

CLINICAL INVESTIGATION

Prostate

**EFFICACY OF IRRADIATION AND EXTERNAL HYPERTHERMIA IN
LOCALLY ADVANCED, HORMONE-REFRACTORY OR RADIATION
RECURRENT PROSTATE CANCER: A PRELIMINARY REPORT**

JOHN A. KALAPURAKAL, M.D., MARGARET PIERCE, R.N., ALAN CHEN, M.D., AND
VYTHIALINGAM SATHIASEELAN, PH.D.

Division of Radiation Oncology, Northwestern University, Robert H. Lurie Cancer Center, Chicago, IL

Purpose: To present a preliminary report on the feasibility, efficacy, and toxicity of irradiation (RT) and hyperthermia (HT) in patients with locally advanced, hormone-refractory prostate cancer (LAHRPC) who may or may not have received prior RT.

Methods and Materials: Between 1997 and 2002, 13 consecutive patients with LAHRPC or RT-recurrent prostate cancer were treated with RT and HT on a Phase I–II protocol. Eight patients had RT-recurrent LAHRPC (Group A) and 5 had LAHRPC without prior RT (Group B). All patients had large and clinically symptomatic tumors. The median RT dose was 39.6 Gy and 66.6 Gy in Groups A and B, respectively. External deep HT was delivered using a BSD-2000 Sigma-60 applicator. The median number of HT treatments was 8 in group A and 10 in group B.

Results: The median follow-up was 14 and 13 months for Groups A and B, respectively. All patients achieved a complete or partial response (CR/PR) and complete palliation of symptoms. Eleven patients had follow-up CT scans that demonstrated a CR in six and a PR in five. Two patients, who died of metastasis, did not have CT scans and had a PR on digital rectal examination. Two patients demonstrated a biochemical CR. The median duration of the CR/PR among Group A patients was 12 months after therapy. Three patients in Group A developed tumor recurrence at 9, 17, and 27 months after repeat RT to doses of 39.6, 36, and 50 Gy, respectively. At last follow-up, no Group B patient developed local recurrence. Grade 1–2 rectal bleeding was noted in 3 patients. RT and HT were generally well tolerated by all patients who had not previously undergone RT. Of the 8 patients who had, 6 (75%) tolerated retreatment well with minimal or no complications. Two patients in the repeat RT group had severe complications. One patient with lymphoma and factor XI deficiency developed Grade 4 hemorrhagic cystitis. Another previously irradiated patient developed a rectovesical fistula 4 months after retreatment, after disappearance of a large, invasive, and necrotic tumor.

Conclusion: This preliminary report demonstrates the feasibility and efficacy of RT and HT in patients with LAHRPC, who may or may not have received prior RT. Presently, such patients who have undergone previous RT have no effective treatment options. RT and HT were generally well tolerated by patients who were not previously undergone RT. Of those who had been, most (6 of 8) tolerated retreatment well with minimal or no complications. The high-risk factors for treatment- and tumor regression-related side effects include the presence of large necrotic tumors, previous RT with a large dose/fraction, and the presence of bleeding disorders. Despite the size of these large tumors, RT and HT resulted in significant tumor shrinkage, rapid serum prostate-specific antigen decline, durable treatment responses, and durable palliation of symptoms. Additional clinical studies are warranted. © 2003 Elsevier Inc.

Prostate cancer, Radiotherapy, Hyperthermia, Hormone refractory, Local recurrence, Palliation, Retreatment.

INTRODUCTION

Patients who experience biochemical relapse after primary irradiation (RT) can have a high survival rate (1). The role of salvage surgery (2), cryosurgery (3), and brachytherapy

(4) in these patients remains to be defined. The effects of antiandrogen therapy are temporary, and most patients develop hormone-refractory disease (5). Patients who develop locally advanced and hormone-refractory prostate cancer (LAHRPC), with or without prior RT, may have significant

Reprint requests to: John A. Kalapurakal, M.D., Division of Radiation Oncology, Northwestern Memorial Hospital, 251 E. Huron St., LC-178, Chicago, IL 60611. Tel: (312) 926-3761; Fax: (312) 926-6374; E-mail: j-kalapurakal@northwestern.edu

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impairment of their quality of life because of tumor invasion into adjacent pelvic organs (6). Presently, such patients who have received prior RT have no effective treatment options. This report is an update of an earlier report (7) on the feasibility, efficacy, and toxicity of RT and hyperthermia (HT) in patients with LAHRPC who may or may not have undergone prior RT.

METHODS AND MATERIALS

Between 1997 and 2002, 13 consecutive patients with LAHRPC or RT-recurrent prostate cancer were treated with RT and HT on a Food and Drug Administration and institutional review board–approved Phase I–II protocol sponsored by the BSD Medical Corporation (Salt Lake City, UT). Of the 13 patients, 8 had RT-recurrent LAHRPC (Group A) and 5 had LAHRPC without prior RT (Group B).

At the initial consultation, a detailed history and physical examination, including a digital rectal examination (DRE), was performed, and blood was drawn for serum prostate-specific antigen (PSA) measurement, complete blood count, and liver and kidney function tests. A pretreatment CT scan of the abdomen and pelvis and bone scan were also obtained. Endoscopy (sigmoidoscopy or cystoscopy) was performed in most patients to document tumor invasion into adjacent organs. A biopsy was obtained to confirm the presence of recurrent prostate cancer. The TNM staging system was used to describe the tumor stage (8).

Informed consent

All patients were presented with the available therapeutic options, including no further treatment, symptomatic management (narcotic analgesics, α -blockers, blood transfusions, etc.), palliative surgical urinary and/or bowel diversion, other Phase I–II chemotherapy protocols, RT alone, or treatment with RT and HT. All patients provided informed consent before enrollment in the study.

Patient and tumor characteristics

The clinical characteristics, treatment, and follow-up data are presented in Table 1. The mean patient age was 76 years (range 54–82). Tumor size was measured from the pretreatment CT scans. The tumor size was expressed as the height by width by AP dimension. Tumor size measurement included the prostate and seminal vesicle and tumor extension into adjacent organs. All patients had large tumors, with a median dimension of 7.5 cm \times 6.5 cm \times 6.5 cm (range 6.5 \times 7.5 \times 6 to 12 \times 13 \times 14). The clinical symptoms at presentation included pelvic pain (13 of 13), hematuria (9 of 13), urinary retention (5 of 13), rectal pain/obstruction (4 of 13), rectal bleeding (2 of 13), and lymphedema (1 of 13). The tumor demonstrated evidence of invasion into the urinary bladder in 8 patients, rectal invasion or obstruction in 6, and pelvic bone/soft tissue invasion in 5 patients. Distant metastasis was present in 8 patients.

Radiotherapy

RT was delivered using 10–18-MV X-rays with CT-based three-dimensional treatment planning techniques and alpha-cradle cast immobilization. In all patients, the planning target volume included the gross tumor volume with a margin of 1–2 cm. RT was delivered at 1.8 Gy/fraction. The prescription isodose line ranged from 95% to 100%. The median total RT dose was 39.6 Gy (range 29.8–50) in Group A and 66.6 Gy (range 59.4–70.2) in Group B. The presence of large tumors with invasion into the rectum and bladder precluded the safe delivery of higher doses to Group B patients.

Hyperthermia

External deep HT was delivered using a BSD-2000 Sigma-60 applicator (BSD Medical, Salt Lake City, UT). A Sigma-60 annular phased-array radiofrequency device operating in the frequency range of 92–72 MHz was used. Both phase and amplitude steering were used to maximize temperatures in the prostate and minimize patient discomfort. Patients were monitored continuously during each treatment for changes in vital signs and for symptoms of heat intolerance such as pain. Power was increased in a stepwise fashion until the patient could no longer tolerate further increases in power. A treatment session lasted for 60 min from the time temperature monitoring was started. A description of this HT delivery system and details about thermometry have been previously published (7, 9).

HT was delivered twice weekly, at least 72 h apart, for a maximum of 10 treatments. HT was administered approximately 1 h after RT. Previous reports have demonstrated the adequacy of endoluminal thermometry (10) and the complications associated with interstitial thermometry (11) in patients with deep-seated pelvic tumors. In this study, interstitial thermometry was not performed, because these patients were already symptomatic from advanced tumors. Furthermore, the main objective of our study was to maximize patient tolerance and thus maintain the HT treatment for at least 1 h. The data obtained from the rectal temperature probes (endoluminal temperatures) thus provided an indirect measure of the temperatures achieved within the prostate gland (11). The rectal temperature probe was placed in a single plastic catheter that was inserted to a distance of 7–8 cm from the anal verge. The temperature probes used included a luxtron optical multisensor probe in 9 patients and a Bowman temperature probe in 4. Thermometry data are given in Table 2 (12). The median number of HT treatments was 8 (range 5–10) in Group A and 10 (range 2–10) in Group B.

Prior therapy

The details of prior therapy, including surgery, RT, hormonal therapy, chemotherapy, and palliative surgery are outlined in Table 1. All patients had hormone-refractory prostate cancer after several years of hormonal therapy with multiple antiandrogens, including leuprolide acetate, bicalutamide, megestrol acetate, and estrogens. Orchiectomy

Table 1. Clinical characteristics, treatment, and follow-up of patients in Groups A and B

Group	Pt. No.	Age at diagnosis (y)	Gleason score	Prior therapy	Presenting signs and symptoms; serum PSA (ng/mL); Tumor size (cm)	RT + HT(n)/completion date	Results (time after RT/HT)	Toxicity
A	1	79	3 + 3	RT (70 Gy, 1988), TAS	LE, hematuria, pelvic pain; 60; 7 × 6 × 6	30.6 Gy, prostate; 38 Gy, LN; + HT (5)/May 1998	CR on DRE and CP (3 mo); CT scan (9 mo) continued CR; DOD	None
	2	80	3 + 3	RT (70 Gy, 1984), orchiectomy, bicalutamide, megestrol acetate, TURP × 3	Bleeding PR and rectal obstruction, pelvic pain, hematuria; 30; 7.5 × 6 × 6 (Fig 1)	36 Gy + HT (7)/October 1998	CP end of RT/HT; CR on DRE (3 mo); CT scan (12 mo) continued CR; endoscopy (13 mo) CR (Fig. 3B); LR in rectum (17 mo)	None; patient alive at last follow-up (4 y)
	3	54	4 + 3	Prostatectomy 1984, RT (60 Gy, 1985), cystectomy (1990) for recurrence, TAS	Pelvic pain; 9.1; 6.5 × 7.5 × 6	50 Gy + HT (8)/December 1998	CP end of RT/HT for 3 y; PSA < 0.1 ng/mL at 3 mo until 20 mo; CT scan—tumor soft-tissue CR, bone PR until 27 mo, then LR	Grade 1 rectal bleeding; patient alive at last follow-up (4 y)
	4	78	3 + 4	RP, RT (60 Gy, 1994), TAS, SPC (February 2000)	Pelvic pain, hematuria, retention; 8 × 7 × 6.5	45 Gy + HT (9)/April 2000	CP 2 mo after RT/HT; tumor PR on CT scan (2 mo); DOD	None
	5	76	3 + 3	TAS, RT hemipelvis (30 Gy/10, June 1998), chemotherapy for NHL; RT hemipelvis 12 Gy/4 f, September 2000	Pelvic pain scale: 5/5, hematuria; 11 × 11 × 8.5	29.8 Gy + HT (8)/November 2000	CP end of RT/HT, CR on DRE, CT scan—soft-tissue CR, bone PR 3 mo; CP (16 mo)	Urethral stricture (6 mo); NHL-related factor XI deficiency; 8 mo later, Grade 4 cystitis, Grade 2 rectal bleeding (14 mo)
	6	80	5 + 5	RT (65 Gy, 1990), TAS, megestrol acetate	Rectal pain, hematuria; 35; 6.5 × 7 × 6	39.6 Gy + HT (10)/October 2000	CP end of RT/HT until death; CR on DRE and endoscopy (5 mo); LR in bladder (9 mo); DOD (14 mo)	Grade 1 rectal bleeding (8 mo)
	7	73	2 + 3	RT (65 Gy, September 1997), TAS, CT, radiolabeled-antibody therapy	Pelvic pain, hematuria, urinary retention, rectal pain and obstruction; 83; 8 × 7 × 9; tumor necrosis present (Fig. 2).	41.4 Gy + HT (10)/October 2001	Decrease in pelvic pain; CT scan CR (4 mo); metastasis in pelvic and abdominal LN	Rectal ulcer (2 mo); urinary fistula with tumor CR (4 mo)
	8	78	5 + 4	RT (66.6 Gy, June 1992), TAS, CT, RT (18 Gy), TURP × 2	Pelvic pain, hematuria, urinary retention, rectal bleeding, pain and obstruction; 319; 7 × 6 × 9	43.2 Gy + HT (10)/May 2002	Decrease in pelvic pain; CT scan 4 mo; after RHT—CR; sigmoidoscopy 5 mo after RHT—CR, with skip lesion above previous tumor site	None
B	1	82	4 + 4	Estrogens, TAS (1994)	Pelvic pain, urinary obstruction, hematuria; 2.7; 8 × 8 × 8	59.4 Gy + HT (2)/January 1998	CP; tumor PR on DRE; no CT scans done; DOD (6 mo)	None
	2	71	4 + 5	TAS (1992)	Rectal obstruction, pain; 318; 7 × 6 × 7	66.6 Gy + HT (10)/October 2000	Tumor CR on DRE (4 mo); CT scan—tumor PR (12 mo); PSA < 0.1 ng/mL (2 mo) until last follow-up (24 mo); CP (Figs. 3, 4)	None
	3	66	3 + 3	Prostatectomy, orchiectomy (1994)	Urinary obstruction, pelvic pain; 13.8; 6.5 × 7 × 9	70.2 Gy + HT (10), bicalutamide/April 2000	DRE, ultrasound scan, CR (6 wk); CT scan—tumor soft-tissue CR, bone sclerosis (4 mo); CP	Grade I rectal bleeding
	4	69	3 + 3	Orchiectomy 1993, bicalutamide	Pelvic pain, ureteral obstruction; 672; 12 × 13 × 14	64.8 Gy + HT (10)/September 2001	CT scan PR (4 mo); significant PSA response from 672 to 56 ng/mL at 14 mo after RT/HT; CP	None
	5	76		TAS (1998)	Hematuria, pelvic pain; 11 × 13 × 12	66.6 Gy + HT (10)/January 2002	CP at end of RT/HT; PR on DRE (3 mo); DOD	None

Abbreviations: PSA = prostate-specific antigen; RT/HT = radiotherapy plus hyperthermia; TAS = total androgen suppression; LE = lymphedema; LN = lymph nodes; CR = complete response; DRE = digital rectal examination; CP = complete palliation (of symptoms); DOD = died of disease; TURP = transurethral resection of prostate; PR = partial response; LR = local recurrence; NHL = non-Hodgkin's lymphoma.

Table 2. Summary of temperature data measured in rectal lumen

Parameter	Group A	Group B
Patients (n)	8	5
Treatments (n)	67	42
Temperature (°C)		
Average	41.1 (41.4–40.7)	41.4 (41.9–41.0)
Maximum	41.6 (42.3–40.8)	42.3 (42.9–41.7)
Minutes \geq 40.0°C (n)	35.8 (49.5–13.1)	42.6 (54.1–26.5)
Minutes \geq 41.0°C (n)	14.6 (25.6–1.8)	31.4 (46.6–17.1)
Minutes \geq 42.0°C (n)	3.4 (7.9–0.0)	6.2 (25.0–0.0)
CEM @ 42.5°C (n)	68.1 (119.0–4.0)	103.0 (262.0–14.0)
CEM @ 43.0°C (n)	35.8 (75.0–2.0)	53.4 (135.0–7.0)

Abbreviation: CEM = cumulative equivalent minutes. Numbers in parentheses are the range.

had been performed in 2 patients. In 1 patient (Table 1, Group B, Patient 2) who underwent orchiectomy, Casodex was added before RT and HT. In all other patients, no new hormonal therapy agent was added during or after RT and HT. The advanced stage of these hormone-refractory tumors was evident by the presence of distant metastasis at presentation in 5 (63%) of 8 Group A patients and 2 (40%) of 5 Group B patients. Furthermore, distant metastasis appeared in 2 additional patients in Group A and 1 patient in Group B.

Follow-up

All patients were followed at 6 weeks after therapy initially and then every 2–4 months after therapy. At each follow-up visit, a detailed clinical examination, including history, physical examination, DRE, and serum PSA estimation, was performed. CT or ultrasound scans of the pelvis were obtained every 3–6 months, if the patient's condition permitted. In patients with tumor invasion into the rectum or bladder, every attempt was made to obtain posttherapy endoscopy to document tumor response, if the patient's condition permitted. Among patients without distant metastasis, the serum PSA half-life after RT and HT was calculated using a previously published formula (13). The Response Evaluation Criteria in Solid Tumor (RECIST) were used to define tumor response. A complete response (CR) was defined as the complete disappearance of the target lesions. A partial response (PR) was defined as at least a 30% decrease in the sum of the longest diameter of the target lesion (14). Late radiation toxicity was scored using the Radiation Therapy Oncology Group (RTOG)/European Organization for Research and Treatment of Cancer late radiation morbidity scoring scheme.

RESULTS

The tumor response and treatment-related toxicity are described in Table 1 and Figs. 1–4. The median follow-up for Group A patients was 14 months (range 4–48) and was 15 months (range 6–32) for Group B patients. Six patients

died of progressive distant metastasis: 4 in Group A and 2 in Group B.

Symptom palliation

Despite the large and clinically symptomatic tumors, all patients achieved complete palliation of symptoms either by the end of treatment (10 of 13) or within 3 months after therapy (3 of 13). The palliation of symptoms was durable in most patients, lasting until the last follow-up visit or death. In 2 Group A patients in whom the tumor relapsed, symptoms of rectal obstruction and pelvic pain reappeared at 17 months and 36 months, respectively, after RT and HT.

Tumor and biochemical response

All patients achieved a CR or PR after RT and HT (Table 1). Eleven patients underwent CT during follow-up. Two patients who died of metastasis did not undergo CT and had a PR by DRE 2–3 months after therapy.

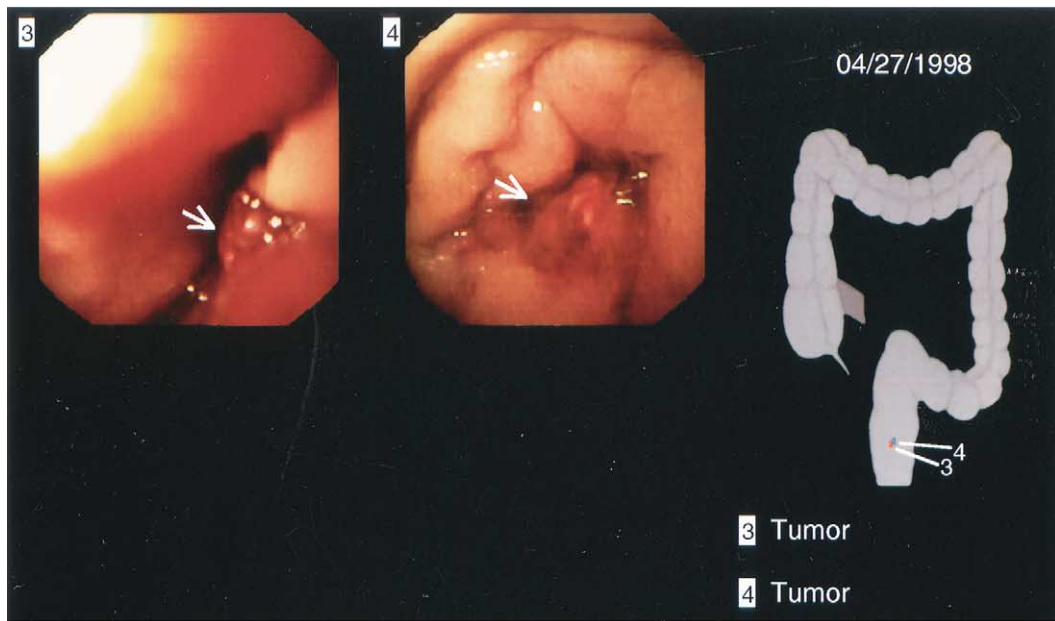
A tumor CR was demonstrated by CT in 6 patients (5 in Group A and 1 in Group B). A tumor CR was demonstrated by CT and endoscopy in 4 Group A patients (Figs. 1 and 2). A tumor PR was demonstrated by CT in 5 patients. Of them, 2 had a CR of the soft-tissue component of the tumor in the pelvis and a PR of the bony component that continued to show bone remodeling after therapy. The other 2 patients had significant tumor shrinkage (Fig. 4). Two patients demonstrated a biochemical CR, achieving undetectable serum PSA levels 2 and 3 months after treatment (Group A, Patient 3 and Group B, Patient 2). One (Group A, Patient 3) had a biochemical relapse 20 months after retreatment; the other continued to maintain biochemical remission 24 months after therapy (Fig. 3).

At last follow-up, the median duration of CR/PR among Group A patients was 12 months (range 4–27) after therapy. Of these, 3 died at 4, 6, and 19 months after retreatment, without local recurrence. Three patients developed tumor recurrence at 9 months (urinary bladder), 17 months (rectum), and 27 months (pelvis) after 39.6, 36, and 50 Gy, respectively. Of the 5 Group B patients, none had local recurrence, and the median duration of CR/PR was 15 months (range 4–32). Two patients died at 6 months of widespread metastasis.

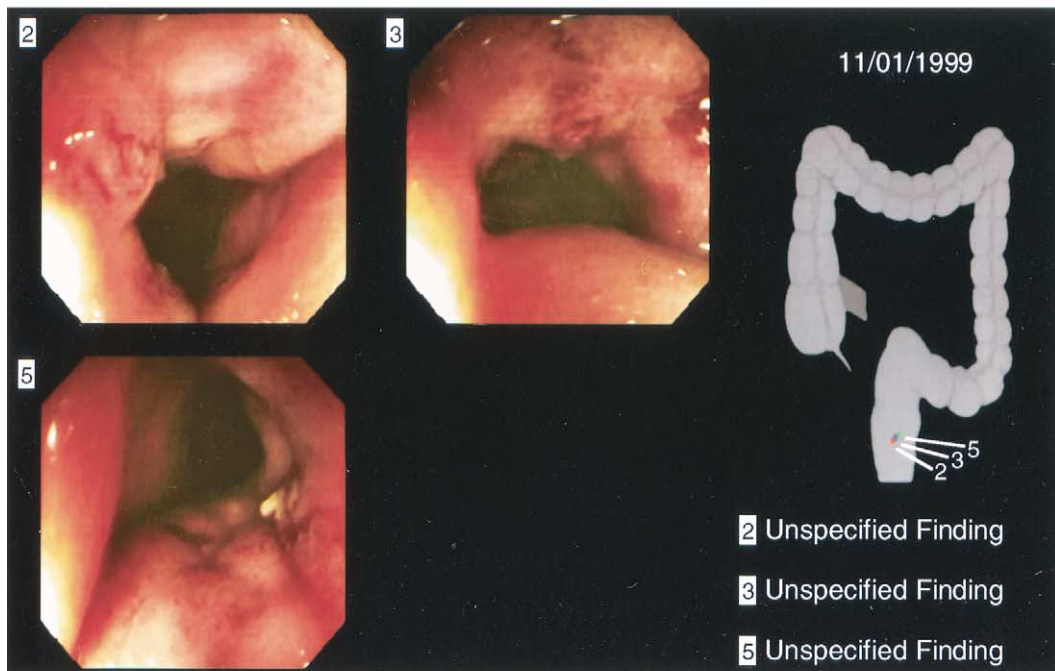
Six patients without distant metastasis demonstrated a rapid decline in serum PSA after treatment (Fig. 3). The PSA half-life in these patients was calculated from plots of the form $\log \text{PSA} = \log A + Bt$, where A is the initial PSA level, B is the rate of PSA decline, and t is time in days. The median half-life was 31.4 days (range 6.8–59.2) (13).

Acute and late toxicity

One patient with lymphedema of the genitalia and extremities developed moist desquamation of the groin after HT and RT to the prostate and inguinal lymph nodes. All other patients tolerated the treatment well. No patient developed hyperthermia-induced skin burns. The delayed toxicity from RT and HT included RTOG Grade 1 rectal bleeding in 2 patients and RTOG Grade 3 rectal bleeding in



(a)



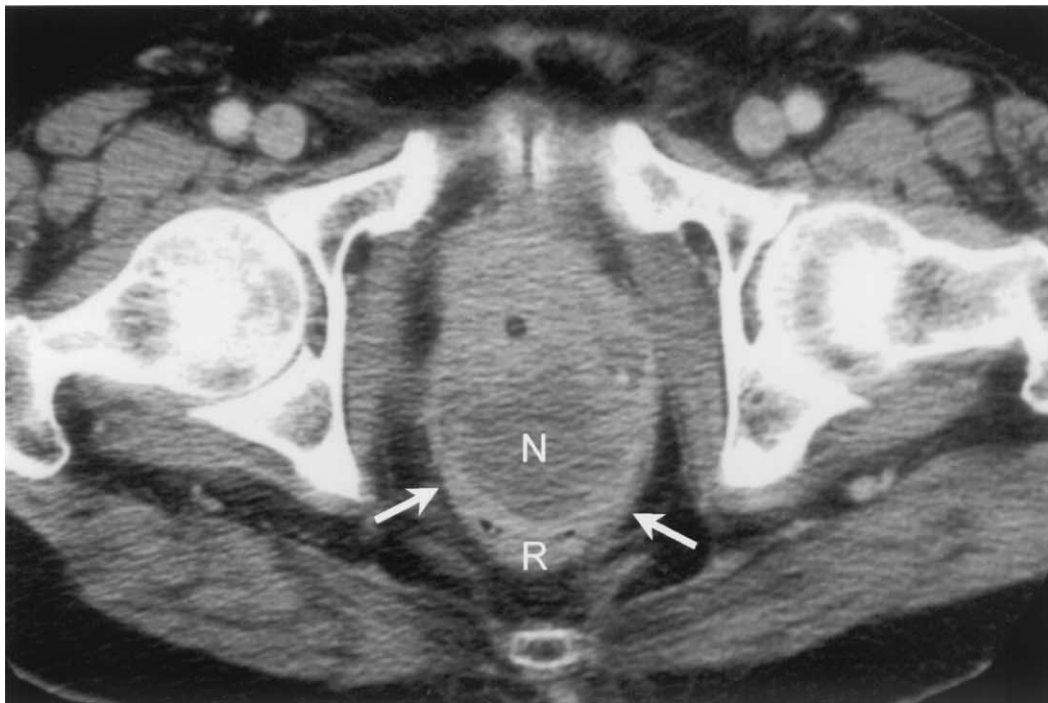
(b)

Fig. 1. Sigmoidoscopy demonstrating CR of RT and hormone-refractory prostate cancer invading rectum (Group A, Patient 2, Table 1). (a) Pretreatment image demonstrating 5 × 5-cm tumor invading rectum. (b) Tumor CR in rectum 13 months after 36 Gy and HT.

1 patient. RT and HT were generally well tolerated by all patients who had not previously undergone RT. Among those who had, most (6 of 8, 75%) tolerated retreatment well with minimal or no complications. Two patients in the repeat RT group had severe complications.

One (Group A, Patient 5) developed urinary stricture after retreatment that required dilation. He also had progressive low-grade non-Hodgkin's lymphoma for which he received

multiagent chemotherapy. After retreatment with RT and HT, he developed a non-Hodgkin's lymphoma-related bleeding diathesis secondary to factor XI deficiency. Eight months after retreatment, he developed Grade 4 hemorrhagic cystitis that was related to repeat RT, chemotherapy, and coagulopathy. He underwent a suprapubic catheter placement and required several hospital admissions for multiple blood transfusions. Fourteen months after retreatment, he developed Grade 2 rectal



(a)

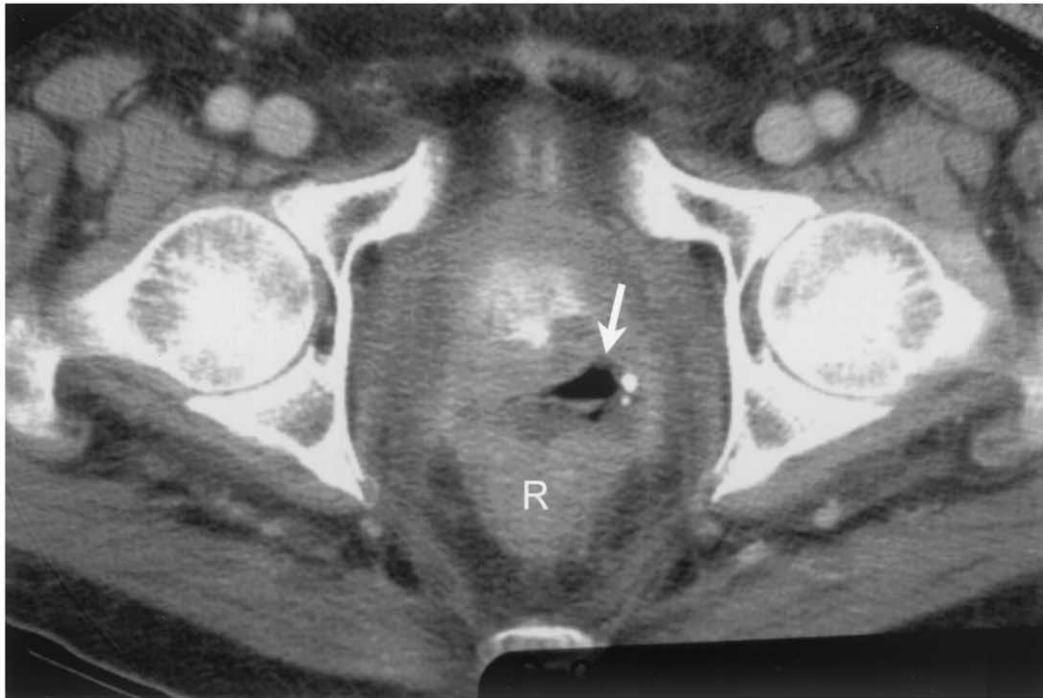


(b)

Fig. 2. Tumor response after RT (41.4 Gy) and HT in Patient 7 (Group A, Table 1). (a, b) Pretreatment CT scans demonstrating $8 \times 7 \times 9$ -cm tumor (arrows) with necrosis (N) obstructing rectum (RE). (c, d) CR of tumor 4 months after RT and HT. Necrotic tumor has disappeared, leaving a fistula in its place (arrow).

bleeding. His symptoms were controlled after transfusions with fresh frozen plasma. This patient had received high-dose/fraction (3 Gy) palliative RT (30 Gy and 12 Gy) on two earlier

occasions before retreatment. Despite his previous treatment, he had intractable pelvic pain owing to recurrent prostate tumor in the pelvic soft tissues and bone, necessitating consid-



(c)



(d)

Fig. 2. (Cont'd)

eration of additional RT. His local symptoms were controlled until he died 19 months later of metastatic prostate cancer and lymphoma.

One previously irradiated patient (Group A, Patient 7)

with a large necrotic tumor invading the bladder and rectum developed a tumor-related rectal ulcer 2 months after therapy. A Gastrografin enema revealed multiple short fistulous tracts extending from the rectum into the prostatic neo-

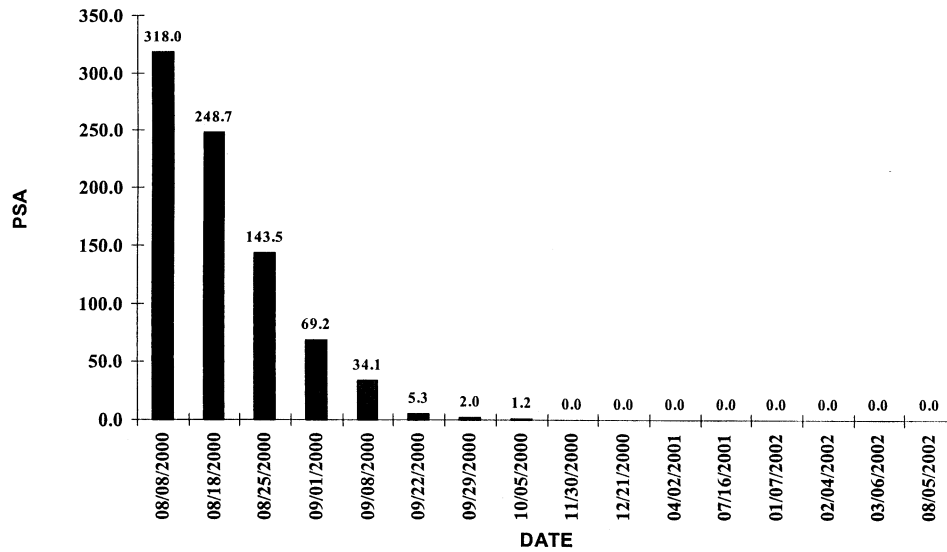


Fig. 3. Serum PSA response during and after RT and HT in Patient 2 (Group B, Table 1). Pretreatment PSA was 318 ng/mL. PSA at conclusion of 66.2 Gy and 10 HT treatments was 1.2 ng/mL. Tumor response illustrated in Fig. 4. Serum PSA half-life was 6.8 days.

plasm. He underwent diversion colostomy. Before retreatment, his tumor was large and had invaded and obliterated the rectal lumen, and he was unable to have daily bowel movements. On DRE, the tumor was very soft and fluctuant owing to tumor necrosis. He continued to self-administer daily enemas even after retreatment against medical advice. This practice most likely resulted in the rectal ulceration secondary to perforation of the fluctuant and necrotic tumor. Four months after RT and HT, he developed a rectovesical fistula after tumor regression and a CR. He then underwent urinary diversion (Fig. 2).

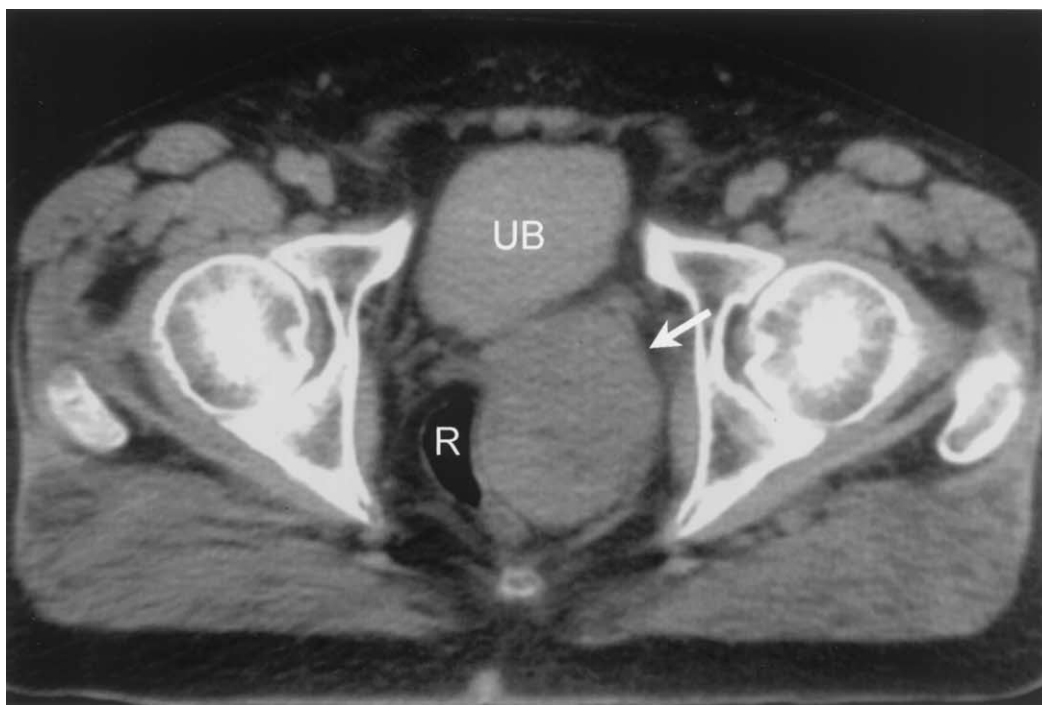
None of the other 12 Group A or B patients developed a treatment-related fistula of the bowel or bladder or developed urinary or bowel incontinence at last follow-up.

DISCUSSION

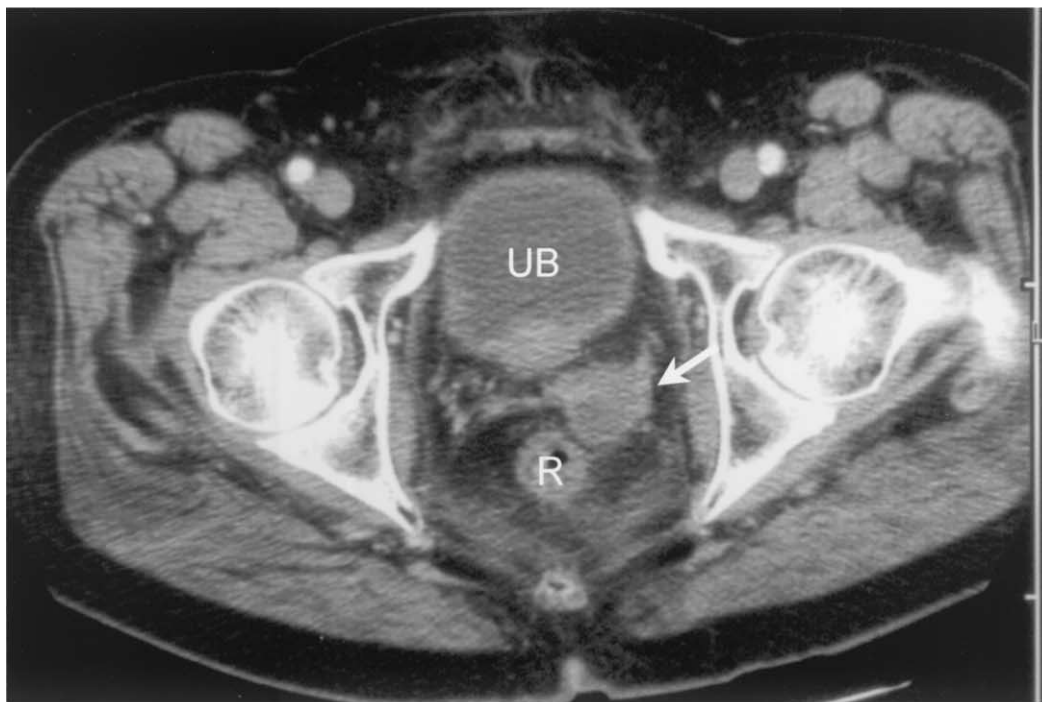
Hormone-refractory prostate cancer is difficult to manage and presents a major therapeutic challenge to all physicians (15). The availability of serum PSA determination has resulted in the early detection of hormone-refractory cancer. Thus, the demographics of patients with hormone-refractory disease are changing, with patients younger and healthier with few comorbid illnesses (15, 16). The role for early intervention with chemotherapy is increasing in an effort to prevent tumor progression and dissemination. However, in patients who can tolerate chemotherapy, the response rates have been low and nondurable, and a survival benefit has yet to be proved (15, 17). Patients with chemotherapy- and hormone-refractory tumors exhibit a slow but relentless pattern of progression, ultimately resulting in death. This pattern of disease progression was evident in all patients included in this report. They had large tumors and debilitating symptoms owing to pelvic tumor progression. Few reports are available on the role of RT in

these patients (18). This is largely because they have either been irradiated previously, as in Group A, or have high serum PSA levels that indicate distant metastasis, as in Group B. The prevalent view that such patients do not require local therapy such as RT needs to be reexamined. In this report, the extent of disease in the Group B patients demonstrated that they could live long enough to develop progressive pelvic disease and debilitating symptoms. Furthermore, the serum PSA response in a few patients (Fig. 3 and Table 1, Group B, Patient 4) would contest the hypothesis that high serum PSA levels is equated with occult/manifest distant metastasis in all patients.

The first priority of patients with locally advanced cancer is to achieve a cure and survive the cancer. Concerns of therapy-related toxicity, although important, are secondary in their view. When considering treatment options, it is important for treating physicians to understand these priorities of patients. A study addressing these issues was conducted among Stage II-IV head-and-neck cancer patients, most of whom were functioning reasonably well before therapy. Most patients ranked being cured (75%) as their top priority. The other top priorities were living as long as possible (56%) and having no pain (35%). Items that related to the toxicity of treatment such as being able to swallow food, keep their natural voice, being able to chew, keeping normal taste were ranked high by 19%, 18%, 8%, and 4% of patients, respectively (19). In another report, the attitudes of cancer patients, doctors, nurses, and the general public to chemotherapy were compared. When asked whether they would accept intensive chemotherapy that would prolong life by 3 months or achieve a relief of symptoms in 1%, approximately 40% of patients answered in the affirmative compared with 0% of radiotherapists and 10% of controls. This suggests that patients with cancer find it difficult to accept circumstances in which no treatment options are



(a)



(b)

Fig. 4. Tumor response after RT (66.6 Gy) and HT in Patient 2 (Group B, Table 1). (a) Pretreatment CT scan demonstrating large ($7 \times 6 \times 7$ cm) tumor (arrows) obstructing rectum (R). UB = urinary bladder. (b) CT scan 12 months after treatment revealing tumor shrunk to residual ($2 \times 2 \times 1.5$ -cm) cystic mass in seminal vesicle. See Fig. 3 for serum PSA response.

available. Moreover, they were willing to undergo treatment that had a minute chance of a possible benefit and to accept a high degree of toxicity to maximize life expectancy and

quality of life (20). In this report, patients with advanced and recurrent prostate cancer sought quality-of-life improvement from debilitating symptoms after treatment with

RT and HT. This goal was met in most patients, except among those with complications such as Grade 4 cystitis and tumor response-related urinary fistula. Even among these patients, a significant and durable tumor response occurred after therapy. It is important to note that these patients had no known alternative treatments that would provide any meaningful tumor response or palliation.

The synergistic role of HT and RT has been demonstrated in randomized clinical trials in locally advanced primary breast cancer (21), malignant melanoma (22) and pelvic tumors (23). The Dutch Deep Hyperthermia Group in a randomized study demonstrated a significantly superior tumor response with deep HT (using the BSD 2000 system) and RT in 358 patients with locally advanced bladder, uterine cervix, and rectal cancer. The CR rate for RT compared with RT plus HT was 39% and 55% ($p < 0.001$), respectively. In patients with cervical cancer, the 3-year survival rate was 27% in the RT group and 51% in the RT plus HT group ($p = 0.009$). The incidence of acute or late radiation toxic effects did not increase with the addition of HT. Interstitial thermometry was used in that study, but no thermometry details were provided (23). In a report from Stanford University, 4 patients with locally recurrent prostate cancer after initial treatment with ^{192}Ir brachytherapy were retreated with deep HT and RT (60 Gy, in two 30-Gy split courses). None of the patients experienced severe rectal or bladder reactions. Three of four achieved a clinical CR at 7–24 months after treatment. The authors concluded that repeat RT and HT had the potential to control local disease with minimal complications (24). In the present study, RT and HT proved successful, with tumor responses (CR plus PR) of 100%, with most being CRs lasting from 9 months to 3 years, among assessable patients. Furthermore, the impact on quality of life has been significant, with durable palliation of disabling symptoms.

Repeat RT is increasingly being used in the management of recurrent tumors at various sites, including the head and neck (25), brain (26), and rectum (27). The local control rates with repeat RT range from 40% to 75% (25–27). Because the repeat RT doses are generally lower, RT is usually administered in combination with radiosensitizing agents such as chemotherapy (25, 27) or HT (28). Whenever repeat RT is used, the risk of acute and late toxicity, including permanent organ damage resulting in tissue necrosis, fistula formation, or life-threatening vascular injury, is increased (25–27). In the RTOG 96-10 study which treated recurrent head-and-neck tumors with RT and concurrent chemotherapy, hematologic Grade 5 toxicity occurred in 7% and 2 patients died secondary to tumor hemorrhage (25). The radiation

tolerance of the different organs and late toxicity after retreatment is not fully known. It depends on a number of factors, including organ type, previous radiation dose, dose per fraction, interval between RT sessions, and use of chemotherapy and/or surgery (29). In a report from Thomas Jefferson University, among patients with RT-recurrent rectal cancer, good palliation of symptoms occurred after low doses of repeat RT and chemotherapy. The Grade 3 and 4 late toxicity rate was 23% and 10%, respectively. Small bowel obstruction, chronic cystitis, and fistula formation was observed in 17%, 6%, and 8%, respectively (27). In the present report, with similar repeat RT doses as in the Jefferson experience, most patients (6 of 8, 75%) tolerated retreatment well with no or minimal complications (2 patients developed Grade 1–2 rectal bleeding). One patient with a lymphoma-related factor XI deficiency that developed after retreatment had Grade 4 hemorrhagic cystitis. Another previously irradiated patient developed a tumor regression-related rectovesical fistula 4 months after retreatment. The patients at higher risk of retreatment or tumor regression-related complications are those with necrotic tumors that destroy tissue planes (Fig. 2), previous RT at a higher dose/fraction, or bleeding disorders. The measures taken to minimize retreatment complications included the use of low-to-moderate doses of RT for retreatment, a lower dose/fraction (1.8 Gy), patient immobilization, and three-dimensional CT treatment planning.

CONCLUSION

This preliminary report demonstrated the feasibility and efficacy of RT and HT in patients with LAHRPC and RT-recurrent prostate cancer. At present, such patients, especially those who have previously been irradiated, have no effective treatment options other than chemotherapy or symptomatic management. RT and HT were generally well tolerated in patients who had not been previously irradiated. Among those who had previously undergone RT, most (6 of 8) tolerated retreatment well with minimal or no complications. The patients at greater risk of retreatment or tumor regression-related complications were those with necrotic tumors that destroyed tissue planes, previous RT at a higher dose/fraction, or bleeding disorders. Despite the large and symptomatic tumors, RT and HT resulted in significant tumor shrinkage, rapid serum PSA decline, durable treatment responses (CRs and PRs), and durable palliation of disabling symptoms. Additional clinical studies are warranted to define the role of this therapy better in the evolving care of patients with hormone-refractory and RT-recurrent prostate cancer.

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