Incidence of Distant Metastasis in Head and Neck Cancer: A Hospital based Study

Prakriti Dayal[1], Ravikiran Ongole[2], Junaid Ahmed[3], Ceena Denny E[4], Deepali Agrawal[5]

[1]Formerly Post Graduate Student, [2]Professor and Head, [3]Associate Dean and Professor, [4]Associate Professor, [5]Post Graduate Student, Oral Medicine and Radiology, Manipal College of Dental Sciences, Mangalore, Manipal Academy Higher Education, Manipal, Karnataka, India

Abstract

Aims and Objectives: To study the incidence of distant metastasis to bone and soft tissues from head and neck cancers and to assess the primary site of head and neck cancer, its clinical staging and its correlation with the site of distant metastasis.

Materials and Methods: Medical records of patients admitted for management of head and neck cancers in Medical and Radiation Oncology for a period of 6 years, were assessed for primary site of the tumour, staging, histopathological diagnosis and the site of distant metastasis.

Results: Out of 125 patient records evaluated, the incidence of distant metastasis was 15.2%. Majority of the patients (60%) presented at Stage III and IV of the disease. Thyroid and tongue malignancies showed the highest incidence of distant metastasis and this incidence was most common in the 5th and 6th decades of life. The most common sites of distant metastasis were to the bones (31.6%) and lungs (15.8%).

Conclusion: Cancers of the head and neck is typically loco-regional in nature, with metastasis to cervical nodes. Distant metastasis, though uncommon, may adversely impact the survival and quality of life of the patient. Understanding the risk factors and incidence for metastatic head and neck cancers may be useful in treatment planning and follow-up protocols for newly diagnosed patients.

Keywords: *Head and neck cancer, distant metastasis, incidence, staging, primary tumor*

Introduction

Cancer remains one of the main reasons of morbidity and mortality globally. A recent Lancet survey draws an alarming picture of increasing mortality (<5lakhs) due to cancer in India in 2010.[1] Among, 1 million new cases reported yearly in India, two hundred thousand affects the craniofacial region[2]. In the global scenario, the prevalence of cancer affecting the craniofacial region is six times more prevalent in India[2], owing to the extensive use of tobacco and its related products and varying lifestyle habits. Cancers of craniofacial region is considered predominantly a loco-regional disease, commonly metastasizing to the lymph nodes of the cervical region. Metastasis to distant sites usually occurs in later stages of the disease progression[3].

Distant metastasis is an intricate process of selection of a certain subpopulation of tumour cells for survival in an unfamiliar and hostile micro-environment.[3] These metastatic tumor cells possess the capacity to invade the basement membrane, extravasate and survive in the systemic circulation. Following which, they invade the microvascular walls and proliferate in a foreign distant organ. Numerous molecular adaptations involving numerous cellular processes such as adhesion,

Corresponding Author:
Ravikiran Ongole
Professor and Head, Oral Medicine and Radiology
Manipal College of Dental Sciences, Mangalore
Manipal Academy of Higher Education
Light House Hill Road, Mangalore 575001
ravikiran.ongole@manipal.edu
+919448430387

proteolysis, apoptosis and angiogenesis occur in order to begin the metastatic disease.[4,5]

The overall clinical frequency of distant metastases in craniofacial malignancies is relatively less in comparison to others, varying from 4.3% to 26% [6,7,8,9]. Leemans et al (1993) mentioned that in autopsy studies there was increased prevalence (40-57%) of metastases to distant areas associated with craniofacial cancer[6]. Lungs and bones are the commonest sites of metastasis from craniofacial cancer[10]. The other areas of metastatic deposits are in the liver, mediastinum, brain and skin although unexpected sites of spread such as cardiac metastasis from carcinoma of the tongue[11,12] and other primary tumours to the peritoneum, oesophagus and spleen, have also been noted. Sites of bone metastases have been found mostly in the vertebrae, skull and ribs[2,10]. This varying rate of metastasis could be influenced by the site of tumour, staging of neoplasm and the degree of involvement of regional nodes[2,3].

Distant metastasis adversely impacts the survival and standard of living in cancer patients. A thorough knowledge about the possible factors for metastatic craniofacial cancers is useful in planning treatment and formulating protocols for follow-up of recently diagnosed patients. The present study is aimed to study the incidence of distant metastasis to bone and soft tissues from head and neck cancers also with an objective to assess the site of primary cancer in craniofacial region, its clinical staging and its correlation with the site of distant metastasis.

Material and Methods

Archival data from the medical records of all patients with cancer in the craniofacial region admitted in the Departments of Medical and Radiation Oncology in the past 6 years were assessed. Patients with clinical and histological diagnosis of malignancy of known primaries of the craniofacial region were included in our study.

The primary site, staging of the tumour, histopathological diagnosis and the site of distant metastasis were recorded from the archival data.

Results

A total number of 125 patient records were assessed. Socio-demographic analysis revealed 44.8% (56) of the study group to be women and 55.2% (69) to be men, aged 10-80 years.

Of all head and neck cancers, thyroid malignancies showed the highest number (34.4%), followed by the maxillary bone and sinus (11.2%), tongue (8.8%), buccal mucosa (8.8%), lymph nodes (7.2%) and the alveolus (4.8%). (Table 1) Among thyroid cancers, papillary variant of thyroid cancer showed the highest percentage (27.2%), while in oral cancers, squamous cell carcinoma (SCC) recorded the highest percentage (well differentiated SCC=12%, whereas poorly differentiated SCC=15.2%). 75 out of 125 patients (60%) presented in advanced stage of the disease (combined Stage III and IV). All patients had been treated with either surgery or chemotherapy or radiotherapy or a combination.

The incidence of distant metastasis recorded in the 125 patient records was 15.2% (19 patients). These metastatic lesions were discovered either incidentally or due to new presenting complaints such as bone pain, cough, loss of appetite or lassitude. A thorough physical examination followed by an appropriate investigation such as a radionuclide scan, CT, MRI, chest x-ray, liver/ thorax ultrasonography was advised.

When comparing the metastatic pattern in relation to the primary site, we found that thyroid malignancies metastasized in 12 cases, tongue in 2, and 1 each was observed from the alveolus, intraosseous mandible, nasal cavity, lymph node and the palate.(Graph 1) Spread of metastasis was more in multiple areas of the same site than localization to a single lesion in a site. The sites of metastasis recorded were to the bones (6 cases, 31.6%), lungs (3 cases, 15.8%), liver (2 cases, 10.5%), to the mid-brain (1 case, 5.3%) and oesophagus (1 case, 5.3%). Lesions were also seen to be metastasizing in a combined manner to lungs and liver (4 cases, 21.1%), lung and bone (1 case, 5.3%), and lungs, liver and bone (1 case, 5.3%). (Table 2) When comparing sites of primaries with sites of metastasis, we found thyroid and tongue malignancies metastasizing to almost all the above mentioned-locations. (Table 3)

Comparing risk factors and its correlation between age of patients and metastasis, revealed that metastasis more common in the 50-60 years age group, followed by 40-50 year age group (Table 4). Only 24% patients'

records had a habit history recorded, out of which 33% patients had a combined habit of smoking cigarette/ beedi, chewing gutkha and consuming alcohol. But a proper correlation between the habit history and incidence of distant metastasis could not be arrived at.

Table 1: Primary site of tumour

Primary site	Frequency	Percentage
Lip	3	2.4
Buccal mucosa	11	8.8
Tongue	11	8.8
Alveolus (maxilla/mandible)	6	4.8
Maxilla and maxillary sinus	14	11.2
Mandible Intraosseous	2	1.6
Nose/nasal cavity	2	1.6
Thyroid	43	34.4
Cervical lymph node	3	2.4
Unknown origin	11	8.8
Nasopharyngeal/ tonsils/ arythenoids, larynx	9	7.2
Palate	2	1.6
Floor of the mouth	1	0.8

Table 2: Sites of Metastasis

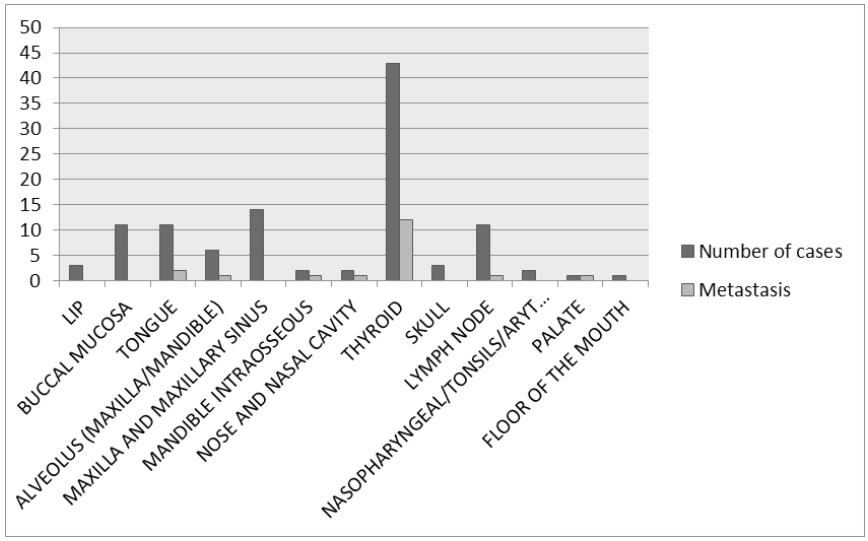
Sites	Frequency	Valid percent
Lung	3	15.8
Liver	2	10.5
Bone	6	31.6
Midbrain	1	5.3
Esophagus	1	5.3
Lung, Liver	4	21.1
Lung, Bone	1	5.3
Lung, Liver, Bone	1	5.3

Table 3: Correlation between primary site of tumor and site of metastasis

Site à Primary site â		Lung	Liver	Bone	Others	Lung, Liver	Lung, Bone	Lung, Liver, Bone
	Tongue	1	0	0	0	0	0	1
	Alveolus	0	0	1	0	0	0	0
	Mandible	0	1	0	0	0	0	0
	Nasal cavity	1	0	0	0	0	0	0
	Thyroid	1	1	4	1	4	1	0
	Lymph node	0	0	1	0	0	0	0
	Palate	0	0	0	1	0	0	0
Total		3	2	6	2	4	1	1

Table 4: Age and metastasis

Age		Frequency	Percent
	<20	5	4.0
	20 -30	6	4.8
	30 -40	13	10.4
	40 -50	31	24.8
	50 -60	34	27.2
	60 -70	26	20.8
	>=70	10	8.0
	Total	125	100.0



Graph 1: Primary site of tumour and metastasis

Discussion

Due to the rich lymphatic drainage in the orofacial region metastasis to the lymph nodes in the immediate vicinity is a common feature associated with head and neck cancers.

Recent reviews have suggested a genetic drive towards early metastatic diffusion to the lymph nodes in the neck[13]. According to the Seed soil theory of metastasis by Stephen Paget, the ''seeds'', or tumor cells grew in the microenvironment of certain organs, ''the soil.''[14,15] Few subpopulations of tumour cells acquire the capacity to invade the surrounding structures and basement membrane of the primary tumour and the local vasculature. Once in the systemic circulation, they must survive and invade the microvasculature of a distant organ. These processes require various molecular level interactions such as activation of receptor tyrosine kinases epidermal growth factor receptor (EGFR), signal transducers and activator of transcription 3 (Stat3) as well as nuclear factor-κB (NF-κB)[4].

Crile (1923) reported 1% prevalence of distant metastases in an autopsy series of craniofacial cancers[16,17]. Series based on clinical material have an incidence varying from 5.3% to 23.7%, whereas autopsy series report distant metastases in 17% to 57% of patients. The prevalence of distant metastasis in cancers of craniofacial region is low when compared to breast and lung cancer (3%-50%).[3] This variation may be due to several reasons like: differing in the assessment of parameters, such as tumour characteristics (primary tumour sites and staging of disease); various treatment modalities, the period of diagnosis of distant metastasis (clinical examination, during the course of disease or during autopsy); staging techniques and the length of follow-up.

Metastatic potential can be an inherited feature of many tumours or can present as an acquired characteristic in the process of tumorigenesis. Accordingly, it may present late onset of the disease or in certain cases, may be a presenting symptom. The prevalence before initial treatment could range from 5% to 17%.[3]

In this population of 125 patients, over a 6-year follow-up period, 15.2% (19) of the patients were found to have distant metastasis, none with an initial presentation of metastasis. These findings find correlation with studies by various studies. Probert and associates (1974) while assessing both clinical and autopsy cases among 749 patients found 12% distant metastasis and also noted that the large lesions were most likely to metastasize.[10] The study of Merino et al. (1977) stated that 10.9% of cancer patients had distant metastases, but the drawback of the study was that it did not take loco-regional status into account[8]. De Bree et al (2000) in his retrospective study among 101 cancer patients scheduled for surgery found that 17% had distant metastasis.[18] Various other authors have reported varying incidence of distant metastasis to be: 12%,2.82%,35%[19,20,21] respectively.

Though studies related to cancer in the craniofacial region have reported primaries in various oral and hypopharyngeal sites, we have not come across thyroid malignancies being included in any study with cancer associated with craniofacial region. Considering the high incidence of thyroid cancer among the Indians and the initial presenting complaint of dysphagia and swelling in the neck, we included various forms of thyroid cancers in our study for a more comprehensive view of cancers of the craniofacial region. In our study, we found an increased frequency of distant metastasis in thyroid cancers when compared to oral squamous cell cancers.

According to Kotwall et al, [22]the common sites of distant metastasis in descending order were: lungs (80%), mediastinal nodes (34%), liver and bone (31% each). Bree et al in their study reported metastasis to lung (12 %), bone metastases (4%) liver metastases (1%)[18]. Our study results were similar to those reported by Merino et al (1977)[8] where they found that the sites of metastasis from primaries originating in the nasopharynx were bone (54%), followed by lungs (23%). Study by Bhandari et al (2013) [2] also showed bone (skull, humerus, femur) to be the most common site of metastasis. However, in our study, bone metastasis was seen originating primarily from the thyroid and the alveolus. Also, vertebral metastasis was common in comparison to other bones.

Cancer research in the past were more focussed on primary tumor features, but in the recent the importance or the focus is more on tumor -specific factors and quality of life of cancer patients.Liao et al[22] in 2006 reported the age at highest risk of metastasis $\leq$ 40 years of age (in cases of tongue cancers) whereas in our study, we found

the age group of 50-60 years to be more commonly affected. Our study also showed metastasis more commonly in females than males. That could be due to the higher number of thyroid malignancies recorded in our study, and a female preponderance of thyroid malignancies. In our study higher rates of metastasis was found in thyroid malignancies. A univariate analysis for distant metastasis of thyroid cancer done by Machens et al revealed distant metastasis in 17 patients (12.69%) from follicular variant of thyroid carcinomas, 16 patients of papillary carcinoma of thyroid (5.6%) and in 40 patients (13.5%) of medullary carcinoma of thyroid.[24] The proposed hypothesis of distant metastasis in these cases is through direct accession of primary tumour cells to extra-thyroidal tissues and the rich blood vessels and an indirect pathway through dissemination via lymphatic channels.

Autopsy series by Kotwall et al.[22] found a correlation between the presence of distant metastasis and primary tumor site. Highest incidence of tumor metastasis in descending order was hypopharynx (63%), base of tongue (53%) and anterior tongue (50%). Papac et al[17] revealed metastasis to the tongue to be 2%. In our study, we found tongue to be the site of metastasis in 10.5% of cases. Our study also found that 60% of the patients who presented with advanced stage of the disease (Stage III and Stage IV) showed metastasis to various sites. This is in accordance with studies by Bhandari et al[2], who reported that 72.7% of cases with metastasis had presented initially with Stage III and IV.

Conclusion

Patients with advanced staging of the cancer have a higher incidence of distant metastasis. Thus such patients should be followed up with proper treatment protocols to evaluate any signs of distant metastasis. A detailed recording of patient demographics, lifestyle habits and tumour characteristics is a pre-requisite for further epidemiologic studies and formulation of a protocol of treatment and follow-up of head and neck cancer patients. Though numerous studies have been done to assess rates of metastasis from nasopharyngeal cancer, data on incidence of distant metastasis from thyroid cancers is lacking. We propose the inclusion of thyroid malignancies along with oral, nasopharyngeal and hypopharyngeal malignancies to study the incidence rates of distant metastasis from the head and neck region, for a more comprehensive data so as to plan appropriate treatment strategies. We also believe a thorough habit history and assessment of nodal status will give an insight into the correlation between development of cancer and distant metastasis to the risk factors.

Funding- Authors declare no funding or source of grant.

Ethical Clearance- Taken from Institutional Ethics committee of MCODS, Mangalore

Conflict of Interest - Nil

References

1. Dikshit R., Gupta PC, Ramasundarahettige C, Gajalakshmi V, Aleksandrowicz L, Badwe R. Cancer mortality in India: a nationally representative survey. Lancet 2012; 379 (9828): 1807-16.
2. Bhandari V, Jain RK. A retrospective study of incidence of bone metastasis in head and neck cancer. J Can Res Ther 2013; 9(1): 90-3.
3. Takes RP, Rinaldo A, Silver CE, Haigentz M Jr., Woolgar JA, Triantafyllou A. Distant metastases from head and neck squamous cell carcinoma. Part I. Basic aspects. Oral Oncol 2012; 48(9): 775–9.
4. Bhave SL, Teknos TN, Pan Q. Molecular parameters of head and neck cancer metastasis. Crit Rev Eukaryot Gene Expr. 2011; 21(2): 143–53.
5. Ellis LM, Fidler IJ. Angiogenesis and metastasis. Eur J Cancer 1996;32(14):2451–60.
6. Leemans CR, Tiwari R, Nauta JJ, van der Waal I, Snow GB. Regional Lymph Node Involvement and Its Significance in the Development of Distant Metastases in Head and Neck Carcinoma. Cancer Jan 1993; 71(2): 452-6.
7. Vikram B, Strong EW, Shah JP, Spiro R. Failure at distant sites following multimodality treatment for advanced head and neck cancer. Head Neck Surg 1984; 6(3):730-3.
8. Merino OR, Lindberg RD, Fletcher GH. An analysis of distant metastases from squamous cell carcinoma of the upper respiratory and digestive tracts. Cancer 1977; 40(1):145-51.
9. Bhatia R, Bahadur S. Distant metastases in malignancies of the head and neck. Laryngol Otol 1987; 101(9):925-8.

10. Probert JC, Thompson RW, Bagshaw MA. Patterns of spread of distant metastases in head and neck cancer. Cancer 1974; 33(1): 127-33.
11. Onwuchekwa J, Banchs J. Early Cardiac Metastasis from Squamous Cell Carcinoma of the Tongue in 2 Patients. Tex Heart Inst J 2012;39(4):565-7.
12. Kavanagh MM, Janjanin S, Prgomet D. Cardiac Métastases and a Sudden Death as a Complication of Advanced Stage of Head and Neck Squamous Cell Carcinoma. Coll Antropol. 2012;36 Suppl 2: 19-21.
13. Leemans CR, Braakhuis BJM, Brakenhoff RH. The molecular biology of head and neck cancer. Nat Rev Cancer 2011;11(1):9-22.
14. Paget S. The distribution of secondary growths in cancer of the breast. Cancer Metastasis Rev 1989;8(2):98–101.
15. Paget S. The distribution of secondary growths in cancer of the breast. Lancet 1889;1:571–3.
16. Crile GW. Carcinoma of the jaws, tongue, cheek, and lips. Surg Gynecol Obsiei 1923; 36:159-184.
17. Papac RJ. Distant Metastases from Head and Neck Cancer. Cancer 1984; 53(2):342-5.
18. de Bree R, Deurloo EE, Snow GB, Leemans CR. Screening for distant metastases in patients with head and neck cancer. Laryngoscope 2000;110(3): 397–401.
19. Jackel MC, Rausch H. Distant metastasis of squamous epithelial carcinomas of the upper aerodigestive tract. The effect of clinical tumor parameters and course of illness. HNO 1999;47(1): 38–44.
20. Kuperman DI, Auethavekiat V, Adkins DR, Nussenbaum B, Collins S, Boonchalermvichian C. Squamous cell cancer of the head and neck with distant metastasis at presentation. Head Neck 2011; 33(5): 714-8.
21. Hauswald H, Simon C, Hecht S, Debus J, Lindel K. Long-term outcome and patterns of failure in patients with advanced head and neck cancer. Radiat Oncol. 2011 Jun 10;6:70.
22. Kotwall C, Sako K, Razack MS, Rao U, Bakamjian V, Shedd DP. Metastatic patterns in squamous cell cancer of the head and neck. Am J Surg 1987;154(4):439–42.
23. Liao CT, Wang HM, Hsieh LL, et al. Higher distant failure in young age tongue cancer patients. Oral Oncol 2006;42(7):718–25.
24. Machens A, Holzhausen HJ, Lautenschlager C, Thanh PN, Dralle H. Enhancement of Lymph Node Metastasis and Distant Metastasis of Thyroid Carcinoma - A Multivariate Analysis of Clinical Risk Factors. Cancer 2003; 98(4): 712–9.