# Distant Metastases and Malignant Cellular Neoplasms Encountered in the Oral and Maxillofacial Region: Analysis of 92 Patients Treated at a Single Institution

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**Abstract.** *Distant metastases to the oral cavity, the face or facial skeleton are rare and/in are usually found in such locations at a late stage of the malignancy. In the majority of cases, the malignancy is already known at the time of admission. However, a distant metastasis as the first sign of a cancer developing in other parts of body may occasionally be found. Malignant cellular neoplasms, in particular those derived from the haematopoetic system, are also rarely diagnosed first in the oral and maxillofacial (OMF) region. Therapy for these patients is difficult. Main parameters of therapy are type of tumour, general health condition and localization of the tumour. The aim of this study was to analyse the types of tumour, the treatment modalities and the outcome of patients who experienced a malignant disease in the OMF region under these conditions. Patients: A total of 92 patients were treated for distant metastases or cellular malignant neoplasms in the OMF region at a single institution (female: 45, male: 47, ratio 1:1.04; mean age: 61.4 years; range: 5 to 88 years). Results: In females, the most frequent primary tumour was breast cancer (40%), followed by malignant lymphoma (17.8%), malignant melanoma and hypernephroma (8.9% each). In males, the most frequent primaries were lymphomas (25.5%), followed by lung cancer and carcinoma of unknown primary site (CUPD syndrome; 17 each). Hypernephroma was the site of origin in 8.5%. Mean survival of patients with solid tumours was 1.28 years and 4.85 years in patients with cellular neoplasm. Survival rates differed significantly in both diagnostic groups (p=0.001). All patients with distant metastases died within 5 years. In patients with malignant cellular neoplasms, significant differences in survival rates were identified. Male survival was calculated to be 90% at 5 years' follow-up, but was poor for females (0%). Conclusion: Prognosis is poor in patients with distant metastases from solid tumours of other body parts to the OMF region. Female patients with malignant cellular neoplasms becoming symptomatic in this region share the fate of patients with solid metastases. Males with this diagnosis have a better prognosis.*

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Distant metastases to the oral cavity, the face or facial skeleton are rare (1, 2) and are usually found in this locations at a late stage of the diseases. In the majority of cases, the malignancy is already known at the time of admission. However, a distant metastasis as the first sign of a cancer developing in other parts of body may occasionally be found. Indeed, in about 30% of cases with distant metastases to the oral and maxillofacial (OMF) region, the diagnosis is not established at the time of referral (3). Malignant cellular neoplasms, in particular those derived from the haematopoetic system, are also rarely diagnosed first in the OMF region. Indeed, it is questionable whether these entities are true examples of metastatic lesions or the tissues of the OMF region give rise to these tumours (2). From a surgical point of view, the clinical aspect of these lesions is usually indistinguishable. However, therapy and outcome may be different. It is difficult to treat these patients. It is general accepted that the demonstration of metastatic lesions in the OMF region involves a grave prognosis. Main parameters of therapy are type of tumour, general health condition, and localization of the tumour. The aim of this study was to analyse the types of tumour, the treatment modalities and the outcome of patients who experienced a distant metastasis or cellular neoplasm in the OMF region.

Table I. *Primary tumours in patients with distant metastases to or cellular neoplasms in the oral and maxillofacial region. There were certain differences between the genders concerning the predisposition to develop metastases to the oral and maxillofacial region.*

| Primary* | Female (45=100%) | Males (47=100%) | Total (92=100%) |
|---|---|---|---|
| Lymphoma | 8 (17.8%) | 12 (25.5%) | 20 (21.7%) |
| Lung | 3 (6.7 %) | 8 (17%) | 11 (12%) |
| CUPD | - | 8 (17%) | 8 (8.7%) |
| Hypernephroma | 4 (8.9%) | 4 (8.5%) | 8 (8.7%) |
| Histiocytoma | 1 (2.2%) | 4 (8.5%) | 5 (5.4%) |
| Rectal | 3 (6.7%) | 3 (6.4%) | 6 (6.5%) |
| Prostate | - | 2 (4.3%) | 2 (2.2%) |
| Plasmacytoma | - | 2 (4.3%) | 2 (2.2%) |
| Colon | - | 1 (2.1%) | 1 (1.1%) |
| Urothelial | - | 1 (2.1%) | 1 (1.1%) |
| Chondrosarcoma | 1 (2.2%) | 1 (2.1%) | 2 (2.2%) |
| Malignant melanoma | 4 (8.9%) | 1 (2.1%) | 5 (5.4%) |
| Breast | 18 (40%) | | 18 (19.6%) |
| Vulva | 1 (2.2%) | | 1 (1.1%) |
| Thyroid | 1 (2.2%) | | 1 (1.1%) |
| Liposarcoma | | | 1 (1.1%) |
| Total | 45 | 47 | 92 |

*Carcinoma if not otherwise specified.

## Patients and Methods

The files of patients treated at a single institution between 1974 and 2002 for a cellular neoplasm or distant metastasis to the OMF region were evaluated. A total of 92 patients fulfilled the inclusion criteria (female: 45, male: 47, ratio 1:1.04; mean age: 61.4 years; range: 5-88 years).

## Results

*All tumours*. Malignant lymphoma was the most frequent diagnosis (n=20, 21.7%), followed by breast cancer (n=18, 19.6%, females only). The third place in tumour frequency was occupied by metastatic lung cancer (n=11, 12%). Other entities were registered in numbers smaller than 10 (Table I).

*Gender and localization of tumour.* The most frequent primary tumour in females was breast cancer (n=18, 40%), followed by malignant lymphoma (17.8%), malignant melanoma and hypernephroma (8.9% each). In males, the most frequent primaries were lymphomas (25.5%), followed by lung cancer and carcinoma of unknown primary site (CUPD syndrome; 17 each). Hypernephroma was the site of origin in 8.5% and 8.6%, respectively (Table I).

*Metastases affecting the facial skeleton*. Osseous metastases were registered in 54 patients (58.7%) and were secondary to breast or lung cancer, or of lymphatic origin (Table II). Simultaneous presence of two or more metastases was noted in 5 patients. In these cases, the calvaria were affected in addition to the jaws. A total of 60 metastases of the facial skeleton were noted. The mandible was by far the most frequent site of metastasis in the whole group (n=39, Table III). Within the large group of mandibular neoplasms, the predilection of the alveolar process was clear (Table IV).

Table II. *Primary sites of tumours metastatic to the facial skeleton.*

| Primary | No. of cases (%) |
|---|---|
| Breast | 12 (22.2%) |
| Lung | 8 (14.8%) |
| Lymphoma | 8 (14.8%) |
| Hypernephroma | 7 (13%) |
| Plasmacytoma | 5 (9.3%) |
| Histiocytoma | 3 (5.6%) |
| Rectal | 3 (5.6%) |
| Prostate | 2 (3.7%) |
| Colon | 1 (1.9%) |
| Thyroid | 1 (1.9%) |
| Malignant melanoma | 1 (1.9%) |
| Urothelial | 1 (1.9%) |
| Chondrosarcoma | 1 (1.9%) |
| CUPD* | 1 (1.9%) |
| Total | 54 (100%) |

CUPD: Carcinoma of unknown primary site. *Adenocarcinoma.

*Metastases affecting the soft tissues*. Distant metastases to the OMF region were situated in the regional lymph nodes in every second patient, followed by the tumourous invasion of the buccal mucosa. Other locations of soft tissue metastasis were rare and showed the major salivary gland as a remarkable site of distant spread (Table V).

*Multiple distant metastases/cellular neoplasm*. Thirteen patients (14.1%) were found with 2 metastases in the OMF region (Table VI). Breast cancer patients constituted the largest subgroup of these patients. Thirty-four patients (37%) developed further metastases in regions outside the OMF region. Table VII summarises the metastases found inside and outside the OMF region related to the primary tumour.

*OMF metastasis as the first finding of advanced stage cancer.* The OMF tumour was diagnostic for cancer in 24 patients (lung: n=5, breast: n=4, lymphoma: n=4, hypernephroma, plasmacytoma or histiocytoma: n=3 each, thyroid or rectal carcinoma: n=1 each. In 8 patients no primary site was found (squamous cell carcinoma: n=7).

*Skeletal radiology*. Standard X-rays of the facial skeleton were performed in 48 patients with osseous invasion of the OMF region. Osteolysis was revealed in 44 patients (91.6%). Two patients with breast cancer showed either osteoplastic or

Table III. *Affected bones of the facial skeleton in patients with distant metastases to or cellular neoplasms in the OMF region.*

| Localization | No. of cases (n=60, 100%) |
|---|---|
| Mandible | 39 (65%) |
| Maxilla | 9 (15%) |
| Calvaria | 8 (13.3%) |
| Orbital walls | 2 (3.3%) |
| Sphenoid | 1 (3.3%) |
| Zygoma | 1 (1.7%) |

Table IV. *Localization of neoplasms invading the mandible.*

| Localization | No. of cases (n=39, 100%) |
|---|---|
| Corpus and alveolar process | 27 (69.2%) |
| Ramus | 6 (15.4%) |
| Condylar process | 3 (7.7%) |
| Mandibular angle/body | 2 (5.1%) |
| Condylar/muscular process and angle | 1 (2.6%) |

Table V. *Soft tissue metastases in the OMF region.*

| Localization | No. of cases (n=46, 100%) |
|---|---|
| Lymph nodes of the neck | 23 (50%) |
| Buccal mucosa | 8 (17.4%) |
| Parotid gland | 4 (8.7%) |
| Submandibular gland | 4 (8.7%) |
| Oral mucosa | 3 (6.5%) |
| Eyelids | 2 (4.3%) |
| Ala of the nose | 2 (4.3%) |

osteoplastic-osteolytic mandibular lesions. In two cases, X-rays failed to demonstrate the osseous invasion properly. A skeletal scintigraphy was performed in 34 out of the 48 patients with osseous metastasis. This technique detected the skeletal affection properly in 32 patients, leaving 2 patients with histologically proven osseous invasion incorrectly diagnosed.

*Clinical presentation*. Symptoms and findings indicative of the stage of disease were predominantly localized swellings, either asymptomatic (n=34) or symptomatic (n=31). Other findings were: restricted opening of the mouth (n=5), paraesthesia or hypaesthesia branches of the trigeminal nerve (n=4), pathological fracture (n=4), oral ulcer (n=4), impaired vision/diplopia (n=3) and rarely pain (n=2). Five patients were incidentally diagnosed.

Table VI. *Multiple metastases of solid tumours or manifestation of cellular neoplasms in the OMF region (n=13).*

| Primary | 1. Metastasis | 2. Metastasis |
|---|---|---|
| Breast | Mandibular ramus | Cervical lymph node |
| Breast | Mandibular body | Cervical lymph node |
| Breast | Mandibular body | Calvaria |
| Breast | Orbital wall | Calvaria |
| Urethral | Mandibular body | Cervical lymph node |
| Prostate | Mandibular body | Calvaria |
| Malignant melanoma | Submandibular gland | Cervical lymph node |
| Chondrosarcoma | Parotid gland | Submandibular gland |
| Plasmacytoma | Maxilla and mandible | Calvaria |
| Lymphoma | Skull base | Cervical lymph node |
| Lymphoma | Oral mucosa | Cervical lymph node |
| Histiocytoma | Mandibular body | Maxilla |
| Lung | Mandibular body | Cervical lymph node |

*Treatment*. Treatment options were palliatively intended and individualised. Therefore all treatment modalities were found in this collective. Surgery was applied in 70.6% of patients. However, adjuvant treatment in addition to surgery was often chosen (Table VIII).

*Survival of patients with solid tumours*. Out of 62 patients with solid tumours, 51 died 1.1 years after admission on average (range of follow-up interval: 0.02-5.34 years). Twenty-four patients were male and 27 were female. Mortality of this subgroup was similar in both sexes (male: 82.8%, female: 81.8%). Analysis of the life table showed a mean survival time of 1.09±0.20 years for males (n=29, 95% confidence interval (CI): 0.69-1.48 years and a median survival time of 0.89±0.21) years (95% CI: 0.47-1.30 years). All male patients were dead after 3 years of follow-up control. Mean survival of females (n=33) was 1.40±0.30 years (median survival time: 0.69±0.12 years, 95% CI: 0.46-0.92 years). No female patient survived for 5 years. Mean and median survival times of females were longer than for males. However, the difference proved to be insignificant (log-rank test: $p$=0.6561, Figure 1).

*Survival of patients with cellular neoplasm*. Six out of 30 patients died within the follow-up period of 1.8±1.9 years (range of follow-up interval: 0.02-6.32 years). Five of these deceased patients were females. Mortality rates related to gender differed in this group (male: 5.6%, female: 41.7%). The 5-year survival rate was calculated as 90.4% for men (n=18, mean survival time: 5.76±0.47 years, 95% CI: 4.84-6.67 years), but declined to zero in women (n=12; mean survival time: 3.20±1.14 years, 95% CI: 0.97-5.43 years; median survival time: 2.16±0.67 years, 95% CI: 0.85-3.46 years). Survival times for females were significantly shorter than for males (log-rank test: $p$=0.0219) (Figure 2).

Table VII. *Metastases and multiple lesions of cellular neoplasms inside and outside the OMF region.*

| Primary | Lesion inside the OMF region | Further lesions outside the OMF region |
|---|---|---|
| Breast | Cervical lymph node, oral mucosa, cheek, mandible, calvaria | Brain, liver, lungs, vertebral column, femur, tibia, pelvis, sternum |
| Hypernephroma | Mandible, parotid gland | Lymph node (psoas), lungs, pelvis, vertebral column |
| Lung | Oral mucosa, mandible, cervical lymph node | Ovary, kidneys, tibia, brain, lungs, mediastinal lymph nodes, vertebral column, femur |
| Malignant melanoma | Mandible, parotid gland, submandibular gland, cervical lymph nodes | Adrenal gland, tibia, lungs |
| Rectal | Mandible | Ribs, pelvis, vertebral column, lungs, liver |
| Chondrosarcoma | Maxilla, parotid gland, submandibular gland | Brain, mediastinal |
| Colon | Maxilla | Retroperitoneal, lungs, liver, ribs, sternum, femur, scapula |
| CUPD | Cervical lymph node, mandible, skull base | Vertebral column |
| Prostate | Mandible, skull base | Clavicula, vertebral column, ribs |
| Lymphoma | Mandible, maxilla | Vertebral column, humerus |
| Plasmacytoma | Calvaria | Femur |

*Comparison of patients with cellular neoplasm and solid tumours*. The median survival time of patients with solid tumours (n=62) was low (0.78±0.20 years, 95% CI: 0.90-1.67 years) and the expectancy of survival for 5 years after diagnosis was 4.4%. On the other hand, the median survival of patients with cellular neoplasm (n=30) was clearly better (6.32±0.0 years, 95% CI: 2.0-5.98 years) and the expectancy of survival for 5 years increased to 35.6%. The calculation of survival according to Kaplan-Meier revealed a mean survival of 1.28±0.20 years, 95% CI: 0.90-1.67 years) for the patients with a solid neoplasm that was statistically significantly lower than the mean survival time of patients with a cellular neoplasm (4.85±0.62 years, 95% CI: 3.63-6.06 years; $p<0.001$). The differences in survival times are shown in Figure 3.

Table VIII. *Treatment for patients with metastases or cellular neoplasms.*

| Treatment | No. of patients (n=92, 100%) |
|---|---|
| Surgery | 41 (44.6%) |
| Surgery and chemotherapy | 12 (13%) |
| Surgery and radiotherapy | 11 (12%) |
| Chemotherapy | 11 (12%) |
| Radiotherapy | 5 (6.5%) |
| Chemotherapy and radiotherapy | 5 (5.4%) |
| Surgery, chemotherapy and radiotherapy | 1 (1.1%) |
| Diagnosis only | 6 (6.5%) |

## Discussion

This study demonstrated a substantial difference concerning the survival rates of patients with solid metastases and patients with cellular neoplasms detected in the OMF region. The composition of the patients did not differ from that of other studies (3).

Breast cancer is the most common source of metastatic spread to the OMF region (2), followed by lung, kidney, bone and colon cancer (1). In this study, breast cancer was found to be the most common metastasizing carcinoma, followed by lung and kidney carcinomas and CUPD. There are differences related to the entity regarding the certainty of the diagnosis in patients with distant metastases to the OMF region. Whereas patients with breast cancer are usually aware of their disease in the situation of tumour manifestations in the OMF region (4), tumours metastatic from the kidney and lung become more frequently first symptomatic due to distant spread (3). In this study, the number of patients with breast, lung or kidney cancer diagnosed following appropriate diagnostics for OMF lesions did not differ. However, regarding the total number of affected patients, the percentage of breast cancer patients already aware of their diagnosis and those with renal cancer not knowing their advanced stage disease was in the expected range. The range of patients with CUPD in this list may be too high with regard to current diagnostic standards, namely positron-emission tomography (PET). Indeed, the time interval of patient recruitment predated PET implementation as a standard diagnostic for CUPD in the head and neck region (5). However, up to 10% of patients with head and neck cancer still were diagnosed as having a CUPD (8.7%, all patients, and 13.3%, carcinoma patients only). CUPD was diagnosed in men only, for unknown reasons.

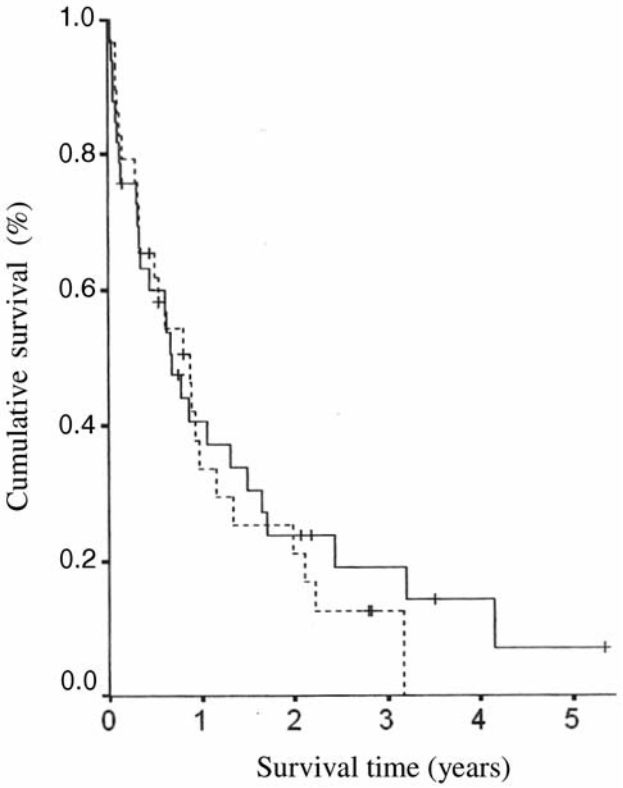


Figure 1. *Survival curves following diagnosis of a solid tumour (females: solid line; males: dotted line). Mean and median survival times were longer for females than for males but differences were statistically not significant.*

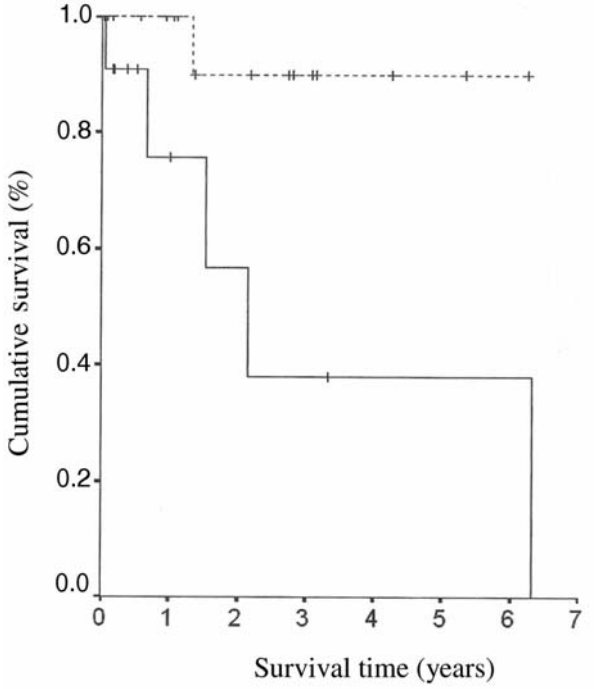


*Figure 2. Survival curves of patients with cellular neoplasms of the OMF region following therapy (females: solid line; males: dotted line). Total survival time was significantly longer in males than in females.*

Lymphoma was the second most frequent diagnosis of the whole group. This result was not surprising owing to the well-known ability of bones to generate blood cells. It still remains debatable whether these tumours arise in this region or are already metastases from other regions of the lymphatic and haematological systems. These patients were included in this evaluation due to the similar clinical aspect that may be seen during physical investigations and on standard X-rays (2). Patients with this diagnosis had a better prognosis than those with a solid tumour. However, this difference was restricted to men only. It was not possible to address the cause of this statistically significant difference between men and women and this argues in favour of further studies on this item.

Skeletal metastases were more often recorded than soft tissue metastases of the OMF region. This distinction may be due to specific routes of metastasis attributable to certain entities, such as prostate, lung or breast cancer, but may also be the result of different ways of referral to specialised clinics. It is well known that the mandible is the predominant target for osseous metastases to the facial skeleton (1, 6). However, in about 1 out of 3 cases, other

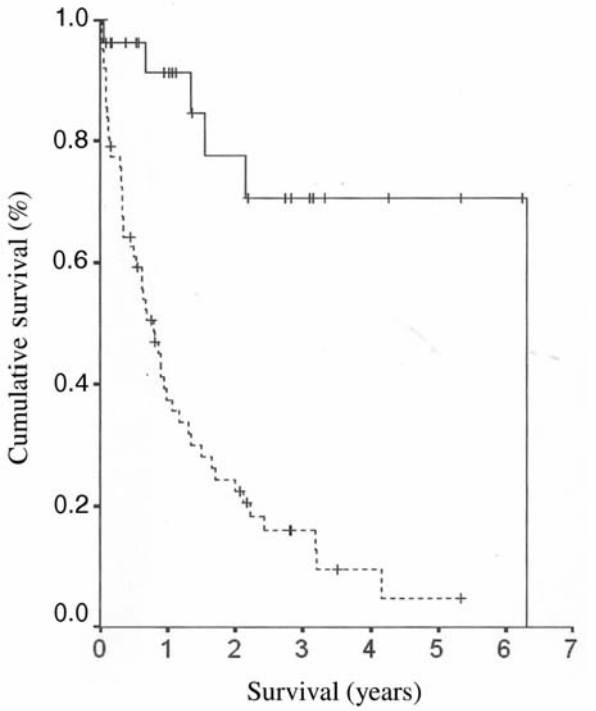


Figure 3. *Comparison of overall survival of two groups of patients with malignancies of the OMF region. The continuous line shows the better survival rate of patients with a cellular neoplasm of the OMF region compared to distant metastases of solid malignancies to the same region.*

skull bones are also invaded by malignant disease. Solitary metastasis is the most common finding in these patients. The diagnosis of simultaneous tumours of the OMF region in this group was low (13/92, 14.1%). However, in 38.5% patients of this subgroup, both bone and soft tissues were affected, demonstrating the need for complementary diagnostics to disclose both soft and hard tissue invasions.

The major salivary glands are regarded to be relatively frequently affected in the course of metastatic spread of malignancies (7, 8). The parotid gland is the predominant salivary gland involved in metastasis. There are substantial differences between the parotid and the submandibular gland regarding the primary site that gives rise to their metastatic involvement. The parotid gland is principally affected by tumours originating in neighbouring organs, such as cutaneous melanoma, squamous cell carcinoma and the nasopharynx (9, 10). On the other hand, distant metastasis to the submandibular gland originates from organs more distant than those affecting the parotid, in particular below the clavicle. This study showed that the knowledge of these differences provide a useful tool for screening patients with an unknown primary tumour, but cannot serve as a standard (11).

## Conclusion

Prognosis is poor in patients with distant metastases of solid tumours of other body parts to the OMF region. Female patients with malignant cellular neoplasms becoming symptomatic in this region share the fates of patients with solid metastases. Males with this diagnosis have a better prognosis.

## References


1 Hirshberg A and Buchner A: Metastatic tumours to the oral region. An overview. Oral Oncol Eur J Cancer *31b*: 355-360, 1995.

2 Shafer WG, Hine M and Levy BM: A Textbook of Oral Pathology, Saunders, Philadelphia, pp. 213-215, 1983.

3 Van der Waal RIF, Buter J and van der Waal I: Oral metastases: report of 24 cases. Br J Oral Maxillofac Surg *41*: 3-6, 2003.

4 Mathis H and Kornrumpf E: Metastasierung in die Kieferknochen und deren Weichteilbedeckung. Dtsch zahnärztl Z *11*: 1374-1382, 1956.

5 Schneider K, Hrasky A, Aschoff P, Bihl H and Hagen R: Significance of PET and integrated PET/CT in the diagnostics of occult primary tumors. Laryngorhinootol *85*: 819-823, 2006 (in German).

6 Frenkel G: Zentrale metastatische Karzinome des Unterkiefers. *In*: K Schuchardt (Hrsg) Fortschritte der Kiefer- und Gesichtschirurgie, Vol. XV, Thieme, Stuttgart, pp. 157-160, 1972.

7 Batsakis JG and Bautina E: Metastases to major salivary glands. Ann Otol Rhinol Laryngol *99*: 501-503, 1990.

8 Gnepp DR: Metastatic disease to the major salivary glands. *In*: Ellis GL, Auclair PL and Gnepp DR (eds.). Surgical Pathology of the Salivary Glands. Philadelphia, WB Saunders: pp. 560-569, 1991.

9 Wanamaker JR, Kraus DH, Biscotti CV and Eliacher I: Undifferentiated nasopharyngeal carcinoma presenting as a parotid mass. Head Neck Surg *16*: 589-593, 1994.

10 Friedrich RE: Immunhistochemische und autoradiographische Untersuchungen zum anaplastischen Karzinom der Kopf- und Hals-Region. Med Diss, Berlin, 1993.

11 Li L, Friedrich RE, Schmelzle R and Donath K: Metachronous bilateral metastases of renal cell carcinoma to the parotid region. J Oral Maxillofac Surg *59*: 434-438, 2001.


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