Late Toxicity and Biochemical Recurrence After External-beam Radiotherapy Combined With Permanent-source Prostate Brachytherapy

Analysis of Radiation Therapy Oncology Group Study 0019

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BACKGROUND. The combination of external-beam radiotherapy and brachytherapy is used commonly to treat men with prostate cancer. In this analysis, the authors examined the rate of biochemical recurrence (BR) and late grade ≥3 genitourinary (GU) and gastrointestinal (GI) toxicity after treatment with external-beam radiotherapy and brachytherapy in a multiinstitutional, cooperative group setting.

METHODS. All eligible patients received external-beam radiotherapy (45 Gray [Gy] in 25 fractions) followed 2 to 6 weeks later by an interstitial implant using iodine-125 to deliver an additional 108 Gy. BR was defined in 2 ways: according to the American Society for Therapeutic Radiology and Oncology (ASTRO) Consensus Definition (ACD) and according to the Phoenix definition (PD) (prostate-specific antigen nadir +2 ng/mL). The Radiation Therapy Oncology Group(RTOG)/European Organization for Research and Treatment of Cancer late radiation morbidity scoring system was used to grade all toxicity.

RESULTS. One hundred thirty-eight patients were enrolled, and 130 were eligible for the current analysis. The median follow-up for surviving patients was 49 months (range, 20–60 months). The 48-month estimate of late grade ≥3 GU/GI toxicity was 15% (95% confidence interval [95% CI], 8–21%), and the 48-month estimate of BR was 19% (95% CI, 12–26%) and 14% (95% CI, 8–20%) according to the ACD and PD, respectively.

CONCLUSIONS. The morbidity observed in this multiinstitutional, cooperative group study was slightly higher than that reported in recent RTOG studies using brachytherapy alone or high-dose external-beam radiotherapy. The BR rate observed in this report was similar to that observed with high-dose external-beam radiotherapy alone in similar patients. ***Cancer* 2007;109:1506–12.**

KEYWORDS: I-125, biochemical recurrence, external-beam radiotherapy, gastrointestinal toxicity, genitourinary toxicity, permanent-source brachytherapy.

The utilization of brachytherapy in the treatment of men with clinically localized prostate cancer has increased dramatically in the past 15 years.[1,2] According to the 1999 Patterns of Care Study, >33% of men with prostate cancer who were treated with radiotherapy received brachytherapy as a component of their treatment.[1] The results from that study also indicated that approximately 50% of men who were treated with brachytherapy received supplemental external-beam radiotherapy. Results from a recent study by the Cancer of the Prostate Strategic Urologic Research Endeavor registry

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of men with prostate cancer indicated that the use of supplemental external-beam radiotherapy has increased over the past decade.[3]

Historically, the combining of external-beam radiotherapy with brachytherapy offered several potential advantages compared with the use of either treatment alone: 1) greater intraprostatic dose than can be achieved with either modality alone, 2) the ability to deliver doses to the periprostatic region that cannot be achieved with brachytherapy alone, and 3) the ability to *fill-in* low-dose regions that may result from inaccurate source placement. At the same time, combination therapy may increase the risk of normal tissue injury compared with either modality alone. For a true improvement in the therapeutic ratio, an increased probability of tumor control should not be overshadowed by an increase in normal tissue complications.

A number of reports describing the efficacy and morbidity of brachytherapy combined with supplemental external-beam radiotherapy have been published.[4–9] The majority of those reports represented retrospective, single-institution experiences, and it is not known whether those results can be generalized to the broader community. Some reports have suggested that the morbidity associated with a combination of external-beam radiotherapy and brachytherapy was not dramatically different than that observed with brachytherapy alone,[10–12] whereas others observed more morbidity after combined brachytherapy and external-beam radiotherapy.[13–15]

It was in this context that the Radiation Therapy Oncology Group (RTOG) designed the current Phase II trial. The objective of the trial was estimate the rate of gastrointestinal (GI) and genitourinary (GU) morbidity after patients received a combination of external-beam radiotherapy and permanent-source, interstitial brachytherapy with iodine-125 (I-125). A preliminary report that examined acute and late toxicity has been published.[16] This report represents an update on the morbidity observed in the study cohort. In addition, the estimated rates of biochemical recurrence (BR) in this population are reported for the first time.

MATERIALS AND METHODS

Participants

Eligible patients had histologically confirmed adenocarcinoma of the prostate gland, and they were required to have clinical stage T1 to T2b. Serum prostate-specific antigen (PSA) levels and a Gleason score were required prior to treatment in all patients. If the Gleason score was <7, then the PSA was required to be >10 ng/mL and ≤ 20 ng/mL. If the Gleason score was 7, then the PSA was required to be ≤ 20 ng/mL. Patients with clinical evidence of extracapsular extension (T3), a pretreatment PSA level >20 ng/mL, or a Gleason score >7 were not eligible.

Additional eligibility criteria required that the prostate volume be ≤ 60 cc on transrectal ultrasound (TRUS) prior to external-beam radiotherapy, and only men with an International Prostate Symptom Score ≤ 18 were eligible. A Zubrod performance status of 0 or 1 was required. No previous pelvic radiation, radical prostate surgery, or chemotherapy was allowed. Short-term androgen deprivation ≤ 6 months was allowed. A history of prior transurethral resection of prostate (TURP) or hip prosthesis made a patient ineligible. All patients completed an informed consent document prior to entering the trial. All institutions that participated were required to have the protocol reviewed by an Institutional Review Board (or equivalent) in accordance with the precepts of the Helsinki declaration. The study was activated in November 2000 and, having met accrual goals, was closed in November 2001.

Patients received a combination of external-beam radiotherapy and interstitial brachytherapy using I-125. The specifics of treatment and quality assurance methods have been described previously.[16] Briefly, patients received a combination of external-beam radiotherapy and interstitial brachytherapy using I-125. External-beam radiotherapy was delivered with megavoltage (MV) photon beams (>6 MV) to the prostate and seminal vesicles (CTV). A CTV-to-block margin from 1.5 cm to 2.0 cm was required. The prescribed dose was 45 Gray (Gy) in 25 fractions (1.8 Gy per fraction). The prescribed dose was defined on the central axis at the intersection of the beams. The permitted dose variation was $\pm 5\%$.

Brachytherapy was completed from 2 to 6 weeks after external-beam radiotherapy. Preplanning methods were required. For treatment-planning purposes, the TRUS volume was considered the CTV. The CTV was enlarged in the anterior, lateral, inferior, and superior dimensions to create a planning target volume (PTV). The CTV was not expanded posteriorly toward the rectum. The prescription dose was 108 Gy and was to be delivered to the PTV. The recommended activity per source was 0.30 to 0.51 U (0.25–0.4 mCi).

Follow-up Studies and Toxicity Evaluation

Patients were evaluated weekly during external-beam radiotherapy for acute toxicity. Follow-up visits were completed 1 month, 3 months, 6 months, 9 months, and 12 months after implantation; every 6 months for the next 2 years; and annually thereafter. History,

physical examination (including digital rectal examination), serum PSA measurement, and toxicity evaluation were performed at each follow-up visit. The RTOG/European Organization for Research and Treatment of Cancer Late Morbidity scale was used to grade all late toxicity. The lead author personally reviewed all cases that reported grade ≥3 toxicity.

Study Endpoints and Statistical Analysis

The primary objective of this study was to estimate the rate of acute and late Grade ≥3 GU and GI toxicity after treatment with external-beam radiotherapy and permanent-source brachytherapy. Secondary endpoints included an estimation of the rates of freedom from BR, disease-specific survival, and overall survival. For the current report, we examined late grade ≥3 GU and GI morbidity and a secondary endpoint, BR.

For the purposes of the current analysis, acute toxicity was defined as toxicity that occurred within 9 months of the beginning of radiotherapy, and late toxicity was defined as toxicity that occurred >9 months after the start of radiotherapy. We believed that this distinction was justified because of the time course of radiation delivery after brachytherapy with I-125. The study was designed to test whether the rate of grade ≥3 GU or GI toxicity was >10% at 18 months after the beginning of radiotherapy. The sample size was determined so that the probability of rejecting the treatment because of excessive late toxicity would be s 90% if the true toxicity rate was 20%. The time to the first occurrence of a late grade ≥3 GU/GI toxicity was estimated by using the cumulative incidence method.

BR was defined in 2 ways; according to the American Society for Therapeutic Radiology and Oncology (ASTRO) Consensus definition (3 consecutive rises with time of recurrence backdated to the midpoint between the PSA nadir and the first PSA rise)[17] and the Phoenix definition (PSA nadir +2 ng/mL).[18] Any PSA rise great enough to provoke the initiation of salvage hormone therapy was considered BR according to either definition. For each definition, the BR rate was estimated by using the cumulative incidence method.[19] Overall survival was estimated according to the Kaplan-Meier method.[20]

RESULTS

Patient Characteristics

One hundred thirty-eight men were entered on the study between November 2000 and November 2001. The outcome of 8 patients was not included in this analysis. Six patients were considered ineligible (3 patients secondary to hormone therapy that violated eligibility criteria, 1 patient had a pretreatment American Urological Association score >18, 1 patient had been treated prior to study entry, and 1 patient had a PSA >20 ng/mL). Two additional patients were not included in the analysis, because 1 patient withdrew consent, and another did not receive any protocol therapy. Late toxicity data were available for all 130 men who were entered and eligible. All radiotherapy data were available for 129 of 130 men, and complete follow-up data were available for 127 of 130 men. This report includes all information received, reviewed, and entered at the RTOG headquarters as of May 2006. Follow-up ranged from 12 months to 60 months (median, 49 months).

TABLE 1
Pretreatment Characteristics of the Study Population (n = 130)

Characteristic	No. of patients	%
Age, y		
Median	67	
Range	40–80	
PSA, ng/mL		
Median	7.6	
Range	1.1–19.7	
Zubrod performance status		
0	122	94
1	8	6
Race		
White	112	86
Hispanic	3	2
African American	10	8
Asian	3	2
Native American	1	1
Unknown	1	1
Tumor classification		
T1c	67	52
T2a/T2b	63	48
PSA, ng/mL		
≤10	83	64
10–20	47	36
Gleason score (institutional)		
≤6	29	22
7	101	78
Prior hormone therapy		
No	95	73
Yes	35	27

PSA indicates prostate-specific antigen.

The pretreatment characteristics of all 130 patients who were entered and eligible are provided in Table 1. The median age of this cohort was 67 years (range, 40–80 years). The vast majority of these men had an excellent performance status, and 86% of them were white. The median PSA for this group was 7.6 ng/mL. Nearly 80% of men in this group had cancers with a Gleason score of 7. Twenty-seven per-

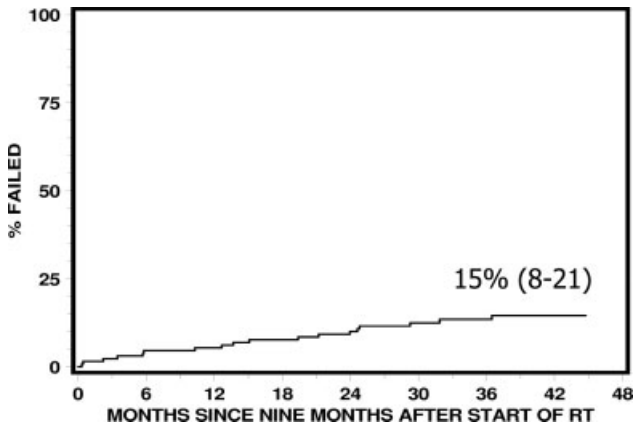

FIGURE 1. Time to late grade ≥3 genitourinary/gastrointestinal toxicity. RT indicates radiotherapy.

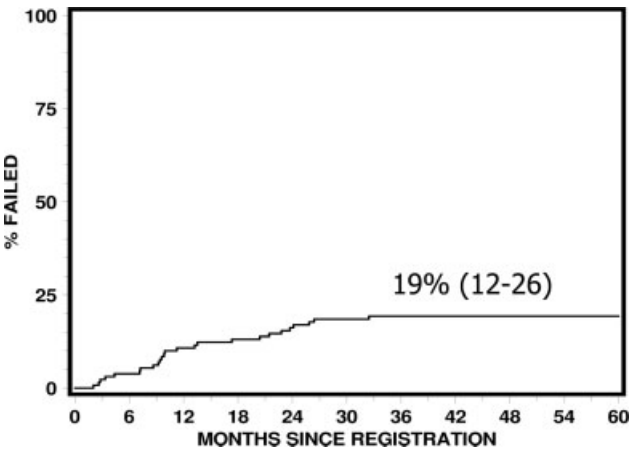

FIGURE 2. Time to biochemical recurrence (American Society for Therapeutic Radiology and Oncology definition).

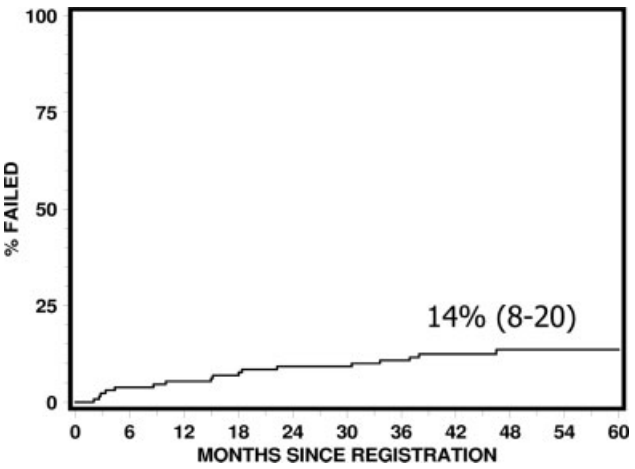

FIGURE 3. Time to biochemical recurrence (Phoenix definition).

cent of men received androgen-deprivation therapy prior to and concurrent with radiotherapy. Greater than 20 institutions contributed patients to this trial. The median number of patients accrued per institution was 5 (range, 1–24 patients per institution). The average monthly accrual was 11 cases per month, and most patients were accrued in the last 6 months that the study was open.

Late Toxicity

No patient experienced grade 5 late toxicity. Grade 4 GU toxicity (bladder necrosis) was reported in 2 patients. In each man, the necrosis occurred in the region of the bladder neck. One man had bladder necrosis that was preceded by a TURP. No grade 4 GI toxicity has been observed. Of the 9 patients who reportedly developed grade 3 late toxicity, 5 patients had urinary toxicity (dysuria in 3 and hematuria in 2), and 4 patients had Grade 3 proctitis. The time to late grade ≥3 toxicity was calculated as the number of months subsequent to 9 months after the start of RT until the event/censoring.

The 18-month month estimate of late grade 3 GU/GI toxicity is 8% (95% confidence interval [95% CI], 3–12%). The null hypothesis that the 18-month late grade ≥3 GU/GI toxicity is >10% was not rejected at the .05 α level (Z-statistic = −4.068; $P = .99$). Given the length of follow-up available, it is also appropriate to report later toxicity. The 48-month estimate of late grade ≥3 GU/GI toxicity is 15% (95% CI, 8–21%). The cumulative incidence estimate of grade ≥3 GU/GI toxicity is illustrated in Figure 1.

BR

Two definitions of BR were used in this analysis, as described above. According to the ASTRO definition, 25 men developed a BR during the period of follow-up. The 48-month estimate of BR using the ASTRO definition is 19% (95% CI, 12–26%). The cumulative incidence estimate of BR according to the ASTRO definition is illustrated in Figure 2.

Using the Phoenix definition, a total of 17 BRs were observed. The 48-month estimate of BR using the Phoenix definition is 14% (95% CI, 8–20%). The cumulative incidence estimate of BR according to the Phoenix definition is illustrated in Figure 3.

Overall Survival and Clinical Recurrence

Twelve men have died during the period of follow-up. There have been no prostate cancer-related deaths reported. The 48-month Kaplan–Meier estimate of overall survival in this cohort is 91% (95% CI, 86–97%). Two clinical recurrences have been documented: One patient developed local recurrence/persistence at 16 months, and another patient

TABLE 2
Reported Late Grade ≥3 Genitourinary/Gastrointestinal Toxicity in Recent Radiation Therapy Oncology Group Trials of Men With Clinically Localized Prostate Cancer

Study no.	Radiotherapy dose	No. of patients	Median FU, mo	% Late grade ≥3 GU/GI toxicity
0019	45 Gy in 1.8-Gy fractions and 108 Gy I–125	130	49	15 at 48 mo
9406 (Level III)	79.2 Gy in 1.8-Gy fractions	170	56–62	1–2 at 24 mo*
9406 (Level V)	78 Gy in 2-Gy fractions	218	29	5–7 at 24 mo*
9509	79.2 Gy in 1.8-Gy fractions	195	66	1–2*
9805	145 Gy I–125	94	64	<3 at 60 mo

FU indicates follow-up; GU/GI, genitourinary/gastrointestinal; Gy, grays; I–125, iodine-125.
* Represents a crude percentage: Actuarial figures are not provided.

developed evidence of distant metastatic disease at 42 months.

DISCUSSION

The primary objective of this study is to estimate the rate of acute and late grade ≥3 GU/GI toxicity after treatment with external-beam radiotherapy and permanent-source brachytherapy. The current analysis indicates that the cumulative incidence of grade 3 and 4 GU/GI toxicity is 15% 4 years after treatment. No grade 5 toxicities have been reported. The most severe toxicity observed has been bladder necrosis in 2 patients; no rectal necrosis or colostomies have been reported. This 15% estimate is higher than a preliminary estimate[16] but is consistent with the time course of radiation-induced GU/GI toxicity observed after external-beam radiotherapy and brachytherapy to pelvic tumors.[21] How does this rate of toxicity compare with other radiation treatment methods studied within the RTOG framework?

Over the past 3 decades, the RTOG has collected toxicity information on a large number of patients who received external-beam radiotherapy alone. Two recent studies provided information that is germane to the results provided in this report. RTOG 94-06 is a Phase I/II dose-escalation study that was designed to determine the maximum tolerated dose that can be delivered to the prostate gland using 3-dimensional conformal radiotherapy. The observed toxicities at all 5 dose levels in that study have been reported.[22–26] The most recent report provided an estimate of grade ≥3 GU/GI toxicity for dose levels III (79.2 Gy in 1.8-Gy fractions) and dose level V (78 Gy in 2-Gy fractions).[25] In that report from Michalski et al, the estimated 24-month incidence of grade ≥3 GU/GI toxicity ranged from 1% to 7% with the higher rates observed at dose level V. This level of toxicity is comparable to the 18-month estimate of 3.3% provided in the preliminary analysis of RTOG 0019.[16] It remains to be determined whether the GU/GI morbidity in RTOG 9406 will increase over the next several years like what has been observed in RTOG 0019.

A second dataset includes patients who were treated on the randomized dose-escalation trial reported by Zietman et al.[27] That study (Proton Radiation Oncology Group/RTOG 9509) included nearly 400 men and randomly assigned them to a control arm (total dose, 70.2 Gy) or an experimental arm (total dose, 79.2 Gy). The final dose (19.8–28.8 Gy) was delivered by proton-beam therapy. At a median follow-up of 5.5 years, the incidence of BR was lower in the experimental arm. Those authors did not provide actuarial estimates, but the crude rate of late grade ≥3 GU/GI toxicity reportedly was from 1% to 2%. No late grade 4 or 5 toxicity was reported.

The RTOG also has collected information on late GU/GI toxicity after permanent-source brachytherapy. In addition to the information provided in this report, the RTOG has completed accrual to another Phase II trial examining the use of permanent low-dose-rate brachytherapy alone, RTOG 9805. That study included men with favorable-risk prostate cancer, and all men were treated with prostate brachytherapy alone (I-125 at a prescription dose of 145 Gy). The preliminary analysis of that study has been published.[28] Ninety-four men were eligible for analysis of late toxicity with a median follow-up of 5.3 years. Two patients developed late grade 3 GU toxicity, and the cumulative incidence of grade 3 GU toxicity was <3% at 5 years. No late grade 3 GI toxicity or grade 4 or 5 GU/GI toxicity was reported.

Table 2 summarizes the late grade ≥3 GU/GI morbidity observed in several recent RTOG trials for men with clinically localized prostate cancer.[25–27] All of those studies used similar reporting methods and toxicity scales. The length of follow-up is approxi-

mately 5 years in all series except for the patients treated at dose level V in RTOG 9406. Although comparisons across series should be undertaken with an abundance of caution, it appears that the observed late grade $\geq$3 GU/GI toxicity is higher in patients treated on RTOG 0019 compared with the toxicity observed in other studies, with the possible exception of dose level V on RTOG 9406.

The increased morbidity of brachytherapy and supplemental external-beam radiotherapy compared with brachytherapy alone has been observed by others. Albert et al. examined the rate of late GU/GI toxicity in men who were treated with magnetic resonance image-guided prostate brachytherapy with or without external-beam radiotherapy. After a median follow-up of 2.8 years, the rate of rectal bleeding and radiation cystitis was significantly greater in the patients who had received supplemental external-beam radiotherapy.[13] Investigators at Duke University observed a similar phenomenon when they examined rectal toxicity after prostate brachytherapy. Those authors studied 134 men and observed that the addition of external-beam radiotherapy was associated with more rectal toxicity.[14] In a recent report from San Antonio, Sarosdy described toxicity in 177 men who received brachytherapy alone (n = 100 patients) or brachytherapy and supplemental external-beam radiotherapy (n = 77 patients). In that study, the rates of rectal bleeding and of fecal and urinary diversion were higher in the men who received both brachytherapy and supplemental external-beam radiotherapy. It is important to point out that increased morbidity of supplemental external-beam radiotherapy has not been observed by all investigators.[10–12] It is interesting to speculate that this lack of consistency may be attributable to subtle differences in dose-volume relationships.

Compared with 3-dimensional conformal radiotherapy, prostate brachytherapy is characterized by a large degree of dose inhomogeneity. It is not unusual to have regions within the prostate gland receiving from 200% to 300% of the prescription dose, although most brachytherapists attempt to minimize these high-dose volumes.[29] The dose-volume-toxicity relationships after prostate brachytherapy are evolving, and no consensus exists to date.[30] Unfortunately, the simple dosimetric evaluation in the current report precludes any meaningful dose-volume analysis.

A secondary objective of the current study was to determine the rate of BR after treatment with external-beam radiotherapy and interstitial brachytherapy. Depending on the definition, either 14% or 19% of men had evidence of BR in the first 48 months after treatment. This result is similar to the results reported in intermediate-risk patients who were treated with high-dose external-beam radiotherapy alone[27,31] or with external-beam radiotherapy and brachytherapy.[4] The rate of BR was slightly lower in the current report but, this is to be expected with the slightly shorter follow-up.

The results from several recent randomized trials provide evidence for a dose response in clinically localized prostate cancer.[27,32,33] Brachytherapy combined with external-beam radiotherapy has been used for nearly 20 years in men with prostate cancer as a strategy to increase the biologic dose. If the therapeutic ratio is be enhanced, however, then normal tissue toxicity should remain low. It is axiomatic that conclusive statements on the toxicity or efficacy of a particular treatment require randomized controlled trials. The results of the current study suggest that the combination of brachytherapy and external-beam radiotherapy is associated with a rate of BR that is similar to that achieved with other dose-escalation strategies (eg, 3-dimensional conformal or intensity-modulated radiotherapy) but may have an increased toxicity profile. The RTOG currently is accruing men with intermediate-risk disease to a randomized trial comparing combined external-beam radiotherapy plus brachytherapy with brachytherapy alone (RTOG 0232; B. Prestidge, Principal Investigator). That trial will determine the value, if any, of external-beam radiotherapy added to brachytherapy; accrual to the trial is vitally important.

In conclusion, the morbidity observed in this multiinstitutional, cooperative group study was slightly higher than that reported in recent RTOG studies using brachytherapy alone or high-dose external-beam radiotherapy. The BR rate observed in this report was similar to that observed with high-dose external-beam radiotherapy alone in similar patients.

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