Comparison of Conventional-Dose vs High-Dose Conformal Radiation Therapy in Clinically Localized Adenocarcinoma of the Prostate
A Randomized Controlled Trial

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THE MAJORITY OF CASES OF prostate cancer now diagnosed in the United States are detected while the disease is still clinically localized. External beam radiation is one of the options used to treat more than 26,000 US men annually.1 There is concern that conventional-dose radiation therapy does not eradicate prostate cancer in a significant proportion of cases, with a resultant increase in prostate-specific antigen (PSA) levels, secondary treatment, and, ultimately, clinical recurrence.2,3

Increasing the delivered radiation dose may increase the probability of local tumor control but carries a risk of greater adverse effects unless the volume of normal tissue treated along with the tumor can be reduced. In the 1990s a number of computed tomography–based techniques became available to deliver radiation more accurately and thus allow the delivery of higher doses. These techniques are together known as “3-dimensional conformal therapy” and include the use of conformal photon beams, intensity-modulated photon beams, and proton beams. Conformal photon-beam therapy has been the standard external radiation therapy, although the more technically challenging intensity-modulated radiation is

Context Clinically localized prostate cancer is very prevalent among US men, but recurrence after treatment with conventional radiation therapy is common.

Objective To evaluate the hypothesis that increasing the radiation dose delivered to men with clinically localized prostate cancer improves disease outcome.

Design, Setting, and Patients Randomized controlled trial of 393 patients with stage T1b through T2b prostate cancer and prostate-specific antigen (PSA) levels less than 15 ng/mL randomized between January 1996 and December 1999 and treated at 2 US academic institutions. Median age was 67 years and median PSA level was 6.3 ng/mL. Median follow-up was 5.5 (range, 1.2-8.2) years.

Intervention Patients were randomized to receive external beam radiation to a total dose of either 70.2 Gy (conventional dose) or 79.2 Gy (high dose). This was delivered using a combination of conformal photon and proton beams.

Main Outcome Measure Increasing PSA level (ie, biochemical failure) 5 years after treatment.

Results The proportions of men free from biochemical failure at 5 years were 61.4% (95% confidence interval, 54.6%-68.3%) for conventional-dose and 80.4% (95% confidence interval, 74.7%-86.1%) for high-dose therapy ($P < .001$), a 49% reduction in the risk of failure. The advantage to high-dose therapy was observed in both the low-risk and the higher-risk subgroups (risk reduction, 51% [$P < .001$] and 44% [$P = .03$], respectively). There has been no significant difference in overall survival rates between the treatment groups. Only 1% of patients receiving conventional-dose and 2% receiving high-dose radiation experienced acute urinary or rectal morbidity of Radiation Therapy Oncology Group (RTOG) grade 3 or greater. So far, only 2% and 1%, respectively, have experienced late morbidity of RTOG grade 3 or greater.

Conclusions Men with clinically localized prostate cancer have a lower risk of biochemical failure if they receive high-dose rather than conventional-dose conformal radiation. This advantage was achieved without any associated increase in RTOG grade 3 acute or late urinary or rectal morbidity.

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Men with high-grade tumors. In the second study, a tumor control advantage was seen in men with intermediate-risk prostate cancer. The latter trial contained only a minority of patients with low-risk disease and was not powered to determine the efficacy of dose escalation in this group, which now constitutes, by far, the most common presentation in the United States. We hypothesized that tumor control could be improved in contemporary patients with prostate cancer, including those with low-risk disease, by the use of higher radiation doses and tested this in a randomized controlled trial. In one group the prostate received a conventional dose of 70.2 Gy; in the other, dose was increased to 79.2 Gy.

**METHODS**

**Study Design**

This randomized controlled trial was designed to compare 2 different radiation doses delivered by conformal techniques. All patients received conformal photon (x-ray) therapy to a fixed dose of 50.4 Gy. The difference between groups was in the boost dose, which was delivered using proton-beam therapy (Figure 1). The unique physical characteristics of this beam allow the treatment of tumors with considerable sparing of normal tissues. The boost dose was either 19.8 Gy or 28.8 Gy, for total doses of either 70.2 Gy (conventional dose) or 79.2 Gy (high dose). All patients received their radiation without the administration of any neoadjuvant, concurrent, or adjuvant hormonal therapy.

**Participants**

Patients were enrolled at 2 centers: Loma Linda University Medical Center, Loma Linda, Calif, and the Massachusetts General Hospital, Boston. Eligible patients with clinically localized adenocarcinoma of the prostate, as defined by criteria available in 1995, were offered entry into this trial. These were men with stage T1b through T2b tumors (using 1992 American Joint Committee on Cancer criteria), serum PSA levels less than 15 ng/mL, and no evidence of metastatic disease as assessed by both whole-body bone scan (with PSA level >10 ng/mL, tumor stage T2b, or Gleason score ≥7) and abdominopelvic computed tomography scan. There was no exclusion from entry on the basis of tumor histology (ie, Gleason score).

All participants provided written informed consent, and the institutional review board at both participating institutions and at the American College of Radiology approved the study protocol. Race/ethnicity data were obtained using investigator-defined classifications, as is required for all studies funded by the National Cancer Institute.

Three hundred ninety-three patients were randomized centrally by the American College of Radiology statistical office on protocol 95-09 of the Proton Radiation Oncology Group between January 1996 and December 1999. Stratification was performed at randomization to ensure balanced groups. Patients were stratified for serum PSA levels less than 4 ng/mL and from 4 to 15 ng/mL and for nodal status NX or N0. In total, only 2 patients underwent a formal node sampling.

**Radiation Treatment**

Conformal radiation therapy was given in 2 phases. Phase 1 used conformal proton beams to treat the prostate alone. The applied proton-beam dose was corrected to a photon equivalent using a radiobiological effectiveness ratio of 1.1. Dose is thus expressed not as gray (Gy) but as gray equivalents (GyE). Either 19.8 GyE or 28.8 GyE was given, depending on randomization, in either 11 or 16 fractions (1.8-GyE fractions). The clinical target volume was the prostate, with a 5-mm margin. An additional 7 to 10 mm was added for a planning target volume, according to the technical requirements of the treating machines at the 2 participating institutions. Thus, the planning target volume varies in order to deliver identical treatment. Planning was performed using 3-dimensional computed tomography–based techniques. Patient position and beam arrangement differed ac-
according to the experience of the participating institutions. At Loma Linda University Medical Center, patients were treated in the supine position using opposed lateral 250-mV proton beams. At the Massachusetts General Hospital, patients were treated in the lithotomy position using a single 160-mV proton beam directed through the perineum.

In phase 2, all men, regardless of trial group, were planned to receive 50.4 Gy delivered with photons in 1.8-Gy fractions to the prostate and seminal vesicles. Patients were treated in the supine position, and radiation was delivered using high-energy (10-23 mV) beams. A combination of 4 beams (anterior, posterior, and right and left lateral) was used. The clinical target volume included the prostate and seminal vesicles, with a margin of 10 mm for potential microscopic infiltration by tumor.

The total treatment time when both phases were combined was 8 weeks in the conventional-dose group and 9 weeks in the high-dose group.

**Patient Immobilization and Treatment Target Imaging**

Patients were immobilized for daily treatment using casts of thermal-setting plastic or body foam. During treatments, a balloon around a Lucite probe was inserted 12 to 15 cm into the rectum and inflated with 25 to 50 mL of saline along its length, as described previously. This procedure immobilized the prostate and displaced the posterior rectal wall out from the path of the beam. Setup error was minimized by obtaining daily portal images throughout the first phase of treatment, imaging the bones and also the metal markers within the Lucite probe that lay against the anterior rectal wall. Portal images were obtained weekly during the second phase.

**Follow-up**

All patients were scheduled to be seen every 3 months for the first year, every 6 months for the next 4 years, and annually after that. Median follow-up for all patients was 5.5 years (range, 1.2-8.2 years). A median of 9 PSA values were available per patient, and the median time between follow-up visits was the same for each group (7 months).

**End Points**

**Biochemical Failure.** This was defined using the American Society for Therapeutic Radiology and Oncology (ASTRO) criteria of 3 successive increases in PSA level, with the failure backdated to a point halfway between the first increase and the last nonincreasing value. Because of concerns that backdating may influence the timing and degree of failure, a second analysis was performed in which no backdating was used.

**Local Control.** Ultrasound-guided sextant prostate biopsy was recommended for men whose postradiation PSA level either did not decrease to 1 ng/mL by 2 years or subsequently increased above that level. A positive biopsy result was taken as evidence of locally persistent or recurrent disease. It was, however, recognized that it is difficult to encourage elderly men to undergo prostate biopsy and that a surrogate for local control would be required. Evidence, reviewed by the ASTRO Consensus Committee on prostate rebiopsy, showed that less than 6% of men with PSA levels less than 1 ng/mL have a positive rebiopsy result. This was therefore taken as surrogate evidence of local control in our trial. All other PSA patterns, in the absence of demonstrable metastatic disease, were judged to be consistent with local failure or persistence of disease unless rebiopsy was performed and showed otherwise.

**Morbidity.** Acute and late genitourinary (GU) and gastrointestinal (GI) morbidity were scored using the Radiation Therapy Oncology Group (RTOG) criteria. This is a 0 to 5 scale in which lower scores equate with fewer symptoms.

**Statistics**

The sample size estimate was calculated to have at least 80% statistical power to detect a 40% to 20% reduction in the 5-year probability of local failure. A 4.5% annual rate of dying without a local failure, 4 years of uniformed accrual, and a 2-sided .05-level log-rank test were assumed and used in the calculation. A sample size of 390 cases provides 80% statistical power to detect a 50% to 30% reduction in the 5-year probability of failure. Actuarial estimates for survival were calculated using Kaplan-Meier methods, and the cumulative incidence method was used to estimate rates of local and biochemical failure. The log-rank test was used to find treatment differences in the overall survival distributions, and the Gray test was used to find differences between the treatment groups for rates of local and biochemical failure over time. Time-to-event methods for right-censored data were used for the primary and secondary analyses. All available information was used in the analysis; analysis was on an intent-to-treat basis. Statistical analyses were performed using SAS version 9.1 (SAS Institute Inc, Cary, NC).

The subgroup analyses performed by risk group were not based on tests of interaction but on published reports of important risk groups and were post hoc analyses. The study was not specifically powered to find differences in the subgroup or overall survival analyses.

**RESULTS**

**TABLE 1** shows the distribution of patients across the 2 study groups by pretreatment prognostic factors (Table 1). It is notable that although patients were stratified by risk parameters available in 1995, they are also balanced for a more contemporary risk stratification.

**Radiation Dose Delivered**

Of 393 patients, 1 refused to participate after randomization and was lost to follow-up, leaving 392 eligible and available for analysis (Figure 1). Of the 197 patients randomized to receive 70.2 GyE, 181 (91.9%) received this dose; 7 (3.6%) received lower and 8 (4.1%) received higher doses. One patient underwent radical prostatectomy rather than radiation therapy because the bowel was too close to the prostate for safe administration of radiation. Of the 195 as-
signed to receive 79.2 GyE, 172 (88.2%) received this dose; 5 (2.6%) received higher and 18 (9.2%) received lower doses. Of these, only 2 received lower doses because of documented toxicity. Four received lower doses because of the development of new medical issues; others did so for a mixture of anxiety, refusal to accept randomization to the higher dose, and convenience.

**Biochemical Outcome**

In the conventional-dose group, 81.0% had a PSA nadir below 1.0 ng/mL, and 44.7% had a nadir below 0.5 ng/mL. In the high-dose group those proportions were 86.6% and 59.8%, respectively. The difference between the proportions with a PSA nadir below 0.5 ng/mL was significant ($P = .003$). Median time to nadir was 28.0 months after conventional-dose and 39.6 months after high-dose therapy.

The 5-year freedom from biochemical failure was 61.4% (95% confidence interval [CI], 54.6%-68.3%) for conventional-dose and 80.4% (95% CI, 74.7%-86.1%) for high-dose therapy ($P < .001$) (Figure 2). This represents a 49% reduction in the risk of failure at 5 years. This advantage for high-dose therapy was seen when those with low-risk disease (PSA level $< 10$ ng/mL, stage $\leq T2a$ tumors, or Gleason score $\leq 6$; $n = 227$ [58% of total]) were examined alone (60.1% in the conventional-dose group and 80.5% in the high-dose group; 51% risk reduction; $P < .001$) (Figure 3). It was also significant for the higher-risk patients (63.4% vs 79.5%; 44% risk reduction; $P = .03$). When the higher-risk patients were broken out into contemporary intermediate- and high-risk subgroups,$^{20}$ the significant difference persisted for the intermediate-risk subgroup (62.7% vs 81%, $P = .02$) but was lost in the small number ($n = 33$) of high-risk patients ($P = .80$).

The backdating used in the ASTRO definition of biochemical failure may affect the timing and rate of failure,$^{13}$ so we performed an analysis without it. The differences between the groups persisted and remained significant (Figure 2). At 5 years it was 66.2% vs 86.4% for conventional-dose and high-dose therapy, respectively ($P < .001$). Significant differences also persisted when men were divided into low-risk (60.6% vs 85.3%, $P < .001$) and intermediate-risk (71.5% vs 89.4%, $P = .008$) subgroups, although again there was no difference seen in the very small number of men with high-risk disease.

Because the 2 involved institutions used different techniques for delivering the proton boost dose, a multivariate Cox model was used to look for any interaction between assigned dose, biochemical outcome, and institution. There was no interaction between these factors ($P = .40$).

In the conventional-dose group, 13 patients have so far received secondary treatment with androgen deprivation therapy, which compared with only 7 in the high-dose group. Treatment was started at the discretion of the oncologist or urologist, usually for increasing PSA level.

**Local Control**

The actuarial estimate of local control at 5 years was 47.6% (95% CI, 40.4%-
54.8%) in the conventional-dose group compared with 67.2% (95% CI, 60.4%-74.0%) in the high-dose group (P < .001). Of those recorded as having local failure or persistence of disease, this was clinically evident or biopsy-confirmed in 24%. In the remainder, the biochemical surrogate alone was used.

**Overall Survival**

At this time, there is no difference in the overall survival rates between the treatment groups (97% vs 96%, P = .80). There were 10 deaths in the conventional-dose group (2 related to prostate cancer) and 8 in the high-dose group (none related to prostate cancer).

**Morbidity**

Table 2 shows morbidity associated with treatment and randomization group. Only 1% of patients receiving conventional-dose and 2% receiving high-dose radiation experienced acute GU or GI (rectal) morbidity of RTOG grade 3 or greater. Forty-two percent

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**Figure 2. Freedom From Biochemical Failure (Increasing PSA Level) Following Either Conventional-Dose (70.2 GyE) or High-Dose (79.2 GyE) Conformal Radiation Therapy**

- **A.** Biochemical Failure With Backdating
- **B.** Biochemical Failure Without Backdating

No. at Risk

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<tr>
<td>Conventional Dose</td>
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</tr>
</tbody>
</table>

Log-Rank P < .001

**Figure 3. Freedom From Biochemical Failure (ASTRO Definition) Following Either Conventional-Dose (70.2 GyE) or High-Dose (79.2 GyE) Conformal Radiation Therapy**

- **Low Risk**
- **Intermediate to High Risk**

No. at Risk

<table>
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<tr>
<th>Group</th>
<th>No. at Risk</th>
</tr>
</thead>
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<td>High Dose</td>
<td>111 111 92 74 64 38 14 4</td>
</tr>
<tr>
<td>Conventional Dose</td>
<td>116 116 111 99 88 56 24 12</td>
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<tr>
<td>High Dose</td>
<td>86 85 79 65 54 38 17 6</td>
</tr>
<tr>
<td>Conventional Dose</td>
<td>76 75 70 61 57 40 19 8</td>
</tr>
</tbody>
</table>

Log-Rank P = .001 Log-Rank P = .02

Analysis of these early cases is by risk subgroup. Low-risk patients have prostate-specific antigen level < 10 ng/mL, stage ≤ T2a tumors, and Gleason scores ≤ 6. ASTRO indicates American Society for Therapeutic Radiology and Oncology; GyE, gray equivalents (see “Methods” section).
and 49% of patients receiving conventional-dose and high-dose therapy, respectively, experienced grade 2 acute GU morbidity (difference not significant by χ² test). The proportions for grade 2 acute GI (rectal) morbidity were 41% and 57%, respectively (P = .004). Proportions for grade 2 late GU morbidity were 18% and 20% (not significant); for grade 2 GI morbidity, they were 8% and 17% (P = .005). Only 2% and 1% of patients receiving conventional-dose and high-dose therapy, respectively, have so far experienced late GU or GI morbidity of RTOG grade 3 or greater. When analyzed as a function of time after treatment, most of the late grade 2 or higher GI morbidity was seen by 3 years. However, GU morbidity continued to accumulate. At 3 years, the actuarial risk of a GU event of grade 2 or greater was 15% and 13% in the conventional-dose and high-dose groups, respectively, increasing to 19% and 18% by 5 years.

**COMMENT**

This randomized trial shows that when men with clinically localized prostate cancer are treated with high-dose rather than conventional-dose external radiation therapy, they are more likely to be free from an increasing PSA level 5 years later and less likely to have locally persistent disease. The data also show that when highly conformal radiation techniques are used, dose escalation to 79.2 Gy can be safely achieved with only a small increase in grade 2 rectal morbidity and no increase in GU morbidity. This study therefore provides evidence to justify trends already emerging in the United States toward conformal technology and higher radiation doses in early-stage disease.21

In 1995, when this trial was designed, early-stage disease was largely defined by tumor stage and PSA level. Since then, more rigorous analysis has developed risk groups, the lowest risk of which are believed to be those that include patients with PSA values less than 10 ng/mL, stage T1-T2a tumors, and Gleason scores of 6 or less.20 Such patients comprised 227 of 393 (58%) of those entered into this trial. Men at intermediate risk comprised the majority of the remainder. The advantage to higher radiation dose was as clear and significant for those with low-risk disease as it was for those with higher risk, and this represents the novel finding of the trial. The advantage was slightly greater for the low-risk group (53% reduction in risk of failure at 5 years, compared with 44%), perhaps reflecting the fact that these men are more likely to have locally confined disease and thus are more likely to benefit from an improved local therapy. Of note, the low- and higher-risk groups appear to have very comparable 5-year freedom from biochemical failure when adjusted for radiation dose. This unexpected finding may result from an unseen bias in more recently recognized prognostic factors, such as percentage of positive biopsy results, percentage of biopsy core involvement, or perineural invasion that were not acknowledged and recorded at the time of the trial design.

Median follow-up was 5.5 years, but this may be regarded as short for a disease whose natural history can spread across decades. Given time, it is therefore possible that the disease-free survival curves could come together. If this proves to be the case, then it would seem that higher doses of radiation delay, rather than prevent, recurrence. Roach et al12 have, however, used a pooled analysis of prostate cancer randomized trials from the RTOG to show that 5-year PSA data correlate strongly with clinical outcome at 15 years. A lengthy delay in recurrence, though not a cure, may also be of clinical benefit to patients, as it delays the use of secondary therapy. In a population of elderly men, a regrowth delay may actually be sufficient to prevent recurrence within the natural lifespan of many patients.

It is most likely that the improvement in biochemical disease-free outcome seen in this trial is due to improved local control. We did not routinely rebiopsy the prostate of all treated patients for several reasons. First, interpretation of prostate biopsy results in the early posttreatment years is unreliable.14 Second, it is ethically difficult to recommend routine prostate rebiopsy, an uncomfortable procedure, when the results are unlikely to influence subsequent management. We therefore used a very stringent surrogate end point for local control, which demanded a PSA of less than 1 ng/mL.

### Table 2

<table>
<thead>
<tr>
<th>Morbidity</th>
<th>70.2 GyE (n = 196)</th>
<th>79.2 GyE (n = 195)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Grade 1</td>
<td>Grade 2</td>
</tr>
<tr>
<td><strong>Acute</strong></td>
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<td></td>
</tr>
<tr>
<td>GU</td>
<td>79 (40)</td>
<td>82 (42)</td>
</tr>
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<td>GI</td>
<td>62 (31)</td>
<td>81 (41)</td>
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<tr>
<td><strong>Late</strong></td>
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<tr>
<td>GU</td>
<td>85 (43)</td>
<td>35 (18)</td>
</tr>
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<td>GI</td>
<td>71 (36)</td>
<td>15 (8)</td>
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**Abbreviations:** GI, gastrointestinal; GU, genitourinary.

*One patient underwent radical prostatectomy rather than radiation therapy because the bowel was too close to the prostate for safe administration of radiation. This patient was excluded from analysis of morbidity.

P = .004 by χ² test.

P = .005 by χ² test.
2 or more years after radiation. This correlates strongly with the likelihood of a negative rebiopsy result in retrospective data, though it has not been prospectively evaluated. This strict end point might represent an underestimate of local control, as patients with PSA values above 1 ng/mL do not always have positive results on rebiopsy. Two prospective Canadian studies that included systematic and regular rebiopsy have, however, reported positive rebiopsy rates of 38% to 53%, consistent with the rates obtained using the biochemical surrogate in the conventional-dose group of our study.

The randomized trial of radiation dose reported by Pollack et al showed higher levels of rectal morbidity, particularly bleeding, in the 78-Gy high-dose group at 5 years. We have also observed this difference at the grade 2 level but not at the more serious grade 3 level. It remains possible that a more sensitive quality-of-life instrument would detect more morbidity than the physician-reported morbidity scales used or that the grade 2 rectal morbidity that we observed may be more bothersome than its low score value would suggest. We are currently performing a cross-sectional study on long-term trial survivors using validated instruments to test these possibilities. Questions regarding sexual function were asked, but these are now recognized to be so prone to bias that the available data have not been presented here.

Although this trial validates the use of proton-beam therapy, it did not test whether this modality is more or less efficacious than other less expensive and more commonly available conformal techniques or, for that matter, than brachytherapy or surgery. Nor do the results justify using doses above 79 Gy outside the context of a clinical trial.

In summary, this randomized controlled trial shows an advantage to high-dose over conventional-dose conformal radiation in terms of freedom from biochemical failure for men with low- and intermediate-risk prostate cancer. This advantage was safely achieved with only a small increase in grade 2 rectal morbidity and no increase in GU morbidity by the use of highly conformal radiation techniques that included 3-dimensional photon and proton beams.

Author Contributions: Dr Zietman had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Zietman, Slater, Rossi, Miller, Shipley.

Acquisition of data: Zietman, Slater, Rossi, Adams.

Analysis and interpretation of data: Zietman, DeSilvio, Rossi, Shipley.

Drafting of the manuscript: Zietman, Slater, Rossi, Critical revision of the manuscript for important intellectual content: DeSilvio, Rossi, Miller, Adams.

Statistical analysis: Zietman, DeSilvio.

Obtained funding: Shipley.

Administrative, technical, or material support: Slater, Rossi, Miller.

Study supervision: Zietman, Slater, Rossi, Shipley.

Financial Disclosures: None reported.

Funding/Support: This trial was supported by National Cancer Institute Institutional Cancer Center Grant 5P30CA013399.

Role of the Sponsor: The National Cancer Institute had no role in the design and conduct of the study; in the collection, analysis, and interpretation of the data; or the preparation, review, or approval of the manuscript.

Acknowledgment: We thank Susan Dean, BS, for her fine data support. We also thank Herman Suit, MD, PhD, Michael Gottei, PhD, and James Slater, MD, for their efforts and inspiration in building the proton beam programs at the 2 sites.

REFERENCES


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data was needed. All of the original data had been collected, stored, and analyzed by the statistics department of the American College of Radiology (ACR). For one secondary analysis, the raw data were obtained from the ACR and the original Kaplan-Meier analysis of cancer-free survival was rerun. This outcome had been defined as freedom from 3 successive increases in the level of prostate-specific antigen (PSA). We were unable to reproduce the curves reported in the JAMA article and brought this to the attention of the ACR statisticians. They traced the problem to an error in the definition of PSA failure coded in the computer program. Although the primary outcome of the study was biochemical failure defined as 3 successive increases (as indicated in the “Methods” section of the article), the computer code identified any 3 increases as biochemical failure. This erroneously identified additional patients as “failures” along with those correctly classified.

The data have now been reanalyzed using the correct definition. The risk of biochemical failure is lower in both arms of the trial than originally reported, although the differences between the 2 arms remain statistically significant. In the post hoc subgroup analyses, the risk reduction is no longer statistically significant for the higher-risk subgroup of patients overall but remains significant for the intermediate-risk subgroup.

On behalf of my research team, I apologize to the JAMA editors and readers for the errors in our study and for any inconvenience caused by the publication of these incorrect data.

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Financial Disclosures: None reported.


Editor’s Note: Corrected results and figures for this article are presented in the Corrections section of this issue of JAMA.

CORRECTION

Incorrect Data Reported in Text and Figure: In the Original Contribution entitled “Comparison of Conventional-Dose vs High-Dose Conformal Radiation Therapy in Clinically Localized Adenocarcinoma of the Prostate: A Randomized Controlled Trial” published in the September 14, 2005, issue of JAMA (2005;294(10):1233-1239), data were incorrectly reported. In the “Results” section of the Abstract on page 1233, the first and second sentences should have read as follows: “The proportions of men free from biochemical failure at 5 years were 78.8% (95% confidence interval, 73.1%-84.6%) for conventional-dose and 91.3% (95% confidence interval, 87.2%-95.4%) for high-dose therapy (P<.001), a 9% reduction in the risk of failure. The advantage to high-dose therapy was statistically significant in the low-risk subgroup (risk reduction, 84% [P<.001]).”

In the “Biochemical Outcome” section on page 1236, the first through third paragraphs should have read as follows:

In the conventional-dose group, 79.2% had a PSA nadir below 1.0 ng/mL, and 41.6% had a nadir below 0.5 ng/mL. In the high-dose group those proportions were 86.6% and 58.8%, respectively. The difference between the proportions with a PSA nadir below 0.5 ng/mL was significant (P=.007). Median time to nadir was 27.0 months after conventional-dose and 39.6 months after high-dose therapy. The 5-year freedom from biochemical failure was 78.8% (95% confidence interval [CI], 73.1%-84.6%) for conventional-dose and 91.3% (95% CI, 87.2%-95.4%) for high-dose therapy (P<.001) (Figure 2). This represents a 59% reduction in the risk of failure at 5 years. This advantage for high-dose therapy was seen when those with low-risk disease (PSA level <10 ng/mL, stage T1b-T2a tumors, or Gleason score ≤6; n=227 [58% of total]) were examined alone (82.6% in the conventional-dose group and 97.3% in the high-dose group; 84% risk reduction; P<.001) (Figure 3). The reduction was not significant for the higher-risk patients taken overall (74.1% vs 81.8%; 30% risk reduction; P=.10). When the higher-risk patients were broken out into contemporary intermediate- and high-risk subgroups,25 significance emerged for the intermediate-risk subgroup (74.5% vs 87.4%;

Figure 2. Freedom From Biochemical Failure (Increasing PSA Level) Following Either Conventional-Dose (70.2 GyE) or High-Dose (79.2 GyE) Conformal Radiation Therapy

A Biochemical Failure With Backdating

- Conventional dose
- High dose

Proportion Free From Biochemical Failure

Time From Randomization, y

No. at Risk

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Gray test P<.001

B Biochemical Failure Without Backdating

- Conventional dose
- High dose

Proportion Free From Biochemical Failure

Time From Randomization, y

No. at Risk

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Gray test P<.001

A, Analysis of outcome using American Society for Therapeutic Radiology and Oncology criteria, in which biochemical failure occurs on the third increase but is backdated to a point midway between the last nonincreasing value and the first increase. B, Same analysis as in A, but without backdating. GyE indicates gray equivalents (see “Methods” section); PSA, prostate–specific antigen. Error bars indicate 95% confidence intervals.
51% risk reduction; \( P = .02 \) but was not observed in the small number (\( n=33 \)) of high-risk patients (\( P = .49 \)). The backdating used in the ASTRO definition of biochemical failure may affect the timing and rate of failure,13 so we performed an analysis without it. The differences between the groups persisted and remained significant (Figure 2). At 5 years it was 81.3% vs 93.2% for conventional-dose and high-dose therapy, respectively (\( P < .001 \)). Significant differences also persisted when men were divided into low-risk (84.7% vs 97.8%, \( P < .001 \)) and intermediate-risk (79.1% vs 90.9%, \( P = .02 \)) subgroups, although again there was no difference seen in the very small number of men with high-risk disease.”

Analysis of these early cases is by risk subgroup. Low-risk patients have prostate-specific antigen level <10 ng/mL, stage ≤T2a tumors, and Gleason score ≤6. ASTRO indicates American Society for Therapeutic Radiology and Oncology; GyE, gray equivalents (see “Methods” section).

In the fourth paragraph of the “Biochemical Outcome” section, the value reported as \( P = .40 \) should have been reported as \( P = .11 \). On page 1237, Figure 2 and Figure 3 should have appeared as shown here. In the “Comment” section on page 1238, the fifth and sixth sentences of the second paragraph should have read “The advantage to higher radiation dose was as clear and significant for those with low-risk disease as it was for those with intermediate risk, and this represents the novel finding of the trial. The advantage was slightly greater for the low-risk group than for the intermediate-risk group (84% reduction in risk of failure at 5 years, compared with 51%), perhaps reflecting the fact that these men are more likely to have locally confined disease and thus are more likely to benefit from an improved local therapy.” See also related letter in this issue.