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Higher scrotal uptake ratio of ^{99m}Tc -MDP on bone scans in newly diagnosed prostate cancer: a reliable indicator of pelvic node metastasis

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Abstract

Objective Pelvic lymph node dissection (PLND) is the gold standard procedure for nodal staging in prostate cancer (PC) but less commonly used due to its invasiveness. More commonly computerized tomography (CT) and magnetic resonance imaging (MRI) are used although these have limited sensitivities and specificities. The aim of this study was to find out the correlation between higher scrotal uptake ratio (SUR) of ^{99m}Tc -methylene diphosphonate (MDP) on bone scan and pelvic node metastasis in patients with PC at high risk for nodal metastasis.

Methods This was a retrospective study which included 68 biopsy proven newly diagnosed PC patients who had bone scan from January 2008 till January 2012. MRI of the pelvis, prostate specific antigen (PSA) and Gleason's score were available in all patients. Whole body bone scan was performed in all patients and SUR was calculated by dividing mean counts over scrotum and soft tissue over lateral aspect of right thigh. PLND was carried out within 2–3 weeks of MRI study in these patients.

Results Mean age of studied males was 71 ± 07 years with a mean PSA level of 65 ± 162 ng/ml. Prostate biopsy revealed adenocarcinoma in all patients with mean Gleason's score 7 ± 1 . Mean SUR was 2.786 ± 0.496 . MRI was positive for pelvic lymphadenopathy in 32/68 (47 %). PLND

revealed evidence of nodal metastasis in 16/68 (24 %) patients. Receiver operating characteristic analysis revealed good diagnostic strength of SUR for nodal metastasis with a cut off value of >2.99 with an area under curve (AUC) 0.708 (95 % CI 0.533–0.847, p value <0.05) and a mean sensitivity of 68.75 % and mean specificity of 80 %. Diagnostic strength of MRI for nodal metastasis was found to be low (AUC 0.566, 95 % CI 0.047–0.657, non-significant p value). No significant correlation was found between SUR and PSA in nodes positive and nodes negative patients.

Conclusion We conclude that in newly diagnosed PC patients, higher SUR on bone scan has a high diagnostic accuracy for pelvic node metastasis. Furthermore, a bone scan with a SUR <2.99 and negative for bone metastasis can stratify newly diagnosed PC patients as low risk.

Keywords Carcinoma prostate · Pelvic node metastasis · Bone scan · Scrotal uptake ratio

Introduction

Prostate cancer (PC) is the most common malignancy and third leading cause of death in American men [1]. Accurate detection of lymph node metastasis in PC is an essential step of approach for treatment and to predict prognosis. Presence of metastasis in one lymph node changes the status of PC from a local to a systemic disease with limited curative options. Bilateral pelvic lymph node dissection (PLND) in patients with intermediate to high risk for nodal metastasis is the standard procedure before radical prostatectomy or curative radiotherapy [2, 3]. CT and MRI have limited sensitivities and specificities due to inability to identify metastases in normal-sized nodes and nodal enlargement secondary to benign reason [4], respectively.

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Table 1 Patients' demographics

Variables	Total population (68)	<i>t</i> test	<i>p</i> value
Age (mean ± SD) years	71 ± 07	83.581	<0.0001*
PSA (mean ± SD) ng/ml	65 ± 162 (0.903–2000)	3.306	0.0015*
Gleason Score (GS) (mean ± SD)	7 ± 1	57.311	<0.0001*
Scrotal uptake on bone scan (mean ± SD)	2.786 ± 0.496	45.487	<0.0001*
Lymphadenopathy on MRI	32/68 (47 %)	173.186	<0.0001*
HP positive in PLND	16/68 (24 %)	88.345	<0.0001*

* *p* < 0.05

MR lymphography using superparamagnetic nanoparticles has reported high accuracy for small nodal deposits [5], but the technique is not widely available and expensive too.

Bone scan is an important tool for the detection of skeletal metastasis in PC patients with a prostate specific antigen (PSA) more than 10 ng/ml [6]. Higher scrotal uptake of Tc-99m MDP has been reported in patients with PC as compared to patients who had bone scans either for some benign or non-prostatic malignant reasons [7].

The objective of this study was to compare the diagnostic strength of scrotal uptake ratio of Tc-99m MDP on bone scan and MRI for nodal metastasis using pelvic nodes biopsies as gold standard in recently diagnosed patients with PC at high risk for nodal metastasis.

Materials and method

This was a retrospective study which included 68 PC patients who underwent PLND because of high risks of having lymph node involvement out of all 119 pathologically proven PC patients. These patients had their bone scans done as a part of staging workup at Nuclear Medicine Section, Department of Radiology, The Aga Khan University Hospital (AKUH), Karachi, Pakistan from January 2008 till January 2012. The study was duly approved by ethical and research committee. The mean age of patients was 71 ± 07 years with a mean PSA level of 65 ± 162 ng/ml (range 0.903–2000). Prostate biopsy revealed adenocarcinoma in all patients with a mean Gleason's score 7 ± 1 (Table 1).

MRI was performed in all patients using 1.5 Tesla scanner (Avanto 76 × 18, Siemens, Germany) and multiplanar and multisequential images of the abdomen and pelvis were obtained with and without intravenous contrast administration (Gadolinium DTPA). T2 weighted (sagittal, coronal, axial), diffusion weighted (DW) axial and post contrast T1-fat-saturation (axial, coronal and sagittal) sequences were acquired. Lymph nodes were reported as malignant if the short-axis diameter was elongated and >10 mm or was rounded and >8 mm, according to standard criteria [8].

Bone scan was performed in all patients with 20–25 mCi (740–925 MBq) of Tc-99m MDP injected intravenously and after 3 h whole body images were acquired under double

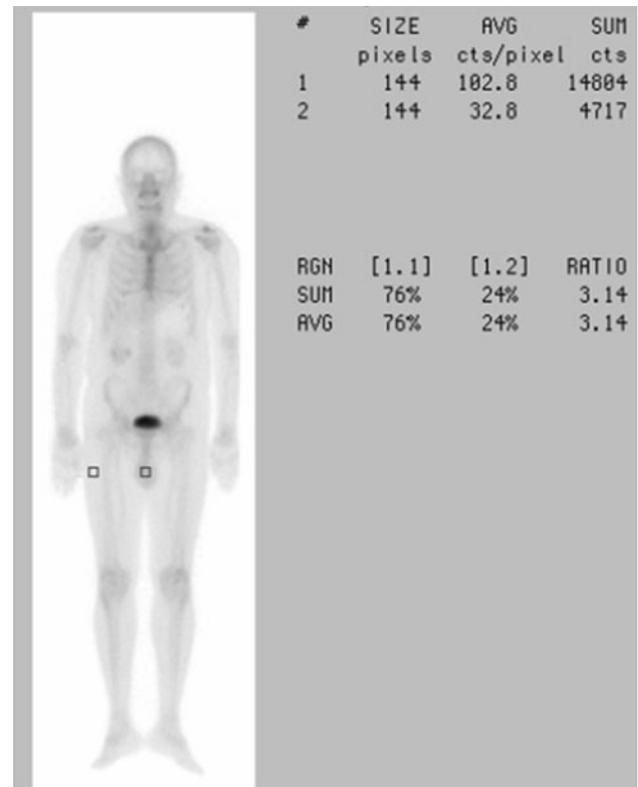


Fig. 1 Whole body bone scan (anterior view) with ROIs over scrotum and lateral aspect of right thigh for estimation of scrotal uptake ratio

head gamma camera fitted with low energy high resolution collimator (Ecam, Siemens, Germany). For quantitative analysis, square-shaped regions of interest (ROIs) of 144 pixels were placed centrally on the scrotum and then on the right thigh laterally (for correction of background) to avoid superimposition of major vessels and bones [7]. Scrotal uptake ratio (SUR), ratio of mean counts of the scrotal and femoral soft tissue ROIs (St/Bg), was calculated in each individual (Fig. 1). PLND was carried out within 2–3 weeks of bone scan and MRI study in patients with PSA >10 ng/ml and GS >6 as these patients are supposed to have higher probability for nodal metastasis. PSA and Gleason's score were also available in all patients.

Data were analyzed using the commercially available statistical software package MedCalc® version 11.3.10 and

SPSS software version 10. For univariate analysis, Chi-square test was performed for discrete and Student's *t* test was used for continuous variables. Receiver operating characteristics curves (ROC) were plotted for diagnostic strength of SUR and MRI against histopathology. Correlation of SUR against PSA was calculated by regression analysis. All *p* values <0.05 were selected as significant.

Results

Mean SUR was 2.86 ± 0.459 . MRI was positive for pelvic lymphadenopathy in 32/68 (47%). PLND revealed evidence of nodal metastasis in 16/68 (24%) patients (Table 1). Based on histopathology results of PLND, the cohort was divided into two groups with (16/68) or without nodal metastasis (52/68). The mean SUR in patients with

nodal metastasis was significantly higher than patients with no nodal metastasis (Table 2).

Receiver operating characteristic analysis for measuring diagnostic strength of SUR for nodal metastasis on histopathology revealed a cut off value of more than 2.99 with an area under curve (AUC) 0.708 (95% CI 0.533–0.847, *p* value <0.05; Table 3) and a mean sensitivity of 68.75% (range 41.4–81.9) and mean specificity of 80% (range 56.3–94.1) (Fig. 2). Figure 3 depicts the diagnostic strength of MRI for nodal metastasis with AUC of 0.566 (95% CI 0.047–0.657, non-significant *p* value; Table 3) with a mean sensitivity of 28.3% (range 16.0–43.5) and mean specificity of 84.9% (range 74.6–92.2). Scatter plot comparing the SUR and PSA in nodes positive and nodes negative patients showed no significant correlation with *r*: 0.227 and 0.104, respectively (non-significant *p* values) (Fig. 4a, b).

Table 2 Comparison of scrotal uptake ratio with nodal status on histopathology

Total PLND (68)	HP positive (16)	HP negative (52)	<i>p</i> value
SUR (mean \pm SD)	3.019 ± 0.409	2.55 ± 0.58	0.0037*

PLND pelvic lymph node dissection, HP histopathology, SUR scrotal uptake ratio, SD standard deviation

* *p* < 0.05

Table 3 Receiver operating characteristics curve analysis

	AUC	Standard error	95% CI	Z statistics	<i>p</i> value
SUR versus HP	0.708	0.089	0.533–0.847	2.334	0.0196*
MRI versus HP	0.566	0.0545	0.047–0.657	2.983	0.0842

AUC area under curve, CI confidence interval, SUR scrotal uptake ratio, HP Histopathology, MRI magnetic resonance imaging

* *p* value <0.05

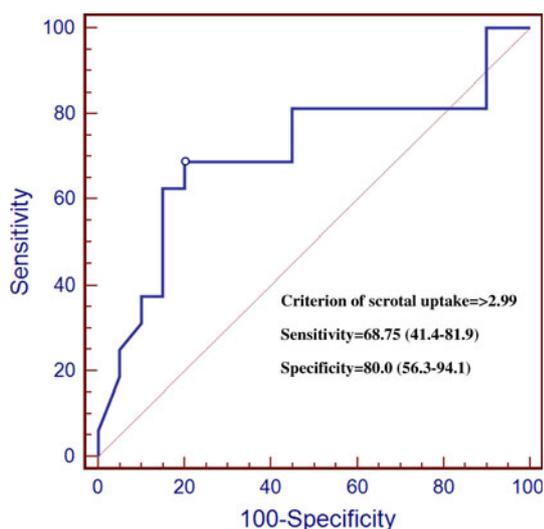


Fig. 2 Receiver operating characteristic analysis of scrotal uptake ratio with histopathology

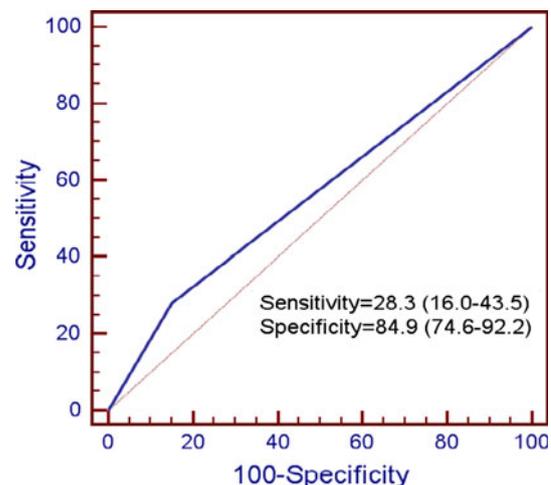


Fig. 3 Receiver operating characteristic analysis of MRI with histopathology

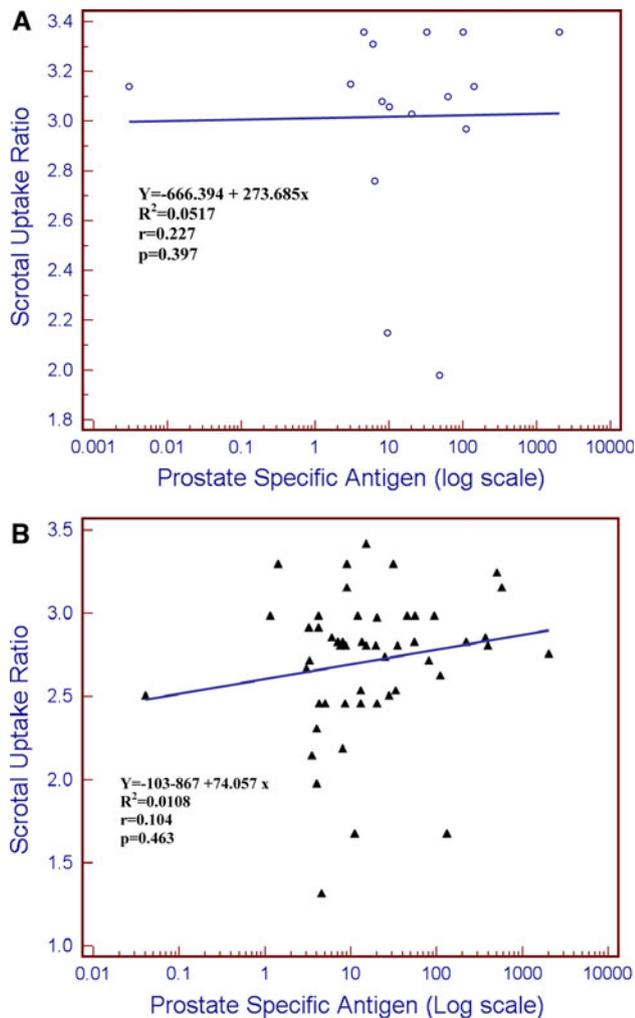


Fig. 4 **a** Scatter plot of scrotal uptake ratio on bone scan against prostatic specific antigen in patients with positive pelvic lymph nodes. **b** Scatter plot of scrotal uptake ratio on bone scan against prostatic specific antigen in patients with negative pelvic lymph nodes

Discussion

In PC, precise determination of nodal involvement is very important as a well localized disease without nodal involvement has the options of radical prostatectomy, watchful waiting, and radiotherapy. Pelvic lymph node dissection is the standard procedure for precise local staging but it is an invasive procedure, carries surgery-related morbidities and increases treatment cost as well. For these reasons, cross-sectional imaging like CT and MRI being non-invasive modalities are primarily used for local staging in PC.

Bone scan is the most common functional imaging which is used for the assessment of bony metastasis in patients with PC. Abnormal soft tissue tracer uptake is not an uncommon finding on bone scan [9]. Higher scrotal uptake of Tc-99m MDP on a bone scan in patients with PC

has been mentioned in the literature [7]. The possible mechanisms for this phenomenon may be either vascular thromboembolism (VTE) due to activation of coagulation system [10, 11] or lymphedema secondary to lymphangitis [12] as prostate and scrotum have common lymphatic drainage pathway [13]. In this study, we have correlated SUR on bone scan with nodal metastasis found on PLND biopsies and lymphadenopathy reported on MRI examinations. Our result showed that a SUR >2.99 has a good diagnostic accuracy for nodal metastasis seen on pelvic node biopsy. The mean sensitivity of 68.75 % for a SUR >2.99 indicates a chance of missing the nodal metastasis in about 31 % (false negative), but high mean specificity ensures its ability to truly diagnose the nodal metastasis. We do not have a precise justification for this phenomenon and assume that lymphangitis due to tumor invasion of regional lymphatic might be the reason as reported in the literature [12, 13]. However, further studies are required for precise evaluation of this important phenomenon. Therefore, patients whom bone scans reveal a SUR >2.99 must be considered as high risk for nodal metastasis and PLND must be considered for precise local staging of PC. Furthermore, in a newly diagnosed PC patient, a negative bone scan for bone metastasis with a SUR <2.99 may be used as a tool for selecting patients with localized disease (low risk group) with expected better outcome.

MRI revealed a weak diagnostic strength (non-significant *p* value) for nodal metastasis found on PLND and this is due to its inability to identify metastasis in normal-sized nodes and nodal enlargement secondary to benign reason [4], respectively. These values are significantly lower than some reported values [8] and the sentinel reason may be the use of 3D T1 weighted image sequences which was not used in this study. However, MR lymphography using superparamagnetic nanoparticles has been reported to have higher sensitivity than conventional MRI (90.5 vs. 35.4 %, *p* < 0.001) [5].

In our study, SUR had no significant correlation with PSA. According to various studies [14, 15] incidence of nodal metastasis with a pretreatment PSA <10 ng/ml and GS ≤6 is very rare. However, in this study, the mean PSA was 56 ± 198 ng/ml with a mean GS 7 ± 1 and theoretically we must have had a significant correlation. The absence of this correlation indicates that lymphedema may not be the only mechanism for higher SUR. The other possible explanation might be an aggressive nature of PC in Asian population preferentially with an early hematogenous spread than nodal metastasis resulting in higher incidence of bone metastasis even at low PSA level and GS as reported by our group [16]. Another plausible reason might be small sample size or sampling error, which is a limitation of this study. A well-designed study to evaluate this aspect of the SUR is really warranted.

To the best of our understanding, this is the first study which correlated SUR on bone scan with nodal metastasis on PLND biopsies and found a good diagnostic accuracy of higher SUR (>2.99) for nodal metastasis in newly diagnosed PC. Limitations of this study are its retrospective design, lower number of patients with PLND and lack of understanding about the precise mechanism of this finding.

We conclude that in newly diagnosed PC higher SUR on bone scan has a high diagnostic accuracy for nodal metastasis seen on PLND. Furthermore, a bone scan with a SUR <2.99 and negative for bone metastasis can stratify newly diagnosed PC patients as low risk.

Conflict of interest The authors declare they have no financial or non-financial competing interests.

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