REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 074-0188

1. AGENCY USE ONLY (Leave blank)	2. REPORT DATE	3. REPORT TYPE AND DATES COVERED
	January 2004	Annual (14 Dec 02-13 Dec 03)

4. TITLE AND SUBTITLE
Development of Internet-Accessible Prediction Models for Prostate Cancer Diagnosis, Treatment, and Follow-Up

5. FUNDING NUMBERS
DAMD17-02-1-0066

6. AUTHOR(S)
Leon L. Sun, M.D., Ph.D., Judd W. Moul, Hongyu Wu, Fatiha Bensouda, Hongyan Wu, Mohammed Berrada

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
Henry M. Jackson Foundation for the Advancement of Military Medicine
Rockville, Maryland 20852-1428

E-Mail: lsun@cpdr.org

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSORING / MONITORING AGENCY REPORT NUMBER

11. SUPPLEMENTARY NOTES
Original contains color plates: All DTIC reproductions will be in black and white.

12a. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited

12b. DISTRIBUTION CODE

13. ABSTRACT (Maximum 200 Words)

The objective of the development of Internet-accessible prediction models is to enhance the diagnosis accuracy, treatment efficacy and prognosis for patients with carcinoma of prostate cancer (CaP). On the basis of the established tools (Oracle database, Internet-accessible data collection applications, and program packages for data retrieval and standardization) in the first year of the support, the roles of a set of variables (race/ethnicity, diagnostic age, labs, delayed treatment interval, treatment types, early and late hormonal therapy, etc.) on the outcome of CaP patients were analyzed. The results show that delayed surgery over 3 months post diagnosis would impact the outcome of patients with high risk disease (submitted to J Urol). Early hormonal therapy can delay clinical metastasis only in men with high risk disease (J Urol, in press). Race, percentage of cancer positive cores over total biopsy cores, surgical margin status and seminal vesicle invasion are independent prognostic variables for men with intermediate risk disease (submitted to J Urol). Race plays an important role in tumor volume and spatial distribution based on 3 dimensional reconstructed models with radical prostatectomy specimens (submitted to J Urol). Post-treatment PSA doubling time < 3 months is a surrogate for prostate cancer specific mortality following surgery or radiation therapy (J Clin Onc 2003). PSA Doubling time calculator and CPDR nomograms were implemented on CPDR website.

14. SUBJECT TERMS	15. NUMBER OF PAGES
Prostate cancer, prediction model, Internet, database	152
	16. PRICE CODE

17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT
Unclassified	Unclassified	Unclassified	Unlimited

AD_____

Award Number: DAMD17-02-1-0066

TITLE: Development of Internet-Accessible Prediction Models for Prostate Cancer Diagnosis, Treatment, and Follow-Up

PRINCIPAL INVESTIGATOR: Leon L. Sun, M.D., Ph.D.
Judd W. Moul
Hongyu Wu
Fatiha Bensouda
Hongyan Wu
Mohammed Berrada

CONTRACTING ORGANIZATION: Henry M. Jackson Foundation for the Advancement of Military Medicine
Rockville, Maryland 20852-1428

REPORT DATE: January 2004

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

Table of Contents

INTRODUCTION

The "prostate specific antigen (PSA) era" (1988 to present) has dramatically altered the epidemiology of prostate cancer [1-2], resulting in CaP diagnosis and treatment at younger age and earlier stage with a longer post-treatment life span. [3]. With approximately 221,000 cases of prostate cancer diagnosed each year in the U.S., two-thirds of which are treated by surgery or radiation therapy, and with as many as 40% of patients eventually relapsing, up to 80,000 men per year may develop a biochemical, or PSA-only, failure [4-8]. Up to 8% of diagnosed men will die due to prostate cancer, the second leading cause of death for men in the United States. The task of advising patients regarding prostate cancer (CaP) treatment options remains extremely challenging because of the great complexity of the interactions among many prognostic factors affecting the clinical course of the disease [9-12]. This study seeks to ameliorate this problem by developing software to examine a comprehensive retrospective database of prostate cancer patients and subjects of prostate cancer screening in order to generate statistical outcome likelihoods for different combinations of prognostic and diagnostic factors and treatment options. The products from this study are aimed to improve early and accurate diagnosis and proper treatment of CaP, thereby lowering healthcare costs and raising survival rates.

For the above purposes, we proposed to: (1) Analyze the data by integrating the most powerful prognostic variables in three regression models: logistic regression, Cox proportional regression, and artificial neural networks; (2) Build clinical models predicting probability of prostate cancer in the diagnosis phase, optimal primary treatment in the treatment phase, and optimal recurrence treatment and outcome in the follow-up phase; (3) Post these models as software on the Internet, accessible by patients and physicians as tools for public education, patient self-test, and physician's decision support reference.

Clinical model development includes five phases: (1) Data preparation: Clinical data will be retrieved from the CPDR National Database, sorted, standardized, and mapped into categories of diagnosis, treatment, follow-up; (2) Data warehousing: The data will be stored into a data warehouse; (3) Data analysis: Traditional statistical methods and/or other new mathematical and computational tools such as decision tree system and artificial neural networks will be used to analyze the effect of each parameter and the interactions of the factors on the CaP clinical process; (4) Data modeling: The probability and confidence range for CaP early detection, optimal primary treatment, treatment of recurrence, and treatment of late-stage disease will be calculated for each of the combinations of the input variables to establish prediction models; (5) Web application development: The developed models will be programmed and posted on the CPDR webpage.

BODY

The development schedule and progress of this project are based on the Statement of Work of the research proposal.

In the second year of the grant proposal we have focused on data analysis, creation of predication models for patients before and after treatment, and creation of prediction models for patients before and after PSA recurrence. Also, the implementation of the nomograms, equations and calculators to CPDR web site accessible through the Internet is ongoing as proposed.

1. Continuation of daily data collection.

As of the end of November 2003, the DoD-CPDR National Database contains 433,083 records on 19,596 men (Table 1). It is one of the largest and most comprehensive longitudinal prostate cancer databases in the nation and world. The data from consented patients was daily collected by well-trained CPDR staff with the standardized database implemented in nine military hospitals across the country and one civilian hospital, Virginia Mason Medical Center (VMMC), that joined CPDR National Database in July 2003 (Table 2). In addition, the retrospective data from the Wright-Patterson Medical Center data is also entered into the database (Table 2).

The multi-center data provides a solid foundation for the project due to the large quantities, varieties of clinical settings, and high analytical assessment power. The results and products derived from this database have every likelihood of being reliable, representative, practical, and beneficial.

Table 1. Records stored in the CPDR National Database (as of the end of November 2003)

Site	BAMC	EAMC	MAMC	MGMC	NMCP	NMCSD	NNMC	VMMC	WHMC	WPAFB	WRAMC	Total
Consent	1704	706	1325	871	806	1701	1521	38	1188	10	3694	13564
Biopsy	2707	913	2239	1761	1766	3037	2468	41	2474	196	5792	23394
Brachytherapy	58	24	67	22	62	36	105	1	217	1	120	713
Cryotherapy	12	3		1	2	4	1	0	1	0	19	43
Follow Up1	10680	2081	12947	7543	14746	25447	26028	12	18694	267	22731	141176
Follow_Up2	7139	1916	9240	2894	14548	24550	9397	12	7826	257	22261	100040
General_Info	2005	737	1838	1526	1299	2301	2324	38	1615	179	5161	19023
Hormone_Therapy	1221	1803	1519	1589	3211	2498	2547	3	5478	75	2514	22458
Lab_Results*								19		572	76531	77122
Med_History	1828	737	1647	1211	1286	2299	1844	38	1599	179	4267	16935
Necropy	182	110	498	210	285	316	435	0	220	17	1596	3869
Pathology	540	241	548	452	426	968	655	11	848	88	1624	6401
Phone_Address	1895	736	1749	1441	1271	2300	2270	38	1614	179	5234	18727
Prostatectomy	549	246	567	487	425	1049	699	13	856	89	1793	6773
Radiation_Dose	262	203	483	106	373	592	588	1	267	68	1460	4403
Radiation_Therapy	280	225	515	218	506	639	930	1	297	71	1676	5358
Registration	2004	737	1906	1548	1300	2301	2419	38	1616	179	5547	19595
Staging	1074	701	1411	\900	1122	1798	1700	24	1554	179	4067	14530
Survey	281	170	313	110	9	572	505	0	103	0	3406	5469
TRUS	2731	917	2289	1770	1788	3034	2385	42	2476	196	6785	24413
Tumor_Size	14	11	22	843	6	466	19	2	346	12	3500	5241
Sum	***35462***	***###***	***39798***	***24632***	***44431***	***74207***	***57319***	***334***	***48101***	***2804***	***176084***	***515683***

Table 2. Hospitals and their locations with an active CPDR database

Abbreviation	Full Name	City	State
BAMC	Brook Army Medical Center	Ft. Sam Houston	Texas
EAMC	Eisenhower Army Medical Center	Ft. Gordon	Georgia
MAMC	Madigan Army Medical Center	Tacoma	Washington
MGMC	Malcolm Grow Medical Center	Andrews AFB	Maryland
NMCP	Naval Medical Center	Portsmouth	Virginia
NMCSD	Naval Medical Center	San Diego	California
NNMC	National Naval Medical Center	Bethesda	Maryland
VMMC	Virginia Mason Medical Center	Seattle	Washington
WHMC	Wilford Hall Medical Center	Lackland AFB	Texas
WPMC	Wright-Patterson Medical Center	Wright-Patterson AFB	Ohio
WRAMC	Walter Reed Medical Center	Washington	District of Columbia

2. Changing face of prostate cancer since the start of the PSA era (submitted to J Urol, accepted as poster presentation in AUA04, see Appendix 1).

PSA screening, especially the mandatory screening for active duty military healthcare system beneficiaries, greatly impacts the epidemiology of prostate cancer in detection, diagnosis, treatment, recurrences and quality of life [13-17]. To build models for prediction of the probabilities of risk of prostate cancer, and outcome, a thorough understanding of the changes of prostate cancer clinical course due to PSA screening is critical.

In this study, we used 10,681 patients diagnosed with prostate cancer between 1990 and 2002 that were registered in the DoD-CPDR national database. Statistical analyses were performed identifying significant trends in patients, their choices of treatment, and their disease-free survivability.

As the PSA era progressed, patients became younger (<70), had lower diagnostic PSA, and were more likely to be diagnosed with clinical T1c disease. The number of diagnostic biopsy cores increased with the percentage of cores containing cancer decreasing over time. Biopsies with a diagnostic Gleason sum of 7 have increased. Patients were almost twice as likely to undergo surgery vs. external beam radiation by the later time of observation. The PSA recurrence-free and clinical metastasis-free survival at 1, 5, and 10 years for radical prostatectomy patients were 88.0 vs. 99.4, 64.0 vs. 96.5, and 38.3 vs. 90.2%, respectively. The clinical metastasis-free survival at 1, 5, and 10 years in external beam radiation therapy was 99.3, 91.4, and 79.3% respectively. Disease-specific mortality has continued to decline over the past twelve-years.

We concluded that prostate cancer is increasingly diagnosed in younger men with clinically localized disease allowing more patients to seek potentially curative treatment. Tumor burden has decreased over the past twelve years. The use of serum PSA as a

screening tool combined with TRUS biopsies to diagnose prostate cancer appears to have reduced disease-specific mortality (see Appendix 1).

3. Racial difference in location, number and volume of prostate cancers based on 3 dimensional reconstructed prostate specimens (submitted to J Urol 2004, accepted as poster presentation in AUA04; see Appendix 2).

This study aimed to identify whether there exists any racial difference between Caucasian (CM) and African American (AA) patients in number, location and volume of prostate cancer. The role of age and pathological stages on the tumor characteristics was clarified.

A total of 176 (135 CM and 41 AA) radical prostatectomy specimens that were obtained between 1993 and 2000, and 3-dimentional (3D) reconstructed were used in this study. Each 3D reconstructed specimen was partitioned into 24 slots and a comprehensive combination of these 24 slots was considered, which resulted in 38 representative zones including peripheral zone, transition zone and central zone. Investigation into potential racial difference in number, location and volume of cancer was performed. We found that no significant overall difference was found in tumor number between the CM and AA patients regardless of their ages. When stratified by pathological stages, however, AA patients (stage T2) were found to have significantly more tumors than CM patients ($P = 0.012$). With or without stratification by pathological T stages, there was no significant difference in tumor location between the two race groups. In the age group of 60 and 65, AA patients were found to have more tumors at the left medial anterior prostate ($p = 0.047$). Further, CM patients 65 or older were found to have significantly more tumors at posterior base ($p = 0.035$). Overall, no significant difference was found in total tumor volume, index tumor volume, and tumor volume at each of the 38 zones between CM and AA patients. When stratified by age, however, we observed an interesting trend: among patients younger than 60, AA patients had consistently larger tumor volumes at most of the 38 zones (Figure 1). Among patients between 60 and 65, there was no apparent racial difference in tumor volumes. For patients older than 65, however, CM patients had consistently larger tumor volumes at most of the 38 zones (Figure 2). Furthermore, CM patients 60 or older were found to have significantly larger tumor volume at a number of zones than their AA counterparts.

We concluded that distribution of prostate cancer can be accurately evaluated using a 3D reconstruction approach. Overall, no significant difference was found in number, location or volume of tumors between CM and AA patients. However, young African American patients had consistently larger tumors compared to young Caucasian men, while this ratio was reversed by ethnicity in older patients.

Figure 1. Racial comparisons of mean tumor volumes at individual zones in men < 60 years old.

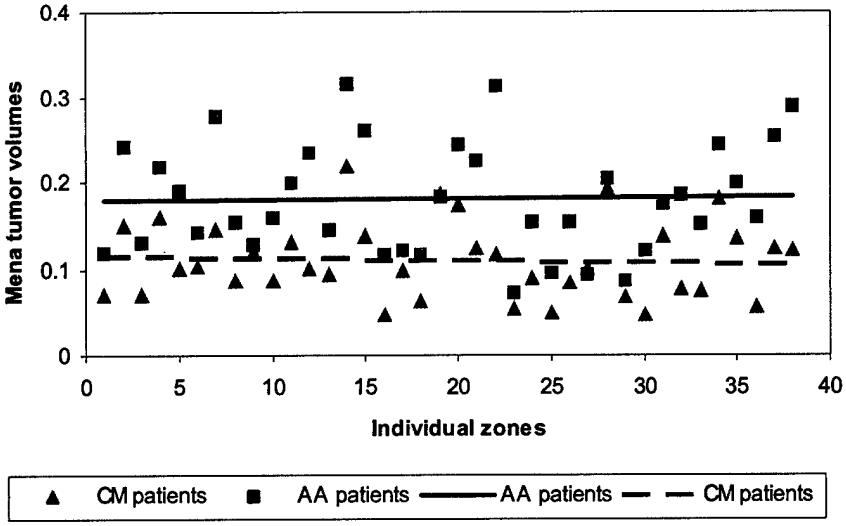
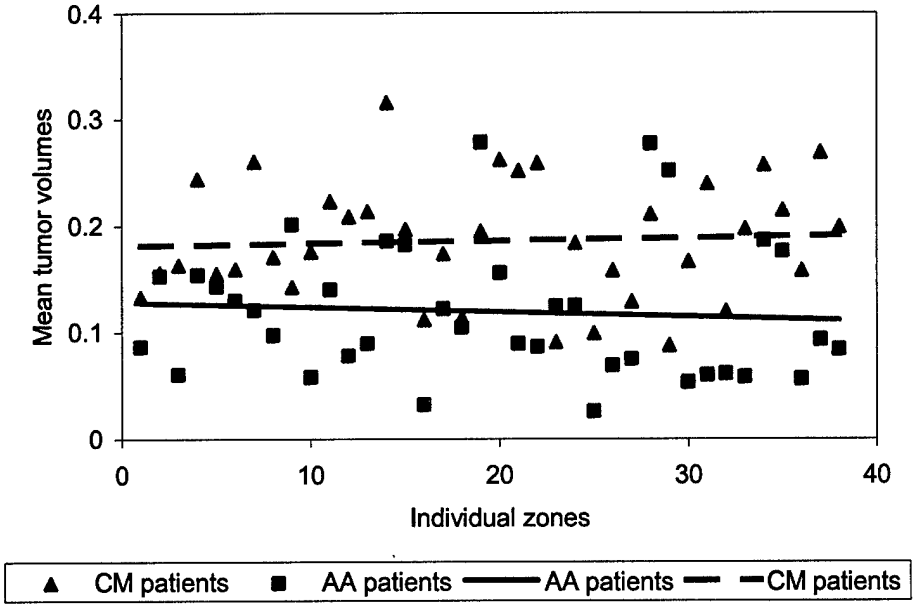


Figure 2. Racial comparisons of mean tumor volumes at individual zones in men > 65 years old.



4. Pre- and post-operative prognostic factors predicting PSA recurrence in intermediate-risk prostate cancer patients (Submitted to J Urol 2004, Accepted as poster presentation in AUA04, see Appendix 3)

Predicting PSA recurrence in patients with intermediate-risk disease (pretreatment PSA 10 - 20 ng/ml, biopsy Gleason sum 7 or clinical stage T2b) treated with radical prostatectomy is an important clinical issue. This study was designed to identify the association of pre- and post-surgery prognostic factors predicting biochemical recurrence. A total of 864 patients who had intermediate-risk disease and received radical prostatectomy from 1989 to 2002 were retrieved from the DoD CPDR Tri-Service Multi-center Database. Patients with neo-adjuvant treatment, post- surgery follow-up time < 6 months or without biopsy core information were excluded. The Kaplan-Meier method was used to estimate the probability of PSA recurrence (PSA > 0.2 ng/ml). Univariate and multivariate Cox proportional hazard analyses were used to evaluate the relative risk of pre- and post-surgery factors for PSA recurrence.

The results showed that the median follow-up for the 864 patients was 4.4 years. Among them, 282 (32.6%) developed PSA recurrence. The 3-year and 5-year PSA-free recurrence rates were 80.3% and 72.0%, respectively. Seventy-four (8.5%) patients developed distant metastasis. In univariate and multivariate analyses on pre-surgery factors: race, percentage of positive biopsy cores, and PSA were significant factors for predicting PSA recurrence ($p < 0.05$). When both pre- and post-surgery factors were pooled together for multivariate analysis, race percentage of positive biopsy cores, pathologic Gleason sum, and margin status were associated with the PSA recurrence ($p < 0.05$).

We concluded that this study provided two sets of prognostic factor sets for potential clinical decision making processes in patients with intermediate-risk disease (Table 3-4). Prior to surgery, race, diagnostic PSA level and percentage of cancer-positive biopsy cores were independent predictors for PSA recurrence. After radical prostatectomy, race, percentage of positive biopsy cores, pathologic Gleason sum and margin status could be used as prognostic factors.

Table 3. Cox regression results of pretreatment factors for PSA recurrence-free time

Factors	Hazard ratio (95% CI)	p
Race		<.0001
AA vs. white & other	1.782 (1.375 – 2.310)	
Diagnostic PSA (ng/ml)		0.0126
> 4 - 10 vs ≤ 4	1.663 (1.138 - 2.429)	
> 10 - 20 vs ≤ 4	1.744 (1.197 – 2.541)	
Percentage of positive biopsy cores		0.0007
> 30 - 50% vs. ≤ 30%	0.897 (0.638 - 1.259)	
> 50% vs. ≤ 30%	1.506 (1.154 – 1.965)	

Table 4. Multivariate Cox regression results of all pre- and post-operative factors for PSA recurrence-free time in the intermediate-risk patients.

Factors	Adjusted hazard ratio (95% CI)	p
Pretreatment factors		
Race		0.0002
AA vs. white & other	1.663 (1.275 – 2.169)	
Diagnostic PSA (ng/ml)		0.0850
> 4 - 10 vs. ≤ 4	1.406 (0.958 – 2.062)	
> 10 - 20 vs. ≤ 4	1.591 (0.980 – 2.581)	
Percentage of positive biopsy cores		0.0054
> 30 - 50% vs. ≤ 30%	0.916 (0.649 – 1.291)	
> 50% vs. ≤ 30%	1.434 (1.091 - 1.885)	
Postoperative factors:		
Pathologic stage		0.0679
PT3/4 vs. PT2	1.427 (0.974 - 2.091)	
Pathologic Gleason sum		0.0041
7 vs. 2 - 6	1.448 (1.103 – 1.901)	
8-10 vs. 2 - 6	1.882 (1.242 – 2.854)	
Capsule		0.5657
Positive vs. negative	1.098 (0.799 – 1.509)	
Margins		0.0345
Positive vs. negative	1.388 (1.024 – 1.881)	
Seminal vesicle		0.4578
Positive vs. negative	1.140 (0.806 – 1.612)	

5. How long should radical prostatectomy be safely delayed (Submitted to J Urol 2004, Accepted as podium presentation, see Appendix 4).

This study was aimed to evaluate the association of delayed radical prostatectomy with PSA recurrence and to identify the prognostic factors and optimal observation interval in different risk groups of prostate cancer. We used 3324 men retrieved from the CPDR National Database who received definitive surgical therapy in the period 1988-2002. The study excluded patients who experienced treatment failure (post-operative PSA never reached nadir or PSA recurrence occurred within 6 months post-operatively), who received adjuvant therapy, or whose follow-up time was less than 6 months. The cohort was then divided into 3 groups based on the delay (<25, 25-75 and > 75 percentiles). Univariate and multivariate Cox regression models were used to evaluate the effect of delay on PSA recurrence (PSA > 0.2 ng/ml) and prognostic variables. Then the patients were regrouped into "low", "intermediate" and "high" risk groups. The "low" risk group included those with Gleason score < 7 and PSA < 4 ng/ml while the "high" risk group consisted of individuals with Gleason score > 7 or PSA > 20 ng/ml. The remainder of the cohort

fell into the "Intermediate" risk category. These groups were then compared to each other to evaluate the effect of delay on PSA recurrence.

Of 3324 patients, mean 5- and 10-year PSA recurrence-free survival were 68.8% (95% CI: 66.7-70.8) and 54.1 %(95% CI: 50.8-57.8), respectively. Overall, delay time was not a significant factor affecting PSA recurrence ($p = 0.099$). Instead, pathological extracapsular extension, surgical margin and seminal vesicle status were prognostic factors ($p < 0.05$). Adjusting the delay time by these three variables showed that delayed surgery was significantly associated with PSA recurrence ($\geq$ 3 months vs < 3 months, adjusted hazard ratio = 1.16, p=0.047). In addition, adjusting the delay time by biopsy Gleason sum and diagnostic tumor stage and PSA level indicated that delayed surgery over 97 days post diagnosis (> 75 percentile of the delay time) had a higher PSA recurrence rate (hazard ratio = 1.23, p=0.042). In high-risk disease, the adjusted hazard ratio of the delayed therapy effect on PSA recurrence was 1.46 ($p = 0.029$).

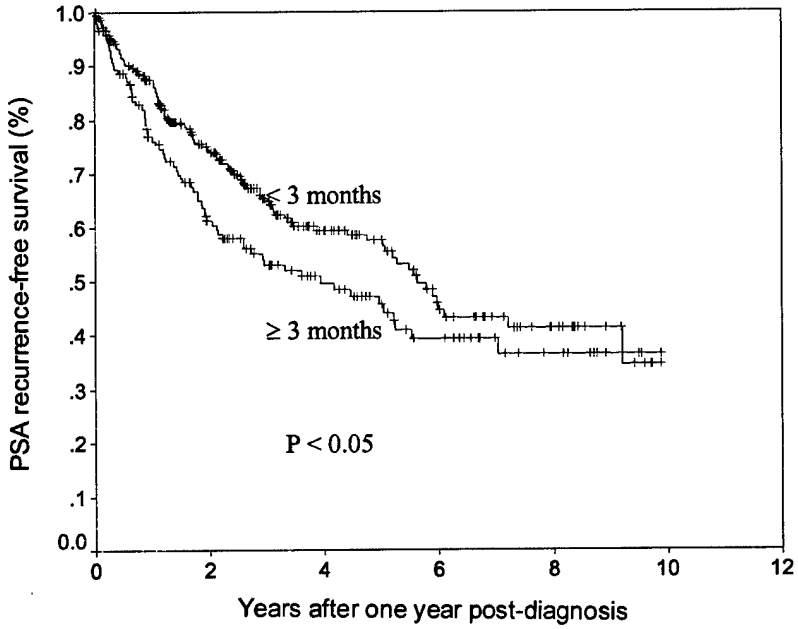
We concluded that although delay was not a significant prognostic factor for all patients, it did influence biochemical outcome for high-risk individuals. In men with high-risk features, a delay greater than approximately 3 months may affect outcome (Table 5 and Figure 3).

Table 5. Crude and adjusted hazard ratio for PSA recurrence by surgical waiting time in quartiles.

Surgical waiting time by quartiles	**Crude hazard ratio**	**95% C.I.**	**p**	**Adjusted hazard ratio**	**95% C.I.**	**p**
< 47 days (< 25%)	1			1		
47-65 (25-50%)	0.991	0.84-1.16	0.911	1.12	0.91-1.38	0.270
66-97 (51-75%)	1.05	0.90-1.23	0.533	1.15	0.94-1.41	0.179
>97(>75%)	1.09	0.93-1.27	0.277	1.23	1.01-1.51	**0.042**

*Adjusted hazard ratio accounted for diagnostic PSA, Gleason sum and diagnostic stage.

Figure 3. Biochemical recurrence-free survival curves of impact of delay in radical prostatectomy



6. Implementation of predicting models in CPDR website accessible through the Internet.

Pre- and post-operative predictive equation. We have posted several biostatistical models predicting the risk of recurrence after radical prostatectomy for clinically localized prostate cancer on the CPDR website. These models were created based on data from 4205 radical prostatectomy patients. In our analysis we evaluated age, race, prostatic acid phosphatase and nuclear grade with the established prognostic variables of pretreatment prostate specific antigen, postoperative Gleason sum and pathological stage (Figures 4 and 5, http://www.cpdr.org/PreOpInput.html **and** http://www.cpdr.org/PostOpInput.html).

Figure 4. Predicting relative risk of PSA recurrence with pretreatment variables

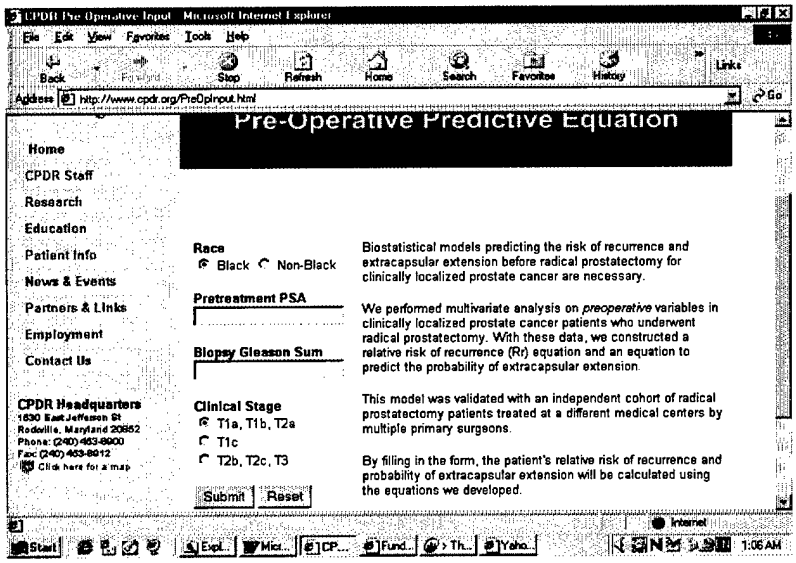
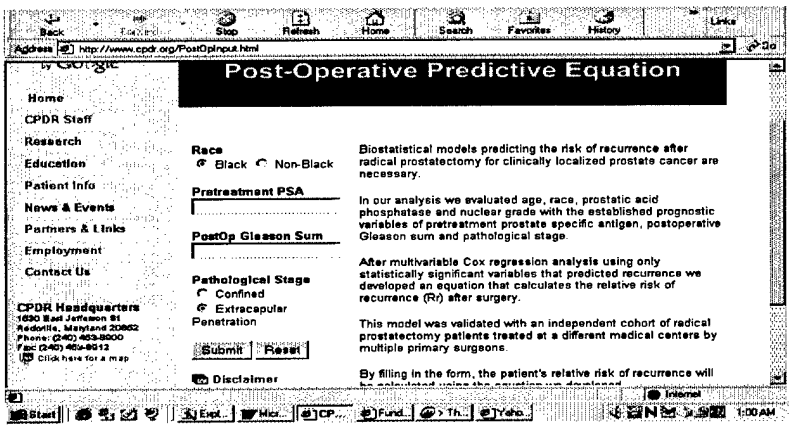


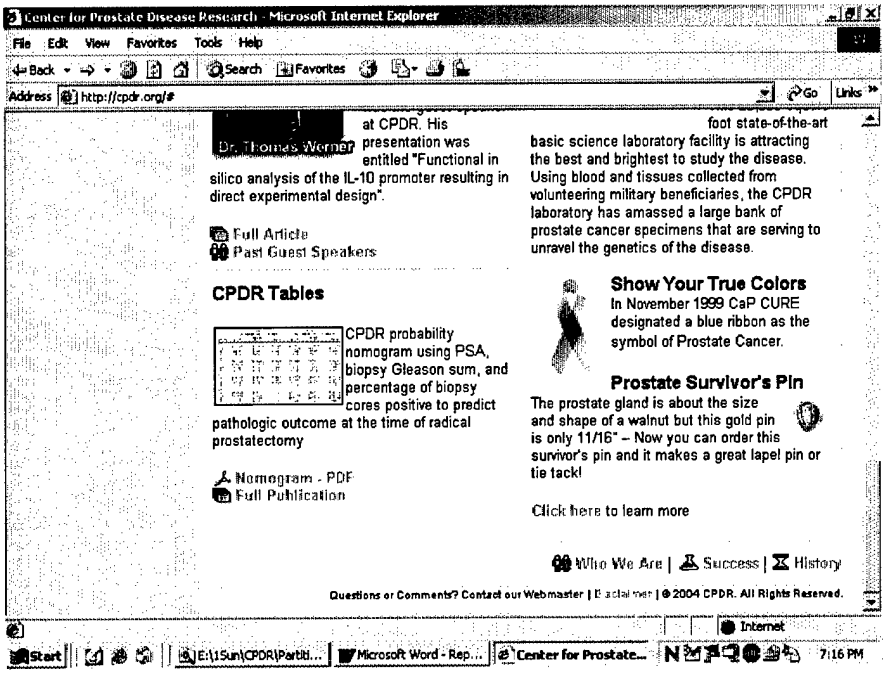
Figure 5. Predicting relative risk of PSA recurrence post radical prostatectomy



PSA doubling time calculator. Our collaborative project with Drs. Peter Caroll at UCSF and Anthony D'Amico at Harvard University revealed that PSA doubling time is an important surrogate marker in predicting the outcome of prostate cancer (see Appendix 5). Therefore we designed and developed the PSA doubling time calculator for patients receiving radical prostatectomy to calculate their PSA doubling time (www.cpdr.org).

CPDR Nomogram. We have developed and posted the CPDR nomogram to the CPDR website (Figure 6). It was designed for patients who have not undergone any treatment to predict pathological stage by using variables of pretreatment PSA, biopsy Gleason sum and the ratio of cancer-positive cores over total biopsy cores (www.cpdr.org/#).

Figure 6. Predicting relative risk of pathological stage



KEY RESEARCH ACCOMPLISHMENTS

- Created an Oracle database, enlarged the data quantity and enhanced the data quality
- Analyzed the impact of delayed surgery on outcome (accepted as podium presentation in AUA 2004)
- Analyzed the roles of pretreatment (PSA, Gleason, Clinical stage, Age, Race, etc) and post-treatment (capsule, margin, node, seminal vesicle invasion) variables on the outcome of prostate cancer (Accepted as poster in AUA 2004)
- Identified the epidemiology characteristics of prostate clinical course since the start of PSA era (Accepted as poster in AUA 2004)
- One article submitted to J Clin Onc in 2003 was under reviewing process (Appendix 5)

- Four articles published in J Urol (2) or J Clin Onc (2) in 2003 (Appendix 6-9)
- Four articles were submitted for publication (Appendix 1-4)
- Six abstracts were accepted as posters by AUA 2004
- One abstract was accepted for podium presentation by AUA 2004
- Three web applications were implemented on the CPDR webpage to predict relative risk of PSA recurrence with pretreatment variables and pathological variables.
- One web application was designed and developed for patients to calculate PSA doubling time.

REPORTABLE OUTCOMES

1. Prostate cancer is increasingly diagnosed in younger men with clinically localized disease allowing more patients to seek potentially curative treatment. Tumor burden has decreased over the past twelve years. The use of serum PSA as a screening tool combined with TRUS biopsies to diagnose prostate cancer appears to have reduced disease-specific mortality.

2. Although delay was not a significant prognostic factor for all patients, it did influence biochemical outcome for high-risk individuals. In men with high-risk features, a delay greater than approximately 3 months may affect outcome.

3. Prior to surgery, race, diagnostic PSA level and percentage of cancer-positive biopsy cores were independent predictors for PSA recurrence. After radical prostatectomy, race, percentage of positive biopsy cores, pathologic Gleason sum and margin status could be used as prognostic factors.

4. Overall, no significant difference was found in number, location or volume of tumors between CM and AA patients. However, young African American patients had consistently larger tumors compared to young Caucasian men, while this ratio was reversed by ethnicity in older patients.

CONCLUSIONS

The epidemiology of prostate cancer clinical course has been changed since the start of the PSA era. Pre- and post-treatment variables can be used to predict disease outcome for patients with intermediate-risk disease. Delayed surgery may impact the outcome for men with high-risk disease. Posttreatment PSA doubling time < 3 months is significantly associated with disease-specific death. Taken together, these studies indicate that using pretreatment and post-treatment variables as well as PSA doubling time to predict CaP outcome is practical. It will lead us to better understand prostate cancer's clinical course and improve decision making and clinical management.

Posting these results on the website accessible through the Internet is possible and practical. A comprehensive effort is underway to develop more prediction models and to post these models on the web, accessible by physicians and patients for their decision making.

REFERENCES

1. Jemal A, Murray T, Samuels A, et al 2003. Cancer statistics. CA Cancer J Clin 53:5-26, 2003

2. Moul JW. Treatment options for prostate cancer. Part I-stage, grade, PSA, and changes in the 1990's. Am J Manag Care 4:1031-6, 1998

3. Moul JW, Wu H, Sun L et al. Epidemiology of radical prostatectomy for localized prostate cancer in the era of prostate-specific antigen: an overview of the Department of Defense Center for Prostate Disease Research national database. Surgery 132:213-9, 2002

4. Moul JW. Prostate specific antigen only progression of prostate cancer. J Urol 163:1632-42, 2000

5. Djavan B, Moul JW, Zlotta A, et al. PSA Progression Following radical prostatectomy and radiation therapy: New Standards in the New Millenium. Eur Urol 43:12-27, 2003

6. Han M, Partin AW, Zahurak M, Piantadosi S, Epstein JI, Walsh PC. Biochemical (prostate specific antigen) recurrence probability following radical prostatectomy for clinically localized prostate cancer. J Urol 169:517-23, 2003

7. Scherr D, Swindle P, Scardino PT. National Comprehensive Cancer Network Guidelines for the Management of Prostate Cancer. Urology 61:14-24, 2003

8. Crawford ED. Early versus late hormonal therapy: debating the issues. Urology 61(2 Suppl 1):8-13, 2003

9. Sun L, Gancarczyk K, McLeod DG, Kane C, Kusuda L, Lance R, Herring J, Foley J, Baldwin D, Bishoff JT, Soderdahl D, Wu H, Xu L, Moul JW. Introduction to department of defense center for prostate disease research (CPDR) multicenter national prostate cancer database with 242,227 records on 11,637 men, and analysis of changes in the PSA-era. *Urol Oncol*, 6:203-209, 2001

10. Vicini FA, Kestin L, Martinez A. Biochemical outcomes of treatment for prostate cancer. *JAMA* 2000; 284:2869

11. Welch HG, Schwartz LM, Woloshin S. Do increased 5-year survival rates in prostate cancer indicate better outcomes? *JAMA* 2000; 284:2053-5

12. Wilt TJ. Uncertainty in prostate cancer care: the physician's role in clearing the confusion. JAMA. 2000 283:3258-60

13. Gann PH, Hennekens CH, Stampfer MJ. A prospective evaluation of plasma prostate-specific antigen for detection of prostatic cancer. *JAMA* 273:289-94, 1995.

14. Burack RC, Wood DP: Screening for prostate cancer. The challenge of promoting informed decision making in the absence of definitive evidence of effectiveness. *Med Clin North Am* 83:1423-42, 1999.

15. Rietbergen JB, Hoedemaeker RF, Boeken K, et al: The changing pattern of prostate cancer at the time of diagnosis: Characteristics of screen detected prostate cancer in a population based screening study. *J Urol* 161(4):1192-8, 1999.

16. Feuer EJ, Mariotto A, Merrill R. Modeling the Impact of the Decline in Distant Stage Disease on Prostate Cancer Mortality Rates. *Cancer* 95:870-80, 2002.

17. Donahue T, Moul J. Diagnostic Accuracy of Prostate Needle Biopsy. *Current Urol Rep* 3:215-21, 2002.

APPENDICES

1. Leon Sun, Judd W. Moul, Corey A. Carter, Xiao Zhao, David G. McLeod, Christopher Amling, Timothy Donahue, Leo Kusuda, Wade Sexton, Keith O'Reilly, John Foley, Andrew Chung, Karen Smith. Changing face of prostate cancer since the start of the PSA-era: Results from the Department of Defense (DoD) Center for Prostate Disease Research (CPDR) database. Submitted to J Urol 2004 (Pending, accepted as poster presentation in AUA 2004)

2. Jianchao Zeng, Leon Sun, Yongmei Chen, Judd J Moul, David G. McLeod, Isabell, Sesterhenn. Racial difference in location, number and volume of prostate cancers based on 3 dimensional reconstructed prostate specimens. Submitted to J Urol 2004 (Pending, accepted as poster presentation in AUA 2004)

3. Yongmei Chen, Leon Sun, Judd W. Moul, David G. McLeod, Gregory Bernsten, Hongyan Wu, Christopher Amling, Robert Douglas, Timothy Donahue, Leo Kusuda, Wade Sexton, Keith O'Reilly, John Foley, Andrew Chung, Karen Smith. Pre- and post-operative prognostic factors predicting PSA recurrence in intermediate-risk prostate cancer patients. Submitted to J Urol 2004 (Pending, accepted as poster presentation in AUA 2004)

4. Judd W. Moul, Leon Sun, Yongmei Chen, Fia Yi, David G. McLeod, Hongyan Wu, Christopher Amling, Timothy Donahue, Leo Kusuda, Wade Sexton, Keith O'Reilly, John Foley, Andrew Chung, Karen Smith. Does Delayed Radical Prostatectomy Impact PSA Recurrence? Submitted to J Urol 2004 (Pending, accepted as podium presentation in AUA 2004)

5. Leon Sun, Judd W. Moul, Julian Wu, David G. McLeod, Christopher Amling, Curt Powell, Thomas Chung, Timothy Donahue, Stephen Jackman, Robert Douglas, Leo Kusuda, Wade Sexton, Keith O'Reilly, Javier Hernandez, John Foley, Andrew Chung, Karen Smith. Clinical Course of Prostate Cancer after Radical Prostatectomy and Prognostic Factors Associated with Post-treatment Distant Metastasis. Submitted to J Clin Onc 2004 (Pending)

6. D'Amico AV, Moul J, Carroll P, Sun L, Lubeck D, Chen M. Cancer specific mortality following surgery or radiation for patients with clinically localized prostate cancer managed during the PSA Era. J Clin Oncol 21:2163-2172, 2003

7. Carter CA, Donahue T, Sun L, Wu H, McLeod DG, Amling C, Lance R, Foley J, Wade S, Kusuda L, Chung A, Soderdahl D, Jackman S, Moul JW. Temporarily Deferred Therapy (watchful waiting) for Men Younger Than 70 Years and With Low-Risk Localized Prostate Cancer in the Prostate-Specific Antigen Era. J Clin Onc 21:4001-8, 2003

8. Judd W. Moul, Hongyu Wu, Leon Sun, David G. McLeod, Christopher Amling, Timothy Donahue, Leo Kusuda, Wade Sexton, Keith O'Reilly, Javier Hernandez, Andrew Chung, Douglas Soderdahl. Early versus delayed hormonal therapy for PSA-only recurrence of prostate cancer after prior radical prostatectomy. J Urol 171, 2004 (in press)

9. Judd W. Moul, Hongyu Wu, Leon Sun, David G. McLeod, Christopher Amling, Timothy Donahue, Leo Kusuda, Wade Sexton, Keith O'Reilly, Javier Hernandez, Andrew Chung, Douglas Soderdahl. Early versus delayed hormonal therapy for prostate specific antigen only recurrence of prostate cancer after prior radical prostatectomy. J Urol 171, 2004.

Appendix 1 (Accepted as poster presentation by AUA 2003 and submitted to J Urol for publication)

CHANGING FACE OF PROSTATE CANCER SINCE THE START OF THE PSA-ERA: RESULTS FROM THE DEPARTMENT OF DEFENSE (DOD) CENTER FOR PROSTATE DISEASE RESEARCH (CPDR) DATABASE.

Leon Sun[1], Judd W. Moul[1], Corey A. Carter[1], Xiao Zhao[1], David G. McLeod[2], Christopher Amling[3], Timothy Donahue[4], Leo Kusuda[5], Wade Sexton[6], Keith O'Reilly[7], John Foley[8], Andrew Chung[9], Karen Smith[1]

1. Center for Prostate Disease Research (CPDR)
   Department of Surgery
   Uniformed Services University of the Health Sciences
   Bethesda, MD 20814

2. Urology Service, Department of Surgery
   Walter Reed Army Medical Center
   Washington, D.C. 20307-5001

3. Department of Urology
   San Diego Naval Medical Center
   San Diego, CA

4. Department of Urology
   National Naval Medical Center
   Bethesda, MD

5. Department of Urology
   Portsmouth Naval Medical Center
   Portsmouth, VA

6. Department of Urology
   Wilford Hall AF Medical Center
   Lackland AFB, TX

7. Urology Service, Dept. of Surgery
   Madigan Army Medical Center
   Tacoma, WA

8. Urology Service, Dept. of Surgery
   Brooke Army Medical Center
   San Antonio, TX

9. Department of Urology
   Malcolm Grow AF Medical Center
   Andrews AFB, MD

10. Urology Service, Dept. of Surgery
    Eisenhower Army Medical Center
    Augusta, GA

*Requests for reprints/correspondence:Judd W. Moul, MD
Leon Sun, MD, PhD
Center for Prostate Disease Research
1530 East Jefferson Street
Rockville, MD 20852
Telephone: (240) 453-8951
Fax: (240) 453-8912
Email: jmoul@cpdr.org
Key Words: Prostate cancer, Epidemiology, PSA recurrence, Metastasis-free survival

Running Title: The Changing Face of Prostate Cancer

The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Departments of the Army, Navy or Air Force or the Department of Defense.

The authors are supported by a grant from the Center for Prostate Disease Research, a program of the Henry M. Jackson Foundation for the Advancement of Military Medicine (Rockville, MD) and the Uniformed Services University of the Health Sciences, funded by the U.S. Army Medical Research and Material Command (DAMD17-02-1-0066).

ABSTRACT

INTRODUCTION: Since the introduction of prostate-specific antigen (PSA) and the increase use of transrectal ultrasound guided (TRUS) biopsies the typical patient who presents with prostate cancer has changed. We attempt to report on the changing trends in prostate cancer's diagnosis, pathology, treatment, and outcomes.
METHODS: Data was collected on 10,681 patients diagnosed with prostate cancer between 1990 and 2002 that were registered in the DoD-CPDR national database. Statistical analyses were performed identifying significant trends in patients, their choices of treatment, and their disease-free survivability.
RESULTS: As the PSA-Ear progressed patients became younger (<70), had lower diagnostic PSA, and were more likely to be diagnosed with clinical T1c disease. The number of diagnostic biopsy cores increased with the percentage of cores containing cancer decreasing over time. Biopsies with a diagnostic Gleason sum of 7 have increased. Patients were almost twice as likely to undergo surgery vs. external beam radiation by the later time of observation. The PSA recurrence-free and clinical metastasis-free survival at 1, 5, and 10 years for radical prostatectomy patients were 88.0 vs. 99.4, 64.0 vs. 96.5, and 38.3 vs. 90.2%, respectively. The clinical metastasis-free survival at 1, 5, and 10 years in external beam radiation therapy was 99.3, 91.4, and 79.3% respectively. Disease-specific mortality has continued to decline over the past twelve-years.
CONCLUSION: Prostate cancer is increasingly diagnosed in younger men with clinically localized disease allowing more patients to seek potentially curative treatment. Tumor burden has decreased over the past twelve years. The use of serum PSA as a screening tool combined with TRUS biopsies to diagnose prostate cancer appears to have reduced disease-specific mortality.

INTRODUCTION

It is estimated that 220,900 men will be diagnosed with prostate cancer in 2003 and there are projected 28,900 deaths from the disease.[1] The Surveillance, Epidemiology, and End Results (SEER) database has shown an increase in the incidence of prostate cancer from 1992 to 1995, and then a subsequent decrease through 1997 to a new stabilized rate.[2] The increase in incidence throughout the early 90s has been directly attributed to the wide use of serum prostate-specific antigen (PSA) testing.

Despite the controversy surrounding prostate cancer population based screening, the American Cancer Society recommends that PSA testing be offered annually (together with digital rectal examination) to men over 50 (45 for African Americans) who have at least a 10-year life expectancy.[3] PSA testing is widely practiced in the United States and it is undisputed that the use of PSA has changed the face of prostate cancer.

PATIENTS AND METHODS

The clinical information for this study is part of the Center for Prostate Disease Research (CPDR) which maintains a research database that is congressionally mandated and funded by the Department of Defense. CPDR registers and follows men being evaluated for and with prostate cancer treated in the military healthcare system described previously by Sun et al.[4] Briefly it uses standardized data collection forms for registration, medical history, primary staging, pathology, treatment, annual questionnaire, and necropsy which have been developed and used. Data has been collected from 9 major hospitals (Table 1) and entered by physicians and data managers, then maintained using MS Access software as the front end and Oracle software as the back end. The CPDR database has been approved by the Uniformed Services University Research Administration, Institutional Review Board (IRB) as well as the IRBs of all participating military hospitals. The original protocol that was in use between 1991-1998 did not require patients to sign a formal informed consent document. However, between 1998 and 1999, the IRBs of all sites required patient informed consent to participate. Data was allowed to be maintained on all entered data prior to 1998-1999 (exact date varies by institution) without gaining the patients' informed consent; however, no new information on existing living patients or new enrollees was entered without consent after these dates.

The data query for this study was performed in February 2003. At this time, the overall database contained 445,740 clinical records on 17,817 patients. Of these 10,681 patients were selected for this study diagnosed during the PSA-era 1990-2002 with complete information on initial diagnostic parameters, progression of disease, and causes of death if any. Patient deaths were confirmed by a private organization (ChoicePoint, Alpharetta, GA) that determines whether an individual is deceased by searching the National Social Security database. The cause of death was determined by acquiring death certificates from individual states' Departments of Vital Records and through the use of the National Death Index (Hyattsville, MD).

The following data points were used from the database for the purpose of this study: number of patients diagnosed each calendar year with prostate cancer (Table 2), initial diagnostic PSAs, age of patient at diagnosis, race of patient, clinical stage at diagnosis using the 1992 TNM system. Biopsy results included the number of cores obtained, and the pathological results which consisted of the percentage of cores that were positive for cancer, and Gleason sums. These data

points were analyzed over time and graphed to determine trends. Data from 1992 and 2002 was categorically analyzed by univariate analysis using chi-square to determine significance. Kaplan-Meier(KM) curves were derived to show survival from both PSA recurrence and metastatic disease. Patients biopsied without evidence of prostate cancer but with evidence high grade PIN was additionally reported on and are not included in the 10,681 patients.

RESULTS

The study includes 10,681 prostate cancer patients with complete clinical information that were diagnosed between 1990 and 2002. A univariate analysis (Table 3) was done showing the demographics of patients diagnosed between 1992 and 2002. Figure 1 reveals a downward trend in diagnostic PSAs greater than 10 and a continual increase in diagnostic PSAs between 4-10 ng/ml. In 1992 approximately 38% of patients had a PSA at diagnosis between 4 and 10, while in 2002 almost 57% ($p<0.0001$) of men did. Figure 2 demonstrates a decrease followed by a leveling off around 1999 of the percentage of men over age 70 diagnosed with prostate cancer. The graph shows a dramatic increase in the percentage of men under the age of 55. This increase began in 1994 and may be continuing to increase. Analysis of patient's age was statistically significant ($p<0.0001$) when comparing 1992 to 2002. Figure 3 demonstrates a trend in the decrease in the percentage of Caucasian men being diagnosed with prostate cancer in relation to the increasing trend of African-American men. This graph is notable for a modest increase in the percentage of men being diagnosed from other racial backgrounds. This trend was significant when comparing the 1992 to 2002 ($p<0.0001$). Figure 4 is a bar graph demonstrating the marked decrease in clinical T2 stage disease and a significant but slower decrease in both T3 and T4 disease. Currently, clinical stage T1C makes up over 53.8% of all diagnosis in our database. Comparing 1992 clinical staging to 2002 resulted in a $p<0.0001$. Figure 5 shows the downward trend in the rate of metastatic disease (T any N + or M1; D1, D2) found at diagnosis over the past twelve years. Almost 8% of cases diagnosed in 1992 had metastatic disease while only 3.5% had it in 2002.

Figure 6 is a graph showing how the mean number of biopsy cores from patients with prostate cancer obtained per year has changed. There was an increase in the mean from 6 in the year 1995 to12 in the year 2002. Figure 7 is a graph of the percent positive of the number of biopsy cores obtained per year. Noted is a continued increase in less than 25% of the cores being positive and a marked decline of patients with more than 50% of the cores positive. Figure 8 demonstrates the percentage of Gleason sums at diagnosis recorded on patients per year which, is then divided into three categories of: 2-6, 7, and 8 or greater. Notable is the increase in the percentage of Gleason 7s. A statistically significant change ($p=0.0033$) was found when comparing Gleason scores from 1992 to 2002. Figure 9 demonstrates the marked increase in the recognition and reporting of prostatic intraepithelial neoplasia (PIN), with the predominate increase in the reporting of high grade PIN.

In 1992, 31% and 27% of all patients electing curative treatment selected radical prostatectomy (RP) and external beam radiation therapy (XRT) respectively. By 2002 surgery was the predominate treatment choice in this database with almost 63% of the patients electing to undergo surgery ($p< 0.0001$). Patients electing brachytherapy, hormonal therapy or watchful waiting were less than 10% between 1990 and 2002 (Figure 10). Figure 11 is the ratio of patients receiving hormonal neoadjuvant therapy who later underwent either RP or XRT. The ratio of

XRT patients rose sharply from 1990 through 1996 and has leveled off since this time, while the ratio of patients who are to undergo radical prostatectomy peaked in 1995 and has steadily fallen to pre-1992 levels. Figure 12 shows the downward trend in disease specific death.

DISCUSSION

Our results have identified and illustrated striking trends in prostate cancer that have occurred over the past twelve years, since the introduction of wide spread PSA testing. Initial PSA measurements at diagnosis, the age of patients, ethnicities of patients, clinical stages, the way patients are biopsied as well as the results of the cores obtained, and the type of treatment were all shown to have changed quite dramatically with time and has resulted in a marked change in the "face" of prostate cancer.

Declining diagnostic PSA level. Widespread screening for prostate cancer has led to prostate cancer being diagnosed earlier and has led to lower diagnostic PSAs. Currently, approximately 80% of patient's in our database were diagnosed with prostate cancer with a PSA less than 10 ng/ml, compared to only 50% of patients in 1992. A similar trend has been reported in a smaller multicenter database by Jani et al[5] which found a decline in PSA at diagnosis of 0.8% per year from 1988 to 1998.

Younger patients. Our data was consistent with other studies that showed an increase in the incidence of younger aged men being diagnosed with prostate cancer and a decrease in the incidence of older aged men.[6] We found in 2002 over 50% of the patients being diagnosed were under the age of 65. The decrease in the age of diagnosis has been thought to be a result of wide spread screening of the population at risk. Some studies have suggested that there is a lead-time of approximately 5.5 years by using PSA measurements to detect prostate cancer.[7] This theory may account for an increase in younger age men being diagnosed, but does not fully account for the increase in men under age 55. Men under the age of 55 are the fastest growing group of men being diagnosed with prostate cancer. This may also reflect a more aggressive approach to screening young men in the military heath care system and a higher proportion of black patients who are known to develop the disease earlier.

Changes in the race of patients. The increase incidence of prostate cancer in African-Americans is well documented in various studies.[8] Our results illustrates an important and continuing trend in prostate cancer: Minority patients continue to be the fastest growing group of prostate cancer patients. Within the minority groups we found that our group labeled "other", which consisted mainly of Hispanics, Filipinos, and Native Americans, more than quadrupled from 1992 to 2002. This increase has occurred in our equal-access health care system. This outcome should lead to further studies on each of the specific minority groups. The increase in the percentage of African American patients as well as other ethnic groups is a result of an increase in public awareness and the prevalent use of PSA as a screening test. This data provides further evidence that there is a higher incidence of prostate cancer in African-Americans and possibly other minorities showing how the face of the prostate cancer patient is continuing to change.

Stage Migration. Screening for cancer may decrease mortality if the cancer is diagnosed earlier, while localized, and at earlier stages when treatment can be sought for a potential cure. Randomized studies have demonstrated that screening for prostate cancer will cause a significant stage reduction.[9] Computer based studies have also confirmed a decline in distant stage disease.[10] We found clinically localized prostate cancer made up over 95% of patients diagnosed in 2002, and of these 54% were T1C disease. Studies done in the Netherlands similarly have reported a marked stage reduction with screening particularly in metastatic cases.[9] SEER data has also confirmed this reduction in metastatic disease.[2] Our results showed a reduction in metastatic cases by more than half over the past ten years. With more prostate cancer being clinically organ confined, more patients can potentially receive curative treatment.

Transrectal Ultrasound Guided Biopsies. The evolution of the transrectal biopsy has occurred over the past 10 years starting from the sextant biopsy protocol to the extended core biopsy schemas focusing on lateral gland directed cores. This has led to an increase in the ability to detect cancer through a more complete sampling of the gland and has led to an increase in the detection of nonpalpable tumors.[11] Increasing the number of samples obtained has, on the other hand, led to decrease in the percentage of positive core samples. Sixty percent of patients had greater than 50 percent positive cores in 1992 to now almost 60 percent of the patients having 25 percent or less positive. In 2000, D'Amico et al[12] reported that patients having greater than 50 percent of their biopsies positive for prostate cancer had an 89% chance of experiencing a PSA recurrence in four years, whereas patients with less than 34 percent of biopsies positive had an 86% chance of remaining free from biochemical recurrence.

Gilliland et al[13] reported on cancer cases between 1983 and 1993 and noted the increase incidence of prostate cancer during this time corresponded to an increase in moderately differentiated tumors. Others have suggested that improvement in the assignment of grade, decrease in the incidence of TURPs, and the use of PSA screening may have resulted in a increase in moderately differentiated tumors.[2] Jani et al[5] noted that there is a decreasing trend in low grade tumors and a increase in the percentage of moderate grade tumors while high grade tumors has remained stable from 1988 to 1998. Similarly, our database showed a slow decrease in reporting of Gleason sums less than seven, a moderate increase in sums of seven, while sums greater than seven remained almost stable.

Changes in PIN: There is an increase risk for patients with high grade PIN to go on to be diagnosed with prostate carcinoma. Autopsy studies have shown that PIN precedes carcinoma by 10 or more years with low-grade PIN emerging first in men during their third decade of life.[14] Bostwick and Prange reported that the chance of progression to prostate cancer is at least 50%.[15] With a link between high grade PIN and prostate cancer, diagnostic follow-up has been recommended within 6 months, 1 year, and thereafter at 12 month intervals for the rest of the patient's life.[16] In review of our database we noted an increase reporting of high grade PIN from 22 cases (2.5%) in 1992 to 144 cases (21.8%) in the year 2002. The increase in reporting of high grade PIN shows an increase in the recognition of this pattern and recognition of the implication of the diagnosis of high grade PIN.

Changes in Treatment. Early detection has allowed for treatment to be accomplished earlier in the progression of the disease. Our database found an increase in the number of patients receiving RP and a decrease in the number of patients undergoing XRT. The SEER data

similarly shows an increase in the percentage of patients receiving RP from approximately 28% of patients to 35% of patients from 1990 to 1997.[2] More patients are choosing to undergo surgery and these patients tend to be younger, have more localized disease, and have greater than a ten year life expectancy.

Hormonal therapy has become the primary management both metastatic and locally advanced prostate cancer. Hormonal therapy has also become a pretreatment strategy for patients undergoing XRT. The results of randomized studies have shown a dramatic downstaging and survival effect from the use of neoadjuvant hormonal therapy for clinically localized disease.[17]. Our database showed an increase in XRT patients receiving neoadjuvant hormonal therapy after 1995 and a leveling off after 1998. Currently, approximately 35% of patients undergoing XRT will receive neoadjuvant therapy.

However, there has been multiple randomized trials showing neoadjuvant therapy has no effect on biochemical relapse in patients undergoing radical prostatectomy.[18] Our data shows a similar movement away from neoadjuvant therapy in patients undergoing RP. There was an increase in use of neoadjuvant therapy up to 1995 and once studies began to show questionable benefit from this treatment there was a downward trend in its use in surgery patients. Milbank et al[19]showed that there is currently little data suggesting that neoadjuvant therapy is beneficial to patients undergoing a RP.

CONCLUSIONS

Prostate cancer is increasingly diagnosed in younger men with clinically localized disease allowing more patients to seek potentially curative procedures. Tumor burden has decreased over the past ten years.

REFERENCES

1. Jemal A, Murray T, Samuels A, et al: Cancer statistics, 2003. CA *Cancer J Clin* 53:5-26, 2003.

2. Stephenson RA, Prostate Cancer Trends in the era of prostate-specific antigen; An update of incidence, mortality, and clinical factors from the SEER database. *Urol Clin North Am* 29:173-81, 2002.

3. Chronological History of ACS Recommendations on Early Detection of Cancer: http://www.cancer.org/docroot/PED/content/PED_2_3X_Chronological_History_of_ACS_Recommendations_on_Early_Detection_of_Cancer.asp?sitearea=PED, *Internet Site*, American Cancer Society, April, 2003.

4. Sun L, Gancarczyk K, Paquette EL, McLeod DG, Kane C, Moul JW: Introduction to Department of Defense Center for Prostate Disease Research Multicenter National Prostate Cancer Database, and analysis of changes in the PSA-Era. *Urol Oncol* 6:203-10, 2001.

5. Jani AB, Vaida F, Hanks G, et al: Changing Face and Different Countenances of Prostate Cancer: Racial and Geographic Differences in Prostate-Specific Antigen (PSA), Stage, and Grade Trends in the PSA Era. *Int J Cancer* 96:363-71, 2001.

6. Pickles T, Coldman A, Phillips N, The changing face of prostate cancer in British Columbia 1988-2000. *Can J Urol* 9:1551-7, 2002.

7. Gann PH, Hennekens CH, Stampfer MJ. A prospective evaluation of plasma prostate-specific antigen for detection of prostatic cancer. *JAMA* 273:289-94, 1995.

8. Burack RC, Wood DP: Screening for prostate cancer. The challenge of promoting informed decision making in the absence of definitive evidence of effectiveness. *Med Clin North Am* 83:1423-42, 1999.

9. Rietbergen JB, Hoedemaeker RF, Boeken K, et al: The changing pattern of prostate cancer at the time of diagnosis: Characteristics of screen detected prostate cancer in a population based screening study. *J Urol* 161(4):1192-8, 1999.

10. Feuer EJ, Mariotto A, Merrill R. Modeling the Impact of the Decline in Distant Stage Disease on Prostate Cancer Mortality Rates. *Cancer* 95:870-80, 2002.

11. Donahue T, Moul J. Diagnostic Accuracy of Prostate Needle Biopsy. *Current Urol Rep* 3:215-21, 2002.

12. D'Amico AV, Whittington R, Malkowicz SB, et al: Clinical Utility of the Percentage of Positive Prostate Biopsies in Defining Biochemical Outcome After Radical Prostatectomy for Patients with Clinically Localized Prostate Cancer. *J Clin Oncol* 18:1164-72, 2000.

13. Gilliland FG, Gleason DF, Hunt WC et al.: Trends in Gleason score for prostate cancer diagnosed between 1983 and 1993. *J Urol* 165:846-50, 2001.

14. Naughton CK, Miller DC, Mager DE, et al.: A prospective randomized trial comparing 6 versus 12 prostatic biopsy cores: impact on cancer detection. *J Urol* 164:388-92, 2000.

15. Prange W, Erbersdobler, Hammerer P: Significance of High Grade Prostatic Intraepithelial Neoplasia in needle biopsy specimens. *Urology* 57:486-90, 2001.

16. Iczkowski KA, Bostwick DG: Prostate Biopsy Interpretation, Current Concepts, 1999. *Urol Clin North Am* 26:435-52, 1999.

17. Fradet Y, The role of neoadjuvant androgen deprivation prior to radical prostatectomy. *Urol Clin North Am* 23:575-85, 1996.

18. Aus G, Abrahamsson PA, Ahlgren G, et al: Hormonal treatment before radical prostatectomy: a 3 year follow-up. *J Urol* 159:2013-17, 1998.

19. Milbank AJ, Dreicer R, Klein EA, Hormonal Therapy for Prostate Cancer: Primum Non Nocere. *Urology* 60:738-41, 2002.

Table 1. Participating multicenter CPDR sites, total cases involved in study.

Abbreviation	Full Name	City	State	Patients
BAMC	Brooke Army Medical Center	Ft. Sam Houston	Texas	1,012
EAMC	Eisenhower Army Medical Center	Ft. Gordon	Georgia	529
MAMC	Madigan Army Medical Center	Tacoma	Washington	1,304
MGMC	Malcolm Grow Medical Center	Andrews AFB	Maryland	609
NMCP	Naval Medical Center Portsmouth	Portsmouth	Virginia	984
NMCSD	Naval Medical Center San Diego	San Diego	California	1,502
NNMC	National Naval Medical Center	Bethesda	Maryland	1,508
WHMC	Wilford Hall Medical Center	Lackland AFB	Texas	1,039
WRAMC	Walter Reed Army Medical Center	Washington	District of Colombia	2,194
OVERALL	CPDR National Database			10,681

Table 2. Patients in the study divided by age and year diagnosed.

Age at diagnosis	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	Total
<55	25	37	40	54	54	68	101	98	109	125	121	111	105	1048
55-60	44	62	81	80	112	112	105	128	114	102	115	96	84	1235
60-65	91	122	195	221	231	218	193	192	209	193	198	175	142	2380
65-70	143	154	202	178	234	197	200	190	208	185	186	197	151	2425
>70	200	280	363	379	407	297	271	257	245	215	231	268	180	3593
Total	503	655	881	912	1038	892	870	865	885	820	851	847	662	10681

Table 3. Univariate analysis of the changing face of prostate cancer

Year	92 ~ 95 (n=3725) # (%)	96 ~ 98 (n=2620) # (%)	99 ~ 2002 (n=3183) # (%)	**p-Value**
Diagnostic PSA				<0.0001
<4	421 (12.3)	429 (17.4)	602 (20.2)	
4-10	1598 (46.5)	1334 (54.2)	1669 (56.2)	
10-20	734 (21.4)	396 (16.1)	445 (15.0)	
>20	682 (19.8)	303 (12.3)	255 (8.6)	
Age at diagnosis				<0.0001
<55	216 (5.8)	308 (11.8)	460 (14.5)	
55 ~ 60	385 (10.3)	347 (13.2)	394 (12.4)	
60 ~ 65	865 (23.2)	594 (22.7)	708 (22.3)	
65 ~ 70	811 (21.8)	598 (22.8)	719 (22.7)	
>70	1446 (38.9)	773 (29.5)	894 (28.2)	
Race				<0.0001
Caucasian	2766 (76.2)	1815 (72.1)	2088 (70.7)	
African American	749 (20.6)	573 (22.8)	654 (22.2)	
Other*	115 (3.2)	129 (5.1)	210 (7.1)	
Clinical stage				<0.0001
T1a/b	175 (5.0)	94 (3.8)	68 (2.4)	
T1c	1102 (31.8)	1092 (44.0)	1495 (52.4)	
T2	1850 (53.3)	1116 (45.0)	1185 (41.6)	
T3 and T4	342 (9.9)	181 (7.3)	104 (3.7)	
Metastatic disease at diagnosis	301 (8.1)	172 (6.6)	119 (3.7)	
Number of cores on biopsy	7.1	8.2	10.1	
Percent of positive cores biopsied				<0.0001
<=25%	589 (29.7)	929 (43.1)	1371 (52.0)	
25-50%	396 (20.0)	496 (23.0)	555 (21.0)	
>50%	997 (50.3)	732 (34.0)	712 (27.0)	
Gleason sum				0.0897
<=6	1994 (65.2)	1500 (64.0)	1581 (61.9)	
7	742 (24.3)	570 (24.3)	665 (26.0)	
>=8	321 (10.5)	275 (11.7)	309 (12.1)	
PIN				<0.0001
High Grade	191 (80.0)	268 (87.9)	694 (91.6)	
Low Grade	41 (17.2)	33 (10.8)	46 (6.1)	
Mixed	7 (2.9)	4 (1.3)	18 (2.4)	
Type of treatment elected				<0.0001
Radical Prostatectomy	1552 (42.5)	636 (25.1)	1544(53.3)	
External Beam Radiation	1243 (34.0)	1158 (45.7)	595 (20.5)	
Watchful Waiting	355 (9.7)	254 (10.0)	220 (7.6)	
Hormonal	393 (10.8)	254 (10.0)	228 (7.9)	
Brachytherapy	66 (1.8)	199 (7.9)	136 (4.7)	
Death from prostate cancer	213 (5.7)	50 (1.9)	20 (0.6)	

*Other races include Hispanic, Filipino, and Native American

Figure 1. Trends in diagnostic PSA levels over time in PSA-era

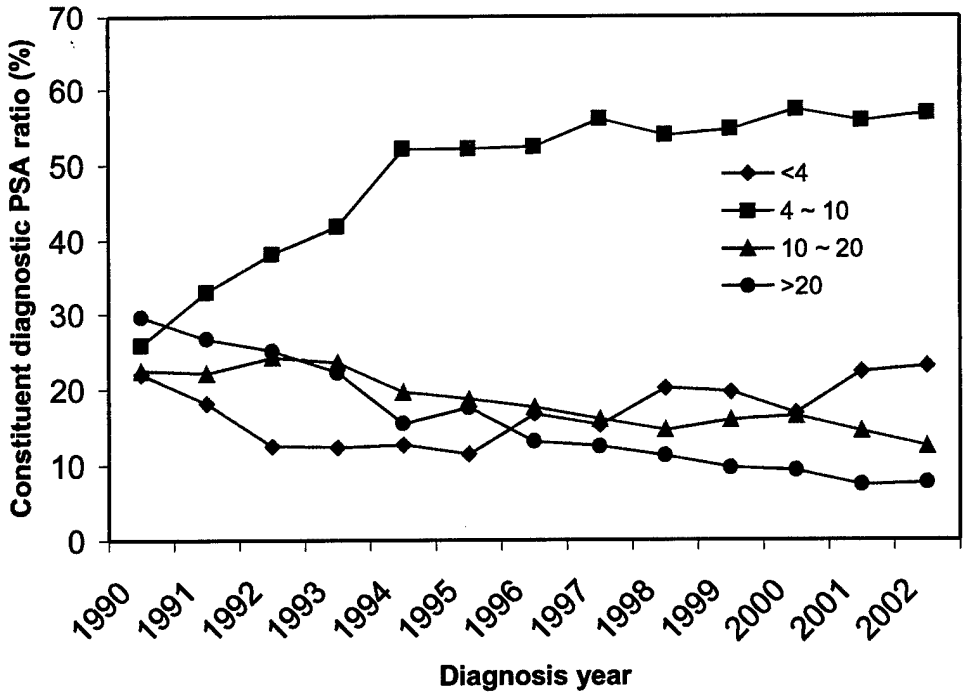


Figure 2. Trends in diagnostic age over time in PSA-era

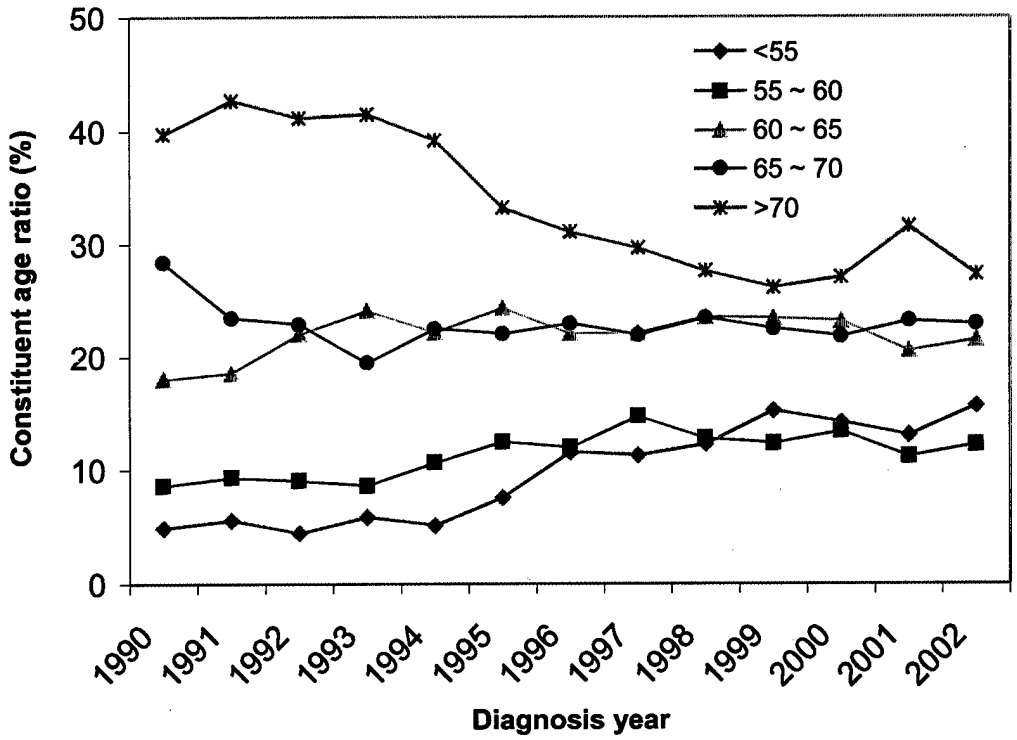


Figure 3. Trends in race/ethnically over time in PSA-era

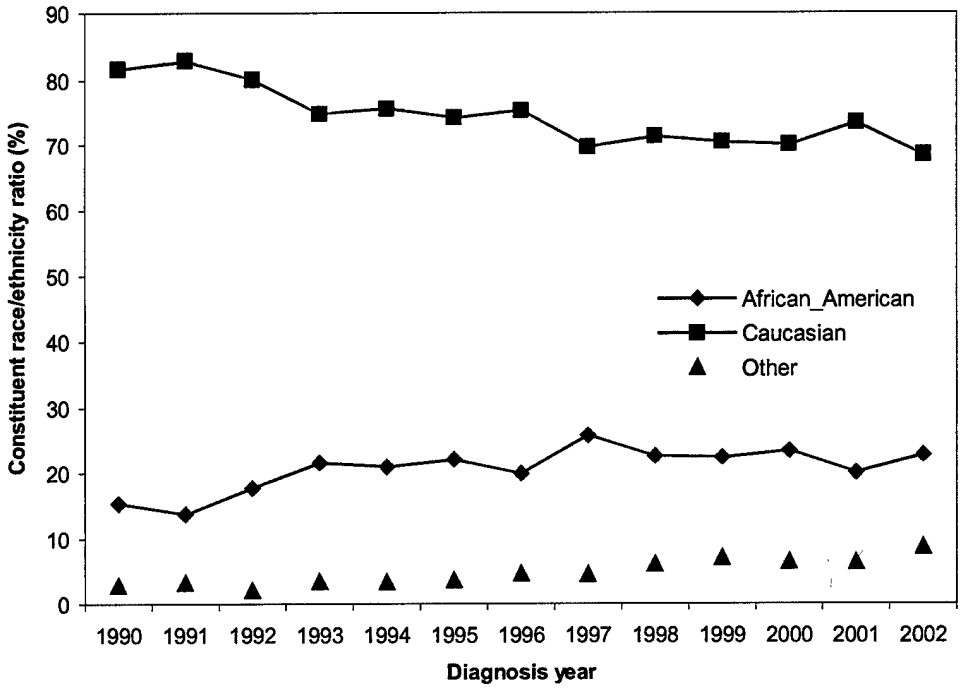


Figure 4. Trends in clinical staging

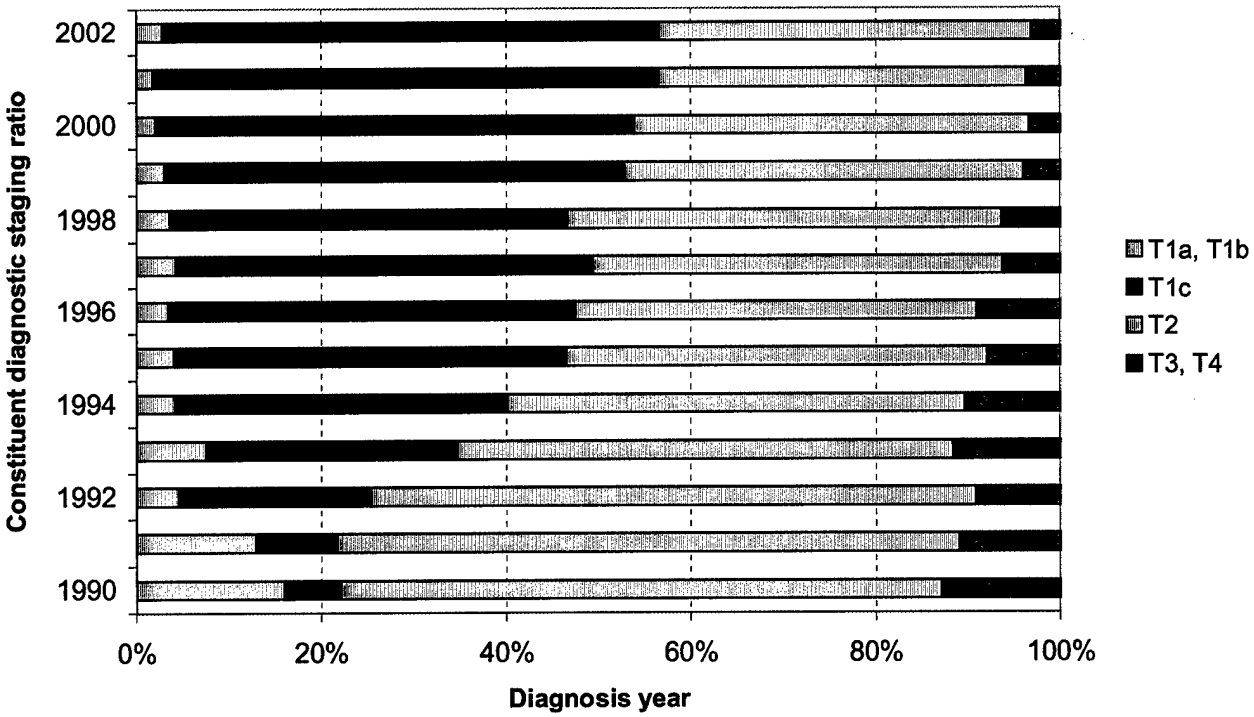


Figure 5. Trends in metastatic disease (clinical stage D1 and D2) at diagnosis

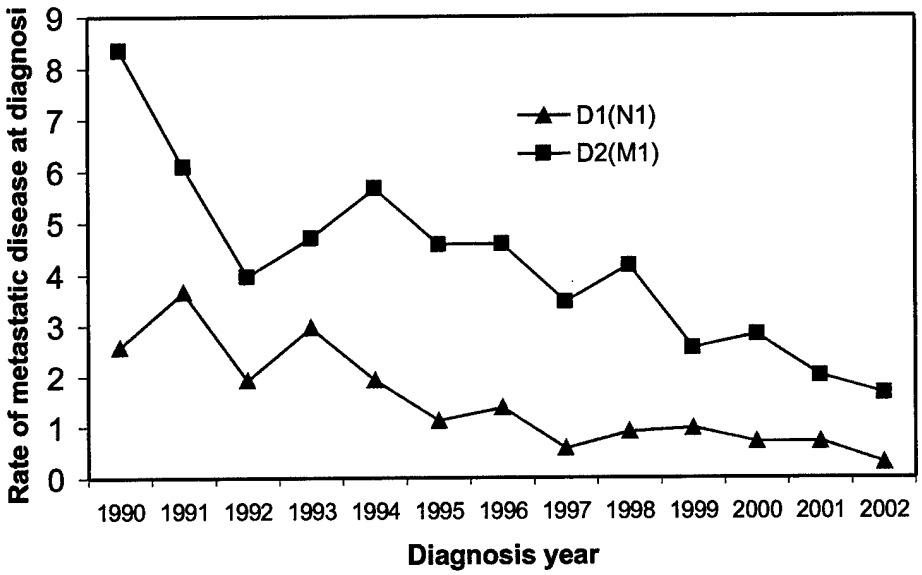


Figure 6. Mean biopsy cores obtained per session from prostate cancer patient

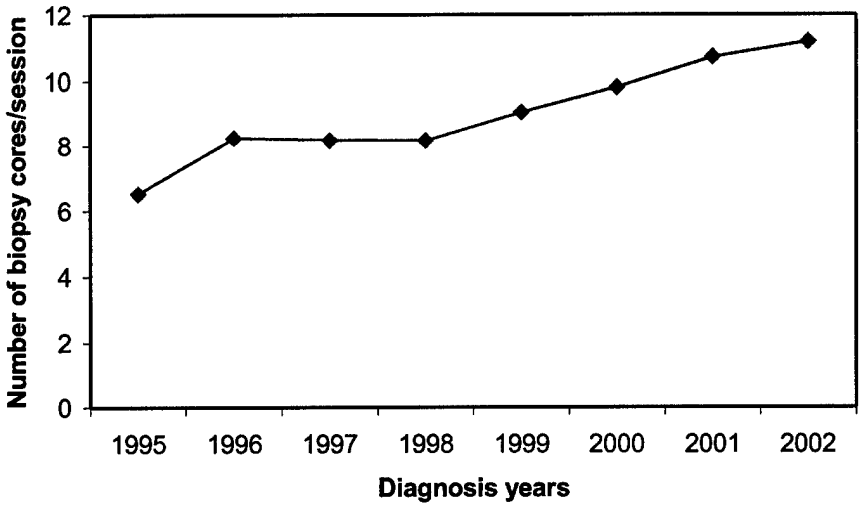


Figure 7. Trends in the percentage of positive cores for prostate cancer

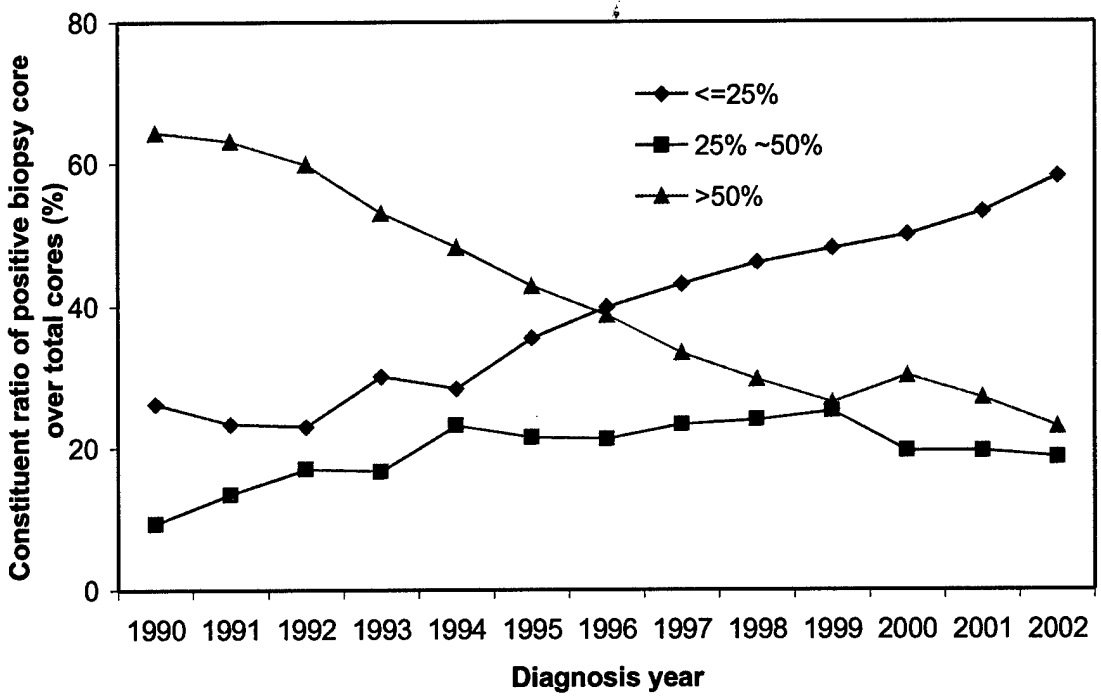
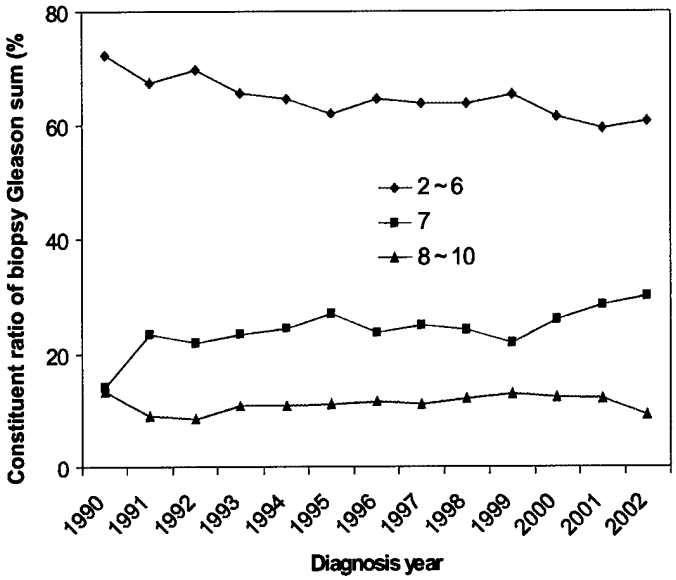


Figure 8. Trends in Gleason sums at diagnosis (A) and at pathology (B)



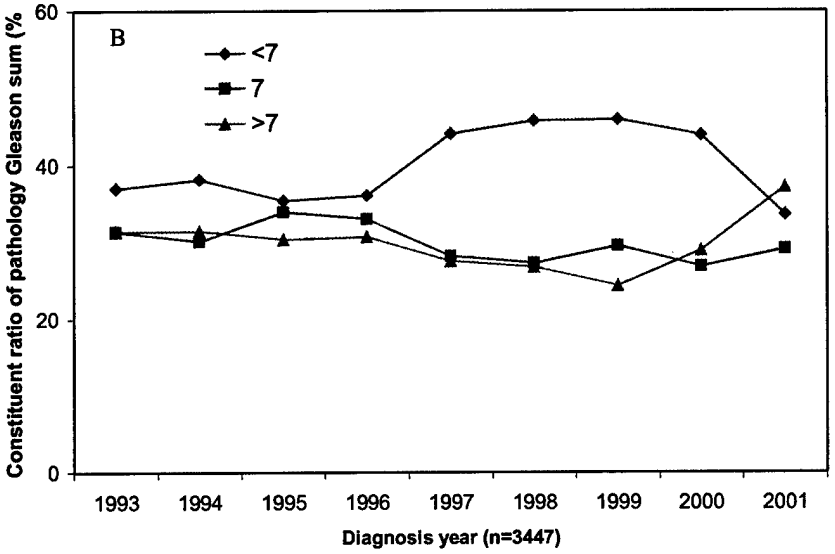


Figure 9. Trends in incidence of prostatic intraepithelial neoplasia (PIN) in the same session of prostate cancer biopsy.

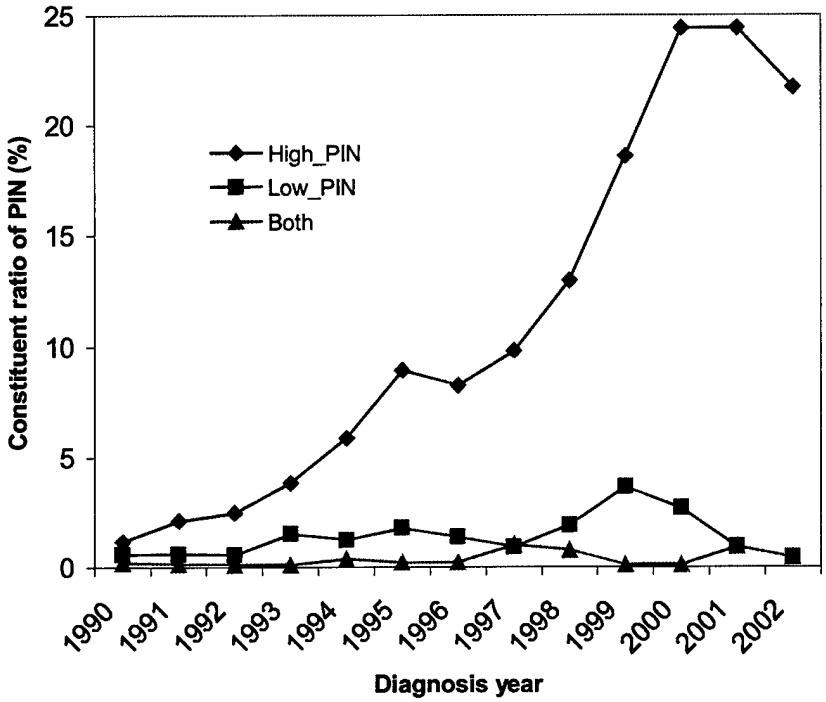


Figure 10. Trends in election of radical prostatectomy (RP) and external radiation therapy (XRT), watchful waiting (WW), brachytherapy (Brachy) and Hormonal therapy (Hormonal)

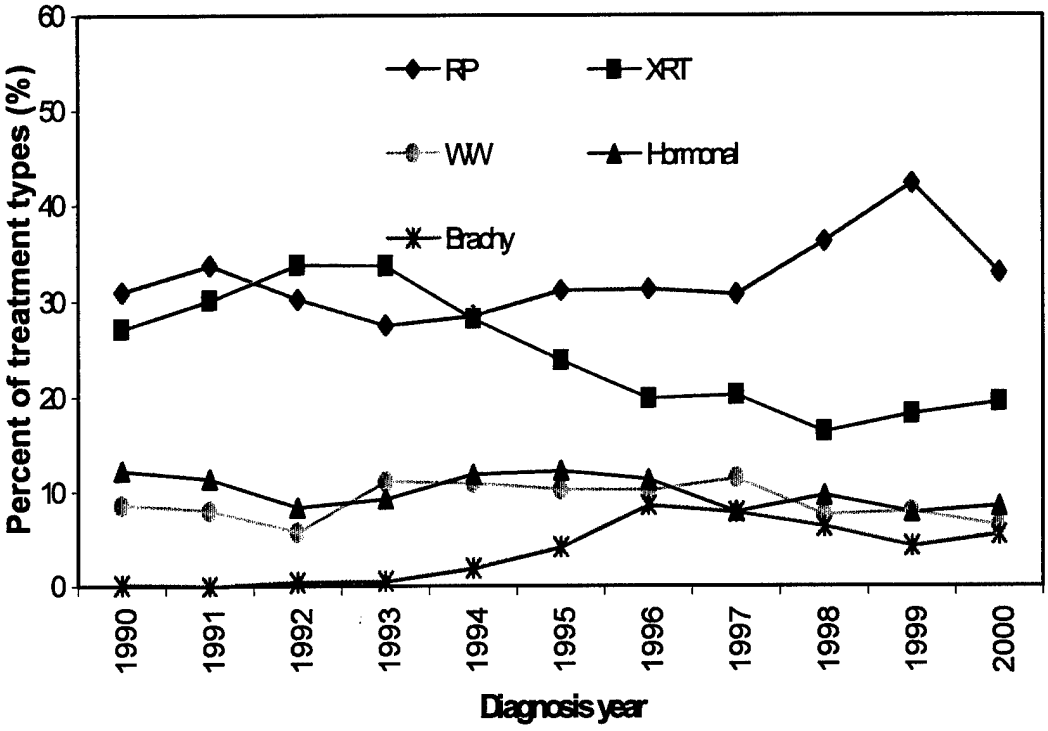


Figure 11. Trends in patients receiving neoadjuvant hormonal therapy

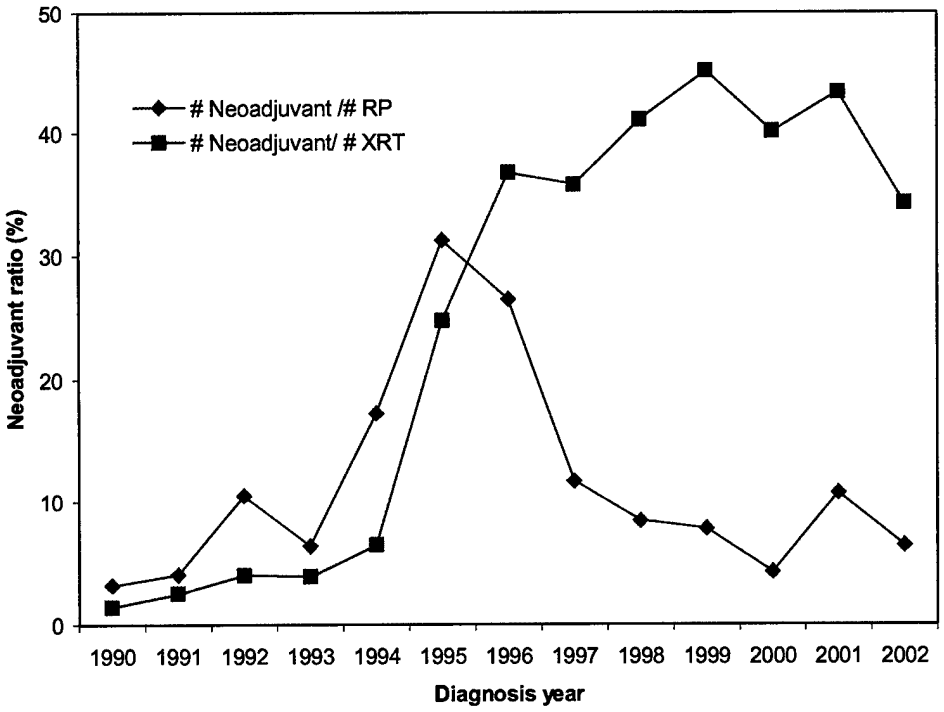
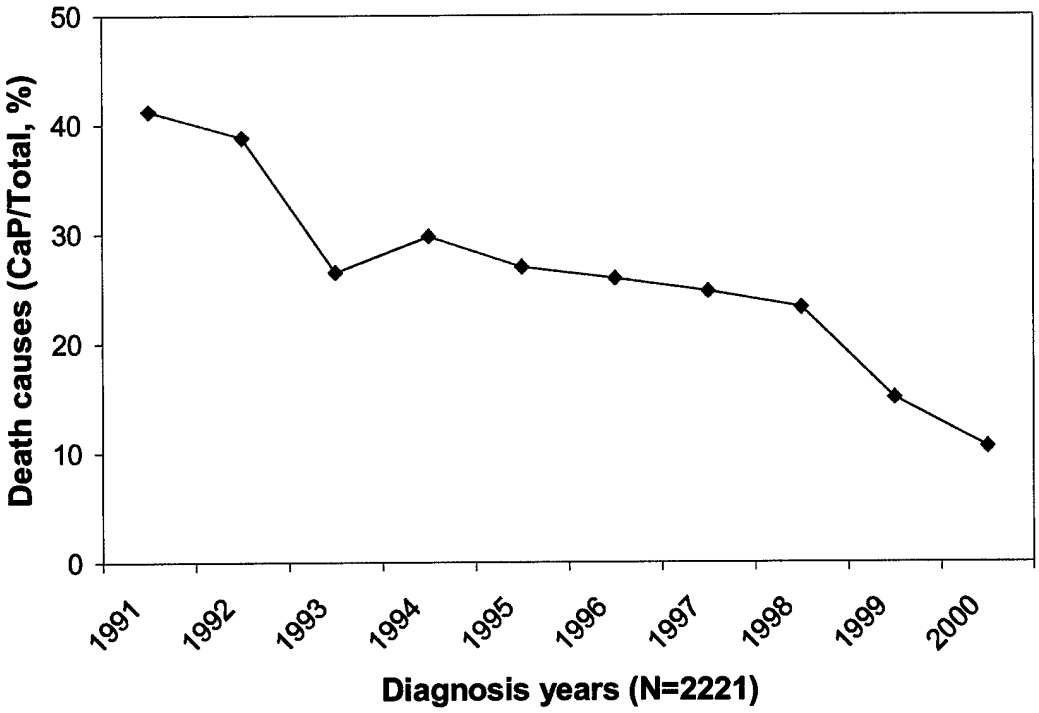


Figure 12. Trends in disease specific death.



Appendix 2 Submitted to J Urol 2004, accepted as poster presentation in AUA 2004).

RACIAL DIFFERENCE IN LOCATION, NUMBER AND VOLUME OF PROSTATE CANCERS BASED ON 3 DIMENSIONAL RECONSTRUCTED PROSTATE SPECIMENS

Jianchao Zeng[1,2], Leon Sun[2], Yongmei Chen[2], Judd J Moul[2,3], David G. McLeod[3], Isabell, Sesterhenn[4]

1. Department of Electrical and Computer Engineering
   Howard University
   Washington, D.C. 20059

2. Center for Prostate Disease Research (CPDR)
   Department of Surgery
   Uniformed Services University of the Health Sciences
   Bethesda, M.D. 20814

3. Urology Service, Department of Surgery
   Walter Reed Army Medical Center
   Washington, D.C. 20307-5001

4. Department of Genitourinary Pathology
   Armed Forces Institute of Pathology (AFIP)
   Washington, DC 20307-6000

*Requests for reprints/correspondence:
Judd W. Moul, MD
Center for Prostate Disease Research
1530 E. Jefferson Street
Rockville, MD 20852
Telephone: 240-453-8951
Fax: 240-453-8922
Email: jmoul@cpdr.org

Key Words: Prostate cancer, Tumor volume, Tumor location, Tumor number, Radical prostatectomy

Running Title: Racial difference in 3D prostate tumor volume, location and numbers

The opinions and assertions contained herein are the private views of the author and are not to be construed as reflective of the views or policies of te US Army Department of Defense.

The authors are supported by a grant from the U.S. Army Medical Research and Material Command (DAMD17-02-1-0066).

ABSTRACT

Objectives: This study aimed to identify whether there exists any racial difference between Caucasian (CM) and African American (AA) patients in number, location and volume of prostate cancer. The role of age and pathological stages on the tumor characteristics was clarified.

Materials and Methods: A total of 176 (135 CM and 41 AA) radical prostatectomy specimens that were obtained between 1993 and 2000, and 3-dimentional (3D) reconstructed were used in this study. Each 3D reconstructed specimen was partitioned into 24 slots and a comprehensive combination of these 24 slots was considered, which resulted in 38 representative zones including peripheral zone, transition zone and central zone. Investigation into potential racial difference in number, location and volume of cancer was performed.

Results: No significant overall difference was found in tumor number between the CM and AA patients regardless of their ages. When stratified by pathological stages, however, AA patients (stage T2) were found to have significantly more tumors than CM patients ($P = 0.012$). With or without stratification by pathological T stages, there was no significant difference in tumor location between the two race groups. In the age group of 60 and 65, AA patients were found to have more tumors at the left medial anterior prostate ($p = 0.047$). Further, CM patients 65 or older were found to have significantly more tumors at posterior base ($p = 0.035$). Overall, no significant difference was found in total tumor volume, index tumor volume, and tumor volume at each of the 38 zones between CM and AA patients. When stratified by age, however, we observed an interesting trend: among patients younger than 60 AA patients had consistently larger tumor volumes at most of the 38 zones. Among patients between 60 and 65, there was no apparent racial difference in tumor volumes. For patients older than 65, however, CM patients had consistently larger tumor volumes at most of the 38 zones. Furthermore, CM patients 60 or older were found to have significantly larger tumor volume at a number of zones than their AA counterparts.

Conclusions: Distribution of prostate cancer can be accurately evaluated using a 3D reconstruction approach. Overall, no significant difference was found in number, location or volume of tumors between CM and AA patients. However, young African American patients had consistently larger tumors compared to young Caucasian men, while this ratio was reversed by ethnicity in older patients.

INTRODUCTION

Although race has been one of the major focuses of much research on prostate cancer[1-5], it is still controversial whether there exists a significant difference in growth pattern of prostate cancer or whether different detection and treatment options should be applied to patients of different races. A literature review on racial aspects of prostate cancer by Alexander and Brawley revealed that equal treatment yielded equal outcomes among patients of different races[6]. Furthermore, research on incidence of positive surgical margins, non-organ-confined tumor, or seminal vesicle invasion found no significant difference between CM and AA patients who underwent radical prostatectomy[7]. By using the NCI SEER cancer registries, a recent study by Polednak did not find significant difference between CM and AA patients with aggressive prostate cancers[8]. Similarly, no significant difference was found between AA and CM patients in terms of transition zone prostate cancer detection[9]. On the other hand, other studies have suggested some significant racial differences in prostate cancer. For example, among 179 patients with positive surgical margins (86 CM and 93 AA), Shekarriz et al. found that AA patients had significantly more positive surgical margins at the base of prostate than CM[10]. With 785 patients, Tiguert et al. also found that AA patients had a greater percentage of anterior tumors than CM patients, and a higher rate of positive surgical margins was observed in patients with anterior tumors, especially among AA patients[11]. In 40 prostatectomy specimens examined, Pettaway et al. found AA patients exhibited a significantly higher incidence of seminal vesicle involvement and cancers with Gleason score of 8 or more[12]. AA patients were also found to have higher incidence of transition zone cancer foci.

In our previous studies, we found significant racial differences of prostate cancer between AA and CM patients. For example, significantly larger tumor volumes were observed in AA than CM patients after radical prostatectomy[13]. In 201 (155 CM and 46 AA) patients, a significant racial difference was noted in pretreatment PSA and 3D tumor volume, with AA patients having higher values in both[14]. In this study, we focus on the comparison of prostate cancer growth patterns between AA and CM patients. We used a total of 176 (135 CM and 41 AA patients) 3D reconstructed radical prostatectomy specimens to carefully investigate tumor distribution in each race group and compared them with respect to number of tumors, location of tumor foci, and tumor volume. Each individual 3D reconstructed prostate specimen was first partitioned into 24 slots according to clinical convention and a comprehensive combination of these slots was then performed to approximate 38 commonly used clinical zonal regions, such as peripheral zone, transition zone, and central zone. Tumor growth patterns were investigated by examining each of these 38 zones across all 176 cases used in this study. Findings of this study and their clinical implications are now reported in this article.

MATERIALS AND METHODS

Between 1993 and 2000, a total of 176 random prostate specimens were obtained from patients who underwent radical prostatectomy (RP) after histologically diagnosed with prostate cancer with biopsy cores. These patients did not receive any other treatments before RP.

3D reconstruction of radical prostatectomy specimens

Three-dimensional reconstruction was performed from a whole-mount, step-sectioned RP specimen with localized cancer in the following 4 steps[15,16].

(a) Physical slicing of the prostate specimen and digitization of each slice. Each prostate specimen was step-sectioned in 4μm sections at 2.25mm intervals and each physical slice was digitized with a scanning resolution of 1,500 dots per inch (dpi). Usually, a prostate specimen can be physically step-sectioned into 10 to 15 slices depending on the size of the specimen.

(b) Outline of contours of relevant structures from the 2D pathological images. Each digitized slice was outlined by a pathologist to identify key pathological structures, including surgical margin, capsule, urethra, seminal vesicles as well as cancer.

(c) Reconstruction of 3D contours by interpolation. The contours of each structure identified on the slices were stacked along the axial direction. The interpolation between each pair of contours was performed using a non-linear elastic contour model.

(d) Final 3D reconstruction from the 3D contours. The final 3D reconstruction of an RP specimen was performed by adding a smooth surface onto the 3D interpolated contours using a deformable modeling technique.

Anatomical locations to be investigated

Each individual 3D reconstructed specimen was partitioned into 24 slots, as shown in Figure 1, according to clinical convention – 3 longitudinal partitions (base, mid, apex), 2 vertical axial partitions (anterior and posterior), and 4 horizontal axial partitions (right lateral, right medial, left medial, left lateral)[17,18].

Each of the 24 slots was labeled as 1 through 24, as shown in Figure 2, in the order from right to left, from posterior to anterior, and from base to apex. For example, the right lateral posterior base was labeled as slot 1, while left lateral anterior apex was labeled as slot 24.

Following this partition, most commonly used clinical zonal regions can be easily approximated with the combination of these 24 slots, as shown in Table 1.

To investigate detailed prostate cancer growth pattern and its potential racial difference, we have examined cancer presence or absence at the 38 zones inside a prostate gland as defined in Table 2. Note that 'Zone#' represents labeling order of the zones, and '#Slots' represents number of slots each zone is composed of.

Statistical analysis

For tumor location evaluation, Chi-square analyses with adjustments for patients were computed to test the null hypothesis of homogeneity of zonal positivity. In case when the number of samples was too small, a Fisher's exact test was used instead of regular Chi-square test. In this case, a two-sided p-value was used instead of the Chi-square p-value. On the other hand, to evaluate tumor volumes, student t-test was used. If the p-value of the equality of variances was less than 0.05, the p-value of unequal variances in the t-test was used. Otherwise, the p-value of equal variances was used. For evaluation of number of tumors, Spearman correlation coefficients were calculated to test the statistical significance.

RESULTS

A total of 176 samples were used in this study with 135 CM (76.7%) and 41 AA (23.3%) patients. The demographic data of the patient cohort are shown in Table 3.

Results on number of tumors are shown in Tables 4. Overall, no significant difference was found between the CM and AA patients in this study regardless of their ages. When the patients were stratified by pathological stages, however, significant difference in number of tumors was found between CM and AA patients with pathological stage T2 ($p = 0.012$).

Overall, no significant difference in tumor location was found between the CM and AA patients, regardless of their pathological stages. When stratified by age, however, AA patients between 60 and 65, were found to have significantly more tumors at left medial anterior ($p = 0.047$). Further, CM patients aged 65 or older had significantly more tumors at posterior base ($p = 0.035$). These results are shown in Table 5.

Total tumor volume, index tumor volume, and tumor volume at each of the 38 zones were evaluated. Figure 3 shows the age-grouped charts of normalized mean tumor volumes at the 38 zones. In order to reduce unbalanced tumor volumes across different zones due to the differences in number of slots each zone occupies, normalization of zonal tumor volumes was performed by dividing the mean tumor volume of a zone with the number of slots this zone occupies (see Table 2). Overall, no significant difference was found between CM and AA patients, regardless of their pathological stages. When stratified by age, however, we observed an interesting trend: among patients younger than 60 AA patients have consistently larger tumor volumes at most of the 38 zones than CM patients. Among patients between 60 and 65, there is no apparent racial difference trend in tumor volumes. Among patients 65 or older, however, CM patients have consistently larger tumor volumes at most of the 38 zones than AA patients. To verify that this trend was not caused by small case number of AA patients in some groups, we regrouped all 176 patients by a new age default: one group includes patients younger than 62 and the other includes the rest. As a result, AA patients were more evenly divided between the two age groups. The same trend in tumor volumes was observed with this regrouping, as shown in Figure 4. Volumes of total and index tumors for both age-based groupings are shown in Figure 5, which had the same trend as zonal tumor volumes.

In addition to the general trend, CM patients aged between 60 and 65 were also found to have significantly larger tumor volumes at right lateral apex (0.037) than their AA counterparts. Further, CM patients of 65 or older had significantly larger tumors at the following 11 zones than their AA counterparts: base (0.0403), central zone (0.028), left lateral (0.0014), left medial (0.016), posterior mid (0.045), posterior left lateral (0.008), posterior left medial (0.007), anterior left lateral (0.004), left lateral mid (0.0003), left medial mid (0.012), and left medial apex (0.045). These results are shown in Table 6.

DISCUSSION

We report the most complex analysis of tumor location and tumor volume to date comparing Caucasian and African American ethnicity men. With the whole-mount, step section, 3-dimensional reconstruction modeling technique, we were able to show that there is no compelling difference in tumor location between the two ethnic groups that would prompt a variation in biopsy schema. However, we did show fascinating total and index tumor volume differences by age and ethnicity. Specifically, young (< 60 or <62 years) African American patients had consistently larger total and index tumor volume than whites. Conversely, the ratio was reversed by ethnicity in older (≥ 62, > 65) men in this equal access series. The exact cause of this finding is unknown, but may be biologic, behavioral, or multifactorial. Specifically, the findings could support the theory put forward by Powell et al that young African American men may have more aggressive disease[19]. Conversely, it could also be due to delay in diagnosis of a disease known to start earlier in Black males. Even though our military population has equal access to care, it is unclear whether the two ethnic groups were being screened equally. Or even

if equally, this data might be used to support earlier start of screening in African American men to attempt to lessen the observed tumor volume disparity in young men.

The finding of greater tumor volume in older white men is interesting as well and heretofore unappreciated. One possibility is that more aggressive tumors in African American men were culled out at an earlier age leaving more small tumors for diagnosis at the older age. This then gives the appearance that older Caucasian men have larger tumors. In fact the tumor volumes in the older white men are remarkably similar to the sizes in the younger African American men. Again, further potential evidence that the disease starts at a younger age in black men.

These new findings point out the prominent role age plays because these trends were not visible without age stratification. Age has been indeed widely used in research on prostate cancer, but we had not noticed that its role could be so clear-cut on racial differences in tumor volumes. We also looked at other factors closely related to tumor volumes for different age groups and listed them in Table 7. Compared to their AA counterparts, CM patients aged 65 or older had, while not statistically significant, higher rate of positive margins, higher rate of worse pathological Gleason scores (> 7), and higher rate of worse pathological stages (T3 or T4), which all supported the new findings. In addition, since the mean prostate volume of the CM patients aged 65 or older was smaller than that of their AA counterparts, CM patients had higher mean tumor-to-prostate ratio (mean tumor volume divided by mean prostate volume) as a result, which also supported our new findings. On the other hand, however, AA patients younger than 60 had higher rate of positive margins, higher rate of worse pathological Gleason score (>7) (p-value = 0.0133), higher rate of worse pathological stages (T3 or T4), and smaller prostate volume, which, again, supported the new findings. For both age groups, AA patients had larger mean PSA values although this difference was not statistically significant. We are planning further studies using a larger patient cohort with more evenly balanced patients from both races.

Our study suggested that there were no overall significant differences between races in number of tumors, tumor location, or tumor volumes. However, significant racial differences were found in tumor volumes at a number of the 38 zones among different age groups. CM patients aged between 60 and 65 were found to have significantly larger tumor volume at right lateral apex (0.037) than their AA counterparts. Also, CM patients of 65 or older have significantly larger tumors at the following 11 zones than their AA counterparts: base (0.0403), central zone (0.028), left lateral (0.0014), left medial (0.016), posterior mid (0.045), posterior left lateral (0.008), posterior left medial (0.007), anterior left lateral (0.004), left lateral mid (0.0003), left medial mid (0.012), and left medial apex (0.045). These zones are shown shaded in Figure 6.

In terms of number of tumors, AA patients with pathological stage of T2 had significantly more tumors than their CM counterparts (p = 0.012). When tumor location is considered, significant difference was observed for the age group younger than 60 at the mid of prostate, with CM patients having more tumors (P = 0.028). In the age group between 60 and 65, AA patients had more tumors at the left medial anterior (p = 0.047). Furthermore, for patients aged 65 or older, CM patients were found to have significantly more tumors at posterior base (p = 0.035).

One limitation of this study is that despite the comprehensive nature of pathologic processing and 3D modeling, the sample size may have been insufficient to detect subtle differences by race and age. Furthermore, the accrual spanned a period of flux in the PSA-era with changes in awareness and use of PSA testing that may obscure changes over time between

AAM and CM. Finally, the observation seen in this equal access health system may not translate to other health settings.

CONCLUSIONS

No significant differences were observed in overall number of tumors, tumor foci locations, and tumor volumes between Caucasian and African American patients. Age and pathological stage, however, played a prominent role in differentiating the two race groups, especially for tumor volumes. Young African American men had larger index and total tumor volume than similar aged Caucasian patients, while this ratio was reversed by ethnicity in older men.

REFERENCES

1. Hoffman RM, Gilliland FD, Eley JW, Harlan LC, Stephenson RA, Stanford JL, Albertson PC, Hamilton AS, Hunt WC, Potosky AL., Racial and ethnic differences in advanced-stage prostate cancer: the Prostate Cancer Outcomes Study, J Natl Cancer Inst. 2001 March, 7; 93(5):388-95.
2. Sawyer R, Berman JJ, Borkowski A, Moore GW. Elevated prostate-specific antigen levels in black men and white men, Mod Pathol. 1996 Nov; 9(11):1029-32.
3. Smith DS, Bullock AD, Catalona WJ, Herschman JD. Racial differences in a prostate cancer screening study, J Urol. 1996 Oct;156(4):1366-9.
4. Sohayda CJ, Kupelian PA, Altsman KA, Klein EA., Race as an independent predictor of outcome after treatment for localized prostate cancer, J Urol. 1999 Oct;162(4):1331-6.
5. Fowler JE Jr, Bigler SA, Bowman G, Kilambi NK. Race and cause specific survival with prostate cancer: influence of clinical stage, Gleason score, age and treatment, J Urol. 2000 Jan;163(1):137-42.
6. Alexander GA, Brawley OW. Prostate cancer treatment outcome in blacks and whites: a summary of the literature. Semin Urol Oncol. 1998 Nov;16(4):232-4.
7. Freedland SJ, Dorey F, Aronson WJ. Multivariate analysis of race and adverse pathologic findings after radical prostatectomy. Urology. 2000 Nov 1;56(5):807-11.
8. Polednak AP. Black-white differences in tumor grade (aggressiveness) at diagnosis of prostate cancer, 1992-1998. Ethn Dis. 2002 Fall;12(4):536-40.
9. Fowler JE Jr, Bigler SA, Kilambi NK, Land SA. Results of transition zone biopsy in black and white men with suspected prostate cancer. Urology. 1999 Feb;53(2):346-50.
10. Shekarriz B, Tiguert R, Upadhyay J, Gheiler E, Powell IJ, Pontes JE, Grignon DJ, Sakr W, Wood DP. Impact of location and multifocality of positive surgical margins on disease-free survival following radical prostatectomy: a comparison between African-American and white men. Urology. 2000 Jun; 55(6):899-903.
11. Tiguert R, Gheiler EL, Tefilli MV, Banerjee M, Grignon DJ, Sakr W, Wood DP Jr, Powell IJ, Pontes JE. Racial differences and prognostic significance of tumor location in radical prostatectomy specimens. Prostate. 1998 Dec 1; 37(4):230-5.
12. Pettaway CA, Troncoso P, Ramirez EI, Johnston DA, Steelhammer L, Babaian RJ. Prostate specific antigen and pathological features of prostate cancer in black and white patients: a comparative study based on radical prostatectomy specimens. J Urol. 1998 Aug;160(2):437-42.
13. Moul JW, Sesterhenn IA, Connelly RR, Douglas T, Srivastava S, Mostofi FK, McLeod DG. Prostate-specific antigen values at the time of prostate cancer diagnosis in African-American men. JAMA. 1995 Oct 25; 274(16):1277-81.
14. Moul JW, Connelly RR, Mooneyhan RM, Zhang W, Sesterhenn IA, Mostofi FK, McLeod DG. Racial differences in tumor volume and prostate specific antigen among radical prostatectomy patients. J Urol. 1999 Aug; 162(2):394-7.
15. Xuan J, Sesterhenn IA, Hayes WS, Wang Y, Adali T, Yagi Y, Freedman MT, Mun SK. Surface reconstruction and visualization of the surgical prostate model. Proc. SPIE 3031. 1997 June; 50-61.
16. Zeng J, Kaplan CR, Xuan J, Sesterhenn IA, Lynch JH, Freedman MT, Mun SK. Optimizing prostate needle biopsy through 3-D simulation. Proc. SPIE 3335. 1998 June; 488-497.

17. Zeng J, Bauer JJ, Yao X, Zhang W, McLeod DG, Sesterhenn IA, Connelly RR, Moul JM, Mun SK. Investigating 3D tumor distribution for optimized diagnosis of prostate cancer. Proc. MMVR. 2000 Jan; 392-398, IOS Press.
18. Opell B, Zeng J, Bauer JJ, Connelly RR, Zhang W, Sesterhenn IA, Mun SK, Moul JW, Lynch JH. Investigating the distribution of prostate cancer using three-dimensional computer simulation. Prostate Cancer and Prostatic Diseases. 2002 Oct; 5: 204-208.

19. Powell IJ, Banerjee M, Novallo M, Sakr W, Grignon D, Wood DP, Pontes JE. Prostate cancer biochemical recurrence stage for stage is more frequent among African-American than white men with locally advanced but not organ-confined disease. Urology. 2000 Feb;55(2):246-51.

LEGENDS

Figure 1. Partition of 3D reconstructed RP specimens into 24 slots

Figure 2. Labeling of the 24 slots in axial view (top half: anterior, bottom half: posterior)

Table 1. Clinical zones approximated by corresponding slots

Table 2. The 38 zones inside a prostate gland for tumor evaluation

Table 3. Demographic data of patient cohort.

Table 4. Number of tumors by age and pathologic T stage

Table 5. Tumor locations by age and race

Table 6. Tumor volumes by age and race

Figure 3. Racial comparisons of mean tumor volumes at individual zones

Figure 4. Verification of racial comparisons of mean tumor volumes at individual zones

Table 7. Other factors for different age groups

Figure 5 Volumes of total and index tumors

Figure 6. Shaded zones with CM patients having significantly larger tumors

Figure 1. Partition of 3D reconstructed RP specimens into 24 slots

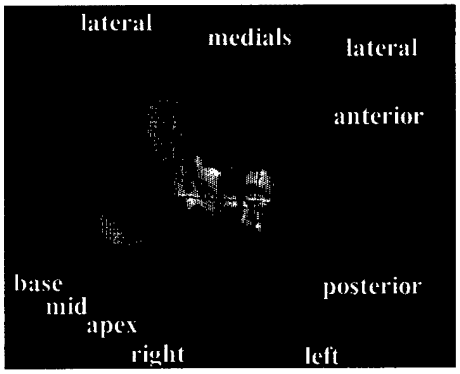


Figure 2. Labeling of the 24 slots in axial view (top half: anterior, bottom half: posterior)

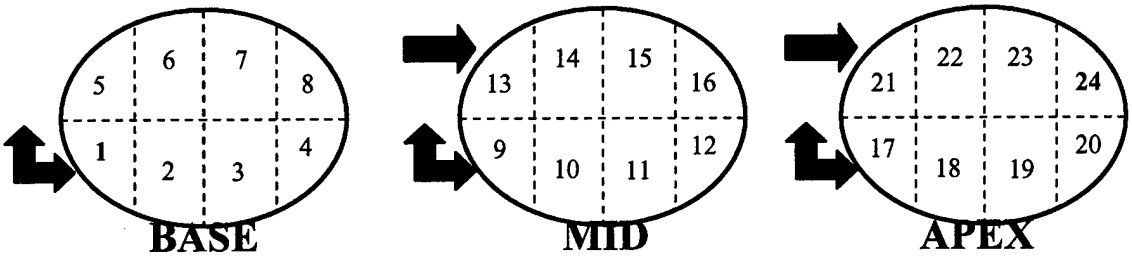


Table 1. Clinical zones approximated by corresponding slots

Zones	***Corresponding slots***
Posterior	1, 2, 3, 4, 9, 10, 11, 12, 17, 18, 19, 20
Anterior	5, 6, 7, 8, 13, 14, 15, 16, 21, 22, 23, 24
Base	1, 2, 3, 4, 5, 6, 7, 8
Mid	9, 10, 11, 12, 13, 14, 15, 16
Apex	17, 18, 19, 20, 21, 22, 23, 24
Lateral	1, 4, 5, 8, 9, 12, 13, 16, 17, 20, 21, 24
Medial	2, 3, 6, 7, 10, 11, 14, 15, 18, 19, 22, 23
Right	1, 2, 5, 6, 9, 10, 13, 14, 17, 18, 21, 22
Left	3, 4, 7, 8, 11, 12, 15, 16, 19, 20, 23, 24
Peripheral	Base: 1, 4, 5, 8 Mid: 9, 12, 13, 16 Apex: 17, 20, 21, 24
Central	Base: 2, 3; Mid: 10, 11; Apex: 18, 19
Transition	Base: 6, 7; Mid: 14, 15; Apex: 22, 23

Table 2. The 38 zones inside a prostate gland for tumor evaluation

Zone#	Zone names	#Slots	Zone#	Zone names	#Slots	Zone#	Zone names	#Slots
1	Anterior	12	14	Posterior mid	4	27	Right lateral base	2
2	Posterior	12	15	Posterior apex	4	28	Right lateral mid	2
3	Base	8	16	Anterior base	4	29	Right lateral apex	2
4	Mid	8	17	Anterior mid	4	30	Left lateral base	2
5	Apex	8	18	Anterior apex	4	31	Left lateral mid	2
6	Peripheral zone	12	19	Posterior right lateral	3	32	Left lateral apex	2
7	Central zone	6	20	Posterior right medial	3	33	Right medial base	2
8	Transition zone	6	21	Posterior left lateral	3	34	Right medial mid	2
9	Right lateral	6	22	Posterior left medial	3	35	Right medial apex	2
10	Left lateral	6	23	Anterior right lateral	3	36	Left medial base	2
11	Right medial	6	24	Anterior right medial	3	37	Left medial mid	2
12	Left medial	6	25	Anterior left lateral	3	38	Left medial apex	2
13	Posterior base	4	26	Anterior left medial	3			

Table 3. Demographic data of patient cohort.

Variable	#Patients(%)	#CM patients (%)	#AA patients (%)	p-value
Total	176	135 (76.7)	41 (23.30)	
Age				0.188
< 60	57 (32.4)	47 (34.8)	10 (24.4)	
60 – 65	65 (36.9)	45 (33.3)	20 (48.7)	
≥ 65	54 (30.7)	43 (31.8)	11 (26.8)	
Dx_PSA				0.001
≤ 4	29 (16.9)	26 (19.8)	3 (7.5)	
> 4 – 10	101 (59.1)	82 (62.6)	19 (47.5)	
> 10	41 (24.0)	23 (17.6)	18 (45.0)	
Pathologic Gleason sum				0.141
< 7	89 (52.7)	72 (55.8)	17 (42.5)	
≥ 7	80 (47.3)	57 (44.2)	23 (57.5)	
Pathologic T stage				0.033
T2	77 (43.7)	65 (48.2)	12 (29.3)	
T3 or T4	99 (56.2)	70 (51.8)	29 (70.7)	
Margin status				0.125
Negative	104 (59.1)	84 (62.2)	20 (48.8)	
Positive	72 (40.9)	51 (37.8)	21 (51.2)	
Capsule				0.058
Negative	104 (59.1)	85 (63.0)	19 (46. 4)	
Positive	72 (40.9)	50 (37.0)	22 (53.6)	

Table 4. The difference of total tumor numbers between AA and CM ethnicity stratified by age and pathologic T stage

	No.	Average number of tumors	Spearman correlation coefficient	p-value
Age				
< 60 (AA vs CM)	57	2.772	-0.175	>0.05
60 – 65 (AA vs CM)	65	2.354	0.124	>0.05
≥ 65 (AA vs CM)	54	2.537	0.169	>0.05
Pathologic T stage				
T2 (AA vs CM)	77	2.61	0.286	0.012
T3 or T4 (AA vs CM)	99	2.49	-0.087	>0.05

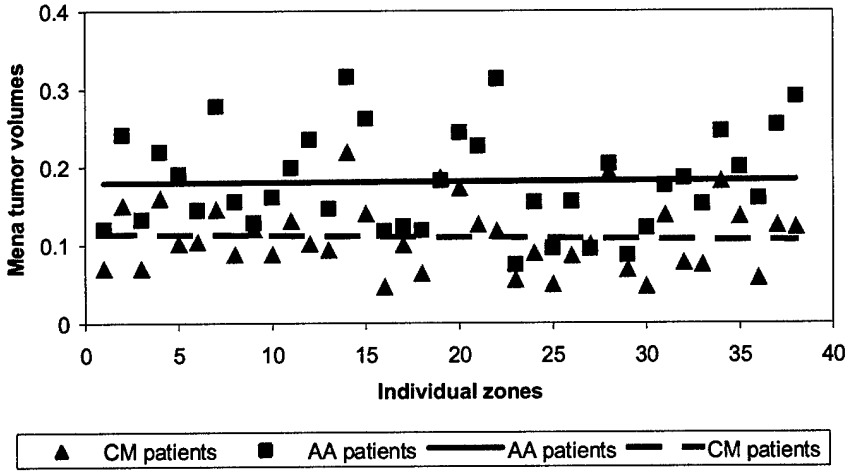
Table 5. Tumor locations by age and race

Location	Age < 60			Age 60 - 65			Age ≥ 65		
	CM (No/Yes)	AA (No/Yes)	p	CM (No/Yes)	AA (No/Yes)	p	CM (No/Yes)	AA (No/Yes)	p
Posterior base	8/39	2/8	>0.05	17/28	4/16	>0.05	6/37	5/6	0.035
Anterior left medial	13/34	3/7	>0.05	18/27	3/17	0.047	10/33	3/8	>0.05

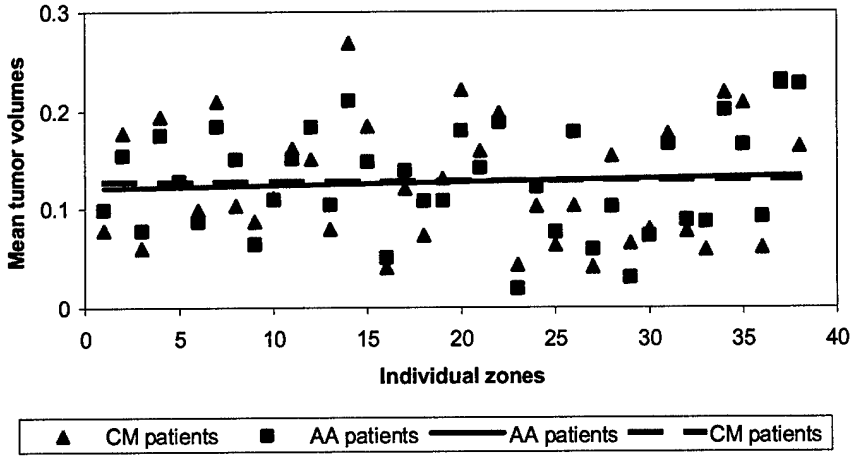
Table 6. Tumor volumes by age and race

		Age < 60				Age 60-65				Age ≥ 65			
Tumor volume	Race	No.	Mean	Std Dev	p-value	No.	Mean	Std Dev	p-value	No.	Mean	Std Dev	p-value
Base	CM	47	0.556	0.923	>0.05	45	0.484	0.946	>0.05	43	1.308	2.282	0.040
	AA	10	1.058	2.127		20	0.622	0.620		11	0.492	0.572	
Central	CM	47	0.873	0.626	>0.05	45	1.262	1.578	>0.05	43	1.569	2.191	0.028
	AA	10	1.672	2.238		20	1.107	0.980		11	0.730	0.540	
Left lateral	CM	47	0.524	0.604	>0.05	45	0.670	0.879	>0.05	43	1.058	1.158	0.001
	AA	10	0.966	1.2		20	0.657	0.754		11	0.352	0.372	
Left medial	CM	47	0.61	0.589	>0.05	45	0.909	1.128	>0.05	43	1.257	1.984	0.016
	AA	10	1.408	1.938		20	1.102	1.515		11	0.472	0.291	
Posterior mid	CM	47	0.876	0.611	>0.05	45	1.076	1.068	>0.05	43	1.265	1.465	0.045
	AA	10	1.265	1.447		20	0.845	0.680		11	0.747	0.387	
Posterior left lateral	CM	47	0.377	0.503	>0.05	45	0.480	0.591	>0.05	43	0.759	0.848	0.008
	AA	10	0.68	0.72		20	0.426	0.499		11	0.271	0.382	
Posterior left medial	CM	47	0.354	0.425	>0.05	45	0.596	0.844	>0.05	43	0.781	1.069	0.007
	AA	10	0.941	1.105		20	0.565	0.583		11	0.261	0.277	
Anterior left lateral	CM	47	0.146	0.259	>0.05	45	0.191	0.337	>0.05	43	0.300	0.432	0.004
	AA	10	0.287	0.53		20	0.231	0.467		11	0.081	0.095	
Right lateral apex	CM	47	0.136	0.201	>0.05	45	0.132	0.181	0.037	43	0.177	0.247	>0.05
	AA	10	0.173	0.224		20	0.062	0.081		11	0.506	0.582	
Left lateral mid	CM	47	0.277	0.346	>0.05	45	0.355	0.483	>0.05	43	0.482	0.576	0.0003
	AA	10	0.352	0.49		20	0.333	0.406		11	0.121	0.102	
Left medial mid	CM	47	0.25	0.228	>0.05	45	0.458	0.576	>0.05	43	0.539	0.823	0.012
	AA	10	0.508	0.773		20	0.462	0.640		11	0.188	0.157	
Left medial apex	CM	47	0.246	0.331	>0.05	45	0.329	0.415	>0.05	43	0.400	0.574	0.045
	AA	10	0.581	0.544		20	0.456	0.593		11	0.170	0.228	

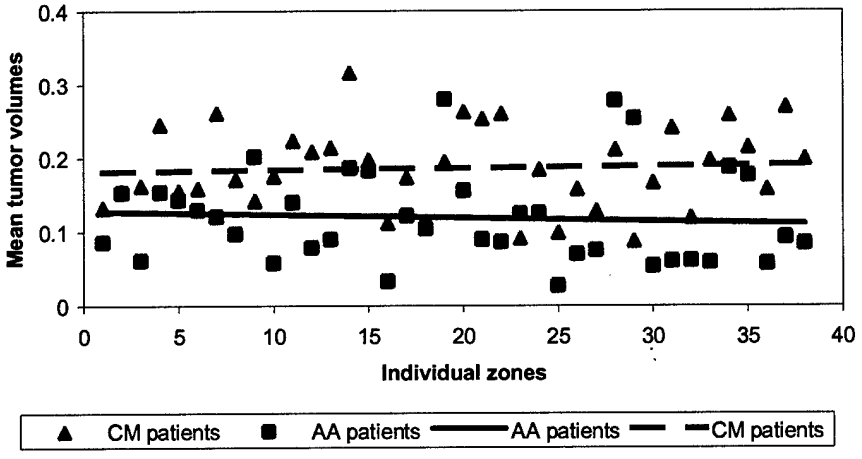
Figure 3. Racial comparisons of mean tumor volumes at individual zones



(a) Age < 60

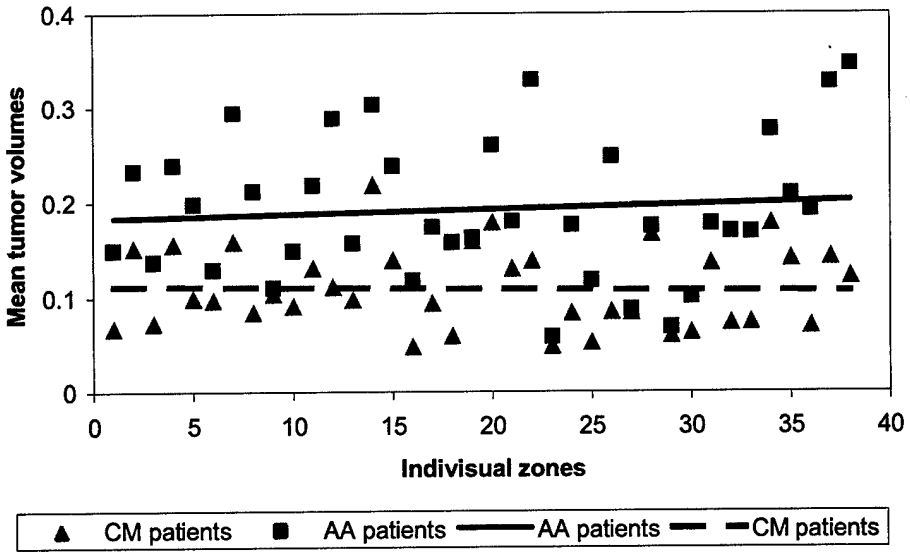


(b) Age 60 - 65

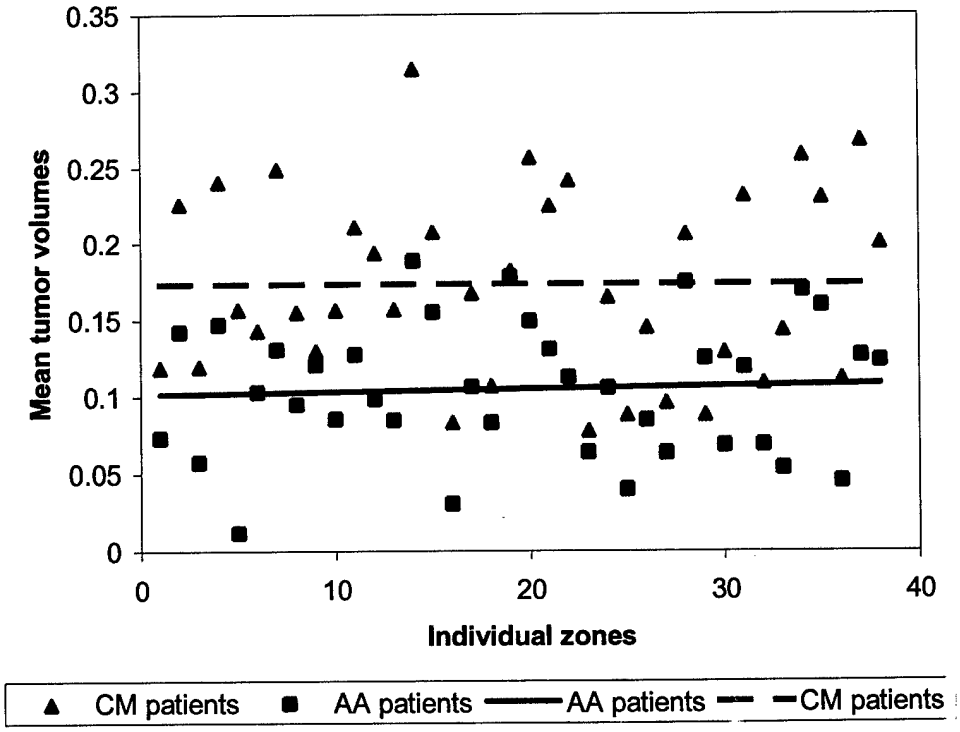


(c) Age ≥ 65

Figure 4. Verification of racial comparisons of mean tumor volumes at individual zones

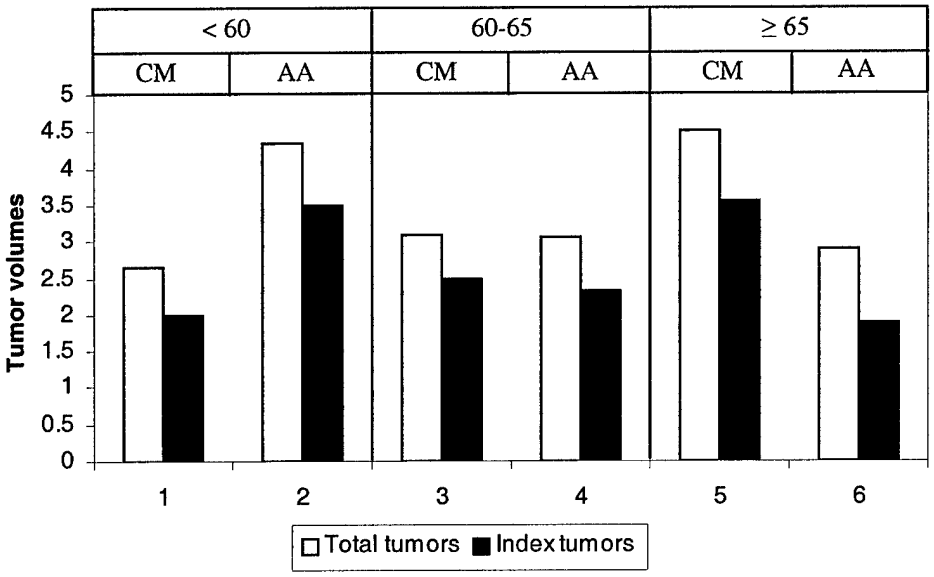


(a) Age < 62

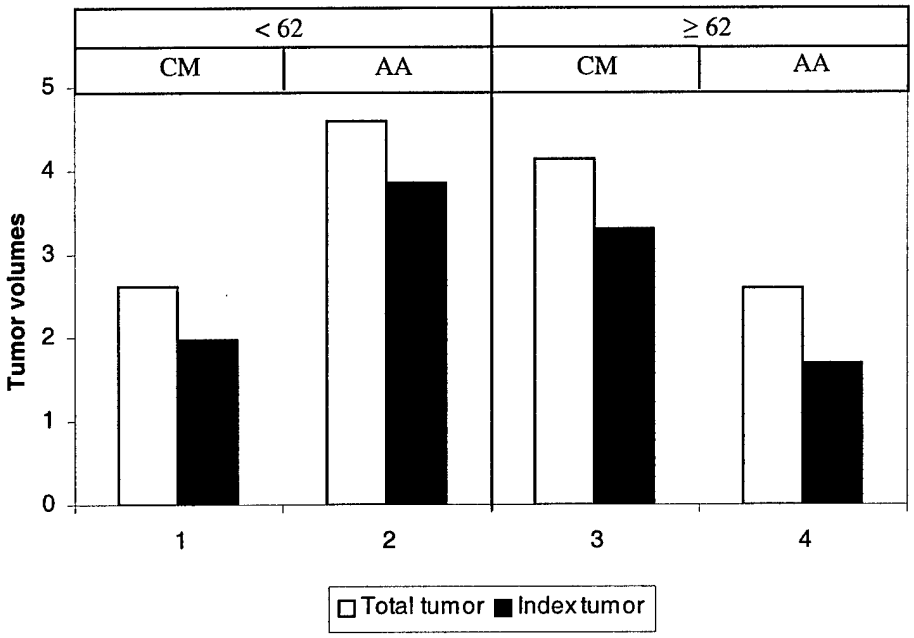


(b) Age ≥ 62

Figure 5. Volumes of total and index tumors



A. For age groups of <60, 60-65 and ≥65

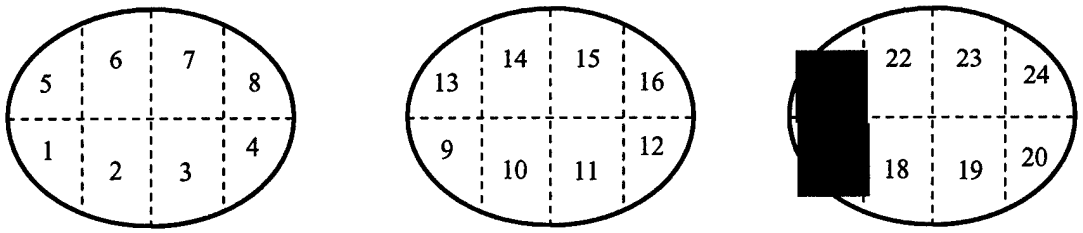


B. For age groups of <62 and ≥ 62

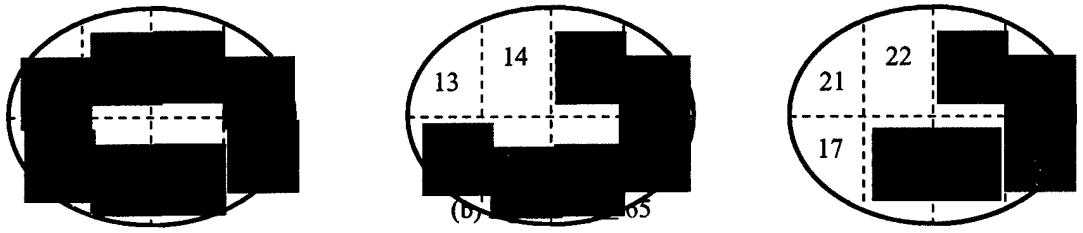
Table 7. Other factors for different age groups

Key factors	Mean values or percentages								
	Age < 60			Age 60 - 65			Age ≥ 65		
	CM	AA	p-value	CM	AA	p-value	CM	AA	p-value
PSA	7.96	10.06	0.5028	8.44	9.88	0.4439	7.87	10.08	0.2597
pStage (T3 or T4)	46.8%	60.0%	0.5045	40.0%	85.0%	0.0008	69.8%	54.5%	0.4752
pGleason (>7)	34.8%	80.0%	0.0133	44.2%	52.6%	0.5389	55.0%	45.5%	0.5743
Prostate volume	28.05	25.69	0.4345	28.43	27.44	0.7416	30.89	32.88	0.6283
Margin positivity	31.9%	40.0%	0.7168	33.3%	70.0%	0.0061	48.8%	27.3%	0.3100

Figure 6. Shaded zones with CM patients having significantly larger tumors



(a) Age group 60-65



(b)

Appendix 3. Submitted to J Urol 2004, accepted as poster presentation in AUA 2004).

PRE- AND POST-OPERATIVE PROGNOSTIC FACTORS PREDICTING PSA RECURRENCE IN INTERMEDIATE-RISK PROSTATE CANCER PATIENTS

Yongmei Chen[1], Leon Sun[1], Judd W. Moul[1], David G. McLeod[2], Gregory Bernsten[2], Hongyan Wu[1], Christopher Amling[3], Robert Douglas[4], Timothy Donahue[4], Leo Kusuda[5], Wade Sexton[6], Keith O'Reilly[7], John Foley[8], Andrew Chung[9], Karen Smith[10]

1. Center for Prostate Disease Research (CPDR)
   Department of Surgery
   Uniformed Services University of the Health Sciences
   Bethesda, MD 20814
2. Urology Service, Department of Surgery
   Walter Reed Army Medical Center
   Washington, D.C. 20307-5001
3. Department of Urology
   San Diego Naval Medical Center
   San Diego, CA
4. Department of Urology
   National Naval Medical Center
   Bethesda, MD
5. Department of Urology
   Portsmouth Naval Medical Center
   Portsmouth, VA
6. Department of Urology
   Wilford Hall AF Medical Center
   Lackland AFB, TX
7. Urology Service, Dept. of Surgery
   Madigan Army Medical Center
   Tacoma, WA
8. Urology Service, Dept. of Surgery
   Brooke Army Medical Center
   San Antonio, TX
9. Department of Urology
   Malcolm Grow AF Medical Center
   Andrews AFB, MD
10. Urology Service, Dept. of Surgery
    Eisenhower Army Medical Center
    Augusta, GA

*Requests for reprints/correspondence:
Judd W. Moul, MD
Leon Sun, MD, PhD
Center for Prostate Disease Research
1530 East Jefferson Street
Rockville, MD 20852
Telephone: (240) 453-8951
Fax: (240) 453-8912
Email: Jmoul@cpdr.org, lsun@cpdr.org

Key Words: Prostate cancer, Prostate-specific antigen recurrence, Radical prostatectomy, Prediction

Running Title: Prediction of recurrence after radical prostatectomy

The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Departments of the Army, Navy or Air Force or the Department of Defense.

The authors are supported by a grant from the Center for Prostate Disease Research, a program of the Henry M. Jackson Foundation for the Advancement of Military Medicine (Rockville, MD) and the Uniformed Services University of the Health Sciences, funded by the U.S. Army Medical Research and Material Command (DAMD17-02-1-0066).

ABSTRACT

Purpose: Predicting PSA recurrence in patients with intermediate-risk disease (pretreatment PSA 10 - 20 ng/ml, biopsy Gleason sum 7 or clinical stage T2b) treated with radical prostatectomy is an important clinical issue. This study was designed to identify the association of pre- and post-surgery prognostic factors predicting biochemical recurrence.

Patients and Methods: A total of 864 patients who had intermediate-risk disease and received radical prostatectomy from 1989 to 2002 were retrieved from the DoD CPDR Tri-Service Multi-center Database. Patients with neo-adjuvant treatment, post- surgery follow-up time < 6 months or without biopsy core information were excluded. The Kaplan-Meier method was used to estimate the probability of PSA recurrence (PSA > 0.2 ng/ml). Univariate and multivariate Cox proportional hazard analyses were used to evaluate the relative risk of pre- and post-surgery factors for PSA recurrence.

Results: The median follow-up for the 864 patients was 4.4 years. Among them, 282 (32.6%) developed PSA recurrence. The 3-year and 5-year PSA-free recurrence rates were 80.3% and 72.0%, respectively. Seventy-four (8.5%) patients developed distant metastasis. In univariate and multivariate analyses on pre-surgery factors: race, percentage of positive biopsy cores, and PSA were significant factors for predicting PSA recurrence ($p < 0.05$). When both pre- and post-surgery factors were pooled together for multivariate analysis, race percentage of positive biopsy cores, pathologic Gleason sum, and margin status were associated with the PSA recurrence ($p < 0.05$).

Conclusions: This study provided two sets of prognostic factor sets for potential clinical decision making processes in patients with intermediate-risk disease. Prior to surgery, race, diagnostic PSA level and percentage of cancer-positive biopsy cores were independent predictors for PSA recurrence. After radical prostatectomy, race, percentage of positive biopsy cores, pathologic Gleason sum and margin status could be used as prognostic factors.

INTRODUCTION

D'Amico, et al [1] have classified clinically-localized prostate cancer patients into low-, intermediate- and high-risk groups based on pretreatment clinical factors to determine the probability of PSA recurrence after radical prostatectomy or external beam radiation therapy. The low-risk group is defined as those with PSA level of 10 ng/ml or less, biopsy Gleason sum of 6 or less, and clinical stage of T1c-2a (AJCC 1992). The intermediate-risk group is defined as those with a PSA level greater than 10 ng/ml but less than 20 ng/ml, or biopsy Gleason sum of 7, or clinical stage of T2b. Since the prognosis of patients with low- and high-risk disease is more certain compared to intermediate-risk disease, identifying additional prognostic factors in the intermediate-risk group patients is clinically important.

While pretreatment PSA level and biopsy Gleason sum are widely accepted prognostic factors, stage migration has rendered the clinical stage a less robust prognostic factor. [2-5] Race or patient ethnicity continues to be a controversial risk factor with some researchers finding African-American race to be associated with worse outcome, while others have not. [4,19,20] Previously published papers from the Center for Prostate Disease Research (CPDR) have found race to contribute significantly to PSA recurrence after radical prostatectomy, but not to survival. [21, 22]

Linson, et al [6] and Yoon, et al [7] have already reported predictive factor analyses of patients with intermediate-risk prostate cancer. They each found that the percentage of biopsy cores positive for prostate cancer was a significant predictor of pathological outcome and recurrence after radical prostatectomy. However, the sample sizes each used were small, and they did not provide overall models for predicting PSA recurrence for the specific intermediate-risk patients.

There is a need to study large multicenter cohorts of intermediate-risk prostate cancer patients to identify the relationship between PSA recurrence and pre- and post-operative factors. This study utilized the Department of Defense (DoD) Center for Prostate Disease Research (CPDR) Multicenter Research Database to find predictive pre- and post-operative factor models for PSA recurrence-free time after radical postatectomy in intermediate-risk prostate cancer patients. We performed a retrospective analysis on a large cohort of prostate cancer patients who were treated with radical prostatectomy from 1989 to 2002 at multiple U.S. military medical centers by a wide variety of urologic surgeons.

PATIENTS AND METHODS

Study group

All localized prostate cancer patients in the intermediate-risk group (defined as diagnostic PSA between 10 and 20 ng/ml, or biopsy Gleason sum 7, or clinical stage T2b (ATCC 1992) who had radical prostatectomy from 1989 to 2002 were retrieved from the DoD CPDR Tri-Service Multicenter Databases that are comprised of patient data from nine combined United States Army, Navy, and Air Force medical centers from across the country.

Exclusion criteria included radiation therapy or hormonal therapy as neoadjuvant treatment before surgery, follow-up after surgery less than six months or incomplete biopsy core information. A final cohort of 864 patients remained for our analysis. The median surgery age was 63 years. Among 864 patients, 282 (32.6%) developed PSA recurrence (PSA > 0.2 ng/ml). Median follow-up after surgery was 4.4 years (0.5 – 13.6 years)]

Definition of PSA Recurrence Time and Clinical Metastasis

The time of PSA recurrence was defined from time of surgery to the first detectable serum PSA >= 0.2 ng/ml obtained after a previously undetectable value. Distant metastases were identified via both nuclear imaging studies (bone scans) and radiographic studies (computed tomography, magnetic resonance imaging, etc.).

Prognostic factors

Pretreatment factors considered included race, age at surgery, clinical stage, diagnostic PSA, biopsy Gleason sum and percent of positive biopsy cores. Postoperative factors included pathologic T stage, pathologic worst Gleason sum, capsule, margin and seminal vesicle status. Diagnostic PSA was divided into three groups: ≤ 4 ng/ml, > 4-10 ng/ml, and > 10-20 ng/ml. Biopsy Gleason sum was divided into two groups: 2 - 6, and 7. Pathologic Gleason sum was divided into three groups: 2 - 6, 7 and 8 – 10. Race was grouped into African-American (AA), and white and other (WO). Percentage of positive biopsy cores (PPBC) was divided into three groups (< 30%, 30 – 50% and $\geq$ 50%). (Table 1)

Statistical Method

The Kaplan-Meier product limit method was used to estimate the probability of PSA recurrence and clinical metastasis. A log rank test was used to test the difference of PSA recurrence-free survival rate stratified by each factor. Time 0 was taken as the first day of radical prostatectomy (RP).

Multivariate Cox proportional hazard ratio analyses were used to report the adjusted relative risk of pre- and post-operative factors predicting the time to PSA recurrence. Probability values of 0.05 or less were considered to be significant.

RESULTS

Among 864 intermediate-risk prostate cancer patients, the median surgery age for patients was 63 years old. The median follow-up time was 4.4 years (range was 0.5 - 13.6 years). Two hundred eighty two (32.6%) patients experienced PSA recurrence. Seventy-four (8.6%) patients developed distant metastasis.

Table 1 shows that there were no significant differences in the distribution of age, biopsy Gleason sum and clinical stage between those with and without PSA recurrence. However, race, diagnostic PSA, percentage of positive biopsy core, pathologic T stage, pathologic Gleason sum, capsule, margin status, and seminal vesicles were found to be related to the PSA recurrence rate at the significant level of 0.05.

Figure 1 shows the Kaplan-Meier survival curve for PSA recurrence in the entire study cohort. The 3-year and 5-year PSA-free recurrence estimates were 80.3% (95% CI: 78.1 - 82.5%) and 72.0% (95% CI: 69.2 – 74.8%), respectively.

Table 2 shows the Kaplan-Meier estimates of all pre- and post-operative factors associated with the PSA recurrence-free time in men with intermediate-risk disease. All factors except surgery age, biopsy Gleason sum and clinical stage were significant for predicting the PSA outcome.

Significant factors from univariate analysis were then used for the multivariate COX proportional hazard ratio regression to select prognostic pretreatment factors which impact the time of post-prostatectomy PSA recurrence. Table 3 shows that race (AA vs. white and other: RR = 1.782, $p < 0.0001$), diagnostic PSA (> 4 - 10 vs. ≤ 4: RR = 1.663, > 10 - 20 vs. ≤ 4: RR =

1.744, p = 0.0126), and percentage of positive biopsy cores (30 – 50% vs. < 30%: RR = 0.897, ≥ 50% vs. < 30%: RR = 1.506, p = 0.0007) are independent pretreatment predictors for PSA recurrence. Surgery age, biopsy Gleason sum and clinical stage were not found to be associated with PSA recurrence by multivariate analysis. Based on diagnostic PSA and percentage of positive biopsy cores, we subdivided the intermediate-risk patients into three pretreatment risk groups: Low-risk: n = 58 (6.7%) with diagnostic PSA 4 ng/ml or less and percentage of positive biopsy core less than 30%; High-risk: n = 519 (60.1%) with diagnostic PSA more than 10 ng/ml, or percentage of positive biopsy core 50% or more; Intermediate-risk: n = 287 (33.2%) who were not in above low- and high-risk groups (Figure 2). The 5-year PSA recurrence-free rates among three risk groups were 79.1% (95% CI: 63.9 – 94.3%), 66.5% (95% CI: 59.4 – 73.6%), and 60.1% (95% CI: 55.2 – 64.8%), respectively (Log rank p = 0.0002).

Adjusted independent variables, both pre- and post-surgery factors, were pooled together and analyzed with multivariate COX regression (Table 4). This analysis found that race (AA vs. white and other: RR = 1.663, p = 0.0002), percentage of positive biopsy cores (30 – 50% vs. < 30%: RR = 0.916, ≥ 50% vs. < 30%: RR = 1.434, p = 0.0054), pathologic Gleason sum (7 vs. 2 - 6: RR = 1.448, 8 - 10 vs. 2 - 6, RR = 1.882, p = 0.0041 and margin status (positive vs negative: RR = 1.388, p = 0.0345) were significant factors affecting PSA recurrence. Diagnostic PSA was not significant when all factors were considered.

Using above pre- and post-surgery prognostic variables, we regrouped the patients to overall risk groups: Low-risk: n = 106 (12.3%) patients with pathologic Gleason sum of 2 – 6, and percentage of positive biopsy cores less than 30% and margin negative; High-risk: n = 506 (58.5%) pathologic Gleason sum of 8 – 10, or percentage of positive biopsy cores 50% or more, or margin positive; intermediate-risk: n = 252 (29.2%) who were not in either group above. The PSA recurrence-free survival rate was estimated based on the re-defined overall risk groups. The 5-year PSA recurrence-free rates among low-, intermediate- and high-risk groups were 78.5% (95% CI: 68.6 – 88.4%), 70.9% (95% CI: 63.8 – 78.0%), and 57.3% (95% CI: 52.3 – 62.3%), respectively (Figure 3, Log rank p < 0.0001).

DISCUSSION

Clinical investigators have developed nomograms and risk groups based on pretreatment clinical factors to determine the probability of PSA recurrence after radical prostatectomy (RP) during the PSA era for patients with clinically localized prostate cancer.[8-15] However, predicting recurrence in specifically in intermediate-risk prostate cancer patients (pretreatment PSA 10-20 ng/ml, or biopsy Gleason sum of 7, or 1992 AJCC clinical stage of T2b) remains a challenging task. Predicting PSA recurrence in this specific group of patients is a clinically significant issue with respect to counseling patients for local treatment versus identifying patients who are optimal candidates for clinical trials evaluating the role of neo-adjuvant systemic therapy.

This study was designed to evaluate whether the pretreatment factors that predict time to PSA recurrence after radical prostatectomy (RP) in all clinically-localized prostate cancer patients (including low-, intermediate- and high-risk patients) could also be used to predict PSA recurrence in specifically the intermediate-risk patients.

This study showed that in the intermediate-risk patients, race, diagnostic PSA level and percentage of positive biopsy cores were the significant pretreatment predictors for PSA

recurrence. Patients with high diagnostic PSA, or a high percentage of cancer-positive biopsy cores over total biopsy cores or AA race were at high risk for PSA recurrence. The significant effects of biopsy Gleason sum and clinical stage on predicting post-prostatectomy PSA recurrence in those specific groups of patients were not found. Previous studies have evaluated the role of percentage of cancer-positive biopsy cores over total biopsy cores in predicting pathologic stage, pathologic Gleason sum, and PSA recurrence. Presti et al found that patients with three or fewer positive biopsy cores were at significantly lower risk of relapse.[16] Huland et al found that the percentage of cancer-positive biopsy cores over total biopsy cores was the best predictor of biochemical failure in multivariate analysis.[17] D'Amico et al evaluated the role of percentage of positive biopsy cores in predicting post-prostatectomy biochemical failure in 960 patients for clinical stage T1 and T2 disease, and found that the percent positive biopsy cores stratified 80% of the intermediate-risk patients into low- or high-risk groups.[18] In this study, the percentage of positive biopsy cores with diagnostic PSA stratified 66.8% intermediate-risk patients to low- or high- risk groups. Our previously published papers have found race to contribute significantly to PSA recurrence after radical prostatectomy, but not to survival. [19-20] In this study, we found race to contribute significantly to PSA-free recurrence survival after radical prostatectomy. Hence, we can use race, diagnostic PSA, and positive biopsy percentage to predict PSA recurrence in intermediate-risk prostate cancer patients before surgery.

Although the analysis of pretreatment-risk factors for predicting PSA outcome for intermediate-risk prostate cancer (Table 3) could be used for patients before any treatment, it is necessary to develop an overall prognostic model by combining pre- and post-operative factors together for patients post radical prostatectomy. After adjusting for pre- and post-operative factors, the race and percentage of cancer-positive biopsy cores over total biopsy cores were still the significant predicting factors for PSA recurrence, as well as the pathologic Gleason sum and margin status entered into the model to predict PSA outcome. The PSA did not enter the overall model (Table 4). Based on percentage of positive biopsy cores, pathologic Gleason sum and margin status, 70.8% intermediate-risk patients was stratified to low- or high-risk patients.

Limitations possibly affecting the outcome include the retrospective nature of this study. The definition of PSA recurrence is not standardized. We used a cut-off of > 0.2. Many clinical investigators feel that with the new highly-sensitive PSA assays, any detectable level constitutes a recurrence while others feel PSA > 0.4 is a better level to document clinically meaningful recurrences. It is possible that some patients having defined recurrence with a PSA > 0.2 ng/mL may actually have detectable PSA due to benign etiology.

This study provided two sets of models to predict the outcome of men with intermediate-risk prostate cancer. One could be used in the pre-treatment phase and the other is for the post-treatment phase. It is concluded that for intermediate-risk patients, race, diagnostic-PSA-level and percentage of cancer-positive biopsy cores over total biopsy cores were the significant independent pre-treatment predictors for post-prostatectomy PSA recurrence. Race, percentage of positive biopsy cores, pathologic Gleason sum and margin status were the independent overall prognostic predicting factors for PSA recurrence.

REFERENCES

1. D'Amico AV, Moul J, Carroll PR, Sun L, Lubeck D, and Chen MH: Cancer specific mortality after surgery or radiation for patients with clinically localized prostate cancer managed during the prostate-specific antigen era. J Clin Oncol, 21(11): 2163-2172, 2003
2. Graefen SM, Karakiewicz PI, Gagiannos I, Quinn DI, Henshall SM, Grygiel JJ, et al: International validation of a preoperative nomogram for prostate cancer recurrence after radial prostatectomy. J Clin Oncol, 20: 3206-3212, 2002
3. Graefen SM, Karakiewicz PI, Gagiannos I, Klein E, Kupelian PA, Quinn DI, et al: Validation study of the postoperative nomogram for recurrence after radical prostatectomy for localized prostate cancer. J Clin Oncol, 20 : 951-954, 2002
4. Grossfeld GD, Latini Dm, Lubeck DP, Broering JM, Li Y, Metha SS, and Caroll PR: Predicting disease recurrence in intermediate and high-risk patients undergoing radical prostatectomy using percent positive biopsy core: results from CaPSURE. Urology, 59: 560-565, 2002
5. D'Amico AV, Whittington R, Malkowicz SB, Schultz D, Fondurulia J, Chen MH, et al: Clinical utility of percentage of positive prostate biopsy core in defining biochemical outcome after radical prostatectomy for patients with clinically localized prostate cancer. J Clin Oncol, 18: 1164-1168, 2000
6. Linson PW, Lee AK, Doytchinova T, Chen MH, Weinstein MH, Richie JP, and D'Amico AV: Percentage of core lengths involved with prostate cancer: does it add to the percentage of positive prostate biopsies in predicting postoperative prostate-specific antigen outcome for men with intermediate-risk prostate cancer? Urology 59(5): 704-708, 2002
7. Yoon JH, Chen MH, Renshaw AA, Richie JP, and D'Amico AV: Predictive factor analysis as the basis for the clinical utility of percent positive prostate biopsies in patients with intermediate-risk prostate cancer. Urology 60(3): 454-457, 2002
8. Kattan MW, Easthan JA, Stapleton AM, Wheeler TM and Scardino PT: A preoperative nomogram for disease recurrence following radical prostatectomy for prostate cancer. J Natl Cancer Inst, 90:766-769,1998
9. D'Amico AV, Cote K, Loffredo M, Renshaw AA, and Chen MH: Pretreatment predictors of time to cancer specific death after prostate specific antigen recurrence. J Urol, 169: 1320-1324, 2003
10. D'Amico AV, Whittington R, Maikowicz SB, Weinstein M, Tomaszewski JE, Schultz D, Rhude M, Rocha S, Wein A, and Richie JP: Predicting prostate specific antigen outcome preoperatively in the prostate specific antigen era. J Urol 166: 2185-2188, 2001
11. D'Amico, AV: Combined-modality staging for localized adenocarcinoma of the prostate. Oncology, 15: 1049-1052, 2001
12. D'Amico AV, Whittington R, Malkowicz SB, et al: Combined modality staging of prostate carcinoma and its utility in predicting pathologic and postoperative prostate specific antigen recurrence. Urology 49: 23-30, 1997
13. Partin AW, Yoo J, Carter HB, et al: The use of prostate specific antigen, clinical stage, and Gleason sum to predict pathological stage in men with localized prostate cancer. J Urol 150:110-114, 1993

14. Kleer E, Larson-Keller JJ, Zincke H, et al: Ability of preoperative serum prostate-specific antigen value to predict pathologic stage and DNA ploidy. Urology 41: 207-216, 1993
15. Sands ME, Zagars GK, Pollack A, et al: Serum prostate specific antigen, clinical stage, pathologic grade, and the incidence of nodal metastases in prostate cancer. Urology 44: 215 - 220, 1994
16. Presti JC, Shinohara K, Bacchetti P, et al: Positive fraction of systematic biopsy core predicts risk of relapse after radical prostatectomy. Urology 52: 1079 – 1084, 1998
17. Huland H, Hammerer P, Rolf-Peter H, et al: Preoperative prediction of tumor heterogeneity and recurrence after radical prostatectomy for localized prostate carcinoma with digital rectal examination, prostate specific antigen and the results of 6 systemic biopsies cores. J Urol 155: 1344 – 1347, 1996
18. D'Amico AV, Whittington R, Malkowicz BS, et al: Clinical utility of the percentage of positive prostate biopsies in defining biochemical outcome after radical prostatectomy for patients with clinically localized prostate cancer. J Clin Oncol 18: 1164 – 1172, 2000
19. Freedland SJ, Amling CL, Dorey F, et al: Race as an outcome predictor after radical prostatectomy: results from the Shared Equal Access Regional Cancer Hospital (SEARCH) database. Urology 60(4): 670 - 674, 2002
20. Moul JW, Connelly RR, Lubeck DP, et al: Predicting risk of prostate specific antigen recurrence after radical prostatectomy with the Center for Prostate Disease Research and Cancer of the Prostate Strategic Urologic Research Endeavor databases. J Urol 166: 1322-1327, 2001

LEGENDS

Table 1. Demographic characteristics of 1516 intermediate-risk prostate patients stratified by PSA recurrence outcome.

Figure 1. Post-prostatectomy PSA recurrence-free Kaplan-Meier survival curve.

Table 2. Kaplan-Meier estimates of PSA recurrence-free time stratified by all prognostic factors.

Table 3. Multivariate COX regression results of pretreatment factors for post-prostatectomy PSA recurrence-free time in the intermediate-risk patients.

Figure 2. Post-prostatectomy PSA recurrence-free Kaplan-Meier survival curve stratified by pre-treatment risk groups.

Table 4. Multivariate COX regression results of all pretreatment and postoperative factors for PSA recurrence-free time in the intermediate-risk patients.

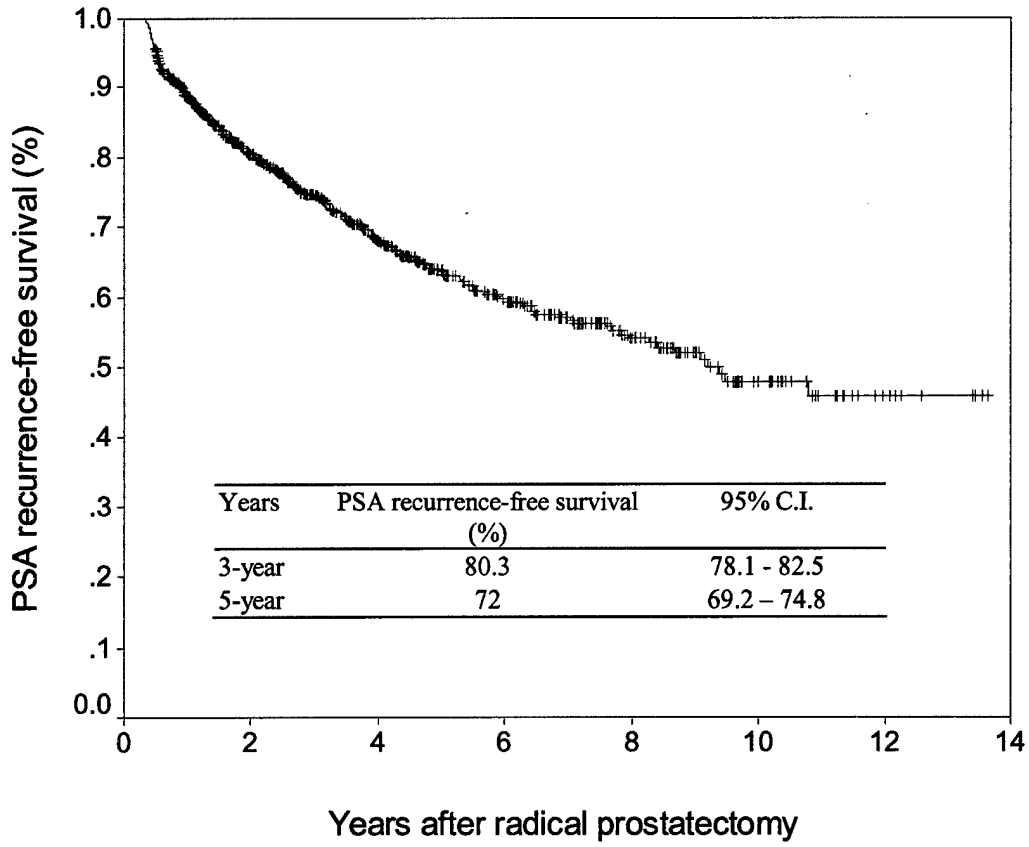
Figure 3. Post-prostatectomy PSA recurrence-free Kaplan-Meier survival curve stratified by overall risk groups.

Table 1. Demographic characteristics of 1516 intermediate-risk prostate patients stratified by PSA recurrence outcome.

	RP Cohort*	Without PSAR**	With PSAR	p
Surgery age (years)				0.3357
< 60	510	200 (34.4)	89 (31.5)	
60 - 70	492	322 (55.3)	170 (60.3)	
> 70	83	60 (10.3)	23 (8.2)	
Race				< .0001
White & other (WO)	683	484 (83.2)	199 (70.6)	
African-American (AA)	181	98 (16.8)	83 (29.4)	
Diagnostic PSA (ng /ml)				0.0006
≤ 4	158	123 (21.1)	35 (12.4)	
> 4 - 10	386	265 (45.5)	121 (42.9)	
> 10 - 20	320	194 (33.3)	126 (44.7)	
Diagnostic Gleason sum				0.4356
2 - 6	385	254(43.6)	131 (46.4)	
7	479	328 (56.4)	151 (53.6)	
Diagnostic T stage				0.6825
T1a-T2a	578	392 (67.4)	186 (66.0)	
T2b	286	190 (32.6)	96 (34.0)	
Percentage of positive biopsy cores				< .0001
< 30%	331	241 (41.4)	90 (31.9)	
30 - 50%	206	152 (26.1)	54 (19.1)	
≥ 50%	327	189 (32.5)	138 (48.9)	
Pathologic Gleason sum				0.0010
2 - 6	314	232 (42.2)	82 (30.4)	
7	430	277 (50.4)	153 (56.7)	
8 - 10	76	41 (7.4)	35 (12.9)	
Pathologic stage				<.0001
pT2	466	363 (63.2)	103 (37.2)	
pT3 + 4	385	211 (36.8)	174 (62.8)	
Capsule				<.0001
Negative	571	424 (72.8)	147 (52.1)	
Positive	293	158 (27.2)	135 (47.9)	
Margin status				<.0001
Negative	580	430 (73.9)	150 (53.2)	
Positive	284	152 (26.1)	132 (46.8)	
Seminal vesicles				<.0001
Negative	778	542 (93.1)	236 (83.7)	
Positive	86	40 (6.9)	46 (16.3)	

*: Radical prostatectomy; **: PSA recurrence.

Figure 1. Post-prostatectomy PSA recurrence-free Kaplan-Meier survival curve



Years	PSA recurrence-free survival (%)	95% C.I.
3-year	80.3	78.1 - 82.5
5-year	72	69.2 – 74.8

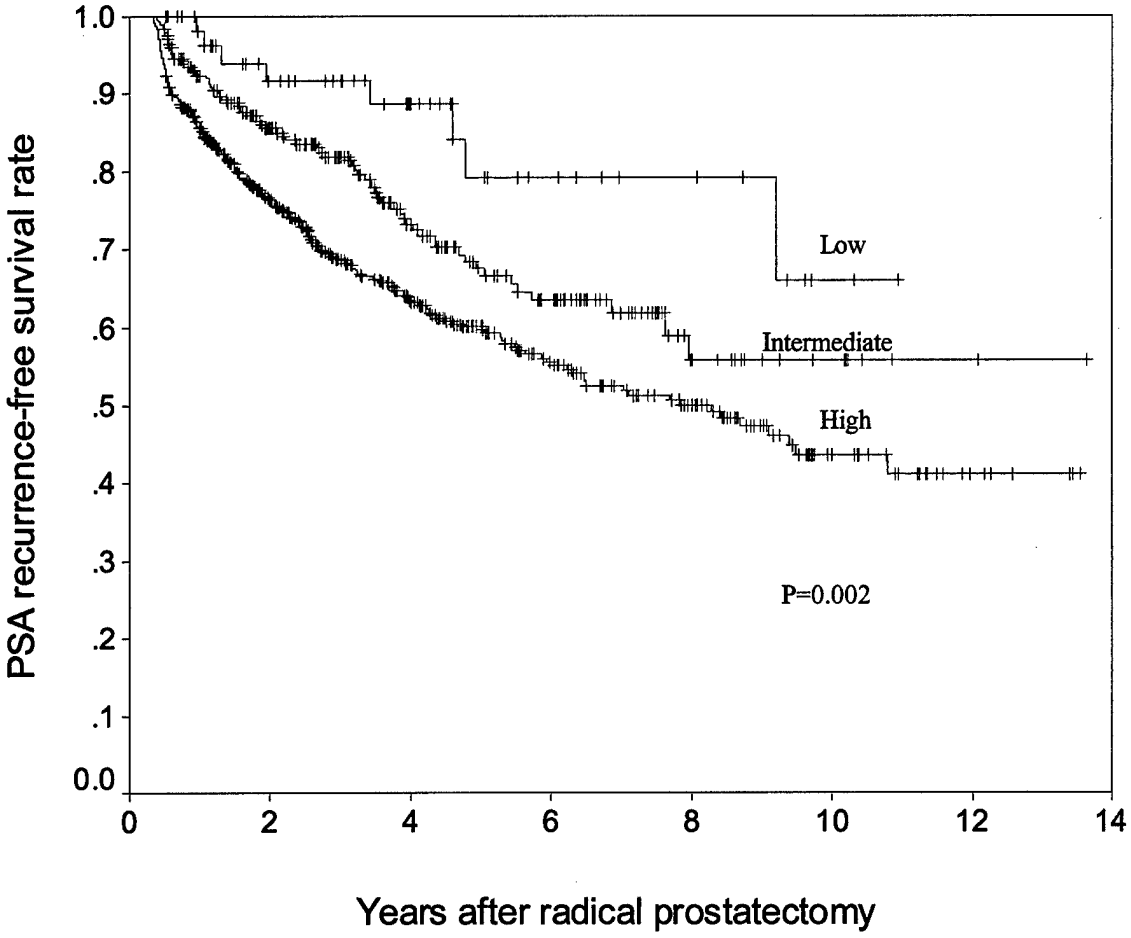
Table 2. Kaplan-Meier estimates of PSA recurrence-free time stratified by each prognostic factor.

Factor	No.	5-year PSA-free survival estimates and 95% CI (%)	p-value
Surgery age (years)			0.2643
< 60	510	63.0 (55.8 – 70.1)	
60 - 70	492	62.3 (57.3 – 67.3)	
> 70	83	72.0 (60.9 – 83.0)	
Race			<.0001
White & other	683	67.4 (63.2 – 71.6)	
African-American	181	50.1 (41.4 – 58.7)	
Diagnostic PSA (ng /ml)			0.0045
≤ 4	158	72.7 (63.8 – 81.7)	
> 4 - 10	386	61.6 (55.5 – 67.6)	
> 10 - 20	320	61.0 (55.0 – 67.0)	
Diagnostic Gleason sum			0.1314
2 - 6	385	67.2 (62.0 – 72.4)	
7	479	60.0 (54.3 – 65.8)	
Diagnostic T stage			0.1640
T1a-T2a	578	62.3 (57.4 – 67.2)	
T2b	286	66.8 (60.6 – 72.9)	
Percentage of positive biopsy cores			0.0004
< 30%	331	67.4 (61.1 – 73.8)	
30 - 50%	206	67.6 (59.7 – 75.5)	
≥ 50%	327	56.7 (50.6 – 62.9)	
Pathologic Gleason sum			<.0001
2 - 6	314	72.7 (66.9 – 78.5)	
7	430	59.2 (53.4 – 64.9)	
8 - 10	76	45.1 (31.9 – 58.2)	
Pathologic stage			<.0001
pT2	466	73.0 (67.9 – 78.0)	
pT3 + 4	385	53.3 (47.6 – 59.0)	
Capsule			<.0001
Negative	571	70.3 (65.6 – 74.9)	
Positive	293	51.5 (45.0 – 58.0)	
Margin status			<.0001
Negative	580	70.3 (65.8 – 74.9)	
Positive	284	50.1 (43.3 – 56.8)	
Seminal vesicles			<.0001
Negative	778	65.7 (61.6 – 69.7)	
Positive	86	45.3 (33.5 – 57.1)	

Table 3. Multivariate COX regression results of pretreatment factors for PSA recurrence-free time

Factors	Hazard ratio (95% CI)	P
Race		<.0001
AA vs. white & other	1.782 (1.375 – 2.310)	
Diagnostic PSA (ng/ml)		0.0126
> 4 - 10 vs ≤ 4	1.663 (1.138 - 2.429)	
> 10 - 20 vs ≤ 4	1.744 (1.197 – 2.541)	
Percentage of positive biopsy cores		0.0007
> 30 - 50% vs. ≤ 30%	0.897 (0.638 - 1.259)	
> 50% vs. ≤ 30%	1.506 (1.154 – 1.965)	

Figure 2. Post-prostatectomy PSA recurrence-free Kaplan-Meier survival curve stratified by pre-treatment risk groups.



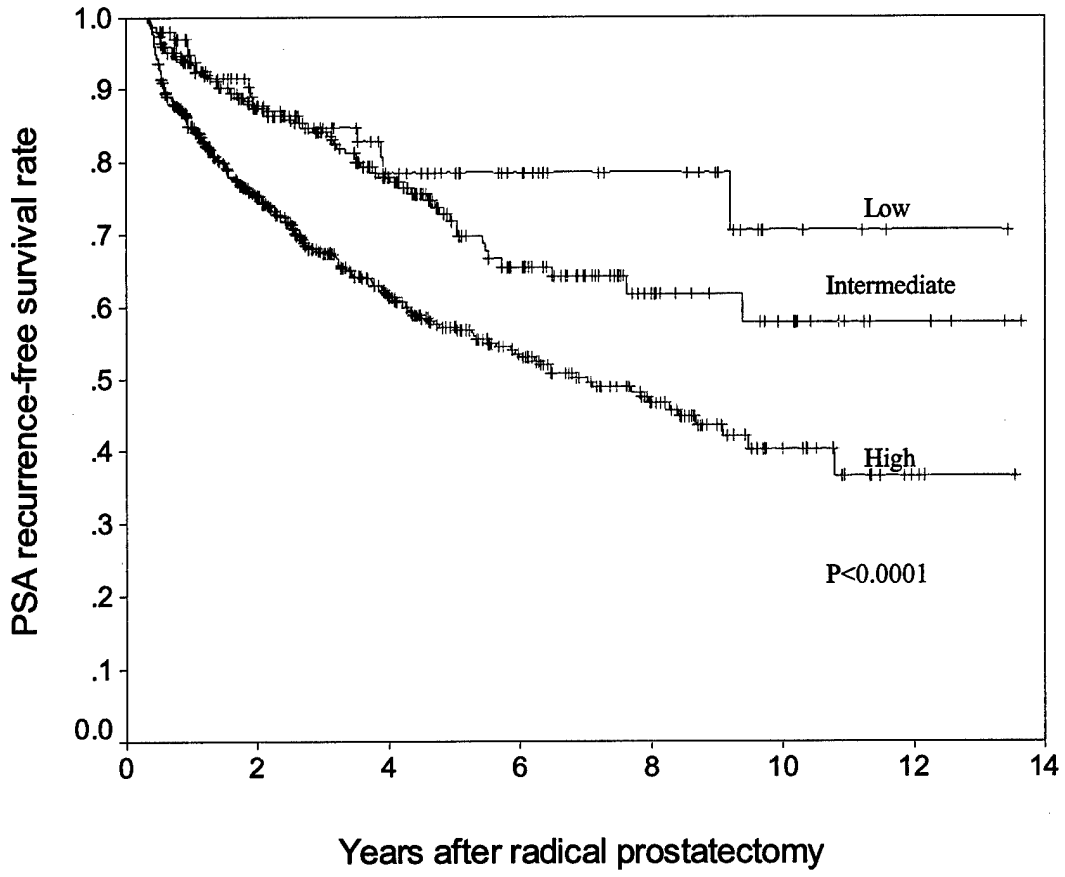
Pre-treatment risk group	Grouping criteria	No (%)
Low	PSA ≤ 4 and PPBC < 30%	58 (6.7)
High	PSA > 10 or PPBC ≥ 50%	519 (60.1)
Intermediate	who were not in either group above	287 (33.2)

* PPBC: Percentage of positive biopsy cores

Table 4. Multivariate COX regression results of all pre- and post-operative factors for PSA recurrence-free time in the intermediate-risk patients.

Factors	Adjusted hazard ratio (95% CI)	P
Pretreatment factors		
Race		0.0002
AA vs. white & other	1.663 (1.275 – 2.169)	
Diagnostic PSA (ng/ml)		0.0850
> 4 - 10 vs. ≤ 4	1.406 (0.958 – 2.062)	
> 10 - 20 vs. ≤ 4	1.591 (0.980 – 2.581)	
Percentage of positive biopsy cores		0.0054
> 30 - 50% vs. ≤ 30%	0.916 (0.649 – 1.291)	
> 50% vs. ≤ 30%	1.434 (1.091 - 1.885)	
Postoperative factors:		
Pathologic stage		0.0679
PT3/4 vs. PT2	1.427 (0.974 - 2.091)	
Pathologic Gleason sum		0.0041
7 vs. 2 - 6	1.448 (1.103 – 1.901)	
8-10 vs. 2 - 6	1.882 (1.242 – 2.854)	
Capsule		0.5657
Positive vs. negative	1.098 (0.799 – 1.509)	
Margins		0.0345
Positive vs. negative	1.388 (1.024 – 1.881)	
Seminal vesicle		0.4578
Positive vs. negative	1.140 (0.806 – 1.612)	

Figure 3. Post-prostatectomy PSA recurrence-free Kaplan-Meier survival curve stratified by overall risk groups.



Overall risk group	Group criteria	No (%)
Low	PSA ≤ 4 and PPBC < 30% and margin negative	106 (12.3)
High	PSA > 10 or PPBC ≥ 50% or margin positive	506 (58.5)
Intermediate	who were not in either group above	252 (29.2)

* PPBC: Percentage of positive biopsy cores

Appendix 4, Submitted to J Urol 2004, accepted as podium presentation in AUA 2004).

Does Delayed Radical Prostatectomy Impact PSA Recurrence?

Judd W. Moul[1], Leon Sun[1], Yongmei Chen[1], Fia Yi[1], David G. McLeod[2], Hongyan Wu[2], Christopher Amling[3], Timothy Donahue[4], Leo Kusuda[5], Wade Sexton[6], Keith O'Reilly[7], John Foley[8], Andrew Chung[9], Karen Smith[10]

6. Center for Prostate Disease Research (CPDR)
Department of Surgery
Uniformed Services University of the Health Sciences
Bethesda, MD 20814

7. Urology Service, Department of Surgery
Walter Reed Army Medical Center
Washington, D.C. 20307-5001

8. Department of Urology
San Diego Naval Medical Center
San Diego, CA

9. Department of Urology
National Naval Medical Center
Bethesda, MD

5. Department of Urology
Portsmouth Naval Medical Center
Portsmouth, VA

6. Department of Urology
Wilford Hall AF Medical Center
Lackland AFB, TX

7. Urology Service, Dept. of Surgery
Madigan Army Medical Center
Tacoma, WA

8. Urology Service, Dept. of Surgery
Brooke Army Medical Center
San Antonio, TX

9. Department of Urology
Malcolm Grow AF Medical Center
Andrews AFB, MD

10. Urology Service, Dept. of Surgery
Eisenhower Army Medical Center
Augusta, GA

*Requests for reprints/correspondence:

Judd W. Moul, MD
Center for Prostate Disease Research
1530 East Jefferson Street
Rockville, MD 20852
Telephone: (240) 453-8951
Fax: (240) 453-8912
Email: jmoul@cpdr.org

Key Words: Prostate cancer, Watchful waiting, Delayed therapy, Radical prostatectomy, PSA recurrence

Running Title: Delayed Radical Prostatectomy

ACKNOWLEDGEMENTS

The opinions and assertions contained herein are the private views of the authors and are not to be constructed as reflecting the official views of the US Army, US Navy, US Air Force or the Department of Defense. The authors are supported by a grant from the U.S. Army Medical Research and Material Command (DAMD17-02-1-0066).

ABSTRACT

Purpose: This study was aimed to evaluate the association of delayed radical prostatectomy with PSA recurrence and to identify prognostic factors and optimal observation interval in different risk groups of prostate cancer.

Materials and Methods: 3324 men were retrieved from the CPDR National Database who received definitive surgical therapy between 1988-2002. Patients with treatment failure (post-operative PSA never reached nadir or PSA recurrence occurred within 6 months post-operatively), received adjuvant therapy, or follow-up time less than 6 months were excluded. The cohort was then divided into 3 groups based on the delay (<25, 25-75 and > 75 percentiles). Univariate and multivariate Cox regression models were used to evaluate the effect of delay on PSA recurrence (PSA > 0.2 ng/ml) and prognostic variables. Then the patients were regrouped into "low", "intermediate" and "high" risk groups. The "low" risk group included those with Gleason score < 7 and PSA < 4 ng/ml while the "high" risk group consisted of individuals with Gleason score > 7 or PSA > 20 ng/ml. The remainder of the cohort fell into the "Intermediate" risk category. These groups were then compared to each other to evaluate the effect of delay on PSA recurrence.

Results: Of 3324 patients, mean 5 and 10-year PSA recurrence free survival were 68.8% (95% CI: 66.7-70.8) and 54.1 %(95% CI: 50.8-57.8), respectively. Overall, delay time was not a significant factor affecting PSA recurrence ($p = 0.099$). Instead, pathological extracapsular extension, surgical margin and seminal vesicle status were prognostic factors ($p < 0.05$). Adjusting the delay time by these three variables showed that delayed surgery was significantly associated with PSA recurrence ($\geq$ 3 months vs < 3 months, adjusted hazard ratio = 1.16, $p=0.047$). In addition, adjusting the delay time by biopsy Gleason sum and diagnostic tumor stage and PSA level indicated that delayed surgery over 97 days post diagnosis (> 75 percentile of the delay time) had a higher PSA recurrence rate (hazard ratio = 1.23, $p=0.042$). In high risk disease, the adjusted hazard ratio of the delayed therapy effect on PSA recurrence was 1.46 ($p = 0.029$).

Conclusions: Although delay was not a significant prognostic factor for all patients, it did influence biochemical outcome for high risk individuals. In men with high risk features, a delay greater than approximately 3 months may affect outcome.

INTRODUCTION

Prostate cancer is the most common solid tumor in United States males and is the second leading cause of cancer death.[1] Since the introduction of the prostate-specific antigen (PSA) screening test in the late 1980s, and increased public awareness of the disease that occurred in the early 1990s, there has been a marked stage migration to a preponderance of clinically localized disease.[2-4] Over two-thirds of men now have localized disease at initial diagnosis and are candidates for primary local therapy with curative intent.[2-4] Options include radical prostatectomy (RP) with or without nerve-sparing to preserve potency, as well as external beam radiotherapy, radioactive seed implant brachytherapy and watchful waiting.[5-7] The use of RP by urologic surgeons has increased dramatically between the mid-1980s and late 1990s. [8-9] Multiple single centers of excellence have reported improved outcomes over time in the PSA-Era including the lowering of stage, shorter operative times, less blood loss, fewer complications, and better survival. [10-11]

Despite these encouraging statistics, a recent preliminary report from Canada found that the median time from diagnosis to surgery was 68 days and that a delay of greater that 3 months was associated with a higher recurrence rate. [12] Because the study only included 645 patients, the findings, while intriguing, were not definitive. In this era of watchful waiting sometimes being offered to young men, [13,14] this topic is of grave importance. Furthermore, with a growing shortage of urologic surgeons and an expanding older, healthier population competing for health resources, delay of definitive therapy may become a greater issue. [15] Finally, delay may be encountered in some patients waiting for surgical care with prominent surgeons or waiting for high tech laparoscopic or robotic surgery. [16]

In an effort to shed more light on this issue, we examined delay in RP using the DoD CPDR Database, which is now sufficiently mature with a large cohort of RP patients enrolled over the last decade to allow meaningful analysis of time trends, risk assessment, surgical data, and impact of delayed operation.

MATERIALS AND METHODS

The clinical information and follow-up have been collected as part of the DoD CPDR Tri-Service Multicenter Prostate Disease Research Database as described previously by Sun et al.[17] Briefly, standardized data collection forms for prostate biopsy, registration, staging, surgery, surgical pathology, radiation treatment, hormonal treatment, cryotherapy, follow-up, and necropsy have been developed and were used. Data was collected and entered by physicians and data managers, then maintained in a relational database using MS Access software as the front end and Oracle software as the back end. The CPDR Database has been approved by the Uniformed Services University Research Administration, Institutional Review Board (IRB) as well as the IRBs of all participating military hospitals. The original protocol in use between 1991-1998 did not require patients to sign a formal informed consent document. However, between 1998 and 1999, the IRBs of all sites required patient informed consent to participate. Data was allowed to be maintained on all entered data prior to 1998-1999 (exact date varies by institution) without gaining the patients' informed consent; however, no new information (except necropsy data) on existing living patients or new enrollees was entered without consent after these dates.

The data query for this study was performed in September 2003. At this time, the overall database had 11360 prostate cancer patients diagnosed between Jan 1, 1988 and Dec 31, 2002. Of these, 3324 underwent a primary RP with complete information and were used for this study. We eliminated patients who never reached an undetectable (< 0.1 ng/ml) nadir PSA postoperatively, patients who experienced a biochemical recurrence ($\geq$ 0.2 ng/ml on two values) within 6 months (180 days) of surgery, patients who received adjuvant radiation or hormonal therapy, and patients who had follow-up time intervals less than 6 months. Table I provides the CPDR Sites, the total number of RP cases included in this study, the percentage of these cases of their entire enrolled cohort during the study interval, and the median delay by site

The data fields analyzed for this study included patient age at surgery, ethnicity/race, clinical stage at diagnosis, pretreatment prostate-specific antigen (PSA) value, clinical (biopsy) and pathologic (surgical) Gleason sum, pathological features from radical prostatectomy, the time (exact date) of diagnostic biopsy to surgery, and the biochemical recurrence status and time to recurrence. Diagnostic PSA on 21 of the 3324 patients were missing from the database. Analyses adjusting for diagnostic PSA levels reflect this fact. The mean follow-up was 4.6 years (range 6 months-15 years). The cohort was divided into groups according to time to treatment after their initial diagnosis with special attention to use the identical criteria as the recent preliminary work of Nam et al. [12]

This time interval was calculated by subtracting the diagnosis date from surgical treatment date. Similar to Nam et al, [12] three different start times for follow up were considered. A start time from date of diagnosis would introduce a bias that would favor the delayed treatment group since they would not be at risk for recurrence for the time until they receive treatment (which could extend up to almost one year from diagnosis). A start time from date of surgery would have a lead-time bias that would make the early treatment group vulnerable for recurrence for a greater amount of time that the delayed treatment group. So a start time from one year after initial date of diagnosis was principally used. In this model a few notable biases come to light. People in the delayed treatment group may have had their surgery beyond the follow up start time. In our cohort, 278 patients qualified for these biases and were eliminated leaving a total cohort of n=3046 for the analyses that involved using the group with the follow up start time from one year after diagnosis. However, this group was considered in the majority of our analysis because it was felt to harbor the least amount of bias, similar to Nam et al [12].

All data analysis including patient pool characteristics and distribution of variables were performed using the SAS system v8 (North Carolina). Mean follow-up time for the entire cohort and primary follow up group (start time=one-year after diagnosis) were calculated using the Cox univariate model. Kaplan-Meier method was employed to determine crude rates for PSA free survival times. Cox univariate and multivariate models were used to calculate the crude and adjusted hazard ratios when determining the effects of the three primary variables being studied (diagnostic PSA, Gleason score and diagnostic Stage). Based on these results we came up with a specific cut-off time to compare the effects of delayed therapy and formulated a working definition of "low", "intermediate" and "high" risk groups. These risk groups were then stratified for the cut-off time and compared.

RESULTS

Table II provides the demographic, clinical, and pathological features of the 3324 patients included in the study. More than 86% of men were between 50 and 70 years of age at the tie of surgery, 80% were Caucasians and other ethnicity, 74% were clinical T1c or T2a, 79% had pretreatment PSA values of less than or equal to 10.0 ng/ml, 94% had a biopsy Gleason grade sum of ≤ 7, 92% had Pathologic Gleason sum ≤ 7, and 62% had pT2 disease.

In Table III, the cohort is examined for delay in time from diagnosis to surgical therapy. For the overall cohort, the median delay was 65 days (mean 87.4 days) and there was a downward trend over time (Figure 1a, Figure 1b). By time interval of delay, 972 (29.2%) had a delay over 3 months. Furthermore, Table I illustrates the delay by institution with a median of 65 days.

The 5 and 10-year PSA-free survival were 68.8% and 54.1%, respectively (C.I. 66.7-70.8 and 50.8-57.8), for the entire cohort. Tables IV and V examine the hazard of recurrence by delay time ($<$ or $\geq$ 3 months) and the known prognostic variables of Gleason sum, pathologic stage factors, and diagnostic PSA level. While Gleason, pathologic variables, and PSA were predictive of recurrence in both crude and adjusted analysis, delay time ($<$ or $\geq$ 3 months) was only significant ($p= 0.047$) in multivariable adjusted hazard analysis.

Table VI further explores the impact of delay on PSA recurrence. Here the surgical waiting time is divided into quartiles ($<$ 47, 47-65, 66-97, and $>$97 days) and analyzed in a crude and adjusted manner. In this experiment, the covariates were PSA level, biopsy worst Gleason sum and clinical stage. In multivariable analysis, a delay greater than 97 days was a significant ($p= 0.042$) predictor of recurrence. Table VII examines a delay ($<$ or $\geq$ 3 months) in relation to PSA level, clinical stage, and biopsy Gleason sum individually. In the setting of clinical T2 disease and a biopsy Gleason sum > 7, a delay greater than 3 months was associated with a higher recurrence probability. Finally, Table VIII examines surgical delay ($<$ or $\geq$ 3 months) by a risk group stratification.

DISCUSSION

The most important finding of this study is that delay in time between diagnosis and the performance of a radical prostatectomy appears to adversely affect the intermediate endpoint of PSA-only or biochemical recurrence rate. This large experience from the DoD CPDR confirms the preliminary suggestions of Nam et al from Canada that delay to surgical therapy may be an important prognostic factor.[12] However, a delay greater than 3 months was only important when examined in the context of established prognostic factors of PSA level, Gleason grade, and clinical stage and their use in contemporary risk assessment. Specifically, a delay appeared to only have a significant impact on biochemical recurrence in the setting of high risk disease features. Significant delay from diagnosis to surgical therapy appears to impact biochemical outcome at 5 years for high risk men with diagnostic PSA > 20 ng/ml, or Gleason sum > 7, or clinical stage T2c.

There are a number of other findings that deserve special comment. In our health care setting of the US military, delay time from diagnosis to surgery decreased over time from 1988 to 2002. This is in contrast to Nam et al who found greater delay time during the latter PSA-era in their Canadian Health care setting[12]. While both the US military and Canadian health systems are socialized, it is unclear why the trends in delay were different over time. It is possible that

military men may have been more definitive in decision making combined with adequate health resources, but this is speculative and requires more study. It is also possible that men in the Nam et al study were more influenced by consideration of watchful waiting that contributed to delayed surgical intervention. [12-14]

Our results may have important implications for the use of watchful waiting to manage localized prostate cancer in the PSA-era. [7,13,14,18,19] Although the majority of men choosing observation are older with low stage, grade and PSA, some are younger men with more adverse disease features. [18,19] It is possible that some men lose their "window of opportunity" for cure imposed by delayed definitive surgical therapy. However, a specific examination of watchful waiting patients who were later treated by radical prostatectomy will be needed to fully address this question.

Our data may also have implications for external beam and brachytherapy treated men. Specifically, in the era before use of neoadjuvant and adjuvant hormonal therapy with radiation, men with adverse disease characteristics i.e. high risk disease received radiation alone. [20,21] The delayed clearance of local cancer as a result of the radiation biology may have contributed to some recurrences. Furthermore, although speculative, this may help explain why neoadjuvant hormones with radiation has been shown to be beneficial but neoadjuvant hormones with radical prostatectomy has not been shown to impact biochemical outcome. [22]

There are a number of limitations to this study. Although this is a very large study with over 3000 patients, the follow-up of just over 5 years, on average, is modest and it is unknown if delay to radical prostatectomy will impact clinical recurrence-free or disease-specific survival. Longer follow-up will be necessary. The healthcare setting of the equal-access military system has the advantage of standardization and good follow-up ability, but the results may not fully translate to the private sector. Finally, due to high penetrance of screening in this health system there were relatively few patients with high risk disease features. Had more of these individuals been available for study, the impact of delay may have been better characterized. Furthermore, the elimination of early recurring patients and neoadjuvant/adjuvant treated patients was necessary to mirror the study of Nam et al and to avoid certain biases, however, it invariably eliminated more high risk men where delay had a greater impact. Despite these limitations, this is the first large study to show that high risk men may be adversely impacted by delayed surgical intervention.

CONCLUSIONS

Delayed radical prostatectomy beyond approximately 3 months was associated with a higher biochemical recurrence rate compared to men who received definitive surgical care earlier than 3 months after adjustment for stage, Gleason sum, and PSA level. The optimal time from diagnosis to radical prostatectomy should be approximately 3 months or less particularly for high risk individuals with PSA > 20 Ng/ml or Gleason sum > 7. Further study will be required to determine if delay impacts clinical metastases or disease-specific survival.

REFERENCES

1. Jemal A, Murray T, Samuels A, Ghafoor A, Ward E, Thun MJ. Cancer statistics, 2003. CA Cancer J Clin. 2003 Jan-Feb;53(1):5-26.
2. Stephenson RA, Prostate cancer trends in the era of prostate-specific antigen. An update of incidence, mortality, and clinical factors form the SEER database. Urol Clin North Am. 2002 Feb;29(1):173-81.
3. Jani AB, Vaida F, Hanks G, Asbell S, Sartor O, Moul JW, Roach M 32d, Brachman D, Kalokhe U, Muller-Runkel R, Ray P, Ignacio L, Awan A, Weichselbaum RR, Vijayakumar S. Changing face and different countenances of prostate cancer: racial and geographic differences in prostate-specific antigen (PSA), stage, and grade trends in the PSA era. Int J Cancer. 2001 Dec 20;96(6):363-71.
4. Farkas A, Scheider D, Perrotti M, Cummings KB, and Ward WS: National trends in the epidemiology of prostate cancer, 1973 to 1974: Evidence for the effectiveness of prostate-specific antigen screening. Urology. 52: 444, 1998.
5. D'Amico AV, Moul J, Carroll PR, Sun L, Lubeck D, Chen MH. Cancer-specific mortality after surgery or radiation for patient with clinically localized prostate cancer managed during the prostate-specific antigen era. J Clin Oncol. 2003 Jun 1;21(11):2163-72.
6. Lee WR, Moughan J, Owen JB, Zelefsky MJ. The 1999 patterns of care study of radiotherapy in localized prostate carcinoma: a comprehensive survey of prostate brachytherapy in the United States. Cancer. 2003 Nov 1:98(9):1987-94.
7. Schroder FH, De Vries SH, Bangma CH. Watchful waiting in prostate cancer: review and policy proposals. BJU Int. 2003 Nov,92(8):851-9.
8. Moul JW, Wu H, Sun L, McLeod DG, Amling C, Lance R, Kusuda L, Donahue T, Foley J, Chung A, Sexton W, Soderdahl D, Rich NM. Epidemiology of radical prostatectomy for localized prostate cancer in the era of prostate-specific antigen: an overview of the Department of Defense Center for Prostate Disease Research national database. Surgery. 2002 Aug;132(2):213-9.
9. Lu-Yao GL, McIerran D, Wasson J and Wennberg JE: An assessment of radical prostatectomy: timetrends, geographic variation, and outcomes. JAMA, 269: 2633-2636, 1993.
10. Han M, Partin AW, Zahurak M, Piantadosi S, Epstein JI, Walsh PC. Biochemical (prostate specific antigen) recurrence probability following radical prostatectomy for clinically localized prostate cancer. J Urol. 2003 Feb;169(2):517-23.
11. Lepor H, Nieder AM, Ferrandino MN: Intraoperative and postoperative complications of radical retropubic prostatectomy in a consecutive series of 1,000 cases. J. Urol., 166: 1729-1733, 2001.
12. Nam RK, Jewett MA, Krahn MD, Robinette MA, Tsihlias J, Toi A, Ho M, Evans A, Sweet J, Trachtenberg J. Delay in surgical therapy for clinically localized prostate cancer and biochemical recurrence after radical prostatectomy. Can J Urol. 2003 Jun;10(3):1891-8.
13. Zietman Al, Thakral H, Wilson L, Schellhammer P. Conservative management of prostate cancer in the prostate specific antigen era: the incidence and time course of subsequent therapy. J Urol. 2001 Nov;166(5):1702-6.
14. Klotz L. Expectant management with selective delayed intervention for favorable risk prostate cancer. Urol Oncol. 2002 Sep-Oct;7(5):175-9.

15. Pace KT, Provan JL, Jewett MA. The urology work force in Ontario for the 21st century: feast or famine? Can J Surg. 1999 Jun;42(3):181-9.
16. Ahlering TE, Skarecky D, Lee D, Clayman RV. Successful transfer of open surgical skills to a laparoscopic environment using a robotic interface: initial experience with laparoscopic radical prostatectomy. J Urol. 2003 Nov;170(5):1738-41.
17. Sun L, Gancarczyk K, Paquette EL, McLeod DG, Kane C, Moul JW: Introduction to Department of Defense Center for Prostate Disease Research Multicenter National Prostate Cancer Database, and analysis of changes in the PSA-Era. Urologic Oncology, 6(5): 203-210, 2001.
18. Carter CA, Donahue T, Sun L, Wu H, McLeod DG, Amling C, Lance R, Foley J, Sexton W, Kusuda L, Chung A, Soderdahl D, Jackman S, Moul JW. Temporarily deferred therapy (watchful waiting) for men younger than 70 years and with low-risk localized prostate cancer in the prostate-specific antigen era. J Clin Oncol. 2003 Nov 1;21(21):4001-8.
19. Harlan SR, Cooperberg MR, Elkin EP, Lubeck DP, Meng MV, Mehta SS, Carroll PR. Time trends and characteristics of men choosing watchful waiting for initial treatment of localized prostate cancer: results from CaPSURE. J Urol. 2003 Nov;170(5):1804-7.
20. Roach M 3rd. Hormonal therapy and radiotherapy for localized prostate cancer: who, where and how long? J Urol. 2003 Dec;170(6 Pt 2):S35-40; discussion S40-1.
21. D'Amico AV, Whittington R, Malkowicz SB, Schultz D, Blank K, Broderick GA, Tomaszewski JE, Renshaw AA, Kaplan I, Beard CJ, Wein A. Biochemical outcome after radical prostatectomy, external beam radiation therapy, or interstitial radiation therapy for clinically localized prostate cancer. JAMA. 1998 Sep 16;280(11):969-74.
22. Gleave ME, La Bianca S, Goldenberg SL. Neoadjuvant hormonal therapy prior to radical prostatactomy promises and pitfalls. Prostate Cancer Prostatic Dis. 2000 Nov;3(3):136-144.

LEGENDS:

Table I. Participating CPDR Sites, Total Prostate Cancer and Total Radical Prostatectomy Cases in the Database between 1988 and 2002.

Table II. Demographic factors in 3324 RP patients operated between 1988-2002 in this study

Table III. Time interval data from date of diagnosis to date of radical prostatectomy in 3324 radical prostatectomy patients between 1988 and 2002.

Table IV. Univariate analyses of above prognostic factors based on three different follow-up start time types.

Table V. Multivariate analyses of above prognostic factors based on three different follow-up start types.

Table VI. Crude and adjusted hazard ratio for PSA recurrence by surgical waiting time in quartiles.

Table VII. Crude and Adjusted hazard ratio for PSA recurrence by delay of surgery ($<, \geq 3$ months) for PSA level, clinical stage, and biopsy Gleason sum.

Table VIII. Hazard ratio of PSA recurrence rates by delay to surgery and risk group stratification.

Figure 1. Downward trend in delayed radical prostatectomy over time
Figure 1a. Median downward trend.
Figure 1b. Mean downward trend.

Figure 2. Kaplan Meier Biochemical Disease-free Survival Curve – of impact at delayed radical prostatectomy
Figure 2a. Overall study cohort
Figure 2b. High-risk cohort

Table I. Participating CPDR sites, total prostate cancer and total radical prostatectomy cases in the CPDR Database between 1988 and 2002.

CPDR Site Name	Total CaP cases	RP cases	RP cases for this study	% of RP/Total	Median delay (days)
Brooke Army Medical Center (BAMC)	940	458	325	0.49	66
Eisenhower Army Medical Center (EAMC)	487	224	149	0.46	57
Madigan Army Medical Center (MAMC)	1129	442	301	0.39	71
Malcom Grow Medical Center (MGMC)	617	330	220	0.53	70
Naval Medical Center Portsmouth (NMCP)	916	356	235	0.39	63
Naval Medical Center San Diego (NMCSD)	1606	893	532	0.56	59
National Navy Medical Center (NNMC)	1464	502	332	0.34	72
Wilford Hall Medical Center (WHMC)	1184	657	501	0.55	59
Walter Reed Army Medical Center WRAMC)	3017	1204	729	0.40	69
CPDR National Database	11360	5066	3324	0.45	65

CaP: Prostate cancer; RP: Radical prostatectomy.

Table II. Demographic factors in 3324 radical prostatectomy patients operated between 1988-2002 in this study

	Number	Percent (%)
Age		
≤ 50	184	5
51-60	987	30
61-70	1736	52
≥ 70	417	13
Race		
Caucasian & other	2667	80
African American	657	20
Clinical stage		
T1	1523	46
T2	1801	54
Diagnostic PSA		
< 4	820	25
4.1-10.0	1795	54
10.1-20.0	502	15
> 20.0	186	6
Diagnostic Gleason sum		
< 7	2409	72
7	733	22
>7	182	5
Pathologic Gleason sum		
< 7	1571	47
7	1138	34
> 7	271	8
Pathology		
Capsule +	1041	31
Margin +	975	29
Seminal Vesicle	220	7
Surgical pathology features		
PT2 (organ confined)	1972	62
PT3-4	1194	38

Table III. Time interval data from date of diagnosis to date of radical prostatectomy in 3324 radical prostatectomy patients between 1988 and 2002.

A. Delay time interval distribution by surgical era.

	Mean	Median time (days)	% of patients with delay >= 3 months
Overall cohort	87.4	65	29.2
By Surgical era			
1988-1990	80	60	17.6
1991-1993	87	74	30.6
1994-1996	99	74	39
1997-1999	111	59	23.9
2000-2002	81	60	25.5

B. Delay time interval (3 month cut point and quartile cut point)

Time interval	Number	Percent
< 3 months	2352	70.8
> 3 months	972	29.2
< 47 days	839	25.2
47-65 days	827	24.9
66-97 days	826	24.8
> 97 days	832	25

C. Significant delay subset (all > 97 days)

Time Interval	Number	Total %	Low-risk %	Intermediate-risk %	High-risk %
98-120	278	33.4	48.0	35.7	16.4
121-180	320	38.5	51.3	33.5	15.2
181-365	149	17.9	48.5	22.4	29.1
>365	85	10.2	37.1	48.6	14.3

Table IV. Univariate analyses of above prognostic factors based on three different follow-up start time types.

Covariant	From 1 year after diagnosis (N=3046)			From date of surgery (N=3324)			From date of diagnosis (N=3324)		
	Hazard ratio	95% C.I.	p	hazard ratio	95% C.I.	p	hazard ratio	95% C.I.	p
Delay time									
< 3 months	1			1			1		
> 3 months	1.159	0.998-1.345	0.0526	1.093	0.958-1.248	0.1847	1.018	0.892-1.161	0.7947
Clinical stage									
T1	1			1			1		
T2	1.244	1.076-1.438	0.0031	1.213	1.069-1.375	0.0026	1.21	1.067-1.372	0.003
Histologic grade									
Gleason 2-6	1			1			1		
Gleason 7	1.535	1.312-1.796	<.0001	1.526	1.331-1.749	<.0001	1.526	1.332-1.750	<.0001
Gleason 8-10	2.037	1.588-2.612	<.0001	1.953	1.572-2.428	<.0001	1.97	1.585-2.449	<.0001
PSA at diagnosis									
< 4.0	1			1			1		
>4.0-10.0	0.927	0.806-1.066	0.2862	0.9	0.796-1.016	0.0894	0.899	0.795-1.015	0.0864
>10.0-20.0	1.358	1.138-1.620	0.0007	1.499	1.290-1.742	<.0001	1.507	1.296-1.751	<.0001
> 20.0	2.131	1.687-2.692	<.0001	2.186	1.788-2.672	<.0001	2.09	1.765-2.638	<.0001
Pathologic stage									
Capsule	1.872	1.627-2.154	<.0001	1.975	1.747-2.232	<.0001	1.981	1.753-2.239	<.0001
Margin	1.81	1.570-2.086	<.0001	1.915	1.693-2.167	<.0001	1.921	1.698-2.174	<.0001
SVI*	2.053	1.639-2.571	<.0001	2.184	1.806-2.640	<.0001	2.171	1.796-2.625	<.0001

*SVI: Seminal vesicle invasion

Table V. Multivariate analyses of above prognostic factors based on three different follow-up start time types.

	From 1 year after diagnosis (N=3046)			From date of surgery (N=3324)			From date of diagnosis (N=3324)		
Covariant	hazard ratio	95% C.I.	p	hazard ratio	95% C.I.	p	hazard ratio	95% C.I.	p
Delay Time			**0.0206**			0.0767			0.5183
< 3 months	1			1			1		
> 3 months	1.193	1.028-1.386		1.127	0.987-1.287		1.045	0.915-1.193	
Clinical stage			0.0048			0.0065			0.0089
T1	1			1			1		
T2	1.243	1.069-1.446		1.2	1.052-1.368		1.191	1.045-1.358	
Histologic grade			<.0001			<.0001			<.0001
Gleason 2-6	1			1			1		
Gleason 7	1.411	1.198-1.663		1.364	1.183-1.574		1.364	1.183-1.574	
Gleason 8-10	1.955	1.511-2.529		1.834	1.463-2.297		1.846	1.473-2.313	
PSA at diagnosis			<.0001			<.0001			<.0001
< 4.0	1			1			1		
>4.0-10.0	1.321	1.095-1.594		1.353	1.143-1.602		1.351	1.141-1.599	
>10.0-20.0	1.569	1.254-1.962		1.758	1.444-2.140		1.762	1.447-2.145	
> 20.0	1.961	1.479-2.602		2.087	1.631-2.670		2.076	1.622-2.656	
Pathologic stage									
Capsule	1.438	1.213-1.706	<.0001	1.455	1.254-1.688	<.0001	1.455	1.255-1.688	<.0001
Margin	1.31	1.101-1.557	0.0023	1.362	1.173-1.582	<.0001	1.368	1.178-1.589	<.0001
SVI*	1.197	0.938-1.528	0.1482	1.268	1.033-1.557	0.0231	1.26	1.026-1.547	0.0274

*: SVI: Seminal vesicle invasion

Table VI. Crude and adjusted hazard ratio for PSA recurrence by surgical waiting time in quartiles.

Surgical waiting time by quartiles	Crude hazard ratio	95% C.I.	p	Adjusted hazard ratio	95% C.I.	p
< 47 days (< 25%)	1			1		
47-65 (25-50%)	0.991	0.84-1.16	0.911	1.12	0.91-1.38	0.270
66-97 (51-75%)	1.05	0.90-1.23	0.533	1.15	0.94-1.41	0.179
>97(>75%)	1.09	0.93-1.27	0.277	1.23	1.01-1.51	**0.042**

*Adjusted hazard ratio accounted for diagnostic PSA, Gleason sum and diagnostic stage.

Table VII. Crude and adjusted hazard ratio for PSA recurrence by delay of surgery (<, ≥ 3 months) for PSA level, clinical stage, and biopsy Gleason sum.

	Crude hazard ratio	p	Adjusted hazard ratio	p
PSA < 4				
< 3 months	1		1	
≥ 3 months	1.07	0.68	1.11	0.54
PSA 4.1-10.0				
< 3 months	1		1	
≥ 3 months	1.1	0.37	1.13	0.25
PSA 10.1-20				
< 3 months	1		1	
≥ 3 months	1.13	0.48	1.15	0.42
PSA >20				
< 3 months	1		1	
≥ 3 months	1.4	0.14	1.46	0.11
Clinical T1				
< 3 months	1		1	
≥ 3 months	0.97	0.81	0.98	0.89
Clinical T2				
< 3 months	1		1	
≥ 3 months	1.33	0.0032	1.31	**0.0055**
Biopsy Gleason sum < 7				
< 3 months	1		1	
≥ 3 months	1.1	0.3	1.11	0.26
Biopsy Gleason sum = 7				
< 3 months	1		1	
≥ 3 months	1.24	0.14	1.19	0.25
Biopsy Gleason sum > 7				
< 3 months	1		1	
≥ 3 months	1.7	0.0352	1.66	**0.0475**

Table VIII. Crude and adjusted hazard ratio of PSA recurrence rates by delay to surgery and risk group stratification.

Risk group	hazard ratio	95% C.I.	p
Low risk (n=1380)			
< 3 months	1		
≥ 3 months	1.037	0.796-1.352	0.7853
Intermediate risk (n=978)			
< 3 months	1		
≥ 3 months	1.156	0.896-1.491	0.2638
High risk (n=444)			
< 3 months	1		
≥ 3 months	1.406	1.043-1.897	**0.0254**

Figure 1. Downward trend in delayed radical prostatectomy over time

Figure 1a. Median downward trend.

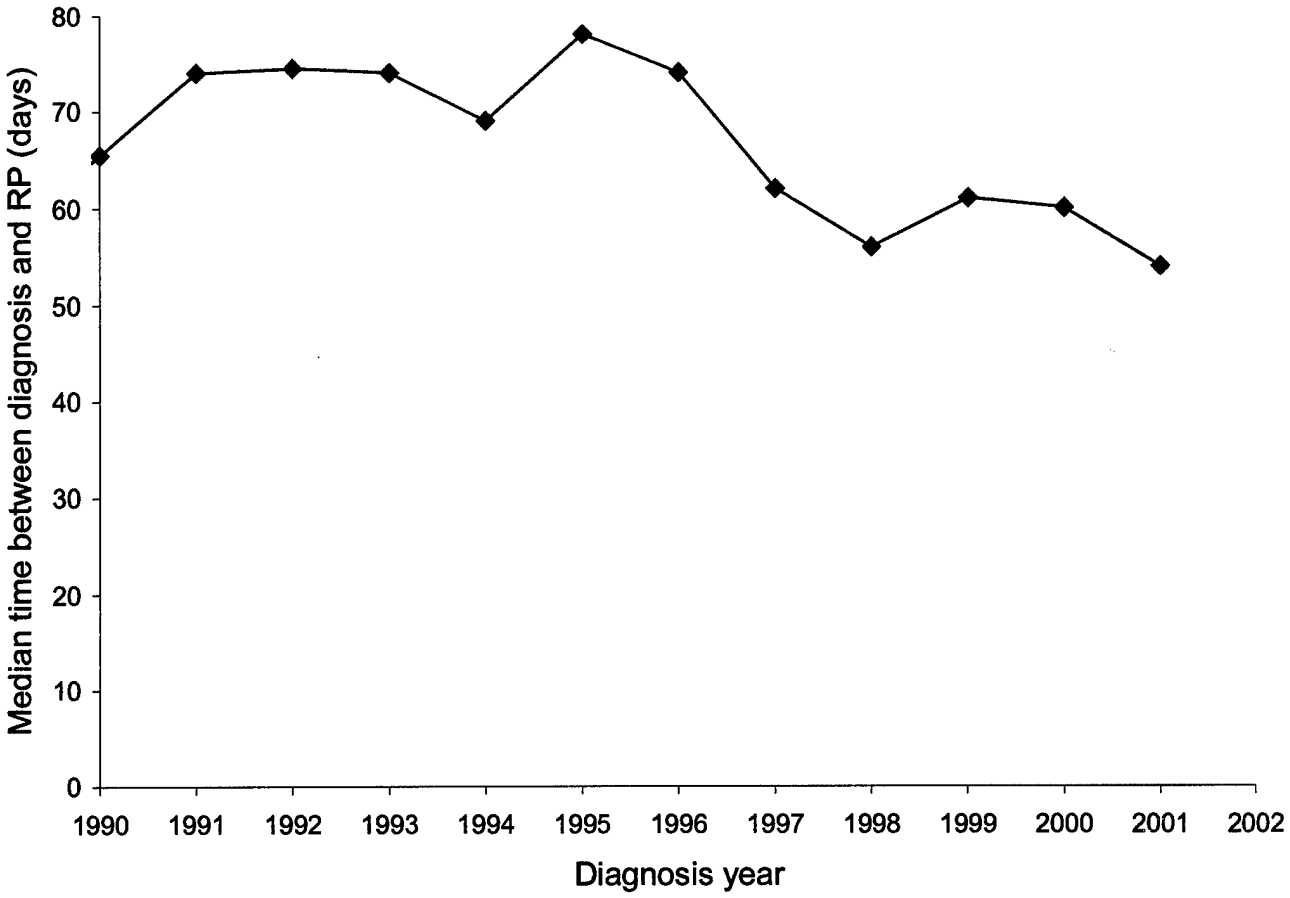


Figure 1b. Mean downward trend over time.

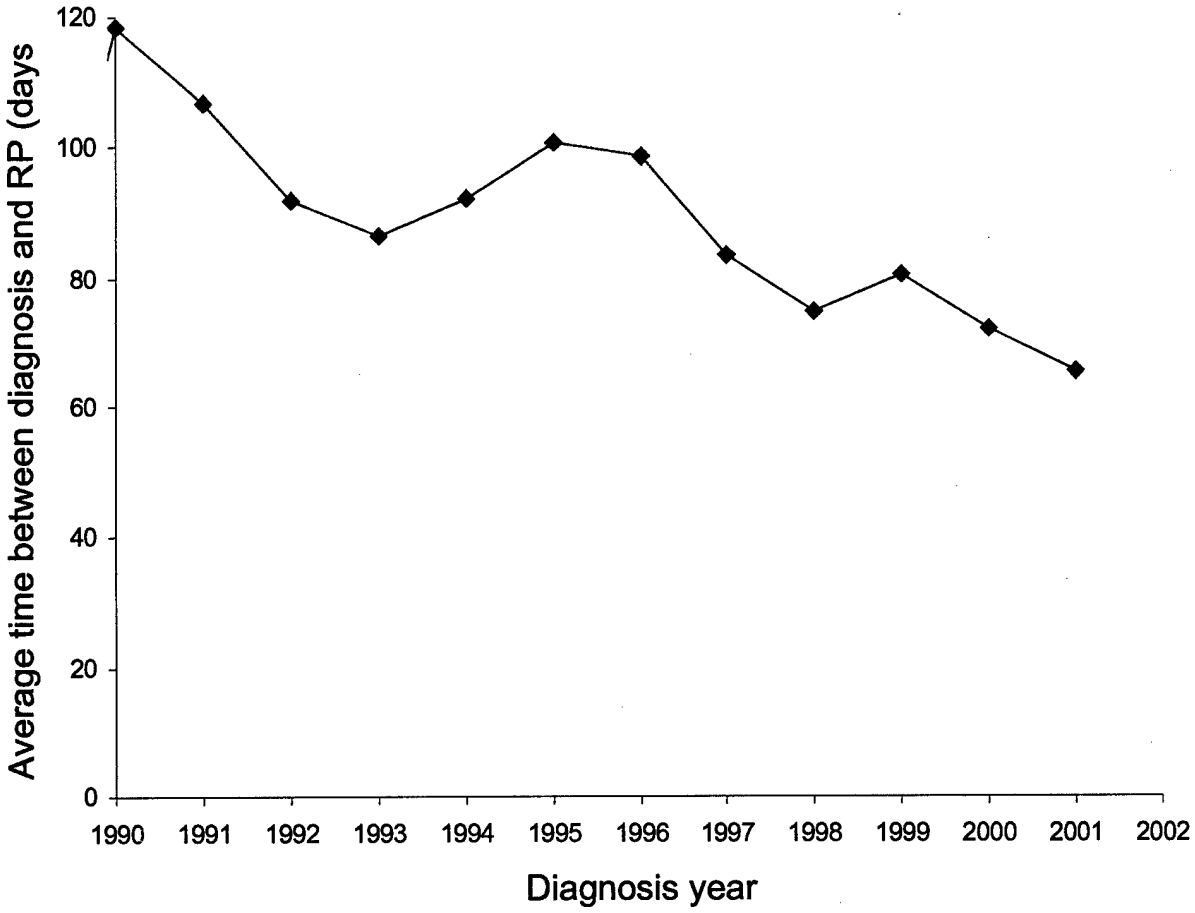


Figure 2. Kaplan Meier Biochemical recurrence-free survival curves of impact of delay in radical prostatectomy

Figure 2a. Overall cohort (n=3046)

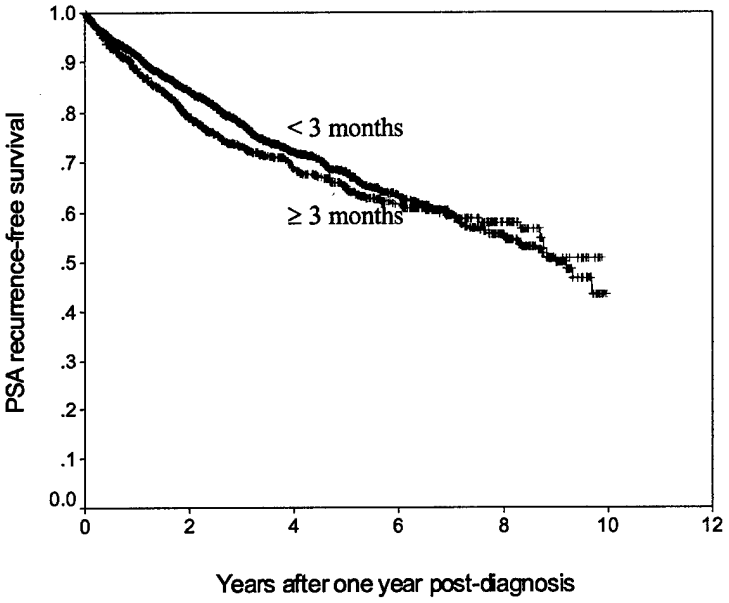
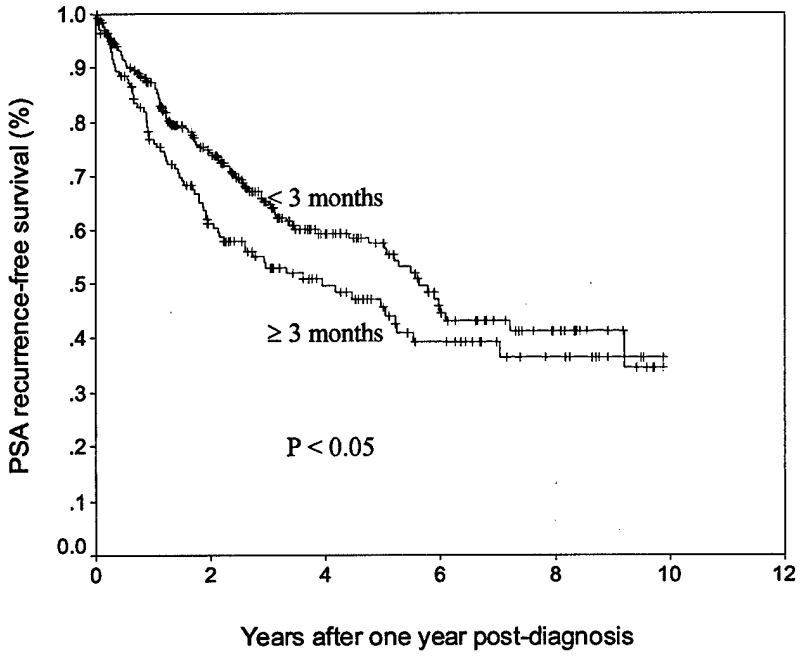


Figure 2b. High-risk cohort (n=444)



Appendix 5, Submitted to J Clin Onc in 2003 (under review)

Clinical Course of Prostate Cancer after Radical Prostatectomy and Prognostic Factors Associated with Post-treatment Distant Metastasis

Leon Sun[1], Judd W. Moul[1], Julian Wu[1], David G. McLeod[2], Christopher Amling[3], Curt Powell[3], Thomas Chung[3], Timothy Donahue[4], Stephen Jackman[4], Robert Douglas[4], Leo Kusuda[5], Wade Sexton[6], Keith O'Reilly[7], Javier Hernandez[8], John Foley[8], Andrew Chung[9], Karen Smith[10]

1. Center for Prostate Disease Research (CPDR)
Department of Surgery
Uniformed Services University of the Health Sciences
Bethesda, MD 20814

2. Urology Service, Department of Surgery
Walter Reed Army Medical Center
Washington, D.C. 20307-5001

3. Department of Urology
San Diego Naval Medical Center
San Diego, CA

4. Department of Urology
National Naval Medical Center
Bethesda, MD

5. Department of Urology
Portsmouth Naval Medical Center
Portsmouth, VA

6. Department of Urology
Wilford Hall AF Medical Center
Lackland AFB, TX

7. Urology Service, Dept. of Surgery
Madigan Army Medical Center
Tacoma, WA

8. Urology Service, Dept. of Surgery
Brooke Army Medical Center
San Antonio, TX

9. Department of Urology
Malcolm Grow AF Medical Center
Andrews AFB, MD

10. Urology Service, Dept. of Surgery
Eisenhower Army Medical Center
Augusta, GA

*Requests for reprints/correspondence:
Judd W. Moul, MD
Center for Prostate Disease Research
1530 East Jefferson Street
Rockville, MD 20852
Telephone: (240) 453-8951
Fax: (240) 453-8912
Email: jmoul@cpdr.org

Key Words: Prostate cancer, Natural history, Radical prostatectomy, Biochemical recurrence, Distant metastasis
Running Title: Clinical course of prostate cancer

The authors are supported by a grant from the U.S. Army Medical Research and Materiel Command (DAMD17-02-1-0066).

ABSTRACT

Purpose: The purpose of this study was to depict the clinical history of prostate cancer after PSA recurrence (> 0.2 ng/ml) with multicenter data.
Patients and Methods: Data from 3731 DoD-CPDR radical prostatectomy patients treated between 1988 and 2002 at nine hospitals across the country were reviewed. Patients having any of the following criteria were excluded: received neoadjuvant or adjuvant radiation or hormonal therapy, positive lymph node at surgery, or post-radical prostatectomy follow-up < 6 months. Kaplan-Meier, univariate and multivariate analyses were used to evaluate the probability of PSA recurrence, distant metastasis and death due to prostate cancer.
Results: Of 3731 patients, 1399 (37.5%) developed PSA recurrence with a median follow-up of 7.9 years. Of these, only 89 patients developed distant metastasis (6.9%) and 16 (1.3%) patients died of prostate cancer. The 5- and 10-year post-PSA recurrence metastasis-free survival rates were 92.4% and 86.3%, respectively. There was no calculable median actuarial time to metastasis from the time of PSA level elevation. The 5- and 10-year prostate cancer-specific survival rates were 98.8% and 96.4 %, respectively. Pathological Gleason sum (≤ 7 vs. > 7) and PSA doubling time (≤ 12 months vs. > 12 months) were associated with distant metastasis (hazard ratio > 2.3, $p < 0.001$).
Conclusion: The period between PSA recurrence and distant metastasis is much greater than a prior single center report, and there is no median year available. Pathological Gleason sum and PSA doubling time were significant independent predictors of distant metastasis for patients having PSA recurrence.

INTRODUCTION

Introduction of the prostate-specific antigen (PSA) screening test induced a marked stage migration to a preponderance of clinically-localized disease.[1] Over two-thirds of men now have localized disease at initial diagnosis and are candidates for primary local therapy with curative intent.[1] In this PSA-era with increasing localized disease, the use of radical prostatectomy (RP) has increased dramatically between the mid-1980s and the late 1990s.[2] However, approximately 35% of men will experience a detectable serum prostate-specific elevation within 10 years following surgery, [3-7] representing the earliest evidence of persistent disease.

There is a need for study of large multicenter cohorts of patients and long-term follow-up to clarify the relationship between PSA failure and distant metastasis and characterize the clinical course of distant metastasis and disease-specific death after PSA failure following radical prostatectomy.[8] Three variables have been identified as predictive of how long a patient may remain free of distant metastasis after PSA recurrence: Time interval to PSA elevation, Gleason sum, and PSA doubling time (PSADT).[9-11]

The objective of this study was to utilize the Department of Defense (DoD) Center for Prostate Disease Research (CPDR) Multicenter Research Database to depict the clinical course of progression after PSA recurrence. We performed a retrospective analysis in a large cohort of prostate cancer patients who were treated with radical prostatectomy from 1988 to 2002 at multiple US military medical centers by a wide variety of urologic surgeons.

PATIENTS AND METHODS

A total of 3731 localized prostate cancer patients undergoing radical prostatectomy from 1988 to 2002 was retrieved from the DoD CPDR Tri-Service Multicenter Database that is comprised of nine combined United States Army, Navy, and Air Force medical centers from across the country. None received neoadjuvant or adjuvant radiation or adjuvant hormonal therapy. The patients having positive lymph node at the time of surgery were excluded. All the patients had post-surgery follow-up for at least 6 months. Among these 3731 patients, 1399 patients developed PSA recurrence (PSA > 0.2 ng/ml). Of the 1399 men, 121 patients were excluded from further study due to lack of follow-up after PSA recurrence. The median follow-up time after PSA recurrence for the remaining 1278 patients was 4.5 years (0.5 -14.2 years). Of these 1278 men, 552 (43.2%) received salvage radiation or hormonal therapy after PSA recurrence and were included in this study.

The candidates of prognostic factors analyzed in this study included ethnicity/race, pretreatment PSA, highest biopsy Gleason sum, age at surgery, pathological stage, highest pathological Gleason sum and post-surgery PSA doubling time. PSA recurrence was defined as PSA □ 0.2 ng/ml.[9] Distant metastasis was identified via both nuclear imaging studies (bone scans) and radiographic studies (computed tomography, magnetic resonance imaging, etc.). For the 1278 patients having PSA recurrence, we used the first detectable PSA and all subsequent PSA values tested before any salvage radiation or hormonal therapy to calculate PSADT. The PSADT could be calculated only for patients with at least two valid PSA measurements. One hundred thirty-five patients had no PSADT due to insufficient PSA values. The median number

of PSA values used to calculate PSADT for the remaining 1130 patients was five. When calculating PSADT by logarithmic transformation and linear regression analysis, a PSA of zero cannot be used because the log of zero is minus infinity. Therefore, in each case in which PSA was reported as undetectable, PSA was arbitrarily assigned a value of 0.01 ng./ml. Doubling time was determined per patient by calculating the logarithm of the PSA values. A simple linear model was created using the formula: Ln(PSA) = A + B ≤ (months after PSA recurrence), where A represents the y intercept and B represents the slope of the curve. Linear regression analysis was then performed to determine the slope and intercept of the best fit curve. From this value we calculated PSADT using the formula: PSADT = Ln(2) ·B. [9-14] The PSADT values that were less than zero (stable, non-increasing, or decreasing PSA levels) and were exceptionally long (eg, >120 months) were assigned a value equal to 120 months. Given the lack of consensus in the published reports regarding appropriate cutoffs for PSADT, [15-18] we arbitrarily defined rapid PSA changes as a PSADT of less than or equal to 12 months, because it represented approximately the 25th percentile for our cohort of patients.

The Kaplan-Meier product limit method was used to estimate the probability of PSA recurrence and distant metastasis. Points estimated were obtained from the Kaplan-Meier curves. The univariate comparison of distributions was performed using a log-rank test. For the patients having PSA recurrence, the multivariate Cox proportional hazard regression analysis was used to test the relationship between distant metastasis-free survival with the other factors: pretreatment PSA, highest pathological Gleason sum, pathological stage, PSADT and the time between RP and PSA recurrence. Probability values of 0.05 or less were considered to be significant. In the Cox model, pretreatment PSA (≤ 10 vs. > 10), highest pathological Gleason sum (≤ 7 vs. > 7), pathological stage (T1 + 2 vs. T3 + 4), PSA recurrence year (≤ 2 vs. > 2) and PSADT (≤ 12 months vs. > 12 months) were categorical variables.

RESULTS

Among 3731 patients, 1399 patients (37.5%) had PSA recurrence. There were 89 (6.9%) patients who developed distant metastasis and 16 patients who died of prostate cancer. The demographic, pretreatment and pathological features of the patient cohort is summarized in Table I. Overall, 59.3% were pathological T1-2, 91.0% had a pathological Gleason grade sum ≤ 7 and 45.7% were followed up more than five years after surgery. For 1278 patients (34.3%) having PSA recurrence and adequate follow-up, 41.6% were pathological T1 - 2, 84.8% had a pathological Gleason grade sum of ≤ 7 and 43.3% were followed up more than five years after PSA recurrence. A total of 64.2% of these 1278 patients experienced the recurrence within two years of surgery and 24.1% had PSADT ≤ 12 months. Five hundred fifty-two of these patients (43.2%) received salvage radiation or hormonal treatment after PSA recurrence. The 5-year and 10-year PSA recurrence-free survival rates for all 3731 patients were 59.6% and 45.4% respectively (Figure I). The median from surgery to PSA recurrence is 7.9 years (Figure I). The time from PSA recurrence to the development of clinically evident metastasis is depicted by actuarial analysis in Figure II. There was no calculable median actuarial time to metastasis from the time of PSA level elevation due to low distant metastasis rate. The 5-year and 10-year distant metastasis-free survival rates were 92.4% and 86.3%, respectively. The 5-year and 10-year post-PSA recurrence prostate cancer-specific survival rates were 98.8% and 96.4 % (Figure III).

Univariate analysis showed that PSADT, pathological Gleason sum and pathological stage were significantly associated with distant metastasis-free survival ($p < 0.01$, Table II). Pretreatment PSA level and time from surgery to PSA recurrence were not significant predictors of distant metastasis (Table II). The significance of pathological Gleason sum on the risk of developing metastatic disease after PSA elevation was illustrated in Figure IV, showing that higher Gleason sum had poorer metastasis-free survival. Figure V demonstrated that the shorter PSADT (≤12 months) had poorer metastasis-free survival rate than longer PSADT.

Table III shows the results of multivariate Cox regression analysis. Highest pathological Gleason sum (≤ 7 vs. > 7, Hazards ratio = 2.71, p=0.0002) and PSADT (≤ 12 months vs. > 12 months, Hazards ratio = 2.39, p = 0.0006) were independent predictors of distant metastasis. Pretreatment PSA, pathological stage and PSA recurrence year were not associated with distant metastasis ($p > 0.05$). In a multivariate Cox model in which treatment after PSA recurrence (XRT or HT) was added to the above analysis to control for the effect of salvage treatment, we found that PSADT and highest pathological Gleason sum were still independent predictors of distant metastasis ($p < 0.001$), but pretreatment PSA, pathological stage and PSA recurrence year still were not (data not shown). Based on the above analysis, we constructed a nomogram to predict the likelihood of developing distant metastasis following PSA recurrence using the highest pathological Gleason sum and PSADT (Table IV).

DISCUSSION

The most important finding from this study is the seeming "disconnect" between PSA failure and the development of clinical metastasis after radical prostatectomy, indicating that early PSA recurrence did not translate into a high rate of clinical metastasis or significant risk of death from prostate cancer. Furthermore, from this large multicenter cohort (N = 3731), the median time from surgery to PSA recurrence was identified (7.9 years). There was no calculable median actuarial time to metastasis from the time of PSA level elevation due to low distant metastasis rate. The finding of high PSA recurrence rate (37.5%) and low clinical metastasis rate (7%) during the 15-year study period (1988 – 2003) indicates a significant improvement of prostate cancer clinical course in the PSA Era. In addition, we found that time to PSA recurrence was not associated with distant metastasis as reported before.[9]

The most prominent study of PSA recurrence after radical prostatectomy has been the Pound et al. experience from Johns Hopkins Hospital.[9] The Pound et al. study of 1997 men showed a low PSA recurrence rate (15%) and a high distant metastasis rate (34%) after PSA recurrence cases during a 15-year study period (1982 – 1997). Pound et al. also identified that the median actuarial time to metastasis was eight years from the time of PSA level elevation.

Why are the results from the two studies so different? Our study attempted to mirror Pound et al. by excluding any patient who had adjuvant radiation or hormones after surgery or who had neoadjuvant hormonal therapy. We used the definition of PSA recurrence as > 0.2 ng/ml as used by Pound et al. One difference between the two studies was our inclusion of men who received salvage radiation or hormonal therapy for PSA recurrence. There was a conscious effort to include these men to reflect the real world setting where many patients demand early treatment for a rising PSA. We recognized that the inclusion of these patients might alter the natural history of the disease after the PSA recurrence, resulting in our low rate of distant metastasis. However, the difference between the two studies is too great to be completely explained by the confounding

effect of salvage radiation or hormonal therapy for PSA recurrence in our overall study, especially considering the lack of consensus about the survival benefit of salvage therapy. In our study, the multivariate analysis showed an insignificant effect of salvage therapy for PSA recurrence on distant metastasis. Patient selection may, however, contribute to the difference. Our study used patients between 1988 and 2002, while Pound et al. used patients between 1982 and 1987; some patients in their cohort represented Pre-PSA Era (the PSA test became available in late 1987). It is not clear how Pound et al. included patients treated between 1982 and 1997 in a study of PSA recurrence when PSA only became available in the late 1980s. The time elapse between the early and late 1980s when PSA first became available for patients may explain the difference in the two studies.

In contrast to Pound et al. we found that the time from primary treatment to PSA recurrence was not significantly associated with distant metastasis both in univariate and multivariate analyses. This may be due to the fact that our PSA failure definition threshold was low (> 0.2 ng/ml), resulting in a "dilution effect" on the PSA recurrence, since many of these patients have a benign clinical course in short- to intermediate-term follow-up.[19] Furthermore, we included men with salvage treatment that may have delayed PSA recurrence, and lessened the impact of PSA recurrence time after primary therapy. Finally, since PSA recurrence is not necessarily associated with distant recurrence, the effect of time to PSA recurrence on distant failure was not evident.

There are a number of other comparisons to other recent studies that deserve comment. The Johns Hopkins group recently updated their experience.[20] Han et al. studied 2091 radical prostatectomy patients finding 360 men (17%) having PSA recurrence with a median follow-up of 5.9 years (range 1 to 17); the 5-year and 10-year PSA recurrence-free survival rates were 84% and 72%. These single-center results regarding biochemical outcome are superior to our multicenter, broad-based study. In our study, there were 89 (6.96%) patients who developed distant metastasis out of a total of 1278 patients having PSA recurrence with the median follow-up of approximately 4.5 years. This was similar to the recent study by Roberts et al. from the Mayo Clinic.[21] For the time interval from RP to PSA recurrence, 64.2% of men in our study developed a PSA failure (>0.2ng/ml) within two years after surgery. This rate was higher than other reports. [9, 21]

In the univariate analysis using the Kaplan-Meier product limit method and multivariate Cox proportional hazard regression analysis, we found that PSADT and pathological Gleason sum were the most significant variables to predict distant metastasis. Pathological stage was significant in the univariate analysis, not significant in multivariate analysis after controlling for other variables. Pretreatment PSA and PSA recurrence timing after primary therapy had no relationship with distant metastasis both in univariate and multivariate analysis. Patients with a PSADT of less than or equal to 12 months had a 5-year metastasis-free survival rate of only 83.3%. In contrast, the 5-year freedom from metastasis with a PSADT of longer than one year was 95.3%. Patients with a pathological Gleason sum of less than or equal to seven had a 5-year metastasis-free survival rate of 93.9%. In contrast, the 5-year freedom from metastasis with a pathological Gleason sum of more than seven was only 84.2%. Using the highest pathological Gleason sum and PSADT, we constructed a nomogram to predict the likelihood of developing distant metastasis following PSA recurrence. Pound et al.[9] combined PSADT, Gleason score, and time to PSA recurrence in an algorithm to predict a man's likelihood of developing metastatic disease. Robert et al.'s study [21] indicated that actual follow-up PSA data allowing calculation of

the PSADT provides an excellent way to predict the likelihood of early clinical progression after a PSA failure[21].

There are a number of limitations to our study. By eliminating the patients who received neoadjuvant hormonal therapy and adjuvant radiation for positive margins, we selected out many men with higher risk of metastatic features. However, we did this in an attempt to pattern our study after Pound et al. to make meaningful comparisons to that investigation. We also used a PSA value > 0.2 ng/ml to define PSA progression as in the Pound et al. study. Amling et al. found that a PSA of > 0.2 ng/ml may not be optimal and suggested a PSA > 0.4 ng/ml to define recurrence.[19] Specifically, Amling et al. found that if 0.2 ng/ml is used, only approximately 50% of patients show clear PSA rise in the three years after 0.2 ng/ml is reached. However, Freedland et al. found that > 0.2 ng/ml was a valid definition of PSA progression.[22] It must be noted that our use of > 0.2 ng/ml resulted in a higher rate of PSA progression than if we had used a definition of > 0.4 ng/ml and some of these "low-level" PSA recurrence cases may have a very benign course. This would invariably be responsible for some of the variability between PSA progression and clinical metastasis. Finally, it may be argued that the patients who received salvage radiation or hormones due to PSA recurrence should not have been included in the study. However, eliminating these men would have created an artificial clinically-meaningless study because so many contemporary men with PSA recurrence do, in fact, get treated prior to clinical metastasis. Future study will further evaluate the role that early hormonal therapy plays in delaying clinical metastasis and improving survival in this cohort.

CONCLUSIONS

Biochemical progression (PSA > 0.2 ng/ml) occurred in greater than one-third (37.5%) of PSA Era radical prostatectomy patients from a broad, multicenter experience. Despite the high rate of biochemical progression, there was a low rate of progression to clinical metastasis and very low rate of death from prostate cancer. Pathological Gleason sum and PSA doubling time were significant independent predictors of distant metastasis for patients having PSA recurrence. These findings may benefit the identification of high-risk patients as candidates for early clinical intervention.

REFERENCES

1. Farkas A, Scheider D, Perrotti M, Cummings KB, and Ward WS: National trends in the epidemiology of prostate cancer, 1973 to 1974: Evidence for the effectiveness of prostate-specific antigen screening. Urol 52:444, 1998

2. Ellison LM, Heaney JA, Birkmeyer JD: Trends in the use of radical prostatectomy for treatment of prostate cancer. Eff Clin Pract 2:228-233, 1999

3. Pound CR, Partin AW, Epstein JI, Walsh PC. Prostate-specific antigen after anatomic radical retropubic prostatectomy: patterns of recurrence and cancer control. Urol Clin North Am 24:395-406, 1997

4. Zincke H, Oesterling JE, Blute ML, Bergstralh EJ, Myers RP, Barrett DM. Long-term (15 years) results after radical prostatectomy for clinically localized (stage T2c or lower) prostate cancer. J Urol 152:1850-1857, 1994

5. Trapasso JG, Dekernion JB, Smith RB, Dorey F. The incidence and significance of detectable levels of serum prostate specific antigen after radical prostatectomy. J Urol 152:1821-1825, 1994

6. Catalona WJ, Smith DS. 5-year tumor recurrence rates after anatomical radical retropubic prostatectomy for prostate cancer. J Urol 152:1837-1842, 1994

7. Ohori M, Goad JR, Wheeler TM, et al. Can radical prostatectomy alter the progression of poorly differentiated prostate cancer? J Urol 152:1843-1849, 1994

8. Amling CL, Blute ML, Bergstralh EJ, Seay TM, Slezak J, Zincke H. Long-term hazard of progression after radical prostatectomy for clinically localized prostate cancer: continued risk of biochemical failure after 5 years. J Urol 164:101-105, 2000

9. Pound CR, Partin AW, Eisenberger MA, Chan DW, Pearson JD, Walsh PC. Natural history of progression after PSA elevation following radical prostatectomy. JAMA 281:1591-1597, 1999

10. Patel A, Dorey F, Franklin J, et al. Recurrence patterns after radical retropubic prostatectomy: clinical usefulness of prostate specific antigen doubling times and log slope prostate specific antigen. J Urol 158:1441-1445, 1997

11. Pruthi RS, Johnstone I, Tu IP, Stamey TA. Prostate-specific antigen doubling times in patients who have failed radical prostatectomy: correlation with histologic characteristics of the primary cancer. Urology 49:737-742, 1997

12. Kakehi Y, Kamoto T, Shiraishi T, et al. Correlation of initial PSA level and biopsy features with PSA-doubling time in early stage prostate cancers in Japanese men. Euro Urol 41:47-53, 2002

13. Stephenson A, Aprikian AG, Souhami L, et al. Utility of PSA doubling time in follow-up of untreated patients with localized prostate cancer. Urology 59:652-656, 2002

14. Soergel TM, Koch MO, Foster RS, et al. Accuracy of predicting long-term prostate specific antigen outcome based on early prostate-specific antigen recurrence results after radical prostatectomy. J Urol 166:2198-2201, 2001

15. Egawa S, Matsumoto K, Suyama K, et al: Observations of prostate-specific antigen doubling time in Japanese patients with nonmetastatic prostate carcinoma. Cancer 86:463-469, 1999

16. Hanks GE, Hanlon AL, Lee WR, et al: Pretreatment prostate-specific antigen doubling times: clinical utility of this predictor of prostate cancer behavior. Int J Radiat Oncol Biol Phys 34:549-553, 1996

17. Nam RK, Klotz LH, Jewett MAS, et al: Prostate-specific antigen velocity as a measure of the natural history of prostate cancer: defining a 'rapid riser' subset. Br J Urol 81:100-104, 1998

18. McLaren DB, McKenzie M, Duncan G, et al: Watchful waiting or watchful progression? Prostate-specific antigen doubling times and clinical behavior in patients with early untreated prostate carcinoma. Cancer 82:342-348, 1998

19. Amling CL, Bergstralh EJ, Blute ML, Slezak JM. Defining prostate-specific antigen progression after radical prostatectomy: what is the most appropriate cut point? J Urol 165:1146-1151, 2001.

20. Han M, Partin AW, Zahurak M, Piantadosi S, Epstein JI, Walsh PC. Biochemical (prostate-specific antigen) recurrence probability following radical prostatectomy for clinically localized prostate cancer. J Urol 169:517-23, 2003

21. Roberts SG, Blute ML, Bergstralh EJ, Slezak JM, Zincke H. PSA doubling time as a predictor of clinical progression after biochemical failure following radical prostatectomy for prostate cancer. Mayo Clin Proc 76:576-81, 2001

22. Jhaveri FM, Zippe CD, Klein EA, Kupelian PA. Biochemical failure does not predict overall survival after radical prostatectomy for localized prostate cancer: 10 year results. Urology 54:884-890, 1999

LEGENDS

Table I. Demographic, clinical and pathological characteristics of different cohorts of patients.

Figure I. Actuarial PSA recurrence-free survival following surgery for radical prostatectomy patients (N = 3731).

Figure II. Actuarial distant metastasis-free survival following PSA recurrence for patients with PSA recurrence (N = 1278).

Figure III. Actuarial prostate cancer-specific survival following PSA recurrence (N = 1278).

Table II. Univariate analysis on the correlation between selected factors and distant metastasis.

Figure IV. Higher pathological Gleason sum (>7) had poorer distant metastasis-free survival than lower Gleason sum (≤7).

Figure V. Shorter PSADT (≤12 months) had poorer metastasis-free survival rate than longer PSADT (>12 months).

Table III. Multivariate Cox proportional hazards model for predictors of distant metastasis.

Table IV. Nomogram for estimating the likelihood of remaining free of distant metastasis using pathologic Gleason sum and PSADT.

Table I. Demographic, clinical and pathological characteristics of study group.

	RP cohort No. (%)	PSA recurrence cohort No. (%)
Total No.	3731	1278
Surgery age		
□ 60	1159 (31.0)	328(25.7)
60.1 - 70	2058 (55.2)	738(57.7)
□ 70	514 (13.8)	212(16.6)
Mean/Median	62.7/63.5	63.7/64.3
Race		
Caucasian and others	2947 (80.6)	973(77.8)
African-American	709 (19.4)	278(22.2)
Pretreatment PSA		
≤ 4	834 (23.7)	169(14.3)
4.1-10	1916 (54.4)	593(50.3)
10.1-20	565 (16.0)	280(23.8)
> 20	206 (5.9)	137(11.6)
Mean/Median	8.4 / 6.0	11.5/7.5
Pathological stage		
T 2	2087 (59.3)	505(41.6)
T3 + 4	1431(40.7)	709(58.4)
Pathological Gleason sum		
≤ 4	315(9.2)	105(9.1)
5 - 6	1640(47.8)	439(37.9)
7	1170(34.1)	438(37.8)
8 - 10	309(9.0)	176(15.2)
Years of follow-up after RP		NA
0.5 - 2	815(21.9)	
2.1 - 5	1210(32.4)	
5.1 - 10	1314(35.2)	
> 10	392(10.5)	
Mean/Median	5.2 / 4.5	
PSA recurrence year	NA	
≤ 2		821(64.2)
2.1 - 5		328(25.7)
5.1 - 10		123(9.6)
> 10		6(0.5)
PSA doubling time (months)	NA	
≤ 12		275(24.1)
> 12		868(75.9)
Mean/Median		67.6/67.2
Years of follow-up after PSA recurrence	NA	
0.5 - 2		277(21.7)
2.1 - 5		448(35.0)
5.1 - 10		474(37.1)
> 10		79(6.2)
Mean/Median		4.8 / 4.5

Figure I. Actuarial PSA recurrence-free survival following surgery for radical prostatectomy patients (N = 3731).

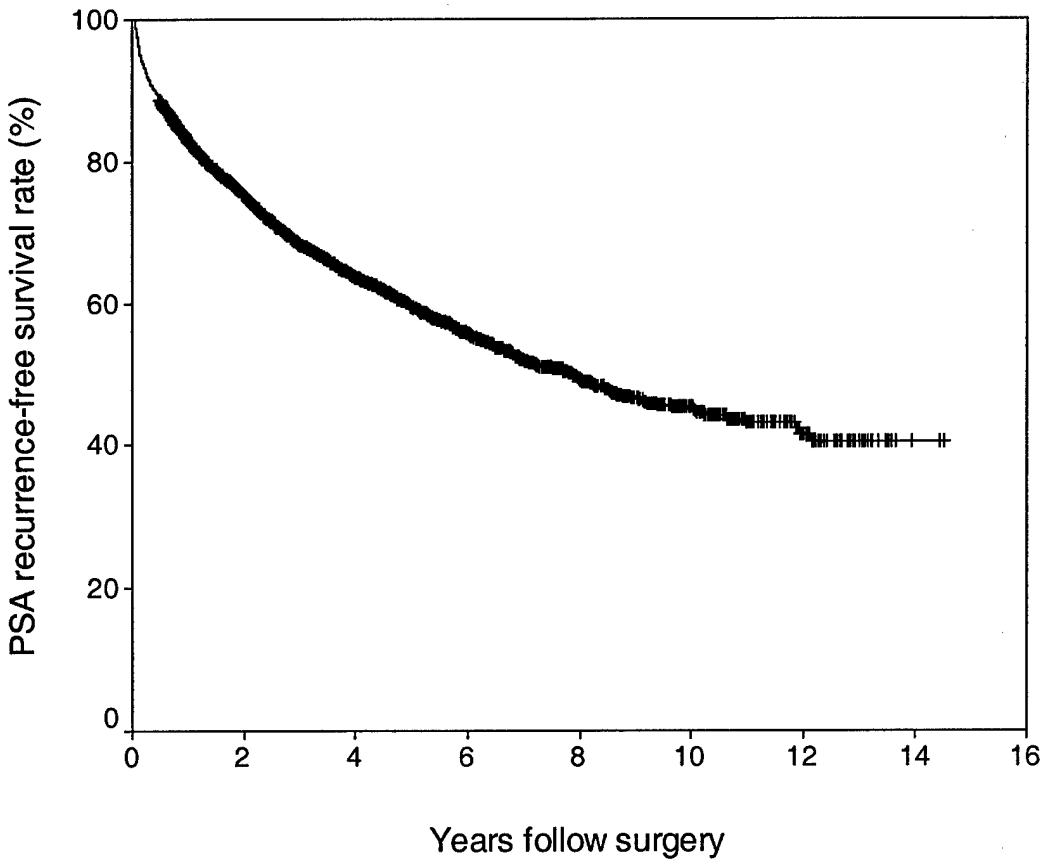


Figure II. Actuarial distant metastasis-free survival following PSA recurrence for patients with PSA recurrence (N = 1278).

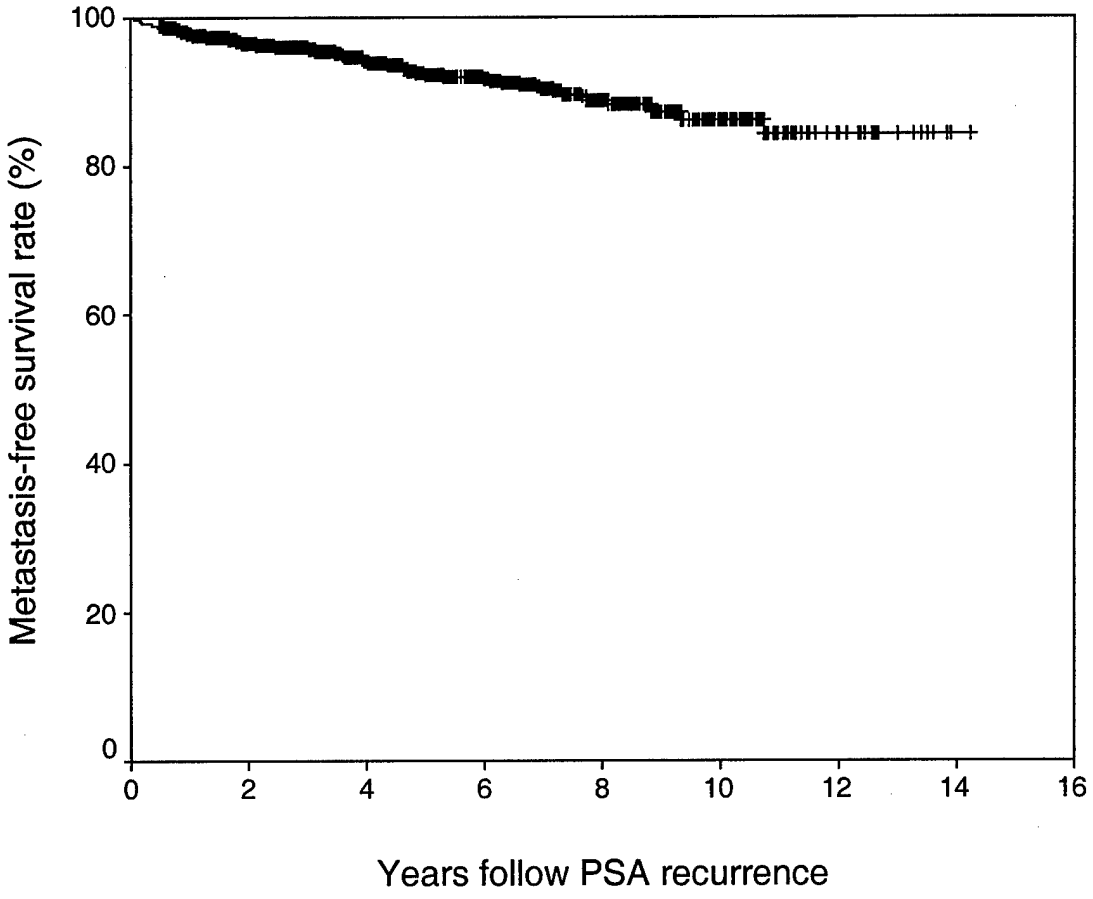


Figure III. Actuarial prostate cancer-specific survival following PSA recurrence (N = 1278).

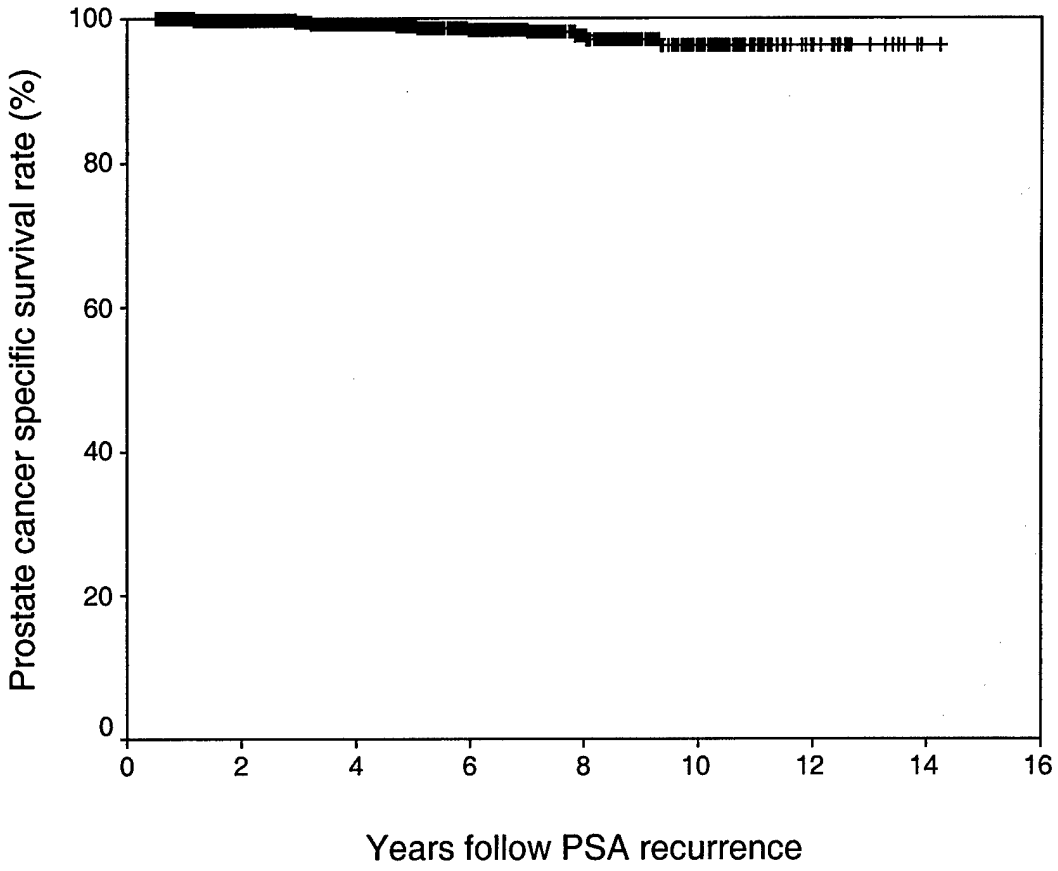


Table II. Univariate analysis on the correlation between selected factors and distant metastasis.

Factor	No. of patients	5-year metastasis-free survival rate (%)	10-year metastasis-free survival rate (%)	p value
Pathologic Gleason Sum				<0.0001
≤ 7	1022	93.9	89.4	
> 7	176	84.2	69.7	
PSADT (months)				<0.0001
≤ 12	275	83.3	76.9	
> 12	868	95.3	90.1	
Pathologic stage				0.005
PT2	505	95.6	91.6	
pT3 + 4	709	90.4	83.5	
PSA recurrence year				0.741
≤ 2	821	92.9	86.5	
> 2	457	91.3	84.7	
Pretreatment PSA (ng/ml)				0.280
≤ 10	762	92.6	90.1	
> 10	417	91.4	82.4	

PSADT: Prostatic-specific antigen doubling time

Figure IV. Higher pathological Gleason sum (> 7) had poorer distant metastasis-free survival than lower Gleason sum (≤ 7).

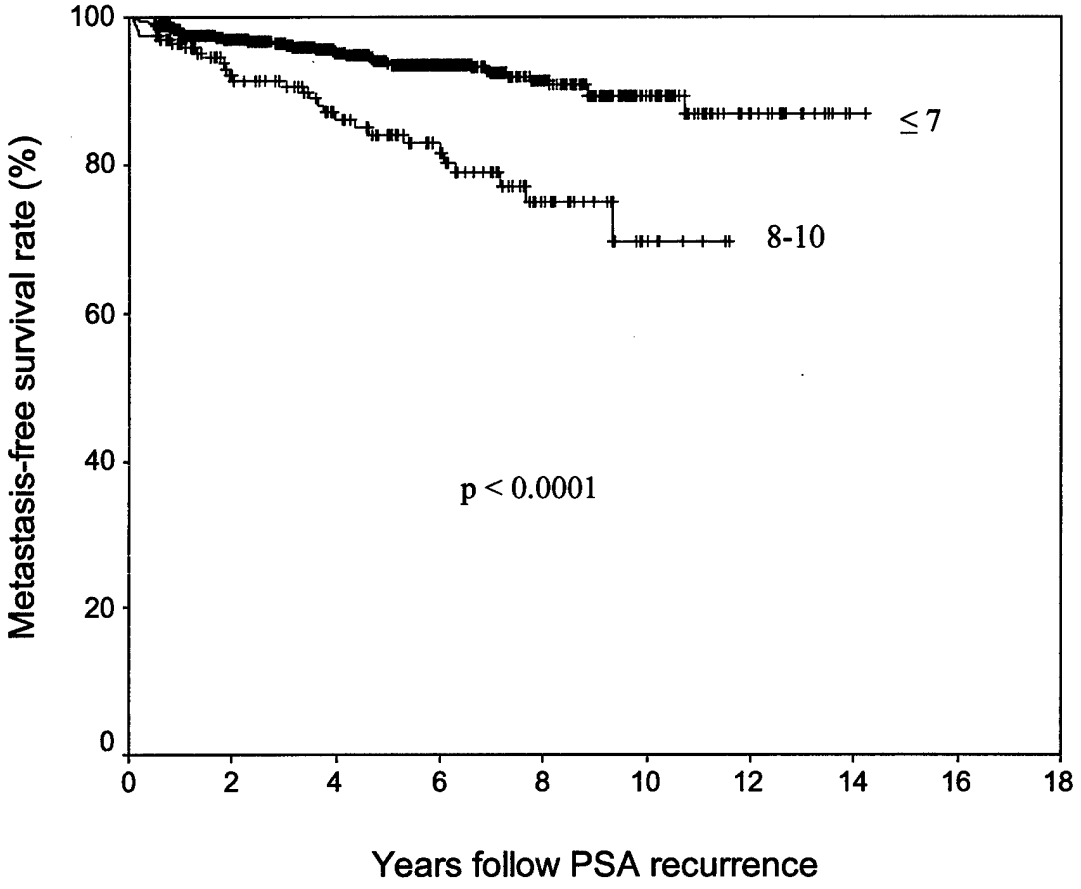


Figure V. Shorter PSADT (≤ 12 months) had poorer metastasis-free survival rate than longer PSADT (> 12 months).

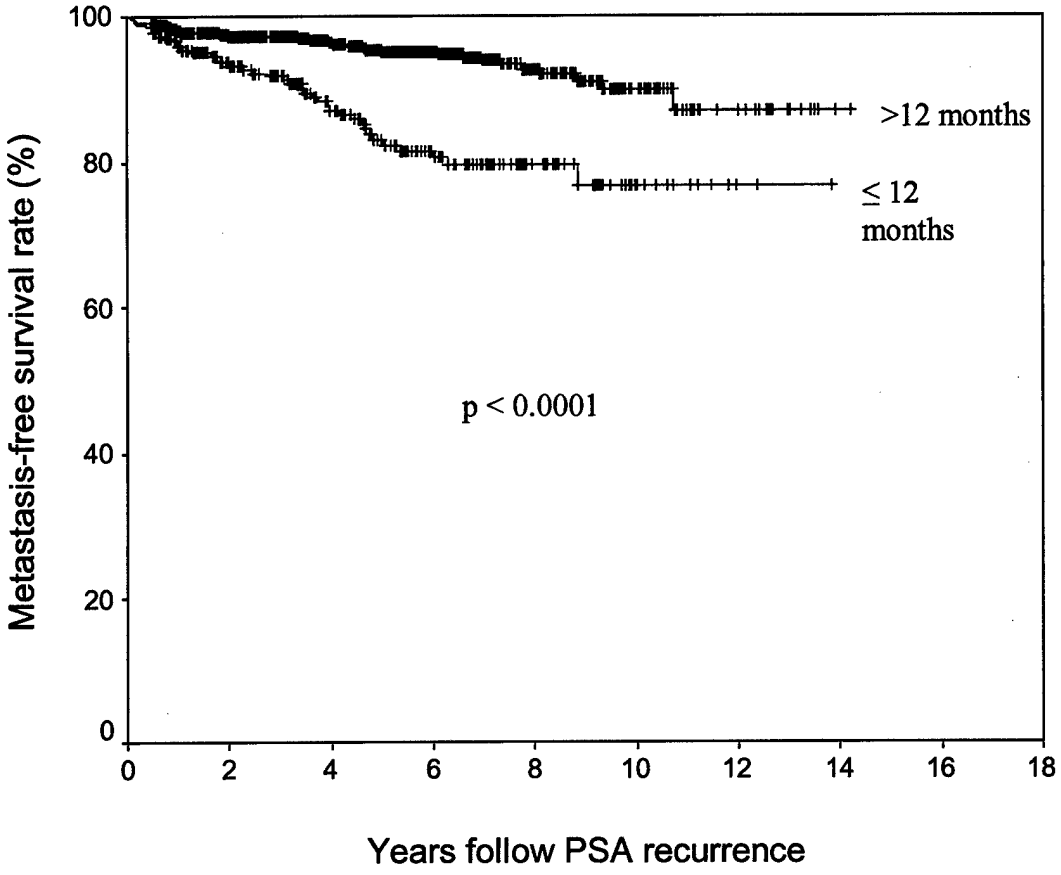


Table III. Multivariate Cox proportional hazards model for predictors of distant metastasis.

	Hazards Ratio	95% CI	p value
Pathological Gleason sum			
> 7 vs. ≤ 7	2.71	1.61-4.55	0.0002
PSA doubling time			
≤ 12 vs. > 12	2.39	1.45-3.95	0.0006
PSA recurrence year			
> 2 vs. ≤2	1.43	0.85-2.40	0.175
Pathological stage			
T3 + 4 vs. T1 + 2	1.26	0.72-2.21	0.426
Pretreatment PSA (ng/ml)			
> 10 vs. ≤10	1.15	0.71-1.87	0.572

Table IV. Nomogram for estimating the likelihood of remaining free from distant metastasis using pathologic Gleason sum and PSADT.

Factor	3-year metastasis-free survival rate and 95% CI (%)	5-year metastasis-free survival rate and 95% CI (%)	10-year metastasis-free survival rate and 95% CI (%)
Pathologic Gleason Sum ≤7			
PSADT (months)			
> 12	97.9 (96.8-98.0)	96.3 (94.7-97.9)	92.2 (88.5-95.9)
≤ 12	91.8 (87.7-95.9)	85.7 (79.8-91.6)	80.5 (70.8-90.2)
Pathologic Gleason Sum >7			
PSADT (months)			
> 12	91.8 (85.5-98.1)	83.7 (74.1-93.3)	70.4 (49.6-91.2)
≤ 12	89.2 (80.9-97.5)	77.9 (65.3-90.5)	68.0 (52.8-83.2)

PSADT: Prostatic-specific antigen doubling time

APPENDIX 6

Cancer-Specific Mortality After Surgery or Radiation for Patients With Clinically Localized Prostate Cancer Managed During the Prostate-Specific Antigen Era

By Anthony V. D'Amico, Judd Moul, Peter R. Carroll, Leon Sun, Deborah Lubeck, and Ming-Hui Chen

Purpose: To determine whether pretreatment risk groups shown to predict time to prostate cancer–specific mortality (PCSM) after treatment at a single institution retained that ability in a multi-institutional setting.

Patients and Methods: From 1988 to 2002, 7,316 patients treated in the United States at 44 institutions with either surgery (n = 4,946) or radiation (n = 2,370) for clinical stage T1c-2, N0 or NX, M0 prostate cancer made up the study cohort. A Cox regression analysis was performed to determine the ability of pretreatment risk groups to predict time to PCSM after treatment. The relative risk (RR) of PCSM and 95% confidence intervals (CIs) were calculated for the intermediate- and high-risk groups relative to the low-risk group.

Results: Estimates of non-PCSM 8 years after prostate-specific antigen (PSA) failure were 4% v 15% (surgery versus radiation; $P_{log\ rank}$ = .002) compared with 13% v 18% (surgery versus radiation; $P_{log\ rank}$ = .35) for patients whose age at the time of PSA failure was less than 70 as compared with ≥ 70 years, respectively. The RR of PCSM after treatment for surgery-managed patients with high- or intermediate-risk disease was 14.2 (95% CI, 5.0 to 23.4; P_{Cox} < .0001) and 4.9 (95% CI, 1.7 to 8.1; P_{Cox} = .0037), respectively. These values were 14.3 (95% CI, 5.2 to 24.0; P_{Cox} < .0001) and 5.6 (95% CI, 2.0 to 9.3; P_{Cox} = .0012) for radiation-managed patients.

Conclusion: This study provided evidence to support the prediction of time to PCSM after surgery or radiation on the basis of pretreatment risk groups for patients with clinically localized prostate cancer managed during the PSA era.

J Clin Oncol 21:2163-2172. © *2003 by American Society of Clinical Oncology.*

THE INTRODUCTION of the serum prostate-specific antigen (PSA) test has changed the presentation of prostate cancer worldwide. Patients now present at a younger age and with lower-grade disease and are more likely to have organ-confined cancers found on pathologic evaluation of the radical prostatectomy specimen.[1] These more favorable clinical and pathologic findings have translated into longer time intervals to PSA failure after either surgical or radiotherapeutic management. Algorithms for predicting PSA outcome after radical prostatectomy (RP) or external-beam radiation therapy (RT) that are based on pretreatment clinical parameters have been validated.[2-4] However, given the competing causes of mortality that exist in men undergoing definitive treatment for localized prostate cancer, many men who sustain PSA failure will not live long enough to develop clinical evidence of distant disease, and far fewer will die from the disease. Although pretreatment risk-based staging systems predicting the end point of prostate cancer–specific mortality (PCSM)[5,6] have been published, none has been validated in the PSA era.

The purpose of this study was to assess whether a pretreatment risk-based staging system that has been shown to predict PCSM after RT delivered at a single institution can also predict PCSM after RP or RT using data gathered from patients treated at 44 institutions during the PSA era. RT and hormonal therapy are now the accepted standard treatments for patients with locally advanced prostate cancer because of the survival benefit shown in a randomized trial;[7] therefore, the focus of this report in which RT was delivered as monotherapy will be on patients with clinically localized disease managed during the PSA era.

PATIENTS AND METHODS

Patient Selection and Treatment

Two multi-institutional databases containing baseline, treatment, and follow-up information on 7,316 men treated with either RP (n = 4,946) or RT (n = 2,370) between 1988 and 2002 at 44 institutions within the United States for clinical stage T1c-2, N0 (RP) or NX (RT), M0 prostate cancer (using the tumor-node-metastasis system of classification) comprised the data with which this study was performed. These two databases included patients from the Cancer of the Prostate Strategic Urologic Research Endeavor[8] and the Center for Prostate Disease Research.[9] The study was

From the Department of Radiation Oncology, Brigham and Women's Hospital and Dana-Farber Cancer Institute, Boston, MA; Department of Surgery and Urology Service, Center for Prostate Disease Research, Uniformed Service University and Walter Reed Army Medical Center, Rockville, MD; Department of Urology, University of California, San Francisco, CA; and Department of Statistics, University of Connecticut, Storrs, CT.

Submitted January 13, 2003; accepted March 17, 2003.

Supported in part by the Department of Defense Center for Prostate Disease Research funded by the United States Army Medical Research and Material Command, Fort Detrick, MD. Cancer of the Prostate Strategic Urologic Research Endeavor is sponsored by TAP Pharmaceuticals Products Inc, Lake Forest, IL, and managed by the Urology Outcomes Research Group at the University of California, San Francisco, CA.

The opinions and assertions contained herein are the private views of the authors and are not to be construed as reflecting the views of the United States Army or Department of Defense.

Address reprint requests to Anthony V. D'Amico, MD, PhD, Brigham and Women's Hospital, Department of Radiation Oncology, 75 Francis St, L-2 Level, Boston, MA 02215; email: adamico@lroc.harvard.edu.

0732-183X/03/2111-2163/$20.00

performed with permission from the human protection committees at each of the individual institutions. To be eligible for study entry, RP-managed patients were permitted to have received up to 3 months of neoadjuvant androgen suppression therapy (AST), given that the 5-year results of a randomized trial[10] have shown no significant effect on cancer control from the addition of 3 months of neoadjuvant AST to RP. The median age of the RP- and RT-managed patients at the time of initial therapy was 63.5 (range, 34.3 to 98.8 years) and 71.3 years (range, 40.5 to 98.3 years), respectively. RP-managed (n = 75) and RT-managed (n = 277) patients with clinical stage T3 or T4 disease were excluded. In addition, any patient with clinical stage T1 or T2 disease who received adjuvant therapy was also excluded (n = 312). The pretreatment clinical characteristics of all patients stratified by the treatment received are shown in Table 1.

Staging

In all patients, staging evaluation involved a history and physical examination including a digital rectal exam (DRE), serum PSA, and transrectal ultrasound-guided needle biopsy of the prostate with Gleason score histologic grading.[11] Patients whose cancer was diagnosed during a transurethral resection of the prostate were excluded. The prostate biopsy was performed using an 18-gauge Tru-Cut needle via a transrectal approach. Before 1996, patients generally had a computerized tomographic scan of the pelvis and bone scan. After 1996, patients with both a pretreatment PSA level less than 10 ng/mL and a biopsy Gleason score of 6 or less did not generally undergo radiologic staging because there was less than a 1% chance that these studies would reveal metastatic disease.[12] The clinical stage was obtained from the DRE findings using the 2002 American Joint Commission on Cancer (AJCC) staging system.[13] Radiologic and biopsy information were not used to determine clinical stage. All PSA measurements were made using the Hybritech (San Diego, CA), Tosoh (Foster City, CA), or Abbott (Chicago, IL) assays.

Table 1. Percentage Distribution of the Pretreatment Clinical Characteristics of the 4,946 Surgery- and 2,370 Radiation-Managed Patients Making Up the Study Cohort

Clinical Characteristic	Surgery (n = 4,946; %)	Radiation (n = 2,370; %)	P_{χ^2}
PSA, ng/mL			
≤ 4	17	10	
> 4-10	59	48	< .0001
> 10-20	17	26	
> 20	7	15	
Biopsy Gleason score			
≤ 6	74	60	
7	21	28	< .0001
8-10	5	12	
2002 AJCC Category			
T1c	40	36	
T2a	34	33	
T2b	21	22	< .0001*
T2c	5	9	
Age, years†			
< 50	4	1	
50-59	27	6	
60-64	28	13	< .0001
65-69	27	22	
70-74	12	34	
75-79	1	20	
≥ 80	< 1‡	4	

Abbreviations: PSA, prostate-specific antigen; AJCC, American Joint Commission on Cancer.

*χ^2 $P < .0001$ despite small numerical differences because of large sample size.

†Age at the time of initial therapy.

‡Percentages may not sum to 100 because of rounding (0.3%).

Follow-Up

The median follow-up for the entire study cohort of 4,946 and 2,370 RP- and RT-managed patients was 4.1 (range, 0.5 to 14.3 years) and 4.4 years (range, 0.8 to 14.3 years), respectively, using the first day of treatment as time zero. For those patients who sustained PSA failure, the median follow-up was 3.9 (range, 0.5 to 12.1 years) and 3.4 years (range, 0.4 to 12.0 years) for RP- and RT-managed patients, respectively, from the date of PSA failure. Before PSA failure, which was defined using the American Society for Therapeutic Radiology and Oncology consensus criteria,[14] patients generally had a serum PSA measurement and DRE performed every 3 months for 2 years, then every 6 months for 3 additional years, and then annually thereafter. A total of 243 deaths occurred after PSA failure was sustained, 157 (102 after RT and 55 after RP) of which were from prostate cancer. No patient died as a result of prostate cancer before PSA failure. The determination of the cause of death was made using death certificates.

Statistical Methods

A Cox regression analysis[15] was used to determine whether the pretreatment risk group (high or intermediate *v* low risk), initial therapy (RT *v* RP), or age at the time of PSA failure (continuous) predicted the time to non-PCSM after PSA failure. For the purpose of illustration, the Cox regression analysis was repeated, defining age at the time of PSA failure as a categorical variable (< 70 *v* ≥ 70 years) to assess whether patients younger than age 70 years selected for RT as compared with RP generally had a higher incidence of competing causes of non–prostate cancer mortality. For these three Cox regression analyses, time zero was defined as the date of PSA failure.

A Cox regression analysis[15] was also performed to determine the ability of the pretreatment risk groups[3] to predict time to PCSM after initial therapy. For the Cox regression analyses, time zero was defined as the day of RP or the last day of RT. The relative risk (RR) of PCSM with 95% confidence intervals (CIs) were calculated for each risk group; the value RR = 1.0 was assigned to the low-risk category. The RR was derived from the coefficients of the Cox model, and the 95% CIs were calculated using a bootstrapping technique[16] with 2,000 replications.

Finally, a Cox regression analysis[15] was also used to determine whether the presence of one, any two, or all three factors that defined intermediate risk affected the time to PCSM after initial therapy. For this analysis, patients with a PSA more than 10 to 20 ng/mL were selected as the baseline group.

For all analyses, the assumptions of the Cox model were tested and satisfied. Estimates of PCSM and non-PCSM were calculated using the cumulative incidence method.[17] Comparisons of PCSM and non-PCSM were evaluated using a log-rank *P* value. The Bonferroni correction[15] was used in the case of multiple comparisons to assess for clinical significance (ie, a significant *P* value was defined as $P < .05/n$, where n is the number of comparisons).

The risk groups were defined using the pretreatment serum PSA level, biopsy Gleason score, and 2002 AJCC tumor category. Specifically, low-risk patients had a PSA level of 10 ng/mL or less, a biopsy Gleason score of 6 or less, and 2002 AJCC category T1c or T2a disease. Intermediate-risk patients

Table 2. *P* Values of the Cox Regression Multivariable Analyses Evaluating Whether the Pretreatment Risk Group (High or Intermediate *v* Low), Initial Therapy (Radiation *v* Surgery), or Age at the Time of PSA Failure ($Age_{PSA\ failure}$) Predicted the Time to Non–Prostate Cancer-Specific Mortality After PSA Failure

Predictor	All Patients	$Age_{PSA\ failure}$ < 70 years	$Age_{PSA\ failure}$ ≥ 70 years
Pretreatment risk group	.58	.67	.68
$Age_{PSA\ failure}$ (continuous)	.0001	.0001	.0001
Initial therapy	.03	.007	.58

Abbreviation: PSA, prostate-specific antigen.

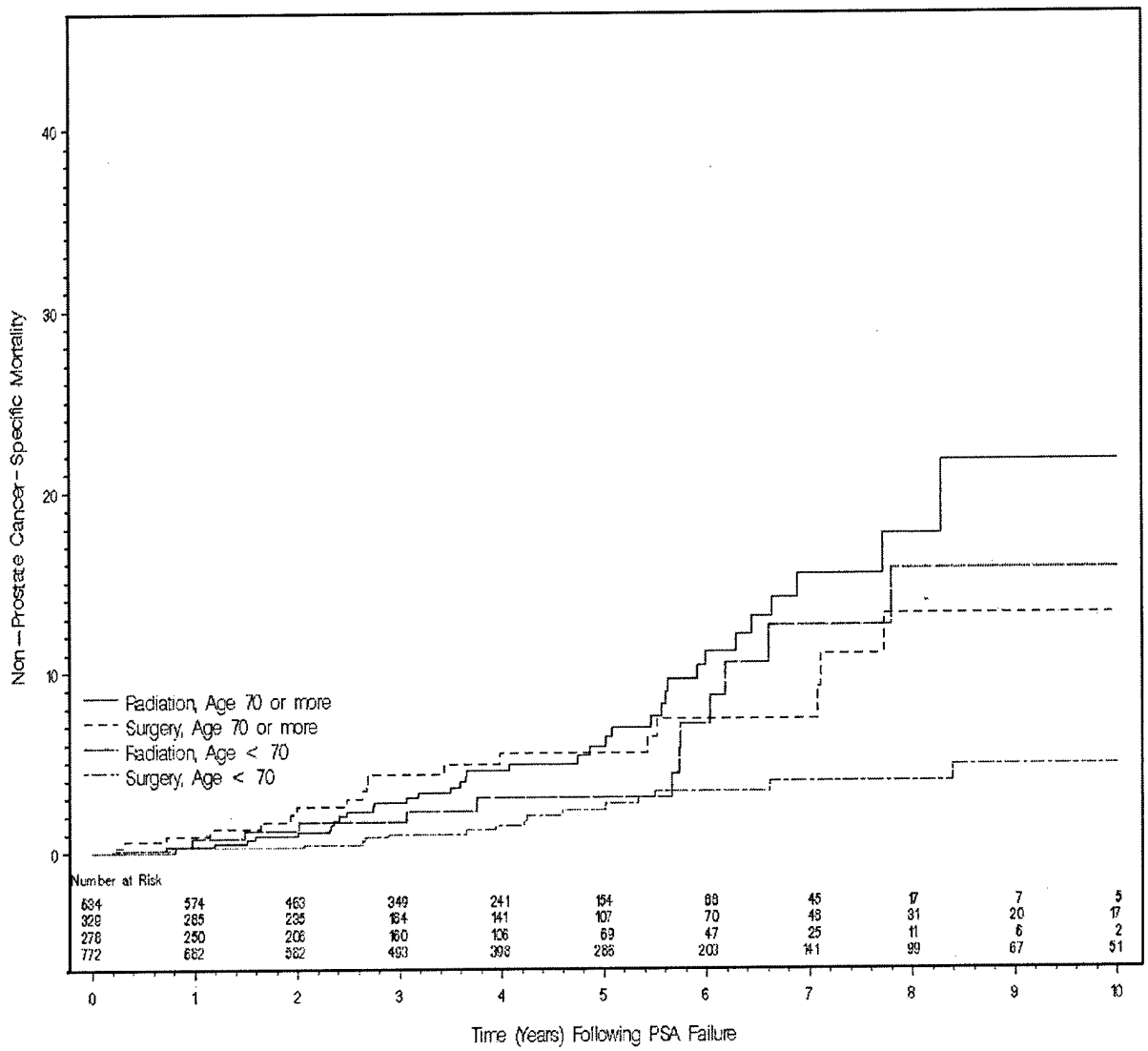


Fig 1. Non–prostate cancer–specific mortality after prostate-specific antigen (PSA) failure stratified by age at the time of PSA failure and initial therapy received. Pairwise *P* values (clinical significance[15] defined as $P < 0.05/6$ or 0.008). All ages are in years. Surgery, age ≥ 70 versus radiation, age ≥ 70; $P = .35$. Surgery, age < 70 versus radiation, age < 70; $P = .002$. Surgery, age ≥ 70 versus surgery, age < 70; $P = .002$. Radiation, age ≥ 70 versus radiation, age < 70; $P = .36$. Radiation, age ≥ 70 versus surgery, age < 70; $P < .0001$. Radiation, age < 70 versus surgery, age ≥ 70; $P = .93$.

had a PSA of more than 10 ng/mL and not more than 20 ng/mL, a biopsy Gleason score of 7, or 2002 AJCC category T2b disease. Finally, high-risk patients had a PSA more than 20 ng/mL, a biopsy Gleason score of 8 to 10, or 2002 AJCC category T2c disease.

Plots of PCSM and non-PCSM are displayed stratified by the initial therapy (RP or RT), the patient's age at the time of initial therapy (< 60, 60 to 64, 65 to 69, and ≥ 70 years), and the pretreatment risk group (low, intermediate, or high).

RESULTS

Rates of Competing Causes of Mortality After PSA Failure

As noted in Table 1, the pretreatment clinical characteristics were less favorable ($P < .0001$), and age at the time of initial therapy was more advanced ($P < .0001$) for RT-managed as compared with RP-managed patients. These differences were

Table 3. Relative Risk (RR) and 95% Confidence Intervals (CIs) of Prostate Cancer–Specific Mortality After Initial Therapy Stratified by the Treatment Received and Pretreatment Risk Group

	Surgery			Radiation		
Risk Group	RR	95% CI	P_{Cox}	RR	95% CI	P_{Cox}
Low	1.0			1.0		
Intermediate	4.9	1.7 to 8.1	.0037	5.6	2.0 to 9.3	.0012
High	14.2	5.0 to 23.4	< .0001	14.3	5.2 to 24.0	< .0001

Table 4. Results (P values) of the Cox Regression Multivariable Analysis Evaluating Whether the Presence of One, Any Two, or All Three Factors That Define Intermediate Risk Predicted the Time to Prostate Cancer–Specific Mortality After Initial Therapy

Predictor	Surgery	Radiation
PSA > 10-20 ng/mL	Baseline	Baseline
Biopsy Gleason score 7	.12	.69
Clinical category T2b	.24	.35
Any two of the three factors	.12	.12
All three factors	.006*	.13

Abbreviation: PSA, prostate-specific antigen.
*The statistical significance of this result did not depend on the choice of the baseline group.

reflected in the increased observed death rate after PSA failure in the RT-managed cohort. Specifically, among RP- and RT-managed patients who experienced PSA failure, 8% and 17% have died, respectively. Age at the time of PSA failure (P_{Cox} = .001) and initial therapy (P_{Cox} = .03) were significant predictors of time to non-PCSM after PSA failure, whereas the pretreatment risk group was not (P_{Cox} = .58), as noted in Table 2. When the predictors of time to non-PCSM were analyzed using Cox regression for patients less than age 70 years at the time of PSA failure, men treated with RT had a shorter time to non-PCSM compared with RP-managed patients (P_{Cox} = .007), whereas initial therapy was not a significant predictor (P_{Cox} = .58) of time to non-PCSM in patients who were 70 years or older at the time of PSA failure. These findings are summarized in Table 2. To illustrate that RT-managed patients younger than age 70 years were generally less healthy than similarly aged RP-managed patients, Fig 1 displays the estimates of non-PCSM 8 years after PSA failure stratified by age at the time of PSA failure and initial therapy. Specifically, these rates were $4\%_{RP}$ *v* $15\%_{RT}$ ($P_{log\ rank}$

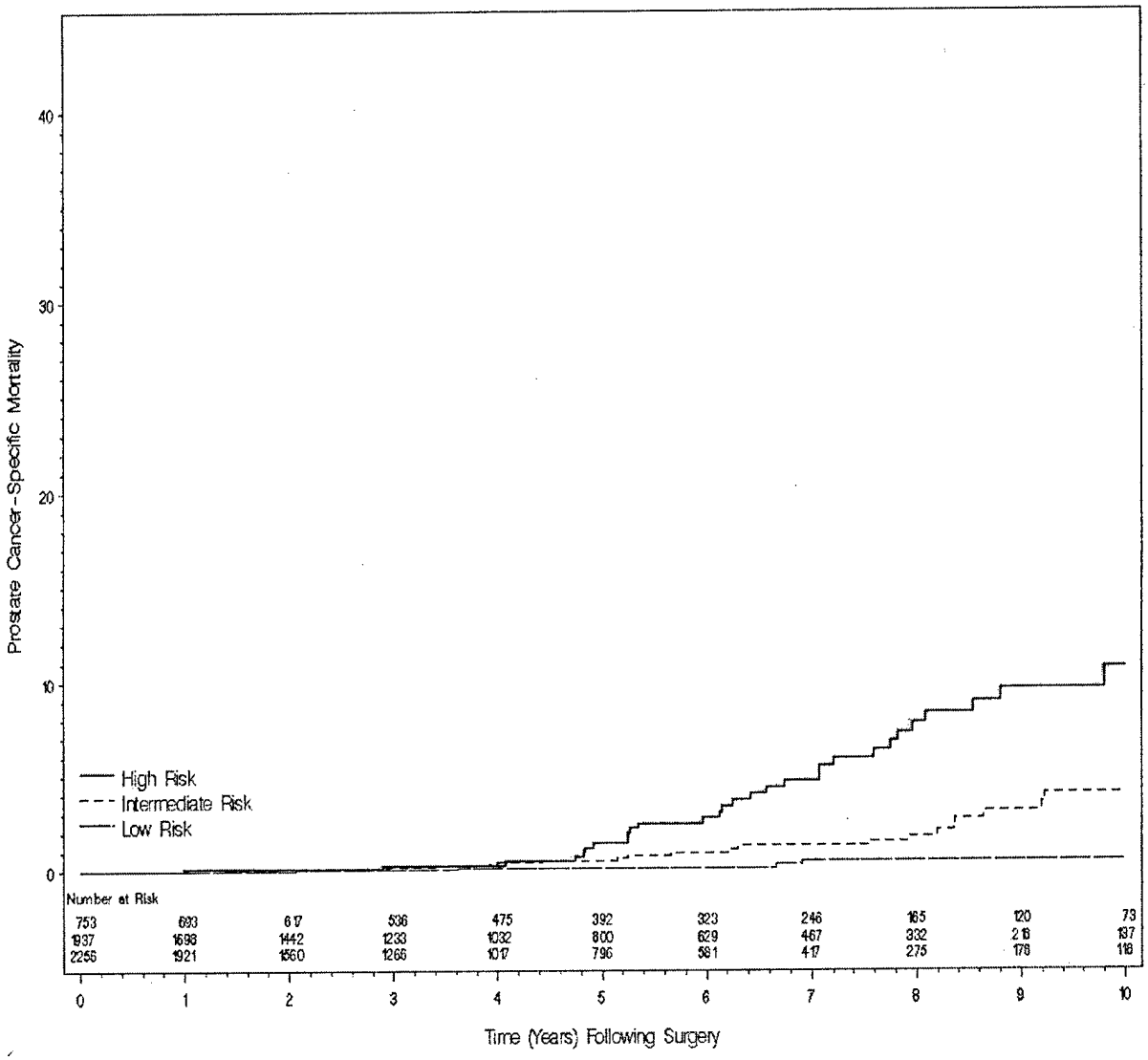


Fig 2. Prostate cancer–specific mortality after radical prostatectomy stratified by the pretreatment risk group. Pairwise *P* values (clinical significance[15] defined as *P* < .05/3 or .017). Intermediate versus low: *P* = .001. High versus low: *P* < .0001. High versus intermediate: *P* < .0001.

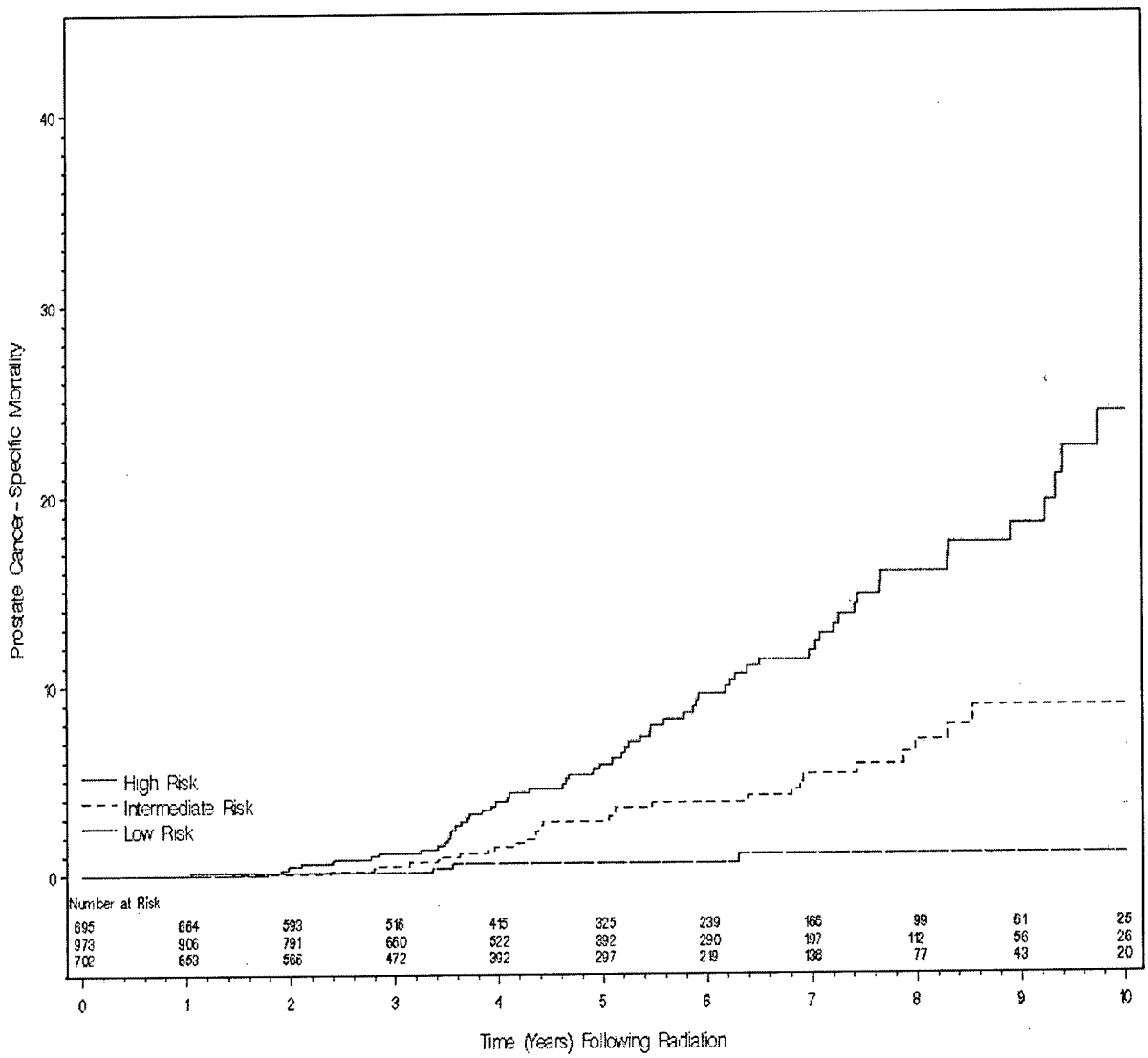


Fig 3. Prostate cancer–specific mortality after radiation therapy stratified by the pretreatment risk group. Pairwise *P* values (clinical significance[15] defined as $P < .05/3$ or .017). Intermediate versus low: $P = .0003$. High versus low: $P < .0001$. High versus intermediate: $P < .0001$.

= .002) compared with $13\%_{RP}$ *v* $18\%_{RT}$ ($P_{\log\ rank} = .35$) for patients whose age at the time of PSA failure was younger than 70 years as compared with ≥ 70 years, respectively.

Relative Risk of Cancer-Specific Mortality by Risk Group

The results of the Cox regression analyses that determined the ability of the pretreatment risk groups to predict time to PCSM after either RP or RT are listed in Table 3 and illustrated in Figs 2 and 3, respectively. The relative risk of PCSM for RP-managed patients with high- or intermediate-risk disease was 14.2 (95% CI, 5.0 to 23.4; $P_{Cox} < .0001$) and 4.9 (95% CI, 1.7 to 8.1; $P_{Cox} = .0037$), respectively. These values were 14.3 (95% CI, 5.2 to 24.0; $P_{Cox} < .0001$) and 5.6 (95% CI, 2.0 to 9.3; $P_{Cox} = .0012$), respectively, for RT-managed patients. Figures 4 and 5 contain the relative contributions of PCSM and non-PCSM after treatment to all causes of mortality stratified by the patient age at the time of initial therapy, the initial therapy received, and the pretreatment risk group.

Patients with intermediate-risk disease were compared using Cox regression to evaluate whether the presence of one, any two, or all three factors affected the time to PCSM after either RP or RT. Specifically, as shown in Table 4, having all three factors was a significant predictor of a shorter time to PCSM after RP ($P_{Cox} = .006$) but not after RT ($P_{Cox} = .13$). The relative statistical significance of these findings remained unchanged if the baseline group in the Cox regression was defined as biopsy Gleason score 7 or clinical category T2b. After multiple comparisons were adjusted for, patients with all three factors had a significantly shorter time to PCSM after RP compared with patients who had any single factor ($P_{\log\ rank} \leq .005$) or any two factors ($P_{\log\ rank} = .004$) that defined intermediate risk. Rates of PCSM for intermediate-risk patients after RP or RT are shown in

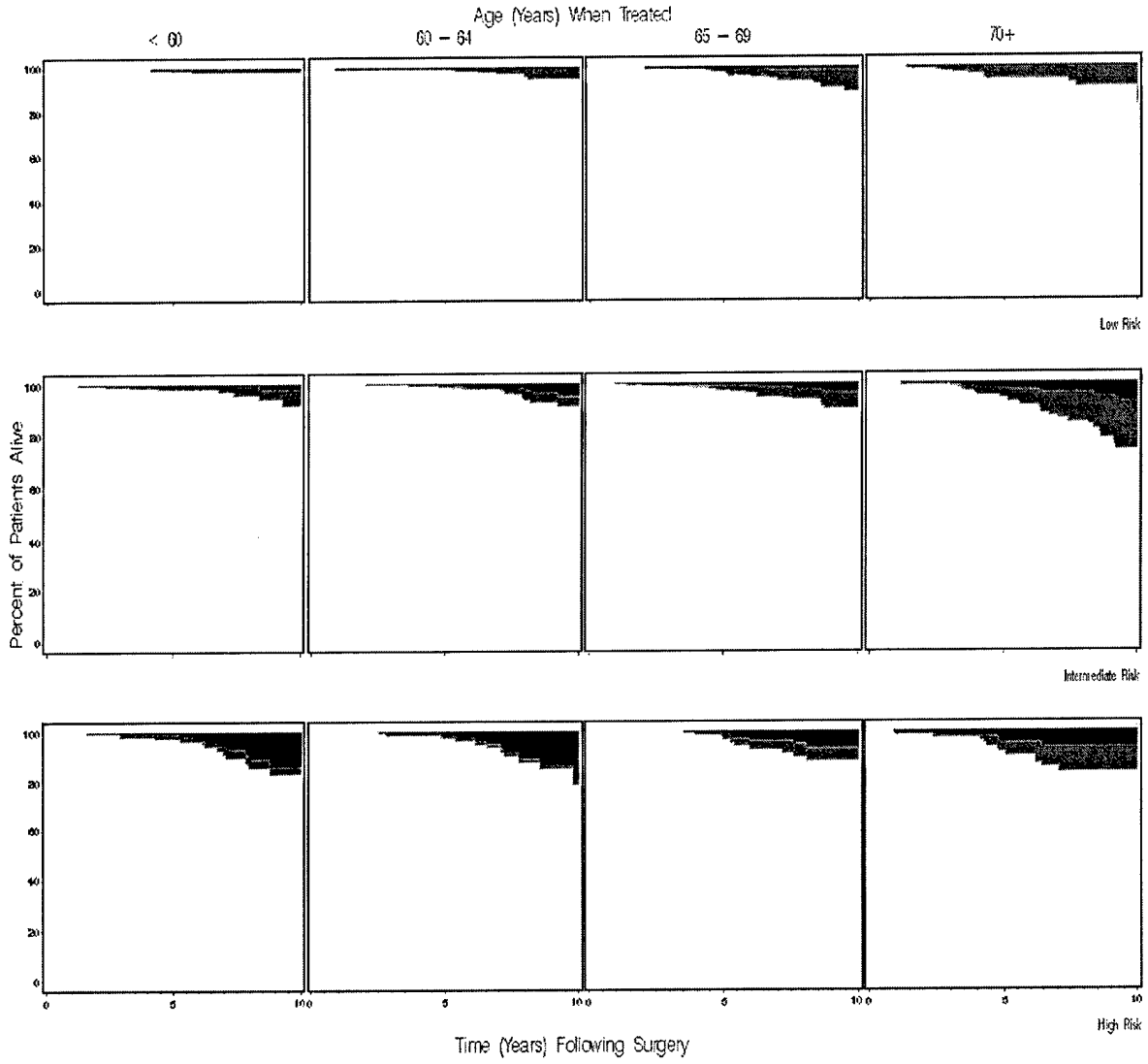


Fig 4. Prostate cancer–and non–prostate cancer–specific mortality after radical prostatectomy stratified by age at the time of initial therapy and the pretreatment risk group. Blue, prostate cancer–specific mortality; red, non–prostate cancer–specific mortality.

Figs 6 and 7, respectively, stratified by the presence of one, any two, or all three factors that defined intermediate-risk patients.

DISCUSSION

The goal of a staging system is to predict cancer-specific survival as accurately as possible using readily available pretreatment parameters that define stages that correspond to rates of disease-specific survival after standard therapy, which increase in a clinically significant manner as the clinical stage decreases. Validated algorithms[2-4] currently exist that provide accurate estimates of PSA failure on the basis of pretreatment clinical parameters after RP or RT for patients with clinically localized disease. However, PSA failure may not translate into mortality from prostate cancer for all patients because men with prostate cancer are generally over the age of 60 years and often have competing causes of mortality.[18] Therefore, a staging system that is constructed on the basis of PSA failure rates may not accurately represent rates of PCSM.

This study provided evidence to support the conjecture that not all men who sustain PSA failure subsequently die as a result of prostate cancer. In particular, within 8 years after PSA failure, estimates of non-PCSM ranged from 4% to 18% (Fig 1). As noted in Table 2, the numerical value of the mortality rate depended on both the age of the patient at the time of PSA failure (P_{Cox} = .001) and the initial therapy received (P_{Cox} = .03) for men who were younger than age 70 years at the time of PSA failure. This latter finding likely reflected the practice pattern in the United States during the study period that patients younger than age 70 years who were selected to undergo RT as opposed to RP were generally less healthy.

Nevertheless, despite the significant rates of non-PCSM after PSA failure, the results of this study that evaluated data obtained

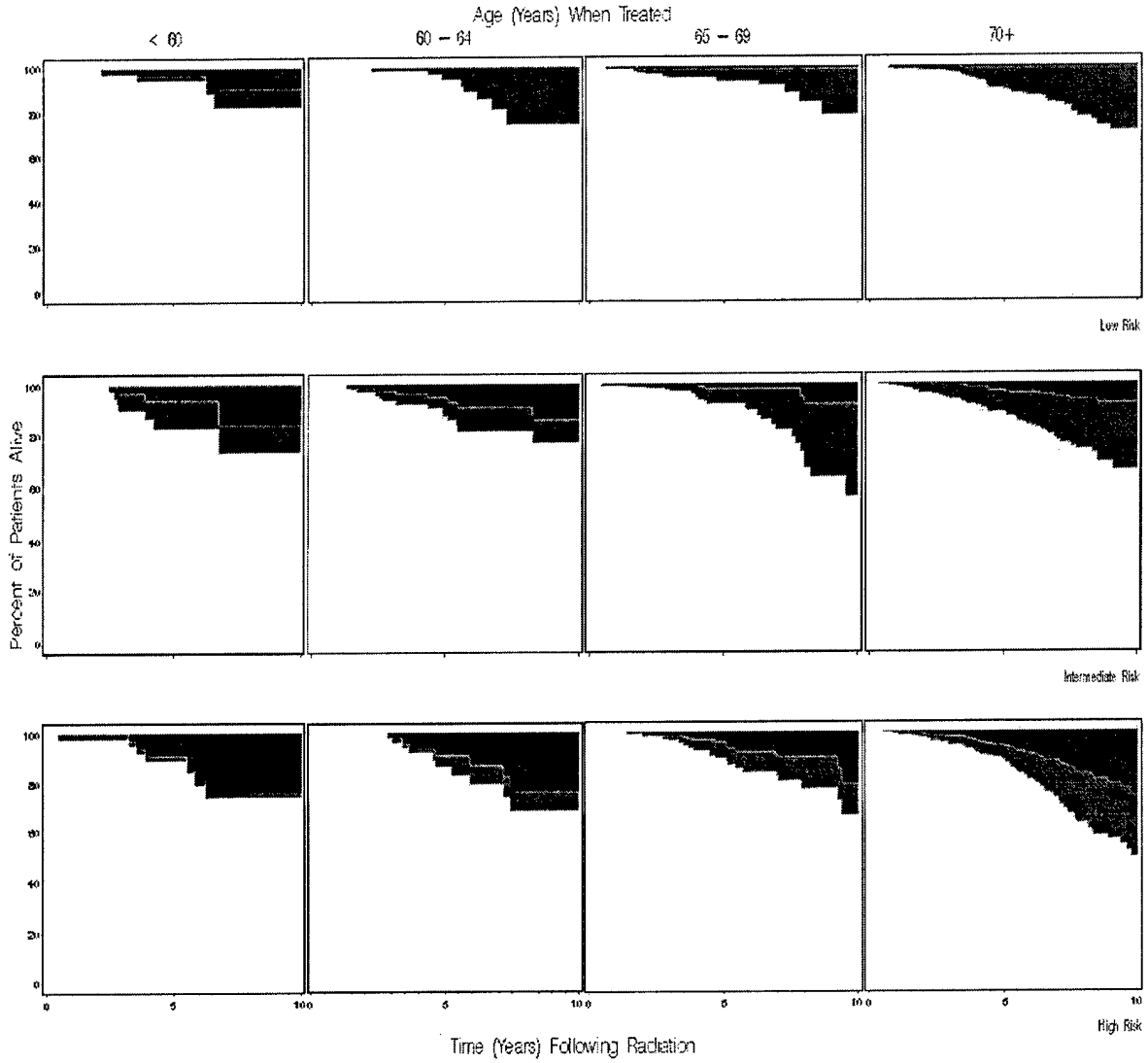


Fig 5. Prostate cancer–and non–prostate cancer–specific mortality after radiation therapy stratified by age at the time of initial therapy and the pretreatment risk group. Blue, prostate cancer–specific mortality; red, non–prostate cancer–specific mortality.

from 44 institutions during the PSA era supported a single institution report[5] indicating that pretreatment risk groups[3] initially derived to predict time to PSA failure after RP or RT could also stratify the time to PCSM after initial therapy. Specifically (Table 3), the RR of PCSM was approximately 14-fold or five-fold higher for patients in the high- or intermediate-risk groups, respectively, as compared with the low-risk group. This increase in the relative risk of PCSM with increasing risk group is illustrated in Figs 4 and 5, respectively, where the contributions from cancer-specific and competing causes to all causes of mortality are shown stratified by age at the time of initial therapy and the pretreatment risk group. In particular, for patients of all ages, PCSM increased with advancing risk group for both RP- and RT-managed patients. In addition, although the relative contribution of non-PCSM to all causes of mortality increased with advancing age as expected, high-risk prostate cancer remained a major cause of death for patients of all ages who were treated with RP or RT.

This study also noted that for patients in the intermediate-risk group who have one or any two of the factors that defined intermediate risk, estimates of PCSM were not significantly different after RP or RT. Patients with all three factors defining intermediate risk, however, had a time to PCSM after RP that was significantly shorter than patients whose definition of intermediate risk was based on a single ($P_{\log\ rank} \leq .005$) or any two factors ($P_{\log\ rank} = .004$; Fig 6). This finding was not replicated for RT-managed patients (Fig 7). Prior investigators have shown a significant increase in PSA failure rates for patients in the intermediate-risk group with two or more of the three defining factors as compared with any single factor.[19] Perhaps with further follow-up, PCSM profiles will more closely approximate the previously reported PSA failure profiles for

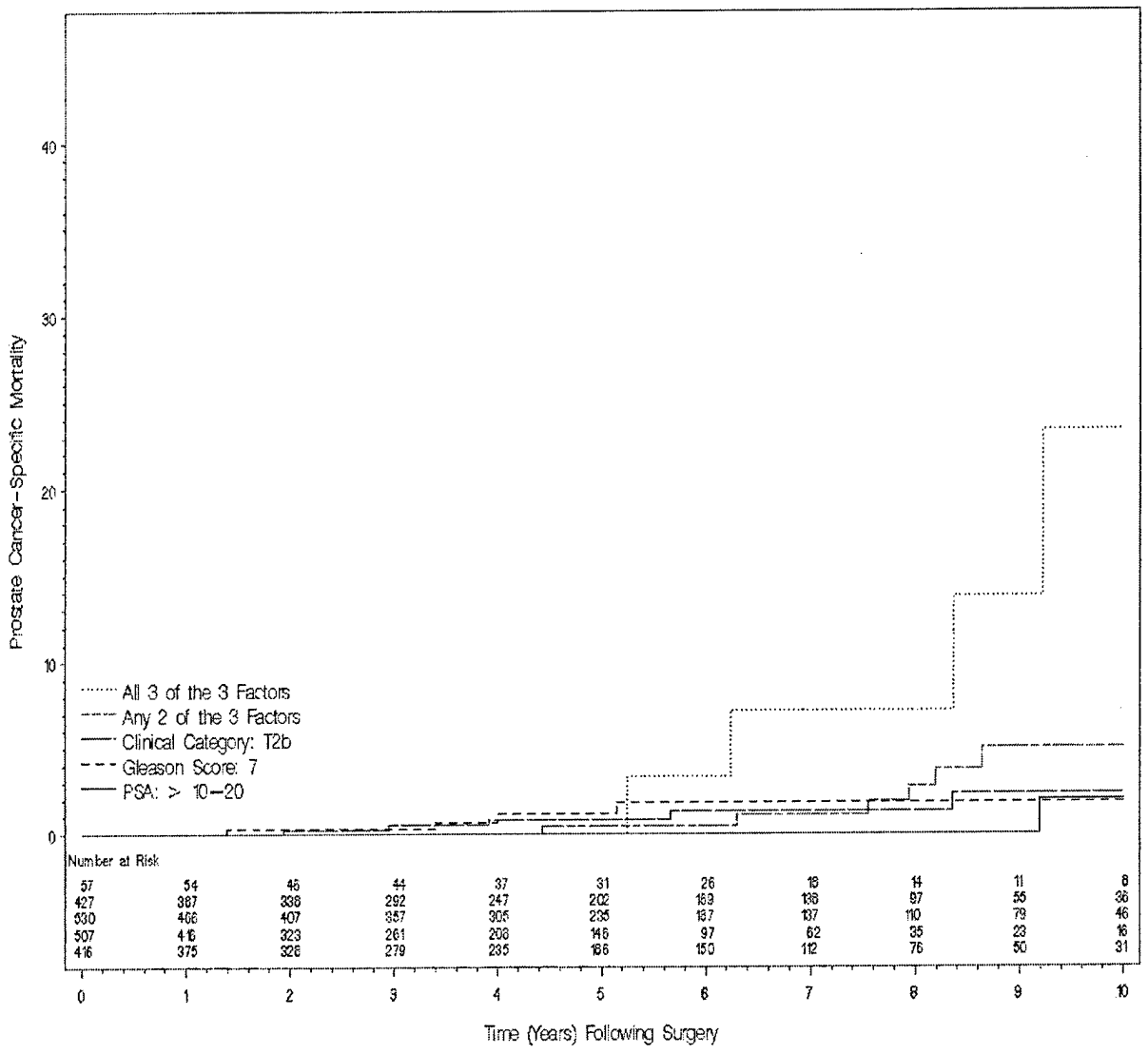


Fig 6. Prostate cancer–specific mortality after radical prostatectomy for patients with 1, any 2, or all 3 factors that define intermediate risk. Pairwise *P* values (clinical significance[15] defined as $P < .05/10$ or .005). Prostate-specific antigen (PSA) > 10 to 20 versus Gleason 7; $P = .05$. PSA > 10 to 20 versus T2b; $P = .19$; PSA > 10 to 20 versus any two factors; $P = .09$. PSA > 10 to 20 versus all three factors; $P < .0001$. Gleason 7 versus T2b; $P = .39$. Gleason 7 versus any two factors; $P = .51$. Gleason 7 versus all three factors; $P = .005$. T2b versus any two factors; $P = .61$. T2b versus all three factors; $P = .003$. Any two factors versus all three factors; $P = .004$.

patients with two or more of factors that define intermediate risk. At present, however, the data in this study only support the placement of the RP-managed patients who possess all three factors that define intermediate risk into the high-risk group.

Several points require further clarification. First, the pretreatment risk groups evaluated in this study represent one of two validated algorithms[2-4] for predicting time to PSA failure after RP or RT for patients with clinically localized prostate cancer. Nomograms that are based on pretreatment factors also have been validated for the prediction of time to PSA failure after RP in this patient population[2,4] and should be studied further to evaluate their ability to predict time to PCSM after RP or RT.

Second, prior studies have shown that by applying the percentage of positive prostate biopsy core information to the intermediate-risk group, a low- and high-risk group for defining time to PSA failure after RP or RT can be defined.[20-22] Therefore, additional studies will be necessary to assess whether adding the percentage of positive prostate biopsy core data to the intermediate-risk group will also succeed in stratifying the time to PCSM after RP or RT into low- and high-risk groups.

Third, the predictions of PCSM using the pretreatment risk groups in this study are only applicable to patients with clinically localized prostate cancer undergoing RP or RT therapy. Therefore, if future studies document a survival benefit for the addition of AST to RT for patients with clinically localized disease, as has been shown for patients with locally advanced prostate cancer,[7] then the ability of the pretreatment risk groups to stratify time to PCSM after RT

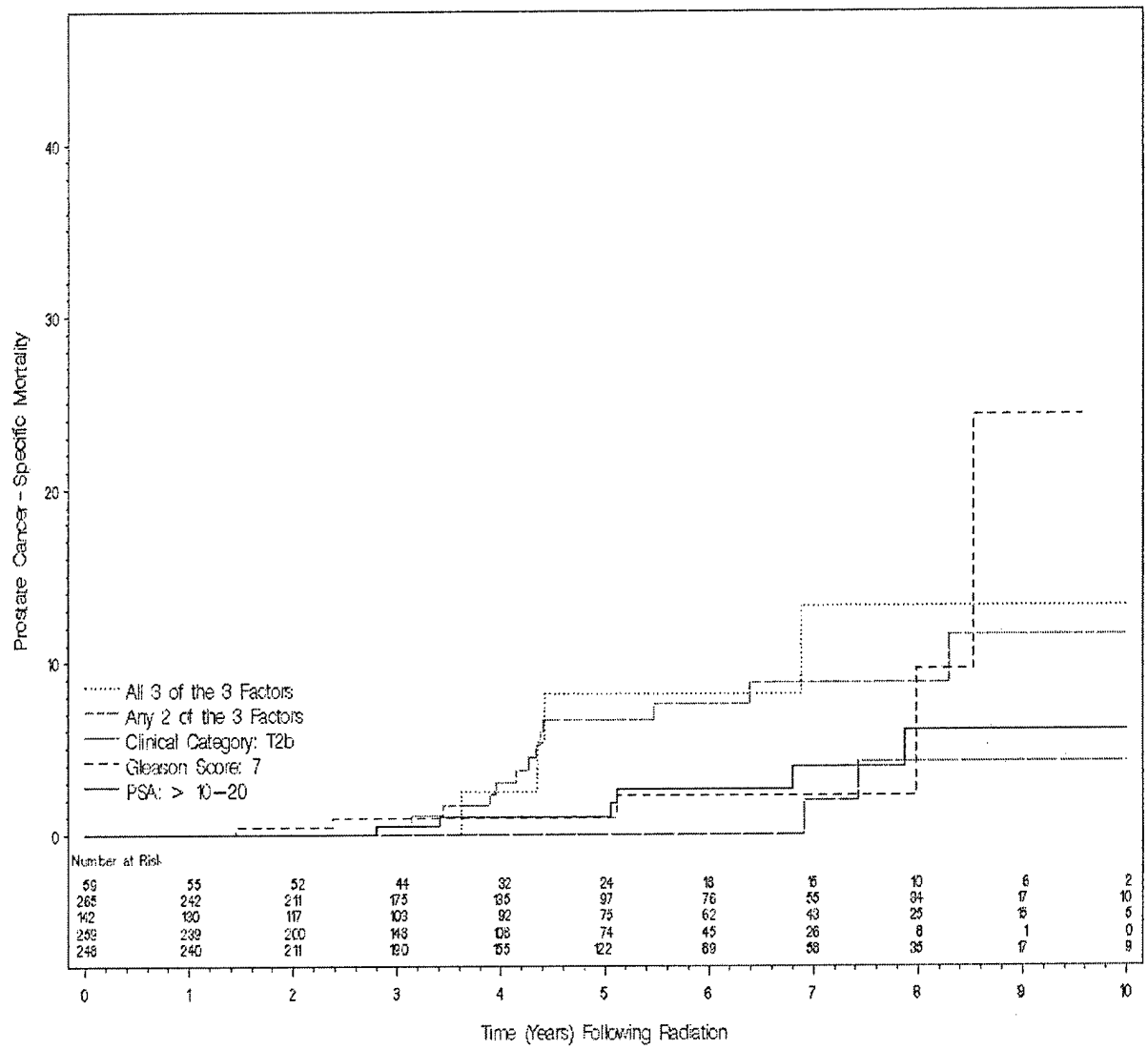


Fig 7. Prostate cancer–specific mortality after radiation therapy for patients with one, any two, or all three factors that define intermediate risk. Pairwise *P* values (clinical significance[15] defined as *P* < .05/10 or .005). Prostate-specific antigen (PSA) > 10 to 20 versus Gleason 7; *P* = .47. PSA > 10 to 20 versus T2b; *P* = .41. PSA > 10 to 20 versus any two factors; *P* = .10. PSA > 10 to 20 versus all three factors; *P* = .08. Gleason 7 versus T2b; *P* = .10. Gleason 7 versus any two factors; *P* = .30. Gleason 7 versus all three factors; *P* = .39. T2b versus any two factors; *P* = .03. T2b versus all three factors; *P* = .02. Any two factors versus all three factors; *P* = .73.

and AST would need to be evaluated in a future study. Finally, whether the specific treatment(s) individual patients received after PSA failure affected the time to PCSM remains unknown and requires clarification in future studies.

In conclusion, this study provided evidence to support the prediction of time to PCSM after RP or RT on the basis of pretreatment risk groups for patients with clinically localized prostate cancer managed during the PSA era.

REFERENCES

1. Catalona WJ, Smith DS, Ratliff TL, et al: Detection of organ-confined prostate cancer is increased through prostate-specific antigen-based screening. J Am Med Assoc 270:948-954, 1993

2. Kattan MW, Easthan JA, Stapleton AMF, et al: A preoperative nomogram for disease recurrence following radical prostatectomy for prostate cancer. J Natl Cancer Inst 90:766-771, 1998

3. D'Amico AV: Combined-modality staging for localized adenocarcinoma of the prostate. Oncology 15:1049-1059, 2001

4. Graefen M, Karakiewicz PI, Cagiannos I, et al: A validation of two preoperative nomograms predicting recurrence following radical prostatectomy. Urol Oncol 7:141-146, 2002

5. D'Amico AV, Cote K, Loffredo M, et al: Determinants of prostate cancer specific survival following radiation therapy for patients with clinically localized prostate cancer. J Clin Oncol 20:4567-4573, 2002

6. Roach M, Lu J, Pilepich MV, et al: Four prognostic groups predict long-term survival from prostate cancer following radiotherapy alone on

Radiation Therapy Oncology Group clinical trials. Int J Radiat Oncol Biol Phys 47:609-615, 2000

7. Bolla M, Collette L, Blank L, et al: Long-term results with immediate androgen suppression and external irradiation in patients with locally advanced prostate cancer (an EORTC study): A phase III randomised trial. Lancet 360:103-106, 2002

8. Lubeck DP, Litwin MS, Henning JM, et al: The CaPSURE database: A methodology for clinical practice and research in prostate cancer—CaPSURE Research Panel: Cancer of the Prostate Strategic Urologic Research Endeavor. Urology 48:773-777, 1996

9. Sun L, Gancarczyk K, Paquette EL, et al: Introduction to Department of Defense Center for Prostate Disease Research Multicenter National Prostate Cancer Database, and analysis of changes in the PSA-era. Urol Oncol 6:203-209, 2001

10. Soloway MS, Pareek K, Sharifi R, et al: Neoadjuvant androgen ablation before radical prostatectomy in cT2bNxMo prostate cancer: 5-year results. J Urol 167:112-116, 2002

11. Gleason DF for the Veterans Administration Cooperative Urological Research Group: Histologic grading and staging of prostatic carcinoma, in Tannenbaum M (ed): Urologic Pathology. Philadelphia, PA, Lea & Febiger, 1977, pp 171-187

12. Lee CT, Oesterling JE: Using prostate-specific antigen to eliminate the staging radionuclide bone scan. Urol Clin North Am 24:389-394, 1997

13. Greene FL, Page DL, Fleming ID, et al. American Joint Committee on Cancer, Manual for Staging Cancer (ed 6). New York, NY, Springer, 2002, pp 337-346

14. Cox JD for the American Society for Therapeutic Radiology and Oncology Consensus Panel: Consensus statement: Guidelines for PSA following radiation therapy. Int J Radiat Oncol Biol Phys 37:1035-1041, 1997

15. Simultaneous inferences and other topics in regression analysis-1, in Neter J, Wasserman W, Kutner M (eds): Applied Linear Regression Models (ed 1). Homewood, IL, Richard D. Irwin, Inc, 1983, pp. 150-153

16. Efron R, Tibsherani R. Introduction to the Bootstrap. New York, NY, Chapman and Hall, 1993

17. Gaynor JJ, Feur EJ, Tan CC, et al: On the use of cause-specific failure and conditional failure probabilities: Examples from clinical oncology data. J Am Stat Assoc 88:400-409, 1993

18. National Center for Health Statistics, Washington, DC: National Vital Statistics report 50:1-120, 2002

19. Zelefsky MJ, Fuks Z, Hunt M, et al: High-dose intensity modulated radiation therapy for prostate cancer: Early toxicity and biochemical outcome in 772 patients. Int J Radiat Oncol Biol Phys 53:1111-1116, 2002

20. D'Amico AV, Whittington R, Malkowicz SB, et al: Clinical utility of the percentage of positive prostate biopsies in defining biochemical outcome after radical prostatectomy for patients with clinically localized prostate cancer. J Clin Oncol 18:1164-1172, 2000

21. Grossfeld GD, Latini DM, Lubeck DP, et al: Predicting disease recurrence in intermediate and high-risk patients undergoing radical prostatectomy using percent positive prostate biopsies: Results from CaPSURE. Urology 59:560-565, 2002

22. D'Amico AV, Schultz D, Silver B, et al: The clinical utility of the percent positive prostate biopsies in predicting biochemical outcome following external beam radiation therapy for patients with clinically localized prostate cancer. Int J Radiat Oncol Biol Phys 49:679-684, 2001

Temporarily Deferred Therapy (watchful waiting) for Men Younger Than 70 Years and With Low-Risk Localized Prostate Cancer in the Prostate-Specific Antigen Era

By Corey A. Carter, Timothy Donahue, Leon Sun, Hongyu Wu, David G. McLeod, Christopher Amling, Raymond Lance, John Foley, Wade Sexton, Leo Kusuda, Andrew Chung, Douglas Soderdahl, Stephen Jackman, and Judd W. Moul

Purpose: **Watchful waiting (WW) is an acceptable strategy for managing prostate cancer (PC) in older men. Prostate-specific antigen (PSA) testing has resulted in a stage migration, with diagnoses made in younger men. An analysis of the Department of Defense Center for Prostate Disease Research Database was undertaken to document younger men with low- or intermediate-grade PC who initially chose WW.**

Patients and Methods: **We identified men choosing WW who were diagnosed between January 1991 and January 2002, were 70 years or younger, had a Gleason score ≤ 6 with no Gleason pattern 4, had no more than three positive cores on biopsy, and whose clinical stage was ≤ T2 and PSA level was ≤ 20. We analyzed their likelihood of remaining on WW, the factors associated with secondary treatment, and the influence of comorbidities.**

Results: **Three hundred thirteen men were identified. Median follow-up time was 3.8 years. Median age was 65.4 years (range, 41 to 70 years). Ninety-eight patients remained on WW; 215 proceeded to treatment. A total of 57.3% and 73.2% chose treatment within the first 2 and 4 years, respectively. Median PSA doubling time (DT) was 2.5 years for those who underwent therapy; those remaining on WW had a median DT of 25.8 years. The type of secondary treatment was associated with the number of patient's comorbidities ($P = .012$).**

Conclusion: **Younger patients who choose WW seemed more likely to receive secondary treatment than older patients. PSA DTs often predict the use of secondary treatment. The number of comorbidities a patient has influences the type of secondary therapy chosen. The WW strategy may better be termed temporarily deferred therapy.**

J Clin Oncol 21:4001-4008.

PROSTATE CANCER (PC) is the most common solid tumor in men in the United States and is the second-leading cause of cancer death.[1] Since the introduction of the prostate-specific antigen (PSA) screening test in the late 1980s and an increase in public awareness of the disease in the early 1990s, there has been a marked stage and age migration; the preponderance of PC is now a clinically localized disease in younger men.[2-4] More than two-thirds of men now have localized disease at initial diagnosis.

The optimal management of clinically localized PC remains controversial. Traditional treatment options for younger men diagnosed with clinically localized PC have focused on definitive therapy, such as radical prostatectomy or radiation therapy.[5-7] Watchful waiting (WW), also known as deferred therapy, has been used as a management strategy primarily in older men.

Both prospective and retrospective studies indicate that patients with localized PC who choose WW may have no loss in life expectancy.[8-11] However, there are inadequate data describing WW in young men with low-grade, low-stage PC. It may be safe to monitor some men expectantly without immediate treatment and the risks associated with definitive therapy.

It is estimated that as many as one-third of patients diagnosed with PC will have low-volume disease (less than 0.5 mL) with no poorly differentiated elements (Gleason score 6 or less). Work done by Epstein et al[12] has helped to identify criteria predictive of small-volume cancers in men with nonpalpable tumors. In that study, if PSA density was less than 0.15 ng/mL and no adverse pathologic findings were present at the time of prostate biopsy, 79% of men had cancers that were small volume (0.5 mL or less), organ confined, and not of high grade. Epstein et al[12] defined the favorable criteria on needle biopsy as Gleason score ≤ 6, no more than three cores positive for cancer, and ≤ 50% involvement of any core with cancer. When these needle

From the Center for Prostate Disease Research, Department of Surgery, Uniformed Services University of the Health Sciences; Department of Urology, National Naval Medical Center, Bethesda; Department of Urology, Malcolm Grow Air Force Medical Center, Andrews Air Force Base, MD; Urology Service, Department of Surgery, Walter Reed Army Medical Center; Urology Service, Department of Surgery, Eisenhower Army Medical Center, Washington, DC; Department of Urology, San Diego Naval Medical Center, San Diego, CA; Urology Service, Department of Surgery, Madigan Army Medical Center, Tacoma, WA; Urology Service, Department of Surgery, Brooke Army Medical Center; Department of Urology, Wilford Hall Air Force Medical Center, Lackland Air Force Base, San Antonio, TX; and Department of Urology, Portsmouth Naval Medical Center, Portsmouth, VA.

Submitted April 11, 2003; accepted August 11, 2003.

Supported by US Army Medical Research and Materiel Command grant PCRP-DAMD17-02-1-0066, funded by the US Department of Defense.

The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Departments of the Army, Navy, or Air Force or the Department of Defense.

Authors' disclosures of potential conflicts of interest are found at the end of this article.

Address reprint requests to Judd Moul, MD, Center for Prostate Disease Research, 1530 E Jefferson St, Rockville, MD 20852; e-mail: jmoul@cpdr.org or *Timothy Donahue, MD, Department of Urology, National Naval Medical Center, Bethesda, MD 20889; e-mail: tfdonahue@bethesda.med.navy.mil.*

0732-183X/03/2121-4001/$20.00

biopsy criteria are used, it is possible to identify men with greater likelihood of low-grade, low-volume PC, in whom WW might be a reasonable option.

The goal of this cohort study was to identify and describe younger men diagnosed with PC with lower-risk features during the PSA era and who chose WW as their initial treatment strategy, and to identify the factors associated with the decision to proceed to definitive therapy.

PATIENTS AND METHODS

The clinical information and follow-up in this study have been collected as part of the Department of Defense Center for Prostate Disease Research (CPDR) Tri-Service Multicenter Prostate Disease Research Database as described previously by Sun et al.[13] In brief, standardized data collection forms for prostate biopsy, registration, staging, WW, surgery, radiation treatment, hormone treatment, cryotherapy, follow-up, and necropsy have been developed and were used. Data were collected and entered by physicians and data managers and maintained in a relational database using Microsoft Access (Microsoft Corp, Redmond, WA) software as the front end and Oracle software (Oracle, Redwood Shores, CA) as the back end. The CPDR Database has been approved by the Uniformed Services University Research Administration institutional review board (IRB), as well as the IRBs of all participating military hospitals. The original protocol in use from 1991 to 1998 did not require each patient to sign a formal informed consent document. However, between 1998 and 1999, the IRBs of all sites required patients to provide informed consent to participate. All data entered before 1998 to 1999 (exact dates vary by institution) without gaining patients' informed consent were allowed to be maintained.

The data query for this study was performed in August 2002. At this time, the overall database contained 345,954 clinical records (eg, transrectal ultrasound, biopsy, staging, WW, follow-up) on 15,063 patients. Of these, 2,074 patients (13.8%) had selected WW as their initial treatment between January 1, 1991, and December 31, 2001, with complete information on progression of the disease. We identified patients who chose WW as their primary treatment strategy and who were believed to be the most suitable candidates for deferred therapy, adapting the criteria developed by Epstein et al.[12] The goal of these selection criteria was to identify patients who were believed to have low-grade, low-stage disease at the time of diagnosis and who were considered to be potential candidates for definitive therapy. These patients had the option of pursuing any type of therapy for their PC and were not hindered in our equal-access military healthcare system because of cost or insurance considerations. Patients older than 70 years or with advanced disease were excluded from analysis to minimize the influence of age and aggressiveness of disease on the decision to pursue WW.

Inclusion criteria for this analysis were the date of diagnosis between January 1991 and January 2002, age $\leq$ 70 years, Gleason score $\leq$ 6 with no Gleason pattern 4, no more than three cores positive on biopsy, clinical stage $\leq$ T2, and PSA level $\leq$ 20 ng/mL at the time of diagnosis. Table 1 provides the number and percentage of WW patients included in this study for each CPDR institution. The discrepancy between the number of patients undergoing WW and those reviewed in this analysis is due to the preponderance of older patients or those with higher-grade disease managed with this strategy of WW.

The data fields analyzed included the patient's age at diagnosis, ethnicity or race, clinical stage at diagnosis, diagnosed PSA level, biopsy Gleason score, number of positive biopsy cores, family history of PC in a first- or second-degree relative, and prior treatment (if any) for symptomatic benign prostate hyperplasia (BPH). Vascular disease risk factors and concurrent comorbidities at diagnosis were analyzed as independent and collective risk factors for progression to secondary treatment. In addition, histologic grading on repeat biopsies, PSA doubling times (DTs), and the type of secondary definitive treatment were also analyzed.

PSA DTs were calculated using the assumption that PSA changes with time in an exponential manner once PC has been diagnosed.[14-16] All patients with at least two PSA levels in the database were used to calculate DTs in a regression analysis to determine the slope of the exponential curve. PSA DTs were calculated for 241 patients, with a median of three PSA entries used (range, two to 28 entries). More than 90% of the 241 patients had at least three PSA entries.

Clinical characteristics of patients who remained on the WW protocol were compared with those of patients who underwent secondary treatment, using χ^2 and Fisher's exact test. These factors were further tested using a log-rank method. In addition, a multivariate Cox proportional hazards regression model was used to assess the predictors of secondary treatment in the total WW cohort. Of the patients who proceeded to definitive treatment, a χ^2 analysis was used to compare the patient's number of comorbidities with the choice of secondary treatment chosen. Treatment curves indicating those patients who were free from secondary treatment were calculated using the Kaplan-Meier (KM) method. The KM curves were further stratified by the patient's PSA DT and clinical stage.

RESULTS

Three hundred thirteen patients met the selective inclusion criteria of this analysis. The mean and median follow-up times were 4.2 and 3.8 years, respectively (range, 0.5 to 10.5 years). Sixty-six percent of the patients were diagnosed before 1997. The median age at diagnosis was 65.4 years (range, 41 to 70 years). Two-thirds of the patients were non-Hispanic white, nearly one fourth were black, and the remaining 9% were Asian (including Filipino) or Hispanic. Two-thirds of patients had nonpalpable disease at the time of diagnosis. The median PSA at diagnosis was 5.1 ng/mL, with a range of 0.5 to 20 ng/mL. Eighty-seven percent of men had a PSA level less than 10 ng/mL at diagnosis, with 20.4% having an initial PSA level less than 4 ng/mL. As an inclusion criterion, no patient had a Gleason score

Table 1. Participating CPDR Sites and Total WW Patient Cases in CPDR Database Between 1991 and 2002

CPDR Institution	Total No. of WW Patient Cases	No. of WW Patient Cases for This Study	WW Patient Cases As Percentage of Total
Brooke Army Medical Center	180	32	17.8
Eisenhower Army Medical Center	69	11	15.9
Madigan Army Medical Center	275	22	8.0
Malcolm Grow Medical Center	107	11	10.3
Naval Medical Center, Portsmouth	155	37	23.9
Naval Medical Center, San Diego	175	48	27.4
National Naval Medical Center	325	26	8.0
Wilford Hall Medical Center	184	36	19.6
Walter Reed Army Medical Center	607	90	14.8
All CPDR institutions	2,077	313	15.1

Abbreviations: CPDR, Center for Prostate Disease Research; WW, watchful waiting.

Table 2. Univariate Analysis of Factors Associated With Secondary Treatment in 313 WW Patients Between 1991 and 2002

Factor	WW With No Secondary Treatment		WW With Secondary Treatment		P
	No. of Patients	%	No. of Patients	%	
Age, years					
≤ 60	21	21.4	54	25.1	.029
60.1-65	23	23.5	76	35.4	
65.1-70	54	55.1	85	39.5	
Clinical stage					
T1a/1b	13	13.3	5	2.3	.0002
T1c	55	56.1	132	61.4	
T2a	26	26.5	46	21.4	
T2b	3	3.1	19	8.8	
T2c	1	1.0	13	6.1	
Treatment for BPH					
No	74	75.5	182	84.7	.020
Yes	24	24.5	33	15.3	
Gleason score*					
Increase or same	15	71.4	51	91.1	.031
Decrease	6	28.6	5	8.9	
PSA doubling time (n = 241)					
< 2	8	8.3	61	42.1	< .0001
2-5	16	16.7	39	26.9	
5.1-50	31	32.3	22	15.2	
> 50	41	42.7	23	15.9	
PSA level at diagnosis					
≤ 4	27	27.5	37	17.1	.23
4.1-6	32	32.7	70	32.6	
6.1-10	30	30.6	78	36.3	
10.1-20	9	9.2	30	14.0	
Gleason score at diagnosis					
≤ 4	9	11.0	10	5.1	.14
5	21	25.6	45	23.1	
6	24	29.3	49	25.1	
TSTG	28	34.1	91	46.7	
No. of positive cores on initial biopsy					
1	60	61.2	139	64.6	.32
2	21	21.4	52	24.2	
3	17	17.3	24	11.2	
Race or ethnicity					
White	68	70.8	141	67.8	.36
Black	20	20.8	56	26.9	
Other	8	8.4	11	5.3	
No. of vascular disease factors per patient					
0	27	27.6	58	27.0	.79
1	36	36.7	91	42.3	
2	27	27.6	51	23.7	
3	8	8.1	15	7.0	
No. of comorbidities per patient					
0	51	52.0	118	54.9	.54
1	25	25.5	60	27.9	
≥ 2	22	22.5	37	17.2	
Deaths					
Related to prostate cancer	1		1		
Related to comorbidity	2		2		
Other known causes	5		2		
Unknown causes	4		6		
Metastatic disease	0		3		

Abbreviations: WW, watchful waiting; BPH, benign prostate hyperplasia; PSA, prostate-specific antigen; TSTG, too small to grade.
*For patients who received repeat biopsy (n = 241).

greater than 6, and no patient had Gleason pattern 4 in any biopsy core. The median Gleason score was 5. Nearly two thirds of patients (63.6%) had only one positive biopsy core at diagnosis. During the period of analysis, there were 23 deaths in the entire cohort of patients. Two of these deaths were related to PC, four were related to comorbid illness, and 17 were as a result of other or unknown causes. Three patients developed metastatic disease.

Table 3. Kaplan-Meier Estimates of Freedom From Secondary Treatment

	No. of Patients	After 2 Years		After 4 Years		P (log-rank test)
		%	SE	%	SE	
All WW patients	313	42.7	2.9	26.8	2.8	
Age, years						
≤ 60	75	38.4	5.8	28.7	5.5	.1929
60.1-65	99	40.9	5.1	15.9	4.3	
65.1-70	139	44.8	4.4	32.6	4.5	
Clinical stage						
T1a/1b	18	72.2	10.6	72.2	10.6	< .0001
T1c	187	43.6	3.7	23.7	3.6	
T2a	72	44.1	6.1	31.7	6.2	
T2b	22	17.9	8.7			
T2c	14	11.9	7.5			
PSA doubling time						
< 2	64	13.9	5.6	2.5	7.1	< .0001
2-5	69	45.1	4.6	21.4	2.4	
5.1-50	55	80.5	6.9	61.9	6.7	
> 50	53	74.9	5.5	56.3	7.2	
PSA at diagnosis						
≤ 4	8	50.0	17.7			.1248
4.1-6	56	47.2	6.7	41.1	6.7	
6.1-10	102	44.3	5.1	27.3	5.0	
10.1-15	108	40.4	4.9	18.9	4.5	
15.1-20	39	30.6	7.7	14.5	6.8	
Race or ethnicity						
White	209	44.0	3.5	29.3	3.4	.0728
Black	76	32.6	5.6	16.6	5.3	
Other	19	52.6	11.5	35.5	13.4	
Family history of disease						
No	252	43.6	3.2	27.2	3.1	.3817
Yes	61	37.3	6.3	22.1	6.2	
No. of comorbidities per patient						
0	169	44.0	3.9	28.5	3.8	.3773
1	85	37.1	5.4	22.4	5.3	
≥ 2	59	47.8	6.8	28.8	6.7	

Abbreviations: WW, watchful waiting; PSA, prostate-specific antigen.

Family history of PC in a first- or second-degree relative was positive in 19.5% of patients. Nearly one-fifth (18.2%) of patients were undergoing active therapy for BPH at the time of diagnosis. Vascular disease risk factors (ie, smoking history, hypertension, and hyperlipidemia) were positive in 51.1%, 45%, and 16.9% of men, respectively. The prevalences of comorbidities were as follows: coronary artery disease, 18.8%; cerebral vascular accident, 5.1%; renal insufficiency, 3.8%; chronic obstructive pulmonary disease, 8.6%; diabetes mellitus, 8.6%; systemic disease, 1.6%; and concurrent malignancy, 16.9%.

Repeat prostate biopsy was performed in 77 (24.6%) of the patients electing to pursue WW. The decision to perform a repeat prostate biopsy was made by the urologist caring for the patient, and its timing was scheduled according to the surgeon's preference. Only 24% of repeat biopsies identified an upgrade in Gleason score from the initial score; 61% remained unchanged, and 14% experienced a decrease in the Gleason score. PSA DTs were calculated and stratified as follows: less than 2 years, 22%; 2 to 5 years, 17.6%; 5 to 10 years, 10.2%; 10 to 20 years, 3.2%; 20 to 50 years, 3.5%; and greater than 50 years, 20.4%.

Table 2 lists a univariate analysis of the demographic and clinical characteristics of the two cohorts in this analysis—namely, those patients who remained on WW and those who elected to proceed with definitive therapy. Under univariate analysis, significant factors that positively affected the decision to move to secondary treatment were the patient's age (P = .029), clinical stage (P = .0002), not receiving treatment for BPH (P = .031), and PSA DT (P < .0001). A finding of same or increased Gleason score on repeat prostate biopsy was also a significant univariate risk factor for progression to secondary treatment (P = .028). Table 3 lists KM estimates for a patient's ability to remain free from secondary treatment. The 2-year and 4-year estimates are shown and are stratified by age, clinical stage, PSA DT, PSA level at diagnosis, race or ethnicity, family history of disease, and number of comorbidities. The long-rank P values shown, which demonstrate both clinical stage and PSA DT, are statistically significant (< .001). Table 4 lists the multivariate analysis conducted using the categorical data; the significant predictors of secondary treatment were found to be the PSA DT and the clinical stage.

Table 5 lists the type of treatment elected by the 215 patients who moved on to secondary treatment. The median time to definitive treatment was 9.6 months. Table 6 compares the number of comorbidities at the time of diagnosis with the choice

Table 4. Cox Proportional Hazards Model for Predictors of Secondary Treatment

Risk of Secondary Treatment	Hazard Ratio	95% CI	P
Clinical stage			
cT1c versus cT1a/b	7.077	1.642 to 30.498	.0087
cT2a versus cT1a/b	5.647	1.260 to 25.302	.0237
cT2b versus cT1a/b	9.184	1.933 to 43.644	.0053
cT2c versus cT1a/b	16.400	3.159 to 85.157	.0009
PSA doubling time			
2-5 versus < 2	0.325	0.202 to 0.523	< .0001
5.1-50 versus < 2	0.116	0.063 to 0.212	< .0001
> 50 versus < 2	0.133	0.073 to 0.242	< .0001
Age, years			
60-65 versus < 60	1.067	0.646 to 1.762	.7997
65-70 versus < 60	0.736	0.428 to 1.268	.2700
PSA at diagnosis			
4.1-10.0 versus 0-4.0	1.311	0.751 to 2.287	.3410
10.1-20.0 versus 0-4.0	1.069	0.523 to 2.184	.8559
Gleason score			
5 versus 2-4	1.017	0.613 to 1.689	.9477
6 versus 2-4	1.450	0.914 to 2.301	.1148
No. of comorbidities per patient			
1 versus 0	1.022	0.649 to 1.610	.9259
2 versus 0	0.861	0.516 to 1.436	.5658
Family history of disease			
Yes versus no	1.376	0.868 to 2.183	.1748
Race			
White versus black	1.131	0.726 to 1.763	.5861

Abbreviation: PSA, prostate-specific antigen.

of secondary treatment chosen by these patients. Patients with fewer comorbidities were more likely to select radical prostatectomy or brachytherapy; those with two or more comorbidities were more likely to undergo external-beam radiation therapy ($P = .012$).

Figure 1 is a KM graph demonstrating the likelihood a patient will remain free from treatment with time. After 2 years, 57% of men had proceeded to secondary therapy, and at 4 years, this portion approached 74%. If a patient remained on WW after 4 years, there was little probability of moving to definitive therapy. Figures 2 and 3 are representative KM curves stratified by DT and the patient's clinical stage. Patients with the fastest PSA DTs (≤ 2 years and 2 to 5 years) and those with palpable disease (cT2a and cT2b/c) more often elected to abandon WW in pursuit of definitive treatment.

Table 5. Patients Who Underwent Secondary Treatment (n = 215)

	No. of Patients	%
Type of treatment		
Radical prostatectomy	104	48.4
External-beam irradiation	57	26.5
Brachytherapy	39	18.1
Androgen deprivation	13	6.0
Cryosurgery	2	0.9
Time to treatment, months		
Mean	15.0	
Median	9.6	
Range	6-81	

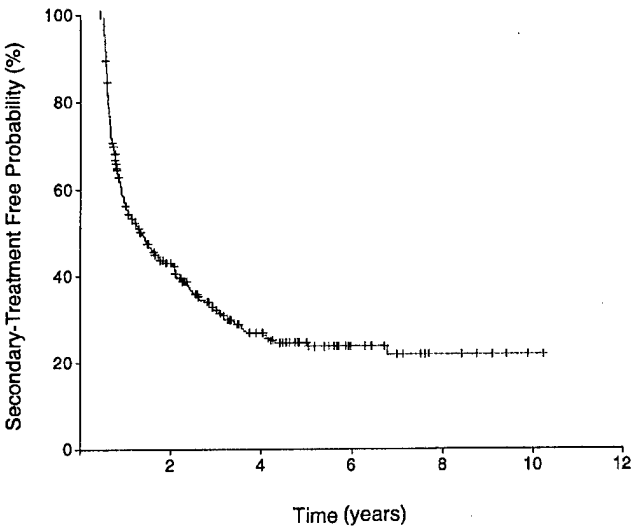


Fig 1. Kaplan-Meier curve indicating those free from secondary treatment of 313 watchful waiting patients.

DISCUSSION

WW has been proposed as a reasonable treatment strategy of localized PC in patients with less than 10 years of life expectancy.[8] In both prospective and retrospective studies, there is indication that patients with localized PC who choose WW may have no loss in life expectancy and that it may be reasonable to defer therapy initially.[8-11] Albertsen et al[11] found in a retrospective analysis of the Connecticut tumor registry that men age 65 to 75 years with conservatively treated low-grade PC can expect to incur no loss of life expectancy. In comparison, men with higher-grade tumors (Gleason scores 5 to 10) experienced a progressively increasing loss of life. Their cohort of men was observed in the era before PSA testing, and a substantial number of men were older than 70 years at the time of diagnosis. There are no data available for WW in those men who would be considered excellent candidates for definitive therapy but who opted to pursue a strategy of deferred therapy. We analyzed the CPDR database to identify a selective cohort of younger men with low-grade, early-stage PC diagnosed during the PSA era who, in general, have a greater than 10-year life expectancy and who elected to pursue WW as their primary treatment. Despite having quite favorable disease characteristics, the vast majority of these men opted to proceed with definitive therapy within 4 years of their diagnosis of PC. The key message is that PSA use has changed the traditional concept of WW from lifelong deferred definitive therapy to temporarily deferred therapy for the majority of men who initially select it.

Koppie et al[17] used the CaPSURE database (University of California, San Francisco, CA) to evaluate both advanced and localized PC patients who chose WW and determined that men who chose WW were more likely to be older than 75 years, have lower serum PSA levels, have organ-confined disease, and have a total Gleason score of ≤ 7. In their group there was a 52% likelihood of secondary treatment within 5 years. Zietman et al[18] retrospectively reviewed 199 records of men with localized

Table 6. Comorbidities by Type of Treatment

Comorbidity (No. per patient)	Radical Prostatectomy		Brachytherapy		External-Beam Irradiation		P
	No.	%	No.	%	No.	%	
0	67	64.4	21	53.9	21	36.8	.012
1	25	24.0	12	30.8	20	35.1	
≥2	12	11.5	6	15.4	16	28.1	

disease who had a median age of 71 years. This study similarly showed a 57% chance of patients proceeding to treatment in 5 years and that therapy was usually triggered by increases in PSA. These series demonstrate the traditionally accepted strategy of WW in older patients. By limiting our analysis to men younger than 70 years and with low- to moderate-grade disease, we have attempted to exclude the majority of patients who continued the WW strategy because of advanced age or more aggressive disease.

We have also tried to evaluate the epidemiology and effectiveness of deferred therapy as a primary treatment strategy in younger men. By choosing WW, these men elected to pursue an initially conservative strategy for managing their PC and thereby avoided the possible side effects associated with surgery or radiation therapy. Despite selecting men with tumor characteristics that would appear favorable for WW, we found that 53% of these younger men abandoned this strategy within 2 years. However, if a patient continued the WW strategy longer than 4 years, there was little likelihood of his progressing to secondary therapy. This is the first study to show that WW in contemporary younger men is temporarily deferred local therapy dictated primarily by PSA level.

As with other investigators,[14,15,18,19] we found that PSA DT is the most significant factor associated with secondary treatment. Nam et al[20] suggested that a rapidly increasing PSA level occurs in as many as 31% of patients who choose WW. We found similar results: 22% of the patients in our analysis had a PSA DT of less than 2 years, and an additional 17.6% of patients had DTs between 2 and 5 years. The patients with the fastest PSA DTs were found to have an 81% chance of abandoning WW to undergo definitive treatment. This may reflect an initial underestimation of the patient's tumor burden or the presence of occult higher-grade cancer, suggesting the patient may not have been a suitable candidate for WW.

Although we found, by univariate analysis, that age was a factor in the choice to pursue secondary treatment, when we analyzed the patients' ages using both the log-rank and the Cox analyses, we found it was not a predictor of secondary treatment for this cohort. In these younger men, PSA level, not age, drives the decision for secondary therapy.

Similar to Koppie et al,[17] we found clinical stage was a highly significant factor for predicting which patients will undergo secondary treatment. Those with palpable disease (cT2b or cT2c) were most likely to abandon WW as their primary treatment strategy. This may reflect a greater burden of tumor than was initially estimated at the time of diagnosis. However, in contrast to Koppie et al,[17] the initial PSA level at diagnosis was not a predictor of secondary treatment. A likely explanation of the difference between our results and those of Koppie et al[17] is that we included only those patients whose initial PSA was less than 20 ng/mL; no exclusionary PSA criteria were used in the review by Koppie et al. For patients in our review, the initial PSA level at the time of diagnosis was not a predictor of progression to secondary therapy.

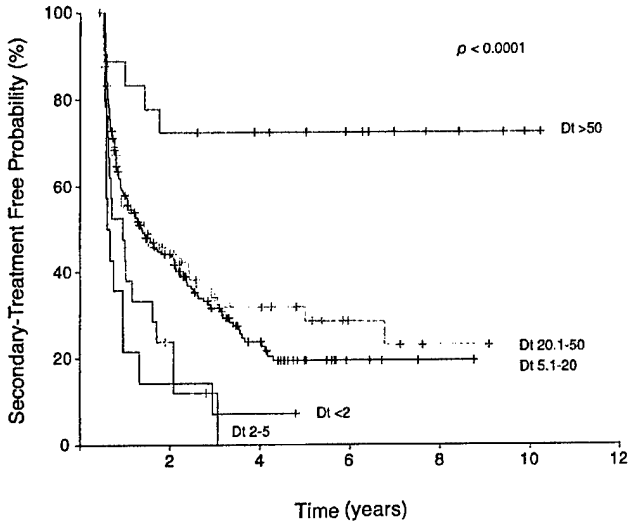


Fig 2. Kaplan-Meier curve indicating those free from secondary treatment, stratified by patients' prostate-specific antigen doubling time (Dt).

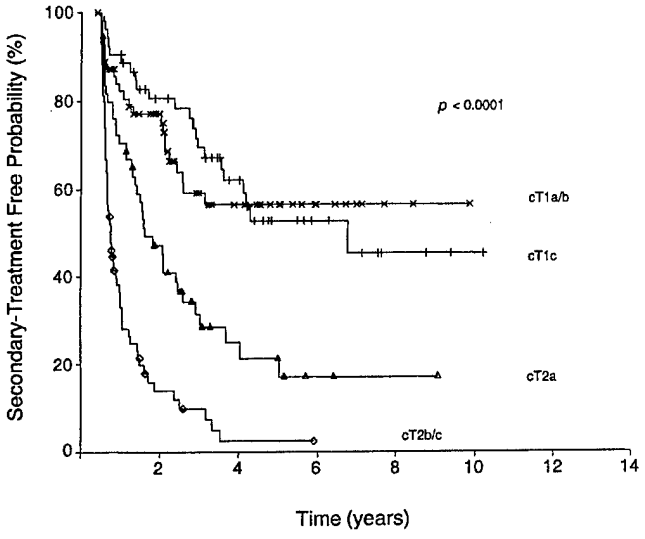


Fig 3. Kaplan-Meier curve indicating those free from secondary treatment, stratified by clinical stage.

Epstein et al[21] demonstrated that men undergoing WW who underwent repeat biopsies showed little evidence of worsening PC grade over the short term. Epstein et al implied that tumor differentiation is not expected to worsen during a 1.5- to 2-year period after initial biopsy. In their study, all 77 men had either an increase or stability in their Gleason score. In our review, 77 patients received repeat biopsies and the decision to undertake the biopsy was made by the attending urologist and patient. Sixty-one percent of patients had the same Gleason score, and 24% had an increase in their Gleason score on repeat needle biopsy. If a higher proportion of the cohort had undergone repeat biopsy, this factor may have been more predictive of secondary treatment. However, the fact that only one fourth of men had a repeat biopsy emphasizes the powerful clinical use of PSA change in this setting.

Bratt et al[22] reported on hereditary PC and found there was no relationship between the clinical characteristics of patients with positive family history, compared with those with sporadic PC. Our analysis found similar results, in that a positive family history did not statistically influence the decision to progress to secondary therapy.

The database does not include reasons patients initially chose WW, but much is known about their initial comorbidities and vascular disease risk factors. It has been documented that comorbidities often influence the initial decision to choose WW.[9,11] Our study tried to determine how comorbidities affect decisions in secondary treatment. It is conceivable that if a patient has multiple comorbidities, both the surgeon and patient would be less likely to opt initially for aggressive therapy, and that these comorbidities could influence the decision to proceed to secondary treatment. Our results, however, suggest there is no relationship between a patient's comorbidities and the ability to remain free from secondary treatment. However, we identified that the number of comorbid illnesses did statistically influence the choice of secondary therapy. Those patients with no comorbidities were most likely to pursue radical prostatectomy or brachytherapy; those with two or more comorbidities chose external-beam radiation therapy.

This study provides a better understanding of patients younger than 70 years who have clinically localized PC. There are many factors that influence both a patient's and a surgeon's decisions to choose WW, as well as many factors that influence the decision to receive secondary treatment. Our review of carefully selected younger men with low-grade, low-stage PC found these men unlikely to pursue this strategy as a long-term treatment. Instead of WW, this approach may better be termed temporarily deferred therapy. The initial PSA level, age, race or ethnicity, family history, and number or type of comorbidities did not predict the progression to secondary treatment. The most predictive factors for a patient's abandoning WW and progressing to definitive therapy were the PSA DT and the initial clinical stage. Those patients with faster DTs (< 5 years) and palpable tumor burden (T2b or T2c) were statistically most likely to move to secondary treatment.

The fact that as many as 73.2% of patients discontinued WW at the 4-year point suggests the necessity of redefining the criteria used for the WW option. Alternatively, this percentage may indicate that PSA level and other factors generate unwarranted concern that needs to be managed more effectively.

The next analysis to be performed in this review is a comparison of the outcomes of the 215 patients who started on a course of WW and moved to definitive therapy with the outcomes of the men who elected immediate, definitive treatment. This study is underway and should provide insight into whether temporarily deferred therapy or WW is a reasonable management strategy for young men during the PSA era.

Despite the encouraging data regarding WW in this clinical setting, caution is in order. The lack of uniformity in the manner of informing patients about the WW option and standardized procedures to manage the implications of changes in PSA level, and other factors, may, over time, create confounding issues. These would be minimized by a prospective study.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The authors indicated no potential conflicts of interest.

REFERENCES

1. Greenlee RT, Hill Harmon MB, Murray T, et al: Cancer statistics, 2001. CA Cancer J Clin 51:15-36, 2002

2. Newcomer LM, Stanford JL, Blumenstein BA, et al: Temporal trends in rates of prostate cancer declining incidence of advanced stage disease, 1974 to 1994, J Urol 158:1427-1430, 1997

3. Stephenson RA: Population-based prostate cancer trends in the PSA-era: Data from the Surveillance, Epidemiology and End Results (SEER) Program. Urol Clin North Am 29:173-181, 2002

4. Farkas A, Scheider D, Perrotti M, et al: National trends in the epidemiology of prostate cancer, 1973 to 1974: Evidence for the effectiveness of prostate-specific antigen screening. Urology 52:444-449, 1998

5. Walsh PC, Lepor H, Eggleston JC: Radical prostatectomy with preservation of sexual function: Anatomical and pathological consideration. Prostate 4:473-485, 1983

6. Barry MJ, Albertsen PC, Bagshaw MA, et al: Outcomes for men with clinically nonmetastatic prostate cancer managed with radical prostatectomy, external beam radiotherapy or expectant management: A retrospective analysis. Cancer 91:2302-2314, 2001

7. Ragde H, Grado GL, Nadie B, et al: Modern prostate brachytherapy. CA Cancer J Clin 50:380-393, 2000

8. Chodak G, Thisted R, Glenn G, et al: Results of conservative management of clinically localized prostate cancer. N Engl J Med 330:242-248, 1994

9. Steinberg G, Bales G, Brendler C: An analysis of watchful waiting for clinically localized prostate cancer. J Urol 159:1431-1436, 1998

10. Johansson JE, Holmberg L, Johansson S, et al: Fifteen-year survival in prostate cancer: A prospective, population study in Sweden. JAMA 277:467-472, 1997

11. Albertson P, Fryback D, Storer B, et al: Long-term survival among men with conservatively treated localized prostate cancer. JAMA 274:626-632, 1995

12. Epstein J, Walsh PC, Carmichael M, et al: Pathologic and clinical findings to predict tumor extent of non-palpable (stage TIc) prostate cancer. JAMA 271:368-374, 1994

13. Sun L, Gancarczyk K, Paquette EL, et al: Introduction to Department of Defense Center for Prostate Disease Research Multicenter National

Prostate Cancer Database, and analysis of changes in the PSA-era. Urol Oncol 6:203-210, 2001

14. Carter H, Morrell C, Pearson J, et al: Estimation of prostatic growth using serial prostate-specific antigen measurements in men with and without prostate disease. Cancer Res 52:3323-3328, 1992

15. McLaren D, McKenzie M, Duncan G, et al: Watchful waiting or watchful progression? Prostate specific doubling times and clinical behavior in patients with early untreated prostate carcinoma. Cancer 82:342-348, 1998

16. Egawa S, Matsumoto K, Suyama K, et al: Observations of prostate specific antigen doubling time in Japanese patients with nonmetastatic prostate carcinoma. Cancer 86:463-469, 1999

17. Koppie T, Grossfeld G, Miller D, et al: Patterns of treatment of patients with prostate cancer initially managed with surveillance: Results from the CaPSURE database. J Urol 164:81-88, 2000

18. Zietman A, Thakral H, Wilson L, et al: Conservative management of prostate cancer in the prostate specific antigen ERA: The incidence and time course of subsequent therapy. J Urol 166:1702-1706, 2001

19. Choo R, Klotz L, Danjoux C, et al: Feasibility study: Watchful waiting for localized low to intermediate grade prostate carcinoma with selective delayed intervention based on prostate specific antigen, histological and/or clinical progression. J Urol 167:1664-1669, 2002

20. Nam R, Klotz L, Jewett M, et al: Prostate specific antigen velocity as a measure of the natural history of prostate cancer: Defining a "rapid riser" subset. B J Urol 81:100-104, 1998

21. Epstein J, Walsh P, Carter H: Dedifferentiation of prostate cancer grade with time in men followed expectantly for stage TIc disease. J Urol 166:1688-1691, 2001

22. Bratt O, Damber J, Emanuelsson M, et al: Hereditary prostate cancer: Clinical characteristics and survival. J Urol 167:2423-2426, 2002

0022-5347/04/1713-0001/0
THE JOURNAL OF UROLOGY®

Vol. 171, ●●●-●●●, March 2004
Printed in U.S.A.
DOI: 10.1097/01.ju.0000113794.34810.d0

EARLY VERSUS DELAYED HORMONAL THERAPY FOR PROSTATE SPECIFIC ANTIGEN ONLY RECURRENCE OF PROSTATE CANCER AFTER PRIOR RADICAL PROSTATECTOMY

JUDD W. MOUL,*† HONGYU WU, LEON SUN, DAVID G. McLEOD, CHRISTOPHER AMLING,‡ TIMOTHY DONAHUE, LEO KUSUDA, WADE SEXTON, KEITH O'REILLY, JAVIER HERNANDEZ,§ ANDREW CHUNG AND DOUGLAS SODERDAHL

From the Department of Surgery, Center for Prostate Disease Research, Uniformed Services University of the Health Sciences (JWM, HW, LS), Department of Urology, National Naval Medical Center (TD), Bethesda, Department of Urology, Malcolm Grow Medical Center, Andrews AFB (AC), Maryland, Urology Service, Department of Surgery, Walter Reed Army Medical Center, Washington, D. C. (JWM, DGM), Department of Urology, San Diego Naval Medical Center, San Diego, California (CA), Department of Urology, Portsmouth Naval Medical Center, Portsmouth, Virginia (LK), Department of Urology, Wilford Hall Medical Center, Lackland AFB (WS), Urology Service, Department of Surgery, Brooke Army Medical Center, San Antonio (JH), Texas, Urology Service, Department of Surgery, Madigan Army Medical Center, Tacoma, Washington (KO), and Urology Service, Department of Surgery, Eisenhower Army Medical Center, Augusta, Georgia (DS)

ABSTRACT

Purpose: Hormonal therapy (HT) is the current mainstay of systemic treatment for prostate specific antigen (PSA) only recurrence (PSAR), however, there is virtually no published literature comparing HT to observation in the clinical setting. The goal of this study was to examine the Department of Defense Center for Prostate Disease Research observational database to compare clinical outcomes in men who experienced PSAR after radical prostatectomy by early versus delayed use of HT and by a risk stratified approach.

Materials and Methods: Of 5,382 men in the database who underwent primary radical prostatectomy (RP), 4,967 patients were treated in the PSA-era between 1988 and December 2002. Of those patients 1,352 men who had PSAR (PSA after surgery greater than 0.2 ng/ml) and had postoperative followup greater than 6 months were used as the study cohort. These patients were further divided into an early HT group in which patients (355) received HT after PSA only recurrence but before clinical metastasis and a late HT group for patients (997) who received no HT before clinical metastasis or by current followup. The primary end point was the development of clinical metastases. Of the 1,352 patients with PSAR clinical metastases developed in 103 (7.6%). Patients were also stratified by surgical Gleason sum, PSA doubling time and timing of recurrence. Univariate and multivariate Cox proportional hazard models were used to evaluate the effect of early and late HT on clinical outcome.

Results: Early HT was associated with delayed clinical metastasis in patients with a pathological Gleason sum greater than 7 or PSA doubling time of 12 months or less (Hazards ratio = 2.12, $p = 0.01$). However, in the overall cohort early HT did not impact clinical metastases. Race, age at RP and PSA at diagnosis had no effect on metastasis-free survival ($p > 0.05$).

Conclusions: The retrospective observational multicenter database analysis demonstrated that early HT administered for PSAR after prior RP was an independent predictor of delayed clinical metastases only for high-risk cases at the current followup. Further study with longer followup and randomized trials are needed to address this important issue.

KEY WORDS: prostatic neoplasms, recurrence, prostate-specific antigen, hormones, prostatectomy

The prostate specific antigen (PSA) era (1988 to present) has dramatically altered the epidemiology of prostate cancer in the United States and many other industrialized countries.[1,2] Diagnosis of clinically localized disease has increased dramatically and radical prostatectomy (RP) rates have increased from 17.4 per 100,000 in 1988 to 54.6 per 100,000 in 1992.[2] By 1992, 36.6% of patients with localized and regional disease received RP and there was a 3 to 4-fold increase in the rate of surgery in men 45 to 59 years old, and a 2 to 3-fold increase in men 60 to 69 years old.[2] Most recently in a large United States military study Moul et al showed that median age at RP had decreased to 62.3 years by 2000 and that more

Accepted for publication September 26, 2003.
The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Departments of the Army, Navy or Air Force or the Department of Defense.
Supported by a grant from the Center for Prostate Disease Research, a program of the Henry M. Jackson Foundation for the Advancement of Military Medicine (Rockville, Maryland) and the Uniformed Services University of the Health Sciences, funded by the United States Army Medical Research and Material Command (DAMD17-02-1-0066).
* Correspondence and requests for reprints: Center for Prostate Disease Research, 1530 East Jefferson St., Rockville, Maryland 20852 (telephone: 240-453-8951; FAX: 240-453-8912; e-mail: jmoul@cpdr.org).
† Financial interest and/or other relationship with Astra Zeneca, TAP and Aventis.
‡ Financial interest and/or other relationship with TAP and Astra Zeneca.
§ Financial interest and/or other relationship with TAP.

Editor's Note: **This article is the __ of __ published in this issue for which category 1 CME credits can be earned. Instructions for obtaining credits are given with the questions on pages __ and __.**

than 40% of men were younger than 60 years at time of surgery.[3] Furthermore, a large number of generally younger men who had already been treated for clinically localized prostate cancer are now experiencing disease recurrence.[4]

With approximately 220,000 cases of prostate cancer diagnosed each year in the United States, two-thirds of which are treated with surgery or radiation therapy, and with as many as 40% of patients eventually experiencing disease relapse, a PSA only early progression up to 60,000 men per year.[4,5] Treatment of early progression after a PSA only or biochemical recurrence after RP is controversial. Localized therapies such as salvage prostate bed radiation are best reserved for men with a high likelihood of having confined disease.[6] Hormonal therapy (HT) is commonly used for the management of PSA only recurrence. However, to date there is little published literature supporting this intervention in the clinical setting. Although Pound et al reported the natural history of observation for PSA recurrence after RP, there was no comparison to men receiving early HT.[7] The goal of this study was to examine the outcome after PSA recurrence (PSAR) in patients who received early HT versus those who received no HT before the occurrence of clinical metastasis or until current followup.

MATERIALS AND METHODS

The Department of Defense Center for Prostate Disease Research Multi-center Prostate Disease Registry Research Database was used for this study and has been described previously.[3,8] In January 2003 a data call was conducted. Specifically, of 12,606 men with prostate cancer enrolled in the database, 5,382 (42.7%) underwent primary RP and 4,967 were treated in the PSA era between 1988 and December 2002. Of those men 1,352 with PSAR (postoperative PSA greater than 0.2 ng/ml) and postoperative followup greater than 6 months were used as the study cohort. Patients were excluded from study due to postoperative followup of less than 6 months (528 patients), lack of PSAR followup (49) or receiving salvage radiation therapy after PSAR (363, fig. 1).

The impact of HT was examined in all patients with PSAR as well as patients with high-risk disease features. The high-risk group was defined by the subgroups of those who had an early PSAR within 12 months after RP (544 patients), patients who had early PSAR between 12.1 and 24 months (288), patients who had a pathological Gleason sum greater than 7 or PSA doubling time of 12 months or less (544) and patients who were considered noncurable by the Johns Hopkins definition (664).[9] Noncurable disease was defined by the conditions that the capsule was positive and pathological Gleason sum was greater than 6, or the surgical margins, lymph nodes or seminal vesicles were positive. Patients with organ confined disease, or those with extracapsular extension only and negative margins with Gleason sum 6 or less were defined as having curable disease.[9]

We did include in the study men who had node positive disease (79) and who underwent RP, and did not receive HT before biochemical recurrence. The data fields analyzed for this study included patient age at treatment, ethnicity/race, clinical stage at diagnosis, pretreatment PSA, highest biopsy Gleason sum, highest pathological Gleason sum, margin status, capsule status and seminal vesicle status. Distant metastases that were identified via nuclear imaging studies and radiographic studies (computerized tomography, magnetic resonance imaging, bone scan and capromab pendetide scans) were used as the end point. Imaging studies were ordered at the discretion of the treating physician based on increasing PSA and/or clinical signs and symptoms. The PSA doubling time (PSA-DT) was calculated assuming first order kinetics and using a minimum of 2 PSA values, each separated by a minimum of 3 months. The mean and median number of PSA values for the study cohort was 6.3 and 5.0, respectively. The minimum PSA value used to calculate the PSA-DT needed to be greater than 0.2 ng/ml for all study patients. Doubling time was determined per patient by calculating the logarithm of PSA values. A simple linear model was created using the formula $Ln(PSA)=A + B * (\text{months after PSA recurrence})$, where A represents the y intercept and B represents the slope of the curve. Linear regression analysis was then performed to determine the slope and intercept of the best fit curve. From this value we calculated PSA-DT using the formula, $PSA\text{-}DT=\ln(2)/B$.

HT included luteinizing hormone releasing hormone (LH-RH) agonist therapy alone, combined HT (LH-RH or orchiectomy plus an oral antiandrogen) or orchiectomy. We did not differentiate between these traditional types of HT because of similar survival rates in advanced disease. After RP the mean/median followup was 5.2/4.7 (range 0.5 to 13.9) years and after PSAR the mean/median followup was 4.2/3.7 (range 0.1 to 13.0) years.

The chi-square test was used to compare differences between patient groups (early HT vs late/no HT) with respect to demographic, clinical and pathological characteristics. The clinical metastasis-free survival was defined as the interval

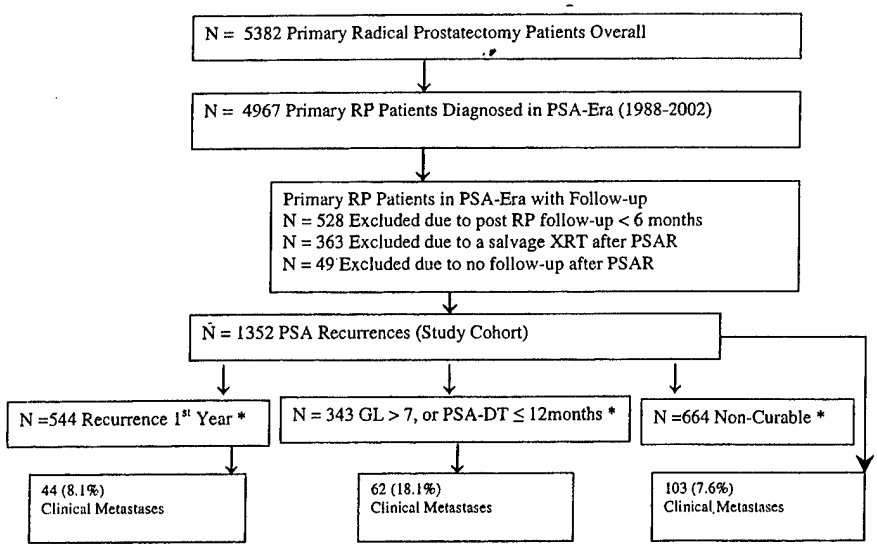


FIG. 1. Study cohort diagram to illustrate patients excluded from and included in study. Asterisk, groups are not mutually exclusive. XRT, external beam radiation therapy.

from PSAR to the time to documented clinical metastasis. The Kaplan-Meier method was used to estimate survival with statistical inferences on actuarial curves made using the log rank test. The relationships between metastasis-free survival and the other factors were analyzed using the univariate and multivariate Cox proportional hazard model with HT status, age at surgery, race, log-transformed pretreatment PSA and pathological status (curable disease: no vs yes). In the Cox model, age at surgery and log transformed pretreatment PSA entered the model as continuous variables. Race (black versus white and other), curable disease (no vs yes) and HT status (early vs late) were categorical variables.

RESULTS

Among the 1,352 patients who had PSAR after RP (PSA greater than 0.2 ng/ml), 355 (26.3%) men received HT after PSAR, with the majority (16.3%) starting HT at PSA between 0.21 and 2.5 ng/ml (fig. 2). The end point of clinical metastases was seen in 103 men (7.6%) overall (fig. 1). Table 1 summarizes the demographic, clinical and pathological features of the PSAR cohort based on clinical and pathological features and by risk group. Specifically, patients (544) were examined by the subgroups of PSAR within postoperative year 1 by high pathological Gleason sum (greater than 7) or having a rapid PSA-DT less than 12 months, and by whether they had non-curable disease the Johns Hopkins criteria based on operative pathological criteria.

The clinical and pathological features by PSA when HT was instituted (greater than 0.2 to 2.5, 2.6 to 5.0, 5.1 to 10.0, greater than 10.0 ng/ml) or no HT during the course of current followup are shown in table 2. Pretreatment PSA, Gleason sum at diagnosis and on surgical pathology, status of capsular extension and surgical margin, seminal vesicle involvement and PSA-DT (less than 1 year) are significantly associated with administration of HT and PSA at start of HT ($p < 0.01$). Age at RP, race/ethnicity and the period between RP and PSAR were not factors affecting HT administration ($p > 0.05$, table 2).

The end point of clinical metastases was analyzed by PSA during PSAR when HT was initiated. For the comparison of PSA 1.0, 2.0, 3.0 and 4.0 ng/ml or less to other cases of PSAR there was no difference between early vs late HT (data not shown). However, early HT administered at PSA 5 ng/ml or less (fig. 3) or at PSA 10 ng/ml or less (fig. 4) showed a significant effect on delaying clinical metastasis in high risk cases (pathological Gleason sum greater than 7 or PSA-DT 12 months or less), compared to late or no HT. In the overall cohort of 1,352 patients with PSAR early HT (5 ng/ml PSA or less, or 10 ng/ml or less [not shown]) did not impact clinical metastases (fig. 5).

Univariate Cox proportional hazard analysis (table 3) shows the prognostic factors predicting clinical metastases in risk stratified groups of patients. In the clinical settings comparing all patients with PSAR or in the setting of early PSAR within postoperative year 1, noncurable disease, a reflection of pathological stage and grade, was the strongest predictor of clinical metastases. In the other clinical setting of men with Gleason greater than 7 or PSA-DT of 12 months or less, early HT either administered at PSA 5 ng/ml or less or at PSA 10 ng/ml or less was a significant predictor of clinical metastasis (Hazards ratio > 2.1, $p < 0.01$). A nearly identical trend of the effect of early HT and curable disease on metastasis-free survival was observed in the multivariate Cox analysis (table 4). Race, age at treatment and pretreatment PSA were not associated with clinical metastasis.

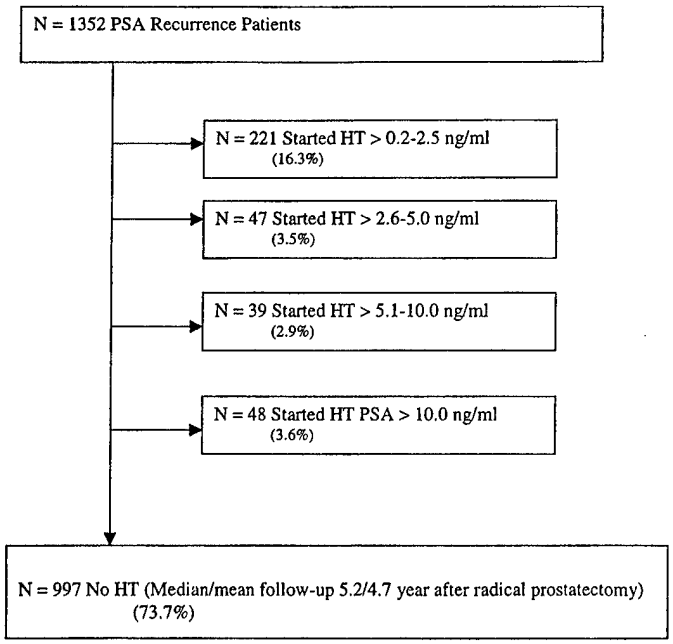


FIG. 2. PSA only recurrence cohort to illustrate PSA at initiation of HT.

DISCUSSION

The most important aspect of this study is that we have attempted, for the first time, to analyze hormonal therapy use in the common clinical setting of PSAR. While we have shown that early HT administered for PSAR after RP can delay the onset of clinical metastases for high risk cases, it must be recognized that this finding was from an observational database and not a randomized controlled trial. Furthermore, the clinical benefit to date is only seen for high-risk cases (Gleason greater than 7 or PSA doubling time less than 12 months) and not in the overall group of cases of biochemical recurrence. It is unknown whether this delaying of clinical metastases will translate into an ultimate survival benefit. Longer followup of this cohort will be necessary and the ultimate benefit of early hormones in this setting must await a prospective randomized trial.

It has previously been shown that the timing of the PSAR, the PSA doubling time during recurrence and the Gleason sum in the RP specimen all impact the natural history of biochemical recurrence to clinical metastases.[7] However, the potential modulating effect of HT in this setting has not been shown previously. We now demonstrate that in the risk stratified settings of high risk disease (pathological Gleason sum greater than 7 or PSA-DT of 12 months or less), early use of HT was a significant and independent predictor of delayed clinical metastases. As previously noted the ultimate clinical value is unknown.

There are a number of potential criticisms of our study that must be addressed. The definition of PSAR itself in the RP setting is controversial. Amling et al have found that a value greater than 0.4 ng/ml was the most appropriate to dictate treatment because this cut point was associated with an approximate 75% chance of further biochemical and/or clinical progression during the next 3 years.[10] However, Freedman et al recently found support in the more conventional cut point of greater than 0.2 ng/ml.[11] We used the 0.2 ng/ml cut point to define biochemical recurrence to mirror the study of Pound et al.[7] However, we recognized that a cut-point of 0.2 ng/ml might mask the effect of early treatment versus observation, especially in shorter followup because many patients will not progress with observation.[10] It is becoming apparent that some men with low level PSA recurrence in the PSA range of 0.2 to 0.5 ng/ml (or even higher) might not always have cancer cells producing PSA, but benign cells/tissue in the prostatic fossa area. It is beyond the

TABLE 1. *Demographic, clinical and pathological characteristics of patients*

	No. (%)			
	All PSAR	PSAR 1 Yr or Less After RP	GL Greater Than 7 or PSA-DT Less Than 12 Mos	Noncurable
Total	1,352 (100)	544 (100)	343 (100)	664 (100)
Age at surgery:				
60 or Younger	353 (26.1)	153 (28.2)	90 (26.2)	166 (25.0)
60. 1–70	767 (56.8)	307 (56.5)	195 (56.9)	379 (57.2)
Older than 70	231 (17.1)	83 (15.3)	58 (16.9)	118 (17.8)
Mean/median	63.7/64.3	63.4/63.9	64.0/64.3	64.0/64.5
Race:				
White + others	1,025 (77.5)	401 (75.1)	260 (78.1)	504 (77.1)
Black	297 (22.5)	133 (24.9)	73 (21.9)	150 (22.9)
Clinical stage:				
T1	505 (38.5)	231 (43.3)	110 (33.4)	243 (37.7)
T2	778 (59.3)	290 (54.3)	209 (63.5)	380 (58.9)
T3+T4	28 (2.1)	13 (2.4)	10 (3.0)	22 (3.4)
Pretreatment PSA:				
4 or Less	240 (19.1)	91 (17.5)	44 (13.7)	79 (12.7)
4–10	624 (49.8)	258 (49.5)	148 (46.1)	299 (48.2)
Greater than 10	390 (31.1)	172 (33.0)	129 (40.2)	243 (39.1)
Mean/median11.1/6.9	12.3/7.4	13.6/8.3	13.2/8.2	
Biopsy Gleason sum:				
6 or Less	561 (64.3)	230 (63.4)	82 (36.9)	237 (53.1)
7	237 (27.2)	104 (28.6)	92 (41.4)	157 (35.2)
8–10	74 (8.5)	29 (8.0)	48 (21.6)	52 (11.7)
Pathological Gleason sum:				
6 or Less	509 (45.8)	212 (45.8)	38 (12.7)	170 (28.6)
7	434 (39.1)	178 (38.4)	92 (30.9)	296 (49.8)
8–10	168 (15.1)	73 (15.8)	168 (56.4)	128 (21.6)
Capsule:				
Neg	800 (59.2)	323 (59.4)	158 (46.1)	178 (26.8)
Pos	552 (40.8)	221 (40.6)	185 (53.9)	486 (73.2)
Surgical margin:				
Neg	845 (62.5)	340 (62.5)	176 (51.3)	157 (23.6)
Pos	507 (37.5)	204 (37.5)	167 (48.7)	507 (76.4)
Seminal vesicle:				
Neg	1,199 (88.7)	476 (87.5)	259 (75.5)	511 (77.0)
Pos	153 (11.3)	68 (12.5)	84 (24.5)	153 (23.0)
Lymph node:				
Neg	1,277 (94.5)	508 (93.4)	302 (88.0)	589 (88.7)
Pos	75 (5.5)	36 (6.6)	41 (12.0)	75 (11.3)

scope of the present study to address this subject further, but this issue may account for a benign clinical course for a proportion of men deemed to have PSAR. At our modest current followup in this study, this factor may help to explain why no benefit was demonstrated for early HT in the overall cohort of men with PSAR.

This concept of "benign" PSAR in the low PSA range may also explain why the early PSAR in the postoperative year 1 group did not demonstrate an effect of early HT. However, in multivariable analysis factoring in the high-risk features, early HT was significant to predict delayed clinical metastases in this early recurrence group. In other words, in men who had early recurrence and other high-risk disease characteristics, early HT delayed clinical metastases. These analyses indicate that just as risk assessment is critical in newly diagnosed clinically localized disease to dictate multimodal therapy in high-risk cases,[12] so is risk assessment critical in biochemical recurrence. Our study confirms the value of high surgical specimen Gleason sum and PSA doubling time to predict the subgroups of biochemical recurrence destined to fail clinically as originally proposed by Pound et al.[7] We now add early HT as an independent predictor for delayed clinical metastases in high risk cases. Early HT is selectively able to alter the natural history of progression to clinical metastases. However, longer followup and randomized trials will be the ultimate judge of clinical value and survival.

There are a number of other limitations to this study. It cannot be overemphasized that this study was observational and the followup is currently limited but ongoing. Study of observational data is limited by selection and detection bias. There is a selection bias as to which patients generally received early hormonal therapy. As the data illustrate, they tended to be high risk cases. Furthermore, HT was not applied at a set time as in a randomized trial. Some men currently reported in the late or no HT group will switch to early HT if the treating physician starts HT for a PSA recurrence if PSA is still less than 5 or 10 ng/ml when treatment is instituted. In this way our observational data will change with time and the findings could also change. Another important limitation is detection bias. Specifically it is possible that patients who have initiation of HT earlier in the disease course may be more likely to receive radiologic testing or more intense followup. This approach would lead to increased detection of clinical outcome and could affect results.

Finally, in this observational database, many comparisons and subgroup analyses were made. Type 1 error must be considered. In other words in this nonrandomized trial setting, significant findings may be due to chance alone at present and not due to clinical value. Despite these limitations the preliminary results are hypothesis generating that cases of high-risk biochemical recurrence may stand to benefit the most from early HT and prompt, risk stratified randomized trials.

The use of early HT in this setting was based on clinical extrapolation from other clinical settings where early HT was found to be superior to delayed HT.[13,16] Most notably, data from the Medical Research Council in the United Kingdom indicate that early HT (LH-RH agonist or orchiectomy) delays disease progression and improves survival compared to delayed treatment in patients with nonmetastatic (M0) and traditional D2 (M1) disease.[13] Further followup confirmed the advantage of immediate HT in terms of improved disease specific survival, but there was a decrease in the overall survival difference reflecting increased mortality from other causes.[14] Unfortunately in the Medical Research Council study some men in the deferred hormonal arm died

TABLE 2. *Comparison of all patients with PSA recurrence with HT based on PSA*

	No. (%)					
	PSA at HT Start				No HT	p Value
	Greater than 0.2–2.5	2.6–5.0	5.1–10.0	Greater than 10.0		
Total	221	47	39	48	997	
Age at surgery:						0.097
60 or Younger	43 (19.5)	12 (25.5)	10 (25.6)	19 (39.6)	269 (27.0)	
60. 1–70	138 (62.4)	26 (55.3)	19 (48.7)	25 (52.1)	559 (56.1)	
Older than 70	40 (18.1)	9 (19.2)	10 (25.6)	4 (8.3)	168 (16.9)	
Mean/median	64.5/64.3	64.1/64.2	65.4/63.9	62.4/62.6	63.5/64.4	
Race:						0.662
White + others	175 (79.2)	36 (80.0)	29 (74.4)	32 (69.6)	753 (77.5)	
Black	46 (20.8)	9 (20.0)	10 (25.6)	14 (30.4)	218 (22.5)	
Clinical stage:						*
T1	73 (33.3)	11 (25.0)	5 (13.2)	9 (20.9)	407 (42.1)	
T2	140 (63.9)	30 (68.2)	30 (78.9)	33 (76.7)	545 (56.4)	
T3+T4	6 (2.8)	3 (6.8)	3 (7.9)	1 (2.4)	15 (1.5)	
Pretreatment PSA:						< 0.0001
4 or Less	20 (9.5)	8 (18.2)	3 (8.6)	6 (15.8)	203 (21.9)	
4–10	107 (50.7)	8 (18.2)	5 (14.3)	8 (21.0)	496 (53.6)	
Greater than 10	84 (39.8)	28 (63.6)	27 (77.1)	24 (63.2)	227 (24.5)	
Mean/median						
Biopsy Gleason sum:						< 0.0001
6 or Less	75 (51.0)	13 (52.0)	9 (42.9)	8 (26.7)	456 (70.3)	
7	54 (36.7)	8 (32.0)	10 (47.6)	18 (60.0)	147 (22.6)	
8–10	18 (12.2)	4 (16.0)	2 (9.5)	4 (13.3)	46 (7.1)	
Pathological Gleason sum:						< 0.0001
6 or Less	49 (25.6)	13 (38.2)	8 (25.0)	6 (16.7)	433 (52.9)	
7	98 (51.3)	14 (41.2)	15 (46.9)	12 (33.3)	295 (36.1)	
8–10	44 (23.0)	7 (20.6)	9 (28.1)	18 (50.0)	90 (11.0)	
Capsule:						< 0.0001
Neg	95 (43.0)	23 (48.9)	19 (48.7)	23 (47.9)	640 (64.2)	
Pos	126 (57.0)	24 (51.1)	20 (51.3)	25 (52.1)	357 (35.8)	
Surgical margin:						< 0.0001
Neg	102 (46.1)	21 (44.7)	20 (51.3)	27 (56.2)	675 (67.7)	
Pos	119 (53.9)	26 (55.3)	19 (48.7)	21 (43.8)	322 (32.3)	
Seminal vesicle:						< 0.0001
Neg	179 (81.0)	35 (74.5)	29 (74.4)	38 (79.2)	918 (92.1)	
Pos	42 (19.0)	12 (25.5)	10 (25.6)	10 (20.8)	79 (7.9)	
Lymph node:						*
Neg	198 (89.6)	39 (83.0)	33 (84.6)	40 (83.3)	967 (97.0)	
Pos	23 (10.4)	8 (17.0)	6 (15.4)	8 (16.7)	30 (3.0)	
PSAR 1 yr or less:						0.495
Yes	88 (39.8)	15 (31.9)	20 (51.3)	20 (41.7)	401 (40.2)	
No	133 (60.2)	32 (68.1)	19 (48.7)	28 (58.3)	596 (59.8)	
PSA-DT greater than 1 yr:						< 0.0001
Yes	90 (47.4)	21 (52.5)	15 (44.1)	27 (67.5)	84 (9.3)	
No	100 (52.6)	19 (47.5)	19 (55.9)	13 (32.5)	815 (90.7)	

* Sample size was too small for chi-square analysis (T3+T4, Lymph node Pos.)

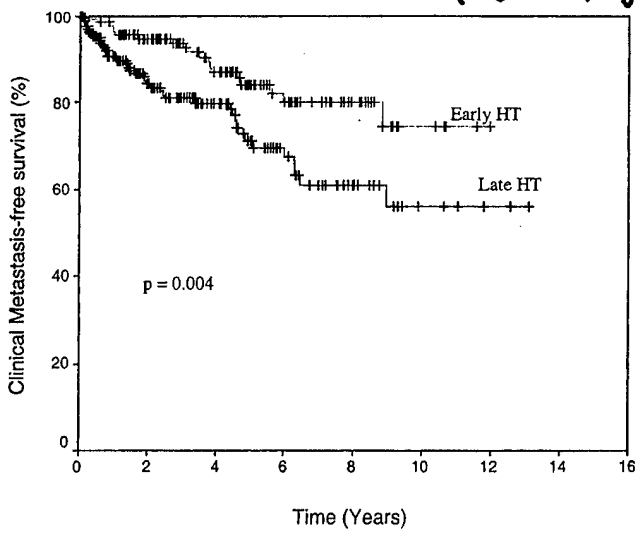


FIG. 3. Early HT (administered at PSA 5 ng/ml or less) affects clinical metastasis survival in patients with pathological Gleason sum greater than 7 or PSA-DT 12 months or less. Time zero is from PSAR time.

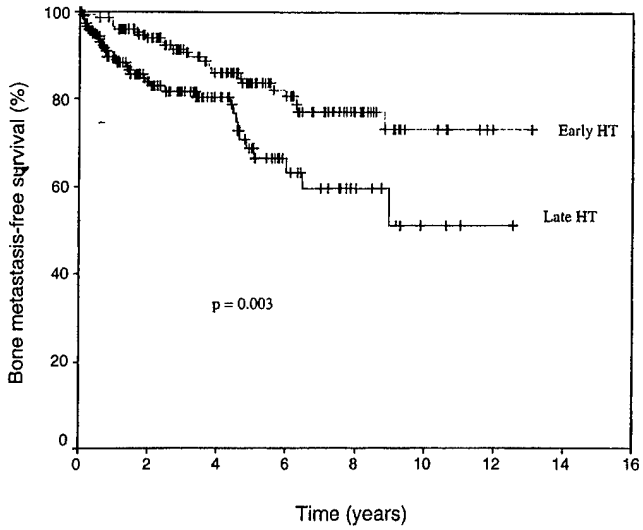


FIG. 4. Early HT (administered at PSA 10 ng/ml or less) affects clinical metastasis-free survival in patients with pathological Gleason sum greater than 7 or PSA-DT 12 months or less. Time zero is from PSAR time.

before receiving any treatment. This event may have biased results to an unknown extent in favor of early therapy. Furthermore, the patients with M0 disease undoubtedly had more advanced disease than the average current patient with PSAR, including those reported here.

Messing et al have also reported results from a random-

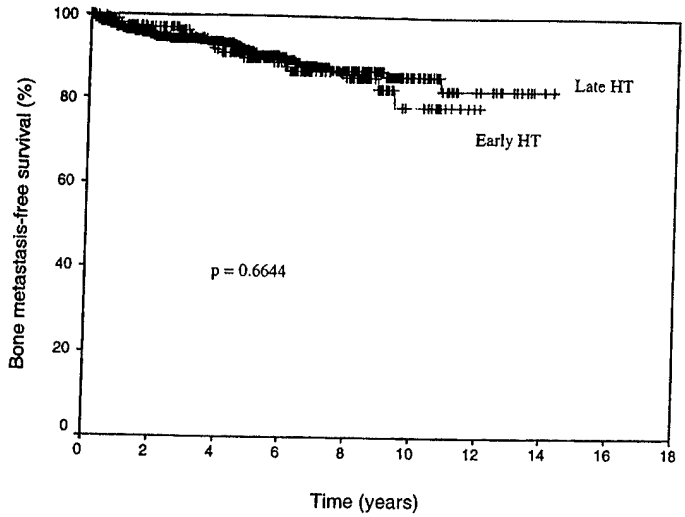


FIG. 5. Early HT (administered at PSA 5 ng/ml or less) did not affect clinical metastasis-free survival in overall cohort of 1,352 patients with PSAR at current followup. Time zero is from PSAR time.

ized, multicenter trial of early versus delayed HT in men who underwent RP and had pelvic lymph node metastases (D1).[15] Those who received immediate HT (LH-RH agonist or orchiectomy) had a 4.3% death rate from prostate cancer at 7-year followup, compared with a death rate of 30.8% in men who were initially observed ($p < 0.01$). Whether these studies can be extrapolated to justify a benefit for early HT for men with PSAR is speculative.

Patients reported on here were treated based on physician belief, and the HT included LH-RH agonist therapy alone, complete HT with a LH-RH agonist and an oral antiandrogen[17] or orchiectomy. Future studies will be required to compare LH-RH alone versus complete HT in this setting as well as the emerging role of nontraditional HT,[18] antiandrogen monotherapy[19] and/or oral combination therapy.[20]

CONCLUSIONS

Retrospective study of a large observational multi-center database suggested that early HT administered for PSA-only recurrence after prior radical prostatectomy was an independent predictor of delayed clinical metastases in high-risk

TABLE 3. *Univariate Cox proportional hazards models for predictors of clinical metastasis in overall and risk stratified groups of patients with PSAR*

	Hazards Ratio	95% CI	p Value
All Pts with PSAR:			
Curable disease No vs yes	2.49	1.62–3.83	<0.0001
Late HT (none or PSA greater than 5) vs early HT (PSA 5.0 or less)	0.91	0.58–1.41	0.665
Black vs white + others	1.04	0.65–1.67	0.870
Log transformed pretreatment PSA	1.03	0.85–1.24	0.791
Pt age at surgery	0.97	0.95–1.00	0.064
Early PSAR (1 yr or less after RP):			
Curable disease No vs yes	2.71	1.40–5.26	0.0032
Late HT (none or PSA greater than 5) vs early HT (PSA 5.0 or less)	1.08	0.52–2.25	0.840
Black vs white + others	0.85	0.41–1.77	0.661
Log transformed pretreatment PSA	1.10	0.81–1.49	0.550
Pt age at surgery	1.00	0.95–1.04	0.900
Pathological Gleason sum greater than 7 or PSA-DT 12 mos or less:			
Late HT (none or PSA greater than 5) vs early HT (PSA 5.0 or less)	2.17	1.26–3.74	0.005
Curable disease No vs yes	2.32	1.14–4.70	0.020
Pt age at surgery	0.98	0.94–1.01	0.263
Black vs white + others	0.46	0.21–1.01	0.052
Log transformed pretreatment PSA	0.90	0.73–1.12	0.337
Pathological Gleason sum greater than 7 or PSA-DT 12 mos or less:			
Late HT (none or PSA greater than 10) vs early HT (PSA 10 or less)	2.14	1.28–3.58	0.004
Curable disease No vs yes	2.32	1.14–4.70	0.020
Black vs white + others	0.46	0.21–1.01	0.052
Pt age at surgery	0.98	0.94–1.01	0.263
Log transformed pretreatment PSA	0.90	0.73–1.12	0.337

TABLE 4. *Multivariate Cox proportional hazard models for predictors of clinical metastasis in overall and risk stratified groups of patients with PSAR*

	Hazards Ratio	95% CI	p Value
All Pts with PSAR:			
Curable disease No vs yes	2.55	1.58–4.11	0.0001
Late HT (none or PSA greater than 5) vs early HT (PSA 5.0 or less)	1.02	0.63–1.63	0.949
Black vs white + others	0.98	0.60–1.62	0.951
Pt age at surgery	0.98	0.95–1.01	0.105
Log transformed pretreatment PSA	0.94	0.78–1.14	0.531
Early PSAR (1 yr or less after RP):			
Curable disease No vs yes	2.73	1.33–5.61	0.0061
Late HT (none or PSA greater than 5) vs early HT (PSA 5.0 or less)	1.38	0.64–2.99	0.410
Black vs white + others	0.84	0.39–1.81	0.656
Pt age at surgery	0.99	0.95–1.04	0.800
Log transformed pretreatment PSA	1.02	0.74–1.39	0.919
Pathological Gleason sum greater than 7 or PSA-DT 12 mos or less:			
Late HT (none or PSA greater than 5) vs early HT (PSA 5.0 or less)	2.12	1.20–3.73	0.010
Curable disease No vs yes	2.54	1.14–5.66	0.023
Black vs white + others	0.48	0.21–1.10	0.080
Pt age at surgery	0.97	0.93–1.01	0.191
Log transformed pretreatment PSA	0.90	0.73–1.12	0.343
Pathological Gleason sum greater than 7 or PSA-DT 12 mos or less:			
Late HT (none or PSA greater than 10) vs early HT (PSA 10 or less)	2.21	1.27–3.83	0.005
Curable disease No vs yes	2.58	1.16–5.75	0.020
Black vs white + others	0.47	0.21–1.06	0.068
Pt age at surgery	0.98	0.93–1.02	0.245
Log transformed pretreatment PSA	0.91	0.73–1.15	0.440

cases with high grade (Gleason sum greater than 7), short (12 months or less) PSA-DT and adverse (noncurable) pathology. Further study and randomized trials will be necessary to determine if this improvement in metastasis-free survival translates into an overall and disease specific survival benefit.

REFERENCES

1. Jemal, A., Murray, T., Samuels, A., Ghafoor, A., Ward, E. and Thun, M. J.: Cancer statistics, 2003. CA Cancer J Clin, **53:** 5, 2003
2. Moul, J. W.: Treatment options for prostate cancer: part I-stage, grade, PSA, and changes in the 1990's. Am J Manag Care, **4:** 1031, 1998
3. Moul, J. W., Wu, H., Sun, L., McLeod, D. G., Armling, C., Lance, R. et al: Epidemiology of radical prostatectomy for localized prostate cancer in the era of prostate-specific antigen: an overview of the Department of Defense Center for Prostate Disease Research national database. Surgery, **132:** 213, 2002
4. Moul, J. W.: Prostate specific antigen only progression of prostate cancer. J Urol, **163:** 1632, 2000
5. Djavan, B., Moul, J. W., Zlotta, A., Remzi, M. and Ravery, V.: PSA progression following radical prostatectomy and radiation therapy: new standards in the new Millenium. Eur Urol, **43:** 12, 2003
6. Katz, M. S., Zelefsky, M. J., Venkatraman, E. S., Fuks, Z., Hummer, A. and Leibel, S. A.: Predictors of biochemical outcome with salvage conformal radiotherapy after radical prostatectomy for prostate cancer. J Clin Oncol, **21:** 483, 2003
7. Pound, C. R., Partin, A. W., Eisenberger, M. A., Chan, D. W., Pearson, J. D. and Walsh, P. C.: Natural history of progression after PSA elevation following radical prostatectomy. JAMA, **281:** 1591, 1999
8. Sun, L., Gancarczyk, K., McLeod, D. G., Kane, C., Kusuda, L., Lance, R. et al: Introduction to department of defense Center for Prostate Disease Research (CPDR) multicenter national prostate cancer database with 242,227 records on 11,637 men, and analysis of changes in the PSA-era. Urol Oncol, **6:** 203, 2001
9. Carter, H. B., Epstein, J. I., Chan, D. W., Fozard, J. L. and Pearson, J. D.: Recommended prostate-specific antigen testing intervals for the detection of curable prostate cancer. JAMA, **277:** 1456, 1997
10. Amling, C. L., Bergstralh, E. J., Blute, M. L., Slezak, J. M. and Zincke, H.: Defining prostate specific antigen progression after radical prostatectomy: what is the most appropriate cut point? J Urol, **165:** 1146, 2001
11. Freedland, S. J., Aronson, W. J., Csathy, G. S., Kane, C. J., Amling, C. L., Presti, J. C., Jr. et al: Comparison of percentage of total prostate needle biopsy tissue with cancer to percentage of cores with cancer for predicting PSA recurrence after radical prostatectomy: results from the SEARCH database. Urology, **61:** 742, 2003
12. D'Amico, A. V.: Combined-modality staging for localized adenocarcinoma of the prostate. Oncology, **15:** 1049, 2001
13. Immediate versus deferred treatment for advanced prostatic cancer: initial results of the Medical Research Council Trial. The Medical Research Council Prostate Cancer Working Party Investigators Group. Br J Urol, **79:** 235, 1997
14. Kirk, D.: Immediate vs. delayed hormone treatment for prostate cancer: how safe is androgen deprivation? BJU Int, suppl., **86:** 220, 2000
15. Messing, E. M., Monola, J., Sarsody, M., Wilding, G., Crawford, E. D. and Trump, D.: Immediate hormonal therapy compared with observation following radical prostatectomy and pelvic lymphadenectomy in men with node-positive prostate cancer. N Engl J Med, **341:** 1781, 1999
16. Bolla, M., Collette, L., Blank, L., Warde, P., Dubois, J. B., Mirimanott, R. O. et al: Long-term results with immediate androgen suppression and external irradiation in patients with locally advanced prostate cancer (an EORTC study): a phase III randomized trial. Lancet, **360:** 103, 2002
17. Maximum androgen blockade in advanced prostate cancer: an overview of the randomized trials. Prostate Cancer Trialists' Collaborative Group. Lancet, **355:** 1491, 2000
18. Hurtado-Coll, A., Goldenberg, S. L., Gleave, M. E. and Klotz, L.: Intermittent androgen suppression in prostate cancer: the Canadian experience. Urology, **60:** 52, 2002
19. See, W. A., Wirth, M. P., McLeod, D. G., Iversen, P., Klimberg, I., Gleason, D. et al: Bicalutamide as immediate therapy either alone or as adjuvant to standard care of patients with localized or locally advanced prostate cancer: first analysis of the early prostate cancer program. J Urol, **168:** 429, 2002
20. Fleshner, N. E. and Trachtenberg, J.: Combination finasteride and flutamide in advanced carcinoma of the prostate: effective therapy with minimal side effects. J Urol, **154:** 1642, 1995

reviewed. approved with minor corrections.

thanks,

JW Moul, MD

12/24/03.

0022-5347/04/1713-0001/0
THE JOURNAL OF UROLOGY®

APPENDIX 9

Vol. 171, ●●●–●●●, March 2004
Printed in U.S.A.
DOI: 10.1097/01.ju.0000113300.74132.8b

WATCHFUL WAITING AND FACTORS PREDICTIVE OF SECONDARY TREATMENT IN LOCALIZED PROSTATE CANCER

HONGYAN WU, LEON SUN,* JUDD W. MOUL,* HONGYU WU, DAVID G. McLEOD, CHRISTOPHER AMLING, RAYMOND LANCE, LEO KUSUDA, TIMOTHY DONAHUE, JOHN FOLEY, ANDREW CHUNG, WADE SEXTON AND DOUGLAS SODERDAHL

From the Department of Surgery, Center for Prostate Disease Research, Uniformed Services University of the Health Sciences (HW, LS, JWM, HW), Department of Urology, National Naval Medical Center (TD), Bethesda, Department of Urology, Malcolm Grow Medical Center, Andrews AFB (AC), Maryland, Urology Service, Department of Surgery, Walter Reed Army Medical Center, Washington, D.C. (DGM), Department of Urology, San Diego Naval Medical Center, San Diego, California (CA), Urology Service, Department of Surgery, Madigan Army Medical Center, Tacoma, Washington (RL), Department of Urology, Portsmouth Naval Medical Center, Portsmouth, Virginia (LK), Urology Service, Department of Surgery, Brooke Army Medical Center, San Antonio (JF), Department of Urology, Wilford Hall Medical Center, Lackland AFB (WS), Texas, and Urology Service, Department of Surgery, Eisenhower Army Medical Center, Augusta, Georgia (DS)

ABSTRACT

Purpose: Watchful waiting remains an important treatment option for some patients with localized prostate cancer. We defined the demographic, clinical and outcome features of men selecting watchful waiting as an initial treatment strategy, and determined factors predictive of eventual progression to secondary treatment.

Materials and Methods: Of 8,390 patients diagnosed with prostate cancer from 1990 to 2001 in the Defense of Department Center for Prostate Disease Research Database, 1,158 patients chose watchful waiting as initial treatment. The demographic and clinical differences between patients on watchful waiting and those choosing other initial treatments were compared using the chi-square test. Secondary treatment-free survival according to various prognostic factors was plotted using the Kaplan-Meier method and differences were tested using the log rank test. A multivariate Cox proportional hazards regression analysis was performed to determine which factors were independent predictors of secondary treatment.

Results: Compared to other patients, those selecting watchful waiting were older, had lower prostate specific antigen (PSA) at diagnosis, and were more likely to have lower stage (cT1) and lower grade (Gleason sum 7 or less) cancers. Age, PSA and clinical stage were all significant and independent predictors of secondary treatment. The relative risk of secondary treatment can be expressed as EXP ($-0.034 \times$ age at diagnosis $+ 0.284 \times$ LOG (diagnostic PSA) $+ 0.271 \times$ clinical stage T2 $+ 0.264 \times$ clinical stage T3).

Conclusions: Men who elect watchful waiting as initial management for prostate cancer are older with lower Gleason sums and serum PSA. In these men, age at diagnosis, serum PSA and clinical stage are the most significant predictors of requiring or selecting secondary treatment.

KEY WORDS: prostatic neoplasms, prognosis, prostate-specific antigen

Prostate cancer is the most common tumor identified in American men and is the second leading cause of cancer related death.[1] Since the introduction of the prostate specific antigen (PSA) screening test in the late 1980s and an increase in public awareness of the disease in the early 1990s, the number of prostate cancer cases diagnosed during the last decade has increased dramatically. This increase has led to a stage migration toward more localized disease and a trend toward younger age at time of diagnosis.[2]

There are several initial treatment options for men with localized disease including radical prostatectomy, external beam radiotherapy, radioactive seed implant brachytherapy, cryotherapy and watchful waiting.[3] Given the relatively slow natural history of some prostate cancers and the advanced age of many men at diagnosis, watchful waiting remains an important treatment option for patients with less than a 10-year life expectancy. It is also a viable option for patients with multiple comorbidities that may preclude active treatment. Retrospective studies have shown that watchful waiting may be a suitable option for those with intermediate or low risk disease based on clinical stage, serum PSA and biopsy Gleason sum.[4] However, while watchful waiting is a relatively common initial treatment for patients in many European countries, it is less commonly reported in this country, and the factors predicting who will be selected for watchful waiting have not been well-defined. It is also uncertain which factors are most likely to prompt the patient or physician to abandon watchful waiting for initiation of secondary treatment.

Accepted for publication September 26, 2003.
Supported by a grant from the Center for Prostate Disease Research, a program of the Henry M. Jackson Foundation for the Advancement of Military Medicine (Rockville, Maryland) and the Uniformed Services University of the Health Sciences, funded by the United States Army Medical Research and Material Command (DAMD17-02-1-0066).
Study received Institutional Review Board of Uniformed Services University approval.
* Correspondence and requests for reprints: Center for Prostate Disease Research, 1530 East Jefferson St., Rockville, Maryland 20852 (telephone: 240-453-8922; FAX: 240-453-8912; e-mail: *lsun@cpdr.org,jmoul@cpdr.org*).

Editor's Note: **This article is the ●●● of ●●● published in this issue for which category 1 CME credits can be earned. Instructions for obtaining credits are given with the questions on pages ●●● and ●●●.**

The Department of Defense Center for Prostate Disease Research (CPDR) Tri-Service Multicenter Database contains a sizeable cohort of patients on watchful waiting enrolled between 1990 and 2001, allowing an analysis of demographic, clinical and early outcome features. Additionally, we determined the factors associated with receiving secondary treatment and built a model to predict the likelihood of secondary treatment in patients on watchful waiting.

MATERIALS AND METHODS

The clinical information and followup have been collected as part of the Department of Defense CPDR Tri-Service Multicenter Database as described previously by Sun et al.[5] Briefly, standardized data collection forms for registration, prostatic biopsy, staging, treatment (watchful waiting, surgery, radiation treatment, hormonal treatment and cryotherapy), followup and necropsy were used. Data were collected and entered by physicians and CPDR full-time, in-hospital data managers, then maintained in a relational database using Oracle software (Oracle Corporation, Redwood Shores, California). This project is under an approved protocol by the Institutional Review Board of Uniformed Services University as well as all participating military hospitals.

The data query for this study was performed in July 2002. At that time, the overall database contained 345,954 clinical records (ie transrectal ultrasound/biopsy, staging, watchful waiting, followup, etc) on 15,063 men. A total of 8,739 patients with prostate cancer diagnosed in the PSA era between January 1, 1990 and December 31, 2001 (12 years) were selected. Of these patients, 1,158 received watchful waiting as initial treatment and 7,232 received other primary treatment. A total of 349 patients were excluded from the study due to confirmed clinical metastasis (M1 disease) at diagnosis. Watchful waiting was defined as no active treatment after diagnosis for at least 9 months. Secondary treatment was defined as clinical intervention (radical prostatectomy, external beam radiation, hormonal treatment and brachytherapy) anytime after watchful waiting. Table 1 summarizes the number of patients and the type of primary treatment. Mean and median followup of the watchful waiting cohort were 3.5 and 2.8 years (range 0.8 to 11.3), respectively.

The data fields analyzed for this study included patient age at diagnoses, ethnicity/race, clinical stage at diagnosis, diagnostic PSA, worst biopsy Gleason sum, family history of prostate cancer in a 1st or 2nd-degree relative. The number of comorbidities were divided into 3 separate groups of patients having no comorbidity, patients with 1 comorbidity and patients with more than 1 comorbidity at diagnosis. Comorbidities collected by CPDR included chronic obstructive pulmonary disease, coronary artery disease, cerebral vascular accident, hypertension, renal insufficiency, diabetes, elevated cholesterol and other cancer.

Demographics and clinical characteristics were compared between patients who remained on the watchful waiting protocol and those who underwent secondary treatment with the chi-square test. The end point was secondary treatment (radical prostatectomy, external beam radiation, hormonal treatment and brachytherapy). Secondary treatment-free survival analysis was performed with the Kaplan-Meier log rank method. Secondary treatment-free survival was further stratified by patient age, race, PSA, Gleason sum, clinical stage, comorbidities and family history of prostate cancer. A multivariate Cox proportional hazards regression model was constructed to assess the prognostic variables for secondary treatment in the watchful waiting cohort.

TABLE 1. *Primary treatment according to CPDR database 1990 to 2001*

	No. Pts (%)
Watchful waiting	1,158 (13.8)
Radical prostatectomy	4,200 (50.1)
External beam radiation	2,230 (26.6)
Hormonal treatment	514 (6.1)
Brachytherapy	284 (3.4)
Cryotherapy	4 (0.1)
Total	8,390 (100.0)

RESULTS

A comparison of the demographic and clinical factors between patients selecting watchful waiting and those choosing initial active therapy is shown in table 2. Compared with the active local therapy group, patients selecting watchful waiting were older at diagnosis (median age 70.9 versus 65.6 years, $p < 0.0001$), had lower diagnostic PSA (median 6.4 versus 7.1 ng/ml, $p < 0.0001$), had higher percentage of stage T1 disease (53.6% versus 41.3%, $p < 0.0001$) and a higher percentage of Gleason sum 7 or less cancers (90.5% versus 84.0%, $p < 0.0001$). Table 3 shows the clinical and demographic features of patients on watchful waiting, comparing those who did or did not receive secondary treatment, and table 4 shows the type of secondary treatment selected. Of 1,158 patients on watchful waiting 453 (39.1%) underwent secondary treatment within the median followup of our watchful waiting cohort (2.8 years).

A univariate analysis of factors associated with eventual progression to secondary treatment is shown in table 5. Patient age ($p = 0.0004$), race ($p < 0.0001$), clinical stage ($p < 0.0001$), diagnosis PSA ($p < 0.0001$) and highest biopsy Gleason sum ($p < 0.0001$) were significant factors associated with secondary treatment. The 2 and 5-year secondary treatment-free survival rates are stratified by age at diagnosis, race, clinical stage, diagnostic PSA, highest biopsy Gleason sum, family history and number of comorbidities (table 6). The results indicate that race, clinical stage and diagnostic PSA all affect the risk of progressing to secondary treat-

TABLE 2. *Patients who elected watchful waiting and active local therapy*

	No. Watchful Waiting (%)	No. Active Local Therapy (%)	p Value
Total	1,158 (13.8)	7,232 (86.2)	
Age at diagnosis:			<0.0001
65 or Younger	306 (26.5)	3,383 (46.8)	
65.1–75	518 (44.8)	3,003 (41.6)	
Older than 75	332 (28.7)	840 (11.6)	
Mean/median	69.8/70.9	65.6/65.6	<0.0001
Race:			0.0079
White + others	917 (82.5)	5,553 (79.0)	
Black	195 (17.5)	1,476 (21.0)	
Clinical stage:			<0.0001
T1	547 (53.6)	2,835 (41.3)	
T2	425 (41.7)	3,547 (51.7)	
T3 + T4	48 (4.7)	477 (6.9)	
Diagnostic PSA:			<0.0001
4 or Less	235 (23.2)	1,162 (16.7)	
4–10	498 (49.3)	3,482 (50.1)	
10 or Greater	278 (27.5)	2,301 (33.1)	
Mean/median	15.1/6.4	15.3/7.1	<0.0001
Highest biopsy Gleason sum:			<0.0001
4 or Less	429 (41.1)	1,603 (23.8)	
5–6	394 (37.8)	2,876 (42.6)	
7	122 (11.6)	1,190 (17.6)	
8–10	99 (9.5)	1,077 (16.0)	
Family history:			<0.0001
No	1,023 (88.3)	6,043 (83.6)	
Yes	135 (11.7)	1,189 (16.4)	
Comorbidity:			0.6056
None	476 (41.1)	2,962 (41.0)	
1	429 (37.1)	2,770 (38.3)	
2 or More	253 (21.8)	1,500 (20.7)	
Death:			<0.0001
Alive	963 (83.2)	6,402 (88.5)	
Disease specific death	23 (2.0)	175 (2.4)	
Died of other causes	172 (14.8)	655 (9.1)	

TABLE 3. *Patients who elected watchful waiting with and without secondary treatment*

	No. Secondary Treatment (%)	No. No Secondary Treatment (%)	p Value (chi-square test)
Total	453 (39.1)	705 (60.9)	
Age at diagnosis:			0.0002
65 or Younger	148 (32.7)	158 (22.5)	
65.1–75	196 (43.3)	322 (45.8)	
Older than 75	109 (24.0)	223 (31.7)	
Mean/median	68.8/70.0	70.5/71.6	0.0004
Race:			0.0044
White + others	346 (78.5)	571 (85.1)	
Black	95 (21.5)	100 (14.9)	
Clinical stage:			<0.0001
T1	192 (45.9)	355 (59.0)	
T2	197 (47.1)	228 (37.9)	
T3 + T4	29 (7.0)	19 (3.1)	
Diagnostic PSA:			<0.0001
4 or Less	62 (14.5)	173 (29.7)	
4–10	217 (50.7)	281 (48.2)	
10 or Greater	149 (34.8)	129 (22.1)	
Mean/median	18.6/7.4	12.5/5.8	<0.0001
Highest biopsy Gleason sum:			0.5034
4 or Less	164 (39.7)	265 (42.0)	
5–6	154 (37.3)	240 (38.0)	
7	49 (11.9)	73 (11.6)	
8–10	46 (11.1)	53 (8.4)	
Family history:			0.9717
No	400 (88.3)	623 (88.4)	
Yes	53 (11.7)	82 (11.6)	
Comorbidity:			0.8491
None	182 (40.2)	294 (41.7)	
1	172 (38.0)	257 (36.5)	
2 or More	99 (21.8)	154 (21.8)	
Death:			0.0762
Alive	389 (85.9)	574 (81.4)	
Disease specific death	10 (2.2)	13 (1.9)	
Died of other causes	54 (11.9)	118 (16.7)	

TABLE 4. *Type of secondary treatment for patients who chose watchful waiting*

	No. Pts (%)
Hormonal treatment	193 (42.6)
External beam radiation	127 (28.0)
Radical prostatectomy	111 (24.5)
Brachytherapy	22 (4.9)

TABLE 5. *Univariate Cox proportional hazards model for predictors of secondary treatment*

	Hazards Ratio	95% CI	p Value
Age	0.981	0.970–0.991	0.0004
Black vs White + others	1.584	1.261–1.990	<0.0001
Clinical stage:			
T2 vs T1	1.503	1.231–1.835	<0.0001
T3 + T4 vs T1	2.089	1.413–3.088	0.0002
LogPSA	1.353	1.242–1.474	<0.0001
Highest biopsy Gleason sum	1.182	1.102–1.267	<0.0001
Family history	1.029	0.773–1.371	0.8447
No. comorbidities	1.052	0.954–1.161	0.3069

ment (log rank p <0.0001). Multivariate Cox regression analysis including age at diagnosis, race, diagnostic PSA, highest biopsy Gleason sum, clinical stage, family history, number of comorbidities found that age, PSA and clinical stage were T7 independent predictors of secondary treatment (table 7).

Using the 3 statistically significant variables predicting secondary treatment in multivariate analysis (age, PSA and stage), an equation to calculate the relative risk (RR) of secondary treatment could be expressed as RR = EXP (−0.034 × age at diagnosis + 0.284 × LOG (diagnostic PSA) + 0.271 × clinical stage T2 + 0.264 × clinical stage T3). Based on RR of secondary treatment patients receiving secondary treatment were divided into 3 risk groups of low (0 to 0.13), intermediate (0.14 to 0.19) and high (greater than 0.19), and their 2, 5 and 7-year secondary treatment-free survival are summarized in table 8. Figure 1 shows overall F1 secondary treatment-free survival curves. Figure 2 shows F2 risk stratified secondary treatment-free survival, revealing significant differences in the risk of secondary treatment among these 3 risk groups (p <0.0001).

DISCUSSION

The most important finding at this multicenter contemporary PSA era experience with a large cohort of patients on watchful waiting is that a large percentage of men progress to active local or systemic therapy in a relatively short time. However, using risk stratification based on PSA, Gleason sum and clinical stage yields a group with low risk of progression that maintains a greater than two-thirds chance of remaining on watchful waiting at 7 years. Furthermore, this clinically useful predictive equation for secondary therapy on watchful waiting is available on the Internet (www.cpdr.org). The equation will give patients and clinicians the ability to estimate the success of a watchful waiting approach given patient age, stage and PSA. The finding that number of comorbidities was not associated with primary or secondary treatment in this data set is interesting. That our comorbidity assessment is not robust may be related to the military setting or that PSA progression is driving care irrespective of patient health. This finding will require further study on other settings.

The choice of treatment for and management of prostate cancer is controversial and no consensus guidelines are available on the proper treatment of the disease, especially for watchful waiting.[6] Different from nearly all other common human cancers, prostate cancer has the features of high incidence of occult disease, affects an expanding elderly population with increased life expectancy and slow natural history. Autopsy studies have shown a high incidence of clinically occult disease in aging men. Approximately 29%, 30%, 40% and 67% of men in their fifth, sixth, seventh and eighth decades of life, respectively, will have occult prostate cancer.[7] It is known from autopsy studies that more than 10 million men in the United States have cancer in the prostate. The majority of prostate cancers are clinically insignificant.[8] Although the annual death rate from prostate cancer is high several studies have noted that tumor progression may not occur or may occur slowly in selected patients with clinically localized cancers left untreated. The probability of tumor progression ranges between 30% and 72% depending on the length of followup. Therefore, the rationale of this study was to illustrate the epidemiological features of watchful waiting in the PSA era and to identify prognostic variables associated with secondary treatment.

Watchful waiting has been proposed as a reasonable treatment strategy of localized prostate cancer. During the last decade many studies of watchful waiting have analyzed the overall survival rate of patients electing such treatment. In these prospective and retrospective studies, there is the indication that patients with localized prostate cancer electing watchful waiting may have no loss in life expectancy, and that it may be reasonable to initially avoid active local treatment.[9–11] In 1997 Johansson et al reported the disease specific outcome of 642 patients diagnosed with prostate cancer in Sweden between 1977 and 1984.[9] Of the 300 men with localized prostate cancer 233 received no initial therapy, followed by delayed treatment for symptomatic progression. Of the men with localized disease 11% died of prostate cancer and the corrected 15-year survival rate was similar for deferred treatment (81%, 95% CI: 72%–89%) to those who were treated at the time of initial diagnosis (81%, 95% CI: 67%–95%). Men with poorly differentiated disease had the highest death rate from prostate cancer (56%) compared to those

TABLE 6. *Secondary treatment-free Kaplan-Meier survival analysis of primary watchful waiting*

	No. Pts	2 Yrs (% ± SE)	5 Yrs (% ± SE)	p Value (log rank test)
Total	1,158	76.3 ± 1.3	55.2 ± 1.7	
Age at diagnosis:				
65 or Younger	306	71.2 ± 2.7	44.9 ± 3.3	0.0002
65.1–75	518	76.0 ± 1.9	56.1 ± 2.6	
Older than 75	332	81.1 ± 2.2	6.3 ± 3.1	
Race:				
White + others	917	77.0 ± 1.4	57.5 ± 1.9	<0.0001
Black	195	70.2 ± 3.4	42.2 ± 4.4	
Clinical stage:				
T1	547	78.5 ± 1.8	59.7 ± 2.5	<0.0001
T2	425	72.0 ± 2.3	48.0 ± 2.9	
T3 + T4	48	58.2 ± 7.4	33.1 ± 7.8	
Diagnosis PSA:				
4 or Less	235	84.6 ± 2.4	71.9 ± 3.4	<0.0001
4–10	498	72.8 ± 2.1	48.0 ± 2.8	
10 or Greater	278	66.3 ± 3.0	34.0 ± 3.7	
Highest biopsy Gleason sum:				
4 or Less	429	78.5 ± 2.0	59.7 ± 2.6	0.0019
5–6	394	76.5 ± 2.2	50.1 ± 3.3	
7	122	72.6 ± 4.2	55.8 ± 5.3	
8–10	99	65.2 ± 5.2	40.2 ± 6.6	
Family history:				
No	1,023	76.3 ± 1.4	55.4 ± 1.8	0.8464
Yes	135	76.5 ± 3.8	54.0 ± 5.3	
Comorbidity:				
None	476	76.4 ± 2.0	55.9 ± 2.6	0.7842
1	429	73.4 ± 2.2	54.1 ± 2.9	
2 or More	253	81.0 ± 2.6	55.9 ± 3.8	

TABLE 7. *Multivariate Cox proportional hazards model for predictors of secondary treatment*

	Parameter	Hazards Ratio	95% CI	p Value
Age at diagnosis	−0.037	0.963	0.950–0.977	<0.0001
LogPSA	0.355	1.427	1.275–1.596	<0.0001
Clinical stage:				
T2 vs T1	0.274	1.315	1.043–1.658	0.0205
T3 + T4 vs T1	0.479	1.615	0.991–2.632	0.0543

with well differentiated (7%) or moderately differentiated (16%) disease.

In 1994 Chodak et al reported a meta-analysis on 828 patients treated conservatively (with observation and delayed hormone therapy but no radical surgery or irradiation) for clinically localized prostate cancer from 6 nonrandomized studies.[11] The 10-year disease specific actuarial survival rates were 87%, 87% and 34% for tumor differentiation of grades I to III, while 10-year metastasis-free survival rates were 81%, 58% and 26%, respectively. This study showed that the strategy of initial conservative management and delayed hormone therapy is a reasonable choice for some men with grade I or II clinically localized prostate cancer, particularly for those who have an average life expectancy of 10 years or less. Their data supported the assertion that watchful waiting results in survival rates similar to those of definitive treatment. Definitive treatment was considered necessary for men with grade III prostate cancer. In 1995 Albertsen et al reported the result from 451 men diagnosed with clinically localized prostate cancer in Connecticut between 1971 and 1976, and with mean followup of 15.1 years.[11] The age adjusted survival for men with Gleason sum 2 to 4 tumors was not significantly different from that of the general population. Maximally estimated lost life expectancy for men with Gleason sum 5 to 7 tumors was 4 to 5 years, and for men with Gleason sum 8 to 10 tumors it was 6 to 8 years. Tumor Gleason sum and patient comorbidities were powerful independent predictors of survival.

Although with watchful waiting an opportunity may be missed to cure or delay disease progression, and it may lead to increased patient anxiety, it may avoid the harmful side effects of early intervention and does not preclude palliative therapy if and when symptomatic disease progression occurs. Therefore, quality of life in many men treated with watchful waiting may be superior to those treated with early intervention. Currently, approximately 11% of patients with newly diagnosed prostate cancer will choose initial watchful waiting rather than initial active local treatment.[12]

What leads men to choose watchful waiting rather than active treatment for prostate cancer is dependent on a number of factors including physician recommendation, patient preference, life expectancy and comorbidities. Diefenbach et al reported initial results from an ongoing longitudinal investigation examining treatment decision making in 654 men diagnosed with early stage prostate cancer.[13] Watchful waiting was chosen by 6% of patients. When asked for the most important reason influencing their treatment decision, patients indicated physician recommendation (51%), advice from friends and family (19%), information obtained from books and journals (18%) or the Internet (7%). McLaren et al followed 113 men who chose watchful waiting after referral to the British Columbia Cancer Agency.[14] Reasons for choosing watchful waiting included patient preference in 37% of cases, physician recommendation in 42%, decreased life expectancy in 19% and contraindication to radiotherapy in 2%. Koppie et al used the Cancer of the Prostate Strategic Urological Research Endeavor database to evaluate patients with advanced and localized prostate cancer on watchful waiting, and determined that men on watchful waiting were more likely to be older than 75 years, have lower serum PSA, have organ confined disease and a total Gleason sum of 7 or less.[15] In agreement with Koppie et al, we noted that men who elected watchful waiting tended to be older, have lower diagnosis PSA and have clinically organ confined disease. Although it has been documented that comorbidities also influence the initial decision to choose watchful waiting,[11] our results suggest that there is no relationship between patient comorbidities and primary treatment selection ($p = 0.6056$). As previously noted this finding is important but puzzling and needs further study.

From our group Bauer et al reported on the hereditary aspects of prostate cancer and found that there was no relationship in the clinical characteristics of cancer between patients who have a family history compared to those in whom sporadic prostate cancer occurs.[16] Kotsis et al even found that men without family history of prostate cancer had

TABLE 8. *Risk group characteristics*

Risk Group	Risk Secondary Treatment	No. Pts	No. Secondary Treatment	Secondary Treatment-Free Survival Rates (%)		
				2-Yr	5-Yr	7-Yr
Low	0.04–0.13	251	62	86.3	72.9	65.4
Intermediate	0.14–0.19	332	142	71.9	48.3	46.7
High	0.19–0.92	331	194	62.8	34.0	23.8

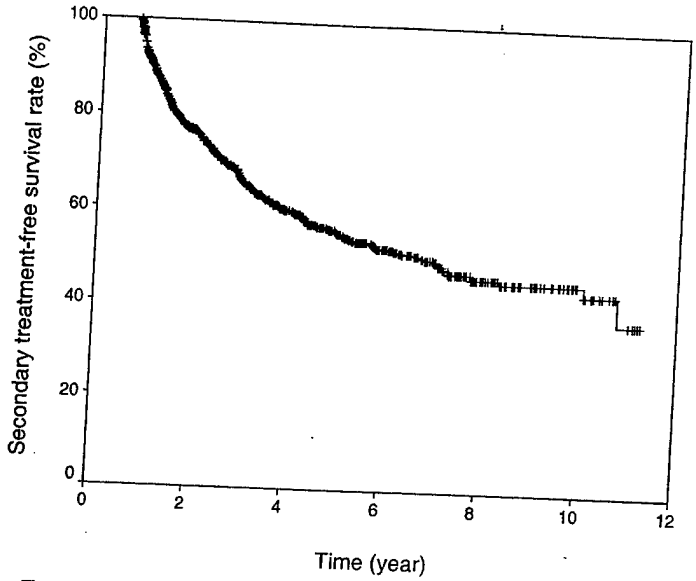


FIG. 1. Overall secondary treatment-free survival rate in patients on watchful waiting.

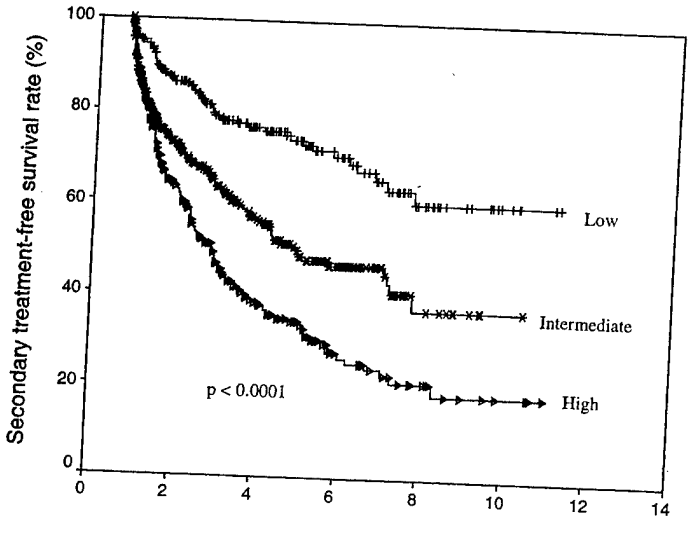


FIG. 2. Secondary treatment-free survival rate in patients on watchful waiting stratified by risk group.

higher grade tumors which are associated with a more serious prognosis.[17] Conversely, our results indicate that patients with family history are more likely to choose active treatment rather than watchful waiting (16.4 versus 11.7, p <0.0001). In contrast to Bauer et al,[16] other studies have found that hereditary prostate cancer may be more aggressive than sporadic disease. This prior conventional wisdom that familial prostate cancer may be a more serious disease and experience of other family members may have led more men to select active treatment.

In our study of 1,158 patients on watchful waiting only 2% died of prostate cancer and 14.9% died of other causes. In the nonwatchful waiting group the disease specific and nonspecific death rate was 2.4% and 9.1%, respectively. These results are similar to those of Koppie et al. They found fewer patients on watchful waiting died of prostate cancer compared to other causes. In their study disease specific death was only in 3 of 23 patients (13%). Our results are also supportive to Johansson's study.[18] Among the 1,158 patients on watchful waiting 23.7% chose a secondary treatment at year 2 and 44.8% at year 5 after prostate cancer diagnosis. In the Koppie et al study population 39% underwent secondary treatment within followup with the likelihood of secondary treatment reaching 52.5%. In our study the most common form of secondary treatment was hormone treatment (42.6%) followed by external beam radiation therapy (17.2%) and radical prostatectomy (10.9%). This result was similar to the findings of Koppie et al.[15]

Currently a policy of watchful waiting with selective active treatment based on predefined criteria of disease progression is feasible.[19] This strategy offers the benefit of an individualized approach based on the demonstrated risk of clinical or biochemical progression over time. Thus, it may decrease the burden of therapy in patients with indolent disease and provides definitive therapy for those with biologically active disease. Characterizing predictive factors for secondary treatment and development of an algorithm to assist decision making has been an area of recent interest. In the study by Koppie et al it is notable that secondary treatment was given more frequently to those with higher serum PSA and those who were younger at diagnosis. In our study significant predictors of secondary treatment were age younger than 65 years, diagnosis PSA (10 ng/ml or more) and clinical stage (T2 or higher). Using only statistically significant variables to predict secondary treatment that were defined in multivariate Cox regression analysis, we developed an equation to calculate the RR of secondary treatment and defined 3 risk groups (low, intermediate and high) based on RR of secondary treatment. The Kaplan-Meier survival analysis (fig. 2) is supportive of this risk stratification ($p < 0.0001$). Using the equations or tables, clinicians can plug in the patient's individual factors to determine risk group. At initial diagnosis the risk stratification can help the clinician and patient make decisions about secondary treatment or better tailoring of followup care.

There are a number of limitations to our study. The followup was short (median 2.8 years) despite the review covering patients diagnosed between 1990 and 2002. This characteristic reflects the increasing number of patients on watchful waiting in recent years. Furthermore, the study was conducted in the military health care system where all patients have equal access to health care for life. That comorbidity did not predict initial or secondary treatment may be related to this setting. Finally, because of these limitations the equation presented should be validated in other cohorts before widespread clinical use.

CONCLUSIONS

Men who elected watchful waiting for prostate cancer tend to be older, have lower serum PSA and lower Gleason sum. The age at diagnosis, PSA and T stage are the most significant predictors of the likelihood of secondary treatment in

patients on watchful waiting. The most common form of secondary treatment was hormonal treatment, followed by external beam radiation and radical prostatectomy. Patients who are younger, have higher diagnostic PSA and clinical stage T2 or higher disease more likely undergo secondary treatment. The model based on these 3 factors may benefit the identification of patients with low risk disease who are better suited for watchful waiting.

REFERENCES

1. Greenlee, R. T., Hill-Harmon, M. B., Murray, T. and Thun, M.: Cancer statistics, 2001. CA Cancer J Clin, **51:** 15, 2001
2. Farkas, A., Schneider, D., Perrotti, M., Cummings, K. B. and Ward, W. S.: National trends in the epidemiology of prostate cancer, 1973 to 1974: evidence for the effectiveness of prostate-specific antigen screening. Urology, **52:** 444, 1998
3. Walsh, P. C., Lepor, H. and Eggleston, J. C.: Radical prostatectomy with preservation of sexual function: anatomical and pathological consideration. Prostate, **4:** 473, 1983
4. Carter, C. A., Donahue, T., Sun, L., Wu, H., McLeod, D. G., Amling, C. et al: Temporary-deferred therapy (watchful waiting) for men younger than 70 years and with low-risk localized prostate cancer in the prostate-specific antigen era. J Clin Oncol, **21:** 4001, 2003
5. Sun, L., Gancarczyk, K., Paquette, E. L., McLeod, D. G., Kane, C., Moul, J. W. et al: Introduction to Department of Defense Center for Prostate Disease Research Multicenter National Prostate Cancer Database, and analysis of changes in the PSA-Era. Urol Oncol, **6:** 203, 2001
6. Kolata, G.: Prostate cancer consensus hampered by lack of data. Science, **236:** 1626, 1987
7. Steinberg, G. D., Bales, G. T. and Brendler, C. B.: An analysis of watchful waiting for clinically localized prostate cancer. J Urol, **159:** 1431, 1998
8. Johansson, J. E.: Watchful waiting for early stage prostate cancer. Urology, **43:** 138, 1994
9. Johansson, J. E., Holmberg, L., Johansson, S., Bergstrom, R. and Adami, H. O.: Fifteen-year survival in prostate cancer. A prospective, population-based study in Sweden. JAMA, **277:** 467, 1997
10. Chodak, G. W., Thisted, R. A., Gerber, G. S., Johansson, J. E., Adolfsson, J., Jones, G. W. et al: Results of conservative management of clinically localized prostate cancer. N Engl J Med, **330:** 242, 1994
11. Albertsen, P. C., Fryback, D. G., Storer, B. E., Kolon, T. F. and Fine, J.: Long-term survival among men with conservatively treated localized prostate cancer. JAMA, **274:** 626, 1995
12. CaPCURE: Observational Database STATISTICAS. San Diego, CaPCURE, 2002
13. Diefenbach, M. A., Dorsey, J., Uzzo, R. G., Hanks, G. E., Greenberg, R. E., Horwitz, E. et al: Decision-making strategies for patients with localized prostate cancer. Semin Urol Oncol, **20:** 55, 2002
14. McLaren, D. B., McKenzie, M., Duncan, G. and Pickles, T.: Watchful waiting or watchful progression? Prostate specific antigen doubling times and clinical behavior in patients with early untreated prostate carcinoma. Cancer, **82:** 342, 1998
15. Koppie, T. M., Grossfeld, G. D., Miller, D., Yu, J., Stier, D., Broering, J. M. et al: Patterns of treatment of patients with prostate cancer initially managed with surveillance: results from the CaPSURE database. J Urol, **164:** 81, 2000
16. Bauer, J. J., Srivastava, S., Connelly, R. R., Sesterhenn, I. A., Preston, D. M., McLeod, D. G. et al: Significance of familial history of prostate cancer to traditional prognostic variables, genetic biomarkers, and recurrence after radical prostatectomy. Urology, **51:** 970, 1998
17. Kotsis, S. V., Spencer, S. L., Peyser, P. A., Montie, J. E. and Cooney, K. A.: Early onset prostate cancer: predictors of clinical grade. J Urol, **167:** 1659, 2002
18. Johansson, J. E.: Expectant management of early stage prostatic cancer: Swedish experience. J Urol, **152:** 1753, 1994
19. Choo, R., Klotz, L., Danjoux, C., Morton, G. C., DeBoer, G., Szumacher, E. et al: Feasibility study: watchful waiting for localized low to intermediate grade prostate carcinoma with selective delayed intervention based on prostate specific antigen, histological and/or clinical progression. J Urol, **167:** 1664, 2002