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Papers

Metastatic Tumours to the Oral Region. An Overview

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Metastatic tumours to the oral region are uncommon. There are more published cases of jawbone metastases than in oral soft tissues. The most common primary sources of metastatic tumours to the oral region are the breast, lung, kidney, bone and colon. The breast is the most common primary site for tumours metastasising to the jawbones, whereas the lung is the most common source for metastases to the oral soft tissues. In the jawbones, the common location of the metastatic lesions is the mandible, with the molar area being the most frequent involved site. In the oral soft tissues, the attached gingiva is the most common affected site followed by the tongue. In nearly 30% of cases, the metastatic lesion in the oral region is the first indication of an undiscovered malignancy at a distant site. The biological basis of the metastatic process is discussed.

Keywords: gingiva, jaws, metastases, mouth neoplasm, oral mucosa

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INTRODUCTION

METASTATIC TUMOURS to the oral region may occur in the soft tissues or in the jawbones. Oral metastatic tumours are uncommon and comprise approximately 1% of malignant oral neoplasms [1]. Because of its rarity, the diagnosis of a metastatic lesion in the oral region is challenging, both to the clinician and to the pathologist, in recognising that a lesion is metastasic and in determining the site of origin.

The purpose of the present article is to review the biological basis of the metastatic process in general, to discuss the possible mechanisms by which metastatic tumours spread to the oral region, and to analyse the information in the literature concerning oral metastatic tumours.

THE BIOLOGICAL BASIS OF THE METASTATIC PROCESS

Metastasis is a complex process that involves sequential steps. In producing a successful metastatic lesion, tumour cells must breach a series of barriers. They must detach from the primary tumour, spread in the tissues, invade the blood or lymphatic vessels, and survive travel through the circulation. The tumour cells then settle in the microvasculature of the target organ, extravasate through the vessel's wall, invade the target organ and proliferate within the recipient tissue.

To accomplish these steps and to produce a successful metastatic colony, tumour cells must gain several properties. They must have a reduced adherence to each other, facilitating their ability to detach from the primary tumour and invade the surrounding tissue. For example, loss of the epithelial cell–cell adhesion molecule E-cadherin, has been found in a variety of carcinomas and its expression is inversely correlated with loss of differentiation and invasive behaviour [2, 3].

Tumour cells must have the ability to adhere and degrade the extracellular matrix elements and be able to move towards the degraded matrix [4]. The interaction between tumour cells and adhesive proteins of the extracellular matrix are mediated through cell surface receptors, such as the integrins, which are a family of transmembrane glycoproteins [5–7]. Several studies have shown that tumour cells express receptors to laminin, type IV collagen, and fibronectin and that when these receptors are blocked, the metastatic potential is inhibited [7–11]. Once tumour cells adhere to the extracellular matrix, further spread depends on their ability to produce proteolytic enzymes that can breakdown the extracellular matrix. Highly metastatic tumour cells release hydrolytic enzymes, such as cathepsin B [12], type IV collagenase [13], elastase [14], heparan sulphate endoglycosidase [15] and plasminogen activator [16]. The ability of tumour cells to degrade the extracellular components of the basement membrane or connective tissue is positively correlated with their metastatic potential [17]. Cell migration plays an important role in the metastatic invasiveness and active cell motility enhances the

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metastatic potential [18]. Motility may be promoted by tumour cell products or by chemotactic factors, such as degradation products of the extracellular matrix molecules [19–22]. Migration of tumour cells involves repetitive steps of attachment and detachment from their matrix support which probably occur through co-ordinated quantitative and qualitative changes of cell surface receptor expression [7].

Angiogenesis, the tumour-induced neovascularisation, plays an important role in expansion of tumour mass and enhancing intravasation of tumour cells into the circulation. In addition to the increased perfusion of blood through the tumour, the new capillary endothelium stimulates tumour cells to produce growth factors [23, 24]. Angiogenesis depends on positive and negative regulators of blood vessel growth [25, 26]. Recent studies suggest that the switch to the angiogenic phenotype of tumour cells is the balance of these positive and negative regulators [26]. Increasing neovascularisation correlates with a rising rate of metastasis [27]. The new proliferating capillaries are permeable and are more likely to be penetrated by tumour cells than mature vessels [28].

In the circulation, most tumour cells are destroyed by mechanical and immunological factors. Only a small number of invading cells survive and are able to colonise in a new metastatic site. The ability of tumour cells to survive travel in the circulation depends, in part, on whether they express histocompatibility antigens [5] or other ligands which enable their recognition by cytotoxic T lymphocytes [29]. It also depends on their ability to induce aggregates of tumour cells which are afforded some protection from anti-tumour host effector cells. Additional protection is achieved by a fibrin covering of tumour cell aggregates in the circulation [30].

Once tumour cells reach the target organ, extravasation occurs. Prior to extravasation, circulating tumour cells are trapped in the capillary network of the target organ. Several mechanisms promote trapping of circulating tumour cells. Tumour cells expressing high levels of hyaluronan are trapped more easily, possibly because hyaluronan enlarges the cell diameter or because hyaluronan on the cell surface interacts with other cells to form a cluster of embolus [31]. In the microvasculature of the target organ, tumour-associated thromboplastic events actively promote the metastatic process [30, 32, 33]. Coagulation and formation of microthrombi around tumour cells form a stationary phase for the tumour cells in the capillaries of the target organ. This allows time for the tumour cells to extravasate [34]. In addition, the reduced blood flow could increase trapping of circulating tumour cells, and fibrin deposits can facilitate and strengthen tumour cell lodgement to the microvasculature. Many of the tumour cell properties which enable them to penetrate blood vessels are similar to those of the white blood cells and their extravasation at inflammation sites [28]. Extravasation of tumour cells involves adhesion to the vascular endothelium, followed by egress through the basement membrane by mechanisms similar to those involved in the invasion process. Further proliferation of the metastatic cells depends on local growth factors, such as the acidic form of fibroblast growth factor and transforming growth factor beta [35]. The metastatic focus may serve as a primary site for further dissemination of tumour cells following the aforementioned cascade.

The metastatic dissemination may be in either a nondiscriminate manner, i.e. the first site encountered will be the most common site of the metastatic colony formation, or as a selective distribution to specific organs [35]. A selective organ distribution for some metastatic tumours has been demonstrated clinically and experimentally. Site specificity of tumour cell dissemination involves several mechanisms that include local growth factors, site-specific adhesion molecules and specific matrix properties [35].

Clinical studies show that tumour cells can undergo a period of dormancy followed by a rapid growth during relapse [36, 37]. Thus, a dormant tumour population remains clinically undetectable for months or years and consequently poses a continuous risk of recurrence. A variety of speculative mechanisms have been proposed, including hormonal, immune, and cell cycle effects, all of which assume that within a dormant tumour the neoplastic cells are not dividing. Recent studies show that metastases remain dormant when tumour cell proliferation is balanced by an equivalent rate of cell death and that angiogenesis inhibitors control metastatic growth by indirectly increasing apoptosis (programmed cell death) of tumour cells [38, 39].

The oral region is an uncommon site for metastatic lesions and probably not preferred for metastatic tumour cell colonisation. Metastatic tumours to the oral region are usually a secondary spread from other metastatic lesions. However, about 30% of oral metastases have been found to be the first sign of a metastatic process [40, 41]. Batson [42] proposed the valveless vertebral venous plexus as a mechanism for bypassing filtration through the lungs. An increase in intrathoracic pressure directs blood flow into this system from the caval and azygous venous system and accounts for the increased distribution of axial skeleton and head and neck metastasis [42, 43].

METASTASES TO THE ORAL REGION

Metastatic tumours to the oral region may manifest in the soft tissues or in the jawbones. In the literature, there are hundreds of single case reports and a small series of cases concerning metastatic lesions to the oral region. The accurate incidence of metastasis to the jawbones is difficult to access since the usual method to determine the distribution of a metastatic tumour in a patient has been by a radiographic skeletal survey. The jawbones are rarely included in such surveys. Thus, it has been suggested that metastatic tumours to the jawbones are far more common than previously noted. In the skeletal bones, the frequency of micrometastasis found in histological sections is higher than that found by conventional methods, such as bone scans and radiographs [44, 45]. In the mandible, microscopical deposits of metastatic tumour cells, not identified in routine radiographic examination, were found in 16% of autopsied carcinoma cases [46].

An attempt to analyse the information in the literature regarding metastatic tumours to the oral region poses several problems. Most of the information is presented in isolated case reports or in a very small series of cases. Moreover, in recent years, mainly unusual cases have been reported, which could cause some bias in favour of unusual cases regarding the primary site and oral site. In the past, several attempts were made to review the literature, but most investigators combined the information for tumours metastatic to the oral soft tissues with that for the jawbones. Recently, several studies have analysed the literature with a special focus on specific oral sites [40, 41, 47–50] and primary sites [51–56].

Differences have been found between various oral sites regarding the primary site and the clinical presentation of the metastatic tumour [40, 41]. There are more published cases of

Table 1. Correlation between site of origin and gender in oral mucosa and jawbone metastases

Primary site	Total	Oral mucosa			Jawbones		
		M	F	U*	M	F	U*
Breast	99	—	14		1	84	
Lung	91	33	7	2	41	7	1
Kidney	53	15	6	1	19	12	
Bone	38	3	6		17	12	
Colo-rectum	34	5	3		8	16	2
Skin	34	14	4	2	6	7	1
Adrenal†	34	—	—		17	17	
Female genital organs‡	25	—	10		—	15	
Prostate	23	1	—		22	—	
Liver	20	6	1		13	—	
Eye	19	1	1		6	9	2
Thyroid	15	—	—		3	12	
Testes	15	5	—		10	—	
Stomach	10	3	2	1	4	—	
Brain	8				3	5	
Oesophagus	7	2	1		4	—	
Bladder	6	—	1		3	2	
Other	16	5	2		7	2	—
Total	547	93	58	6	184	200	6

*U, unknown gender; †adrenal—all cases of neuroblastoma, including 4 cases from the retroperitoneum and 2 from the mediastinum; ‡female genital organs—uterus, ovaries, cervix, fallopian tubes. Data taken from [24, 25].

jawbone metastases than in oral soft tissues [41]. In their files, Summerlin *et al.* [57] found 124 cases of metastasis to the oral region. Most lesions were in the jawbones and only 16% were soft tissue metastases.

AGE AND GENDER

Most metastatic tumours to the oral region are found in patients in their fifth to seventh decade [40, 41]. However, the mean age in patients with metastases to the jawbones (45 years) is lower compared with patients with metastases to the oral soft tissues (54 years). The difference in the mean age between the two groups is probably due to cases of metastatic neuroblastoma to the jawbones in children, which have the propensity to metastasise to bones.

PRIMARY SITE

Almost any metastatic malignant tumour can potentially colonise in the oral region. The common primary sources of the metastatic tumours to the oral region are shown in Table 1. The most common are the breast, lung, kidney, bone and colon, which are also the most common malignant tumours in general.

Table 1 exhibits differences in oral site preference of metastatic tumour cells from different sources. The breast is the most common primary site for tumours metastasising to the jawbones, whereas the lung is the most common source for metastases to the oral soft tissues. The differences in oral site distribution is probably due to the different individual preferences of each tumour. For example, the breast prefers bone as its target organ [58]. Metastatic tumours from the adrenal, prostate, eye, and thyroid, which are more prevalent in the jawbones, are not found in the oral soft tissues. These tumours prefer skeletal bones as their metastatic target [58].

The primary site differs between genders. In males, the most common primary sites are the lung, followed by the kidney, bone and the colo-rectum, whereas in females, the most common primary sites are the breast, followed with much less frequency by the female genital organs and kidneys.

Race was not studied as a factor in the metastatic process in the oral region. However, Nishimura *et al.* [59], in a review of the Japanese literature, found that the uterus is the most common primary site in Japanese women, not the breast.

ORAL SITE

In the jawbones, the common location of metastatic lesions is the mandible, with the molar area being the most frequent involved site, followed by the premolar area [41]. The pathogenesis of the metastatic process in the jawbones is not clear. In the skeleton, bones with a red marrow are the preferential sites for metastatic deposits [60–62]. The jawbones, especially in old age, are poor in active marrow which is usually found in the posterior part of the mandible. Hashimoto *et al.* [46] suggest that haematopoietic areas in the mandible favour an early deposition of tumour cells. Remnants of haematopoietic marrow can also be detected in an edentulous mandible in cases of focal osteoporotic bone marrow defects [63]. These haematopoietically active sites may attract metastatic tumour cells.

In the oral soft tissues, the attached gingiva is the most common affected site, followed by the tongue, and with much less frequency by the remaining sites of the oral soft tissues [40]. The possible role of inflammation in the attraction of metastatic cells towards the attached gingiva has been suggested [40]. Malignant cells may be entrapped by the rich capillary network of chronically inflamed gingiva. The proliferating capillaries have a fragmented basement membrane

and are leaky, making them more penetrable by tumour cells than mature vessels [28].

The tongue is the second most common oral soft tissue site involved in the metastatic process. Baden *et al.* [48], in an extensive literature review, found 77 cases in which metastatic tumours were located in the tongue. The review shows that the mobile tongue has a slightly higher incidence of metastases than the base and/or posterior border. Although muscle is known to be resistent to metastasis, the tongue is well-vascularised and may have the potential to attract metastatic tumour cells.

A peculiar site for metastasis is the post-extraction site. Hirshberg *et al.* [47], when analysing the literature, found 55 cases in which tooth extraction preceded the discovery of the metastases. In many of these cases the metastatic tumour was assumed to be present in the area before extraction. However, in some cases, metastasis probably developed after extraction.

CLINICAL PRESENTATION

The clinical presentation of the metastatic lesion differs between the various sites in the oral region. In the jawbones, most patients complain of swelling, pain and paresthesia which develop in a relatively short time. A lytic radiolucent lesion with ill-defined margins is the common radiographic presentation [41, 57]. Occasional osteoblastic lesions are also observed. However, in approximately 5% of the cases, radiographs do not reveal any pathological changes [41].

The early manifestation of gingival metastases resembles a hyperplastic or reactive lesion, such as a pyogenic granuloma, peripheral giant cell granuloma, or fibrous epulis. In other locations in the oral soft tissues, and especially in the tongue, the clinical presentation is that of a submucosal mass.

In patients with a known malignant disease, the clinical presentation may favour the pre-operative diagnosis of metastasis. However, in nearly 30% of patients, the metastatic lesion in the oral region is the first indication of an undiscovered malignancy at a distant site. Moreover, lack of radiographic changes do not exclude the possible presence of a small metastatic deposit in the jawbone [41, 64].

METASTASES TO THE SALIVARY GLANDS

The major salivary glands are considered to be a relatively common site for metastatic involvement. Several extensive reviews have recently been published [49, 65]. The parotid gland is the most common salivary gland involved in the metastatic process, followed with a much lower incidence by the submandibular gland. The incidence of metastatic involvement of the salivary glands ranges between 3 and 25% of all epithelial malignancies affecting the salivary glands. The principal malignant tumours metastasising to the parotid gland originate from neighbouring structures. Cutaneous squamous cell carcinomas and melanomas are the most frequent offenders. However, in the sumandibular gland most metastatic tumours originate from distant organs, below the clavicles. This difference between the two salivary glands is most likely related to the absence of lymph nodes within the submandibular gland and the rich lymphatic plexus found within the parotid gland.

Clinically, most metastatic tumours in the salivary glands mimic primary salivary gland tumours. In cases where malignant lymphoepithelial lesion of the parotid is suspected, examination of the nasopharynx is mandatory in order to rule out metastatic undifferentiated nasopharyngeal carcinoma [66].

DIFFERENTIAL DIAGNOSIS

Attention should be given to differentiating primary intraoral malignancies from metastatic tumours. Several primary intraoral malignancies, especially those originating from salivary glands, have similar histological features to tumours occurring in distant organs. For example, primary ductal carcinoma of salivary gland origin versus metastatic breast carcinoma; primary intraoral clear cell tumour of salivary gland origin versus metastatic renal cell carcinoma; and primary intraoral squamous cell carcinoma versus metastatic squamous cell carcinoma from the lung. In addition, malignant soft tissue tumours may originate intraorally but, because of their relatively uncommon occurrence in the oral region, metastatic origin should be considered. A careful history and physical examination, as well as a thorough histological examination in these cases could eliminate most of the potential problems.

Whitaker *et al.* [55] suggest a structural approach to the evaluation of oral soft tissue metastasis, which would ensure that no relevant clinicopathological information is overlooked. The diagnostic algorithm for evaluation of oral soft tissue metastases constitute the following steps:

(1) Review clinical history.
(2) If there is a history of a previous tumour, obtain the slides and reports for review.
(3) Review available radiographic material.
(4) Perform a biopsy of the lesion and obtain an intraoperative evaluation of a frozen section.
(5) Evaluate the light microscopic features of the neoplasm. Based on the histological features, determine the need for special studies, i.e. histochemical stains, immunohistochemistry, electron microscopy.
(6) Plan the treatment protocol based on the clinical, pathological and radiographical information.

It is of interest to note that in some cases, in spite of vigorous investigation, no evidence of a primary tumour is found during the patient's lifetime. These cases are designated as "tumours of unknown origin".

TREATMENT AND PROGNOSIS

Oral metastases are usually evidence of a widespread disease and indicate a grave prognosis. The time from the appearance of the metastasis to death is no longer than a few months [41]. However, in some cases where the oral metastasis is the single metastatic site, adequate surgical treatment can improve prognosis [52].

Oral metastatic lesions, especially those located in the soft tissues, cause progressive discomfort. Pain, bleeding, superinfection, dysphagia, interference with mastication, and disfiguring are some of the main complaints of the patients. Therefore, even in cases with advanced malignant disease, paliation is necessary to improve the "quality of life". The best results can be achieved, whenever it is possible, with surgical excision.

In his review of the literature, Zachariades [67] found that the most popular treatment for oral metastases was irradiation

followed by no treatment at all, chemotherapy, surgery or a combination of irradiation and chemotherapy. In cases of widespread metastatic disease, Keller and Gunderson [68] suggest irradiation therapy as a paliative procedure; the dose and duration of irradiation being dependent on the patient's life expectancy.

The present treatment modalities of advanced metastatic disease are limited to paliation, because of the difficulty in delivering drugs to specific tumour locations, the inherent resistance of tumour cells to drugs, and the toxicity associated with the poor selectivity of anti-tumour compounds. Advances in molecular biology have provided new insight into the potential approach to therapy and substantial efforts are invested at the present time in translating the new knowledge of molecular mechanisms to new therapeutic modalities [69].

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