Application of bone scans for prostate cancer staging: Which guideline shows better result?

Ari Chong, MD;[*] Insang Hwang, MD;[†] Jung-min Ha, MD;[*] Seong Hyeon Yu, MD;[†] Eu Chang Hwang, MD;[†] Ho Song Yu, MD;[†] Sun Ouck Kim, MD;[†] Seung-Il Jung, MD;[†] Taek Won Kang, MD;[†] Dong Deuk Kwon, MD;[†] Kwangsung Park, MD[†]

[*]Department of Nuclear Medicine, Chosun University Hospital, Republic of Korea; [†]Department of Urology, Chonnam National University Hospital, Republic of Korea

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Abstract

Introduction: We evaluated the accuracy of current guidelines by analyzing bone scan results and clinical parameters of patients with prostate cancer to determine the optimal guideline for predicting bone metastasis.

Methods: We retrospectively analyzed patients who were diagnosed with prostate cancer and who underwent a bone scan. Bone metastasis was confirmed by bone scan results with clinical and radiological follow-up. Serum prostate-specific antigen, Gleason score, percent of positive biopsy core, clinical staging and bone scan results were analyzed. We analyzed diagnostic performance in predicting bone metastasis of the guidelines of the European Association of Urology (EAU), American Urological Association (AUA), and the National Comprehensive Cancer Network (NCCN) guidelines as well as Briganti's classification and regression tree (CART). We also compared the percent of positive biopsy core between patients with and without bone metastases.

Results: A total 167 of 806 patients had bone metastases. Receiver operating curve analysis revealed that the AUA and EAU guidelines were better for detecting bone metastases than were Briganti's CART and NCCN. No significant difference was observed between AUA and EAU guidelines. Patients with bone metastases had a higher percent positive core than did patients without metastasis (the cut-off value >55.6).

Conclusion: The EAU and AUA guidelines showed better results than did Briganti's CART and NCCN for predicting bone metastasis in the enrolled patients. A bone scan is strongly recommended for patients who have a higher percent positive core and who meet the EAU and AUA guidelines.

Introduction

A bone scan is recommended for prostate cancer staging to identify possible bone metastasis.[1-5] However, a recent cross-sectional study showed poor adherence to imaging guidelines,[6] although applying a bone scan according to guidelines showed a better result.[7] Inappropriate bone scans of patients at low risk of bone metastasis[8] and underuse of bone scans in patients with high risk[9] have also been reported. Additionally, current Western guidelines should be applied to Asian patients with caution.[10,11]

Therefore, we evaluated the accuracy of the current guidelines by analyzing bone scan results and clinical parameters of patients with prostate cancer to determine the optimal guideline for predicting metastasis. Additionally, we examined the value of adding the percentage of positive biopsy core to predict bone metastasis.

Methods

Patient selection

This clinical retrospective observational study was carried out in accordance with the Declaration of Helsinki. We enrolled all patients at a single hospital with prostate cancer confirmed by transrectal ultrasonographic prostate biopsy from 2009 to 2011. All patients underwent a bone scan at staging. Bone metastasis was confirmed by bone scan findings with clinical and radiological follow-up of 2 to 4 years.

Data collection

Clinical, pathological and radiological data were collected. Clinical data, such as serum prostate-specific antigen (PSA) level, Gleason score (GS), percent of the positive biopsy core, and clinical staging by magnetic resonance imaging (MRI) were analyzed.

Bone scan

Tc-99m Hydroxymethylene diphosphonate (650 MBq) was injected intravenously, and scanning was performed 3 hours

later. Planar images were obtained using a large field-of-view dual-head gamma camera (Millennium VG, GE, Milwaukee, WI). The scan was read by qualified nuclear physicians.

Confirmation of bone metastasis

Bone metastasis was confirmed by both bone scan findings and clinical follow-up. Clinical follow-up included bone scan and computed tomography (CT) or MRI for suspicious lesions.

Guidelines for recommending a bone scan

We examined the European Association of Urology (EAU) guidelines,[3] American Urological Association (AUA) PSA best practice policy,[1] the guidelines of the National Comprehensive Cancer Network (NCCN),[4] and the classification and regression tree (CART) by Briganti and colleagues.[2]

According to the EAU guidelines, a bone scan may not be indicated in asymptomatic patients with a well or moderately differentiated tumour if the serum PSA level is <20 ng/mL. Based on the AUA guidelines, a bone scan is unnecessary with localized disease when the serum PSA level is <20 ng/mL and there is no clinical evidence of bone metastasis. A bone scan is appropriate according to the NCCN guidelines for symptomatic patients and/or those with life expectancy >5 years when they have any of the following: T1 disease with PSA >20 ng/mL or T2 disease with PSA >10 ng/mL, GS ≥8, or T3 or T4 or symptomatic disease. According to Briganti's CART, a bone scan should be considered only for patients with a GS >7 or serum PSA level >10 ng/mL with a palpable tumour (cT2/T3).

Analysis

We analyzed whether a bone scan should be recommended for each patient by comparing the results with each guideline. We compared the level of percent positive biopsy core between patients with and without a bone metastasis, and identified the cut-off value for positive biopsy core percentage for predicting bone metastasis using receiver operating curve (ROC) analyses. The McNemar test was used to compare sensitivity and specificity. Medcalc version 11.3.1.0 statistical software (MedCalc Software, Mariakerke, Belgium) was used.

Results

Patients with bone metastasis

A total of 806 patients were enrolled, and all of them underwent a bone scan. Among them, 167 (20%) had bone metastasis at staging (Table 1). Patients with bone metastasis were older, had higher PSA levels, and had a higher percent positive biopsy core compared to those without metastasis.

The number of patients for whom a bone scan was recommended by each of the guidelines was as follows: 409 (50.7%) patients by the EAU guidelines, 409 (50.7%) by the AUA guidelines, 531 (65.9%) by Briganti's CART, and 523 (64.9%) by the NCCN guidelines (61 patients were not available to be classified by the NCCN guidelines).

Comparison among guideline results

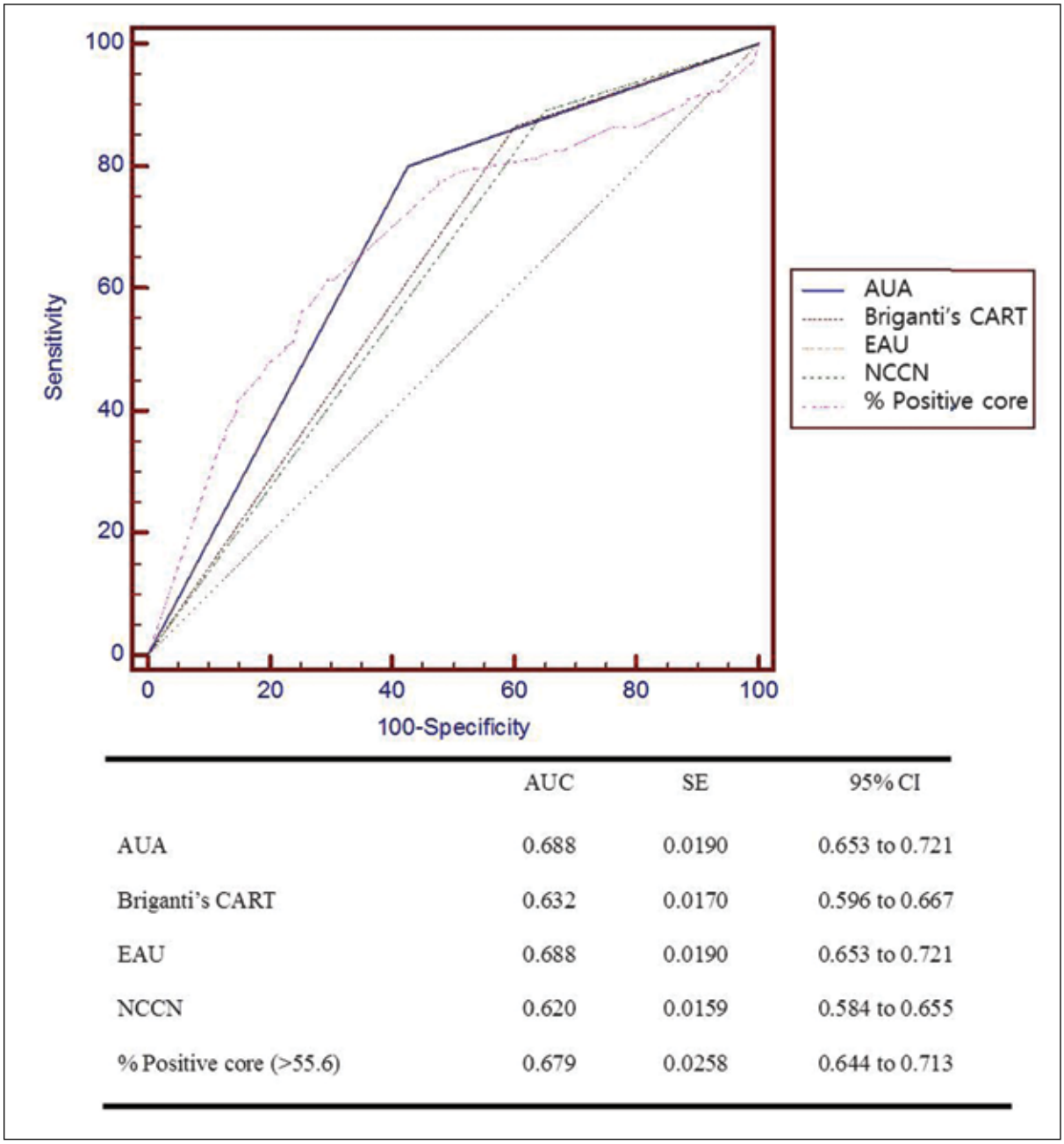
The EAU and AUA guidelines showed 100% agreement in recommending a bone scan. However, the McNemar test showed that the bone scan recommendations differed significantly in other comparisons (EAU vs. Briganti's CART, EAU vs. NCCN, Briganti's CART vs. AUA, Briganti's CART vs. NCCN, and AUA vs. NCCN; all $p < 0.0005$).

Pairwise comparisons of the ROC curves showed that the AUA and EAU guidelines had larger areas under the curve than did the other guidelines (Fig. 1). No significant differ-

Table 1. Patient characteristics

	Patients with bone metastasis (n = 167)	Patients without bone metastasis (n = 639)	*p* value
Age (mean ± SD)	73.31 ± 6.92	71.76 ± 7.21	0.013
PSA (ng/mL) (mean ± SD)	252.87 ± 345.67	39.41 ± 94.14	<0.001
PSA (ng/mL), no.			
0–4.0	1	38	
4.01–10.0	24	261	
10.01–20.0	22	138	
>20	120	202	
Gleason score, no.			
≤7	66	466	<0.001
>7	101	173	
Percent of positive core (mean ± SD)	67.57 ± 32.07	46.74 ± 29.05	<0.0001

SD: standard deviation; PSA: prostate-specific antigen.



	AUC	SE	95% CI
AUA	0.688	0.0190	0.653 to 0.721
Briganti's CART	0.632	0.0170	0.596 to 0.667
EAU	0.688	0.0190	0.653 to 0.721
NCCN	0.620	0.0159	0.584 to 0.655
% Positive core (>55.6)	0.679	0.0258	0.644 to 0.713

Fig. 1. Receiver operating characteristic (ROC) curve analyses (AUA, Briganti's CART, EAU, NCC, percent positive core). Note: Pairwise comparison of ROC curves shows significant result with $p < 0.05$ in AUA vs. Briganti's CART, AUA vs. NCCN, Briganti's CART vs. EAU, Briganti's CART vs. percent positive core, EAU vs. NCCN, NCCN vs. percent positive core. AUA: American Urological Association; EAU: European Association of Urology; NCCN: National Comprehensive Cancer Network; Briganti's CART: Briganti's classification and regression tree.

ence was detected between the AUA and EAU guidelines. Among the 806 patients, 16 (2%) had bone metastasis even though none of guidelines recommended a bone scan.

Cut-off value of percent of positive biopsy core for bone metastasis

Patients with bone metastases had a higher percent of positive biopsy core than did those without a metastasis (67.6 ± 32.1 vs. 46.7 ± 29.1, $p < 0.0001$). The cut-off value for percent positive biopsy core was >55.6 by ROC analysis, with sensitivity of 62.9% and specificity of 70.7% (Table 2). A combination of a cut-off value of 55.6% positive core and each guideline showed lower specificity and compatible sensitivity than did each guideline alone (Table 2).

Table 2. Results of each guidelines and the combinations with percent positive core (>55.6)

	Sensitivity (%)		Specificity (%)		NPV (%)	Accuracy (%)
EAU[3]	80.84		57.12		91.38	62.03
AUA[1]	80.84		57.12		91.94	62.03
NCCN[4]	89.10		34.80		92.34	46.17
Briganti's CART[2]	87.43		39.75		92.36	49.62
% Positive core (>55.6)	62.87		70.74		87.90	
Combination with % Positive core (>55.6)						
	Sensitivity (%)	***p****	**Specificity (%)**	***p****	NPV (%)	Accuracy (%)
EAU	82.04	0.5	49.77	<0.0001	91.38	56.45
AUA	82.04	0.5	49.77	<0.0001	91.38	56.45
NCCN	89.74	¥	32.26	0.0001	92.23	44.30
Briganti's CART	88.62	0.5	35.99	<0.0001	92.37	46.90

*p value: each guideline versus the combination of each guideline and percent positive core (>55.6). ¥Could not perform the test; AUA: American Urological Association; EAU: European Association of Urology; NCCN: National Comprehensive Cancer Network; Briganti's CART: Briganti's classification and regression tree; NPV: negative predictive value

Discussion

Prior studies have compared current guidelines in terms of their recommendation of a bone scan for prostate cancer staging.[12,13] In 2012, De Nunzio and colleagues[13] compared Briganti's CART to the EAU guidelines in 313 patients with prostate cancer (6.4% had bone metastasis). They reported that Briganti's CART was significantly more accurate than the EAU guideline for predicting bone metastasis using ROC analyses.[13] However, in our study, the EAU and AUA guidelines showed a better result than the Briganti's CART (Fig. 1). De Nunzio and colleagues, however, used the 2008 EAU guidelines,[14] whereas we used those published in 2011.[3] However, details related to bone scan recommendations for staging were the same.[3,14] Ito and colleagues[12] analyzed 508 patients (3.5% had bone metastasis) and reported that the EAU guidelines showed the best accuracy compared with those of the Japanese Urological Association, NCCN, AUA/American Joint Committee on Cancer, and the American College of Radiology.[12] Similar to our study, the EAU guideline results offered the best prediction, but those authors reported that the EAU guidelines were better than the AUA guidelines.

Due to the high rate of false-positive bone scans, we radiologically and clinically confirmed bone metastasis in our study. We followed patients for 2 to 4 years and used CT or MRI in some patients. The false-positive rate was higher in our study (20%) than in previous studies,[12,13] perhaps due to the higher percentage of patients with bone metastasis in our study. However, other studies have reported even higher percentages of bone metastasis, including studies by Al-Ghazo and colleagues[15] (98 patients, 39.7% had bone metastasis), Lai and colleagues[16] (116 patients, 29.3% with metastasis), Kosuda and colleagues[17] (1294 patients, 22% with metastasis), and Lee and colleagues[11] (579 patients, 14.3% with metastasis). Therefore, the percentage of bone metastasis in our study was not unusually high.

Several studies have suggested that a bone scan can be omitted for prostate cancer staging if the serum PSA level and GS satisfy the following: PSA ≤20 ng/mL and GS <8;[15] PSA <20 ng/mL and GS <8;[18] PSA ≤10;[16] PSA ≤10 or Gleason grade ≤2 or GS ≤6;[17] and PSA ≤20 and GS ≤6.[19] However, other reports have suggested that some patients with low PSA and GS had bone metastasis.[20] Zaman and colleagues[10] identified Asian patients with PSA ≤20 and GS <8 who had bone metastasis and suggested that we should be cautious when adopting Western guidelines for bone scans to an Asian population. The incidence and mortality rate of prostate cancer are lower in Asians than in northern European and Caucasian Americans.[16] Lai and colleagues[16] suggested that guidelines for Asians might differ from those for Caucasians. Lee and colleagues[11] showed the need for a bone scan in patients with PSA values of 10 to 20 ng/mL and suggested that new guidelines might be needed for Asians. In our study of Korean patients, 16 (2% of total patients) had bone metastases, even though none of the 4 guidelines recommended a bone scan for them. Racial differences between studies might be the cause of discrepancies in the results between studies that applied these guidelines. Further studies including those looking at racial differences in each guideline are needed.

In 2009, Ritenour and colleagues[21] suggested that the PSA threshold should be adjusted according to the GS for recommending a bone scan in newly diagnosed patients with prostate cancer; they recommended a bone scan for GS ≤7 and PSA >30 ng/mL and for GS ≥8 to 10 and PSA >10 ng/mL.[21] In our study, we determined whether the percent of positive biopsy core could enhance the predictability of bone metastasis. However, combining the percent of positive biopsy core with the guidelines resulted in comparable sensitivity, but lower specificity (Table 2).

Our study has several limitations. We did not confirm bone metastasis by biopsy. Although the clinical follow-up included a bone scan and CT or MRI for suspicious lesions,

the possibility of false-positive or false-negative results existed. Additionally, patients with a negative bone scan were not followed. Even though the specificity of a bone scan is high, the possibility of false-negative results existed.

Conclusion

Based on our study of Korean patients, the EAU and AUA guidelines showed better results than did Briganti's CART and the NCCN guidelines for predicting bone metastasis. A bone scan is strongly recommended in patients who have a higher percent positive biopsy core, as per the EAU and AUA guidelines.

Competing interests: Dr. Chong, Dr. I. Hwang, Dr. Ha, Dr. S. Yu, Dr. E. Hwang, Dr. H. Yu, Dr. Kim, Dr. Jung, Dr. Kang, Dr. Kwon, and Dr. Park all declare no competing financial or personal interests.

This paper has been peer-reviewed.

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Correspondence: Dr. Insang Hwang, Department of Urology, Chonnam National University Hospital, Republic of Korea; hwanginsang@gmail.com