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Predicting bone scan positivity after biochemical recurrence following radical prostatectomy in both hormone-naive men and patients receiving androgen-deprivation therapy: results from the SEARCH database

DM Moreira[1], **MR Cooperberg**[2], **LE Howard**[3,4], **WJ Aronson**[5,6], **CJ Kane**[7], **MK Terris**[4,8], **CL Amling**[9], **M Kuchibhatla**[3], and **SJ Freedland**[4,10,11]

[1]The Arthur Smith Institute for Urology, North Shore Long Island Jewish Health System, New Hyde Park, NY, USA

[2]Departments of Urology, and Epidemiology and Biostatistics, University of California, San Francisco and Urology Section, Department of Surgery, Veterans Affairs Medical Center, San Francisco, CA, USA

[3]Department of Biostatistics and Bioinformatics, Duke University School of Medicine, Durham, NC, USA

[4]Urology Section, Veterans Affairs Medical Center, Durham, NC, USA

[5]Urology Section, Department of Surgery, Veterans Affairs Medical Center, Los Angeles, CA, USA

[6]Department of Urology, University of California at Los Angeles Medical Center, Los Angeles, CA, USA

[7]Division of Urology, Department of Surgery, University of California at San Diego Medical Center, San Diego, CA, USA

[8]Urology Section, Division of Surgery, Veterans Affairs Medical Centers and Division of Urologic Surgery, Department of Surgery, Medical College of Georgia, Augusta, GA, USA

[9]Division of Urology, Department of Surgery, Oregon Health and Science University, Portland, OR, USA

[10]Division of Urology, Department of Surgery, and the Duke Prostate Center, Duke University School of Medicine, Durham, NC, USA

[11]Department of Pathology, Duke University School of Medicine, Durham, NC, USA

Abstract

Correspondence: Dr DM Moreira, The Arthur Smith Institute for Urology, North Shore Long Island Jewish Health System, 450 Lakeville Road, New Hyde Park, NY 11042, USA. dmoreira@nshs.edu.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

BACKGROUND—To evaluate the factors associated with positive bone scans after biochemical recurrence (BCR) following radical prostatectomy in both hormone-naive subjects and subjects after androgen-deprivation therapy (ADT).

METHODS—Retrospective analysis of 380 bone scans of 301 hormone-naive subjects and 214 bone scans of 137 subjects after ADT following BCR from the Shared Equal Access Regional Cancer Hospital database. Generalized estimating equations and local regression plots were used to evaluate bone scan positivity by patients' demographics, pathological features, PSA levels and kinetics.

RESULTS—Among hormone-naive subjects and subjects on ADT, bone scan positivity was seen in 24 (6%) and 65 (30%) subjects, respectively. In hormone-naive subjects, the higher prescan PSA, higher PSA velocity (PSAV) and shorter PSA doubling time (PSADT) were significantly associated with positive scans (P =0.008, P<0.001 and P<0.001, respectively). In subjects after ADT, the prescan PSA, PSAV and PSADT were significantly associated with positive scans (P =0.011, P<0.001 and P =0.002, respectively). Regression plots showed increased scan positivity with increasing PSA levels and shortening PSADT (all P<0.001) for both hormone-naive subjects and subjects after ADT. For a given PSA level and PSADT, subjects on ADT had higher bone scan positivity.

CONCLUSIONS—In both hormone-naive subjects and subjects after ADT, more aggressive and advanced disease identified by higher PSA levels, higher PSAV and shorter PSADT were associated with higher bone scan positivity. For the same PSA level and PSADT, subjects after ADT had higher bone scan positivity than hormone-naive subjects. Therefore, PSA levels and kinetics may be used as selection criteria for bone scan in these patients.

Keywords

disease-free survival; metastasis; mortality; prostatectomy; PSA

INTRODUCTION

Bone scans are routinely used to detect metastasis in patients with prostate cancer; however, most scans are negative.[1] Multiple studies in untreated subjects with prostate cancer suggest that higher PSA levels, higher Gleason scores and more advanced clinical stages are associated with higher risk of a positive bone scan.[2-12] Patients after biochemical recurrence (BCR) following radical prostatectomy are at a higher risk of disease progression and the development of bone metastasis.[13] However, presently it is unclear as to when the screening for bone metastasis should start, how frequent bone scans should be performed and whether the scans should be done at regular time intervals or triggered by changes in clinical or biochemical variables. To answer these important questions, one needs to first identify the factors associated with the development of metastasis and positive bone scans. Previously, Gleason score, clinical stage and PSA kinetics, such as PSA velocity (PSAV) and PSA doubling time (PSADT), have all been correlated with the risk that a given scan will show bone metastasis among hormone-naive men.[14-17] Similarly, in men with castration-resistant nonmetastatic prostate cancer, higher PSA levels and adverse kinetics were independently associated with faster progression to metastatic disease and death.[18,19] These findings

suggest that the above variables could be used to select subjects for bone scan, potentially minimizing the number of negative and perhaps unnecessary scans. However, there are limited tools to stratify patients according to their risk of positive bone scan for metastasis. Therefore, the primary objective of the present study is to determine the factors associated with positive bone scans after BCR following radical prostatectomy in both hormone-naive men and those who had received or were receiving androgen deprivation therapy (ADT) (henceforth 'after ADT') from the Shared Equal Access Regional Cancer Hospital (SEARCH) database. The secondary objective of the study is to use PSA levels and PSADT to stratify bone scans according to the risk of positivity.

MATERIALS AND METHODS

Study population

After obtaining institutional review board approval from each institution, data from prostate cancer patients with BCR following radical prostatectomy undergoing bone scan for suspicion of metastatic disease between 1995 and 2012 at six Veteran Affairs Medical Centers (West Los Angeles, Palo Alto and San Diego, CA; Augusta, GA; Durham and Asheville, NC) were included in the study database.[20] The database included information on the patients' age at the time of bone scan, race, height, weight, preoperative PSA levels, surgical specimen pathology (specimen weight, tumor grade, stage and surgical margin status), follow-up PSA, bone scans and secondary treatments after surgery. Patients treated with preoperative ADT or radiotherapy were excluded from the study. Bone scans following a positive bone scan were excluded. A total of 1 303 bone scans (from 665 subjects) after BCR (defined as a single PSA above 0.2 ng ml^{-1}, 2 PSA at 0.2 ng ml^{-1} or secondary treatment for an elevated PSA level) following radical prostatectomy were identified.[21] Of these, 97 (7%) scans were done after a positive scan and were excluded from the study. A total of 694 (58%) scans had complete data including PSA levels and PSA kinetics at the time of the scan. Of these, 100 scans (8%) with negative PSAV were excluded given that these likely had PSAV determined during the start of ADT when PSA level was declining. Such PSA kinetics do not reflect the long-term PSA trends, they only demonstrate the acute effect of ADT on PSA levels. This resulted in a final study sample of 594 (49%) bone scans (from 401 subjects). Of these, 380 (64%) bone scans were done among 301 men who had not received ADT and 214 (36%) scans were done in 137 subjects after ADT. Bone scans done within 30 days after the start of ADT were considered before ADT. Supplementary Figures S1 and S2 show the number of scans per patient. Secondary treatments for recurrence were at the discretion of the patient and the treating physician. The number and interval of bone scans were also at the discretion of the patient and the treating physician. Bone scans were read by nuclear medicine radiologists. Radiologists were not blinded to patients' demographics, laboratory, radiologic or pathologic results. Bone scan reports were coded as positive or negative based on the radiology report (equivocal scans were considered negative unless confirmed positive by a secondary imaging modality).

Statistical analysis

PSADT was calculated using the natural log of two (0.693) divided by the slope of the linear regression of the natural log of PSA levels over time (in months). Subjects with calculated

PSADT >120 were assigned 120 months for the ease of analysis. PSAV was calculated as the slope of the linear regression of PSA levels over time in years. Subjects were required to have at least two values separated by at least 3 months to have PSA kinetics calculated. All available PSA levels before the bone scan and before ADT but after BCR (that is, >0.2 ng ml^{-1}) were used to calculate preADT PSA kinetics. All available PSA levels before bone scan but after ADT were used to calculate postADT PSA kinetics. Subjects with three or more PSA values over the 3 months or more had PSA kinetics calculated. Statistical analysis was done by stratifying bone scans based on ADT status, that is, whether they were done in hormone-naive subjects or in subjects after ADT. Given the repeated-measures nature of our data, generalized estimating equations were used to compare patients' demographics, pathological features, PSA levels and kinetics between negative and positive scans, grouping by patient (primary objective). PSA levels were then arbitrarily broken down into four groups: 0.0–4.9, 5.0–9.9, 10.0–19.9 and ≥20.0 ng ml^{-1}. Similarly, PSADT was divided into three groups: ≥9, 3–8.9 and <3 months (based on previous studies correlating these values with mortality).[22] Bar plots were used to demonstrate the relative prevalence of positive bone scans by PSA and PSADT groups stratified by ADT status and linear trends were evaluated with generalized estimating equations. We also used local regression (LOESS) plots to graphically represent the relationship between bone scan positivity and PSA level and PSADT as continuous variables stratified by ADT status. Finally, a table of point estimates and 95% confidence intervals for probability of bone scan positivity by PSA and PSADT groups stratified by ADT status were estimated from the generalized estimation equations (secondary objective). All statistical analyses were two-tailed and performed using Stata 11.2 (StataCorp, College Station, TX, USA). A $P<0.05$ was considered statistically significant.

RESULTS

Of the 308 bone scans done among hormone-naive subjects, 24 (6%) scans were positive and 356 (94%) were negative for metastasis (Table 1). The median time from surgery to recurrence was 5 years. A higher pathological Gleason score was observed among positive scans: 50% of the positive scans were done in subjects with Gleason scores of 4 + 3 or 8–10 and only 34% of the negative scans were done in subjects with high-grade Gleason scores. This difference, however, was not statistically significant. Similarly, the prevalence of positive surgical margins, extracapsular extension and seminal vesicle invasion were all higher among positive bone scans but the differences were not statistically significant. The median PSAV values among subjects with positive scans (8.8 ng ml^{-1} per year) was statistically significantly higher than those with negative scans (0.6 ng ml^{-1} per year, $P<0.001$). The median prescan PSA values were significantly higher for positive bone scans (2.9 ng ml^{-1}) compared with negative bone scans (1.1 ng ml^{-1}, $P=0.008$). The median prescan PSADT of subjects with positive bone scans was significantly shorter than those with negative scans (4.7 versus 13.0 months, respectively, $P<0.001$).

Of the 214 bone scans done among subjects after ADT, 65 (30%) scans were positive and 149 (70%) were negative for metastasis (Table 2). The median time from surgery to recurrence and that from surgery to ADT were 6.4 and 11.3 years, respectively. Similar to bone scans done among hormone-naive subjects, the median prescan PSA and PSAV values

were considerably higher (31.0 ng ml^{-1} and 13.4 ng ml^{-1} per year, respectively) for positive bone scans compared with negative bone scans (2.1 ng ml^{-1} and 1.7 ng ml^{-1} per year, correspondingly; all $P<0.05$). The median prescan PSADT for positive bone scans was 3.7 months compared with 7.2 months for negative scans ($P=0.002$).

In both hormone-naive subjects and those after ADT, there was an increase in bone scan positivity with an increase in prescan PSA levels (all P for trend <0.001, Figure 1a). Similarly, among both groups there was an increase in bone scan positivity with shortening prescan PSADT (all P for trend <0.001, Figure 1b). Figure 2a shows the relationship between prescan PSA levels and bone scan positivity. For a given prescan PSA level, the bone scan positivity risk was considerably higher in subjects after ADT compared with hormone-naive subjects. For example, in the postADT setting, a PSA of 25 ng ml^{-1} corresponded to nearly 40% risk of a positive scan, whereas in the hormone-naive setting, the PSA level needed to be >50 ng ml^{-1} before a 40% risk of a positive scan was achieved. Figure 2b shows the relationship between prescan PSADT and bone scan positivity. For a given PSADT, the bone scan positivity was likewise noticeably higher among subjects after ADT compared with hormone-naive subjects.

Given prescan PSA levels and PSA kinetics were the two strongest predictors of bone scan positivity, we developed a table that estimates bone scan positivity by prescan PSA levels and prescan PSADT stratified by ADT status (Table 3). For example, among bone scans done in hormone-naive subjects with PSADT ≥9 months, the estimated bone scan positivity was 5% or less compared with 10% or greater for those with PSADT <9 months. In scans done among subjects after ADT, for the same PSA level and PSADT, the scan positivity was higher compared with scans done in hormone-naive subjects with no group (even PSA <5ng ml^{-1} and PSADT >9 months) having an estimated bone scan positivity risk <10%.

DISCUSSION

With the advances in chemo- and immunotherapies for metastatic prostate cancer in recent years, early detection of metastasis has become more and more important. However, it is not clear when and how patients should be screened for metastasis. Bone scans are routinely used to detect metastasis in patients with prostate cancer; however, a significant number of these scans are negative. To better select patients for bone scans, we evaluated the predictors of positive bone scans. We found that the factors associated with more aggressive and advanced disease such as higher PSA levels, higher PSAV and shorter PSADT were associated with positive bone scans in both hormone-naive subjects and those after ADT. In other words, in both groups there was a statistically significant increase in bone scan positivity with an increase in prescan PSA levels and shortening PSADT. Importantly, for the same prescan PSA level and PSADT, the bone scan positivity was much higher among subjects after ADT. These results suggest that more aggressive and/or advanced diseases are associated with higher risk of a positive bone scan. Furthermore, they suggest that the factors associated with aggressive and advanced disease such as high PSA levels and short PSADT may be used to stratify patients based on risk of a positive bone scan. Indeed, we created a table combining PSA levels and PSADT to predict the risk of a positive bone scan

that may help clinicians estimate the risk of a positive bone scan to help guide imaging for men with BCR after surgery.

Only a few studies evaluated the use of PSA levels and PSA kinetics to predict metastatic disease in patients with recurrent disease after primary treatment for prostate cancer (radical prostatectomy and/or radiotherapy). Slovin *et al*[14] found baseline PSA levels and PSADT were independently predictive of metastatic progression. However, in their study, they did not evaluate different PSA and PSADT cut points. Also, they did not include patients receiving ADT. Similarly, Okotie *et al*,[15] studying hormone-naive patients after BCR following radical prostatectomy, found the risk of metastasis to have increased with PSADT shorter than 6 months (especially those with PSA levels >10 ng ml^{-1}). Likewise, Dotan *et al*,[16] also studying hormone-naive patients, found PSA levels and kinetics to be associated with the risk of a positive bone scan. They used pathological and biochemical variables to create a nomogram to predict bone scan positivity. In our study of patients after BCR following radical prostatectomy, we also observed an association between PSA levels and PSA kinetics with bone metastasis. Furthermore, we evaluated the prevalence of positive bone scans across multiple PSA and PSA-kinetic groups. Our results suggest that, for hormone-naive subjects, screening should start once PSADT is shorter than 9 months, given the risk of a positive bone scan in subjects with PSADT ≥9 months is 2% or less. Even among men with high PSA values, the estimated risk of a positive bone scan in hormone-naive men with a long PSADT was very low. For subjects after ADT, we were unable to identify a subgroup where the risk of a positive scan was that low. Even the lowest risk groups (that is, low PSA levels and long PSADTs) had a risk of a positive scan of 10% or greater. This suggests that bone scan for patients after ADT should begin early—even before the PSA level reaches 5 ng ml^{-1} regardless of PSADT. Assuming the initial bone scan is negative, PSA levels and PSADT can be used to estimate the risk of a positive bone scan in these patients and help guide the timing of subsequent imaging.

The main limitation of the present study is its retrospective nature. Consequently, we were not able to decide when and how bone scans were performed. It is plausible that patients with more advanced and aggressive disease at baseline had more and earlier bone scans in comparison to those with less advanced and aggressive disease for whom the bone scan may have been deferred to a later point of time. If this hypothesis is true, some patients with worse disease were more likely to be diagnosed with metastasis, whereas a number of patients with more favorable disease may have been excluded from the study, given they have never had a single bone scan. Similarly, we had no control over when and how patients were treated with ADT. Moreover, nearly 40% of our sample had missing PSA kinetics and were excluded from the study. In addition, PSA measurements were not systematic and were at the discretion of the treating physician, which also adds noise and unwanted variability to the study. Also, repeated measures were present in our data (that is a single patient had more than one bone scan), which increase the complexity of our statistical analysis. In addition, the small number of events—especially in the hormone-naive population, resulted in large confidence intervals in our ability to estimate bone scan positivity as a function of PSA and PSADT. Finally, although bone scans are very sensitive to detect metastasis, false positive

and negative do occur, but we were unable to identify them given the confirmatory imaging was not available for all patients in our sample.[23]

In conclusion, among prostate cancer patients with BCR following radical prostatectomy, for a given PSA level and PSADT, subjects after ADT had a higher risk of bone scan positivity. More aggressive and advanced disease identified by higher PSA levels, higher PSAV and shorter PSADT were associated with higher risk of a positive bone scan. Therefore, PSA level and PSA kinetics may be used as selection criteria for performing bone scans in both hormone-naive subjects and subjects after ADT.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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DISCLAIMER

The views and opinions of, and endorsements by, the author(s) do not reflect those of the US Army or the Department of Defense.

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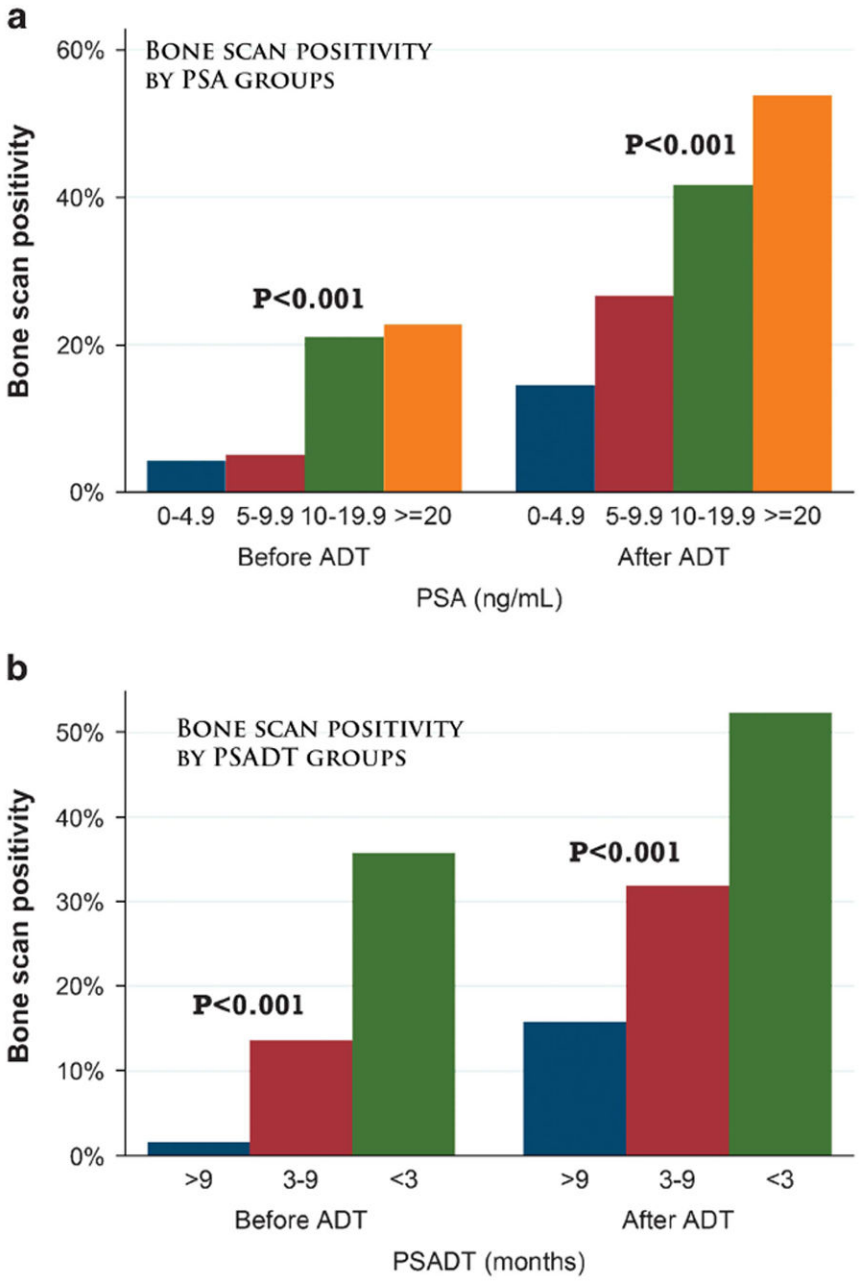

Figure 1.

Bone scan positivity by prescan PSA (**a**) and PSADT (**b**) groups. ADT, androgen-deprivation therapy; PSADT, PSA doubling time.

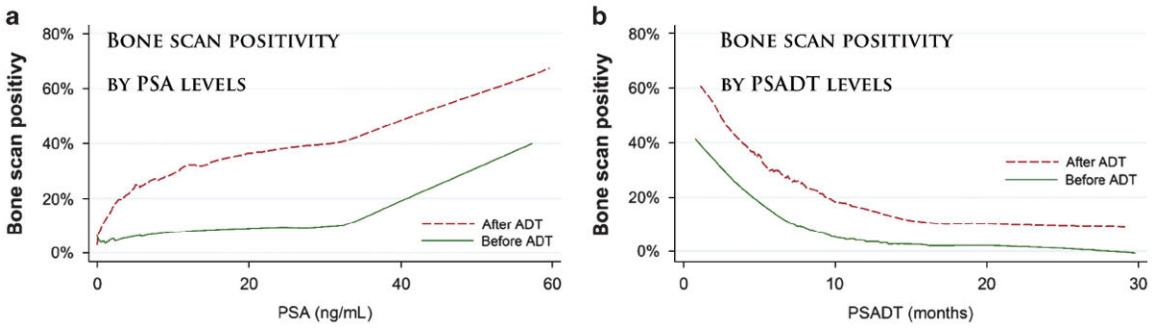

Figure 2.

Bone scan positivity by prescan PSA (**a**) and PSADT (**b**) levels. ADT, Androgen deprivation therapy; PSADT, PSA doubling time.

Table 1

Bone scans done after BCR and before ADT

Variables	Positive bone scan	Negative bone scan	OR (95% CI)[a]	P[b]
Bone scans, Total *N* (%)	24 (6)	356 (94)	—	—
Age (years), median (Q1, Q3)	69 (65, 77)	68 (64, 74)	1.03 (0.97–1.08)	0.352
Race, N (%)				0.628
White	16 (67)	231 (65)	ref.	
Black	6 (25)	109 (31)	0.79 (0.30–2.07)	
Other	2 (8)	16 (4)	1.81 (0.38–8.49)	
Year of scan (years), median (Q1, Q3)	2004 (1998, 2008)	2004 (1999, 2007)	0.98 (0.90–1.07)	0.704
Preoperative PSA (ng ml^{-1}), median (Q1, Q3)	11.9 (7.2, 18.2)	9.2 (5.7, 16.7)	1.00 (0.996–1.003)	0.808
Pathological Gleason score, N (%)				0.411
2–6	3 (17)	76 (25)	ref.	
3+4	6 (33)	127 (41)	1.20 (0.29–4.93)	
4+3, 8–10	9 (50)	107 (34)	2.13 (0.56–8.13)	
Positive surgical margins, *N* (%)	11 (61)	162 (56)	1.23 (0.46–3.24)	0.681
Extracapsular extension, *N* (%)	11 (58)	104 (36)	2.46 (0.97–6.23)	0.057
Seminal vesicle invasion, *N* (%)	5 (26)	64 (20)	1.45 (0.51–4.15)	0.486
Lymph nodes, N (%)				0.932
Positive	1 (4)	11 (3)	1.45 (0.18–11.91)	
Negative	16 (73)	257 (73)	ref.	
Unknown	5 (23)	85 (24)	0.94 (0.34–2.65)	
Prescan PSA (ng ml^{-1}), median (Q1, Q3)	2.9 (0.6, 12.3)	1.1 (0.4, 3.4)	1.03 (1.01–1.05)	0.008
Prescan PSADT (months), median (Q1, Q3)	4.7 (3.1, 7.8)	13.0 (7.9, 23.9)	0.25 (0.14–0.47)[c]	<0.001
Prescan PSAV (ng ml^{-1} per year), median (Q1, Q3)	8.8 (1.7, 42.0)	0.6 (0.2, 1.5)	1.06 (1.03–1.09)	<0.001
Time from BCR to scan (months), median (Q1, Q3)	31.5 (21.7, 62.0)	30.1 (13.3, 59.8)	1.00 (0.99–1.01)	0.848

Abbreviations: ADT, androgen-deprivation therapy; BCR, biochemical recurrence; CI, confidence interval; OR, odds ratio; PSADT, PSA doubling time; PSAV, PSA velocity; Q1, 25th percentile; Q3, 75th percentile; ref., reference group.

Missing values indicate that the model did not converge.

[a] Odds ratios are estimated using GEE logistic regression.

[b] *P*-values are for the significance of the covariate in predicting risk of a bone scan being positive, across all patients.

[c] log-transformed PSADT was used in this analysis.

Table 2

Bone scans done after BCR and after ADT

Variables	Positive bone scan	Negative bone scan	OR (95% CI)[a]	P[b]
Bone scans, *N* (%)	65 (30)	149 (70)	—	—
Age (years), median (Q1, Q3)	71 (65, 76)	70 (64, 77)	1.01 (0.98–1.05)	0.502
Race, N (%)				0.550
White	47 (73)	98 (66)	ref.	
Black	15 (24)	45 (30)	0.70 (0.36–1.36)	
Other	2 (3)	6 (4)	0.71 (0.14–3.63)	
Year of scan (years), median (Q1, Q3)	2006 (2001, 2008)	2006 (2003, 2008)	0.94 (0.88–1.01)	0.088
Preoperative PSA (ng ml^{-1}), median (Q1, Q3)	10.5 (6.4, 17.9)	9.4 (6.4, 15.2)	1.00 (0.9998–1.0002)	0.391
Pathological Gleason score, N (%)				0.097
2–6	9 (15)	9 (7)	ref.	
3+4	14 (23)	45 (33)	0.30 (0.10–0.90)	
4+3, 8–10	38 (62)	80 (60)	0.44 (0.16–1.18)	
Positive surgical margins, *N* (%)	33 (57)	75 (60)	0.86 (0.46–1.60)	0.631
Extracapsular extension, *N* (%)	33 (58)	60 (49)	1.42 (0.76–2.66)	0.272
Seminal vesicle invasion, *N* (%)	29 (48)	57 (41)	1.31 (0.73–2.35)	0.361
Lymph nodes, N (%)				0.941
Positive	6 (9)	16 (11)	0.84 (0.31–2.26)	
Negative	51 (80)	116 (78)	ref.	
Unknown	7 (11)	17 (11)	0.95 (0.37–2.41)	
Prescan PSA (ng ml^{-1}), median (Q1, Q3)	31.0 (5.6, 151.3)	2.1 (0.4, 13.2)	1.002 (1.0006–1.004)	0.011
Prescan PSADT (months), median (Q1, Q3)	3.7 (2.9, 6.9)	7.2 (4.1, 13.9)	0.58 (0.41–0.82)[c]	0.002
Prescan PSAV (ng ml^{-1} per year), median (Q1, Q3)	13.4 (4.3, 48.9)	1.7 (0.44, 6.0)	1.011 (1.005–1.016)	<0.001
Time from BCR to scan (months), median (Q1, Q3)	55.6 (33.8, 107.6)	71.8 (39.4, 105.5)	0.998 (0.991–1.004)	0.491

Abbreviations: ADT, androgen deprivation therapy; BCR, biochemical recurrence; CI, confidence interval; OR, odds ratio; PSADT, PSA doubling time; PSAV, PSA velocity; Q1, 25th percentile; Q3, 75th percentile; ref., reference group.

Missing values indicate that the model did not converge.

[a] Odds ratios are estimated using GEE logistic regression.

[b] *P*-values are for the significance of the covariate in predicting risk of a bone scan being positive, across all patients.

[c] log-transformed PSADT was used in this analysis.

Table 3

Percent risk of positive scan by PSA and PSADT groups stratified by ADT status

PSADT (months)	Before ADT				After ADT			
	PSA (ng ml^{-1})				PSA (ng ml^{-1})			
	0–4.9	5–9.9	10–19.9	≥20	0–4.9	5–9.9	10–19.9	≥20
≥9	1 (1–2)	1 (0–6)	5 (2–15)	3 (1–10)	10 (8–13)	17 (8–32)	30 (21–40)	39 (32–47)
3–8.9	11 (9–14)	10 (3–27)	31 (16–53)	24 (14–37)	19 (16–22)	30 (17–48)	47 (36–58)	57 (52–62)
< 3	24 (11–43)	22 (5–60)	53 (26–79)	44 (22–68)	26 (20–33)	40 (22–61)	57 (45–69)	67 (61–73)

Abbreviations: ADT, androgen deprivation therapy; PSADT, PSA doubling time.