

Distant metastasis from oral cancer: A review and molecular biologic aspects

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Abstract

Oral squamous cell carcinoma (OSCC) has been estimated to be the sixth most common cancer worldwide. The distant metastasis plays a critical role in the management and prognosis in oral cancer patients. Regarding the distant metastasis from the oral cancer, the hypopharynx is the most common primary site, followed by the base of tongue and anterior tongue. The present review article analyzes the characteristics of the distant metastases from the oral cavity from 1937 to 2015.

Key words: *Incidence, metastasis, molecular biology, oral cancer*

INTRODUCTION

Oral squamous cell carcinoma (OSCC) has been estimated to be the sixth most common cancer worldwide.^[1] The distant metastasis plays a critical role in the management and prognosis of oral cancer patients.^[2] Regarding the distant metastasis from the oral cancer, the hypopharynx is the most common primary site (60%), followed by the base of tongue (53%) and anterior tongue (50%).^[3]

The present article reviews the characteristics of distant metastases from the oral cavity to analyze all available information in the English language literature from 1937 to 2015. Metastases from the major salivary glands are not included in this review. In addition, metastasis to the cervical lymph nodes was not included.

BIOLOGY OF METASTASIS

Metastasis means the spread of the disease from one organ to another not directly connected to it. Cancer cells enter the vascular or lymphatic channels.^[4] Metastasis starts from detaching the cancer cells from the primary site, spreading in the tissue, moving away through the extracellular matrix, invading blood vessels, and settling in the microvasculature, and finally, extravasating through the vessel wall and proliferating in the recipient tissue.^[5] Epithelial-mesenchymal transition (EMT) promotes metastasis due to loss of cell-cell adhesion and secretion of matrix metalloproteinases (MMPs) to degrade the extracellular matrix (ECM).^[6-8] Anoikis, a specific form of apoptosis, occurs after detachment of the cells from the ECM^[9] and facilitates metastasis.^[10] Angiogenesis is another step for cancer metastasis as

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tumor cells should be transported via blood and/or lymph vessels.^[11] Overexpression of vascular endothelial growth factors (VEGFs) has been reported in the cancers.^[12] Tumor cells lining blood vessels “mosaic vessels” or “vasculogenic mimicry” may be another way for spreading cancer cells.^[13] After surviving the immune system, the tumor cells extravasate into the organ parenchyma to establish a micrometastasis.^[14]

There are a few theories about the mechanism of metastasis. First, the “organ selection” theory suggesting the growth factors in the metastatic site may determine the establishment of successful metastasis. The second theory “adhesion theory” proposes that tissue specific adhesion molecules, expressing on endothelial cells of target organs, set up a pre-metastatic niche by anchoring migrating cancer cells to develop a metastatic tumor. Another is the “chemoattraction theory” that suggests that cancer cells express chemokine receptors.^[15] Another theory proposes that the site and histopathological type of the primary cancer determine the organ distribution patterns, which first was reported by Paget in 1889, who proposed the concept of “seed” for metastatic tumor cells and of “soil” for the secondary site.^[16] A pre-metastatic niche is a recently suggested concept, and according to the concept, prior to colonization, the primary tumor induces the remodelling of an organ microenvironment by circulating tumor cells (CTCs). Then, a metastatic niche is produced to support disseminated tumor cells (DTCs) to localize them.^[17,18] A metastatic niche is a microenvironment that supports and facilitates the invasion and growth of metastasis.^[19]

Finally, there is a new theory that explains the relationship between the primary and metastatic sites as a bidirectional pathway, rather than unidirectional. According to this theory, the surviving cancer cells in the secondary tumor site have the ability to return to the primary site to accelerate the primary tumor progression.^[20,21]

RESULTS

Of the 107 case reports of distant metastasis, 67 were in men and 36 in women. The male and female patients’ age ranged from 20–92 and 6–79 years, respectively. Distant soft tissue metastases most commonly occurred in the lung with 23 cases, followed by the heart with 10 cases. Metastasis to different bones occurred in 23 cases, with a higher incidence to vertebral bones in 11 cases. In 8 cases, the primary and secondary tumors were discovered at the same time. In 16 cases, the distant metastasis occurred bilaterally, and in 2 cases there were multiple metastases. In 13 cases, the distant metastasis occurred in the contralateral side. In 6 cases, the distant metastasis was the first sign of the presence of a malignancy. In 47 cases, the distant metastasis occurred in more than one site, more commonly in the lung with 22 cases. The most common histologic type was SCC with 55 cases for soft tissue metastases, and ameloblastoma with 23 cases for jaw bone metastases. In addition, there were 18 cases of distant metastasis from the oral cavity minor salivary gland tumors.

The details are summarized in Tables 1-3 to aid comparison.

Table 1: Demographic characteristics of distant metastasis from the oral cancer among 67 males

Primary site (No. of patients)	Secondary site	References
Mandible (17)	Lung, penis, skull, femur, kidney, skin, pelvis, vertebra, submandibular area	(22-38)
Tongue (8)	Heart, axillary LN , penis, skin	(39-46)
Upper gingiva (8)	Retropharyngeal LN, parapharyngeal space , lateral pharyngeal LN, lung	(47-50)
Buccal mucosa (7)	Cerebral, ankle, eyelid, talus, thyroid, vertebra, adrenal	(51-57)
Lower lip (6)	Vertebra, leptomeninge, lung, infratemporal area	(58-60)
Hard palate (5)	Lung, skin, liver, neck, eyelid	(61-65)
Maxilla (4)	Rib, lung, heart	(39, 66, 67)
Floor of mouth (3)	Axillary LN, breast, percutaneous endoscopic gastrotomy	(68-70)
Tonsil (3)	Cerebellum, leptominange, retroperitoen	(71-73)
Lower alveolus (2)	Hand and finger, phalange	(74, 75)
Oral mucosa (2)	Skin, soft palate	(76, 77)
Retromolar area (1)	Heart	(78)
Soft palate (1)	Lung	(79)
Lower gingiva (1)	Lateral pharyngeal LN	(50)
Mandible and maxilla (1)	Lung	(80)

LN=Lymph node

Table 2: Demographic characteristics of distant metastasis from the oral cancer among 36 females

Primary site (No. of patients)	Secondary site	References
Mandible (10)	Axilla, vertebra, submandibular region, skull, lung, ileum, eye	(81-90)
Buccal mucosa (6)	Vertebra, neck, thyroid, lung, heart	(91-96)
Hard palate (6)	Abdomen, lung, pleura, skin	(97-101)
Upper gingiva (4)	Kidney, parapharyngeal space, retropharyngeal LN	(47, 48, 50, 102)
Tongue (3)	Heart, lung	(103, 104)
Maxilla (2)	Lung, skin	(105, 106)
Tonsil (2)	Breast, CNS	(71)
Soft palate (1)	Retropharyngeal LN	(47)
Floor of mouth (1)	Parieto-occipital	(69)
Lower alveolus (1)	Heart	(107)
Upper lip (1)	Pleura	(108)
Retromolar area (1)	Skin	(109)

LN=Lymph node, CNS=Central nervous system

Table 3: Demographic characteristics of distant metastasis from the oral cancer among patients with unknown gender

Primary site (No. of patients)	Secondary site	References
Lower gingiva (2)	Vertebra	(110)
Maxilla (1)	Vertebra	(110)
Retromolar area (1)	Vertebra	(110)

DISCUSSION

There is a high risk of developing a second primary tumor in oral cancer patients.^[111] Distant metastasis is another problem with oral cancer which is not so common and correlates with advanced stages of oral cancer.^[112] Although the tongue is considered to be the most common site for cancer development, the present review indicated that the gingiva was the most frequent primary site for distant metastasis. A previous study showed that the rate of distant metastasis from the tongue was 4.1%, and was lower than that from upper gingiva carcinomas (6.6%).^[113] The lip cancer comprises 30% of the oral cancer and 2.06% of all cancer cases.^[114,115] The lip carcinoma shows regional lymph node metastasis in 3–29% of cases. In the present review, only 1 case of lip carcinoma metastasis to the lung has been found.

Although ameloblastoma is histologically a benign and slow growing tumor mostly in the mandible, it can metastasize to the cervical lymph nodes and distant sites.^[116] In the present review, 22 cases (20.5%) of distant metastasis from ameloblastoma have been reported. In 15 cases (68%), the distant metastasis was developed in the lungs. In addition, there was a case of mandibular ameloblastoma, metastasizing to the

eye. Metastatic head and neck tumor to the brain is the rare.^[69] A previous study has shown that metastasis to the brain occurred in 6% of head and neck cancer patients.^[117] In the current review, metastasis to the brain and skull was detected in 10 (9.3%) cases.

In conclusion, distant metastasis from the oral cavity is not so common an event, however, because it mostly occurs in the advanced stages of a malignancy, careful examination of the patient during primary cancer treatment has a significant impact on a patient's life.

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Conflicts of interest

There are no conflicts of interest.

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