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# FREQUENCY AND NUMBER OF BONE LESIONS ON BONE SCAN IN CASE OF HEPATOCELLULAR CARCINOMA

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## Abstract

***Objective:***
*To determine the frequency and number of bone lesions on bone scan in cases of hepatocellular carcinoma.*

***Methodology:***
*This Cross-sectional study was carried out from December 2024 to May 2025 at the Department of Nuclear Medicine, Multan Institute of Nuclear Medicine and Radiotherapy, Multan.*
*A total of 114 patients with hepatocellular carcinoma aged 18-60 years were included. Bone scintigraphy was performed after intravenous administration of technetium-99m methyl diphosphonate. Presence, number and anatomical distribution of metastatic bone lesions were recorded. Data were analysed by using IBM Statistical Package for Social Sciences version 26.*

***Results:***
*The mean age of patients was 48.49 ± 11.62 years. Bone metastasis were detected in 11 patients giving frequency of 11 (9.60%). Vertebral involvement was present in 11 (100.0%) patients, pelvic involvement in 10 (90.9%) and rib involvement in 4 (36.4%) patients. Mean number of lesions was 0.27 ± 0.96. Significant association was observed between bone metastasis and duration of disease (p=0.049), stage of hepatocellular carcinoma (p=0.002) and previous chemotherapy or radiotherapy (p=0.009).*

***Conclusion:***
*Bone metastasis is not uncommon in hepatocellular carcinoma and bone scintigraphy is useful for early detection of skeletal involvement, especially in advanced disease.*

## INTRODUCTION

Hepatocellular carcinoma is one of the commonest types of primary cancer of the liver and an important cause of death from cancer all over the world.[1] It commonly occurs in individuals who have chronic conditions of liver like hepatitis B, hepatitis C and liver cirrhosis.[2] Individuals can suffer from symptoms like abdominal pain, weight loss, jaundice and weakness but sometimes individuals do not show any symptoms at early stages of the disease.[3] In later stages, hepatocellular carcinoma can metastasize to other parts of the body including lungs, lymph nodes and bones.[4]

Bone metastases are an adverse effect associated with hepatocellular carcinoma, and bone scans are widely used for diagnosing such lesions.[5] Bone scan is termed a sensitive diagnostic technique since it can diagnose the presence of metastatic lesions in various parts of skeleton before developing severe symptoms.[6] Lesions may be single or multiple in nature affecting the vertebrae, ribs, pelvis, and long bones. Individuals suffering from numerous lesions generally develop severe bone pain, limited movement, and pathological fractures.[7] Diagnosing the presence of multiple lesions by bone scan is clinically significant as it aids in staging the disease and treatment plan.

The frequency and number of bone lesions in hepatocellular carcinoma was different in various studies depending on the stage of the disease and the method used for diagnosis.[8] Advanced hepatocellular carcinoma patients have a higher likelihood of developing multiple bone lesions through bone scans than early-stage patients.[9] The development of many bone metastases indicates poor quality of life and low survival rates.[10] Bone scan is essential for patient monitoring because it shows the progress of metastatic diseases.

Bone metastases in HCC patients are highly morbid and have poor prognosis, but there are very few studies from our region describing the prevalence and number of bone metastasis detected by bone scan among HCC patients. Early detection of bone metastasis is important for the purpose of staging, treatment planning, and improved management of the patients. The current study will be helpful to understand the pattern of bone involvement in HCC patients. Therefore, this study is being conducted to determine the frequency and number of bone lesions on bone scan in patients of hepatocellular carcinoma.

## METHODOLOGY:

This cross-sectional study was carried out at the Department of Nuclear Medicine, Multan Institute of Nuclear Medicine and Radiotherapy from December 2024 to May 2025. Approval of the study was taken from the ethical committee, research board and Research Evaluation Unit of CPSP Karachi before starting the data collection. The sample size was calculated as 114 patients by using OpenEPI online calculator for population proportion while taking prevalence of skeletal involvement in hepatocellular carcinoma as 8.03%[11] with 95% confidence interval.

Inclusion criteria: Patients of both genders aged 18-60 years and undergoing bone scan for hepatocellular carcinoma were included in the study. Hepatocellular carcinoma was labelled on the basis of clinical findings, imaging and medical records documented by the treating consultant.

Exclusion criteria: Patients who refused to participate, pregnant and lactating women, patients having contraindication to bone scan and patients with history of any other primary malignancy on medical history and medical record were excluded from the study.

Written informed consent was taken from all patients after explaining the purpose, importance and possible risks of the study. Baseline demographic details including age, gender, duration of disease, stage of HCC and previous history of chemotherapy or radiotherapy were recorded. Detailed clinical history and relevant examination findings were also noted. Bone scintigraphy was performed after intravenous administration of 744 MBq of Tc-99m methyl diphosphonate and whole-body anterior and posterior images were obtained after 3 hours of tracer injection. Low-dose CT imaging was done in selected patients where clarification of suspicious findings on bone scintigraphy was required or where any specific body region needed further evaluation. All scans were reviewed and reported by an experienced nuclear medicine physician or nuclear medicine qualified radiologist. Bone metastasis, the number of metastatic bone lesions, and the anatomic sites of lesions were noted in the study proforma. Presence of bone metastasis was defined based on the presence of abnormal accumulation of the radiotracer indicating metastasis to bones in the bone scan examination, supported by CT where applicable. The number of metastatic bone lesions was noted based on the total number of abnormal lesions seen in the bone scintigraphy.

. Numerical variables including age, duration of HCC and number of lesions were presented as

mean ± standard deviation. Categorical variables including gender, stage of HCC, history of chemotherapy or radiotherapy, presence of metastatic lesion on bone scan and involvement of vertebrae, pelvis or ribs were presented as frequency and percentage. Confounding variables including age, gender, duration and stage of HCC were controlled through stratification. Post-stratification chi-square test was applied and p-value less than 0.05 was taken as statistically significant.

**RESULTS**:

The study included a total of 114 patients with hepatocellular carcinoma (HCC). The mean age of the patients were 48.49 ± 11.62 years, and the mean duration of HCC were 3.15 ± 2.04 years. Majority of the patients were male, accounting for 86 (75.4%) of the total, while 28 (24.6%) were female. Regarding the stage of disease, most patients has Stage II HCC, which were 46 (40.4%), followed by Stage III in 42 (36.8%) patients. Stage I were observed in 16 (14.0%) and Stage IV in 10 (8.8%) patients. With respect to previous treatment, 49 (43.0%) patients had received prior chemotherapy or radiotherapy, whereas 65 (57.0%) had not received any such treatment (Table-I). On bone scan, metastatic bone lesions were detected in 11 patients, which corresponds to a frequency of 9.60%, while the remaining 103 patients (90.40%) showing no evidence of bone metastasis (Table-II). Among the 11 patients in whom bone metastasis were identified, vertebrae or spine involvement were present in all 11 patients, representing a frequency of 100.00%. Pelvic involvement was noted in 10 patients (90.90%), and ribs were affected in 4 patients (36.40%). The mean number of bone lesions across the entire study population were calculated as 0.27 ± 0.96 (Table-III)

Longer duration of HCC (more than 3 years) were significantly associated with higher frequency of bone metastasis as compared to shorter duration (p=0.049). Advanced stage of disease also shown a significant association, where bone lesions were absent in Stage I and II but were present in 8 (19.0%) of Stage III and 3 (30.0%) of Stage IV patients (p=0.002). Prior chemotherapy or radiotherapy were also significantly associated with presence of bone metastasis, with 9 (18.4%) of treated patients showing lesions compared to only 2 (3.1%) in untreated group (p=0.009). Age and gender did not shown any statistically significant association with bone metastasis (Table-IV).

**Table- I: Patient Demographics (n=114)**

| **Demographics** | **Mean ± SD / n** (%) |
|---|---|
| Age (Years) | 48.49 ± 11.62 |
| Duration of HCC (Years) | 3.15 ± 2.04 |
| **Gender** | |
| Male n (%) | 86 (75.4%) |
| Female n (%) | 28 (24.6%) |
| **Stage of HCC** | |
| Stage I n (%) | 16 (14.0%) |
| Stage II n (%) | 46 (40.4%) |
| Stage III n (%) | 42 (36.8%) |
| Stage IV n (%) | 10 (8.8%) |
| **Previous Chemotherapy / Radiotherapy** | |
| Yes n (%) | 49 (43.0%) |
| No n (%) | 65 (57.0%) |

**Table- II: Frequency of Bone Lesions on Bone Scan in Cases of Hepatocellular Carcinoma n=114**

| Metastatic Bone Lesion Present | Frequency | % age |
|---|---|---|
| Yes | 11 | 9.60% |
| No | 103 | 90.40% |
| Total | 114 | 100% |

**Table- III: Distribution of Bone Lesions by Site in Hepatocellular Carcinoma**

| Bone Site Involved | Frequency / Mean ± SD | % age |
|---|---|---|
| Vertebrae / Spine | 11 | 100.00% |
| Pelvis | 10 | 90.90% |
| Ribs | 4 | 36.40% |
| **Number of Lesions** | 0.27 ± 0.96 | |

**Table- IV: Association of Metastatic Bone Lesion with Clinical Factors in Hepatocellular Carcinoma**

| Clinical Factors | Subgroup | Metastatic Lesion Present | | p-value |
|---|---|---|---|---|
| | | Yes n(%) | No n(%) | |
| Age (years) | ≤40 | 3 (10.7%) | 25 (89.3%) | 1.000* |
| | >40 | 8 (9.3%) | 78 (90.7%) | |
| Gender | Male | 6 (7.0%) | 80 (93.0%) | 0.135* |
| | Female | 5 (17.9%) | 23 (82.1%) | |
| Duration of HCC | ≤3 Years | 4 (5.4%) | 70 (94.6%) | 0.049* |
| | >3 Years | 7 (17.5%) | 33 (82.5%) | |
| Stage of HCC | Stage I | 0 (0.0%) | 16 (100.0%) | 0.002* |
| | Stage II | 0 (0.0%) | 46 (100.0%) | |
| | Stage III | 8 (19.0%) | 34 (81.0%) | |
| | Stage IV | 3 (30.0%) | 7 (70.0%) | |
| Previous Chemo / Radiotherapy | Yes | 9 (18.4%) | 40 (81.6%) | 0.009* |
| | No | 2 (3.1%) | 63 (96.9%) | |

*Fischer Exact Test

**DISCUSSION:**

The current research was conducted to determine the prevalence and distribution of bone metastases on bone scan in patients suffering from hepatocellular carcinoma. It has been found that the prevalence rate of bone metastasis among the participants was 9.60%. This shows that bone involvement is not rare in HCC patients, and therefore it should be taken into account in both staging and management of the disease. This observation can be explained by the biological characteristics of HCC cells, which are able to spread to other organs via invasion of vascular channels, especially portal and hepatic veins.[12] The prevalence rate of metastasis of the spine and pelvis among the HCC patients was 100% and 90.90%, respectively. This result is biologically feasible due to rich red bone marrow content and blood supply through Batson's venous plexus in the vertebrae and pelvis.[13]

The frequency of metastatic bone lesions in the present study were found to be 9.60% (n=11), which is somewhat consistent with findings of Sakr *et al.* [14] who reported bone metastases in 10.9% of HCC patients, suggesting that skeletal involvement occurs in a comparable proportion of cases across different populations. However, this figure is lower than that reported by Iqbal *et al.* [15] who detected skeletal metastases in 18% of patients undergoing bone scintigraphy, and also lower than the broader range of 3%–20% cited by

Jin *et al.* [16] This variation in frequency may be attributable to differences in disease stage at presentation, study population characteristics, and the sensitivity of imaging modality used for detection.

Regarding site distribution, vertebral or spinal involvement were present in all 11 (100%) metastatic patients, and pelvic involvement were seen in 10 (90.90%) cases, which shows strong similarity with findings of Sakr *et al.* [14] who reported vertebral involvement in 79% of cases, and with Chen *et al.* [17] who demonstrated that vertebral metastases accounted for the majority of all bone lesions. Iqbal *et al.* [15] also reported vertebrae as the most common metastatic site, occurring in 67% of their patients. The predominance of axial skeletal involvement, particularly spine and pelvis, has been well recognised in literature and is scientifically explained by the rich vascularity of these regions and the role of Batson's paravertebral venous plexus, which provides a low-pressure route for haematogenous tumour dissemination from abdominal organs *via* retrograde venous flow.

The significant association of bone metastasis with advanced HCC stage (p=0.002) in the present study is in agreement with the general understanding supported by Ozer *et al.* [18] who demonstrated that tumour characteristics including degree of differentiation significantly influenced metastatic behaviour and survival outcomes. Advanced stage tumours are biologically more aggressive, with greater capacity for vascular invasion and extrahepatic spread, which explains the absence of bone metastasis in Stage I and II patients and its presence in 8 (19.0%) Stage III and 3 (30.0%) Stage IV patients in this study.

The significant association between prior chemotherapy or radiotherapy and higher frequency of bone metastasis (18.4% vs 3.1%, p=0.009) observed in present study may reflects the fact that patients who had received prior treatment already had more advanced disease burden at baseline, which is indirectly supported by Ozer *et al.* [18] who showed that chemotherapy was administered in 39.5% of patients with bone metastases, indicating that treated patients tends to have more aggressive disease course. Similarly, longer disease duration of more than 3 years was significantly associated with higher bone metastasis rate (17.5% vs 5.4%, p=0.049), which is biologically plausible as prolonged disease course allows more opportunity for tumour progression,[19,20] clonal evolution and eventual distant metastatic spread, a concept further supported by Jin *et al.* [16] who demonstrated genetic heterogeneity between primary HCC and metastatic bone lesions, suggesting ongoing tumour evolution over time.

There were a number of limitations in this current study that need to be discussed. First of all, this is a single centre study, and this may affect the generalizability of the findings to a wider population. The number of subjects involved in this study was limited to only 114 patients, and this may reduce the validity of the findings. Also, bone scintigraphy was utilized in this case, and even though it has been found to be widely used for diagnosing bone metastases, it does have some limitations regarding the accuracy and the specificity. In addition to that, the study design was cross-sectional, and this means that the progress of bone metastases cannot be studied.

**Conclusion**:

In conclusion, this study has found that bone metastasis in hepatocellular carcinoma cases is common, and bone scan can be a valuable diagnostic technique for detecting it. The most common sites where bone metastases occur include the spine and the pelvis. In addition, it was also found that advanced disease stage, history of HCC for a longer period, and chemotherapy or radiotherapy treatment history are important factors that lead to bone metastasis in such cases.

**Disclaimer:**

Not needed for this study.

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maintaining patient files and arranging study data made this work easy to complete.

**Ethical Approval:**
Approval for conducting this research was obtained from the ethical review committee before start of study. All procedures of study were carried out according to committee instruction and Helsinki declaration principle.

**Patient Consent:**
Written informed consent was obtained from every patient before inclusion in study. Patients were told that all information will be kept secret and they can leave the study at any stage without any problem.

**Conflict of Interest:**
The author stated that they have no conflict of interest concerning this research study.

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