Original Investigation

Failure-Free Survival and Radiotherapy in Patients With Newly Diagnosed Nonmetastatic Prostate Cancer

Data From Patients in the Control Arm of the STAMPEDE Trial

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IMPORTANCE The natural history of patients with newly diagnosed high-risk nonmetastatic (M0) prostate cancer receiving hormone therapy (HT) either alone or with standard-of-care radiotherapy (RT) is not well documented. Furthermore, no clinical trial has assessed the role of RT in patients with node-positive (N+) M0 disease. The STAMPEDE Trial includes such individuals, allowing an exploratory multivariate analysis of the impact of radical RT.

OBJECTIVE To describe survival and the impact on failure-free survival of RT by nodal involvement in these patients.

DESIGN, SETTING, AND PARTICIPANTS Cohort study using data collected for patients allocated to the control arm (standard-of-care only) of the STAMPEDE Trial between October 5, 2005, and May 1, 2014. Outcomes are presented as hazard ratios (HRs) with 95% CIs derived from adjusted Cox models; survival estimates are reported at 2 and 5 years. Participants were high-risk, hormone-naive patients with newly diagnosed M0 prostate cancer starting long-term HT for the first time. Radiotherapy is encouraged in this group, but mandated for patients with node-negative (N0) M0 disease only since November 2011.

EXPOSURES Long-term HT either alone or with RT, as per local standard. Planned RT use was recorded at entry.

MAIN OUTCOMES AND MEASURES Failure-free survival (FFS) and overall survival.

RESULTS A total of 721 men with newly diagnosed M0 disease were included: median age at entry, 66 (interquartile range [IQR], 61-72) years, median (IQR) prostate-specific antigen level of 43 (18-88) ng/mL. There were 40 deaths (31 owing to prostate cancer) with 17 months' median follow-up. Two-year survival was 96% (95% CI, 93%-97%) and 2-year FFS, 77% (95% CI, 73%-81%). Median (IQR) FFS was 63 (26 to not reached) months. Time to FFS was worse in patients with N+ disease (HR, 2.02 [95% CI, 1.46-2.81]) than in those with N0 disease. Failure-free survival outcomes favored planned use of RT for patients with both N0M0 (HR, 0.33 [95% CI, 0.18-0.61]) and N+M0 disease (HR, 0.48 [95% CI, 0.29-0.79]).

CONCLUSIONS AND RELEVANCE Survival for men entering the cohort with high-risk M0 disease was higher than anticipated at study inception. These nonrandomized data were consistent with previous trials that support routine use of RT with HT in patients with N0M0 disease. Additionally, the data suggest that the benefits of RT extend to men with N+M0 disease.

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT00268476; ISRCTN78818544

JAMA Oncol. 2016;2(3):348-357. doi:10.1001/jamaoncol.2015.4350
Published online November 25, 2015. Corrected on February 11, 2016.

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The STAMPEDE Trial (MRC PR08, CRUK/06/019) has recruited men starting first-line long-term hormone therapy (HT) for the first time for prostate cancer with or without metastases. The STAMPEDE population therefore includes a cohort of men with newly diagnosed nonmetastatic (M0) disease that is either high risk localized or node positive (N+); approximately 40% of trial entrants have no metastases. The trial uses a multiarm, multistage design to test the addition of further treatments to HT-based therapy, including docetaxel, zoledronic acid, celecoxib, abiraterone acetate, enzalutamide, and, only in patients with newly diagnosed metastatic (M1) disease, local radiotherapy (RT). Research arms have recruited at overlapping times, but, throughout, the control arm has consistently been use of HT, with RT where appropriate.[1-8]

This article describes the prognosis for men with newly diagnosed, high-risk M0 disease, split by nodal involvement, to complement the outcomes that we have reported for patients with metastatic disease allocated to the control arm of the trial.[7] We also considered the effect of radical RT on time to progression, by nodal involvement. A detailed understanding of these effects will underpin the interpretation of the trial's comparative outcomes as the study matures.

There is limited information on the natural history of patients with newly diagnosed, high-risk M0 prostate cancer receiving androgen deprivation therapy (ADT) either alone or with RT. Since the trial commenced, 2 large randomized clinical trials, SPCG-7[9] and PR07,[10] have shown that RT to the prostate with or without the pelvis, in addition to ADT, reduces risk of prostate cancer death by approximately 50%; both studies have more limited populations than STAMPEDE. First, SPCG-7 was exclusively in node-negative (N0) disease and largely at the lower end of the risk spectrum (maximum prostate-specific antigen [PSA] level, 80 ng/mL, but median PSA, approximately 20 ng/mL). Second, PR07 did not mandate nodal staging but was only for N0 disease if staging had been performed; the trial had no PSA level cap. Therefore, there remains uncertainty about the role of RT in men with N0M0 disease and higher PSA levels, and in men with N+M0 disease. To date, no randomized clinical trials have looked at the role of RT in patients with N+M0 disease, and to our knowledge none are planned. The STAMPEDE Trial has recruited and observed many such patients.

When STAMPEDE started, patients with N0M0 disease had the option of RT with HT. Radiotherapy was to be given approximately 6 to 9 months after randomization, to allow adequate time for hormone response and avoid combination of RT and docetaxel for relevant patients. Starting November 15, 2011, RT became mandatory for this node-negative patient subset on the basis of the SPCG-7 and PR07 trial reports. For patients with N+M0 disease, RT (also after 6-9 months) has been optional throughout.

The intended use of RT is a stratification factor at trial entry. The trial control arm provides a suitable cohort, with prospectively collected data in which to undertake an exploratory multivariate analysis to opportunistically investigate possible impact of radical RT in patients with these disease characteristics at entry, in particular, N0, high PSA level, and N+, in a nonrandomized fashion. We hypothesized that RT was associated with better prognosis in men with M0 disease, regardless of nodal involvement.

At a Glance

- This research describes the prognosis of men with newly diagnosed, nonmetastatic (M0) prostate cancer and considers the effect of radiotherapy on failure-free survival by nodal involvement (N0 vs N+).
- We hypothesized that radiotherapy was associated with better prognosis in men with M0 prostate cancer, regardless of nodal involvement.
- Survival for men with high-risk M0 disease was higher than anticipated at study inception, with 80% still alive at 5 years.
- Failure-free survival outcomes favored planned use of radiotherapy for patients with both N0M0 (hazard ratio, 0.33 [95% CI, 0.18-0.61]; consistent with previous reported randomized trials) and N+M0 disease (hazard ratio, 0.48 [95% CI, 0.29-0.79]).
- Radiotherapy was tolerable and the toxic effects profile was as expected.

Methods

Overall Trial Recruitment and Eligibility

Patients joined the STAMPEDE Trial from more than 100 sites across the United Kingdom and Switzerland. To be eligible, patients must have prostate cancer that was either high-risk newly diagnosed N0M0 disease, newly diagnosed M1 or N+ disease, or disease (previously treated with radical surgery and/or RT) that was relapsing at the time of randomization. All patients were intended for first-line treatment with long-term HT for the first time, and this must have started no longer than 12 weeks prior to randomization. Baseline investigations must have been completed prior to randomization, which included computed tomography or magnetic resonance imaging (MRI) of the pelvis and abdomen; bone scan or equivalent, for example, whole-body MRI; chest x-ray if chest was not included in the computed tomography or MRI; electrocardiogram; and PSA test. There were no age restrictions; patients had to be fit for chemotherapy and have no significant cardiovascular history.

Study Population

For this cohort analysis, we selected men with newly diagnosed prostate cancer, which we defined as being diagnosed within 6 months prior to randomization, that was nonmetastatic, and who were randomized to the control arm of the STAMPEDE Trial between October 2005 and May 2014. All patients were planned for treatment with standard-of-care HT, according to local practice, which comprised either orchiectomy or use of luteinizing hormone–releasing hormone agonists or antagonists with or without long-term oral antiandrogens. Hormone therapy was to continue for at least 2 years or until disease progression. Treatment after these points was at the discretion of the consulting clinician. We further divided this cohort to investigate the effects of RT: for men with

N0M0 disease we selected those randomized prior to November 15, 2011, after which RT became compulsory for this group (the "N0M0 subcohort"); and for patients with N+M0 disease, for whom RT remains optional, we selected men randomized at least 12 months before the data cutoff of May 2014, to ensure sufficient follow-up (the "N+M0 subcohort").

Data Collection

Baseline data included patient demographic characteristics, regional lymph node status, Gleason sum score, World Health Organization (WHO) performance status, pre-HT PSA level, and planned RT. Details of disease progression were obtained from progression forms. Details of reported RT were obtained from the RT (detail) form. The protocol can be found at http://www.stampedetrial.org. The trial was registered as NCT00268476 and ISRCTN78818544 and had the relevant regulatory approval, national ethics approval, and local practical site approval. All patients gave written, informed consent.

Radiotherapy Techniques

Exact RT technique was at site discretion. Guidance was given within the trial protocol (section 6.15) such that for patients with negative nodes on axial imaging, clinicians may choose between irradiating prostate and seminal vesicles alone or include pelvic nodes. Additional staging tests, such as pelvic node sampling, may aid decision making. Conformal or intensity-modulated radiotherapy (IMRT) should be used in all patients. Where patients have good clinical evidence that nodes are tumor free or where nodal radiotherapy is contraindicated (eg, significant bowel disease), treatment may be given to the prostate gland and seminal vesicles only. Recommended dosing is 74 Gy in 37 fractions to the prostate and seminal vesicles or the equivalent using hypofractionated schedules, with optional pelvic node dose of 46 to 50 Gy in 2-Gy fractions or equivalent; suggested dose is 55 Gy in 37 fractions with IMRT. Higher doses may be considered if the department is experienced at using IMRT for nodal RT. No formal lymph node size was given to define normality/abnormality, but generally an upper limit of normality of 10 mm is used[11]; for most pelvic lymph node sites 8 mm is the cutoff used. Conventionally an upper limit of 10 mm in short axis dimension is used to define normal size lymph node.

Outcome Measures

The trial's definitive and intermediate primary outcome measures were overall survival and failure-free survival (FFS), respectively.[12] These outcome measures formed the primary focus of this cohort analysis. Survival was defined as time from randomization to death from any cause. Failure-free survival was defined as time from randomization to the first of the following events: biochemical failure (as defined herein); progression either locally, in lymph nodes, or in distant metastases; or death from prostate cancer.

Biochemical failure, based on the PSA nadir in the first 24 weeks after randomization, was defined as:

1. 50% above nadir and at least 4 ng/mL if PSA nadir is less than 4 ng/mL;
2. 50% above nadir if PSA nadir is at least 50% lower than the last pretreatment PSA but remaining greater than 4 ng/mL; or
3. Failure at time zero if PSA nadir is greater than 50% of the last pretreatment PSA level.

Cause of death was determined by central review without reference to the allocated treatment. Death was taken as being from prostate cancer when classified by the reviewer as "definitely" or "probably" prostate cancer. The site investigator's determination was used for deaths not yet reviewed.

Statistical Analyses

These analyses are nonrandomized and post hoc. Analyses were performed using Stata, version 13, using standard survival analysis methods. Kaplan-Meier estimates were used to produce survival curves. Cox models were used to investigate effects by subgroup; models were adjusted for initial Gleason sum score category (≤7, ≥8, unknown), log-transformed pre-ADT PSA level, age at randomization (<60, 60-64, 65-69, ≥70 years), and WHO performance status (0 vs 1-2) at randomization. Median follow-up was determined through reverse censoring on death.

The main time-to-event analyses were calculated as time from randomization to the outcome of interest, with those not experiencing the event being censored at the time of last contact. The analyses of reported RT use employed a landmark approach,[13,14] in which analyses were timed from 6 months after randomization, to allow for RT to be started. Patients were included in the landmark analysis if they had follow-up 6 months from randomization and had not experienced the outcome of interest within the first 6 months; patients with progression, death, or withdrawal of consent prior to 6 months, or less than 6-months' follow-up reported, were therefore excluded from the landmark analysis.

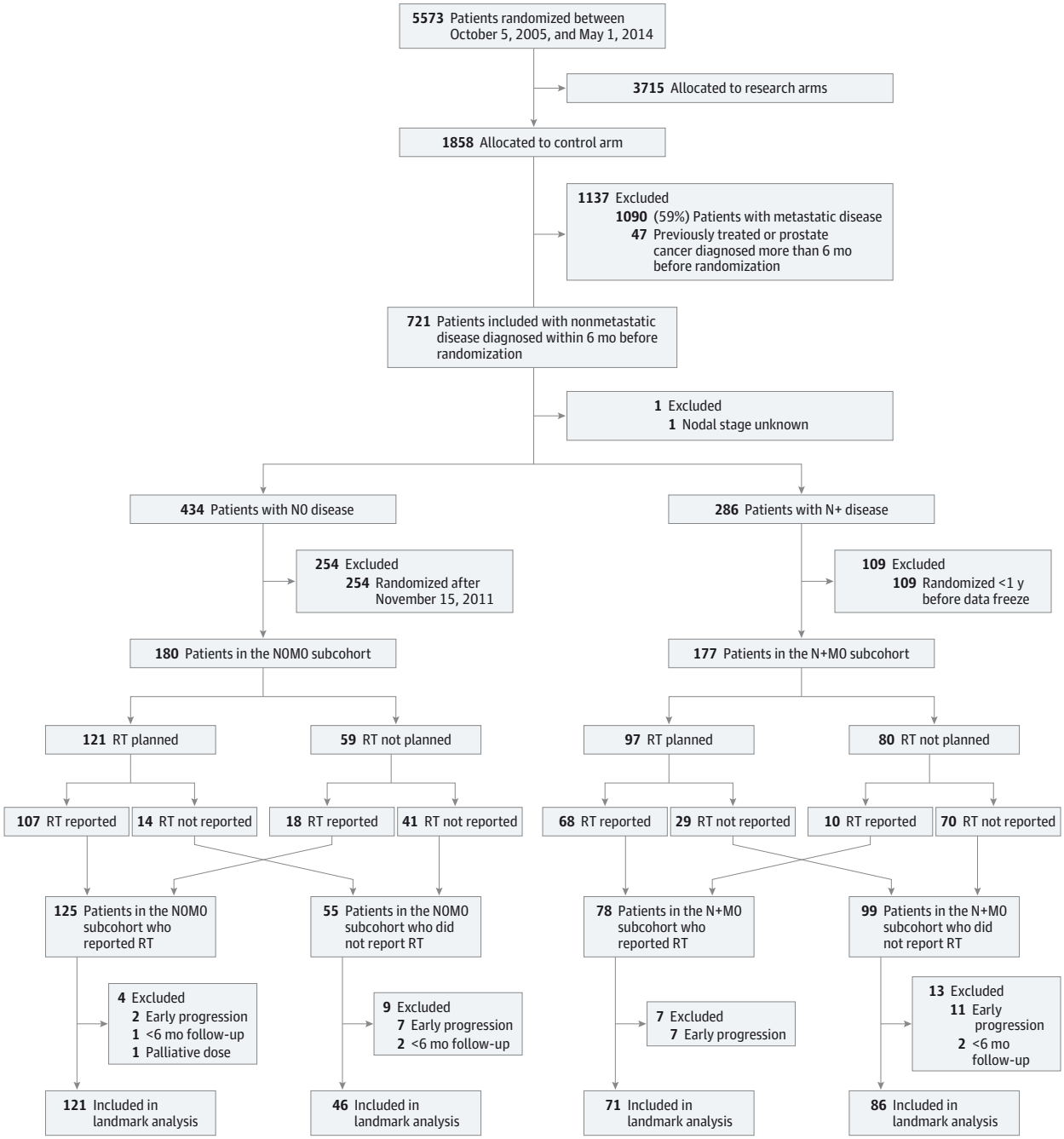
Outcomes were considered according to the following groupings: presence of regional lymph node involvement (N0 vs N+), year of randomization, and both planned and reported radical RT. Radiotherapy schedules were grouped according to field and fractionation (conventional or hypofractionated).

Results

Patient Cohort

Figure 1 shows the cohort selection process. Of 5573 eligible patients randomized to the trial from October 5, 2005, to May 1, 2014, 1858 were allocated to the control arm. Of these, 721 (13% of all randomized men) had nonmetastatic prostate cancer, newly diagnosed within 6 months prior to randomization, and were included in the main analytic cohort. The data set was frozen in May 2014, with median (interquartile range [IQR]) follow-up of 17 (6-36) months in this cohort, and 1380.5 patient-years total follow-up. From these, 357 of 721 (50%) patients met our time criteria for inclusion in the "RT analyses." **Table 1** shows the baseline characteristics of the whole M0 cohort and the N0 and N+ subcohorts, split by planned RT status.

Figure 1. Cohort Selection for Full M0 Cohort and Patient Selection for the Radiotherapy Analysis, in NOM0 and N+M0 Subcohorts



Survival and Failure-Free Survival Outcomes—Full M0 Cohort

eFigure 1 in the Supplement shows overall survival and FFS for all 721 patients. Forty of 721 had died; 31 of 40 (78%) deaths were attributed to prostate cancer. Two-year survival was 96% (95% CI, 93%-97%), with 80% (95% CI, 72%-86%) still alive at 5 years. One hundred fifty-one of 721 reported at least 1 FFS event, with 81% (123 of 151) reporting PSA failure only as their first FFS event. Median (IQR) FFS was 63 (26 to not reached) months; 2-year FFS was 77% (95% CI, 73%-81%). Failure-free survival was worse in patients reporting nodal involvement at randomization, with 27% of patients with N+ disease reporting an event compared with 17% of patients with N0 disease (HR, 2.02 [95% CI, 1.46-2.81]). Five-year FFS for patients with N+ disease was 47% (95% CI, 36%-58%), compared with 60% (95% CI, 50%-68%) for patients with N0M0 disease. There was no evidence of a difference in FFS by year of randomization (likelihood ratio test $P = .88$); there were insufficient data yet to explore survival.

Table 1. Patient Characteristics at Baseline, Overall, and in NOMO and N+MO Subcohorts

Randomized Patient Characteristic	No. (%)[a]				
		Radiotherapy			
	Full M0 Cohort October 5, 2005, to May 1, 2014 (N = 721)	NOMO Subcohort Before November 15, 2011		N+M0 Subcohort at Least 1 Year Before Data Freeze	
		None Planned (n = 59)	Planned (n = 121)	None Planned (n = 80)	Planned (n = 97)
Age group, y					
<60	133 (19)	13 (22)	31 (26)	17 (21)	21 (22)
60-64	145 (20)	10 (17)	26 (21)	22 (28)	27 (28)
65-69	189 (26)	11 (19)	34 (28)	16 (20)	30 (31)
≥70	254 (35)	25 (42)	30 (25)	25 (31)	19 (20)
Age at randomization, median (IQR), y	66 (61-72)	68 (61-73)	65 (59-69)	65 (60-71)	65 (60-68)
Gleason Sum Score					
<8	156 (22)	15 (25)	29 (24)	21 (26)	18 (19)
≥8	535 (74)	44 (75)	91 (75)	56 (70)	76 (78)
Unknown	30 (4)	0	1 (1)	3 (4)	3 (3)
World Health Organization performance status					
0	611 (85)	47 (80)	114 (94)	69 (86)	85 (88)
≥1	110 (15)	12 (20)	7 (6)	11 (14)	12 (12)
Nodal stage					
N0	434 (60)	59 (100)	121 (100)	0	0
N+	286 (40)	0	0	80 (100)	97 (100)
NX	1 (0.1)	0	0	0	0
PSA before ADT, median (IQR)					
ng/mL	43 (18-88)	90 (58-164)	45 (22-75)	40 (17-98)	28 (15-67)
Log-transformed	3.8 (2.9-4.5)	4.5 (4.1-5.1)	3.8 (3.1-4.3)	3.7 (2.8-4.6)	3.3 (2.7-4.2)

Abbreviations: ADT, androgen deprivation therapy; IQR, interquartile range; M0, nonmetastatic; M1, metastatic; N+, node positive; N0, node negative; PSA, prostate-specific antigen; RT, radiotherapy.

[a] Data are reported as number (percentage) unless otherwise specified. Percentages may not total 100% because of rounding.

Of 151 patients with an FFS event, there were 33 deaths with median (IQR) 18 (7-37) months' follow-up from FFS event. Median survival from FFS event was not reached; however, 74% (95% CI, 63%-82%) were still alive 2 years after first FFS event, with 51% (95% CI, 32%-66%) alive at 5 years.

Impact of Radiotherapy on Failure-Free Survival

Figure 2 shows time from 6-month landmark to FFS by reported radical RT status, split by time-specified nodal status at baseline.

NOMO Subcohort

There were 180 patients with NOMO disease randomized prior to November 15, 2011. Two-year survival in this NOMO subcohort was 97% (95% CI, 93%-99%), with 84% (95% CI, 74%-91%) still alive after 5 years.

Figure 1 shows the men planned for and receiving RT. Fourteen of 121 (12%) did not report receiving their planned RT: 2 experienced disease progression within 6 months of randomization, and 12 had no RT data. Median (IQR) time to starting RT was 5.8 (4.5-6.9) months from randomization (eFigure 2 in the Supplement).

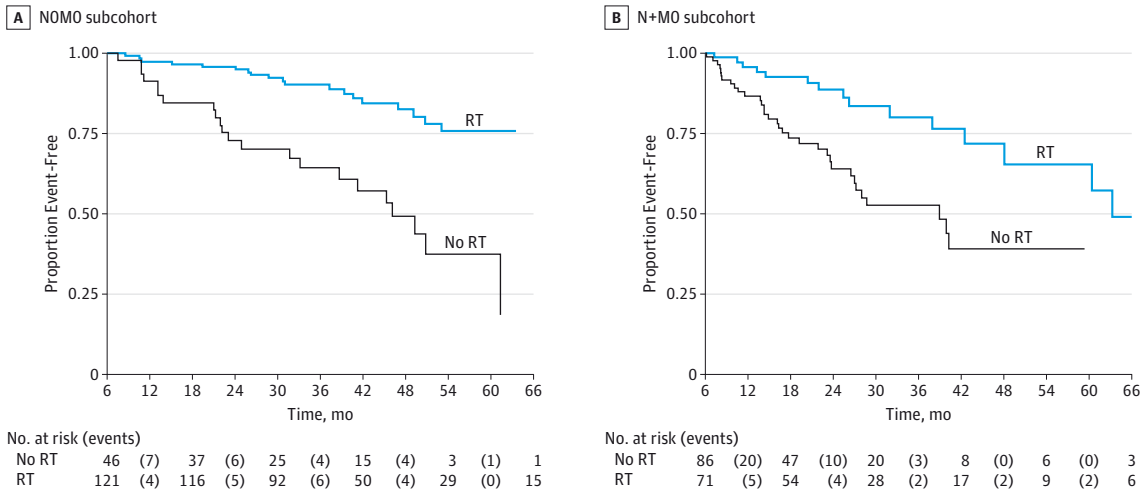
Failure-free survival was better among patients planned for radical RT against those not planned, with adjusted HR, 0.33 (95% CI, 0.18-0.61). Two-year FFS was 93% (95% CI, 87%-97%) in patients planned for RT compared with 68% (95% CI, 54%-78%) of patients not planned for RT (eFigure 3A in the Supplement).

The exploratory landmark analysis (selection in Figure 1), timed from 6 months after randomization, compared patients who received RT against those not reporting RT (regardless of planned use). A total of 167 patients were failure free and uncensored at 6 months, so included in this analysis, 121 receiving RT and 46 not reporting RT. Failure-free survival was better with received RT: adjusted HR, 0.25 (95% CI, 0.13-0.49) with 2-year FFS of 96% (95% CI, 90%-98%) in patients receiving RT compared with 73% (95% CI, 57%-84%) in those not reporting RT (Figure 2A).

N+MO Subcohort

There were 177 patients with N+M0 disease randomized at least 1 year prior to the data freeze. Two-year survival in this N+M0 subcohort was 93% (95% CI, 88%-96%), with 71% (95% CI, 56%-82%) still alive after 5 years. Figure 1 shows the patients planned for and receiving RT. Twenty-nine of 97 patients planned for RT did not report receiving it: 5 experienced disease progression within 6 months after randomization, and 24 had no RT data. Median (IQR) time to starting RT was 6.1 (4.7-8.5) months from randomization (eFigure 2 in the Supplement).

Figure 2. Failure-Free Survival for Reported Radical Radiotherapy Status, in N0M0 and N+M0 Subcohorts



Failure-free survival was better among those planned for radical RT than those not planned: adjusted HR, 0.48 (95% CI, 0.29-0.79), with 2-year FFS of 81% (95% CI, 71%-87%) and 53% (95% CI, 40%-65%), respectively (eFigure 3B in the Supplement).

A total of 157 patients were event free and uncensored at 6 months and included in the landmark analysis by reported RT (regardless of planned use). Failure-free survival was better among patients receiving RT: adjusted HR, 0.35 (95% CI, 0.19-0.65), with 2-year FFS of 89% (95% CI, 77%-94%) and 64% (95% CI, 51%-75%), respectively (Figure 2B).

Radiotherapy Field and Fractionation

Reported RT is summarized for the subcohorts in **Table 2**. For the 71 patients with N+M0 disease, kept in the landmark analysis and reporting RT, 82% (58 of 71) reported receiving RT to both prostate and pelvis, with conventional fractionation for all but 8 patients. For the 121 patients with N0M0 disease, kept in the landmark analysis and reporting RT, 43% (52 of 121) received RT to both prostate and pelvis, with conventional fractionation for all but 14 patients.

Reported Radiation Therapy Oncology Group Late Toxic Effects

Table 2 also shows adverse effects associated with radical RT, using Radiation Therapy Oncology Group late toxic effect grading, for all patients receiving RT, split by nodal subcohorts. Reported adverse effects were similar for patients with and without nodal involvement, with no grade 4 or 5 adverse effects reported.

Discussion

We selected a cohort of men with nonmetastatic, newly diagnosed, hormone-naive prostate cancer, at high risk of dying from the disease, who were treated with long-term ADT with or without RT. We found median FFS of 63 months for the full M0 cohort, from study entry. Two-year FFS and survival were 77% and 96%, respectively, and 80% were still alive at 5 years. We report a clear improvement in FFS with RT.

Comparisons with other published series must be made with caution because of differences in case mix and the start time of estimate (**Table 3**). The GETUG-12 trial, comparing ADT + RT (74 Gy in 37 fractions) with or without 4 cycles of docetaxel and estramustine in a high-risk nonmetastatic population, recently reported results in its control arm and showed 5-year relapse-free survival of approximately 80%; this is an obviously different patient group from the STAMPEDE control arm.[17] Older RT series focused on generally lower-risk N0M0 cases, for example, GETUG-01,[16] which examined the role of nodal RT in patients with clinically node-negative disease and which had only approximately 11% Gleason score 8 or greater and 25% T3 tumors (in comparison with our population in Table 1). Nonetheless, median FFS reported here is comparable to median PFS reported for the higher-risk subgroup in GETUG-01, with similar progression criteria.

The standard-of-care therapy for the STAMPEDE control arm was initially envisaged as ADT alone. When the trial was launched in October 2005, a decision was made to permit RT at the individual investigator's discretion and to stratify by intended RT use. Guidelines on RT doses and volumes were included in the protocol in an attempt to standardize practice. Despite publication of SPCG-7 in 2009,[9] the proportion of men with N0M0 disease being offered RT within the trial remained stable at approximately 60%. With publication of PR07 in 2011,[18] the trial management group took the positive decision to mandate RT in this subgroup to ensure that the trial standard of care was updated to reflect the new evidence base.

Within the N0M0 and N+M0 subcohorts, both planned and reported radical RT was associated with prolonged FFS, even after adjustment for initial Gleason sum score category, log-transformed pre-HT PSA level, age at randomization, and WHO performance status at randomization. Multivariate HRs for FFS, both by stated RT intention (HR, 0.33 [95% CI, 0.18-0.61]) and landmark analysis (HR, 0.25 [95% CI, 0.13-0.49]),

Table 2. Reported Radiotherapy Field and Fractionation, and Worst Reported Radiation Therapy Oncology Group (RTOG) Late Toxic Effects Grading for Those Landmark Patients Reporting Radiotherapy, in NOMO and N+MO Subcohorts

Reported Radiotherapy Details	Subcohort, No. (%) NOMO (n = 121)	N+MO (n = 71)
Radiotherapy Prostate Fractionation[a]		
Hypofractionated		
Prostate only	13 (11)	5 (7)
Prostate and pelvis	1 (1)	3 (4)
Conventionally fractionated		
Prostate only	56 (46)	8 (11)
Prostate and pelvis	51 (42)	55 (78)
Missing	0	0
RTOG Late Adverse Effect and Grade[b]		
Diarrhea		
0	90 (79)	48 (78)
1	19 (17)	10 (16)
2	4 (3)	4 (6)
3	1 (1)	0
Missing	7	9
Proctitis		
0	94 (82)	53 (86)
1	10 (9)	4 (6)
2	8 (7)	5 (8)
3	2 (2)	0
Missing	7	9
Cystitis		
0	109 (96)	55 (89)
1	2 (2)	4 (6)
2	2 (2)	3 (5)
3	1 (1)	0
Missing	7	9
Hematuria		
0	108 (95)	58 (94)
1	2 (2)	2 (3)
2	3 (3)	1 (2)
3	1 (1)	1 (2)
Missing	7	9
Rectal-anal stricture		
0	114 (100)	62 (100)
1	0	0
2	0	0
3	0	0
Missing	7	9
Urethral stricture		
0	113 (99)	62 (100)
1	1 (1)	0
2	0	0
3	0	0
Missing	7	9
Rectal ulcer		
0	112 (98)	62 (100)
1	1 (1)	0
2	0	0
3	1 (1)	0
Missing	7	9
Bowel obstruction		
0	114 (100)	62 (100)
1	1 (1)	0
2	0	0
3	0	0
Missing	7	9

Abbreviations: M0, nonmetastatic; M1, metastatic; N+, node positive; N0, node negative.

[a] Hypofractionated dose is defined as greater than 2 Gy per fraction. Conventionally fractionated dose is defined as 2 Gy or less per fraction.

[b] The purpose of the second part of this table is to indicate the long-term toxic effects; it is not to facilitate comparisons of toxic effects across the subgroups. Note that all patients in the NOMO cohort had been in the trial for at least 2.5 y by the time of the data freeze; the patients in the N+MO cohort had been in the trial for at least 1 y. No patients reported grade 4 or 5 RTOG toxic effects.

are reassuringly consistent with corresponding data in PR07 (HR, 0.31 [95% CI, 0.25-0.39]) and SPCG-7 (PSA recurrence-only: HR, 0.16 [95% CI, 0.12-0.20]).

It is thus of interest that the HR for FFS for RT in the N+M0 subcohort is also strongly in favor of RT, in both RT intention (HR, 0.48 [95% CI, 0.29-0.79]) and reported RT use (HR, 0.35 [95% CI, 0.19-0.65]). Previous widespread concerns that RT was inappropriate in patients with high-risk nonmetastatic disease, due to high probability of occult metastases, thus appear to be misplaced, although RT could act by an abscopal effect. We are testing this latter hypothesis in patients with metastatic disease within STAMPEDE.[19] In addition, the reported late RT adverse event toxicity profile appears similar for patients with N0 and N+ disease, in keeping with recently published modern RT series that include GETUG-01 and PR07.[10,16]

Within the N+M0 group, there are still no randomized data on the role of radical RT, and we are not aware of any ongoing trials. However, the data presented here show a substantial effect of RT on FFS, consistent with that seen in the patients with NOMO disease within the same data set, and also the published randomized data in patients with NOMO disease. It is thus plausible that a similar benefit for RT, as seen in patients with N0 disease, exists for patients with N+M0 disease as well. Table 2 lists the RT fractionation to prostate and seminal vesicles and to lymph nodes. As expected, few patients with N+ disease received prostate-only RT, whereas inclusion of the pelvis in RT to patients with N0 disease was in less than half of the patients.

The data presented here are further consistent with the recent study published using retrospective, observational data

Table 3. Results in Context With Data From Previously Published Studies

Source	Data Type	Population	Deaths, No./ Patients, No.	Radiotherapy Effect, HR (95% CI)[a]	Treatment Groups	Estimates	
						Progression	Survival
Comparative Data							
SPCG-7,[9] 2009	R	Low risk, N0M0	116/875	0.16 (0.12-0.20)	ADT only	10-y PSA-FS, 25%	10-y OS, 61%
					ADT+RT	10-y PSA-FS, 74%	10-y OS, 70%
NCIC PR.3/MRC PR07,[10] 2011/2015[b]	R	N0M0	465/1205	0.31 (0.25-0.39)	ADT only	10-y PFS, 46%	10-y OS, 49%
					ADT+RT	10-y PFS, 74%	10-y OS, 55%
National Cancer Database,[15] 2015	NR	High-risk M0	?/636[c]	0.50 (0.37-0.67)	ADT only	Not given	5-y OS, 53%
					ADT+RT	Not given	5-y OS, 72%
STAMPEDE, 2015[c]	NR	N0M0	16/180	0.25 (0.13-0.49)	ADT only	5-y FFS, 38%	5-y OS, 86%
					ADT+RT	5-y FFS, 76%	5-y OS, 90%
STAMPEDE, 2015[d]	NR	N+M0	22/177	0.35 (0.19-0.65)	ADT only	5-y FFS, 39%	5-y OS, 82%
					ADT+RT	5-y FFS, 65%	5-y OS, 82%
Reference Data							
GETUG-01,[16] 2007	R	N0M0	36/352	Not relevant	RT to pelvis + prostate	5-y PFS, 66%	5-y OS, 87%
					RT to prostate only	5-y PFS, 65%	5-y OS, 88%
GETUG-12,[17] 2015	NR	High-risk M0	49/206	Not relevant	ADT with or without RT	8-y RFS, ~50%	8-y OS, ~83%
STAMPEDE, 2015[d]	NR	Newly diagnosed M0	40/721	Not relevant	ADT with or without RT	5-y FFS, 55%	5-y OS, 80%

Abbreviations: FFS, failure-free survival; HR, hazard ratio; M0, nonmetastatic; N+, node positive; N0, node negative; NR, nonrandomized; OS, overall survival; PFS, progression-free survival; R, randomized; RT, radiotherapy.

[a] Effect on progression unless otherwise stated.

[b] PR07 had no mandatory nodal staging.

[c] Patients matched by propensity scoring; number of deaths unknown; no analysis on progression.

[d] Data presented within this article.

from the US National Cancer Data Base, which reported data on men who received a diagnosis between 2004 and 2006.[15] Using propensity-score matching in approximately 600 patients with cN+M0 prostate cancer, they reported an advantage in overall survival.

STAMPEDE is now collecting randomized data on the value of prostate RT in patients with newly diagnosed distant metastatic disease at the time of trial entry.[8,19] Approximately 1800 patients will contribute to this randomized comparison, which targets a relative improvement in overall survival of 25%; more than 1300 patients have already been randomized. If the results are positive, this will be likely to help further elucidate the data for the N+M0 setting.

The main strengths of our cohort include the fact that patients were from multiple centers and that data were collected in a consistent, prospective fashion. However, there are limitations. First, our substantive cohort was drawn from the control arm of a clinical trial, inevitably applying eligibility restrictions. Second, this is not a formally planned, randomized comparison and so numbers are small, and there are likely to be unmeasured confounders not accounted for in the analyses and potentially important differences in baseline characteristics because only men who were considered fit for RT were planned for RT and definitions of fitness for RT may have varied by site. We therefore might expect men planned for RT to have better prognosis than men not planned for RT, and the treatment effect seen here to be an overestimate of the benefit, but the consistency of effect with those previously published randomized trials enforces confidence in there being a positive effect of RT. Third, median follow-up within this cohort is only 17 months and survival data are still immature; recruitment was ongoing when this data set was frozen, with only 40 deaths in total (16 in the N0M0 subcohort, 22 in the N+M0 subcohort, and 2 in patients not included in the analyzed subcohorts).

Although using data from a trial's control arm invariably has limitations, there is need for a randomized clinical trial within the N+M0 population to address questions prospectively. No such trial has reported or is planned to report, and construction of one would be at great financial cost while taking many years to provide reliable long-term data. The control arm of a high recruiting trial, such as STAMPEDE, therefore makes efficient use of the wealth of data collected for the trial while incurring no extensive additional costs and simultaneously providing treatment safety and efficacy answers. Also, as highlighted herein, there is reassurance in the fact that the results we present for the N0M0 subcohort are consistent with those presented for similar patients in both PR07 and SPCG-7; this gives us confidence in the results for the N+M0 subcohort. Such results, along with the ever-evolving accuracy of RT imaging tools, present an important contribution to the treatment of men with locally advanced prostate cancer. We show here that a combination of both early ADT and RT, in suitable men, is effective in delaying time to first relapse, as well as being tolerable in terms of acute toxicity.[20-24]

Conclusions

Survival outcomes in this cohort of men with nonmetastatic, newly diagnosed disease were shown to be good, with time to progression increased by RT to the prostate with or without the pelvis, for patients both with and without nodal involvement. The data presented support routine use of RT in patients with N+ nonmetastatic prostate cancer. Investigators and funders should be aware that this improved survival may delay results in ongoing clinical trials.

ARTICLE INFORMATION

Accepted for Publication: September 10, 2015.

Correction: This article was corrected on February 11, 2016, to fix an error in the corresponding author's address.

Published Online: November 25, 2015. doi:10.1001/jamaoncol.2015.4350.

Open Access: This article is published under *JAMA Oncology*'s open access model and is free to read on the day of publication.

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Obtained funding: James, Clarke, Mason, Parmar, Sydes.
Administrative, technical, or material support: James, Clarke, Ritchie, Schiavone, de Bono.
Study supervision: James, Clarke, Dearnaley, Attard, de Bono, Srihari, Parmar, Sydes.

Conflict of Interest Disclosures: None reported.

Funding/Support: Cancer Research UK, Medical Research Council, Novartis, Sanofi, Pfizer, Janssen, and Astellas all provided research support for the trial. Professor Dearnaley, Drs Parker and Attard, and Professor de Bono all acknowledge support from Royal Marsden and the Institute of Cancer Research National Institute for Health Research, Biomedical Research Centre.

Role of the Funder/Sponsor: The funding sources and sponsor had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Previous Presentation: Preliminary results were presented at the Annual Meeting of the American Society for Therapeutic Radiology and Oncology; September 14-17, 2014; San Francisco, California; and European Society for Medical Oncology Congress; September 26-30, 2014; Madrid, Spain.

Additional Contributions: It was the decision of the trial management group to submit the manuscript for publication. Access to summary data and reports was available to all other co-authors. All individuals involved in the data analysis are identified as authors for the article.

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Invited Commentary

Pelvis Plus Prostate Radiation Therapy and the Risk of Death in Men With Newly Diagnosed Node-Positive Prostate Cancer

Anthony V. D'Amico, MD, PhD

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Both single-institutional retrospective series and a multi-institutional observational study[1,2] find a significant association between a reduced risk of death and treatment of node-positive prostate cancer using both external-beam radiation treatment (EBRT) of the prostate and pelvic lymph nodes (LNs) and androgen deprivation therapy (ADT) compared with ADT alone. However, whether this association is causal remains unanswered and requires testing in a prospective randomized trial. In this issue of *JAMA Oncology*, James and colleagues[3] use data from the control arm in the Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy (STAMPEDE) Trial to investigate this issue.

Specifically, they perform a Cox regression multivariable analysis[4] evaluating the risk of failure-free survival where failure is defined as prostate-specific antigen (PSA) level; local, regional, or distant treatment failure; or death from prostate cancer, adjusting for highest initial Gleason score category (≤7, ≥8, unknown), log-transformed pre-ADT PSA level (continuous), age (<60, 60-64, 65-69, ≥70 years), and World Health Organization performance status (0 vs 1 or 2) at randomization. Among 177 men with node-positive prostate cancer, 97 were planned for EBRT and 68 of these, plus 10 men not originally slated for EBRT, were recorded as having received EBRT to the prostate with or without pelvic LNs. After a median follow-up of 17 months in the overall study cohort, 20 men with node-positive prostate cancer experienced a failure event. The authors report that both planned and delivered prostate with or without pelvic EBRT was associated with reduced risk of failure, with adjusted hazard ratios of 0.48 (95% CI, 0.29-0.79) and 0.35 (95% CI, 0.19-0.65), respectively.

There are several reasons to interpret these results with caution. First, as the authors note, EBRT use was prescribed by physician choice and therefore nonrandomized. In addition, the short median follow-up of 17 months in a study in which at least 2 years of ADT was required and a primary end point (ie, failure-free survival) that is likely driven by PSA-related failure events at this short median follow-up time make it difficult to predict what effect a reduction in mostly PSA failure-free survival will have on overall survival. Moreover, given the low event rate (20 of 177 [11.3%]), the authors were not able to analyze overall survival as an end point or adjust for all known prostate cancer prognostic factors in their model, such as tumor category, tertiary grade 5 in men with Gleason score 7 prostate cancer, and percent positive biopsies. Also, with 40 deaths in the overall study cohort of which 9 could not be attributed to prostate cancer, a competing risk[5] and not Cox regression analysis[4] would have been more appropriate to analyze the end point of time to first failure or prostate cancer death. Finally, treatment use varied, in that some men could have received irreversible and life-long testosterone suppression via bilateral orchiectomy as compared with 2 years of reversible ADT using a luteinizing hormone-releasing hormone agonist. Moreover, in men in whom EBRT was delivered, the prostate was always treated whereas the pelvic LNs were only treated in a subset and the dose fractionation scheme for EBRT delivery varied. Both the variations in EBRT and ADT can affect time to first failure. Ideally, to account for these variations in treatment an adjustment in the model using a treatment propensity score would have been used, but the short median follow-up and consequently a low event rate would likely not permit the inclusion of the treatment propensity score and other known prostate cancer prognostic factors without running the risk of overfitting the model.

Given these limitations, the conclusion that the addition of prostate and pelvic EBRT to ADT in the treatment of node-positive prostate cancer reduces the risk of failure, while probably true, cannot be rigorously concluded from the present analysis because of the short median follow-up, low event rate, nonrandomized data, and lack of adjustment for treatment variation and some known prostate cancer prognostic factors. Moreover, to affect clinical practice, at a minimum one should provide evidence in a model powered for survival and adjusted for age, comorbidity, known prostate cancer prognostic factors, and type and duration of ADT that treatment using both pelvic and prostate RT and ADT as compared with