Magnetic Resonance Image-guided Salvage Brachytherapy After Radiation in Select Men Who Initially Presented With Favorable-risk Prostate Cancer

A Prospective Phase 2 Study

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BACKGROUND. The authors prospectively evaluated the late gastrointestinal (GI) and genitourinary (GU) toxicity and prostate-specific antigen (PSA) control of magnetic resonance imaging (MRI)-guided brachytherapy used as salvage for radiation therapy (RT) failure.

METHODS. From October 2000 to October 2005, 25 men with a rising PSA level and biopsy-proven, intraprostatic cancer at least 2 years after initial RT (external beam in 13 men and brachytherapy in 12 men) who had favorable clinical features (Gleason score ≤7, PSA <10 ng/mL, negative pelvic and bone imaging studies), received MRI-guided salvage brachytherapy to a minimum peripheral dose of 137 gray on a phase 1/2 protocol. Estimates of toxicity and cancer control were calculated using the Kaplan-Meier method.

RESULTS. The median follow-up was 47 months. The 4-year estimate of grade 3 or 4 GI or GU toxicity was 30%, and 13% of patients required a colostomy and/or urostomy to repair a fistula. An interval <4.5 years between RT courses was associated with both outcomes with a hazard ratio of 12 (95% confidence interval [95% CI], 1.4–100; P = .02) for grade 3 or 4 toxicity and 25 (95% CI, 1.1–529; P = .04) for colostomy and/or urostomy. PSA control (nadir definition) was 70% at 4 years.

CONCLUSIONS. The current results indicated that MRI-guided salvage brachytherapy in men who are selected based on presenting characteristics and postfailure PSA kinetics can achieve high PSA control rates, although complications requiring surgical intervention may occur in 10% to 15% of patients. Prospective randomized studies are needed to characterize the relative cancer control and toxicity after all forms of salvage local therapy. Cancer 2007;110:1485–92. © 2007 American Cancer Society.

KEYWORDS: salvage therapy, brachytherapy, magnetic resonance imaging, local neoplasm recurrence, prostate cancer, prostate-specific antigen.

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Among men who experience prostate-specific antigen (PSA) failure after radiation therapy (RT) for prostate cancer, many will harbor occult distant metastases, but a significant minority will have a local-only recurrence and potentially may be cured with a salvage local therapy.1–3 Although imaging modalities, such as bone scans and pelvic computed tomography (CT) scans, can help screen out patients who have gross metastases at the time of PSA failure, PSA kinetics can help further to identify which patients are most likely to have local-only disease. Specifically, local-only failures have been associated with longer intervals to PSA failure (≥2–3 years)4,5 and protracted PSA doubling times (PSA-DT) (≥8–12 months).1,6 In addition, patients who presented initially with lower risk clinical features (eg, Gleason score <8 or a pretreatment PSA velocity <2 ng/mL per year) prior to their initial treatment are less likely to harbor distant micrometastases at the time of PSA failure.4,5,7–9

One approach to local failure after RT is to perform a salvage radical prostatectomy (RP). However, this approach has a substantial risk of serious treatment side effects that include urinary incontinence in approximately 40% of patients, bladder neck stricture in approximately 25%, and the potential for rectal injury.2,10,11 Cryosurgery has been used as an alternative local salvage modality, but the treatment-related toxicity also may be considerable, including complete urinary incontinence in approximately 35% of patients, as well as bladder stricture, fistula, and penile and/or perineal pain.11–13 Attempts at using transrectal ultrasound (TRUS)-guided brachytherapy as a salvage modality have led to the avoidance of some of these side effects and less incontinence overall, although complete urinary incontinence still was reported in up to 31% of men in 1 series,14 and problems continue to occur with bladder neck stricture, late urinary toxicity, and rectal injury.11,15,16

A technologic advancement that could improve further on the side-effect profile of TRUS-based brachytherapy is the magnetic resonance imaging (MRI)-guidance system that currently is being used for prostate brachytherapy at our institution. It has been demonstrated that this method provides excellent PSA control with minimal acute morbidity in the definitive primary treatment setting.17,18 Negligible, if any, bladder or rectal toxicity has been observed with an extended 4 years of reported follow-up, and late urinary toxicity was decreased when an MRI-guided, urethral-sparing technique was used.19–21

Therefore, the use of the MRI-guided brachytherapy technique in the salvage setting has the potential to improve the therapeutic benefit/risk ratio compared with the other currently available salvage local therapies. In this report, we present our data on late treatment-related toxicity and early PSA outcome from a prospective phase 2 study of MRI-guided brachytherapy in men who were believed to have local-only failure based on biopsy, imaging studies, and clinical prognostic factors.

MATERIALS AND METHODS

Patient Selection

From October 2000 through October 2005, 25 men were enrolled on a prospective phase 2 study of salvage MRI-guided prostate brachytherapy. The initial accrual goal for the phase 1 portion of the study was 20 patients. On May 1, 2004, the toxicity rate at 12 months for the initial 20 enrollees was lower than expected; therefore, permission was granted to enroll additional patients into a combined phase 1/2 study. All of the patients had received prior external beam RT or interstitial brachytherapy for clinically localized prostate cancer and had experienced PSA failure based on the 1997 American Society for Therapeutic Radiology and Oncology (ASTRO) consensus definition of 3 consecutive rises after a nadir.22

Requirements for eligibility included: biopsy-proven, locally recurrent prostate cancer at least 2 years after initial RT; no history of a transurethral resection of the prostate (TURP); a biopsy Gleason score ≤7 prior to initial RT; a PSA level <10 ng/mL within 3 months of registration; bone scans that were negative for distant metastases; pelvic CT or MRI studies that were negative for lymph node disease; an Eastern Cooperative Oncology Group performance status of 0 to 2; age >30 years; no history of uncontrolled diabetes mellitus; no contraindications to spinal or general anesthesia; and no indwelling pacemakers. In addition, enrollment required a cystoscopy study that showed the absence of muscle-invasive bladder cancer, no significant benign prostatic hyperplasia that caused ≥90% narrowing of the urethra, no urethral stricture that required a TURP, and no bladder neck contracture that required prior surgical correction. A presalvage PSA level >10 ng/mL after an invasive procedure, such as prostate biopsy, colonoscopy, or cystoscopy, did not exclude a patient from eligibility as long as a subsequent serum PSA level <10 ng/mL was noted within 3 months of registration. The pretreatment baseline characteristics of the 25 trial participants are listed in Table 1.

Treatment

No patient received neoadjuvant or adjuvant hormone therapy with their salvage implant. Patients
were placed in the lithotomy position under general anesthesia. A Foley catheter was inserted and clamped. An MR-compatible perineal template was secured to the MR table and placed against the patient’s perineum. A rectal obturator was placed to allow for the passage of intrarectal gas. Axial, coronal, and sagittal images of the prostate were acquired at 5-mm intervals using an MR pelvic coil in a 0.5-Tesla magnetic field (General Electric Medical Systems, Milwaukee, Wis). The prostate gland, anterior rectal wall, and prostatic urethra were identified on each axial slice by an experienced genitourinary MRI radiologist. Based on the prostate gland and juxtaposed normal tissue volumes and the desired minimum prescription dose, an initial treatment plan and needle loading was determined as described previously elsewhere.18

Needles were then loaded and placed under real-time MRI guidance with dosimetric feedback. During the insertion of each catheter containing preloaded 125I sources, its position was identified in real time and was compared with its planned location. The range of activity was from 0.35 to 0.45 mCi/source with a median of 0.40 mCi/source. Adjustments to account for prostate motion, edema, or catheter divergence could be made before source deposition. The process was repeated in an iterative fashion for all planned catheters. The cumulative dose-volume histograms for the prostate gland, anterior rectal wall, and prostatic urethra were evaluated after each catheter insertion, which allowed for adjustments to the treatment plan intraoperatively if necessary. The prescribed minimum dose to the MRI-defined target volume (prostate only) was 137 gray (Gy). This dose was calculated according to the method published by the American Association of Physicists in Medicine Task Group 43 and was equivalent to the standard 160 Gy calculated by prior methods.23 Adjustments were made to ensure that the intraoperative V100 (fractional volume of the target that receives ≥100% of the prescribed dose) was ≥100% and that the D90 (dose that covers ≥90% of the target) was at least the full prescribed dose. Changes caused by intraoperative edema were minimal in these previously irradiated prostates, and postoperative dosimetry performed on Day 0 and at 6 weeks also met these requirements.

Follow-up

The median follow-up was 47 months (range, 14–75 months).24 Follow-up was calculated from the date of the salvage implant. Patients typically were seen in follow-up after 1 month, then every 3 months for the first year, then every 6 months until Year 5, and annually thereafter. Follow-up visits included a complete history and physical examination, including a digital rectal examination (DRE) and a PSA test. In addition, we recommended that patients have a flexible sigmoidoscopy at 3 months, 15 months, and 27 months to screen for rectal toxicity and to evaluate for the need for any medical interventions. Flexible sigmoidoscopy was done sooner and more often for patients who had evidence of rectal bleeding. All endoscopies were performed by a single endoscopist (D.L.C.-L.) for continuity and standardization. Finally, patients were asked at study entry to complete a prospectively validated quality-of-life questionnaire to establish baseline sexual, urinary, and bowel function.

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>Clinical Characteristics of the Study Cohort Prior to Salvage Therapy (N = 25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristic</td>
<td>No. of patients (%)</td>
</tr>
<tr>
<td>Median initial PSA [range], ng/mL</td>
<td>7.45 [4.2–18.4]</td>
</tr>
<tr>
<td>0 to &lt;4</td>
<td>0 (0)</td>
</tr>
<tr>
<td>4 to &lt;10</td>
<td>23 (92)</td>
</tr>
<tr>
<td>10–20</td>
<td>2 (8)</td>
</tr>
<tr>
<td>Initial Gleason score</td>
<td></td>
</tr>
<tr>
<td>2+3 = 5</td>
<td>1 (4)</td>
</tr>
<tr>
<td>3+3 = 6</td>
<td>18 (72)</td>
</tr>
<tr>
<td>3+4 = 7</td>
<td>6 (24)</td>
</tr>
<tr>
<td>Initial clinical tumor (T) classification</td>
<td></td>
</tr>
<tr>
<td>T1c</td>
<td>17 (68)</td>
</tr>
<tr>
<td>T2a</td>
<td>7 (28)</td>
</tr>
<tr>
<td>Unknown</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Initial RT received</td>
<td></td>
</tr>
<tr>
<td>External beam RT (66–70.2 Gy)</td>
<td>12 (48)</td>
</tr>
<tr>
<td>Brachytherapy (137 Gy; MRI-guided)</td>
<td>11 (44)</td>
</tr>
<tr>
<td>External beam RT + brachytherapy</td>
<td>1 (4)</td>
</tr>
<tr>
<td>External beam RT + hormones (4 mo)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Median presalvage PSA doubling time [range], mo</td>
<td>9.46 [1.9–39.9]</td>
</tr>
<tr>
<td>&lt;3</td>
<td>2 (8)</td>
</tr>
<tr>
<td>3 to &lt;6</td>
<td>5 (20)</td>
</tr>
<tr>
<td>6 to &lt;12</td>
<td>10 (40)</td>
</tr>
<tr>
<td>≥12</td>
<td>8 (32)</td>
</tr>
<tr>
<td>Median interval between RT [range], y</td>
<td>5.2 [2.5–12.8]</td>
</tr>
<tr>
<td>&lt;2</td>
<td>0 (0)</td>
</tr>
<tr>
<td>2 to &lt;5</td>
<td>10 (40)</td>
</tr>
<tr>
<td>5 to &lt;10</td>
<td>13 (52)</td>
</tr>
<tr>
<td>≥10</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Median age at salvage therapy [range], y</td>
<td>65 [56–82]</td>
</tr>
<tr>
<td>ECOG performance status</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>25 (100)</td>
</tr>
<tr>
<td>1</td>
<td>0 (0)</td>
</tr>
<tr>
<td>2</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Median PSA at salvage [range], ng/mL</td>
<td>5.5 [1.4–11.6]</td>
</tr>
<tr>
<td>0 to &lt;4</td>
<td>9 (36)</td>
</tr>
<tr>
<td>4–10</td>
<td>15 (60)</td>
</tr>
<tr>
<td>10–20</td>
<td>1 (4)</td>
</tr>
</tbody>
</table>

PSA indicates prostate-specific antigen; RT, radiation therapy; Gy, grays; MRI, magnetic resonance imaging; ECOG, Eastern Cooperative Oncology Group.
and this was readministered at 3 months and then annually for 3 years after therapy.25

Endpoints
The primary endpoint of this study was the time to late grade 3 or 4 gastrointestinal (GI) or genitourinary (GU) toxicity, as defined by the Radiation Therapy Oncology Group (RTOG)/Late Effects Normal Tissue Task Force criteria.26 Secondary endpoints included the time to surgery required to correct late GI or GU injuries from radiation and the time to PSA failure using the updated 2006 RTOG-ASTRO (Phoenix) Consensus Definition, in which PSA failure is scored on the day the PSA rises by 2 ng/mL above the posttreatment nadir.27

Statistical Methods
Time zero was defined as the date of the salvage implant. Kaplan-Meier analysis was used to estimate the percent of men who developed late grade 3 or 4 GI or GU toxicity and PSA failure-free survival.28 A Cox regression analysis was used to determine whether the time to development of grade 3 or 4 toxicity was associated with the time interval between the initial and salvage radiation treatments or with whether the patient had received a prior interstitial implant (compared with external beam RT) as his first radiation treatment.29 The time between radiation treatments was analyzed first as a continuous variable and then as a categorical value with a cutoff point of 4.5 years, which was the median time interval when these data first were analyzed and presented.30 These same analyses were repeated for the endpoint of time to surgical intervention for any GI or GU toxicity.

When this study was designed, the prognostic value of the post-RT PSA-DT had not yet been appreciated; consequently, PSA-DT was not used as an inclusion or exclusion criterion. Therefore, the PSA-DT at the time of PSA failure was evaluated as a continuous and categorical variable (ie, PSA-DT <3 months vs all others) to test for an association between PSA-DT and the time to PSA failure after salvage MRI-guided prostate brachytherapy. The cutoff point of 3 months was chosen, because a PSA-DT <3 months has been associated with a short time to prostate cancer-specific mortality, with a median of 6 years between PSA failure and death; therefore, these men likely harbor micrometastatic disease.5,31

For all Cox regression analyses, the assumption of the proportional-hazards model was tested, and no evidence of violation of the proportional-hazards assumption was observed. Adjusted and unadjusted hazards ratios (HRs), along with the associated 95% confidence interval (95% CI) and \( P \) value were reported for each covariate that was tested in the Cox model. All statistical tests were 2-sided. Analyses were performed using SAS software (version 9.1.3; SAS Institute, Inc, Cary, NC); a 2-sided \( P \) value <.05 was used to determine statistical significance.

RESULTS
GI and GU Toxicity
Seven patients experienced late grade 3 or 4 GI or GU toxicity. Two patients had GI toxicity (radiation proctopathy that was controlled successfully by endoscopically applied argon plasma coagulation), 2 patients had GU toxicity, and 3 patients had both GI and GU toxicity in the form of a fistula between the urinary and rectal tracts that required surgery to correct. The specific toxicities are outlined in Table 2. The actuarial estimate of grade 3 or 4 GI and/or GU toxicity was 30% at 48 months (Fig. 1). The time to the development of grade 3 or 4 GI or GU toxicity was associated significantly with an interval <4.5 years between radiation courses (HR, 12; 95% CI, 1.4–100; \( P = .02 \)) but was not associated with implantation as the prior type of radiation treatment (\( P = .14 \)).
Complications Requiring Surgical Intervention

Three patients required a colostomy and urostomy for repair of a fistula between the GI and GU tracts. These events occurred at 11 months, 12 months, and 29 months after salvage therapy. The actuarial estimate of the rate of GI or GU toxicity requiring surgery was 13% at 48 months (Fig. 2). The time to surgery was associated significantly with an interval <4.5 years between radiation courses (HR, 25; 95% CI, 1.1–529; \( P = .04 \)). Of the remaining 22 men, we noted that none developed urinary incontinence.

Estimates and Predictors of PSA Recurrence

After a median follow-up of 47 months (interquartile range, 31–57 months), 7 of 25 men had experienced PSA failure. The estimated actuarial PSA failure-free survival rate was 70% at 48 months (Fig. 3). Presalvage PSA-DT was not associated significantly with the time to PSA failure as a continuous variable (\( P = .66 \)). However, the ability to measure this association was limited by the sample and event size. A PSA-DT <3 months, however, did approach significance for its association with the time to postsalvage brachytherapy PSA failure (HR, 8.9; 95% CI, 0.8–99; \( P = .08 \)).

DISCUSSION

In this prospective phase 1/2 study of 25 men with favorable prognostic features who failed initial RT for clinically localized prostate cancer and received MRI-guided salvage brachytherapy, we observed a 4-year PSA failure-free survival rate of 70%. By 4 years, 30% of the men had developed grade 3 or 4 GI or GU toxicity, and 13% required a colostomy and urostomy as a result of the formation of a fistula. Of the 22 men who did not require surgery, we observed that none experienced urinary incontinence.
To our knowledge, this is the first reported prospective study evaluating the efficacy and toxicity of salvage brachytherapy. The importance of the prospective nature of this study is 2-fold. First, we were able to limit the study population to men whose clinical prognostic features made them most likely to have a local-only failure at the time of PSA failure. Second, we were able to capture information regarding toxicity more reliably than is possible from a retrospective review.

Our PSA control rate generally was numerically better than or at least comparable to the rates reported in other published salvage brachytherapy series, although the results are difficult to compare directly because of the varied definitions of PSA failure and the lack of randomization (Table 3). For example, our 4-year PSA control rate of 70% was higher than the approximately 38% 4-year PSA control rate obtained in the largest salvage brachytherapy series of 49 patients by Grado et al. and was comparable to the 75% rate at 4-years reported by Wong et al. We required a biopsy-proven local recurrence that developed ≥2 years after the initiation of radiation, an initial presenting Gleason score ≤7, a presalvage

<table>
<thead>
<tr>
<th>Institution</th>
<th>Reference</th>
<th>Years treated</th>
<th>No. of patients</th>
<th>Image guidance</th>
<th>Median follow-up, mo</th>
<th>PSA failure definition</th>
<th>4-year PSA control, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mayo Clinic</td>
<td>Grado et al., 1998</td>
<td>1990–1996</td>
<td>49</td>
<td>Ultrasound</td>
<td>64</td>
<td>Two rises above nadir*</td>
<td>38</td>
</tr>
<tr>
<td>Uro-Radiology Prostate Institute</td>
<td>Koutrouvelis et al., 2003</td>
<td>1995–2002</td>
<td>31</td>
<td>CT-guided + STAD</td>
<td>30</td>
<td>ASTRO</td>
<td>83</td>
</tr>
<tr>
<td>Mount Sinai</td>
<td>Lo et al., 2005</td>
<td>NR</td>
<td>30</td>
<td>Ultrasound</td>
<td>59</td>
<td>ASTRO</td>
<td>57 (Crude)</td>
</tr>
<tr>
<td>DFCI/Brigham and Women's</td>
<td>Current study</td>
<td>2000–2005</td>
<td>25</td>
<td>MRI-guided</td>
<td>47</td>
<td>Phoenix</td>
<td>70</td>
</tr>
<tr>
<td>UCSF</td>
<td>Lee et al., 2007</td>
<td>1998–2005</td>
<td>21</td>
<td>Ultrasound HDR</td>
<td>19</td>
<td>ASTRO</td>
<td>89 (2-y)</td>
</tr>
<tr>
<td>Dattoli Cancer Center</td>
<td>Dattoli et al., 1997</td>
<td>1991–1994</td>
<td>17</td>
<td>Ultrasound + STAD</td>
<td>38</td>
<td>PSA &gt; 1.0 ng/mL</td>
<td>65 (Crude)</td>
</tr>
<tr>
<td>Mayo Clinic</td>
<td>Wong et al., 2006</td>
<td>1999–2004</td>
<td>17</td>
<td>Ultrasound + STAD</td>
<td>44</td>
<td>ASTRO</td>
<td>75</td>
</tr>
</tbody>
</table>

PSA indicates prostate-specific antigen; CT, computed tomography; STAD, 3 months of neoadjuvant, short-term androgen-deprivation therapy; NR, not reported; ASTRO, American Society for Therapeutic Radiology and Oncology; DFCI, Dana Farber Cancer Institute; MRI, magnetic resonance imaging; UCSF, University of California-San Francisco; HDR, high-dose rate.

* Failure was backdated to the date of the first rising PSA after nadir.

1 According to the 1997 ASTRO consensus definition, failure required 3 consecutive PSA rises after a nadir. Failure was backdated to the midpoint between the nadir and the first rise (ASTRO, 1997).

2 Crude failure was calculated as the number of patients who did not fail divided by the total number of patients and did not account for the time of failure. Both series with crude outcome were presented in abstract form.

3 According to the 2006 Radiation Therapy Oncology Group/ASTRO Phoenix Consensus Conference definition, failure was scored on the day the PSA rose above the nadir by at least 2 ng/mL.
PSA level <10 ng/mL, and a negative bone scan and MRI or CT studies. Despite these favorable characteristics, 30% of men in this study subsequently experienced PSA failure at 4 years, suggesting that they either had radioresistant disease or, perhaps more likely, that they already had harbored micrometastases at the time of salvage. One possible explanation for this is that we had not excluded patients who had 2 additional factors that recently have been associated with prostate cancer-specific mortality: namely, a PSA-DT <3 months and an initial pretreatment PSA velocity >2.0 ng/mL per year.5,7,9,31

Although we do not have information on the initial pretreatment PSA velocity, the median PSA-DT was 9.5 months, and 28% of men had a PSA-DT <6 months. We observed that having a PSA-DT <3 months was had an almost significant association with the time to PSA failure (HR, 8.9; P = .08), highlighting the need to include the PSA-DT as a selection criteria for future prospective studies of salvage local therapy. For any local salvage candidate, the probability of subsequent PSA control will be a function of the clinical features and PSA kinetics both prior to the initial presentation and after the initial PSA failure, and both sets of factors should be considered in the decision of whether or not to offer a man a salvage local therapy.

In terms of toxicity, the 30% grade 3 or 4 GI or GU toxicity rate observed at 4 years with MRI-guided salvage brachytherapy was comparable to the up to 47% reported in the retrospective salvage brachytherapy series.15,16,32,34 The most serious complications were rectal-prostatic fistulas leading to colostomy and urostomy, which occurred in 3 men (13% actuarial at 4 years). This rate is comparable to the up to 15% rates reported for rectal injury in prostatectomy series10,44 and up to 11% rectal-prostatic fistulas in salvage cryotherapy series.45 We also observed that the development of such a complication was associated with an interval <4.5 years between radiation treatments (HR, 25; P = .04), suggesting that a longer interval may allow for the repair of normal tissues that were damaged by the initial radiation.46

In conclusion, MRI-guided salvage brachytherapy in men who are selected based on presenting characteristics and postfailure PSA kinetics can produce high PSA control rates, although complications that require surgical intervention may occur in 10% to 15% of men. Further study is needed to elucidate the factors that will identify the men who are most likely to develop grade 4 complications from this modality, and prospective randomized studies are needed to characterize the relative cancer control and toxicity after all forms of salvage local therapy.

REFERENCES


