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Watchful waiting and quality of life among prostate cancer survivors in the Physicians' Health Study

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Abstract

Purpose—We examined patient-reported outcomes among prostate cancer patients managed by watchful waiting (WW) in a nationwide cohort.

Materials and Methods—We collected treatment information and patient-reported outcomes from 1230 prostate cancer patients diagnosed with T1-T2 prostate cancer in the Physicians' Health Study; 125 were initially managed by WW. Cox proportional-hazards regression was used to identify predictors of treatment initiation among WW patients. Logistic regression was used to calculate odds ratios (OR) and 95% confidence intervals (CI) to assess disease-targeted quality of life by initial treatment or WW.

Results—At 7.3 years' mean follow-up, 41% of WW patients remained free of treatment while 34% underwent radiotherapy or brachytherapy, 16% underwent primary hormonal therapy, and 10% underwent prostatectomy. Younger age, higher clinical stage, higher Gleason score, and

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higher PSA at diagnosis predicted progression to treatment. Watchful waiting compared to immediate treatment was associated with less urinary incontinence (3.5% vs 10%) and impotence (68% vs 78%) but more common obstructive urinary symptoms (22% vs 13%) in univariate analyses ($p < 0.05$ for each), with incontinence and impotence differences remaining significant after adjustment for age, comorbidity, and time after cancer diagnosis. Quality of life outcomes among men who underwent delayed treatment after initially waiting were not worse than among men who underwent immediate treatment.

Conclusions—Our findings suggest quality of life benefits subsequent to WW among select patients with early-stage prostate cancer compared to men treated immediately following diagnosis. Younger age and greater cancer severity at diagnosis predicted progression to treatment.

Keywords

watchful waiting; prostate cancer; prospective study; quality of life; outcomes

INTRODUCTION

Differences between prostate cancer incidence and mortality reflect that clinically indolent prostate cancer is commonplace.^{1, 2} Randomized prostate cancer screening trials, showing that more than 12 men are treated to prevent one prostate cancer death, have exposed that overtreatment undercuts the survival benefits of early detection.^{2, 3} Watchful waiting (WW), or deferring immediate treatment at diagnosis, represents a prostate cancer care alternative that has the potential to mitigate overtreatment for screening-detected cancers while retaining survival benefits of early detection.⁴

Clinical guidelines to identify suitable candidates for active surveillance, another clinical approach to deferred treatment,⁵ rely on the assumption that men with low-risk disease who delay treatment can still receive curative therapy if signs of cancer aggressiveness become evident.^{6, 7} However, limited information has been described regarding progression to treatment and cancer control after WW or active surveillance in the community-based setting.^{8, 9} Moreover, while immediate initial treatment can benefit men with a potentially lethal cancer,¹⁰ it can also cause adverse effects that impair quality of life (QOL),^{11, 12} and information regarding QOL outcomes after WW is sparse.^{13–15}

We therefore sought to characterize, in a multiregional American community-based setting, the long-term clinical patterns of progression to treatment and patient-reported QOL among early-stage prostate cancer patients who opted for WW compared to men treated immediately after initial diagnosis. Prior multi-regional, American studies of outcomes after deferred treatment for prostate cancer have been limited to two cohorts: CaPSURE and the Health Professionals Follow-up Study,^{8, 9} with the former including general QOL evaluation at short-term follow-up.¹² In order to elucidate long-term quality of life consequences in deferred treatment or WW as compared to immediate treatment, we interrogated patient-reported outcomes among prostate cancer survivors within the Physicians' Health Study.

MATERIALS AND METHODS

Study population

The Physicians' Health Study (PHS) I and II were randomized, placebo-controlled, double-blind trials in the prevention of cardiovascular disease and cancer. The PHS I evaluated aspirin and β -carotene among 22,071 U.S. male physicians aged 40–84 years in 1982¹⁶ In

1997, the PHS II randomized 7,641 physicians from PHS I and 7000 new physicians to vitamin E, vitamin C, and multivitamins.¹⁷ All arms of the trial have ended except the multivitamin component;^{17–19} participants continue follow-up as an observational cohort.

Incident cases of prostate cancer were confirmed by medical record review. In 2005, a sample of the 3313 prostate cancer survivors diagnosed in PHS I and II were invited to complete a supplemental questionnaire regarding prostate cancer treatment and outcome. Of the 1366 who completed the questionnaire, patients were excluded due to incomplete treatment information (n=38), missing clinical stage (n=16), or clinical stage T3–T4 or N1/M1 (n=82), leaving 1230 patients for the current analysis. This study is compliant with the Institutional Review Board of Partners Healthcare.

Treatment evaluation and clinical factors

We ascertained date of initial treatment from medical records and from the list of treatment options reported in the 2005 questionnaire. We defined WW as the absence of treatment for at least one year after diagnosis; similar to other studies.^{8, 9, 20} We could not discern active surveillance from WW, so all patients who deferred treatment for at least one year are referred to as WW. Medical records of prostate cancer-related diagnostic or therapeutic encounters were reviewed to ascertain appropriate assignment of treatment type and date; all available records for the WW group were additionally reviewed by a study physician to confirm accuracy.

We recorded clinical stage, Gleason score, and prostate specific antigen (PSA) at diagnosis from medical records, and secondarily from patient self-report. Occurrence of bone metastasis after diagnosis (up to 2008) was assessed by self-report, followed by medical record review. Cause and date of death (through May 2010) was assigned from medical records, death certificates, and information from family.

Patient-reported outcomes

QOL was assessed on the 2005 questionnaire by a symptoms checklist asking men to report the occurrence (never, mild, moderate, severe) of 13 conditions or symptoms experienced in the past year: urinary leakage or incontinence, nocturia, increased urinary frequency or urgency, decreased force of urinary stream, hematuria, fatigue, hot flashes, impotence, reduced sexual desire, rectal urgency, diarrhea, abdominal and/or perineal pain, and nausea and/or vomiting. This set of QOL questions included items from the UCLA Prostate Cancer Index (PCI)²¹ and EPIC;¹⁵ however, neither the entire PCI nor EPIC were able to be administered due to length restrictions of the PHS questionnaire, thereby limiting our analyses to individual items querying specific symptoms.

We also calculated a comorbidity score using a modified Charlson Comorbidity Index.^{22, 23}

Statistical analyses

Clinical and lifestyle characteristics were compared between earlystage (T1–T2) WW patients (n=125) versus those who were treated within one year of diagnosis (n=1105) using t-tests, chi-square tests, Fisher exact tests, or Wilcoxon rank-sum tests. Cox proportional hazards regression was used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) to identify predictors of treatment initiation among early-stage WW patients. We considered the following variables: age at diagnosis, race/ethnicity, BMI, clinical stage, PSA at diagnosis, Gleason score, and time of diagnosis (to control for stage migration after introduction of PSA screening).²⁴ Data for each covariate was missing in <9% of men.

We used modified D'Amico criteria to form three prognostic risk categories for early-stage WW patients by combining PSA at diagnosis and Gleason score: low risk (Gleason score 2–6 and PSA < 10 ng/ml; n=76), intermediate risk (Gleason score 2–6 and PSA 10 to < 20 ng/ml, or Gleason score 7 and PSA < 20 ng/ml; n=36), and high risk (Gleason score 8–10 or PSA ≥ 20 ng/ml; n=9) risk.²⁵ The modified criteria do not take into account T stage since all patients were early-stage (T1–T2), and we were unable to discern T2a from T2b due to a high proportion of missing information on subcategories of T2. Four patients could not be classified due to missing data. Kaplan-Meier estimates were used to plot the cumulative incidence of treatment initiation across prognostic risk groups.

Twenty-four (2%) patients did not respond to the entire QOL questionnaire and were excluded from QOL analyses; responses to individual items were missing for 5–13%. We compared WW patients to those treated within one year post-diagnosis across QOL measures (never/mild vs. moderate/severe) using chi-square or Fisher's exact tests. The nausea and/or vomiting category was eliminated since only two men reported moderate/severe symptoms. Logistic regression was used to calculate odds ratios (ORs) and 95% CIs for the association between WW and QOL, compared to treatment within one year of diagnosis. Models were adjusted for age at diagnosis, comorbidity index, and time from diagnosis to QOL assessment, and Wald tests were used to evaluate statistical significance. As an exploratory analysis, we compared QOL among WW patients who later received treatment (n=72) to those treated within one year.

All p-values were 2-sided; p-values < 0.05 were considered statistically significant. Analyses were conducted using SAS (version 9.1, SAS Institute, Cary, North Carolina).

RESULTS

Among 1230 early-stage prostate cancer patients, 125 (10.2%) opted for WW or deferred treatment for at least one year. (Table 1). Patients in the WW group were significantly older (mean 72.3 versus 68.1 years, respectively) and had a lower PSA level and Gleason score at diagnosis compared to patients initially treated.

Fifty-one (40.8%) of the WW patients remained untreated for a mean of 7.6 years (Table 2). Radiation therapy was the most common delayed treatment among initially WW patients. Mean time from diagnosis to treatment initiation was shortest for external beam radiation (2.3 years) and longest for hormone therapy (6.1 years). Treatment initiation was associated with younger age at diagnosis, higher clinical stage, higher PSA at diagnosis, and higher Gleason score (Supplementary Table available at www.bidmc.org/prostate). When race/ethnicity was added to the final model, it was not a significant predictor of treatment initiation and did not appreciably change the other risk estimates. Prognostic risk categories combining PSA at diagnosis and Gleason score were associated with treatment initiation: compared to low risk men, the HRs (95% CI) were 1.71 (1.03, 2.86) for intermediate risk and 2.56 (1.18, 5.57) for high risk, adjusting for age at diagnosis (Figure 1).

Lethal disease (defined as prostate cancer-specific death or bone metastasis)^{26, 27} occurred in one of 125 WW patients and 42 of 1105 immediately treated patients (p = 0.10). Crude incidence rates for all-cause mortality were similar between the two groups: 10.84 events per 1000 person-years for WW patients and 11.72 events per 1000 person-years for initially treated patients (p = 0.83).

WW patients were less likely to report moderate-to-severe symptoms of urinary leakage/incontinence (3.5% versus 10.0%, respectively; p-value=0.024) and impotence (67.9% versus 78.2%, respectively; p-value=0.015), and more likely to report reduction of urinary stream force (21.8% versus 13.0%, respectively; p-value=0.011) compared to initially

treated patients (Table 3). After adjusting for age at diagnosis, comorbidity score, and time from diagnosis to QOL assessment in the regression model, WW patients remained less likely to report urinary leakage/incontinence (OR=0.33; 95% CI: 0.12, 0.91; p-value=0.033) and impotence (OR=0.41; 95% CI: 0.26, 0.65; p-value<0.001) compared to those initially treated. No significant differences in QOL outcomes were observed among the subset of WW patients who progressed to treatment compared to patients treated within a year after diagnosis (data not shown), though we had <80% power to detect differences across all 12 domains.

DISCUSSION

Among men diagnosed with prostate cancer who were participants in the Physicians' Health Study, one in ten opted for WW for at least one year. Over half of the men on WW eventually underwent treatment, most commonly radiation therapy. Early-stage WW patients who were later treated tended to be younger and had a less favorable prognostic risk profile compared to those who remained untreated during follow-up. Adverse QOL measures, notably urinary leakage/incontinence and impotence, were less prominent among WW patients compared to those initially treated.

Our results are consistent with other studies of WW and predictors of subsequent treatment, including the Health Professionals Follow-up Study,⁸ CaPSURE,^{9, 28} and Department of Defense Center for Prostate Disease Research Database,²⁹ that also had found that WW patients were older at diagnosis and had less aggressive cancers than those who chose immediate therapy. However, our prostate cancer survivorship analysis of the PHS extends beyond the scope of these prior American studies by concurrently evaluating clinical outcomes and QOL consequences of WW.

In the PHS, we observed long-term reduction in risk of urinary leakage/incontinence and impotence among the WW group compared to those initially treated. Our QOL findings in the PHS cohort extend to a substantially longer period of follow-up (mean 7.3 years) than was observed by two prior studies that had evaluated early follow-up after diagnosis: In CaPSURE, men on WW tended to have better or equivalent urinary and sexual function after 2 years of follow-up compared to treated men,²⁰ and in a sub-study of the Prostate Cancer Intervention Versus Observational Trial, incontinence scores were better in WW (n=20) versus curative therapy (n=41) patients at a mean of 2 years of follow-up.¹³

In contrast to benefits of WW in urinary incontinence and sexual QOL domains, WW has been associated with detrimental consequences in urinary obstructive outcomes. The Scandinavian Prostate Cancer Group-4 trial comparison of 187 WW and 189 radical prostatectomy patients showed that obstructive urinary symptoms were more common among WW patients.¹¹ We also noted a 29% increased risk of weak urinary stream among the WW group in our study, but this result was not significant in the adjusted model. One possible explanation for why we did not detect a urinary obstructive benefit with treatment, as had been observed by Steineck et al,¹¹ is that we compared WW to any initial treatment without discerning relative effects of different primary treatments (e.g. prostatectomy, radiotherapy).

QOL among WW patients has been prospectively evaluated from time of diagnosis in three studies.^{12, 20, 30} Two of these studies showed that QOL remained relatively stable during the first year following diagnosis among WW patients.^{20, 30} The CaPSURE study, however, observed declines in sexual function during five years following diagnosis among WW patients that were greater than potentially attributable to aging.¹² Though we were unable to assess change in QOL over time, we found that impotence was less likely among WW

versus initially treated patients, after controlling for age at diagnosis and time from diagnosis to QOL assessment. This difference may partially be explained by radiation as the most common delayed treatment among the WW group.

Our study has limitations. First, due to limitations of questionnaire length that precluded use of an entire validate HRQOL instrument, our analyses were restricted to evaluating responses to single items, and not scorable multi-item domain sets. Moreover, baseline urinary and sexual status prior to prostate cancer diagnosis or treatment was not available, and such baseline information is a key determinant of outcome. Our findings, therefore, do not provide conclusive evidence to reliably predict outcome for an individual patient, but instead suggest focal points for more definitive, prospective QOL assessment in studies of WW. Second, our study excluded 25% of prostate cancer patients from the PHS who died (proportion due to prostate cancer: 40%) before the patient-report questionnaire was distributed in 2005, as well as non-responders. The QOL profile of excluded patients may have differed from those included in the current analysis, thus limiting generalizability. Third, recall bias is a concern among WW patients since we relied largely on a self-reported data for radiation and hormone therapy, in contrast to studies such as CaPSURE which has longitudinally followed newly diagnosed patients since 1999.²⁸ We attempted to limit the potential bias by assigning a study physician to carefully review all available medical records for these patients. Fourth, while the PHS participants represent the major geographical regions of the US,¹⁶ they are physicians and thus the distribution of treatment choices may or may not be representative of the general population. Furthermore, the PHS began as a clinical trial for cardiovascular disease and cancer prevention, which could have also influenced the participants' timing and choice of treatments. Fifth, we combined all patients who deferred treatment into one group (referred to as WW) because we could not discern WW from active surveillance. Lastly, we were unable to examine lethal prostate cancer as an endpoint since only 43 deaths or bone metastases occurred in the four years following questionnaire return.

CONCLUSIONS

WW or active surveillance for low risk prostate cancer seeks to harness the survival benefits of treatment while optimizing QOL by selectively treating only those cancers that show aggressive biological features during vigilant follow-up. Our observations that only one prostate cancer-specific death occurred among 125 early-stage WW patients, and that 41% of WW patients remained treatment-free during a mean follow-up of over seven years, validate the rationale for deferring initial treatment. Furthermore, our pilot evaluation of patient-reported QOL suggested possible benefit in urinary incontinence and sexual QOL status among WW patients compared to that of patients treated within one year of diagnosis. These findings support the suitability of WW as a prostate cancer care option for select patients at low risk of disease progression.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Number of men on watchful waiting for prostate cancer at risk of treatment initiation:

Prognostic risk group	Duration of Follow-up			
	0 (at diagnosis)	5 years	10 years	15 years
High risk	9	2	1	0
Intermediate risk	36	12	6	0
Low risk	76	30	12	5

Figure 1.

Cumulative incidence of treatment initiation by prognostic risk group among early-stage (clinical stage T1–T2) prostate cancer patients who underwent watchful waiting for at least one year after diagnosis, Physicians' Health Study, 1982–2006. Prognostic risk groups were categorized using a modification of the D'Amico criteria: low risk (Gleason score 2–6 and PSA at diagnosis < 10 ng/ml); intermediate risk (Gleason score 2–6 and PSA at diagnosis 10 to < 20 ng/ml, or Gleason score 7 and PSA at diagnosis < 20 ng/ml); high risk (Gleason score 8–10 or PSA at diagnosis ≥ 20 ng/ml).

Table 1

Characteristics of men diagnosed with early-stage prostate cancer from 1982 to 2004 in the Physicians' Health Study

	Total (n=1230)	Watchful waiting for at least one year after diagnosis (n=125)	Any treatment within a year after diagnosis (n=1105)	p-value [†]
Mean follow-up time, years ²	7.3	7.8	7.2	0.199
Age at diagnosis, years				
Mean	68.5	72.3	68.1	<0.0001
Categories, %				
< 60	11.2	4.8	11.9	<0.0001
60 to 69	48.6	29.6	50.7	
70	40.2	65.6	37.4	
Race / ethnicity, % ³				
White	95.6	96.5	95.4	0.345
Black	0.9	0.0	1.0	
Asian	1.4	0.0	1.6	
Other	2.1	3.5	2.0	
BMI (kg/m ²) at diagnosis, % ³				
< 21	6.0	4.3	6.2	0.726
21 to 24.9	42.0	42.7	41.9	
25 to 29.9	43.5	46.2	43.2	
30	8.5	6.8	8.7	
Clinical stage, %				
T1	54.0	56.0	53.8	0.633
T2	46.0	44.0	46.2	
PSA at diagnosis (ng/ml) ³				
Median	6.6	6.0	6.7	0.051
Categories, %				
< 4	13.3	22.4	12.3	0.021
4 to 9.9	60.7	52.6	61.6	
10 to 19.9	18.9	17.2	19.1	
20	7.1	7.8	7.0	
Gleason score, % ³				
2 to 5	21.7	39.8	19.6	<0.0001
6	44.3	36.6	45.2	
7	24.6	21.2	25.0	
8 to 10	9.4	2.4	10.2	

¹Two-sided p-value for chi-square test, Fisher exact test, t-test, or Wilcoxon rank-sum test.

²Time from diagnosis to return of patient-reported outcomes questionnaire.

³Missing data not shown for race/ethnicity (n=105), BMI (n=53), PSA at diagnosis (n=42), and Gleason score (n=27).

Table 2

Average time to treatment among early-stage prostate cancer patients who underwent watchful waiting for at least one year, Physicians' Health Study, 1982–2006

	n	%	Average time to treatment or end of follow-up (years)	
			Median	Mean $\pm$ standard deviation
Radical prostatectomy	12	9.6	1.5	2.6 $\pm$ 2.7
External beam radiation alone	19	15.2	2.0	2.3 $\pm$ 1.6
Brachytherapy alone	11	8.8	1.9	2.5 $\pm$ 1.2
Hormones with external beam radiation or brachytherapy	12	9.6	1.4	2.3 $\pm$ 2.5
Hormones alone	20	16.0	5.0	6.1 $\pm$ 4.3
Untreated during follow-up	51	40.8	6.6	7.6 $\pm$ 4.8
Total	125	100.0	3.3	5.1 $\pm$ 4.4

Table 3

Quality of life measures comparing early-stage prostate cancer patients who underwent watchful waiting for at least one year to those who were treated within one year after diagnosis, Physicians' Health Study, 1982–2006

	Watchful waiting for at least one year after diagnosis (n=121)	Any Treatment within one year after diagnosis (n=1085)	p-value ^I
Urinary leakage or incontinence			
% moderate or severe	3.5	10.0	0.024
OR (95% CI) ²	0.33 (0.12,0.91)	1.00 (referent)	0.033
Nocturia			
% moderate or severe	27.6	21.3	0.118
OR (95% CI) ²	1.07 (0.68,1.68)	1.00 (referent)	0.775
Increased urinary frequency or urgency			
% moderate or severe	16.1	15.0	0.761
OR (95% CI) ²	0.94 (0.54,1.63)	1.00 (referent)	0.829
Decreased force of urinary stream			
% moderate or severe	21.8	13.0	0.011
OR (95% CI) ²	1.34 (0.80,2.23)	1.00 (referent)	0.269
Hematuria			
% moderate or severe	1.9	1.9	1.000
OR (95% CI) ²	0.62 (0.14,2.89)	1.00 (referent)	0.545
Fatigue			
% moderate or severe	12.2	8.9	0.272
OR (95% CI) ²	0.98 (0.50,1.90)	1.00 (referent)	0.945
Hot flashes			
% moderate or severe	5.7	7.3	0.534
OR (95% CI) ²	0.54 (0.22,1.31)	1.00 (referent)	0.171
Impotence			
% moderate or severe	67.9	78.2	0.015
OR (95% CI) ²	0.41 (0.26,0.65)	1.00 (referent)	< 0.001
Reduced sexual desire			
% moderate or severe	55.7	47.2	0.099
OR (95% CI) ²	1.00 (0.65,1.53)	1.00 (referent)	0.994
Rectal urgency			
% moderate or severe	7.6	8.4	0.780
OR (95% CI) ²	0.75 (0.35,1.63)	1.00 (referent)	0.463

	Watchful waiting for at least one year after diagnosis (n=121)	Any Treatment within one year after diagnosis (n=1085)	p-value ¹
Diarrhea			
% moderate or severe	2.9	3.3	1.000
OR (95% CI) ²	0.73 (0.21,2.51)	1.00 (referent)	0.614
Abdominal and/or perineal pain			
% moderate or severe	1.0	1.2	1.000
OR (95% CI) ²	0.78 (0.09,6.40)	1.00 (referent)	0.815

¹Two-sided p-value from the chi-square test, Fisher's exact test, or Wald test comparing watchful waiting patients to those treated within one year after diagnosis.

²Odds of reporting moderate or severe symptoms among watchful waiting patients compared to those treated within one year post-diagnosis. Adjusted for age at diagnosis (continuous), comorbidity score (continuous), and time from diagnosis to quality of life assessment (continuous).