Re-irradiation and external hyperthermia in locally advanced, radiation recurrent, hormone refractory prostate cancer: a preliminary report

J A KALAPURAKAL, MD, B B MITTAL, MD and V SATHIASEELAN, PhD

Division of Radiation Oncology, Robert H Lurie Comprehensive Cancer Center, Northwestern Memorial Hospital, 251 East Huron Street, Galter Pavilion LC-178, Chicago, IL 60611, USA

Abstract. The purpose of this report is to present the preliminary results of re-irradiation and external hyperthermia in patients with locally advanced, previously irradiated, hormone refractory prostate cancer. Three consecutive patients with symptomatic, locally advanced, previously irradiated and hormone refractory prostate cancer were treated with further irradiation (30.6–50 Gy) and external hyperthermia (5–8 treatments). All patients had complete resolution of symptoms lasting for 12–24 months. Significant tumour shrinkage, including complete tumour response, was demonstrated by CT and endoscopy. In one case, at 2 years after re-treatment, there is continued tumour regression and bone regeneration in the pelvis. Two patients had local control of tumour, which continued until most recent follow-up at 12 months and more than 24 months, respectively. Another case developed local recurrence at 17 months. At most recent follow-up, no patient has experienced significant treatment-related side effects. In these patients with no other therapeutic alternatives, re-irradiation and hyperthermia can provide durable tumour response for more than a year, resulting in significant improvement in quality of life. Further clinical studies are warranted.

There are at present no effective treatment options in patients with locally advanced, previously irradiated and hormone refractory prostate cancer [1]. The purpose of this study is to present the preliminary results of re-irradiation and external hyperthermia in such patients.

Materials and methods

In 1997, a programme of re-irradiation and hyperthermia for patients with locally advanced, clinically symptomatic, previously irradiated and hormone refractory prostate cancer was started at Northwestern Memorial Hospital. This report describes the treatment and the tumour response of the first three consecutive patients who have a minimum follow-up of 1 year after retreatment.

Case 1

A 79-year-old White male initially presented with stage B2 adenocarcinoma of the prostate in 1988. He received external beam irradiation to a dose of 70 Gy. He relapsed 4 years later, with a rising serum prostate specific antigen (PSA), and was placed on total androgen suppression with leuprolide acetate and flutamide. His PSA began to rise 2 years later while on anti-androgens. In 1997 he developed haematuria. Cystoscopy showed invasive tumour in the bladder, which was resected cystoscopically. Later that year he developed lymphoedema of the lower extremities and scrotum. He also had significant difficulty in walking owing to pain and lymphoedema. He had bilateral inguinal and femoral lymphadenopathy. A large, hard nodular tumour mass in the prostate and seminal vesicles with invasion into the rectal wall without ulceration of the rectal mucosa, was palpated on digital rectal examination (DRE). CT in March 1998 showed a large prostate measuring 7 cm × 6 cm × 6 cm invading the urinary bladder (Figure 1a). There were multiple enlarged lymph nodes in the inguinal, femoral and iliac regions bilaterally. The maximum size of the nodes was 3 cm × 3 cm (Figure 2a). CT also showed liver metastases. His serum PSA was 60 ng ml⁻¹. No skeletal metastases were shown on a radionuclide bone scan.

CT treatment planning and immobilization with an alpha cradle cast was employed. The planning target volume (PTV) included the gross tumour volume (GTV) plus a margin of 2 cm. He received 38 Gy in 20 fractions to both iliac and inguinofemoral regions using 18 MeV electrons over 3 weeks in April and May 1998. The dose...
was prescribed to the 90% isodose. The prostate gland was treated with bilateral arc fields (10 cm × 13 cm) to a dose of 30.6 Gy at 1.8 Gy per fraction. He also received five external deep hyperthermia treatments, twice weekly, 30–45 min after radiation.

During treatment he developed progressive worsening of the extremity and genitalia oedema. CT and venography ruled out obstructive uropathy or venous thrombosis as potential causes for this increase in swelling. He developed urinary retention requiring insertion of a Foley catheter. He also developed moist desquamation in the groin. The urinary catheter was removed 2 weeks after re-treatment. The moist desquamation healed 1 month later. At 3 months post treatment there was complete resolution of scrotal and extremity lymphoedema. CT of the pelvis 9 months post treatment showed reduction in tumour size in the prostate, with no bladder invasion. The prostate gland measured 5 cm × 4 cm × 4 cm and there was no invasion of the bladder or rectum (Figure 1b). There was complete resolution of inguinal and femoral lymphadenopathy (Figure 2b). Urinalysis at that time did not show any microscopic haematuria. He had no pain, urinary obstruction, difficulty in walking or rectal bleeding. However, he developed progression of metastases in the liver, bones and paraaortic lymph nodes. He died 12 months after re-treatment, with no evidence of locoregional recurrence or lymphoedema in the scrotum. He had good urinary function, with no haematuria, or urinary or faecal incontinence.

Case 2

An 80-year-old man was initially diagnosed with stage B2, moderately differentiated adenocarcinoma of the prostate in 1983. He received external beam irradiation to a dose of 70 Gy in 1984. Approximately 2 years later he developed tumour recurrence in the prostate gland. He had a transurethral resection (TURP) in 1986 for urinary outlet obstruction followed by bilateral orchietomy. He was asymptomatic for approximately 3 years, after which he again developed
urinary outlet obstruction requiring TURP in 1992 and 1995, which subsequently left him with urinary incontinence. In 1998 he experienced worsening constipation. Sigmoidoscopy in April 1998 demonstrated a 5 cm × 5 cm circumferential mass in the rectum with constriction of the rectal lumen. Biopsy of the tumour showed prostatic adenocarcinoma, with positive immunohistochemical staining for PSA. Rectal examination demonstrated a 6 cm × 6 cm hard fixed mass in the anterior rectal wall with near total obliteration of the rectal lumen. CT of the pelvis in September 1998 showed a 7.5 cm × 6 cm × 6 cm tumour arising in the region of the seminal vesicles, invading and narrowing the rectum (Figure 3a). At this time he had symptoms of rectal bleeding and pelvic pain. His serum PSA was 30 ng ml⁻¹ before treatment. CT of the abdomen as well as bone scan showed a right-sided hydronephrosis and hydrourerter secondary to ureteral obstruction by tumour, but there was no evidence of distant metastases.

CT treatment planning and immobilization with an alpha cradle cast was employed. The PTV included the GTV plus a margin of 2 cm. He received external beam irradiation to a dose of 36 Gy in 20 fractions over 4 weeks. He was treated with 10 MV X-rays with a four-field technique, using field sizes of 13 cm × 16 cm and 15.5 cm × 16 cm. He also received seven hyperthermia treatments.

He tolerated the treatment well. By the end of his treatment he had complete resolution of rectal bleeding and pelvic pain, with significant reduction of the rectal mass. At 3 month follow-up the rectal tumour had completely regressed on DRE and his serum PSA had decreased from 30 ng ml⁻¹ prior to treatment to 3.3 ng ml⁻¹. In July 1999, approximately 9 months after treatment, his PSA was 1.8 ng ml⁻¹ and in November 1999 there was further reduction to 0.6 ng ml⁻¹. CT in October 1999, 1 year after treatment, showed complete resolution of the tumour in the seminal vesicles and rectum and complete resolution of hydronephrosis. The prostate gland measured 5 cm × 4 cm × 4 cm, with no evidence of tumour invasion into the bladder and rectum (Figure 3b). Sigmoidoscopy 13 months after treatment demonstrated complete resolution of the tumour in the rectum. There was no evidence of radiation proctitis. Small mucosal erosions in the rectum at the site of the previous tumour were biopsied and were consistent with prostate adenocarcinoma with positive immunostaining for PSA. In March 2000, local tumour recurrence was detected on DRE and was confirmed by flexible sigmoidoscopy and CT of the pelvis. CT also showed liver metastases. The serum PSA level had risen to 7.9 ng ml⁻¹.

Case 3

A 54-year-old White male was diagnosed with adenocarcinoma of the prostate in 1984. Radical prostatectomy on 14 October 1984 showed a Gleason 4+3 adenocarcinoma of the prostate with tumour extension beyond the left apex and invasion into the membranous urethra. He received adjuvant post-operative radiation to a dose of 60 Gy in 30 fractions, which was completed in January 1985. He was without clinical evidence of recurrence until 1990, when he was noted to have a rising serum PSA level. CT of the pelvis showed recurrent tumour nodules in the bladder,
and a radical cystectomy was performed. He was then placed on total hormone suppression with leuprolide acetate and bicalutamide. Approximately 4 years later his tumour became androgen refractory and the serum PSA rose to 9.1 ng ml$^{-1}$ in August 1998. At that time he also had pain in the left pelvis. DRE demonstrated a hard nodular tumour mass in the left pelvic sidewall. CT in September 1998 demonstrated a 6.5 cm $\times$ 7.5 cm $\times$ 6 cm pelvic sidewall tumour invading bone. There was enlargement of the left obturator internus muscle, and the mass was contiguous with a region of destruction of the left pubic symphysis and left inferior pubic ramus. Both sclerotic and lytic lesions were present in this area (Figure 4a). Biopsy of the lesion confirmed recurrence of prostate adenocarcinoma. Isotope bone scan showed increased uptake in this region corresponding to the CT. There was no evidence of distant visceral or skeletal metastases.

CT treatment planning and immobilization with an alpha cradle cast was employed. The PTV included the GTV plus a margin of 2 cm. He was treated in the supine position. Between 24 November 1998 and 30 December 1998 he received 50 Gy in 25 fractions to the left hemipelvis. The first 40 Gy was delivered using 10 MV X-rays with an anteroposterior–posteroanterior technique to a field size of 12 cm $\times$ 16 cm. The next 10 Gy boost was delivered with the same technique to a field size of 11 cm $\times$ 16 cm. He also received eight hyperthermia treatments.

He tolerated the re-treatment well. Pelvic pain disappeared by the end of treatment. At 3 months after re-treatment his serum PSA was <0.1 ng ml$^{-1}$. CT in October 1999 at 10 months after re-treatment showed reduction in size of the tumour in the left pelvic sidewall and soft tissues. The tumour measured 5.5 cm $\times$ 4.5 cm $\times$ 4.5 cm and there was evidence of bone regrowth. A radionuclide bone scan at this time showed decreased uptake in this region, consistent with tumour shrinkage. 1 year after treatment he developed minimal rectal bleeding (RTOG grade 1) approximately once a week. Colonoscopy 14 months after treatment showed mild radiation proctitis. Barium enema demonstrated thickening of the sigmoid colon with no evidence of bowel obstruction. His serum PSA continued to be undetectable until 20 months after re-treatment when the PSA was 0.2 ng ml$^{-1}$. CT 2 years after re-treatment demonstrated continued tumour shrinkage and bone regeneration (Figure 4b). He was then started on bicalutamide and he now has an undetectable PSA. He currently has no pelvic pain, numbness or weakness of the extremities. Bone densitometry in April 2000 showed mild osteopenia in the left hip (88th percentile of age-matched control).

**Hyperthermia treatment (Table 1)**

Hyperthermia was delivered using a BSD-2000 system and a Sigma-60 applicator (BSD Medical Corporation, Salt Lake City, UT). This system consists of four synchronous amplifiers operating in the frequency range 60–120 MHz, each amplifier capable of delivering 500 W. The Sigma-60 applicator array consists of eight dipole antennae, equally spaced on a transparent cylindrical plastic shell. All patients were treated according to a Food and Drug Administration and Institutional Review Board approved phase I/II protocol. All hyperthermia sessions were started within 1 h after irradiation. A single, closed end thermometry catheter was introduced into the rectal

![Figure 4](image-url). CT of the pelvis (Case 3) (a) before treatment and (b) 2 years after re-treatment demonstrating tumour shrinkage in the pelvic sidewall and pubic bone regeneration (arrows).
lumen beyond the level of the tumour in the prostate. Luxtron multisensor optical temperature probes were placed inside these catheters and temperatures were recorded at three to four points, 1.0 cm apart, during each treatment. The objective of treatment was to obtain a minimum tumour temperature of 42 °C. If this was achieved, the power was regulated to maintain this temperature for 30–60 min. If this was not achieved, the power was increased to maximum tolerated levels for 30–60 min. The hyperthermia treatment characteristics are shown in Table 1.

### Discussion

Prostate cancer is the commonest malignancy and the second leading cause of cancer death among men in the USA. In the year 2000, it was estimated that 180 400 new cases of prostate cancer would be diagnosed and that 31 900 patients would die of this disease [3]. The overall incidence of biochemical progression following treatment with radical prostatectomy, radiation therapy or radiation plus hormone treatment is 15–40% [4–6]. A significant number of patients will therefore develop recurrent prostate cancer after irradiation.

Patients with recurrent prostate cancer after irradiation are commonly retreated with anti-androgens or orchietomy [1]. The anti-tumour effects of such hormonal treatment last for approximately 1–2 years, after which time the tumours become hormone refractory [7]. Prostate cancer has a long natural history, and patients with early biochemical failure following radiation, without other clinical evidence of local or systemic progression, are expected to have an average survival of 5–10 years [1, 8]. As a consequence of the long survival and lack of treatment options for hormone refractory disease, some of these patients develop symptoms due to disease progression in the pelvis. Tumour invasion into the urethra and urinary bladder causes urinary outlet obstruction, haematuria and hydronephrosis. Tumour invasion into the rectum may result in bleeding, fistula formation and rectal obstruction. Tumour invasion into the pelvic lymphatic channels and lymph nodes can cause lymphoedema in the pelvis, external genitalia and extremities. Tumour invasion into the pelvic nerves and pelvic bones may result in intractable pelvic and perineal pain as well as pathological fracture [9].

The treatment options presently available for locally advanced, previously irradiated, hormone refractory prostate cancer include palliative surgical procedures such as TURP, ureteric stenting, cystoscopic tumour fulguration to limit urinary bleeding and colostomy/urinary diversion to overcome rectal/ bladder obstruction or fistulae. The medical measures utilized in these patients include narcotic or non-narcotic analgesics, antidepressants and blood transfusions [9]. Chemotherapy has been used in hormone refractory prostate cancer, but the tumour response rates are low and short lived. In a report of 42 patients treated with oral etoposide and estramustine, the overall response rate was 36% and the average duration of serum PSA decline was 8 weeks among responders [10, 11].

Re-irradiation has been used for treatment of previously irradiated tumours in several sites including head and neck, breast and brain. The local control rates achieved with re-irradiation range from 40–75% [12–14]. Re-irradiation has generally been used in combination with radiosensitizing agents such as chemotherapy and hyperthermia [12, 13]. Re-irradiation has also been used for the re-treatment of pelvic tumours such as recurrent rectal cancer [15]. In a report from Thomas Jefferson University, patients with recurrent rectal cancer were re-treated to a median dose of 30.6 Gy plus 5-fluorouracil chemotherapy. Bleeding, pain and mass effect were palliated in 100%, 65% and 24%, respectively. The RTOG grade 3 and 4 late toxicity rates were 23% and 10%, respectively. Small bowel obstruction occurred in 17%, with only 3% requiring re-operation. 6% developed chronic cystitis and 8% developed fistula formation [15]. Re-irradiation of locally advanced pelvic tumours may therefore result in significant palliation with tolerable side effects. In this study we have used similar doses to those used in the Jefferson series.

Randomized clinical trials have demonstrated the efficacy of radiation and hyperthermia in locally advanced primary breast cancer [16] and malignant melanoma [17]. All these tumour sites

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**Table 1. Summary of treatment**

<table>
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<tr>
<th>Case</th>
<th>Frequency (MHz)</th>
<th>Average power (W)</th>
<th>Max. cumulative min at 42.5 °C in rectal probe</th>
<th>CumMinT10@41.0°C in rectal probe</th>
<th>Mean (and range) measured max. rectal temperature (°C)</th>
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</thead>
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<tr>
<td>1</td>
<td>92</td>
<td>464.4</td>
<td>21.3</td>
<td>75.0</td>
<td>42.0 (40.5–43.3)</td>
</tr>
<tr>
<td>2</td>
<td>72</td>
<td>496.4</td>
<td>355.7</td>
<td>242.0</td>
<td>43.7 (41.8–45.3)</td>
</tr>
<tr>
<td>3</td>
<td>82</td>
<td>639.0</td>
<td>32.5</td>
<td>123.0</td>
<td>42.0 (41.1–43.7)</td>
</tr>
</tbody>
</table>

*aCumulative minutes of temperature exceeding 41 °C in 10% of the measured points [2].
are superficially located, thus enabling adequate heating of the tumour bed. The clinical value of deep hyperthermia was not proven until recently. A prospective randomized trial from the Dutch Deep Hyperthermia Group demonstrated significantly superior results with hyperthermia and irradiation in 358 patients with locally advanced bladder, uterine cervix and rectal cancer. The complete response (CR) rates, duration of CR and the local tumour control rates were significantly higher when radiation was combined with hyperthermia. There was also a survival advantage for patients with cervical cancer treated with radiation and hyperthermia [18].

There are a few reports of deep hyperthermia and radiation in patients with untreated prostate cancer [19–21]. In the Duke University series, 18 patients with newly diagnosed stage T3 or T4 prostate cancer were treated with definitive irradiation (65–70 Gy) and deep hyperthermia. The 3-year local control and treatment failure free survival were 93% and 68%, respectively [20]. The only report of re-irradiation and external hyperthermia for prostate cancer was from Stanford University. These patients were initially treated with $^{192}$Ir implantation. Four patients were treated with hyperthermia and re-irradiation to a dose of 60 Gy, in two 30 Gy split courses. None of the patients experienced severe rectal or bladder reactions and three patients achieved complete clinical response at 7–24 months after re-treatment [21].

This report is the first to describe the response to re-irradiation and hyperthermia in clinically symptomatic, locally advanced, hormone refractory prostate cancer following full dose external beam irradiation. The risks of re-treatment in patients with large recurrent tumours should be weighed against the immediate threat posed by tumour progression. The very high likelihood of significant deterioration of quality of life owing to unhindered tumour progression necessitates the judicious use of re-treatment. In this preliminary report, all three patients had good responses that lasted for 1–2 years. So far no patient has had significant late toxicity. Further follow-up is required before any definite statements on late toxicity can be made. Most re-irradiation reports use radiosensitizing chemotherapy to potentiate the effects of the lower radiation doses used for re-treatment. In recurrent hormone refractory prostate cancer, as the efficacy of radiosensitizing chemotherapy is unproven, the choice of deep hyperthermia as a radiosensitizer is appropriate. Based on these results, a multicentre randomized study is being planned to further evaluate the role of hyperthermia and re-irradiation in such patients.

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References


