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Trends and practices for managing low-risk prostate cancer: a SEER-Medicare study

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Abstract

Background—Expectant management (EM) has been widely recommended for men with low-risk prostate cancers (PCa). We evaluated trends in EM and the sociodemographic and clinical factors associated with EM, initiating a National Comprehensive Cancer Network guideline-concordant active surveillance (AS) monitoring protocol, and switching from EM to active treatment (AT).

Methods—We used the SEER-Medicare database to identify men ages 66+ diagnosed with a low-risk PCa (PSA < 10 ng/mL, Gleason ≤ 6, stage ≤ T2a) in 2010–2013 with ≥1 year of follow-up. We used claims data to capture (1) PCa treatments, including surgical procedures, radiotherapy, and hormone therapy, and (2) AS monitoring procedures, including PSA tests and prostate biopsy. We defined EM as receiving no AT within 1 year of diagnosis. We used multivariable regression techniques to identify factors associated with EM, initiating AS monitoring, and switching to AT.

Results—During the study period, EM increased from 29.4% to 49.0%, $p < 0.01$. Age < 77, being married/partnered, non-Hispanic ethnicity, higher median ZIP code income, lower PSA levels, stage T1c, and more recent year of diagnosis were associated with EM. Nearly 39% of the EM cohort initiated AS monitoring; age <77, White race, being married/partnered, higher median ZIP code income, and lower PSA levels were associated with initiating AS. By three years after diagnosis, 21.3% of the EM cohort had switched to AT, usually after undergoing AS monitoring procedures.

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Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

Ethical approval The research project was approved by the University of Iowa Human Subjects Review Board, IRB number 01. The study was performed in accordance with the Declaration of Helsinki.

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Discussion—We found increasing uptake of EM over time, though over 50% still received AT. About 60% of EM patients did not initiate AS monitoring, even among those with life expectancy >10 years, implying that a substantial proportion was being managed by watchful waiting. AS monitoring was associated with switching to AT, suggesting that treatment decisions likely were based on cancer progression.

Introduction

The widespread use of PSA testing since the late 1980s raised concerns that a substantial number of men were being overtreated for indolent prostate cancers [1]. Consequently, active surveillance has emerged in the United States and Europe as a widely recommended initial therapy for healthy men with a low-risk prostate cancer and the preferred treatment for healthy men with a very low-risk cancer [2, 3]. By selecting active surveillance, men may reduce the like-lihood of undergoing unnecessary treatment without increasing their risk for prostate cancer mortality [4–7]. Watchful waiting, which offers only palliative treatment for symptoms of clinically progressive cancer, is recommended for men with a life expectancy less than 5–10 years, and typically involves less intensive surveillance testing [2, 3]. Numerous studies have shown that increasing proportions of men with a low-risk prostate cancer are initially being managed expectantly, i.e., not undergoing active treatment [8–15]. These studies, though, were unable to distinguish between active surveillance and watchful waiting because they lacked data on the monitoring procedures that define active surveillance.

Several studies of men who underwent initial surveillance monitoring suggest that longer-term adherence with recommended surveillance protocols has been poor. Loeb et al., using SEER-Medicare data from 2001 to 2009, reported that fewer than 13% of men on active surveillance underwent a biopsy beyond the first 2 years [16]. Luckenbaugh et al., using 2012–2013 data from a statewide registry in Michigan, found that only 30.6% of their active surveillance cohort underwent a guideline-concordant biopsy at a median follow-up of 2 years [17]. The European Prostate Cancer Research International Active Surveillance study, which followed men from 2006 through 2015, found substantially decreasing compliance with biopsies over time [18]. These findings are concerning because unmonitored men may have undiagnosed higher-grade prostate cancer or may progress to advanced-stage disease that is less likely to respond to treatment.

We used a cancer database of men over age 66 years with low-risk prostate cancer in combination with claims data to (1) quantify trends in the use of expectant management (EM), defined as not undergoing active treatment within 1 year of diagnosis, (2) to describe uptake of active surveillance monitoring procedures and switches to active treatment among the EM cohort, and (3) to determine sociodemographic and clinical factors associated with EM, initiating active surveillance monitoring concordant with the National Comprehensive Cancer Network (NCCN) guideline [2], and switching to active treatment.

Patients and methods

Data sources

We used the linked Surveillance, Epidemiology, and End Results (SEER)-Medicare database for the years 2010, when SEER first provided biopsy core data to define very low-risk cancers, through 2014 for our analyses. The SEER program is a population-based registry that collects cancer incidence and survival data in 19 US geographic areas representing about 35% of the US population [19]. SEER data include patient demographics, tumor characteristics, initial course of treatment, and vital status.

Study population

We used the SEER-Medicare Patient Entitlement and Diagnosis Summary File (PEDSF) file to identify men ages 66 and older who were diagnosed with malignant prostate adenocarcinoma (SEER ICD-O-3/WHO site recode of prostate and ICD-O-3 histology code 8140) between January 1, 2010, and December 31, 2013, with follow-up through December 31, 2014 (Fig. 1). Guidelines during this study period supported active surveillance as an option for men with a low-risk prostate cancer [20, 21]. We excluded men who did not survive at least 1 year after diagnosis, those who did not have at least 1 year of continuous Medicare Part A and Part B insurance without HMO coverage before and after diagnosis, and those who had no professional, hospital, or outpatient Medicare claims in the year following diagnosis.

Risk groups

We used SEER collaborative stage variables and American Joint Committee on Cancer (AJCC) 7th edition T-stage data on disease characteristics (PSA, Gleason grade, and clinical stage) [22]. We defined low-risk prostate cancer as PSA < 10 ng/mL, Gleason = 6, and stage T1c or T2a. We defined very low risk as PSA < 10 ng/mL, Gleason = 6, stage T1c, and <25% positive biopsy cores. SEER staging is based on the best available data, which may include pathological staging data obtained following surgery.

Study variables

We used patient-level variables from the PEDSF file to determine sociodemographic characteristics, including age, race, ethnicity, marital status, and ZIP code level census data on population median income. We extracted data from the Medicare claims files (Medicare Provider and Analysis Review, Carrier Claims, and Outpatient facility claims) and used the NCI Combined Index to calculate a comorbidity score [23–25]. We used SEER data, ICD-9-CM codes, and HCPCS (Healthcare Common Procedure Coding System) codes to identify treatments and surveillance procedures (Supplementary Table 1). Prostate cancer treatments included radical prostatectomy, radiotherapy (external beam radiotherapy or brachytherapy), cryotherapy, and androgen deprivation therapy. We defined EM as no prostate cancer treatment for the first year following diagnosis. Among men initially managed expectantly, we determined whether they underwent surveillance monitoring, including PSA tests, prostate biopsies, and pelvic MRI imaging. In tracking surveillance monitoring, we avoided misclassifying diagnostic procedures as surveillance procedures by counting only those that

took place at least 3 months after diagnosis and before starting treatment (among men who subsequently switched to active treatment). PSA tests and biopsies had to be separated by 30 days and MRIs had to be separated by 180 days to be considered a new procedure.

Statistical analyses

Cochran-Armitage tests were used to assess temporal trends in the proportion of patients receiving each management modality during the first year following diagnosis. The primary management modality was defined as the most aggressive treatment approach based on the following hierarchy from most to least aggressive: surgery, radiation, cryotherapy, hormone therapy, or no treatment. Because cryotherapy and hormone therapy were infrequently used as the primary management modality, we combined them under the category of "other" in the figures. Logistic regression models were applied to determine the effect of baseline sociodemographic and clinicopathologic variables on receiving no active treatment for at least 12 months post-diagnosis. For all multivariable analyses, we stratified age at 77, when actuarial tables estimate that life expectancy drops below 10 years and when guidelines preferentially recommend observation over active surveillance [2, 26].

Among patients who were managed expectantly, we estimated the cumulative incidences of surveillance procedure utilization and subsequent treatment using Fine and Gray's method. In addition, Cox regression models were used to estimate the association of baseline sociodemographic and clinicopathologic variables on time to initiating NCCN-concordant active surveillance monitoring, which was operationally defined as ≥1 biopsy and ≥2 PSA tests within 2 years of diagnosis [2]. Time was calculated from the end of the 12-month no treatment period to the time by which the active surveillance monitoring criteria were met; treatment initiation before meeting the criteria and death were considered competing risks. Patients who did not meet the monitoring criteria were censored at change in insurance coverage or the end of the study period, whichever occurred first.

Cox regression models were also used to estimate the effect of baseline sociodemographic and clinicopathologic variables as well as receipt of surveillance monitoring procedures on time to initiating active treatment (switching from EM). We used time-dependent covariates for surveillance monitoring procedures (PSA, biopsy or MRI) occurring after the initial 12-month period of no treatment following diagnosis (deferment period). Time was calculated from the end of the deferment period to treatment initiation; death was considered a competing risk and patients who did not receive treatment were censored at change in insurance coverage or the end of the study period, whichever occurred first.

To account for the possible dependency between patients from each SEER registry, we used generalized estimating equations with a compound symmetry structure and a robust sandwich variance estimate for the logistic and Cox regression models, respectively. Estimated effects of predictors are reported as odds ratios or hazard ratios (HR) along with 95% confidence intervals (CIs). All tests were two-sided and assessed for significance at the 5% level using SAS v9.4 (SAS Institute, Cary, NC).

Results

We identified 7573 men from the SEER-Medicare database who were diagnosed with a low-risk prostate cancer in the years 2010–2013 and a subset of 2551 men with a very low-risk cancer. Table 1 shows baseline sociodemographic and clinical characteristics for the cohort of men with a low-risk prostate cancer, overall and stratified by whether they underwent any active treatment during the first year following diagnosis. The median age was 71 years, 87.3% were White, 5.7% were Hispanic, 80.3% were married/ partnered, about a third lived in ZIP code areas with a median income > $60000, and 58.7% had a comorbidity score of 0.

Figure 2 shows the treatment patterns for the most aggressive treatment received in the year following diagnosis of a low-risk prostate cancer in the years 2010–2013. The proportion initially selecting EM (not receiving active treatment for at least one year following diagnosis) increased over time from 29.4% to 49.0%, $p < 0.01$. The proportion undergoing radiation therapy decreased from 60.8% to 42.3%, $p < 0.01$, while the proportions undergoing surgery, cryotherapy, or hormone therapy remained consistently low. Among the cohort of men with very low-risk cancers, the proportion initially selecting EM increased from 36.4% to 60.1%, $p < 0.01$ (Supplementary Fig. 1).

We evaluated factors associated with EM (Table 2).Multivariable analysis identified not being married/partnered, being of non-Hispanic ethnicity, having a ZIP code in the highest two tertiles of median income compared to the lowest tertile, lower stage cancer (T1c vs. T2a), lower PSA levels (<4 ng/mL vs 4–9.9 ng/mL), and a more recent year of diagnosis (2011–2013 vs. 2010) as significantly associated with EM.

Among men being managed expectantly, the cumulative incidences for undergoing PSA testing, prostate biopsy, and pelvic MRI at 2 years after diagnosis were 91.8% (95% CI, 90.7–92.8%), 41.0% (95% CI, 39.1–42.9%), and 10.2% (95% CI, 9.0–11.3%), respectively. The cumulative incidence of men managed expectantly who initiated NCCN-concordant active surveillance monitoring, defined as undergoing ≥ one prostate biopsy and ≥ two PSA tests within 2 years of diagnosis, was 38.6% (95% CI, 36.7–40.4%). Men younger than 77 were more likely than older men to initiate active surveillance, 42.4% vs. 23.0%, $p < 0.01$. On multivariable analysis, the factors associated with initiating active surveillance monitoring were White race (compared to Black race), being younger than 77, being married/partnered, having a ZIP code in the highest two tertiles of median income compared to the lowest tertile, and having a PSA < 4 ng/mL vs 4–9.9 ng/mL (Table 3). We also found that 5.6% (95% CI, 4.7–6.5%) of the EM cohort underwent PSA testing and at least one MRI without repeating a prostate biopsy.

The cohort of men with a low-risk prostate cancer who were initially managed expectantly had a median 34 months of follow-up time. The cumulative incidence of switching to active treatment by 3 years following diagnosis was 21.3% (95% CI, 19.6–23.1%). The most frequent primary treatment modality was radiation therapy (17.1%, 95% CI 15.3–18.9%) followed by surgery (6.1%, 95% CI 5.1–7.3%) (Supplementary Fig. 2). In the multivariable analysis, the factors associated with switching were non-Hispanic ethnicity vs. Hispanic

ethnicity (HR = 1.67, 95% CI, 1.25–2.22), initial PSA of <4.0 ng/mL vs. 4.0–9.9 ng/ mL (HR = 1.64, 95% CI, 1.28–2.05), and undergoing any surveillance monitoring procedure, particularly prostate biopsy (HR = 5.85, 95% CI, 4.45–7.50).

Discussion

Using SEER-Medicare linked data for prostate cancer diagnoses from 2010 through 2013, we found that the proportion of men with a low-risk prostate cancer who were initially managed expectantly (no active treatment within the first 12 months after diagnosis) significantly increased from 29.4% to 49.0%, $p < 0.01$. The proportion was even higher for men with a very low-risk prostate cancer, reaching 60.1% by 2013. Within 2 years of diagnosis, 38.6% in the EM cohort, including 42.4% of those <77, initiated NCCN-concordant active surveillance monitoring. Among men who deferred active treatment for 1 year, 21.3% subsequently received active treatment by 3 years following diagnosis; undergoing surveillance monitoring was the strongest factor associated with switching to active treatment.

Professional guidelines have been recommending EM, either active surveillance for healthy men or watchful waiting for men with a limited life expectancy, as a primary management option for men with a low-risk prostate cancer since 2007 [21]. Our finding that increasing proportions of men with a low-risk prostate cancer did not receive initial active treatment demonstrates a changing approach to management over time and expands on the results of previous studies by providing more recent SEER-Medicare management data, including for men with very low-risk prostate cancers [8–15]. We found that older age, not being married/ partnered, living in a ZIP code area with higher median income, non-Hispanic ethnicity, more recent year of diagnosis, and having less aggressive disease characteristics were associated with being expectantly managed. Other studies have identified similar predictors of EM, particularly disease characteristics, as well as lower comorbidity and family history [10–13, 27].

Among men diagnosed with a low-risk prostate cancer, we found significantly decreased use of radiotherapy and consistently low levels of cryotherapy and primary ADT, which has been reported by others [8, 13–15, 28]. We also found consistent use of radical prostatectomy, but at a much lower level (<10%) than the 31–46% reported by studies using SEER data [12, 14, 29] and the ~50% reported by studies using the National Cancer Database (NCDB) [11, 14]. One explanation for this difference is that the SEER-Medicare cohort skews toward older men who are less likely to undergo surgery [30].

By using Medicare data, we were able to determine that 38.6% of men managed expectantly initiated monitoring concordant with the NCCN active surveillance guideline. We are unaware of any recent national-level reports similarly characterizing active surveillance uptake. The NCDB and SEER datasets have a treatment indicator variable for EM, but the variable does not distinguish active surveillance from watchful waiting. We found that being younger than 77, White race (compared to Black race), being married, living in a census tract with higher median income, and a lower PSA level, were associated with initiating active surveillance monitoring. The age stratification finding is notable

because it corresponds to a 10-year actuarial life expectancy and aligns with guidelines considering active surveillance to be less appropriate for men with a shorter life expectancy. SEER-Medicare analyses of men with a localized prostate cancer diagnosed in the 2000s found younger age, higher socioeconomic status, lower comorbidity, and favorable disease characteristics associated with surveillance monitoring [16, 31].

Studies using the SEER Watchful Waiting database have found no racial differences in EM after adjusting for socioeconomic status [32–34]. However, the decreased initiation of surveillance monitoring among Black men, only 23.8% among those <77, is potentially concerning because observational data suggest that Black men are more likely than White men to be reclassified through surveillance biopsies with higher-grade disease [35]. Studies also suggest that Black men eligible for active surveillance who undergo initial prostatectomy are more likely than White men to have adverse pathological outcomes, including positive surgical margins or upstaging [36, 37]. A VA study did find that Black men on active surveillance were not at increased risk for metastatic disease or prostate cancer mortality [38]. However, all men underwent at least one surveillance biopsy. Lower adherence with surveillance monitoring protocols, particularly undergoing biopises, could lead to poorer clinical outcomes, heightening existing racial disparities for mortality [39].

We found that 5.6% of the EM cohort underwent repeat PSA testing and at least one MRI without repeating a prostate biopsy. Although some urologists may consider using MRI as a substitute for repeat biopsy for men on active surveillance, that practice is controversial and may not be strongly supported by evidence [40]. Professional society guidelines continue recommending a surveillance biopsy that can be augmented but not replaced by MRI [2, 41].

Overall, 21.3% of the cohort who did not undergo active treatment for 1 year following diagnosis switched to active treatment by the end of the subsequent two-year period. Most of these men underwent radiotherapy as their primary treatment modality. We found that undergoing surveillance testing was most strongly associated with switching. Test results are not available in the SEER-Medicare data, but the finding is consistent with data suggesting that the majority of men switching from AS do so because there is evidence of disease progression [42].

Our study had some inherent limitations. We were able to determine whether patients received active treatment during the first year following diagnosis, but we do not know whether the initial intent of the patient and physician was to actually manage the cancer expectantly, particularly with active surveillance. In 2010, SEER introduced a treatment variable documenting an initial intention for EM, but it was not available in the SEER-Medicare dataset that we received. However, the SEER Watchful Waiting Database does not distinguish between active surveillance and watchful waiting [34, 43]. While linking with Medicare provides data not captured by the population-based SEER registry, including comorbidity, receipt of primary androgen deprivation, surveillance procedures, and treatments occurring more than 1 year following diagnosis, the results are not necessarily generalizable to those younger than 66 years of age where management patterns may differ. Furthermore, the analyzed SEER-Medicare cohort is not population-based given the various eligibility requirements and our exclusion of men with incomplete staging information.

With a median follow-up duration of 34 months, we were not able to assess long-term continuation of active surveillance monitoring or evaluate clinical outcomes.

We found increasing uptake of EM among men with a low-risk prostate cancer over time. However, by 2013 over 50% of patients were still receiving active treatment within the first year of diagnosis. Within 2 years of diagnosis, just over 40% of those age <77 managed expectantly met initial criteria for undergoing guideline-concordant active surveillance monitoring. Men who do not monitor their cancers could potentially have undiagnosed higher grade cancers that might progress to advanced stages that are more difficult to treat. Surveillance procedures, particularly biopsy, were associated with switching to active treatment suggesting that treatment decisions were likely based on cancer progression.

Data availability

The data that support the findings of this study are available from the National Cancer Institute, but restrictions apply to the availability of these data, which are under license for the study, and so are not publicly available.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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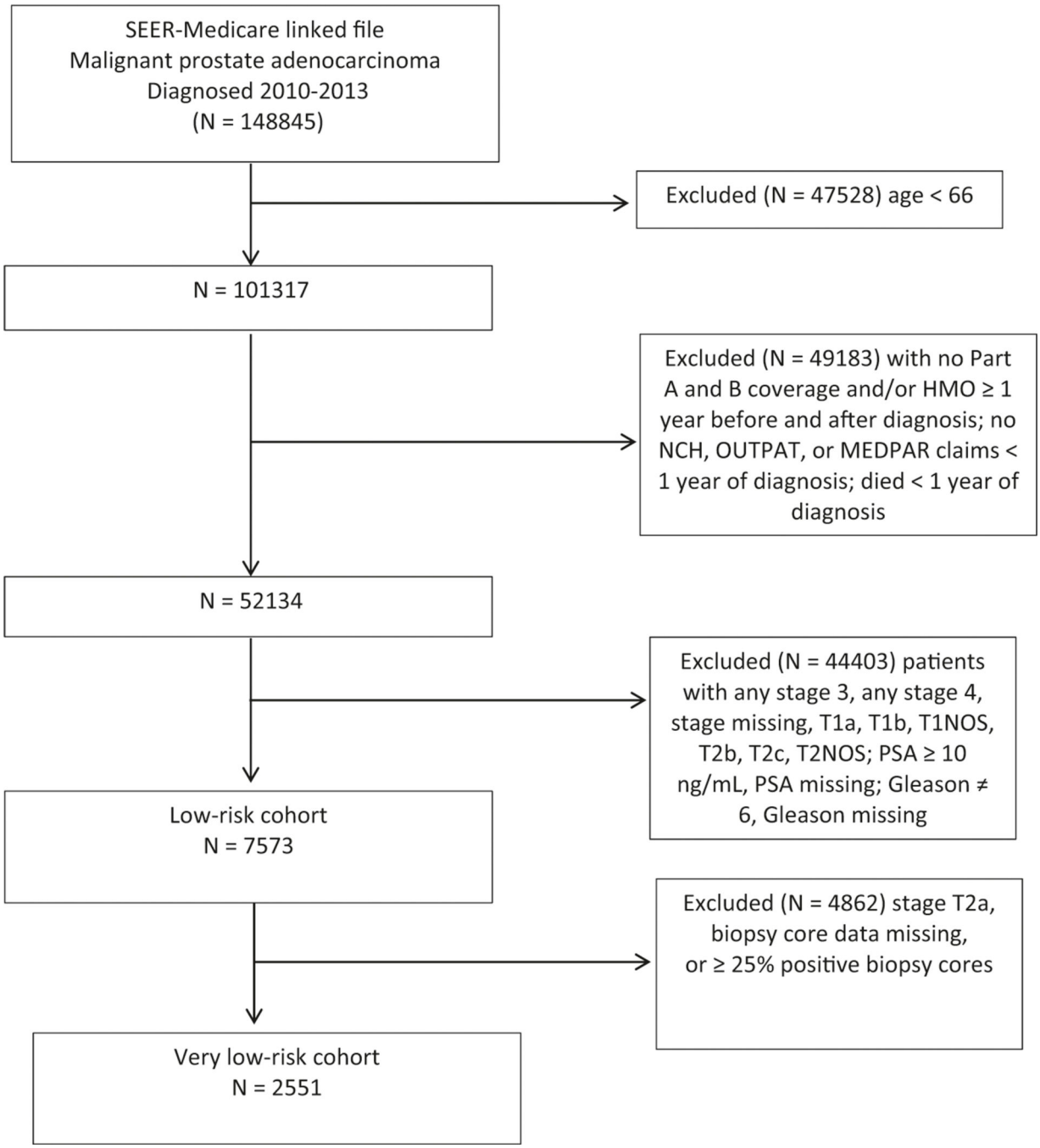

Fig. 1.

Subject flow sheet, SEER-Medicare cohorts of men with low-risk and very low-risk prostate cancers, 2010–2013.

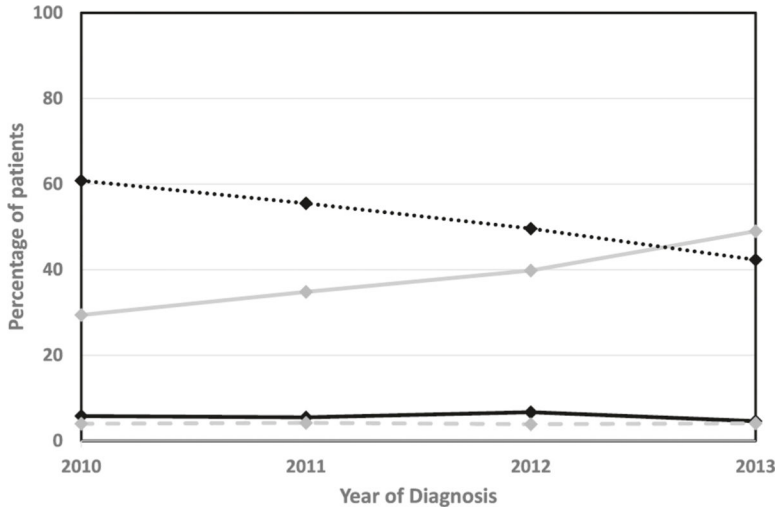

Fig. 2.

Treatment patterns over time for men with a low-risk prostate cancer. No treatment Radiation Surgery Other .

Table 1

Patient characteristics, SEER-Medicare cohort diagnosed with low-risk prostate cancer 2010–2013, overall and by receipt of treatment within one year following diagnosis.

Variable	Level	Overall	Active treatment during 1st year	
		***N*= 7573**	**No (*N*= 2796)**	**Yes (*N*= 4777)**
Age	<77	6404 (84.6)	2262 (80.9)	4142 (86.7)
	77+	1169 (15.4)	534 (19.1)	635 (13.3)
Race	Black	727 (9.8)	237 (8.8)	490 (10.4)
	Other	212 (2.9)	88 (3.3)	124 (2.6)
	White	6446 (87.3)	2371 (87.9)	4075 (86.9)
	Missing	188	100	88
Ethnicity	Hispanic Non-Hispanic	432 (5.7)	113 (4.0)	319 (6.7)
		7141 (94.3)	2683 (96.0)	4458 (93.3)
Married/partner	No	1276 (19.7)	489 (21.2)	787 (18.9)
	Yes	5188 (80.3)	1818 (78.8)	3370 (81.1)
	Missing	1109	489	620
Income (ZIP code median)	<$40,000	2389 (33.5)	724 (27.6)	1665 (36.9)
	$40–60,000	2458 (34.5)	931 (35.5)	1527 (33.9)
	>$60,000	2285 (32.0)	970 (37.0)	1315 (29.2)
	Missing	441	171	270
Charlson comorbidity index	0	4396 (58.7)	1673 (60.9)	2723 (57.4)
	1 2+	1751 (23.4)	628 (22.9)	1123 (23.7)
	Missing	1340 (17.9)	444 (16.2)	896 (18.9)
		86	51	35
PSA (ng/mL)	<4	1104 (14.6)	460 (16.5)	644 (13.5)
	4–9.9	6469 (85.4)	2336 (83.5)	4133 (86.5)
Derived AJCC 7th Edition stage	T1c	6711 (88.6)	2595 (92.8)	4116 (86.2)
	T2a	862 (11.4)	201 (7.2)	661 (13.8)
Year of diagnosis	2010	2265 (29.9)	666 (23.8)	1599 (33.5)
	2011	2261 (29.9)	786 (28.1)	1475 (30.9)
	2012	1620 (21.4)	645 (23.1)	975 (20.4)
	2013	1427 (18.8)	699 (25.0)	728 (15.2)

Table 2

Univariable and multivariable models evaluating expectant management for low-risk prostate cancer, n= 6001 (multivariable).

Variable	Level	Univariable odds ratio (95% CI)	*p* value	Multivariable odds ratio (95% CI)	*p* value
Age	<77	Reference	<0.01	Reference	<0.01
	77+	1.53 (1.30, 1.80)		1.32 (1.19, 1.45)	
Race	White	Reference	0.46	-	-
	Black	0.86 (0.66, 1.12)			
	Other	1.07 (0.91, 1.25)			
Ethnicity	Non-Hispanic	Reference	<0.01	Reference	<0.01
	Hispanic	0.51 (0.40, 0.66)		0.76 (0.67, 0.86)	
Married/partner	Yes	Reference	0.07	Reference	0.02
	No	1.13 (0.99, 1.30)		1.09 (1.01, 1.16)	
Income (ZIP code median)	<$40,000	Reference	<0.01	Reference	<0.01
	$40–60,000	1.42 (1.24, 1.61)		1.26 (1.13, 1.40)	
	>$60,000	1.79 (1.50, 2.12)		1.37 (1.20, 1.57)	
Comorbidity	2+	Reference	0.02	Reference	0.06
	0	1.18 (1.05, 1.33)		1.08 (1.01, 1.16)	
	1	1.10 (1.00, 1.21)		1.08 (0.99, 1.16)	
PSA (ng/mL)	4–9.9	Reference	<0.01	Reference	<0.01
	<4	1.27 (1.10, 1.48)		1.25 (1.11, 1.41)	
Derived AJCC stage	T2a	Reference	<0.01	Reference	<0.01
	T1c	2.19 (1.91, 2.53)		1.77 (1.60, 1.96)	
Year of diagnosis	2010	Reference	<0.01	Reference	<0.01
	2011	1.28 (1.15, 1.42)		1.15 (1.05, 1.27)	
	2012	1.61 (1.49, 1.72)		1.39 (1.30, 1.49)	
	2013	2.33 (1.98, 2.74)		1.61 (1.43, 1.82)	

Table 3

Univariable and multivariable models evaluating initial adherence with guideline-concordant active surveillance monitoring protocol[a] *n*= 2067 (multivariable).

Variable	Level	Univariable hazard ratio (95% CI)	*p* value	Multivariable hazard ratio (95% CI)	*p* value
Age	<77	Reference	<0.01	Reference	<0.01
	77+	0.48 (0.42, 0.55)		0.45 (0.39, 0.52)	
Race	White	Reference	<0.01	Reference	<0.01
	Black	0.50 (0.36, 0.70)		0.58 (0.38, 0.87)	
	Other	0.81 (0.62, 1.06)		0.79 (0.59, 1.06)	
Ethnicity	Non-Hispanic	Reference	0.34	-	-
	Hispanic	0.80 (0.50, 1.27)			
Married/partner	Yes	Reference	<0.01	Reference	0.02
	No	0.69 (0.54, 0.88)		0.75 (0.59, 0.96)	
Income (ZIP code median)	<$40,000	Reference	<0.01	Reference	<0.01
	$40–60,000	1.41 (1.15, 1.74)		1.47 (1.15, 1.86)	
	>$60,000	1.97 (1.68, 2.31)		2.04 (1.71, 2.44)	
Comorbidity	2+	Reference	0.08	Reference	0.08
	0	1.44 (1.04, 2.00)		1.18 (0.87, 1.59)	
	1	1.33 (1.03, 1.72)		1.26 (0.99, 1.62)	
PSA (ng/mL)	4–9.9	Reference	<0.01	Reference	<0.01
	<4	1.21 (1.13, 1.29)		1.11 (1.03, 1.20)	
Derived AJCC T stage	T2a	Reference	0.97	-	-
	T1c	0.99 (0.63, 1.55)			
Year of diagnosis	2010	Reference	0.03	Reference	0.22
	2011	0.94 (0.75, 1.17)		0.98 (0.81, 1.17)	
	2012	1.01 (0.87, 1.18)		0.98 (0.85, 1.13)	
	2013	1.14 (1.04, 1.24)		1.12 (1.00, 1.26)	

[a] ≥ one biopsy and ≥ two PSA tests within 24 months of diagnosis.