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TIME TRENDS AND CHARACTERISTICS OF MEN CHOOSING WATCHFUL WAITING FOR INITIAL TREATMENT OF LOCALIZED PROSTATE CANCER: RESULTS FROM CAPSURE*

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ABSTRACT

Purpose: Watchful waiting (WW) is one option for men with clinically localized prostate cancer. We examined temporal trends in the use of WW, as well as sociodemographic and clinical profiles of men who choose this form of management.

Materials and Methods: The Cancer of the Prostate Strategic Urologic Research Endeavor is a national registry of patients with various stages of prostate cancer. Between 1989 and 2000, 5,365 men in the database were diagnosed with localized disease and elected either WW or active treatment within 9 months of diagnosis. Of these men 402 elected WW as initial disease management. We analyzed time trends in WW use, and sociodemographic and clinical predictors of WW using chi-square tests and multivariate logistical regression.

Results: In examining 3-year intervals, use of WW increased from 7.5% in 1989 to 1991 to 9.5% in 1992 to 1994, and then decreased during the next 6 years to 5.5% in 1998 to 2000 ($p = 0.001$). With time there was a significant increase in the proportion of WW patients with T1 disease and prostate specific antigen of 10 ng/ml or less. Compared to patients choosing active treatment, patients opting for WW were more likely to have low risk disease. After controlling for clinical factors WW patients were also more likely to be 75 years old or older, to have Medicare insurance and to have greater comorbidity.

Conclusions: During the prostate specific antigen era rates of WW for the initial treatment of prostate cancer have been decreasing despite considerable downward stage migration. We expect that as prostate cancer risk assessment and surveillance strategies continue to improve, more patients may benefit from this approach to management.

KEY WORDS: prostatic neoplasms, therapy, trends

Prostate specific antigen (PSA) screening has resulted in more frequent early detection of prostate cancer with more tumors amenable to potentially curative local treatment at diagnosis. However, the natural history of the disease may be protracted especially in the context of cancer screening, and only 25% to 33% of men who are diagnosed actually die of prostate cancer.[1,2] Moreover, all available treatments can negatively affect patient health related quality of life.[3] Analysis of tumor registries in the United States[4] and Sweden[5] with followup as long as 15 years has demonstrated that patients with low grade tumors may expect prolonged survival without definitive treatment. Therefore, interest has focused increasingly on watchful waiting (WW) as a viable alternative for the initial management of the disease, particularly in men with low stage and low risk clinical features.[6,7]

However, a recent cross-sectional analysis found that despite downward stage migration only 8.2% of patients with newly diagnosed prostate cancer in the United States in fact pursue watchful waiting, and these are mostly older patients and those with favorable risk parameters.[8] We determined whether rates of WW are increasing or decreasing with time, and characterized further sociodemographic and clinical variables which predict WW versus active treatment.

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MATERIALS AND METHODS

Description of data set. CaPSURE is a longitudinal, observational database of men with biopsy proven prostate adenocarcinoma recruited from 40 academic and community based urology practices in the United States. Patients with prostate cancer are recruited consecutively by participating urologists who report clinical data and followup information on diagnostic tests and treatments. Patients are treated according to usual physician practices and are followed until time of death or withdrawal from study. Completeness and accuracy of data are assured by random sample chart review every 6 months. Additional details of the project methodology have been reported previously.[9]

Of the 8,685 men enrolled in CaPSURE as of August 2002, we identified 5,365 who were diagnosed between 1989 and 2000 with localized disease (clinical stage T3a or less with no evidence of lymph node involvement or metastases) who chose either WW or an active treatment (radical prostatectomy, external beam or interstitial radiation therapy, cryotherapy, or androgen deprivation therapy) within 9 months of prostate cancer diagnosis. There were 402 men who elected WW and 4,963 who opted for active treatment. The 402 men

choosing WW excluded those who had active treatment before or within 6 months after initiating WW. An additional 152 treatment delayers waited more than 9 months from diagnosis before initiating active treatment. These men were treated at a median of 14 months after diagnosis. They were excluded from study because based on preliminary analysis they had significantly higher risk disease (42% of treatment delayers were high risk vs 27% of WW patients, chi-square test $p = 0.009$).

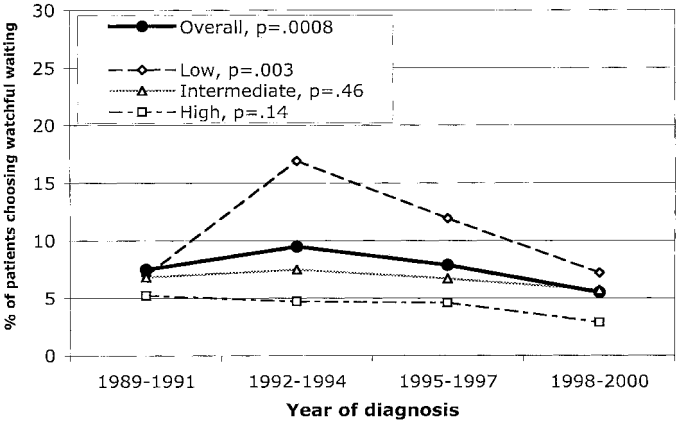
Statistical analysis. Time trends were examined by year of diagnosis and categorized into 3-year intervals (1989 to 1991, 1992 to 1994, 1995 to 1997 and 1998 to 2000). Clinical variables assessed at diagnosis included PSA, Gleason score and clinical T-stage (1997 definition). Based on these variables patients were categorized into low, intermediate and high risk groups. Low risk patients had a PSA of 10 ng/ml or less, Gleason sum less than 7 and clinical stage T1 or T2a. Intermediate risk patients had a PSA between 10.1 and 20 ng/ml, Gleason sum 7 or clinical stage T2b. High risk patients had a PSA greater than 20 ng/ml, Gleason sum greater than 7, or clinical stage T3 or T4.[10] Sociodemographic variables analyzed included patient age at diagnosis, ethnicity, education, income, relationship status, type of insurance and Charlson comorbidity index, as well as physician practice type (community vs academic or Veterans Affairs Medical Center).

We first examined temporal trends in the percent of patients electing watchful waiting. This analysis was performed for all men on WW and then stratified by risk group. Significance of time trends was measured with the Mantel-Haenszel chi-square test for trend. Because not all study sites contributed patients in each year (ie site withdrawal or enrollment occurred during the study) and each contributed different numbers of patients, we were concerned that practice patterns at a few sites might unduly influence the results of analysis. Therefore, we also examined the effect of time period on WW using logistical regression. We ran a model controlling for study site only, and one with study site, risk group, age, comorbidity and insurance (selection via backward stepwise analysis) to determine whether the effect of time period remained after controlling for potential changes in case mix through the years. Odds ratios (OR) for electing WW by time period were calculated with 95% confidence intervals (CI).

We also examined time trends in sociodemographic and clinical characteristics among the 402 WW patients. We used the chi-square test to look for univariate differences in patient characteristics followed by a backward stepwise logistical regression to determine which of the characteristics to include in a multivariate final model. Odds ratios adjusting for the other variables in the model were calculated with 95% confidence intervals.

RESULTS

Time trends in use of WW for localized prostate cancer are presented in the figure. After an initial increase from 7.5% in 1989 to 1991 to 9.5% in 1992 to 1994, overall rates of WW decreased to 7.9% in 1995 to 1997 and then to 5.5% in 1998 to 2000 ($p = 0.0008$). After controlling for risk group, age, comorbidity, insurance status and study site, patients diagnosed in 1995 to 1997 were 1.8 times as likely (CI 1.3–2.5) as those diagnosed in 1998 to 2000 to choose WW. Patients diagnosed in 1992 to 1994 were also 1.8 times as likely (CI 1.3–2.6) to choose WW. However, patients diagnosed in 1989 to 1991 were not more or less likely to elect WW than those diagnosed in 1998 to 2000 after adjustment for study site and other variables (OR 1.09, CI 0.7–1.7). The most striking changes occurred among the low risk population (see figure), among whom rates of WW increased from 7.0% to 16.9% between 1989 to 1991 and 1992 to 1994, and then decreased to 11.9% in 1995 to 1997 and further to 7.2% in 1998 to 2000 ($p = 0.003$). Trends among the intermediate and high risk patients were not significant.



Global time trends in patient choice of watchful waiting. Percentages of patients electing watchful waiting in each time period are presented for all patients in data set and divided by clinical risk group. Mantel-Haenszel chi-square test for trend used to calculate p values.

In general we found few significant temporal trends in the clinical and sociodemographic profile of WW patients. Notable exceptions were that the frequency of T1 disease increased from 35% in 1989 to 1991 to 66% in 1998 to 2000 ($p = 0.0003$), and the proportion of patients with a PSA of 10 ng/ml or less increased from 59% to 73% during the same time period ($p = 0.005$). In addition, the proportion of WW patients in academic rather than community practices increased from 5% in 1989 to 1992 to 15% in 1998 to 2000 ($p = 0.008$).

Patient characteristics predictive of WW or active treatment are presented in the table. By univariate analysis all factors but practice site were significantly different between the 2 groups. WW patients tended to be older, white, less educated and single. They tended to have lower risk disease, less income, more comorbidity and to be covered by Medicare rather than private insurance. In multivariate analysis risk, age, comorbidity and insurance status remained in the model. Low risk patients are 5.1 times as likely as high risk patients to pursue WW (CI 3.8–6.9). Patients older than 75 years are much more likely than those younger than 65 to choose WW (adjusted OR 14.3, CI 9.1–22.5), while those with comorbidity index scores greater than 1 are more likely than those with scores of 0 to 1 to elect WW (adjusted OR 1.43, CI 1.1–1.8). In contrast those with private insurance are less likely than those with Medicare to pursue watchful waiting (OR 0.7, CI 0.5–1.0).

A preliminary analysis of global treatment trends over time finds that WW use has decreased from 1992 to 1994, to 1998 to 2000. During the same time period use of external beam radiotherapy has decreased from 19.2% to 8.8% while that of brachytherapy has risen from 3.9% to 22.0%, and that of primary androgen deprivation therapy has increased from 13.1% to 16.3%. Rates of radical prostatectomy have remained fairly stable accounting for 47.1% and 45.7% of patients in each time period.

DISCUSSION

Recent trials have explored the feasibility of initial observation for greater numbers of patients with prostate cancer. Efforts have centered primarily on those with low risk tumor characteristics in whom initial selection of active monitoring may not entail significant risk of disease progression, nor sacrifice curative intent. Such an approach could preserve quality of life and achieve significant cost savings without impairing long-term oncological outcomes.

Characteristics of patients pursuing active treatment or watchful waiting

	No. Active Treatment (%)	No. WW (%)	p Value (chi-square)*	Adjusted OR for WW Choice (95% CI)
Total pts	4,963	402		
Risk group:				
Low	1,427 (34)	178 (55)	<0.0001	5.13 (3.83–6.87)
Intermediate	862 (20)	61 (19)		1.81 (1.27–2.57)
High	1,931 (46)	87 (27)		Reference
Practice site:				
Academic/Veterans Affairs	386 (8)	32 (8)	0.90	Not significant
Community	4,577 (92)	370 (92)		
Age:				
Younger than 65	1,902 (38)	43 (11)	<0.0001	Reference
65–74	2,239 (45)	144 (36)		2.57 (1.65–4.02)
75* or Older	822 (17)	215 (53)		14.32 (9.09–22.54)
Ethnicity:				
Black	504 (10)	29 (7)	0.03	Not significant
White	4,279 (86)	365 (91)		
Other/unknown	180 (4)	8 (2)		
Education:				
Unknown	872 (18)	74 (18)	0.03	Not significant
Less than high school graduate	768 (15)	75 (19)		
High school graduate	1,848 (37)	160 (40)		
College graduate	1,475 (30)	93 (23)		
Income:				
Unknown	1,409 (28)	119 (30)	0.01	Not significant
Less than $30,000	1,373 (28)	131 (33)		
$30–$50,000	923 (19)	79 (20)		
$50,000 or Greater	1,258 (25)	73 (18)		
Relationship status:				
Unknown	1,055 (21)	79 (20)	0.0001	Not significant
In relationship	3,535 (71)	269 (67)		
Not in relationship	373 (8)	54 (13)		
Insurance:				
Medicare	2,744 (55)	311 (77)	<0.0001	Reference
Private	1,910 (38)	64 (16)		0.70 (0.48–1.00)
Other/none/unknown	309 (6)	27 (7)		1.38 (0.82–2.34)
Comorbidity index:				
Unknown	691 (14)	60 (15)	<0.0001	1.48 (1.01–2.06)
0–1	2,251 (45)	130 (32)		Reference
2 or More	2,021 (41)	212 (53)		1.42 (1.09–1.85)

* Univariate p values are calculated from chi-square test.

Choo et al recently reported on a cohort of 206 low risk patients pursuing WW with an overall median followup of 29 months. The majority of these patients (67%) remained on WW without evidence of disease progression. Of the 69 patients who discontinued the study no patient had evidence of metastasis and only 36 (17%) had evidence of clinical or biochemical progression. Of the remainder, 23 voluntarily withdrew, 6 had protocol violations and 4 died of other causes.[11] Carter et al likewise observed 81 patients with low risk disease with a median followup of 23 months. At 2-year followup with repeat biopsy and PSA measurement 31% had evidence of disease progression. A total of 13 men ultimately underwent radical prostatectomy, of whom 12 had potentially curable cancers (greater than 70% survival at 10 years expected based on pathological features). Therefore the initial period of WW did not appear to compromise potential for cure. The higher rate of progression seen in this trial may be an artifact of requiring only sextant biopsies at study entry with higher grade disease simply not sampled at initial biopsy.[6]

Holmberg et al recently reported the results of a randomized trial comparing radical prostatectomy to WW for clinically localized prostate cancer. They found that prostatectomy yielded a 6.6% decrease in disease specific mortality at 8 years of followup ($p = 0.02$). A 6.3% decrease in overall survival was not statistically significant ($p = 0.31$), although the study was likely underpowered with respect to this secondary outcome.[12] It is important to note that the patients in this trial were identified before the PSA era and, thus, potentially harbored more advanced disease than contemporary cohorts of lower risk patients. The ongoing randomized Prostate Cancer Intervention Versus Observation Trial is enrolling patients with T1 or T2 tumors of any Gleason grade to address the same question.[13]

A previous cross-sectional analysis from CaPSURE found that 8.2% of patients, principally those who were older and had favorable risk characteristics, opted for initial observation of prostate tumors. More than half of these patients underwent secondary treatment within 5 years, especially those who were younger or had higher PSA scores at diagnosis.[8] Another single institution study of 199 older patients with low risk tumors following a surveillance protocol found that 44% underwent treatment within 5 years with a disease specific survival rate of 98% at 7 years.[14] More recent reports suggest that patients may pursue watchful waiting for up to 10 years without adverse psychological impact.[15]

We found that contemporary patients pursuing WW are more likely than earlier groups to have clinical stage T1 disease and a PSA of 10 ng/ml or less. These trends reflect recognized shifts in prostate cancer risk characteristics at diagnosis.[16,17] Despite this downward risk migration, with more patients potentially excellent candidates for WW, we have shown a 42% decrease in actual rates of WW during the PSA era. An overall decrease from 9.5% in 1992 to 1994, to 5.5% in 1998 to 2000 was observed, with the most rapid decrease noted among the low risk patients, the best candidates for WW. The initial increase in WW use in the early 1990s may be explained by the sharp increase in the incidence of early stage tumors due to the introduction of widespread PSA screening. Explanations for the subsequent decrease in WW are less clear, likely reflecting a combination of patient desire and physician guidance. Based on our preliminary analysis it seems likely that many patients previously pursuing WW now receive brachytherapy or primary androgen deprivation therapy. Detailed analysis is ongoing regarding treatment trends for these low risk patients.[18]

CaPSURE tracks use and outcome patterns in actual practice without the constraints imposed by clinical trial proto-

cols. While CaPSURE practice sites have not been chosen at random and, thus, cannot be assumed to represent a statistically valid sample of the United States patient population, they do represent a broad range of geographic locales, heavily weighted toward community practices. CaPSURE data are submitted only by patients and urologists, therefore, any treatments by other practitioners which are not reported by patients either to their urologists or in their questionnaires may be missed. Extant quality assurance mechanisms, including chart review of all hospital admissions and the use of patient questionnaires detailing treatment, minimize this problem. Data before 1995 were entered retrospectively, which could potentially have biased comparisons between patients with early or late dates of diagnosis.

Finally, we excluded 152 patients from study for whom no treatment was recorded within 9 months of diagnosis. Our initial analysis suggested that they represented a different clinical group than our WW cohort. They were similar in all regards to those receiving more immediate treatment and, therefore, most likely represented patients who simply delayed final treatment decisions. Moreover, prior studies have found that among those electing WW median time to treatment was greater than 6 years,[14] and greater than 3 years even among high risk patients[8] with virtually no patients undergoing treatment in the first year. Because the excluded patients underwent treatment at a much shorter median interval we are confident in the decision to exclude them. However, the possibility remains that this decision may limit the ability of our analysis to generalize to other patients who do not meet our stricter definition of watchful waiting. Despite these caveats we believe our data provide the best available description of temporal trends in WW for prostate cancer, and of differences between patients choosing WW and active treatment.

Recent studies have raised the concern that PSA screening has led to the overdiagnosis of prostate cancer with the identification of many tumors that are unlikely to affect the length or quality of life in affected men.[19] However, overdiagnosis is primarily a concern only to the extent that it leads to overtreatment. Given the increasing number of patients diagnosed with low risk prostate cancer, the prolonged natural history of the disease, the adverse quality of life impact of all available active treatments and the apparent low risk of disease progression with active surveillance, it seems likely that more patients should be considered for WW.

CONCLUSIONS

Use of WW as initial management for prostate cancer is decreasing, particularly in low risk patients. This decrease comes at a time when trials are demonstrating a potentially increased role for this management strategy for low risk disease. Long-term results from these cohorts are needed, as are data from multi-institutional trials underway. These results may provide confirmation that cancer control is not compromised and that quality of life is in fact preserved by deferring active intervention for select patients with prostate cancer.

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