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ORIGINAL ARTICLE

Salivary gland hybrid tumour revisited: could they represent high-grade transformation in a low-grade neoplasm?

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Abstract Salivary gland hybrid tumour, first described in 1996, is a very rare neoplasm for which exact morphological criteria have not been universally agreed upon. In contrast, the concept of high-grade transformation (HGT) in salivary neoplasms has been widely accepted during the last decade, and the number of reported cases is rapidly increasing. A review of the literature revealed 38 cases of hybrid tumour reported in 22 publications. During approximately the same time period, well over 100 cases of HGT in salivary neoplasms have been reported. There are important histological similarities between hybrid tumours and salivary tumours with HGT. In the latter, containing one tumour component of low-grade malignancy and the other of high grade, the two tumour components are not entirely separated and appear to originate in the same area. Virtually, all cases reported as hybrid tumour had no clear lines of demarcation between the two tumour types. We are inclined to suggest that most of the 38 cases of hybrid tumours described in the literature would today better be called tumour with HGT rather than hybrid tumour. The relative proportion of the two components may vary, and the high-grade component is sometimes very small, which emphasises the importance of very generous sampling of the surgical specimen. The molecular genetic mechanisms responsible for HGT, including what used to be called hybrid tumour, remain largely unknown. Abnormalities of a few genes (including *p53*, *C-MYC*, *cyclin D1*, *HER-2/neu*) have been documented. As insufficient data exist on gene abnormalities in these lesions, conclusions as to whether or not they have a common origin and which mechanisms are involved in transformation cannot be drawn. Due to the small number of cases reported, many of which lack follow-up details; indicators of prognosis of hybrid tumours are not available, but their behaviour seems to be similar to that of tumours with HGT, i.e. an accelerated aggressive course. HGT of salivary gland neoplasms greatly influences macroscopic and microscopic evaluation of the specimen but also, given the high incidence of metastases and morbidity, carries significant treatment implications.

Keywords Salivary gland neoplasms · Hybrid tumour · High-grade transformation · Dedifferentiation · Salivary glands

Introduction

The so-called salivary hybrid tumour, or hybrid carcinoma, is a very rare neoplasm and appears to have been reported in the English literature first in 1996 by Ballestin et al. [1]. The same year Seifert and Donath published their seminal paper, providing a detailed description of five cases. They defined hybrid tumour as "a neoplasm composed of two separate different tumour entities, each one of which conforms to an exactly defined tumour category, arising within the same topographical area. Both tumour entities are not separated but have an identical origin in the same topographical area" [2]. The exact criteria for a hybrid tumour/carcinoma have not been universally agreed upon and with the growing awareness of high-grade transformation; the validity of the term hybrid tumour might be questioned.

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Two decades have passed since the observation of Seifert and Donath, but only some 33 further cases of hybrid tumour have been reported. During approximately the same period of time, the concept of high-grade transformation in salivary gland neoplasms became widely accepted, and the number of reported cases is rapidly increasing. Previous personal observations [3, 4] and increasing awareness of high-grade transformation in salivary gland cancers [5] prompted us to critically review published cases of hybrid tumour/carcinoma and compare them with salivary tumours with high-grade transformation. The concept of high-grade transformation (previously also called dedifferentiation) in neoplasms was introduced in 1971 when Dahlin and Beabout described a low-grade chondrosarcoma associated with a high-grade sarcoma [6]. High-grade transformation in salivary neoplasms most commonly creates a poorly differentiated adenocarcinoma or undifferentiated carcinoma (hence the older term dedifferentiation). Dedifferentiation is defined as the abrupt transformation of low-grade (LG) well-differentiated carcinoma into high-grade (HG) morphology, lacking the original distinct histological and immunohistochemical features [7]. The LG and HG areas may be clearly demarcated, but a transitional zone is usually present. In contrast to what has been published in bone and soft tissue sarcomas, in salivary gland tumours but also lymphomas, a line of demarcation is not always obvious. Therefore, high-grade transformation (HGT) seems a more appropriate term than dedifferentiation.

The present study is a critical review of published cases of salivary gland hybrid tumours and salivary gland tumours with HGT. Although HGT in a salivary tumour was first reported already in 1988 in an acinic cell carcinoma [8], we limited inclusion of hybrid tumours to those reported after the Seifert and Donath paper, the only exception being the case reported by Ballestin et al. [1] (a case of a combined acinic cell carcinoma and mucoepidermoid carcinoma). The paucity of hybrid tumour reports, and the histological similarities with salivary gland tumours with HGT do question the validity of the term hybrid tumour. Hybrid tumour was mentioned but not included as a separate entity in the latest 2005 WHO Classification [9]. Our hypothesis is that some cases, or perhaps most, reported as hybrid tumours may have represented HGT in a pre-existing salivary neoplasm, and a change in terminology may be warranted.

Review of the literature

We found 22 publications together describing 38 cases of hybrid tumour [1, 2, 10–28]. Almost 70 % of reported cases were located in the parotid gland. Three cases were located in submandibular glands, one in a sublingual gland, five in the palate, two in the maxillary sinus, and one each in the upper lip, larynx, and lacrimal gland. A review of the literature of salivary neoplasms published as HGT so far revealed more than 100 cases, i.e. HGT in acinic cell carcinoma (ACC) [8, 29–34], adenoid cystic carcinoma (AdCC) [35–53], epithelial-myoepithelial carcinoma (EMC) [54–58], polymorphous low-grade adenocarcinoma (PLGA) [59–61], mucoepidermoid carcinoma (MEC) [62], myoepithelial carcinoma (MC) [63, 64], hyalinising clear cell carcinoma (HCCC) [65, 66] and mammary analogue secretory carcinoma (MASC) [67, 68].

Hybrid salivary gland tumour

Some clinicopathological features of the 38 cases of the so-called hybrid tumour are summarised in Table 1. Seifert and Donath retrieved and described five very rare tumours from the Salivary Gland Registry in Hamburg, at that time containing more than 6600 tumours, and outlined their definition and proposed the term hybrid tumour. All tumours were described as a single tumour mass, four were circumscribed and one even encapsulated and the tumour components were not separated from each other [2].

One of the cases in the original study by Seifert and Donath showed a combination of EMC and AdCC. Another nine cases with the same combination of EMC and AdCC have been reported subsequently [10, 12, 16, 18, 19, 21, 23, 27, 28]. Hence, in approximately 25 % of reported hybrid tumours, the two tumour components were EMC and AdCC. In another 11 cases, AdCC was mixed with another tumour component [2, 3, 11–13, 15, 17, 18, 24, 25]. AdCC therefore constituted one of the malignant components in more than 50 % of the 38 cases. SDC was the second most common carcinoma component and was found in 16 cases (44 %) [2, 11–13, 15, 17, 22, 24, 26] (Table 1). In one case, four malignant components were described (PLGA, ACC, AdCC and SDC) [15] and in another case in a single parotid tumour, three types of carcinoma, EMC, basal cell adenocarcinoma (BCAC) and AdCC [27]. Myoepithelial carcinoma (MC), ACC and mucoepidermoid carcinoma (MEC) have both been described in two cases, whilst squamous cell carcinoma (SCC), adenocarcinoma NOS (ANOS) and lymphoepithelial carcinoma (LEC) have occurred once only. Of the 38 cases, 24 (>60 %) were located in the parotid gland and five in the palate. The submandibular gland was the third most common site with three reported cases. There was male/female ratio of 1.6/1, and the age span was 26 to 81 years with a mean of 56 years (Table 1). The text and/or illustrations provided in the different publications rather convincingly showed all tumour components to be located within one single tumour mass without any clear separation or lines of demarcation between the different components. These descriptions of the growth pattern are compatible with HGT of one of the components. Woo et al. [19] reported a tumour that might have represented two malignancies arising as a carcinoma ex pleomorphic adenoma. The patient had an operation in the same area (right nasal

Table 1 Clinicopathological features of hybrid tumours reported in the literature

Case	Authors	Age	Sex	Localisation	Histology
1.	Seifert and Donath 1996 [2]	70	M	Parotid	BCA and CA
2.		60	M	Parotid	WT and SebLA
3.		62	M	Parotid	BCA and AdCC
4.		53	M	Parotid	ACC and SDC
5.		66	F	Palate	EMC and AdCC
6	Ballestin et al. 1996 [1]	67	M	Parotid	ACC and MEC
7	Seifert and Simpson 1997 [10]	62	F	Parotid	EMC and AdCC
8.	Kamio et al. 1997 [11]	51	M	Palate	AdCC and SDC
9.	Croitoru et al. 1999 [12]	53	M	Parotid	MEC and AdCC
10.		71	M	Parotid	EMC and AdCC
11.		28	M	Parotid	EMC and SDC
12.		51	M	Palate	AdCC and SDC
13.	Snyder and Paulino 1999 [13]	36	F	Submandibular	AdCC and SDC
14.	Chetty et al. 2000 [14]	58	M	Parotid	EMC and MEC
15.	Zardawi 2000 [15]	78	F	Parotid	PLGA, ACC, AdCC and SDC
16.	Hayashi et al. 2001 [16]	69	F	Parotid	EMC and AdCC
17.	Nagao et al. 2002 [17]	74	F	Parotid	EMC and BCAC
18.		56	M	Parotid	EMC and BCAC
19.		73	F	Parotid	EMC and SDC
20.		40	M	Parotid	AdCC and SDC
21.		81	F	Submandibular	AdCC and SDC
22.		65	M	Parotid	MC and SDC
23.		42	M	Parotid	ACC and SDC
24.		66	M	Parotid	SCC and SDC
25.		54	F	Lacrimal	SCC and SDC
26.	Ruiz-Godoy et al. 2003 [18]	49	F	Palate	MEC and AdCC
27.		71	M	Palate	EMC and AdCC
28.	Woo et al. 2004 [19]	26	F	Maxillary sinus	EMC and AdCC
29.	Piana et al. 2004 [20]	?	F	Parotid	EMC and LEC (EBV+)
30.	Murphy et al. 2006 [3]	68	F	Parotid	BCAC and AdCC
31.	Mosqueda-Taylor et al. 2010 [21]	65	M	Upper lip	EMC and AdCC
32.	Kainuma et al. 2010 [22]	74	M	Parotid	EMC and SDC
33.	Falbo et al. 2011 [23]	78	M	Submandibular	EMC and AdCC
34.	Eichhorn et al. 2013 [24]	56	F	Sublingual	AdCC and SDC
35.	Karasmanis et al. 2013 [25]	53	M	Larynx	AdCC and ANOS
36.	Atay et al. 2014 [26]	71	M	Parotid	MC and SDC
37.	Sabri et al. 2015 [27]	51	M	Parotid	BCAC, EMC and AdCC
38.	Tran et al. 2015 [28]	68	M	Maxillary sinus	EMC and AdCC

ACC acinic cell carcinoma, *AdCC* adenoid cystic carcinoma, *ANOS* adenocarcinoma NOS, *BCA* basal cell adenoma, *BCAC* basal cell adenocarcinoma, *CA* canalicular adenoma, *EBV+* Epstein Barr virus positive, *EMC* epithelial-myoepithelial carcinoma, *LEC* lymphoepithelial carcinoma, *MC* myoepithelial carcinoma, *MEC* mucoepidermoid carcinoma, *PLGA* polymorphous low-grade adenocarcinoma, *SCC* squamous cell carcinoma, *SDC* salivary duct carcinoma, *WT* Warthin tumour

cavity/maxillary sinus; tumour diagnosed as a pleomorphic adenoma), 2 years before the tumour described in the paper. The surgical specimen showed a carcinoma composed of EMC with an AdCC component, and the illustrations are compatible with the two components being intermingled. Development of carcinoma ex pleomorphic adenoma cannot

totally be excluded in this case, although 2 years is a rather short period of time for such development, and the report does not mention any remnants of pleomorphic adenoma [19]. We are inclined to regard also this case as HGT of an EMC into AdCC.

High-grade transformation in salivary gland neoplasms

We were able to retrieve from the literature more than 100 cases of different salivary tumour with HGT. Histologically, salivary gland tumour HGT is characterised by a residual component of a conventional salivary gland tumour entity and another distinct more anaplastic cell population, often a poorly differentiated adenocarcinoma, or another tumour entity of higher degree of malignancy (e.g. epithelial-myoepithelial carcinoma transformed to foci of salivary duct carcinoma). The two (or more) components are intermingled (as seen in hybrid tumours), but smaller additional separate foci can be present. There is often an altered immunohistochemical marker profile as well as a considerably higher Ki-67 labelling index in the higher grade component. Mitoses are frequent and necrosis often extensive [7].

The first case of HGT in acinic cell carcinoma was described in 1988, and since then, more than 40 cases of ACC-HGT have been reported [8, 29–34]. In most cases, the high-grade component was a poorly differentiated adenocarcinoma (Fig. 1).

HGT in adenoid cystic carcinoma (AdCC-HGT) was first described in 1999 by Cheuk and associates who described three cases [35]. Since then, another 41 cases were published, and all were recently presented in great detail in multi-author review. Most of the 44 cases involved a submandibular gland, paranasal sinus or palate [69]. Also, in cases with AdCC-HGT, the HG component was usually a poorly differentiated adenocarcinoma with large pleomorphic cells, high mitotic rate and necrosis (Fig. 2).

HGT of polymorphous low-grade adenocarcinoma (PLGA) was first described in 1995, but only a few cases have been reported since [59–61]. More than 20 cases of HGT in epithelial-myoepitelial carcinoma (EMC) have been reported since 1999 [5, 54–58]. HGT was also reported in low-grade mucoepidermoid carcinoma (MEC) [62, 64], myoepithelial carcinoma (MC) [63], hyalinising clear cell carcinoma [65, 66] and mammary analogue secretory carcinoma (MASC) [67, 68] (Fig. 3).

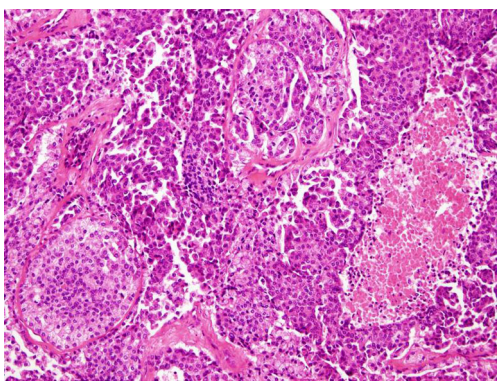

Fig. 1 ACC-HGT consisting of a poorly differentiated pleomorphic adenocarcinoma with necrosis

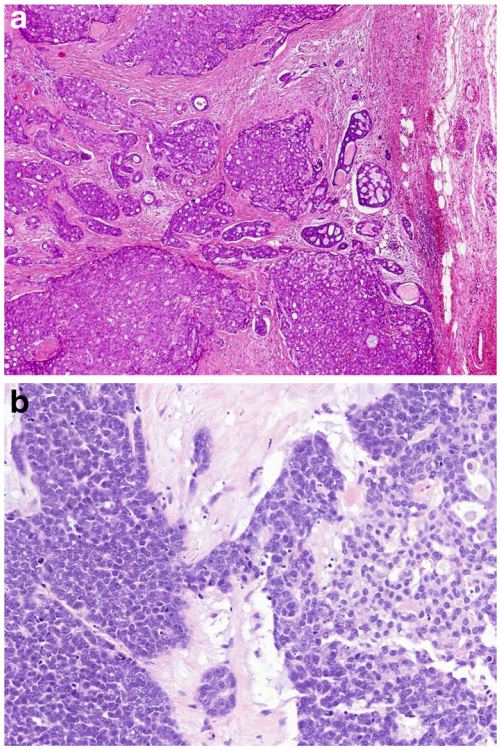

Fig. 2 **a** AdCC-HGT where the HG component is predominantly solid while the conventional AdCC reveals cribriform structures. **b** The HG component of this AdCC-HGT has undifferentiated basophilic cells with polymorphic nuclei, distinct nucleoli and high apoptotic activity

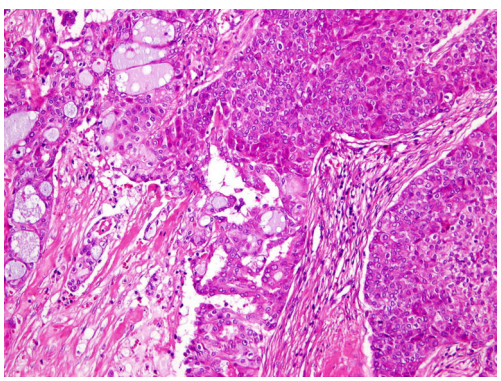

Fig. 3 MASC-HGT with two distinct components, partly delineated, partly intermingled. Conventional MASC shows microcystic and vacuolated pattern with characteristic secretion, while the HG component exhibits solid growth without secretory activity

Discussion

The diagnosis of hybrid tumour or HGT in a salivary gland tumour is almost always reached only after examination of the postoperative surgical specimen, which has been meticulous and often of the entire specimen is included for histological examination. Hybrid tumours as defined by Seifert and Donath [2] differ from biphasically differentiated salivary neoplasms (e.g. epithelial-myoepithelial carcinoma and adenoid cystic carcinoma), collision tumours (the meeting of two neoplasms arising at independent topographical sites; usually a carcinoma and a sarcoma and/or lymphoma, e.g. observed in multiple sites such as cardia, cervix and urinary bladder) and synchronous and multiple (often recurrent) salivary gland tumours and to a certain extent, carcinomas with metaplastic changes. Rare cases of primary salivary tumours with metastatic localization of extra-salivary primaries exist, e.g. pleomorphic adenoma in a parotid next to metastasis from renal carcinoma, but such cases are beyond the scope of this review.

HGT in AdCC may occur first in recurrent AdCC [35]. There should be a clear distinction between a solid type of AdCC and AdCC-HGT, and to this end, histological criteria were outlined by Seethala et al. [43]. Most reports indicate that the prognosis for AdCC-HGT is even worse than for a solid type of conventional AdCC [43, 5, 69, 70], and therefore, HGT recognition is important for management of the individual patient. The cells in the solid type of AdCC have small hyperchromatic nuclei and a basaloid appearance, whilst the cells in AdCC-HGT have larger and more pleomorphic vesicular nuclei. Moreover, the cells in a solid type AdCC express some of the myoepithelial immunohistochemical markers. The HG component, which usually is either a poorly differentiated adenocarcinoma or, less commonly, an undifferentiated carcinoma, shows cells with large pleomorphic nuclei and a high mitotic rate. The nuclei contain vesicular chromatin with conspicuous nucleoli. Necrosis (also comedonecrosis) is common as is desmoplastic stroma and tumour calcification. Squamous areas and micropapillary growth are unique patterns seen exclusively in AdCC-HGT as compared to conventional AdCC [43]. There are suggestions that AdCC-HGT has a high propensity for lymph node metastasis, which have been reported in up to 57 % of patients compared to 5–25 % of patients with conventional AdCC [43]. The risk for tumour extension into lymph nodes in AdCC-HGT is distinctly higher than in conventional AdCC, as lymph nodes in conventional AdCC are often involved by direct extension from the primary tumour rather than by metastasis. In the study of AdCC-HGT by Seethala et al. in all cases with cervical lymph node metastases, these were not single but multiple and all with extracapsular spread [43]. HGT in salivary tumours of low-grade malignancy, such as acinic cell carcinoma (ACC), is associated with a higher propensity for local recurrence and lymph node metastasis along with worse prognosis. While ACC has the best prognosis of all salivary malignancies (10-year survival of almost 90 %), in patients with ACC-HGT, the mean survival has been reported as short as 4.3 years [31, 34, 71]. A recent review of the head and neck AdCC-HGT concluded that its clinical course is progressive with a high propensity for lymph node metastasis, drastically different from that of conventional AdCC. The study concludes that elective neck dissection in patients with AdCC-HGT is mandatory [69].

In some cases, particularly in cases of EMC and basal cell adenoma, the possibility of multidirectional differentiation, mediated through intercalated duct hyperplasia, has been suggested [72–75]. We tend to consider in such cases multidirectional differentiation also as a form of HGT. Grenko et al. [76] described three AdCCs and two EMCs and discussed criteria for hybrid tumours. They showed in AdCCs regions of clear cell change of basal/myoepithelial cells and prominent ductal structures mimicking EMC. Conversely, EMCs had AdCC-like regions. The authors concluded that AdCC-like regions in EMC and EMC-like regions in AdCC should be regarded as anomalous differentiation but not as hybrid tumour. They further suggested that the only two tumour types that might be included in the hybrid tumour category to be adenosquamous carcinoma and carcinosarcoma [76]. It is noteworthy that in 10 of the 38 cases of hybrid tumour described in the literature, the two tumour components were EMC and AdCC (Table 1). Further support for a common differentiation pathway, i.e. HGT, comes from a case report of a salivary gland type hybrid carcinoma arising within a Bartholin's gland adenoma, in which the tumours consisted of an EMC and an AdCC [77]. In this context, one should bear in mind that occurrence of areas of EMC within an AdCC is not extremely unusual, as is MC associated with EMC (these tumour entities share a common origin). In our optinion, cases with these two carcinoma components that have been called hybrid tumour should possibly regarded as HGT carcinomas.

One argument that has been used in favour of the term hybrid tumours/carcinomas has been the consistent presence of a transitional feature between the two, suggesting that the two components have an identical origin [2, 11, 17]. This feature can also be found in HGT of salivary gland neoplasms. In the 36 so-called hybrid tumours (Table 1) with at least one malignant component, AdCC was the high-grade component in 21 cases (58 %). Salivary duct carcinoma was the high-grade component in 16 (45 %) of these 36 cases. The latter finding makes it tempting to draw parallels with the development of carcinoma in situ ex pleomorphic adenoma and carcinoma ex pleomorphic adenoma, where SDC is one of the more common malignant components [78, 79].

The molecular genetic mechanisms responsible for the development of hybrid tumours and for HGTs remain largely unknown. Very few genomic studies have been performed on hybrid tumours. The nine cases of hybrid tumour studied

by Nagao et al. [40] reported diffusely positive p53 immunoreactivity in four cases, restricted to the more aggressive component. Molecular analysis showed that of the p53-positive cases, three had loss of heterozygosity at a p53 microsatellite locus and one *TP53* gene point mutation, only in the p53-immunoreactive carcinoma component. The authors suggest that such molecular-genetic events might induce the transformation from histologically lower to higher grade tumour during the development of a hybrid carcinoma [40]. We tend to interpret this statement as "hybrid tumours are examples of HGT." In cases of HGT of salivary gland neoplasm abnormalities, a few genes have been documented, for example *TP53* gene mutation and C-MYC amplification [38, 46, 64, 70]. Cyclin D1 overexpression, as well as p53 abnormalities in combination with HER-2/neu overexpression or loss of pRb expression, has been implicated in HGT of AdCC [35, 38, 40]. Some studies have implicated *C-MYC* amplification but also oncogenes on chromosome 17q23 in HGT of AdCC, and these warrant further investigation [70, 80]. One study of AdCC-HGT reported that MYB/NFIB translocation is not necessarily an early event in or fundamental for HGT in AdCC [47]. Skálová et al. [67] recently reported the HG component of MASC to have strong immunostaining for *EGFR*, Beta-catenin, S-100 and *cyclin D1*, whereas *HER-2/neu* was absent. Analysis of *TP53* and *CTNNB1* gene mutations in the HG component of MASCs as well as detection of copy number aberration of *EGFR* and *CCND1* gene did not harbour any abnormalities. However, both high- and low-grade components of MASC contained the *ETV6-NTRK3* fusion transcript. Overall, only *TP53* alterations have been shown in both hybrid tumours and HGT, and this is insufficient evidence to firmly conclude that hybrid tumours in fact represent HGT.

Our review of hybrid tumours and HGT in salivary tumours emphatically demonstrates the importance of very generous sampling of the surgical specimens and meticulous microscopic examination, as the HG component may represent as little as 5–10 % or even less of the tumour. Ideally, the entire surgical specimen should be examined. Virtually, all cases reported as hybrid tumours had no clear lines of demarcation between the different tumour types. We contend that most, if not all (apart from the two cases with two benign tumour entities—see Table 1) of the 38 cases of hybrid tumour described in the literature, would today probably better be called tumours with HGT. We suggest that the term hybrid tumour is reserved for those rare occasions, as originally proposed, of two benign tumours (or also perhaps as suggested by Grenko et al. [76], adenosquamous carcinoma and carcinosarcoma) arising in the same topographical area and are not separated from each other (which is not the same as a collision tumour). The concept of HGT in salivary gland tumours has important consequences for macroscopic and microscopic evaluation of a specimen, but also carries significant treatment implications given the high incidence of metastases [81].

We conclude that salivary hybrid tumours and salivary gland neoplasms with HGT share many morphological and clinical similarities and conclude that hybrid tumours do exist and that the concept is valid, but also that most cases published so far are not true hybrid tumours but salivary neoplasms with HGT. Careful examination including generous sampling of the surgical specimen is essential, as missing the high-grade component has important implications for treatment and prognosis. Further, molecular genetic studies are necessary to unambiguously determine whether or not salivary hybrid tumours and salivary gland neoplasms with HGT are distinct entities or biologically identical.

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