Role of Baseline Bone Scintigraphy in the Evaluation of Skeletal Metastases of Newly Diagnosed Lung Carcinoma Patients

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ABSTRACT

Objective: **Lung carcinoma is the most common cancer worldwide with high potentiality of being metastasized to bone. Technetium-99m methylene diphosphonate (99mTc MDP) bone scintigraphy is a sensitive nuclear medicine imaging study to detect the skeletal metastases. The utilization of bone scan upon diagnosis of lung cancer appears to help in accurate staging of patients and planning treatment. The aim of the present study was to see the role of baseline bone scintigraphy in the newly diagnosed lung carcinoma patients and also to see the number, pattern and sites of involvement of bone as well as to evaluate the skeletal metastases according to the different histological types of lung carcinoma.**

Patients and Methods: **This observational study was carried out at the Institute of Nuclear Medicine & Allied Sciences (INMAS), Sylhet during the period of July 2014 to June 2015. A total number of 59 lung carcinoma patients who attended at the scintigraphy division of INMAS, Sylhet within three months of their histopathological diagnosis were included in this study. Clinical staging was done from clinical evaluation (history and physical examination) and also form available investigation reports. Skeletal scintigraphy was performed by dual-head gamma camera using low-energy all purpose collimator, 2-3 hours after IV administration of 20-30 mCi of 99mTc MDP. Interpretation was done by recording the distribution of radiotracer within the skeleton along with correlation of history, physical examination, FNAC or biopsy reports and other relevant investigation findings.**

Results: **Out of 59 patients, 43 (72.9%) were male and 16 (27.1%) were female. The age range of the patients was from 37 to 85 years with a mean (± SD) of 59.10 ± 10.43 years. The rate of lung carcinoma was highest in the age group of 55-64 years (45.7%), followed by 45-54 years (27.1%) and 65-74 years (11.9%). Incidence was lowest in patients below 45 years (6.8%) and above 75 years (8.5%). Skeletal metastases were detected in 52.54% of lung carcinoma patients where multiple lesions were seen in 87.1% of cases and solitary lesion in 12.9%. Among the metastatic lesions, 82.9% lesions were distributed in axial skeleton and 17.1% lesions were distributed in appendicular skeleton. Spine was the most frequent site of metastatic involvement in the present study which was 37.8% followed by ribs 28.0%, sternum 9.7% and pelvic bones 7.3%. Thoracic spine was found to be involved more (58.1%). Regarding patterns of metastatic lesions, 23 patients (74.1%) showed hot lesions, two patients (6.5%) showed cold lesions, four patients (12.9%) showed superscan and two patients (6.5%) showed pattern of hypertrophic osteoarthropathy. Bone metastasis was found in 75% cases of small cell lung carcinoma (SCLC) and 49.2% cases of non-small cell lung carcinoma (NSCLC). Among NSCLC, adenocarcinoma showed 62.9% metastases followed by 36.8% squamous cell carcinomas and 20.0% large cell carcinomas. In this series, clinical staging was done and 11 patients (18.6%) were found in stage I, 21 patients (35.6%) in stage II, 23 patients (39.0%) in stage III and 04 patients (6.8 %) in stage IV. Skeletal scintigraphy detected metastatic lesions in six of 11 cases (54.5 %) in clinical stage I, five of 21 cases (23.8 %) in clinical stage II, 16 of 23 cases (69.6 %) in clinical stage III and in all patients (100%) with clinical stages IV showing higher rate of bone metastases with advanced clinical stages.**

Conclusion: **In this study, skeletal scintigraphy changed clinical staging of 27 patients. Early diagnosis of lung carcinoma, followed by bone scanning without delay helps to diagnose skeletal metastases, the presence of which is a major determinant in subsequent pathological staging and treatment planning.**

INTRODUCTION

Lung carcinoma is the most common cancer worldwide (1). It is the most common cause of cancer related mortality for both men and women, causing approximately 1.2 million deaths per year (2). It is generally believed that the high mortality rate of lung cancer cases may be a result of the aggressiveness, invasiveness and metastatic potential of the disease and the fact that it is not easily detectable until it reaches

the advanced stages (3). Lung cancer frequently has bone metastasis at presentation or during follow-up, adding to both morbidity and prognostic impact (4).

The most commonly used screening test for the assessment of bone metastases is 99mTc methylene diphosphonate (MDP) bone scintigraphy which is a sensitive nuclear medicine imaging procedure for identifying osseous metastases regardless of symptoms. This method depends upon the relatively high uptake of radioisotope in areas of bone with high mineral turnover and reflects the metabolic state of the bone. It provides total skeletal examination, has a relative low cost, and thus is often the initial imaging modality for detection of bone metastases (5). Staging is an integral part of the work up in any newly diagnosed case of cancer and its real impact is to assess for operability if the patient presents in the early stages. This may ultimately lead to more appropriate treatment strategies for individuals diagnosed with lung cancer (6). Because the choice of treatment strategy is influenced by the presence or absence of bone metastases, the correct interpretation of bone scan is important. The goals of imaging are to identify sites of metastases and to evaluate them for the presence of, or potential for, complications such as pathological fractures and spinal cord compression.

Lung cancers are classified according to histological types, as Small cell lung cancer (SCLC) and Non-small cell lung cancer (NSCLC). The histopathology or cell differentiation type of lung cancer could influence the frequency of skeletal involvement and it is important because it provides a basis for epidemiology, prognosis and therapeutic approach. Molecular and cellular biological characteristics of the tumor cells and the tissues to which they metastasize are of paramount importance and influence the pattern of metastatic spread (7).

The present study was performed to see the role of baseline bone scintigraphy in the newly diagnosed lung carcinoma patients and also to see the number, pattern and sites of involvement of bone as well as to evaluate the skeletal metastases according to the different histological types of lung carcinoma.

PATIENTS AND METHODS

This observational study was carried out at the Institute of Nuclear Medicine &Allied Sciences (INMAS), M A G Osmani Medical College Hospital Campus, Sylhet during the period of July 2014 to June 2015. A total of 59 lung carcinoma patients who attended the scintigraphy division of INMAS, Sylhet within three months of their histopathological diagnosis were included in this study. Clinical staging was done from a clinical evaluation (history and physical examination) and also form available investigation reports. Skeletal scintigraphy was performed by dual-head gamma camera using low-energy all purpose collimator, 2-3 hours after IV administration of 20-30 mCi of 99mTc MDP. Scanning was accomplished by obtaining both anterior and posterior views. Interpretation was done by recording the distribution of radiotracer within the skeleton along with correlation of history, physical examination, FNAC or biopsy reports and other relevant investigation findings.

RESULTS

Bone scintigraphy was done in 59 lung carcinoma patients within three months of their histopathological diagnosis. The age range of the patients was from 37 to 85 years with a mean (± SD) of 59.10 ± 10.43 years. Out of 59 patients, 43 (72.9%) were male and 16 (27.1%) were female. Incidence of lung carcinoma was highest in the age group of 55-64 years, (45.7%), followed by 45-54 years, (27.1%) and 65-74 years (11.9%). Incidence was lowest in patients below 45 years and above 75 years (Figure 1).

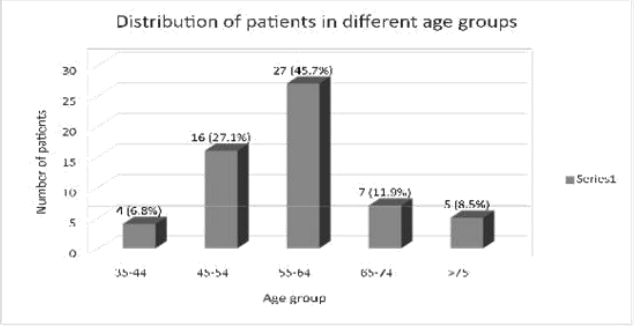

Figure 1. Distribution of patients according to age groups.

Out of 59 breast cancer patients, 64.4% patients had positive bone scans and 35.6% patients had negative bone scans. Among positive scan findings, 52.5% patients showed metastatic bone lesions and 11.9% patients showed non-metastatic bone lesions (Table 1).

Table 1: Distribution of study population according to bone scan findings (n=59).

Bone scan findings		Number (%)
Negative bone scan		21 (35.6%)
Positive bone scan	Metastatic bone lesions	31 (52.5%)
	Non-metastatic bone lesions	07 (11.9%)

Overall rate of metastases detected was 52.54%, where multiple lesions were seen in 87.1% cases and solitary lesion was seen in 12.9% cases.

A total of 82 lesions were reported as metastatic and among them 68 (82.9%) lesions were distributed in axial skeleton and 14 (17.1%) lesions in appendicular skeleton. Spine was the most frequent site of metastatic involvement in the present study which was37.8% followed by ribs 28.0%, sternum 9.7% and pelvic bones 7.3% (Table 2).

Table 2. Distribution of metastatic lesions according to anatomical sites of skeleton (n=82)

Site	Spine	Rib	Sternum	Pelvis	Skull & Facial bones	Joint	Extremity
Number of lesions (%)	31 (37.8%)	23 (28.0%)	08 (9.8%)	06 (7.3%)	06 (7.3%)	04 (4.9%)	04 (4.9%)

Thoracic spine was found to be involved more (58.1%) followed by cervical, lumbar and sacrum (Table 3).

Table 3. Distribution of number of lesions according to spinal distribution of lesions (n=31)

Spinal region	Number of lesions (%)
Cervical	5 ((16.1)
Thoracic	18 (58.1)
Lumbar	5 (16.1)
Sacrum	3 (9.7)

Regarding patterns of metastatic positive bone scans, 23 patients (74.1%) showed hot lesions, two patients (6.4%) showed cold lesions, four patients (12.9%) showed superscan and two patients (6.4%) showed pattern of hypertrophic osteoarthropathy (Table 4).

Table 4. Distribution of study subjects according to patterns of metastatic bone lesions (n=31)

Patterns of metastases	Number of patients (%)
Hot spot	23 (74.1)
Cold lesion	2 (6.5)
Superscan	4(12.9)

Among the study subjects, eight patients had small cell lung carcinoma and 51 had non-small cell carcinoma. Among 51 NSCLC, 27 had adenocarcinoma, 19 had squamous cell carcinoma and 5 had large cell carcinoma. Skeletal metastases were more common in small cell lung carcinoma, where six out of eight cases showed metastases (75%). On the other hand, 25 out of 51 cases of non-small cell carcinoma had skeletal metastases (49.01%) and among them rate of skeletal metastases was highest (62.9%) in adenocarcinoma (17 out of 27), followed by 36.8% in squamous cell carcinoma (7 out of 19) and 20% in large cell carcinoma (01 out of 05) (Table 5).

Table 5. Distribution of study population according to histological types of lung carcinoma and their metastases (n=59)

Histological types of lung carcinoma		Number of skeletal metastases (%)
Small cell lung carcinoma (n=8)		6(75)
Non small cell lung carcinoma (n=51)	Adenocarcinoma (n=27)	17(62.9)
	Squamous cell carcinoma (n=19)	7(36.8)
	Large cell carcinoma (n=5)	1(20.0)

In this series, clinical staging was done and 11 patients (18.6%) were in stage I disease , 21 patients (35.6%) in stage II disease, 23 patients (39.0%) in stage III disease and four patients (6.8 %) in stage IV disease. Skeletal scintigraphy detected metastatic lesions in six of 11 cases (54.5 %) in clinical stage I, five of 21 cases (23.8 %) in clinical stage II, 16 of 23 cases (69.6 %) in

clinical stage III and in all patients (100%) with clinical stages IV showing higher involvement of bone metastases with advanced clinical stages (Table 6).

Table 6. Distribution of study population according to rate of bone metastases in relation to clinical stages (n=59)

Clinical Stages	Status of Skeletal Metastases		Total
	Positive No (%)	Negative No(%)	
Stage - I	6(54.5)	5(45.5)	11
Stage - II	5(23.8)	16(76.2)	21
Stage - III	16(69.6)	7(30.4)	23
Stage - IV	4(100.0)	0	4
Total	**31**	**28**	**59**

DISCUSSION

In this study, mean (± SD) age of lung carcinoma patients was 59.10 (±10.43) years, ranging from 37 to 85 years. The occurrence of lung carcinoma was highest in the age group of 55-64 years. This finding was consistent with Akhtar et al. where highest occurrence (> 85%) was at and above 50 years of age, and Harald et al. where the mean age of the patients at the time of the diagnosis of osseous metastasis of lung carcinoma was 64 years (8, 9).

In the current study, 72.9% of the study subjects were male and 27.1% were female which is similar to Harald et al. where among 338 patients, 232 (69%) were male and 106 (31%) were female (11). It is also similar to Begum et al. where among 123 patients, 104 (84.6%) were male and 19 (15.4%) were female (10).

In the present study, overall rate of metastases detection was 52.54% where multiple lesions were seen in 87.1% of cases and solitary lesion was seen in 12.9% of cases. Similar result was reported by others - rate of metastases was 56% reported by Wang and Zhan, 62.5% reported by Kakhi et al. and 30-65% by Coleman (7, 11, 12). Begum et al. showed bone metastases in 80.5% cases of lung cancer, multiple metastases in 59.6% and solitary lesion in 18.2% cases (10). This difference might be due to inclusion of patients in advanced stages in their study.

In this study, 82.9% metastatic lesions were distributed in axial skeleton and 17.1% were distributed in appendicular skeleton. Wang and Zhan also reported higher incidence of metastases in axial skeleton (49.6%) than appendicular skeleton (36%) (11). The preference of involvement of axial skeleton can be explained by the presence of red bone marrow in this site. In case of lung cancer metastasis may occur easily to an axial bone through the vertebral vein system at an early stage and then to an appendicular bone in more advanced stages of the disease (13).

Spine was the most frequent site of metastatic involvement in the present study which was found in 37.8% cases followed by ribs (28.0%), sternum (9.7%) and pelvic bones (7.3%). These findings slightly differ from Begum et al. (12) who showed the involvement of bone metastases from lung cancer to be highest in ribs (75%) followed by spine (54%) and pelvis (23%). Distribution of bone metastases from lung cancer was reported to be more frequent in ribs followed by spines and pelvis by several other authors (4, 11, 12).

In this study, thoracic spine was the most involved site 18/31 (58.1%) among the spinal distribution of the lesions followed by cervical spine (16.1%) and lumbar spine (16.1%). This finding is nearly consistent with the previous observations, where 70% of symptomatic lesions were located in thoracic vertebra, 20% in lumbar vertebra and only 10% in the cervical spine (14, 15).

In this study, adenocarcinoma was most common histological type, which was consistent with the findings of Harald et al. (9) where adenocarcinoma was the most frequently diagnosed histological subtype. In another study, adenocarcinoma surpassed squamous cell carcinoma as the most common histological type of lung carcinoma (16). Merrick (17) reported that the prevalence of bone metastases was 63% for adenocarcinoma, 57% for large cell carcinoma and 50% for squamous cell carcinoma which is similar to the present study where adenocarcinoma showed more skeletal metastases (62.9%) followed by squamous cell carcinoma (36.8%) and large cell carcinoma (20%). These

findings are dissimilar to Salvatierra et al. (18) who reported higher frequency of bone metastases in large cell carcinoma (20%) and adenocarcinoma (16%) compared to squamous cell carcinoma (10%). The differences of the findings may be due to different study population, different geographical areas with environmental variation and different presenting stages of the disease.

Sugiura et al. (13) reported the incidence of bone metastases from NSCLC to be around 15-40%. Morgan et al. (19) and Lardinois et al. (20) found bone metastases at initial presentation in 60% cases with NSCLC. These findings are nearly similar to the present study where incidence of bone metastases from NSCLC was about 49.2%and from SCLC was about 75%.

In this series, clinical staging was done and 11 patients (18.6%) were in stage I disease , 21 patients (35.6%) in stage II disease, 23 patients (39.0%) in stage III disease and four patients (6.8 %) in stage IV disease. Skeletal scintigraphy detected metastatic lesions in six out of 11 cases (54.5 %) in clinical stage I, five out of 21 cases (23.8 %) in clinical stage II, 16 out of 23 cases (69.6 %) in clinical stage III and in all patients (100%) with clinical stages IV showing higher involvement of bone metastases with advanced clinical stages. Thus bone scintigraphy changed staging of 27 patients- 6 from stage I to stage IV, 11 from stage II to stage IV and 16 from stage III to stage IV and thereby helped to modify their treatment plan. Sun et al. (21) showed the incidence of bone metastases at initial diagnosis was 48% in stage IV NSCLC. Kosteva and Langer (22) revealed an incidence of skeletal metastases is 24% with the majority of those (66%) detected at the time of initial staging.

CONCLUSION

From the findings of this study, it can be concluded that bone scintigraphy has important role at initial presentation of lung carcinoma patients by detecting bone metastases and also demonstrating number, sites of bony involvement as well as specific pattern of distribution of metastatic lesions. Early diagnosis of lung carcinoma, followed by bone scanning without delay helps to diagnose skeletal metastases, the presence of which is a major determinant in subsequent pathological staging and treatment planning. The routine bone scan may help to prevent futile thoracotomies with apparently operable lung cancer. Baseline bone scan after initial diagnosis of lung carcinoma also provides prognostic value in subsequent follow up of the patient.

REFERENCES

1. Jemal A, Bray F and Center MM. Global cancer statistics. CA Cancer J Clin 2011;61:69-90.
2. Parkin DM, Bray F, Ferlay J and Pisani P. Global cancer statistics 2002. CA Cancer J Clin 2005;55:74-108.
3. Bulk E, Sargin B and Krug U.S100A2 induces metastasis in non-small cell lung cancer. Clin Cancer Res 2009;1:22-29.
4. Memon AG, Jaleel A and Aftab J. Pattern of prostatic carcinoma metastasis in bones detected by bone scan using Technetium 99m Methyle Diphosphonate (Tc-99m-MDP) imaging technique. PAK J Med Sci 2006;22:180-183.
5. Hsiang-Hsuan MY, Ya-Yu T, and Sarah EH. Overview of Diagnosis and Management of Metastatic Disease to Bone. Cancer Control 2012;19:84-91.
6. Hetzel M, Hetzel J and Arslandemir C. Reliability of symptoms to determine use of bone scans to identify bone metastases in lung cancer: prospective study. Brit Med J 2004;328:1051-1052.
7. Coleman RE. Clinical features of metastatic bone disease and risk of skeletal morbidity.Clin Cancer Res 2006;12:6243-6249.
8. Akhtar PS, Masud ZM, Alam T and Begum M. Profile of Lung Cancer: A One-Year Report. J Med 2011;12:488.
9. Harald R, Marc B, Thomas B, ThomasW, Vasileios A, Stefan R et al. The stability of osseous metastases of the spine in lung cancer – a retrospective analysis of 338 cases. Radiation Oncology 2013;8:200.
10. Begum SMF, Jabin Z,Perveen R, Sultana N, Banu LS et al . Tc99m-MDP Bone Scan in Lung Cancer: Predilection Sites for Metastasis. Bang J Nucl Med 2014;17:120-124.
11. Wang CY and Zhan XY. 99m Tc MDP whole body bone imaging in evaluation of the characteristics of bone metastases of primary lung cancer.Zhong Zhong Liu Zai 2010;32:382-386.
12. Kakhi VRI, Anvari K, Sadeghi R, Mahmoudian AS and Torabian-Kakhi M. Pattern and distribution of bone metastases in common malignant tumors. Nucl Med Rev Cent East Eur 2013;16:66-69.
13. Sugiura H, Yamada K, Sugiura T, Hida T and Mitsudomi T. Predictors of survival in patients with bone metastasis of lung cancer. Clin Orthop Relat Res 2008;466:729-736.
14. Kosteva J and Langer C. Incidence and distribution of skeletal metastases in the era of PET. Lung Cancer 2004;46:45-86.
15. Tsuya A, Kurata T, Tamura K and Fukuoka M. Skeletal metastases in non-small cell lung cancer: a retrospective study. Lung Cancer 2007;57:229-232.
16. Vaporciyan AA, Nesbitt JC, Lee J, Stevens C, Komaki R and Roth JA. Cancer of the lung. Cancer Medicine. 5thed. Lewiston NY: Decker, 2000.
17. Merick MV. Bone scintigraphy in lung cancer: a reappraisal. Br J Radiol1986;59:1185-1194.
18. Salvatierra A, Baamonde C and Llamas JM. Extra thoracic staging of bronchogenic carcinoma. Chest 1990;97:1052-1058.
19. Morgan JWM, AdcockKM and Donohue RE. Distribution of skeletal metastases in prostate and lung cancer. Urology 1990;36:31-34.
20. Lardinois D, Weder W and Hany TF. Staging of non-small-cell lung cancer with integrated positron-emission tomography and computed tomography. N Engl J Med 2003;348:2500-2507.
21. Sun JM, Ahn JS and Lee S. 'Predictors of skeletal-related events in non-small cell lung cancer patients with bone metastases', Lung Cancer 2011; 71: 89-93.
22. Kosteva Jand Langer C. 'Incidence and distribution of skeletal metastases in the era of PET', Lung Cancer 2004; 46:45-86.