Randomized Phase III Noninferiority Study Comparing Two Radiotherapy Fractionation Schedules in Patients With Low-Risk Prostate Cancer


See accompanying editorial on page 2323

ABSTRACT

Purpose
Conventional radiotherapy (C-RT) treatment schedules for patients with prostate cancer typically require 40 to 45 treatments that take place from > 8 to 9 weeks. Preclinical and clinical research suggest that hypofractionation—fewer treatments but at a higher dose per treatment—may produce similar outcomes. This trial was designed to assess whether the efficacy of a hypofractionated radiotherapy (H-RT) treatment schedule is no worse than a C-RT schedule in men with low-risk prostate cancer.

Patients and Methods
A total of 1,115 men with low-risk prostate cancer were randomly assigned 1:1 to C-RT (73.8 Gy in 41 fractions over 8.2 weeks) or to H-RT (70 Gy in 28 fractions over 5.6 weeks). This trial was designed to establish (with 90% power and an α of .05) that treatment with H-RT results in 5-year disease-free survival (DFS) that is not worse than C-RT by more than 7.65% (H-RT/C-RT hazard ratio [HR] < 1.52).

Results
A total of 1,092 men were protocol eligible and had follow-up information; 542 patients were assigned to C-RT and 550 to H-RT. Median follow-up was 5.8 years. Baseline characteristics were not different according to treatment assignment. The estimated 5-year DFS was 85.3% (95% CI, 81.9 to 88.1) in the C-RT arm and 86.3% (95% CI, 83.1 to 89.0) in the H-RT arm. The DFS HR was 0.85 (95% CI, 0.64 to 1.14), and the predefined noninferiority criterion that required that DFS outcomes be consistent with HR < 1.52 was met (P < .001). Late grade 2 and 3 GI and genitourinary adverse events were increased (HR, 1.31 to 1.59) in patients who were treated with H-RT.

Conclusion
In men with low-risk prostate cancer, the efficacy of 70 Gy in 28 fractions over 5.6 weeks is not inferior to 73.8 Gy in 41 fractions over 8.2 weeks, although an increase in late GI/genitourinary adverse events was observed in patients treated with H-RT.

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INTRODUCTION

External beam radiotherapy (RT) is commonly used to treat localized prostate cancer. Conventional schedules use 1.8 to 2 Gy per treatment, administered 5 days per week for > 8 to 9 weeks (40 to 45 treatments), for total doses that range from 70 to 81 Gy. Preclinical and clinical research published during the last 15 years has suggested that the sensitivity of prostate cancer to RT is such that hypofractionation—fewer treatments but at a higher dose per treatment—may increase the biologic effective dose and improve patient outcomes. Several observational studies of hypofractionated RT (H-RT) have suggested its safety, but the lack of a randomized comparison with conventional RT (C-RT) has limited inference on the efficacy of this approach. Results from these observational studies have informed the development of several contemporary randomized clinical trials (RCTs) that compare...
C-RT with H-RT. The majority of these studies tested the hypothesis that hypofractionation would improve efficacy.6-9 The published results, however, have not demonstrated increased efficacy with hypofractionation.

In addition to potentially increasing the efficacy of RT, the smaller number of treatments with hypofractionation increases convenience for the patient and decreases use and health care costs. The desire to explore hypofractionation in prostate cancer is analogous to a research paradigm in breast cancer, in which RCTs have now established its safety and noninferiority to C-RT treatment schedules,10-12

In 2004, the Radiation Therapy Oncology Group (RTOG) decided to compare an H-RT treatment schedule with a C-RT schedule in an RCT. Given the enhanced patient convenience and the reduced costs associated with hypofractionation, a noninferiority hypothesis was chosen. The purpose of NRG Oncology RTOG 0415 was to determine whether the efficacy of a hypofractionated treatment schedule was not worse than a conventional schedule in men with low-risk prostate cancer. To our knowledge, this is the first report of this study.

**PATIENTS AND METHODS**

**Trial Design and Participants**

Men age ≥ 18 years with prostate adenocarcinoma were eligible if they met the following criteria: a clinical classification of T1b to T2c (according to American Joint Committee on Cancer staging system, 6th edition),11 a Gleason score of 2 to 6, and a prostate-specific antigen (PSA) < 10. Additional criteria were no nodal or distant metastatic disease, Zubrod performance status < 2, and no prior bilateral orchectomy, chemotherapy, RT, cryosurgery, or definitive surgery for prostate cancer. Patients with another invasive cancer, other than localized basal or squamous cell skin carcinoma, were not eligible unless continually free of that cancer for a minimum of 5 years. Before study entry, evaluation required history and physical examination, including digital rectal examination, and a serum PSA within 180 days before registration. Androgen suppression was not allowed other than as a salvage therapy in the case of prostate cancer recurrence.

After institutional review board approval at each center, participants were recruited at community-based and tertiary medical sites that were members of the RTOG. Membership was established and maintained through a quality control system that was 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.

**Random Assignment**

This was a multicenter, stratified, parallel-group study with 1:1 random assignment approved and sponsored by the US National Cancer Institute. Participants were stratified according to PSA level (< 4 ng/mL vs 4 to 10 ng/mL), Gleason score (2 to 4 vs 5 to 6), and radiation modality (three-dimensional conformal RT [3D-CRT] vs intensity-modulated RT [IMRT]). Participants were then randomly assigned by using the permuted block method to either a C-RT treatment schedule (73.8 Gy in 41 fractions over 8.2 weeks) or to an H-RT schedule (70 Gy in 28 fractions over 5.6 weeks).

**Treatment**

RT was to be initiated within 6 weeks of registration, using either 3D-CRT or IMRT. Daily field alignment with intraprostatic fiducial markers or other means to the prostate was required. The clinical target volume was the prostate as identified on computed tomography (CT) scan at the time of treatment planning simulation. A 3D expansion of the clinical target volume by 4 to 10 mm was used to create the planning target volume (PTV). Participants were assigned either to 73.8 Gy (C-RT) or to 70 Gy (H-RT) fraction, which was the minimum dose to ≥ 98% of the PTV. Adherence to this specification required that the maximum dose to the PTV could not exceed the prescription dose by more than 7%. Maximum dose > 7% but < 10% was a minor, acceptable variation, and ≥ 10% was a major, unacceptable variation. Dose constraints to normal tissues (bladder, rectum, penile bulb) as listed in the protocol are available in the Data Supplement.

No attempt was made to treat the seminal vesicles or pelvic lymph nodes. All RT plans were submitted as digital DICOM files to the Image-guided Therapy quality assurance Center for central quality assurance review. CT scans, target volumes, organ-at-risk contours, radiation dose distributions, dose volume histograms, and dose statistics were reviewed for compliance with protocol guidelines.

**Patient Assessment and End Points**

Adverse event monitoring occurred weekly during RT. History and physical examination, assessment of adverse events, and PSA measurement were performed every 3 months for the first 2 years, every 6 months for the next 3 years, and annually thereafter. Any findings noted between scheduled evaluations were also recorded. Prostate biopsy, radionuclide bone scan, CT, or magnetic resonance imaging was used to investigate clinical findings or serum PSA elevation. These same tests, with history, examination, and serum PSA, were to be performed if there was evidence of disease progression.

The primary study aim was to compare the disease-free survival (DFS) rate between the two treatment arms. DFS events included local progression, distant metastatic progression, biochemical recurrence as defined by the RTOG Phoenix definition,12 or death from any cause. Patients who experienced second primary cancers remained under observation for DFS events. Death was attributed to prostate cancer if certified primarily as such, disease progressed on salvage androgen suppression, or death resulted from an adverse effect of therapy.

Additional end points with specified noninferiority hypotheses were overall survival, prostate cancer–specific survival, time to local progression, and time to biochemical recurrence. The frequency of adverse events as defined by National Cancer Institute Common Terminology Criteria for Adverse Events (version 3) were compared between treatment arms. This report reflects information reported to the NRG Oncology Statistics and Data Management Center as of March 31, 2015.

**Statistical Methods**

Sample size was determined by assuming an 85% 5-year DFS with C-RT. The trial was designed to establish with 90% power and an α of .05 that H-RT results in a 5-year DFS that is not lower than C-RT by more than 7.65% (hazard ratio [HR] < 1.52). The noninferiority margin was chosen to be approximately one half of the absolute difference in 5-year DFS observed in contemporary superiority trials of dose escalation (15%) in similar patients. Under assumed failure rates and guarding against a 10% ineligible or lack of data rate, the final targeted accrual was 1,067 patients, with definitive analysis to occur after 238 DFS events. The trial was expected to accrue 20 patients per month and to reach primary end point reporting at 11 years from the start of accrual. Interim reports were provided to the external Data Monitoring Committee every 6 months. Three interim analyses were planned after 60, 120, and 179 DFS events for early rejection of both the null hypothesis and the alternative hypothesis. The boundaries for rejecting the null hypothesis were based on a Lan and DeMets α spending function approach with properties similar to the O'Brien-Fleming boundary.13 The futility testing used the method by Harrington et al14 of testing to reject the alternative. At the third interim analysis, the Data Monitoring Committee recommended that results of the trial be disclosed. On the basis of the event information at that time
(185 [78%] of 238 events required for definitive analysis), stopping to reject the null hypothesis of inferiority required a test statistic $P$ value of $\leq .011$, and this condition was satisfied.

All eligible patients with follow-up were included and analyzed according to assignment (modified intent-to-treat analysis), with time-to-event duration originating at random assignment. Overall survival and DFS distributions were calculated using the Kaplan-Meier method. The cumulative incidence estimator was used for all other end points to account for competing risks. Treatment efficacy for DFS and other end points were tested by comparing cause-specific hazards with the log-rank statistic. Noninferiority hypotheses for each secondary end point were defined in the study protocol. HRs with 95% CI were computed using the Cox proportional hazards regression model for the end point–specific hazard. Frequency distributions of grade (0 to 5) for selected adverse events were compared using $\chi^2$ tests. To evaluate the differences in risk of grade 2 or 3 events by treatment arm, 2 $\times$ 2 subtables were formed and relative risk (RR) estimates with 95% CIs were computed. Median follow-up time was computed using the Kaplan-Meier estimate of time to last follow-up date, with death considered the censoring event (reverse Kaplan-Meier method).

### RESULTS

#### Demographic Characteristics

Between April 2006 and December 2009, 1,115 participants were enrolled as outlined in Figure 1, and 23 were excluded from analysis (16 who underwent treatment with C-RT and seven with H-RT). Baseline characteristics of 1,092 analyzable participants with follow-up are listed in Table 1. The median age was 67 years and the median pretreatment PSA was 5.4 ng/mL. Among patients, > 90% had no physical limitations (Zubrod performance score, 0). Baseline characteristics were well balanced, with no substantial between-group differences.

### Radiation Treatment Delivery

Of 1,092 eligible patients, 1,079 received RT, and 13 patients (eight from the C-RT arm and five from H-RT) received no RT, in most cases because of refusal. Of the 1,079 patients who were treated with RT, 1,030 (98%) were treated according to protocol or with acceptable variation. There were no differences in compliance according to treatment assignment.

#### Outcomes

Study end points and between-group comparisons are listed in Table 2. Median follow-up duration was 5.8 years. At the time of analysis, there were 185 DFS events; 99 in the C-RT arm and 86 in the H-RT arm. The estimated 5-year DFS was 85.3% (95% CI, 81.9 to 88.1) in the C-RT arm and 86.3% (95% CI, 83.1 to 89.0) in the H-RT arm (Fig 2). The HR comparing DFS between the two arms

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Fig 1. CONSORT diagram. Enrollment, random assignment, and follow-up of the study participants. C-RT, conventional radiotherapy; H-RT, hypofractionated radiotherapy; PSA, prostate-specific antigen.
The observed early (within 90 days of RT completion) and late GI or genitourinary (GU) adverse events according to treatment assignment are provided in Table 3. No differences in early GI or GU adverse events were observed. Late grade 2 and 3 GI adverse events were approximately 60% more likely in men who were assigned to treatment with H-RT (RR, 1.55 to 1.59). Similarly, late grade 2 and 3 GU adverse events were more likely in men assigned to treatment with H-RT (RR, 1.31 to 1.56). No differences in more severe events were observed.

Additional protocol-specified clinical end points included local progression (seven patients in the C-RT arm, two patients in the H-RT arm), and prostate cancer–specific survival (two deaths in the C-RT arm, one death in the H-RT arm). As a result of the low frequency of these events, additional analyses are not presented.

Adverse Events

The sensitivity of prostate cancer to the RT dose administered at each treatment session has been the subject of considerable controversy and intense interest since a provocative commentary by Brenner and Hall19 was published in 1999. Soon afterward, investigators designed RCTs on the basis of the hypothesis that a higher dose per treatment, that is, hypofractionated external RT, would increase the efficacy of RT compared with conventionally delivered external RT. The results reported to date have not fulfilled that hypothesis.8,20 Rather than improving the efficacy, albeit with an increase in late GU and GU adverse effects. Our results indicate that the shorter course provides similar efficacy, albeit with an increase in late GI and GU adverse events.

At the time of analysis, 100 men had died; 51 in the C-RT arm and 49 in the H-RT arm. The estimated 5-year overall survival was 93.2% (95% CI, 90.7 to 95.1) in the C-RT arm and 92.5% (95% CI, 89.9 to 94.5) in the H-RT arm. The HR comparing overall survival between the two arms was 0.95 (95% CI, 0.64 to 1.41). The protocol specified noninferiority criteria was met (HR > 1.54 rejected; P = .008). The most frequent causes of death were cardiovascular disease and second cancers.

DISCUSSION

The sensitivity of prostate cancer to the RT dose administered at each treatment session has been the subject of considerable controversy and intense interest since a provocative commentary by Brenner and Hall19 was published in 1999. Soon afterward, investigators designed RCTs on the basis of the hypothesis that a higher dose per treatment, that is, hypofractionated external RT, would increase the efficacy of RT compared with conventionally delivered external RT. The results reported to date have not fulfilled that hypothesis.8,20 Rather than improving the efficacy of RT, the current trial was designed to demonstrate that a shorter, more convenient treatment schedule could be accomplished without compromising cure or causing additional adverse effects. Our results indicate that the shorter course provides similar efficacy, albeit with an increase in late GI and GU adverse events.
This trial is unique in that it focused exclusively on patients with low-risk prostate cancer, using RT alone—androgen suppression was not allowed. As such, this trial complements other research yet provides unique findings with generalizability and immediate relevance. It was developed coincident with a debate about the use of early intervention compared with active surveillance for this group of patients. On the basis of what is known about prostate cancer–specific mortality in low-risk disease, a noninferiority design was a prudent use of resources. A noninferiority trial is typically warranted when an investigational treatment is hypothesized to have efficacy that is comparable to the standard treatment, but with safety, convenience, cost, and/or other advantages.

### Fig 2. Estimates of disease-free survival (DFS) according to treatment assignment. The hazard ratio (HR) comparing DFS between the two arms (hypofractionated radiotherapy/ conventional radiotherapy) is 0.85 (95% CI, 0.64 to 1.14). The prespecified noninferiority criterion was met (null hypothesis HR > 1.52 rejected; P < .001). 3D-CRT, three-dimensional conformal radiotherapy; IMRT, intensity-modulated radiotherapy.

<table>
<thead>
<tr>
<th>Time Since Random Assignment (years)</th>
<th>73.8 Gy</th>
<th>70.0 Gy</th>
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<tr>
<td>1</td>
<td>542</td>
<td>550</td>
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<td>2</td>
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<td>6</td>
<td>387</td>
<td>395</td>
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<td>7</td>
<td>212</td>
<td>225</td>
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<tr>
<th>No. of Patients</th>
<th>Fail</th>
<th>Censored</th>
<th>HR (95% CI)</th>
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<tr>
<td>3D-CRT/IMRT</td>
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<tr>
<td>73.8 Gy</td>
<td>542</td>
<td>99</td>
<td>0.85 (0.64 to 1.14)</td>
</tr>
<tr>
<td>70.0 Gy</td>
<td>550</td>
<td>86</td>
<td>Referent</td>
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</tbody>
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### Fig 3. Cumulative incidence of biochemical recurrence according to treatment assignment. The hazard ratio (HR; hypofractionated radiotherapy [H-RT]/conventional radiotherapy [C-RT]) comparing biochemical recurrence between the two arms was 0.77 (95% CI, 0.51 to 1.17), and the protocol-specified noninferiority criterion was met (H-RT/C-RT HR > 1.67 rejected; P < .001). 3D-CRT, three-dimensional conformal radiotherapy; IMRT, intensity-modulated radiotherapy.

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<th>70.0 Gy</th>
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<td>7</td>
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<tr>
<td>70.0 Gy</td>
<td>550</td>
<td>39</td>
<td>Referent</td>
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These findings have important implications for men with low-risk prostate cancer who are considered for external beam RT. If disease control is similar, reducing the number of treatments from 41 to 28 and reducing the duration of therapy by 2.5 weeks (a nearly one-third reduction) provides greater patient convenience and reduced cost. The observed increase in late GI and GU adverse events in patients assigned to treatment with H-RT, however, suggests that increased convenience leads to more treatment-related toxicity. Previous randomized trials that used conventional fractionation have demonstrated that dose escalation decreases biochemical recurrence, with an increase in GI toxicity of a magnitude similar to that observed in this study.\(^2,26\) Despite the increase in toxicity, dose escalation has become the standard of care. It remains to be seen whether the specialty will accept an increase in toxicity without an increase in efficacy. Several patient-reported outcomes, including health-related quality of life, anxiety, and depression, were collected as a component of this study but have not been analyzed to date. It will be of great interest to determine whether patients themselves report differences according to assigned treatment.

The increased late toxicity after treatment with H-RT in this study is somewhat surprising as most of the RCTs have not observed excess GI and GU toxicity with hypofractionation,\(^2,23\) although the power of these studies to detect a small difference is limited. Prior work (RTOG 9406) has suggested that an increase from 1.8 Gy to 2 Gy may increase toxicity,\(^27\) and we intend to perform exploratory analyses in the future to examine whether dose-volume relationships exist when the fraction size is further increased to 2.5 Gy. We also intend to examine whether the use of IMRT has any effect on late toxicity compared with 3D-CRT. The only study that reported excess toxicity with hypofractionation was the Pollack trial, and this effect was only observed for GU toxicity in men with preexisting urinary dysfunction. We did collect baseline information on urinary function, and we intend to complete an exploratory analysis in the near future.

Some design elements of this trial may be criticized. First, although the noninferiority margin was prespecified, some may view the margin (7.5% absolute difference or HR < 1.52) as too great. The observed HR of 0.85 (95% CI, 0.64 to 1.14) for DFS and 0.77 (95% CI, 0.51 to 1.17) for biochemical recurrence favors the hypofractionated regimen and should mitigate concerns that it is actually worse than the conventional regimen. Second, some may contend that the prescription dose in the conventional arm was too low, but this dose was specified such that > 98% of the prostate received \(\geq 73.8\) Gy. Because the protocol allowed \(\pm 7\%\) inhomogeneity, portions of the prostate received doses > 76 Gy. A recent analysis of > 12,000 men with low-risk prostate cancer found no evidence that doses > 75.6 Gy improve overall survival.\(^28\) Perhaps the most important criticism is that many of these men with low-risk prostate may not need any treatment at all. Active surveillance is an appropriate initial strategy for men with low-risk disease and has increased in use during the last 5 years;\(^29\) however, a significant proportion of men with low-risk disease still opt for definitive treatment even today, and these results should inform those who elect external beam RT.\(^29\)

This trial includes men with low-risk disease only; therefore, these results should not be extrapolated to men with intermediate- or high-risk disease. It is important to remember that the PTV included the prostate only; the seminal vesicles and pelvic lymph nodes were not irradiated. Two other noninferiority trials that have completed accrual include men with intermediate- and high-risk disease treating larger volumes, and the results are expected soon.\(^20\) It is also important to note that all participants had low-risk disease and were allocated to immediate intervention. It may not be appropriate to extend these results to men who progress beyond low-risk disease after a period of active surveillance, as evidence is lacking in this context.

In conclusion, the results of this trial demonstrate that in men with low-risk prostate cancer, the efficacy of 70 Gy delivered in 28 fractions over 5.5 weeks is not inferior to 73.8 Gy delivered in 41 fractions over 8.25 weeks, although an increase in late grade 2 and 3 GI and GU adverse events was observed.

### Table 3. Early and Late GI and GU Adverse Events According to Treatment Assignment

<table>
<thead>
<tr>
<th>Adverse Event Class</th>
<th>3D-CRT/IMRT 73.8 (n = 534)</th>
<th>3D-CRT/IMRT 70 Gy (n = 545)</th>
<th>RR (95% CI)*</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum grade of early GI toxicity</td>
<td>None reported 327 (61.2)</td>
<td>311 (57.1)</td>
<td>—</td>
<td>.54†</td>
</tr>
<tr>
<td>1</td>
<td>152 (28.5)</td>
<td>176 (32.3)</td>
<td>1.10 (0.74 to 1.63)</td>
<td>.68</td>
</tr>
<tr>
<td>2</td>
<td>52 (9.7)</td>
<td>54 (9.9)</td>
<td>1.03 (0.73 to 1.46)</td>
<td>.85</td>
</tr>
<tr>
<td>3</td>
<td>3 (0.6)</td>
<td>3 (0.6)</td>
<td>0.58 (0.61 to 1.36)</td>
<td>.2</td>
</tr>
<tr>
<td>4</td>
<td>0 (0.0)</td>
<td>2 (0.3)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Maximum grade of late GI toxicity</td>
<td>None reported 204 (38.2)</td>
<td>206 (37.8)</td>
<td>—</td>
<td>.83†</td>
</tr>
<tr>
<td>1</td>
<td>185 (34.6)</td>
<td>192 (35.2)</td>
<td>1.03 (0.82 to 1.28)</td>
<td>.663</td>
</tr>
<tr>
<td>2</td>
<td>132 (24.7)</td>
<td>129 (23.7)</td>
<td>0.99 (0.82 to 1.21)</td>
<td>.95</td>
</tr>
<tr>
<td>3</td>
<td>13 (2.4)</td>
<td>18 (3.3)</td>
<td>1.36 (0.67 to 2.74)</td>
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<tr>
<td>4</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>—</td>
<td>—</td>
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<tr>
<td>Maximum grade of late GU toxicity</td>
<td>None reported 350 (65.7)</td>
<td>300 (54.4)</td>
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<td>.002†</td>
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<tr>
<td>1</td>
<td>108 (20.3)</td>
<td>121 (22.3)</td>
<td>1.08 (0.86 to 1.34)</td>
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<td>2</td>
<td>61 (11.4)</td>
<td>99 (18.3)</td>
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<td>13 (2.4)</td>
<td>22 (4.1)</td>
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<td>1 (0.2)</td>
<td>0 (0.0)</td>
<td>—</td>
<td>—</td>
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<tr>
<td>Maximum grade of early GU toxicity</td>
<td>None reported 255 (47.8)</td>
<td>227 (41.9)</td>
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<td>.06†</td>
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<td>1</td>
<td>157 (29.4)</td>
<td>154 (28.4)</td>
<td>1.03 (0.78 to 1.35)</td>
<td>.74</td>
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<tr>
<td>2</td>
<td>109 (20.5)</td>
<td>142 (26.2)</td>
<td>1.31 (1.07 to 1.61)</td>
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<td>3</td>
<td>11 (2.1)</td>
<td>19 (3.5)</td>
<td>1.56 (0.76 to 3.18)</td>
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<tr>
<td>4</td>
<td>1 (0.2)</td>
<td>0 (0.0)</td>
<td>—</td>
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</table>

NOTE. Data are given as No. (%) unless otherwise noted. Abbreviations: 3D-CRT, three-dimensional conformal radiotherapy; GU, genitourinary; IMRT, intensity-modulated radiotherapy; RR, relative risk.

*RR, 95% CI, and P for comparison by treatment group of \(\geq\) grade 2 versus < grade 2 and \(\geq\) grade 3 versus < grade 3.

†Test of difference in overall frequency distribution of grade by treatment group.

Disclosures provided by the authors are available with this article at www.jco.org.
Hypofractionation for Prostate Cancer

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GLOSSARY TERMS

**hypofractionation**: fractionation scheme for delivery of ionizing radiation in which the dose per fraction is > 2 Gy or radiation treatment in which the total dose of radiation is divided into large doses and treatments are given less than once a day. Also called hypofractionated radiation therapy.

**intensity-modulated radiation therapy**: radiation treatment using beams with nonuniform fluence profiles that shape the dose distribution in the target volume and adjacent normal structures. Beam modulation is typically achieved via multileaf collimators or custom-milled compensators to achieve the appropriate fluence profiles calculated by inverse optimization algorithms. The radiation beam is divided into beamlets of varying intensity such that the sum from multiple beams via inverse planning results in improved tumor targeting and normal tissue sparing. A technique of radiation therapy delivery in which the intensity of each beamlet of radiation coming from a specific angle can be adjusted to provide a desired dose distribution when the doses delivered from all beamlets are added from a single angle and from all dose delivery angles. An advanced type of high-precision radiation therapy, which aims to improve the coverage of the radiation therapy target and/or minimize radiation dose to surrounding normal tissue.

**prostate-specific antigen (PSA)**: a protein produced by cells of the prostate gland. The blood level of PSA is used as a tumor marker for men who may be suspected of having prostate cancer. Most physicians consider 0 to 4.0 ng/mL to be the normal range. Levels of 4 to 10 ng/mL and 10 to 20 ng/mL are considered slightly and moderately elevated, respectively. PSA levels have to be complemented with other tests to make a firm diagnosis of prostate cancer.
Hypofractionation for Prostate Cancer

AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Randomized Phase III Noninferiority Study Comparing Two Radiotherapy Fractionation Schedules in Patients With Low-Risk Prostate Cancer

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