Is quantitative analysis of planar bone scan useful in assessment of response in bone metastases?

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Abstract:

Background: One of most common and economical method for identifying bone metastases in clinical workflow is a bone scan. However, its clinical significance for determining how well patients with advanced metastatic bone disease are responding to therapy is still restricted, partly due to the absence of a reliable approach for measuring changes in bone scans.

Objectives: using quantitative analysis of planar images as compared to qualitative assessment in cancer patients receiving treatment for bone metastasis, radiotracer uptake was observed between first and follow-up scans. This method of imaging interpretation can be used to produce a more reliable and consistent manner of patient follow-up analysis, which is essential for researching.

Methods: This prospective study involved 37 patients who were known to have primary malignant tumor and osseous metastases. They underwent two bone scintigraphies before and after the therapy, each involved certain osseous lesion for further analysis by planar images. 47 osseous lesions were interpretated firstly by visual assessment by 3 physicians and interpretated by (progressive, regressive, stationary) opinion. Secondly, the same osseous lesions analyzed by quantifications of planar images were added by measuring mean and maximum of standardized uptake value of osseous lesions (SUV mean and max). All of quantification is considered progressive (more than 30% rise), regressive (more than 30% reduction) and stationary (rest in between). The results of agreement between 3 readers visually and between visual and quantitative assessment was done using Cohen's kappa test.

Results: Inter-observer agreement of the visual analysis between readers 1 and 2 was in 32 lesions of total 47 lesions, k = 0.519 (moderate degree) for planar scintigraphy. By the same way the agreement between readers 1 and 3 was in 36 lesions, k= 0.662 (substantial degree). In addition, inter-method agreement between reader 2 and reader 3 was in 27 lesions k = 0.358 (fair degree). On the other side, 19 (40.4%) of the total 47 lesions had visual and quantitative assessments that were in agreement. The quantitative and visual analyses' intra-method agreement was k= 0.049. (Poor degree).

Conclusions: For up to 57% of the total lesions, visual assessment of bone scintigraphy for changes in tumor metabolism produced conflicting results. In addition, visual analysis revealed moderate to significant inter-observer agreement. This suggests that, to maximize consistency in treatment planning, continuous monitoring of bone scanning for variations in the tracer uptake of lesions should be carried out using quantification of tracer uptake rather than just by visual evaluation.

Keywords: Bone scan, quantitative analysis, visual assessment, assessment of response.

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Introduction:

Bone is one of the most often sites of distant metastasis in patients with cancer, in addition to the lung and liver[1]. Hematogenous spread of cancer cells is the primary cause of most bone metastases. For identifying and classifying bone metastases, numerous anatomical and functional imaging techniques are employed. One of them is bone scintigraphy, which is

frequently carried out using 99mtechnetium methylene diphosphonate (99mTc-MDP). It is a routine imaging technique that offers a full-body skeletal survey at a reasonable cost and is typically the first imaging technique for the detection of bone metastatic lesions [2].

The excellent sensitivity of bone scintigraphy in the assessment of metastatic osseous lesions is highlighted in numerous papers. However, newly accessible bone scan SPECT-CT systems combine tomographic scintigraphy and CT, creating a special fusion of both anatomical and functional sets of data [3]. These devices enable the alignment of the CT scan's field of view with the SPECT result. It has been demonstrated that SPECT-CT is useful for a variety of indications and for varied areas [4].

Quantitative nuclear medicine measurements are used to quantitatively evaluate the local concentrations of radiotracers and, if necessary, their wider spread. Increased tracer uptake in bone reflects two physiological processes: blood flow and the degree of osteogenesis. The limitations of a merely visual analysis may be overcomed by quantitative assessment [5]. The purpose of this study was to compare the difference between visual and quantitative methods for assessing response of treatment in patients with metastatic bone lesions.

Patients and Methods:

Study design and population:

Between November 2021 and November 2022, the Nuclear Medicine Unit of the South Egypt Cancer Center conducted this prospective study. It contained 37 patients, with a mean age of 50.5 years and a gender ratio of 34 females (91.9%). (SD: 9.9). All cancer patients who referred for bone scintigraphy and their planar whole-body scans revealed metastatic osseous lesions were recruited. Three experienced nuclear medicine doctors (Reader 1:7-year experience; Reader 2:10-year experience; Reader 3:11-year experience) who were aware of the study's purpose separately read the data, and the results were recorded by consensus opinion in between readings to evaluate the final visual opinion on planar images. The local ethics committee gave approval for the project.

Patients' selection

The selection criteria included the patients who met the criteria listed below, and it was accepted by the ethical committee.

Inclusion criteria:

- All patients with known primary neoplasm metastasizing to bone proved by bone scan presented to assess the response after interval therapy.
- Patient who received interval treatment (systemic and/or local).
- At least 6-8 month time frame between two studies.
- Having access to the estimated administered activity, the measurement's timing, the injection's timing, and the syringe's remaining activity.
- There were no statistically significant variations between the baseline and follow-up studies in the acquisition parameters.

Exclusion criteria:

- Osseous lesions in non-neoplastic patients.
- Neoplastic patients with benign osseous lesions.
- Interval surgical osseous intervention.
- Newly developed osseous lesion.
- Patients below 18 years.

Methodology and data collection

- Data was collected for all patients from their medical records in the department’s clinic and completed on the day of the scan.

Demographic characters and data collected included:

- Age
- Gender
- Telephone number
- Referring department
- Case Diagnosis
- History of radiotherapy and chemotherapy.
- History of trauma or fractures

Nuclear medicine Data Acquisition:

It was carried out by the nuclear medicine unit team of physicist and technicians. The tracer was also prepared daily by the same team of physicists.

Radiopharmaceuticals Used and Dose:

- Technetium99m diphosphonate (MDP), intravenous injection of 20 mCi (740 MBq).
- Site of injection was chosen to prevent pathological condition that was known or suspected.

Technique of scanning

Patients were advised to drink at least 1.5 liters of water following tracer injection to hydrate properly. Patients were instructed to void immediately before delayed imaging (2-4 hours post injection). Patients were instructed to take care as urinary contamination frequently confuses or obscures potential lesion sites. All metal (such as coins or belts) were taken off and sites of trauma or surgery were documented. To reduce movement during the acquisition, the patients were instructed to lie supine with their arms down and immobilized. The entire skeleton's anterior and posterior pictures were captured. Images were acquired on the140 keV photopeak with a 20% symmetrical window and matrix size was 256 × 1024.Whole-body scan (table rate ≈ 12 cm/min).

Data analysis:

The study was done on total 37 patients who were known to have primary tumor proved by pathology, 34 females and 3 males. Most of female patients (32 females) were known to have breast cancer with percentage of 86.5%.

Total defined osseous lesions by planar images of 47 lesions were defined and selected for further qualitative and quantitative analysis.

Follow-Up Examination:

Following the initial scan, every 6 to 8 months, the patients with metastatic bone lesions underwent a follow-up examination in our department to monitor the changes in radiotracer uptake brought on by changes in the bone metastases' metabolic activity. To prevent a potential flare phenomenon, which commonly manifested 2 to 18 weeks after the initiation of treatment, the interval between therapy and patient scanning was adjusted. The assessment of the therapeutic response to radiotherapy was done two months after the therapy was completed. These factors are crucial for appropriately assessing therapy efficacy and determining the degree of osseous involvement.

Qualitative evaluation:

The planar images from first bone scintigraphy (BS1) and follow up second bone scintigraphy (BS2) were performed and assessed for clearly identifiable metastatic bone lesions. The criteria were a clearly increase of uptake, with more focal metastases preferable.

In the following step, the BS1 and BS2 images were viewed together, and the uptake in the target lesions was visually evaluated and categorized as progression, regression, or stationary lesion.

Three nuclear medicine physicians worked separately to complete this analysis for planar scintigraphy. Then the final visual interpretations were recorded by consistency in between them.

Quantitative evaluation:

Sensitivity of gamma camera was calculated as the count rate per unit activity to improve the detection effectiveness. It was carried out using a fat plastic dish (petri dish) having a diameter of 15 cm. This is positioned 10 cm away from the collimator and contains (0.908mci) activity of the (tc99m). The overall count rate is calculated by dividing the number of counts throughout the entire image and the defined circular ROI by the acquisition duration (20 minutes). The background count rate was then subtracted from this count rate to account for background. To achieve sensitivity in cps/MBq or cpm/Ci, the background-corrected count rate is finally divided by the source activity at the beginning of the acquisition time[6].

Quantitative analysis of two (BS) were done by using the region of interest (ROI) analysis which measured the mean of average number of counts in a group of contiguous pixels in the image. In this study, A ROI was drawn around the area of defined osseous lesion in both bone scans on anterior and posterior images, Furthermore, a standard ROI was drawn on a corresponding area with no increased tracer uptake as a standard location. The mean average counts per pixel (counts/pixel) of each lesion on both the anterior and posterior imaging were retrieved. Using the counts/pixel of the ROI, the average of the relative activity of each region can be determined. Then square root for anterior and posterior mean of each lesion and the standard reference bone were calculated. Ratio between square root of anterior and posterior mean for both osseous lesion to standard reference bone were calculated. Finally, a percentage of difference between mean of both ratio in (BS1) and (BS2) was calculated. [7]

The results were evaluated like the Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) criteria in CT and suggested positron emission tomography response criteria in solid tumors version 1.0 (PERCIST criteria) in FDG-PET. The lesions were then again classified as progressive (more than 30 % increase), regressive (more than 30 % reduction), and stable (in between). This classification was carried out using both the absolute quantification and the ratios mentioned above. [8, 9].

Statistical analysis:

Statistical Package for Social Sciences (SPSS) version 25 was used for data management and analysis. The normality of numerical data was verified before being statistically reported using the mean (standard deviation) or median (range), if necessary. Categorical data were presented as percentages and numbers. When comparing proportions of categories yielded by each classification methods; planar scintigraphy, and/or clinical decision, Mc Nemar-Boker test for paired categorical data (more than 2x2 tables) was performed. Inter- and intra-method agreement as well as inter-raters' agreements was done using Cohen's kappa and the strength of agreement was considered as follows ($k = 0.00–0.20$ is poor to slight degree, $k = 0.21–0.40$ is fair degree, $k = 0.41–0.60$ is moderate degree, $k = 0.61–0.80$ is a substantial degree, and $k = 0.81–1.00$ is almost perfect degree of agreement). P-value 0.05 was regarded as statistically significant for all two-tailed tests.

Results:

Demographic data:

This study included thirty-seven patients, [34 females (91.9%) & 3 males (8.1%)] with age ranged from 29 to 72 years, mean age of 50.5 years and SD 9.9 (Table 1).

Clinical characteristics of patients:

- All the patients were known to have primary tumor that confirmed by histopathological analysis and recorded as shown in (table 2).
- Each patient underwent 2 Bone scans with planar images which were defined as (BS1) and (BS2), first one was done before therapy to identify the presence and sites of bone metastases, the second one was done after the therapy to assess response to treatment.
- The defined metastatic lesions were 47 lesions, and their distributions are shown in (Table 3).
- Each lesion was interpretated visually and by quantitative analysis.

Scan interpretation:

Each defined lesion of 47 lesions was evaluated visually by 3 readers of physicians of nuclear medicine department (reader1 (R1), reader2 (R2), reader3 (R3)) to assess response to therapy between (BS1) and (BS2) and was recorded as (progression, regression, stationary).

The results for assessment of total lesions (47) by reader 1 were 16 lesions interpretated as progression, 11 lesions were described as stationary, and 20 lesions were assessed as regression. In the same way, the results for reader 2 were described as 10 lesions progression, 22 lesions stationary, and 15 lesions regression for planar images. In addition, for reader 3 the results of interpretation were 15 lesions were described as progression, 16 were stationary and 16 were regression for planar images (figure 1). (Table 4).

For evaluation of lesions by quantitative analysis of planar images, estimation of response to therapy was recorded as [progression (>30% increase, regression (>30% decrease), stationary (in-between)].

Analytical data:

Inter-observers' agreement

Inter-observers' agreement between 3 readers was recorded by percentage and by using Cohen's kappa method.

The inter-observer agreement of the visual interpretation between readers 1 and 2 was k = 0.519 (p 0.01).

By the same way, the degree of agreement in opinion between readers 1 and 3 was k= 0.662 by 36 lesions.

In addition, the visual analysis between readers 2 and 3 had an inter-method agreement of k = 0.358 by 27 lesions. (Table 6).

Comparison of visual assessment and quantitative assessment:

Agreement between quantification and visual assessment occurred in 19 (40.4 %) lesions of total 47 lesions with Kappa = 0.049 (p-value=0.397).

Table 1: Demographic features of the studied patients

		Number	Percentage	Total	Age
Gender	**Male**	3	8.1	**37**	**50.5 years ± 11**
	Female	34	91.9		

Table 2: Primary tumor distributions of patients

Primary tumor	Number of patients	Percentage
Breast	32	(86.5)
Endometrium	1	(2.7)
Liver	1	(2.7)
Prostate	1	(2.7)
Stomach	1	(2.7)
Suprarenal	1	(2.7)

Table 3: Distribution sites of lesions (n:47)

Site	N	%
Skull	**2**	**(4.2)**
Clavicle	**1**	**(2.1)**
Humerus	**1**	**(2.1)**
Scapula	**1**	**(2.1)**
Sternum	**6**	**(12.8)**
Ribs	**2**	**(4.2)**
Cervical vertebrae	**1**	**(2.1)**
Dorsal vertebrae	**9**	**(19.1)**
Lumbar vertebrae	**9**	**(19.1)**
Pelvis	**14**	**(29.8)**
Femur	**1**	**(2.1)**

Table 4: Summary of visual analysis of planar images for 47 lesions by 3 readers

	Reader 1	Reader 2	Reader3
Progression	**16**	**10**	**15**
Stationary	**11**	**22**	**16**
Regression	**20**	**15**	**16**

Table 5: Results of lesions interpretations by quantification

Quantification	Planar images
Progression	3
Stationary	42
Regression	2

Table 6: Summary for inter-reader's agreements (n: 47)

Method	N	%	Kappa	p-value	Degree
Planar images					
Reader 1 vs. Reader 2	32	68	0.519	<0.001*	Moderate
Reader 1 vs. Reader 3	36	76.6	0.662	<0.001*	Substantial
Reader 2 vs. Reader 3	27	57.4	0.358	<0.001*	Fair

* Statistically significant at p-value < 0.05 level

Table 7: Intra-method comparison for quantitative vs Visual opinion (n=47 lesions)

Method	N	%	Kappa	p-value
Quantitative vs. Visual	19	40.4	0.049	0.397

Discussion:

One of the most popular and economical methods for identifying bone metastases in clinical workflow is a bone scan. However, its clinical significance for determining how well patients with advanced metastatic disease are responding to therapy is still restricted, partly due to the absence of a reliable approach for measuring changes in bone scans [8]. For a very long time, the primary approach of imaging interpretation has been qualitative analysis, which provides sufficient data and reliability for patient diagnosis and follow-up. The lack of objective data, particularly for research and patient follow-up, and the interobserver variability, Beck et al. [10] have highlighted the need to establish a quantitative approach of molecular imaging analysis that can offer clear, quantifiable, and reproducible results. It is difficult to establish a clinically appropriate intensity threshold to detect changes in the target lesions because there are large inter- and intra-reader variability in the interpretation of the uptake of the lesions [11].

In our study, the total defined osseous lesions were 47 lesions, and their distribution was mainly in spine (19 lesions, 40.4%) then pelvis (14 lesions, 29.8%), and sternum (6 lesions, 12.8%). This distribution matches with results of distribution of metastatic bone lesions in VRD Kakhki et al [12] which revealed that the most affected area was the spine (30 lesions,18.8 %), followed by ribs and pelvis. In breast and GI malignancies, the spine was the most often affected bone metastasis site. Except for the spine, ribs and the sternum were the most typical sites for bone metastases from breast cancer. The most common sites for prostate cancer were the spine and pelvis, with comparable incidences [12].

In our study, Visual assessment of total 47 lesions by three nuclear medicine physicians resulted in an agreement between readers 1 and 2 in 32 lesions (68%), between R2 and reader 3 (R3) in 27 (57.4%) lesions, and between R1 and R3 in 36 (76.6%) lesions as regarding planar images evaluation as (progressive /regressive and stable disease), by Kappa results, it was 0.51, 0.35 and 0.66 respectively (moderate, fair and

substantial degree). While Ishii et al. [13] evaluated the response to specific therapy (zoledronic acid) for bone metastases in the same way of interobserver agreement between 3 readers, for BS, the interobserver agreement rates between Readers 1 and 2, Readers 1 and 3, and Readers 2 and 3 were 84%, 80%, and 88% (= 0.648, 0.561, and 0.766), respectively. On the other hand, M Shackleton et al. [14] and as part of the assessment of the efficiency of X-rays and bone scintigraphy for the evaluation of changes in osseous metastases in cases of breast cancer, revealed that nuclear medicine doctors had a significant degree of agreement regarding the variations between sequential bone scans (k=0.62).

For quantitative assessment, we assessed SUV mean and max of bone lesions in initial and follow-up bone scans for each patient to assess the response to therapy, according to Philipp Ritt et al. [15], positron emission tomography (PET) and single-photon emission computed tomography (SPECT) allowed the precise measurement of the radioactivity concentration within a given volume of tissue in absolute units, such as kilobecquerels per cubic centimeter, this allows for the descriptions of the distribution of radioactivity within the scanned skeleton.

Furthermore, for determining the basic concepts of tumor response criteria (anatomic and functional) and the appearance of bone metastatic lesions as they respond to treatment or progress, we considered by quantification analysis that if osseous uptake (>30% increase) it was considered progression, (> 30% decrease) it was regression and in between was stationary , and this depended on Colleen M. Costelloe et al [16] described Cancer Response Criteria and Bone Metastases :RECIST 1.1, MDA and PERCIST for solid tumors and descried response as (complete, partial ,progressive and stable disease) according to metabolic and anatomical changes that can be assessed by CT, MRI or BS.

Based on our small data, we could demonstrate that there was a great difference between visual and quantitative methods, producing conflicting findings in as many as 59.6% of the investigated lesions in planar pictures. On the other hand, 19 (40.4%) of the total 47 lesions with a Kappa value of 0.049 for planar scintigraphy showed agreement between visual and quantitative assessment (poor degree).

As far as we know there is one study which compared visual analysis and quantification of bone scintigraphy of response to therapy, Michael Beck et al. [17] revealed that the agreement between visual analysis and quantification was only moderate, with an average Cohen's kappa of 0.42 for planar scintigraphy.

Our findings together with those from the literature provide strong evidence that semi-quantitative or quantitative evaluation should be used with visual evaluation of bone scanning for further variations in tracer uptake of the target lesions [18].

Limitations:

It is challenging to evaluate the clinical relevance of our findings because of the relatively small patient group and the lack of consensus on radiotracer uptake variations in the quantitative analysis of planar data sets due to the paucity of data in the literature.

Conclusion:

Visual analysis of bone scintigraphy for alteration in tumor uptake produced variable results in up to 57% of the total lesions when compared to assessing tracer uptake in absolute unit. In addition, visual analysis revealed moderate to significant inter-observer agreement. This shows that to maximize consistency in patient management, longitudinal monitoring of bone scans for alteration in tracer uptake of specific lesions should be undertaken utilizing quantification of tracer uptake rather than making decision based on visual judgement only.

References:

1. Disibio G, French SW. Metastatic patterns of cancers: results from a large autopsy study. Arch Pathol Lab Med. 2008 Jun;132(6):931-9.
2. Yang HL, Liu T, Wang XM, Diagnosis of bone metastases: a meta-analysis comparing 18 FDG PET, CT, MRI and bone scintigraphy. Eur Radiol. 2011 Dec;21(12):2604-17.
3. Histed SN, Lindenberg ML, Mena E, et al. Review of functional/anatomic imaging in oncology. Nucl Med Commun. 2012 Apr; 33(4): 349–361.
4. Le Bihan D, Johansen-Berg H. Diffusion MRI at 25: exploring brain tissue structure and function. Neuroimage. 2012 Jun;61(2):324-41.
5. Gherghe M, Mutuleanu MD, Stanciu AE, et al. Quantitative Analysis of SPECT-CT Data in Metastatic Breast Cancer Patients-The Clinical Significance. Cancers (Basel). 2022 Jan 6;14(2):273.
6. Khalil MM. Positron emission tomography (PET): Basic principles. In: Basic sciences of nuclear medicine, Springer-Verlag Heidelberg Dordrecht London New York, 2011, pp. 179-213.
7. Saridin CP, Raijmakers P, Becking AG. Quantitative analysis of planar bone scintigraphy in patients with unilateral condylar hyperplasia. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2007 Aug;104(2):259-63.
8. Wahl RL, Jacene H, Kasamon Y, et al. From RECIST to PERCIST: evolving considerations for PET response criteria in solid tumors. J Nucl Med. 2009 May;50 Suppl 1(Suppl 1):122S-50S.
9. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009 Jan;45(2):228-47.
10. Beck M, Sanders JC, Ritt P, et al. Longitudinal analysis of bone metabolism using SPECT/CT and 99m Tc-diphosphono-propanedicarboxylic acid: comparison of visual and quantitative analysis. EJNMMI Res. 2016 Dec;6(1):60.
11. Hirschmann MT, Wagner CR, Rasch H, et al. Standardized volumetric 3D-analysis of SPECT/CT imaging in orthopaedics: overcoming the limitations of qualitative 2D analysis. BMC Med Imaging. 2012 Mar 29;12:5.

12. Kakhki VR, Anvari K, Sadeghi R, et al. Pattern and distribution of bone metastases in common malignant tumors. Nucl Med Rev Cent East Eur. 2013;16(2):66-9.
13. Ishii S, Kikuchi K, Miyajima M, et al. Validation of therapeutic response assessment by bone scintigraphy in patients with bone-only metastatic breast cancers during zoledronic acid treatment: comparison with computed tomography assessment. Fukushima J Med Sci. 2015;61(1):23-31.
14. Shackleton M, Yuen K, Little AF, et al. Reliability of X-rays and bone scans for the assessment of changes in skeletal metastases from breast cancer. Intern Med J. 2004 Nov;34(11):615-20.
15. Ritt P, Vija H, Hornegger J, et al. Absolute quantification in SPECT." Eur J Nucl Med Mol Imaging. 2011 May;38 Suppl 1:S69-77.
16. Costelloe CM, Chuang HH, Madewell JE, et al. Cancer response criteria and bone metastases: RECIST 1.1, MDA and PERCIST. J Cancer. 2010 Jun 28;1:80-92.
17. Beck M, Sanders JC, Ritt P, et al. Longitudinal analysis of bone metabolism using SPECT/CT and 99mTc-diphosphono-propanedicarboxylic acid: comparison of visual and quantitative analysis. EJNMMI Res. 2016 Dec;6(1):60.
18. Woolf D, Padhani A, Makris A. Assessing response to treatment of bone metastases from breast cancer: what should be the standard of care? Ann Oncol. 2015 Jun;26(6):1048-1057.