

Metastasis to the oral soft tissues: A review of 412 cases

Soussan Irani

Dental Research Center, Department of Oral Pathology, Dental Faculty, Hamadan University of Medical Sciences, Hamadan, Iran

Corresponding author (email: <soussanirani@gmail.com>)

Dr. Soussan Irani, Dental Faculty, Shahid Fahmideh Street, Hamadan, Iran.

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Abstract

The present review article analyzes the characteristics of metastases to the oral soft tissues from 1937 to 2015. An extensive literature search was performed. All variables such as age, gender, and primary and secondary tumor sites were analyzed. Metastases to the major salivary glands were not included in this review. In general, there were 412 metastatic lesions developed in the oral soft tissues. The male-to-female ratio was approximately 1.8:1. The mean age of the patients at diagnosis was 58. The lung was the most common primary site and the gingiva was the most common metastatic site. The greater part of the histological examination yielded adenocarcinoma. The diagnosis of a metastatic lesion in the oral cavity is a challenge to the clinicians due to the lack of pathognomonic signs and symptoms. Oral metastases usually occur in the advanced stages of cancers, and the interval between appearance and death is usually short. The oral soft tissue metastasis can be easily recognized compared to the metastasis of jawbones. Early detection of oral lesions is important in the case of being the first sign of a malignancy in other parts of body.

Key words: *Metastasis, mouth, soft tissue*

INTRODUCTION

Metastasis to the oral cavity is a rare event and constitutes 1% of all oral cavity malignancies.^[1] Oral cavity metastases are mostly observed in the jaws compared to the soft tissues, particularly in the posterior area of the mandible.^[2-4] Only 33% of oral metastatic lesions are seated in the soft tissues.^[3] A specific site for metastasis is the post-extraction site.^[5] Clinically, early gingival metastases are polypoid or exophytic, highly vascularized, and resemble hyperplastic or reactive lesions such as pyogenic granuloma, giant cell granuloma, and peripheral fibroma.^[6,7] In other locations, especially on the tongue, they appear as

submucosal masses.^[3] Metastasis to the oral cavity is one of the complications of systemic cancer and usually develops in the end stage of a cancer lesion.^[8] Oral cavity metastases are an increasingly critical cause of morbidity and mortality in cancer patients. Thus, oral cavity metastasis presents a therapeutic challenge and is a physically debilitating event for the patient. Early diagnosis and treatment of oral cavity metastasis may enhance the quality of the patient's life and prolong survival. Dentists play a crucial role in the diagnosis and management of cancer patients, especially in those patients in whom oral metastasis is the first sign of undiscovered cancer in other parts of the body.^[8] The purpose of the present article was to review the

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characteristics of the oral soft tissues metastases to analyze all available information. A relevant English Literature search in PubMed, Scopus, and Google Scholar was performed. The keywords “oral cavity,” “soft tissue,” and “metastasis” were searched in the title/abstract of publications limited to 1930 to 2015. Only the relevant publications were included. All variables such as age, gender, and primary and secondary tumor sites were analyzed. In some of reports, especially in case series, most of the variable assessments were incomplete.

RESULTS

In general, there were 412 metastatic lesions that developed in the oral soft tissues. Lung cancers mostly metastasized to the gingiva with 46 cases (11.1%), followed by the tonsil and tongue with 11 cases each (2.6%). Majority of liver cancers metastasized to the gingiva in 26 cases (72.2%) of all metastatic lesions from liver cancer. Breast cancers also mostly metastasized to the gingiva in 20 cases (60.6%) of all metastatic lesions from breast cancer. However, kidney cancers mostly metastasized to the tongue (19 cases of all metastatic lesions from kidney cancer; 36.5%). Most of the gingival metastases were detected in posterior areas. The anterior gingiva was only involved in 16 cases (3.9%). The presence of teeth was the most frequent finding in gingival metastases. Metastasis in edentulous cases was found in only 7 cases (1.7%). In 14 cases (3.4%), oral metastasis developed in a tooth extraction site. Metastatic tumors were distributed equally in the right and left sides. In 19 cases (4.6%), metastatic tumors developed in the anterior region and in 11 cases (2.6%) developed bilaterally. In 62 cases (15%), the metastatic lesion developed in the contralateral side of the primary tumor. In 69 cases (16.7%), underlying bone tissue was also involved. The greater part of the histological examination yielded adenocarcinoma ($n = 93$; 22.5%), followed by variants of renal carcinoma ($n = 54$; 13.2%), hepatocellular carcinoma ($n = 41$; 10%), and in lower numbers, malignant melanoma ($n = 21$; 5%) and squamous cell carcinoma ($n = 18$; 4.4%). There were 5 cases of osteosarcoma, 4 cases of chondrosarcoma, and 3 cases of Ewing's sarcoma. Most reported cases were from the United States of America with 63 cases (15.2%), followed by Korea and Spain with 45 (11%) and 32 cases (7.8%), respectively. The results of the literature search of cases of oral soft tissue metastases are summarized in Tables 1 and 2. Table 3 shows the comparison of the results of this review with those of the previous reviews.

DISCUSSION

The incidence of metastasis is rising with the increase in the survival of cancer patients. At present, cancer patients live longer due to advances in cancer diagnosis and management.^[259] The majority of head and neck cancer cases are related to tobacco use and heavy alcohol consumption. Other possible risk factors include viral infections, infection with *Candida* species, and a number of bacterial species.^[260] The oral cavity is an uncommon site for metastasis.^[5] The criteria for the diagnosis of a metastatic tumor are as follows; first, the primary tumor must be histologically verified. Second, the metastatic tumor and primary tumor must be of the same histological type. Finally, the possibility of direct local spread from the primary tumor must be excluded.^[261] Metastasis to distant organs is not a random event, and is regulated by a site-specific process.^[262] For example, breast and prostate cancers usually metastasize to the jaw bones, however, lung carcinomas commonly metastasize to the oral soft tissues.^[263,264] There are a few reports of oral metastases from the tumors with high mortality rate such as pancreatic cancer probably due to patient's death before the appearance of a metastatic lesion. In this review, there were only 2 cases of metastatic pancreatic cancer. In the cases of bone involvement, it is not clear whether the cancer cells directly metastasize to the gingiva, or a bone metastasis subsequently extends into the gingiva, or the patient had both gingival and bone metastases;^[265] however, it is suggested that the cancers first metastasize to the gingiva, and then cancer cells invade to the underlying bone. In the current review, the involvement of both gingiva and bone was found in 69 cases. The gingiva is the most common site for metastasis; inflammatory reaction such as gingivitis or periodontitis could be critical factors to facilitate metastasis. Some degree of inflammation in the gingival tissue can be found in most people. In chronically inflamed gingiva, the capillary network constantly proliferates and develops fragmented basement membranes.^[266] The role of inflammation in the attraction of metastatic cells has been suggested previously, and it might be the reason for a higher frequency of metastases in the attached gingiva. On the other hand, there are some reports of metastases to the post-extraction site, which indicate the role of local factors in the extraction or wound area that may attract circulating tumor cells. Tooth extraction may serve as a promoting factor in metastasis as it creates a microenvironment rich in growth factors. It is suggested that tooth extraction site is a microenvironment rich with local growth factors which favor the growth of metastatic cells.^[267] The tongue is also a highly

Table 1: A summary of oral metastasis in men

| Primary site (No. of patients) | Age range (years) | The time intervals from primary tumor detection to diagnosis of an oral metastasis | Range of time duration of development of a metastatic lesion | The time intervals between diagnosis of primary tumor to death | References |
|--------------------------------|-------------------|--|--|--|----------------------------|
| Lung (61) | 14-84 | Same time*-90 months | 1 week-5 months | 1 week-2 years | (4, 9-43) |
| Kidney (43) | 35-78 | 1 month-19 years | 1 week-3 years | 3 weeks -31 months | (4, 22, 28, 31, 34, 44-73) |
| Liver (33) | 52-74 | 1 month-100 months | 2 weeks-4 months | 1 month-13 months | (22, 28, 31, 74-89) |
| Skin (16) | 21-86 | 8 months-12 years | 3 weeks-2 months | 4 months-10.2 years | (90-100) |
| Unknown (12) | 2-72 | 1 month-5 months | 1 month | 7months-58 months | (27, 29, 41) |
| Prostate (12) | 53-85 | 1 month-7 years | 3 weeks-2 months | 1 month-1 year | (22, 29, 54, 101-105) |
| Stomach (10) | 42-72 | Same time-1 year | 2 weeks-3 months | 1 month-2 years | (7, 22, 106-112) |
| Colon (9) | 42-73 | 1 month-5.3 years | 3 weeks-2 months | 1 month-9 months | (19, 22, 30, 113-118) |
| Esophagus (8) | 30-67 | 1 month-5 months | 1 week -5 months | Few days-6 weeks | (19, 41, 119-124) |
| Rectum (6) | 45-80 | 2 years-5 years | 1 week | 5 months-14 months | (41, 125-129) |
| Urinary bladder (5) | 56-75 | 2 years | 2-4 months | 1 month | (54, 130-132) |
| Testes (4) | 25-63 | Same time-2 years | 3 weeks-3 months | 7 months | (133-136) |
| Bronchus (4) | 25-66 | 5 months | 1 week-6 months | 3 weeks-2 months | (137-140) |
| Adrenal glands (3) | 2-65 | 4 months | 3 weeks-2 months | 3 weeks-1 year | (141-143) |
| Thyroid (3) | 65-83 | 28.5 months-104 months | 4 months | 2 months-12 months | (34, 128, 144) |
| Leg (3) | 55-60 | 2 months-5.3 years | 1 month-6 months | 9 months | (30, 145, 146) |
| Forearm (2) | 14,69 | 12 months- 18 months | 2 months | 6 months | (147, 148) |
| Parotid (2) | 36,67 | 11 months,-21 years | 5 months | 1 month | (149, 150) |
| Pleural cavity (2) | 65,75 | 1 years-2 years | 6 weeks-2 months | 3 months | (151, 152) |
| Urethra (2) | 61 | No data | No data | No data | (101) |
| Femur (2) | 22,49 | 14 months-2 years | 6 months | 4 months | (34, 153) |
| Pancreas (2) | 61,71 | No data | No data | 19 months | (28, 34) |
| Tibia (2) | 17,18 | 6 months-1 year | 2 weeks-2 months | 1 week | (148, 154) |
| Breast (2) | 60,86 | 2 years | 2-4 month | 4 months-1 year | (155, 156) |
| Mediastinum (1) | 23 | 3 years | 3 months | Alive at the time of report | (157) |
| Colorectal (1) | 71 | 1 year | 1 month | 1 month | (158) |
| Brain (1) | 8 | 18 months | No data | Alive at the time of report | (159) |
| Cecum (1) | 44 | First sign | 2 months | Alive at time of report | (160) |
| Chest (1) | 68 | 5 months | 1 month | 3 weeks | (161) |
| Foot (1) | 43 | 6 years | 2 weeks | Alive at the time of report | (162) |
| Hard palate (1) | 52 | 17 months | 2 weeks | Alive at the time of report | (98) |
| Nasal septum (1) | 57 | 4.2 years | No data | 4 years | (93) |
| Rib (1) | 24 | 4 years | 2 months | No data | (163) |
| Sacrum (1) | 18 | 6 years | 1 week | 1 week | (164) |
| Thigh (1) | 27 | 1 year | 2 months | 2 months | (165) |
| Thorax (1) | 61 | 15 months | No data | No data | (166) |
| Wrist (1) | 57 | 18 months | 4 months | Alive at the time of report | (167) |
| Gluteal (1) | 32 | 28 months | No data | 38 months | (34) |
| Lower extremities (1) | 61 | No data | No data | No data | (28) |
| Nasal fossa (1) | 69 | First sign | No data | 44 months | (34) |
| Shoulder (1) | 68 | 8 months | 2 weeks | Alive at the time of report | (168) |

vascular organ, and hence, the high incidence of metastatic tumors can be explained. These findings are in agreement with the role of both inflammation and angiogenesis in cancer metastasis.^[268,269]

According to a review by Yoshitomi *et al.* the tongue is a frequent site for Renal Cell Carcinoma metastasis and usually indicates a widespread disease.^[51] In the present

series, there were 58 cases of metastasis from the kidney, and in 19 cases the tongue was the metastatic site. The second most common primary site metastasized to the tongue was the lung with 11 cases. Some other studies revealed that the most common tumors metastases to the tonsil are malignant melanoma and small-cell bronchogenic carcinomas.^[270-272] For example, the majority of lung cancers metastasizing to the tonsils

Table 2: A summary of oral metastasis in women

| Primary site (No. of patients) | Age range (years) | The time intervals from primary tumor detection to diagnosis of an oral metastasis | Range of time duration of development of a metastatic lesion | The time intervals between diagnosis of primary tumor to death | References |
|--------------------------------|-------------------|--|--|--|-------------------------------|
| Breast (31) | 25-74 | Same time-24 years | 2 weeks-6 months | 2 weeks-3 years | (4, 24, 29, 30, 33, 169-190) |
| Lung (14) | 46-83 | Same time-2 years | 1 week-8 months | 6 weeks-20 months | (29,34,128,191-201) |
| Thyroid (13) | 40-73 | 4 months-15 years | 1 month-1 year | 3-9 months | (27,28, 31, 34, 101, 200-206) |
| Kidney (12) | 46-87 | 6 months-10 years | 3 weeks-4 months | 1 month-3 years | (4,31,62,101,207-211) |
| Skin (12) | 16-84 | 1 week-8 years | 1 week-2 months | 2 months-3 years | (101, 212-216,270) |
| Unknown (8) | 44-87 | 3-4 months | 1-3 months | 1-6 months | (4,27,31,41,217,218) |
| Colon (7) | 35-80 | 1 year-56 months | 1-3 months | 3 months-1 year | (22,29,220-224) |
| Rectum (7) | 37-79 | 1-49 months | 1 week-2 months | 3 weeks-4 months | (27,225-230) |
| Uterus (6) | 45-75 | 28.5 months | 1-9 months | 2 weeks-21 months | (14,29, 128, 231-233) |
| Stomach (6) | 48-88 | 1-14 years | 3 months-1 year | 2 weeks-1 year, | (22,28,234-237) |
| Endometrium (4) | 26-78 | 6 months-7 years | 1-3 weeks | 2 months-6.5 months | (238-241) |
| Ovary (3) | 46-60 | 5 years | 1 month | 3 weeks | (14, 242, 243) |
| Genital organ (3) | 48 | No data | No data | No data | (28) |
| Liver (3) | 23-78 | 1-6 years | 2 weeks-1month | 3 months-2 years | (244-246) |
| Gluteus (2) | 66-68 | 6 months | No data | 44 months | (27, 34) |
| Bronchus (1) | 70 | 2 weeks | No data | 2 years | (247) |
| Cervix (1) | 44 | 1 year | 1 month | 1 year | (219) |
| Elbow (1) | 82 | 10 months | No data | 2 months | (34) |
| Eye (1) | 76 | 6 years | No data | Alive at the time of report | (248) |
| Femur (1) | 15 | 4 years | 2 months | 2 months | (249) |
| Gallbladder (1) | 62 | 1 year | No data | 2 months | (250) |
| Hip (1) | 47 | 8 years | 2 months | Alive at the time of report | (251) |
| Knee (1) | 45 | 3 years | No data | 1 month | (252) |
| Parotid (1) | 80 | 28.5 months | No data | 3 months | (128) |
| Vagina (1) | 44 | 1 year | 1 week | 1 week | (148) |
| Rib (1) | 12 | 10 months | No data | 2 months | (253) |
| Shoulder (1) | 31 | 3 years | 3 months | 2 months | (254) |
| Phalanx (1) | 89 | 18 months | 1 week | 1 week | (255) |
| Spheno-occipital (1) | 33 | 6 years | 2 months | Alive at the time of report | (256) |

are of the small cell type, thus, adenocarcinomas rarely metastasize to the tonsil.^[138] However, this review indicated that most of the metastatic tumors to the tonsil were adenocarcinomas (14 cases), followed by malignant melanoma (11 cases), and there were only 2 small cell carcinomas metastasizing from the lung. Providing an exact diagnosis is very challenging for a pathologist. If the history of a previous cancer exists, the histopathological findings of the metastatic lesion should be compared with those of the primary cancer. Special staining such as immunohistochemistry can be helpful in identifying the nature of the primary tumor.

In addition to the Batson's plexus, the other possible routes of oral metastasis include arterial, venous, and lymphatic circulations. However, in cases such as lung

cancer, direct extension by aspiration, access to the pulmonary vein, and drain to the left side of the heart has been suggested. Majority of all metastatic deposits occur in the lungs and liver. Cancer cell clusters drain into the portal vein and then travel to the heart and finally deposit in the lungs.^[273] In cases of gastric cancer, stomach contents are also considered as the routes of dissemination. In addition, retrograde dissemination of the tumor to the tongue with involvement of regional lymph nodes is another possible route in the cases of tongue metastasis. As the palatine tonsils do not have afferent lymphatic vessels, the metastatic pathway is difficult to determine in palatal tonsil metastases. Furthermore, retrograde transportation of tumor cells has been suggested.^[274-278] Metastasis to the oral cavity mostly occurs in the advanced stage of the disease

Table 3: Comparison of the results with those of previous reviews

| Reference No. | Age (years) | Male/female ratio | Most common primary sites | Most common metastatic site(s) | Most common histological tumor type | Oral metastasis as the first sign |
|----------------|-------------|-------------------|--|------------------------------------|-------------------------------------|-----------------------------------|
| Current review | 58 | 1.8:1 | Lung (men), breast and reproductive system (women) | Gingiva, tongue | Adenocarcinoma | 23.3% |
| (5) | 42 | 2:1 | Lung, kidney, liver, and prostate in men, the breast, genitals, kidney, and colorectum in women. | Gingiva, tongue | Not mentioned | 23% |
| (3) | 54 | 1.6:1 | Lung (men), breast and reproductive system (women) | Gingiva, tongue | No difference | 20.4% |
| (257) | 54 | 3.6:1 | Lung, kidney, skin | Gingiva, tongue | Not mentioned | 30% |
| (29) | 54.7 | 1.28:1 | Lung, breast, kidney, liver, and prostate | gingiva | Adenocarcinoma | 29% |
| (28) | 55.2 | 1.9:1 | liver, female genital organs, and thyroid | Gingiva, tongue | Hepatocellular carcinoma | 26.8% |
| (34) | 65 | 2.3:1 | Lung, kidney | Gingiva or alveolar mucosa, tongue | Carcinoma | 26.1% |
| (31) | 62.3 | 1.1:1 | Kidney, lung, and breast | Gingiva, tongue | Adenocarcinoma | 25.6% |
| (258) | 53.9 | 2:1 | Lung, kidney, skin | Gingiva, tongue | Carcinoma | 27% |
| (22) | 64.8 | 5:1 | Liver, lung stomach | Gingiva, tonsil | Carcinoma | 34% |

and indicates widespread disease. The prognosis and treatment depends on the site of primary tumor and degree of metastatic spread.^[273] The metastatic lesion should be treated by surgical resection, radiation, chemotherapy, or a combination of these methods. Palliative treatment reduces the patient's pain, size of tumor, and preserves oral function.^[8]

CONCLUSION

The diagnosis of a metastatic lesion in the oral cavity is a challenge to the clinicians due to the lack of pathognomonic signs and symptoms. Oral metastases usually occur in the advanced stages of cancers, and the interval between appearance and death is usually short. Therefore, due to a high mortality rate, patients with oral lesions, particularly those with a history of a malignancy, deserve a careful diagnostic procedure. Even with the diagnosis of a primary lesion, it is necessary to make a definite diagnosis of oral lesions for

appropriate treatment. The oral soft tissue metastasis can be easily recognized compared to jawbones metastasis. Early detection of oral lesions is important in the case of being the first sign of a malignancy in other parts of the body.

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Conflicts of interest

There are no conflicts of interest

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