Original Article

Conservative Management of Low-Risk Prostate Cancer Among Young Versus Older Men in the United States: Trends and Outcomes From a Novel National Database

Amandeep R. Mahal, BS [1]; Santino Butler, BA [2]; Idalid Franco, MD, MPH[2]; Vinayak Muralidhar, MD, MSc[2]; Dalia Larios, BS[3]; Luke R. G. Pike, MD, DPhil[2]; Shuang G. Zhao, MD[4]; Nina N. Sanford, MD[5]; Robert T. Dess, MD [4]; Felix Y. Feng, MD[6]; Anthony V. D'Amico, MD, PhD[2]; Daniel E. Spratt, MD [4]; James B. Yu, MD, MHS [1]; Paul L. Nguyen, MD[2]; Timothy R. Rebbeck, PhD[2,7]; and Brandon A. Mahal, MD [2]

BACKGROUND: Management for men aged ≤55 years with low-risk prostate cancer (LRPC) is debated given quality-of-life implications with definitive treatment versus the potential missed opportunity for cure with conservative management. The objective of this study was to define rates of conservative management for LRPC and associated short-term outcomes in young versus older men in the United States. **METHODS:** The nonpublic Surveillance, Epidemiology, and End Results Prostate with Active Surveillance/Watchful Waiting (AS/WW) Database identified 50,302 men who were diagnosed with LRPC from 2010 through 2015. AS/WW rates in the United States were stratified by age (≤55 vs ≥56 years). Prostate cancer-specific mortality and overall mortality were defined by initial management type (AS/WW vs definitive treatment [referent]) and age. **RESULTS:** AS/WW utilization increased from 8.61% (2010) to 34.56% (2015) among men aged ≤55 years (*P* for trend <0.001) and from 15.99% to 43.81% among men aged ≥56 years (*P* for trend <.001). Among patients who had ≤2 positive biopsy cores, AS/WW rates increased from 12.90% to 48.78% for men aged ≤55 years and from 21.85% to 58.01% for men aged ≥56 years. Among patients who had ≥3 positive biopsy cores, AS/WW rates increased from 3.89% to 22.45% for men aged ≤55 years and from 10.05% to 28.49% for men aged ≥56 years (all *P* for trend <.001). Five-year prostate cancer-specific mortality rates were <0.30% across age and initial management type subgroups. **CONCLUSIONS:** AS/WW rates quadrupled for patients aged ≤55 years from 2010 to 2015, with favorable short-term outcomes. These findings demonstrate the short-term safety and increasing acceptance of AS/WW for both younger and older patients. However, there are still higher absolute rates of AS/WW in older patients (*P* < .001), suggesting some national ambivalence toward AS/WW in younger patients. ***Cancer* 2019;125:3338-3346**. © *2019 American Cancer Society*.

KEYWORDS: active surveillance, conservative treatment, low-risk prostate cancer, prostatic neoplasms, watchful waiting.

INTRODUCTION

Historically, the standard of care for localized prostate cancer has been definitive radical prostatectomy (RP) or radiation therapy (RT).[1] However, conservative management of low-risk prostate cancer (LRPC) with active surveillance or watchful waiting (AS/WW) has been shown to be an efficacious alternative to definitive treatment and is now a National Comprehensive Cancer Network guideline-approved standard of care.[2-5] Although AS/WW can reduce over-treatment of indolent disease,[3,5-7] concern about a greater risk of development of metastatic disease has led to reexamination of AS/WW for LRPC.[8] AS/WW is particularly controversial for younger patients with LRPC given the small number of younger patients in conservative management trials for whom the risk-to-benefit ratio is not well elucidated.[7,9-11]

The management dilemma for younger patients with low-risk disease stems from their longer projected life expectancy; therefore, they may be at greater risk of prostate cancer death, yet they also have better baseline sexual, genitourinary, and gastrointestinal function and may be at greater risk of adverse quality-of-life outcomes with definitive treatment.[6,12,13] In an effort to reduce potential over-treatment and over-detection of indolent disease in younger patients, the US Preventative Services Task Force recommends against prostate-specific antigen (PSA) screening in men

Corresponding author: Brandon A. Mahal, MD, Department of Radiation Oncology, Dana-Farber Cancer Institute, 75 Francis Street, Boston, MA 02115; brandon_mahal@dfci.harvard.edu

[1]Department of Therapeutic Radiology, Yale School of Medicine, New Haven, Connecticut; [2]Department of Radiation Oncology, Dana-Farber Cancer Institute/Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts; [3]Harvard Medical School, Boston, Massachusetts; [4]Department of Radiation Oncology, University of Michigan, Ann Arbor, Michigan; [5]Department of Radiation Oncology, University of Texas Southwestern Medical Center, Dallas, Texas; [6]Helen Diller Family Comprehensive Cancer Center, University of California at San Francisco, San Francisco, California; [7]Harvard T. H. Chan School of Public Health, Boston, Massachusetts.

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aged ≤55 years.[14,15] Nevertheless, nearly 20% of men aged ≤55 years still undergo PSA screening, and this group comprises approximately 10% of patients with low-risk disease.[16] As such, the appropriate management of younger men with LRPC remains an area of debate with little data to inform practice and policy.

Therefore, we sought to define the national rates of conservative management for LRPC and associated short-term population-based outcomes in young men (aged ≤55 years) versus older men (aged ≥56 years) using the largest currently available cohort of young patients who were managed conservatively.

MATERIALS AND METHODS

Study Cohort

We identified 50,302 men diagnosed who had LRPC (clinical American Joint Committee on Cancer [*AJCC Cancer Staging Manual*, seventh edition] tumor classification T1-T2a, clinical/biopsy Gleason score 6, and PSA <10 ng/mL)[2] and known initial management/treatment status between January 2010 and December 2015 using the US Surveillance, Epidemiology, and End Results (SEER) Program Prostate with AS/WW Database, which represents approximately 28% of the US population.[17] The study period was determined by the inclusion of the novel AS/WW variable into the custom data set in which all SEER prostate with AS/WW data were available. These data are unique from the publicly available SEER database, requiring a proposal and approval of analyses by SEER before release.

Patients with unknown T-classification, Gleason score, PSA, or initial management approach were excluded. If patients were conservatively managed,[18] then they were identified as received "active surveillance/watchful waiting" by treating facilities. This variable was quality-assured by SEER and collected as a North American Association of Central Cancer Registries metric.

The SEER Prostate with AS/WW Database captures initial management approach, defined as AS/WW (as defined by SEER), and definitive treatment (SEER-defined RP or RT, including any type of brachytherapy or external-beam radiotherapy). SEER also provides data on the number of positive cores; however, the percentage by volume of core cancer involvement is not reported. These data evaluated socioeconomic status (SES) using the validated Yost index (higher Yost index scores correspond with higher SES).[19] Insurance status was classified as non-Medicaid insurance, Medicaid, uninsured, and unknown insurance.

Statistical Analyses

Baseline characteristics

Baseline characteristics were summarized through descriptive statistics stratified by age and initial management. Medians and interquartile ranges (IQRs) were reported across subgroup analyses for continuous variables. For categorical variables, column percentages were calculated with the denominator being the total number of patients within age and initial management subgroups. To compare the distribution of continuous and categorical covariates, we used the Wilcoxon rank-sum test and the Fisher exact test, respectively.

AS/WW trends and associations by age

The primary endpoint was the US rate of AS/WW utilization over time for LRPC stratified by age ≤55 versus ≥56 years. Utilization rates were defined as the sum of patients managed with AS/WW divided by the sum of patients with LRPC. Similarly, AS/WW rates were stratified by the number of positive cores (very-low-risk disease [≤2 positive biopsy cores] vs standard low-risk disease [≥3 positive biopsy cores]) in addition to age.[2] In total, there were 39,020 patients with a known number of cores.

Multivariable logistic regression for AS/WW was used to characterize the association between AS/WW utilization rates and patient characteristics—variables of age (≤55 [referent] vs ≥56 years), number of positive cores (≤2 vs ≥3 [referent]), year of diagnosis (2013-2015 vs 2010-2012 [referent], based on recommendations against PSA screening in 2012),[20] age at diagnosis (per year increase), insurance status (uninsured status or Medicaid-insured [referent], unknown insurance status, and non-Medicaid insurance), and Yost index (per unit increase). Adjusted odds ratios, 95% CIs, and *P* values were calculated for each covariate in the regression model. For subgroup analyses, the multivariable logistic regression described above was repeated after stratification by age ≤55 versus ≥56 years.

Estimates of prostate cancer-specific mortality and overall mortality with AS/WW by age

Multivariable Fine-Gray competing risks regression and Cox regression were used to analyze prostate cancer-specific mortality (PCSM) and overall mortality (OM), respectively, for patients who had at least 1 month of follow-up (N = 49,770 patients) from the date of diagnosis. Analyses were stratified by age (≤55 vs ≥56 years) and initial management type (AS/WW vs RP or RT). Adjustments were made for the aforementioned variables in the above-described logistic regression models. As an

TABLE 1. Distribution of Baseline Characteristics by Age (≤55 vs ≥56 Years) and Initial Management Type (Active Surveillance/Watchful Waiting vs Definitive Treatment With Radical Prostatectomy or Radiation Therapy) Among 50,302 Patients in the United States Diagnosed With National Comprehensive Cancer Network Low-Risk Prostate Cancer From 2010 to 2015

	Patients Aged ≤55 Years		Patients Aged ≥56 Years	
Characteristic	AS/WW, N = 1957	RP or RT, N = 8016	AS/WW, N = 11,527	RP or RT, N = 28,802
Age: Median [IQR], y	53 [50-54]	52 [49-54]	65 [61-69]	64 [60-68]
PSA: Median [IQR], ng/mL	4.8 [4-6]	4.8 [3.9-6]	5.5 [4.5-6.9]	5.5 [4.4-6.9]
No. of positive cores (%)[a]				
≤2	1310 (66.9)	3141 (39.2)	7526 (65.3)	11,280 (39.2)
≥3	411 (21.0)	2956 (36.9)	2273 (19.7)	10,123 (35.1)
Unknown	236 (12.1)	1919 (23.9)	1728 (15.0)	7399 (25.7)
Year of diagnosis: No. (%)[a]				
2010-2012	800 (40.9)	5345 (66.7)	4974 (43.2)	18,887 (65.6)
2013-2015	1157 (59.1)	2671 (33.3)	6551 (56.8)	9915 (34.4)
Insurance status: No (%)[a]				
Non-Medicaid insured	1764 (90.1)	7275 (90.8)	10,384 (90.1)	25,902 (89.9)
Medicaid	67 (3.4)	286 (3.6)	304 (2.6)	965 (3.3)
Uninsured	23 (1.2)	114 (1.4)	136 (1.2)	234 (0.8)
Unknown	103 (5.3)	341 (4.2)	701 (6.1)	1701 (5.9)
Yost index: Median [IQR]	11,363 [10,815-11,628]	11,105 [10,581-11,567]	11,340 [10,815-11,598]	11,070 [10,537-11,559]

Abbreviations: AS/WW, active surveillance/watchful waiting; IQR, interquartile range; PSA, prostate-specific antigen; RP, radical prostatectomy; RT, radiation therapy.
[a]Percentages (%) indicate the proportion of patients within each categorical variable among the column-stratified group.

exploratory analysis, we evaluated the potential for an interaction between age and initial management type with respect to OM using an age × initial management type interaction term.

We also examined subgroup analyses stratified by the number of positive biopsy cores (≤2 vs ≥3) among 38,573 patients who had at least 1 month of follow-up from the date of diagnosis and a known number of positive biopsy cores. Cumulative incidence plots were generated using the PCSM multivariable regression models described above, and survival curves were generated using the Kaplan-Meier method.

Statistical Tests

For regression analyses, adjusted hazard ratios and adjusted odds ratios with 95% CIs and *P* values were calculated. All analyses were performed with a 2-sided level of significance set at $P = .05$. Statistical analyses were performed with STATA/SE version 15.1 (StataCorp). Permission for this study was granted by The Dana-Farber/Harvard Cancer Center Institutional Review Board.

RESULTS

Baseline Characteristics

In a total of 50,302 patients who were diagnosed with LRPC between 2010 and 2015, 19.8% were aged ≤55 years (N = 9973). Across the study period, among patients aged ≤55 years, 19.6% (N = 1957) were managed with AS/WW, 60.6% (N = 6041) were managed with definitive RP, and 19.8% (N = 1975) were managed with definitive RT. Among patients aged ≥56 years (N = 40,329), 28.6% (N = 11,527), 35.9% (N = 14,471), and 35.5% (N = 14,331) were managed with AS/WW, definitive RP, and definitive RT, respectively. The median PSA was 4.8 ng/mL (IQR, 3.9-6 ng/mL) among men aged ≤55 years versus 5.5 ng/mL (IQR, 4.4-6.9 ng/mL) among men aged ≥56 years ($P < .001$) Baseline characteristics stratified by age and initial management type are shown in Table 1. Initial management type was further stratified by RP and RT (see Supporting Tables 1 and 2 and Supporting Fig. 1).

AS/WW Trends and Associations by Age

AS/WW utilization for LRPC increased from 8.61% in 2010 to 34.56% in 2015 among men aged ≤55 years and similarly increased from 15.99% to 43.81% among men aged ≥56 years (*P* for trend <.001 for both) (Fig. 1A,B). Rates of definitive RP and RT decreased from 69.71% and 21.68% to 48.38% and 17.06% from 2010 to 2015, respectively, among men aged ≤55 years (*P* for trend <.001) (Fig. 1A,B). Similarly, among men aged ≥56 years, rates of definitive RP and RT decreased from 41.95% and 42.06% to 27.5% and 28.64%, respectively, from 2010 to 2015 (*P* for trend <.001) (Fig. 1A,B). Among patients with ≤2 positive biopsy cores, rates of AS/WW utilization increased from 12.90% to 48.78% for

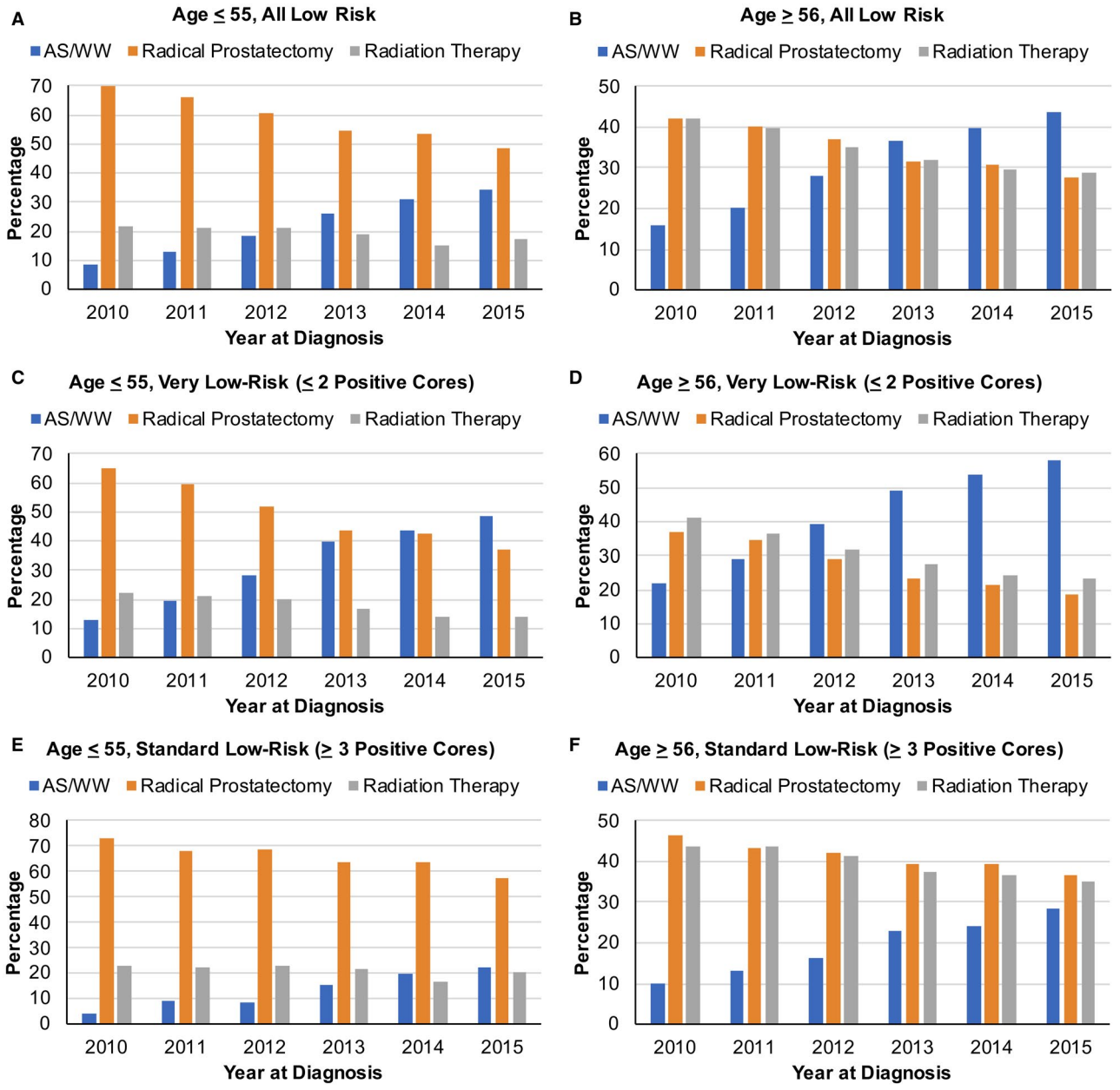

Figure 1. Initial management rates (active surveillance/watchful waiting [AS/WW] vs initial definitive radical prostatectomy or radiation therapy) are illustrated for National Comprehensive Cancer Network low-risk prostate cancer diagnosed in the United States from 2010 to 2015 (N = 50,302) among (A) all men aged ≤55 years with low-risk prostate cancer (N = 9973), (B) all men aged ≥56 years with low-risk prostate cancer (N = 40,329), (C) men aged ≤55 years with very-low-risk disease and ≤2 positive cores (N = 4451), (D) men aged ≥56 years with very-low-risk disease and ≤2 positive cores (N = 18,806), (E) men aged ≤55 years with standard low-risk disease and ≥3 positive cores (N = 3367), and (F) men aged ≥56 years with standard low-risk disease and ≥3 positive cores (N = 12,396). Note that 39,020 of the total 50,302 patients had known numbers of positive cores. *P* for trend <.001 for all subgroups (A-F).

men aged ≤55 years and from 21.85% to 58.01% for men aged ≥56 years (Fig. 1C,D). Among patients with ≥3 positive biopsy cores, rates increased from 3.89% to 22.45% for men aged ≤55 years and from 10.05% to 28.49% for men aged ≥56 years (*P* for trend <.001 for all groups examined) (Fig. 1E,F). Notably, factors associated with AS/WW utilization included ≤2 positive cores, higher SES, age ≥56 years, and diagnosis after 2012 (Table 2).

TABLE 2. Multivariable-Adjusted Odds of Receiving Active Surveillance/Watchful Waiting by Age (≤55 vs ≥56 Years) Among 50,302 Patients in the United States Diagnosed With National Comprehensive Cancer Network Low-Risk Prostate Cancer From 2010 to 2015

	AS/WW					
	All Patients, N = 50,302		Patients Aged ≤55 Years, N = 9973		Patients Aged ≥56 Years, N = 40,329	
Characteristic	AOR (95% CI)	*P*	AOR (95% CI)	*P*	AOR (95% CI)	*P*
Age, y						
≤55	1.0 (Ref)		—	—	—	—
≥56	1.63 (1.54-1.72)	<.001	—	—	—	—
Age at diagnosis, per y increase	—	—	1.02 (1.01-1.04)	.003	1.04 (1.03-1.05)	<.001
PSA, ng/mL increase	1.02 (1.01-1.03)	<.001	1.01 (0.98-1.04)	.60	1.01 (0.99-1.02)	.35
No. of positive cores						
≤3	1.0 (Ref)		1.0 (Ref)		1.0 (Ref)	
≤2	3.15 (3.00-3.32)	<.001	3.26 (2.87-3.70)	<.001	3.15 (2.98-3.33)	<.001
Unknown	1.20 (1.13-1.29)	<.001	1.08 (0.91-1.29)	.36	1.21 (1.13-1.30)	<.001
Year of diagnosis						
2010-2012	1.0 (Ref)		1.0 (Ref)		1.0 (Ref)	
2013-2015	2.65 (2.54-2.76)	<.001	3.10 (2.78-3.45)	<.001	2.61 (2.49-2.74)	<.001
Insurance status						
Uninsured or Medicaid insured	1.0 (Ref)		1.0 (Ref)		1.0 (Ref)	
Non-Medicaid insured	1.02 (0.92-1.14)	.67	0.99 (0.77-1.27)	.95	1.00 (0.89-1.13)	.96
Unknown	0.91 (0.79-1.04)	.18	1.06 (0.76-1.50)	.71	0.81 (0.70-0.95)	.007
Yost index, for socioeconomic status	1.00 (1.00-1.00)	<.001	1.00 (1.00-1.00)	<.001	1.00 (1.00-1.00)	<.001

Abbreviations: AOR, adjusted odds ratio; AS/WW, active surveillance/watchful waiting; PSA, prostate-specific antigen; ng/mL, nanograms per milliliter; Ref, referent.

Estimates of PCSM and OM With AS/WW by Age

The median follow-up was 41 months (maximum follow-up was 71 months). The median follow-up for patients aged ≤55 versus ≥56 years was 42 and 41 months, respectively. There were 9 prostate cancer deaths among men aged ≤55 years (9 among men managed with definitive treatment vs 0 among men managed with AS/WW) and 64 among men aged ≥56 years (53 among men managed with definitive treatment vs 11 among men managed with AS/WW).

No difference in PCSM by initial management existed ($P = .40$) (Table 3); however, for patients who were managed with AS/WW, there was a higher risk of OM (adjusted hazard ratio, 1.24; 95% CI, 1.05-1.47; $P = .01$). In addition, no difference in PCSM ($P = .78$) or OM ($P = .11$) existed among men aged ≤55 years compared with those aged ≥56 years (Table 3).

Five-year PCSM rates were <0.30% across age and initial management type subgroups (Fig. 2A). Specifically, the 5-year PCSM rates were 0% (no events), 0.14% (95% CI, 0.06%-0.27%), 0.22% (95% CI, 0.10%-0.44%), and 0.30% (95% CI, 0.22%-0.39%) for patients aged ≤55 years managed with AS/WW, patients aged ≤55 years managed with RP or RT, patients aged ≥56 years managed with AS/WW, and patients aged ≥56 years managed with RP or RT, respectively (*P* value for overall comparison <.001 in the setting of no events in patients aged ≤55 years managed with AS/WW). Furthermore, the 5-year Kaplan-Meier estimates of overall survival were 98.8% (95% CI, 97.5%-99.5%), 98.9% (95% CI, 98.6%-99.2%), 96.1% (95% CI, 95.4%-96.7%), and 97.1% (95% CI, 96.8%-97.4%) for patients aged ≤55 years managed with AS/WW, patients aged ≤55 years managed with RP or RT, patients aged ≥56 years managed with AS/WW, and patients aged ≥56 years managed with RP or RT, respectively (*P* for overall comparison = .53) (Fig. 2B). On exploratory Cox regression analysis for OM, there was no interaction between age and initial management approach (*P* for interaction = .88).

DISCUSSION

Between 2010 and 2015, AS/WW utilization rates in the United States more than quadrupled for patients aged ≤55 years with LRPC. Similarly, AS/WW rates have nearly tripled for patients aged ≥56 years with low-risk disease. Although there was a greater rate of uptake of AS/WW in younger patients with low-risk disease over time, the absolute utilization of AS/WW remained lower in younger patients than in older patients (34.56% vs 43.81% by 2015, respectively). Furthermore, RP remained the favored initial management strategy among younger men with a 48.38% utilization rate by the end

TABLE 3. Distribution of Prostate Cancer-Specific Mortality Deaths by Age (≤55 vs ≥56 Years) and Multivariable-Adjusted Hazard Ratio for Prostate Cancer-Specific Mortality and Overall Mortality Among 49,770 Patients in the United States Diagnosed With National Comprehensive Cancer Network Low-Risk Prostate Cancer From 2010 to 2015[a]

	Age ≤55 Years			Age ≥56 Years			PCSM		Overall Mortality	
Characteristic	No. Men	No. PCa Deaths	No. Competing Deaths	No. Men	No. PCa Deaths	No. Competing Deaths	AHR (95% CI)	*P*	AHR (95% CI)	*P*
Age ≤55 y (by treatment strategy)[b]										
Definitive treatment[c]	7966	9	50	—			1.0 (Ref)			
AS/WW	1909	0	10	—			No events	—	1.14 (0.57-2.30)	.71[d]
Age ≥56 y (by treatment strategy)[b]										
Definitive treatment[c]	—			28,610	53	465	1.0 (Ref)			
AS/WW	—			11,285	11	178	0.77 (0.39-1.53)	.46	1.24 (1.05-1.49)	.01[d]
Age, y										
≥56	—			39,895	64	643	1.0 (Ref)			
≤55	9875	9	60	—			1.14 (0.45-.91)	0.78	1.29 (0.95-1.75)	.11
Treatment strategy										
Definitive treatment[c]	7966	9	50	28,610	53	465	1.0 (Ref)			
AS/WW	1909	0	10	11,285	11	178	0.68 (0.35-1.33)	.40	1.24 (1.05-1.47)	.01
Age at diagnosis per y increase	9875	9	60	39,895	64	643	1.05 (1.01-1.10)	.01	1.08 (1.07-1.10)	<.001
PSA, ng/mL increase	9875	9	60	39,895	64	643	1.09 (0.96-1.23)	.18	1.05 (1.01-1.09)	.02
No. of positive cores										
≥3	3335	2	22	12,260	23	198	1.0 (Ref)			
≤2	4401	4	22	18,577	23	264	0.77 (0.44-1.32)	.34	0.80 (0.680.95)	.01
Unknown	2139	3	16	9058	18	181	0.96 (0.54-1.73)	.91	1.00 (0.83-1.20)	.96
Year of diagnosis										
2010-2012	6142	8	53	23,852	57	551	1.0 (Ref)			
2013-2015	3733	1	7	16,043	7	92	0.68 (0.30-1.54)	.36	0.99 (0.79-1.24)	.93
Insurance status										
Non-Medicaid insured	8960	8	49	35,918	57	548	1.0 (Ref)			
Medicaid	345	1	8	1257	3	38	1.52 (0.53-4.32)	.43	2.00 (1.50-2.67)	<.001
Uninsured	136	0	1	364	0	5	0.00 (0.00-0.00)	<.001	0.91 (0.41-2.04)	.82
Unknown	434	0	2	2356	4	52	1.04 (0.38-2.90)	.93	1.47 (1.12-1.93)	.005
Yost index	9875	9	60	39,895	64	643	0.99 (0.99-1.00)	.22	0.99 (0.99-1.00)	<.001

Abbreviations: AHR, adjusted hazard ratio; AS/WW, active surveillance/watchful waiting; NR, not reported; PCa, prostate cancer; PCSM, prostate cancer-specific mortality; PSA, prostate-specific antigen; Ref, referent.

[a]Patients had at least 1 month of follow-up.

[b]Analyses were stratified by age (≤55 vs ≥56 years) and initial management type (AS/WW vs definitive management).

[c]Definitive management was defined as initial management with either radical prostatectomy or radiation therapy).

[d]*P* for interaction = .88, where the interaction term was defined as age (≤55 vs ≥56) * initial management type (AS/WW vs definitive management).

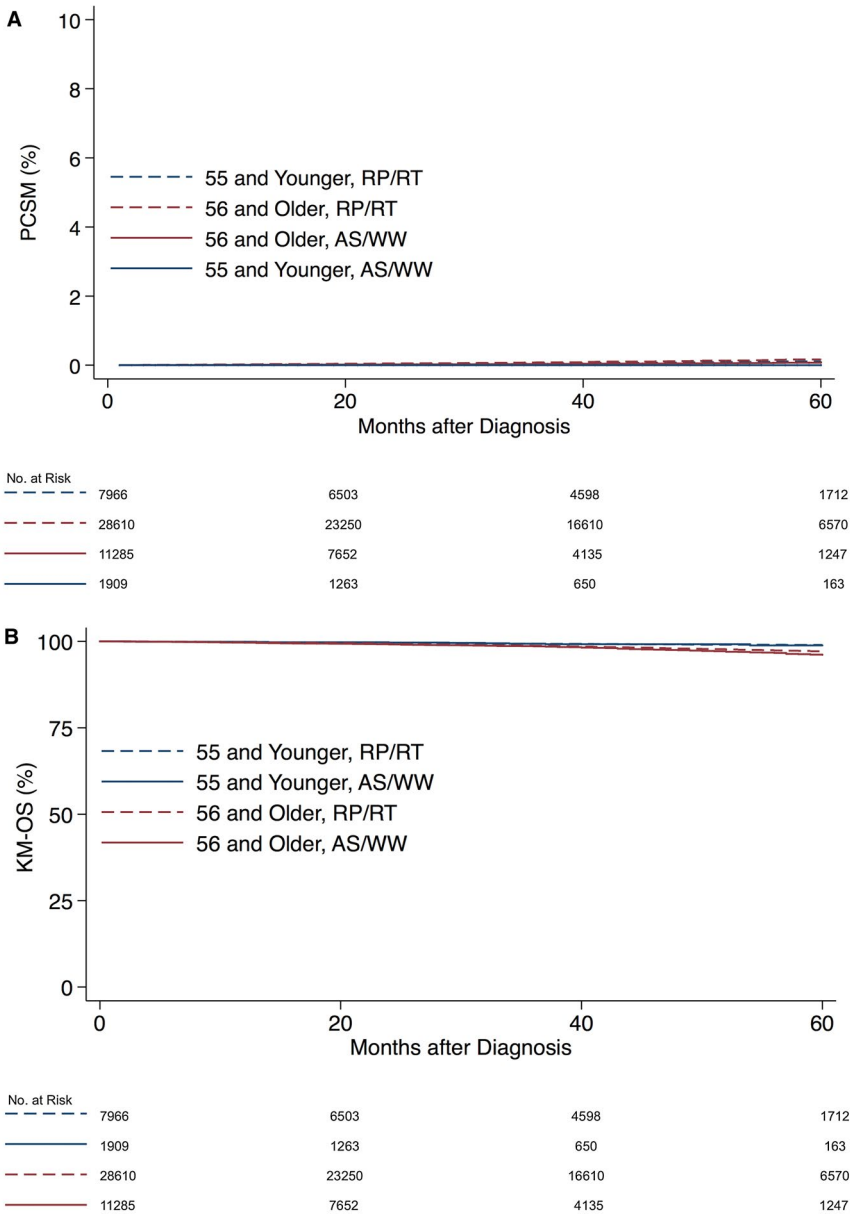

Figure 2. (A) The cumulative incidence of prostate cancer-specific mortality (PCSM) and (B) Kaplan-Meier curves for overall survival (KM-OS) are illustrated by age (≤55 vs ≥56 years) and initial management approach (active surveillance/watchful waiting [AS/WW] vs initial definitive radical prostatectomy or radiation therapy [RP/RT]) among patients diagnosed with low-risk prostate cancer in the United States from 2010 to 2015 (N = 49,770). Note that patients had to have at least 1 month of follow-up to be included in survival analyses (N = 49,770 of 50,302 patients).

of the study period, whereas AS/WW transitioned from the least to the most common initial management approach for older patients (43.81%). Among patients with very-low-risk disease (≤2 positive biopsy cores), AS/WW became the most common initial management approach by 2015 regardless of age, whereas RP remained the favored initial management approach regardless of age for patients with standard-risk features (≥3 positive biopsy cores) despite significant uptake of AS/WW.

Controversy surrounding the use of AS/WW as initial management for younger patients is rooted in the dilemma of longevity: potentially greater quality-of-life implications with definitive treatment versus potentially greater opportunity for disease progression and missed

opportunity for cure without treatment.[21,22] On the basis of the results of this study, it appears that clinicians and patients feel AS/WW is a reasonable alternative to definitive treatment for low-risk disease, resulting in an increasing preference toward AS/WW across age groups. Furthermore, 5-year PCSM rates were <0.30% across age and initial management type subgroups (similar to 5-year rates reported in randomized clinical trials[5,7,23]), suggesting that AS/WW may afford acceptable outcomes in younger men, although studies with a median follow-up of at least 10 years are needed to make a better determination.[9]

Increasing AS/WW utilization for younger patients is likely a result of efforts to avoid overtreatment of indolent disease,[14,20] especially given that younger patients may be at an increased risk of sexual and urinary dysfunction with definitive treatment.[10,12] Thus, the study trends suggest that preservation of quality-of-life by avoiding or delaying treatment-related complications may be increasingly a predominant driver in treatment decisions for both younger and older patients. Importantly, initial AS/WW does not appear to hinder the ability to perform curative treatment with surgery or radiation at a later time,[4] which might also explain the observed uptrend in AS/WW as the initial management approach. Moreover, as multiparametric magnetic resonance imaging and genomic risk stratification become increasingly integrated with active surveillance protocols, initial definitive treatment will likely be more readily delayed.[24]

Conversely, our evidence also supports potential clinician and patient ambivalence toward missed opportunity for cure. This is evident from poor AS/WW utilization rates among both young and older men with ≥3 positive biopsy cores (a standard low-risk feature). Furthermore, lower absolute rates of AS/WW utilization in younger patients suggests that there is more ambivalence and uncertainty toward managing younger patients than older patients with conservative management. This uncertainty likely arises from a theoretical threat of disease progression.[4,25] When uncertainty arises, it may be beneficial to further evaluate with advanced magnetic resonance imaging-targeted biopsy[26] or the addition of genomic tests that assess disease risk.[3]

Our study comes at a critical time in the current debate regarding optimal treatment management for patients with LRPC, especially in younger men.[12,27,28] For the majority of men aged ≤55 years who are diagnosed with low-risk disease, there has been insufficient evidence to demonstrate the efficacy for conservative management compared with definitive treatment given that young men are underrepresented in trials and retrospective studies because of their lower likelihood of prostate cancer diagnosis. For example, our study has a higher total number and proportion of patients aged ≤55 years compared with recent large randomized controlled trials in prostate cancer. Specifically, the ProtecT trial (Prostate Testing for Cancer and Treatment) included 11% (N = 58), 12% (N = 69), and 11% (N = 62) of men aged ≤54 years who received active monitoring, RP, and RT, respectively,[29] whereas our study included 14.5% (N = 1957), 29.5% (N = 6041), and 12.1% (N = 1,975) of men aged ≤55 years younger who received AS/WW, RP, and RT, respectively. Moreover, other large US national database studies have used a proxy for AS/WW to compare conservative management with other treatment, rather than using a validated variable for AS/WW.[30] To address these limitations, the current study represents the largest inclusion of young patients with a quality-assured AS/WW variable. Therefore, our findings could serve as a national standard for comparing utilization and outcomes associated with AS/WW in LRPC across age groups.

Several limitations exist. First, our analyses lack quality-of-life measures to determine whether choices for AS/WW were driven by baseline quality of life or whether younger patients had better preserved sexual and urinary function.[12] Second, SEER does not indicate comorbidity status—which could drive management decisions for or against AS/WW. Third, although SEER provides the number of cores involved by tumor, SEER does not collect information on the percentage of biopsy core involved by tumor; therefore, our analyses for "standard" low-risk and "very-low-risk" disease represent proxies for those risk groups. Fourth, although this custom database includes information on AS/WW as initial management choice, it does not include information on adherence to AS/WW. Fifth, given the retrospective nature of the study design, potential confounding factors other than age could have contributed to the study findings. Finally, our secondary exploratory survival analyses were limited by short follow-up—with a maximum follow-up of 71-months. Future studies with longer follow-up will be needed to determine whether the long-term outcomes of AS/WW presented in this study persist.

Despite potential limitations, our study demonstrates that there has been a rapid uptake of AS/WW as initial management, and AS/WW may be a reasonable approach for both younger and older patients with low-risk disease. Despite a more rapid uptake of AS/WW in younger patients, there are still higher absolute rates of AS/WW in older patients, and RP remains the favored

initial management approach for younger patients. Overall, these findings demonstrate the early safety and increasing acceptance of AS/WW for both younger and older patients with LRPC.

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CONFLICT OF INTEREST DISCLOSURES

Luke R. G. Pike reports personal fees from Third Rock Ventures. Shuang G. Zhao reports travel fees and expenses from GenomeDx Biosciences and has a patent on gene signatures in prostate cancer with the University of Michigan and GenomeDx Biosciences. Felix Y. Feng reports personal fees for Dendreon, Genzyme, Ferring Pharmaceuticals, Janssen Biotech, EMD Serono, Bayer Healthcare, Sanofi-Aventis, GenomeDx Biosciences, and Medivation/Astellas, as well as compensation for speaking for Clovis Oncology, cofounder of PFS Genomics, and a patent with the University of Michigan ("Compositions and Methods for the Analysis of Radiosensitivity"; patent publication number EP3047037). Daniel E. Spratt reports personal fees from Janssen and Blue Earth. James B. Yu reports research funding from 21st Century Oncology. Paul L. Nguyen reports personal fees from Ferring, Genome DX, Medivation, and Nanobiotix and research funding from Janssen and Astellas. The remaining authors made no disclosures.

AUTHOR CONTRIBUTIONS

All authors listed have contributed sufficiently to the project to be included as authors, and all those who are qualified to be authors are listed in the author byline. All authors have read and approved the article. The authors of this study have not published or submitted any related articles from this study. This article is not under consideration elsewhere.

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