^{99m}Tc-MDP renal parenchymal retention on bone scan in hepatocellular carcinoma patients

Pakistan Journal of Nuclear Medicine
Volume 10(1):31–37

Pakistan Society of Nuclear Medicine
contact@psnmed.com
https://pjnmed.com

Muhammad Shahzad Afzal[1*], Muhammad Babar Imran[1], Samen Fatima[1], Muhammad Iqbal[1], Farkhanda Gillani[1], Nayyar Rubab[1], Owais Qadeer Gill[1], Muhammad Naeem[1]

ABSTRACT

Background: Hot kidneys had been reported on bone scan in few patients with hepatocellular carcinoma (HCC), but their cause is unknown. This study was conducted to compare the ^{99m}Tc-MDP renal parenchymal retention on bone scan in HCC patients with normal controls and chronic liver disease (CLD) patients and to correlate it in HCC patients with glomerular filtration rate (GFR).

Methods: Fifteen normal, 15 CLD, and 85 HCC patients with normal serum urea and creatinine underwent bone scan. Renal parenchymal retention index (PRI) in terms of the kidney-to-lumbar vertebrae counts ratio was calculated, and its mean was compared between these three groups by using Student's *t*-test. Last consecutive 25 HCC patients underwent ^{99m}Tc DTPA dynamic renal scan, and mean PRI in patients with normal GFR (group I, $n = 6$) was compared with those with deranged GFR (group II, $n = 19$).

Results: Mean PRI was 26.8% higher in CLD patients than control group ($p = 0.000$). Mean PRI in HCC group was 99.7% higher than control ($p = 0.000$) and 59.6% higher than that of CLD group ($p = 0.004$). GFR was deranged in 76% of HCC patients. Mean PRI was 36.9% higher in group II than group I at $p = 0.023$.

Conclusion: Renal parenchymal retention on bone scan is significantly higher in HCC patients than normal control and CLD patients. In HCC patients, it was significantly higher in patients with reduced GFR than those with normal GFR.

Keywords: Hot kidney, renal parenchymal retention of MDP, hepatocellular CA, HCC, renal parenchymal retention index.

Received: 30 December 2019 **Accepted:** 07 July 2020
Type of Article: ORIGINAL ARTICLE
https://doi.org/10.24911/PJNMed.175-1574674085

Correspondence to: Muhammad Shahzad Afzal
*PINUM (Punjab Institute of Nuclear Medicine) Cancer Hospital, Faisalabad, Pakistan.
Email: msamirza@yahoo.com
Full list of author information is available at the end of the article.

Introduction

Hepatocellular carcinoma (HCC) represents about 7% of the total number of cancers diagnosed and is the third leading cause of cancer death, after the lung and stomach [1]. In most of the cases, it occurs in patients with underlying cirrhosis, especially in those having hepatitis B and hepatitis C. The frequency of cirrhosis in patients with HCC is about 80%-90% [3,4]. The incidence of HCC is on the rise in the world because of the high incidence of hepatitis C [4,5]. Its mortality is very high with survival rate less than 16% [1,6,7]. Most tumors are diagnosed in intermediate to advanced stage. The pattern of the distribution of metastases from HCC has also changed, and skeletal metastases from HCC are now more frequently being observed than mentioned in the textbooks (20% *vs.* 5.8%) [8–11]. In bone scan performed after 3 hours after i/v injection of ^{99m}Tc MDP, the kidneys are usually faintly visualized in nuclear medicine practice. An increased diffuse cortical renal parenchymal retention, also termed as "hot kidney," has been reported in patients due to different causes in literature. It has also been reported in patients with cirrhosis, and exact mechanism is not established yet. Hepatorenal syndrome causing renal parenchymal insult leading to raised serum urea and creatinine levels has been reported as its probable cause [9–16]. Only very limited work had been done in HCC cases to assess the diffuse renal parenchymal retention of ^{99m}Tc-MDP. These limited studies had also shown that a significant number of HCC and chronic liver disease (CLD) patients with hot kidneys had normal serum urea and creatinine levels [14,17]. Hence, there is a need to investigate this subgroup of patients with normal serum urea and creatinine for the probable cause of hot kidneys. In this study, we probed HCC cases for high diffuse renal parenchymal retention of ^{99m}Tc-MDP and investigated its probable cause.

The first objective was to quantify the renal parenchymal retention of ^{99m}Tc-MDP on whole body bone scan and compare the results in the patients of HCC with those of patients with CLD and normal human volunteers. The

second objective was to measure the glomerular filtration rate (GFR) and compare the parenchymal retention in terms of parenchymal retention index (PRI) in patients with normal GFR with those having deranged GFR in HCC patients.

Material and Methods

The study was approved by the Ethical Review Committee of Punjab Institute of Nuclear Medicine (PINUM) Cancer Hospital. A total of 115 human subjects were selected for the study, of which 62 were males and 48 females. An informed written consent was obtained from all the subjects included in this study. They were divided into control, CLD, and HCC groups. Their demographic characteristics are shown in Table 1.

In control group, healthy human volunteers (n = 15) were included which has no systemic disease, and their routine clinical laboratory reports were normal. In CLD group (n = 15), only those CLD patients were included, whose ultrasonography (USG) revealed chronic liver parenchymal changes along with enlarged spleen and/or dilated portal vein with the absence of any focal lesion in the liver. In HCC group (n = 85), only those patients were included, whose HCC diagnosis was confirmed on the basis of prior performed triphasic computed tomography (CT) abdomen, and they did not fit in the exclusion criteria. The patients with focal liver mass but not proved HCC on the triphasic CT; those with abnormal kidneys on ultrasonography; those having deranged serum urea, creatinine, and/or blood urea nitrogen (BUN) concentration; patients with systemic disease which may affect the renal functions, e.g., diabetes mellitus and hypertension, critically ill patients, pregnant ladies, and lactating mothers reluctant or unwilling to stop lactation after bone/renal scan for a specified period were excluded from the study.

All the patients underwent detailed clinical history, clinical examination, laboratory investigations [complete blood picture, urine C/E, renal function tests (serum urea, serum creatinine, and BUN), serum calcium, serum iron, liver function tests, and serum alpha feto protein (AFP)], and ultrasonography. All clinical information and investigations were evaluated carefully to make sure that patients fall within the selection criteria. The selected patients underwent ^{99m}Tc-MDP whole body bone scan, which was performed 3 hours after i/v injection of 20 mCi ± 5% ^{99m}Tc-MDP on GE Dual Head SPECT/CT Gamma Camera (Hawkeye 2) installed with low-energy high-resolution collimator by using 20 cm/minutes scan speed, zoom 1, energy window 140 keV ± 15%, and 256 × 1024 matrix size. Xeleris Functional Imaging Workstation 4600 was used to display the posterior projections. Renal, background, and first to third lumbar vertebrae region of interest were drawn as shown in Figure 1, and the average counts per pixel were calculated.

Parenchymal retention index for each kidney was calculated by using Equation 1. In subjects where there were metastases in lumbar vertebrae, ROI was drawn on sacrum instead of lumbar vertebrae.

$$\text{PRI} = \frac{\text{Background corrected kidney counts}}{\text{Background corrected lumbar/sacral counts}} \quad (1)$$

The relative PRI (RPRI) for the right and left kidney was calculated by using Equation 2 as follows:

$$\text{RPRI} = \frac{\text{One kidney PRI}}{\text{Sum of Both kidney PRI}} \times 100 \quad (2)$$

Last consecutive 25 HCC patients underwent ^{99m}Tc-DTPA dynamic renal scan for renal function assessment. After taking preinjection 1 minute counts of syringe containing 2 mCi ± 5% of ^{99m}Tc-DTPA in 1 ml of volume, radiophrmaceutical was injected as a compact bolus, and the data were acquired in frame mode on a dedicated computer as dynamic sequential study, consisting of initial 30 frames of 2 seconds each, followed by 120 frames of 15 seconds each. The study was performed using the setup described above except with different collimator i.e Low energy all purpose (LEAP) and matrix size (128 mm × 128 mm). At the end of study, post injection 1 minute counts were also taken to calculate net injected counts.

Xeleris Functional Imaging Workstation 4600 system was used to draw renal and background ROIs on suitable summed image, and time activity curves (renograms) were generated. Total and divided GFR was calculated by using computer algorithm based on modified Gates method. Xeleris System generated expected normal GFR and its lower normal limit for every patient were recorded to calculate the mean normal expected GFR (101.50 ml/minute) and its lower normal limit (77.90 ml/minute). All the patients included in this specific part of the study were divided into two groups based on the lower normal limit for GFR, i.e., 77.90 ml/minute. Group I consisted of six patients (mean age = 53.33 ± 11.25 years, male = 4, female = 2) with GFR above the lower normal limit, and Group II consisted of 19 patients (mean age = 59 ± 9.87

Table 1. Demographic characteristics of the control, CLD, and HCC groups.

CATEGORY	NUMBER OF PATIENTS (*N*)	AGE (YEARS)		GENDER	
		RANGE	MEAN ± SD	MALE *N* (%)	FEMALE *N* (%)
Control group	15	19-75	50.73 ± 16.66	6 (40)	9 (60)
CLD group	15	40-75	50.67 ± 12.24	8 (54.3)	7 (46.7)
HCC group	85	38-82	59.14 ± 9.50	52 (61.2)	33 (38.8)

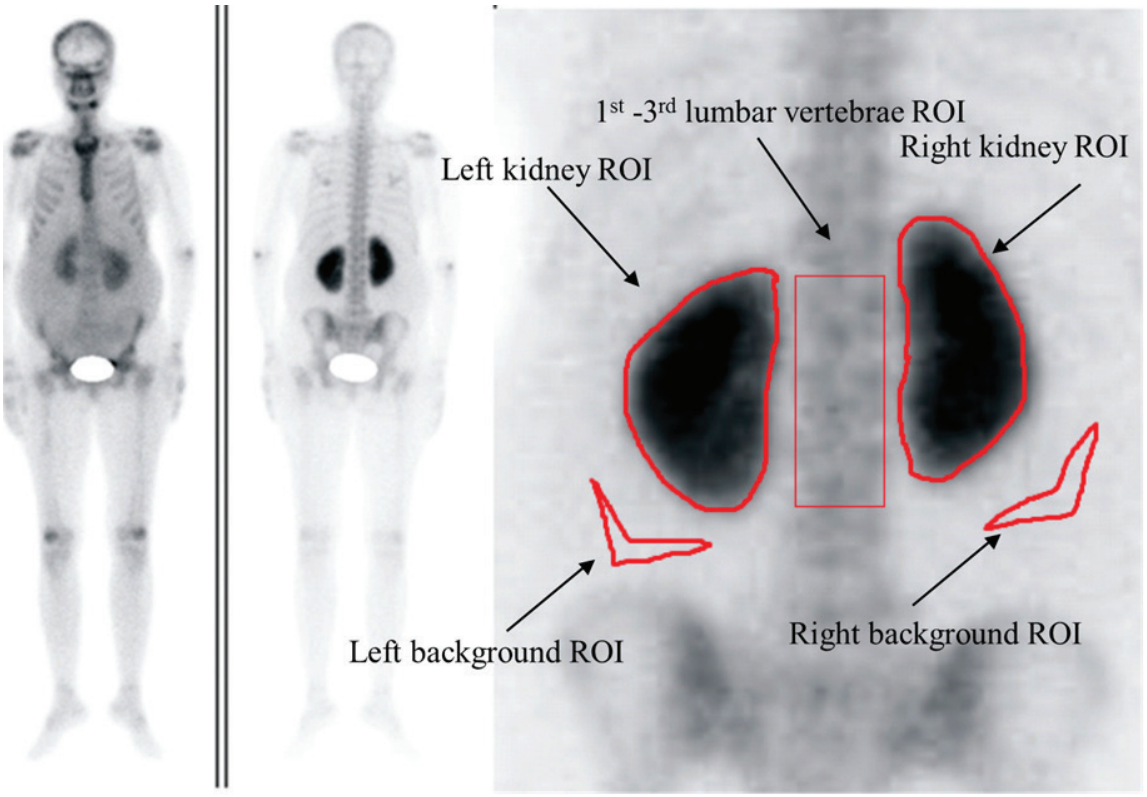

Figure 1. *^{99m}Tc MDP whole body bone scan and its posterior lumbar view showing ROI on kidneys, background, and lumber vertebrae.*

years, male = 10, female = 19) with GFR below this lower normal limit. According to KIDGO classification [18] in group II, 12 patients were in class 2 (GFR 60-89 ml/minute) and 7 were in class 3 (GFR 30-59 ml/minute).

All the processing and calculation of quantitative renal parameters of the bone scan were done by two independent observers. The average values calculated by both observers were used to compare the results between control, CLD, and HCC groups. The statistical analyses were performed on Windows workstation using the SPSS version 20.0 software. Mean and SD was calculated for quantitative parameters for each group. Two-tailed independent student's *t*-tests were used to compare the means of PRI and difference of means between the groups, and a *p*-value of less than 0.05 was considered to be statistically significant.

Results

Serum urea, serum creatinine, serum BUN concentration, serum calcium, serum iron, and serum hemoglobin were normal in all the patients included in this study. Out of 85 patients included in HCC group, 74 (87%) were positive for viral hepatitis, 68 (91.8%) patients had HCV, and 6 (8.1%) HBV. Serum AFP was within normal limits in control, almost three times higher in CLD group and more than 50 times higher in HCC group than control. Serum alkaline phosphatase in control and CLD group patients was within normal limits and almost two times higher in HCC group. Other LFT parameters were normal in all control group patients and abnormal in many of the CLD and HCC group cases. All subjects were having normal kidneys on USG.

An interobserver variation in the calculation of PRI and GFR was less than 5%. RPRI of the right and left kidneys differ from one another by less than 5% as shown in Table 2. Considering patients individually, none of the patients in all the groups showed the difference in RPRI value more than 5%.

Figure 2 graphically shows the mean PRI values in control, CLD, and HCC groups. Mean PRI value was 26.8% higher in CLD group than control group (0.52 ± 0.15 *vs.* 0.41 ± 0.11), which is statistically significant (t = 3.295, p = 0.002). Mean PRI values in HCC group were almost twice (99.7% higher) as compared to that of control group (0.82 ± 0.58 *vs.* 0.41 ± 0.10). the independent-student's *t*-test showed that this difference in the means of PRI between control and HCC groups is statistically very significant (t = 3.947, p = 0.000). Mean PRI value of HCC group was 59.6% higher than that of CLD group (0.83 ± 0.58 *vs.* 0.52 ± 0.15), which is statistically very significant (t = 2.89, p = 0.004).

In subgroup of HCC patients, in which ^{99m}Tc-DTPA renal scintigraphy was performed (n = 25), although serum BUN, urea, and creatinine were normal, GFR was reduced in 76% (n = 19) of patients (group II) and normal in only 24% (n = 6) of patients (group I). GFR was 60.76 ± 15.04 in group II, whereas 89.02 ± 10.28 in group I. As

shown in Figure 3, the mean PRI in group II was 36.99% higher than that in group I (0.97 ± 0.44 *vs.* 0.66 ± 0.21). The independent student's *t*-test showed that this difference in the means of PRI between group I and II is statistically significant ($t = -2.349$, $p = 0.023$).

Discussion

Hepatocellular carcinoma is the most common primary malignancy of the liver in this region of world. Bone scan is routinely used for skeletal metastatic survey in patients with known malignancy. Usually the kidneys are faintly visualized on routine bone scan images. The incidence of diffuse increased renal parenchymal retention of ^{99m}Tc-MDP (hot kidneys) in literature varies from 1% to 1.4% in general patients who underwent bone scintigraphy in nuclear medicine setups [16]. Only limited work had been done in HCC cases to assess the diffuse renal parenchymal retention of ^{99m}Tc-MDP and its correlation with

Table 2. Relative renal PRI in percentage.

GROUPS	RIGHT KIDNEY	LEFT KIDNEY	DIFFERENCE
Control	48.91 ± 2.18	51.09 ± 2.18	2.18
CLD	48.77 ± 1.71	51.23 ± 1.71	2.46
HCC	51.73 ± 5.01	48.27 ± 5.01	3.50

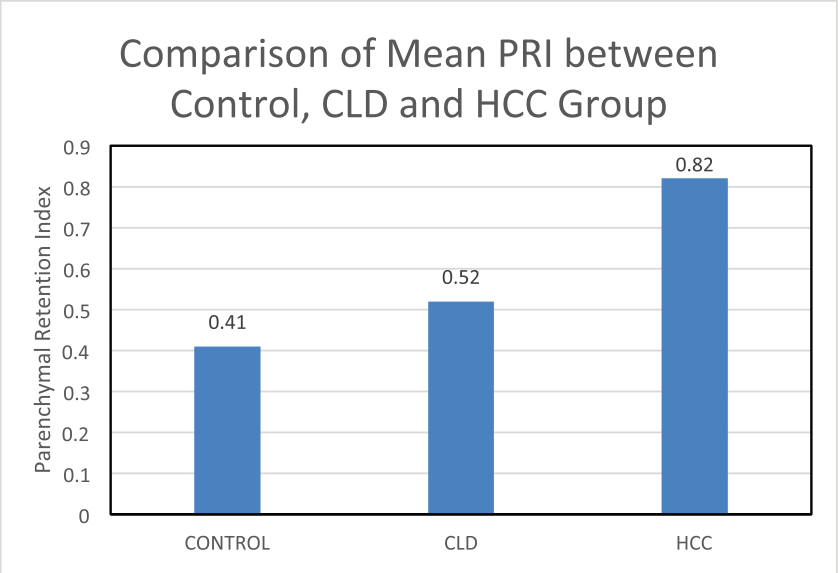

Figure 2. *Mean PRI of control, CLD, and HCC groups.*

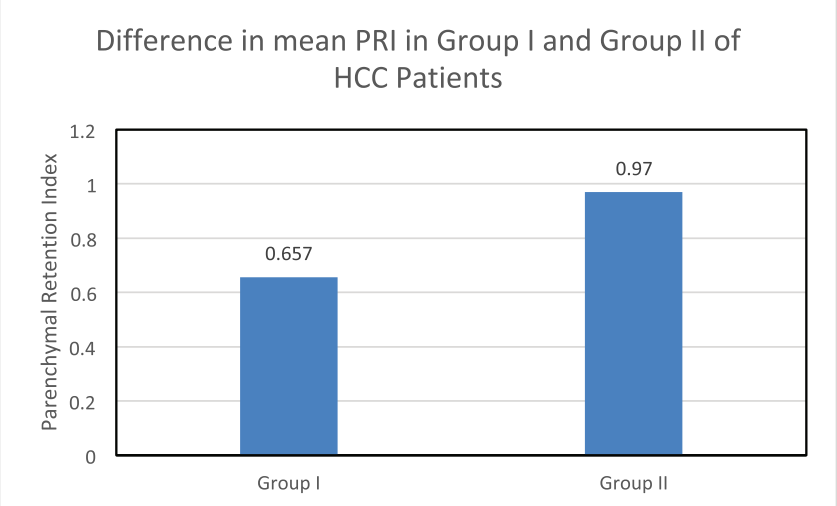

Figure 3. *Mean PRI in group I and group II of HCC patients who underwent ^{99m}Tc-DTPA renal scintigraphy and GFR analysis (25 patients).*

renal function. Even in such reported studies, researchers confined their work on the qualitative assessment of renal uptake of tracer and correlated them with blood urea and creatinine [17]. Population reported in these studies was heterogeneous with reference to urea and creatinine levels. Blood urea and creatinine levels are deranged only when more than 50% of renal function has been knocked out [19]. Hence, these are not optimal parameters for research correlation. The direct measurement of GFR is rather a better criterion. This study is one of those limited studies which quantify diffuse renal parenchymal retention of ^{99m}Tc-MDP in patient population with normal serum urea and creatinine and correlate it with GFR obtained from DTPA renal scan to investigate the probable cause of high ^{99m}Tc-MDP renal parenchymal retention.

In this study, control, CLD, and HCC groups showed a less than 5% difference between RPRI values of the right and left kidneys. It is in accordance with acceptable limits for relative renal function of normal kidneys [20] and denotes that both the kidneys were having almost similar PRI values. We found a statistically significant 26.8% higher mean PRI value in CLD than control group (p = 0.002), which represents high diffuse renal parenchymal retention of ^{99m}Tc-MDP in CLD patients than that in control group. The results agree with the results of different researchers. Koizumi et al. [21] found intense bilateral renal uptake in 13 patients, of which four were of cirrhosis. Erhamamcı et al. [17] observed hot kidneys in 20 (43.5%) of 50 consecutive patients with end-stage CLD; however, among their 46 adult patients, 45 were having HCC (97.6%), and they did not compare their patients with normal control subjects.

The results showed that the mean PRI of HCC group was almost two times higher than that of control group and almost 1.5 times higher than that of CLD group. Very limited work has been done on bilateral diffuse renal parenchymal ^{99m}Tc-MDP retention in HCC patients. In one case series bilateral diffuse MDP parenchymal retention on bone scan is already reported [22].

The differential diagnosis of hot kidneys on bone scan include nephrocalcinosis, hypercalcemia, hyperparathyroidism, chemotherapy, iron overload (sickle-cell disease), acute renal injury due to ATN and nonsteroidal anti-inflammatory drugs (NSAIDs), recent radiotherapy, and use of antineoplastic drugs and secondary to aluminum breakthrough of ^{99}Mo- ^{99m}Tc generator [12–16]. The exact mechanism leading to abnormal high renal tracer parenchymal retention has not been established, and researchers proposed different mechanics [23,24]. The patients with hepatorenal syndrome are characterized by severe cirrhosis, glomerular hypofiltration, and low arterial pressure. Renal failure is a common major complication in patients with advanced cirrhosis [15]. In this study, all the patients had normal renal function tests (BUN, urea, and creatinine). They were having normal kidneys on USG and CT. They did not reveal any chronic disease other than that of CLD/cirrhosis. The effects of chemotherapeutics, antibiotics, radiations, NSAIDs, and chronic diseases causing iron overload are excluded. These cases were normotensive and normocalcemic which made the diagnosis of metabolic and vascular pathologies unlikely.

We could find only one study in literature which qualitatively assessed diffuse renal parenchymal retention of ^{99m}Tc-MDP in 46 adult patients of cirrhosis, of which 45 (97.8%) had HCC [14]. This study differs from this study with respect to the MDP retention paralleled to the severity of parenchymal damage since they have relied on serum urea and creatinine. They proposed that any significant retention of tracer in the kidney might forecast future renal function deterioration [14]. A higher PRI value is probably a predictor/marker of deranged renal function and very high risk of subsequent rapid deterioration in renal function which may lead to hepatorenal syndrome.

This study showed that in spite of normal serum BUN, urea, and creatinine levels in HCC patients who underwent ^{99m}Tc-DTPA renal scintigraphy, 76% of them had reduced GFR. Hence, the biochemical renal function tests underestimate the renal function in these HCC patients. It is because serum urea, BUN, and creatinine rise above the upper normal limit only when more than half of the functions of the kidneys have been knocked out. Moreover, as creatinine is synthesized within the liver, in compromised cirrhotic liver, its production can be significantly less than that of normal individual and hence is not a reliable parameter to evaluate the renal function [25,26]. In few of the patients, water retention in the body leading to expansion of volume of distribution may be another cause [27]. This study showed a statistically significant difference in the mean PRI ($p < 0.05$) of group I (patients with normal GFR) and group II (patients with GFR less than lower normal limit). This study suggests that, in HCC patients having normal serum BUN, urea, and creatinine levels, the diffuse renal parenchymal retention of ^{99m}Tc-MDP on bone scan is inversely related with GFR.

HCC patients frequently have coexisting cirrhosis that makes patients more vulnerable to renal damage. Cirrhosis compensatory mechanism leads to the preservation of renal perfusion pressure. As cirrhosis advances, hepatic vascular resistance due to fibrosis and systemic vasodilatation becomes high, and the kidneys are hypoperfused due to the vasoconstriction of renal circulation and decreased renal flow, which may lead to renal insult leading to renal function impairment and drop in GFR [28,29]. The rapid diagnosis of renal function impairment and its management are important since it can offer the patient time for liver transplantation. HCC patients with normal serum urea and creatinine levels, showing high diffuse increased renal cortical ^{99m}Tc-MDP on bone scan, should

be considered at high risk of subsequent rapid deterioration in renal function. It may be an early marker of renal dysfunction or a predictor of hepatorenal syndrome. In such patients, renal scintigraphy should be used to assess the renal function in terms of GFR, which helps in the early and reliable detection of renal function impairment than routine renal function tests.

Confounding factors for RPI include time to image after i/v injection of Tc-99m MDP and body mass index (BMI). Time to image can affect PRI because of renal and background clearance. To avoid the impact of this factor on PRI, time to image for bone scan was kept 3 hours post injection. High BMI results in high background activity and it may affect the RPI. It might not be in case of HCC because these patients commonly present with weight loss.

Conclusion

In HCC patients, diffuse renal parenchymal retention of ^{99m}Tc-MDP on bone scan is significantly higher than that of normal volunteers and CLD patients. GFR is reduced in many HCC patients with normal blood biochemistry renal function tests, which suggest that blood biochemistry renal function tests underestimate renal function. In HCC patients with normal blood biochemistry renal function tests, the diffuse renal parenchymal retention of ^{99m}Tc-MDP on bone scan is significantly higher in patients with reduced GFR than those with normal GFR. In those with high diffuse renal parenchymal ^{99m}Tc-MDP uptake in the presence of normal serum BUN, urea, and creatinine, a higher PRI value is a strong predictor/marker of reduced renal function and very high risk of subsequent rapid deterioration in renal function which may lead to hepatorenal syndrome.

Clinical Implication

In HCC patients with high diffuse renal parenchymal retention of ^{99m}Tc-MDP on bone scan, BUN, serum urea, and creatinine are not reliable parameters to assess renal function. High diffuse renal parenchymal retention of ^{99m}Tc-MDP on bone scan is a strong predictor of deranged renal function which may not be detectable by routine blood biochemistry renal function tests. In such cases, ^{99m}Tc-DTPA renal scintigraphy should be used to assess the renal function reliably.

Limitation

In this study, the number of cases of CLD was small, and most of the CLD patients had an early stage of cirrhosis. ^{99m}Tc-DTPA renal scan was not performed in CLD patients and normal controls, and we could not correlate higher PRI values in CLD group than control group with renal function in terms of GFR. Renal scan was not performed in all HCC patients. We did not investigate the possible causes of high diffuse renal parenchymal retention of ^{99m}Tc-MDP due to tumor itself.

List of Abbreviations

CLD	Chronic Liver Disease
DTPA	Diethylene Triamine Penta Acetic Acid
GFR	Glomerular Filtration Rate
HCC	Hepatocellular Carcinoma
LEAP	Low Energy All Purpose
MDP	Methylene Diphosphonate
PRI	Parenchymal Retention Index
RPRI	Relative Parenchymal Retention Index

Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this article.

Funding

None.

Consent for publication

Informed written consent was taken from all the patients included in this study.

Ethical approval

The approval of this study was obtained from the Ethical committee of PINUM Cancer Hospital before start of the study.

Author details

Muhammad Shahzad Afzal[1], Muhammad Babar Imran[1], Samen Fatima[1], Muhammad Iqbal[1], Farkhanda Gillani[1], Nayyar Rubab[1], Owais Qadeer Gill[1], Muhammad Naeem[1]

1. PINUM Cancer Hospital, Faisalabad, Pakistan.

References

1. Pascual S, Herrera I, Irurzun J. New advances in hepatocellular carcinoma. World J Hepatol. 2016;8(9):421–38. https://doi.org/10.4254/wjh.v8.i9.421
2. Kim JU, Shariff MIF, Crossey MME, Romero MG, Holmes E, Cox IJ, et al. Hepatocellular carcinoma: review of disease and tumor biomarkers. World J Hepatol. 2016;8(10):471–84. https://doi.org/10.4254/wjh.v8.i10.471
3. Simonetti RG, Cammà C, Fiorello F, Politi F, D'Amico G, Pagliaro L. Hepatocellular carcinoma. A worldwide problem and the major risk factors. Dig Dis Sci. 1991;36(7):962–72. https://doi.org/10.1007/BF01297149
4. Parkash O, Hamid S. Next big threat for Pakistan hepatocellular carcinoma (HCC). J Pak Med Assoc. 2016;66(6):735–9.
5. Tsuchiya N, Sawada Y, Endo I, Saito K, Uemura Y, Nakatsura T. Biomarkers for the early diagnosis of hepatocellular carcinoma. World J Gastroenterol. 2015;21(37):10573–83. https://doi.org/10.3748/wjg.v21.i37.10573
6. Poon D, Anderson BO, Chen LT, Tanaka K, Lau WY, Van Cutsem E, et al. Management of hepatocellular carcinoma in Asia: consensus statement from the Asian Oncology Summit 2009. Lancet Oncol. 2009;10:1111–8. https://doi.org/10.1016/S1470-2045(09)70241-4
7. Cook GJ, Azad GK, Goh V. Imaging bone metastases in breast cancer: staging and response assessment. J Nucl Med. 2016;57:27S–33S. https://doi.org/10.2967/jnumed.115.157867
8. Özdoğan Ö, Pınar Karahan N, Sarıoğlu S, Durak H. Acute kidney injury secondary to NSAID diagnosed on 99mTc MDP bone scan. Mol Imaging Radionucl Ther. 2013;22(2):66–9. https://doi.org/10.4274/Mirt.95
9. Bernard MS, Hayward M, Hayward C, Mundy L. Evaluation of intense renal parenchymal activity ("hot kidneys") on

bone scintigraphy. Clin Nucl Med. 1990;15(4):254–6. https://doi.org/10.1097/00003072-199004000-00010
10. Gambaro G, Perazella MA. Adverse renal effects of anti-inflammatory agents: evaluation of selective and nonselective cyclooxygenase inhibitors. J Intern Med. 2003;253(6):643–52. https://doi.org/10.1046/j.1365-2796.2003.01146.x
11. Choy D, Murray IP, Hoschl R. The effect of iron on the biodistribution of bone scanning agents in humans. Radiology. 1981;140(1):197–202. https://doi.org/10.1148/radiology.140.1.6264545
12. Ohta H. Liver uptake and increased renal uptake of Tc-99m HMDP in a patient with iron overload. Clin Nucl Med. 2001;26(2):164–5. https://doi.org/10.1097/00003072-200102000-00024
13. Bernard MS, Hayward M, Hayward C, Mundy L. Evalution of intense renal parenchymal activity on bone scintigraphy. Clin Nucl Med. 1990;15(4):254–6. https://doi.org/10.1097/00003072-199004000-00010
14. Erhamamcı S, Aktaş A, Bahçeci T, Kavak K. Osseous and nonosseous bone scan findings in liver transplant candidates with end-stage chronic liver disease. Mol Imaging Radionucl Ther. 2013;22(2):23–31. https://doi.org/10.4274/Mirt.29292
15. Mauss S, Berg T, Rockstroh J, Sarrazin C, Wedemeyer H. Hepatology: A Clinical Text book. 10th Edition. Flying Publisher, Germany. 2020:197–207.
16. Hafeez Bhatti AB, Dar FS, Waheed A, Shafique K, Sultan F, Shah NH. Hepatocellular carcinoma in Pakistan: national trends and global perspective. Gastroenterol Res Pract. 2016;2016:1–10. https://doi.org/10.1155/2016/5942306
17. 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. https://doi.org/10.1007/s10555-013-9454-4
18. Levey AS, Jong PE, Coresh J, Nahas ME, Astor BC, Kunihiro Matsushita K, et.al. The definition, classification, and prognosis of chronic kidney disease: a KDIGO Controversies Conference report. Kidney Int. 2011;80(1):17–28. https://doi.org/10.1038/ki.2010.483
19. Shokeir AA, Gad HM, El-Diasty T. Role of radioisotope renal scans in the choice of nephrectomy side in live kidney donors. J Urol. 2003;170(2 Pt 1):373–6. https://doi.org/10.1097/01.ju.0000074897.48830.58
20. Koizumi K, Tonami N, Hisaha K. Diffusly increased Tc-99m uptake in both kidneys. Clin Nucl Med. 1981;6(8):362–5. https://doi.org/10.1097/00003072-198108000-00006
21. Afzal MS, Imran MB, Akhtar MS, Iqbal M. Increased renal parenchymal retention of 99mTc-MDP (hot kidneys) in two patient of hepatocellular cancer: one with and other without osseous metastases. EJMCR. 2017;1(2):74–8 https://doi.org/10.24911/ejmcr/1/19
22. Kondakov AK, Kharina DS, Servuli EA, Znamenskiy IA. Hot kidneys; artifact on bone scan: incidence and approach to quantification. In: 28th Annual EANM Congress of the European Association of Nuclear Medicine, Hamburg, Germany; 2015. pp 42.
23. Tarsarya S, Marwah A, Shah H, Jaiswar R. Non-osseous uptake on Tc99m methylene diphosphonate in multiple muscles confirmed on SPECT/computed tomography. Indian J Nucl Med. 2012;27(3):205–7
24. Francoz C, Glotz D, Moreau R, Durand F. The evaluation of renal function and disease in patients with cirrhosis. J Hepatol. 2010;52(4):605–13. https://doi.org/10.1016/j.jhep.2009.11.025
25. Ayan AK, Varoglu E, Keles M, Seven B, Uyanik A, Örsal E. Comparison of glomerular filtration rate measurements with the two-plasma sample technique using Tc-99m DTPA and other methods in donor candidates for renal transplantation. Turkish J Med Sci. 2016;46:1025–32. https://doi.org/10.3906/sag-1403-58
26. Ginès P, Schrier RW. Renal failure in cirrhosis. N Engl J Med. 2009;361(13):1279–90. https://doi.org/10.1056/NEJMra0809139
27. Slack A, Yeoman A, Wendon J. Renal dysfunction in chronic liver disease. Crit Care. 2010;14(2):214. https://doi.org/10.1186/cc8855
28. Tandon BN. Tropical hepato-gastroenterology. 2nd ed. Amsterdam, The Netherlands: Elsevier Health Sciences; 2012. 804 p.
29. Hsu CY, Huang YH, Su CW, Lin HC, Chiang JH, Lee PC, et al. Renal failure in patients with hepatocellular carcinoma and ascites. Liver Int. 2010;30(1):77–84. https://doi.org/10.1111/j.1478-3231.2009.02128.x