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Bone metastasis in head and neck squamous cell carcinoma – 5-year experience of an Indian Cancer Institute

Diptajit Paul[1], Sheeba Bhardwaj[1], Sumit S. Chatterjee[2], Abhirup Chanda[1]

[1]*Pandit BD Sharma Post Graduate Institute of Medical Sciences, Rohtak, Haryana, India*
[2]*College of Medicine & JNM Hospital, Kalyani, India*

Introduction. Bone metastasis (BM), a common and awful complication of advanced malignancy, is comparatively infrequent in head and neck squamous cell carcinoma (HNSCC). Having a discouraging survival of around 6-months only, BM decreases the quality of life in such patients. We reported 13 cases of BM in HNSCC patients in respect to clinical patterns, treatment modalities and outcome.

Material and methods. This is a retrospective study conducted in a tertiary cancer institute of India. Records of all HNSCC patients reviewed and patients having BM were identified.

Results. Total 13 cases of BM were found over a 5-year period; 5 patients having synchronous BM and the rest had developed metastasis later. Monostotic and polyostotic diseases were found in 8 and 5 patients, respectively, bone exclusive disease was seen in 6 patients only. Overall median survival was 6.7 months.

Conclusions. Palliation seems to be the only option once BM is diagnosed in HNSCC. All of our patients received local palliative radiation, and systemic chemotherapy to increase survival. As there is no standardized treatment for such occurrence, more case series and prospective studies are welcomed.

Key words: bone metastasis, head and neck cancer, monostotic, polyostotic, radiotherapy

Introduction

Bone metastasis (BM) is a dreadful complication of advanced malignancy; incidence of bone involvement by cancerous cells depends mainly on the primary site. Nearly 90% cases of BM are seen in primary breast, prostate and lung cancer [1]. Other relatively less common primary sites include the thyroid, melanoma, kidney and gastrointestinal malignancies [1]. Overall, distant metastasis in primary head and neck carcinoma (HNC) is infrequent [2–4]. Involvement of the bone as a metastatic site, although second in order only after lungs, is relatively rare [3–5]. Few studies state a median overall survival of around 6 months in patients of BM with primary HNC [5, 6]. Advanced local disease burden, multiple metastatic sites and poor performance status (PS) of the patient limit the treatment options in such patients. In this article we report the clinical course of 13 cases of head and neck malignancy with bone metastasis.

The purpose of this study is to report a comparatively rare occurrence, i.e., bone metastasis in squamous cell head and neck carcinoma. Our main objectives were:

- to assess the patient's characteristics and etio-pathological factors,
- to describe the patterns of bone metastasis in HNC,
- to evaluate the treatment outcomes in them.

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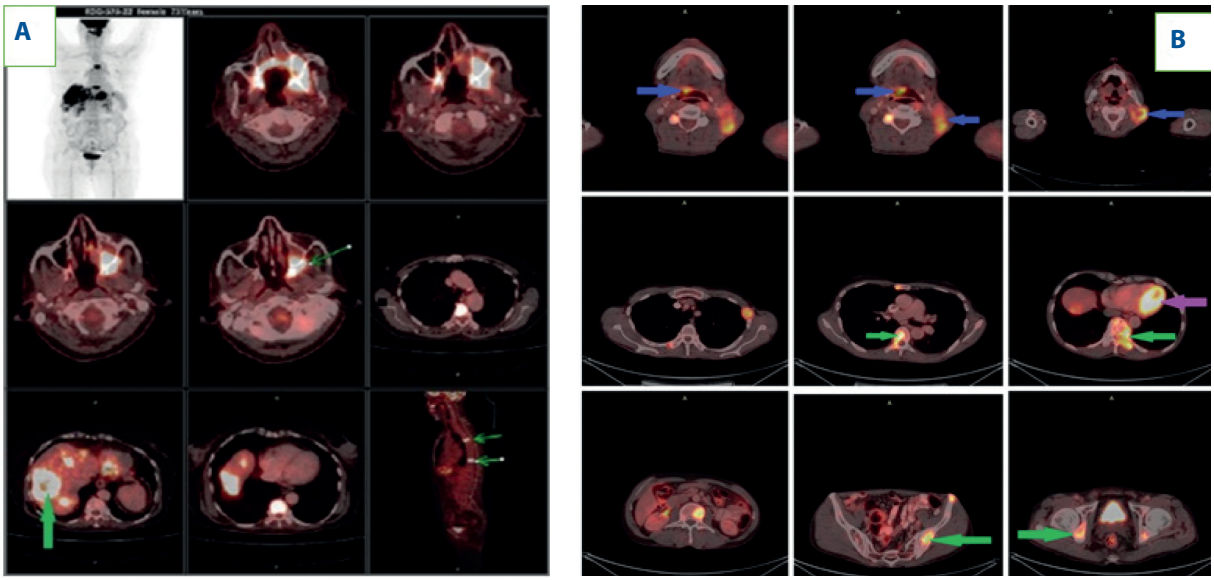

Figure 1. FDG-PET scan showing: (**A**) vertebral metastasis (D5 and D10, green arrow) in a patient with left maxillary sinus squamous cell carcinoma; (**B**) metastatic lesions in multiple pelvic bones, vertebra (green arrow) in a patient of base of tongue squamous cell carcinoma (blue arrow). The purple arrow indicates associated liver metastasis in the same patient

Material and methods

This is a retrospective analysis done in a tertiary cancer institute of India. Permission from the Institutional Review board was taken and informed consent was provided from the live patients as far as possible. Records of all patients of HNC registered in the institute over a period of 5 year were reviewed manually and patients having bone metastasis were identified. Only those patients were included in this series, in whom bone metastasis was confirmed either by histopathological proof (cytology or biopsy) or by imaging (bone scintigraphy or positron emission tomography [PET] scan) (fig. 1). Details of their records were evaluated using analytical software and compared with published literature.

Results

A total of 13 cases of squamous cell carcinoma of the head and neck region associated with bone metastasis are reported in this case series. Details of the patient's characteristics are illustrated in table I. The mean age of presentation was 64.3 years; the range was from 38 to 76 years. Male preponderance was seen in our case series, with male to female ratio being 3.3:1. Most of the patients were from a rural background. The mean duration of symptoms was 5.5 months.

Table II depicts the involved bones in all the patients along with different treatment received by them for primary as well metastatic lesions and final outcome. Bone metastasis was present in 5 out of 13 patients at initial presentation i.e., synchronous metastasis; while, the remaining 8 patients developed bone metastasis during the course of treatment. Overall, axial skeleton involvement by tumour spread was observed. The most commonly involved bone was vertebrae. Single bone involvement, i.e., monostotic metastasis was seen in only 5 patients (38.5%). Radical chemo-radiation to primary tumour was given to 3 patients, all of them were non-metastatic initially and had a good general condition. For metastatic bone lesions, all patients received palliative radiation therapy (RT); mostly to relieve pain and decrease the risk of complication (impending fracture, cord prolapse). Most common RT schedules was 20 Gy/5 fractions over 5 consecutive days. Salvage chemotherapy, to counter the overall local as well metastatic disease burden, in the form of either

Table I. Demographic profile of patients having bone metastasis with head and neck squamous cell carcinoma

Characteristics	Parameters	Number of patients
total patients		13
gender	male	10
	female	3
age	range	38–76 years
	mean	64.3 years
	median	68 years
background	rural	9
	urban	4
addiction	smoker	10
	alcoholic	7
ECOG performance status	0–1	1
	2	4
	3	8
presenting symptoms	difficulty in swallowing	6
	throat pain	5
	neck mass	4
	others	3

ECOG – Eastern Cooperative Oncology Group

Table II. Treatment profile and outcome in patients of bone metastasis with primary head and neck carcinoma

Involved metastatic bone(s)	Duration from primary to bone metastasis (in months)	Primary treatment received		Treatment for bone metastasis		Outcome
		RT	chemotherapy	RT	chemotherapy	
lumbar vertebrae	12 months	70 Gy/35 fr	NACT – TPF CCT – cisplatin	20 Gy/5 fr	salvage – oral Mtx	death
multiple (bilateral pelvic bones, femurs, scapula and sternum)	3 months	20 Gy/5 fr	salvage – TPF	20 Gy /5 fr	salvage – TPF	death
multiple (dorso-lumbar vertebrae, right acetabulum and femur, few bilateral ribs)	at diagnosis	20 Gy/5 fr	salvage – oral gefitinib	20 Gy/5 fr	salvage – oral sefitinib	death
multiple (cervico-dorsal vertebrae, right mandible and occipital condyle)	at diagnosis	20 Gy/5 fr	nil	20 Gy/5 fr	nil	death
right femur	at diagnosis	20 Gy/5 fr f/b supplementary 20 Gy/5 fr	salvage – oral Mtx	8 Gy single session	salvage – oral Mtx	PR (residual disease)
D5 and D10 vertebrae and bilateral 6th ribs	at diagnosis	20 Gy/5 fr f/b supplementary 20 Gy/5 fr	salvage – TPF f/b – oral Mtx	20 Gy/5 fr	salvage – TPF f/b – oral Mtx	PR (residual disease)
multiple pelvic bones, both femur, multiple cervical, dorsal and lumbar vertebrae, left scapula and sternum	at diagnosis	20 Gy/5 fr	salvage – oral Mtx	20 Gy/5 fr	salvage – oral Mtx	death
multiple vertebrae, ribs	3 months	20 Gy/5 fr f/b supplementary 20 Gy/5 fr	salvage – oral Mtx	8 Gy single session	salvage – oral Mtx	death
left femur	8 months	66 Gy/33 fr	CCT – cisplatin salvage – TPF f/b oral gefitinib	20 Gy/5 fr	salvage – TPF f/b oral gefitinib	PR (residual disease)
single vertebrae	5 months	66 Gy/33 fr	NACT-TPF – CCT – cisplatin	20 Gy/5 fr	salvage – oral cyclophosphamide	PR (residual disease)
multiple pelvic bones, sacrum	4 months	20 Gy/5 fr	salvage – oral Mtx	20 Gy/5 fr	salvage – oral Mtx	death
scapula	5 months	44.4 Gy/12 fr (quad shot regimen)	salvage – oral gefitinib	8 Gy single session	salvage – oral gefitinib	death
multiple vertebrae, pelvic bones	at diagnosis	20 Gy/5 fr	salvage – cisplatin	8 Gy single session	salvage – cisplatin	death

CCT – concurrent chemotherapy; f/b – followed by; fr – fractions; Gy – Gray; Mtx – methotrexate; NACT – neoadjuvant chemotherapy; PR – partial response; RT – radiotherapy, TPF – taxane, platinum, 5-fluorouracil

an oral metronomic or intravenous combination regimen, was advised to all the patients according to their general condition and disease status.

A summary of all the cases was illustrated in tabulated format (tab. III). The involvement of the oropharyngeal structure (tonsil, base of tongue, soft palate and lateral pharyngeal wall) was seen in 7 out of 13 patients (fig. 2). Eight patients were in locally advanced stage initially, the rest had metastatic disease. The median survival time was 6.7 months. Four patients were alive at the time of reporting this series; however, they have residual disease and were on oral metronomic agents.

Discussion

The development of bone metastasis in any malignancy is associated with poor survival outcome and poses a therapeutic challenge for the treating oncologist. BM usually leads to a dismal prognosis and affect patients' quality of life [7, 8]. Once BM is diagnosed, palliative treatment of symptoms becomes the desired treatment. On average, 20% of cases of head and neck squamous cell carcinoma metastasize to distant organ throughout the time of the disease's course [2–4, 9]. Bone is the second-most frequent organ involved by metastasis, the first being the lungs, and it accounts for nearly 15–39% of distant metastases

Table III. Summary of important parameters in bone metastasis patients with primary head and neck squamous cell carcinoma

Primary site – subsite	Histopathological grade (differentiation)	TNM stage at presentation	Type of bone metastasis	Bone-exclusive metastasis	Survival after bone metastasis diagnosed
oropharynx – tonsil	MDSCC	T3N2M0 (IVA)	monostotic	no (lung, liver)	5 months
oropharynx – base of tongue	PDSCC	T3N3M0 (IVB)	polyostotic	yes	3 months
oropharynx – tonsil and soft palate	PDSCC	T4N2M1 (IVC)	polyostotic	yes	5 months
oropharynx – tonsil	MDSCC	T4N1M1 (IVC)	polyostotic	yes	2 months
hypopharynx – post cricoid region	MDSCC	T3N2M1 (IVC)	monostotic	no (abdominal lymph nodes, ascending colon)	>24 months
para nasal sinus – left maxillary sinus	MDSCC	T4N0M1 (IVC)	polyostotic	no (liver)	6 months
oropharynx – base of tongue	PDSCC	T4N3M0 (IVB)	polyostotic	no (lung)	3 months
larynx – supraglottis	PDSCC	T3N2M0 (IVA)	polyostotic	yes	4 months
oral cavity – anterior tongue	MDSCC	T3N1M0 (III)	monostotic	yes	9 months
hypopharynx – posterior pharyngeal wall	PDSCC	T2N2M0 (IVA)	monostotic	no (liver)	7 months
oropharynx – tonsil and base of tongue	MDSCC	T4N3M0 (IVB)	polyostotic	no (lung, liver)	5 months
oropharynx – lateral pharyngeal wall	PDSCC	T3N2M0 (IVA)	monostotic	no (lung)	8 months
hypopharynx – right pyriform sinus	PDSCC	T3N2M1 (IVC)	polyostotic	yes	4 months

MDSCC – moderately differentiated squamous cell carcinoma; PDSCC – poorly differentiated squamous cell carcinoma

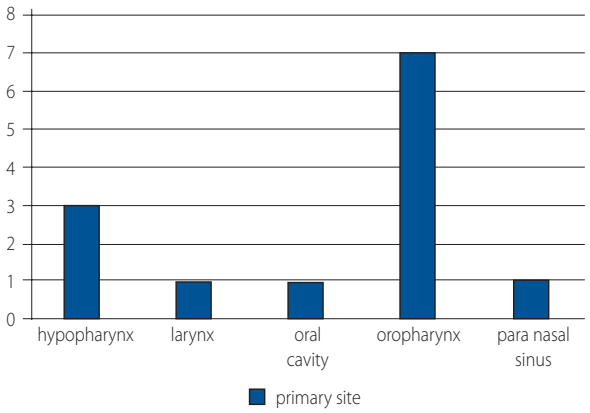

Figure 2. Distribution of all patients according to primary site

cases [3–5, 10, 11]. Nowadays, in Western countries, routine use of fluoro-deoxy-glucose positron emission tomography (FDG-PET) scan and bone scintigraphy as part of metastatic work up in HNSCC has increased the detection rate of clinically relevant BM [11, 12]. Primary HNC having bony involvement has a relatively shorter survival compared to that from primary breast and prostate malignancy [5–7].

The frequency of osseous dissemination in HNC depends greatly upon the primary tumor size (T) and regional nodal (N) involvement. T and N staging also affects the prognosis of such patients [13]. It is reported that the primary site (hypopharynx *vs.* others) and size (less in T1 tumors), tumor grade (well *vs.* moderately *vs.* poorly differentiated), nodal status (more in N3 node and highly prevalent in disease with extra-capsular extension), prognostic stage (higher incidence in stage IV disease than others) are contributory risk factors for the development of distant bone metastasis [4, 14]. As far as the primary site of the tumor is concerned, the prevalence of distant metastasis, bone as well as other organs, is highest in the tumor of the hypopharynx, followed by oropharynx (base of tongue) [4, 15]. Bhandari et al. [16] reported that among different primary sites of head and neck tumors, the hypopharynx is more likely to develop distant metastases with a probability of 20.5–60% and thus has a poorer prognosis. Outcomes in metastatic HNSCC also have a significant connection with old age, poorly differentiated tumors, higher nodal stage, race (more in black Afro-Americans) and multiple metastatic sites [14, 17].

Our study revealed that most of the cases have high tumors (T3 and T4 cases mostly, only 1 patient had T2 disease) and nodal stage (≥N2 in 10 patients) at the time of presentation. Except a single case, all the patients' neck nodes revealed tumor infiltration and were stage IV disease. This correlates well with other studies [4, 13, 14]. In our study, most patients had primary lesion in the oropharyngeal region, which is not matched with the global documentation of higher metastatic cases in hypopharyngeal cancer [4, 15]. This is most probably due to the relatively higher incidence of carcinoma oropharynx in our institution. In our study, distribution of MDSCC and PDSCC are nearly equal, 6 and 7 cases respectively. Most patients presented in advanced age with the median age being 67 years.

In general, the axial skeleton is the most prevalent site of bone metastasis involving the spine, pelvis and ribs frequently; the lumbar spine is the single most frequent site as documented in literature [1, 18]. Involvement of bone from primary HNSCC is thought to be the result of a systematic spread of tumour cells and the site distribution matches the red marrow distribution in the skeletal system [13, 19, 20]. The patient may present with pain originating from the bone as well as associated skeletal-related events (SREs) such as fractures, cord compression, and, obviously, hypercalcemia. Grisanti et al. [21] reported skeletal related events (SRE) were in 9% of nasopharyngeal cancer cases (NPC) and in 27% of non-NPC patients. As a result, subsequent median survival decreased from 25 months in nasopharyngeal cancer patients to 6 months in non-NPC patients, respectively [21]. They also opined that bone-directed treatments (bisphosphonates and denosumab) and radiotherapy are good options in improving survival for these patients.

Radiological changes of BM from HNSCC are variable. Skeletal metastasis invariably incites the process of bone resorption and bone formation, and depending upon the dominant process, radiologic appearance can be lytic, sclerotic or mixed type. Al-Bulushi et al. [12] and Basu et al. [19] recorded that more than 80% of cases of BM showed an osteolytic lesion; while Nakanishi et al. [10] and Kim et al. [20] documented osteoblastic and inter-trabecular types in nearly 60% of cases of their analyses. Prognosis in metastatic disease is determined by multiple factors. In a large case series over an 11-year period, single site BM, a good PS (ECOG 0-1) and a systemic chemotherapy receiver were found to be independent factors for comparatively prolonged survival; yet the median survival remained 11 months in that analysis [22]. It is obvious that a patient with favourable general condition (good PS) is likely to have a lower chance of lung infection and a greater stamina to tolerate more aggressive systemic therapy. A comparatively fair PS also suggests that the BM may not be that extensively distributed so as to hamper daily activities [23–25].

Recent published articles have mentioned that neither metastasis of monostotic origin nor bone-exclusive metastasis are rare in HNC; with the former having a frequency of 24–50% and the latter of 24–46% [12, 19, 20]. Suzuki et al. [5] found favourable prognosis in patients with bone-exclusive and monostotic metastases compared with patients with multi-organ or polyostotic metastases, with an average survival time of 18.2 months and 5.7 months, respectively.

Bony dissemination as a result of distant metastasis in HNC are crucial in clinical practice because they serve as a major cause of misery in such patients, such as severe refractory pain, pathological fractures, spinal cord compression and hypercalcemia. Palliation with the help of both radiation and salvage chemotherapy is the routine therapeutic strategy for patients with HNSCC who have distant organ involvement; platinum-based systemic chemotherapy has been reported to improve outcomes to a certain degree [6, 26–29]. Radiotherapy to the involved bone, either single session or multi-fractionation regimen, is usually employed in all BM patients, along with systemic chemotherapy or bone directed treatment (zoledronic acid) [21, 26]. Once BM develops in these patients, median survival time becomes significantly less [2–4].

The management strategy of such patients having bone metastases, requires a multidisciplinary team from different fields including but not limited to medical and radiation oncologists, orthopedicians, neuro-vascular surgeons, interventional radiologists and pain specialist to dispense the best therapeutic approach, appropriate measures to prevent further damage, and the treatment of SREs. A few classes of drugs like bisphosphonates and denosumab, have bone-directed mechanism of action and revealed to decrease the risk of SREs remarkably in patients having bone metastases from common solid primaries like prostate, breast and lung cancer, and multiple myeloma [30]. The addition of zoledronic acid to chemotherapy in patients with nasopharyngeal carcinoma having distant osseous involvement was correlated with a lower rate of symptomatic skeletal events and better survival in comparison to chemotherapy alone [31]. Patel et al. [32] showed that surgery and radiation therapy, when used in patients with distant metastatic disease, can improve survival. Operative intervention, in terms of decompression surgery in spinal cord compression cases or internal fixation in pathological fractures, can be performed in BM patients when non-surgical therapies have failed. Compared with lung metastases and locoregional recurrence, systemic chemotherapy is more effective in bone involvement from HNSCC. This can be justified by richer blood supply of bone marrow compared with the lung and local area. Sakisuka et al. [22] reported the statistically significant prognostic influence of systemic chemotherapy in HNC patients with BM; unfortunately, this influence is limited on survival. This was also pointed out by Suzuki et al. [5] that neither chemotherapy nor radiotherapy could significantly prolong the overall survival of HNC patients with BM. Therefore, the adverse effects of adding systemic chemotherapy in patients of BM from HNSCC should be carefully looked at and the decision should be taken on an individual basis.

In our study, most patients presented in advanced stage and received palliative radiotherapy to the primary site and bone metastasis. Incidence of synchronous bone metastasis and bone-exclusive metastasis were 38.5% and 46%, respectively in our analysis. Both of these values are similar to analysis done by another Asian country [22]. Around 40% of cases were monostotic metastases and the rest showed polyostotic metastasis. Median survival for the patients with solitary bone metastasis was 11 months, while in patients with multiple bone metastases it was only 4 months. The overall median survival value closely matched with the other published articles [5]. Nine patients expired due to the progression of the disease; surprisingly one patient, with maintenance oral metronomic chemotherapy, is still regularly followed up with more than 2 year survival.

Conclusions

Bone metastasis in primary HNSCC is an occurs infrequently. Palliation is the only option after BM occurs in these patients. Survival is usually discouraging. However, high palliative radiotherapy to both the local and metastatic site as well as systemic chemotherapy can improve their quality of life as well as survival. More case series and prospective trials in this topic will highlight the standard treatment guidelines for these patients.

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Diptajit Paul
Pandit BD Sharma Post Graduate Institute of Medical Sciences
Rohtak, Haryana
124001 Rohtak, India
e-mail: diptajitpaul.91@gmail.com

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