More Judicious Use of Expectant Management for Localized Prostate Cancer during the Last 2 Decades

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Abbreviations and Acronyms

ADT = androgen deprivation therapy

AS = active surveillance

CEASAR = Comparative Effectiveness Analysis of Surgery and Radiation

PCa = prostate cancer

PCOS = Prostate Cancer Outcomes Study

PCSM = prostate cancer specific mortality

PSA = prostate specific antigen

SEER = Surveillance, Epidemiology, and End Results

WW = watchful waiting

Purpose: Urologists have been criticized for overtreating men with low risk prostate cancer and for passively observing older men with higher risk disease. Proponents of active surveillance for low risk disease and critics of watchful waiting for higher risk disease have advocated for more judicious use of observation. Thus, we compared 2 population based cohorts to determine how expectant management has evolved during the last 2 decades.

Materials and Methods: A total of 5,871 men with localized prostate cancer were enrolled in the PCOS (Prostate Cancer Outcomes Study) or the CEASAR (Comparative Effectiveness Analysis of Surgery and Radiation) study. We compared the use of definitive treatment vs expectant management (watchful waiting or active surveillance) across cohorts, focusing on the influence of disease risk, age and comorbidities.

Results: Use of watchful waiting or active surveillance was similar in PCOS and CEASAR (14% in each). Compared to the PCOS, more men in the CEASAR study with low risk disease selected watchful waiting or active surveillance (25% vs 15%, respectively), whereas fewer men with intermediate (7% vs 14%) and high risk (3% vs 10%) disease chose watchful waiting or active surveillance ($p < 0.001$ for each). The association of disease risk with watchful waiting or active surveillance was significantly larger in CEASAR than in PCOS (OR 7.3, 95% CI 3.4 to 15.7). Older age was associated with watchful waiting or active surveillance in both cohorts but there was no association between comorbidity and watchful waiting or active surveillance in the CEASAR study.

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Conclusions: Use of watchful waiting or active surveillance was more aligned with disease risk in CEASAR compared to PCOS, suggesting there has been a pivot from watchful waiting to active surveillance. While older men were more likely to be observed, comorbidity had little, if any, influence.

Key Words: prostatic neoplasms, watchful waiting, antineoplastic protocols, risk assessment

ALTHOUGH prostate cancer remains the second leading cause of cancer death in men,[1] the natural history of localized PCa varies from indolent to aggressive.[2] Deciding whether to treat or observe localized PCa depends on accurate estimation of prostate cancer specific mortality and other cause mortality.[3]

Failure to balance these competing risks has resulted in widespread overtreatment of low risk disease and under treatment of high risk disease among elderly men.[4–6] However, during the last decade some thought leaders have promoted active surveillance as a means to reduce the harms associated with overtreatment of low risk disease, and urological guidelines panels have adjusted their recommendations accordingly.[7] Similarly, recent attention has focused on the under treatment of older men with higher risk disease, who may be placed on watchful waiting rather than being offered curative treatment.[6]

In this study we determined the extent to which evidence-based recommendations regarding more judicious use of expectant management have been implemented at the population level. We compared the use of treatment and observation in 2 large, population based studies, the CEASAR study, accrued in 2011 to 2012, and the PCOS, accrued in 1994 to 1995. Our aim was to determine how the use of observation has changed with respect to disease risk, age and comorbidity, and to determine whether there is evidence of a pivot from the WW modality toward AS in this interval.

MATERIALS AND METHODS

Patients

The analytic cohort was drawn from PCOS and CEASAR, 2 population based PCa cohorts. The PCOS enrolled 5,424 patients from 6 participating SEER sites (Connecticut, Utah and New Mexico as well as the metropolitan areas of Atlanta, Georgia; Los Angeles, California and Seattle-Puget Sound, Washington) in 1994 to 1995.[8] The CEASAR study used similar accrual mechanisms to enroll 3,691 men in 2011 to 2012 from 5 SEER registries (Atlanta, Los Angeles, Louisiana, New Jersey and Utah) as well as newly accrued CaPSURE™ (Cancer of the Prostate Strategic Urologic Research Endeavor) study participants.[9]

Inclusion in CEASAR was restricted to men younger than age 80 years, with clinically localized disease (cT1 or T2) and PSA less than 50 ng/ml, whereas PCOS was less restricted. Therefore, in order to create a homogenous analytic cohort of men who might be eligible for treatment or observation, the current study included the 2,625 men from the PCOS and 3,246 men from the CEASAR study who were between 40 and 75 years old at enrollment, had a baseline survey, a 6-month or a 12-month survey, PSA less than 50 ng/ml, nonmissing Gleason score, clinical stage T1 or T2 disease and sufficient treatment information.

Data Collection

At baseline, demographic and clinical information was collected. Functional status was assessed with the UCLA-PCI (University of California Los Angeles-Prostate Cancer Index) in the PCOS and the Expanded Prostate Cancer Index Composite-26 in the CEASAR study. The 2 questionnaires asked similar, but slightly different questions regarding sexual, urinary and bowel function. Thus, we normalized functional domain scores to the cohort mean and standard deviation.

Data were abstracted from medical records 12 months after diagnosis.[10] Treatment choice was determined by the most reliable source of information available in the order of medical chart abstraction, patient reported treatment selection and SEER registry data. WW/AS was defined as no record of definitive treatment within 1 year after diagnosis, or documentation of WW/AS in the medical chart or patient reported WW/AS in the absence of treatment. Patients on androgen deprivation monotherapy were initially grouped with those undergoing definitive treatment and were omitted in subsequent sensitivity analyses.

Statistical Analysis

Patient and disease characteristics were compared across cohorts. Rates of definitive treatment vs WW/AS were compared by cohort across recurrence risk strata. The odds of choosing WW/AS in CEASAR and PCOS were compared using a logistic regression model. Covariates of interest included age, number of comorbidities and modified D'Amico risk score. The comorbidities assessed common to both cohorts were heart failure, angina, stroke, heart attack, hypertension, diabetes, colitis and lung disease. The number of comorbidities was grouped as 0, 1, or 2 or more. In the CEASAR study the low modified D'Amico risk score was defined as PSA less than 10 ng/ml, Gleason sum less than 7 and T1 clinical stage. In the PCOS cases were considered low risk using the same PSA and Gleason sum cutoffs, but with a clinical stage of T1 or T2 to account for the fact that some in the PCOS were coded as T1/T2. The model included 2-way interaction terms between risk factors (age, comorbidities and modified D'Amico risk group) and cohort (PCOS vs CEASAR), and adjusted for race, functional status, study site and

socioeconomic factors (marital status, education, inflation adjusted income, insurance and employment status).

Sensitivity analysis was performed for patients treated at sites common to PCOS and CEASAR. In a separate sensitivity analysis patients who only received ADT were excluded.

To determine the intensity of post-diagnostic surveillance we tallied post-diagnosis PSA testing and repeat biopsies in patients in the CEASAR study. These data were not available for patients in the PCOS. As a secondary analysis we computed 15-year overall survival probability and PCa specific mortality for patients in the PCOS. These data were not available for patients in the CEASAR study.

All p values were 2-sided with $p < 0.05$ considered statistically significant. R software v3.1.0 (R Foundation, Vienna, Austria) was used for all statistical analysis. Estimates are reported with 95% CIs.

RESULTS

The 2,625 PCOS subjects and 3,246 CEASAR subjects were demographically similar (table 1). In terms of disease characteristics more men in CEASAR had nonpalpable disease than in PCOS (76% vs 32%, respectively, $p < 0.001$) but fewer men in CEASAR harbored Gleason 6 or lower tumors (51% vs 66%, respectively, $p < 0.001$, table 2). Of note, even if the 24% of cases of uncertain clinical T-stage in PCOS were classified as T1, the percentage with nonpalpable disease would still be lower than in CEASAR. The differences in T-stage and Gleason sum at presentation likely reflect the stage migration during the interval between studies[11] as well as changes in the Gleason classification system, which was updated in 2005.[12]

Overall rates of WW/AS were similar between cohorts (14% vs 14%, p=0.85). However, its use across disease risk strata changed markedly (fig. 1). Men with low risk disease were far more likely to be on WW/AS in CEASAR than in PCOS (25% vs 15%, $p < 0.001$), whereas a lower percentage of men with intermediate or high risk disease were on WW/AS in CEASAR (7% vs 14% for intermediate risk disease, $p < 0.001$, and 3% vs 10% for high risk disease, $p < 0.001$). Grouping primary ADT and WW/AS together demonstrated that nondefinitive management for high risk disease decreased from 25% in the PCOS to 6% in the CEASAR study ($p < 0.001$).

In the multivariable model men in the CEASAR study were significantly more likely to select WW/AS compared to those in the PCOS ($p < 0.0001$). Disease risk was strongly associated with selecting WW/AS in CEASAR (OR for low risk vs high risk 17.5 [9.3, 32.9]). While having low risk disease was also a strong predictor of WW/AS in the PCOS (OR 2.4 [1.6, 3.7]), it was much more important in the CEASAR study (ratio of OR in CEASAR-to-OR in PCOS 7.3 [3.4, 15.7], table 3). This interaction between disease risk and cohort indicates that risk is used much differently in CEASAR vs PCOS (p-interaction < 0.001).

Table 1. *Demographic characteristics of study cohort*

	CEASAR	PCOS	p Value
Median pt age (Q1, Q3)	64 (59, 70)	66 (59, 71)	<0.001
% Race (No.):			
White	73 (2,343)	70 (1,849)	<0.001
Black	15 (487)	16 (425)	
Hispanic	7 (225)	13 (351)	
Other	4 (139)	0 (0)	
% No. comorbidities (No.):			
0	34 (891)	50 (1,311)	<0.001
1	41 (1,088)	30 (799)	
2 or More	25 (664)	19 (515)	
% Income (No.):			
$30,000 or Less	22 (591)	24 (582)	<0.001
$30,001—$100,000	51 (1,370)	58 (1,378)	
More than $100,000	27 (730)	18 (420)	
% Education (No.):			
Less than grade school	5 (135)	9 (232)	<0.001
Less than high school	6 (158)	11 (297)	
High school graduate	21 (604)	20 (527)	
Some college	22 (635)	24 (627)	
College graduate	23 (652)	15 (387)	
Advanced degree	24 (675)	20 (520)	
% Employment (No.):			
Full-time	41 (1,306)	28 (726)	<0.001
Part-time	8 (249)	9 (245)	
Retired	46 (1,484)	59 (1,526)	
Other	5 (163)	4 (97)	
% Marital status (No.):			
Married	80 (2,275)	81 (1,929)	0.164
Not married	20 (575)	19 (442)	
% Insurance (No.):			
Private or health maintenance organization	47 (1,489)	49 (1,187)	<0.001
Medicare	48 (1,514)	45 (1,075)	
Veterans Affairs or military	1 (39)	4 (97)	
Medicaid	2 (53)	1 (15)	
Other	1 (45)	1 (26)	
No insurance	1 (46)	0 (12)	
% Self-reported overall health (No.):			
Excellent	19 (614)	19 (449)	0.256
Very good	38 (1,239)	37 (866)	
Good	31 (1,002)	31 (737)	
Fair	9 (306)	11 (257)	
Poor	2 (78)	2 (57)	

Table 2. *Clinical characteristics by cohort*

	CEASAR	PCOS	p Value
Median ng/ml PSA (Q1, Q3)	5.5 (4.3, 7.6)	7.5 (5.2, 11.9)	<0.001
% Clinical T-stage (No.):			
T1	76 (2,453)	32 (831)	<0.001
T2	24 (783)	44 (1,164)	
T1 or T2	0 (0)	24 (630)	
% Biopsy Gleason score (No.):			
6 or Less	51 (1,658)	66 (1,734)	<0.001
7	38 (1,236)	25 (669)	
8—10	11 (352)	8 (222)	
% Risk of recurrence (No.):			
Low	44 (1,426)	49 (1,277)	0.004
Intermediate	39 (1,254)	35 (907)	
High	17 (558)	17 (441)	

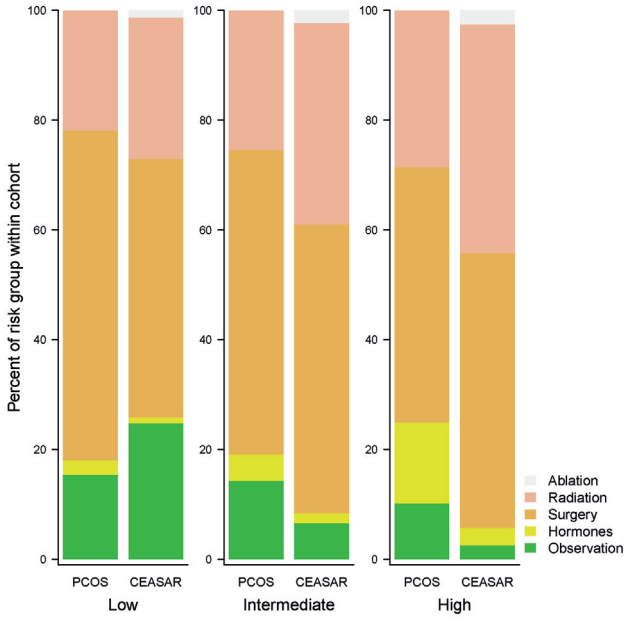

Figure 1. Percentage of men selecting given treatment by risk classification and cohort in unadjusted analysis.

The association between advanced age (older than 70 years) and WW/AS was stronger in PCOS than in CEASAR (p-interaction=0.008, table 3). The corresponding cohort specific results for the number of comorbidities were closer to the null value and to each other (p-interaction=0.16). There was a significant association for 0 vs 2 comorbid conditions but only in the PCOS data.

In sensitivity analyses no difference in outcomes was observed after excluding patients receiving ADT. The findings were also similar when restricting the analysis to participants from SEER sites common to PCOS and CEASAR.

The model enables us to compare estimates of the likelihood of WW/AS across cohorts based on disease risk, age and comorbidity (fig. 2). For example, a 60-year-old man with no comorbidities and low risk disease had a 33% (25, 43) chance of WW/AS in CEASAR vs 9% (6, 13) in PCOS. On the other end of the life expectancy spectrum a 75-year-old man with 2 or more comorbidities with low risk disease had a 69% (57, 78) chance of WW/AS in CEASAR vs 53% (41, 66) in PCOS, while a similar patient with high risk disease had an 11% (6, 21) chance of WW/AS in CEASAR vs 32% (21, 46) in PCOS.

After a median followup of 13 months 90% of men in the CEASAR cohort had at least 1 subsequent PSA measurement and 35% underwent prostate biopsy after diagnosis, suggesting most of these men were on AS rather than WW. Median overall survival in the PCOS observation group was 11.5 years (95% CI 9.6–12.6). At 15 years after enrollment the overall mortality rate was 68.8% (62.5–75.0) and the PCSM rate was 16.6% (12.0–22.6) (see supplementary figures, http://jurology.com/).

DISCUSSION

In this study we found that the use of observation changed substantially between the PCOS era (1994 to 1995) and the CEASAR era (2011 to 2012). While observation was used in a comparable proportion in each cohort (14%), it was used much more frequently for low risk disease in CEASAR and much less frequently for intermediate and high risk disease. The high rates of subsequent testing in the CEASAR cohort suggest that the majority of patients on observation with a diagnosis in 2011 to 2012 were indeed on AS, while the high PCSM in the PCOS suggests that WW was applied to men with a high risk of progression in the 1990s. Taken together, these findings suggest that the modality of

Table 3. *Factors associated with an observational strategy in a multivariable model*

	CEASAR		PCOS		Difference in Effect between Cohorts	
	OR (95% CI)	p Value*	OR (95% CI)	p Value*	OR/OR (95% CI)†	p Value*
Age:						0.008
70 vs 60 yrs	2.66 (2.10, 3.38)	<0.001	3.98 (3.08, 5.14)	<0.001	0.67 (0.50, 0.90)	
Comorbidities:						0.16
1 vs 0	0.78 (0.56, 1.03)	0.103	1.09 (0.78, 1.52)	0.604	0.71 (0.46, 1.11)	
2+ vs 0	1 (0.71, 1.43)	0.979	1.54 (1.08, 2.22)	0.019	0.65 (0.4, 1.06)	
Disease risk:						<0.001
Intermediate vs low	0.18 (0.14, 0.25)	<0.001	0.65 (0.48, 0.89)	0.007	0.28 (0.18, 0.44)	
High vs low	0.06 (0.03, 0.11)	<0.001	0.42 (0.27, 0.64)	<0.001	0.14 (0.06, 0.29)	
Disease risk (other pairwise comparisons):						
Low vs high	17.48 (9.29, 32.88)	<0.001	2.39 (1.55, 3.68)	<0.001	7.32 (3.41, 15.71)	<0.001
Intermediate vs high	3.23 (1.67, 6.23)	<0.001	1.55 (0.99, 2.43)	0.054	2.08 (0.94, 4.60)	

Adjusted for site, race, income, marital status, education, employment, sexual and urinary domain scores, insurance status and overall health.
* p Value for ANOVA test of overall interaction effect.
† Ratio of effect of risk factor for CEASAR vs PCOS.

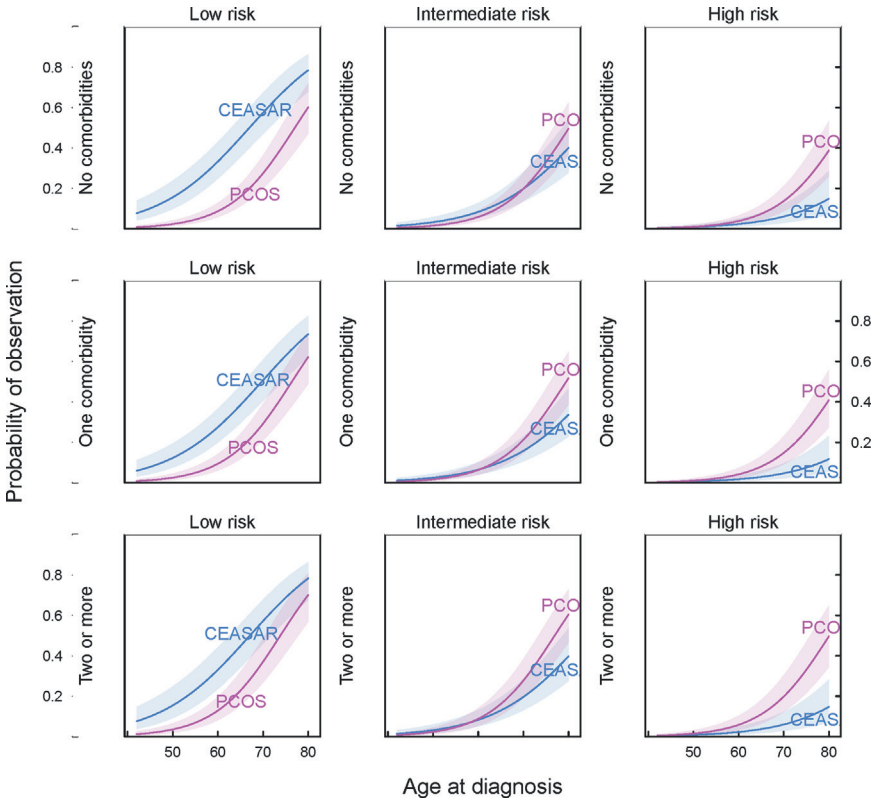

Figure 2. Cohort differences in effects of age, comorbidity and recurrence risk on probability of choosing WW/AS strategy for localized PCa. Estimates based on multivariable logistic regression and calculated for men with median values of demographic and health characteristics.

observation evolved during this interval from WW to AS, in accord with the available evidence and guidelines.

We also found that older age was associated with a likelihood of being on observation in both eras but its effect was smaller in the CEASAR study. This may suggest that physicians and patients have become more comfortable with the concept of AS in younger men, rather than reserving observation as a palliative strategy for those at high risk for other cause mortality (WW). Comorbidity did not have a significant effect on decisions to treat vs observe in the CEASAR study and its effect did not change significantly from the PCOS.

Concerns regarding the over detection and overtreatment of low risk PCa developed after the spike in the incidence of PCa due to the adoption of PSA screening in the early 1990s.[13] During the last 2 decades evidence has accrued demonstrating the harms of aggressive treatment, the safety of AS for low risk disease and the absence of a survival benefit for the treatment of low risk disease.[14–18] These factors have prompted guideline panels to expand the indications for expectant management to include AS for the management of low risk PCa, even in men with a long life expectancy.[7]

However, population based studies have suggested that, until recently, definitive treatment for low risk disease was the norm.[4,19] More recent evidence suggests that the use of WW/AS for low risk disease is increasing in some scenarios. For example, the use of WW/AS is increasing in the Medicare beneficiary population and among practices engaged in a quality collaborative in Michigan.[20,21] In CaPSURE, a PCa registry which collects data primarily from community practices, the rate of WW/AS among men with low risk disease increased from 6.7% to 14.3% in 1990 to 2009 to 40.4% in 2010 to 2013.[22] The current study of 2 large population based cohorts with carefully curated data sets confirms that the use of WW/AS for men with low risk disease has expanded significantly between the early PSA era and the contemporary era (PCOS 15% vs CEASAR 25%), and demonstrates that observation is increasing nationally, not just at academic centers, among the elderly and in quality collaboratives. Furthermore, it demonstrates a transition in the mode of observation from WW to AS. Finally, it demonstrates that, to some degree, disease risk is taking precedence over age and comorbidities in treatment vs observation decisions.

While overtreatment of low risk disease is widely publicized, that older men with high risk disease are often under treated is less commonly acknowledged. However, data suggest that approximately half of men with high risk disease are under treated, with 60% to 67% of men older than age 75 with high risk disease receiving no therapy or ADT alone to their apparent detriment.[4,5,23–25] Our data indicate an encouraging trend away from WW/AS among men with intermediate or high risk disease.

A rational approach to treatment selection for localized PCa would take into account age and comorbidity status to determine other cause mortality risk in addition to PCSM risk.[3] However, treatment decisions often fail to account adequately for comorbidity, and it is not clear how best to improve attention to comorbidity.[26] Our data indicate that more needs to be done to incorporate comorbidity and life expectancy into treatment decisions.

The study results must be interpreted in the context of the study design and available data. There are some important differences between the 2 cohorts that are worth considering. Due to stage migration, changes in biopsy techniques (ie more thorough sampling) and changes in the Gleason scoring system,[11,12] the distribution of men classified as low risk in the PCOS contains some considered intermediate risk in the CEASAR study, and the Will Rogers phenomenon may explain a portion of the difference in the use of WW/AS in men with low risk disease.[27] In addition, unmeasured confounders may have differed between cohorts, and modulated the relationship between cohort and selection of WW/AS. For instance, biopsy findings such as the number of positive cores or length of cancer in a core are inclusion criteria for some AS programs, and could confound the association between cohort and use of AS. Finally, we could not reliably distinguish between AS and WW in either data set, although in the CEASAR study the use of PSA measurements and prostate biopsies after diagnosis suggests that the majority of men were on AS and the high rate of PCSM in the PCOS suggests many of those men were on WW. Nonetheless, the similarity in data collection strategies and the richness of the data sets enabled us to expand on the findings of prior studies that used only administrative and registry data, and those based on selective registries.

CONCLUSIONS

Men diagnosed with localized PCa in the contemporary era experience more judicious use of expectant management compared to men diagnosed in the mid 1990s. The use of WW/AS was more aligned with disease risk in the contemporary cohort such that men with low risk disease were more likely to be on WW/AS while those with intermediate and high risk disease were more likely to undergo treatment compared to the cohort accrued in the 1990s. In addition, we found evidence of a pivot from WW to AS. While older age was a strong predictor of WW/AS in both cohorts, its use was different in CEASAR vs PCOS. Comorbidity status remains underused in deciding whom to observe. Overall these findings suggest a growing acceptance of WW/AS for men with low risk disease and definitive therapy for intermediate or high risk disease, and a pivot from WW to AS during this interval, which may be a prerequisite for realizing the potential advantages of prostate cancer screening. While our results are encouraging, there remains substantial room for improvement in continuing to increase the use of WW/AS in low risk disease and integrating comorbidity information into decision making.

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