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Original Article

Practice patterns and outcomes of equivocal bone scans for patients with castration-resistant prostate cancer: Results from SEARCH

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KEYWORDS
Castration-resistant prostate cancer;
Equivocal test result;
Bone scan;
Radiology report;
Follow-up imaging;
Neoplasm metastasis

Abstract *Objective:* To review follow-up imaging after equivocal bone scans in men with castration resistant prostate cancer (CRPC) and examine the characteristics of equivocal bone scans that are associated with positive follow-up imaging.
Methods: We identified 639 men from five Veterans Affairs Hospitals with a technetium-99m bone scan after CRPC diagnosis, of whom 99 (15%) had equivocal scans. Men with equivocal scans were segregated into "high-risk" and "low-risk" subcategories based upon wording in the bone scan report. All follow-up imaging (bone scans, computed tomography [CT], magnetic resonance imaging [MRI], and X-rays) in the 3 months after the equivocal scan were reviewed. Variables were compared between patients with a positive *vs.* negative follow-up imaging after an equivocal bone scan.
Results: Of 99 men with an equivocal bone scan, 43 (43%) received at least one follow-up imaging test, including 32/82 (39%) with low-risk scans and 11/17 (65%) with high-risk scans ($p = 0.052$). Of follow-up tests, 67% were negative, 14% were equivocal, and 19% were positive. Among those who underwent follow-up imaging, 3/32 (9%) low-risk men had metastases *vs.* 5/11 (45%) high-risk men ($p = 0.015$).
Conclusion: While 19% of all men who received follow-up imaging had positive follow-up imaging, only 9% of those with a low-risk equivocal bone scan had metastases versus 45% of those with high-risk. These preliminary findings, if confirmed in larger studies, suggest follow-up imaging tests for low-risk equivocal scans can be delayed while high-risk equivocal scans should receive follow-up imaging.
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1. Introduction

Metastatic evaluations for castration-resistant prostate cancer (CRPC) routinely rely on technetium-99m (^{99m}Tc) bone scintigraphy for identifying bone metastases, in order to guide clinical decision-making. Roughly one in four bone scans, however, is equivocal: Neither definitive for metastases nor definitively normal [1]. Though treatment options for non-metastatic CRPC patients have advanced some in recent years, determining whether these equivocal lesions are likely to be metastases is crucial, considering that there continue to be vast differences in prognosis and treatment options for metastatic *vs.* non-metastatic CRPC [2].

Despite this, few studies have examined characteristics of equivocal ^{99m}Tc bone scans that may correspond to a greater or lesser risk of a future positive scan. Furthermore, no guidelines exist regarding whether or not to conduct repeat imaging after an equivocal bone scan or which type of imaging test should follow an equivocal bone scan.

To address this limitation in the literature, we reviewed follow-up imaging tests after an equivocal ^{99m}Tc bone scan in men with M0 CRPC (meaning a patient had no distant metastasis at the time of castration-resistance) and examined factors associated with metastases on follow-up imaging. We considered demographic and clinical variables such as prostate-specific antigen (PSA) and PSA doubling time (PSADT) at the time of equivocal bone scan, as well as aspects of the equivocal bone scan itself, such as the language used in the radiology report pertaining to the likelihood of metastases.

2. Materials and methods

2.1. Data collection

After obtaining approval from the Institutional Review Board of the Durham Veterans Affairs Health Care System, we identified 1191 patients with M0 CRPC being treated at Veterans Affairs Hospitals in five cities in the United States (Durham, North Carolina; Augusta, Georgia; San Diego, California; San Francisco, California; West Los Angeles, California) between 2000 and 2015. CRPC was defined per the PSA Working Group 2 criteria: A $\geq$25% PSA increase and an absolute $\geq$2 ng/mL increase from the post-androgen deprivation therapy (ADT) nadir while being castrated [3]. Patients with metastases prior to CRPC were not included in order to limit the study to M0 CRPC patients. We defined castration as a testosterone level of $<$1.74 nmol/L, a bilateral orchiectomy, or the continuous receipt of a luteinizing hormone-releasing hormone (LHRH) agonist or antagonist. Detailed methods on the selection of our M0 CRPC population have been published previously [4]. Once patients with M0 CRPC were identified, we collected information on demographic, clinical, and pathological characteristics, as well as all imaging after M0 CRPC diagnosis from their electronic medical records. Of the 1 191 men with M0 CRPC, 836 (70%) had at least one imaging test after diagnosis of M0 CRPC. Of these, 639 (76%) had one or more ^{99m}Tc bone scans of which 99 (15%) had a bone scan that was equivocal for metastases. For patients with more than one equivocal bone scan, only the first

equivocal scan was included. Charts were reviewed to find all follow-up imaging (bone scan, computed tomography [CT], magnetic resonance imaging [MRI], and/or X-ray targeted to the suspicious lesion) pertaining to the equivocal lesions within 3 months of the equivocal scan. Imaging tests were ordered at the discretion of the treating physician.

Bone scans and all follow-up imaging tests were coded by trained personnel as positive, equivocal, or negative for metastases based upon the language of the radiology report, similar to previous studies of equivocal bone scans [1,5]. Personnel were blinded to follow-up imaging when determining the protocols for categorizing the language of imaging reports. An imaging report was considered negative if it did not mention metastases or if it stated that no metastases were present. A report was considered positive if it stated that metastases were present or if metastases were described as being at least possible and no alternative diagnosis was mentioned. Scans where metastases were the only option put forth by the radiologist were considered positive. An imaging report was considered equivocal if two or more possible diagnoses including metastases were mentioned, or if the imaging report was otherwise interpreted as being inconclusive for metastases (*e.g.* "these findings are of unknown significance and would be an unusual presentation of metastatic disease") (additional examples are provided in Appendix 1). In addition, we created two subcategories of equivocal bone scan reports, "high-risk" equivocal and "low-risk" equivocal, to distinguish between radiology reports of equivocal bone scans that were inconclusive but suggested a high likelihood of metastases (*e.g.* "…suspicion for a metastasis, although it could also represent degenerative change"), and those which were inconclusive but suggested a low likelihood of metastases (*e.g.* "…more suggestive of Paget's disease than mets, although the latter or a combination of both cannot be excluded"). These categories are defined further in Appendix 1. Patients receiving multiple follow-up imaging tests in the 3-month window after the equivocal scan were considered as positive for metastases if any positive imaging was found. Equivocal follow-up imaging tests were considered negative for analysis.

2.2. Statistical analysis

PSADT was calculated by dividing the natural log of two (0.693) by the slope of the linear regression of the natural log of PSA over time in months. PSADT was calculated using all available PSA values in the two years leading up to the equivocal bone scan, or starting at the time of CRPC diagnosis if the equivocal scan occurred within 2 years of CRPC diagnosis.

Patient characteristics were summarized among all men who had an equivocal bone scan as well as those who had follow-up imaging within 3 months, stratified by follow-up imaging test results, using median, 25th and 75th percentiles for continuous variables and frequencies and percentages for categorical variables. The association between clinical and demographic factors and follow-up imaging test result was tested using Wilcoxon rank sum tests for continuous variables and Fisher's exact test for categorical variables. Similarly, characteristics were compared between those who received follow-up imaging *vs.* those who did not. Factors that were tested included age (continuous), year of equivocal bone scan (continuous), PSA at time of equivocal bone scan (continuous, log-transformed), PSADT leading up to equivocal bone scan (continuous), risk rating of the equivocal scan (high-risk *vs.* low-risk), and whether the follow-up scan was within 1 week (yes *vs.* no). We tabulated the number of each follow-up imaging test performed (X-ray, CT, MRI, bone scan) and the number of these that were positive for metastases. Of note, patients with multiple follow-up imaging tests were counted more than once in this analysis. The proportion of positive follow-up imaging following a low-risk equivocal bone scan was compared to that of high-risk scans.

Analyses were performed using Stata 12.1 (Stata, Corp., College Station, TX, USA). The $p < 0.05$ was used to indicate statistical significance.

3. Results

Of 639 men who received at least one ^{99m}Tc bone scan after diagnosis of M0 CRPC, 99 (15%) had an equivocal bone scan. The median age of these 99 patients was 78 years, and 39% of patients were African American (Table 1). Median PSA prior to equivocal scan was 9.2 ng/mL, and median PSADT leading up to equivocal scan was 11.0 months, among those patients with sufficient PSA values to calculate doubling time ($n = 74$). Follow-up imaging tests were ordered for 43 (43%) of the 99 men, including 32 (39%) of the 82 men with low-risk equivocal bone scans and 11 (65%) of the 17 men with high-risk equivocal bone scans ($p = 0.052$). Patients who received a follow-up imaging test had similar age, year, race, PSA, PSADT, and risk rating of equivocal scan compared to patients who did not receive follow-up imaging ($p > 0.05$, data not shown). Of all follow-up imaging tests, 67% were negative, 14% were equivocal, and 19% were positive. Follow-up imaging tests included 32 X-rays, eight bone scans, five MRIs, and 10 CTs. The number of scans is greater than the number of men, as nine men received multiple follow-up imaging tests.

Of the patients who received a follow-up imaging test, eight (19%) had a positive follow-up imaging test (Table 2). Among 32 men with a low-risk equivocal bone scan and subsequent follow-up imaging, only three (9%) had follow-up imaging that was positive for metastases. In contrast, of 11 men with a high-risk equivocal bone scan and follow-up imaging, five (45%) had metastases on follow-up imaging. Patients with high-risk equivocal bone scans were more likely to have metastases on follow-up imaging compared to patients with low-risk equivocal scans (45% *vs.* 9%, $p = 0.017$). Median PSADT was 11.1 months (Q1—Q3: 6.2—15.8) among men with negative follow-up imaging and 16.7 months (Q1—Q3: 4.4—28.8) among men with positive follow-up imaging; however, no statistically significant difference was detected ($p = 0.608$). Similarly, median PSA at equivocal bone scan was 7.9 ng/mL (Q1—Q3: 5.4—14.8) among men with negative follow-up imaging and 14.4 ng/mL (Q1—Q3: 9.6—27.8) among men with positive follow-up imaging, but the difference was not statistically significant ($p = 0.086$). No statistically significant differences were detected between follow-up imaging result and age, year, or follow-up scan within 1 week (all $p > 0.6$).

Table 1 Patient characteristics at time of equivocal bone scan.

Characteristic	Data (n = 99)
Age (year)	78 (69–84)
Year	2006 (2004–2010)
Race	
non-African American	60 (61%)
African American	38 (39%)
PSA (ng/mL)	9.2 (4.8–21.2)
PSADT[a] (month)	11.0 (5.1–27.6)
Risk rating of equivocal scan	
Low	82 (83%)
High	17 (17%)
Received follow-up imaging	43 (43%)
Negative	29 (67%)
Equivocal	6 (14%)
Positive	8 (19%)
Type of follow-up imaging[b]	
X-ray	32 (58%)
Bone scan	8 (15%)
MRI	5 (9%)
CT	10 (18%)

Table displays median (25th percentile, 75th percentile) for continuous variables and frequencies (%) for categorical variables. CT, computed tomography; MRI, magnetic resonance imaging; PSA, prostate-specific antigen; PSADT, prostate-specific antigen doubling time.

[a] Among 74 patients with sufficient PSA values to calculate doubling time.

[b] Total count of follow-up imaging tests is greater than the number of men who received follow-up imaging, as nine men received multiple follow-up imaging tests.

Overall, each follow-up imaging modality was more likely to be positive among those with a high-risk equivocal bone scan rating *vs*. those with low-risk rating (Table 3). However, regardless of risk-rating, men receiving X-rays had a low rate of positive follow-up imaging, although numbers were small (≤14% positive).

Table 3 Type of follow-up imaging test and outcome stratified by low- and high-risk.

Type	Low-risk	High-risk
	positive/performed (%)	positive/performed (%)
X-ray	2/25 (8)	1/7 (14)
Bone scan	2/6 (33)	1/2 (50)
MRI	1/3 (33)	1/2 (50)
CT	1/7 (14)	2/3 (67)

CT, computed tomography; MRI, magnetic resonance imaging.

4. Discussion

Equivocal bone scans are common for men with M0 CRPC, occurring in 15% of the men in our study. Despite this, there are no clear follow-up imaging guidelines for M0 CRPC patients with equivocal scans. While detecting metastases is crucial for clinical decision-making, few studies have examined predictors of positive follow-up imaging after an equivocal bone scan. Only 43% of men in the current study who had equivocal bone scans received targeted follow-up imaging within 3 months. Of these men, 19% were diagnosed with metastases on follow-up imaging. The only factor related to positive follow-up imaging was a "high-risk" rating based on interpretation of the equivocal bone scan radiology report. Among those who underwent repeat imaging, only 9% of patients with a low-risk equivocal bone scan had metastases, whereas 45% of those with high-risk equivocal bone scans had metastases. While numbers are small and require confirmation, if validated, these findings suggest follow-up imaging tests for men with low-risk equivocal scans can be delayed while high-risk equivocal scans should receive follow-up imaging.

In our study of men with M0 CRPC receiving one or more bone scans within the United States Veterans Affairs Health Care System, the rate of equivocal ^{99m}Tc bone scans was 15%. This is in line with previous studies, which reported rates of equivocal scans ranging from 14% to 56% among various cohorts of patients being treated for prostate cancer, with most

Table 2 Associations between clinical factors and follow-up imaging test outcome.

Clinical factors	Follow-up imaging test result		p-Value
	Negative, n = 35 (81%)	Positive, n = 8 (19%)	
Age (year)	80 (71–84)	71 (67–78)	0.091
Year	2006 (2004–2010)	2006 (2005–2009)	0.851
PSA (ng/mL)	7.9 (5.4–14.8)	14.4 (9.6–27.8)	0.086
PSADT[a] (month)	11.1 (6.2–15.8)	16.7 (4.4–28.8)	0.608
High-risk equivocal bone scan rating			0.017
Low	29 (91%)	3 (9%)	
High	6 (55%)	5 (45%)	
Follow-up scan within 1 week			0.612
No	29 (81%)	7 (19%)	
Yes	6 (86%)	1 (14%)	

Table displays median (25th percentile, 75th percentile) for continuous variables and frequencies (%) for categorical variables.
p-Value calculated using Fisher's exact test or rank sum test.
PSA, prostate-specific antigen; PSADT, prostate-specific antigen doubling time.

[a] Data only available on 33 patients.

studies reporting rates of 20%—30% (excluding studies with fewer than 10 equivocal scans) [1,5—9]. However, most of these studies examined men with either newly diagnosed prostate cancer or men with rising PSA after primary therapy. No prior study has examined the rate of equivocal bone scans in the castration-resistant population. Thus, it is difficult to directly compare rates across studies; nonetheless, our rate of equivocal scans was similar to prior studies.

Among the 99 patients with an equivocal bone scan in our study, 43 (43%) received follow-up imaging of the equivocal lesion(s) within 3 months. Most prior studies of equivocal bone scans did not evaluate the frequency of follow-up imaging after equivocal bone scans or were prospective studies with protocol-mandated follow-up imaging for all patients (*i.e.* 100% follow-up imaging). However, one observational study of newly diagnosed patients reported that 60% of patients with equivocal bone scans received additional imaging within 6 weeks before or after the equivocal bone scan, with the majority occurring after the bone scan [1]. This is very similar to the rate of follow-up imaging we found for men with high-risk equivocal scans (65%). In contrast, the low rate of follow-up imaging for men with low-risk equivocal scans (39%) in the current study suggests perhaps that clinicians who treated these patients viewed these scans as negative rather than equivocal with no immediate follow-up required.

Of 43 patients in our study with follow-up imaging after an equivocal bone scan, eight (19%) had metastases on follow-up imaging, including three (9%) of 32 patients with low-risk equivocal scans and five (45%) of 11 patients with high-risk equivocal scans. Prior studies have suggested that the rate of finding metastases among men with an equivocal bone scan ranges from 14% to 62% [1,6—9]. This wide range likely reflects the diverse methods used for follow-up imaging, small sample sizes, and significant differences among the patient populations being studied, none of which were limited to castration-resistant men, though in general, these results were in line with our findings.

Few prior studies examined factors associated with positive follow-up imaging after an equivocal bone scan. In our study, the lack of association between PSA and PSADT and a positive follow-up imaging test was somewhat surprising considering the strong link between PSA, PSADT, and bone metastases seen in other settings, including predicting positive imaging in the initial bone scan in our cohort [4,10—12]. Though these findings may relate to the limited number of patients, nonetheless, given that standard variables (*i.e.* PSA, PSADT) were not associated with positive follow-up imaging, we evaluated the wording within the bone scan report. Our finding that "high-risk" equivocal bone scans are more likely than "low-risk" equivocal bone scans to be followed by a positive imaging test is unsurprising, but may be very clinically useful. While some clinicians may have access to dedicated genitourinary radiologists who can provide direction following an equivocal bone scan, clinicians lacking this resource may find the distinction between high-risk and low-risk equivocal bone scans to be a helpful "rule of thumb". Specifically, if the high-risk *vs.* low-risk distinction is confirmed in future studies, this suggests follow-up imaging tests for men with low-risk equivocal scans may be delayed while high-risk equivocal scans should receive follow-up imaging.

While our data provide some insight into which patients have a high risk of positive follow-up imaging after an equivocal bone scan and should thus receive immediate follow-up imaging, the question of which imaging modality should follow an equivocal bone scan is less clear. Although the small sample size of the study prevents us from making strong conclusions, plain film radiographs (X-rays) were not often positive for metastases with only 8% positive in the low-risk group and 14% in the high-risk group. The other tests (bone scan, MRI, CT) were more likely to show metastases with all being roughly equally likely to be positive. These findings suggest that follow-up imaging with plain X-rays is less helpful and that using cross sectional imaging (CT or MRI) for follow-up imaging is more likely to be diagnostic, though this requires further study in larger data sets. Importantly, the field of imaging for prostate cancer is rapidly evolving and thus, the best technique(s) for both initial scan and follow-up after an equivocal bone scan remain unclear [13].

This study looks at imaging that took place from 2000 to 2015. More recent imaging techniques, such as whole-body MRIs and Gallium-68 prostate-specific membrane antigen (PSMA) positron emission tomography (PET)/CT imaging, which were not widely used in prostate cancer staging for the majority of the period of the study, were not included in the analysis. Ideally, future studies would apply these methods to results from new imaging modalities to evaluate factors that may indicate a higher risk of positive imaging after an equivocal PET scan or full-body MRI, though the higher sensitivity of these techniques may mean that overall number of equivocal scans is reduced [14,15].

Our study has several limitations. First, since this was an observational study, not all patients had follow-up imaging, and patients who did have follow-up imaging were not a random sample of those with equivocal bone scans. The associations that were found do not take into account the probability that a patient receives a follow-up scan or any possible confounders. Furthermore, the follow-up imaging tests did not always evaluate all of the equivocal lesions that had been described on the equivocal bone scan. This may lead to underestimation of the rate of positive follow-up since, and in fact, some of the lesions did not receive follow-up imaging. In addition, the restriction of follow-up imaging to tests that occurred within 3 months is somewhat arbitrary. Patients included in this study received care at five separate facilities and physician experience and practice may have varied between sites [16]. Indeed, we have previously published on practice patterns within the MO CRPC space, though the focus of this study was on identifying which factors can help guide the follow-up to an equivocal scan [17]. Given this limitation, future prospective studies are needed to validate our definition of high-risk *vs.* low-risk equivocal scans. As this was an observational study with a small size, it limits the strengths of the conclusions that can be drawn and may have influenced some of our more surprising results, such as the lack of association of PSA and/or PSADT. Moreover, though we had a sizable percentage of African American, the small overall numbers precluded us from analyzing race-specific results. Though we previously found race does not predict the development of metastases for men with non-metastatic CRPC, future studies are needed to assess whether race affects the follow-up rate of men with equivocal scans. Also,

given the small numbers, it is possible there are other important clinical predictors of future scan positivity that we lacked sufficient power to detect and this should be assessed in future larger studies [18]. We only reviewed ^{99m}Tc bone scans, but bone scans using sodium fluoride or novel markers (*i.e.* PSMA-PET) may be more sensitive and may have detected fewer equivocal scans. The relationship between newer modalities such as PET/CT and ^{99m}Tc bone scans warrant further investigation. However, ^{99m}Tc bone scans continue to have widespread use and remain recommended by some guidelines as front-line tests for detecting bone metastases [19]. Likewise, none of our follow-up imaging included sodium fluoride or novel markers. How this would change the detection of metastases on follow-up requires further study. The heterogeneity of the follow-up imaging in itself is also a limitation, since some types of follow-up imaging, such as X-rays, may be less sensitive to metastases. Follow-up data regarding treatments received after the equivocal scan were not readily available limiting us from assessing whether the equivocal scan resulted in a change in therapy. Finally, we were unable to reliably capture information on symptoms such as bone pain that may have influenced the frequency of follow-up imaging and the likelihood that the subsequent imaging would be positive.

5. Conclusion

In summary, we found that 15% of M0 CRPC patients receiving ^{99m}Tc bone scans have at least one equivocal bone scan, of which only 43% received targeted follow-up imaging within 3 months. While 19% of all men who received follow-up imaging had metastases, only 9% of those with a low-risk equivocal bone scan had metastases, compared to 45% of those with a high-risk equivocal bone scan. Though numbers are small, plain X-rays were less likely than other modalities to be positive when used as a follow-up to an equivocal bone scan. These preliminary findings suggest follow-up imaging tests for men with low-risk equivocal scans can be delayed while high-risk equivocal scans should receive follow-up imaging, though confirmation in larger studies is required.

Author contributions

Study design: Brian Hanyok, Lauren Howard, Stephen Freedland.
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Conflicts of interest

The authors declare no conflict of interest.

Appendix 1 Definitions of "low-risk" and "high-risk" ratings of equivocal bone scan radiology reports.

	Definition	Example(s)
High-risk equivocal definition	The radiology report identifies two or more possible diagnoses, but it suggests that prostate cancer metastases are more likely than the alternatives.	(a) "…suspicion for a metastasis, although it could also represent degenerative change." (b) "…concern is for metastases, however trauma cannot be excluded." (c) "…consistent with metastatic disease given the patient's history, however, the differential diagnosis does include Paget's disease."
Low-risk equivocal definition, Part 1	The radiology report identifies two or more possible diagnoses, but it suggests that prostate cancer metastases are less likely than the alternatives.	(a) "This is likely degenerative, however an early metastasis cannot be entirely excluded." (b) "…may be due to post-traumatic changes or less likely a small met." (c) "…more suggestive of Paget's disease than mets, although the latter or a combination of both cannot be excluded."
Low-risk equivocal definition, Part 2	The radiology report suggests that prostate cancer metastases and another diagnosis are equally likely.	"…nonspecific and may result from focal metastasis or fracture."

(*continued on next page*)

Appendix 1 (*continued*)

	Definition	Example(s)
Low-risk equivocal definition, Part 3	The radiology report does not specifically identify prostate cancer metastases as a possible diagnosis, but it describes the findings as abnormal in the context of a prostate cancer metastatic evaluation.	"Abnormal radiotracer uptake in a linear vertical configuration within the sternum."
Low-risk equivocal definition, Part 4	The radiology report identifies only prostate cancer metastases as a possible explanation of abnormal findings, but it explicitly states that metastases are unlikely.	"These findings are of unknown significance and would be an unusual presentation of metastatic disease."

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