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Review

Multiple Tumours of the Salivary Glands—Terminology and Nomenclature

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Multiple tumours of the salivary glands are very rare and their combinations according to histological classification of the tumours, localisation and origin (origin in independent topographical areas or in the same tissue) are diverse.

The following two categories can be distinguished: common occurrence of multiple salivary gland tumours with identical histology, or with different histology. In either group the tumours can be unilateral or bilateral, synchronous or metachronous. The most common multiple tumours with an identical histology are Warthin tumours and pleomorphic adenomas. Bilateral occurrence has been observed especially in oncocytomas, acinic cell carcinomas and basal cell adenomas. In the group of multiple tumours with differing histology, Warthin tumours and pleomorphic adenomas show a number of combinations with other adenomas or carcinomas of the salivary glands. Notable also is the simultaneous occurrence of salivary gland tumours with other oral tumours or extraglandular tumours, especially thyroid carcinomas and breast carcinomas.

Multiple salivary gland tumours must be distinguished by nomenclature from tumours with biphasic differentiation and hybrid tumours. Tumours with biphasic differentiation are defined as regular, recurring mixtures of two cellular components in the same tumour and have a corresponding term in the tumour classification. Hybrid tumours are very rare and are composed of two different tumour entities within the same topographical area. Each of the tumour entities conforms with an exactly defined tumour category.

Keywords: multiple tumours, salivary glands, biphasic tumours, hybrid tumours

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INTRODUCTION

As a rule, salivary gland tumours are individual tumours in one salivary gland. In contrast to this quite common occurrence, double or multiple tumours of the salivary glands are unusual and in some observations extremely rare. An analysis of the cases reported in the literature shows a diversity of combinations according to the histological classification of the tumours, their localisation and whether development was in independent topographical areas or in the same tissue [1–4]. Awareness of the possibility of multiple tumours can avoid an incorrect interpretation with regard to malignancy. To clarify the different terminology and nomenclature, this review summarises the publications in the literature and the evaluation of the Salivary Gland Register in Hamburg.

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TERMINOLOGY

Occurrence of salivary gland tumours with identical histology

With regard to the localisation of identical tumours of the salivary glands, the following topographical situations must be distinguished: (1) *unilateral* occurrence in one or several salivary glands; and (2) *bilateral* occurrence in one or several salivary glands. Multiple tumours, especially of the parotid gland, are more frequent bilaterally than unilaterally [5–7].

An additional factor is the time of development, whether *synchronous* (*simultaneous*) or *metachronous*. But this is very difficult to establish in most observations.

The most common tumour to occur unilaterally or bilaterally, is the *Warthin tumour*, 100 cases of which have been reported in the literature [8–16]. Bilateral Warthin tumours were observed in 7.5% of all Warthin tumours [9]. The incidence of bilateral Warthin tumours in men was very high (male:female 6.3:1). Four per cent of all Warthin tumours were unilateral and multifocal. This means that multiple

adenomas had developed which were clearly separated from each other by parotid tissue free of tumours. Most of the bilateral Warthin tumours were defined as metachronous, but some cases were also defined as synchronous and/or simultaneous [17–20].

Other *bilateral* salivary gland tumours are pleomorphic adenomas with about 35 cases reported in the literature [15, 21–23], oncocytomas with about 12 reported cases [15, 24–28], acinic cell carcinomas with 12 reported cases [29–34] and basal cell adenomas with 6 reported cases [35].

Sporadic observations of bilateral carcinomas concern epithelial–myoepithelial carcinoma [36], mucoepidermoid carcinoma [37], acinic cell carcinoma [38], adenoid cystic carcinoma [39], polymorphous low-grade adenocarcinoma [40] and other adenocarcinomas with different pathohistology [41].

Unilateral multiple salivary gland tumours are mostly Warthin tumours (29 cases) and less frequently pleomorphic adenomas [15, 42, 43], developing particularly in two or more major salivary glands.

Multiple foci—mostly unilateral—were observed in basal cell adenoma (especially the membranous subtype with multicentric occurrence in 50% of the cases and with about 12 microadenomas in each case) [35, 44]. Further examples are canalicular adenoma, mostly of the upper lip [45–47], and adenoid cystic carcinoma, especially of the lip [48]. The multifocal occurrence of oncocytoma [49] must be compared with the multifocal adenomatous oncocytic hyperplasia of the parotid gland, a tumour-like lesion which may be the prestage of an oncocytoma occurrence [50–52].

Occurrence of salivary gland tumours with different histology

The most common combination is *pleomorphic adenoma* with Warthin tumour [53–56]. Not so frequent is the common occurrence of pleomorphic adenoma with the following tumour entities: mucoepidermoid carcinoma [15, 57]; epithelial–myoepithelial carcinoma [58]; oncocytoma [59]; oncocytic carcinoma [60]; acinic cell carcinoma [31]; and adenoid cystic carcinoma [61].

Warthin tumour is the most frequently observed synchronous tumour occurring with other salivary gland tumours, which is probably attributable to its multifocality. The syntropy of Warthin tumour was observed with the following tumour entities [15]: pleomorphic adenoma (about 20 cases [62]); oncocytoma (about 9 cases; [63]); basal cell adenoma [64]; acinic cell carcinoma [15]; adenoid cystic carcinoma [15]; mucoepidermoid carcinoma [65–67]. An isolated observation was the combination of an adenoid cystic carcinoma with a clear cell carcinoma of the palate [68]. In another rare case the occurrence of an adenoid cystic carcinoma with an epithelial–myoepithelial carcinoma was observed [69], but the author discussed the probability of two separate tumours having developed or even a hybrid tumour.

Occurrence of salivary gland tumours with other extraglandular tumours

The common occurrence of salivary gland tumours with other *oral tumours* is very rare. The casuistic reports of the literature contain the following observations: Warthin tumour and ameloblastoma of the mandible and/or acinic cell carcinoma and ameloblastoma of the mandible [70]; pleomorphic adenoma and haemangiopericytoma [71]; pleomorphic adenoma and malignant lymphoma [72]; Warthin tumour and malignant lymphoma [9]; Warthin tumour and squamous cell carcinoma [71].

An interesting point is the occurrence of *primary salivary gland tumours* with *secondary extraglandular carcinomas*. Predominantly the following associations between salivary gland carcinomas and other carcinomas were registered: breast cancer with a four–five-fold increased risk, subsequent to the first primary salivary gland tumour [73–76], of thyroid cancer [77–80], cancers of the respiratory tract and of the ovaries [81].

The occurrence of secondary thyroid carcinomas follows in some cases after a long interval of irradiation of the neck area [80]. From our own observations, a secondary papillary thyroid carcinoma developed in a child 5 years after surgery and irradiation of a carcinoma in a pleomorphic adenoma. In 1 case [77] four distinct head and neck tumours occurred simultaneously (Warthin tumour and mucoepidermoid carcinoma of the parotid gland together with an oral squamous cell carcinoma and a thyroid carcinoma).

In comparison to the salivary glands, squamous carcinomas of the head and neck show an increased association with carcinomas of the upper respiratory tract, the lung, the oesophagus or colon with a variety of 3–10% or more in the different studies [82–86].

Occurrence of salivary gland tumours with biphasic differentiation

This tumour group is characterised by a regular, and always recurring, mixture of two cellular components in the same tumour with a corresponding term in the tumour classification. Examples of biphasically differentiated salivary gland tumours are [87]: epithelial–myoepithelial carcinoma; mucoepidermoid carcinoma; basaloid-squamous carcinoma; adenosquamous carcinoma; carcinoma in pleomorphic adenoma with differentiation as squamous carcinoma as well as adenocarcinoma; and sarcomatoid carcinoma ("carcinosarcoma").

Epithelial–myoepithelial carcinomas are composed of variable proportions of two cell types which form typically duct-like structures: an inner layer of duct-lining cells and an outer layer of clear myoepithelial cells [88–90].

Mucoepidermoid carcinomas are characterised by their composition of two cell types (mucus-producing cells and epidermoid and/or intermediate cells) with a great variety in the proportion of these two cell types [4, 91].

Basaloid-squamous carcinomas show a biphasic differentiation as a squamous cell carcinoma and a solid type of adenoid cystic carcinoma. This rare carcinoma is mostly localised at the base of the tongue and the floor of mouth or the palate [92, 93].

Adeno-squamous carcinoma is constructed on an epidermoid component and glandular features with true lumina in separate and well-defined areas [94]. The development of primary adeno-squamous carcinomas from the minor salivary glands or the oral mucosa has been the subject of controversial discussion [4].

Secondary carcinomas in pre-existing pleomorphic adenomas show different histological types of carcinoma, but often demonstrate a mixed differentiation as squamous cell carcinoma and adenocarcinoma [95].

The histogenetical classification of *carcinosarcoma* was controversially disputed for a very long time [96], but new experimental data, and results of electron microscopy and

immunohistochemistry, corroborate the hypothesis that totipotential stem or reserve cells exist in any tissue and have the ability to pursue epithelial, mesenchymal or mixed lineages of differentiation [97]. Electron microscopic studies of the sarcomatous components of carcinosarcoma have shown an admixture of cells having epithelial properties with others manifesting a mesenchymal phenotype. Immunohistochemistry often demonstrates the presence of cytokeratin, epithelial membrane antigen (EMA) or both in mesenchymal components of carcinosarcomas. Therefore, malignant tumours with apparently mixed carcinomatous and sarcomatous phenotypes are examples of so-called *sarcomatoid carcinomas* with varying degrees of divergent differentiation. Sarcomatoid carcinoma should be the preferred nomenclature for use in diagnostic reports. In addition, the term "biphasic sarcomatoid carcinoma" should be used [98]. Sarcomatoid carcinomas of the salivary glands, which were called carcinosarcomas in the earlier publications, are very rare [99, 100]. Carcinomas of the salivary glands with focal sarcomatoid stromal reaction contain mostly osteoclastic multinuclear giant cells [101, 102]. A curiosity is the association of a carcinoma in a pleomorphic adenoma with a giant cell tumour [103].

Collision tumours

The old term "collision tumour" was determined in 1919 by Meyer [104]. In his original definition, a collision tumour was a meeting of two malignant neoplasms arising at independent topographical sites. During further growth, the two tumours invade each other, especially in the border zone. Such rare collisions have been described in various locations, including the oral cavity [105]. Other areas are the gastric cardia, anorectal junction, lung, cervix, urinary bladder and liver. In most of the reported cases the collisions have been between adenocarcinomas and sarcomas or lymphomas, collisions between two types of carcinomas are very rare.

Hybrid tumours

Hybrid tumours are very rare tumours which are composed of two different tumour entities within the same topographical area. Each of the tumour entities conforms with an exactly defined tumour category. In contrast to the collision tumour, both tumour entities of a hybrid tumour are not separate but have an identical origin in the same tissue. Hybrid tumours are very rare with a percentage of less than 0.1% of all salivary gland tumours. Examples of hybrid tumours are: basal cell adenoma and canalicular adenoma; basal cell adenoma and adenoid cystic carcinoma; Warthin tumour and sebaceous adenoma; epithelial–myoepithelial carcinoma and adenoid cystic carcinoma; and acinic cell carcinoma and salivary duct carcinoma.

NOMENCLATURE

The exact terminology of the different types of multiple salivary gland tumours is the basis for a clearly defined nomenclature.

Multiple tumours of the salivary glands

The tumours can be localized in one or more salivary glands. The tumours have developed in different topographical areas and are separated from each other by tumour-free salivary gland tissue.

With regard to the *localisation*, the following two possibilities can be distinguished: unilateral and bilateral.

With regard to the *histological typing*, two groups can be defined: multiple salivary gland tumours with identical histology or different histology. The most common uni- or bilateral tumour is the Warthin tumour. Other mostly bilateral tumours are pleomorphic adenoma, oncocytoma, acinic cell carcinoma and basal cell adenoma. In the group of tumours with different histology the most frequent combination is between pleomorphic adenomas and Warthin tumours.

With regard to the *timing*, synchronous (simultaneous) and metachronous tumours can be distinguished. The development of tumours is more often metachronous, but the clarification of this point has proved to be very difficult in many observations.

Salivary gland tumours with other extraglandular tumours

Simultaneous occurrence with other *oral tumours* is very rare. Occurrence with secondary *extraglandular carcinoma* has been observed, especially with breast carcinoma, thyroid carcinoma, carcinoma of the respiratory tract and of the ovaries.

Salivary gland tumours with biphasic differentiation

This tumour group is characterised by a regular, constantly recurring mixture of two cellular components in the same tumour with a corresponding term in the tumour classification. Examples are epithelial–myoepithelial carcinoma, mucoepidermoid carcinoma, basaloid-squamous carcinoma and adeno-squamous carcinoma. Biphasic sarcomatoid carcinoma is a malignant tumour with mixed carcinomatous and sarcomatous phenotypes, and with varying degrees of divergent differentation. Rather than the older term "carcinosarcoma" the term "sarcomatoid carcinoma" is preferred. The sarcomatoid stromal component mostly contains osteoclastic multinuclear giant cells.

Collision tumour

The old term "collision tumour" is defined as a meeting of two malignant neoplasms arising at independent topographical sites. During further growth the two tumours invade each other. The collision is mostly between adenocarcinomas and either sarcomas or lymphomas.

Hybrid tumours

The very rare hybrid tumours are composed of two different tumour entities within an identical topographical area. Each of the tumour entities conforms with an exactly defined tumour category. In contrast to the collision tumour, both entities of a hybrid tumour are not separated but have an identical origin in the same tissue.

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