Annals of Hepatology 29 (2024) 101545

Contents lists available at ScienceDirect

Annals of Hepatology

journal homepage: www.elsevier.es/annalsofhepatology

Original article

Limited utility of routine bone scintigraphy in the staging of patients with hepatocellular carcinoma: A cross-sectional study

Fatima Rodriguez-Alvarez[a,b,c], Blanca Zuleima Mota-Ayala[a], Ramiro Villavicencio-Martínez[d], Eric Kauffman-Ortega[a], Lucero Selene Téllez-Morán[e], Graciela Castro-Narro[a], Eleazar Ignacio-Alvarez[f], Jesús Alejandro Gabutti-Thomas[e], Carlos Moctezuma-Velazquez[a,g,*]

[a] *Gastroenterology Department, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán. Vasco de Quiroga 15, Belisario Domínguez Secc 16, Tlalpan. Mexico City, CP 14080, Mexico*
[b] *Liver Unit, Hospital Clinic, University of Barcelona, Barcelona, Spain. Street Villarroel, 170, L'Eixample, 08036 Barcelona, Spain*
[c] *Faculty of Medicine and Health Sciences, Doctoral Program in Medicine and Translational Research, University of Barcelona, Barcelona, Spain. Street Casanova, 143, L'Eixample, 08036 Barcelona, Spain*
[d] *Surgery Department, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán. Vasco de Quiroga 15, Belisario Domínguez Secc 16, Tlalpan. Mexico City, CP 14080, Mexico*
[e] *Radiology Department, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán. Vasco de Quiroga 15, Belisario Domínguez Secc 16, Tlalpan. Mexico City, CP 14080, Mexico*
[f] *Nuclear Medicine Department, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán. Vasco de Quiroga 15, Belisario Domínguez Secc 16, Tlalpan. Mexico City, CP 14080, Mexico*
[g] *Department of Medicine - Division of Gastroenterology (Liver Unit), University of Alberta. Edmonton, Alberta, Canada. 8540 112 Street NW, Zeidler Ledcor Centre, Room 1-20B, Edmonton, Alberta, T6G 2×8, Canada*

ARTICLE INFO

Article History:
Received 8 February 2024
Accepted 15 July 2024
Available online 13 August 2024

Keywords:
Hepatocellular carcinoma
Bone scintigraphy
Liver cirrhosis
Bone metastases

ABSTRACT

Introduction and Objectives: The most widely used staging system for hepatocellular carcinoma (HCC) is the Barcelona Liver Clinic Cancer (BCLC) system, which considers tumor burden, performance status, and liver function. Tumor burden is assessed with cross sectional imaging of the abdomen and chest, controversy surrounds the routine use of bone scintigraphy (BS) for detecting extrahepatic metastases. This study evaluated the role of BS in staging HCC in Mexican patients.
Patients and Methods: Retrospective cross-sectional study of all adults with HCC at a Mexican referral center from 2000 to 2018. Staging included abdominal computed tomography (CT) or magnetic resonance imaging, chest CT, and BS. The main outcome was the impact of BS on staging and/or therapy plans.
Results: Among 238 patients, 2 with fibrolamellar variant and 44 with incomplete data were excluded. Median age was 66 years, 84 % had cirrhosis, and the predominant etiology was hepatitis C virus (43 %). BCLC stages were distributed as follows: A (14 %), B (7 %), C (68 %), and D (11 %). Extrahepatic disease was present in 18 %; only 8 % patients had a positive BS. Among the positive cases, 4 were true positives, but they did not alter staging or therapy plans.
Conclusions: Routine BS in HCC staging demonstrated low yield, with a notable rate of false positives. Considering the implications of extrahepatic disease, BS may be justified for liver transplant candidates outside conventional criteria. Our study highlights the limited role of BS in early-stage HCC and advocates for a more selective utilization.
© 2024 Fundación Clínica Médica Sur, A.C. Published by Elsevier España, S.L.U. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/)

1. Introduction

Hepatocellular carcinoma (HCC) is the most common type of liver cancer, and it is the third leading cause of cancer-related death. Its global incidence is decreasing, mainly in Asia, but it is on the rise in Latin America [1]. Diagnosis is usually based on imaging, without the need for a biopsy, and staging is performed based on the Barcelona Liver Clinic Cancer (BCLC) algorithm, which considers three aspects: liver synthetic function, performance status, and tumor burden [2]. The tumor burden includes the size and number of lesions, as well as the presence of vascular invasion and extrahepatic spread. The most common sites of extrahepatic metastases are the lungs, regional lymph nodes, and bones [3,4]. Therefore, staging is based on cross

Abbreviations: BCLC, Barcelona clinic liver cancer; BS, bone scintigraphy; CT, computed tomography; HCC, hepatocellular carcinoma

* Corresponding author.
E-mail address: moctezum@ualberta.ca (C. Moctezuma-Velazquez).

https://doi.org/10.1016/j.aohep.2024.101545
1665-2681/© 2024 Fundación Clínica Médica Sur, A.C. Published by Elsevier España, S.L.U. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/)

sectional imaging of the thorax and abdomen. Regarding bone scintigraphy (BS), the most recent Mexican Consensus on Hepatocellular Carcinoma recommends its routine use for staging [5], whereas the European Society of Medical Oncology [6] and the National Comprehensive Cancer Network [7] recommend against its routine use (*i.e.* reserve it for patients with skeletal symptoms), while the American Association for the Study of the Liver [8] and the European Association for the Study of the Liver [9] make no specific recommendation. Therefore, the aim of this study was to assess the role of BS in the staging of HCC in Mexican patients.

2. Patients and methods

This was a cross-sectional study that comprised all adult patients with a new diagnosis of HCC assessed at a referral center in Mexico between the years 2000 and 2018. We excluded patients without BS or with incomplete data that would preclude adequate staging. For the purpose of this study, HCC diagnosis was based on imaging criteria on multiphase computed tomography (CT) or magnetic resonance image in patients with cirrhosis; a liver biopsy was required in cases with atypical imaging features and in all patients without cirrhosis. Imaging-based diagnosis of HCC in patients with cirrhosis was determined based on the European Association for the Study of the Liver guidelines [9]. A liver lesion was considered HCC if it exhibited arterial phase hyperenhancement and washout in the portal and/or delayed phases. Cirrhosis was diagnosed using one or more of the following criteria: histological evidence, radiological findings (ultrasound or cross-sectional imaging showing a lobulated liver and/or unequivocal signs of portal hypertension), or transient elastography with a liver stiffness measurement greater than 14 kPa.

Relevant data was gathered from each patient's medical record. At our hospital, after diagnosis, all HCC cases are staged with a cross sectional study of the abdomen (either CT or magnetic resonance image), a chest CT, and a BS. The main outcome of the study was the proportion of cases in which the result of the BS modified the stage and/or therapy plan of a patient.

2.1. Bone scintigraphy

BSs were performed 3 h after intravenous injection of 744 MBq of Tc-99 m methyl diphosphonate. Anterior and posterior whole-body images were acquired. In addition, single-photon emission computed tomography (SPECT) with a dual-head gamma camera (Siemens, Symbia T2 SPECT/CT) was acquired on a case-by-case basis in some body regions when there was diagnostic uncertainty. Low-dose CT imaging was used when relevant, in a targeted fashion on review of BS findings. All studies at our center are interpreted by experienced nuclear medicine physicians. For the purpose of this study, all BSs that showed abnormal findings were reviewed by an experienced nuclear radiologist (EIA), who adjudicated the findings as compatible or not with bone metastasis based on the review of the BS and available CT, SPECT, magnetic resonance imaging, plain radiographs, and also based on the behavior of the lesion over time. Positive BS results, referring to any abnormal uptake that was interpreted in the original report as compatible or suspicious for bone metastasis, were categorized as true-positives when confirmed to be a bone metastasis, or false-positives when the abnormal uptake was due to another reason. This adjudication was done by the nuclear radiologist based on the characteristics of the abnormal uptake, the presence or absence of lesions interpreted as arthritis, osteophytes, or benign compression fractures, and/or the clinical course of the abnormal uptake areas over time. A lesion with a central cold defect was considered malignant.

2.2. Sample size and statistical analyses

Continuous variables were reported with medians and interquartile ranges, and categorical variables with absolute and relative values. We estimated a sample size of 125 patients to detect a change in staging of 7 % of cases (*i.e.,* proportion of cases migrating from BCLC stage A or B to C), considering a type 1 error of 0.05, and a type 2 error of 0.20 [10].

2.3. Ethical statements

The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the Ethics Committee of hour hospital (GAS-4137-22-23-1). The need for informed consent was waived due to its observational and retrospective nature.

3. Results

We reviewed the chart of 238 patients with diagnosis of HCC; we excluded 2 patients who had a primary diagnosis of fibrolamellar variant and 44 patients because of incomplete data (33 without BS, 7 cases where we could not retrieve their imaging studies, 2 with incomplete laboratory results to assess liver function, and 2 due to incomplete clinical/demographic data).

Median age of the population was 66 years (IQR 59-71), 113 were male (59 %), 161 (84 %) had cirrhosis, and the most common etiology of liver disease was hepatitis C virus infection in 70 (43 %) patients. Regarding the stage of HCC, 26 (14 %), 14 (7 %), 131 (68 %), and 21 (11 %) were BCLC A, B, C, and D, respectively. The rest of the general characteristics of the patients can be found in Table 1.

Thirty-five patients (18 %) had extrahepatic disease. Overall, only 15 (8 %) patients had a positive BS, and of these, only four were true positives for bone metastasis. In two of these cases, the BS showed ribcage lesions that had been missed on cross-sectional imaging, and in the other two, the BS showed lesions in bones that are not routinely visualized when staging HCC (*i.e.*, humerus, femur, skull). In these four cases, the presence of bone metastasis did not change the stage of the disease since the patients were already classified as BCLC stage C due to the presence of extrahepatic non-bone metastases. A false positive BS led to a bone biopsy that ruled out metastasis. Table 2 describes each of the cases with a positive BS.

4. Discussion

The most common HCC staging system is the BCLC, which considers tumor burden, performance status, and hepatic function [2]. The recommended workup for staging includes imaging of the chest and abdomen, but there is inconsistency amongst the international societies regarding the utility of the routine use of BS, as bone metastases are described as the second or third most common site of extrahepatic disease after the lung and lymph nodes [3,4]. On its most recent version of the HCC Consensus, the Mexican Association of Hepatology recommends staging of HCC with BS in all patients [5] with early HCCs undergoing a potentially curative treatment. Therefore, the aim of this study was to assess the role of BS in the staging of HCC in Mexican patients. In our study, we found that most positive BS were false positives, and the 4 true positive BSs did not change the stage or the therapy plan, suggesting there is no role for routinely ordering this study. Our results are in line with those of Koneru B, *et al*., who studied the utility of BS in 117 patients with early-stage HCC being considered for liver transplantation. In their study, none of the BS were positive, but 9 % were considered indeterminate, and recurrent disease after liver transplant was not different between those with normal and indeterminate BSs (5 % *versus* 7 %, respectively) [11].

Table 1
General characteristics of patients (n = 192).

Age, years, med (IQR)	66 (59–71)
Male, n (%)	113 (59)
Cirrhosis, n (%)	161 (84)
Underlying liver disease, n (%)	
-Chronic hepatitis C virus	70 (43)
-Chronic hepatitis B virus	4 (2)
Alcohol	17 (11)
MASLD or cryptogenic	52 (32)
Other	18 (11)
AFP, ng/ml, med (IQR)	57.5 (9.6–1212.9)
MELD, med (IQR)	10 (8–12)
MELD-Na, med (IQR)	12 (10–15)
Child-Pugh Score, n (%)	
-A	84 (44)
-B	95 (49)
-C	13 (7)
Size of biggest liver lesion, mm, med (IQR)	45 (25–81)
Number of lesions, med (IQR)	1 (1–3)
Number of lesions, n (%)	
–1	99 (52)
–2–3	66 (34)
->3	27 (13)
Tumor thrombus, n (%)	20 (10)
Lymphatic metastasis, n (%)	16 (8)
Pulmonary metastasis, n (%)	22 (12)
Positive bone scintigraphy, n (%)	15 (8)
-True positive for bone metastases	4/15
-False positive for bone metastases	11/15
Eastern Clinical Oncology Group Performance Status, n (%)	
–0	54 (28)
–1	108 (56)
–2	17 (9)
–3	12 (6)
Barcelona Clinic Liver Cancer stage, n (%)	
-A	26 (14)
-B	14 (7)
-C	131 (68)
-D	21 (11)

IQR: Interquartile range. MASLD: Metabolic dysfunction-associated steatotic liver disease. MELD: Model for end-stage liver disease.

Table 2
Patients with bone scintigraphy with abnormal findings.

	BCLC pre-BS	BCLC post-BS	Interpretation and comments
1	C	C	True positive. The BS showed a metastasis in the left femur. The staging CT had previously shown vascular invasion, pulmonary and lymphatic metastases, so overall did not change stage or treatment.
2	D	D	False positive. The BS showed uptake in L1 and this was due to a compression fracture.
3	C	C	True positive. The BS showed metastases in several spots of the ribcage. The staging CT had previously shown pulmonary metastasis, so overall did not change stage or treatment.
4	C	C	True positive. Metastases were found in the ribcage, right femur, and right humerus. The staging CT had previously shown pulmonary, lymphatic, and bone metastases in the ribcage, so overall did not change stage or treatment.
5	B	B	False positive. Uptake was due to degenerative bone disease. There was increased tracer uptake in the right glenohumeral joint, in one rib, in T12, L5, and right femur, with no morphological evidence of bone metastases on the CT. After 2 years, the patient is still alive with no evidence of extrahepatic spread.
6	A	A	False positive. Increased tracer uptake in a rib was due to a previous rib fracture.
7	A	A	False positive. Increased uptake of the tracer in two ribs, but there was no morphological evidence of bone metastasis on those ribs in the chest CT.
8	C	C	True positive. The staging CT had already shown pulmonary metastasis so overall did not change the stage or treatment.
9	B	B	False positive. Irregularities in the tracer uptake were due to degenerative bone disease, with no evidence of bone metastasis on CT. Patient had a follow up of >2 years with no manifestations of bone disease.
10	B	B	False positive. Increased uptake in a rib was found to be due to an enchondroma that was better characterized on the chest CT.
11	A	A	False positive. The BS showed increased uptake in a dorsal and a lumbar vertebra, but a biopsy was negative for metastasis.
12	C	C	False positive. Positivity in a costovertebral joint and in L3 were found to be due to degenerative bone disease, with no evidence of metastasis on CT.
13	C	C	False positive. Abnormal areas of uptake in the ribcage were due to previous rib trauma, no abnormalities were found on the chest CT.
14	C	C	False positive. Abnormal areas of uptake in the ribcage were due to degenerative bone disease with no evidence of bone metastasis on chest CT
15	C	C	False positive. Abnormal areas of uptake in ribcage were due to previous rib fractures

BCLC: Barcelona Clinic Liver Cancer. BS: Bone scintigraphy. CT: Computed tomography.

The proportion of patients with bone metastases in our study was only 2 %,which is lower than the 4–24 % reported in other studies [12–17], and this can be because we also included patients with early stage disease. Risk factors for developing extrahepatic disease are those representing the tumor burden (*i.e.* tumor size, number of nodules, lymph node involvement, intrahepatic metastases, extrahepatic non-bone metastases, and presence of vascular invasion) [4], so it is very unlikely to have bone metastases in early HCC [11,17]. For example, Kutaiba *et al.* reported 0 % of true-positive BSs in 186 patients awaiting liver transplant [18], and Witjes *et al.* found bone metastases in only 2 % of 137 patients prior to HCC resection [19]. Therefore, BS should be better reserved for patients outside conservative transplant criteria (*e.g.* Milan) or for patients that are being considered for downstaging, as a positive BS would have a significant impact in the therapy plan of these patients. Symptom guided investigations are also appropriate, as suggested by case reports of patients with HCC and with atypical initial presentations attributed to bone metastases [20–23], and by series showing that almost all patients with bone disease will be symptomatic [4,24].

In addition to the relatively low frequency of bone metastases, the performance of BS in the specific case of HCC patients is not optimal. Sensitivity is hampered in HCC because most bone metastases are osteolytic in nature [15,25]. In one multicenter study of 211 patients with HCC, 82 % of bone metastases were osteolytic, and the rest were distributed between osteoblastic and mixed [26]. Poor specificity was also evident in our study, in which most positive studies were attributed to non-metastatic bone disease, mainly traumatic and degenerative in nature. Poor specificity may result in over-staging and over-diagnosing, which may result in harm, such as not offering a liver transplant to a patient who otherwise would be an acceptable candidate. Likewise, positive BSs may lead to unnecessary invasive diagnostic procedures and risks, like in our series, in which a patient underwent a bone biopsy. The specificity can be improved by pairing it with a SPECT/CT [27], which can better characterize uptake areas in the BS. However, since bone metastasis is a relatively infrequent event in patients with HCC, and as shown in our study, they usually

happen in patients with advanced tumors, there does not seem to be a role for proactively searching for bone metastases in the absence of symptoms. Moreover, as suggested by other authors, routine BS is not cost effective [11,19], and adding SPECT/CT in all cases would increase healthcare costs. Finally, BS interpretation is subject to interobserver variability, adding further uncertainty when using it to stage patients [28].

Our study does have limitations. Due to its retrospective and cross-sectional nature, we were unable to assess if patients with bone metastases were symptomatic, and/or if the findings of the BSs led to any specific interventions, such as palliative radiotherapy, which would further support ordering BSs based on clinical suspicion. In addition, we could not determine the reasons why 33 patients were missing BS results. One of the major limitations is that all BSs were reviewed by a single nuclear radiologist, and as mentioned, interpretation of BSs is subject to interobserver variability. In the particular case of bone metastasis, kappa coefficients are described between 0.53 and 0.88 [29]. However, because the objective of our study was to assess the role of BS in staging, it may be that interobserver variability was not as significant in our study. The nuclear radiologist was able to interpret the findings in light of other available imaging studies and the progression of lesions over time so that any abnormal finding could be retrospectively adjudicated as a bone metastasis.

5. Conclusions

In conclusion, the yield of routinely doing BS as part of the staging of patients with HCC is low and can lead to a significant rate of false positive results. Therefore, we favor a more customized approach, ordering BS on a case-by-case basis based on clinical suspicion. Based on the implications of having extrahepatic disease, BS can also be considered in patients being assessed for liver transplants when outside of conventional criteria. A prospective study focused on this group of patients, intentionally investigating any abnormal findings, would provide important information.

Author contributions

FRA was involved in data curation, methodology, project administration, and investigation. BZMA, RVM, EKO, and LSTM were involved in data curation, writing (original draft), and investigation. GCN, EIA, JAGT were involved in conceptualization, writing (review, editing), and supervision. CMV was involved in conceptualization, writing (review, editing), formal analysis, and supervision and is responsible for the integrity of the work as a whole.

Data availability

Data supporting the findings of this study are available from the corresponding author upon request.

Conflicts of interest

None.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References

[1] Singal AG, Kanwal F, Llovet JM. Global trends in hepatocellular carcinoma epidemiology: implications for screening, prevention and therapy. Nat Rev Clin Oncol 2023;20(12):864–84 Epub 20231026PubMed PMID: 37884736. https://doi.org/10.1038/s41571-023-00825-3.

[2] Reig M, Forner A, Rimola J, Ferrer-Fàbrega J, Burrel M, Garcia-Criado Á, et al. BCLC strategy for prognosis prediction and treatment recommendation: the 2022 update. J Hepatol 2022;76(3):681–93 Epub 20211119PubMed PMID: 34801630; PubMed Central PMCID: PMC8866082. https://doi.org/10.1016/j.jhep.2021.11.018.

[3] Uchino K, Tateishi R, Shiina S, Kanda M, Masuzaki R, Kondo Y, et al. Hepatocellular carcinoma with extrahepatic metastasis: clinical features and prognostic factors. Cancer 2011;117(19):4475–83 Epub 20110322PubMed PMID: 21437884. https://doi.org/10.1002/cncr.25960.

[4] Kanda M, Tateishi R, Yoshida H, Sato T, Masuzaki R, Ohki T, et al. Extrahepatic metastasis of hepatocellular carcinoma: incidence and risk factors. Liver Int 2008;28(9):1256–63 Epub 20080715PubMed PMID: 18710423. https://doi.org/10.1111/j.1478-3231.2008.01864.x.

[5] Cisneros-Garza LE, González-Huezo MS, Moctezuma-Velázquez C, Ladrón de Guevara-Cetina L, Vilatobá M, García-Juárez I, et al. The second Mexican consensus on hepatocellular carcinoma. Part II: treatment. Rev Gastroenterol Mex 2022;87(3):362–79 Epub 20220628PubMed PMID: 35778341. https://doi.org/10.1016/j.rgmxen.2022.01.004.

[6] Vogel A, Cervantes A, Chau I, Daniele B, Llovet JM, Meyer T, et al. Hepatocellular carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2018;29(Suppl 4):iv238–iv55 Epub 2018/10/05PubMed PMID: 30285213. https://doi.org/10.1093/annonc/mdy308.

[7] National Comprehensive Cancer Network (NCCN). NCCN clinical practice guidelines in oncology. Hepatocellular carcinoma version 2.2023. National Comprehensive Cancer Network; 2024. Jan 10Available from https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1514.

[8] Singal AG, Llovet JM, Yarchoan M, Mehta N, Heimbach JK, Dawson LA, et al. AASLD practice guidance on prevention, diagnosis, and treatment of hepatocellular carcinoma. Hepatology 2023 Epub 20230522PubMed PMID: 37199193. https://doi.org/10.1097/HEP.0000000000000466.

[9] European Association for the Study of the Liver. Electronic address eee, European Association for the Study of the L. EASL Clinical Practice Guidelines: management of hepatocellular carcinoma. J Hepatol 2018;69(1):182–236 Epub 2018/04/10PubMed PMID: 29628281. https://doi.org/10.1016/j.jhep.2018.03.019.

[10] Machin D, Campbell MJ, Tan SB, Tan SH. Sample size tables for clinical studies. Oxford: Wiley-Blackwell; 2009 3r[d] editor.

[11] Koneru B, Teperman LW, Manzarbeitia C, Facciuto M, Cho K, Reich D, et al. A multicenter evaluation of utility of chest computed tomography and bone scans in liver transplant candidates with stages I and II hepatoma. Ann Surg 2005;241(4):622–8 PubMed PMID: 15798464; PubMed Central PMCID: PMC1357066. https://doi.org/10.1097/01.sla.0000157267.27356.80.

[12] Uka K, Aikata H, Takaki S, Shirakawa H, Jeong SC, Yamashina K, et al. Clinical features and prognosis of patients with extrahepatic metastases from hepatocellular carcinoma. World J Gastroenterol 2007;13(3):414–20 PubMed PMID: 17230611; PubMed Central PMCID: PMC4065897. https://doi.org/10.3748/wjg.v13.i3.414.

[13] Buijs JT, van der Pluijm G. Osteotropic cancers: from primary tumor to bone. Cancer Lett 2009;273(2):177–93 Epub 20080715PubMed PMID: 18632203. https://doi.org/10.1016/j.canlet.2008.05.044.

[14] Nakashima T, Okuda K, Kojiro M, Jimi A, Yamaguchi R, Sakamoto K, et al. Pathology of hepatocellular carcinoma in Japan. 232 Consecutive cases autopsied in ten years. Cancer 1983;51(5):863–77 PubMed PMID: 6295617. https://doi.org/10.1002/1097-0142(19830301)51:5<863::aid−cncr2820510520>3.0.co;2-d.

[15] Kuhlman JE, Fishman EK, Leichner PK, Magid D, Order SE, Siegelman SS. Skeletal metastases from hepatoma: frequency, distribution, and radiographic features. Radiology 1986;160(1):175–8 PubMed PMID: 3012630. https://doi.org/10.1148/radiology.160.1.3012630.

[16] Iguchi H, Yokota M, Fukutomi M, Uchimura K, Yonemasu H, Hachitanda Y, et al. A possible role of VEGF in osteolytic bone metastasis of hepatocellular carcinoma. J Exp Clin Cancer Res 2002;21(3):309–13 PubMed PMID: 12385570.

[17] Guo X, Xu Y, Wang X, Lin F, Wu H, Duan J, et al. Advanced hepatocellular carcinoma with bone metastases: prevalence, associated factors, and survival estimation. Med Sci Monit 2019;25:1105–12 Epub 20190210PubMed PMID: 30739123; PubMed Central PMCID: PMC6378855. https://doi.org/10.12659/MSM.913470.

[18] Kutaiba N, Ardalan Z, Patwala K, Lau E, Goodwin M, Gow P. Value of bone scans in work-up of patients with hepatocellular carcinoma for liver transplant. Transplant Direct 2018;4(12):e408. Epub 20181123PubMed PMID: 30584589; PubMed Central PMCID: PMC6283090. https://doi.org/10.1097/TXD.0000000000000846.

[19] Witjes CD, Verhoef C, Kwekkeboom DJ, Dwarkasing RS, de Man RA, Ijzermans JN. Is bone scintigraphy indicated in surgical work-up for hepatocellular carcinoma patients? J Surg Res 2013;181(2):256–61 Epub 20120720PubMed PMID: 22831566. https://doi.org/10.1016/j.jss.2012.07.013.

[20] Ruiz-Morales JM, Dorantes-Heredia R, Chable-Montero F, Vazquez-Manjarrez S, Méndez-Sánchez N, Motola-Kuba D. Bone metastases as the initial presentation of hepatocellular carcinoma. Two case reports and a literature review. Ann Hepatol 2014;13(6):838–42 PubMed PMID: 25332273.

[21] Piccirillo M, Granata V, Albino V, Palaia R, Setola SV, Petrillo A, et al. Can hepatocellular carcinoma (HCC) produce unconventional metastases? Four cases of extrahepatic HCC. Tumori 2013;99(1):e19–23 PubMed PMID: 23549015. https://doi.org/10.1177/030089161309900127.

[22] Monteserin L, Mesa A, Fernandez-Garcia MS, Gadanon-Garcia A, Rodriguez M, Varela M. Bone metastases as initial presentation of hepatocellular carcinoma. World J Hepatol 2017;9(29):1158–65 PubMed PMID: 29085559; PubMed Central PMCID: PMC5648989. https://doi.org/10.4254/wjh.v9.i29.1158.

[23] Belli A, Gallo M, Piccirillo M, Izzo F. Bone metastases as initial presentation of hepatocellular carcinoma. Lancet Oncol 2019;20(9):e549. PubMed PMID: 31486371. https://doi.org/10.1016/S1470-2045(19)30417-6.
[24] Harding JJ, Abu-Zeinah G, Chou JF, Owen DH, Ly M, Lowery MA, et al. Frequency, morbidity, and mortality of bone metastases in advanced hepatocellular carcinoma. J Natl Compr Canc Netw 2018;16(1):50–8 PubMed PMID: 29295881. https://doi.org/10.6004/jnccn.2017.7024.
[25] Longo V, Brunetti O, D'Oronzo S, Ostuni C, Gatti P, Silvestris F. Bone metastases in hepatocellular carcinoma: an emerging issue. Cancer Metastasis Rev 2014;33 (1):333–42 PubMed PMID: 24357055. https://doi.org/10.1007/s10555-013-9454-4.
[26] Santini D, Pantano F, Riccardi F, Di Costanzo GG, Addeo R, Guida FM, et al. Natural history of malignant bone disease in hepatocellular carcinoma: final results of a multicenter bone metastasis survey. PLoS ONE 2014;9(8):e105268 Epub 20140829PubMed PMID: 25170882; PubMed Central PMCID: PMC4149423. https://doi.org/10.1371/journal.pone.0105268.
[27] Suppiah S, Mohd Rohani MF, Zanial AZ, Ahmad Shahrir AD, Khairuman KA, Vinjamuri S. A review on the usage of bone single-photon emission computed tomography/computed tomography in detecting skeletal metastases in the post-COVID-19 era: is it time to ditch planar and single-photon emission computed tomography only gamma camera systems? Indian J Nucl Med 2023;38(2):191–200 Epub 20230608PubMed PMID: 37456181; PubMed Central PMCID: PMC10348494. https://doi.org/10.4103/ijnm.ijnm_142_22.
[28] Sadik M, Suurkula M, Höglund P, Järund A, Edenbrandt L. Improved classifications of planar whole-body bone scans using a computer-assisted diagnosis system: a multicenter, multiple-reader, multiple-case study. J Nucl Med 2009;50(3):368–75 Epub 2009 Feb 17. PMID: 19223423. https://doi.org/10.2967/jnumed.108.058883.
[29] Ore L, Hardoff R, Gips S, Tamir A, Epstein L. Observer variation in the interpretation of bone scintigraphy. J Clin Epidemiol 1996;49(1):67–71 PMID: 8598513. https://doi.org/10.1016/0895-4356(95)00056-9.