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# Effect of Standard vs Dose-Escalated Radiation Therapy for Patients With Intermediate-Risk Prostate Cancer
## The NRG Oncology RTOG 0126 Randomized Clinical Trial

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**IMPORTANCE** Optimizing radiation therapy techniques for localized prostate cancer can affect patient outcomes. Dose escalation improves biochemical control, but no prior trials were powered to detect overall survival (OS) differences.

**OBJECTIVE** To determine whether radiation dose escalation to 79.2 Gy compared with 70.2 Gy would improve OS and other outcomes in prostate cancer.

**DESIGN, SETTING, AND PARTICIPANTS** The NRG Oncology/RTOG 0126 randomized clinical trial randomized 1532 patients from 104 North American Radiation Therapy Oncology Group institutions March 2002 through August 2008. Men with stage cT1b to T2b, Gleason score 2 to 6, and prostate-specific antigen (PSA) level of 10 or greater and less than 20 or Gleason score of 7 and PSA less than 15 received 3-dimensional conformal radiation therapy or intensity-modulated radiation therapy to 79.2 Gy in 44 fractions or 70.2 Gy in 39 fractions.

**MAIN OUTCOMES AND MEASURES** Time to OS measured from randomization to death due to any cause. American Society for Therapeutic Radiology and Oncology (ASTRO)/Phoenix definitions were used for biochemical failure. Acute (≤90 days of treatment start) and late radiation therapy toxic effects (>90 days) were graded using the National Cancer Institute Common Toxicity Criteria, version 2.0, and the RTOG/European Organisation for the Research and Treatment of Cancer Late Radiation Morbidity Scoring Scheme, respectively.

**RESULTS** With a median follow-up of 8.4 (range, 0.02-13.0) years in 1499 patients (median [range] age, 71 [33-87] years; 70% had PSA <10 ng/mL, 84% Gleason score of 7, 57% T1 disease), there was no difference in OS between the 751 men in the 79.2-Gy arm and the 748 men in the 70.2-Gy arm. The 8-year rates of OS were 76% with 79.2 Gy and 75% with 70.2 Gy (hazard ratio [HR], 1.00; 95% CI, 0.83-1.20; $P = .98$). The 8-year cumulative rates of distant metastases were 4% for the 79.2-Gy arm and 6% for the 70.2-Gy arm (HR, 0.65; 95% CI, 0.42-1.01; $P = .05$). The ASTRO and Phoenix biochemical failure rates at 5 and 8 years were 31% and 20% with 79.2 Gy and 47% and 35% with 70.2 Gy, respectively (both $P < .001$; ASTRO: HR, 0.59; 95% CI, 0.50-0.70; Phoenix: HR, 0.54; 95% CI, 0.44-0.65). The high-dose arm had a lower rate of salvage therapy use. The 5-year rates of late grade 2 or greater gastrointestinal and/or genitourinary toxic effects were 21% and 12% with 79.2 Gy and 15% and 7% with 70.2 Gy ($P = .006$ [HR, 1.39; 95% CI, 1.10-1.77] and $P = .003$ [HR, 1.59; 95% CI, 1.17-2.16], respectively).

**CONCLUSIONS AND RELEVANCE** Despite improvements in biochemical failure and distant metastases, dose escalation did not improve OS. High doses caused more late toxic effects but lower rates of salvage therapy.

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Author Audio Interview

Supplemental content

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External-beam radiation therapy is an established curative treatment option for men with localized prostate cancer. Prior to the availability of modern radiation therapy (RT) techniques such as 3-dimensional conformal radiation therapy (3DCRT) or intensity-modulated radiation therapy (IMRT), it was difficult to safely deliver high doses of radiation to the prostate gland without excessive toxic effects. Using modern technologies, prospective phase 3 dose escalation trials have demonstrated a dose response for improved biochemical and local tumor control.[1-5] NRG Oncology RTOG 0126 is the largest randomized clinical trial that evaluates the effect of radiation dose escalation in localized prostate cancer. Only 1 of the previously reported trials was powered to determine a difference in overall survival (OS).

The primary objective of NRG Oncology RTOG 0126 was to determine whether 3DCRT or IMRT to 79.2 Gy in 44 fractions compared with 70.2 Gy in 39 fractions would lead to improved OS in patients treated for intermediate-risk prostate cancer. At study inception, it was expected that an improvement in local therapy for this group of patients would affect OS rates. Secondary objectives of the trial were to determine the freedom from biochemical (prostate-specific antigen [PSA] level) failure, prostate cancer mortality, and local and distant progression and to assess the incidence of grade 2 or greater genitourinary (GU) and gastrointestinal (GI) acute and late toxic effects.

### Key Points

**Question** Does dose-escalated radiation therapy improve outcomes for men treated for localized prostate cancer?

**Findings** In this randomized clinical trial, dose escalation was associated with a significant improvement in the rates of clinical end points such as biochemical control and distant metastases, but there was no significant improvement in overall survival. Patients who received high-dose radiation therapy had less need for salvage local or systemic therapy.

**Meaning** Radiation dose escalation did not improve overall survival but reduced the need for secondary therapies.

## Methods

### Trial Design and Participants

This randomized clinical trial compared dose-escalated (79.2 Gy) with standard dose (70.2 Gy) 3DCRT or IMRT. Men with histologically confirmed prostate cancer diagnosed within 180 days of study randomization, a Zubrod performance scale of 0 to 1, clinical stage T1b to T2b with either a Gleason score of 2 to 6 and a PSA of at least 10 and less than 20 ng/mL (1:1 conversion to micrograms per liter) or Gleason score of 7 and a PSA of less than 15 ng/mL were eligible. Patients could not have metastases, received prior treatment for prostate cancer, previous pelvic irradiation, chemotherapy, or hormonal therapy (such as luteinizing hormone-releasing hormone agonists, antiandrogens, estrogens, or surgical castration). Before study entry, evaluation included history and physical examination (including digital rectal examination) and a serum PSA test (within 120 days prior to registration).

Participants were recruited at academic, community-based, and tertiary medical site members of the then RTOG, now NRG Oncology, after institutional review board approval at each center. Membership was established and maintained through a quality control system compliant with National Cancer Institute guidelines. All participants provided written informed consent before registration and were to receive protocol-specified care and follow-up at a member site. Participants did not receive compensation for joining the study, and no commercial support was provided.

### Randomization

This was a multicenter, stratified phase 3 trial with 1:1 random assignment and approved and sponsored by the National Cancer Institute. Participants were stratified according to clinical risk group (Gleason score of 2-6 with a PSA level ≥10 but <20 ng/mL or a Gleason score of 7 and PSA <15 ng/mL) and treatment modality (3DCRT or IMRT). A permuted-block randomization treatment allocation scheme described by Zelen[6] was used to balance patient factors other than institution. Patients were randomly assigned to standard dose (70.2 Gy in 39 fractions over 7.8 weeks) or dose-escalated RT (79.2 Gy in 44 fractions over 8.8 weeks). The selection of 79.2 Gy as the experimental dose followed results of the preceding phase 1/2 dose escalation trial, RTOG 9406.[7]

### Treatment

At the outset of the trial, only 3DCRT was allowed, as the quality assurance criteria for IMRT were under development. On September 18, 2003, the protocol (Supplement 1) was amended to allow IMRT and treatment modality (3DCRT vs IMRT) was added as a stratification factor. Protocol treatment was to be initiated within 4 weeks of registration.

Details of the RT planning have been previously reported.[8] For patients receiving 3DCRT, the clinical target volume included the prostate and seminal vesicles for the first 55.8 Gy, followed by a boost to the prostate only, to a total of 79.2 Gy. For patients receiving IMRT, there was a single clinical target volume consisting of the prostate and the proximal 1 cm of seminal vesicle tissue based on data demonstrating that 93% of 344 prostatectomy specimens had no cancer beyond the first 1 cm.[9] All clinical target volumes were required to have a planning target volume margin of 0.5 to 1.0 cm surrounding them to account for organ motion or setup uncertainties.

### Patient Assessment and End Points

Patients were monitored weekly during RT for adverse events and tolerance to treatment. Following treatment, they underwent interval history, physical examination with assessment of specific GU and GI morbidity, and PSA level testing at each visit starting 3 months after RT and then every 3 months for 2 years, every 6 months for the next 3 years, and annually thereafter. Acute (within ≤90 days after treatment start) and late RT toxic effects (>90 days after treatment start) were graded using the National Cancer Institute common toxicity criteria, version 2.0, and the RTOG/European Organisation for the Research and Treatment of Cancer Late Radiation Morbidity Scoring Scheme, respectively.

Overall survival was the primary end point, with time to OS measured from the date of randomization to the date of death due to any cause. For biochemical failure (BF), both the American Society for Therapeutic Radiology and Oncology (ASTRO) (BF-ASTRO)[10] and Phoenix (BF-Phoenix)[11] definitions of PSA failure were used. BF-ASTRO is defined as having 3 consecutive elevations of posttreatment PSA level or starting hormones after 1 or more elevations in posttreatment PSA but before 3 consecutive elevations were documented. The failure date was the midpoint between last nonincreasing PSA and first PSA increase. BF-Phoenix is defined as a PSA level equal to or greater than the PSA nadir plus 2 ng/mL or the initiation of salvage hormone therapy. The failure date is the first PSA value meeting this criterion or the start of hormone therapy. A bone scan was obtained in the event of a PSA (biochemical) failure or if the patient developed symptoms suggestive of metastatic disease. A needle biopsy of the prostate at the time of failure was encouraged. Clinical criteria for local failure were progression (LP) (increase in palpable abnormality) at any time and redevelopment of a palpable abnormality after complete disappearance of previous abnormalities. Distant metastasis (DM) was determined if clinical or bone scan evidence of disease was demonstrated. The time to distant failure was measured from the date of randomization to the date of documented regional nodal recurrence or development of distant disease. Patients with evidence of BF, but a negative prostate biopsy result, were considered as having experienced distant failure only. Time to distant metastasis-free survival (DMFS) was measured from the date of randomization to the date of DM or death due to any cause. Time to prostate cancer mortality was measured from the date of randomization to the date of death due to prostate cancer. Death due to prostate cancer was defined as primary cause of death due to prostate cancer, or death in association with any of the following conditions: further clinical tumor progression occurring after initiation of "salvage" antitumor (eg, androgen suppression) therapy, and increase (that exceeds 1.0 ng/mL) in the serum PSA level on at least 2 consecutive occasions that occurred during or after salvage androgen suppression therapy, or disease progression in the absence of any antitumor therapy.

A review panel consisting of the principal investigator (J.M.M.) and 5 other investigators (J.-P.B., H.L., M.P., D.H., and H.S.) reviewed data describing the causes of death of all patients who died. Initially, 2 members of this panel (J.-P.B., H.L., M.P., and/or D.H.) independently reviewed the reported cause of death, the information provided to NRG Oncology headquarters regarding the circumstances of death, the PSA level history, and any salvage (ie, hormone therapy) therapies administered. The principal investigator (J.M.M.) and disease committee chair (H.S.) were not involved in the first level of review. When there was disagreement between the initial 2 panel members, the cases were discussed by teleconference among the 6 panel members to reach consensus. Deaths were attributed to prostate cancer when there was documented and irrefutable evidence of cancer progression by PSA test, imaging, salvage therapy, or clinical examination and history; or death related to treatment-associated toxic effects. Deaths due to other causes were determined when there was evidence of specific causes contributing to death unrelated to prostate cancer or effects of treatment. When insufficient evidence was available to determine the cause of death, it was scored as unknown. If it was believed to be unlikely to be related to prostate cancer, for example, with an undetectable PSA level and no salvage therapy or reported toxic effects within 3 months of death, that death was recorded as unknown but unlikely related to prostate cancer.

### Statistical Methods

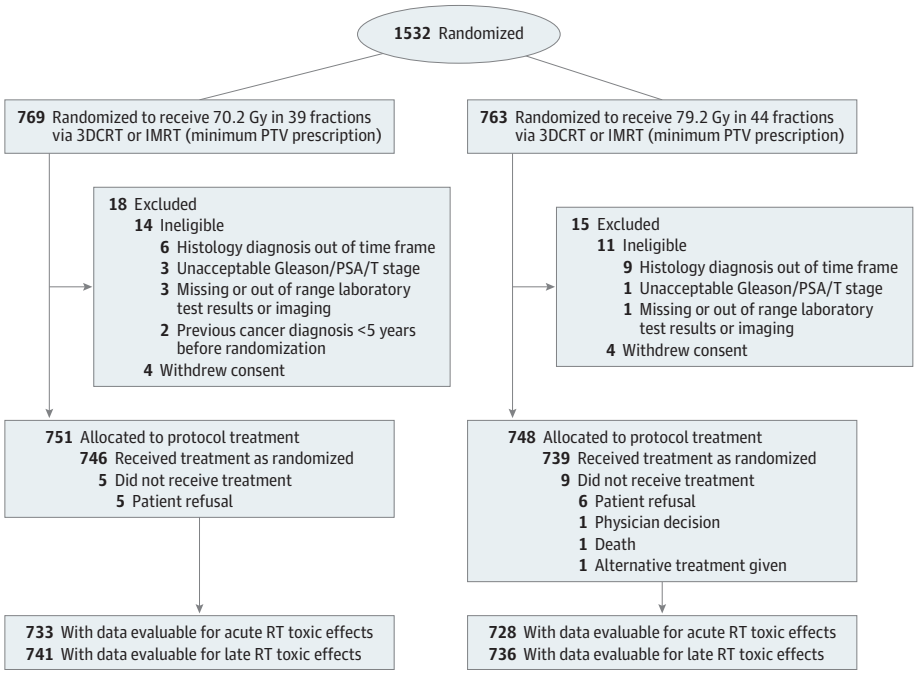
Target sample size was determined to be 1520 cases to reach the required 715 deaths to test the hypothesis of superior efficacy in terms of OS for the high-dose (79.2 Gy) arm over the standard dose (70.2 Gy) arm. The trial was designed to detect a hazard ratio (HR) of 1.30 (standard/high-dose) with 90% statistical power at a 1-sided significance level of .025. Five interim analyses (at 85, 186, 320, 478, and 640 deaths) were planned with early stopping for efficacy based on O'Brien-Fleming type boundaries, and the definitive primary analysis at 715 deaths. The monitoring plan also specified a conditional power rule for futility, where if the conditional power was found to be to less than 10% at any interim analysis, trial reporting would be recommended. The futility rule was subsequently revised based on the lower inefficacy boundary rule of Freidlin, Korn, and Gray.[12] This rule provides the opportunity to terminate early for evidence that the experimental arm will not prove superior, but protects against aggressive early termination for treatment effect sizes smaller than planned.

The Kaplan-Meier[13] approach was used to estimate OS and DMFS, and the log-rank test[14] was used to compare treatment arms. Cumulative incidence[15(pp247-277)] was used to estimate BF-ASTRO and BF-Phoenix LP, DM, prostate cancer mortality, and time to late GU and GI toxic effects, and the Gray[16] test was used to compare treatment arms. The univariate Cox proportional hazards regression model[17] approach was used to obtain HRs for OS and DMFS. Univariate Fine-Gray[18] regression was used obtain HRs for BF-ASTRO and BF-Phoenix LP, DM, prostate cancer mortality, and time to late GI and GU toxic effects. A multivariable Cox proportional hazards regression model was also performed for OS adjusting for the stratification variables of Gleason score, PSA level, and radiation modality. Treatment was coded such that an HR greater than 1 indicates an increased risk of failure for the 79.2-Gy arm. The analyses were based on data received at NRG Oncology Statistical and Data Management Center through March 17, 2016. All analyses were conducted using SAS, version 9.4.

## Results

Between March 21, 2002, and August 20, 2008, a total of 1532 patients were randomized from 104 institutions. Thirty-three patients were excluded from analysis; 25 were ineligible and 8 withdrew consent. There were 1499 eligible and analyzable patients (**Figure 1**). Pretreatment characteristics

Figure 1. CONSORT Diagram[a]




[a] Information regarding number of patients assessed for eligibility is missing because NRG (as well as its predecessor RTOG) does not require institutions to collect these data when they are assessing patients for potential participation in a trial.

3DCRT indicates 3-dimensional conformal radiation therapy; IMRT, intensity-modulated radiation therapy; PSA, prostate-specific antigen; PTV, planning target volume; RT, radiation therapy.

were balanced and are summarized in **Table 1**. The median age was 71 years (range, 33-87 years), and 1371 (91.5%) patients had no physical limitations (Zubrod performance score of 0). Disease characteristics were consistent with an intermediate-risk population, with 1257 (83.9%) patients having a Gleason score of 7 and PSA level less than 15 ng/mL and 242 (16.1%) a Gleason score of 2 to 6 and 10 ng/mL ≤ PSA < 20 ng/mL. A total of 993 (66.2%) patients were treated with 3DCRT, with the remainder receiving IMRT. For patients with a Gleason score of 7, the distribution of 3 + 4 was similar for the 2 arms ($P$ = .64): 459 (72.4%) and 443 (71.2%) for the 70.2- and 79.2-Gy arms, respectively.

The RT plans for all patients were centrally reviewed. Tumor and RT target volumes were defined per protocol or with an acceptable variation in 675 (89.9%) and 669 (89.4%) patients for the 70.2- and 79.2-Gy arms, respectively. Organs at risk were defined per protocol or with an acceptable variation in 1397 (93.2%) patients. Tumor dose-volume coverage was per protocol or with a minor variation in 1304 (87.0%) patients, with no differences between treatment arms. All participating centers successfully irradiated an anthropomorphic phantom from the Radiological Physics Center to ensure accurate treatment delivery capabilities.

## Interim Analyses

No boundaries were crossed for efficacy or futility of the OS primary end point at either the first (June 2009) or second (January 2012) interim analysis, so additional follow-up was recommended by the Data Monitoring Committee. At the time of the third interim analysis, there were 329 events (46% of the total 715 events). The third interim analysis futility boundary was exceeded when the observed experimental/control HR of 1.00 exceeded the predetermined threshold of 0.986. Based on their review of the study data, including these results, the Data Monitoring Committee recommended early reporting of the trial.

## Outcomes

The median follow-up for all patients was 8.4 (range, 0.02-13.0) years and for alive patients was 8.8 (range, 0.02-13.0) years. There was no difference in OS between the 2 arms (**Figure 2**A). The 5- and 8-year OS was 89% and 75% for the 70.2-Gy arm and 88% and 76% for the 79.2-Gy arm, respectively (HR for 79.2 vs 70.2 Gy, 1.00; 95% CI, 0.83-1.20; $P$ = .98). Prostate cancer was the cause of death in 51 patients (3.4% of all patients enrolled) and accounted for 11.8% of the 431 recorded deaths (eTable 1 in Supplement 2). The 5- and 8-year cumulative incidence of prostate cancer mortality was 1% and 4% for the 70.2-Gy arm and 1% and 2% for the 79.2-Gy arm (HR for 79.2 vs 70.2 Gy, 0.66; 95% CI, 0.38-1.15; $P$ = .14) (Figure 2B). There was a statistically significant difference between treatment arms for ASTRO-BF favoring the high-dose arm (**Figure 3**A). The 5- and 8-year cumulative incidence of ASTRO-BF was 40% and 47% for the 70.2-Gy arm and 25% and 31% for the 79.2-Gy arm, respectively (HR, 0.59; 95% CI, 0.50-0.70; $P$ < .001). The 5- and 8-year cumulative incidence of Phoenix-BF was 20% and 35% for the 70.2-Gy arm and 13% and 20% for the 79.2-Gy arm, respectively (HR, 0.54; 95% CI, 0.44-0.65; $P$ < .001) (Figure 3B).

There were statistically significant differences between treatment arms for LP and DM. The 5- and 8-year cumulative incidence of LP was 4% and 6% for the 70.2-Gy arm and 2% and 3% for the 79.2-Gy arm, respectively (HR, 0.41; 95% CI, 0.25-0.66; $P$ < .001) (eFigure 1 in Supplement 2). The 5- and

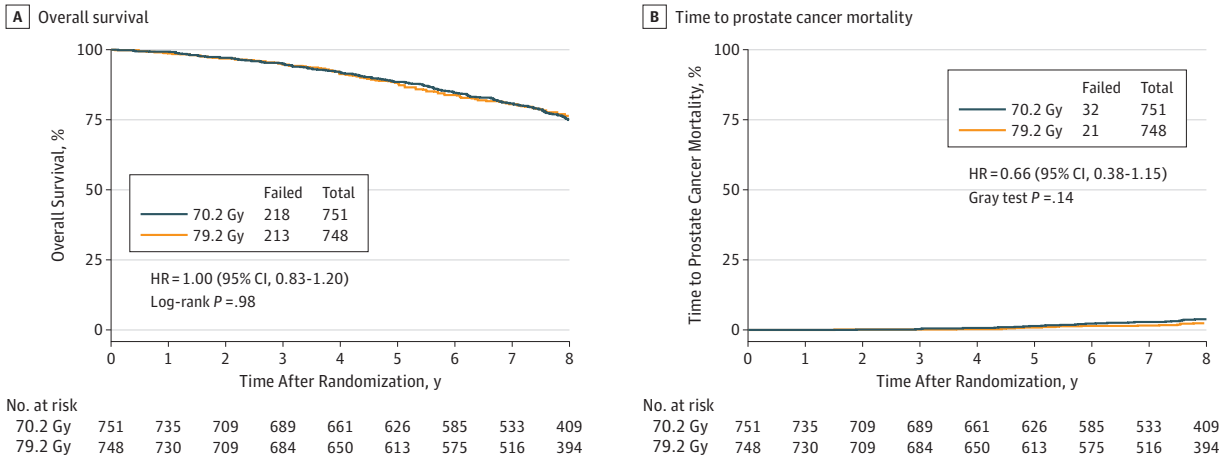
Table 1. Pretreatment Characteristics

| Characteristic | Value | | |
|---|---|---|---|
| | 70.2 Gy (n = 751) | 79.2 Gy (n = 748) | Total (N = 1499) |
| Age, median (range), y | 71 (33-86) | 71 (49-87) | 71 (33-87) |
| Race, No. (%) | | | |
| American Indian or Alaskan Native | 2 (0.3) | 5 (0.7) | 7 (0.5) |
| Asian | 7 (0.9) | 10 (1.3) | 17 (1.1) |
| Black or African American | 84 (11.2) | 104 (13.9) | 188 (12.5) |
| Native Hawaiian or other Pacific islander | 0 | 1 (0.1) | 1 (0.1) |
| White | 643 (85.6) | 609 (81.4) | 1252 (83.5) |
| >1 Race | 2 (0.3) | 1 (0.1) | 3 (0.2) |
| Unknown | 13 (1.7) | 18 (2.4) | 31 (2.1) |
| Ethnicity, No. (%) | | | |
| Hispanic or Latino | 24 (3.2) | 24 (3.2) | 48 (3.2) |
| Not Hispanic or Latino | 682 (90.8) | 687 (91.8) | 1369 (91.3) |
| Unknown | 45 (6.0) | 37 (4.9) | 82 (5.5) |
| Zubrod Performance Status, No. (%) | | | |
| 0 | 679 (90.4) | 692 (92.5) | 1371 (91.5) |
| 1 | 72 (9.6) | 56 (7.5) | 128 (8.5) |
| PSA level at study entry, ng/mL | | | |
| Median (range) | 7.7 (0.1-19.9) | 7.4 (0.3-19.7) | 7.6 (0.1-19.9) |
| No. (%) | | | |
| <10 | 525 (69.9) | 517 (69.1) | 1042 (69.5) |
| 10 to <15 | 195 (26.0) | 187 (25.0) | 382 (25.5) |
| 15 to 20 | 31 (4.1) | 44 (5.9) | 75 (5.0) |
| Combined GS, No. (%) | | | |
| 2-6 | 116 (15.4) | 126 (16.8) | 242 (16.1) |
| 7 | 635 (84.6) | 622 (83.2) | 1257 (83.9) |
| PSA and GS at study entry | | | |
| GS 2-6 and 10 ng/mL ≤ PSA < 20 ng/mL | 116 (15.4) | 126 (16.8) | 242 (16.1) |
| GS 7 and PSA < 15 ng/mL | 635 (84.6) | 622 (83.2) | 1257 (83.9) |
| T Stage | | | |
| T1 | 430 (57.3) | 423 (56.6) | 853 (56.9) |
| T2 | 321 (42.7) | 325 (43.4) | 646 (43.1) |
| N Stage | | | |
| N0 | 715 (95.2) | 712 (95.2) | 1427 (95.2) |
| NX | 36 (4.8) | 36 (4.8) | 72 (4.8) |
| M Stage | | | |
| M0 | 729 (97.1) | 734 (98.1) | 1463 (97.6) |
| MX | 22 (2.9) | 14 (1.9) | 36 (2.4) |
| Urinary incontinence at study entry (severity) | | | |
| Grade 0 | 715 (95.2) | 699 (93.4) | 1414 (94.3) |
| Grade 1 | 31 (4.1) | 39 (5.2) | 70 (4.7) |
| Grade 2 | 5 (0.7) | 6 (0.8) | 11 (0.7) |
| Grade 3 | 0 | 1 (0.1) | 1 (0.1) |
| Unknown | 0 | 3 (0.4) | 3 (0.2) |
| Urinary frequency/urgency at study entry (severity) | | | |
| Grade 0 | 481 (64.0) | 494 (66.0) | 975 (65.0) |
| Grade 1 | 217 (28.9) | 211 (28.2) | 428 (28.6) |
| Grade 2 | 49 (6.5) | 38 (5.1) | 87 (5.8) |
| Grade 3 | 2 (0.3) | 3 (0.4) | 5 (0.3) |
| Unknown | 2 (0.3) | 2 (0.3) | 4 (0.3) |
| Radiation therapy modality | | | |
| 3-Dimensional conformal radiation therapy | 502 (66.8) | 491 (65.6) | 993 (66.2) |
| Intensity-modulated radiation therapy | 249 (33.2) | 257 (34.4) | 506 (33.8) |

Abbreviations: GS, Gleason score; PSA, prostate-specific antigen.

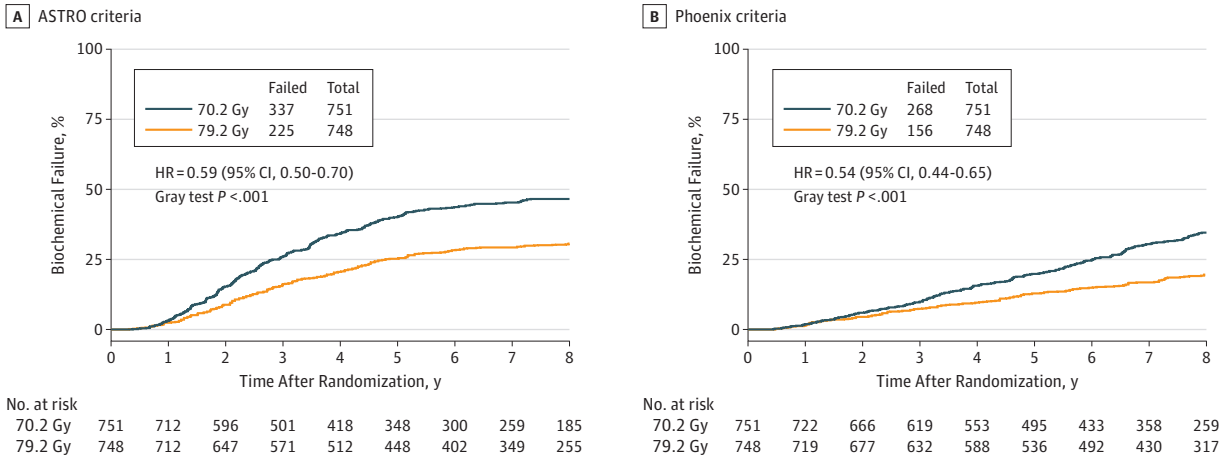
SI conversion factor: PSA level, 1:1 conversion to micrograms per liter.

Figure 2. Overall Survival and Time to Prostate Cancer Mortality After Either Conventional-Dose (70.2 Gy) or High-Dose (79.2 Gy) Radiation Therapy




HR indicates hazard ratio.

Figure 3. Biochemical Failure (American Society for Therapeutic Radiology and Oncology [ASTRO] Consensus Definition and Phoenix Criteria) After Either Conventional-Dose (70.2 Gy) or High-Dose (79.2 Gy) Radiation Therapy




HR indicates hazard ratio.

8-year cumulative incidence of DM was 3% and 6% for the 70.2-Gy arm and 2% and 4% for the 79.2-Gy arm, respectively (HR, 0.65; 95% CI, 0.42-1.01; $P$ = .05) (eFigure 2 in Supplement 2). There was no statistically significant difference between the treatment arms for DMFS (HR, 0.97; 95% CI, 0.81-1.17; $P$ = .78).

Patients in the 70.2-Gy arm were more likely (169 [22.5%]) to undergo a salvage therapy (eg, androgen deprivation, cryosurgery, brachytherapy) than patients in the 79.2-Gy arm (111 [14.8%]; $\chi^2$ $P$ < .001) (eTable 2 in Supplement 2). The 5- and 8-year cumulative incidence of salvage therapy was 15% and 22% for the 70.2-Gy arm and 9% and 14% for the 79.2-Gy arm (HR, 0.63; 95% CI, 0.50-0.80; $P$ < .001) (eFigure 3 in Supplement 2).

## Adverse Events

There were no significant differences in frequency of acute GI or GU toxic effects (**Table 2**). Patients in the 79.2-Gy arm experienced significantly higher rates of late grade 2 or greater GU and GI toxic effects than those in the 70.2-Gy arm (Table 2 and eFigures 4a and 5a in Supplement 2). The 5-year cumulative incidence of late grade 2 or greater GI toxic effects was 15% for the 70.2-Gy arm compared with 21% (HR, 1.39; 95% CI, 1.10-1.77; $P$ = .006) for the 79.2-Gy arm. The 5-year cumulative incidence of late grade 2 or greater GU toxic effects was 7% for the 70.2-Gy arm compared with 12% (HR, 1.59; 95% CI, 1.17-2.16; $P$ = .003) for the 79.2-Gy arm. Time to late GU and GI toxic effects of grade 3 or greater is shown in eFigures 4b and 5b in Supplement 2.

Table 2. Gastrointestinal (GI) and Genitourinary (GU) Toxic Effects[a]

| Toxic Effects | No. (%) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 70.2 Gy | | | | | 79.2 Gy | | | | |
| | Grade 1 | Grade 2 | Grade 3 | Grade 4 | Grade 5 | Grade 1 | Grade 2 | Grade 3 | Grade 4 | Grade 5 |
| **Acute** | **(n = 733)** | | | | | **(n = 728)** | | | | |
| GU[b] | 146 (20) | 113 (15) | 10 (1) | 0 | 0 | 136 (19) | 116 (16) | 10 (1) | 0 | 0 |
| GI[c] | 61 (8) | 33 (5) | 2 (<1) | 0 | 0 | 50 (7) | 50 (7) | 1 (<1) | 0 | 0 |
| **Late** | **(n = 741)** | | | | | **(n = 736)** | | | | |
| GU | 21 (3) | 52 (7) | 15 (2) | 0 | 0 | 16 (2) | 81 (11) | 19 (3) | 3 (<1) | 0 |
| GI | 23 (3) | 93 (13) | 23 (3) | 0 | 1 (<1) | 26 (4) | 119 (16) | 34 (5) | 3 (<1) | 2 (<1) |

[a] Acute toxic effects were graded with National Cancer Institute Common Toxicity Criteria, version 2.0. Late toxic effects were graded with RTOG/European Organisation for the Research and Treatment of Cancer late toxicity criteria.

[b] Acute GU grade 2 or greater toxic effects seen in 17% of the 70.2-Gy group vs 17% of the 79.2-Gy group; $\chi^2$ $P$ = .79.

[c] Acute GI grade 2 or greater toxic effects seen in 5% of the 70.2-Gy group vs 7% of the 79.2-Gy group; $\chi^2$ $P$ = .07.

## Discussion

This randomized clinical trial showed that the OS of men treated for localized intermediate-risk prostate cancer was not improved with radiation dose escalation. This is despite the fact that dose escalation significantly reduced the rates of BF, local progression, and DM. Unlike previous randomized clinical trials evaluating dose escalation,[1-5] this trial, the largest thus far, was powered to detect an OS difference in this patient population. The reduction in biochemical and clinical failure with dose escalation was accompanied by an increase in late grade 2 or greater GI and GU toxic effects.

As in the recently published ProtecT trial from the United Kingdom, it is noteworthy that the rate of prostate cancer mortality in this trial was lower than expected.[19] The ProtecT trial compared management with radical prostatectomy, RT, or active monitoring for patients with low- and intermediate-risk disease. Patients who were treated with RT received 74 Gy conventionally fractionated dose with 3 to 6 months of androgen deprivation therapy (ADT). The prostate cancer mortality was only 1%, with no significant differences between the arms. Despite the attempt to select a patient population with clinically significant intermediate-risk disease, only 3% of all evaluable patients died of prostate cancer. The growing availability of systemic salvage therapies has prolonged the natural history of this disease. Patients experiencing a biochemical or clinical failure may go on to receive several life-prolonging systemic agents, which may negate any clinical advantage from a more effective primary local therapy. Indeed, patients receiving the standard dose were significantly more likely to receive salvage therapy compared with those treated with dose escalation.

A reduction in use of salvage therapies has important implications because the morbidity associated with both local and systemic treatments is substantial. The advantage of avoiding or delaying the adverse effects of these therapies has to be weighed against the increased rate of RT-related morbidity with dose escalation. We have identified physical and clinical factors that are associated with late morbidity that can be used to minimize this risk in selected patients.[7] For example, IMRT is associated with a significant reduction in grade 2 or greater GI and GU toxic effects. Keeping less than 15% of the volume of rectum receiving more than 70 Gy reduces late rectal toxic effects.

In contrast to dose escalation, the use of short-term ADT has improved OS and disease-specific survival in men with intermediate-risk prostate cancer.[20,21] The use of ADT may be particularly relevant for men with intermediate risk with unfavorable features. Zumsteg and Zelefsky[22] proposed a risk classification system that improves the prognostic discrimination of intermediate-risk prostate cancer more than the earlier criteria by D'Amico et al.[23] Patients with a predominant Gleason pattern 4, percentage of positive biopsy cores of 50% or greater, or multiple intermediate risk factors (cT2b-c, PSA level of 10-20 ng/mL, or Gleason score of 7) have a distinctly worse prognosis and benefit from ADT.

Recently, the ASCENDE-RT trial examined dose escalation using low dose rate brachytherapy compared with dose escalation with external-beam RT in patients with high-risk prostate cancer also receiving short-term ADT. While a boost with brachytherapy improved biochemical control, it did not improve clinical or OS but it did increase the rates of grade 2 or greater GU toxic effects.[24] Collectively, dose escalation trials using x-rays, protons, or brachytherapy have improved biochemical outcomes but none have affected OS.

The 15% absolute reduction at 8 years in Phoenix-BF is consistent with other reports of dose escalation from other trial groups. As in the present study, those improvements in biochemical outcomes were accompanied by an increase in morbidity but not an improvement in survival. However, despite the increased risk of adverse effects with high-dose RT in this trial, the risk of severe morbidity (grade ≥3) remains acceptably low. Dose and volume criteria that are associated with grade 2 or 3 GU or GI toxic effects have been previously published.[8] Maintaining the volume of rectum exceeding 70 or 75 Gy to less than 15% and 10%, respectively, reduces the incidence of grade 2 or greater GI toxic effects. No similar threshold dose volume criteria have been identified for GU toxic effects. An article addressing patient-reported outcomes collected as part of this trial is forthcoming.

### Limitations

This trial enrolled a narrow population of patients with intermediate risk features including patients with Gleason score of 6 and a PSA level of 10 to 20 ng/mL or those with a Gleason score of 7 and a PSA less than 15. Whether this can be extrapolated to a broader population is not known. In addition, the accrual and follow-up periods of the trial spanned 6 and 9 years, respectively. In that period, advances in staging, adjustments in grading, and improvements in systemic salvage therapies could influence the survival rate beyond the effect of dose escalation. In addition, there have been improvements in radiation treatment delivery that have decreased the rates of toxic events.

## Conclusions

Dose escalation has several clinical advantages including improved rates of biochemical and clinical cancer control. These benefits do not translate into improved OS. The decision to deliver high radiation dose must be balanced against the risk of morbidity in the individual patient.

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