Original Article

Detection of bone metastasis in nasopharyngeal carcinoma by bone scintigraphy: A retrospective study in perspective of limited resource settings

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ABSTRACT

Background: Nasopharyngeal carcinoma (NPC) is an aggressive tumor with a significant proportion of patients presenting with distant metastasis. The skeleton is one of the most common sites of distant failure. This retrospective study was performed to analyze the incidence and patterns of skeletal metastasis in NPC detected by bone scintigraphy in resource-poor settings. **Materials and Methods:** We analyzed records of 301 NPC patients attending our oncology outpatient department from January 2002 to December 2012. Of these, 33 patients who presented with bony pain underwent bone scan (BS) for suspect of skeletal metastasis. In patients with positive scans, histological diagnosis to confirm metastasis was attempted. **Results:** Bone metastasis (BM) was found in 19 patients (57.6% of patients undergoing BS, 6.3% of total NPC patients). About 36.8% and 15.8% of BM cases were in the age group 20-29 and 30-39 years, respectively ($P = 0.27$). 63.1% of metastatic cases were of World Health Organization type-II histology ($P = 0.021$). Of the patients diagnosed with BM, 52.6% belonged to stage IV at presentation ($P = 0.022$). Spine was involved in 56% of the positive cases, followed by the pelvis (32%), and ribs (24%). On univariate analysis, histology ($P < 0.001$), stage at diagnosis ($P = 0.007$) and age group ($P = 0.001$) were identified as significant factors affecting BM. However, on multivariate analysis, only stage ($P = 0.001$) was a significant factor. **Conclusion:** Bone scintigraphy can be considered in limited resource settings for the evaluation of distant metastasis in the patients of advanced NPC.

Key words: Bone metastasis, bone scintigraphy, nasopharyngeal cancer

INTRODUCTION

Nasopharyngeal carcinoma (NPC) is a tumor notorious for its predilection for hematogenous dissemination. Distant metastasis is found in 6% of the patients of the NPC at presentation. More importantly, the cause of death in more than 30% of patients with advanced disease is distant failure.[1] Usually up to 30% patients with NPC will eventually develop distant metastasis, while only one-sixth patients with metastasis are diagnosed at their initial diagnosis, and another one-third are identified within 3 months after diagnosis.[2,3] With significant improvement in local control by use of high-precision radiotherapy techniques, distant failure is expected to become an increasingly important cause of death from NPC. Skeletal metastasis has been reported as the most common site of distant failure in various studies.[4,5]

NPC is classified by the World Health Organization (WHO) according to the histological subtype. Type-I NPC denotes keratinizing, well-differentiated tumor cells; whereas, nonkeratinizing, differentiated tumor cells are found in type-II NPC. Type-III NPC is characterized by nonkeratinizing, undifferentiated carcinoma, (referred to as lymphoepitheliomas), and represents 63-95% of NPC tumors worldwide.[6] Human papillomavirus (HPV) has been detected in NPCs, particularly in the keratinizing WHO type-I NPC.[7-9] However, the role of HPV in WHO type-II and III NPC is not well understood. While HPV is less commonly found in WHO-II or -III NPCs, co-infection with HPV

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and Epstein–Barr virus has been reported in these nonkeratinizing NPC types.[7,10]

Imaging work-up, preferably in the form positron emission tomography (PET)-computed tomography (CT) has been recommended for evaluation of distant metastasis, especially in patients presenting with high-risk features.[11] These include nonkeratinizing histology, endemic phenotype, N2–N3 disease and stage III-IV disease. However, PET-CT is an expensive investigation not readily available in developing countries. Bone scan (BS) has been used in our center in patients of NPC to identify bone metastasis (BM) at presentation. It is a useful tool to identify the disease spread and thus has the potential to alter the treatment decisions. It is also a cheaper option than PET scan and widely available, thus of special importance in countries with limited resources. However, it suffers from the inherent disadvantage of being false positive considering the widespread prevalence of degenerative spine diseases. In addition, it may miss a pure osteolytic lesion in the absence of uptake of tracer in such a lesion. This retrospective study was designed to find out the incidence and patterns of BM diagnosed by BS in patients of NPC at initial presentation.

MATERIALS AND METHODS

A total of 301 NPC patients who attended our oncology outpatient department from January 2002 to December 2012 and whose records were available for analysis were selected for this retrospective study. 33 NPC patients symptomatic for bone pain at the time of initial presentation underwent BS for suspect of skeletal metastasis. Scintigraphy was performed by Nucline™ SPIRIT DH-V variable angle dual head camera (Mediso Medical Imaging Systems, Budapest, Hungary) with technetium-99 m methylene diphosphonate. The patients were stratified according to age groups, stage and histology of the disease. In patients with positive BS, histological correlation was attempted by taking fine needle aspiration cytology of the lesion, wherever possible. In cases of involvement of the spine, X-ray and/or magnetic resonance imaging of the involved spine was performed. Patients with a confirmed metastasis were treated with local radiotherapy (30 Gy in 10 fractions in 2 weeks) followed by chemotherapy for the systemic disease. In patients with a poor general condition, 800cGy single fraction was used to provide symptomatic relief. Frequency tables were drawn, and correlations between various variables were calculated using the Chi-square test. Crosstabs' statistics was used to measure the association for two-way tables. Univariate and multivariate analysis was performed to identify the factors that may affect metastasis to the bones. All statistical calculations were performed using SPSS software for windows, version 20.0 (IBM Corp., Armonk, NY, USA).

RESULTS

Bone scan led to the identification of suspected bony lesions in 21 patients. However, on correlating with history and X-ray/magnetic resonance imaging/histology, BM were confirmed in total 19 patients. Thus, the specificity of BS was 90.4% in our patient cohort. The two cases, which were false positive, were diagnosed to be suffering from degenerative spine disease in addition to NPC. The incidence of BM in NPC overall at presentation was 6.3% (19/301). Table 1 describes the characteristics of study patients. The patients of younger age groups had higher incidence of BM; out of 19 BM, 7 (36.8%) patients were of age group 20-29 years, 15.8% 30-39 years, 10.5% of 40-49 years, 21% of 50-59 years while 15.8% patients of 60-69 year age group had skeletal metastasis (P = 0.238). However, no patient of >70 years age was found to have BM [Figure 1]. Most of the patients with BM (52.6%) were stage IV, 36.8% stage III and 10.5% were stage II at the presentation and start of the treatment (P = 0.001). 12 BM patients (63.1%) were of WHO type-II histology (nonkeratinizing carcinoma); 5 (26.3%) of WHO type-III histology (undifferentiated carcinoma) and 2 (10.5%) of WHO type-I (squamous cell carcinoma) (P < 0.001). The most common site of BM was spine (56%) followed by the pelvis (32%), and ribs (24%). Overall, isolated single BM was identified in 14 patients (73.6%) withisolated involvement of the spine being 24% [Figure 2]. On univariate analysis, histology (P < 0.001), stage at diagnosis (P = 0.007) and age group (P = 0.001) were identified as significant factors affecting BM [Table 2]. However, on multivariate analysis, only stage (P = 0.001) was a significant factor [Table 3].

Table 1: Characteristics of the patients

Feature	Total patients (%)	Patients undergoing bone scan (%)	Confirmed BM (%)	χ^2 value	P
Sex					
Male	264 (87.7)	30 (90.9)	17 (89.5)	0.59	0.809
Female	37 (12.3)	3 (9.1)	2 (10.5)		
Age (years)					
10-19	48 (15.9)	4 (12.1)	2 (10.5)	6.78	0.238
20-29	62 (20.6)	9 (27.3)	5 (26.3)		
30-39	29 (9.6)	7 (21.2)	4 (21.0)		
40-49	22 (7.3)	6 (18.2)	3 (15.8)		
50-59	57 (18.9)	4 (12.1)	3 (15.8)		
≥60	83 (27.5)	3 (9.1)	2 (10.5)		
Stage					
I	26 (8.6)	2 (6.1)	0 (0)	16.05	0.001
II	74 (24.6)	8 (24.2)	2 (10.5)		
III	144 (47.8)	11 (33.3)	7 (36.8)		
IV	57 (8.9)	12 (36.4)	10 (52.6)		
Histology					
WHO type-I	74 (24.6)	9 (27.3)	2 (10.5)	50.48	<0.001
WHO type-II	36 (11.9)	15 (45.5)	12 (63.2)		
WHO type-III	191 (63.4)	9 (27.3)	5 (26.3)		

WHO: World Health Organization, BM: Bone metastasis

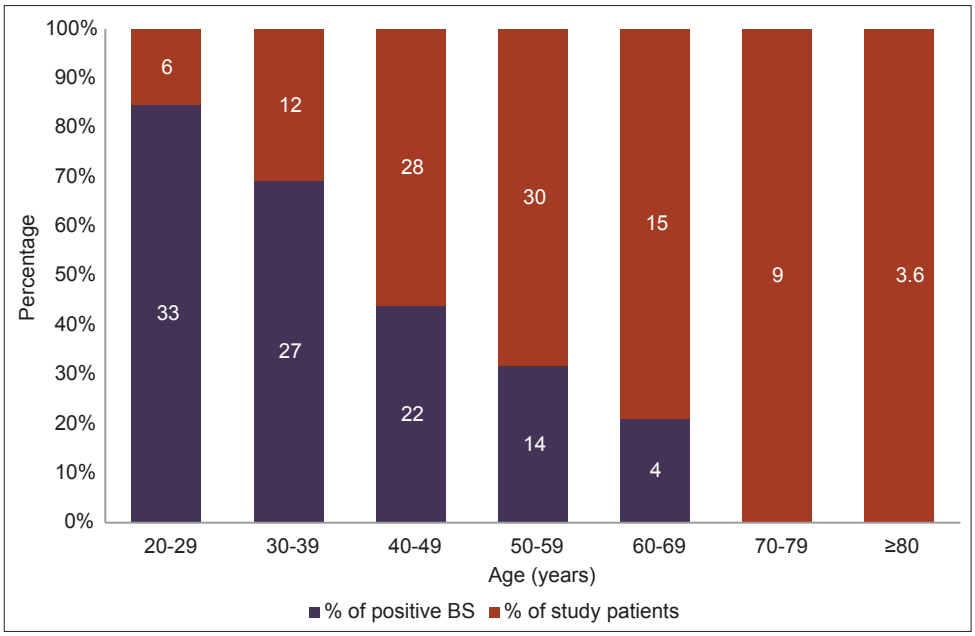

Figure 1: The number of patients with positive bone scan against the age group of the patients

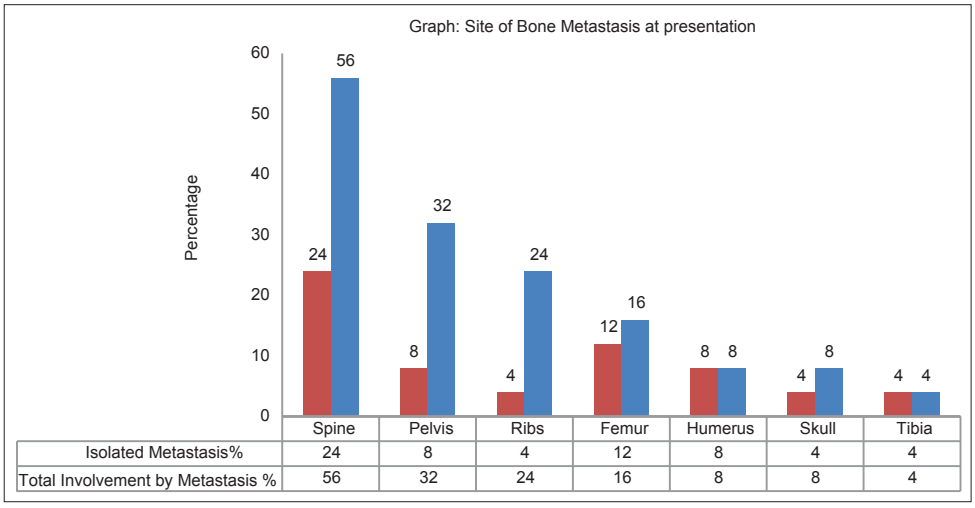

Figure 2: Bar diagram showing percentage distribution of site of bone metastasis involved overall (in blue) and in isolation (in red)

Table 2: Univariate analysis of the variables that may affect bone metastases

Tests of between-subjects effects Dependent variable: Bone mets					
Source	**Type-III sum of squares**	**df**	**Mean square**	***F* test**	**Significant**
Histology	0.509	2	0.254	12.734	0.000
Stage	0.250	3	0.083	4.172	0.007
Age group	0.449	5	0.090	4.497	0.001
Sex	0.024	1	0.024	1.183	0.278

df: Degree of freedom

Table 3: Multivariate analysis of the variables that may affect bone metastases

Tests of between-subjects effects						
Source	**Dependent variable**	**Type-III sum of squares**	**df**	**Mean square**	***F* test**	**Significant**
Bone mets	Histology	1.080	1	1.080	1.479	0.225
	Stage	8.576	1	8.576	12.175	0.001
	Age group	6.017	1	6.017	1.760	0.186
	Sex	0.006	1	0.006	0.058	0.809

df: Degree of freedom

DISCUSSION

Nasopharyngeal carcinoma, being a tumor of the high propensity for hematogenous dissemination, requires proper staging work-up. Hui *et al.* reported distant metastasis to be the most common mode of failure, identified in 13% patients ($n = 379$) with a 5 years actuarial rate of 14.9%.[4] The commonest metastatic site was bone (22%), followed by liver (16%) and lung (10.8%).

Sundram *et al*. reported 23% (33/143) incidence of BM in newly diagnosed NPC patients (within 2 months of initial diagnosis) had evidence of bone metastases on evaluation by bone scintigraphy (BS).[5] Various guidelines, including widely followed National Comprehensive Cancer (NCCN) recommend the use of PET/CT and/or other imaging modalities for the initial work-up for distant metastasis in NPC with high-risk features. BS has been used in our center for this purpose, and we present a retrospective review of these cases.

Caglar *et al*. have reported 11.3% incidence of BM in NPC.[12] In their study, out of 230 patients, 171 were examined for skeletal metastases with BS prior to therapy and at 1-year intervals. BS detected increased uptake in 29 patients, which was reported as suggestive of metastases or equivocal. Twenty-six of these were true-positive, confirmed by radiography or clinical follow-up. They also recommend that BS be used in determining the presence of BM, but its utilization should be preserved for those with nodal involvement. In our study, the incidence of BM at presentation was found in 6.3% (19 out of 301) of total NPC patients. High incidence of distant metastases was also found by Ahmad and Stefani, who reviewed the records of 256 patients with NPC to determine the incidence and location of distant metastases.[13] The incidence of distant metastases was 36% overall and 51% in the autopsy patients. Bones, distant lymph nodes, liver, and lungs were the most common sites of distant metastases, while liver was the most common site in the autopsy patients. Of those patients who developed distant metastases, 98% were discovered within 3 years or earlier.

Yang *et al*. found that although PET/CT was found to be more sensitive on lesion level than BS (sensitivity 70.0 vs. 42.0%; P = 0.044), there were still 14 metastatic (28.0%) lesions that could be detected by BS, while negative in PET/CT imaging and concluded that there was no statistical difference between PET/CT and BS.[11] In a recently published retrograde study, Zhao *et al*. reported that in 70 patients who had been preliminarily diagnosed with BM, the incidence of BM in N0, N1, N2 and N3 stage was 5.7%, 17.2%, 50.2%, and 25.7%, respectively, while the incidence in T0, T1, T2 and T3 stage was 0%, 23.8%, 47.6% and 28.6% respectively.[14] In their study, BM occurred in most common in the vertebral column, rib, sternum, ilium and femur. We found that 52.6% of the patients diagnosed to have BM were already stage IV at presentation (P = 0.004). Spine was involved in 56% of the positive cases followed by the pelvis (32%), and ribs (24%). In a recent study by Kumar *et al*., patients with spinal metastases from NPC had relatively good survival prognosis when compared to patients with visceral metastasis.[15]

In our study, the patients of younger age groups had higher incidence of BM; 36.8% bone metastatic patients were of age group 20-29 years while it was 15.8% patients for 60-69 years. However, the data failed to reach the significance level (P = 0.27). Ahmad and Stefani found that undifferentiated carcinoma had the highest incidence of bone, but lowest incidence of lung metastases compared with other major histological subtypes.[13] NCCN guidelines recommend the use of imaging modalities for distant metastasis in NPC patients with nonkeratinizing histology, stage III-IV disease, N2-N3 disease and endemic phenotype. In a study by Micheau *et al*., about 40% of nonkeratinizing NPC patients with advanced N-stage disease (N2 or N3) had tumor invasion in the bone marrow as demonstrated by transiliac biopsy.[16] In our study, we found that 63.1% BM patients were of WHO type-II histology (nonkeratinizing carcinoma) and 26.3% of WHO type-III histology (undifferentiated carcinoma; P = 0.015). Thus, nonkeratinizing histology was found to have significantly higher association with BM. Furthermore, 52.6% patients with confirmed BM were of stage IV and 36.8% of stage III at the presentation. Other studies have also found a strong correlation between advanced locoregional disease and distant metastasis.[12] Thus, we were able to corroborate the locally advanced disease with higher incidence of BM stressing on the need of careful work-up in these patients as this may alter the treatment intent and primary therapeutic modality; chemotherapy being preferred over radiation for metastatic disease.

The results of this study needs to be interpreted with caution as BS was not performed in all the patients due to financial considerations in a limited resource setting. Caglar *et al*. reported that BM was present in 33% asymptomatic patients of NPC.[12] Thus, there may have been missed cases of distant metastasis explaining its lower incidence in our study (6.3%) versus 11.3% in the study by Caglar *et al*. Various studies have demonstrated PET/CT as a superior staging modality for M-stage compared with conventional staging work-up, in terms of specificity, sensitivity, and accuracy.[16,17] Approximately, 20% of cases will be found to have distant metastases on PET at diagnosis. However, BS is a cheaper option than PET scan and also widely available, thus of special importance in developing countries and limited resource settings.

CONCLUSIONS

Bone scintigraphy can be considered for evaluating patients of advanced NPC in developing countries with limited resource settings. Randomized controlled trials with head on comparison of BS with PET scan are required to confirm the findings of this retrospective study.

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