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Characterising potential bone scan overuse amongst men treated with radical prostatectomy

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Objectives

To characterise bone scan use, and potential overuse, after radical prostatectomy (RP) using data from a large, national integrated delivery system. Overuse of imaging is well documented in the setting of newly diagnosed prostate cancer, but whether overuse persists after RP remains unknown.

Patients and methods

We identified 12 269 patients with prostate cancer treated with RP between 2005 and 2008 using the Veterans Administration Central Cancer Registry. We used administrative and laboratory data to examine rates of bone scan use, including preceding prostate-specific antigen (PSA) levels, and receipt of adjuvant or salvage therapy. We then performed multivariable logistic regression to identify factors associated with post-RP bone scan use.

Results

At a median follow-up of 6.8 years, one in five men (22%) underwent a post-RP bone scan at a median PSA level of 0.2 ng/mL. Half of bone scans (48%) were obtained in men who did not receive further treatment with androgen-deprivation or radiation therapy. After adjustment, post-RP bone scan was associated with a prior bone scan (adjusted odds ratio [aOR] 1.55, 95% confidence interval [CI] 1.32–1.84), positive surgical margin (aOR 1.68, 95% CI 1.40–2.01), preoperative PSA level (aOR 1.02, 95% CI 1.01–1.03), as well as Hispanic ethnicity, Black race, and increasing D'Amico risk category, but not with age or comorbidity.

Conclusion

We found a substantial rate of bone scan utilisation after RP. The majority were performed for PSA levels of <1 ng/mL where the likelihood of a positive test is low. More judicious use of imaging appears warranted in the post-RP setting.

Keywords

prostatic neoplasms, prostatectomy, radionuclide imaging, diagnostic imaging, neoplasm metastasis

Introduction

Many men diagnosed with prostate cancer will undergo diagnostic imaging at some point, either as part of initial staging or to investigate rising PSA levels after treatment. Guidelines recommend radionuclide bone scan use for newly diagnosed men at high risk of metastasis or with symptoms concerning for metastatic disease, and after treatment in the setting of persistent or rising PSA [1,2].

While bone scan use amongst the majority of newly diagnosed men is unlikely to yield useful clinical information (i.e., change treatment options), it remains common [3–10]. In fact, recent regional and national quality improvement initiatives target bone scan overuse amongst newly diagnosed men [11,12]. Whether similar initiatives are warranted to promote high-value imaging use after radical prostatectomy (RP) remains unknown. On the one hand, persistent (e.g., >0.2 ng/mL) or rising PSA levels after RP define biochemical recurrence prompting imaging recommendations. On the

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other hand, although men with metastatic disease may present with low PSA levels, most patients at these PSA levels are asymptomatic and the likelihood of bone scans finding metastatic disease amongst a cohort of post-RP men before PSA levels exceed 10 ng/mL is well below 10%, except in cases with extremely brisk PSA-doubling times [13–18]. While patients with local recurrence may be candidates for salvage therapy, a PSA level threshold of 10 ng/mL remains too high to inform clinical decision-making in many men with recurrence but low PSA levels.

In this context, we examined bone scan use after RP in a national integrated delivery system. We characterised adjuvant and salvage therapy rates, investigated PSA levels at the time of bone scan, and identified predictors associated with post-RP bone scan use. A better understanding of bone scan use after prostate cancer treatment will inform high-value use of current imaging resources, and identify considerations for emerging, expensive next-generation imaging techniques [19,20].

Patients and methods

Study population

We used data from the Veterans Affairs Central Cancer Registry (VACCR) to identify men with pathologically confirmed incident diagnoses of prostate cancer between the years 2005 and 2008, and available follow-up through 2013. These records were linked with administrative files to obtain clinical data. We excluded men with <2 years of follow-up, a history of other malignancy, those enrolled in a hospice within 30 days of diagnosis or who died within 6 months of diagnosis, and those who were diagnosed at autopsy. Our sample was then restricted to men who underwent RP as their primary therapy per the VACCR, yielding a cohort of 12 269 patients.

Imaging use, biochemical recurrence, salvage and adjuvant therapy

We identified receipt of imaging using the Healthcare Common Procedure Coding System (HCPCS; codes 78300, 78305, 78315, 78320). We defined pre-treatment imaging use as any bone scan ordered from the 6 months prior to diagnosis until the date of RP. All bone scans ordered after the date of RP were categorised as postoperative. We considered the last PSA level obtained prior to the treatment date from the laboratory data as the pre-treatment PSA level [21]. We also assessed the post-treatment PSA nadir, as well as the PSA level at the time of bone scan.

To better understand post-RP treatment patterns influencing bone scan use, we defined biochemical recurrence as a PSA level of ≥0.2 ng/mL in accordance with national guidelines [1]. We used claims and pharmacy data to classify any subsequent treatments as androgen-deprivation therapy (ADT) or radiation therapy (XRT). Next, we characterised XRT according to timing after RP to better understand whether it was intended as adjuvant or salvage. We defined adjuvant therapy as occurring at ≤1 year of RP, and salvage therapy as occurring >1 year after RP. Lastly, we identified PSA levels at the time of post-RP ADT or XRT use.

Statistical analysis

We used descriptive statistics to characterise our cohort according to post-RP bone scan use. We examined a range of demographic and clinical covariates, including age, race (Black, White, Other), ethnicity (Hispanic, non-Hispanic, unknown), marital status (married, divorced, single/never married, widowed, unknown), VACCR Gleason score, D'Amico risk group, surgical margin status (positive, negative, unknown), and Charlson Comorbidity Index (CCI) score. Next, we examined rates of, and time to, adjuvant and salvage therapy, as well as the corresponding PSA levels at the time of each therapy. Finally, we used multivariable logistic regression to assess factors associated with receipt of bone scan after RP. We selected variables a priori including: age, race, ethnicity, marital status, D'Amico risk group, CCI score, pretreatment PSA level, history of prior bone scan, and surgical margin status.

All analyses were performed using the Statistical Analysis System (SAS), version 9.4 (SAS Institute, Cary, NC, USA). Statistical significance was evaluated using a significance level of 0.05. This study was approved by the VA Ann Arbor Healthcare System Institutional Review Board.

Results

Demographic characteristics of the 12 269 men treated with RP are shown in Table 1. The mean age in this cohort was 62 years, and most men were diagnosed with low- or intermediate-risk disease at a median PSA level of 5.6 ng/mL. The median follow-up for the entire cohort was 81.4 months, and all patients were followed for ≥5 years.

While one-third of the men in this cohort received a preoperative bone scan (33%), one in five (22%) received at least one bone scan (median 1, range 1–13) after RP, and 30% of men who received a bone scan underwent more than one. As shown in Fig. 1, most patients undergoing a post-RP bone scan had low- (22%) and intermediate-risk (40%) prostate cancer. Moreover, the median PSA level at the time of post-RP bone scan was 0.2 ng/mL, with 78% of bone scans performed in men with PSA levels of <1 ng/mL. While nearly half of patients (48%) undergoing a bone scan received no subsequent treatment, men with low-risk disease were less likely, and those with high-risk disease more likely,

Table 1 Demographic characteristics of 12 269 men treated with RP for incident diagnoses of prostate cancer stratified by receipt of postoperative bone scan.

Demographics	Bone scan	No bone scan	*P*
Number of patients	2652	9617	
Age, years, mean (SD)	62.4 (8.0)	62.1 (7.2)	0.049
Race, %			
Black	26	22	<0.001
White	71	75	
Other/unknown	3	3	
Ethnicity, %			
Hispanic	7	4	<0.001
Non-Hispanic	92	95	
Other/unknown	1	1	
Marital status, %			
Married	54	57	0.033
Divorced/separated	31	29	
Single/never	8	8	
Widowed	7	6	
Other	<1	<1	
Employment status, %			
Full-time	13	16	<0.001
Part-time	5	4	
Retired	38	41	
Self-employed	3	4	
Unemployed	40	34	
Active military	<0.1	0	
Unknown	1	1	
CCI score, %			
0	54	51	<0.01
1	25	24	
2	21	25	
PSA level at diagnosis, ng/mL, median (range)	6.3 (0.1–96.4)	5.5 (0.1–97.2)	<0.001
Gleason Score, %			
6	30	44	<0.001
7	47	47	
8–10	23	9	
D'Amico risk group, %			
Low	22	35	<0.001
Intermediate	40	42	
High	38	23	
Positive surgical margins, %	31	19	<0.001
Follow-up, months, median (IQR)	83.3 (71.5–95.0)	80.9 (69.5–93.5)	<0.001

to have subsequent treatment with either ADT or XRT ($P < 0.001$).

As shown in Table 2, both adjuvant and salvage XRT were more common in men who received bone scans ($P < 0.001$), although time to XRT did not differ based on receipt of bone scan. Men who received bone scans were also more likely to receive ADT and do so later after RP. The receipt of bone scan was associated with significantly higher PSA levels at treatment for both salvage and adjuvant XRT, but not for ADT. After multivariable adjustment, factors significantly associated with bone scan were positive surgical margins, preoperative PSA level, Hispanic ethnicity, Black race, increasing D'Amico risk group, and history of a prior bone scan (Table 3). After adjustment, we found no differences in post-RP bone scan use according to patient comorbidity or age. Rates of pre- and postoperative bone scan varied widely across facilities, and did not appear to be correlated within individual facilities (Fig. 2).

Discussion

One in five men in this large national integrated delivery system underwent at least one postoperative bone scan following RP. Nearly half of these scans were performed in men who did not receive any additional treatment. The median PSA level amongst men who received bone scans was 0.2 ng/mL, which suggests that half of the patients who underwent a bone scan after RP did so before their PSA level had reached the level of a biochemical recurrence. Even after adjustment for patient and disease characteristics, receipt of preoperative bone scan was a significant predictor of postoperative imaging, which suggests that there may be non-clinical variables (e.g., provider preference for 'baseline' studies) influencing the decision to pursue bone scan. The wide range of usage across facilities further suggests an opportunity for increased standardisation. Taken together, these results suggest that there is opportunity for more judicious use of postoperative bone scan, just as in the pretreatment setting.

These findings suggest a higher rate of post-RP bone scan use than found in prior studies and are reminiscent of imaging overuse in the pretreatment setting [19]. While imaging overuse in the evaluation of newly diagnosed prostate cancer has been extensively studied, there is a paucity of literature investigating post-treatment use. Interestingly, our present findings are from an integrated delivery system that lacks incentives for imaging, potentially underestimating bone scan use in fee-for-service systems, and justifying post-treatment efforts to decrease low value imaging. Our present results regarding ethnicity are somewhat surprising given that studies from other settings have found that minority populations generally receive a lower intensity of follow-up, and we did observe differences based on race/ethnicity with African-American/Hispanic men more likely to undergo a bone scan [22]. However, these findings may be reflective of more aggressive disease in these men possibly incompletely controlled for in our model [23].

For this population-based study, we were able to use PSA levels prompting bone scan use amongst men treated with RP. Unfortunately, our finding of low PSA levels at the time of imaging indicates the results were unlikely to be clinically useful. In other words, a negative imaging test at low PSA levels is unable to differentiate local vs distant metastatic disease and therefore adds little value to clinical decision-making for men with biochemical recurrence as currently defined. In fact, guidelines recommend consideration of bone scan in the setting of biochemical recurrence; however, indicate the likelihood of a positive result in the absence of

Fig. 1 Distribution of postoperative bone scans across categories of adjuvant or salvage treatment and D'Amico risk group with median prostate-specific antigen (PSA) levels at the time of bone scan. Most bone scans were obtained in men who did not receive postoperative therapy, and most scans were in men with PSA levels <1 ng/mL.

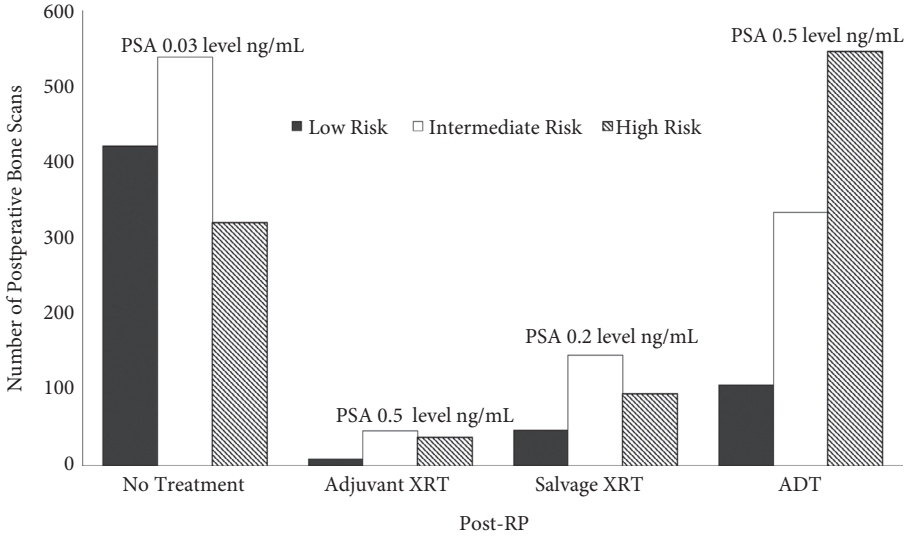


Table 2 Treatment type and PSA levels amongst men who received additional therapy after RP stratified by receipt of postoperative bone scan.

Characteristic	Bone scan	No bone scan	*P*
Number of patients	2652	9617	
Any therapy, %	51.6	11.8	<0.001
XRT, %	14.3	3.6	<0.001
Adjuvant	3.5	1.1	<0.001
Salvage	10.8	2.5	<0.001
Time to XRT, months, median (IQR)	23.8 (12.5–46.4)	21.0 (10.6–43.0)	0.06
Adjuvant	8.1 (5.8–9.9)	7.7 (5.4–9.8)	0.6
Salvage	33.4 (20.2–52.7)	33.8 (18.9–49.6)	0.3
PSA level at XRT, ng/mL, median (range)	0.3 (0.0–0.9)	0.2 (0.0–3.7)	<0.001
Adjuvant	0.5 (0.0–9.1)	0.1 (0.0–3.7)	<0.001
Salvage	0.3 (0.0–9.4)	0.2 (0.0–3.3)	<0.001
ADT, %	37.3%	8.2%	<0.001
PSA level at ADT, ng/mL, median (range)	0.9 (0–2513)	0.2 (0–598)	0.1
Time to ADT, months, median (IQR)	12.2 (2.9–38.6)	8.3 (1.8–36.6)	0.05

symptoms and with PSA levels of <10 ng/mL is low [1]. For example, one study found that men with PSA levels of <10 ng/mL had positive bone scan rates ranging from 0% to 11%, depending on if PSA-doubling time was greater or less than 6 months, and another estimated the probability of a positive bone scan at <5% until PSA levels exceeded 40 ng/mL [14,17]. However, this situation is made more complicated by results suggesting that up to one in four men with bone metastases after RP present with PSA levels of <10 ng/mL [13]. Post-RP bone scan is likely warranted in men with rapidly rising PSA levels or levels closer to 10 ng/mL; however, that still excludes the many men in our present cohort who received bone scans at far lower values. Interestingly, studies suggest that implementation of salvage XRT earlier in the postoperative period and at lower PSA levels may confer benefits in the form of lower rates of additional recurrence and metastasis [24]. In light of this, eliminating bone scan altogether and proceeding directly to salvage therapy for men with biochemical recurrence but low PSA levels could be an approach to lower the use of uninformative imaging while improving clinical outcomes.

Our present findings are also relevant to emerging diagnostic techniques posited to improve post-treatment prostate cancer surveillance, namely, positron emission tomography (PET) imaging. Early findings suggest PET-based approaches may improve staging of lymph nodes and distant metastases (e.g., bone) for men with newly diagnosed prostate cancer [25,26]. Relevant to our work, PET imaging is also increasingly used to evaluate biochemical recurrence. The inability of current

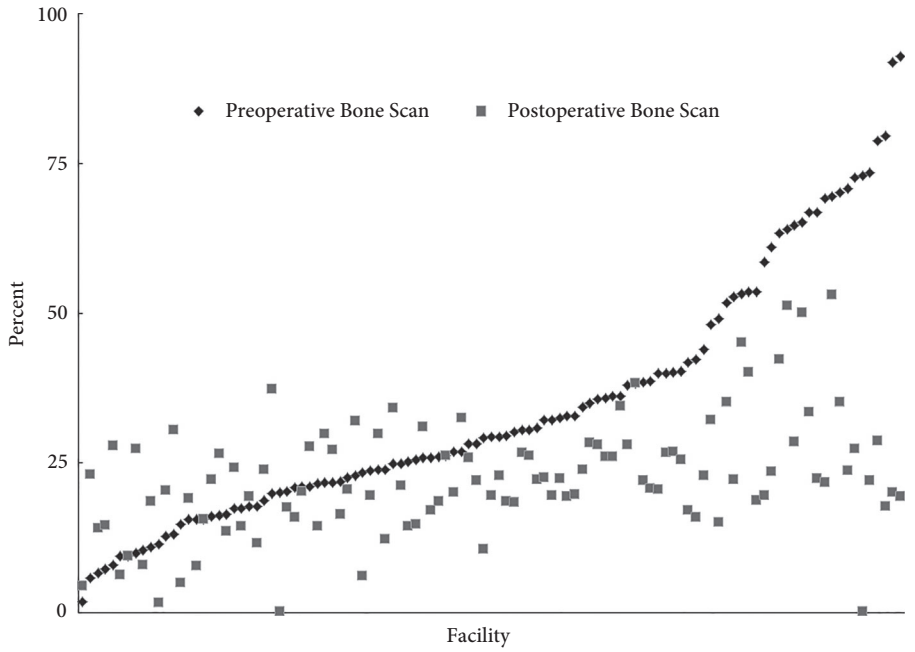
Table 3 Multivariable logistic regression results modelling the receipt of bone scan after RP.

Covariate	Adjusted odds ratio (95% CI)
Age	0.99 (0.98–1.01)
Race	
White	Referent
Black	1.32 (1.10–1.59)
Other	0.81 (0.51–1.30)
Ethnicity	
Non-Hispanic	Referent
Hispanic	1.58 (1.22–2.05)
Marital status	
Married	Referent
Divorced/separated	0.95 (0.79–1.13)
Never married	0.79 (0.58–1.07)
Widowed	0.97 (0.68–1.38)
D'Amico risk group	
Low	Referent
Intermediate	1.44 (1.16–1.77)
High	1.88 (1.49–2.36)
CCI score	
0	Referent
1	0.85 (0.71–1.03)
2	1.12 (0.91–1.38)
Positive surgical margin	1.68 (1.40–2.01)
Preoperative PSA	1.02 (1.01–1.03)
Prior bone scan	1.55 (1.32–1.84)

bone scan imaging techniques to adequately assess the source of low but detectable PSA levels after surgery may be frustrating for clinicians, spurring the promise and use of PET imaging [27,28]. PET imaging utilising prostate-specific membrane antigen (PSMA), in particular, appears to hold promise in the evaluation of biochemical recurrence, especially at lower PSA levels where the traditional bone scan has been of limited use. Recent data from Gadzinski et al. [29] suggest that nearly half of post-RP men with a PSA level of 0.2 ng/mL may have detectable lesions using PSMA-PET, with the detection rate improving to 100% amongst included men with PSA levels of >6 ng/mL. Continuing work should help to clarify the most effective ways to apply this new technology and identify those men most likely to benefit. Next-generation PET imaging could be harnessed to improve the value of care by identifying patients with metastases who would not benefit from local therapies such as salvage XRT. However, the ability of advanced imaging techniques to improve decision-making and clinical outcomes for these patients remains to be fully explored.

While significant efforts are directed towards decreasing imaging overuse in prostate cancer staging, we found similar issues post-treatment that are not being addressed. From a clinical perspective, a negative postoperative bone scan may alleviate patient and clinician concerns about rising, although low, PSA levels. It could also lead to salvage treatment with XRT, as many scans in these data may have been ordered to verify the absence of disseminated disease before localised XRT. However, using negative bone scans as reassurance and to differentiate local vs distant disease when it is unlikely to yield accurate results could mislead patients and clinicians resulting in misuse and overuse of treatment. These risks must be weighed against the benefit of possible discovery of some metastatic disease. In addition, we found that a

Fig. 2 Preoperative and postoperative bone scan rates across VHA facilities. The range of preoperative bone scan rates is large, with little apparent correlation between the facility level use of preoperative and postoperative bone scan.



previous bone scan was associated with post-RP bone scan use, suggesting that some may be ordered based on non-clinical factors such as provider perception or preference. Lastly, consideration should be given to the natural history of PSA progression after RP and to the life expectancy of patients with biochemical recurrence years after their RP, as we found age was not a factor in our adjusted analyses [30]. Better understanding competing risks for individual patients, and how best to approach de-implementation of low-value imaging in light of these risks appears warranted.

There are limitations to the present study. This study did not include an assessment of PSA kinetics found to be at least as important as PSA levels in predicting bone scan positivity after biochemical recurrence. A subset of the patients in the present study likely had rapid doubling times prompting imaging despite low PSA levels. However, given the median PSA level at bone scan of 0.2 ng/mL, our overall conclusions regarding the extent to which imaging is potentially low value is unchanged. The data used in the present study lack information about the indication for which imaging was obtained. It is possible that a number of scans were obtained to evaluate common benign conditions, such as persistent low back pain, to exclude malignancy as an aetiological factor. It is unlikely that many men in the present study would have had symptoms from metastasis-related back pain due to the low PSA levels at the time of bone scan. Additionally, prior studies examining bone scan positivity after biochemical recurrence did not observe an association between common symptoms, such as fatigue or back pain, and bone scan results [15]. Next, whether recent advances in the management of locally recurrent and metastatic prostate cancer might have impacted imaging use amongst prostate cancer survivors in our present study remains unknown. However, use of advanced therapies would theoretically only increase bone scan use to monitor treatment effects. We also did not exclude men participating in clinical trials. Lastly, we did not have results of the bone scan studies. However, as many men were not treated after the bone scan it was unlikely that these scans were positive for disease. As ADT was the most commonly used salvage treatment, it remained unclear whether this was used to target biochemical recurrence, an increasingly scrutinised practice [31], or metastatic disease to the bone, which would be unusual for most PSA levels prompting bone scans in the present study.

Despite these limitations, our present study has important implications for current and future practice. While the AUA has partnered with the American Board of Internal Medicine's *Choosing Wisely* campaign to help reduce the routine use of bone scans in the staging of men with low-risk prostate cancer, it appears that the potential for imaging overuse in this population may persist in the postoperative phase. As a point of comparison from another osteophilic malignancy, historic data recommended obtaining serial post-treatment bone scans in women after treatment for breast cancer. Subsequent evidence has led to guidelines recommending against the use of routine follow-up imaging in otherwise asymptomatic women [32,33]. Focusing increased attention on this aspect of prostate cancer survivorship care will help decrease the burdens of unnecessary testing and procedures. As imaging paradigms in prostate cancer evolve, it will be critically important to leverage these insights in guidelines and best practices. The application of carefully considered testing thresholds will help to minimise low-yield evaluations amongst prostate cancer survivors, even as technology enables improved diagnostic efficiency at lower PSA levels. De-implementation of unnecessary imaging in the post-RP setting will spare asymptomatic prostate cancer survivors inconvenience and cost, likely without compromising quality and quantity of life.

We found relatively high rates of bone scan use following RP, with many performed at PSA levels below the threshold for biochemical recurrence. Our present results emphasise the need to optimise post-RP imaging practices, much like those amongst newly diagnosed men.

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Conflict of Interest

None declared.

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Abbreviations: ADT, androgen-deprivation therapy; CCI, Charlson Comorbidity Index; PET, positron emission tomography; PSMA, prostate-specific membrane antigen; RP, radical prostatectomy; VACCR, Veterans Affairs Central Cancer Registry; XRT, radiation therapy.

