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REVIEW ARTICLE

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.

Methods

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

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

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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].

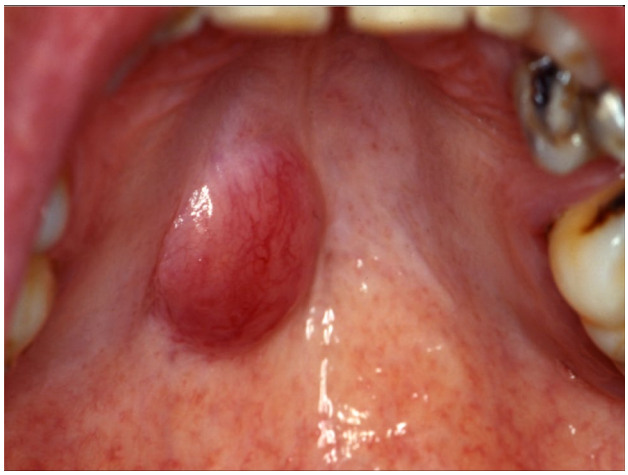


Fig. 1 PAC of the hard palate in a male aged 37 years. (Courtesy of Associate Professor Panagiota Economopoulou, University of Athens, Greece)

Most patients with a PAC show a mass with a mean size at presentation of 2.1 cm (± 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 afore-mentioned for small sized incisional or punch-type biopsies are common. The presence of hyaline globules surrounded by 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.

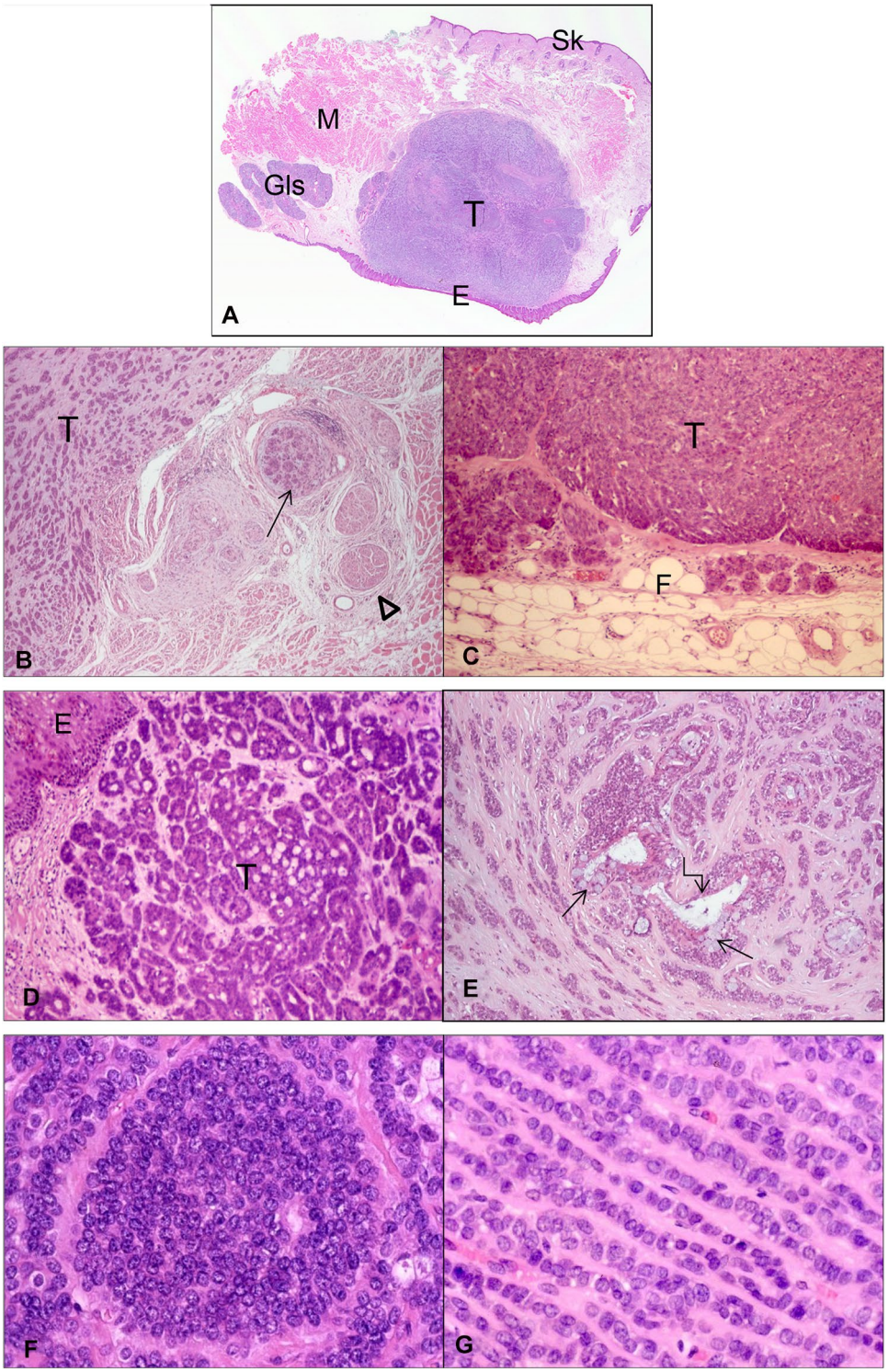
Despite the rather poor performance of FNAC, it should be emphasized that its main goal is distinguishing benign from malignant tumours, with a reported specificity of more than 90% in salivary glands in general [72]. A balanced approach on the value of FNAC and CNB in pre-operatively assessing salivary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

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**

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

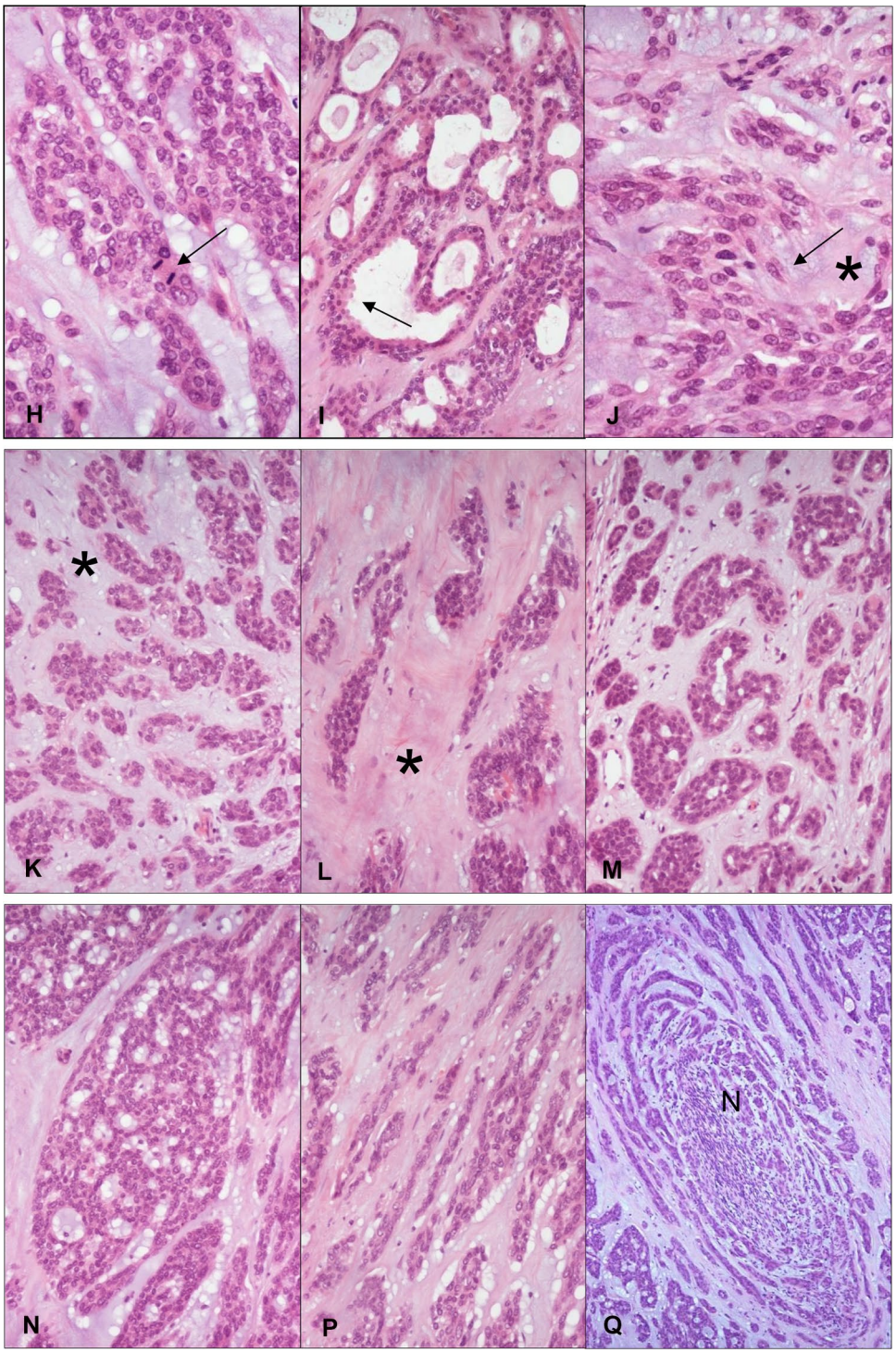


Fig. 2 (continued)

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

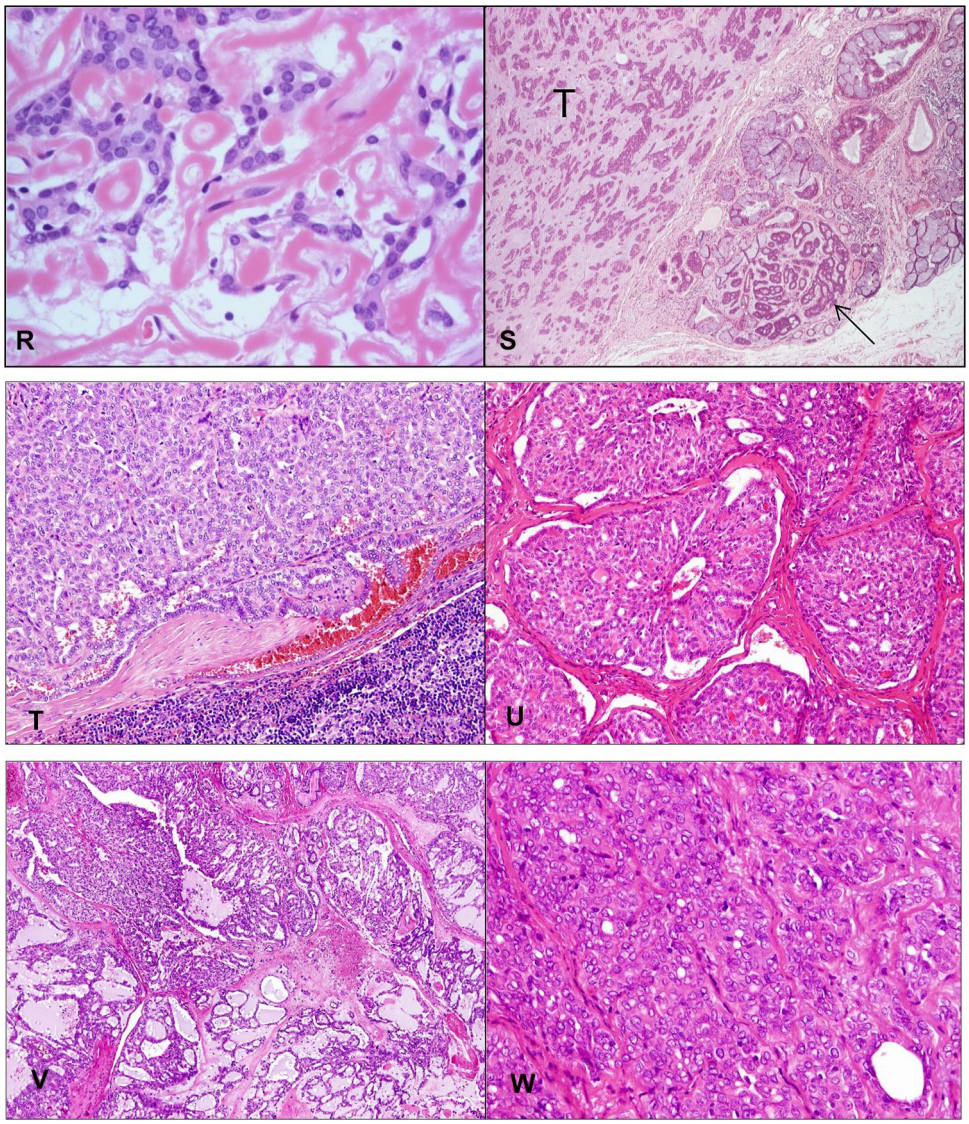


Fig. 2 (continued)

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 cytoarchitectural 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 pseudocribriform 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 canalicular 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-cribriform 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 β1, β2, and β3 can be detected in the pseudocribriform 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 growth, further sustained by anti-apoptotic and anti-senescence signals [89]. The Ki67 (MIB-1) proliferation index is usually less than 5% [90, 91].

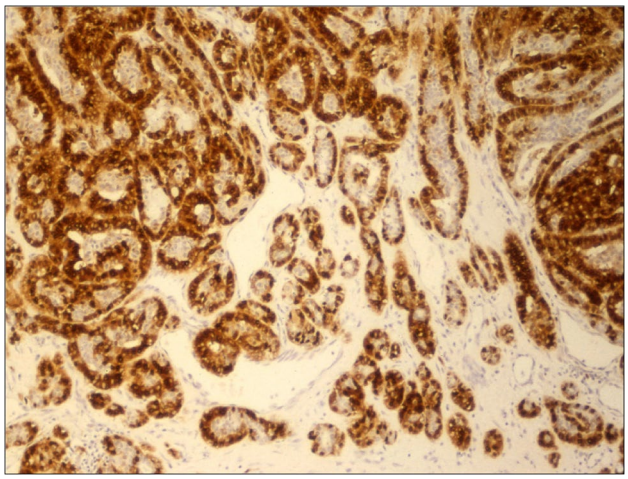


Fig. 3 Expression of S-100 protein in PAC

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 mammaglobin 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 myofilament 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 that 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-cribriform 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 sinusal 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-cribriform 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 (≥ 10%)	DFS [54]	DFS [54]
Cribriform component (≥ 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.

References

1. Coca-Pelaz A, Rodrigo JP, Bradley PJ et al (2015) Adenoid cystic carcinoma of the head and neck—an update. Oral Oncol 51:652–661. https://doi.org/10.1016/j.oraloncology.2015.04.005
2. Coca-Pelaz A, Rodrigo JP, Triantafyllou A et al (2015) Salivary mucoepidermoid carcinoma revisited. Eur Arch Oto Rhino Laryngol 272:799–819. https://doi.org/10.1007/s00405-014-3053-z
3. Vander Poorten V, Triantafyllou A, Thompson LDR et al (2016) Salivary acinic cell carcinoma: reappraisal and update. Eur Arch Oto Rhino Laryngol. https://doi.org/10.1007/s00405-015-3855-7
4. Freedman PD, Lumerman H (1983) Lobular carcinoma of intraoral minor salivary gland origin. Oral Surg Oral Med Oral Pathol 56:157–165. https://doi.org/10.1016/0030-4220(83)90282-7
5. Batsakis JG, Pinkston GR, Luna MA et al (1983) Adenocarcinomas of the oral cavity: a clinicopathologic study of terminal duct carcinomas. J Laryngol Otol 97:825–835. https://doi.org/10.1017/S0022215100095062
6. Evans HL, Batsakis JG (1984) Polymorphous low-grade adenocarcinoma of minor salivary glands a study of 14 cases of a distinctive neoplasm. Cancer 53:935–942. https://doi.org/10.1002/1097-0142(19840215)53:4<935::AID-CNCR2820530420>3.0.CO;2-V
7. Seifert G, Sobin L (1991) Histological typing of salivary gland tumours. World Health Organization International Histological Classification of Tumours, 2nd edn. Springer, New York
8. Hellquist HB, Tytor M (1991) Polymorphous low-grade adenocarcinoma: a "new" salivary gland tumour. ORL J Otorhinolaryngol Relat Spec 53:52–56
9. Ellis G, Auclair P (1996) Salivary gland tumors: malignant epithelial tumors. In: Ellis, G, Auclair P (eds) Atlas of tumor pathology. Tumors of the salivary glands. Third series, seventienth fascicle. Armed Forces Institute of Pathology, Washington DC, pp 155–228
10. Castle JT, Thompson LDR, Frommelt RA, et al (1999) Polymorphous low grade adenocarcinoma: a clinicopathologic study of 164 cases. Cancer 86:207–219. https://doi.org/10.1002/(SICI)1097-0142(19990715)86:2<207::AID-CNCR4>3.0.CO;2-Q
11. Hellquist H, Skálová A, Barnes L et al (2016) Cervical lymph node metastasis in high-grade transformation of head and neck adenoid cystic carcinoma: a collective international review. Adv Ther 33:357–368. https://doi.org/10.1007/s12325-016-0298-5
12. Skalova A, Sima R, Vanecek T et al (2009) Acinic cell carcinoma with high-grade transformation: a report of 9 cases with immunohistochemical study and analysis of TP53 and HER-2/neu genes. Am J Surg Pathol 33:1137–1145. https://doi.org/10.1097/PAS.0b013e3181a38e1c
13. Simpson RHW, Reis-Filho JS, Pereira EM et al (2002) Polymorphous low-grade adenocarcinoma of the salivary glands with transformation to high-grade carcinoma. Histopathology 41:250–259. https://doi.org/10.1046/j.1365-2559.2002.01439.x
14. Fonseca FP, de Carvalho MV, de Almeida OP et al (2012) Clinicopathologic analysis of 493 cases of salivary gland tumors in a Southern Brazilian population. Oral Surg Oral Med Oral Pathol Oral Radiol 114:230–239. https://doi.org/10.1016/j.oooo.2012.04.008
15. Fonseca I, Assaad A, Katabi N et al (2017) Polymorphous adenocarcinoma. In: El-Naggar AK, Chan JKC, Grandis JR, Takata T, Slootweg PJ (eds) World Health Organization (WHO) Classification of Head and neck tumours. IARC Press, Lyon, pp 168–169
16. Seethala RR, Stenman G (2017) Update from the 4th edition of the World Health Organization classification of head and neck tumours: tumors of the salivary gland. Head Neck Pathol 11:55–67. https://doi.org/10.1007/s12105-017-0795-0

17. Michal M, Skálová A, Simpson RHW et al (1999) Cribriform adenocarcinoma of the tongue: a hitherto unrecognized type of adenocarcinoma characteristically occurring in the tongue. Histopathology 35:495–501. https://doi.org/10.1046/j.1365-2559.1999.00792.x
18. Luna MA, Wenig BM (2005) Pathology and genetics of head and neck tumours. In: Barnes L, Eveson JW, Reichart P, Sidransky D (eds) WHO classification of tumours. International Agency for Research on Cancer (IARC), Lyon, France, pp 224–225
19. Skálová A, Sima R, Kaspirkova-Nemcova J et al (2011) Cribriform adenocarcinoma of minor salivary gland origin principally affecting the tongue: characterization of new entity. Am J Surg Pathol 35:1168–1176. https://doi.org/10.1097/PAS.0b013e31821e1f54
20. Skalova A, Gnepp DR, Lewis JS et al (2017) Newly described entities in salivary gland pathology. Am J Surg Path 0:1–15. https://doi.org/10.1097/PAS.0000000000000883
21. Bradley PJ, McGurk M (2013) Incidence of salivary gland neoplasms in a defined UK population. Br J Oral Maxillofac Surg 51:399–403. https://doi.org/10.1016/j.bjoms.2012.10.002
22. de Araujo VC, Passador-Santos F, Turssi C et al (2013) Polymorphous low-grade adenocarcinoma: an analysis of epidemiological studies and hints for pathologists. Diagn Pathol 8:6. https://doi.org/10.1186/1746-1596-8-6
23. Carvalho AL, Nishimoto IN, Califano JA, Kowalski LP (2005) Trends in incidence and prognosis for head and neck cancer in the United States: a site-specific analysis of the SEER database. Int J Cancer 114:806–816. https://doi.org/10.1002/ijc.20740
24. Van Eycken L (2015) Head and neck. Cancer Burden in Belgium. Brussels, p 32
25. Tian Z, Li L, Wang L et al (2010) Salivary gland neoplasms in oral and maxillofacial regions: a 23-year retrospective study of 6982 cases in an eastern Chinese population. Int J Oral Maxillofac Surg 39:235–242. https://doi.org/10.1016/j.ijom.2009.10.016
26. Wang X, Meng L, Hou T, Zheng C (2015) Frequency and distribution pattern of minor salivary gland tumors in a northeastern chinese population: a retrospective study of 485 patients. J Oral Maxillofac Surg 73:81–91. https://doi.org/10.1016/j.joms.2014.08.019
27. Bjørndal K, Krogdahl A, Therkildsen MH et al (2012) Salivary gland carcinoma in Denmark 1990–2005: outcome and prognostic factors: results of the Danish Head and Neck Cancer Group (DAHANCA). Oral Oncol 48:179–185. https://doi.org/10.1016/j.oraloncology.2011.09.005
28. Patel TD, Vazquez A, Marchiano E et al (2015) Polymorphous low-grade adenocarcinoma of the head and neck: a population-based study of 460 cases. Laryngoscope 125:1644–1649. https://doi.org/10.1002/lary.25266
29. Evans HL, Luna MA (2000) Polymorphous low-grade adenocarcinoma: a study of 40 cases with long-term follow up and an evaluation of the importance of papillary areas. Am J Surg Pathol 24:1319–1328
30. Buchner A, Merrell PW, Carpenter WM (2007) Relative frequency of intra-oral minor salivary gland tumors: a study of 380 cases from northern California and comparison to reports from other parts of the world. J Oral Pathol Med 36:207–214. https://doi.org/10.1111/j.1600-0714.2007.00522.x
31. Weinreb I, Piscuoglio S, Martelotto LG et al (2014) Hotspot activating PRKD1 somatic mutations in polymorphous low-grade adenocarcinomas of the salivary glands. Nat Genet 46:1166–1169. https://doi.org/10.1038/ng.3096
32. Elhakim MT, Breinholt H, Godballe C et al (2016) Polymorphous low-grade adenocarcinoma: a Danish national study. Oral Oncol 55:6–10. https://doi.org/10.1016/j.oraloncology.2016.02.005
33. Hagiwara M, Nusbaum A, Schmidt BL (2012) MR assessment of oral cavity carcinomas. Magn Reson Imaging Clin N Am 20:473–494
34. Lee DH, Yoon TM, Lee JK, Lim SC (2013) Polymorphous low-grade adenocarcinoma of the maxillary sinus. J Craniofac Surg 24:e213–e214. https://doi.org/10.1097/SCS.0b013e31827ff1a2
35. Zhang Y, Wang C, Zhang G et al (2015) Case report of polymorphous low-grade adenocarcinoma in the trachea with metastasis to the right middle lobe bronchus. Thorac Cancer 6:220–223. https://doi.org/10.1111/1759-7714.12157
36. Jafarian AH, Khazaeni K, Rahpeyma A, Khajehahmadi S (2013) Polymorphous low-grade adenocarcinoma of the larynx: a rare case report. Arch Iran Med 16:560–562
37. Larbcharoensub N, Sanpaphant S, Witoonpanich P et al (2016) Polymorphous low-grade adenocarcinoma of the epiglottis: a case report. Mol Clin Oncol 779–782. https://doi.org/10.3892/mco.2016.780
38. Ramesh G, Manohar R, Raghunath V, Nagarajappa R (2012) Intraosseous polymorphous low-grade adenocarcinoma of mandible: a rare entity. Dent Res J (Isfahan) 9:499–503
39. Young S, Leon M, Talerman A et al (2003) Polymorphous low-grade adenocarcinoma of the vulva and vagina: a tumor resembling adenoid cystic carcinoma. Int J Surg Pathol 11:43–49. https://doi.org/10.1177/106689690301100113
40. Sato T, Indo H, Takasaki T et al (2001) A rare case of intraosseous polymorphous low-grade adenocarcinoma (PLGA) of the maxilla. Dentomaxillofac Radiol 30:184–187. https://doi.org/10.1038/sj.dmfr.4600596
41. Asioli S, Marucci G, Ficarra G et al (2006) Polymorphous adenocarcinoma of the breast. Report of three cases. Virchows Arch 448:29–34. https://doi.org/10.1007/s00428-005-0084-2
42. Boonsarngsuk V, Suwatanapongched T, Rochanawutanon M et al (2009) Primary polymorphous low-grade adenocarcinoma of the bronchus: complete tumor removal with bronchoscopic resection. Lung Cancer 63:301–304. https://doi.org/10.1016/j.lungcan.2008.06.001
43. Brierley D, Hons BDS, Green D, Bs MB (2015) Cribriform adenocarcinoma of the minor salivary glands arising in the epiglottis d a previously undocumented occurrence. Oral Surg Oral Med Oral Pathol Oral Radiol 120:e174–e176. https://doi.org/10.1016/j.oooo.2015.02.480
44. Pogodzinski MS, Sabri AN, Lewis JE, Olsen KD (2006) Retrospective study and review of polymorphous low-grade adenocarcinoma. Laryngoscope 116:2145–2149. https://doi.org/10.1097/01.mlg.0000243200.35033.2b
45. Chi AC, Neville BW (2015) Surface papillary epithelial hyperplasia (rough mucosa) is a helpful clue for identification of polymorphous low-grade adenocarcinoma. Head Neck Pathol 9:244–252. https://doi.org/10.1007/s12105-014-0572-2
46. Seethala RR, Johnson JT, Barnes L, Myers EN (2010) Polymorphous low-grade adenocarcinoma. Arch Otolaryngol Head Neck Surg 136:385–392
47. Vincent SD, Hammond HL, Finkelstein MW (1994) Clinical and therapeutic features of polymorphous low-grade adenocarcinoma. Oral Surg Oral Med Oral Pathol 77:41–47. https://doi.org/10.1016/S0030-4220(06)80105-2
48. Mahdura M, Veerendra Kumar B, Suma S, Sarita Y (2016) Cribriform adenocarcinoma of minor salivary gland: a mimic of polymorphous lowgrade adenocarcinoma. J oral Maxillofac Pathol 20:536–539. https://doi.org/10.4103/0973
49. Hannen EJM, Bulten J, Festen J et al (2000) Polymorphous low grade adenocarcinoma with distant metastases and deletions on chromosome 6q23-qter and 11q23-qter: a case report. J Clin Pathol 53:942–945. https://doi.org/10.1136/jcp.53.12.942
50. Olusanya AA, Akadiri OA, Akinmoladun VI, Adeyemi BF (2011) Polymorphous low grade adenocarcinoma: literature

review and report of lower lip lesion with suspected lung metastasis. J Maxillofac Oral Surg 10:60–63. https://doi.org/10.1007/s12663-011-0185-1
51. Tanaka F, Wada H, Inui K et al (1995) Pulmonary metastasis of polymorphous low-grade adenocarcinoma of the minor salivary gland. Thorac Cardiovasc Surg 43:178–180. https://doi.org/10.1055/s-2007-1013795
52. Thomas KM, Cumberworth VL, McEwan J (1995) Orbital and skin metastases in a polymorphous low grade adenocarcinoma of the salivary gland. J Laryngol Otol 109:1222–1225. https://doi.org/10.1017/S0022215100132517
53. Thennavan A, Rao L, Radhakrishnan R (2013) Polymorphous low-grade adenocarcinoma of maxillary alveolus metastasising to the abdomen: the role of immunomarkers in diagnosis. BMJ Case Rep 2013:1–4. https://doi.org/10.1136/bcr-2013-009633
54. Xu B, Aneja A, Ghossein R, Katabi N (2016) Predictors of outcome in the phenotypic spectrum of polymorphous low-grade adenocarcinoma (PLGA) and cribriform adenocarcinoma of salivary gland (CASG). Am J Surg Path 40:1526–1537
55. Bertagna F, Nicolai P, Maroldi R et al (2015) Diagnostic role of 18 F-FDG-PET or PET/CT in salivary gland tumors: a systematic review. Rev Española Med Nucl e Imagen Mol (English Ed 34:295–302. https://doi.org/10.1016/j.remnie.2015.07.008
56. Kato H, Kanematsu M, Makita H et al (2014) CT and MR imaging findings of palatal tumors. Eur J Radiol 83:e137–e146. https://doi.org/10.1016/j.ejrad.2013.11.028
57. Spiro RH (1998) Management of malignant tumors of the salivary glands. Oncology (Williston Park) 12:671–680 **(discussion 683)**
58. Madani G, Beale T (2006) Tumors of the salivary glands. Semin Ultrasound CT MRI 27:452–464. https://doi.org/10.1053/j.sult.2006.09.004
59. Chen AY, Myers JN (2001) Cancer of the oral cavity. Dis Month 47:266–361. https://doi.org/10.1016/S0011-5029(01)90005-7
60. King AD, Tse GMK, Ahuja AT et al (2004) Necrosis in metastatic neck nodes: diagnostic accuracy of CT, MR imaging, and US. Radiology 230:720–726. https://doi.org/10.1148/radiol.2303030157
61. Sumi M, Kimura Y, Sumi T, Nakamura T (2007) Diagnostic performance of MRI relative to CT for metastatic nodes of head and neck squamous cell carcinomas. J Magn Reson Imaging 26:1626–1633. https://doi.org/10.1002/jmri.21187
62. Digonnet A, Hamoir M, Andry G et al (2013) Follow-up strategies in head and neck cancer other than upper aerodigestive tract squamous cell carcinoma. Eur Arch Otorhinolaryngol 270:1981–1989. https://doi.org/10.1007/s00405-012-2220-3
63. El-Naaj IA, Leiser Y, Wolff A, Peled M (2011) Polymorphous low grade adenocarcinoma: case series and review of surgical management. J Oral Maxillofac Surg 69:1967–1972. https://doi.org/10.1016/j.joms.2010.10.010
64. Kimple AJ, Austin GK, Shah RN et al (2014) Polymorphous low-grade adenocarcinoma: a case series and determination of recurrence. Laryngoscope 124:2714–2719. https://doi.org/10.1002/lary.24788
65. Vander Poorten V, Hunt J, Bradley P et al (2014) Recent trends in the management of minor salivary gland carcinoma. Head Neck 36:444–455. https://doi.org/10.1002/HED
66. Pfeiffer J, Ridder GJ (2012) Diagnostic value of ultrasound-guided core needle biopsy in patients with salivary gland masses. Int J Oral Maxillofac Surg 41:437–443. https://doi.org/10.1016/j.ijom.2011.12.005
67. Gibbons D, Hossein Saboorian M, Vuitch F, et al (1999) Fine-needle aspiration findings in patients with polymorphous low grade adenocarcinoma of the salivary glands. Cancer 87:31–36. https://doi.org/10.1002/(SICI)1097-0142(19990225)87:1<31::AID-CNCR6>3.0.CO;2-G
68. Sáenz-Santamaría J, Catalina-Fernandez I (2004) Polymorphous low grade adenocarcinoma of the salivary gland. Diagnosis by fine needle aspiration cytology. Acta Cytol 48:52–56
69. Gailey MP, Bayon R, Robinson RA (2014) Cribriform adenocarcinoma of minor salivary gland: a report of two cases with an emphasis on cytology. Diagn Cytopathol 42:1085–1090. https://doi.org/10.1002/dc.23111
70. Kapur U, Wojcik EM (2007) Follicular neoplasm of the thyroid—vanishing cytologic diagnosis? Diagn Cytopathol 35:525–528. https://doi.org/10.1002/dc.20676
71. Sahai K, Kapila K, Dahiya S, Verma K (2002) Fine needle aspiration cytology of minor salivary gland tumours of the palate. Cytopathology 13:309–316. https://doi.org/10.1046/j.1365-2303.2002.00429.x
72. Colella G, Cannavale R (2010) Fine-needle aspiration cytology of salivary gland lesions: a systematic review. YJOMS 68:2146–2153. https://doi.org/10.1016/j.joms.2009.09.064
73. Howlett DC, Triantafyllou A (2016) Evaluation: fine needle aspiration cytology, ultrasound-guided core biopsy and open biopsy techniques. Adv Otorhinolaryngol 78:39–45. https://doi.org/10.1159/000442123
74. Pittman CB, Zitsch RP (2002) Polymorphous low-grade adenocarcinoma of the tonsil: report of a case and review of the literature. Am J Otolaryngol Head Neck Med Surg 23:297–299. https://doi.org/10.1053/ajot.2002.124194
75. Regezi JA, Zarbo RJ, Stewart JCB, Courtney RM (1991) Polymorphous low-grade adenocarcinoma of minor salivary gland. A comparative histologic and immunohistochemical study. Oral Surg Oral Med Oral Pathol 71:469–475. https://doi.org/10.1016/0030-4220(91)90432-C
76. González-García R, Rodríguez-Campo FJ, Muñoz-Guerra MF et al (2005) Polymorphous low-grade adenocarcinoma of the palate: report of cases. Auris Nasus Larynx 32:275–280. https://doi.org/10.1016/j.anl.2005.03.019
77. Woolgar J, Triantafyllou A (2011) Contemporary salivary clinical pathology—facts and dilemmas. In: Bradley P, Guntinas-Lichius O (eds) Salivary gland disorders and diseases: diagnosis and management, 1st edn. Thieme, Stuttgart, pp 27–41
78. Colmenero CM, Patron M, Burgueño M, Sierra I (1992) Polymorphous low-grade adenocarcinoma of the oral cavity: a report of 14 cases. J Oral Maxillofac Surg 50:595–600. https://doi.org/10.1016/0278-2391(92)90440-B
79. Triantafyllou A, Hunt JL, Devaney KO, Ferlito A (2014) A perspective of comparative salivary and breast pathology. Part I: microstructural aspects, adaptations and cellular events. Eur Arch Oto Rhino Laryngol 271:647–663. https://doi.org/10.1007/s00405-013-2488-y
80. Dardick I (1996) Color Atlas/text of salivary gland tumor pathology. Jgaku-Shoin, New York
81. Sedassari BT, dos Santos HT, Pigatti FM et al (2016) Doing more with less: the challenging diagnosis of polymorphous low-grade adenocarcinoma in incisional biopsy samples. Histopathology 68:1046–1054. https://doi.org/10.1111/his.12880
82. Takhar AS, Simmons A, Ffolkes L, Hyde N (2015) Not just another paediatric neck lump: metastatic cribriform adenocarcinoma of the palate in an adolescent. J Laryngol Otol 129:194–197. https://doi.org/10.1017/S0022215114002643
83. Laco J, Kamarádová K, Vítková P et al (2012) Cribriform adenocarcinoma of minor salivary glands may express galectin-3, cytokeratin 19, and HBME-1 and contains polymorphisms of RET and H-RAS proto-oncogenes. Virchows Arch 461:531–540. https://doi.org/10.1007/s00428-012-1320-1
84. Mariano FV, Varanda F, Schultz L (2017) Cribriform adenocarcinoma of the soft palate with multiple lymph node metastasis and long-term follow-up. Oral Surg Oral Med Oral

Pathol Oral Radiol 123:e117–e122. https://doi.org/10.1016/j.oooo.2016.10.017
85. Marotta Reis de Vasconcellos L, Avila Sarmento Silveira V, Eduardo Blumer Rosa L et al (2006) Immunohistochemistry as a fundamental tool for the differential diagnosis of polymorphous low-grade adenocarcinoma. Quintessence Int 37:565–573
86. Araújo V, Sousa S, Jaeger M et al (1999) Characterization of the cellular component of polymorphous low-grade adenocarcinoma by immunohistochemistry and electron microscopy. Oral Oncol 35:164–172. https://doi.org/10.1016/S1368-8375(98)00102-X
87. Araújo VC, Loducca SVL, Sousa SOM et al (2001) The cribriform features of adenoid cystic carcinoma and polymorphous low-grade adenocarcinoma: cytokeratin and integrin expression. Ann Diagn Pathol 5:330–334. https://doi.org/10.1053/adpa.2001.29339
88. Rosa ACG, Soares AB, Santos FP et al (2016) Immunoexpression of growth factors and receptors in polymorphous low-grade adenocarcinoma. J Oral Pathol Med 45:494–499. https://doi.org/10.1111/jop.12402
89. Soares AB, Martinez EF, Ribeiro PFA et al (2017) Factors that may influence polymorphous low-grade adenocarcinoma growth. Virchows Arch. https://doi.org/10.1007/s00428-017-2085-3
90. Skálová A, Simpson RHW, Lehtonen H, Leivo I (1997) Assessment of proliferative activity using the MIB1 antibody helps to distinguish polymorphous low grade adenocarcinoma from adenoid cystic carcinoma of salivary glands. Pathol Res Pract 193:695–703. https://doi.org/10.1016/S0344-0338(97)80029-5
91. McHugh JB, Visscher DW, Barnes EL (2009) Update on selected salivary gland neoplasms. Arch Pathol Lab Med 133:1763–1774
92. Leader R, Deol-Poonia RK, Sheard J, Triantafyllou A (2014) Immunohistochemical localization of WT1 in epithelial salivary tumors. Pathol Res Pract 210:726–732. https://doi.org/10.1016/j.prp.2014.06.029
93. Beltran D, Faquin WC, Gallagher G, August M (2006) Selective immunohistochemical comparison of polymorphous low-grade adenocarcinoma and adenoid cystic carcinoma. J Oral Maxillofac Surg 64:415–423. https://doi.org/10.1016/j.joms.2005.11.027
94. Prasad ML, Barbacioru CC, Rawal YB et al (2008) Hierarchical cluster analysis of myoepithelial/basal cell markers in adenoid cystic carcinoma and polymorphous low-grade adenocarcinoma. Mod Pathol 21:105–114. https://doi.org/10.1038/modpathol.3800983
95. Rooper L, Sharma R, Bishop JA (2015) Polymorphous low grade adenocarcinoma has a consistent p63+/p40− immunophenotype that helps distinguish it from adenoid cystic carcinoma and cellular pleomorphic adenoma. Head Neck Pathol 9:79–84. https://doi.org/10.1007/s12105-014-0554-4
96. Montalli VAM, Passador-Santos F, Martinez EF et al (2017) Mammaglobin and DOG-1 expression in polymorphous low-grade adenocarcinoma: an appraisal of its origin and morphology. J Oral Pathol Med 46:182–187. https://doi.org/10.1111/jop.12491
97. Owosho AA, Aguilar CE, Seethala RR (2016) Comparison of p63 and p40 (ΔNp63) as basal, squamoid, and myoepithelial markers in salivary gland tumors. Appl Immunohistochem Mol Morphol AIMM 24:501–508. https://doi.org/10.1097/PAI.0000000000000222
98. Skalova A, Michal M, Simpson RH (2017) Newly described salivary gland tumors. Mod Pathol 30:S27–S43. https://doi.org/10.1038/modpathol.2016.167
99. Mantripragada K, Caley M, Stephens P et al (2008) Telomerase activity is a biomarker for high grade malignant peripheral nerve sheath tumors in neurofibromatosis type 1 individuals. Genes Chromosomes Cancer 47:238–246. https://doi.org/10.1002/gcc
100. Seethala RR (2017) Salivary gland tumors. Surg Pathol Clin 10:155–176. https://doi.org/10.1016/j.path.2016.11.004
101. Skálová A, Stenman G, Simpson RHW et al (2017) The role of molecular testing in the differential diagnosis of salivary gland carcinomas. Am J Surg Pathol 0:1. https://doi.org/10.1097/PAS.0000000000000980
102. Persson M, Andren Y, Mark J et al (2009) Recurrent fusion of MYB and NFIB transcription factor genes in carcinomas of the breast and head and neck. Proc Natl Acad Sci USA 106:18740–18744. https://doi.org/10.1073/pnas.0909114106
103. Andersson MK, Afshari MK, Andrén Y et al (2017) Targeting the oncogenic transcriptional regulator MYB in adenoid cystic carcinoma by inhibition of IGF1R/AKT signaling. J Natl Cancer Inst https://doi.org/10.1093/jnci/djx017
104. Persson F, Fehr A, Sundelin K et al (2012) Studies of genomic imbalances and the MYB-NFIB gene fusion in polymorphous low-grade adenocarcinoma of the head and neck. Int J Oncol 40:80–84. https://doi.org/10.3892/ijo.2011.1190
105. Brill LB, Kanner WA, Fehr A et al (2011) Analysis of MYB expression and MYB-NFIB gene fusions in adenoid cystic carcinoma and other salivary neoplasms. Mod Pathol 24:1169–1176. https://doi.org/10.1038/modpathol.2011.86
106. Seethala RR (2017) Basaloid/blue salivary gland tumors. Nat Publ Gr 30:S84–S95. https://doi.org/10.1038/modpathol.2016.190
107. Hellquist H, Skalova A (2014) Polymorphous low-grade adenocarcinoma. In: Hellquist H, Skalova A (eds) Histopathology of the salivary glands. Springer, Berlin, pp 319–345
108. Nagao T (2013) "Dedifferentiation" and high-grade transformation in salivary gland carcinomas. Head Neck Pathol 7:37–47. https://doi.org/10.1007/s12105-013-0458-8
109. Pelkey TJ, Mills SE (1999) Histologic transformation of polymorphous low-grade adenocarcinoma of salivary gland. Am J Clin Pathol 111:785–791
110. Singh M, Bhushan A, Kumar N, Chand S (2013) Obturator prosthesis for hemimaxillectomy patients. Natl J Maxillofac Surg 4:117–120. https://doi.org/10.4103/0975-5950.117814
111. Fife TA, Smith B, Sullivan CA et al (2013) ScienceDirect polymorphous low-grade adenocarcinoma: a 17 patient case series. Am J Otolaryngol Neck Med Surg 34:445–448. https://doi.org/10.1016/j.amjoto.2013.03.012
112. Browne JD, Butler S, Rees C (2011) Functional outcomes and suitability of the temporalis myofascial flap for palatal and maxillary reconstruction after oncologic resection. Laryngoscope 121:1149–1159. https://doi.org/10.1002/lary.21747
113. Chang EI, Hanasono MM (2016) State-of-the-art reconstruction of midface and facial deformities. J Surg Oncol 113:962–970. https://doi.org/10.1002/jso.24150
114. Kim JH, Hyun CL, Lim GC (2015) Polymorphous low-grade adenocarcinoma of the tongue base treated by transoral robotic surgery. Case Rep Otolaryngol 2015:981436. https://doi.org/10.1155/2015/981436
115. Meulemans J, Vanclooster C, Vauterin T et al (2017) Up-front and salvage transoral robotic surgery for head and neck cancer: a belgian multicenter retrospective case series. Front Oncol 7:15. https://doi.org/10.3389/fonc.2017.00015
116. Appukutty SJ, Di Palma S, Daborn L et al (2015) Cribriform adenocarcinoma of minor salivary glands. Diagn Histopathol 21:380–382
117. Robbins K, Clayman G, Levine P et al (2002) Neck dissection classification update. Revisions proposed by the American Head and Neck Society and the American Academy of Otolaryngology-Head and Neck Surgery. Arch Otolaryngol Head Neck Surg 128:751–758
118. Crean SJ, Bryant C, Bennett J, Harris M (1996) Four cases of polymorphous low-grade adenocarcinoma. Int J Oral Maxillofac Surg 25:40–44

119. Sathyanarayanan R, Suresh V, Therese Thomas BA (2015) Polymorphous low-grade adenocarcinoma of the palate: a rare case report. Iran J Cancer Prev. https://doi.org/10.17795/ijcp-3447
120. Terhaard CHJ (2007) Postoperative and primary radiotherapy for salivary gland carcinomas: indications, techniques, and results. Int J Radiat Oncol Biol Phys 69:52–55. https://doi.org/10.1016/j.ijrobp.2007.04.079
121. Chen AM, Bucci MK, Quivey JM et al (2006) Long-term outcome of patients treated by radiation therapy alone for salivary gland carcinomas. Int J Radiat Oncol Biol Phys 66:1044–1050. https://doi.org/10.1016/j.ijrobp.2006.06.050
122. Uemaetomari I, Tabuchi K, Tobita T et al (2007) The importance of postoperative radiotherapy against polymorphous low-grade adenocarcinoma of the parotid gland: case report and review of the literature. Tohoku J Exp Med 211:297–302. https://doi.org/10.1620/tjem.211.297
123. Lombardi D, McGurk M, Vander Poorten V et al (2017) Surgical treatment of salivary malignant tumors. Oral Oncol 65:102–113. https://doi.org/10.1016/j.oraloncology.2016.12.007
124. Garden AS, Weber RS, Ang KK, et al (1994) Postoperative radiation therapy for malignant tumors of minor salivary glands. Outcome and patterns of failure. Cancer 73:2563–2569. https://doi.org/10.1002/1097-0142(19940515)73:10<2563::AID-CNCR2820731018>3.0.CO;2-X
125. Vander Poorten VLM, Balm AJM, Hilgers FJM, et al (2000) Stage as major long term outcome predictor in minor salivary gland carcinoma. Cancer 89:1195–1204. https://doi.org/10.1002/1097-0142(20000915)89:6<1195::AID-CNCR2>3.0.CO;2-J
126. Rosenberg L, Weissler M, Hayes DN et al (2012) Concurrent chemoradiotherapy for locoregionally advanced salivary gland malignancies. Head Neck 34:872–876. https://doi.org/10.1002/hed.21831
127. Mifsud MJ, Tanvetyanon T, Mccaffrey JC et al (2016) Adjuvant radiotherapy versus concurrent chemoradiotherapy for the management of high-risk salivary gland carcinomas. Head Neck 38:1628–1633. https://doi.org/10.1002/hed.24484
128. Paleri V, Robinson M, Bradley P (2008) Polymorphous low-grade adenocarcinoma of the head and neck. Curr Opin Otolaryngol Head Neck Surg 16:163–169. https://doi.org/10.1097/MOO.0b013e3282f70441
129. Papadogeorgakis N, Parara E, Petsinis V et al (2011) A retrospective review of malignant minor salivary gland tumors and a proposed protocol for future care. Craniomaxillofac Trauma Reconstr 4:1–10. https://doi.org/10.1055/s-0030-1268515
130. Borowski-Borowy P, Dyduch G, Papla B et al (2011) Cribriform adenocarcinoma of the tongue. Pol J Pathol 62:168–171

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