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ORIGINAL REPORT

Randomized Trial of a Hypofractionated Radiation Regimen for the Treatment of Localized Prostate Cancer

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ABSTRACT

Purpose
Men with localized prostate cancer often are treated with external radiotherapy (RT) over 8 to 9 weeks. Hypofractionated RT is given over a shorter time with larger doses per treatment than standard RT. We hypothesized that hypofractionation versus conventional fractionation is similar in efficacy without increased toxicity.

Patients and Methods
We conducted a multicenter randomized noninferiority trial in intermediate-risk prostate cancer (T1 to 2a, Gleason score ≤ 6, and prostate-specific antigen [PSA] 10.1 to 20 ng/mL; T2b to 2c, Gleason ≤ 6, and PSA ≤ 20 ng/mL; or T1 to 2, Gleason = 7, and PSA ≤ 20 ng/mL). Patients were allocated to conventional RT of 78 Gy in 39 fractions over 8 weeks or to hypofractionated RT of 60 Gy in 20 fractions over 4 weeks. Androgen deprivation was not permitted with therapy. The primary outcome was biochemical-clinical failure (BCF) defined by any of the following: PSA failure (nadir + 2), hormonal intervention, clinical local or distant failure, or death as a result of prostate cancer. The noninferiority margin was 7.5% (hazard ratio, < 1.32).

Results
Median follow-up was 6.0 years. One hundred nine of 608 patients in the hypofractionated arm versus 117 of 598 in the standard arm experienced BCF. Most of the events were PSA failures. The 5-year BCF disease-free survival was 85% in both arms (hazard ratio [short *v* standard], 0.96; 90% CI, 0.77 to 1.2). Ten deaths as a result of prostate cancer occurred in the short arm and 12 in the standard arm. No significant differences were detected between arms for grade ≥ 3 late genitourinary and GI toxicity.

Conclusion
The hypofractionated RT regimen used in this trial was not inferior to conventional RT and was not associated with increased late toxicity. Hypofractionated RT is more convenient for patients and should be considered for intermediate-risk prostate cancer.

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INTRODUCTION

External beam radiotherapy (RT) is a treatment option for men with localized prostate cancer and is commonly used alone for patients with intermediate-risk disease.[1] Toward the end of the 20th century, hypofractionated RT, given over a shorter time than standard RT with larger doses per fraction, was proposed for prostate cancer.[2,3] In 2005, we reported the results of a Canadian trial that compared conventional RT (66 Gy in 33 fractions) with hypofractionated RT (52.5 Gy in 20 fractions) in prostate cancer.[4] The rationale for the shorter treatment was increased patient convenience and optimized use of resources. The study was also supported by data from the linear-quadratic model of radiation dose response that prostate cancer exhibits a low α/β-value, which suggests that RT of fewer and larger fractions would increase therapeutic efficacy.[5,6] The total doses of radiation in both arms were suboptimal by current standards and associated with high rates of recurrence.[4]

In recent years, three-dimensional conformal RT or intensity-modulated RT delivered with daily image guidance onto the prostate gland have resulted in improved RT precision. Thus, by avoiding radiosensitive normal tissues, such as the

ASSOCIATED CONTENT

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bladder and rectum, substantially higher doses of RT can be given with reduced treatment-related toxicity.[7,8] External RT for localized prostate cancer typically delivers 37 to 42 fractions of 1.8 to 2.0 Gy/fraction given 5 days/week over 7.5 to 8.5 weeks.[9-12]

Concerns with hypofractionated RT for prostate cancer are increased toxicity and reduced tumor control. Modern RT techniques may potentially be used to deliver hypofractionated RT without increased toxicity. We hypothesized that with an $\alpha/\beta \leq 1.5$, a moderately hypofractionated RT regimen of 60 Gy in 20 fractions over 4 weeks would demonstrate noninferior disease control versus a standard regimen of 78 Gy in 39 fractions over 8 weeks for men with intermediate-risk prostate cancer. We further hypothesized that there would be no increase in treatment-related toxicity if highly conformal image-guided external beam radiation techniques were used.

PATIENTS AND METHODS

Study Design

A randomized noninferiority trial was conducted in men with intermediate-risk prostate cancer at 27 centers (14 in Canada, 12 in Australia, and one in France). The study protocol was approved by the institutional review board at each center.

Patients

Eligible patients had a histologic diagnosis of intermediate-risk carcinoma of the prostate (T1 to 2a, Gleason score ≤ 6, and prostate-specific antigen [PSA] = 10.1 to 20 ng/mL; T2b to 2c, Gleason ≤ 6, and PSA ≤ 20 ng/mL; or T1 to 2, Gleason = 7, and PSA ≤ 20 ng/mL) without evidence of disease spread to the lymph nodes or bone. Exclusion criteria were prostate cancer diagnosis > 6 months before study entry, previous therapy for prostate cancer other than biopsy or transurethral resection, > 12 weeks of hormone therapy for treatment of prostate cancer, any malignancy diagnosed within 5 years of entry except for nonmelanoma skin cancer, radiation treatment plan that did not meet dose constraints for the hypofractionation arm of the trial, and previous pelvic RT or inflammatory bowel disease. Written informed consent was obtained from patients before random assignment.

Random Assignment

Random assignment was performed centrally through the Ontario Clinical Oncology Group coordinating center in Hamilton, Ontario, Canada. Random assignment was stratified by the use of neoadjuvant hormone therapy (yes/no); risk of seminal vesicle involvement ($< 15\%$, $> 15\%$) calculated by Partin's risk nomogram,[13] which uses pretreatment PSA, Gleason score, and T category; and treatment center. A computer-generated randomization schedule assigned patients to either the shorter hypofractionated radiation group or the standard radiation group within concealed permuted block sizes of four.

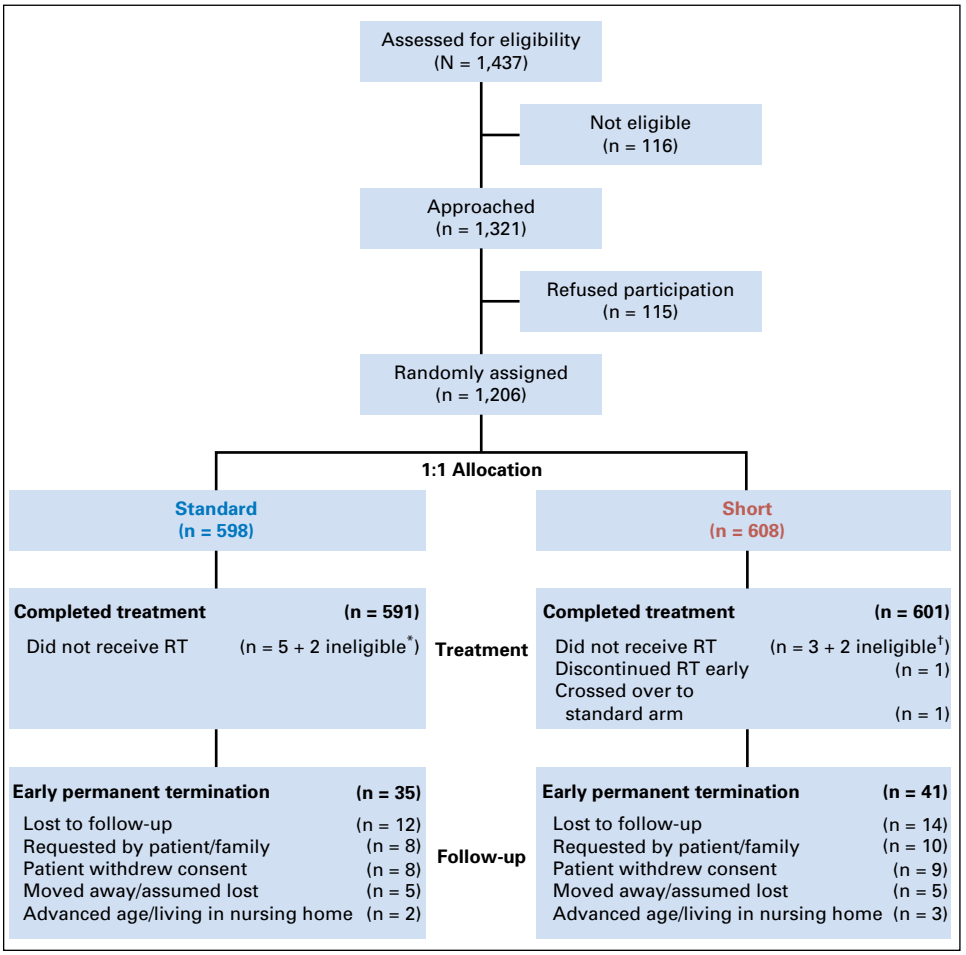

Fig 1. CONSORT diagram. *One patient had a previous cancer; in one patient, radiotherapy (RT) dose constraints were exceeded. †Both found after random assignment not to be of intermediate risk.

Radiation Treatment

Patients were allocated to receive 60 Gy in 20 fractions 5 days/week over 4 weeks to the prostate or 78 Gy in 39 fractions 5 days/week over 7 to 8 weeks. Androgen deprivation therapy was not permitted. Treatment was to a risk-adapted clinical target volume (CTV) defined as the prostate gland alone if the risk of seminal vesicle involvement was < 15% by Partin's nomogram.[13] The CTV was expanded to include the distal 10 mm of the seminal vesicles for patients with an involvement risk > 15%. A non-uniform planning target volume was created by expanding the CTV 7 mm posteriorly and 10 mm in other directions. The CTV was planned to receive at least 100% of the intended dose and the planning target volume at least 95%.

Patients were planned and treated each day with the use of a bowel and bladder preparation protocol. Centers declared at accreditation the radiation treatment technique that they would use for the trial. Intensity-modulated RT was encouraged, although three-dimensional conformal RT was permitted provided that all protocol-mandated normal tissue dose constraints were met. The delineation for normal tissue structures and the dose constraints used for the target and normal tissues are described in the Appendix (online only).

Treatment was delivered with high-energy linear accelerators and daily image guidance onto the target. Permitted image guidance techniques included implanted fiducial markers, cone beam computed tomography, and ultrasound guidance. Before activation, all participating centers underwent accreditation that required submission of a facility questionnaire, description of institutional quality control and image guidance processes, and successful planning of five test cases for the 60-Gy treatment arm. All cases were required to undergo real-time central RT review before the third treatment fraction.[14]

Follow-Up

Patients were followed according to a prescribed schedule. Toxicity assessments were performed weekly during RT followed by telephone assessments to week 14 and again at follow-up visits scheduled every 6 months after random assignment; PSAs were collected starting with the 6-month post–random assignment visit; and health-related quality of life (HRQoL) assessments were performed at baseline, 24 months, and 48 months after random assignment.

Outcomes

The primary outcome was biochemical-clinical failure (BCF) defined as the first occurrence of any of the four outcomes: PSA failure, hormonal intervention, clinical evidence of failure (local or distant), and death as a result of prostate cancer.[4] At the time of protocol development in 2004, PSA failure that was based on the American Society of Therapeutic Radiology and Oncology (ASTRO) definition was the standard approach (post-treatment nadir plus three consecutive PSA rises, with backdating the time to failure).[15] Secondary outcomes were BCF that used the Phoenix definition (nadir plus a ≥ 2 ng/mL increase),[16] prostate cancer–specific mortality, genitourinary (GU) and GI toxicity assessed by the Radiation Therapy Oncology Group toxicity score administered by the physician or clinical designee, and HRQoL based on the Expanded Prostate Cancer Index Composite[17] and the 12-Item Short Form Health Survey.[18] The results of the comparison of HRQoL between treatment groups will be presented in a subsequent manuscript.

The independent Data Safety Monitoring Board (DSMB) was to perform a single interim analysis at 3 years after study commencement. It would recommend early discontinuation for safety if there was greater late grade ≥ 3 bladder or rectal toxicity in the short arm or for efficacy if the hazard ratio (HR) for BCF (short arm relative to standard arm) exceeded 1.0. In either case, a one-sided $P < .001$ would trigger the recommendation.

In January 2016, the study steering committee wrote to the DSMB to request that the definition of PSA failure be switched from the ASTRO definition to the Phoenix definition and that PSA failure on the basis the ASTRO definition be relegated to a secondary outcome measurement for BCF. This request was made without knowledge of the outcome data. The main reason was that in almost all contemporary prostate cancer hypofractionation trials, the Phoenix definition was used.[12,19-22] In the original study protocol, we had recognized that the definition of PSA failure could change and that the definition current at the time of the analysis should be used. At the time of the DSMB letter, the study was on track for the prespecified number of BCF events with the ASTRO definition. By switching to the Phoenix definition, the power to support noninferiority could be jeopardized because fewer PSA failures would be expected. Nonetheless, the steering committee asked the DSMB that the analysis proceed in March 2016 because the study funding was finishing, and the results of three other hypofractionated RT trials in prostate cancer had been presented.[12,19,21] The DSMB agreed with both requests. PSA failures were determined using computer algorithms.

Statistical Analysis

In the sample size determination, we based the HR (experimental relative to the standard regimen) on the 5-year BCF probability. From the results of previous studies,[23-25] we estimated 30% BCF at 5 years in the standard arm. We postulated that patients would be accrued over 4 years and that the last patient would be followed for at least 5 years. For a noninferiority design, we estimated that with 1,144 patients (572 per

Table 1. Baseline Characteristics by Treatment Group

Characteristic	Treatment Group, No. (%)	
	Short	Standard
No. of subjects	608	598
Age (years)		
Median (IQR)	72 (68-75)	71 (67-75)
Range	48-87	50-88
Strata: neoadjuvant hormone therapy, risk of seminal vesicle involvement (%)		
Yes, ≤ 15	28 (5)	22 (4)
Yes, > 15	9 (1)	9 (2)
No, ≤ 15	529 (87)	526 (88)
No, > 15	42 (7)	41 (7)
PSA, ng/mL		
< 5	103 (17)	116 (19)
5-10	302 (50)	303 (51)
10.1-20	203 (33)	179 (30)
Gleason score		
3 + 3	57 (9)	56 (9)
3 + 4	382 (63)	380 (64)
4 + 3	169 (28)	162 (27)
Clinical stage		
T1a, T1b	4 (< 1)	3 (< 1)
T1c	328 (54)	308 (52)
T2a	163 (27)	159 (27)
T2b	73 (12)	91 (15)
T2c	40 (7)	37 (6)
Myocardial infarction history	57 (9)	72 (12)
Treatment history*		
Hypertension that required medication	360 (59)	327 (55)
Diabetes	99 (16)	107 (18)
Bowel disorder	21 (3)	19 (3)
Bladder disorder	14 (2)	15 (3)
Medical history within 5 years*		
Cardiac	337 (55)	342 (57)
Respiratory	73 (12)	59 (10)

Abbreviations: IQR, interquartile range; PSA, prostate-specific antigen.
*Subjects may fit into more than one category.

arm), 370 BCF events overall, and a one-sided α of 5%, we would have 85% power to demonstrate that the experimental arm would be no worse than the standard arm by a maximally tolerable HR of 1.32 (corresponding to a 7.5% noninferiority margin). By allowing 5% for loss, noncompliance, and death unrelated to prostate cancer, a minimum of 1,204 patients would need to be recruited. This 7.5% noninferiority margin at 5 years was the same as that used in our earlier study.[4]

The primary assessment of noninferiority was based on the estimated HR with respect to BCF using a Cox proportional hazards regression model[26] with treatment as the sole predictor adjusted for the stratification factors neoadjuvant hormone therapy, risk of seminal vesicle involvement, and center. For declaration of noninferiority, the upper limit of the two-sided 90% CI needed to be < 1.32.

All time-to-event data were summarized using Kaplan-Meier methods, and comparisons between treatment arms were undertaken using stratified Cox proportional hazards regression modeling. The assumption of proportional hazards was tested using the Cox method.[26] Toxicity (acute and long term) was compared using Mantel-Haenszel tests that adjusted for the clinical stratification factors. For overall survival and toxicity outcomes, statistical significance was based on a two-sided α of 5%. The full analysis set that adhered to the intention-to-treat principle and SAS 9.4 statistical software (SAS Institute, Cary, NC) were used for all analyses.

Role of the Funding Source

The Canadian Institutes for Health Research provided a grant-in-aid to the investigators that supported coordination and data management by the Ontario Clinical Oncology Group and data collection at the study sites. The funder played no role in the study design; data collection, analysis, and interpretation; and writing of the manuscript. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

RESULTS

Between May 26, 2006, and November 9, 2011, 1,206 patients at 27 centers (14 in Canada, 12 in Australia, and one in France) were randomly assigned (608 to the hypofractionated RT group [short arm] and 598 to the control RT group [standard arm]). Twelve patients received no RT (five in the short arm and seven in the standard arm). In the short arm, one patient received standard RT, and one missed the last four fractions. Overall, 76 patients were terminated early from the study (41 [6.7%] in the short arm and 35 [5.9%] in the standard arm; Fig 1). Median follow-up in both arms was 6.0 years (interquartile range, 4.9 to 7.3 years), and the maximum was 10 years. The baseline characteristics were comparable between groups (Table 1). The patients were predominantly elderly (median age, 71 years), 82% had PSA ≥ 5 ng/mL, 63% had 3 + 4 Gleason scores, and 79% had T1c to T2a disease.

As a first event, 109 of 608 patients in the short arm compared with 117 of 598 in the standard arm experienced a BCF. The BCF event types are listed in Table 2; most were PSA failure. The 5-year BCF disease-free survival was 85% (95% CI, 82% to 88%) in both arms (Fig 2). The HR (short *v* standard) adjusted on stratification factors was 0.96 (90% CI, 0.77 to 1.20). Regardless of the BCF definition, the hypofractionated regimen was found to be noninferior to the standard regimen (Appendix).

There were 154 deaths in the cohort (76 in the short arm and 78 in the standard arm). Overall, 10 deaths as a result of prostate cancer were observed in the short arm compared with 12 in the standard arm (HR, 0.76; 95% CI, 0.32 to 1.82; Fig 3).

Toxicity data were available for all patients. GU toxicities (Table 3) were similar in both treatment arms. In the acute period, only 4% of patients in both arms had grade ≥ 3 GU toxicity; in the late period, 3.0% of patients in the standard arm and 2.1% in the short arm experienced grade ≥ 3 toxicity.

For GI toxicities (Table 4), the proportion of patients with acute grade ≥ 3 toxicity was low in both arms. Late grade ≥ 3 toxicity was not significantly different between groups, but a trend toward higher levels in the standard arm ($P = .10$) was observed. A significant increase in acute grade ≥ 2 toxicity occurred in the short arm ($P = .003$); conversely, for late grade ≥ 2 toxicity, a significant increase occurred in the standard arm ($P = .006$).

Table 2. Biochemical-Clinical Failure Component Outcomes by Treatment Arm

Outcome (as first event)	Treatment Arm (No. of subjects)		
	Short (n = 608)	Standard (n = 598)	Total (N = 1,206)
Biochemical-clinical failure	109	117	226
PSA failure (Phoenix definition)	97	100	197
Death as a result of prostate cancer	4	4	8
Local recurrence	2	2	4
Distant recurrence	3	5	8
Started hormonal therapy	3	6	9

Abbreviation: PSA, prostate-specific antigen.

DISCUSSION

The results support the primary hypothesis that a moderately hypofractionated RT regimen of 60 Gy in 20 3-Gy fractions over 4 weeks is noninferior to a standard regimen of 78 Gy in 39 2-Gy fractions over 8 weeks for intermediate-risk prostate cancer. The upper bound for the HR of the BCF composite outcome is within

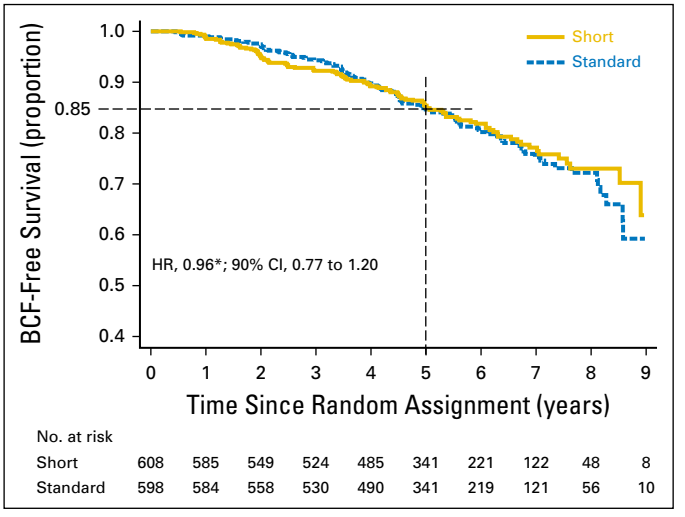

Fig 2. Biochemical-clinical failure (BCF)–free survival. Short (hypofractionated) radiotherapy, 60 Gy in 20 fractions over 4 weeks. Standard radiotherapy, 78 Gy in 39 fractions over 8 weeks. *Estimate based on stratified Cox proportional hazards regression model; test of the hazard proportionality assumption $P = .16$. HR, hazard ratio.

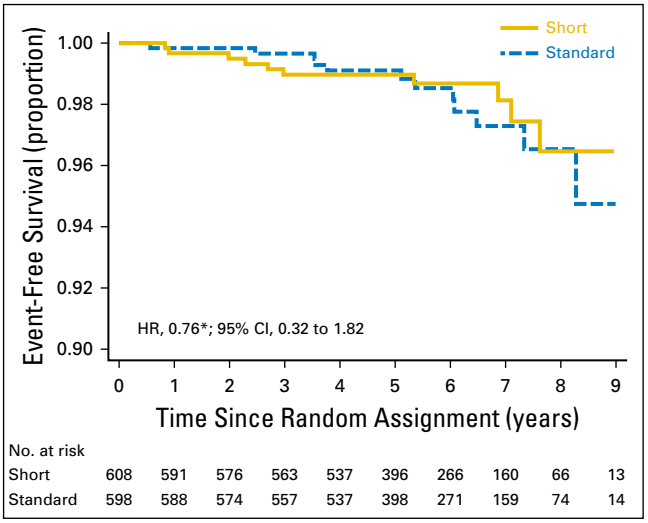

Fig 3. Freedom from prostate cancer–related death. Short (hypofractionated) radiotherapy, 60 Gy in 20 fractions over 4 weeks. Standard radiotherapy, 78 Gy in 39 fractions over 8 weeks. *Estimate was based on stratified Cox proportional hazards regression model. HR, hazard ratio.

the predefined limit of 1.32 for noninferiority. BCF accounted for 87% of the events. The data are mature, with a median follow-up of 6 years.

The results are consistent with two recently published randomized noninferiority trials that compared moderately hypofractionated RT regimens with conventionally fractionated regimens for localized prostate cancer. Lee et al[12] reported that 70 Gy in 28 2.5-Gy fractions over 5.6 weeks was noninferior to 73.8 Gy in 41 1.8-Gy fractions over 8.2 weeks in low-risk prostate cancer. In many jurisdictions, however, active surveillance is commonly used in low-risk prostate cancer. Dearnaley et al[21] compared 60 Gy in 20 fractions over 4 weeks (the same regimen as the current trial) and 57 Gy in 19 fractions over 3.8 weeks, with 74 Gy in 38 fractions over 7.6 weeks in predominantly intermediate-risk patients who also all received 6 months of androgen deprivation therapy before and during RT. The same regimen as ours was noninferior to standard, but the other hypofractionated regimen was not. The standard arm used a lower radiation dose (74 Gy) compared with the 78 Gy used in the standard arm in our trial, which is more commonly used in North America.

Avoidance of excessive toxicity, particularly late radiation GU and GI toxicity, is essential for hypofractionated regimens to be adopted into standard practice. Our hypothesis, that no increase would be seen in toxicity with hypofractionated RT delivered by highly conformal image-guided techniques, was supported. No differences were detected between treatment arms for grade ≥ 3 late GU and GI toxicity. Significantly less grade ≥ 2 late GI toxicity in the hypofractionated arm than in the standard arm was observed. The reduction in late toxicity with the hypofractionated regimen is consistent with the linear-quadratic model that would predict a lower biologically equivalent dose for normal tissues with an α/β of 3 to 5. This finding is supported by the trial conducted by Dearnaley et al,[21] who reported a lower 5-year incidence of grade ≥ 2 GI toxicity for both hypofractionated arms compared with standard. These results are in contrast to those by Lee et al,[12] who reported an increase in both GI and GU grade ≥ 2 late events in the hypofractionated arm. The normal tissue dose constraints permitted for the hypofractionated arm were liberal compared with the other trials and may account for this finding.[12] The Dutch Hypofractionated Versus Conventionally Fractionated Radiotherapy for Patients With Prostate Cancer (HYPRO) trial, which compared standard fractionation with 39 fractions of 2 Gy in 8 weeks (five fractions per week) or hypofractionation with 19 fractions of 3.4 Gy in 6.5 weeks (three fractions per week) demonstrated increased GU and GI late toxicity in the hypofractionated arm.[19] This trial was designed to have a biologically higher dose in the experimental treatment arm, which likely accounts for these findings.

The maximally tolerable HR of 1.32 for BCF was chosen because patients who experience PSA failure usually are treated with hormonal therapy, which often delays disease progression for an extended period. The combination of a long natural disease history and long periods of disease control with hormonal intervention implies that the 7.5% noninferiority margin on the basis of the surrogate marker of PSA failure would translate to a clinically acceptable difference in a clinical cancer outcome.

A strength of this trial is the attention given to quality assurance, which included center accreditation before activation and real-time RT review.[14] This quality assurance may have contributed to the favorable toxicity profile in both treatment arms.

A couple of issues with the recently reported hypofractionation trials are that the follow-up was relatively short, and the occurrence of any increase in late local failures or toxicities associated with the hypofractionated treatments could have been missed. In another trial, Dearnaley et al[27] compared conventional-dose with dose-escalated RT by using conventional fractionation in men with localized prostate cancer. At a median follow-up of

Table 3. Genitourinary Toxicity by Period, Treatment, and Grade

	Acute* Toxicity (No. [%])		Late† Toxicity (No. [%])	
Grade	Short (n = 608)	Standard (n = 598)	Short (n = 608)	Standard (n = 598)
None	150 (25)	143 (24)	310 (51)	299 (50)
1	273 (45)	272 (46)	162 (27)	165 (28)
2	161 (27)	159 (27)	123 (20)	116 (19)
3	24 (3.9)	24 (4.0)	12 (2.0)	17 (2.8)
4	0	0	1 (0.2)	1 (0.2)

*Acute period = worst grade during the first 14 weeks.
†Late period = worst grade from 6 months onward.

Table 4. GI Toxicity by Period, Treatment, and Grade

	Acute* Toxicity (No. [%])		Late† Toxicity (No. [%])	
Grade	Short (n = 608)	Standard (n = 598)	Short (n = 608)	Standard (n = 598)
None	249 (41)	286 (48)	355 (58)	311 (52)
1	260 (43)	250 (42)	199 (33)	204 (34)
2	95 (16)	59 (10)	45 (7.4)	66 (11)
3	4 (0.7)	3 (0.5)	9 (1.5)	16 (2.7)
4	0	0	0	1 (0.2)

*Acute period = worst grade during the first 14 weeks.
†Late period = worst grade from 6 months onward.

10 years, no increases in local failures were detected in the dose-escalated arm relative to the standard treatment arm. In addition, the incidence of late GI toxicity decreased after 5 years.[28] Long-term toxicity data have been reported recently from two studies of hypofractionated radiation in prostate cancer.[29,30] Most late events with moderate hypofractionation occurred within the first 48 months. Occasionally, very late bladder events occurred with hypofractionated doses higher than those used in the Prostate Fractionated Irradiation Trial (PROFIT). However, patients in the current trial should be followed for at least 10 years.

The switch from the ASTRO definition[15] to the Phoenix failure definition[16] was a practical decision. The change was made to be consistent with contemporary practice and trials. As expected, fewer BCF events occurred with the Phoenix failure definition, but the inference with regard to noninferiority of the investigational arm was not altered. By delaying the analysis and reporting the results, the PROFIT potentially would no longer be relevant. Furthermore, that study funding was coming to an end was a practical issue.

The results should not be extended to patients with high-risk disease. Incrocci et al[31] studied predominantly high-risk disease in the HYPRO trial and failed to show superiority of the hypofractionated regimen. Similarly, the current results cannot be used to support adoption of extreme hypofractionation regimens, which are being investigated (ClinicalTrials.gov identifiers NCT01794403 and NCT01584258).

In conclusion, results of this study provide evidence to support the use of moderate hypofractionated RT in patients with intermediate-risk prostate cancer.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

AUTHOR CONTRIBUTIONS

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Appendix

Delineation Protocol for Radiation Planning Technique

The clinical target volume (CTV) is the prostate gland with or without the base 1 cm of the seminal vesicles, which depends on risk stratification. The planning target volume is created by expanding the CTV by 10 mm but limiting this to 7 mm posteriorly.

Delineated organs at risk include the bladder, rectum, and both femoral heads. Bladder and rectum are contoured as hollow organs with both the internal and the external organ wall delineated. The bladder and rectal wall delineation is extended 18 mm above and below the CTV (Tables A1 and A2).

Definition for Biochemical-Clinical Failure

On the basis of the American Society of Therapeutic Radiology and Oncology definition, the hazard ratio (short *v* standard radiotherapy) for biochemical-clinical failure was 1.08 (90% CI, 0.91 to 1.27; $P_{\text{noninferiority}} = .023$; Table A3).

Table A1. Dose-Volume Criteria for 60 Gy in 20 Fractions

Volume of Interest	Metric	Gy Value
Target volume		
Clinical	D99	≥ 60
Planning	D99	≥ 57
	Maximum dose to 1 mL	≤ 63
Rectum wall	D30	≤ 46.0
	D50	≤ 37.0
Bladder wall	D30	≤ 46.0
	D50	≤ 37.0
Left/right femoral head	D5	≤ 43.0

Table A2. Dose-Volume Criteria for 78 Gy in 39 Fractions

Volume of Interest	Metric	Gy Value
Target volume		
Clinical	D99	≥ 78
Planning	D99	≥ 74.1
	Maximum dose to 1 mL	≤ 81.9
Rectum wall	D30	≤ 71.0
	D50	≤ 53.0
Bladder wall	D30	≤ 71.0
	D50	≤ 53.0
Left/right femoral head	D5	≤ 53.0

Table A3. Biochemical-Clinical Failure Components by Treatment Arm

	Treatment Arm (No.)		
Outcome (as first event)	Short (n = 608)	Standard (n = 598)	Total (N = 1,206)
Biochemical-clinical failure	195	185	380
PSA failure (ASTRO definition)	167	157	324
Death as a result of prostate cancer	4	4	8
Local recurrence	3	1	4
Distant recurrence	6	7	13
Started hormonal therapy	15	16	31

Abbreviations: ASTRO, American Society of Therapeutic Radiology and Oncology; PSA, prostate-specific antigen.