

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 $\leq T2$ 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. © 2003 by American Society of Clinical Oncology.

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 al¹² 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 al¹² defined the favorable criteria on needle biopsy as Gleason score ≤ 6 , no more than three cores positive for cancer, and $\leq 50\%$ 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.

© 2003 by American Society of Clinical Oncology.

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	

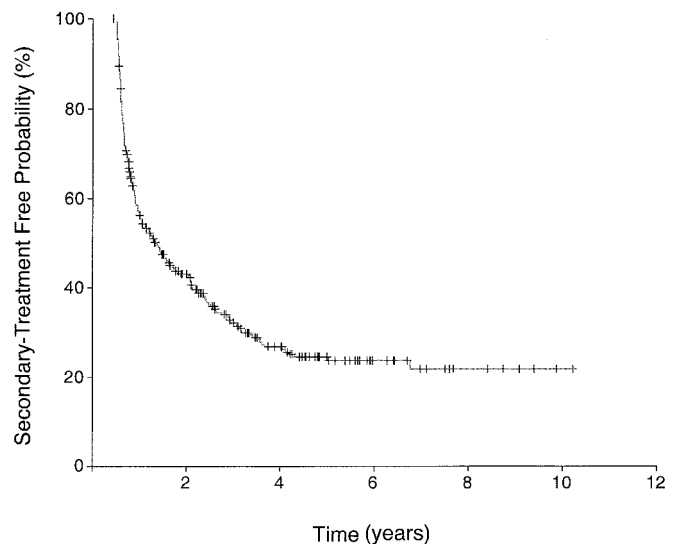


Fig 1. Kaplan-Meier curve indicating those free from secondary treatment of 313 watchful waiting patients.

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 al¹¹ 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 al¹⁷ 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 al¹⁸ 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 al²⁰ 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 al¹⁷ 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.

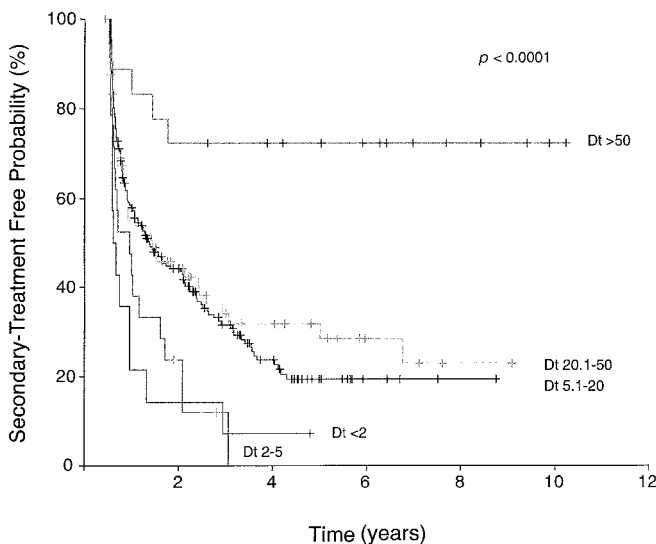


Fig 2. Kaplan-Meier curve indicating those free from secondary treatment, stratified by patients' prostate-specific antigen doubling time (Dt).

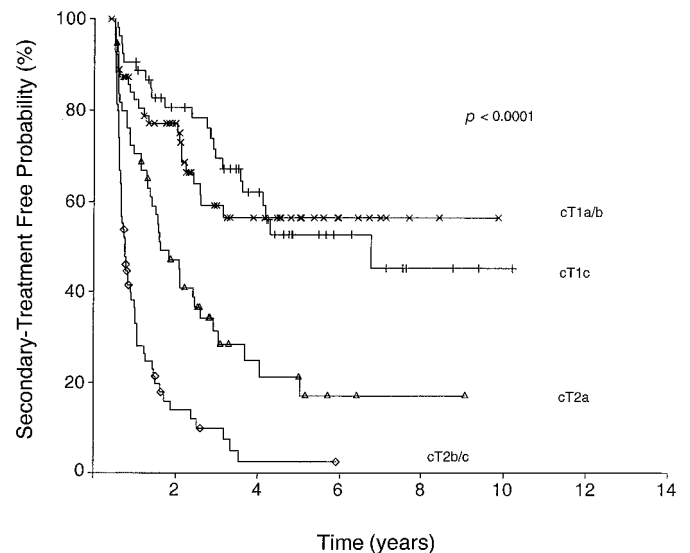


Fig 3. Kaplan-Meier curve indicating those free from secondary treatment, stratified by clinical stage.

Epstein et al²¹ 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 al²² 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

- Greenlee RT, Hill-Harmon MB, Murray T, et al: Cancer statistics, 2001. *CA Cancer J Clin* 51:15-36, 2002
- 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
- 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
- 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
- Walsh PC, Lepor H, Eggleston JC: Radical prostatectomy with preservation of sexual function: Anatomical and pathological consideration. *Prostate* 4:473-485, 1983
- 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
- Ragde H, Grado GL, Nadie B, et al: Modern prostate brachytherapy. *CA Cancer J Clin* 50:380-393, 2000
- 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
- Steinberg G, Bales G, Brendler C: An analysis of watchful waiting for clinically localized prostate cancer. *J Urol* 159:1431-1436, 1998
- 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
- Albertson P, Fryback D, Storer B, et al: Long-term survival among men with conservatively treated localized prostate cancer. *JAMA* 274:626-632, 1995
- Epstein J, Walsh PC, Carmichael M, et al: Pathologic and clinical findings to predict tumor extent of non-palpable (stage T1c) prostate cancer. *JAMA* 271:368-374, 1994
- 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 T1c 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