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Endocrine treatment, with or without radiotherapy, in locally advanced prostate cancer (SPCG-7/SFUO-3): an open randomised phase III trial

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Summary

Background Several studies have shown the efficacy of endocrine therapy in combination with radiotherapy in high-risk prostate cancer. To assess the effect of radiotherapy, we did an open phase III study comparing endocrine therapy with and without local radiotherapy, followed by castration on progression.

Methods This randomised trial included men from 47 centres in Norway, Sweden, and Denmark. Between February, 1996, and December, 2002, 875 patients with locally advanced prostate cancer (T3; 78%; PSA<70; N0; M0) were centrally randomly assigned by computer to endocrine treatment alone (3 months of total androgen blockade followed by continuous endocrine treatment using flutamide; 439 patients), or to the same endocrine treatment combined with radiotherapy (436 patients). The primary endpoint was prostate-cancer-specific survival, and analysis was by intention to treat. This study is registered as an international standard randomised controlled trial, number ISRCTN01534787.

Findings After a median follow-up of 7·6 years, 79 men in the endocrine alone group and 37 men in the endocrine plus radiotherapy group had died of prostate cancer. The cumulative incidence at 10 years for prostate-cancer-specific mortality was 23·9% in the endocrine alone group and 11·9% in the endocrine plus radiotherapy group (difference 12·0%, 95% CI 4·9–19·1%), for a relative risk of 0·44 (0·30–0·66). At 10 years, the cumulative incidence for overall mortality was 39·4% in the endocrine alone group and 29·6% in the endocrine plus radiotherapy group (difference 9·8%, 0·8–18·8%), for a relative risk of 0·68 (0·52–0·89). Cumulative incidence at 10 years for PSA recurrence was substantially higher in men in the endocrine-alone group (74·7% *vs* 25·9%, p<0·0001; HR 0·16; 0·12–0·20). After 5 years, urinary, rectal, and sexual problems were slightly more frequent in the endocrine plus radiotherapy group.

Interpretation In patients with locally advanced or high-risk local prostate cancer, addition of local radiotherapy to endocrine treatment halved the 10-year prostate-cancer-specific mortality, and substantially decreased overall mortality with fully acceptable risk of side-effects compared with endocrine treatment alone. In the light of these data, endocrine treatment plus radiotherapy should be the new standard.

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Introduction

Hormone therapy alone or radiotherapy alone have for decades been acceptable treatments for locally advanced prostate cancer. The addition of hormonal therapy to radiation adds survival benefits compared with radiation alone,[1–5] but the effect of this approach is still unclear.[6] Whether the benefits of combining these treatment strategies are due to hormone-induced radiosensitisation or due to an effect on micro-metastases remains to be proven. Despite an increase of local aggressive treatment in prostate cancer, and although more than 10 years has passed since the design of this study, the issue of whether local radiotherapy adds to hormonal treatment alone in locally advanced prostate cancer is still open.

After a hearing with the providers of the antiandrogen drugs flutamide and bicalutamide, presenting their latest data, the anti-androgen therapy was chosen in 1995, due to the early results showing similar efficacy in non-metastatic prostate cancer and the decrease in side-effects. The effect of bicalutamide has been better documented than has flutamide, but to our knowledge no strong documentation has been provided that flutamide is less effective. Both drugs have a similar mechanism of action. In the Swedish randomised POSAPROCA study with 468 patients with metastatic prostate cancer, flutamide 250 mg three times a day was compared with total androgen blockade, and results showed no difference in overall survival at 5-year follow-up. On progression, flutamide was supplemented with luteinising-hormone releasing hormone-agonist (LHRH) as castration treatment (Jonas Hugosson, Gothenburg University, Sweden, personal communication).

The bicalutamide early prostate cancer programme shows that early antiandrogen treatment is better than deferred treatment in locally advanced prostate cancer (SPCG-6).[7] The same programme showed that long-term bicalutamide in combination with radiation treatment improves outcome compared with radiation alone. Based

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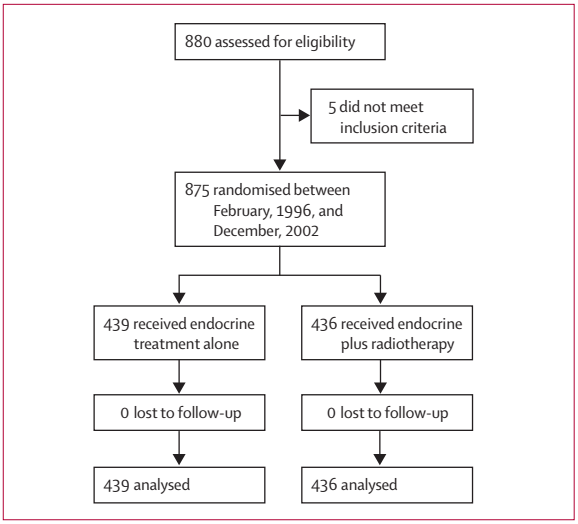

Figure 1: **Trial profile**

	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.

Table 1: **Baseline characteristics**

on the results from early prostate cancer trials,[8] antiandrogen treatment has become the preferred treatment in patients with non-metastatic locally advanced prostate cancer who are not suitable for curative treatment. However, antiandrogens are not recommended for treatment of early localised prostate cancer since survival benefit has not been shown.[7–12]

To assess the importance of local radiotherapy in patients with high-risk prostate cancer, in 1996 the Scandinavian Prostate Cancer Group and the Swedish Association for Urological Oncology started a phase III trial that explored the role of local radiotherapy in addition to endocrine treatment in patients with high-risk prostate cancer. The SPCG-7/SFUO 3 trial randomised patients to endocrine treatment alone or radiotherapy of the prostate together with endocrine treatment. After a median observation time of almost 8 years, we now present the results of the first analysis.

Methods

Patients

This trial included men from 47 centres in Norway, Sweden, and Denmark. Eligibility criteria were histological-proven prostate cancer in men younger than 76, who had a good performance status, a life expectancy of more than 10 years, and were categorised as clinical T1b–T2, G2–G3, or T3 (TNM-classification 1992), any WHO Grade 1–3. Participants had a prostate specific antigen (PSA) of 70 ng/mL or less, and no evidence of metastases as determined by bone scanning and pulmonary radiography. Participants with a PSA of 11 ng/mL or more had a pelvic lymph node dissection (fossa obturatoria); patients with nodal disease were not eligible for the trial. Ethics approval was granted by Umeå University, Medical Faculty Ethical Committee. All participants gave written informed consent before participation in the study.

Procedures

Patients were randomly assigned to receive either endocrine alone or endocrine plus radiotherapy, with stratification according to study centre, T stage, and grade. Randomisation was by computer with a block size of four through a telephone service at the Oncology Centre at Umeå University.

After randomisation, all patients were given endocrine treatment with total androgen blockade with an LHRH-agonist, leuprorelin (Procren depot; Abbott, 3·75 mg a month or 11·25 mg every 3 months), for 3 months and were simultaneously treated with 250 mg of an oral antiandrogen, flutamide (Eulexin, Schering-Plough) three times a day. After 3 months of total androgen blockade, patients continued using flutamide until progression or death. After 3 months, patients in the endocrine plus radiotherapy group started radiotherapy. When antiandrogen treatment side-effects were evident, flutamide was stopped and then reinstituted with stepwise increased dose to at least 500 mg. If this treatment failed, antiandrogen was changed to bicalutamide (150 mg once a day). 80% of all patients received breast irradiation to prevent gynecomastia.[13]

Initially, castration was recommended at time of appearance of clinical symptoms related to progression. No change of treatment was recommended in the event of PSA increase only. After the first publication of the SPCG-6 data in 2002,[14] the addition of leuprorelin was

allowed before clinical progress when the PSA level was more than 10 µg/mL.

A standard 3D conformal radiotherapy 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 immobilisation could be achieved, the margins were reduced accordingly. A 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. 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, but some of the obturatorious nodes were included in the standard target volume.

The primary objective was to explore if addition of radiotherapy to endocrine treatment would improve cancer-specific survival at 7 years compared with endocrine treatment alone. Secondary objectives were PSA recurrence (the time from randomisation to first occurrence of a PSA recurrence or death from prostate cancer), overall mortality (time from randomisation to death irrespective of cause), and quality of life.

The primary endpoint was prostate-cancer-specific mortality, defined as the time from randomisation to death from prostate cancer or death from another cause with prostate cancer as a significantly contributing factor; deaths from other causes were treated as censoring events.

To ensure complete follow-up regarding survival status, all included patients were linked to nationwide population registries in Sweden, Norway, and Denmark (Feb 22, 2008). No patient was lost from follow-up due to emigration. For each patient that had died during follow-up, the responsible physician classified the cause of death into one of five categories: (1) death from prostate cancer; (2) death from another main cause with prostate cancer as a significantly contributing factor; (3) death from anticancer therapy; (4) death from another main cause without prostate cancer as a significantly contributing factor; and (5) death from unknown cause.

According to the protocol, PSA progression was defined as an increase in PSA on two consecutive measurements with at least 1 month between them. Since new recommendations define biochemical recurrence according to the 2006 American Society of Therapeutic Radiology (ASTRO) consensus, this definition was changed accordingly and defined as an increase of PSA of 2 ng/mL or more above nadir.[15]

Quality of life was assessed using the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaire, with analysis done according to the EORTC recommendations.[16] The questionnaires were filled out before any treatment (baseline), at 3 and 6 months, and thereafter at 1, 2, 4, 8, and 10 years after start of treatment. We now report on quality of life information obtained at baseline and 4 years after the start of treatment.

	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.

Table 2: **Proportion of patients reporting specific levels of distress or dysfunction as reported by treating doctor at baseline and 5 years after treatment start**

Sample size

Initially, we aimed to include 660 patients to provide a statistical power of 80% to detect an increased cause-specific survival of 10% after 7 years of follow-up in the endocrine plus radiotherapy group compared with 65% in the endocrine group. In a blinded analysis of 716 enrolled patients by an independent Data Safety Monitoring Committee in February, 2002, the overall mortality was lower than anticipated. Therefore, the study steering board decided to extend the target sample size to 880 patients to achieve a total of 198 prostate cancer deaths after 7 years of follow-up. In February, 2008, after a median follow-up of 7·6 years, the total number of prostate cancer deaths

	Endocrine (N=439)	Endocrine plus radiotherapy (N=436)	Absolute risk reduction (95% CI)	Relative risk (95% CI)	p value
Disease-specific mortality					
Total number of events	79	37	..	..	..
Mean follow-up, years	7·4	7·6	..	..	..
7 years of follow-up, % (95% CI)	9·9 (7·1 to 12·8)	6·3 (3·9 to 8·6)	3·7 (0·0 to 7·4)	..	..
10 years of follow-up, % (95% CI)	23·9 (18·4 to 29·4)	11·9 (7·4 to 16·5)	12·0 (4·9 to 19·1)	0·44 (0·30 to 0·66)	<0·001
Overall mortality					
Total number of events	132	94	..	..	..
Mean follow-up, years	7·4	7·6	..	..	..
7 years of follow-up, % (95% CI)	20·1 (16·2 to 23·9)	16·5 (12·9 to 20·1)	3·6 (−1·7 to 8·8)	..	..
10 years of follow-up, % (95% CI)	39·4 (33·0 to 45·7)	29·6 (23·3 to 36·0)	9·8 (0·8 to 18·8)	0·68 (0·52 to 0·89)	0·004
PSA recurrence					
Total number of events	285	77	..	..	..
Mean follow-up, years	3·8	6·3	..	..	..
7 years of follow-up, % (95% CI)	71·1 (66·3 to 75·9)	17·6 (13·6 to 21·5)	53·5 (47·3 to 59·7)	..	..
10 years of follow-up, % (95% CI)	74·7 (69·6 to 79·8)	25·9 (19·3 to 32·6)	48·8 (40·4 to 57·2)	0·16 (0·12 to 0·20)	<0·001

* Analysis of cumulative incidence was done with the cmprsk package developed by Gray.[19] Relative risks were derived from Cox proportional-hazard models. Absolute risk reduction and relative risk are for endocrine plus radiotherapy treatment compared with endocrine treatment alone. Gray's test was used for p values.

Table 3: **Cumulative incidence of main endpoints and corresponding relative risks***

was 116. Therefore, a new independent Data Safety Monitoring Committee was assigned to blindly explore the present power of the study. Because of a much higher than expected cancer-specific survival in the complete cohort of patients (overall cancer-specific survival was 90% after 7 years compared with an assumed overall survival of 70%), the committee concluded that the study had more than adequate power to detect an increased cancer-specific survival of 10% and recommended the study steering board to break the randomisation code and publish the results.

Statistical analysis

According to the study protocol, no interim analysis was done. All analyses were prespecified with an intention-to-treat approach. To acknowledge the presence of competing risks, we calculated cumulative incidence for each endpoint.[17] Gray's test[18] was used to test the hypothesis that there was no difference between the treatment groups. Differences in cumulative incidence (with 95% CIs) and relative risks (with 95% CIs) were used as measures of effect for each endpoint. The relative risks were estimated using the Cox proportional-hazards model, and the cumulative incidence analysis was done using the "cmprsk" package developed by Gray.[19] Effect modification was tested by a Cox proportional-hazards model, which included an interaction term between subgroup category and treatment group. Subgroups assessed for effect modification were age at diagnosis, PSA level at diagnosis, and T stage. Comparisons of quality of life scores within and between treatments groups were done with the Wilcoxon rank-sum and signed-rank test, respectively. Differences between categorical variables were assessed by the χ^2 test. All reported p values are based on two-sided hypothesis with a p value of less than 0·05 considered to indicate statistical significance.

This study is registered as an International Standard Randomised Controlled Trial, number ISRCTN01534787).

Role of the funding source

The Scandinavian Prostate Cancer Group, as the sponsor, has received unrestricted grants from: Schering-Plough and Abbott Scandinavia. Funding has also been provided from the Nordic Cancer Union, Swedish Cancer Society (070604), Norwegian Cancer Society, Lions Cancer Foundation, and Umeå University. Neither the sponsor nor any of the grants providers had any role in the design, data collection, data analysis, data interpretation, and writing of the report. Widmark as the corresponding author and the statistician (Wiklund) had full access to all data in the study and, together with the Study Board, had the final responsibility for the decision to submit for publication.

Results

Between February, 1996, and December, 2002, 880 patients were randomised and 875 analysed (figure 1). Baseline demographics and clinical characteristics were balanced between the groups (table 1). 35 (8%) men in the endocrine group and 58 (13·3%) men in the endocrine plus radiotherapy group had their dose of flutamide reduced, and 77 (17·5%) men in the endocrine group and 88 (20·2%) in the endocrine plus radiotherapy group had their treatment changed to bicalutamide.

All patients in the radiotherapy group received curative radiotherapy with a prescribed dose to the planning target volume (PTV1 [prostate]) of 70·0 Gy or higher, 27 patients receiving 74 Gy or more. The median dose of PTV1 (prostate) was 70·0 Gy with an interquartile range of 69·5–70·6 Gy. No patients in the endocrine-alone group received radiotherapy with curative intent, although six patients later received palliative radiotherapy due to local progression.

Follow-up started on date of randomisation and concluded on Feb 22, 2008, or on the date of death. Every 3 months for the first year and every 6 months thereafter, a clinical examination and assessment of PSA, liver function, and blood cell counts was done. Additionally, at each visit adverse events, assessed by the treating physician, were recorded according to a modified scale of the Radiation Therapy Oncology Group (table 2). Completeness of PSA follow-up was 95% in the endocrine group and 94% in the endocrine plus radiotherapy group. The study was not blinded and the physicians assessing the patients were aware of which study group the patient was allocated to.

With a median follow-up of 7·6 years (range 0·2–11·9 years), 79 of the 439 (18·0%) patients in the

endocrine-alone group and 37 of the 436 (8·5%) patients in the endocrine plus radiotherapy group died of prostate cancer. Of the 116 men that were classified as dead from prostate cancer, 28 (20 in the endocrine-alone group and eight in the endocrine plus radiotherapy group) were classified as dead from other causes but with prostate cancer substantially involved. The number of deaths from causes other than prostate cancer was 52 in the endocrine-alone group and 56 patients in the endocrine plus radiotherapy group. For two patients (one in each group) the cause of death could not be established.

The cumulative incidence at 7 years for cancer-specific mortality was 9·9% (95% CI 7·1–12·8%) in the endocrine group 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 with a significant difference between treatment groups (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 treatment group (table 3, figure 2).

As for cancer-specific mortality, overall mortality was higher in the endocrine group than in the endocrine plus radiotherapy group. Radiotherapy treatment yielded an absolute improvement of 3·6% (95% CI –1·7 to 8·8%) at 7 years and 9·8% (0·8–18·8%) at 10 years. The relative risk of overall death was 0·68 (0·52–0·89, p=0·004) in favour of the endocrine plus radiotherapy treatment group (table 3, figure 2).

PSA recurrence revealed strikingly higher rates in the endocrine group than in 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 treatment group (table 3, figure 2).

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. Subgroup analysis stratified by T stage, PSA level, and inclusion age uniformly revealed decreased 10-year cumulative incidence of prostate-cancer-specific mortality in the radiotherapy group. In particular, this decrease was evident in patients with T1b–T2 tumours, where the mean absolute risk reduction was 16·0% (95% CI 3·7–28·2; figure 3).

Table 2 presents the doctor-assessed moderate and severe side-effects at 5-year follow-up compared with baseline. Significantly more patients in the endocrine plus radiotherapy group had urinary incontinence, urgency, urethral stricture, and erectile dysfunction. The difference in intestinal symptoms was not significant (p=0·075). 18 serious adverse events were reported: diarrhoea (4), liver toxicity (6), photosensitivity (4), interstitial fibrosis of the lung (1), thrombocytopenia (1), deep venous throm-

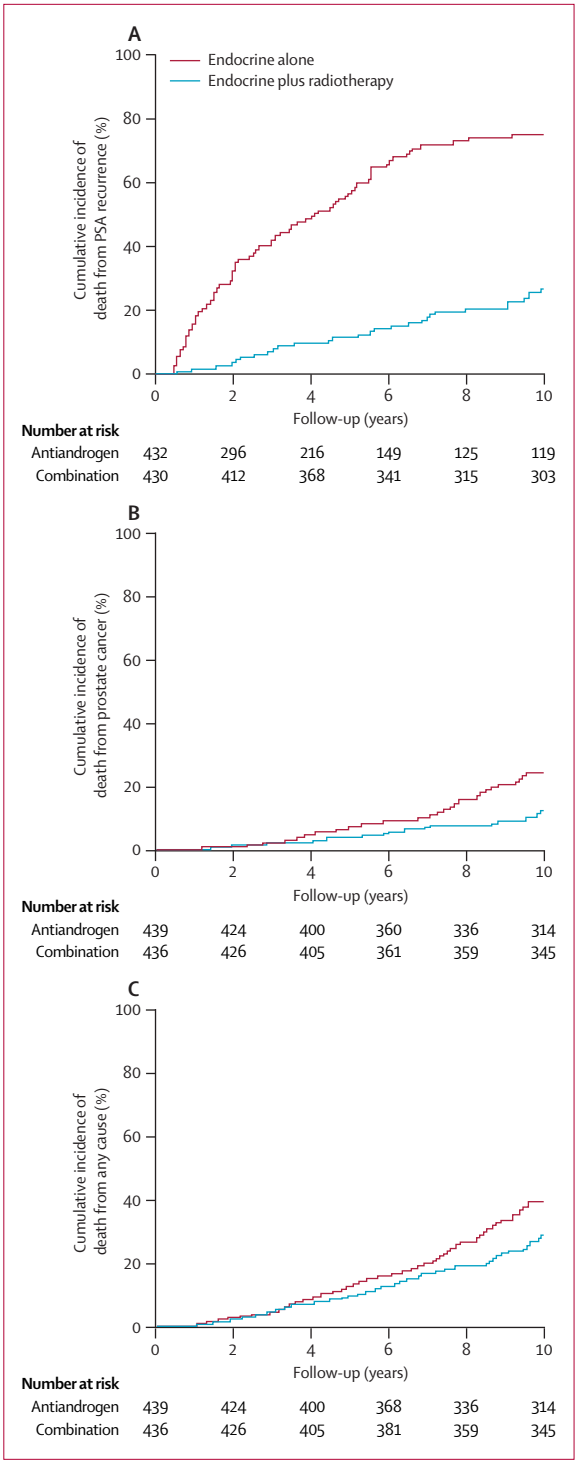

Figure 2: **Cumulative incidence of (A) PSA recurrence, (B) death from prostate cancer, and (C) death from any cause**

bosis (1), and urinary retention due to carcinosarcoma in the prostate (1). Events were evenly distributed between the two groups (11 in the endocrine alone group and seven in the endocrine plus radiotherapy group).

The proportion of missing questionnaires at baseline and during follow-up was equally distributed between treatment groups. At the 4-year follow-up 340 of 399 (85%) men in the endocrine group and 359 of 401 (89%) men in the endocrine plus radiotherapy group returned the questionnaire (table 4). No significant difference in global health and quality of life score was seen 4 years post-treatment.

Social function was the only function scale, whereas diarrhoea was the only symptom that differed substantially between the two groups at 4 years (table 4). Moderate or severe diarrhoea at 4 years were reported by 32 of 337 (9·5%) patients in the endocrine only group, whereas 39 of 355 (11·6%) in endocrine plus radiotherapy group reported the same side-effect (p=0·003). Emotional function was significantly improved at the 4-year follow-up (mean 85) compared with the baseline assessment (mean 82) in the endocrine plus radiotherapy group (p=0·006; table 4).

Dyspnoea and fatigue were the only symptoms on the QLQ-C30 questionnaire that increased significantly between baseline and 4-year follow-up in both groups (table 4). The most pronounced change was seen in dyspnoea, where the absolute increase between baseline and 4 years was 21% in the endocrine group and 24% in the endocrine plus radiotherapy group. However, dyspnoea and fatigue increased substantially in both groups between baseline and 3 months.

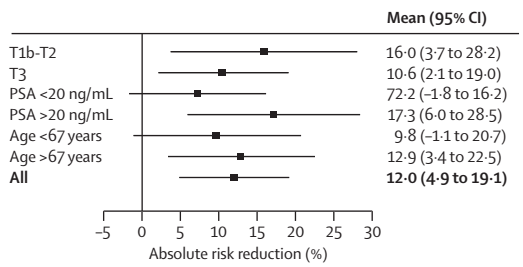

Figure 3: **Absolute risk reduction in 10-year cumulative incidence of prostate-cancer-specific mortality in the endocrine plus radiotherapy group as compared to the endocrine alone group stratified by T stage, diagnostic PSA level, and age at start of treatment**

	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.

Table 4: **Quality of life scores (EORTC QLQ-C30) in endocrine group and endocrine plus radiotherapy group**

Discussion

The present study indicates a significant superiority of the endocrine plus radiotherapy treatment compared with endocrine treatment alone in patients with locally advanced prostate cancer. The endocrine treatment plus radiotherapy resulted in a substantial reduction in prostate cancer mortality. This significant difference, which at 10 years reached 12%, also translated into improved difference in overall survival (9·8%). 37 patients in the endocrine plus radiotherapy group died from prostate cancer compared with 79 patients in the endocrine alone group.

Several large randomised studies have shown that the combination of radiotherapy and androgen-deprivation improves outcome over radiotherapy alone in high-risk prostate cancer. Survival benefit depends on the duration of the hormonal treatment,[2,20] and was also reported by the Early Prostate Cancer Programme using adjuvant antiandrogen treatment.[8] In studies with androgen deprivation of short or intermediate duration (less than 3 years), survival prolongation has only been reported in subgroups.[3,21,22] In the present study, the survival at 10 years increased from 60·6% to 70·4% in favour of the endocrine plus radiotherapy treatment, and the improvement was achieved without excess long-term toxicity. These results clarify the importance of local radiotherapy treatment in high-risk patients with prostate cancer.

Recent reports suggest that the risk of cardiometabolic problems with long-term castration deprivation therapy could counteract the benefits of hormonal therapy,[23,24] although this has also been questioned.[25] Using anti-androgens might be a way to avoid these difficulties and could reduce risk of osteoporosis, flush, and impotence.

This study has a few limitations. In some parts of the world, medical or surgical castration is still the preferred treatment of locally advanced prostate cancer. Due to the pronounced side-effects of surgical and medical castration, the role of monotherapy with oral antiandrogens has been

explored during the past two decades. In non-metastatic patients, no difference in efficacy and survival was seen between antiandrogens and medical castration with a median follow-up time of 6·3 years, and patients treated with antiandrogens had significantly fewer side-effects than patients treated with castration.[10] The Early Prostate Cancer Program showed that the use of antiandrogen reduced mortality in patients with locally advanced disease.[8] On the basis of these results, the use of non-steroidal antiandrogen therapy in M0 patients has been well established in clinical routine in Europe and is considered an alternative to castration according to the European Association of Urology guidelines. In the present study, the endocrine treatment was 3 months of total androgen blockade (LHRH plus antiandrogen) followed by non-steroidal antiandrogens. Castration treatment (total androgen blockade) was then reinstituted on PSA progression. In 1995, when our study was designed, the choice of antiandrogen was based on preliminary reports on outcomes comparable with that after castration, but less side-effects.[9] In the present study, we see no separation of survival curves until 4 years after randomisation, indicating the time taken for patients with locally advanced prostate cancer to develop hormone refractory disease (figure 2). A further separation was seen after 7 years. We know of no comparative studies that have assessed radiation combined with antiandrogens or LHRH-agonists versus such endocrine treatment alone.

At the start of the present study, the standard radiation dose to the prostate was 70 Gy. With the invention of intensity-modulated and image-guided radiotherapy, radiation doses of 78 Gy or higher are now possible, and randomised studies have shown that biochemical relapse-free survival improves with high radiation doses. The clear overall survival benefit might increase further with the larger radiation doses now safely available.[26–29]

Since the combination of surgery and androgen deprivation has not shown any increased efficacy over surgery alone, other mechanisms might be of importance for the radiation-induced improvement in local control and survival.[30] Our results cannot directly be implemented for prostatectomy. Appropriate trials addressing this issue need to be undertaken.

The Scandinavian Prostate Cancer Group Study 4 (SPCG-4) in localised disease reported a small absolute difference in overall survival of 5% after a 12 year follow-up after radical prostatectomy when compared with deferred treatment.[31] The present study shows a difference of 9·8% at 10 years. The present study also shows a benefit in favour of the endocrine plus radiotherapy treatment in T2 tumours (absolute risk reduction 16%; figure 3).

The benefits of the endocrine therapy plus radiotherapy should be weighed against the expected adverse events. Our study shows a small but significant increase of moderate to severe late effects related to urinary and sexual function. The patient-reported diarrhoea was significantly different at 4 years, which probably could explain the decreased social function in the radiotherapy group. This finding has also been reported earlier.[32,33] Fatigue increased over time in both groups, consistent with a recent report.[34] Patient acceptability was high (over 85%), and the side-effects of adding radiotherapy are acceptable in comparison to the survival gain achieved.

Compared with endocrine treatment alone, the addition of definitive prostate radiotherapy reduces the 10-year cancer-specific and overall mortality by 12·0% and 9·8%, respectively, in non-metastatic prostate cancer patients with locally advanced tumours or tumours that are prostate-confined but with aggressive histology. The quality of life and adverse effect profile is acceptable. We therefore suggest that endocrine treatment plus radiotherapy should be the new standard of care for these patients.

Contributors

The study was designed by AW (principal investigator), OK, SDF, and JED. FW, PF, and AW had full access to all data and were responsible for data analyses. AW and SDF wrote the first draft of the paper with revision by the other authors.

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Conflict of interest statement

AW (sanofi-aventis), AA (Astra-Zeneca, sanofi-aventis), MH (Novo Nordisk, sanofi-aventis), and SDF (Astra-Zeneca, Novartis) have received lecture fees of less than US$2000. The other authors declare that they have no conflict of interest.

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References

1 Boustead G, Edwards SJ. Systematic review of early vs deferred hormonal treatment of locally advanced prostate cancer: a meta-analysis of randomized controlled trials. *Br J Urol Int* 2007; **99:** 1383–89.

2 Granfors T, Modig H, Damber JE, Tomic R. Long-term followup of a randomized study of locally advanced prostate cancer treated with combined orchiectomy and external radiotherapy versus radiotherapy alone. *J Urol* 2006; **176:** 544–47.

3 Horwitz EM, Bae K, Hanks GE, et al. Ten-year follow-up of radiation therapy oncology group protocol 92-02: a phase III trial of the duration of elective androgen deprivation in locally advanced prostate cancer. *J Clin Oncol* 2008; **26:** 2497–504.

4 Roach M, DeSilvio M, Lawton C, et al. Phase III trial comparing whole-pelvic versus prostate-only radiotherapy and neoadjuvant versus adjuvant combined androgen suppression: Radiation Therapy Oncology Group 9413. *J Clin Oncol* 2003; **21:** 1904–11.

5 D'Amico AV, Chen MH, Renshaw AA, Loffredo M, Kantoff PW. Androgen suppression and radiation vs radiation alone for prostate cancer: a randomized trial. *JAMA* 2008; **299:** 289–95.

6 Lawton CA, DeSilvio M, Roach M, et al. An update of the phase III trial comparing whole pelvic to prostate only radiotherapy and neoadjuvant to adjuvant total androgen suppression: updated analysis of RTOG 94-13, with emphasis on unexpected hormone/radiation interactions. *Int J Radiat Oncol Biol Phys* 2007; **69:** 646–55.

7 Iversen P, Johansson J-E, Lodding P, et al. Bicalutamide 150 mg in addition to standard care for patients with early non-metastatic prostate cancer: updated results from the Scandinavian Prostate Cancer Period Group-6 Study after a median follow-up period of 7·1 years. *Scand J Urol Nephrol* 2006; **40:** 441–52.

8 McLeod DG, Iversen P, See WA, Morris T, Armstrong J, Wirth MP. Bicalutamide 150 mg plus standard care vs standard care alone for early prostate cancer. *BJU Int* 2006; **97:** 247–54.

9 Iversen P, Tyrrell CJ, Kaisary AV, et al. Casodex (bicalutamide) 150-mg monotherapy compared with castration in patients with previously untreated nonmetastatic prostate cancer: results from two multicenter randomized trials at a median follow-up of 4 years. *Urology* 1998; **51:** 389–96.

10 Iversen P, Tyrrell CJ, Kaisary AV, et al. Bicalutamide monotherapy compared with castration in patients with nonmetastatic locally advanced prostate cancer: 6·3 years of followup. *J Urol* 2000; **164:** 1579–82.

11 Boccon-Gibod L, Fournier G, Bottet P, et al. Flutamide versus orchidectomy in the treatment of metastatic prostate carcinoma. *Eur Urol* 1997; **32:** 391–95.

12 Seidenfeld J, Samson DJ, Hasselblad V, et al. Single-therapy androgen suppression in men with advanced prostate cancer: a systematic review and meta-analysis. *Ann Intern Med* 2000; **132:** 566–77.

13 Widmark A, Fosså SD, Lundmo P, et al. Does prophylactic breast irradiation prevent antiandrogen-induced gynecomastia? Evaluation of 253 patients in the randomized Scandinavian trial SPCG-7/SFUO-3. *Urology* 2003; **61:** 145–51.

14 Iversen P, Tammela TL, Vaage S, et al. A randomised comparison of bicalutamide ('Casodex') 150 mg versus placebo as immediate therapy either alone or as adjuvant to standard care for early non-metastatic prostate cancer. First report from the Scandinavian Prostatic Cancer Group Study Number 6. *Eur Urol* 2002; **42:** 204–11.

15 Roach M, Hanks G, Thames H, et al. Defining biochemical failure following radiotherapy with or without hormonal therapy in men with clinically localized prostate cancer: recommendations of the RTOG-ASTRO Phoenix Consensus Conference. *Int J Radiat Oncol Biol Phys* 2006; **65:** 965–74.

16 Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst* 1993; **85:** 365–76.

17 Kalbfleisch JD, Prentice RL. The statistical analysis of failure time data, 2nd edn. Hoboken, NJ, USA: Wiley, 2002.

18 Gray RJ. A class of K-sample tests for comparing the cumulative incidence of a competing risk. *Ann Stat* 1988; **16:** 1141–54.

19 Gray RJ. cmprsk Package serial on line] 2001. Boston: Department of Biostatistical Science, Dana-Farber Cancer Institute. http://biowww.dfci.harvard.edu (accessed June 2001).

20 Bolla M, Collette L, Blank L, et al. Long-term results with immediate androgen suppression and external irradiation in patients with locally advanced prostate cancer (an EORTC study): a phase III randomised trial. *Lancet* 2002; **360:** 103–06.

21 Pilepich MV, Winter K, John MJ, et al. Phase III radiation therapy oncology group (RTOG) trial 86-10 of androgen deprivation adjuvant to definitive radiotherapy in locally advanced carcinoma of the prostate. *Int J Radiat Oncol Biol Phys* 2001; **50:** 1243–52.

22 Pilepich MV, Winter K, Lawton CA, et al. Androgen suppression adjuvant to definitive radiotherapy in prostate carcinoma—long-term results of phase III RTOG 85–31. *Int J Radiat Oncol Biol Phys* 2005; **61:** 1285–90.

23 D'Amico AV, Renshaw AA, Loffredo B, Chen MH. Duration of testosterone suppression and the risk of death from prostate cancer in men treated using radiation and 6 months of hormone therapy. *Cancer* 2007; **110:** 1723–28.

24 Tsai HK, D'Amico AV, Sadetsky N, Chen MH, Carroll PR. Androgen deprivation therapy for localized prostate cancer and the risk of cardiovascular mortality. *J Natl Cancer Inst* 2007; **99:** 1516–24.

25 Roach M. Regarding the influence of adjuvant suppression therapy for prostate cancer on the frequency and timing of fatal myocardial infarction: how real is the risk? *J Clin Oncol* 2007; **25:** 5325–26.

26 Pollack A, Zagars GK, Starkschall G, et al. Prostate cancer radiation dose response: results of the M. D. Anderson phase III randomized trial. *Int J Radiat Oncol Biol Phys* 2002; **53:** 1097–105.

27 Dearnaley DP, Sydes MR, Graham JD, et al. Escalated-dose versus standard-dose conformal radiotherapy in prostate cancer: first results from the MRC RT01 randomised controlled trial. *Lancet Oncol* 2007; **8:** 475–87.

28 Kuban DA, Tucker SL, Dong L, et al. Long-term results of the M. D. Anderson randomized dose-escalation trial for prostate cancer. *Int J Radiat Oncol Biol Phys* 2008; **70:** 67–74.

29 Zietman AL, DeSilvio ML, Slater JD, et al. Comparison of conventional-dose vs high-dose conformal radiation therapy in clinically localized adenocarcinoma of the prostate: a randomized controlled trial. *JAMA* 2005; **92:** 1233–39.

30 Aus G, Abrahamsson PA, Ahlgren G, et al. Three-month neoadjuvant hormonal therapy before radical prostatectomy: a 7-year follow-up of a randomized controlled trial. *BJU Int* 2002; **90:** 561–66.

31 Bill-Axelson A, Holmberg L, Filén F, et al. Radical prostatectomy versus watchful waiting in localized prostate cancer: the Scandinavian prostate cancer group-4 randomized trial. *J Natl Cancer Inst* 2008; **100:** 1144–54.

32 Fransson P, Damber JE, Tomic R, Modig H, Nyberg G, Widmark A. Quality of life and symptoms in a randomized trial of radiotherapy versus deferred treatment of localized prostate carcinoma. *Cancer* 2001; **92:** 3111–19.

33 Mavroidis P, al-Abany M, Helgason AR, et al. Dose-response relations for anal sphincter regarding fecal leakage and blood or phlegm in stools after radiotherapy for prostate cancer. Radiobiological study of 65 consecutive patients. *Strahlenther Onkol* 2005; **181:** 293–306.

34 Pirl WF, Greer JA, Goode M, Smith MR. Prospective study of depression and fatigue in men with advanced prostate cancer receiving hormone therapy. *Psychooncology* 2008; **17:** 148–53.