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CLINICAL INVESTIGATION **Prostate**

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. © 2011 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 μm 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 ≤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 ≤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 ≥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.

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.

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.

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

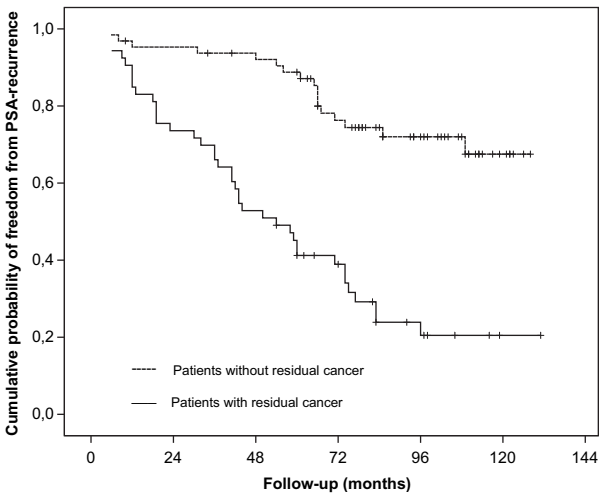

Fig. Cumulative probability of freedom from prostate-specific antigen (PSA) recurrence in biopsy-positive and -negative prostate cancer patients treated with endocrine therapy alone or in combination with radiotherapy.

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 $\geq$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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