Radiotherapy and hyperthermia in the treatment of patients with locally advanced prostate cancer: preliminary results

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Accepted for publication 15 August 2003

OBJECTIVE

To report an interim clinical evaluation of combined external beam irradiation (EBRT) and interstitial or regional hyperthermia in the treatment of locally advanced prostate cancer.

PATIENTS AND METHODS

From 1997 to 2001, 26 patients with T3-4/NX/0M0 prostate carcinoma were treated with a combination of conformal EBRT and hyperthermia. Fourteen patients received five weekly regional hyperthermia treatments within an optimization (phase II) study, using the coaxial transverse electrical magnetic system. Twelve patients received one interstitial hyperthermia treatment within a feasibility study (phase I), using the multi-electrode current source system. Irradiation was delivered using a conformal three-field technique, administering 70 Gy in 2-Gy fractions in 7 weeks.

RESULTS

The mean initial prostate-specific antigen level was 26 ng/mL. Three patients had a T4 and 23 a T3 tumour; the tumours were classified as well (four), moderately (16) and poorly (six) differentiated. The mean follow-up was 36 months. In the combined treatments there was no toxicity of more than grade 2. In regional hyperthermia the mean index temperature (T_{90} and T_{50}, i.e. exceeded by 90% and 50% of the measurements) was 40.2 °C and 40.8 °C, and for interstitial hyperthermia 39.4 °C and 41.8 °C, respectively. All patients survived; seven patients had a biochemical relapse (27%), three in the regional and four in the interstitial group. The actuarial probability of freedom from biochemical relapse was 70% at 36 months for all patients together, 79% for regional and 57% for interstitial. No factors were found that could be used to predict relapse.

CONCLUSIONS

The clinical outcome in these patients with advanced localized prostate cancer seems to compare favourably with most series using irradiation alone, and the treatment caused no severe complications.

KEYWORDS

prostate carcinoma, hyperthermia, regional interstitial, radiotherapy, follow-up, hyperthermia dose

INTRODUCTION

The outcome of treatment for locally advanced prostate carcinoma (T3,4 NX/0 M0) using conventional radiotherapy alone is insufficient. Zagars *et al.* [1] described a 10-year biochemical relapse rate of 76% after conventional external beam irradiation (EBRT). An improvement in local control may result in a better disease-specific survival [2]. Local control can be enhanced by androgen suppression with local irradiation [3] or by increasing the radiation dose [4], e.g. by using intensity-modulated radiotherapy.

Adding hyperthermia to conventional radiotherapy may also improve local control in prostate carcinoma. Hyperthermia is known to enhance the radiation effect in prostate cancer cells *in vitro* [5]. One study suggested a gain from hyperthermia in newly diagnosed patients [6], and Kalapurakal *et al.* [7] reported a benefit for relapsed hormone-refractory patients. Furthermore, additional hyperthermia does not seem to decrease the quality of life of patients with prostate carcinoma [8].

Different hyperthermia techniques can be used to treat prostate carcinoma; promising methods include both interstitial [9] and regional hyperthermia [6,10]. Transurethral and/or transrectal hyperthermia produces a highly variable heat distribution, because of the limited heat penetration depth [11]. Algan *et al.* [12] used transrectal hyperthermia and reported no improvement in treatment outcome. The feasibility of interstitial and regional hyperthermia for locally advanced prostate carcinoma was reported earlier by us [13,14].

Because added hyperthermia for treating locally advanced prostate cancer seems promising, the possibilities were evaluated for future randomized trials (20th European Society for Hyperthermic Oncology conference, Bergen, Norway, 23–25 May, 2002). Only a few studies have described the clinical results after prostate hyperthermia [6,12]. Although we realise that data on the clinical outcome of phase I/II studies are inconclusive and that the results remain preliminary, they might serve to support future discussions.

PATIENTS AND METHODS

From December 1997 to October 2001, 26 men with locally advanced prostate cancer (T3,4 NX/0 M0) received EBRT combined with regional or interstitial hyperthermia. The toxicity in all patients was measured using the Common Toxicity Criteria (CTC, version 2.0). All patients were irradiated using CT-planned

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three-dimensional (3D) conformal EBRT in a linear accelerator. Then the clinical target volume (CTV) was defined as the prostate and seminal vesicles; 66–70 Gy in 2-Gy fractions (five fractions/week) were delivered to the CTV. The seminal vesicles were excluded from the irradiation field after 50 Gy when they were not invaded by tumour. A conformal three-field isocentric technique was applied, using 6 and 18 MV photons and a multileaf collimator. The dose was prescribed according to ICRU-50 [15]. The dose was 100% at the reference point, the allowed dose gradient within the planning target volume was ± 5%; the 95% isodose line was at 8 mm from the CTV.

HYPERTHERMIA

There were two studies of hyperthermia, one using regional and one interstitial treatment. The selection criteria, evaluation of the feasibility and quality of life of the patients are described elsewhere [8,13,14]. The local ethical committee has approved both studies. Briefly the studies were as follows.

Fourteen patients were treated in an optimization study (phase II) with regional hyperthermia during the radiotherapy course [13]. Hyperthermia was delivered with the coaxial transverse electrical magnetic system, one treatment/week, for five treatments. Thermometry was used in the bladder, urethra and rectum, and in the oesophagus to measure body temperature. Invasive temperatures in the prostate were measured in one or two treatments for each patient by placing a central and a peripheral catheter transperineally. A mean (range) of 8 (2–11) invasive sensors were available per treatment. All patients completed the five hyperthermia treatments for 75 min, except two who had five treatments of 60 min because of back pain when upright for treatment. Absorbers (agar-bound saline blocks) placed on the skin were used to reduce local pain caused by 'hot spots'. The invasive and tumour-related intraluminal temperatures were compared; there was a heterogeneous distribution of temperatures in the prostate because the mean perfusion was 14 (±2) mL/100 g/min [16]. Intraluminal thermometry could not reliably predict the invasive temperatures. It was concluded that regional hyperthermia for locally advanced prostate carcinoma is clinically feasible. For guidance and optimizing treatment urethral temperatures are sufficient, but invasive thermometry remains compulsory to estimate the thermal dose for each patient.

Twelve patients were treated to assess the technical feasibility (phase I) of one interstitial hyperthermia treatment in the last week of the EBRT, as outpatients [14]. Hyperthermia was delivered with the 27 MHz multi-electrode current source interstitial hyperthermia technique (MECS-IHT) lasting 60 min. Guided by TRUS, a mean of 12 (7–16) catheters were placed in the prostate through a template. A probe containing two electrodes was inserted and thermometry used within the probes for online temperature control; a mean of 84 (49–112) sensors were available per treatment. The temperature was also measured in the prostate, rectum, urethra and bladder. A reconstruction of the implant was created using ultrasonography. Only when a sufficient temperature decline was measured could the full 3D temperature distribution be calculated using the treatment planning system. This was possible in eight patients, and considerable experience was required for successful implantation, verifying the position, reconstruction and temperature simulation. It was concluded that MECS-IHT is technically feasible and significant normal tissue protection was possible. Because of a high perfusion (47 ± 5 mL/100 g per min) and limitations to implantation near the rectum and bladder, there as a very heterogeneous temperature distribution. This resulted in under-dosed regions and therefore interstitial hyperthermia is unlikely to be sufficient when the target volume is the entire prostate. However, a high minimum temperature was possible in the macroscopic tumour regions. Further technical optimization of MECS-IHT seems possible.

Thermal variables were calculated from the invasively measured temperature in each treatment. The temperature T_x, exceeded by x% (where $x = 90$, 50) of the measurements, was determined and termed the index temperature [17]. Index temperatures give an indication of the quality of the hyperthermia treatment, like the mean and minimum temperature reached and the temperature heterogeneity. To estimate a thermal dose the cumulative time at T_{90} of >40.5 °C (CM T_{90}) was calculated [17], as was the cumulative equivalent minutes (CEM) at a T_{90} of 43 °C for each treatment [18].

Only a few thermometry sensors were available in the prostate for regional hyperthermia (mean eight), which makes the calculation of T_{90} each minute less reliable. For interstitial hyperthermia there were more sensors (mean 100) [14]. Thus the thermal variables are only shown for the eight treatments with a calculated 3D temperature distribution. The calculated 3D T_{90} temperature was converted into the CEM T_{90} and CM T_{90}, as used by others [19].

Before treatment all patients provided a history and were physically examined. The primary tumour was assigned a T-category based on a DRE and TRUS; four patients had no TRUS. All patients had abdominopelvic CT to exclude the presence of nodal metastases. Eight patients also had a pelvic lymphadenectomy. The metastatic evaluation included a bone scan for all patients. The latest American Joint Committee classification system was used for staging [20].

Patients attended for a follow-up 4 weeks after completing the combined hyperthermia-radiotherapy treatment. Subsequently, they were assessed every 3 months for 2 years, and at 6-month intervals thereafter. At each follow-up a history was taken and they were physically examined. PSA was measured at least twice per year; other investigations were used only when indicated by symptoms.

The major criteria for disease outcome were relapse or an increasing PSA level [21]. Patients were classified as free of disease if there was no clinical or radiographic evidence of local or distant disease, and if the PSA was not rising. An increase in the PSA on two consecutive measurements was considered a relapse [21]. Curves of freedom from (biochemical) relapse were calculated using the Kaplan-Meier method [22], and proportional hazards regression analysis used to determine which factors were associated with time to relapse [23].

RESULTS

The patients' characteristics for both groups are shown in Table 1. The prostate volume was measured using CT data, which were available for both groups. Only one patient in each group received adjuvant hormonal therapy. Irradiation doses were according to the department protocol at the time. Although the patient groups differed in prognostic factors, both had stage III tumours. Therefore

both patient groups were also evaluated together (Table 1), with a mean follow-up of 36 months.

	Regional	Interstitial	All
No. of patients	14	12	26
Mean (range):			
age, years	65 (56–75)	65 (45–74)	65 (45–75)
prostate vol., mL	64 (35–128)	46 (32–66)	56 (35–128)
EBRT dose, Gy	69.4 (66–70)	70	69.9 (66–70)
Follow-up, months	38 (16–60)	33 (25–42)	36 (16–60)
Initial PSA, ng/mL	32 (4–86)	20 (9–60)	26 (4–86)
No. with PSA, ng/mL, of			
0–20	7	7	14
21–80	5	5	10
> 81	2	–	2
Clinical stage (23)			
T3	11	12	23
T4	3	–	3
Differentiation			
Well	1	3	4
Moderate	8	8	16
Poor	5	1	6
Hormonal therapy	1	1	2

TABLE 1
The patients' characteristics

TOXICITY

Because there were no significant differences in the distribution of side-effects between hyperthermia techniques (data not shown) and no complications above grade 2, the CTC scores of the combined radiotherapy-hyperthermia treatments are shown for all patients together in Table 2. No late complications worse than grade 2 occurred, although the follow-up is still limited.

After regional hyperthermia, acute complications consisted of local pain (46 of 70 treatments), mostly in the pubic region, but sometimes also at the hips, sacrum and in the testicles. Absorbers were used successfully to reduce pain to an acceptable level, although in 10 cases an additional power reduction was required. In two of 70 treatments systemic stress, caused by general discomfort, limited the treatment [13]. No infections or bleeding occurred from the invasive procedures. To investigate the effect of absorbers, invasive thermometry in the pubic region was applied during regional hyperthermia. This resulted, on three of five occasions, in a palpable mass (1–3 cm) developing over several days and lasting up to a year, probably resulting from a combination of trauma from the needle insertion and fibrosis. During interstitial treatments there were no side-effects [14], and afterwards all patients noticed self-limiting transperineal pain.

CTC item	0	1	2
Constitutional: fatigue	19	69	12
Renal/genitourinary:			
urinary frequency urgency	12	69	19
urinary retention	96	4	0
bladder spasms	92	8	0
incontinence	96	4	0
haematuria	88	12	0
dysuria	46	50	4
Gastrointestinal:			
proctitis	8	69	23
(peri-)rectal pain	73	23	4
sexual function: erectile dysfunction*	32	47	21

TABLE 2
CTC score of the combined treatments

**Score for 19 patients, as seven already had erectile dysfunction before treatment.*

TEMPERATURES

The thermal variables are shown in Table 3; for regional hyperthermia the mean (SD) temperature range (over each minute, all treatments) was 1.1 (0.2) °C, indicating a heterogeneous temperature distribution. For interstitial hyperthermia there was a very heterogeneous temperature distribution, with high temperature peaks on the heating catheters (up to 60 °C) and low temperatures between the catheters and at the prostate border (some areas as low as 37 °C). The differences in temperature heterogeneity between the techniques can be explained by differences in calculated perfusion values and the differences in technique.

Mean (SD) or (range)	Regional (70)	Interstitial (8)
T_{90}, °C	40.2 (0.6)	39.4 (0.9)
T_{50}, °C	40.8 (0.6)	41.8 (1.6)
CM T_{90}, min	22 (0–50)	0
CEM T_{90}, min	1.9 (0.2–6.1)	0.47 (0.0–1.4)

TABLE 3
Thermal variables per treatment

All patients survived during a mean (range) follow-up of 36 (16–60) months. Three patients in the regional group had a biochemical relapse; two of them had T4 grade 3 tumours with PSA values of 86 and 30 ng/mL, and were treated with an irradiation dose of 66 Gy. In the interstitial group four patients had a biochemical relapse. Fig. 1a shows the actuarial probability of freedom from biochemical relapse for both groups and together. For the combined group the 36-month freedom from biochemical relapse rate was 70%, for the regional 79% and for the interstitial 57%.

Distant metastases were detected in one patient from the regional group and in two in the interstitial group (Fig. 1b). For all patients together the actuarial probability of freedom from distant metastasis after 36 months was 86%. There were two local recurrences, both in the interstitial group; for all patients

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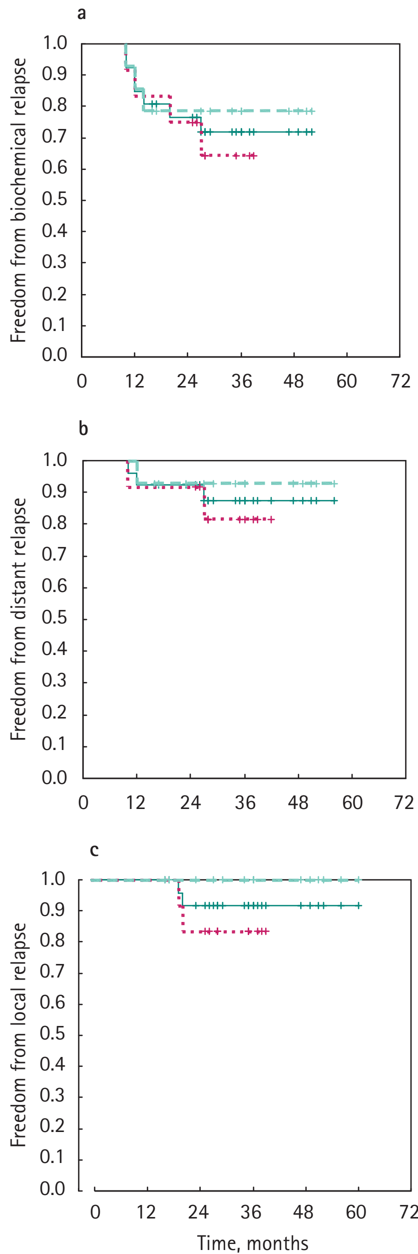
FIG. 1. Freedom from (a) biochemical relapse, (b) distant metastasis, and (c) local relapse for all patients (green line), and the interstitial (red dotted line) and regional (light green dashed line) hyperthermia groups.



together the actuarial probability of freedom from local relapse was 91% after 36 months (Fig. 1c).

The proportional hazards regression analysis of the items in Table 1 showed that no factor was significantly associated with time to biochemical relapse, mainly because there were too few patients and events, and the short follow-up.

DISCUSSION

There is a strong rationale for adding hyperthermia to EBRT in men with locally advanced prostate carcinoma. Treatment results after conventional irradiation alone are unsatisfactory [1,3,24,25]. A thermal enhancement ratio has been established for prostate cancer [5]. Early studies on hyperthermia for prostate carcinoma showed evidence for an improved clinical outcome [6,7] and prostate hyperthermia does not seem to decrease the quality of life [8]. Although the present data on clinical outcome are preliminary, they might serve to support present discussions on future randomized trials.

The toxicity of the combined hyperthermia-radiotherapy treatment is acceptable; no toxicity above grade 2 was reported. The side-effects of the hyperthermia treatments were mild, as was also reported by others [6,9,10].

The 36-month freedom from biochemical relapse rate was 70% for all 26 patients (Fig. 1a), with actuarial probabilities of freedom from local relapse rate of 91% (Fig. 1c) and from distant metastasis of 86% (Fig. 1b). Anscher *et al.* [6] delivered regional hyperthermia to 18 patients with newly diagnosed prostate cancer; the actuarial local control and freedom from distant failure at 36 months were 93% and 68%, respectively. The results of Anscher *et al.* [6] and the present results on clinical outcome compare favourably with series of patients treated with radiotherapy alone [1,3,24,25]. Zagars *et al.* [1] reported a 50% freedom from PSA relapse rate after 36 months in 260 patients with T3 NXM0 disease. Pilepich *et al.* [24] found in 230 patients with T2–T4 tumours that ≈40% were free from local relapse and 70% free from distant metastases after 3 years.

To date the optimal treatment temperature, the required number of hyperthermia treatments and treatment duration remain unclear. Thus we report the clinical results of both groups separately and together; it is inappropriate to compare the clinical results of both groups. There were differences between the groups in the number of hyperthermia treatments, treatment duration, thermal variables and temperature distribution [13,14], perfusion [16] and applied selection criteria [8]. Furthermore, both groups comprised few patients. The regional hyperthermia study was phase II, focusing on optimization. Most feasibility aspects were already investigated and the treatments administered according to the current standards and quality-assurance protocols. Interstitial hyperthermia was a phase I study mainly of technical feasibility, which resulted in an insufficient temperature distribution, using the criteria of Emami *et al.* [26] for prostate cancer treatment. Further optimization of the interstitial hyperthermia technique is necessary before it can be used in clinical trials.

The thermal dose concept was developed to evaluate the quality of the hyperthermia [17,18]. A more homogeneous temperature distribution seems to produce better clinical results. There was a strong correlation between the minimum thermal dose, tumour coverage, local control and duration of control [17,26]. It is likely that the minimum temperature in the entire prostate volume will also be clinically relevant. In 83% of men prostate cancer has more than one cancer focus and 95% of these are situated in both the peripheral and the central or transitional zone [27].

There are limitations to the thermal dose variables T_{90}, T_{50}, CM T_{90} and CEM T_{90} [17,18]. Most of these concepts are based on the availability of very sparse thermometry data [28]. Because of this it is likely that the minimum temperatures in the tumour will be missed, and that the thermal dose will be overestimated. In the regional treatments only a mean of eight invasive sensors was present, whereas there were many for interstitial hyperthermia and a 3D temperature distribution could be calculated. In Table 3 the mean CEM T_{90} was 0.47 min for interstitial hyperthermia using only the mean T_{90}. However, especially in the catheter tracts, high temperatures were reached, up to 60 °C, which must have caused severe thermal damage [14]. When averaging the thermal dose in the entire prostate volume, the CEM T_{90} could be 13–45 000 min. Thus temperature heterogeneity is not properly incorporated in the CEM T_{90} and CM T_{90} formulae. A comparison between these hyperthermia methods is therefore not valid using the present thermal dose concepts.

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There is a marked improvement in treatment outcome in locally advanced prostate carcinoma when using androgen suppression as an adjuvant to conventional irradiation [1,3,24,25]. In the present study only two of the 26 patients received adjuvant androgen suppression. This has the advantage of showing an adjuvant effect of hyperthermia more clearly than in patients also treated with adjuvant androgen suppression. The combination of hyperthermia, androgen suppression and radiotherapy may further improve the clinical outcome. Quality of life is now widely recognized as important in evaluating the effectiveness of prostate cancer therapies [29]. Androgen suppression severely compromises the quality of life [30], whereas hyperthermia does not seem to do so [8].

In conclusion, hyperthermia is a promising therapy in conjunction with irradiation for locally advanced prostate carcinoma. There are probably fewer short-term relapses with adjuvant hyperthermia than with irradiation alone. The toxicity is acceptable and randomized studies are needed to confirm these beneficial effects.

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Abbreviations: **EBRT**, external beam radiotherapy; **CTC**, Common Toxicity Criteria; **3D**, three-dimensional; **CTV**, clinical target volume; **MECS-IHT**, multi-electrode current source interstitial hyperthermia technique; **C(E)M**, cumulative (equivalent) minutes.

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