Late-Stage Prostate Cancer and Prostate Cancer Mortality

A Population-Based Study

Sven Löffeler

Thesis for the degree of Philosophiae Doctor (PhD)
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Scientific environment

Most of the work in this thesis was conducted at the *Section of Urology, Vestfold Hospital Trust* in the period 2011 to 2019. Parts of the work were carried out in cooperation with the *Oslo Center for Biostatistics and Epidemiology*, Research Support Services, Oslo University Hospital, Oslo, Norway, the *Norwegian Cancer Registry*, Oslo, Norway and the *Cause of Death Registry*, Health Data and Digitalization, Norwegian Institute of Public Health, Bergen, Norway.
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Abstract

Aims

The aim of this thesis was to provide a better understanding of the final stages of PCa, metastatic castration resistant PCa and PCa death. We further aimed to address the consequences of possible undertreatment of elderly PCa patients.

Patients and Methods

Paper I: The study was a retrospective analysis of a consecutive sample of patients with mCRPC seen at the urological unit of a local hospital from 2000 to 2005, their mCRPC diagnosis based on rising prostate-specific antigen (PSA) during androgen depletion treatment (ADT). Several easily accessible parameters were identified and their prognostic value was tested.

Paper II: The study included all 764 patients from Vestfold County who had PCa and who died in 2009-2014. The true cause of death of all patients was evaluated based on patient medical records.

Paper III: Retrospective analysis of 117 patient records (PCa death, Vestfold County, M0 at diagnosis, no radical treatment). Decision rationales at diagnosis with regard to treatment were identified. Local and systemic complications during the further course of the disease were registered. National data from the Cancer Registry of Norway (CRN, N=1874, ≥75 years at diagnosis, localized high-risk/ locally advanced PCa, WHO 0, diagnosed 2009-2017) were obtained and PCa specific survival was analyzed in patients who had received local treatment versus patients with no local treatment.

Results

Paper I: Median overall survival for the entire cohort of mCRPC patients was 12.3 months (range 0.2-108 months), while 3-year survival was 16.9% (95% confidence interval 0.11-0.24). Two patients were alive at the end of follow-up. PSA doubling time following the onset of mCRPC, hemoglobin and alkaline phosphatase levels at

the onset of mCRPC and PSA nadir during ADT prior to the onset of mCRPC were strong predictors of overall survival.

Paper II: Over-reporting of PCa deaths in patients whose death certificate indicated that they died of PCa was 33% while under-reporting in the two groups who according to their death certificates died of other causes was 19% and 5%, respectively. The correlation between registered and observed causes of death was 0.81 (95% confidence interval 0.78-0.83). Misattribution of prostate cancer deaths increased significantly with patient age and decreasing Gleason score.

Paper III: For the cohort of Vestfold patients age was the reason for choosing conservative treatment in 37% of patients (N=43), despite good health and functional status. Ninety percent of patients developed local complications attributable to PCa growth. National CRN data suggested a significant survival benefit for patients aged 75-79 years who had received local treatment. 5-year cause-specific survival of 98.9 percent (CI 96.7-99.7) compared to 90.8 percent in patients who had received no local treatment (CI 86.9-93.6).

Conclusions

Late stage PCa (mCRPC) is a heterogeneous condition with diverse survival. Its natural course can be defined by easily accessible parameters.

PCa death reported on death certificates is unreliable particularly among the elderly and it is unsuitable as a stand-alone, population-based outcome measure in Norway.

There are indications of undertreatment at diagnosis both in patients who later develop late-stage PCa and in patients who die of PCa and decisions with regard to radical treatment for patients with NMPCa are unduly influenced by patient age. The majority of elderly patients with high risk or locally advanced NMPCa who are not treated with local therapy suffer considerable local complications

List of Publications

I. Löffeler S, Weedon-Fekjaer H, Wang-Hansen MS, Sebakk K, Hamre H, Haug ES, Fosså SD. "Natural course" of disease in patients with metastatic castrate-resistant prostate cancer: Survival and prognostic factors without life-prolonging treatment. Scandinavian Journal of Urology. 2015. 49(6):440-445

II. Löffeler S, Halland A, Weedon-Fekjær H, Nikitenko A, Ellingsen CL, Haug ES. High Norwegian prostate cancer mortality: evidence of over-reporting. Scandinavian Journal of Urology. 2018. 52(2):122-128

III. Löffeler S, Fawad H, Halland A, Beisland C, Haug ES. Non-metastatic prostate cancer: Rationale for conservative treatment and impact on disease related morbidity and mortality in the elderly. 2019. Article submitted for review

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Abbreviations

ADT	Androgen deprivation therapy
BCR	Biochemical recurrence
CAPRA	Cancer of the Prostate Risk Assessment
CRN	Cancer Registry of Norway
cT	Clinical T-stage
DRE	Digital rectal examination
EAU	European Association of Urology
ERSPC	European Randomised Study of Screening for Prostate Cancer
LHRH	Luteinizing hormone-releasing hormone
LN	Lymph node
mCRPC	Metastatic, castration-resistant prostate cancer
MP-MRI	Multi-parametric magnetic resonance imaging
MSKCC	Memorial Sloan Kettering Cancer Centre
NMPCa	Non-metastatic prostate cancer
NoTreat/Age	Patient group who did not receive curative treatment due to age (paper III)
NoTreat/Other	Patient group who did not receive curative treatment due to other reasons (paper III)
OM	Overall mortality
PCa	Prostate cancer
PCSM	Prostate cancer specific mortality
PI-RADS v2	**P**rostate **I**maging - **R**eporting **a**nd **D**ata **S**ystem Version 2
PIVOT	**P**rostate cancer **I**ntervention **V**ersus **O**bservation **T**rial
PLCO	**P**rostate**, L**ung, **C**olon, **O**vary (cancer screening trial)
PLND	Pelvic lymph node dissection
PRECISION	**PR**ostate **E**valuation for **C**linically **I**mportant Disease: **S**ampling Using **I**mage-guidance **O**r **N**ot trial
PROMIS	**Pro**state **M**RI **I**maging **S**tudy
ProtecT	**Pro**state **Te**sting for **C**ancer and **T**reatment

PSA	Prostate-specific antigen
RARP	Robot-assisted radical prostatectomy
REK	Regional Committee for Medical and Health Research Ethics
RP	Radical prostatectomy
RT	Radiotherapy
SOC	Standard of care
TNM	Tumour Node Metastasis (classification system)
TRUS	Transrectal ultrasound
US	Ultrasound
USPSTF	US Preventive Services Task Force
WW	Watchful waiting

1. Introduction

Historically, the prospects for patients diagnosed with prostate cancer (PCa) were grim. In a 1933 article Benjamin Stockwell Barringer -the first chief of urology at Memorial Hospital in New York City- lamented: "*There is a peculiar fascination in backing lost causes. The reason for this is that medical science considers no cause wholly and irrevocably lost; it believes that there is no disease that which sooner or later may not be controlled. Prostatic carcinoma is today fairly firmly established in the lost-cause column.*" He reported on 241 consecutive patients, 221 of whom had advanced or metastatic disease at diagnosis. Only 20 (8%) were deemed to have early stage PCa, meaning limited to the prostate gland or "prostate region" (1). This unsatisfactory state of affairs was also reflected in the scientific and clinical work of Hugh H. Young (head of urology at Johns Hopkins Brady Urological Institute from 1897-1940), an early proponent of radical perineal prostatectomy, a procedure he had developed and published on for the first time in 1905 (2). In 1932, he summarized his experience: Over a period of twenty years, he had operated on just 42 patients, which implies that on average only two patients a year had had sufficiently localised tumours to warrant the procedure. Perioperative mortality was about ten percent in this series prior to the advent of antibiotics and proper aseptic procedures (3).

Without effective treatment options such as hormone therapy, patients diagnosed with PCa usually died of the disease with an average survival of just 30 months (4).

The suffering of these early patients and the often-forlorn efforts of the pioneers of PCa treatment have been motivation and warning for generations of urologists and oncologists. The prospects of the "lost cause"-patients have improved considerably, but for many patients the disease still carries great suffering and the outcome remains often fatal.

The following pages contain a short summary of the current state of practice before moving on to attempting to address a few questions that remain unanswered.

1.1 Epidemiology

1.1.1 Incidence and prevalence

PCa is the second-most common cancer worldwide and by far the most common cancer in the developed world. Estimated incidence rates worldwide are increasing, from an estimated 900 000 new cases in 2008 (5) to 1.1 million in 2012 (6). More than two-thirds of these new cases (N~760 000) were diagnosed in developed countries where just 17 percent of the world male population live. There is a broad consensus that changes in diagnostic practices, namely the introduction of PSA testing, have been a major cause of rising PCa incidence in the developed world (7). Countries with a PSA screening program, such as the United States and Canada, observed a PCa incidence peak in the first half of the 1990s followed by a sharp decline, while PCa incidence in other Western countries that adopted PSA screening more gradually appear to be rising still and no incidence peak has been observed yet (6).

In Norway, PCa is the most common form of cancer among men, with approximately 5000 new cases every year between 2011 and 2017. PCa incidence has risen considerably from 3848 cases in 2004 to the peak incidence year of 2016, when the *Cancer Registry of Norway* (CRN) reported 5253 new cases. The sharpest increase in PCa incidence in Norway was observed in 2011 when more than 700 extra cases were diagnosed compared to 2010 (8). Every year considerably more men are diagnosed with PCa than die of PCa. Consequently, prevalence numbers for PCa have more than doubled during the last one and a half decades: In 2004 just over 20 000 men lived with PCa in Norway. By 2017, this number had increased to 49 000 (8).

1.1.2 Mortality and survival

PCa was the fifth leading cause of cancer death worldwide with an estimated 300 000 fatalities in 2012. Approximately half of the PCa deaths occurred in developed countries (N~140 000). The highest mortality rates were reported in the Caribbean and sub-Saharan Africa (6). The published data suggest a slight increase in PCa deaths worldwide since 2008 when an estimated 260 000 PCa deaths occurred. This

development was driven exclusively by increasing PCa deaths in non-industrialised countries. In the developed world, PCa deaths have been either stable or decreasing (5).

In Norway, *absolute* numbers of PCa deaths have been relatively stable during the last 15 years (8): The number of PCa deaths reported in 2004 was 1026 and 934 in 2016. Most developed countries report similar findings. The reported decrease in PCa mortality of 2-4 percent annually for Norway and other developed countries during the last 10-15 years thus refer to *age-adjusted mortality rates*, rather than absolute PCa mortality (7). In the United States, the annual reduction in age-adjusted PCa mortality has recently flattened out (9).

Relative survival is defined as the ratio of the proportion of observed survivors in a cohort of cancer patients to the proportion of expected survivors in a comparable set of cancer free individuals. Relative survival rates have improved significantly for PCa. In Norway for the period 1978-1982, the five-year relative survival for all PCa patients was less than sixty percent. These numbers had improved with more than fifty percent during 2013-2017 (five-year relative survival 94%) (10). There are some caveats related to survival in PCa that will be discussed later (see chapter 1.6)

1.1.3 Age

While patient age at diagnosis in Norway was stable for the time period 1983-1997 (median age 74 years), it has since dropped considerably with a median age of 69 years during the latest observational period (2013-2017) (10). However, this is not an expression of a true age shift nor the manifestation of a more aggressive behaviour of PCa, but rather the result of commonplace screening for early PCa of asymptomatic men. In the United States, where an organised screening program has been in place for more than two decades, the average age at diagnosis is 66 years (11). Figure 1 illustrates the incidence of PCa per age group in Norway in 2017.

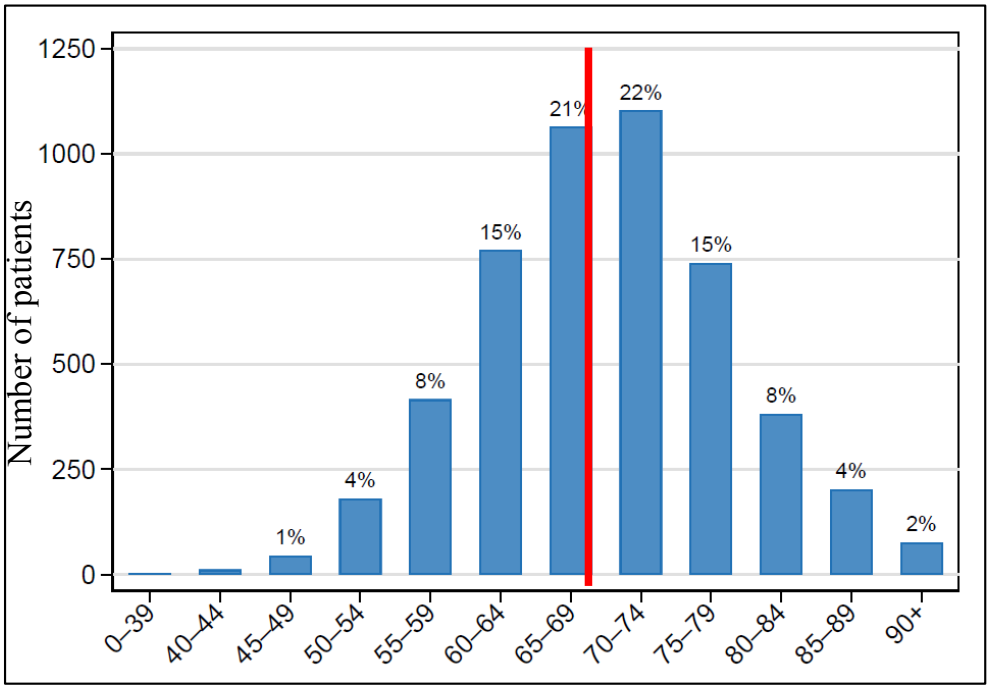

Figure 1: Incidence of PCa in Norway in 2017 per age group. The red line indicates the median age of 69 years.
Source: Cancer Registry of Norway. Adapted and modified from the annual report of the Norwegian quality register for PCa (2017)

In contrast to patient *age at diagnosis*, *age at death* has been rather unchanged over time and unaffected by screening. With a median age of 82 years at death, PCa as a cause of death in Norway affects mostly elderly men. The same holds true for other developed countries: In the United States, more than 70 percent of PCa deaths occur in men older than 75 years of age (11). Figure 2 illustrates the age of patients at death in Norway in 2017.

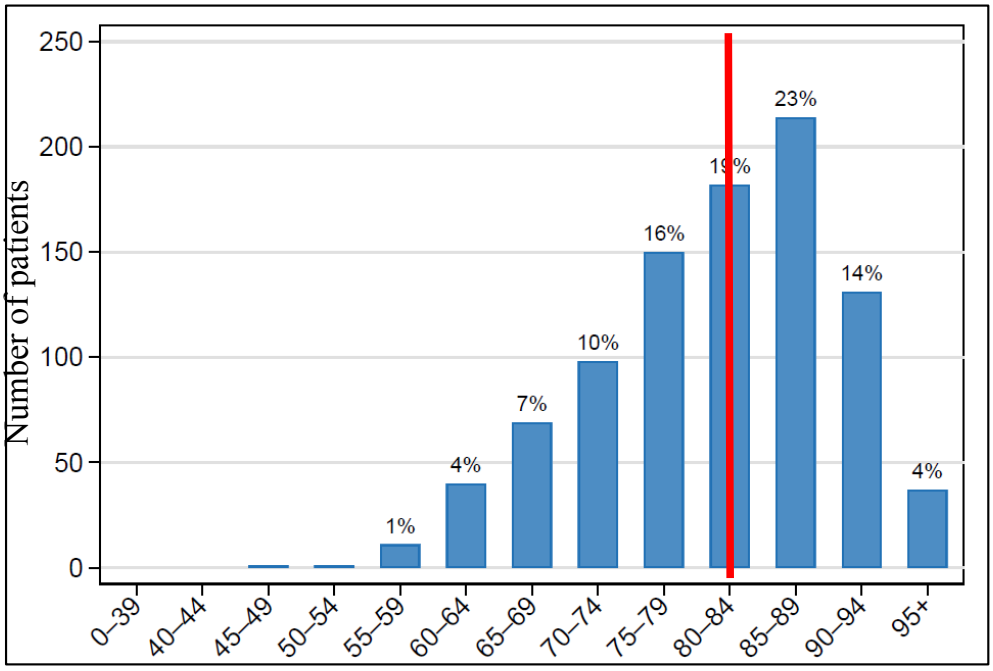

Figure 2: PCa deaths in Norway in 2017 per age group. The red line indicates the median age of 82 years. Source: Cancer Registry of Norway. Adapted and modified from the annual report of the Norwegian quality register for PCa (2017)

1.2 Staging, grading and classification

The heterogeneous nature of PCa and the need to better define the potential risk of individual tumours inspired Donald Gleason to design the histological grading that bears his name (12). For the clinician, the problem was described by Willet Whitmore in his *Cancer* paper from 1973: "*Clinical judgment involves selecting the appropriate treatment . . . in the individual patient. Only with better methods for defining the natural history of the particular tumor, more sophisticated means for anticipating the life expectancy of the individual host, and good data on the effects of various treatments. . . will it be possible to inject more science into the extant art of treatment of the prostatic cancer patient . . . ".* (13)

The decades that have passed since, have brought better staging, grading and risk-classification systems to aid the clinician with the task of finding the appropriate treatment for the individual patient.

1.2.1 Staging of prostate cancer

As is the case for most cancers, PCa is staged using the **T**umor **N**ode **M**etastasis (TNM) classification by either the International Union Against Cancer (UICC) (14) or the American Joint Commission on Cancer (AJCC) (15). Originally, both classifications described exclusively the anatomical extension of PCa. In its 2016 edition, the AJCC has introduced prognostic stage groups that incorporate non-anatomic parameters, such as PSA and tumor grade (16). The EAU refers to the UICC TNM classification in its guidelines on PCa (17). The current criteria and definitions of the UICC clinical TNM classification are listed in table 1.

T categorization

In contrast to EAU risk classification, in the UICC classification, clinical staging of the primary tumor (cT) includes only findings from digital, rectal examination of the prostate (DRE). Information from imaging studies (e.g. capsular infiltration/ penetration) and from biopsies (e.g. tumor localization) should not be taken into account for cT categorization of PCa (16). It is likely that particularly MRI imaging will eventually improve cT staging of PCa, but due to a number of unresolved issues and somewhat conflicting and contradictory findings in clinical trials, imaging has not been incorporated into cT categorization of PCa yet (18).

Table 1: Categories and definitions of the UICC clinical TNM staging system.
Source: Reproduced from the EAU guidelines on prostate cancer (17)

T - Primary Tumour	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Clinically inapparent tumor that is not palpable
	T1a Tumor incidental histological finding in 5% or less of tissue resected
	T1b Tumor incidental histological finding in more than 5% of tissue resected
	T1c Tumor identified by needle biopsy (e.g. because of elevated prostate-specific antigen [PSA])
T2	Tumor that is palpable and confined within the prostate
	T2a Tumor involves one half of one lobe or less
	T2b Tumor involves more than half of one lobe, but not both lobes
	T2c Tumor involves both lobes
T3	Tumor extends through the prostatic capsule*
	T3a Extracapsular extension (unilateral or bilateral) including microscopic bladder neck involvement
	T3b Tumor invades seminal vesicle(s)
T4	Tumor is fixed or invades adjacent structures other than seminal vesicles: external sphincter, rectum, levator muscles, and/or pelvic wall
N - Regional Lymph Nodes1	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
M - Distant Metastasis2	
M0	No distant metastasis
M1	Distant metastasis
	M1a Non-regional lymph node(s)
	M1b Bone(s)
	M1c Other site(s)

*Invasion into the prostatic apex or into (but not beyond) the prostatic capsule is not classified as T3, but as T2.
1 Metastasis no larger than 0.2 cm can be designated pNmi.
2 When more than one site of metastasis is present, the most advanced category is used. (p)M1c is the most advanced category.

N categorization*:*

The assessment of pelvic lymph nodes (LN) is in many respects the "blind spot" of PCa staging. The gold standard for lymph node evaluation is still extended pelvic lymph node dissection (ePLND), but it requires an invasive procedure and may nevertheless underestimate the extent of lymph node involvement (19). The risk of LN metastasis is commonly assessed using statistical nomograms (20, 21). Ideally, LN status would be assessed by imaging studies. However, traditionally available imaging has performed poorly (22). With the advent of novel molecular imaging techniques, LN staging has become more reliable and accurate. There is emerging evidence, that PSMA (Prostate-specific membrane antigen) PET/CT imaging for detection of LN metastasis is superior to other molecular imaging techniques (23).
Currently there is no method to predict N-status reliably in PCa patients. However, it is likely that future imaging studies will provide sufficient sensitivity and specificity to replace ePLND as the gold standard for N-staging.

M categorization

Accurate staging and in particular accurate determination of metastatic status (M1 or M0) is vital for choosing adequate therapy for PCa patients. Extra nodal metastases from PCa develop primarily as sclerotic lesions in the bone while visceral metastases are rare in castrate-sensitive PCa (24, 25). There is clear evidence that the extent and the pattern of PCa metastasis has implications for the effects of local and systemic treatments (26, 27).
According to EAU guidelines, imaging studies for detection of metastatic PCa ought to be reserved for high-risk patients (i.e. PSA levels ≥ 20 ng/ml, Gleason score ≥ 8, cT≥3) (17). International guidelines still regard bone scans as the standard imaging procedure for detection of bone metastasis and patient follow-up (17, 28). It is based on Technetium 99m-methyl diphosphonate (99mTc-MDP) that accumulates at points in the bone with high osteoblastic activity. Small metastases with little osteoblast

activity can thus be overlooked. The sensitivity of bone scans is generally acceptable with reported numbers of 62 to 89 percent (29, 30), while false-positive results can occur due to other metabolic disturbances in the bone that lead to increased osteoblast activity, such as trauma and inflammation. This is the reason why bone scanning achieves low and unsatisfactory specificity levels (31, 32).
The current EAU guidelines acknowledge that choline PET/CT, MRI and PSMA PET/CT are more sensitive in detecting bone metastases than bone scan and CT (17). However, since the benefit of maximum precision in detecting early metastasis is unclear, more advanced imaging techniques for primary M-staging are currently not endorsed (33).

1.2.2 Grading of prostate cancer

The original Gleason score from 1974 described the architectural composition of a tumor without any reference to cellular properties. The grading system, in combination with clinical staging, showed strong correlation with PCa death for high scores and differentiated patients with good prognosis from patients with lethal outcomes (12). The simplicity of the system and its strong predictive qualities lead to the rapid introduction of the Gleason score into clinical practice. It remains the cornerstone of PCa grading.
The original Gleason score was revised in 2004 by a consensus group of urological pathologists (34) and in 2014 by an expert panel consisting of pathologists and clinicians (35). Figure 3 illustrates the resulting changes with regard to pattern evaluation. Particularly the changes made in 2004, while clarifying several areas of uncertainty, lead to a so-called Gleason shift with a general upgrading of tumors across the board. In a 2005 publication, Albertsen and colleagues showed that in a population of patients diagnosed with PCa in 1991-92, upgrades of Gleason scores outnumbered downgrades with a ratio of 4:1 when the original biopsy slides were reexamined according to the 2004 revision (36). This, in turn, has consequences for risk models that incorporate Gleason score in their calculations (see chapter 1.4).

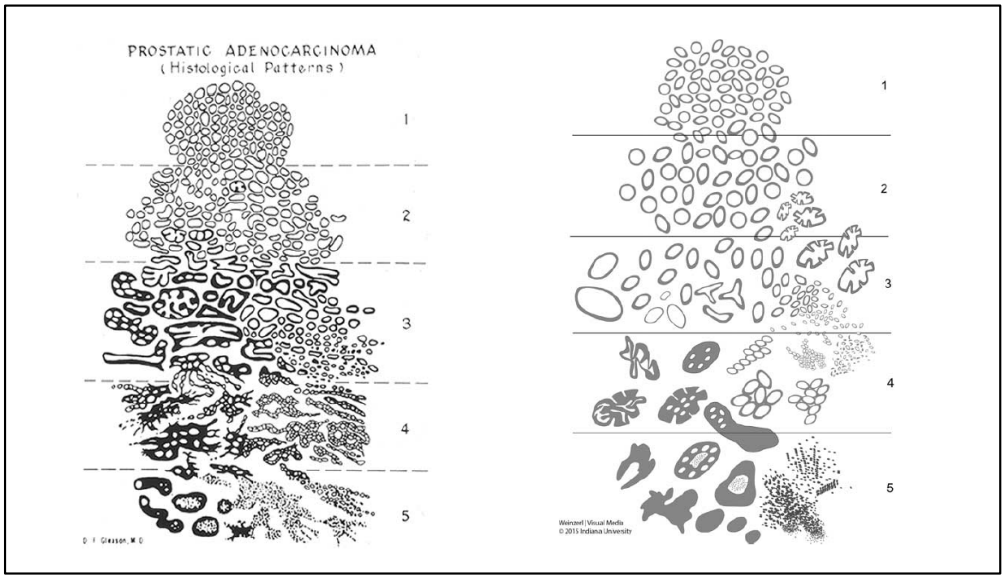

Fig. 3: The original Gleason scoring system with corresponding tissue patterns (left) and the modified current version (right) (courtesy of David Grignon, Indiana University Medical Center).

According to the Gleason score revisions, Gleason grades 1 and 2 are no longer assigned. This means that the lowest Gleason score according to current practice is 3+3=6. There is also consensus that Gleason 3+4=7a and Gleason 4+3=7b are different entities with different prognostic implications (37). A new grading system has thus been introduced which consists of grade groups 1-5 (International Society of Urological Pathology, ISUP): Gleason score 2–6 (Group 1); Gleason score 3+4=7 (Group 2); Gleason score 4+3=7 (Group 3); Gleason score 8 (Group 4); and Gleason scores 9–10 (Group 5).

The ISUP grade groups have been endorsed by the WHO and it is recommended that both Gleason score and ISUP grade group should be reported simultaneously for the foreseeable future (38).

1.3 Diagnostic evaluation

According to the EAU guidelines on PCa, the diagnostic workup of patients referred for evaluation, includes PSA blood test, digital rectal examination (DRE) and transrectal, ultrasound (TRUS) guided, systematic biopsies. The increasing role of MRI imaging in the diagnostic process is acknowledged (17).

1.3.1 Prostate-specific antigen (PSA)

Prostate-specific antigen (PSA) is a glycoprotein enzyme encoded by the KLK3 gene in humans. It is also known as gamma-seminoproteine or kallikrein-3 (KLK3). It is exclusively secreted by the epithelial cells of the prostate where it serves to liquefy semen and thus allows sperm cells to move effectively (39). PSA is detectable in serum in all men and is commonly elevated in the presence of benign disorders (e.g. benign prostate hyperplasia, infection) and PCa (40).

PSA in diagnostic workup

PSA levels correlate largely with PCa stage (41, 42) and are thus a valuable tool in the primary assessment of patients. PSA levels of >100μG/L strongly suggest metastatic disease (22).

Used judiciously, PSA can be useful in assessing the need for further evaluations with biopsies and imaging studies. With the increasing use of PSA testing in primary health care, an elevated PSA level between 2 and 10 μG/L alone in the presence of normal findings on palpation should not automatically lead to a prostate biopsy in order to reduce over- diagnosis of PCa (17). Instead, patients should be counseled using risk assessment tools and nomograms that are validated for predicting indolent PCa (43). PSA density (PSA value divided by prostate volume) can serve as an important and easy-to-use trigger, as values below 0.15 in combination with a negative DRE indicate that the presence of aggressive PCa is unlikely (44). At the same time, it is important to remember that there is no “safe” PSA threshold, as clinical trials demonstrated that even very low PSA levels do not rule out aggressive PCa (45). In patients with large

tumor volume, low PSA levels are indicative of aggressive disease associated with a bleak prognosis (46).

PSA in screening and early detection of prostate cancer

The goal of PSA screening is the detection of PCa at an early and potentially curable stage. There is consensus that the gradual reduction of PCa mortality in the US has at least in part been due to organized, PSA-based screening (47).

The three major trials investigating the benefits of screening and early detection of PCa (PLCO Cancer Screening Trial, ERSPC, Gothenburg randomized population-based prostate cancer screening trial) generated inconclusive and partially contradictory results (48-50).

Screening and early detection of PCa remains thus one of the most debated topics in the urological community (51), particularly after the US Preventive Services Task Force (USPSTF) issued its D-recommendation in 2011, discouraging screening for PCa in healthy men (52). The increasing use of active surveillance has since let the USPSTF to soften its stance and the D-recommendation has been upgraded to a C-recommendation. The task force's current suggestion leaves the decision for or against screening for men aged 55-69 to the individual patient after careful information about the benefits and harms of PSA-based screening. The new recommendation acknowledges that there may be a small survival benefit. However, the D-recommendation for screening of men older than 70 years remains unchanged (53).

In general, the debate is still unresolved if screening for PCa of asymptomatic, healthy men strikes the right balance between benefits and harms.

1.3.2 Digital rectal examination

Digital rectal examination (DRE) is still a cornerstone of clinical tumor staging. It assesses areas of increased firmness on the posterior surface of the prostate facing the rectum. The majority of tumors are located in this area. However, anterior tumors and tumors with a volume of less than 0.2 ml are easily missed (54). Positive DRE findings

in the absence of elevated PSA levels often indicate the presence of aggressive tumors (46, 55).

1.3.3 Prostate biopsy

Prostate biopsies need to reflect accurately the actual Gleason score to avoid misclassification.

Standard of care is the ultrasound-guided, systematic biopsy performed by either the transrectal or the transperineal approach, sampling ten to twelve cores. However, since ultrasound does not visualize PCa reliably, the procedure is performed without information about the location of PCa. This biopsy strategy leads to over-diagnosis of clinically insignificant disease and under-diagnosis of potentially aggressive cancers (56).

There is evidence that MRI-guided biopsies can enhance biopsy accuracy significantly, particularly after prior negative biopsies (57, 58). Targeted biopsies can be performed cognitively (by visualization of tumor or anatomical landmarks on TRUS), by real-time MRI targeted biopsy (with the patient placed in the MRI machine) or with MRI-TRUS fusion systems. All three approaches have overall cancer detection rates comparable to systematic biopsies, but with higher detection rates of clinically significant PCa and lower detection rates of clinically insignificant PCa (59).

1.3.4 Imaging

Grey-scale ultrasound (US) is useful in visualizing the prostate and in guiding systematic core biopsies. However, it does not reliably identify PCa in the prostate (60). It is therefore unlikely that US based strategies alone can replace systematic biopsies. New US based modalities such as sonoelastography and contrast-enhanced US have been introduced recently but are not recommended for routine use (17).

The advent of multi-parametric MRI (MP-MRI) has gradually led to a paradigm shift in PCa imaging and the primary diagnostic evaluation of patients. Ahmed and colleagues demonstrated (PROMIS study) that MRI and targeted biopsies improved detection of clinically significant PCa while reducing over-diagnosis of non-significant

PCa (56). The results supported the notion that MRI of the prostate should be routinely performed *prior* to biopsies. Similar conclusions were reached by the PRECISION trial that showed that in biopsy-naïve patients, MRI prior to biopsy followed by MRI-targeted biopsies was superior to systematic TRUS-guided biopsies in men at clinical risk for PCa (61).

However, despite the introduction of a standardized system for reporting suspicious lesions on MRI (PI-RADS v2) (62), inter-observer variability remains high (63). The EAU in its most recent guideline update on PCa recommends MRI of the prostate prior to initial biopsies, but acknowledges that "systematic biopsy is an acceptable approach if mpMRI is unavailable" (17).

1.4 Risk-stratification of prostate cancer

The heterogeneous natural history of PCa makes defining risk categories both mandatory and challenging: On the one hand, there is a large group of indolent tumors, which are usually asymptomatic, have little or no metastatic potential and are not lethal during a normal life span. On the other side of the spectrum, we find extremely aggressive tumors, which develop in the course of weeks and months, metastasize early and lead to a rapid demise of the patient despite aggressive treatment (64).

1.4.1 Risk-stratification models

The recognition that not just anatomical, but also histological and biochemical parameters define patient outcome, lead to the introduction of integrated risk prediction models. Anthony D'Amico introduced the most commonly used risk stratification model in 1998 (65). He combined pre-treatment information on PSA, clinical T-stage (AJCC) and Gleason score to divide patients into low-, intermediate- and high-risk groups.

Importantly, the model primarily defined risk for biochemical recurrence (BCR, increasing PSA levels over a defined limit) following therapy. The D'Amico risk groups correlate with metastatic disease and prostate-cancer specific mortality (PCSM)

(66). The EAU guidelines on PCa promote a three-tier risk-group system which follows the basic principles of the D'Amico risk classification (17).
A further risk stratification system that has achieved widespread use in clinical practice is the Cancer of the Prostate Risk Assessment (CAPRA) score. It, too, integrates pre-treatment information on PSA, cT-stage and Gleason score and assigns low-, intermediate- and high-risk groups. The underlying scale of 0 to 10, however, allows for further differentiation of patient risk. The CAPRA score also appreciates the different prognostic outlooks of Gleason 7a and Gleason 7b, adding 1 and 3 points respectively to the final score (67). The CAPRA score, as the D'Amico 3-level system, predicts primarily BCR following treatment, but has also been demonstrated to predict metastasis, PCSM and overall mortality (OM) after surgery, radiation therapy and androgen deprivation therapy (68).

1.4.2 Nomograms and calculators

In the field of PCa, there is a plethora of prediction tools. Over one hundred nomograms have been designed that predict a great variety of outcomes such as: Positive biopsies with or without prior negative biopsies; prediction of pathological outcomes before surgery; prediction of biochemical endpoints before and after surgery; prediction of biochemical and clinical endpoints before radiation therapy and prediction of metastases and survival among patients with recurrent disease after primary treatment (69) . Particularly the Partin tables which predict postoperative, pathological stage based on clinical stage, PSA and biopsy Gleason score, have reached widespread use in pre-therapeutical decision making (70).
The majority of nomograms predict outcome based solely on tumor characteristics and do not take into account patient factors. This can complicate decision-making in a patient group with comorbidities and an often-limited life expectancy. A commonly used tool that takes into consideration both patient and tumor factors is the life-expectancy-calculator by the Memorial Sloan Kettering Cancer Centre (MSKCC). It generates for a group of hundred men with given tumor characteristics and comorbidities a probability of overall survival, PCa death and death of other causes

(see figure 4) (71). This model helps the clinician to illustrate for patients the *actual* risk their particular PCa represents in a setting that takes into account patient health and life expectancy.

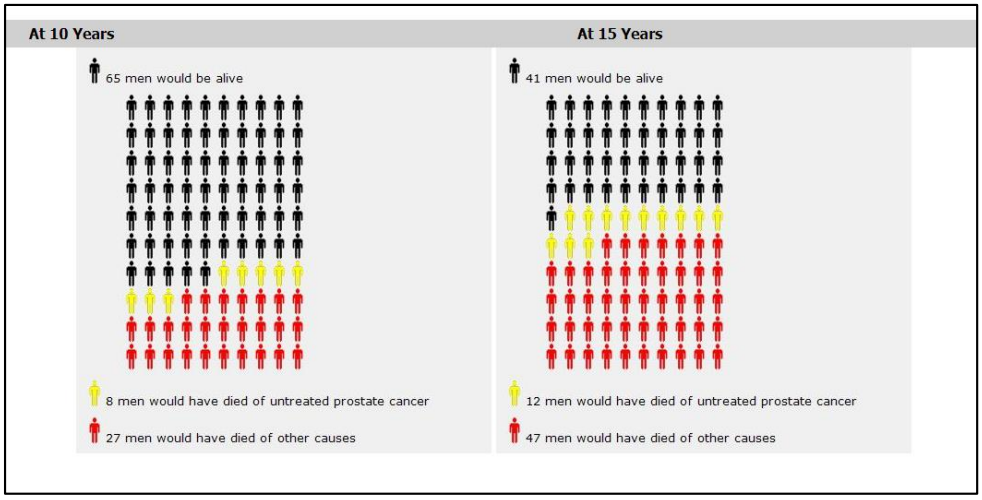

Fig. 4: Illustration of risk of dying of untreated PCa (yellow) and dying of other causes (red) at 10 and at 15 years for an otherwise healthy 70-year-old man with PCa, clinical stage T1c, PSA 12, Gleason 7b. Black illustrates men alive.
Source: Life-expectancy calculator, MSKCC, www.mskcc.org/nomograms/prostate

1.4.3 Challenges with current risk-classifications

In the common risk-stratification models, only PSA is a constant variable while Gleason grade and T-stage have been subject to significant changes over time. The modifications of the Gleason grading system that resulted in a general upgrading of tumors have already been outlined (see chapter 1.2.2). The increasing use of MRI has led to similar changes of the clinical T-staging (cT) of tumors. Particularly intermediate-risk tumors are prone to upgrading following MRI, affecting approximately 25 percent of patients (72).

Gleason shift and upstaging of PCa by MRI thus regularly lead upgrading of tumors to a higher risk group. This has the net effect of improving the average prognosis in both groups, by removing the tumors with the worst prognosis in the lower risk group and

adding patients with a better prognosis than average in the higher risk group. This statistical effect is called the Will Rogers phenomenon

1.5 Treatment

Two main treatment strategies have evolved over the last decades to improve the prognostic outlook of PCa patients:

I. Early detection (see chapter 1.3.1) combined with local treatment with curative intent.
II. Improvement of hormonal treatment and introduction of novel cytotoxic agents in the treatment of patients with advanced disease.

Today, due to PSA testing of men, most patients present with localized PCa, which is potentially curable.

1.5.1 Treatment of non-metastatic prostate cancer

In principle, there are three therapeutic options for patients with non-metastatic PCa (NMPCa) depending on the stage and aggressiveness of the disease: Radical prostatectomy (RP), radiotherapy (RT) and active surveillance (AS). A fourth approach, watchful waiting (WW), is feasible only for patients with a very limited life-expectancy either due to age or considerable comorbidity.

Radical prostatectomy

Patients treated with RP during the first half of the 20th century, were usually subjected to the procedure not to attempt cure but to achieve alleviation of obstructive symptoms (73).

The role of surgery changed in 1983 when Patrick Walsh described a modified version of retropubic RP, which preserved the neuro-vascular bundle and consequently some form of erectile function in the majority of patients. The prospect of less side effects with reduced impact on quality of life and the simultaneous increase in early-stage

PCa due to PSA screening, led to a rapid increase in the number of RPs during the late 1980s and early 1990s (74).

RP entails the removal of the entire prostate gland and the seminal vesicles, preservation of the sphincter and the reestablishment of a drainage pathway by a vesico-urethral anastomosis. The goal of the procedure is the removal of the tumor with free surgical margins while preserving as much of the neurovascular bundle (erectile nerves) as possible to preserve erectile and continence function. Nerve-sparing surgery can be performed in patients with localized PCa but may be associated with an increased rate of positive margins in patients with pT2 tumors if the procedure is performed bilaterally (75).

In case of a preoperative risk of lymph node metastasis of five percent or more, as calculated by e.g. the Briganti nomogram (20) or the Roach formula (76), an extended pelvic lymph node dissection (ePLND) is indicated (17).

RP can be performed by open, laparoscopic or robot-assisted techniques (RARP). There is consistent evidence that RARP is associated with shorter hospital stay and less blood loss (77, 78). However, there are no differences in short- or long-term functional and oncological outcomes between the three approaches (77-79).

For almost two decades there was no evidence from randomized clinical trials that RP was associated with a survival benefit. In 2002, Holmberg and colleagues published results from the SPCG 4 trial that had randomized men with localized PCa diagnosed in 1989-1999 to either RP or WW. The participants had clinically and not PSA-detected PCa. SPCG 4 demonstrated a significant reduction in PCSM but not in OM. The risk-reduction was most pronounced in men younger than 65 years at diagnosis and patients with intermediate-risk PCa (80). More recent and more mature data from the SPCG 4 trial showed better OS, reduced risk of metastases and less use of androgen deprivation therapy (ADT) favoring RP over WW (81).

A corresponding trial (PIVOT), conducted by Wilt and colleagues who had randomized patients diagnosed in the early PSA era to either RP or WW, found no significant differences in OM and PCSM (82). The most recent trial, ProtecT, that randomized patients to either AS, RP or RT showed few PCa deaths in general after

ten years of follow up and no significant differences in OM and PCSM between the three groups. However, AS was associated with higher incidence of progression and metastasis (83).

Radiotherapy

Radiotherapy (RT) of the prostate as a palliative measure was first reported at the beginning of the 20th century (84). It utilizes ionizing radiation to target and kill cancer cells. Today, it is employed with both curative and palliative intent.

Photon-based external beam radiotherapy (EBRT) and brachytherapy are the mainstay of treatment in a curative setting.

External beam radiotherapy

EBRT uses photons generated by a linear accelerator. EBRT was initially insufficient therapy because the first delivery systems did not generate enough energy to penetrate to deep-seated neoplasms such as PCa. First in the 1950's, when higher energy cobalt machines managed to reach deeper levels of tissue, EBRT received renewed attention. The curative potential of EBRT for PCa was established by the trials of Bagshaw and colleagues (85, 86).

Today, standard treatment consists of fractionated radiation with individual doses of 1.8–2.0 Gy and total dosages of 74.0–80.0 Gy (87). Dose escalation of up to 80 Gy is associated with increased toxicity and accuracy of radiation therapy within a moving organ has thus become increasingly important. Intensity modulated radiotherapy is a form of improved standard treatment, where different volumes of the irradiated area are treated with different doses, largely sparing surrounding healthy tissue (88). CT-guided targeting of the prostate with the help of implanted markers (e.g. gold markers) allows for correction of both patient and organ movement, resulting in better targeting and potentially reduced side effects (89).

EBRT in combination with neoadjuvant androgen deprivation therapy (ADT) has been standard of care for many years for patients with locally advanced NMPCa with documented benefits in terms of recurrence-free survival and OS (90, 91). For patients

with high-risk and locally advanced PCa, two to three years with neoadjuvant ADT are recommended (92), while patients with intermediate-risk PCa only require six months of ADT (93).
Recent data published by the STAMPEDE trial group indicated that a subgroup of patients with metastatic PCa might may benefit from EBRT of the prostate in combination with systemic therapy in terms of survival (26).

Brachytherapy
The principle of low-dose brachytherapy entails implantation of permanent radioactive seeds. The initial trials on brachytherapy with open implants of iodine-containing titanium cylinders demonstrated that the procedure was feasible, but there were serious challenges with inconsistent dose distributions and major complications as a consequence with high rates of local failure (94). First in 1983, with the introduction of ultrasound-guided implantation of radioactive seeds (95), did brachytherapy establish itself as a viable treatment alternative for patients with localized PCa (96). However, only patients with localized low-risk or low-volume intermediate risk are eligible for low-dose brachytherapy (97) with active surveillance as the preferred option for these patients today (see below).
With high-dose brachytherapy, a radioactive source is temporarily introduced into the prostate via the perineum. Radiation is delivered either in single or multiple fractions. One randomized clinical trial reported promising results of combined high-dose brachytherapy plus EBRT versus EBRT alone (98), but the results need to be interpreted with caution since the control group (EBRT alone) was treated with sub-standard radiation doses (55 Gy, 20 fractions).

Side effects of radical treatment
Radical treatment of PCa has side effects that can have a significant impact on patients' quality of life (99). This was one of the motivations behind the introduction of active surveillance instead of radical treatment for patients with low-risk PCa (see below).

A recent publication of patient-reported outcome measures from the ProtecT trial demonstrated that patients after RP had consistently higher rates of urinary incontinence than after RT or under active surveillance (AS) (100). Forty-six percent of patients used pads six months after treatment (AS: 4%, RT: 5%).
After six years of follow-up, 17% of men in the RP group were using pads (AS: 8%, RT: 4%). At baseline, 67% of patients reported erectile function sufficient for intercourse. A significant decline was observed in all groups after six months (AS: 52%, RT: 22%, RP: 12%). Erectile function remained worse in the RP group during the entire study period despite some recovery.
RP and AS did not affect bowel function, bowel bother scores and bowel-related quality of life, while these outcomes were worse in the radiotherapy group, particularly at 6 months. However, after two years, RT patients only experienced more bloody stools while all other parameters were comparable to RT and AS.
Studies in selected patients from high-volume centers show better results for RP than ProtecT with preserved sexual function in over eighty percent of patients (101).

Active surveillance

Active surveillance (AS), also known as active monitoring or deferred treatment, has become an increasingly acknowledged alternative for selected patients with localized PCa. Particularly patients with PCa diagnosed on the basis of an elevated PSA without any other symptoms or findings, will in many instances not benefit from radical treatment (102). AS offers patients a path to avoiding the side effects that come with radical treatment while reducing risk by continuous and close surveillance of the tumor. In contrast to watchful waiting, these patients will be candidates for radical treatment if their tumors show signs of progression beyond predefined thresholds.
Klotz and colleagues from Toronto, Canada, conducted one of the largest studies (N=980) on AS to date and with the longest follow-up. Inclusion criteria were stage T1c or T2a, a PSA $\leq$ 10 ng/mL and a Gleason score of $\leq$ 6 at diagnosis and age younger than 70 years. For patients older than 70 years, a Gleason score of seven was permissible (103). MRI imaging was not part of the diagnostic process or follow-up.

After a median follow-up of 6.3 years (range 0-20 years) 30 patients (3%) developed metastasis and 15 patients (1.5%) died of PCa. Disease-specific survival after 10 and 15 years was 98 and 94 percent respectively. Twenty-seven percent of patients underwent radical treatment due to progression (104).

Researchers from Johns Hopkins conducted a comparable AS trial in the US with a large cohort of patients and long follow-up. Patients eligible for the trial had to fulfill more stringent inclusion criteria than the Toronto patients and the disease-specific survival was accordingly higher. After 10 and 15 years of follow-up disease-specific and metastasis-free, survival was close to 100 percent. Thirty-six percent of patients underwent radical treatment eventually, of which approximately 25 percent in the absence of progression (patient preference) (105).

Acceptance of AS has been slow, partly due to reports of adverse pathological features (higher Gleason/ T-stage in prostatectomy specimens) in patients who were eligible for AS but opted for surgery instead (106). However, there is little evidence that these adverse *pathological* outcomes translate into adverse *clinical* outcomes (107).

The role of MRI in increasing accuracy at diagnosis and safety under follow-up for patients under AS remains currently undefined (108, 109).

In general, AS appears to be a safe alternative to radical therapy for most patients with low-risk PCa and an option for selected patients with intermediate-risk PCa.

Watchful waiting

There is still some confusion about the role of watchful waiting (WW) as compared to AS and the terms are often used synonymously. In contrast to AS, patients under WW are not candidates for radical treatment, with hormone therapy as the primary treatment option if their PCa becomes symptomatic or metastatic. It is frequently the preferred option for the oldest patients and patients with multiple comorbidities.

It is also important to bear in mind that the landmark studies that tested radical treatment versus observation followed control groups with WW and not AS (81, 82).

1.5.2 Treatment of metastatic prostate cancer

The incidence of metastatic PCa at diagnosis in the US is approximately 50 percent lower now than in 1988 and there is broad consensus that this stage shift is due to aggressive PSA screening. However, during the last decade the incidence of metastatic PCa has stabilized which means that a considerable number of patients still present with metastasis at diagnosis (110). In Norway, approximately half of the patients who later die of PCa initially present with metastatic disease (111). In a recent publication, metastatic patients in the control arm of the STAMPEDE trial (ADT only as primary therapy) had a median OS of 3.5 years (112) .

Hormone therapy

ADT has been the mainstay of treatment for metastatic PCa for decades. Surgical castration used to be the primary treatment option but has since been largely replaced by other therapeutical agents that achieve similar outcomes: Luteinizing hormone-releasing hormone (LHRH) antagonists and LHRH agonists (113). However, for patients with impeding spinal cord compression, surgical castration or LHRH agonists are recommended as primary treatment because of their immediate effect on testosterone levels and tumor growth (17).

In the metastatic setting, monotherapy with non-steroidal anti-androgens has no accepted place with evidence pointing to unfavorable outcomes compared to LHRH in terms of OS, clinical progression and treatment failure (114). However, anti-androgens appear to convey a moderate survival benefit in combination with LHRH (complete androgen blockade) (115).

Intermittent ADT is a treatment option in patients with good response to hormone therapy in order to alleviate the side effects of ADT. Intermittent ADT appears to be non-inferior to continuous ADT (116).

Other systemic therapies in metastatic prostate cancer

Primary treatment of metastatic PCa has undergone significant changes during the last five years and is fast turning into a complex matter. Three large randomized trials

(GETUG-15, CHAARTED, and STAMPEDE) have demonstrated the importance of adding docetaxel to ADT as primary treatment for patients with metastatic PCa (27, 117, 118). While GETUG-15 failed to show a significant survival benefit, both CHAARTED (Median OS 57.6 vs 44 months, HR 0.61) and STAMPEDE (Median OS 60 vs 45 months, HR 0.76) demonstrated conclusively a significant survival benefit of the combined treatment approach. The reason for the conflicting outcomes in these three trials is currently unknown. The EAU guidelines on PCa strongly recommend the addition of docetaxel to ADT in the treatment of PCa patients with metastatic disease (17). Two further trials documented comparable effects of abiraterone when given in combination with ADT in hormone-naïve M1 patients (119, 120) and their use is equally recommended by the EAU in patients unfit for chemotherapy.

Local treatment of the prostate in metastatic disease

In a recently published trial from the STAMPEDE group, with over 2000 men randomized to either standard of care (SOC) or SOC plus radiotherapy to the prostate, the latter combination conveyed no significant survival benefit in unselected patients. However, patients with a low metastatic burden showed improved survival after radiotherapy to the prostate (26).

1.5.3 Treatment of metastatic castration-resistant prostate cancer

Metastatic, castration-resistant PCa (mCRPC) is the preterminal stage of PCa. Castration-resistant PCa is currently defined by either biochemical progression with three consecutive rises in PSA one week apart resulting in two 50% increases over the nadir, or by radiological progression with the appearance of either two or more new bone lesions on bone scan or a new soft tissue lesion in patients on ADT. The definition of CRPC requires a serum testosterone at castration level with values of 50 ng/dl or less (17). Until the introduction of docetaxel, roughly fifteen years ago, no life-prolonging treatment existed and survival was limited after the onset of mCRPC.

First-line treatment

The simultaneous publication of the SWOG 99-16 and TAX 327 2008 trials in 2004 represented a watershed moment in the treatment of patients with mCRPC which had traditionally shown little response to conventional chemotherapy regimens. Both studies showed a significant OS benefit of two to three months for patients who received docetaxel every three weeks plus prednisolone 5mg BID compared to controls (121, 122). Therefore, docetaxel has become primary treatment for chemotherapy-naïve mCRPC patients.

More recently, two additional substances have been added to the therapeutic arsenal for chemotherapy-naïve mCRPC patients: Abiraterone and enzalutamide. Both substances target pathways related to the androgen-receptor and are commonly referred to as second-generation antiandrogens.

Abiraterone demonstrated a significant reduction of radiographic progression and an OS benefit of 35 months in the treatment group versus 30 months in the control group (123).

The PREVAIL trial found similar results for enzalutamide in chemotherapy-naïve patients with an OS benefit of approximately four months and a reduction of radiographic progression of 68 percent (124).

Sequencing and second-line treatment

Almost all patients with mCRPC will progress despite effective first-line treatment. Further significant delays of disease progression can be achieved by different sequences of second-line therapies. The benefits of second-line therapies need to be weighed against side effects, realistic treatment objectives, quality of life, costs and patient age and comorbidity.

Two large randomized, placebo-controlled trials (COU-AA-301, AFFIRM) demonstrated significant survival benefits of 4-5 months in patients with progressive disease after docetaxel therapy who had received abiraterone (COU-AA-301) or enzalutamide (AFFIIRM) compared to patients on placebo (125, 126). Furthermore,

both therapies were superior compared to placebo in terms of secondary objectives such as soft-tissue response, biochemical (PSA) and clinical progression.
Cabazitaxel is a second-generation taxane with effect in docetaxel-resistant PCa. The TROPIC trial (randomized phase III) demonstrated a survival benefit of cabazitaxel of approximately 2.5 months compared to SOC (127). However, toxicity and cost are factors that have so far hampered the widespread adaptation of this treatment option.
Radium-223 is an α-emitter with high affinity to bone. A large randomized, placebo-controlled phase III trial (ALSYMPCA) demonstrated a survival benefit of Radium-223 in patients who progressed on or were unfit for docetaxel of roughly 3.5 months compared to placebo. It also prolonged time to first skeletal event, lead to improvement in pain scores and in quality of life (128).

1.6 Knowledge gap

Defining patients' risk for dying of PCa and finding adequate and effective ways of reducing that risk remains a challenge for the clinician, despite the introduction of advanced diagnostic tools.
We usually assess and predict risk through the lens of risk-stratification models and nomograms. However, to be able to grasp the risk PCa patients are exposed to completely, we need to have a thorough understanding of both the outcome that we aim to change and our outcome measures and their limitations. Furthermore, appreciation of the natural course of PCa at its various stages is necessary to make effective and meaningful treatment decisions for our patients.

1.6.1 Natural course of prostate cancer

In order to affect outcomes, it is important for the clinician to understand the natural course of PCa and to appreciate when and how it can be altered by therapeutic interventions.
Although we have for PCa in general a relatively good picture of the natural course of the disease from the first diagnosis to death on a population level (129), important stages of this trajectory remain poorly explored.

The preterminal stage of PCa is mCRPC. By extension, reducing patients' risk of developing mCRPC would equally reduce the risk of dying of PCa. However, the "baseline" natural course of mCRPC patients without life-prolonging treatment (Docetaxel, Abiraterone, etc.) is currently undefined on a population base and our knowledge about this patient group stems from the control arms of clinical, randomized trials with significant patient selection.
Our perception of the natural course of PCa is also influenced by patient factors, namely patient age and comorbidities. High patient age and/ or several comorbidities can lead the clinician to conclude that patients will not live long enough to suffer the negative impact of their PCa in terms of morbidity and mortality. In Norway 15-20 years ago, this understanding of patient factors lead to relatively strict age limits for radical treatment with very few patients >75 years receiving such treatment at the time (8). If this policy benefited the elderly patients has to our knowledge not been evaluated.

1.6.2 Mortality and Survival

Survival is generally an unsuitable outcome measure in most PCa patients. Rising PCa incidence numbers due to PSA testing have likely led to a dilution effect where better survival data are the result of adding new patient groups with a considerably better prognosis rather than real improvements in treatment and outcome. However, survival can be a good measure of treatment effects in more stable subgroups of PCa patients, e.g. de-novo metastatic (M+) PCa patients. A recent report showed no marked improvement of survival for these patients over a 20-year period (130).
The main outcome measure of PCa treatment at all stages is PCa specific-mortality (PCSM). Most Western countries have seen a gradual decline of age-adjusted PCSM over the last ten to twenty years, as previously outlined (see chapter 1.1.2).
PCSM is reported age-adjusted to allow for comparisons of PCa population over time and between countries. A complicating factor is the definition of PCa death. In clinical trials, PCa death is commonly determined by a cause-of-death committee consisting of clinicians that have to agree upon the cause of death of any deceased trial

participant (131, 132). On a population level PCa mortality numbers are based exclusively on death certificates of deceased men. It is crucial for the quality of population-based PCa mortality numbers that death certificates contain reliable information on patients' death.

Misattribution of cause of death may for instance have implications for the relatively high PCa mortality in Norway compared to other countries. However, to date thorough audits of death certificates have not been conducted.

1.6.3 Summary

To provide patients with good advice and a realistic picture of the nature and the inherent risk their PCa represents, we ourselves need to have a better understanding of the final stages of PCa and PCa death. In particular, we need to

- Broaden our understanding of mCRPC
- Evaluate if current PCa mortality statistics give a realistic picture of outcome in Norway
- Better understand the characteristics of patients who die of PCa and the course of their disease
- Evaluate the effects of treatment decisions based on strict patient criteria on the further course of PCa

2. Aims of the thesis

General aims

The aim of this thesis was to provide a better understanding of the final stages of PCa, metastatic castration resistant PCa and PCa death. We further aimed to address the consequences of possible undertreatment of elderly PCa patients.

Paper I

The aim of this study was to determine survival in unselected patients with metastatic castrate-resistant prostate cancer (mCRPC), who never received life-prolonging treatment. The study aimed to define the natural course of mCRPC without life-prolonging treatment and provide prognostic factors for better risk-stratification in a population representative for Norway.

Paper II

PCa mortality statistics are based on information from death certificates. This study aimed to evaluate the quality of death certificates related to PCa and assessed the level of misattribution on a population level.

Paper III

In paper III we aimed to define the rationales for choosing conservative treatment in a cohort of men with NMPCa, the consequences in terms of local complications and the need for systemic treatment. On a national level we aimed to study survival of elderly patients (>75 years) who had received local therapy at diagnosis compared to patients who had been treated conservatively.

3. Material and methods

3.1 Permissions and ethical considerations

All papers were submitted and approved by the *Regional Committee for Medical and Health Research Ethics in South-Eastern Norway* (REK South East) (REK number, paper I: S-06282a; paper II and III: 2014/2203)

3.2 Study Population

All three papers included retrospective analyses of PCa patients in Vestfold County, Norway. Vestfold County has approximately 240 000 inhabitants (Mean 2009-14: 235 000) representing roughly five percent of the Norwegian population. There is one hospital (Vestfold Hospital Trust) serving the entire county with the exception of the peripheral municipalities of Sande and Svelvik. Vestfold Hospital Trust has a urological department with eight senior consultants who are responsible for treatment and follow-up of PCa patients in Vestfold County. At the time of the study, there were no urologists or oncologists in private practice. Thus, almost all relevant information about patients' PCa treatment and follow-up could be obtained from the hospital's patient records allowing for high quality, population-based retrospective studies.
The male population of Vestfold County has a higher proportion of men ≥70 years compared to the rest of the country. Other relevant socioeconomic factors are comparable.
Table 2 lists the characteristics of the male population of Vestfold County in comparison to the male population of the entire country.

The context of all three papers is illustrated in figure 5.

Table 2: Sociodemographic comparison between the male population of Vestfold County and Norway for the years 2009-2014. Unless otherwise stated, the numbers are the mean of the observations for the years 2009-2014.

	Vestfold County	**Norway**
Population, males (mean 2009-2015)	117,088	2,497,670
% of the male population >= 70 years	9.7	8.8
Estimated life expectancy (years), males (2011-2015)	79.3	79.7
ASDR all causes, males	1220/100,000	1209/100,000
ASDR prostate cancer (official statistics)	71/100.000	67/100.000
Percentage of males >16 years with more than 12 years education	24.5	26.9
Occupation, males (2011-2015)		
Predominantly non-manual, ISCO group 1-5 (%)	52.7	52.8
Predominantly manual, ISCO group 5-10 (%)	47.3	47.2
Mean gross income, persons (M+F) above 17 years (NOK)	364.100	383.700

Source: Statistics Norway, Norwegian Cause of Death Registry; Norwegian Institute of Public Health; ASDR: Age-standardized death rate. Eurostat's European Standard Population (ESP2013)

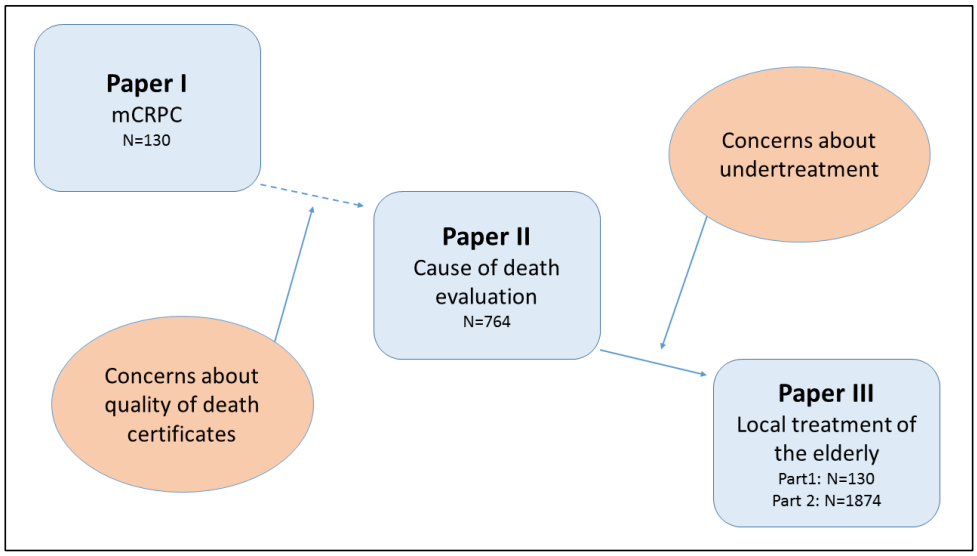

Fig. 5: Illustration of the context of papers I-III

Paper I

Vestfold County hospital's patient administrative system was used to identify all patients registered with diagnosis C61 (Prostate cancer, International Classification of Diseases, 10th revision, ICD-10), who had been seen at Vestfold Hospital Trust between 2000 and 2005 (N=1460). The medical records of these patients were screened to identify patients with mCRPC (N=168). Thirty-eight patients who had received docetaxel, abiraterone, enzalutamide or radium-223 were excluded from the study, leaving 130 patients for further evaluation.

According to guidelines at the time, CRPC was defined by a continuous rise in serum prostate-specific antigen (PSA) levels, progression of pre-existing disease and/or the appearance of new metastases (133). The date of the first rising PSA during either chemical (LHRH) or surgical ADT followed by continuously rising PSA values was defined as the onset date of mCRPC. For patients who had non-measurable PSA values during ADT, the first PSA value above 0.1 mg/l was defined as the onset of CRPC. Supportive treatment that was SOC consisted of bicalutamide, prednisolone, biphosphonates and/or palliative radiotherapy.

The observation time ranged from the onset date of mCRPC until death or 31 December 2012, whichever event occurred first.

Paper II

For the six-year period 2009–2014, names and dates of birth of all deceased men in Vestfold County, registered with either PCa as the immediate/underlying cause of death (PCD, N=341) or other significant condition at death (OCD, part II of the death certificate, N=127) were obtained from the Norwegian Institute of Public Health. Furthermore, data on all deceased men in Vestfold County with a diagnosis of PCa, but whose diagnosis was not mentioned on the death certificate were obtained from the Cancer Registry of Norway (CRN). The latter group of patients was designated PC-DCneg (prostate cancer, no mention of PCa on death certificate).
The three study populations are illustrated in figure 6.

Paper III

In the study population of paper II, we identified 139 patients who had non-metastatic PCa (NMPCa) at diagnosis, but who died of PCa. In the first part of paper III we investigated 117 (84%) of these patients who had not received local/ curative treatment. Metastatic status was determined by the imaging method available at the time of diagnosis (bone scan, CT, MRI).
For the second part of paper III, CRN provided national data on 1874 patients who were seventy-five years or older at diagnosis, had localized high-risk or locally advanced PC, normal functional status (WHO performance status 0) and had either received effective local treatment or no local treatment in the time period 2009-2017. We defined effective local treatment as radical prostatectomy ≤12 months after diagnosis or radiation of ≥60Gy to the prostate ≤15 months after diagnosis following CRN selection procedures.
Paper II and paper III have overlapping study populations and are illustrated in figure 6.

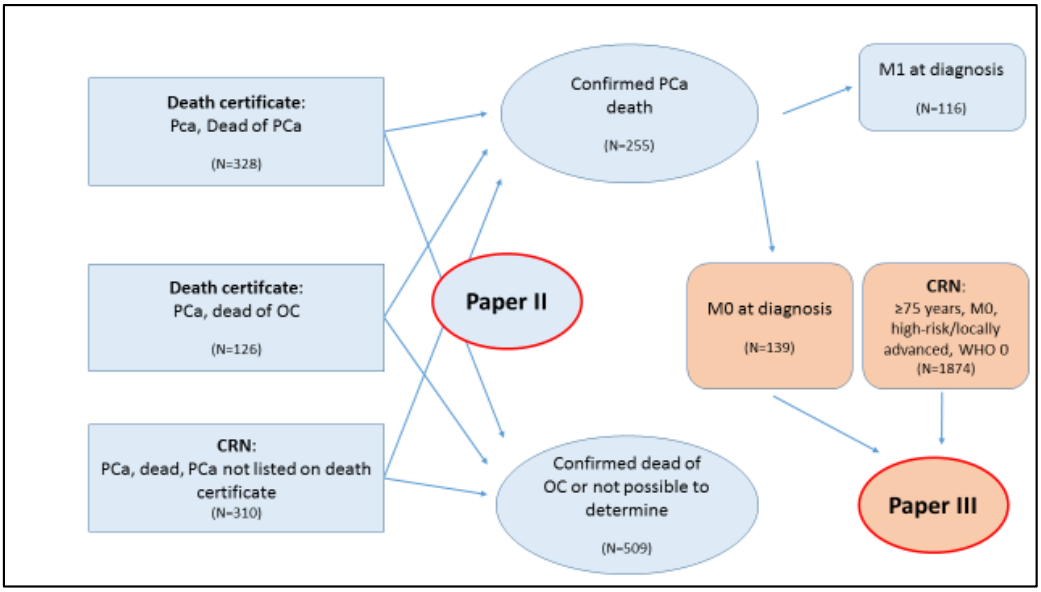

Fig. 6: Flow chart of the study populations of paper II and paper III. PCa: prostate cancer, OC: other causes, CRN: Cancer Registry of Norway

3.3 Methods

Paper I

All data were extracted from patient records.

Prior to the onset of mCRPC:

- Date of PCa diagnosis, age, metastatic status and Gleason score at diagnosis
- PSA nadir during ADT, duration of hormonal treatment until onset of mCRPC

At the onset of mCRPC:

- PSA, alkaline phosphatase and hemoglobin
- PSA doubling time (PSA nadir value plus next two consecutive PSA),
- Date and vital status at last observation.

We defined “effective hormone time” as the time from initiation of any hormonal treatment (including bicalutamide monotherapy) until the first rising PSA under ADT with persistently rising values afterwards.

For patients registered with WHO classification instead of Gleason score (51%), we performed the following conversions: WHO I to Gleason 6, WHO II to Gleason 7 and WHO III to Gleason 8. We estimated PSA doubling time based on PSA values early after the diagnosis of mCRPC using the online calculator of the Memorial Sloan Kettering Cancer Center (134).

We defined cut-off values for age at diagnosis, effective hormone time, PSA doubling time, PSA at CRPC and PSA nadir by trichotomization of their statistical distributions. For the Gleason score analysis, patients with a high-risk profile (Gleason 8–10) were separated from a group with expected lower risk (Gleason ≤7). The levels of hemoglobin were dichotomized with the lower limit value of the normal range as the cut-off value (≥13.4 vs <13.4 g/dl)

Paper II

The main challenge in this study was to specify the cause of death as correctly and objectively as possible in patients with often-complex medical histories. We thus formed a review committee consisting of three urologists and one oncologist. Patient hospital records provided sufficient information on medical histories for the great majority of patients. For twelve patients, we obtained additional information from nursing homes or family doctors. We conducted three consecutive reviews of the study population. The first review served as a filtering process to identify patients with an unambiguous, immediate cause of death and a clear underlying disease process, separating out patients ascribed as dead either from PCa (PCD) or as dead from other causes (OCD). The first author conducted this review, with a blinded audit of 50 random patients in the sample by two other committee members demonstrating perfect correlation. We assumed PCD when the immediate cause of death was caused by systemic or local complications of the disease process or cancer-directed treatment and comorbidities were either absent or of obvious minor importance. We defined OCD by the criteria listed in table 3.

Table 3: First review of patient history - definition of death of other causes and results for patients with prostate cancer as an immediate or underlying cause of death (PCD), N=328

No histological or clinical diagnosis of prostate cancer	15 (4.6 %)
Watchful waiting with no significant disease activity	13 (4 %)
Previous radical treatment with no disease recurrence and an immediate cause of death not related to treatment	5 (1.5 %)
Hormone therapy with complete response to treatment and an immediate cause of death unrelated to hormone therapy, and other	33 (10.1 %)
Other, clinically more significant metastatic malignancies	4 (1.2 %)
Total	70 (21.3 %)

We included patients who we could not assign to either of the above categories in the second review for further evaluation. Patients with autopsy results were registered with the underlying cause of death given on the autopsy report, and no further review of the cause of death was conducted (N=16).

For the second review, committee members independently analyzed patient histories unaware of the conclusions from the other reviewers. We assigned the following categories when answering the question of whether the patient's death was due to PCa: 'Yes/No' (preferable category), 'Likely/Unlikely' (if a definite answer was not possible) or 'Not possible to determine' (if any qualified answer was impossible to

give, owing to numerous and competing comorbidities). We included patients with conflicting conclusions in the third review.

For the third review, we discussed patients whose underlying cause of death was still undetermined in consensus meetings with all members of the committee present. We reviewed patient histories in plenum and reached a consensus decision, which all committee members could agree upon. Assignment of labels followed the same principles as outlined under the second review of patient history.

For the end result, we collapsed patients with the label 'Yes' or 'Likely' into category 'Yes' (dead from PCa). Accordingly, we collapsed patients labeled 'No' or 'Unlikely' into category 'No' (not dead from PCa). We upheld 'Not possible to determine' as an independent category.

Paper III

We deducted the rationales for choosing radical versus non-radical treatment from the patient records at the time of diagnosis based on the stated or implied reasoning of the treating doctor. We assigned patients to two groups according to the decision rationale: Patients who had not received curative treatment due to their age (*NoTreat/Age*) and patients who had not received curative treatment due to other reasons (*NoTreat/Other*).

We assessed patient performance status retrospectively using the Eastern Cooperative Oncology Group score (ECOG) (135) and recorded comorbidity using the Charlson comorbidity index (CCI) and estimated 10-year survival using the age-adjusted Charlson-score (CS) (136).

We collected data on survival, tumor characteristics at diagnosis, use of systemic therapy/ radiation to bone/ prostate and local complications during the course of the disease from patient records.

CRN provided survival data and statistics for the 1874 national patients.

3.4 Statistics

All statistical analyses of the Vestfold patient cohort were performed using SPSS for Windows, versions 18, 22 and 23 (IBM Corp., Armonk, NY, USA) and the R statistical package (137).

Paper I: We tested differences in baseline variables using Mann–Whitney tests and calculated survival curves, three- and five-year survival and median survival using Kaplan–Meier estimation, with 95% confidence intervals (CIs) and 5% significance level to assess statistical uncertainty and significance. We calculated Kaplan– Meier confidence intervals using log-minus-log transformation. Factors that were statistically significant in the univariate analysis were included in the multivariate Cox regression analysis. We used Markov chain, Monte Carlo (MCMC) multiple logistic regression imputation to check the effect of missing values on Cox regression estimates.

Paper II: We described baseline data and PCa death misclassification rates by median, range, percentages, and calculated confidence intervals (CIs) for percentages using Wilson score interval with Yates' continuity correction. The effect of age and study year on the risk of misclassifying cause of death was studied by binary logistic regression. Subgroup analysis was performed by dividing patients into seven age groups (<65, 65–70, 70–75, 75–80, 80–85, 85–90, and >90 years). We calculated correlation between the cause-of-death methods using Cohen's kappa.

Paper III: We described baseline data by median, interquartile range and percentages. For the CRN data, cause-specific survival was estimated using the Kaplan-Meier estimator, where the 95 % confidence intervals were based on Greenwood's formula. The patients' follow-up time was left-truncated at 15 months after their date of diagnosis, since local treatment was defined as treatment within 15 months after diagnosis. Within each age group, a likelihood ratio test was performed to test the significance of local treatment using Cox proportional hazards models adjusting for age and year of diagnosis. CRN analyses were conducted using Stata 15.1.

4. Results

4.1 Paper I

The great majority of the 130 patients who were treated for mCRPC at Vestfold Hospital Trust in 2000-2005 were over 70 years old when diagnosed with PCa (median age 73 years, range 46–89 years). Sixty-six percent (N=86) presented with metastatic disease at diagnosis.

At the onset of mCRPC, patients were 75 years old, a median time of 19 months (range 0-134 months) after the initial PCa diagnosis. Effective hormone time lasted for a median of 17 months (range 0-108 months). Twenty-eight patients were initially followed with watchful waiting (time from diagnosis until initiation of any therapy >6 months). Only one patient had initially received treatment with curative intent (high-dose radiotherapy).

4.1.1 Survival

Median survival after onset of mCRPC was 12.3 months (range 0.2–108 months, 95% CI 8.5–16.1). Two patients were alive at the end of the observation time. Eight patients (6 %, 95% CI 0.03–0.11) lived for 5 years or longer. Eight patients with a very short effective hormone time of 3 months or less had a median survival of only five months after onset of mCRPC (range 3.3–10.9 months, 95% CI 4.4–5.8). Figure 7 illustrates patient survival after the onset of mCRPC.

4.1.2 Prognostic factors

In univariate analyses, the following variables were associated with a favorable prognosis: PSA nadir during ADT of less than 1.1 mg/l, PSA doubling time of more than 3 months during the early period of mCRPC, and alkaline phosphatase and hemoglobin within the normal range at the onset of mCRPC. Effective hormone time of less than 10 months, PSA doubling times of less than 1.6 months or a PSA nadir of greater than 11 mg/l during ADT predicted short survival times. Age, Gleason score

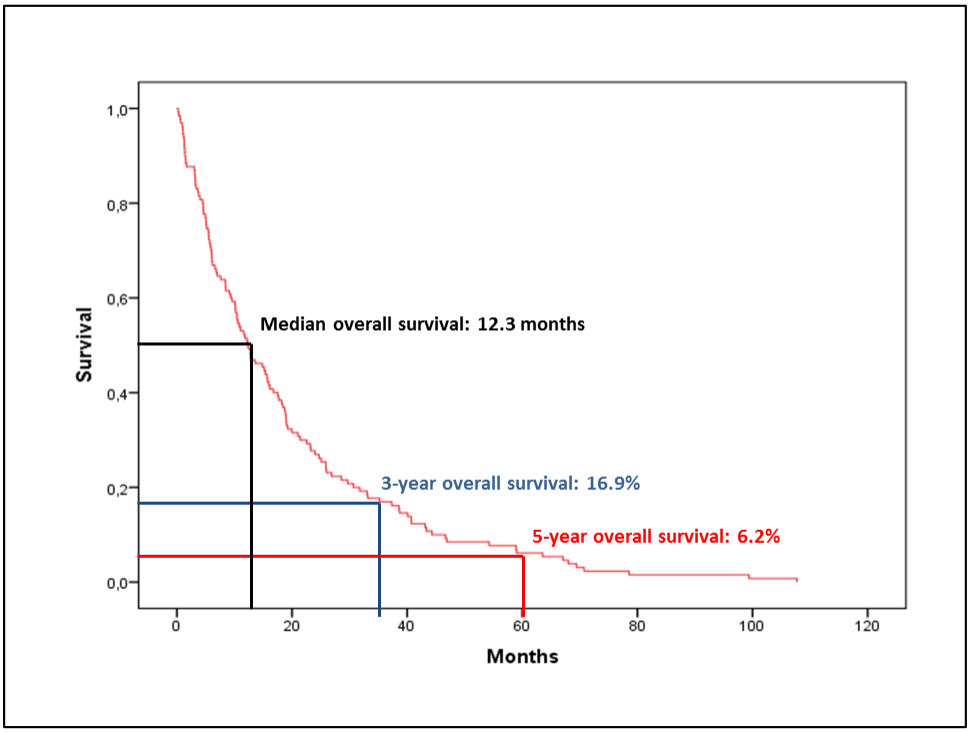

Fig. 7: Kaplan–Meier curve with median, three- and five-year overall survival of patients with metastatic castration-resistant PCa (mCRPC).

and metastatic status at diagnosis and PSA at mCRPC had no significant impact on survival. In the multivariate Cox-regression model, effective hormone time did not reach statistical significance ($p = 0.5$). On the other hand, PSA doubling time, PSA nadir during ADT, hemoglobin and alkaline phosphatase levels at CRPC remained strong prognostic factors.

4.2 Paper II

The majority of patients in all three study groups (PCD, OCD, PC-DCneg) were elderly (>80 years) at death. The median age at death was 84 years in all groups. In the PCD group, 21 percent of patients were younger than 75 years at death, with corresponding numbers of 14 percent in the OCD group and 16 percent in the PC-

DCneg group. Fourteen percent of patients in the PCD group, 20 percent in the OCD group and 14 percent in the PC-DCneg group were older than 90 years at death.

4.2.1 Patients registered as dead of prostate cancer (PCD group)

The final results of the review process demonstrated that 32 percent (N=105) of the 328 patients in the PCD group had died of other causes than PCa. Logistic regression demonstrated a statistically significant increase in misattribution rates with increasing age in the PCD group ($p<0.001$, OR 1.8 per 5 years, 95% CI 1.4–2.1). Among patients younger than 75 years, 10 percent (7/70) were incorrectly labeled as dead from PCa while the misattribution rate increased to 63% in patients aged 90 years and older (29/46). Misattribution of cause of death per age group in the PCD group is illustrated in Figure 8.

4.2.2 Patients registered as dead of other causes (OCD group)

The final results of the review process indicated that 18 percent of patients (N=23) had actually died of PCa. Logistic regression showed a statistically non-significant decreasing trend of misattribution by age in the OCD group ($p=0.33$, OR 1.2 per 5 years, 95% CI 0.9–1.6).

4.2.3 Patients with prostate cancer, not registered on the death certificate (PC-DCneg)

Among the 310 PC-DCneg patients, the review process identified 5 percent (N=14) who had died of PCa.

4.2.4 Overall misattribution

Underreporting of PCa deaths in the OCD and PC-DCneg groups was 18 and 5 percent respectively, while over-reporting in the PCD group was 32 percent. The net result was an over-reporting of PCa deaths of approximately 20 percent. The correlation between reported patient death and observed patient death was 0.81 (95% CI 0.78–

0.83), with Cohen's kappa (0.4, 95% CI 0.3–0.5) showing a moderate correlation between registered and true PCa death.

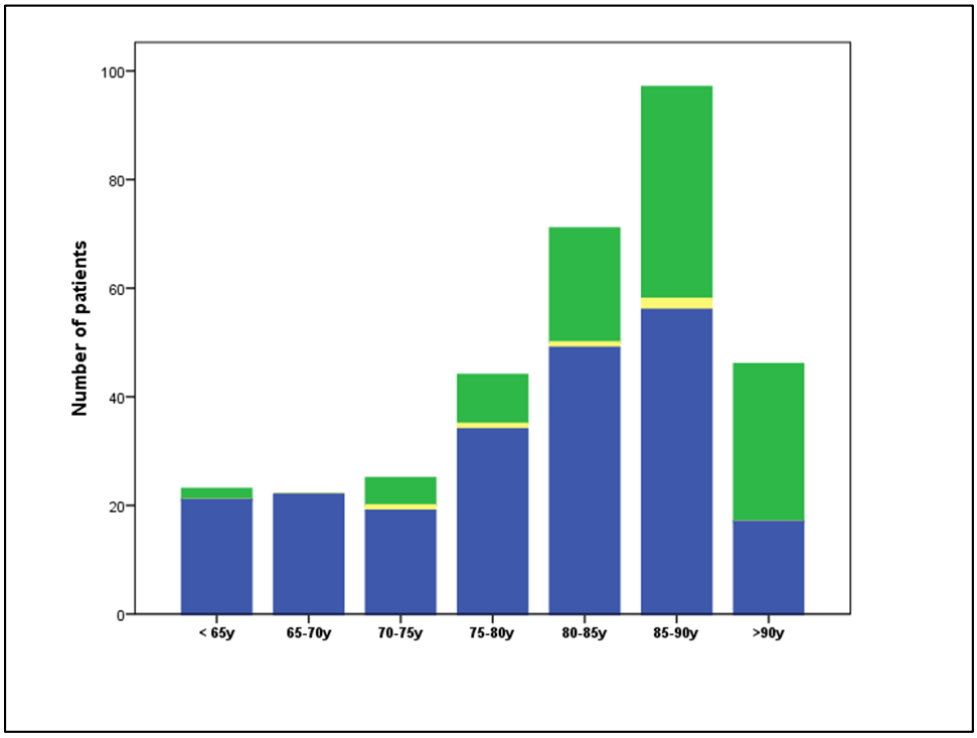

Fig. 8: Patients registered as dead from PCa (PCD) per age group: patients actually dead from PCa (blue), patients dead from other causes (green) and patients whose cause of death was not possible to determine (yellow).

4.3 Paper III

4.3.1 Vestfold cohort

Of the 117 patients from paper II who were included in the study (M0 at diagnosis, no curative treatment), 73 (62%) were initially treated with hormones, while 44 patients (38%) were followed with WW.

Further analysis of the decision process identified age as the main reason for abstaining from radical treatment (*NoTreat/Age*, N=43, 37%). Patients in this subgroup

represented 17 percent of the total PCa mortality in Vestfold County during the study period. All rationales for choosing hormone therapy or WW (*NoTreat/Other*, N=74, 63%) are illustrated in figure 9.

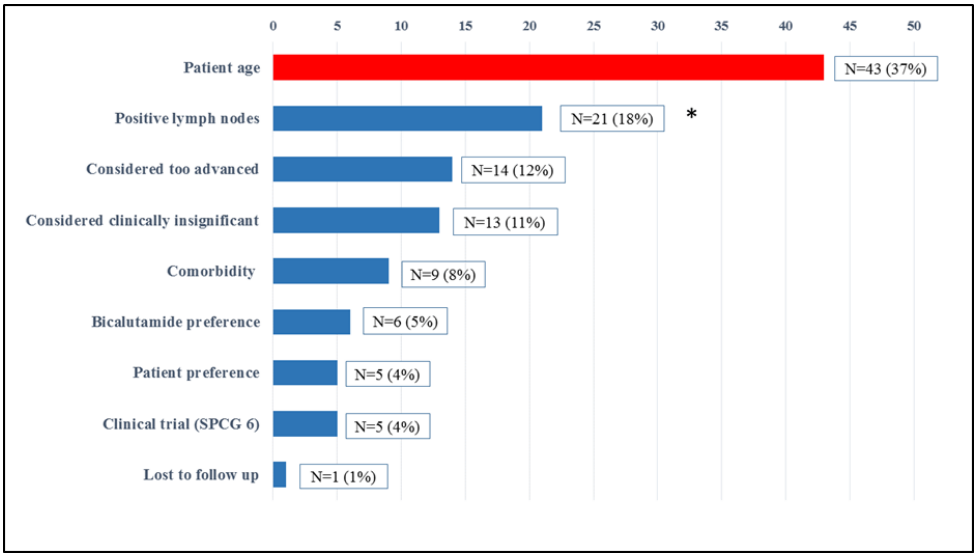

Fig. 9: Rationales for offering hormone therapy or WW in non-metastatic patients in the Vestfold Mortality Study (N=117)
* positive lymph nodes detected by surgical staging

The median age at diagnosis in the *NoTreat/Age* and *NoTreat/Other* groups was 79 and 70 years respectively, and the median time from diagnosis to death seven and eight years. Most patients in the *NoTreat/Age* group were in good functional shape at the time of diagnosis with an ECOG score of one or less. In terms of comorbidity, *NoTreat/Age* patients were in good health at diagnosis, with a Charlson comorbidity index (CCI) of zero or one (Fig. 3).

Almost all *NoTreat/Age* patients had either locally advanced or localized high-risk PCa at diagnosis. The median year of diagnosis for all patients was 2003 (IQR 2001-2007). Median year of diagnosis for patients in the *NoTreat/Age* group was 2005 and for patients in the *NoTreat/Other* group 2002.

In addition to dying of PCa, 86 percent of patients in the *NoTreat/Age* group developed local complications during the course of their disease. More than half of the patients needed bladder catheterization, twenty percent a nephrostomy and ten percent a colostomy (see fig. 10).

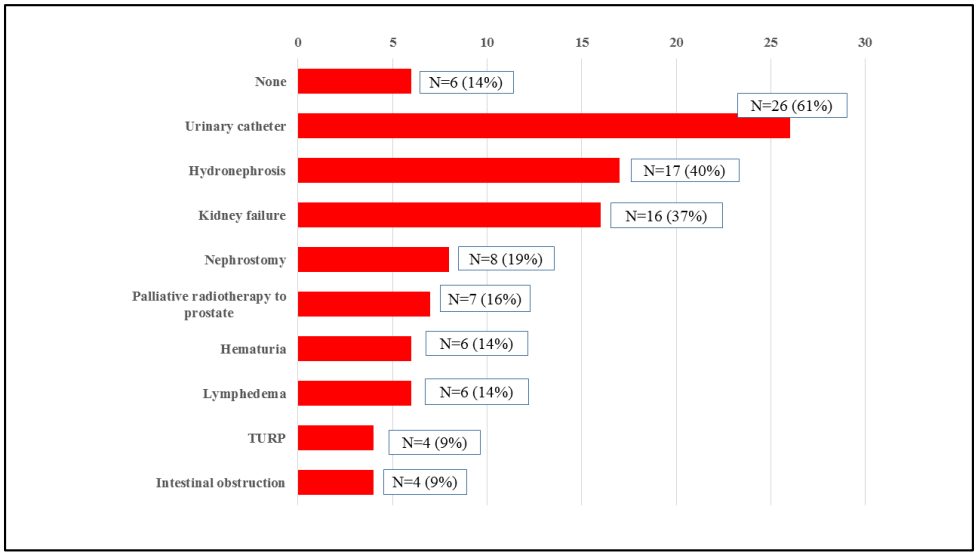

Fig. 10: Local complications during the course of the disease in patients with no local/ curative treatment due to age (*NoTreat/Age*, N=43). The total incidence of >100% is a result of the occurrence of two or more complications in a single patient.

Nineteen percent of patients received radiation to the bone (N=8), 7 percent were treated with docetaxel alone (N=3) and 14 percent were treated with various combinations of palliative therapies. Almost 60 percent of *NoTreat/Age* patients received neither docetaxel nor radiation to the bone nor any other second-line treatment (N=25). Only one patient (2%) received abiraterone alone and no patient received enzalutamide alone. Forty-seven percent of *NoTreat/Age* patients (N=20) received blood transfusions at least once due to cancer-induced anemia.

4.3.2 National data on treatment in elderly NMPCa patients, 2009-17

Among the 1874 CRN patients (age ≥ 75 years, WHO functional status 0, high-risk or locally advanced PCa, diagnosed 2009-2017), 748 patients had received local treatment of the prostate. There were 152 PCa deaths, 12 among patients with local treatment and 140 among patients without local treatment.

There was a significant survival benefit for patients aged 75-79 years who had received local treatment with a 5-year cause-specific survival of 99 percent (CI 97-100) versus 91 percent (CI 87-94, $p<0.001$). A similar difference was observed for patients aged 80+ with a 5-year cause-specific survival of 95 percent (CI 82–99) versus 80 percent (CI 76–85, $p=0.02$), but with too few PCa deaths to draw definite conclusions.

5. Discussion

5.1 Metastatic, castration-resistant prostate cancer (mCRPC) - Paper I

In a cohort of 130 consecutive patients with mCRPC at Vestfold Hospital Trust during the six-year period 2000-2005, we examined the natural course of this preterminal stage of PCa, which is heterogeneous. In order to address the need for risk-stratification of patients with mCRPC, we aimed to provide easily accessible, statistically independent prognostic factors from an unselected, population-based cohort of patients.

The median survival of approximately one year illustrates that mCRPC without life-prolonging treatment is a condition with a grim prognosis for the majority of patients. We identified a subgroup of mCRPC patients (6%, N=8) with extremely rapid progression of the disease whose median survival after the onset of mCRPC was only five months. These patients had virtually no effect of ADT (median effective hormone time 3 months) prior to the onset of mCRPC. On the opposite side of the spectrum we found a considerable number of long-time survivors with a survival time of three years and more following the onset of mCRPC (17%; N=22) which means that survival shows very heterogenous trajectories in patients with mCRPC (see fig. 7).

This "true natural course" of mCRPC without life-prolonging treatment other than ADT, was what nearly all patients had to face a mere fifteen years ago.

The landscape of mCRPC has changed considerably since. We conducted our study after the introduction of new therapeutic agents, which had demonstrated survival benefits for patients with mCRPC (see chapter 1.5.3). The trials investigating docetaxel (121, 122), abiraterone (138) and enzalutamide (139) as well as radium-223 (ALSYMPCA) (128) used control patients with mCRPC who received placebo and had otherwise only been treated with ADT. In theory therefore, control group survival

across these five trials should have been similar. However, median overall survival in the control groups ranged from eleven to thirty months.

Crossover from placebo to treatment arms and subsequent antineoplastic treatment was permitted in some trials and may explain some of the longer survival times.

However, bearing in mind the very heterogeneous trajectories of mCRPC patients that we documented in our study, one can also speculate that in the trials with the longest survival, patients were included during the early stages of mCRPC, while the contrary may have been the case in the trials with shorter survival. A further explanation for the considerable survival differences between our study and the abovementioned randomized clinical trials may be that patients with the most rapid progression of mCRPC and very short survival times identified by our study, were probably not included in any clinical trial. Table 4 lists treatment details and median survival of the abovementioned trials.

Table 4: Median survival of patients in the placebo arm of pre- and post- docetaxel trials.

Study	Trial drug	Antineoplastic treatment, placebo group	Median survival, mo
SWOG 99-16 (122)	Docetaxel	antineoplastic therapy permitted on progression	15.6
TAX 327 (121)	Docetaxel	Cross-over to trial drug permitted	16.5
PREVAIL (139)	Enzalutamide	antineoplastic therapy permitted, cross-over to trial drug permitted after unblinding	30.2
COU-AA-302 (138)	Abiraterone	Docetaxel permitted on progression, cross-over to trial drug permitted after unblinding	30.1
ALSYMPCA (128)	Radium 223	Majority of patients post-docetaxel (57%), post-trial drug treatment not documented	11.3

There have been repeated attempts to risk-stratify patients with mCRPC by prognostic factors resulting in the publication of several nomograms (140-143). When we evaluated these historic nomograms, we found that they incorporated patient populations with largely *symptomatic* mCRPC. The median survival was accordingly low (8-16 months from inclusion). With late stage selection being a significant issue in these older studies, it was doubtful that they were representative for current mCRPC patients who are usually seen at an earlier phase of mCRPC. Since the subjects incorporated in these nomograms were all participants in clinical trials at major referral centers, we also suspected a significant level of selection bias in patient populations. We thus clearly identified a need to better describe patients with mCRPC on a population-level and to provide risk-stratification tools to better predict individual risk and allow for better randomization procedures in clinical trials.

In our study, we confirmed the value of hemoglobin and alkaline phosphatase levels as prognostic markers. Low hemoglobin levels and high alkaline phosphatase levels likely reflect extensive cancer infiltration of bone marrow and are probably therefore associated with a poor prognosis. Short PSA doubling times after the onset of mCRPC and insufficient PSA nadir during ADT showed further negative impact on survival in our multivariate analysis.
Patients with the shortest survival times (< 6 months) were thus defined by PSA nadirs during ADT of more than >11 µG/L, PSA doubling times of less than 1.6 months, alkaline phosphatase above normal (>105 U/L) and low hemoglobin levels (<13.5 G/dL) at mCRPC. In clinical practice, patients with these characteristics would likely need early and aggressive treatment in order to delay the invariably fatal course of the disease. On the other hand, long-term survivors were characterized by excellent ADT responses with PSA nadirs ≤1 µG/L, PSA doubling times > 3 months and normal hemoglobin and alkaline phosphatase levels at the onset of mCRPC. With median survival times of three years, aggressive therapy may be delayed in these patients and even initial follow-up with watchful waiting could be considered.

The introduction of new therapeutical agents in the hormone-*naïve* setting since the publication of our study may have affected the natural course of mCRPC as we defined it. Three trials, CHAARTED (27), GETUG-AFU15 (117) and STAMPEDE (118), addressed the role of early docetaxel in addition to ADT (see chapter 1.4.2) with significant benefits in OS in CHAARTED and STAMPEDE. As a result, docetaxel upfront in combination with ADT is now SOC in patients with hormone-naïve M1 disease. Similar results for abiraterone were documented in the LATITUDE (119) and STAMPEDE trial (120).

With their documented effect on the course of PCa in terms of overall survival, it is likely that these agents and their use *prior to* the onset of mCRPC also affect the course of mCRPC. The validity of our prognostic factors will thus need to be evaluated anew under the changed circumstances.

However, despite the need for adjustment, it is likely that the prognostic factors we suggest still retain their usefulness for the clinician who needs to address individual patient risk.

A further aspect of paper I deserves notice: Among the 130 patients included in this study, 44 patients had non-metastatic disease (NMPCa) at diagnosis. Although this study does not further elaborate on how advanced these tumors were, it is striking that only one of the 44 NMPCa patients had received radical treatment. Patients were diagnosed with PCa between 1991 and 2005 and it is possible that the apparent underuse of radical treatments reflect the fact that surgery and radiotherapy were not yet firmly established treatment modalities in Norway for many study patients at the time of diagnosis. However, it is also possible that the inclusion criteria for radical treatment at the time did not reliably identify patients who were at real risk of developing late-stage PCa in the absence of aggressive treatment.

5.2 Defining prostate cancer death – Paper II

During the process of identifying patients with mCRPC in paper I, we evaluated the medical records of all patients with PCa during the study period (N=1460). The death certificates of the deceased patients that were available for review, raised quality and validity concerns.

In paper II, we documented that in a cohort of 328 consecutive patients with PCa listed as cause of death on the death certificate, one-third died of other causes. In contrast, among 436 patients with PCa whose death certificate indicated that they died of other causes, approximately one-tenth died of PCa. The net result was a considerable over-registration of PCa deaths in Vestfold County during the years 2009–2014.

Our study therefore casts considerably doubt on the validity of official PCa mortality statistics. The problem is exacerbated by our findings that misattribution rates were largest in the oldest age groups (see fig. 7) who represent the large majority of PCa deaths.

PCa mortality is reported as an age-adjusted number. In order to understand *age-adjusted PCa* mortality as an outcome it is important to understand the process and the data it is based upon. The terms that are used can be confusing. The following text and figures illustrate the process in which *absolute mortality numbers* are first computed into *age-specific death rates* and finally into *age-adjusted death rates*. Figure 11 shows the *absolute numbers* of PCa deaths in Norway in 2002 (blue columns) and in 2013 (red columns).

In most age groups, there was an increase in PCa deaths over this twelve-year period, with the exception of three age groups that saw slight decreases (50-54 yr, 60-64 yr, 80-84 yr) and one age groups with a large decrease (75-79 yr).

In order to acquire *age-specific mortality rates*, PCa mortality numbers from each age group are divided by the number of men in the respective age group in Norway (total number of men at risk) and then multiplied by 100 000. Figure 12 illustrates the resulting *age-specific mortality rates* for each age group for the same PCa populations as in figure 10 (2002 versus 2013).

We now see a decline in *age-specific PCa mortality rates* in almost every age group with the most pronounced changes between the ages of 75 and 94 years. This decline is –except for age group 75-79 years- mostly caused by an increase of the population at risk (denominator of the rate calculation), rather than a decline in absolute mortality numbers (numerator of the rate calculation).

A "standard" population distribution is finally used to adjust the *age-specific* rates. Several standard populations have been introduced; the most commonly used is the WHO standard population (144). The Cancer Registry of Norway (CRN) uses a Norwegian standard (mid-year population in 2014) (10). The resulting *age-adjusted rates* are rates that would have existed if the population under study had the same age distribution as the "standard" population. In our example, *age-adjusted PCa mortality* in 2002 was 56/ 100 000, while it decreased to 50/100 000 in 2013.

In spite of the final age-adjustment, it is important to realize that changes in *age-adjusted mortality* are a result of the underlying differences in *age-specific mortality rates*.

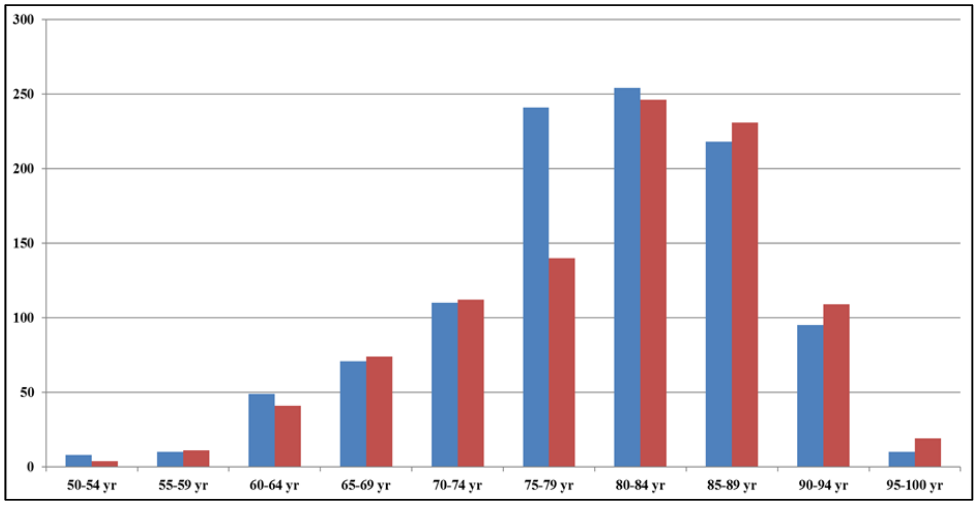

Fig. 11: Absolute numbers of PCa deaths in Norway per age group in 2002 (blue) and in 2013 (red); *Source: Statistics Norway (Statistisk Sentralbyrå, SSB)*

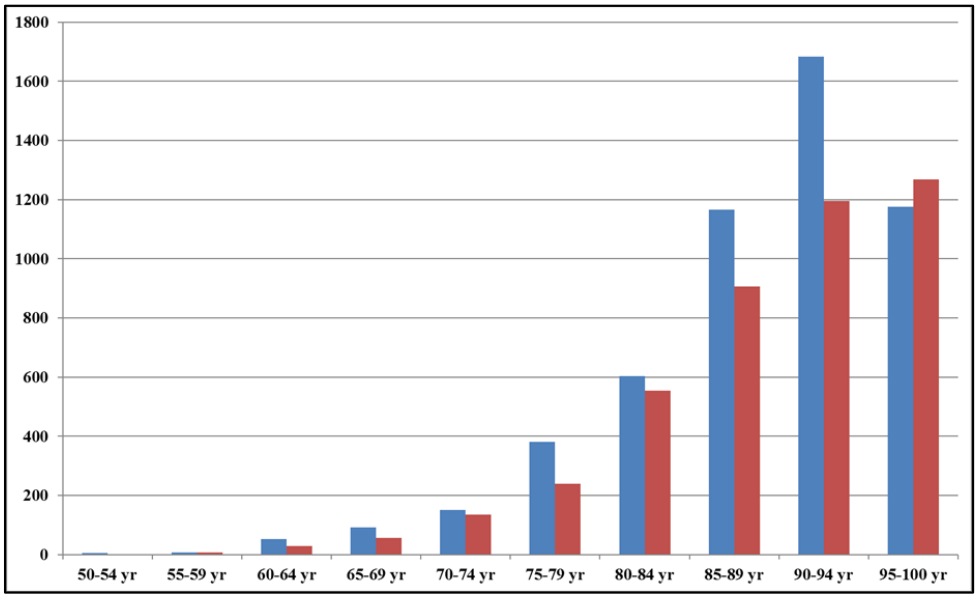

Fig. 12: age-specific PCa death rates (per 100 000 men) in Norway per age group in 2002 (blue) and 2013 (red); *Source: Statistics Norway (Statistisk Sentralbyrå, SSB)*

As mentioned above, the decrease in PCa mortality that has been observed in Norway between 2002 and 2013 was most pronounced in the oldest age groups in which we documented the largest misattribution rates of PCa deaths. Changes in PCa mortality should therefore be interpreted with caution. However, there is an inclination among urologists and oncologists to see improvements in PCa mortality exclusively as a consequence of improved screening and treatment methods (145). This is also illustrated by the reactions to the most recent report of cancer statistics in the US which showed a slight increase in PCa mortality for the first time since the early 1990's (146). The immediate responses on social media by respected capacities in PCa treatment suggest that this slight increase in PCa mortality is seen as a consequence of reduced PSA screening after the implementation of the D-recommendation by the USPSTF (147, 148). However, a recent review of modeling studies that analyzed population trends and extrapolated results from clinical trials, concluded that PSA screening can explain only 45% of the PCa mortality decline in the US while changes in primary treatment can explain 33% (47). This would leave 20% of the mortality decline unexplained. It is also unclear in which age groups the recent increase in PCa mortality occurred, as misattribution of cause of death may be one possible explanation. However, the misattribution rates for PCa as cause of death in the US are unknown.

Temporal changes of the underlying risk of PCa death in the male population, independent of screening and early treatment (reduced risk in the population at risk) and insufficient quality of death certificates can all lead to significant distortions of mortality statistics. This is especially important when interpreting the apparently high PCa mortality in Norway compared to other Western countries (149, 150).

It is possible that these differences are due to genetic factors (151). However, with the current definitions of genetic PCa (17), one would expect higher PCa mortality among men younger than seventy years in Norway compared to e.g. the United States. Yet differences in *age-specific mortality rates* between the two countries first become apparent in men older than 70 years (see figure 13).

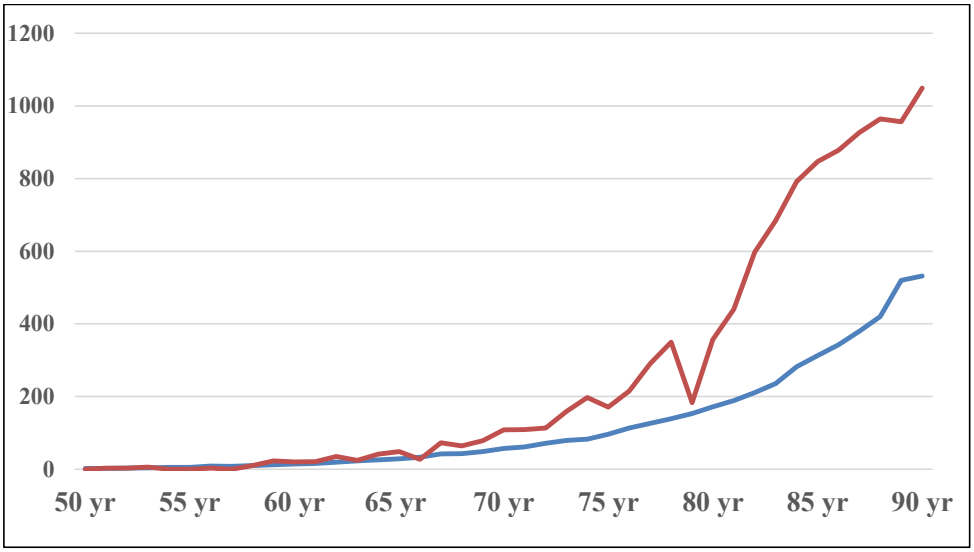

Fig. 13: Age-specific PCa mortality rates (per 100 000 men) for Norway (red) and the US (blue) in 2013
Source: Statistics Norway (SSB, Norwegian data), Center for Disease Control and Prevention (CDC, US data)

Although one cannot rule out that genetic dispositions or different screening and treatment policies are the main cause of this surplus PCa mortality, our results imply that it can partly be explained by over-reporting of PCa deaths.

The doctor who confirms the patient's death must fill out death certificates in Norway. These are usually junior hospital doctors or on-call doctors at the municipal primary care emergency departments (Legevakt) and nursing homes, who rarely have intimate knowledge of the patient's medical history. In contrast to the Norwegian practice, in the US the coroner's office determines the cause of death while in Germany the family doctor makes the decision. It is possible that the latter systems result in improved cause of death determination.

The increasing age of PCa patients seems to have impacted this problem further: The majority of PCa deaths thirty years ago occurred in hospitals where determination of

the cause of death is usually more accurate (152), while only one third occurred in nursing homes. By 2014, these numbers were reversed, with more than 60% of PCa deaths occurring in nursing homes and only 23% in hospitals (2016 mail correspondence with the Norwegian Institute of Public Health).

Our findings of subpar PCa death reporting stand in contrast to earlier studies, which showed that PCa mortality statistics based on death certificates, were relatively reliable in Norway (153, 154). However, these studies were register-based without access to patient records. Furthermore, they evaluated PCa deaths that occurred in 1996, prior to the considerable increase in PCa prevalence that has been observed since. PCa prevalence in this context appears to have a clear impact on PCa mortality: Studies from the early PSA era in the US showed that rising and falling PCa prevalence rates were mirrored directly by corresponding changes in mortality rates (155). The most likely explanation was that a fixed percentage of the rising and falling pool of newly diagnosed PCa patients was mislabeled as dying of the disease. If similar misattribution mechanisms apply to Norway, then misattribution rates have likely increased considerably during the past fifteen years which have seen a doubling of PCa prevalence in Norway, probably due to increasing PSA testing (8).
Further publications of death certificate audits are available from Finnish, Swedish and UK PCa trials (156-159). They consistently show high accuracy of death certificates, while a similar evaluation in a group of PCa patients in the US showed more ambivalent results (131). However, PCa deaths that were evaluated in these studies occurred within the framework of clinical trials and patients were on average significantly younger at death than PCa patients in the general population (*maximum* age at death 74–77 years in the Finnish and Swedish trials versus *median* age at death 83 years in the Norwegian population).

There is a further aspect of PCa death that may be controversial: That not every PCa death is an event that must be prevented. The in-depth review of patient histories that formed the basis of paper II showed that quite regularly PCa death is not only a normal

but also sometimes a welcome and natural end to a long life. This is mirrored both by the fact that almost twenty percent of patients had dementia at the time of death and the abovementioned high percentage of patients who die at nursing homes. Many of the patients also had several competing comorbidities with short expected survival. The concept of "acceptable" PCa death is difficult to define in an academic setting and it is not incorporated in our prediction tools. However, it is an important aspect to address when patients have to weigh the side effects of early treatment against the benefit of reducing their risk of dying of PCa.

Finally, enforcing our findings from paper I, we documented that only a small number of patients with NMPCa at diagnosis and potentially curable disease had received radical treatment (16%). This consistent finding led to the more thorough investigation of the rationales behind decision treatments for patients with NMPC that represents the background for paper III.

5.3 Treatment decisions and consequences in elderly prostate cancer patients – Paper III

We documented in this study that many patients with lethal PCa but potentially curable disease at diagnosis did not receive radical treatment based on their chronological age alone (≥75 years). In addition to dying of PCa, most of these patients experienced considerable morbidity caused by local PCa complications. Our analysis of national data suggest that local treatment of elderly PCa patients with good functional status may reduce PCa specific mortality (PCSM).

There is increasing evidence that elderly cancer patients in general are undertreated, particularly with regard to local, curative therapy (160-162). In PCa, elderly men with NMPCa have been treated with hormone therapy or followed with watchful waiting, partly due to the lack of documented benefit of radical treatment (163). In our study, we documented that in addition to age, stringent national thresholds (PSA, lymph node

status) for radical treatment ten to fifteen years ago, excluded patients that would be eligible for radical treatment according to current guidelines (17).

Contradicting the notion that NMPCa in elderly patients is harmless, there is increasing evidence that locally advanced and high-risk NMPCa is often deadly regardless of age. A US study, based on SEER-Medicare data, demonstrated a 10-year PCSM of 27 percent for patients ≥75 years with high-risk, localized PCa (164). In Sweden, a register-based study found that even in patients ≥85 years, untreated, locally advanced PCa with Gleason 8-10 was associated with a mortality rate of 42 percent (46).
The nationwide data from our study suggest that effective local treatment of the prostate may reduce PCSM in patients ≥75 years. Several other studies support this notion. A Swedish, nationwide, register-based study indicated that radiotherapy had the potential of improving PCSM in elderly patients (165). Sheng and colleagues also found a positive impact of local treatment on PCSM in elderly American patients (aged ≥ 75 years, locally advanced PCa, SEER database). However, the benefit was only seen in patients with cT3b/4 tumors, Gleason score 8–10, negative lymph nodes or PSA > 10 ng/ml (166). In Australia, a register-based study also found that radical treatment reduced the risk of PCSM even in patients >80 years (167).

The risk of developing high-risk and locally advanced PCa increases with age (46, 168). Somewhat paradoxically, elderly men with PCa are less likely to receive radical treatment (165, 169). A recent publication of data from the US National Cancer Database (NCDB) documented that increasing age was significantly associated with decreased likelihood of radical treatment in patients with intermediate and high-risk PCa. Interestingly, despite the claim of undertreatment of the elderly, the study showed that more than half of patients older than 80 years had received some form of local treatment, mostly radiotherapy (170). This contrast sharply with treatment policies in Norway: While in 2004, less than five percent of patients aged 75-79 years had received radical treatment, these numbers increased gradually during the following

twelve years (~50% radical treatment in 2016). However, even in 2016 only slightly more than 10 percent of patients older than 80 years had received radical therapy (radiotherapy, ≥70Gy, ≤12 months of diagnosis) (8). This appears to have been even more pronounced in Sweden. In a nationwide cohort study with over 120 000 men aged 55 to 95 years, diagnosed with PCa in 1998 to 2012, virtually no man >80 years had received radical treatment (171).

What may be the reason for the apparent reluctance to treat elderly patients with NMPCa radically? First, it is possible that findings from SPCG4 left the impression that radical treatment did not confer a survival benefit for patients older than 65 years (81). However, most patients included in SPCG4 had intermediate-risk PCa and the results should therefore not be extrapolated to patients with high-risk or locally advanced PCa. Of note, SPCG4 demonstrated reduced incidence of metastasis and ADT use also in patients older than 65 years.

Furthermore, none of the major randomized clinical trials on radical treatment versus hormone therapy or watchful waiting included patients older than 75 years (81-83, 172). Only one of the randomized trials investigating radiotherapy in combination with ADT versus ADT alone included patients 75-80 years of age (173). This leaves us with no level 1 evidence for determining the role of radical treatment in the elderly.

A further reason for deferring radical treatment is underestimation of patients' life expectancy (174, 175). The background for this may be a misconception about life expectancy statistics in general. In most Western European countries life expectancy for men is somewhere in the range between 77 and 80 years (176). Intuitively, treating patients in this age group radically with little documented benefit of treatment for the first years can seem futile and unnecessary. However, the abovementioned life expectancy numbers refer to life expectancy *at birth*. Life expectancy later in life is a different matter. For example, a 75-year-old Norwegian man in 2018 had a mean life expectancy of 11.7 years, while an 80-year-old still had a mean life expectancy of 8.5 years (Source: Statistics Norway, www.ssb.no).

Local complications of PCa have been a focus area with regard to treatment effects (100) but there is little literature on complications caused by uninhibited local tumor progression. This aspect of the disease is difficult to address in registry-based studies that do not have access to these kind of data. An unintended consequence could be that complications and side effects caused by treatment receive more consideration when we give advice to patients than complications caused by local, uninhibited tumor growth.

We documented in our study that almost all of the elderly NMPCa patients that had not received local treatment of the prostate experienced some form of local complication during the further course of the disease. Local treatment of the prostate has the potential to alleviate or even avoid these complications altogether. However, the possible benefits of treatment must be weighed against the side effects. Ideally, the issue should be addressed in the setting of a clinical trial.

Our findings lend further support to the notion that elderly patients who are in good health and have good functional status and who are diagnosed with high-risk or locally advanced PCa should be considered for radical therapy regardless of their chronological age. Future clinical trials investigating the effects of local treatment should not exclude patients based on their chronological age alone.

6. Strengths and limitations

6.1 Strengths

All three papers describe patient populations from Vestfold County, which only has one department of urology and had no urologists or oncologists in private practice at the time. This allowed for a comprehensive analysis of patient records and for access to high-quality data despite the retrospective design of the studies. All analyses were performed in consecutive and unselected patient groups.

In paper II, the direct access to patient records instead of registry information provided a high level of accuracy in determining patients' cause of death.

The CRN data in paper III allow for an extended view on a nation-wide level. CRN has coverage of more than 99 percent of cancers in Norway (177) which means that analyses of CRN data can be performed with a high degree of accuracy.

6.2 Limitations

The comparatively small size and regional restriction of the patient population in Vestfold County are limitations, particularly with regard to the generalizability of our finding to the national level.

Furthermore, the retrospective nature of our analyses prohibited the collection of some important data. This was a limiting factor particularly in paper I, in which we could not quantify metastatic burden and describe metastatic sites. The medical records lacked systematic documentation of patient performance and pain status, which are established prognostic factors. Furthermore, the calculations of PSA doubling times and description of PSA nadirs were probably influenced by the variation of time intervals between analyses, which is a major difference between clinical trials and daily clinical practice that our analyses were based upon.

Furthermore, the imaging studies used at the time (mostly bone scans) may have resulted in an under-diagnosis of metastatic disease compared to current MRI based imaging.

Furthermore, the 38 patients who had received docetaxel as second line treatment and who were excluded from paper I were younger at diagnosis and at mCRPC, which may have biased the results. A further limitation of paper I was that not all parameters were available for every patient. However, MCMC multiple logistic regression imputation showed that this did not significantly affect the Cox multivariate analyses. In paper II, the clinical decision-making process to identify the correct cause of death was potentially biased. This may have led to either over-estimation or under-estimation of PCa mortality.

The committee members in this study treated PCa patients daily. A different mix of specialties may have led to different conclusions for some of the patients.

Paper III makes a point for providing more local treatment of the prostate in elderly patients, but does not provide a measure of overtreatment such an approach would likely entail.

7. Conclusions; Prostate cancer morbidity and mortality in Norway

The three papers in our study demonstrate that defining late stage PCa and describing and interpreting PCa mortality correctly is complex. Several lessons and conclusions can be drawn from our work:

- Late stage PCa (mCRPC) is a heterogeneous condition with diverse survival.
- Its natural course can be defined by easily accessible parameters
- PCa death reported on death certificates is unreliable particularly among the elderly and it is unsuitable as a stand-alone outcome measure in Norway
- There are indications of undertreatment at diagnosis both in patients who later develop late-stage PCa and in patients who die of PCa.
- Decisions with regard to radical treatment for patients with NMPCa are unduly influenced by patient age and by underestimation of patient life expectancy
- The majority of elderly patients with high risk or locally advanced NMPCa not treated with local therapy suffer considerable local complications
- PCSM in elderly patients who are in good health, who present with good functional status and who are diagnosed with high risk or locally advanced NMPCa may be reduced with local therapy
- Randomized, clinical trials investigating the effects of local treatment of PCa should not exclude patients based on their chronological age.

8. Future perspectives

- There is a need to supplement PCa mortality with other public health outcome measures. To this purpose, a nation-wide registry of patients who have late-stage PCa ***and*** who receive life-prolonging oncologic treatment could be established. Such a registry has several advantages over PCa mortality as a stand-alone measure. First, very old and frail patients who die of PCa at e.g. nursing homes and who are unsuited for active oncologic treatment would not be registered. This would introduce some differentiation of PCa death, between death that is "natural" and death that should be prevented if possible. Second, risk-stratification models could be better tailored to identify patients who are at risk for developing late-stage PCa and the need for active oncologic treatment rather than patients who are at risk of a "natural" PCa death. Finally, the suggested registry would enable a continuous evaluation of treatment effects, treatment side effects and disease-related side effects over time.

- We identified the need for a randomized clinical trial investigating local treatment versus no local treatment in NMPCa patients ≥75 years who have normal functional status and good health. Such a trial would give better guidance on who would benefit from treatment, give a measure of overtreatment and clarify the potential of local treatment to reduce PCa mortality and morbidity.

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ORIGINAL ARTICLE

High Norwegian prostate cancer mortality: evidence of over-reporting

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ABSTRACT

Objective: This study aimed to determine the level of misattribution of prostate cancer deaths in Norway based on the county of Vestfold in the years 2009–2014.

Materials and methods: The study included 328 patients registered as dead from prostate cancer (PCD; part I of death certificate), 126 patients with prostate cancer as other significant condition at death (OCD; part II of death certificate) and 310 patients who died with a diagnosis of prostate cancer not registered on the death certificate (PC-DCneg) in Vestfold County in 2009–2014. The complete cohort with patients' names and dates of birth was provided by the Norwegian Institute of Public Health and the Norwegian Cancer Registry. The true cause of death of all patients was evaluated based on patient journals.

Results: Over-reporting of prostate cancer deaths in the PCD group was 33% while under-reporting in the OCD and PC-DCneg groups was 19% and 5%, respectively. The correlation between registered and observed causes of death was 0.81 (95% confidence interval 0.78–0.83). Misattribution of prostate cancer deaths increased significantly with patient age and decreasing Gleason score.

Conclusions: Prostate cancer mortality statistics in Norway are relatively accurate for patients aged <75 years at death. However, overall accuracy of cause of death assignment is significantly reduced by misattribution among older patients (>75 years), who represent the large majority of prostate cancer deaths. Over-reporting of prostate cancer deaths among elderly people may not be an exclusively Norwegian phenomenon and may affect prostate cancer mortality statistics in other countries.

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Introduction

Official cancer mortality statistics strongly influence the perception of different cancers, their impact on public health and the effects of treatment efforts [1]. The accurate determination of cancer deaths and high quality of death certificates are essential for achieving reliable mortality statistics. However, such high-quality information is commonly only available in clinical trials or hospital series.

Norway and other Scandinavian countries report consistently higher prostate cancer mortality rates than other Western countries [1,2]. Several explanations for this have been suggested, among them a potentially higher underlying risk of prostate cancer death and differences in national health strategies regarding screening and treatment [2]. In 1981, Percy et al. documented that misattribution of cause of death in death certificates may bias mortality statistics [3]. Several studies have since corroborated this evidence [4–6]. For prostate cancer, there is compelling evidence that increasing prevalence due to screening has significantly affected misattribution of prostate cancer deaths [7].

Several Scandinavian studies have addressed the quality of death certificates with regard to prostate cancer, demonstrating relatively reliable results with misattribution rates of 10% or less [8–11]. However, previous audits of prostate cancer deaths have been either registry based [10,11] or conducted in study patients who were considerably younger at death than the majority of men dying of prostate cancer [8,9]. Correct attribution of the underlying cause of death becomes more challenging with increasing age owing to competing comorbidities [12]. A recent Norwegian study, comparing relative and cause-specific survival for several cancer sites, documented significant differences for older prostate cancer patients, suggesting incorrect coding of the underlying cause of death [13].

Increasing prostate cancer incidence rates in Norway and the likely corresponding increase in prevalence of non-lethal cancers may potentially exacerbate this problem of misattribution bias.

The aim of this population-based study was to determine the level of misattribution of Norwegian prostate cancer

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Supplemental data for this article can be accessed here.

deaths based on data from the county of Vestfold in the years 2009–2014.

Materials and methods

Study population

Vestfold Hospital Trust is the only hospital in Vestfold County, which has approximately 230,000 inhabitants representing approximately 5% of the Norwegian population. Vestfold County has a somewhat higher proportion of men older than 70 years than the rest of Norway, but is otherwise representative of the entire country in terms of relevant socioeconomic factors (see supplementary material).

For the 6 year period 2009–2014, names and dates of birth of all deceased men in Vestfold County, registered with either prostate cancer as the immediate/underlying cause of death (part I of the death certificate, $n = 341$) or another significant condition at death (part II of the death certificate, $n = 127$), were obtained from the Norwegian Institute of Public Health, while data on all deceased men with prostate cancer whose diagnosis was not mentioned on the death certificate were obtained from the Norwegian Cancer Registry.

Prostate cancer care for almost all patients in the county of Vestfold is provided at Vestfold Hospital Trust, including diagnosis, treatment and follow-up. Patients from two peripheral municipalities, who routinely receive their prostate cancer care elsewhere, were excluded from the study. This resulted in a study population of 328 patients with prostate cancer as an immediate or underlying cause of death (part I of the death certificate), referred to as PCD; 126 patients with prostate cancer as other significant condition (part II of the death certificate), referred to as OCD; and 310 patients with prostate cancer without any mention of prostate cancer on the death certificate, referred to as PC-DCneg (Norwegian Cancer Registry).

Assessment of cause of death

A review committee was formed consisting of three urologists and one oncologist, all of whom were experienced in treating prostate cancer patients. Three consecutive reviews of the study population were conducted. Patient hospital records provided sufficient information on medical histories for the great majority of patients. For 12 patients, additional information had to be obtained from nursing homes or family doctors.

First review of patient history

The first review served as a filtering process and identified patients with an unambiguous, immediate cause of death and a clear underlying disease process, separating out patients ascribed as either dead from prostate cancer (PCD) or dead from other causes (OCD). The review was conducted by the first author, with a blinded audit of 50 random patients in the sample by two other committee members demonstrating perfect correlation.

Table 1. First review of patient history: definition of death from other causes for patients with prostate cancer as underlying of immediate cause of death (PCD, $n = 328$) and corresponding results.

	No. of patients (%)
No histological or clinical diagnosis of prostate cancer	15 (4.6)
Watchful waiting with no significant disease activity	13 (4)
Previous radical treatment with no disease recurrence and an immediate cause of death not related to treatment	5 (1.5)
Hormone therapy with complete response to treatment and an immediate cause of death unrelated to hormone therapy, and other	33 (10.1)
Other, clinically more significant metastatic malignancies	4 (1.2)
Total	70 (21.3)

Prostate cancer death was assumed when the immediate cause of death was caused by systemic or local complications of the disease process or cancer-directed treatment and comorbidities were either absent or only of minor importance. Death from other causes was defined by the criteria listed in Table 1.

Patients who could not be placed with certainty in either of the above categories were included in the second review for further evaluation.

Patients who had been autopsied were registered with the underlying cause of death given on the autopsy report, and no further review of the cause of death was conducted ($n = 16$).

Second review of patient history

Patients were independently reviewed by committee members unaware of the other reviews. Prostate cancer death was assumed when the immediate cause of death was due to systemic or local complications of the disease process or cancer-directed treatment. The following categories were assigned, answering the question of whether the patient's death was due to prostate cancer: 'Yes/No' (preferable category), 'Likely/Unlikely' (if a definite answer was not possible) or 'Not possible to determine' (if any qualified answer was impossible to give, owing to numerous and competing comorbidities). Patients on whom committee members reached conflicting conclusions were included in the third review.

Third review of patient history

Patients whose underlying cause of death was still undetermined after the first two reviews were discussed in a consensus meeting with all members of the committee present. Patient histories were reviewed in plenum and a consensus decision was reached upon which all committee members could agree. Assignment of labels followed the same rules as outlined under the second review of patient history.

Final result

All patients with the label 'Yes' or 'Likely' after the third review were collapsed into the final Yes category (dead from prostate cancer). Patients labeled 'No' or 'Unlikely' were

Table 2. Comparison of clinical characteristics of patients with prostate cancer as the immediate or underlying cause of death according to the death certificate (PCD), patients with prostate cancer as other significant condition at death (OCD) and patients with prostate cancer with no mention of the diagnosis on the death certificate (PC-DCneg).

	PCD patients	OCD patients	PC-DCneg patients
All patients			
No. of patients	328	126	310
Age at death (years)	84 (50–97)	84 (59–98)	83 (57–101)
Patients with prostate cancer			
No. of patients	313	111	308
Year of diagnosis	1989–2014 (2007)	1988–2014 (2005)	1985–2013 (2005)
Age at diagnosis (years)	76 (48–96)	76 (52–93)	75 (55–96)
Age at death (years)	83 (50–97)	83 (59–98)	83 (57–101)
PSA at diagnosis (µg/l)	34 (0–10 000)	21 (1–2853)	15 (0–4400)
Gleason score at diagnosis			
≤6	29 (9)	23 (21)	106 (35)
7	102 (33)	36 (32)	119 (39)
8–10	128 (41)	34 (31)	54 (18)
Unknown	54 (17)	18 (16)	29 (9)
T stage			
T1	44 (14)	21 (19)	117 (38)
T2	41 (13)	14 (13)	65 (21)
T3	140 (45)	59 (53)	100 (33)
T4	48 (15)	9 (8)	17 (6)
Unknown	40 (13)	8 (7)	9 (3)
Metastatic status at diagnosis			
Yes	106 (34)	18 (16)	30 (10)
No	178 (57)	85 (77)	268 (87)
Unknown	29 (9)	8 (7)	10 (3)
Metastatic status at death			
Yes	230 (74)	26 (23)	22 (7)
No	63 (20)	84 (76)	279 (91)
Unknown	21 (6)	1 (1)	7 (2)
Primary treatment			
Hormone therapy	223 (71)	55 (50)	110 (36)
Radical prostatectomy	11 (4)	9 (8)	26 (8)
Radiation therapy	15 (5)	9 (8)	31 (10)
Watchful waiting	61 (20)	37 (33)	115 (37)
Active surveillance			5 (2)
Autopsy finding			2 (1)
Cystoprostatectomy (bladder cancer)			15 (5)
Other	3 (1)	1 (1)	4 (1)
Time from diagnosis to death (years)	5 (0–22)	6 (0–22)	6 (0–27)
Hormone therapy at death	284 (91)	82 (74)	143 (46)
mCRPC at death	200 (64)	39 (35)	40 (13)

Data are shown as *n*, median (range) or *n* (%).
PSA: prostate-specific antigen; mCRPC: metastatic castration-resistant prostate cancer.

collapsed into the final No category (not dead from prostate cancer). 'Not possible to determine' was upheld as an independent category.

Statistics

Baseline data and prostate cancer death misclassification rates were described by median, range and percentages. Confidence intervals (CIs) for percentages were calculated using Wilson score interval with Yates' continuity correction. The effect of age and study year on the risk of misclassifying cause of death was studied by binary logistic regression. Subgroup analysis was performed by dividing patients into seven age groups (<65, 65–70, 70–75, 75–80, 80–85, 85–90, and >90 years). All statistical analyses were conducted using SPSS statistics, version 23 (IBM Corp., Armonk, NY, USA) and the R statistical package [14]. Correlation between the cause-of-death methods was calculated using Cohen's kappa.

Ethics

The study was approved by the Regional Committee for Medical Research Ethics (REK).

Results

The median age at death was 83–84 years in all groups. In the PCD group, 21% of patients were younger than 75 years at death, with corresponding numbers of 14% in the OCD group and 16% in the PC-DCneg group ($n = 70$, $n = 18$, $n = 50$), while 14% of patients in the PCD group, 20% in the OCD group and 14% in the PC-DCneg group were older than 90 years at death ($n = 46$, $n = 25$, $n = 43$). Dementia had been diagnosed in 18% of the PCD patients, 11% of the OCD patients and 10% of the PC-DCneg patients ($n = 58$, $n = 14$, $n = 32$). Fifteen patients in both the PCD and OCD groups and two patients in the PC-DCneg group had no clinical or histological diagnosis of prostate cancer. The clinical characteristics of all patients are listed in Table 2.

Death from prostate cancer (PCD)

The first review of the PCD group identified 21% of patients ($n = 70$) who had died of causes other than prostate cancer. Their prostate cancer status at death is listed in Table 1. The final result of the review process demonstrated that 32% of

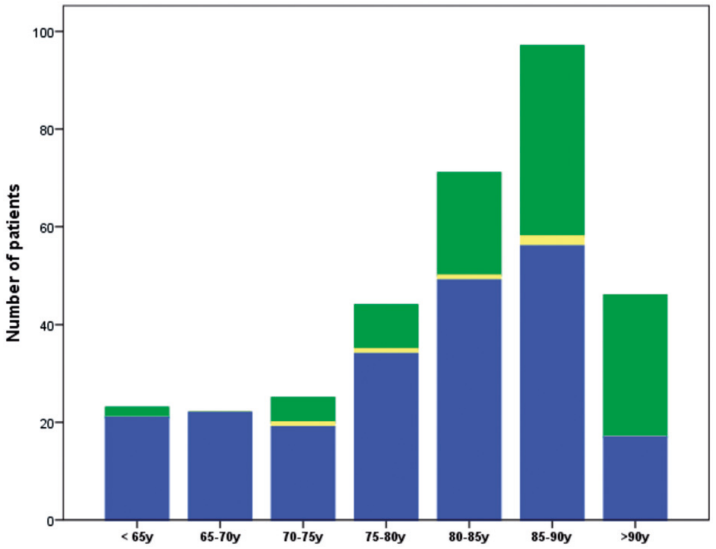

Figure 1. Total number of patients registered as dead from prostate cancer per age group: patients dead from prostate cancer (blue), patients dead from other causes (green) and patients whose cause of death was not possible to determine (yellow).

patients ($n = 105$) in the PCD group had died of other causes. Logistic regression demonstrated a statistically significant increase in misattribution rates with increasing age in the PCD group ($p < 0.001$, OR 1.8 per 5 years, 95% CI 1.4–2.1). Among patients younger than 75 years, 10% (7/70) were incorrectly labeled as dead from prostate cancer while the misattribution rate increased to 63% in patients aged 90 years and older (29/46). Misattribution of cause of death per age group in the PCD group is illustrated in Figure 1. Logistic regression revealed a statistically significant impact on misattribution rates by Gleason grade ($p = 0.007$, OR 0.7, 95% CI 0.5–0.9). There was no statistically significant variation in misattribution rates for the years of diagnosis 2009–2014 ($p = 0.25$, OR 1.1, 95% CI 1.0–1.2) or for tumor stage at diagnosis ($p = 0.12$, OR 0.8, 95% CI 0.6–1.1).

Death from other causes (OCD)

In the OCD group, the final results of the review process indicated that 18% of patients ($n = 23$) had died of prostate cancer. Logistic regression showed a statistically non-significant decreasing trend of misattribution by age in the OCD group ($p = 0.33$, OR 1.2 per 5 years, 95% CI 0.9–1.6). Misattribution of cause of death per age group in the OCD group is illustrated in Figure 2. Gleason grade had a statistically significant impact on misattribution ($p = 0.006$, OR 0.5, 95% CI 0.3–0.8). There was no statistically significant variation in misattribution rates for year of diagnosis ($p = 0.18$, OR 0.8, 95% CI 0.6–1.1) or stage at diagnosis ($p = 0.25$, OR 0.7, 95% CI 0.4–1.3).

The review process of PCD and OCD patients and its results are illustrated in Tables 3 and 4.

Patients with prostate cancer not registered on the death certificate (PC-DCneg)

Among the 310 PC-DCneg patients, the review process identified 5% ($n = 14$) who had died of prostate cancer.

Underreporting of prostate cancer deaths in the OCD and PC-DCneg groups was 18% and 5%, respectively, while over-reporting in the PCD group was 32% (Figure 3). The correlation between reported patient death and observed patient death was 0.81 (95% CI 0.78–0.83), with Cohen's kappa (0.4, 95% CI 0.3–0.5) showing a moderate correlation between registered and true prostate cancer death.

Discussion

In a cohort of 328 consecutive patients with prostate cancer as cause of death, this study found that one-third died of other causes, while among 436 patients with prostate cancer who died of other causes approximately one-tenth died of prostate cancer. The net result was a considerable over-registration of prostate cancer deaths in Vestfold County for the years 2009–2014.

This study has several strengths: its population-based design, the consecutive cohort of patients, the 6 year study period and rich clinical data for the majority of patients. The weaknesses of the study are its limited geographical scope and the difficult clinical decision-making process, which might be biased. The committee members in this study treat prostate cancer patients daily. A panel of physicians from other specialties may have come to different conclusions for some of the study patients.

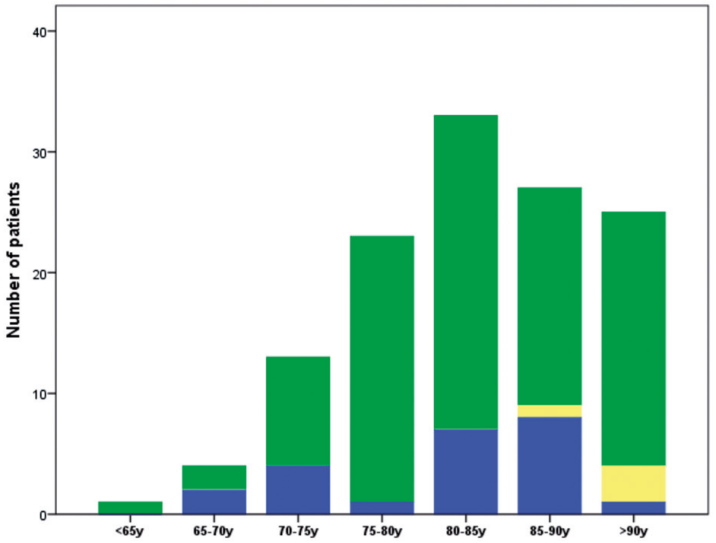

Figure 2. Total number of patients registered as dead from other causes per age group: patients dead from prostate cancer (blue), patients dead from other causes (green) and patients whose cause of death was not possible to determine (yellow).

Table 3. Results of the review process for patients with prostate cancer as the immediate or underlying cause of death (PCD) ($n = 328$).

Prostate cancer death	First review		Second review		Third review		Final result	
	% (95% CI)	*n*	% (95% CI)	*n*	% (95% CI)	*n*	% (95% CI)	*n*
Yes	58 (52–63)	189	60 (54–65)	195	62 (56–67)	202	67 (61–72)	218
No	21 (17–26)	70	26 (21–31)	85	29 (24–34)	94	32 (27–37)	105
Likely	–	–	2 (1–4.5)	7	5 (3–8)	16	–	–
Unlikely	–	–	0.3 (0–2)	1	3 (2–6)	11	–	–
Not possible to determine	–	–	0.6 (0–2)	2	2 (1–4)	5	2 (1–3)	5
Further discussion needed	21 (16–26)	69	12 (8–16)	38	–	–	–	–

CI: confidence interval.

Table 4. Results of the review process for patients with prostate cancer as other significant condition at death (OCD) ($n = 126$).

Prostate cancer death	First review		Second review		Third review		Final result	
	% (95% CI)	*n*	% (95% CI)	*n*	% (95% CI)	*n*	% (95% CI)	*n*
Yes	14 (8–21)	17	15 (10–23)	19	16 (10–24)	20	18 (12–26)	23
No	66 (57–74)	83	72 (63–79)	90	75 (66–82)	94	79 (70–85)	99
Likely	–	–	0.8 (0–5)	1	2 (1–7)	3	–	–
Unlikely	–	–	2 (0–6)	2	4 (2–10)	5	–	–
Not possible to determine	–	–	0.8 (0–5)	1	3 (1–8)	4	3 (1–8)	4
Further discussion needed	21 (14–29)	26	10 (6–17)	13	–	–	–	–

CI: confidence interval.

The findings seem to contradict previous studies which documented relatively reliable mortality numbers for prostate cancer in Norway [10,11]. However, these studies were register based and evaluated prostate cancer deaths that occurred in 1996, before the PSA-induced increase in prostate cancer prevalence. Feuer et al. demonstrated during the early PSA era that rising prostate cancer prevalence rates were mirrored directly by corresponding changes in mortality rates [7]. The authors hypothesized that a fixed percentage of the rising and falling pool of newly diagnosed prostate cancer patients was mislabeled as dying of the disease [7]. According to this theory, it is likely that misattribution rates in Norway have increased considerably during the past decade (2004–2013) as prostate cancer prevalence has doubled at least partly owing to extensive PSA testing [15]. Prostate cancer prevalence is equal in Vestfold County and on the national level, suggesting that misattribution rates may be comparable [16]. A more recent study by the Norwegian Cancer Registry demonstrated that relative survival estimates for prostate cancer were consistently above cause-specific survival estimates for all but the very youngest patients, with the most marked differences among the oldest patients (>85 years) [13]. One explanation suggested by the authors is that prostate cancer patients in Norway are somewhat healthier

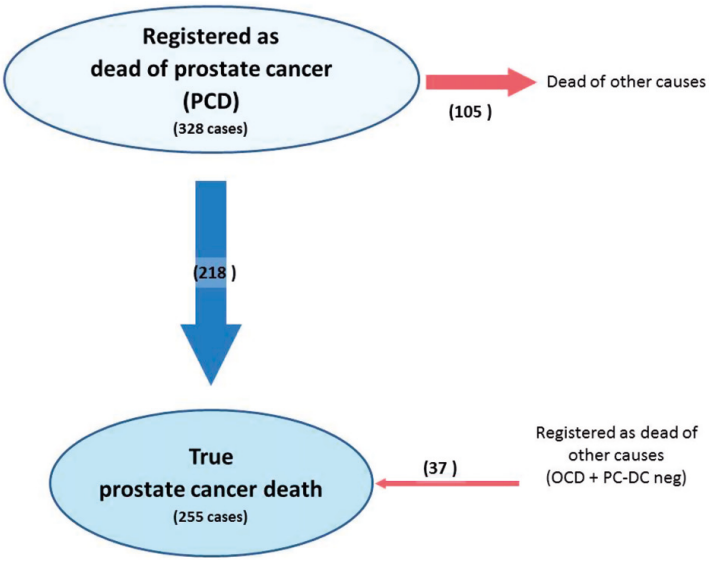

Figure 3. Patient transition from the original group of patients registered as dead from prostate cancer (PCD) and formation of the group of patients observed dead from prostate cancer. OCD: dead from other causes; PC-DCneg: prostate cancer not registered on the death certificate.

than the general population. However, as the observed effect is strongest among the oldest patients, the reported differences are more likely to be due to incorrect coding of the underlying cause of death. This is mirrored by the patients in the present study whose cause of death could not be determined during the first review: the median age in this subgroup was 86 years and for the majority a cause of death could first be determined after the third review. For patients younger than 75 years, on the other hand, results were relatively reliable, with a 90% concordance between cause of death on the death certificate and cause of death based on committee evaluation. However, these patients were a clear minority in the PCD group (21%), where 75% of patients were older than 77 years at death.

A further explanation for the high misattribution rates in this study may be found in the Norwegian proceedings for death certification [17,18]. In contrast to many other Western countries, death certificates in Norway are filled out by the doctor who confirms the patient's death. These are usually the most junior doctors at the hospitals or on-call doctors at the municipal primary care emergency departments and nursing homes, who rarely have intimate knowledge of the patient's medical history. In 1986, 57% of Norwegian prostate cancer deaths occurred in hospitals, where determination of the cause of death is usually more accurate [19], while only 29% occurred in nursing homes. By 2014 these numbers were reversed, with more than 60% of prostate cancer deaths occurring in nursing homes and only 23% in hospitals (2016 mail correspondence between the Norwegian Institute of Public Health and the first author). This change may have impacted the accuracy of death certificates considerably. Furthermore, it seems that not all doctors are fully confident with the concepts of immediate, underlying and contributory causes of death. In addition, the guidelines from the WHO state that in certain circumstances a specific diagnosis in part II of the death certificate may be registered as the underlying cause of death instead of an unspecific diagnosis in part I. This will have little impact on the actual cause of death in patients with a cancer diagnosis and few or no comorbidities. However, in patients with several comorbidities, usually older patients, this lack of knowledge may have a considerable impact on accuracy.

A key issue is the interpretation of the results and the question of whether over-registration of prostate cancer deaths is a specific Norwegian problem. In this case, prostate cancer mortality may not be significantly higher in Norway than in other Western countries. A Swedish registry-based study, evaluating the quality of official cause of death diagnoses of prostate cancer patients diagnosed in 1987–1999 and deceased before 2003, documented a relatively high reliability (correlation of 0.86%) of official cause of death statistics [20]. However, the hallmarks of misattribution of cause of death are similar to those in the present study, with high correlation among the youngest patients and increasing misattribution with increasing age. The higher misattribution rates seen in the current study may be due to the more recent timeframe of this study, with higher underlying prevalence rates of prostate cancer.

Further results of death certificate audits have been published for Finnish, Swedish and UK prostate cancer patients [8,9,21,22], demonstrating high accuracy of death certificates in those countries, while a similar evaluation in a group of US prostate cancer patients showed more ambivalent results [23]. However, patients evaluated in these studies were participants in clinical trials and were on average significantly younger at death than prostate cancer patients in the

general population (maximum age at death 74–77 years in the Finnish and Swedish clinical trials). The majority of prostate cancer deaths occur in patients older than 80 years and thus similar quality issues as described in the present study may negatively affect the prostate cancer mortality statistics in the above-mentioned countries. In this case, prostate cancer mortality may still be relatively high in Norway, with excess mortality among patients older than 80 years. This may be due to national therapy recommendations where, until recently, a strict age limit (75 years) for recommending radical therapy has been observed.

Prostate cancer mortality statistics in Norway must be interpreted with caution and may have to be supplemented by additional parameters (e.g. statistics on patients with castration-resistant prostate cancer) that may better reflect disease burden and intervention effects in the general population.

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