ORIGINAL ARTICLE

SURVIVAL IMPACT OF SKELETAL METASTASIS ON BONE SCINTIGRAPHY IN PATIENTS WITH GERM CELL TUMOURS

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Abstract

Objective: Our aim was to determine the frequency of skeletal metastasis in germ cell tumours (GCT) at baseline and relapse on conventional technetium-99m methylene diphosphonate (Tc-99m MDP) whole body bone scan (bone scan) and to evaluate the effect of bone metastases on survival.

Materials and Methods: Electronic medical records of histologically proven GCT over 64 months were retrospectively analysed. Basic demographic and histologic information were correlated with the presence of osseous and visceral metastases. 5-year disease-free survival (DFS) and overall survival (OS) were calculated in presence, the absence of bone metastases at baseline and at relapse.

Results: A total of 130 gonadal and extragonadal GCT patients underwent Tc-99m MDP bone scans; four with insufficient data were excluded from the study. 47% were females and 53% were males with the age range of 1 month – 72 years. 105 (83%) were under 18 years of age. Osseous metastasis was detected in 12 (9.5%). Two (17%) had solitary and 10 (83%) had multifocal skeletal metastases. Clinically, 83% had localised bone pain. Osseous metastases were more frequently associated with mixed GCT and yolk sac tumour. 50% of mediastinal GCT developed bone metastases. 42% died within 4–18 months. There was a statistically significant impact of visceral metastases on DFS and OS. OS at 5 years in patients without bone metastases, with bone metastases at baseline and bone metastases at relapse, was 77%, 38% and 75%, respectively. 5-year DFS for the same cohort groups was 63%, 38% and 20%, respectively.

Conclusion: Osseous involvement was found in 9.5% of GCT patients undergoing diagnostic Tc-99m MDP bone scan. Baseline skeletal evaluation for metastases should be done, particularly in the case of bone pains or known systemic metastases. Although skeletal relapses are rare, they have a grim outcome.

Key words: Bone scintigraphy, germ cell tumours, skeletal metastases

Introduction

Germ cell tumours (GCTs) are one of the most common malignant tumours, comprising 1% of all the solid tumours in young male adults.[1] GCT usually metastasizes to retroperitoneal lymph nodes. Osseous metastases are a rare entity, particularly at primary diagnosis and its true incidence remains unknown. It is usually a late manifestation, with synchronous haematogenous spread to the lung, liver, and brain and the overall prognosis of bone involvement is as poor as hepatic or central nervous system (CNS) metastases.[2] Moreover, non-pulmonary metastases are considered poor prognosticators. For patients with metastatic GCT, prognostic factors at primary diagnosis are well recognised and the international germ cell cancer consensus cooperative group (IGCCCG) guidelines are followed to determine treatment regimens for chemotherapy. Bone metastases classify the patient into high-risk (HR) (non seminomatous) group or intermediate risk (IR) (seminomatous) group.[3]

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Conventional Technetium-99m methylene diphosphonate (Tc-99m MDP) whole body bone scan (bone scan), computerised tomography (CT), and magnetic resonance imaging (MRI) are various modalities for diagnosing bone metastases as indicated.[4] The incidence of osseous involvement, its responsiveness to chemotherapy and long-term prognosis remain poorly defined.[5]

Objective

The main objectives of this study were as follows:

1. To determine the frequency of skeletal metastases in patients with newly diagnosed GCT and/or relapsed after first-line chemotherapy.1.
2. To explore the characteristics, potential risk factors for skeletal metastases and overall and disease-free survival (DFS) after chemotherapy in patients with and without bone metastases.

Materials and Methods

Electronic medical records of 130 consecutive patients treated at our institution for histologically proven gonadal or extragonadal GCT between October 2010 and February 2016 were retrospectively analysed. All patients underwent Tc-99m MDP bone scan as part of staging workup, or when relapse was suspected following initial high-dose chemotherapy. Where suspicious, the osseous uptake on Tc-99m MDP bone scan was further correlated with additional radiological imaging.

The association of bone metastases was assessed with gender, age, histopathology, stage and risk stratification according to International Germ Cell Consensus Classification guidelines formulated in 1997,[3] tumour marker elevation including lactate dehydrogenase/LDH (Normal = 240–480 IU/L), alpha-fetoprotein/AFP (cutoff 10kU/L), and human chorionic gonadotropins/B-HCG (cutoff 2 U/L). Overall survival (OS), DFS and treatment response were evaluated in patients with bone metastases at baseline and relapse and compared to those without metastases and those with non-osseous, visceral metastases.

Imaging

Baseline Tc-99m MDP planar whole body bone scans were acquired 2.5 h after the intravenous administration of Tc-99m MDP. Since 2013, a SPECT/CT scan was also acquired to better specify the cause of uptake if needed. The scans were reported by experienced nuclear physicians. Bone involvement was diagnosed by radioisotope uptake. Foci of uptake were confirmed by one or more radiological imaging modality including plain radiograph, CT scan, MRI scan or 18F-FDG PET-CT as indicated clinically.

HR and IR GCT were further evaluated for concurrent systemic metastasis. Chemotherapy was administered according to UKCCSG GCIII (Extracranial GCT guidelines January 2011-Phase III Trial) protocol.

The Institutional Review Board approved the study.

Statistical analysis

All the relevant statistical data were entered into SPSS software version. 20 (IBM, USA). Continuous variables were presented as mean or median with ranges. Categorical variables were presented as absolute and relevant frequencies. The correlative analysis was performed using the Chi-square or Log-rank test (categorical variables). $P < 0.05$ was considered statistically significant. Survival rates were analysed using the method of Kaplan–Meier (Kaplan and Meier 1958).

Results

A total of 130 GCT patients underwent Tc-99m MDP bone scan between October 2010 and February 2016. Four were excluded due to incomplete information. Of the remaining 126, 59 (47%) were females and 67 (53%) were males. Mean age was 18 years (range: 1 month – 72 years). 105 (83%) were of paediatric age group (under 18 years) at the time of initial diagnosis. Patient characteristics are summarised in Table 1.

Characteristics of patients with bone metastases

Overall, 9.5% (12/126) had bone metastases either at primary diagnosis or relapse. While classifying by the IGCCC guidelines, four (33%) had IR and eight (67%) had HR GCT.

Of the 12 with bone metastases; five (42%) had mixed GCT, three (25%) yolk sac tumour, two (17%) immature

Table 1: Characteristics of GCT patients with or without bone metastases

Variable	Total patients *n*=126 (%)	Patients with bone metastases *n*=12 (%)	IR/HR patients without bone metastases *n*=80 (%)
Age range (years)	1 month–72 years	1–29	1 month–54 years
Male/Female ratio	1:1	2:1	1:1
Site of primary			
Gonadal (ovary/testes)	73 (58)	5 (42)	55 (68.8)
Mediastinal	6 (5)	3 (25)	3 (3.7)
Sacrococcygeal	12 (10)	2 (17)	7 (8.8)
Abdominopelvic	22 (17)	2 (17)	15 (18.7)
Others	13 (10)	0 (0)	0 (0)
Histology			
Yolk sac tumour	41 (33)	3 (25)	33 (41)
Mixed GCT	34 (27)	5 (42)	22 (27.7)
Seminoma/Germinoma	23 (18)	1 (8)	14 (17.5)
Malignant teratoma	23 (18)	2 (17)	8 (10%)
Non seminomatous GCT	3 (2.4)	1 (8)	1 (1.3)
Embryonal carcinoma	2 (1.6)	0 (0.0)	2 (2.5)
Tumour markers elevation			
AFP	74 (59)	8 (67)	56 (70)
B-HCG	7 (5.5)	0 (0)	7 (8.7)
LDH	27 (21.4)	6 (50)	18 (22.5)
Non-osseous metastatic sites			
Nodal	55 (44)	8 (67)	47 (59)
Lung	26 (21)	4 (33)	22 (27.5)
Liver	13 (10.2)	1 (8.3)	12 (15)
CNS	1 (0.8)	0 (0.0)	1 (1.3)
IGCCC at initial diagnosis			
Low	34 (27)	0 (0.0)	0 (0.0)
Intermediate	52 (41)	4 (33)	48 (60)
High	40 (32)	8 (67)	32 (40)
Response to first-line chemotherapy			
CR/NED*	55 (43)	0 (0.0)	21 (26)
CR/SD** with no relapse	36 (29)	3 (25)	33 (40)
CR/SD after treating relapse	14 (11)	4 (33)	10 (12.5)
PD***	21 (17)	5 (42)	16 (21)
Disease free interval (months)			
Median (range)	21 (3–62)	22 (4–52)	23 (3–60+)

*Complete response/no evidence of disease, **Complete response/radiologically stable disease, ***Progressive disease. GCT: Germ cell tumours, IR/HR: Intermediate risk/High risk, AFP: Alpha-fetoprotein, B-HCG: β-Human chorionic gonadotropins, LDH: Lactate dehydrogenase, CNS: Central nervous system, IGCCC: International germ cell cancer consensus cooperative

teratoma and one each of seminoma (8%) and non-seminomatous GCT (8%). Tumour markers elevation of either LDH or AFP (α−fetoprotein) was seen in 92%. All the 12 were non β-HCG secreting tumours.

Bone metastases were found at diagnosis in seven and five at relapse. A most frequent site of bone metastases was thoracolumbar spine (58%) with cord compression in 57% of them. Other sites included pelvis in 50%, ribs 42%

and long bones in 42%. Bone metastases were solitary in 17% and multifocal in 83%. Clinically, 83% of patients were symptomatic with localised bone pains.

In the seven with osseous metastases at baseline, additional sites of metastases included; lymph nodes (n = 4), lung (n = 2) and liver (n = 1). In five with bone metastases at relapse, concomitant metastatic sites were lymph node (n = 4), lung (n = 4) and liver (n = 1).

Table 2 outlines the risk category, treatment and outcome of patients with bone metastases.

Tc-99m MDP bone scan findings were confirmed by CT scan in eight, MRI in six and radiograph in two. An MRI scan was used for assessing cord compression in four.

Treatment and outcome of patients with bone metastases

Nearly 42% of patients with bone metastases received only first-line chemotherapy, while 33% with progressive disease and relapse received additional second-line and 25% third-line chemotherapies. Table 2 outlines the chemotherapy regimens used and the outcome of patients with bone metastases.

There was no significant correlation between the presence of bone metastases at diagnosis and the subsequent lines of chemotherapy received. Response assessment after chemotherapy showed stable disease in 33%, partial response with the primary irresectable disease in 25% and progressive disease in 42%. One with partial response was lost to follow-up. A neurological compromise was seen in the form of cord compression in four. In these patients, palliative management was done with lumbar spine radiation therapy (XRT) in one and laminectomy in another.

Five had irresectable primary tumours; two mediastinal and three sacrococcygeal/pelvic. XRT was given to three primary tumour sites. Based on the last clinical follow-up, five died due to progressive disease (median survival – 9 months; range: 4–18 months); five had no evidence of disease after first-line chemotherapy, one required second-line chemotherapy due to disease relapse and one was lost to follow-up. Out of five who died, four had bone metastases at primary diagnosis with concurrent nodal and pulmonary metastases. One developed bone metastases at relapse but had no concurrent visceral metastases. One with bone metastases at relapse was lost to follow-up during third-line chemotherapy. 50% remained stable with a median follow-up duration of 29 months (Range: 17–52 months). Survival plots according to Kaplan–Meier are presented in Figures 1-5.

Table 2: Chemotherapy regimens, IGCCC-defined risk and outcome in GCT patient with bone metastases

Patient	Chemotherapyregimen	IGCCC-defined risk	Outcome
Bone metastases at baseline staging			
1	1,2*	High	Died due to disease
2	1, 2, 3	High	Died due to disease
3	1	High	Alive
4	1, 2	High	Died due to disease
5	1	Intermediate	Alive
6	1	High	Alive
7	1, 2	High	Died due to disease
Bone metastases at relapse			
1	1, 2, 3	High	Lost to follow-up
2	1	Intermediate	Alive
3	1,2	Intermediate	Alive
4	1,2,3	High	Died due to disease
5	1	Intermediate	Alive

*1. First-line chemotherapy: Four cycles of BEP (Bleomycin, Etoposide and Cisplatin) in adults and 4–6 cycles of JEB (Carboplatin, Etoposide and Bleomycin) in paediatric patients, 2: Second-line chemotherapy: VeIP (Vinblastine, Ifosfamide and Carboplatin), 3: Third-line chemotherapy: Gemcitabine and Oxaliplatin. IGCCC: International germ cell cancer consensus cooperative, GCT: Germ cell tumours

Characteristics of patients without bone metastases

Nearly 94% had no bone metastases at baseline. Out of these, 30% had low-risk (LR)/Stage I disease, 42% IR and 28% HR disease. Details of histological breakup and tumour marker status of the 80 with IR and HR without bone metastases are shown in Table 1.

Nearly 24% of patients had irresectable primary tumour site. Synchronous retroperitoneal/mediastinal nodal,

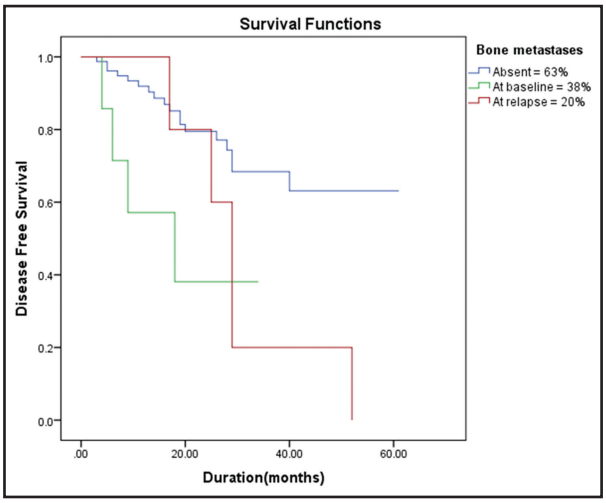

Figure 1: Kaplan–Meier curve displaying the 5-year disease-free survival in intermediate risk and high-risk germ cell tumours (No bone metastases, 63%; bone metastases at baseline, 38% and bone metastases at relapse, 20%). The log-rank test showed a statistically significant difference in percent survival of patients with and without bone metastases both at baseline or relapse

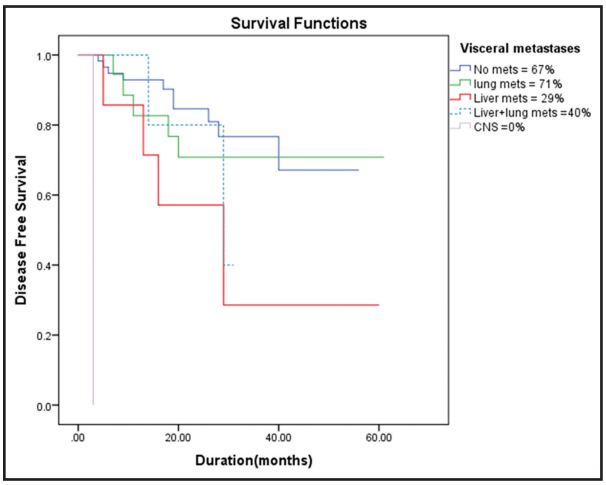

Figure 3: Kaplan–Meier curve showing the 5-year disease-free survival in intermediate risk and high-risk germ cell tumours in relation to visceral metastases other than bone involvement (No metastases, 67%; only lung metastases, 71%; only liver metastases, 29%; lung + liver metastases, 40% and central nervous system involvement, 0%). The log-rank test showed a statistically significant difference in percent survival of patients with and without visceral metastases ($P = 0.0001$)

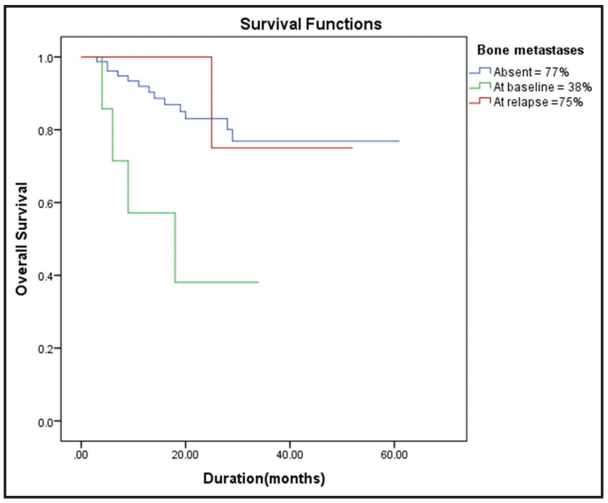

Figure 2: Kaplan–Meier curve showing the 5-year overall survival in intermediate risk and high-risk germ cell tumours (No bone metastases, 77%; bone metastases at baseline, 38% and bone metastases at relapse, 75%). The log-rank test showed a statistically significant difference in percent survival of patients with and without metastases at baseline ($P = 0.02$)

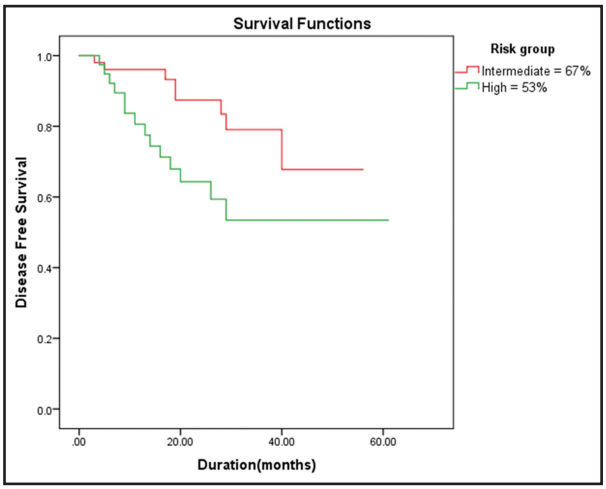

Figure 4: Kaplan–Meier curve showing the 5-year disease-free survival of germ cell tumours in relation to international germ cell cancer consensus cooperative defined risk assessment (intermediate risk [IR], 67% and high risk [HR], 53%). The log-rank test showed a statistically significant difference in percent survival of patients with IR versus HR ($P = 0.02$)

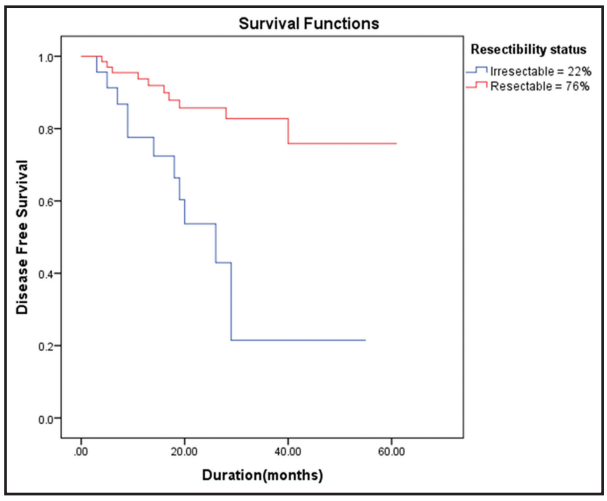

Figure 5: Kaplan–Meier curve showing the 5-year disease-free survival of intermediate risk high-risk germ cell tumours in relation to resectibility of primary tumour site (irresectable, 22% and respectable, 76%). The log-rank test showed a statistically significant difference in percent survival of patients with resectable versus irresectable disease ($P = 0.0001$)

pulmonary, hepatic and CNS metastases were seen in 59%, 27.5%, 15% and 1%, respectively at baseline staging.

Treatment and outcome of patients without bone metastases

All Stage I/LR was treated with complete resection of primary tumour only or followed by a few cycles of systemic chemotherapy with subsequent surveillance with tumour markers. At the end of follow-up, all were alive and disease free.

Of 80 with IR or HR, 70% were treated with only first-line chemotherapy while the rest received either second- or third-line chemotherapy due to progressive disease. XRT was given to four irresectable primary mediastinal/abdominal tumours, two with para-aortic nodal masses and one with brain metastases.

About 32.5% had disease relapse, out of which 16 had progressive disease, rest remained in remission. Seven (9%) were lost to follow-up.

13 died with a median OS of 13 months (Range: 3–29 months); of these two died due to bleomycin toxicity. The remaining 59% remained progression free with a median OS of 21 months (range: 6–60+months). Ten with relapse remained in remission with a median OS of 28 months (range: 11–60 months).

DFS and OS of patients with and without metastases

Comparing those with bone metastases to those without metastases, the following correlations were found:

By spearman's two-tailed test, patients with bone metastases had an equal chance of presenting with visceral (lung, liver or both) metastases and various histologic subtypes, as the difference was not statistically significant ($P = 0.06$).

On bivariate analysis, tumour histology ($P = 0.02$), site of primary tumour ($P < 0.0001$), the risk group ($p = 0.02$), tumour resectibility status ($P < 0.001$), presence of bone metastases at baseline ($P < 0.0001$) and visceral involvement at baseline ($P < 0.0001$) had significant influence on DFS and OS. Survival plots according to Kaplan–Meier curves are presented in Figures 1-5.

The 5-year OS in the absence of bone metastases, with bone metastases at baseline and bone metastases at relapse, was 77%, 38% and 75%, respectively. The 5-year DFS for the same cohort groups is 63%, 38% and 20%, respectively.

Discussion

Bone metastasis is a rare event in GCT, detected in 5% of patients at primary diagnosis.[3] Based on current treatment guidelines, the outcome of non-osseous metastatic GCT is good, achieving an overall cure rate of over 80% after standard chemotherapy. However, a patient with osseous metastases achieves 5-year survival rate in the range of 45–55% after cisplatin-based combination chemotherapy.[5,6] Although bone metastases are rare in GCT, prompt and accurate diagnosis are very crucial since there is a significant treatment failure rate after first-line chemotherapy. Osseous metastases mainly affect young males and lead to morbidity in the form of pain and cord compression, necessitating the use of radiotherapy in chemoresistant cases.[7]

In routine practice, screening of bone metastases is generally not endorsed in adult cases of GCT. Patients do not always present with bony symptoms related to metastases; they are usually detected incidentally on

imaging. Jamal-Hanjani *et al*.[2] found incidental bone metastases in 58%.

In our study, 83% of symptomatic patients had osseous metastases on Tc-99m MDP bone scans. Studies have suggested that back pain can be a manifestation of para-aortic lymphadenopathy;[8] however, consideration should always be given to metastatic disease especially if bone tenderness is present.

Hitchins *et al*.[5] reported 3% incidence of bone metastases in gonadal and extragonadal GCT at primary diagnosis and 9% at relapse with concomitant retroperitoneal and pulmonary metastases in all. Oechsle *et al*.[9] found primary bone metastases in 40/434 (9%) patients, with frequent histology of primary mediastinal tumours, yolk sac and synchronous liver metastases. In our study, 50% of non-seminomatous mediastinal GCT had bone metastases. In addition, 67% had retroperitoneal nodal diseases, 33% had synchronous lung metastases and 8.3% had lung and liver metastases, suggesting simultaneous lymphatic and haematological spread. Tumour markers elevation was more frequently seen in the presence of bone metastases (92%) as compared to the rest of the study population (79%). Bokemeyer *et al*.[10] concluded that non-seminomatous histology, mediastinal primary site, presence of non-pulmonary visceral metastases or marked elevation of serum tumour markers are poor prognosticators. In another study by Mead *et al*.[11] found a 3-year survival rate of 68% in 33% of patients with raised markers (either AFP>1000 kU/L or β-HCG >10,000 IU/L) among other poor prognostic factors versus 93% survival rate in 67% without raised markers. However, in our study none of the patients with bone metastases had HCG secreting features.

Relapse in patients with primary bone metastases is less common than failure of cisplatin-based chemotherapy leading to progressive disease. In our study, five patients with bone metastases died due to progressive disease <1 year after diagnosis. The 5-year OS of patients with bone disease at relapse was significantly better; 75% versus 38% in primary bone metastases.

In our study, three patients had isolated bone metastases without synchronous nodal/visceral metastases, out of which one was a case of testicular seminoma rarely reported in literature.[4,12-14]

Seven patients with bone metastases did not respond to cisplatin-based chemotherapy and were switched to second- and third-line regimens with radiotherapy to local disease sites. In addition to progression in bone metastases, relapse with new-onset lung metastases in three and liver disease in one patient was seen. Two of these patients had isolated skeletal metastases at baseline with no extraskeletal disease. By the end of follow-up, five died despite salvage treatment with a median survival of 9 months, one was stable with an irresectable primary pelvic mass and one was lost to follow-up. Hence, the optimal treatment approach to bone metastases in patients with bone metastases remains elusive.

Limitations of this study are primarily related to the fact that data were gathered retrospectively. However, since bone metastases in GCT are not frequent, prospective data collection would not be easy. We were able to reach meaningful outcomes from this data set. Our hospital did not have a SPECT/CT scanner before September 2013; therefore, only planar scintigraphy was acquired before that and correlative radiologic imaging was performed separately where needed.

There were some variations in protocols over the course of this study. Since 2013, all patients underwent Tc-99m MDP bone scan, before that although most had bone scintigraphy, some who did not were excluded from this study.

Conclusion

Skeletal metastases were found in 9.5% of GCT patients, 7.6% at baseline staging and 5.4% at relapse in IR or HR GCT. Based on our findings, baseline skeletal evaluation for metastases; especially in the presence of bone pain or known systemic metastases should be done because although skeletal relapses are rare, they have a dismal outcome. IGCCCG defined risk stratification, primary tumour resectability and visceral metastases are a better predictors of survival.

Conflict of Interest

The authors declare that they have no conflict of interest.

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