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ORIGINAL ARTICLE

Side-effects of post-treatment biopsies in prostate cancer patients treated with endocrine therapy alone or combined with radical radiotherapy in the Scandinavian Prostate Cancer Group-7 randomized trial

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Abstract

Objective. Post-treatment prostate biopsy side-effects were evaluated in patients with locally advanced prostate cancer on endocrine therapy alone or combined with radiotherapy in the Scandinavian Prostate Cancer Group-7 randomized trial. *Material and methods.* One-hundred and twenty patients underwent transrectalultrasound-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 patients (91%) (endocrine therapy only 52%, combined endocrine therapy and radiotherapy 48%). Previous therapy had no significant influence on pain, urinary flow, haematuria or haematospermia. Pain at biopsy was reported in 63% (mild, 57%; moderate, 5.6%; severe, one patient) and pain at follow-up in 31% (mild, 27%; moderate, four patients). Haematuria (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). Haematospermia 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 and 2.2 days, respectively ($p = 0.031$). In logistic regression analysis, a trend towards increased rectal bleeding was found in patients on combined endocrine therapy and radiotherapy (odds ratio 2.4, $p = 0.050$). *Conclusion.* Patient-reported post-treatment prostate biopsy side-effects were mild and self-limiting.

Key Words: *Endocrine therapy, post-treatment 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 post-treatment prostate biopsies is used to select patients for salvage therapy [4–6], there are no published reports on post-treatment prostate biopsy complications.

Haematuria, rectal bleeding and haematospermia, 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,

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urinary retention and urinary tract infections(UTIs) 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 randomized 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 transrectal ultrasound (TRUS)-guided post-treatment prostate biopsies [18]. This paper presents patient-reported biopsy-related side-effects experienced in a 7 day period following the procedure.

Material and methods

The SPCG-7 study inclusion criteria and study population have been described previously [17]. All the 875 included patients received 3 months' total androgen blockade (TAB) with 3 monthly injections of a luteinizing hormone-releasing hormone (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 3 months of TAB in patients randomized to endocrine therapy combined with radiotherapy. Eleven out 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 Organization (WHO) performance status 0–1 and no medical contraindications to biopsy underwent TRUS-guided post-treatment prostate biopsies. All patients received antibiotic prophylaxis with three doses of 500 mg ciprofloxacin. The first dose was taken 1 h before 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 occurring within 7 days after the biopsy procedure. The single questionnaire items were chosen on the basis of diagnostic prostate biopsy side-effects reported in previous studies [11,12,19,20].

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 15 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 experienced at the time of the procedure was graded by the patient according to the following verbal rating scale [21]: 0 = no pain; 1 = slight pain (analgesics not necessary); 2 = moderate pain (analgesics necessary); 3 = severe pain. Postbiopsy pain experienced during the 7 day-follow-up period was graded on an identical scale.

Experienced change in urinary flow (obstruction) in the 7 daystudy period was graded on the following scale: 0 = no change; 1 = slightly increased obstruction; 2 = severely increased obstruction; 3 = urinary retention.

The occurrence of UTI and pyrexia and the use of antibiotics, as well as the occurrence and duration (days) of haematuria, rectal bleeding and haematospermia in the 7 dayperiod were recorded.

Furthermore, the patients were requested to record the reason for any contact with a general practitioner or hospital, and to describe in their own words any other medical problem that occurred during the 7 days.

Statistical analyses

Categorical variables were compared using Pearson's chi-squared or Fisher's exact test. Continuous variables were compared using the Student's t test. If data were not normally distributed, the Mann–Whitney U test was used. Pain intensity was graded according to the scale used in theEuropean 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 [22]. Furthermore, biopsy-related side-effects (pain, urinary obstruction and bleeding complications) were transformed into dichotomous variables. The associations between these dichotomous variables and therapy (endocrine therapy only vs. combined endocrine therapy and radiotherapy), age at biopsy and number of biopsy cores taken (fewer than eight vs. eight or more) were first assessed in univariable logistic regression. Variables with a p value <0.1 for an association were

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

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

Results

Eleven hospitals participated in the biopsy side-study. These hospitals included 415 patients in the SPCG-7 trial of which 120 (29%) patients accepted inclusion in the biopsy side-study and underwent post-treatment prostate biopsy.The side-effects questionnaire was returned by 109 (91%) of the 120 biopsy study patients (Figure 1), while the compliance with single questionnaire items varied from 94 to 100%.

There were no significant differences in baseline characteristics at randomization between the total SPCG-7 study population and the 109 respondents (Table I), of whom 57 patients (52%) received endocrine therapy alone and 52 (48%) additional radiotherapy.

The biopsies were performed between March 2001 and October 2005 at a median of 44 months, with a range of 30–97 and an interquartile range (IQR) of 37–60 months from start of treatment.

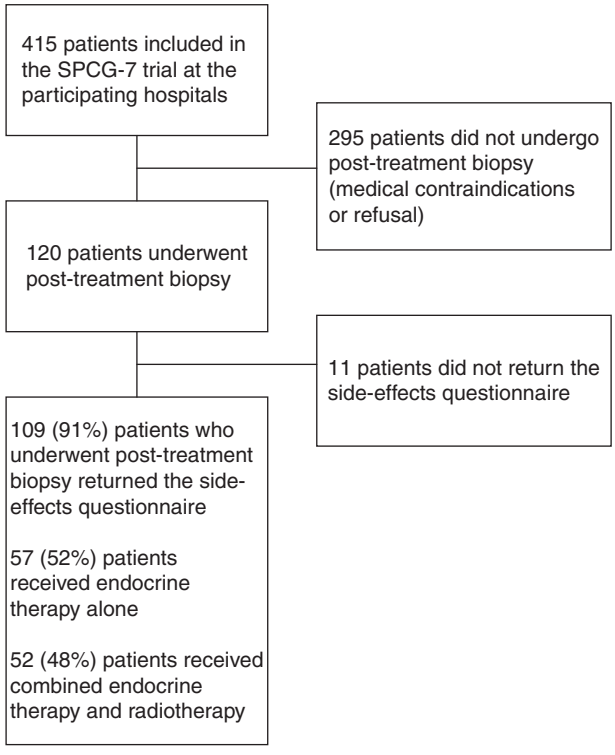

Figure 1. Patients in the Scandinavian Prostate Cancer Group-7 (SPCG-7) study who underwent post-treatment biopsy and returned the side-effects questionnaire.

In patients given endocrine therapy alone, the mean age at biopsy was 71.5 (range 56–83) years compared with 68.8 (range 51–80) years in patients treated with combined endocrine therapy and radiotherapy (difference 2.7, 95% CI 0.45–4.91 years, p = 0.019). A median of 8 biopsy cores (range 2–11, IQR 6–8) was obtained in both groups. All patients received antibiotic prophylaxis, and 19% (n = 21) were given periprostatic local anaesthesia. The histopathological results have been reported in detail previously [18]. In the 109 respondents, residual prostate cancer was found in 37 patients (65%) on endocrine therapy alone, and in 12 patients (23%) on combined endocrine therapy and radiotherapy ($p < 0.0001$).

Biopsy result, the number of biopsy cores taken and age at biopsy had no significant influence on the incidence of self-reported side-effects. Moreover, therapy (endocrine therapy alone vs. combined endocrine therapy and radiotherapy) was not associated with biopsy-related pain, change in urinary flow, haematuria or haematospermia. 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 patients (64%) (Table II), and 33 patients (31%) reported pain during follow-up (Table III).

Table I. Baseline characteristics of the 875 men enrolled in the Scandinavian Prostate Cancer Group-7 (SPCG-7)study and of the 109 patients who responded to the post-treatment prostate biopsy side-effects questionnaire.

Characteristic	Patients enrolled in the SPCG-7 study	Patients who underwent post-treatment prostate biopsy
Age (years), mean ± SD	65.8 ± 5.4	66.1 ± 5.9
PSA (ng/ml), median (IQR)	16 (9–27)	16 (8–27)
Tumour stage, *n* (%)		
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, *n* (%)	203 (23.2)	22 (20)
WHO grade, *n* (%)		
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)

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

Table II. Intensity of pain during the post-treatment biopsy procedure reported by 108 prostate cancer patients treated with either endocrine therapy alone or combined with external beam radiotherapy.

Pain (grade[a]) reported at biopsy	Therapy	
	Endocrine therapy alone (n = 57)[b]	Combined therapy (n = 51)[c]
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

Except for mean score, data are shown as number of patients (%).
[a]0 = No pain; 1 = slight pain; 2 = moderate pain; 3 = severe pain;
[b]11 patients (19%) received local anaesthesia; [c]10 patients (20%) received local anaesthesia.

Table IV. Subjective change in urinary flow during 7 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.

Subjective change (grade[a]) in urinary flow	Therapy	
	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

Data are shown as number of patients (%).
[a]0 = No change; 1 = slightly increased obstruction; 2 = severely increased obstruction; 3 = urinary retention.

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

Haematuria was reported in 26 of 56 patients (46%) on endocrine therapy alone and in 18 of 52 patients (35%) on combined endocrine therapy and radiotherapy, with a mean duration of 2.2 (range 1–7) days. In one patient given combined therapy with persistent haematuria at completion of the questionnaire, a duration of 7 days was recorded. Haematuria was not found to be significantly associated with reduced urinary flow.

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

Ten of 56 patients (18%) on endocrine therapy alone reported rectal bleeding compared with 18 of 52 patients (35%) on combined endocrine therapy and radiotherapy (p = 0.047, Pearson's chi-squared test), whereas the mean duration in patients who bled was 1.6 (range 1–4) days and 2.2 (range 1–7) days, 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, 95% CI 1.0–5.9, p = 0.050).

No patient had UTI. Only the patient with acute grade 3 biopsy-related perineal pain was admitted to hospital. In addition, one patient contacted his general practitioner because of haematuria, and one for reasons not related to the biopsy procedure. No patient required therapeutic intervention owing to bleeding complications in the study period.

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.

Pain (grade[a]) reported during 7 days' follow-up	Therapy	
	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

Except for mean score, data are shown as number of patients (%).
[a]0 = No pain; 1 = slight pain; 2 = moderate pain; 3 = severe pain.

Discussion

The self-reported side-effects were mild and self-limiting in the majority of patients who underwent post-treatment 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 [8–10,23].

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 has previously been reported to be 11–30% [7,12,19,20], corresponding with the 12% incidence in the present study (Table II). 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. However, no significant effect of local anaesthesia and a low incidence of severe pain (grade 3) may be due to a reduced sensibility, as both endocrine therapy and radiotherapy have been shown to 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 haematuria 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 bleedingcompared with pretreatment biopsy, late radiation toxicity may lead to proctitis with ulceration and bleeding and thus a more vulnerable rectal mucosa [27,28]. The present study showed a trend towards an increased risk of rectal bleeding in patients treated with radiotherapy.

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

UTI, which may be complicated by pyrexia and sepsis, has been reported in 0.3–11% following diagnostic prostate biopsy, even if antibiotic prophylaxis was used [7–13]. However, a single dose of oral ciprofloxacin has been shown to prevent infection following prostate biopsy in a randomized 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 UTIs were not observed. Based on this result, administering two or three doses of ciprofloxacin, starting 1 h before post-treatment biopsy, seems to be a safe regime for prevention of UTI.

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 post-treatment prostate biopsy may have been underestimated owing to a relatively small samplesize. 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 pretreatment and post-treatment biopsy side-effects was not planned. If patients who experienced major side-effects of biopsy at diagnosis or patients with severe therapy related side-effects refused post-treatment biopsy, a selection bias is possible.Pain intensity was assessed using a four-point verbal rating scale, but 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 [21]. 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 are likely to reflect those commonly seen in clinical practice, and the respondents seems to be representative of the SPCG-7 study patients (Table I).

Notwithstanding that the results of studies with small samplesizes must be interpreted with care, the main conclusion from this study 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 modestly increased risk of rectal bleeding compared with patients on endocrine therapy alone. In Norway, post-treatment biopsy is mandatory to select patients with residual tumours who may gain advantage from salvage therapy [4]. To the authors' knowledge, this is the first study to report on the side-effects of this procedure, and these results may be helpful in patient counselling.

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