalation has been shown to reduce recurrence and improve overall survival (118-121). A dosage of minimum 74 Gy, with no

distinction between risk groups, is today considered mandatory for cure in Norway, whereas target doses of at least 70 Gy were viewed as sufficient before 2009 (122).

The proportion of patients treated with RAD have remained relatively stable in intermediate- and high-risk patients in Norway in the past decade (15). Due to increased perioperative morbidity in senior men, definitive RAD has been the preferred curative treatment option in patients ≥70 years. Norwegian PCa patients aged 70-74 years are now, however, equally treated with primary RP and RAD (15).

Adjuvant RAD

Patients with the high pathological Gleason scores, extracapsular extension and/or positive surgical margins following RP have an increased risk of developing BCR (123-125). Adjuvant RAD, provided immediately after RP, may prolong PSA progression-free survival, but the impact on clinical progression is uncertain (126, 127). An increasing body of evidence shows that close observation followed by early salvage radiotherapy for BCR, does not increase the risk of metastatic progression or death compared to adjuvant RAD (128, 129). In patients with unfavorable tumour characteristics and low-volume pN1-disease (≤2 positive nodes), and in patients with intermediate-volume pN1-disease (3-4 positive nodes), adjuvant RAD may reduce PCSM and OM (130).

Radical prostatectomy vs radiotherapy

The ProtecT study is the only RCT comparing survival outcomes of primary RP and RAD in patients with localised PCa, with no observed differences in ten-year PCSM in patients with low- and intermediate-risk tumours (25). Observational studies have indicated better survival after RP compared to RAD in patients with non-metastatic PCa, however, insufficient adjustment for patient- and tumour heterogeneity within the treatment groups limit interpretation of results (88, 131, 132). Robinson and colleagues observed a smaller difference in PCa mortality between RP and RAD compared to previous studies after adjustment for clinical covariates (133). Formal comparison between RP and RAD in patients up to 75 years of age with locally advanced T3-tumours will be made in the ongoing randomized SPCG-15 trial (NCT02102477).

Active surveillance

The concept of active surveillance (AS) was first described in 2002 (134). AS, more recently referred to as deferred active treatment (DAT), is a strategy that involves deferring curative treatment in selected patients with localised PCa and long LE, aiming to delay or avoid treatment-related side-effects without compromising PCa-specific survival (135-137). According to contemporary guidelines, patients with low-, and selected patients with intermediate-risk disease, can be managed with AS (33). Patients in AS are monitored according to a predefined schedule, including regular DRE, PSA-testing, MRI and re-biopsies. The optimal AS regime is unknown, and ongoing studies are investigating various inclusion criteria, monitoring regimes, reclassification criteria and triggers for active treatment (135-141) (NCT02914873). In a large European study, 52% and 73% of patients had discontinued AS after five and ten-year follow-up, mainly because of protocol-based re-classification (138). Although AS avoids physical side-effects from curative treatment, and the majority of men report good quality of life with untreated cancer, patients with intermediate-risk disease have an overall increased risk of worsened oncological outcomes when active treatment is deferred (111, 137, 140-143). Since AS was first recorded in the NoPCR in 2009, an increasing proportion of low-risk patients are managed with AS in Norway (15).

1.4.2. Non-curative treatment

Deferred treatment

Watchful waiting (WW) is a deferred treatment strategy in which patients who are ineligible for curative treatment, or asymptomatic patients with LE <10 years, are managed with observation only and treated with ADT and/or other palliative measures as indicated by symptoms or rapidly progressing disease (33).

Androgen deprivation therapy

In 1941, C. Huggins and colleagues demonstrated that the growth of PCa could be retarded by androgen (testosterone) deprivation. He was awarded the Nobel Prize for Physiology or Medicine for his discovery (144). Androgen deprivation from castration is achieved either by surgical removal of the testicles or by suppressing the testicular androgen production with

medical agents (Lutenizing hormone-releasing hormone (LHRH) agonists or antagonists). The effect of androgen deprivation may be further achieved by inhibiting the action of circulating androgens at the receptor level (antiandrogens) or by blocking the production of testosterone from the adrenal glands. Castration is the standard of care for PCa patients with distant metastases (33). In patients with high-risk PCa, adding RAD to ADT reduces long-term PCa mortality compared to ADT alone (145, 146). Temporary ADT is used in conjunction with definitive RAD in patients with intermediate- and high-risk PCa.

1.4.3. Prostate cancer patient pathway

Based on a Danish model, the Norwegian Directorate of Health implemented in 2015 a cancer patient pathway (CPPs) for PCa patients (147). This fast-track system defines upper time limits for diagnostic activities and treatment, starting from the time PCa is suspected in the specialized health care service to initiation of primary treatment when PCa is diagnosed. The CPP aims to optimize patient flow and avoid unnecessary delays and is supervised by a coordinating nurse at the hospitals. For PCa patients, whose primary treatment consists of RP or definite RAD, treatment should be initiated within 32 days of decision-making, usually calculated from the time of the multidisciplinary team meeting. No distinctions regarding time limits are made according to patient or tumour risk profile. AS and medical treatment should commence within three days of decision. According to quality indicators defined by the Directorate of Health, minimum 70% of patients with a new diagnosis of PCa should be included in the CPP and receive timely treatment (147, 148).

1.5. Secondary treatment

Local salvage treatments

Persistent PSA or any sustained rise in PSA from an undetectable level post-RP may indicate tumour activity, either persistent local or pre-existing metastatic disease. Traditionally, the definition of BCR post-RP has been two consecutive PSA values of ≥0.2 ng/ml and rising from an undetectable level, but has recently been re-defined to include all rise in PSA (33). After definitive RAD, the PSA level drops to a minimum, referred to as the nadir level. An increase in PSA ≥2 ng/ml above the nadir level is considered disease recurrence. PSA recurrence after curative treatment in PCa patients often precedes clinical recurrence by many years, and categorization of patients into risk groups based on pathological Gleason score, interval to biochemical failure and PSA doubling time, may aid prediction of metastases and PCSM (149, 150). In patients with persistent or rising PSA post-RP, early salvage radiotherapy provides a possibility of cure in patients without metastases and high risk of disease progression (151, 152). Salvage RAD is today combined with hormone treatment (153). Alternative locoregional salvage therapies are being explored; salvage RP, salvage PLND, RAD to pelvic lymph nodes, brachytherapy and cryotherapy. Patients with locoregional recurrence who have low risk of clinical progression or who are ineligible for salvage treatments can be managed with observation or ADT.

1.6. Outcomes

Assessment of functional and oncological outcomes in PCa patients can provide information about the quality of PCa care, stratified for different treatments. The most commonly used oncological outcome measures in PCa patients include surgical margin status, biochemical/clinical recurrence after curative treatment, local/symptomatic/metastatic progression, need for secondary cancer treatments, acute and long-term adverse side-effects, mortality and survival. In this thesis, we evaluate the following outcomes after primary treatment in PCa patients without distant metastases; surgical margin status, use of post-RP pelvic or mamillary RAD as a minimum estimate of recurrence (the latter as a proxy indicator for start of anti-androgen hormone treatment), PCSM and OM.

1.6.1. Functional outcomes

Functional outcomes after treatment for PCa are not assessed in this thesis, but constitute an important aspect in clinical decisions-making, since improved oncological outcomes after curative treatment may come at a cost of long-term side-effects, ultimately reducing the patients´ quality of life. RP may result in deterioration of sexual function and incontinence. Preservation of potency and continence are included in the trifecta and pentafecta systems for post-RP outcome reporting (154, 155). Radiotherapy may result in worsening of sexual function and bowel symptoms, and limited worsening of urinary continence (155). Considerable heterogeneity in patient-reported functional outcomes is observed among subgroups of patients (155). Higher age has been associated with worse functional outcomes after curative treatment for PCa (156-159), although the total impact of age on self-reported toxicities from radical treatments may be marginal (158). Distinguishing between function and bother, and pre- vs post-treatment evaluation scores, has gained increased attention in recent years (155, 159, 160). A significant proportion of senior men have erectile dysfunction prior to treatment, and treatment-related worsening of erectile function may not impact on quality of life to a similar extent as in younger men (161).

1.6.2. Histopathological outcomes

The post-prostatectomy surgical margin status is considered positive if tumour cells are in contact with the ink on the surface of the RP specimen. Positive surgical margins are associated with increased likelihood of BCR and secondary cancer treatments after RP, however, the impact on metastatic progression and PCSM is less clear (125, 162-167). The presence of negative surgical margins in the RP specimen is considered a measure of surgical quality and is included in the post-RP pentafecta assessment, along with freedom of BCR and complications, and preserved potency and continence (154). The association between NS and surgical margin status in unclear (100, 168). In Norway, the presence of tumor-free margins in pT2 specimens is regarded as a quality indicator, and 17% of patients with pT2 tumours had PSMs in 2018 (15). The increasing proportion of high-risk patients operated with RP, along with use of NS surgical technique, may increase the rate of PSM, however in a large meta-analysis, NS did not increase the risk of PSMs in patients with pT2 or pT3 disease (100, 168). Abern et al demonstrated that time from biopsy to RP beyond nine months was associated with greater risk of PSM in intermediate-risk patients (169).

1.6.3. Mortality/survival

Mortality and survival are key measures in PCa patients. Although related, there are important differences in how mortality and survival estimates are calculated, related to what purpose they serve; policy making, research and/or clinical decision-making. Death may occur from a specific disease or from any cause, and the population at risk may refer to the general population or to a specified diseased cohort, the latter the case for most clinical studies. Overall survival estimates can be compared to a matched group in the general population to gain information on net survival.

Prostate cancer-specific mortality rates in Norwegian men are provided by the CRN, the Association of Nordic Cancer Registries (ANCR) and the International Agency for Research on Cancer (IARC). Estimates are presented as *absolute numbers* of PCa deaths per year (e.g. 934 PCa deaths in Norway in 2017), or as *crude PCa mortality rates*, referring to the number of PCa deaths per 100 000 persons in the general population per year. These measures provide information on the burden of PCa in the population and allow evaluation of changes over

time. The crude mortality rates do not consider the age distribution of PCa-specific mortality, which is done by calculation of *age-specific* and *age-standardized mortality rates*.

Considering the distribution of PCa-specific mortality, the *absolute numbers, the crude and the age-standardized mortality rates* increased in Norway up to the mid 1990s, with a slight decrease thereafter (Figure 5) (14). In Norway approximately thousand men die each year from of PCa (discussed in section 1.1.). The median age at PCa death is 83 years, and two out of three men who die from PCa are ≥80 years old at the time of death (15). Over the past three decades, there has been a shift in *age-specific mortality rates* in Norway (7). Theories for the observed decrease in mortality rates in patients <85 years and increase in mortality rate among patients aged ≥85 years, include increased diagnostic and treatment-related efforts among younger men and increased misattribution of cause of death, mainly affecting the senior population.

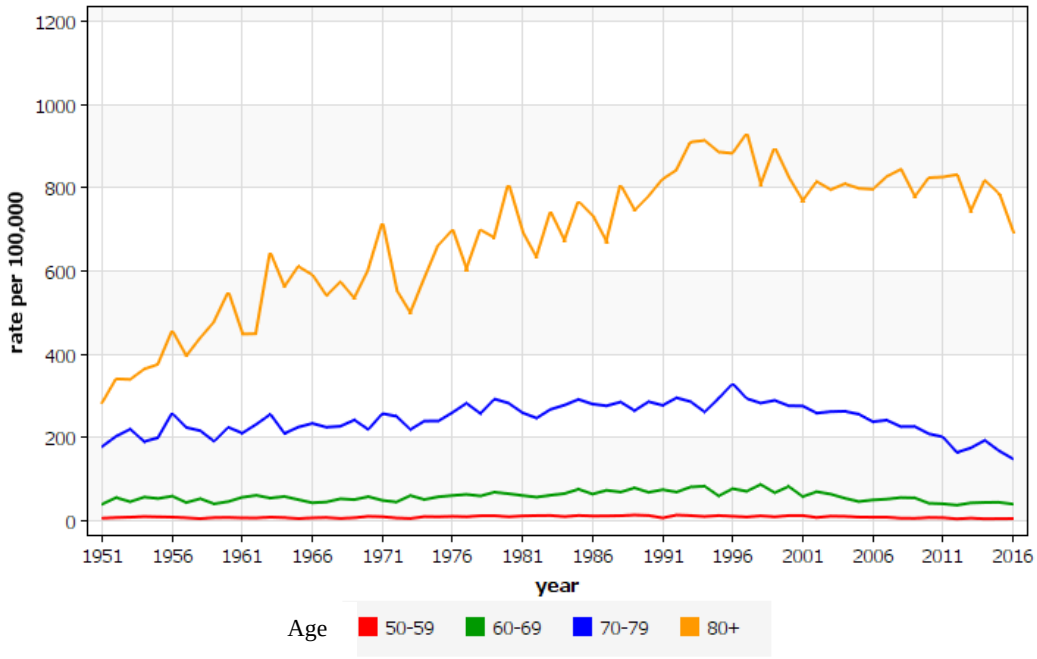


Figure 5. PCa mortality rates in Norway over time according to age (14). Copyright has been obtained.

Prostate cancer-specific mortality (PCSM) refers to the probability of PCa-specific death in PCa patients in a specified time period after diagnosis. It is a useful measure to assess prognosis and treatment efficacy within subgroups of PCa patients. The Kaplan-Meier and competing risk models can be used to estimates disease-specific mortality probabilities over time (time-to-event endpoint). Since the median time from diagnosis to PCa death is 13 years, PCa patients, particularly those with localised disease, require long-term follow-up when assessing mortality (15). In patients with high-risk PCa, however, treatment-related survival differences may become evident with shorter observation times.

PCSM trends in Norway are reported by the NoPCR (15). For patients diagnosed in 2009-2018, the risk of death from PCa increased with age, markedly in patients aged ≥75 years, and with increasing risk group. Patients who did not undergo curatively intended treatment had higher PCSM and other cause mortality compared with patients who underwent RP, RAD or AS. With data from the CRN, Fosså et al documented 5-year PCa-specific survival of >99%, 96.3-99.5% and 85.9-97.7 in the low-, intermediate- and high-risk groups, respectively, in Norwegian men ≤75 years diagnosed with non-metastatic PCa in 2004-2005 (78). Wæhre et al documented 15-year PCSM of 15% (95% confidence interval (CI) 10-19%) in all patients, and 24% (95% CI 16-32%) in the high-risk group, operated with RP in a Norwegian tertiary referral cancer center between 1987 and 2004 (170).

The latest update from the Nordic SPCG-4 trial documented 23-year PCSM in patients ≤75 years with localised PCa; 19.6% in the RP group and 31.3% in the WW group (106). The SPCG-7 study documented ten- and 15-year PCSM in Scandinavian men ≤75 years diagnosed with high-risk PCa in 1996-2002; 19.1% and 34.3% in patients randomized to lifelong endocrine treatment alone and 8.9% and 17.4% in patients who received endocrine treatment combined with RAD (146).

The evidence for impact of age at diagnosis on PCSM is conflicting. The majority of studies demonstrate a positive association between increasing age and PCSM, but not when adjusted for PCa characteristics, health status and treatment. In a report from the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) database, Bechis et al reported that age ≥75 years was a univariate predictor of PCSM and OM, but did not independently predict PCSM when controlling for risk category and treatment (171). Similar results have been

published based on a large study from the Surveillance, Epidemiology, and End Results (SEER) database (172) and Sun et al´s analyses (173). On the contrary, a population-based study from the Veterans Affairs database in the U.S. demonstrated that higher age was associated with increased PCa-specific death, independent of PSA level at diagnosis, though without adjustment for other clinically relevant covariates or treatment type (26). Other studies have shown decreased PCSM with increasing age. In a study with extended follow-up of men <75 years with localised PCa who were managed conservatively, Albertsen et al showed that increasing age was associated with decreasing risk of PCSM and increasing risk of death from other causes compared with younger men (69). In a study by the Radiation Therapy Oncology Group (RTOG) including men with locally advanced disease treated with RAD, age >70 years was associated with decreased overall survival, but also decreased prostate-cancer specific mortality compared with men ≤70 years when adjusted for other covariates, suggeting that senior men harbour less aggressive disease (174).

Overall mortality refers to the proportion of patients in a group who have died within a certain time interval after diagnosis or initiation of treatment. It can be calculated by use of the Kaplan Meier method. Because the majority of PCa patients are senior adults with increased risk of death from other causes than PCa, OM is an important measure to be considered when evaluating the prognosis related to the disease and effect of treatment in PCa patients.

Relative survival (RS) is defined as the observed survival in a group of patients with a specific disease in a defined unit of time divided by the expected survival in a comparable group in the general population matched on key factors such as age, sex and calendar year. RS is referred to as the net survival since it represents the net effect of the cancer i.e. the chances of survival in the absence of other causes of death. RS benefit from not relying on cause of death registration and is widely used by cancer registries (6). The main challenge when estimating RS, however, is to select a comparable group, as demonstrated for patients with localised PCa who have 5-year RS >100%.

Defined as a quality indicator of PCa care, the estimated 5-year RS in patients diagnosed with high-risk PCa in Norway is 96.3%. The RS for patients with localised PCa has increased in Norway over time; 1979-83: 72.7%, 2014-18: 102 % (6). Compared with men <70 years, RS

is markedly reduced from the time of diagnosis in patients aged ≥80 years and decreases in men aged 70-79 years from five years after diagnosis (Figure 6) (6). These findings suggest that senior patients have a higher likelihood of dying from PCa compared to younger patients, possibly due to delayed diagnosis and less treatment. Similar findings were reported in a population-based study from the Netherlands (175).

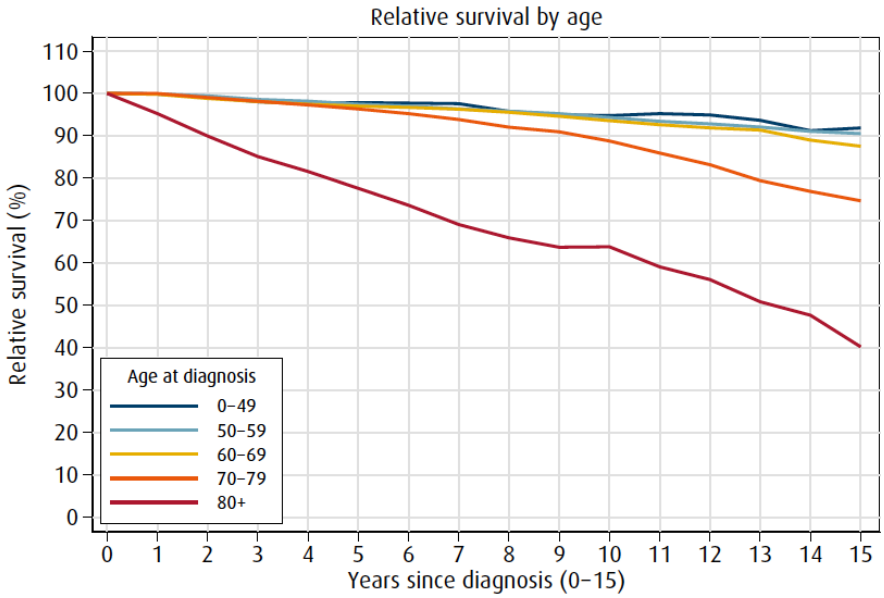


Figure 6: Relative survival by age up to 15 years after PCa diagnosis, 2014-2018 (6)

2. Thesis

2.1. Aims

The planning of a research project investigating patterns of care in patients with non-metastatic PCa in Norway had already commenced by the time I was invited to take part in this project in 2015. Based on data from the initial registrations in the NoPCR, Fosså et al had in 2014 documented five-year survival in a cohort of Norwegian men diagnosed with non-metastatic PCa in 2004-2005 (78). Long-term mortality in Norwegian PCa patients without distant metastases, treated with both curative and non-curative intent, had not previously been documented within a scientific population-based study, and the first paper in this thesis aimed to update survival data in the previously reported cohort. We also wanted to identify prognostic factors associated with ten-year PCSM, with particular attention to the recently defined ISUP grade groups.

During the study period, the CPP for PCa patients was implemented at the hospitals in 2015. It proved difficult to comply with the rigid time limits set by the CPP, and nonetheless, no evidence demonstrated improved survival with reduced time from diagnosis to curative treatment. We therefore aimed to investigate the impact of increasing time interval from diagnosis to RP on PCSM and secondarily on histopathological findings in the RP specimen and the likelihood of receiving post-RP RAD.

With aging of the population and increasing LE, a significant rise in PCa incidence was expected, particularly among senior adults. At the same time, it was evident that these patients had more unfavorable disease characteristics, received less curative treatment and were less likely to be included in clinical trials compared to younger men. Further, it was unclear to what extent older patients tolerated radical treatment and whether they had a survival gain from attempted cure. With this background we wanted to investigate patterns of primary treatment and mortality in senior adults with high-risk PCa, comparing results to those of younger men.

In summary, the overall aim of this project was to generate new evidence-based knowledge to assist clinicians in pre-treatment counselling and management of men diagnosed with PCa without distant metastases. The specific objectives were to investigate the association between

curative treatment vs non-curative treatment and PCSM, with emphasis on senior adults, and the timing of such treatment, along with prognostic factors readily available at the time of diagnosis.

With the above background, we aimed to answer the following research questions based on available data from the CRN;

2.1.1. Paper I

Research questions

- What is the ten-year PCSM and OM in patients diagnosed with PCa without distant metastases in Norway in 2004-2005 when stratified according to risk group and primary treatment (curative treatment (RP, RAD) vs no curative treatment)?
- Which clinical factors influence on the above associations?

Expected outcomes

We expected that curative treatment compared to non-curative treatment would reduce ten-year PCSM and OM. We further expected increasing Gleason score/GGG to be a strong predictor of ten-year PCSM.

2.1.2. Paper II

Research questions

- Is post-diagnosis delay of RP up to 180 days (RP-interval) associated with increased PCSM?
- What is the impact of such increasing RP-interval on histopathological findings in the RP specimen and the likelihood of receiving post-RP pelvic or mamillary RAD (the latter indicating the start of antiandrogens)?

Expected outcomes

We did not expect increasing RP-interval up to 180 days to be associated with increased PCSM.

2.1.3. Paper III

Research questions

- Do senior adults (≥70 years) with high-risk PCa have more unfavorable disease characteristics (higher PSA, ISUP grade groups, cT-categories) than younger men (<70 years), and what proportion of men within each age group receive curative treatment?
- Is PCSM and OM significantly reduced in senior PCa patients receiving curative treatment compared to younger patients, taking into account available risk factors?

Expected outcome

We expected that the use of curative treatment would increase with time and be associated with reduced PCSM and OM in all patients, with greatest survival benefit in younger men.

2.2. Material and methods

2.2.1. Data sources

Data was extracted from the National Cancer Registry of Norway (CRN), the Norwegian Prostate Cancer Registry (NoPCR) and the Radiotherapy Database. Reporting to the CRN is mandatory by law, and the registry contains almost all cancer cases in Norway since 1953. The CRN receives clinical notifications and pathology reports from health care institutions involved in cancer diagnosis and treatment (6). Monthly updates on dates of deaths and emigration are received from the National Population Registry, and cause of death information is regularly updated by the Cause of Death Registry.

The NoPCR was established as a sub-registry in the CRN in 2004 and became a national quality registry in 2009, in line with quality statues in the health care service defined by the Norwegian Directorate of Health (84, 176). Availability of population-based prognostic and therapeutic variables, combined with survival data, allows continuous evaluation of the quality in the management of Norwegian PCa patients. The NoPCR contains information on individual demographic and clinical information (including date of diagnosis, ECOG/WHO PS, T-, N-, M-categories, PSA level at the time of diagnosis, histological WHO grade, Gleason score since 2004 and histopathological findings in the RP specimen), primary treatment (e.g. RP, RAD, AS and hormone therapy started within four months of diagnosis), date and cause of death (84). Information on treatment provided to patients outside Norway, disease recurrence or progression or complete data on second-line therapies are not available from the NoPCR.

The Radiotherapy Database within the CRN contains information since 1997 from all the eight radiotherapy centers in Norway (177). The responsible radiotherapist at the institutions registers information according to codes about type of cancer treated, irradiated anatomical regions, start and end dates for all RAD series provided, total and daily doses, number of fractions, treatment intention (curative, local control, prophylactic, palliative, or unknown) and optional free-text (177). Until 2020, no data on newer RAD techniques (MVAT, IMRT, use of fiducial markers) or toxicity was routinely collected in the registry, and information on brachytherapy was not easily accessible. Further, reliable data on irradiation to pelvic lymph nodes cannot be extracted from the database.

2.2.2. Study design

All studies in this thesis are observational studies with historically prospective population-based cohorts of PCa patients registered in the CRN.

2.2.3. Ethical considerations

The project was approved by the Regional Committee for Medical and Health Research Ethics (2011/1746). Reporting to the CRN is mandatory by law and does not require patient consent. De-identified data was extracted from the CRN and the NoPCR. Each individual patient was assigned a project-specific number and the key to personal identification was securely contained within the CRN. Data was handled according to the General Data Protection Regulation (GDPR).

2.2.4. Patients and data management

Men with a new diagnosis of PCa in Norway 2001-2016 were identified in the CRN and the NoPCR. In all papers, patients were excluded if they had no histological or cytological verification of cancer or if diagnosis was based on cysto-prostatectomy or autopsy. Only patients with adenocarcinomas of the prostate were included. Patients with documented distant metastases and/or a PSA value >100 ng/ml, indicating metastatic disease, were excluded.

Paper I

Patient selection

This follow-up study provided updated information (per June 30, 2015) on a previously described cohort of men diagnosed with PCa in Norway in 2004-2005 (78). Patients not viewed as candidate for curative treatment were excluded; >75 years at diagnosis, ECOG PS >3, major comorbidity in the free-text field and/or those having cT4-tumours. The N-status was not considered because of incomplete information. Patients who lacked information on

basic clinical variables (PSA, cT-category, Gleason score) needed for risk grouping were not eligible for analyses. Patients treated outside Norway were included in the study, but with no primary treatment recorded in the NoPCR.

Data management

Patients were stratified according to ECOG PS, Gleason score/GGG, 2017 EAU risk groups (low, intermediate, high localised, high locally advanced) and primary treatment. Patients with unknown cT2-subcategory (615 patients) were risk classified according to PSA and Gleason score/GGG. Primary RP was performed within <12 months of diagnosis. Primary RAD was defined as pelvic RAD started within 18 months of diagnosis with a target dose of ≥70 Gy. Patients who were not treated with primary RP or RAD were allocated to the no standard curative treatment group.

Paper II

Patient selection

In this study, patients diagnosed with PCa in 2001-10 and operated with RP ≤180 days from the first cancer-positive biopsy were identified. Aside from the general exclusion criteria described above, patients with biopsy Gleason score <5 and missing variables necessary for EAU risk grouping were excluded. Patients of all ages and with any ECOG PS were eligible for inclusion. Further, we included eight patients with cT4 tumours. The N-status was not evaluated because of incomplete information. Only patients operated with RP in Norway were included.

Data management

Patients were stratified according to the 2017 EAU risk groups and time from biopsy to RP (<60, 61-90, 91-120, 121-180 days). Like paper I, patients were classified according to PSA level and Gleason score if the cT2-subcategory was unknown (n=618). Pathological upstaging was defined as T-category increasing by ≥2 categories for cT1-tumours and ≥1 category for ≥cT2-tumours. Pathological upgrading was defined as an increase in Gleason score by ≥1 (separating Gleason score 7a and 7b) compared to the first biopsy. Receiving post-RP RAD, either pelvic RAD indicating locoregional recurrence or mamillary RAD indicating initiation of antiandrogen treatment, during the observation period was considered RP-failure.

Paper III

Patient selection

In this study we included patients diagnosed with 2017 EAU high-risk PCa in 2005-2016. The general exclusion criteria described above were applied. Patients with no high-risk features were excluded. Unlike paper I, patients of all ages, with any ECOG PS and all cT-categories were included.

Data management

Patients were stratified according to diagnostic period (2005-2008, 2009-2012, 2013-2016), age (<70, 70-74, 75-79, ≥80 years) and treatment (RP, RAD, no curative treatment). RP was performed within 12 months of diagnosis and RAD was given with prostatic doses ≥74 Gy, with or without (neo-) adjuvant ADT, within 15 months of diagnosis in patients diagnosed in 2005-2013 and within 12 months in patients diagnosed in 2014-2016. Patients who did not meet the time-based criteria for RP or RAD were allocated to the no curative treatment group.

2.2.5. Statistical methods

In all three papers we used standard descriptive methods (frequencies/proportions, medians/ranges, means). In paper III, we used a Chi-square test to test for intergroup differences in clinical variables available at diagnosis. In paper II, we used the Chi-squared test to test for intergroup differences in pathological outcomes. In paper III, a multivariable logistic regression model estimated the odds ratios (ORs) and 95% confidence intervals (CIs) for curative treatment.

In the time-to-event analyses in paper I and III, patients were observed from the date of diagnosis until emigration, death or end-of-study, whatever occurred first. Treatment was included as a time-varying covariate. In paper II, patients were followed from the date of RP until RP-failure, emigration, death or end-of-study.

The Aalen-Johansen estimator was used to calculate PCSM and RP-failure, treating death from other causes and death from any causes as competing risks for PCSM and RP-failure, respectively (178). To compare estimates, we used univariate Fine-Gray regression models.

To estimate OM, we used the Kaplan Meier method (179), and the log rank method tested for difference among groups. Mortality estimates were reported with 95% CIs.

In paper I, a standard likelihood ratio test was used to assess the impact of clinical variables in multivariate analyses. Flexible parametric methods with five degrees of freedom for baseline hazard were used to estimate hazard ratios (HRs) for PCSM in both univariate and multivariate analyses, and the proportional hazards assumption was not validated. The same models calculated probabilities of PCSM, incorporating death from other causes as competing risks. In paper II, multivariable Cox proportional hazard regressions documented the impact of RP-interval on PCSM and RP-failure, adjusting for primary treatment and co-existing clinical variables available at the time of diagnosis. In paper III, a multivariable Fine-Gray model tested the relationship (sub-distribution hazard ratios (SHRs) and CIs) between primary treatment and PCSM, treating death from other cause as a competing risk. Cox regressions tested the relationship between primary treatment and OM, adjusting for co-existing variables.

For all three papers we used significance level of $p<0.05$. Data were analysed using the IBM Statistical Package for the Social Sciences (SPSS) Statistics version 23/25/26 and Stata version 14.2.

2.4. Main findings

2.4.1. Paper I

In total, 3449 patients were eligible for the study. The risk group distribution was 26/31/42% for low-, intermediate- and high-risk disease, respectively. Of all patients, 26% underwent RP (n=913), 39% underwent RAD (n=1334) and 35% received no curative treatment (n=1202). There was significant heterogeneity between the treatment groups; RP patients had lower age and better ECOG PS compared to patients managed with RAD or no curative treatment. Only 15% of RP patients had high-risk disease compared to 59% in the RAD group and 46% in the no curative treatment group. Of patients in the RP group, 89% had Gleason score 6-7a/GGG 1-2 cancers.

After a median follow-up of ten years (range 0-11), the PCSM was 8.5%, increasing with increasing risk group allocation within all treatment groups. The ten-year OM was 25.5% for all patients; three times higher than the PCSM. Independent of treatment, the all-cause mortality was 8-fold increased compared to PCSM the low-risk group, while patients in the high-risk group had similar ten-year risk of death from PCa and other causes. Curative treatment reduced the risk of PCSM and OM compared to no curative treatment, with markedly higher absolute differences in the high-risk groups compared to the low-risk group.

In univariate analyses, all clinical variables were significantly associated with ten-year PCSM. In multivariate analyses, primary treatment was associated with ten-year PCSM, with a 4-6-fold increased risk of PCSM in the no curative treatment group compared to curatively treated patients. Age was not significantly associated with PCSM, neither when including all patients or patients receiving curative treatment, or when excluding ECOG from the analyses. ECOG PS ≥1 was independently prognostic of ten-year PCSM, also in the curative treatment group, increasing the risk by almost 50% compared with ECOG 0. The PSA level was not associated with PCSM, nor was the cT-category in patients who underwent curative treatment. Increasing Gleason score/GGG was strongly associated with increased PCSM in all patients and those receiving curative treatment.

2.4.2. Paper II

A total of 5163 patients were eligible for the study. High-risk disease was present in 28% of patients. The distribution of patients within the RP-intervals of 0-60, 61-90, 91-120 and 121-180 days were 17%, 31%, 26% and 27%, respectively. The median RP-interval was 93 days (range 1-180). The age and risk groups were distributed evenly in the RP-interval groups. Among high-risk patients, a higher proportion was treated in the last RP-interval compared to the first (26% vs 18%).

The median follow-up time was 7.9 years (range 0-15). During this time, 1.9% of the patients had died from PCa. For all patients the five- and ten-year PCSM was 0.7% and 2.5%. For intermediate and high-risk patients, no association between RP-interval and PCSM was observed. Mortality analysis in the low-risk groups was hindered by event paucity. For all patients, no worsening of the histopathological findings was seen in the prostatectomy specimens with increasing RP-interval. Totally 22%, 34% and 28% of patients experienced upstaging, upgrading, PSMs, respectively. In all patients, 24.7% experienced RP-failure, and increasing time from diagnosis to RP reduced the likelihood of this event.

2.4.3. Paper III

A total of 19 763 patients were eligible for the study. More than half of the patients diagnosed with high-risk PCa were aged ≥70 years. Compared to younger men, senior adults had poorer ECOG performance status and more unfavorable disease characteristics (higher PSA levels, higher ISUP grade groups, higher cT-categories).

The most marked increase in use of curative treatment from the first to the last diagnostic period was seen in senior adults, with RP increasing 4-fold in patients aged 70-74 years and a 7-fold increase in irradiated patients aged 75-79 years. For all patients, the likelihood of receiving curative treatment decreased with earlier diagnostic period, increasing age and ECOG PS, prior cancer and PSA >20 ng/ml. Patients with ISUP grade group 1 tumours were less likely to receive curative treatment compared to patients with ISUP grade group ≥2 tumours.

Median follow-up time was five years (range 0-13 years). PCSM decreased with time in all patients, but for diagnostic period three only in the senior population. Both PCSM and OM increased with age at diagnosis. Not receiving curative treatment increased the risk of PCa death three-fold and the risk of death from any cause two-fold in both senior adults and younger men. Increasing ISUP grade group was significantly prognostic for PCa death, more so in younger patients.

2.5. Methodological considerations

2.5.1. Data quality

The strengths of the data in this thesis include the use of large population-based cohorts. Data from the CRN with the NoPCR and the Radiotherapy Database were not coupled with data from other public registries, although details on comorbidity using data from the NPR and complete information on hormonal treatment from the National Prescription Database, would have enriched the interpretation of our findings, particularly in the senior patient population.

Norwegian Prostate Cancer Registry

The quality of data in cancer registries can be assessed by completeness, timeliness, comparability and validity of data (180, 181). According to a Norwegian Public Health Act passed in 1983, the CRN is legally obliged to evaluate the quality of their registrations.

The completeness of data in the CRN refers to data coverage, i.e. the proportion of PCa patients registered in the CRN, and the rate of clinical reporting, i.e. the proportion of patients in which the registry has received clinical information and the completeness of these registrations. The mandatory national reporting and the complementary data acquisition from multiple sources at multiple time points should ensure completeness of data. Complementary information from the NPR allows inclusion of unreported cancer cases. A review of data from 2008 found that 313/16 907 men (1.9%) registered with PCa in the NPR had no registration in the CRN (182). The estimated coverage of all PCa patients in the CRN was 99.3% in 2012-2016 (15).

In 2018, the rate of clinical reporting for PCa patients was 79% for diagnosis notifications and 90% for surgery notifications (15). The CRN, however, is a dynamic registry, continuously being updated when new clinical information is acquired, and the completeness of recent data may be delayed beyond the annual reports released by the registry. In 2018, the Norwegian Directorate of Health evaluated national registrations of PCa treatment provided to patients in 2008-2015, and by comparing data with the NPR, they reported 97.7% completeness for prostatectomies in the CRN (183).

In terms of comparability, the CRN coding and classification systems largely follow international standards, and the internal coding of collected data is manually performed by trained coders at the CRN. Continuous quality assurance is an integrated part of the work flow in the CRN, ensuring internal validation of data. Further, data from the CRN is frequently used by researchers, providing opportunities for feed-back on data registrations. For the time period 2001-2005, completeness, comparability, validity and timeliness of PCa data in the registry had favorable values for the above-mentioned quality measures (184).

A limitation with registry data is that researches have limited influence on data collection and monitoring, and registered data may not provide answers to all clinical research questions. A dedicated clinical expert group advises the NoPCR on data collection, quality indicators and presentation of data in the annual report released by the registry.

Radiotherapy Database

Interpretation and validation of RAD data in the CRN for use in clinical research and surveillance demand in-depth knowledge about multidisciplinary treatment of PCa patients. In a previously described external validation analysis, conducted by the Norwegian Directorate of Health in 2018, 99.6% completeness for radiotherapy registrations in the CRN was documented (183).

Cause of Death Registry

Statistics Norway has been responsible for death registration routines in Norway from 1925 until the Norwegian Institute for Public Health took over the processing of data in 2001 and the operation of the Cause of Death Registry in 2014 (185). The registry collects death certificates for all deaths that occur in Norway and registers deaths of Norwegians who die abroad. In Norway, death is declared by a doctor, usually the hospital or community doctor on call or the patients´ general practitioner. Death certificates are filled in according to the principles established by the WHO and the International Classification of Diseases and Related Health Problems coding system. A computer program or a professional coder assists in determining the underlying cause of death (the disease or injury which initiated the train of morbid events leading directly to death), which is used for statistics. The coverage of deaths in the Cause of Death Registry is assumed to be >98%. Not specified for PCa, extensive use

of unspecified codes has been reported (185), but the registry ranks high in international quality reviews (186-188).

Misattribution of the underlying cause of death may introduce attribution bias in studies relying on PCa death reporting. Supported by international findings, concerns have been raised as to the accuracy of the cause of death reporting in Norwegian men with PCa, particularly those >75 years at the time of death (189-191). When comparing survival estimates, Skyrud et al demonstrated significant differences between 5-year RS and cancer-specific survival in Norwegian PCa patients; RS estimates being higher compared to CSS (192). These differences increased with age and time since diagnosis, suggesting inaccuracies in cause of death reporting in the oldest patients and difficulties establishing the cause of death when time from diagnosis increases. In other Scandinavian countries and the UK, however, reports have shown high accuracy for official death certificates (65, 193-196). A Swedish registry-based study found that the proportion of PCa patients classified as having died from PCa was 3.3 % higher in the official death certificates compared to a medical record review, with overreporting occurring primarily among patients aged ≥75 years at the time of diagnosis (193). Validation studies from the U.S. have demonstrated concordance rates of 87-96% for PCa death between death certificates and medical records, concluding that PCa mortality could be reliably classified in most patients (191, 197).

2.5.2. Study design

The observational design of our studies provides real-life data of large historical population-based patient cohorts with long-term follow-up. Population-based pattern of care studies, combined with survival analyses, can be used to evaluate national therapeutic strategies and results, and are useful in determining the magnitude of over- and under-treatment in patients with PCa. The observational study design, however, can merely describe the outcomes in different treatment groups, and conclusions as to differences between therapeutic effectiveness of specific treatments cannot be made.

2.5.3. Patients and data management

In all papers, patients were classified according to the 2017 EAU risk grouping (56), which is identical to the contemporary version (33). This risk classification system differs from the D´Amico system concerning the PSA cut-off value in the low-risk group (EAU: PSA <10 vs D´Amico: ≤10 ng/ml) and inclusion of patients with cT3-4 tumours and N1 disease in the EAU high-risk locally advanced group (56). Variables increasingly used for risk stratification beyond the three-tiered system, including PSA density, length and number of positive/negative biopsies and MRI findings, were not readily available from the CRN.

In our papers, we included only patients with information on all variables needed for risk classification; cT-category, PSA value and Gleason score. In paper III, 8347 potential high-risk patients without distant metastases and high-risk features were excluded due to insufficient data required for risk grouping. To avoid exclusion of patients with missing cT2 subcategory data in paper I and II, we decided to risk classify these patients based on PSA and Gleason score alone. The routine implementation of pre-biopsy MRI of the prostate is likely to have affected cT-categorization in the third diagnostic period (2013-2016) in paper III, potentially resulting in upstaging of tumours compared to DRE. In contrast to paper I, patients with cT4-tumors were considered potential candidates for curative treatment in paper III. Complete information on clinical N-category was not available in the CRN and could not reliably be used for risk classification, but patients coded with N1-disease were included in the high-risk cohort in paper III. A significant proportion of patients had unknown M-status, and in line with other studies, we used PSA levels >100 ng/ml as an indicator of distant metastases, and the remaining ´MX´-patients were regarded as M0. For most patients we had several PSA-values (up to four) from the initial work-up, and the highest value was reported. In line with the EAU risk classification, we categorized the PSA values into three categories; PSA <10, 10-20 and >20 ng/ml.

The ´Gleason shift´ since 2005, with an overall upgrading and upward risk group migration, may have contributed to a survival improvement in patients classified by tumour grade, an effect referred to as the Will Rogers phenomenon (198). A number of patients who today would have been classified as Gleason score 7/ISUP 2-3 could have been categorized as Gleason score 6/ISUP grade group 1 in our papers. The time of implementation of the Gleason modifications at different Pathology Departments in Norway has not been mapped,

although we expect pathologists regularly attending international conferences and as soon as possible introducing these modifications in clinical practice. The pathology reports were made by multiple pathologists around the country, and no central reviews of biopsies were performed. We had only information on Gleason score in the first cancer-positive biopsy (or TURP specimen), although patients may have undergone re-biopsies with a resultant change in Gleason score affecting final treatment decisions.

No data on comorbidity other than WHO/ECOG PS and other cancer diagnosis was available from the CRN, and ECOG PS was used as a surrogate for comorbidity in paper I and III. In the first paper, we viewed patients ≤75 years as candidates for curative treatment, although, as demonstrated in paper III, patients ≥75 years with high-risk disease have increasingly received curative treatment and may benefit from such treatment.

In paper I and III, patients were categorized into three treatment groups; RP or RAD (curative treatment) or no curative treatment. RP was performed ≤12 months of diagnosis. No information on the reasons for timing of RP within this time period was available from the CRN. With the introduction of the CPP in 2015, today´s RP-intervals would be expected to be shorter compared to time periods covered by these papers. Performance of PLND was not reliably documented in the CRN, but a therapeutic effect of PLND has not been reported.

In paper I, RAD was defined as pelvic RAD with target doses of ≥70 Gy started within 18 months of diagnosis. More than one third of patients received a RAD dose of 70 Gy, a dose that today would be considered suboptimal (120). In the third paper, comprising high-risk patients only, we considered pelvic RAD with target dose ≥74 Gy as curative, and patients receiving lower doses were included in the no curative treatment group, potentially improving survival outcomes in this subgroup as compared to no local treatment. The discrepancies in our definitions of curative RAD relate to the change in guidelines in the time period covered by this thesis, based on the increasing evidence from comparative effectiveness studies that higher RAD doses increase survival (120). Importantly, we provided information of RAD doses. For paper III, RAD was started ≤15 months of diagnosis in patients diagnosed 2005-2013 and ≤12 months in patients diagnosed 2014-2016, because of the CPP reducing wait times for initiation of treatment. For patients in the RAD groups, we had no information on the concomitant use of ADT, although common practice was 3-6-months neo-adjuvant ADT,

followed by 1-3 years adjuvant ADT, depending on the risk group. Although, less likely, patients receiving curative treatment could have been managed with initial AS for a short time period.

In paper I and III, patients not fulfilling the criteria for primary RP or RAD were allocated to the no curative treatment group. In paper I, no distinction could be made between AS and WW in the no curative treatment group, because AS was not registered in the NoPCR until 2009, nor could use of primary ADT be identified. AS, however, was less commonly applied in low-risk patients compared to today´s practice. The main distinction was made between curative treatment and no curative treatment in papers I and III. In the CRN, no direct information on disease recurrence, progression or secondary cancer treatments is available. In paper II, post-RP pelvic or mamillary RAD served as a minimum estimate of recurrence and is further discussed in section 2.6.2. (199).

In paper I, we had satisfactory follow-up of median 10 years. In paper II, longer follow-up time could have influenced the results regarding long-term impact of delayed RP on PCSM, admitting that this patient group has excellent long-term prognosis. In this paper, we had too few deaths in the low-risk group to estimate differences in PCSM related to RP-interval. In paper III, survival differences emerged with a median follow-up of five years, but the results regarding the impact of curative versus non-curative treatment on PCSM, could change with longer observation times, particularly in patients with longer LE.

2.5.4. Statistical methods

Despite limitations of cause of death registration, we used PCSM for survival analyses, partly because we did not have access to correct national lifetables. We know that early detection of PCa is related to socioeconomic status (200), and thus, we should have life tables stratified on socioeconomic status in order to correctly estimate relative survival in patients with non-metastatic PCa. When applying standard life tables, which are stratified on sex, calendar year and age, it is not uncommon to see relative survival estimates >100% in these patients, which is not correct and also not clinically relevant. For individual patients, we believe PCSM gives better estimates of prognosis compared to RS. PCSM estimates also allow comparisons with international cohorts.

To avoid immortal time bias, we analyzed treatment as a time-varying covariate, meaning that patients remained in the no curative treatment group until the date they received curative treatment with RP or RAD. In all papers, we used the Kaplan-Meier (KM) method to estimate overall survival probabilities over time. For estimation of PCSM we used the Aalen Johansen estimator. The type of method used to estimate cancer-specific mortality may have great implications for interpretation of results (201, 202). When using the KM method to estimate PCSM, patients experiencing an event (drop out, death from other causes) during the study period are censored, assuming that these events are independent of the outcome of interest (uninformative censoring) and that the patients who are censored during the study period have the same prognosis as those who are still followed. In real life, however, these events are competing, and the assumption is likely invalid, merely representing a hypothetical situation and not the reality experienced by patients. The risk of overestimating the probability of the event of interest using the KM method increases as the risk of noncancer-specific mortality increases (201). This issue is particularly relevant in cohorts of PCa patients, because these patients often are old, have comorbidities and generally good long-term PCa-related prognosis. For these reasons, competing risk methods were considered more appropriate for the present studies. In these models, non-PCa deaths are considered competing events (203).

In paper III we included older patients with high risk of death from other causes than PCa. We therefore used a multivariable Fine-Gray model to test the relationship between primary treatment and PCSM since our primary aim was to assess the prognostic value of clinical parameters, rather than investigating the causal association between clinical variables and PCa death. The Cox proportional hazards model may be more appropriate in etiologic research, while the Fine-Gray model may provide more relevant information in prognostic research (202).

2.5.5. Errors and bias

Errors can be classified as random or systematic. Random errors are fluctuations in measurements that occur by chance. They reduce towards zero as the study size increases (204) and will be limited in our studies due to large cohort sizes. Systematic errors may occur at any level of data flow, and may be caused by e.g. errors in reporting or coding. Such errors

may induce biases in estimates and could potentially result in erroneous associations between exposure and outcome. Systematic errors include selection bias, information bias and confounding.

The CRN is a national registry and the completeness in the registry avoids *selection bias* when extracting population-based data. Non-randomized patient stratification according to treatment type, however, introduces selection bias because subgroups are coherently heterogenous, as demonstrated in paper I and III. Differences in overall and PCSM mortality among treatment groups will therefore have to be viewed with great caution. In multivariate analyses, attempts were made to adjust for differences in basic patient- and disease-related factors within the treatment groups.

Information bias is one type of systematic error that occurs when the available information about the study participants is misclassified. The general view is that for CRN data, information bias is limited by reports from multiple sources for each patient and internal quality control. The data collection and quality control of CRN data are discussed in sections 2.2.1. and 2.5.1.

Confounding bias occurs when a third variable (a confounder) affects both the independent and the dependent variable, resulting in a distorted association between the exposure and the outcome, in which the variables are associated, but not causally related. The lack of in-depth information on comorbidity may have introduced a confounding bias when investigating the association between age and mortality outcomes, as comorbidity is associated with both variables. The ECOG PS, although a crude measure, was used as a proxy for comorbidity in these papers and adjusted for in multivariate analyses, using both competing and non-competing risk models.

We have no reasons to believe that missing information in the datasets followed particular patterns introducing biases in our results. The cohorts were large with less than 10% missing data, and we deemed imputation unnecessary. In paper I, we performed survival analyses in patients excluded because of missing data (incomplete group), and found no differences in mortality compared to the main cohort.

2.6. Discussion of main findings

2.6.1. Paper I

With ten-year OM being three times higher than PCSM, the results from this population-based cohort clearly demonstrate the considerable risk of death from other causes than PCa and high-light the importance of individual outcome assessment when considering curative treatment in patients with PCa without distant metastases. Discrepancies between PCSM and OM were highest in patients with low-risk disease and smallest in patients with high-risk disease.

The ten-year PCSM estimates from this study are comparable to results from other population-based observational studies from the Surveillance, Epidemiology, and End Results (SEER) registry (40, 88), the National Cancer Database (120) and the Swedish National Prostate Cancer Registry (111, 205). PCSM estimates were higher compared to those of the ProtecT trial, however, significant differences in patient characteristics exist between these cohort and direct comparisons are not justified (25). Comparisons with previous Norwegian population-based cohorts cannot be made due to lack of data.

Despite competing risks of death, not receiving curative treatment clearly increased the risk of death from PCa, mainly in intermediate- and high-risk patients. In agreement with previous reports, high-risk patients benefit the most from curative treatment, and survival differences between treated and untreated emerge within five years of diagnosis (78, 88). A surprisingly high proportion of patients with high-risk disease (37%) did not receive curative treatment, although management of PCa patients diagnosed in 2004-2005 would not be representative for today´s practice. As demonstrated in paper III, an increasing proportion of Norwegian high-risk patients has been treated with curative intent from 2005-2008 onwards, and a decrease in PCSM has been observed in these patients. A minor reduction in PCSM was observed in low-risk patients receiving curative treatment, many of whom today would be considered for AS. Although the non-random allocation to treatment groups did not allow direct comparisons of treatment modalities, we observed almost a doubling in the risk of PCa death in patients treated with RAD compared to RP, even when adjusted for available

covariates. Unidentified covariates contributing to further heterogeneity within treatment groups may have impacted results. Further, the RAD doses considered curative in this study (<74 Gy), would today be considered suboptimal. The definition of curative RAD was re-defined in paper III.

The prognostic factors evaluated in this study are easily available at the time of diagnosis. Risk group and biopsy Gleason score/GGG categorization have previously been shown to be prognostic for PCSM (40, 58). Increasing risk group was significantly associated with increased ten-year PCSM in all patients, also in the curatively treated men. Of the clinical variables included in the three-tiered risk classification, Gleason score/GGG appeared to be the most important prognostic factor for PCSM. The significant additional predictive effect when evaluating GGG 1-3 within the intermediate risk group and GGG 1-5 within the high-risk group in patients treated with curative intent, demonstrates the high predictive value of GGGs. Increasing cT-category was associated with increased likelihood of PCSM, however, not significantly in men who received curative treatment. Unlike demonstrated in other studies, the PSA level at diagnosis was not prognostic of PCSM when adjusted for available covariates (26, 27). We did, however, evaluate PSA as a categorical variable (<10, 10-20, >20 ng/ml) and not a continuous measure. Further, we did not explore the prognostic impact of clinical variables in the no curative treatment group separately.

ECOG PS was in this study shown to be an independent covariate of ten-year PCSM in both univariate and multivariate analyses, also in patients receiving curative treatment. Although the impact of ECOG PS on PCSM was unexpected, one explanation could be that patients with increasing ECOG scores receive less secondary cancer treatments. Further, there were relatively fewer PCa deaths in the curative treatment groups, in which the association of ECOG and PCSM were highest, compared to all patients. The impact of ECOG PS on PCSM within the treatment groups would need further confirmation. ECOG is a crude measure of health status in clinical practice, limited by interobserver variability, but its prognostic value and ease of registration adds value in a population-based registry.

Age was prognostic of PCSM in univariate analysis. This relationship can be explained by the positive associations between increasing age and more unfavourable disease characteristics and less curative treatment compared to younger men. When adjusting for other covariates, age was not an independent predictor of PCSM. One explanation could be an interaction

effect between age and PS in multivariate analysis, but when excluding ECOG PS from the analysis, age estimates remained unchanged. Our results are in line with findings in international literature (171-173) and support the notion that age alone should not exclude patients from curative treatment.

Our patient cohort was diagnosed with PCa fifteen years ago, and changes in diagnostic methods and disease classifications may imply important differences when comparing these patients to contemporary cohorts. As a result of the Gleason shift and increased use of radiological staging, patients diagnosed with intermediate- and high-risk PCa today may have a more favorable prognosis compared to similar patients in this study. Risk stratification is continuously improving with identification of new prognostic variables available at the time of diagnosis. Furthermore, changes in patient selection for treatment and refinements in curative treatment techniques, along with increased LE, are likely to impact PCSM in contemporary cohorts. Within a rapidly evolving medical field, this will always be the case for data with long-term follow-up. Findings from this study allow comparisons with international estimates and will permit comparisons with more recent Norwegian PCa patient cohorts.

2.6.2. Paper II

In this cohort of more than 5000 patients, of which 28.8% had high-risk disease and 8.8% had locally advanced tumours, delayed RP up to 180 days after diagnosis was not associated with increased PCSM, worse histopathological findings in the RP specimen (more upgrading/upstaging/positive survival margins), or increased likelihood of post-RP pelvic or mamillary RAD in any risk group. These findings are consistent with previous reports that have not documented worse survival with longer RP-intervals (206-209). Furthermore, results are in agreement with studies demonstrating no adverse effects of increasing RP-interval on histopathological findings or BCR rates (209-213), although such associations have previously been reported (45, 169, 206, 214, 215).

Surprisingly, we found that increased RP-interval was associated with less likelihood of post-RP pelvic or mamillary RAD. The reasons for delayed RP were not known, and the even

distribution of age and tumour characteristics within the four RP-interval groups did not indicate prioritization of specific patient groups. We hypothesize that patients operated late had more favorable disease characteristics not visualized by our covariates. Post-RP pelvic or mamillary RAD must be regarded as a minimum estimate of recurrence in this study, as patients may have experienced recurrence without receiving pelvic RAD, started anti-androgen treatment without preceding mamillary RAD or progressed to metastatic disease directly. Further, we could not separate adjuvant from salvage radiotherapy. Limitations of this study include the lack of post-RP PSA values and information on hormonal treatment.

Similar to findings from paper I, Gleason score and risk group were highly prognostic of PCSM in multivariate analyses, but age and PSA were not. No changes in PCSM were seen across time periods and PCSM estimates were comparable to international cohorts (40, 88, 111, 205).

In our study, only 17% of patients were operated within the CPP recommendations. A large study from Canada from the same period as ours showed similar RP-intervals with a median of 83 days (212). With the implementation of the CPP, the median RP-interval of 93 days in this study would be expected to be significantly shorter today, however, the time limits for initiation of treatment in the prostate CPP have proven difficult to implement in clinical practice and were only complied with in 45.2% of patients treated with RP in the third period of 2019 (147, 216).

There are several reasons why the performance of RP may be extended beyond 32 days from decision-making. These factors may be patient-related, hospital-related or external. Firstly, the patient may wish time to consider curative treatments options and seek second opinions before deciding on RP. Some patients may want to defer treatment because of upcoming important events in their lives. Patients with comorbidities may require time to optimize health status or recover from acute illness. Further, with more senior patients, there is increasing interest in pre-habilitation prior to surgery to improve post-RP recovery. Finally, the hospitals may need to prioritize based on limited internal resources or due to external events (e.g. pandemics) reducing the operative capacity.

The health care service´s strict adherence to defined time limits does not necessarily reflect quality in PCa care. Pre-set time limits may even be contradictory to value-based health care

if compliance with time limits compromises the needs and wishes of the patient. Patients may further experience unnecessary distress when the time limits are not adhered to, fearing that prognosis will worsen.

Although oncological outcomes do not worsen with increased RP-intervals up to six months, the CPP is likely to bring about several important improvements related to patient care. Patients and their relatives experience a well-organized and predictable diagnostic and therapeutic path with avoidance of unnecessary delays and wait times. Having a dedicated, coordinating contact person at the hospital may solve practical issues and provide a sense of security. For the hospitals, stream-lining services and planning resources may improve efficacy and possibly reduce costs. The authorities can ensure equal handling across regions and keep an overview of local practices to plan improvement efforts.

Patients considered for RP would be expected to have a LE of minimum ten years and extended follow-up beyond eight years could possibly have revealed survival differences within the RP-interval groups. In this cohort, 28.2% and 42.9% of patients had low- and intermediate-risk disease, respectively, many of whom today would be considered for deferred active treatment. More importantly, contemporary RP-patients have more unfavorable disease characteristics compared to earlier cohorts, and findings from this study may be highly relevant for patient counselling and RP planning today.

2.6.3. Paper III

In this large population-based cohort of men with high-risk PCa diagnosed in Norway in 2005-2016, the use of curative treatment increased with time, more in senior men (≥70 years), and was accompanied by decreased PCSM and OM in both senior and younger patients.

Several studies have documented more unfavorable disease with increasing age at diagnosis (43, 175, 217). In this study, we demonstrate that also within the high-risk group, senior adults have more unfavorable disease, and that significant heterogeneity as to medical variables exists among high-risk patients.

The use of curative treatment increased across diagnostic periods, more in senior than in younger adults. These findings are in line with increasing LE in the population and the rising attention among health care professionals to biological rather than chronological patient age. Furthermore, increased documentation that high-risk patients considerably benefit from modern curative treatment techniques is likely to have influenced decisions.

Increased use of curative treatment was accompanied with a decrease in PCSM across the diagnostic periods. In multivariate analyses, using both standard and competing risk methods, curative treatment was associated with a reduced risk of death from PCa in both senior and younger patients, similar for RP and RAD. Of note, we could not identify patients receiving primary treatment with RP and adjuvant RAD, however, multimodal treatment was not common at this time, at least not in the first two diagnostic periods (218). Importantly, curative treatment was also associated with a reduced risk of all-cause mortality in senior adults.

Unlike demonstrated in paper I, increasing ECOG status was not associated with increased likelihood of PCSM when analyzed in a competing risk setting in senior adults with high-risk PCa. As previously shown, when unadjusted, increasing age was associated with increased likelihood of PCa death in senior men, but only in men ≥80 years in multivariate analysis. Adjusted for other covariates, PSA >20 ng/ml and cT3-4 tumours were poor prognostic factors in both senior and younger men. Surprisingly, the increasing risk of dying of PCa with increasing ISUP grade groups was more prominent in younger compared to senior adults. An association between testosterone levels and PCa was proposed in a study demonstrating lower risk of PCa in men with lower circulating free testosterone (219).

The results of our study are important because of the limited number of studies investigating the impact of curative treatment on PCSM in senior adults with high-risk PCa, and with increasing LE in the population, particularly important in patients aged ≥75 years. At present, there is no consensus on the optimal treatment strategy in senior adults with high-risk PCa and considerable variations are permitted in clinical practice. Similar to our findings, several studies indicate undertreatment of senior men eligible for curative treatment, resulting in excess morbidity and mortality in this subgroup of patients (90, 91).

2.7. Conclusions

2.7.1. Paper I

- In patients diagnosed with PCa without distant metastases in Norway in 2004-2005, the ten-year PCSM was 8.5% and the OM was 25.5%. The ten-year PCSM was 1.7% in the low-risk group, 4.5% in the intermediate-risk group, and 13.1% and 17.3% in the high-risk localised and locally advanced groups, respectively.
- When adjusted for available covariates, ECOG performance status ≥1, increasing cT-category, Gleason score/GGG and EAU risk group and not receiving curative treatment were independent prognostic factors associated with increased ten-year PCSM. In patients receiving curative treatment, the GGGs added predictive value supplementary to traditional risk grouping.

2.7.2. Paper II

- A delay of RP up to 180 days after PCa diagnosis was not associated with increased PCSM, worse histopathological findings in the RP-specimen or increased likelihood of receiving post-RP pelvic or mamillary RAD (the latter indicating start of anti-androgen treatment).

2.7.3. Paper III

- Among high-risk patients, senior adults (≥70 years) had more unfavorable disease characteristics compared to younger men (<70 years).
- Use of curative treatment in patients with high-risk PCa increased in Norway from 2005-2008 to 2013-2016, more in senior adults (from 15 to 51%) than in younger men (from 65 to 81%).
- Curative treatment significantly reduced PCSM and OM when adjusted for available covariates, and unlike the expected outcome, to a similar extent in both senior and younger adults.

2.8. Clinical implications and future studies

- The population-based ten-year PCSM and OM in men with PCa without distant metastases documented in this thesis should be compared with comparable outcomes in more recent Norwegian cohorts.
- The high prognostic value of biopsy-based ISUP grade groups for PCSM compared to other basic clinical variables should increasingly be considered when making treatment decisions in PCa patients without distant metastases.
- The observed higher prognostic value of ISUP grade groups for PCSM in younger men (<70 years) compared with senior adults (≥70 years) needs further confirmation.
- Patients and clinicians can be reassured that delay in RP, whatever reason, up to six months will not significantly reduce survival.
- The time limit for performance of RP as primary treatment in the current prostate CPP should be reconsidered.
- Exploration of the impact of time from diagnosis to start of definitive RAD on PCSM is warranted.
- The patients´ satisfaction with the CPP should be evaluated in a national study.
- Particularly in senior adults, decisions regarding treatment should as a minimum be based on assessment of age, performance status and comorbidity, ideally with formal health screening, together with risk stratification, to identify who will gain benefit from curative treatment, expressed by survival in this thesis.
- Increased use of curative treatment with RP or RAD in eligible men with high-risk PCa, even in senior adults with LE < ten years, may reduce PCSM and OM and should be further explored in future studies including senior adults and quality of life outcomes.

3. References

1. Aas K, Axcrona K, Kvale R, Moller B, Myklebust TA, Axcrona U, et al. Ten-year Mortality in Men With Nonmetastatic Prostate Cancer in Norway. Urology. 2017;110:140-7.

2. Aas K, Fossa SD, Kvale R, Moller B, Myklebust TA, Vlatkovic L, et al. Is time from diagnosis to radical prostatectomy associated with oncological outcomes? World J Urol. 2019;37(8):1571-80.

3. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394-424.

4. Moch H, Humphrey PA, Ulbright TM, Reuter VE. WHO Classification of Tumours of the Urinary System and Male Genital Organs. 4th ed 2016.

5. World Health Organization. Estimated number of incident cases from 2018 to 2040, prostate, males.: International Agency for Research on Cancer; 2018 [Cancer statistics]. Available from: https://gco.iarc.fr.

6. Cancer Registry of Norway. Cancer in Norway 2018 - Cancer incidence, mortality, survival and prevalence in Norway. Oslo: Cancer Registry of Norway; 2019.

7. Kvale R, Myklebust TA, Engholm G, Heinavaara S, Wist E, Moller B. Prostate and breast cancer in four Nordic countries: A comparison of incidence and mortality trends across countries and age groups 1975-2013. Int J Cancer. 2017;141(11):2228-42.

8. Engholm G, Ferlay J, Christensen N, Bray F, Gjerstorff ML, Klint A, et al. NORDCAN--a Nordic tool for cancer information, planning, quality control and research. Acta Oncol. 2010;49(5):725-36.

9. Danckert B FJ, Engholm G , Hansen HL, Johannesen TB, Khan S, Køtlum JE, Ólafsdóttir E, Schmidt LKH, Virtanen A, Storm HH. NORDCAN: Cancer Incidence, Mortality, Prevalence and Survival in the Nordic Countries. Version 8.2 (26.03.2019).

10. Kicinski M, Vangronsveld J, Nawrot TS. An epidemiological reappraisal of the familial aggregation of prostate cancer: a meta-analysis. PLoS One. 2011;6(10):e27130.

11. Leitzmann MF, Rohrmann S. Risk factors for the onset of prostatic cancer: age, location, and behavioral correlates. Clin Epidemiol. 2012;4:1-11.

12. Allott EH, Masko EM, Freedland SJ. Obesity and prostate cancer: weighing the evidence. Eur Urol. 2013;63(5):800-9.

13. Vidal AC, Freedland SJ. Obesity and Prostate Cancer: A Focused Update on Active Surveillance, Race, and Molecular Subtyping. Eur Urol. 2017;72(1):78-83.

14. World Health Organization Department of Information Evidence and Research. Cancer Mortality database 2019 [Available from: https://www-dep.iarc.fr/whodb/whodb.htm

15. Cancer Registry of Norway. Annual Report 2018 with Results and Improvements from the Norwegian Prostate Cancer Registry. 2019.

16. Borden LS, Jr., Wright JL, Kim J, Latchamsetty K, Porter CR. An abnormal digital rectal examination is an independent predictor of Gleason > or =7 prostate cancer in men undergoing initial prostate biopsy: a prospective study of 790 men. BJU Int. 2007;99(3):559-63.

17. Bozeman CB, Carver BS, Caldito G, Venable DD, Eastham JA. Prostate cancer in patients with an abnormal digital rectal examination and serum prostate-specific antigen less than 4.0 ng/mL. Urology. 2005;66(4):803-7.

18. Draulans C, Everaerts W, Isebaert S, Gevaert T, Oyen R, Joniau S, et al. Impact of Magnetic Resonance Imaging on Prostate Cancer Staging and European Association of Urology Risk Classification. Urology. 2019;130:113-9.

19. van der Poel H, van der Kwast T, Aben K, Mottet N, Mason M. Imaging and T Category for Prostate Cancer in the 8th Edition of the Union for International Cancer Control TNM Classification. Eur Urol Oncol. 2019.

20. Thompson IM, Pauler DK, Goodman PJ, Tangen CM, Lucia MS, Parnes HL, et al. Prevalence of prostate cancer among men with a prostate-specific antigen level < or =4.0 ng per milliliter. N Engl J Med. 2004;350(22):2239-46.

21. Harvey P, Basuita A, Endersby D, Curtis B, Iacovidou A, Walker M. A systematic review of the diagnostic accuracy of prostate specific antigen. BMC Urol. 2009;9:14.

22. Verma A, St Onge J, Dhillon K, Chorneyko A. PSA density improves prediction of prostate cancer. Can J Urol. 2014;21(3):7312-21.

23. Guazzoni G, Nava L, Lazzeri M, Scattoni V, Lughezzani G, Maccagnano C, et al. Prostate-specific antigen (PSA) isoform p2PSA significantly improves the prediction of prostate cancer at initial extended prostate biopsies in patients with total PSA between 2.0 and 10 ng/ml: results of a prospective study in a clinical setting. Eur Urol. 2011;60(2):214-22.

24. Rider JR, Sandin F, Andren O, Wiklund P, Hugosson J, Stattin P. Long-term outcomes among noncuratively treated men according to prostate cancer risk category in a nationwide, population-based study. Eur Urol. 2013;63(1):88-96.

25. Hamdy FC, Donovan JL, Lane JA, Mason M, Metcalfe C, Holding P, et al. 10-Year Outcomes after Monitoring, Surgery, or Radiotherapy for Localized Prostate Cancer. N Engl J Med. 2016;375(15):1415-24.

26. MacKintosh FR, Sprenkle PC, Walter LC, Rawson L, Karnes RJ, Morrell CH, et al. Age and Prostate-Specific Antigen Level Prior to Diagnosis Predict Risk of Death from Prostate Cancer. Front Oncol. 2016;6:157.

27. Thurtle DR, Greenberg DC, Lee LS, Huang HH, Pharoah PD, Gnanapragasam VJ. Individual prognosis at diagnosis in nonmetastatic prostate cancer: Development and external validation of the PREDICT Prostate multivariable model. PLoS Med. 2019;16(3):e1002758.

28. Rao AR, Motiwala HG, Karim OM. The discovery of prostate-specific antigen. BJU Int. 2008;101(1):5-10.

29. Kvale R, Auvinen A, Adami HO, Klint A, Hernes E, Moller B, et al. Interpreting trends in prostate cancer incidence and mortality in the five Nordic countries. J Natl Cancer Inst. 2007;99(24):1881-7.

30. Breidablikk HJM, E.; Aakre, K.M.; Førde, O.H. PSA-måling og prostatakreft - overdiagnostisering og overbehandling? Tidsskr Nor Legeforen. 2013(16):1711-6.

31. Pettersson A, Robinson D, Garmo H, Holmberg L, Stattin P. Age at diagnosis and prostate cancer treatment and prognosis: a population-based cohort study. Ann Oncol. 2018;29(2):377-85.

32. Hodge KK, McNeal JE, Terris MK, Stamey TA. Random systematic versus directed ultrasound guided transrectal core biopsies of the prostate. J Urol. 1989;142(1):71-4; discussion 4-5.

33. European Association of Urology. Oncology Guidelines Prostate Cancer 2020 [Available from: https://uroweb.org/guideline/prostate-cancer/.

34. Gleason DF, Mellinger GT. Prediction of prognosis for prostatic adenocarcinoma by combined histological grading and clinical staging. J Urol. 1974;111(1):58-64.

35. Bailar JC, 3rd, Mellinger GT, Gleason DF. Survival rates of patients with prostatic cancer, tumor stage, and differentiation--preliminary report. Cancer Chemother Rep. 1966;50(3):129-36.

36. Epstein JI, Allsbrook WC, Jr., Amin MB, Egevad LL, Committee IG. The 2005 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason Grading of Prostatic Carcinoma. Am J Surg Pathol. 2005;29(9):1228-42.

37. Epstein JI, Egevad L, Amin MB, Delahunt B, Srigley JR, Humphrey PA, et al. The 2014 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason Grading of Prostatic Carcinoma: Definition of Grading Patterns and Proposal for a New Grading System. Am J Surg Pathol. 2016;40(2):244-52.

38. Epstein JI, Zelefsky MJ, Sjoberg DD, Nelson JB, Egevad L, Magi-Galluzzi C, et al. A Contemporary Prostate Cancer Grading System: A Validated Alternative to the Gleason Score. Eur Urol. 2016;69(3):428-35.

39. Pierorazio PM, Walsh PC, Partin AW, Epstein JI. Prognostic Gleason grade grouping: data based on the modified Gleason scoring system. BJU Int. 2013;111(5):753-60.

40. Pompe RS, Davis-Bondarenko H, Zaffuto E, Tian Z, Shariat SF, Leyh-Bannurah SR, et al. Population-based validation of the 2014 ISUP Gleason grade groups in patients treated with radical prostatectomy, brachytherapy, external beam radiation or no local treatment. Prostate. 2017.

41. Leapman MS, Cowan JE, Simko J, Roberge G, Stohr BA, Carroll PR, et al. Application of a Prognostic Gleason Grade Grouping System to Assess Distant Prostate Cancer Outcomes. Eur Urol. 2017;71(5):750-9.

42. International Agency for Research on Cancer. WHO Classification of Tumours of the Urinary System and Male Genital Organs. 4th ed2016.

43. Scosyrev E, Messing EM, Mohile S, Golijanin D, Wu G. Prostate cancer in the elderly: frequency of advanced disease at presentation and disease-specific mortality. Cancer. 2012;118(12):3062-70.

44. Pepe P, Pennisi M. Gleason score stratification according to age at diagnosis in 1028 men. Contemp Oncol (Pozn). 2015;19(6):471-3.

45. Kvale R, Moller B, Wahlqvist R, Fossa SD, Berner A, Busch C, et al. Concordance between Gleason scores of needle biopsies and radical prostatectomy specimens: a population-based study. BJU Int. 2009;103(12):1647-54.

46. Amin MB ES, Greene F, Byrd DR, Brookland RK, Washington MK, Gershenwald JE, Compton CC, Hess KR, Sullivan DC, Jessup JM, Brierley JD, Gaspar LE, Schilsky RL, Balch CM, Winchester DP, Asare EA, Madera M, Gress DM, Meyer LR. AJCC Cancer Staging Manual Eight Edition. 8 ed. Switzerland: Springer; 2017.

47. Brierley JD GM, Wittekind C. TNM Classification of Malignant Tumours, 8th Edition. 8 ed: Wiley-Blackwell; 2017.

48. Kiss B, Thoeny HC, Studer UE. Current Status of Lymph Node Imaging in Bladder and Prostate Cancer. Urology. 2016;96:1-7.

49. Perera M, Papa N, Roberts M, Williams M, Udovicich C, Vela I, et al. Gallium-68 Prostate-specific Membrane Antigen Positron Emission Tomography in Advanced Prostate Cancer-Updated Diagnostic Utility, Sensitivity, Specificity, and Distribution of Prostate-specific Membrane Antigen-avid Lesions: A Systematic Review and Meta-analysis. Eur Urol. 2020;77(4):403-17.

50. Gandaglia G, Ploussard G, Valerio M, Mattei A, Fiori C, Fossati N, et al. A Novel Nomogram to Identify Candidates for Extended Pelvic Lymph Node Dissection Among Patients with Clinically Localized Prostate Cancer Diagnosed with Magnetic Resonance Imaging-targeted and Systematic Biopsies. Eur Urol. 2019;75(3):506-14.

51. Partin AW, Mangold LA, Lamm DM, Walsh PC, Epstein JI, Pearson JD. Contemporary update of prostate cancer staging nomograms (Partin Tables) for the new millennium. Urology. 2001;58(6):843-8.

52. Mohler JL, Antonarakis ES, Armstrong AJ, D'Amico AV, Davis BJ, Dorff T, et al. Prostate Cancer, Version 2.2019, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2019;17(5):479-505.

53. NICE Guidance - Prostate cancer: diagnosis and management: (c) NICE (2019) Prostate cancer: diagnosis and management. BJU Int. 2019;124(1):9-26.

54. Gnanapragasam VJ, Bratt O, Muir K, Lee LS, Huang HH, Stattin P, et al. The Cambridge Prognostic Groups for improved prediction of disease mortality at diagnosis in primary non-metastatic prostate cancer: a validation study. BMC Med. 2018;16(1):31.

55. Sanda MG, Cadeddu JA, Kirkby E, Chen RC, Crispino T, Fontanarosa J, et al. Clinically Localized Prostate Cancer: AUA/ASTRO/SUO Guideline. Part I: Risk Stratification, Shared Decision Making, and Care Options. J Urol. 2017.

56. Mottet N, Bellmunt J, Bolla M, Briers E, Cumberbatch MG, De Santis M, et al. EAU-ESTRO-SIOG Guidelines on Prostate Cancer. Part 1: Screening, Diagnosis, and Local Treatment with Curative Intent. Eur Urol. 2017;71(4):618-29.

57. D'Amico AV, Whittington R, Malkowicz SB, Schultz D, Blank K, Broderick GA, et al. Biochemical outcome after radical prostatectomy, external beam radiation therapy, or interstitial radiation therapy for clinically localized prostate cancer. JAMA. 1998;280(11):969-74.

58. Boorjian SA, Karnes RJ, Rangel LJ, Bergstralh EJ, Blute ML. Mayo Clinic validation of the D'amico risk group classification for predicting survival following radical prostatectomy. J Urol. 2008;179(4):1354-60; discussion 60-1.

59. Heidenreich A, Bellmunt J, Bolla M, Joniau S, Mason M, Matveev V, et al. [EAU guidelines on prostate cancer. Part I: screening, diagnosis, and treatment of clinically localised disease]. Actas Urol Esp. 2011;35(9):501-14.

60. Heidenreich A, Bastian PJ, Bellmunt J, Bolla M, Joniau S, van der Kwast T, et al. EAU guidelines on prostate cancer. part 1: screening, diagnosis, and local treatment with curative intent-update 2013. Eur Urol. 2014;65(1):124-37.

61. Zelic R, Garmo H, Zugna D, Stattin P, Richiardi L, Akre O, et al. Predicting Prostate Cancer Death with Different Pretreatment Risk Stratification Tools: A Head-to-head Comparison in a Nationwide Cohort Study. Eur Urol. 2020;77(2):180-8.

62. Krishnan V, Delouya G, Bahary JP, Larrivee S, Taussky D. The Cancer of the Prostate Risk Assessment (CAPRA) score predicts biochemical recurrence in intermediate-risk prostate cancer treated with external beam radiotherapy (EBRT) dose escalation or low-dose rate (LDR) brachytherapy. BJU Int. 2014;114(6):865-71.

63. Cucchiara V, Cooperberg MR, Dall'Era M, Lin DW, Montorsi F, Schalken JA, et al. Genomic Markers in Prostate Cancer Decision Making. Eur Urol. 2018;73(4):572-82.

64. Cooperberg MR, Carroll PR, Dall'Era MA, Davies BJ, Davis JW, Eggener SE, et al. The State of the Science on Prostate Cancer Biomarkers: The San Francisco Consensus Statement. Eur Urol. 2019;76(3):268-72.

65. Johansson JE, Andren O, Andersson SO, Dickman PW, Holmberg L, Magnuson A, et al. Natural history of early, localized prostate cancer. JAMA. 2004;291(22):2713-9.

66. Droz JP, Albrand G, Gillessen S, Hughes S, Mottet N, Oudard S, et al. Management of Prostate Cancer in Elderly Patients: Recommendations of a Task Force of the International Society of Geriatric Oncology. Eur Urol. 2017;72(4):521-31.

67. Boyle HJ, Alibhai S, Decoster L, Efstathiou E, Fizazi K, Mottet N, et al. Updated recommendations of the International Society of Geriatric Oncology on prostate cancer management in older patients. Eur J Cancer. 2019;116:116-36.

68. Tewari A, Johnson CC, Divine G, Crawford ED, Gamito EJ, Demers R, et al. Long-term survival probability in men with clinically localized prostate cancer: a case-control, propensity modeling study stratified by race, age, treatment and comorbidities. J Urol. 2004;171(4):1513-9.

69. Albertsen PC, Hanley JA, Fine J. 20-year outcomes following conservative management of clinically localized prostate cancer. JAMA. 2005;293(17):2095-101.

70. Lee JY, Lee DH, Cho NH, Rha KH, Choi YD, Hong SJ, et al. Impact of Charlson comorbidity index varies by age in patients with prostate cancer treated by radical prostatectomy: a competing risk regression analysis. Ann Surg Oncol. 2014;21(2):677-83.

71. Albertsen PC, Moore DF, Shih W, Lin Y, Li H, Lu-Yao GL. Impact of comorbidity on survival among men with localized prostate cancer. J Clin Oncol. 2011;29(10):1335-41.

72. Wilson JR, Clarke MG, Ewings P, Graham JD, MacDonagh R. The assessment of patient life-expectancy: how accurate are urologists and oncologists? BJU Int. 2005;95(6):794-8.

73. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40(5):373-83.

74. Albertsen PC, Fryback DG, Storer BE, Kolon TF, Fine J. The impact of co-morbidity on life expectancy among men with localized prostate cancer. J Urol. 1996;156(1):127-32.

75. Kastner C, Armitage J, Kimble A, Rawal J, Carter PG, Venn S. The Charlson comorbidity score: a superior comorbidity assessment tool for the prostate cancer multidisciplinary meeting. Prostate Cancer Prostatic Dis. 2006;9(3):270-4.

76. Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5(6):649-55.

77. Kelly CM, Shahrokni A. Moving beyond Karnofsky and ECOG Performance Status Assessments with New Technologies. J Oncol. 2016;2016:6186543.

78. Fossa SD, Nilssen Y, Kvale R, Hernes E, Axcrona K, Moller B. Treatment and 5-year survival in patients with nonmetastatic prostate cancer: the Norwegian experience. Urology. 2014;83(1):146-52.

79. Statistics Norway. Life tables, by sex and age 1966-2019. 2020 [Available from: https://www.ssb.no/en/statbank/table/07902.

80. Eurostat. Life expectancy at birth, 1980-2017. 2019 [Available from: https://ec.europa.eu/eurostat/statistics-explained/index.php?title=File:Life_expectancy_at_birth,1980-2017_(years).png#file.

81. Mottet N, et al. EAU-EANM-ESTRO-ESUR-SIOG Guidelines on Prostate Cancer 2019 [Available from: https://uroweb.org/wp-content/uploads/EAU-Pocket-Guidelines-Prostate-Cancer-2019.pdf.

82. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology - Prostate Cancer Version 4.2019 2019 [Available from: https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf.

83. Gandaglia G, Bray F, Cooperberg MR, Karnes RJ, Leveridge MJ, Moretti K, et al. Prostate Cancer Registries: Current Status and Future Directions. Eur Urol. 2016;69(6):998-1012.

84. Hernes E, Kyrdalen A, Kvale R, Hem E, Klepp O, Axcrona K, et al. Initial management of prostate cancer: first year experience with the Norwegian National Prostate Cancer Registry. BJU Int. 2010;105(6):805-11; discussion 11.

85. Helsedirektoratet. Nasjonalt handlingsprogram med retningslinjer for diagnostikk, behandling og oppfølging av prostatakreft. 2015.

86. Memorial Sloan Kettering Cancer Centre. Male Life Expectancy Survey. Online. [Available from: https://webcore.mskcc.org/survey/surveyform.aspx?preview=true&excelsurveylistid=4

87. National Health Service UK. Predict Prostate. Online. [Available from: https://prostate.predict.nhs.uk

88. Abdollah F, Schmitges J, Sun M, Jeldres C, Tian Z, Briganti A, et al. Comparison of mortality outcomes after radical prostatectomy versus radiotherapy in patients with localized prostate cancer: a population-based analysis. Int J Urol. 2012;19(9):836-44.

89. Abdollah F, Sun M, Schmitges J, Thuret R, Bianchi M, Shariat SF, et al. Survival benefit of radical prostatectomy in patients with localized prostate cancer: estimations of the number needed to treat according to tumor and patient characteristics. J Urol. 2012;188(1):73-83.

90. Loffeler S, Halland A, Fawad H, Beisland C, Haug ES. Non-metastatic prostate cancer: rationale for conservative treatment and impact on disease-related morbidity and mortality in the elderly. Scand J Urol. 2020:1-5.

91. Bratt O, Folkvaljon Y, Hjalm Eriksson M, Akre O, Carlsson S, Drevin L, et al. Undertreatment of Men in Their Seventies with High-risk Nonmetastatic Prostate Cancer. Eur Urol. 2015;68(1):53-8.

92. Horwich A, Hugosson J, de Reijke T, Wiegel T, Fizazi K, Kataja V, et al. Prostate cancer: ESMO Consensus Conference Guidelines 2012. Ann Oncol. 2013;24(5):1141-62.

93. Kuchler J. Uber Prostatavergroserungen. Deutsch Klin. 1866;18:458-65.

94. Young H. The early diagnosis and radical cure of carcinoma of the prostate. Being a study of 40 cases and presentation of a radical operation which was carried out in 4 cases. Johns Hopkins Hosp Bull. 1905;16:315.

95. Millin T. Retropubic prostatectomy; a new extravesical technique; report of 20 cases. Lancet. 1945;2(6380):693-6.

96. Schuessler WW, Schulam PG, Clayman RV, Kavoussi LR. Laparoscopic radical prostatectomy: initial short-term experience. Urology. 1997;50(6):854-7.

97. Brennhovd B. AK. Robotassistert laparoskopisk prostatektomi ved prostatacancer. Kirurgen. 2009.

98. Alemozaffar M, Sanda M, Yecies D, Mucci LA, Stampfer MJ, Kenfield SA. Benchmarks for operative outcomes of robotic and open radical prostatectomy: results from the Health Professionals Follow-up Study. Eur Urol. 2015;67(3):432-8.

99. Ficarra V, Novara G, Ahlering TE, Costello A, Eastham JA, Graefen M, et al. Systematic review and meta-analysis of studies reporting potency rates after robot-assisted radical prostatectomy. Eur Urol. 2012;62(3):418-30.

100. Nguyen LN, Head L, Witiuk K, Punjani N, Mallick R, Cnossen S, et al. The Risks and Benefits of Cavernous Neurovascular Bundle Sparing during Radical Prostatectomy: A Systematic Review and Meta-Analysis. J Urol. 2017;198(4):760-9.

101. Choi WW, Freire MP, Soukup JR, Yin L, Lipsitz SR, Carvas F, et al. Nerve-sparing technique and urinary control after robot-assisted laparoscopic prostatectomy. World J Urol. 2011;29(1):21-7.

102. Fossati N, Willemse PM, Van den Broeck T, van den Bergh RCN, Yuan CY, Briers E, et al. The Benefits and Harms of Different Extents of Lymph Node Dissection During Radical Prostatectomy for Prostate Cancer: A Systematic Review. Eur Urol. 2017;72(1):84-109.

103. Cooperberg MR, Hilton JF, Carroll PR. The CAPRA-S score: A straightforward tool for improved prediction of outcomes after radical prostatectomy. Cancer. 2011;117(22):5039-46.

104. Iversen P, Madsen PO, Corle DK. Radical prostatectomy versus expectant treatment for early carcinoma of the prostate. Twenty-three year follow-up of a prospective randomized study. Scand J Urol Nephrol Suppl. 1995;172:65-72.

105. Bill-Axelson A, Holmberg L, Garmo H, Rider JR, Taari K, Busch C, et al. Radical prostatectomy or watchful waiting in early prostate cancer. N Engl J Med. 2014;370(10):932-42.

106. Bill-Axelson A, Holmberg L, Garmo H, Taari K, Busch C, Nordling S, et al. Radical Prostatectomy or Watchful Waiting in Prostate Cancer - 29-Year Follow-up. N Engl J Med. 2018;379(24):2319-29.

107. Bill-Axelson A, Holmberg L, Ruutu M, Haggman M, Andersson SO, Bratell S, et al. Radical prostatectomy versus watchful waiting in early prostate cancer. N Engl J Med. 2005;352(19):1977-84.

108. Wilt TJ, Brawer MK, Jones KM, Barry MJ, Aronson WJ, Fox S, et al. Radical prostatectomy versus observation for localized prostate cancer. N Engl J Med. 2012;367(3):203-13.

109. Wilt TJ, Jones KM, Barry MJ, Andriole GL, Culkin D, Wheeler T, et al. Follow-up of Prostatectomy versus Observation for Early Prostate Cancer. N Engl J Med. 2017;377(2):132-42.

110. Albertsen PC, Hanley JA, Penson DF, Barrows G, Fine J. 13-year outcomes following treatment for clinically localized prostate cancer in a population based cohort. J Urol. 2007;177(3):932-6.

111. Stattin P, Holmberg E, Johansson JE, Holmberg L, Adolfsson J, Hugosson J, et al. Outcomes in localized prostate cancer: National Prostate Cancer Register of Sweden follow-up study. J Natl Cancer Inst. 2010;102(13):950-8.

112. Abdollah F, Sun M, Schmitges J, Tian Z, Jeldres C, Briganti A, et al. Cancer-specific and other-cause mortality after radical prostatectomy versus observation in patients with prostate cancer: competing-risks analysis of a large North American population-based cohort. Eur Urol. 2011;60(5):920-30.

113. Fossa SD, Beyer B, Dahl AA, Aas K, Eri LM, Kvan E, et al. Improved patient-reported functional outcomes after nerve-sparing radical prostatectomy by using NeuroSAFE technique. Scand J Urol. 2019;53(6):385-91.

114. Leow JJ, Leong EK, Serrell EC, Chang SL, Gruen RL, Png KS, et al. Systematic Review of the Volume-Outcome Relationship for Radical Prostatectomy. Eur Urol Focus. 2018;4(6):775-89.

115. Helsedirektoratet. Kreftkirurgi i Norge. 2015. Contract No.: IS-2284.

116. Bolla M, Van Tienhoven G, Warde P, Dubois JB, Mirimanoff RO, Storme G, et al. External irradiation with or without long-term androgen suppression for prostate cancer with high metastatic risk: 10-year results of an EORTC randomised study. Lancet Oncol. 2010;11(11):1066-73.

117. Telhaug R, Fossa SD, Ous S. Definitive radiotherapy of prostatic cancer: the Norwegian Radium Hospital's experience (1976-1982). Prostate. 1987;11(1):77-86.

118. Kuban DA, Levy LB, Cheung MR, Lee AK, Choi S, Frank S, et al. Long-term failure patterns and survival in a randomized dose-escalation trial for prostate cancer. Who dies of disease? Int J Radiat Oncol Biol Phys. 2011;79(5):1310-7.

119. Michalski JM, Moughan J, Purdy J, Bosch W, Bruner DW, Bahary JP, et al. Effect of Standard vs Dose-Escalated Radiation Therapy for Patients With Intermediate-Risk Prostate Cancer: The NRG Oncology RTOG 0126 Randomized Clinical Trial. JAMA Oncol. 2018;4(6):e180039.

120. Kalbasi A, Li J, Berman A, Swisher-McClure S, Smaldone M, Uzzo RG, et al. Dose-Escalated Irradiation and Overall Survival in Men With Nonmetastatic Prostate Cancer. JAMA Oncol. 2015;1(7):897-906.

121. Zietman AL, Bae K, Slater JD, Shipley WU, Efstathiou JA, Coen JJ, et al. Randomized trial comparing conventional-dose with high-dose conformal radiation therapy in early-stage adenocarcinoma of the prostate: long-term results from proton radiation oncology group/american college of radiology 95-09. J Clin Oncol. 2010;28(7):1106-11.

122. Helsedirektoratet. Nasjonalt handlingsprogram med retningslinjer for diagnostikk, behandling og oppfølging av prostatakreft. 2009. Report No.: IS-1777.

123. Jiang WZ, L; Wu, B; Zha, Z, Zhao, H; Feng, Y. Prognostic roles of extraprostatic extension in evaluating biochemical recurrence after radical prostatectomies: PRISMA-compliant systematic review and meta-analysis. Int J Clin Exp Med. 2019;12(5):4550-62.

124. McCormick BZ, Mahmoud AM, Williams SB, Davis JW. Biochemical recurrence after radical prostatectomy: Current status of its use as a treatment endpoint and early management strategies. Indian J Urol. 2019;35(1):6-17.

125. Karakiewicz PI, Eastham JA, Graefen M, Cagiannos I, Stricker PD, Klein E, et al. Prognostic impact of positive surgical margins in surgically treated prostate cancer: multi-institutional assessment of 5831 patients. Urology. 2005;66(6):1245-50.

126. Hackman G, Taari K, Tammela TL, Matikainen M, Kouri M, Joensuu T, et al. Randomised Trial of Adjuvant Radiotherapy Following Radical Prostatectomy Versus Radical Prostatectomy Alone in Prostate Cancer Patients with Positive Margins or Extracapsular Extension. Eur Urol. 2019;76(5):586-95.

127. Bolla M, van Poppel H, Tombal B, Vekemans K, Da Pozzo L, de Reijke TM, et al. Postoperative radiotherapy after radical prostatectomy for high-risk prostate cancer: long-term results of a randomised controlled trial (EORTC trial 22911). Lancet. 2012;380(9858):2018-27.

128. Vogel MME, Kessel KA, Schiller K, Devecka M, Gschwend JE, Weichert W, et al. Adjuvant versus early salvage radiotherapy: outcome of patients with prostate cancer treated with postoperative radiotherapy after radical prostatectomy. Radiat Oncol. 2019;14(1):198.

129. Fossati N, Karnes RJ, Boorjian SA, Moschini M, Morlacco A, Bossi A, et al. Long-term Impact of Adjuvant Versus Early Salvage Radiation Therapy in pT3N0 Prostate Cancer Patients Treated with Radical Prostatectomy: Results from a Multi-institutional Series. Eur Urol. 2017;71(6):886-93.

130. Abdollah F, Karnes RJ, Suardi N, Cozzarini C, Gandaglia G, Fossati N, et al. Impact of adjuvant radiotherapy on survival of patients with node-positive prostate cancer. J Clin Oncol. 2014;32(35):3939-47.

131. Sooriakumaran P, Nyberg T, Akre O, Haendler L, Heus I, Olsson M, et al. Comparative effectiveness of radical prostatectomy and radiotherapy in prostate cancer: observational study of mortality outcomes. BMJ. 2014;348:g1502.

132. Wallis CJD, Saskin R, Choo R, Herschorn S, Kodama RT, Satkunasivam R, et al. Surgery Versus Radiotherapy for Clinically-localized Prostate Cancer: A Systematic Review and Meta-analysis. Eur Urol. 2016;70(1):21-30.

133. Robinson D, Garmo H, Lissbrant IF, Widmark A, Pettersson A, Gunnlaugsson A, et al. Prostate Cancer Death After Radiotherapy or Radical Prostatectomy: A Nationwide Population-based Observational Study. Eur Urol. 2018;73(4):502-11.

134. Choo R, Klotz L, Danjoux C, Morton GC, DeBoer G, Szumacher E, et al. Feasibility study: watchful waiting for localized low to intermediate grade prostate carcinoma with selective delayed intervention based on prostate specific antigen, histological and/or clinical progression. J Urol. 2002;167(4):1664-9.

135. Lam TBL, MacLennan S, Willemse PM, Mason MD, Plass K, Shepherd R, et al. EAU-EANM-ESTRO-ESUR-SIOG Prostate Cancer Guideline Panel Consensus Statements for Deferred Treatment with Curative Intent for Localised Prostate Cancer from an International Collaborative Study (DETECTIVE Study). Eur Urol. 2019;76(6):790-813.

136. Klotz L. Active surveillance for low-risk prostate cancer. Curr Opin Urol. 2017;27(3):225-30.

137. Klotz L. Active surveillance in intermediate-risk prostate cancer. BJU Int. 2020;125(3):346-54.

138. Bokhorst LP, Valdagni R, Rannikko A, Kakehi Y, Pickles T, Bangma CH, et al. A Decade of Active Surveillance in the PRIAS Study: An Update and Evaluation of the Criteria Used to Recommend a Switch to Active Treatment. Eur Urol. 2016;70(6):954-60.

139. Soeterik TFW, van Melick HHE, Dijksman LM, Biesma DH, Witjes JA, van Basten JA. Active Surveillance for Prostate Cancer in a Real-life Cohort: Comparing Outcomes for PRIAS-eligible and PRIAS-ineligible Patients. 2018;1(3):231-7.

140. Musunuru HB, Yamamoto T, Klotz L, Ghanem G, Mamedov A, Sethukavalan P, et al. Active Surveillance for Intermediate Risk Prostate Cancer: Survival Outcomes in the Sunnybrook Experience. J Urol. 2016;196(6):1651-8.

141. Yamamoto T, Musunuru HB, Vesprini D, Zhang L, Ghanem G, Loblaw A, et al. Metastatic Prostate Cancer in Men Initially Treated with Active Surveillance. J Urol. 2016;195(5):1409-14.

142. Bellardita L, Valdagni R, van den Bergh R, Randsdorp H, Repetto C, Venderbos LD, et al. How does active surveillance for prostate cancer affect quality of life? A systematic review. Eur Urol. 2015;67(4):637-45.

143. Godtman RA, Holmberg E, Khatami A, Pihl CG, Stranne J, Hugosson J. Long-term Results of Active Surveillance in the Goteborg Randomized, Population-based Prostate Cancer Screening Trial. Eur Urol. 2016;70(5):760-6.

144. Huggins C, Hodges CV. Studies on prostatic cancer. I. The effect of castration, of estrogen and androgen injection on serum phosphatases in metastatic carcinoma of the prostate. CA Cancer J Clin. 1972;22(4):232-40.

145. Mason MD, Parulekar WR, Sydes MR, Brundage M, Kirkbride P, Gospodarowicz M, et al. Final Report of the Intergroup Randomized Study of Combined Androgen-Deprivation Therapy Plus Radiotherapy Versus Androgen-Deprivation Therapy Alone in Locally Advanced Prostate Cancer. J Clin Oncol. 2015;33(19):2143-50.

146. Fossa SD, Wiklund F, Klepp O, Angelsen A, Solberg A, Damber JE, et al. Ten- and 15-yr Prostate Cancer-specific Mortality in Patients with Nonmetastatic Locally Advanced or Aggressive Intermediate Prostate Cancer, Randomized to Lifelong Endocrine Treatment Alone or Combined with Radiotherapy: Final Results of The Scandinavian Prostate Cancer Group-7. Eur Urol. 2016;70(4):684-91.

147. Helsedirektoratet. Pakkeforløp for prostatakreft 2020 [23/06/20]. Available from: https://www.helsedirektoratet.no/statistikk/kvalitetsindikatorer/kreft-pakkeforlop/pakkeforløp-for-prostatakreft.

148. Nilssen Y, Brustugun OT, Eriksen MT, Haug ES, Naume B, Moller B. Patient and tumour characteristics associated with inclusion in Cancer patient pathways in Norway in 2015-2016. BMC Cancer. 2020;20(1):488.

149. Tilki D, Preisser F, Graefen M, Huland H, Pompe RS. External Validation of the European Association of Urology Biochemical Recurrence Risk Groups to Predict Metastasis and Mortality After Radical Prostatectomy in a European Cohort. Eur Urol. 2019;75(6):896-900.

150. Van den Broeck T, van den Bergh RCN, Arfi N, Gross T, Moris L, Briers E, et al. Prognostic Value of Biochemical Recurrence Following Treatment with Curative Intent for Prostate Cancer: A Systematic Review. Eur Urol. 2019;75(6):967-87.

151. Fossati N, Karnes RJ, Cozzarini C, Fiorino C, Gandaglia G, Joniau S, et al. Assessing the Optimal Timing for Early Salvage Radiation Therapy in Patients with Prostate-specific Antigen Rise After Radical Prostatectomy. Eur Urol. 2016;69(4):728-33.

152. Preisser F, Chun FKH, Pompe RS, Heinze A, Salomon G, Graefen M, et al. Persistent Prostate-Specific Antigen After Radical Prostatectomy and Its Impact on Oncologic Outcomes. Eur Urol. 2019.

153. Shipley WU, Seiferheld W, Lukka HR, Major PP, Heney NM, Grignon DJ, et al. Radiation with or without Antiandrogen Therapy in Recurrent Prostate Cancer. N Engl J Med. 2017;376(5):417-28.

154. Patel VR, Sivaraman A, Coelho RF, Chauhan S, Palmer KJ, Orvieto MA, et al. Pentafecta: a new concept for reporting outcomes of robot-assisted laparoscopic radical prostatectomy. Eur Urol. 2011;59(5):702-7.

155. Avila M, Patel L, Lopez S, Cortes-Sanabria L, Garin O, Pont A, et al. Patient-reported outcomes after treatment for clinically localized prostate cancer: A systematic review and meta-analysis. Cancer Treat Rev. 2018;66:23-44.

156. Mandel P, Graefen M, Michl U, Huland H, Tilki D. The effect of age on functional outcomes after radical prostatectomy. Urol Oncol. 2015;33(5):203 e11-8.

157. Mandel P, Chandrasekar T, Chun FK, Huland H, Tilki D. Radical prostatectomy in patients aged 75 years or older: review of the literature. Asian J Androl. 2017.

158. Payne HA, Hughes S. Radical radiotherapy for high-risk prostate cancer in older men. Oncologist. 2012;17 Suppl 1:9-15.

159. Hampson LA, Cowan JE, Zhao S, Carroll PR, Cooperberg MR. Impact of age on quality-of-life outcomes after treatment for localized prostate cancer. Eur Urol. 2015;68(3):480-6.

160. Storas AH, Sanda MG, Ferrer M, Loge JH, Dahl AA, Steinsvik EA, et al. Localized prostate cancer in Norway, the United States, and Spain: between-country differences of variables before treatment among patients eligible for curative treatment. Clin Genitourin Cancer. 2014;12(4):e117-25.

161. Hamilton AS, Stanford JL, Gilliland FD, Albertsen PC, Stephenson RA, Hoffman RM, et al. Health outcomes after external-beam radiation therapy for clinically localized prostate cancer: results from the Prostate Cancer Outcomes Study. J Clin Oncol. 2001;19(9):2517-26.

162. Kvale R, Myklebust TA, Fossa SD, Aas K, Ekanger C, Helle SI, et al. Impact of positive surgical margins on secondary treatment, palliative radiotherapy and prostate cancer-specific mortality. A population-based study of 13 198 patients. Prostate. 2019;79(16):1852-60.

163. Stephenson AJ, Eggener SE, Hernandez AV, Klein EA, Kattan MW, Wood DP, Jr., et al. Do margins matter? The influence of positive surgical margins on prostate cancer-specific mortality. Eur Urol. 2014;65(4):675-80.

164. Mithal P, Howard LE, Aronson WJ, Terris MK, Cooperberg MR, Kane CJ, et al. Positive surgical margins in radical prostatectomy patients do not predict long-term oncological outcomes: results from the Shared Equal Access Regional Cancer Hospital (SEARCH) cohort. BJU Int. 2016;117(2):244-8.

165. Boorjian SA, Karnes RJ, Crispen PL, Carlson RE, Rangel LJ, Bergstralh EJ, et al. The impact of positive surgical margins on mortality following radical prostatectomy during the prostate specific antigen era. J Urol. 2010;183(3):1003-9.

166. Preisser F, Mazzone E, Knipper S, Nazzani S, Bandini M, Shariat SF, et al. Rates of Positive Surgical Margins and Their Effect on Cancer-specific Mortality at Radical Prostatectomy for Patients With Clinically Localized Prostate Cancer. Clin Genitourin Cancer. 2019;17(1):e130-e9.

167. Wright JL, Dalkin BL, True LD, Ellis WJ, Stanford JL, Lange PH, et al. Positive surgical margins at radical prostatectomy predict prostate cancer specific mortality. J Urol. 2010;183(6):2213-8.

168. Preston MA, Breau RH, Lantz AG, Morash C, Gerridzen RG, Doucette S, et al. The association between nerve sparing and a positive surgical margin during radical prostatectomy. Urol Oncol. 2015;33(1):18 e1- e6.

169. Abern MR, Aronson WJ, Terris MK, Kane CJ, Presti JC, Jr., Amling CL, et al. Delayed radical prostatectomy for intermediate-risk prostate cancer is associated with biochemical recurrence: possible implications for active surveillance from the SEARCH database. Prostate. 2013;73(4):409-17.

170. Waehre H, Vlatkovic L, Cvancarova M, Paus E, Fossa SD, Danielsen HE. Fifteen-year mortality after radical prostatectomy: which factors are available for patient counselling? Scand J Urol. 2014;48(2):123-30.

171. Bechis SK, Carroll PR, Cooperberg MR. Impact of age at diagnosis on prostate cancer treatment and survival. J Clin Oncol. 2011;29(2):235-41.

172. Gandaglia G, Karakiewicz PI, Abdollah F, Becker A, Roghmann F, Sammon JD, et al. The effect of age at diagnosis on prostate cancer mortality: a grade-for-grade and stage-for-stage analysis. Eur J Surg Oncol. 2014;40(12):1706-15.

173. Sun L, Caire AA, Robertson CN, George DJ, Polascik TJ, Maloney KE, et al. Men older than 70 years have higher risk prostate cancer and poorer survival in the early and late prostate specific antigen eras. J Urol. 2009;182(5):2242-8.

174. Hamstra DA, Bae K, Pilepich MV, Hanks GE, Grignon DJ, McGowan DG, et al. Older age predicts decreased metastasis and prostate cancer-specific death for men treated with radiation therapy: meta-analysis of radiation therapy oncology group trials. Int J Radiat Oncol Biol Phys. 2011;81(5):1293-301.

175. Vernooij RWM, van Oort I, de Reijke TM, Aben KKH. Nationwide treatment patterns and survival of older patients with prostate cancer. J Geriatr Oncol. 2019;10(2):252-8.

176. Nasjonalt servicemiljø for medisinske kvalitetsregistre. Om medisinske kvalitetsregistre. Online [Available from: https://www.kvalitetsregistre.no/om-medisinske-kvalitetsregistre-0.

177. Asli LM, Kvaloy SO, Jetne V, Myklebust TA, Levernes SG, Tveit KM, et al. Utilization of radiation therapy in Norway after the implementation of the national cancer plan--a national, population-based study. Int J Radiat Oncol Biol Phys. 2014;90(3):707-14.

178. Aalen O. Nonparametric estimation of partial transition probabilities in multiple decrement models. Annals of Statistics. 1978;6(3):534-45.

179. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. Journal of the American Statistical Association. 1958;53(282):457-81.

180. Bray F, Parkin DM. Evaluation of data quality in the cancer registry: principles and methods. Part I: comparability, validity and timeliness. Eur J Cancer. 2009;45(5):747-55.

181. Parkin DM, Bray F. Evaluation of data quality in the cancer registry: principles and methods Part II. Completeness. Eur J Cancer. 2009;45(5):756-64.

182. Bakken IJ, Gystad SO, Christensen OO, Huse UE, Laronningen S, Nygard J, et al. Comparison of data from the Norwegian Patient Register and the Cancer Registry of Norway. Tidsskr Nor Laegeforen. 2012;132(11):1336-40.

183. Helsedirektoratet. Nasjonal tjeneste for validering og dekningsgradsanalyser Årsrapport 2018. 2018.

184. Larsen IK, Smastuen M, Johannesen TB, Langmark F, Parkin DM, Bray F, et al. Data quality at the Cancer Registry of Norway: an overview of comparability, completeness, validity and timeliness. Eur J Cancer. 2009;45(7):1218-31.

185. Pedersen AG, Ellingsen CL. Data quality in the Causes of Death Registry. Tidsskr Nor Laegeforen. 2015;135(8):768-70.

186. Mahapatra P, Shibuya K, Lopez AD, Coullare F, Notzon FC, Rao C, et al. Civil registration systems and vital statistics: successes and missed opportunities. Lancet. 2007;370(9599):1653-63.

187. Mathers CD, Fat DM, Inoue M, Rao C, Lopez AD. Counting the dead and what they died from: an assessment of the global status of cause of death data. Bull World Health Organ. 2005;83(3):171-7.

188. Phillips DE, Lozano R, Naghavi M, Atkinson C, Gonzalez-Medina D, Mikkelsen L, et al. A composite metric for assessing data on mortality and causes of death: the vital statistics performance index. Popul Health Metr. 2014;12:14.

189. Loffeler S, Halland A, Weedon-Fekjaer H, Nikitenko A, Ellingsen CL, Haug ES. High Norwegian prostate cancer mortality: evidence of over-reporting. Scand J Urol. 2018;52(2):122-8.

190. Feuer EJ, Merrill RM, Hankey BF. Cancer surveillance series: interpreting trends in prostate cancer--part II: Cause of death misclassification and the recent rise and fall in prostate cancer mortality. J Natl Cancer Inst. 1999;91(12):1025-32.

191. Albertsen PC, Walters S, Hanley JA. A comparison of cause of death determination in men previously diagnosed with prostate cancer who died in 1985 or 1995. J Urol. 2000;163(2):519-23.

192. Skyrud KD, Bray F, Moller B. A comparison of relative and cause-specific survival by cancer site, age and time since diagnosis. Int J Cancer. 2014;135(1):196-203.

193. Fall K, Stromberg F, Rosell J, Andren O, Varenhorst E, South-East Region Prostate Cancer G. Reliability of death certificates in prostate cancer patients. Scand J Urol Nephrol. 2008;42(4):352-7.

194. Godtman R, Holmberg E, Stranne J, Hugosson J. High accuracy of Swedish death certificates in men participating in screening for prostate cancer: a comparative study of official death certificates with a cause of death committee using a standardized algorithm. Scand J Urol Nephrol. 2011;45(4):226-32.

195. Makinen T, Karhunen P, Aro J, Lahtela J, Maattanen L, Auvinen A. Assessment of causes of death in a prostate cancer screening trial. Int J Cancer. 2008;122(2):413-7.

196. Turner EL, Metcalfe C, Donovan JL, Noble S, Sterne JA, Lane JA, et al. Contemporary accuracy of death certificates for coding prostate cancer as a cause of death: Is reliance on death certification good enough? A comparison with blinded review by an independent cause of death evaluation committee. Br J Cancer. 2016;115(1):90-4.

197. Penson DF, Albertsen PC, Nelson PS, Barry M, Stanford JL. Determining cause of death in prostate cancer: are death certificates valid? J Natl Cancer Inst. 2001;93(23):1822-3.

198. Albertsen PC, Hanley JA, Barrows GH, Penson DF, Kowalczyk PD, Sanders MM, et al. Prostate cancer and the Will Rogers phenomenon. J Natl Cancer Inst. 2005;97(17):1248-53.

199. Vatne K, Stensvold A, Myklebust TA, Moller B, Svindland A, Kvale R, et al. Pre- and post-prostatectomy variables associated with pelvic post-operative radiotherapy in prostate cancer patients: a national registry-based study. Acta Oncol. 2017:1-7.

200. Tomic K, Ventimiglia E, Robinson D, Haggstrom C, Lambe M, Stattin P. Socioeconomic status and diagnosis, treatment, and mortality in men with prostate cancer. Nationwide population-based study. Int J Cancer. 2018;142(12):2478-84.

201. Tan KS, Eguchi T, Adusumilli PS. Competing risks and cancer-specific mortality: why it matters. Oncotarget. 2018;9(7):7272-3.

202. de Glas NA, Kiderlen M, Vandenbroucke JP, de Craen AJ, Portielje JE, van de Velde CJ, et al. Performing Survival Analyses in the Presence of Competing Risks: A Clinical Example in Older Breast Cancer Patients. J Natl Cancer Inst. 2016;108(5).

203. Putter H, Fiocco M, Geskus RB. Tutorial in biostatistics: competing risks and multi-state models. Stat Med. 2007;26(11):2389-430.

204. Rothman KJ. Epidemiology: An introduction. 2nd ed: New York, USA: Oxford University Press; 2012.

205. Holmstrom B, Holmberg E, Egevad L, Adolfsson J, Johansson JE, Hugosson J, et al. Outcome of primary versus deferred radical prostatectomy in the National Prostate Cancer Register of Sweden Follow-Up Study. J Urol. 2010;184(4):1322-7.

206. van den Bergh RC, Albertsen PC, Bangma CH, Freedland SJ, Graefen M, Vickers A, et al. Timing of curative treatment for prostate cancer: a systematic review. Eur Urol. 2013;64(2):204-15.

207. Redaniel MT, Martin RM, Gillatt D, Wade J, Jeffreys M. Time from diagnosis to surgery and prostate cancer survival: a retrospective cohort study. BMC Cancer. 2013;13:559.

208. Graefen M, Walz J, Chun KH, Schlomm T, Haese A, Huland H. Reasonable delay of surgical treatment in men with localized prostate cancer--impact on prognosis? Eur Urol. 2005;47(6):756-60.

209. Sun M, Abdollah F, Hansen J, Trinh QD, Bianchi M, Tian Z, et al. Is a treatment delay in radical prostatectomy safe in individuals with low-risk prostate cancer? J Sex Med. 2012;9(11):2961-9.

210. van den Bergh RC, Steyerberg EW, Khatami A, Aus G, Pihl CG, Wolters T, et al. Is delayed radical prostatectomy in men with low-risk screen-detected prostate cancer associated with a higher risk of unfavorable outcomes? Cancer. 2010;116(5):1281-90.

211. Korets R, Seager CM, Pitman MS, Hruby GW, Benson MC, McKiernan JM. Effect of delaying surgery on radical prostatectomy outcomes: a contemporary analysis. BJU Int. 2012;110(2):211-6.

212. Patel P, Sun R, Shiff B, Trpkov K, Gotto GT. The effect of time from biopsy to radical prostatectomy on adverse pathologic outcomes. Res Rep Urol. 2019;11:53-60.

213. Zanaty M, Alnazari M, Lawson K, Azizi M, Rajih E, Alenizi A, et al. Does surgical delay for radical prostatectomy affect patient pathological outcome? A retrospective analysis from a Canadian cohort. Can Urol Assoc J. 2017;11(8):265-9.

214. Berg WT, Danzig MR, Pak JS, Korets R, RoyChoudhury A, Hruby G, et al. Delay from biopsy to radical prostatectomy influences the rate of adverse pathologic outcomes. Prostate. 2015;75(10):1085-91.

215. Zanaty M, Alnazari M, Ajib K, Lawson K, Azizi M, Rajih E, et al. Does surgical delay for radical prostatectomy affect biochemical recurrence? A retrospective analysis from a Canadian cohort. World J Urol. 2018;36(1):1-6.

216. Nilssen Y, Brustugun OT, Tandberg Eriksen M, Gulbrandsen J, Skaaheim Haug E, Naume B, et al. Decreasing waiting time for treatment before and during implementation of cancer patient pathways in Norway. Cancer Epidemiol. 2019;61:59-69.

217. Brassell SA, Rice KR, Parker PM, Chen Y, Farrell JS, Cullen J, et al. Prostate cancer in men 70 years old or older, indolent or aggressive: clinicopathological analysis and outcomes. J Urol. 2011;185(1):132-7.

218. Vatne K, Stensvold A, Myklebust TA, Moller B, Svindland A, Kvale R, et al. Pre- and post-prostatectomy variables associated with pelvic post-operative radiotherapy in prostate cancer patients: a national registry-based study. Acta Oncol. 2017;56(10):1295-301.

219. Watts EL, Appleby PN, Perez-Cornago A, Bueno-de-Mesquita HB, Chan JM, Chen C, et al. Low Free Testosterone and Prostate Cancer Risk: A Collaborative Analysis of 20 Prospective Studies. Eur Urol. 2018;74(5):585-94.

I

ERRATA PAPER I

Introduction:

Reference seven (page 2, line 15) should be replaced by;

Bill-Axelson A, Holmberg L, Ruutu M, Haggman M, Andersson SO, Bratell S, et al. Radical prostatectomy versus watchful waiting in early prostate cancer. N Engl J Med. 2005;352(19):1977-84.

Material and methods:

Patients with PSA ≤100 ng/ml were included in the study (unlike PSA <100 ng/ml).

Treatment performed abroad was not recorded (unlike patients who were treated outside Norway were excluded).

Ten-year Mortality in Men With Nonmetastatic Prostate Cancer in Norway

Kirsti Aas, Karol Axcrona, Rune Kvåle, Bjørn Møller, Tor Åge Myklebust, Ulrika Axcrona, Viktor Berge, and Sophie Dorothea Fosså

OBJECTIVE To provide population-based data on 10-year prostate cancer-specific mortality (PCSM), overall mortality (OM), treatment, and prognostic factors in patients with nonmetastatic prostate cancer (PCa).

MATERIALS AND METHODS Based on data from the Norwegian Prostate Cancer Registry, we calculated 10-year PCSM and OM in 3449 patients diagnosed with nonmetastatic PCa in 2004-2005 who underwent radical prostatectomy (n = 913), radiotherapy (n = 1334), or no local treatment (n = 1202). Patients were stratified according to risk group, Gleason grade group (GGG), and Eastern Cooperative Oncology Group (ECOG) performance status. Aalen-Johansen and Kaplan-Meier estimates and proportional hazards regressions were used.

RESULTS The 10-year PCSM rate was 8.5% (radical prostatectomy: 1.5, radiotherapy: 6.2%, no local treatment: 16.3%) and the OM rate was 25.5%. In the low-risk group, the risk of dying from other causes was 8-fold increased compared with death from PCa, the comparable factor being approximately 2 among high-risk patients. Patients with high-risk factors seemed to benefit the most from local treatment. Within each risk group, the 5 GGGs improved the prediction of PCSM. Having an ECOG performance status of ≥1 doubled the risk of PCSM compared with patients with an ECOG performance status of 0.

CONCLUSION For all patients, the 10-year OM was about 3 times higher than PCSM, the greatest and lowest discrepancies emerging among patients with low- and high-risk tumors, respectively. The results support increased use of local treatment in high-risk patients. GGGs should be implemented in clinical practice. The role of ECOG performance status as prognostic factor has to be validated in future studies. UROLOGY 110: 140–147, 2017. © 2017 Elsevier Inc.

Norway is among the countries with the highest incidence of prostate cancer (PCa) in Europe.[1] In 2015, 90% of the patients presented with nonmetastatic PCa.[2] These men may be candidates for curative treatment, including radical prostatectomy (RP) and high-dose radiotherapy (RAD) with or without hormonal treatment (HT), in some cases preceded by a period of active surveillance (AS).[3]

To aid the prediction of prostate cancer-specific mortality (PCSM) and to guide therapeutic decisions, patients with nonmetastatic disease are stratified into low-, intermediate-, and high-risk groups based on the clinical T-category (cT category), the PSA level, and the Gleason score (GS) at the time of diagnosis.[3] However, the cancer cases within each of these risk groups are heterogeneous. Particularly, the intermediate- and high-risk groups allow varying combinations of the cT-category, the PSA level, and the GS, each combination possibly having its own prognostic significance. An important conclusion of an international conference held by the International Society of Urological Pathology (ISUP) was therefore to separate GS 7a (Gleason grade 3 + 4) from GS 7b (Gleason grade 4 + 3).[4] Mainly based on the histopathology of prostatectomy specimens, the ISUP introduced in 2014 Gleason grade grouping: Gleason grade group (GGG)1: GS ≤6, GGG2: GS 7a (3 + 4), GGG3: GS 7b (4 + 3), GGG4: GS 8 (4 + 4, 3 + 5, 5 + 3), and GGG5: GS 9 or 10 (4 + 5, 5 + 4, 5 + 5).[4,5] In several studies, this new 5-tiered classification has shown prognostic significance even beyond the older 3-tiered

Financial Disclosure: *The authors declare that they have no relevant financial interests.*
Funding Support: *This study was supported by the Norwegian Cancer Society (fund no. 5781243) and the Radium Hospital Foundation (project no. 335007).*

From the Department of Surgery, Vestre Viken Hospital Trust, Bærum Hospital, Drammen, Norway; the Department of Surgery, Akershus University Hospital, Lørenskog, Norway; the Department of Oncology, Haukeland University Hospital, Bergen, Norway; The Cancer Registry of Norway, Norway; the Department of Pathology, The Norwegian Radium Hospital/Oslo University Hospital, Oslo, Norway; the Department of Surgery, Oslo University Hospital, Oslo, Norway; the Department of Oncology, The Norwegian Radium Hospital/Oslo University Hospital, Oslo, Norway; and the Faculty of Medicine, University of Oslo, Norway

Address correspondence to: Kirsti Aas, M.D., Department of Surgery, Vestre Viken Hospital Trust, Bærum Hospital, Drammen 3004, Norway. E-mail: kirstiaas@hotmail.com

Submitted: May 9, 2017, accepted (with revisions): July 25, 2017

© 2017 Elsevier Inc.
All rights reserved.
https://doi.org/10.1016/j.urology.2017.07.048
0090-4295

risk grouping (6-8). However, more studies are needed to document its prognostic significance if used in addition to clinical parameters (age and comorbidity) and traditional risk grouping, in particular, if the Gleason grade grouping is performed in biopsies.

The impact of comorbidity on overall mortality (OM) is obvious, but its association with PCSM is less clear, in part because this clinical variable most often is not reported in public registries. The ECOG performance status, assessing an individual's functional status, is widely used in oncology and may serve as a surrogate for comorbidity. In Fosså et al's analysis of a population-based cohort of patients with nonmetastatic PCa, ECOG was an independent prognostic covariate of 5-year PCSM.[6] However, as also shown in other studies,[7,8] the need for a longer follow-up was expressed in an accompanying comment.

The current observational study therefore provides 10-year PCSM and OM of the previously reported population-based cohort of patients with nonmetastatic PCa stratified for treatment modalities, risk groups, and performance status, with emphasis on PCSM.[6] A further aim was to document the prognostic significance of Gleason grade grouping if used in addition to traditional risk groups.

MATERIALS AND METHODS

Data Sources

The Cancer Registry of Norway with its RAD data and the Norwegian Prostate Cancer Registry (NoPCR) provided updated information (per June 30, 2015) for the previously described population-based cohort of patients who were viewed as candidates for the curative treatment of PCa diagnosed in Norway in 2004-2005.[6] Due to the dynamic character of these registries, changes in previously recorded treatments may occur. The individual case record form contains information on the cT-category, the PSA level, the primary and secondary Gleason grades, and the ECOG performance status at the time of diagnosis. In 2004-2005, no data on systemic therapy, such as HT, or information enabling a valid separation of AS from watchful waiting (WW) were collected. The study was approved by the Regional Committee for Medical and Health Research Ethics.

Patients

Candidates for curative treatment as their primary therapy were characterized by age ≤75, cT-category of <4, PSA level of <100 ng/mL, ECOG performance status of <4, and no record of major comorbidity in the free-text comment field of the NoPCR case record form. In this report, patients were not eligible for inclusion if information was lacking on the cT-category, the PSA level, or the GS. Patients who were treated outside Norway or those whose diagnosis was based on autopsy or cystoprostatectomy specimens were excluded.

Data Management

According to the risk stratification model of the contemporary European Association of Urology (EAU) Guidelines 2016 patients were categorized as belonging to the low-, intermediate-, or high-risk groups.[3]

- Low-risk: cT1-T2a and PSA <10 ng/mL and GS <7
- Intermediate-risk: all others
- High-risk localized: cT2c or PSA >20 ng/mL or GS >7
- High-risk locally advanced: cT3

For 615 patients, data from the NoPCR could not identify the subgroups within the cT2-category. In the present study, a patient recorded with a cT2x cancer was therefore allocated to the localized high-risk group if he had a GS of >7 or a PSA level of >20 ng/mL, and tumors with a GS of <7 and PSA level of <10 ng/mL were included in the low-risk group. All other cT2x tumors were included in the intermediate-risk group. Data on GS from the NoPCR enabled classification of patients into GGGs 1-5. Patients with GS 5 (n = 231) were included in GGG1. No patients had a GS of <5. The separation between GS 7a and 7b, along with the omitted use of GS 2-4, was implemented into clinical practice in Norway in 2004-2005. Norwegian pathologists from the main hospitals regularly attended international conferences, including the 2005 ISUP conference,[9] and gradually implemented clinical modifications in line with international practice.

Three principal types of treatment were recorded: RP, RAD, or no local treatment (NoLocTrt). Patients included in the RP group had to be treated with RP within 12 months of diagnosis. In the RAD group, RAD had been started within 18 months of diagnosis with the background of a 6-month period of neoadjuvant HT in the majority of patients, often preceded by a diagnostic obturatory lymphadenectomy. Patients in the RAD group underwent pelvic radiation with a target dose of ≥70 Gy, applied as daily fractions of 2 Gy with 5 fractions per week (24%: 76 or 78 Gy; 38%: 72 or 74 Gy; 38%: 70 Gy). Following Bolla et al, RAD was in more than 95% of the patients combined with (neo-) adjuvant HT lasting for 3 years.[10] The NoLocTrt group included unidentifiable patients with AS, WW, or primary HT, without exact quantification of the number of patients within the therapeutic subcategories.

Statistical Methods

Standard descriptive methods were applied. The Aalen-Johansen estimator was used to calculate 10-year PCSM rates, treating death from other causes as a competing risk.[11] Treatment was included as a time-varying covariate where it was applicable. A standard likelihood ratio test was used to assess the importance of each variable in the multivariate analyses. Kaplan-Meier estimates were used to calculate the OM rates.[7] The observation times ranged from the date of diagnosis to the date of death, emigration, or end of the study (June 30, 2015), whatever occurred first. Flexible parametric models with 5 degrees of freedom were used to estimate hazard ratios (HRs), for both univariate and multivariate analyses. The proportional hazards assumption was not validated. The same models were used for predicting actual probabilities of PCa-specific death but, for this purpose, incorporating death from other causes as competing risks. A P value of <0.05 was considered statistically significant. Data were analyzed using the IBM Statistical Package for the Social Sciences (SPSS) Statistics version 23 and Stata version 14.2.

RESULTS

Of the previously described 3486 men, 3449 patients remained eligible for the present study. Out of these patients, 913 (26%) underwent RP, 1334 (39%) underwent RAD, and 1202 (35%) received NoLocTrt (Supplementary

Table 1. 10-Year PCa-specific and overall mortality

Treatment	RP (n = 913)	RAD (n = 1334)	NoLocTrt (n = 1202)	Total (N = 3449)
Dead*	90 (10)	282 (21)	551 (46)	923 (27)
PCa	15 (2)	83 (6)	198 (17)	296 (9)
Other causes	75 (8)	199 (15)	353 (29)	627 (18)
PCa deaths or all deaths				
All risk groups	15/90 (17†)	83/282 (29)	198/551 (36)	296/923 (32)
Low risk	1/24 (4)	2/26 (8)	12/83 (15)	15/133 (11)
Intermediate risk	7/44 (16)	12/70 (17)	29/122 (24)	48/236 (20)
High risk localized	5/19 (26)	23/61 (38)	57/131 (44)	85/211 (40)
High risk locally advanced	2/3 (67)	46/125 (37)	100/215 (47)	148/343 (43)
PCa-specific mortality				
All risk groups	1.5 (0.9-2.5)‡	6.2 (5.0-7.6)	16.3 (14.2-18.4)	8.5 (7.6-9.4)
Low risk	0.3 (0-1.4)	1.2 (0.2-3.9)	3.4 (1.9-5.7)	1.7 (1.0-2.7)
Intermediate risk	1.5 (0.6-3.1)	3.3 (1.8-5.5)	10.3 (7.1-14.2)	4.5 (3.4-5.9)
High risk localized	4.9 (1.8-10.2)	7.6 (4.9-11.1)	24.0 (18.6-29.7)	13.1 (10.6-15.9)
High risk locally advanced	6.5 (1.1-18.6)	9.2 (6.8-12.0)	30.7 (25.7-35.9)	17.3 (14.8-19.9)
Overall mortality				
All risk groups	9.3 (7.6-11.4)	20.5 (18.4-22.8)	42.4 (39.6-45.3)	25.5 (24.1-27.0)
Low risk	6.2 (4.2-9.2)	15.2 (10.5-21.7)	21.6 (17.7-26.3)	14.1 (12.0-16.6)
Intermediate risk	10.0 (7.4-13.5)	17.8 (14.2-22.1)	38.9 (33.5-45.0)	20.9 (18.5-23.5)
High risk localized	17.8 (11.6-26.8)	20.1 (15.9-25.2)	52.5 (46.1-59.3)	32.0 (28.5-35.8)
High risk locally advanced	9.7 (3.2-27.1)	24.5 (20.9-28.6)	62.6 (57.2-68.0)	38.7 (35.5-42.1)

NoLocTrt, no local treatment; PCa, prostate cancer; RAD, radiotherapy; RP, radical prostatectomy.
* n (%).
† % dead due to PCa.
‡ Mortality rate % (95% confidence interval).

Table S1). Only 15% of the patients in the RP group had a high-risk disease compared with 59% in the RAD group and 46% in the NoLocTrt group, and the median age at diagnosis in this group was significantly lower compared with the other 2 groups (RP 62, RAD 66, and NoLocTrt 69). The proportion of patients with an ECOG score of 0 was highest in the RP group (93%) and lowest in the NoLocTrt group (72%). Only 15 patients, all in the NoLocTrt group, presented with an ECOG 3 performance status.

After a median observation period of 10 years (range 0-11), the PCSM of all patients was 8.5%, the comparable percentage for OM being 25.5% (Table 1). As expected, the PCSM and the OM rates increased with the increasing risk group allocation. In the NoLocTrt group, PCSM was at least 3-fold and OM was around 2-fold higher than the rates in the groups receiving local treatment. Among the deceased patients in the low-risk group, the risk of dying from other causes was increased by a factor of 8 as compared with death from PCa, the comparable factor being approximately 2 among high-risk patients. Admittedly, based on relatively small numbers in the low-risk group, patients with high-risk tumors seemed to benefit the most from local treatment, not separating RP from RAD.

For all patients, Figure 1 depicts the 10-year PCSM stratified for clinical parameters. In the univariate analysis, all clinical parameters apart from ages 61-65 compared with age ≤60 emerged as significant risk factors (Supplementary Table S2).

On multivariate analysis including all patients, the HR of 10-year PCSM was 1.7 in irradiated men compared to those undergoing RP (Table 2). The comparable risk was more than 6-fold in patients without local treatment. With the low-risk group as the reference, the increasing risk group was associated with significantly increasing numerical HRs. Age was not significantly associated with the risk of PCSM, with the lowest risk for men aged 61-65 years. When excluding ECOG from the multivariate analysis to eliminate an interaction effect of age and performance status, age estimates remained unchanged. Both the cT-category and the GGG were significantly correlated with PCSM with an almost doubling of HR for patients with GGG2 vs GGG3 and GGG4 vs GGG5. HRs were similar in all PSA categories; that is, PSA was not an independent factor. Presenting with an ECOG status of ≥1 resulted in a significant increase in the risk of PCa death by almost 50% compared with ECOG 0.

Principally similar risk estimations emerged when the multivariate analysis was restricted to prostatectomized and irradiated patients (Table 2). RAD, risk group, GGG, and ECOG status were significantly associated with an increased risk of PCSM. The highest HRs were observed for GGG4 (HR: 9.0) and GGG5 (HR: 19.7), respectively. Furthermore, the risk of PCSM doubled significantly for patients with an ECOG status of ≥1 compared with patients with an ECOG status of 0.

In Table 3, the predicted probabilities of PCa-specific death in the local treatment groups are shown utilizing risk group allocation combined with significant factors from Table 2. In both treatment groups, all percentages increased with increasing risk and grade group. Within each

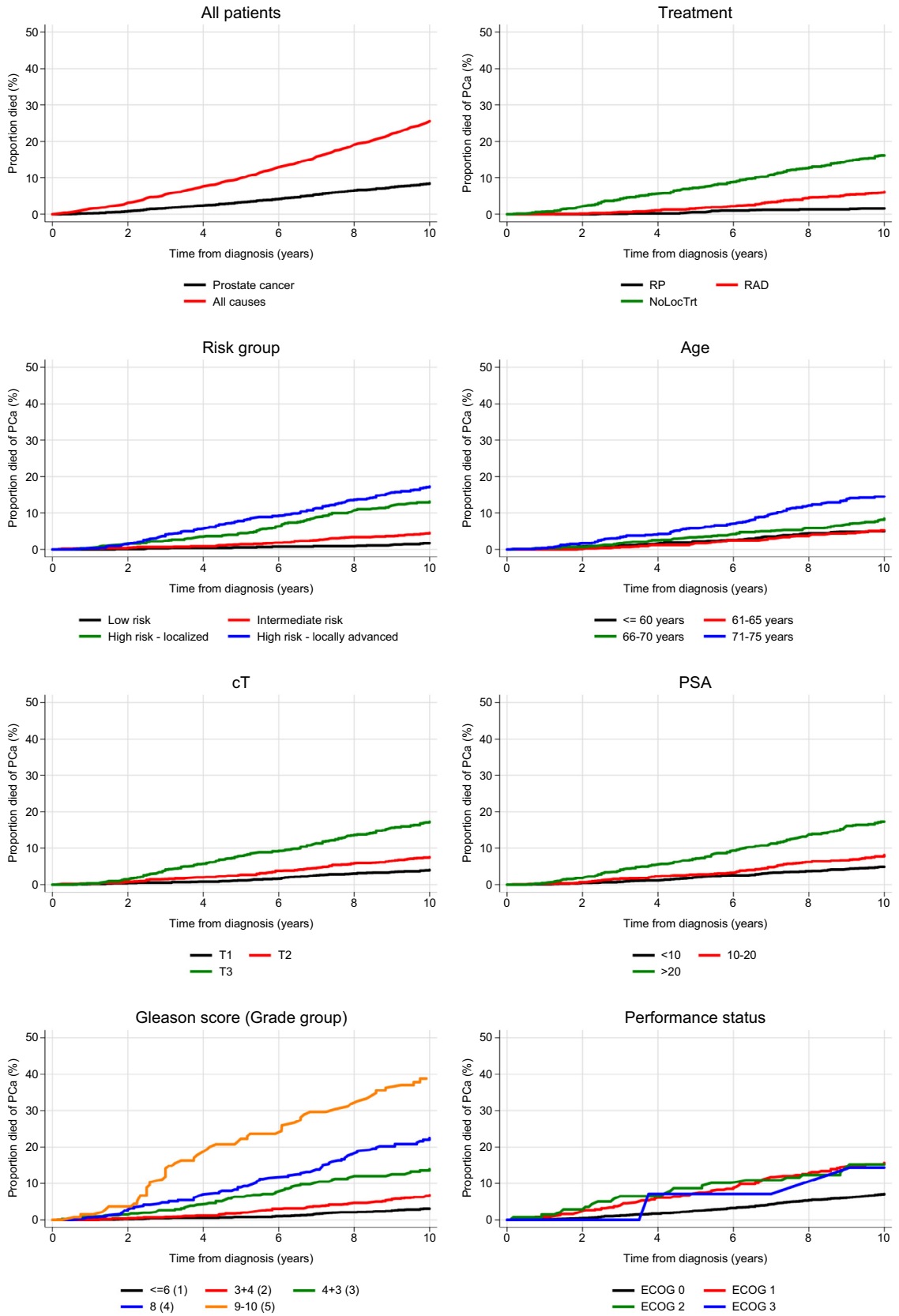


Figure 1. Ten-year overall (top left) and prostate cancer-specific mortality for patients with nonmetastatic prostate cancer according to initial treatment, risk group, age, cT-category, PSA, Gleason score (grade group), and ECOG performance status. cT-category, clinical T-category; ECOG, Eastern Cooperative Oncology Group; NoLocTrt, no local treatment; PCa, prostate cancer; PSA, prostate-specific antigen; RAD, high-dose radiotherapy with or without adjuvant hormonal therapy; RP, radical prostatectomy. (Color version available online.)

Table 2. Multivariate analysis of 10-year PCa-specific mortality

	All Treatment Groups HR (95% CI)	*P* Value	Local Treatment Groups HR (95% CI)	*P* Value
Treatment RP	1		1	
RAD	1.7 (0.95-2.99)		2.0 (1.03-3.69)	
NoLocTrt	6.4 (3.66-11.35)	<.001		.034
Risk group* Low	1		1	
Intermediate	3.5 (1.95-6.28)		4.0 (1.17-13.54)	
High localized	9.5 (5.42-16.50)		10.3 (3.06-34.92)	
High locally advanced	12.4 (7.23-21.37)	<.001	12.9 (3.84-43.31)	<.001
Age (y) ≤ 60	1		1	
61-65	0.9 (0.59-1.34)		0.7 (0.40-1.21)	
66-70	1.0 (0.70-1.49)	0.398	0.8 (0.44-1.29)	0.600
≥71	1.2 (0.81-1.72)		0.8 (0.40-1.40)	
cT-category T1	1		1	
T2	1.6 (1.15-2.28)		1.4 (0.77-2.44)	
T3	2.0 (1.41-2.76)	<.001	1.9 (1.10-3.41)	.057
PSA (ng/mL) <10	1		1	
10-20	1.1 (0.82-1.52)		0.8 (0.49-1.24)	
>20	1.2 (0.91-1.69)	0.399	0.9 (0.49-1.46)	0.574
GS (GGG) ≤6 (1)	1		1	
3 + 4 (2)	2.2 (1.45-3.17)		3.4 (1.66-6.93)	
4 + 3 (3)	4.3 (2.87-6.41)		5.6 (2.57-11.98)	
8 (4)	6.1 (4.12-9.00)		9.0 (4.23-19.03)	
9-10 (5)	11.6 (7.57-17.69)	<.001	19.7 (8.62-44.91)	<.001
ECOG 0	1		1	
≥1	1.4 (1.12-1.86)	.006	2.0 (1.23-3.20)	.008

CI, confidence interval; cT-category, clinical T-category; ECOG, Eastern Cooperative Oncology Group; GGG, Gleason grade group; GS, Gleason score; HR, hazard ratio.

* Due to high correlation, the effect estimate of the risk group is obtained from a model where the cT-category, the PSA, and the GS are excluded. Equivalently, the effect estimates on the cT-category, the PSA, and the GS are estimated excluding the risk group from the model.

Table 3. 10-Year probability of PCa-specific death in patients treated with radical prostatectomy (%) and radiotherapy (%)

Risk Group	Low		Intermediate		High Localized		High Locally Advanced	
Radical prostatectomy								
ECOG	0	≥1	0	≥1	0	≥1	0	≥1
GGG								
1	0.4	0.9	0.8	1.6	1.2	2.5	1.6	3.4
2			2.0	4.2	3.2	6.6	4.3	8.7
3			3.2	6.6	4.9	10.1	6.6	13.4
4					6.8	13.6	9.1	17.7
5					14.2	27.0	18.7	34.0
Radiotherapy								
ECOG	0	≥1	0	≥1	0	≥1	0	≥1
GGG								
1	0.7	1.4	1.1	2.3	1.8	3.6	2.4	4.8
2			3.0	5.9	4.6	9.2	6.2	12.1
3			4.6	9.2	7.2	14.2	9.6	18.4
4					9.7	18.4	12.9	23.4
5					19.9	35.0	25.8	42.7

GGG, worsening of the ECOG status generally doubled the probability of PCa death.

COMMENT

Based on mature 10-year mortality data, our population-based study among patients with nonmetastatic PCa shows that the 10-year OM is almost 3 times higher than PCSM. This discrepancy is greatest among patients with low-risk cancers and lowest among men with high-risk cancers. Within each risk group, for prostatectomized as well as for irradiated patients, the stratification by the 5 GGGs improved the prediction of PCSM. Patients having an ECOG performance status of ≥1 had twice the risk of a 10-year PCSM compared with patients with an ECOG performance status of 0.

Our overall results are comparable with the findings from other observational studies covering patients with PCa

diagnosed 10-20 years ago (Supplementary Table S3). In particular, based on the Surveillance, Epidemiology, and End Results registry, Pompe et al provided 8-year PCSM rates in the different treatment groups (RP: 1.7%; RAD 5.6%; NoLocTrt: 10.3%) similar to our findings. Our PCSM rates are, however, inferior to those from prospective randomized trials in patients with intraprostatic tumors,[8,12,13] most probably as our cohort covers 844 patients (24%) with T3 tumors. Further, only about 30% of the PCa diagnoses were based on PSA screening. Higher mortality rates were demonstrated in men with advanced disease not eligible for participation in the ProtecT trial, of which 10% were dead from PCa and 26% were dead from all causes at a median follow-up of 7.4 years.[14]

No statistically significant difference in 5-year PCSM between RP and RAD was reported in the prior publication concerning our patient group.[6] In the present study, the PCSM was lower in the RP group compared with that in the RAD group in both univariate and multivariate analyses. The difference became evident after 6-7 years of observation, demonstrating the importance of long observation times before evaluating the treatment with curative intent in these patients. However, the numerical difference in PCSM between the RP and the RAD group should be viewed with great caution due to the considerable intergroup variations. For example, 37% of patients in the RAD group had a high-risk locally advanced disease compared to 4% in the RP group. Furthermore, the radiation doses applied to the prostate in this cohort (≤74 Gy) are today considered suboptimal. Our data merely demonstrate mortality risks for patients treated with any of the 3 therapeutic modalities. The results indicate that patients with high-risk tumors benefit the most from local treatment if compared with men without such therapy. These findings are in agreement with the final reports from Mason et al and Fossa et al on the beneficial impact of RAD in patients with high-risk tumors, in whom local treatment approximately halved the 10-year PCSM.[15,16] The results from these studies were, however, not available in 2004-2005, probably explaining why as many as 37% of patients with high-risk tumors did not receive local treatment. Retrospectively, and based on today's guidelines, omission of local treatment in these patients most often reflects undertreatment. Whether RP or RAD should be used in high-risk patients has to be documented by randomized trials, for example, the ongoing SPCG-15 trial (NCT02102477).

As shown in another large study, age up to 75 years was not significantly associated with PCSM in the multivariate analysis,[17] whereas other studies have demonstrated a higher PCSM with increasing age.[18,19] One explanation could be a strong correlation between age and performance status; however, no significant associations emerged in a multivariate analysis including age, but not performance status. Based on these findings a good performance status (or no comorbidity) is more important for PCSM after local treatment than age alone. Our findings support omitting any age limitation for a curatively intended local treatment of patients with PCa, a good performance status, and a life expectancy of ≥10 years. This finding is in line with EAU guidelines and recommendations from the International Society of Geriatric Oncology.[3,20]

We documented a significant difference in PCSM between patients with a functional status of ECOG 0 compared with those with a functional status of ECOG ≥1. This difference was obvious in all risk groups and their histologic subgroups. Although the impact of a reduced ECOG status on OM was expected, we were surprised about the significant association between the ECOG status and PCSM in all risk groups. The individual categorization of the ECOG status is based on the clinician's subjective estimation with inherent interobserver variability, not measurable in our registry-based study.[21] One explanation for our observation as to ECOG being a prognostic factor could be that patients with ECOG ≥1 had more comorbidities and were older (median 69 years) than patients with ECOG 0 (median 65 years), resulting in fewer patients being candidates for second-line treatment. There is limited literature evaluating the association between comorbidity or performance status and PCSM, although this evaluation is considered important in the pretreatment assessment of patients and in the final treatment decisions. Several studies have not been able to demonstrate a correlation between comorbidity and PCMS.[8,22-26] Albertsen et al showed in their study that a higher Charlson Comorbidity Index was associated with a higher overall mortality and a lower PCa-specific mortality.[27] Assessing the impact of comorbidity and estimating the life expectancy of a patient remains a challenge to clinicians.[28,29] At the present time, we consider the use of ECOG to be a simple and clinically significant tool for assessing comorbidity in population-based registries of patients with PCa. Admittedly, our finding as to the prognostic significance of the ECOG performance status has to be validated in an external cohort.

Results from multivariate analysis demonstrate the varying significance of the individual parameters used for traditional risk grouping, with the GS emerging as the most important prognostic factor. Our findings as to the significant prognostic impact of GGGs performed in biopsies before RP or RAD are in agreement with Pompe et al's report from the Surveillance, Epidemiology, and End Results registry.[30] Separating GGG2 from GGG3 and GGG4 from GGG5 provided prognostic information within each of the EAU-defined risk groups to be taken into account in daily practice. Our findings thus support the clinical implementation of Gleason grade grouping as a prognostic tool in addition to traditional risk grouping when decisions are to be made.

There are several limitations to the present study. First, based on the data from the NoPCR, it was not possible to distinguish between AS, WW, or primary HT. In 2004-2005, most clinicians in Norway were reluctant to offer local treatment to patients aged ≥70 years and patients with locally advanced PCa, preferring the use of HT. Second, no review of the biopsy specimens' histopathology was performed, performing Gleason grade grouping with originally recorded primary and secondary Gleason grades based on ISUP

recommendations from 2004. Third, in the present study, the exact T2 subgroup was unknown in 1 of 5 patients. T-categorization was mainly based on digital rectal examination, making it difficult to distinguish between subgroups of T2 tumors and hence correct risk group allocation. Fourth, data on disease progression or second-line treatment were not available from the NoPCR. Finally, our analysis of PCSM is based on data from a population-based registry and displays the limitations connected to such registration. In particular, the cause of death may be uncertain in older patients as shown in a previous report from the Cancer Registry of Norway.[31] The strengths of the present study include its population-based design with long-term follow-up analyzing prognostic factors that are easily available at the time of diagnosis (risk group, GGG, and ECOG performance status).

CONCLUSION

The 10-year PCSM and OM rates for patients with nonmetastatic PCa who were candidates for curative treatment diagnosed in Norway in 2004-2005 were 8.5% and 25.5%, respectively. Local treatment with curative intent was associated with a reduction in 10-year PCSM, possibly with the greatest benefit for patients with high-risk tumors. Independent of allocation to either RP or RAD, GGG provides prognostic information supplementary to traditional risk grouping. If validated externally, the ECOG performance status provides additional prognostic information to be taken into account in clinical practice.

References

1. Center MM, Jemal A, Lortet-Tieulent J, et al. International variation in prostate cancer incidence and mortality rates. *Eur Urol*. 2012;61:1079-1092.
2. Cancer Registry of Norway. Cancer incidence, mortality, survival and prevalence in Norway. Available at: https://www.kreftregisteret.no/globalassets/cancer-in-norway/2015/cin2015-special_issue-web.pdf. Accessed June 15, 2017.
3. Mottet N, Bellmunt J, Bolla M, et al. EAU-ESTRO-SIOG guidelines on prostate cancer. Part 1: screening, diagnosis, and local treatment with curative intent. *Eur Urol*. 2016;71:618-629.
4. Epstein JI, Egevad L, Amin MB, et al. The 2014 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason Grading of Prostatic Carcinoma: definition of grading patterns and proposal for a new grading system. *Am J Surg Pathol*. 2016;40:244-252.
5. Egevad L, Delahunt B, Srigley JR, Samaratunga H. International Society of Urological Pathology (ISUP) grading of prostate cancer—an ISUP consensus on contemporary grading. *APMIS*. 2016;124:433-435.
6. Fossa SD, Nilssen Y, Kvale R, Hernes E, Axcrona K, Moller B. Treatment and 5-year survival in patients with nonmetastatic prostate cancer: the Norwegian experience. *Urology*. 2014;83:146-152.
7. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc*. 1958;53:457-481.
8. Wilt TJ. The Prostate Cancer Intervention Versus Observation Trial: VA/NCI/AHRQ Cooperative Studies Program #407 (PIVOT): design and baseline results of a randomized controlled trial comparing radical prostatectomy with watchful waiting for men with clinically localized prostate cancer. *J Natl Cancer Inst Monogr*. 2012;2012:184-190.
9. Epstein JI, Allsbrook WC Jr, Amin MB, Egevad LL, Committee IG. The 2005 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason Grading of Prostatic Carcinoma. *Am J Surg Pathol*. 2005;29:1228-1242.
10. Bolla M, Collette L, Blank L, et al. Long-term results with immediate androgen suppression and external irradiation in patients with locally advanced prostate cancer (an EORTC study): a phase III randomised trial. *Lancet*. 2002;360:103-106.
11. Aalen O. Nonparametric estimation of partial transition probabilities in multiple decrement models. *Ann Stat*. 1978;6:534-545.
12. Hamdy FC, Donovan JL, Lane JA, et al. 10-year outcomes after monitoring, surgery, or radiotherapy for localized prostate cancer. *N Engl J Med*. 2016;375:1415-1424.
13. Bill-Axelson A, Holmberg L, Garmo H, et al. Radical prostatectomy or watchful waiting in early prostate cancer. *N Engl J Med*. 2014;370:932-942.
14. Johnston TJ, Shaw GL, Lamb AD, et al. Mortality among men with advanced prostate cancer excluded from the protect trial. *Eur Urol*. 2017;71:381-388.
15. Fossa SD, Wiklund F, Klepp O, et al. Ten- and 15-yr prostate cancer-specific mortality in patients with nonmetastatic locally advanced or aggressive intermediate prostate cancer, randomized to lifelong endocrine treatment alone or combined with radiotherapy: final results of the Scandinavian Prostate Cancer Group-7. *Eur Urol*. 2016;70:684-691.
16. Mason MD, Parulekar WR, Sydes MR, et al. Final report of the intergroup randomized study of combined androgen-deprivation therapy plus radiotherapy versus androgen-deprivation therapy alone in locally advanced prostate cancer. *J Clin Oncol*. 2015;33:2143-2150.
17. Bechis SK, Carroll PR, Cooperberg MR. Impact of age at diagnosis on prostate cancer treatment and survival. *J Clin Oncol*. 2011;29:235-241.
18. Tward JD, Lee CM, Pappas LM, Szabo A, Gaffney DK, Shrieve DC. Survival of men with clinically localized prostate cancer treated with prostatectomy, brachytherapy, or no definitive treatment: impact of age at diagnosis. *Cancer*. 2006;107:2392-2400.
19. Sun L, Caire AA, Robertson CN, et al. Men older than 70 years have higher risk prostate cancer and poorer survival in the early and late prostate specific antigen eras. *J Urol*. 2009;182:2242-2248.
20. Droz JP, Albrand G, Gillessen S, et al. Management of prostate cancer in elderly patients: recommendations of a task force of the International Society of Geriatric Oncology. *Eur Urol*. 2017;doi:10.1016/j.eururo.2016.12.025.
21. Kelly CM, Shahrokni A. Moving beyond Karnofsky and ECOG performance status assessments with new technologies. *J Oncol*. 2016;2016:6186543.
22. Abdollah F, Schmitges J, Sun M, et al. Comparison of mortality outcomes after radical prostatectomy versus radiotherapy in patients with localized prostate cancer: a population-based analysis. *Int J Urol*. 2012;19:836-844.
23. Briganti A, Spahn M, Joniau S, et al. Impact of age and comorbidities on long-term survival of patients with high-risk prostate cancer treated with radical prostatectomy: a multi-institutional competing-risks analysis. *Eur Urol*. 2013;63:693-701.
24. Daskivich TJ, Chamie K, Kwan L, et al. Comorbidity and competing risks for mortality in men with prostate cancer. *Cancer*. 2011;117:4642-4650.
25. Daskivich TJ, Litwin MS, Penson DF. Effect of age, tumor risk, and comorbidity in a U.S. population-based cohort of men with prostate cancer. *Ann Intern Med*. 2013;159:370.
26. Lee JY, Lee DH, Cho NH, et al. Impact of Charlson comorbidity index varies by age in patients with prostate cancer treated by radical prostatectomy: a competing risk regression analysis. *Ann Surg Oncol*. 2014;21:677-683.
27. Albertsen PC, Moore DF, Shih W, Lin Y, Li H, Lu-Yao GL. Impact of comorbidity on survival among men with localized prostate cancer. *J Clin Oncol*. 2011;29:1335-1341.

28. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987;40:373-383.
29. Froehner M, Koch R, Hubler M, Wirth MP. Validation of an age-adjusted prostate cancer-specific comorbidity index. *Eur Urol*. 2016;69:764-766.
30. Pompe RS, Davis-Bondarenko H, Zaffuto E, et al. Population-based validation of the 2014 ISUP Gleason grade groups in patients treated with radical prostatectomy, brachytherapy, external beam radiation or no local treatment. *Prostate*. 2017;77:686-693.
31. Skyrud KD, Bray F, Moller B. A comparison of relative and cause-specific survival by cancer site, age and time since diagnosis. *Int J Cancer*. 2014;135:196-203.

APPENDIX

Supplementary Data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.urology.2017.07.048.

Supplementary Table S1: Patient characteristics

Treatment	RP	RAD	NoLocTrt	Total
No. of Patients (%)	913 (26)	1334 (39)	1202 (35)	3449
Risk group				
Low	377 (41)	169 (13)	369 (31)	915 (26)
Intermediate	400 (44)	378 (28)	287 (24)	1065 (31)
High localized	104 (11)	294 (22)	227 (19)	625 (18)
High locally advanced	32 (4)	493 (37)	319 (27)	844 (24)
Age (y)				
Median (range)	62 (43-74)	66 (41-75)	69 (47-75)	66 (41-75)
≤60	407 (45)	338 (25)	159 (13)	904 (26)
61-65	304 (33)	380 (28)	215 (18)	899 (26)
66-70	184 (20)	394 (30)	409 (34)	987 (29)
≥71	18 (2)	222 (17)	419 (35)	659 (19)
cT-category				
T1	491 (54)	389 (29)	588 (49)	1468 (43)
T2a	83 (9)	86 (6)	49 (4)	218 (6)
T2b	47 (5)	84 (6)	24 (2)	155 (4)
T2c	60 (7)	51 (4)	38 (3)	149 (4)
T2x	200 (22)	231 (17)	184 (15)	615 (18)
T3	32 (4)	493 (37)	319 (27)	844 (24)
PSA level (ng/mL)				
Median (range)	7.2 (1-92)	12.5 (1-100)	12.0 (1-100)	10.0 (1-100)
<10	714 (78)	503 (38)	554 (46)	1771 (51)
10-20	180 (20)	503 (38)	287 (24)	970 (28)
>20	19 (2)	328 (25)	361 (30)	708 (21)
GS (GGG)				
≤6 (1)	570 (62)	492 (37)	650 (54)	1712 (50)
3+4 (2)	247 (27)	406 (30)	227 (21)	880 (26)
4+3 (3)	63 (7)	206 (15)	139 (12)	408 (12)
8 (4)	26 (3)	172 (13)	115 (10)	313 (9)
9-10 (5)	7 (1)	58 (4)	71 (6)	136 (4)
ECOG performance status[1]				
0	851 (93)	1117 (84)	869 (72)	2837 (82)
1	32 (4)	144 (11)	202 (17)	378 (11)
2	17 (2)	37 (3)	84 (7)	138 (4)
3	0	0	15 (1)	15 (0)
Missing	13 (1)	36 (3)	32 (3)	81 (2)

Abbreviations: RP: radical prostatectomy; RAD: radiotherapy; NoLocTrt: no local treatment; cT-category: clinical T-category; GS: Gleason score; GGG: Gleason grade group, ECOG: Eastern Cooperative Oncology Group

[1] *0: Fully active, able to carry on all pre-disease performances without restriction ;1: Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature ;2: Ambulatory and capable of all self-care but unable to carry out any work activities; up about >50% of waking hours; 3: Capable of only limited self-care; confined to bed or chair >50% of waking hours*

Oken M, Creech R, Tormey D, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5:649-655.

Supplementary Table S2: Univariate analysis of 10-year prostate cancer-specific mortality

Variable	HR	95% CI	P-value
Treatment			
RP	1		
RAD	3.9	2.27-6.81	<0.001
NoLocTrt	12.7	7.52-21.49	<0.001
Age (y)			
≤60	1		
61-65	1.1	0.68-1.64	0.810
66-70	1.7	1.19-2.56	0.004
≥71	3.6	2.54-5.22	<0.001
cT-category			
T1	1		
T2	1.9	1.37-2.64	<0.001
T3	4.8	3.58-6.51	<0.001
PSA (ng/mL)			
<10	1		
10-20	1.8	1.30-2.37	<0.001
>20	4.4	3.30-5.77	<0.001
GS (GGG)			
≤6 (1)	1		
3+4 (2)	2.3	1.59-3.34	<0.001
4+3 (3)	5.4	3.69-7.80	<0.001
8 (4)	9.0	6.32-12.88	<0.001
9-10 (5)	19.2	13.09-28.18	<0.001
Risk group			
Low	1		
Intermediate	2.8	1.59-5.06	<0.001
High localized	9.3	5.37-16.10	<0.001
High locally advanced	12.5	7.38-21.34	<0.001
ECOG performance status			
0	1		
≥1	2.5	1.94-3.19	<0.001

Abbreviations: CI: confidence interval; cT-category: clinical T-category; ECOG: Eastern Cooperative Oncology Group; GGG: Gleason grade group; GS: Gleason score; HR: hazard ratio; NoLocTrt: no local treatment; PCa: prostate cancer, RAD: radiotherapy; RP: radical prostatectomy

Supplementary Table S3: Studies evaluating prostate cancer-specific mortality (PCSM)

Author year (ref)	Study design	No. patients	Gleason score ≤6 (%)	cT-categories	Treatment groups	10-year PCSM (%)
Aas et al 2017 (present study)	OS	3449	50	T1-T3	RP RAD O	1.5 6.2 16.3
Pompe et al 2017 (1)	OS	268 406	46.9	T1-T3+ (N+)	RP RAD O	1.7 (8-year PCSM) 2.6-5.6 10.3
Sooriakumaran et al 2014 (2)	OS	34 515	63	T1-T4 (N+M+)	RP RAD	0.4-10.3 % dead from PCa at 10 yrs 1.1-12.5
Hoffman et al 2013 (3)	OS	1655	59-64	T1-T2	RP/RAD	18.3% dead from PCa at 15 yrs
Abdollah et al 2012 (4)	OS	68 665		T1-T2	RP RAD	1.4-6.8 3.9-11.5
Abdollah et al 2011 (5)	OS	44 694		T1-T2	RP O	2.8 5.8
Stattin et al 2010 (6)	OS	6849	86	T1-T2	RP RAD O	2.4 3.3 3.6
Albertsen et al 2007 (7)	OS	1618	57-78	T1-T2	RP RAD O	3-10 7-20 10-30
Hamdy et al 2016 (8)	RT	1643	77	T1-T2	RP RAD O	1.0 0.4 1.2
Fosså et al 2016 (9)	RT	436	15	T1-T3	RAD+ET ET	17 (15-year PCSM) 34
Mason et al 2015 (10)	RT	1205	63.2% <GS 8	T1-T4	RAD+ET ET	32 % dead from PCa at 8 yrs 52%
Bill-Axelsons et al 2014 (11)	RT	695		T1-T2	RP O	17.7 % dead from PCa at 18 yrs 28.7%
Wilt et al 2012 (12)	RT	731	75	T1-T2	RP O	5.8% dead from PCa at 10 yrs 8.4%

Abbreviations: ET: endocrine treatment, O: observation, OS: observational study, RAD, radiotherapy, RP: radical prostatectomy, RT: randomized trial, yrs: years, *mean

References Supplementary Table S3

1. Pompe RS, Davis-Bondarenko H, Zaffuto E, Tian Z, Shariat SF, Leyh-Bannurah SR, et al. Population-based validation of the 2014 ISUP Gleason grade groups in patients treated with radical prostatectomy, brachytherapy, external beam radiation or no local treatment. Prostate. 2017.
2. Sooriakumaran P, Nyberg T, Akre O, Haendler L, Heus I, Olsson M, et al. Comparative effectiveness of radical prostatectomy and radiotherapy in prostate cancer: observational study of mortality outcomes. BMJ. 2014;348:g1502.
3. Hoffman RM, Koyama T, Fan KH, Albertsen PC, Barry MJ, Goodman M, et al. Mortality after radical prostatectomy or external beam radiotherapy for localized prostate cancer. J Natl Cancer Inst. 2013;105(10):711-8.
4. Abdollah F, Schmitges J, Sun M, Jeldres C, Tian Z, Briganti A, et al. Comparison of mortality outcomes after radical prostatectomy versus radiotherapy in patients with localized prostate cancer: a population-based analysis. Int J Urol. 2012;19(9):836-44.
5. Abdollah F, Sun M, Schmitges J, Tian Z, Jeldres C, Briganti A, et al. Cancer-specific and other-cause mortality after radical prostatectomy versus observation in patients with prostate cancer: competing-risks analysis of a large North American population-based cohort. Eur Urol. 2011;60(5):920-30.
6. Stattin P, Holmberg E, Johansson JE, Holmberg L, Adolfsson J, Hugosson J, et al. Outcomes in localized prostate cancer: National Prostate Cancer Register of Sweden follow-up study. J Natl Cancer Inst. 2010;102(13):950-8.
7. Albertsen PC, Hanley JA, Penson DF, Barrows G, Fine J. 13-year outcomes following treatment for clinically localized prostate cancer in a population based cohort. J Urol. 2007;177(3):932-6.
8. Hamdy FC, Donovan JL, Lane JA, Mason M, Metcalfe C, Holding P, et al. 10-Year Outcomes after Monitoring, Surgery, or Radiotherapy for Localized Prostate Cancer. N Engl J Med. 2016;375(15):1415-24.
9. Fossa SD, Wiklund F, Klepp O, Angelsen A, Solberg A, Damber JE, et al. Ten- and 15-yr Prostate Cancer-specific Mortality in Patients with Nonmetastatic Locally Advanced or Aggressive Intermediate Prostate Cancer, Randomized to Lifelong Endocrine Treatment Alone or Combined with Radiotherapy: Final Results of The Scandinavian Prostate Cancer Group-7. Eur Urol. 2016;70(4):684-91.
10. Mason MD, Parulekar WR, Sydes MR, Brundage M, Kirkbride P, Gospodarowicz M, et al. Final Report of the Intergroup Randomized Study of Combined Androgen-Deprivation Therapy Plus Radiotherapy Versus Androgen-Deprivation Therapy Alone in Locally Advanced Prostate Cancer. J Clin Oncol. 2015;33(19):2143-50.
11. Bill-Axelson A, Holmberg L, Garmo H, Rider JR, Taari K, Busch C, et al. Radical prostatectomy or watchful waiting in early prostate cancer. N Engl J Med. 2014;370(10):932-42.
12. Wilt TJ. The Prostate Cancer Intervention Versus Observation Trial: VA/NCI/AHRQ Cooperative Studies Program #407 (PIVOT): design and baseline results of a randomized controlled trial comparing radical prostatectomy with watchful waiting for men with clinically localized prostate cancer. J Natl Cancer Inst Monogr. 2012;2012(45):184-90.

II

World Journal of Urology (2019) 37:1571–1580
https://doi.org/10.1007/s00345-018-2570-6

ORIGINAL ARTICLE

Is time from diagnosis to radical prostatectomy associated with oncological outcomes?

Kirsti Aas[1] · Sophie Dorothea Fossa[2,3,4] · Rune Kvåle[2,5,10] · Bjørn Møller[2] · Tor Åge Myklebust[2,6] · Ljiljana Vlatkovic[7] · Stig Müller[4,8] · Viktor Berge[9]

Received: 17 September 2018 / Accepted: 15 November 2018 / Published online: 27 November 2018
© Springer-Verlag GmbH Germany, part of Springer Nature 2018

Abstract

Purpose To study the association between time from diagnosis to radical prostatectomy (RP-interval) and prostate cancer-specific mortality (PCSM), histological findings in the RP-specimen and failure after RP (RP-failure).

Methods Patients diagnosed with non-metastatic prostate cancer (PCa) in 2001–2010 and prostatectomized within 180 days of biopsy were identified in the Cancer Registry of Norway and the Norwegian Prostate Cancer Registry. Patients were stratified according to risk groups and RP-intervals of 0–60, 61–90, 91–120 and 121–180 days. Aalen-Johansen and Kaplan–Meier methods estimated curves for PCSM, RP-failure and overall mortality. Multivariable Cox regressions and Chi-square tests were used to evaluate the impact of RP-interval on outcomes.

Results In 5163 eligible patients, the median time from diagnosis to RP was 93 days (range 1–180). Risk group distribution was similar in all RP-interval groups. With almost eight years of observation, no association was found between RP-interval and PCSM in the intermediate-or high-risk groups. Increasing RP-interval did not increase the rate of adverse histological outcomes or incidence of RP-failure.

Conclusions Increasing RP-interval up to 180 days was not associated with adverse oncological outcomes at eight years follow-up. These findings should be considered when planning for prostatectomy.

Keywords Mortality · Outcomes · Prostate cancer · Radical prostatectomy · Timing

Introduction

More than 90% of men diagnosed with prostate cancer (PCa) today have no distant metastases [1]. Patients with a life expectancy of 10 or more years are considered candidates for curative treatment with radical prostatectomy (RP) or high-dose radiotherapy (RAD) [2]. Treatment is

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00345-018-2570-6) contains supplementary material, which is available to authorized users.

✉ Kirsti Aas
kirstiaas@hotmail.com

1 Department of Surgery, Vestre Viken Hospital Trust, 3004 Drammen, Norway

2 Cancer Registry of Norway, Ullernchausseen 64, 0379 Oslo, Norway

3 Department of Oncology, Oslo University Hospital, Postboks 4950 Nydalen, 0424 Oslo, Norway

4 University of Oslo, Boks 1072 Blindern, 0316 Oslo, Norway

5 Department of Oncology, Haukeland University Hospital, Jonas Lies Vei 65, 5021 Bergen, Norway

6 Department of Research and Innovation, Møre and Romsdal Hospital Trust, Åsehaugen 1, 6026 Ålesund, Norway

7 Department of Pathology, Oslo University Hospital, Postboks 4950 Nydalen, 0424 Oslo, Norway

8 Department of Surgery, Akershus University Hospital, Sykehusveien 25, 1478 Lørenskog, Norway

9 Department of Urology, Oslo University Hospital, Postboks 4950 Nydalen, 0424 Oslo, Norway

10 Department of Health Registries, Norwegian Institute of Public Health, Oslo, Norway

generally provided as soon as possible after diagnosis, or in selected low-risk patients preceded by a period of active surveillance (AS).

It is a common perception among patients, physicians and decision-makers that delay in cancer treatment adversely affects oncological outcomes. Reports documenting analyzes of the association between time-to-treatment and clinical outcomes, however, show equivocal findings among different cancer types [3–7]. The length of time from diagnosis to RP ('RP-interval') has not been shown to impact long-term oncological outcomes, even when months and years have elapsed since diagnosis [8–11]. In contrast, other studies have shown unfavorable effects on pathological outcomes [8, 12] and biochemical recurrence (BCR) rates [8, 13].

For cancer patients, delays in diagnosis and treatment may aggravate psychological distress [14]. In line with other European countries, the Norwegian health authorities implemented in 2015 a fast track cancer patient pathway (CPP) for patients with suspected PCa, providing upper limits for time intervals from referral to diagnosis and start of treatment (Online Appendix 1).Such standardized CPPs may possibly meet the emotionalneeds and expectations of the patients. However, currently there is little scientific evidence to support that RP beyond a certain time will adversely affect oncological outcomes in PCa patients.

With this background, our observational study primarily investigates the relation between the length of the RP-interval and PCa-specific mortality (PCSM). Secondarily, we evaluated the association between RP-intervals and adverse histological findings in the RP specimen and incidence of failure after RP ('RP-failure').

Material and methods

Data sources

Data were extracted from the Cancer Registry of Norway (CRN) and the Norwegian prostate cancer registry (NoPCR). For prostatectomized patients, these registries contain demographic data and basic diagnostic variables, including the date of the first cancer-positive biopsy and RP, along with histopathological findings in the RP specimen [15]. The referral and treatment decision dates are not recorded in the CRN. Data on radiotherapy and death statistics can be extracted, but information on disease progression or post-RP systemic therapy is not available. The study was approved by the Regional Committee for Medical and Health Research Ethics (2011/1746).

Patients

Eligible patients had to meet the following criteria:

- Diagnosis of non-metastatic PCa in the time period 2001–2010
- RP within 180 days of the first cancer-positive biopsy
- PSA ≤ 100 ng/mL
- Biopsy Gleason score (GS) ≥ 5
- Information on clinical (c) T-category, PSA and GS to allow risk group categorization

Patients whose diagnosis was based on cysto-prostatectomy or who were treated abroad were ineligible.

Data management

Patients were divided into RP-interval groups according to the time from the first cancer-positive biopsy to RP (0–60, 61–90, 91–120 and 121–180 days). Considering time from biopsy to treatment decision, the first RP-interval is in accordance with the maximum RP waiting time of 32 days depicted in the CPP.

Patients were stratified into low-, intermediate-or high-risk groups according to the European Association of Urology Guidelines 2017 [2].

Low-risk: PSA < 10 ng/mL and GS < 7 and cT1–T2a
Intermediate-risk: PSA 10–20 ng/mL or GS 7 or cT2b
High-risk localised: PSA > 20 ng/mL or GS > 7 or cT2c
High-risk locally advanced: any PSA, any GS, cT3–4

In less than 10% of the cohort ($n = 439$) data for risk group categorization was missing, and imputation was deemed unnecessary.

If a patient was recorded with an unknown cT2 subgroup ($n = 618$), he was allocated to the localized high-risk group if he had a GS >7 or PSA > 20 ng/mL, and to the low-risk group if he had a GS < 7 and PSA< 10 ng/mL. All other cT2x tumors were included in the intermediate-risk group. Information on the node (N) category was not available, but performing RP in patients with known N+ disease was not common practice in this time period.

Based on the routinely recorded histopathology of the RP specimen, we considered tumors to be upstaged if the T-category increased by ≥ 2 categories in cT1 patients (pathological ≥ T3) and ≥ 1 category in ≥ cT2 patients. Patients were stratified into biopsy GS-categories (GS 5–6, GS7a, GS7b, GS8, GS9–10). Tumors were considered upgraded if the pathological GS increased by at least one category compared to the biopsy GS. Patients were furthermore divided

Table 1 Patient characteristics

Time from diagnosis to RP (days)	≤ 60	61–90	91–120	121–180	Total
Median (range)	50 (1–60)	76 (61–90)	105 (91–120)	145 (121–180)	93 (1–180)
No. of patients (%)	854 (16.5)	1584 (30.7)	1314 (25.5)	1411 (27.3)	5163 (100)
Year of diagnosis					
2001–2007	453 (53.0)	859 (54.2)	640 (48.7)	666 (47.2)	2618 (50.7)
2008–2010	401 (47.0)	725 (45.8)	674 (51.3)	745 (52.8)	2545 (49.3)
Risk group					
Low	242 (28.3)	441 (27.8)	368 (28.0)	406 (28.8)	1457 (28.2)
Intermediate	347 (40.6)	677 (42.7)	580 (44.1)	613 (43.4)	2217 (42.9)
High localized	195 (22.8)	313 (19.8)	251 (19.1)	274 (19.4)	1033 (20.0)
High locally advanced	70 (8.2)	153 (9.7)	115 (8.8)	118 (8.4)	456 (8.8)
Age (years)					
Median (range)	62 (39–75)	62 (39–76)	62 (42–77)	62 (42–76)	62 (39–77)
60	400 (46.8)	721 (45.5)	619 (47.1)	606 (42.9)	2346 (45.4)
61–65	261 (30.6)	506 (31.9)	456 (34.7)	497 (35.2)	1720 (33.3)
66–70	177 (20.7)	322 (20.3)	216 (16.4)	267 (18.9)	982 (19.0)
71	16 (1.9)	35 (2.2)	23 (1.8)	41 (2.9)	115 (2.2)
cT-category					
T1	383 (44.8)	718 (45.3)	614 (46.7)	712 (50.5)	2427 (47.0)
T2	401 (47.0)	713 (45.0)	585 (44.5)	581 (41.2)	2280 (44.2)
T3–4[a]	70 (8.2)	153 (9.7)	115 (8.7)	118 (8.4)	448 (8.7)
PSA level					
< 10	594 (69.6)	1102 (69.6)	942 (71.7)	943 (66.8)	3581 (69.4)
10–20	219 (25.6)	408 (25.8)	309 (23.5)	389 (27.6)	1325 (25.7)
> 20	41 (4.8)	74 (4.7)	63 (4.8)	79 (5.6)	257 (5.0)
Gleason score					
5–6	385 (45.1)	741 (46.8)	591 (45.0)	717 (50.8)	2434 (47.1)
7a	243 (28.5)	502 (31.7)	448 (34.1)	430 (30.5)	1623 (31.4)
7b	116 (13.6)	188 (11.9)	157 (11.9)	167 (11.8)	628 (12.2)
8	92 (10.8)	114 (7.2)	89 (6.8)	75 (5.3)	370 (7.2)
9–10	18 (2.1)	39 (2.5)	29 (2.2)	22 (1.6)	108 (2.1)
Other cancer at the time of diagnosis[b]					
0	816 (95.6)	1517 (95.8)	1251 (95.2)	1353 (95.9)	4937 (95.6)
≥ 1	38 (4.4)	67 (4.2)	63 (4.8)	58 (4.1)	226 (4.4)
Dead all causes	73 (8.5)	141 (8.9)	98 (7.4)	92 (6.5)	404 (7.8)
Cause of death					
PCa	18 (2.1)	42 (2.7)	20 (1.5)	19 (1.3)	99 (1.9)
Other	53 (6.2)	97 (6.1)	75 (5.7)	72 (5.1)	297 (5.8)
Unknown	2 (0.2)	2 (0.1)	3 (0.2)	1 (0.1)	8 (0.2)

[a]Eight patients had cT4 tumors

[b]Except basal cell carcinoma

into groups based on the time of diagnosis (2001–2007 and 2008–2010) to account for the implementation of the 2005 International Society of Urological Pathology (ISUP) GS modifications in Norway [16].

RP-failure, as available from the CRN, was defined as having received post-RP pelvic RAD (≥ 50 Gy) or mammillary RAD, whatever occurred first, indicating BCR. In the time of this cohort, prophylactic mammillary RAD was common practice before initiation of anti-androgen treatment.

Statistical analyzes

Patients were followed from the date of RP until the date of study outcomes (death from PCa or RP-failure), death from other causes, emigration or end of follow-up (December 31st 2015), whichever came first. Overall mortality was estimated using the Kaplan–Meier method. The Aalen–Johansen estimator estimated PCSM, treating death from other causes as a competing risk, and RP-failure, treating death from any

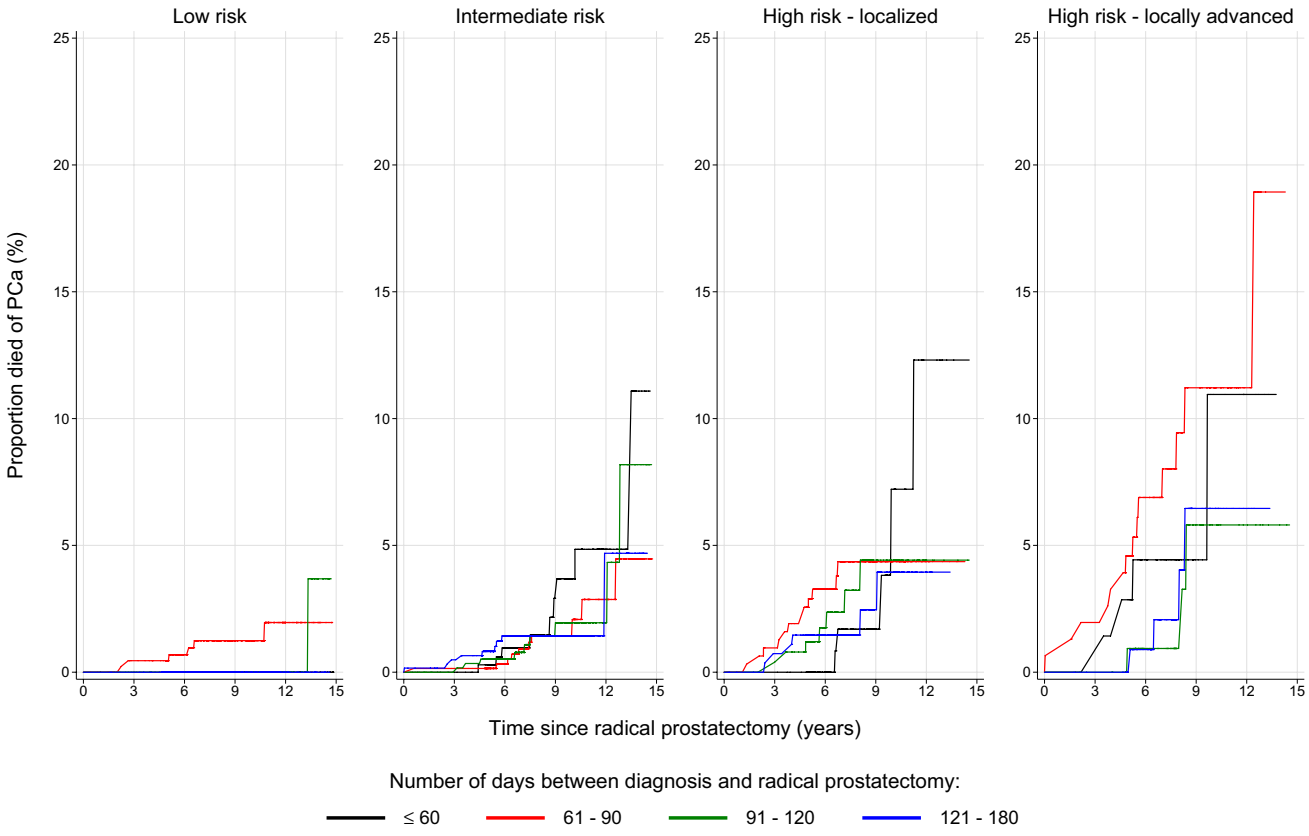


Fig. 1 Prostate cancer-specific mortality in patients with non-metastatic prostate cancer according to risk group and number of days between diagnosis and radical prostatectomy. *PCa* prostate cancer

cause as a competing risk. To compare PCSM- and RP-failure development across patient groups we estimated a univariable Fine-Gray regression and performed a Wald test of equality of coefficients. Multivariable Cox-regressions documented the impact of RP-interval on the cause-specific hazard of PCa death, as well as the cause-specific hazard of RP-failure, adjusting for potential confounding factors. Standard chi-square tested the association between the RP-interval groups and the rates of upstaging, upgrading and surgical margin status. A p value of < 0.05 was considered statistically significant. Data were analyzed using the IBM Statistical Package for the Social Sciences (SPSS) version 23 and Stata version 14.2.

Results

In the 5163 evaluable patients, 17%, 31%, 26% and 27% of patients underwent RP 0–60, 61–90, 91–120 and 121–180 days from diagnosis (Table 1). The median time from diagnosis to RP was 93 days (range 1–180). The age and risk group distribution were similar in all RP-interval groups. Of all patients included in this cohort, 29% had high-risk disease. Among these, 18% were treated with RP within 60 days compared to 26% between 121–180 days from diagnosis.

After a median follow-up of 7.9 years (range 0–15), 99 patients (1.9%) had died from PCa (Table 1). For all patients, the 5-year and 10-year PCSM rates were 0.7% and 2.5%, respectively, without any significant difference between time periods (Supplementary Table 5, Supplementary Fig. 3). In the intermediate-risk, high-risk localized and high-risk locally advanced groups, there were no significant differences in PCSM according to RP-interval (Fig. 1). A statistically significant difference emerged for patients in the low-risk group ($p < 0.001$), but this analysis was regarded as invalid due to event paucity. On multivariate analysis cT-category, biopsy GS and risk group were associated with PCSM, but not RP-interval, PSA, age group or year of diagnosis (Table 2a, b).

No associations between the length of the RP-interval and the rate of upstaging (22%) or upgrading (34%) were demonstrated (Tables 3, 4). The surgical margins were positive in 28% of the RP specimens (low-risk: 23%, high-risk:

Table 2 Multivariate analysis of PCa-specific mortality

	HR (95% CI)	*p* value
(a)		
RP-interval		
1	1	
2	1.46 (0.83–2.54)	0.186
3	0.94 (0.49–1.78)	0.840
4	0.89 (0.46–1.71)	0.729
Age (year)		
< 60	1	
≥ 60	1.44 (0.91–2.29)	0.118
cT-category		
T1	1	
T2	1.63 (1.00–2.65)	0.048
T3	2.62 (1.46–4.71)	0.001
T4	–	–
PSA (ng/mL)		
<10	1	
10–20	1.46 (0.96–2.22)	0.076
>20	1.03 (0.41–2-60)	0.953
GS		
5–6	1	
7a	1.80 (0.98–3.31)	0.055
7b	4.79 (2.54–9.03)	0.000
8	7.9 (4.15–15.14)	0.000
9–10	18.60 (9.20–37.60)	0.000
Time of diagnosis		
2001–07	1	
2008–10	1.01 (0.62–1.65)	0.966
(b)		
RP-interval		
1	1	
2	1.24 (0.71–2.15)	0.452
3	0.78 (0.41–1.47)	0.441
4	0.70 (0.37–1.35)	0.289
Risk group		
Low	1	
Intermediate	4.01 (1.78–9.02)	0.001
High localized	8.14 (3.55–18.68)	0.000
High locally advanced	13.98 (6.02–32.49)	0.000
Age (year)		
< 60	1	
≥ 60	1.54 (0.98–2.43)	0.064
Time of diagnosis		
2001–2007	1	
2008–2010	1.15 (0.71–1.87)	0.575

35%). Increasing RP-interval was not associated with higher rates of positive surgical margins (PSM) in any risk group (Tables 3, 4).

After a median time of 1.9 years (range 0.1–12.5) after RP, 1273 patients (24.7%) experienced RP-failure. Of these, 528 (41.5%) belonged to the high-risk group at the time of diagnosis. In all risk groups, increasing RP-interval was significantly associated with decreased probability of RP-failure (Fig. 2). This finding was confirmed in multivariate analysis (Online Appendix 2). With low-risk group as reference increasing risk group was associated with significantly increasing hazard ratios of RP-failure (Online Appendix 2).

Discussion

In this population-based cohort with a follow-up time of almost eight years, increasing RP-interval up to 180 days was not associated with increased PCSM in intermediate-or high-risk patients, or with adverse histological outcomes or RP-failure in any risk group.

Our findings are in agreement with a systematic review by Van den Bergh et al. concluding that an association between the timing of RP and PCSM has not yet been documented [8]. The majority of reviewed studies included low and intermediate-risk patients only. Importantly, as shown by Korets et al. and Redaniel et al., this finding confirmed by us, is also valid for high-risk patients [9, 17].

The documented PCSM rates in this cohort are comparable to other observational studies covering patients diagnosed in the same time period [18–22]. As expected with a large proportion of high-risk patients, the PCSM is higher than demonstrated in the Protect trial including only screening-detected patients with intra-capsular tumors [23]. Despite a shift towards a larger proportion of prostatectomized patients having high-risk disease (2001–2007: 25.2%, 2008–2010: 32.6%), we observed no difference in PCSM for patients diagnosed in the early versus late period, possibly explained by a decrease in the rate of PSM and intensified adjuvant and salvage treatment in the late period [24].

The observation that increasing RP-interval was not associated with adverse pathological outcomes in our study is in agreement with Sun et al. who found that timing of RP did not affect the rate of upstaging [25]. Neither did Korets et al. find an impact of time from the last positive biopsy to RP on the rate of upgrading or pT-categorization [17]. On the contrary, Berg et al. observed, in patients from the same institution, a significant increase in the proportion of adverse pathological outcomes (upstaging, seminal vesicle invasion, positive lymph nodes, upgrading, PSM) with RP beyond 75 days, ranging from 30 to 150 days depending on the GS and PSA level at the time of diagnosis [12]. In terms of recurrence, Abern et al. found that a delay beyond 9 months was significantly related to PSM and BCR in low- and intermediate risk patients [27], while Zanaty et al. found a positive association between increasing time to RP and

Table 3 Histological outcomes (biopsy versus RP specimen) according to EAU contemporary risk group and RP-interval for patients diagnosed 2001–2007

Risk group	Low						Intermediate						High					
RP-interval (days)	60	61–90	91–120	121–180	Total	*p* values	60	61–90	91–120	121–180	Total	*p* values	60	61–90	91–120	121–180	Total	*p* values
Upstaging (%)																		
cT1- pT3	15.6[a]	9.7	9.9	17.4	12.8	0.18	27.1	25.3	25.2	18.8	23.8	0.61	47.6	50.0	31.6	33.3	41.9	0.30
cT2- pT3	16.2	11.7	19.0	17.2	15.3		22.1	22.7	31.5	33.1	27.3		22.2	13.5	19.5	16.0	17.1	
cT3-pT4													0	0	0	0	0	
Upgrading (%)																		
Biopsy GS 5–6	36.7	40.3	44.7	42.3	41.2	0.42	45.8	44.3	62.3	48.4	49.4	0.53	62.9	55.7	64.9	62.0	60.6	0.49
Biopsy GS 7a							18.2	22.2	20.4	25.9	21.9		12.5	23.5	40.0	37.5	30.1	
Biopsy GS 7b							9.7	8.5	7.3	14.6	10.0		0	9.5	23.5	21.4	13.2	
Biopsy GS 8													15.6	11.1	6.9	13.8	11.9	
Positive margins (%)																		
Yes	29.7	23.1	27.9	26.3	26.2	0.41	32.6	34.5	27.8	22.9	29.5	0.02	39.3	42.7	32.4	31.9	36.8	0.06
No	60.1	67.1	65.6	69.0	65.9		62.9	61.5	67.5	71.2	65.7		51.3	50.2	61.5	61.5	56.1	
Unknown	10.1	9.8	6.5	4.7	7.8		4.5	4.0	4.7	5.9	4.7		9.4	7.0	6.1	6.6	7.1	

Missing pT-category = 2.7%

Missing GS in RP specimen = 1.4%

[a]Percentage

Table 4 Histological outcomes (biopsy versus RP specimen) according to EAU contemporary risk group and RP-interval for patients diagnosed 2008–2010

Risk group	Low						Intermediate						High					
RP-interval (days)	≤ 60	61–90	91–120	121–180	Total	*p* values	≤ 60	61–90	91–120	121–180	Total	*p* values	60	61–90	91–120	121–180	Total	*p* values
Upstaging (%)																		
cT1-pT3	10.9[a]	12.2	11.4	18.4	13.8	0.61″	23.1	29.6	30.3	23.8	26.9	0.95	30.0	46.6	45.8	45.7	43.0	0.67
cT2-pT3	20.0	16.1	10.0	13.0	14.2		27.7	29.9	30.4	40.6	32.7		33.3	34.9	44.2	31.8	36.3	
cT3-pT4													0	1.3	1.6	0	0.9	
Upgrading (%)																		
Biopsy GS 5–6	41.7	55.5	49.0	52.8	50.9	0.19	63.3	56.7	63.8	66.2	62.7	0.14	63.2	73.0	71.8	73.3	71.6	0.05
Biopsy GS 7a							18.8	18.7	22.2	26.5	21.9		48.6	25.3	29.2	30.6	31.2	
Biopsy GS 7b							20.9	13.9	13.0	13.8	14.8		7.7	22.0	13.3	28.1	18.6	
Biopsy GS 8													13.3	15.4	10.0	19.6	14.3	
Positive margins (%)																		
Yes	20.2	21.2	17.6	12.4	17.2	0.13	29.6	30.4	23.1	21.1	25.5	0.02	27.7	34.4	33.9	35.7	33.4	0.46
No	76.2	75.3	75.2	85.0	78.6		62.7	65.0	70.6	73.4	68.7		64.9	57.3	63.3	60.0	60.9	
Unknown	3.6	3.4	7.2	2.6	4.2		7.7	4.6	6.3	5.6	5.8		7.4	8.3	2.8	4.3	5.7	

Missing pT-category = 20.9%

Missing GS in RP specimen = 0.7%

[a]Percentage

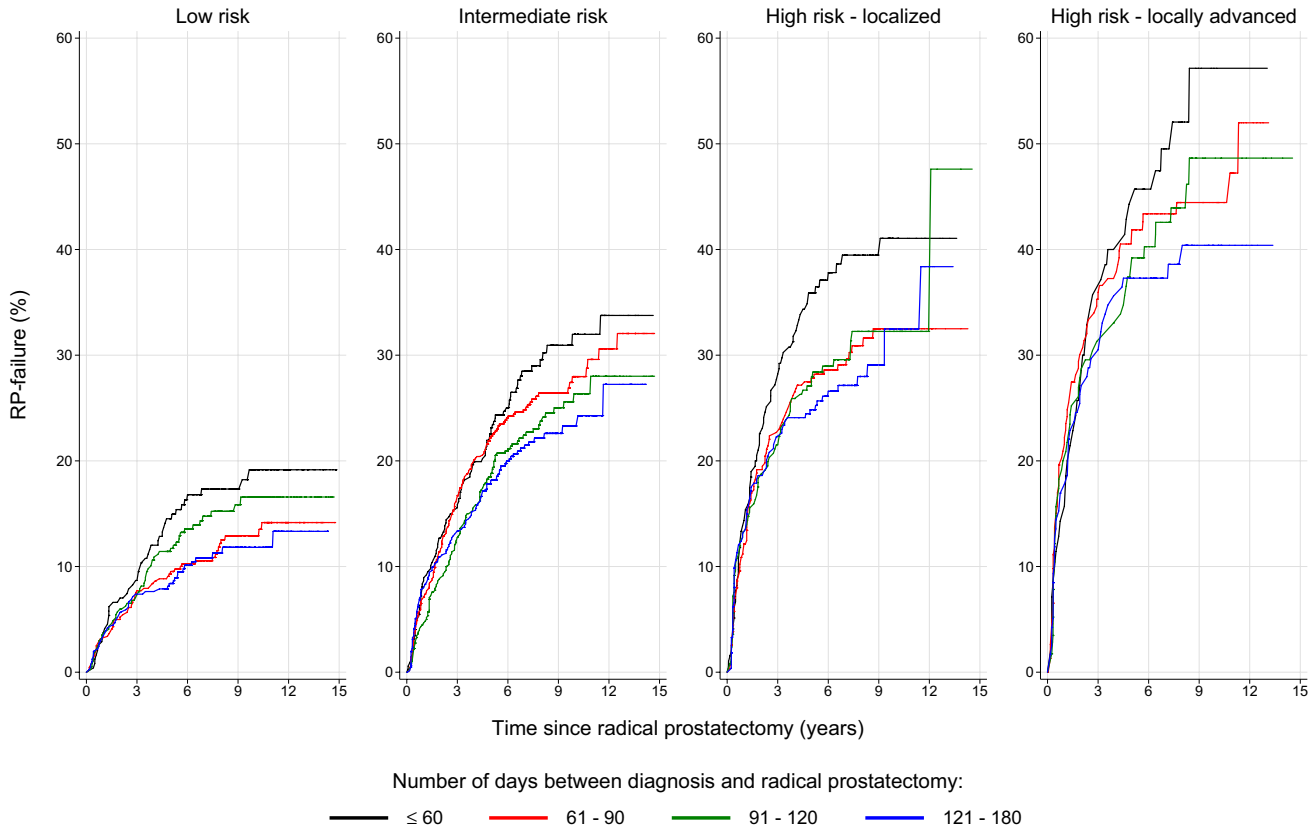


Fig. 2 RP-failure in patients with non-metastatic prostate cancer according to risk group and number of days between diagnosis and radical prostatectomy.*RP-failure* failure after radical prostatectomy

BCR in the high-risk group beyond 90 days [13]. The majority of studies, however, do not show increased incidence of BCR with increasing RP-interval, and our findings support these data [8]. We were surprised to find that the risk of RP-failure decreased with increasing RP-interval. This finding may indicate that patients with shorter RP-intervals had more aggressive disease than reflected by our co-variates (e.g., the number of biopsy cores involved with cancer, the percentage of cancer within each biopsy core, PSA doubling time).

We do not know the reasons for increasing RP-interval in this cohort. National guidelines were not implemented in Norway until 2009, and clinical decisions were mainly based on preferences of the treating physician. Increasing age, a co-existing cancer diagnosis or more favorable tumor characteristics did not explain increasing RP-intervals. AS was not formally recorded in the CRN at this time.

The implementation of CPPs in Norway is a political initiative based on the Danish model aiming to improve quality of PCa care [28]. By streamlining services, patients are provided with an efficient and predictable path in close dialog with the hospital, avoiding unnecessary delays. The CPP may facilitate better hospital organization and planning based on available resources and ensure equal cancer handling across regions.

There are, however, challenges with the implementation of the CPP. The time limits for diagnosis and treatment of PCa have proven difficult to put in practice and are currently complied with in about half of the cases. Contrary to the intention of the CPP, patients may suffer additional distress from treatment delay as they anticipate worse prognosis with RP beyond 32 days [29]. The medical rationale behind the time limit for RP, being independent of individual risk assessment, is questioned by clinicians. Medically related delay, like health status optimization or extensive pre-operative planning, may be necessary in selected patients. Moreover, in a time with emerging therapeutic options, patients may wish to seek second opinions before deciding on treatment. Patient preferences and expectations regarding treatment are highly dependent on in-depth counseling by the treating physicians. In our opinion, these priorities, although time-consuming, better reflect quality of PCa care than strict adherence with time limits for RP.

There are several limitations to this study. Firstly, although the registration of new cases of PCa in the CRN is close to complete, the reporting of post-diagnosis outcomes

is less exhaustive [1]. Secondly, histological evaluation of prostate biopsies was performed by multiple pathologists without central review, and patients diagnosed before the implementation of the 2005 ISUP modifications were evaluated according to the old Gleason grading system. Third, information on eventual re-biopsies or pre-RP changes in PSA or clinical stage was not available. Fourth, our data on RP-failure underestimates the true incidence of BCR, because the CRN and NoPCR provided no information on post-RP PSA or androgen-deprivation therapy for distant metastasis. Fifth, in older patients, the cause of death may be uncertain as shown in a previous report from the CRN [30]. Finally, this study did not investigate the associations between increasing RP-interval and functional or psychological outcomes. The strength of this study is the long-term follow-up of a large population-based cohort of patients with RP as initial treatment, of which almost one third of the patients had high-risk disease.

Conclusions

Based on the above, the time from diagnosis to RP performed within 6 months of diagnosis is not associated with adverse oncological outcomes at eight years follow-up. These findings should be taken into consideration when counseling candidates for prostatectomy and planning surgical resources at the hospitals. Our study warrants revision of the length of the RP-interval in the current Norwegian CPP for PCa.

Acknowledgements We would like to thank the Norwegian Cancer Society (Fund no. 5781243), the Radium Hospital Foundation (Project no. 335007) and the Vestre Viken Hospital Trust (Project no. 2503002) for financial support.

Author contributions KA: Protocol/project development, Data collection or management, Data analysis, Manuscript writing/editing. SDF: Protocol/project development, Data collection or management, Data analysis, Manuscript writing/editing. RK: Data analysis, Manuscript writing/editing. BM: Protocol/project development, Data collection or management, Data analysis, Manuscript writing/editing. TÅM: Data collection or management, Data analysis, Manuscript writing/editing. LV: Data collection or management, Manuscript writing/editing. SM: Data analysis, Manuscript writing/editing. VB: Protocol/project development, Data analysis, Manuscript writing/editing.

Funding This study was funded by the Norwegian Cancer Society (Fund no. 5781243), the Radium Hospital Foundation (Project no. 335007) and the Vestre Viken Hospital Trust (Project no. 2503002).

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Cancer Registry of Norway (2017) Annual Report 2016 with Results and Improvements from the Norwegian Prostate Cancer Registry. https://www.kreftregisteret.no/globalassets/publikasjoner-og-rapporter/arsrapporter/publisert-2017/arsrapport-2016_prostatakreft.pdf. Accessed Oct 2018
2. Mottet N, Bellmunt J, Bolla M et al (2017) Guidelines on Prostate Cancer. Part 1: screening, diagnosis, and local treatment with curative intent. Eur Urol 71(4):618–629. https://doi.org/10.1016/j.eururo.2016.08.003
3. Neal RD, Tharmanathan P, France B et al (2015) Is increased time to diagnosis and treatment in symptomatic cancer associated with poorer outcomes? Systematic review. Br J Cancer 112(Suppl 1):S92–S107. https://doi.org/10.1038/bjc.2015.48
4. Bruins HM, Aben KK, Arends TJ, Heijden AG, Witjes AJ (2016) The effect of the time interval between diagnosis of muscle-invasive bladder cancer and radical cystectomy on staging and survival: a Netherlands Cancer Registry analysis. Urol Oncol 34(4):e161–e166. https://doi.org/10.1016/j.urolonc.2015.11.006
5. Jensen AR, Nellemann HM, Overgaard J (2007) Tumor progression in waiting time for radiotherapy in head and neck cancer. Radiother Oncol 84(1):5–10. https://doi.org/10.1016/j.radonc.2007.04.001
6. Jooste V, Dejardin O, Bouvier V et al (2016) Pancreatic cancer: wait times from presentation to treatment and survival in a population-based study. Int J Cancer. 139(5):1073–1080. https://doi.org/10.1002/ijc.30166
7. Bourgade V, Drouin SJ, Yates DR et al (2014) Impact of the length of time between diagnosis and surgical removal of urologic neoplasms on survival. World J Urol. 32(2):475–479. https://doi.org/10.1007/s00345-013-1045-z
8. van den Bergh RC, Albertsen PC, Bangma CH et al (2013) Timing of curative treatment for prostate cancer: a systematic review. Eur Urol 64(2):204–215. https://doi.org/10.1016/j.eururo.2013.02.024
9. Redaniel MT, Martin RM, Gillatt D, Wade J, Jeffreys M (2013) Time from diagnosis to surgery and prostate cancer survival: a retrospective cohort study. BMC Cancer 13:559. https://doi.org/10.1186/1471-2407-13-559
10. O'Callaghan ME, Shi Z, Kopsaftis T, Moretti K (2017) Prostate cancer outcomes and delays in care. Int Urol Nephrol 49(3):449–455. https://doi.org/10.1007/s11255-017-1508-z
11. Morini MA, Muller RL, de Castro Junior PCB, de Souza RJ, Faria EF (2018) Time between diagnosis and surgical treatment on pathological and clinical outcomes in prostate cancer: does it matter? World J Urol 36(8):1225–1231. https://doi.org/10.1007/s00345-018-2251-5
12. Berg WT, Danzig MR, Pak JS et al (2015) Delay from biopsy to radical prostatectomy influences the rate of adverse pathologic outcomes. Prostate 75(10):1085–1091. https://doi.org/10.1002/pros.22992
13. Zanaty M, Alnazari M, Ajib K et al (2018) Does surgical delay for radical prostatectomy affect biochemical recurrence? A retrospective analysis from a Canadian cohort. World J Urol 36(1):1–6. https://doi.org/10.1007/s00345-017-2105-6
14. Seklehner S, Hladschik-Kermer B, Lusuardi L, Schabauer C, Riedl C, Engelhardt PF (2013) Psychological stress assessment of patients suffering from prostate cancer. Scand J Urol 47(2):101–107. https://doi.org/10.3109/00365599.2012.700946
15. Hernes E, Kyrdalen A, Kvale R et al (2010) Initial management of prostate cancer: first year experience with the Norwegian National Prostate Cancer Registry. BJU Int. 105(6):805–811. https://doi.org/10.1111/j.1464-410X.2009.08834.x**discussion 811**

16. Epstein JI, Allsbrook WC Jr, Amin MB, Egevad LL, Committee IG (2005) The 2005 International Society of Urological Pathology (ISUP) consensus conference on gleason grading of prostatic carcinoma. Am J Surg Pathol 29(9):1228–1242. https://www.ncbi.nlm.nih.gov/pubmed/16096414. Accessed Oct 2018
17. Korets R, Seager CM, Pitman MS, Hruby GW, Benson MC, McKiernan JM (2012) Effect of delaying surgery on radical prostatectomy outcomes: a contemporary analysis. BJU Int 110(2):211–216. https://doi.org/10.1111/j.1464-410X.2011.10666.x
18. Pompe RS, Davis-Bondarenko H, Zaffuto E et al (2017) Population-based validation of the 2014 ISUP Gleason grade groups in patients treated with radical prostatectomy, brachytherapy, external beam radiation or no local treatment. Prostate. https://doi.org/10.1002/pros.23316
19. Abdollah F, Schmitges J, Sun M et al (2012) Comparison of mortality outcomes after radicalprostatectomy versus radiotherapy in patients with localized prostate cancer: a population-based analysis. Int J Urol 19(9):836–844. https://doi.org/10.1111/j.1442-2042.2012.03052.x
20. Stattin P, Holmberg E, Johansson JE et al (2010) Outcomes in localized prostate cancer: National Prostate Cancer Register of Sweden follow-up study. J Natl Cancer Inst 102(13):950–958. https://doi.org/10.1093/jnci/djq154
21. Aas K, Axcrona K, Kvale R et al (2017) Ten-year mortality in men with nonmetastatic prostate cancer in Norway. Urology 110:140–147. https://doi.org/10.1016/j.urology.2017.07.048
22. Holmstrom B, Holmberg E, Egevad L et al (2010) Outcome of primary versus deferred radical prostatectomy in the National Prostate Cancer Register of Sweden Follow-Up Study. J Urol 184(4):1322–1327. https://doi.org/10.1016/j.juro.2010.06.008
23. Hamdy FC, Donovan JL, Lane JA et al (2016) 10-year outcomes after monitoring, surgery, or radiotherapy for localized prostate cancer. N Engl J Med 375(15):1415–1424. https://doi.org/10.1056/NEJMoa1606220
24. Vatne K, Stensvold A, Myklebust TA et al (2017) Pre- and post-prostatectomy variables associated with pelvic post-operative radiotherapy in prostate cancer patients: a national registry-based study. Acta Oncol. https://doi.org/10.1080/0284186X.2017.1314006
25. Sun M, Abdollah F, Hansen J et al (2012) Is a treatment delay in radical prostatectomy safe in individuals with low-risk prostate cancer? J Sex Med 9(11):2961–2969. https://doi.org/10.1111/j.1743-6109.2012.02806.x
26. Kvale R, Moller B, Wahlqvist R et al (2009) Concordance between Gleason scores of needle biopsies and radical prostatectomy specimens: a population-based study. BJU Int 103(12):1647–1654. https://doi.org/10.1111/j.1464-410X.2008.08255.x
27. Abern MR, Aronson WJ, Terris MK et al (2013) Delayed radical prostatectomy for intermediate-risk prostate cancer is associated with biochemical recurrence: possible implications for active surveillance from the SEARCH database. Prostate 73(4):409–417. https://doi.org/10.1002/pros.22582
28. Sundhedsstyrelsen (2016) Pakkeforløb for prostatakræft. https://www.sst.dk/da/sygdom-og-behandling/kraeft/pakkeforloeb/~/media/086DCAA5E5B14713BA08556124EB4681.ashx. Accessed Oct 2018
29. Norwegian Directorate of Health (2016) Pakkeforløp for prostatakreft. https://helsedirektoratet.no/retningslinjer/pakkeforlop-for-prostatakreft. Accessed Oct 2018
30. Skyrud KD, Bray F, Moller B (2014) A comparison of relative and cause-specific survival by cancer site, age and time since diagnosis. Int J Cancer 135(1):196–203. https://doi.org/10.1002/ijc.28645

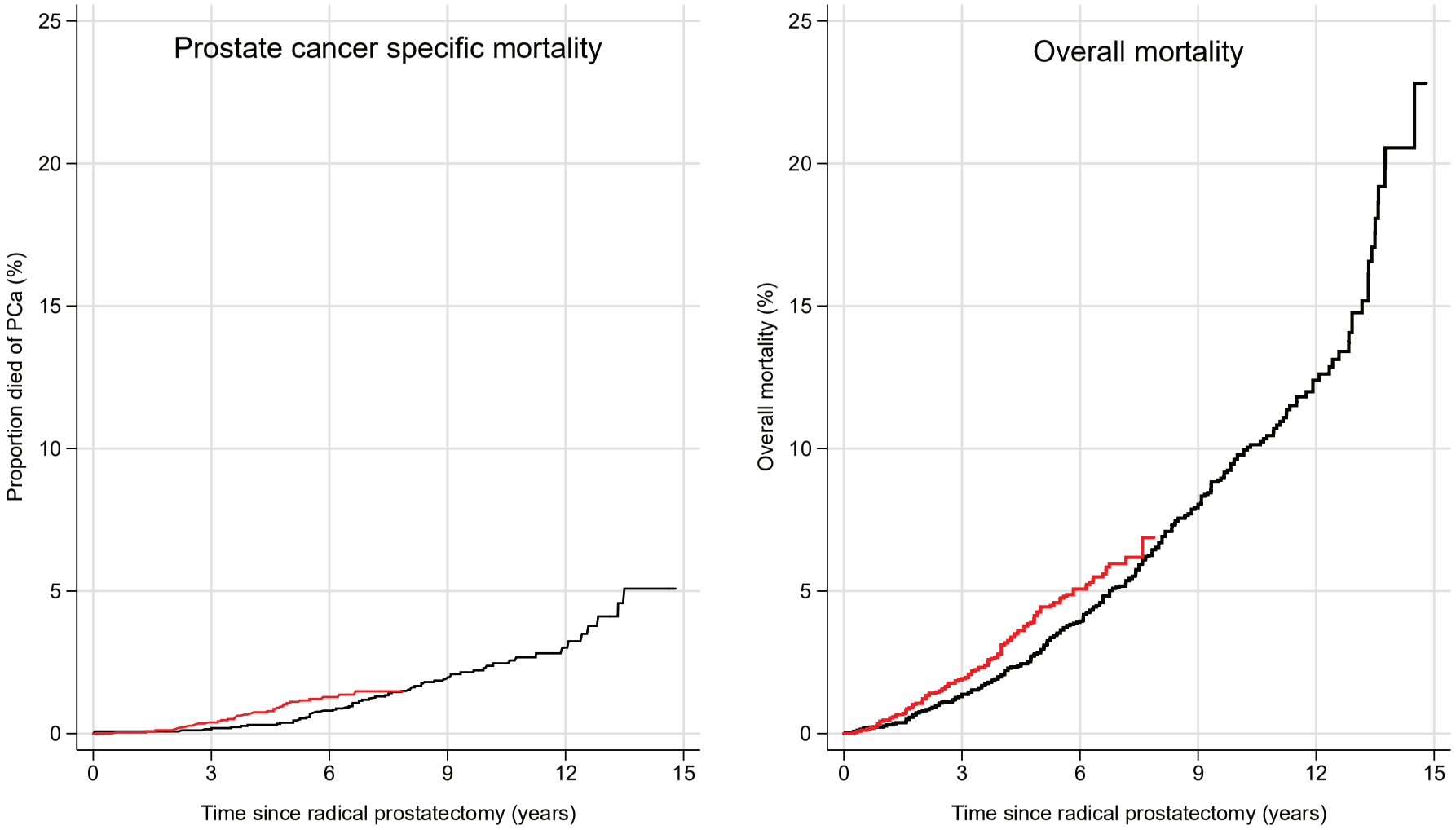
Supplementary Table 5: 5-year and 10-year PCSM according to risk group

PCSM Risk group	5-year*	10-year
Low	0.14 (0.03-0.48)	0.39 (0.15-0.88)
Intermediate	0.45 (0.23-0.81)	2.21 (1.45-3.23)
High localized	1.56 (0.93-2.47)	4.70 (2.93-7.08)
High locally advanced	2.21 (1.14-3.89)	8.49 (5.24-12.72)
All	0.74 (0.53-1.01)	2.54 (2.01-3.18)

*Numbers correspond to % (95% confidence interval)

Abbreviation: PCSM; prostate cancer-specific mortality

SUPPLEMENTARY FIGURE 3



Prostate cancer-specific mortality (left) and overall mortality (right) in men treated with radical prostatectomy within 180 days of prostate cancer diagnosis

Appendix 1: Prostate cancer patient pathway

Description	Treatment	Maximum time (calendar days)
From referral to first meeting with the specialist services		10
From first meeting to complete work-up and treatment decision		24
From treatment decision to treatment start	Surgical treatment	32
From treatment decision to treatment start	Medical treatment	3
From treatment decision to treatment start	Radiotherapy	32
From treatment decision to treatment start	Active surveillance	3
From referral to treatment start	Surgical treatment	66
From referral to treatment start	Medical treatment	37
From referral to treatment start	Radiotherapy	66
From referral to treatment start	Active surveillance	37

Appendix 2: Multivariate analysis of RP-failure

	HR (95% CI)	P-value
RP-interval		
1	1	
2	0.82 (0.70-0.96)	0.011
3	0.79 (0.67-0.93)	0.004
4	0.70 (0.59-0.83)	0.000
Risk group		
Low	1	
Intermediate	1.98 (1.68-2.33)	0.000
High localized	2.77 (2.32-3.31)	0.000
High locally advanced	4.30 (3.53-5.23)	0.000
Age (years)		
<60	1	
≥60	0.94 (0.84-1.06)	0.064
Time of diagnosis		
2001-07	1	
2008-10	1.18 (1.05-1.32)	0.004

Abbreviations: HR; hazard ratio, RP; radical prostatectomy

III

Received: 8 May 2020 | Revised: 21 June 2020 | Accepted: 22 June 2020

DOI: 10.1002/cam4.3297

ORIGINAL RESEARCH

Cancer Medicine Open Access WILEY

Increased curative treatment is associated with decreased prostate cancer-specific and overall mortality in senior adults with high-risk prostate cancer; results from a national registry-based cohort study

Kirsti Aas[1] | **Sophie Dorothea Fossåa**[2,3,4] | **Tor Åge Myklebust**[3,5] | **Bjørn Møller**[3] | **Rune Kvåle**[6,7] | **Ljiljana Vlatkovic**[8] | **Viktor Berge**[4,9]

[1]Department of Surgery, Vestre Viken Hospital Trust, Drammen, Norway

[2]Department of Oncology, Oslo University Hospital (OUH), Oslo, Norway

[3]Cancer Registry of Norway, Oslo, Norway

[4]University of Oslo, Oslo, Norway

[5]Department of Research and Innovation, Møre and Romsdal Hospital Trust, Alesund, Norway

[6]Department of Oncology, Haukeland University Hospital, Bergen, Norway

[7]Department of Health Registry-based Research and Development, Norwegian Institute of Public Health, Bergen, Norway

[8]Department of Pathology, OUH, Oslo, Norway

[9]Department of Urology, OUH, Oslo, Norway

Correspondence
Kirsti Aas, Department of Surgery, Vestre Viken Hospital Trust, Postboks 800, 3004 Drammen, Norway.
Email: kirstiaas@hotmail.com

Funding information
The Vestre Viken Hospital Trust (project no 2503002), the Norwegian Cancer Society (fund no 5781243) and the Radium Hospital Foundation (project no 335007) have provided financial support.

Abstract

Background: The association between curative treatment (CurTrt) and mortality in senior adults (≥70 years) with high-risk prostate cancer (PCa) is poorly documented. In a population-based cohort we report temporal trends in treatment and PCa-specific mortality (PCSM), investigating the association between CurTrt and mortality in senior adults with high-risk PCa, compared to findings in younger men (<70 years).

Methods: Observational study from the Cancer Registry of Norway. Patients with high-risk PCa were stratified for three diagnostic periods (2005-08, 2009-12 and 2013-16), age (<70, vs ≥70) and primary treatment (CurTrt: Radical prostatectomy (RP), Radiotherapy (RAD) vs no curative treatment (NoCurTrt)). Competing risk and Kaplan-Meier methods estimated PCSM and overall mortality (OM), respectively. Multivariable logistic regression models estimated odds for CurTrt, and multivariable Fine Gray and Cox regression models evaluated the hazard ratios for PCSM and OM.

Results: Of 19 763 evaluable patients, 54% were aged ≥70 years. Senior adults had more unfavorable PCa characteristics than younger men. Across diagnostic periods, use of CurTrt increased from 15% to 51% in men aged ≥70 and 65% to 81% in men aged < 70 years. With median five years follow-up, PCSM decreased in all patients ($P < .05$), in the third period restricted to senior adults. In all patients NoCurTrt was associated with three-fold higher 5-year PCSM and two-fold higher OM compared to CurTrt.

Conclusions: In high-risk PCa patients, increased use of CurTrt, greatest in senior men, was observed along with decreased PCSM and OM in both senior and younger adults. CurTrt should increasingly be considered in men ≥70 years.

KEYWORDS
elderly, mortality, prostate cancer, senior adults, treatment

This is an open access article under the terms of the Creative Commons Attribution License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.
© 2020 The Authors. *Cancer Medicine* published by John Wiley & Sons Ltd.

1 | INTRODUCTION

Prostate cancer (PCa) is a major cause of cancer mortality in senior men worldwide.[1,2] Due to demographic changes, the number of new PCa cases in men ≥ 70 years is expected to double within year 2040.[3] According to the literature, a higher proportion of senior adults have high-risk disease at presentation compared to younger men.[4-6]

Elderly patients are underrepresented in clinical trials, and there is no consensus on the optimal treatment strategy in senior adults with high-risk PCa.[7,8] The Scandinavian Prostate Cancer Group (SPCG) 4 study demonstrated a survival benefit from radical prostatectomy (RP) compared to watchful waiting in both senior and younger men with localized disease and long life expectancy (LE).[9] In patients with high-risk disease, there is level 1 evidence that androgen deprivation therapy (ADT) combined with radiotherapy (RAD) improves survival compared to either modality alone, also in senior adults.[10-13] Patients without distant metastases and LE > 5-10 years, should be considered for curatively intended treatment with RP and extended pelvic lymph node dissection or high-dose RAD combined with (neo-) adjuvant ADT.[14-18] Those who are unwilling or ineligible for curative treatment (CurTrt), may be managed with watchful waiting or ADT.[14-18]

Senior adults with high-risk PCa comprise a heterogeneous group of patients in terms of PCa characteristics, health status, and LE. Any life-prolonging effect from CurTrt must in these patients be weighed against the risk of adverse treatment-related effects and death from other causes than PCa.[19-21] Studies have indicated that treatment decisions in PCa patients are primarily based on chronological age rather than biological age.[7,22-27] Undertreatment of healthy senior adults with high-risk PCa may thus contribute to the described high incidence of death from PCa in the elderly population.[5,6,20,21]

With this background, we compare patient characteristics, primary treatment, and prostate cancer-specific mortality (PCSM) in senior adults (≥70 years) and younger men (<70 years) diagnosed with high-risk PCa in Norway. Furthermore, we investigate the association between CurTrt and mortality in the two age groups.

2 | METHODS

2.1 | Data sources

The Norwegian Prostate Cancer Registry is a national clinical quality registry managed by the Cancer Registry of Norway.[28] The registry codes individual demographic and clinical information, including date of PCa diagnosis, Eastern Cooperative Oncology Group (ECOG) performance status, PSA level, Gleason score, clinical TNM-categories, and date of RP. The Radiotherapy Database contains information on start of RAD, target site, and target dose from all radiotherapy centers in Norway. Information on the date and cause of death is collected from the Cause of Death Registry. The study was approved by the Regional Committee for Medical and Health Research Ethics (2011/1746).

2.2 | Patients

Patients diagnosed from 2005 to 2016 with PCa without distant metastases were identified (Appendix 1). For inclusion in the study, the European Association of Urology high-risk group criteria had to be met, including both localized and locally advanced disease.[29] Detailed information on clinical N-category was not available in the registry. Patients were stratified according to diagnostic period (2005-08, 2009-12, 2013-16), age at diagnosis (<70, 70-74, 75-79, ≥80 years), and curative treatment (CurTrt: RP, RAD vs no curative treatment (NoCurTrt)). RP was performed in ≤ 12 months of diagnosis. Performance of pelvic lymph node dissection was not reliably documented. RAD was in the current study defined as RAD doses of ≥ 74 Gy, with or without (neo-) adjuvant ADT, started ≤ 15 months of diagnosis in patients diagnosed 2005-13 and ≤ 12 months in patients diagnosed 2014-16. Patients not fulfilling the criteria for primary RP or RAD were allocated to the NoCurTrt group. Treatment was analyzed as a time-varying covariate. Patients were observed from the time of diagnosis to emigration, death, or end of study date (31st December 2017).

2.3 | Statistical methods

Standard descriptive methods were applied (frequencies/proportions, medians/ranges). The Chi square tested intergroup differences. Multivariable logistic regression models estimated the odds ratios (ORs) and 95% confidence intervals (CIs) for performance of CurTrt. PCSM was estimated using the Aalen-Johansen estimator, and mortality estimates were compared using a univariate Fine-Gray regression model. Overall survival was assessed with the Kaplan-Meier method. Multivariable Fine-Gray and Cox regression models tested the relationship (subdistribution hazard ratios (SHRs), hazard ratios (HRs) and CIs) between primary treatment and PCSM and OM, respectively, adjusting for relevant clinical confounding variables available at the time of diagnosis. The level of significance was $P < .05$. Data were analysed using the IBM Statistical Package for the Social Sciences Statistics version 26 and Stata version 14.2.

3 | RESULTS

3.1 | Disease characteristics

In total, 19 763 patients with high-risk PCa were evaluable for the present study (Appendix 1,2). More than half of the patients were aged ≥ 70 years (Table S1). Compared to younger patients, senior adults had poorer ECOG performance status, higher PSA levels, and more unfavorable International Society of Urological pathology (ISUP) grade groups and cT-categories. Decrease in PSA levels and increase in ISUP grade groups were observed across diagnostic periods, similar for senior and younger patients.

3.2 | CurTrt vs NoCurTrt

In all patients the use of CurTrt increased from 37% in 2005-08 to 66% in 2013-16, with a larger increase in senior adults (≥70 years; 15 to 51%, <70 years: 65 to 81%) (Table 1). Compared to 24% of the younger men, 67% of high-risk senior adults did not receive CurTrt. Use of RP increased fourfold in patients aged 70-74 years, and RAD increased sevenfold in patients aged 75-79 years, whereas RP doubled in the younger ones parallel with decrease in RAD.

Patients in the NoCurTrt group were older, had poorer ECOG performance status and higher PSA-levels compared to curatively treated patients (Table S2). In both the CurTrt and NoCurTrt groups, one in two patients had ISUP grade group ≥ 4 tumors.

In multivariable analyses, the odds of receiving CurTrt increased sixfold across the diagnostic periods in senior adults compared to a twofold increase in younger patients (Table 2). For all patients, the probability of receiving CurTrt decreased with increasing age, ECOG status ≥ 1, and a prior cancer diagnosis. In both senior and younger patients, having ISUP grade group ≥ 2 tumors doubled the odds for treatment compared to ISUP grade group 1 tumors.

3.3 | Mortality

For all patients, PCSM decreased within the observation period ($P < .05$), although a decrease in the last diagnostic period was observed only in patients ≥ 70 years (Figure 1). The 5-year PCSM was 8.8% and OM was 21.8%, both increasing with age at diagnosis (Table 3). With a median follow-up time of five years (range 0-13 years), about two of five deaths were caused by PCa in both senior and younger adults (1825/4650 and 570/1307 deaths respectively) (Table 3, Figure 2).

In multivariable analyses, NoCurTrt was associated with more than threefold increased risk of PCa death in all patients, with similar results for RP and RAD (Table 4, Figure S1). Time-dependent decreasing probabilities of PCa death

TABLE 1 Primary treatment in patients diagnosed with high-risk prostate cancer in Norway

Diagnostic period	2005-2008				2009-12				2013-16					
Age (y)	<70	70-74	75-79	≥80	All	<70	70-74	75-79	≥80	All	<70	70-74	75-79	≥80	All	Total
Patients (n)	2677	1159	1164	1268	6268	3052	1238	1032	1207	6529	3352	1439	1100	1075	6966	19 763
Primary treatment																
RP	824 (31)[a]	72 (6)	11 (<1)	2 (<1)	909 (15)	1484 (49)	231 (19)	20 (2)	2 (<1)	1737 (27)	1972 (59)	433 (30)	66 (6)	0	2471 (36)	5117 (26)
RAD	903 (34)	379 (33)	83 (7)	3 (<1)	1368 (22)	971 (32)	577 (47)	323 (31)	36 (3)	1907 (29)	742 (22)	672 (47)	536 (49)	124 (12)	2074 (30)	5349 (27)
NoCurTrt	950 (36)	708 (61)	1070 (92)	1263 (>99)	3991 (64)	597 (20)	430 (35)	689 (67)	1169 (97)	2885 (44)	638 (19)	334 (23)	498 (45)	951 (89)	2421 (35)	9297 (47)

Abbreviations: NoCurTrt, no curative treatment; post-RP RAD, post radical prostatectomy radiotherapy; RP, radical prostatectomy.

[a]Number of patients (% of patients within diagnostic period and age group).

TABLE 2 Logistic regression with curative treatment (RP or RAD) as dependent variable

Age (y)	<70			≥70		
	7567			8571		
Patients analyzed (n)	Odds ratio	95% CI	*P*-value	Odds ratio	95% CI	*P*-value
Diagnostic period						
2005-08	1			1		
2009-12	2.20	1.92-2.53	.000	3.44	2.96-4.00	.000
2013-16	2.10	1.83-2.42	.000	6.44	5.49-7.55	.000
Age						
<60	1					
60-64	0.89	0.76-1.04	.140			
65-69	0.78	0.67-0.91	.001			
70-74				1		
75-79				0.26	0.23-0.30	.000
≥80				0.03	0.03-0.04	.000
ECOG						
0	1			1		
1	0.68	0.58-0.81	.000	0.53	0.46-0.60	.000
≥2	0.24	0.19-0.31	.000	0.16	0.13-0.20	.000
Prior cancer						
No	1			1		
Yes	0.75	0.60-0.93	.009	0.70	0.58-0.84	.000
PSA (ng/mL)						
<10	1			1		
10-20	1.01	0.87-1.18	.889	0.84	0.72-0.97	.022
>20	0.44	0.39-0.50	.000	0.41	0.36-0.48	.000
ISUP grade group						
1	1			1		
2	2.17	1.81-2.58	.000	2.26	1.81-2.83	.000
3	2.05	1.69-2.48	.000	2.56	2.03-3.23	.000
4	1.83	1.55-2.18	.000	2.44	1.97-3.01	.000
5	1.33	1.10-1.62	.003	2.26	1.80-2.84	.000
cT-category						
1-2	1			1		
3-4	0.73	0.65-0.82	.000	0.89	0.79-1.01	.066

Abbreviations: CI, confidence interval; cT-category, clinical tumor-category; ECOG, Eastern Cooperative Oncology Group functional status; ISUP grade group, International Society of Urological Pathology grade group; PSA, prostate specific antigen; RAD, radiotherapy; RP: radical prostatectomy.

with increasing diagnostic periods were further reduced if primary treatment was excluded from the analysis (data not shown). Having ISUP grade group five vs one increased the HR of death from PCa almost four times (95% CI 2.9-4.3) in men ≥ 70 years compared to 13 times (95% CI 8.5-22.1) in men < 70 years (Table 4). In both senior and younger adults, NoCurTrt more than doubled the overall 5-year risk of death (Table 5). The HR of OM decreased with increasing diagnostic period in senior adults (Table 5), also when defining death from PCa as a competing risk (data not shown).

4 | DISCUSSION

In this population-based cohort of high-risk PCa patients, increased use of CurTrt, greatest in senior men, was observed

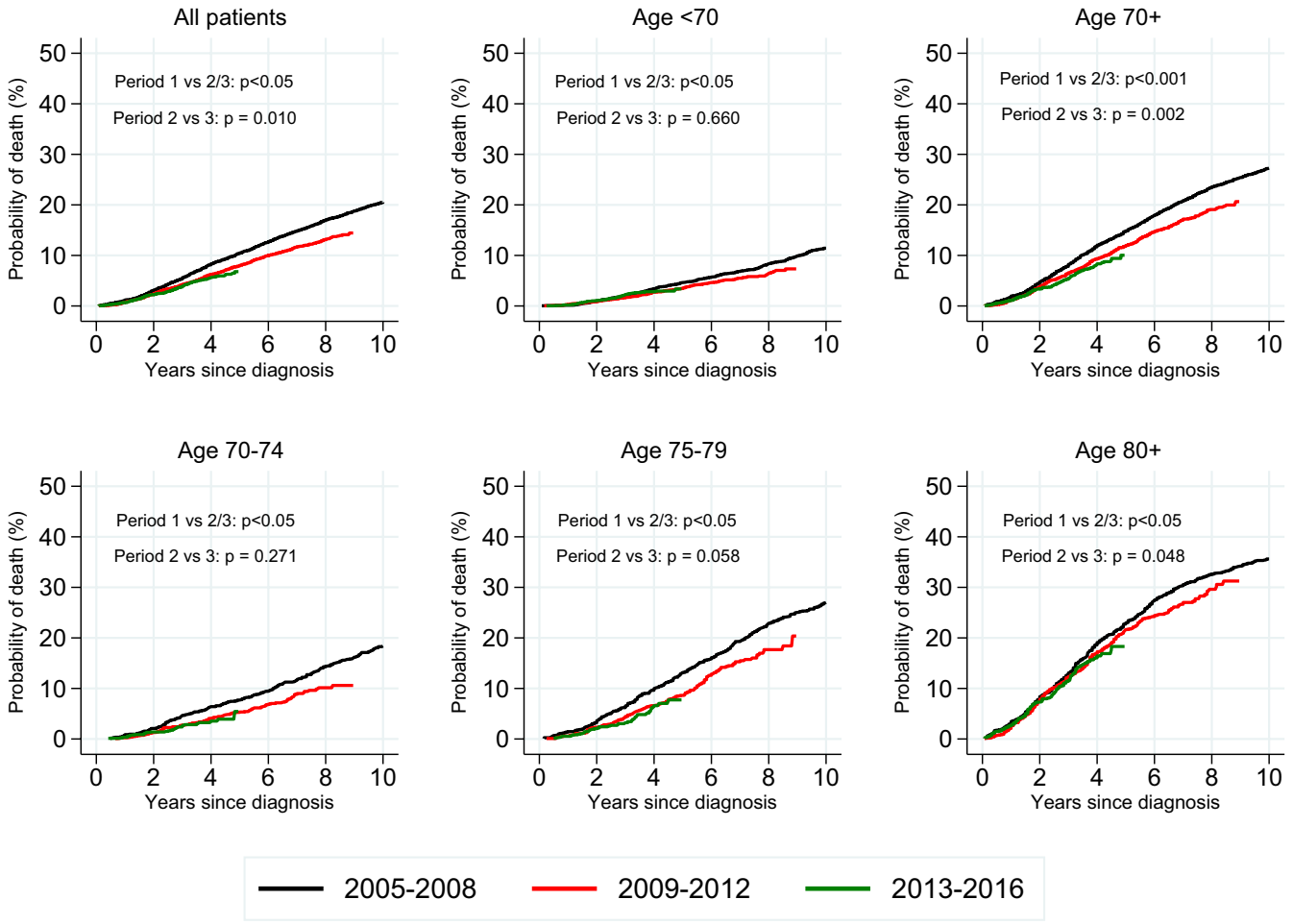


FIGURE 1 Prostate cancer-specific mortality according to age group and diagnostic period in patients diagnosed with high-risk prostate cancer in Norway 2005-16

with time, along with decreased PCSM and OM in both senior and younger adults.

4.1 | Disease characteristics

Our findings are in agreement with previous studies demonstrating higher prevalence of high-risk disease in senior adults compared to younger men.[4,5] Admittedly, more aggressive histology observed with time in all patients, may relate to gradual implementation of the 2005 ISUP Gleason score modifications and increased use of targeted biopsies.

4.2 | Treatment

In our study, we observed a striking increase in the use of RP in patients up to 75 years of age and RAD in senior adults. Improvements in CurTrt techniques with lower toxicity, along with increasing LE in the population, may have influenced physicians´ decisions. Furthermore, increased use of CurTrt may relate to a 2012 consensus, stating that CurTrt should be discussed with high-risk patients having LE more than 5 years.[18]

Recommendations advocating management of senior adults according to health status rather than chronological age, were not implemented in the European Association of Urology Guidelines until 2016, but preceding discussions within the uro-oncological community may have guided clinical practice earlier.[30] Furthermore, the overall increase in use of CurTrt across diagnostic periods reflects the increase in ISUP grade groups, being a strong predictor of unfavorable outcomes.[31]

4.3 | Mortality

The decrease in PCSM coincides with the increase in use of CurTrt during the observation period, without

TABLE 3 5-year prostate cancer-specific and overall mortality in patients diagnosed with high-risk prostate cancer

(A)				
Treatment	**RP**	**RAD**	**NoCurTrt**	**All**
Dead PCa				
All ages	110/5117 (2)[a]	209/5349 (4)	2076/9297 (22)	2395/19763 (12)
<70	90/4280 (2)	123/2616 (5)	357/2185 (16)	570/9081 (6)
70-74	19/736 (3)	60/1628 (4)	307/1472 (21)	386/3836 (10)
75-79	1/97 (1)	23/942 (2)	505/2257 (22)	529/3296 (16)
≥80	0/4	3/163 (2)	907/3383 (27)	910/3550 (26)
Dead any cause				
All ages	330/5117 (6)	733/5349 (14)	4894/9297 (53)	5957/19763 (30)
<70	251/4280 (6)	360/2616 (14)	696/2185 (32)	1307/9081 (14)
70-74	70/736 (10)	236/1628 (14)	691/1472 (47)	997/3836 (26)
75-79	7/97 (7)	121/942 (13)	1234/2257 (55)	1362/3296 (41)
≥80	2/4 (50)	16/163 (9)	2273/3383 (67)	2291/3550 (65)
(B)				
Treatment	**RP**	**RAD**	**NoCurTrt**	**All**
PCa-specific mortality				
All	1.4 (1.0-1.8)[b]	2.2 (1.8-2.7)	15.6 (14.9-16.4)	8.8 (8.4-9.3)
<70	1.1 (0.8-1.5)	2.4 (1.8-3.1)	11.0 (9.6-12.5)	4.0 (3.6-4.5)
70-74	2.8 (1.5-4.7)	2.0 (1.4-3.0)	11.3 (9.7-13.1)	6.1 (5.3-7.0)
75-79	2.8 (0.2-12.4)	2.0 (1.1-3.5)	13.1 (11.7-14.7)	10.4 (9.3-11.6)
≥80	—	3.3 (0.8-8.9)	22.6 (21.1-24.1)	22.1 (20.6-23.6)
Overall mortality				
All	4.7 (4.0-5.5)	8.4 (7.6-9.3)	36.2 (35.1-37.2)	21.8 (21.2-22.5)
<70	3.8 (3.1-4.6)	7.0 (6.0-8.1)	19.9 (18.1-21.8)	8.9 (8.3-9.7)
70-74	10.4 (7.7-14.0)	8.9 (7.5-10.7)	26.5 (24.2-29.0)	16.9 (15.6-18.3)
75-79	7.9 (2.8-21.3)	11.2 (8.9-14.1)	31.8 (29.8-33.9)	26.8 (25.2-28.6)
≥80	25.0 (4.0-87.2)	20.4 (12.2-33.0)	55.1 (53.3-57.0)	54.2 (52.4-56.0)

Abbreviations: NoCurTrt: no curative treatment; PCa: prostate cancer; RAD: radiotherapy; RP: radical prostatectomy.

[a]Mortality rate % (95% confidence interval).

[b]Number of patients (% within treatment group).

differences for RP and RAD. Adjusted for well-known prognostic risk factors, CurTrt was associated with reduced likelihood of 5-year PCSM and OM in both senior and younger adults. In contrast with our findings, the SPCG-4 trial did not show a survival benefit until more than 20 years follow-up with RP compared to watchful waiting in patients aged 65-75 years, however, only 3% had Gleason score 8-10 tumors.[9,32] Our results are in agreements with retrospective series, demonstrating reduced 5-10-year PCSM with local treatment in patients aged ≥ 75 years with ISUP grade group ≥ 2 and locally advanced tumors.[33,34]

In line with our findings regarding PCSM, relative survival is reduced in Norwegian PCa patients aged > 70 years at diagnosis, with a marked reduction in patients ≥ 80 years.[35] Similarly, a previous population-based study demonstrated reduced 10-year relative survival in senior adults compared with younger men, with more pronounced differences in high-risk patients.[6] Unlike previously reported, ECOG status was no longer an independent predictor of PCSM in senior adults when analyzed in a competing risk setting (Table 4, Table S3).[36] Surprisingly, increasing ISUP grade groups were associated with higher risk of PCa death in younger than in senior men (Table 4). We speculate whether this finding may be related to underlying host-related differences, such as reduced free testosterone levels, associated with age.[37-39]

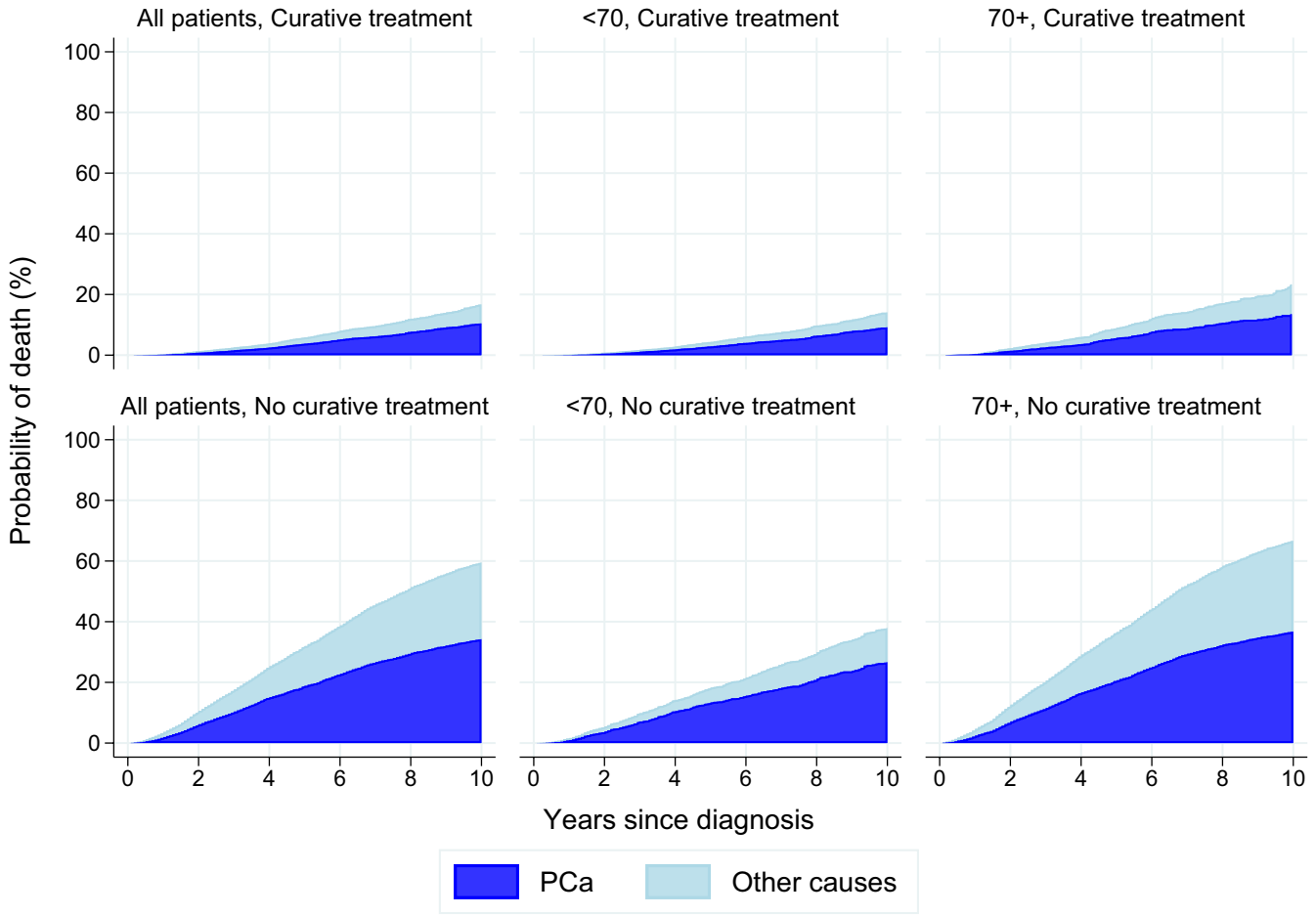


FIGURE 2 Prostate cancer and other cause mortality according to age group and primary treatment in men diagnosed with high-risk prostate cancer in Norway 2005-16. PCa; prostate cancer

4.4 | Undertreatment of senior adults

Even in the most recent period in this study, almost half of the senior adults with high-risk PCa did not receive CurTrt. Comparable to findings by Rider et al and Albertsen et al, a considerable proportion of these patients died from PCa.[20,21] Similar to younger men, senior adults in the NoCurTrt group had a twofold increased risk of overall death within five years of diagnosis compared to patients treated curatively. The considerable 5-year PCSM rates, along with the high proportion of patients having ISUP grade group ≥ 4 tumors and ECOG status ≤ 1 in the NoCurTrt group, suggest the likelihood of undertreatment, as also emphasized in other studies.[27,4026]

4.5 | Treatment decisions in senior adults

Higher age is associated with more peri-operative complications and poorer functional outcomes after radical treatment,[4,19,41,42] although, several studies report tolerable side-effects with CurTrt in senior adults.[43,44] The possibility of undertreatment and early death from high-risk PCa may imply that the selection criteria for CurTrt are too strict and LE may be underestimated. When CurTrt is considered in senior adults, formal health assessment and individual in-depth patient counseling are obligatory to facilitate optimal patient selection.

4.6 | Limitations and strengths

This registry-based cohort study has several limitations. Our cohort presents a minimum estimate since data were insufficient for risk grouping in 8347 of the initial 26 819 patients without distant metastases (31%). A case mix, with stage and grade migration, may have occurred during the study period, resulting from improvements in diagnostic methods. Major limitations include the lack of detailed comorbidity data. Furthermore, complete data on ADT use, disease progression and second-line cancer treatments were not available in the Norwegian Prostate Cancer Registry. Estimation of PCSM was based on official cause of death registration and over-/underreporting of PCa as cause of death, particularly in senior

TABLE 4 Multivariable Fine-Gray regression with prostate cancer-specific mortality as dependent variable in patients diagnosed with high-risk prostate cancer

Age (years)	<70						≥70					
Patients analyzed (n)	7567						8563					
	Univariable			Multivariable			Univariable			Multivariable		
Analysis	SHR	95% CI	*P*-value	SHR	95% CI	*P*-value	SHR	95% CI	*P*-value	SHR	95% CI	*P*-value
Diagnostic period												
2005-08	1			1			1			1		
2009-12	0.74	0.61-0.89	.002	0.72	0.58-0.91	.006	0.69	0.63-0.77	.000	0.70		.000
2013-16	0.79	0.59-1.04	.097	0.64	0.42-0.92	.017	0.53	0.46-0.62	.000	0.48		.000
Treatment												
RP	1			1			1			1		
RAD	1.71	1.30-2.24	.000	1.02	0.75-1.40	.893	1.12	0.69-1.81	.648	0.90	0.52-1.53	.685
NoCurTrt	6.02	4.76-7.62	.000	3.16	2.36-4.23	.000	6.93	4.47-10.74	.000	3.69	2.24-6.09	.000
Age												
<60	1			1								
60-64	1.10	0.87-1.38	.419	0.91	0.70-1.19	.498						
65-69	1.17	0.94-1.45	.158	0.91	0.71-1.18	.490						
70-74							1			1		
75-79							1.59	1.40-1.81	.000	1.08	0.94-1.25	.283
≥80							2.75	2.44-3.09	.000	1.35	1.17-1.56	.000
ECOG												
0	1			1			1			1		
1	2.03	1.62-2.55	.000	1.43	1.11-1.83	.006	1.46	1.30-1.64	.000	1.11	0.98-1.26	.100
≥2	1.54	1.03-2.30	.034	0.79	0.50-1.24	.303	1.80	1.59-2.04	.000	1.07	0.93-1.23	.357
PSA (ng/mL)												
<10	1			1			1			1		
10-20	1.47	1.14-1.89	.003	1.11	0.84-1.46	.474	1.29	1.09-1.53	.003	1.06	0.89-1.26	.535
>20	2.27	1.83-2.82	.000	1.50	1.17-1.92	.002	1.86	1.61-2.15	.000	1.27	1.08-1.48	.003
ISUP grade group												
1	1			1			1			1		
2	2.46	1.54-3.93	.000	2.57	1.59-4.15	.000	1.18	0.95-1.47	.131	1.24	0.99-1.55	.067
3	4.20	2.64-6.69	.000	3.67	2.25-5.98	.000	1.59	1.28-1.97	.000	1.63	1.29-2.05	.000
4	5.55	3.59-8.59	.000	5.73	3.65-8.99	.000	1.96	1.61-2.38	.000	2.15	1.75-2.65	.000
5	16.72	10.89-25.67	.000	13.38	8.49-22.08	.000	3.54	2.93-4.29	.000	3.61	2.93-4.46	.000
cT-category												
1-2	1			1			1			1		
3-4	2.05	1.70-2.46	.000	1.45	1.18-1.78	.000	1.45	1.31-1.60	.000	1.30	1.17-1.45	.000

Abbreviations: CI, confidence interval; cT-category, clinical tumor-category; ECOG, Eastern Cooperative Oncology Group functional status; ISUP grade group, International Society of Urological Pathology grade group; NoCurTrt, no curative treatment; PSA, prostate specific antigen; RAD, radiotherapy, SHR, sub-distribution hazard ratio; RP, radical prostatectomy.

adults, must be considered.[45-48] The strengths of this study include real-life data from a large population-based cohort of senior adults with high-risk PCa, assessing the association between CurTrt and PCSM.

5 | CONCLUSION

Use of CurTrt increased with time and was associated with decreased PCSM and OM in senior adults with high-risk

TABLE 5 Cox regression with overall mortality as dependent variable in patients diagnosed with high-risk prostate cancer

Age (y)	<70			≥70		
	7567			8563		
Patients analyzed (n)	**HR**	**95% CI**	***P*-value**	**HR**	**95% CI**	***P*-value**
Diagnostic period						
2005-08	1			1		
2009-12	0.95	0.81-1.10	.458	0.86	0.80-0.93	.000
2013-16	1.00	0.79-1.27	.991	0.81	0.72-0.92	.001
Treatment						
RP	1			1		
RAD	1.29	1.07-1.55	.007	0.96	0.73-1.26	.762
NoCurTrt	2.74	2.29-3.28	.000	2.25	1.73-2.93	.000
Age						
<60	1					
60-64	1.15	0.96-1.39	.133			
65-69	1.50	1.27-1.78	.000			
70-74				1		
75-79				1.30	1.18-1.43	.000
≥80				2.14	1.95-2.35	.000
ECOG						
0	1			1		
1	1.81	1.55-2.11	.000	1.31	1.21-1.41	.000
≥2	2.34	1.91-2.87	.000	1.79	1.64-1.94	.000
PSA (ng/mL)						
<10	1			1		
10-20	1.31	1.10-1.54	.002	1.14	1.02-1.27	.019
>20	1.52	1.30-1.78	.000	1.34	1.22-1.47	.000
ISUP grade group						
1	1			1		
2	1.30	1.06-1.61	.013	1.07	0.94-1.21	.296
3	1.51	1.21-1.88	.000	1.27	1.12-1.43	.000
4	1.73	1.41-1.12	.000	1.48	1.32-1.66	.000
5	2.95	2.39-3.65	.000	1.94	1.73-2.19	.000
cT-category						
1-2	1			1		
3-4	1.15	1.01-1.30	0.035	1.18	1.10-1.26	0.000

Note: Abbreviations: CI: confidence interval; cT-category: clinical tumor-category; ECOG: Eastern Cooperative Oncology Group functional status; HR: Hazard ratio; ISUP grade group: International Society of Urological Pathology grade group; NoCurTrt: no curative treatment; PSA: prostate specific antigen; RAD: radiotherapyRP: radical prostatectomy.

PCa, suggesting that CurTrt may benefit appropriately selected patients.

6 | CREDIT AUTHOR STATEMENT

Aas: Conceptualization, methodology, formal analysis, investigation, writing – original draft, writing – review and editing, visualization, project administration, funding acquisition. **Fosså**: Conceptualization, methodology, formal analysis, investigation, writing – original draft, writing – review and editing, visualization, supervision, project administration, funding acquisition. **Myklebust:** Methodology, formal analysis, investigation, writing – review and editing, visualization. **Møller:** Conceptualization, methodology, investigation, writing – review and editing. **Kvåle**: writing – review

and editing. **Vlatkovic:** writing – review and editing. **Berge:** Conceptualization, methodology, writing – original draft, writing – review and editing, visualization, supervision, project administration.

ACKNOWLEDGMENTS

For financial support, we thank the Vestre Viken Hospital Trust (project no 2503002), the Norwegian Cancer Society (fund no 5781243) and the Radium Hospital Foundation (project no 335007).

CONFLICTS OF INTEREST

None of the authors have conflicts of interests to disclose.

AUTHORS CONTRIBUTION

All authors listed on the title page have made substantial contributions to the manuscript and agree to the submission to Cancer Medicine.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the Cancer Registry of Norway Restrictions apply to the availability of these data, which were used under license for this study. Data are available from the authors with the permission of the Cancer Registry of Norway.

ORCID

Kirsti Aas https://orcid.org/0000-0002-2125-227X

REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, et al. GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2018;68(6):394-424. https://doi.org/10.3322/caac.21492
2. International Agency for Research on Cancer. Estimated number of deaths in 2018, worldwide, all cancers, males, ages 70+. 2019; http://gco.iarc.fr/today/online-analysis-pie?v=2018&mode=cancer&mode_population=continents&population=900&populations=900&key=total&sex=1&cancer=39&type=1&statistic=5&prevalence=0&population_group=0&ages_group%5B%5D=14&ages_group%5B%5D=17&nb_items=7&group_cancer=1&include_nmsc=1&include_nmsc_other=1&half_pie=0&donut=0&population_group_globocan_id=. Accessed November, 2019.
3. International Agency for Research on Cancer. Estimated number of incident cases from 2018 to 2040, prostate, males, ages 70+. Cancer Tomorrow 2019; Global cancer statistics. Available at: https://gco.iarc.fr/tomorrow/graphic-isotype?type=0&population=900&mode=population&sex=1&cancer=39&age_group=65%2B&apc_male=0&apc_female=0. Accessed November, 2010.
4. Brassell SA, Rice KR, Parker PM, et al. Prostate cancer in men 70 years old or older, indolent or aggressive: clinicopathological analysis and outcomes. *J Urol*. 2011;185(1):132-137. https://doi.org/10.1016/j.juro.2010.09.014
5. Scosyrev E, Messing EM, Mohile S, Golijanin D, Wu G. Prostate cancer in the elderly: frequency of advanced disease at presentation and disease-specific mortality. *Cancer*. 2012;118(12):3062-3070. https://doi.org/10.1002/cncr.26392
6. Vernooij RWM, van Oort I, de Reijke TM, Aben KKH. Nationwide treatment patterns and survival of older patients with prostate cancer. *J Geriatr Oncol*. 2019;10(2):252-258. https://doi.org/10.1016/j.jgo.2018.06.010
7. Fung C, Dale W, Mohile SG. Prostate cancer in the elderly patient. *J Clin Oncol*. 2014;32(24):2523-2530. https://doi.org/10.1200/JCO.2014.55.1531
8. Dunn C, Wilson A, Sitas F. Older cancer patients in cancer clinical trials are underrepresented. Systematic literature review of almost 5000 meta- and pooled analyses of phase III randomized trials of survival from breast, prostate and lung cancer. *Cancer Epidemiol*. 2017;51:113-117. https://doi.org/10.1016/j.canep.2017.11.002
9. Bill-Axelson A, Holmberg L, Garmo H, et al. Radical prostatectomy or watchful waiting in prostate cancer - 29-year follow-up. *N Engl J Med*. 2018;379(24):2319-2329. https://doi.org/10.1056/NEJMoa1807801
10. Mason MD, Parulekar WR, Sydes MR, et al. Final report of the intergroup randomized study of combined androgen-deprivation therapy plus radiotherapy versus androgen-deprivation therapy alone in locally advanced prostate cancer. *J Clin Oncol*. 2015;33(19):2143-2150. https://doi.org/10.1200/JCO.2014.57.7510
11. Bolla M, Van Tienhoven G, Warde P, et al. External irradiation with or without long-term androgen suppression for prostate cancer with high metastatic risk: 10-year results of an EORTC randomised study. *Lancet Oncol*. 2010;11(11):1066-1073. https://doi.org/10.1016/S1470-2045(10)70223-0
12. Fosså SD, Wiklund F, Klepp O, et al. Ten- and 15-yr prostate cancer-specific mortality in patients with nonmetastatic locally advanced or aggressive intermediate prostate cancer, randomized to lifelong endocrine treatment alone or combined with radiotherapy: final results of The Scandinavian Prostate Cancer Group-7. *Eur Urol*. 2016;70(4):684-691. https://doi.org/10.1016/j.eururo.2016.03.021
13. Warde P, Mason M, Ding K, et al. Combined androgen deprivation therapy and radiation therapy for locally advanced prostate cancer: a randomised, phase 3 trial. *Lancet*. 2011;378(9809):2104-2111. https://doi.org/10.1016/S0140-6736(11)61095-7
14. Mottet N, et al. EAU-EANM-ESTRO-ESUR-SIOG Guidelines on Prostate Cancer. 2019; https://uroweb.org/wp-content/uploads/EAU-Pocket-Guidelines-Prostate-Cancer-2019.pdf. Accessed November, 2019.
15. Network NCC. NCCN Clinical Practice Guidelines in Oncology - Prostate Cancer Version 4.2019. 2019; https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf. Accessed November, 2019.
16. European Society for Medical Oncology. eUpdate - Prostate Cancer Algorithms. 2016; https://www.esmo.org/Guidelines/Genitourinary-Cancers/Cancer-of-the-Prostate/eUpdate-Treatment-Algorithms. Accessed November, 2019.
17. Association AU. Clinically Localized Prostate Cancer: AUA/ASTRO/SUO Guideline (2017). 2017; https://www.auanet.org/guidelines/prostate-cancer-clinically-localized-guideline. Accessed November, 2019.

18. Horwich A, Hugosson J, de Reijke T, et al. Prostate cancer: ESMO Consensus Conference Guidelines 2012. *Ann Oncol*. 2013;24(5):1141-1162. https://doi.org/10.1093/annonc/mds624
19. Mandel P, Chandrasekar T, Chun FK, Huland H, Tilki D. Radical prostatectomy in patients aged 75 years or older: review of the literature. *Asian J Androl*. 2019;21(1):32. https://doi.org/10.4103/aja.aja_43_17
20. Rider JR, Sandin F, Andren O, Wiklund P, Hugosson J, Stattin P. Long-term outcomes among noncuratively treated men according to prostate cancer risk category in a nationwide, population-based study. *Eur Urol*. 2013;63(1):88-96. https://doi.org/10.1016/j.eururo.2012.08.001
21. Albertsen PC, Hanley JA, Fine J. 20-year outcomes following conservative management of clinically localized prostate cancer. *JAMA*. 2005;293(17):2095-2101. https://doi.org/10.1001/jama.293.17.2095
22. Bechis SK, Carroll PR, Cooperberg MR. Impact of age at diagnosis on prostate cancer treatment and survival. *J Clin Oncol*. 2011;29(2):235-241. https://doi.org/10.1200/JCO.2010.30.2075
23. de Camargo CM, Comber H, Sharp L. Age remains the major predictor of curative treatment non-receipt for localised prostate cancer: a population-based study. *Br J Cancer*. 2013;109(1):272-279. https://doi.org/10.1038/bjc.2013.268
24. Droz J-P, Albrand G, Gillessen S, et al. Management of prostate cancer in elderly patients: recommendations of a task force of the international society of geriatric oncology. *Eur Urol*. 2017;72(4):521-531. https://doi.org/10.1016/j.eururo.2016.12.025
25. Hamilton AS, Fleming ST, Wang D, et al. Clinical and demographic factors associated with receipt of non guideline-concordant initial therapy for nonmetastatic prostate cancer. *Am J Clin Oncol*. 2016;39(1):55-63. https://doi.org/10.1097/COC.0000000000000017
26. Bratt O, Folkvaljon Y, Hjälm Eriksson M, et al. Undertreatment of men in their seventies with high-risk nonmetastatic prostate cancer. *Eur Urol*. 2015;68(1):53-58. https://doi.org/10.1016/j.eururo.2014.12.026
27. Loffeler S, Halland A, Fawad H, Beisland C, Haug ES. Non-metastatic prostate cancer: rationale for conservative treatment and impact on disease-related morbidity and mortality in the elderly. *Scand J Urol*. 2020;54(2):105-109. https://doi.org/10.1080/21681805.2020.1732463
28. Hernes E, Kyrdalen A, Kvåle R, et al. Initial management of prostate cancer: first year experience with the Norwegian National Prostate Cancer Registry. *BJU Int*. 2010;105(6): 805-811. https://doi.org/10.1111/j.1464-410X.2009.08834.x
29. Mottet N, Bellmunt J, Bolla M, et al. Guidelines on prostate cancer. Part 1: screening, diagnosis, and local treatment with curative intent. *Eur Urol*. 2017;71(4):618-629. https://doi.org/10.1016/j.eururo.2016.08.003
30. Eurostat. Life expectancy at birth 1980–2017 (years). 2019; Available at: https://ec.europa.eu/eurostat/statistics-explained/index.php?title=File:Life_expectancy_at_birth,1980-2017_(years).png#file, 2020.
31. Pompe RS, Davis-Bondarenko H, Zaffuto E, et al. Population-based validation of the 2014 ISUP gleason grade groups in patients treated with radical prostatectomy, brachytherapy, external beam radiation, or no local treatment. *Prostate*. 2017;77(6):686-693.
32. Bill-Axelson A, Holmberg L, Garmo H, et al. Radical prostatectomy or watchful waiting in early prostate cancer. *N Engl J Med*. 2014;370(10):932-942. https://doi.org/10.1056/NEJMoa1311593
33. Bandini M, Pompe RS, Marchioni M, et al. Radical prostatectomy or radiotherapy reduce prostate cancer mortality in elderly patients: a population-based propensity score adjusted analysis. *World J Urol*. 2018;36(1):7-13. https://doi.org/10.1007/s00345-017-2102-9
34. Sheng W, Kirschner-Hermanns R, Zhang H. Elderly patients aged >/= 75 years with locally advanced prostate cancer may benefit from local treatment: a population-based propensity score-adjusted analysis. *World J Urol*. 2019;37(2):317-325. https://doi.org/10.1007/s00345-018-2389-1
35. Cancer Registry of Norway. Cancer in Norway 2018 - Cancer incidence, mortality, survival and prevalence in Norway. 2019.
36. Aas K, Axcrona K, Kvåle R, et al. Ten-year mortality in men with nonmetastatic prostate cancer in Norway. *Urology*. 2017;110:140-147. https://doi.org/10.1016/j.urology.2017.07.048
37. Salinas CA, Tsodikov A, Ishak-Howard M, Cooney KA. Prostate cancer in young men: an important clinical entity. *Nat Rev Urol*. 2014;11(6):317-323. https://doi.org/10.1038/nrurol.2014.91
38. Harman SM, Metter EJ, Tobin JD, Pearson J, Blackman MR. Baltimore longitudinal study of A. Longitudinal effects of aging on serum total and free testosterone levels in healthy men. Baltimore Longitudinal Study of Aging. *J Clin Endocrinol Metab*. 2001;86(2):724-731. https://doi.org/10.1210/jcem.86.2.7219
39. Hamstra DA, Bae K, Pilepich MV, et al. Older age predicts decreased metastasis and prostate cancer-specific death for men treated with radiation therapy: meta-analysis of radiation therapy oncology group trials. *Int J Radiat Oncol Biol Phys*. 2011;81(5):1293-1301. https://doi.org/10.1016/j.ijrobp.2010.07.2004
40. Chen RC, Carpenter WR, Hendrix LH, et al. Receipt of guideline-concordant treatment in elderly prostate cancer patients. *Int J Radiat Oncol Biol Phys*. 2014;88(2):332-338. https://doi.org/10.1016/j.ijrobp.2013.11.004
41. Preisser F, Mazzone E, Nazzani S, et al. Impact of age on perioperative outcomes at radical prostatectomy: a population-based study. *Eur Urol Focus*. 2018. https://doi.org/10.1016/j.euf.2018.12.006
42. Mandel P, Graefen M, Michl U, Huland H, Tilki D. The effect of age on functional outcomes after radical prostatectomy. *Urol Oncol*. 2015;33(5):203.e11-203.e18. https://doi.org/10.1016/j.urolonc.2015.01.015
43. Hampson LA, Cowan JE, Zhao S, Carroll PR, Cooperberg MR. Impact of age on quality-of-life outcomes after treatment for localized prostate cancer. *Eur Urol*. 2015;68(3):480-486. https://doi.org/10.1016/j.eururo.2015.01.008
44. Payne HA, Hughes S. Radical radiotherapy for high-risk prostate cancer in older men. *Oncologist*. 2012;17(Suppl 1):9-15. https://doi.org/10.1634/theoncologist.2012-S1-09
45. Fall K, Stromberg F, Rosell J, Andren O, Varenhorst E. South-East Region Prostate Cancer G. Reliability of death certificates in prostate cancer patients. *Scand J Urol Nephrol*. 2008;42(4):352-357. https://doi.org/10.1080/00365590802078583
46. Loffeler S, Halland A, Weedon-Fekjaer H, Nikitenko A, Ellingsen CL, Haug ES. High Norwegian prostate cancer mortality: evidence of over-reporting. *Scand J Urol*. 2018;52(2):122-128. https://doi.org/10.1080/21681805.2017.1421260
47. Skyrud KD, Bray F, Moller B. A comparison of relative and cause-specific survival by cancer site, age and time since diagnosis. *Int J Cancer*. 2014;135(1):196-203. https://doi.org/10.1002/ijc.28645

48. Nguyen-Nielsen M, Moller H, Tjonneland A, Borre M. Causes of death in men with prostate cancer: Results from the Danish Prostate Cancer Registry (DAPROCAdata). *Cancer Epidemiol*. 2019;59:249-257. https://doi.org/10.1016/j.canep.2019.02.017

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Aas K, Dorothea Fosså S, Åge Myklebust T, et al. Increased curative treatment is associated with decreased prostate cancer-specific and overall mortality in senior adults with high-risk prostate cancer; results from a national registry-based cohort study. *Cancer Med*. 2020;00:1–12. https://doi.org/10.1002/cam4.3297

Table S1: Characteristics of patients diagnosed with high-risk prostate cancer in Norway 2005-16

Diagnosis period	2005-08			2009-12			2013-16			All periods		
Age group (years)	**<70**	**≥70**	**All**	**<70**	**≥70**	**All**	**<70**	**≥70**	**All**	**<70**	**≥70**	**All**
Number of patients	2677 (43)	3591 (57)	6268	3052 (47)	3477 (53)	6529	3352 (48)	3614 (52)	6966	9081 (46)	10682 (54)	19763
ECOG												
0	2095 (78)	1561 (44)	3656 (58)	2145 (70)	1436 (41)	3581 (55)	2313 (69)	1620 (45)	3933 (57)	6553 (72)	4617 (43)	11170 (57)
1	284 (11)	1000 (28)	1284 (21)	317 (10)	900 (26)	1217 (19)	283 (8)	727 (20)	1010 (15)	884 (10)	2627 (25)	3511 (18)
≥2	104(4)	774 (22))	878 (14)	114 (4)	638 (18))	752 (12)	82 (2)	410 (11)	492 (7)	300 (3)	1822 (17)	2122 (11)
Missing	194 (7)	256 (7)	450 (7)	476 (16)	503 (15)	979 (15)	674 (20)	857 (24)	1531 (22)	1344 (15)	1616 (15)	2960 (15)
Prior cancer												
No	2519 (94)	3169 (88)	5688 (91)	2835 (93)	3019 (87)	5854 (90)	3137 (94)	3085 (85)	6222 (89)	8491 (94)	9273 (87)	17764 (90)
Yes	158 (6)	422 (12)	580 (9)	217 (7)	458 (13)	675 (10)	215 (6)	529 (15)	744 (11)	590 (7)	1409 (13)	1999 (10)
PSA (ng/mL)												
<10	845 (32)	527 (15)	1372 (22)	1142 (37)	681 (20)	1823 (28)	1634 (49)	1015 (28)	2649 (38)	3621 (40)	2223 (21)	5844 (30)
10-20	671 (25)	790 (22)	1461 (23)	729 (24)	878 (25)	1607 (25)	656 (20)	888 (25)	1544 (22)	2056 (23)	2556 (24)	4612 (23)
>20	1053 (39)	2131 (59)	3184 (51)	936 (31)	1619 (47)	2555 (39)	700 (21)	1122 (31)	1822 (26)	2689 (30)	4872 (46)	7561 (38)
Missing	108 (4)	143 (4)	251 (4)	245 (8)	299 (9)	544 (8)	362 (11)	589 (16)	951 (14)	715 (8)	1031 (10)	1746 (9)
ISUP grade group												
1	616 (23)	546 (15)	1162 (19)	371 (12)	334 (10)	705 (11)	331 (10)	218 (6)	549 (8)	1318 (15)	1098 (10)	2416 (12)
2	566 (21)	803 (22)	1498 (24)	682 (22)	539 (16)	1221 (19)	741 (22)	487 (14)	128 (18)	2118 (23)	1829 (17)	3947 (20)
3	695 (26)	551 (15)	960 (15)	498 (16)	541 (16)	1039 (16)	516 (15)	530 (15)	1046 (15)	1423 (16)	1622 (15)	3045 (15)
4	409 (15)	918 (26)	1497 (34)	963 (32)	1185 (34)	2148 (33)	1053 (31)	1249 (35)	2302 (33)	2595 (29)	3352 (31)	5947 (30)
5	579 (22)	614 (17)	884 (14)	496 (16)	802 (23)	1298 (20)	686 (21)	1078 (30)	1764 (25)	1452 (16)	2494 (23)	3946 (20)
Missing	270 (10)	159 (4)	267 (4)	42 (1)	76 (2)	118 (2)	25 (<1)	52 (1)	77 (1)	175 (2)	287 (3)	462 (2)
cT-category												
1-2	1190 (45)	1440 (40)	2630 (42)	1644 (54)	1675 (48)	3319 (51)	1691 (50)	1477 (41)	3168 (46)	4525 (50)	4592 (43)	9117 (46)
3-4	1419 (53)	1934 (54)	3353 (54)	1174 (39)	1493 (43)	2667 (41)	1293 (39)	1542 (43)	2835 (41)	3886 (43)	4969 (47)	8855 (45)
Missing	68 (3)	217 (6)	285 (5)	234 (8)	309 (9)	543 (8)	368 (11)	595 (17)	963 (14)	670 (7)	1121 (11)	1791 (9)

Abbreviations: cT-category: clinical tumor-category; ECOG: Eastern Cooperative Oncology Group functional status; ISUP grade group: International Society of Urological Pathology grade group; PSA: prostate specific antigen

Table S2: Characteristics of patients with high-risk disease according to primary treatment and diagnostic period

	CurTrt			NoCurTrt		
Diagnostic period	**2005-08**	**2009-12**	**2013-16**	**2005-08**	**2009-12**	**2013-16**
Number of patients	2277	3644	4545	3991	2885	2421
Age (years)						
Median (range)	65 (42-84)	67 (45-86)	68 (40-87)	76 (44-100)	78 (46-98)	77 (40-96)
<70	1727 (76)[a]	2455 (67)	2714 (60)	950 (24)	597 (21)	638 (26)
>70	550 (24)	1189 (33)	1831 (40)	3041 (76)	2288 (79)	1783 (74)
ECOG						
0	1799 (79)	2530 (69)	2997 (66)	1857 (47)	1051 (36)	936 (39)
1	256 (11)	474 (13)	530 (12)	1028 (26)	743 (26)	480 (20)
≥2	61 (3)	94 (3)	118 (3)	817 (21)	658 (23)	374 (15)
Missing	161 (7)	546 (15)	900 (20)	289 (7)	433 (15)	631 (26)
Prior cancer						
Yes	130 (6)	262 (7)	383 (8)	450 (11)	413 (14)	361 (15)
No	2147 (94)	3382 (93)	4162 (92)	3541 (89)	2472 (86)	2060 (85)
PSA (ng/mL)						
Median (range)	13 (0-100)	13 (1-100)	10 (1-100)	26 (0-100)	23 (0-100)	17 (1-100)
<10	809 (36)	1342 (37)	2021 (45)	563 (14)	481 (17)	628 (26)
10-20	676 (30)	967 (27)	1093 (24)	785 (20)	640 (22)	451 (19)
>20	702 (31)	1059 (29)	944 (21)	2482 (62)	1496 (52)	878 (36)
Missing	90 (4)	276 (8)	487 (11)	161 (4)	268 (9)	464 (19)
ISUP grade group						
1	504 (22)	342 (9)	245 (5)	658 (17)	363 (13)	304 (13)
2	636 (28)	817 (22)	889 (20)	862 (22)	404 (14)	339 (14)
3	340 (15)	612 (17)	750 (17)	620 (16)	427 (15)	296 (12)
4-5	711 (31)	1841 (51)	2636 (58)	1670 (42)	1605 (56)	1430 (59)
Missing	86 (4)	32 (1)	25 (1)	181 (5)	86 (3)	52 (2)
cT-category						
1-2	1065 (47)	1988 (55)	2154 (47)	1565 (39)	1331 (46)	1014 (42)
3-4	1171 (51)	1391 (38)	1892 (42)	2182 (55)	1276 (44)	943 (39)
Missing	41 (2)	265 (7)	499 (11)	244 (6)	278 (10)	464 (19)

Abbreviations: CurTrt: curative treatment; ECOG: Eastern Cooperative Oncology Group functional status; ISUP grade group: International Society of Urological Pathology grade group; NoCurTrt: no curative treatment; PSA: prostate specific antigen; cT-category: clinical T-category

[a] Number of patients (% within treatment group and diagnostic period)

Table S3: Multivariable Cox regression with prostate cancer-specific mortality as dependent variable in patients with high-risk prostate cancer

Age (years)	<70			≥70		
Patients analyzed (n)	7567			8563		
	Hazard ratio	**95% CI**	**p-value**	**Hazard ratio**	**95% CI**	**p-value**
Diagnostic period						
2005-08	1			1		
2009-12	0.80	0.63-1.01	0.063	0.78	0.69-0.88	0.000
2013-16	0.75	0.50-1.12	0.157	0.66	0.54-0.82	0.000
Treatment						
RP	1			1		
RAD	1.03	0.76-1.41	0.838	0.82	0.48-1.41	0.467
NoCurTrt	3.41	2.57-4.52	0.000	3.71	2.23-6.17	0.000
Age						
<60	1					
60-64	0.94	0.73-1.22	0.657			
65-69	0.97	0.76-1.25	0.838			
70-74				1		
75-79				1.16	1.00-1.35	0.047
≥80				1.81	1.56-2.10	0.000
ECOG						
0	1			1		
1	1.59	1.24-2.03	0.000	1.20	1.06-1.36	0.004
≥2	1.00	0.66-1.51	0.998	1.41	1.23-1.62	0.000
PSA (ng/mL)						
<10	1			1		
10-20	1.14	0.87-1.50	0.332	1.09	0.91-1.30	0.356
>20	1.55	1.21-1.97	0.000	1.37	1.17-1.60	0.000
ISUP grade group						
1	1			1		
2	2.60	1.60-4.21	0.000	1.24	0.98-1.56	0.070
3	3.76	2.31-6.13	0.000	1.72	1.37-2.17	0.000
4	5.83	3.70-9.17	0.000	2.34	1.89-2.88	0.000
5	14.01	8.90-22.04	0.000	4.13	3.34-5.10	0.000
cT-category						
1-2	1			1		
3-4	1.43	1.17-1.75	0.000	1.36	1.22-1.51	0.000

Abbreviations: CI: confidence interval; cT-category: clinical T-category; ECOG: Eastern Cooperative Oncology Group functional status; ISUP grade group: International Society of Urological Pathology grade group; n: number; NoCurTrt: no curative treatment; PSA: prostate specific antigen; RAD: radiotherapy; RP: radical prostatectomy

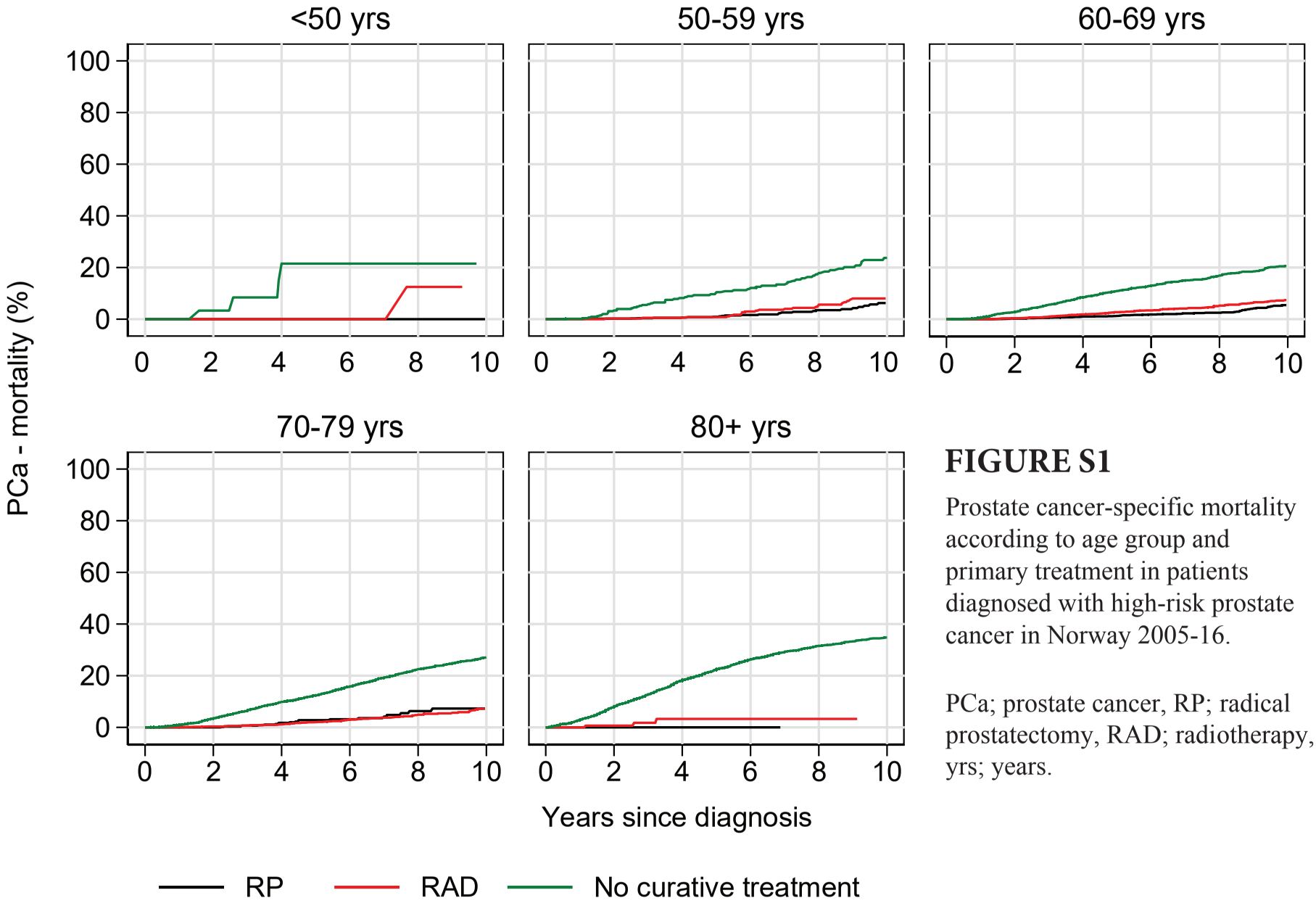
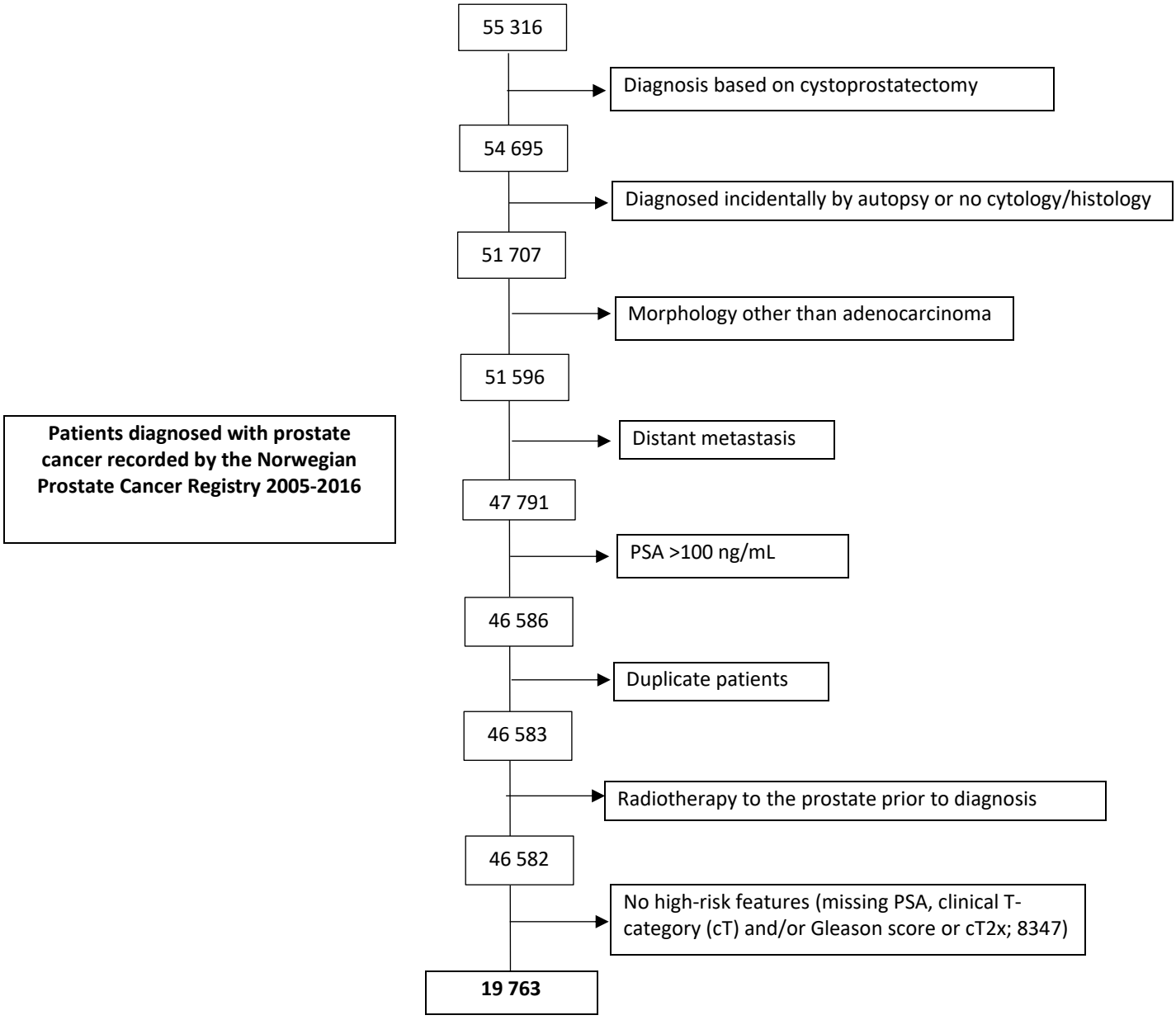


FIGURE S1

Prostate cancer-specific mortality according to age group and primary treatment in patients diagnosed with high-risk prostate cancer in Norway 2005-16.

PCa; prostate cancer, RP; radical prostatectomy, RAD; radiotherapy, yrs; years.

Appendix 1: Patient cohort



Appendix 2: Patients with high-risk disease among all men diagnosed with prostate cancer without distant metastasis in Norway 2005-16

Diagnostic period	2005-08		2009-12		2013-16		All periods	
Risk group	**High-risk**	**All**	**High-risk**	**All**	**High-risk**	**All**	**High-risk**	**All**
	6268 (47)[a]	13341	6529 (42)	15718	6966 (40)	17523	19763 (42)	46582
Age group								
<70	2677 (37)[b]	7149	3052 (33)	9310	3352 (33)	10168	9081 (34)	26627
70-74	1159 (49)	2348	1238 (45)	2772	1439 (41)	3478	3836 (45)	8598
75-79	1164 (59)	1959	1032(55)	1866	1100 (50)	2185	3296 (55)	6010
≥80	1268 (67)	1885	1207 (68)	1770	1075 (64)	1692	3550 (66)	5347

[a] Number of patients (% within diagnostic period)
[b] Number of patients (% within diagnostic period and age group)

VITENSKAPELIG SAMMENDRAG

Prostatakreft er den hyppigst forekomne kreftformen blant menn i Norge. De fleste (>90%) av pasientene har ikke fjernspredning på diagnosetidspunktet og kan være kandidater for kurativ behandling med radikal prostatektomi (RP) eller strålebehandling (RAD), hos enkelte etterfulgt av en periode med aktiv overvåkning.

1) *Bakgrunn/mål første artikkel:* Pasienter med prostatakreft uten fjernspredning har generelt høy langtidsoverlevelse. For å vurdere eventuell overlevelsesgevinst av kurativ behandling, er det ofte nødvendig med lang observasjonstid. Ikke tidligere dokumentert i Norge, ønsket vi i en vitenskapelig populasjonsbasert studie å undersøke ti-års prostatakreft-spesifikk og total dødelighet hos norske pasienter diagnostisert med prostatakreft uten fjernspredning, inndelt etter risikogruppe og primærbehandling. Vi ønsket videre å undersøke den prognostiske betydningen av kliniske variabler tilgjengelig på diagnosetidspunktet.
2) *Bakgrunn/mål andre artikkel:* Ifølge Pakkeforløp for prostatakreft som ble innført av norske helsemyndigheter i 2015, skal pasienter opereres innen 32 dager fra beslutning om RP. Det finnes i dag ikke evidens for at RP innen angitt forløpstid øker overlevelsen. Vi ønsket derfor å undersøke sammenhengen mellom tid fra diagnose til RP og primært prostatakreft-spesifikk dødelighet og sekundært ugunstige histopatologiske funn i operasjonspreparatet og bruk av post-operativ bekken- eller mamille-bestråling, sistnevnte en indikator for oppstart av antiandrogen behandling.
3) *Bakgrunn/mål tredje artikkel:* Antall eldre menn (≥70 år) som diagnostiseres med prostatakreft øker. Sammenliknet med yngre menn (<70 år), har eldre pasienter mer ugunstige sykdomsparametere samtidig som de har mer komorbiditet og kortere forventet gjenstående levetid. Det finnes i dag lite evidens for overlevelsesgevinst av kurativ behandling og ingen konsensus for optimal behandling av eldre menn med høy-risiko prostatakreft. Med denne bakgrunnen ønsket vi å sammenlikne kliniske variabler relatert til pasient og kreftsykdom, primærbehandling og prostatakreft-spesifikk dødelighet hos eldre menn sammenliknet med yngre pasienter og undersøke sammenhengen mellom kurativ behandling og dødelighet i begge aldersgruppene.

I prosjektet brukte vi data fra Kreftregisteret, inkludert data fra Nasjonalt kvalitetsregister for prostatakreft og Stråledatabasen, som omfattet menn diagnostisert med prostatakreft uten fjernspredning i Norge 2001-2016. Pasientene ble stratifisert for risikogruppe og primærbehandling (kurativ behandling; RP eller RAD versus ingen kurativ behandling). Aalen-Johansen metoden beregnet prostatakreft-spesifikk dødelighet og sannsynlighet for postoperativ strålebehandling og

Kaplan Meier metoden beregnet total dødelighet. Regresjonsanalyser undersøkte sammenhengen mellom primærbehandling og kliniske variabler ved diagnosetidspunkt og dødelighet.

1) *Resultater første artikkel:* For 3449 pasienter diagnostisert med prostatakreft uten fjernmetastaser i 2004-2005 var ti-års prostatakreft-spesifikk dødelighet 8,5% og total dødelighet 25,5%. For pasienter med lav-risiko prostatakreft var total dødeligheten åtte ganger høyere enn prostatakreft-spesifikk dødelighet, tilsvarende faktor var to for pasienter med høy-risiko pasienter. Kurativ behandling reduserte prostatakreftspesifikk dødelighet, mest hos pasienter med høy-risiko sykdom. Pasienten funksjonsstatus og kreftens lokale utbredelse, aggressivitet (Gleason score) og risikogruppe var assosiert med ti-års dødeligheten.
2) *Resultater andre artikkel:* Etter åtte års median oppfølging av 5163 pasienter operert med RP i perioden 2001-2010, hvorav 28.8% hadde høy-risiko sykdom, fant vi at økende tidsintervall opptil 180 dager fra diagnose til RP ikke økte sannsynligheten for prostatakreft-spesifikk dødelighet, ugunstige funn i operasjonspreparatet eller bruk av post-RP strålebehandling, uavhengig av risikogruppe.
3) *Resultater tredje artikkel:* Av totalt 19 763 pasienter diagnostisert med høy-risiko prostatakreft i Norge i perioden 2005-2016, var mer enn halvparten ≥70 år. Eldre pasienter hadde redusert funksjonsstatus og mer ugunstige kreftparametere (høyere PSA, mer aggressiv kreft og mer utbredt lokal sykdom) sammenliknet med yngre menn. Andelen pasienter som fikk kurativ behandling økte fra 15-51% hos pasienter ≥70 år og fra 65-81% hos yngre menn fra perioden 2005-2008 til 2013-2016. Med en median oppfølgingstid på fem år, var kurativ behandling assosiert med redusert prostatakreft-spesifikk og total dødelighet hos både eldre og yngre pasienter. Den kreftspesifikke dødeligheten sank med tiden, mest hos de eldre.

Total ti-års dødelighet var tre ganger så høy som prostatakreft-spesifikk dødelighet hos pasienter diagnostisert i med prostatakreft uten fjernspredning i 2004-2005, og pasienter med høy-risiko sykdom hadde størst overlevelsesgevinst av kurativ behandling. Gleason score var en viktig prognostisk faktor for PCSM. Pasienter og klinikere bør vite at økt tid fra diagnose til RP opptil seks måneder ikke forverrer prostatakreft-spesifikk overlevelse, heller ikke for høy-risiko pasienter. Økt prostatakreft-spesifikk og total overlevelse etter kurativ behandling ble også observert hos eldre pasienter med høy-risiko prostatakreft, som i økende grad bør vurderes for slik behandling.