Scholars Journal of Applied Medical Sciences
Abbreviated Key Title: Sch J App Med Sci
ISSN 2347-954X (Print) | ISSN 2320-6691 (Online)
Journal homepage: https://saspublishers.com/journal/sjams/home

OPEN ACCESS

Pathology

Histopathological Study of Metastatic Bone Tumours

Dr. Annapoorani Varadarajan[1], Dr. Dhaval Jetly[2*]

[1]Resident, Pathology Department, Gujarat Cancer and Research Institute (GCRI), Ahmedabad, India
[2]Associate professor and head of Pathology Department, Gujarat Cancer and Research Institute (GCRI), Ahmedabad, India

***Corresponding author:** Dr. Dhaval Jetly
| **Received:** 15.01.2019 | **Accepted:** 25.01.2019 | **Published:** 30.01.2019
DOI: 10.36347/sjams.2019.v07i01.072

Abstract **Original Research Article**

Bone metastasis is frequently the first sign of malignancy when the primary has not been discovered. Thus, histopathological examination of the affected bone helps in its characterization and localization of primary site. A study of 110 patients with metastatic bone tumors was done. Histopathological diagnosis of biopsy tissues was obtained on formalin fixed, paraffin embedded tissue and stained with hematoxylin and eosin. Decalcification was done with nitric acid. The mean age of patients was 47.5 years with 63 males and 47 females. Bone pain and haematological abnormalities (thrombocytopenia, bicytopenia and pancytopenia) were the most common presenting symptoms. 84 patients (76.4%) were found to have multiple metastatic lesions in their skeleton. The most common location of metastasis in our study is spine, followed by pelvis. Sixty eight patients had their metastatic disease diagnosed in Core biopsy specimens while Trephine biopsy was used in 42 patients. Metastatic adenocarcinoma was the most common tumour diagnosed, making up 69.1% (76 patients) of the total. The primary site varied between the genders. Lung was the most common primary in males followed by Prostate, while in females, it was Breast followed by Lung.

Keywords: Metastatic bone tumours, unknown primary, histopathology, metastasis, most common primary, India.

INTRODUCTION

Metastatic Bone tumors are the commonest malignancies to affect the skeletal system[1]. Patients of all age groups can suffer from skeletal metastases; however, they predominantly occur in the elderly age group[2]. A vast majority of patients present with bone pain at the affected site[3]. The metastatic disease weakens the bone as it progresses, which may result in pathological fracture[4]. Lesions occurring in the vertebrae may lead to spinal cord compression resulting in paraplegia and loss of bowel and bladder functions[5]. Certain cancers such as lung, breast, kidney, thyroid and prostate are known to produce skeletal metastases[1,6]. On the other hand, a vast majority of tumours such as ovary and colon rarely spread to bone. In the case of Prostate carcinoma, the skeletal spread is known to occur via valveless venous communication between Prostate and vertebral column through Batson's plexus[7]. Flat bones such as pelvis and skull, along with long bones such as femur are the favoured sites of skeletal metastases[8]. This is probably due to the presence of red bone marrow with abundant vascularity in these bones as they are actively involved in haematopoiesis. Plain radiograph is the initial diagnostic intervention used in most patients. Radiographically, the metastatic lesions may be classified as lytic, blastic or mixed depending on whether lesions cause either bone destruction, bone formation or both respectively[9]. Mixed presentation is the most common radiographic pattern in skeletal metastasis[2]. However, renal and thyroid carcinomas are known to produce lytic metastasis while prostate cancers classically result in blastic metastasis[10]. Establishing a diagnosis of metastatic bone lesion is extremely important as further diagnostic workup and treatment plan will be based on it[11]. Depending on the primary process characteristics, therapy for bone metastases includes chemotherapy, radiotherapy, immunotherapy, hormonal therapy, bisphosphonate therapy, and various operative procedures. Hence it is essential to identify the primary site. The two common differentials for skeletal metastases in elderly age group are multiple myeloma and non-Hodgkin's lymphoma. Both of them can present with bone pain and lytic lesions similar to metastases. If a metastatic lesion is suspected, the pathologist must try to characterize the lesion in the basic H & E preparation. In those patients with history of established primary neoplasm, the diagnosis is fairly straight forward. However, a substantial number of patients do present with unknown primary lesion[12]. These patients usually present a diagnostic challenge and the pathologist must be able to

guide the clinician to look for possible sources of primary neoplasm. Our aim was to Study the Histopathological Features and Demographic Characteristics of patients presenting with Metastatic Bone Tumour, to Correlate Histopathological findings with Clinical and Radiographic features of the Metastatic Bone Tumors and to locate the primary site with histopthological analysis without the use of immunohistochemistry.

MATERIALS AND METHODS

The study of 110 cases, was conducted at the Department of Pathology, The Gujarat cancer and research institute (GCRI) between September 2015 and October 2017. The study was approved by the Ethical committee. All patients of all age groups with histopathologically confirmed skeletal metastases with both unknown and known primary neoplasm were included in the study. Patients with primary bone tumors including Ewing's sarcoma and patients with multiple myeloma or lymphoma were excluded. Biopsies were fixed in 10% neutral formal saline, decalcified in 5% nitric acid, embedded in paraffin 4 micrometer thick sections were cut using microtome and fixed in egg albumin coated slide kept at 60^{o}c in hot air oven for tissue fixation stained with hematoxylin and eosin using autostainer *VARISTAIN*^{TM}by *Thermoscientific*. After light microscopic examination of the routinely stained section, a histopathological diagnosis is formulated.

RESULTS AND DISCUSSION

Biopsy specimens (both trephine and core biopsies) of 110 patients with metastatic bone tumors were analyzed. The mean age of patients was 47.5 years. The mean age of our patients is less compared to other studies (Table 1). The age range in our study is 2 to 80 years. Majority of patients in our study fell in the 40 to 60 years age group (Figure 1).

Table-1: Comparison of different studies with present study with respect to mean age and number of patients

Authors	No. of patients	Mean Age
Present study	110	47.5 years
Tomas *et al*. [13]	78	57 years
Xu *et al*. [14]	390	55.7 years
Ugras *et al*. [15]	33	64 years
Takagi *et al*. [16]	286	65.2 years

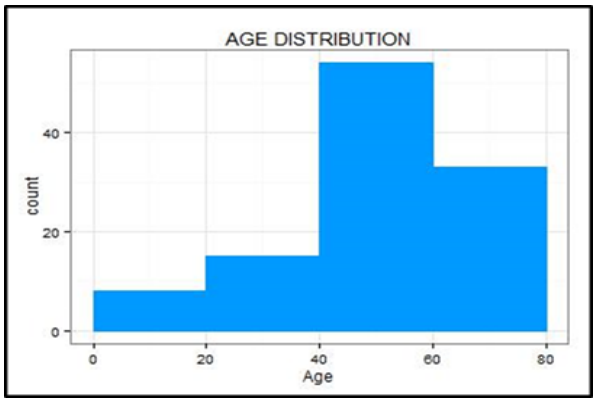

Fig-1: Bar diagram depicting the age distribution of patients presenting with bone metastases

In total, there were 63 males and 47 females. The male: female ratio was 1.34. As in other studies, metastatic bone disease is more common in males than females (Table 2).

Table-2: **Comparison of different studies with present study with respect to sex distribution**

Authors	Sex distribution(male: female)
Present study	63: 47
Tomas *et al.* [13]	47: 31
Xu *et al*. [14]	265:125
Ugras *et al*. [15]	26: 7
Takagi *et al*. [16]	174: 112

The presenting complaints are depicted in the table below (Table 3):

Table-3: Summary of presenting complaints in the present study

Presenting complaint	Number of patients (n= 110)
Asymptomatic	10
Bone pain	67
Pathological fracture	3
Swelling	3
Anemia	1
Thrombocytopenia	12
Bicytopenia	8
Pancytopenia	6

On evaluation, 84 patients (76.4%) were found to have multiple metastatic lesions in their skeleton. Majority of the lesions were either mixed (53 lesions) or lytic (42 lesions) on radiographs. 68 patients had their metastatic disease diagnosed in Core biopsy specimens while Trephine biopsy was used in 42 patients. Spine (77 lesions) remained the most favoured site of metastasis, followed by pelvis (41 lesions) and femur (13 lesions) .Of the blood parameters assessed, Serum Alkaline Phosphatase (ALP) was most useful as it was elevated in 61% of patients. Forty two patients (38.1%) had any one of the tumour markers elevated. The histopathological diagnosis based on routine H& E staining is elaborated in the table below (Table 4). Metastatic adenocarcinoma was the most common tumour diagnosed, making up 69.1% (76 patients) of the total.

Table-4: Summary of histopathological diagnosis in the present study

Diagnosis	Number of patients (n= 110)
Metastatic Squamous cell carcinoma , Lung	1
Metastatic Carcinoma	3
Metastatic adenocarcinoma , Stomach	2
Metastatic adenocarcinoma, Breast Ductal origin	20
Metastatic Adenocarcinoma , Breast – Lobular origin	1
Metastatic Adenocarcinoma, Prostate	8
Metastatic Adenocarcinoma , Gall Bladder	1
Metastatic Adenocarcinoma, Lung	10
Metastatic Adenocarcinoma	35
Malignant round cell tumour	5
Metastatic follicular carcinoma of thyroid	3
Metastatic medullary carcinoma thyroid	1
Metastatic papillary carcinoma thyroid	1
Metastatic poorly differentiated carcinoma	9
Metastatic renal cell carcinoma	3
Metastatic small cell carcinoma ,Lung	3
Metastatic neuroblastoma	4

Five patients had known primary from Thyroid with Three patients being known case of Follicular carcinoma of Thyroid, one patient who was a known case of medullary carcinoma of thyroid and one had papillary carcinoma of thyroid (Figure 1). Three patients had a known primary in Kidney which was of Clear cell variant. Three patients were known case of Small cell carcinoma of Lung (Figure 2). Four paediatric patients had neuroblastoma with bone metastases.

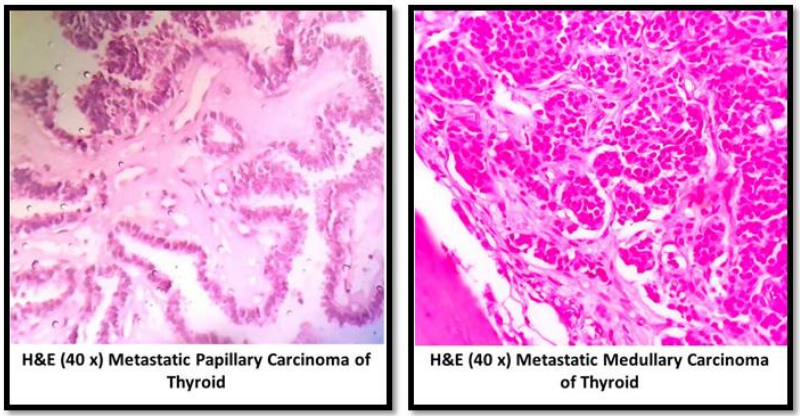

Fig-1: H & E slides under 40 x showing Metastatatic Papillary Carcinoma of Thyroid & Metatstatic Medullary carcinoma of Thyroid

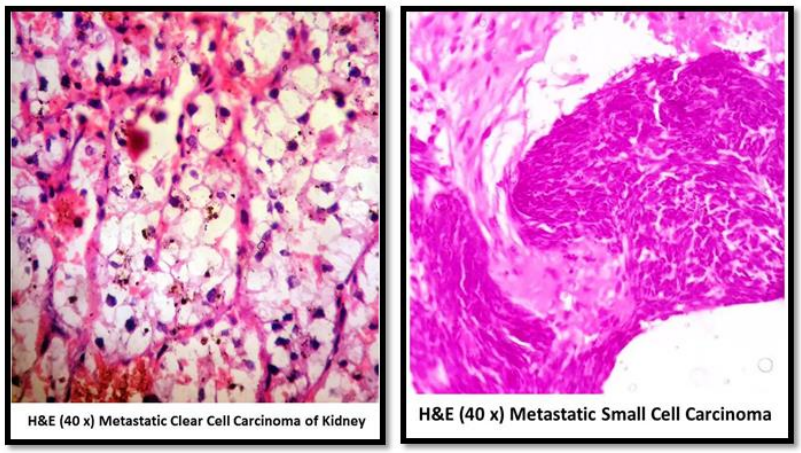

Fig-2: H & E slides under 40 x showing Metastatatic Clear Cell Carcinoma of Kidney & Metatstatic Small Cell Carcinoma

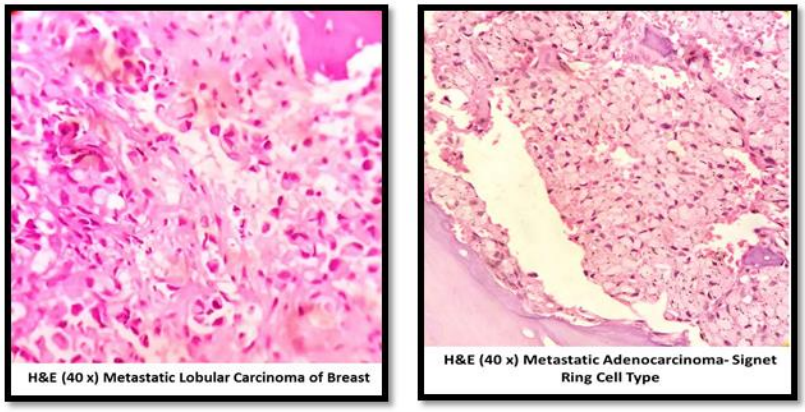

Fig-3: H & E slides under 40 x showing Metastatatic Lobular Carcinoma of Breast & Metatstatic Adenocarcinoma – Signet Ring Cell type

One patient was a known case of Squamous cell carcinoma Lung. Among 78 patients with Metastatic Adenocarcinoma 22 patients had a primary from breast of Ductal origin, one patient had metastases from lobular carcinoma of breast, 10 patients had a known primary in Lung, two patients had primary in Stomach and one patient had primary in gall bladder (Figure 3).

In our study, Breast was the most common source of primary, followed by Lung and Prostate which was comparable with literature data (Table 4). The primary site varied between the genders. Lung was the most common primary in males followed by Prostate, while in females, it was Breast followed by Lung. There was variation in most common site with respect to age group as well. Neuroblastoma is the most common primary in less than 20 years age group, Ca

Breast was the most common between 20 to 60 years and Ca Lung was the commonest beyond 60 years of age. Primary was identified in 58 patients with histopathology alone out of which 50 patients had a known primary in which histopatholoigical examination helped in confirming the presence of metastates. Among remaining 8 patients, two patients had signet ring cell type adenocarcinoma with mass in stomach, hence possibility of stomach primary was suggested, four patients had osteoblastic metastatses with elevated PSA levels and mass in prostate, two patients had mass in lung.

Table-4: **Comparision of different studies with present study with respect to common primary site**

Authors	Most common primary	2nd most common primary
Present study	Breast	Lung
Tomas *et al*. [13]	Breast	Lung
Xu *et al*. [14]	Lung	Prostate
Ugras *et al*. [15]	Lung	Kidney
Takagi *et al*. [16]	Lung	Prostate

CONCLUSION

The aim of the study was to compare some basic data on metastatic bone tumors with literature reports. The prevalence, age and sex distribution, and most common localizations of metastatic bone tumors were determined. Our results showed that Indian patients present at a relatively younger age with bone metastases compared to other published literature. This is an important finding as clinicians should consider metastases as a possible differential even among young individuals in India. Our study is limited only to histopathological analysis, which without immunohistochemistry, failed in identifying primary in 52 cases. However, we could confirm the presence of bone metastases and suggest possible primary sites. If applied, immunohistochemistry would have helped in identifying primary in these cases. Also many of these cases lacked adequate clinical information which could have helped in arriving at a diagnosis. Hence, close cooperation and MDT (Multi- Disciplinary Team) approach are required for appropriate diagnosis of metastatic bone tumours.

To conclude, histopathology of metastatic bone tumours is a useful tool in confirming diagnosis and guide the physician regarding possible sites of primary malignancy.

REFERENCES

1. Hage WD, Aboulafia AJ, Aboulafia DM. Incidence, location, and diagnostic evaluation of metastatic bone disease. Orthop Clin North Am. 2000;31(4):515–28.
2. Mangham DC, Tyrrell PNM, Cool WP. The surgical pathology of skeletal metastases. Diagn Histopathol. 2009;15(9):444–453.
3. Riccio AI, Wodajo FM, Malawer M. Metastatic carcinoma of the long bones. Am FAM Physician. 2007;76(10).
4. Coleman RE. Metastatic bone disease: clinical features, pathophysiology and treatment strategies. Cancer Treat Rev. 2001;27(3):165–176.
5. Berenson J, Rajdev L, Broder M. Pathophysiology of bone metastases. Cancer Biol Ther. 2006;5(9):1078–1081.
6. Li S, Peng Y, Weinhandl ED, Blaes AH, Cetin K, Chia VM, Stryker S, Pinzone JJ, Acquavella JF, Arneson TJ. Estimated number of prevalent cases of metastatic bone disease in the US adult population. Clinical epidemiology. 2012;4:87.
7. Harada M, Iida M, Yamaguchi M, Shida K. Analysis of Bone Metastasis of Prostatic Adenocarcinoma in 137 Autopsy Cases [Internet]. In: Prostate Cancer and Bone Metastasis. Springer, Boston, MA; 1992 [cited 2017 Dec 2]. page 173–82.Available from: https://link.springer.com/chapter/10.1007/978-1-4615-3398-6_18
8. Jacofsky DJ, Frassica DA, Frassica FJ. Metastatic disease to bone. Hosp Physician. 2004;39:21–28.
9. Ibrahim T, Flamini E, Fabbri L, Serra P, Mercatali L, Ricci R, Sacanna E, Falasconi MC, Casadei R, Galassi R, Giannini M. Multidisciplinary approach to the treatment of bone metastases: Osteo-Oncology Center, a new organizational model. Tumori Journal. 2009 May;95(3):291-7.
10. Rosenthal DI. Radiologic diagnosis of bone metastases. Cancer 1997;80(S8):1595–1607.
11. Galasko CSB. Diagnosis of skeletal metastases and assessment of response to treatment. In: Metastatic Bone Disease. Springer; 1994. page 93–108.
12. Holmes FF, Fouts TL. Metastatic cancer of unknown primary site. Cancer 1970;26(4):816–20.
13. Tomas D, Kruslin B, Matejcic A, Kejla Z, Belicza M. Metastatic bone tumors in biopsy specimens. Acta Clin Croat. 2003;42(1):35–40.
14. Xu DL, Zhang XT, Wang GH, Li FB, Hu JY. Clinical features of pathologically confirmed metastatic bone tumors–a report of 390 cases. Ai Zheng Aizheng Chin J Cancer. 2005;24(11):1404–1407.
15. Ugras N, Yalcinkaya U, Akesen B, Kanat O. Solitary bone metastases of unknown origin. Acta Orthop Belg. 2014;80(1):139–143.
16. Takagi T, Katagiri H, Kim Y, Suehara Y, Kubota D, Akaike K, Ishii M, Mukaihara K, Okubo T, Murata H, Takahashi M. Skeletal metastasis of

unknown primary origin at the initial visit: a retrospective analysis of 286 cases. PloS one. 2015 Jun 26;10(6):e0129428.