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Doctoral Thesis

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Trondheim, March 2011

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**Metoder for å måle utfall av behandling hos pasienter med prostatakreft uten spredning.**

Prostatakreft uten påvist spredning kan behandles med operasjon, strålebehandling med eller uten hormonbehandling, eller hormonbehandling alene. Svært mange menn med nylig påvist prostatakreft vil imidlertid kunne leve i mange år uten plager av sykdommen også uten behandling, og en stor andel dør til slutt av helt andre årsaker enn prostatkreft. Man mangler imidlertid helt sikre metoder for å velge ut pasienter som ikke trenger behandling, men i noen tilfeller hvor sykdommen er i tidlig fase er et regelmessig kontrollopplegg hvor kurativ behandling iverksettes først hvis sykdomen viser tegn til utvikling, forsvarlig. Imidlertid kan prostatakreft også være en agressiv sykdom med stor risiko for spredning og forkortet levetid. Pasienter med nylig påvist prostatakreft uten spredning og intermediær til høy risiko for progresjon regnes derfor å være behandlingstrengende.

Det kan ta mange år før man merker symptomer på et tibakefall etter en behandling som ikke har gitt ønsket kurasjon. Da vil sykdommen ofte ha kommet for langt til å kunne helbredes. Påvisning av manglende behandlingseffekt før et tilbakefall av sykdommen gir symptomer er imidlertid kun viktig hvis det da finnes effektiv tileggsbehandling. Siden overlevelse vanligvis ansees som det viktigste effektmålet ved kurativ kreftbehandling, blir det også viktig å avklare om det å påvise et tidlig tilbakefall eller manglende behandlingseffekt virkelig kan forutsi om pasienten på sikt vil utvikle plager av kreftsykdommen og i verste fall dø av den. I tillegg er det også svært viktig at bivirkningene ved utredning og behandling er så lite plagsomme som mulig.

Denne avhandlingen omhandler metoder for å måle effekt/utfall av behandling hos pasienter med prostatakreft uten spredning. Avhandlingen inbefatter 4 studier hvor hovedvekten er lagt på resultater av vevsundersøkelser av prostatkjertelen etter åpen radikal prostatectomi (operasjon) samt resultater i form av overlevelse og bivirkninger når kombinert strålebehandling og hormonbehandling sammenlignes med hormonbehandling alene. Videre undersøkes hvor hyppig det påvises kreftceller i systematiske vevsprøver fra prostata 3-4 år etter at de to sistnevne behandlingene ble iverksatt. Endelig undersøkes bivirkninger av vevsprøvetakning etter kombinert strålebehandling og hormonbehandlig sammenlignet med hormonbehandling alene.

Resultatene av studiene viser at andel pasienter som fikk prostatakreften fullstendig fjernet ved operasjon bedømt ut fra kirurgiske marginer gradvis økte de første årener etter at operasjonsmetoden ble innført. Det gir en indikasjon på at operasjonsteknikken bedret seg vesentlig i samme periode.

Strålebehandling kombinert med hormonbehandling ga vesentlig bedre totaloverlevelse enn hormonbehandling alene. Kombinasjonsbehandlingen ga en lett øktning av bivirkninger, men bivirkningene var akseptable.

De pasientene som fikk denne kombinasjonsbehandlingen hadde vesentlig skjeldnere gjenværende kreftceller i vevsprøvene sammenlignet med de som bare fikk hormonbehandling. Videre hadde pasienter med gjennværende kreftceller i prostatakjertelen vesentlig høyere risiko for tilbakefall påvist med blodprøve (stigende PSA) .

Bivirkningene ved å ta systematiske vevsprøver fra prostata etter hormonbehandling med eller uten stråleterapi var små og gikk stort sett over i løpet av en uke.

***Navn kandidat:*** ***Arne Solberg***
***Institutt:*** ***Institutt for Kreftforskning og Molekylær Medisin***
***Veileder(e):*** ***Anders Angelsen og Olav Anton Haugen***

*Ovennevnte avhandling er funnet verdig til å forsvares offentlig*
*for graden PhD i klinisk medisin*
*Disputas finner sted i Auditoriet,Medisinsk Teknisk Forskningssenter.*
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# CONTENTS

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# LIST OF PAPERS

1. Solberg A, Viset T, Haugen OA, Mjønes J, Klepp O, Angelsen A. Histopathological outcome in 167 patients operated on with radical retropubic prostatectomy. Scand J Urol Nephrol. 2005;39(4):283-8

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3. Solberg A, Haugen OA, Viset T, Ahlgren G, Widmark A, Angelsen A. Residual prostate cancer in patients treated with endocrine therapy with or without radical radiotherapy: A side study of the SPCG-7 randomised trial. Int J Radiat Oncol Biol Phys. 2010 Jun 30. [Epub ahead of print]

4. Arne Solberg, Anders Widmark, Ilker Tasdemir, Göran Ahlgren, Anders Angelsen: Side effects of posttreatment biopsies in prostate cancer patients treated with endocrine therapy alone or combined with radical radiotherapy in the SPCG-7 randomised trial. *Submitted.*

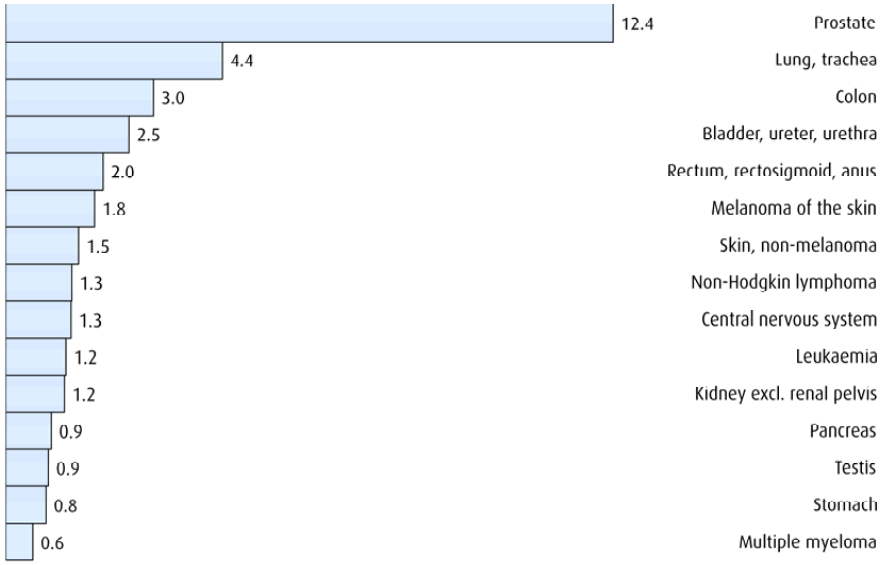
# ABBREVIATIONS

| | |
|---|---|
| **ADT** | **Androgen-deprivation therapy** |
| **AR** | **Androgen receptor** |
| **ASTRO** | **American Society of Therapeutic Radiology** |
| **CSS** | **Cancer specific survival** |
| **CKHMW** | **High-molecular-weight-cytokeratin** |
| **CI** | **Confidence interval** |
| **CT** | **Computer tomography** |
| **DFS** | **Disease free survival** |
| **DHT** | **Dihydrotestosterone** |
| **DRE** | **Digital rectal examination** |
| **EBRT** | **External beam radiotherapy** |
| **HIFU** | **High intensity focused ultrasound** |
| **HR** | **Hazard ratio** |
| **IQR** | **Interquartile range** |
| **LHRH** | **Luteinising-hormone releasing hormone** |
| **MRI** | **Magnetic resonance imaging** |
| **OR** | **Odds ratio** |
| **OS** | **Over all survival** |
| **PET** | **Positron emission tomography** |
| **PFS** | **Progression free survival** |
| **PLND** | **Pelvic lymph node dissection** |
| **PSA** | **Prostate specific antigen** |
| **QOL** | **Quality of life** |
| **PSADT** | **PSA doubling time** |
| **RCT** | **Randomized controlled trial** |
| **RFS** | **Recurrence-free survival** |
| **RP** | **Radical prostatectomy** |
| **RPC** | **Residual prostate cancer** |
| **RRP** | **Radical retropubic prostatectomy** |
| **RT** | **Radiotherapy** |
| **SPCG** | **Scandinavian Prostate Cancer Group** |
| **TNM** | **Tumour Node Metastasis** |
| **TAB** | **Total androgen blockade** |
| **TRUS** | **Transrectal ultrasonography** |
| **TUR-P** | **Transurethral resection of the prostate** |
| **WHO** | **World Health Organisation** |

# INTRODUCTION

Prostate cancer is the most common malignancy in Norwegian males with 4168 new cases diagnosed in 2008. The annual incidence in Norway has been rapidly increasing since 1990 coinciding with the introduction of the serum Prostate specific antigen (PSA) test. The majority of patients are now diagnosed with non-metastatic disease whereas regional and/or distant metastases are diagnosed in approximately 15%. Moreover, the incidence increases rapidly with age from the fifth decade, and approximately one in eight Norwegian men will be diagnosed with prostate cancer before the age of 75 (figure 1).

Figure 1. Cumulative risk (%) of developing cancer in Norwegian males by the age of 75 for selected cancers - 2004-2008 [1]



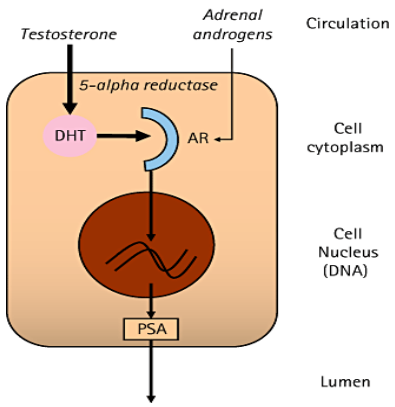

Although prostate cancer is the second most frequent cause of cancer death responsible for 1090 of 5655 male cancer deaths in 2008, the prevalence in Norway is doubled in the last decade. As of December 31st 2008, 27570 patients diagnosed with the disease were alive. The 5 years relative survival in localised disease exceeded 95% in 2004-08 as compared to 70% in 1988-93. In patients with distant metastasis, the trend was relatively stable with only a few

percentage points increase in 5 years relative survival, reaching 30% in 2004-08. Whereas the prostate cancer mortality rate increased steadily from the 1970s until 1996, there is now evidence that the rate is declining [1]. The increasing prostate cancer incidence seems to be closely related to measurement of PSA in serum (s-PSA), and the improved survival can in part be explained by a stage migration towards localised disease with more indolent and slowly progressing tumours ("insignificant cancers") at diagnosis. On the other hand, it is likely that curative therapy contributes to the favourable trend observed in the recent years [2].

## Etiology

Huggins and Hodges demonstrated the testosterone dependent nature of prostate cancer in the early 1940s [3]. In benign prostatic stromal and epithelial cells as well as in cancer cells, testosterone entering from circulation is reduced to dihydrotestosterone (DHT) and act as a growth factor forming a complex with the androgen receptor (AR) which enters the nucleus (figure 2). The modified DHT-AR complex combines with specific parts of the DNA and stimulates m-RNA formation, successive protein synthesis (e.g. PSA) and cell proliferation [4-6], whereas androgen depletion leads to apoptosis [7, 8].

Figure 2. The physiological mechanism of androgenic stimulation of prostate cancer cells [9].



A positive family history is identified as the strongest prostate cancer risk factor with a 11-fold higher risk in men with three first-degree relatives previously diagnosed with the disease [10]. Moreover, American men of African origin has an almost 60% increased relative risk of developing prostate cancer and a doubled risk of prostate cancer death as compared to those of European origin [11]. Although the genetic mechanisms in hereditary prostate cancer are not fully understood, several prostate cancer tumour suppressor genes have been identified [12-15].

In addition, there is some evidence from observational studies that diet and lifestyle may contribute to prostate cancer development. However, the associations seems to be weak, especially in localized disease [16]. In a recent meta-analysis, a relative risk of 1.05 per 5 $kg/m^2$ increment of body mass index was found [17], suggesting that obesity may be a prostate cancer risk factor. Although a high intake of n-6 fatty acids is proposed to increase prostate cancer risk [16], the association between diet and prostate cancer remains unclear. For instance, supplemental and dietary calcium was found to be associated with an increased risk in two observational studies [18, 19], whereas a possible protective effect was found in a randomized controlled trial (RCT) in which patients were allocated to a daily intake of supplementary calcium or placebo [20]. A high dietary or supplemental intake of several nutrients such as vitamin E, selenium as well as lycopene which is found in tomatoes is suggested to be associated with prostate cancer risk reduction [21-23].

## Diagnosis

Localised prostate cancer is most commonly asymptomatic, but some men may experience lower urinary tract symptoms. In Norwegian men, the diagnosis of non-metastatic prostate cancer is most commonly established following s-PSA measurement and/or digital rectal examination (DRE) due to concern about prostate cancer, and rarely due to urinary symptoms [24].

**Prostate specific antigen**

The serine protease PSA is secreted from the prostate glands into the seminal fluid. PSA is responsible for semen liquefaction, and was characterized and detected in serum around 1980 [25, 26]. Measurement of s-PSA has become an important diagnostic tool as an elevated serum level is strongly associated with prostate cancer [27]. On the other hand, benign prostatic disorders such as benign prostatic hyperplasia and prostatitis are also associated with elevated s-PSA [28]. Moreover, there is no distinct s-PSA cut-off value below which the prostate cancer diagnosis can be excluded. In the US Prostate Cancer Prevention Trial, Thompson et al. found prostate cancer in 15% of men with a s-PSA value of <4 ng/ml, of which 15% had histological aggressive tumours (Gleason score of $\geq$7) [29]. In attempt to increase the sensitivity and specificity of the s-PSA test as well as its ability to predict prognosis, several modifications have been introduced. A PSA velocity (increasing PSA over time) of >0.75 ng/ml/year is predictive of prostate cancer in undiagnosed patients [30], whereas a PSA doubling time (PSADT) >4 years indicates a favourable prognosis in diagnosed patients [31]. Moreover, a low percentage of free s-PSA (%fPSA) is shown to be predictive of cancer diagnosis and histological aggressiveness [32]. However, the sensitivity, specificity and predictive properties of these tests are restricted [33], and the cancer diagnosis cannot be based solely on s-PSA testing.

The issue of PSA-screening in healthy men has been a matter of debate since the introduction of the test. Recently, the European Randomized Study of Screening for Prostate Cancer demonstrated a 20-30% reduced relative risk of dying from prostate cancer in men randomized to PSA-screening with a cut-off value of 3-4 ng/ml [34, 35]. However, PSA-screening resulted in substantial overdiagnosis and overtreatment in patients with insignificant cancer. More than 1000 men had to be screened to prevent one prostate cancer death, and a total of 48 men had to undergo radical treatment. Furthermore, no difference in prostate cancer mortality was found in the North American randomized Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial in which a PSA cut-off level of 4.0ng/ml was used

[36]. By contrast, a much lower number needed to screen (293) and number needed to treat (12) to prevent one prostate cancer death was found in the recently published Göteborg randomised population-based prostate-cancer screening trial [37]

According to the recently published Norwegian Directory of Health's guidelines on diagnosis, treatment and monitoring of prostate cancer, the PSA test can be offered on an individual basis, but should not be taken unless the patient is fully informed about the consequences. Population based PSA-screening is not implemented in the official Norwegian health care program [38] .

**Trans rectal ultrasound-guided prostate biopsy**

The suspicion of prostate cancer should be verified by a histopathological diagnosis. In order to decrease the false-negative rate following prostate biopsy, systematic trans rectal ultrasound (TRUS)-guided biopsy (sextant biopsy) was introduced in the 1980s [39]. Currently, dependent on prostate volume, 10-12 biopsy cores are usually taken as a higher number of biopsy cores is shown to increase the detection rate. In a series of 1051 men with a serum-PSA of 4-10 ng/ml that underwent sextant biopsy and 2 additional transition zone biopsies the detection rate of cancer was 22%. In patients with negative biopsies, the detection rates in successive biopsies were 10, 5 and 4%, respectively [40]. Moreover, repeated biopsy with up to 40 cores (saturation prostate biopsy) in previously biopsy-negative men with a high suspicion of cancer yield detection rates of 13.5-41% [41-48]. In men with an elevated s-PSA and negative random biopsies, magnetic resonance spectroscopic imaging as well as dynamic contrast-enhanced magnetic resonance imaging may be used to localise tumour foci as targets for successive TRUS-guided biopsies [49].

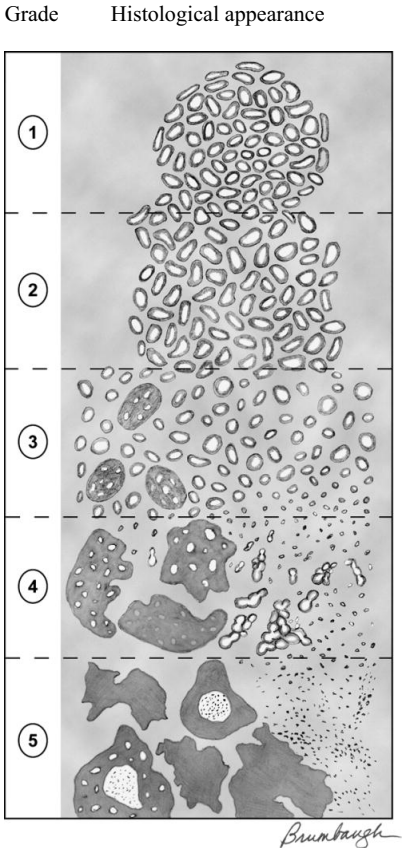
**Histopathology**

The vast majority of malignant prostate tumours are adenocarcinomas arising from the glandular epithelium, and histological tumour grade is shown to be a significant prognostic factor [50]. In the World Health Organisation (WHO) system, the tumour is graded on a 3-point scale based on evaluation of nuclear anaplasia and glandular differentiation. A higher tumour grade corresponds with increasingly malignant morphologic appearance, and WHO-grade 1-3 denotes well, intermediate and poorly differentiated tumours, respectively [51]. The Gleason grading system is based on the histological architecture of the tumour in which the growth pattern is graded on a scale from 1 to 5. Increasing grade corresponds to increasing infiltrative growth and loss of glandular formation, and grade 5 denotes the most malignant histopathological pattern (Table 1, Figure 3). [52]. Finally, the tumour is assigned a Gleason score defined as the sum of the two most commonly occurring grade patterns [51, 53]. The Gleason system appears to be superior to the WHO system in assessing the prognostic impact of tumour grade, and is internationally accepted as the reference grading system [54, 55].

Table 1. The Gleason grading system [52]

| |
|---|
| Pattern 1: |
| Circumscribed nodule of closely packed but separate, uniform, rounded to oval, medium-sized acini (larger glands than pattern 3) |
| Pattern 2: |
| Like pattern 1, fairly circumscribed, yet at the edge of the tumor nodule there may be minimal infiltration |
| Glands are more loosely arranged and not quite as uniform as Gleason pattern 1 |
| Pattern 3: |
| Discrete glandular units |
| Typically smaller glands than seen in Gleason pattern 1 or 2 |
| Infiltrates in and amongst nonneoplastic prostate acini |
| Marked variation in size and shape |
| Smoothly circumscribed small cribriform nodules of tumor |
| Pattern 4: |
| Fused microacinar glands |
| Ill-defined glands with poorly formed glandular lumina |
| Large cribriform glands |
| Cribriform glands with an irregular border |
| Hypernephromatoid |
| Pattern 5: |
| Essentially no glandular differentiation, composed of solid sheets, cords, or single cells |
| Comedocarcinoma with central necrosis surrounded by papillary, cribriform, or solid masses |

Figure 3. Schematic diagram of the modified Gleason grading system [52]

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**Staging**

Patients diagnosed with prostate cancer should undergo a staging procedure according to the Tumour Node Metastasis (TNM) classification system of malignant tumours (Table 2) in order to select those eligible for curative treatment, and to exclude patients with metastasis from inappropriate local therapy [56].

The clinical tumour (cT) stage is usually assessed by a DRE and transrectal ultrasonography (TRUS) [57]. Pathological tumour (pT) stage as assessed following radical prostatectomy resembles cT-stage, although the cT1 categories are excluded. Localised disease include non-metastatic T1 and T2 (organ confined) and locally advanced tumours that penetrate beyond the prostatic capsule into adjacent tissues ($\geq$T3) [56].

Table 2. TNM clinical classification for tumours of the prostate

| | |
|---|---|
| **T - Primary Tumour** | |
| TX | Primary tumour cannot be assessed |
| T0 | No evidence of primary tumour |
| T1 | Clinically inapparent tumour not palpable or visible by imaging |
| T1a | Tumour incidental histological finding in 5 % or less of tissue resected |
| T1b | Tumour incidental histological finding in more than 5 % of tissue resected |
| T1c | Tumour identified by needle biopsy (e.g., because of elevated PSA) |
| T2 | Tumour confined within prostate[1] |
| T2a | Tumour involves one half of one lobe or less |
| T2b | Tumour involves more than one half of one lobe, but not both lobes |
| T2c | Tumour involves both lobes |
| T3 | Tumour extends throughout the prostatic capsule[2] |
| T3a | Extracapsular extension (unilateral or bilateral) |
| T3b | Tumour invades seminal vesicle(s) |
| T4 | Tumour is fixed or invades adjacent structures other than seminal vesicles: Bladder neck, external sphincter, rectum, levator muscles, or pelvic wall |
| **N - Regional Lymph Nodes** | |
| NX | Regional lymph nodes cannot be assessed |
| N0 | No regional lymph node metastasis |
| N1 | Regional lymph node metastasis |
| **M - Distant Metastasis** | |
| MX | Distant metastasis cannot be assessed |
| M0 | No distant metastasis |
| M1 | Distant metastasis |

1. Tumour found in one or both lobes by needle biopsy, but not palpable or visible by imaging, is classified as T1c

2. Invasion into the prostatic apex or into (but not beyond) the prostatic capsule is not classified as T3, but as T2

The regional lymph nodes lie within the confines of the true pelvis [56]. Imaging techniques such as magnetic resonance imaging (MRI) and computer tomography (CT) are frequently used in lymph node staging. Although the relatively low sensitivity and specificity of these techniques may be improved with contrast-enhanced MRI and positron emission tomography (PET) [58, 59], a pelvic lymph node dissection (PLND) is regarded to be the gold standard of nodal staging [60]. The PLND may be performed as an open or laparoscopic procedure, either prior to definitive local therapy (e.g. radiotherapy) or simultaneously with prostatectomy [61-63]. The majority of lymph node metastases are found outside the obturator fossa. Thus, according to recent guidelines, the PLND should be extended to include the area up to the bifurcation of the common iliac artery and down to the epigastric artery [60, 61].

As haematogenous prostate cancer dissemination most frequently affects the skeleton, a bone scan has traditionally been used to determine the M-stage. Although the sensitivity is high, the specificity may be further improved using MRI as a supplement [64, 65].

**Risk assessment in presumed non-metastatic prostate cancer**

Several models and nomograms combining s-PSA, clinical tumour (cT) stage and Gleason score have been developed in order to predict likelihood of organ confined disease, extraprostatic tumour extension, seminal vesicle involvement, lymph node metastasis as well as relapse following radical therapy. The risk of an unfavourable pT and pN stage and outcome increases with serum level of PSA, higher Gleason score and advanced cT-stage [66-70]. Moreover, 3 risk categories for treatment failure following curative therapy have been identified (Table 3) [71]. All three criterions must be fulfilled in the low risk group, whereas one criterion is sufficient in the intermediate and high risk groups.

Table 3. Risk group categories in presumed localised prostate cancer, according to D'Amico [71].

| Risk group | PSA | GS | cT-stage |
|---|---|---|---|
| Low | < 10 ng/ml | $\leq$ 6 | $\leq$ T2a |
| Intermediate | >10 and $\leq$ 20 ng/ml | 7 | T2b |
| High | > 20 ng/ml | 8-10 | $\geq$ T2c |

## Measures of outcome in non-metastatic prostate cancer

Survival is commonly regarded to be the most important time-dependent end-point in curative cancer therapy [72]. In general, modeling of time to event data is done using various methods of survival analysis. The event of interest in *overall survival* (OS) is death of any cause. All other patients are censored at the time of last follow-up. When *cancer specific survival* (CSS) is estimated, patients who died from other causes are censored at the time of death [73]. Other commonly reported outcomes are *disease-free survival* (DFS), *progression-free survival* (PFS) and *recurrence free-survival* (RFS) in which the events of interest are lack of cure, progression and recurrence, respectively. In these instances, also death of any cause is defined as an event. Moreover, in prostate cancer, *biochemical* DFS, PFS and RFS relates to a threshold PSA-value above which the event is defined to have occurred [74]. *Clinical* DFS, PFS and RFS denote survival without local recurrence or metastasis, whereas *metastasis-free survival* (MFS) is an estimate of the probability of surviving without metastasis. Often, time-dependent clinical outcomes in terms of probabilities of recurrence, progression and metastasis are reported in clinical trials using survival analysis. In these cases, only recurrence or progression are defined as events, and patients who die without the event are censored [75].

However, otherwise healthy men with newly diagnosed prostate cancer may have a life expectancy of many years even without therapy [76], and a high proportion will eventually die from other causes without clinical symptoms of their cancer [77-79]. On the other hand, clinically apparent (symptomatic) relapse or disease progression may occur after several years following therapy [80, 81]. In these patients, an earlier diagnosis of treatment failure is beneficial only if effective therapy is available. Thus, a key question is how well surrogate outcome measures such as histopathological outcome and biochemical recurrence following therapy predict survival [75].

In patients with non-metastatic prostate cancer, morbidity may be caused by progressive disease as well as side-effects from diagnostic procedures and therapy. Thus, a survival benefit gained from diagnosis and successive therapy must always be weighed against adverse effects on quality of life (QOL). This is particularly important in non-metastatic prostate cancer due to the long natural history of the disease [76].

**Therapeutic options and survival**

In non-metastatic prostate cancer the ultimate goal of various treatment strategies is cure, or at least to prevent morbidity such as symptomatic local recurrence and/or metastasis. Whereas active surveillance is an option in carefully selected low risk-patients, the treatment modalities include androgen deprivation therapy (ADT), radical prostatectomy (RP) and radiotherapy (RT) with curative intent [60].

*Active surveillance*

According to the Norwegian guidelines [38], eligibility criteria for active surveillance are PSA <10ng/ml, ≤2 positive biopsies with less than 50% cancer in at least 8 cores with normal length, cT-stage ≤2b and Gleason score ≤6. All criteria should be fulfilled. The surveillance scheme includes s-PSA control every 3 months for two years and then biannually as well as re-biopsy 1, 4 and 7 years after diagnosis. Commonly used criteria for progression are PSADT <3 years, GS ≥7 or ≥2 positive biopsies. Progressing patients (one criterion is sufficient) should be offered therapy with curative intent. Although not tested in RCTs, the prognosis in eligible patients who complied with this scheme in observational studies was excellent, and the vast majority will eventually die of other causes than prostate cancer [77-79].

*Androgen deprivation therapy*

ADT in prostate cancer constitute castration including orchiectomy and luteinising-hormone releasing hormone (LHRH) agonist or antagonist therapy as well as non-steroid antiandrogen

therapy (flutamide, bicalutamide, nilutamide) [82]. The term total androgen blockade (TAB) denotes combinations of castration and a peroral antiandrogen.

Several RCTs have explored the effect of immediate versus deferred ADT mono-therapy (orchiectomy or LHRH-agonist) in locally advanced and/or metastatic prostate cancer [83-87]. In a meta-analysis including these studies, a modest OS benefit (estimated 10% relative risk reduction) in favour of immediate treatment was found [88].

Antiandrogen monotherapy yield equal survival as compared to castration therapy (LHRH-agonist) in M0 prostate cancer [89]. Furthermore, in the Scandinavian Prostate Cancer Group (SPCG) Study 6, patients with M0 prostate cancer were randomised to either antiandrogen (bicalutamide 150mg daily) or placebo. Whereas a trend towards reduced OS was found in patients with organ confined disease on antiandrogen monotherapy, the opposite trend as well as an improved PFS (43% relative risk reduction in favour of bicalutamide) was observed in patients with locally advanced disease [90].

Three RCTs have compared external beam radiotherapy (EBRT) with and without 3-6 months neoadjuvant ADT (LHRH-agonist or TAB) [91-93]. In all studies, a biochemical and clinical DFS benefit was found in favour of neoadjuvant therapy. In a recent meta-analysis, the estimated relative risk reductions were 37 and 31%, respectively [94], whereas no difference in survival was found in a recently published RCT comparing 3 and 8 months neoadjuvant ADT prior to 64 Gy EBRT [95]. By contrast, prostatectomy patients do not benefit from neoadjuvant ADT. Ten RCTs have compared RP ± neoadjuvant ADT (LHRH-agonist, antiandrogen or TAB). No difference in survival was found [94].

Although the role of ADT adjuvant to RP in non-metastatic disease is not explored in RCTs, immediate ADT (orchiectomy or LHRH-agonist) in pN+ patients is shown to improve OS with a 46% relative risk reduction as compared to ADT given at detection of symptomatic local recurrence and/or distant metastases [96]. Moreover, there is substantial evidence from RCTs that endocrine treatment adjuvant to EBRT in locally advanced and/or lymph node positive prostate cancer improves survival as compared to EBRT alone. In 3 of these studies

an absolute OS benefit of 10-20% at was found in favour of adjuvant therapy [97-99], whereas an absolute CSS benefit of 6% was found in one study [100]. These studies are, however, heterogeneous with respect to radiation dose (65-70Gy), tumour stage as well as timing (started prior to, under or after local therapy), duration (6 months to indefinitely) and type (orchiectomy vs LHRH agonist ± antiandrogen) of ADT. Moreover median follow-up ranged from 4.5 to more than 15 years. Nonetheless, there seems to be a clear interaction between local therapy and adjuvant ADT. A recent meta analysis which included the RT studies as well as the study on RP plus immediate vs. delayed ADT [96] estimated the relative risk reduction of death from any cause to be 31% in favour of adjuvant therapy [88]. In the Early Prostate Cancer Program, patients with M0 prostate cancer were randomized to receive a daily dose of antiandrogen (150 mg bicalutamide) or placebo in addition to standard care. A sub-group analysis demonstrated a 35% relative risk reduction of death from any cause in patients with locally advanced prostate cancer treated with RT and bicalutamide [101]. One RCT has examined short (6 months) vs. long (3 years) duration of ADT started simultaneously with EBRT. In this trial a small absolute OS benefit (3.8%) in favour of 3 years ADT was found [102].

*Radical prostatectomy*

Patients with clinically localised prostate cancer and a life expectancy >10 years have been treated with surgery for decades [60] although only one published RCT has compared RP with observation alone ("watchful waiting"). The SPCG-4 study which included men with presumed organ confined prostate cancer (T1-T2b N0 M0) demonstrated a risk reduction of metastasis, cancer specific mortality as well as a 5% absolute reduction in over all mortality at 10 years in favour of open radical retropubic prostatectomy (RRP) [103]. However, the overall mortality risk reduction was no longer statistically significant after an additional three years follow-up [104].

In the past decade, minimal invasive techniques such as laparoscopic RP [105], and more recently robot-assisted laparoscopic RP [106], have been introduced. RCTs comparing

the various RP techniques with respect to oncological outcome are, however, non-existent [107].

*Radiotherapy*

Several RCTs have shown that escalation of the EBRT dose from the traditionally used 64-70 Gy to 74-79.2 Gy with conventional fraction doses (1.8 – 2.0 Gy) improves biochemical outcome (10-27% absolute risk reduction of biochemical recurrence) [108-111]. Although none of these studies demonstrated an OS benefit, there seems to be a clear dose-response relationship in radiotherapy for prostate cancer. In high dose-rate brachytherapy, radioactive iridium ($^{192}$Ir) probes are temporarily implanted in the prostate gland, usually delivering 10-20 Gy in 2-4 fractions combined with conventional fractionated 45-54 Gy EBRT [112]. In low dose-rate brachytherapy, permanent radioactive Iodine ($^{125}$I) or Palladium ($^{103}$Pd) implants are used, preferably in low-risk patients [113]. By both techniques, a normalized dose equivalent of 2 Gy per fraction of more than 100 Gy may be delivered safely [114, 115]. However the efficacy of brachytherapy is not compared with dose escalated EBRT in RCTs.

In hypofractionated EBRT, radiation doses biologically equivalent to those given with conventionally fractionated irradiation are delivered over a shorter period of time. Two RCTs have compared hypofractionationated with conventionally fractionated (2 Gy in 32-33 fractions) EBRT. Equal survival was reported in both studies [116, 117].

Although the pelvic lymph nodes received 44-50 Gy irradiation in the RCTs that compared RT +/- long term ADT, [97, 99, 100, 102], the role of prophylactic pelvic lymph node irradiation is controversial. One large RCT demonstrated a PFS benefit of whole pelvic as compared to prostate only irradiation but no difference in OS. However, two other RCTs failed to demonstrate a survival benefit in favour of pelvic lymph node irradiation [118-120].

Three RCTs have explored to role of adjuvant radiotherapy following RP in locally advanced prostate cancer. An improved biochemical DFS was found in two studies in which patients with pT3 and/or margin positive tumours were randomised to 60-64 Gy RT adjuvant or observation [121, 122]. In the Southwest Oncology Group (SWOG) trial number 8794,

patients with pT3N0M0 prostate cancer were randomized to receive either 60-64 Gy adjuvant EBRT or observation. At long-term follow up (median 12.7 and 12.5 years in the two groups, respectively) a 29% relative risk reduction of metastasis as well as an 11% absolute improved OS was found in favour of adjuvant RT [123].

Whether the observed survival benefit from combined EBRT and ADT as primary treatment in M0 disease was due to the ADT alone was until recently unresolved. This issue is addressed in study 2 in this thesis, and will be discussed in detail in subsequent sections.

**Surrogate measures of outcome in non metastatic prostate cancer**

Several surrogate outcome measures have been introduced to detect persistent cancer following therapy in asymptomatic patients at an early and potentially curable stage.

*Post-treatment PSA in outcome assessment*

Following RP, s-PSA should remain below the detection level as an indication of no residual cancer. Two consecutive s-PSA measurements of $\geq$0.2 ng/ml is a generally accepted definition of biochemical recurrence [60, 124]. Following RP, biochemical recurrence occurs in around one per cent in low-risk patients and in more than 60% high-risk patients [125-128]. In a retrospective study by Uchio et al, biochemical recurrence after RP was found to be a significant predictor of prostate cancer mortality with an absolute increased risk of 21% at 15 years [129]. Moreover, Pound et al. reported in their retrospective study which included 1997 men operated on with RP that an early biochemical recurrence ($\leq$ 2 years vs. > 2 years) as well as a short PSADT (cut-off 10 months) was significant predictors of distant metastasis [81].

A detectable s-PSA level following curative RT does not necessarily imply treatment failure, as PSA may be produced in residual benign prostate tissue. Variations in post-RT s-PSA levels not due to disease progression is most commonly observed the first two years after RT [130]. According to the 2006 American Society of Therapeutic Radiology (ASTRO) recommendation, PSA-recurrence post-RT is defined as a ≥2.0 ng/ml increase above a

previous nadir-value [131]. Dependent on radiation dose, biochemical recurrence following EBRT occurs in 16-35% [108-111]. Consistent with data on RP, biochemical recurrence after EBRT is found to be a significant predictor of prostate cancer mortality. In a retrospective study, patients with biochemical recurrence according to the ASTRO-definition were found to have a 41% higher absolute risk of dying from prostate cancer at 15 years as compared to patients without biochemical failure [129]. In another cohort study with retrospective design, patients with an early biochemical recurrence (<18 months) had a 5-year prostate cancer mortality of 36% as compared to 6% in late PSA-relapsing patients [132]. In addition, biochemical recurrence with a short PSADT is found to be an independent predictor of clinical recurrence and cancer specific mortality in several observational studies [132-134].

Biochemical progression in castration resistant prostate cancer is highly predictive of prostate cancer mortality, especially in patients with a short PSADT [135]. In a prospective study, patients with non-metastatic prostate cancer and biochemical progression on castration therapy only had a median metastasis-free survival of approximately 30 months. PSA velocity was an independent predictor of time to first bone metastasis, metastasis-free and overall survival [136]. On the other hand, the natural history of biochemical progression in non-metastatic prostate cancer on antiandrogen monotherapy is poorly described in the literature [89, 90, 137].

*Histopathological outcome*

In RTCs, neoadjuvant ADT given prior to RP is shown to improve local control in terms of negative surgical margins, although no survival benefit was observed [138-141]. However, central pathology review of the prostatectomy specimens in a subgroup analysis of the European Organisation for Research and Treatment of Cancer (EORTC) trial 22911 (adjuvant RT vs. observation following RP in pT3 and/or margin positive cancer) demonstrated a 29% absolute improved biochemical DFS in favour adjuvant irradiation in patients with positive surgical margins. On the other hand, no benefit from RT was found in patients with margin negative disease [142]. Moreover, a positive surgical margin is shown to predict clinically

important outcomes such as local recurrence, distant metastasis and prostate cancer mortality [143, 144]. This includes one large population based cohort study of more than 65,000 patients operated on with RP in which the incidence of positive surgical margins ranged from17-43% depending on pT-stage and to a lesser extent tumour grade. In the total study population, a 61% relative risk reduction of prostate cancer mortality was found in favour of negative margins [144]. In contrast, in the SPCG-4 randomized trial, positive margins which were found in 35% was not an independent predictor of prostate cancer mortality. Extracpsular tumour growth (pT3-stage) was, however, found in 46% of the RP-specimens and gave a 14-fold relative risk of prostate cancer death as compared to lower pT-stages. Moreover, patients with high-grade tumours (Gleason score $\geq$ 8) had a more than 4 times increased relative risk of dying from prostate cancer as compared to patients with GS 7 tumours [104]. The combination of locally advanced and histological aggressive disease seems to yield a particularly unfavourable prognosis in younger men. In a large population based cohort study which included more than 100,000 RP-patients aged 35-74 years, the youngest (age 34-44 years) men with pT3, Gleason score $\geq$8 tumours had an at least 5-fold relative risk of dying from prostate cancer as compared to their older counterparts [145]. Moreover, data from recently published observational studies suggest that length of positive margin is predictive of biochemical recurrence [146, 147], although this findings have not been confirmed in other studies [148, 149]. The prognostic value of tumour volume in RP-specimens is also controversial. Whereas some studies report a high tumour volume to be predictive of an adverse clinical outcome, no association was found in other studies [150, 151].

There is substantial evidence of a dose-response relationship in EBRT for non-metastatic cancer prostate cancer as assessed by posttreatment biopsy. A significantly reduced incidence of biopsy verified residual prostate cancer (RPC) following escalation of the radiation dose was demonstrated in a prospective observational study in the late 1990s [152].

Moreover, ADT given neoadjuvant to EBRT was shown to improve local tumour control as assessed by posttreatment biopsy in a RCT [153].

In retrospective studies, RPC after EBRT is found to be predictive of distant metastasis as well as prostate cancer mortality. In one of these studies, the 10 year distant metastasis free survival in patients with and without RPC was 61% and 77%, respectively [154]. Another retrospective study demonstrated an 11% absolute difference in 10 years CSS (96 vs. 85%) in favour of patients without RPC [155]. In a recently published RCT exploring the effect of two different neoadjuvant ADT schemes prior to EBRT in non-metastatic prostate cancer, biopsy verified RPC was found to be significantly predictive of biochemical DFS with an approximately 40% absolute difference in favour of negative biopsy [95]. However, RCP is not shown to predict clinical DFS, CSS or OS in prospective studies. Moreover, the incidence and clinical implications of biopsy verified RPC in patients treated with endocrine therapy alone is unknown.

**Side effects from diagnostic procedures and therapy**

Diagnostic procedures as well as therapy in non-metastatic prostate cancer are associated with considerable side effects which may affect QOL and even be fatal. Although there is a vast body of literature on this issue including retrospective and prospective observational studies, RCTs comparing different treatment modalities with main focus on side effects have been virtually non-existent. Comparisons of side effects from different treatment modalities are hampered by the methodological variability in data acquisition (different questionnaires), reporting (physician vs. patient reported), and definition of function as well patient characteristics in the published studies [107, 156-158].

Widespread PSA measurement in asymptomatic men results in a considerable over-diagnosis of “insignificant tumours” as well as false positives [34, 36], resulting in psychological distress as well as unnecessary and often repeated diagnostic procedures, treatment and follow-up [40, 159].

Transient hematuria, rectal bleeding and hematospermia as well as mild pain are frequent and usually self-limiting side effects in diagnostic prostate biopsy. Moderate to severe pain is reported in 11-30 % [160-163], whereas complications that require medical or surgical intervention such as major bleeding, urinary retention and complicated urinary tract infections are rare (<1-2%) in diagnostic biopsy [160, 164-166]. However, there are no published reports on posttreatment prostate biopsy complications.

The most frequent complication to PLND is symptomatic pelvic lymphocele which is reported in 3-18%, depending on the extent of dissection [62, 63, 167]. Other complications such as thrombosis and pulmonary embolism, haematoma, wound infection and sepsis are reported in up to 6% [62].

The vast majority of patients on castration therapy experience loss of sexual function [168], and 80% report hot flashes [169]. Moreover, castration is associated with loss in bone-mineral density, and in a large population-based study the number needed to harm with respect to bone fracture within 12 to 60 months from start of therapy was estimated to be 28 and 16 for LHRH-agonist and orchiectomy, respectively [170]. Also, castration is significantly associated with an increase in total cholesterol and triglyceride serum levels [171]. In a population-based cohort study including more than 22,000 men with prostate cancer, patients on castration therapy for more than 1 year had a 20% higher relative risk of cardiovascular morbidity compared to untreated patients [172]. Furthermore, neoadjuvant TAB is reported to be associated with increased mortality in patients with a history of myocardial infarction or congestive heart failure due to coronary heart disease [173], although no difference in cardiovascular mortality was found in RCTs comparing long term adjuvant castration with no ADT in patients receiving EBRT [97, 174]. However, the risk of cardiovascular morbidity in patients treated with antiandrogens is unknown, whereas mineral density in patients on antiandrogen monotherapy was found to be maintained at 6 years in a prospective cohort study [175]. Moreover, bicalutamide was superior to castration with respect to maintained physical capacity and sexual interest in a RCT. However, gynecomastia

occurred in 50% of patients on bicalutamide and in <5% following castration. [89]. Although rarely severe, ADT is associated with elevations in aminotransferases, slight anaemia and diarrhoea [176, 177].

In patients operated on with RP, difference in functional outcome between open and minimally invasive procedures (laparoscopy) is not documented [107]. Anastomotic stricture is reported in less than 10% in prospective non-randomized studies [178, 179], whereas between 30 and 50% of patients report some degree of urinary incontinence at 3 months follow-up. However, successive improvement occurs in the majority, and 80-92% of patients are continent within one year [180-184]. In a RCT, intensive pelvic floor muscle training is shown to enhance urinary control [184]. The reported incidence of erectile dysfunction (partial or complete) varies considerably in the literature from less than 10% up to 100% [185]. The incidence depends on surgical technique, and is low in patients selected for nerve sparing procedures [186, 187]. Moreover, recovery frequently occurs within two years or more [188]. Postoperative inguinal hernia following open RP occurs in 12-20%, most frequently within the first two years. The risk seems to be higher in patients previously operated on with hernioplasty and in patients with postoperative wound infections [189-192]. The reported incidence of other rare, although potentially serious complications, such as rectal injury, unexpected bleeding and venous thomboembolism is around 1% or less [193], whereas the 30-day mortality is estimated to be 0.5% [194].

Following RT, symptoms of acute radiation cystitis and prostatitis with increased frequency, dysuria and incomplete emptying as well as proctitis (rectal discomfort and increased defecation frequency) are usually transient with gradual recovery within a few weeks. Recovery may, however, be prolonged in patients receiving brachytherapy [193, 195-197]. Late radiation side effects develop over years due to gradual nerve damage and changes in the small vessels resulting in hypoxia, mucosal thinning and fibrosis as well as telangiectasia formation. The risk of late toxicity is dependent on several factors including total irradiation dose and volume [193, 197, 198]. In a retrospective study on late urinary and

intestinal side effects occurring within 24-56 months after irradiation for prostate cancer, 200 patients were compared with an age-matched control population using a self-assessment questionnaire. In the patient group, 50% reported some kind of urinary problems as compared to of 25% the controls (urgency 42 vs. 19%; starting problems 33 vs. 22%; leakage 32 vs. 11%). Intestinal problems in the patient and control groups were reported in 14 and 59%, respectively (mucus 38% vs. 4%; cramp 14% vs. 5%; leakage 27% vs. 2%; blood 36% vs. 2%). However, 90% of the irradiated patients reported the problems to be minor [199]. Radiation to the penile bulb and neurovascular bundles may lead to erectile dysfunction caused by venous insufficiency and direct nerve damage. In a prospective cohort study, 286 and 901 prostate cancer patients aged 55–74 years received EBRT without ADT and radical prostatectomy, respectively. Although potency declined in both groups, erectile dysfunction was more prevalent in the RP group at 5 years (79 vs. 64%). On the other hand, some recovery was observed in the RP group between 2 and 5 years follow-up, whereas the function continued to decline in the EBRT group [200]. In the EBRT dose-escalation RCTs, no or moderately increased late side effects was found in patients receiving the higher doses [108-111]. Radiation induced secondary cancer is a rare, although serious side effect. A population-based cohort study of nearly 18000 prostate cancer patients treated with EBRT (47%) and prostatectomy (53%) evaluated incident cases of cancer diagnosed 60 months or later after therapy. The incidence of pelvic malignity such as bladder and rectal cancer as well as lung cancer was significantly higher patients treated with EBRT. The absolute difference in risk of being diagnosed these malignancies was found to be 3.9, 2.4 and 5.2%, respectively [201].

# AIMS OF THE STUDIES

The aim of this thesis is to evaluate outcomes following therapy and a diagnostic procedure in patients treated for non-metastatic prostate cancer in order to answer the following specified research questions:

1. Histopathological outcome following RRP in terms of locally advanced (pT3) tumours and intra- and extra capsular tumour margins. Research questions:
    A) Is there evidence that histopathological outcome improves over time following the implementation of RRP?
    B) Does patient selection and/or surgical technique influence on the histopathological outcome?
2. Clinical outcome (survival and side effects) in patients treated with either ADT alone or combined with EBRT. Research questions:
    A) Does the addition of EBRT to ADT improve survival?
    B) Does the addition of EBRT to ADT have an impact on therapy side effects?
3. Histopathological outcome assessed by posttreatment biopsy in patients treated with either ADT alone or combined with EBRT. Research questions:
    A) Does the addition of EBRT to ADT improve local tumour control?
    B) Does residual prostate cancer in patients on ADT plus EBRT or ADT alone predict clinical outcome and survival?
4. Clinical outcome in terms of patient-reported side effects from posttreatment prostate biopsy in patients treated with either ADT alone or combined with EBRT. Research questions:
    A) What is the incidence of posttreatment biopsy side effects?
    B) Are posttreatment prostate biopsy side effects increased in patients on ADT plus EBRT compared to side effects in patients on ADT alone?

# MATERIAL AND METHODS

## Study 1

### Rationale

The aim of study 1 was to evaluate the initial experience with open RRP at Trondheim University Hospital. When this study was initiated, the prognostic significance of pT-stage and surgical margins were not evaluated in prospective studies, although histopathological outcome following RP was frequently reported as "oncological outcome" [202, 203]. However, there was some evidence, based on retrospective studies, that a pT3-stage as well as positive surgical margins and a high Gleason score predicted an unfavourable DFS [204-208]. Thus, histopathological outcome in terms of pT-stage, margin status and tumour grade was chosen as outcome measures.

### Study design

A retrospective cohort study.

### Study population

Open RRP was implemented at Trondheim University hospital in 1996. As of December 31 2001, a total of 183 patients had undergone the operation. The RRP-specimens from the initial 16 patients were not available for re-examination. Thus, the study population consists of the subsequent 167 consecutive patients with no evidence of metastasis operated on with RRP by three surgeons, divided into three chronological cohorts as follows:

Cohort I (n= 55; 33%) operated on between December 1996 and March 1998.

Cohort II (n= 56; 33.5%) operated on between April 1998 and July 1999.

Cohort III (n=56; 33.5%) operated on between August 1999 and December 2001.

Data on diagnosis and baseline characteristic (age, TNM-stage and s-PSA) were recorded from the patients' medical records. The cT staging was made by performing digital rectal examination and TRUS, whereas a bone scan and chest X-ray was used to assess M-stage.

### Histopathological evaluation

For microscopic evaluation, six to 10 transverse sections from each of the 167 RP specimens were randomly assigned for re-examination by one of two pathologists following a strictly defined protocol, without any knowledge of the clinical data or the original histopathology report. Tumour grade (Gleason score), pT stage and the tumour involvement of the surgical margins were recorded. Positive tumour margins were classified as either extra- or intracapsular. The site of positive tumour margins with respect to the prostate gland was recorded at the following locations: anterior, posterior, posterolateral, apex and base.

## Study 2

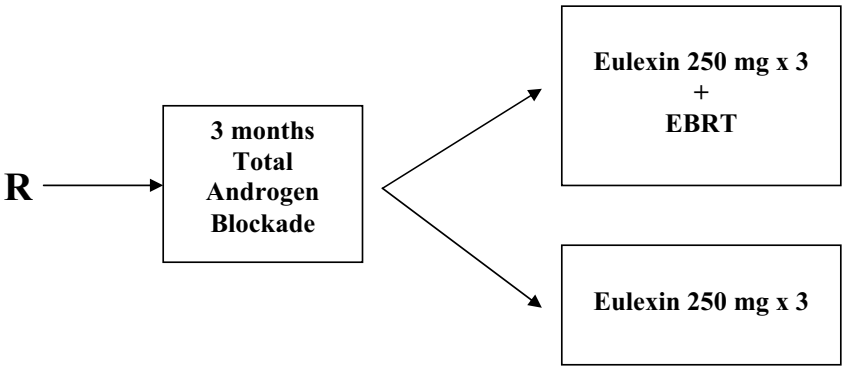
### Rationale

For decades, both RT and ADT alone have been acceptable treatments for locally advanced prostate cancer. When this study was initiated, the effect of these treatment modalities were not compared in prospective trials, and the independent role of prostatic irradiation with respect to survival was controversial. To address this issue, the SPCG and the Swedish Association for Urological Oncology initiated the SPCG-7 study in 1995. The primary objective was to evaluate if CSS can be improved in patients treated with a combination of EBRT and ADT as compared to ADT alone. The secondary objectives were to evaluate time to biochemical progression, time to symptoms related to local progression, time to symptoms related to distant progression, and to evaluate side effects with special focus on sexual function, urinary and gastrointestinal morbidity.

**Design**

An open randomised prospective clinical trial with comparative parallel design. Eligible patients were randomised to receive three months with neoadjuvant TAB followed by either antiandrogen therapy alone or combined with EBRT (Figure 4). Stratification was according to study centre, cT-stage, and WHO tumour grade.

Figure 4. Study design, SPCG-7.




**Study population**

The inclusion criteria were histological verified prostate cancer cT3 (WHO tumour grade 1-3) N0M0 or cT1b-T2 (WHO tumour grade 2-3) N0M0, age ≤75 and a life expectancy of ≥10 years. All patients with a serum PSA value ≥11.0 ng/ml underwent a diagnostic PLND to select the eligible pN0 patients. Patients with a s-PSA value ≤10.9 ng/ml were defined as N0. The M0 status was established by bone scanning and chest X-ray.

**Study treatment and follow-up**

Three months neoadjuvant TAB consisted of a LHRH agonist (leuprorelin 3.75 mg a month for 3 months or one 11.25 mg injection) combined with an oral antiandrogen (flutamide 250 mg three times a day). After 3 months of TAB, flutamide was continued in all patients until progression or death. No change of treatment was recommended in case of biochemical progression only. The recommended treatment of local progression was optional: Surgical castration or treatment with a LHRH agonist, transurethral resection of the prostate (TUR-P) or palliative RT. In distant progression, castration well as discontinuation of the anti-andogen was recommended.

A standard three-dimensional conformal EBRT technique was applied with a prescribed central dose of 50 Gy to the prostate and the seminal vesicles. A sequential boost of at least 20 Gy was added to the prostate, which received a total dose of minimum 70 Gy. A margin of 20 mm (15 mm in posterior direction) was added. If optimum immobilization could be achieved, the margins were reduced accordingly. Dose heterogeneity of 95–107% was allowed. To compensate for internal prostate movement and uncertainty in daily setup, a geometrical margin (2 cm) was established between the CT-verified prostate or seminal vesicles and the edge of the field. When invasion to the seminal vesicles was detected using palpation or TRUS-guided biopsy, 70 Gy was given to the prostate as well as the seminal vesicles. If more than half of the rectal cross-section received an accumulated dose higher than 50 Gy, the posterior margin was reduced. Pelvic lymph nodes were not intentionally irradiated.

A clinical examination and assessment of PSA, liver function, and blood cell counts was done every 3 months for the first year and every 6 months thereafter. The ASTRO-definition of PSA recurrence (increase in PSA $\geq$2 ng/ml above nadir) was used [131]. Adverse events concerning pain, use of analgesics, nausea/vomiting, breast tenderness, hot flushes, urinary problems, sexual function, bowel problems, were recorded by the treating physician at each visit (Appendix 1). Patient-reported quality of life was assessed using the

European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaire (Appendix 2) [209]. The questionnaires were filled out at baseline, at 3 and 6 months, and thereafter at 1, 2, 4, 8, and 10 years after start of treatment.

All included patients were linked to the nationwide population registries in Sweden, Norway, and Denmark (Feb 22, 2008) to ensure complete follow-up regarding survival.

## Study 3

### Rationale

In 2001, the SPCG-7 study board initiated a side study:" Posttreatment prostatic biopsies after antiandrogen treatment with or without radiotherapy of locally advanced prostatic cancer", abbreviated *Biopsy side-study*.

At that time, the clinical significance of post-radiotherapy RPC was controversial [210, 211], although there was some emerging evidence that RPC could predict biochemical outcome following EBRT [212]. The beneficial effect on local control following EBRT plus neoadjuvant ADT was recently demonstrated in a RCT [153], and a prospective observational study had demonstrated a dose-response relationship with respect to local control for EBRT [152]. However, the incidence and predictive value of RPC in posttreatment biopsies following long term ADT alone or combined with EBRT was not evaluated prospectively.

The primary objective was to evaluate the incidence of residual prostate cancer in post-treatment prostate biopsies in patients treated with either endocrine therapy alone or combined endocrine and radiotherapy. Secondary objectives were to assess clinical implications of residual cancer.

### Design

Prospective design. Sub-group analysis of a RCT.

**Study population**

The *Biopsy side-study* population constitute a sub-group of patients previously included in the SPCG-7 trial at 11 Norwegian and Swedish hospitals. Whereas all patients fulfilled the inclusion criteria of SPCG-7 trial at baseline and received protocol treatment, the *Biopsy-side study* inclusion criteria were WHO performance-status 0-1 and no medical contra-indications for prostate biopsy.

**Biopsy procedure**

All patients were given prophylactic antibiotics according to local practice prior to the transrectal ultrasound guided biopsy procedure. At least two biopsies were taken from the primary lesion, followed by posterolateral sextant biopsies.

**Histopathological evaluation**

All prostate needle biopsies were fixed in neutral buffered 4% formaldehyde solution, dehydrated and separately embedded in paraffin. From all specimens 5 micron thick sections were cut and one section from each core stained with hematoxylin-eosin-saffron for histological examination performed by two pathologists without any knowledge of the clinical data or the original histopathological reports. Based on the results of microscopic evaluation, representative sections from each case were incubated with antiserum to high-molecular-weight-cytokeratin (CKHMW) to distinguish residual tumour from benign glands with radiotherapy effect [213]. Gleason score was settled by agreement using the two most prevailing growth patterns. Each tumour-containing core was graded separately. Finally each case was given an overall score according to recent guidelines [52].

**Definition of events**

PSA-recurrence: A PSA-increase ≥2.0 ng/ml above nadir-value according to the 2006 American Society of Therapeutic Radiology (ASTRO) recommendation [131].

Local progression: Increasing urinary problems (frequency, urgency, obstruction) of such a magnitude that change of treatment was necessary.

Distant recurrence: Metastases verified by X-ray, CT scan, bone scan, MRI or histological examination.

Clinical recurrence: Either local progression, distant recurrence or both.

The cause of death was classified into one of five categories: 1. Death from prostate cancer; 2. Death from other causes with prostate cancer significantly contributing; 3. Death from anticancer therapy; 4. Death from other causes without prostate cancer significantly contributing; 5. Death from unknown cause. Cancer-specific death was defined as items 1 and 2.

# STUDY 4

**Rationale**

In 2001, RPC in posttreatment biopsy following RT had been used as a surrogate outcome measure following RT for decades [214], and histological evaluation of posttreatment prostate biopsies was recommended to select patients for salvage therapy [215, 216]. Although the side effects from diagnostic prostate biopsy were well known [160-163], local ADT effects as well as late radiation injury may theoretically have influenced on posttreatment biopsy complications [197, 217]. There were, however, no published reports on posttreatment prostate biopsy side effects. The objectives of study 4 were to estimate and compare incidences of posttreatment biopsy side effects in prostate cancer patients treated with ADT alone or combined with EBRT.

**Design**

Prospective design. Sub-group analysis of a RCT.

**Study population**

The *Biopsy side-study* patients (study 3) were requested to complete a non-validated questionnaire concerning biopsy related side effects seven days after the biopsy procedure. Respondents to the questionnaire constitute the study population.

**Evaluation of side effects**

The intensity of biopsy related pain was graded by the patient using the following verbal rating scale [218]: 0-no pain; 1-slight pain (analgesics not necessary); 2-moderate pain (analgesics necessary); 3-severe pain. Post biopsy pain intensity experienced during the seven days follow-up period was graded on an identical scale. Experienced change in urinary flow (obstruction) in the seven days study period was graded on the following scale: 0-no change; 1-slightly increased obstruction; 2-severely increased obstruction; 3-urinary retention. The occurrence of urinary tract infection, pyrexia and the use of antibiotics were recorded. The occurrence and duration (days) of hematuria and rectal bleeding were recorded as well as the experience of hematospermia. Furthermore, the patients were requested to record the reason for any contact with general practitioner or hospital, and to describe in their own words any other medical problem that occurred in the seven days period.

# STATISTICAL CONSIDERATIONS

**Estimation of sample size**

Based on an assumed 65% 7-years CSS in patients on ADT alone, study 2 initially aimed to include 660 patients to detect a 10% difference between treatment groups ($\alpha = 0.05$, $1\text{-}\beta = 0.8$). When 716 patients were included, an independent Data Safety Monitoring Committee found a lower overall mortality than expected in a blinded analysis (February, 2002), and the sample size was extended to 880 patients to achieve a total of 198 prostate cancer deaths at 7 years. After 7.6 years median follow-up (February, 2008), 116 patients had died from prostate cancer. A new independent Data Safety Monitoring Committee blindly explored the power of the study. As the CSS was found to be much higher than expected (7-years OS was 90% compared with an assumed 70%) in the total study population, the committee concluded that the study had sufficient power and recommended that the results should be analyzed and published.

**Statistical analyses**

In general, categorical variables were compared using the $\chi^2$ or Fisher's exact tests. Continuous variables were compared using the Student's t-test. If not normally distributed, the Mann-Whitney U test was applied.

In study 2, the EORTC QLQ-C30 questionnaire data were transformed linearly into a 0-100 scale and analysed according to the EORTC recommendations [219]. The Wilcoxon rank-sum test was used to compare QOL scores within groups, whereas scores between groups were compared using the sign-rank test. In study 4, Pain intensity was graded according to the scale used in the EORTC QLQ-30 questionnaire, and the recommended linear transformation into a 0-100 scale was made to obtain a pain score in each case.

Moreover, all analyses in study 2 were made according to the intention to treat principle. Cumulative incidence of each endpoint was calculated, and the hypothesis that there was no difference between treatment groups was tested using Gray's test. Differences in cumulative incidence with 95% confidence intervals (CIs) were used as measures of effect.

In study 3, associations between biopsy status and time dependent outcomes were assessed in univariable analysis using the log-rank test and Kaplan-Meier curves of biochemical recurrence probability was estimated.

The associations between potential predictive variables and time independent endpoints in terms of Odds ratio (OR) with a 95% CI were assessed in multivariable analysis using logistic regression models, whereas associations with time dependent endpoints in terms of Hazard ratio (HR) with a 95% CI were assessed in multivariable analysis using Cox proportional-hazards models. Only covariates that were considered clinically relevant were included in regression analysis. In study 2, the term relative risk, synonymous to HR, was used. Moreover, interaction between treatment group and the following variables: Age, PSA level and T-stage at diagnosis were tested by a Cox proportional-hazards model in study 2. In study 3 and 4, covariates with a p-value of 0.1 or less for an association with outcome in univariable analysis were included in the final regression models. As five events per variable is suggested to be sufficient in regression analysis [220], a maximum of two variables were included in the regression models in study 3 and 4 in case of 10 to 30 events. Otherwise, a maximum of one variable per 10 events was included.

A two-sided p-value $<0.05$ was considered statistically significant in all the analyses.

# RESULTS

## Study 1

### Patients

The prostate cancer diagnosis was verified by biopsy in 152 (91%), TUR-P specimens in 12 (7%) and cytology in 3 (2%) patients, respectively. Whereas 164 (98%) had organ confined tumours (cT-stage 1-2) at pre-operative staging, 3 (2%) patients had cT3 tumours. Mean pre-operative PSA was 10.2 (range 1.6-39.2) ng/ml, and significantly higher in cohort I compared to cohorts II and III: 13.2, 9.0 and 8.5 ng/ml, respectively ($p<0.05$).

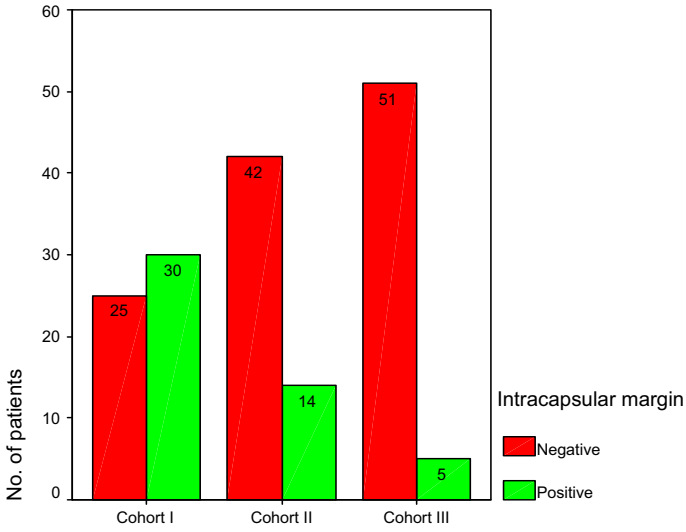
### Histopathology

Locally advanced (pT3a-b) tumours were significantly more common in cohort I (44%) compared to cohorts II and III (20% in both cohorts), $p<0.05$.

The proportion with positive tumour margins were higher in cohort I, compared to cohorts II and III (58, 30 and 13%, respectively), $p<0.05$. Moreover, positive intracapsular tumour margins (Figure 5) were found in 55% of the RRP specimens in cohort I, compared to 25% in cohort II and 8.9% in cohort III, $p<0.05$, whereas pT2 tumours with positive margins in cohorts I-III was found in 57%, 26% and 8.9%, respectively, $p<0.05$.

Low-grade tumours (Gleason score 4-6) were statistically significant more common in Cohort III (58.9%) compared to cohorts I (31.5%) and II (34%).

Figure 5. Intracapsular tumour margins in cohort I-III.



# Study 2

**Patients**

Whereas a total of 880 patients were assessed for eligibility after written informed consent, 875 met the inclusion criteria and were included in the study (figure 6). The treatment groups were well balanced with respect to clinical baseline characteristics and demographics (table 4).

Figure 6. SPCG-7 trial profile [221]

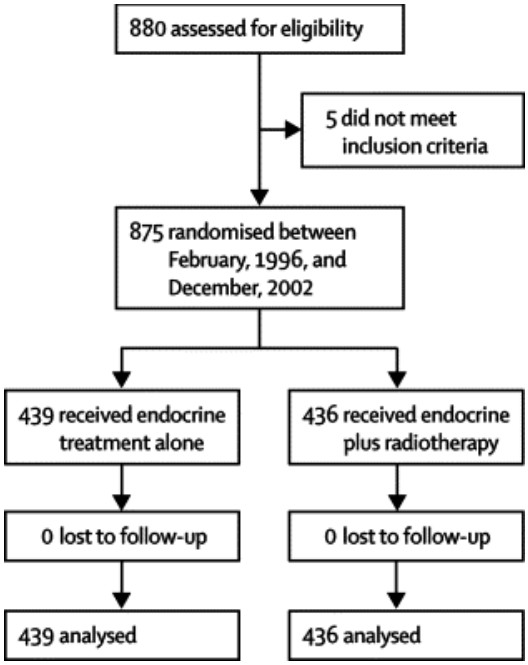


Table 4. Baseline characteristics of patients included in the SPCG-7 study [221].

| | Endocrine (N=439) | Endocrine plus radiotherapy (N=436) |
|---|---|---|
| Age in years, mean (SD) | 66·2 (5·1) | 65·7 (5·5) |
| Median PSA (IQR), ng/mL | 16·0 (8·9–27·0) | 16·0 (9·0–26·7) |
| Mean PSA, ng/mL | 19·8 | 19·9 |
| Tumour stage, number (%) | | |
| T1b | 1 (0·2) | 2 (0·5) |
| T1c | 7 (1·6) | 9 (2·1) |
| T2 | 83 (18·9) | 86 (19·7) |
| T3 | 347 (79) | 335 (76·8) |
| Unknown | 1 (0·2) | 4 (0·9) |
| WHO grade, number (%) | | |
| I | 66 (15) | 65 (14·9) |
| II | 283 (64·5) | 289 (66·3) |
| III | 84 (19·1) | 80 (18·3) |
| Unknown | 6 (1·4) | 2 (0·5) |
| Seminal vesicle involvement, number (%) | 107 (24·4) | 96 (22·0) |
| PSA level, number (%) | | |
| <4 ng/mL | 26 (5·9) | 22 (5·0) |
| 4–10 ng/mL | 104 (23·7) | 110 (25·2) |
| 10·1–20 ng/mL | 132 (30·1) | 132 (30·3) |
| 20·1–30 ng/mL | 90 (20·5) | 85 (19·5) |
| >30 ng/mL | 87 (19·8) | 87 (20·0) |

PSA=prostate specific antigen.

**Study therapy**

All patients allocated to the endocrine plus radiotherapy group received EBRT according to protocol with a median dose of 70 Gy with an interquartile range (IQR) of 69.5–70.6 Gy. The flutamide dose was reduced in 35 (8%) in the endocrine and 58 (13.3%) patients in the endocrine plus radiotherapy group, whereas 77 (17.5%) in the endocrine and 88 (20.2%) patients in the endocrine plus radiotherapy group had their treatment changed to bicalutamide.

**Survival analysis**

No patient was lost from follow-up due to emigration. At a median follow-up of 7.6 years (range 0.2–11.9 years), a total of 224 patients had died of whom 116 patients died of prostate cancer.

The cumulative 7-years cancer-specific mortality incidence was 9.9% (95% CI 7.1–12.8%) in the endocrine and 6.3% (3.9–8.6%) in the endocrine plus radiotherapy group (difference 3.7%, 0.0–7.4%). At 10 years, the cumulative incidence for cancer-specific mortality increased to 23.9% in the endocrine group and to 11.9% in the endocrine plus radiotherapy group (difference 12.0%, 4.9–19.1%). The relative risk of cancer-specific death was 0.44 (0.30–0.66, $p<0.0001$) in favour of the endocrine plus radiotherapy group.

Moreover, the addition of EBRT to ADT yielded an absolute over all mortality difference of 3.6% (95% CI –1.7 to 8.8%) at 7 years and 9.8% (0.8–18.8%) at 10 years with a relative risk of overall death of 0.68 (0.52–0.89, $p=0.004$) in favour of the endocrine plus radiotherapy group.

At 7 and 10 years, the cumulative incidence of PSA recurrence was 71.1% (95% CI 66.3–75.9%) and 74.7% (69.6–79.8%) in the endocrine group, and 17.6% (13.6–21.5%) and 25.9% (19.3–32.6%) in the endocrine plus radiotherapy group. The relative risk of PSA recurrence was 0.16 (0.12–0.20, $p<0.0001$) in favour of the endocrine plus radiotherapy group.

No significant effect modification of the combined treatment according to T stage, PSA level at diagnosis, or age at inclusion was seen for any of the endpoints.

**Side effects and quality of life**

As assessed by the treating physician at 5 years follow-up, significantly more patients in the endocrine plus radiotherapy group had urinary incontinence, urgency, urethral stricture, and erectile dysfunction compared to patients in the endocrine group, (table 5).

Table 5. Proportion of patients reporting specific levels of distress or dysfunction as reported by treating doctor at baseline and 5 years after treatment start [221].

| | Endocrine | Endocrine plus radiotherapy | p value |
|---|---|---|---|
| **Bladder obstruction/sclerosis (yes*)** | | | |
| Baseline | 14/428 (3%) | 11/425 (3%) | 0·686 |
| 60 months | 6/269 (2%) | 6/329 (2%) | 0·775 |
| **Urethral stricture (yes*)** | | | |
| Baseline | 1/428 (0%) | 1/425 (0%) | 1·000 |
| 60 months | 0/269 (0%) | 6/329 (2%) | 0·035 |
| **Urinary frequency per 24 h (>10)** | | | |
| Baseline | 59/424 (14%) | 71/420 (17%) | 0·253 |
| 60 months | 47/265 (18%) | 58/328 (18%) | 1·000 |
| **Urgency (yes*)** | | | |
| Baseline | 29/428 (7%) | 29/425 (7%) | 1·000 |
| 60 months | 21/269 (8%) | 47/329 (14%) | 0·014 |
| **Incontinence, urinary (moderate or total†)** | | | |
| Baseline | 2/428 (0%) | 8/424 (2%) | 0·063 |
| 60 months | 7/269 (3%) | 22/330 (7%) | 0·022 |
| **Intestinal symptoms (moderate or severe‡)** | | | |
| Baseline | 0/430 (0%) | 1/425 (0%) | 0·497 |
| 60 months | 2/269 (1%) | 10/331 (3%) | 0·075 |
| **Erection (not enough or no erection)** | | | |
| Baseline | 112/337 (33%) | 112/314 (36%) | 0·563 |
| 60 months | 173/213 (81%) | 236/266 (89%) | 0·027 |
| **Sexual activity (last year or not last year)** | | | |
| Baseline | 143/307 (47%) | 152/288 (53%) | 0·140 |
| 60 months | 158/187 (84%) | 194/227 (85%) | 0·784 |

*Not graded. †Use diaper or total incontinence. ‡Diarrhoea requiring parasympatholytic drugs (>5 stools a day). Sometimes medication with imodium or pred-clysma; grade 2 toxicity. The following recorded symptoms were not significantly different between groups and are therefore not included in table 3: pain, analgesics, nausea/vomiting, hot flushes, diarrhoea, macroscopic haematuria, and other symptoms.

There was no difference in compliance to the EORTC QLQ-C30 questionnaire (table 6) at baseline and during follow-up. The questionnaire was retuned by 85% in the endocrine and 89% in the endocrine plus radiotherapy group at 4 years. Social function was the only function scale whereas diarrhoea was the only symptom that differed significantly between the two groups. Mean social function score in the endocrine group was 80.7 compared to 76.2 in the endocrine plus radiotherapy group (p=0.01), and moderate or severe diarrhoea were reported by 32 of 337 (9.5%) in the endocrine and 39 of 355 (11.6%) patients in the endocrine plus radiotherapy group, p=0.003.

Emotional function was significantly improved at 4-year follow-up (mean score 85) compared with the baseline assessment (mean score 82) in the endocrine plus radiotherapy

group, p=0.006. Dyspnoea and fatigue were the only symptoms that increased significantly between baseline and 4-year follow-up in both groups (table 5).

Table 6. Quality of life scores (EORTC QLQ-C30) in endocrine group and endocrine plus radiotherapy group[221]

| | Endocrine | | | Endocrine plus radiotherapy | | | p (group) | |
|---|---|---|---|---|---|---|---|---|
| | Baseline (N=413) | 4 year (N=340) | p (time)† | Baseline (N=423) | 4 year (N=359) | p (time)† | Baseline (group)‡ | 4 year (group)§ |
| **Functioning scale QLQ-C30*** | | | | | | | | |
| Physical function | 98·0 | 96·0 | <0·001 | 97·7 | 95·6 | <0·001 | 0·666 | 0·305 |
| Role function | 87·0 | 81·0 | <0·001 | 84·2 | 79·7 | 0·010 | 0·120 | 0·674 |
| Emotional function | 84·6 | 85·8 | 0·098 | 81·5 | 84·6 | 0·006 | 0·031 | 0·422 |
| Cognitive function | 88·1 | 82·1 | <0·001 | 85·8 | 80·8 | <0·001 | 0·033 | 0·362 |
| Social function | 88·0 | 80·7 | <0·001 | 85·7 | 76·2 | <0·001 | 0·092 | 0·010 |
| Global health/ quality of life | 78·4 | 76·1 | 0·189 | 77·5 | 73·1 | 0·005 | 0·661 | 0·059 |
| **Single symptom QLQ-C30¶** | | | | | | | | |
| Fatigue | 17·1 | 26·4 | <0·001 | 20·6 | 27·9 | <0·001 | 0·235 | 0·528 |
| Nausea/vomiting | 2·2 | 3·6 | 0·054 | 2·5 | 3·6 | 0·095 | 0·934 | 0·843 |
| Pain | 10·5 | 11·6 | 0·551 | 12·3 | 11·1 | 0·440 | 0·603 | 0·400 |
| Dyspnoea | 12·7 | 23·0 | <0·001 | 13·0 | 25·5 | <0·001 | 0·866 | 0·402 |
| Insomnia | 14·8 | 19·3 | 0·004 | 16·7 | 19·1 | 0·222 | 0·096 | 0·905 |
| Appetite loss | 4·0 | 4·4 | 0·469 | 5·0 | 5·9 | 0·628 | 0·114 | 0·228 |
| Constipation | 10·7 | 12·9 | 0·314 | 9·9 | 14·9 | 0·003 | 0·598 | 0·186 |
| Diarrhoea | 13·0 | 14·0 | 0·931 | 12·0 | 18·6 | <0·001 | 0·314 | 0·003 |
| Financial difficulties | 5·5 | 5·8 | 0·538 | 5·8 | 7·4 | 0·135 | 0·859 | 0·319 |

*On function and global quality of life scales, higher scores indicate better function or better quality of life. †Comparison between baseline and 4 years within the different groups; Mann-Whitney test. ‡Comparison between endocrine and endocrine plus radiotherapy at baseline. §Comparison between endocrine and endocrine plus radiotherapy at the 4-year follow-up. ¶Higher scores indicate more severe symptoms.

# Study 3

### Patients

The 11 participating hospitals recruited 47% (n = 415) of the SPCG-7 study population. Of these, 120 (29%) patients were successively enrolled in the *Biopsy side-study* and underwent posttreatment biopsies at a median of 45 months (range 30-97) follow-up. Thus, the *Biopsy*

*side-study* included 14% of the SPCG-7 study patients. Sixty-four patients were allocated to endocrine therapy alone and 56 patients to combined therapy. One patient allocated to endocrine therapy alone had PSA-recurrence six months after randomisation and started curative RT with a total dose of 70Gy 38 months prior to biopsy. Thus, of the included patients, 63 (53%) were in the endocrine and 57 (47%) were in the combined therapy group receiving a median radiation dose of 70Gy (range 70-78Gy).

There were no significant differences in clinical baseline characteristics (age, s-PSA, cT-stage and WHO tumour grade) between the total SPCG-7 study population and the 120 patients in the *Biopsy side-study*. Except for age (mean 67.1 vs. 64.9 years in patients on endocrine therapy alone in patients on combined therapy, respectively, p=0.047) there were no significant differences in baseline characteristics between therapy groups in the *Biopsy side-study*.

**Histopathology**

A median of 8 biopsy cores (range 2-10) were taken. No prostate tissue was found at biopsy in one patient in the endocrine and two patients in the combined therapy group. Consequently, biopsies from 117 patients (62 patients in the endocrine and 55 patients in the combined therapy group) were available for histological evaluation. Residual cancer was found in 66% (n = 41) and 22% (n = 12), respectively, $p<0.0001$. The majority of positive biopsies in the endocrine and all in the combined therapy group contained poorly differentiated (Gleason score $\geq$ 8) cancer (Table 7).

In logistic regression analysis, significant predictors of residual prostate cancer were: Endocrine therapy alone, OR 7.49 (3.18-17.7), $p<0.0001$, and baseline-PSA, OR 1.03 (1.00-1.07), p=0.044.

Table 7. Biopsy results in 117 patients with locally advanced prostate cancer treated with endocrine therapy alone or combined endocrine and radical radiotherapy.

| Biopsy result | Patients treated with endocrine therapy alone (n=62) | | Patients treated with combined endocrine and radiotherapy (n=55) | | p-value |
|---|---|---|---|---|---|
| **Residual cancer, n (%)** | **41** | **(66)** | **12** | **(22)** | **<0.001*** |
| **Time to biopsy, months (range)** | **43** | **(32-81)** | **45** | **(30-97)** | **0.27†** |
| **Median number of biopsy cores taken (range)** | **7** | **(2-10)** | **8** | **(3-11)** | **0.40†** |
| **Median number of tumour-containing biopsy cores in patients with residual cancer, (range)** | **3** | **(1-8)** | **4** | **(1-9)** | **0.45†** |
| **Gleason score, median (range)** | **8** | **(6-10)** | **8** | **(8-8)** | |
| **Gleason score 6, number (%)** | **1** | **(2.4)** | **0** | | |
| **Gleason score 7, number (%)** | **7** | **(17)** | **0** | | |
| **Gleason score 8, number (%)** | **14** | **(34)** | **12** | **(100)** | |
| **Gleason score 9, number (%)** | **15** | **(37)** | **0** | | |
| **Gleason score 10, number (%)** | **4** | **(9.8)** | **0** | | |

**Subgroups compared using *$\chi^2$ test, †Mann-Whitney U test.**

## Survival analysis

Median follow-up time for survival was 101.5 months with a range of 54 to 140 months and an inter quartile range (IQR) of 86.5 to 117.8 months, and 97 months (range 10-134, IQR 80.0-112.75) for other clinical events. Incidences of clinical events and univariable intergroup comparisons in patients with and without residual cancer are shown in Table 8.

In multivariable Cox-regression analysis, factors significantly associated with PSA-recurrence were: Residual cancer, HR 2.69 (1.45-4.99), p=0.002; Endocrine therapy alone HR 3.45 (1.80-6.62), p< 0.0005; Baseline serum PSA level, HR 1.02 (1.00-1.04), p=0.014. For local progression, a significant association with endocrine therapy alone was found, HR 11.6

(1.38-97.2), p=0.024. Also, endocrine therapy alone was significantly associated with clinical recurrence, HR 3.86 (1.30-11.5), p=0.015.

Table 8. Clinical events in 117 patients with positive and negative post-treatment biopsy performed at a median of 45 months follow-up. Except for time to PSA*-recurrence, the values shown represent number of patients with percentages in parenthesis

| Clinical event, n (%) | Patients with residual cancer (n=53) | | Patients without residual cancer (n=64) | | p-value |
|---|---|---|---|---|---|
| PSA-recurrence[†] | 39 | (74) | 17 | (27) | < 0.001[††] |
| Time from Randomisation to PSA-recurrence, months (IQR[§]) | 37 | (13-59) | 65 | (39.5-69) | 0.03 |
| PSA-recurrence at biopsy | 19 | (36) | 3 | (4.7) | <0.001[¶] |
| Local progression[#] | 14 | (26) | 3 | (4.7) | 0.002[††] |
| Distant recurrence** | 9 | (17) | 6 | (9.4) | 0.27[††] |
| Clinical recurrence*[†] | 19 | (36) | 8 | (13) | 0.006[††] |
| Cancer specific death*[§] | 10 | (19) | 3 | (4.7) | 0.025[††] |

*Prostate specific antigen. [†]PSA increase of 2 ng/ml or more above nadir-value. [§]Inter quartile range. [#]Increasing urinary frequency, urgency, or obstruction of such a magnitude that change of treatment was necessary. 12 patients had PSA-recurrence. **Metastases verified radiologically or histologically All patients had PSA-recurrence. *[†]Either local progression, distant recurrence, or both. *[§]Death from prostate cancer or other causes with prostate cancer significantly contributing. Subgroups compared using [††]log-rank test, [‡]Mann-Whitney U test, [¶]$\chi^2$ test.

# Study 4

### Patients

Of the 120 *Biopsy side-study* patients, 109 (91%) returned the side effects questionnaire. The compliance to single questionnaire items varied from 94-100%.

There were no significant differences in baseline characteristics (age, s-PSA, cT-stage and WHO tumour grade) between the total SPCG-7 study population and the 109 respondents, of

whom 57 (52%) patients received endocrine therapy alone, and 52 (48%) additional RT. A median of 8 biopsy cores (range 2-11, IQR 6-8) were obtained in both therapy groups. All patients received antibiotic prophylaxis, and 19% (n=21) were given periprostatic local anaesthesia. In the endocrine and combined therapy group, the mean age at biopsy was 71.5 (range 56-83) years and 68.8 (range 51-80) years, respectively (difference 2.7, 95% CI 0.45-4.91 years), p=0.019.

**Side effects**

The number of biopsy cores taken (less than eight cores vs. eight or more) and age at biopsy had no significant influence on the incidence of self-reported side effects. Moreover, therapy group had no significant influence on biopsy related pain (Table 9), change in urinary flow (Table 10), hematuria or hematospermia. The use of local anaesthesia had no significant impact on the incidence and degree of pain at biopsy. No patient reported complete urinary retention (grade 3).

Hematuria was reported in 26 of 56 patients (46%) in the endocrine therapy and in 18 of 52 patients (35%) in the combined therapy group. The mean duration was 2.2 days (range 1-7. Hematospermia was reported in two patients in each therapy group and unknown in 62 (60%) of 108 patients. Ten of 56 patients (18%) on endocrine therapy alone reported rectal bleeding compared to 18 of 52 patients (35%) on combined therapy (p=0.047). The mean duration was 1.6 days (range 1-4) and 2.2 days (range 1-7), respectively, p=0.031. In logistic regression analysis, a trend towards a significant association between combined therapy and rectal bleeding was found, OR 2.4 (1.0-5.9), p=0.050.No patient had urinary tract infection.

Table 9. Intensity of pain during the post-treatment biopsy procedure reported by 108 patients. Except for mean score, the figures shown represent number of patients with percentages in parenthesis

| | Therapy | |
|---|---|---|
| Pain (grade*) reported at biopsy | Endocrine therapy alone n = 57[†] | Combined therapy n = 51[‡] |
| 0 | 23 (40) | 16 (31) |
| 1 | 32 (56) | 30 (59) |
| 2 | 2 (4) | 4 (8) |
| 3 | 0 | 1 (2) |
| Mean score (SD) | 21.1 (18.5) | 26.8 (22.1) |

*** 0: No pain, 1: Slight pain, 2: Moderate pain, 3: Severe pain. [†]11 patients (19%) received local anaesthesia. [‡]10 patients (20%) received local anaesthesia. Abbreviation: SD = standard deviation.**

Table10. Patient-reported subjective change in urinary flow during seven days follow-up after post-treatment biopsy in 103. The figures shown represent number of patients with percentages in parenthesis.

| | **Therapy** | |
|---|---|---|
| **Subjective change (grade*) in urinary flow** | **Endocrine therapy n = 54** | **Combined therapy n = 49** |
| **0** | **44 (81)** | **38 (78)** |
| **1** | **11 (19)** | **9 (18)** |
| **2** | **0** | **2 (4)** |
| **3** | **0** | **0** |

***0: No change, 1: Slightly increased obstruction, 2: Severely increased obstruction, 3: Urinary retention**

# DISCUSSION

## Survival following therapy

The principal finding in the SPCG-7 study (study 2) was that the addition of EBRT to ADT in locally advanced or histological aggressive prostate cancer significantly improved OS with acceptable side effects. The estimated absolute OS benefit of 9.8% at 10 years was driven by a 12% increased CSS in favour of the combined therapy.

However, the optimal local therapy in non-metastatic prostate cancer remains controversial. After a median of 8.2 years follow-up, Bill-Axelson et al. found a modestly reduced absolute 10-year over all mortality of 5% in favour of prostatectomy in the SPCG-4 randomised study which compared open RRP with watchful waiting [103], whereas the difference was not statistically significant after an additional three years follow-up [104]. Although these results may seem inferior to that of study 2, the comparison may be severely biased by the fact the majority of the SPCG-4 study patients were diagnosed before the PSA-era and may not be representative of currently treated patients. Recently, a long term follow-up of the SWOG randomized trial number 8794 demonstrated an OS benefit from EBRT adjuvant to prostatectomy in high-risk (pT3 and/or positive surgical margin) patients [123]. In this study reported by Thompson et al., the estimated 8% absolute improved OS at 10 years was of the same magnitude as the 9.8% improvement found in study 2. Thus, both radiotherapy (if combined with ADT in locally advanced and/or histological aggressive disease) and prostatectomy (if followed by adjuvant therapy in high-risk patients) seems to be acceptable local therapies.

Although the survival curves in study 2 started to separate after 4 years follow-up, the difference was not statistically significant at 7 years. A further separation occurred after 7 years, and the difference in survival eventually became statistically significant at 10 years. Similar observations have been reported in other non-metastatic prostate cancer RCTs. The

reduced risk of metastasis and prostate cancer death found at a median follow-up of 6.2 years in the SPCG-4 study [222] translated into an OS benefit when the patients were followed for an additional three years [103]. In the SWOG 8794 randomized study on EBRT adjuvant to prostatectomy, no differenced in OS was found at 10.6 years median follow-up [223], whereas the OS benefit in favour of adjuvant EBRT was demonstrated at long term (median 12.7 years) follow-up [123]. Two other RCTs evaluated the effect of EBRT adjuvant prostatectomy. With a median follow-up of 5 and 10.6 years, respectively, a benefit in terms of DFS was found for adjuvant irradiation, although there were no significant differences in OS [121, 122]. Thus, long term follow-up is needed to detect clinically important effects of radical therapy in non-metastatic prostate cancer. This reflects the long natural history of the disease [76], and radical therapy is most likely of little value in patients with a short life expectancy (<5 years). On the other hand, a life expectancy of 10 years, which was required in the SPCG-4 and 7 studies [222], may be a too strict criterion.

The optimal scheme of ADT combined with EBRT in non-metastatic prostate cancer is still unresolved. Although several RCTs have demonstrated an OS benefit in favour of this combination over EBRT alone, these studies are heterogeneous with respect to the timing of ADT. Whereas D'Amico et al. gave TAB for six months initiated two months prior to EBRT [98], Bolla et al. started the 3 years a LHRH agonist treatment simultaneously with radiotherapy [224]. In the RCT reported by Granfors et al., ADT consisted of orchietomy 4-5 weeks prior to EBRT [99]. Moreover, a sub-group analysis of the early prostate cancer program demonstrated an OS benefit from antiandrogen therapy if given in addition to radiotherapy in patients with locally advanced disease [101]. There is, however, evidence that the effect of adjuvant ADT depends on duration. Bolla et al. found that 3 years ADT (LHRH agonist initiated on the first day of irradiation) combined with EBRT yielded superior OS over 6 months adjuvant treatment [102]. The absolute OS benefit was, however, less than 5%, and the effect of long term castration on survival should thus be weighed against side effects such as bone fractures due to loss in bone-mineral density, reduced sexual function and

cardiovascular disease [168, 170]. There is some evidence that antiandrogen therapy is superior to castration with regard to side effects [89, 175], whereas no difference in survival was found in a RCT comparing castration and antiandrogen monotherapy [89]. Withdrawal of LHRH agonists results in testosterone recovery within 3-4 months in the majority of patients on short term (≤6 months) therapy [225]. In study 2, castration therapy was only given for three months, whereas long term ADT consisted of an antiandrogen. Most likely, the patients in study 2 benefited from long term ADT, although spared from the side effects of long term castration.

## Histopathological outcome; the importance of local tumour control

Whereas the overall incidence of locally advanced (pT3) tumours found at histopathological examination in study 1 was 28%, the incidence was reduced from 52% in cohort I to 20% in cohorts II and III. The reported incidence of pT3-tumours ranges between 10 and almost 70% in previous and successive studies [104, 203, 226, 227]. However, the comparison between various patient series is hampered by the heterogeneity of preoperative risk factors such as cT-stage, Gleason score and s-PSA. Accordingly, the observed pT-stage migration in study 1 was most likely due to a stricter preoperative patient selection. This is reflected by a significantly higher preoperative s-PSA in cohort I as compared to cohorts II and III as well as successively reduced proportion of palpable tumours (cT2-3) in the study period. A similar stage migration driven by preoperative patient selection was reported by Ung et al. in a study that included over 1000 RRP-patients which were divided into three chronological cohorts [226].

Positive tumour margins were found in 33% of the RRP-specimens in study 1, consistent with the incidence of 35% reported in the SPCG-4 randomised trial [104]. On the other hand, Eggelstone and Walsh reported positive margins in only 7% of their 100 first

patients operated on with nerve sparing RRP [228]. However, comparisons of tumour margin status reported in different patient series are most likely biased by differences in pre-operative risk factors. As for pT3 tumours, the proportions of RRP-specimens with positive tumour margins declined significantly in the study period from 58% in cohort I to 31% in cohort II and 13% in cohort III. Consistently, Ung et al. reported a successive reduction in positive tumour margins in their three cohorts of RRP-patients (32, 26 and 14%, respectively) [226].

The decline in positive tumour margins in study 1 may be explained by the observed pT-stage migration towards organ confined tumours (≤pT 2). However, the proportions of RRP-specimens with positive intracapsular margins also declined significantly in the study period (55, 25 and 9%, respectively), whereas the proportion of pT3 tumours (20%) was similar in cohorts II and III. This successive reduction in positive intracapsular margins was most likely due to an improved surgical technique, which is further illustrated by the successively reduced incidence of margin positive pT2-tumours in the three cohorts (57, 26 and 9%, respectively). Guilloneau and Vallancien found 11% margin-positive pT2 tumours in patients operated on with laproscopic RP [203], whereas Salomon et al. found an incidence of 19% margin-positive pT2 tumours following open RRP [202]. This excludes the margin-positive pT3 tumours and is thus comparable to the results for cohort III in study 1.

Both the locally advanced and margin-positive tumours had a higher incidence of a Gleason score of ≥7 compared to the organ-confined and margin-negative tumours in study 1. As a high tumour grade has been shown to be a predictor of an unfavourable pathological tumour stage, this result is consistent with previous reports [66].

The most important finding in study 1 was that the surgical technique seemed to improve significantly in the study period, which resulted in a more favourable histopathological outcome in terms of negative tumour margins. This study evaluated a single institutions initial experience with a new operative technique, and the results suggest that an adequate number of operations were needed to achieve the necessary experience with the operative procedure in order to improve cancer control. The importance of experience was

demonstrated in a retrospective cohort study by Vickers et al. published in 2007, in which PSA-recurrence rates in 7765 patients treated with RRP by 72 surgeons were evaluated. The surgeons experience was found to be significantly predictive of biochemical DFS, and the estimated learning curve was steep until a surgeon had completed approximately 250 operations [229]. Vickers et al. also compared tumour margins in RRP-specimens from patients treated by inexperienced (10 previous RRP procedures) and experienced (250 previous procedures) surgeons. A 15% absolute risk reduction of positive margins in favour of patients treated by experienced surgeons was found [230]. Moreover, a positive margin following prostatectomy was convincingly shown to be a negative predictor of CSS in a large population based study [144], and it is highly likely that the patients will benefit from the improved surgical technique demonstrated in study 1.

The principal finding in study 3 was that patients on endocrine therapy alone had a three times higher incidence of local residual prostate cancer compared to patients on combined therapy. Residual cancer was significantly associated with PSA- recurrence. Whereas 78% of patients treated with EBRT plus ADT had biopsy verified local tumour control, negative biopsies were found in only 33% of patients treated with ADT alone. The proportions mimicked almost exactly the final 10 years figures on PSA recurrence in the treatment arms of the SPCG-7 trial.

In prostate cancer patients treated with EBRT, previous studies have reported local tumour control rates assessed by posttreatment biopsies ranging from 40 to over 90% [152, 155, 211, 212, 214, 231]. Comparisons of the different patient series are obviously biased, as the incidence of RPC in posttreatment biopsies depends on several factors. Tumour regression following RT occurs gradually, and a higher rate of positive and indeterminate biopsies showing treatment effect is obtained if taken earlier than two years of follow-up, whereas a significant proportion will eventually become negative if biopsy is repeated [153, 210, 212, 214]. In a three armed RCT reported by Laverdiere et al., 64 Gy EBRT alone was compared with EBRT plus either 3 months neoadjuvant TAB or 3 months neoadjuvant, concomitant and

6 months adjuvant TAB. RPC in 24 months posttreatment biopsies was found in 65, 28 and 5%, respectively, and the incidence was significantly reduced in patients who received ADT [153]. In the prospective non-randomized Memorial Sloan-Kettering Cancer Center dose-escalation study, patients with T1c-T3 tumours underwent prostate biopsy at a median of 3.3 years following EBRT with doses between 64.8 and 81 Gy in successive increments of 5.4 Gy. As reported by Zelefsy et al., a radiation dose of 75.6Gy was inferior to 81Gy in terms of local control (positive biopsy in 48% vs. 7%) [152]. This dose-response relationship seems to be dependent on risk factors like clinical tumour stage, pre-treatment PSA and tumour grade, as high risk patients require significantly larger doses to achieve biopsy verified local control [232]. Notwithstanding these possible biases, the 78% biopsy-verified local control rate in patients on combined EBRT and ADT in study 3 is in accordance with the 76% negative posttreatment biopsies taken at minimum of 2.5 years follow-up in a subgroup of patients treated with ADT plus an EBRT dose of 70.2 Gy or less reported by Zelefsky et al. [155].

Although not directly comparable [233], the tumours in study 3 were considerably less aggressive at diagnosis. Whereas more than 80% of the cancers initially were WHO grade I or II, the residual tumours were high-grade with a Gleason score $\geq$8 in all residual tumours in the combined and in 80% in the endocrine group. The shift towards a high-grade malignancy observed in this study may be caused by a gradual dedifferentiation over time, eradication of low-grade tumour elements, or a combination.

The association of residual tumour with PSA-recurrence probability observed in study 3 corresponds with previous reports [95, 154, 155, 231], including one RCT in which Crook et al. randomly assigned patients to receive either 3 or 8 months ADT neoadjuvant to 64 Gy EBRT. In this study, 24 months preplanned posttreatment biopsies were taken, and an approximately 40% absolute difference in 7 years biochemical DFS was found in favour of negative biopsy [95]. Corresponding with the results of study 3, biopsy status was shown to be predictive of biochemical DFS in a multivariable analysis which included the following covariates: biopsy status, pretreatment PSA, tumour grade and cT-stage. However, residual

cancer as well as an early PSA-recurrence is reported to be predictive of distant metastases and prostate cancer mortality in retrospective studies [132, 154, 155]. This finding was not confirmed in study 3, and the RCT conducted by Crook et al. also failed to demonstrate a significant association between RPC and clinical recurrence, CSS and OS in multivariable analysis. A significant associations between biopsy verified RPC and these clinically important outcomes remains to be demonstrated prospectively, and an extended follow-up of patients in these studies may be required. However, a survival benefit from local irradiation was clearly demonstrated in the SPCG-7 trial, and the patients in the present study constitute a subgroup of the SPCG-7 study population with similar baseline prostate cancer risk-factors and clinical outcome. Most likely, post-treatment biopsies would be required from a substantially larger patient cohort to explore the influence of residual cancer on distant metastases and survival with sufficient statistical power.

In patients unsuccessfully treated with radiotherapy for prostate cancer, eradication of the residual tumour may still be achieved with salvage prostatectomy, cryosurgery, brachytherapy or high intensity focused ultrasound (HIFU) [234-238]. However, these salvage therapies are associated with substantial morbidity, whereas cure is less likely in patients with histologically highly malignant (Gleason score $\geq$ 9) residual tumours. Thus, posttreatment biopsies are recommended by several authors to select eligible patients [215, 216, 237].

## Side effects

In study 2, physician-assessed urinary and sexual problems (urethral strictures, urgency, incontinence and impotency) at 5 years follow-up were significantly increased in patients treated with combined ADT and EBRT as compared to patients on ADT alone. The differences between the two groups were, however small (range 2-8%). Whereas approximately 50% of the study patients were sexually active at baseline, impotency was

reported in the vast majority (89 vs. 81%, respectively) at 5 years. Urinary frequency >10 times pr 24 h was the second most common problem at 5 years, although considerably less frequent (reported in 18%) and equally distributed in the two groups.

The compliance to the EORTC QLQ-C30 questionnaire was high (85%). Consistent with a recent report, fatigue was increased in both groups [219]. The same trend was observed for dyspnoea, whereas the mean scores for diarrhoea at 4 years was significantly higher in patients on combined therapy as compared both with baseline (mean score difference 6.6) and with the mean score at 4 years in patients on endocrine therapy alone (difference 4.6). In accordance with a previous report [239], increased diarrhoea may possibly explain the reduced social function score of 4.5 at 4 years in patients on combined ADT and radiotherapy as compared to patients treated with ADT alone. The late toxicity observed in study 2 is consistent with several previous reports [89, 193, 197-199, 239]. All differences between the treatment groups were, however, small and of marginal clinical significance [240], and must be deemed acceptable considering the survival benefit achieved when EBRT is added to ADT. On the other hand, further improvement of local control as well as a maintained low level of serious side effects may be achieved by dose-escalation if image guided radiotherapy as well as intensity modulated radiotherapy techniques are applied [241, 242].

The self-reported side effects were mild and self-limiting in the majority of patients who underwent posttreatment prostate biopsy. In accordance with reports on prostate biopsy side effects in previously untreated patients, the incidence of severe side effects was low, and not increased if more than eight biopsy cores were taken [164-166, 243].

More than 60 % of the patients reported biopsy related pain, whereas no more than 10% required analgesics, and only one patient reported severe (grade 3) pain. The incidence of moderate to severe pain following diagnostic prostate biopsy is previously reported to be 11-30 % [160, 161, 163, 243]. This study was not designed to evaluate the effect of local anaesthesia, and the use was infrequent and optional. Even though no significant effect on biopsy related pain was observed, local anaesthesia may still have been beneficial for some

patients. In addition, the low incidence of severe pain (grade 3) may be due to a reduced sensibility as endocrine therapy and radiotherapy reduce the prostate volume and cause fibrosis of the rectal wall [197, 198, 217].

Although 20% of the patients reported decreased urinary flow, no patient reported urinary retention. These findings do not differ from those reported in patients undergoing diagnostic prostate biopsy, with a 0.7-1.6 % reported incidence of post biopsy urinary retention [160, 161, 165, 166, 244]. Urinary tract infection which may be complicated with pyrexia and sepsis has been reported in 0.3-11% following diagnostic prostate biopsy, even if antibiotic prophylaxis was used [160, 161, 164-166, 244]. On the other hand, a single dose of oral ciprofloxacin is shown to prevent infection following prostate biopsy in a randomised placebo controlled trial [245], and orally administered ciprofloxacin concentrates in the prostatic tissue [246]. In this study, all patients received antibiotic prophylaxis with Ciprofloxacin, and clinically urinary tract infections were not observed. Based on this result, two to three doses of ciprofloxacin, starting one hour prior to posttreatment biopsy, seems to be a safe regime for prevention of urinary tract infection.

Obviously, the low incidence of hematospermia observed in study 4 was due to a low degree of sexual activity in a senior study population on prostate cancer therapy. Corresponding with the results of the present study, the incidence of minor hematuria and rectal bleeding related to prostate biopsy in previously untreated patients is reported to be 14 - 74 % and 2-40%, respectively [160, 161, 165, 166, 244]. Although therapy induced prostate gland shrinkage and fibrosis may theoretically decrease the risk of prostate bleeding as compared to pretreatment biopsy, late radiation toxicity may lead to proctitis with ulceration and bleeding and thus a more vulnerable rectal mucosa [247, 248]. Study 4 showed a trend towards an increased risk of rectal bleeding in patients treated with radiotherapy. However, the clinical significance of this finding is limited because no patient had major rectal bleeding and the mean difference in duration was less than one day.

## Limitations and strengths of the studies.

### Study 1

A logistic regression model including cohorts and preoperative risk factors (tumour grade, cT-stage and s-PSA) may have produced a more reliable estimate of the independent association between cohorts and tumour margins in study 1. However, selection biases other than an uneven distribution of these measurable preoperative risk factors may still be present in this retrospective study. For instance, the operations were performed by one of three surgeons whereas the skill of the individual surgeon may have influenced on histopathological outcome [230]. Furthermore, some patients with positive margins and/or pT3 tumors will not experience relapse [249], and clinical DFS and mortality were not evaluated in this study. Histopathological outcome as assessed in study 1 is, however, shown to be significant predictors of such clinically important outcomes in large population based studies [144, 145].

A major strength of the study is the histopathological re-examination of the RRP-specimens which was blinded with respect to the clinical data and the original histopathology report. By this approach, the risk of a detection bias is minimal. The risk of selection bias may also have been reduced by the fact that the study included all consecutive patients operated on with open RRP in the study period. Moreover, only objectively measurable variables were analyzed. This eliminates recall bias, which is an inherent problem in retrospective studies.

### Study 2

A suboptimal radiation dose of 70Gy was used, as the study was initiated before any of the dose-escalation RTCs were published [108-111]. The current EBRT standard dose of 78 Gy might increase the benefit from radiotherapy even further. This study was necessarily unblinded, which opens the possibility of detection biases, especially with regard to physician-assessed side effects. In general, physician-assessed side effects may be

problematic. Recently, Steinsvik et al. reported on discrepancies between patient and physician ratings of adverse events in the SPCG-7 trial. Although an acceptable accordance was generally found, physicians tended to over-report minor bowel problems after EBRT, whereas other symptoms, such as urinary problems, were usually under-reported [250]. Moreover, urinary and sexual problems are not directly addressed in the EORTC QLQ-C30 questionnaire. Thus, the incidence of urogenital side effects was underestimated in study 2. This was demonstrated in a subsequent analysis of the SPCG-7 patients, in which Fransson et al. assessed urinary and bowel symptoms as well as sexual function using the validated prostate-cancer symptom scale (PCSS) self-assessment questionnaire [251]. At 4 years, significantly more patients in the combined therapy group reported moderate or severe urinary problems as compared to patients on endocrine therapy alone (18 vs. 12%) Also, bowel and sexual problems were more common in patients treated with EBRT. However the intergroup difference in symptom severity was generally small and considered clinically insignificant by the authors [247].

In general, randomization reduces selection bias to a minimum. The RCT design and completeness of survival data constitutes the major strength of the SPCG-7 study. Moreover, the patient population was well characterized as all patients with a s-PSA ≤10.9 ng/ml underwent PLND to select the eligible pN0-patients, whereas all patients had negative chest X-rays and bone scans. In addition to cT3 tumours, histologically aggressive cT 1-2 tumours were eligible. Accordingly, the vast majority of the study population would currently be classified as intermediate or high-risk patients according to the risk-group classification proposed by D'Amico et al. [71], whereas patients in the low-risk group eligible for active surveillance were not included [78]. Thus, the SPCG-7 study population seems to be representative of current prostate cancer patients treated with combined ADT and EBRT, and the external validity of the study is most likely high.

**Study 3**

The amount of remaining and biologically aggressive cancer may have been overestimated in study 3. In animal studies, cancer cells remaining after irradiation may not be functionally active because they do not proliferate even after testosterone stimulation [252]. In this study, cell proliferation was not examined. Although the morphology of the individual remaining cancer cells in study 3 was that of poorly differentiated tumours, Gleason score may be artificially upgraded and thus unreliable in posttreatment biopsies due to therapy induced gland shrinkage, especially following endocrine therapy [253]. However, a high Gleason score in prostate biopsies following radiotherapy is shown to strongly predict recurrence after salvage cryotherapy [215]. Furthermore, high-molecular-weight cytokeratin (CKHMW) staining was used to distinguish therapy-induced atypia in benign glands from malignancy [213]. Thus, the false-positive biopsy rate was most likely low. By contrast, the amount of residual cancer may be underestimated because a more extended number of biopsy cores may have detected additional small tumour foci [40]. The number of biopsies taken in study 3 is, however comparable with previous reports. Zelfsky et al. performed sextant biopsy [155], whereas minimum sextant biopsy was taken by Crook et al [95]. Thus, a high false-negative biopsy rate seems unlikely. The number of patients examined with biopsy (n=117) was suboptimal with an inclusion rate of 29%. In comparison, Zelefsky et al. included 339 of 1773 patients (19%) in a study reporting on posttreatment biopsy results following EBRT for prostate cancer [155], whereas Crook et al. obtained posttreatment biopsies from 205 of 378 patients (54%) in their RCT [95]. Even though prostate cancer risk-factors were well balanced in the study population, intergroup-comparisons should be interpreted with caution because a low inclusion rate may yield a selection bias. In patients with residual cancer, median follow-up to PSA-recurrence was 37 months compared to 65 months in patients without residual cancer, whereas the biopsies were performed at a median of 45 months. Consequently, PSA-recurrence had occurred at the time of biopsy in 36% of patients with residual cancer and in only 4.7% with negative biopsy result. However, according to the written informed consent,

the biopsy result was not available for the treating physicians or the patients. Thus, it is unlikely that a selection bias has been introduced by an intention of allocating patients with PSA-recurrence and biopsy-verified residual cancer to salvage therapy. In summary, these possible limitations are unlikely to affect the general conclusions.

A major strength of the study is the prospective design with well balanced groups, which reduces the risk of selection bias. Moreover, a detection bias seems highly unlikely because the pathologist was blinded of which therapy the individual patients were allocated to and had no knowledge of any of the clinical data, whereas the number of biopsy cores obtained in patients with positive and negative biopsy was equal.

**Study 4**

Study 4 has some limitations. The self-assessment questionnaire used was not validated. However, to our knowledge, validated self-assessment questionnaires on prostate biopsy side effects have not been developed. Although the compliance to the questionnaire was high (91%), the true incidence of infrequently occurring serious complications in patients undergoing posttreatment prostate biopsy may have been underestimated due to a relatively small sample-size. For instance, no patient had rectal bleeding that required therapy, a complication which is reported to occur in less than 1% following diagnostic prostate biopsy [160, 165, 166]. Moreover, a comparison between pre- and posttreatment biopsy side effects was not planned. If patients who experienced major side effects of biopsy at diagnosis refused posttreatment biopsy, a selection bias is possible. Pain intensity was assessed using a 4-point verbal rating scale, whereas a visual analogue or a numeric rating scale may have given a more reliable estimate. However, the validity of verbal rating scales in pain intensity assessment is well documented [218]. Although the questionnaire assessed clinically important change in urinary flow (severe reduced flow and retention) subjectively, uroflowmetry was not performed, and minor changes may have been underestimated.

Notwithstanding that the results of study 4 must be interpreted with care because of these limitations, the respondents seems to be representative of the SPCG-7 study population, and the patient-reported posttreatment biopsy side effects in study 4 most likely reflect those commonly seen in clinical practice. Posttreatment biopsy has been recommended to select patients with residual tumours who may take advantage from salvage therapy [215, 216]. In Norway, salvage HIFU has been offered to patients with locally radiorecurrent prostate cancer and no metastasis since 2006. A positive posttreatment biopsy taken at least 18 months after irradiation is a mandatory eligibility criterion [237]. To our knowledge, study 4 is the first to report posttreatment prostate biopsy side effects, and the results may be helpful in patient counselling.

# CONCLUSIONS

- As assessed by histopatholgical examination of open RRP-specimens, locally advanced prostate cancers and positive tumour margins were significantly reduced over time in the initial 5 years cohort of patients treated at Trondheim University Hospital. Reduced incidence of intracapsular tumour margins and margin positive pT2 tumours over time imply that the surgical technique improved in the study period.
- The addition of 70Gy EBRT to ADT significantly improved disease free, cancer specific and overall survival in patients with locally advanced or histologically aggressive non-metastatic prostate cancer with acceptable side effects.
- The addition of 70 Gy EBRT to ADT in patients with locally advanced or histologically aggressive non-metastatic prostate cancer significantly improved local tumour control as assessed by posttreatment biopsy. Significantly more patients with histologically proven residual disease died of prostate cancer. In multivariable analysis, residual cancer was predictive of recurrence.
- Posttreatment prostate biopsy can be performed safely with a low risk of major complications. Patients who receive combined endocrine therapy and EBRT may have a modestly increased risk of rectal bleeding as compared to patients on endocrine therapy alone.

# ISSUES FOR FUTURE RESEARCH

Although prostatectomy and radiotherapy are acceptable local therapies in non-metastatic prostate cancer, the optimal local therapy in is still to be defined as the efficacy of these modalities has not been compared in RCTs. However, several issues must be taken into consideration in future prostate cancer trials. Whereas active surveillance is acceptable in low-risk patients [77-79], the optimal RP procedure (open RP vs. minimal invasive procedures such as robot-assisted RP) is still controversial [107]. The addition of ADT in high risk patients as well as dose-escalation beyond 72 Gy is recommended in the intermediate and high risk groups if EBRT is chosen, whereas the role of ADT combined with dose-escalated RT in intermediate risk patients is unclear [60]. Furthermore, at least 60Gy adjuvant EBRT should be offered patients with pT3 and/or margin positive tumours following prostatectomy [123]. Finally, chemotherapy (docetaxcel) has become standard therapy in castration resistant metastatic prostate cancer [254], and adjuvant docetaxcel after prostatectomy and EBRT is currently evaluated in the SPCG 12 and 13 randomized studies. Thus, future multimodal management of non-metastatic prostate cancer may include several treatment modalities, and to adequately design a RCT comparing the efficacy and side effects of prostatectomy and radiotherapy will certainly not be straightforward.

Whether irradiation of the pelvic lymph nodes is necessary in high risk prostate cancer treated with radiotherapy is still controversial, as a PFS benefit was demonstrated in only one of several RCTs [118-120]. A study with sufficient power to demonstrate a CSS and OS benefit from pelvic lymph irradiation, if any, is warranted. Evaluation of side effects will be essential.

Although not compared with EBRT in RCTs, dose-escalation may also be achieved with brachytherapy [113, 115]. Moreover, dose-escalation with hypofractionated EBRT is shown to yield acceptable side effects and survival in non-randomised studies [255], and the efficacy and toxicity is currently evaluated in ongoing RCTs comparing conventional

fractionation and hypofractionation schemes. The dose-escalation strategies to be tested in future radiotherapy studies may thus imply conventionally fractionated and hypofractionated, EBRT, brachytherapy as well as combinations.

Castration and antiandrogen monotherapy yields equal survival in M0 prostate cancer [89], and both therapies are shown to improve survival if combined with EBRT. Whereas several RCTs have shown the beneficial effect of castration in this setting [88], antiandrogen therapy (bicalutamide) was demonstrated to be superior to placebo in a subgroup analysis of a large randomized trial [101]. Although long term antiandrogen therapy was used in the SPCG-7 trial, RCTs comparing castration with antiandrogens in combination with irradiation for non-metastatic prostate cancer do not exist. The burden of evidence seems to lie on the antiandrogens, and a RCT with non-inferiority design appears to be appropriate way to compare antiandrogen therapy with castration in this setting.

Although immediate castration improves OS in pN+ patients operated on with prostatectomy [96], the role of adjuvant ADT in lymph node-negative patients is unclear. Possibly, the beneficial effect of ADT obtained when given in addition to local radiation therapy may also be achieved following prostatectomy. This remains to be demonstrated in a randomized study.

The predictive value of post radiation prostate biopsy is still controversial. Although study 3 as well as the prospective study conducted by Crook et al. demonstrated that a positive biopsy predicted biochemical recurrence [95], the association with metastasis and mortality remains to be shown prospectively. The predictive value of RPC with respect to these clinically important outcomes demonstrated in retrospective studies [155] remains unreliable because such studies may be severely biased. In future prospective radiotherapy studies, pre-planned posttreatment biopsies may resolve this issue if taken in a sufficient number of patients. This clarification is particularly important if posttreatment biopsies are used to select patients for post-radiation salvage therapies. Kattan et al. have developed a nomogram to predict treatment failure following EBRT [69], and recently Spiess et al.

presented a pretreatment nomogram to predict biochemical failure following salvage cryotherapy in patients with post-EBRT relapse [256]. Predictor variables included in these nomograms were cT-stage, pretreatment s-PSA, pretreatment biopsy Gleason score as well as radiation dose and the use of ADT. In a phase I/II study, a high Gleason score in post-EBRT biopsy verified residual tumour was shown to be a predictor of recurrence following salvage cryotherapy [215]. Thus, the addition of posttreatment biopsy status might possibly increase the predictive value of pre-salvavage treatment nomograms. Such nomograms should be evaluated in prospective studies.

Study 4 suggests that posttreatment prostate biopsy can be performed with a low risk of serious complications. However, the sample-size was relatively small, and this finding should be verified in a larger cohort in order to estimate the true incidence of rare and serious complications using validated self-assessment questionnaires as well as objective methods such as flowmetry. Moreover, the efficacy of local anaesthesia and antibiotic prophylaxis should be evaluated in randomised trials in the posttreatment biopsy setting.

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CLINICAL INVESTIGATION

# RESIDUAL PROSTATE CANCER IN PATIENTS TREATED WITH ENDOCRINE THERAPY WITH OR WITHOUT RADICAL RADIOTHERAPY: A SIDE STUDY OF THE SPCG-7 RANDOMIZED TRIAL

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**Purpose:** The Scandinavian Prostate Cancer Group-7 randomized trial demonstrated a survival benefit of combined endocrine therapy and external-beam radiotherapy over endocrine therapy alone in patients with high-risk prostate cancer. In a subset of the study population, the incidence and clinical implications of residual prostate cancer in posttreatment prostate biopsy specimens was evaluated.

**Methods and Materials:** Biopsy specimens were obtained from 120 of 875 men in the Scandinavian Prostate Cancer Group-7 study.

**Results:** Biopsies were performed at median of 45 months follow-up. In 63 patients receiving endocrine treatment only and 57 patients receiving combined treatment, residual cancer was found in 66% ($n = 41$) and 22% ($n = 12$), respectively ($p < 0.0001$). The vast majority of residual tumors were poorly differentiated (Gleason score ≥8). Endocrine therapy alone was predictive of residual prostate cancer: odds ratio 7.49 (3.18–17.7), $p < 0.0001$. In patients with positive vs. negative biopsy the incidences of clinical events were as follows: biochemical recurrence 74% vs. 27% ($p < 0.0001$), local progression 26% vs. 4.7% ($p = 0.002$), distant recurrence 17% vs. 9.4% ($p = 0.27$), clinical recurrence 36% vs. 13% ($p = 0.006$), cancer-specific death 19% vs. 9.7% ($p = 0.025$). In multivariable analysis, biochemical recurrence was significantly associated with residual cancer: hazard ratio 2.69 (1.45–4.99), $p = 0.002$, and endocrine therapy alone hazard ratio 3.45 (1.80–6.62), $p < 0.0001$.

**Conclusions:** Radiotherapy combined with hormones improved local tumor control in comparison with endocrine therapy alone. Residual prostate cancer was significantly associated with serum prostate-specific antigen recurrence, local tumor progression, clinical recurrence, and cancer-specific death in univariable analysis. Residual cancer was predictive of prostate-specific antigen recurrence in multivariable analysis. © 2010 Elsevier Inc.

**Prostate cancer, Radiotherapy, Endocrine therapy, Posttreatment biopsy, Outcome.**

## INTRODUCTION

In locally advanced prostate cancer, antiandrogen monotherapy is equally efficient to luteinising-hormone releasing hormone agonist therapy (1), and survival is improved if external-beam radiotherapy (EBRT) is combined with endocrine therapy (2–5). Randomized trials have shown that dose-escalated radiation therapy decrease recurrence rates, especially in patients with unfavourable clinical tumor stage, pretreatment serum prostate-specific antigen (PSA), and tumor grade (6–8). To explore the role of EBRT in locally

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advanced prostate cancer, the Scandinavian Prostate Cancer Group (SPCG) initiated the SPCG-7 trial in 1995 in which patients were randomized to endocrine therapy either alone or combined with EBRT. Combined therapy improved overall survival and reduced the10-year cancer-specific mortality by 50% (9).

Variations in serum PSA levels that may be misinterpreted as treatment failure (PSA bouncing) are commonly observed the first 2 years of follow-up in patients successfully treated with radiotherapy (10). The PSA recurrence definition is thus based on an increasing PSA above the nadir value (11). Whereas a PSA recurrence does not distinguish between local and distant failure, biopsy-verified residual prostate cancer enhances the risk of PSA recurrence, metastatic disease, and prostate cancer mortality (12–15). Moreover, the residual cancer incidence in patients treated with radiotherapy is dependent on radiation dose (15, 16), and the addition of endocrine therapy reduces the incidence in comparison with EBRT alone (15, 17). However, the incidence and clinical significance of residual cancer in patients with locally advanced tumors treated with endocrine therapy alone is unknown.

The primary aim of this prospective study was to evaluate the incidence of residual prostate cancer in posttreatment prostate biopsy specimens in patients treated with either endocrine therapy alone or combined endocrine and radiotherapy in the SPCG-7 trial. Secondary objectives were to assess the clinical implications of residual cancer.

## METHODS AND MATERIALS

### *Patients*

Locally advanced or local aggressive tumors were included in the SPCG-7 study (9). Patients were randomly assigned to receive either endocrine therapy alone or endocrine therapy plus EBRT. A total of 875 patients from Norway, Sweden, and Denmark recruited at 47 centers met the inclusion criteria and were randomized from February 1996 until December 2002. The present biopsy side-study aimed to include all consecutive patients at 11 of the 47 hospitals at approximately 30 to 42 months of follow-up. Posttreatment prostate biopsies were performed in patients with World Health Organisation (WHO) performance status 01 unless there were medical contraindications. Before inclusion, all participants received oral and written information and gave their written informed consent. The study was approved by the Regional Committee for Medical and Health Research Ethics of Middle-Norway, conducted according to the Declaration of Helsinki, and is registered as a Current Controlled Trials study (registration number ISRCTN76301727).

### *Study therapy*

After randomization, all patients were given 3 months of neoadjuvant total androgen blockade (TAB) with antiandrogen therapy (flutamide 250 mg three times daily) plus leuproline 11.25 mg subcutaneously, followed by the same flutamide dose continuously. In case of PSA recurrence only, no change of treatment was recommended. Local progression was optionally treated with medical or surgical castration, transurethral resection of the prostate, or palliative radiotherapy. If metastases were diagnosed, castration was added, and discontinuation of the antiandrogen was recommended on further progression. In patients with unacceptable side effects of flutamide, the drug was stopped and then restarted with gradually increasing doses to at least 500 mg daily. If the side effects recurred, the antiandrogen therapy was changed to bicalutamide 150 mg daily. After three months of TAB, patients allocated to combined therapy received a minimum of 70 Gy conformal EBRT with a dose of 2 Gy per fraction (9).

### *Follow-up*

Clinical examination and assessment of serum PSA was made in all patients every 3 months the first year and every 6 months thereafter. Follow-up concluded by the end of February 2008 or on the date of death. Survival status was controlled against the nationwide population registries in Sweden and Norway. No patient was lost from follow-up as a result of emigration.

### *Definition of clinical events*

*PSA recurrence.* A PSA increase $\geq$2.0 ng/mL above nadir value according to the 2006 American Society for Therapeutic Radiology and Oncology recommendation (11).

*Local progression.* Increasing urinary problems (frequency, urgency, obstruction) of such a magnitude that change of treatment was necessary.

*Distant recurrence.* Metastases verified by X-ray, computed tomography, bone scan, magnetic resonance imaging, or histologic examination.

*Clinical recurrence.* Local progression, distant recurrence, or both.

The cause of death was classified into one of five categories: (1) death from prostate cancer, (2) death from other causes with prostate cancer significantly contributing, (3) death from anticancer therapy, (4) death from other causes without prostate cancer significantly contributing, and (5) death from unknown cause. Cancer-specific death was defined as items 1 and 2.

### *Prostate biopsy procedure*

All patients were given prophylactic antibiotics according to local practice before the transrectal ultrasound-guided biopsy procedure. At least two biopsy specimens were taken from the primary lesion, followed by posterolateral sextant biopsies.

### *Histologic examination*

All prostate needle biopsy specimens were fixed in neutral buffered 4% formaldehyde solution, dehydrated, and separately embedded in paraffin. From all specimens, sections 5 $\mu$m thick were cut, and one section from each core was stained with hematoxylin-eosin-saffron for histologic examination performed by two pathologists (OAH and TV) who had no knowledge of the clinical data or the original histopathologic reports. On the basis of the results of microscopic evaluation, representative sections from each case were incubated with antiserum to high-molecular-weight cytokeratin to distinguish residual tumor from benign glands with radiotherapy effect (18). Gleason score was settled by agreement using the two most prevailing growth patterns. Each tumor-containing core was graded separately. Finally, each case was given an overall score according to recent guidelines (19).

### *Statistics*

Categoric variables were compared using the chi-square or Fisher's exact tests. Continuous variables were compared using the Student's $t$ test. If the distribution was not normal, the Mann-Whitney $U$ test was

applied. The association between residual cancer and therapy group, and baseline prostate cancer risk factors (serum PSA, WHO grade III, clinical stage T3, and seminal vesicle tumor involvement) was assessed in univariable analysis. Variables with a $p$ value of $\leq 0.1$ were evaluated simultaneously in a logistic regression model. Odds ratio (OR) with a 95% confidence interval (CI) was used as effect measure. The association between clinical events and residual cancer was assessed using the log-rank test. Kaplan-Meier curves of freedom from PSA recurrence probability were estimated in patients with and without residual cancer. Furthermore, the influence of therapy group and baseline prostate cancer risk factors on clinical events was assessed in univariable analysis. Variables with a $p$ value $\leq 0.1$ were analyzed simultaneously with the biopsy result using a Cox proportional-hazards model. Hazard ratio (HR) with a 95% CI was used as effect measure.

Given that five events per variable is suggested to be sufficient in regression analysis (20), a maximum of two variables were included in the regression models in the case of 10 to 30 events. Otherwise, a maximum of one variable per 10 events was included. A two-sided $p$ value <0.05 was considered statistically significant.

## RESULTS

### *Study population*

Eleven Norwegian and Swedish hospitals participated in the biopsy study. Of 875 patients included in the SPCG-7 trial, these hospitals recruited 415 (47%) patients. Posttreatment prostate biopsy was performed in 120 (29%) patients in these hospitals. Sixty-four patients were allocated to endocrine therapy alone and 56 patients to combined therapy. One patient allocated to endocrine therapy alone had PSA recurrence 6 months after randomization and started curative radiotherapy with a total dose of 70 Gy 38 months before biopsy. Thus, of the included patients, 63 (53%) were in the endocrine group and 57 (47%) were in the combined therapy group receiving a median radiation dose of 70 Gy (range 70–78 Gy). Three patients received more than 70 Gy.

All patients completed neoadjuvant TAB. In the endocrine therapy group, 25 patients had the flutamide dose modified in the follow-up. In 10 of these patients the antiandrogen was later changed to bicalutamide 150 mg. The corresponding figures in the combined therapy group were 21 and 8 patients. Additionally, the antiandrogen was changed to bicalutamide without flutamide dose modifications in 1 patient in the combined therapy group.

Median follow-up time for survival was 101.5 months (range, 54–140 months) and an inter quartile range (IQR) of 86.5 to 117.8 months, and 97 months (range, 10–134; IQR, 80.0–112.75) for other clinical events.

There were no statistically significant differences in clinical baseline characteristics between the total SPCG-7 study population and the 120 patients in the biopsy study (Table 1). Except for age, there were no significant differences in baseline characteristics between therapy groups in the biopsy study (Table 2).

### *Biopsy result*

A median of 8 biopsy cores (range, 2–10) were taken at a median of 45 months (range, 30–97 months) follow-up.

Table 1. Baseline characteristics of 875 men enrolled in the SPCG-7 study and of 120 patients who underwent posttreatment prostate biopsy

| Characteristic | SPCG-7 study | | Posttreatment prostate biopsy | |
|---|---|---|---|---|
| Age (y), mean (SD) | 65.8 | (5.4) | 66.1 | (6.1) |
| Median PSA, ng/mL (IQR) | 16 | (9–27) | 15.5 | (8–26.75) |
| Tumor stage, *n* (%) | | | | |
| T1b | 3 | (0.3) | 0 | |
| T1c | 16 | (1.8) | 4 | (3.3) |
| T2 | 169 | (19.3) | 18 | (15) |
| T3 | 682 | (77.9) | 98 | (81.7) |
| Unknown | 5 | (0.6) | 0 | |
| Seminal vesicle involvement, *n* (%) | 203 | (23.2) | 24 | (20) |
| WHO grade, *n* (%) | | | | |
| I | 131 | (17) | 25 | (20.8) |
| II | 572 | (65.4) | 71 | (59.2) |
| III | 164 | (18.7) | 23 | (19.2) |
| Unknown | 8 | (0.9) | 1 | (0.8) |

*Abbreviations:* SD = standard deviation; PSA = prostate-specific antigen; IQR = interquartile range.

The biopsy specimens from 1 patient in the endocrine group and 2 patients in the combined therapy group contained no prostate tissue. Consequently, biopsy specimens from 117 patients (62 patients in the endocrine group and 55 patients in the combined therapy group) were available for histologic evaluation. In 62 patients receiving endocrine treatment only and 55 patients receiving combined treatment, residual cancer was found in 66% ($n = 41$) and 22% ($n = 12$), respectively ($p < 0.0001$). The majority of positive biopsy specimens in the endocrine group and all in the combined therapy group contained poorly differentiated (Gleason score $\geq 8$) cancer (Table 3). There was no significant difference in baseline prostate cancer risk factors in patients with and without residual cancer (Table 4). In logistic regression analysis, significant predictors of residual prostate cancer were as follows: endocrine therapy alone, OR 7.49 (3.18–17.7), $p < 0.0001$, and baseline PSA, OR 1.03 (1.00–1.07), $p = 0.044$.

### *Clinical events*

Incidences of clinical events and univariable intergroup comparisons in patients with and without residual cancer are shown in Table 5.

### *PSA recurrence*

The median nadir PSA value in the study population was 0.1 ng/mL (IQR 0.1-0.1), and the level was not significantly influenced by biopsy-proven residual cancer. Moreover, the 48% incidence ($n = 56$) of PSA recurrence observed in this study was not significantly different from the 41% ($n = 362$) incidence in the total SPCG-7 study population. The estimated Kaplan-Meier curves of freedom from PSA recurrence probability in patients with and without residual cancer are shown in Fig. 1. In Cox regression analysis, factors significantly associated with PSA recurrence were as follows: residual cancer, HR 2.69 (1.45–4.99), $p = 0.002$; endocrine

Table 2. Baseline characteristics of 120 men enrolled in the SPCG-7 study who underwent posttreatment prostate biopsy

| Characteristic | Endocrine therapy alone | | Combined endocrine and radiotherapy | | *p*value |
|---|---|---|---|---|---|
| Included patients, *n* | 63 | | 57 | | |
| No prostate tissue, *n* | 2 | | 1 | | |
| Analyzed patients, *n* | 62 | | 55 | | |
| Age (y), mean (SD) | 67.1 | (5.7) | 64.9 | (6.4) | 0.047* |
| Median PSA, ng/mL (IQR) | 14.5 | (8–26.8) | 16.5 | (8–26.8) | 0.94† |
| Tumor stage, *n* (%) | | | | | 0.21‡ |
| T1c | 2 | (3.2) | 2 | (3.5) | |
| T2 | 13 | (20.6) | 5 | (8.8) | |
| T3 | 48 | (76.2) | 49 | (87.7) | |
| Seminal vesicle involvement, *n* (%) | 9 | (14.3) | 15 | (26.3) | 0.11§ |
| Unknown, *n* (%) | 1 | (1.6) | 0 | | |
| WHO grade, *n* (%) | | | | | 0.49§ |
| I | 16 | (25.4) | 9 | (15.8) | |
| II | 36 | (57.1) | 35 | (61.4) | |
| III | 11 | (17.5) | 12 | (21.1) | |
| Unknown, *n* (%) | 0 | | 1 | (1.8) | |

*Abbreviations:* SD = standard deviation; PSA = prostate-specific antigen; IQR = interquartile range; WHO = World Health Organization.

* Student's *t* test.
† Mann-Whitney *U* test.
‡ Fisher's exact test.
§ Chi-square test.

Table 3. Biopsy results in 117 patients with locally advanced prostate cancer treated with endocrine therapy alone or combined endocrine and radical radiotherapy

| Biopsy result | Endocrine therapy alone (*n* = 62) | | Combined endocrine and radiotherapy (*n* = 55) | | *p* value |
|---|---|---|---|---|---|
| Residual cancer, *n* (%) | 41 | (66) | 12 | (22) | <0.001* |
| Time to biopsy, mo (range) | 43 | (32–81) | 45 | (30–97) | 0.27† |
| Median number of biopsy cores taken (range) | 7 | (2–10) | 8 | (3–11) | 0.40† |
| Median number of tumor-containing biopsy cores in patients with residual cancer (range) | 3 | (1–8) | 4 | (1–9) | 0.45† |
| Gleason score, median (range) | 8 | (6–10) | 8 | (8–8) | |
| Gleason score 6, *n* (%) | 1 | (2.4) | 0 | | |
| Gleason score 7, *n* (%) | 7 | (17) | 0 | | |
| Gleason score 8, *n* (%) | 14 | (34) | 12 | (100) | |
| Gleason score 9, *n* (%) | 15 | (37) | 0 | | |
| Gleason score 10, *n* (%) | 4 | (9.8) | 0 | | |

* Chi-square test.
† Mann-Whitney *U* test.

therapy alone, HR 3.45 (1.80–6.62), $p < 0.0005$; baseline serum PSA level, HR 1.02 (1.00–1.04), $p = 0.014$.

*Local progression*

Two patients with biopsy-verified residual cancer in the endocrine therapy group had local progression with rising PSA, but not yet PSA recurrence according to the American Society for Therapeutic Radiology and Oncology definition. All other patients with local progression had PSA recurrence. Local progression was found in 3 patients without residual cancer, of whom all had PSA progression and 1 was later diagnosed with metastasis. Although Cox regression analysis showed no statistically significant association between residual cancer and local progression, a significant association with endocrine therapy alone was found: HR 11.6 (1.38–97.2), $p = 0.024$.

*Distant recurrence*

All patients with distant recurrence had PSA recurrence, among whom 5 patients also had local progression. Although patients with residual cancer more often had distant recurrence (17 vs. 9.4%), the difference was not statistically significant (Table 5).

*Clinical recurrence*

In patients with residual cancer ($n = 63$), clinical recurrence was more common than in patients without residual tumor ($p = 0.006$) (Table 5). However, in Cox regression analysis, only endocrine therapy alone was significantly associated with clinical recurrence: HR 3.86 (1.30–11.5), $p = 0.015$.

*Mortality*

At the cutoff point of follow-up, 26 patients had died. Whereas 13 patients died of other causes than prostate cancer, the incidence of cancer-specific death was 11% ($n = 13$), compared with 13% ($n = 362$) in the total SPCG-7 study population ($p = 0.5$). Of patients with residual cancer, 5 died of prostate cancer and 5 died of other causes with prostate cancer significantly contributing. The corresponding figures in patients without residual cancer were 2 patients and 1 patient, respectively. Although cancer-specific death occurred more frequently ($p = 0.025$) in patients with residual cancer (Table 5), no significant association was found when residual tumor and therapy group were evaluated simultaneously in Cox regression analysis.

## DISCUSSION

The principal finding in this study was that patients receiving endocrine therapy alone had a three times higher incidence of local residual prostate cancer than did patients

Table 4. Baseline prostate cancer risk factors in 117 patients with and without local residual prostate cancer

| Characteristic | With residual prostate cancer ($n$ = 53) | | Without residual prostate cancer ($n$ = 64) | | $p$ value |
|---|---|---|---|---|---|
| Median PSA, ng/mL (IQR) | 13 | (7–25.8) | 16 | (9.5–29) | 0.11* |
| Tumor stage, $n$ (%) | | | | | 0.70† |
| T1c | 2 | (3.8) | 1 | (1.6) | |
| T2 | 9 | (17) | 9 | (14) | |
| T3 | 42 | (79) | 54 | (84) | |
| Seminal vesicle involvement, $n$ (%) | 7 | (13) | 17 | (27) | 0.11‡ |
| Unknown, $n$ (%) | 0 | | 1 | (1.6) | |
| WHO grade, $n$ (%) | | | | | 0.81‡ |
| I | 10 | (19) | 15 | (23) | |
| II | 33 | (62) | 36 | (56) | |
| III | 10 | (19) | 12 | (19) | |
| Unknown, $n$ (%) | 0 | | 1 | (1.6) | |

*Abbreviations:* PSA = prostate-specific antigen; IQR = interquartile range.

* Mann-Whitney $U$ test.

† Fisher's exact test.

‡ Chi-square test.

receiving combined therapy (Table 3). Residual cancer was significantly associated with PSA recurrence. The proportions mimicked almost exactly the final 10-year figures on PSA recurrence in the treatment arms of the SPCG-7 trial (9).

The biopsy-verified local control rate in the combined therapy group was 78%. Previous studies have reported local tumor control assessed by posttreatment biopsy in 40–80% of patients receiving 70 Gy or less (12, 13, 15, 21, 22). The residual prostate cancer incidence is, however, reduced if EBRT is combined with endocrine therapy, indicating a radiosensitizing effect (15, 17, 23). In accordance with the present study results, Zelefsky *et al*. reported a local control rate of 76% in patients treated with a radiation dose of 70.2 Gy or less combined with endocrine therapy (15). In contrast, biopsy-verified local control was achieved in only 33% of patients treated with endocrine therapy alone in the present study. Although radiotherapy constitutes an essential therapeutic element, this finding illustrates the additive effect of endocrine therapy.

Tumor regression after radiotherapy occurs gradually, and a higher rate of positive and indeterminate biopsy specimens showing treatment effect is obtained if specimens are taken earlier than 2 years of follow-up. A significant proportion will eventually become negative if biopsy is repeated (13, 21, 24). In contrast to previous findings, inconclusive biopsy specimens were not observed in this study with a median of 42 months follow-up from radiotherapy to biopsy.

Although not directly comparable (25), the tumors were considerably less aggressive at diagnosis, inasmuch as more than 80% of the cancers initially were WHO grade I or II. The shift toward high-grade malignancy (Table 3) observed in this study may be caused by a gradual dedifferentiation over time, eradication of low-grade tumor elements, or a combination of both.

Table 5. Clinical events in 117 patients with positive and negative posttreatment biopsy performed at a median of 45 months follow-up

| Clinical event, $n$ (%) | With residual cancer ($n$ = 53) | | Without residual cancer ($n$ = 64) | | $p$ value |
|---|---|---|---|---|---|
| PSA recurrence* | 39 | (74) | 17 | (27) | <0.001‖ |
| Time from randomization to PSA recurrence, mo (IQR) | 37 | (13–59) | 65 | (39.5–69) | 0.03** |
| PSA recurrence at biopsy | 19 | (36) | 3 | (4.7) | <0.001†† |
| Local progression# | 14 | (26) | 3 | (4.7) | 0.002‖ |
| Distant recurrence‡ | 9 | (17) | 6 | (9.4) | 0.27‖ |
| Clinical recurrence§ | 19 | (36) | 8 | (13) | 0.006‖ |
| Cancer-specific death¶ | 10 | (19) | 3 | (4.7) | 0.025‖ |

*Abbreviations:* PSA = prostate-specific antigen; IQR = interquartile range.

Except for time to PSA recurrence, the values shown represent number of patients with percentages in parentheses.

* PSA increase of 2 ng/mL or more above nadir value.

# Increasing urinary frequency, urgency, or obstruction of such a magnitude that change of treatment was necessary. 12 patients had PSA recurrence.

§ Either local progression, distant recurrence, or both.

‡ Metastases verified radiologically or histologically All patients had PSA recurrence.

¶ Death from prostate cancer or other causes with prostate cancer significantly contributing.

‖ Log-rank test.

** Mann-Whitney $U$ test.

†† Chi-square test.

The association of residual tumor with PSA recurrence observed in this study corresponds with previous reports (12, 14, 15). However, residual cancer and early PSA recurrence are reported to be predictive of distant metastases and prostate cancer mortality (15, 26). Although study patients with residual cancer had earlier PSA recurrence than did patients with negative biopsy specimens, residual cancer had no influence on other clinical endpoints in multivariable analysis. Nevertheless, a survival benefit in favor of combined therapy was clearly demonstrated in the SPCG-7 trial (9), and the patients in the present study constitute a subset of the SPCG-7 study population with similar baseline prostate cancer risk factors and clinical outcome. Most likely, posttreatment biopsies would be required in a substantially larger cohort to explore the influence of residual cancer on distant metastases and survival with sufficient statistical power.

In patients unsuccessfully treated with radiotherapy, eradication of the residual tumor may still be achieved with cryosurgery, salvage prostatectomy, or high-intensity focused ultrasound (27–29). However, the optimal salvage therapy is unknown, and randomized trials comparing available treatment modalities are warranted. Posttreatment prostate biopsy may be useful to select eligible patients.

The study has some possible limitations. The amount of remaining and biologically aggressive cancer may be overestimated. In animal studies, cancer cells remaining after

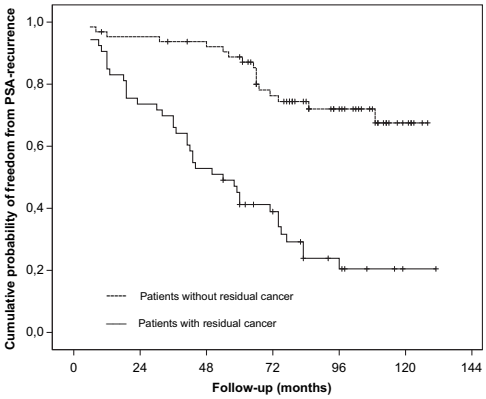


Figure 1. Cumulative probability of freedom from prostate-specific antigen (PSA) recurrence in biopsy-positive and -negative prostate cancer patients treated with endocrine therapy alone or in combination with radiotherapy.

irradiation may not be functionally active because they do not proliferate even after testosterone stimulation (30). In this study, cell proliferation was not examined. Moreover, Gleason scores may be artificially upgraded and thus unreliable in posttreatment biopsy specimens because of therapy-induced gland shrinkage, especially after endocrine therapy (31). The morphology of the individual remaining cancer cells (Table 3) was, however, that of poorly differentiated tumors (Gleason score ≥8 in all residual tumors in the combined group and in 80% in the endocrine group). Furthermore, high-molecular-weight cytokeratin staining was used to distinguish therapy-induced atypia in benign glands from malignancy (18). Thus, the false-positive biopsy rate was most likely low.

By contrast, the amount of residual cancer may be underestimated because a more extended number of biopsy cores may have detected additional small tumor foci (32, 33). However, the number of biopsy cores obtained in patients with positive and negative biopsy results was equal. Moreover, the pathologist was blinded to which therapy the individual patients were allocated to. Thus, a high false-negative biopsy rate seems unlikely, as does detection bias.

The 70-Gy radiation dose used is suboptimal. Dose escalation is necessary to improve local control and clinical outcome (6–8, 15, 16, 34), and today 78 Gy is mostly used in Scandinavian EBRT.

A suboptimal number of patients was examined with biopsy. The inclusion rate was 29%. In comparison, Zelefsky *et al.* included 339 of 1773 patients (19%) in a study reporting on posttreatment biopsy results after EBRT for prostate cancer (15). Even though prostate cancer risk factors were well balanced in the study population, intergroup comparisons should be interpreted with caution because a low inclusion rate may yield a selection bias.

Timing of posttreatment biopsy. In patients with residual cancer, the median follow-up to PSA recurrence was 37 months, compared with 65 months in patients without residual cancer, whereas the biopsies were performed at a median of 45 months. Consequently, PSA recurrence had occurred at the time of biopsy in 36% of patients with residual cancer and in only 4.7% with negative biopsy results. However, according to the written informed consent, the biopsy result was not available for the treating physicians or the patients. Thus, it is unlikely that a selection bias was introduced by an intent to allocate patients with PSA recurrence and biopsy-verified residual cancer to salvage therapy.

In summary, these possible limitations are unlikely to affect the general conclusions.

In conclusion, combined therapy with EBRT and antiandrogen gave a superior biopsy-verified local tumor control in comparison with endocrine therapy alone. The vast majority of residual tumors were poorly differentiated. Residual prostate cancer was significantly associated with serum PSA recurrence, local tumor progression, clinical recurrence, and cancer-specific death in univariable analysis. Multivariable analysis showed that residual cancer was predictive of PSA recurrence.

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# Paper 4

**Side effects of posttreatment biopsies in prostate cancer patients treated with endocrine therapy alone or combined with radical radiotherapy in the SPCG-7 randomised trial.**

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**Running head:** Posttreatment prostate biopsy side effects

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**Abstract**

**Objectives:** Posttreatment prostate biopsy side effects were evaluated in locally advanced prostate cancer patients on endocrine therapy alone or combined with radiotherapy in the SPCG-7 randomised trial.

**Materials and Methods**: 120 patients underwent transrectal, ultrasound-guided biopsy, and were requested to complete a questionnaire on side effects occurring within 7 days follow-up.

**Results:** The questionnaire was returned by 109 (91%) patients (endocrine therapy only 52%, combined therapy 48%). Therapy group had no significant influence on pain, urinary flow, hematuria or hematospermia. Pain at biopsy was reported in 63% (mild: 57%, moderate: 5.6%, severe: one patient), pain at follow-up in 31% (mild: 27%, moderate: four patients). Hematuria (mean duration 2.2 days) was reported in 41%, and reduced urinary flow in 20% (mild: 18%, severe: four patients, no patient had urinary retention). Hematospermia was scarce. No patient reported urinary tract infection. Rectal bleeding occurred in 18 % in the endocrine and 35 % in the combined therapy group ($p=0.047$) with a mean duration of 1.6 vs. 2.2 days, respectively, $p=0.031$. In logistic regression analysis, a trend towards increased rectal bleeding was found in patients on combined therapy (odds ratio 2.4, $p=0.050$).

**Conclusions:** Patient-reported posttreatment prostate biopsy side effects were mild and self-limiting.

**Key words:** Endocrine therapy; Posttreatment biopsy; Prostate cancer; Radiotherapy; Side effects.

## Introduction

Biopsy verified residual prostate cancer in patients treated with endocrine therapy and radical external beam radiotherapy (EBRT) is a predictor of biochemical and clinical relapse as well as cancer related mortality (1-3). Eradication of unsuccessfully treated local tumours is, however, possible with cryosurgery, salvage prostatectomy or high intensity focused ultrasound. Although histological evaluation of posttreatment prostate biopsies is used to select patients for salvage therapy (4-6), there are no published reports on posttreatment prostate biopsy complications.

On the other hand, hematuria, rectal bleeding and hematospermia as well as mild discomfort and pain are frequent and usually self-limiting side effects in diagnostic prostate biopsy, whereas the incidence of major bleeding, urinary retention and urinary tract infections is low (7-10). Antibiotic prophylaxis prevents bacteriuria following prostate biopsy and is commonly used (11-13). Local anaesthesia may be applied to reduce pain (14-16).

Although prostate cancer has been treated with endocrine therapy and curative radiotherapy for decades, the role of EBRT was controversial until the results of the Scandinavian Prostate Cancer Group (SPCG) 7 study were published recently. This trial, in which patients with locally advanced or aggressive non-metastatic prostate cancer were randomised to receive either endocrine therapy alone or combined with EBRT, demonstrated a superior survival in favour of the combined therapy (17).

A side study to the SPCG-7 trial was undertaken to evaluate the incidence and clinical implications of residual prostate cancer in trans-rectal ultrasound (TRUS) guided post-treatment prostate biopsies (18). This paper presents patient-reported biopsy related side effects experienced in a seven days period following the procedure.

**Materials and methods**

The SPCG-7 study inclusion criteria and study population is described previously (17). All the 875 included patients received three months total androgen blockade (TAB) with three monthly injections of an LHRH agonist (Leuprorelin) combined with an antiandrogen (Flutamide 250 mg three times per day), followed by the same dose of antiandrogen continuously. EBRT to the prostate with a minimum dose of 70 Gy in 35 fractions was started after the three months TAB in patients randomised to combined therapy. Eleven of 47 hospitals participated in the present side study which aimed to include all consecutive patients at approximately 30-42 months from randomization. Patients with World Health Organisation (WHO) performance status 0-1 and no medical contraindications to biopsy underwent TRUS-guided posttreatment prostate biopsies. All patients received antibiotic prophylaxis with three doses of 500 mg ciprofloxacin**.** The first dose was taken one hour ahead of the biopsy procedure. The use of local anaesthesia was optional dependent on local practice. All patients were requested to complete a non-validated questionnaire concerning biopsy related side effects seven days after the biopsy procedure.

All participants received oral and written information about the study and gave their written informed consent before inclusion. The study was approved by The Regional Committee for Medical and Health Research Ethics of Middle-Norway on the 15$^{th}$ of August 2000 (ref: 112-2000) and conducted according to the Helsinki Declaration of 1975, as revised in 1983.

Collection of side effect data

The intensity of biopsy related pain was graded by the patient according to the following verbal rating scale (19): 0-no pain; 1-slight pain (analgesics not necessary); 2-

moderate pain (analgesics necessary); 3-severe pain. Post biopsy pain experienced during the seven days follow-up period was graded on an identical scale.

Experienced change in urinary flow (obstruction) in the seven days study period was graded on the following scale: 0-no change; 1-slightly increased obstruction; 2-severely increased obstruction; 3-urinary retention.

The occurrence of urinary tract infection, pyrexia and the use of antibiotics was recorded.

The occurrence and duration (days) of hematuria and rectal bleeding was recorded as well as the experience of hematospermia.

Furthermore, the patients were requested to record the reason for any contact with general practitioner or hospital, and to describe in their own words any other medical problem that occurred in the seven days period.

**Statistical analyses**

Categorical variables were compared using Pearson's Chi-square or Fisher's exact tests. Continuous variables were compared using the Students T-test. If not normally distributed, the Mann Whitney U-test was used. Pain intensity was graded according to the scale used in the European Organization for Research and Treatment of Cancer (EORTC) QLQ-30 questionnaire, and the recommended linear transformation into a 0-100 scale was made to obtain a pain score in each case (20). Furthermore, biopsy related side effects (pain, urinary obstruction and bleeding complications) were transformed into dichotomous variables. The associations between these dichotomous variables and therapy group, age at biopsy and number of biopsy cores taken (less than eight vs. eight or more) were first assessed in univariable logistic regression. Variables with a p-value of $<0.1$ for an association were

included in a multivariable logistic regression model. Odds ratio with a 95% confidence interval (CI) was used as effect measure.

A two-sided p-value <0.05 was considered statistically significant.

**Results**

The participating hospitals recruited 415 (47%) of the SPCG-7 trial patients of which 120 (29%) patients accepted inclusion in the biopsy study. The 109 (91%) patients who returned the questionnaire constitute the study population in which the compliance to single questionnaire items varied from 94-100%. There were no significant differences in baseline characteristics at randomisation between the total SPCG-7 study population and the 109 respondents (Table I), of whom 57 (52%) patients received endocrine therapy alone, and 52 (48%) additional radiotherapy.

The biopsies were performed between March 2001 and October 2005 at median of 44 months with a range of 30-97 and an inter-quartile range (IQR) of 37-60 months from start of treatment. A median of 8 biopsy cores (range 2-11, IQR 6-8) were obtained in both therapy groups. All patients received antibiotic prophylaxis, and 19% (n=21) were given periprostatic local anaesthesia. In the endocrine and combined therapy group, the mean age at biopsy was 71.5 (range 56-83) years and 68.8 (range 51-80) years, respectively (difference 2.7, 95% CI 0.45-4.91 years), p=0.019.

The number of biopsy cores taken and age at biopsy had no significant influence on the incidence of self-reported side effects. Moreover, therapy group was not associated with biopsy related pain, change in urinary flow, hematuria or hematospermia. The use of local anaesthesia had no significant impact on the incidence and intensity of pain at biopsy.

Pain during the biopsy procedure was reported in 69 (64%) patients (Table II), and 33 (31%) patients reported pain during follow-up (Table III).

Change in urinary flow was reported in 21 (20%) patients (Table IV). No patient reported complete urinary retention (grade 3).

Hematuria was reported in 26 of 56 patients (46%) in the endocrine therapy and in 18 of 52 patients (35%) in the combined therapy group with a mean duration of 2.2 days (range 1-7). In one patient on combined therapy with persistent hematuria at completion of the questionnaire, seven days duration was recorded.

Hematospermia was reported in two patients in each therapy group and unknown in 62 (60%) of 108 patients.

Ten of 56 patients (18%) on endocrine therapy alone reported rectal bleeding compared to 18 of 52 patients (35%) on combined therapy (p=0.047, Pearson's Chi squared test), whereas the mean duration in patients who bled was 1.6 days (range 1-4) and 2.2 days (range 1-7), respectively (p=0.031, Mann-Whitney U-test). In logistic regression analysis, a trend towards a significant association between combined therapy and rectal bleeding was found, OR 2.4 (1.0-5.9), p=0.050.

No patient had urinary tract infection. Only the patient with grade 3 pain was admitted to hospital. Additionally, one patient contacted his general practitioner because of hematuria, and one of reasons not related to the biopsy procedure. No patient required therapeutic intervention due to bleeding complications in the study period.

**Discussion**

The self-reported side effects were mild and self-limiting in the majority of patients who underwent posttreatment prostate biopsy. In accordance with reports on prostate biopsy side effects in previously untreated patients, the incidence of severe side effects was low, and not increased if more than eight biopsy cores were taken (8-10, 21).

This study has some limitations. Although the compliance to the side effect questionnaire was high (91%), the true incidence of infrequently occurring serious complications in patients undergoing posttreatment prostate biopsy may have been underestimated due to a relatively small sample-size. For instance, no patient had rectal bleeding that required therapy, a complication which is reported to occur in less than 1% following diagnostic prostate biopsy (7, 9, 10). Moreover, a comparison between pre- and posttreatment biopsy side effects was not planned. If patients who experienced major side effects of biopsy at diagnosis refused posttreatment biopsy, a selection bias is possible. Pain intensity was assessed using a 4-point verbal rating scale, whereas a visual analogue or a numeric rating scale may have given a more reliable estimate. However, the validity of verbal rating scales in pain intensity assessment is well documented (19). Although the questionnaire assessed clinically important change in urinary flow (severe reduced flow and retention) subjectively, uroflowmetry was not performed, and minor changes may have been underestimated. Despite these limitations, the patient-reported side effects in the present study most likely reflect those commonly seen in clinical practice, and the respondents seems to be representative of the SPCG-7 study patients (Table I).

More than 60 % of the patients reported biopsy related pain, whereas no more than 10% required analgesics, and only one patient reported severe (grade 3) pain (Table II). The incidence of moderate to severe pain following diagnostic prostate biopsy is previously reported to be 11-30 % (7, 12, 22, 23), corresponding with the 12% incidence in the present study (Table 2). This study was not designed to evaluate the effect of local anaesthesia, and the use was infrequent and optional. Even though no significant effect on biopsy related pain was observed, local anaesthesia may still have been beneficial for some patients. In addition, the low incidence of severe pain (grade 3) may be due to a reduced sensibility as endocrine

therapy and radiotherapy reduce the prostate volume and cause fibrosis of the rectal wall (24-26).

Although 20% of the patients reported decreased urinary flow (Table III), no patient reported urinary retention. These findings do not differ from those reported in patients undergoing diagnostic prostate biopsy, with a 0.7-1.6 % reported incidence of post biopsy urinary retention (7, 9, 10, 12, 13).

Corresponding with the results of the present study, the incidence of minor hematuria and rectal bleeding related to prostate biopsy in previously untreated patients is reported to be 14 -74 % and 2-40%, respectively (7-9, 12, 13). Although therapy induced prostate gland shrinkage and fibrosis may theoretically decrease the risk of prostate bleeding as compared to pretreatment biopsy, late radiation toxicity may lead to proctitis with ulceration and bleeding and thus a more vulnerable rectal mucosa (27, 28). Our study showed a trend towards an increased risk of rectal bleeding in patients treated with radiotherapy.

Hematospermia was only reported by four patients and unknown in the majority (60%) even though the compliance to this questionnaire-item was high (99%). In comparison, a 10% incidence was reported during seven days follow-up after prostate biopsy in 1051 untreated patients (7). Obviously, the low incidence observed in the present study was due to a low degree of sexual activity in our senior study population on prostate cancer therapy.

Urinary tract infection which may be complicated with pyrexia and sepsis has been reported in 0.3-11% following diagnostic prostate biopsy, even if antibiotic prophylaxis was used (7-13). On the other hand, a single dose of oral ciprofloxacin is shown to prevent infection following prostate biopsy in a randomised placebo controlled trial (11), and orally administered ciprofloxacin concentrates in the prostatic tissue (29). In this study, all patients received antibiotic prophylaxis with Ciprofloxacin, and clinically urinary tract infections were

not observed. Based on this result, two to three doses of ciprofloxacin, starting one hour prior to posttreatment biopsy, seems to be a safe regime for prevention of urinary tract infection.

Notwithstanding that the results of small sample-size studies must be interpreted with care, our main conclusion is that post treatment prostate biopsy can be performed safely with a low risk of major complications. Patients who receive combined endocrine therapy and EBRT may, however, have a modest increased risk of rectal bleeding as compared to patients on endocrine therapy alone. In Norway, posttreatment biopsy is mandatory to select patients with residual tumours who may take advantage from salvage therapy (4). To our knowledge this is the first study that report on side effects of this procedure, and our results may be helpful in patient counselling.

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Table I. Baseline characteristics of the 875 men enrolled in the SPCG-7 study and of the 109 patients who responded to the posttreatment prostate biopsy side effects questionnaire.

| **Characteristic** | **Patients enrolled in the SPCG-7 study** | | **Patients who underwent post treatment prostate biopsy** | |
|---|---|---|---|---|
| Age in years, mean (SD) | 65.8 | (5.4) | 66.1 | (5.9) |
| Median PSA in ng/ml (IQR) | 16 | (9-27) | 16 | (8-27) |
| Tumour stage, number (%) | | | | |
| T1b | 3 | (0.3) | 0 | |
| T1c | 16 | (1.8) | 4 | (3.7) |
| T2 | 169 | (19.3) | 16 | (14.7) |
| T3 | 682 | (77.9) | 89 | (81.7) |
| Unknown | 5 | (0.6) | 0 | |
| Seminal vesicle involvement, number (%) | 203 | (23.2) | 22 | (20) |
| WHO grade, number (%) | | | | |
| I | 131 | (17) | 24 | (22) |
| II | 572 | (65.4) | 64 | (58.7) |
| III | 164 | (18.7) | 20 | (18.3) |
| Unknown | 8 | (0.9) | 1 | (0.9) |

Abbreviations: SD = Standard deviation, IQR = Inter quartile range, PSA = Prostate specific antigen

Table II. Intensity of pain during the post-treatment biopsy procedure reported by 108 prostate cancer treated patients treated with either endocrine therapy alone or combined with external beam radiotherapy. Except for mean score, the figures shown represent number of patients with percentages in parenthesis.

| | Therapy | |
|---|---|---|
| Pain (grade[1]) reported at biopsy | Endocrine therapy alone n = 57[2] | Combined therapy n = 51[3] |
| 0 | 23 (40) | 16 (31) |
| 1 | 32 (56) | 30 (59) |
| 2 | 2 (4) | 4 (8) |
| 3 | 0 | 1 (2) |
| Mean score (SD) | 21.1 (18.5) | 26.8 (22.1) |

[1] 0: No pain, 1: Slight pain, 2: Moderate pain, 3: Severe pain. [2]11 patients (19%) received local anaesthesia. [3]10 patients (20%) received local anaesthesia. Abbreviation: SD = standard deviation

Table III. Intensity of pain during 7 days follow-up after post-treatment biopsy procedure reported in 106 patients with locally advanced prostate cancer treated with either endocrine therapy alone or combined with external beam radiotherapy. Except for mean score, the the figures shown represent number of patients with percentages in parenthesis.

| | Therapy | |
|---|---|---|
| Pain (grade[1]) reported during 7 days follow-up | Endocrine therapy alone n = 55 | Combined therapy n = 51 |
| 0 | 37 (67) | 36 (71) |
| 1 | 18 (33) | 11 (21) |
| 2 | 0 | 4 (8) |
| 3 | 0 | 0 |
| Mean score (SD) | 10.9 (15.8) | 12.4 (21.0) |

[1]0: No pain, 1: Slight pain, 2: Moderate pain, 3: Severe pain. Abbreviation: SD = standard deviation

Table IV.

Subjective change in urinary flow during seven days follow-up after post-treatment biopsy in 103 patients with locally advanced prostate cancer treated with either endocrine therapy alone or combined with external beam radiotherapy. The figures shown represent number of patients with percentages in parenthesis.

| | Therapy | |
|---|---|---|
| Subjective change (grade[1]) in urinary flow | Endocrine therapy n = 54 | Combined therapy n = 49 |
| 0 | 44 (81) | 38 (78) |
| 1 | 11 (19) | 9 (18) |
| 2 | 0 | 2 (4) |
| 3 | 0 | 0 |

[1]0: No change, 1: Slightly increased obstruction, 2: Severely increased obstruction, 3: Urinary retention

# APPENDICES

## Appendix 1. Grading of physician-assessed side effects in study 2

## Appendix 2. Quality of life questionnaire EORTC QLQ-C30

# Grading of physician-assessed side effects in study 2

| Items | Grading scale | | | | | |
|---|---|---|---|---|---|---|
| | 0 | 1 | 2 | 3 | 4 | 5 |
| Pain intensity | None | Mild | Moderate | Severe | Intolerable | |
| Use of analgesics | None | Non-opioids occationally | Non-opioids regularly | Opioids occationally | Opioids regularly | 100% increased opioid dose or epidural administration |
| Nausea/vomiting | None | Nausea | Transient vomiting | Vomiting requiring therapy | Intractable vomiting | |
| Hot flushes | None | 1-3 times per day | 4-10 times per day | >10 times per day | | |
| Daytime urinary frequency[1] | <5 | 6-8 | 9-12 | >12 | | |
| Nighttime urinary frequency[1] | 0-1 | 2 | 3 | ≥4 | | |
| Urinary incontinence[1] | None | Slight, do not use diper | Moderate, use diper | Total incontinence | | |
| Macroscopic haematuria[1] | No | Yes | | | | |
| Urinary urgency[1] | No | Yes | | | | |
| Uretral stricture[1,2] | No | Yes | | | | |
| Bladder obstruction[1] | No | Yes | | | | |
| Diarrhoea | None | ≤2/day | >2/day | Requiering therapy | Haemorrhagic, dehydration | |
| Other intestinal symptoms | None | Increased frequency or rectal discomfort not requiring therapy. Sometimes mucus and/or blood | Diarrhoea (>5 stools/day) requiring parasymptholytic drugs. Sometimes medication with Imodium or Pred-clysma | Problems in daily routines. Continued medication with Imodium or repeated Cortison treatments | More extensive bleedings necessitating investigation or transfusions | Problems demanding surgical intervention (for example colostomy, perforation, fistula) |
| Erection | Normal | Not enough for intercourse | None | | | |
| Sexual activity | Last week | Last month | Last year | Not last year | | |

[1]During the last two weeks. [2]Evaluated with cystoscopy.

# EORTC QLQ-C30

**(Versjon 3.0)**

Pasientnummer: ☐☐☐

Dato for utfylling: ☐☐.☐☐.☐☐

Vi er interessert i forhold vedrørende deg og din helse. Vær så vennlig å besvare hvert spørsmål ved å sette et kryss x i den boksen som best beskriver din tilstand. Det er ingen «riktige» eller «gale» svar. Alle opplysningene vil bli behandlet konfidensielt.

---

| | **Ikke i det hele tatt** | **Litt** | **En del** | **Svært mye** |
|---|---|---|---|---|
| 1. Har du vanskeligheter med å utføre anstrengende aktiviteter, slik som å bære en tung handlekurv eller en koffert? | ☐ | ☐ | ☐ | ☐ |
| 2. Har du vanskeligheter med å gå en lang tur? | ☐ | ☐ | ☐ | ☐ |
| 3. Har du vanskeligheter med å gå en kort tur utendørs? | ☐ | ☐ | ☐ | ☐ |
| 4. Er du nødt til å ligge til sengs eller sitte i en stol i løpet av dagen? | ☐ | ☐ | ☐ | ☐ |
| 5. Trenger du hjelp til å spise, kle på deg, vaske deg eller gå på toalettet? | ☐ | ☐ | ☐ | ☐ |

| **I løpet av den siste uka:** | **Ikke i det hele tatt** | **Litt** | **En del** | **Svært mye** |
|---|---|---|---|---|
| 6. Har du hatt redusert evne til å arbeide eller utføre andre daglige aktiviteter? | ☐ | ☐ | ☐ | ☐ |
| 7. Har du hatt redusert evne til å utføre dine hobbyer eller andre fritidsaktiviteter? | ☐ | ☐ | ☐ | ☐ |
| 8. Har du vært tung i pusten? | ☐ | ☐ | ☐ | ☐ |
| 9. Har du hatt smerter? | ☐ | ☐ | ☐ | ☐ |
| 10. Har du hatt behov for å hvile? | ☐ | ☐ | ☐ | ☐ |
| 11. Har du hatt søvnproblemer? | ☐ | ☐ | ☐ | ☐ |
| 12. Har du følt deg slapp? | ☐ | ☐ | ☐ | ☐ |
| 13. Har du hatt dårlig matlyst? | ☐ | ☐ | ☐ | ☐ |
| 14. Har du vært kvalm? | ☐ | ☐ | ☐ | ☐ |

**Bla om til neste side**

Pasientnummer:
☐☐☐

| I løpet av den siste uka: | Ikke i det hele tatt | Litt | En del | Svært mye |
|---|---|---|---|---|
| 15. Har du kastet opp? | ☐ | ☐ | ☐ | ☐ |
| 16. Har du hatt treg mage? | ☐ | ☐ | ☐ | ☐ |
| 17. Har du hatt løs mage? | ☐ | ☐ | ☐ | ☐ |
| 18. Har du følt deg trett? | ☐ | ☐ | ☐ | ☐ |
| 19. Har smerter påvirket dine daglige aktiviteter? | ☐ | ☐ | ☐ | ☐ |
| 20. Har du hatt problemer med å konsentrere deg, f.eks. med å lese en avis eller se på TV? | ☐ | ☐ | ☐ | ☐ |
| 21. Har du følt deg anspent? | ☐ | ☐ | ☐ | ☐ |
| 22. Har du vært engstelig? | ☐ | ☐ | ☐ | ☐ |
| 23. Har du følt deg irritabel? | ☐ | ☐ | ☐ | ☐ |
| 24. Har du følt deg deprimert? | ☐ | ☐ | ☐ | ☐ |
| 25. Har du hatt problemer med å huske ting? | ☐ | ☐ | ☐ | ☐ |
| 26. Har din fysiske tilstand eller medisinske behandling påvirket ditt familieliv? | ☐ | ☐ | ☐ | ☐ |
| 27. Har din fysiske tilstand eller medisinske behandling påvirket dine sosiale aktiviteter? | ☐ | ☐ | ☐ | ☐ |
| 28. Har din fysiske tilstand eller medisinske behandling gitt deg økonomiske problemer? | ☐ | ☐ | ☐ | ☐ |

Som svar på de neste spørsmålene, sett et kryss i den boksen fra 1 til 7 som best beskriver din tilstand.

29. Hvordan har din helse vært i løpet av den siste uka?

☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7

Svært dårlig — Helt utmerket

30. Hvordan har livskvaliteten din vært i løpet av den siste uka?

☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7

Svært dårlig — Helt utmerket



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39. Petter C. Borchgrevink: MAGNESIUM AND THE ISCHEMIC HEART.
40. Kjell-Arne Rein: THE EFFECT OF EXTRACORPOREAL CIRCULATION ON SUBCUTANEOUS TRANSCAPILLARY FLUID BALANCE.
41. Arne Kristian Sandvik: RAT GASTRIC HISTAMINE.
42. Carl Bredo Dahl: ANIMAL MODELS IN PSYCHIATRY.

**1989**

43. Torbjørn A. Fredriksen: CERVICOGENIC HEADACHE.
44. Rolf A. Walstad: CEFTAZIDIME.
45. Rolf Salvesen: THE PUPIL IN CLUSTER HEADACHE.
46. Nils Petter Jørgensen: DRUG EXPOSURE IN EARLY PREGNANCY.
47. Johan C. Ræder: PREMEDICATION AND GENERAL ANAESTHESIA IN OUTPATIENT GYNECOLOGICAL SURGERY.
48. M. R. Shalaby: IMMUNOREGULATORY PROPERTIES OF TNF-α AND THE RELATED CYTOKINES.
49. Anders Waage: THE COMPLEX PATTERN OF CYTOKINES IN SEPTIC SHOCK.
50. Bjarne Christian Eriksen: ELECTROSTIMULATION OF THE PELVIC FLOOR IN FEMALE URINARY INCONTINENCE.
51. Tore B. Halvorsen: PROGNOSTIC FACTORS IN COLORECTAL CANCER.

**1990**

52. Asbjørn Nordby: CELLULAR TOXICITY OF ROENTGEN CONTRAST MEDIA.
53. Kåre E. Tvedt: X-RAY MICROANALYSIS OF BIOLOGICAL MATERIAL.
54. Tore C. Stiles: COGNITIVE VULNERABILITY FACTORS IN THE DEVELOPMENT AND MAINTENANCE OF DEPRESSION.
55. Eva Hofsli: TUMOR NECROSIS FACTOR AND MULTIDRUG RESISTANCE.
56. Helge S. Haarstad: TROPHIC EFFECTS OF CHOLECYSTOKININ AND SECRETIN ON THE RAT PANCREAS.
57. Lars Engebretsen: TREATMENT OF ACUTE ANTERIOR CRUCIATE LIGAMENT INJURIES.
58. Tarjei Rygnestad: DELIBERATE SELF-POISONING IN TRONDHEIM.
59. Arne Z. Henriksen: STUDIES ON CONSERVED ANTIGENIC DOMAINS ON MAJOR OUTER MEMBRANE PROTEINS FROM ENTEROBACTERIA.
60. Steinar Westin: UNEMPLOYMENT AND HEALTH: Medical and social consequences of a factory closure in a ten-year controlled follow-up study.
61. Ylva Sahlin: INJURY REGISTRATION, a tool for accident preventive work.
62. Helge Bjørnstad Pettersen: BIOSYNTHESIS OF COMPLEMENT BY HUMAN ALVEOLAR MACROPHAGES WITH SPECIAL REFERENCE TO SARCOIDOSIS.
63. Berit Schei: TRAPPED IN PAINFUL LOVE.
64. Lars J. Vatten: PROSPECTIVE STUDIES OF THE RISK OF BREAST CANCER IN A COHORT OF NORWEGIAN WOMAN.

**1991**

65. Kåre Bergh: APPLICATIONS OF ANTI-C5a SPECIFIC MONOCLONAL ANTIBODIES FOR THE ASSESSMENT OF COMPLEMENT ACTIVATION.

66. Svein Svenningsen: THE CLINICAL SIGNIFICANCE OF INCREASED FEMORAL ANTEVERSION.
67. Olbjørn Klepp: NONSEMINOMATOUS GERM CELL TESTIS CANCER: THERAPEUTIC OUTCOME AND PROGNOSTIC FACTORS.
68. Trond Sand: THE EFFECTS OF CLICK POLARITY ON BRAINSTEM AUDITORY EVOKED POTENTIALS AMPLITUDE, DISPERSION, AND LATENCY VARIABLES.
69. Kjetil B. Åsbakk: STUDIES OF A PROTEIN FROM PSORIATIC SCALE, PSO P27, WITH RESPECT TO ITS POTENTIAL ROLE IN IMMUNE REACTIONS IN PSORIASIS.
70. Arnulf Hestnes: STUDIES ON DOWN´S SYNDROME.
71. Randi Nygaard: LONG-TERM SURVIVAL IN CHILDHOOD LEUKEMIA.
72. Bjørn Hagen: THIO-TEPA.
73. Svein Anda: EVALUATION OF THE HIP JOINT BY COMPUTED TOMOGRAMPHY AND ULTRASONOGRAPHY.

**1992**

74. Martin Svartberg: AN INVESTIGATION OF PROCESS AND OUTCOME OF SHORT-TERM PSYCHODYNAMIC PSYCHOTHERAPY.
75. Stig Arild Slørdahl: AORTIC REGURGITATION.
76. Harold C Sexton: STUDIES RELATING TO THE TREATMENT OF SYMPTOMATIC NON-PSYCHOTIC PATIENTS.
77. Maurice B. Vincent: VASOACTIVE PEPTIDES IN THE OCULAR/FOREHEAD AREA.
78. Terje Johannessen: CONTROLLED TRIALS IN SINGLE SUBJECTS.
79. Turid Nilsen: PYROPHOSPHATE IN HEPATOCYTE IRON METABOLISM.
80. Olav Haraldseth: NMR SPECTROSCOPY OF CEREBRAL ISCHEMIA AND REPERFUSION IN RAT.
81. Eiliv Brenna: REGULATION OF FUNCTION AND GROWTH OF THE OXYNTIC MUCOSA.

**1993**

82. Gunnar Bovim: CERVICOGENIC HEADACHE.
83. Jarl Arne Kahn: ASSISTED PROCREATION.
84. Bjørn Naume: IMMUNOREGULATORY EFFECTS OF CYTOKINES ON NK CELLS.
85. Rune Wiseth: AORTIC VALVE REPLACEMENT.
86. Jie Ming Shen: BLOOD FLOW VELOCITY AND RESPIRATORY STUDIES.
87. Piotr Kruszewski: SUNCT SYNDROME WITH SPECIAL REFERENCE TO THE AUTONOMIC NERVOUS SYSTEM.
88. Mette Haase Moen: ENDOMETRIOSIS.
89. Anne Vik: VASCULAR GAS EMBOLISM DURING AIR INFUSION AND AFTER DECOMPRESSION IN PIGS.
90. Lars Jacob Stovner: THE CHIARI TYPE I MALFORMATION.
91. Kjell Å. Salvesen: ROUTINE ULTRASONOGRAPHY IN UTERO AND DEVELOPMENT IN CHILDHOOD.

**1994**

92. Nina-Beate Liabakk: DEVELOPMENT OF IMMUNOASSAYS FOR TNF AND ITS SOLUBLE RECEPTORS.
93. Sverre Helge Torp: *erb*B ONCOGENES IN HUMAN GLIOMAS AND MENINGIOMAS.
94. Olav M. Linaker: MENTAL RETARDATION AND PSYCHIATRY. Past and present.
95. Per Oscar Feet: INCREASED ANTIDEPRESSANT AND ANTIPANIC EFFECT IN COMBINED TREATMENT WITH DIXYRAZINE AND TRICYCLIC ANTIDEPRESSANTS.
96. Stein Olav Samstad: CROSS SECTIONAL FLOW VELOCITY PROFILES FROM TWO-DIMENSIONAL DOPPLER ULTRASOUND: Studies on early mitral blood flow.
97. Bjørn Backe: STUDIES IN ANTENATAL CARE.
98. Gerd Inger Ringdal: QUALITY OF LIFE IN CANCER PATIENTS.
99. Torvid Kiserud: THE DUCTUS VENOSUS IN THE HUMAN FETUS.
100. Hans E. Fjøsne: HORMONAL REGULATION OF PROSTATIC METABOLISM.
101. Eylert Brodtkorb: CLINICAL ASPECTS OF EPILEPSY IN THE MENTALLY RETARDED.
102. Roar Juul: PEPTIDERGIC MECHANISMS IN HUMAN SUBARACHNOID HEMORRHAGE.
103. Unni Syversen: CHROMOGRANIN A. Phsysiological and Clinical Role.

**1995**

104. Odd Gunnar Brakstad: THERMOSTABLE NUCLEASE AND THE *nuc* GENE IN THE DIAGNOSIS OF *Staphylococcus aureus* INFECTIONS.

105. Terje Engan: NUCLEAR MAGNETIC RESONANCE (NMR) SPECTROSCOPY OF PLASMA IN MALIGNANT DISEASE.
106. Kirsten Rasmussen: VIOLENCE IN THE MENTALLY DISORDERED.
107. Finn Egil Skjeldestad: INDUCED ABORTION: Timetrends and Determinants.
108. Roar Stenseth: THORACIC EPIDURAL ANALGESIA IN AORTOCORONARY BYPASS SURGERY.
109. Arild Faxvaag: STUDIES OF IMMUNE CELL FUNCTION *in mice infected with* MURINE RETROVIRUS.

**1996**

110. Svend Aakhus: NONINVASIVE COMPUTERIZED ASSESSMENT OF LEFT VENTRICULAR FUNCTION AND SYSTEMIC ARTERIAL PROPERTIES. Methodology and some clinical applications.
111. Klaus-Dieter Bolz: INTRAVASCULAR ULTRASONOGRAPHY.
112. Petter Aadahl: CARDIOVASCULAR EFFECTS OF THORACIC AORTIC CROSS-CLAMPING.
113. Sigurd Steinshamn: CYTOKINE MEDIATORS DURING GRANULOCYTOPENIC INFECTIONS.
114. Hans Stifoss-Hanssen: SEEKING MEANING OR HAPPINESS?
115. Anne Kvikstad: LIFE CHANGE EVENTS AND MARITAL STATUS IN RELATION TO RISK AND PROGNOSIS OF CANCER.
116. Torbjørn Grøntvedt: TREATMENT OF ACUTE AND CHRONIC ANTERIOR CRUCIATE LIGAMENT INJURIES. A clinical and biomechanical study.
117. Sigrid Hørven Wigers: CLINICAL STUDIES OF FIBROMYALGIA WITH FOCUS ON ETIOLOGY, TREATMENT AND OUTCOME.
118. Jan Schjøtt: MYOCARDIAL PROTECTION: Functional and Metabolic Characteristics of Two Endogenous Protective Principles.
119. Marit Martinussen: STUDIES OF INTESTINAL BLOOD FLOW AND ITS RELATION TO TRANSITIONAL CIRCULATORY ADAPATION IN NEWBORN INFANTS.
120. Tomm B. Müller: MAGNETIC RESONANCE IMAGING IN FOCAL CEREBRAL ISCHEMIA.
121. Rune Haaverstad: OEDEMA FORMATION OF THE LOWER EXTREMITIES.
122. Magne Børset: THE ROLE OF CYTOKINES IN MULTIPLE MYELOMA, WITH SPECIAL REFERENCE TO HEPATOCYTE GROWTH FACTOR.
123. Geir Smedslund: A THEORETICAL AND EMPIRICAL INVESTIGATION OF SMOKING, STRESS AND DISEASE: RESULTS FROM A POPULATION SURVEY.

**1997**

124. Torstein Vik: GROWTH, MORBIDITY, AND PSYCHOMOTOR DEVELOPMENT IN INFANTS WHO WERE GROWTH RETARDED *IN UTERO*.
125. Siri Forsmo: ASPECTS AND CONSEQUENCES OF OPPORTUNISTIC SCREENING FOR CERVICAL CANCER. Results based on data from three Norwegian counties.
126. Jon S. Skranes: CEREBRAL MRI AND NEURODEVELOPMENTAL OUTCOME IN VERY LOW BIRTH WEIGHT (VLBW) CHILDREN. A follow-up study of a geographically based year cohort of VLBW children at ages one and six years.
127. Knut Bjørnstad: COMPUTERIZED ECHOCARDIOGRAPHY FOR EVALUTION OF CORONARY ARTERY DISEASE.
128. Grethe Elisabeth Borchgrevink: DIAGNOSIS AND TREATMENT OF WHIPLASH/NECK SPRAIN INJURIES CAUSED BY CAR ACCIDENTS.
129. Tor Elsås: NEUROPEPTIDES AND NITRIC OXIDE SYNTHASE IN OCULAR AUTONOMIC AND SENSORY NERVES.
130. Rolf W. Gråwe: EPIDEMIOLOGICAL AND NEUROPSYCHOLOGICAL PERSPECTIVES ON SCHIZOPHRENIA.
131. Tonje Strømholm: CEREBRAL HAEMODYNAMICS DURING THORACIC AORTIC CROSSCLAMPING. An experimental study in pigs.

**1998**

132. Martinus Bråten: STUDIES ON SOME PROBLEMS REALTED TO INTRAMEDULLARY NAILING OF FEMORAL FRACTURES.
133. Ståle Nordgård: PROLIFERATIVE ACTIVITY AND DNA CONTENT AS PROGNOSTIC INDICATORS IN ADENOID CYSTIC CARCINOMA OF THE HEAD AND NECK.

134. Egil Lien: SOLUBLE RECEPTORS FOR **TNF** AND **LPS**: RELEASE PATTERN AND POSSIBLE SIGNIFICANCE IN DISEASE.
135. Marit Bjørgaas: HYPOGLYCAEMIA IN CHILDREN WITH DIABETES MELLITUS
136. Frank Skorpen: GENETIC AND FUNCTIONAL ANALYSES OF DNA REPAIR IN HUMAN CELLS.
137. Juan A. Pareja: SUNCT SYNDROME. ON THE CLINICAL PICTURE. ITS DISTINCTION FROM OTHER, SIMILAR HEADACHES.
138. Anders Angelsen: NEUROENDOCRINE CELLS IN HUMAN PROSTATIC CARCINOMAS AND THE PROSTATIC COMPLEX OF RAT, GUINEA PIG, CAT AND DOG.
139. Fabio Antonaci: CHRONIC PAROXYSMAL HEMICRANIA AND HEMICRANIA CONTINUA: TWO DIFFERENT ENTITIES?
140. Sven M. Carlsen: ENDOCRINE AND METABOLIC EFFECTS OF METFORMIN WITH SPECIAL EMPHASIS ON CARDIOVASCULAR RISK FACTORES.

**1999**

141. Terje A. Murberg: DEPRESSIVE SYMPTOMS AND COPING AMONG PATIENTS WITH CONGESTIVE HEART FAILURE.
142. Harm-Gerd Karl Blaas: THE EMBRYONIC EXAMINATION. Ultrasound studies on the development of the human embryo.
143. Noèmi Becser Andersen:THE CEPHALIC SENSORY NERVES IN UNILATERAL HEADACHES. Anatomical background and neurophysiological evaluation.
144. Eli-Janne Fiskerstrand: LASER TREATMENT OF PORT WINE STAINS. A study of the efficacy and limitations of the pulsed dye laser. Clinical and morfological analyses aimed at improving the therapeutic outcome.
145. Bård Kulseng: A STUDY OF ALGINATE CAPSULE PROPERTIES AND CYTOKINES IN RELATION TO INSULIN DEPENDENT DIABETES MELLITUS.
146. Terje Haug: STRUCTURE AND REGULATION OF THE HUMAN UNG GENE ENCODING URACIL-DNA GLYCOSYLASE.
147. Heidi Brurok: MANGANESE AND THE HEART. A Magic Metal with Diagnostic and Therapeutic Possibilites.
148. Agnes Kathrine Lie: DIAGNOSIS AND PREVALENCE OF HUMAN PAPILLOMAVIRUS INFECTION IN CERVICAL INTRAEPITELIAL NEOPLASIA. Relationship to Cell Cycle Regulatory Proteins and HLA DQBI Genes.
149. Ronald Mårvik: PHARMACOLOGICAL, PHYSIOLOGICAL AND PATHOPHYSIOLOGICAL STUDIES ON ISOLATED STOMACS.
150. Ketil Jarl Holen: THE ROLE OF ULTRASONOGRAPHY IN THE DIAGNOSIS AND TREATMENT OF HIP DYSPLASIA IN NEWBORNS.
151. Irene Hetlevik: THE ROLE OF CLINICAL GUIDELINES IN CARDIOVASCULAR RISK INTERVENTION IN GENERAL PRACTICE.
152. Katarina Tunòn: ULTRASOUND AND PREDICTION OF GESTATIONAL AGE.
153. Johannes Soma: INTERACTION BETWEEN THE LEFT VENTRICLE AND THE SYSTEMIC ARTERIES.
154. Arild Aamodt: DEVELOPMENT AND PRE-CLINICAL EVALUATION OF A CUSTOM-MADE FEMORAL STEM.
155. Agnar Tegnander: DIAGNOSIS AND FOLLOW-UP OF CHILDREN WITH SUSPECTED OR KNOWN HIP DYSPLASIA.
156. Bent Indredavik: STROKE UNIT TREATMENT: SHORT AND LONG-TERM EFFECTS
157. Jolanta Vanagaite Vingen: PHOTOPHOBIA AND PHONOPHOBIA IN PRIMARY HEADACHES

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158. Ola Dalsegg Sæther: PATHOPHYSIOLOGY DURING PROXIMAL AORTIC CROSS-CLAMPING CLINICAL AND EXPERIMENTAL STUDIES
159. xxxxxxxxx (blind number)
160. Christina Vogt Isaksen: PRENATAL ULTRASOUND AND POSTMORTEM FINDINGS – A TEN YEAR CORRELATIVE STUDY OF FETUSES AND INFANTS WITH DEVELOPMENTAL ANOMALIES.
161. Holger Seidel: HIGH-DOSE METHOTREXATE THERAPY IN CHILDREN WITH ACUTE LYMPHOCYTIC LEUKEMIA: DOSE, CONCENTRATION, AND EFFECT CONSIDERATIONS.
162. Stein Hallan: IMPLEMENTATION OF MODERN MEDICAL DECISION ANALYSIS INTO CLINICAL DIAGNOSIS AND TREATMENT.

163. Malcolm Sue-Chu: INVASIVE AND NON-INVASIVE STUDIES IN CROSS-COUNTRY SKIERS WITH ASTHMA-LIKE SYMPTOMS.
164. Ole-Lars Brekke: EFFECTS OF ANTIOXIDANTS AND FATTY ACIDS ON TUMOR NECROSIS FACTOR-INDUCED CYTOTOXICITY.
165. Jan Lundbom: AORTOCORONARY BYPASS SURGERY: CLINICAL ASPECTS, COST CONSIDERATIONS AND WORKING ABILITY.
166. John-Anker Zwart: LUMBAR NERVE ROOT COMPRESSION, BIOCHEMICAL AND NEUROPHYSIOLOGICAL ASPECTS.
167. Geir Falck: HYPEROSMOLALITY AND THE HEART.
168. Eirik Skogvoll: CARDIAC ARREST Incidence, Intervention and Outcome.
169. Dalius Bansevicius: SHOULDER-NECK REGION IN CERTAIN HEADACHES AND CHRONIC PAIN SYNDROMES.
170. Bettina Kinge: REFRACTIVE ERRORS AND BIOMETRIC CHANGES AMONG UNIVERSITY STUDENTS IN NORWAY.
171. Gunnar Qvigstad: CONSEQUENCES OF HYPERGASTRINEMIA IN MAN
172. Hanne Ellekjær: EPIDEMIOLOGICAL STUDIES OF STROKE IN A NORWEGIAN POPULATION. INCIDENCE, RISK FACTORS AND PROGNOSIS
173. Hilde Grimstad: VIOLENCE AGAINST WOMEN AND PREGNANCY OUTCOME.
174. Astrid Hjelde: SURFACE TENSION AND COMPLEMENT ACTIVATION: Factors influencing bubble formation and bubble effects after decompression.
175. Kjell A. Kvistad: MR IN BREAST CANCER – A CLINICAL STUDY.
176. Ivar Rossvoll: ELECTIVE ORTHOPAEDIC SURGERY IN A DEFINED POPULATION. Studies on demand, waiting time for treatment and incapacity for work.
177. Carina Seidel: PROGNOSTIC VALUE AND BIOLOGICAL EFFECTS OF HEPATOCYTE GROWTH FACTOR AND SYNDECAN-1 IN MULTIPLE MYELOMA.

**2001**

178. Alexander Wahba: THE INFLUENCE OF CARDIOPULMONARY BYPASS ON PLATELET FUNCTION AND BLOOD COAGULATION – DETERMINANTS AND CLINICAL CONSEQUENSES
179. Marcus Schmitt-Egenolf: THE RELEVANCE OF THE MAJOR hISTOCOMPATIBILITY COMPLEX FOR THE GENETICS OF PSORIASIS
180. Odrun Arna Gederaas: BIOLOGICAL MECHANISMS INVOLVED IN 5-AMINOLEVULINIC ACID BASED PHOTODYNAMIC THERAPY
181. Pål Richard Romundstad: CANCER INCIDENCE AMONG NORWEGIAN ALUMINIUM WORKERS
182. Henrik Hjorth-Hansen: NOVEL CYTOKINES IN GROWTH CONTROL AND BONE DISEASE OF MULTIPLE MYELOMA
183. Gunnar Morken: SEASONAL VARIATION OF HUMAN MOOD AND BEHAVIOUR
184. Bjørn Olav Haugen: MEASUREMENT OF CARDIAC OUTPUT AND STUDIES OF VELOCITY PROFILES IN AORTIC AND MITRAL FLOW USING TWO- AND THREE-DIMENSIONAL COLOUR FLOW IMAGING
185. Geir Bråthen: THE CLASSIFICATION AND CLINICAL DIAGNOSIS OF ALCOHOL-RELATED SEIZURES
186. Knut Ivar Aasarød: RENAL INVOLVEMENT IN INFLAMMATORY RHEUMATIC DISEASE. A Study of Renal Disease in Wegener's Granulomatosis and in Primary Sjögren's Syndrome
187. Trude Helen Flo: RESEPTORS INVOLVED IN CELL ACTIVATION BY DEFINED URONIC ACID POLYMERS AND BACTERIAL COMPONENTS
188. Bodil Kavli: HUMAN URACIL-DNA GLYCOSYLASES FROM THE UNG GENE: STRUCTRUAL BASIS FOR SUBSTRATE SPECIFICITY AND REPAIR
189. Liv Thommesen: MOLECULAR MECHANISMS INVOLVED IN TNF- AND GASTRIN-MEDIATED GENE REGULATION
190. Turid Lingaas Holmen: SMOKING AND HEALTH IN ADOLESCENCE; THE NORD-TRØNDELAG HEALTH STUDY, 1995-97
191. Øyvind Hjertner: MULTIPLE MYELOMA: INTERACTIONS BETWEEN MALIGNANT PLASMA CELLS AND THE BONE MICROENVIRONMENT
192. Asbjørn Støylen: STRAIN RATE IMAGING OF THE LEFT VENTRICLE BY ULTRASOUND. FEASIBILITY, CLINICAL VALIDATION AND PHYSIOLOGICAL ASPECTS

193. Kristian Midthjell: DIABETES IN ADULTS IN NORD-TRØNDELAG. PUBLIC HEALTH ASPECTS OF DIABETES MELLITUS IN A LARGE, NON-SELECTED NORWEGIAN POPULATION.
194. Guanglin Cui: FUNCTIONAL ASPECTS OF THE ECL CELL IN RODENTS
195. Ulrik Wisløff: CARDIAC EFFECTS OF AEROBIC ENDURANCE TRAINING: HYPERTROPHY, CONTRACTILITY AND CALCUIM HANDLING IN NORMAL AND FAILING HEART
196. Øyvind Halaas: MECHANISMS OF IMMUNOMODULATION AND CELL-MEDIATED CYTOTOXICITY INDUCED BY BACTERIAL PRODUCTS
197. Tore Amundsen: PERFUSION MR IMAGING IN THE DIAGNOSIS OF PULMONARY EMBOLISM
198. Nanna Kurtze: THE SIGNIFICANCE OF ANXIETY AND DEPRESSION IN FATIQUE AND PATTERNS OF PAIN AMONG INDIVIDUALS DIAGNOSED WITH FIBROMYALGIA: RELATIONS WITH QUALITY OF LIFE, FUNCTIONAL DISABILITY, LIFESTYLE, EMPLOYMENT STATUS, CO-MORBIDITY AND GENDER
199. Tom Ivar Lund Nilsen: PROSPECTIVE STUDIES OF CANCER RISK IN NORD-TRØNDELAG: THE HUNT STUDY. Associations with anthropometric, socioeconomic, and lifestyle risk factors
200. Asta Kristine Håberg: A NEW APPROACH TO THE STUDY OF MIDDLE CEREBRAL ARTERY OCCLUSION IN THE RAT USING MAGNETIC RESONANCE TECHNIQUES

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201. Knut Jørgen Arntzen: PREGNANCY AND CYTOKINES
202. Henrik Døllner: INFLAMMATORY MEDIATORS IN PERINATAL INFECTIONS
203. Asta Bye: LOW FAT, LOW LACTOSE DIET USED AS PROPHYLACTIC TREATMENT OF ACUTE INTESTINAL REACTIONS DURING PELVIC RADIOTHERAPY. A PROSPECTIVE RANDOMISED STUDY.
204. Sylvester Moyo: STUDIES ON STREPTOCOCCUS AGALACTIAE (GROUP B STREPTOCOCCUS) SURFACE-ANCHORED MARKERS WITH EMPHASIS ON STRAINS AND HUMAN SERA FROM ZIMBABWE.
205. Knut Hagen: HEAD-HUNT: THE EPIDEMIOLOGY OF HEADACHE IN NORD-TRØNDELAG
206. Li Lixin: ON THE REGULATION AND ROLE OF UNCOUPLING PROTEIN-2 IN INSULIN PRODUCING ß-CELLS
207. Anne Hildur Henriksen: SYMPTOMS OF ALLERGY AND ASTHMA VERSUS MARKERS OF LOWER AIRWAY INFLAMMATION AMONG ADOLESCENTS
208. Egil Andreas Fors: NON-MALIGNANT PAIN IN RELATION TO PSYCHOLOGICAL AND ENVIRONTENTAL FACTORS. EXPERIENTAL AND CLINICAL STUDES OF PAIN WITH FOCUS ON FIBROMYALGIA
209. Pål Klepstad: MORPHINE FOR CANCER PAIN
210. Ingunn Bakke: MECHANISMS AND CONSEQUENCES OF PEROXISOME PROLIFERATOR-INDUCED HYPERFUNCTION OF THE RAT GASTRIN PRODUCING CELL
211. Ingrid Susann Gribbestad: MAGNETIC RESONANCE IMAGING AND SPECTROSCOPY OF BREAST CANCER
212. Rønnaug Astri Ødegård: PREECLAMPSIA – MATERNAL RISK FACTORS AND FETAL GROWTH
213. Johan Haux: STUDIES ON CYTOTOXICITY INDUCED BY HUMAN NATURAL KILLER CELLS AND DIGITOXIN
214. Turid Suzanne Berg-Nielsen: PARENTING PRACTICES AND MENTALLY DISORDERED ADOLESCENTS
215. Astrid Rydning: BLOOD FLOW AS A PROTECTIVE FACTOR FOR THE STOMACH MUCOSA. AN EXPERIMENTAL STUDY ON THE ROLE OF MAST CELLS AND SENSORY AFFERENT NEURONS

**2003**

216. Jan Pål Loennechen: HEART FAILURE AFTER MYOCARDIAL INFARCTION. Regional Differences, Myocyte Function, Gene Expression, and Response to Cariporide, Losartan, and Exercise Training.

217. Elisabeth Qvigstad: EFFECTS OF FATTY ACIDS AND OVER-STIMULATION ON INSULIN SECRETION IN MAN
218. Arne Åsberg: EPIDEMIOLOGICAL STUDIES IN HEREDITARY HEMOCHROMATOSIS: PREVALENCE, MORBIDITY AND BENEFIT OF SCREENING.
219. Johan Fredrik Skomsvoll: REPRODUCTIVE OUTCOME IN WOMEN WITH RHEUMATIC DISEASE. A population registry based study of the effects of inflammatory rheumatic disease and connective tissue disease on reproductive outcome in Norwegian women in 1967-1995.
220. Siv Mørkved: URINARY INCONTINENCE DURING PREGNANCY AND AFTER DELIVERY: EFFECT OF PELVIC FLOOR MUSCLE TRAINING IN PREVENTION AND TREATMENT
221. Marit S. Jordhøy: THE IMPACT OF COMPREHENSIVE PALLIATIVE CARE
222. Tom Christian Martinsen: HYPERGASTRINEMIA AND HYPOACIDITY IN RODENTS – CAUSES AND CONSEQUENCES
223. Solveig Tingulstad: CENTRALIZATION OF PRIMARY SURGERY FOR OVARAIN CANCER. FEASIBILITY AND IMPACT ON SURVIVAL
224. Haytham Eloqayli: METABOLIC CHANGES IN THE BRAIN CAUSED BY EPILEPTIC SEIZURES
225. Torunn Bruland: STUDIES OF EARLY RETROVIRUS-HOST INTERACTIONS – VIRAL DETERMINANTS FOR PATHOGENESIS AND THE INFLUENCE OF SEX ON THE SUSCEPTIBILITY TO FRIEND MURINE LEUKAEMIA VIRUS INFECTION
226. Torstein Hole: DOPPLER ECHOCARDIOGRAPHIC EVALUATION OF LEFT VENTRICULAR FUNCTION IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION
227. Vibeke Nossum: THE EFFECT OF VASCULAR BUBBLES ON ENDOTHELIAL FUNCTION
228. Sigurd Fasting: ROUTINE BASED RECORDING OF ADVERSE EVENTS DURING ANAESTHESIA – APPLICATION IN QUALITY IMPROVEMENT AND SAFETY
229. Solfrid Romundstad: EPIDEMIOLOGICAL STUDIES OF MICROALBUMINURIA. THE NORD-TRØNDELAG HEALTH STUDY 1995-97 (HUNT 2)
230. Geir Torheim: PROCESSING OF DYNAMIC DATA SETS IN MAGNETIC RESONANCE IMAGING
231. Catrine Ahlén: SKIN INFECTIONS IN OCCUPATIONAL SATURATION DIVERS IN THE NORTH SEA AND THE IMPACT OF THE ENVIRONMENT
232. Arnulf Langhammer: RESPIRATORY SYMPTOMS, LUNG FUNCTION AND BONE MINERAL DENSITY IN A COMPREHENSIVE POPULATION SURVEY. THE NORD-TRØNDELAG HEALTH STUDY 1995-97. THE BRONCHIAL OBSTRUCTION IN NORD-TRØNDELAG STUDY
233. Einar Kjelsås: EATING DISORDERS AND PHYSICAL ACTIVITY IN NON-CLINICAL SAMPLES
234. Arne Wibe: RECTAL CANCER TREATMENT IN NORWAY – STANDARDISATION OF SURGERY AND QUALITY ASSURANCE

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235. Eivind Witsø: BONE GRAFT AS AN ANTIBIOTIC CARRIER
236. Anne Mari Sund: DEVELOPMENT OF DEPRESSIVE SYMPTOMS IN EARLY ADOLESCENCE
237. Hallvard Lærum: EVALUATION OF ELECTRONIC MEDICAL RECORDS – A CLINICAL TASK PERSPECTIVE
238. Gustav Mikkelsen: ACCESSIBILITY OF INFORMATION IN ELECTRONIC PATIENT RECORDS; AN EVALUATION OF THE ROLE OF DATA QUALITY
239. Steinar Krokstad: SOCIOECONOMIC INEQUALITIES IN HEALTH AND DISABILITY. SOCIAL EPIDEMIOLOGY IN THE NORD-TRØNDELAG HEALTH STUDY (HUNT), NORWAY
240. Arne Kristian Myhre: NORMAL VARIATION IN ANOGENITAL ANATOMY AND MICROBIOLOGY IN NON-ABUSED PRESCHOOL CHILDREN
241. Ingunn Dybedal: NEGATIVE REGULATORS OF HEMATOPOIETEC STEM AND PROGENITOR CELLS
242. Beate Sitter: TISSUE CHARACTERIZATION BY HIGH RESOLUTION MAGIC ANGLE SPINNING MR SPECTROSCOPY
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