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Prostate cancer radiotherapy

Young age under 60 years is not a contraindication to treatment with definitive dose escalated radiotherapy for prostate cancer ☆

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ABSTRACT

Background: It is widely believed that younger prostate cancer patients are at greater risk of recurrence following radiotherapy (RT).
Methods: From 1992 to 2007, 2168 (395 age ⩽60) men received conformal RT alone for prostate cancer at our institution (median dose = 76 Gy, range: 72–80). Multivariable analysis (MVA) was used to identify significant predictors for BF and PCSM. Cumulative incidence was estimated using the competing risk method (Fine and Gray) for BF (Phoenix definition) and PCSM to account for the competing risk of death.
Results: With a median follow-up of 72.2 months (range: 24.0–205.1), 8-year BF was 27.1% for age ⩽60 vs. 23.7% for age >60 ($p = 0.29$). Eight-year PCSM was 3.0% for age ⩽60 vs. 2.0% for age >60 ($p = 0.52$). MVA for BF identified initial PSA [adjusted HR = 1.7 (PSA 10–20), 2.6 (PSA >20), $p < 0.01$], Gleason score [adjusted HR = 2.1 (G7), 1.9 (G8–10), $p < 0.01$], T-stage [adjusted HR = 1.7 (T2b–c), 2.6 (T3–4), $p < 0.01$], and initial androgen deprivation therapy (ADT) [adjusted HR = 0.38 (ADT >12 months), $p < 0.01$] as significant, but not age or ADT <12 months. MVA for PCSM identified Gleason score [adjusted HR = 3.0 (G8–10), $p = 0.01$] and T-stage [adjusted HR = 8.7 (T3-4), $p < 0.01$] as significant, but not age, PSA, or ADT.
Conclusion: This is the largest, most mature study of younger men treated with RT for prostate cancer that confirms young age is not prognostic for BF.
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Prostate cancer is diagnosed at increasingly earlier ages, possibly the result of increased awareness or early detection through PSA screening [1,2]. Despite little published evidence comparing efficacy of radiotherapy (RT) to other treatments, only 10–15% of men <60 years of age undergo primary RT [3,4].

Concern exists that younger men, due to their longer life expectancy, may be at relatively increased risk for long-term prostate cancer recurrence after radiotherapy. Rosser bolstered these concerns in his retrospective study of prostate cancer patients receiving RT, finding a significantly increased rate of biochemical failure (BF) in 98 patients aged ⩽60 vs. 866 older men [5]. However, a subsequent publication by Zelefsky showed no significant difference in biochemical free survival for 644 men >60 years vs. 96 younger men receiving definitive prostate EBRT [6], concluding that young age does not necessarily increase failure risk following definitive radiation.

In this study, we reviewed the records of patients receiving external beam radiation therapy to the prostate to examine the impact of age on BF. Our large prospective prostate cancer database allowed us to expand on the previous work of Rosser and Zelefsky with greater patient numbers, longer follow-up, and a greater proportion of patients receiving dose-escalated radiation. We also investigated risk factors for BF and prostate cancer specific mortality (PCSM) in this group of patients.

Material and methods

Between January 1992 and June 2007, 3362 men with localized prostate cancer were treated with definitive 3D conformal radiotherapy (3DCRT) or intensity modulated radiation therapy (IMRT) at Fox Chase Cancer Center. Men were excluded from analysis if they had (1) missing staging or treatment-related data, (2) <24 months follow-up, (3) radiation dose <72 Gy, or (4) metastatic or node-positive disease. A total of 2168 men met these criteria, of which 395 were aged 60 or younger.

All patients underwent a complete workup and staging evaluation prior to treatment, including a transrectal ultrasound-guided biopsy of the prostate gland. All slides for cases diagnosed in referring institutions that represent the majority of the material were reviewed at Fox Chase Cancer Center. Most cases were examined by an oncologic pathologist with a special experience in urologic pathology. Cases with discrepancy in diagnosis or grading with the outside

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institutions were examined by a panel of oncologic pathologists until a consensus diagnosis was reached. T-stage was determined solely by the clinical digital rectal exam; MRI was not used for staging evaluation. PSA data was obtained prior to treatment and serially following completion of treatment. All patients were treated with 3DCRT or IMRT; our techniques have been previously reported [7,8]. Dose was prescribed to the 95% isodose line, and normalized such that 95% of the PTV received 100% of the dose. Patients receiving androgen deprivation were given an LHRH agonist.

Following treatment, serum PSA was typically measured at 4 months and then at 6-month intervals thereafter, unless there was concern for disease progression. Digital rectal exam was performed at every follow-up visit, first at three to 4 months after completion, then every 6–12 months thereafter. Biochemical failure (BF) was defined by the Phoenix definition (PSA nadir + 2 ng/mL) [9].

We used χ^2 tests to examine bivariate associations between patient characteristics and age group. Primary endpoints were time from start of RT to BF, and start of RT to cause-specific death. We estimated cumulative incidence using the competing risk method [10], adjusting for death as a competing risk. This method takes into account that patients who die are no longer at risk for the endpoint and accounts for censoring among those who do not have an event during the follow-up interval. Cumulative incidence curves by age group were compared using Gray's test [10]. For multivariable analyses, we used competing risks proportional hazards regression models [11] to estimate relative risk associated with age group (reported as adjusted hazard ratio, HR) when considered with other covariates. A p value <0.05 was considered statistically significant. We estimated the detectable effect size for this study's parameters (for type I error = 0.05 (two-sided), power = 85%) using a simple Cox model as an approximation to the competing risk regression model. Analyses were done using SAS/STAT software for Windows, version 9.1 (SAS Institute Inc., Cary, NC), R version 2.5.1 (R Foundation for Statistical Computing, Vienna, Austria), and STATA/IC 10.0 for Windows (StataCorp LP, College Station TX).

Results

Patient and treatment characteristics are summarized in Table 1. Risk groups are as assigned by the Fox Chase single factor model [12]. Pre-treatment PSA, radiation dose, incidence and duration of androgen deprivation were not significantly different between the two age groups. There were more high-risk patients in the older age group (27.7% vs. 20.8%, $p = 0.006$), with significantly higher T-stages and Gleason scores as compared to their younger counterparts. There were significantly more African–American patients in the younger group (22% vs. 9%, $p < 0.001$). Median follow-up was 72.2 months (range: 24–205 months).

Fig. 1 shows the cumulative incidence of biochemical failure for younger vs. older men. Five and 8-year cumulative incidence of BF in men aged 60 and younger was 13.9% (95% CI: 10.4–18.1%) and 27.3% (95% CI: 20.1–34.2%), respectively, compared to 12.8% (95% CI: 11.1–14.6%) and 23.3% (95% CI: 20.6–26.1%) in the older patients. The 8-year PCSM rate was 3.0% (95% CI: 1.0–7.1%) for age ⩽60 vs. 2.0% (95% CI: 1.3–3.0%) for age >60, as seen in Fig. 2.

Tables 2 and 3 show the results of the multivariable analysis (MVA) for BF and PCSM, respectively. T-stage, Gleason score, PSA, and androgen deprivation were all significantly associated with BF. Gleason score and T-stage were identified as significant independent predictors for prostate cancer specific mortality. Age ⩽60 was not an independent predictor for BF or PCSM. With 2168 men, of whom 18.2% were ⩽60 years and 81.8% were >60 years, our study had 85% power to detect a hazard ratio of 1.51 or greater for BF. Overall, RT dose ⩾78 Gy (vs. 72–75.9 vs.

Table 1
Patient characteristics.

Characteristic	Men ⩽60 yo	Men >60 yo
N	395	1773
Median age (range)	57.4 (36-60)	70.3 (61–88)
Caucasian race*	295 (75.6)	1573 (89.5)
African–American	87 (22.3)	151 (8.6)
Other race	8 (2.1)	33 (1.9)
Gleason score 2–6*	252 (63.8)	988 (55.7)
7	116 (29.4)	553 (31.2)
8–10	27 (6.8)	232 (13.1)
T1, 2a*	284 (71.9)	1149 (64.8)
T2b–c	63 (16.0)	401 (22.6)
T3–4	25 (6.3)	141 (8.0)
preTx PSA <10	262 (66.3)	1094 (61.7)
10-20	83 (21.0)	460 (25.9)
>20	50 (12.7)	219 (12.4)
Median preTx PSA	6.7 (0.4-93.4)	8.1 (0.7-186)
Low risk*	154 (40.1)	513 (29.7)
Int risk	150 (39.1)	735 (42.6)
High risk	80 (20.8)	477 (27.7)
No ADT	293 (74.2)	1253 (70.7)
ADT <12 months	44 (11.1)	225 (12.7)
ADT > 12 mo	58 (14.7)	295 (16.6)
Dose 72–75.9 Gy	175 (44.3)	813 (45.9)
76–77.9 Gy	134 (33.9)	509 (28.7)
78+ Gy	86 (21.8)	451 (25)
Median follow-up	66.3 months	73.3 months

Abbreviations: PSA, prostate specific antigen; ADT, androgen deprivation therapy.
* $p < 0.05$, Considered statistically significant.

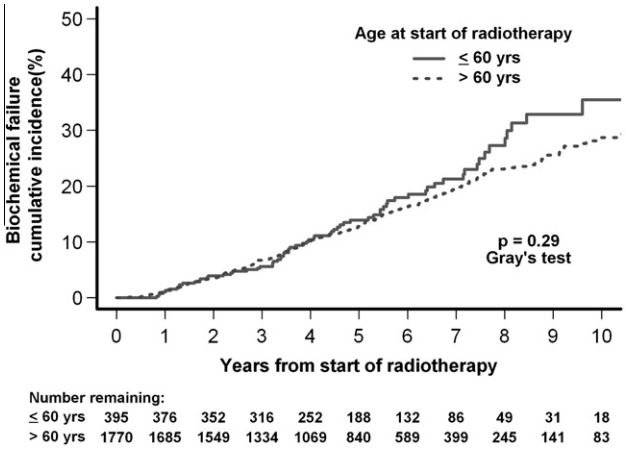

Fig. 1. Cumulative incidence of biochemical failure for patients ⩽60 vs. >60.

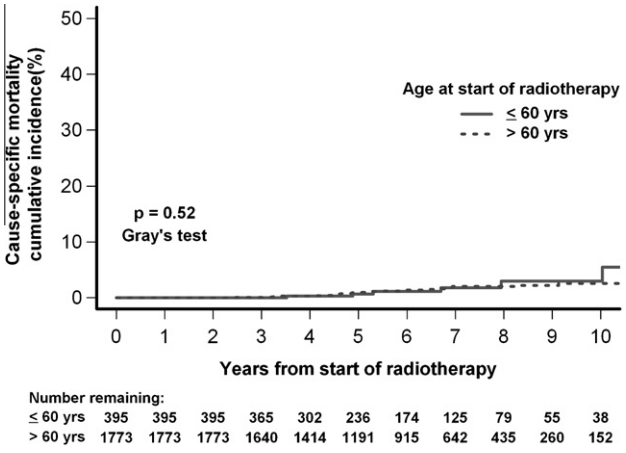

Fig. 2. Prostate cancer specific mortality for patients ⩽60 vs. >60 years old.