



Increasing Utilization of Multiparametric Magnetic Resonance Imaging in Prostate Cancer Active Surveillance

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OBJECTIVE	To characterize the use of multiparametric magnetic resonance imaging (mpMRI) in male Medicare beneficiaries electing active surveillance for prostate cancer. mpMRI has emerged as a tool that may improve risk-stratification and decrease repeated biopsies in men electing active surveillance. However, the extent to which mpMRI has been implemented in active surveillance has not been established.
METHODS	Using Surveillance, Epidemiology, and End Results registry data linked to Medicare claims data, we identified men with localized prostate cancer diagnosed between 2008 and 2013 and managed with active surveillance. We classified men into 2 treatment groups: active surveillance without mpMRI and active surveillance with mpMRI. We then fit a multivariable logistic regression models to examine changing mpMRI utilization over time, and factors associated with the receipt of mpMRI.
RESULTS	We identified 9467 men on active surveillance. Of these, 8178 (86%) did not receive mpMRI and 1289 (14%) received mpMRI. The likelihood of receiving mpMRI over the entire study period increased by 3.7% ($P = .004$). On multivariable logistic regression, patients who were younger, white, had lower comorbidity burden, lived in the northeast and west, had higher incomes and lived in more urban areas had greater odds of receiving mpMRI (all $P < .05$).
CONCLUSION	From 2008 to 2013, use of mpMRI in active surveillance increased gradually but significantly. Receipt of mpMRI among men on surveillance for prostate cancer varied significantly across demographic, geographic, and socioeconomic strata. Going forward, studies should investigate causes for this variation and define ideal strategies for equitable, cost-effective dissemination of mpMRI technology. UROLOGY 130: 99–105, 2019. © 2019 Elsevier Inc.

Active surveillance is the gold standard for men with lower risk prostate cancer. Traditional active surveillance protocols rely on transrectal ultrasound-guided biopsies to accurately risk-stratify patients. More recently, new imaging modalities¹ and genomic classifiers² have supplemented traditional protocols to attempt to improve this risk stratification.

Multiparametric resonance imaging (mpMRI) is one of these tools, but its use in active surveillance remains uncharacterized. The potential for mpMRI to improve the monitoring of patients on active surveillance by detecting clinically significant cancers³ and limiting the number of repeat biopsies,^{4,5} may drive widespread uptake. Alternatively, concerns that mpMRI may add unnecessary expense, inconvenience, and anxiety may limit acceptance and use of mpMRI.^{6,7} While most urologists believe mpMRI is beneficial in the management of prostate cancer, many feel that limited access and prohibitive cost are significant barriers to incorporating mpMRI into standard practice.⁸ Where there is uncertainty, there is often variation in practice. As with other expensive technologies,^{4,6} mpMRI use may be more prevalent among higher socioeconomic groups, or within certain regions of the country.^{9,10}

For these reasons, we sought to characterize the use of mpMRI among men on active surveillance using population-level data from the Surveillance, Epidemiology, and

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End Results (SEER)-Medicare data. Understanding factors associated with the adoption of mpMRI represent an initial step in developing strategies to optimize cost-effective and equitable dissemination.

METHODS

Study Population

The SEER-Medicare data files were used to identify men with nonmanaged care Medicare coverage age 66 years or older, and localized prostate (International Classification of Diseases ninth Edition code 185) between 2008 and 2013. Methods for cohort identification closely adhered to prior work using SEER-Medicare data to study prostate cancer active surveillance.¹¹ We included patients 66 years or older who were continuously enrolled in Medicare Parts A and B during the 12 months prior and after diagnosis (henceforth “entitlement criteria”). Patients who did not undergo any definitive treatment within the first year of diagnosis (ie, no surgery, radiation, cryotherapy, or hormone therapy) and who had at least 1 prostate-specific antigen level and/or 1 prostate biopsy in the 2 years after diagnosis were assigned to active surveillance, based on previously described work¹¹ as well as recent data supporting the high sensitivity of this definition for men on prostate cancer active surveillance.¹² We excluded patients who had Gleason score of 4 + 3 = 7 or greater pathology as surveillance is not a recommended management strategy for this group.¹³

Outcomes

The primary outcome of this analysis is receipt of mpMRI as part of active surveillance. To define this outcome, we identified whether men received a pelvic MRI during active surveillance (Healthcare Common Procedure Coding System codes 72195, 72196, 72197, and 72198 with or without MRI guidance for needle placement [Healthcare Common Procedure Coding System 77021]) after their first biopsy (henceforth “index biopsy”).

Patient demographic and pathological information were obtained using the SEER Patient Entitlement and Diagnosis Summary File. Local census tract information (ie, ZIP code-level educational attainment, population of the county of residence, and ZIP code-level median household income) were obtained. Geographic region (northeast, south, central, and west) was categorized based on SEER region at the time of prostate cancer diagnosis. Pathologic information included tumor grade and stage classification based on the 2005 International Society of Urological Pathology Consensus.¹⁴ Patient comorbidity was determined using the Charlson-Klabunde method in the 12 months leading up to diagnosis.¹⁵

Statistical Analysis

We summarized demographic, socioeconomic, and pathologic characteristics of men in the cohort, stratified by receipt of mpMRI, using frequencies and percentages. Tests for associations were conducted using Chi-square or Fisher exact tests for categorical variables, and Students *t* tests or Wilcoxon Rank-Sum tests for continuous variables. Strength and direction of associations between covariates and receipt of mpMRI were assessed using odds ratios and 95% confidence intervals. Unadjusted odds ratios were calculated based on unadjusted logistic regression models. We then fit a multivariable logistic regression model to examine patient factors that were independently associated with receipt of mpMRI. We included variables from the unadjusted

analysis with a *P* < .05 and also enhanced the model by adding additional factors into the multivariable model whose effects were deemed clinically important (ie, age, sex, race, comorbidity, marital status, stage, and grade). We then used this model to calculate the adjusted yearly probability of receiving mpMRI. To test the hypothesis that MRI uptake may be greater in men with Gleason 3 + 4 disease, we assessed for an interaction between Gleason score and MRI use/year. We also performed a sensitivity analysis calculating the adjusted yearly probability of receiving MRI stratified by Gleason 3 + 3 and 3 + 4.

All analysis were performed using SAS v9.4 (Cary, NC) and R (version 3.4.1) using the packages dplyr¹⁶ for data management, compareGroups¹⁷ for descriptive tables, and ggplot2¹⁸ for graphics. Statistical significance was set at 0.05. The study protocol was deemed exempt by the University of Pittsburgh Institutional Review Board.

RESULTS

We identified 9467 male Medicare beneficiaries diagnosed with prostate cancer and managed with active surveillance between 2008 and 2013. Of these, 1289 (14%) received mpMRI. The demographic, socioeconomic, and clinical information for the men in the prostate cancer surveillance cohort is summarized in Table 1. Overall, most of the men in the cohort were under 75 years, white, married, had low comorbidity burden, Gleason score 3 + 3, lived in higher educational attainment areas, higher income areas, densely populated areas, and there was greater representation in SEER from the northeast and west (Table 1). Median time on surveillance was 44 months overall (interquartile range [IQR] 29-63 months). MRI took place at a median of 14.1 months from the time of diagnosis (IQR 3.8-27 months). Most (62%) MRI were performed after the initial biopsy establishing diagnosis, but before the first biopsy on surveillance (sometimes referred to as “confirmatory biopsy”).¹⁹ However, 494 (38%) MRI were performed after the confirmatory biopsy. Within the cohort, follow-up ceased because of mortality (all-cause) in 8%, treatment in 24% (and end of entitlement criteria 68%. Among the men having MRI, 394 were treated after receiving MRI and 194 of these treatment events (49%) occurred within 90 days post-MRI. Among the 1289 men receiving mpMRI, the median number of mpMRI performed was 0.38 per year (IQR 0.25-0.61) presenting approximately 1 mpMRI every 3 years. This corresponds to 950 (74%) men receiving 1 MRI during surveillance, 256 (20%) men receiving 2 MRI, and 83 (6%) receiving ≥3 MRI.

The results of the unadjusted and multivariable analyses are shown in Table 2. Men who were younger, white, healthier, lived in more populated communities, higher income communities, lived in the northeast or west (compared to the south and midwest), and those diagnosed more recently had greater odds of receiving an mpMRI (Table 2). Gleason score and education level were not significantly different for those who did or did not receive an mpMRI (Table 2). There was no interaction in the model between Gleason score and MRI use over time. Similarly, when the yearly probability of receiving MRI was recalculated by Gleason score, there was no difference in direction of effect or effect size.

The adjusted probability of receiving an mpMRI during the study period increased from 11.8% to 15.5% from 2008 to 2013, representing an overall increase of 3.7% for the entire study period (*P* = .004; test for trend, Fig. 1).

Table 1. Characteristics of the Medicare cohort on active surveillance stratified by receipt of multiparametric MRI (mpMRI)

	No mpMRI (N = 8178)	mpMRI (N = 1289)	P value*
Age at diagnosis (%)			<.001
66-69	1664 (20)	422 (33)	
70-74	2661 (33)	497 (39)	
75-79	2155 (26)	267 (21)	
80 and older	1698 (21)	103 (7)	
Race (%)			<.001
White	6861 (84)	1119 (87)	
Black	788 (10)	76 (6)	
Other	529 (6)	94 (7)	
Marital status (%)			<.001
Married	4196 (51)	771 (60)	
Not married	1191 (15)	171 (13)	
Unknown	2791 (34)	347 (27)	
Comorbidity (%)			<.001
0	4721 (58)	892 (69)	
1	1941 (24)	246 (19)	
2 or more	1516 (18)	151 (12)	
Gleason score (%)			.002
3 + 3 or less	6184 (76)	1027 (80)	
3 + 4	1994 (24)	262 (20)	
Education level in the ZIP code of residence (%)			<.001
Low (<75% with high school education)	882 (11)	92 (7)	
High (>75% with high school education)	7296 (89)	1197 (93)	
County of residence population (%)			<.001
1,000,000 or more	4420 (54)	861 (66)	
250,000-999,999	1378 (17)	214 (17)	
Less than 250,000	2380 (29)	214 (17)	
Median household income in ZIP code of residence, \$ (%)			<.001
\$60,000 or less	4221 (52)	422 (33)	
\$60,001 or more	3957 (48)	867 (67)	
U.S. geographic region (%)			<.001
Northeast	1322 (16)	366 (28)	
South	2060 (25)	170 (14)	
Central	1608 (20)	120 (9)	
West	3188 (39)	633 (49)	
Year of diagnosis (%) ¹			<.001
2008	1346 (17)	165 (13)	
2009	1382 (17)	205 (16)	
2010	1457 (18)	199 (15)	
2011	1536 (19)	243 (19)	
2012	1212 (14)	233 (18)	
2013	1245 (15)	244 (19)	

* Due to the requirement of 2 years claims data follow-up, rates of AS in the later study years should not be taken as a true denominator.

DISCUSSION

In this population-based study we characterize patterns of mpMRI utilization for men on surveillance for localized prostate cancer between 2008 and 2013. There are several key implications from this analysis. First, mpMRI was uncommon, with only 14% of men on surveillance receiving mpMRI. Second, the uptake of mpMRI in active surveillance was relatively slow with an increase of only 3.7% over the 5 years analyzed. Finally, use of mpMRI varied significantly across geographic regions and among socioeconomic strata.

There are several factors that may explain the slow uptake of mMRI from 2008 to 2013. During this time period, there was considerable variation in the way prostate MRI sequences were reported.²⁰ This variation likely contributed to the slow adoption of this technology due

to difficulty of interpretation by both radiologists and urologists. The prostate imaging reporting and data system classification for structured reporting of the probability of cancer risk was introduced in 2012.²¹ Prostate imaging reporting and data system version 2 further refined the classification system and allowed for more confident and uniform reporting of MRI-detected prostate lesions.²² With better uniformity of reporting and interpretation, we suspect that provider confidence and application of this technology will increase and will be reflected in future population-based studies.

In addition to codification of mpMRI reporting, process-based improvements may yield greater uptake of mpMRI in prostate cancer surveillance in subsequent years relative to this cohort. For example, the 3 Tesla magnet improved imaging quality and eliminated the

requirement for an uncomfortable endorectal coil, both of which were potential barriers to use of mpMRI. Patient adherence to prostate cancer surveillance, which relies on serial testing, places a high premium on any improvement in patient comfort.²³ Moreover, the widespread use of MRI-ultrasound fusion-guided biopsies did not occur until after 2013.^{24,25} Other MRI-guided biopsies are challenged by lack of accuracy (eg, cognitive biopsy) or patient discomfort (eg, in-bore biopsy) as compared to fusion-guided biopsies.²⁶ As the use of fusion technology increases, given its advantages over other biopsy techniques,¹⁹ we hypothesize that mpMRI use in active surveillance will continue to accelerate and will be reflected in future population-based studies.

Finally, there is still a significant ideological barrier to adoption of mpMRI. While most urologists feel it is beneficial in the management of prostate cancer, many believe that access and cost are significant barriers to incorporating this technology into routine practice.⁸ The manner in which mpMRI access improves, and costs diminish, may also determine the extent of use in the future.

Our multivariable analysis suggests that mpMRI use varies significantly across racial, socioeconomic, and geographic groups. This observation is concordant with investigations of other costly technologies (ie, stereotactic body radiation for prostate cancer), which demonstrate greater use among white, higher socioeconomic groups, and within certain regions of the country.^{9,10,27} In this analysis, increasing income was associated with higher

Table 2. Unadjusted and adjusted logistic regression models assessing odds of receiving mpMRI among Medicare beneficiaries on active surveillance for localized prostate cancer

Covariate	Unadjusted Analysis		Multivariable Analysis*	
	Odds Ratio (95% CI)	P value	Adjusted Odds Ratio (95% CI)	P value
Age at diagnosis		<.001		<.0001
66-69	Reference		Reference	
70-74	0.74 (0.64-0.85)		0.77 (0.66-0.89)	
75-79	0.49 (0.41-0.58)		0.54 (0.45-0.63)	
80 or more	0.24 (0.19-0.30)		0.26 (0.21-0.33)	
Race (self-reported)		<.001		.04
White	Reference		Reference	
Black	0.59 (0.46-0.75)		0.72 (0.55-0.93)	
Other	1.09 (0.86-1.36)		0.99 (0.78-1.26)	
Marital status		<.001		.006
Married	Reference		Reference	
Not married	0.78 (0.65-0.93)		0.88 (0.73-1.06)	
Unknown	0.68 (0.59-0.77)		0.80 (0.69-0.92)	
Charlson-Klabunde comorbidity index		<.001		<.0001
0	Reference		Reference	
1	0.67 (0.58-0.78)		0.73 (0.63-0.86)	
2 or more	0.53 (0.44-0.63)		0.66 (0.54-0.79)	
Gleason score		.002		.593
3+3 or less	Reference		Reference	
3+4	0.79 (0.68-0.91)		1.04 (0.90-1.21)	
Education level in the ZIP code of residence		<.001		.864
Low (<75% with high school education)	Reference		Reference	
High (>75% with high school education)	1.57 (1.26-1.98)		0.98 (0.76-1.26)	
County of residence population		<.001		.0008
1,000,000 or more	Reference		Reference	
250,000-999,999	0.80 (0.68-0.94)		0.86 (0.72-1.01)	
Less than 250,000	0.46 (0.39-0.54)		0.71 (0.59-0.86)	
Median household income in ZIP code of residence		<.001		.0001
\$60,000 or less	Reference		Reference	
\$60,001 or more	2.19 (1.94-2.48)		1.36 (1.16-1.59)	
U.S. geographic region		<.001		<.0001
Northeast	Reference		Reference	
South	0.30 (0.25-0.36)		0.40 (0.32-0.49)	
Central	0.27 (0.22-0.33)		0.35 (0.28-0.45)	
West	0.72 (0.62-0.83)		0.75 (0.65-0.88)	
Year of diagnosis		<.001		.004
2008	Reference		Reference	
2009	1.21 (0.97-1.51)		1.19 (0.95-1.49)	
2010	1.11 (0.89-1.39)		1.02 (0.81-1.28)	
2011	1.29 (1.05-1.60)		1.16 (0.93-1.44)	
2012	1.57 (1.27-1.94)		1.39 (1.11-1.73)	
2013	1.60 (1.29-1.98)		1.39 (1.12-1.74)	

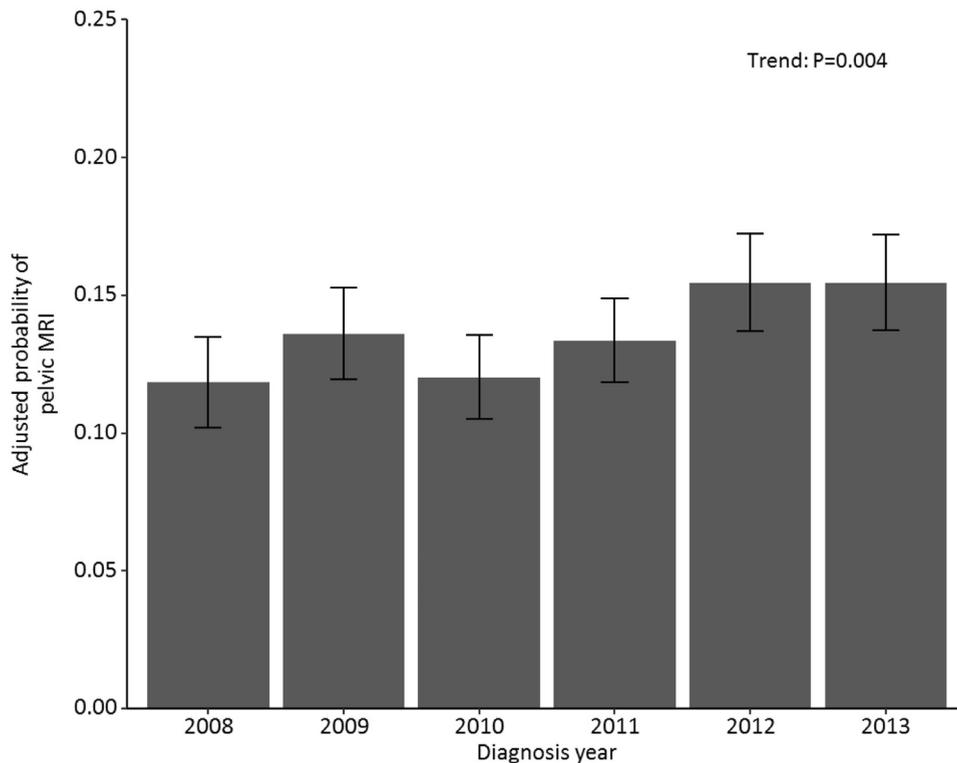


Figure 1. *Adjusted for age, race, marital status, Charlson-Klabunde comorbidity index, Gleason score, ZIP code-level educational attainment, county population, ZIP code-level median household income, and geographic region.

odds of receiving mpMRI. The finding that black men had lower odds of receiving mpMRI is concerning given the large body of evidence supporting worse prostate cancer outcomes overall, and surveillance outcomes specifically, among this group.²⁸ Finally, mpMRI use was more likely in the US northeast and west regions compared to the midwest and south. The northeast and west regions contain markets with high hospital and physician capacity in close geographic proximity²³ which results in significant market competition. This competition may drive increased adoption of new technologies in order to gain a competitive advantage and increase market share.²⁹ Thus, the market dynamic of these regions may explain greater use of mpMRI compared to other regions.

The findings of this study should be considered in the context of several limitations. Using claims data, it is difficult to distinguish active surveillance from watchful waiting as prostate cancer management strategies. However, we took several measures to limit misclassification. Our definition of active surveillance has prior precedent,¹¹ and required evidence of surveillance with billing claims for prostate-specific antigen or prostate biopsy, which would be less commonly performed in men on watchful waiting. Recent work validates the ability of this definition to detect surveillance in administrative claims data.¹² In addition, we limited our cohort to patients with Gleason score $\leq 3 + 4 = 7$ to eliminate patients with higher risk disease, who would be more likely to receive watchful waiting in

lieu of active surveillance. An additional limitation is that there is no specific billing code for prostate MRI. MRI of the pelvis can be performed for other indications beyond prostate cancer surveillance. However, we restricted our cohort to men with billing codes for pelvic MRI and prostate cancer as their only cancer diagnosis, thus minimizing misclassification of MRIs ordered for other malignancies. While pelvic MRI could theoretically be ordered for non-malignant indications, this is likely rare in this patient population. Lastly, our findings are based on retrospective administrative and registry data, which is limited by coding errors, uncaptured claims and unmeasured confounding that may not be fully adjusted for in our multivariable models. Furthermore, we were not able to account for the impact of hospital and provider characteristics in this analysis (eg, academic center, provider volume). However, we adjusted for several measurable clinical and nonclinical factors to minimize confounding, such as age, comorbidity, and Gleason score.

CONCLUSION

From 2008 to 2013, the use of mpMRI in prostate cancer active surveillance in the Medicare population increased incrementally, but significantly. The overall rate of mpMRI use was 14% and increased by a mere 3.7% over the 5 years analyzed. Receipt of mpMRI among men on surveillance for prostate cancer varied significantly across

demographic and socioeconomic strata. This may represent provider uncertainty and access disparities and is a potential target for future work determining ideal implementation of mpMRI technology in prostate cancer active surveillance.

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EDITORIAL COMMENT



The pace of innovation in medical technology continues to accelerate and it can be a challenge for practicing urologists to choose which to adopt.

A study published in this month's issue examined the pattern of use of multiparametric magnetic resonance imaging (mpMRI) in prostate cancer surveillance over a period of 2008-2013.¹ The rate of increase over the 5-year period was 3.7% with only 14% of men on surveillance receiving mpMRI.

There have been many publications in the last few years discussing the role of mpMRI in prostate cancer detection and active surveillance. The American Urological Association suggests that mpMRI be considered during surveillance² and the UK National Institute for Clinical Excellence (NICE) recommends that mpMRI be used for both the selection of men in active surveillance, and during follow-up.³

So why has there not been greater uptake in the use of mpMRI? There are many possible reasons. The first is that this study covered a period from 2008 to 2013. As the authors mentioned, the prostate imaging reporting and data system version 2 classification came out in 2016,⁴ and studies on the use of MRI-ultrasound fusion-guided biopsies occurred after the study period. It is therefore quite likely that the rate of uptake is now higher than this study suggests.

However, mpMRI has not been universally embraced. This may be partly because there isn't a great deal of information on the natural history of prostate cancer findings on serial mpMRI. There remain concerns about false negative mpMRIs that may be related to the quality of the scans or their interpretation.⁵ Cost and availability of this technology are important factors impacting adoption, and the most appropriate imaging schedule is still unknown.

Despite these challenges, it is expected that the use of mpMRI will only increase. A better knowledge of the natural history across timelines will help guide the indications for intervention. Easier accessibility and lowered costs will also drive uptake. Patients who have a strong preference for a non-invasive imaging test rather than an invasive prostate biopsy will demand it. In the end, greater patient awareness will drive increased utilization.

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