Changing the referral criteria for bone scan in newly diagnosed prostate cancer patients

¹C MCARTHUR, MBChB, ¹G MCLAUGHLIN, MBChB, FRCR and ²R N MEDDINGS, MBChB, FRCS

¹Department of Radiology, Ayr Hospital, Ayr, UK, and ²Department of Urology, Ayr Hospital, Ayr, UK

Objectives: The aim of this study was to correlate the prostate-specific antigen (PSA) level and Gleason score with staging bone scan result in patients with a new diagnosis of prostate cancer in order to establish the feasibility of implementing the European Association Urology guidelines, which state that a bone scan may not be indicated when PSA <20 in well-moderately differentiated tumours.

Methods: We identified 633 patients retrospectively and 186 patients prospectively with a new diagnosis of prostate cancer undergoing a staging bone scan between March 2005 and January 2010. Patients were excluded if there was no Gleason score available or if the PSA level was checked over 3 months prior to bone scan. Bone scan results were analysed with respect to age, PSA level and Gleason score. In the case of an equivocal result, subsequent imaging was taken into consideration or the initial bone scan was re-reviewed. In persistently equivocal cases, all relevant imaging was assessed by a blinded panel of radiologists to allow a final decision to be made.

Results: Of 672 patients aged 39–93 years (median 71 years), who fulfilled the inclusion criteria, 54 (8%) had evidence of bony metastases. PSA level and Gleason score were both independent predictors of bone scan positivity and their predictive value was additive $p < 0.01$. None of the 357 patients with a PSA level of <20 and a Gleason score of <8 had a positive bone scan.

Conclusion: Staging bone scans in newly diagnosed prostate cancer patients with a PSA level of <20 and a Gleason score of <8 can be safely omitted, with these criteria having a negative predictive value of 100% in our series.

Received 20 April 2010

Revised 14 July 2010

Accepted 15 July 2010

DOI: 10.1259/bjr/79184355

© 2012 The British Institute of Radiology

Prostate cancer is currently the most common malignancy diagnosed in men in the UK [1] and bone is the second most common site of metastasis [2]. Bone metastases are present in up to 14% of patients at presentation [3] and in 80–85% of those who die of the disease [4], and they therefore affect morbidity, reflect prognosis and significantly influence decisions with regard to patient management.

Sensitivity of planar bone scan for the detection of bone metastases is 72–77% in adults [5, 6] and is currently the investigation of choice. However, it lacks diagnostic specificity, with indeterminate results often prompting the need for further imaging.

Prostate-specific antigen (PSA) level is an established prognostic marker that correlates with bone scan positivity, and various studies demonstrate a low risk of a positive bone scan in newly diagnosed patients with a low PSA level [3, 4, 7–13]. Gleason score is also of important prognostic significance and has been shown to be an independent predictor of bone scan results on multivariate analysis [4, 7, 12, 14]. There is still a lack of consensus, however, on the referral criteria for bone scan in low-risk patients, with different authors supporting various cut-off levels of PSA, with some including Gleason score and clinical stage. The European Association of Urology (EAU) guidelines, updated in March 2009,

recommend that staging bone scan may not be indicated in patients with a PSA level of <20 with moderately to well-differentiated tumours in the absence of bony symptoms [15], while the American Urological Association and American Joint Committee on Cancer (AJCC) both recommend that staging bone scan is indicated in patients with a Gleason score of >7 or a PSA level of >20 prior to treatment [14].

Despite this, there remains a large demand for isotope bone scanning in patients with a new diagnosis of prostate cancer regardless of risk stratification based on these prognostic tools.

The purpose of the current study was to correlate PSA levels and Gleason scores with bone scan results in patients with newly diagnosed prostate cancer, with the aim of identifying a subgroup of patients who did not require staging bone scan, and assess the feasibility and safety of implementing EAU guidelines.

Methods and materials

The local ethics committee was consulted about the study and no formal ethical approval was required.

Patients

819 consecutive patients with newly diagnosed prostate cancer, who underwent a staging bone scan between

Address correspondence to: Dr Claire McArthur, Department of Radiology, Ayr Hospital, Dalmellington Road, Ayr KA6 6DX, UK. E-mail: claire.mcarthur@nhs.net

Table 1. PSA level, Gleason score and age results in negative and positive scans

Results	Negative, n=618	Positive, n=54
PSA level, mean (SD) median	29.7 (76.8) 11.7	186.3 (427.3) 53
Gleason score, mean (SD) median	7.1 (1.2) 7	8.6 (0.9) 9
Age (years), mean (SD) median	70.1 (7.9) 71	71.5 (8.6) 71.5

PSA, prostate specific antigen; SD, standard deviation.

March 2005 and January 2010 at our institution, were identified. Data were collected retrospectively in the first 633 patients and prospectively in 186 patients from November 2009. Patients were excluded if there was no Gleason score available ($n=80$) in order to avoid bias as the majority did not undergo biopsy and were felt to represent a higher risk group, or if the PSA level was measured over 3 months prior to the bone scan, unless assessed within 1 month following the scan in the absence of treatment with no significant difference in PSA level before and after the scan ($n=65$). In patients with high PSA levels or high Gleason scores, hormone therapy was occasionally commenced prior to the bone scan and two further patients were excluded as hormone therapy was commenced over 1 month prior to the scan.

Data were gathered on age, PSA level, Gleason score, bone scan and associated imaging results. PSA assessment, histological grading and isotope bone scanning were performed in the same manner for all remaining 672 patients.

Bone scan

Whole body scanning was performed 3–4 h after injection of 600 MBq ^{99m}Tc methyldiphosphonate using a matrix size of 256×1024 at a scan speed of 10 cm min^{-1} and an energy window of 15% at 140 keV (Siemens Symbia T; Siemens, Chicago, IL). Reporting of bone scans was performed by one of six experienced consultant radiologists at our hospital. The decision to refer for bone scan was made by the urology clinicians and specialist nurses.

Bone scan results were initially recorded as negative, equivocal or positive for the presence of metastases. In equivocal cases, further imaging including radiographs, CT and MRI scans, and subsequent bone scans were taken into consideration. If these were not performed, a single consultant radiologist reviewed the initial bone

scan. In persistently equivocal cases, a blinded panel of four consultant radiologists reviewed all relevant imaging to allow a final decision, if possible, to be made with respect to the likely presence of bone metastases. Any outstanding indeterminate cases were treated as negative—all in patients with PSA levels of >20 or Gleason scores of >7 .

Gleason

Pathological samples were obtained by transrectal ultrasound-guided biopsy (TRUS) in 615 patients from a minimum of 8 sample sites, and following transurethral resection of prostate in the remaining 57. Specimens were analysed using the Gleason grading system and reviewed by one of two experienced pathologists at our institution prior to multidisciplinary team discussion.

Prostate-specific antigen

The ADVIA Centaur two site sandwich immunoassay (Siemens) was used for PSA determination for the duration of the study period. PSA levels were determined prior to bone scan and prior to biopsy in TRUS cases in all but one patient.

Statistics

PSA was subdivided into 4 groups for analysis: PSA levels of <10 , PSA levels of 10–19.9, PSA levels of 20–49.9 and PSA levels of >50 , with Gleason scores subdivided into <7 , 7 and >7 . These parameters were based on previous literature and with consideration of EAU guidelines.

A χ^2 test for linearity was used to assess the relationship between PSA levels, Gleason score and bone scan

Figure 1. Positive vs negative scans in each prostate-specific antigen (PSA) bracket.

Figure 2. Positive vs negative scans in each Gleason bracket.

result, and used a cut-off of PSA levels of <20 and a Gleason score of <8 . Logistic regression analysis of age, log PSA and Gleason score was performed to assess the independent and additive effects of these parameters. A p -value of ≤ 0.05 was taken to indicate statistical significance.

Results

Of 672 patients aged 39–93 years (median 71 years), 54 (8.0%) had evidence of bony metastatic disease. Table 1 shows PSA level, Gleason score and age for the negative and positive groups.

Figures 1 and 2 and Tables 2 and 3 demonstrate the relationship between PSA levels, Gleason score and bone scan results.

A χ^2 test for linearity found that the relationship was strong and significant for both PSA and Gleason ($p < 0.01$).

Table 4 shows the rate of bone scan positivity by PSA level combined with Gleason score and with a Gleason score of 7 divided into major Grade 3 or 4.

Using sequential logistic regression with scan result as the dependent variable and age, log PSA and Gleason scores as independent variables was carried out to determine whether PSA levels and Gleason scores were additive. Log PSA was used to counter the skewness observed earlier. In the final model, both log PSA and Gleason score were statistically significant predictors of bone scan result and their predictive value was additive ($p < 0.01$). Age was not a predictive factor.

None of the 357 patients with a PSA level of <20 and a Gleason score of <8 had a positive bone scan; therefore,

there was a clear significant relationship between these cut-off criteria and scan results. The 95% confidence interval for positive scans resulting when PSA levels and Gleason scores are below these cut-off values gives a population upper limit of 1.32% [16].

Using PSA levels of <20 and Gleason scores of <8 in the absence of bony pain as criteria for avoiding staging bone scan (EAU guidelines), 355 (53%) scans could have been avoided, allowing for 2 patients in this group with bony symptoms. 66 (18.5%) patients in this subgroup had initial equivocal bone scan findings to some degree, none of which had a high degree of suspicion, resulting in additional plain radiographs in 44, CT in 3 and MRI in 3. In 60, the possibility of metastases was refuted on review of the imaging or on subsequent investigation. In six, the blinded, pooled radiological consultant opinion was of a non-metastatic process.

Discussion

PSA levels of <20 combined with a Gleason score of <8 , in our cohort, had a negative predictive value for bone metastases of 100%. Our results strongly suggest that staging isotope bone scan is not indicated in patients with a new diagnosis of prostate cancer with these characteristics. These findings support the application of EAU guidelines, and this would lead to a reduction in staging bone scans of 53% in our sample if taking symptomatic bony pain into account. The results also validate the use of AUA and AJCC recommendations in this respect.

The results are in keeping with previous work in that PSA level and Gleason score are independent predictors of bone scan positivity. Like O'Sullivan et al [12] and

Table 2. Number of negative and positive scans in each PSA subgroup

PSA level	Scan		Total n (%)
	Negative, n (%)	Positive, n (%)	
0–9.9	251 (40.6)	7 (13.0)	258 (38.4)
10–19.9	180 (29.1)	5 (9.3)	185 (27.5)
20–49.9	115 (18.6)	15 (27.8)	130 (19.3)
>50	72 (11.7)	27 (50)	99 (14.7)
Total	618	54	672

PSA, prostate specific antigen.

Table 3. Number of negative and positive scans per Gleason subgroup

Gleason score	Scan		Total, n (%)
	Negative, n (%)	Positive, n (%)	
<7	257 (41.6)	2 (3.7)	259 (38.5)
7	173 (28.0)	5 (9.3)	178 (26.5)
>7	188 (30.4)	47 (87.0)	235 (35.0)
Total	618	54	672

Table 4. Bone scan results for each PSA and GS subgroup combined

PSA	GS <7	GS <7	GS 7				GS>7	GS>7
	Total grade	Mets, n (%)	n 3+4		n 4+3		Total grade	Mets, n (%)
			Total grade	Mets, n (%)	Total grade	Mets, n (%)		
0–9.9	149	0 (0.0)	46	0 (0.0)	19	0 (0.0)	44	7 (15.9)
10–19.9	80	0 (0.0)	42	0 (0.0)	21	0 (0.0)	42	5 (11.9)
20–49.9	16	1 (6.3)	19	1 (5.3)	15	1 (6.7)	80	12 (15)
≥50	14	1 (7.1)	4	1 (25.0)	12	2 (16.7)	69	23 (33.3)

GS, Gleason; PSA, prostate specific antigen.

Ayyathurai et al [13], but at variance with others [2, 3, 10, 11], we found that PSA level and pathological grade had a higher predictive value in combination.

Our overall rate of bony metastases differs from that of a large contemporary study by Briganti et al [14]: 8% *vs* 2.8%. The rate of positive bone scans in patients with PSA levels <10 was 2.7%, slightly higher than that quoted in previous studies, ranging from 0% to 1.7% [3, 4, 8–12], although the rate in patients with PSA levels of 10–19.9 at 2.7% is comparable with these studies, which range from 1 to 8%. This discrepancy most likely reflects the fact that 35% of patients in our study population overall had a Gleason sum of >7, a higher proportion than in other studies: Briganti et al [14] 10%, Lin et al [4] 14%, O'Sullivan et al [12] 18% and Pal et al [3] 30%.

Unlike O'Sullivan et al [12] and Ayyathurai et al [13], major Gleason Grade 4 *vs* 3 made no difference to the rate of bone scan positivity with PSA levels <20.

Briganti et al [14] recently carried out external validation of the EAU and AUA/AJCC guidelines with respect to bone scan referral in a cohort of 853 consecutive patients and found an accuracy of 79.7% and 82.6%, respectively, and a negative predictive value of 99% and 99.3%, respectively. Using their own regression model, patients with a Gleason score ≤7, a PSA level ≤10 and clinical stage T2/3 had a rate of bone metastases of 1.3% while those with a Gleason score ≤7 and clinical stage T1 (regardless of PSA level) had a positive rate of 0.2% [14]. Clinical stage was not included in our analysis partly owing to limitations with data collection; however, EAU recommendations do not consider clinical stage if PSA levels are <20 in well-moderately to differentiated tumours and AUA/AJCC guidelines also do not include this information in the decision for bone scan referral. Several previous authors have found no statistically significant relationship between clinical stage and bone scan positivity [3, 8] or survival [2].

In the low-risk group, 18.5% of patients had initial equivocal bone scan findings to some degree, which often necessitated further imaging investigations and thus resulted in delays in management decisions and uncertainty for the patient. In the current climate, where there is a demand for decreasing times from diagnosis to treatment and from request to reporting of radiological examinations, it is important to ensure that patients who do require evidence-based investigation are imaged promptly. The avoidance of unnecessary bone scans would allow more dedicated studies to be performed in appropriate cases and would decrease all patients' journey times. The significant financial savings would also be an obvious benefit.

To our knowledge, this is the largest series to date from the United Kingdom that correlates PSA level and Gleason score with bone scan results in newly diagnosed patients with prostate cancer. It is partly a retrospective analysis with associated limitations with respect to data collection and potential bias. However, it is based on consecutive patients presenting to a single institution; therefore, PSA assay, pathological analysis and radiological interpretation are all very well standardised.

Unlike several other studies, we did not exclude all patients who commenced hormonal therapy prior to bone scan, only those in whom hormonal treatment was introduced over 1 month before the scan. It was felt that treatment in this time period would not significantly affect the bone scan result, and this situation invariably arose in patients with high PSA levels and/or a Gleason score of >7 and would therefore not affect the outcome in the low-risk group.

Further research regarding patients in this low-risk category presenting with bony symptoms would be of value.

In conclusion, we recommend that staging isotope bone scans in newly diagnosed patients with prostate cancer with PSA levels of <20 and a Gleason score of <8 in the absence of bony symptoms can be safely omitted.

Acknowledgments

We are grateful to Dr Mario Hair, Statistics Consultant, NHS Ayrshire and Arran, for assistance with statistical analysis, and to Eleanor Ferguson, Urology Audit Department, NHS Ayrshire and Arran, for assistance with data collection.

References

1. UK. CR. Prostate cancer statistics—key facts. Cancer Research UK site [cited 20 May 2010]. Available from: <http://info.cancerresearchuk.org/cancerstats/types/prostate/>
2. Haukaas S, Roervik J, Halvorsen OJ, Foelling M. When is bone scintigraphy necessary in the assessment of newly diagnosed, untreated prostate cancer? *Br J Urol* 1997;79:770–6.
3. Pal RP, Thirudaian T, Khan MA. When is a bone scan study appropriate in asymptomatic men diagnosed with prostate cancer? *Asian J Androl* 2008;10:890–5.
4. Lin K, Szabo Z, Chin BB, Civelek AC. The value of a baseline bone scan in patients with newly diagnosed prostate cancer. *Clin Nucl Med* 1999;24:579–82.
5. Eustace S, Tello R, DeCarvalho V, Carey J, Wroblecka JT, Melhem ER, et al. A comparison of whole-body turboSTIR MR imaging and planar 99mTc-methylene diphosphonate

- scintigraphy in the examination of patients with suspected skeletal metastases. *AJR Am J Roentgenol* 1997;169:1655–61.
6. Sadik M, Suurkula M, Hoglund P, Jarund A, Edenbrandt L. Quality of planar whole-body bone scan interpretations—a nationwide survey. *Eur J Nucl Med Mol Imaging* 2008;35:1464–72.
 7. Lee N, Fawaaz R, Olsson CA, Benson MC, Petrylak DP, Schiff PB, et al. Which patients with newly diagnosed prostate cancer need a radionuclide bone scan? An analysis based on 631 patients. *Int J Radiat Oncol Biol Phys* 2000;48:1443–6.
 8. Gleave ME, Coupland D, Drachenberg D, Cohen L, Kwong S, Goldenberg SL, et al. Ability of serum prostate-specific antigen levels to predict normal bone scans in patients with newly diagnosed prostate cancer. *Urology* 1996;47:708–12.
 9. Huncharek M, Muscat J. Serum prostate-specific antigen as a predictor of radiographic staging studies in newly diagnosed prostate cancer. *Cancer Invest* 1995;13:31–5.
 10. Oesterling JE, Martin SK, Bergstralh EJ, Lowe FC. The use of prostate-specific antigen in staging patients with newly diagnosed prostate cancer. *JAMA* 1993;269:57–60.
 11. Chybowski FM, Keller JJ, Bergstralh EJ, Oesterling JE. Predicting radionuclide bone scan findings in patients with newly diagnosed, untreated prostate cancer: prostate specific antigen is superior to all other clinical parameters. *J Urol* 1991;145:313–18.
 12. O'Sullivan JM, Norman AR, Cook GJ, Fisher C, Dearnaley DP. Broadening the criteria for avoiding staging bone scans in prostate cancer: a retrospective study of patients at the Royal Marsden Hospital. *BJU Int* 2003;92:685–9.
 13. Ayyathurai R, Mahapatra R, Rajasundaram R, Srinivasan V, Archard NP, Toussi H. A study on staging bone scans in newly diagnosed prostate cancer. *Urol Int* 2006;76:209–12.
 14. Briganti A, Passoni N, Ferrari M, Capitanio U, Suardi N, Gallina A, et al. When to perform bone scan in patients with newly diagnosed prostate cancer: external validation of the currently available guidelines and proposal of a novel risk stratification tool. *Eur Urol* 2009;57:55–8.
 15. Heidenreich A, Bolla M, Joniau S, van der Kwast TH, Matveev V, Mason MD, et al. Guidelines on prostate cancer. Arnhem, The Netherlands: European Association of Urology; 2009.
 16. Agresti A, Coull BA. Approximate is better than 'exact' for interval estimation of binomial proportions. *Am Statist* 1998;52:119–26.