

CLINICAL INVESTIGATION

Prostate

EFFECT OF AGE ON BIOCHEMICAL DISEASE-FREE OUTCOME IN PATIENTS WITH T1-T3 PROSTATE CANCER TREATED WITH DEFINITIVE RADIOTHERAPY IN AN EQUAL-ACCESS HEALTH CARE SYSTEM: A RADIATION ONCOLOGY REPORT OF THE DEPARTMENT OF DEFENSE CENTER FOR PROSTATE DISEASE RESEARCH<sup>1</sup>

PETER A. S. JOHNSTONE, M.D., M.A.,<sup>\*†</sup> ROBERT H. RIFFENBURGH, PH.D.,<sup>\*</sup> JUDD W. MOUL, M.D.,<sup>‡§</sup> LEON SUN, M.D., PH.D.,<sup>‡</sup> HONGYU WU, M.D., M.P.H.,<sup>‡</sup> DAVID G. MCLEOD, M.D.,<sup>‡§</sup> CHRISTOPHER J. KANE, M.D.,<sup>\*||</sup> DOUGLAS D. MARTIN, M.D.,<sup>||</sup> LEO KUSUDA, M.D.,<sup>||</sup> RAYMOND LANCE, M.D.,<sup>#</sup> ROBERT DOUGLAS, M.D.,<sup>\*\*</sup> TIMOTHY DONAHUE, M.D.,<sup>\*\*</sup> MICHAEL G. BEAT, M.D.,<sup>††</sup> JOHN FOLEY, M.D.,<sup>††</sup> ANDREW CHUNG, M.D.,<sup>‡‡</sup> DOUGLAS SODERDAHL, M.D.,<sup>†</sup> JASON DO, B.S.,<sup>\*</sup> AND CHRISTOPHER L. AMLING, M.D.<sup>\*</sup>

<sup>\*</sup>Naval Medical Center, San Diego, CA; <sup>†</sup>Emory University School of Medicine, Atlanta, GA; <sup>‡</sup>Center for Prostate Disease Research, Department of Surgery, Uniformed Service University, Bethesda, MD; <sup>§</sup>Walter Reed Army Medical Center, Washington DC; <sup>||</sup>University of California, San Francisco, School of Medicine, San Francisco, CA; <sup>||</sup>Naval Medical Center, Portsmouth, VA; <sup>#</sup>Madigan Army Medical Center, Tacoma WA; <sup>\*\*</sup>National Naval Medical Center, Bethesda, MD; <sup>††</sup>Brooke Army Medical Center, San Antonio, TX; <sup>‡‡</sup>Malcolm Grow Medical Center, Andrews AFB, MD

**Purpose:** It has traditionally been a common perception that young age is a negative prognostic factor in prostate cancer (CaP). Furthermore, many urologists believe that younger patients are better suited to surgery rather than radiotherapy (RT) because of this perception. However, the data on the effect of age on outcome in patients with CaP are unclear. The records of the Department of Defense Center for Prostate Disease Research were queried for the biochemical disease-free results of patients after definitive RT and analyzed by age.

**Methods and Materials:** The records of 1018 patients with T1-T3 CaP treated with definitive RT between 1988 and 2000 were reviewed. The records of patients receiving adjuvant hormonal therapy or adjuvant or salvage RT postoperatively were excluded. Biochemical failure was calculated by the American Society for Therapeutic Radiology and Oncology criteria. The median potential follow-up was 85.3 months as of December 31, 2001.

**Results:** Age did not affect biochemical disease-free survival significantly when considered as <60 vs. ≥60 years ( $p = 0.646$ ), by decade ( $p = 0.329$ ), or as a continuous variable (correlation coefficient  $r = 0.017$ , regression slope = 0.007, with  $p = 0.588$  and  $R^2 < 0.001$ ). Using multiple regression analysis, age was still not significant ( $p = 0.408$ ). Other variables analyzed were pretreatment prostate-specific antigen level ( $p < 0.001$ ), Gleason sum ( $p = 0.023$ ), stage ( $p = 0.828$ ), and RT dose ( $p = 0.033$ ).

**Conclusion:** Age and biochemical disease-free survival after RT for CaP are not related. Age may not be a valid factor in choosing between primary treatment options for CaP. © 2003 Elsevier Science Inc.

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INTRODUCTION

Risk assessment using multiple prognostic factors is a growing area of concern in prostate cancer (CaP). The traditional prognostic factors of stage and grade have been broadened

by newer factors, including prostate-specific antigen (PSA) level at presentation. The role of tumor volume, perineural invasion, and race are still the subject of investigation. The effect of age at presentation is generally a subject of some unease, because, in the pre-PSA era, patients presenting

Reprint requests to: Peter A. S. Johnstone, M.D., c/o Clinical Investigation Department (KCA), Naval Medical Center San Diego, 34800 Bob Wilson Dr., Ste. 5, San Diego, CA 92134-1005. Tel: 619-532-7274; Fax: 619-532-8178. E-mail: pajohnstone@nmcscd.med.navy.mil

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with CaP at a young age were considered to be subject to lesions of a more virulent biology, with attendant poorer outcomes. Grabstald (1), Rosenberg (2), and Cook and Watson (3) concluded in the mid-1960s that CaP was more aggressive in the younger patient. This was refuted by work by Whitmore (4). Clearly, however, although age is a continuous variable, “young age” is subject to considerable interpretation.

In the Department of Defense (DoD), patients are eligible for free or low-cost medical care while on active duty or retired or as a dependent of either category. A 1991 congressional mandate provided funding for the DoD Center for Prostate Disease Research (CPDR), with offices and research facilities in Rockville, MD, starting in 1992. A clinical center was built at Walter Reed Army Medical Center in Washington, DC; others are anticipated in San Diego and San Antonio, sites of large military retirement populations.

Funding for CPDR has supported basic science research and a large database containing demographic, prognostic, and outcomes data from the largest military medical treatment facilities (Naval medical centers in San Diego, Bethesda, and Portsmouth, VA, Army medical centers [AMC] in Washington, DC [Walter Reed AMC], Tacoma, WA [Madigan AMC], Augusta, GA [Eisenhower AMC], and San Antonio [Brooke AMC], and Air Force medical centers in San Antonio [Lackland Air Force Base (AFB)], and Washington, DC [Andrews AFB]). Data collection with informed patient consent is under the auspices of the institutional review board at the Uniformed Services University (Bethesda, MD), with the full concurrence of the individual institutional review board at each medical treatment facility.

Nearly all CPDR clinical publications to date have been related to the population of patients receiving radical prostatectomy (RP). This report is the second CPDR collaboration concerned with outcome after radiotherapy (RT); the first addressed the relationship between ethnicity and biochemical disease-free (bNED) outcomes after definitive RT (5). Prior DoD publications have reported short- and long-term outcomes (6–8) and quality of life (9) after definitive RT in the single-institution setting.

## METHODS AND MATERIALS

A data call was submitted to the CPDR requesting information on age and outcome in patients with T1-T3 CaP after definitive RT in the PSA era. Patients receiving adjuvant or salvage RT after RP were excluded. Data were collected for patients who had received definitive RT (defined as an RT dose of  $\geq 60$  Gy), but who had never received hormonal therapy before PSA recurrence, if any. bNED failure was determined according to the American Society for Therapeutic Radiology and Oncology criteria (10); patients with fewer than three follow-up PSA values were excluded from analysis. The records of 1018 eligible patients were reviewed.

Table 1. Unified staging system

Stage	Description
T1a	Tumor incidental histologic finding in $\leq 5\%$ of tissue resected
T1b	Tumor incidental histologic finding in $> 5\%$ of tissue resected
T1c	Tumor identified by needle biopsy (e.g., because of an elevated PSA)
T2a	Tumor involves one-half or less of one prostate lobe
T2b	Tumor involves more than one-half of one lobe, but not both lobes
T2c	Tumor involves both lobes
T3a	Unilateral extension of tumor outside prostate
T3b	Bilateral extension of tumor outside prostate
T3c	Tumor invading one or both seminal vesicles
T4	Tumor is fixed or invades adjacent structures other than seminal vesicles: bladder neck, external sphincter, rectum, levator muscles, and/or pelvic wall

Abbreviation: PSA = prostate-specific antigen.

The uniform staging system used was the American Joint Commission on Cancer system in place when the database was begun in 1992 (Table 1). The RT dates varied between February 1988 and October 2000; the median follow-up was 85.3 months as of December 31, 2001. Demographic data are presented in Table 2.

The urology departments at the participating medical centers maintain the CPDR databases. The radiation dose entries are consistently provided; the median dose delivered was 68.4 Gy (range 60–81). Only 1 patient received a dose  $> 72$  Gy and only 2 received  $< 64$  Gy.

No data are collected on prescription points. Although the “technique” portion of the database is incomplete in almost 20% of entries, CT scans were available at all sites for the duration of this study, and 2.5–3-dimensional treatment

Table 2. Demographics of the CPDR RT population

	Age* by decade (n)			
	<60	61–70	71–80	>80
Stage				
T1	6	24	30	4
T2	47	303	450	33
T3	10	35	36	7
Gleason sum				
2–4	6	69	85	8
5,6	25	136	178	7
7	10	70	104	11
8–10	11	15	45	2
Presenting PSA (ng/mL)				
<4.0	5	29	37	4
4.1–10	17	99	141	11
10.1–20	7	52	88	11
>20	4	32	43	7

Abbreviations: CPDR = Center for Prostate Disease Research; RT = radiotherapy; PSA = prostate-specific antigen.

\* Number of patients by age: 41–50,  $n = 3$ ; 51–60,  $n = 64$ ; 61–70,  $n = 368$ ; 71–80,  $n = 538$ ; 81–90,  $n = 41$ ;  $\geq 90$ ,  $n = 4$ .

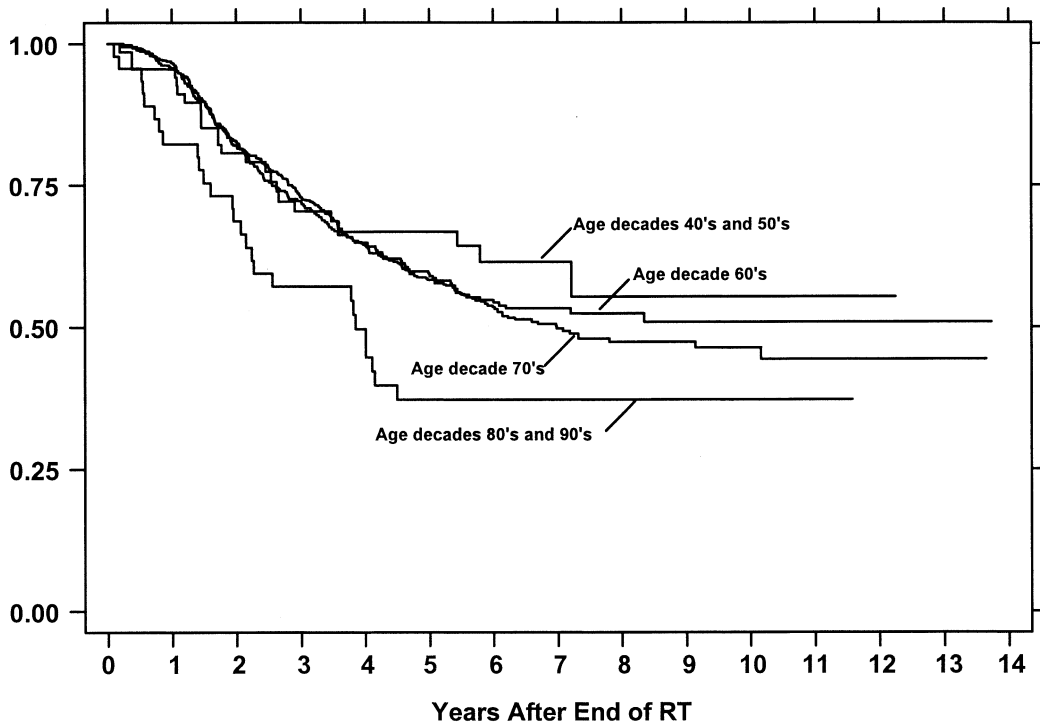


Fig. 1. Kaplan-Meier plots of bNED survival by age decade.

planning became available at all sites between 1993 and 1995. Intensity-modulated RT is not yet available throughout the military radiation oncology system.

A distribution analysis of the data set was performed to examine the mean and median of the parameters. Simple

descriptive statistics were calculated where required. Disease-free survival was determined using the technique of Kaplan and Meier. The comparison between survival curves used the log-rank test. Rank tests were used for age group comparisons. Multiple regression analysis was used to assess bNED status as

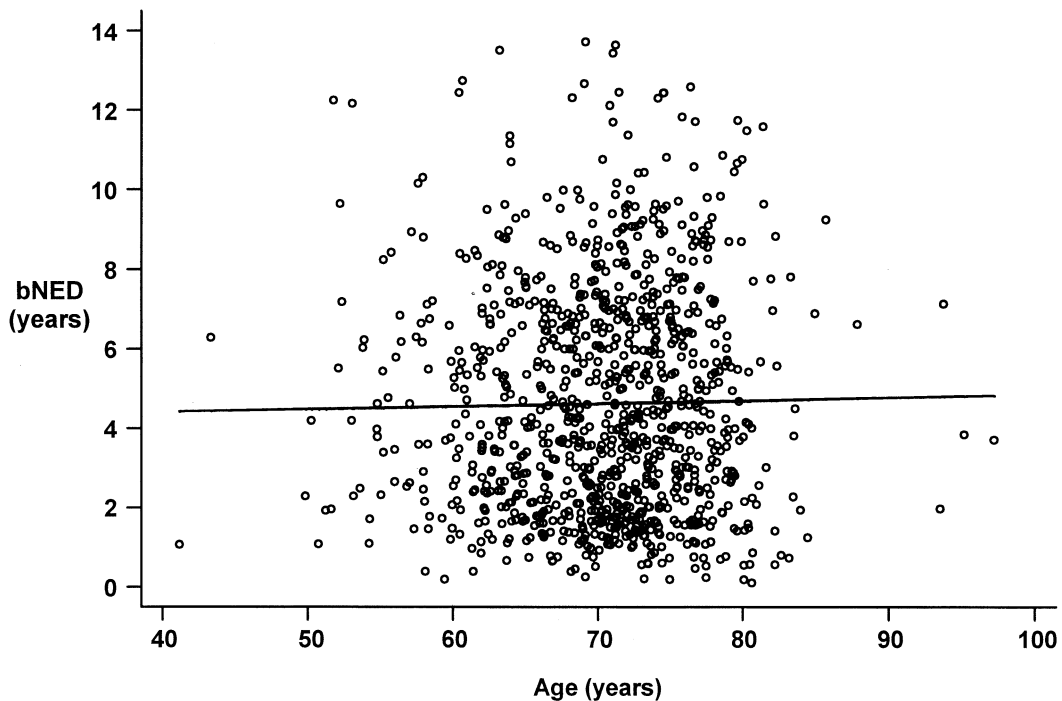


Fig. 2. Scatterplot of bNED survival plotted against age, with the almost horizontal regression line superposed.

Table 3. Outcomes in younger CaP patients (pre-PSA era)

Authors	Year	Tx	Age (y)	n	Result (%)	Age (y)	n	Result (%)
Tjaden <i>et al.</i> (17)	1965	V	<50	51	12.5 5-y crude OS			
Byar and Mostofi (18)	1969	V	<50	34	86 5-y crude OS	>50	210*	63 5-y crude OS
Silber and McGavran (19)	1971	V <sup>†</sup>	<56	28	77 5-y crude OS	>56	38	21 5-y crude OS
		V <sup>‡</sup>	<56	37	23 5-y crude OS	>56	78	21 5-y crude OS
Johnson <i>et al.</i> (20)	1972	V	<50	26	14.3 5-y crude OS	>50	599 <sup>§</sup>	43 5-y crude OS
Harrison (21)	1983	V	<60	46	46 5-y crude OS	65–74	193	38 5-y crude OS
Benson <i>et al.</i> (22)	1987	V	<45	14	47 10-y crude OS			
Aprikian <i>et al.</i> (23)	1994	V	<50	151	35 10-y DFS			
Kerr and Zincke (24)	1994	RP	≤55	191	93 10-y CSS	≥75	51	100 5-y CSS
Riopol <i>et al.</i> (25)	1995	RP	<50	85	“Less evidence of disease progression ( $p = 0.04$ )”	>50	458	

**Abbreviations:** CaP = prostate cancer; PSA = prostate-specific antigen; Tx = treatment; V = various; OS = overall survival; DFS = disease-free survival; RP = radical prostatectomy; CSS = cause-specific survival.

\* From the Veterans Administration Cooperative Urological Research Group (26).

<sup>†</sup> Cases limited to prostate.

<sup>‡</sup> Cases with fixed or metastatic prostate cancer.

<sup>§</sup> From Johnson and Jackson (27).

related to age, RT dose, PSA level, stage, and Gleason sum; age as related to RT dose, PSA level, stage, and Gleason sum; and RT dose as related to PSA level, stage, and Gleason sum.

## RESULTS

Kaplan-Meier plots of bNED survival by age decade are given in Fig. 1 ( $p = 0.073$ , log-rank test).

Age did not affect the bNED survival time significantly when considered as <60 vs. ≥60 years (rank sum test,  $p = 0.646$ ), by decade of age (Kruskal-Wallis,  $p = 0.329$ ), or as a continuous variable (correlation coefficient  $r = 0.017$ , regression slope = 0.007,  $p = 0.588$ , and  $R^2 < 0.001$ ). Figure 2 shows the bNED survival plotted against age, with the almost horizontal regression line superposed.

When bNED survival was considered in multiple regression analysis to reduce the effect of other variables, age was still not significant ( $p = 0.408$ ). Other variables assessed for their predictive capability were pretreatment PSA level ( $p < 0.001$ , significant), Gleason sum ( $p = 0.023$ , significant), stage ( $p = 0.828$ , not significant), and RT dose ( $p = 0.033$ , significant).

Regression analysis gave insignificant  $p$  values for other variables as related to age (PSA, 0.466; Gleason sum, 0.780; stage, 0.797; and RT dose, 0.117). Significant  $p$  values arose from RT dose as predicted by (regressed on) PSA ( $p < 0.001$ ), Gleason sum ( $p = 0.002$ ), and stage ( $p < 0.001$ ), indicating that RT dose was influenced by the presenting clinical indicators.

An argument could be made that our younger patients could have a markedly shorter follow-up in this cohort, because of the effect of PSA testing. The length of follow-up was calculated and compared for younger (<60 years) vs. older (≥60 years) patients. The median follow-up for 67 patients <60 years was 6.6 years. The median follow-up for patients ≥60 years was 7.8 years. The  $p$  value from the rank sum test was 0.013, showing that follow-up

was significantly longer for older patients. The clinical importance of this is questionable, because both values represent mature follow-up compared with the most recent studies of CaP.

## DISCUSSION

Our data reveal that age does not confer a negative bNED bias in CaP patients treated with RT within an equal-access health care system. Prior reports are summarized in Tables 3 to 5.

The data from the pre-PSA era (Table 3) are more variable and less valuable than the more recent data. The data presented here are most properly compared with two recent studies. Carter and associates (11) reported the results of RP in 492 patients with T1c disease. In that population, younger age was considered to be a strong positive predictor of cure (Table 4). In a prior CPDR study investigating the effect of age in a RP cohort, Smith and colleagues (12) reported that patients ≤50 years had fewer recurrences and better recurrence-free survival than did older patients (Table 5).

Two survey studies are also instructional. In 1982, Huben and associates (13) reported the results from the American College of Surgeons CaP survey. Of >20,150 patients, 168

Table 4. Cure rates in 492 CaP patients after prostatectomy

PSA (ng/mL)	Age 40–50 y (%)	Age 51–60 y (%)	Age 61–73 y (%)
2.5–4.0	89	83	78
4.1–6.0	87	81	74
6.1–8.0	84	78	71
8.1–10.0	83	75	67
>10.0	73	57	49

Abbreviations as in Table 3.  
Data from Carter *et al.* (11).

Table 5. Outcomes in 477 CaP patients after prostatectomy

Age (y)	n	Recurrence (n)	5-y bNED survival (%)
≤50	79	6	90
>50	398	107	66

Abbreviations: CaP = prostate cancer; bNED = biochemical disease-free (result).

Data from Smith *et al.* (12).

were <50 years old. The only difference in overall survival between the younger and older cohorts was noted in Stage B patients, in whom youth provided an advantage (83.8% vs. 68% at 5 years). Austin and Convery (14) reported an analysis of the Connecticut Tumor Registry. In their data, men <60 years had a nonsignificant ( $p = 0.06$ ) 5-year survival advantage (72% vs. 61%) compared with men >60 years. When taken in sum, these studies clearly support our conclusion that young age is not a negative prognostic factor in CaP.

Our data did not allow us to comment directly on the therapeutic adequacy of RT vs. RP in younger patients. The differences between RP and RT populations in terms of patient performance status, nodal status, and clinical vs. pathologic stage and grade are well documented (15). A contemporary bias is that younger patients should be offered RP, but little clinical evidence is available to support this bias. Werthman and colleagues (16), in their report of CaP patients <50 years, described a “statistically higher failure rate among RT patients with Stage B and C disease than among the surgical patients.” An analysis of their data revealed that this statement is based on only 12 patients, of whom only 4 received surgery. If we compare the data presented here with data presented previously from the CPDR database for patients <50 years receiving RP (12), a visual inspection of the curves show vastly different 5-year

actuarial bNED rates (60% for RT, 88% for RP). Small patient numbers, the nonrandomized nature of the data, and the potential difference between the surgical and RT series mentioned above render valid comparison impossible.

We previously published 20-year outcomes in terms of overall and disease-specific survival after RT for CaP (8). That study compared results with surgical series more properly, because all of those patients were young and fit enough to undergo staging pelvic lymphoidectomy, and all had negative lymph nodes. The median follow-up of these patients was 13.9 years. In that comparison, the rare surgical series of sufficient maturity boasted somewhat better survival rates, but were hindered by a much shorter median follow-up (8).

There are potential drawbacks from such a database analysis in terms of how the study population was selected. Not including patients receiving neoadjuvant hormonal therapy might cloud data for a population of patients with locally advanced disease presenting after 1996, because they may be excluded from analysis, but we considered this necessary to maintain the most accurate bNED survival data based on RT alone. Similarly, the cutoff of 60 Gy as the lowest level of definitive therapy is certainly subject to debate; it must be remembered, however, that RT doses for CaP increased dramatically in this era. These points notwithstanding, given these data, there still seems to be little justification to infer that young age is a negative prognostic factor after definitive RT for CaP.

## CONCLUSION

Young age does not consistently confer a negative prognosis in DoD patients who are the beneficiaries of an equal-access health care system with the subspecialty care required for CaP. Physicians counseling patients regarding potential therapies should not be biased by patient age.

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