Original Article - Retrospective Study

Impact of Early Diagnosis of Maxillofacial Metastases on Treatment and Patient Outcomes - A Retrospective Study

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Abstract

Introduction: Maxillofacial metastases from distant primary sites account for less than 1% of cancer in the head-and-neck region and are often misdiagnosed as benign or inflammatory conditions. The purpose of this study was to describe the clinical characteristics of patients with maxillofacial metastases, treatment and outcomes. **Materials and Methods:** Subjects with head-and-neck cancer were identified from the institutional database. Descriptive statistics were employed. **Results:** Of 532 patients with head-and-neck cancer between 2008 and 2020, 15 (2.8%) had histologically verified metastatic lesions, of which 53.33% males with a mean age of 69 years. The median time from symptom onset to diagnosis was 17 days (range: 7–60). The mandible was the most common location (40%), followed by the parotid gland (33.33%) and maxilla (13.33%). Adenocarcinoma was the most frequent histology (60%), and half of the patients had extraoral manifestations. Tumour origin was gastrointestinal, lung (33.33% each), prostate (20%) and breast (13.3%). No predilection for tumour type or histology and location were seen. Radiographic features were non-specific, with computed tomography (CT) demonstrating periosteal reaction, bone expansion and lytic lesions and high variability in Positron Emission Tomography (PET) standardised uptake value (minimum: 2.0, maximum: 10.93 and mean: 4.14). Diagnosis led to altered treatment in 60%, more in extraoral than intraoral manifestations (71% vs. 37.5%); 40% received radiotherapy, 20% systemic treatment and none underwent surgery. Over half of the patients passed away within 6 months, median survival was 5 months, shorter in patients with intraoral than extraoral disease (3 vs. 13.2 months, $P < 0.05$). **Discussion:** Maxillofacial metastases have elusive manifestations and often warrant specific treatment. Prospective data should evaluate associations between timely diagnosis and symptomatic improvement and survival.

Keywords: Adenocarcinoma, cancer early diagnosis, head-and-neck cancer, metastasis, oral cancer, squamous cell carcinoma

Introduction

Metastases of systemic malignancies in the maxillofacial region are rare, accounting for approximately 1% of all newly diagnosed head-and-neck cancer (HNC).[1-3] Although these may arise from different distant locations, breast, prostate and lung cancer are most frequent.[4] Within the maxillofacial region, the mandible is the most common site to harbour metastases, particularly the angle, premolar and condylar parts.[5] Symptoms are non-specific and include swelling and pain, but a complaint of paraesthesia warrants higher suspicion for malignancy.[6] Due to the often misleading clinical presentation, it is recommended to consider potential metastatic lesions when evaluating other benign and inflammatory lesions, as well as other primary malignancies.[7,8] Moreover, they should be verified histologically to confirm similarity to primary tumour, are often diagnosed months after their appearance and portend a poor prognosis, with up to 90% mortality.[9]

The undertaking of this study was based on three main hypotheses. First, metastatic lesions to the maxillofacial region are highly misdiagnosed owing to other more likely diagnoses in the population of oncological patients. Second,

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their distribution within the maxillofacial area is not well understood with regard to patterns and routes of cancer spread. Finally, information from tissue biopsies may alter the treatment delivered to patients. The aim of our study was to explore the hypotheses by characterising proven metastases harboured within the maxillofacial region by histological type and origin of the primary tumour and subsequently to explore treatment modalities and patient outcomes.

Materials and Methods

This retrospective study was conducted between 2008 and 2020, in the Department of Oral and Maxillofacial Surgery of Rambam Health Care Campus. Files of all patients admitted with HNC were initially evaluated. Those with histologically proven metastases and known distant primary tumour were included in the study. Data concerning patient demographics, site of primary tumour and metastasis, histology, symptoms, imaging report, treatment and outcomes were collected from the hospital database. Oral cavity lesions were registered in appropriate subsite division. Extraoral lesions were registered by the tissue or organ involved. Time elapsed between the report of symptom onset to the diagnosis of metastasis was also recorded. Treatment modalities and protocols were examined, and survival outcomes were determined. All patients included had to have undergone either head-and-neck focussed computed tomography (CT) or total-body positron emission tomography (PET) scans. Patients with current or past primary HNC, history of osteomyelitis of the jaws or previous radiation to the head and neck area, were excluded.

Descriptive statistics were performed, along with evaluation of clinical and demographic variables using Grubb's and paired *t*-tests. Correlation between variables was examined with univariate regression models. The level of significance was 5%. The study was approved by the institutional ethics committee (RMB-0458-22) and granted a waiver for patient consent due to its retrospective nature.

Results

A total of 532 HNC patients were identified in the hospital database. Of these, 15 patients (2.8%) met inclusion criteria. Clinical, demographic and treatment-related parameters are presented in Table 1. Time to diagnosis ranged from 1 week to 60 days with an average of 22 days and a median of 17 days. Six patients (40%) experienced symptoms including trismus and swelling with no paraesthesia reported. Seven patients (46.67%) had intraoral manifestations, ranging from classic oral ulcerations similar to squamous cell carcinoma (SCC) lesions, to diffuse erythroplakia and exophytic lesions with or without local swelling [Figure 1]. Eight patients (53.33%) had extraoral presentation, which manifested as diffuse swelling in the pre-auricular area and angle of the mandible resulting from metastatic lesions in the ramus area and the parotid gland. These lesions were diagnosed 5 days later on average than the intraoral metastases. The distribution of the primary tumour

Table 1: Patient, tumour and metastases characteristics

Maxillofacial metastasis (*n*=15)	*n* (%)	*P*
Patient demographics		
Age at diagnosis (years)		
Mean (SD)	69 (6.14)	
Median (range)	78 (43–88)	
Gender, *n* (%)		
Male	8 (53.33)	
Female	7 (46.67)	
Ethnicity, *n* (%)		
Jewish	8 (53.33)	
Arab	7 (46.67)	
Time to diagnosis (days)*		
Average	22	
Median (range)	17 (7–60)	
Intraoral lesion	18.3	
Extraoral lesion	23	
Manifestation, *n* (%)		
Extraoral	8 (53.33)	
Intraoral	7 (46.67)	
Primary tumour		
Primary tumour location, *n* (%)		
Lung	4 (26.67)	>0.05
Breast	2 (13.33)	
Prostate	3 (20)	
Kidney	1 (6.67)	
Skin	1 (6.67)	
GI	4 (26.67)	
All locations	15 (100)	
Primary tumour histology, *n* (%)		
Adenocarcinoma	9 (60)	<0.05
SCC	3 (20)	
Undifferentiated	1 (6.67)	
Angiosarcoma	1 (6.67)	
RCC	1 (6.67)	
Metastasis		
Metastatic site, *n* (%)		
Mandible	6 (40)	>0.05
Maxilla	2 (13.33)	
Parotid	5 (33.33)	
Gingiva	1 (6.67)	
Sinuses	1 (6.67)	
Radiology of metastasis		
Imaging modality, *n* (%)		
CT	13 (86.67)	
PET-FDG	7 (46.67)	
SUV		
Minimum	2.0	
Maximum	10.93	
Mean average	4.14	
Maximum average	5.82	
Hard-tissue findings on CT (*n*=6), *n* (%)		
Lysis	3 (50)	
Expansion	3 (50)	
Periosteal reaction	2 (33.33)	
Soft-tissue findings on CT (*n*=4), *n* (%)		

Contd...

Table 1: Contd...

Maxillofacial metastasis ($n=15$)	*n* (%)	*P*
Solid	3 (75)	
Central necrosis	1 (25)	
Treatment and outcome		
Additional treatment, *n* (%)		
Yes	9 (60)	
No	6 (40)	
Radiation treatment to metastasis, *n* (%)		
Yes	6 (40)	
No	9 (60)	
Systemic treatment, *n* (%)		
Yes	2 (13.33)	
No	13 (86.67)	
Immunotherapy, *n* (%)		
Yes	1 (6.67)	
No	14 (93.3)	
Survival (months)**		
Minimum	0.5	<0.05
Maximum	84	
Average	13.75	
Median	5	
Intraoral average	3.0	
Extraoral average	13.2	

*Time to diagnosis refer to the days elapsed between report of symptom onset in maxillofacial region to diagnosis of metastasis, **Survival refers to the time elapsed between diagnosis of metastasis and time of death. SUV: Standard uptake value, SCC: Squamous cell carcinoma, CT: Computed tomography, PET: Positron emission tomography, RCC: Renal cell carcinoma, GI: Gastrointestinal, SD: Standard deviation, FDG: Fluorodeoxyglucose

and metastatic target site are shown in Table 1 and Figure 2. The mandible and parotid gland were the most common target sites in hard and soft tissue (40% and 33.33%, respectively).

Significant radiological findings were seen in 10 subjects. Periosteal reaction, bone expansion and lytic lesions were encountered in 33.3%, 50% and 50% respectively amongst patients with hard-tissue metastases [Figure 3]. PET scans did not reveal consistent findings. Several lesions showed high FDG standardised uptake values (SUVs), with a maximal value of 10.93, mean SUV 4.14 and minimal value of 2.0. Adenocarcinoma was the most commonly observed histological subtype accounting for 60% ($P < 0.05$), followed by SCC (20%), undifferentiated carcinoma (6.6%), angiosarcoma (6.6%) and renal cell carcinoma (6.6%). Table 2 summarises the distribution of primary tumour and histology to the target site.

Over half of patients (60%) had altered therapy after diagnosis of the metastasis. Radiotherapy to the metastatic lesion was delivered in 40% with doses ranging from 30 to 70 Gy. Three patients had a systemic therapy regimen change, two to paclitaxel chemotherapy and one to pembrolizumab immunotherapy. Patients with intraoral metastases were twice as likely to receive any type of treatment than extraoral lesions (71% and 37.5%, respectively). No patients included in the study underwent surgical intervention since diagnosis of metastasis.

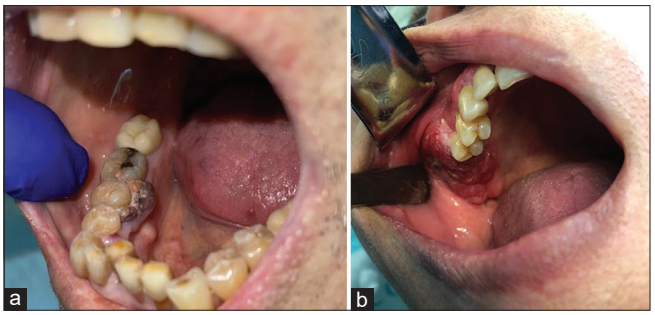

Figure 1: (a) Oral manifestations of metastatic primary lung angiosarcoma, (b) gastrointestinal squamous cell carcinoma

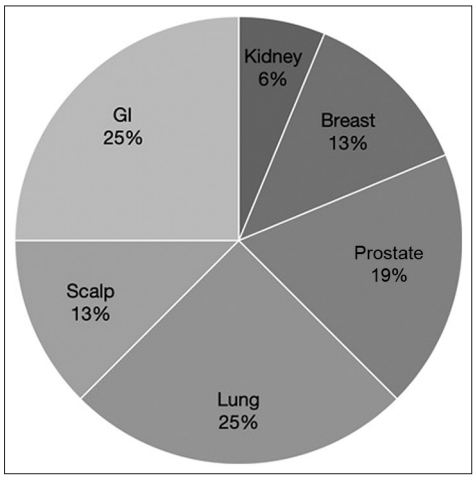

Figure 2: Primary cancer site distribution

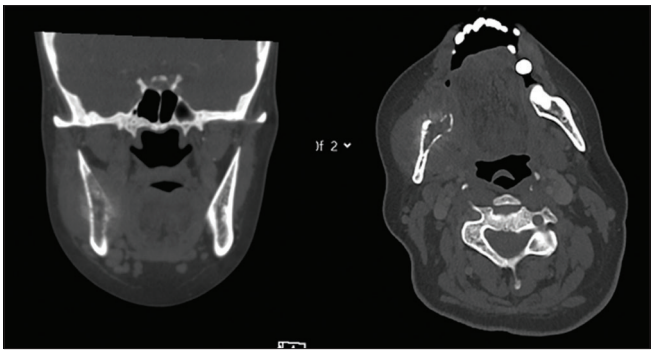

Figure 3: Radiological changes showing lysis cortical perforation and periosteal reaction along the right mandible. Note the pre-auricular and mandibular extraoral swelling

Median survival after diagnosis of metastasis was 5 months. Over half (60%) of patients in the study group lived fewer than 6 months [Figure 4]. No correlation was found between time to diagnosis and survival. Survival rates amongst patients with intraoral metastases were significantly lower than patients who had extraoral lesions ($P < 0.05$).

Discussion

In this retrospective analysis over 12 years, 15 patients (2.8%) were identified with histology-proven metastatic lesions to the

head-and-neck region. The average time to diagnosis of the metastasis was over 3 weeks, and while adenocarcinoma was the most common histology, clinical and radiographic features were non-specific, and no particular primary tumour or target site predilection was noted. Over half of the patients in the study received specific treatment, often radiotherapy, and survival after diagnosis was poor. The first hypothesis of this study was that head-and-neck metastases are misdiagnosed as more common diagnoses are considered first, such as medication-related osteonecrosis of the jaws, and second primary malignancy. When treating a patient with no oncological background, a suspicious lesion should be biopsied as soon as possible. In the present study, the average time to diagnosis was 22 days. Reasons for the delay may be low suspicion amongst physicians, patient compliance and treatment in multiple medical institutions. These perpetuate the time patients suffer from pain and functional problems and delay effective treatment. Other studies show the difficulty in differentiating between benign, inflammatory and potentially malignant lesions, but did not report the actual time to diagnosis.[8]

As to the second hypothesis, certain malignancies are more prone to spread through haematologic or lymphatic vasculature and colonise in head-and-neck areas, such as breast, lung and prostate cancer.[10,11] Here, the most common primary tumours were gastrointestinal (GI), lung and prostate. In recent years, head-and-neck metastases of GI cancers are increasingly reported.[12] This may be explained by new treatment modalities and anticancer agents being introduced to these patients, resulting in longer survival and increasing the chances of developing late metastases to uncommon sites.[13] As in this work, there is no clear evidence for a predilection of spread from a primary site to a specific target metastatic location.[14-16] No specific site-to-source connection was found, and each site was equally likely to give rise to soft- or hard-tissue metastases. However, of target sites in the maxillofacial area, the prevalence of mandible followed by parotid and maxilla here are consistent with previous works.[17] The third hypothesis was the importance of tissue biopsy. The most common metastatic tumour pathology within the maxillofacial region was adenocarcinoma, from different primary sites. Once a cancer patient presents for examination with a suspected lesion in the jaws, it should be considered a potential metastasis, and a biopsy should be recommended in advance. Amongst the advantages of performing a tissue biopsy soon is the option to treat the cause of symptoms. Moreover, a diagnosis of a second primary such as oral SCC may indicate a surgical intervention. In the metastatic patient, however, careful judgement is required when assuming that a suspicious lesion is probably a metastasis of the existing primary tumour. The advantage of early tissue diagnosis could indicate an additional treatment modality or change in the current treatment regimen.

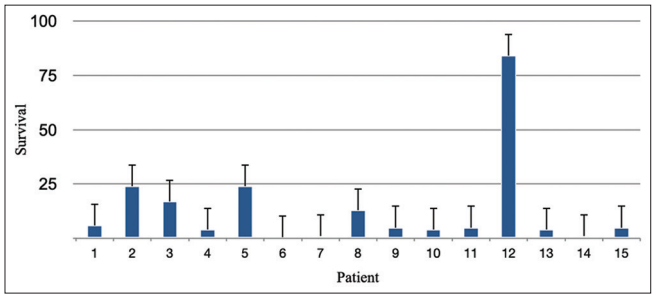

Figure 4: Vertical axis: survival in months, horizontal axis: numbers representing patients in the study

Sixty per cent of patients in this study received additional treatment related to the metastatic lesion, most commonly radiation. It is known that radiation therapy, systemic chemotherapy and surgery that are added to or replace current treatment regimens, are used to alleviate symptoms related to the metastasis in the maxillofacial area, improve quality of life and improve survival.[18] Furthermore, radiation therapy plays a major role in the treatment of maxillofacial metastases, especially in those with high proximity to important organs such

Table 2: Primary tumour, histology, demographics and treatment

Primary tumour	Gender	Age	Histology	Metastatic site	Treatment
Kidney	Male	88	RCC	Parotid	
Breast	Male	49	Adenocarcinoma	Parotid	
Prostate	Male	81	Adenocarcinoma	Mandible	RT (30 Gy)
Lung	Female	64	Adenocarcinoma	Maxilla	
Prostate	Male	71	Adenocarcinoma	Mandible	
Breast	Female	43	Adenocarcinoma	Gingiva	Paclitaxel
Lung	Male	55	Adenocarcinoma	Maxilla	Pembrolizumab
Skin	Male	79	SCC	Parotid	RT (30 Gy)
GI	Female	43	SCC	Mandible	RT (30 Gy)
Prostate	Male	84	Adenocarcinoma	Parotid	RT (70 Gy)
GI	Female	79	SCC	Mandible	
GI	Female	86	Adenocarcinoma	Frontal	
Lung	Male	78	Undifferentiated	Mandible	RT (30 Gy)
Lung	Male	78	Angiosarcoma	Mandible	Paclitaxel
GI	Male	61	Adenocarcinoma	Parotid	

RCC: Renal cell carcinoma, SCC: Squamous cell carcinoma, GI: Gastrointestinal, RT: Radiation therapy

as the eyes, carotid artery and airway tract.[19] In the current study, different radiation protocols ranging from 30 to 70 Gy were used in cases of metastatic lesions in the mandible-ramus and parotid gland, both hard and soft tissue, respectively. Median survival in our study was 5 months, and 60% of the patients lived fewer than 6 months. Previous data have likewise reported poor survival rates of patients with maxillofacial metastases ranging between 6 and 52 months;[20] in one study, the average time of death after the discovery of a maxillofacial metastasis from a distant site was 4 months and no longer than 1 year.[11] Therefore, the presentation of maxillofacial metastases should be considered a sign of advanced disease. An increased period of survival in some patients can be explained by specific targeted and biologic therapy that allows prolonged survival.[21] Previous studies have found that in 25%–62% of cases, metastases to the jaws were the first indicator of a primary disease, but a comparison between the target sites in terms of diagnosis and outcome was not carried out.[11,12] In the present study, we found that intraoral metastases were identified and diagnosed earlier than extraoral metastases. In addition, the intraoral lesions were twice as likely to be treated systemically or with radiotherapy. More importantly, patients with intraoral lesions had significantly lower survival rates than those with extraoral lesions. Intraoral metastatic lesions may be more aggressive, present in later stage of the disease and more prone to cause discomfort requiring treatment.

Professional guidelines for surgical treatment of HNC often exclude surgical intervention in cases of advanced stage of disease such as tumour involvement of the base of the skull and carotid sheath or metastases. As in any other surgical intervention in the oncological patient, the operation is dependent on the performance status of the patient. However, there are no clear guidelines for patients with maxillofacial metastasis, who have low survival rates and advanced disease. The role of surgical ablation for cure at the metastatic site becomes questionable in terms of improving survival. However, improving quality of life and alleviating pain caused directly from the metastasis is important, and surgical intervention should be considered to achieve this goal. In several cases in our study, the metastatic lesion was exposed in the oral cavity or cutaneous area and allowed simple surgical access. Having said that, we find surgical intervention in the metastatic patient being relevant for palliation only. The limitations of this study are single institution research and small sample size.

Conclusions

Metastases to maxillofacial region are rare but should always be taken into consideration, especially when treating patients with metastatic cancer. Clinical signs are not specific; however, metastases presenting in the oral cavity show more aggressive characteristics with significantly worse prognosis. There is a high importance of tissue diagnosis that may lead to a change in treatment and ultimately improve patient outcomes.

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Conflicts of interest

There are no conflicts of interest.

References

1. Ho DP, Wilkinson PE, Vogel RI, Gopalakrishnan R, Argyris PP. Metastatic tumors to the oral soft tissues and jawbones: A retrospective analysis of 40 cases and review of the literature. Head Neck Pathol 2022;16:802-13.
2. Gupta S, Jawanda MK, Ganganna A, Basavaraju S, Kashav N, Dhawan J, *et al.* Jaw bone metastasis from lung cancer as sole primary source: A systematic review. J Clin Exp Dent 2022;14:e573-93.
3. Lopes AM, Freitas F, Vilares M, Caramês J. Metastasis of malignant tumors to the oral cavity: Systematic review of case reports and case series. J Stomatol Oral Maxillofac Surg 2023;124:101330.
4. Kaplan I, Raiser V, Shuster A, Shlomi B, Rosenfeld E, Greenberg A, *et al.* Metastatic tumors in oral mucosa and jawbones: Unusual primary origins and unusual oral locations. Acta Histochem 2019;121:151448.
5. Labrador AJ, Marin NR, Valdez LH, Sanchez KB, Zabarburu W, Ibazetta KA, *et al.* Metastasis to the oral and maxillofacial region. A systematic review. J Stomatol Oral Maxillofac Surg 2022;123:e474-83.
6. do Amaral-Silva GK, Leite AA, Mariz BA, Dos Santos Moreira F, Lopes MA, Ribeiro AC, *et al.* Metastatic neuroblastoma to the mandible of children: Report of two cases and critical review of the literature. Head Neck Pathol 2021;15:757-68.
7. Hirshberg A, Leibovich P, Buchner A. Metastases to the oral mucosa: Analysis of 157 cases. J Oral Pathol Med 1993;22:385-90.
8. Murillo J, Bagan JV, Hens E, Diaz JM, Leopoldo M. Tumors metastasizing to the oral cavity: A study of 16 cases. J Oral Maxillofac Surg 2013;71:1545-51.
9. Kirschnick LB, Schuch LF, Cademartori MG, Vasconcelos AC. Metastasis to the oral and maxillofacial region: A systematic review. Oral Dis 2022;28:23-32.
10. Hirshberg A, Shnaiderman-Shapiro A, Kaplan I, Berger R. Metastatic tumours to the oral cavity – Pathogenesis and analysis of 673 cases. Oral Oncol 2008;44:743-52.
11. McClure SA, Movahed R, Salama A, Ord RA. Maxillofacial metastases: A retrospective review of one institution's 15-year experience. J Oral Maxillofac Surg 2013;71:178-88.
12. Hirshberg A, Berger R, Allon I, Kaplan I. Metastatic tumors to the jaws and mouth. Head Neck Pathol 2014;8:463-74.
13. Biller LH, Schrag D. Diagnosis and treatment of metastatic colorectal cancer: A review. JAMA 2021;325:669-85.
14. Erra S, Costamagna D. Breast cancer metastatic to the submandibular gland. Case report. G Chir 2011;32:194-8.
15. Duncan M, Monteiro M, Quante M. Bilateral parotid gland metastases from carcinoma of the breast that presented 25 years after initial treatment. Br J Oral Maxillofac Surg 2015;53:94-6.
16. Sauerborn D, Vidakovic B, Baranovic M, Mahovne I, Danic P, Danic D. Gastric adenocarcinoma metastases to the alveolar mucosa of the mandible: A case report and review of the literature. J Craniomaxillofac Surg 2011;39:645-8.
17. Hashimoto N, Kurihara K, Yamasaki H, Ohba S, Sakai H, Yoshida S. Pathological characteristics of metastatic carcinoma in the human mandible. J Oral Pathol 1987;16:362-7.
18. Teymoortash A, Rassow S, Bohne F, Wilhelm T, Hoch S. Clinical impact of radiographic carotid artery involvement in neck metastases from head and neck cancer. Int J Oral Maxillofac Implants 2015;45:422-6.
19. Yen SH, Wang LW, Lin YH, Jen YM, Chung YL. Phenylbutyrate mouthwash mitigates oral mucositis during radiotherapy or chemoradiotherapy in patients with head-and-neck cancer. Int J Radiat Oncol Biol Phys 2012;82:1463-70.
20. Shen H, Wang X, Shao Z, Liu K, Xia XY, Zhang HZ, *et al.* Alterations of high endothelial venules in primary and metastatic tumors are correlated with lymph node metastasis of oral and pharyngeal carcinoma. Cancer Biol Ther 2014;15:342-9.
21. Duan S, Buxton IL. Evolution of medical approaches and prominent therapies in breast cancer. Cancers (Basel) 2022;14:2450.