Histologic Classification and Molecular Signature of Polymorphous Adenocarcinoma (PAC) and Cribriform Adenocarcinoma of Salivary Gland (CASG)

An International Interobserver Study

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Abstract: Polymorphous adenocarcinoma (PAC) shows histologic diversity with streaming and targetoid features whereas cribriform adenocarcinoma of salivary gland (CASG) demonstrates predominantly cribriform and solid patterns with glomeruloid structures and optically clear nuclei. Opinions diverge on whether CASG represents a separate entity or a variant of PAC. We aimed to assess the level of agreement among 25 expert Head and Neck pathologists in classifying these tumors. Digital slides of 48 cases were reviewed and classified as: PAC, CASG, tumors with ≥50% of papillary architecture (PAP), and tumors with indeterminate features (IND). The consensus diagnoses were correlated with a previously reported molecular alteration. The consensus diagnoses were PAC in 18/48, CASG in16/48, PAP in 3/48, and IND in 11/48. There was a fair interobserver agreement in classifying the tumors (κ = 0.370). The full consensus was achieved in 3 (6%) cases, all of which were classified as PAC. A moderate agreement was reached for PAC (κ = 0.504) and PAP (κ = 0.561), and a fair agreement was reached for CASG (κ = 0.390). IND had only slight diagnostic concordance (κ = 0.091). PAC predominantly harbored *PRKD1* hotspot mutation, whereas CASG was associated with fusion involving *PRKD1*, *PRKD2*, or *PRKD3*. However, such molecular events were not exclusive as 7% of PAC had fusion and 13% of CASG had mutation. In conclusion, a fair to moderate interobserver agreement can be achieved in classifying PAC and CASG. However, a subset (23%) showed indeterminate features and was difficult to place along the

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morphologic spectrum of PAC/CASG among expert pathologists. This may explain the controversy in classifying these tumors.

Key Words: polymorphous adenocarcinoma, cribriform adenocarcinoma of salivary gland, salivary gland neoplasm

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Polymorphous adenocarcinoma (PAC) is a salivary gland malignancy described by Batsakis et al in 1983[1] and Evans and Batsakis in 1984.[2] It is characterized histologically by cytologic uniformity and architectural diversity.[3] It commonly affects minor salivary glands of the upper aerodigestive tract and constitutes the second most common intraoral salivary gland carcinoma. Histologically, PAC typically contains a single tumor cell type arranged in cords, single file, trabeculae or tubules swirling or concentrically layered around nerves or vasculature. In general, PAC is considered as a low-grade carcinoma with an overall recurrence rate of 19%, a risk of regional lymph node metastasis of 13% to 17%, and low rate of distant metastasis.[4–8]

In 1999, Michal et al[9] described the cribriform adenocarcinoma of tongue. In their original series, cribriform adenocarcinoma of tongue occurred exclusively in the tongue, had an infiltrative lobular growth pattern and prominent cribriform, solid or glomeruloid architecture, and was associated with a high risk (over 60%) of lymph node metastases. Subsequently, the same authors reported cribriform adenocarcinoma in other minor salivary gland sites, modifying the diagnostic term to cribriform adenocarcinoma of minor salivary gland.[8,10–12] A couple of recent publications have reported 2 cases of cribriform adenocarcinoma in the major salivary gland.[8,13] Therefore, cribriform adenocarcinoma of salivary gland (CASG) has been suggested as a better term to describe this tumor. In the third and fourth editions of the World Health Organization (WHO) classification, CASG was considered a variant of PAC.[3,14] However, several groups have proposed classifying CASG as a distinct entity separate from PAC based on its unique histologic appearance and a much higher rate of nodal metastasis.[9–11,15]

Recently, the underlying molecular signatures of PAC and CASG has been discerned by Weinreb and colleagues.[13,16] A hotspot activating p.Glu710Asp mutation affecting *PRKD1* (protein kinase D1) has been detected in > 70% of PAC, whereas a translocation involving *PRKD1*, *PRKD2*, or *PRKD3* gene was found to be a frequent finding in CASG reportedly detected in 80% CASG, 6% PAC, and 45% of tumors with indeterminate features (IND). The facts that typical CASG and PAC are associated with activation of *PRKD1* but via different mechanisms adds fuel to the ongoing debates on whether PAC and CASG are 2 separate tumors or a single entity.[17]

The ability to precisely evaluating the clinical behaviors and molecular signature of CASG and PAC relies heavily on the pathologists' ability to accurately separate these tumors histologically. To date, there has been no study addressing the diagnostic concordance and reliability to distinguish PAC and CASG. Therefore, we conducted this large-scale international study to assess the interobserver agreement among expert head and neck (HN) pathologists using whole slide images (WSIs) from 48 cases in the spectrum of PAC and CASG.

MATERIALS AND METHODS

Case and Slide Selection

The study was approved by the Institutional Review Board of Memorial Sloan-Kettering Cancer Center (MSKCC, New York, NY). A total of 48 cases of PAC/CASG spectrum from 1993 to 2016 were retrieved from the MSKCC pathology archive, 45 of which were previously reported,[8] and reviewed by 2 HN pathologists (B.X. and N.K.). One or 2 hematoxylin and eosin slides of the most representative tumor sections per case were digitally scanned to WSI using an Aperio ScanScope AT2 scanner (Leica Biosystems Inc., Buffalo Grove, IL) at ×20 magnification (0.50 μm/pixel).

Participants and Study Design

The anonymized WSIs were distributed along with a score sheet to the study pathologists, which consisted of 25 subspecialty expert HN pathologists, from the United States, Canada, and Europe. A brief 4-question survey was distributed to collect basic demographic data of the participants, including (1) country of practice; (2) experience determined by the year of practice; (3) practice pattern being subspecialized with at least 50% of practice in HN pathology; and (4) perception of CASG/PAC before the current study.

Representative illustrations and pertinent diagnostic criteria from previous publications of CASG and PAC[3,8,10,11,13] were circulated before the case review. The cases were independently categorized into 1 of the 4 predefined categories: (1) PAC: a carcinoma characterized by cytologic uniformity, architectural diversity and frequent swirling and targetoid arrangement of tumor cells (Fig. 1); (2) CASG: a carcinoma with lobulated growth, solid, cribriform, and/or microcystic architecture, peripheral palisading, peripheral clefting, glomeruloid appearance, and pale optically clear nuclei; (3) PAP: tumor with predominant ($\geq$ 50%) of papillary architecture; and (4) IND: tumors with indeterminate features defined as tumor within CASG/PAC spectrum but difficult to subclassify into any of the other 3 categories. Three of the participants have felt that a few tumors did not fit into the PAC/CASG spectrum and used diagnoses outside of the 4 provided categories using free text to classify some tumors. Such diagnoses were captured as "others." Any additional comments and explanatory notes were collected and reviewed.

Consensus Classification and Statistical Analysis

The consensus diagnosis was determined using the classification agreed upon by at least 50% of participants, or as IND when a predominant diagnosis could not be reached. All statistical analyses were performed using the SPSS software 24.0 (IBM Corporation, New York, NY). Interobserver agreement among all participants followed

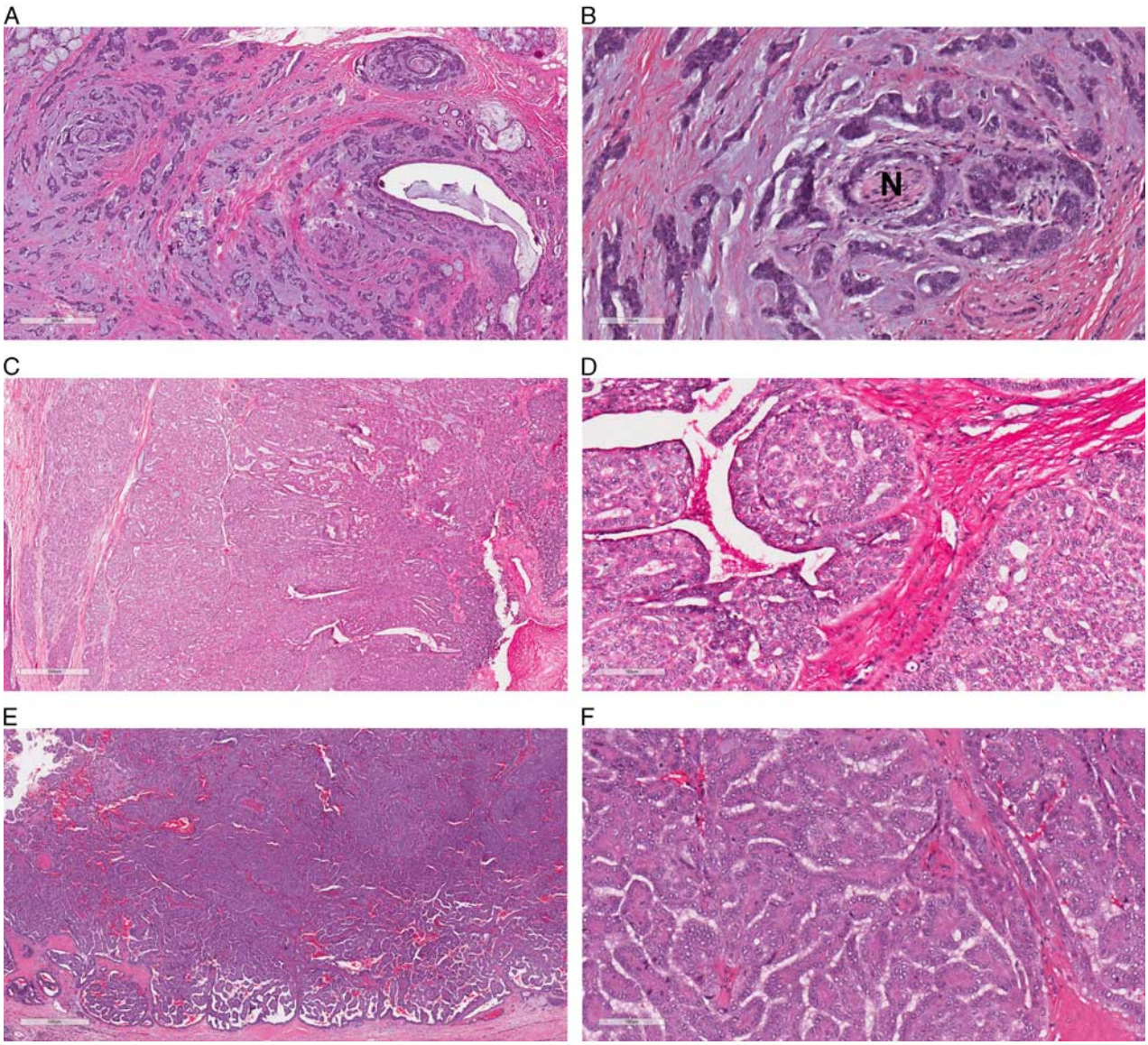

FIGURE 1. Histologic features of PAC, CASG, and PAP. A and B, PAC (case #1) is characterized by tubular targetoid arrangements of tumor cells surrounding nerves (N). C and D, CASG (case #19) contains lobules with cribriform and solid growth separated by thin fibrous septa. Prominent peripheral palisading, clefting, and glomeruloid appearance are noted on high power (D). E and F, PAP (case #36) is characterized by prominent papillary growth. Of note, all 3 tumors are composed of 1 type of cell that is characterized by uniform nuclei with chromatin clearing.

by sub-stratification according to practice pattern and perception of CASG/PAC was calculated using Fleiss' κ analysis with κ values interpreted as follows: 0.01 to 0.20 slight agreement; 0.21 to 0.40 fair agreement, 0.41 to 0.60 moderate agreement, 0.61 to 0.80 substantial agreement, and 0.81 to 0.99 almost perfect agreement.

Detection of PRKD1 Hotspot Mutation and PRKD1/PRKD2/PRKD3 Fusion and Correlation With Consensus Classification

Thirty-seven cases with sufficient DNA retrieved from archived paraffin blocks were tested in our prior study[18] for *PRKD1* hotspot mutation using real-time polymerase chain reaction and *PRKD1*, *PRKD2*, and *PRKD3* fusion using fluorescent in situ hybridization. The findings were subsequently correlated with the current consensus classification to determine the rate of mutation and fusion within each diagnostic category.

RESULTS

Characteristics of the Cases and Consensus Classification

The results are summarized in Figure 2. The majority of the tumors originated from minor salivary glands of the upper aerodigestive tract, whereas 4 tumors (8%) were

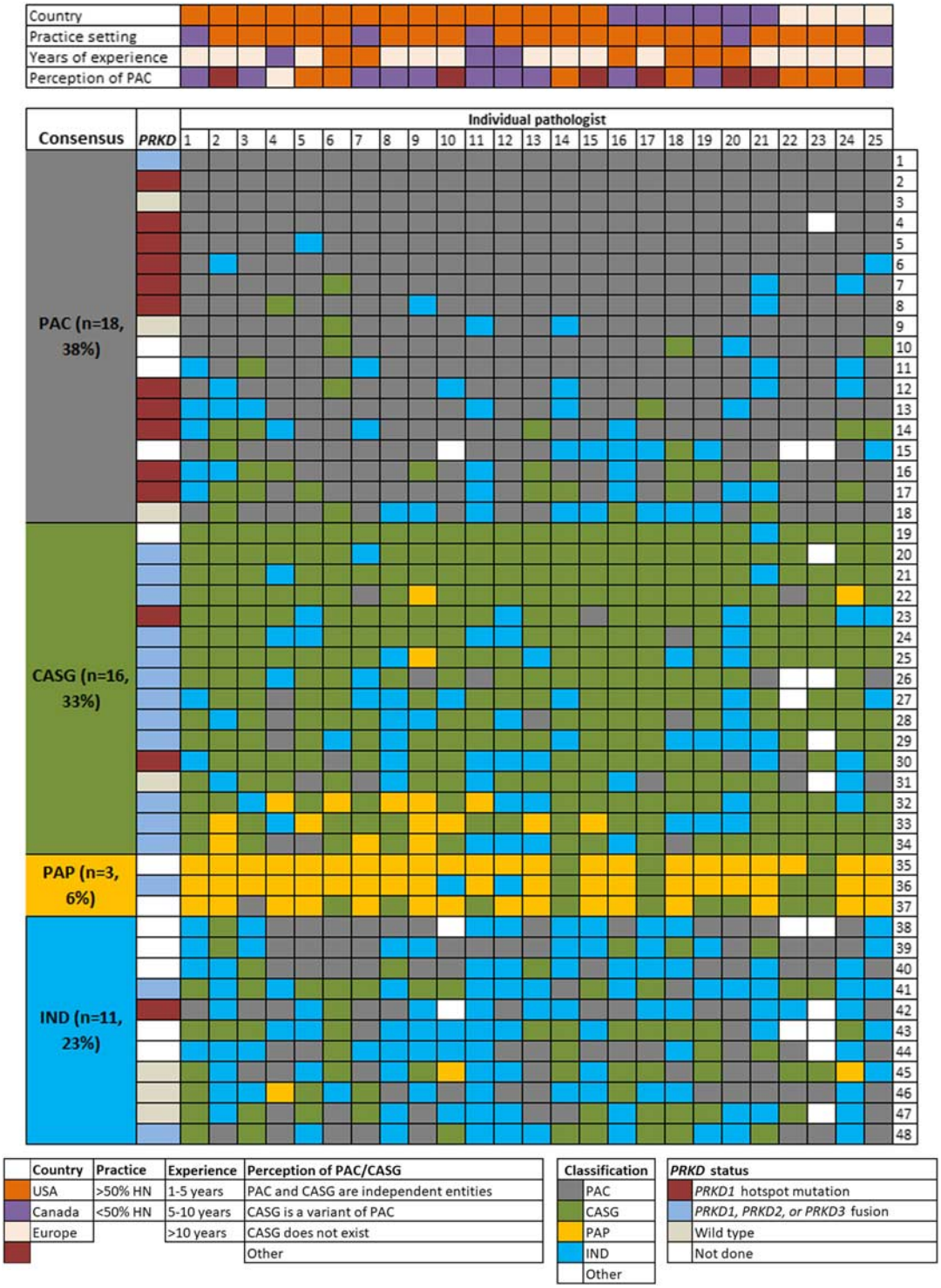

FIGURE 2. Heat map of consensus classification and individual diagnosis.

located in the parotid gland. Common affected sites were palate (n = 24, 50%), other intraoral mucosal site (n = 9, 19%), base of tongue (n = 6, 13%), and sinonasal tract (n = 4, 8%). In 2 CASGs (cases #29 and #37), the primary tumor was not available for WSI digitalization, and the lymph node metastases were scanned and included in the current study.

In 37 cases (77%), a consensus diagnosis, defined as a classification that was agreed upon by the majority (> 50%) of the participants, was reached. The consensus

diagnoses of these cases were PAC (18/48), CASG (16/48), and PAP (3/48). The remaining 11 cases (23%) were classified as IND. The full consensus was achieved in 3 (6%) cases, all of which were classified as PAC. In 19 cases (40%), the diagnosis was agreed upon by at least 20 participating pathologists with ≤ 5 disagreements, including 11 of 17 PAC (65%), 7 of 16 CASG (44%), and 1 of 3 PAP (33%).

Among the 4 parotid gland tumors, the consensus diagnoses were IND (n = 2), CASG (n = 1), and PAC (n = 1).

Interobserver Agreement Determined Using Fleiss' κ Statistics

The interobserver concordance expressed as κ values and 95% confidence interval are shown in Table 1. Overall, there was a fair interobserver agreement among all participants in classifying the tumors ($\kappa = 0.370$). A moderate agreement was achieved for PAC ($\kappa = 0.504$) and PAP ($\kappa = 0.561$) and a fair agreement for CASG ($\kappa = 0.390$). In contrast, IND had only a slight diagnostic concordance ($\kappa = 0.091$).

The demographic data of the 25 participated pathologists was as follow:(1) geographic distribution: United States, n = 15; Canada, n = 6, and Europe, n = 4; (2) practice setting: HN pathology accounts for >50% of practice, n = 20 and <50% of practice, n = 5; (3) years of practice: <5 years, n = 6; 5 to 10 years, n = 3; and >10 years, n = 16; and (4) perception of PAC/CASG before the study: PAC and CASG were independent entities, n = 7; CASG was a variant of PAC, n = 11; CASG did not exist, n = 1; and other, n = 6. Among the 6 participants who answered "other": 3 were uncertain; 2 suggested that PAC and CASG are a spectrum; and 1 thought that CASG and PAC were distinct but too interrelated to classify them as separate entities.

The interobserver agreement was not significantly altered based on country of practice (United States: $\kappa = 0.381$; Canada: $\kappa = 0.366$; and Europe: $\kappa = 0.368$), practice pattern (<50% of HN specialty sign out $\kappa = 0.354$; and >50%: $\kappa = 0.372$), years of practice (<5 y: $\kappa = 0.359$; 5 to 10 y: $\kappa = 0.385$; and >10 y: $\kappa = 0.383$), and perception of CASG/PAC and their morphologic spectrum before the study (independent entities: $\kappa = 0.320$; variant: $\kappa = 0.421$ and other: $\kappa = 0.343$).

TABLE 1. Correlation of Molecular Alterations With Consensus Diagnosis in 37 Tumors

Consensus Diagnosis	Total (N = 37)	Mutation (N = 14)	Fusion (N = 16)	Wild-Type (N = 7)	*P*
PAC*	15	11 (73)	1 (7)	3 (20)	0.001
CASG*	15	2 (13)	12 (80)	1 (7)	
PAP*	1	0	1 (100)	0	
IND*	6	1 (17)	2 (33)	3 (50)	

*For PRKD mutation or fusion status of each tumor category, the values are expressed as number of cases harboring the molecular alteration (percentage of the cases positive for molecular alteration within that tumor category).

Indeterminate Lesions: Obstacles in Classification

None of the 48 cases included in this study had a predominant diagnosis of IND. Eleven tumors (23%) were classified as IND because a consensus diagnosis among at least 50% of participants was not achieved.

In 3 cases (#39, #42, and #46), the diagnostic uncertainty may be partially attributed to specimen integrity with tissue fragmentation, making it difficult to accurately evaluate the architectural pattern which is a key histologic feature to distinguish between PAC and CASG. Furthermore, case #46 had marked thermal artifacts marking nuclear features.

In addition, some of these tumors exhibited mixed features, rendering a definite distinction between CASG and PAC difficult even in resection specimens. For example, case #48, a parotid tumor contained areas that were typical of both CASG and PAC (Fig. 3). The diagnoses of this tumor were PAC by 8, CASG by 8, and IND by 9 participants, respectively.

PRKD1 Hotspot Mutation and PRKD1, PRKD2, and PRKD3 Fusion in PAC/CASG Spectrum of Tumors

Among the 37 tumors previously tested in our prior study,[18] 14 (38%) harbored P*RKD1* hotspot mutations, 16 (43%) contained fusion involving *PRKD1*, *PRKD2*, or *PRKD3*, while the remaining 7 (19%) were *PRKD* wild-type. The molecular findings of each tumor in correlation with the consensus diagnoses are shown in Figure 2 and Table 1. The consensus diagnoses of these 37 tumors were: PAC, n = 15; CASG, n = 15; PAP, n = 1; and IND, n = 6.

The majority (11/15, 73%) of PACs had *PRKD1* mutation, whereas a single PAC (7%) contained *PRKD3* fusion. This fusion-positive PAC arose in the palate and was 1 of the 3 cases which achieved full consensus among all participants. In contrast, most CASGs (12/15, 80%) showed fusions involving *PRKD1*, *PRKD2*, or *PRKD3* (Fisher exact test, $P = 0.001$), although *PRKD1* mutation was also detected in a small number of CASG cases (2/15, 13%). Among the 6 tested IND, 1 (17%) had *PRKD1* mutation, 2 (33%) had fusion (*PRKD1* in 1 and *PRKD3* in another), while the remaining 3 (50%) were wild-type. The 1 tested PAP showed *PRKD1* fusion.

Of the 2 parotid gland tumors tested, 1 showed *PRKD1* fusion and was classified as CASG (case #21); the other contained *PRKD2* translocation and was classified as IND (case #48, Fig. 3).

DISCUSSION

This is the first study that examined the reproducibility of diagnosing the tumors within the PAC and CASG spectrum. Our results showed that a moderate interobserver agreement can be achieved in classifying the morphologic spectrum of PAC/CASG with complete or near-complete consensus in a proportion of but not all cases. Practice patterns, experience, and prestudy perception of CASG/PAC have no significant impacts on the interpretation.

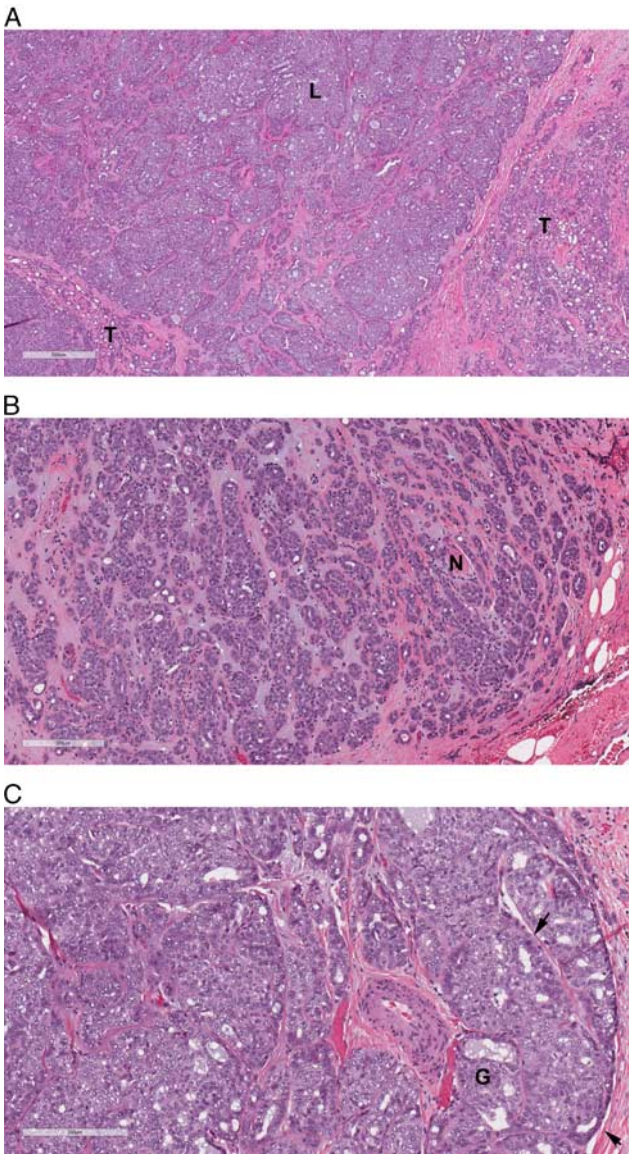

FIGURE 3. A *PRKD2*-rearranged tumor with indeterminate features involving the parotid gland (case #48). A, At low power, the tumor shows typical features of CASG (lobules [L] of solid and cribriform architectures, separated by thin fibrous bands) intermixed with PAC regions with streaming tubules (T). B, PAC area: monotonous tumor cells form tubules, trabeculae, and single files arranged circumferentially around a nerve (N). C, CASG area contains lobules of various sizes, with peripheral palisading and clefting (arrows) forming glomeruloid structure (G).

The ability of pathologists to reliably distinguish PAC and CASG is not irrelevant as several studies have shown that CASG is associated with a high rate (up to 72%) of lymph node metastasis,[9,11,12,19] compared with 10% to 17% rate in classical PAC.[4,5] Similarly, in our cohort, the risk of nodal metastases was 6% for PAC, and 31% for CASG. Therefore, regardless of the terminology controversy, it seems important to recognize typical CASG in daily practice. Further, identifying CASG may help to avoid misinterpreting this tumor as a different entity and to better classify salivary gland neoplasms. Our study showed that the classification of a given tumor as PAC or CASG is possible based on histologic features when the hallmark morphologic features of these tumors as detailed in Figure 1 are identified.

In our study, PAC and PAP showed a higher level of concordance compared with CASG. Several potential reasons may have contributed to such a difference. First, PAC is a well-recognized entity that has been described >30 years ago[2] and included in several editions of WHO classification.[3,14] In contrast, CASG described in 1999, is relatively rare and is not universally accepted even among expert HN pathologists,[9] which may result in a relatively low diagnostic reproducibility for this tumor. In addition, compared with the category of PAP which has been clearly defined in this study using a single criterion (>50% of papillae), there is no well-accepted concise criteria for CASG. Most of the prior series of CASG, including the very first report, have only provided a detailed histologic description results in significant diagnostic subjectivity.[9–12,15]

A subset (23%) of tumors were classified as IND, defined in this study as tumors belonging within CASG/PAC spectrum but difficult to subclassify into 1 specific entity. In 3 cases, the diagnostic uncertainty was likely related to the sample quality and size (eg, incisional biopsy), tissue fragmentation and thermal artifacts. However, such difficulties are similar to what pathologists encounter in their daily practice. In small samples, the definitive distinction between CASG and PAC may therefore not always be possible. Nevertheless, in most IND cases, a consensus diagnosis was not reached because tumors showed mixed features of classical PAC and CASG. IND were previously reported by 2 recent studies, accounting for 32% to 35% of all CASG/PAC spectrum of tumors.[8,13] Because of subjectivity and diagnostic uncertainty, not surprisingly, this group of lesions is associated with poor to almost absent interobserver agreement even among expert HN pathologists.[8] Moreover, the fact that some of these tumors show mixed features of both PAC and CASG may also have attributed to the inability to classify these tumors into a single category. Furthermore, there is an ongoing debate regarding the diagnosis of PAC with significant papillary architecture.

From a molecular perspective, PAC predominantly has *PRKD1* hotspot mutation, whereas CASG mostly harbors *PRKD1*, *PRKD2*, or *PRKD3* fusion. Our findings were consistent with what have been previously reported.[13,16] However, we clearly demonstrated that the fusion or mutation was not exclusive for CASG or PAC. Weinreb et al[13] has previously reported *PRKD1*, *PRKD2*, or *PRKD3* fusion in a small percentage of classic PAC, which is confirmed by the current study. Herein, we document 2 cases of CASG that harbored *PRKD1* hotspot mutation.

Tumors with predominant papillary patterns have been described before as low-grade papillary adenocarcinoma (LGPA) by Allen et al in 1974[20] and subsequently by Mills

et al in 1984[21] but have not been included in the recent WHO classification. Similar to classical PAC, these tumors are composed of a single cell type with optically cleared nuclei but with a prominent papillary architecture. Previous studies, including our own, have shown that the presence of ≥10% true papillae or "more than focal papillary area" is associated with a higher risk of regional metastasis and/or recurrence.[8,22,23] To date, little is known about the underlying molecular mechanisms in LGPA, in part because the entity is not well-defined and is not widely accepted as a diagnostic category. Some pathologists accept this entity as part of the spectrum of CASG. In the study by Weinreb and colleagues, *PRKD1*, *PRKD2*, or *PRKD3* fusion was identified in 26 cases of which 9 contained papillary architecture, 8 were CASG, and 1 was classified as IND. In view of the similar nuclear features and that papillary architecture can be seen in both CASG and PAC, it is likely that LGPA belongs to the CASG/PAC histomorphologic spectrum of tumors. In this study, we had a separate category of PAP which included only 6% (3/48) of the tumors. One tumor was subjected to molecular testing and was found to harbor *PRKD1* fusion. The fact that the tumors with extensive papillary growth may harbor *PRKD1* fusion further supports that they should be classified as part of the PAC/CASG spectrum of tumors. The number of cases tested in this study was too small to determine if PAP is molecularly akin to CASG or PAC, although in our observation, PAP seems to be more closely related to CASG.

Of interest, 4 tumors in this study cohort were identified in the parotid gland. These 4 tumors were classified as IND (n = 2), PAC (n = 1), and CASG (n = 1). Two tumors (1 CASG and 1 IND) were subjected to molecular testing and both were found to have fusion involving *PRKD1* and *PRKD2*, a molecular alteration that is characteristic for CASG.[16] These findings are consistent with previous studies suggesting that PAC and CASG may rarely occur in the major salivary gland and should be considered in the differential diagnosis of major salivary gland neoplasms.[8,13,16]

There were several potential weaknesses of this study. The diagnosis was rendered by evaluating the digitalized WSI of 1 to 2 preselected representative tumor slides per tumor rather than the actual glass slides of the entire tumor. The purpose of this study design is to facilitate the distribution of the materials and to reduce the time required to review the entire tumor. Recent studies have shown that WSI is noninferior to microscopy for diagnostic purposes, which lead to approval by the US Food and Drug Administration (FDA).[24,25] However, limiting the material to 1 or 2 slides per case may potentially introduce selection bias and reduce the diagnostic certainty (ie, a tendency towards IND). In addition, it was noted by the participants that a small percentage (5/48, 10%) of cases, including 3 IND and 2 PAC, had tissue fragmentation (3 cases), cautery artifacts (1 case), poor scan quality (1 case), and/or small tumor sample size (1 case), which in part resemble problems pathologists encounter in real life but at the same time may compromise the diagnostic accuracy. Last, we recognize that the participants are all experts in HN pathology. Therefore, the generalization of our results in the wider pathology community may require further exploration.

In conclusion, in this study which involved a large international group of expert HN pathologists, we have shown that a fair to moderate interobserver agreement can be achieved in classifying the morphologic spectrum of PAC/CASG. The diagnosis of classic PAC or CASG could be rendered based on the histopathologic features of the tumor. A subset of these tumors (23%) showed indeterminate features and had a poor interobserver agreement and were difficult to classify. This may explain the controversy in classifying these tumors, which results in diagnostic uncertainty and poor interobserver agreement in this subgroup of tumors. The majority of PACs contained *PRKD1* hotspot mutation and most CASGs showed *PRKD1*, *PRKD2*, or *PRKD3* fusion; however, these molecular events did not appear to be exclusive to either PAC or CASG. The molecular analysis generally but not perfectly corroborated the histologic classification.

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