Published in final edited form as:

Int J Radiat Oncol Biol Phys. 2011 December 1; 81(5): 1293–1301. doi:10.1016/j.ijrobp.2010.07.2004.

OLDER AGE PREDICTS DECREASED METASTASIS AND PROSTATE CANCER-SPECIFIC DEATH FOR MEN TREATED WITH RADIATION THERAPY: META-ANALYSIS OF RADIATION THERAPY ONCOLOGY GROUP TRIALS

Daniel A. Hamstra, M.D., PH.D.[*], **Kyounghwa Bae, PH.D.**[†], **Miljenko V. Pilepich, M.D.**[‡], **Gerald E. Hanks, M.D.**[¶], **David J. Grignon, M.D.**[§], **David G. McGowan, M.D.**[**], **Mack Roach, M.D.**[††], **Colleen Lawton, M.D.**[‡‡], **R. Jeffrey Lee, M.D.**[¶¶], and **Howard Sandler, M.D.**[§§]

[*]University of Michigan, Ann Arbor, Michigan

[†]Radiation Therapy Oncology Group, Philadelphia, Pennsylvania

[‡]UCLA Medical Center, Los Angeles, California

[¶]Fox Chase Cancer Center, Philadelphia, Pennsylvania

[§]Indiana University-Purdue University Indianapolis, Indiana

[**]Cross Cancer Institute, Edmonton, Alberta, Canada

[††]UCSF, San Francisco, California

[‡‡]Medical College of Wisconsin, Milwaukee, Wisconsin

[¶¶]Intermountain Medical Center, Salt Lake City, Utah

[§§]Cedars-Sinai Medical Center, Los Angeles, California

Abstract

Purpose—The impact of age on prostate cancer (PCa) outcome has been controversial; therefore, we analyzed the effect of age on overall survival (OS), distant metastasis, prostate cancer-specific death (PCSD), and nonprostate cancer death (NPCD) on patients with locally advanced PCa.

Methods and Materials—Patients who participated in four Radiation Therapy Oncology Group (RTOG) phase III trials, 8531, 8610, 9202, and 9413, were studied. Cox proportional hazards regression was used for OS analysis, and cumulative events analysis with Fine and Gray's regression was used for analyses of metastasis, PCSD, and NPCD.

Reprint requests to: Daniel A. Hamstra, M.D., Ph.D., Department of Radiation Oncology, University of Michigan Medical Center, UHB2C490, 1500 East Medical Center Drive, Ann Arbor, MI 48109-5010. Tel: (734) 936-7810; Fax: (734) 763-7370; dhamm@umich.edu.

An online CME test for this article can be taken at http://astro.org/MOC.

Presented in part at the American Society of Clinical Oncology Genitourinary Cancers Symposia, Orlando, FL, Feb 26–28, 2009.

Conflict of interest: none.

Results—Median follow-up of 4,128 patients with median age of 70 (range, 43-88 years) was 7.3 years. Most patients had high-risk disease: cT3 to cT4 (54%) and Gleason scores (GS) of 7 (45%) and 8 to 10 (27%). Older age (≤70 vs. >70 years) predicted for decreased OS (10-year rate, 55% vs. 41%, respectively; $p < 0.0001$) and increased NPCD (10-year rate, 28% vs. 46%, respectively; $p < 0.0001$) but decreased metastasis (10-year rate, 27% vs. 20%, respectively; $p < 0.0001$) and PCSD (10-year rate, 18% vs. 14%, respectively; $p < 0.0001$). To account for competing risks, outcomes were analyzed in 2-year intervals, and age-dependent differences in metastasis and PCSD persisted, even in the earliest time periods. When adjusted for other covariates, an age of >70 years remained associated with decreased OS (hazard ratio [HR], 1.56 [95% confidence interval [CI], 1.43-1.70] $p < 0.0001$) but with decreased metastasis (HR, 0.72 [95% CI, 0.63-0.83] $p < 0.0001$) and PCSD (HR, 0.78 [95% CI, 0.66-0.92] $p < 0.0001$). Finally, the impact of the duration of androgen deprivation therapy as a function of age was evaluated.

Conclusions—These data support less aggressive PCa in older men, independent of other clinical features. While the biological underpinning of this finding remains unknown, stratification by age in future trials appears to be warranted.

Keywords

Prostate cancer; Radiation therapy; Hormonal ablation; Age; Metastasis

INTRODUCTION

The incidence of prostate cancer (PCa) increases significantly as men age, but the impact of age on prognosis is not clear. Some investigators have suggested worse outcomes with increasing age (1–6), and others have reported better outcomes in older men (7–10), while still others found no impact of age (11–13).

The Radiation Therapy and Oncology Group (RTOG) conducted a series of phase III trials evaluating the role, timing, and duration of androgen deprivation therapy (ADT) in combination with radiation therapy (RT) in the treatment of men with predominantly locally advanced PCa (14, 15, 16, 17). In this study, we used a meta-analysis of patient treatment data from these trials to evaluate the impact of age.

METHODS AND MATERIALS

Patient evaluation and treatment

Patients were enrolled in four RTOG Phase III PCa trials, 8531 (14), 8610 (15), 9202 (16), and 9413 (17) and were included in this analysis. Details of these trials have been published previously. Briefly, all studies used radiation doses between 65 and 70.2 Gy and included protocols consisting of RT alone vs. RT plus indefinite ADT (RTOG 8531), RT alone vs. RT plus 4 months of neoadjuvant and concurrent ADT (RTOG 8610), RTwith 4 months of neoadjuvant or adjuvant ADT with or without pelvic RT (RTOG 9413), and RT with 4 months of ADT vs. RTwith 28 months of ADT (RTOG 9202).

Statistical methods

The event for overall survival (OS) was defined as death due to any cause, while that for PCa-specific death (PCSD) was defined as death due to PCa, not including unknown causes of death, while non-PCa death (NPCD) was defined as death due to any cause other than PCa. The event for distant metastasis was defined as documented metastatic disease. Time to failure was measured from the date of randomization to the date of the event.

A heterogeneity test was performed to assess the homogeneity of the data and to establish whether one estimate could be used to represent the metadata from four different trials. The chi-square test was applied to assess heterogeneity at the significance level of 0.1. To take into account the differences among the trials, such as the patient population, treatment delivered, and period of accrual, metadata were stratified by the trial. Hazard ratios (HR) were used as estimators for time to failure. Pooled HR estimator values (18,19) with the weight of the inverse of variance of the estimator were used.

Chi-square test values were used to determine if there was a difference with respect to pretreatment characteristics and outcomes of patients with and without missing data. These test values were also used to compare pretreatment characteristics of patients. The Kaplan-Meier method (20) was used to estimate the OS rate, and the log-rank test (21, 22) was used to test the differences between categories. In order to account for competing risks of all causes, mortality with other endpoints, the cumulative incidence method (23) was used to estimate metastasis, PCSD, and NPCD rates, and Gray's test (23) was used to test differences between categories. To determine whether age was independently associated with outcomes, the Cox proportional hazards regression model (24) was used for OS rate, and Fine and Gray's regression models (25) were used for metastasis, PCSD, and NPCD rates. The following covariates were considered in the models: age (≤70 years old [the reference level {RL}) vs. >70 years old or continuous), nodal status (none or not assessed [RL] vs. present), Gleason score (GS; 2–6 [RL] vs. 7 vs. 8–10), clinical stage (T1 or T2 [RL] vs. T3 or T4), race (white [RL] vs. non-white), hormone therapy duration (none [RL] vs. ≤6 months vs. >6 months), and trial (RTOG 8531 [RL] vs. 8610 vs. 9202 vs. 9413). Unadjusted and adjusted HRs were calculated for all covariates by using the appropriate multivariate regressions models with associated 95% confidence intervals (CIs) and *p* values. All statistical tests were two-sided, and a *p* value of <0.05 was considered statistically significant. Statistical Analysis System (SAS Institute, Cary, NC) and R software programs were used.

RESULTS

Patient population and follow-up

There were 69 (1.6%) patients with missing data, who were excluded from analysis. The remaining 4,128 subjects comprised the patient group. There were 930 patients in RTOG trial 8531; 449 patients in trial 8610; 1,474 patients in trial 9202; and 1,275 patients in trial 9413. There were no differences between patients with and without missing data except for race, GS, and hormone duration (data not shown, $p < 0.001$, $p < 0.001$, and $p < 0.004$, respectively). However, there were no differences in outcomes between those patients with

and without missing data. Median follow-up was 7.3 years for all patients, which was greater in those ≤70 years of age (7.7 years) than in those >70 years of age (7.0 years). At last follow-up, 1,988 (48%) of the men were still alive, and 2,140 (52%) of patients had died. Death due to PCa occurred in 649 (16%) patients; 1,243 (30%) of the patients died of other causes, and 248 (6%) of the patients died of unknown causes. A total of 947 (23%) men had metastasis prior to death.

Pretreatment characteristics

This was a high-risk group of patients (Table 1), in which only 5% of patients had clinical stage T1 disease, and 54% of patients had clinical T3 to T4 disease. GSs were 7 to 10 in 72% of patients, and 9% of patients had positive lymph nodes. Clinical characteristics were similar for T stage, GS, and duration of ADT delivered to men in each age group. There was a greater proportion of younger black men (19%) than older black men (12%; $p < 0.0001$) in the group. Finally, younger men were more likely to have positive lymph nodes than older men (12% vs. 5%, respectively, $p < 0.0001$). Since prostate-specific antigen (PSA) screening was not an enrollment criterion for RTOG 8531, we did not include PSA test results in this analysis. Two studies (RTOG 8531 and 8610) randomized patients to receive RT alone compared to those who received RT plus ADT, while two other studies (RTOG 9202 and 9413) assessed the timing or duration of ADT. Therefore, 17% (690) of patients were treated with RT alone, while 83% of patients received ADT, which ran for ≤6 months in 57% (2,367) of patients and for >6 months in 26% (1,071) of patients.

Impact of age on PCa outcomes

Trial results were homogeneous for the impact of age upon OS, PCSD, NPCD, and metastasis ($p > 0.1$) (Table 2). Older patients (>70 years old) were more likely to have died than younger patients (HR = 1.55 [95% CI, 1.42-1.69]). The 10-year OS rate was 55% (95% CI, 52-57) in younger men compared to 41% (95% CI, 38–43) in older men (Fig. 1a). A portion of this difference was accounted for by the fact that older men were more likely to have died of causes other than PCa (HR = 1.85 [95% CI, 1.67-2.06]). The 10-year rate of NPCD was 28% (95% CI, 25-30) in younger men compared to 45% (95% CI, 43-48) in older men (Fig. 1b). However, older patients were statistically significantly less likely to have died of a PCSD (HR = 0.77 [95% CI, 0.65-0.90]) or to have metastasis (HR = 0.71 [95% CI, 0.62-0.82]). This was reflected in a 10-year metastasis rate of 27% (95% CI, 25–29) in men ≤70 years old compared to 20% (95% CI, 18-22) in older men (Fig. 1c). Men >70 years old also exhibited a lower 10-year rate of PCSD (Fig. 1d) of 14% (95% CI, 12-15) than that for men ≤70 years old, which was 18% (95% CI, 16-19, $p < 0.0001$).

Prostate cancer outcomes by time interval

Given excess NPCD rates in older men, it is likely that parts of the differences in metastasis and PCSD were due to men dying of other causes. Therefore, absolute rates of metastasis, PCSD, and NPCD were analyzed by 2-year intervals (Fig. 2a–c). Throughout the first 10 years, rates of metastasis and PCSD were greater in the younger age group, while NPCD rates were greater in the older age group. However, the difference in NPCD rates was not sufficient to explain excess metastasis in younger men. As shown in Fig. 2, in the first 2-

year period, there was a 2.1% greater rate of death from other causes in older men and a 2.1% greater rate of metastasis in younger men. Therefore, the lower rate of metastasis in older men could only be explained if all of the men who died of causes other than PCa in the first 2 years would have had metastasis if they had lived. These men would have needed to have a metastasis rate of 100% (a 14-fold higher rate than that observed during this time period) for the increased rate of NPCD to explain the decrease in metastasis during the first 2-year period. Analyzed over the first 6 years, a similar trend was observed in that differences in metastasis rates in older men could only be explained if those who died of NPCD had an observed rate of metastasis that was 6- to 14-fold greater than that actually observed. A similar trend was observed for PCSD in that the difference in NPCD would not account for the entirety of the excess PCSD in younger men. Therefore, the lower rates of metastasis and NPCD in older men are not explained by the higher rates of death due to other causes.

Prostate cancer outcomes as a function of age and pathologic grade

We next evaluated the interaction between age and tumor grade (Table 3). As expected, younger men were more likely to be alive than older men, with 10-year OS rates of 63%, 57%, and 42% compared to 46%, 44%, and 30% for GSs of 2 to 6, 7, and 8 to 10, respectively. In men ≤70 years old, both GS 7 and GSs 8 to 10 carried a greater risk of all-cause mortality than GSs of 2 to 6, while this increased risk of overall mortality was observed only for older men in the GS 8 to 10 subgroup.

Both the metastasis and PCSD rates also exhibited age- and GS-dependent differences. In all cases, older age was associated with lower metastasis and PCSD rates, while a higher GS was associated with higher metastasis and PCSD rates. For men with GSs 2 to 6, the 10-year rate of metastasis was 17% in men ≤70 years old vs. 11% for men >70 years old. Increasing GS was correlated with an increased risk of metastatic disease, which was independent of patient age, with the HR for metastasis for GS 7 in men ≤70 years old of 1.52 (95% CI, 1.21-1.90) and 1.82 (95% CI, 1.34-2.47) in men >70 years old. GS 8-to-10 disease carried an even higher risk of metastatic disease, with HRs of 2.38 (95% CI, 1.89-3.01) and 3.22 (95% CI, 2.37-4.37) in younger and older men, respectively. Not surprisingly, PCSD increased with GS but was consistently lower at each pathologic grade as a function of age, with 10-year rates of PCSD in younger and older men of 9%, 16%, and 31% compared to 6%, 11%, and 27% for GSs 2 to 6, 7, and 8 to 10, respectively.

Multivariate analysis of risk factors affecting outcomes

To assess the relative impact of age on outcomes, multivariate analyses were performed for OS, local failure, metastasis, PCSD, and NPCD, adjusting for age (continuous), race, clinical T stage, nodal status, GS, and ADT duration. Cox proportional hazards models, which do not account for competing risks, were initially evaluated (data not shown) and indicated that for each additional year of age, there was a 2% decline in metastasis ($p < 0.0005$) and a 1% decline in PCSD ($p = 0.12$), with a 7% increase in the risk of NPCD ($p < 0.0001$). Due to the confounding influence of NPCD, multivariate analyses were performed using Fine and Gray's analyses, which account for competing risks of intercurrent events. As shown in Table 4, after adjustments were made for other variables, each year of increasing age was

directly correlated with a 7% increased risk for NPCD (HR = 1.07 [95% CI, 1.06-1.08], $p < 0.0001$) which resulted in a 4% increase in the relative risk of all-cause mortality (HR = 1.04 [95% CI, 1.03-1.05], $p < 0.0001$). Only older age and non-white race predicted for increased NPCD, while age, non-white race, higher GS, higher clinical stage, and presence of nodal disease were all adverse prognostic factors for all OS. The use of ADT for >6 months was associated with a significant decrease in the risk of death overall (HR = 0.72 [95% CI, 0.62-0.83], $p < 0.0001$) compared to no ADT, while there was a trend toward improved survival with a shorter duration of ADT, ≤6 months, that did not achieve statistical significance (HR = 0.91 [95% CI, 0.79-1.06], $p > 0.2$). The use or duration of ADT did not appear to influence rates of NPCD.

Similar trends were observed for clinical failure with higher GS, higher clinical stage, and positive lymph nodes, all predicting for metastasis. Metastases were reduced by ADT and were proportional to the duration with a greater reduction for ADT delivered for >6 months (HR = 0.46 [95% CI, 0.37-0.56]) than for ≤6 months (HR = 0.78 [95% CI, 0.61-0.92]). Importantly, after accounting for competing risks, we found a decline in metastasis with age, with a 3% decrease in the relative risk of metastasis for each increasing year of age (HR = 0.97 [95% CI, 0.96-0.98], $p < 0.0001$). In addition to metastasis, local failure was also increased in younger patients, with a 10-year rate of local failure of 18% (95% CI, 16-19) in men ≤70 years old compared to 15% (95% CI, 14-17, $p < 0.03$) in men >70 years old at diagnosis (HR = 0.82 [95% CI, 0.70-0.96], $p < 0.02$).

Similar results were seen when PCSD was analyzed with higher GS, higher clinical stage, and the presence of nodal disease, all of which predicted increased risk of PCSD. The use of ADT as well as its duration also demonstrated significant reductions in the rate of PCSD in a duration-dependent manner (HR = 0.78 [95% CI, 0.61-0.99]) for ADT regimens of ≤6 months (HR = 0.50 [95% CI, 0.39-0.64]) and for ADT regimens of >6 months. Finally, older age was associated with a decreased likelihood of dying of PCa, with a 2% reduction in the relative risk of PCSD for each increasing year of age (HR = 0.98 [95% CI, 0.97 – 0.99], $p < 0.0001$).

Interaction between ADT duration and patient age

Finally, the effects of ADT use and duration as stratified by age was evaluated. In men ≤70 years old, use of ADT resulted in reductions in both metastasis and PCSD, with an increase in OS ($p < 0.001$) (Table 5). For each of these three endpoints, a longer duration of ADT (≤6 months vs. >6 months) resulted in a greater reduction in the risk of each event, with 75% to 80% of the effect observed with ADT duration of ≤6 months and a greater effect observed with >6 months of ADT. It is noteworthy that OS was increased with both shorter and longer ADT durations in younger men ($p < 0.0001$), while there was no change in NPCD ($p > 0.1$). For men >70 years old, both shorter and longer ADT regimens were associated with decreases in metastasis and PCSD ($p < 0.001$) (Table 5). However, in contrast to younger men, only ADT delivered for >6 months provided a benefit in OS (HR = 0.73 [95% CI, 0.61-0.86], $p < 0.0004$) in older men, while ADT for ≤6 months did not improve OS in older men (0.96 [95% CI, 0.82-1.13], $p > 0.6$). Similar to outcomes in younger men, there were no differences in NPCD based upon the use of ADT ($p > 0.1$).

DISCUSSION

For locally advanced PCa, older age carries a decreased risk of both metastasis and PCSD. Univariate analysis revealed a 7% absolute decrease in metastasis (10-year rate, 27% vs. 20%, respectively) and a 4% absolute decrease in the risk for PCSD (10-year rate, 18% vs. 14%, respectively) for men older then 70 years of age compared to those ≤70 years old. As expected, older men had a higher rate of death due to other causes; nevertheless, the decreased risk of PCa events is not simply an artifact because of excess NPCD. When metastasis, PCSD, and NPCD were analyzed in 2-year intervals, differences in metastasis and PCD as functions of age were observed even in the earliest time periods and were not explained by the excess rate of NPCD throughout the first 10 years. In addition, when multivariate models were evaluated (taking into account competing risks), age-dependent differences in metastasis and PCSD remained. This also was not simply a matter of analysis at a single-age cut-off point because when age was used as a continuous variable, analysis revealed a decrease of 3% per year in the relative risk of metastasis and a decrease of 2% per year in the relative risk of PCSD.

Despite a decreased rate of metastasis and PCSD in older men, treatment for locally advanced PCa in men >70 years of age is warranted. Even with treatment, there was a 20% risk of metastasis and a 14% risk for PCSD at 10 years, and these risks were higher with GS 8-to-10 disease, with 10-year rates of metastasis and PCSD of 34% and 27%, respectively. These results are similar to conclusions reached in the study by Nguyen *et al.* (26), which determined that comorbid illness rather than age was the determining factor in the benefit of adding ADT to RT in men with intermediate- or high-risk PCa and that treatment of healthier men over the age of >70 with higher-risk PCa was still warranted.

A number of different opinions have been suggested as to why there might be age-dependent differences in PCa outcomes. First, some studies have attributed these differences among men undergoing RT to differences between clinical and pathologic staging or referral bias relative to RT in younger men who were restricted to the pre-PSA screening era (12). Second, some investigators have hypothesized that in older men, higher-grade PCa develops in the setting of “andropause,” thus leading to more aggressive clinical behavior and an earlier transition to androgen independence (16). Third, worse outcomes for older patients have been identified based upon population registries, with older patients being less likely to receive appropriate care (3, 5, 6). Since all patients in this analysis were treated in prospective trials and received the same level of care independent of age, treatment biases in regard to RT and ADT would not explain the differences. Furthermore, a recent subset analysis of patients treated in both the RTOG trial 9202 and trial 9413 demonstrated no association between basal testosterone levels and either GS or clinical outcomes (27). In addition, the majority of patients in that analysis were treated once PSA screening had been adopted in the United States, and age-dependent differences persisted across all trials. More recently, based upon the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) database, an analysis of more than 310,000 patients treated for PCa between 1988 and 2003 revealed increased PCSD in younger men with high-risk PCa regardless of the type of treatment delivered (4). When that SEER analysis was limited to patients treated with radical prostatectomy and complete surgical staging, the adverse impact of younger age

persisted and may even have increased (4). Therefore, it does not appear that these results are explained by “andropause,” referral bias, understaging, or type of treatment used.

Finally, the present results are similar to those observed in another multiinstitutional evaluation of patients treated with RT (9). Proust-Lima *et al.* (9) evaluated 4,247 men (median age, 70 years old) treated with RT between 1987 and 2004. Most men had localized disease, with 92% clinical T1 or T2, and all patients were treated with RTalone (without ADT) to a median RT dose of 66 Gy (range, 58–80 Gy). In that analysis, younger age predicted for a higher rate of clinical failure (defined as either local or metastatic), even when adjusted for baseline clinical characteristics. For 2 patients with the same baseline prognostic factors and the same pattern of PSA response following treatment but a 10-year age difference, the younger patient had a 36% higher risk of clinical recurrence (HR = 1.36 [95% CI,1.16–1.60]). That finding is similar to the 30% higher risk of metastasis (HR = 1.30 [95% CI, 1.20-1.40]) we observed for a 10-year age difference between patients.

Weaknesses in the current study include the retrospective nature of the analysis as well as the inability to adjust for PSA as a risk factor. Age was not a stratification factor in any of the RTOG studies represented here, and as such, this analysis is hypothesis-generating. However, the use of prospectively collected data from patients treated in cooperative trials in a multiinstitutional setting with uniform follow-up lends credence to the conclusions. PSA values were not available for all patients, so the multivariate models were performed without adjusting for PSA. Nevertheless, it is unlikely that the inclusion of PSA values would significantly alter these results, as PSA level is less closely linked to clinical outcome than GS, which was included in the analysis. In addition, PSA values tend to be higher in older men than in younger men, which is not likely to explain improved outcomes in older patients (28). Furthermore, for the current analysis, only three of the four trials included PSA values, which were, therefore, only available for 77% of the patients (3,178 /4,128 patients). Nevertheless, we recently analyzed patients treated in two of these trials (RTOG trials 9202 and 9413), which included 2,729 patients (or 86% of the patients with PSA data), to assess the effect of baseline differences in testosterone level on clinical outcome. In that analysis, adjusting for other clinical variables (including PSA level), we also observed better clinical outcome in older patients, confirming the results obtained in the present study without adjusting for PSA values (29). Finally, in the analysis performed by Proust-Lima *et al.* (9), even when they adjusted for both baseline and posttreatment PSA level, they still observed worse clinical outcome for younger patients treated with external beam radiation therapy.

CONCLUSIONS

The biologic mechanism underlying the more aggressive clinical disease in younger men identified in this study remains to be elucidated. Given the availability of tissue for molecular analysis of factors associated with radiation response and/or metastasis for patients treated in these trials (30), potential correlations between age at diagnosis and molecular features demonstrated to predict for more aggressive clinical behavior are ongoing.

Acknowledgments

This work was supported by RTOG Grant U10 CA21661 and National Cancer Institute Grants CCOP U10 CA37422 and Stat U10 CA32115.

REFERENCES

1. Carter HB, Epstein JI, Partin AW. Influence of age and prostate-specific antigen on the chance of curable prostate cancer among men with nonpalpable disease. Urology. 1999; 53:126–130. [PubMed: 9886601]
2. Herold DM, Hanlon AL, Movsas B, et al. Age-related prostate cancer metastases. Urology. 1998; 51:985–990. [PubMed: 9609637]
3. Jonsson E, Sigbjarnarson HP, Tomasson J, et al. Adenocarcinoma of the prostate in Iceland: a population-based study of stage, Gleason grade, treatment and long-term survival in males diagnosed between 1983 and 1987. Scand J Urol Nephrol 2006. 40:265–271.
4. Lin DW, Porter M, Montgomery B. Treatment and survival outcomes in young men diagnosed with prostate cancer: A population-based cohort study. Cancer. 2009; 115:2863–2871. [PubMed: 19466697]
5. Gondos A, Holleczek B, Arndt V, et al. Trends in population-based cancer survival in Germany: To what extent does progress reach older patients? Ann Oncol. 2007; 18:1253–1259. [PubMed: 17470450]
6. Brenner H, Arndt V. Recent increase in cancer survival according to age: Higher survival in all age groups, but widening age gradient. Cancer Causes Control. 2004; 15:903–910. [PubMed: 15577292]
7. Merrill RM, Bird JS. Effect of young age on prostate cancer survival: A population-based assessment (United States). Cancer Causes Control. 2002; 13:435–443. [PubMed: 12146848]
8. Mayer R, Pummer K, Quehenberger F, et al. Analysis of competing risk parameters in irradiated prostate cancer patients. Strahlenther Onkol. 2003; 179:452–457. [PubMed: 12835881]
9. Proust-Lima C, Taylor JM, Williams SG, et al. Determinants of change in prostate-specific antigen over time and its association with recurrence after external beam radiation therapy for prostate cancer in five large cohorts. Int J Radiat Oncol Biol Phys. 2008; 72:782–791. [PubMed: 19014779]
10. Aaronson D, Cowan J, Carroll P, et al. Association of age and response to androgen-deprivation therapy with or without radiotherapy for prostate cancer: Data from CaPSURE. BJU Int. 2009
11. Jani AB, Gratzle J. Analysis of impact of age and race on biochemical control after radiotherapy in different prostate cancer settings. Urology. 2005; 66:124–129. [PubMed: 15992908]
12. Parker CC, Gospodarowicz M, Warde P. Does age influence the behaviour of localized prostate cancer? BJU Int. 2001; 87:629–637. [PubMed: 11350402]
13. Jani AB, Johnstone PA, Liauw SL, et al. Age and grade trends in prostate cancer (1974-2003): A Surveillance, Epidemiology, and End Results Registry analysis. Am J Clin Oncol. 2008; 31:375–378. [PubMed: 18845997]
14. Pilepich MV, Caplan R, Byhardt RW, et al. Phase III trial of androgen suppression using goserelin in unfavorable-prognosis carcinoma of the prostate treated with definitive radiotherapy: Report of Radiation Therapy Oncology Group protocol 85-31. J Clin Oncol. 1997; 15:1013–1021. [PubMed: 9060541]
15. Pilepich MV, Winter K, John MJ, et al. Phase III radiation therapy oncology group (RTOG) trial 86-10 of androgen deprivation adjuvant to definitive radiotherapy in locally advanced carcinoma of the prostate. Int J Radiat Oncol Biol Phys. 2001; 50:1243–1252. [PubMed: 11483335]
16. Hanks GE, Pajak TF, Porter A, et al. Phase III trial of long-term adjuvant androgen deprivation after neoadjuvant hormonal cytoreduction and radiotherapy in locally advanced carcinoma of the prostate: The Radiation Therapy Oncology Group Protocol 92-02. J Clin Oncol. 2003; 21:3972–3978. [PubMed: 14581419]
17. Roach M 3rd, DeSilvio M, Lawton C, et al. Phase III trial comparing whole-pelvic versus prostate-only radiotherapy and neoadjuvant versus adjuvant combined androgen suppression: Radiation Therapy Oncology Group 9413. J Clin Oncol. 2003; 21:1904–1911. [PubMed: 12743142]

18. Smith CT, Williamson PR, Marson AG. Investigating heterogeneity in an individual patient data meta-analysis of time to event outcomes. Stat Med. 2005; 24:1307–1319. [PubMed: 15685717]
19. Collett, D. Modelling survival data in medical research. Chapman & Hall; New York: 1994.
20. Kaplan E, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc. 1958; 53:457–481.
21. Mantel N. Evaluation of survival data and two new rank order statistics arising in its consideration. Cancer Chemother Rep. 1966; 50:163–170. [PubMed: 5910392]
22. Kim K, Tsiatis AA. Study duration for clinical trials with survival response and early stopping rule. Biometrics. 1990; 46:81–92. [PubMed: 2350572]
23. Gray R. A class of K-sample tests for comparing the cumulative incidence of a competing risk. Annual Statistics. 1988; 16:1141–1143.
24. Cox D. Regression models and life tables. J R Stat Soc. 1972; 34:187–202.
25. Fine J, Gray R. A proportional hazards model for the subdistribution of a competing risk. J Am Stat Assoc. 1999; 94:496–509.
26. Nguyen PL, Chen MH, Renshaw AA, et al. Survival following radiation and androgen suppression therapy for prostate cancer in healthy older men: Implications for screening recommendations. Int J Radiat Oncol Biol Phys. 2009
27. Taussky D, Bae K, Bahary JP, et al. Does timing of androgen deprivation influence radiation-induced toxicity? A secondary analysis of radiation therapy oncology group protocol 9413. Urology. 2008; 72:1125–1129. [PubMed: 18314175]
28. Oesterling JE, Jacobsen SJ, Chute CG, et al. Serum prostate-specific antigen in a community-based population of healthy men. Establishment of age-specific reference ranges. JAMA. 1993; 270:860–864. [PubMed: 7688054]
29. Roach M III, Bae K, Lawton C, et al. Baseline serum testosterone in men treated with androgen deprivation therapy and radiotherapy for localized prostate cancer. Int J Radiat Oncol Biol Phys. doi:10.1016/j.ijrobp.2009.09.073; 2010 [Epub ahead of print].
30. Pollack A, Bae K, Khor LY, et al. A model for distant metastasis incorporating tissue biomarkers from prostate cancer patients in Radiation Therapy Oncology Group (RTOG) 92-02. Int J Radiat Oncol Biol Phys. 2008; 72(Suppl):S58.

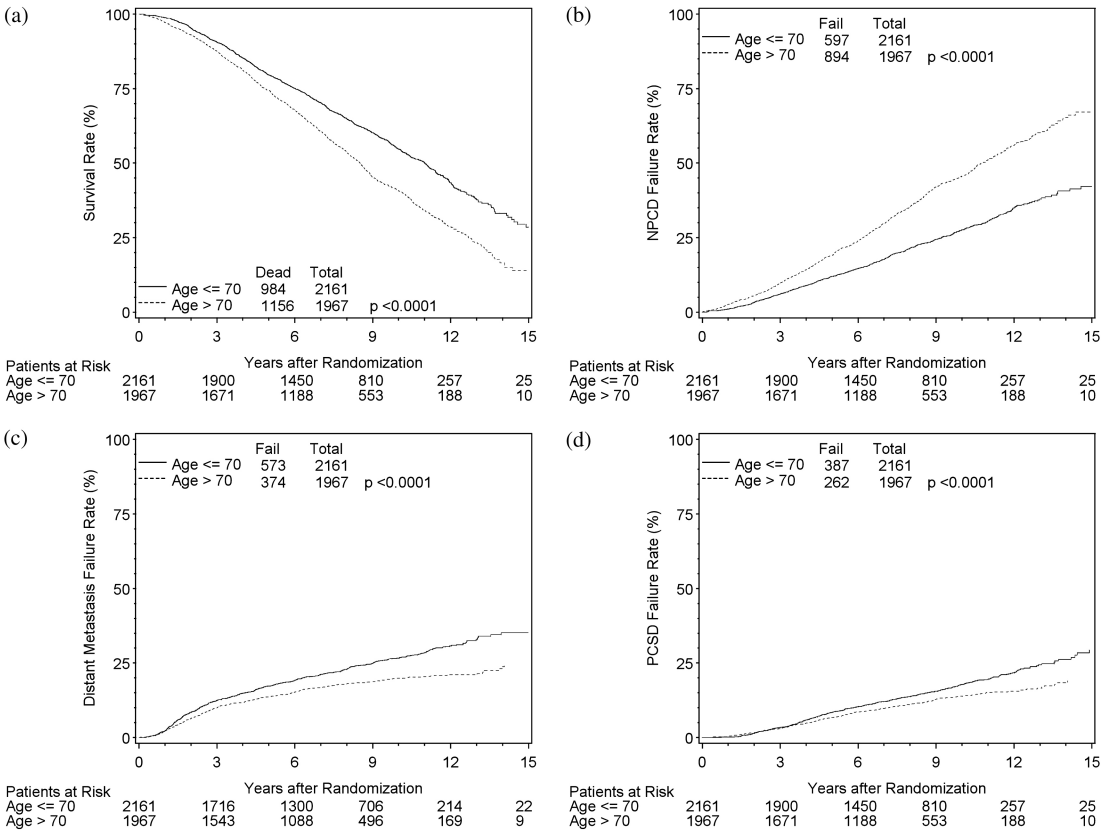

Fig. 1.

(a) Overall survival as a function of age. (b) Nonprostate cancer death as a function of age. (c) Distant metastases as a function of age. (d) Prostate cancer-specific death as a function of age.

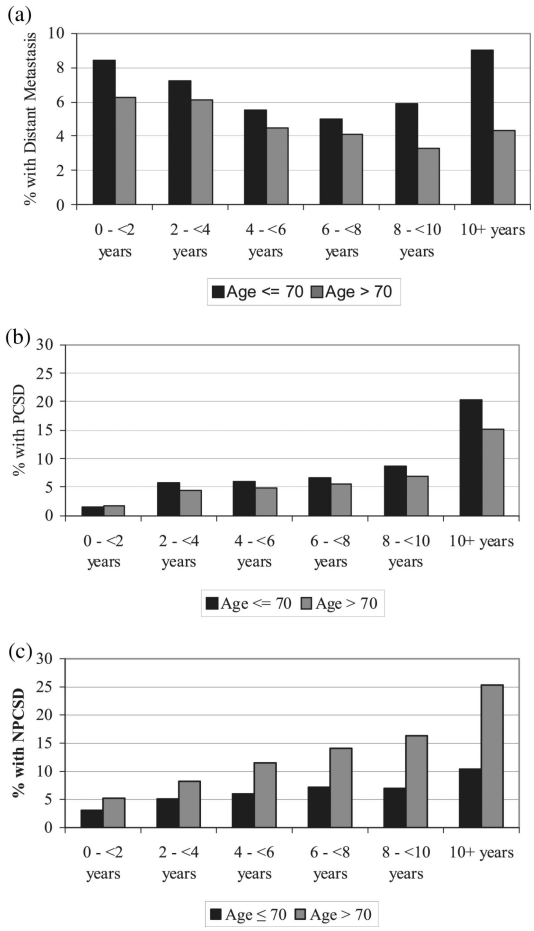

Fig. 2.

(a) Distant metastasis as a function of time since enrollment, as stratified by age. (b) Prostate cancer-specific death as a function of time since enrollment, as stratified by age. (c) Non-prostate cancer-specific death as a function of time since enrollment, as stratified by age.

Table I

Pretreatment Characteristics By Age

	Age ≤ 70 (n=2161)	Age > 70 (n=1967)	Total (n=4128)	p-value*
Race				
White	1689 (78%)	1691(86%)	3380 (82%)	< 0.0001
Black	406 (19%)	238 (12%)	644 (16%)	
Other	66 (3%)	38 (2%)	104 (3%)	
Clinical T Stage				
T1	113 (5%)	86 (4%)	199 (5%)	0.4
T2	888 (41%)	821 (42%)	1709 (41%)	
T3	1116 (52%)	1029 (52%)	2145 (52%)	
T4	44 (2%)	31 (2%)	75 (2%)	
Gleason Score				
2-6	593 (27%)	551 (28%)	1144 (28%)	0.9
7	988 (46%)	884 (45%)	1872 (45%)	
8-10	580 (27%)	532 (27%)	1112 (27%)	
Nodal Status				
None	1895 (88%)	1866 (95%)	3761 (91%)	< 0.0001
Present	266 (12%)	101 (5%)	367 (9%)	
Hormone Duration				
None	360 (17%)	330 (17%)	690 (17%)	0.4
≤ 6 months	1221 (56%)	1146 (58%)	2367 (57%)	
> 6 months	580 (27%)	491 (25%)	1071 (26%)	

*The p-value is from Chi-square test statistics.

Table II

Heterogeneity Testing By Age (≤ 70 (RL) vs. >70)

	Adjusted Hazard Ratio**							
	Overall Survival		Distant Metastasis		PCSD		NPCD	
Trial	Hazard Ratio (95% CI*)	p-value	Hazard Ratio (95% CI*)	p-value	Hazard Ratio (95% CI*)	p-value	Hazard Ratio (95% CI*)	p-value
RTOG 8531	1.66 (1.39-1.98)	< 0.0001	0.71 (0.56-0.92)	<0.008	0.80 (0.59-1.09)	0.16	1.89 (1.53-2.35)	<0.0001
RTOG 8610	1.62 (1.30- 2.01)	< 0.0001	0.83 (0.62-1.11)	0.21	0.89 (0.64-1.24)	0.50	1.88 (1.41-2.52)	<0.0001
RTOG 9202	1.48 (1.29-1.70)	< 0.0001	0.62 (0.48-0.79)	<0.0002	0.65 (0.48-0.85)	<0.002	1.93 (1.63-2.28)	<0.0001
RTOG 9413	1.52 (1.25-1.85)	< 0.0001	0.75 (0.54-1.04)	<0.09	0.82 (0.54-1.27)	0.37	1.68 (1.35-2.08)	<0.0001
	T.S= 1.14	0.38	T.S. = 2.47	0.24	T.S=2.67	0.22	T.S=1.07	<0.04
Pooled HR† (95% CI)	1.55 (1.42-1.69)		0.71 (0.62-0.82)		0.77 (0.65-0.90)		1.85 (1.67-2.06)	

* CI = Confidence Interval; RL = Reference Level as Age ≤ 70.

** Adjusted for race, Gleason score, clinical stage, nodal status:

† This is a pooled estimate.

Table III

Prostate Cancer Outcomes By Age and Gleason Score

Outcome	Gleason Score	10-year survival/failure rate	HR**	p-value
Overall Survival				
≤ 70	2 - 6	63% (59-68)	RL	
	7	57% (54-61)	1.20 (1.02-1.41)	<0.03
	8 – 10	42% (37-46)	1.92 (1.62-2.27)	< 0.0001
> 70	2 - 6	46% (41-51)	RL	
	7	44% (40-48)	1.11 (0.96-1.28)	>0.1
	8 – 10	30% (25-34)	1.74 (1.49-2.02)	< 0.0001
Distant Metastasis				
≤ 70	2 - 6	17% (14 -20)	RL	
	7	25% (22- 28)	1.50 (1.20-1.88)	<0.0005
	8 – 10	40% (35-44)	2.67 (2.12-3.35)	< 0.0001
> 70	2 - 6	11% (8-14)	RL	
	7	17% (14-20)	1.65 (1.22-2.23)	<0.002
	8 – 10	34% (30- 38)	3.56 (2.27-4.80)	< 0.0001
PCSD				
≤ 70	2 - 6	9% (7-12)	RL	
	7	16% (13-18)	1.56 (1.18-2.10)	<0.002
	8 – 10	31% (27-35)	3.37 (2.54-4.48)	< 0.0001
> 70	2 - 6	6% (4-9)	RL	
	7	11% (8-13)	1.78 (1.20-2.62)	<0.004
	8 – 10	27% (23-31)	4.94 (3.40-7.16)	< 0.0001
NPCD				
≤ 70	2 - 6	28% (24-32)	RL	
	7	27% (24-31)	0.96 (0.79-1.16)	0.67
	8 – 10	28% (24-32)	1.00 (0.81-1.23)	0.98
> 70	2 - 6	48% (43-52)	RL	
	7	45% (42-49)	0.95 (0.82-1.11)	0.51
	8 – 10	44% (39-48)	0.91 (0.76-1.08)	0.27

Actuarial estimates for overall survival were calculated using Kaplan-Meier methods and the cumulative incidence method was used to estimate distant metastasis, prostate cancer specific death and non-prostate cancer specific death.

** HR: Hazard ratio; RL= reference level

Table IV

Multivariate Hazards Models of Prostate Cancer Outcomes

		Overall Survival		Distant Metastasis		PCSD		NPCD	
Covariate	**Comparison**	**HR (95% C.I.)**	**p-value***	**HR (95% C.I.)**	**p-value†**	**HR (95% C.I.)**	**p-value†**	**HR (95% C.I.)**	**p-value†**
Age	Continuous	1.04(1.03-1.05)	< 0.0001	0.97(0.96-0.98)	< 0.0001	0.98(0.97-0.99)	< 0.0001	1.07(1.06, 1.08)	<0.0001
Race	White vs.	RL		RL		RL			
	Non-white	1.13(1.01-1.28)	<0.04	0.86(0.71-1.0)	>0.1	0.82(0.64-1.04)	>0.1	1.23(1.07, 1.42)	0.003
Gleason Score	2-6 vs.	RL		RL		RL			
	7	1.17(1.05-1.31)	<0.004	1.70(1.42-2.02)	< 0.0001	1.74(1.38-2.19)	< 0.0001	0.95(0.85, 1.08)	> 0.1
	8-10	1.78(1.59-2.00)	< 0.0001	2.99(2.48-3.58)	< 0.0001	3.87(3.09-4.86)	< 0.0001	0.93(0.81, 1.07)	> 0.1
Clinical Stage	T1/T2 vs.	RL		RL		RL			
	T3/T4	1.19(1.08-1.30)	< 0.0003	1.44 (1.25-1.67)	< 0.0001	1.35(1.13-1.61)	<0.0009	1.05(0.95, 1.17)	> 0.1
Nodal	None vs.	RL		RL		RL			
	Present	1.48(1.28-1.72)	< 0.0001	1.68(1.35-2.07)	< 0.0001	1.83(1.44-2.33)	< 0.0001	1.03(0.85, 1.26)	> 0.1
Hormone duration	None vs.	RL		RL		RL			
	0-6 months	0.91(0.79-1.06)	>0.2	0.78(0.61-0.92)	<0.007	0.78(0.61-0.99)	0.047	1.05(0.87, 1.26)	> 0.1
	> 6 months	0.72(0.62-0.83)	< 0.0001	0.46(0.37-0.56)	<0.0001	0.50(0.39-0.64)	<0.0001	1.00(0.84, 1.19)	> 0.1
Trial	8531 vs.	RL		RL		RL			
	8610	1.13(0.98, 1.31)	0.0962	1.42 (1.15, 1.75)	0.0001	1.74(1.37, 2.2)	< 0.001	0.86(0.71, 1.03)	> 0.1
	9202	0.94 (0.82, 1.08)	0.3720	0.73 (0.59, 0.91)	0.004	0.97(0.75, 1.26)	0.8400	0.92(0.78, 1.08)	> 0.1
	9413	0.92 (0.77, 1.10)	0.3365	0.51 (0.39, 0.67)	< 0.001	0.57(0.40, 0.80)	0.0013	0.99(0.80, 1.22)	> 0.1

+ HR=Hazard ratio, C.I. = confidence interval.

* p-value is from the Cox-Proportional Hazard models

† p-value is from Fine Gray's regression models

Table V

Impact of Hormone Duration By Age[**]

	Overall Survival		Distant Metastasis		PCSD		NPCSD	
Covariate	**Adjusted HR (95% C.I.)**	**p-value***	**Adjusted HR (95% C.I.)**	**p-value†**	**Adjusted HR (95% C.I.)**	**p-value†**	**Adjusted HR (95% C.I.)**	**p-value†**
Age ≤70								
Hormone Duration								
None	RL		RL		RL		RL	
≤ 6 months	0.72 (0.61-0.85)	< 0.0001	0.48 (0.39-0.60)	< 0.0001	0.64 (0.49-0.83)	<0.001	0.90 (0.73-1.11)	0.34
> 6 months	0.59 (0.50-0.71)	< 0.0001	0.38 (0.30-0.48)	< 0.0001	0.49 (0.37-0.65)	< 0.0001	0.85 (0.67-1.07)	0.16
Age>70								
Hormone duration								
None	RL		RL		RL		RL	
≤ 6 months	0.96 (0.82-1.13)	**>0.6**	0.53 (0.41-0.69)	<0.0001	0.53 (0.39-0.72)	<0.0001	1.15 (0.96-1.38)	0.13
> 6 months	0.73 (0.61-0.86)	<0.0004	0.29 (0.21-0.40)	<0.0001	0.31 (0.22-0.44)	<0.0001	1.11 (0.91-1.35)	0.30

[+] HR=Hazard ratio, C.I. = confidence interval.

[**] Adjusted for race, Gleason score, clinical stage, nodal status

[*] p-value is from the Cox-Proportional Hazard models

[†] p-value is from Fine Gray's regression models