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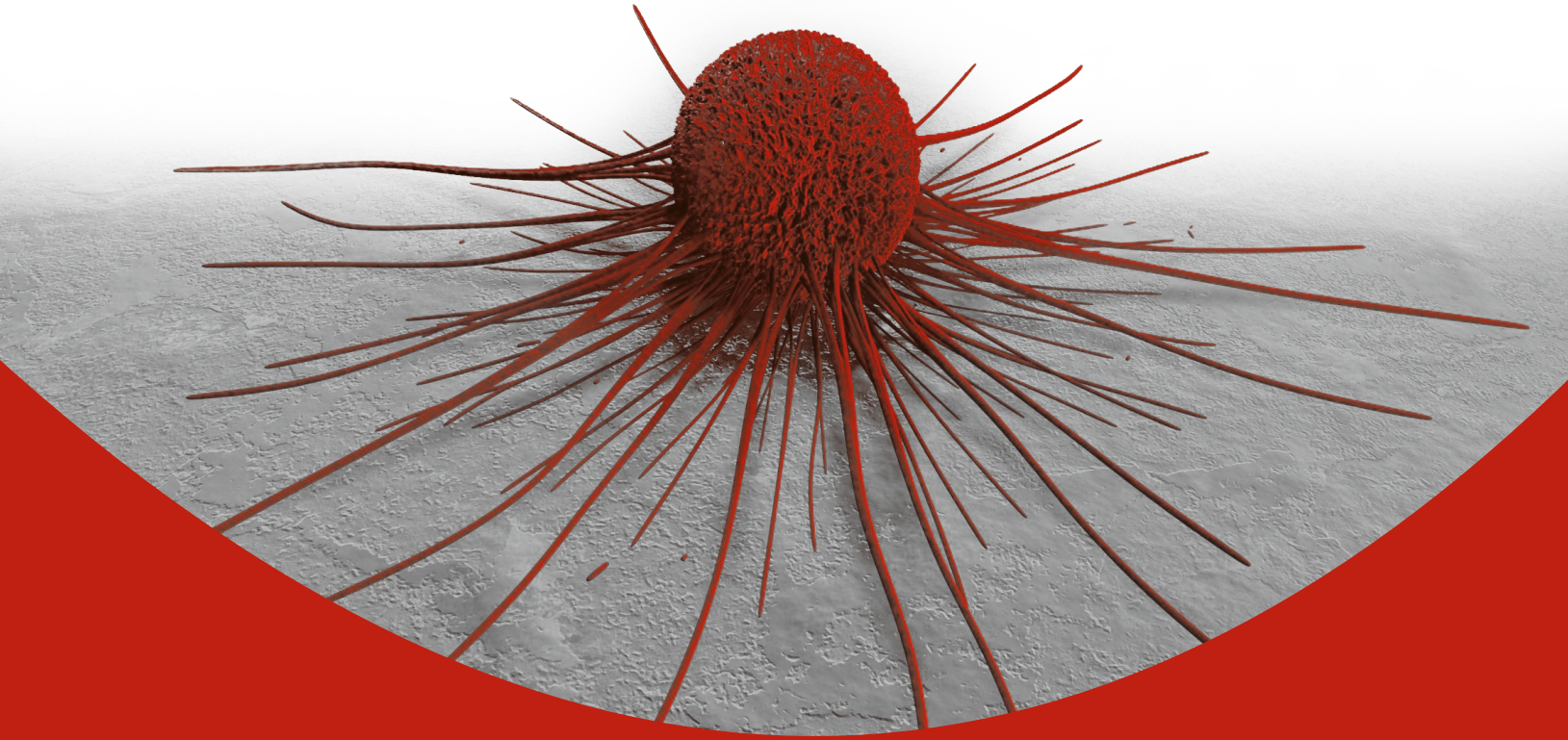

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Original Article

Analysis of bone metastasis in head and neck squamous cell carcinoma: Experience of a regional cancer center

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ABSTRACT

Background: Bone metastasis is a rare occurrence in head and neck squamous cell carcinoma (HNSCC). This retrospective study was performed to analyze the frequency and patterns of skeletal metastasis in HNSCC. **Materials and Methods:** We analyzed records of 8326 HNSCC patients attending our oncology outpatient department from January 2000 to December 2013. All statistical calculations were performed using MedCalc software for windows, version 12.5.0 (Osterd, Belgium). **Results:** Bone metastasis was found in 25 patients (0.3% of total HNSCC patients, nasopharynx excluded). 10 patients (0.66%) of carcinoma tonsil had skeletal metastasis. The patients of younger age groups had higher frequency of bone metastasis; 1.56% patients of age group 20–29 years while 0.26% patients of 60–69 years age group had skeletal metastasis ($P < 0.001$). However, no patient of >70 years age was found to have bone metastasis. Most common site of metastasis was spine (56%) followed by pelvis (32%). Isolated involvement of a single bony site was present in 64% of the metastatic cases. **Conclusion:** Bone metastasis though very rare, should be considered for evaluation in patients of HNSCC especially in younger patients.

Key words: Bone metastasis, bone scintigraphy, head and neck squamous cell cancer

INTRODUCTION

Head and neck squamous cell carcinoma (HNSCC) is the sixth most common cancer worldwide.[1] In India, it accounts for one-fourth of male cancers and one-tenth of female cancers.[2] The incidence of HNSCC is about 6 times higher in India as compared to western countries probably due to oral consumption of tobacco in various forms, use of lime with betel nut and leaves and smoking.

The incidence of distant metastasis is around 14% in Indian scenario.[3] In our regional cancer center, up to 75% cases of metastasis to bones originate from the primary in breast and lung. Other primaries contributing to metastasis to bones include prostate, renal, and thyroid. The rarer primaries include the cervix, gastrointestinal tract, urinary bladder, and hematological malignancies including myeloma and lymphoma. Despite its higher incidence, HNSCC is an uncommon primary source of skeletal metastases. The lungs are the most common site of distant metastases in HNSCC.[4] With the improvement in treatment and resultant increasing duration of survival of these patients, however, increases the probability of late bone involvement.[5]

Recent data have confirmed the role of human papillomavirus (HPV) as an independent risk factor for oral and oropharyngeal carcinomas.[6,7] In ASTRO 2014, a news release stated that HPV-positive SCC of the oropharynx patients experiences distant metastases after initial treatment at a later date, in more subsites and more atypical sites compared to HPV-negative patients.[8] In meeting of ASCO 2014, a press release

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stated that HPV-positive oropharyngeal cancer patients may receive lower radiation dose improving outcomes and causing fewer long-term side effects.[9] In another abstract of ASCO 2014, Law *et al*. concluded that at median follow-up of 18–25 months, there was no difference in the overall rate of distant metastasis for HPV-positive HNSCC compared to HPV-negative/unknown ($P = 0.21$) but there was a significant difference in the rate of distant metastasis to the lung ($P = 0.012$).[10] Thus, the exact role of HPV in bone metastasis remains a subject of debate but there is consensus at present that HPV positivity confers good responsiveness of the HNSCC to chemo and radiotherapy.

For HNSCC, bone metastases traditionally have only come to the attention through pain symptoms, pathologic fractures, or abnormal laboratory test results, all of which are insensitive for early lesions.[11] Due to the low frequency of bone metastases and the high percentage of equivocal findings, bone scintigraphy (BS) is not routinely performed for staging HNSCC.[12,13] Screening for distant metastases at sites other than the lungs is, usually, not recommended for HNSCC.[12,14] However, BS is an important investigation to identify skeletal metastases in advanced HNSCC with suggestive symptoms. In this study, we aimed to find out the frequency of skeletal metastasis in patients of HNSCC as indicated by BS or other imaging modalities, and study its correlation with age and site of the disease.

MATERIALS AND METHODS

A total of 8326 HNSCC patients who attended our oncology outpatient department from January 2000 to December 2013 and whose records were available for analysis were selected for this retrospective analysis. Nasopharyngeal carcinoma (NPC) patients were not included in this study due to the high incidence of undifferentiated carcinoma in this subgroup and thus, authors have presented similar study in NPC in a separately devoted article.[15] 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. Other imaging modalities used for the diagnosis included plain radiographs, computed tomography (CT)/magnetic resonance imaging, and positron emission tomography/CT (PET/CT). The determination of HPV status was not done in most of the patients as it was not included in the previous protocols of the institute. The patients were stratified according to age groups and site of the primary disease. In patients with equivocal findings on imaging studies, biopsy was performed to establish bone secondaries. The patients were also screened for second primary malignancy which could have given rise to bone metastasis. The patients with established skeletal metastasis were treated with local radiotherapy (30 Gy in 10 fractions in 2 weeks) followed by chemotherapy for the systemic disease. In patients with poor general condition, 800 cGy single fraction was used to provide symptomatic relief. Frequency tables were drawn, and associations between various variables were calculated using the Chi-square test. All statistical calculations were performed using MedCalc software for windows, version 12.5.0 (Osterd, Belgium).

RESULTS

Skeletal metastasis was identified in 25 patients (0.3%) out of total 8326 HNSCC cases [Figure 1]. Table 1 shows age wise and Table 2 shows site wise distribution of study patients and patients with bony metastasis. The patients of younger age groups had higher frequency of bone metastasis; 1.56% patients of age group 20–29 years, 0.69% of 30–39 years, 0.18% of 40–49 years, 0.13% of 50–59 years while 0.26% patients of 60–69 years age group had skeletal metastasis ($P < 0.001$) [Figure 2]. However, no patient of >70 years age was found to have bone metastasis. Ten patients out of 1497 (0.66%) carcinoma tonsil cases had skeletal metastasis. Nine cases out of 3600 (0.25%) carcinoma tongue patients were found to have metastasis to bones. Besides, two each of pyriform fossa and alveolus, 1 each of larynx and lip cancer had skeletal

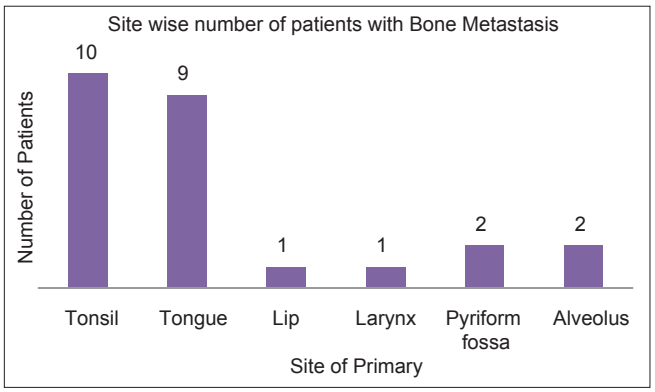

Figure 1: Bar diagram showing number of positive bone scans versus site of primary disease

Table 1: Age wise distribution of study patients and patients with bony metastasis

Age group	Patients with bone metastasis	Total number of patients	Percentage of bone metsw
20-29	8	512	1.56
30-39	7	1003	0.69
40-49	4	2243	0.18
50-59	3	2373	0.13
60-69	3	1165	0.26
70-79	0	730	0
≥80	0	300	0

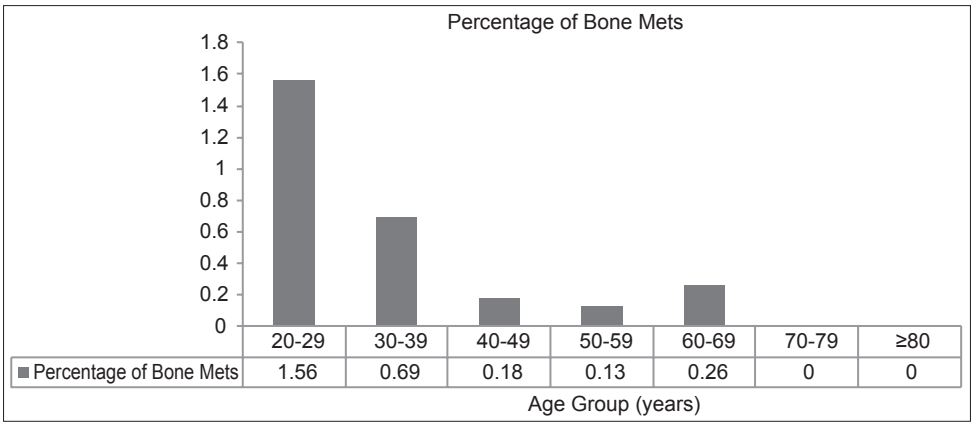

Figure 2: Bar graph showing percentage of bone metastasis versus age group (out of total 8326patients

Table 2: Site wise distribution of study patients and patients with bony metastasis

Site of primary	Patients with bone metastasis	Total number of patients	Percentage of bone mets
Tonsil	10	1497	0.67
Tongue	9	3600	0.22
Lip	1	24	4.16
Larynx	1	1750	0.06
Pyriform fossa	2	887	0.22
Alveolus	2	242	0.82
Others	0	326	0

metastasis. Most common site of bone involvement was spine (56%) followed by pelvis (32%) ($P < 0.001$). However, isolated involvement of spine and pelvis was 24% and 8%, respectively [Figure 3]. Overall, isolated involvement of a single bony site was present in 64% of the metastatic cases. All the patients with bony involvement were found to be suffering from locally advanced HNSCC.

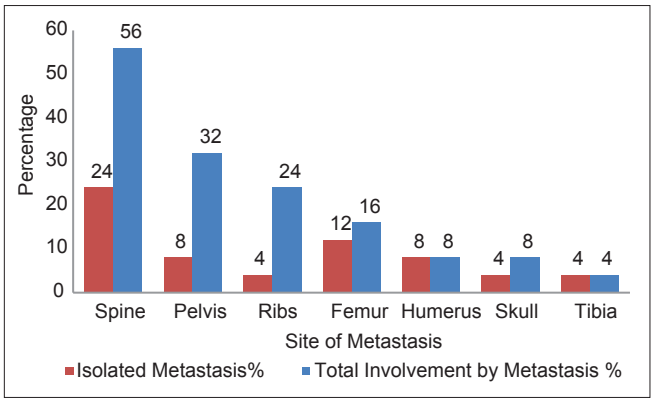

Figure 3: Bar diagram showing siteof bone metastasis (overall and isolated involvement)

DISCUSSION

The prime route of spread for HNSCC is lymphatic with nonlymphatic distant spread accounting for approximately 10% of the cases.[16] The lungs, bones (especially the vertebrae, ribs, and skull) and the liver are the most common sites of hematogenous distant metastases from HNSCC.[16,17] In a study by Gowen and Desuto-Nagy, 6.2% of the patients were diagnosed of having distant metastasis during the follow-up period after the initial treatment.[17] The most common sites of distant metastasis were the lungs (58%) and the bones (22%). Similarly, Holsinger *et al*., from the Anderson Cancer Center in Houston, provided a panel of clinical and histopathological predictors that can identify patients at the greatest risk for development of distant metastases in HNSCC.[18] In their study, the 5-year incidence of distant metastasis was 15.1% (94/622). Pulmonary metastases were most commonly found: 65.9% to the lung, 4.2% to the mediastinum, 2.1% to the pleura. Metastases to bone (22.3%) and to the liver (9.5%) were the next most commonly encountered. 31.9% patients with distant metastases presented with more than one metastatic site. The most common site for bony metastasis was the spine (12.7%), followed by skull (4.2%), rib (3.1%), and axial bones (femur, humerus; each 2.1%). In our study also, spine was the most common site followed by pelvic bones and ribs. A possible reason for preferential axial involvement could be the greater vascularity of the red marrow in the axial skeleton as opposed to the yellow marrow in the appendicular bones. More than half of patients with osseous metastases presented with multiple sites. Many of the patients complained of bone pain, which may be due to multiple mechanisms including release of chemical mediators, elevated intra-osseous pressure and elevation of periosteum. Fractures and impending fractures are also an important source of pain, especially in weight-bearing bones. Such fractures are more common in areas involved with lytic metastases rather than blastic ones. Trilling *et al*. could identify only 19 patients of HNSCC reported to have spinal metastasis from 1965 to 2009 with thoracic vertebra being the most common site (17/19, 89.47%) exemplifying the ill reporting of the issue.[19]

In our study, mainly primaries located in tonsil and tongue showed metastasis to bones. These were also the most common sites of HNSCC registered in our hospital. Overall, 0.3% HNSCC patients had skeletal metastases in this study. In a study by Bhandari and Jain, out of 624 patients of head and neck cancers, 6 (0.96%) developed metastasis to solitary or multiple bones during the course of the disease.[20] In a study by Li *et al*., it was found that primary tumor site, level of tumor invasion and also numbers of levels with positive lymph node are closely related to the occurrence of distant metastasis in HNSCC.[21] Lesions arising in the larynx and hypopharynx have a greater predilection to metastasize than oral lesions, although true vocal cord lesions infrequently metastasize as demonstrated by Snow *et al*.[22] In data of Merino, 8% of all patients who had local control developed metastases, while 23% of those with T3 to T4 lesions had local control and developed distant spread.[23] The time interval between the diagnosis of distant metastasis and death is <2 years in >90% of such cases.

Another important observation in this study is the prevalence of the higher metastasis in younger age; 1.56% in 20–29 years and 0.69% in 30–39 years age group. All other groups had bone metastasis in <0.3%. This could point toward the most aggressive nature of the disease in younger patients.

Because distant metastasis has an important impact on survival, early detection of this unfavorable status in HNSCC is substantial for therapeutic strategy regulation.[23] As the lungs, bones and the liver are the most common sites of distant metastases from HNSCC, routine examination about these organs should be performed for high-risk patients. The prevalence of metastases at autopsy (37–57%) is much higher than in clinical studies (4–26%).[24] This suggests that distant metastases in head and neck cancer are often asymptomatic. In the absence of useful screening tests, metastases are, usually, detected by specific investigation of suspicious symptoms. Plain X-rays, CT and BS are the most frequently used investigations. Since the introduction of technetium-based scan agents, approximately 30 years ago, the radioisotope bone scan has been the standard method for detection of bony metastases. Radioisotope scanning is more sensitive than radiography for detection of most metastases.[25] Tracer accumulates in the reactive new bone that is formed in response to the lesion. Thus, most metastatic lesions are "hot;" however, "cold" lesions due to a complete absence of reactive bone may be encountered in aggressive metastases. Furthermore, the amount of accumulation is directly proportional to the level of blood flow. Diffuse accumulation of tracer throughout the skeleton due to disseminated skeletal disease (known as super scan) may lead to the false impression of a normal scan. Despite the sophisticated mechanism, the BS suffers from a lack of specificity.[26] Tracer accumulation may occur in any skeletal location with an elevated rate of bone turnover and thus, may accompany trauma, infection or arthropathy. The probability that an abnormal scan represents metastatic tumor is directly linked to the number of abnormal foci. In a patient with foci of increased uptake and a known primary tumor, the scan strongly suggests metastases. A small number (<4) of abnormalities is more likely to represent metastatic disease in some locations than others, with rib lesions being particularly low-yield.[27] Only 50% of solitary foci represent metastases, even among patients with cancer. This lack of specificity is well-known and has led to recommendations that positive scans be accompanied by radiographic correlation. However, given the greater sensitivity of the bone scan, a positive radiograph may confirm a finding, but a negative radiograph does not exclude a metastasis.

Positron emission tomography-computed tomography with fluorodeoxyglucose F18 (^{18}F-FDG-PET/CT) is another widely used investigation to evaluate patients with HNSCC. PET/CT can provide early and accurate detection of bone metastases from HNSCC. Use of FDG-PET/CT in restaging HNSCC allows for detection of occult lung, live and bone metastases, and this early detection frequently influences therapeutic decision making. In a study by Basu *et al*., the identification of bone metastases by PET/CT influenced therapeutic decisions in 5 of 13 cases (38%).[25] Some studies have also compared PET with BS. Fujimoto *et al*. reported that diagnostic accuracy of bone metastasis was comparable in PET and BS.[26] BS is cheaper and more readily available. Furthermore, PET may miss solitary bone metastasis in the skull bone and lower limbs as field of visualization in PET is, usually, from face to upper thigh. However, BS may miss purely osteolytic bony metastases.

Knowledge of the natural history of various cancers and the factors that contribute to distant metastases as well as good judgment are essential for cost-effective treatment planning and decision making with regard to both pre- and post-operative evaluation for distant metastases in cancer of the head and neck. Distant bone metastases are infrequent despite the increasing overall survival of patients with these carcinomas, but should be considered in any patient with a concurrent or past diagnosis of HNSCC. The very short time from discovery of bone dissemination to death in most of these patients should be considered when contemplating operative intervention or radical radiotherapy. As metastasis to osseous tissue is the

second most common presentation of distant metastases in HNSCC, BS is an important and sensitive test. It may be particularly helpful in younger age groups.

CONCLUSIONS

The frequency of bone metastasis in HNSCC in our patient cohort was 0.3%. Though very rare, it should be considered for evaluation in patients of HNSCC especially in younger patients. This needs to be confirmed by well-designed prospective trials.

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