Journal of Clinical Periodontology
Official Journal of The European Federation of Periodontology
Founded by the British, Dutch, French, German, Scandinavian, and Swiss Societies of Periodontology

J Clin Periodontol 2009; 36: 488–492 doi: 10.1111/j.1600-051X.2009.01407.x

Metastatic tumours to the oral cavity: a survival study with a special focus on gingival metastases

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Seoane J, Van der Waal I, Van der Waal RIF, Cameselle-Teijeiro J, Antón I, Tardio A, Alcázar-Otero JJ, Varela-Centelles P, Diz P. Metastatic tumours to the oral cavity: a survival study with a special focus on gingival metastases. J Clin Periodontol 2009; 36: 488–492. doi: 10.1111/j.1600-051X.2009.01407.x.

Abstract

Aims: To describe survival from oral metastases, particularly gingival metastases, and to identify clinical prognostic variables.

Materials and Methods: A series of 39 patients were studied, analysing age, gender, primary tumour site, oral metastases site and histological type.

Results: Mean age: 62.3 ± 9.2 years, with similar prevalence by gender. The most frequent sites for primary tumours were the kidney (20.5%), lung (20.5%) and breast (20.5%). Gingival metastases represented 63.6% of all oral soft tissue metastases (7/11). The average time between primary tumour diagnosis and appearance of the gingival metastases was 9.7 ± 13.4 months. The median survival time since gingival metastases appearance was 5.2 months [95% confidence interval (CI) = 0–13.6]; no statistically significant difference with other oral locations was found by the Kaplan–Meier curves (log rank: 0.29; $p > 0.05$). Oral metastases involving the gingiva were more frequently found in the maxilla (85.7% *versus* 14.3%), whereas intra-osseous metastatic tumours were more frequent in the mandible (77.8% *versus* 22.2%; $p < 0.05$; odds ratio = 21; 95% CI = 2.0–210.1). None of the variables considered had a prognostic value as indicated by the Kaplan–Meier test.

Practical implications: The data in this paper show that 25% (and in other studies up to 37%) of oral metastases came from unknown primary tumours; thus a biopsy with histopathologic analysis is mandatory for every patient with a gingival mass.

Conclusions: This study reinforces the significance of gingival metastases as a poor prognosis indicator. Dental practitioners should suspect that gingival masses mimicking benign or inflammatory lesions may represent a sign of underlying malignant tumours.

Key words: gingiva; jaw; mouth neoplasms; neoplasm metastasis; survival analysis

Accepted for publication 3 March 2009

Oral metastatic tumours are uncommon and account for approximately 1% of malignant oral neoplasms (Meyer & Shklar 1965). Metastatic tumours to the oral region may occur in the jawbones. Alternatively, metastases may involve the soft tissues, usually the gingivae (Hirshberg et al. 1993, 1994, Hirshberg & Buchner 1995, Sánchez-Jiménez et al. 2005). There is no information on survival from gingival metastases in the literature, probably due to the fact that only isolated case reports or very small series of cases are available (Hirshberg et al. 1993, 1994, Hirshberg & Buchner 1995, Ostrosky et al. 2003, Ramón Ramírez et al. 2003, Sánchez-Jiménez et al. 2005, Park et al. 2006, Bernabé et al. 2008, Pozzi et al. 2008). Almost any metastatic malignant tumour can develop in the oral region. In patients with oral metastases, the most common primary tumours are located in the breast, lung, kidney, bone and colon, these also being the most prevalent in the general

Conflict of interest and source of funding statement

The authors declare that they have no conflict of interests.
This study has been self-supported by the authors.

population (Hirshberg & Buchner 1995). Variations in the incidence of primary tumour location may be due to several factors, including geographic influences and genetic mutations (D'Silva et al. 2006). The aims of this study were to describe survival from oral metastases from extraoral primary tumours of a series of Spanish and Dutch patients, with a special focus on gingival metastases, and to identify the clinical variables that influence prognosis.

Materials and Methods

A retrospective study based on histopathological and medical records from patients diagnosed with oral metastatic tumours was carried out. According to Clausen & Poulsen (1963) criteria, only cases of metastatic lesions with information regarding the primary tumours, oral location, clinical presentation and histological confirmation were included. Oral metastatic tumours were diagnosed in 15 patients at the Galician Health Service Hospitals (Galicia, Spain) from March 1978 to February 2007; while 24 patients, whose clinical data have been previously published (Van der Waal et al. 2003), were diagnosed at the VU University Medical Centre of Amsterdam (the Netherlands) from January 1970 to January 2001. A survival study was performed starting on the day the oral metastases were diagnosed and ending with either death (caused by the neoplasm) or survival at the end of the follow-up period.

The variables recorded were age, gender, site of primary tumour, site of oral metastases and histological type. Metastatic tumours to the jawbones (maxilla or mandible) and to the oral mucosa were considered. The cases where the oral location was in the jawbone with secondary invasion to the oral soft tissues were considered metastasic tumours to the jawbones.

A descriptive analysis of the data was performed, along with a survival analysis using Kaplan–Meier curves (log-rank test for comparison among curves). The Kruskal–Wallis test was used for comparing whole survival times in terms of the site of the primary tumour. The significance level established was 0.05.

Results

The mean age at diagnosis was 62.3 ± 9.2 years, ranging between 48 and 90. A similar prevalence by gender was observed (53.8% males and 46.2% females). The most frequent sites for primary tumours were the kidney (20.5%), lung (20.5%) and breast (20.5%). Adenocarcinoma was the most common histological type (53.8%). In most cases, the primary tumour was already known before the oral metastatic lesion appeared. Nevertheless, in 10 patients (25.6%) the oral lesion was diagnosed before the primary tumour was detected (Table 1). In 28 patients (71.8%), oral metastases were intra-osseous and the remaining 11 patients (28.2%) showed metastases to the oral mucosa.

Gingival metastases represented 63.6% (7/11) of all soft tissue metastases. The mean age of these patients was 65.2 ± 8.5, with a significant male predominance (71.4% male *versus* 28.6% female). Only one out of 11 cases of gingival metastases were diagnosed earlier than the primary tumour. Such primary tumours were mainly located in the lung (28.6%), liver (28.6%) and breast (28.6%). Oral metastases with gingival involvement were significantly more frequent in the maxilla than in the mandible (85.7% *versus* 14.3%), whereas intra-osseous metastatic tumours were more frequent in the mandible [77.8% mandible *versus* 22.2% maxilla; $p < 0.05$; odds ratio = 21; 95% confidence interval (CI) = 2.0–210.1].

The average time between the diagnosis of the primary tumour and the appearance of the oral metastases was 13.5 ± 21.3 months. The average time between the diagnosis of the primary tumour and appearance of the gingival metastases was 9.7 ± 13.4 months.

The mean survival time since the diagnosis of oral metastases was 6 months (95% CI = 4.5–7.5) (Fig. 1). The mean survival time since the diagnosis of gingival metastases was 5.2 months (95% CI = 0–13.6); no statistically significant difference with other oral locations was found by the Kaplan–Meier curves (log rank: 0.29; $p > 0.05$) (Fig. 2).

Age, gender, site of the primary tumour and site for oral metastases (maxilla *versus* mandible and jawbones *versus* oral mucosa) were not recognized as prognostic variables for survival (Table 2). No statistically significant differences were found in the mean survival times according to the site of the primary tumour (χ^2: 7.88; $p > 0.05$).

Discussion

A mean age of 54 years (range 9–88) has been suggested for patients with oral metastases by several review studies (Hirshberg et al. 1993, Hirshberg & Buchner 1995). Younger patients tend to show oral metastases from nervous system primary tumours (Hirshberg & Buchner 1995), as with the child with a cerebellum tumour in the present series. The male:female ratio is usually slightly higher for men (1.6:1) (Hirshberg et al. 1993, 1994, Hirshberg & Buchner 1995). However, in the present series, a significant predominance of males in cases of gingival metastases was detected (5:2).

The most common primary sites are the kidney and the lung, these also being the most common locations of malignant tumours in the general population (Hirshberg et al. 1993, 1994, Hirshberg & Buchner 1995). As in this series, the most frequent oral metastases are adenocarcinomas, but hypernephromas, seminomas, chorioepitheliomas and, in lower numbers, sarcomas, melanomas and neuroblastomas have also been described (Zachariades 1989, Hirshberg & Buchner 1995, Valdivieso et al. 1999).

In this series, all gingival metastases were from primary epithelial tumours, which are consistent with malignancies of epithelial origin accounting for >80% of all primary cancers, regardless of the tumour site (Keller & Gunderson 1987).

There are more published cases of jawbone metastases than oral soft tissue metastases (Keller & Gunderson 1987, Zachariades 1989, Hirshberg et al. 1993, 1994, Hirshberg & Buchner 1995, Valdivieso et al. 1999). The most common location of intra-osseous metastatic tumours was the mandible, while the gingiva and tongue were the most common sites in the soft tissues. These locations are in accord with those described elsewhere in the English language literature (Hirshberg et al. 1993, 1994, Hirshberg & Buchner 1995).

The gingival metastases seem to be located more often in the upper jaw (6/7), although in some series the gingival lesions were almost equally distributed between the maxilla and the mandible (Hirshberg et al. 1993). The jawbones and their adjacent gingiva share a common blood supply through the maxillary artery. In the maxilla, it is through the antero- and postero-superior alveolar arteries, and in the mandible only through the inferior alveolar artery. The role of inflammation in the attrac-

Table 1. Clinicopathological features of the oral metastases ($n = 39$)

Site of oral metastasis	Age (years) at time of diagnosis	Gender	Site of primary tumour	Histological type	Metastases found before primary tumour	Time from primary tumour diagnosis to death or end point (months)
Soft tissues						
Upper gingival	69	Male	Kidney	Clear cell carcinoma	No	43.8
Upper gingival	48	Female	Breast	Adenocarcinoma	No	20
Upper gingiva	62	Female	Breast	Adenocarcinoma	Yes	2
Upper gingival	68	Male	Lung	Squamous cell carcinoma	No	28
Upper gingival	65	Male	Liver	Hepatocellular carcinoma	No	14.7
Upper gingival	71	Male	Liver	Hepatocellular carcinoma	No	1.1
Lower gingiva	74	Male	Lung	Large cells carcinoma	No	8.5
Tongue	58	Female	Thyroid	Papillary thyroid carcinoma	Yes	118.5
Tongue	45	Female	Unknown primary	Undifferentiated carcinoma	No	4
Soft palate	62	Female	Kidney	Clear cell carcinoma	No	7
Bucal mucosa	67	Male	Kidney	Clear cell carcinoma	No	31
Jawbones						
Mandible	54	Male	Lung	Adenocarcinoma	No	9.7
Mandible	60	Male	Kidney	Clear cell carcinoma	Yes	3.2
Mandible	66	Female	Breast	Adenocarcinoma	No	15.5
Mandible	57	Female	Breast	Adenocarcinoma	Yes	17.6*
Mandible	69	Female	Thyroid	Papillary thyroid carcinoma	No	25.0
Mandible	59	Male	Colon	Adenocarcinoma	No	24.3
Mandible	87	Female	Unknown primary	Adenocarcinoma	Yes	0.8
Mandible	54	Female	Breast	Adenocarcinoma	No	18
Mandible	57	Female	Breast	Adenocarcinoma	No	69
Mandible	61	Female	Breast	Adenocarcinoma	No	108
Mandible	63	Female	Breast	Adenocarcinoma	No	114
Mandible	55	Male	Lung	Squamous cell carcinoma	Yes	12
Mandible	60	Male	Lung	Adenocarcinoma	Yes	25
Mandible	78	Male	Lung	Adenocarcinoma	Yes	3
Mandible	48	Male	Kidney	Clear cell carcinoma	No	53
Mandible	53	Female	Unknown primary	Adenocarcinoma	No	5
Mandible	77	Male	Unknown primary	Adenocarcinoma	No	11
Mandible	64	Male	Prostate	Adenocarcinoma	No	13
Mandible	74	Male	Prostate	Adenocarcinoma	No	20
Mandible	90	Male	Prostate	Adenocarcinoma	No	20
Mandible	8	Female	Cerebellum	Medulloblastoma	No	13
Mandible & maxilla	59	Male	Lung	Squamous cell carcinoma	Yes	2
Maxilla	52	Male	Kidney	Clear cell carcinoma	No	25.6
Maxilla	74	Male	Kidney	Clear cell carcinoma	Yes	1.0*
Maxilla	64	Female	Kidney	Clear cell carcinoma	No	8
Maxilla	61	Female	Lung	Adenocarcinoma	No	10.9
Hard palate	70	Female	Colon	Adenocarcinoma	No	49
Hard palate	60	Male	Oesophagus	Adenocarcinoma	No	17

*Survivors.

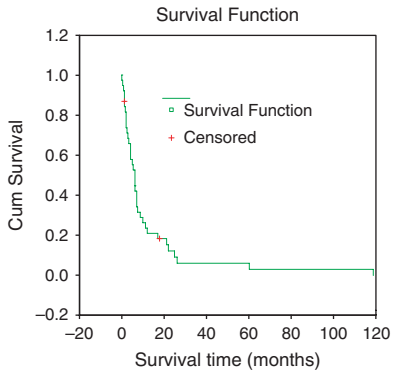

Fig. 1. Survival function for oral metastases from extraoral primary tumours.

tion of metastatic cells towards the attached gingiva has been suggested (Hirshberg et al. 1993). Malignant cells may be entrapped by the rich capillary network of the chronically inflamed gingival (Nagy et al. 1989). However, the pathogenesis of the preference of gingival metastases for maxillary locations and bone metastases for mandibular ones remains unclear. Equally, the precise mechanism of metastases of infradiaphragmatic neoplasms to the oral region is poorly understood. It is believed that the portal haematogenous route is the preferred mode for oral metastases. However, oral metastases have been documented in the absence of pulmonary lesions. In an attempt to explain metastases to the oral region from a primary tumour in the lower part of the body, especially in the absence of lung metastases, the valveless vertebral venous plexus (Batson's plexus) has been proposed as a mechanism for bypassing filtration through the lungs (Batson 1940, Appenzeller et al. 1971). This hypothesis has not been confirmed.

The early manifestation of gingival metastases may resemble a hyperplastic or a reactive lesion, such as a pyogenic granuloma, peripheral giant cell granuloma or fibrous epulis (Hirshberg & Buchner 1995). Some authors have proposed that the rapid and expansive growth that is generally present in the gingival metastases could be used as a differential characteristic (Kanazawa & Sato 1989). However, this clinical finding can also be observed in pyogenic granulomas (Neville et al. 1995). In up

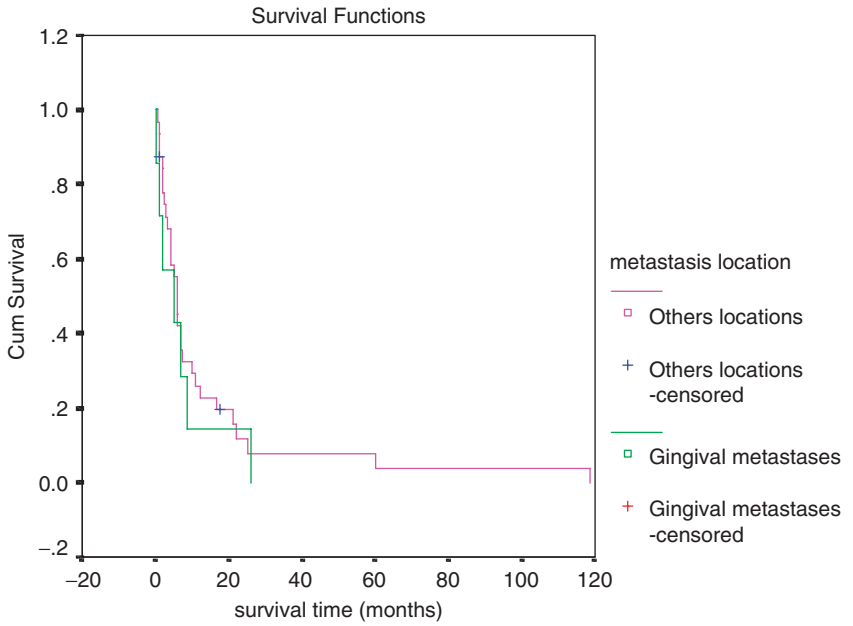

Fig. 2. Survival function for gingival metastases *versus* other oral locations.

Table 2. Influence of the variables considered on survival (Kaplan–Meier test)

Variable	Survival time (months) mean	Standard error	95% CI	Log rank
Age (years)				
⩽60	16.88	8.27	0.68–33.08	0.405
>60	9.35	2.98	2.60–7.93	
Sex				
Male	8.64	1.85	5.01–12.27	0.714
Female	19.07	8.47	2.47–35.67	
Oral metastases site				
Oral mucosa	17.78	10.41	0.0–38.17	0.572
Jawbones	9.90	2.69	4.63–15.17	
Jawbones metastasis				
Maxilla	6.68	2.12	2.53–10.82	0.570
Mandible	10.97	3.25	4.59–17.34	

CI, confidence interval.

to 37% of patients, oral metastases have been found to be the first sign of a metastatic process (Sanchez-Aniceto et al. 1990, Hirshberg et al. 1993, 1994, Hirshberg & Buchner 1995, Cardona et al. 2000). In this series, a 25% occurrence was observed, but with only in 1 case of gingival metastasis. Therefore, an incorrect diagnosis based on clinical features may result in delayed or inappropriate treatment of the oral lesions.

The average time between the diagnosis of the primary tumour and appearance of the jawbone metastases was estimated to be 39.5 months (Hirshberg et al. 1994). Zachariades (1989) reported that in up to 45% of cases, an oral metastasis occurred within 1 year of the diagnosis of a primary tumour and increased to 73% of cases within 4 years of diagnosis. These finding are similar to those reported in this paper.

Most patients with a metastatic tumour in the oral cavity have also developed metastases at other sites, often leaving no other option for treatment than palliation (Van der Waal et al. 2003). The prognosis is poor. Most patients die within the first year after the diagnosis of metastases, with a 4-year survival rate of 10% (Hirshberg et al. 1994). In the present series, most patients with gingival metastases died within the first 6 months following diagnosis.

The survival time was not affected by the gender of the patient, the site of the primary tumour or the site of the oral osseous metastases (maxilla *versus* mandible). Our results also suggest the absence of a prognostic value for the classification of metastatic tumours in terms of soft *versus* hard tissues within the oral region. Furthermore, this study reinforces the significance of gingival metastases as evidence of a widespread disease and indicates a poor prognosis.

Dental practitioners should recognize that gingival masses mimicking benign or inflammatory lesions may represent an initial sign of underlying malignant tumours. The data in this paper show that 25% (and in other studies up to 37%) of oral metastases came from unknown primary tumours; thus, biopsy with histopathologic analysis is mandatory for every patient with a gingival mass.

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Clinical Relevance

Scientific rationale for the study: To the best of our knowledge, specific information on gingival metastases is very scarce and based on isolated cases or very small series with no reported survival studies.

Principal findings: Gingival metastases appear more frequently in the upper jaw, and are an indicator of a poor prognosis [the mean survival time since the diagnosis of gingival metastases was 5.2 months (95% CI = 0–13.6)].

Practical implications: The data in this paper show that 25% (and in other studies up to 37%) of oral metastases came from unknown primary tumours; thus, a biopsy with histopathologic analysis is mandatory for every patient with a gingival mass.