



Metastatic Tumors have Become the Most Important Entity in Parotid Gland Cancer

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Abstract

Aim: Lymphatic tissue enclosed in the parenchyma is the precondition for metastases to the parotid gland. Significance and clinical parameters of metastatic tumors are presented.

Methods: The clinical data of 837 patients over a period of 40 years who received a parotidectomy for a tumor disease are analyzed. Two 20 years intervals are compared.

Results: Of those, 144 tumors were malignant (17.2%) and 72 were metastases. The proportion of metastases was 24.4% in the first two decades and 61.6% in the second. Metastatic parotid tumor affected male patients in 75% with a mean age of 71.1 (23 and 93 years). At 81.8% metastatic tumors were squamous cell carcinoma. Metastatic tumors were in 51 cases cutaneous tumors of the head and neck, in 8 cases carcinoma of the oral cavity or pharynx and in 4 of the outer ear canals, in 6 cases the primary tumor was located below the clavicle and another 4 cases were diagnosed as CUP syndromes.

Discussion: Metastatic tumors have become the most important entity in malignant parotid tumors of our patients. Indications of a metastatic disease are older age, male sex, actinically damaged skin, histological findings and tumor diseases, in particular skin carcinomas, in history.

Conclusion: Distinguishing between glandular primary and parotid metastasis is an essential precondition for stratifying risk, planning treatment and aftercare in malignant parotid neoplasms.

Keywords: Parotid gland; Malignant tumors; Metastases; Epidemiology; Diagnostic

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Introduction

200-300 neck lymph nodes are topographically assigned to seven groups (Level I–VII), the currently valid nomenclature dates back to the year 2000. In addition, there are superficial lymph nodes around the external jugular vein, which are particularly relevant in metastatic skin cancers, and lymph nodes in the Parotid Gland (PG). The lymph nodes drain the lymph of the head and neck region in a relatively constant manner [1,2].

The PG differs from the other large salivary glands by the lymphatic tissue, which is partially diffuse in the parenchyma and partially forms lymph nodes. The presence of this lymphatic tissue is the precondition for the formation of metastatic tumors and malignant lymphomas, but also some benign tumors, e.g., cystadenolymphoma [1,2].

The purpose of the presented study is to investigate the significance and clinical parameters of metastatic tumors in the spectrum of malignant tumors of the PG.

Patients and Methods

In order to carry out the investigation submitted, the clinical data from the patient records of 892 patients receiving a parotidectomy are presented. Catchment area of our clinic, a University Medical Centre, is the northwest part of Brandenburg. The data of a period of 40 years from 1980 to 2020 are evaluated; two 20 years intervals are compared. The results are discussed on the background of the available literature.

During this period, 892 patients received a parotidectomy at least once. Included in this study are 837 patients who were operated for PG tumors, 55 patients operated on for chronic infection (sialadenitis) were excluded. The tumors are classified according to the valid WHO classification.

The modifications made between 1972 and the current version of 2017 affect numerous benign and malignant entities, but essentially not the metastatic tumors relevant in this study. Within the malignant tumor entities, glandular carcinomas, metastatic tumors and malignant lymphomas are distinguished. Epidemiology, clinical parameters, therapy and outcome are studied.

Results

Of 837 consecutive parotid gland tumors, 144 were malignant (17.2%) and 72 were metastases (8.6%); (Table 1). Therefore, 50% of all malignant parotid tumors were metastases and only 30.5% (n=44) primary epithelial parotid tumors or malignant lymphoma at 19.4% (n=28).

The total number of parotid tumors rose over the observation period from 358 parotid tumors in the first two decades to 479 in the second (Table 1).

The incidence of malignant parotid neoplasms simultaneously rose from 45 malignancies before 2000 to 99 malignancies after 2000 (Table 1) accounting for 12.6% of all parotid tumors and 20.7% respectively.

In the first two decades before 2000, the proportion of metastases among malignant parotid tumors was 24.4% (11 out of 45), in the second two decades 61.6% (61 out of 99). Considering all tumors, the number of parotid metastases rose from 3.1% to 12.7%.

Parotid metastases were found in 54 male patients (75%) and 18 female patients (25%) between the ages of 23 and 93 years, with a mean age of 71.1 years. The mean age of patients presenting with squamous cell carcinoma of the skin alone was 75.6 years.

The histological diagnosis was usually confirmed after parotidectomy was carried out. Metastatic tumors were squamous cell carcinoma at 81.8% (n=59) malignant melanoma at 11.1% (n=8), adenocarcinoma (n=3), RCC and oat cell carcinoma (n=1 each) of all metastatic lesions.

66 out of 72 cases (91.6%) primary tumors were located in the head and neck, with 51 of them located in the facial skin or scalp, 8 in the oral cavity or pharynx and 4 in the ear canal. Thus, primary cancers of the skin counted for 71% (51 out of 72) of PG metastases. Another 4 cases were diagnosed as CUP syndromes. Six distant primary tumors were located in the lung (n=3), the kidney (n=1), distal esophagus (n=1) and breast (n=1).

The period between diagnosis of the primary tumor and the parotid metastasis was 12 months on average (range 0 to 144 months).

We performed partial parotidectomy (n=38), total parotidectomy (n=23), or radical parotidectomy in 2 patients presenting with facial nerve palsy. Four patients had open biopsy alone. Exact type of

Table 1: Distribution of parotid gland tumors within a 40 years period (1980-2020) and two 20 years sections.

Period	1980-2020	1980-2000	2000-2020
All tumors	837	358	479
benignant tumors	693	313	380
malignant tumors	144	45	99
-glandular tumors	44	26	18
-metastatic tumors	72	11	61
-malignant lymphoma	28	8	20



Figure 1: Squamous cell carcinoma of the forehead and metastasis within the left parotid gland.

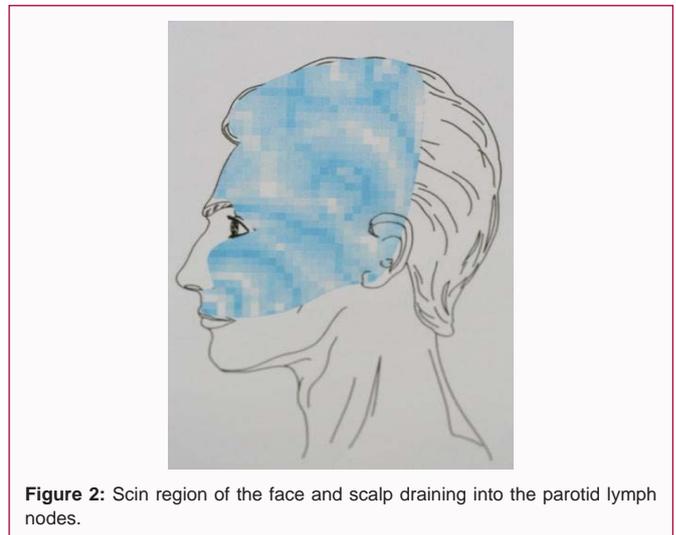


Figure 2: Scin region of the face and scalp draining into the parotid lymph nodes.

parotidectomy remained uncertain in five patients. Parotidectomy with concurrent excision of a skin tumor was performed in only one third of those cases.

A contemporaneous (limited) neck dissection was carried out in 39 out of 72 cases (54%) and adjuvant radiotherapy in 48 out of 72 patients (67%) of metastatic parotid tumors.

In 49 out of 72 cases with metastatic disease (68%), we observed tumor progression after completion of the therapy. This accounts for 100% of infraclavicular primary tumors, 6 out of 8 cases of carcinoma of the oral cavity or pharynx (75%), one out of 4 in the ear canal and none of 4 cases that were diagnosed as CUP syndromes. Concerning skin cancer, metastases we found tumor progression in eight out of eight cases of malignant melanoma and in 28 out of 43 cases of cutaneous squamous cell carcinoma.

Discussion

In our patient group over a 40-year period, 50% of malignant tumors in the parotid were metastases with a rise from 24% between 1980 and 2000 to 60% between 2000 and 2020 (Table 1).

These results differ from those of older studies and the statements

of most textbooks as the proportion of primary glandular tumors among malignant parotid gland tumors is thought to be 50% to 70%, the others are thought to be metastases or lymphoma [3-7].

On the other hand, Bergersen and colleagues already 35 years ago observed of a high number of metastatic tumors within Australian patients [8]. The results have been confirmed by other investigators for Australia. A rising proportion of parotid metastases was reported by others in North America more recently [9-12]. Our results, which we already reported in 2015, were currently confirmed by Mayer et al. for a population of southern Germany [13,14].

When malignant parotid tumors were previously recorded in large epidemiologic studies, it stands out that metastatic tumors are not being mentioned at all [15,16].

As observed by us: Squamous cell carcinomas are generally the most frequent metastatic tumors into the PG. Furthermore, in our patient group 42% malignant tumors were squamous cell carcinomas representing the most frequent histological type at all. This was first described in multiple studies from Australia with a high prevalence of metastatic cutaneous squamous cell carcinoma of the white population [8-11]. Increases of the entity were reported from Europe [17], Western China [18] and North America [19].

The available literature on squamous cell carcinomas of the parotid gland includes two large epidemiologic studies [15,16]. The result of the US population-based study carried out by Boukheris et al. [15] is a proportion of squamous cell carcinoma in men of 20% and in women of 15%. The entity was found to be the most common histological type, like in our patient group.

For the interpretation of these results, it is crucial that the data of the studies are based on the International Classification of Diseases for Oncology, Third Edition (ICD-O-3). However, with this classification it cannot be coded whether a squamous cell carcinoma of the parotid gland is a primary parotid malignancy or a metastasis. In so far, the background of data can be looked upon as the essential limitation of these studies. Since diagnosis of a primary parotid squamous cell carcinoma is a diagnosis of exclusion, it is reasonable to conclude that the majority of squamous cell carcinomas are metastases [20].

According to the results of other researchers, malignant melanoma is the second most common histologic entity metastasizing into the parotid gland (11% of our cases). In this context it must be considered that malignant melanoma represents only 10% of malignant skin tumors. Primary malignant melanomas of the parotid gland are very rare. Beyond cutaneous melanoma, mucosal melanoma and choroidal melanoma may be primary lesions. Knowledge about metastatic tumors to the PG results above all from reports about squamous cell carcinoma; reports about metastatic melanoma are rare [21-24].

In our patient group, a wide majority (>90%) of primary tumors metastasizing into the parotid gland are located in the head and neck. Most common were skin tumors (71%) located within the lymphatic drainage area of the parotid lymph nodes [10,25,26]. A distinction between metastases to the intraparotid lymph nodes and within the parenchyma itself, as suggested by Donath et al. [1] was not made. This corresponds to the procedure practiced by most investigators. While we assume hematogenous metastasis for the infraclavicular primary tumors presented (see below), the series presented does not include any parotid carcinomas that metastasize to parotid lymph nodes.

The definition of metastasis also counts for direct infiltration from a skin tumor into the parotid gland. In our patient's group, two cases of squamous cell carcinoma of the buccal skin are included. (Squamous cell) carcinoma of the ear canal are usually regarded as a distinct entity, although they are ultimately skin carcinomas. Reasons for this are amongst others different growth patterns and a poorer overall prognosis. The latter aspect is not confirmed by our findings.

In only 11%, accounting for less than 1% of all, metastatic tumors of our patients the primary lesions were located in the upper aerodigestive tract. In 75% of those cases respectively, a carcinoma of the oropharynx and a relapse situation was found. The number of reports of parotid metastases of the upper aerodigestive tract is limited [3,27].

(Squamous cell) carcinoma of the ear canal is rare. In advanced cancer situation it may be difficult to distinguish those from tumors of the helix or the middle ear. We performed parotidectomy in either case and found metastases in every second case. Systematic research about the entity is missing. Nevertheless, parotidectomy seems to be recommended at least in advanced primary tumors [28].

According to the available literature, the frequency of distant metastases to the PG is between 10 and 20% of all parotid metastases. The most significant primary tumor locations are the lung, breast and kidney, as seen in our patients. Of less importance are the gastrointestinal tract, prostate and infraclavicular skin. The comparably low frequency in our group (6 cases) may be explained by the rising importance of cutaneous primary tumors [29,30].

Concerning four cases of squamous cell carcinoma, we established a separate category: Carcinoma of unknown primary. In these patients a primary could not be detected after extensive search, but histological aspect (e.g., lack of infiltrative tumor growth, lymphatic tissue with contact to the tumor) was untypical for primary carcinoma. Moreover, in two cases patients had a history of skin tumors of unknown histologic specification [20].

The majority of primary tumors of our group became manifest prior to the clinical manifestation of the parotid metastases. The average period was 12 months with a wide variety (0 to 144 months) demonstrating the very diverse clinical course and the importance of meticulous medical history taking. We found parotid metastases from breast cancer 9 years and renal cell carcinoma 6 and 12 years (in the same patient) after diagnoses of the primary tumor without local relapse or secondary primary tumors.

Concerning our patients with squamous cell carcinomas of the skin, the diagnosis of the skin carcinoma was made in 60% of cases between 6 and 24 months prior to parotid metastasis.

The association between the skin tumor and the parotid lesions was not recognized or unknown to the patient and the referring or admitting clinician. Accordingly, the conclusion is obvious that a significant number of these patients were operated on their primary skin tumors without appropriate staging or follow up [7,11].

Our results reveal that the option of a metastatic process should be considered if a non-clearly glandular malignant tumor is diagnosed by histological examination. In particular, this applies to squamous cell carcinoma, malignant melanoma, adenocarcinoma, clear and out cell carcinoma. If the primary tumor is not obvious this can be difficult on the background of the large number of histologic entities of PG tumors. Otherwise, the distinction is highly relevant for

therapy and prognosis.

Indication of malignant tumor growth are infiltration of surrounding structures and facial nerve palsy. The latter symptom is comparably rare as we observed two cases within our patient group. When searching for a primary tumor, medical history of the patient, results of clinical examination and morphological/histological aspects with a growing importance of molecular pathology must be considered. Depending on the histological result search of the primary tumor should include the skin of face and scalp and the oral and pharyngeal mucosa, but also the lung, kidney and breast [26,29].

Easily accessible clinical data can be a first important indication of whether it is a metastatic process. Metastatic tumors are more common in male (75%). This finding is different to non-malignant entities and patients with malignant primary parotid tumors or parotid lymphoma. In our patient's group, male predominance of metastatic disease results from higher incidence in squamous cell carcinoma of the skin and the head and neck. Moreover, metastatic parotid tumors are more common in older age. Mean age of patients with metastatic disease is 71.1 years and even 75.6 years patients with squamous cell carcinomas of the skin. Only eight of our 72 patients were younger than 50 years of age. By contrast, in metastatic melanoma we found a wide age range of age between 23 years and 93 years [7,11,31].

Histopathology characteristics of metastatic disease are close topographical relationship of the tumor to intraglandular lymph nodes without infiltration of the parenchyma. Similarly, multiple tumor manifestations in the parotid and direct infiltration from a skin tumor highly indicative metastatic disease [20,32].

Knowledge about therapy and prognosis mainly results from single institution reports. Multimodal therapy comprises resection of the primary tumor if still present and the parotid metastasis including the lymph nodes at least of the upper neck (level II). Elective parotidectomy and neck dissection in cases of advanced squamous cell carcinoma and malignant melanoma are discussed controversially. Nevertheless, parotidectomy may improve regional control and to prevent facial nerve damage resulting from a relapse in the parotid gland [24].

Adjuvant radiotherapy following surgical treatment seems to be associated with an improvement in overall survival [33-35].

Depending on final tumor staging results chemotherapy may be indicated in many cases. By our experiences especially in cases of cutaneous squamous cell carcinoma, patients are often too old for (platin-based) chemotherapy. New systemic therapy approaches are reported particularly for advanced squamous cell carcinoma [36-39].

According to current literature, we found metastatic disease to be associated with a high rate of local recurrence and consequently a poor prognosis. Indications of an unfavorable course are metastasis of 6 cm or more in diameter and facial nerve palsy [40].

We observed a better outcome in patients who had parotidectomy and neck dissection when first presenting with a cutaneous carcinoma. Moreover, clinical and histological N0 neck was associated with a more favorable result. Interestingly, a brief interval (9 months or less) between detection of primary tumor and detection of a metastasis in squamous cell carcinoma of the scalp seems to be an unfavorable prognostic factor [41]. Increasing number of nodal metastases may be associated with an increased risk of distant metastases and a

worse outcome [42]. As the result of their meta-analysis, the authors detected a significantly poorer prognosis in immunosuppressed patients and those with extracapsular extension of metastases [33]. However, a commonly accepted staging system stratifying the risk of skin cancer does not exist [43].

From our results and the current literature, we draw the conclusion that the lymph nodes of the neck and the PG should urgently be included in the staging of head and neck skin cancer [23,25,26,44].

Isolated distant metastases to the PG are rare but often an expression of disseminated tumor disease and associated with a poor prognosis. In our collective, a metastatic process was not expected when parotidectomy was carried out. The primary tumors were known in some cases, or the parotid metastasis was the first clival presentation of the primary tumor. Parotidectomy in patients with infraclavicular primary tumors may be appropriate for symptom control but is rarely considered curative. In renal cell carcinoma, surgery is still an important element of metastases treatment [29,30].

There are only few reports about parotid metastases of mucosal primary carcinoma. The results suggest a poor prognosis [3,27]. We explain an unfavorable outcome in our patients by a relapse situation found in 75% of cases. Contrary to expectations, our results of metastatic tumors of the ear canal were good possibly ascribed by early stage of primary cancer [28].

According to our results, in patients with malignant melanoma parotid metastases are an unfavorable prognostic sign. Survival differences after (elective) parotidectomy could not be proved so far [23,24].

Conclusion

Metastatic tumors have become the most important entity in malignant parotid tumors of our patients.

Indications of a metastatic tumor of the parotid gland are older age, male sex, histological findings and tumor diseases, in particular (cutaneous) squamous cell carcinomas, in history.

Distinguishing between glandular primary and parotid metastasis is of high prognostic relevance and an essential precondition for stratifying risk, planning treatment and aftercare.

Ethical Considerations

All data presented within the investigations are based on retrospective data analysis. Thus, formal ethical approval was not required. All patients admitted to the hospital agree formally to scientific evaluation of clinical data. The treatment of all patients included was carried out according to accepted clinical practice as well as medical principles of the Declaration of Helsinki and German Federal Law.

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