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Quality of Life and Functional Outcomes in Men with Localized Prostate Cancer

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Abstract
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Quality-of-life and functional outcomes are important in the choice of treatment for men with localized prostate cancer. These issues were investigated in the present thesis.

All living 400 men randomized to radical prostatectomy or watchful waiting from 1989 to 1999 in the Scandinavian Prostate Cancer Group Number 4 (SPCG-4) were included. An additional 281 men compromised an age-matched control group. Physical symptoms, symptom-induced stress, sense of well-being and self-assessed quality of life were evaluated by a study-specific questionnaire.

Results showed that prostate cancer men, regardless if they were allocated to radical prostatectomy or watchful waiting were suffering of long term adverse effects, mainly erectile dysfunction, urinary leakage and voiding symptoms. In the prostatectomy group, erectile dysfunction and urinary leakage were often consequences of surgery; in the watchful waiting group the side-effects could be caused by tumor progression. The quality of life deteriorated over time. High self-assessed quality of life was reported by 35 % in the radical, 34 % in watchful-waiting, and 43 % in the control groups after a median follow-up time of 12.2 years. The SPCG-4 men significantly more often reported anxiety than did controls. Erectile dysfunction was associated with the most negative influence on quality of life in both SPCG-4 groups. Men in the prostatectomy group were more distressed by erectile dysfunction than watchful waiting. Androgen deprivation therapy had negative effects on all psychological parameters, including quality of life, for the watchful waiting but not for the prostatectomy group. Information about the prostate-cancer disease was significantly higher in the radical-prostatectomy group than in watchful waiting. Check-ups were associated with worry, especially for those on androgen deprivation therapy. Open radical prostatectomy led to an increased rate of inguinal hernia compared with robot-assisted technique.

In conclusion, the data of this thesis emphasize that it takes more than a decade to understand the patterns of adverse effects and time dimension of their occurrence for each treatment. Consideration of quality of life has a high priority to aid the ageing man through the shifting scenarios of localized prostate cancer.

Keywords: prostate cancer, radical prostatectomy, watchful waiting, quality of life, erectil dysfunction, androgen deprivation therapy, robot-assisted radical prostatectomy, inguinal hernia, information, randomized

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"The term quality of life extends not only to the impact of treatment and side-effects, but to the recognition of the patient as an individual and as a whole person, body, mind and spirit"

KC Calman

List of papers

1. **Johansson E**, Bill-Axelson A, Holmberg L, Onelöw E**,** Johansson JE, Steineck G. Time, Symptom Burden, Androgen Deprivation, and Self-Assessed Quality of Life after Radical Prostatectomy or Watchful Waiting: The Randomized Scandinavian Prostate Cancer Group Study Number 4 (SPCG-4) Clinical Trial. *EurUrol* 2009; 55(2):422-430.

2. **Johansson E**, Steineck G, Holmberg L, Johansson JE, Nyberg T, Ruutu M, Bill-Axelson A. Long-term quality-of-life outcomes after Radical Prostatectomy or Watchful Waiting: The Scandinavian Prostate Cancer Group-4 Randomized Trial. *Lancet Oncology. Published Online August, 5, 2011.*

3. **Johansson E**, Steineck G, Holmberg L, Johansson JE, Nyberg T, Ruutu M, Bill-Axelson A. Quality of life after Radical Prostatectomy or Watchful Waiting with or without Androgen Deprivation Therapy: The Scandinavian Prostate Cancer Group-4 Randomized Trial. *In manuscript.*

4. Stranne J, **Johansson E**, Nilsson A, Bill-Axelson A, Carlsson S, Holmberg L, Johansson JE, Nyberg T, Ruutu M, Wiklund NP, Steineck G. Inguinal Hernia after Prostatectomy for Prostate Cancer: Results from a Randomized Setting and a Nonrandomized Setting. *EurUrol* 2010; 58(5) 719-726.

Contents

Abbreviations

ADT	Androgen deprivation therapy
BMI	Body mass index
CI	Confidence interval
HR	Hazard ratio
IH	Inguinal hernia
LUTS	Lower urinary tract symptoms
NA	Not applicable
NAD	Non-androgen deprivation
PCa	Prostate cancer
PSA	Prostate specific antigen
RARP	Robot-assisted radical prostatectomy
NPCR	National Prostate Cancer Register
RP	Radical prostatectomy
RR	Relative risk
RRP	Retropubic radical prostatectomy
SPCG-4	Scandinavian Prostate Cancer Group Study Nr 4
T1a	Tumor found in less than 5% of prostate tissue resected
T1b	Tumor found in more than 5% of prostate tissue resected
T1c-tumors	Tumor found in a needle biopsy performed due to an elevated serum PSA
T2-tumors	Palpable, but not spread outside the prostate
T3-tumors	Extracapsular growth
T4-tumors	The tumor has invaded other nearby structures
TX-tumors	Cannot be evaluated primary tumor
TUR-P	Transurethral resection of the prostate
VDS	Visual digital scale
WW	Watchful waiting

Introduction

This thesis is based on three articles on different aspects of quality of life in men with prostate cancer and a fourth article exploring the risk of developing a hernia after prostate cancer surgery. The papers are all based on a clinical trial of the Scandinavian Prostate Cancer Group Study Number 4 (SPCG-4), a group of men with localized prostate cancer who were randomized to radical prostatectomy or watchful waiting between 1989 and 1999. The SPCG-4 study's main endpoints were: death from any cause, death from prostate cancer, and death from distant metastasis [1,2,3,4]. Data on quality of life were collected at a median follow-up time of 4.1 years and 12.2 years to more fully understand the advantages and consequences of the two different treatment alternatives from the patient's perspective.

The overall aim of this research was to investigate if physical and psychological symptoms related to prostate cancer and treatment of the cancer differed between the groups and if they influenced self-assessed quality of life in men randomized to radical prostatectomy or watchful waiting.

Background

The number of prostate cancer survivors in the world is rapidly rising. Intensified diagnostic activity following prostate specific antigen (PSA) testing since the beginning of the 1990s has increased prostate cancer incidence. More than half a million men in the world get a prostate cancer diagnosis yearly, mostly in Europe, USA, Canada, and Australia.

In Sweden, prostate cancer accounts for 34 percent of all male cancers and is thereby the most common form of cancer among men. According to the 2009 statistics from The National Prostate Cancer Register (NPCR) as many as 10404 men in Sweden were diagnosed with prostate cancer, and 42 percent of these men were diagnosed due to follow-up after opportunistic PSA screening. Prostate cancer deaths have been relatively stable since the beginning of 1970 with 2404 in 2009. More than 50 percent of the men that are diagnosed with prostate cancer are over the age of 70 and less than 100 men are under the age of 50 (Figure 1). Mortality rates increase with age.

PSA testing as a preliminary means screening of men without any symptoms has led to an increased detection of prostate cancer, especially of T1c- tumors. A T1c-tumor is localized to the prostate, non-palpable, detected due to an elevated PSA, and requires for diagnosis the finding of one or more positive core biopsies. The most common tumors being diagnosed today are T1c-tumors.

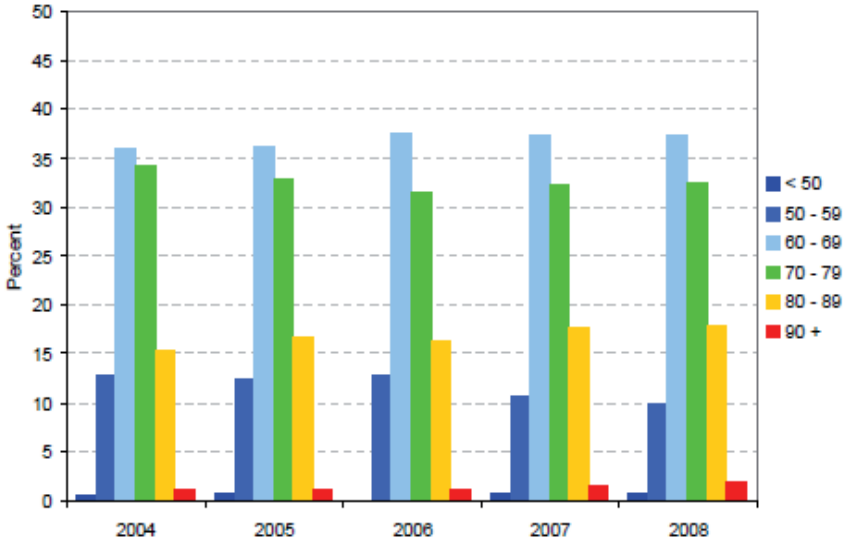


Figure 1. Age at diagnosis of prostate cancer, 2004-2008, in Sweden

Prostate cancer localized within the prostate gland is potentially curable but if the cancer extends outside the prostate capsule (locally advanced) there is a much lower chance of curability. If an effort is to be made to cure the cancer, the patient's options are surgery (radical prostatectomy) or radiation therapy. Radical prostatectomy can be performed with open surgery, or by using a laparoscopic or robot assisted approach. Dr Hugh Hampton Young at Johns Hopkins Hospital in the USA performed the first perineal radical prostatectomy in 1904. In the beginning surgery was associated with large blood loss, incontinence, and impotence as side effects. Later on at the same hospital, Dr Patrick C. Walsh introduced a nerve-sparing technique in the 1980s to preserve erectile function [5] and he refined the techniques of radical prostatectomy to minimize blood loss and incontinence. In spite of the development of these techniques, the side effects of surgery are still primarily the risk of erectile dysfunction ranging from 30-80 percent in different studies and also urinary leakage, with a range of 10-45 percent [6,7,8]. A globally agreed definition for erectile dysfunction and urinary leakage is lacking and this makes comparison between studies difficult.

The15-year survival rate for patients with localized prostate cancer is high and therefore an expectancy approach is a third option. Watchful waiting is a program of expectant management with no intention to cure. The patients are followed clinically and they are treated if the disease progresses, locally with a resection of the prostate (TUR-P) or antiandrogens and, in the case of metastasis, with androgen deprivation therapy as the standard treatment. The present method that has replaced watchful waiting for healthier men under the age of 75 years is called active monitoring or active surveillance and is employed in order to reduce over-treatment of insignificant tumors. In active monitoring curative treatment is instigated when a sign of disease progression occurs or when the patient requests that treatment be started [9]. For the tumors that have spread to lymph nodes or bones at the time of diagnosis only palliative treatment can be considered.

At present in Sweden, 36-40 percent of men with localized prostate cancer choose treatment intended to cure while expectant management stays around 25 percent (Figure 2). T1c and T2 tumors are the two most common T- categories (Figure 3).

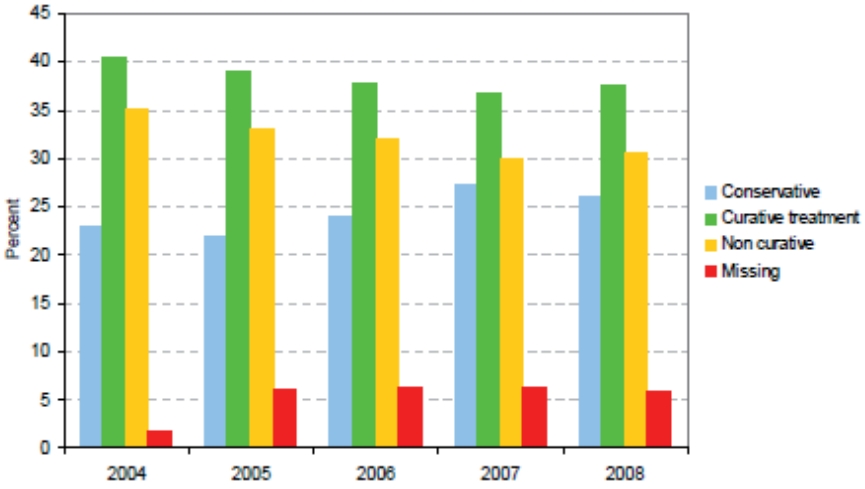


Figure 2. The distribution of primary treatments of prostate cancer, 2004- 2008, in Sweden

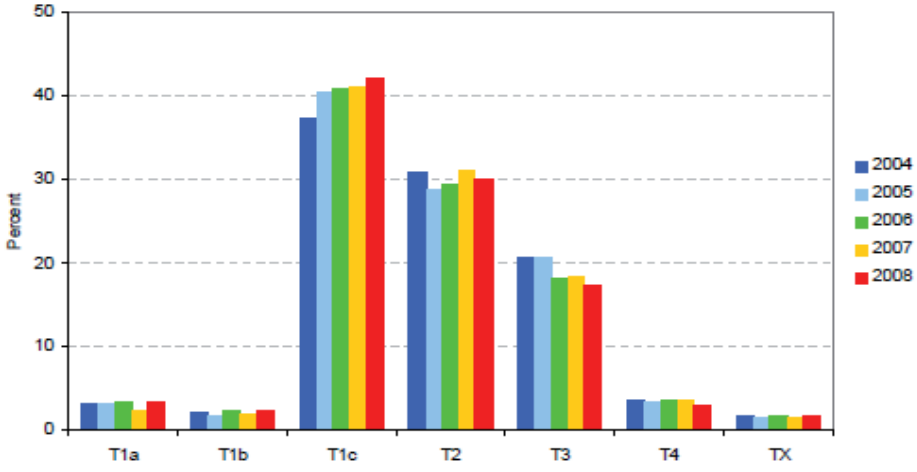


Figure 3. Distribution of T category in prostate cancer, 2004-2008, in Sweden

The widespread use of PSA testing increases the risk of overdiagnosis and overtreatment of clinically irrelevant tumors. Men with a low-risk, low volume cancer probably have a lead-time of around 12 years or more [10,11] compared with men diagnosed with a T2 tumor. It is difficult to find a balance between the risk of over-treatment leaving the patient with potential negative side effects and if no treatment with a risk of cancer progression, reduced quality of life and a premature death. The long-term quality-of-life outcomes for prostate cancer survivors with a life expectancy of two decades or more have not been investigated.

Quality of life

Quality of life is a challenging subject. It is subjective, difficult to define, and difficult to measure. Any review of the literature does demonstrate that the number of different definitions is so large as to make comparisons difficult. According to the World Health Organisation quality of life is the individual's perception of his or her position in life in the context of the culture and the value system in which he/she lives and in relation to the individual's goals, expectations, standards, and, concerns [12]. Medical research requires that quality of life be carefully defined if it is to be measured. In modern medicine quality of life is regarded as an important subject of research as shown by the results from a search in PubMed in 2011, which gives almost 160.000 hits for "quality of life". The term quality of life extends not only to the impact of treatment and side-effects, but to the recognition of the patient as an individual and as a whole person, body, mind and spirit [13].

There are many standardized and validated forms that have been developed to measure quality of life in clinical trial. One of the most commonly used forms is The Medical Outcomes Study Short Form-36 Health Survey (SF-36). It contains an 8-scale profile of functional health and well-being scores as well as psychometrically-based physical and mental health summary measures and a preference-based health utility index. It is a generic measure, as opposed to one that targets a specific age, disease, or treatment group. In prostate cancer the UCLA prostate cancer index is widely used to measure health-related quality of life (HRQOL). It employs six scales containing 20 disease-targeted items that address impairment in the urinary, bowel, and sexual domains [14]. The International Prostate Symptom Score (IPSS) specifically measures lower urinary tract symptoms (LUTS). In many parts of the world clinician's use IPSS routinely when evaluating LUTS in a patient [15]. The International index of erectile function (IIEF) addresses five domains of male sexual function (erectile function, orgasmic function, sexual desire, intercourse satisfaction, and overall satisfaction), using 15 questions. These are all psychometric scales. The patient answers several questions and points assigned to the specific answer to each question may be summed to produce one or more specific scores**.** That score then is the measure of the patient's quality of life, LUTS, or potency. The psychometric scores are validated and examined for sensitivity, specificity, reliability, and construct validity.

In my research, quality of life was analysed by employing an approach that differs from the methods described above. No summary scores were

used because each question required answering in a statement. The patient self-reports and self-assesses his quality of life. One reason for employing self-assessment is that two patients with the same objective health status can view their quality of life completely differently and with our method we can capture that difference. In our research it was also possible to explore the field further since the questionnaire is tailored for the cohort being studied. The approach that I employed is described in "measuring quality of life" on page 26. The advantages with the psychometric scales are that they can be used in different studies in the world, they are pre-validated, and the scores can be compared.

SPCG-4

The SPCG-4 study was started in 1989 because radical prostatectomy was gaining popularity in international medical practice even though no studies had been made to demonstrate that there was a survival benefit compared with watchful waiting. At that time watchful waiting was the most common regime and was regarded as the gold standard for handling prostate cancer. The physician followed the patient with regular check-ups and treatment was only given if local progression or metastatic disease developed; the treatment employed was intended to be palliative. The SPCG-4 trial was designed to determine if there is an over-all survival benefit for men with localized prostate cancer treated with radical prostatectomy as compared with watchful waiting [1,2,3,4]. For the over-all mortality at 15 years the cumulative incidences of death were 46.1 percent in the radical-prostatectomy group and 52.7 percent in the watchful-waiting group (an absolute difference of 6.6 percent). For cancer-specific mortality at 15 years the cumulative incidences of death were 14.6 percent in the radical-prostatectomy group and 20.7 percent in the watchful-waiting group (an absolute difference of 6.1 percent), [1]. The prognosis for a well to moderately well differentiated localized prostate cancer, regardless of treatment regime, is good and the absolute difference in survival in the Scandinavian study was relatively modest.

Quality of life among men with prostate cancer has been rather well investigated [7, 16] but data on the long-term effects are limited and data are lacking from randomized settings. Since the 15-year survival rate is high, regardless of treatment, the long-term effects on quality of life have become an increasingly important factor to consider in the decision making process after a cancer diagnosis. Increasing knowledge of long-term effects on functional outcome and quality of life can help the patient to make a more informed decision about his treatment and also prepare him for future difficulties. As physicians we can care for our patients in the best possible way to help them maintain their quality of life while living with a prostate cancer diagnosis and the potential negative side effects of the cancer disease and its treatment.

Hernia and radical prostatectomy

During the last two decades the number of men undergoing radical surgery for prostate cancer has increased substantially in the world. In Sweden 2707 men were treated with radical prostatectomy in 2009. Of that total 1410 operations were performed with laparoscopic technique and 1287 of these were robotic-assisted. The open retropubic prostatatectomy via midline abdominal incision accounted for 1297 operations. Robotic assisted surgery is now a more common approach than open radical prostatectomy. With the robotic approach, surgeons aim to provide better control of the cancer and reduce adverse effects than is provided by open surgery. However, no one technique has yet proved to be superior to the others.

Although much work has been focused on improving the surgical technique, including nerve-sparing procedures, to minimize post-surgical complications and long-term side effects such as incontinence and impotence, major problems are still experienced after prostate surgery. In 1996, Regan and co-workers proposed for the first time that inguinal hernia should be included as a potential complication after retropubic radical prostatectomy [(17)]. In their study of 92 consecutive patients, an incidence of postoperative inguinal hernia of 12 percent was reported within 6 months after the prostatectomy. In a study from 2001, Lodding and co-workers confirmed that there is a relationship between retropubic radical prostatectomy and inguinal hernia [(18)]. Later reports have indicated that an incidence of 12-21 percent of inguinal hernias within 2-3 years can be expected after retropubic prostatectomy using a lower midline incision [(19,20,21,22,23)].

Inguinal hernia is about ten times more common in men than in women. Two types occur, medial (direct) and lateral (indirect) hernias. The pathogenesis of the two types is different. The medial or direct hernia is acquired and produces through the transversalis fascia. The mechanism behind the hernia is a weakness of the transversalis fascia of the posterior wall of the inguinal canal. An increased intra-abdominal pressure is a contributing factor for the development of this type of hernia. The lateral or indirect hernia is the more common of the two types. This hernia is congenital in origin. Two abnormalities are necessary for the development of an indirect hernia, namely a patent processus vaginalis and a defect in the annulus internus (internal ring). The annulus internus is composed of the transversalis fascia and suspended by the transversalis muscle [(24)]. It has been suggested that the internal ring acts like a U-shaped valve and when the intra-abdominal pressure rises

the valve works like a shutter to prevent herniation, the so-called shutter mechanism [19]. Injuries of the structures of the internal ring or damage of their nerve supply are suggested as causative factors for indirect inguinal herniation associated with retropubic prostatectomy and the midline incision is postulated to be the main cause of the damage [19].

The abdominal muscles and aponeuroses are illustrated in Figure 4 and the so-called shutter mechanism is shown in Figure 5. These two illustrations are taken from Johan Stranne´s dissertation (2009) with the permission of the author.

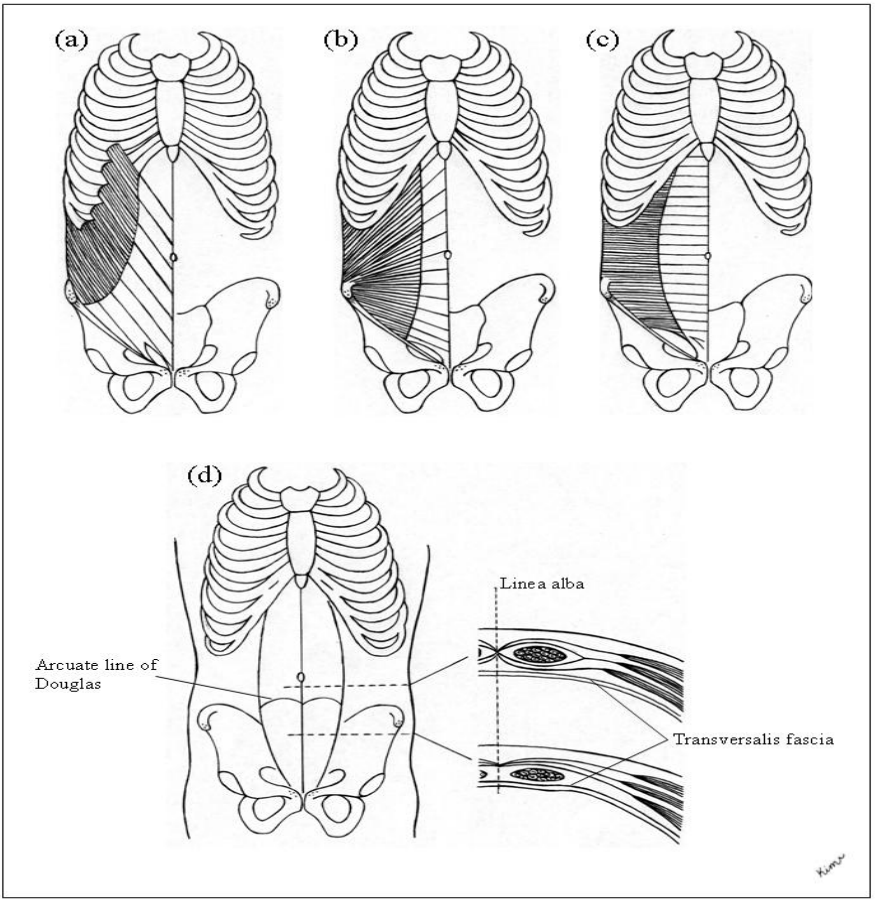


Figure 4. Muscular and aponeurosal layers of the abdominal wall: a) external oblique muscle b) internal oblique muscle c) transversalis muscle d) rectus muscle above and below arcuate line of Douglas. Note that the linea alba is separated from transversalis fascia at all levels.

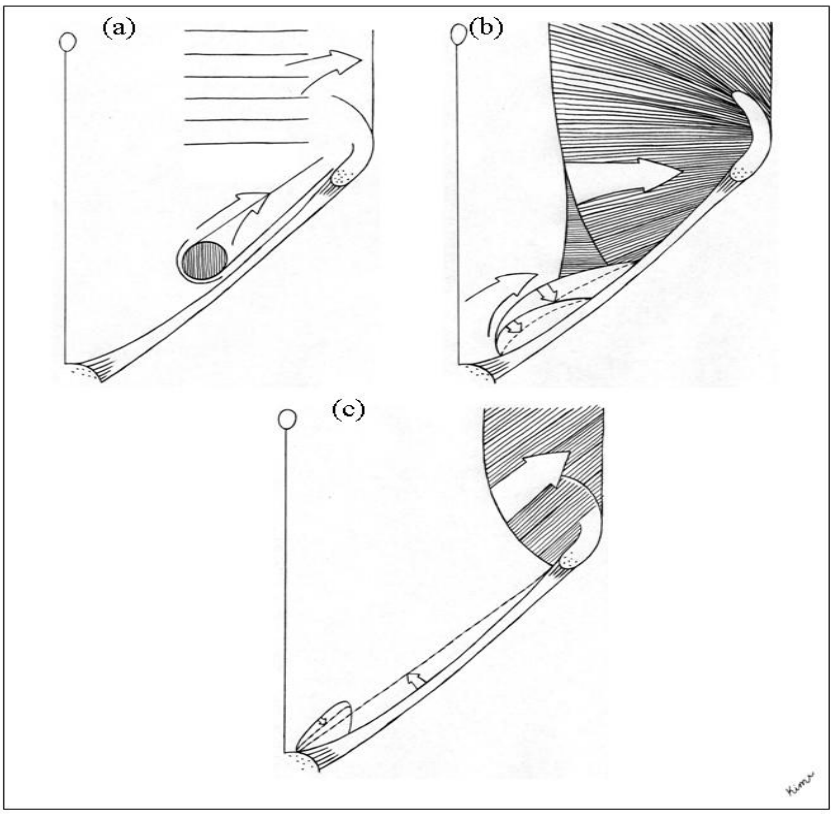


Figure 5. Shutter mechanism: a) lateral tension of the crurae from transverse muscles moves annulus internus craniolaterally b) tension of the transversalis and inner oblique muscles lovers the conjoined tendon towards inguinal ligament c) tension of external oblique muscles raises inguinal ligament.

It has been shown that a previous unilateral hernioplasty is a predisposing factor to develop hernia after radical retropubic prostatectomy [18,20]. These facts reflect the congenital origin of the lateral, indirect type of inguinal hernia and strengthen the need to consider the contralateral groin in cancer patients undergoing radical surgery who have a previous hernioplasty. In 1996, when Regan and co-workers described for the first time the association between radical retropubic prostatectomy and an increased risk of inguinal hernia, they also pointed out that repairing of the contralateral groin is to be recommended. Postoperative wound infection was identified as another risk factor for developing inguinal hernia after radical retropubic prostatectomy [20]. To minimize wound-related problems it is therefore important to take special care to avoid wound infection after open radical surgery for prostate cancer. The risk of developing inguinal hernia is also increased by higher patient age at the time of operation. As older patients are prone to increased morbidity from abdominal wall hernias, inguinal hernia is a disease that has to be considered in prostate cancer patients.

Aims of the studies

I. To evaluate how follow-up time, number of physical symptoms and presence of androgen deprivation affected quality of life among men randomized to radical prostatectomy or watchful waiting.

II. To evaluate how men randomized to radical prostatectomy or watchful waiting assessed quality of life after a median follow-up of 12.2 years and to identify physical and psychological factors of importance for this outcome. To evaluate the impact of leaving a prostate cancer in place, we enrolled a population-based group to be compared with the watchful-waiting group in addition to the radical-prostatectomy group.

III. To evaluate the effect of androgen deprivation on quality-of-life outcomes in men randomized to radical prostatectomy or watchful waiting after a median follow-up of 12.2 years. A further aim was to explore if the provision of more and better information plays a role in the patient's ability to cope with his cancer disease and to determine how the patients experienced medical checks-ups. For comparison a population-based control group of a similar age without a prostate-cancer diagnosis was enrolled.

IV. To compare the incidence of inguinal hernia after retropubic and robot-assisted radical prostatectomy with that of non-operated patients with localized prostate cancer and with that of a population-based control group.

Patients and methods

Paper I

The study group comprised all 376 living men who were included in the Swedish part of the Scandinavian Prostate Cancer Group Study Number 4 (SPCG-4) [3] between January 1, 1989 and February 29, 1996. The data were collected at least 12 months after surgery and 14 months after randomization throughout 1997 and in the beginning of 1998. The mean follow-up time was 4.1 years (range: 1-8 years). The appropriate ethics committees approved the study.

Inclusion criteria for the SPCG-4 trial were age less than 75 years, a newly diagnosed, localized T0d, T1 or T2 tumor according to the 1978 criteria of the International Union against Cancer, and after 1994 men with T1c-tumors according to the revised criteria of 1987 were also accepted [25,26]. The tumor had to be identified on the basis of a core-biopsy or needle-aspiration as being well to moderately well differentiated according to the definition established by the World Health Organization. PSA had to be less than 50 ng per milliliter. A negative bone scan, a health status that would permit a radical prostatectomy and a life expectancy of more than 10 years were also required. **(**The protocol is available at www.roc.se). After informed consent was received from eligible patients each was randomly assigned to undergo radical prostatectomy or watchful waiting through a telephone service outside the clinics. For men randomized to radical prostatectomy the surgical procedure started with examination of frozen sections of the regional lymph nodes; only if the lymph nodes were tumor free was the prostate gland excised according to the Walsh-Lapore technique [5]. Tumor radicality was prioritized over preserved potency.

Urologists followed patients in both groups regularly (every 6 months for 2 years, then annually) with a physical examination, digital rectal examination and blood tests, including PSA. A bone scan was obtained annually. Hormonal treatment was recommended for local histologically verified recurrence in the radical-prostatectomy group and for disseminated disease in both groups. In the watchful-waiting group transurethral resection was recommended for urinary obstruction.

After an introductory letter and contact by telephone, the Swedish patients who agreed to participate in this quality-of-life study were mailed a questionnaire. The assistant who made all the phone calls was blinded to the allocation

of the patients. The questionnaire was developed on the basis of interviews with patients, tested for face validity on 30 men, and further validated in a small pilot study. Our developing of a study-specific questionnaire has been described in previous methodological and empirical articles and is based on a one concept - one question method [7,27,28,29,30]. The questionnaire contained 77 questions. The Spielberger´s Trait measure from the State-Trait Anxiety Inventory was used to measure anxiety while the Centre for Epidemiological Studies Measure of Depression was used to assess depression [31,32].

The psychological symptoms (anxiety, depressed mood), sense of well-being and quality of life were assessed on seven-point visual digital scales. The men marked one of seven numbers on a line anchored by, for example, no sense of well-being to best possible sense of well-being, with seven as the most favourable outcome. For anxiety and depressed mood one on the scale indicated no anxiety/depression and seven the worst outcome. Additional information was collected on potential confounders and effect modifying factors, such as concurrent diseases and treatments, including androgen deprivation. Psychological symptoms were related to the following physical symptoms; erectile dysfunction, weak urinary stream, urinary leakage, and fecal leakage.

Statistical Methods

The intention-to-treat principle was followed. Outcome variables were dichotomized utilizing cut-off values previously used by our group, one and two = low, three to five = moderate, and six and seven = high intensity [7]. The results were presented as percentages and relative risks. Estimated relative risks and associated 95% confidence intervals were calculated according to the Mantel-Haenszel method [33,34]. Mantel-Haenszel chi square tests were used to evaluate if symptoms changed with different follow-up time. A p-value< 0.05 (two-sided) indicated statistical significance. To assess whether the morbidity (calculated as relative risks) was different for androgen deprived and non-androgen deprived men, a test for homogeneity was performed. The men who did not respond to a question were not included in the analyses of that specific variable. SPSS was the computer package used for calculations.

Papers II and III

In the SPCG-4 study (previously described in detail)[4] 695 men younger than 75 years, with clinically localized prostate cancer[25] and a life expectancy of more than 10 years were randomized to radical prostatectomy or watchful waiting between October 1, 1989 and February 28, 1999. (The protocol is available at www.roc.se.). The randomization of the study population and population control group is shown in the enclosed flow chart (Figure 6).

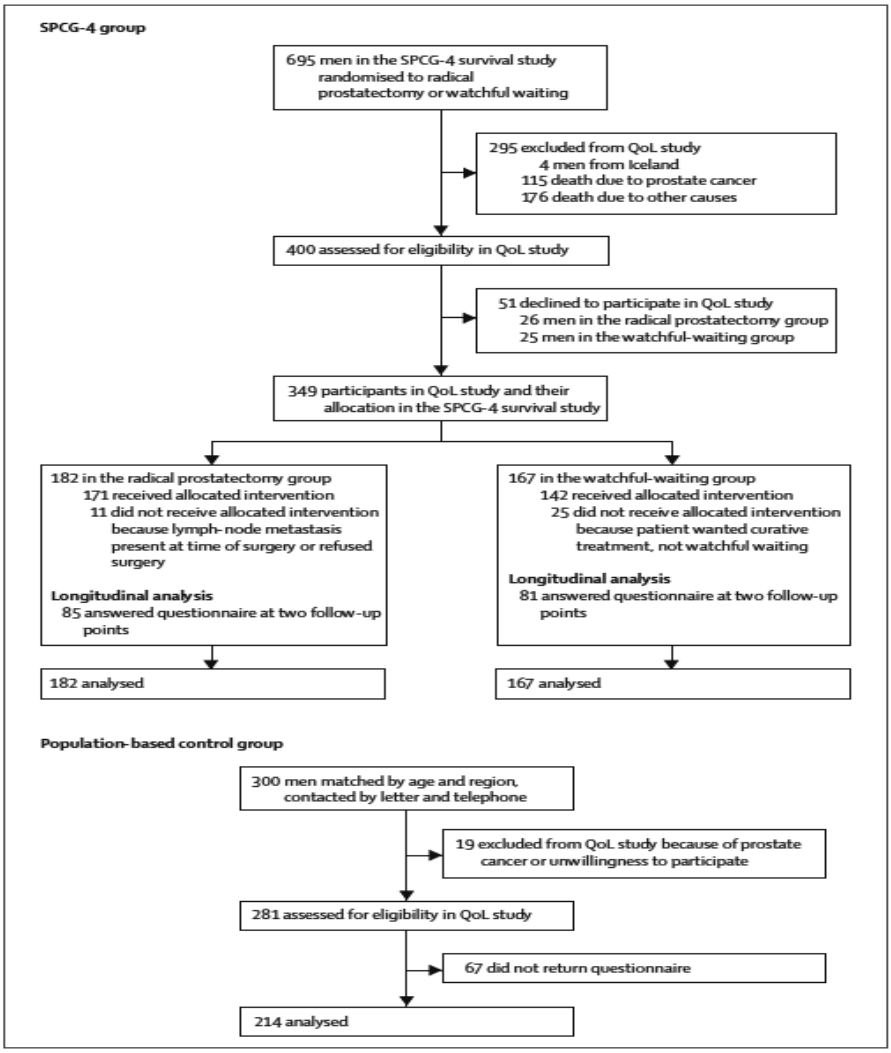


Figure 6. Flow chart for the SPCG-4 trial and for the population-based contol group.

The study population for papers II and III comprised all 400 living Swedish and Finnish men included in SPCG-4. The four men randomized in Iceland were excluded due to practical reasons (translating and validating the questionnaire for only four patients). An age (by interval of 4 years) and region-matched control group of 300 Swedish men was sampled from the Total Population Register. The 4-year interval is the closest matching given by the Total Population Register. A research assistant contacted the 300 men by letter and telephone; 19 were excluded due to prostate cancer or unwillingness to participate. Of the 400 men in the SPCG-4 study 166 answered a questionnaire at two follow-up points, first in 1997-1998 at a median follow-up of 3.7 years and, second, at a median follow-up of 13.4 years, thus giving

us longitudinal information (paper II) [7,35] .The follow-up in 1997-1998 was restricted to Swedish men, thus, the longitudinal group comprised the 166 Swedish men who were alive to answer both questionnaires.

All patients agreeing in a telephone contact to participate were mailed a study-specific questionnaire, distributed between October 2006 and November 2008. The questionnaire was developed after interviews with men with prostate cancer. The questions were tested on both patients and healthy men for face validity, with one investigator (EJ) accompanying them while they completed the questionnaire. Questions that were not immediately understood were discussed (according to the method "think aloud") and then edited so as to be interpreted as the participant intended. The questionnaire was further validated in a pilot study. This questionnaire is also validated in other studies [36,37] .The questionnaire used throughout 1997 and 1998 contained 77 questions. The second, refined version contained 141 questions and is shown in the appendix in this thesis. The questions assessing quality of life and functional outcome were identical in both questionnaires. The population-based control group answered 111 questions in a modified version in which specific cancer-related questions were excluded. The questionnaires explored psychological symptoms (anxiety, depressed mood), sense of wellbeing and quality of life on a seven-point visual digital scale: one and two on this scale were assessed as low intensity, three to five as moderate and six and seven as high intensity. The following categories of physical symptoms were probed: erectile dysfunction, weak urinary stream, urinary leakage, and nocturia. The questionnaire contained questions about quality, frequency, and intensity of each physical symptom and assessed distress according to a verbal scale. Summary questions were asked about distress from compromised sexual function and urinary symptoms (paper II). Additional information was collected on potential confounders and effect-modifying factors such as concurrent diseases and treatments, including androgen deprivation.

Paper III also contained questions on how much information the patient received from his doctor about prostate cancer and its course, about treatment alternatives for cancer, about the side effects (undesirable effect) of the various treatment alternatives, and about how the different treatments affected his daily life (quality of life). The following four answering alternatives were possible, no information, a little information, quite a lot of information, and very much information. A group of questions explored how the patient experienced the out-patient visits in connection with medical checks-ups.

Statistics paper II

All analyses followed the intention-to-treat principle. In assessment of the distress caused by a symptom, the denominator included all men who answered the question in the respective group. Outcome variables were dichotomized with cutoff values previously used by our group. We estimated

age-adjusted relative risks of the dichotomized outcomes with associated 95% confidence intervals for risk comparisons between groups using a log-binomial regression [38]. When adjusting for age the categories were ≤64, 65-69, 70-74, 75-79 and ≥80. In the analyses of longitudinal data, we presented the number of men with an increase, no change, or decrease in severity or number of symptoms between the two follow-ups. We tested homogeneity in the signs of differences within study groups using the sign test (excluding patients for whom there had been no change) [39]. All calculations were done with the SAS version 9.2 and all tests were done at the 5% significance level. Individuals who did not respond to a question were excluded from analyses of that specific variable.

Statistics paper III

All analyses followed the intention-to-treat principle. Outcome variables were dichotomized utilizing cutoff values previously used by our group. We estimated age-adjusted relative risks of the dichotomized outcomes with associated 95% confidence intervals for risk comparisons between groups using a log-binomial regression [38]. All calculations were done with the SAS 9.2 computer. All tests were done at the 5% significance level. Individuals who failed to respond to a question were excluded in the analyses of that specific variable.

Paper IV

In paper IV the occurrence of inguinal hernia after radical prostatectomy was studied. For this aim two study groups were used. The material and inclusion criteria in study group 1 were identical with those used in the SPCG-4 study. SPCG-4 including 400 men randomized to retropubic radical prostatectomy or watchful waiting. Study group 2 consisted of 1411 consecutive patients who underwent radical retropubic prostatectomy (n=465) or laparoscopic robot-assisted radical prostatectomy (n=946) at Karolinska University Hospital. A comparison group for each study group was composed of men without prostate cancer matched for age and regions as controls.

The retropubic radical prostatectomy used on those in study group 2 was based on the same technique that was used in group 1 (Walsh-Lepor technique). The robot-assisted technique used was described previously by Nilsson and co-workers in 2006 [40]. In none of the procedures was an intraoperative repair of an inguinal hernia included. All patients were admitted to the same urologic ward and the majority of the patients were operated on by the same urologists.

Information on the occurrence of inguinal hernia after prostatectomy operations was collected from the questionnaire described above. Concerning hernia the questionnaire contained the following questions:

- Have you a hernia now, or have you had a hernia?
- When did you first notice that you had a hernia?
- Have you had surgery for hernia?
- Where on your body have you now or have you had a hernia?

The last question had five alternatives: inguinal hernia, scrotal hernia, umbilical hernia, incisional hernia and other hernia. All patients who answered the first question affirmatively were included in the analysis. Of these patients who also answered "inguinal hernia" on the last question and gave a date confirming that the hernia was detected after prostate surgery had been carried out were registered as having an inguinal hernia during the follow-up. Data in group 1 were collected throughout 2006 and in the beginning of 2007 and in group 2 during 2007.

Statistics paper IV

The intention-to-treat principle was followed for group 1. Kaplan- Meier survival analysis was used to estimate the cumulative free survival of inguinal hernia for each group. As group 1 had a much longer follow-up time, the cumulative occurrence for development of inguinal hernia was calculated with 95% confidence intervals at 48 months after inclusion/operation and at the end of follow-up for comparison between the groups. Confidence intervals were estimated with the log-log transformation method. Log-rank (Mantel-Cox) test was used to analyse differences in inguinal hernias between the groups. The hazards ratio of inguinal hernia-development for investigated factors and influence of potential effect-modifying/confounding factors was estimated from the univariable and multivariable Cox proportional hazards model. A statistical significance level of 0.05 was used. The statistical analyses were carried out using the SPSSv.17 software package.

Methodological considerations

General aspects

In this thesis I have worked in an epidemiology tradition as transferred into the field of quality of life by the hierarchal step-model for causation of bias [30]. To conduct this research I have used both qualitative and quantitative methods.

The perfect study exists only as a utopia but the intention must be to strive to come as close as possible to this utopian ideal. The validity of an effect-measure depends on the absence of errors. In our research group we have traditionally been using a hierarchal step-model for causation of bias [30]. The model contains four main steps (confounding, misrepresentation, misclassification, and analytical adjustment) towards the adjusted effect measure.

1) Confounding

A confounding factor is associated with the exposure and an independent risk factor for the outcome. A confounding factor may hide an actual association between the exposure and the outcome. The research for this thesis (paper I-III) was done within the framework of a randomized trial. A randomized trial tends to give comparable groups at baseline minimizing the risk of possible confounders.

2) Misrepresentation

This step can induce bias due to non-participation and a selection-induced problem may occur (difference between targeted person-time and observed person-time). To minimize non-participation, the response rate is crucial. Non-participants result in a loss of information and we do not know if the non-responders differ from the responders. A high non-participation rate will lower the validity of the study. In SPCG-4 the participation rate was very high throughout (86 to 88 percent).

3) Misclassification

A systemic error can be introduced if the information collected is incorrect (due to measuring errors). The instrument used, in our case the questionnaire, was of greatest importance. The questions and answering alternatives were constructed to measure what we aimed to detect (sensitivity), for ex-

ample, urinary leakage, but not to misclassify men without urinary leakage as incontinent (specificity).

4) Analytical adjustment
Statistics were used to estimate effects of an association and to adjust for differences between the groups to avoid errors. The difference between the radical-prostatectomy group and the watchful-waiting group was often presented as a relative risk. These groups were randomized and therefore comparable at baseline. However, the population control group was younger, and in order to minimize bias, age was adjusted for.

Measuring quality of life

In this thesis quality of life was self-assessed and self-reported and is based on a one concept - one question method. No summary scores were used. The questionnaires explored psychological symptoms (anxiety, depressed mood), sense of wellbeing and quality of life on a seven-point visual digital scale (VDS): one and two on this scale were assessed as low intensity, three to five as moderate and six and seven as high intensity. The patients marked one of seven numbers on a line anchored by, for example, no sense of well-being to best possible sense of well-being.

Preparation - qualitative phase

Interviews

The base for this research was the interviews with prostate cancer patients. In this way I explored prostate cancer from the view of the patient and not of the physician. The patients were completely free to speak about symptoms and anything connected with being a cancer patient. The interviews were ongoing until the patient felt that he had nothing more to share; on average they took one to two hours. The interviews were then summarized on paper but not published. The interviews were neither structured nor semi-structured but the men themselves formed themes such as: the cancer diagnosis, the treatment choice, the side-effects of treatment, and life before and after the cancer.

From this knowledge hypotheses were formed.
1) On average, radical prostatectomy improves sense of well-being, self-assessed quality of life and sense of meaningfulness as compared with watchful waiting.

2) The total symptom burden from the disease and the palliative treatments increase more rapidly over time among men managed by watchful waiting than among those treated with radical prostatectomy.
3) Quality of life is higher following radical prostatectomy than watchful waiting due to the quality and duration of counselling from the managing doctor – urologic surgeon. Counselling will improve the long-term ability to cope with symptoms induced by surgery or by the disease.
4) The therapeutic intervention is much less drastic following watchful waiting than radical prostatectomy. As a consequence, men treated with radical prostatectomy benefit from a higher awareness and stronger support from their relatives and other members of their social network.

Study-specific questionnaire

Based on the interviews, our hypothesis, our clinical knowledge, the literature, and the previous SPCG-4 questionnaire from 2002, a study-specific questionnaire was constructed.

The questionnaire from the 2002 SPCG-4 study contained 77 questions and the final questionnaire contained 141 questions divided into the following sections:

1. Introductory questions
2. Quality of life
3. Dejection and worry
4. Urinary tract – questions on how you urinate
5. Sex life – questions about your sexual functioning
6. Sex aides and impotency medicine
7. Intestines – questions about your intestinal functioning
8. Diagnosis and treatment
9. Check-ups – questions about prostate cancer check-ups
10. Castration – questions about castration and its significance
11. Hernia and abdominal problems
12. Illnesses, treatment, and medication

The questionnaire contained questions about incidence, prevalence, intensity, duration, and bother of the symptoms where appropriate**.** The questionnaire was based on a "one concept - one question" method; no summary scores were used.

Face-to-face validity

The questionnaire was tested for face-to-face validity on both patients and healthy men. I accompanied them while they were completing the questionnaire. Questions that were not immediately understood were discussed (according to the method "think aloud") and then edited so as to be interpreted

as the participant intended. Quite a few questions dealt with very intimate issues and the wording of these questions was discussed and changed to be accurate but while not offending the participant. This process was ongoing until no more changes were suggested.

Pilot study

The questionnaire was tested for logistics and response rate in a pilot study. Twenty men with prostate cancer were sampled from the Swedish Cancer Register. Ten men were treated with radical prostatectomy and ten men followed the regime of watchful waiting. The response rate was 18/20 (90 percent). Since the pilot study went well it was decided to move on to the main study. To be able to include the Finnish men in the SPCG-4 study the questionnaire was translated into the Finnish language under the supervision of Professor Mirja Ruutu.

Main study - quantitative phase

This thesis is based on three different data collections:

1. 1997-1998 quality of life data from the Swedish men in the SPCG-4 study. Collected by Gunnar Steineck and co-workers.
2. 2006-2008 quality of life data from the Swedish and Finnish men in the SPCG-4 study and an age- and region-matched population control group. Collected by Eva Johansson and Mirja Ruutu.
3. 2006-2007 quality of life data from consecutive patients who underwent open radical prostatectomy or robot-assisted radical prostatectomy at Karolinska University Hospital and an age-matched population control group. Collected by Andreas Nilsson.

All collectors belonged to the research team of Clinical Cancer Epidemiology at Karolinska Institutet. A standardized method was used. An introductory letter was sent out to all potential participants. One week later a research assistant contacted them by phone. If informed oral consent occurred the participants received a posted study-specific questionnaire. Each questionnaire contained an identification number except for the population controls, who remained anonymous. The research assistant contacted all participants within a week if they had not returned the questionnaire. After three weeks a combined thank you and "reminding of the study" post-card was sent out. Additional phone calls were made to those who still had not returned the questionnaire. The research assistant was blinded to the patient's allocation in the SPCG-4 study and took no part in the analysis of the data.

Data entry

All data from the questionnaires were transferred into the freeware data and validated program Epi-Data 3.02 (www.epidata.dk). For validation of the accuracy of the data entry the ten first entrees were entered twice. Three people did all the entrées and they worked together on several questionnaires to unify the process.

The approach for identifying long-term outcome is summarized in Figure 7.

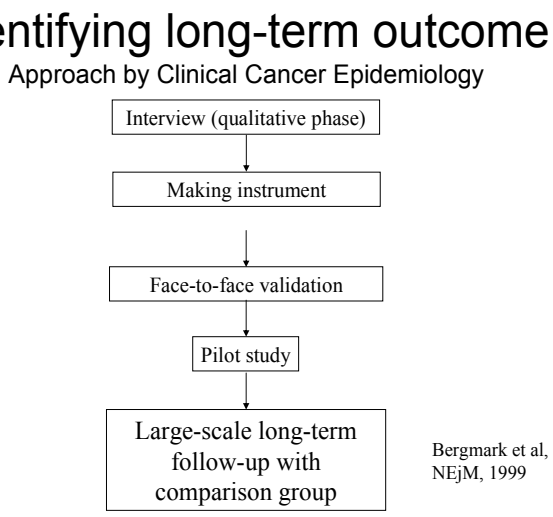


Figure 7. The approach for identifying long-term outcome.

Results

Paper I

The participation rate in men assigned to radical prostatectomy was 88%, (166 of 189) and 86% (160 of 187) in the watchful-waiting group. The mean age at randomization was 64.1 and 64.8 years respectively for the two study groups. Mean time from randomization to completion of questionnaire was 50.2 months and 48.7 months, respectively. In the radical-prostatectomy group 80% had the prostate gland removed, the remaining 20% were mostly node-positive. In the watchful-waiting group 6% ultimately underwent a radical prostatectomy.

In the radical-prostatectomy group 20 patients were androgen deprived for a mean time of 2.8 years. Of those 70% (14/20) had bone metastasis. In the watchful-waiting group 25 men had had androgen deprivation therapy for a mean time of 1.7 years. Of those 80% (29/25) were diagnosed with bone metastasis. Androgen deprivation therapy had a significantly negative effect on the levels of depressed mood, sense of well-being and quality of life in the watchful-waiting group, whereas men in the radical-prostatectomy group scored at the same level as those not being androgen deprived. After a mean observation time of 4.1 years 24% of men treated with androgen deprivation therapy in the watchful-waiting group reported a high self-assessed quality of life compared with 60% in the radical-prostatectomy group. The effect of androgen deprivation therapy on anxiety, depressed mood, sense of well-being and self-assessed quality of life is shown in Table 1 and Figure 8.

Table 1. The effect of androgen deprivation on anxiety, depressed mood, well-being, and quality of life.

	Androgen deprived		RR	Non–androgen deprived		RR	p value*
	WW	RP		WW	RP		
Anxiety	16/25 (64%)	5/20 (25%)	2.6 (1.1–5.8)	32/132 (24%)	32/144 (22%)	1.1 (0.7–1.7)	0.07
Depressed mood	17/25 (68%)	7/20 (35%)	1.9 (1.0–3.7)	43/132 (32%)	50/144 (35%)	0.9 (0.7–1.3)	0.05
Low sense of well-being†	18/25 (72%)	6/20 (30%)	2.4 (1.1–4.7)	39/132 (29%)	51/144 (35%)	0.8 (0.6–1.2)	0.01
Low self-assessed quality of life†	19/25 (76%)	8/20 (40%)	1.9 (1.1–3.4)	49/126 (39%)	56/139 (40%)	1.0 (0.7–1.3)	0.04

WW = watchful-waiting group; RP = radical prostatectomy; RR = relative risk (WW vs RP).

* Androgen deprived versus non–androgen deprived.

† Low-to-moderate self-assessed quality of life and well-being represents a score of 1–5 on a 1–7 visual digital scale.

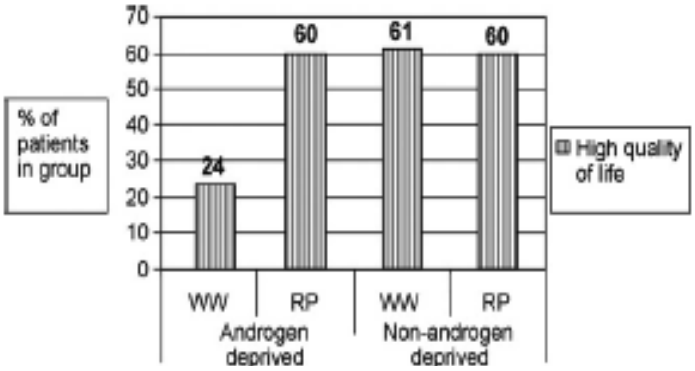


Figure 8. High quality of life in relation to allocated intervention and androgen deprivation treatment.

The self-assessed quality of life was dependent on the number of physical symptoms (erectile dysfunction, weak urinary stream, urinary leakage, and fecal leakage) in both groups and it became progressively worse with each added symptom (Figure 9). In analysis stratified on the basis of the number of these symptoms anxiety and depressed mood were less common and sense of well-being and quality of life were better in the radical-prostatectomy group than in the watchful-waiting group.

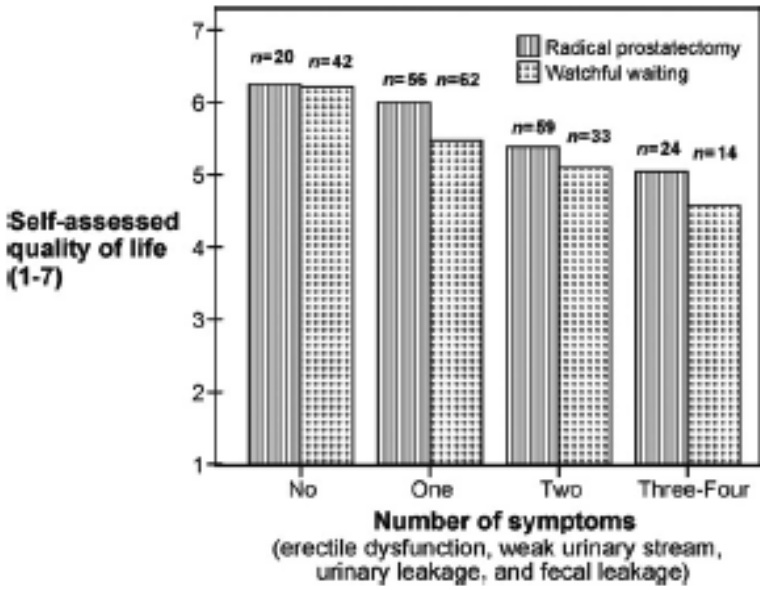


Figure 9. Mean values of quality of life in relation to number of symptoms

Erectile dysfunction was reported by 80% and urinary leakage by 42%, of the prostatectomy group and the numbers remained stable. In the watchful-waiting group these symptoms were less common initially (37% erectile

dysfunction, 11% urinary leakage) but 6-8 years after randomization 55% of these patients reported an erectile dysfunction and 25% a urinary leakage.

Anxiety, depressed mood and low sense of well-being remained stable at different follow-up times in both groups. After 6-8 years a significant decrease in quality of life (p=0.03) was seen in the watchful-waiting group but not in the radical-prostatectomy group (p=0.41). After 6-8 years 56% of men in the watchful-waiting group reported low to moderate quality of life. The corresponding figure for the radical-prostatectomy group was 42%.

Paper II

The number of participants in the radical-prostatectomy group was 182/208 (88%) and in the watchful-waiting group167/192 (87%). The follow-up time varied from 7 to 17 years (median 12.2 years). The median age at randomization was 64.0 and 65.0 years, respectively, and the median age when the questionnaire was completed was 77.0 and 78.0 years. In the population-control group 214 of 281 (76%) answered the questionnaire at a median age of 71.0 years. The 166 men (85 radical prostatectomy, 81 watchful waiting) answering the questionnaire twice did so at median follow-up times of 3.7 and 13.4 years. Social status and education level were similarly distributed between the randomized groups and the population-control group (Table 2).

Tabel 2. Patient characteristics.

	Study groups		Longitudinal analysis		Population-based control group
	RP	WW	RP	WW	
Eligible for study	208	192	85	81	281
Patients who responded to questionnaire*	182 (88%)	167 (87%)	85	81	214 (76%)
Age at randomisation (years)					
Mean	64·1	65·3	63·5	65·3	NA
Median	64·0	65·0	64·0	65·0	NA
Range	49·0–75·0	45·0–75·0	51·0–73·0	51·0–73·0	NA
Age when questionnaire was distributed (years)					
Mean	76·2	77·2	76·8	78·5	72·3
Median	77·0	78·0	77·0	79·0	71·0
Range	63·0–85·0	61·0–88·0	66·0–85·0	63·0–88·0	64·0–86·0
Time from randomisation to completion of questionnaire at the second follow-up point (months)					
Mean	149·3	147·0	163·2	162·5	NA
Median	147·0	144·5	161·0	157·4	NA
IQR	125·9–173·3	125·7–166·4	145·5–181·3	144·5–181·6	NA
Range	95·0–205·1	93·2–202·7	129·9–204·2	130·4–201·7	NA
Treatment received					
Radical prostatectomy	171 (94%)	25 (15%)	78 (92%)	10 (12%)	NA
Androgen-deprivation treatment	34 (19%)	47 (28%)	15 (18%)	24 (30%)	NA
Antiandrogen treatment	21 (12%)	38 (23%)	9 (11%)	15 (19%)	NA
Time from randomisation to surgery (months)†					
Mean	1·9	27·4	1·8	37·7	NA
Median	1·3	6·0	1·3	3·9	NA
IQR	0·85–2·0	1·35–39·6	0·85–1·87	0·85–81·4	NA
Range	0·03–28·0	0·26–163·5	0·16–28·0	0·26–163·5	NA
Social status					
Married or living with partner	142 (78%)	117 (70%)	69 (81%)	53 (65%)	156 (73%)
Partner but not living together	8 (4%)	11 (7%)	3 (4%)	2 (2%)	17 (8%)
Living alone without partner	14 (8%)	13 (8%)	7 (8%)	7 (9%)	17 (8%)
Widowed	16 (9%)	21 (13%)	6 (7%)	17 (21%)	21 (10%)
Unknown	2 (1%)	5 (3%)	0	1 (1%)	3 (1%)
Educational level					
High-school graduate	93 (51%)	94 (56%)	39 (46%)	48 (59%)	101 (47%)
College graduate	54 (30%)	46 (28%)	30 (35%)	24 (30%)	65 (30%)
Higher studies at university	31 (17%)	23 (14%)	15 (18%)	7 (9%)	43 (20%)
Unknown	4 (2%)	4 (2%)	1 (1%)	1 (1%)	5 (2%)

Data are n (% of those who responded to questionnaire), unless otherwise specified. RP=radical prostatectomy group. WW=watchful-waiting group. NA=not applicable.
*Percentages are of eligible patients. †Restricted to the men who underwent radical prostatectomy.

Number of physical symptoms

The number of physical symptoms was similarly distributed between the two SPCG-4 groups: 94% (171 of 181) and 94% (155 of 165) reported one to four for the physical symptoms erectile dysfunction, weak urinary stream, urinary leakage or nocturia. In the population-control group the corresponding figure was 65% (139 of 213).

In the analysis of longitudinal data 45% (38 of 85) of men allocated to radical-prostatectomy reported an increase in the number of physical symptoms between the two observations (p=0.036), and in men allocated to watchful-waiting 60% (48 of 80) reported an increase in the number of physical symptoms (p<0.0001) for the change from the first to second follow-up.

Sexual functional consequences

The prevalence of erectile dysfunction defined as an inability to have erection spontaneously or when elicited was 84% (146 of 173) among men allocated to radical prostatectomy and 80% (122 of 153) in men allocated to watchful waiting. The corresponding number in the population-control group was 46% (95 of 208). In a multivariate analysis of the four probed physical symptoms, inability to achieve an erection was associated with the highest relative risk of a low to moderate quality of life, adjusted RR = 1.7 (1.2-2.2). In the two SPCG-4 groups 59% (101 of 170) and 55% (84 of 152), respectively, believed their sexuality to be part of their manhood, as did 63% (125 of 198) in the population-control group. Moderate to great distress in the overall group due to loss of erection was reported by 48% (80 of 168) of men allocated to radical prostatectomy, 36% (56 of 154) allocated to watchful waiting, and 37% (76 of 208) in the population-control group. Distress from lower self-esteem due to diminished erection was seen in 39% (67 of 171), 23% (36 of 157), and 19% (39 of 207), respectively.

In the longitudinal analysis, a complete loss of erectile function was reported by 66% (54 of 82) at four years and 81% (67 of 83) at 12 years in the radical-prostatectomy group (p=0.023 for difference between the first and second follow-up), while the corresponding numbers in the watchful-waiting group were 24% (19 of 80) and 75% (56 of 75) (p<0.0001).

Urinary function and consequences

Urinary leakage at least once daily was reported by 41% (71 of 173) of men allocated to radical prostatectomy and 11% (18 of 164) of the men allocated to watchful waiting. In the population-control group the corresponding number was 3% (6 of 209). Nighttime urinary leakage once a week or more was reported by 20% (36 of 177), 8% (13 of 163), and 1% (2 of 209). A moderate to severe urinary leakage was reported by 23% (41 of 177), 11% (18 of 164), and 0.5% (1 of 209), respectively. Use of protection for urinary leakage was reported by 54% (94 of 175) in the radical-prostatectomy group, 25% (41 of 163) in the watchful-waiting group and 8% (16 of 209) in the population-control group. Moderate to great distress due to daytime urinary leakage was seen in 28% (48 of 174), 15% (25 of 162), and 9% (19 of 209), respectively.

A weak stream on more than half of all occasions was reported by 29% (50 of 174), 40% (64 of 160), and 26% (56 of 212) and nocturia twice a night or more by 49% (87 of 178), 63% (101 of 160), and 42% (89 of 212), respectively.

Men in the longitudinal analysis allocated to radical prostatectomy reported incontinence daily or more often at four years in 27% (23 of 84) of cases and at 12 years in 41% (32 of 80; p=0.243 for the difference between the first and second follow-up). The corresponding numbers were 4% (3 of 80) and 10% (8 of 80) in the watchful–waiting group (p=0.608). Going from no pad at first follow-up to using a pad at second follow-up was reported by 15% (13 of 85) in the radical-prostatectomy group (p=0.021 for the difference between the first and second follow-up) and by 19% (15 of 81) in the watchful-waiting group (p=0.0005).

Overall psychological measurements

High self-assessed quality of life was experienced by 35% (62 of 179) in the radical-prostatectomy group and 34% (55 of 160) in the watchful-waiting group and 45% (93 of 208) in the population-control group. Moderate to high level of anxiety was reported by 43% (77 of 178) and (69 of 161) in both SPCG-4 groups and by 33% (68 of 208) in the population-control group. The corresponding values for depressed mood were 47% (85 of 180), 52% (82 of 159), and 40% (84 of 207), respectively.

In the men followed longitudinally, high self-assessed quality of life was reported at 4 years by 70% (57 of 82) and at 12 years by 36% (31 of 85) in the radical-prostatectomy group and by 69% (53 of 77) and 24% (19 of 78) in the watchful-waiting group. A reduction of quality of life during longitudinal follow-up was reported by 61% (50 of 82) in the radical-prostatectomy group and 64 % (47 of 74) men in the watchful-waiting group ($p<0.0001$ for both groups for difference between the first and second follow-up). Men followed longitudinally are shown in Figure 10.

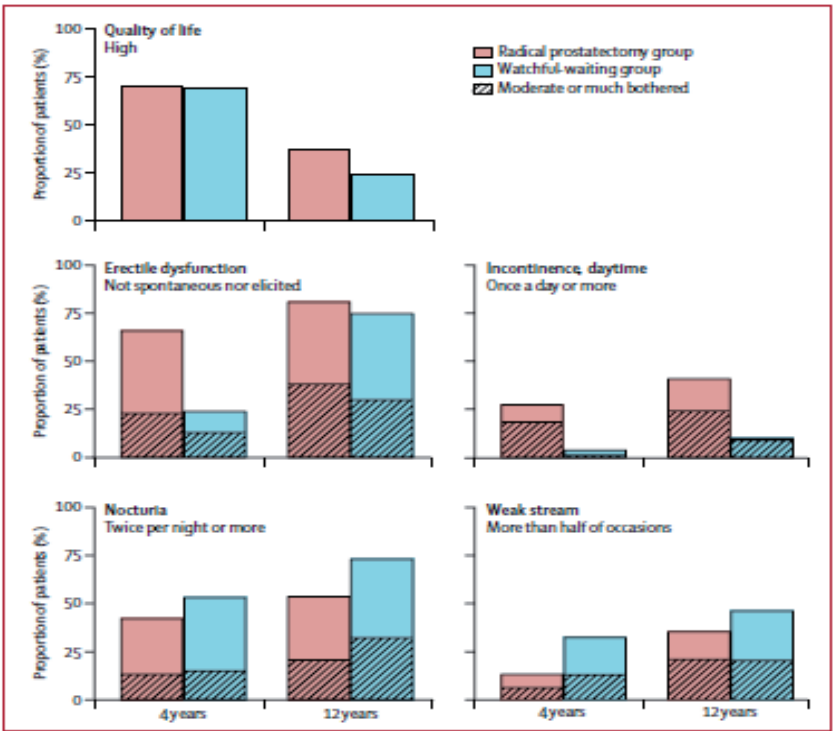


Figure 10. Changes in self-assessed quality of life, physical symptoms, and bother in 166 men answering the questionnaire at two follow-up points, 9 years apart.

Paper III

The number of participants in the radical-prostatectomy group was 182/208 (88%) and in the watchful-waiting group167/192 (87%). The follow-up time varied from 7 to 17 years (median 12.2 years). The median age at randomization was 64.0 and 65.0 years, respectively, and the median age when the questionnaire was completed was 77.0 and 78.0 years. In the population-control group 214 of 281 (76%) answered the questionnaire at a median age of 71.0 years. Social status and education level had a similar distribution between the randomized groups and population control group.

Among men assigned to radical prostatectomy 94% (171 of 182) had the prostate removed, the rest were node positive at the time of surgery or declined surgery. In the watchful-waiting group 15% (25 of 167) ultimately had a radical prostatectomy. At the time of answering the questionnaire 26% (48 of 182) of the radical-prostatectomy group and 40% (66 of 167) of the watchful-waiting group had ongoing treatment with androgen deprivation. Among androgen deprived men in the radical prostatectomy-group 73% (35 of 48) had bone metastasis; the corresponding number for men in the watchful waiting-group was 85% (56 of 66).

Self-assed quality of life and psychological parameters

In the SPCG-4 groups the highest scores for all psychological parameters were reported by men in the watchful-waiting group without androgen deprivation and the lowest scores were found among men in the same group who were androgen deprived. High quality of life for men without androgen treatment was reported in 36% (48/132) of men in radical prostatectomy and in 44% (42/95) of men in watchful waiting. In the population-control group high quality of life was reported by 45% (93/208). In the radical prostatectomy-group the scores for all the psychological domains including depression and anxiety showed no statistical difference between men with or without androgen treatment. In the watchful waiting-group there was a statistical significant difference, favouring men without androgen deprivation therapy compared with the androgen deprived. A relative risk (95% confidence interval, CI) for high self-assessed quality of life of 2.21 (1.29-3.78) was found comparing no androgen deprivation with androgen deprivation for men in the watchful-waiting group.

Information

The amount of information– from diagnosis until answering the questionnaire - the patients received on their cancer disease, different treatment options, potential side effects, and its impact on quality of life varied. Of four possible answers, no or little information was compared with quite a lot of and very much information. Men allocated to radical prostatectomy were statistically significantly more informed throughout than men allocated to watchful waiting (data not shown). When looking at information in relation to the SPCG-4 groups with or without androgen deprivation therapy, androgen deprived men in the radical-prostatectomy group reported being more informed throughout. The percentage of men who reported receiving no or little information about the prostate cancer disease and its course was 17% (8/47) among androgen deprived men in radical prostatectomy and 39% (24/62) among androgen deprived men in watchful waiting. The corresponding rates for no or little information about side-effects were 21% (9/42) and 45% (28/62), respectively.

Experiences at medical check-ups

In connection with medical check-ups at the urological out-patient clinic, androgen deprived men felt significantly more worry than men without androgen deprivation, regardless of intervention group and at a median follow-up of 12.2 years. The least amount of worry throughout was reported by men in the radical-prostatectomy group with no androgen deprivation. Of androgen deprived men in the radical-prostatectomy group 73% (32/44) felt wor-

ried about the result of the PSA-test compared with 72% (47/65) of androgen deprived men in the watchful waiting-group. For men without androgen deprivation the corresponding numbers were 34% (42/125) and 51% (49/96), respectively.

Paper IV

The results of this paper are based on study of two groups. Group 1 was composed of 400 Swedish and Finnish living men included in the SPCG-4 study, randomly assigned to open radical prostatectomy or watchful waiting between 1989 and 1999. Group 2 consisted of 1411 consecutive patients who underwent radical prostatectomy for localized cancer between 2002 and 2006 at Karolinska University Hospital; 465 with open technique and 946 with robot-assisted laparoscopic technique. In both groups population controls were included; 281 in group 1 and 442 in group 2 (Table 3).

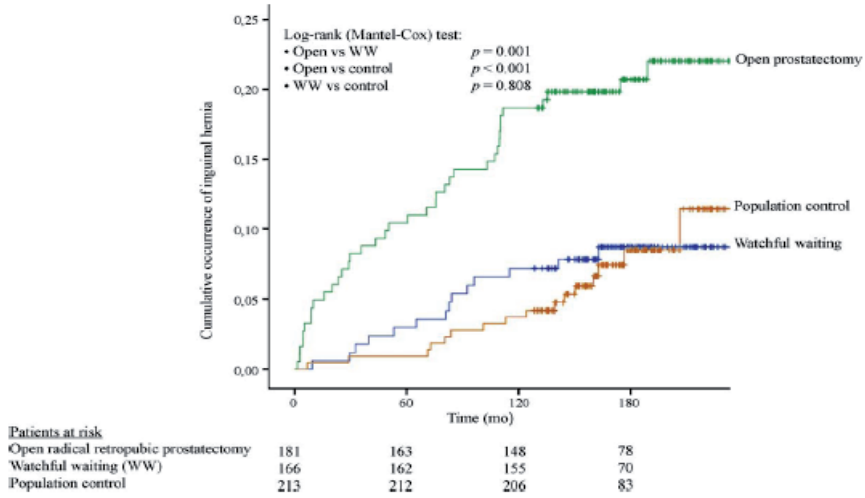
Table 3. Patient charecteristics.

Characteristics	Study group 1			Study group 2		
	Open prostatectomy	Watchful waiting	Population control	Open prostatectomy	Robot-assisted prostatectomy	Population control
Eligible patients, No.	208	192	281	465	946	442
Questionnaires returned, No. (%)	182 (87.5)	167 (87.0)	214 (76.2)	424 (91.2)	864 (91.3)	350 (79.0)
Age at randomization/surgery, yr						
Mean	64.2	65.2	60.0	63.0	61.9	60.2
Median	64.6	65.3	59.4	62.9	62.2	59.4
Range	49.3–75.0	45.1–74.7	48.3–74.7	46.7–77.6	36.7–77.5	47.2–75.4
Age at questionnaire, yr						
Mean	76.6	77.5	72.7	66.2	63.9	63.4
Median	77.1	77.9	71.5	66.2	64.2	62.8
Range	63.4–87.2	61.0–88.6	63.6–86.5	48.7–79.2	4.3–78.8	48.8–77.9
Follow-up time, mo						
Mean	148.9	147.0	152.9	38.3	23.6	38.7
Median	146.9	144.5	151.8	39.7	20.3	36.5
Range	95.0–205.1	93.2–202.7	96.3–218.0	3.7–64.0	4.6–63.2	14.7–75.9
BMI						
Mean	NA[1]	NA[1]	NA[1]	26.6	25.8	26.1
Median	NA[1]	NA[1]	NA[1]	26.2	25.5	25.7
Range	NA[1]	NA[1]	NA[1]	17.7–58.6	17.7–58.3	16.1–48.5
Comorbidity, No. (%)	17 (9)	21 (13)	23 (11)	137 (32)	202 (23)	98 (28)
Civil status, No. (%)						
Married or spouse	142 (78)	117 (70)	156 (73)	313 (74)	670 (78)	227 (65)
Living alone without partner	14 (8)	13 (8)	17 (8)	38 (9)	67 (8)	67 (19)
Living alone with occasional partner	8 (4)	11 (7)	17 (8)	22 (5)	53 (6)	28 (8)
Widower	16 (9)	21 (13)	21 (10)	13 (3)	10 (1)	7 (2)
Employment status, No. (%)						
Employed	3 (2)	3 (2)	20 (9)	143 (34)	429 (50)	182 (56)
Old-age pensioner	176 (97)	160 (96)	185 (86)	258 (61)	383 (44)	130 (37)
Long-term sick leave	0 (0)	0 (0)	5 (2)	4 (1)	16 (2)	5 (2)
Disability pension	0 (0)	1 (1)	4 (2)	15 (4)	22 (3)	9 (3)
Highest education, No. (%)						
Primary school (9 yr)	93 (51)	94 (56)	101 (47)	81 (19)	118 (14)	63 (18)
Secondary school (3 yr)	54 (30)	46 (28)	65 (30)	151 (36)	307 (36)	111 (32)
College or university	31 (17)	23 (14)	43 (20)	153 (36)	373 (43)	154 (44)
PSA, ng/ml						
Mean	12.0	11.1	NA[2]	8.3	7.7	NA[2]
Median	9.7	8.8	NA[2]	7.2	6.5	NA[2]
Range	0.1–48.0	0.1–44.0	NA[2]	0.4–60	0.4–50	NA[2]
Volume, ml						
Mean	NA[1]	NA[1]	NA[2]	43.4	40.8	NA[2]
Median	NA[1]	NA[1]	NA[2]	39.0	37.0	NA[2]
Range	NA[1]	NA[1]	NA[2]	15–206	10.0–145.0	NA[2]
Gleason score, No. (%)						
<5	56 (31)	59 (35)	NA[2]	15 (4)	40 (5)	NA[2]
6	51 (28)	37 (22)	NA[2]	150 (35)	335 (39)	NA[2]
7	31 (17)	32 (19)	NA[2]	175 (41)	384 (44)	NA[2]
8	5 (3)	6 (4)	NA[2]	18 (4)	23 (3)	NA[2]
9–10	1 (1)	0 (0)	NA[2]	22 (5)	16 (2)	NA[2]
Clinical stage, No. (%)						
T1	40 (22)	48 (29)	NA[2]	155 (37)	483 (56)	NA[2]
T2	141 (77)	118 (71)	NA[2]	122 (29)	277 (32)	NA[2]
T3	NA[3]	NA[3]	NA[2]	32 (8)	24 (3)	NA[2]

BMI = body mass index; NA = not applicable; PSA = prostate-specific antigen.
[1] Data on BMI and prostate volume not recorded according to protocol for study group 1 (Scandinavian Prostate Cancer Group Study Number 4 [SPCG-4]).
[2] PSA, prostate volume, Gleason score, or clinical stage not applicable for population control without diagnosed prostate cancer.
[3] Clinical stage T3 not eligible according to protocol for study group 1 (SPCG-4).

The overall participation rate in the two study groups was 82.7% and 88.4%, respectively, including the controls. The average age of the patients in group 1 was 64.7 years, in group 2 it was 62.3 years.

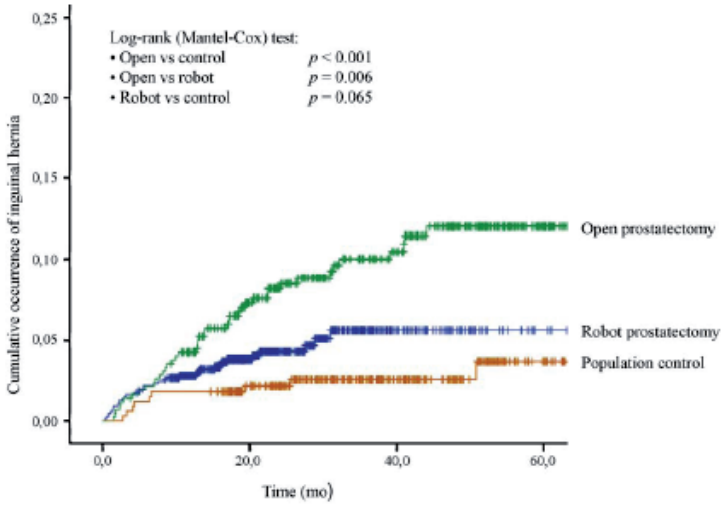
Inguinal hernia 48 months after retropubic radical prostatectomy was reported in 9.3% and 12.2%, respectively, in the two study groups. Men undergoing watchful waiting had an incidence of 2.4% and men operated on with robot-assisted laparoscopic technique reported an occurrence of 5.8%. In the controls the occurrence was 0.9% and 2.6%, respectively. The cumulative occurrence of inguinal hernia in the two study groups is illustrated in Figures 11and 12. The figures show that the incidence of inguinal hernia remained higher after open prostatectomy.



Patients at risk

Open radical retropubic prostatectomy	181	163	148	78
Watchful waiting (WW)	166	162	155	70
Population control	213	212	206	83

Figure 11. Cumulative occurrence of inguinal hernia after open prostatectomy and watchful waiting.



Patients at risk

Open radical retropubic prostatectomy	387	294	163	26
Robot-assisted prostatectomy	806	388	65	3
Population control	331	280	136	46

Figure 12. Cumulative occurrence of inguinal hernia after open and robot-assisted prostatectomy.

There was a statistically significant higher occurrence of inguinal hernias among men after open radical prostatectomy than among those undergoing watchful waiting or robot-assisted laparoscopic radical prostatectomy. No statistically significant differences in the occurrence of hernia were found between men undergoing watchful waiting and controls in study group 1 or

between men who underwent robot-assisted laparoscopic operation and controls in study group 2.

Estimated hazard ratios showed that there was 2.7 times higher risk for prostate cancer men to develop inguinal hernia after open radical prostatectomy than after undergoing watchful waiting. In comparison with open versus robot-assisted laparoscopic prostatectomy the corresponding

Discussion

Papers I and III

Androgen deprivation therapy affected the SPCG-4 men differently depending on the treatment arm. We found the same pattern after a median follow-up of 4 years (paper I) and 12 years (paper III). Androgen deprived men in the watchful-waiting group reported lower levels of self-assessed quality of life, sense of well-being and a higher prevalence of depressed mood. In contrast, men in the prostatectomy group were less affected and scored at a similar level as the SPCG-4 men without androgen deprivation therapy.

Androgen deprivation therapy is well documented as causing negative effects on general health and quality of life, even when used for a short period of time [16,41,42,43]. The different psychological reactions to androgen deprivation therapy for men in the radical-prostatectomy and watchful-waiting groups were novel findings but the reasons behind the difference are unknown. The difference in response to androgen deprivation therapy was not explained by a more severe illness in the watchful-waiting group compared with the prostatectomy group. The protocol stipulated androgen deprivation therapy for local, histological verified recurrence in the radical-prostatectomy group and for disseminated disease in both groups. In the watchful-waiting group a TUR-P was recommended for urinary obstruction. A majority (70 to 80 percent) in both groups had bone metastasis at the time of androgen deprivation therapy. In paper I we therefore hypothesized that sense of well-being, self-assessed quality of life and the ability to cope with negative symptoms and treatments were substantially influenced by having, or not having, undergone primary therapy with a curative intention. The quality and duration of counselling from the managing doctor could have been higher in the radical-prostatectomy group (during the time of surgery and medical check-ups postoperatively). A radical prostatectomy has much greater immediate consequences for the patients and his surrounding than watchful waiting. Therefore, men treated with radical prostatectomy could have benefited from a higher level of awareness of their cancer diagnosis and stronger support from their relatives and members of their social network. Knowledge that the primary tumor has been removed might influence the perception and the interpretation of symptoms, whether or not the symptoms were related to the underlying disease, favouring the radical-prostatectomy group. If there was a recurrence, men in the radical-

prostatectomy group might, in contrast with men assigned to watchful waiting, benefit from a higher level of initial awareness of cancer, more information, and from knowing that they have done all they could to rid themselves of the tumor. This could lead to a higher preparedness in times of cancer progression, better coping and understanding of negative side-effects including androgen deprivation therapy. From these hypotheses new questions were formed and sent out for the 12 year quality-of-life follow-up.

In paper III it was shown that the amount of information– from diagnosis until answering the questionnaire – received by the patients about their cancer concerning different treatment options, potential side effects, and its impact on quality of life was statistically significantly higher for men allocated to radical prostatectomy than for those assigned to watchful waiting. Examination of the level of information in relation to study group with or without androgen deprivation therapy shows that androgen deprived men in the radical-prostatectomy group reported the highest scores throughout. More information was associated with less psychological morbidity for men treated with androgen deprivation therapy. A recent Australian study showed that patients with advanced cancer had unmet needs for psychological help and medical information [(44)]. Our results in conjunction with reports from other scientific groups indicate that there is room for improvement in counselling prostate cancer patient during all stages of the disease.

Although watchful waiting patients received less cancer-specific information, paper III showed that living under the regime of watchful waiting was associated with the best scores in all psychological domains, including self-assessed quality of life. These men - diagnosed 7 to 17 years ago – had not progressed to the point of needing additional androgen deprivation therapy. They had also avoided the potential immediate side effects of surgery, especially erectile dysfunction and urinary leakage. However, when men allocated to watchful waiting needed androgen deprivation therapy they reported the worst scores for all the psychological domains. These results indicate that information about the cancer disease is less important when all is going well and the consequences of the disease are few but if progression occurs, these less well informed patients are ill prepared to meet the challenges.

The results in paper I showed that the number of physical symptoms influenced quality of life. Each added symptom lowered the level of self-assessed quality of life, and having anxiety and depressed mood were also more commonly reported. This finding is in contrast with earlier research that has shown that patients adapt to side-effects. For example, Shrader-Bogen and co-workers showed that having more symptoms did not necessarily result in poorer quality of life[(45)]. Many patients undergoing radical prostatectomy experienced immediate adverse and lasting sexual dysfunction and urinary incontinence. The watchful-waiting group had fewer physical symptoms with a short follow-up but after 6-8 years somewhat more than

half reported erectile dysfunction and urinary incontinence. The results of paper I indicated that the men who had a prostatectomy got their side-effects more or less in direct connection to surgery whereas those in the watchful-waiting group experienced an ongoing increase in these afflictions over a longer time. Quality of life was statistically significantly lower with time for the watchful-waiting group. These results should be interpreted cautiously since we took cross-sectional data and made subgroups based on time from randomization until answering the first quality-of- life questionnaire.

In our SPCG-4 study more than 80 percent of men were detected on the basis of clinical symptoms and with the presence of a palpable tumor. This study population is therefore not directly comparable with men diagnosed only on the basis of PSA. Today, the majority of men diagnosed with prostate cancer are asymptomatic with T1c tumors (non-palpable prostate cancer detected due to elevated PSA). These low-volume tumors are unlikely to produce physical symptoms until much later, if at all. Active monitoring has more and more replaced watchful waiting for healthier men under the age of 75 years in order to reduce over-treatment of insignificant tumors. In active monitoring curative treatment is instigated when a sign of disease progression occurs or when the patient chooses treatment [(46)]. This can lead to different evaluation of quality-of-life outcomes than those made in our study. Active surveillance may be associated with better outcomes than both watchful waiting and surgery; studies are needed to determine if this might be the result of active surveillance.

Repeated medical checks-ups are routinely used for many cancer patients, including men with prostate cancer. Paper III showed that medical check-ups were largely associated with worry, especially for those treated with androgen deprivation. The least amount of worry was reported by men in the radical-prostatectomy group with no hormonal therapy. It is noteworthy that the PSA value at clinical check-ups was of great concern for the SPCG-4 men even though the median age was 77 years and the men had had regular check-ups once or twice a year for up to 17 year. Our results indicate that medical check-ups never become simply a routine matter for patients and are associated with worry about the status of their cancer disease.

Our results from paper I and III underline the importance of minimizing negative side-effects of different types of treatment of prostate cancer. They also point to the necessity of providing understandable information about the prostate-cancer disease. With more knowledge the ability to cope with the disease and a progression seems to improve. The reactions to androgen deprivation therapy can both be a psychological as well as a physiological response that can improve with good clinical information. Worry at medical check-ups is common even for men that have been cancer patients for more than a decade.

Paper II

A principal finding of this study was that living with negative symptoms ensuing from prostate cancer and its treatment was associated with persisting psychological stress. Even after a median follow-up time of 12 years, prostate cancer patients, whether allocated to prostatectomy or watchful waiting, had lower scores for all psychological parameters, including quality of life, compared with population controls. Anxiety was statistically significantly higher for the SPCG-4 men. There was a higher occurrence of erectile dysfunction and urinary leakage after radical prostatectomy than after watchful waiting but urinary-emptying symptoms were more common in watchful waiting. Despite different patterns and onset of side-effects related to the cancer disease and its treatment there was no difference in self-assessed quality of life for the SPCG-4 groups. For the SPCG-4 men providing information at two points, nine years apart, the occurrence of negative physical symptoms increased and a majority reported a decreased quality of life.

Our data showed in a multivariate analysis that erectile dysfunction was associated with the most negative relative effect on quality of life. This was true for both SPCG-4 groups. This finding underlines that loss of sexual ability is a serious and persisting psychological problem even among older men. A majority in the radical-prostatectomy group had erectile dysfunction as a consequence of surgery and had lived with this side-effect for 7 to 17 years. They reported significantly more stress related to erectile dysfunction than did men in the watchful-waiting group, who lost their sexual ability more gradually. More than 80% of men in the SPCG-4 reported a loss of erectile function at a median follow-up of 12 years. A majority of cancer patients in this study also expressed their sexuality as an essential part of their manhood. Recent studies have shown that men in older ages keep their sexual activity to a great extent [47,48]. Our findings emphasized the importance of nerve sparing radical prostatectomies to prevent erectile dysfunction when it can be performed without compromising tumor radicality [5,49]. Furthermore, these findings highlight the need for an open communication about sexuality with the elderly patient, before treatment choice and continuously.

Leaving the tumor in place was associated with an increased risk of erectile dysfunction, urinary leakage, and emptying problems. There was a higher occurrence of these side-effects among men in the watchful-waiting group than in population controls. It is likely that these complications are due to a direct effect of growth of the tumor left in place and/or an effect of additional hormonal treatment or LUTS. In our study most of the cancers were clinically diagnosed and with earlier diagnosis using PSA screening these symptoms will appear later or maybe never.

There was a significant difference in urinary leakage between the two study groups favouring men in the watchful-waiting group. In the surgical group, 44% reported urinary leakage at least once a day. This can be at least

partly explained by the fact that the prostate cancer men included in our SPCG-4 trial were operated on during the 1990s when the surgical technique in radical prostatectomies was less well developed among urologists than it is today [7,35]. The definition of urinary leakage was also quite strict. The status of urinary leakage was not static, longitudinal data showed that about every 6th man started to use a pad as an aid in dealing with urinary leakage between the two follow-ups, regardless of treatment group. Feeling distress from urinary leakage was significantly more common for men in the radical-prostatectomy group, maybe due to more severe leakage and the fact that 20% reported nightly leakage. We are not aware of any corresponding data from similar settings.

The participants in the SPCG-4 groups had lower scores in all psychological parameters and significantly more worry and anxiety in comparison with population controls. In our study, the negative effects of symptoms and treatment of prostate cancer were more strongly associated with persistent stress and anxiety than with quality of life. Observational studies have shown similar results, men with prostate cancer are more affected by stress from an increased burden of negative symptoms than changes in quality of life [16,50]. This could be due to a psychologically new attitude to life after receiving a cancer diagnosis where you value your life more but are living with the increased stress of a life-threatening disease.

In this SPCG-4 trial almost all patients had tumors detected due to symptoms. When the cancer was left *in situ* under a policy of watchful waiting it was obvious that this regime had a similar negative effect on the self-assessed quality of life as performing a prostatectomy where radicality was given priority over nerve-sparing surgery. Our findings give important information that may be used in making treatment decisions for men with palpable tumors as well as for asymptomatic men diagnosed by PSA-testing who have small-volume cancers. Once negative side effects start, they are likely to progress over a long follow-up time and might cause more distress than can be expected in a background population. This underlines that counselling for prostate cancer should not be limited to the period around diagnosis and in recent guidelines The American Cancer Society recommends an informed decision-making process even before taking the PSA-test [51]. In our study the distress in the watchful-waiting group was related to tumor-progression symptoms and side-effects of treatment. Such symptoms will appear much later, if at all, in men under active surveillance with a low-volume cancer**.** On the other hand today's surgical techniques applied to small tumors will lower the risk of urinary leakage and erectile dysfunction. This can balance quality of life between surgery and active surveillance differently than in our trial, especially for the first decade of follow-up. However, our data emphasized that choice of therapy must be guided by complete information and understanding of patient preferences since the interventions involve complex scenarios that are not directly comparable.

Paper IV

The present study further confirmed that inguinal hernia is a complication after retropubic radical prostatectomy. The incidence of inguinal hernias within four years after open radical surgery using lower midline incision was five-fold to ten-fold higher than in non-surgical groups or population controls. The incidence of inguinal hernias was based on patients´ self-reporting, probably indicating that the incidence is underestimated. The significantly lower occurrence of inguinal hernia after prostatectomy with laparoscopic technique than after an open procedure supports the assumption that the abdominal incision is the factor behind hernia development. Other studies have also shown that the occurrence of inguinal hernias increased in men after operations with lower midline incision for both benign and malign urological diseases [19,52]. These findings support the hypothesis that a midline incision *per se* is causative for development of postoperative inguinal hernia [19]. Contributing mechanical factors for formation of postoperative hernias might be tissue damage caused by self-retaining retractors [18,52] but the duration of surgery seems to be without importance [19].

The length of the incision probably plays a role for the development of inguinal hernia after ”lower” abdominal surgery. The present study showed that laparoscopic procedure, performed through five-six shorter incisions, was associated with lower incidence of postoperative hernias than open prostatectomy. Our results differed from those recently reported from Rabbani and co-workers who did not find any differences in incidence of inguinal hernia between men who underwent open or laparoscopic approaches [53]. However, in their study the majority of the open operations were performed as “mini-laparotomies”. Their results are also in accordance with those described by Koie and co-workers who reported only an incidence of 2.9 percent after “mini-laparotomy”[54]. A shorter length of the midline incision thus seems to reduce the risk of postoperative inguinal hernias after retropubic radical prostatectomy. Another way to minimize the risk of developing inguinal hernia after prostatectomy might be to choose the perineal approach. Using this manoeuvre Matsuba and co-workers reported in 2007 a postoperative incidence of 1.8 percent [55].

It was clear from our data that the cumulative hernia-free survival was significantly lower for patients operated on with retropubic radical prostatectomy than those who underwent watchful waiting or constituted controls. A significant lower hernia-free survival existed also for patients after robot assisted prostatectomy in comparison with those who were operated on with open procedure. The results for the SPCG-4 study group, a group with long follow-up, showed that there was an annual increase in postoperative hernias for several years, indicating that some hernias develop late and parallel with an increased age of the patients.

Our study has shown that development of inguinal hernia after open radical prostatectomy using lower midline incision is a risk factor to consider. The complication contributes to discomfort and suffering and often a need of further surgery in form of hernioplasty. In surgical treatment of localized prostate cancer the choice of procedure should be viewed also from the point of the risk of a hernia.

General discussion

The SPCG-4 trial gave us a unique opportunity to utilize a study population, randomized to radical prostatectomy and watchful waiting, to evaluate the consequences of the different treatment principles in relation to the patients´ self-assessed quality of life. We could investigate the long-term quality-of life outcomes since randomization occurred between the years 1989 to 1999. An increased knowledge of the functional outcome and its association with quality of life is of the greatest importance in guiding prostate cancer patients in their choice of therapy. In modern medicine, quality of life has taken an important position when the impact of different treatments and their side-effects is to be evaluated. Consideration of quality-of- life aspects is essential for patients with long expected survival time, as is often true for men with prostate cancer, regardless of the treatment chosen. To cure or treat with the least amount of harm to the patient must be a goal. We need to listen to our patients telling us about life after a cancer diagnosis. This thesis has explored the functional outcomes and quality-of-life aspects in men with localized prostate cancer.

The SPCG-4 trial provided long-term data showing that negative side effects of both interventions were common and also showed that patients experienced more stress than can be expected from a background population. The onset of side effect differed between the groups. In the radical-prostatectomy group erectile dysfunction and urinary leakage were often consequences of surgery and in the watchful-waiting group side effects were due to tumor progression, hormonal treatment or LUTS. The SPCG-4 groups had similar levels of anxiety, depressed mood, and sense of well-being at a median follow-up of 4.1 years. When we looked at quality of life in relation to time from randomization until answering the questionnaire, a significant reduction after 6-8 years was found in the watchful-waiting but not in the radical-prostatectomy group (paper I). Reasons for this difference could include that more men in the watchful-waiting group had a progressive disease treated with androgen deprivation therapy, known to lower quality of life. These results were from cross-sectional data and should be interpreted with caution.

With a median follow-up of 12.2 years the level of high self-assessed quality of life was similar in the SPCG-4 groups (35 and 34 percent, respectively) but lower than at 4 years [7]. Data from SPCG-4 men, who provided information at two time-points, also showed deterioration in quality of life

with a $p<0.0001$ for the reduction between the first and second follow-up for both groups (paper II). The reduction in quality of life could be an effect of normal aging. However, more men in the control group reported high level of quality of life (43 percent). Statistical significance was not found but statistical power was relatively low. Living with a prostate cancer diagnosis caused deterioration in quality of life over time and gave more anxiety than could be expected from the background population**.** This aspect should be considered, as PSA screening is more and more common. In Sweden today almost half of men are diagnosed on the basis of PSA screening and of these men only 50 percent are informed about the PSA test in advance according to NPCR data from 2009.

Androgen deprivation is a cornerstone in prostate cancer treatment. The treatment is often effective but the patients are at risk for side effects including cardio-vascular disease, diabetes, bone loss, potency problems, depression [56,57,58], emotional changes, and sense of fatigue [59,60]. Androgen deprivation therapy lowers quality of life for men with localized prostate cancer even when used for a limited time [16]. In this thesis, a novel finding was that prostate cancer patients in the SPCG-4 groups reacted differently to androgen deprivation therapy. The emotional reaction of men in the watchful-waiting group was more negative than in men in the prostatectomy group (papers I and III). The same pattern was reported both after a median follow-up of 4 years (paper I) and 12 years (paper III). It is likely that the prostatectomized men were mentally better prepared to cope with a progressive disease and side-effects from the additional hormonal therapy. Paper III showed that men allocated to prostatectomy were more informed about the cancer disease and the side-effects of treatment, especially the androgen deprived men in the surgery group. It can therefore not be excluded that there was an association between a higher amount of information and a better ability to cope with a progressive cancer. Such a suggestion is supported by a recent study from Australia indicating that patients with advanced cancer has unmet needs of psychological help and medical information [44]. An intriguing thought is that providing more and better information and increased clinical communication can alter the psychological effects of androgen deprivation therapy.

Urinary and sexual complications are common in men with prostate cancer. The risk of when these side-effects may occur depends on treatment choice. A radical prostatectomy, regardless of surgical approach, is a technically advanced operation. Both in the past and at present, the patients are at high risk of erectile dysfunction. For most men the erection after a radical prostatectomy with nerve-sparing intent has a lesser tumescence than preoperatively and if the nerves are cut the erection is lost. Urinary leakage is also a side-effect of surgery but less common than erectile dysfunction. The literature provides reports showing a great variability of these adverse effects. Results can be hard to compare since there is no consensus on the def-

inition of urinary incontinence and erectile dysfunction. Our aim was to identify and report a wide range of symptoms, as they could be important in influencing persistent stress and quality of life. We reported for example urinary leakage as once a week or more, this liberal attitude was reflected in our reported rates of physical complications.

Our results showed that the addition of adverse symptoms lowered the level of self-assessed quality of life in addition to raising levels of anxiety and depressed mood in both SPCG-4 groups (paper I). The level of bother from these adverse symptoms remained over time. We found no indication of patients coping with side-effects as has been reported by others [45]. Erectile dysfunction was associated with the most negative influence on quality of life. Our randomized setting showed that a sudden loss of sexual ability after surgery had a more severe psychological impact than a gradual loss due to ageing, or due to tumor growth or androgen deprivation. It is noteworthy that the distress from erectile dysfunction remained even at a median age of 77 and when the problem could have persisted for up to 17 years. Studies of older men show that men are sexually active into their 80s [47,48]. For the majority of SPCG-4 men and population controls sexuality was an important part of their manhood. Our findings underline the importance of reducing adverse effects as well as performing nerve-sparing surgery to preserve sexual function when this can be done without compromising tumor radicality [5,49].

Watchful waiting refers to a regime with observation and no treatment until there are signs of progression or metastasis of the prostate cancer disease. A major finding (paper III) was that men living under this regime - without need for androgen deprivation therapy- reported the best scores for all psychological parameters, including self-assessed quality of life. They reported high quality of life (44 percent) at the same level as population controls, despite the fact that men in the watchful-waiting group had an increased risk of erectile dysfunction, urinary leakage and emptying problems. Maybe these men were the winners. They were diagnosed with a cancer, avoided the potential side effects of surgery, and did not progress to the point of needing androgen deprivation therapy. However, the advantage of living with a high quality of life has to be weighted against the disadvantage in survival. The SPCG-4 survival study at 15 years follow-up showed that there was an absolute risk reduction in disease-specific mortality with 6.1% in men randomized to surgery compared with those following the watchful waiting treatment [1].

It is well recognized that inguinal hernia is a potential complication after retropubic radical prostatectomy [18] and several reports have shown that there is a relationship between retropubic radical prostatectomy and inguinal hernia [19,20,21,22]. Concurrently with the increase in the number of prostate cancer men undergoing surgery during the past decade or two, inguinal hernia has become a complication that must be given greater consideration; it is

of special importance to pay attention to older men who are prone to increased morbidity from inguinal hernia. In Sweden today a majority of radical prostatectomies are preformed by robot-assisted technique and the numbers of open surgery are decreasing in Sweden and the western world.

Paper IV confirmed that that there is an increased risk of developing inguinal hernia after retropubic radical prostatectomy; 48 months after surgery the cumulative occurrence was 9.3 percent compared with 2.4 and 0.9 percent for watchful waiting and population controls, respectively. The results also documented that there was a significantly lower occurrence of inguinal hernia after prostatectomy performed with robot assisted laparoscopic technique. These findings support the assumption that the lengths of the abdominal incision are crucial for the development of inguinal hernias after radical prostatectomy. Our results were in accordance with those described by Koie and co-workers who reported a low incidence (2.9 percent) of inguinal hernias after mini-laparotomy [(54)].

Thus, our study has emphasized that development of inguinal hernia after open radical prostatectomy using lower midline incision is a risk factor to consider. Inguinal hernia is far from a harmless disease and older patients run an increased morbidity and mortality risk, especially if the hernia requires emergency operation including intestinal resection. Although hernias remain uncomplicated they contribute to discomfort negatively influencing the patient´s quality of life, and there is often a need of surgery in form of hernioplasty. In surgical treatment of localized prostate cancer the choice of procedure should be taken into consideration.

Results from paper III showed that providing good information and communicating well with the patients have a central role in modern medicine. Cancer patients face many stressors during the course of the illness and they are not fully satisfied with present levels of clinical communication and information. Our findings reflected different attitudes among physicians in communicating cancer questions, with prostate cancer patients. The amount of information given to the patient varied not only individually but also depending on the treatment received. We suggest that when patients experience negative changes in their disease they have a need for more information and emotional support.

Clinical checks-ups have a routine role for many cancer patients, including men with prostate cancer. However, the results from paper III emphasized that the check-ups were associated with psychological strains and worry, especially for those treated with androgen deprivation therapy. The PSA value at clinical check-ups was of great concern for the SPCG-4 men even though the median age was 77 years and the men had had regular check-ups once or twice a year for up to 17 year. Counselling for prostate cancer should not be limited to the period around diagnosis and improving clinical communication between the doctor and the patient and his close social network

can strengthen the patients understanding of his disease and maybe lower worry in connection with check-ups at the out-patient clinic.

The strengths of this thesis included the randomized setting, the face-validated study-specific questionnaire, the high participation rate, the long follow-up time, and the longitudinal data. The use of an age-matched population control group explored the effects of ageing and leaving a prostate in place. The analyses of data with the intention-to-treat principle maintained the random allocation but were confounded by the planned treatment. We also made analyses based on treatment actually received and for per- protocol but this did not alter the results. Quality of life was a later addition to the SPCG-4 study and therefore we lack base-line data. This is a limitation but randomization tends to account for comparable groups at base line concerning possible confounders. Still, it would have been a great strength to have had base line data on the patient's physical and psychological status. Statistical power was lost by dichotomizing the outcome but was used to get a clear-cut measure of the effect and to gain clinical relevance. The stress/bother of a symptom was measured for the whole group (that answered that specific question) as a denominator to make the comparison on a group level.

In summary, the SPCG-4 trial provides long-term data showing that negative side-effects of both radical prostatectomy and watchful waiting are common and that both interventions add more stress than is seen in the background population. The onset of side-effects differs between the treatment groups. In the radical prostatectomy group, erectile dysfunction and urinary leakage are often consequences of surgery, whereas in the watchful-waiting group, side-effects are due to tumor progression, hormonal therapy, or LUTS. Still, there is a change in functional outcome with time in both groups. Loss of sexual ability is a persisting psychological problem, especially if the loss emerges after surgery. Our results underline that counselling for prostate cancer should not be limited to the period around diagnosis. Improving clinical communication and the amount of information about the cancer disease is important especially for patients with a progressive disease. Every side effect added results in an additional lowering of the quality of life in both SPCG-4 groups. The findings reported in this thesis document the importance of trying to reduce adverse side-effects with all possible means.
Our data emphasize that the choice of treatment has to be guided by complete information and understanding of patient preferences since radical prostatectomy and watchful waiting involve complex scenarios that are not directly comparable.

Conclusions

- The number of side-effects increased with time, especially in the watchful-waiting group. With each added side-effect quality of life decreased in both SPCG-4 groups. Androgen deprivation therapy lowered quality of life and increased anxiety and depressed mood in the watchful-waiting group but not in the radical-prostatectomy group.

- Negative side-effects were common in both SPCG-4 groups and added more stress than was reported in the population control group. In the radical-prostatectomy group, erectile dysfunction and urinary leakage were often consequences of surgery. In the watchful-waiting group side-effects could be caused by tumor progression. Side-effects increased with time both in number and severity and at a higher rate than was caused by normal ageing. Loss of sexual ability was a persisting psychological problem for both interventions.

- After a median follow-up of 12.2 years, men in the watchful–waiting group without androgen deprivation reported the best quality-of-life scores, comparable with those in the population control group. However, after androgen deprivation therapy the watchful-waiting group reported the worst scores. Men in the prostatectomy group had similar scores for all psychological parameters, whether treated with androgen deprivation or not. Men in the radical-prostatectomy group were better informed throughout than men in the watchful-waiting group. Medical check-ups were associated with worry, especially for those treated with androgen deprivation**.**

- Radical prostatectomy using lower midline incision led to an increased risk for development of inguinal hernia. Laparoscopic robot assisted radical prostatectomy lowered the risk of inguinal hernia as compared with the risk from open surgery.

Future perspectives

Studies of quality of life remain a high priority to aid clinical decision making under the shifting scenarios of management for prostate cancer. My work with this thesis has changed the way I look at patients with prostate cancer and the way I treat them. The patients' values in life need to play a more important role during the course of the disease and in making the treatment decisions. To live with prostate cancer is like being on a journey with constant changes.

We have found some answers as a result of this research, but new ones have surfaced:

- Active surveillance is increasing as a way to monitor men with low-risk tumors in order to reduce over-treatment. Little is known of the optimal follow-up schedule and the impact on quality of life and anxiety. In the Study of Active Monitoring in Sweden (SAMS) a standard follow-up schedule is compared with an experimental program (more extensive re-biopsy, less intensive surveillance). Quality of life is followed longitudinally by using a web-based questionnaire and compared results with men who have chosen immediate curative treatment. We are focusing on investigating the potential stress of living with the uncertainty of an untreated cancer.

- The SPCG-4 patients answered a questionnaire on health and quality of life at each follow-up time. These longitudinal data are being analysed and give us the opportunity to look at changes in quality of life before and after events like androgen deprivation therapy and metastasise as well as general changes over time.

- Information to the prostate-cancer patient strengthened the patient especially when dealing with a progressive disease. To further investigate this finding it would be interesting to do an intervention study to compare regular information with extra information to patients with progressive disease to analyse the effect on anxiety, depression and quality of life.

- Radical prostatectomy often has a negative influence on sexual function. To investigate the psychological effect of that impairment

among men that has undergone radical prostatectomy and their wife's or partners is of interest.

- Men with prostate cancer are one a journey of changes with an interaction of a cancer disease and the process of ageing. To meet these changes I believe we need multidisciplinary units with urologists, oncologists, specially trained nurses, and psychologists to optimize the care for prostate cancer patients.

Summary in Swedish – sammanfattning på svenska

Bakgrund

Vid lokaliserad prostatacancer kan patienterna välja en kurativt syftande behandling eller enbart expektans.

I den skandinaviska prostatacancerstudien (SPCG-4) fördelades (randomiserades) män till radikal prostatektomi eller expektans under åren 1989 till 1999. Denna patientgrupp (kohort) följs årligen fram till patientens död. Studien har hittills visat att även om radikal prostatektomi sänker dödligheten i cancer jämfört med exspektans är den absoluta överlevnadsvinsten endast 6 procent efter en uppföljningstid av 15 år. Överlevnadsvinsten gäller framför allt män som behandlas före 65 års ålder. En nyhet är att män med s.k. lågrisktumörer, som uppvisar relativt låga värden av tumörmarkören PSA (prostataspecifikt antigen), även har en behandlingsvinst.

Medelåldern vid prostatacancerdiagnos i Sverige är idag 69 år och årligen diagnostiseras cirka nio- till tiotusen män med prostatacancer. Antalet nydiagnostiserade har stigit kraftigt på grund av blodprovstagning av PSA under 1990- och 2000-talen. De flesta män kommer inte att avlida till följd av prostatacancer, men många män kommer att leva 10 till 30 år efter cancerdiagnosen.

Livskvalitetsaspekten är en viktig och många gånger avgörande faktor i ställningstagandet till prostatacancerns behandling. Vi saknar dock långtidsdata från randomiserade studier. I min forskning har en livskvalitetsstudie utförts inom ramen för SPCG-4-studien med det övergripande syftet att undersöka livskvalitet och funktionella resultat hos män med lokaliserad prostatacancer som randomiserats till radikal prostatektomi eller expektans.

Syftet med de olika delarbetena:

I. Att undersöka hur uppföljningstid, antal biverkningar av behandling och hormonell kastration påverkar livskvalitet hos män randomiserade till radikal prostatektomi eller expektans.

II. Att undersöka hur män som randomiserats till radikal prostatektomi eller expektans bedömer sin livskvalitet efter en uppföljningstid på i medeltal 12 år och att identifiera viktiga fysiska och psykiska faktorer som påverkar detta utfall. För att förstå hur normalt åldrande påverkar män både fysikiskt och psykiskt inkluderades en åldersmatchad kontrollgrupp av män utan prostatacancer.

III. Att undersöka hur hormonbehandling påverkar livskvalitet hos män som randomiserats till radikal prostatektomi eller expektans jämfört med dem som inte behandlats efter en uppföljningstid på i medeltal 12 år. Betydelsen av information om cancersjukdomen har undersökts för män med och utan hormonbehandling och hur patienterna upplever sina cancerkontroller.

IV. Att analysera om det föreligger någon skillnad i förekomst av ljumskbråck (inguinalbråck) mellan patienter som opererats för sin prostatacancer med endera öppen eller laparoskopisk (titthålsoperation) radikal prostatektomi. Jämförelse har gjorts med cancerpatienter som inte opererats liksom med åldersmatchade män ingående i en kontrollgrupp.

Metod

I studierna har kvalitativa och kvantitativa metoder integrerats. Kvalitativt har detta skett genom intervjuer som jag gjort med patienter med prostatacancer. Här har givits fritt utrymme för patienten att berätta om sina upplevelser och symtom under sin tid som prostatacancerpatient. Sammanställningen av intervjuverna har inte publicerats, utan den ligger till grund för det utarbetade frågeformuläret. Ett "kvantitativt" frågeformulär har utvecklats och underkastats en grundlig test vad gäller validitet efter de metoder som är accepterade enligt epidemiologisk tradition för att studera livskvalitet. Frågeformuläret som jag utvecklat bygger på det formulär som användes vid en tidigare livskvalitetsundersökning (N. Engl. J. Med, 2002).

Formuläret har genomgått "face-to-face" validitetskontroll. Patienterna har fyllt i frågeformuläret tillsammans med undertecknad och då har bedömmnig gjorts om frågorna uppfattats på ett korrekt sätt. Om så inte är fallet diskuteras de enligt ”think aloud” metoden och frågeformuläret har omarbetats tills samtliga frågor är lättförståliga och klara. Frågeformuläret dokumenterar förekomsten av urinvägsbesvär, tarmbesvär, sexuella besvär, upplevelser vid cancerdiagnos, cancerkontroller, symtom och upplevelser av hormonbehandling, förekomst av bråck och bukbesvär. I samma frågeformulär efterfrågas olika variabler på välbefinnande: total livskvalitet, ångest, depression, energi med mera. Innan frågeformuläret slutligen

fastställdes testades det i en pilotstudie på 20 patienter med en svarsfrekvens på 90 procent (18/20).

Studien innefattar alla levande svenska och finska män (n= 400/695) som randomiserats till radikal prostatektomi eller expektans i SPCG-4- studien. Dessutom har inkluderats en populationsbaserad kontrollgrupp med 300 ålders- och regionalt matchade män utan prostatacancer. Detta för att kunna särskilja vilka symtom som härrör från prostatacancer och vilka symtom som beror på normalt åldrande.

Eftersom jag har velat koppla livskvalitén till den ursprungliga SPCG-4 studien och tidigare livskvalitetuppföljning har varje frågeformulär ett identitetsnummer. Den åldersmatchade kontrollgruppen är anonym. Analyser och tolkningar har gjorts med epidemiologisk metodik.

Sammanfattning av resultaten:

I. Efter 4 års medeluppföljning påverkade hormonbehandling män olika beroende av randomiseringen. Hormonbehandlade män i expektansgruppen hade signifikant lägre livskvalitet, mer ångest och depressiva besvär jämfört med dem som opererats. Män i den opererade gruppen påverkades mycket lite av hormonbehandling. Resultaten visade att ju fler biverkningar desto sämre livskvalitet i bägge SPCG-4 grupperna. Biverkningsprofilen ändrade sig över tid, framförallt i expektansgruppen.

II. Efter 12.2 års medianuppföljning (7-17) var män som randomiserats till radikal prostatektomi mer stressade av erektil dysfunktion och urininkontinens än män i expektansgruppen. Nivån av självskattad livskvalitet var likartad för män i den opererade gruppen och expektansgruppen men lägre än för kontrollgruppen. Oro och ångest var signifikant vanligare bland SPCG-4-männen än hos kontrollgruppen. Antalet biverkningar var många i bägge SPCG-4 grupperna och ökade över tid i både antal och intensitet. Försämrad sexuell förmåga var ett kvarstående psykologiskt problem för bägge SPCG-4 grupperna.

III. Efter 12.2 års medianuppföljning uppvisade icke hormonbehandlade män i expektansgruppen den högsta livskvalitén, i nivå med kontrollgruppens, men vid hormonbehandling förändrades bilden och männen i expektansgruppen upplevde då den lägsta livskvaliteten. I den opererade gruppen påverkades livskvaliteten däremot mycket lite av hormonbehandling. Män som opererats upplevde sig ha fått signifikant mer information om prostatacancersjukdomen och dess förlopp än män i expektansgruppen. Mest information ansåg sig opererade män som hor-

monbehandlats ha fått. Trots att de flesta haft en cancerdiagnos i över tio år var kliniska återbesök förenade med oro, framför allt för hormonbehandlade män oavsett om de tillhörde operationsgruppen eller expektansgruppen.

IV. Öppen radikal prostatektomi ledde till en ökad risk för ljumskbråck. Laparoskopisk radikal prostatektomi minskade bråckrisken.

Sammanfattningsvis har avhandlingen visat att komplikationer till behandling av prostatacancer är vanliga och ökar i antal och intensitet över tid. Livskvalitén försämras. Detta gäller för patienter oavsett de behandlats med operation eller expektans. Oro och ångest var vanligare bland cancerpatienterna än bland män i en åldersmatchad kontrollgrupp. Försämrad sexuell förmåga var ett kvarstående psykologiskt problem för cancerpatienter vid 77 års ålder. Ökad information om cancersjukdomen, dess behandling och risker kan minska patienternas oro, speciellt vid en spridd sjukdom. Det finns en ökad rik för ljumskbråck efter öppen operation jämfört med robotassisterad radikal prostatektomi.

Att vara fullt informerad om de olika biverkningsriskerna och dess påverkan på livskvaliten är viktigt för att en man med lokaliserad prostatacancer skall kunna göra ett klokt behandlingsval utifrån sin egen livssituation. Ett behandlingsval som han sedan ska leva med i många år.

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The cover picture is a photograph taken in 1924 at the operating theatre at Akademiska Hospital, Uppsala, Sweden.
Photograph: Uppsala Medical Historical Museum.

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Appendix:
The questionnaire

Appendix

Health and Quality of life
A questionnaire for the SPCG-4 men

This questionnaire contains questions about urinary tract, sexual and intestinal disorders. In connection with prostate disorders one may experience symptoms from all of these organ systems. We want to find out what problems you as a patient have been affected by, and how you experience them. In this questionnaire, we will ask questions about your disease, treatment and how you experience the role of a patient. With greater knowledge we hope to be able to minimize these inconveniences in the future

The questions are most often formulated so that you answer by putting a cross in the box for the answer that best corresponds with your experience. Some of the questions may be answered by choosing several alternatives that are listed after the question. ***We would appreciate it if you would try to provide answers to all of the questions.*** You are also given the chance to write your own comments.

It is easy to skip a question or perhaps even an entire page when you are answering the questionnaire so feel free to take a second look at the questions.

Some of the questions about, among other things, sex and sexuality, may seem to be a bit too intimate. It is important, however, to ensure that correct information can be given to future patients even about these matters.

If you need help or if you have questions, contact project assistant Else Lundin 020-49 11 34: the call

is free.

Thanks in advance

INTRODUCTORY QUESTIONS

Questions about yourself

Put a cross in the box for the alternative that best corresponds with your situation or experience – **only one alternative**. Write your answer on the dotted line.

1) What year were you born? 19……

2) Is it correct that you have had prostate cancer?

- ❑ No
- ❑ Yes

Note! If your answer was **NO** to the question above, contact our project assistant Else Lundin at telephone number 020-49 11 34 or return the questionnaire in the accompanying envelope.

Today's date.....

3) What year were you diagnosed with prostate cancer?

Year 19.....

4) Are you currently:

- ❑ Married or sharing a household
- ❑ Living alone without a partner
- ❑ Living alone but have a partner
- ❑ Widower

5) Are you currently:

- ❑ Employed
- ❑ Retired
- ❑ On long term sick leave
- ❑ Retired due to a health condition

6) What is your level of education? Check your highest level of education:

- ❑ Compulsory schooling or equivalent
- ❑ High school or equivalent
- ❑ University or college

Feel free to write your own comments about yourself

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QUALITY OF LIFE

Questions about your quality of life during the past 6 months

7) ***During the past 6 months,*** how has your quality of life been?

Put a circle around the number that corresponds best with your evaluation

1----------2----------3----------4----------5----------6----------7
No quality of life The best possible quality of life

8) ***During the past 6 months,*** has your life felt meaningful?

Put a circle around the number that corresponds best with your evaluation

1----------2----------3----------4----------5----------6----------7
Never All of the time

9) ***During the past 6 months***, how well have you been able to manage physically?

Put a circle around the number that corresponds best with your evaluation

1----------2----------3----------4----------5----------6----------7
Only with great difficulty Extremely well

10) ***During the past 6 months,*** have you felt dejected or depressed?

Put a circle around the number that corresponds best with your evaluation

1----------2----------3----------4----------5----------6----------7
Never All of the time

11) ***During the past 6 months,*** have you felt worried or suffered from anxiety?

Put a circle around the number that corresponds best with your evaluation

1----------2----------3----------4----------5----------6----------7
Never All of the time

12) ***During the past 6 months,*** how has your psychological state of well being been?

Put a circle around the number that corresponds best with your evaluation

1----------2----------3----------4----------5----------6----------7
No sense of well being Best possible sense of well being

13) ***During the past 6 months,*** how has your physical health been?

Put a circle around the number that corresponds best with your evaluation

1----------2----------3----------4----------5----------6----------7
Worst possible physical health Best possible health

14) ***During the past 6 months,*** how has your self esteem been?

Put a circle around the number that corresponds best with your evaluation

1----------2----------3----------4----------5----------6----------7
No self esteem Best possible self esteem

DEJECTION AND WORRY

Questions about how you have felt during the past 6 months

15) ***During the past 6 months*****,** have you had difficulty in sleeping at night?

- ❑ No, never
- ❑ Yes, at least once during the past 6 months
- ❑ Yes, at least once a month
- ❑ Yes, at least once a week
- ❑ Yes, at least 3 times a week
- ❑ Yes, every night

16) ***During the past 6 months***, have you awakened some time during the night with a feeling of worry, anxiety or discomfort?

- ❑ No, never
- ❑ Yes, at least once during the past 6 months
- ❑ Yes, at least once a month
- ❑ Yes, at least once a week
- ❑ Yes, at least 3 times a week
- ❑ Yes, every night

17) ***During the past 6 months***, have you experienced periods of intense unrest, anxiety or panic (for example with heart palpitation, breathing distress or dizziness)?

- ❑ No, never
- ❑ Yes, at least once during the past 6 months
- ❑ Yes, at least once a month
- ❑ Yes, at least once a week
- ❑ Yes, at least 3 times a week
- ❑ Yes, every day

18) ***During the past 6 months,*** have you experienced a feeling that something terrible is happening?

- ❑ No, never
- ❑ Yes, at least once during the past 6 months
- ❑ Yes, at least once a month
- ❑ Yes, at least once a week
- ❑ Yes, at least 3 times a week
- ❑ Yes, every day

19) ***During the past 6 months,*** have you taken sleeping pills?

- ❑ No, never
- ❑ Yes, at least once during the past 6 months
- ❑ Yes, at least once a month
- ❑ Yes, at least once a week
- ❑ Yes, at least 3 times a week
- ❑ Yes, every night

20) ***During the past 6 months,*** have you taken medicine (sedatives) to calm you down?

- ❑ No, never
- ❑ Yes, at least once during the past 6 months
- ❑ Yes, at least once a month
- ❑ Yes, at least once a week
- ❑ Yes, at least 3 times per week
- ❑ Yes, every day

21) ***During the past 6 months,*** have you taken anti-depressive medicine (medication for anxiety and depression)?

- ❑ No, never
- ❑ Yes, every day

22) Are you depressed?

- ❑ No, I am not depressed
- ❑ Yes, I am a little depressed
- ❑ Yes, I am moderately depressed
- ❑ Yes, I am very depressed

Feel free to write your own comments about how you feel

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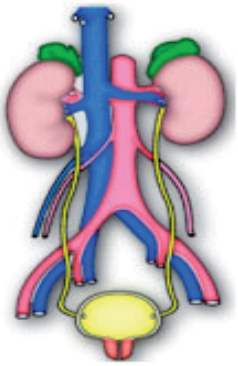
URINARY TRACT



Questions about how you urinate

Put a cross in the box for the alternative that best matches your experience – **only one alternative**

23) ***During the past 6 months,*** how often have you had a feeling that your bladder has not been emptied even though you have urinated?

- ❑ Never
- ❑ On **fewer** than half of the occasions when I have urinated
- ❑ On **more** than half of the occasions when I have urinated
- ❑ Always

24) ***During the past 6 months,*** how often have you needed to urinate within two hours?

- ❑ Never
- ❑ On **fewer** than half of the occasions I have had to urinate within two hours
- ❑ On **fewer** than half of the occasions I have had to urinate within two hours
- ❑ Always

25) ***During the past 6 months,*** how often have you noticed that you have experienced involuntary interruption of flow when you are urinating?

- ❑ Never
- ❑ On **fewer** than half of the occasions I experience involuntary interruption of flow
- ❑ On **more** than half of the occasions I experience involuntary interruption of flow
- ❑ Always

26) ***During the past 6 months,*** how often have you noticed that your urine stream was weak when you urinated?

- ❑ Never
- ❑ My urine stream has been weak on **fewer** than half of the occasions
- ❑ My urine stream has been weak on **more** than half of the occasions
- ❑ Always

27) ***During the past 6 months,*** how often have you had to exert pressure in order to begin urinating?

- ❑ Never
- ❑ I have had to exert pressure on **fewer** than half of the occasions
- ❑ I have had to exert pressure on **more** than half of the occasions
- ❑ Always

28) ***During the past 6 months,*** how often have you gotten up to urinate during a **typical night**?

- ❑ Never
- ❑ Approximately once
- ❑ Approximately twice
- ❑ Approximately 3 times
- ❑ Approximately 4 times
- ❑ Approximately 5 or more times

29) ***During the past 6 months,*** have you had a sudden feeling (a bladder urgency) that you needed to urinate immediately?

- ❑ Never
- ❑ At least once during the past 6 months
- ❑ Yes, at least once a month
- ❑ Yes, at least once a week
- ❑ Yes, at least 3 times a week
- ❑ Yes, at least once a day
- ❑ Yes, at least twice a day

30) If you, for the rest of your life, have to live with the same **overall** problems with urination, how would you feel?

- ❑ *Not relevant,* I do not have any difficulty urinating

- ❑ This would not affect me at all
- ❑ This would affect me a little
- ❑ This would affect me moderately
- ❑ This would affect me very much

31) ***During the past 6 months,*** have your problems with urination led to your avoiding doing something that really interests you (for example a leisure time activity or accepting an invitation)?

- ❑ *Not relevant,* I do not have any difficulty urinating

- ❑ No
- ❑ Yes, at least once during the past 6 months
- ❑ Yes, at least once a month
- ❑ Yes, at least once a week
- ❑ Yes, at least 3 times a day
- ❑ Yes, at least once a day
- ❑ Yes, at least twice a day

32) ***During the past 6 months,*** have you leaked urine during **the day**?

- ❑ *Not relevant,* I do not leak urine during the day

- ❑ Yes, at least once during the past 6 months
- ❑ Yes, at least once a month
- ❑ Yes, at least once a, I leak urine
- ❑ Yes, at least 3 times a week
- ❑ Yes, at least once a day
- ❑ Yes, at least twice a day

33) ***During the past 6 months,*** have you experienced urine leakage during exertion, for example when you lift something heavy, cough, or sneeze?

- ❑ No
- ❑ Yes, **only** during exertion
- ❑ Yes, **both** during exertion and without exertion

34) ***During the past 6 months,*** how much urine have you leaked during **theday**?

- ❑ *Not relevant*, I do not leak urine during the day

- ❑ A little
- ❑ Moderate
- ❑ Very much

35) ***During the past 6 months,*** have you leaked urine during **the nig**ht?

- ❑ No, never
- ❑ Yes, at least once during the past 6 months
- ❑ Yes, at least once a month
- ❑ Yes, I have leaked urine during the night at least once a week
- ❑ Yes, at least 3 times a week
- ❑ Yes, at least once a night
- ❑ Yes, at least twice a night

36) ***During the past 6 months,*** how much urine do you leak during the **night?**

- ❑ *Not relevant*, I do not leak urine during the night

- ❑ A little
- ❑ Moderate
- ❑ Very much

37) ***During the past 6 months,*** have you used one or more of the following aids to keep from leaking urine into your clothes? (*Answer all of the following questions)*

❑ *Not relevant*, I do not leak urine

A) Incontinence pads	❑ No ❑ Yes
B) Diapers	❑ No ❑ Yes
C) Uridome	❑ No ❑ Yes
D) Other protection	❑ No ❑ Yes

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…… Feel free to write your own comments about protection

38) ***During the past 6 months,*** how many times have you changed incontinence pads, diapers or other protection because of leakage of urine during **a typical day**?

❑ *Not relevant*, I use neither incontinence pads, diapers, nor other protection

❑ Less often than once a day
❑ About once a day
❑ Approximately 2 to 3 times a day
❑ Approximately 4 to 5 times a day
❑ Approximately 6 or more times per day

39) ***During the past 6 months*** when you change an incontinence pad, diaper or other protection how wet are they?

❑ *Not relevant,* I use neither incontinence pads, diapers nor any other protection

❑ A little damp
❑ Moderately wet
❑ Very wet

40) ***During the past 6 months*** if you have experienced leakage of urine **during the day** and you were to have to live with this for the rest of your life, how would this affect you?

❑ *Not relevant* – I have not experienced leakage of urine during the day

❑ This would not affect me at all
❑ This would affect me slightly
❑ This would affect me moderately
❑ This would affect me very much

41) ***During the past 6 months*** if you have experienced leakage of urine **during the night** and you were to have to live with this the rest of your life, how would you experience this?

- ❑ *Not relevant,* I do not experience leakage of urine during the night

- ❑ This would not affect me at all
- ❑ This would affect me slightly
- ❑ This would affect me moderately
- ❑ This would affect me very much

42) **Before** you got the diagnosis of prostate cancer, did you experience leakage of urine?

- ❑ No
- ❑ Yes

43) **If** during the rest of your life you were to **both control urination and to urinate** as you have done in the past 6 months, how would you experience this?

- ❑ *Not relevant*, I do not have any problems controlling urination or urinating

- ❑ This would not affect me at all
- ❑ This would affect me slightly
- ❑ This would affect me moderately
- ❑ This would affect me very much

44) ***During the past 6 months,*** have you experienced leakage of urine in combination with sexual activity?

- ❑ *Not relevant*, I am not sexually active

- ❑ No, never
- ❑ Yes, I experience leakage of urine on **fewer** than half of the occasions of sexual activity
- ❑ Yes, I experience leakage of urine on **more** than half of the occasions of sexual activity
- ❑ Yes, always

45) Does leakage of urine affect your sex life?

- ❑ *Not relevant,* I am not sexually active and do not have any leakage of urine

- ❑ No, not at all
- ❑ Yes, a little
- ❑ Yes, moderately
- ❑ Yes, very much

Feel free to write your own comments on problems with your urination

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SEX LIFE

Sex life is an important part of life for many people while for others it is not so important. Sexual functioning can be affected by prostate disease. Sex is not simply sexual intercourse but can also involve close physical contact, other erotic experiences or one's own personal satisfaction.

We want once again to remind you that this study is covered by the laws on secrecy

Questions about your sexual functioning

We ask you about your experiences on the average during ***the past 6 months***

Put a cross in the box for the alternative that best corresponds with our experience – **only one alternative**

About sexual desire:

46) ***During the past 6 months,*** have you had thoughts about sex?

- ❑ No, never
- ❑ Approximately once during the past 6 months
- ❑ Approximately once a month
- ❑ Approximately once a week
- ❑ Approximately 3 times a week
- ❑ Approximately once a day

About stiffness of the penis

47) ***During the past 6 months***, how stiff has your penis been during sexual activity?

- ❑ *Not relevant, I have note been sexually active*

- ❑ My penis has never been sufficiently stiff for intercourse
- ❑ My penis has been sufficiently stiff for intercourse on **fewer** than half of the occasions
- ❑ My penis has been sufficiently stiff for intercourse on **more** than half of the occasions
- ❑ My penis has always been sufficiently stiff for intercourse

48) ***During the past 6 months,*** if you have had an erection in the morning, how stiff was your penis?

- ❑ *Not relevant*, I have not had a morning erection

- ❑ My penis has never been sufficiently stiff for intercourse
- ❑ My penis has been sufficiently stiff for intercourse on **fewer** than half of the occasions
- ❑ My penis has been sufficiently stiff for intercourse on **more** than half of the occasions
- ❑ My penis has always been sufficiently stiff for intercourse

49) ***During the past 6 months,*** how often during sexual activity have you reached orgasm?

- ❑ *Not relevant*, I have not been sexually active during the past 6 months

- ❑ Never
- ❑ I have reached orgasm during **fewer** than half of the occasions
- ❑ I have reached orgasm during **more** than half of the occasions
- ❑ Always

50) **If** your erection has become worse compared with what it was previously and if this condition were to continue for the rest of your life, what do you think about that?

- ❑ *Not relevant,* my erection has not become worse
- ❑ This would not affect me at all
- ❑ This would affect me slightly
- ❑ This would affect me moderately
- ❑ This would affect me very much

51) **If** your erection has worsened or disappeared, has this affected your self esteem?

- ❑ *Not relevant,* my erection has not become worse

- ❑ No, this has not affected my self esteem at all
- ❑ Yes, this has affected my self esteem slightly
- ❑ Yes, this has affected my self esteem moderately
- ❑ Yes, this has affected my self esteem very much

52) **If** your erection has worsened or disappeared, has this affected your relationship with your partner?

- ❑ *Not relevant*, I do not have a partner
- ❑ *Not relevant*, my erection has not worsened

- ❑ No, this has not affected our relationship at all
- ❑ Yes, this has affected our relationship slightly
- ❑ Yes, this has affected our relationship moderately
- ❑ Yes, this has affected our relationship very much

53) **Before** you received the diagnosis of prostate cancer, had you experienced diminished erection?

- ❑ No
- ❑ Yes

54) Is your penis shorter now than when you were 30 years old?

- ❑ No
- ❑ Yes

55) **If** your penis is shorter now compared with when you were 30 years old and if this condition were to continue for the rest of your life, what do you think of that?

- ❑ *Not relevant*, my penis is not shorter

- ❑ This would not affect me at all
- ❑ This would affect me slightly
- ❑ This would affect me moderately
- ❑ This would affect me very much

On sexual intercourse

56) ***During the past 6 months,*** how often have you had sexual intercourse?

- ❑ Never
- ❑ Approximately once during the past 6 months
- ❑ Approximately 1 to 2 times a month
- ❑ Approximately 3 to 4 times a month
- ❑ Approximately 5 or more times a month

57) ***During the past 6 months,*** if you have had sexual intercourse **less often** than in the past and if this situation were to continue for the rest of your life, what do you think of that?

- ❑ *Not relevant*, I have not had intercourse less often than in the past

- ❑ This would not affect me at all
- ❑ This would affect me slightly
- ❑ This would affect me moderately
- ❑ This would affect me very much

On orgasm and the volume of semen

58) ***During the past 6 months,*** how often, on the average, have you had an orgasm?

- ❑ *Not relevant*, I have not been sexually active during the past 6 months

- ❑ Never
- ❑ Approximately once during the past 6 months
- ❑ Approximately 1 to 2 times a month
- ❑ Approximately 3 to 4 times a month
- ❑ Approximately 5 or more times a month

59) ***During the past 6 months,*** if the number of orgasms has been **fewer** than before and if this would continue for the rest of your life, what do you think of that?

- ❑ *Not relevant*, the number of orgasms has not changed

- ❑ This would not affect me at all
- ❑ This would affect me a little
- ❑ This would affect me moderately
- ❑ This would not affect me very much

60) ***During the past 6 months,*** if you have had an orgasm, how satisfying was that experience?

- ❑ *Not relevant*, I have not had an orgasm during the past 6 months.

- ❑ Not at all satisfying
- ❑ Slightly satisfying
- ❑ Moderately satisfying
- ❑ Very satisfying

61) ***During the past 6 months***, If your experience of orgasm has been **less** satisfying compared with the past and if this condition were to prevail for the rest of your life, what do you think about that?

- ❑ *Not relevant*, my experience of orgasm has not changed
- ❑ *Not relevant*, I have not had an orgasm during the past 6 months

- ❑ This would not affect me at all
- ❑ This would affect me a little
- ❑ This would affect me moderately
- ❑ This would affect me very much

62) ***During the past 6 months***, how often have you experienced pain during orgasm?

- ❑ *Not relevant,* I have not had an orgasm during the past 6 months

- ❑ Never
- ❑ I have experienced pain on **fewer** than half of the occasions
- ❑ I have experienced pain on **more** than half of the occasions
- ❑ Always

63) ***During the past 6 months***, if you have had an ejaculation, how much semen has come out during the ejaculation?

- ❑ *Not relevant*, I have not had an ejaculation

- ❑ None at all
- ❑ A little bit
- ❑ A moderate amount
- ❑ A large amount

64) ***During the past 6 months,*** if the amount of semen has been **less** compared with the amount earlier, what do you think about this?

- ❑ *Not relevant,* the amount of semen has not decreased
- ❑ *Not relevant,* I have not had an ejaculation

- ❑ This would not affect me at all
- ❑ This would affect me slightly
- ❑ This would affect me moderately
- ❑ This would affect me very much

Questions about sexuality

65) ***During the past 6 months,*** have you had a partner with whom you have been sexually active?

- ❑ No
- ❑ Yes

66) ***During the past 6 months,*** have you felt that you could sexually satisfy your partner?

- ❑ *Not relevant*, I do not have a partner

- ❑ No, I never satisfy my partner
- ❑ Yes, I satisfy my partner **fewer** than half of the times I try
- ❑ Yes, I satisfy my partner **more** than half of the times I try
- ❑ Yes, I can always satisfy my partner

67) How important is sex for you at present?

- ❑ Not at all important
- ❑ Of slight importance
- ❑ Moderately important
- ❑ Very important

68) Do you believe that sexuality is part of your being a man (manhood)?

- ❑ No
- ❑ Yes

69) ***During the past 6 months***, have you avoided sexual activity because of fear that you would fail?

- ❑ No, not true at all
- ❑ Yes, this is somewhat true
- ❑ Yes, this is largely true
- ❑ Yes, this is completely true

70) If ***during the past 6 months***, your sexual capacity has been **worse** in comparison with what it previously was and if it could be expected to remain that way for the rest of your life, what would you think about that?

- ❑ *Not relevant*, my sexual capacity has not become worse

- ❑ That would not affect me at all
- ❑ That would affect me a little
- ❑ That would affect me moderately
- ❑ That would affect me very much

Feel free to write your own comments on sexuality

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SEX AIDS AND IMPOTENCY MEDICINE

Both mechanical aids and impotency medicine can improve erection and prolong the time during which you can have an erection

71) Have you had a discussion with your doctor about using mechanical aids or potency medicine to improve or prolong your erections?

- ❑ No
- ❑ Yes

72) Would you have liked it if a doctor had given you information about mechanical aids or medicine in order to improve or prolong your erections?

- ❑ Not relevant, my doctor informed me.

- ❑ No
- ❑ Yes

73) Have you used mechanical aids or medicine to improve or retain erection?
*(A series of follow-up questions are listed below, A-G. Answer **yes** or **no** to every question. If the answer is yes also put a cross in the box if you have used aids during the **past 6 months** or in the box for **further back in time**)*

A) Medicine (for example Viagra, Cialis, Levitra)?
❑ No ❑Yes ❑During the past 6 months ❑ Further back in time

B) Medicine from Natural Health stores, so called natural medicine?
❑ No ❑Yes ❑ During the past 6 months ❑ Further back in time

C) Medicine that is introduced into the urethra (*for example Muce*)?
❑ No ❑Yes ❑During the past 6 months ❑ Further back in time

D) Vacuum pump?
❑ No ❑Yes ❑During the past 6 months ❑ Further back in time

E) Injection treatment (with, for example, Caverject, Prostivas, or Papaverin)?
❑ No ❑Yes ❑During the past 6 months ❑ Further back in time

F) Elastic band on the root of the penis?
❑ No ❑Yes ❑During the past 6 months ❑ Further back in time

G) Prosthesis surgically inserted in the penis?
❑ No ❑Yes❑During the past 6 months ❑ Further back in time

H) Other aids?
❑ No ❑Yes ❑During the past 6 months ❑ Further back in time

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(Feel free to write comments about aids you have used)

74) **If** you use mechanical aids or medicine to improve the stiffness of your penis, how stiff does your penis become as a result of this?

❑ *Not relevant*, I do not use mechanical aids or medicine in order to improve stiffness of my penis

❑ My penis never becomes stiff enough to have intercourse
❑ My penis becomes stiff enough to have intercourse **fewer** than half of the times I want to have intercourse
❑ My penis becomes stiff enough to have intercourse **more** than half of the times I want to have intercourse
❑ My penis always becomes stiff enough to have intercourse

75) Have you **stopped** using mechanical aids or impotency medicine?

- ❑ *Not relevant,* I have never used mechanical aids or impotency medicine

- ❑ No
- ❑ Yes

76) What do you think about mechanical aids or medicine to improve potency?

(A series of statements appear below, A-G. Put a cross in the box for each question for the answer that best matches your views.)

- ❑ *Not relevant,* I have never used mechanical aids or potency medicine (*Go to question 77*)

A) Too expensive?

- ❑ Nor at all true
- ❑ A little bit true
- ❑ Somewhat true
- ❑ Completely true

B) Mechanical aids or medicine did not improve my erection enough?

- ❑ Not at all true
- ❑ A little bit true
- ❑ Somewhat true
- ❑ Completely true

C) The mechanical aid or medicine caused troublesome side effects?

- ❑ Not at all true
- ❑ A little bit true
- ❑ Somewhat true
- ❑ Completely true

D) Sex with the use of mechanical aids or medicine feels unnatural?

- ❑ Not at all true
- ❑ A little bit true
- ❑ Somewhat true
- ❑ Completely true

E) I was not interested in having sex with the help of mechanical aids or medicines?

- ❑ Not at all true
- ❑ A little bit true
- ❑ Somewhat true
- ❑ Completely true

F) My partner was not interested in having sex with the help of mechanical aids or medicine?

- ❑ Not at all true
- ❑ A little bit true
- ❑ Somewhat true
- ❑ Completely true

G) I am satisfied with my mechanical aids or medicine?

- ❑ Not at all true
- ❑ A little bit true
- ❑ Somewhat true
- ❑ Completely true

Feel free to write your own comments on aids and medication.

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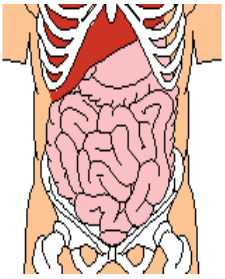
INTESTINES



Questions about your intestinal functioning

We ask you what you have experienced in general ***during the past 6 months***

Put a cross in the box for the alternative that best corresponds with your experience – **only one alternative.**

77) ***During the past 6 months***, have you had loose stools?

- ❑ No
- ❑ Yes, at least once during the past 6 months
- ❑ Yes, at least once a month
- ❑ Yes, at least once a week
- ❑ Yes, at least 3 times a week
- ❑ Yes, at least once a day

78) ***During the past 6 months***, have you experienced hard stools that are difficult to pass (constipation)?

- ❑ No, never
- ❑ Yes, at least once during the past 6 months
- ❑ Yes, at least once a month
- ❑ Yes, at least once a week
- ❑ Yes, at least 3 times a week
- ❑ Yes, at least once a day

79) ***During the past 6 months,*** how often have had to rush to the toilet because of a pressing need to empty the bowels?

- ❑ Never
- ❑ At least once during the past 6 months
- ❑ At least once a month
- ❑ At least once a week
- ❑ At least 3 times a week
- ❑ Yes, at least once a day

80) ***During the past 6 months***, how often have you had blood or mucus in your stools?

- ❑ Never
- ❑ At least 1 time during the past 6 months
- ❑ At least once a month
- ❑ At least once a week
- ❑ At least 3 times a week
- ❑ Yes, at least once a day

81) ***During the past 6 months***, how often have you had pain in your genitals (for example, when you sit down)?

- ❑ No, never
- ❑ Yes, at least once during the past 6 months
- ❑ Yes, at least once a month
- ❑ Yes, at least once a week
- ❑ Yes, at least 3 times a week
- ❑ Yes, at least once a day

82) ***During the past 6 months,*** how often do you experience involuntary fecal leakage?

- ❑ *Not relevant*, I do not experience involuntary fecal leakage

- ❑ At least once during the past 6 months
- ❑ At least once a month
- ❑ At least once a week
- ❑ At least 3 times a week
- ❑ At least once a day

83) What kind of fecal leakage do you have?

- ❑ *Not relevant*, I do not have fecal leakage

A) I leak hard stools ❑No ❑Yes
B) I leak soft stools ❑No ❑Yes
C) I leak normally formed stools ❑No ❑Yes

84) How much fecal leakage do you experience?

- ❑ *Not relevant*, I do not have fecal leakage

- ❑ A little
- ❑ Moderate
- ❑ Very much

85) ***During the past 6 months,*** have you been using incontinence pads or diapers for fecal incontinence?

- ❑ No
- ❑ Yes

86) ***During the past 6 months***, how many times have you changed your incontinence pad or diaper because of fecal leakage during ***a typical day?***

- ❑ *Not relevant*, I use neither an incontinence pad nor a diaper

- ❑ At least once a day
- ❑ At least 2 to 3 times a day
- ❑ At least 3 to 4 times a day
- ❑ At least 5 to 6 times a day
- ❑ At least 7 times a day

87) ***During the past 6 months***, how often have you had problems with flatulence (”farts”) that you could not control?

- ❑ *Not relevant,* I can control my flatulence

- ❑ At least once during the past 6 months
- ❑ At least once a month
- ❑ At least once a week
- ❑ At least 3 times a week
- ❑ At least once a day

88) **If** you were to have to live the rest of your life with the same problem with fecal leakage that you now experience, how would this affect you?

- ❑ *Not relevant,* I do not have fecal leakage

- ❑ It would not affect me at all
- ❑ It would affect me a little
- ❑ It would affect me moderately
- ❑ It would affect me very much

89) **If** you were to have to live the rest of your life with **the same set** of problems with bowel movements that you now have, how would this affect you?

- ❑ *Not relevant,* I have no intestinal problems

- ❑ It would not affect me at all
- ❑ It would affect me a little
- ❑ It would affect me moderately
- ❑ It would affect me very much

90) **Before** you got the diagnosis of prostate cancer had you experienced intestinal problems?

- ❑ No
- ❑ Yes

Feel free to write your own comments about intestinal problems

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DIAGNOSIS AND TREATMENT

Questions about prostate cancer – diagnosis and treatment

Put a cross in the box for the answers that are most appropriate for you

91) When your doctor told you personally that you had prostate cancer was this done in a good way?

- ❑ *Not relevant,* I have never been informed by a doctor
- ❑ No
- ❑ Yes

92) Was someone close to you with you when you got the diagnosis of your cancer?

- ❑ No
- ❑ Yes

93) **If** someone close to you was with you, who was that or who were they?
(Put a cross in the box for the answer to each question)

❑ *Not relevant*, I did not have anyone close to me with me when I got the diagnosis about my cancer

	No	Yes
A) Wife, a partner, a partner not living with me	❑	❑
B) Child	❑	❑
C) Friend	❑	❑
D) Work colleague	❑	❑
E) Another individual	❑	❑

94) **If** you were alone when you got the diagnosis about your cancer would you have preferred to have someone who is close to you with you?

- ❑ *Not relevant,* I was not alone when I got the diagnosis of my cancer.
- ❑ No
- ❑ Yes

95) **How much** information have you received from your doctor?

(A series of questions are listed below. Put a cross in the box for each row that best fits your experience)

	No information	**A little information**	**Quite a lot of information**	**Very much information**
A) About prostate cancer and its course of development?				
B) About treatment alternatives for cancer?				
C) About the side effects (undesirable effect) of the various treatment alternative?				
D) About how the different treatments affect your daily life (your quality of life)?				

96) To what extent have you had the chance to influence the decision about treatment of your cancer?

- ❑ Not at all
- ❑ A little
- ❑ Moderately
- ❑ Very much

97) Are you satisfied with your participation in making the decision about your cancer treatment?

- ❑ No, I would have preferred to have been **less involved** in the decision about my cancer treatment
- ❑ No, I would have preferred taking a **greater** role in the decision about my cancer treatment
- ❑ Yes, I am satisfied

98) Have you chosen to tell someone close to you about your cancer?

- ❑ No
- ❑ Yes

99) **If** you have talked about your prostate cancer who have you told?
(Put a cross in the box indicating your answer to each question)

- ❑ Not relevant, I have not told anyone about my cancer

		No	Yes
A)	Wife (or a partner living with you or living apart from you)	❑	❑
B)	Children	❑	❑
C)	Grandchildren	❑	❑
D)	Close friend/friends	❑	❑
E)	Fellow worker/workers	❑	❑
F)	Another individual	❑	❑

100) If you have chosen **not** to talk about your prostate cancer **or** have only told **a** few close relatives or friends**, what are the reasons for this?**

(A series of follow-up questions appear below A-G. Put a cross in the box for each question indicating which best describes your response)

❑ *Not relevant*, I have told **all** in my environment about my cancer, *(Go to question 101)*

A) Too private? ❑No ❑Yes

B) In order to spare my closest friends or relatives? ❑No ❑Yes

C) I wanted to hide my cancer from my close friends or relatives? ❑ No ❑Yes

D) I myself have not accepted my cancer? ❑ No ❑Yes

E) I believe/believed that people would behave differently toward me if they know/knew that I had cancer? ❑ No ❑Yes

F) I believe/I believed that my career opportunities at my place of employment would become worse? ❑ No ❑Yes

G) Another reason? ❑No ❑Yes

Specifically……...

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(Feel free to write your own comments on the reason)

CHECKUPS

Questions about prostate cancer checkups

Place a cross indicating the alternative or alternatives that correspond best with what you experience.

101) I go in for regular checkups for my prostate cancer.

- ❑ No
- ❑ Yes

102) Before these checkups I feel

(A number of questions appear below, A-E. Place a cross in the box for each questions that best corresponds with your experience.)

		No	**Yes**
A)	Secure?		
B)	Worried that my prostate cancer has returned?		
C)	Worried that the cancer has spread to another place in my body?		
D)	Worried that results from blood tests (among others PSA test) have deteriorated?		
E)	Worried that the physical problems I experience have been caused by my prostate cancer		

CASTRATION

Questions about castration and its significance

103) I have had my testicles surgically removed as one step in the treatment of my prostate cancer.

- ❑ No
- ❑ Yes

104) For my prostate cancer I receive ongoing hormone treatment by injections.

- ❑ No
- ❑ Yes

105) I receive hormone treatment for my prostate cancer consisting only of pills.

- ❑ No
- ❑ Yes

106) I receive ongoing hormone treatment with **both** injections and hormone pills.

- ❑ No
- ❑ Yes

107) I have had **both** an operation to remove my testicles and treatment requiring that I take hormone pills every day.

- ❑ No
- ❑ Yes

108) When you found out that you needed to be treated for your prostate cancer by undergoing an operation removing your testicles or by being giving ongoing hormone treatment, **how did you feel then**?

(A series of questions follow below, A-F. Put a cross in the box for each question that best corresponds with your feelings).

❑ *Not relevant,* I have not been treated by undergoing an operation removing my testicles nor have I received ongoing hormone treatment *(Go to question 109)*

		No	**Yes**
A)	Secure?		
B)	Disappointed?		
C)	Troubled?		
D)	Conscious for the first time of the fact that I really had cancer?		
E)	I regretted that at the time of the diagnosis I was not offered or did not choose another treatment for cancer?		
F)	Satisfied with the treatment that I was offered at the time of the diagnosis of my cancer?		

109) What treatment were you given when your prostate cancer **was discovered**?

(A number of follow up questions appear below, A-D. Put a cross in the box for each question that best corresponds with your treatment.)

A) Periodic control visits	❑ No ❑ Yes
B) Surgical removal of the entire prostate, radical prostatectomy	❑ No ❑Yes
C) Radiation treatment of the prostate	❑No ❑Yes
D) Other treatment	❑ No ❑Yes

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(Feel free to write your own comments about your treatment)

110) Do you notice in your daily life that you have been castrated or given hormone treatment?

❑ *Not relevant,* I have not been castrated or given hormone treatment

❑ No
❑ Yes, a little
❑ Yes, moderately
❑ Yes, very much

111) **How** do you notice that you have been castrated or given hormone treatment?

(A series of questions follow below A-I. Put a cross in a box at the end of every line for the answer that best corresponds with your experience)

❑ *Not relevant*, I have not been castrated or given hormone treatment (*Go to question 112*)

A)	Sweating, "hot flushes"?	❑ No	❑ Yes
B)	Weight gain?	❑ No	❑ Yes
C)	Less physically active than before?	❑ No	❑ Yes
D)	Less active socially than before?	❑ No	❑ Yes
E)	Feeling down more than before?	❑ No	❑ Yes
F)	Less interested in sex than before?	❑ No	❑ Yes
G)	Increase in size of breasts?	❑ No	❑ Yes
H)	More satisfied and content than before?	❑ No	❑ Yes
I)	Anything else you have observed?	❑ No	❑ Yes

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(Feel free to write your own comments on what you have observed)

112) Do you feel that you have changed as an individual since you were castrated or given hormone treatment?

❑ *Not relevant*, I have not been castrated or given hormone treatment

❑ No
❑ Yes, a little
❑ Yes, moderately
❑ Yes, very much

113) **If** you were free to choose, which treatment for your prostate cancer would you choose **today?**

- ❑ *Not relevant*, I am satisfied with my treatment
- ❑ No treatment
- ❑ Ongoing examination and treatment when there is a problem
- ❑ Surgical removal of the entire prostate (radical prostatectomy)
- ❑ Radiation treatment of the prostate
- ❑ Hormone treatment with pills or injections
- ❑ Some other treatment, specifically

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…… (Feel free to describe which kind of treatment)

Feel free to write additional comments on castration and hormone treatment

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HERNIA AND ABDOMINAL PROBLEMS

Men who have their prostate surgically removed have an elevated risk for hernia

114) Have you had or do you have a hernia?

- ❑ No
- ❑ Yes

115) In what year did you first discover that you had a hernia?

- ❑ *Not relevant,* I do not have a hernia

Year …….

116) Where in your body do you have or have you had a hernia?

(Listed below are terms for the specific position of the hernia. Place a cross in the box that is best suited for each of the lines)

- ❑ *Not relevant,* I do not have a hernia

a)	Abdominal hernia?	❑ No	❑ Yes
b)	Scrotal hernia?	❑ No	❑ Yes
c)	Umbilical hernia?	❑ No	❑ Yes
d)	Hernia in a surgical incision?	❑ No	❑ Yes
e)	Other hernia?	❑ No	❑ Yes

Specifically……..

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(Feel free to write your own comments on where your hernia is located)

117) Have you been operated on for a hernia?

- ❑ *Not relevant*, I do not have a hernia

- ❑ No
- ❑ Yes

118) ***During the past six months,*** have you had pain in the lower part of your abdomen?

- ❑ No, never
- ❑ Yes, at least once in the past six months
- ❑ Yes, at least once a month
- ❑ Yes, at least once a week
- ❑ Yes, at least three times a week
- ❑ Yes, at least once a day

119) **When** did you first discover that you had pain in the lower part of your abdomen?

- ❑ *Not relevant*, I do not have any pain in my lower abdomen

Year…….

120) ***During the past 6 month,*** how strong has the pain been in your abdomen when it was at its worst?

(Circle the number that matches your experience)

1……....2…...…3…...….4……..…5…..….6…..…..7
No pain The worst possible pain

121) ***During the past 6 months,*** have you felt the need to take pain medication to deal with pain in your abdomen?

- ❑ *Not relevant*, I do not have any abdominal pain.

- ❑ No
- ❑ Yes

122) Have you been operated on in your abdomen or genitals?

- ❑ No
- ❑ Yes

123) **What** was the operation you had and in **what year** did you have the operation?
(Note only operations in the abdomen and genitals)

❑ *Not relevant,* I have not had any operation in my abdomen or genitals

Year..... Operation ……

Year…… Operation …….....

Year……. Operation ……

Year……. Operation ……

Write your own comments about hernia and abdominal problems

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ILLNESSES, TREATMENT, AND MEDICATION

124) Has your prostate been reduced surgically (transurethral resection, TUR-P)?

- ❑ No
- ❑ Yes

125) Are you being given hormone pills or hormone injections for prostate cancer?

- ❑ No
- ❑ Yes

126) Have your testicles been surgically removed?

- ❑ No
- ❑ Yes

127) Have you had radiation therapy for prostate cancer?

- ❑ No
- ❑ Yes

Have you had one or more of the following illnesses during the past year?

128) High blood pressure? No ❑ Yes ❑

Do you take any medicine for this? No ❑ Yes ❑

Which?.....

129) Congestive heart failure? No ❑ Yes ❑

Do you take any medicine for this? No ❑ Yes ❑

Which?.....

130) Angina? No ❑ Yes ❑

Do you take any medicine for this? No ❑ Yes ❑

Which?.....

131) Heart attack? No ❑ Yes ❑

Do you take any medicine for this? No ❑ Yes ❑

Which?.....

132. Blood clot or bleeding in the brain or the consequences of this? No ❑ Yes ❑

Do you take any medicine for this? No ❑ Yes ❑

Which?.....

133) Any other neurological illness? No ❑ Yes ❑

Do you take any medicine for this? No ❑ Yes ❑

Which?.....

134) Lung problems of any kind? No ❑ Yes ❑

Do you take any medicine for this? No ❑ Yes ❑

Which?.....

135) Ulcers or other stomach problems? No ❑ Yes ❑

Do you take any medicine for this? No ❑ Yes ❑

Which?.....

136) Diabetes? No ❑ Yes ❑

Do you take any medicine for this? No ❑ Yes ❑

Which?.....

137) Psychological problems or illness? No ❑ Yes ❑

Do you take any medicine for this? No ❑ Yes ❑

Which?.....

138) Long lasting pain? No ❑ Yes ❑

Do you take medicine for this? No ❑ Yes ❑

Which?.....

139) Any other cancer? No ❑ Yes ❑

Do you take medicine for this? No ❑ Yes ❑

Which?.....

130) Do you take blood thinning medicine (anticoagulant medicine)? No ❑ Yes ❑

If yes, which?.....

141) Do you have any other illness or medication? No ❑ Yes ❑

Do you take medicine for this? No ❑ Yes ❑

Which?.....

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You have contributed your time and your experience to cancer research.
We express our thanks to you for your participation!

We want once again to remind you that the questionnaire is by law a secret document. The results will be transmitted in such a way that no individual can be identified.

It is easy to mistakenly skip over a question or even a whole page. Feel free to go through the entire questionnaire one last time.

If you have missed an entire section in the questionnaire, may we contact you in order get a supplementary answer?

❑ Yes
❑ No

Identification number:_____

Your questionnaire has been given an identification number to make it possible for us to follow up (track) important findings (information) from the main Scandinavian Study.

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