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Conservative Management of Low-Risk Prostate Cancer among Young versus Older Men in the United States: Trends and Outcomes from a Novel National Database

Running Title: Surveillance of Low-Risk Prostate Cancer

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Precis: Debate exists regarding active surveillance/watchful waiting (AS/WW) for low-risk prostate cancer, particularly in younger men. We demonstrate that there is increasing acceptance of conservative management with AS/WW for both younger and older patients in the U.S. with favorable short-term outcomes.

Keywords: Conservative Treatment, Watchful Waiting, Prostatic Neoplasms

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Background: Management for men age ≤55 with low-risk prostate cancer (LRPC) is debated given quality of life implications with definitive treatment versus potential missed opportunity for cure with conservative management. We sought to define rates of conservative management for LRPC and associated short-term outcomes in young versus older men in the United States (U.S.).
Methods: The non-public Surveillance, Epidemiology, and End Results Prostate with Active Surveillance/Watchful Waiting (AS/WW) Database identified 50,302 men diagnosed with LRPC from 2010-2015. AS/WW rates in the U.S. were stratified by age

(≤55 versus ≥56). Prostate cancer-specific mortality (PCSM) and overall mortality were defined by initial management type (AS/WW versus definitive treatment [referent]) and age.

Results: AS/WW utilization increased from 8.61% (2010) to 34.56% (2015) among men ≤55 (P_{trend}<0.001) and from 15.99% to 43.81% among men ≥56 (P_{trend}<0.001). Among patients with ≤2 positive biopsy cores, AS/WW rates increased from 12.90% to 48.78% for men ≤55 and from 21.85% to 58.01% for men ≥56. Among patients with ≥3 positive biopsy cores, AS/WW rates increased from 3.89% to 22.45% for men ≤55 and from 10.05% to 28.49% for men ≥56 (all P_{trend}<0.001). Five-year PCSM rates were below 0.30% across age and initial management type subgroups.

Conclusion: AS/WW rates quadrupled for patients age ≤55 from 2010-2015, 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<0.001), suggesting some national ambivalence toward AS/WW in younger patients.

Background

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 (NCCN) guideline-approved standard of care.[2–5] Though 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 and thus 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 (USPSTF) recommends against PSA screening in men age 55 years and younger.[14,15] Nevertheless, nearly 20% of men age ≤55 still undergo PSA-screening and this group comprises approximately 10% of patients with low-risk disease.[16] As such, appropriate management of younger men with LRPC remains an area of debate with little data to inform practice and policy.

We therefore sought to define the national rates of conservative management for LRPC and associated short-term population-based outcomes in young (age ≤55) versus older (age ≥56) men using the largest currently available cohort of young patients managed conservatively.

Methods

Study Cohort

We identified 50,302 men diagnosed with LRPC (clinical AJCC 7th Edition Tumor Stage T1-T2a, clinical/biopsy Gleason 6, and Prostate-Specific Antigen [PSA] <10 ng/mL)[2] and known initial management/treatment status between January 2010 and December 2015 using the U.S. Surveillance, Epidemiology, and End Results (SEER) Program Prostate with Active Surveillance/Watchful Waiting Database, which represents approximately 28% of the U.S. population.[17] The study period was determined by the inclusion of the novel AS/WW variable into the custom dataset in which all SEER Prostate with AS/WW data was available. This data is unique from the publicly available SEER database, requiring a proposal and approval of analyses by SEER before release.

Patients with unknown T stage, Gleason score, PSA, or initial management approach were excluded. If patients were conservatively managed[18] they were identified as "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 (NAACCR) 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 number of positive cores; however, percentage by volume of core cancer involvement is not reported. This 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. Median and interquartile range 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 Fisher Exact test, respectively.

Active Surveillance / Watchful Waiting (AS/WW) trends and associations by Age

The primary endpoint was U.S. rate of AS/WW utilization for LRPC stratified by age ≤55 versus age ≥56, over time. 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 number of positive cores (very low-risk disease [≤2 positive biopsy cores] versus standard low-risk disease [≥3 positive biopsy cores]) in addition to age.[2] There were N=39,020 patients with 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] versus ≥56), number of positive cores (≤2 versus ≥3 [referent]), year of diagnosis (2013-2015 versus 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 (AOR), 95% confidence intervals (CI's) and P-values were

calculated for each covariate in the regression model. For subgroup analyses, the above multivariable logistic regression was repeated after stratification by age ≤55 versus age ≥56.

Estimates of Prostate Cancer-Specific Mortality (PCSM) and Overall Mortality (OM) 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 with at least 1-month follow-up (N=49,770 patients) from date of diagnosis. Analyses were stratified by age (≤55 versus ≥56) and initial management type (AS/WW versus RP or RT). Adjustments were made for the aforementioned variables in the above logistic regression models. As an exploratory analysis, we evaluated the potential for an interaction between age and initial management type with respect to OM via an age x initial management type interaction term.

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

Statistical Tests

For regression analyses, adjusted hazard ratios (AHR) and AOR with 95% CIs and P-values were calculated. All analyses were performed with two-sided level of significance set at P=0.05. Statistical analyses were performed with STATA/SE 15.1 (StataCorp, College Station, TX, USA). Permission for study was granted by The Dana-Farber/Harvard Cancer Center Institutional Review Board.

Results

Baseline Characteristics

With a total of 50,302 patients diagnosed with LRPC between 2010-2015, 19.8% were age ≤55 (N=9,973). Across the study period, among patients age ≤55, 19.6% (N=1,957) were managed with AS/WW, 60.6% (N=6,041) with definitive RP and 19.8%

(N=1,975) with definitive RT. Among patients ≥56 (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 (ng/mL) was 4.8 (IQR 3.9-6) among men age ≤55 versus 5.5 (IQR 4.4-6.9) among men age ≥56 (P<0.001) Baseline characteristics stratified by age and initial management type are shown in Table 1. Initial management type was further stratified by RP and RT in Supplemental Tables A and B.

Active Surveillance / Watchful Waiting (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 ≤55, and similarly increased from 15.99% to 43.81% among men ≥56 (P_{trend} for both <0.001; Figure 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 ≤55 (P_{trend}<0.001, Figure 1a-b). Similarly, among men ≥56, 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_{trend}<0.001, Figure 1a-b). Among patients with ≤2 positive biopsy cores, rates of AS/WW utilization increased from 12.90% to 48.78% for men ≤55 and from 21.85% to 58.01% for men ≥56 (Figure 1c-d). Among patients with ≥3 positive biopsy cores, rates increased from 3.89% to 22.45% for men ≤55 and from 10.05% to 28.49% for men ≥56; P_{trend} was <0.001 for all groups examined (Figure 1e-f). Notably, factors associated with AS/WW utilization included ≤2 positive cores, higher SES, age ≥56, and diagnosis after 2012 (Table 2).

Estimates of Prostate Cancer-Specific Mortality (PCSM) and Overall Mortality (OM) with AS/WW by Age

Median follow-up time was 41 months (maximum follow-up was 71 months). Median follow-times among patients age ≤55 versus ≥56 were 42 and 41 months, respectively. There were 9 prostate cancer deaths among men age ≤55 (N=9 among men managed with definitive treatment versus N=0 among men with AS/WW) and 64 among men age ≥56 (N=53 among men managed with definitive treatment versus N=11 among men with AS/WW).

No difference in PCSM by initial management existed (P=0.40; Table 3); however, for patients managed with AS/WW there was a higher risk of OM (AHR 1.24, 95%CI 1.05-1.47, P=0.01). Additionally, no difference in PCSM (P=0.78) or OM (P=0.11) existed among men age ≤55 compared to men ≥56 (Table 3).

Five-year PCSM rates were below 0.30% across age and initial management type subgroups (Figure 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 age ≤55 managed with AS/WW, patients age ≤55 managed with RP or RT, patients age ≥56 managed with AS/WW, and patients age ≥56 managed with RP or RT, respectively (P-value for overall comparison <0.001 in the setting of no events in patients age ≤55 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 age ≤55 managed with AS/WW, patients age ≤55 managed with RP or RT, patients age ≥56 managed with AS/WW, and patients age ≥56 managed with RP or RT, respectively ($P_{\text{overall comparison}}$=0.53; Figure 2b). On exploratory Cox regression analysis for OM, there was no interaction between age and initial management approach ($P_{\text{interaction}}$=0.88).

Conclusions

Between 2010-2015, AS/WW utilization rates in the U.S. have more than quadrupled for patients 55 and younger with LRPC. Similarly, AS/WW rates have nearly tripled for low-risk patients 56 and older. Though 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% versus 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 of the study period, while AS/WW transitioned from least to 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—while 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] Based on 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 below 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—though 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]

On the other hand, 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 MRI 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 age 55 years and younger diagnosed with low-risk disease, there has been insufficient evidence to demonstrate efficacy for conservative management compared with definitive treatment given that young men are underrepresented in trials and retrospective studies due to their lower likelihood of prostate cancer diagnosis. For example, our study has a higher total number and proportion of patients ≤55 as compared to recent large RCTs in prostate cancer. Specifically, the ProtecT trial included 11% (N=58), 12%(N=69), and 11%(N=62) of men age 54 and younger receiving active monitoring, RP, and RT, respectively,[29] whereas our study included 14.5%(N=1,957), 29.5%(N=6,041), 12.1%(N=1,975) of men age 55 and younger who received AS/WW, RP, and RT, respectively. Moreover, other large U.S. national database studies have used a proxy for AS/WW to compare conservative management with other treatment, rather than a validated variable for AS/WW.[30] To address these limitations, the present 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.

A number of limitations exist. First, our analyses lack quality-of-life measures to determine if choice for AS/WW were driven by baseline quality-of-life or if 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, though SEER provides number of cores involved by tumor, SEER does not collect information on percentage of biopsy core involved by tumor and therefore our analyses for "standard" and "very low" -risk disease represent proxies for those risk groups. Fourth, though 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. Lastly, 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 if the long-term outcomes of AS/WW presented in this study persist.

Despite potential limitations, our present 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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Veterans Affairs Integrated Health Care System From 2005-2015. *JAMA*. 2018;319(21):2231. doi:10.1001/jama.2018.5616.

Figure 1. Initial management rates (active surveillance/watchful waiting [AS/WW] versus initial definitive radical prostatectomy or radiation therapy) for NCCN low-risk prostate cancer diagnosed in the United States from 2010-2015 (N= 50,302*), among **(A)** all men age ≤55 with low-risk prostate cancer (N= 9,973), **(B)** all men age ≥56 with low-risk prostate cancer (N=40,329), **(C)** men age ≤55 with very low-risk disease / ≤ 2 positive cores (N= 4,451), **(D)** men age ≥56 with very low-risk disease / ≤ 2 positive cores (N=18,806), **(E)** men age ≤55 with standard low-risk disease / ≥ 3 positive cores (N=3367), and **(F)** men age ≥56 with standard low-risk disease / ≥ 3 positive cores (N=12,396). *N=39,020 patients had known number of positive cores. P_{trend}<0.001 for all subgroups (A-F).

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

Table 1. Distribution of baseline characteristics by age (Age ≤55 years versus Age ≥56 years) and initial management type (AS/WW versus Definitive Treatment with radical prostatectomy or radiation therapy) among 50,302 patients in the U.S. diagnosed with NCCN low-risk prostate cancer, from 2010-2015.

Characteristic	Age ≤55, AS/WW (N= 1,957)	Age ≤55, RP or RT (N= 8,016)	Age ≥56, AS/WW (N= 11,527)	Age ≥56, RP or RT (N= 28,802)
Age (median with IQR, years)	53 (50-54)	52 (49-54)	65 (61-69)	64 (60-68)
PSA (median with IQR, ng/mL)	4.8 (4-6)	4.8 (3.9-6)	5.5 (4.5-6.9)	5.5 (4.4-6.9)
Number Positive Cores				
≤2	1,310 (66.9)	3,141 (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)	1,728 (15.0)	7399 (25.7)
Year of Diagnosis, N (%)				
2010-2012	800 (40.9)	5345 (66.7)	4,974 (43.2)	18,887 (65.6)
2013-2015	1,157 (59.1)	2671 (33.3)	6,551 (56.8)	9915 (34.4)
Insurance Status				
Non-Medicaid Insured	1,764 (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 with 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; RP, radical prostatectomy; RT, radiation therapy; IQR interquartile range; N, number; %, percentage within categorical variable among column-stratified group; PSA, prostate-specific antigen; ng/mL, nanograms per milliliter; SEER, Surveillance, Epidemiology, and End Results.

Table 2. Multivariable-adjusted odds of receiving AS/WW by age (Age ≤55 years versus Age ≥56 years) among 50,302 patients in the U.S, diagnosed with NCCN low-risk prostate cancer, from 2010-2015.

Characteristic		AS/WW, All (N= 50,302)		AS/WW, Age ≤55 (N= 9,973)		AS/WW, Age ≥56 (N= 40,329)	
		AOR (95% CI)	P	AOR (95% CI)	P	AOR (95% CI)	P
Age							
	Age ≤55	1.0 (Ref)		-	-	-	-
	Age ≥56	1.63 (1.54-1.72)	<0.001	-	-	-	-
Age at Diagnosis (per year increase)		-	-	1.02(1.01 – 1.04)	0.003	1.04 (1.03-1.05)	<0.001
PSA (ng/mL increase)		1.02 (1.01-1.03)	<0.001	1.01 (0.98 – 1.04)	0.60	1.01 (0.99-1.02)	0.35
Number of Positive Cores							
	≥3	1.0 (Ref)		1.0 (Ref)		1.0 (Ref)	
	≤2	3.15 (3.00-3.32)	<0.001	3.26 (2.87 – 3.70)	<0.001	3.15 (2.98-3.33)	<0.001
	Unknown	1.20 (1.13-1.29)	<0.001	1.08(0.91 – 1.29)	0.36	1.21 (1.13-1.30)	<0.001
Year of Diagnosis							
	2010-2012	1.0 (Ref)		1.0 (Ref)		1.0 (Ref)	
	2013-2015	2.65 (2.54-2.76)	<0.001	3.10 (2.78 – 3.45)	<0.001	2.61 (2.49-2.74)	<0.001
Insurance Status							
	Uninsured or Medicaid Insured	1.0 (Ref)		1.0 (Ref)		1.0 (Ref)	
	Non-Medicaid Insured	1.02 (0.92-1.14)	0.67	0.99 (0.77 – 1.27)	0.95	1.00 (0.89–1.13)	0.96
	Unknown	0.91 (0.79-1.04)	0.18	1.06 (0.76 – 1.50)	0.71	0.81 (0.70–0.95)	0.007
Yost Index (for socioeconomic status)		1.00 (1.00 – 1.00)	<0.001	1.00 (1.00 – 1.00)	<0.001	1.00 (1.00–1.00)	<0.001

Abbreviations: AS/WW, Active Surveillance/Watchful Waiting; AOR, Adjusted Odds Ratio; CI, Confidence Interval; N, number; P, P-value; %, percentage within categorical variable among column-stratified group; PSA, prostate-specific antigen; ng/mL, nanograms per milliliter; Ref, Referent

Table 3. Distribution of PCSM-deaths by age (Age ≤55 years versus Age ≥56 years) and multivariable-adjusted hazard ratio for PCSM and OM among 49,770 patients in the U.S. diagnosed with NCCN low-risk prostate cancer, from 2010-2015. Patients had at least 1 month of follow-up.

Characteristic		(Age ≤55) No. Men / No. PCa Deaths / No. Competing Deaths	(Age ≥56) No. Men / No. PCa Deaths / No. Competing Deaths	Prostate Cancer-Specific Mortality		Overall Mortality	
				AHR (95% CI)	P	AHR (95% CI)	P
Age ≤55 (by Treatment Strategy) †							
	Definitive Treatment ‡	7966 / 9 / 50	-	1.0 (Ref)			
	AS/WW	1,909 / 0 / 10	-	No events	-	1.14 (0.57-2.30)	0.71§
Age ≥56 (by Treatment Strategy) †							
	Definitive Treatment ‡	-	28,610 / 53 / 465	1.0 (Ref)			
	AS/WW	-	11,285 / 11 / 178	0.77 (0.39 – 1.53)	0.46	1.24 (1.05-1.49)	0.01§
Age							
	≥56	-	39,895 / 64 / 643	1.0 (Ref)			
	≤55	9,875 / 9 / 60	-	1.14 (0.45– 2.91)	0.78	1.29 (0.95 – 1.75)	0.11
Treatment Strategy							
	Definitive Treatment ‡	7966 / 9 / 50	28,610 / 53 / 465	1.0 (Ref)			
	AS/WW	1,909 / 0 / 10	11,285 / 11 / 178	0.68 (0.35 – 1.33)	0.40	1.24 (1.05 – 1.47)	0.01
Age at Diagnosis (per year increase)		9,875 / 9 / 60	39,895 / 64 / 643	1.05 (1.01 — 1.10)	0.01	1.08 (1.07 – 1.10)	<0.001
PSA (ng/mL increase)		9,875 / 9 / 60	39,895 / 64 / 643	1.09 (0.96 – 1.23)	0.18	1.05 (1.01 – 1.09)	0.02
Number 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)	0.34	0.80(0.68 – 0.95)	0.01

	Unknown	2139/3/16	9058/18/181	0.96(0.54 – 1.73)	0.91	1.00 (0.83 – 1.20)	0.96
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)	0.36	0.99 (0.79 – 1.24)	0.93
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)	0.43	2.00 (1.50 – 2.67)	<0.001

Table 3 Continued.

	Uninsured	136/0/1	364/0/5	0.00 (0.00-0.00)	<0.001	0.91(0.41 – 2.04)	0.82
	Unknown	434/0/2	2356/4/52	1.04 (0.38 – 2.90)	0.93	1.47 (1.12 – 1.93)	0.005
Yost Index		9,875 / 9 / 60	39,895 / 64 / 643	0.99 (0.99-1.00)	0.22	0.99 (0.99-1.00)	<0.001

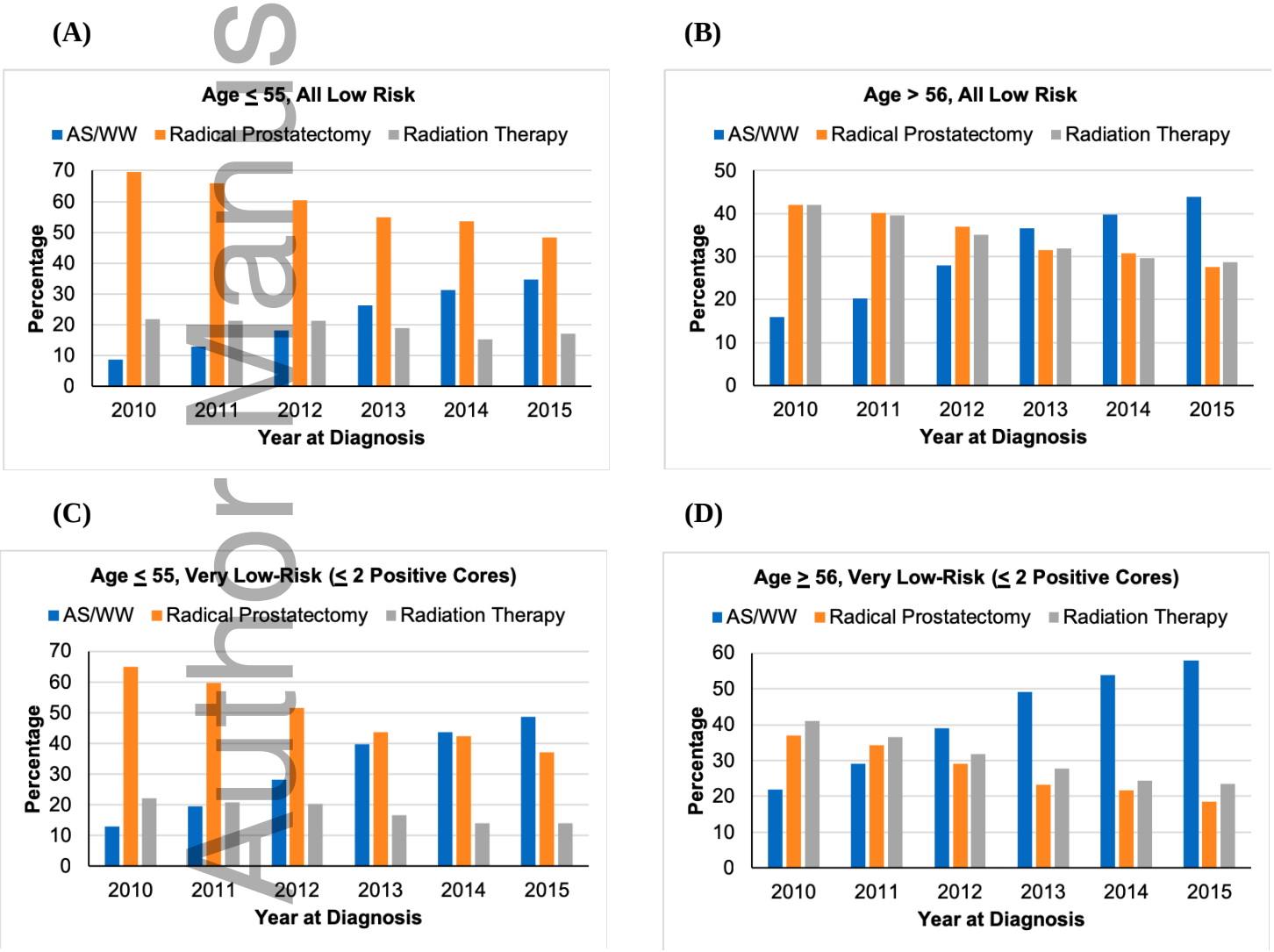
Abbreviations: AS/WW, Active Surveillance/Watchful Waiting; AHR, adjusted hazard ratio; CI, Confidence Interval; No., number; NR, not reported; OM, overall mortality; PCSM, prostate cancer-specific mortality; PCa, prostate cancer; P, P-value; %, percentage within categorical variable among column-stratified group; PSA, prostate-specific antigen; ng/mL, nanograms per milliliter; Ref, Referent; SEER, Surveillance, Epidemiology, and End Results

† Analyses stratified age (≤55 versus ≥56) and initial management type (AS/WW versus Definitive management‡)

‡ Definitive management: initial management with either radical prostatectomy or radiation therapy

§ $P_{interaction}$=0.88, where the interaction term was defined as Age (≤55 versus ≥56) * Initial management type (AS/WW versus Definitive management‡)

Figure 1. Initial management rates (active surveillance/watchful waiting [AS/WW] versus initial definitive radical prostatectomy or radiation therapy) for NCCN low-risk prostate cancer diagnosed in the United States from 2010-2015 (N= 50,302*), among **(A)** all men age ≤55 with low-risk prostate cancer (N= 9,973), **(B)** all men age ≥56 with low-risk prostate cancer (N=40,329), **(C)** men age ≤55 with very low-risk disease / ≤ 2 positive cores (N= 4,451), **(D)** men age ≥56 with very low-risk disease / ≤ 2 positive cores (N=18,806), **(E)** men age ≤55 with standard low-risk disease / ≥ 3 positive cores (N=3367), and **(F)** men age ≥56 with standard low-risk disease / ≥ 3 positive cores (N=12,396). *N=39,020 patients had known number of positive cores. P_{trend}<0.001 for all subgroups (A-F).



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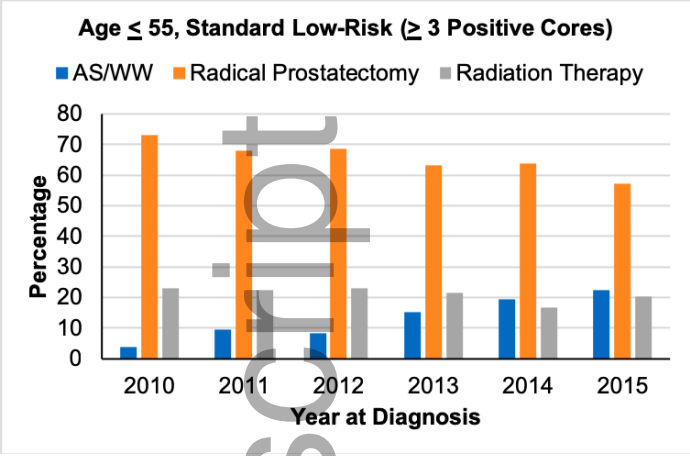

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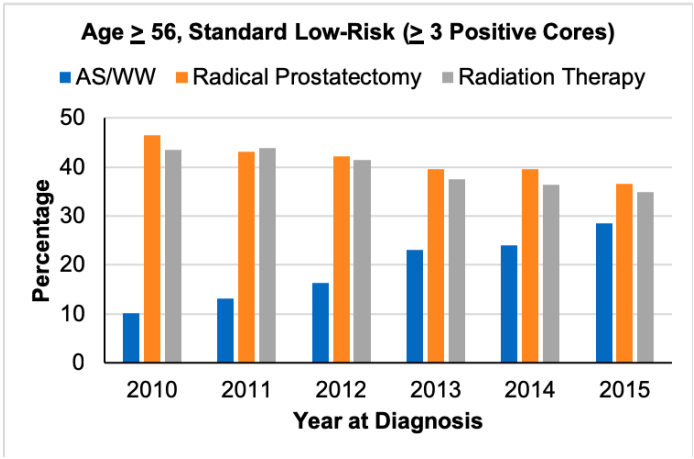

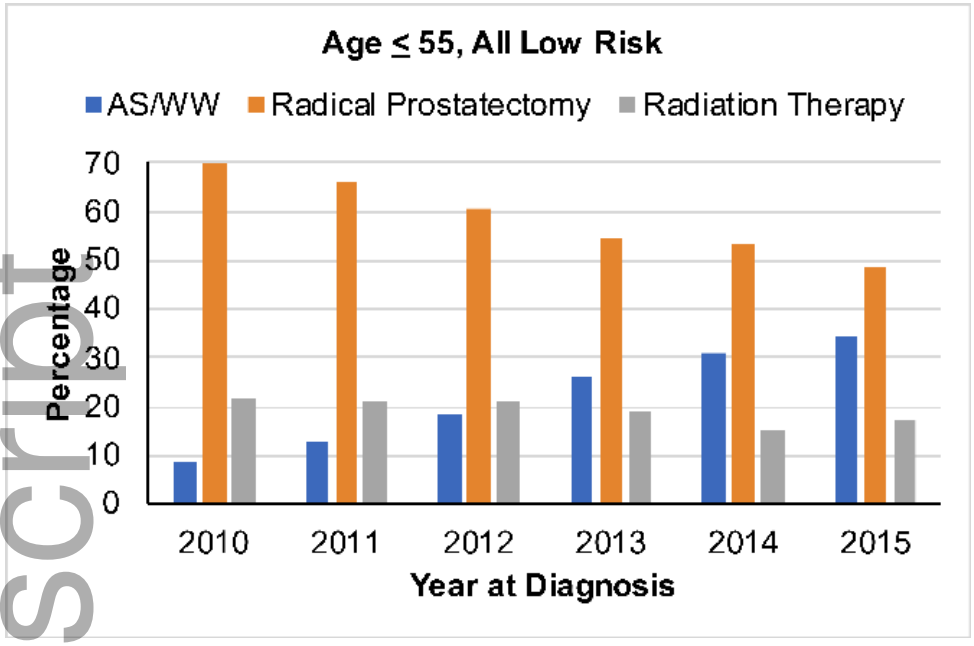

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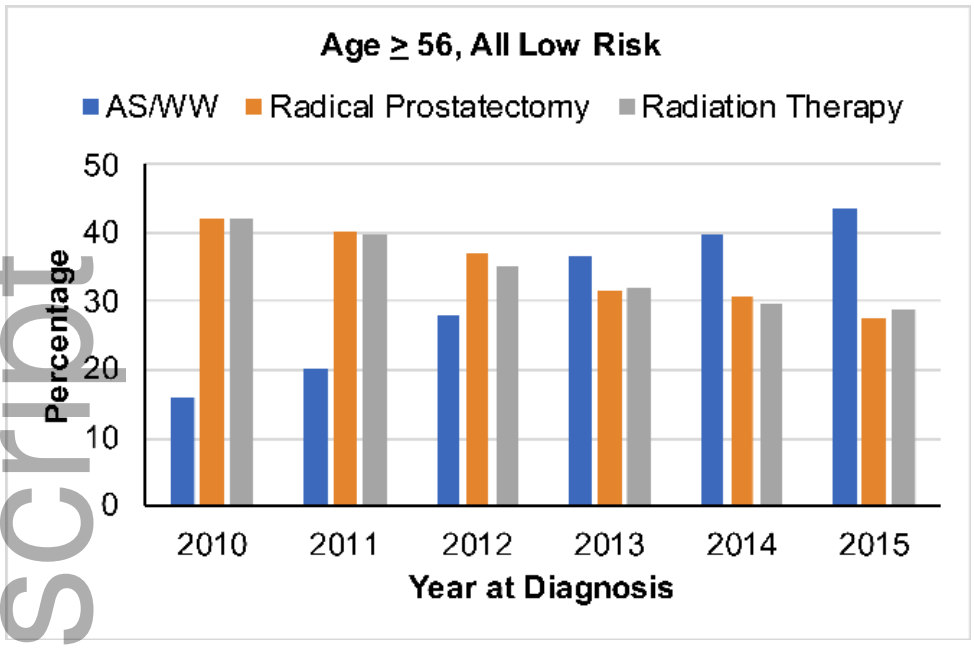

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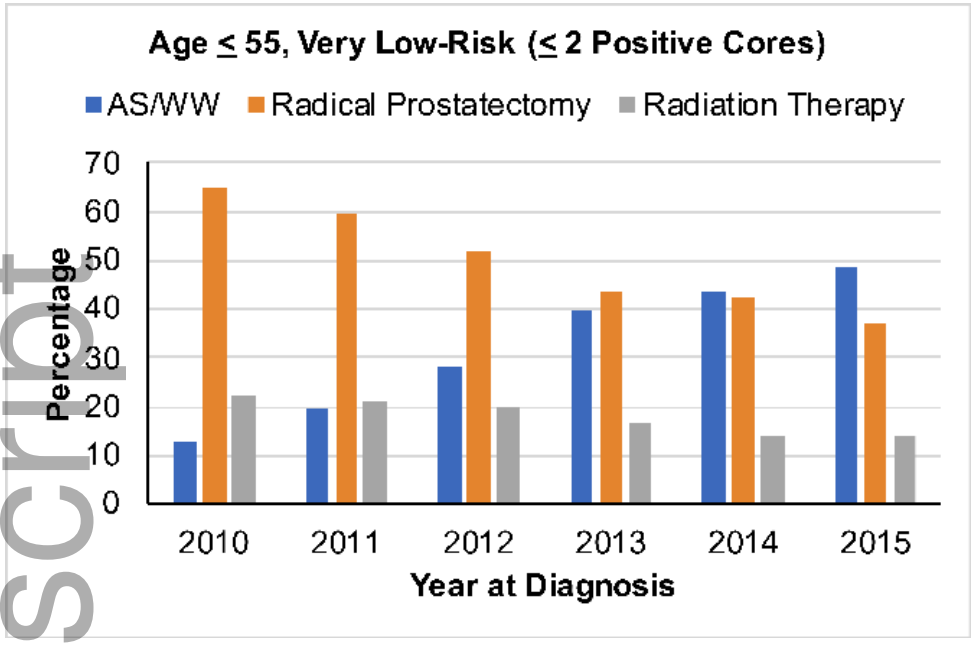

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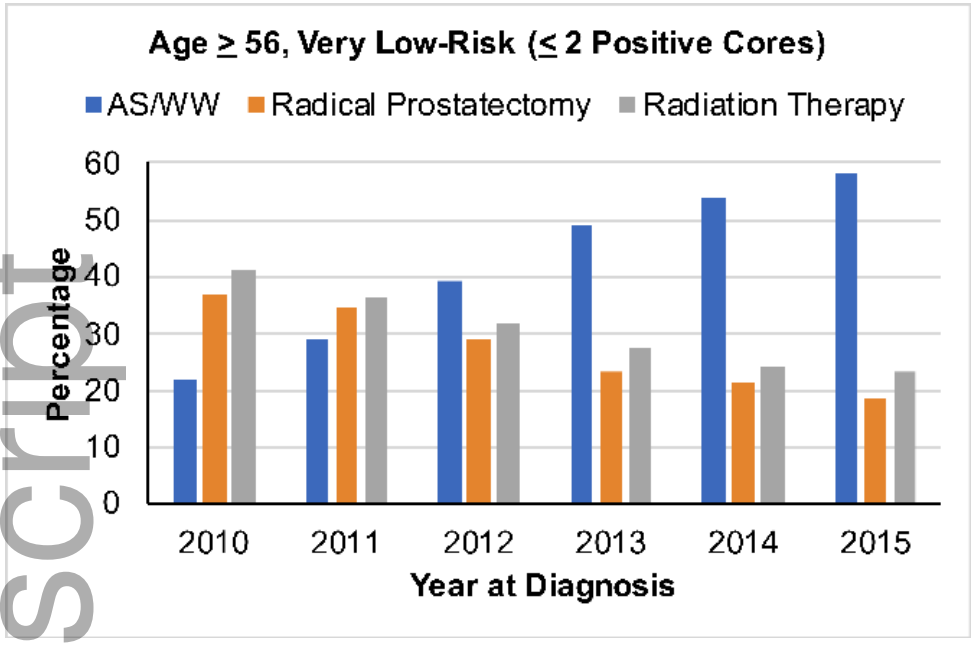

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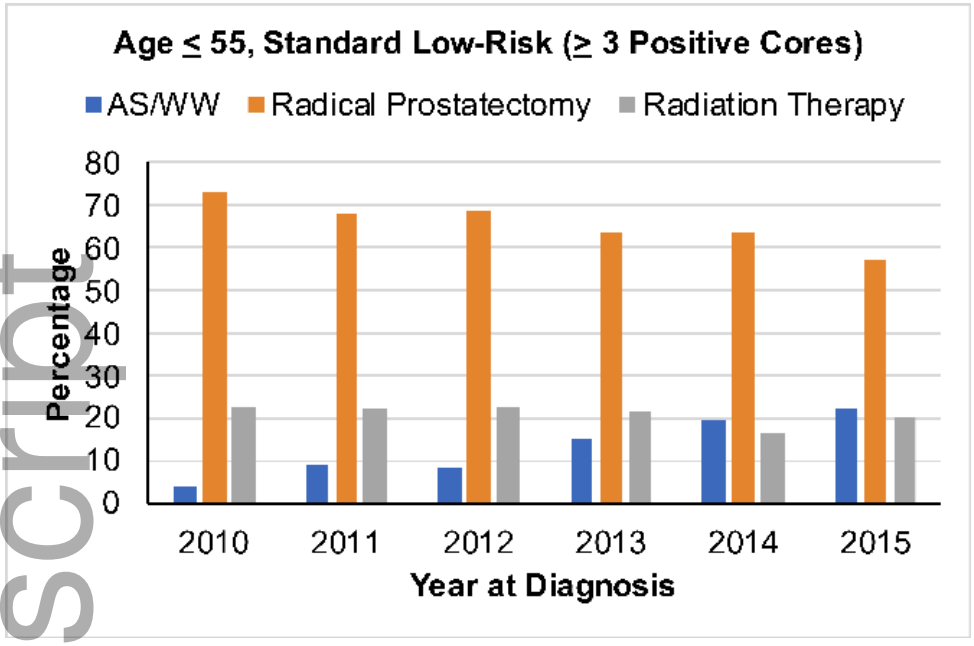

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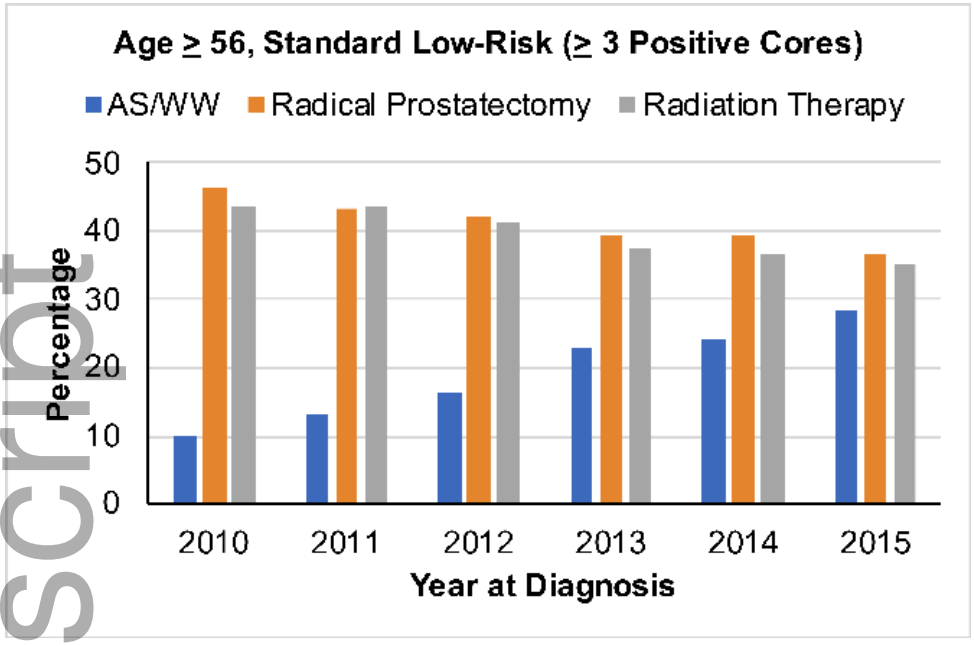

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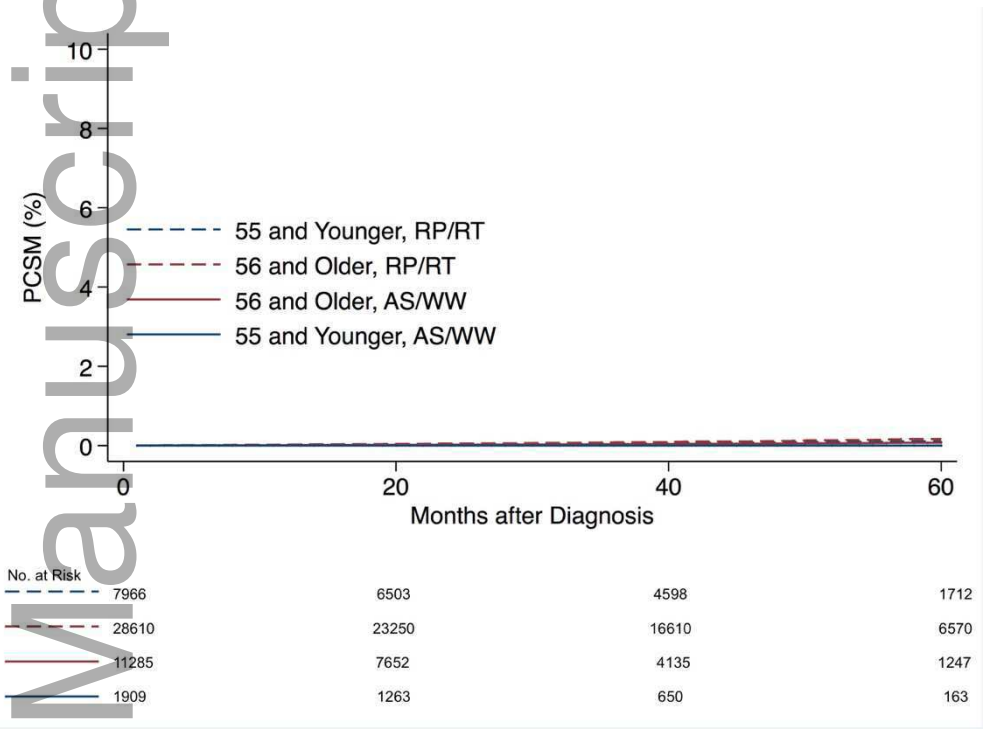
Figure 2. Cumulative incidence of prostate cancer-specific mortality **(A)** and Kaplan-Meier curves for overall survival **(B)** by age (Age ≤55 versus Age ≥56) and initial management approach (active surveillance/watchful waiting [AS/WW] versus initial definitive radical prostatectomy or radiation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

(A)



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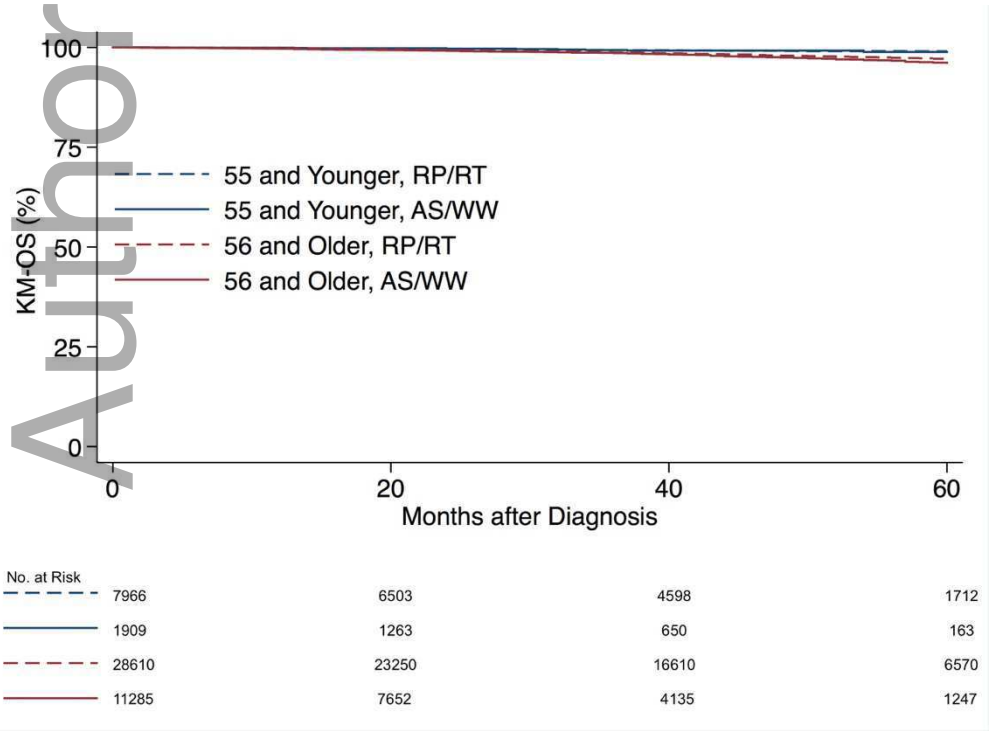

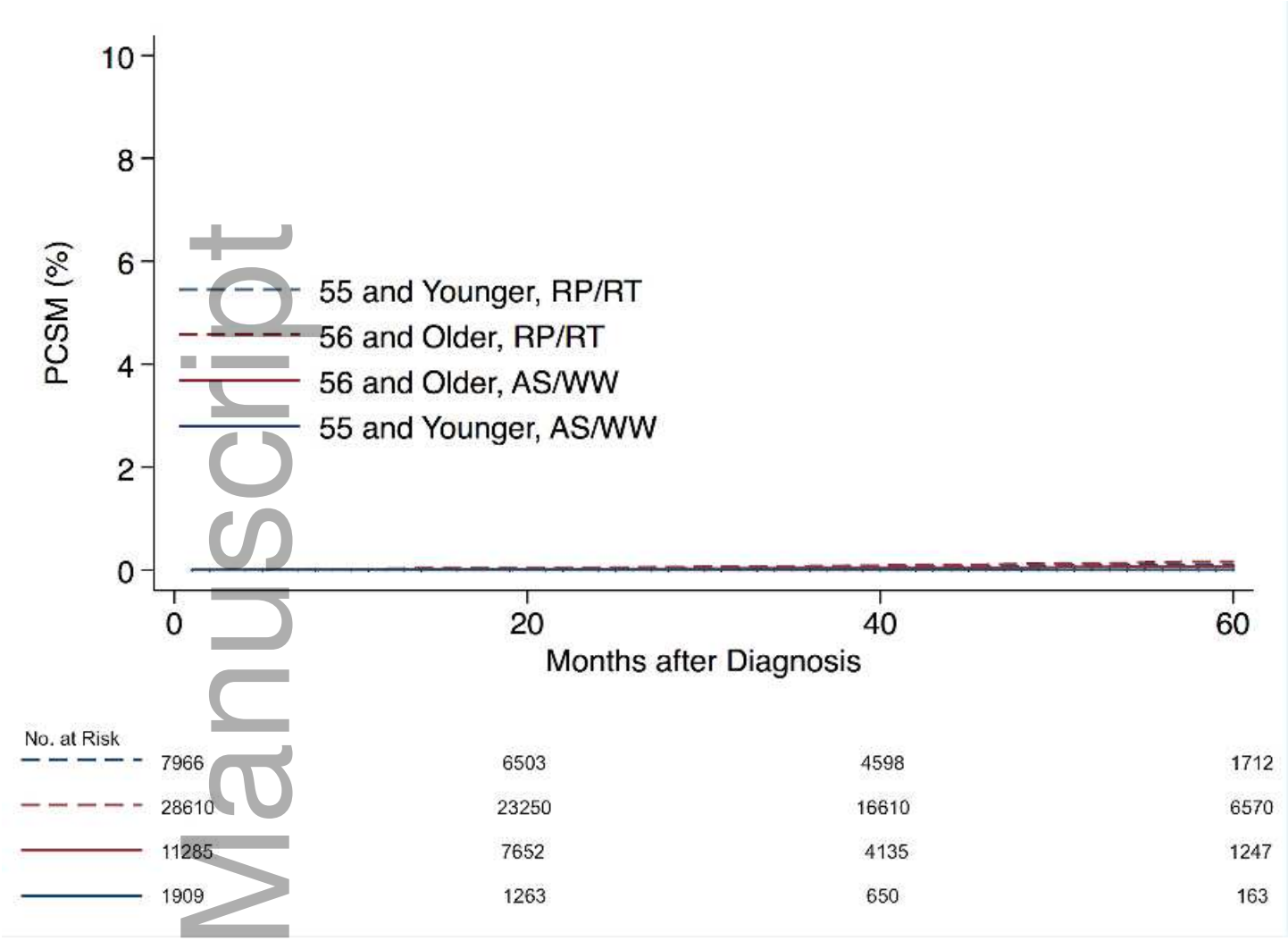

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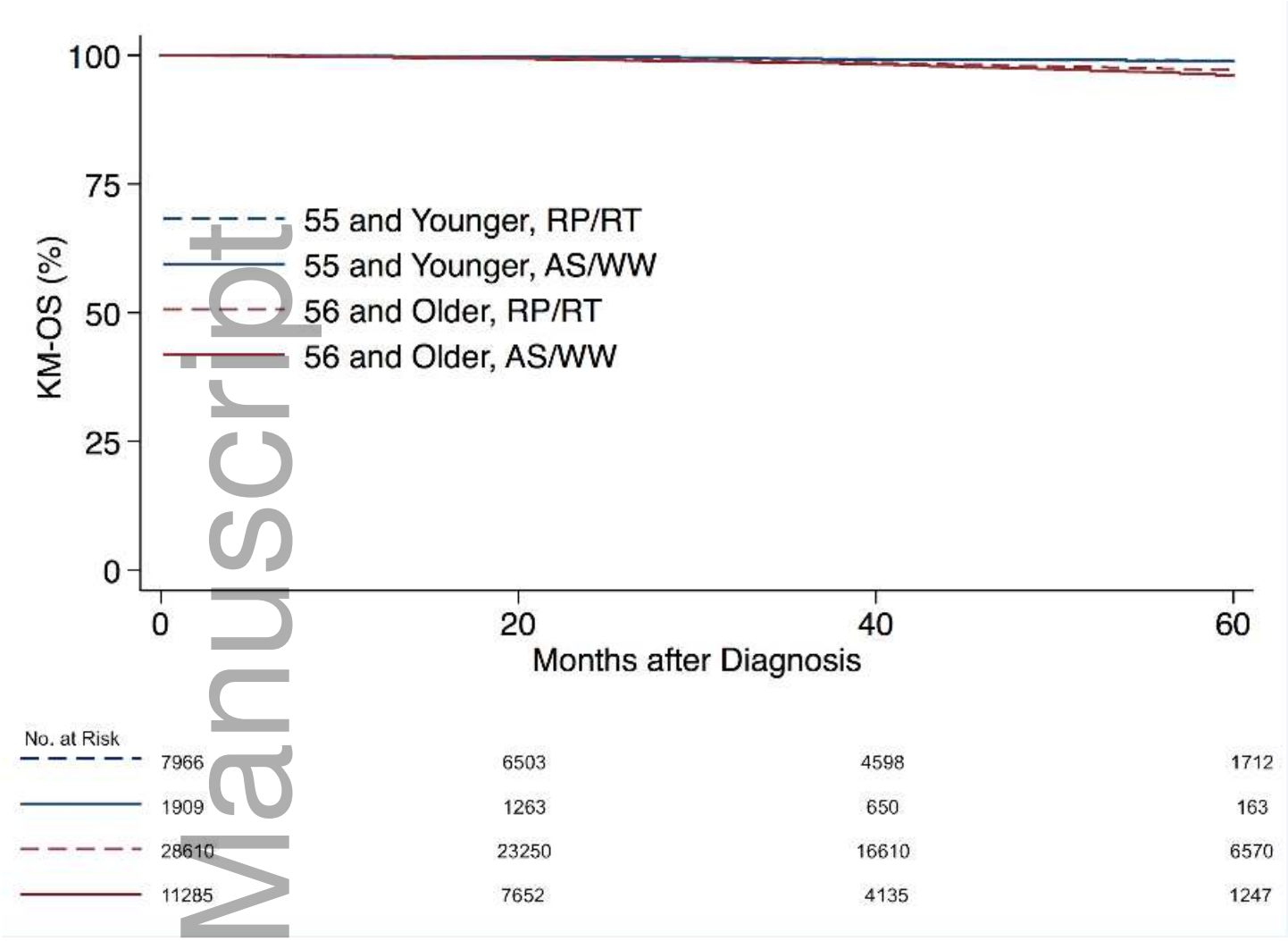

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