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Non-primary salivary malignancies: A 22-year retrospective study

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ABSTRACT

Purpose: Most salivary gland malignancies are primary tumors, but in our medical center one of six is non-primary. The relative scarcity of such reports justifies studying them.
Subjects & methods: We studied patients' demographic and clinical parameters, salivary tumors/metastasis, diagnosis and treatment, and survival rates.
Results: Of all our salivary malignancy patients over the last 22 years, 15% (18/119) had non-primary malignant tumors, all located in the parotid glands. Of these, nine had skin cancer (SCC), 3 malignant solid tumors and 6 hematological systemic malignancies. Four had concomitant second malignancy. Mean age was 70.2 ± 13.8 years, 66.7% of the patients were males, 27.8% were smokers, none reported alcohol use. The most prevalent diagnostic tools used were CT (16 patients), FNA (13) and PET-CT (12). Eleven of 18 patients died from the disease despite receiving therapy: 6 SCC patients, 2 CLL patients and all 3 with solid tumors. All four lymphoma patients survived as did another three SCC patients.
Conclusions: Chemotherapy and radiotherapy for systemic disease prolonged life rather than surgery. Patients with poor prognosis non-primary salivary tumors should be treated conservatively; surgery should be for those without widespread metastases or systemic disease. Sometimes a palliative patient may benefit from tumor debulking.
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1. Introduction

The great majority of salivary gland malignancies are primary tumors which have been often studied and reported (Ng-Cheng-Hin et al., 2018; Zbären et al., 2018). These tumors vary significantly in their histological and biological nature, yet most of them (approximately 90%) belong to well known groups such as mucoepidermoid carcinoma, acinic cell carcinoma, adenoid cystic carcinoma, adeno carcinoma, polymorphous low grade adeno carcinoma and salivary squamous cell carcinoma (Jones et al., 2008; De Oliveira et al., 2009; Speight and Barrett, 2009).

However, there is another subset of malignant salivary tumors encountered by the clinician which is seldom discussed or studied, the non-primary malignant tumors (both metastatic and not metastatic) (Jackson et al., 2015; Wang et al., 2017; Mezei et al., 2018). Analyzing this cohort of patients is important since their number is quite significant: In our medical center the salivary malignancy of one of every six patients was a non-primary tumor. The relative scarcity of reports dealing with such patients justifies studying them.

In order to be able to specify the therapy recommended for non-primary tumor patients, it is important to understand that surgical removal of a primary salivary tumor is performed following proper imaging, whether CT or MRI. Surgery carries a risk for various operative and post-operative complications, among them the facial nerve which should be carefully preserved when it is not infiltrated. Adjuvant radiotherapy is sometimes administered in high-risk situations such as proximal invaded margins, perineural, lymphatic and vascular spread, lymph-node metastasis or aggressive high-grade and high stage tumors (Andry et al., 2012; Thiagarajan et al., 2018).

The purpose of the current study was to examine characteristics related to the systemic medical and oncological background of these patients.

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2. Material and methods

2.1. Study design, patients and statistics

In the current study we analyzed the 18 patients diagnosed with non-primary salivary malignancies, out of 119 total salivary malignancy patients who were admitted to our medical center during the past 22 years. In other words, 15% of salivary malignancies were non-primary tumors. We studied various demographic and clinical parameters related to the patients as well as factors related to their salivary tumors/metastasis, diagnosis and treatment. Finally, we looked at these patients' survival rates.

Survival analysis was performed for all patients using the Kaplan-Meier model to calculate the probability of cancer specific survival (CSS) as a function of time.

3. Results

Interestingly, in all 18 cases the disease was located in the parotid glands. This is in contrast to the malignant salivary tumors as primary tumors, which are typically found in all of the various salivary glands, major and minor. Of our 18 patients, nine were skin cancer (SCC) patients whose original skin tumor sites were either in the scalp or in proximal facial regions (mainly the pre-auricular and ear regions). Accordingly, their parotid tumors may be considered a regional metastasis. Another three of the 18 patients had malignant solid tumors with metastases spread to various organs including the parotid glands: two patients with renal cell carcinoma and one with breast carcinoma. Their parotid tumors are considered distant metastasis. The remaining six patients had hematological systemic malignancies: four with lymphomas (2 with MALT lymphoma, one with B Cell lymphoma and one with large cell lymphoma) and 2 with chronic lymphocytic leukemia (CLL). The parotid tumors of these patients were part of malignant lymphatic masses found in various organs and sites throughout the body and as such should be considered as part of the systemic disease (Table 1).

3.1. Demographic and medical analysis

The baseline demographic and habit variables for age, age at diagnosis, gender, ethnic group, and cigarette and alcohol use, for patients with secondary disease are presented in Table 2. Mean age of the 18 patients was 70.2 ± 13.8 years (median 70.0) while the mean age at diagnosis was 66.5 ± 16.4 years (median 65.5). About two thirds of the patients were male and one third female. About one quarter of the patients were smokers. None of the patients reported alcohol use. As for comorbidities, seven of the 18 patients also suffered from hypertension, 6 from CVA and/or cardiological problems and 5 from diabetes. Four of the patients had a concomitant second malignancy: a patient with skin SCC also had BCC (another less aggressive form of skin cancer), one with breast carcinoma also had parotid lyposarcoma, a patient with CLL also had skin SCC and the other patient with CLL also had Merkel tumor (a rare type of skin cancer).

Table 1
Cancer patients with non primary malignant parotid tumors.

Oncology type	Renal cell carcinoma	2
	Breast carcinoma	1
	MALT lymphoma.	2
	B cell lymphoma	1
	Large cell lymphoma	1
	Ch. lymphocytic leukemia (CLL)	2
	Skin SCC	9

One patient with Skin SCC also had a BCC lesion. One CLL patient also had a small Skin SCC lesion. Ch. = Chronic.

3.2. Tumor and diagnostic analysis

The diagnostic tools used are presented in Table 3. These included tissue diagnosis based on open biopsy or FNA, either US-guided or non-guided, accompanied by various imaging techniques such as US, MRI, CT and PET-CT. The most prevalent diagnostic tools used were CT (in 16 patients), and PET CT and FNA, in 12 and 13 patients respectively.

The characteristics of the tumors are presented in Table 4a–c.

Median tumor size was 2.0 cm (mean 2.4 cm). In nine patients tumor size was 2 cm or less (≤2 cm), and in only one patient was the tumor size larger than 4 cm (Table 4a).

In four patients the tumor located in the parotid gland was accompanied by lymph node metastasis to the neck (Table 4b). Six of the SCC patients were diagnosed with high grade disease and three SCC patients with low grade disease. Noteworthy is that in nine patients the grading was unknown or considered irrelevant (one SCC patient, one lyposarcoma patient, 2 renal cell carcinoma patients and 5 hematological malignancy patients). Three of the patients were diagnosed with perineural invasion and three with extra parenchymal spread (Table 4c).

3.3. Survival

The cancer specific survival of the non-primary parotid tumors is depicted in Fig. 1. In total, eleven of these 18 patients died from the disease, in spite of the therapy administered. These included six of the SCC patients, the two CLL patients and all three patients with solid tumors whose parotid masses were one of their distant metastases. All four lymphoma patients survived, as did another two SCC patients. The Kaplan-Meir analysis of these patients revealed that the probability of Cancer Specific Survival (CSS) of patients with non primary salivary tumors at 60 months (5 years) post first treatment date was 0.52 (with 95% C.I. of [0.08–0.84]).

The probability of Cancer Specific Survival (CSS) of these patients at 120 months (10 years) post first treatment date was 0.52 as well (with 95% C.I. of [0.08–0.84]).

3.4. Therapy

The treatment modalities used for these 18 patients included surgery, radiotherapy and chemotherapy as presented in Table 5. In almost all cases (i.e. in 16/18 patients) the surgery included removal of the parotid tumor, performed by employing various surgical techniques, including local excision or various forms of parotidectomy as shown in Table 5. The local removal of the tumor was

Table 2
Summary of demographic characteristics.

Demographic Characteristic		
Age at the end of the study (years)	Median	70.0
	Mean±SD	70.2 ± 13.8
	Range	[50–92]
Age at diagnosis (years)	Median	65.5
	Mean ± SD	66.5 ± 16.4
	Range	[39–90]
Gender	M	12
	F	6
Smoker		5
Alcohol		0
Ethnic – Arab		2
Ethnic – Jewish		16

Table 3
Summary of diagnosis examination.

Diagnosis examination	
CT	16
FNA	13
PET CT	12
US	7
MRI	4
Biopsy	4
FNAguUS (US guided)	3

augmented in eight of the cases with neck dissection (mostly 1–4 levels). Whenever possible, the original skin SCC lesion was removed prior to or concomitantly with the salivary SCC mass. Adjuvant therapy was administered as well: in 12 patients radiotherapy was added and in 8 patients chemotherapy was added. Three of these patients received combined treatment of chemotherapy and radiotherapy. The 12 patients who received radiotherapy were the nine SCC patients, the two renal cell carcinoma patients and one patient with CLL. The eight patients who received chemotherapy included the four lymphoma patients, the two renal cell carcinoma patients and two of the SCC patients who suffered from advanced diseases (both had stage 3–4 and highly differentiated disease).

4. Discussion

In the current study it was interesting to find that a relatively high proportion of our patients were diagnosed with non-primary salivary malignant tumors (15% of all salivary malignancies) and that these patients may be divided into three major subgroups: those with proximal skin cancer, those with remote distant solid tumors and those with systemic hematological disease. Also very interesting was the fact that all these patients' tumors were located in the parotid glands. This is in contrast to what we know for *primary* malignant salivary tumors; some are found in the parotid glands but most are in the other major and minor salivary glands. Actually, most parotid tumors are benign rather than malignant. For example, in the cohort of concomitant 101 primary salivary malignant tumors treated in our hospital over the same period of time, only 59% were located in the parotid (data not shown), while the others were found in other major and minor salivary glands. Another interesting finding was the high proportion of patients with non-primary tumors belonging to one of two groups, either those with skin SCC (in the scalp and/or proximal facial sites, 50% of the patients) or with hematological lymphocyte-related diseases (various forms of lymphomas or CLL, 33% of the patients). Perhaps the lymph vessels drained at the parotid gland site explains this finding; they act as major lymph node cancer drainage junctions where mutagenic lymphocytes concentrate, as in lymphomas or CLL or in a similar manner for regional metastasis of solid tumors (in neck nodes, axillary nodes, inguinal nodes (. This general phenomenon of lymph cancer metastasis to the parotid glands is also supported by the three other distant metastasizing solid tumors (two renal cell carcinoma patients and one breast carcinoma patient) which metastasized to the parotid gland as well as to other remote sites including the lungs and skeleton. It is well established that renal cell carcinoma in particular is characterized by its tendency toward distant metastasis, sometimes in unexpected sites throughout the body (Zhang et al., 2018) The same holds true for the other significant group: six hematological patients with proliferating malignancies characterized by lymphocyte aggregates gathering in various nodes throughout the body. Chronic lymphocytic leukemia (CLL) is the most common leukemia in adults. It starts in lymphocytes in the bone marrow which later spread into the blood and further to other parts of the body, including the lymph nodes, liver, and spleen (Hallek, 2015), and, as we report here, also (rarely) to the parotid glands. In this group of hematologic oncology patients, malignant lymphocytic aggregates were found throughout the body - in the neck, above and beneath the clavicle, in the axilla, mediastinum, peritoneum, pelvis and appendix. All these patients underwent surgical removal of the parotid mass accompanied by chemotherapy.

In many of the 18 cases presented here, local removal of the parotid tumor was accompanied by neck dissection (50% of the cases) and often with adjuvant radiotherapy, chemotherapy or both. This treatment regime is also the therapy of choice administered in our institute for primary salivary malignant tumors and for oral SCC tumors. As noted here, 11/18 (61%) patients died from the disease. Thus the survival rate of our patients was rather low, only 39%. This is in contrast to a much better survival rate found in our concomitant primary tumor patients (the probability of cancer specific survival at 180 months of the 101 primary salivary tumors was 61% (data not shown)). Among the subsets of the patients in the "non-primary" cohort, there were differences in the survival tendencies among the sub groups. Only 33% (3/9) of the patients with SCC lesions survived, and as previously mentioned all four

Table 4a
Summary of tumor parameters.

Tumor parameters		
T size (cm)	Median	2.0
	Mean±SD	2.4 ± 1.3
	Range	[0.8–5.7]
	UK (patients)	2
T size (cm)	≤2 cm, patients (%)	9
	≤4	6
	≤6	1
	UK	2
N lymph nodes (LN)	NO (no lymph nodes)	14
	Cervical lymph node metastasis:	4
	3-N2b: Metastasis in multiple ipsilateral lymph nodes, none>6 em in greatest dimension	3
	4 - N2c: Metastasis in bilateral orcontralateral lymph	1

UK = Un Known, CM = Centimeter, SD = Standard deviation.

Table 4b
Summary of tumor parameters.

Tumor parameters		N = 18
Grading	Low grade SCC	3
	High grade SCC	6
	UK or non-relevant	9
Perineural invasion		3
Extra Parenchymal spread		3

UK = Un Known, SCC = Squamous Cell Carcinoma.

Table 4c
Summary of tumor parameters by study group.

Tumor parameters		N = 18
Side	Right	3
	Left	14
	Bilateral	1
Location	Parotid	18
Sub-location	Parotid tail	2
	Parotid superficial lobe	13
	Parotid deep lobe	2
	Parotid (sublocation Unknown)	1

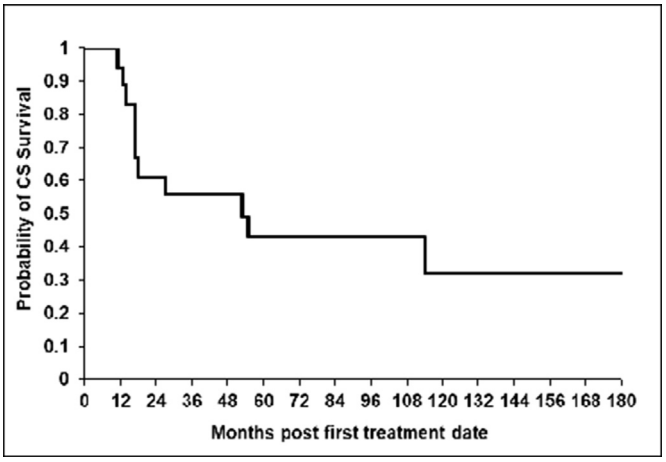

Fig. 1. Probability of cancer specific survival (CSS) of patients with non primary malignant disease.

lymphoma patients survived as well (a 100% survival rate). In contrast, none of the three patients with distant solid tumor metastasis to the parotid glands survived, nor did the two CLL patients (0% survival rate in these subgroups). This latter finding should be of no surprise, since these diseases in the advanced stages are known to have very low survival rates (Keegan et al., 2012; Redig and McAllister, 2013; Hallek, 2015). Also, it is not surprising that the lymphoma patients survived since it is well known that these patients, when treated properly and systemically, often survive for a long period of time, especially those with MALT lymphoma (Defrancesco and Arcaini, 2018; Godfrey et al., 2018). We do not know, however, what distinguished the six SCC patients who died from the other three SCC patients who survived. Obviously, these six patients had a far more aggressive disease (stage 3–4, poorly differentiated SCC), but still the question is why. SCC of the skin is often diagnosed at early stages since it is obvious and external. In such circumstances and if not metastasized, skin SCC is less lethal than SCC in the mucosa, as evidenced in oral SCC where the 5Y survival rates are often only 50% (Rivera, 2015; Kaboodkhani et al., 2016). The same is true for skin melanoma, considered at higher adversity when in the oral cavity mucosa than when in the skin (Kuk et al., 2016). In our study we witnessed patients whose skin SCC was mediatizing (to the parotid glands) and as such, was of an aggressive nature to begin with. Thus, it is not surprising that these patients' survival rate was only 33%.

The fact that four of the 18 patients had other concomitant malignancies besides the salivary non-primary tumors may indicate a systemic background that plays a role in the pathogenesis of the disease. Perhaps this occurs in patients suffering from a systemic weakness of their anti -cancer immunological capacity or in those exposed to aggressive not-yet-specified carcinogens. This phenomenon is known in other forms of cancer such as in oral SCC, as we have reported in the past (Nagler et al., 2002). Another interesting finding is the relatively high prevalence of patients with skin cancer (mainly SCC but also BCC and Merkel carcinoma) among the 18 salivary non-primary tumor patients. Perhaps this is the reason that the non-primary salivary malignant tumors were found only in the parotid. And if so, is lymphatic drainage the reason, as we suggested earlier, or perhaps other factors such as similarity of structural and biochemical elements in the skin and the salivary epithelium. To the best of our knowledge, there is only one case in the professional literature where the salivary gland involved as a distant metastasis was not the parotid and this was a case report of a breast carcinoma metastasizing to the submandibular gland (Cain et al., 2001).

Concerning the therapy administered to non-primary salivary malignancies, quite clearly the cases can be divided into the salvageable and the non-salvageable diseases. Palliative and conservative therapy should be administered to the incurable patients, and surgical removal avoided in most cases due to its related morbidity and complications. In our lymphoma patients, clearly the systemic chemotherapy saved the patients and not the local surgical removal of the parotid mass. Thus, in lymphoma patients receiving chemotherapy, surgical removal of the parotid tumor is not required unless it somehow interferes with quality of life. The same principles dictate the therapy recommended for other patients with extremely low prognosis, the CLL patients and those with solid tumors with spreading metastasis. In these instances, systemic chemotherapy and/or radiotherapy should be the therapy of choice. In contrast, in cases of parotid SCC, complete surgical removal of the tumor seems to be mandatory and this should be accompanied with neck dissection and adjuvant radio- and/or chemotherapy. The spread of the cutaneous metastasis to intraparotid and peri-parotid lymph nodes and to cervical lymph nodes is known (Yilmaz et al., 2012); however, sometimes parotid SCC can be successfully treated in this manner as evidenced by the three of our nine patients who survived. The literature is rather contradictory in this respect, i.e. survival rates of salivary SCC related to skin cancer was reported to be rather high (Dalal et al., 2018), attributed to the relatively less aggressive nature of skin SCC as opposed to mucosal SCC (Green and Olsen, 2017; Parekh and Seykora, 2017). Other reports (Akhtar et al., 2013; Shao et al., 2014), however, also presented a relatively small subset of patients in whom the parotid SCC was aggressive and the disease unsalvageable, perhaps the result of a far more pathological behavior of the malignancy rendered by its biological characteristics. This was suggested to result from an epidermal growth factor receptor overexpression (Veness et al., 2007; Bumpous, 2009; Kinouchi et al., 2018), and recommended therapies were sentinel lymph node biopsy, microarray gene analysis and adjuvant chemotherapy in these patients.

Table 5
Summary of treatment modalities.

Tumor parameters		N = 18
Surgical Technique	Local excision superficial/partial	1
	Parotidectomy	6
	Total parotidectomy	7
	Wide local excision	2
	No parotid gland surgery	2
Neck dissection	Yes	8
	No	10
Chemotherapy	Yes	8
Radiotherapy	Yes	9
Chemotherapy and Radiotherapy	Yes	3

5. Conclusions

Patients with poor prognosis non-primary salivary tumors should be treated in a conservative and palliative manner, while the surgical option should be reserved for those who do not show spread of metastases or systemic disease. However, some palliative patients may benefit from tumor debulking.

Author contributions

YI: Co-wrote the first draft, analyzed data, approved submission.

AR: Co-wrote the first draft, interpreted data, approved submission.

KG: Acquisition, analysis & interpretation of data, approved submission.

RN: Conception and design of the study, acquisition of data, critical review of the manuscript, approved submission.

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Conflicts of interest

None of the authors declare any conflict of interest, financial or otherwise.

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