OPEN

Value of Bone Scans in Work-up of Patients With Hepatocellular Carcinoma for Liver Transplant

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Background. The purpose of this study was to review the value of bone scans (BS) in the assessment of bone metastases from early-stage hepatocellular carcinoma (HCC) in patients assessed or waiting for liver transplant (LTx). **Methods.** We reviewed BS studies performed at our center for patients with early-stage HCC either being assessed for LTx, or on the waiting list for LTx, from January 2010 to May 2017. The BS findings were classified as positive, equivocal, or negative. Correlation with final outcome based on clinical and radiological follow-up was performed. **Results.** There were 360 BS performed in 186 patients during the study period with a mean age of 58.7 years (range, 34.9-70.4 years) and most were male patients (161/186 [86.6%]). None of the BSs resulted in delisting of patients from the LTx waiting list. Three BSs were reported as positive for metastases. All 3 were proven to be false positives on follow-up. Fourteen studies reported equivocal findings, none of which were confirmed to be metastases on follow-up. There was 1 false-negative BS: a bone metastasis was detected incidentally on magnetic resonance imaging and proven on biopsy. **Conclusions.** We have demonstrated that the diagnostic yield of BS in early HCC patients who are candidates for LTx is minimal, challenging the current inclusion of BS in guidelines for staging these HCC patients.

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Hepatocellular carcinoma (HCC) is a growing global problem[1,2] and represents the second leading cause of cancer-related death worldwide.[3] Curative treatments, such as resection, ablation, and liver transplantation (LTx), are offered for patients with early-stage tumors and for patients fulfilling criteria for liver transplant outcome and survival are excellent.[4] The current American Association for the Study of Liver Diseases (AASLD) and European Association for the Study of the Liver (EASL) clinical practice guidelines for staging patients with HCC before LTx include chest computed tomography (CT) and bone scan (BS) for assessment of extrahepatic disease including bone metastases.[5,6] The rationale for this assessment is that patients with extrahepatic disease will be excluded from LTx. However, the current 2011 Organ Procurement and Transplantation Network Policies (9.3.F.ii) no longer include BS in the assessment of extrahepatic disease after it was removed from the 1998 policies which previously included them.[7] The use of BS in patients with early-stage HCC has already been challenged.[8,9] However, many LTx centers, including our own, continue to use them in staging before LTx and on 6 monthly basis while on the waiting list in accordance with existing guidelines.

Bones represent the third most frequent site, after lungs and lymph nodes, for extrahepatic metastases seen in HCC.[10-12] The majority of bone metastases involve the spine, pelvis, and ribs.[13-15] These are sites covered by conventional CT imaging of the chest, abdomen, and pelvis. The aim of our study is to review the value of BS in assessment of extrahepatic metastases from early-stage HCC in patients assessed for and on LTx waiting list.

MATERIALS AND METHODS

Patients

The study was approved by our institutional review board. We retrospectively reviewed the medical records of patients

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with HCC who had at least 1 BS performed between January 2010 and May 2017. All patients in the study were assessed for and/or on the LTx waiting list. At our center, the protocol for screening for metastatic disease, in patients listed for LTx for HCC is to perform a BS and a chest CT on initial assessment and then 6 monthly while on the LTx waiting list.

The diagnosis of HCC was based on radiological findings with histopathological confirmation when necessary in accordance with AASLD guidelines. Our HCC prospective database and medical charts were reviewed for demographics and clinical characteristics of patients including etiology of liver disease, Child-Turcotte-Pugh (CTP) class, number of active tumors at the time of study and presence of extrahepatic disease. The outcome of patients with regard to transplantation, mortality, and follow-up was also recorded. We only included patients who were considered for LTx and excluded patients who had already undergone BS with known advanced-stage HCC or extrahepatic disease. We also excluded patients who had a BS as part of staging before HCC surgical resections.

Bone Scintigraphy

Bone scans were performed 3 hours postintravenous injection of 744 MBq of Tc-99m methyl diphosphonate. Anterior and posterior whole-body images acquired. In addition, single-photon emission computed tomography (SPECT) with a dual-head gamma camera (GE Discovery NM/CT 670 Pro or Siemens Symbia TruePoint SPECT/CT) was occasionally acquired in some body regions. Low-dose CT imaging was used where relevant in a targeted fashion on review of bone scintigraphy findings. Targeted SPECT and SPECT/CT imaging were used when standard planar BS imaging revealed a finding that required clarification or when there was a specific question regarding a body region. Studies were reported by an experienced nuclear medicine physician or nuclear medicine qualified radiologist.

The reports of each BS were reviewed by 1 radiologist who was blinded to patients' HCC burden and outcome. The results were classified into negative, equivocal or positive for bone metastases. Scans with findings explained by physiological change, inflammation, degenerative changes, and/or trauma were considered negative. Clinical and radiological follow-up with radiographs, CT and magnetic resonance imaging (MRI), were used to assess the accuracy of BS findings.

Cost Analysis

A cost analysis was performed. Costs for BS, additional imaging or procedures required for further assessment of BS findings and hospital stay were obtained from the Australian Medicare Benefits Schedule and from the Benefit Requirements (Department of Health, Australian Government). Costs for imaging and procedures including BS did not change over the study period. Costs related to additional physician visits or time spent to correlate BS positive or equivocal findings with other imaging in multidisciplinary meetings were not incorporated into cost estimates. Individual items costs are listed in Table 4. All costs are reported in Australian dollars. For the purposes of this simplified analysis, estimates of total costs in US dollars are also provided using an average of historical exchange rates over the study period obtained from Westpac Banking Corporation (https://www.westpac.com.au/personal-banking/services/historical-rates).

Descriptive results are presented in frequencies and percentages. Continuous variables are presented as mean with range and medians with interquartile range (IQR) where relevant. No statistical comparisons were required or performed for the purposes of this study.

RESULTS

A total of 186 patients were included in this study with a mean age of 58.7 years (range, 34.9-70.4 years) and most were male patients (161/186 [86.6%]). The etiology of liver disease, CTP class, number of viable HCC tumors at the time of BS is given in Table 1. A total of 113 (60.8%) of 186 patients received a transplant during the study period. Fifteen of 73 patients who were not transplanted were still awaiting transplant at the time of assessment (Table 2). Median (IQR) follow-up was 2.3 years (1.1-3.9).

There were 360 BS performed in 186 patients during the study period. Ninety-two patients underwent 1 BS with 94 patients having 2 or more BSs. The majority of BSs (306/360) were performed without SPECT or SPECT/CT imaging, while 46 BSs were performed with SPECT/CT and 8 were performed with SPECT only.

None of the BSs resulted in delisting of patients from LTx waiting list. Three BSs were reported positive for metastases. In 1 of these 3 studies, the patient was reported to have a skull

TABLE 1.

Demographics and clinical characteristics of patients

Variables	Total = 186 patients
Age (range)	58.7 years (34.9-70.4)
Gender	n (%)
• Male	161 (86.6%)
• Female	25 (13.4%)
Etiology	
• HCV	107 (57.5%)
• HBV	33 (17.7%)
• EtOH	19 (10.2%)
• NASH	15 (8.1%)
• Others	12 (6.5%)
CTP class	
• A	82 (42.9%)
• B	61 (31.9%)
• C	48 (25.1%)
No. viable HCCs[a]	
• Nil[b]	78 (41.9%)
• Single	62 (33.3%)
• Multiple	46 (24.7%)
Size of viable HCCs[c]	2.7 cm (1.5-4)
Beyond Milan criteria at listing	14 (7.5%)
AFP	5.3 ng/mL (2.85-17)
MELD	12 (8-16)
Locoregional therapy	
• No therapy	26 (14%)
• Combination of therapies	81 (43.5%)
• TACE	69 (37.1%)
• Ablation	10 (5.4%)

[a] Assessment at time of most recent BS.

[b] Previously treated tumor(s)—not viable at time of BS.

[c] Median size (IQR) of viable tumor burden per patient at time of most recent BS.

HCV, hepatitis C virus; HBV, hepatitis B virus; EtOH, ethanol; NASH, nonalcoholic steatohepatitis; AFP, alpha-fetoprotein; TACE, transarterial chemoembolization.

TABLE 2.
Outcome of patients

Outcome	n/N (%)
Transplanted	113/186 (60.8%)
• Time to transplant[a]	15 months (9-27)
• Alive	103/113 (91.2%)
○ Disease free	103
○ Recurrent HCC	0
• Not alive	10/113 (8.8%)
○ HCC-related	5
○ Non-HCC related	3
○ Postoperative	2
Not transplanted	73/186 (39.2%)
• Time to delisting	9 mo (4-14)
• Time to death[b]	6 mo (3-8)
• Alive	45/73 (61.6%)
○ Awaiting liver transplant	15
○ Delisted	30
▪ Advanced HCC[c]	15
▪ Sustained remission	5
▪ Social reasons	5
▪ Cholangiocarcinoma	3
▪ Other	2
• Not alive	28/73 (38.4%)
○ HCC-related	11
○ Cirrhosis-related	13
○ Other causes	4

[a] Time from first HCC diagnosis to transplant.

[b] For patients who died while on waiting list.

[c] Of 15 patients delisted for advanced HCC, 11 were discharged back to their referring hospitals within 12 months of their BSs—presumably not alive.

metastasis and underwent an excisional biopsy which revealed a benign sclerotic lesion and was negative for metastasis. The remaining 2 patients with suspected rib and scapular metastases had no diagnostic CT correlates for the suspected metastases and were followed up with repeat BSs which showed resolution of the findings. All 3 studies were considered false-positive BSs (Table 3).

One patient had a BS to investigate an incidental L3 vertebral body focal lesion identified on lumbar spine MRI performed for evaluation of L1 crush fracture through a known hemangioma (Figure 1). The L3 lesion did not show increased activity on BS (Figure 2) but went on to have a CT-guided biopsy which demonstrated a metastatic HCC deposit. This was considered a false negative BS.

Fourteen studies reported equivocal findings; none of which were confirmed to be metastases on radiographic, CT, MRI, BS, and/or clinical follow-up. Out of these 14 studies, 10 (71.4%) abnormalities were rib lesions, 3 (21.4%) were lumbosacral spine lesions, 1 was in a humeral shaft, and 1 was in a femoral head. The remainder of BSs were negative (Table 3). Among the negative scans, 67 BSs reported benign findings including arthritic changes and rib fractures.

The use of BS as part of initial and ongoing staging of HCC patients for LTx generated an expenditure of A$185298.30(US $171854.30). Costs for 4 patients who required further imaging and 1 patient who required a surgical biopsy were A$3471.60 (US $3219.72). The grand total costs of BS and additional work-up was A$188769.90 (US $175074) resulting in an average per patient cost of A$1014.89 (US $941.25) (Table 4).

DISCUSSION

The rise in incidence and recognition of bone metastases in HCC patients is attributed to improved survival of HCC patients in general due to improvements in primary tumor control.[16] However, the incidence of such metastases remains very low in early-stage HCC, the cohort considered for LTx.[8,9,17]

Our study reviewed the results of BS in assessment of patients with early-stage HCC considered for LTx and has confirmed previously reported data.[8,9] In our cohort of patients, BS showed no true bone metastases. We encountered 3 false positives, 14 equivocal findings, and 1 false-negative BS. None of the patients who had positive or equivocal findings were found to have bone metastases on clinical and radiological follow-up. The findings confirm the very low incidence of bone metastases in early-stage HCC with only 1 (0.5%) of 186 patients developing a bone metastasis which was not detected by BS.

Sensitivity, specificity, positive predictive value and negative predictive value of BS were not provided given the absence of a true positive finding on BS and the very low incidence (1 of 186) in this cohort. There was slight heterogeneity in the acquisition of BS with the majority of patients (306 of 360) receiving planar imaging only and some patients (54 of 360) receiving SPECT and SPECT/CT imaging. SPECT/CT imaging is known to improve the specificity, and to a lesser extent sensitivity, of BS.[18] However, it is unlikely that performing SPECT/CT on all of these patients would have resulted in improved BS accuracy due to the very low prevalence of bone metastases. In the only case with a bone metastasis in our cohort, a diagnostic CT study could not identify the metastasis despite direct correlation with the MRI study in which the metastasis was detected and therefore performing a SPECT/CT might not have improved the detection of this metastasis.

It is no surprise that BS offers limited additional value in staging patients with early-stage HCC.[17] Bone metastases from HCC are osteolytic in the majority of cases.[10,11,19] The osteolytic nature of these metastases may lead to false-negative results which have been reported in 27% of patients with HCC-related bone metastases.[20] The majority of such metastases are in the axial skeleton involving ribs, thoracic and lumbar spine and pelvis and assessment of such regions can still be made with routine CT imaging performed for primary tumor and chest evaluation.

Whether BS still has a role in staging patients beyond LTx criteria is debatable. The additional value of detecting bone

TABLE 3.
Results of 360 BSs in 186 patients with follow-up

	Bone metastasis		
BS results	Present	Absent	Total
Positive	0	3 (0)	3
Equivocal	0	14 (9)	14
Negative	1[a] (0)	342 (45)	343
Total	1	359	360

Number in parenthesis indicates studies performed with SPECT/CT.

[a] False negative BS for a focal lesion in L3 vertebral body—visible on MRI and not seen on diagnostic CT.

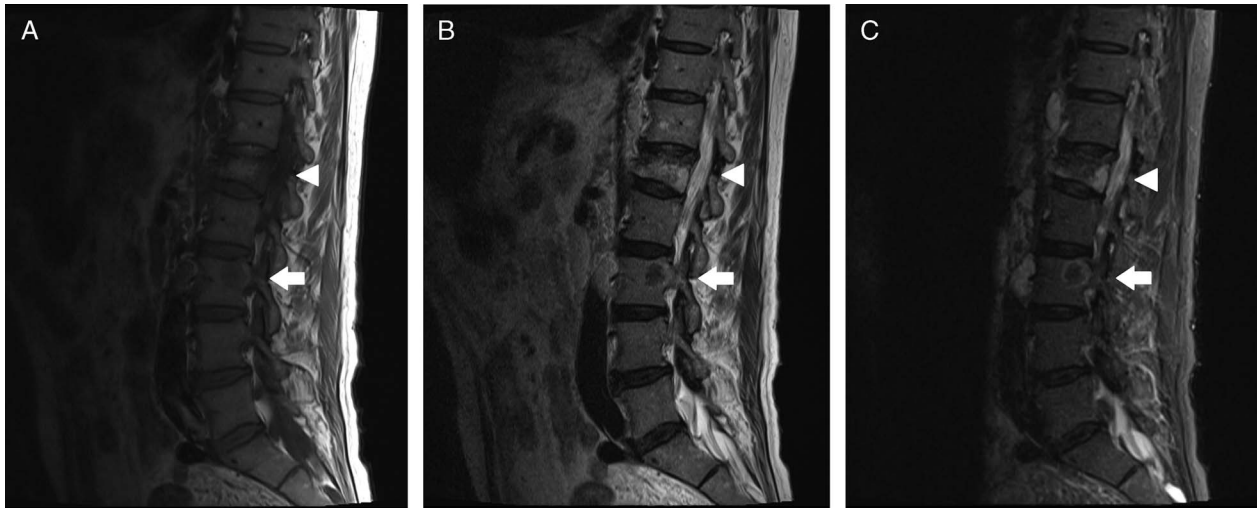

FIGURE 1. Lumbar spine sagittal MRI for assessment of a crush fracture through L1 vertebral body known hemangioma (arrowhead) demonstrating an incidental lesion in L3 vertebral body (arrow) which is low intensity on T1 (A) and T2 (B) sequences with peripheral high intensity on STIR sequence (C). The L3 lesion was biopsied under CT guidance confirming HCC metastasis.

metastases in patients with advanced-stage/metastatic HCC is probably minimal and symptomatic patients will receive targeted radiographic and cross-sectional imaging which probably negates the routine use of whole-body BS.

Our cohort findings confirm findings from similar cohorts with limited value of routine use of BS in early-stage HCC. Koneru et al[8] in 2005 first described the limited role of BS in a similar cohort of 117 LTx candidates and found no bone metastases in their patients.[8] Rodriguez et al[9] assessed a cohort of 328 patients with a total number of 259 patients receiving a BS as part of their assessment for LTx. 276 of their patients were transplanted with 207 of transplanted patients receiving BSs before LTx. They showed no difference in

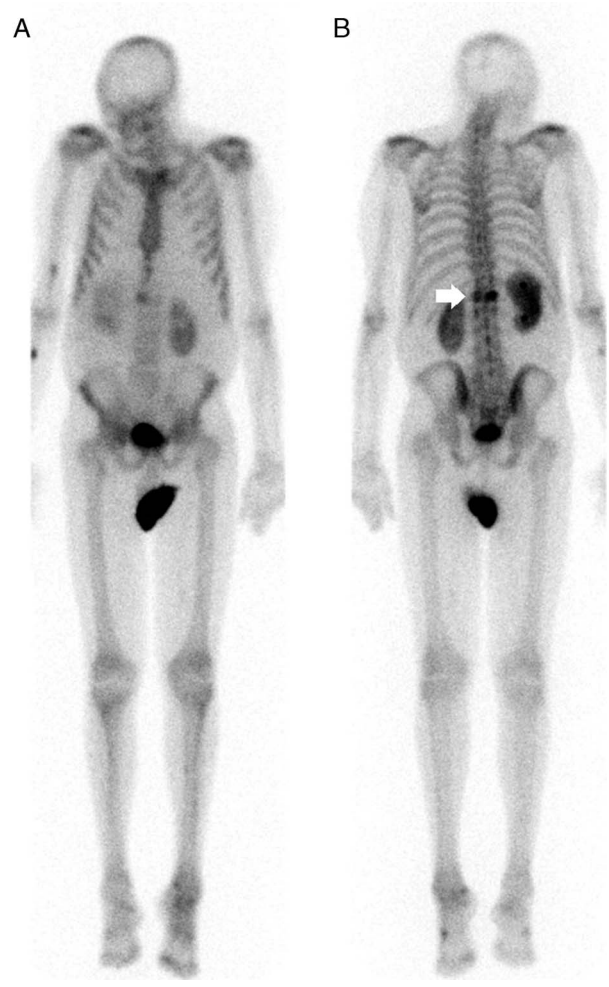

FIGURE 2. Whole-body BS anterior (A) and posterior (B) views performed 8 days after lumbar spine MRI, demonstrating increased uptake at L1 crush fracture site (arrow) and no increased uptake at L3 metastasis detected on MRI.

TABLE 4.

Costs of BS and additional work-up for positive and equivocal BS findings

Unit	Number	Unit cost (A$)	Total (A$)
BS	306	496.95	152066.70
BS with SPECT/CT	54	615.40	33231.60
Total			185298.30 (US $171 854.30)
Additional work-up			
(1) False positive skull lesion			
CT with contrast	1	250.00	250.00
Surgical biopsy	1	1511.60	1511.60
Hospital stay	1	356.00 per night	356.00
Histopathology	1	417.20	417.20
(2) Equivocal S3 vertebral lesion			
MRI with contrast	1	358.40	358.40
(3) Equivocal L1 vertebral lesion			
MRI with contrast	1	358.40	358.40
(4) Equivocal acromion lesion			
CT shoulder	1	220.00	220.00
Total			3471.60 (US $3219.72)
Grand total			188769.90 (US $175074)
Average cost per patient			A$1014.89 (US $941.25)

outcome between patients who underwent and did not undergo a BS before LTx. In their cohort, 1 patient developed a bone metastasis before LTx but the patient was symptomatic, and the metastasis was visible on BS as well as targeted imaging. Our study assessed a smaller number compared to the study by Rodriguez et al but the total number of BSs was larger as our patients had repeat BS every 6 months while on the LTx. Data regarding staging of early-HCC patients before surgical resection[17,21] and on initial staging for new diagnosis of HCC[22] confirm the low diagnostic yield of BS in early-stage HCC.

Patients with HCC undergo multiple diagnostic and therapeutic radiological procedures. The effects of radiation exposure are usually weighed against the benefit of diagnostic work-up and treatments. However, patients with HCC who undergo evaluation for LTx receive significantly high ionizing radiation including from BS.[23] If transplanted, such patients have reasonably improved life expectancy and efforts should be made to decrease unnecessary ionizing radiation before transplantation. Furthermore, the costs associated with BS in such cohorts have already been highlighted in 2 similar cohorts.[8,9] Omitting unnecessary BS and downstream tests from false positive and equivocal findings can provide significant savings to healthcare systems.

Our study has some limitations. This was a single-center retrospective review of patients who had received at least 1 BS study and were on the LTx assessment/waiting list. Some of our patients were delisted for LTx due to disease progression or other causes and were not followed-up at our institution and data on their mortality was unclear. However, this scenario would not have influenced the results of our study question.

In conclusion, we have demonstrated that the diagnostic yield of BS in early-HCC patients who are candidates for LTx is minimal. Healthcare costs related to unnecessary BS and additional tests and biopsies incurred from false positive and equivocal results are unjustified. In our opinion, clinical assessment for symptomatic patients with targeted imaging rather than routine BS use would be more appropriate for suspected bone metastases. We doubt that randomized-controlled trials assessing the role of BS in such cohorts would yield different results. Given our findings and evidence from previous studies, we recommend that routine ordering of BS in the LTx staging work-up for early-HCC patients is removed from current AASLD and EASL guidelines.

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