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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 1992–2007, 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). 8-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 mo), 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.

Conclusions—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.

Keywords

prostatic neoplasms; prostate; radiotherapy; conformal; age factors

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INTRODUCTION

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 versus 866 older men [5]. However, a subsequent publication by Zelefsky showed no significant difference in biochemical free survival for 644 men >60 yrs versus 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, 3,362 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 2,168 men met these criteria, of which 395 were age 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 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 four months and then at six-month intervals thereafter, unless there was concern for disease progression. Digital rectal exam was performed at every follow-up visit, first at three to four months after completion, then every six to twelve months thereafter. Biochemical failure (BF) was defined by the Phoenix Definition (PSA nadir + 2 ng/mL) [9].

We used Chi-square 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

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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).

Figure 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 Figure 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 2,168 men, of whom 18.2% were ≤60 yrs and 81.8% were >60 yrs, 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. 76–77.9 Gy) was associated with significantly decreased risk of PCSM (adjusted HR=0.36, p=0.04).

Toxicity information was available for 2,124 men in our study population, of which 387 were ≤60 years old. Acute and late toxicities were graded by a modification of the RTOG Acute and Late Morbidity Scoring Criteria [13]. Late GI toxicity (≥Grade 2) was slightly but significantly higher in older men, 10.1 vs. 5.7% (p=0.009). There was no significant difference between age groups for early ≥Grade 2 and ≥Grade 3 GI or GU toxicity, or for late ≥Grade 2 and ≥Grade 3 GU toxicity.

DISCUSSION

This study, to our knowledge, is the largest to report outcomes for men under 60 years old (n=395) who received modern definitive EBRT for prostate cancer. It is also the first study

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examining the relationship between age and post-RT BF utilizing the Phoenix definition for BF, which has been shown to be superior to the ASTRO consensus definition [9, 14].

There are limited data available in the recent literature investigating outcomes for young prostate cancer patients treated with external beam radiation. Our institutional experience, initially published in 1996, compared the biochemical outcomes of 30 men under age 65 with 139 men aged 65 years and older receiving definitive external beam radiation for T1–T2 prostate cancer [15]. With 3-year median follow-up, freedom from biochemical failure (FFBF) was equivalent between the younger and older men, with 5-year actuarial biochemical control rates of 89% and 84%, respectively [15]. A subsequent matched pair analysis of 252 men treated with prostate 3DCRT at our institution showed no difference in FFBF between men ≤55, 60–70, and ≥70 years old [16]. A European retrospective analysis of 39 prostate EBRT patients aged ≤55 years of age demonstrated an 88% 5 year disease free survival [17]. The Department of Defense Center for Prostate Disease Research retrospectively investigated the effect of age on biochemical outcomes for 1,018 patients receiving definitive radiotherapy [18]. With a median follow-up of 85 months, their findings showed no significant relationship between age and BF, whether age was considered as a continuous variable (p=0.59), a discrete variable based on decade (p=0.07), or divided into <60 or ≥60 years old (p=0.65) [18].

In 2002, Rosser and colleagues compared biochemical outcomes for 98 men 60 years of age or younger to those of 866 men older than 60 years who underwent definitive prostate EBRT at the MD Anderson Cancer Center. With a median follow-up of 48 months, the younger men were found to have a statistically higher rate of biochemical failure at 5 and 7 years (45% vs. 35% for 5 years, p <0.05 and 53% vs. 41% for 7 years, p <0.05) [5]. The following year, Zelefsky et al published the Memorial Sloan-Kettering Cancer Center experience of definitive prostate EBRT for 96 men aged ≤60 compared to 644 men >60. Unlike Rosser, Zelefsky found no difference in biochemical failure rates between younger and older men. With a median follow up of 88 months, the 5 and 7 year biochemical failure rates were 18% and 21% in younger men, versus 21% and 22% in men >60 [6]. At first glance, these results (like ours) seem to conflict directly with those published by Rosser. However, as noted by Zelefsky, the median RT dose in Rosser's study population was 66 Gy, considerably lower than median dose from Zelefsky et al. (75.6 Gy) and the current study (76 Gy). Furthermore, 85% of patients included in Rosser's analysis received 70 Gy or less. Dose escalation >70 Gy significantly reduces the incidence of BF [19]. Zelefsky examined the relationship between dose and his institutions' BF rates, finding that doses less than 75.6 Gy were associated with an 8-fold increased BF risk in men <60 yrs. When radiation was delivered at dose-escalated ranges, BF was equivalent between younger and older patients. The results of our study support Zelefsky's conclusion that, at sufficiently high RT doses, biochemical control is equivalent between both age groups. The failure of our analysis to show a significant relation between RT dose and BF may be, in part, attributable to the fact that only patients who received at least 72 Gy were included. Interestingly, we were able to show a significant PCSM benefit associated with dose ≥78 Gy.

Although our study was limited to patients receiving external beam photon RT, men under 60 years old undergoing brachytherapy seed implants or proton beam therapy also have comparable biochemical control compared to older men. With an average of 56 months follow-up, Shapiro et al. [20] found no age-related difference in biochemical failure rates after brachytherapy in all risk groups. 10-year biochemical progression free survival for men <60 as compared to older men was 91.3% vs. 91.8%, 80.0% vs. 83.4%, and 70.2% vs. 72.1% respectively for low, intermediate, and high risk patients [20]. Similarly, Hinnen et al. [21] demonstrated no significant difference in 10 year in FFBF or PCSM after prostate brachytherapy for men ≤60 compared to older men. Burri et al. [22] found no difference in 5

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or 8 year FFBF for 378 men age ≤60 (95% and 92%, respectively) as compared to 1287 men >60 (93% and 97%, respectively) receiving low-dose-rate brachytherapy [22]. In 2004, investigators at Loma Linda University Medical Center showed that age did not significantly impact FFBF following definitive proton beam radiotherapy to the prostate. With a median follow up of 62 months, 8 year FFBF was 75% for men <60 years, and 74% for men ≥60 years [23].

It has been well-documented that prostate cancer patients under the age of 60 overwhelmingly choose radical prostatectomy as their treatment modality of choice [4, 24]. This may reflect an underlying assumption in patients and physicians that radical prostatectomy offers superior long-term disease control [25]. Unfortunately, randomized data comparing the relative efficacy of different treatment modalities is lacking. The single randomized trial comparing RP to EBRT is not applicable to the modern prostate cancer patient, having been published in 1982, long before the era of PSA, conformal radiation and dose escalation [26]. A Cochrane meta-analysis intended to synthesize all available data to formulate valid comparisons between treatment modalities was unable to draw any conclusions regarding the comparative efficacy of EBRT versus RP, citing inconsistent definition of biochemical failure between nonrandomized studies [27]. While direct comparisons can not be made, FFBF for men aged ≤60 reported in this study appear consistent with those reported in several recent prostatectomy series [28–32].

The strength of our conclusion is limited by the retrospective nature of our data and relatively small patient numbers. Selection bias may lead to unaccountable imbalances between the younger and older men. Our statistical methods and survival endpoints were chosen to minimize the impact of comorbidities and competing causes of death. Another potential shortcoming of this study is the higher proportion of low-risk patients in the younger age group. Low-risk patients have by definition a lower risk of BF, which may be more difficult to detect in a retrospective study of this size. And, low-risk patients may require more extended follow-up [33]. It is however, important to note that the multivariable analysis used in this study would account to difference in risk factors between younger and older men. An additional noteworthy finding was the nearly equivalent use of ADT in the older age group despite higher risk disease, indicating that a larger proportion of high risk men in the younger age group received ADT. The role of long-term ADT for high-risk patients was demonstrated in 1997 with the publication of EORTC 22863 [34, 35], which randomized patients with locally advanced prostate cancer to radiation with concurrent and adjuvant ADT for 3 years versus radiation alone. At the time of publication, patients receiving ADT demonstrated a highly significant survival advantage, with 78% of the ADT group alive at 5 years compared to 62% of the control group. Over the next few years, additional randomized studies confirmed the benefit of androgen deprivation therapy in higher risk prostate cancer patients, and by the time RTOG 92-02 demonstrated the superiority of long-term over short-term ADT in 2003, adjuvant ADT had become well-established as the standard of care for high-risk patients [36, 37]. Of the 112 high-risk patients treated from 1992–1996, only 45% received ADT; less than one-third of these patients received ADT >12 months. From 1997 to 2002, only 54% of our high-risk patients received ADT >12 months, and 25% received no ADT at all. Very few (14%) of the high risk patients treated from 2003–2007 were not given ADT, while 70% received ADT >12 months. Imbalances in ADT use across age and risk groups were accounted for in the multivariable analysis, which did not show a relationship between age and BF or PSCM.

The decision to proceed with a particular therapy for localized prostate cancer depends on more than just which modality offers the best likelihood of disease control. Factors such as comorbidities, potential complications, quality of life, and patient preference must be considered as well. Many younger patients, particularly those with demanding work

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schedules, are unable to accommodate eight weeks of daily radiation treatments. Other young patients may opt for surgery based on the possibility that a radiation-induced secondary malignancy could manifest years later, although the clinical magnitude of this risk is currently undefined [38–41]. Still others may choose surgery for psychological assurance that the disease has been removed, and to escape the uncertainties of having a detectable post-treatment PSA. Alternatively, some patients may proceed with radiation therapy to avoid an invasive procedure or to lessen their risk of urinary incontinence.

CONCLUSION

The results of this study suggest that young men receiving definitive radiation therapy fare just as well as their older counterparts, when it comes to biochemical control and prostate cancer specific survival. As such, young age should not preclude prostate cancer patients from receiving definitive radiation treatment.

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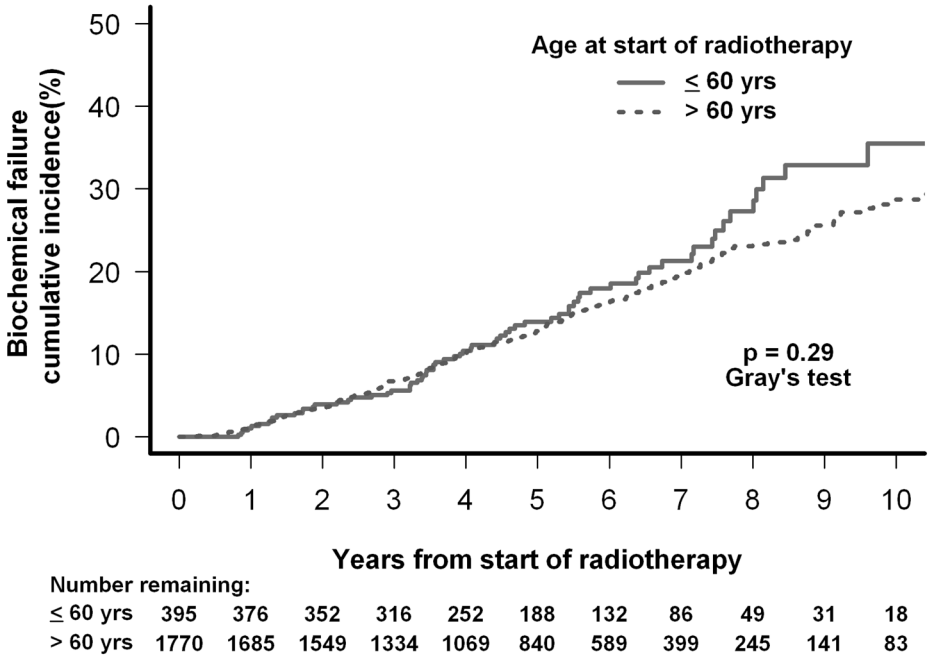

Figure 1.
Cumulative Incidence of Biochemical Failure for Patients ≤60 vs. >60

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Figure 2.
Prostate Cancer Specific Mortality for Patients ≤60 vs. >60 years old.

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Table 1

Patient Characteristics

Characteristic	Men ≤ 60 yo	Men > 60 y.o
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 mo	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

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Table 2

Adjusted hazard ratios for biochemical failure

		HR (95% CI)	***p***
Age	61+	1.00	
	36–60	1.21 (0.92–1.59)	0.17
Gleason Score	2–6	1.00	
	7	2.09 (1.64–2.67)	<.0001
	8–10	1.91 (1.24–2.93)	0.003
T Stage	T1-T2a	1.00	
	T2b-T2c	1.69 (1.31–2.19)	<.0001
	T3–T4	2.64 (1.76–3.96)	<.0001
PSA	<10	1.00	
	10–20	1.33 (1.03–1.71)	0.031
	>20	2.58 (1.93–3.44)	<.0001
ADT	None	1.00	
	<12 mo	0.77 (0.54–1.11)	0.16
	>12 mo	0.38 (0.25–0.57)	<.0001
RT Dose	72–75.9	1.000	
	76–77.9	1.15	0.25
	78+	0.88	0.36

Results of multivariable competing risk regression analysis

Abbreviations: PSA = Prostate Specific Antigen; ADT = Androgen Deprivation Therapy; RT = Radiation Therapy

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Table 3

Adjusted hazard ratios for prostate cancer specific mortality

		HR (95% CI)	***p***
Age	61+	1.00	
	36–60	1.46 (0.61–3.49)	0.40
Gleason Score	2–6	1.00	
	7	1.96 (0.85–4.52)	0.11
	8–10	2.98 (1.26–7.06)	0.01
T Stage	T1-T2a	1.00	
	T2b-T2c	2.03 (0.73–5.64)	0.18
	T3–T4	8.66 (3.14–23.9)	<.0001
PSA	<10	1.00	
	10–20	0.77 (0.33–1.81)	0.55
	>20	0.99 (0.39–2.52)	0.97
ADT	None	1.00	
	<12 mo	0.98 (0.39–2.46)	0.96
	>12 mo	0.64 (0.26–1.59)	0.34
RT Dose	72–75.9	1.00	
	76–77.9	0.89 (0.34–2.31)	0.81
	78+	0.36 (0.14–0.96)	0.04

Results of multivariable competing risk regression analysis

Abbreviations: PSA = Prostate Specific Antigen; ADT = Androgen Deprivation Therapy; RT = Radiation Therapy