Adverse effects and global quality of life after curative treatment for prostate cancer

A population-based cross-sectional survey

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ERRATUM
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Definitions and abbreviations

ADT: Androgen deprivation therapy
ATC: Anatomical Therapeutic Classification
AUA: American Urological Association
CF: Chronic fatigue
CI: Confidence interval
CRN: Cancer Registry of Norway
CT: Computed tomography
CTCAE: Common Terminology Criteria for Adverse Events
CurCands: Candidates for curative treatment
EAU: European Association of Urology
ECOG: Eastern Cooperative Oncology Group
EORTC: European Organization for Research and Treatment of Cancer
FACT: Functional Assessment of Cancer Therapy scale
Gn-RH-agonists: Gonadotropin-releasing hormone agonists
Gy: Gray
HTcont: Definitive radiotherapy with ongoing neoadjuvant/adjuvant androgen deprivation therapy (hormone therapy continued)
HTdis: Definitive radiotherapy with discontinued neoadjuvant/adjuvant androgen deprivation therapy (hormone therapy discontinued)
HRQoL: Health Related Quality of Life
IARC: The International Agency of Research and Treatment of Cancer
IPSS: The International Prostate Symptom Score
Late/long-term adverse effects: Adverse effects persisting or occurring one year or more after start of local treatment
Localized prostate cancer: in the current thesis the term refers to both localized and locally advanced prostate cancer (T1-3, N0-X, M0)
LHRH-analogs: Luteinizing hormone releasing hormone-analogs
MRI: Magnetic Resonance Imaging
NCCN: National Comprehensive Cancer Network
(neo)adjuvant androgen deprivation therapy: expression used to describe hormone treatment received before and/or after definitive radiotherapy. (Neoadjuvant and/or adjuvant hormone therapy)

NoPCR: Norwegian Prostate Cancer Registry
NorPD: The Norwegian Prescription Database
NPPC: National Program for Prostate Cancer
PCa: Prostate cancer
PSA: Prostate specific antigen
RAD: Definitive radiotherapy as monotherapy
RADHT: CurCands with definitive radiotherapy with neoadjuvant and or adjuvant hormone therapy
RADNoHT: CurCands with definitive radiotherapy as monotherapy
RP: Radical prostatectomy
RTOG: Radiation Therapy Oncology Group
SF-12: The Short-Form Health Survey-12
SF-36: The Short-Form Health Survey-36
SPCG-4: Scandinavian Prostate Cancer Group, study number 4
TNM: Tumor, Node, Metastasis
TUR-P: Trans-urethral resection of the prostate
Typical adverse effects: urinary, sexual and bowel adverse effects
QoL: Quality of Life
WHO: World Health Organization
List of papers

I:
Initial management of prostate cancer: first year experience with the Norwegian National Prostate Cancer Registry

II:
Kyrdalen AE, Dahl AA, Hernes E, Cvancarova M, Fosså SD
Fatigue in hormone-naïve prostate cancer patients treated with radical prostatectomy or definitive radiotherapy

III:
Kyrdalen AE, Dahl AA, Hernes E, Hem E, Fosså SD
Fatigue in prostate cancer survivors treated with definitive radiotherapy and LHRH analogs

IV:
Kyrdalen AE, Dahl AA, Hernes E, Cvancarova M, Fosså SD
A national study of adverse effects and global quality of life among candidates for curative treatment for prostate cancer.
[Submitted: British Journal of Urology International]
Chapter 1: Introduction

1.1 Prostate cancer epidemiology

Epidemiology of prostate cancer (PCa) the last three decades requires an understanding of the impact of prostate-specific antigen (PSA) testing. Since the late 1980ies the PSA test has enabled the detection of PCa and is most frequently used in developed countries [1]. The widespread use of the PSA test has contributed to a dramatic rise in PCa incidence. The period after its introduction is in clinical medicine often referred to as the PSA-era (in Norway starting early in the 1990ies) [2]. With the help of PSA testing latent cancers are increasingly detected affecting the interpretation of PCa incidence and survival data [3]. As early cases are more often diagnosed, survival will increase, even in the absence of benefits from therapy [4]. However, the availability of PSA testing of asymptomatic men will detect a large proportion of PCa which would never been clinically diagnosed (over-diagnosis). Despite available PSA testing, 12% of PCa patients in the United Kingdom are still diagnosed with metastases [5]. In Norway, which is also without a national PSA screening program, 13% of the patients had metastases at diagnosis in 2005 [6]. In the PSA-era 30-45% of patients, initially clinically diagnosed with PCa confined within the prostate, had extracapsular growth when evaluating the histopathology of a prostatectomy specimen [7, 8].

In 2002 PCa was the fifth most common cancer in the world with 679000 new cases [9]. PCa is mainly a disease of older men and the incidence increases with age [10]. In 2005 in Norway, barely 1% of newly diagnosed men were younger than 50 years at diagnosis, 11% were between 50 and 59 years and 88% were 60 years and older [11]. Based on rates from 2004-2008 the lifetime risk of PCa is estimated to be 16.48% (1 in 6 men) for men born today [12].

The worldwide incidence of PCa varies across countries and shows distinct ethnical differences [1]. PCa represented 15.3% of new cancer cases in men in developed countries and 4.3% in developing countries in the year 2000, but the incidence has increased for several years in both groups. Some of the highest incidences of PCa are observed in the USA and in the Scandinavian countries, and one of the lowest incidences are observed in China [13]. The varying incidence of PCa is dependent upon etiological factors affecting the true prevalence (detected and undetected) of the disease, the intensity of diagnostic procedures including PSA testing and on the registration routines.
The International Agency of Research and Treatment of Cancer (IARC) estimated that worldwide 221000 men died from PCa in 2002 [9]. The estimated age-specific PCa mortality rates (deaths per 100 000 person years) increase with advancing age; 0.1 (15-44 years), 1.9 (45-54 years), 11.8 (55-64 years) and 100.4 (65 years and more) [14]. Mortality rates also vary between populations and are low in Asian populations and in North Africa. The highest mortality rates are found in the Caribbean, Southern and Central Africa, Northern and Western Europe, Australia, and North and South America [9]. PCa mortality has been quite stable even in the presence of large increases in incidence, but has started to decrease in countries which started early with an extensive use of the PSA test and increased use of curative therapy [9, 15]. The relation between reduced mortality and increased use of curative therapy is however not definitely established.

1.2 Prostate cancer in Norway

PCa is a major cause of morbidity and mortality of the Norwegian male population. Data from the Cancer Registry of Norway (CRN) show that over 3800 new cases were diagnosed in 2004 which is the cohort this thesis concerns. The average new number of cases per year had risen to 4145 for the five-year period 2005-2009 [16]. No national PSA screening program exists in Norway, but the test is widely used as part of health control in men without any symptoms (opportunistic screening). The Norwegian PCa mortality rates are among the highest in the world and only a slight decline can be seen the recent years (Figure 1) [16].

1.3 Etiological factors

The etiological factors and causal mechanisms of PCa are not well understood, but consist of both endogenous and exogenous factors and the interaction between them [17]. Most of the prostate consists of glandular cells, and histologically, PCa is usually an adenocarcinoma. The development of PCa requires circulating androgens and the function of a cytoplasmatic androgen receptor. Testosterone is taken up from the blood and converted to dihydrotestosterone through the enzymatic process driven by the enzyme 5-alpha reductase [18]. Dihydrotestosterone binds to the androgen receptor which is activated and the molecule translocates to the nucleus [19]. The dihydrotestosterone-androgen receptor complex binds to DNA within regulatory regions of the target genes, a process which is necessary for cell proliferation and tissue maintenance in both PCa and normal prostate tissue.
Heredity is estimated to account for around 5-10% of all PCa cases and 10-20% of PCa diagnosed before 60 years of age [20, 21]. Men with two or three first-degree relatives previously diagnosed with PCa have an 11-fold increased risk of developing the disease in their lifetime [22]. However associations found between relevant genes and risk of PCa are modest and sometimes inconsistent [17].

Since PCa probably develops after androgen influence of long duration, an unavoidable risk factor for PCa is age. An important notice is that autopsy studies have also found latent PCa in younger men (21-30 years) and that the prevalence of latent cancers across countries varies much less than incidence figures [23-25]. Risk factors may therefore also include factors which can stimulate the development of latent PCa into symptomatic disease.

Figure 1: Trends in PCa incidence and mortality rates and 5-year relative survival proportions. From Cancer in Norway 2009 [16].
Specific exogenous factors which increase the risk of PCa have not been identified. However, there are many indications that dietary and lifestyle factors may influence on the risk of PCa. Migration studies show that if Japanese men move to America their risk of clinical PCa will approach that of American men, which is generally much higher than in Japanese men [26, 27]. This indicates that environmental or lifestyle factors are involved in the development of clinical PCa. Dietary elements which are suggested to increase risk of PCa are for example high consumption of saturated fat, heterocyclic amines, milk and dairy products [28]. Several potential protective dietary factors have been under study such as tomatoes/lycopene, vitamin E, selenium, lignans and isoflavones among others [29]. As a result, consumption of cooked tomatoes [30] and omega-3 fatty acids [31] shows a small, but significant association with reduced risk of PCa.

1.4 The natural history of prostate cancer

The natural history of PCa is extremely varying, which complicates the debate concerning both screening and treatment. Some PCa tumors are aggressive and can develop into lethal metastatic disease within short time. However, most PCa remain confined to the prostate for a long time and may never represent a problem during a man’s lifetime [32]. Exact criteria for determining if a PCa tumor requires treatment are not identified and expected prognosis of untreated PCa is today determined from Gleason Score [33], level of PSA [34] and extent of the disease related to the primary tumor, and regional and distant metastases (TNM classification system for prostate cancer [35]). On the basis of prognostic studies in large cohorts these factors separate non-metastatic patients into risk groups which among other aspects determine further interventions [36].

PCa usually develops in the peripheral zone of the prostate gland. As it grows it extends through the prostatic capsule and may gradually infiltrate the seminal vesicles. Sometimes the tumor advances locally and grows into the urinary bladder or the rectum. The PCa tumor cells can acquire the abilities to migrate from the primary tumor into the blood stream and/or through the lymphatic system. This dissemination of tumor cells is a step in the process of developing distant and/or regional lymphatic metastases [37]. Typically, PCa metastasizes to the skeleton. However, the malignancy can spread to other organs such as lung and liver [38]. Patients with distant metastases cannot be cured and metastases are the most important cause of substantial morbidity and mortality in these patients [37]. In some patients, the dissemination of tumor cells and the development of distant metastases take
place early in the tumor development [39]. However, metastases from PCa can also develop several years after curative treatment, probably because of early dissemination of tumor cells which remain dormant for long periods [7, 40]. Search for new diagnostic and prognostic tools which better discriminate between “significant” and “insignificant” PCa is continuing and when this project was initiated the prostate cancer antigen 3 (PCA3) test was showing promising results [41].

1.5 Staging

In the present thesis the latest TNM (Tumor, Node, Metastasis) classification available at the time the patients under study were diagnosed was the 6\textsuperscript{th} edition from 2002 (Table 1) [35].

\textbf{T-staging:} The local extent of the tumor is evaluated using digital rectal examination of the patient as the standard procedure. Transrectal ultrasound visualizes the suspicious lesion and assists biopsy performance. Stage T1c denotes a non-palpable tumor detected on the basis of elevated PSA.

\textbf{N-staging:} Definite statement as to pelvic lymph node status requires lymphadenectomy with histopathological examination of the resected tissue. Stage NX is used for patients without such diagnostic procedure. Evaluation of lymph node involvement is recommended only in those patients in whom a positive finding will influence on the decision of curative treatment. According to the European Association of Urology (EAU) guidelines from 2003 [38], lymph nodes on such patients should be examined unless patients have a low risk (<10\%) of nodal metastases (T2a or less, PSA < 20 ng/ml and Gleason score 6 or less).

\textbf{M-staging:} Distant metastases at diagnosis are most often found in the axial skeleton (85\% of the cases) [42] and are assessed by bone scan. Metastases in soft tissue can be detected by computed tomography (CT) or magnetic resonance imaging (MRI). PSA exceeding 100ng/mL has proven to be highly associated with metastases [43]. According to the EAU guidelines from 2003, diagnostics to search for distant metastases is not required in asymptomatic patients with well-, or moderately differentiated tumors if the serum PSA level is less than 20 ng/mL.
Table 1: The 2002 TNM (Tumor Node Metastasis) classification system for prostate cancer [35]

<table>
<thead>
<tr>
<th>Evaluation of the primary tumor (T)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>TX: Primary tumor cannot be assessed</td>
<td></td>
</tr>
<tr>
<td>T0: No evidence of primary tumor</td>
<td></td>
</tr>
<tr>
<td>T1: Clinically inapparent tumor not palpable or visible by imaging</td>
<td></td>
</tr>
<tr>
<td>T1a Tumor incidental histological finding in 5% or less of tissue resected</td>
<td></td>
</tr>
<tr>
<td>T1b Tumor incidental histological finding in more than 5% of tissue resected</td>
<td></td>
</tr>
<tr>
<td>T1c Tumor identified by needle biopsy (e.g. because of elevated PSA level)</td>
<td></td>
</tr>
<tr>
<td>T2: Tumor confined within the prostate</td>
<td></td>
</tr>
<tr>
<td>T2a Tumor involves one half of one lobe or less</td>
<td></td>
</tr>
<tr>
<td>T2b Tumor involves more than half of one lobe, but not both lobes</td>
<td></td>
</tr>
<tr>
<td>T2c Tumor involves both lobes</td>
<td></td>
</tr>
<tr>
<td>T3: Tumor extends through the prostatic capsule</td>
<td></td>
</tr>
<tr>
<td>T3a Extracapsular extension (unilateral or bilateral)</td>
<td></td>
</tr>
<tr>
<td>T3b Tumor invades seminal vesicle(s)</td>
<td></td>
</tr>
<tr>
<td>T4: Tumor is fixed to or invades adjacent structures other than seminal vesicles; bladder neck, external sphincter, rectum, levator muscles and/or pelvic wall</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Evaluation of the regional lymph nodes (N)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>NX: Regional lymph nodes cannot be assessed</td>
<td></td>
</tr>
<tr>
<td>N0: No regional lymph node metastasis</td>
<td></td>
</tr>
<tr>
<td>N1: Regional lymph node metastasis</td>
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<table>
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<tr>
<th>Evaluation of distant metastasis (M)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>MX: Distant metastasis cannot be assessed</td>
<td></td>
</tr>
<tr>
<td>M0: No distant metastasis</td>
<td></td>
</tr>
<tr>
<td>M1: Distant metastasis</td>
<td></td>
</tr>
<tr>
<td>M1a Non-regional lymph nodes</td>
<td></td>
</tr>
<tr>
<td>M1b Bone(s)</td>
<td></td>
</tr>
<tr>
<td>M1c Other site(s)</td>
<td></td>
</tr>
</tbody>
</table>

1 Tumor found in one or both lobes by needle biopsy, but not palpable or visible by imaging, is classified as T1c.
2 Invasion into the prostatic apex, or into (but not beyond) the prostate capsule, is not classified as T3, but as T2.
3 Metastasis no larger than 0.2 cm can be designated pN1mi.
4 When more than one site of metastasis is present, the most advanced category should be used.
1.6 Prostate specific antigen

PSA is a glycoprotein produced, almost exclusively, by the epithelial cells in the prostate. The serine protease is secreted from the prostate glands and into the seminal fluid. PSA is responsible for liquefaction of the semen when a man ejaculates. An elevated PSA is an indication of prostate disease, but is not PCa specific [44]. There is no generally accepted cut-off level for serum PSA in diagnostics of non-palpable PCa, however <4 ng/mL is commonly used as a threshold in studies [38].

1.7 Histopathological grading

Tissue from adenocarcinoma of the prostate is graded microscopically using the Gleason grading system [45] which describes how much the microscopic picture resembles normal prostatic tissue based on the growth pattern. The grading system ranges from 1 (good resemblance) to 5 (poor resemblance), thus making the tumor more aggressive with increasing grade. The Gleason score is given as the Gleason grade of the most common tumor pattern added with the Gleason grade of the second most common tumor pattern. This also implies that Gleason score 3+4=7 has a better prognosis than Gleason score 4+3=7 [46]. The most common tumor pattern must constitute of more than 50% of the tumor tissue seen and the second most common tumor pattern must constitute of less than 50%, but at least 5% of the tumor tissue seen. In 2005 a Gleason consensus conference recommended that the presence of Gleason grade 5 should always be scored (even if less than 5% of the tissue seen), because of a potentially poorer prognosis [47].

1.8 Tumor risk groups

Non-metastatic PCa is usually classified into prognostic categories before the optimal treatment strategy is considered. In this thesis we classified non-metastatic patients by the D’Amico risk group classification [2, 48] which takes into account the T-category, Gleason grade and the PSA level of the patient categorizing them into three prognostic groups:

- Low-risk: T1-T2a, PSA ≤10 ng/mL, Gleason score ≤6.
- Intermediate-risk: Not comprised by the low- or high-risk group definitions
- High-risk: T2c or PSA >20 or Gleason score ≥8.
Though not included in the original risk-categories of D’Amico et al [48] all T3 tumors are commonly classified to the high-risk group [49]. Compared to low-risk the relative risk of PCa specific mortality for intermediate- and high-risk PCa is approximately 5 and 14, respectively, for both radical prostatectomy (RP) and definitive radiotherapy [36]. The latter study with a median follow-up time of 4.1 years (range 0.5-14.3 years) for RP and 4.4 years (range 0.8-14.3 years) for definitive radiotherapy.

### 1.9 Guidelines

Medical guidelines (also called clinical guidelines) are documents providing consensus statements on best practice concerning specific areas of healthcare. Guidelines should evaluate the highest quality evidence available and discuss it in relation to prevention, diagnosis, treatment, prognosis and aftercare. The benefits from using guidelines are standardization of medical care and provision of the best available practice to unselected patients. Guidelines are not intended to replace individual treatment decisions. However, the considerations leading to management decisions deviating from guidelines should be recorded in the medical record.

Medical guidelines in oncology are developed for PCa patients, some as a result of an international consensus and some at national or hospital level [50]. The EAU PCa guidelines were first published in 2001, with updated versions in 2003, 2005, 2007, 2009 (full revision), 2010 and 2011. The American Urological Association (AUA) published “Report on the Management of Clinically Localized Prostate Cancer” in 1995 [51], with total revision in 2007 and an update in 2009. The main activity of the organization National Comprehensive Cancer Network (NCCN) is to develop clinical guidelines in oncology. NCCN is a cooperative organization of twenty-one cancer centers in the United States, most of which are designated as comprehensive cancer centers. Guidelines for specific cancer sites are free of charge and accessible from the NCCN’s website. The NCCN guidelines for PCa were first developed in 1995 and are updated annually. In Norway national guidelines for PCa were published in 2009 and at the time the patients in this thesis were diagnosed and treated, only the EAU guidelines from 2003 were relevant.
1.10 Treatment

1.10.1 Treatment with curative versus palliative intention

Localized and locally advanced PCa (from now collectively referred to as localized) (T1-3, N0-X, M0) are considered to be potentially curable. The decision whether or not to give curative treatment for localized PCa depended in 2004 upon the responsible physician’s evaluation of life expectancy (age and co-morbidity) and patients’ preferences. According to EAU guidelines from 2003 a life expectancy of at least 10 years was recommended if curative therapy was to be offered [38]. In 2004-2005 standard curative treatment modalities for localized PCa were RP and definitive radiotherapy, the latter with or without neoadjuvant and/or adjuvant [(neo)adjuvant] androgen deprivation therapy (ADT). The risk of dying from a diagnosed localized PCa for men older than 70 years decreases with increasing co-morbidity and age [33] and careful considerations as to treatment benefits are emphasized in the EAU guidelines with no rigid limits. In 2004 most clinicians would consider patients with N+ disease to be beyond curability, this view being reflected in Paper I, recognizing the later years’ gradual change of this principal view [52-54].

Men with metastatic PCa can be offered palliative treatment with the intention to prolong life and relieve symptoms, but without attempting to cure the disease. Palliative treatment can for example be a trans-urethral resection of the prostate (TUR-P) to relieve urinary-obstructive symptoms, low dose radiotherapy to relieve pain from metastases or hormonal treatment to delay disease progression. Palliative treatment is not further described, as this thesis mainly concerns men with non-metastatic PCa.

1.10.2 Conservative management

In the current thesis conservative management of PCa is divided into watchful waiting and active surveillance. Watchful waiting is offered patients where a decision is made not to provide curative treatment, but to initiate palliative therapy at the time of eventual progression. The indication for watchful waiting can for example be high age and/or co-morbidity. The active surveillance group is principally different from the watchful waiting group as it consists of men who are considered to have “insignificant PCa” at the time of diagnosis. A decision is made to postpone curative treatment until the disease shows signs of progression. Indication for active surveillance is usually favorable prognostic factors.
combined with a small tumor volume and informed consent from the patient. In 2004 active surveillance was not implemented as a routine curative treatment strategy in Norway, but could occasionally be used. The separation into two types of conservative management is dependent upon knowledge of the treatment decision process, as both groups consist of patients with localized PCa.

1.10.3 Radical prostatectomy

RP is the surgical removal of the prostate gland with tumor-free margins usually including the seminal vesicles. Thereafter the urethra is reattached to the bladder neck. Depending on the extent of the tumor the surgeon might also remove the regional lymph nodes to perform a histopathological examination [55]. In 2004 regional lymph node dissection was in Norway confined to the obturatory lymph nodes. The outcome concerning adverse effects after RP depends upon the anatomy of the patient, the skills of the surgeon and his/her team and might also be influenced by the surgical technique [56]. At the discretion of the operating surgeon unilateral or bilateral nerve sparing technique can be applied to preserve nerves important for erectile and urinary function.

In Norway the most common surgical procedure for RP in 2004/2005 was the retropubic approach. In 2004 two Norwegian hospitals had started to perform laparoscopic RP and one hospital introduced robot-assisted laparoscopic RP in December 2004.

1.10.4 Definitive radiotherapy

Definitive radiotherapy is an alternative to RP and is often combined with ADT in patients with high-risk PCa. Definitive radiotherapy can be applied as external radiotherapy, brachytherapy or as a combination. The gold standard for definitive radiotherapy is three-dimensional conformal radiotherapy as much as possible sparing the rectum and the bladder. The radiation series are normally given over 7-8 weeks, five days a week. PCa cells are relatively radio-resistant [57] and high doses have to be applied ranging from 70-78 Gray (Gy) in 2 Gy fractions. Dose escalation can reduce the risk of biochemical failure [58, 59] and improve survival [60]. The innovation of intensity modulated radiotherapy enables a more complex distribution of radiation within the treatment fields and helps to minimize radiation
dose to organs at risk, such as bladder and rectum [61]. In Norway three-dimensional conformal radiotherapy was the mainstay treatment in the period of study and is still standard treatment today. The usual practice is to apply an initial dose of 46-50 Gy to a larger volume with risk of tumor growth, for example the true pelvis, and a higher dose to the prostate itself (boost) [6]. Low-dose rate brachytherapy with iodine 131 was not offered at any Norwegian hospital in the period of study. High-dose rate brachytherapy combined with external radiotherapy was introduced in December 2004 [62].

1.10.5 Hormonal therapy

As PCa cells are dependent upon the availability of androgens, their proliferation can be delayed and even stopped if the androgens, mainly testosterone, are removed from the blood stream. Even regression of existing tumor lesion can be observed during ADT. Alternatively one can inhibit the cellular uptake of testosterone by antiandrogens. Antiandrogens prevent the binding of circulating testosterone to the androgen receptor and thus remove androgen stimulation of the PCa cell. Removal of testosterone can be done either by surgical or medical castration, the latter causing discontinuation of the testicular testosterone production. The most common medication is the application of gonadotropin-releasing hormone agonists (Gn-RH-agonists) also called luteinizing hormone releasing hormone-analogs (LHRH-analogs) which prevent the production of luteinizing hormone in the pituitary gland with subsequent termination of testosterone production [18].

A randomized trial has concluded that patients with locally advanced PCa benefit from treatment with LHRH-analogs combined with definitive radiotherapy [63]. This combination has become the standard treatment for locally advanced PCa. Radiotherapy combined with (neo)adjuvant LHRH-analogs for six months has proven to be superior with respect to survival compared to definitive radiotherapy as monotherapy (RAD) in localized PCa, excluding low-risk patients [64]. However, the optimal duration of LHRH-treatment for PCa risk-categories is not evaluated in randomized trials. Neoadjuvant ADT can reduce the pre-radiotherapy target volume and reduce the radiation field thus sparing adjacent tissue [65]. As the LHRH-analogs during the first weeks of their initiation are followed by a transient increase of testosterone production (flare), patients use anti-androgens two weeks prior to start of medical castration and for two weeks thereafter. A recent randomized trial has also shown that definitive radiotherapy combined with ADT is better that ADT alone [66].

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Treatment with anti-androgens given adjuvant to definitive radiotherapy has been investigated in men with PCa confined to the prostate (T1-2, N0/x) and in men with locally advanced disease (T3-4, any N or any T, N+) [67, 68]. Anti-androgens are generally well tolerated as to adverse effects compared to castration and can be an alternative to LHRH-analogs. No study directly compares outcomes after anti-androgens or LHRH-analogs in combination with definitive radiotherapy in patients with localized PCa.

1.10.6 Survival and prognosis

In the absence of large randomized trials, conclusive evidence of benefit from any curative treatment for localized PCa compared to conservative management is lacking. No curative treatment option for PCa had proved to be superior to the other in terms of survival [69] until Bill-Axelson et al [40] in 2005 reported from a randomized study that RP reduced PCa mortality and risk of metastases compared to “conservative management” in patients with localized PCa. However, the majority of patients in the study by Bill-Axelson et al was diagnosed in the pre-PSA era and is not representative for patients diagnosed today. Widmark et al found in a randomized study that definitive radiotherapy and (neo)adjuvant ADT halved the 10-year PCa specific mortality compared to ADT alone in men with locally advanced PCa (T3, N0, M0) [66]. A few population-based observational studies indicate that curatively treated men may have a higher chance of survival compared to conservatively managed patients with localized PCa [70, 71]. In spite of all uncertainty as to benefits in particular in low-risk patients curative treatment is today widely used. The 15-year mortality from low-risk screen detected PCa in men aged 55-74 years at diagnosis treated with conservative management has been estimated to be 1% [3]. The cancer specific survival after curative treatment in low-risk PCa is therefore predestined to be extremely good with a marginal benefit. Any 15-year survival benefit of curative treatment for low-risk PCa compared to conservative management has been estimated to be less than 1% [3]. To demonstrate survival benefits of PCa local treatment studies with long observation-time (10-12 years) are needed.

Until results from randomized trials are presented, the reports from population-based observational studies can indicate treatment effect on survival. Observational studies estimating the overall 10-year PCa-specific survival show 95% confidence intervals (CIs) in the range 73-93% for prostatectomized patients, 61-83% for definitive radiotherapy and 66-88% for conservative management [72] [71], with subgroups performing substantially
different according to clinical T-category, Gleason Score and preoperative PSA level. A nomogram reports the estimated risk of recurrence after PCa treatment. Nomograms which show estimated risk of recurrence stratified by PSA level, Gleason Score and T-category have been developed both after RP [73, 74] and after radiotherapy [75] and reveal that some PCa tumors are highly aggressive. Nomograms to predict indolent PCa are also available [76]. However, nomograms do not evaluate the beneficial effect of treatment. With today’s evidence RP and definitive radiotherapy must be considered as equally effective, comparing patients with similar risk-groups of PCa.

There are two ongoing comparative randomized trials for localized PCa treatment. The Prostate Testing for Cancer and Treatment trial (ProtecT) [77] is performed in the United Kingdom and compares active surveillance, RP and definitive radiotherapy and will publish its main results in 2016 concerning effectiveness of PCa treatment in men with PSA detected disease. The Prostate Cancer Intervention versus Observation Trial (PIVOT) [78] compares watchful waiting with RP in PSA detected PCa diagnosed in the United States. The results from the PIVOT study have not yet been published in a peer-reviewed journal. Nevertheless, it cannot be ignored that the first findings from PIVOT were presented by Dr. Wilt in the plenary session of the 2011 annual meeting of AUA as late breaking news [79]. With the caution of referring to unpublished results the PIVOT study shows no survival benefit from RP in low PSA or low-risk early stage PCa compared to observation. In his presentation at AUA Wilt added:” Results suggest a benefit from surgery in men with higher PSA or higher risk of disease”. Unfortunately it is not possible to have an opinion on these findings as the study is not available for critical review.

1.11 Registration and availability of data in national health registries

1.11.1 The Cancer Registry of Norway/Norwegian Prostate Cancer Registry

All new cancer cases in Norway have been reported to the CRN by law since 1953. Main sources of information are the copies of all histological/cytological reports with a cancer diagnosis which are routinely sent to the CRN for registration. Additionally, completion of a case record form is required containing coded clinical information from the physician responsible for the cancer diagnosis of the patient. Cancer cases are registered by a person’s unique personal identification number which also allows linkage to other public registries.
Cancer incidents in the CRN are coded manually based on all available reports (clinical reports, pathology reports) which are visible for the coding personnel either as a paper copy or electronic version. Sometimes reports are missing and the diagnosis is registered the best possible way according to available sources. The CRN has focused on tumor status at the time of diagnosis and on initial treatment. Apart from time and cause of death the CRN does not contain systematically collected follow-up data on cancer recurrence, adverse effects or global quality of life (QoL). Initial treatment for PCa is routinely documented in broad terms (RP, radiotherapy, planned hormonal treatment). A sub-registry of the CRN contains individualized data concerning radiation therapy, provided by all radiotherapy units in Norway. The completeness of registered cancer cases in the CRN has been thoroughly documented and was estimated to be 99.8% for PCa in the period 2001-2005 [80].

TNM status, PSA value and Gleason score are essential variables in PCa diagnostics and treatment. Before 2004 the case record form was the same for all cancer types and did not include prostate specific variables. The Gleason grading system was recommended by a World Health Organization (WHO) consensus already in 1993 [45] and in 2003 nearly all pathologists in Norway had converted to the Gleason system. The Gleason score was nevertheless only available from the scanned images of histopathological reports in the CRN, which was inconvenient for research purposes [81]. PSA value at diagnosis was not reported to the CRN. The increasing demand for clinically important data for this patient group led to the establishment of a Norwegian Prostate Cancer Registry (NoPCR). The purpose of the NoPCR was to provide improved report on the new PCa cases at diagnosis, but did not aim to provide follow-up data. The establishment of a sub-registry for PCa in 2004 represented a necessary innovation. With the establishment of NoPCR several clinically important PCa specific variables became available, such as T category, PSA level and Gleason score. In addition the new PCa specific case record form (Appendix A) contained improved registration of diagnostic examinations as well as performance status (at diagnosis). An additional field enabled the registration of major co-morbidity with impact on treatment decision, such as the presence of another cancer or dementia. The NoPCR aimed to separate men treated with conservative management into watchful waiting or active surveillance. In order to achieve the highest possible completeness of essential data, careful manual review of available reports sometimes provided missing information. By this task and multiple reminders to hospitals and pathology laboratories, registration in the CRN/NoPCR became as complete as possible for the first year.
1.11.2 The Norwegian Prescription Database

The Norwegian Prescription Database (NorPD) was established on 1st of January 2004 and contains information on dispensed drugs prescribed in Norway. Records for each prescription contain several available variables such as product name, active ingredient and Anatomical Therapeutic Classification (ATC) code, prescription date, amount/size of prescription and a code for reimbursement purposes. For studies meeting the aims of NorPD individualized data can be released after application, in 2004 restricted to patients who have provided informed consent.

1.12 Adverse effects and global quality of life after prostate cancer treatment

The term health-related quality of life (HRQoL) refers to WHO’s definition of health; “A state of complete physical, mental, and social well-being not merely the absence of disease or infirmity” [82]. Measures of health and evaluation of health care should therefore include dimensions of physical, mental and social well-being, which is denoted as “generic QoL” or “global QoL” in this thesis. In addition to global QoL cancer patients might develop cancer specific adverse effects related to the type of malignancy or its treatment. Long-term adverse effects after cancer treatment can be explained as health problems starting during cancer treatment and persisting more than one year after treatment termination. Additionally, health problems caused by cancer or its treatment which arise one year or later after treatment are called late adverse effects. In this two year cross-sectional survey the terms late and long-term adverse effects are used similarly. Long-term adverse effects can impact on global QoL and both types of measures are important and should be assessed separately.

As the prognosis for men with a localized PCa diagnosis is good, most men live for many years with the adverse effects after curative treatment. Today’s PCa patients are encouraged to take part in the process of choosing between treatment options with similar prognosis [83]. They are therefore interested in possible side effects. Erectile, urinary and bowel dysfunction are considered as “typical adverse effects” after curative treatment for PCa and each treatment modality is related to specific patterns of symptoms. Differences as to late adverse effects may therefore impact on patients’ final treatment decision. Conservative management might be an option for some men with low-risk PCa and may for some patients be the optimal strategy to avoid adverse effects and thereby preserving global QoL. However, this approach may result in psychological symptoms as uncertainty and mental stress [84, 85].
Some of the symptoms described as treatment related adverse effects may also be experienced by PCa patients who never had treatment [86].

1.12.1 Measurement of adverse effects and global quality of life

Adverse effects and global QoL can be measured by an external observer or by the patient himself. In both situations validated instruments should be used. Examples of instruments based on an external observer are the Common Terminology Criteria for Adverse Events (CTCAE) [87] and the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer (RTOG/EORTC) scale [88]. Karlsdóttir et al used the RTOG instrument to study late gastrointestinal and genitourinary morbidity after three-dimensional conformal radiotherapy for PCa [89]. The benefit of using an external observer can be better communication with patients about treatment related adverse effects.

Studies have shown that subjectively experienced cancer related morbidity is best reported by the patient as physicians tend to underestimate morbidity as summarized in several review articles [90, 91]. Assessment of global QoL and disease specific symptoms are thus today mainly done by the patients themselves, requiring validated psychometrically tested instruments. A validated instrument is a questionnaire which by psychometric measures (factor analysis, reliability and validity testing) has proven to accurately measure what it aimed to do. A reliable instrument should for example reproduce similar results at repeated measurements. Instruments usually contain questions that are organized into scales of certain domains [92]. The responses in a multi-items domain should show a high grade of internal consistency, usually assessed by the Cronbach’s alpha coefficient which also is a type of reliability testing. Resulting values should range from 0.6 to 0.9 to avoid inconsistency (<0.6) or unnecessary item replication (>0.9). Clinicians usually use either a complete questionnaire package or a combination of instruments to assess global QoL and typical adverse effects. It is recommended to use validated instruments or at least select complete domains, and avoid the application of ad hoc questions as much as possible. Measurement of adverse effects can be reported as a score, or dichotomized into groups using clinically meaningful cutoff-values. Results from dichotomized scales are usually easier to communicate to patients (percentage of patients with a specific symptom) than results from scores which mirror severity.

Global QoL instruments assess the patients own perception of their health status. Several validated instruments are available [93-96]. The Short Form Health Survey-36 (SF-
The Short Form Health Survey-12 (SF-12) instruments are universally applicable in the general population. Other instruments are disease specific such as the Functional Assessment of Cancer Therapy scale (FACT) and the EORTC QLQ-C30 scale, designed for cancer patients in general. SF-36, FACT and QLQ-C30 all contain a dimension of energy or vitality comparable to fatigue. For more comprehensive measurement of fatigue a separate fatigue-specific instrument is recommended.

For localized PCa the most typical cancer-specific adverse effects are urinary, bowel and sexual dysfunction. According to some, but not all published studies adverse effects should generally be separated into function and bother [97]. Several validated instruments based on patient report of symptoms have been developed for PCa patients. The incidence and prevalence of “typical adverse effects” is frequently documented in the literature, but the figures vary considerably in the absence of standardized methods for measuring and reporting these adverse effects as problematised in Bhatnagar et al’s review article [98]. Bhatnagar et al concludes that it is difficult to provide accurate estimations of risk of adverse effects due to biased patient selection and various study designs. The extensive use of curative therapy warrants standardized measures of adverse effects which enables comparison between treatment modalities and between populations.

When evaluating QoL or even adverse effects after cancer treatment, response shift has to be accounted for [99]. Response shift concerns the impact life changes have on how a person perceives his or her health and QoL. For non-metastatic PCa patients response shift can cause gradual acceptance of treatment-related adverse effects and change of expectations as to global QoL. This would result in a relatively satisfying global QoL in spite of considerable adverse effects. It is even suggested that psychological adjustment in patients both lead to greater awareness and reporting of adverse effects, nevertheless with a maintained or elevated global QoL perception [100]. Quantification of response shift requires repeated measurements.
1.12.2 Global quality of life

A study of Norwegian men representative for the general population showed that subjects of 70 years or older had the lowest scores on all scales of the SF-36 except for mental health and vitality. Low education, not being married and report of a disease and/or current health problem were associated with lower score in all scales [101]. Based on the literature, men newly diagnosed with localized PCa in the PSA-era are in general healthy, reflected by a global QoL not different from that of the general age-matched population [102, 103]. However, studies report that global QoL declined from baseline both at one and three months following treatment [104, 105]. Approximately one year post-treatment global QoL had recovered to baseline in most cases regardless of treatment modality [104, 105]. However, little is known about the association between global QoL and “typical adverse effects” after PCa treatment. Presence of slight to moderate urinary, bowel or sexual dysfunctions are not necessarily associated with reduced global QoL [103], however in some studies they are [106]. An explanation for this inconsistency can be cultural variations concerning the importance of these functions for participation in daily and individually preferred activities. Response shift may also explain the insensitivity of global QoL to variations of typical adverse effects [99].

1.12.3 Sexual dysfunction

Sexual functioning is dependent upon both psychological and physiological factors. The most common sexual problems reported by American men aged 57-74 years are erectile dysfunction, early ejaculation, lack in sexual interest and anxiety of performance [107]. Erectile function is not synonym to, but a part of sexual function. However, in many studies of PCa patients only erectile function is reported. Erectile dysfunction is the condition defined as the persistent inability to attain and maintain penile erection sufficient for sexual intercourse [108]. Causes of erectile dysfunction can be hormonal deficiency, disorders of the nervous system, inadequate penile blood supply and psychological problems [109]. Some sexual problems increase with age, and based on published estimates 39-51% of men aged 65-74 years suffer from erectile dysfunction. Major co-morbidity as diabetes and vascular disease contribute to sexual problems, in the general population, also increasing the prevalence of erectile dysfunction [107, 110]. The condition of the partner and the strength of the relationship can also play an important role for sexual functioning and may be altered after a
cancer diagnosis [111]. Decline in erectile function occurs both after RP and radiotherapy for PCa [112]. Further, the addition of LHRH-analogs has shown to be negatively associated with several domains of sexual function [113].

Erectile dysfunction after RP is often related to the damage of nerves and blood vessels which lie close to the prostate and usually occurs shortly after the operation. Estimates of complete erectile dysfunction after RP range between 26% and 100% [114]. Erectile dysfunction present at one year after RP treatment can be considered permanent though slight improvement might occur during the second year [115]. A recently published paper from the Scandinavian Prostate Cancer Group study number 4 (SPCG-4) reports significantly higher erectile dysfunction rate among prostatectomized men compared to men assigned to observation, after a median follow-up of more than 12 years [116]. In a systematic literature review from 2006 it was found that after a bilateral nerve-sparing procedure erectile function is preserved in 31-86% of sexually active men with organ-confined disease [117].

Except for psychological impact gradually decreasing penile blood supply is believed to be the major reason for post-radiotherapy erectile dysfunction. The neurovascular bundles, the internal pudendal arteries and the proximal penile structures are exposed to radiation. Low doses of radiation to these structures cause slow destruction of tissue and development of fibrosis with narrowing of the arterial volume [118]. Estimates of complete erectile dysfunction after definitive radiotherapy range between 8% and 85% [114]. The sexual function after radiotherapy steadily decreases during the five years after PCa diagnosis [119, 120]. The inclusion of men who received adjuvant hormonal therapy may obscure the results by increasing the occurrence of erectile dysfunction.

The addition of (neo)adjuvant LHRH-analog treatment impairs erectile function in most patients by lowering testosterone needed for sexual functioning to a castrational level [121, 122]. Few PCa patients regain their baseline erectile function and sexual desire after radiotherapy combined with use of ADT, often concurrent with a slow recovery of testosterone level [123, 124]. Recovery of erectile function is, however, dependent upon age and the duration of ADT. Detailed studies of recovery of erectile function after short-term ADT and radiotherapy are rare.

Treatment for erectile dysfunction is available such as PDE5-inhibitors, intracavernous injections and vacuum devices. Not all studies report if sexual function is measured with or without treatment for erectile dysfunction. PDE5-inhibitors have proven to be effective both after bilateral nerve-sparing RP [125] and after radiotherapy [126] though not for all patients. Overall 62% of men with bilateral nerve-sparing RP reported improved erection after 12
weeks of tadalafil, compared to 23% in the placebo group [125]. Successful intercourse was possible for 41% of patients in the RP group versus 19% in the placebo group. Incrocci et al found that 67% of men with erectile dysfunction reported improvement after six weeks of tadalafil use compared to 20% in the placebo group [126]. Successful intercourse was possible in 48% of radiotherapy patients and 9% of men in the placebo group. Many men with improvement in erectile function will therefore still be defined as having erectile dysfunction. Stephenson et al [127] found that about 50% of patients following treatment for localized PCa had used medication for erectile dysfunction during the five years after diagnosis and overall Sildenafil helped a lot in 12% of those who used it.

1.12.4 Urinary dysfunction

Urinary dysfunction is commonly reported after curative treatment for PCa and the nature of the dysfunction varies with the type of treatment. Based on the available literature urinary incontinence should be separated from irritative-obstructive urinary symptoms [128-130]. Both urinary incontinence and irritative-obstructive urinary symptoms increase in prevalence with advancing age [131, 132]. Irritative-obstructive urinary symptoms are often related to enlargement of the prostate and are present in 29% of Norwegian men 55-69 years in moderate to severe degree [133]. Male urinary incontinence is usually urge-incontinence caused by an overactive bladder.

Urinary incontinence is an acute/immediate and late adverse effect after RP with small, if any, increased risk after definitive radiotherapy [119, 134, 135]. Urinary incontinence after RP has its onset immediately after the operation with improvement during the first post-operative year [134]. Estimates of urinary incontinence after RP defined as daily leakage range from 16% to 24%, admittedly from published studies with widely different follow-up time [119, 134, 135]. The stabilization of urinary incontinence occurs around one year after RP with only slight improvement thereafter [115].

Irritative-obstructive urinary symptoms, such as slow or difficult urination, are more frequently reported by men after radiotherapy compared to men after RP [119]. The irritative-obstructive urinary symptoms after radiotherapy have gained far less attention than RP related urinary incontinence in the literature concerning acute and late adverse effects after primary treatment for localized PCa.
1.12.5 Bowel dysfunction

Bowel dysfunction reported by PCa patients concerns fecal leakage, bowel urgency, chronic diarrhea, blood or mucus in stool, painful defecation, painful hemorrhoids, tenesmus and frequent defecation.

Acute bowel dysfunction after definitive radiotherapy occurs early after treatment and is mainly caused by damage of the intestinal rectal mucosa [136]. This dysfunction may worsen during the first post-treatment months with gradual recovery thereafter. Bowel dysfunction is significantly worse six months post-treatment compared to one year post-treatment [115].

Onset of more long-lasting bowel dysfunction usually starts within two years after radiotherapy [115, 119]. In irradiated patients late bowel dysfunction is a consequence of radiation to the rectum and intestinal tract located in the true pelvis. Increasing small vessel obliteration and development of fibrosis in the rectum/bowel wall are etiological factors of the late bowel dysfunction, together with radiation-induced nerve damage. The severity of bowel dysfunction after definitive radiotherapy is dependent upon the volume of treated rectum and the maximum radiation dose to the rectum [137].

Bowel dysfunction after RP is rarely the focus of studies of adverse effects, probably because it seldom is a major problem for the patients. Post-treatment bowel dysfunction (rectal bleeding, abdominal pain or cramps, loose stools and bowel urgency) was significantly worse after definitive radiotherapy than after RP both 6 months and 12 months after diagnosis [134]. In the previous study bowel urgency approximately one year after diagnosis was present in 26-30% of radiotherapy patients and 6-7% of RP patients [134]. Potosky et al [112] found the difference to be smaller, as 30.5% of radiotherapy and 16.1% of RP patients reported bowel urgency. Estimated bowel urgency after twelve months was 19% after radiotherapy and 6% after RP in a publication by Talcott et al with yet another definition of the symptom and other criteria for patient selection [138].
1.12.6 Fatigue and chronic fatigue

Cancer-related fatigue has been defined by the NCCN as: "a distressing persistent, subjective sense of physical, emotional and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning." NCCN summarizes the problem as follows: “Persistent cancer-related fatigue affects quality of life, as cancer patients become too tired to fully participate in the roles and activities that make life meaningful.” Fatigue has been reported as the most distressing late adverse effect after cancer and its treatment [139]. It has been estimated that fatigue during a course of definitive radiotherapy may be experienced in as many as 90% of all cancer patients. However, and more important, fatigue becomes a chronic condition in about 30% of cancer survivors [140].

Several instruments for assessing fatigue are available [141-147]. If fatigue has persisted for six months or more it can be defined as chronic fatigue (CF) [146]. Most fatigue instruments do not include the duration of fatigue and only measure the presence of severe/moderate fatigue. Though the concepts of fatigue and CF are associated, NCCN states that it is the persistent fatigue which affects QoL contrary to acute short-lasting fatigue. Measurements of fatigue should therefore include a measure of the duration.

The etiology of fatigue in cancer patients is unknown. As fatigue is not limited to one specific cancer type or treatment it is probably a result of multiple factors. Several mechanisms have been proposed to be important for the development of fatigue in cancer patients. The activation of pro-inflammatory cytokines is suggested to play a role in the onset of fatigue [148] and elevated levels of some cytokines are associated with fatigue in cancer patients [149]. Pro-inflammatory cytokines are thought to signal the central nervous system with subsequent behavioral effects as reduced activity, increased pain sensitivity and cognitive alterations [150]. Functioning of the hypothalamic-pituitary-adrenal (HPA) axis is necessary for release of cortisol and mobilization of energy resources when exposed to stress. Dysregulation of the HPA-axis may play a role in the chronic inflammatory process [148]. In extension to this hypothesis, disturbance of the intestinal tract may have causal relationship with CF, and both altered intestinal microbiota and dysfunction in the mucosal barrier is observed in fatigued persons [151-153]. In brief, any inflammation can increase the permeability of the gut membrane to lipopolysaccharides produced by gram negative bacteria, which may again increase the production of pro-inflammatory cytokines. Several cancer
therapies can possibly cause intestinal inflammation; especially relevant for localized PCa is the use of radiation therapy to the pelvis [154].

In the general Norwegian male population CF was positively correlated with older age and was reported by 16.8% of men older than 60 years [155]. In the same paper by Loge et al, lower education, being unemployed or having a disease and/or current health problem were associated with increased risk of CF among men. The high prevalence of CF in the general population is important for the interpretation of the symptom prevalence in PCa populations.

Before 2005 fatigue in PCa patients was mostly identified as a complication during ADT [156, 157] often described as “loss of vitality” or “energy loss”. Fatigue was rarely reported as a late adverse effect after RP and definitive radiotherapy for localized disease. Largely, existing studies concerning fatigue and definitive radiotherapy focused on the presence of fatigue only during radiotherapy treatment [158]. Nevertheless, the persistence of increased fatigue twelve months after radiotherapy was reported by Beard et al, already in 1997 [159]. An often cited study comparing long-term morbidity and QoL among RP and definitive radiotherapy patients showed that fatigue was common in both treatment groups with a prevalence of 10% and 15%, respectively [103]. Severe fatigue as a long-term effect after definitive radiotherapy (> 1 year after radiotherapy) was also reported by Vordermark et al in 2002 [160] who found the prevalence of severe fatigue among men with definitive or post-operative radiotherapy to be 18.7% after a median of 2.1 years, measured with the Brief Fatigue Inventory [147]. Weaknesses with these studies are that additional treatment such as ADT was not taken into account and that the studies include patients with recurrence. There is no doubt that fatigue can occur during long-lasting ADT, but whether fatigue persists after discontinuation of adjuvant ADT and for how long time is not assessed in the literature.
1.13 Status at the start of the thesis

1. Since 2000 there was an increasing recognition among Norwegian urologists and oncologists that the conventional CRN registration of recently diagnosed PCa had become insufficient for clinical research. New from January 1\textsuperscript{st} 2004 is the NoPCR registry which should offer new opportunities to study patients using more modern principles of risk-categorization related to treatment.

2. Fatigue is recognized as a frequent long-term effect after cancer, but few studies are performed in men with curative treatment for PCa. The literature suggested that fatigue was more common after definitive radiotherapy than after RP, however the studies were methodologically weak as they included patients with (neo)adjuvant ADT.

3. Published estimates of adverse effects and global QoL vary considerably. No population-based Norwegian estimates are available. Further, published figures of prevalence of adverse effects are confounded by age and co-morbidity as well as (neo)adjuvant hormone treatment, cancer recurrence or use of PDE5-inhibitors. The relationship between adverse effects and global QoL is rarely investigated.
Chapter 2: The current thesis

2.1 Background

In 2003 an interdisciplinary group of PCa experts in Norway formed the National Program for Prostate Cancer (NPPC) with the agenda to work out a national strategy for research on PCa. The establishment of the NoPCR was the first result of NPPC’s strategy. NoPCR was established and running by January 2004. The CRN/NoPCR could from 2004 theoretically inform about the annual number of RP and radiotherapy courses, but research had to document the quality of this registry and indicate eventual future improvement strategies. In particular it seemed necessary to assess whether the additional registration allowed allocation of patients into risk-groups, requiring different treatment strategies and the treatment adherence to the existing EAU guidelines.

In 2006 the medical literature provided much information about the “typical adverse effects” after RP and definitive radiotherapy, the latter with or without ADT. Except for one study addressing such patients [103] little information was available for Norwegian patients treated in the first decade of the 21st century. At the same time, more and more Norwegian men planned for RP or definitive radiotherapy asked for evidence-based information about adverse effects and global QoL to be expected after their treatment.

Further, the prevalence of CF was not sufficiently explored in patients during or after curative treatment for PCa, though post-cancer fatigue had been recognized as a frequent long-term effect in several groups of cancer patients with significant impact on global QoL.

Finally, on the background of the growing interest in active surveillance and watchful waiting it was desirable to achieve more information on “typical adverse effects” in patients without local curative treatment.

In summary, there was an increasing demand for follow-up data on adverse effects and global QoL data for patients with localized PCa. As a joined decision of the NPPC and the Norwegian Urological Cancer Group (NUCG) a cross-sectional survey among PCa survivors in the 2004 cohort was sent out in October 2006.
2.2 Study aims

Based on the background outlined above the thesis had the following aims:

I. To perform a quality control of the NoPCR established in 2004, aiming to achieve most complete categorization of the patients into risk-groups with therapeutic consequences. A particular question of interest was whether patients could be identified who should be offered curative treatment. A secondary aim was to monitor to what degree recommendations were followed as published in the 2003 EAU guidelines with emphasis on patients who were candidates for curative treatment.

II. In a cross-sectional study to investigate the prevalence of CF in PCa patients after RP and RAD as monotherapy and to investigate the associations between CF and medical and psychosocial variables.

III. To assess the post radiotherapy prevalence of CF in patients with ongoing hormonal therapy compared to patients who had discontinued hormonal therapy at the time of the survey. Secondly, we aimed to investigate associations between CF and selected medical and psychosocial variables.

IV. To provide population-based two year estimates of “typical adverse effects”, such as urinary, bowel and sexual dysfunction in non-metastatic recurrence-free PCa patients in relation to treatment modality also including a group without treatment. Secondly we aimed to describe associations between these “typical adverse effects” and global QoL, to study patients’ use of medication for erectile dysfunction and the relation between such use and global QoL.
2.3 Materials and methods

2.3.1 Data sources

National population-based postal survey

In 2005 the NPPC and the NUCG agreed to perform a cross-sectional survey among PCa survivors diagnosed in 2004 and registered in the NoPCR. The survey aimed to study “typical adverse effects” and global QoL and was designed by using data from the NoPCR and the NorPD. The survey was designed in 2005 as a questionnaire based cross-sectional study. Eligible patients were identified by the CRN and were per mail invited to complete a questionnaire dealing with sociodemographic items and typical adverse effects as well as global QoL and fatigue. After about one year of preparation the study patients were invited by mail by their responsible physician to participate in the survey if they fulfilled the following eligibility criteria:

- Alive in 2006
- Considered to be approachable by the responsible physician who approved a list of names with possible participants
- Not diagnosed after a cystoprostatectomy
- The patients did not have an uncertain diagnose or were under evaluation
- Known address in Norway

Fourteen private urologists and 41 public hospitals accepted the offer to participate with their patients. Lists of eligible patients were sent to each institution and the patients were invited to participate in the national postal survey by a physician at the health-institution where the patient was first diagnosed. Twenty institutions contacted ≥50 patients, 14 institutions contacted between 20-49 patients and 21 institutions contacted less than 20 patients. The patients received a letter of information together with the questionnaire, and were also asked to sign a written informed consent if they wanted to participate in the survey. The survey responses were scanned and digitally read. One reminder was sent out to non-compliant patients. 2998 patients were initially invited to participate and of these 34 men either had died during the distribution process or were reconsidered by their responsible physician not to be eligible before the reminder was sent out. The invitation process and responses are depicted in Figure 2.

For consenting patients, the results from the questionnaire were connected to data from the CRN/NoPCR and the NorPD, based on the unique personal identification number.
Data from the Cancer Registry of Norway/Norwegian Prostate Cancer Registry
The following patient and cancer “baseline” data were collected from the CRN/NoPCR: date of diagnosis, age at diagnosis, curative treatment (RP or definitive radiotherapy), other treatment, date of treatment start, PSA at diagnosis, Gleason score from biopsy, clinical TNM category, Eastern Cooperative Oncology Group (ECOG) performance-status at diagnosis, and other cancer diagnosis. High-dose rate brachytherapy combined with external radiotherapy was introduced in 2004 [62], but is in this thesis not separated from conventional
radiotherapy. The data files were provided in June 2008 and contain combined information reported to the CRN and NoPCR by this date, which can be different from equivalent data extracted at another date because the registry is continuously updated. The interpretation and reporting of the CRN data are the sole responsibility of the authors, and no endorsement by the CRN is intended nor should be inferred.

**Data from the Norwegian Prescription Database**

In paper II variables from the NorPD were essential for identification of hormone-naive men. All patients with any prescription of PCa related use of hormones between diagnosis and the survey were excluded. Such differentiation could not be done for non-participants as NorPD data were not released for these men. In paper III and IV prescription data from the NorPD identified patients with continuous use of LHRH-analogs and were used to assess the duration of such treatment. Further, in paper IV patients with prescribed medication for erectile dysfunction were identified, including use of PDE5 inhibitors, Alprostadil urethral sticks and Papaverin injections.

### 2.3.2 Study populations

**Paper I (Population of men with a prostate cancer diagnosis from 2004)**

In this descriptive study all patients with a PCa diagnosis in 2004 were included regardless of the basis of the diagnosis, tumor extent or missing data. The data file was extracted from the CRN and NoPCR in June 2008. Patients who were diagnosed by autopsy, death certificate only or cystoprostatectomy were excluded from analyses of initial treatment as this could not be followed by a therapeutic treatment decision (Figure 3). Patients entitled as “candidates for curative treatment” met the following criteria: T1-3 N0-X M0 category, PSA level ≤ 100 ng/mL, any Gleason score, age ≤ 75 years at diagnosis, ECOG performance status 0-1, no other cancer, no known co-morbidity at diagnosis as assessed from a voluntary commentary field. Initial local treatment was defined if RP was performed within six months or definitive radiotherapy was performed within 14 months.
Prostate cancer diagnosis in 2004

N=3833

Not assessed for initial treatment
- Reported by death certificate only: n=22
- Incidental finding by autopsy: n=30
- Incidental finding by cystoprostatectomy: n=37

n=89 (2%)

Candidates for curative treatment
n=1650 (43%)

Basic diagnostics missing
n=295 (8%)

Advanced disease
n=833 (22%)

Ineligibility criteria for curative treatment*
n=966 (25%)

N=3744
Assessed for initial treatment

* high age (>75 years), ECOG performance status ≥2 or performance status missing, other cancer, serious co-morbidity reported

Figure 3: Patients diagnosed in 2004

Paper II-IV (PCa survivors participating in the national survey)
The survey conducted in October 2006 primarily included all eligible survivors from the 2004 cohort. The focus of the current thesis was restricted to compliant non-metastatic patients belonging to defined treatment categories and without other adjuvant treatment or evidence of recurrence (Table 2). The use of adjuvant or salvage treatment was known from the CRN/NoPCR, the CRN’s radiotherapy registry and by linkage to the NorPD. Further, study populations were restricted to survey participants with complete data on relevant instruments.
Table 2: Relevant treatment groups for papers II-IV

<table>
<thead>
<tr>
<th></th>
<th>RP</th>
<th>RAD hormone-naïve</th>
<th>RAD+ADT* with discontinued hormone treatment</th>
<th>RAD+ADT* with ongoing hormone treatment</th>
<th>No treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paper II</td>
<td>×</td>
<td>×</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paper III</td>
<td>×</td>
<td>×</td>
<td>×</td>
<td>×</td>
<td></td>
</tr>
<tr>
<td>Paper IV</td>
<td>×</td>
<td>×</td>
<td>×</td>
<td>×</td>
<td>×</td>
</tr>
</tbody>
</table>

*RAD+ADT: definitive radiotherapy with (neo)adjuvant hormone treatment

Paper II
Among survey participants with a valid Fatigue Questionnaire (FQ), PCa patients treated with RP or RAD who never had received ADT or orchiectomy were included in the study. No supplementary PCa treatment was received in addition to the RP or RAD treatment before the survey. Twelve months or more had elapsed between start of initial curative treatment and the survey. A control group from the Norwegian male population aged ≥ 60 years was used for comparison [155].

Paper III
Among survey participants with a valid FQ, patients were eligible if they had radiotherapy with (neo)adjuvant ADT (RADHT). Eligible patients started continuous treatment with LHRH-analogs (with or without simultaneous anti-androgens) up to eight months prior to start of radiotherapy. Men still using LHRH-analogs at the time of the survey (HTcont) were separated from men who had their last prescription of LHRH-analogs at least 6 months before the survey (HTdis). Any other ADT-use led to exclusion, e.g. those who had intermittent use of LHRH-analogs or those who started anti-androgen monotherapy after discontinuation of LHRH-analogs. Start and end of LHRH-analog treatment was estimated by using the date of the first prescription and the amount of prescribed medication (1 or 3 month’s depot effect), as documented in the NorPD. The previously described hormone-naïve RAD patients were included as a control group.

Paper IV
The study was performed among study participants with a valid SF-12 who were “candidates for curative treatment”, as defined in Paper I. Further, eligible patients had to belong to one
of the following treatment categories of initial treatment without any other PCa specific therapy: 1) No treatment, 2) RP, 3) RAD without hormones, 4) RADHT with hormone therapy of 3-24 months duration, the last three-month LHRH-depot injection prescribed at least 6 months prior to the survey. Start of the defined local treatment had to be one year prior to the survey and all treatment had to be discontinued before the survey. For the “No treatment” group the date of diagnosis represented the start of treatment.

2.3.3 Measures and instruments

In general, the design of the final questionnaire was a joined task of the project group of NPPC and it is rendered in its entirety in Appendix B. As it was necessary to combine different views and priorities of members in the NPPC, the project leader could not always meet the requirement of using only validated and formally translated items or domains. However, in principal the questionnaire reflects this intention. The population-based survey thus contains selected items from previously published validated questionnaires and some supplementary study specific questions.

The Short-Form Health Survey 12

Global QoL was measured by the physical and mental summary scores of the validated instrument SF-12 [94]. The scores of PCS and MCS were transformed by linear T-transformation and standardized to have a mean score of 50 and a standard deviation of 10. In paper II we used the SF-12 single item of bodily pain. In paper IV low global QoL was defined as having a PCS and/or MCS of 40 or below. The SF-12 has previously been translated to Norwegian, and validated in a Norwegian population [161].

Urinary adverse effects

The International Prostate Symptom Score (IPSS)

IPSS measures irritative-obstructive urinary symptoms [162, 163]. Three IPSS categories were defined using recommended cut-off levels; none/mildly symptomatic (0-7), moderately symptomatic (8-19) and severely symptomatic (20-35). In paper IV the categories were further dichotomized (0: no symptoms/mildly symptomatic and 1: moderately or severely symptomatic). The IPSS has previously been translated to Norwegian [133].
Urinary incontinence
Urinary incontinence was defined as “leaking urine at least once a day”. In paper II and III irritative symptoms and urinary incontinence were combined in a variable called “urinary dysfunction”, while in paper IV the two items were analyzed separately.

Bowel dysfunction
Intestinal irritative symptoms
Intestinal irritative symptoms were defined as having at least one of the following traits: 1) defecation ≥3 times a day, 2) at least 50% of the times; diarrhea, blood or mucus in stool or painful defecation, 3) ≥2 times a week cramps or fecal urgency.

Fecal leakage
Presence of fecal leakage was defined as fecal leakage once a week or more. In paper II and III intestinal irritative symptoms and fecal leakage were combined in a variable called “intestinal dysfunction”. In paper IV the two items were analyzed as separate variables.

The Brief Male Sexual Function Inventory (BSFI)
BSFI is an eleven-item inventory that assesses five dimensions of sexual function: drive, erection, ejaculation, problem assessment and overall satisfaction with sexual life [164]. Mykletun et al have shown that BSFI can serve as an overall measure of sexuality, excluding overall satisfaction [165]. The instrument is translated into Norwegian and is validated [165]. The items are scored on a five-point Likert-scale and the total score ranges from 0-40. A higher BSFI total score implies a better sexual function. The BSFI was used in paper II and III as a continuous variable. In paper IV we used the following cut-off levels to define “Caseness” for drive and erection; poor sexual drive ≤3 and poor erectile function ≤7 [166].

The Fatigue Questionnaire
FQ evaluates physical fatigue (seven items) and mental fatigue (four items) [146]. Total Fatigue Score is the sum of all eleven items. Items are measured on a four-point Likert-scale (0-3) where higher scores imply more fatigue. Physical, mental and total fatigue ranges from 0-21, 0-12 and 0-33, respectively. Two questions concern the duration of the fatigue. Caseness of CF is defined as the sum-score of ≥4 after dichotomization of the FQ symptom scores (0-1=0, 2-3=1) and with duration of six months or more. The FQ was used in paper II
and III and used the translation by Loge et al who validated the FQ and provided normative data in a Norwegian representative sample in 1997 [155].

**Eysenck Personality Questionnaire (EPQ-18)**

As symptom-reporting and physical complaints may be influenced by a person’s neuroticism, we included a measure of this personality trait. Neuroticism describes if a person generally feels anxious or safe. People with a high degree of neuroticism are likely to interpret even normal situations as problematic or threatening [167]. An abbreviated version of the Eysenck Personality Questionnaire (EPQ-18) measured neuroticism [168]. The EPQ-18 was translated and validated in a Norwegian population in 1990 [169]. Six items comprise the personality trait neuroticism (range 0-6) which covers the dimension from feeling safe (score 0) to feeling maximally nervous (score 6). In paper II and III we defined “low neuroticism” as score 0-4 and “high neuroticism” as score 5-6 [170]. In paper IV we categorized neuroticism into “low neuroticism” (score 0-1) “moderate neuroticism” (score 2-3) and “high neuroticism” (score 4-6).

**Missing responses**

Missing responses in the questionnaire were replaced with the mean value within a domain if at least half of the items were valid. Otherwise, domain scores were considered as missing [171].

**2.3.4 Ethical considerations**

All parts of the present thesis were approved by the Regional Committee for Medical Research Ethics, the protocol review of committee of the Norwegian Radium Hospital, and the Norwegian Data Inspectorate. All participants in the national survey provided written informed consent including permission to the use of their NorPD data.

An ethical challenge occurred while collecting data for the survey. After the first invitation of 2998 patients 33 persons (1%) responded that they did not have a PCa diagnosis. The physicians at the medical centers where the PCa was diagnosed and who approved their participation were informed of the situation. We recognized that the problem mostly concerned patients with “insignificant” PCa (micro focus). Before a reminder was posted to non-responders we provided a list of these patients to the responsible doctor and asked for a confirmation that the patients were informed of their PCa diagnosis. The fact that some men
were not informed of their “insignificant” PCa or had not perceived it as a PCa diagnosis was an unforeseen problem. In addition, other studies have shown that some cancer patients might deny their diagnosis [172]. In either way it was stressful for these men to be contacted in relation to a PCa diagnosis and every attempt should be made to avoid such situations in the future. Our experiences should be a reminder for other groups working with similar studies to be precautious when contacting persons identified through a health registry.

2.3.5 Statistics

Median and range were calculated to describe data with skewed distributions. Mean and standard deviation were calculated to describe data with normal distributions. Continuous variables were compared using t-tests and analysis of variance (ANOVA) if normally distributed and Mann-Whitney Wilcoxon if skewed. Categorical variables were analyzed with Chi-square tests. Multivariate analyses were performed using logistic regression analysis. The strength of an association was expressed as an odds ratio with a 95% CI. All tests were two-sided. The analyses were performed using versions of the Statistical Package for Social Science (SPSS version 15 and PASW version 18, Chicago, IL)

2.4. Main findings

2.4.1 Paper I

In this paper we analyzed the compliance to the NoPCR and assessed initial treatment of men with a PCa diagnosis in Norway in 2004.

The first year experience with registration of prognostic and therapeutic variables in the NoPCR showed a compliance-rate of 96%, admittedly after sending many reminders to the hospitals. To achieve as high completeness as possible interpretation of all available information was essential, even though such data were not always submitted to the CRN on structured case record forms. Nevertheless, missing information caused that 295 non-metastatic patients could not be classified to risk-groups (Table 3). Forty patients with basic diagnostics missing received definite curative treatment.

Of 3833 patients diagnosed in 2004 we defined 1650 men as candidates for curative treatment (Figure 3). A total of 966 patients were ineligible as candidates for curative treatment due to old age, poor performance status, major co-morbidity or other cancer and
85% of these were categorized as intermediate or high-risk patients. Of these 966 ineligible patients, 73 (8%) did receive definite curative treatment.

In total 1022 (62%) of CurCands received curative treatment (RP: 360, definitive radiotherapy: 662). RP was administered in 18 different hospitals (1-10 prostatectomies: 8 hospitals. 11-24 prostatectomies: 3 hospitals. ≥25 prostatectomies: 7 hospitals). Definitive radiotherapy was administered in seven different hospitals. Among CurCands 500 (30%), 453 (27%) and 697 (42%) patients were categorized to the low-, intermediate- and high-risk group, respectively. The proportions curatively treated patients were 57%, 68% and 61% for the low-, intermediate and high-risk group, respectively. In the low-risk group patients with T2 tumors had higher risk of receiving curative treatment than men with T1 tumors. In the intermediate- and high-risk groups the probability to undergo curative treatment significantly decreased with increasing PSA. In the two latter groups increased age also significantly reduced the probability of curative treatment.

Table 3: Description of treatment and missing variables in 295 non-metastatic patients with missing basic diagnostics (PSA, Gleason score, T category)

<table>
<thead>
<tr>
<th>Patient descriptives</th>
<th>Missing basic diagnostics</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=295</td>
</tr>
<tr>
<td>Prognostic factors missing, N (%)</td>
<td></td>
</tr>
<tr>
<td>Missing PSA only</td>
<td>45 (15)</td>
</tr>
<tr>
<td>Missing Gleason Score only</td>
<td>100 (34)</td>
</tr>
<tr>
<td>Missing T category only</td>
<td>92 (31)</td>
</tr>
<tr>
<td>Missing two or more prognostic factors</td>
<td>58 (20)</td>
</tr>
<tr>
<td>Curative treatment, N (%)</td>
<td></td>
</tr>
<tr>
<td>RP within 6 months</td>
<td>15 (5)</td>
</tr>
<tr>
<td>Definitive radiotherapy within 14 months</td>
<td>25 (8)</td>
</tr>
</tbody>
</table>
2.4.2 Compliance to the national survey (paper II-IV)

In the current survey 2998 men were invited to answer the questionnaire in October 2006 and of these 73% (N=2194) participated. Compliers had median age 69 years [range: 44-94 years] and non-compliers had median age 74 years [42-96 years], p<0.001. Men aged ≤75 years had a compliance rate of 80%. The compliance rates for RP, definitive radiotherapy and CurCands, from Paper II-IV, were 87%, 85% and 78% respectively. The compliance rate was highest for men with non-metastatic disease compared to those with metastatic PCa or unknown metastasis status (Figure 4).

![Figure 4: Compliance rates to the national survey stratified for metastasis status. Numbers and proportions for compliers are given at the green section and non-compliers at the blue section of the bars.](image-url)
2.4.3 Paper II

In this paper the prevalence of CF was compared in patients with RP or RAD as monotherapy more than one year after treatment start. We identified 521 patients with curative monotherapy (RP: 337, RAD: 184). RP patients were significantly younger at diagnosis compared to RAD patients (RAD: median 66 years, RP: median 62 years). RAD patients more often belonged to the intermediate or high-risk group (60%) compared to RP (47%). At survey co-morbidity and pain was reported by 55% and 60% of the RAD patients, respectively, compared to 39% and 44% in the RP group. The prevalence of urinary and intestinal dysfunction was 30% and 21% among RP patients and 21% and 48% among RAD, respectively. RAD patients had a significantly better sexual function compared to RP in unadjusted analyses.

Physical, mental and total fatigue was significantly higher in RAD patients compared to RP. The proportion of patients with CF was 13.4% after RP and 26.1% after RAD. In multivariate analyses patients after RAD had a doubled risk of CF compared to RP. Younger age, presence of high neuroticism, co-morbidity, pain, urinary and intestinal dysfunction were positively and significantly associated with increased risk of CF. Risk-group was not significantly associated with CF. The difference in CF between RP and RAD was largest in patients with the longest observation times.

2.4.4 Paper III

In this paper we investigated the prevalence and severity of CF in definitive radiotherapy patients with ongoing or discontinued (neo)adjuvant ADT. As control group we used the RAD group from Paper II. Of 239 consenting, evaluable patients treated with RADHT, 82 were still on hormone therapy (HTcont) and 157 men had discontinued hormone treatment (HTdis) at the time of the survey.

In the HTcont group 19% and 80% of patients belonged to the intermediate- and high-risk group, respectively. This was significantly different from the HTdis group where 27% and 64% belonged to the intermediate- and high-risk group, respectively (p<0.001). The median duration of (neo)adjuvant ADT was 27 months in HTcont and 6 months in HTdis patients (p<0.001).

Patients in the HTcont group had the highest prevalence of CF (39.0%) compared to 22.3% in the HTdis group and 26.1% in the control group. In the adjusted analysis belonging to the HTcont group doubled the risk of CF compared to the hormone-naïve controls, whereas
men from the HTdis group had no elevated risk of CF. Younger age, presence of pain and high neuroticism as well as urinary, intestinal and sexual dysfunction increased the risk of CF. Exclusively looking at patients who had discontinued their LHRH-analog treatment, treatment duration >6 months, younger age and urinary, intestinal and sexual dysfunction increased the risk of CF.

2.4.5 Paper IV

This paper provides information on global QoL and prevalence of typical adverse effects in non-metastatic PCa patients who were candidates for curative treatment. After approximately two years since diagnosis totally 771 patients were eligible (NoTreat: 180, RP: 293, RADNoHT: 156 and RADHT: 142). NoTreat patients were oldest with median age 70 years compared to 62, 67 and 66 years in RP, RADNoHT and RADHT patients respectively. High-risk PCa was significantly more common in RADHT (61%), compared to 23%, 12% and 16% in NoTreat, RP and RADNoHT respectively. The NoTreat and RADNoHT group presented the highest prevalence of co-morbidity at survey (53%) and RP patients the lowest (37%). Prostatectomized men reported significantly more urinary incontinence (24%), but the lowest prevalence of irritative-obstructive urinary symptoms (23%) compared to the other treatment groups (Table 4). The two groups of irradiated men reported more irritative intestinal symptoms (RADNoHT: 47%, RADHT: 42%) and fecal leakage (14%) compared with RP and the NoTreat group. A rather high proportion of men from the NoTreat group experienced urinary incontinence (13%) and irritative-obstructive urinary symptoms (50%). Poor erectile function was common in all treatment groups ranging from 76%-89%. Presence of irritative-obstructive urinary symptoms and poor sexual drive were associated with approximately doubled risk of low global QoL in adjusted analyses.

Compared to the other treatment groups, prostatectomized men had more often used medication for erectile dysfunction at least once between treatment and survey (84%). In addition prostatectomized men initiated such treatment earlier compared to men belonging to other treatment groups. Use of medication for erectile dysfunction was not significantly associated with global QoL.
Table 4: Prevalence of "typical adverse effect” and low global quality of life (QoL) stratified per treatment group*

<table>
<thead>
<tr>
<th></th>
<th>NoTreat</th>
<th>RP</th>
<th>RADNoHT</th>
<th>RADHT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse effects</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Irritative/obstructive**</td>
<td>50</td>
<td>23</td>
<td>44</td>
<td>35</td>
</tr>
<tr>
<td>Incontinence</td>
<td>13</td>
<td>24</td>
<td>10</td>
<td>6</td>
</tr>
<tr>
<td>Intestinal</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Irritative symptoms</td>
<td>21</td>
<td>20</td>
<td>47</td>
<td>42</td>
</tr>
<tr>
<td>Leakage</td>
<td>3</td>
<td>3</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>Sexual</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poor sexual drive</td>
<td>55</td>
<td>61</td>
<td>71</td>
<td>69</td>
</tr>
<tr>
<td>Poor erectile function</td>
<td>76</td>
<td>89</td>
<td>83</td>
<td>84</td>
</tr>
<tr>
<td>Low global QoL</td>
<td>27</td>
<td>18</td>
<td>30</td>
<td>24</td>
</tr>
</tbody>
</table>

*Given as percentage of patients with the specified condition in each treatment group

**Moderate to severe symptoms

2.5. Discussion

2.5.1 Methodological considerations

Biases

Bias is a term used for describing any systematic error in a study and can be classified into three main categories: selection bias, information bias and confounding [173]. Randomized trials reduce most sources of bias, but with the disadvantage that they cannot be generalized to all patient groups. In our case men in the RADNoHT group may never have been candidates for RP and thus would have been excluded from a randomized trial. In such cases population-based studies with well-described patients are suitable because they describe the condition in the community setting. Our population-based survey is based on information available in the CRN when the patients were contacted in 2006. At that time the CRN data for diagnosed PCa in 2004 were close to complete regarding the number of patients. The CRN is dynamic and data are continuously updated if new information is available. The high quality as to proportion of patients being registered can partially be explained by the CRN’s access to multiple sources of information such as case record forms, histopathological reports, radiotherapy data and death certificates. Due to the high completeness of the CRN as to number of cancer cases per year, we consider selection bias in this context to be minimal.
However, 8% of non-metastatic patients could not be categorized into risk-groups because of missing data for T-category, PSA and/or Gleason score, which might be a source of selection bias.

Selection bias might also be present in papers II-IV which rely on self-selection of patients to respond to a survey. Unfortunately NorPD data were only released for consenting study compliers, which prevented us from doing an attrition analysis. The associations we have studied and the prevalences we have described might differ between compliers and non-compliers to the survey. We can speculate that heavily fatigued men were less likely to respond to the survey due to the burden the questionnaire completion may represent. On the other hand, men volunteering to complete the questionnaire might be especially bothered by symptoms related to PCa and its treatment. In extension to this, men without bothersome problems or dysfunction may have considered survey participation as irrelevant.

The information bias present in the study is most probably non-differential; meaning that misclassification of exposure is unrelated to the occurrence or presence of the dependent variable. For example, misclassification of patients in categories of adverse effects may only reduce the observed association with global QoL, compared to correctly classified data. Some known confounding factors are accounted for in multivariate analyses; however, unknown confounding factors can be a problem in cross-sectional studies. *Confounding by indication* is a relevant term when discussing biases in the present study. It relates to the fact that those who receive a specific treatment generally differ from those who receive another treatment, according to the medical indication of the treatments. In the present study we attempted to remove this type of bias by adjusting for risk group, co-morbidity and age in adjusted analyses. However, the NoTreat group in Paper IV comprises patients who remain untreated due to different indications (watchful waiting and active surveillance), which could not principally be separated from each other.

**Validity of the study**

The internal validity of a study deals with the degree to which results can be attributed to the effect under study, or can be a product of sampling error and alternative explanations. Unknown confounding factors can be differently distributed between groups introducing systematical bias. When comparing treatment groups we have controlled for available confounding factors, such as known co-morbidity and age. Unknown confounding factors and
more precise measures of known confounders may have altered our results, in particular the unknown severity of pre-treatment co-morbidity influencing treatment decisions.

External validity concerns the question if our results can be generalized to other populations. Considering the high response rate of our study and the nature of our unselected cohort we probably have a high generalizability of our study results to PCa patients which are similar in indication for and selection of curative treatment as in our patients from 2004. This means that the results can be used to foresee adverse effects in two-year recurrence-free patients without any supplementary treatment beyond that provided initially. However, several limitations have to be considered.

Most importantly any consideration of our results’ external validity requires some aspects of selection of patients for RP versus RAD without ADT. Though we have no pre-treatment data, the higher prevalence of chronic co-morbidity in the RAD patients makes us believe that these group’s data, especially concerning CF, are valid only if patients are selected for RAD on the same background as anticipated in this study, including more severe co-morbidity, which did not allow major surgery.

When the patients in the 2004 cohort were treated with RP this was mainly open retropubic technique, however two hospitals in Norway used laparoscopic technique already in 2004. Laparoscopic RP and robotic assisted laparoscopic RP are performed by less time and with less blood loss compared to retropubic RP [174]. In addition the surgeon has a better visualization of anatomical structures which in theory could affect outcomes as free surgical margins, urinary incontinence and erectile function, however randomized studies showing such differences are lacking [175]. No significant differences in survival between the different operative techniques have been documented [174]. Further, our data did not separate patients based on nerve sparing procedure. However, taking into account the prevalence of self-reported erectile dysfunction among patients prostatectomized in Norway in 2009 [176] we believe our results can be used with caution also with today’s operative techniques. Steinsvik et al report that 86% of patients prostatectomized in 2009 suffer from poor erection one year after RP [176].

The vast majority of definitive radiotherapy patients were treated with external beam radiotherapy and the results may differ after the use of brachytherapy.
2.5.2 Discussion of main results

**Paper I**

Paper I indicates issues of future improvement as to registration of variables into the NoPCR. At least for non-metastatic patients all essential variables (PSA, Gleason score, T category) should be collected for adequate risk-group allocation. Missing variables and missing case record forms should be chased as soon as possible by the coding staff at the CRN, as a delay in registration complicates the task to provide correct information from the time of diagnosis, both for the responsible doctor and for the CRN. Improvement in data collection is also needed for better separation of active surveillance as a part of curative treatment and watchful waiting in a palliative setting. The NoPCR data registration of diagnostics and treatment must be under continuous evaluation by dedicated persons who know about the advancing practices concerning PCa. The NoPCR should at any time contain all essential variables which are needed for evaluating patients according to the current guidelines. For future years the above experiences indicate the need for improved registration of essential data and continuous control of their completion either by manual or electronic procedures. Registration of ADT in the CRN is difficult as these data are complex concerning type of medication, duration, amount of ADT and application method. If possible, individualized NorPD data concerning cancer treatment should be made available to the CRN, which would be a practical way to collect detailed and very important clinical information lacking today.

Another issue to discuss is whether RP, definitive radiotherapy or active surveillance is the most appropriate treatment considering the different risk-groups. Only randomized trials can show the superiority of either treatment, but such trials are lacking. As a next to optimal alternative very long-term follow-up of unselected and well characterized patient cohorts can be studied, with the possibility to include comparable patients without any initial local treatment. This latter aspect is of particular relevance for the low-risk group. Improved data collection in the NoPCR will probably enable such comparative survival analyses.

Further, our population-based registry study revealed patterns of the cancer management which might be issues for improvement. Firstly the data indicated over-treatment of low-risk PCa, as 57% received definite local therapy within the first 6 months (RP) or 14 months (definitive radiotherapy). Today’s literature suggests that at least some of these patients from the low-risk group can be included in an active surveillance policy, without reducing the prognosis, but minimizing the burden of typical adverse effects [177, 178]. This
is probably especially valid for patients >65 years for whom the results of RP were equal to those of conservative management. A registry study from Sweden reported the 10-year cancer-specific mortality for those with low-risk disease to be 2.4% and 0.7% in conservatively managed patients and patients treated with curative intent, respectively [179]. In the previous Swedish study 60% of patients in the low-risk group were treated with curative intention. Local treatment may thus be justified in some men with low-risk tumors, in particular in the youngest. The extensive use of local treatment in 2004 is difficult to defend, seen with today’s knowledge, especially in men close to their 70ies, for whom survival was not prolonged in the SPCG-4 study [177, 178]. Any survival benefit from therapy in low-risk patients is bound to be small, however randomized studies are needed. Follow-up studies in the NoPCR are needed to prove whether the treatment pattern has changed the most recent years.

Secondly the data suggest under-treatment of intermediate and high-risk patients defined as CurCands as only 68% and 61% received definite curative treatment, respectively. At the localized stage PCa is still a potentially curable disease. The probability to undergo curative treatment decreased with increasing PSA level in the intermediate- and high-risk groups. Recent data indicate that local treatment may be beneficial in these patients, even though not always curative [66]. Widmark et al found that patients with high-risk PCa treated with definitive radiotherapy and ADT had significantly better PCa specific survival and overall survival compared to patients treated with ADT alone [66].

Finally, the paper documented that Norwegian urologists and oncologists in general followed the recommendations stated in the 2003 EAU guidelines, both in patients who were planned for curatively intended treatment, but also for those with metastatic treatment. At the same time the paper documented the fact that some hospitals have a small annual number of prostatectomies per year and thereby surgeons with low-volume of RP procedures. This issue is worth mentioning since an association between high-volume surgeons and better post-prostatectomy outcomes has been found where low, medium and high volume are defined as <18 RPs, 18-52 RPs and >52 RPs a year, respectively [180]. If desirable a cancer registry could be used for such surveillance purposes on hospital and/or surgeon level related to outcome variables.
In Norway in 2004 RP was the preferred treatment for the majority of men with low-risk PCa, but if co-morbidity and age did not allow this surgical procedure, RAD without adjuvant hormone therapy was the most often used curatively intended treatment. Such selection bias can also explain why hormone-naïve RAD patients report significantly more CF (26.1%) compared to men after RP (13.4%). Interestingly, only 40% of RAD monotherapy patients were in the low-risk group and as many as 16% were high-risk patients. Though we only have information on post-treatment co-morbidity, the nature of reported conditions suggests that many patients suffered from these diseases already at the time of diagnosis and prior to treatment decision. Co-morbidity and high age probably had a high impact on the treatment decision. However, we cannot exclude that our findings reflect an etiological relationship between radiotherapy and CF. High-dose radiotherapy induces long-lasting inflammatory processes [181, 182], with chronic overproduction of cytokines and subsequent long-term development of fibrosis and necrosis in normal tissue [183], which might be connected to CF. In contrast to the patients with (neo)adjuvant ADT, patients with RAD as monotherapy probably are less likely to recover from CF with time. Moreover, the comparison of the prevalence of post-RP fatigue with that of the normal population may be debatable. RP patients are usually selected based on their good health and a life expectancy of more than 10 years. Pre-treatment CF is probably less of a problem for RP candidates compared to the normal population. The prevalence of post-RP CF which is only slightly above that of the normal population may thus reflect true increase compared to the pre-treatment level.

A cross sectional study from the United Kingdom, similar to Paper II, investigated “clinically-relevant fatigue” in recurrence free patients >1 year after RP or radiotherapy [184]. Storey et al found the prevalence of “clinically relevant fatigue” to be 33% (95% CI: 27% to 39%) after radiotherapy and 22% (95% CI: 16% to 30%) after RP. Patients in this study are not well characterized at baseline except from age, which in this case was not significantly associated with “clinically relevant fatigue”. All radiotherapy patients also had three months of neoadjuvant ADT which may have influenced the prevalence of fatigue. However the largest difference compared to our study was the high prevalence of “clinically relevant fatigue” in the RP group. Only randomized prospective studies can prove whether and to what degree radiotherapy can cause CF more than RP.

The addition of hormones did not increase the risk of CF in the HTdis group compared to hormone-naïve RAD. The two mentioned groups had similar age distribution and
proportion with co-morbidity and therefore one might suspect that radiation treatment in itself was the most important factor in the development of CF. However, we believe that most of our hormone-naive RAD patients might have been at poorer health at baseline, disqualifying them from RP. On the other hand patients receiving RADHT had this combined treatment due to more advanced disease and not as a result of more co-morbidity. The relatively high estimate of CF in the HTdis group (22.3%) might thus be a result of previous ADT.

The HTcont group had the highest proportion of CF (39.0%) reflecting a well-known negative influence of long lasting hormone treatment on vitality, which has to be balanced against inhibition of PCa cells by castration levels of testosterone [185]. ADT for PCa, with corresponding low serum testosterone level, has proved to be associated with several adverse effects as hot flashes [186], skeletal problems [187, 188], sexual dysfunction [189, 190], metabolic changes [191-193] with subsequent increased cardiovascular risk [194], possible cognitive impairment [195] and fatigue [156, 157]. Most adverse effects will be reversed with subsequent recovery of testosterone production when ADT is discontinued. Normalization of testosterone levels appears to be dependent upon ADT duration, baseline testosterone level and the age of the patient at initiation of ADT treatment [124]. However, the optimal duration of ADT related to the individual patient’s risk-group is uncertain. With treatment duration shorter than three years 65% of patients return to their baseline level of testosterone after a median follow-up of 18 months [196]. A longer interval to testosterone recovery might prolong the duration of adverse effects; however long-term ADT has shown to be associated with a lower risk of PCa death in men with minimal co-morbidity [197]. The median time during which the HTdis group had been without ADT was 18 months and some would therefore not have reached their baseline level of testosterone thus explaining the CF even after several months without ADT.

Unexpectedly, age was negatively associated with CF in both Paper II and III. As an explanation we suggest that CF at a greater extent prevents performance of daily chores and leisure activity in younger pre-treatment active men than in older more sedate men. On the other hand, the pattern for CF in the normal population is that CF increases with advancing age.
The study population in Paper IV differs slightly from patients in Paper II and III, as only CurCands were included. The NoTreat group consisted of both true active surveillance patients and of men on watchful waiting who were candidates for palliative treatment if the disease progressed. Results should not be extrapolated to patients outside our CurCands definition or to patients with treatment for PCa recurrence. Separate studies should be performed for these patient groups. A rather high number (73 patients) received curatively intended therapy, but were by us not defined as CurCands due to old age, poor performance status, major co-morbidity or other cancer. This result may reflect that clinicians perform individualized evaluations of patients where old age and poor health condition are considered unimportant compared to for example the patients’ wishes.

The treatment strategies we studied (NoTreat, RP, RADNoHT, RADHT) showed distinct patterns of prevalence of typical adverse effects. The investigations were restricted to study functional aspects of adverse effects, not taking into account the persons bother. It is known that similar degrees of urinary incontinence can be experienced as a great bother or not as bothersome depending on the individual [198].

Men in the NoTreat group were not spared from urinary incontinence or irritative-obstructive urinary symptoms. Irritative-obstructive urinary symptoms in these patients most probably originated from malignant and benign growth of the prostate. We can not exclude that some men were treated with TUR-P before survey which may have affected our estimates concerning urinary function. Low prevalence of irritative-obstructive urinary symptoms among men in the RP group may point toward that treatment with RP relieves post-treatment irritative-obstructive urinary symptoms, not quite unusual in men above the age of 50 years. However, the RP group had a significantly higher prevalence of urinary incontinence compared to all other groups. Interestingly, irritative-obstructive urinary symptoms were associated with increased risk of low global QoL and should be recognized as a typical adverse effect of similar significance as urinary leakage. The significance of irritative-obstructive urinary symptoms has also been emphasized by Sanda et al [129] and Pardo et al [130]. Pardo et al found that irritative-obstructive symptoms were relieved in 64% three years after RP, however the prevalence of such symptoms at baseline is not reported.

Poor sexual drive and poor erectile function were common in all treatment groups though we stress that there might be subgroups performing better for example those operated with a nerve-sparing technique [199, 200]. Surprisingly, poor erectile function was not
significantly associated with global QoL in our study. However our categorization of patients according to use of medication for erectile dysfunction suggests that men have reported sexual function without the use of aids, which may have confounded the calculated association between erectile function and global QoL. Poor sexual drive was significantly associated with low global QoL, probably because it is a more general symptom related to vitality and energy. Not surprisingly poor sexual drive was most common among RADNoHT patients (71%) supporting our suggestion that this group has a poorer health condition. Poor sexual drive was also common among men who had (neo)adjuvant ADT who may still suffer from a low testosterone level. Logically men with poor sexual drive were less likely to try medication for erectile dysfunction compared to men with normal sexual drive, reflecting their lack of motivation to try such treatment.

**Neuroticism**

Neuroticism was included as a variable in Paper II-IV and was associated with CF in Paper II and III and with global QoL in paper IV, even in adjusted analyses. CF in the general population is associated with neuroticism through genetic mechanisms [201] and some PCa patients may therefore be predisposed to develop CF under the stress from PCa treatment and adverse effects. Evidently this personality trait also plays a role in symptom reporting and how a man perceives his health status [167].

The public health significance of neuroticism is discussed by Lahey [202] in a review article which states that neurotic trait is robustly correlated to many physical and mental disorders and a person’s use of public health services. Lahey considers neuroticism to be of enormous importance to the public health and suggests intensive research to understand relations and mechanisms among neuroticism, mental health, physical health and QoL. Previously, Costa &McCrae have stated: «…it (author’s remark: neuroticism) is intimately linked to health perceptions and behaviors, and thus to every interaction of the individual with the health care system» [167]. The role of this personality trait in clinical and public health research has nevertheless not been finally established.

Recognition of a nervous personality can be of value during pre-treatment counseling having in mind that this condition increases the perception of unavoidable adverse effects. Including a measure of neuroticism into pre-treatment counseling can potentially help clinicians to provide improved individualized information which render realistic expectations as to life after curative treatment for PCa.
2.6 Conclusions

- The initial management of PCa in Norway was largely in accordance with the 2003 EAU guidelines. There was some evidence of over-treatment of low-risk patients and undertreatment of intermediate and high-risk patients. If the NoPCR shall be a research tool and function as a source of enhancement of medical care of PCa patients in Norway, the routine registration of the essential diagnostic variables must be improved and kept at least as complete as in 2004. Revision of the case record form is necessary, for example for better separation of conservatively managed patients into active surveillance and watchful waiting.

- Our findings support a possible role of definitive radiotherapy in the development of CF in PCa patients, but the observations may be confounded for example by unknown pre-treatment co-morbidity. As many as 26.1% of hormone-naïve RAD patients had CF approximately two years after treatment, which is a substantial proportion and more than one would intuitively presume given the total absence of ADT. In addition 30% of men in this group had low global QoL. Regardless of the influence of confounding factors this treatment group is characterized by distinct health problems and should receive special attention during aftercare. Younger age, high neuroticism, co-morbidity, pain and urinary and intestinal dysfunction significantly increased the risk of CF implicating that management of CF requires pain and symptom relieve.

- The high prevalence of CF in RADHT patients with ongoing adjuvant ADT is an incentive to keep the duration of such treatment as short-lasting as possible without reducing the cure rate.

- Our findings support that different treatment modalities are followed by distinct patterns of adverse effects. However, patients who are without treatment also experience symptoms viewed as “typical” after curative treatment for PCa. The presence of irritative-obstructive urinary symptoms and poor sexual drive are associated with increased risk of low global QoL. Irritative-obstructive symptoms should thus be recognized as a distinct adverse effect in PCa patients. Our results further suggest that the personality trait neuroticism is related to global QoL and CF. The use of medication for erectile dysfunction is most common after RP treatment, but does not seem to be related to global QoL. To study the effect of medication for erectile dysfunction requires that the relevant questionnaire specifically ask for sexual function with or without the use of such medication.
2.7 Future perspectives

- The prevalence of typical adverse effects and their impact on global QoL should be studied prospectively in a national study, using validated questionnaires and comparing the results with similar studies from other cultures. After the initiation of this cross-sectional study a prospective national study of adverse effects in Norwegian PCa patients treated with curative treatment was initiated.

- As a consequence of the first experiences with the use of the NoPCR data, a new version of the PCa specific case record form was developed and put into use for patients diagnosed from 2009 and forward.

- Few studies are published which describe the typical adverse effects ten years or more after curative treatment. Though prospective studies including pre-treatment data are important, our well-described cohort of men is in our opinion too valuable to be left uninvestigated. We also recommend that survival analyses for 2004 patients are performed stratified for treatment modality and risk-group.

- In extension to the studies we did on CF, adverse effects and global QoL as single outcomes after curative treatment for PCa, we recommend that future research projects describe the total symptom burden reported by the individual and also identify men who are without any burden after their curative treatment for PCa. Such information would be more relevant for patient counseling purposes than the information on individual single adverse effects.

- As a last comment we had an enormous advantage of the access to the NorPD data as it was crucial for identification of treatment groups. The NorPD provided information on ADT use and on the use of medication for erectile dysfunction. The access to use NorPD data was unreasonably difficult and required written informed consent from the patients. In the future, access to these data should be made easier, especially those related to the outcome of cancer. In our view the level of sensitivity is the same as for other treatment already recorded in the CRN as for example orchiectomy, which does not require the individual patient’s consent.
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A national study of adverse effects and global quality of life among candidates for curative treatment for prostate cancer

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SUMMARY

OBJECTIVES

- To provide population-based estimates of “typical adverse effects” (AEs) such as urinary, bowel and sexual dysfunction in patients with non-metastatic recurrence-free prostate cancer (PCa) by curative treatment modality, including observation.
- To describe associations between typical AEs and global quality of life (QoL), to study patients’ use of medication for erectile dysfunction (EDmed) and the relation between such use and global QoL

PATIENTS AND METHODS

- In October 2006 a national population-based sample of PCa survivors diagnosed in 2004 was invited to a postal survey focusing on treatment-related AEs and global QoL 12-32 months after treatment start. All had completed their initial treatment.
- In the present study 771 compliers were categorized into four groups of localized or locally advanced PCa related to the treatment they completed: 1) No treatment, 2) Radical prostatectomy (RP), 3) Radiotherapy without hormones and 4) Radiotherapy with hormone therapy of 3-24 months duration.
- Measurement of AEs was restricted to function, using selected items from the EPIC-50 and the Brief Sexual Function Inventory (BSFI) among others, whereas global QoL was measured with SF-12.
- National prescription data enabled assessment of adjuvant hormone application and EDmed use.

RESULTS

- Prostatectomized men reported more urinary incontinence (24%) compared to the other treatment groups, but had the lowest level of moderate/severe urinary irritative-
obstructive symptoms. Men from the “No treatment” group had the highest level of moderate/severe irritative-obstructive urinary symptoms. Irradiated men reported higher levels of irritative intestinal symptoms and fecal leakage compared to RP and the group without treatment.

- In all treatment groups poor sexual drive and poor erectile function were common AEs; with men treated with RP reporting the highest prevalence of poor erectile function (89%).

- Presence of irritative-obstructive urinary symptoms and poor sexual drive were independently associated with low global QoL in multivariate analyses.

- Fifty percent of the study group had ever used EDmed after treatment start, but only 47% of them were still using EDmed at the time of the survey. Use of EDmed was not significantly associated with global QoL.

CONCLUSION

- PCa survivors after curative treatment, but also patients without any anti-cancer therapy, report high levels of urinary and sexual AEs.

- Irritative-obstructive urinary symptoms and poor sexual drive were significantly associated with low global QoL, whereas erectile function and use of EDmed were not.

Keywords: curative treatment, adverse effects, global quality of life, neuroticism, medication for erectile dysfunction
INTRODUCTION

Erectile, urinary and bowel dysfunction are “typical adverse effects” (AEs) after local treatment for prostate cancer (PCa) (radical prostatectomy [RP] and radiotherapy [RAD]) though the published estimates vary considerably [1-8]. Missing information about additional androgen deprivation therapy (ADT) and relapse make interpretation of these findings challenging. The prevalence of AEs depends on treatment modality, baseline characteristics, time elapsed since treatment and assessment methodology, which eventually should separate function from bother [9]. After RP, most AEs develop immediately after treatment with gradual improvement during the first year, whereas AEs after RAD develop more slowly. Maximum recovery is usually achieved during the first two post-treatment years [3]. Simultaneous use of adjuvant ADT decreases sexual function and leads to increasing fatigue [6]. Further, some of the symptoms described as treatment-related AEs may be experienced by PCa patients who never had treatment, such as erectile dysfunction (ED) and urinary urgency and frequency [10]. In Europe, reports on typical AEs are usually based on mono-institutional experience or multi-center studies, performed at high volume university-affiliated hospitals. Estimates published on AEs include patients with recurrence and additional treatment. It is debatable to what extent such studies can serve as basis for counseling regarding typical AEs in unselected patients.

Global quality of life (QoL) describes physical and mental health status as reported by the patient, separate from typical AEs. Though AEs are reported as bothersome to patients, they are not always associated with reduced global QoL when other factors such as co-morbidity and age are taken into account [11]. Further, results from cross-cultural studies indicate that cultural and national differences influence such associations [12,13]. In Norwegian PCa patients for example sexual function was not significantly associated with global QoL after radiotherapy [14] contrary to the findings in an American study [4]. More
information is therefore needed regarding the relationship between global QoL and typical AEs in patients in different cultures preferably derived from population-based studies.

Lastly, neuroticism is a personality trait which is closely linked to health perception [15] and should be accounted for in this context. Of the personality traits presented in the five-factor model of Costa and McCrae [16], neuroticism has proven to be robustly correlated to several mental and physical health outcomes [17]. An individual’s degree of neuroticism develops from early childhood and remains relatively stable after young adulthood. Elderly men facing the physical and mental health challenges from a PCa diagnosis do so with their established degree of neuroticism. In previous studies from our research group neuroticism has proven to be a relevant variable when assessing symptoms (e.g. sexual bother) and global QoL [18,19].

ED is one of the most frequently reported AEs after treatment for PCa. Treatment for ED is available such as the use of phosphodiesterase type 5 inhibitors (PDE5 inhibitors). In an American study about half of PCa patients treated for localized disease tried/received treatment for ED once or more during a five year follow-up period [20]. Differences in the use of PDE5 inhibitors may exist between different cultures [21], also related to reimbursement possibilities for these expensive drugs. In Norway, medication for ED (EDmed) has to be paid by the patients themselves. Use of PDE5 inhibitors have shown to improve functional and psychosocial aspects of sexual life and may therefore be important for global QoL [22]. Thus, the question is open as to what proportions of PCa patients in a population-based sample use these agents and whether EDmed use is related to global QoL.

With this background our population-based study of non-metastatic PCa patients who had completed their planned intervention (No treatment, RP, RAD without ADT or RAD with ADT) had two aims:
1) To estimate the prevalence of typical AEs and low global QoL in relation to treatment. Based on the available literature, we hypothesized following a period of median 23 months after local treatment that fewer RAD than RP patients without ADT would experience sexual and urinary AEs, but more of them would report bowel AEs. Further, we expected adjuvant ADT to increase the prevalence of ED, without significant impact on bowel or urinary AEs.

2) Independently of treatment group, to explore the association between typical AEs and low global QoL. In a sub-analysis we investigated the use of EDmed and the relation between such use and global QoL.

**PATIENTS AND METHODS**

**Data sources**

Based on the unique personal identification number assigned to each Norwegian citizen data were obtained by merging two population-based registries, the Norwegian Prescription Database (NorPD) and the Cancer Registry of Norway (CRN) with its radiotherapy and PCa registries. *Candidates for curative treatment* (CurCands) were identified among patients diagnosed with PCa in 2004 (T1–3 N0-XM0 category, PSA level ≤ 100 ng/mL, any Gleason score, age ≤ 75 years, ECOG performance status 0–1, no other cancer, no major pre-treatment co-morbidity reported on the registration form to the CRN in the optional field for comments [23].

**Treatment**

Information about RP and RAD was obtained from the CRN. The decision on whether or not to apply curative treatment depends upon the patient’s preference and the doctor’s evaluation
of the medical situation, with “no curative treatment” being one of the options. The pattern of care for men who were to receive curative treatment for PCa in Norway in 2004 is summarized as follows based on D’Amico risk groups [23,24]: **Low risk:** RP or RAD without hormones. **Intermediate risk:** RP or RAD with ADT of variable duration depending on patient preference, but not longer than 2 years. **High risk:** RAD with 2-3 years ADT duration.

In October 2006 a national cross-sectional survey of all Norwegian PCa survivors diagnosed during 2004 was conducted. Survivors were invited to complete a questionnaire concerning global QoL, AEs, lifestyle and psychosocial issues. The present study covers responding PCa patients whose eligibility criteria are depicted in Figure 1.

The following groups were defined based on the patient’s local treatment:

- **Group 1:** Patients who did not receive any form of anti-cancer treatment (NoTreat). For this group the date of diagnosis served as “treatment start”.

- **Group 2:** RP as monotherapy (RP). Except for the date of RP (“treatment start”) no information was available about the operative procedure.

- **Group 3:** Definitive radiation therapy without any additional treatment (RADNoHT).

- **Group 4:** Definitive radiation therapy combined with (neo-)adjuvant ADT, the last 3-month luteinizing hormone-releasing hormone (LHRH) depot injection applied at least 6 months before the survey (RADHT).

All irradiated patients received a target dose of $\geq 70$ Gy to the prostate. “Treatment start” was defined as the day of the first session of radiation.

**Measurements**

**Patient characteristics**

Patients were divided into risk categories using a slightly modified D’Amico risk assessment where T2x was categorized as T2a, and all T3 cancers were allocated to the high-risk group
Age was included as a continuous variable. Paired relationship was present if patients were married or cohabiting. Higher education was defined as > 12 years of education. Co-morbidity at the time of the survey implied the report of at least two of 18 co-morbid conditions listed in the questionnaire, such as myocardial infarction and diabetes.

AEs
The survey questionnaire was developed in 2005 and after discussion with experienced oncologists and urologists it was decided to use selected items from published questionnaires and supplementary study-specific ad hoc questions. For the current study only items concerning function were selected and AEs were dichotomized into clinically meaningful groups.

The International Prostate Symptom Score (IPSS) [25] measures irritative-obstructive urinary symptoms. The IPSS categories used were; none/mildly symptomatic (0-7), moderately symptomatic (8-19) and severely symptomatic (20-35) [26], with further dichotomization (0: no symptoms/mildly symptomatic and 1: moderately/severely symptomatic). Internal consistency for IPSS was 0.75.

Urinary incontinence (UI) was defined as “leaking urine at least once a day”, categorizing the degree of leakage into “dribbling” versus “more than just dribbling”.

Irritative intestinal symptoms, measured with selected questions from the EPIC-50 [27], were defined as experiencing one or more of the following problems; (1) defecation three times a day or more; (2) about half the time or more often diarrhea, blood or mucus in stool or painful defecation; (3) At least two times a week cramps or fecal urgency.

Presence of fecal leakage was defined if occurring at least once a week.

Sexual function was evaluated with the validated instrument Brief Sexual Function Inventory (BSFI) [28,29]. Only the drive and erection ratings from BSFI were used, ranging
from 0-8 and 0-12, respectively. Higher scores indicated better function. Sexual drive rated as ≤3 was defined as “caseness/poor” as was erectile function rated ≤7 [30]. The questionnaire did not specify if sexual function was reported with or without the use of EDmed. Internal consistencies for drive and erection were 0.85 and 0.94, respectively.

Global QoL was measured by the physical and mental component summary scores (PCS and MCS) of the SF-12 [31] validated in a Norwegian population [32]. Internal consistency was 0.77 for PCS and 0.77 for MCS. The scores of PCS and MCS were T-transformed with a mean score of 50 for the general population and a standard deviation (SD) of 10. Low global QoL was defined as PCS and/or MCS of 40 or below.

As symptom-reporting and physical complaints may be influenced by a person’s neuroticism, we also measured this personality trait. Neuroticism describes if a person generally feels anxious or safe. People with high neuroticism are likely to interpret even normal situations as problematic or threatening [15]. An abbreviated version of the Eysenck Personality Questionnaire (EPQ-18) measures neuroticism [33,34]. Six items comprise this personality trait (range 0-6) which ranges from feeling safe (score 0) to feeling quite nervous (score 6). Internal consistency for the EPQ-18 neuroticism was 0.73. Three categories were defined; low neuroticism: score 0-1, moderate neuroticism: score 2-3 and high neuroticism: score 4-6.

Prescribed EDmed (PDE5 inhibitors, Alprostadil urethral sticks and Papaverin injections) were identified using the NorPD database. Patients who had no records of prescription of EDmed between treatment and survey were defined as “never users”. Men with any EDmed prescription between treatment start and survey were defined as “ever users”, independent of the number and amount of prescribed medication. “Ever users” were further divided into those who reported use of EDmed during the last four weeks prior to
survey ("still users") and those who did not ("discontinued users"). All but eight men (96 %) who stated use of EDmed in the self-report questionnaire were identified in the NorPD data.

**STATISTICS**

The dataset was described with mean and SD for continuous, normally distributed variables and with median and range for variables with skewed distributions. Categorical variables were described with proportions and percentages. Crude associations between pairs of variables were assessed using t-tests, Mann-Whitney-Wilcoxon tests, Chi-square tests and One-way ANOVA. Adjusted associations between pairs of variables in different treatment groups were explored with logistic regression analyses. Internal consistencies of scales were given by Cronbach’s coefficient alpha. Factor analyses were not performed.

Univariate and multivariate associations between typical AEs and low global QoL were explored with logistic regression analyses. Due to limitations of statistical power it was not possible to include all AEs and significant confounders in one logistic regression model. A separate multivariate regression analysis was performed for each AE to investigate its association with low global QoL. Each sub-analysis was adjusted for age, education, co-morbidity and level of neuroticism. The associations between AEs and low global QoL were assumed to be similar for all treatment modalities, and therefore all treatment groups were combined in the regression analyses (treatment group was not included as a variable).

All tests were two-sided and the level of significance was set at p<0.01 due to multiple testing. The dataset was analyzed using PASW version 18 (IBM, Chicago, IL).

**ETHICS**

The study was approved by the Regional Ethics Committee of Southern Norway.
RESULTS

After one reminder 2193 (73%) of 2998 invited patients responded to the national survey. Of these, 771 patients were eligible for the present study (Figure 1). At the time of the survey the median age of the total sample was 66 years (range 45-75), and a median of 23 months (range 12-32) had elapsed since start of local treatment. RADHT patients had used ADT for a median of six months [range: 3-24 months] and had received their last 3-month LHRH depot injection a median of 21 months [range: 7-30 months] before the survey. NoTreat patients were significantly older and RP patients were significantly younger than the other treatment groups (Table 1). As expected, significantly more men with RADHT belonged to the high risk group (61%), compared to the other treatment groups. Of the whole study population 45% reported co-morbidity, with significantly lower prevalence in the RP group compared to NoTreat and RADNoHT, the latter two groups displaying the highest prevalence of co-morbidity (53%). Neuroticism was evenly distributed among the treatment groups.

AEs

Statistically significantly fewer RP patients reported moderate/severe irritative-obstructive urinary symptoms (23%) compared to NoTreat (50%) and RADNoHT (35%) when adjusted for age, risk-group and co-morbidity. Among RP patients 24% had UI, significantly higher than the other groups (Table 2A, Figure 2A).

Intestinal symptoms and fecal leakage were most common in irradiated patients; the estimates were significantly higher compared to the NoTreat and RP group (Table 2A, Figure 2B).

Poor sexual drive was common (>50%) in all treatment groups, with significantly lower prevalence (55%) in the NoTreat group. Poor erectile function was also frequently reported in all treatment groups (>75%). The highest proportion of poor erectile function was
observed among RP patients (89%), which was significantly higher than both the NoTreat group and the RADNoHT group (Table 2A, Figure 2C).

**Global QoL**

Compared to the other groups RP patients had the lowest proportion of men with PCS ≤ 40 (11%), the statistical difference disappeared after adjustment for age, risk-group and co-morbidity. The proportion of men with MCS ≤ 40 was similar in all treatment groups (11% for all groups combined). The prevalence of low global QoL was 18% in the RP group (Table 2B), with the RADNoHT group reaching a statistically significantly higher level (30%).

**Associations with global QoL**

All typical AEs (moderate/severe IPSS, UI, irritative intestinal symptoms, fecal leakage, poor sexual drive and poor erectile function) were significantly associated with low global QoL in univariate analyses (Table 3B). Low educational level, co-morbidity and moderate or high neuroticism were all statistically significantly associated with low global QoL in univariate analyses (Table 3A). No significant associations with global QoL were observed for age, paired relationship and D’Amico risk group. Age was considered an important confounder and was therefore adjusted for in the multivariate analyses.

In the multivariate analyses (Table 3B) the presence of moderate/severe irritative-obstructive urinary symptoms and poor sexual drive were each statistically significantly associated with increased risk of low global QoL. Urinary incontinence, intestinal symptoms, fecal leakage and poor erectile function did not reach statistical significance in the adjusted analyses. In all six logistic regression analyses, neuroticism was the variable with the highest point estimate of association with low global QoL (data not shown).
EDmed

Of 767 evaluable patients 385 (50%) had ever used EDmed, but only 24% were “still users”. “Never users” of EDmed were significantly older than the “discontinued” and “still user” groups and had a higher prevalence of co-morbidity compared to “still users” (Table 4). Poor sexual drive was significantly more prevalent among “never users” (71%), compared to “still users” (50%). The prevalence of poor erectile function was similar in men from the three EDmed groups. Between the three groups of EDmed users no significant differences emerged for low global QoL when co-morbidity and age were adjusted for.

Significantly more men in the RP group were “ever users” of EDmed compared to the NoTreat, RADNoHT and RADHT groups (Table 5). Men in the RP group were prescribed EDmed closer to treatment start compared to men in the other treatment groups.

DISCUSSION

Our population-based study documents that cure from PCa has its price, but that “no treatment” is also associated with symptoms similar to “typical AEs”. Two types of urinary AEs emerged with different patterns in the treatment groups. While the prevalence of UI was highest after RP (24%) irritative-obstructive symptoms were most often recorded by irradiated or NoTreat patients (35-50%). Intestinal AEs were more common after RAD compared to RP or NoTreat. More than half of the patients in all groups reported poor sexual drive, though it was significantly less often reported by NoTreat patients. Poor erectile function was reported by more than 75% of men in all treatment groups, most often after RP. Despite having typical AEs, the global QoL of men with discontinued curative treatment was good for 75%. In adjusted analyses irritative-obstructive urinary symptoms and poor sexual drive each approximately doubled the risk of low global QoL, whereas UI, intestinal symptoms and poor erectile function were not significantly associated with low global QoL.
EDmed was most often used by prostatectomized patients. Such use was not significantly associated with global QoL.

Our results should be interpreted on the background of the treatment policies valid in Norway around 2004. Firstly, today’s surveillance strategy was not implemented as a national recommendation. We suspect that high age and chronic pre-treatment co-morbidity allocated many men to our NoTreat group. Secondly, the RADNoHT group consisted mainly of patients with intraprostatic tumors whose co-morbidity probably did not allow a major surgical procedure, which would have been the treatment of choice in Norway at that time. These policies explain our high rates of post-treatment co-morbidity and high proportion of men with PCS≤40 in the NoTreat and RADNoHT groups. The high proportion of PCS≤40 (23%) in the RADHT group, not different from estimates in the NoTreat and RADNoHT groups, is likely due to ADT’s negative impact on physical health, persisting for several months after discontinuation of ADT.

The duration of adjuvant ADT is a matter of ongoing debate. As ADT often leads to physical and mental AEs, such treatment should be as short-lasting as possible without reduction of its beneficial effect on survival. In real-life planned long-lasting hormone treatment is often prematurely discontinued in a patient with severe ADT-related AEs, possibly explaining the varying duration of adjuvant ADT in our RADHT group.

This study adds to the growing evidence that irritative-obstructive urinary symptoms represent late AEs which impact on a PCa patient’s global QoL. Published studies have emphasized the impact of irritative-obstructive urinary symptoms on satisfaction with treatment outcome and global QoL [6,8]. In our study men in the NoTreat and RADNoHT groups were more likely to experience these AEs compared to prostatectomized men. Similar results were found in the prospective study by Pardo and colleagues where irritative-obstructive symptoms were reduced in about half of the patients three years after RP [8]. The
prevalence of moderate/severe irritative-obstructive urinary symptoms was highest in our NoTreat group, probably related to the growth of the prostate gland, though not significantly different from the RADNoHT group.

UI has been the main focus of many studies and, as expected, it was most common after RP, but only 10% of our prostatectomized patients described their UI as “more than just dribbling”. Prevalence of UI found in the Prostate Cancer Outcomes Study [4] after 24 months of follow-up was 4.7%, 3.3% and 21.5% for watchful waiting, RAD and RP respectively. Steineck et al [10] found that 18% of men randomized to RP and 2% of men randomized to watchful waiting reported a moderate to severe degree of urinary leakage after a mean follow-up of four years. Our high prevalence of UI in the NoTreat group (13%) and severe leakage (8%) must be viewed on the basis of this group’s heterogeneity.

In addition to irritative-obstructive urinary symptoms, poor sexual drive was significantly associated with a doubled risk of having low global QoL. Interestingly, and contrary to Penson et al’s study [4], the association between poor erectile function and low QoL did not reach our level of significance. This may be related to cultural differences in patients’ view concerning sexual functioning with increasing age. Response shift must also be considered as a possible explanation [35,36]. Response shift reflects the gradual acceptance of treatment-related AEs and change of expectations as to global QoL. Based on our results we speculate that response shift related to low global QoL develops less easily with regard to irritative-obstructive urinary symptoms and poor sexual drive. This is probably because these AEs are more disturbing and interfere with the general perception of health.

Age, education, co-morbidity and neuroticism were identified as confounding factors which moderated the observed association between AEs and low global QoL. Even though the confounding effect of neuroticism was moderate, level of neuroticism consequently had the strongest association with low global QoL (data not shown) which gives further strength
to its importance in QoL research. A person’s presence of a moderate or high level of neuroticism was more important for reporting low global QoL than erectile or intestinal dysfunction or UI. This result also implies that personality should be taken into account when informing patients about functional AEs, as nervous men might experience more symptoms concurrent with a low QoL, than less neurotic ones.

Even though treatment for ED is available only about half of our patients had used such medication after PCa treatment, most men in the RP group (84%) and fewest in the NoTreat group (19%). We cannot decide whether these differences primarily are due to varying patients’ demands or if they reflect prescription patterns differing between urologists and oncologists. Both explanations are most probably relevant. With today’s knowledge of the importance of early activation of nervous pathways responsible for erectile function [37] early and more frequent post-treatment management of ED is challenging, also after RAD. About half of “ever-users” report that they had not used EDmed within four weeks prior to the survey which may indicate that today’s EDmed is not effective for many of these patients. Of special interest, and admittedly based on small figures, is the fact that almost two thirds of patients from the RADNoHT group were “still users” as compared to less than half in the other groups. This may indicate that these drugs are particularly effective after RAD as monotherapy. While erectile function was similar in “ever-users” and “never-users”, poor sexual drive was significantly more prevalent in the latter group, probably reflecting their lack of motivation to try EDmed. Low global QoL was not significantly associated with EDmed use and the small proportion of “still users” with low QoL is explained by their younger age and fewer co-morbid conditions.

Several limitations concerning our cross-sectional study should be mentioned, such as the lack of pre-treatment data. Not recognized inter-group variability in pre-treatment dysfunctions and low global QoL could have introduced a systematic bias. Our choice to
select single domains from different instruments for the survey questionnaire instead of one complete validated questionnaire is today questionable. Our solution has to be viewed as a compromise between interests of oncologists and urologists for whom self-report of AEs was a new methodology in 2004. Further, there is uncertainty to whether or not the questions about ED have been answered disregarding the use of EDmed. Since 85% of “still users” report poor erectile function similarly to “never users” and “discontinued users”, the majority has probably reported their function in absence of sexual aids. We propose that future questionnaires should clearly separate the patient’s report on erectile function related to the use of EDmed.

The major strengths of our study are the population-based design and the comparison of three of today’s major treatment modalities in addition to a “no treatment” group. Further, the described typical AEs are those emerging after completion of planned initial treatment alone, without the use of adjuvant or salvage treatment. Finally, the reported prevalences of typical AEs and low global QoL are probably persistent ones, as several studies have shown that PCa related QoL stabilizes 6-12 months post treatment [4,38,39].

In conclusion, PCa survivors after curative treatment, but also patients without any therapy, report considerable rates of sexual, urinary and intestinal AEs. Irritative-obstructive urinary symptoms and poor sexual drive each approximately double the risk of low global QoL. Use of EDmed was most common among men in the RP group, and was not associated with global QoL.
ACKNOWLEDGEMENTS

This project has been financially supported by the Norwegian ExtraFoundation for Health and Rehabilitation through EXTRA funds. The study has used data from the Cancer Registry of Norway. The interpretation and reporting of these data are the sole responsibility of the authors, and no endorsement by the Cancer Registry of Norway is intended nor should be inferred.


FIGURES AND TABLES:

![Diagram]

**Figure 1:** Attrition analysis leading from all 2193 complying patients to the 771 eligible Candidates for Curative treatment (yellow fields). The gray fields cover patients who are ineligible due to medical or therapeutic reasons, whereas the red fields reflect study-related eligibility criteria.
Figure 2: Percentage of typical side effects per treatment group; A) Moderate/severe irritative-obstructive urinary symptoms and urinary incontinence. B) Intestinal symptoms and fecal leakage. C) Poor sexual drive and poor erectile function.
Table 1: Descriptives: Demographics and diagnostics (A) and physical and psychosocial condition at survey (B)

<table>
<thead>
<tr>
<th>A) Demographics and diagnostics</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>Group 4</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>NoTreat</td>
<td>N=180</td>
<td>N=293</td>
<td>N=156</td>
<td>N=142</td>
<td>N=771</td>
</tr>
<tr>
<td>RP</td>
<td>N=266</td>
<td>N=136</td>
<td>N=100</td>
<td>N=67</td>
<td>N=463</td>
</tr>
<tr>
<td>RADNoHT</td>
<td>N=136</td>
<td>N=74</td>
<td>N=36</td>
<td>N=27</td>
<td>N=207</td>
</tr>
<tr>
<td>RADHT</td>
<td>N=130</td>
<td>N=85</td>
<td>N=25</td>
<td>N=16</td>
<td>N=111</td>
</tr>
<tr>
<td>Total</td>
<td>685</td>
<td>70</td>
<td>685</td>
<td>70</td>
<td>771</td>
</tr>
</tbody>
</table>

| Paired relation, N (%)         | 153 (87)  | 266 (92)  | 136 (90)  | 130 (94)  | 685 (91)   |
| Higher education               | 84 (47)   | 186 (64)  | 74 (47)   | 78 (55)   | 422 (55)   |
| Risk group, N (%)*             | 92 (51)   | 157 (54)  | 64 (41)   | 15 (11)   | 328 (43)   |
| Low risk                       | 106 (61)  | 178 (63)  | 80 (54)   | 74 (54)   | 437 (59)   |
| Intermediate risk              | 46 (26)   | 100 (34)  | 67 (43)   | 40 (28)   | 253 (33)   |
| High risk                      | 41 (23)   | 36 (12)   | 25 (16)   | 87 (61)   | 189 (25)   |

| B) Physical and psychosocial condition at survey |
| Co-morbidity, N (%)*               | 84 (47)^2 | 186 (64)^1,3 | 74 (47)^2 | 78 (55) | 422 (55) |
| Yes                              | 96 (53)   | 107 (37)   | 82 (53)   | 64 (45) | 349 (45) |

| Neuroticism, N (%)               | 105 (61)  | 178 (63)  | 80 (54)   | 74 (54) | 437 (59) |
| Low                              | 46 (27)   | 71 (25)   | 42 (28)   | 48 (35) | 207 (28) |
| Moderate                         | 20 (12)   | 35 (12)   | 27 (18)   | 16 (12) | 98 (13) |

*At least one significant difference at p<0.01.
1, 2, 3, 4: indication of groups whose results differ significantly from the actual group.
Table 2: Prevalence of adverse effects (A) and Global Quality of Life outcomes (B) stratified per treatment group

A) Adverse effects

<table>
<thead>
<tr>
<th>Urinary</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>Group 4</th>
<th>Total N=771</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NoTreat</td>
<td>RP</td>
<td>RADNoHT</td>
<td>RADHT</td>
<td></td>
</tr>
<tr>
<td>N=180</td>
<td>N=293</td>
<td>N=156</td>
<td>N=142</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Irritative-obstructive, N (%)*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None/Mild sympt.</td>
<td>88 (50)</td>
<td>225 (77)</td>
<td>87 (56)</td>
<td>93 (66)</td>
<td>493 (65)</td>
</tr>
<tr>
<td>Moderate/severe sympt.</td>
<td>87 (50)</td>
<td>67 (23)</td>
<td>68 (44)</td>
<td>49 (35)</td>
<td>271 (36)</td>
</tr>
<tr>
<td>Incontinence, N (%)*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>157 (87)</td>
<td>223 (76)</td>
<td>140 (90)</td>
<td>134 (94)</td>
<td>654 (85)</td>
</tr>
<tr>
<td>Yes</td>
<td>23 (13)</td>
<td>70 (24)</td>
<td>16 (10)</td>
<td>8 (6)</td>
<td>117 (15)</td>
</tr>
<tr>
<td>Drops</td>
<td>9 (5)</td>
<td>40 (14)</td>
<td>13 (8)</td>
<td>2 (1)</td>
<td>64 (8)</td>
</tr>
<tr>
<td>More than drops</td>
<td>14 (8)</td>
<td>30 (10)</td>
<td>3 (2)</td>
<td>6 (4)</td>
<td>53 (7)</td>
</tr>
<tr>
<td>Intestinal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Irritative symptoms, N (%)*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>140 (79)</td>
<td>233 (80)</td>
<td>83 (53)</td>
<td>82 (58)</td>
<td>538 (70)</td>
</tr>
<tr>
<td>Yes</td>
<td>38 (21)</td>
<td>59 (20)</td>
<td>73 (47)</td>
<td>60 (42)</td>
<td>230 (30)</td>
</tr>
<tr>
<td>Fecal leakage, N (%)*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>172 (97)</td>
<td>283 (97)</td>
<td>133 (86)</td>
<td>120 (86)</td>
<td>708 (93)</td>
</tr>
<tr>
<td>Yes</td>
<td>5 (3)</td>
<td>8 (3)</td>
<td>21 (14)</td>
<td>19 (14)</td>
<td>53 (7)</td>
</tr>
<tr>
<td>Sexual</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal sexual drive, N (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N=763</td>
<td>78 (45)</td>
<td>113 (39)</td>
<td>45 (29)</td>
<td>44 (31)</td>
<td>280 (36)</td>
</tr>
<tr>
<td>Poor sexual drive</td>
<td>97 (55)</td>
<td>180 (61)</td>
<td>109 (71)</td>
<td>97 (69)</td>
<td>483 (63)</td>
</tr>
<tr>
<td>Erectile function (N=753)*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal erectile funct. N (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N=753</td>
<td>41 (24)</td>
<td>33 (11)</td>
<td>25 (17)</td>
<td>23 (17)</td>
<td>122 (16)</td>
</tr>
<tr>
<td>Poor erectile function</td>
<td>131 (76)</td>
<td>258 (89)</td>
<td>126 (83)</td>
<td>116 (84)</td>
<td>631 (84)</td>
</tr>
<tr>
<td>(B) Global QoL outcomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCS ≤ 40, N (%)</td>
<td>37 (21)</td>
<td>32 (11)</td>
<td>33 (21)</td>
<td>32 (23)</td>
<td>134 (17)</td>
</tr>
<tr>
<td>MCS ≤ 40, N (%)</td>
<td>19 (11)</td>
<td>33 (11)</td>
<td>22 (14)</td>
<td>8 (6)</td>
<td>82 (11)</td>
</tr>
<tr>
<td>Low global QoL, N (%)*</td>
<td>49 (27)</td>
<td>54 (18)</td>
<td>47 (30)</td>
<td>34 (24)</td>
<td>184 (24)</td>
</tr>
</tbody>
</table>

*At least one significant difference at p<0.01 when adjusted for age, risk-group and comorbidity.

1, 2, 3, 4: indication of groups whose results differ significantly from the actual group
Table 3: Univariate associations between possible confounders and low global QoL (A) and univariate and multivariate logistic regression analyses for each AE, with low global QoL as dependent variable (B).

### A) Univariate

<table>
<thead>
<tr>
<th></th>
<th>OR (95% CI OR)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (continuous)</td>
<td>1.02 (0.99-1.05)</td>
<td>.196</td>
</tr>
<tr>
<td>Paired relation (yes=ref)</td>
<td>1.88 (1.12-3.17)</td>
<td>.017</td>
</tr>
<tr>
<td>Education (high=ref)</td>
<td>1.66 (1.16-2.36)</td>
<td>.006</td>
</tr>
<tr>
<td>Risk group (D'Amico) (low risk=ref)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermediate risk</td>
<td>0.97 (0.65-1.44)</td>
<td>.860</td>
</tr>
<tr>
<td>High risk</td>
<td>1.57 (1.05-2.36)</td>
<td>.028</td>
</tr>
<tr>
<td>Co morbidity (no=ref)</td>
<td>3.02 (2.14-4.28)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Neuroticism (low=ref)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>3.47 (2.27-5.29)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>High</td>
<td>15.26 (9.14-25.47)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

### B) Univariate and Adjusted*

<table>
<thead>
<tr>
<th></th>
<th>Univariate</th>
<th>Adjusted*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI OR)</td>
<td>p-value</td>
</tr>
<tr>
<td>Moderate/severe irritative-obstructive urinary symptoms (no/mild = ref)</td>
<td>3.02 (2.14-4.26)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Urinary incontinence (no=ref)</td>
<td>2.32 (1.53-3.51)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Intestinal symptoms (no=ref)</td>
<td>2.23 (1.58-3.14)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fecal leakage (no=ref)</td>
<td>2.93 (1.66-5.18)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Poor sexual drive (normal=ref)</td>
<td>2.60 (1.76-3.84)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Poor erectile function (normal=ref)</td>
<td>3.02 (1.65-5.51)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Adjusted for age, education, co-morbidity and level of neuroticism
Table 4: Comparison of men not using medication for erectile dysfunction (EDmed) with those who had used, but discontinued EDmed between start of local treatment and survey** and those still using EDmed at survey

<table>
<thead>
<tr>
<th></th>
<th>N=382</th>
<th>“Ever users” N=385</th>
<th>“Never users” N=382</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, median [range]</strong></td>
<td>68 [50-75]</td>
<td>63 [45-75]</td>
<td>63 [48-75]</td>
</tr>
<tr>
<td><strong>Co-morbidity, N (%)</strong></td>
<td>197 (52)</td>
<td>87 (43)</td>
<td>64 (35)</td>
</tr>
<tr>
<td><strong>Poor sexual drive</strong></td>
<td>266 (71)</td>
<td>124 (62)</td>
<td>92 (50)</td>
</tr>
<tr>
<td><strong>Poor erectile function</strong></td>
<td>306 (83)</td>
<td>167 (84)</td>
<td>155 (85)</td>
</tr>
<tr>
<td><strong>Low QoL, N (%)</strong></td>
<td>102 (27)</td>
<td>51 (25)</td>
<td>31 (17)</td>
</tr>
</tbody>
</table>

*At least one significant difference at p<0.01.
1, 2, 3: indication of groups whose results differ significantly from the actual group.
** The NoTreatment group is calculated from the time of diagnosis as a substitute for start of local treatment.
‡adjusted for age and co-morbidity
Table 5: Post-treatment use of Medication for Erectile Dysfunction (EDmed) in 771 evaluable men**

<table>
<thead>
<tr>
<th>Group</th>
<th>N=180</th>
<th>N=293</th>
<th>N=156</th>
<th>N=142</th>
<th>N=771</th>
</tr>
</thead>
<tbody>
<tr>
<td>NoTreat</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ever users, N (%)*</td>
<td>35 (19)</td>
<td>246 (84)</td>
<td>57 (37)</td>
<td>51 (36)</td>
<td>389 (51)</td>
</tr>
<tr>
<td>Discontinued users*†, N (%)</td>
<td>19 (54)</td>
<td>129 (53)</td>
<td>20 (35)</td>
<td>33 (66)</td>
<td>201 (52)</td>
</tr>
<tr>
<td>Still users†, N (%)</td>
<td>14 (40)</td>
<td>116 (48)</td>
<td>37 (65)</td>
<td>17 (34)</td>
<td>184 (47)</td>
</tr>
</tbody>
</table>

Months to first prescription after treatment start, median [range]

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>Group 4</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NoTreat</td>
<td>RP</td>
<td>RADNoHT</td>
<td>RADHT</td>
<td></td>
</tr>
<tr>
<td>Ever users, N (%)*</td>
<td>6 [0-29]</td>
<td>2 [0-19]</td>
<td>7 [0-19]</td>
<td>9 [0-24]</td>
<td>3 [0-29]</td>
</tr>
</tbody>
</table>

*At least one significant difference at p<0.01, adjusted for age and co-morbidity.
1, 2, 3, 4: indication of groups whose results differ significantly from the actual group
** Calculated from date of start of local treatment (Group 2-4) or date of diagnosis (Group 1)
†Proportion of ever users. Percentages do not summarize to 100 because of missing categorization of patients.
Appendix A:

Case record form for prostate cancer. This form was in use at the Cancer Registry of Norway for patients diagnosed from January 2004 to October 2008.
## INSTITUSJON (sykehus/avdeling/legepraksis)

### ÅRSAK TIL UTREDNING

<table>
<thead>
<tr>
<th>Årsak</th>
<th>Valgt</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. PSA initiert av</td>
<td>lege, pasient, ukjent</td>
</tr>
<tr>
<td>2. Palpasjonsfunn (rektal eksplorasjon)</td>
<td></td>
</tr>
<tr>
<td>3. Urineissymptomer</td>
<td></td>
</tr>
<tr>
<td>4. Metastasemistanke</td>
<td></td>
</tr>
<tr>
<td>5. Tilfeldig funn v/ TUR-P</td>
<td></td>
</tr>
<tr>
<td>6. Andre årsaker</td>
<td>sjefsunderskrift</td>
</tr>
</tbody>
</table>

### DATO FOR HENVISNING TIL SPEISIALISTHELSETJENESTEN

<table>
<thead>
<tr>
<th>Gleason score</th>
<th>Morfologisk basis</th>
<th>biopsi</th>
<th>TUR-P</th>
<th>metastase</th>
<th>andre</th>
</tr>
</thead>
</table>

### DIAGNOSEGRUNNLAG

<table>
<thead>
<tr>
<th>PSA ved diagnosetidspunkt</th>
<th>Skjellettscintigrafi</th>
<th>positivt funn</th>
<th>negativt funn</th>
<th>ikke utført</th>
<th>hvilken</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultryd prostata</td>
<td>annen bildediagnostikk</td>
<td>utført</td>
<td>ikke utført</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymfadenektomi</td>
<td>pN</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### PLANLAGTE TILTAK

<table>
<thead>
<tr>
<th>Pasienten observeres</th>
<th>alder</th>
<th>dårlig almenntilstand</th>
<th>pasienten ønsker ikke behandling</th>
<th>ikke medisinsk indikasjon</th>
<th>andre</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Pasienten får</th>
<th>behandling/ behandling planlagt</th>
<th>(meldes på ordinært meldeskjema)</th>
</tr>
</thead>
</table>

### STUDIEINKLUSJON

<table>
<thead>
<tr>
<th>Er pasienten inkludert i studie</th>
<th>Ja</th>
<th>Nei</th>
<th>hvilken</th>
</tr>
</thead>
</table>

### TILLEGGSOPPLYSNINGER

<table>
<thead>
<tr>
<th>Dag</th>
<th>Mnd</th>
<th>År</th>
<th>Pasientansvarlig lege (Etternavn, fornavn - trykte bokstaver)</th>
<th>Legens underskrift</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Id. nummer</td>
<td>Id. nummer</td>
</tr>
</tbody>
</table>
VEILEDNING TIL UTFYLLING AV SKJEMAET
MERK AT DETTE ER ET TILLEGGSKSKJEMA TIL ORDINÆRT MELDESKJEMA TIL KREFTREGISTERET. BEGGE SKJEMAER MÅ FYLLES UT.

Årsak til utredning: Under dette punktet oppgir man de viktigste årsakene til at pasienten ble utredet med hensyn på prostatacancer. Det kan krysses av på flere punkter hvis dette er nødvendig.


Diagnosegrunnlag: De diagnostiske prosedyrer som danner grunnlaget for diagnosen prostatacancer. Usikkert funn etter skjelletscintigrafi skal oppgis som negativt funn og eventuelt kommenteres i feltet "tilleggsopplysninger" nederst på meldeskjemaet.

Planlagte tiltak: Utført og planlagt primærbehandling rapporteres også på ordinært meldeskjema.


T | Primaer tumor
---|---
TX | Primærtumor kan ikke vurderes.
T0 | Primærtumor ikke påvist.
T1 | Klinisk ikke erkjennbar tumor, ikke palpabel eller påvisbar ved bildediagnostikk.
T1a | Tumor, tilfeldig funn i 5% eller mindre av resesert vev.
T1b | Tumor, tilfeldig funn i mer enn 5% av resesert vev.
T1c | Tumor påvist ved nålebiopsi (f.eks. på grunn av forhøyet PSA).
T2 | Tumor begrenset til prostata.
T2a | Tumor omfatter en halv lapp eller mindre.
T2b | Tumor omfatter mer enn halvparten av en lapp, men ikke begge lapper.
T2c | Tumor omfatter begge lapper.
T3 | Tumor vokser gjennom prostatakapselen.
T3a | Ekstrakapsulær vekst (unilateral eller bilateral).
T3b | Tumor vokser inn i sædblære(r).
T4 | Tumor er fiksert eller vokser inn i nabostruktur(er) annet enn sædblære(r): blærehals, musculus sphincter externus, rectum,levator-musculatur og/eller er fiksert til bekkenveggen.

N | Regionale lymfeknuter: Lymfeknuter i det lille bekken (mellom bifurkaturen av arteria iliaca communis og lyskebåndet). Lateralitet påvirker ikke N-klassifikasjonen.
NX | Spredning til regionale lymfeknuter kan ikke vurderes.
N0 | Ingen regionale lymfeknutemetasastaser.
N1 | Regional(e) lymfeknutemetasastase(r).

M | Fjernmetastaser (fjerne lymfeknutemetasastaser og organmetastaser)
MX | Fjernmetastasering kan ikke vurderes.
M0 | Ingen fjernmetastaser.
M1 | Fjernmetastase(r).
M1a | Metastase(r) til fjern(e) lymfeknute(r).
M1b | Metastase(r) til skjelett.
M1c | Annen/andre fjernmetastase(r), med eller uten skjelettmetastaser.

Veiledningen er à jour pr. 01.01.2004. Se eventuelle oppdateringer på Kreftregisterets hjemmeside: www.kreftregisteret.no. Kreftmeldingen er hjemlet i Kreftregisterforskriften, i kraft fra 01.01.2002.
Appendix B:

National population-based survey in Norwegian
Etter at du fikk prostatakreft - hvordan går det med deg?


Dine svar blir behandlet fortrolig, og de vil bare bli brukt til forskning. Svarene blir bearbeidet sammen med alle de andre svarene, slik at enkeltpersoner ikke kan gjenkjennes i undersøkelsen.


1. Bruk bare blå eller sort kulepenn (ikke blyant)
2. Sett bare ett kryss for hvert spørsmål, hvis ikke annet er oppgitt
3. Sett kryss innenfor rutene: X
4. Skriv tallene slik: 1 2 3 4 5 6 7 8 9 0
5. Skjemaet må ikke brettes
Hvordan er helsen din?


1. Stort sett, vil du si at din helse er:
   Utmerket .................................. 
   Meget god ..................................
   God ........................................
   Nokså god .................................
   Dårlig ......................................

2. De to neste spørsmålene handler om aktiviteter som du kanskje utfører i løpet av en vanlig dag. Er din helse slik at den begrenser deg i utførelsen av disse aktivitetene nå?
   Moderate aktiviteter som å flytte et bord, støvsuge, gå en tur eller drive med hagearbeid..................... Ja, begrenser meg mye  
   Gå opp trappen flere etasjer.......................... Ja, begrenser meg litt  
   Nei, begrenser meg ikke i det hele tatt

3. I løpet av de siste 4 ukene, har du hatt noen av følgende problemer i ditt arbeid eller i andre av dine daglige gjøremål på grunn av din fysiske helse?
   Du har utrettet mindre enn du ønsket.............................. Ja  
   Nei
   Du har vært hindret i å utføre visse typer arbeid eller gjøremål.............................. Nei

4. I løpet av de siste 4 ukene, har du hatt noen av følgende problemer i ditt arbeid eller i andre av dine daglige gjøremål på grunn av følelsesmessige problemer (som for eksempel å være deprimert eller engstelig)?
   Du har utrettet mindre enn du ønsket.............................. Nei
   Du har utført arbeidet eller andre gjøremål mindre grundig enn vanlig............ Nei

5. Hvor sterke kropplige smørrer har du hatt i løpet av de siste 4 ukene?
   Ingen........................................
   Meget svake................................
   Svake....................................
   Moderate................................
   Sterke ................................... 
   Meget sterke.............................

T 2 T
6. I løpet av de siste 4 ukene, hvor mye har smerter påvirket ditt vanlige arbeid? (gjelder både arbeid utenfor hjemmet og arbeid i hjemmet)

 Ikke i det hele tatt.........................
 Litt...........................................
 En del........................................
 Mye............................................
 Svært mye...................................

7. De tre neste spørsmålene handler om hvordan du har følt deg og hvordan du har hatt det de siste 4 ukene. For hvert spørsmål, vennligst velg det svaralternativet som best beskriver hvordan du har hatt det. Hvor ofte i løpet av de siste 4 ukene har du:

<table>
<thead>
<tr>
<th>Følt deg rolig og harmonisk?</th>
<th>Hele tiden</th>
<th>Nesten hele tiden</th>
<th>Mye av tiden</th>
<th>En del av tiden</th>
<th>Litt av tiden</th>
<th>Ikke i det hele tatt</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hatt mye overskudd?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Følt deg nedfor og trist?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
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</tr>
</tbody>
</table>

8. I løpet av de siste 4 ukene, hvor mye av tiden har din fysiske helse eller følelsesmessige problemer påvirket din sosiale omgang (som det å besøke venner, slektninger osv.)?

<table>
<thead>
<tr>
<th>Hele tiden</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Nesten hele tiden</td>
<td></td>
</tr>
<tr>
<td>En del av tiden</td>
<td></td>
</tr>
<tr>
<td>Litt av tiden</td>
<td></td>
</tr>
<tr>
<td>Ikke i det hele tatt</td>
<td></td>
</tr>
</tbody>
</table>

9. Har du hatt vektforandringer siden du fikk prostatakreft?

- [ ] Nei, ingen forandringer
- [ ] Ja, gått opp i vekt
- [ ] Ja, gått ned i vekt

Hva er din høyde? 

[ ] [ ] [ ] cm

Hva er din vekt i dag? 

[ ] [ ] [ ] kg

Hva var din vekt i 2004 da du fikk påvist prostatakreft? 

[ ] [ ] [ ] kg
**Hvordan er vannlatingen din?**

Det er bare situasjonen de siste 4 ukene du skal ta i betraktning.

10. Hvor ofte har du:

<table>
<thead>
<tr>
<th></th>
<th>Aldri</th>
<th>1 av 5 ganger</th>
<th>1 av 3 ganger</th>
<th>Annenhver gang</th>
<th>2 av 3 ganger</th>
<th>Nesten altid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Følelsen av at blæren ikke er blitt fullstendig tømt etter avsluttet vannlating?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Måttet late vannet på nytt mindre enn 2 timer etter forrige vannlating?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Måttet stoppe og starte flere ganger under vannlatingen?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hatt vansker med å holde igjen når du har følt trang til å late vannet?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hatt svak urinstråle?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Måttet trykke eller presse for å begynne vannlatingen?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Ingen</td>
<td></td>
</tr>
<tr>
<td>1 gang</td>
<td></td>
</tr>
<tr>
<td>2 ganger</td>
<td></td>
</tr>
<tr>
<td>3 ganger</td>
<td></td>
</tr>
<tr>
<td>4 ganger eller mer</td>
<td></td>
</tr>
</tbody>
</table>

Hvis du må opp om natten for å late vannet, hvordan opplever du det?

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Ikke noe problem</td>
<td></td>
</tr>
<tr>
<td>Litt plaget</td>
<td></td>
</tr>
<tr>
<td>Mye plaget</td>
<td></td>
</tr>
<tr>
<td>Svært stort problem</td>
<td></td>
</tr>
</tbody>
</table>

12. Har du urinlekkasje?  □ Ja □ Nei Hvis ”Nei”, gå videre til nummer 13

Hvor ofte har du urinlekkasje?

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Mer enn én gang per dag</td>
<td></td>
</tr>
<tr>
<td>Omtrent én gang per dag</td>
<td></td>
</tr>
<tr>
<td>Mer enn én gang i uken</td>
<td></td>
</tr>
<tr>
<td>Omtrent én gang i uken</td>
<td></td>
</tr>
<tr>
<td>Sjeldnere</td>
<td></td>
</tr>
</tbody>
</table>

Hvor mye urin lekker du vanligvis hver gang?

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Dråper</td>
<td></td>
</tr>
<tr>
<td>Små skvetter</td>
<td></td>
</tr>
<tr>
<td>Større mengder</td>
<td></td>
</tr>
</tbody>
</table>
Hvor mange truseinnlegg eller bleier bruker du per dag for å kontrollere urinlekkasje?

Ingen ........................................... ☐
1 per dag ................................... ☐
2 per dag ................................... ☐
3 eller flere per dag ....................... ☐

I hvilke situasjoner har du lekkasje av urin? (ett eller flere kryss)

Ingen bestemte ................................... ☐
Hosting, nysing, latter ....................... ☐
Tunge løft ..................................... ☐
Reise deg fra sittende til stående ....... ☐
Gange på flat mark ............................ ☐
Andre situasjoner .................................. Hvilke?

Hvordan opplever du urinlekkasjen din?

Ikke noe problem ................................... ☐
Litt plaget ....................................... ☐
En del plaget .................................... ☐
Mye plaget ....................................... ☐
Svært stort problem ............................. ☐

13. Har du behov for hjelpemidler for å late vannet? (ett eller flere kryss)

Nei .................................................. ☐
Ja, kateter gjennom urinrøret av og til ☐
Ja, kateter gjennom urinrøret hele tiden ☐
Ja, pose med slange inn i flanken .......... ☐
Ja, annet hjelpemiddel ....................... ☐ Hvilket?

14. Hvis du resten av livet måtte leve med de vannlatingsproblemene du har nå, hvordan ville du føle det?

Ikke relevant: har ikke vannlatingsproblemer ☐
Være meget godt fornøyd .................................. ☐
Være fornøyd ........................................... ☐
Være for det meste fornøyd ....................... ☐
Ha blandete følelser ................................... ☐
Være for det meste misfornøyd .................... ☐
Være misfornøyd ...................................... ☐
Ha det forferdelig .................................... ☐

Hvordan er tarmfunksjonen din?
Det er bare situasjonen de siste 4 ukene du skal ta i betraktning.

15. Hvor mange ganger har du avføring på en vanlig dag?

2 eller færre ..................................... ☐
3 til 4 ............................................ ☐
5 eller flere .................................... ☐
16. Hvor ofte har du:

- Tynn avføring eller diarré? □ Aldri □ Sjelden □ Omtrent annenhver gang □ Vanligvis □ Alltid
- Blod i avføringen? □ Aldri □ Sjelden □ 1 gang i uken □ 2-3 ganger i uken □ Omtrent daglig □ Flere ganger daglig
- Slim i avføringen? □ Aldri □ Sjelden □ □ □ □ □ □
- Smerter ved avføring? □ Aldri □ Sjelden □ 1 gang i uken □ 2-3 ganger i uken □ Omtrent daglig □ Flere ganger daglig

Krampeligende smerter i magen, underlivet eller endetarmen? □ Aldri □ Sjelden □ 1 gang i uken □ 2-3 ganger i uken □ Omtrent daglig □ Flere ganger daglig

Plutselig kraftig avføringstrang (følt at du skulle ha avføring uten at det kom noe)? □ Aldri □ Sjelden □ 1 gang i uken □ 2-3 ganger i uken □ Omtrent daglig □ Flere ganger daglig

17. Har du lekkasje av avføring? □ Ja □ Nei Hvis "Nei", gå videre til nummer 18

Hvor ofte har du lekkasje av avføring?
- Flere ganger daglig □
- Omtrent daglig □
- 2-3 ganger i uken □
- 1 gang i uken □
- Sjeldnere □

I hvilke situasjoner har du hatt lekkasje av avføring? (ett eller flere kryss)
- Ingen bestemte □
- Hosting, nysing, latter □
- Tunge løft □
- Reise seg fra sittende til stående □
- Ved luftavgang □
- Andre situasjoner □ Hvilke?

18. Hvis du resten av livet måtte leve med de avføringsproblemen du har nå, hvordan ville du føle det?

- Ikke relevant: har ikke avføringsproblemer □
- Være meget godt fornøyd □
- Være fornøyd □
- Være for det meste fornøyd □
- Ha blandete følelser □
- Være for det meste misfornøyd □
- Være misfornøyd □
- Ha det forferdelig □
Hormoneffekter

Vi ber deg svare på spørsmålene uansett om du får hormonbehandling eller ikke (spørsmål om behandling kommer senere). Det er bare situasjonen de siste 4 ukene du skal ta i betraktning.

19. Har du hetetokter?
   Ikke i det hele tatt.................. ☐
   Litt............................................. ☐
   En del.......................................... ☐
   Svært mye...................................... ☐

   Hvis du har hetetokter, opplever du dette som et problem?
   Ikke noe problem ☐
   Ganske lite problem ☐
   Lite problem ☐
   Middels problem ☐
   Stort problem ☐

20. Har du fått forstørrede bryst?
   Ikke i det hele tatt.................... ☐
   Litt............................................... ☐
   En del............................................ ☐
   Svært mye.................................... ☐

   Hvis du har fått forstørrede bryst, opplever du dette som et problem?
   Ikke noe problem ☐
   Ganske lite problem ☐
   Lite problem ☐
   Middels problem ☐
   Stort problem ☐

21. Har du fått ømme bryst?
   Ikke i det hele tatt.................... ☐
   Litt............................................... ☐
   En del............................................ ☐
   Svært mye.................................... ☐

   Hvis du har fått ømme bryst, opplever du dette som et problem?
   Ikke noe problem ☐
   Ganske lite problem ☐
   Lite problem ☐
   Middels problem ☐
   Stort problem ☐
**Trettet**

De neste 12 spørsmålene handler om du har følt deg sliten, svak eller i mangel av overskudd de siste 4 ukene. Vi ber om at du besvarer spørsmålene selv om du ikke har hatt slike problemer.

22. Vi spør om hvordan du har følt deg i det siste, og ikke hvordan du følte deg for lenge siden. Hvis du har følt deg sliten lenge bør vi deg om at du sammenligner deg med hvordan du følte deg sist du var bra:

<table>
<thead>
<tr>
<th>Spørsmål</th>
<th>Mindre enn vanlig</th>
<th>Ikke mer enn vanlig</th>
<th>Mer enn vanlig</th>
<th>Mye mer enn vanlig</th>
</tr>
</thead>
<tbody>
<tr>
<td>Har du problemer med at du føler deg sliten?.....</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trenger du mer hvile?....................................</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Føler du deg søvnig eller døsig?..........................</td>
<td></td>
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<tr>
<td>Har du problemer med å komme i gang med ting?</td>
<td></td>
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</tr>
<tr>
<td>Mangler du overskudd?.....................................</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Har du redusert styrke i musklene dine?.......</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Føler du deg svak?........................................</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Har du vansker med å konsentrere deg? .....................</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Forsnakker du deg i samtaler?.......................</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Er det vanskeligere å finne det rette ordet?.............</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hvordan er hukommelsen din?...............................</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

**Hvis du føler deg sliten for tiden, omtrent hvor lenge har det vart?**

- Mindre enn 1 uke .................. □
- Mindre enn 3 måneder .......... □
- Mellom 3 og 6 måneder ........ □
- 6 måneder eller mer............. □
Hvordan er seksualiteten din?

La oss definere seksualdrift som en følelse som kan omfatte ønske om seksuell aktivitet (onani eller samleie), tanken på å ha sex eller frustrasjon som følge av mangel på sex.

23. Seksualdrift:

Hvor mange dager har du følt seksualdrift de siste 4 ukene?

- Ingen dager ............................................
- Bare noen få dager ......................................
- Noen dager ................................................
- De fleste dagene ........................................
- Nesten hver dag ..........................................

Hvordan vurderer du nivået på seksualdriften din de siste 4 ukene?

- Ingen drift ..............................................
- Lav drift ................................................
- Middels drift ...........................................
- Middels sterk drift ......................................
- Sterk drift ...............................................  

24. Reisning:

Hvis du er blitt seksuelt stimulert på noen måte de siste 4 ukene; hvor ofte har du hatt delvis eller full reisning?

- Aldri ......................................................
- Noen få ganger .........................................
- Ganske ofte ...............................................
- Vanligvis ...................................................
- Alltid .....................................................

Hvis du har hatt reisning de siste 4 ukene; hvor ofte var penis stiv nok til at du kunne ha samleie?

- Aldri ......................................................
- Noen få ganger .........................................
- Ganske ofte ...............................................
- Vanligvis ...................................................
- Alltid .....................................................

Hvor store vansker har du hatt med å få reisning de siste 4 ukene?

- Har ikke fått reisning .............................
- Store vansker ..........................................  
- Noen vansker .........................................
- Få vansker .............................................
- Ingen vansker ........................................
25. Sæduttømming:

Hvor store vansker har du hatt med å få sæduttømming når du er blitt seksuelt stimulert de siste 4 ukene?

<table>
<thead>
<tr>
<th>Vanse</th>
<th>□</th>
</tr>
</thead>
<tbody>
<tr>
<td>Har ikke hatt</td>
<td></td>
</tr>
<tr>
<td>Seksuell stimulering de siste 4 ukene</td>
<td></td>
</tr>
<tr>
<td>Store vansker</td>
<td></td>
</tr>
<tr>
<td>Ingen vansker</td>
<td></td>
</tr>
</tbody>
</table>

I hvilken grad har du over de siste 4 ukene sett på mengden sæd ved uttømming som et problem for deg?

<table>
<thead>
<tr>
<th>Vanse</th>
<th>□</th>
</tr>
</thead>
<tbody>
<tr>
<td>Har ikke hatt</td>
<td></td>
</tr>
<tr>
<td>Sæduttømming</td>
<td></td>
</tr>
<tr>
<td>Stort problem</td>
<td></td>
</tr>
<tr>
<td>Middels problem</td>
<td></td>
</tr>
<tr>
<td>Lite problem</td>
<td></td>
</tr>
<tr>
<td>Ikke noe problem</td>
<td></td>
</tr>
</tbody>
</table>

26. I hvilken grad har du over de siste 4 ukene:

Sett på manglende seksualdrift som et problem?.....

<table>
<thead>
<tr>
<th>Grad</th>
<th>□</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stort problem</td>
<td></td>
</tr>
<tr>
<td>Middels problem</td>
<td></td>
</tr>
<tr>
<td>Lite problem</td>
<td></td>
</tr>
<tr>
<td>Ganske lite</td>
<td></td>
</tr>
<tr>
<td>Ikke noe problem</td>
<td></td>
</tr>
</tbody>
</table>

Vurdert din evne til å få og beholde reisning som et problem?..............................

<table>
<thead>
<tr>
<th>Grad</th>
<th>□</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stort problem</td>
<td></td>
</tr>
<tr>
<td>Middels problem</td>
<td></td>
</tr>
<tr>
<td>Lite problem</td>
<td></td>
</tr>
<tr>
<td>Ganske lite</td>
<td></td>
</tr>
<tr>
<td>Ikke noe problem</td>
<td></td>
</tr>
</tbody>
</table>

Sett på din sæduttømming som et problem?..............

<table>
<thead>
<tr>
<th>Grad</th>
<th>□</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stort problem</td>
<td></td>
</tr>
<tr>
<td>Middels problem</td>
<td></td>
</tr>
<tr>
<td>Lite problem</td>
<td></td>
</tr>
<tr>
<td>Ganske lite</td>
<td></td>
</tr>
<tr>
<td>Ikke noe problem</td>
<td></td>
</tr>
</tbody>
</table>

27. Hvor tilfreds har du samlet sett vært med ditt seksualliv de siste 4 ukene?

<table>
<thead>
<tr>
<th>Grad</th>
<th>□</th>
</tr>
</thead>
<tbody>
<tr>
<td>Veldig utilfreds</td>
<td></td>
</tr>
<tr>
<td>For det meste</td>
<td></td>
</tr>
<tr>
<td>Utilfreds</td>
<td></td>
</tr>
<tr>
<td>Omtrent like</td>
<td></td>
</tr>
<tr>
<td>Tilfreds</td>
<td></td>
</tr>
<tr>
<td>Svarr tilfreds</td>
<td></td>
</tr>
</tbody>
</table>

28. Hjelpemidler:

Har du brukt hjelpemidler for å få og beholde reisning i løpet av de siste 4 ukene? (ett eller flere kryss)

<table>
<thead>
<tr>
<th>Grad</th>
<th>□</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nei</td>
<td></td>
</tr>
<tr>
<td>Ja, tablett (for eksempel Viagra)</td>
<td></td>
</tr>
<tr>
<td>Ja, sprøyter/injeksjoner (eks. Caverject)</td>
<td></td>
</tr>
<tr>
<td>Ja, gel inn i urinrøret (eks. Bondil)</td>
<td></td>
</tr>
<tr>
<td>Ja, vakumpumpe</td>
<td></td>
</tr>
<tr>
<td>Ja, annet</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Grad</th>
<th>□</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hva?</td>
<td></td>
</tr>
</tbody>
</table>

Hvis du i løpet av de siste 4 ukene har brukt hjelpemidler for å forbedre reisning, har dette fungert tilfredsstillende?

<table>
<thead>
<tr>
<th>Grad</th>
<th>□</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ja, fullt ut</td>
<td></td>
</tr>
<tr>
<td>Ja, delvis tilfredsstillende</td>
<td></td>
</tr>
<tr>
<td>Nei</td>
<td></td>
</tr>
</tbody>
</table>
**Hva slags behandling har du fått for prostatakreften?**

Det er ikke alltid lett å ha full oversikt over hva slags behandling man har fått fordi noen får flere typer behandling, enten samtidig eller etter hverandre, mens andre får ingen behandling.


**29. Observasjon, "vente-og-se"**

Sett kryss hvis du **aldri** har fått behandling for din prostatakreft: □ Hvis kryss, gå videre til nummer 35

**30. Operasjon**

<table>
<thead>
<tr>
<th>Ja</th>
<th>Nei</th>
<th>Vet ikke</th>
<th>Mnd</th>
<th>År</th>
</tr>
</thead>
<tbody>
<tr>
<td>Operasjon med fjerning av hele prostatakjertelen</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Operasjon gjennom urinrøret med fjerning av deler av prostatakjertelen (transuretral reseksjon)</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
</tbody>
</table>

**31. Strålebehandling**

<table>
<thead>
<tr>
<th>Ja</th>
<th>Nei</th>
<th>Vet ikke</th>
<th>Mnd</th>
<th>År</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strålebehandling mot <strong>prostata</strong> for å fjerne all kreften</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Strålebehandling mot <strong>prostata</strong> for å lindre plagene</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Første strålebehandling mot <strong>skelelet</strong> for å lindre plagene</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Strålebehandling mot <strong>krystvortene</strong> for å hindre plagene</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
</tbody>
</table>

**32. Hormonbehandling**

<table>
<thead>
<tr>
<th>Ja</th>
<th>Nei</th>
<th>Vet ikke</th>
<th>Mnd</th>
<th>År</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hormonsprøyter (f.eks. Zoladex, Procrin, Enantone)</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Hormontabletter (f.eks. Casodex, Eulexin)</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Østrogener</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Kortison (f.eks. Prednisolon)</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
</tbody>
</table>

Bruker du hormonsprøyter i dag? □Ja □Nei □Vet ikke

Bruker du hormontabletter i dag? □Ja □Nei □Vet ikke
33. Annet

<table>
<thead>
<tr>
<th>Fjernet testiklene</th>
<th>Ja</th>
<th>Nei</th>
<th>Vet ikke</th>
<th>Mnd</th>
<th>År</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cellogift (f.eks. Taxotere, Mitoxantrone)</th>
<th>Ja</th>
<th>Nei</th>
<th>Vet ikke</th>
<th>Mnd</th>
<th>År</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Benstyrkende medisiner (f.eks. Zometa)</th>
<th>Ja</th>
<th>Nei</th>
<th>Vet ikke</th>
<th>Mnd</th>
<th>År</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Kalktilskudd</th>
<th>Ja</th>
<th>Nei</th>
<th>Vet ikke</th>
<th>Mnd</th>
<th>År</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Innsprøytning av stråleaktivt stoff (Strontium)</th>
<th>Ja</th>
<th>Nei</th>
<th>Vet ikke</th>
<th>Mnd</th>
<th>År</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Annen behandling eller alternativ behandling</th>
<th>Ja</th>
<th>Nei</th>
<th>Vet ikke</th>
<th>Mnd</th>
<th>År</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Hvis "Ja", hvilke(n):

34. Har du fått behandling(er) for prostatakreften i utlandet?  

<table>
<thead>
<tr>
<th>Ja</th>
<th>Nei</th>
</tr>
</thead>
</table>

Hvis "Ja", hvilke(n):

35. Hvordan har prostataprøven – PSA – vært hos deg?

PSA måles ved hjelp av en blodprøve, og kan være forhøyet ved prostatakreft.

Hva var PSA-verdien da du fikk påvist prostatakreft i 2004?  

<table>
<thead>
<tr>
<th>Ble ikke målt</th>
<th>Ble målt, men husker ikke verdien</th>
<th>Vet ikke</th>
</tr>
</thead>
</table>

Hvis PSA ble målt da du fikk påvist prostatakreften, ble det gjort på grunn av:

☐ Helsesjekk med blodprøve, jeg hadde ingen plager eller annet som ga mistanke om prostatakreft
☐ Helsesjekk hvor legen kjente en kul i prostata, jeg hadde ingen plager
☐ Plager som kunne gi mistanke om prostatakreft; f.eks. vannlatingsplager, smerter
☐ Noe annet: ________________________________________________________________________

☐ Jeg husker ikke om jeg hadde plager eller ikke da prostatakreften ble påvist

Hvis PSA ble målt da du fikk påvist prostatakreften, ble du før målingen informert av lege/helsepersonell om denne spesielle blodprøven?

<table>
<thead>
<tr>
<th>Ja</th>
<th>Nei</th>
<th>Husker ikke</th>
</tr>
</thead>
</table>

Hva er siste PSA-verdi målt hos deg?  

<table>
<thead>
<tr>
<th>(hele tall)</th>
<th>Mnd</th>
<th>År</th>
</tr>
</thead>
</table>

☐ Måler ikke PSA
36. Hvilke andre sykdommer har du, eller har du noen gang hatt?

<table>
<thead>
<tr>
<th>Sykdom</th>
<th>Ja</th>
<th>Nei</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hjerteinfarkt</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angina pectoris (hjertekrampe)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hjertesvikt</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Annen hjertesykdom</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hjerneslag, hjerneblødning</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes (sukkersyke)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nyresykdom</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Astma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kronisk bronkitt, emfysem eller KOLS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Annen kreftisykdom</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Magesår, irritabel tarm eller annen tarmsykdom</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benskjørhet (ostheoporose)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leddgikt (reumatoid artritt)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Slitasjegikt (artrose)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Andre langvarige skjelett-, ledd- eller muskelsykdommer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epilepsi</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psykiske plager du har søkt hjelp for</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Annen langvarig sykdom</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Hvis "Ja", hvilke?________________________________________

(ikke regn med prostatakreften)

37. Bruker du noen av følgende medisiner?

<table>
<thead>
<tr>
<th>Medisin</th>
<th>Ja, daglig</th>
<th>Iblant</th>
<th>Nei</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smertestillende</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sovemedisin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beroligende medisin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medisin mot depresjon</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blodtrykksmedisin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kolesterolenkende medisin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Andre medisiner</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Hvis andre medisiner, hvilke?________________________________________

(ikke regn med prostatakreften)
38. Hvordan er dine leveår?

Hvilke av følgende passer best på ditt nåværende forhold?

- Er gift eller samboende
- Er i fast forhold, men bor ikke sammen
- Er ikke i noe fast forhold

Hvilken utdanning er den høyeste du har fullført?

- Grunnskole 7-10 år, framhaldsskole, folkehøyskole
- Realskole, middelskole, yrkesskole, 1-2 år videregående skole
- Artium, økonomisk gymnas, allmennfaglig retning i videregående skole
- Høyskole/universitet mindre enn 4 år
- Høyskole/universitet, 4 år eller mer

Er du for tiden i inntektsgivende arbeid? (ett eller flere kryss)

- Ja, fulltid/deltid
- Nei, alderspensjonert
- Nei, sykmeldt
- Nei, uføretrygdet
- Nei, annet

Har det i løpet av det siste året hendt at husholdningen har hatt vansker med å klare de løpende utgifter til mat, transport, bolig og lignende?

- Ja, ofte
- Ja, av og til
- Ja, en sjelden gang
- Nei, aldri

39. Driver du med mosjon?

Med mosjon mener vi at du f.eks. går tur, går på ski, svømmer eller driver trening/idrett.

Hvor ofte driver du med mosjon? (ta et gjennomsnitt)

- Aldri
- Sjeldnere enn en gang i uken
- En gang i uken
- 2-3 ganger i uken
- Omtrent hver dag

Dersom du driver slik mosjon så ofte som en eller flere ganger i uken: Hvor hardt mosjonerer du? (ta et gjennomsnitt)

- Tar det rolig uten bli andpusten eller svett
- Tar det så hardt at jeg blir andpusten eller svett
- Tar meg nesten helt ut
Hvor lenge holder du på hver gang? (ta et gjennomsnitt)

☐ Mindre enn 15 minutter
☐ 15-29 minutter
☐ 30 minutter - 1 time
☐ Mer enn 1 time

Har du vanligvis minst 30 minutter fysisk aktivitet daglig på arbeid og/eller i fritiden? (regn med alle daglige aktiviteter)

☐ Ja
☐ Nei

Omtrent hvor mange timer sitter du i ro på en vanlig hverdag? (regn med både jobb og fritid)

☐ ☐ timer

40. Røyker du?

☐ Nei, jeg har aldri røykt
☐ Nei, jeg har sluttet å røyke
☐ Ja, sigaretter av og til (fest, ferie; ikke daglig)
☐ Ja, sigarer, cigarillos eller pipe av og til
☐ Ja, sigaretter daglig
☐ Ja, sigarer, cigarillos eller pipe daglig

41. Hva er typiske væremåter for deg?

Spørsomlene nedenfor handler om hvordan du vanligvis er. Vennligst kryss av for enten ”ja” eller ”nei” for hvert spørsmål. Svar hurtig og ikke tenk for lenge over den nøyaktige meningen med hvert spørsmål.

Er du ofte bekymret? .................. ☐ Ja ☐ Nei

Bli din følelse lett såret? .................. ☐ Ja ☐ Nei

Hender det ofte at du ”går trøtt”? .................. ☐ Ja ☐ Nei

Har du ofte følt deg trøtt og giddesløs uten grunn? ☐ Ja ☐ Nei

Bekymrer du deg lenge etter en pinlig opplevelse? ☐ Ja ☐ Nei

Bekymrer du deg for at fryktelige ting kan skje? ☐ Ja ☐ Nei

42. Helt til slutt,

Kjenner du til Prostatakreftforeningen (PROFO)? ☐ Ja ☐ Nei

Er du medlem av PROFO? .................. ☐ Ja ☐ Nei

Tusen takk for hjelpen!
Erratum

Paper 3: The correct institution for affiliation number 4 is the following: National Resource Center for Late Effects, Department of Oncology, Oslo University Hospital and University of Oslo, Norway.