Localized Prostate Cancer

Results From a Randomized Clinical Trial

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Abstract


The aims of the thesis were to

• explore whether radical prostatectomy is beneficial compared with watchful waiting in survival and disease progression
• find possible effect modifiers
• evaluate a protocol of multiple biopsies and investigate if men with previous benign prostate biopsies are a group at risk for later prostate cancer
• inquire into patients’ and clinicians’ experiences of randomization in order to find out what made this study possible to conduct, and thereby contribute to improve randomization in the future

The background material was a large randomized clinical trial, the Scandinavian Prostatic Cancer Group Study Number 4, or SPCG-4, which was open for inclusion from February 1989 through December 1999. It comprised 695 men in Sweden, Finland and Iceland who had localized prostate cancer and were randomized to either radical prostatectomy or watchful waiting.

After a mean follow-up time of 6.2 years the first analyses, according to intention-to-treat, showed that radical prostatectomy reduced disease specific mortality, risk of metastases and risk of local progression but did not statistically significantly reduce overall mortality.

The second analyses confirmed our earlier findings and furthermore, at ten years, radical prostatectomy also statistically significantly reduced overall mortality. Age appeared as an independent effect modifier that will be further investigated.

A total of 547 men, with a suspicion of prostate cancer that had undergone multiple biopsies, and whose biopsies had benign histology were later compared with the background population to evaluate whether they were a group at risk of developing prostate cancer. Within six years of follow-up, there was no increased risk of prostate cancer.

Patients as well as clinicians used individual strategies to cope with the situation. The randomizing clinician has to understand the patient’s strategy and his expectations in order to individualize the information accordingly.

Keywords: prostate cancer, localized, randomized, biopsies, interviews

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Abbreviations

BPH  Benign prostate hyperplasia
DRE  Digital rectal examination
MRC (PRO6)  Medical research council prostate cancer trial no six
PCPT  Prostate cancer prevention trial
PSA  Prostate specific antigen
RCT  Randomized clinical trial
RP  Radical prostatectomy
SCB  Statistiska centralbyrån
SPCG-4  Scandinavian Prostatic Cancer Group study no.4
T1a-b  Non-palpable tumor detected at transurethral resection of the prostate
T1c  Non-palpable tumor detected through elevated PSA
T2  Palpable tumor within the prostate capsule
TNM  Tumor stage classification according to UICC (1) tumor stage, node, metastases
TRUS  Transrectal ultrasound
TUR-P  Transurethral resection of the prostate
WW  Watchful waiting
Introduction

The present thesis comprises three topics and is connected to the Scandinavian Prostatic Cancer Group study number four (SPCG-4), a randomized clinical trial comparing radical prostatectomy with watchful waiting in localized prostate cancer.

The first and second paper focus on the efficacy of treatment for well- to moderately well differentiated localized prostate cancer, and contain the first and second evaluation of differences in prostate cancer mortality, risk of metastases, risk of local progression and overall mortality between men randomized to radical prostatectomy and those randomized to watchful waiting. In the second paper we further explored three subgroups as possible independent effect modifiers. The third paper focuses on the risk of underdiagnosis of clinical prostate cancer. The fourth paper concerns the randomization process; with interviews where we inquire into how patients and clinicians perceived the randomized study.

Background

Prostate cancer is the most common malignancy in Swedish men, accounting for 35 percent of all male cancer. In 2003 a total of 9035 men were diagnosed with prostate cancer with a mean age at diagnosis of 71 years. The age-standardized incidence has increased by approximately 3.2 percent per year during the last ten years (2). The increase in prostate cancer incidence is mainly due to the intensified diagnostic activity with serum analyses of prostate-specific antigen (PSA) in men with voiding symptoms and an opportunistic screening in men without symptoms. This notion is supported by an almost doubled incidence of PSA-detected, non palpable tumors (T1C) in the last five years (fig. 1). The cumulative probability to be diagnosed with prostate cancer for a Swedish man is 3.6 percent, 11 percent and 20.2 percent before the age 65, 75 and 85 years, respectively (2).

Prostate cancer mortality in Sweden represents five percent of all causes of death in men and 20 percent of male cancer deaths. The age-standardized mortality from prostate cancer is the same as ten years ago, but the number of deaths from prostate cancer has increased by 10 percent (2138 deaths in 1992 and 2352 death in 2002) (3). This increase in prostate cancer deaths is explained by the dramatic decrease in coronary deaths in the increasingly
elderly population (3); more men live long enough to die from their prostate cancer.

One major concern in prostate cancer is the large discrepancy between histological evidence of the disease, clinically detected and mortality from the disease. The estimated risk for a US man 50 years old, with a life expectancy of 25 years, of microscopic, clinical and fatal prostate cancer is 42 percent, 9.5 percent and 2.9 percent respectively (4). Thus, if we strive to detect all histological cancers we will end up diagnosing a high amount of non-fatal cancers.

Digital rectal examination (DRE), prostate-specific antigen (PSA) and transrectal ultrasound (TRUS) are important diagnostic tools for selecting patients who should be further investigated with prostate biopsies. Histological or cytological evidence is mandatory for the diagnosis, and the golden standard is histology from TRUS guided core biopsies. The diagnostic tests have limits, mainly due to low specificity with the consequence that a number of men are unnecessarily worried and referred to urologist for further investigation with prostate biopsies. When it comes to diagnosis there are two major problems. Firstly, the number of false negative biopsies is high, since the biopsies only sample around 1/100 000 of the prostate. Secondly, the risk of detecting insignificant tumours if the number of biopsies is increased or the procedure repeated too many times. However, nobody knows the optimal number of biopsies or how often they should be repeated, if negative. The denotation “insignificant tumours” can be used in different

Figure 1. Proportion of T1c category in prostate cancer, 1999 – 2003
ways but is in this thesis defined according to Stamey, as small-volume cancers (less than 0.5 cc) (5).

TRUS-guided core biopsies are the golden standard for diagnosing prostate cancer. The random systematic biopsies have been standard ever since Hodge and colleagues in 1989 showed its superiority compared with lesion-directed (6). They used a standardized protocol with six biopsies (sextant protocol) that became widespread and remained standard for more than a decade. However, a number of studies have investigated whether the sextant protocol is optimal (7, 8). Stroumbakis et al. elegantly evaluated the sextant protocol by repeating the sextant biopsies in men, already diagnosed with prostate cancer, who were undergoing radical prostatectomy. They found 30 percent of the men to have false negative biopsies (9).

An increased number of cancers are detected by extending the sextant biopsy protocol (8) and by using more lateral biopsies (10). Furthermore, repeated biopsies, after previous benign biopsies, detect prostate cancer the second, third and even the fourth time. Djavan et al. asked in their title “Prospective evaluation of prostate cancer detected on biopsies 1, 2, 3 and 4: When should we stop?” (11). That question can only be answered when different biopsy protocols have been evaluated with long-term follow up to estimate the risk of undetected fatal cancers.

The high proportion of false negative biopsies has led to the recommendation in the European Association of Urology guidelines to repeat biopsy in all patients with a consistently elevated PSA (12). However, with extensive biopsy protocols and repeated biopsies one could even come close to the high autopsy incidence, where small foci of histological cancer are detected already in the third and fourth decade of age (27 percent) and continues to increase with increasing age (13). In the recently published Prostate Cancer Prevention Trial (14), 25 percent of the men in the placebo arm (men, with no clinical or biochemical suspicion of prostate cancer at allocation) were diagnosed with prostate cancer within seven years of follow-up. With this background it is somewhat surprising that there have been no studies on the long-term incidence of clinically detected prostate cancers after previous negative biopsies.

Treatment & options for localized prostate cancer

The diagnostic and curative treatment activity has increased each year in most Western countries the last decade despite lack of evidence from any randomized trial that curative treatment is beneficial compared with watchful waiting. In Sweden the number of radical prostatectomies has more than tripled in the last five years (502 in the year 1998 and 1818 in the year 2003) and the number of men who underwent curative radiation therapy increased from 342 to 959 during the same time period (15). In the US alone, an estimated 80 000 radical prostatectomies are carried out each year.
The two currently accepted forms of treatment with curative intent for prostate cancer are radical prostatectomy and radiotherapy. However, curative treatments are controversial and have been hotly debated during the last decades since there has been limited knowledge of how these treatments compare in terms of survival as well as quality of life. The majority of studies that have been conducted are observational in design and consequently all sorts of bias might be present. Treatment comparisons are also inappropriate since the patient characteristics are so diverse, for instance patients undergoing surgery are usually younger and have less co-morbidity than men in watchful waiting or radiotherapy. In the literature there are only two randomized clinical trials (RCT) comparing treatments for localized prostate cancer. However, due to methodological drawbacks, they could not lead to any treatment recommendations. One compared radical prostatectomy and radiotherapy in men with localized prostate cancers in the early 1980s (16). The number of patients recruited was small (97), and there was no intention-to-treat analysis. The authors concluded that radical prostatectomy led to a better outcome, but they had treatment failure as primary endpoint and long-term outcome was not evaluated. The other RCT compared radical prostatectomy with watchful waiting (17, 18). This study also had a number of methodological drawbacks with small numbers of patients and insufficient statistical power to compare cancer-specific survival between groups. In a pooled analysis from six nonrandomized studies of 828 men in watchful waiting for clinically localized prostate cancer, Chodak et al. reported ten-year disease-specific survival rates of 87 percent (19). Two more recently published large observational studies (20) (21) reported a disease-specific ten-year survival of 75 and 70 percent, respectively, following watchful waiting, 67 and 62 percent following radiation therapy and 86 and 90 percent following radical prostatectomy.

Radical prostatectomy
Radical prostatectomy was for the first time carried out in 1905 by Young with a perineal approach but the surgical procedure was experienced more dangerous than the disease. In 1947 Millin was the first to describe radical retropubic prostatectomy and in the 1980s with the introduction of a nerve sparing technique (22), which reduced adverse effects, radical prostatectomy became widely used. The adverse effects with erectile dysfunction and incontinence after open radical prostatectomy vary in different studies but range from 30-80 percent erectile dysfunction, and 10-45 percent incontinence and are strongly age-dependent (23-25). More lately the laparoscopic and recently the robot-assisted radical prostatectomy were introduced. So far neither laparoscopic nor robotic radical prostatectomy has been compared with open radical prostatectomy within a randomized study. In a prospective study of robotic radical prostatectomy Menon and colleagues reported continence rates of 94 percent at three months after surgery (26). After radical
prostatectomy, 5-, 10- and 15-year biochemical recurrence-free survival rates were 84%, 72% and 61%, respectively (27).

Radiation therapy
Radiation therapy started as a curative treatment for prostate cancer in 1960, with the introduction of high energy X-ray, but with unacceptable high doses in adjacent tissues as the rectum and bladder. Since then the radiotherapy techniques have changed and radiotherapy has been claimed to be equal to radical prostatectomy in 10-year outcome (28). However, there is no evidence from any randomized study supporting this hypothesis and a randomized study is required before a conclusion can be made. Most studies are observational and usually retrospective, with 10 year survival ranging from 22 to 86 percent (28, 29). The radiotherapy is fast evolving with a number of different techniques introduced, i.e. brachytherapy with combined external and internal radiation, seed implants and 3D conformal radiation. This heterogeneity adds to the difficulties in comparing radiation therapies with surgery or watchful waiting. In a study by Little et al. the reported adverse effects three years after external radiation therapy were erectile dysfunction (41-55%), incontinence (6-35%), and bowel dysfunction (30-35%) dominated by urgency of bowel movement (19-26%), and rectal bleeding was common (30 percent)(30).

Watchful waiting
Watchful waiting or conservative management, also referred to as expectant management, implies that the patient is followed up but receives no curative therapy. If he develops local progression with obstructive symptom he is treated with TUR-P, likewise if there is disease progression with metastases hormonal treatment is indicated. Watchful waiting has been an option for older men with well- or moderately well differentiated tumors and for men with a life expectancy less than 10 years. One argument for this conservative approach is the excellent 10-year disease-specific prognosis demonstrated in a pooled analysis (of six non-randomized studies) where only 13 percent died of prostate cancer within ten years. Two different cohorts in watchful waiting are from Sweden. Patients from both cohorts show similar 10-year disease-specific survival as in the pooled analyses for men with well- to moderately well differentiated tumors (31) (32). In the study by Johansson et al. the relative risk to die from prostate cancer increased 58 times for patients with poorly differentiated tumors (high graded, Gleason score 8-10, WHO grade III) (31). However, only a small amount of prostate cancers are poorly differentiated (high graded); in Sweden only five percent of all men less than 75 years, diagnosed with prostate cancers have Gleason score 8-10 (15).

The majority of men diagnosed with prostate cancer have so called “good risk” prostate cancers defined by Klotz as Gleason score of 6 or less and PSA<10-15 and tumor stage T1C-T2a (33) and the majority of these tumors
will never cause disease-specific morbidity or mortality. Unnecessary curative treatment is a cost for both patients and society. However, since it cannot be predicted which tumors will progress and cause morbidity and mortality of these so called “good risk” prostate cancers, a modified version of watchful waiting is becoming more widely used where the patient is closely followed and, if signs of disease progression, offered curative therapy. This active monitoring or active surveillance strategy is currently investigated in a randomized clinical trial, the PROTECT study (34).

Randomization

Randomization is accepted as the best research method for minimizing selection bias and to reduce known and unknown confounders when comparing treatments, with differences in patient characteristics evenly distributed between the groups. However, recruitment to randomized studies of both patients and clinicians is difficult involving a risk of breaking studies in advance and subsequently making them invalid due to too low statistical power (35). One recent example is the Medical Research Council Prostate Cancer trial no six (MRC, PRO 6) that randomized patients to radiation therapy, watchful waiting or radical prostatectomy. The patient should be randomized between two of the three treatments in order to give an element of freedom for patient’s or clinician’s preferences. However, this did not succeed and the study was recently discontinued having recruited only 35 of the planned 1800 patients.

Difficulties with information, unwillingness to let chance decide treatment and patient’s preference of a particular treatment have been found as possible obstacles among patients (35). Patients with severe and potentially life-threatening diseases such as cancer are more vulnerable than patients with benign diseases and possibly more reluctant to accept randomized treatment. Among doctors, perception of an impaired patient-doctor relationship, lack of time, doctors’ reluctance to recruit severely ill patients, feeling of personal responsibility should the patient not benefit from the allocated treatment and loss of clinical autonomy, have all been suggested as important problems (35). Information from successfully conducted randomized trials is scarce which motivated our investigation of these issues. The aim was to facilitate participation of both patients and clinicians in the future.
Aims of the studies

I. To investigate if radical prostatectomy reduces prostate cancer mortality, lowers the risk of metastasis and local progression and affects overall mortality.

II. To investigate if radical prostatectomy affects overall mortality and to do subgroup analyses of possible independent effect modifiers

III. To investigate the incidence of prostate cancer after negative TRUS guided multiple biopsies and to estimate the sensitivity of TRUS-guided multiple biopsies.

IV. To investigate patients’ and clinicians’ experiences of randomization with the aim of facilitating future trial participation.
Patients and Method

Paper I & Paper II

From 1989 to 1999, after approval from the regional ethic committees, 14 centers in Sweden, Finland and Iceland, recruited 698 men, with a life expectancy of more than ten years and newly diagnosed untreated localized prostate cancer, to a randomized trial comparing radical prostatectomy with watchful waiting. Inclusion criteria were age less than 70 years, well or moderately well differentiated tumors, clinical stage T1b–T1c (24 percent) and T2 (76 percent), PSA less than 50 ng/ml and no evidence of metastases on bone scan (table 1).

For men in the radical prostatectomy group surgery started with a pelvic lymph-node dissection and if there were no metastases in frozen section the operation was continued with a retro-pubic radical prostatectomy. The men in the watchful-waiting group received no immediate treatment in addition to the TUR-P some already had received. In the radical-prostatectomy group, systematic hormonal treatment was recommended in case of symptomatic and histologically confirmed tumor recurrence. In the watchful-waiting group TUR-P was the first treatment for local progression with obstructive voiding symptoms. Systemic hormonal treatment was recommended in both groups if metastases were verified.

All patients were followed up twice a year during the first two years and then annually with a clinical examination, blood samples for hemoglobin, creatinine, PSA and alkaline phosphatases levels. A bone scan was carried out annually and during the first two years also a chest X-ray. All records were reviewed for the first analysis at the end of year 2000, and for those who had died; an extended search for medical information was made. This procedure was repeated after year 2003 for the second analysis. An independent end-point committee determined cause of death based on standardized extractions from the patient files where treatment group was not revealed. They classified all deaths in one of six categories. 1, death from prostate cancer; 2, death from other main cause but with distant metastases, regardless of local status; 3, death from other cause, without distant metastases, but with local progression; 4, death from other cause with unknown status of distant metastases but with local progression; 5, death without evidence of tumor recurrence; and 6, death from other cause but within the first month after randomization. Four main end points were used for the analysis:
Disease-specific mortality, occurrence of distant metastasis, occurrence of local progression and overall mortality. All analyses were carried out in accordance with the intention-to-treat principle.

Table 1. Base-line characteristics of the 695 at inclusion

<table>
<thead>
<tr>
<th></th>
<th>Radical prostatectomy</th>
<th>Watchful waiting</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N 347</td>
<td>(N 348)</td>
</tr>
<tr>
<td>Age mean, years (SE)</td>
<td>64.7 +/- (5.1)</td>
<td>64.7 +/- (5.1)</td>
</tr>
<tr>
<td>PSA mean, ng/ml</td>
<td>13.5</td>
<td>12.3</td>
</tr>
<tr>
<td>Tumor stage* (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1b</td>
<td>33 (9.5)</td>
<td>50 (14.4)</td>
</tr>
<tr>
<td>T1c</td>
<td>43 (12.4)</td>
<td>38 (10.9)</td>
</tr>
<tr>
<td>T2</td>
<td>270 (77.8)</td>
<td>259 (74.4)</td>
</tr>
<tr>
<td>Unknown</td>
<td>1 (0.3)</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>WHO Grade (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>168 (48.4)</td>
<td>166 (47.7)</td>
</tr>
<tr>
<td>2</td>
<td>178 (51.3)</td>
<td>182 (52.3)</td>
</tr>
<tr>
<td>Unknown</td>
<td>1 (0.3)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Gleason score ** (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2-4</td>
<td>45 (13.0)</td>
<td>46 (13.2)</td>
</tr>
<tr>
<td>5-6</td>
<td>165 (47.5)</td>
<td>166 (47.7)</td>
</tr>
<tr>
<td>7</td>
<td>77 (22.2)</td>
<td>82 (23.6)</td>
</tr>
<tr>
<td>8-10</td>
<td>14 (4.0)</td>
<td>21 (6.0)</td>
</tr>
<tr>
<td>Unknown ***</td>
<td>46 (13.3)</td>
<td>33 (9.5)</td>
</tr>
<tr>
<td>Mode of detection (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Screening</td>
<td>18 (5.2)</td>
<td>18 (5.2)</td>
</tr>
<tr>
<td>En passant</td>
<td>87 (25.1)</td>
<td>91 (26.1)</td>
</tr>
<tr>
<td>TUR-P</td>
<td>40 (11.5)</td>
<td>56 (16.1)</td>
</tr>
<tr>
<td>Symptoms</td>
<td>152 (43.8)</td>
<td>138 (39.7)</td>
</tr>
<tr>
<td>Other</td>
<td>49 (14.1)</td>
<td>44 (12.6)</td>
</tr>
<tr>
<td>Unknown</td>
<td>1 (0.3)</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>PSA, ng/ml (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;4</td>
<td>43 (12.4)</td>
<td>63 (18.1)</td>
</tr>
<tr>
<td>4&lt;7</td>
<td>60 (17.3)</td>
<td>60 (17.2)</td>
</tr>
<tr>
<td>7-10</td>
<td>68 (19.6)</td>
<td>67 (19.3)</td>
</tr>
<tr>
<td>&gt;10-20</td>
<td>100 (28.8)</td>
<td>95 (27.3)</td>
</tr>
<tr>
<td>&gt;20</td>
<td>69 (19.9)</td>
<td>60 (17.2)</td>
</tr>
<tr>
<td>Unknown</td>
<td>7 (2.0)</td>
<td>3 (0.9)</td>
</tr>
</tbody>
</table>

*T1b indicates an incidental histologic finding in more than 5 percent of tissue resected (in 1978, this was classified as stage T0d); stage T1c indicates a tumor identified by needle biopsy because of elevated serum prostate specific antigen levels (in 1978 this classification did not exist). In palpable carcinoma confined to the prostate, T2 indicates a tumor confined within the prostate (in 1978, this was classified as T1 or T2).

** This score was assigned during histopathological review; Gleason score range 2-10 where 10 is most severe

*** Diagnosis was made by cytologic examination only in 55 patients; a biopsy specimen could not be retrieved in 24 patients
Three men were excluded; two due to wrong diagnosis (one from each group) and one man with a prior cancer diagnosis (from the radical prostatectomy group). In all, 347 men randomized to radical prostatectomy and 348 men randomized to watchful waiting were included. The characteristics at inclusion were similar in the two study groups and most of the men had palpable tumors (table 1).

Statistics, Paper I
We calculated cumulative cause-specific hazard rates with the use of the negative log transformation of the Kaplan-Meier estimator for each endpoint. The 95 percent confidence intervals for the differences between the point estimates at five and eight years for the cumulative hazard rates for the study groups are reported (table 2). The log-rank test was used for comparisons between groups; a P value of less than 0.05 (two-sided) was considered to indicate statistical significance. Relative hazards with 95 percent confidence intervals were estimated with the use of Cox proportional-hazard models. The influence of any imbalance in age, tumor stage, Gleason score as determined by the review, or PSA levels was checked in a multivariate Cox model for disease-specific mortality. SAS statistical software was used for all calculations.

Statistics, Paper II
From a Cox proportional-hazard model relative risks (with 95% confidence intervals) and differences in cumulative incidence (with 95% confidence intervals) were estimated and used as effect measures for each endpoint. Gray’s test (10) was used to test the hypothesis that there was no difference in cumulative incidence between the treatment groups, with a P-value of less than 0.05 (two sided) to indicate statistical significance. Cumulative incidence (integrated sub-density) rather than cumulative hazard (integrated sub-hazard) was used to acknowledge the influence of competing risks (11).

Subgroup analyses
Effect modification was first investigated through simple stratified analyses. For all endpoints, three pre-specified subgroup analyses were carried out: 1/ analysis by age at diagnosis, under 65 years compared with 65 years and older (since mean age in the study was 65 years); 2/ analysis by PSA at diagnosis, lower than or equal to 10 ng per milliliter compared with level higher than 10 ng per milliliter; 3/ analysis by Gleason score in the pre-randomization biopsies, lower than 7 compared with equal to or higher than 7. Any modification by subgroup of the effect of radical prostatectomy was tested by a Cox proportional-hazard model including an interaction term between subgroup category and randomization group. In a second step, we explored the interaction by including the possible effect modifier (age, PSA...
level at diagnosis or Gleason score) as continuous variable. When there was an indication of effect modification, we further controlled for PSA level at diagnosis, tumor stage, Gleason score and year at inclusion by adding these as additional covariates in the Cox proportional hazards model. We further made a regression model of the effect modifier (36).

Paper III

Men with elevated PSA and/or abnormal DRE, who were potential candidates for the SPCG-4 study, were referred to a radiologist (MN), for an extensive investigation with TRUS and multiple biopsies. All men whose biopsies were negative for cancer (578) were included in the cohort after approval from the regional ethic committee and compared with an age-standardized background population.

According to the biopsy protocol, defined by one of the authors (MN), systematic biopsies were taken from four standardized locations in each lobe (fig.3). Additional biopsies were taken from hypo- and hyper-echoic lesions, as well as areas where there was a loss of a distinct border between the peripheral and transition zone. A total of 5155 biopsies were taken with a mean of nine in each patient (range 6-14).

We linked our cohort to the Swedish Cancer Register to find the number of patients eventually diagnosed with prostate cancer and obtained a follow up of our cohort through December 2001. We also used the register to calculate the expected number of new prostate cancers for an age matched background population in Uppsala County. To ensure that there was no increased mortality due to undiagnosed prostate cancer in the cohort, we further registered the number of deaths in our cohort and compared this with expected mortality calculated from the matched background population.

Excluded from the cohort of 578 men were 29 men that had a previous cancer diagnosis, and therefore were deemed to have false negative TRUS-guided biopsies and two men that were rebiopsied within six month due to high suspicion of cancer already at the initial biopsy. In all, 547 men without evidence of prostate cancer were included in the cohort with a mean age at biopsy of 64 years.

Statistics, Paper III

The standardized incidence ratio (SIR) was calculated as the ratio of the observed to expected cases in every age and calendar year group using data from the Swedish Cancer Register and Uppsala County as reference popula-
tion (37). The SAS software program was used for calculation of the SIR and Brynard’s approximation was used to evaluate statistical significance as well as the 95 percent confidence interval (38). The relative survival was also calculated as observed to expected survival and the five-year sensitivity of TRUS-guided multiple biopsies was calculated using the 1459 men in the entire database.

Paper IV

In the year 2000, after approval from the regional ethics committees, nine patients (five participants and four non-participants in the SPCG-4 study) and five clinicians randomizing for the SPCG-4 study in Sweden were selected for interviews. The patients were selected from the population of men asked to participate in the SPCG-4 study at two major Swedish randomization centers between 1992 and 1998, with variation concerning: age, time from diagnosis, treatment and participating or not in the SPCG-4 study. The clinicians were selected in order to ensure variation in relation to number of recruited patients and hospital size.

The interviews were conducted by a cancer specialist nurse with psychotherapy training, who used a semi-structured checklist of topics. The interviews lasted for 40-80 minutes, were audio-taped, and transcribed verbatim and analyzed using content analysis (39). The analyzing researcher listened to the tapes, read through the transcriptions several times, picked out statements that corresponded to the study’s purpose, grouped statements that concerned the same issues in categories and labeled them.
Results

Paper I
At the end of year 2000, after a mean follow-up time of 6.2 years, 25 men in the radical-prostatectomy group had not undergone surgery and 30 men were treated with curative intent in the watchful-waiting group. During follow-up, 115 men died, 53 in the radical-prostatectomy group and 62 in the watchful-waiting group. In all, 47 died of prostate cancer, 16 in the radical-prostatectomy group and 31 in the watchful-waiting group. Deaths from other causes were 37 in the radical prostatectomy group and 31 in the watchful-waiting group.

The cumulative hazard functions for death from prostate cancer and the corresponding five-year and eight-year point estimates showed a difference that increased over time.

Disease-specific mortality:
The absolute difference was 2.0 percent (95 percent confidence interval, -0.8 to 4.8) at five years and 6.6 percent (95 percent confidence interval, 2.1 to 11.1) at eight years in favor of radical prostatectomy. The relative hazard for men assigned to radical prostatectomy compared with expectancy was 0.50 (95 percent confidence interval, 0.27 to 0.91; P= 0.02).

Distant metastases:
The cumulative hazard analysis showed similar results in the two groups at five years but an absolute difference at eight years of about 14 percent in favor of radical prostatectomy (P=0.03) and the relative hazard was 0.63 (95 percent confidence interval, 0.41 to 0.96).

Local progression:
The cumulative hazard rate of local progression was statistically significantly different in the two groups already at five years in favor of radical prostatectomy and the relative hazard at eight years was 0.31 (95 percent confidence interval 0.22 to 0.44)
Overall mortality:
The absolute difference at eight years was 6.3 percent in favor of radical
prostatectomy and the relative hazard of death from any cause was 0.83 (95
percent confidence interval, 0.57 to 1.2; P=0.31).

Radical prostatectomy significantly reduced disease-specific mortality,
risk of metastases and risk of local progression. However, there was no sta-
tistically significant difference for overall mortality.

Paper II
At the end of year 2003, 21 men randomized to radical prostatectomy had
not undergone surgery, whilst 42 men in the watchful-waiting group had
undergone curative treatment.

During follow-up, 30 men in the radical-prostatectomy group died of
prostate cancer compared to 50 in the watchful-waiting group. As for causes
of death other than prostate cancer, the number was similar in the two groups
(53 versus 56). Considering all causes of death, 23 more men died in the
watchful-waiting group.

Disease-specific mortality:
The difference between the two groups in cumulative incidence of death
from prostate cancer was 5.4 percent (95 percent confidence interval, -0.3-
11.0) after ten years in favor of radical prostatectomy. The relative risk for
men assigned to radical prostatectomy compared with watchful waiting was
0.56 (95 percent confidence interval, 0.36-0.88) (table 2).

Distant metastases:
The absolute risk reduction was after ten years of follow-up 10.2 percent (95
percent confidence interval, 3.1-17.2) in the radical-prostatectomy group,
corresponding to a relative risk of 0.60 (95 percent confidence interval, 0.42-
0.46) (Table 2).

Local progression:
The absolute reduction after 10 years was 25.1 percent (95 percent confi-
dence interval, 17.6-32.6), corresponding to a relative risk of 0.33
(95 percent confidence interval, 0.25-0.44) in the radical-prostatectomy group
(Table 2).

Overall mortality:
The absolute risk reduction after ten years was 5.1 percent (95 percent confi-
dence interval, -2.8-13.0) corresponding to a relative risk of 0.74 (95 percent
confidence interval, 0.56-0.99) after randomization to radical prostatectomy (Fig.2, Table 2).

Other treatments:
Hormonal treatment was less common in the radical-prostatectomy group (110 vs. 177 patients). The mean time to introduction of hormonal treatment was 4.5 and 4.8 years for the radical-prostatectomy group and watchful-waiting group, respectively. Palliative radiation was also less common in the radical-prostatectomy group (29 vs. 38) as well as laminectomy (4 vs. 11).

Figure 2. Cumulative incidence of death
Table 2. Cumulative incidence and differences between the two groups

<table>
<thead>
<tr>
<th>Disease specific mortality</th>
<th>Radial prostatectomy</th>
<th>Watchful waiting</th>
<th>Difference five- and ten-year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease specific mortality</td>
<td>Total no. of events</td>
<td>30</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>5-years follow-up, % (95% CI)</td>
<td>2.3 (1.2-4.6)</td>
<td>4.3 (2.6-7.1)</td>
</tr>
<tr>
<td></td>
<td>10-years follow-up, % (95% CI)</td>
<td>9.6 (6.5-14.2)</td>
<td>14.9 (11.2-19.8)</td>
</tr>
<tr>
<td>RR (95% CI)</td>
<td>P=0.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Distance metastases</td>
<td>Total no. of events</td>
<td>50</td>
<td>79</td>
</tr>
<tr>
<td></td>
<td>5-years follow-up, % (95% CI)</td>
<td>8.1 (5.7-11.6)</td>
<td>9.8 (7.1-13.5)</td>
</tr>
<tr>
<td></td>
<td>10-years follow-up, % (95% CI)</td>
<td>15.2 (11.4-20.3)</td>
<td>25.4 (20.4-31.5)</td>
</tr>
<tr>
<td>RR (95% CI)</td>
<td>P=0.004</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Local progression</td>
<td>Total no. of events</td>
<td>64</td>
<td>149</td>
</tr>
<tr>
<td></td>
<td>5-years follow-up, % (95% CI)</td>
<td>8.1 (5.7-11.5)</td>
<td>27.2 (22.8-32.3)</td>
</tr>
<tr>
<td></td>
<td>10-years follow-up, % (95% CI)</td>
<td>19.2 (15.0-24.6)</td>
<td>44.3 (38.8-50.5)</td>
</tr>
<tr>
<td>RR (95% CI)</td>
<td>P&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall mortality</td>
<td>Total no. of events</td>
<td>83</td>
<td>106</td>
</tr>
<tr>
<td></td>
<td>5-years follow-up, % (95% CI)</td>
<td>7.8 (5.4-11.2)</td>
<td>9.8 (7.1-13.5)</td>
</tr>
<tr>
<td></td>
<td>10-years follow-up, % (95% CI)</td>
<td>27.0 (21.9-33.1)</td>
<td>32.0 (26.9-38.2)</td>
</tr>
<tr>
<td>RR (95% CI)</td>
<td>P=0.04</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Subgroup analyses:

We found that the benefit of radical prostatectomy on disease-specific mortality differed by age group, but not by PSA level at diagnosis, or Gleason score. A Cox model containing randomization group, age split in two groups and an interaction term showed a statistically significant interaction between age group and randomization group. The cumulative incidence of death from prostate cancer in men less than 65 years in the watchful-waiting group was markedly higher than for all other subgroups (figure 3). Men older than 65 years had the same low cumulative incidence of prostate cancer mortality as men less than 65 years who had undergone radical prostatectomy. This is also shown in the cumulative regression analysis (fig.4).
**Figure 3.** Cumulative incidence of prostate cancer death for different age categories

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>2</th>
<th>4</th>
<th>6</th>
<th>8</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Years</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Probability</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>No. At Risk</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radical prostatectomy Age &lt; 65</td>
<td>157</td>
<td>156</td>
<td>151</td>
<td>135</td>
<td>110</td>
<td>66</td>
</tr>
<tr>
<td>Watchful waiting Age &lt; 65</td>
<td>166</td>
<td>161</td>
<td>153</td>
<td>128</td>
<td>96</td>
<td>56</td>
</tr>
<tr>
<td>Radical prostatectomy Age ≥ 65</td>
<td>190</td>
<td>187</td>
<td>181</td>
<td>149</td>
<td>100</td>
<td>52</td>
</tr>
<tr>
<td>Watchful waiting Age ≥ 65</td>
<td>182</td>
<td>180</td>
<td>173</td>
<td>151</td>
<td>102</td>
<td>48</td>
</tr>
</tbody>
</table>
Radical prostatectomy conveys a statistically significant reduction in disease-specific mortality, overall mortality, risk of metastases and risk of local progression. The absolute risk reduction in mortality is modest within ten years while the reduction of metastases and local tumor progression is substantial. Age was found to be an independent effect modifier and must be further investigated.

**Paper III**

We found eleven men diagnosed with prostate cancer in our cohort after a median observation time of six years. The expected number during this time in an age-standardized male population was 14.6 which resulted in an SIR of 0.8 (95% CI 0.4 to 1.2). Only two of 547 (0.3%) men in the cohort were diagnosed with advanced disease. The sensitivity of TRUS with multiple biopsies as evaluated in a five-year follow-up was 95.7% (95% CI 94.2% to

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*Figure 4. Age effect on prostate cancer mortality in the radical prostatectomy group and watchful waiting group*
96.8%). The relative survival was more than one hundred percent indicating a selection of men more healthy than average and deemed fit for surgery.

Figure 5. Flow diagram of all biopsied men in the database.

Conclusion: Among men with suspicion of prostate cancer who are examined with multiple biopsies (mean 9) and whose TRUS-guided biopsies are negative for cancer, the incidence of clinical prostate cancer is not increased within six years compared with an age matched male population. The five-year sensitivity of the extended protocol was high.
Paper IV

We found four categories of importance for our study aim for both patients and clinicians

1. Treatment preference
The patients’ attitudes varied from no set treatment preference at all to a strong preference. Those with a strong treatment preference had commonly had previous contact with prostate cancer through friends or relatives.

   “I didn’t know anything...you have to trust the doctor who’s taking care of you.”

   “I had a neighbor who was suffering terribly before he died, so for me it wasn’t difficult to opt for surgery.”

2. Decision making
The patients used different strategies for their decisions. Some of them saw any medical decision as the doctor’s responsibility. Others found it impossible to let chance decide their treatment or were reluctant to let someone else decide, they wanted to be responsible for their own decision.

   “Well since I didn’t know anything I pretty much told him it was up to him to decide. After all he knows more than I do.”

   “In the end I can only trust my own judgment.”

3. Attitudes towards research
The patients’ attitudes ranged from considering research very important and an altruistic willingness to be part of it to feeling that patients were used as guinea pigs for the doctors’ own benefit.

   “If it can make it easier for somebody in the future, count me in.”

   “It is for the doctors’ interest and not for mine.”

4. The randomization process
All patients kept well in mind the information of the different treatment possibilities. However, their memories about the randomization process varied from no memories at all to a vivid recollection of the information received many years ago.

   “They just asked me if I wanted to participate. However I don’t recall much about it since I did not spend much time thinking about it.”
"There were some guys in Stockholm who were supposed to make the decision. I didn’t like that. They had one group that would get surgery and one group that did not.”

1. Decision making
The clinicians’ attitudes varied from the position that ultimately the patient is, and should be, left to make his own decision, to the view that in a fundamental way the doctor always, depending on how he chooses to inform the patient, influences and steers the patient’s choice.

“It is always the doctor who makes the decision depending on how he informs the patient.”

“If the patient makes the decision he’s more content and cannot blame anybody else.. but it can also be harder to have decided something that turned out badly.”

2. Strategies
The clinicians had developed individual strategies to increase the patients’ acceptance of randomization. Early mentioning of the trial to the patients was important in order to accustom them to the study. Sometimes a second clinician was present at the consultation for discussion on treatment options in the hope of helping the patient feel more confident and open to considering randomization. Some clinicians used extra consultations, away from stressful surroundings with the aim of giving the patient, and often his spouse, additional time for reflection. Careful wording when describing the randomization process was thought to decrease the risk for misunderstanding. Some doctors took care to individualize the information, based on the patient’s preformed opinion in order to lead him in the direction of equipoise. Informing about the study’s potential implications for future patients was thought to increase awareness in the patients’ of their own contribution. The clinicians avoided reminding the included patients of the randomization procedure in the hope of reducing feelings of randomness. Instead, they actively strengthened their trust in the allocated therapy.

“In this situation it’s important to make them understand that the three alternatives are equivalent and if a patient preferred surgery I stressed out the risks with surgery. The point is to get the patient neutral not until then is he fully informed and at the same level as current knowledge.”

“We were usually two urologists who informed about the disease and the study and evaluated the tumor stage. We perceived it helpful and I think the patients experienced it as something positive that they were so well taken care of”
3. Attitudes towards research
The attitudes ranged from clinical studies being extremely important to clinical studies being a routine part of the job. All clinicians believed the research question had to be relevant, the time consumed reasonable and the paperwork kept to a minimum. They all stressed that the principal issue was always the individual patient and his well-being.

“A study that is accepted on all levels and is really important and where the hospital has agreed to partake, then your own opinion is subordinate.”

“I think that in order to learn more we need to do trials, otherwise we might do the wrong things for 50 years without knowing it.”

4. Equipoise
The SPCG-4 study was open for inclusion over a period of ten years, and during this time diagnostic procedures and treatments changed. Several clinicians expressed difficulty in maintaining equipoise, whether having initially had a preference for surgery or watchful waiting, or having been neutral. One strategy that facilitated the preservation of equipoise was the regular meetings with the SPCG-4 study group, meetings that also served as a motivation booster for the attendant.

“Unconsciously you get influenced during the years passing.”

“I have tried to be active and participate in all meetings with the study group and steering committee, for different reasons, but the most important was to maintain my interest and motivation for the study and be updated on the current discussion.”

➢ To establish a good platform for randomization the clinician needs to know about the patient’s individual strategy and expectations to individualize information accordingly. The strategies developed by the clinicians were perceived as helpful and could be tried nested in an intervention study.
General Discussion

This thesis has explored different aspects of localized prostate cancer as well as the randomized study procedure used. In the first paper we found that radical prostatectomy significantly reduced disease specific mortality, risk of metastases and local progression but did not statistically significantly reduce overall mortality. In the second paper after another three years of follow up, we found that at ten years, radical prostatectomy significantly reduced all endpoints above including overall mortality. We further found in a subgroup analyzes that age was an independent effect modifier. This finding however, must be further investigated with longer follow up and confirmed in other studies before any changes in clinical practice can be considered. In the third paper we found that a man with a suspicion of prostate cancer who had undergone one set of multiple biopsies that were benign, had the same baseline risk of a later diagnosis of prostate cancer as the background population within six years of follow-up. In the fourth paper we found that in order to recruit patients to a randomized study, the clinicians must explore the patient’s response and expectation to be able to individualize the information accordingly. Furthermore we found different strategies developed by the clinicians’ that were probably a key element to make the study feasible.

Methodological considerations

Paper I & Paper II

Randomized intervention study

The randomized study is the best way to reduce selection bias and the influence of both known and unknown confounders and thus only evaluate the intervention; in the SPCG-4 study, the treatment efficacy of radical prostatectomy. In Sweden the randomization was handled by a randomization secretariat, outside the clinic and in Finland by a secretary at the hospital in Helsinki.
When SPCG-4 started in 1989 all ethic committees had agreed to the study. In all but two centers randomization was done according to Zelen (40). This model was supposed to simplify the procedure and stated that only patients randomized to the experimental group needed full information, while those randomized to standard treatment only received the treatment they would have received under normal circumstances and did not have to be fully informed. However, from 1990 Zelen’s randomization model was abandoned, since the clinicians did not find it easier or necessary for randomization, but preferred to give all patients full information before randomization.

An independent end-point committee, of two experienced urologists and one pathologist, was selected to decrease the risk of observer bias in determining cause of death. They received standardized extracts from the patients’ files, where group assignment and treatment received were not revealed. They classified all deaths individually and then had a consensus meeting about unclear cases.

A potential problem in a randomized trial is the frequency of cross-over from the assigned group to the other group. Since the most accepted way to analyze a randomized study is by intention-to-treat, cross-over patients dilute the study findings. However, so far this has not been a problem in the SPCG-4 study. In the first analysis there were less than 10 percent in both groups who were not compliant with their allocated treatment and in the second analysis less than 10 percent in the radical prostatectomy group were in watchful waiting, and of men randomized to watchful waiting 12 percent had received curative treatment.

Cumulative hazard rates and cumulative incidence
We changed from cumulative hazard rates (paper I) to cumulative incidence (paper II) to better acknowledge competing risks (41). Since mortality in prostate cancer and overall mortality is so low the change of method at this time did not significantly change our results. But cumulative hazards overestimate the risk in the long run as the proportion of men experiencing an event increases.

Subgroup analyses
The subgroup analyses in paper II were pre-specified but not defined in the protocol. They were based on the hypothesis that Gleason score, PSA and age at inclusion could be subgroups of importance as effect modifiers. Performing multiple tests and dividing the study population into subgroups increase the risk of chance findings as well as the risk of false negative findings due to reduced statistical power. In the SPCG-4 study the 80 men who died in prostate cancer during follow up were divided into four groups instead of the two intended in the study design (42) (43). Subgroup analyses should be interpreted cautiously especially if there is a no-benefit group, and
must be reproduced in other trials before clinical practice can be changed. The reduced power could explain the no-benefit group of men 65 years and older and the findings that PSA and Gleason score were not independent effect modifiers.

Paper III

Register-based cohort studies
Since 1958 all newly diagnosed cancer cases in Sweden are registered in the Swedish Cancer Register by mandatory notification from both pathologists and clinicians. The completeness of the register is at the level of 95-98% of all tumors reported (44). Errors in personal identification numbers are few, below one percent (45). This completeness makes the register population-based and free from selection bias. We could link our cohort to the Swedish Cancer Register and get both observed and expected number of new prostate cancers, age-standardized and for the same calendar-years which gave us a standardized incidence ratio. The lack of information concerning intervention during the patients’ follow-up is a potential confounder in our study and in order to minimize known confounders (such as regional differences in diagnostic activity) we used the same reference population (Uppsala County) that the cohort originated from. Furthermore, we eliminated possible differences in diagnostic activity due to age and time period by using age-standardization and adjusting for the calendar-years of follow-up.

Case-Control study
To investigate if the men who were later diagnosed with prostate cancer had cancer in their biopsies the first time but were misjudged, we conducted a case-control study nested in the cohort. Cases were the men diagnosed with prostate cancer after previous benign biopsies. Through a computer algorithm we randomly selected four controls for each case from the cohort, matched for the time-at-risk variable only. The pathologist who reviewed the diagnostic biopsies was blinded for case and control status in order to eliminate the risk of observer bias and further increase the validity of our findings.

Sensitivity and specificity
To get a true sensitivity we would need to take out all the prostates and evaluate the number of microscopic prostate cancers present. However, in this study we did not want to find all microscopic cancers, since we know that the prevalence is so high and non-fatal cancers are in majority. What we wanted to know was the sensitivity of clinically important cancers, in other words, whether we missed potentially fatal cancers with this biopsy protocol.
In this sense the high sensitivity of the protocol could even be underestimated since we counted all cancers that were later detected as clinically important, while only two men in the cohort actually presented with advanced disease and probably had fatal cancers missed at biopsy.

Paper IV

Qualitative interview study of patients’ and clinicians’ experiences of the trial

The interview is a way to explore and understand how patients and clinicians perceived the randomized study. The interviews were conducted by a cancer specialist nurse with psychotherapy training, who was not involved in the SPCG-4 study, in order to minimize observer bias. She used a semi-structured checklist of topics. The interviews lasted for 40-80 minutes, were audio-taped and transcribed verbatim.

Qualitative content analyzes

There are a number of different methods to interpret the interviews and we chose content analysis. Content analysis aims to find conflicting opinions regarding procedures (39).

Credibility focuses on how well the data analyses address the study aim. We selected the patients to ensure a variety in aspects like treatment, age, participation status. However, socioeconomic factors were not available in the patient files. Although the number of interviewees was small we were able to find a number of possible key elements of interest, which can be tested in a future randomized trial.

Findings and implications

Radical prostatectomy is for the first time found to affect the natural course of localized prostate cancer and to reduce disease-specific as well as overall mortality.

At five years the only statistically significant difference was for local progression but at ten years a statistically significant difference in all endpoints had emerged. The ten-year disease-specific mortality after radical prostatectomy was 9.6 percent compared with 14.9 percent following watchful waiting which corresponds to an absolute reduction of 5.4 percent and a relative reduction of 44 percent following radical prostatectomy. As for the risk of distant metastases, the absolute difference between radical prostatectomy and watchful waiting was larger (10.2 percent) and since metastases almost always precede death in prostate cancer it is possible that a greater survival advantage will follow after ten years (46).
After the first analyses of the SPCG-4 study, the question was how to interpret our findings, since the disease specific mortality was affected but overall mortality was not statistically significantly reduced. The study was not mature to answer whether overall mortality was also affected. According to the study-protocol the first analyses should be undertaken at this time, and the main end-point was disease-specific mortality. However, the second analyses made it clear that radical prostatectomy significantly reduces both disease-specific and overall mortality. This finding is important since it is one of the cornerstones in all screening interventions. There is no point in screening for a disease if there is no cure or possibility to reduce morbidity. However, our study does not answer whether screening or even early detection is beneficial but there will be results from the ongoing screening trials in the US, Canada and Europe within a few years.

The SPCG-4 study comprises chiefly patients with symptomatic disease and palpable tumors whereas most prostate cancers diagnosed today are PSA detected non-palpable tumors. They are detected earlier and, to a larger extent, organ-confined (47). However, the lead-time of 6-12 years (48) gained by earlier detection, must be added to the ten-years time in our study. The patient invests time in a potential survival benefit 15-25 years ahead, during which time he might suffer from erectile dysfunction and incontinence.

With an absolute reduction in overall mortality of 5.1 percent, 19 patients have to undergo radical prostatectomy in order to prevent one death within 10 years. In year 2003 in Sweden, 1818 men underwent radical prostatectomy. If they have the same risk of death within ten years as those randomized to radical prostatectomy in the SPCG-4 study, 96/1818 will be saved who would otherwise have died within ten years. 316/1818 will die from other causes within ten years, and 180/1818 will die in prostate cancer within ten years in spite of operation. An even larger amount of overtreatment is likely to prevail in today’s settings, where many or most cancers are detected by means of PSA testing among asymptomatic men. The risk of overtreatment raises the most important challenge in contemporary prostate cancer research – to find prognostic markers in order to separate those who will benefit from surgery from those who will not develop fatal cancer.

We found age to modify the effect of radical prostatectomy. Men under 65 years, who were in watchful waiting, had a markedly higher cumulative incidence of mortality than the other groups. The clinicians randomizing in the SPCG-4 study were not blinded for the patients’ age and thus they might have selected younger patients on different premises than older men, and the finding of age as an independent effect modifier could in fact be a result of selection bias. Or, there could be differences in tumor-aggressiveness related to age in for example apoptosis or angiogenesis. In any case, age at diagnosis has to be further explored before any changes in clinical practice can be made. Gleason score as well as PSA level are known to influence prognosis (49), but they were not found to be independent effect modifiers. It could be
that even though the absolute benefit of radical prostatectomy differs between high and low Gleason scores as well as between high and low PSA values at randomization, the relative benefit of radical prostatectomy is the same. However, this will be further investigated at the next follow up, when there is increased statistical power due to more events.

Quality of life is a factor of greater importance in the treatment for prostate cancer than in most other cancer treatments, because of the high risk of overtreatment. In a quality-of-life study on a subgroup of the SPCG-4 study population, Steineck et al. (24) found clear effects on quality of life in both groups. The radical prostatectomy group had more erectile dysfunction and incontinence and the watchful waiting group more local progression with obstructed voiding symptoms, but average self-assessed quality of life and sense of well-being was similar between the groups. Erectile dysfunction and incontinence in the watchful-waiting group was higher than expected, which is probably a result of the locally growing tumor and, in addition, the more frequent use of hormonal therapy.

Local progression, hormonal treatment and palliative radiation increased more in frequency in the watchful-waiting group than in the radical prostatectomy group; all with side effects that influence quality of life and well-being. Thus, the more immediate – but stable – side effects of operation (50) are balanced by an increasing incidence of symptoms and treatments following disease progression in the watchful-waiting group. These findings will be further investigated by new questionnaires in the quality-of-life group of the study.

The extended protocol with a mean of nine biopsies did not have many false negative biopsies. The five-year sensitivity for detecting prostate cancer was 95%. Our estimate of sensitivity is not directly comparable to the sensitivity of the repeat biopsy studies where as many as 20% of rebiopsied men are diagnosed with prostate cancer (51). However, knowledge about sensitivity and risk estimates of spontaneously detected prostate cancer after a long-term follow up is important for clinical practice and necessary for the designing of follow-up protocols and patient information. The evaluated protocol, at the time considered extended, is now rather the gold standard and most urologists take 8-10 biopsies (52). Our preconceived hypothesis was that this cohort was a high risk group for later development of prostate cancer, considering the high number of prostate cancers detected at repeat biopsy shown by Djavan et al.(11) and that almost all men had elevated PSA or abnormal DRE. Our findings support a less aggressive policy of repeat biopsies; those are not indicated if previous multiple biopsies showed only benign histology, since the detection of insignificant tumors increases with the number of repeat biopsies (11).

The median follow-up time of six years is fairly short when it comes to prostate cancer. However, a mean age at biopsy of 64 years corresponds to a mean age of 70 years at the follow-up. Considering the long natural history
of localized prostate cancer, later detected localized cancers are less likely to be fatal. Nevertheless, the cohort will be followed up in the cancer register again when mean follow-up time reaches ten years.

The patients’ differed in their responses or strategies in decision-making, and their expectations of the clinician. Their responses could be sorted in three ways: 1/ making his own decision responsible for the outcome, 2/ preferring the clinician to make any medical decision, 3/ not letting chance decide treatment group. The clinicians used individual strategies focused on increasing the patients understanding and acceptance of allocation. At first, it is easy to assume that the patients, who prefer the clinician to make the decision are the ones randomized in the study. But this is not the case. The variation in strategies used by the clinicians probably enabled them to adjust the information to the different patients’ needs. In order to adjust information the clinician has to find out each patients response and expectation of the doctor. For example patients in category 1, who wanted to make their own decision, are more likely to accept allocation if they are informed of the study purpose and implication, and maybe have the possibility of a second clinician as a “second opinion” to debate pros and cons etc. Patients’, who prefers the clinician to make the decision, are probably more open to inclusion if they are convinced that their clinician not favors any of the treatment possibilities. Patients in the third category are probably the most difficult to allocate into a randomized study since the chance factor they want to avoid is the whole point.

What made the clinicians motivated to work so hard for the study? One reason was the same for all of them – the desire to know whether radical prostatectomy is better than watchful waiting. Since the study was open for inclusion during so many years, there was a problem with maintaining equipoise. Even though there was no new evidence during this time that radical prostatectomy was beneficial, radical prostatectomy became more and more common and gained acceptance without evidence. However, one way to reduce the difficulties with equipoise was to have regular meetings with the study group and steering-committee where these issues could be discussed.

The randomized MRC study (Pro6) was recently closed in advance after ten years of inclusion. It accrued 35 of the intended 1800 patients. Two explanations given for the poor recruitment were clinicians’ difficulties with equipoise and patients’ reluctance towards randomization. These barriers were also present in the SPCG-4 study but were found to be reduced by some of the strategies that were used.

Some of the strategies must have worked well in the SPCG-4 study, since the randomizing clinicians succeeded to include 698 patients into this very difficult trial. Hopefully, experiences from the SPCG-4 study will help reduce early closure of future studies.

Cancerförändringar i prostatan är vanliga och även innan man började behandla prostatacancer avled de flesta män med prostatacancer av någonting annat. Att prostatacancer är så vanligt och ofta relativt godartad gör att risken för överdiagnostik och överbehandling är stor.

Det finns tre principiellt skilda sätt att behandla prostatacancer: radikal prostatektomi varvid hela prostatan och sädesblåsorna opereras bort, strålbehandling och expektans (endast behandling av symptom). Tidigare studier har inte kunnat säkerställa en skillnad mellan behandlingarna avseende överlevnad och livskvalitet och man har därför inte heller kunnat ge några välgrundade rekommendationer. Trots att det inte funnits några säkra vetenskapliga belägg för att en kurativt syftande behandling skulle vara bättre än expektans har man sedan slutet av 1980-talet i ökad utsträckning utfört radikal prostatektomi vid lokaliserad prostatacancer. Radikal prostatektomi är idag i USA, Canada och på många ställen i Europa en standardmetod vid lokaliserad prostatacancer. Radikal prostatektomi har dock en hög andel biverkningar i form av inkontinens och impotens. För att undersöka om radikal prostatektomi är bättre än expektans beträffande överlevnad och risk för metastaser och lokal tillväxt beslutade man inom Skandinaviska prostatecancer gruppen att göra en gemensam randomiserad studie. En randomiserad studie innebär att slumpen avgör om man opereras eller inte och genom detta får man en jämn fördelning av faktorer som annars skulle kunna påverka resultatet som tex rökning, motion, andra sjukdomar etc. Att genomföra randomiserade studier har dock många gånger visat sig svårt då det krävs stort engagemang från både läkare och patienter.

I Sverige, Finland och Island startades efter godkännande av etiska kommittéer en gemensam randomiserad studie för att undersöka om radikal prostatektomi var bättre än expektans (SPCG-4 studien) avseende sjukdoms
specifik mortalitet (prostatacancerdöd), risk för metastaser, risk för lokal tumörtillväxt och total mortalitet. Män med lokaliserad prostatacancer, högt till medelhögt differentierad, med en förväntad överlevnad på mer än 10 år och prostataspecifikt antigen under 50 ng/ml tillfrågades om de ville delta i studien. Studien stängdes februari 1999 då 698 män inkluderas.

Arbete 1
Den första analysen av SPCG-4 studien, efter 6.2 års uppföljning visade att radikal prostatektomi minskade risken för död i prostatacancer, risken för metastaser och risken för lokal tumörtillväxt. Däremot fann vi ingen statistiskt signifikant skillnad mellan grupperna vad gällde total dödlighet.

Arbete 2
I den andra analysen av SPCG-4 studien, efter ytterligare tre års uppföljning, fann vi att radikal prostatektomi minskar risken för prostatacancer död, risk för metastaser och lokal tumörtillväxt samt också statistiskt signifikant minskade total dödlighet. Vi fann också att ålder modifierar effekten av behandlingen, där män under 65 år befann ha störst nytta av operation. Detta fynd måste dock undersökas vidare innan några definitiva slutsatser kan dras.

Arbete 3
I detta arbete undersökte vi om män som genomgått biopsier av prostata för misstanke om prostatacancer, där biopsierna varit godartade; om dessa män har en högre risk än andra män att senare få prostatacancer. Vi undersökte därför en grupp av män (549), som genomgått undersökning av prostata med i medeltal 9 biopsier utan tecken på cancer och jämförde med män i samma ålder för att se om de senare i livet hade ökad risk för att få prostatacancer. Vi fann att dessa män inte hade någon ökad risk att senare få prostatacancer jämfört med män i samma ålder.

Arbete 4
För att kunna förbättra deltagandet av både patienter och randomiserande läkare i framtiden undersökte vi faktorer som varit viktiga för deltagandet i vår studie.
Vi intervjuade både män som hade tackat ja till att delta i SPCG-4 studien och män som hade tackat nej till att delta. Vi intervjuade också fem läkare som randomiserat i studien.


Läkarna å andra sidan använde sig av strategier för att underlätta för patienten att fatta beslut och känna sig trygga

Radikal prostatektomi har för första gången visats påverka utvecklingen av prostatacancer gynnsamt. Operationen minskar risken att dö i sjukdomen, risken för spridning och även den totala risken att dö inom 10 år. Det tar tio år innan denna effekt blir synlig och då är det bara ett litet antal i båda grupperna som har dött av sjukdomen (30 i operationsgruppen och 50 i opektsgruppen). Den absoluta skillnaden på fem procent mellan grupperna innebär att för att rädda en man från att dö inom tio år måste man operera 19. Denna överbehandling med risk för komplikationer som impotens och inkontinens kan bara minska om vi kan finna subgrupper som har större nytta av operation än andra. Våra resultat tyder på att det kan vara män under 65 år som har störst nytta av operation, men detta resultat måste först bekräftas med längre uppföljning och från andra studier innan det kan ändra vår behandlingspolicy. Vi behöver också hitta prognostiska markörer som möjliggör att skilja ut de män som har en potentiellt dödlig prostatacancer från dem som har en stillsam cancer som inte kommer växa till eller sprida sig.

Män med misstänkt prostatacancer, som genomgått utredning med multipla biopsier som varit godartade har inte någon ökad risk att senare få prostate cancer.

För att kunna randomisera patienter till en studie måste läkaren först förstå vilken strategi patienten använder och vilka förväntningar patienten har på läkarens roll i beslutet för att kunna anpassa informationen därefter.

SPCG-4 studien kunde genomföras tack vare Cancerfondens finansiella stöd och ett stort engagemang från både läkare och patienter.
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