International Journal of Radiation Oncology biology • physics

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Clinical Investigation

Dose Escalation for Prostate Adenocarcinoma: A Long-Term Update on the Outcomes of a Phase 3, Single Institution Randomized Clinical Trial

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Received Nov 8, 2018. Accepted for publication Feb 21, 2019.

Summary

At a median follow-up of more than 14 years, this is one of the most mature randomized dose-escalation trials that continues to demonstrate significant improvement in biochemical or clinical failure, particularly distant metastases. This improvement translated into a significant improvement in prostate cancer mortality and decreased salvage therapy requirement and maintenance of a low incidence of secondary malignancies.

Purpose: To determine the long-term outcomes for prostate adenocarcinoma when escalating radiation dose from 70 Gy to 78 Gy.

Methods and Materials: Between 1993 and 1998, 301 patients with biopsy-proven clinical stage T1b-T3 prostate adenocarcinoma, any prostate-specific antigen level, and any Gleason score were randomized to 70 Gy in 35 fractions versus 78 Gy in 39 fractions of photon radiation therapy using a 4-field box technique without hormone deprivation therapy. The primary outcome was powered to detect a 15% difference in biochemical or clinical failure. Secondary outcomes included survival, prostate cancer mortality, biochemical failure, local failure, nodal failure, distant failure, and secondary malignancy rates.

Results: With a median follow-up of 14.3 years, the cumulative incidence of 15-year biochemical or clinical failure was 18.9% versus 12.0% in the 70 Gy versus 78 Gy arms, respectively (subhazard ratio [sHR], 0.61; 95% confidence interval [CI], 0.38-0.98; Fine-Gray $P = .042$). The 15-year cumulative incidence of distant metastasis was 3.4% versus 1.1%, respectively (sHR, 0.33; 95% CI, 0.13-0.82; Fine-Gray $P = .018$). The 15-year cumulative incidence of prostate cancer-specific mortality was 6.2% versus 3.2%, respectively, (sHR, 0.52; 95% CI, 0.27-0.98; Fine-Gray $P = .045$). There were no differences in overall survival (HR, 1.10; 95% CI, 0.84-1.45; log rank $P = .469$) or other-cause

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Supported in part by grants CA 06294 and CA 16672 awarded by the National Cancer Institute, U.S. Department of Health and Human Services; DOD Grant DAMD 17-98-1-8483; and the Prostate Cancer Research Program at MD Anderson Cancer Center.

Disclosures: A.P., S.J.F., and C.T. disclose funding support by Varian Medical Systems.

Supplementary material for this article can be found at https://doi.org/10.1016/j.ijrobp.2019.02.045.

Int J Radiation Oncol Biol Phys, Vol. 104, No. 4, pp. 790–797, 2019
0360-3016/$ - see front matter
https://doi.org/10.1016/j.ijrobp.2019.02.045

survival (sHR, 1.33; 95% CI, 0.99-1.79; Fine-Gray $P = .061$). Salvage therapy was more common in the 70 Gy arm, at 38.7% versus 21.9% in the 78 Gy arm ($P = .002$). There was a 2.3% secondary solid malignancy rate (1 bladder, 6 rectal) within the radiation treatment field, which was not significantly different between treatment arms.

Conclusions: Dose escalation by 8 Gy (78 Gy vs 70 Gy) provided a sustained improvement in biochemical and clinical failure, which translated into lower salvage rates and improved prostate cancer-specific mortality, but not overall survival. Long-term follow-up demonstrated a low incidence of potential solid tumor secondary malignancies.

Introduction

External beam radiation therapy is a curative treatment option for localized prostate cancer and is used in roughly a quarter of all treated cases in the United States.[1] Based on quantitative biological modeling studies[2,3] and supported by clinical observations,[4] it is well established that high doses of radiation are necessary for adequate prostate cancer cell killing to achieve cure. However, until 3-dimensional conformal radiation therapy (3DCRT) and intensity modulated radiation therapy (IMRT) techniques could be implemented clinically, dose escalation to the prostate was limited out of concern for toxicity to surrounding organs at risk. Although several randomized controlled trials have examined dose escalation in prostate cancer,[5-9] none report median follow-up beyond 10 years. Moreover, these trials had heterogeneous use of concurrent androgen deprivation therapy, which is now the standard of care for many patients. Given the frequently indolent nature of the disease and protracted time to failure, extensive follow-up may provide unique and valuable insight. Here, we present long-term follow-up of a prospective trial involving patients with localized prostate adenocarcinoma treated without hormonal therapy, randomized to standard versus dose escalated radiation therapy.

Methods and Materials

Protocol eligibility and participants

Between 1993 and 1998, patients at our high-volume academic institution were enrolled in an institutional review board–approved phase 3 randomized trial (CRT 93-001). Informed consent was obtained from each participant. Eligibility criteria included clinical stage T1-T3, N0, M0 prostate cancer based on the 1992 American Joint Commission on Cancer staging system; a documented pretreatment serum prostate-specific antigen (PSA) measurement $\leq$30 ng/mL; histopathologic confirmation of diagnosis and Gleason score at our institution; and no history of pelvic radiation, radical prostatectomy, or androgen therapy. A bone scan or computed tomography (CT) scan was performed for pretreatment PSA levels $>$10 ng/mL or $>$20 ng/mL, respectively. Stratification at protocol entry was done based on pretreatment PSA level: PSA $\leq$10, 10-20, and $>$20 ng/mL. Randomization was done 1:1 using a permuted block randomization allocation scheme performed by the Data Management Section in the Department of Clinical Radiotherapy. Follow-up schedule was a digital rectal examination and PSA measurement every 3 months for 2 years, every 6 months for 3 years, and then annually. In later years, patients were followed through clinical visits or yearly letters to determine status.

The Consolidated Standards of Reporting Trials diagram demonstrates that out of a total of 305 patients, 301 met the eligibility criteria and were enrolled in the study (Fig. E1; available online at https://doi.org/10.1016/j.ijrobp.2019.02.045). The 4 nonassessable patients include 2 who withdrew consent before starting radiation therapy, 1 who chose surveillance, and 1 who lacked pathologic confirmation review at our institution. Of the 301 assessable patients, 150 were randomized to 70 Gy in 35 fractions and 151 were randomized to 78 Gy in 39 fractions. There were 4 protocol violations with 2 who received adjuvant androgen blockade and 2 who were randomized to receive 78 Gy but instead received 70 Gy. We report outcomes on an intent-to-treat basis.

Radiation treatment

All patients were prescribed 2 Gy per day to the isocenter, and the clinical target volume (CTV) included the prostate and seminal vesicles. Planning was done based on a pretreatment pelvic CT scan. Pelvic lymph nodes were not included in the target volume. A conventional 4-field box design was used for the initial 46 Gy in both treatment arms. The general anteroposterior field size was 11 $\times$ 11 cm, and the lateral fields were 11 $\times$ 9 cm with a small block over the anterior bladder and posterior half of the rectum. After 46 Gy, the 70 Gy arm had a field reduction to 9 $\times$ 9 cm using a 4-field design whereas the 78 Gy arm had a 6-field 3DCRT design. Margins from the CTV to the block edge were 1.25 to 1.5 cm in the anteroinferior dimension and 0.75 to 1.0 cm in the posterosuperior dimension. 3DCRT included Beam's Eye View shaping with generous margins around the CTV to account for uncertainty. A CT scan was done during the first week of treatment to confirm appropriate CTV coverage.

Endpoints and statistical analysis

The primary endpoint of the study was biochemical or clinical disease failure (freedom from failure [FFF]). Secondary endpoints include overall survival (OS), prostate cancer specific-mortality (PCSM), local failure (LF), nodal failure (NF), and distant metastatic failure (DMF). Assuming direct causality from differences in local tumor control, the protocol was designed with 150 patients per treatment arm to detect a 15% difference in FFF.[10] Interim analyses were performed after 180 and 250 patients were enrolled using actuarial freedom from rising PSA as the main endpoint. A biopsy 2 years after completion of radiation therapy was planned to confirm eradication of disease.

Biochemical failure (BF) was defined by the American Society for Therapeutic Radiology and Oncology Phoenix criteria of PSA nadir + 2 ng/mL[11] on post hoc analysis given that this is the modern standard of care. BF at the time of the clinical trial was defined as 3 or more PSA increases on follow-up visit per the 1997 American Society for Therapeutic Radiology and Oncology criteria,[12] which is no longer commonly used in practice. On post-hoc analysis, we stratified patients into risk groups based on the National Comprehensive Cancer Network (NCCN) guidelines, which define low risk (Gleason $\leq$6, PSA $<$10 ng/mL, and clinical $\leq$T2a), high risk (Gleason $\geq$8 or PSA $>$20 ng/mL or clinical T3), and intermediate risk (any patient not meeting low-risk or high-risk criteria) groups. Clinical failure was defined as local, nodal, or distant recurrence before PSA failure or the initiation of salvage hormonal therapy. LF was defined as palpable evidence of disease or positive biopsy because of rising serum PSA; NF was defined as positive lymph nodes noted on CT scan; DMF was based on CT scan or bone scan; PCSM was defined as death at time of progressive metastatic disease or death while actively receiving prostate cancer treatment; other-cause mortality was defined as all causes of death minus prostate-cancer specific mortality; and distant metastatic-free survival (DMFS) was defined as distant metastases or death as an event. Patients who died from other causes, those without a documented cause of death and last PSA $\leq$1.0 ng/mL without metastases, or those on prostate cancer treatment (eg, androgen deprivation) were classified as dying from other causes. Cause of death was determined by death certificate as recorded in the National Death Index database or by the institutional tumor registry

Table 1 Intention to treat patient, disease, and treatment characteristics by treatment arm

	70 Gy arm	78 Gy arm
Total no. of patients	150	151
Median age at diagnosis (range), y	69 (50-79)	69 (48-81)
Race		
White	124 (82.7%)	132 (86.1%)
Black	16 (10.7%)	12 (7.9%)
Hispanic	7 (4.7%)	4 (2.7%)
Asian	3 (2%)	3 (2%)
Median pretreatment PSA, (range), ng/mL	7.50 (1.1-32.5)	7.80 (0.6-86.1)
Pretreatment PSA grouping, ng/mL		
$\leq$10	98 (65.3%)	98 (64.9%)
10-20	42 (28%)	47 (31.1%)
$>$20	10 (6.7%)	6 (4%)
Gleason total		
$<$6	13 (8.7%)	15 (9.9%)
6	57 (38%)	59 (39.1%)
7	54 (36%)	50 (33.1%)
8	19 (12.7%)	22 (14.6%)
9	5 (3.3%)	5 (3.3%)
10	2 (1.3%)	0
AJCC tumor stage		
T1	45 (30%)	43 (28.5%)
T2	79 (52.7%)	74 (49%)
T3	26 (17.3%)	34 (22.5%)
NCCN risk group		
Low	31 (20.7%)	31 (20.5%)
Intermediate	71 (47.3%)	67 (44.4%)
High	48 (32%)	53 (35.1%)
Lost to follow-up	8 (5.3%)	14 (9.3%)

Abbreviations: AJCC = American Joint Commission on Cancer; NCCN = National Comprehensive Care Network; PSA = prostate-specific antigen.

Table 2 Cumulative incidence of clinical and/or biochemical failure, biochemical failure, local failure, distant metastasis failure, other-cause mortality, prostate cancer-specific mortality, and overall survival hazard ratios by treatment arm

	Outcome type								
	Clinical and/or biochemical failure			Biochemical failure			Local failure		
		Univariate			Univariate			Univariate	
	15-year (%)	sHR (95% CI)	*P* value	15-year (%)	sHR (95% CI)	*P* value	15-year (%)	sHR (95% CI)	*P* value
70 Gy arm	18.9	1 [Ref]	.042	12.3	1 [Ref]	.051	11.3	1 [Ref]	.326
78 Gy arm	12.0	0.61 (0.38-0.98)		7.1	0.56 (0.31-1.00)		8.4	0.72 (0.39-1.37)	

Abbreviations: CI = confidence interval; HR = hazard ratio; Ref = reference; sHR = subhazard ratio.

that regularly contacts patients regarding disease and vital status.

A competing risk analysis was done using the Fine-Gray test for cumulative incidence of clinical and/or biochemical failure, BF, LF, DMF, other-cause mortality, and PCSM.[13] The competing event for all of these analyses is death without failure. Univariate competing risk regression analysis was used to obtain subhazard ratios (sHRs) for clinical and/or biochemical failure, BF, LF, DMF, PCSM, and other-cause mortality. Multivariate competing risk regression analysis was also done. Kaplan-Meier analysis was carried out to determine OS and DMFS; comparisons between groups were done using the log-rank test. Univariate Cox regression analysis was used to obtain hazard ratios for OS and DMFS. Differences in prognostic patient characteristics and stratification criteria between treatment groups were assessed using a χ^2 or Wilcoxon rank-sum test. A P value of .05 or less was considered to be statistically significant. Statistical tests were based on a 2-sided significance level. All statistical analyses were performed using Stata/MP 15.1 (College Station, TX).

Results

As of January 2018, the median follow-up was 14.3 years and median time since last contact among living patients was 1 month (range, 0-43 months). Of the 301 patients, 71% (214) were confirmed to be deceased and 7.3% (22) requested to stop contact and/or were lost to follow-up (>48 months since last contact). Examining the patients lost to follow-up more closely, 8 versus 14 were in the 70 Gy versus 78 Gy arm, respectively, which was not significantly different (P = .682). On subgroup analysis, there were no differences in the lost-to-follow-up group in terms of age, ethnicity, pretreatment PSA, Gleason score, American Joint Committee on Cancer tumor staging, or NCCN risk classification. The patient and tumor characteristics are outlined in Table 1. The median age at diagnosis was 69 years. There was no difference between treatment arms in age, ethnicity, pretreatment PSA, Gleason score, American Joint Committee on Cancer tumor staging, or NCCN risk stratification. The majority of patients were intermediate (45.8%) or high risk (33.6%) per NCCN risk stratification. One patient in the low-dose and high-dose group received unplanned adjuvant hormone therapy after radiation therapy.

Table 2 summarizes the univariate hazard ratios, P values, and 15-year survival percentages for the major outcomes in the 70 Gy versus 78 Gy groups. Figure 1 demonstrates that the primary study endpoint of biochemical and/or clinical failure was significantly better for the 78 Gy arm as compared to the 70 Gy arm (sHR, 0.61; 95% CI, 0.38-0.98; Fine-Gray P = .042). The 15- and 20-year cumulative incidences were 18.9% and 19.2% for the 70 Gy arm as compared to 12.0% and 12.2% for the 78 Gy arm, respectively. Based on competing risk univariate regression analysis, factors aside from dose that were significantly associated with worse biochemical or clinical failure included T2 stage (sHR, 2.11; 95% CI, 1.10-4.03; P = .024) and NCCN low-risk disease (sHR, 0.45; 95% CI, 0.23-0.90; P = .025). On multivariate analysis, dose (sHR, 0.33; 95% CI, 0.13-0.82; P = .018), higher Gleason score (sHR, 2.14; 95% CI, 1.45-3.16; P < .001), T3 stage (sHR, 15.34; 95% CI, 3.43-68.55; P < .001), pretreatment PSA (sHR, 1.08; 95% CI, 1.06-1.11; P < .001), and pretreatment PSA >10 ng/mL (sHR, 4.08; 95% CI, 1.76-9.49; P = .001) remained significant (Table EA; available online at https://doi.org/10.1016/j.ijrobp.2019.02.045). Clinical and/or biochemical failure was not significantly different between the 70 Gy and 78 Gy arms (Fig. 2) when stratifying by NCCN low risk (Fine-Gray P = .064), intermediate risk (Fine-Gray P = .344), and high-risk disease (Fine-Gray P = .223). Tables EG, EH, and EI (available online at https://doi.org/10.1016/j.ijrobp.2019.02.045) provide additional information on clinical outcomes when stratifying by treatment arm and NCCN risk grouping.

The cumulative incidence of BF at both 15 and 20 years (Fig. E2; available online at https://doi.org/10.1016/j.ijrobp.2019.02.045) was 12.3% and 12.3% versus 7.1% and 7.1% in the 70 Gy versus 78 Gy arm, respectively (sHR, 0.56; 95% CI, 0.31-1.00; Fine-Gray P = .051). Out of the total of 69 biochemical failures, 29% (20) were biopsy proven. On univariate competing risk regression

Table 2 Cumulative incidence of clinical and/or biochemical failure, biochemical failure, local failure, distant metastasis failure, other-cause mortality, prostate cancer-specific mortality, and overall survival hazard ratios by treatment arm *(continued)*

Outcome type											
Distant metastatic failure			Other-cause mortality			Prostate cancer-specific mortality			Overall survival		
	Univariate			Univariate			Univariate			Univariate	
15-year (%)	sHR (95% CI)	P value	15-year (%)	sHR (95% CI)	P value	15-year (%)	sHR (95% CI)	P value	15-year (%)	HR (95% CI)	P value
3.4	1 [Ref]	.018	45.7	1 [Ref]	.061	6.2	1 [Ref]	.045	53.4	1 [Ref]	.469
1.1	0.33 (0.13-0.82)		55.6	1.33 (0.99-1.79)		3.2	0.52 (0.27-0.98)		48.9	1.10 (0.84-1.45)	

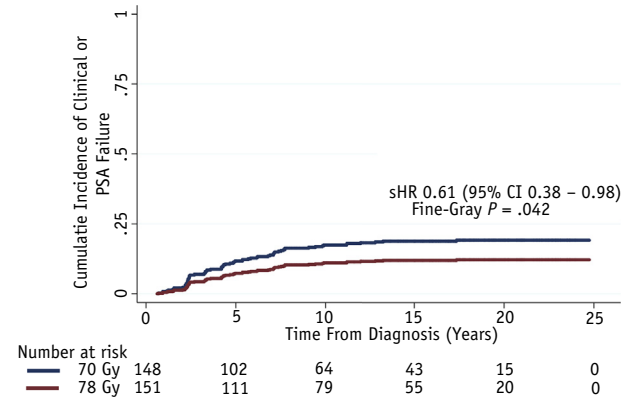

Fig. 1. Cumulative incidence of biochemical or clinical failure for the entire patient cohort treated to 70 Gy versus 78 Gy. Biochemical or clinical failure at 15 and 20 years was significantly better for patients receiving 78 Gy (red line; 12.0% and 12.2%, respectively) compared to 70 Gy (blue line; 18.9% and 19.2%, respectively) (subhazard ratio, 0.61; 95% confidence interval, 0.38-0.98; Fine-Gray $P = .042$). (A color version of this figure is available at https://doi.org/10.1016/j.ijrobp.2019.02.045.)

analysis, dose was the only factor associated with BF; on multivariate analysis, pretreatment PSA was the only significant factor (Table EB; available online at https://doi.org/10.1016/j.ijrobp.2019.02.045). At 15 years without adjuvant or neoadjuvant androgen deprivation, 6.1% versus 5.4% of patients had an NF in the 70 Gy versus 78 Gy arm, respectively.

Figure 3 demonstrates that the cumulative incidence of DMF at 15 and 20 years was significantly higher for the 70 Gy arm at 3.4% and 4.2% versus 1.1% and 1.4% in the 78 Gy arm, respectively (sHR, 0.33; 95% CI, 0.13-0.82; Fine-Gray $P = .018$). Of the patients who had a DMF, 75% (18 of 24) were high risk, 17% (4 of 24) were intermediate risk, and 8% (2 of 24) were low risk. On univariate competing risk regression analysis, total Gleason score, dose, T3 stage, NCCN risk grouping, pretreatment PSA, and pretreatment PSA >10 ng/mL were factors associated with DMF. On multivariate analysis, total Gleason score and pretreatment PSA >10 ng/mL remained significant (Table EC; available online at https://doi.org/10.1016/j.ijrobp.2019.02.045). Patients in the NCCN high-risk group who received 70 Gy versus 78 Gy were more likely to experience DMF at 15 years, at 8% versus 2.6%, respectively (sHR. 0.32; 95% CI, 0.11-0.89; Fine-Gray $P = .03$).

There was no difference in the cumulative incidence of other-cause mortality, also known as non–prostate-cancer death, for patients receiving 70 Gy versus 78 Gy (Fig. E3; available online at https://doi.org/10.1016/j.ijrobp.2019.02.045). The 15- and 20-year cumulative incidences were 45.7% and 64.5% for the 70 Gy arm as compared to 55.6% and 74.8% for the 78 Gy arm, respectively (sHR, 1.33; 95% CI, 0.99-1.79; Fine-Gray $P = .061$). On univariate competing risk regression analysis, age at diagnosis was the only factor associated with other-cause mortality; on multivariate analysis, total Gleason score and age at diagnosis remained (Table ED; available online at https://doi.org/10.1016/j.ijrobp.2019.02.045). As demonstrated in Figure 4, the cumulative incidence of PCSM was significantly higher for patients receiving 70 Gy versus 78 Gy. The 15- and 20-year cumulative incidences were 6.2% and 10.2% for the 70 Gy arm versus 3.2% and 5.4%, respectively (sHR. 0.52; 95% CI, 0.27-0.98; Fine-Gray $P = .045$). On univariate competing risk regression analysis, factors significantly associated with PCSM were year of diagnosis, total Gleason score, dose, tumor stage, NCCN risk grouping, and pretreatment PSA. On multivariate analysis, only total Gleason score remained significant (Table EE; available online at https://doi.org/10.1016/j.ijrobp.2019.02.045). Overall survival was not significantly different between the 70 Gy and 78 Gy arm (HR, 1.10; 95% CI, 0.84-1.45; log rank $P = .469$). Distant metastasis-free survival (Fig. E4; available online at https://doi.org/10.1016/j.ijrobp.2019.02.045) was not significantly different between the 70 Gy and 78 Gy arm (log rank $P = .613$).

Patients in the 70 Gy arm were significantly more likely ($P = .002$) (38.7% [58 of 150]) than those in the 78 Gy arm

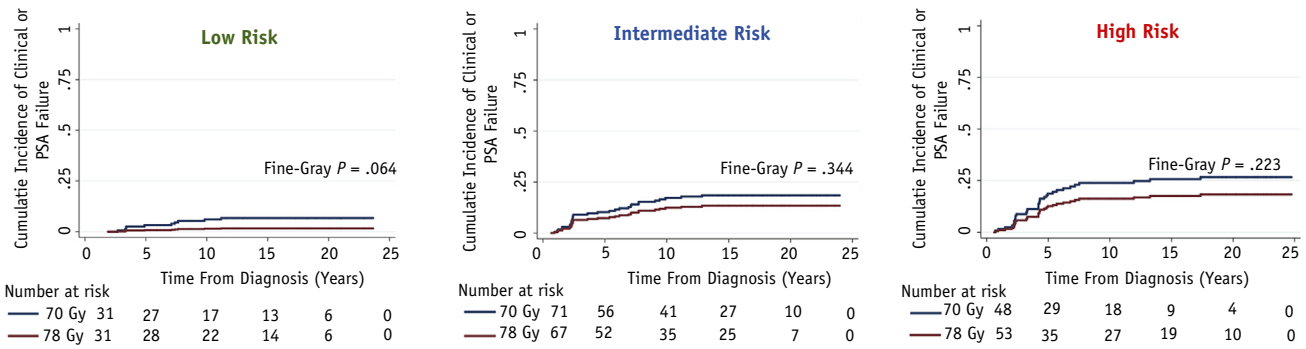

Fig. 2. Cumulative incidence of biochemical or clinical failure for low-, intermediate-, and high-risk patients treated to 70 Gy versus 78 Gy. Subgroup analysis demonstrated no difference in the cumulative incidence of biochemical or clinical failure in patients with low-risk (Fine-Gray $P = .064$), intermediate-risk (Fine-Gray $P = .344$), and high-risk (Fine-Gray $P = .223$) disease per the National Comprehensive Cancer Network risk stratification criteria.

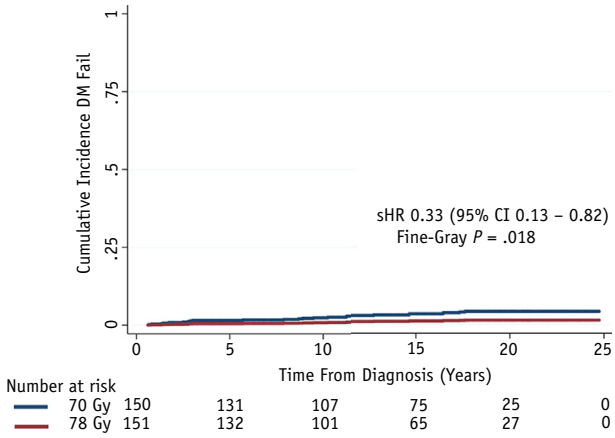

Fig. 3. Cumulative incidence of distant metastatic failure for the entire patient cohort treated to 70 Gy versus 78 Gy. Distant metastatic failure at 15 and 20 years was significantly better for patients receiving 78 Gy (red line; 1.1% and 1.4%, respectively) compared to 70 Gy (blue line; 3.4% and 4.2%, respectively) (subhazard ratio. 0.33; 95% confidence interval. 0.13-0.82; Fine-Gray $P = .018$). (A color version of this figure is available at https://doi.org/10.1016/j.ijrobp.2019.02.045.)

(21.9% [33 of 151]) to undergo salvage therapy such as androgen deprivation, chemotherapy, and/or surgery (Table EF; available online at https://doi.org/10.1016/j.ijrobp.2019.02.045). There was no significant difference in the time to salvage therapy: Patients in the 70 Gy group had a median time of 62.9 months (9.0-257.5 months) versus

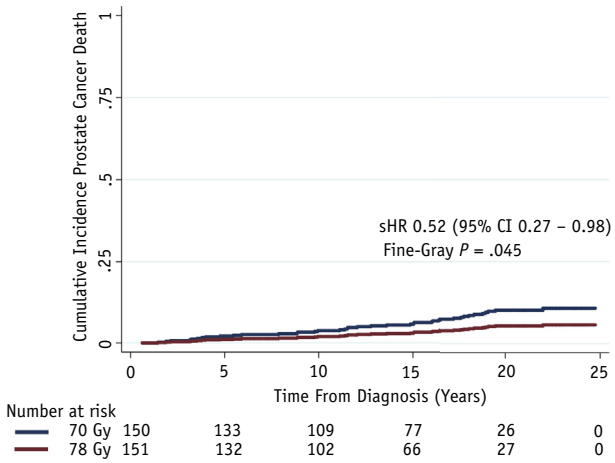

Fig. 4. Cumulative incidence of prostate cancer–specific mortality for the entire patient cohort treated to 70 Gy versus 78 Gy. Cumulative incidence of prostate cancer–specific mortality at 15 and 20 years was significantly higher in the patients receiving 70 Gy (blue line; 6.2% and 10.2%, respectively) compared to 78 Gy (red line; 3.2% and 5.4%, respectively) (subhazard ratio, 0.52; 95% confidence interval, 0.27-0.98; Fine-Gray $P = .045$). (A color version of this figure is available at https://doi.org/10.1016/j.ijrobp.2019.02.045.)

52.2 months (7.7-210.3 months) in the 78 Gy group ($P = .157$). Of 301 patients, 31.2% (94 of 301) had additional malignancies in their lifetime and 2.3% (7 of 301) had possible prostate radiation-related, in-field, secondary malignancies: 1 rectal and 6 bladder cancer cases, without a statistically significant difference between treatment arms. The median time to malignancy was 14 years (range, 6-20 years). Two patients developed a sarcoma in their lifetime, and neither was in the radiation treatment field.

Discussion

The long-term results of this phase 3 randomized, single institution trial found that increasing the radiation dose from 70 to 78 Gy without androgen deprivation resulted in a significant improvement in the primary endpoint of biochemical or clinical failure, with significant reductions in the development of distant metastases, the need for subsequent therapy, and death from prostate cancer at a median follow-up of 14 years. Radiation therapy was associated with a 2.3% incidence of in-field secondary malignancy, such as bladder or rectal cancer, for the overall patient cohort.

Dose escalation[5-9] has become widely adopted as the standard of care for external beam radiation therapy for prostate cancer in the United States,[14] despite relatively little level 1 evidence related to survival or survival without prostate cancer to support this approach. Given the indolent nature of localized prostate adenocarcinoma and its propensity for late biochemical or clinical failures, the true benefit, if any, of radiation dose escalation can only be determined after many years of follow-up. With a median follow up of more than 14 years, our study reports one of the longest follow-up intervals available in a group of prospectively treated patients enrolled in a study designed to test the value of dose escalation for prostate cancer. Moreover, the present study did not include the use of neoadjuvant or concurrent androgen deprivation therapy, which offers an unfettered view of the absolute benefit of dose-escalated radiation therapy.

Consistent with previous updates, these results demonstrate improved FFF in those treated with dose escalation.[15,16] Aside from biochemical failure, dose escalation also significantly lowered the cumulative incidence of DMF at 15 and 20 years in the setting of no hormone deprivation therapy. As a result, the improvement in biochemical and distant relapses translated into lower salvage rates and an improvement in prostate cancer mortality for the dose-escalated group. The discrepancy in higher prostate cancer–specific mortality compared to the cumulative incidence of DMF can likely be accounted for by the fact that patients died while on systemic therapy, which was initiated for a rising PSA without overt evidence of distant disease on bone scan or CT scan, as was commonly done during this era of less advanced imaging techniques. The decrease in salvage rates with dose escalation are

particularly important given the associated morbidity and detrimental effects on quality of life with systemic and even local salvage therapy options.[17-19] The advantage of reducing the need for salvage therapy by approximately 15% should be weighed against the small, but measurable, increase in gastrointestinal and genitourinary toxicity that has been reported by our group in the past.[15,16] Recent prospective studies demonstrate encouraging results that brachytherapy may be an effective local salvage therapy with decreased toxicity as compared to historical reports and should be further explored in larger patient cohorts.[20] Moreover, reduction in late toxicity has been further enhanced in recent years with the implementation of IMRT, improvements in image guided radiation therapy, and other modern radiation techniques.

However, despite the significant gains in biochemical and distant control that have conferred decreased prostate-cancer mortality, dose escalation did not translate to an overall survival benefit. This finding may be due, in part, to an elderly patient cohort at the time of enrollment or the relatively low number of prostate cancer−specific deaths compared to other causes. Moreover, the lack of a survival benefit may be due to the successful nature of salvage therapy, which can include hormonal therapy, cryotherapy, and surgical intervention first line. Similar studies[6,8,9] have not demonstrated an overall survival benefit for dose escalation alone, but the addition of neoadjuvant hormone deprivation therapy to lower doses (65-70 Gy) of radiation therapy does have a purported survival benefit.[21] Similar to salvage therapy, the benefits should be balanced through careful patient selection[22] given the known side effects of androgen deprivation therapy,[19] which can be detrimental to quality of life. The present study may provide some guidance to clinicians contemplating the use of external beam radiation alone in patients with relative contraindications to androgen deprivation therapy.

A median follow-up time of 14.3 years allows for the detection of secondary malignancies that may be associated with a history of radiation therapy; this effect becomes most apparent $\geq$10 years after completion of treatment.[23] Given a 2.3% incidence of in-field solid secondary malignancies, our clinical findings are well within the range of 1.4% to 4% in previous studies.[24-26] Of the 7 recurrences, 4 patients (1.3%) died of the secondary malignancy, 1 of blunt trauma, and 2 were unknown. As a comparison, in the ProtecT trial, 4.0% (22 of 545) active monitoring, 4.5% prostatectomy (25 of 553), and 4.2% radiation therapy (23 of 545) patients died of a neoplasm other than prostate cancer.[27] We would expect these numbers to dwindle even further with modern techniques.[28]

The present study does suffer from some weaknesses. The lack of modern radiation techniques, such as IMRT and/or brachytherapy boost, is certainly a limitation; this study was conducted during an earlier era using a 4-field box/3-dimensional conformal technique. Similarly, the omission of androgen deprivation in the present study does not reflect the modern standard of care for unfavorable intermediate- and high-risk patients. Therefore, these results are less generalizable to a present-day cohort of patients. Salvage therapy was initiated at the clinician's discretion as opposed to a standardized threshold. Additionally, the lack of standardized imaging and follow-up long-term may bias the results. Moreover, long-term side effects were not tracked in a prospective manner beyond 10 years and, therefore, are not reported in this manuscript. Although we acknowledge that the patient cohort 20 years after study completion is small because of drop out and death, this will likely still be the case even with future, more contemporary treatment. Nonetheless, the reported outcomes should add valuable insight on the absolute benefit of high-dose external beam radiation therapy alone for patients with low- and high-risk prostate cancer and should help to guide future trial design in this patient population.

Conclusions

Moderate dose escalation from 70 to 78 Gy demonstrates sustained improvement in clinical or biochemical disease control, which translated into lower salvage rates and prostate cancer mortality. Long-term follow-up also shows a low incidence of related solid tumor secondary malignancies.

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