Head and Neck Pathology (2019) 13:415–422
https://doi.org/10.1007/s12105-018-0964-9

HISTORICAL PERSPECTIVES IN PATHOLOGY

Historical Evolution of the Polymorphous Adenocarcinoma

Juan C. Hernandez-Prera[1]

Received: 29 July 2018 / Accepted: 3 September 2018 / Published online: 5 September 2018

Abstract
The 2017 World Health Organization Classification of Head and Neck Tumors introduced for the first time the diagnostic terminology "cribriform variant of polymorphous adenocarcinoma". This nomenclature attempts to reconciliate the ongoing taxonomical controversy related to cribriform adenocarcinoma of tongue. In order to better understand this classification conundrum, it is imperative for pathologist to comprehend the historical evolution of polymorphous adenocarcinoma formerly known as polymorphous "low grade" adenocarcinoma. This review highlights our understanding of these tumors since their origins.

Keywords Polymorphous low grade adenocarcinoma · Cribriform adenocarcinoma of tongue · Polymorphous adenocarcinoma · Cribriform variant of polymorphous adenocarcinoma · Minor salivary gland · PRDK1 · PRDK2 · PRKD3

The Origin of Polymorphous "*Low Grade*" Adenocarcinoma (PLGA)

PLGA was first characterized as a distinctive entity by two independent groups in 1983 (Fig. 1). In their manuscript, Freedman and Lumerman designated their tumors as lobular carcinoma of minor salivary glands primarily based on the single cell pattern of growth akin to that seen in lobular carcinoma of the breast [1]. Batsakis et al. coined the name terminal duct carcinoma to refer to same tumor apparently reflecting a presumptive origin from intercalated ducts [2]. Regardless, of the nomenclature both publications depicted an oral cavity minor salivary gland neoplasm composed of uniform cells with low-grade cytomorphology arranged in multiple architectural patterns that despite of infiltrative growth was associated with an indolent behavior with no reported recurrences or metastasis [1, 2]. Both groups stressed that this tumor represented a hitherto unrecognized type of intraoral salivary gland adenocarcinoma; however it should be noted that descriptions of carcinomas with similar morphology were reported in the literature as far back as 1961 [3].

Following its initial description, in 1984 Evans and Batsakis coined the term and created the unifying concept of PLGA [4]. Subsequent independent publications confirmed and further delineated the clinico-pathologic characteristics of PLGA [5–15]. Consequently, the WHO classification of salivary gland tumors from 1991 accepted PLGA as distinct tumor and adopted this terminology (Fig. 1) [16]. The description of PLGA was that of an invasive epithelial neoplasm with no evidence of encapsulation (Fig. 2a) composed of small to medium sized cells with oval nuclei with pale vesicular chromatin and inconspicuous to small nucleoli devoid of significant nuclear pleomorphism, increased mitotic activity and/or necrosis (Fig. 2e). A highlighted feature was the presence of diverse morphological patterns (polymorphous) seen between different tumors and within each individual case. The described growth patterns included single cell filing, lobular, papillary or papillary-cystic, cribriform, trabecular and duct-like. Neurotropism associated with concentric whorls or targetoid arrangements of tumor cells was listed as a striking histological finding (Fig. 2c). Importantly, despite the microscopic evidence of invasion including extensive perineural invasion, PLGA was regarded as an adenocarcinoma with low metastatic potential [17]. Since 1991, the term PLGA has been ingrained in our diagnostic lexicon and its very good clinical outcomes perpetuated among clinicians.

✉ Juan C. Hernandez-Prera
juan.hernandez-prera@moffitt.org

[1] Department of Anatomic Pathology, Moffitt Cancer Center, Tampa, FL, USA

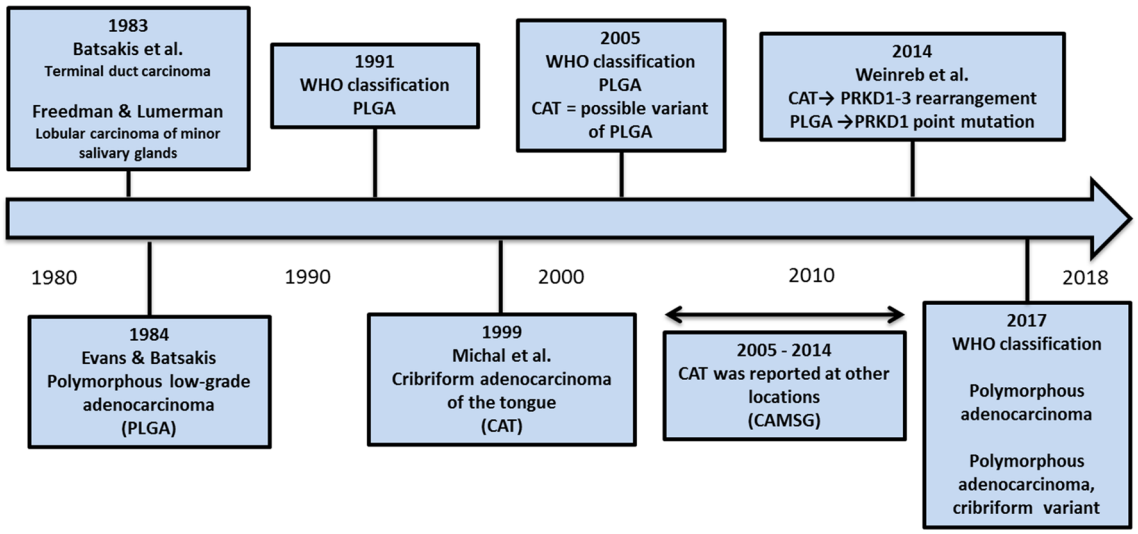

Fig. 1 In summary, polymorphous adenocarcinoma (PA) was first described by two different groups in 1983 as terminal duct carcinoma and lobular carcinoma of minor salivary glands. Subsequently, it was renamed as polymorphous low-grade adenocarcinoma (PLGA) in 1984 and included as such in the 1991 WHO classification of salivary gland tumors as a distinct entity. In 1999, cribriform adenocarcinoma of the tongue (CAT) was proposed as different and distinct entity, based on its localization to the base of the tongue, morphologic features including glomeruloid/cribiform structures and nuclear features reminiscent of papillary thyroid carcinoma, and clinical behavior including the presence of synchronous lymph node metastasis. The 2005 WHO classification did not recognize CAT as a distinct tumor but as a possible variant of PLGA. Since them CAT has been reported at other anatomic sites. In 2014 rearrangements in *PRKD 1–3* were reported in CAT and *PRDK1* point mutations in PLGA. In the 2017 WHO classification, a terminology change was presented to include renaming PLGA as PA and owing to overlapping morphological and molecular features to subsume CAT within the classification of PA and referring to it as the cribriform variant of PA

Parallel to the evolution of PLGA, different authors contributed to the concept of low-grade papillary adenocarcinoma (LGPA) of the oral cavity [18]. LGPA was described as an intraoral salivary gland carcinoma with marked predilection to the palate and predominately characterized by simple to complex papillary proliferations with solid, microcystic and cribriform foci. The papillae were typical lined by bland uniform low cuboidal cells. It was described that in areas the papillary structures had a more compacted arrangement and protruded into cystic spaces giving the impression of renal glomeruli [18–20]. The aforementioned histological features and the absence of whorling fascicles was the argument proposed by some authorities to conclude that there were sufficient morphological differences between LGPA and PLGA to classify them as independent tumor types [18–20]. Moreover, the reported cases of LGPA appeared to follow a more aggressive clinical course including local and distant metastasis, as well as reported tumor related deaths [18–20].

Whether the LGPA represented a distinct entity or a "predominantly papillary" subtype of PLGA was extensively discussed [4, 13, 20, 21]. Evans and Batsakis strongly argued that this neoplasm fell within the histologic spectrum of PLGA and this view was also adopted by the WHO in 1991 [4, 17]. Nevertheless, some authorities disagreed with this concept and stated that LGPA harbored morphological (predominant/exclusive papillary growth) and clinical (distant metastasis and tumor related deaths) differences that warranted distinction form PLGA and proposed classifying this tumor as papillary cystadenocarcinoma [22]. Since then the term LGPA lost popularity; however some authors still use it and the discussion of the clinical significance of papillary structures in PLGA continued with conflicting results [23–26].

The Origin of Cribriform Adenocarcinoma of the Tongue (CAT)

In 1999, a manuscript by Michal et al. from the Czech Republic presented a series of adenocarcinomas initially diagnosed as PLGAs but exclusively arising in the tongue (Fig. 1) [27]. These tumors were predominately characterized by a cellular proliferation divided by fibrous septa into irregularly shaped and sized nodules (Fig. 2b). The tumor nodules showed variable proportions of cribriform, tubular and solid architecture. Some tumor nodules exhibited hyperchromatic peripheral palisading and some were detached from the surrounding fibrous stroma and peripheral cell layer creating a glomeruloid appearance (Fig. 2d). The tumors were composed of one cell type showing clear to light eosinophilic cytoplasm and overlapping nuclei with pale

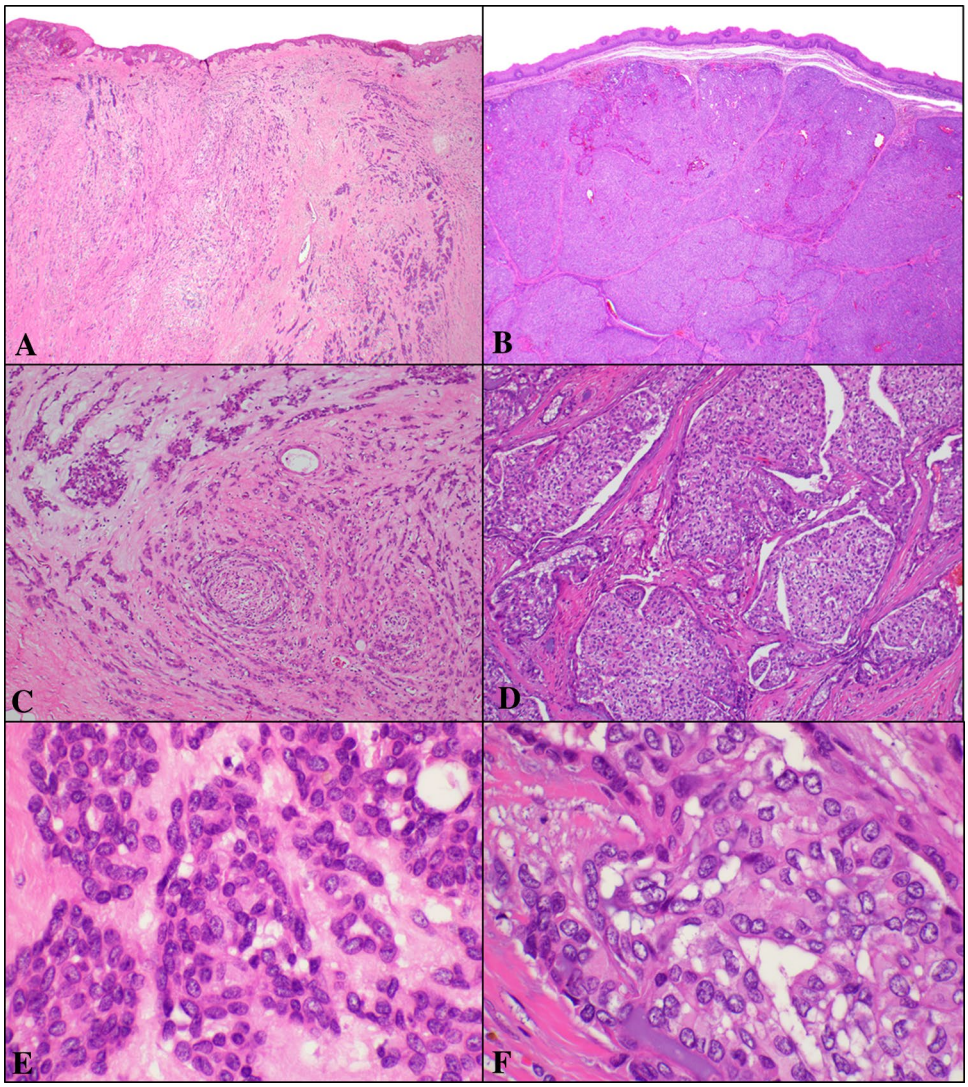

Fig. 2 Polymorphous adenocarcinoma (PA) is classically characterized by an invasive unencapsulated neoplastic proliferation showing diverse morphological patterns (**a**, Hematoxylin & Eosin [H&E] stained slide at 2×10 magnification); single cell filing and perineural invasion with concentric whorling are commonly identified (**c**, H&E stained slide at 10×10 magnification); tumor cells are bland, small to medium in size and have oval nuclei with open chromatin and inconspicuous to small nucleoli (**e**, H&E stained slide at 60×10 magnification). Cribriform variant of PA is predominately characterized by a cellular proliferation divided by fibrous septa into tumor nodules (**b**, H&E stained slide at 2×10 magnification); some nodules are detached from the surrounding fibrous stroma imprinting a glomeruloid appearance (**d**, H&E stained slide at 10×10 magnification); tumor cells are bland with clear to light eosinophilic cytoplasm and overlapping nuclei showing optical clearing reminiscent nuclei features of papillary thyroid carcinoma (**f**, H&E stained slide at 60×10 magnification)

vesicular chromatin resulting in a ground glass appearance (Fig. 2f). Due to the growth pattern, the nuclear features and the presence of occasional psammomatoid calcifications, the authors mentioned that tumors were reminiscent variants of the papillary thyroid carcinoma and alluded to a possible thyroglossal duct anlage origin. However, these tumors were negative for thyroglobulin. The authors proposed the catchy terminology of "CAT" for these tumors [27].

In addition to its anatomic distribution and morphological features, the main argument that Michal et al. presented to assert that CAT represented a distinctive type of adenocarcinoma was its clinical behavior [27]. All cases included in their series presented regional lymph node metastasis at the time of diagnosis. This high rate of synchronous lymphatic spread to cervical nodes was in contradistinction to the clinical findings association with PLGA [17]. However, despite advanced stage at presentation, all patients were alive with no evidence of locoregional recurrence after resection and radiation therapy [27].

In their discussion Michal et al. made references to reported cases of PLGAs associated with positive lymph nodes that, in their view, could have represented potential cases of CATs [24, 28–30]. Interestingly, the glomeruloid structures described in CAT were previously reported in LGPA [19–21]. Published illustrations depicted in early reports of PLGA without lymph node metastasis showed histologic features reminiscent of CAT as well as showing tumors with mixed morphological features between CAT and PLGA [2, 4, 6, 13]. These overlapping morphological characteristics raised the question whether CAT truly was a distinct entity from PLGA or simply a more aggressive variant of PLGA with greater capability for metastatic spread. It should be noted that most of published case series of PLGA before 1999 lacked extended follow to fully understand its clinical behavior, in particular its metastatic potential.

The Origin of the Controversy

By the time 2005 WHO Classification of Head and Neck Tumors was published two major studies with larger numbers of cases (n = 204) and long-term follow-up were available for review [25, 30]. Those studies provided a more detailed delineation of the clinical behavior of PLGA highlighting its excellent overall survival. Local recurrence was reported between 9% and 32%, regional lymph node metastases ranged from 0 to 15% and collectively seven patients died from disease [25, 31]. In addition, it was also evident that high grade transformation was a rare event in PLGA that conveyed a less favorable outcome [32]. By 2005, the study by Michal et al. was the only one addressing the potential existence of CAT and therefore this tumor was mentioned in the WHO Blue Book as possible variant of PLGA (Fig. 1) [33].

Since then other cases of CATs with clinical follow-up have been reported in the literature and it has been recognized at other intraoral locations besides the tongue (Table 1) [34–47]. The latter has led to the proposed name cribriform adenocarcinoma of minor salivary gland origin (CAMSG) [36]. Alternative names used in the literature include cribriform adenocarcinoma of the tongue and minor salivary glands (CATMSG) and cribriform adenocarcinoma of salivary glands (CASG) [45, 48]. Regardless of the location the reported cases have aimed to highlight the importance of separating cribriform adenocarcinoma from PLGA due to its increased rate of lymph node metastasis. In summary, the published cases as CASG show a predilection to occur in the tongue; however tumors arising in the parotid and sinonasal tract have been described [27, 34–47]. A key clinical feature that have been recurrently reported is that more than half of the patients have lymph node metastasis at time of presentation and in many instances a neck mass was the initial symptom of the patients [27, 34–47]. The local recurrence rate and distant metastatic potential is rare and only two reported patients have died from disease [27, 34–47].

Despite the distinct regional metastatic capacity of CASG, it was been argued that the numbers are statistically insufficient and the overall survival is not different from PLGA [49]. A fact attributed to the limited extended follow-up of most published cases of CASG. In addition, recent studies have reported tumors with overlapping histology where the distinction between PLGA and CASG is not feasible [45, 50, 51]. Moreover, other authors have proposed that the early metastatic potential of CASG may be attributed to its predilection to affect the base of the tongue which is rich in lymphatic spaces [50].

With the advent of molecular pathology, it was expected that the debate relative to whether CASG is a variant of PLGA or an independent tumor type could be resolved (Fig. 1). In 2014, Weinreb et al. reported for the first time that 80% of tumors classified as CASG harbor rearrangements in the *PRKD* genes (*PRKD1, PRKD2* and *PRKD3*), including *ARID1A-PRKD1* and *DDX3X-PRKD1* gene fusions [51]. However, in their cohort 45% of cases with overlapping histology including admixed foci of CASG and PLGA, as well as a single case of a pure PLGA also showed similar rearrangements [51]. Subsequently, Weinreb et al. reported that 72.9% of PLGA harbor *PRKD1* activating mutations resulting from an amino acid substitution, p.Glu710Asp [52]. Far from resolving the aforementioned controversy, these studies further muddied the proverbial waters. Currently, there is evidence to argue that PLGA and CASG are related at the molecular level through different mechanisms. *PRKD1* mutations appear to define PLGA, while rearrangements in the same family of genes primarily cluster in CASG as well as cases with indeterminate histologic features. Unfortunately, it was out of the scope of these studies to address the relationship of the molecular alterations with the clinical behavior.

The Current Classification Approach

In 2017, the 4th edition of the WHO Classification of Head and Neck Tumors was released. As expected, one of the sources for contention was whether to recognize CASG as a distinct entity or not. The determination in the 2017 WHO classification was to continue classify CASG within the histological spectrum of PLGA (Fig. 1) [53]. This decision was made on the basis of the morphological and molecular overlap between both tumors and their shared excellent overall survival despite the increased rate of lymph node metastasis in CASG. Concurrent with the decision to classify CASG as a variant of PLGA, there was a terminology change that included omitting the adjective "*low-grade*" from PLGA and using the designation polymorphous adenocarcinoma (PA). By so doing, there was an acknowledgement of a spectrum of tumors within the PLGA classification with varying aggressiveness including those with indolent behavior (classical PA) and those tumors with more aggressive behavior (cribriform variant of PA and tumors with high grade transformation).

At present, the 2017 WHO Blue Book approach appears to solve the taxonomic issues revolving around PLGA, however it is important to appraise the clinical consequences of these changes in nomenclature. Histological grading continues to be an important predictor of outcome in salivary gland adenocarcinomas and a required reporting element per the College of American Pathologists [54–57]. PLGA has been inherently conceived as a "low grade" adenocarcinoma and therefore the mainstay of treatment has been wide surgical

Table 1 Reported cases of CASG with clinical follow-up

Authors	Year	Terminology	Number of cases	Location	Number of cases with positive LN at presentation	Number of cases with regional LN recurrence	Number of cases with local recurrence	Number of cases with distant metastasis	Reported deaths attributable to disease	Follow-up
Michal et al. [26]	1999	CAT	8	Tongue (8/8)	8	0	0	0	0	2–6 years
Prasad et al. [33]	2004	CAT	1	Tongue	0	0	0	0	0	18 months
Čoček et al. [34]	2010	CAT	1	Tongue	1	0	0	0	0	3 years
Skalova et al. [35]	2011	CAMSG	23	Tongue (17/23) Soft palate (3/23) Buccal mucosa (2/23) Upper lip (1/23)	15	1	1	0	0	2 months–13 years
Borowsky-Borowy et al. [36]	2011	CAT	1	Tongue	0	1	1	0	0	2 years
Laco et al. [37]	2012	CAMSG	5	Tongue (4/5) Floor of mouth (1/4)	4	2	0	0	0	8–45 months
Gailey et al. [38]	2014	CAMSG	2	Tongue (2/2)	1	0	0	0	0	6–8 months
Worral et al. [39]	2014	CATMSG	1	Palatine tonsil	1	0	0	0	0	2 months
Appukutty et al. [40]	2015	CAMSG	1	Palate	1	0	0	0	0	18 months
Brierley et al. [41]	2015	CAMSG	1	Laryngeal surface epiglottis	0	0	0	0	0	26 months
Madhura et al. [42]	2016	CAMSG	1	Tongue	0	0	0	0	0	10 months
Majewska et al. [43]	2016	CAMSG	1	Tongue	1	0	0	0	0	10 moths
Xu et al. [44]	2016	CASG	21	Tongue (5/21) Buccal mucosa (1/21) Oral cavity, NOS (1/21) Palate (8/21) Parotid (1/21) Sinonasal (2/21)	2	1	2	2	1	10–217 months
Mariano et al. [45]	2017	CATMSG	1	Palate	0	1	1	1	1	11 years
Pagano et al. [46]	2017	CAMSG	1	Tonsil	1	0	0	0	0	6 months

CAT cribriform adenocarcinoma of the tongue, *CAMSG* + cribriform adenocarcinoma of minor salivary gland origin, *CATMSG* cribriform adenocarcinoma of the tongue and minor salivary glands, *CASG* cribriform adenocarcinoma of salivary glands, *LN* lymph node

excision without neck dissection, except for the cases with clinically positive lymph nodes [58, 59]. Nevertheless, due to the high rate of synchronous nodal metastasis in the cribriform variant of PA, it is reasonable that an elective neck dissection should be considered even in patients with clinically negative lymph nodes. Further, the WHO recommendation relative to histologic grading of PA is to do so on a case-by-case basis; however no specific grading system was proposed [53]. Therefore, albeit imperfect, a grading approach based on traditional cytomorphological features could be a practical solution. Tumors with minimal cytologic atypia, low mitotic rate and no tumor necrosis could be regarded as low grade; tumors with moderate cytologic atypia, increased mitotic rate and/or tumor necrosis as intermediate grade; while high grade tumors would be lesions showing any evidence of high transformation as described by Simpson et al. [32].

Conclusion and the Future

Understanding the historical evolution of PA and its cribriform variant allows pathologists to comprehend the current changes adopted by the 2017 WHO Classification of Head and Neck Tumors and provides them with the knowledge necessary to engage in multidisciplinary discussion of patients with these tumors. Further studies are required to address emerging gaps such as the development of a specific grading system, the correlation of molecular findings and clinical behavior, and the management of cases with intermediate morphology. Moreover, it is imperative to establish strict and reproducible diagnostic criteria for classical PA and its cribriform variant so that their biology (similarities and/or differences) can be better documented over the next several years. The on-going evolution of our understanding of these tumors continues with the hope that in the future new information will be unearthed allowing for the determination whether CASG does or does not fall within the spectrum of PLGA as this controversy has not at present been definitively resolved. To be continued…

References

1. Freedman PD, Lumerman H. Lobular carcinoma of intraoral minor salivary gland origin. Report of twelve cases. Oral Surg Oral Med Oral Pathol. 1983;56(2):157–66.
2. Batsakis JG, Pinkston GR, Luna MA, Byers RM, Sciubba JJ, Tillery GW. Adenocarcinomas of the oral cavity: a clinicopathologic study of terminal duct carcinomas. J Laryngol Otol. 1983;97(9):825–35.
3. Chaudhry AP, Vickers RA, Gorlin RJ. Intraoral minor salivary gland tumors. An analysis of 1414 cases. Oral Surg Oral Med Oral Pathol. 1961;14:1194–226.
4. Evans HL, Batsakis JG. Polymorphous low-grade adenocarcinoma of minor salivary glands. A study of 14 cases of a distinctive neoplasm. Cancer 1984;53(4):935–42.
5. Mitchell DA, Eveson JW, Ord RA. Polymorphous low-grade adenocarcinoma of minor salivary glands—a report of three cases. Br J Oral Maxillofac Surg. 1989;27(6):494–500.
6. Wenig BM, Harpaz N, DelBridge C. Polymorphous low-grade adenocarcinoma of seromucous glands of the nasopharynx. A report of a case and a discussion of the morphologic and immunohistochemical features. Am J Clin Pathol. 1989;92(1):104–9.
7. Regezi JA, Zarbo RJ, Stewart JC, Courtney RM. Polymorphous low-grade adenocarcinoma of minor salivary gland. A comparative histologic and immunohistochemical study. Oral Surg Oral Med Oral Pathol. 1991;71(4):469–75.
8. Nicolatou O, Kakarantza-Angelopoulou E, Angelopoulos AP, Anagnostopoulou S. Polymorphous low-grade adenocarcinoma of the palate: report of a case with electron microscopy. J Maxillofac Surg. 1988;46(11):1008–13.
9. Gnepp DR, Chen JC, Warren C. Polymorphous low-grade adenocarcinoma of minor salivary gland. An immunohistochemical and clinicopathologic study. Am J Pathol. 1988;12(6):461–8.
10. Anderson C, Krutchkoff D, Pedersen C, Cartun R, Berman M. Polymorphous low grade adenocarcinoma of minor salivary gland: a clinicopathologic and comparative immunohistochemical study. Mod Pathol. 1990;3(1):76–82.
11. Dardick I, van Nostrand AW. Polymorphous low-grade adenocarcinoma: a case report with ultrastructural findings. Oral Surg Oral Med Oral Pathol. 1988;66(4):459–65.
12. Simpson RH, Clarke TJ, Sarsfield PT, Gluckman PG, Babajews AV. Polymorphous low-grade adenocarcinoma of the salivary glands: a clinicopathological comparison with adenoid cystic carcinoma. Histopathology 1991;19(2):121–9.
13. Frierson HF Jr, Mills SE, Garland TA. Terminal duct carcinoma of minor salivary glands. A nonpapillary subtype of polymorphous low-grade adenocarcinoma. Am J Clin Pathol. 1985;84(1):8–14.
14. Aberle AM, Abrams AM, Bowe R, Melrose RJ, Handlers JP. Lobular (polymorphous low-grade) carcinoma of minor salivary glands. A clinicopathologic study of twenty cases. Oral Surg Oral Med Oral Pathol. 1985;60(4):387–95.
15. Waldron CA, el-Mofty SK, Gnepp DR. Tumors of the intraoral minor salivary glands: a demographic and histologic study of 426 cases. Oral Surg Oral Med Oral Pathol. 1988;66(3):323–33.
16. Seifert G, Brocheriou C, Cardesa A, Eveson JW. WHO international histological classification of tumours. Tentative histological classification of salivary gland tumours. Pathol Res Pract. 1990;186(5):555–81.
17. Seifert G. Histological classification of salivary gland tumours. Histological typing of salivary gland tumours. Berlin: Springer; 1991. pp. 9–10.
18. Allen MS Jr, Fitz-Hugh GS, Marsh WL Jr. Low-grade papillary adenocarcinoma of the palate. Cancer 1974;33(1):153–8.
19. Mills SE, Garland TA, Allen MS Jr. Low-grade papillary adenocarcinoma of palatal salivary gland origin. Am J Surg Pathol. 1984;8(5):367–74.
20. Slootweg PJ, Muller H. Low-grade adenocarcinoma of the oral cavity. A comparison between the terminal duct and the papillary type. J Cranio-Maxillofac Surg. 1987;15(6):359–64.
21. Batsakis JG, El-Naggar AK. Terminal duct adenocarcinomas of salivary tissues. Ann Otol Rhinol Laryngol. 1991;100(3):251–3.
22. Wenig BM, Gnepp DR. Polymorphous low-grade adenocarcinoma of minor salivary glands. In: Ellis GL, Auclair PL, Gnepp DR, editors. Surgical pathology of the salivary glands major problems in pathology. vol 25. Philadelphia: W. B. Saunders Company; 1991. pp. 409–10.
23. Slootweg PJ. Low-grade adenocarcinoma of the oral cavity: polymorphous or papillary? J Oral Pathol Med. 1993;22(7):327–30.

24. Colmenero CM, Patron M, Burgueno M, Sierra I. Polymorphous low-grade adenocarcinoma of the oral cavity: a report of 14 cases. J Oral Maxillofac Surg. 1992;50(6):595–600.
25. Evans HL, Luna MA. 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. 2000;24(10):1319–28.
26. Hunter JB, Smith RV, Brandwein-Gensler M. Low-grade papillary adenocarcinoma of the palate: the significance of distinguishing it from polymorphous low-grade adenocarcinoma. Head Neck Pathol. 2008;2(4):316–23.
27. Michal M, Skalova A, Simpson RH, Raslan WF, Curik R, Leivo I, et al. Cribriform adenocarcinoma of the tongue: a hitherto unrecognized type of adenocarcinoma characteristically occurring in the tongue. Histopathology 1999;35(6):495–501.
28. Perez-Ordonez B, Linkov I, Huvos AG. Polymorphous low-grade adenocarcinoma of minor salivary glands: a study of 17 cases with emphasis on cell differentiation. Histopathology 1998;32(6):521–9.
29. Yajima M, Yamazaki T, Minemura T, Kotani A. Tubular adenocarcinoma of the apex of the tongue. J Oral Maxillofac Surg. 1989;47(1):86–8.
30. Crocker TP, Kreutner A Jr, Othersen HB Jr, Garvin AJ. Papillary adenocarcinoma of minor salivary gland origin in a child. Arch Otolaryngol. 1983;109(12):827–31.
31. Castle JT, Thompson LD, Frommelt RA, Wenig BM, Kessler HP. Polymorphous low grade adenocarcinoma: a clinicopathologic study of 164 cases. Cancer 1999;86(2):207–19.
32. Simpson RH, Pereira EM, Ribeiro AC, Abdulkadir A, Reis-Filho JS. Polymorphous low-grade adenocarcinoma of the salivary glands with transformation to high-grade carcinoma. Histopathology 2002;41(3):250–9.
33. Luna MA, Wenig BM. Polymorphous low-grade adenocarcinoma. In: Barnes EL, Eveson JW, Reichart P, Sidransky D, editors. World health organization classification of tumours pathology and genetics of head and neck tumours. Lyon: IARC Press; 2005. pp. 223–4.
34. Prasad KC, Kaniyur V, Pai RR, Nesari SS. Pedunculated cribriform adenocarcinoma of the base of the tongue. ENT J 2004;83(1):62–64.
35. Čoček A, Hronková K, Voldánová J, Šach J, Skálová A, Ambruš M, et al. Cribriform adenocarcinoma of the base of the tongue and low-grade, polymorphic adenocarcinomas of the salivary glands. Oncol Lett. 2011;2(1):135–8.
36. Skalova A, Sima R, Kaspirkova-Nemcova J, Simpson RH, Elmberger G, Leivo I, et al. Cribriform adenocarcinoma of minor salivary gland origin principally affecting the tongue: characterization of new entity. Am J Surg Pathol. 2011;35(8):1168–76.
37. Borowski-Borowy P, Dyduch G, Papla B, Gabryś I, Składzień J, Okoń K. Cribriform adenocarcinoma of the tongue. Pol J Pathol. 2011;62(3):198–71.
38. Laco J, Kamarádová K, Vítková P, Sehnálková E, Dvořáková Š, Václavíková E, et al. 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. 2012;461(5):531–40.
39. Gailey MP, Bayon R, Robinson RA. Cribriform adenocarcinoma of minor salivary gland: a report of two cases with an emphasis on cytology. Diagn Cytopathol. 2014;42(12):1085–90.
40. Worrall DM, Brant JA, Chai RL, Weinstein GS. Cribriform adenocarcinoma of the tongue and minor salivary gland: transoral robotic surgical resection. ORL. 2015;77(2):87–92.
41. Appukutty SJ, Di Palma S, Daborn L, Bagwan I, Beeslaar S. Cribriform adenocarcinoma of minor salivary glands. Diagn Histopathol. 2015;21(9):380–2.
42. Brierley D, Green D, Speight P. Cribriform adenocarcinoma of the minor salivary glands arising in the epiglottis—a previously undocumented occurrence. Oral Surg Oral Med Oral Pathol Oral Radiol. 2015;120(3):e174–6.
43. Madhura MG, Kumar BV, Suma S, Sarita Y. Cribriform adenocarcinoma of minor salivary gland: a mimic of polymorphous low-grade adenocarcinoma. J Oral Maxillofac Pathol. 2016;20(3):536–9.
44. Majewska H, Skalova A, Weinreb I, Stodulski D, Hyrcza M, Stankiewicz C, et al. Giant cribriform adenocarcinoma of the tongue showing PRKD3 rearrangement. Pol J Pathol. 2016;67(1):84–90.
45. Xu B, Aneja A, Ghossein R, Katabi N. Predictors of outcome in the phenotypic spectrum of polymorphous low-grade adenocarcinoma (PLGA) and cribriform adenocarcinoma of salivary gland (CASG): a retrospective study of 69 patients. Am J Surg Pathol. 2016;40(11):1526–37.
46. Mariano FV, Varanda RF, Schultz L, Correa MB, de Almeida OP, Altemani A, et al. Cribriform adenocarcinoma of the soft palate with multiple lymph node metastasis and long-term follow-up. Oral Surg Oral Med Oral Pathol Oral Radiol. 2017;123(4):e117–22.
47. Pagano A, Dennis K. Cribriform adenocarcinoma of the minor salivary gland arising in the tonsil with metastasis to a cervical lymph node: a case report with description of fine needle aspiration cytology. Diagn Cytopathol. 2017;45(5):468–71.
48. Michal M, Kacerovska D, Kazakov DV. Cribriform adenocarcinoma of the tongue and minor salivary glands: a review. Head Neck Pathol. 2013;7(Suppl 1):3–11.
49. Seethala RR, Stenman G. Update from the 4th edition of the world health organization classification of head and neck tumours: tumors of the salivary gland. Head Neck Pathol. 2017;11(1):55–67.
50. Seethala RR, Johnson JT, Barnes EL, Myers EN. Polymorphous low-grade adenocarcinoma: the University of Pittsburgh experience. Arch Otolaryngol Head Neck Surg. 2010;136(4):385–92.
51. Weinreb I, Zhang L, Tirunagari LM, Sung YS, Chen CL, Perez-Ordonez B, et al. Novel PRKD gene rearrangements and variant fusions in cribriform adenocarcinoma of salivary gland origin. Genes Chromosom Cancer 2014;53(10):845–56.
52. Weinreb I, Piscuoglio S, Martelotto LG, Waggott D, Ng CK, Perez-Ordonez B, et al. Hotspot activating PRKD1 somatic mutations in polymorphous low-grade adenocarcinomas of the salivary glands. Nat Genet. 2014;46(11):1166–9.
53. Fonseca I, Assaad A, Katabi N, Seethala RR, Weinreb I, Wenig BM. Polymorphous adenocarcinoma. In: El-Naggar A, Chan JKC, Grandis J, Takata T, Slootweg PJ, editors. World health organization classification of tumours: pathology and genetics of head and neck tumours. 4th ed. Lyon: IARC Press; 2017. pp. 167–8.
54. National Comprehensive Cancer Network. Head and neck cancers (Version 2.2018) 2018. https://www.nccn.org/professionals/physician_gls/pdf/head-and-neck.pdf.
55. Nam SJ, Roh J-L, Cho K-J, Choi S-H, Nam SY, Kim SY. Risk factors and survival associated with distant metastasis in patients with carcinoma of the salivary gland. Ann Surg Oncol. 2016;23(13):4376–83.
56. Huang AT, Tang C, Bell D, Yener M, Izquierdo L, Frank SJ, et al. Prognostic factors in adenocarcinoma of the salivary glands. Oral Oncol. 2015;51(6):610–5.
57. Seethala RR, Bullock MJ, Carlson DL, Ferris RL, Harrison LB, McHugh JB, et al. Protocol for the examination of specimens from patients with carcinomas of the major salivary glands. Northfield, IL: College of American Pathologists; 2017.

58. Patel TD, Vazquez A, Marchiano E, Park RC, Baredes S, Eloy JA. Polymorphous low-grade adenocarcinoma of the head and neck: a population-based study of 460 cases. Laryngoscope 2015;125(7):1644–9.

59. Kimple AJ, Austin GK, Shah RN, Welch CM, Funkhouser WK, Zanation AM, et al. Polymorphous low-grade adenocarcinoma: a case series and determination of recurrence. Laryngoscope 2014;124(12):2714–9.