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ORIGINAL ARTICLE

Secondary malignant tumors of the parotid gland: not a secondary problem!

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Summary

Purpose: *To present the clinical features of patients with parotid gland metastasis, and compare the results with previously published series. Most of the relevant literature arises from case reports, while there are only few series reported, as secondary neoplastic lesions of the parotid gland are uncommon.*

Methods: *The medical records of patients with parotid gland metastasis, treated at the ENT Department of the University Hospital of Ferrara, between January 1st 1965 and December 31th 2014, were retrospectively reviewed. Fine needle aspiration cytology (FNAC) and biopsy results were compared. Localization of the primary tumor was searched in all cases. Lymphomatous lesions have been excluded from the study.*

Results: *A total of 66 patients with parotid gland metastasis were evaluated. There were 53 males and 13 females with mean age 68.2 ± 13.5 years. Histopathologic analysis of the lesions revealed that 47 (71.2%) were parotid gland metastasis from cutaneous head and neck tumors, 8 (12.1%) from the upper aero-digestive tract, 7 (12.1%) from locations out of facial-cervical region, 1 from a conjunctival melanoma, while in 3 (4.5%) cases the primary tumor origin remained unknown. FNAC results were compared with the final histopathologic diagnosis, showing an overall concordance of 71.9%.*

Conclusion: *The present study is one of the largest series of parotid gland metastasis available so far. During the diagnostic work-up of a parotid tumor, the possibility of a metastasis should also be considered. FNAC can be a useful tool for the preoperative assessment of parotid lesions.*

Key words: *fine needle aspiration cytology, head and neck, metastasis, oncology, parotid gland, secondary tumor*

Introduction

Parotid secondary malignant tumors represent a rare condition. Metastasis can reach the parotid gland via lymphatics and haematogeneous routes, and can develop in the intraghiandular nodes or intraparenchymally. Parotid metastasis usually arises from head and neck primary tumors, the majority of which are primaries head and neck cutaneous squamous cell carcinomas or cutaneous melanomas of the cervico-facial region. However, metastasis from tumors in other locations have also been rarely reported [1-3].

The purpose of this study was to present the clinical features of patients with parotid gland metastasis, and compare the results with relevant previously published series.

Methods

We retrospectively reviewed the clinical records of patients with parotid gland metastasis, treated at the ENT Department of the University Hospital of Ferrara, between January 1st 1965 and December 31th 2014. Those affected by lymphoma were excluded from this study. Written informed consent was obtained from each patient prior to surgery and the search has

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been conducted in compliance with the Declaration of Helsinki.

For each patient the following information was collected: personal data with previous medical history, date of surgery, side affected, histology and the origin of metastasis. The diagnostic workup consisted of echography of the parotid with FNAC, head and neck CT and/or MRI scans, while in selected cases a total body PET/CT was performed. For each case, we evaluated if the primary tumor was synchronous with the parotid gland metastasis or metachronous. We also considered and compared the FNAC results with the final histopathological diagnosis. Data concerning the types of treatment performed (surgery, radiotherapy, chemotherapy) have also been registered. In particular, types of parotidectomies performed were: superficial/partial parotidectomy; total parotidectomy with facial nerve preservation; total parotidectomy with facial nerve sacrifice; and total parotidectomy with neck dissection. Types of neck dissection performed were radical neck dissection (RND), modified radical neck dissection (MRND), and selective neck dissection (SND).

FNAC results were divided into 4 categories: benign cytological sample=S0; non-diagnostic cytology sample= S1; cytology sample showing a benign neoplasm=S2; cytological sample with atypical cytological findings, suspicious for malignancy=S3; cytological sample showing a malignant neoplasm= S4.

Follow-up of the treated patients ranged from 24 to 36 months (median 30±6). Patients were followed on a regular basis with clinical evaluation, neck echography and imaging (MRI and/or CT scans in relation to the clinical status).

Since it was not possible to assess the overall survival rates of the whole studied group, due to the non homogeneous diagnosis (many different types of primary tumors), we decided to compare the overall survival outcome of the two larger groups of patients, those affected by parotid metastasis of head and neck cutaneous tumors with those affected by parotid metastasis of head and neck melanoma.

Statistics

The observed survival rate was estimated separately for two tumor histologies, cutaneous squamous cell carcinoma and melanoma. Survival was evaluated with Kaplan-Mayer method and log rank test was used to search for significant differences. A p value <0.05 was considered as statistically significant. All analyses were performed using the SPSS software (v.12.0; SPSS Inc, Chicago, Ill, USA) for Windows.

Results

Sixty-six patients were affected by parotid gland metastasis. Fifty-three of them (80.3%) were men and 13 (19.7%) women with mean age 68.2 ± 13.5 years.

The primary sites were:

1) head and neck cutaneous tumors in 47 cases (32 squamous cell carcinomas, 13 melanomas, 1 angiosarcoma, 1 Kaposi's sarcoma);

2) conjunctival melanoma in 1 case;

3) mucosal cancer of the upper aero-digestive tract in 8 cases (oropharynx squamous cell carcinoma in 2 cases; 1 case of squamous cell carcinoma and 1 case of lymphoepithelial carcinoma from rhinopharynx; larynx squamous cell carcinoma in 2 cases; retromolar trigone squamous cell carcinoma in 1 case; septal nose squamous cell carcinoma in 1 case);

4) in 7 cases, the primary tumor was outside the head and neck area (pancreatic adenocarcinoma 1 case, bronchial origin 5, neuroendocrine carcinoma, squamous cell carcinoma 2 and small cell carcinoma of the lung 2, breast cancer 1 case); interestingly the primary pancreatic adenocarcinoma gave bilateral parotid gland metastasis.

In the remaining 3 cases, the primary site remained unknown (Table 1).

The majority of primary tumors were located in the head and neck region. Thirty-two patients (48.5%) had a primary cutaneous squamous cell carcinoma. In particular, among head and neck cutaneous cancer sites, the locations of those spread to the parotid gland were: auricular pinna (14), temple (3), forehead (10), scalp (2), zygomatic region (1), neck (1), and cheek (1). The 2 cases of scalp tumors were a trichilemmal carcinoma and a malignant cylindroma. Among head and neck melanomas, the location of the primary tumor site was: auricular pinna (4), neck (4), forehead (2), temple (1), cheek (1), scalp (1), and eye conjunctiva (1). In 1 squamous carcinoma and 2 melanomas, the primary origin remained unknown.

Signs and symptoms at the time of diagnosis were: sudden parotid swelling in 44 cases, intractable head and neck pain in 13 cases, facial nerve palsy in 3 cases (2 cases affected by a grade II lesion according to House-Brackmann and 1 affected by a grade III House-Brackmann lesion), and skin ulceration in one case.

Cytological diagnosis was available for all parotid gland metastases. The final histopathological diagnosis was compared to the preoperative FNAC results and the concordance between FNAC and final histopathological diagnosis was 71.9%. In particular, concordance for squamous cell carcinoma metastasis was 81.6%, and for melanoma metastasis 43.7%; other cyto-histological concordances are shown in Table 2 (A and B).

Diagnosis of primary tumor and parotid

Table 1. Histopathology and primary tumor location of the parotid gland metastasis

Primary tumor location	*n*	*%*
Head and neck cutaneous cancer	47	71.2
Squamous cell carcinoma	32	48.5
Cutaneous melanoma	13	19.7
Angiosarcoma (forehead)	1	1.5
Kaposi's sarcoma (external acoustic meatus)	1	1.5
Upper aero-digestive tract mucosal cancer	8	12.1
Oral cavity	1	1.5
Oropharynx	2	3
Larynx	2	3
Hypopharynx	-	-
Nasopharynx	2	3
Nasal septum	1	1.5
Eye (conjunctival melanoma)	1	1.5
Non-head & neck tumors	7	10.6
Pancreas (adenocarcinoma)	1	1.5
Lung (1 neuroendocrine carcinoma, 2 squamous cell carcinoma and 2 small-cell carcinoma)	5	7.6
Breast (adenocarcinoma)	1	1.5
Unknown primary (2 melanoma, 1 squamous cell carcinoma)	3	4.6
Total	66	100.0

gland metastasis was synchronous in 6 cases (3 were skin squamous cell carcinoma and 3 cutaneous melanoma). In the remaining 60 cases, parotid gland metastasis was identified 18 months on average after the primary tumor diagnosis, during follow-up.

The therapeutic approach was defined for each case, according to the preoperative clinical staging. While 2 patients were treated by radiotherapy alone, 64 underwent a parotidectomy. In particular, 37 cases underwent total parotidectomy with neck dissection (facial nerve sacrifice was necessary in 8 cases - 3 of them already presented facial nerve palsy prior to surgery), 20 cases total parotidectomy without neck dissection and 7 cases partial parotidectomy. Adjuvant radiotherapy was delivered in 28 cases.

Recommendation for adjuvant postoperative radiotherapy were: concomitant metastasis in neck lymph node(s), locally advanced disease and low grade of differentiation G3-G4. However, 17 patients could not complete adjuvant radiotherapy, due to the following reasons:

1) early disease recurrence with concomitant systemic metastasis (5 cases); 2) concomitant presence of other melanoma metastasis (10 cases); 3) development of skin angiosarcoma metastasis, not responsive to radiotherapy (1 case); 4)

Table 2. Final histopathological diagnosis compared to the preoperative FNAC results

A *Histology*	*Freq*	*%*	*Conc*	*%*
Metastasis of squamous cell carcinoma	38	59.4	31	81.6
Metastasis of melanoma	16	25	7	43.7
Metastasis of angiosarcoma	1	1.5	1	100
Metastasis of pancreatic adenocarcinoma	1	1.5	1	100
Metastasis of undifferentiated neuroendocrine carcinoma (lung)	1	1.5	1	100
Metastasis of trichilemmal carcinoma	1	1.5	1	100
Metastasis of undifferentiated lymphoepithelial carcinoma	1	1.5	1	100
Metastasis of malignant cylindroma	1	1.5	1	100
Metastasis of poorly differentiated squamous cell carcinoma (lung)	1	1.5	1	100
Metastasis of small-cell carcinoma (lung)	2	3.1	1	50
Kaposi's sarcoma	1	1.5	0	0
Total	64	100	46	71.9

Freq: frequency, Conc: concordance

B *Cytology*	*n*
S0 = non neoplastic lesion	2
S1 = inadequate	17
S2 = benign neoplasm	1
S3 = atypic cells/suspicious for maligancy	2
S4 = malignant neoplasm	44
Total	66

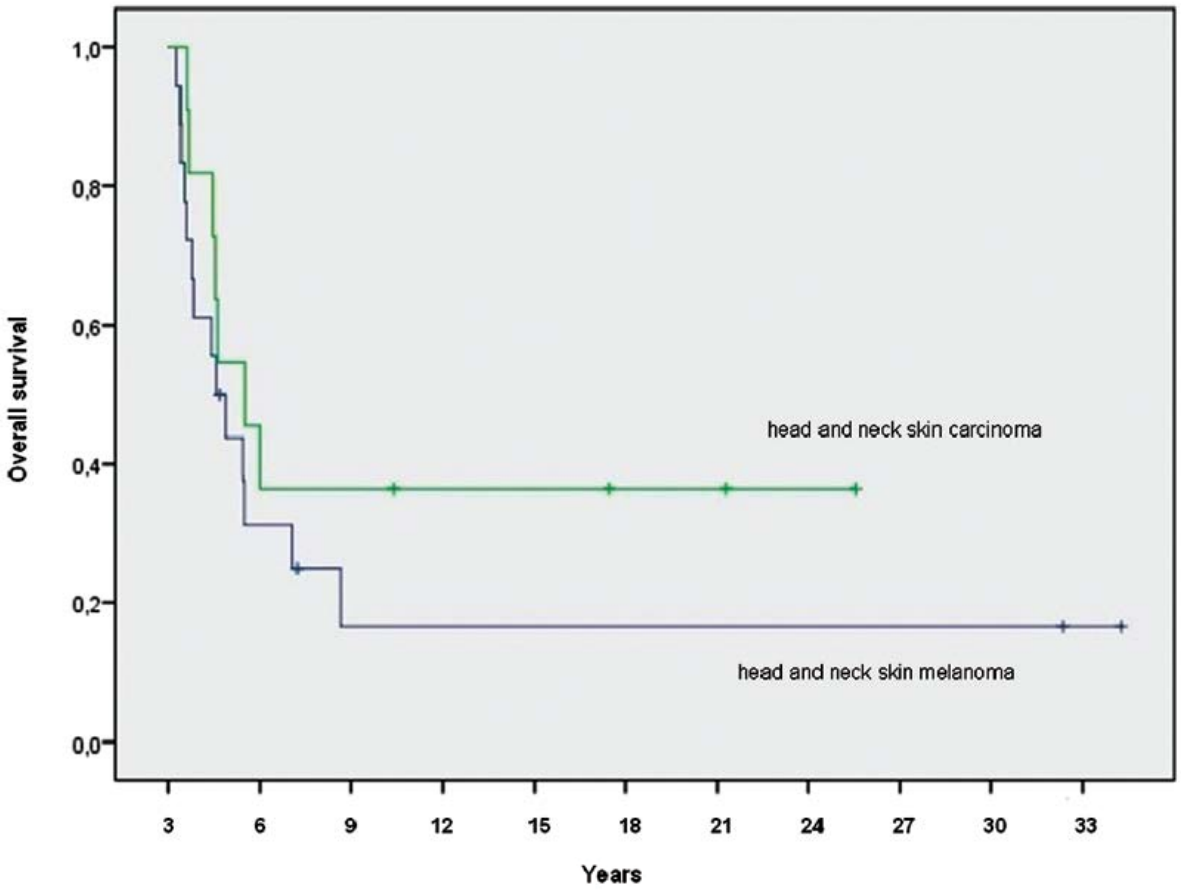

Figure 1. Overall survival rate of patients with parotid metastasis from head and neck skin carcinoma and from head and neck skin melanoma were 16.7% and 36.4%, respectively (p=0.282).

death before treatment onset (1 case).

Finally, a total of 8 patients were administered chemotherapy postoperatively**.** Of these, 5 cases with a metastasis of an undifferentiated squamous cell carcinoma were also treated by concomitant radiotherapy, and 3 cases with a melanoma metastasis with chemotherapy alone.

The overall survival of those with parotid metastasis from head and neck skin squamous cell carcinoma and with head and neck melanoma was 16.7 and 36.4%, respectively. Log rank test showed no statistical difference between the two conditions (Figure 1).

Discussion

Secondary neoplastic lesions of the parotid gland are not very common, with an average incidence of 6-8 % of all parotid tumors [1,2,3,5]. As already said, the vast majority of primary tumors, giving metastasis to the parotid gland, are most frequently located in the head and neck region [1,2,3,6-10]. The parotid gland can be considered as a target of metastasis from cutaneous squamous cell carcinomas or melanomas located in the face, scalp and neck, as the drainage of these anatomical regions include lymph nodes anterior and lateral to the parotid [1-3,5-12]. However, rarely, distant primary tumors have been reported to spread to the parotid; these can be situated in the upper respiratory tract, the upper digestive tract, the lung, colon, breast and pancreas [1-3,5-18]. In the present series, 32 of 66 patients (48.5%) had head and neck cutaneous squamous cell carcinoma and 13 of 66 (19.7%) head and neck cutaneous melanoma. As in other reports [1,3,7-9], we also found a preponderance of metastasis in men.

In the present series, parotid gland metastases were identified, on average, 18 months after the primary tumor diagnosis; this data is in concordance with other reports (reported average time of identification: 12-20 months) [1-3,7,10]. A continuous and regular monitoring and follow-up of these patients is always recommended.

When dealing with a parotid tumor, the distinction between a primary tumor and a metastasis is of crucial importance for diagnostic work-up, treatment planning and prognosis [1-3,7] and FNAC is a useful tool in this issue [19,20]. In a previous study we showed that FNAC may be a

good technique for the preoperative assessment of parotid lesions [21] and in the present study FNAC sensitivity was 71.9%. However, cytologic data should always be correlated to other information retrieved from history, clinical examination and imaging, in order to achieve a correct differential diagnosis for each patient. Indeed, in some cases, only histopathological analysis (by using different immunohistochemistry stainings) may provide clues to identify the origin of the primary tumor [1-3,5-10].

Treatment of malignant parotid tumors is preferably surgery, followed by radiotherapy [1-3,7]. The approach to the patient should always be multidisciplinary, and ENT surgeons should co-operate with oncologists and radiotherapists in order to evaluate and provide the best therapeutic option. Parotid metastasis from primary tumors of the head and neck is usually treated by total parotidectomy and neck dissection [1-3,7]. However, there is no international consensus about the therapeutic strategy of parotid malignant metastasis [7], and the definition of a standard treatment of parotid metastasis is a difficult challenge due to the complexity of variables (i.e. different histological types) that can affect patient survival [22,23]. Recently, Thom et al. have also included deep lobe parotidectomy, apart from neck dissection and adjuvant therapy, in the surgical planning of metastatic squamous cell carcinomas and melanomas to the parotid gland [12]. The role of surgery can still be considered crucial, however only the early and adequate surgical treatment (including lymph node dissection as well as parotidectomy) has been advocated to offer the best survival chances [11].

The prognosis of parotid gland metastasis is generally reported to be very poor. When available, the 5-year overall survival rate is reported to range from 11.5 to 43% [6,7]. The prognosis seems to be very poor particularly for malignant melanomas, as the presence of metastasis usually means advanced disease [7]. Interestingly, metastatic cutaneous squamous cell carcinoma has been reported to have a significantly worse prognosis when involving both the parotid gland and neck lymph nodes, than in cases with disease in the parotid gland alone [24]. The overall survival rates in the present series, when available, were very poor, either for patients with head and neck cutaneous carcinoma or for those affected with by head and neck melanoma.

The major drawback of this study is the very long time interval (49 years) for recruiting patients; however, even if the diagnostic tools as well as the therapeutic approaches have evolved through the years, the prognosis of these tumors still remains poor.

Conclusions

To the best of our knowledge, the present series is one of the largest on metastasis to the parotid available so far. When facing a parotid tumor, also a metastasis should also be considered during the diagnostic work-up. A precise history taking and a careful examination of the different head and neck regions can help reveal the primary tumor. Furthermore, comparison between the current histological findings and all the other clinical and radiological data availabe can be of great value in order to disclose a parotid metastasis. Also FNAC can be considered a useful tool for the preoperative assessment of parotid lesions.

Conflict of interests

The authors declare no confict of interests.

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