

# Late Genitourinary and Gastrointestinal Toxicity after Magnetic Resonance Image-Guided Prostate Brachytherapy with or without Neoadjuvant External Beam Radiation Therapy

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**BACKGROUND.** This study was designed to estimate the rates of late genitourinary (GU) and rectal toxicity after magnetic resonance image (MRI)-guided prostate brachytherapy exclusively or in conjunction with external beam radiation therapy (EBRT).

**METHODS.** Between November 1997 and April 2002, 201 patients with category T1C prostate carcinoma (according to the 2002 American Joint Committee on Cancer staging criteria), prostate specific antigen levels < 10 ng/mL, and biopsy Gleason score 3 + 4 disease were treated with MRI-guided brachytherapy exclusively or in conjunction with EBRT. The MRI-guided technique was designed to spare the urethra based on delivery of the prescription dose to the peripheral zone exclusively. The Kaplan-Meier method was used to estimate rates of freedom from late GU and rectal toxicity. Comparisons were made using a log-rank test.

**RESULTS.** At a median follow-up of 2.8 years (range, 0.5–5.0 years), the 4-year estimates of rectal bleeding requiring coagulation for patients who underwent implantation therapy, compared with patients who received combined-modality therapy, were 8% versus 30%, respectively (log-rank *P* value = 0.0001). Although erectile dysfunction was common (range, 82–93%), with the use of sildenafil citrate (Viagra®), it was estimated that at least two-thirds of patients had erectile function comparable to or superior to baseline function, independent of whether they received monotherapy or combined-modality therapy (*P* = 0.46). The 4-year estimate of freedom from radiation cystitis was 100% versus 95% (*P* = 0.01) for patients who received monotherapy and patients who received combined-modality therapy, respectively. No urethral strictures were observed, and no patients underwent postimplantation transurethral resection of the prostate.

**CONCLUSIONS.** In the current study, rectal bleeding after MRI-guided prostate brachymonotherapy was infrequent, and urethral and bladder toxicity is reported to be rare and may be attributed to the urethral-sparing technique of the MRI-guided approach. *Cancer* 2003;98:949–54. © 2003 American Cancer Society.

**KEYWORDS:** prostate carcinoma, brachytherapy, magnetic resonance imaging (MRI), late toxicity.

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**T**ransperineal prostate brachytherapy has become an increasingly popular method of treatment for patients with clinically localized adenocarcinoma of the prostate.<sup>1</sup> This current treatment approach employs transrectal ultrasound (TRUS) image guidance for the placement of permanent radioactive sources into the prostate gland.<sup>1</sup> New approaches have been developed in the last decade that include improved multidimensional imaging using TRUS-based technology, intraoperative dosimetry,<sup>2</sup> and a new image-guided approach using magnetic resonance image (MRI) guidance.<sup>3</sup> These developments have reduced the likelihood of inadvertent source misplacement in two ways. First, intraoperative dosimetry has eliminated the need to reproduce the patient position in the operating room. Second, MRI guidance has provided improved imaging of both the normal tissues and the prostate gland, particularly at the apex, which has reduced the dose to normal juxtaposed, and interposed tissues.

Since 1997, 201 patients have undergone MRI-guided prostate brachytherapy. This technique includes both real-time MRI imaging and intraoperative dosimetry. The objective of this investigation was to estimate the rates of late rectal bleeding and genitourinary (GU) dysfunction in patients who were treated using MRI-guided prostate brachytherapy alone or in conjunction with 5 weeks of neoadjuvant external beam radiation therapy (EBRT). In a companion study,<sup>4</sup> prostate specific antigen (PSA) control is presented for the 151 patients who were treated using brachytherapy in the current study by a single investigator in addition to patients who were treated using the same technique by other members of the Genitourinary Radiation Oncology Group.

## **MATERIALS AND METHODS**

### **Patient Selection and Staging**

Between 1997 and 2002, 201 patients underwent MRI-guided prostate brachytherapy treatment at the Brigham and Women's hospital. The median age of the patient population was 63 years (range, 48–79 years). Patient selection for monotherapy with MRI-guided brachytherapy included men with PSA levels < 10 ng/mL; a biopsy Gleason score  $\leq 3 + 4$ ; category T1C disease according to the 2002 American Joint Committee on Cancer staging system; endorectal coil MRI T2 disease; and, after June 1999, < 50 % positive prostate biopsies. Patient selection for MRI-guided brachytherapy in conjunction with EBRT included patients with either a PSA level > 10–13 or  $\geq 50$  % positive biopsies starting in June 1999, or MRI evidence of extracapsular extension at the midgland or the apex. Informed consent was obtained from all patients. The

**TABLE 1**  
Percent Distribution According to Clinical Characteristics of 151 Patients Who Received Implant Monotherapy and 50 Patients Who Received Combined-Modality Therapy

Characteristic	Implant monotherapy (%)	Combined-modality therapy (%)
No. of patients	151	50
PSA		
$\leq 4$ ng/mL	23	12
4–10 ng/mL	75	64
> 10 ng/mL	2	24
Biopsy Gleason score		
$\leq 6$	14	90
3 + 4	86	10
Percent positive biopsies		
< 34%	85	62
34–50%	9	16
> 50%	6	22

PSA: prostate specific antigen.

pretreatment clinical characteristics of the group are listed in Table 1.

### **Treatment and Follow-Up**

The entire course of treatment was described in a prior report.<sup>3</sup> The minimal peripheral dose prescribed for monotherapy was 137 grays (Gy) and was 77 Gy for combination EBRT and brachytherapy according to the American Association of Physicist in Medicine Radiation Therapy Committee Task Group No. 43 specifications.<sup>5</sup> When EBRT was used, it was delivered to 45 Gy using a 4-field, three-dimensional, conformal technique. Follow-up was performed approximately at 3 months, every 6 months thereafter for 5 years, and annually thereafter. At the time of each follow-up, a digital rectal examination was performed, and a PSA level was obtained within 2 weeks prior to follow-up. The median follow-up was 2.8 years (range, 0.5–5.0 years).

### **Assessment of Late Toxicity**

#### **Rectal**

Patients were asked whether they had experienced any rectal bleeding at each follow-up by a specialty oncology nurse. All rectal bleeding was analyzed with colonoscopy, and evidence of proctitis had to be confirmed endoscopically before grading the rectal bleeding as an event related to radiation. In all instances, the date that the patient reported the first evidence of rectal bleeding was noted as the event date. The following scales were used to quantify the rectal bleeding: Grade 1, no clinical evidence of rectal bleeding but evidence of mild proctitis seen on screening colonoscopy; Grade 2, cortisone ene-

mas necessary for eradication of rectal bleeding; and Grade 3, argon plasma coagulation (APC)<sup>6,7</sup> necessary for the eradication of bleeding. Data on other late gastrointestinal toxicities, such as rectal urgency, were not collected in this study.

### Erectile

At baseline and at each subsequent follow-up visit, patients were asked about their ability to have an erection sufficient for vaginal intercourse and, specifically, how this ability compared with their erectile function prior to treatment. Erectile function was noted as the same as baseline function, worse than baseline function, or better than baseline function. Information on the use of erectile function aids and their efficacy was collected. A standardized questionnaire was not used.<sup>8</sup> The date that the patient reported the first evidence of any decrease in erectile function compared with baseline function was noted as the event date.

### Urinary

Prior to treatment and at each subsequent follow-up visit, patients were asked whether they had noted any blood in the urine. All patients who presented with hematuria were evaluated with a urine analysis and culture to rule out a urinary tract infection (UTI). Once a UTI had been excluded, a cystoscopy was performed to determine the etiology of the hematuria. In addition, patients were asked about the strength of their urinary stream and the frequency of voiding, nocturia, hesitancy, and urgency as well as the presence of any urinary incontinence. In patients who reported a significant change in their voiding pattern, a cystoscopy and urodynamic studies were performed to assess for a urethral stricture or the need for transurethral resection of the prostate (TURP).

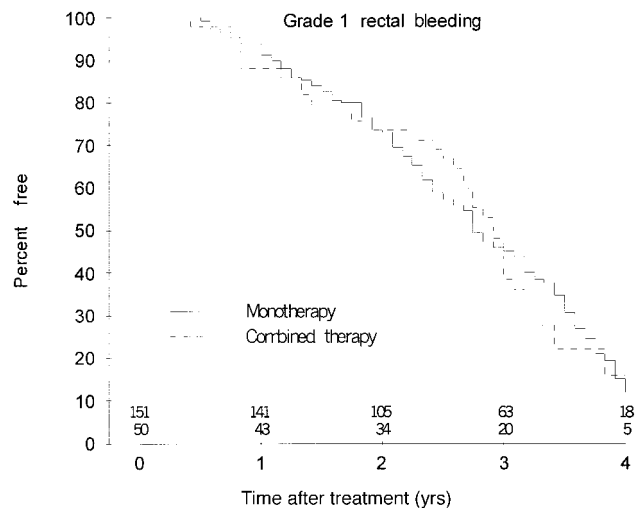
### Statistical Methods

Freedom from rectal bleeding, freedom from radiation cystitis, freedom from urethral stricture, freedom from the need for a postimplantation TURP, and freedom from any decrease in erectile function compared with baseline function were computed using the actuarial method of Kaplan and Meier. Comparisons were made using a log-rank test. One patient was not evaluable for rectal toxicity, and four patients were not evaluable for erectile dysfunction, all due to lack of information in the patients' charts.

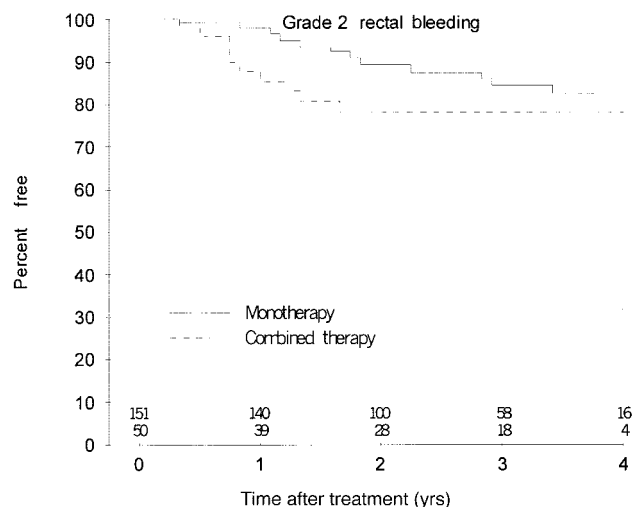
## RESULTS

### Rectal Bleeding

Estimates of Grade 1, Grade 2, and Grade 3 rectal bleeding stratified by implantation monotherapy or combined-modality therapy are shown in Figures 1–3,



**FIGURE 1.** Estimates of Grade 1 rectal bleeding after magnetic resonance image-guided implant monotherapy or combined-modality therapy (log-rank  $P$  value = 0.88).

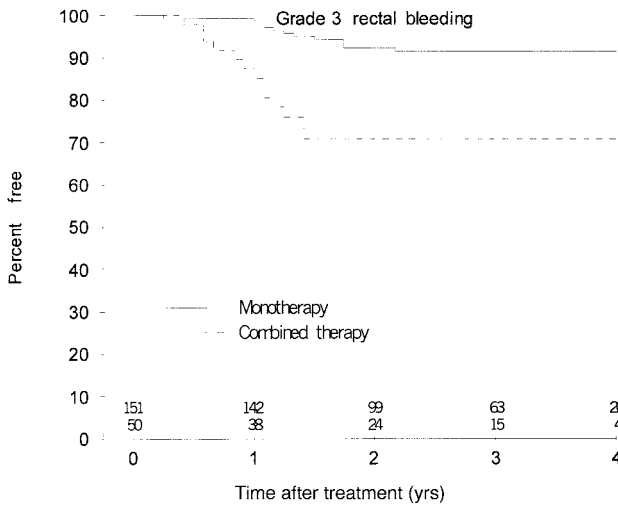


**FIGURE 2.** Estimates of Grade 2 rectal bleeding after magnetic resonance image-guided implant monotherapy or combined-modality therapy (log-rank  $P$  value = 0.88).

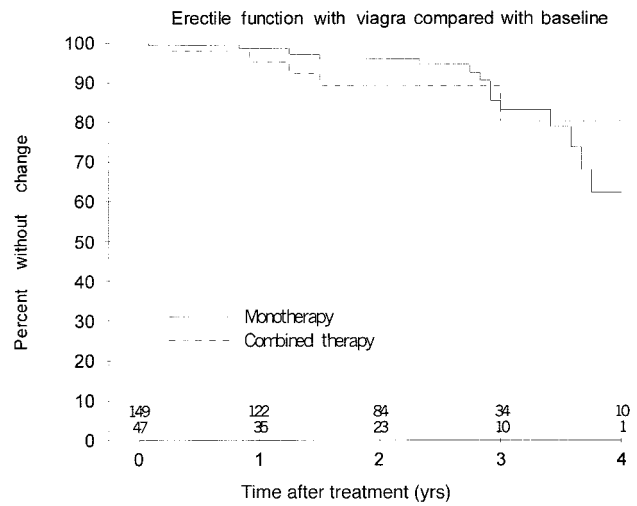
respectively. Four years after initial therapy, estimates of the rate of Grade 1, Grade 2, and Grade 3 rectal bleeding were 80% versus 85% (log-rank  $P$  value = 0.88), 18% versus 22% (log-rank  $P$  value = 0.16), and 8% versus 30% (log-rank  $P$  value = 0.0001) for patients who received implantation therapy versus combined-modality therapy, respectively. All patients who sustained Grade 2 or 3 of rectal bleeding were controlled using cortisone enemas or APC.

### Erectile Dysfunction

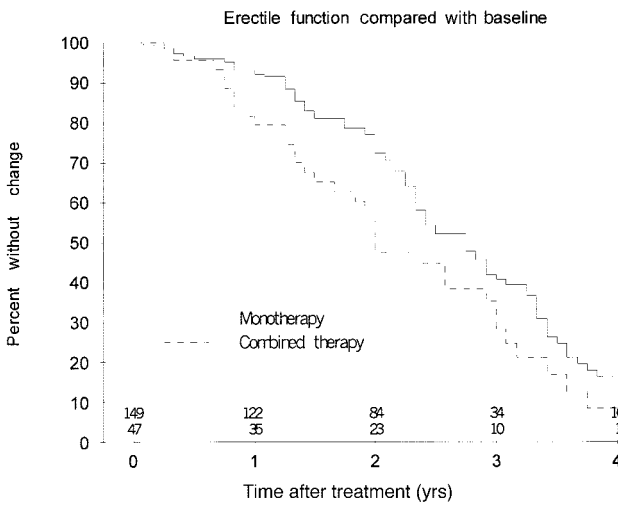
Five patients (2 monotherapy, 3 combined therapy) could not have erections sufficient for vaginal inter-



**FIGURE 3.** Estimates of Grade 3 rectal bleeding after magnetic resonance image-guided implant monotherapy or combined-modality therapy (log-rank *P* value = 0.0001).



**FIGURE 5.** Estimates of erectile function with sildenafil citrate compared with baseline after magnetic resonance image-guided implant monotherapy or combined-modality therapy (log-rank *P* value = 0.46).



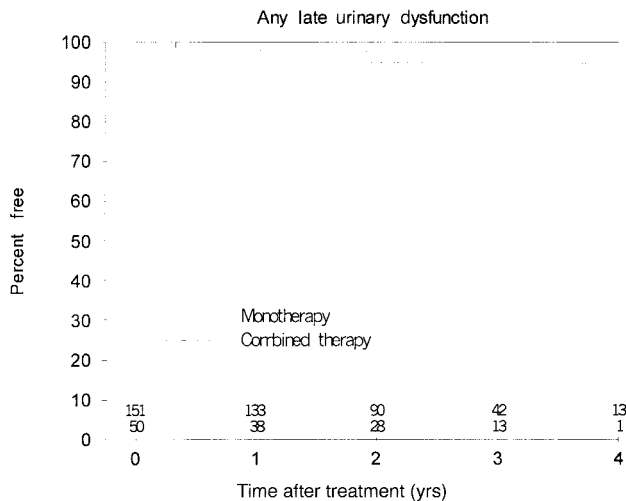
**FIGURE 4.** Estimates of erectile function compared with baseline after magnetic resonance image-guided implant monotherapy or combined-modality therapy (log-rank *P* value = 0.03).

course at time of initial treatment. Figure 4 illustrates the estimated rate at which patients experienced any decrease in their ability to have an erection sufficient for vaginal intercourse compared with baseline function stratified by initial therapy. Although there was a significant difference (log-rank *P* value = 0.03) between patients who received monotherapy and patients who received combined-modality therapy in the estimates of erectile dysfunction, it was estimated that essentially all patients (82–93%) experienced some degree of erectile dysfunction compared with baseline function within 4 years after therapy. However, as

shown in Figure 5, when erectile function aids were used, which was sildenafil citrate (Viagra®; Pfizer, Groton, CT) in 95% of patients, at least two-thirds of patients reported rates of erectile function comparable to or superior to baseline function by 4 years after either implantation or combined-modality therapy (log-rank *P* value = 0.46).

**Radiation Cystitis**

In two prior reports,<sup>9,10</sup> a decrease in acute urinary retention and urinary obstructive and irritative symptoms were reported for patients who received MRI-guided therapy compared with patients who received TRUS-guided prostate brachytherapy. In the current study, there were no late events with regard to bladder or urethral dysfunction after patients received implantation monotherapy. Specifically, no patient required a postimplantation TURP. In addition, urethral strictures and radiation cystitis were not documented. However, two patients who received combined-modality therapy presented with radiation cystitis. Specifically, cystoscopy performed after a single episode of macroscopic hematuria confirmed this finding. The first patient presented in the setting of a UTI, and the hematuria resolved and did not recur after the administration of an antibiotic. The other patient’s hematuria resolved after bladder irrigation. Neither patient had recurrent symptoms 3 years after the initial presentation of macroscopic hematuria. Figure 6 illustrates the 100% versus 95% estimates (log-rank *P* value = 0.01) of freedom from radiation cystitis 4 years



**FIGURE 6.** Estimates of freedom from any late urinary dysfunction after magnetic resonance image-guided implant monotherapy or combined-modality therapy (log-rank  $P$  value = 0.01).

after treatment for patients who received monotherapy or combined-modality therapy, respectively.

## DISCUSSION

MRI-guided prostate brachytherapy was developed with the goal of improved radioactive source placement within the prostate gland given the ability to have real-time MR imaging in the operating room. Concurrent with that goal, the preservation of normal tissues that were juxtaposed (i.e., rectum, neurovascular bundles, and penile bulb) or interposed (i.e., urethra) with function also was expected. The results of this study suggest that the ability of the MRI-guided approach to keep the dose to any point on the urethra at < 200 Gy spared the urethra. In particular, urethral and/or bladder toxicity was rare. Specifically, there were no reports of macroscopic hematuria, or the need for a postimplantation TURP, or documentation of urethral stricture for patients who were treated with monotherapy; and it was estimated that only 5% of patients had radiation cystitis 4 years after they received combined-modality therapy that resolved with minimal intervention (antibiotics by mouth and bladder irrigation). These very low rates of late urinary toxicity, coupled with the low rates of acute urinary retention<sup>10</sup> and the need for postimplantation Flomax, support the urethral-sparing effect of MRI-guided brachytherapy. Although estimates of Grade 3 rectal bleeding were low in the implantation monotherapy group, 30% of patients who received combined-modality therapy had Grade 3 rectal bleeding by 4 years

after treatment. Therefore, consideration should be given to decreasing the implantation brachytherapy boost dose or employing a different form of dose escalation. Observing a decrease in erectile function compared with baseline was very common and may have been due to both the combination of aging and the treatment, because the median age of the study cohort was 63 years (range, 48–69 years). However, 4 years after therapy, sildenafil citrate at doses of 25–100 mg was effective in returning erectile function to levels comparable to or superior to baseline function in two-thirds of patients independent of whether they had received combined-modality therapy or monotherapy (log-rank  $P$  value = 0.46), as shown in Figure 5.

Potential limitations of the study include the relatively short median follow-up of 2.9 years. Previous studies from the gynecologic oncology literature<sup>11,12</sup> suggested that late urethral and bladder toxicity can occur beyond 5 years after initial therapy. However, rectal and erectile dysfunctions usually are noted within the first 3 years after therapy. Therefore, the estimates of rectal bleeding and of diminution in erectile function compared with baseline reported in this study likely reflect the true extent of these late effects, whereas the urethral and bladder toxicities may be underestimates of the true long-term rates. The second potential limitation of this study relates to the manner in which the information on toxicity was acquired. Because a standardized questionnaire was not used, under-reporting is possible. However, the acquisition of rectal, urethral, and bladder function was rigorous, in that colonoscopic and/or cystoscopic confirmation of radiation proctitis and/or cystitis was necessary to establish the etiology of the rectal bleeding and/or macroscopic hematuria, and the assessment of erectile function was made based on office visit questioning. It is interesting to note, however, that, despite this form of information acquisition, nearly all patients (82–93%) reported a decrease in erectile function compared with baseline function by 4 years after treatment. It is equally important to note that most patients (greater than two-thirds) returned to baseline functioning or better with the simple use of oral sildenafil citrate. Therefore, although the manner in which the erectile function information was obtained may not have been optimal and may have led to under-reporting, it is unlikely that underestimates of the impact of both treatment and aging on erectile function were made.

## Conclusions

Although estimates of Grade 3 rectal bleeding were low after implant monotherapy, they were significantly higher after combined-modality therapy.

Nearly all patients experienced a decrease in erectile function compared with baseline function; however, the vast majority of patients returned to at least baseline function with the use of sildenafil citrate. Urethral and bladder toxicity were rare, which may be attributed to the urethral-sparing technique of the MRI-guided approach.

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