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Practice Patterns and Predictors of Followup Imaging after a Negative Bone Scan in Men with Castration Resistant Prostate Cancer: Results from the SEARCH Database

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Abbreviations and Acronyms

ADT = androgen deprivation therapy

CRPC = castration resistant prostate cancer

M0 = nonmetastatic

PC = prostate cancer

PSADT = PSA doubling time

PSAV = PSA velocity

VA = Veterans Affairs

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Purpose: We investigated imaging practice patterns in men with nonmetastatic (M0) castration resistant prostate cancer.

Materials and Methods: We analyzed data on 247 patients with documented M0 CRPC from the SEARCH database. Patients were selected regardless of primary treatment modality and all had a negative bone scan after a castration resistant prostate cancer diagnosis. Cox models were used to test associations of time to a second imaging test with several demographic and clinical factors.

Results: During a median followup of 29.0 months (IQR 12.9–43.5) after a post-castration resistant prostate cancer bone scan was negative, 190 patients (77%) underwent a second imaging test. On univariable analysis patients with higher prostate specific antigen (HR 1.13, $p = 0.016$), shorter prostate specific antigen doubling time (HR 0.79, $p < 0.001$) and faster prostate specific antigen velocity (HR 1.01, $p < 0.001$) were more likely to undergo a second imaging test. Treatment center was also a significant predictor of a second imaging test ($p = 0.010$). No other factor was a significant predictor. Results were similar on multivariable analysis. It was estimated that approximately 20% of men with a prostate specific antigen doubling time of less than 3 months did not undergo an imaging test in the first year after a post-castration resistant prostate cancer negative bone scan. However, 50% of patients with prostate specific antigen doubling time 15 months or greater underwent a second imaging test in the first year.

Conclusions: Clinicians use some known predictors of positive imaging tests to determine which patients with M0 castration resistant prostate cancer undergo a second imaging test . However, there may be under imaging in those at high risk and over imaging in those at low risk. Further studies are needed to identify risk factors for metastasis and form clear imaging guidelines in patients with M0 castration resistant prostate cancer.

Key Words: prostatic neoplasms, prostate specific antigen, radionuclide imaging, neoplasm metastasis, physician's practice patterns

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THE natural history of M0 CRPC is not well characterized. Clear universal practice guidelines are unavailable, providing little guidance of when and how often imaging should be performed to screen for metastasis. The CUA (Canadian Urological Association) recommends that in patients with M0 CRPC and PSADT less than 8 months scanning should be performed every 3 to 6 months and if PSADT is greater than 12 months, scanning should be performed every 6 to 12 months.[1] However, there is little evidence to suggest that these guidelines influence practice patterns. Having better information on imaging practice patterns in patients with M0 CRPC may help guide future practices.

Practice patterns for metastasis screening in PC have not been well explored since most groups have examined practice patterns for newly diagnosed tumors but not M0 CRPC.[2–7] Moreover, studies in the M0 CRPC population have focused on characteristics predicting a positive bone scan but not on imaging practice patterns.[8–10] Similarly other groups investigated predictors of a positive scan at multiple PC stages.[11]

Although such studies identifying factors predictive of metastasis are important, they do not address which factors are actually used by clinicians when making decisions on imaging for metastasis. Studies of imaging patterns in patients newly diagnosed with PC suggest overuse in those at low risk[2–7] and underuse in those at high risk.[2,4,7] Therefore, we evaluated the timing of imaging for metastasis in men with M0 CRPC in the SEARCH (Shared Equal Access Regional Cancer Hospital) database. Specifically in patients with a negative bone scan after CRPC diagnosis we determined which factors predict time to a second imaging test (primary outcome) or time to a second bone scan (secondary outcome) and how this correlates with known predictors of positive imaging tests.

MATERIALS AND METHODS

Study Design

After obtaining institutional review board approval we identified patients with PC who received ADT and had PSA 2 ng/ml or greater at some point after ADT at 2 VA hospitals (San Diego, California and Durham, North Carolina). Data on these patients were combined into SEARCH. After identifying 4,549 patients with ADT we examined the records to identify 668 (14.7%) in whom CRPC developed between 2000 and 2013, and who were classified with M0 disease at that time (fig. 1).

CRPC was defined as a 25% or greater PSA increase and an absolute 2 ng/ml or greater increase from the post-ADT nadir while being castrate.[12] We defined castration as testosterone less than 50 ng/dl, bilateral orchiectomy, or continuous receipt of luteinizing hormone-releasing hormone agonist or antagonist. M0 was defined as an absent positive imaging test for distant metastasis at or before CRPC diagnosis.

We then restricted our cohort to patients proven to have M0 by excluding those without a negative bone scan after CRPC, leaving a cohort of 269 (40.3%). In these

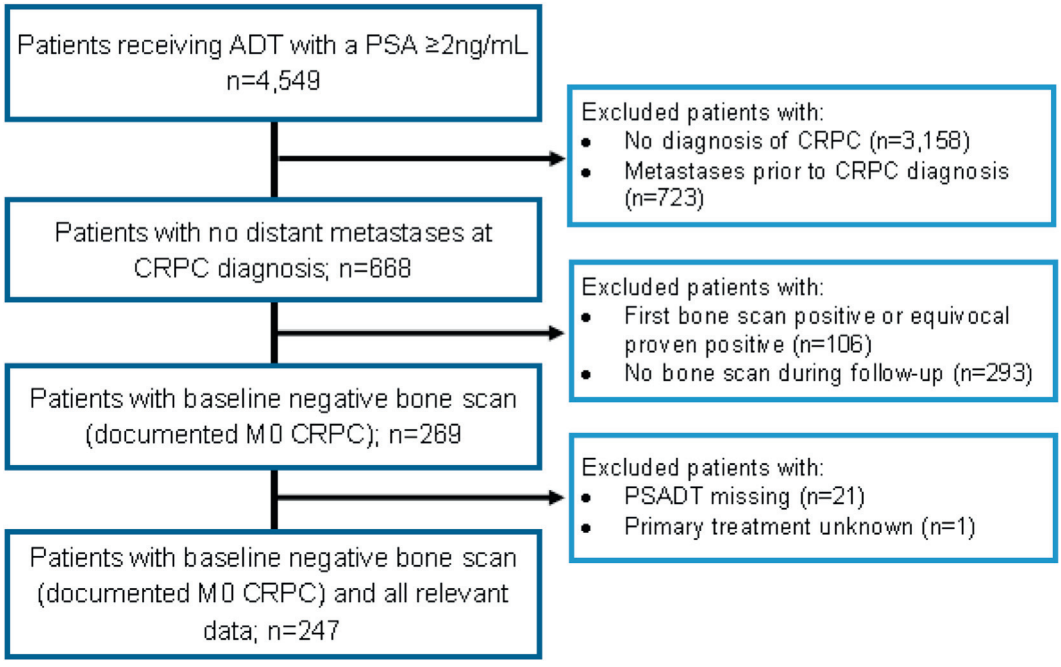

Figure 1. Study cohort CONSORT diagram

patients data were collected on all relevant imaging after CRPC diagnosis up to and including the first positive imaging test, which was coded as positive or negative based on the radiology report. Equivocal tests were considered negative unless confirmed to be positive by a secondary imaging modality/biopsy. Relevant imaging included bone scan, abdomen/pelvic magnetic resonance imaging/computerized tomography, spine imaging and any other imaging tests positive for PC metastasis.

Patients without a second imaging test were censored at the last known followup. We considered a second imaging test any of the relevant imaging tests already defined. Time zero was at the first post-CRPC negative bone scan. Finally, we excluded 21 patients from the study without enough PSA measurements to calculate PSADT or PSAV and 1 with unknown primary treatment. Thus, the study population included 247 patients with documented M0 CRPC.

Statistical Analysis

PSADT was calculated by the natural log of 2 (0.693) divided by the slope of the linear regression of the natural log of PSA with time in months. Patients with PSADT greater than 120 months were assigned a time of 120 months to facilitate analysis. PSAV was calculated as slope of the linear regression of PSA with time in years. PSAV less than the 10th percentile (−4.6 ng/ml per year) or greater than the 90th percentile (64.3 ng/ml per year) were assigned the values of the 10th or 90th percentile, respectively, to facilitate analysis. PSADT and PSAV were calculated using all available PSA values from the CRPC diagnosis to 6 months after the post-CRPC negative bone scan or until the first followup imaging, whichever was first. The rationale for using all of these PSAs was twofold. 1) Physicians are likely to use PSA values after a negative scan to determine the need for followup imaging and 2) this allowed us to calculate PSA kinetics and, thus, include 58 more patients in the study. To calculate PSA kinetics at least 2 PSA values were needed in at least 3 months.

Overall patient characteristics are summarized as the median with the 25th and 75th percentiles for continuous variables, and the frequency and percent for categorical variables. Separate Cox proportional hazards models were used to test associations between predictors and time from post-CRPC negative bone scan to second imaging. We tested certain predictor variables, including age (continuous), year (continuous), race (black vs nonblack), treatment center (center 1 vs 2), biopsy Gleason score (2–6 vs 3 + 4 vs 4 + 3, 8–10), primary localized treatment (none vs radical prostatectomy with or without radiation vs radiation alone), time from ADT to CRPC (continuous), PSA at CRPC diagnosis (continuous and log transformed), time from CRPC to post-CRPC negative bone scan (continuous), PSA (continuous and log transformed), PSADT (continuous and log transformed) and PSAV (continuous). To find the strongest predictors of time to the second imaging test we used forward selection with an entry criterion of $\alpha < 0.10$. Time from the post-CRPC negative bone scan to the second imaging test was compared among PSADT groups using Kaplan-Meier curves and the log rank test.

Sensitivity analysis was done to test whether predictors of time to a second imaging test differed from predictors of time to a second bone scan. To examine this all analyses described were performed using time to a second bone scan as the outcome rather than time to any second imaging test. Statistical analysis was done with Stata® 13.0.

RESULTS

Patient Characteristics

Median followup was 29.0 months (IQR 12.9–43.5). Of our 247 patients with a post-CRPC negative bone scan 190 (77%) and 146 (59%) had a second imaging test and a second bone scan, respectively (table 1). Median age was 76 years and the median year of the post-CRPC negative bone scan was 2007. Of the patients 86 (34%) were black and 164 (66%) were nonblack.

Time to Second Study

Imaging test (primary outcome). On univariable analysis patients with higher PSA (HR 1.13, 95% CI 1.02–1.25, p = 0.016), shorter PSADT (HR 0.79, 95% CI 0.71–0.88, p <0.001) and faster PSAV (HR 1.01, 95% CI 1.01–1.02, p <0.001) were more likely to undergo a second imaging test (table 2). Center 2 patients were more likely to undergo a second imaging test compared to center 1 patients (HR 1.46, 95% CI 1.10–1.95, p = 0.010). However, no other covariates were associated with time to a second imaging test.

Table 1. *Patient characteristics at post-CRPC negative bone scan*

No. pts (%)	247	
Age	76	(68–83)
Median yr (IQR)	2007	(2004–2010)
No. race (%):		
Nonblack	164	(66)
Black	86	(34)
No. treatment center (%):		
1	110	(45)
2	137	(55)
No. biopsy Gleason score (%):		
2–6	45	(18)
3 + 4	45	(18)
4 + 3, 8–10	74	(30)
Unknown/no biopsy	83	(34)
No. primary treatment (%):		
None (watchful waiting/ADT)	105	(43)
Radical prostatectomy ± radiation	65	(26)
Radiation alone	77	(31)
ADT-CRPC interval (mos)	46.4	(25.1–79.1)
PSA at CRPC (ng/ml)	3.9	(2.7–7.5)
Time since CRPC diagnosis (mos)	8.8	(3.9–19.8)
PSA (ng/ml)	7.8	(3.7–18.1)
PSADT (mos)	12.7	(5.6–120.0)
PSAV (ng/ml/yr)	4.4	(0.1–14.7)
2nd Test:		
Imaging	190	(77)
Bone scan	146	(59)
Mean mos followup (IQR)	29.0	(12.9–43.5)

Table 2. *Univariable analysis of second imaging test and second bone scan after post-CRPC negative bone scan*

Predictor	Imaging		Bone Scan	
	HR (95% CI)	p Value (Cox proportional hazards model)	HR (95% CI)	p Value (Cox proportional hazards model)
Age	0.99 (0.97–1.00)	0.098	0.99 (0.97–1.01)	0.166
Yr	1.01 (0.96–1.05)	0.810	1.01 (0.96–1.06)	0.691
Race:				
Nonblack	Referent		Referent	
Black	0.85 (0.63–1.16)	0.303	0.89 (0.62–1.26)	0.497
Treatment center:				
1	Referent		Referent	
2	1.46 (1.10–1.95)	0.010	0.93 (0.67–1.29)	0.662
Biopsy Gleason score:				
2–6	Referent		Referent	
3 + 4	1.07 (0.65–1.74)	0.799	1.17 (0.66–2.07)	0.593
4 + 3, 8–10	1.42 (0.94, 2.15)	0.098	1.62 (0.99, 2.64)	0.055
Unknown/no biopsy	1.13 (0.74–1.71)	0.574	1.26 (0.77–2.05)	0.356
Primary treatment:				
None (watchful waiting/ADT)	Referent		Referent	
Radical prostatectomy ± radiation	1.27 (0.88–1.82)	0.201	1.35 (0.90–2.02)	0.143
Radiation alone	1.17 (0.84–1.64)	0.360	0.98 (0.67–1.45)	0.939
ADT-CRPC interval	1.00 (1.00–1.00)	0.687	1.00 (1.00–1.01)	0.379
Log transformed PSA at CRPC	1.00 (1.00–1.01)	0.109	0.89 (0.72–1.11)	0.303
Time since CRPC diagnosis	1.00 (0.98–1.01)	0.440	1.00 (0.99–1.01)	0.702
Log transformed PSA	1.13 (1.02–1.25)	0.016	1.17 (1.05–1.31)	0.006
Log transformed PSADT	0.79 (0.71–0.88)	<0.001	0.77 (0.68–0.87)	<0.001
PSAV	1.01 (1.01–1.02)	<0.001	1.01 (1.01–1.02)	0.001

Using forward selection only age, treatment center, PSA and PSADT were entered in the model (table 3). Younger age (HR 0.98, 95% CI 0.97–1.00, p = 0.029), treatment at center 2 (HR 1.74, 95% CI 1.28–2.35, p <0.001) and shorter PSADT (HR 0.81, 95% CI 0.73–0.91, p <0.001) were associated with an increased likelihood of a second imaging test. Although not significant, there was a trend between higher PSA and an increased risk of a second imaging test (HR 1.11, 95% CI 1.00–1.24, p = 0.054).

Figure 2 shows Kaplan-Meier curves of time to a second imaging test stratified by previously described PSADT cutoff points (log rank p = 0.0006).[13] It was estimated that approximately 20% of men with PSADT less than 3 months did not undergo a scan within year 1 after the post-CRPC negative bone scan despite a presumed 16-fold or greater increase in PSA, that is at least 4 doublings in 12 months. In contrast, almost half of the patients with PSADT 15 months or greater underwent a second imaging test within the first year after a post-CRPC negative bone scan.

Bone scan (secondary outcome). Patients who had higher PSA at the post-CRPC negative bone scan (HR 1.17, 95% CI 1.05–1.31, p = 0.006), shorter PSADT (HR 0.77, 95% CI 0.68–0.87, p <0.001) and faster PSAV (HR 1.01, 95% CI 1.01–1.02, p = 0.001) were more likely to undergo a second bone scan (table 2). However, using forward selection only PSADT significantly correlated with a second bone scan (HR 0.77, 95% CI 0.68–0.87, p <0.001, table 3). Figure 3 shows time to a second bone scan stratified by previously described PSADT cutoffs (log rank p = 0.0007).[13] One year after a post-CRPC negative bone scan only about half of the patients with PSADT less than 3 months (corresponding to a greater than 16-fold PSA increase in 1 year) had undergone a second

Table 3. *Multivariable analysis of second imaging test and second bone scan after post-CRPC negative bone scan with variables based on forward selection*

Predictor	Imaging		Bone Scan	
	HR (95% CI)	p Value (Cox proportional hazards model)	HR (95% CI)	p Value (Cox proportional hazards model)
Age	0.98 (0.97–1.00)	0.029	–	–
Treatment center:			–	–
1	Referent			
2	1.74 (1.28–2.35)	<0.001		
Log transformed PSA	1.11 (1.00–1.24)	0.054	–	–
Log transformed PSADT	0.81 (0.73–0.91)	<0.001	0.77 (0.68–0.87)	<0.001

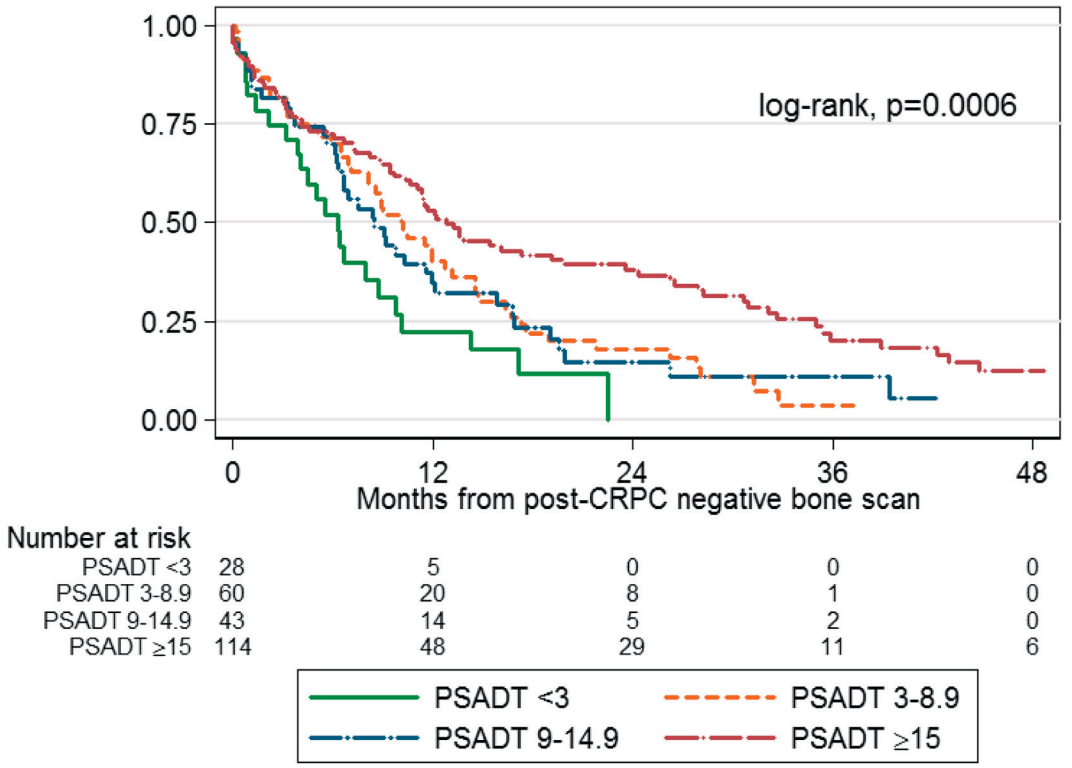

Figure 2. Kaplan-Meier curve of time to second imaging test

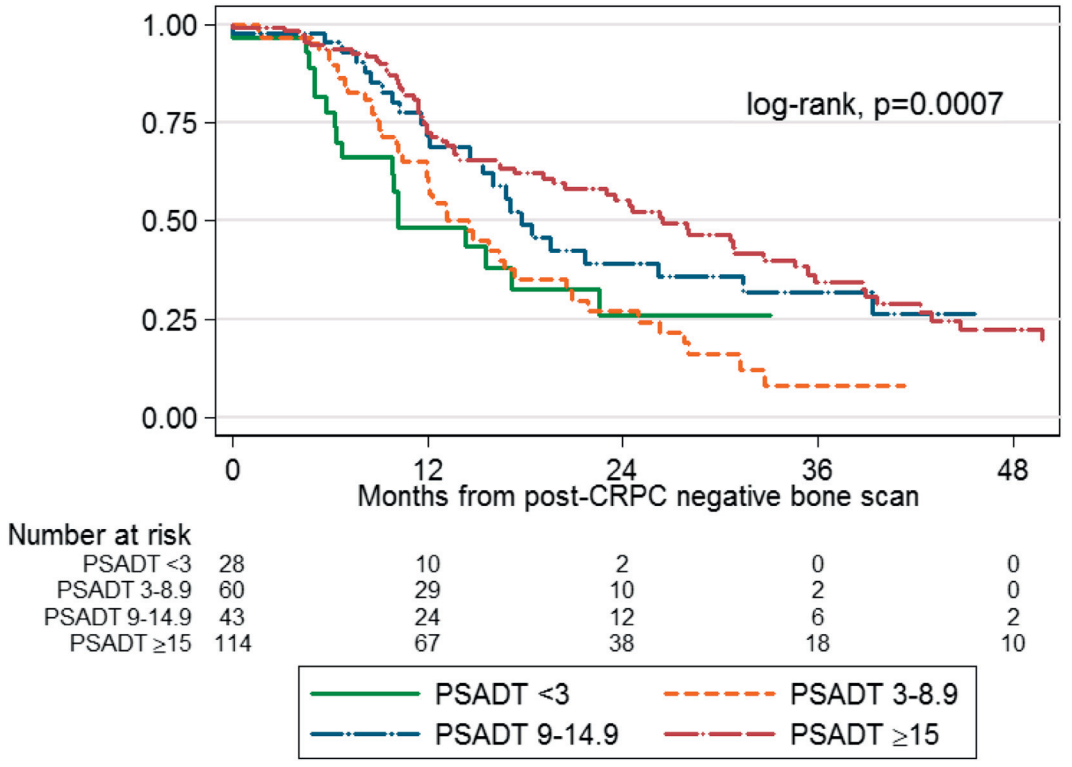

Figure 3. Kaplan-Meier curve of time to second bone scan

bone scan. In contrast, about a quarter of the patients with PSADT 15 months or greater underwent a second bone scan within 1 year after a CRPC negative bone scan, during which period PSA would not have even doubled.

DISCUSSION

Three prior studies in men with M0 CRPC show that higher PSA, shorter PSADT and faster PSAV predict a positive bone scan.[8,9,11] However, 2 of these studies were clinical trials in which regular imaging was protocol mandated, which does not reflect real world practice patterns.[8,9] The third study, which was done by our group, included a subset of men in the current study but examined only surgical patients who received bone scans.[11] Thus, to our knowledge there is no literature on how frequently physicians order imaging tests or what characteristics predict an imaging test in men with M0 CRPC.

Our results suggest that in men with documented M0 CRPC (ie negative imaging after CRPC diagnosis) clinicians use PSA and PSA kinetics as indications for additional imaging. In our cohort a second imaging test (primary outcome) was significantly associated with shorter PSADT and faster PSAV. However, the correlations were weak and in fact much weaker than in prior studies showing that these variables predict metastasis. Thus, while clinicians use known predictors of metastasis to drive imaging, we saw patterns suggesting over scanning in men at low risk and under scanning in men at high risk.

Based on new recommendations from a multidisciplinary group that were published after our data accrued, scanning should be done at each PSA doubling.[14] Based on this recommendation in the first year after documented M0 CRPC the scanning rates should be 100% in men with PSADT less than 3 months and 0% in men with PSADT greater than 15 months. However, only about half of patients with PSADT less than 3 months underwent a followup bone scan within 1 year and approximately 20% underwent no imaging. Conversely of men with PSADT greater than 15 months a quarter underwent a bone scan and almost 50% underwent some imaging in the first year. According to CUA guidelines in patients with PSADT less than 8 months the recommendation would be to scan within 3 to 6 months.[1] However, we found that only 12 of 82 patients (15%) underwent a second bone scan within 6 months. Given the strong prognostic value of PSADT,[11] this likely represents over scanning in men at low risk and under scanning in men at high risk. These observations are consistent with prior literature suggesting that imaging in men newly diagnosed with PC is over used in those at low risk[2–7] and under used in those at high risk.[2,4,7]

This has implications for costs and for patient health. Based on our observations, PSADT is clearly associated with imaging frequency but not at the optimal level. This can best be seen by evaluating the prognostic role of PSADT. In the current results PSADT predicted a second bone scan, although associations were modest (HR 0.79). In contrast, in men with CRPC and no prior imaging, which included all men in the current study, our group previously found that shorter PSADT strongly predicted metastasis (HR 0.53).[15]

Screening patterns varied between the centers, suggesting that nononcological factors drive practice patterns. The 2 centers are academic affiliated VA institutions where there are similar infrastructures and presumably similar knowledge about prognostic factors for metastasis. However, our results are consistent with those of prior studies showing geographic and intercenter variation in PC imaging,[4–6] including a prior VA study.[5] Another VA study of PSA screening practices also identified practice variation, which was notably driven by academic affiliations, the ratio of mid level providers to physicians, and geographical location.[16] Further research is needed to better understand patient, physician and facility level drivers of imaging in men with M0 CRPC.

Similar to prior studies in men with newly diagnosed PC[5] we found that younger men were more likely to undergo a second bone scan. There are several possible explanations. Older men are more likely to have health problems that make it difficult to perform imaging. These comorbidities lead to greater risk of competing mortality, which perhaps results in lower willingness to spend resources to monitor for asymptomatic metastasis. While comorbidity data were unavailable, prior research shows that comorbidities do not strongly influence PC treatment patterns but rather age is the main factor contributing to treatment variation.[17]

Guidelines provide a standardized approach for clinicians to provide care in a consistent and effective manner. Unfortunately there are no universally accepted imaging guidelines in men with documented M0 CRPC. Consequently we found that practice patterns only loosely matched known predictors of metastasis and varied by center. Appropriate scanning is important in men with M0 CRPC because unnecessary screening can be costly and under screening misses early detection of metastasis. Because life extending drugs for CRPC are only approved for metastatic cancer, it is important to detect metastasis early, enabling life extending and complication preventing agents to be used earlier.

The use of guidelines is promising to refine practice patterns and bring them in line with known best practices. For example, a recent study showed that when physicians reviewed imaging guidelines for newly diagnosed PC, they engaged in practice patterns more closely aligned to those guidelines.[18] Hopefully studies such as this that highlight the current state of M0 CRPC imaging patterns will spur interest in developing imaging guidelines in men with M0 CRPC.

One strength of this study is that all men were from the VA and, thus, they had equal access to medical care. However, this also limits the findings to a specific medical environment, which may not reflect universal practice patterns. Because our study was retrospective, we were limited by the information available in the medical records. Thus, we could not distinguish routine imaging tests from those done for cause (ie bone pain). We also did not account for later treatments such as ketoconazole, which may affect PSA and thereby PSA kinetics. In addition, because we collected data through 2013, we could not account for the fact that some men may not have undergone a second imaging test simply because CRPC developed more recently.

We did not evaluate which patients had a positive second imaging test. Therefore, although our data suggest over imaging in men at low risk and under imaging in men at high risk, we cannot definitely state that the imaging practices were inappropriate. Finally, the number of men in this study was small, especially in the group with PSADT less than 3 months. Thus, further studies are needed for validation.

CONCLUSIONS

There is a correlation between known predictors of positive imaging tests and factors used by clinicians to determine the timing of followup imaging tests. However, correlations were modest, suggesting over imaging in men at low risk and under imaging in men at high risk. This likely reflects the lack of clear guidelines to inform imaging practices. Analyses of practice patterns such as this study could help elucidate current practices and inform future practices.

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