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ORIGINAL ARTICLE

Observational Study

Incidence of exclusive extrapelvic skeletal metastasis in prostate carcinoma on bone scintigraphy

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Abstract

BACKGROUND

Bone is one of the common sites of metastasis from prostate carcinoma. Bone scintigraphy (BS) is one of the most sensitive imaging modalities currently used for bone metastatic work-up. Skeletal metastasis in prostate carcinoma commonly involves pelvic bones but rarely involves extrapelvic-extraspinal sites.

AIM

To retrospectively analyze the BS data to determine the pattern of skeletal metastases in the prostate carcinoma.

METHODS

This retrospective observational study involves patients with biopsy-proven prostate carcinoma referred for BS for staging assessment. Patients with abnormal BS were evaluated for the pattern of skeletal involvement and data were presented in descriptive format in the form of percentages.

RESULTS

A total of 150 patients with biopsy-proven prostate cancer who were referred for staging were included in the study. Thirteen of 150 patients (8.67%) had no abnormal uptake on planar images, ruling out metastatic disease. Twenty-four patients (16%) had heterogeneous uptake in the spine with distribution characteristic of degenerative disease and no scan pattern of metastatic disease. Thirty patients (20%) had multifocal uptake involving both pelvic and extra pelvic bones

on planar images typical for skeletal metastasis and were considered metastatic. Eighty-three out of 150 patients (55.3%) had increased tracer uptake, which was indeterminate, thus, single photon emission computed tomography-computed tomography (SPECT-CT) was acquired, which showed 51 with metastatic disease, 31 benign lesions, and one indeterminate finding. Seven of 150 patients had exclusive pelvic bone uptake, which was found to be metastatic in 4/7 patients in SPECT-CT. Fifty six out of 150 patients showed exclusive extrapelvic tracer uptake, of which only 3 had vertebral metastatic disease. None of the patients with increased uptake exclusively in the extrapelvic-extraspinal location was metastatic.

CONCLUSION

The incidence of exclusive extrapelvic skeletal metastatic disease in prostate carcinoma is 2% (excluding one patient with indeterminate findings). Further, none of the patients in the current study had exclusive extrapelvic-extraspinal metastasis. Thus, exclusive extrapelvic-extraspinal focal abnormality on planar BS carries a very low probability of metastatic disease and hence, further imaging or SPECT-CT can be safely avoided in such cases.

Key Words: Pelvic; Prostate cancer; Bone scan; Single photon emission computed tomography-computed tomography; Skeletal metastasis

Core Tip: The current study analyzed bone scintigraphy (BS) data from 150 patients with biopsy-proven prostate carcinoma to determine skeletal metastasis patterns. The most common site of skeletal metastasis was pelvis. The incidence of exclusive extrapelvic skeletal metastatic disease was 2%, excluding one indeterminate case. Additionally, no patients in the study had exclusive extrapelvic-extraspinal metastasis. Therefore, exclusive extrapelvic-extraspinal focal abnormalities on planar BS have a very low likelihood of being metastatic, making further imaging or single photon emission computed tomography-computed tomography often unnecessary.

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INTRODUCTION

Prostate carcinoma (PCa) is one of the most common cancers worldwide and stands as the second most commonly diagnosed cancer in men. It constitutes the 5th most common cause of cancer-related death[1]. The prevalence of PCa increases with age. About less than 5% of individuals under the age of 30 years harbor PCa, while this rises to greater than 59% in those with age above 80 years[2-4]. Skeleton is the most common site for metastatic disease involvement in PCa. Radionuclide bone scintigraphy (BS) is one of the most sensitive investigations for screening of skeletal metastases in PCa with the added advantage of low cost and the ability to screen the entire skeleton in a single study[5,6].

In PCa, pelvic bones, followed by the spine, represent the most common site of metastatic bone disease. This can be attributed to the low resistance venous connection between the periprostatic venous plexus and valveless vertebral venous plexus of Batson and the presence of a highly conducive microenvironment due to abundant red marrow, particularly in the pelvic bones providing the ideal "soil" for metastatic disease development[7-9]. Involvement of other bones without involvement of pelvic bones and spine is rarely encountered. We retrospectively analyzed the BS data to determine the pattern of bone metastases in PCa[5,10,11].

MATERIALS AND METHODS

The study involved a retrospective analysis of BS data of prostate cancer patients referred to the Department of Nuclear Medicine who underwent whole-body skeletal scintigraphy between August 2016 to June 2023. All patients with histopathologically proven PCa referred for whole-body BS for metastatic work-up were reviewed. Patients' details, clinical history, result of other imaging modalities and follow-up of the patients were recorded. The study was performed in accordance with the Declaration of Helsinki and after receiving approval from the institutional ethical committee (No. T/IM-NF/Nucl.Med/23/187).

Inclusion criteria

(1) Histopathologically proven PCa; (2) Patient referred for initial staging work-up; and (3) No history of prior hormonal therapy, radiotherapy, chemotherapy, or any other form of systemic therapy.

Exclusion criteria

(1) Histopathological diagnosis not available; or (2) History of prior systemic therapy.

Image acquisition

BS imaging protocol: Whole body BS was performed after intravenous administration of 20-25 mCi (740-925 MBq) of Tc-99m methylene diphosphonate (MDP) following SNMMI Procedure Standard for BS 4.0. Images were acquired on a dual-head gamma camera (Discovery NM/CT 670, GE Healthcare) using a low energy high-resolution parallel hole collimator with an energy window width of 20% centered at 140 KeV. Whole body planar images were acquired 3 hours after tracer injection in anterior and posterior views with a matrix size of 1024 × 256[12].

Regional single-photon emission computed tomography (SPECT)-computed tomography (CT) was acquired in patients with indeterminate and suspicious lesions on planar images. The SPECT was acquired in a step-and-shoot manner with 60 stops, 25 seconds/stop, and angular movement of 3 degrees/head/stop using a matrix size of 128 × 128 and co-registered with CT (low-dose non-contrast 16 slice CT acquired keeping 120 KVp, 50 mAs tube energy setting). The images were analyzed using the Xeleris 4.0 workstation. SPECT-CT images were processed with 8 iterations and sub-sets and co-registration with CT was done on Volumetric MI software to form fused 3D images[12].

Image interpretation

The scans were interpreted individually by two experienced nuclear medicine physicians. The scans were categorized as positive, negative, or suspicious/indeterminate for skeletal metastases on planar studies. The tracer uptake on planar BS was reported positive for metastasis when there is a classical pattern for metastatic disease involvement, like multiple foci of uptake. The scan was reported as negative when it conforms to the physiological distribution of the tracer or to the typical pattern of benign disease viz degenerative changes, arthritis, *etc.* In suspicious/indeterminate uptake, SPECT/CT of the corresponding region was available in all cases. SPECT/CT was interpreted as positive, negative or indeterminate for metastasis. In case of discordancy of results, the help of a third nuclear medicine physician was sought, and the final result was made on the basis of consensus.

Statistical analysis

The data were analysed on a per-patient basis, and the incidence of multiple metastases, including pelvic and extrapelvic, exclusive extrapelvic, and exclusive extrapelvic/extraspinal metastasis, was recorded. The data are presented in descriptive format in the form of percentages.

RESULTS

A total of 150 patients with biopsy-proven prostate cancer for staging were included in the study. The median age of included patients was 68.7 years (range: 42-86 years). A total of 81/150 patients showed metastatic disease.

Thirteen of 150 patients (8.67%) had no abnormal uptake on planar images ruling out metastatic disease. Twenty-four patients (16%) had heterogenous uptake in the spine with distribution characteristic of degenerative disease and no scan pattern of metastatic disease. Thirty patients (20%) had multifocal uptake involving both pelvic and extra pelvic bones on planar images typical for skeletal metastasis and were considered metastatic (Table 1).

Eighty-three out of 150 patients (55.3%) had increased tracer uptake on whole-body planar images, which were indeterminate or suspicious for metastatic disease. Thus, SPECT-CT was acquired to characterize the uptake further (Table 2). Forty-four of 83 patients (53%) had more than five foci of abnormally increased osteoblastic activity involving all pelvic, spinal, and extraspinal sites, and SPECT-CT was performed to confirm the metastatic disease. All of these patients were found to be metastatic on SPECT-CT. Focal osteoblastic activity localizing exclusively to the pelvis was seen in 7 patients, with 4 patients proven to be metastatic, and 3 patients having benign uptake on SPECT-CT. Thus, pondering a very high relative risk of isolated pelvic focal osteoblastic activity being malignant. The remaining 32 out of 83 patients showed abnormal exclusive extra pelvic tracer uptake. These included 20 patients with vertebral (17 benign and 3 metastatic) as shown in Figure 1, and 12 patients with exclusive extrapelvic extraspinal uptake (11 benign and 1 indeterminate) as shown in Figures 2-4. None of the patients with osteoblastic abnormality exclusively in the extrapelvic-extraspinal regions on planar BS was metastatic. One patient had focal uptake in the skull and was deemed indeterminate on SPECT-CT.

Exclusive extrapelvic

Thus, in total, of all patients showing exclusive extrapelvic uptake (56 patients), only three were metastatic (all vertebral metastatic disease) (Table 3). Exclusive extrapelvic/extraspinal uptake was found in a total of 12 patients, of which locations of uptake were ribs (7/12), sternum and manubriosternal joint (2/12), and skull (3/12). None of these exclusive extra pelvic-extraspinal sites of abnormal tracer uptake was malignant on SPECT-CT. Thus, pondering a negligible risk of metastatic skeletal disease in absence of pelvic and spinal bones involvement. Table 4 elaborates the SPECT-CT findings in solitary extra pelvic uptake. Most common site for metastatic disease involvement were pelvic bones followed by vertebrae and ribs (Table 5).

Table 1 Planar bone scintigraphy findings

Pattern of uptake on bone scan	Number of patients among, *n* = 150
No abnormal increased osteoblastic activity	13
Increased uptake with pattern typical of degenerative changes/benign uptake	24
Multifocal increased uptake typical for metastatic disease	30
Indeterminate or suspicious for metastatic uptake where SPECT-CT was performed	83

SPECT-CT: Single photon emission computed tomography-computed tomography.

Table 2 Single photon emission computed tomography-computed tomography findings

Lesion	Number of patients among, *n* = 83
Benign	31
Metastatic	51
Indeterminate	1

Table 3 Location of uptake and characterization in patients with exclusive extrapelvic uptake

Site of uptake	Benign	Metastatic	Indeterminate
Vertebra	41	3	0
Ribs	7	0	0
Sternum and manubriosternal region	2	0	0
Skull	2	0	1

Table 4 Single photon emission computed tomography-computed tomography characterization of isolated extrapelvic uptake

Serial No.	Age in years	Site of uptake	SPECT-CT findings	Final diagnosis
1	67	Left 1st rib	Arthritis	Benign
2	83	Right 5th rib	Fibrous dysplasia	Benign
3	66	Right 6th rib	Fracture line likely post traumatic	Benign
4	63	Right 11th rib	Fracture line likely post traumatic	Benign
5	72	Right 6th rib	Fracture line likely post traumatic	Benign
6	60	Sternum	Manubriosternal joint	Benign
7	76	Right parietal bone	Subtle sclerosis not typical for metastatic disease	Indeterminate

SPECT-CT: Single photon emission computed tomography-computed tomography.

DISCUSSION

In this study, we found pelvic bones and vertebrae to be the most common sites of metastatic disease in PCa. Further, this study demonstrates that the risk of a metastatic disease of an extra-pelvic/extraspinal uptake in PCa is negligible. Exclusive extrapelvic osteoblastic activity localizing to the spine has a less but significant risk of metastatic disease (15%).

PCa is relatively indolent and has slow growth. Thus, PCa has a favorable prognosis. The 5-year survival rates approach nearly 100% for localized as well as locoregional disease. However, this reduces to almost 34% once the patient has metastatic disease. Thus, marking the importance of early diagnosis of metastatic disease in PCa. With the implementation of early detection strategies like prostate-specific antigen screening programs, the majority of the cases are diagnosed in the early stages[2,6,13-15]. At diagnosis, about 78% of the patients have localized disease, while 16% of patients have locoregional lymph nodal involvement, and only 6% of cases have metastatic disease.

Table 5 Site of metastatic disease on bone scintigraphy

Site	Number of patients
Super-scan	10
Pelvic bones	68
Vertebrae	63
Ribs	55
Sternum	42
Femur	41
Scapula	41
Skull	32
Clavicle	29
Humerus	23
Others	7 (4 tibia, 2 forearm bones, 1 maxilla)

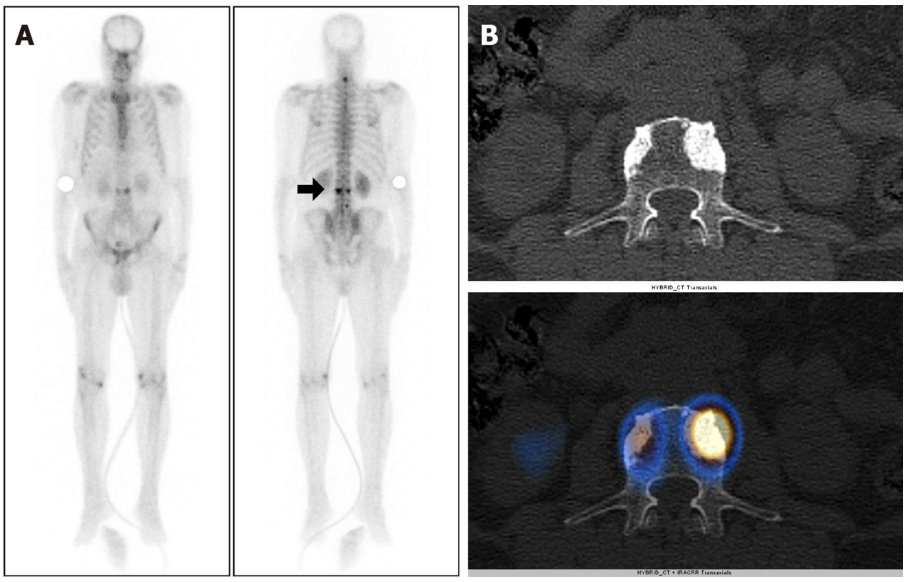

Figure 1 A 74-year-old male, with a newly diagnosed case of carcinoma of the prostate [Gleason's Score 7 (4 + 3)] with serum prostate-specific antigen level 491 ng/mL and underwent whole body bone scintigraphy. A: ^{99m}Tc methylene diphosphonate Whole body planar images show focal increased tracer uptake involving the cervical and lumbar vertebrae (arrow) raising the suspicion of metastatic disease; B: Axial computed tomography (CT) and fused single photon emission computed tomography (SPECT)-CT images show tracer localization to sclerotic lesion involving L3 vertebrae suggestive of metastatic disease. No metastatic disease was seen in pelvic bones on SPECT-CT.

Bone and bone marrow, providing the ideal site for metastatic disease development, constitute the most common site for metastatic disease involvement of PCa. Lymph nodes, lung and liver follow this. Approximately 60% of patients progress to metastatic disease throughout management, and approximately 80% of patients with fatal progressive PCa harbor bone metastasis[16,17]. Bone metastasis commonly localizes to pelvic bones. This is hypothesized to be secondary to the retrograde spread of the tumor *via* the venous communication between the low resistance periprostatic venous plexus and Batson's plexus. BS is the most commonly used imaging modality for the assessment of bone metastasis in PCa staging. BS can be performed using 99m-Tc MDP and 99m-Tc HDP (hydroxymethylene diphosphonate). These radiopharmaceuticals, when injected intravenously, get rapidly chemisorbed onto the hydroxyapatite crystals and more so at the sites of increased osteoblastic activity, thus highlighting the skeletal involvement with high sensitivity[8,18-20].

However, not all areas of increased osteoblastic activity are metastatic, and they may represent some benign pathology. Thus, emanating its limited specificity. The use of targeted SPECT/CT offers more specific diagnostic options in this subgroup of patients. It adds anatomical information of CT with functional information of SPECT and can help rule out benign causes of increased tracer uptake and confirm the metastatic disease. SPECT/CT, however, is associated with increased patient radiation burden by its CT component and adds to the total scan time. It adds approximately 0.5 to 2.6 mSv of radiation dose to the patient and approximately ≥ 12 mins to the acquisition time, depending on the area imaged. Thus, employing the need for caution while performing SPECT/CT[21-23]. Further, it is not always available in all

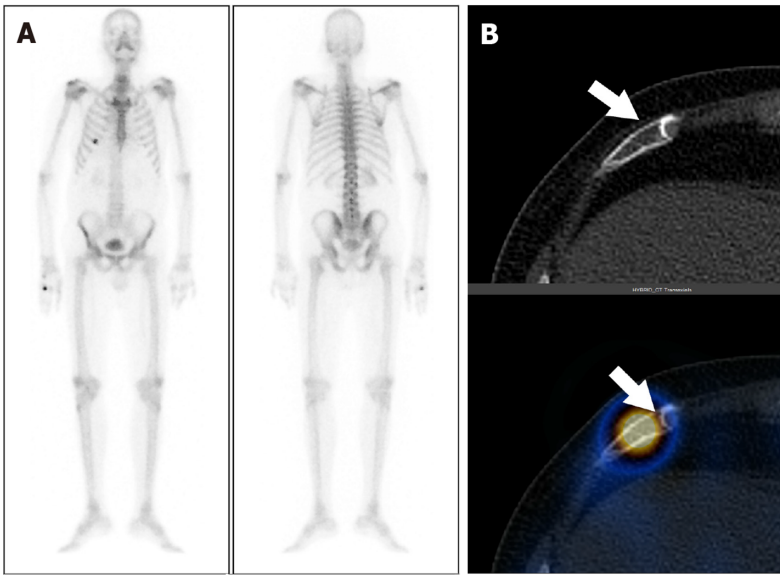

Figure 2 A 66-year-old male with carcinoma of the prostate and serum prostate-specific antigen of 23.3 ng/mL. A: Staging with whole body bone scintigraphy show focal areas of increased tracer uptake involving the right 6th rib; B: Axial computed tomography (CT) and fused single photon emission computed tomography-CT images show tracer localization to the right 6th rib anteriorly with a fracture line (arrow). The uptake was thus secondary to rib fracture post traumatic. There was no other abnormal uptake anywhere in the bones on whole body study.

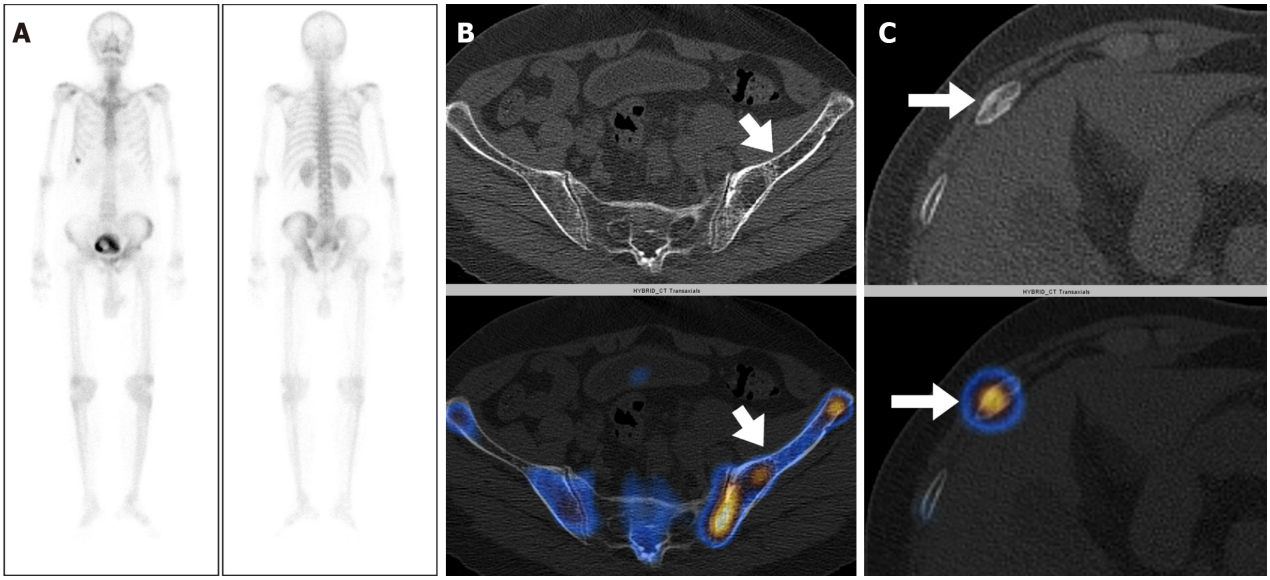

Figure 3 A 77-year-old male with carcinoma of the prostate and a Gleason's Score 8 (4 + 4) and serum prostate-specific antigen level of 100 ng/mL. A: Staging whole body bone scintigraphy show heterogeneously increased tracer uptake involving the left hemipelvis and focal areas of increased tracer uptake involving the right 8th rib raising the suspicion of metastatic disease; B and C: Axial computed tomography (CT) and fused single photon emission computed tomography-CT images localizes the tracer to the left iliac bone with cortical thickening and bony expansion consistent with Paget's disease (arrow in B) and to the right 8th rib anteriorly with a fracture line (arrow in C).

Nuclear Medicine departments.

Skeletal metastasis from PCa commonly localizes to pelvic bones followed by vertebrae. Isolated focal areas of uptake, apart from these regions, are rarely due to skeletal metastasis[13,14,17]. Wang *et al*[24] studied the distribution of skeletal metastasis in PCa and found vertebrae and pelvis to be the most frequent sites to harbor metastasis. Only 1% of patients had exclusive extrapelvic-extraspinal metastasis. The present study revealed metastatic disease involvement only in 3 patients (2%) with extra-pelvic skeletal disease in the absence of pelvic bone involvement. All three patients had involvement of vertebrae. None of the 150 patients had exclusive extrapelvic-extraspinal skeletal metastasis.

In an autopsy study by Mintz and Smith[25], including 100 patients of PCa, 21 patients had bone metastasis, and all the cases had involvement of the axial skeleton, with no incidence of isolated appendicular skeleton involvement. The pelvis was the most common site for metastatic disease and was involved in 13/21 cases. Similar results were observed by Roth *et al*[14] where axial skeleton involvement was found in all the patients (n = 54), while pelvic involvement was observed

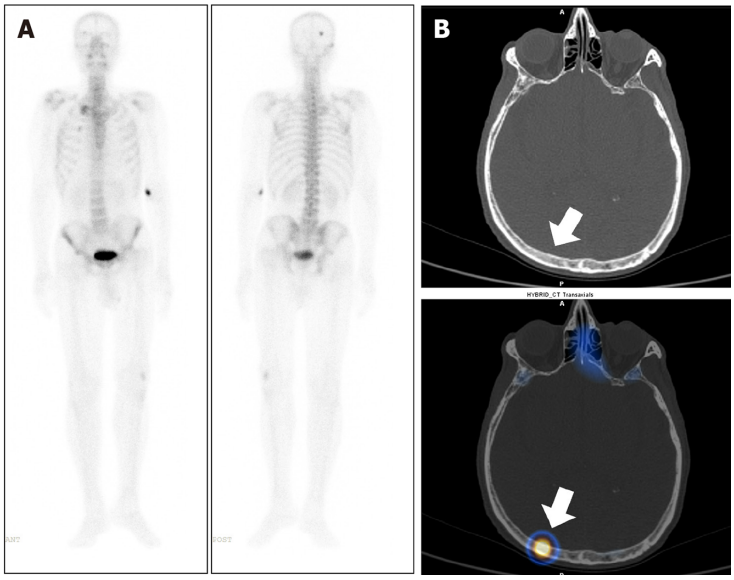

Figure 4 A 76-year-old male, with a newly diagnosed case of carcinoma of the prostate underwent whole body bone scintigraphy. A: ^{99m}Tc methylene diphosphonate Whole body planar images show solitary focal area of increased tracer uptake involving skull bone on the right side; B: Axial computed tomography (CT) and fused single photon emission computed tomography-CT images show tracer localization to the right parietal bone (arrow) with no significant CT abnormality to suggest of metastatic disease involvement. The lesion was thus considered indeterminate.

in 92.5% (n = 50) of patients. Also, in another autopsy study by Bubendorf *et al*[6], the axial skeleton was the predominant site of skeletal metastasis, with exclusively extrapelvic-extraspinal metastasis skeleton being rarely involved. Thus, fortifying the hypothesis of the current study.

The current study's limitations include a retrospective design, limited sample size, lack of survival data, and lack of histopathology confirmation of the BS findings.

CONCLUSION

The incidence of exclusive extrapelvic skeletal metastatic disease in PCa is 2% (excluding one patient with indeterminate findings). None of the patients in the current study had exclusive extrapelvic-extraspinal metastasis. Thus, exclusive extrapelvic-extraspinal focal abnormality on planar BS carries a very low probability of metastatic disease, and hence, further imaging or SPECT/CT can be safely avoided in such cases.

FOOTNOTES

Author contributions: Singh P and Agrawal K contributed to conception and design; Singh P and Singhal T contributed to drafting the manuscript; Agrawal K, Parida GK and Gnanasegaran G contributed to analysis and interpretation of data; Rahman A contributed to data collection, interpretation of data; All authors have confirmed the final approval.

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