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Polymorphous adenocarcinoma of the salivary glands: reappraisal and update

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Abstract

Although relatively rare, polymorphous adenocarcinoma (PAC) is likely the second most common malignancy of the minor salivary glands (MiSG). The diagnosis is mainly based on an incisional biopsy. The optimal treatment comprises wide surgical excision, often with adjuvant radiotherapy. In general, PAC has a good prognosis. Previously, PAC was referred to as polymorphous low-grade adenocarcinoma (PLGA), but the new WHO classification of salivary gland tumours has also included under the PAC subheading, the so-called cribriform adenocarcinoma of minor salivary glands (CAMSG). This approach raised controversy, predominantly because of possible differences in clinical behaviour. For example, PLGA (PAC, classical variant) only rarely metastasizes, whereas CAMSG often shows metastases to the neck lymph nodes. Given the controversy, this review reappraises the definition, epidemiology, clinical presentation, diagnostic work-up, genetics, treatment modalities, and prognosis of PAC of the salivary glands with a particular focus on contrasting differences with CAMSG.

Keywords Polymorphous adenocarcinoma · Pathology · Salivary glands · Therapy · Prognosis · Polymorphous low-grade adenocarcinoma · Cribriform adenocarcinoma of minor salivary glands

Introduction

Polymorphous adenocarcinoma (PAC) of the minor salivary glands (MiSG) is a rare head and neck cancer, which generally has a good prognosis following adequate multidisciplinary treatment. Regarding this entity, recently, the histopathological landscape has been redesigned. Most PACs were previously known as “polymorphous low-grade adenocarcinoma” (PLGA), but the recent WHO classification of salivary gland tumours includes under the PAC heading, besides the classical PLGA, also the so-called “cribriform adenocarcinoma of minor salivary glands” (CAMSG). This approach has met controversy predominantly because of purported important differences in clinical behaviour. For

example, PLGA (PAC, classical variant) only rarely metastasizes, whereas CAMSG often shows regional metastases.

In view of the controversy, this review by the International Head and Neck Scientific Group (IHNSG) aims to critically reappraise the recent literature on PAC, and to integrate recent findings into the existing knowledge base, predicated on extensive clinical experience. Comparable efforts have been already published for adenoid cystic carcinoma, mucoepidermoid carcinoma and acinic cell carcinoma [1–3]. The definition, epidemiology, clinical presentation, diagnostic work-up, genetics, treatment modalities, and prognosis of PAC are revisited, with a particular focus on contrasting differences between PLGA and CAMSG. In this manuscript, the term PAC refers to PLGA or “PAC, classical variant”, whenever studies containing data from before the latest WHO classification are referred to.

This paper was written by members and invitees of the International Head and Neck Scientific Group (<http://www.IHNSG.com>).

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Methods

A literature search was conducted using PubMed and ScienceDirect, based on the MeSH terms “polymorphous low-grade adenocarcinoma”, “polymorphous low-grade papillary

adenoma”, “salivary lobular carcinoma”, “salivary terminal-duct adenocarcinoma”, “polymorphous adenocarcinoma”, and “cribriform adenocarcinoma of the minor salivary gland”, spanning the period 1984–2017. Based on title and abstract, a total of 462 manuscripts were included in the final database that provided the basis for this review. An additional 13 manuscripts were added through reference tracking.

Historical survey and definition

Freedman and Lumerman should be credited with the first clinicopathological description of what is now referred to as “polymorphous adenocarcinoma” (PAC) in 1983, though they suggested the term “lobular carcinoma” to emphasize similarities with the single-file (‘Indian-file’) cellular infiltrates seen in breast lobular carcinoma [4]. The same year Batsakis et al. reported a series of similar tumours as “terminal-duct adenocarcinoma” to reflect their purported origin from the intercalated (terminal/distal) segment of salivary ducts [5]. Previously, it is likely that PAC had been diagnosed as non-specific adenocarcinoma or adenoid cystic carcinoma (AdCC). In 1984, however, Evans and Batsakis suggested the term “polymorphous low-grade adenocarcinoma” (PLGA) for this group of largely MiSG tumours that were characterized by blunt/uniform cytology, but histologically diverse architectural patterns (see “[Microscopic features](#)” below) [6]. The latter varied both within and among the individual tumours [6]. The term PLGA enjoyed widespread endorsement and in 1991 the World Health Organization (WHO), in its 2nd classification of histological typing of salivary gland tumours, adopted it to emphasize the polymorphous histology and rather indolent clinical behaviour [7]. Between the original reports and the 1991 WHO publication, approximately 130 cases of PLGA were reported in the English literature [8]. The interest in PLGA gained momentum and culminated with the publication in 1996 of the Armed Forces Institute of Pathology volume on tumours of the salivary glands by Ellis and Auclair [9]. This text provided a good review of the literature together with a detailed pathological description, illustrations, and differential diagnosis, and became the standard reference.

Increasing clinical experience eventually indicated that PLGA is not always as indolent as initially thought [10]. In addition and similarly to other salivary carcinomas (e.g., AdCC [11], acinic cell carcinoma [12]), high-grade transformation of PLGA was described [13]. Differences in histopathological interpretation and factors such as pT and site apart, it was on those grounds, that in 2017, the WHO opted for the term PAC and defined it as “a malignant epithelial tumour characterized by cytological uniformity, morphological diversity, and an infiltrative growth pattern” [14–16]. The value of this decision remains to be seen.

In 1999, a type of adenocarcinoma occurring in the posterior lateral/base of tongue and frequently showing synchronous metastases in cervical lymph nodes, was described [17]. It was named “cribriform adenocarcinoma of the tongue” (CAT) and, given some histological resemblance to papillary thyroid carcinoma (PTC), was hypothesized to arise from the thyroglossal duct anlage [17]. This concept, however, was not universally accepted, arguments against being that the thyroglossal duct is not lateral, the site possibly influenced the rate of metastases, and that CAT shared histological features with conventional PLGA. Accordingly, the 2005 WHO publication classified CAT as a subtype of PLGA [18]. Interestingly, CAT was later reported in MiSGs other than the ones located in the tongue (see “[Clinical features](#)” below), and was thus renamed “cribriform adenocarcinoma of minor salivary gland origin” (CAMSG) [19]. Despite the purported similarity of CAMSG cells to PTC, the differences in site distribution, the higher regional aggressiveness, and partly different genetic alterations found in PLGA (PAC, classical variant) and CAMSG (see “[Genetic analysis](#)” below), the 2017 WHO classification decided to retain CAMSG under the PAC subheading [15, 20]. This is supported by the histologic and immunophenotypic similarities, the existence of tumours with histologic features of both PLGA (PAC, classical variant) and CAMSG, comparable survival rates, absence of distant metastasis in both entities, and the observation that PLGA (PAC, classical variant) and CAMSG are driven by genes of the same family (see “[Genetic analysis](#)” below). Debate on whether to separate CAMSG from PAC or not is still ongoing [20] and more research is desirable to make conclusive decisions [16]. In view of the ongoing debate, CAMSG will be separately treated in this review.

Epidemiology

Obviously, available epidemiological studies date back to the time period before the recent definition of PAC, and mainly focus on PLGA (PAC, classical variant), and not on the rare entity of CAMSG. The recently reported increased proportion of these tumours [21–23] should be interpreted with caution, since this may reflect improved diagnostics. Salivary cancers account for 5.9% of the yearly incidence of head and neck cancers [24]. Approximately 0.44–2.47% of all benign and malignant salivary gland tumours are PLGAs [14, 21, 25, 26]. De Araujo et al. performed an extensive literature review of mainly institution-based series between 1992 and 2012, and found a varying frequency of PLGAs among MiSG carcinomas, calculating an average proportion of 6.3% (431 cases out of a total of 6891) [22]. This number is obviously subjected to both

referral and diagnostic biases within centres and among centres, and it is, therefore, better to focus on population-based registries. Considering “all salivary gland malignancies” in a population-based registry in the UK, PLGA constitutes about 11.5% [21]. Given the almost exclusive MiSG origin [27], the proportion of 41% of MiSG carcinomas is clinically the most meaningful one [21]. Thus, PLGA (PAC, classical variant) with or without CAMSG inclusive is the second most common intraoral salivary cancer after mucoepidermoid carcinoma. The recent analysis of the United States National Cancer Institute’s Surveillance, Epidemiology, and End Results (SEER) Database on PLGA (2001–2011) provides the most accurate epidemiologic information and reports an annual incidence rate of 0.051 PLGA per 100,000 [28].

The tumour predominantly affects women, with an F:M ratio of around 2–1 [10, 28–32]. Over 90% of PLGAs occur above 40 years of age, with comparable incidence rates per decade from 40 to 79 years, and a mean age at diagnosis of 61.3 years [28]. The site is discussed below. Over 75% of PLGAs were diagnosed in whites, approximately 20% in coloured people, and less than 2% in Asians [28].

Regarding CAMSG, only around 50 cases have been described, which limits epidemiological conclusions. CAMSG affects males and females approximately equally and age at diagnosis ranges from 25 to 85 years (mean 53 years) [20].

Clinical features

For consistency with the latest WHO classification, the term PAC will be used, but it is re-emphasized that data were collected in the era when the tumour was referred to as PLGA. PAC is mainly described in the posterior hard and soft palate (Fig. 1) [25, 28, 33]. Labial and buccal mucosa are also involved [10, 25, 28]. Up to 9% of PACs have been reported to originate from major salivary glands, with the parotid affected in more than half of these cases [21, 28], but in our collective experience; however, bona fide PACs of the major salivary glands are rare. Even less frequently, PAC of the nasal cavity and paranasal sinuses has been described [28, 34]. Cases of laryngeal, tracheal, bronchial, breast, intramandibular, intramaxillary, lacrimal, and synchronous bilateral oral presentation of PAC have been reported as well [35–42]. PAC-like tumours in other sites are outside the scope of this review.

CAMSG predominantly involves the base of the tongue, but has been described in the retromolar region, palate, upper lip and tonsils [19]. Recently, a case of CAMSG originating from the epiglottis has been reported [43].

Fig. 1 PAC of the hard palate in a male aged 37 years. (Courtesy of Associate Professor Panagiota Economopoulou, University of Athens, Greece)

Most patients with a PAC show a mass with a mean size at presentation of 2.1 cm ($\pm$ SD 1.3 cm) (Fig. 1) [28]. PAC of the lip is likely smaller at first presentation, probably due to easier visualisation [10]. Conversely, CAMSG, being at a less visible site, typically is approximately 1 cm larger than PAC at presentation [19]. Only a minority presents with pain, ulceration, bleeding or ill-fitting dentures [44]. When experienced and on average, symptoms are present for over 2 years [10]. A possible presentation may be of stippled mucosa overlying the tumour, attributable to surface papillary epithelial hyperplasia [45]. Bone invasion may be occasionally seen in the hard palate and nasopharynx [46].

An apparent difference between PLGA (PAC, classical variant) and CAMSG is the pattern of metastasis: only 1 in 10 PLGA (PAC, classical variant) patients presents with nodal metastasis [28, 29, 47], as opposed to 7 in 10 patients with CAMSG [19]. In the latter, nodal disease can even be the first symptom [48]. As already noted, the particular site may account for this and the rich lymphatic network therein may also be significant [46]. Approximately 4% of PLGAs (PAC, classical variant) have distant metastases at diagnosis [28], mainly in the lungs, but abdominal, orbital and skin metastases have also been described [49–53]. Only one CAMSG case with lung and bone metastases has been reported [54].

Pre-operative assessment: imaging

Similar to other salivary malignancies, the imaging techniques pre-operatively used for treatment planning are ultrasound (US), computed tomography (CT), magnetic resonance imaging (MRI), and positron-emission tomography

combined with CT (PET-CT) [55]. PAC has non-specific imaging features [56], but the main goal is to assess the local extent including bone and cartilage involvement (especially when the tumour arises in the palate, sinuses, nasopharynx or larynx), and any regional lymph node involvement (particularly for tumours at the base of tongue) rather than providing a specific diagnosis [33, 55, 57]. US cannot differentiate PAC from most other carcinomas, as most show similar echotexture [58], but can be helpful in guiding fine-needle aspiration (FNA) of suspicious lymph nodes [59]. MRI should be performed in all salivary tumours and typically, PAC has a low T1 signal intensity and a high- to iso-T2 intensity [34]. CT has proved to be better in assessing bone erosion [33, 58] and shows PAC as an irregular, low-density lesion with irregular enhancement or bone involvement [40]. MRI suffers less from metallic artefacts (e.g., dental amalgam restorations) and is superior to CT for pre-operative assessment of tumour border, bone invasion, nodal metastases [60, 61], and perineural spread. For the latter, the preferred sequence is the contrast-enhanced fat-suppressed T1-weighted image [56]. ^{18}F -FDG-PET or PET/CT may also be useful to stage and restage PAC, but given the low rate of M+ disease, its added value compared to conventional imaging is questionable [55]. A chest X-ray or, preferably, a low-dose chest CT, is recommended for pre-operative staging of lung metastases [49–51, 62].

Pre-operative assessment: biopsy and cytology

Pre-operative tissue diagnosis for PAC of the oral cavity and oropharynx, primarily relies on an incisional biopsy including a margin of normal tissue [63–65]. The biopsy should be of adequate surface diameter and depth to allow a confident diagnosis; small sized incisional or punch-type biopsies may result in a differential diagnosis only and diagnostic difficulties because of the diverse cyto-architectural patterns.

For evaluation of major salivary gland lesions and suspicious neck nodes, FNA cytology (FNAC) and, less frequently, core needle biopsy (CNB) are used [66]. In cell-rich smears, irregular sheets and clusters of branching papillae may be seen. The nuclei are round to oval with scattered chromatin, inconspicuous nucleoli, whereas the cytoplasm is eosinophilic, dense, and moderate in amount [67, 68]. The matrix is myxohyaline [67, 68], often with bare nuclei in the background [67]. Aspirates show super-imposed nuclei with an irregular shape, punctate nucleoli and fine granular chromatin [69, 70]. The differential diagnoses include AdCC, pleomorphic adenoma (PA), and monomorphic adenoma (MA) [67, 71], and difficulties similar to the aforementioned for small sized incisional or punch-type biopsies are common. The presence of hyaline globules surrounded by

Fig. 2 **a** PAC of the lip. Histological section scanned to allow appreciation of the ‘low-grade’, somewhat lobulated and deceptively ‘pushing’, though asymmetrical silhouette of the tumour (T). (E), labial epithelium; Gls, labial salivary glands M, orbicularis oris; Sk, skin. (Unless otherwise specified, the photomicrographs are from sections stained with haematoxylin and eosin.) **b, c** Deep portion of PACs of minor salivary glands. The invasive qualities of the tumour (T) can be appreciated. A satellite tumour nodule (arrow) and penetration of the superficial submucosal fat (F) are seen. The arrowhead indicates nerve bundles subadjacent to the tumour. **d** Superficial portion of PAC (T) of A minor salivary gland. The characteristic involvement of the lamina propria is seen. (E), oral epithelium. **e** PAC involves pre-existing salivary mucous acini (straight arrows) and ducts (zigging arrow). The increased eosinophilia of the ducts allows distinction from the tumour parenchyma. **f, g** Cytological detail. H. The arrow indicates a mitotic figure. **i, j** Luminal ‘apocrine’ and non-luminal spindled phenotypes. The spindled cell (arrow) seems in the process of fraying-off into myxoid stroma (asterisk). Various architectural arrangements of the tumour cells. Largely solid islets in myxoid stroma (asterisk) (**k**); solid cords in fibrous stroma (asterisk) (**l**); luminal structures (**m**); pseudo-cribriform arrangements (**n**); single-file (‘Indian file’) arrangements (**p**); targetoid infiltration around a nerve (**q**). The non-rigid, collapsed and/or irregular silhouette of tumour lumina is appreciated in **m** and **n**. **r** ‘Pink’, eosinophilic annuli and bands of newly formed elastin (‘elastosis’) are present in the tumour stroma. **s** Canalicular adenoma (arrow) adjacent to a PAC (T) of the lip. **t** Nodal metastasis in CAMSG. **u–w** Primary CAMSG. While pseudo-cribriform appearance is dominant in **u, v**, solid patterns are seen in **w**. Note similarities to PTC nuclei in **w**; these are also appreciated in **t**

tumour cells should probably tip the scales towards AdCC, but the results for diagnosing PAC by FNAC seem poor, with one study finding a specificity of 14% (1 out of 7) for palatal tumours [71]. Cytologic samples of CAMSG share some features (e.g., super-imposed nuclei) with PTC; this may be puzzling in a patient presenting with a neck node metastasis from an unknown primary tumour [69, 70], though thyroglobulin immunohistochemistry can be performed on samples and may resolve the issue.

Despite the rather poor performance of FNAC, it should be emphasized that its main goal is distinguishing benign from malignant tumours, with a reported specificity of more than 90% in salivary glands in general [72]. A balanced approach on the value of FNAC and CNB in pre-operatively assessing salivary neoplasia is given by Howlett and Triantafyllou [73].

Pathology

Macroscopic features

PAC, classical variant, typically is firm to solid, with an ovoid, unencapsulated, though grossly circumscribed, contour. The tumour often lies in close proximity to the overlying surface epithelium [10]. The cut surface is white or tan [74], whereas central tumour necrosis and haemorrhage are

rare [10, 75, 76]. CAMSG is rubbery in consistency and white to gray in cut surface [17, 19, 20].

Microscopic features

The macroscopically described contour is reflected on whole mount preparations of PAC (Fig. 2a) and accords

with a low-grade behaviour, but satellite nodules can be seen (Fig. 2b). The tumour invades adjacent salivary lobules/fat (Fig. 2c) and is characteristically flooding the overlying lamina propria to reach the surface epithelium (Fig. 2d); the latter is in contrast to intraoral metastatic adenocarcinomas that are often submucosal [77]. Another common and characteristic feature is the continuation of

Fig. 2 (continued)

tumour to pre-existing parenchyma (Fig. 2e) [9]. It is not known whether this phenomenon reflects secondary spreading into or de novo origin from normal glandular parenchyma.

In PAC, the tumour cells per se show a uniform appearance: shaped round or polygonal and small to medium sized with indistinct boundaries, slightly increased nuclear: cytoplasmic ratio, round or oval vesicular nuclei showing dispersed chromatin and inconspicuous nucleoli, and usually

Fig. 2 (continued)

eosinophilic cytoplasm (Fig. 2f, g). The nuclear and cytoplasmic features result in an overall ‘pale’ appearance of the tumour parenchyma, which was considered a useful diagnostic criterion in the past. Nuclear atypia or mitoses are not common (Fig. 2h) [6, 10, 29, 76, 78]; which had been overemphasized. Apocrine and spindled cell phenotypes can be seen (Fig. 2i, j), whereas oncocytes are exceedingly rare [79]. The spindled phenotypes may reflect attempts at myoepithelial differentiation and/or epithelial–mesenchymal transition.

As previously noted, PAC may show various cyto-architectural patterns within a single tumour and between different tumours. The patterns vary in ratio, and include solid islands and cords, tubules, pseudo-cribriform aggregates, and “Indian-file” infiltrates (Fig. 2k–p). The pseudo-cribriform arrangements in PAC should be distinguished

from the classic cribriform pattern of AdCC; they reflect true lumina, whereas the pattern in AdCC results from stromal cores trapped within the tumour parenchyma and thus outlined by basement membrane [80]. Papillary arrangements are less common and never dominant. Finally, a targetoid pattern, concentrically around a small nerve bundle is not rare (Fig. 2q); this neurotropism has often been highlighted. Perivascular arrangements can also be seen [10, 13, 46, 47, 81].

PAC is set in variously myxoid fibrous/hyalinised or elastotic stroma with inconspicuous inflammation (Fig. 2k, l, r) [6, 10, 75]. Tyrosine-rich crystalloids and microcalcifications can be observed [79]. PAC-like components are not unusual in the context of carcinoma ex PA, whereas canaliculic adenomas can be seen adjacent to PAC of the lip (Fig. 2s).

Features of CAMSG are illustrated in Fig. 2t–w. The tumour cells often show pale and vesicular nuclei with ground-glass appearance which often overlap and thus resemble the Orphan Annie Eye-nuclei of PTC (Fig. 2w). This may be a pitfall especially when such cells are found in a lymph node metastasis, when the primary tumour is unknown (Fig. 2t). Again, immunohistochemistry for thyroglobulin should be used when in doubt. The cytoplasm is often abundant and clear to eosinophilic. As in PAC, cellular atypia and mitotic figures are rare [19, 82, 83]. The architecture of CAMSG is, however, considered different. A dominance of a pseudo-cirriiform pattern may point towards CAMSG. Furthermore, CAMSG may be divided into cellular, solid or microcystic lobules by fibrous septa. Solid cellular aggregates often show a chromatically accentuated peripheral layer, consisting of palisaded tumour cells arranged perpendicular to the contour of the aggregate. These peripheral areas are frequently detached from the rest of the tumour mass, which may render the tumour a papillary or glomeruloid appearance (Fig. 2u, v). The microcystic aggregates may have an alternating cribriform or tubular architecture, with the latter displaying monolayered, secretion containing, similarly sized, luminal structures [10, 17, 48, 84]. CAMSGs often invade the muscular tissue of the tongue and/or adjacent tissues and display lymphatic and occasionally also vascular invasion [19, 20, 69]. CAMSG is also set in hyalinized fibrous stroma with areas of myxoid matrix [17, 43, 69]. The features of nodal metastases resemble those of the primary (Fig. 2t).

The latest WHO recommendations, however, still question the validity of these observations [15].

Immunohistochemistry

Concerning cytoskeleton and cytoplasmic filaments, PAC cells stain for vimentin and CK 7. CKs 8 and 18 are found in most solid nests, though only focally in predominantly papillary tumours, where CK 14 is more frequently expressed. CKs 10, 13, and 19 are not expressed [85, 86].

Integrins $\beta 1$, $\beta 2$, and $\beta 3$ can be detected in the pseudo-cirriiform areas [87]. The growth factors FGF-2, PDGF-A, and PDGF-B and the receptors FGFR1, PDGFRA, and EGFR are more highly expressed in PAC than in normal salivary parenchyma [88].

Regarding cell cycle proteins, the anti-apoptotic markers BCL2 and survivin are strongly positive in PAC, while expression of the pro-apoptotic protein Bax is variable. The autophagy markers Beclin and LC3B, the most used marker of autophagosomes, are variably positive. The senescence markers p21 and p16 are predominantly negative or weakly positive. Taken together, these findings suggest that in PAC, autophagy, as a mechanism of cell survival under nutrient depletion and hypoxia, plays a role to support tumour

Fig. 3 Expression of S-100 protein in PAC

growth, further sustained by anti-apoptotic and anti-senescence signals [89]. The Ki67 (MIB-1) proliferation index is usually less than 5% [90, 91].

S-100 protein is expressed in almost all PACs, the immunoreactivity being diffuse and strong (Fig. 3) [75, 76]. Up to 80% of the cells may stain for WT1 [92]. In contrast, expression of smooth muscle actin (SMA) is inconsistent [93, 94]. A p63 positivity and absence of p40 immunostaining have also been reported [95].

The expression of mamaglobin and DOG-1 in PAC has been regarded as consistent with an origin from the intercalated (terminal/distal) segment of salivary ducts [5, 96].

As in PAC, CAMSG is strongly positive to CK7, CK8, CK18, S-100 protein, and vimentin. Furthermore, AE1-3, SOX10, and CAM5.2 are strongly expressed in CAMSG. A significant KIT expression is seen in almost half of the cases. Basal and myoepithelial markers such as p63, calponin, CK14, SMA, and CK5/6 are variably positive in all CAMSG, preferentially in the peripheral palisaded cells. Like PAC, CAMSG is also consistently p40 negative [97]. In contrast to PAC, CK19 stains in most CAMSG, though in a mild-to-moderate way. Immunostaining of p16 in CAMSG typically exhibits a patchy pattern, staining both cytoplasm and nuclei with variable portions of positive cells [19, 83, 98].

Electron microscopy

This has been summarized by Dardick [80]. He notes various proportions of luminal and non-luminal cells between regions of the same tumour and between individual cases. The non-luminal cells may express features of basal or myoepithelial cells, but their proportional volumes have not been calculated. In spite of this and the results of myofibrillar immunohistochemistry (see above), the ultrastructural

findings have been interpreted as indicative of a biphasic structural organization, for PAC, similar to other epithelial salivary tumours and the distal (acinar and intercalated ductal) segment of normal glandular parenchyma.

Genetic analysis

More than 70% of PAC exhibit activating mutations in the *PRKD1* gene, that is a single-nucleotide variant (E710D), which affects a highly conserved amino acid in the catalytic loop of the kinase domain. The mutation increases both the kinase activity and cell proliferation and is likely to act as a driver of PAC [31]. One case with a *PRKD2* rearrangement has also been described [99]. Thus, *PRKD1* mutations define a large subset of PAC and may be used to distinguish it from its mimics.

In contrast to PAC, 80% of CAMSGs show rearrangements rather than mutations in *PRKD* genes (*PRKD1-3*). The rearrangements result in recurrent *ARID1A-PRKD1* and *DDX3X-PRKD1* gene fusions, but the exact molecular consequences remain to be determined. Cases with mixed PAC and CAMSG features may show either types of molecular alterations [98–101].

Differential diagnosis

This has been addressed by Ellis and Auclair [9] and Dardick [80] on a variously histological basis. Guidance on distinguishing between PAC and AdCC, based on contour of tumour-cell aggregates, nature/contour of luminal spaces, and cytology, has also been tabulated [77]. Of the immunohistochemical markers S-100 protein, WT1 and SMA are very helpful in distinguishing PAC from its mimics (see above). For example, S-100 protein and WT1 are regularly expressed in PAC, as opposed to AdCC, where staining for SMA is, however, more consistent [92–94]. These markers seem preferable over cKIT, p63 and p40 to distinguish between the two tumours. In addition, MYB overexpression is a hallmark of AdCC [101–103], but absent in PAC [104], which is rather identified by *PRKD* gene family alterations [31, 95, 100, 105, 106]. As regards distinction from PA, particularly when faced with small sized incisional and punch biopsies, CNBs and FNAC, a negative GFAP-staining would favour PAC [107]. PA also shows concordant p63 and p40 expression (either both positive for both negative), whereas PAC is consistently p63 positive and p40 negative [95]. However, p40 does not feature in the immunohistochemical panel of every pathology laboratory.

There are no immunohistochemical markers distinguishing PAC from CAMSG, adding to the ongoing discussion whether CAMSG should be regarded as a variant of PAC with dominant pseudo-cirriiform component, or as a separate entity. In metastatic lesions, CAMSG may be confused

with PTC: the thyroid follicular markers thyroglobulin (see above) and TTF-1 are positive in PTC, but negative in CAMSG [19, 83].

High-grade transformation

High-grade transformation in PAC is rare, but has been reported, especially in recurrent tumours, where radiotherapy may be a causative factor. It is characterized by a predominantly solid growth pattern, nuclear atypia, prominent nucleoli, a high mitotic count, necrosis and frequent central haemorrhage [13, 108, 109]. To date, no cases of high-grade transformation have been described in CAMSG.

Management

Surgery

Primary wide surgical excision provides the best locoregional control for PAC (classical variant) and CAMSG [28, 34, 64, 65]. Even with a radical approach, one in three patients will have positive resection margins, possibly linked to the neurotropism that results in a tumour that escapes out of the surgical field, similar to what is observed in AdCC [64]. On the other hand, the local recurrences in the Mayo Clinic series all occurred despite negative surgical margins [44]. Prevention of recurrence is particularly important in PAC, since recurrent PAC may behave more aggressively [29]. Surgical excision is also the mainstay to treat recurrent tumours [10].

Palatal PAC with bone invasion often requires variably extended maxillectomy [63] combined with an obturator or an anatomical reconstruction to restore functionality [110]. Reconstruction can either be done immediately after the resection or delayed, following a disease-free time interval [63]. Different flaps and bone grafts have been proposed including myofascial temporalis flaps [111, 112], rotational flaps, vascularized fibular free flaps, iliac crest, and scapular osteocutaneous free flaps [63, 111]. Use of an obturator, when possible, has the advantages of potentially allowing an early detection of recurrence and a lower postoperative complication rate [63]. This should be weighed against the better functionality associated with free-flap reconstruction [113]. To achieve complete excision of CAMSG at the base of the tongue, transoral laser microscopic or robotic surgery may be preferred for smaller lesions, since it avoids the use of a mandibulotomy or suprahyoid release [65, 114, 115].

Since metastases to the neck lymph nodes are rare in PAC, neck dissection should generally be performed only in case of positive lymph nodes, observed clinically and/or on imaging [44, 76]. For PAC at the base of the tongue [46] and CAMSG [116], bilateral elective selective neck dissection

of levels II–III–IV can be considered, given the propensity for cervical nodal metastases [117].

Radiotherapy (RT)

RT is most often used postoperatively [28], in patients with extensive primary tumours or when section margins are not clear, when there is perivascular or perineural spread ahead of the main front in the resected specimen [118], and/or when cervical nodal metastases are found [63, 119]. Radiotherapy is used both in PAC and CAMSG. Currently, intensity-modulated radiotherapy (IMRT) is the standard, usually with a total dose to a tumour bed of 60 Gy (in completely excised tumours/R0 resection) or 66 Gy (when there is a microscopically involved/R1 resection) [65, 120]. Further improvement in terms of toxicity and dosimetric profile over conventional photon beam radiotherapy can be expected with the use of protons as monotherapy in patients with their tumour close to critical structures such as the orbital apex, those unfit for surgery or those with an unresectable tumour [65, 121]. IMRT has been proposed as a useful adjuvant therapy in parotid PAC when being conservative towards the facial nerve and/or in advanced-stage primary tumours [122, 123]. For MiSG tumours in general, radiotherapy has also been recommended as adjuvant therapy in tumours with advanced T and/or N status, when bone or muscle invasion is found, or when the tumour has a paranasal sinus localization [65, 124, 125]. Thus far, type-specific data supporting the use of adjuvant radiotherapy in PAC or CAMSG are lacking.

Chemotherapy

In general, the use of chemotherapy in malignant MiSG tumours is restricted to palliative cases [65]. It may be used concomitantly with radiotherapy for unresectable MiSG tumours, when the patient refuses surgery or is inoperable, or in the postoperative setting [10, 65, 126, 127]. No type-specific evidence supporting the use of chemotherapy in PAC or CAMSG is currently available [10, 47].

Follow-up

Patients treated for PAC should have regular assessments for any recurrence [44, 63, 128]. Initially, the follow-up is not different from other head and neck malignancies [62], but a minimum of 15–20 years has been suggested, since recurrence may well occur after 5 years [44, 111]. Clinical examination and MRI are the recommended tools for locoregional monitoring [129]. Use of ^{18}F -FDG-PET or PET/CT has also been proposed for post-surgical follow-up, but this may not be cost effective [55]. Chest X-ray or low-dose chest CT should be performed periodically, to detect pulmonary metastases early [49, 62].

Local recurrence has been described in CAMSG, as well as delayed cervical lymph node metastasis, necessitating a comparable follow-up scheme [19, 84, 130].

Prognosis

In general, patients affected by PAC have a good prognosis. This accords with the low Ki67 index of PACs (see above), which is suggestive of slow growth. The SEER database analysis showed a 5- and 10-year disease-specific survival (DSS) of 98.6 and 96.4%, respectively [28]. However, PAC should not be complacently regarded as a uniformly low-grade tumour, since it may recur, metastasize and even cause death [54]—hence, the decision of the WHO to rename PLGA into PAC [15]. Local recurrence of PAC has been reported to be 5.3–33% over a 5–10 year period [10, 16, 28, 46], the average time interval being approximately 70 months. Nevertheless, recurrences have been described even 24 years after primary tumour removal [64].

Table 1 summarizes statistically corroborated adverse prognosticators for PAC in a statistically significant way, mainly assessed by univariate analysis. These include site, angiolymphatic-, perineural- or bone invasion, necrosis, size, UICC stage, papillary and pseudo-ciribiform components, positive resection margins and the use of radiotherapy without surgery [28, 32, 46, 54]. Probably, the latter is influenced by a negative selection bias; radiotherapy without surgery is usually reserved for patients not fit for surgery or those with advanced-stage disease [28].

CAMSG has also a good prognosis [17, 84]. Local recurrence rates of 10–30% have been reported, while cervical lymph node metastasis may occur years after excision of the primary tumour [19, 20]. So far, one death due to CAMSG has been reported [54].

Epilogue

PAC seems the second most common MiSG cancer. Large population-based studies confirm its usually good prognosis. Nevertheless, the occurrence of regional metastasis in especially the CAMSG spectrum of the disease, as well as the possible high-grade transformation in PAC underlie the recent decision of the WHO to remove the “low-grade” indication from the term. Further research should focus on improving the treatment, while more evidence is necessary to make a conclusive decision whether to regard CAMSG as a separate entity or part of the PAC spectrum. These two entities remain grouped under one umbrella in the latest edition of the WHO classification, but further investigations are desirable and may provide different options for future targeted therapy.

Table 1 Adverse prognosticators in PAC

	Univariate identification of prognostic value of factor for certain adverse outcomes	Multivariate verification of prognostic value of factor for certain adverse outcomes
Tumour		
Extrapalatal site	DFS [46]	
Hard palate	RFS [7] OS [25]	
Size	DSS [25], DFS [54]	
Advanced-stage disease	OS, DSS [25]	
Histology		
Angiolymphatic invasion	DFS [54]	
Large nerve perineural invasion	OS [29]	
Bone invasion	DFS [54]	
Papillary component ($\geq 10\%$)	DFS [54]	DFS [54]
Cribriform component ($\geq 30\%$)	DFS [54]	DFS [54]
Necrosis	DFS [54]	
Treatment		
Radiotherapy without surgery	DSS [25]	
Positive resection margins	RFS [29]	

DFS disease-free survival, DSS disease-specific survival, RFS recurrence free survival, OS overall survival

Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

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