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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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 item 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
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 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. Bone metastases from HCC are osteolytic in the majority of cases. 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. 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 2

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

<sup>a</sup> Time from first HCC diagnosis to transplant.

<sup>b</sup> For patients who died while on waiting list.

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

### Table 3

Results of 360 BSs in 186 patients with follow-up

| BS results | Present | Absent | Total |
|------------|---------|--------|-------|
| Positive   | 0       | 3 (0)  | 3     |
| Equivocal  | 0       | 14 (9) | 14    |
| Negative   | 1* (0)  | 342 (49) | 343   |
| Total      | 1       | 359    | 360   |

Number in parenthesis indicates studies performed with SPECT/CT.

<sup>*</sup> False negative BS for a focal lesion in L3 vertebral body—visible on MRI and not seen on diagnostic CT.
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. 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

| 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 repeated BS every 6 months while on the LTxs. Data regarding staging of early-HCC patients before surgical resection\footnote{[17-21]} and on initial staging for new diagnosis of HCC\footnote{[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.\footnote{[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.\footnote{[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 received at least 1 BS study and were on the LTx assessment/waiting list. Some of our patients were delisted for LTxs 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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