西京医院 XIJING HOSPITAL

PATH 西京病理

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

An International Interobserver Study

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BACKGROUND

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多形性腺癌Polymorphous Adenocarcinoma (PAC)

【定义】

以细胞学一致性、形态学多样性、浸润性生长为特点的涎腺上皮性恶性肿瘤

【ICD-O 】及【曾用名】

8525/3，低级别多形性腺癌

【流行病学】

是口腔内第二常见的恶性涎腺肿瘤，[illegible]1：2，年龄从16岁至94岁，平均59岁，70%以上的患者在50-70岁，

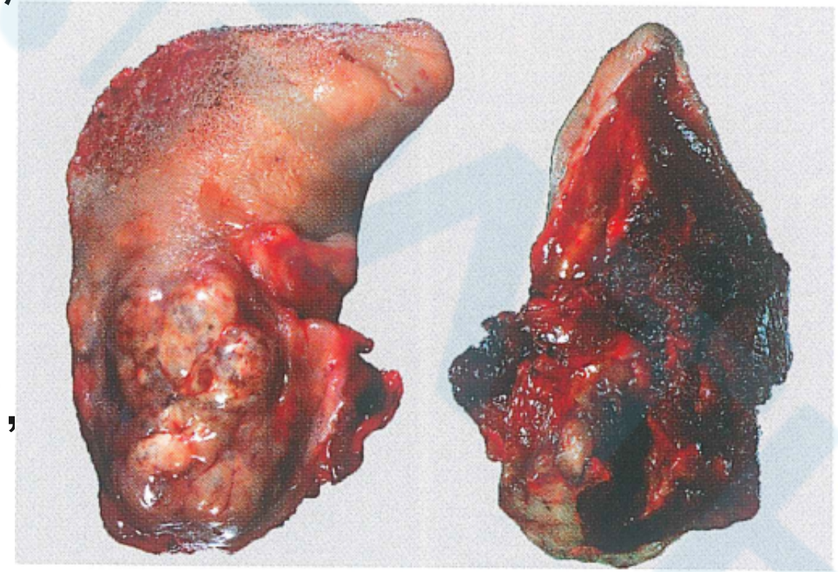


Fig. 7.10 Polymorphous adenocarcinoma. Note the multinodular surface and the haemorrhage.

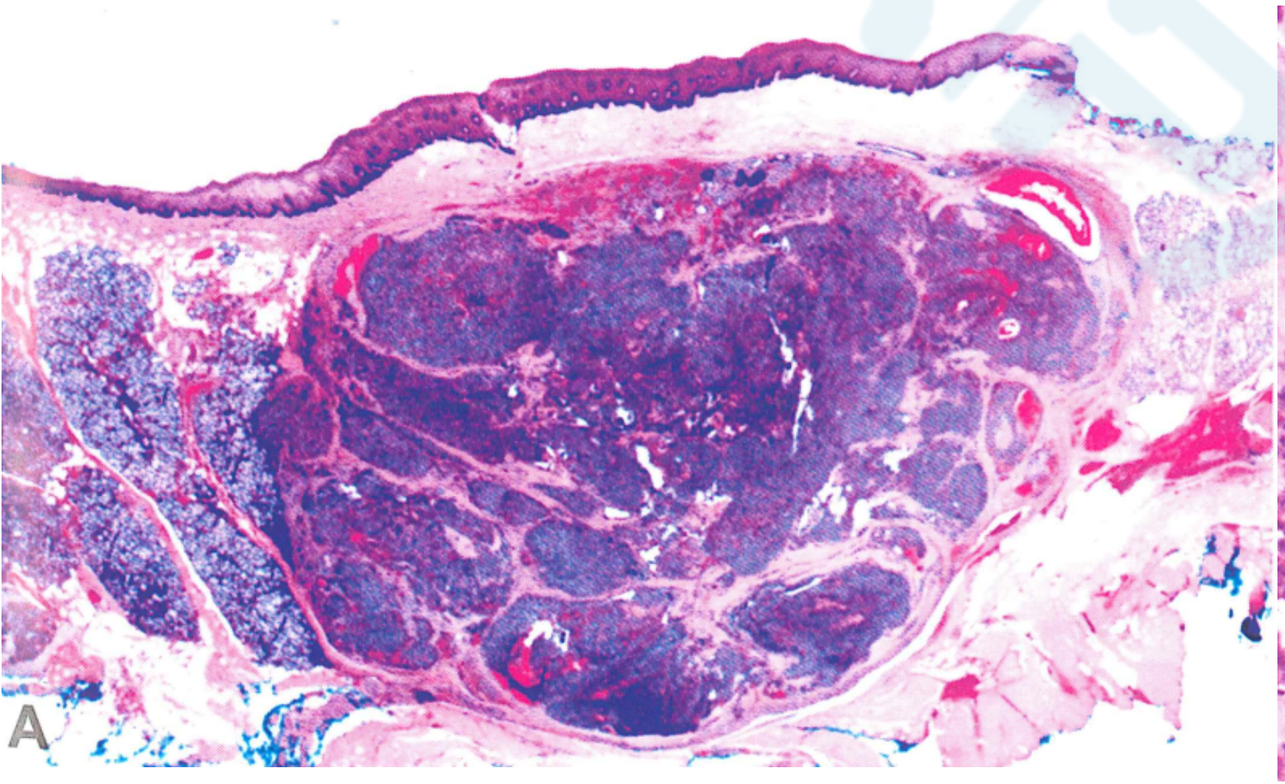
【部位】

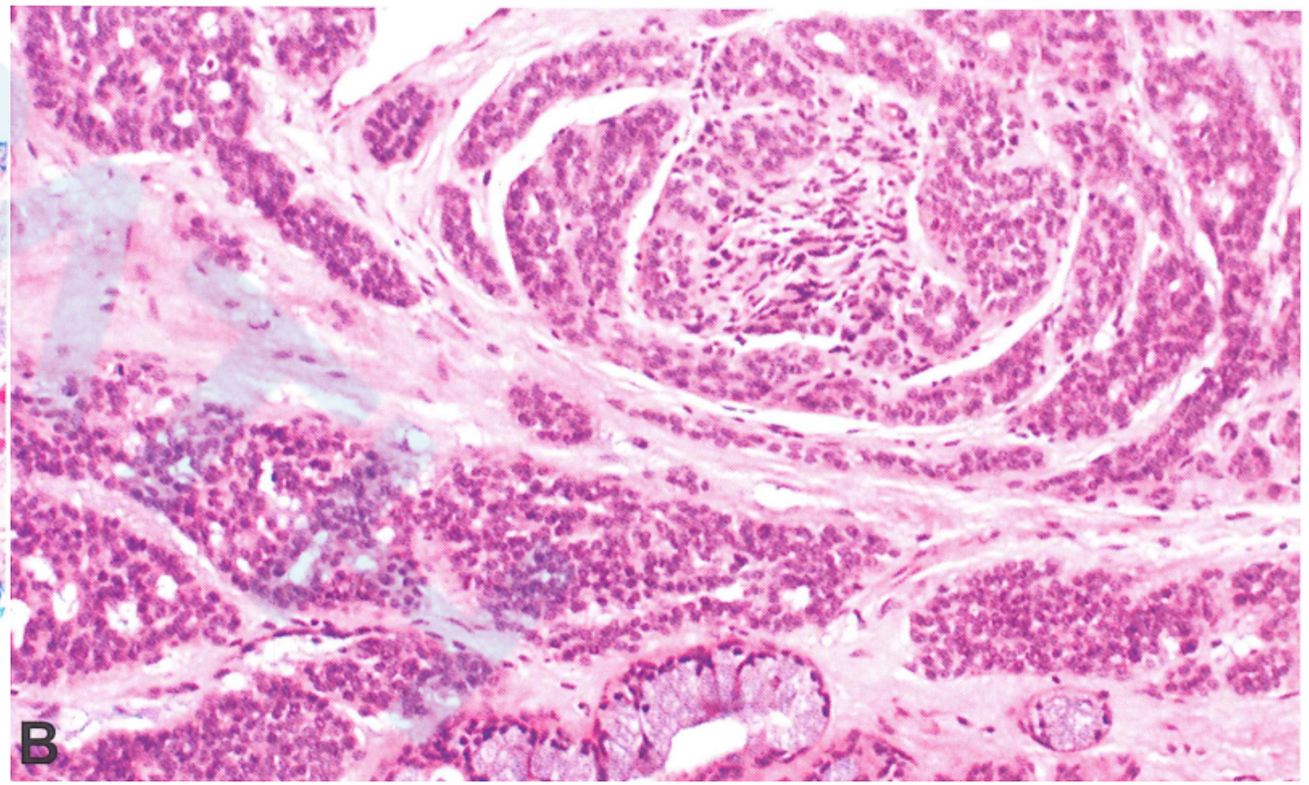
大部分发生于鄂部（60%），其他部位包括颊粘膜、磨牙后区、上唇、舌根

WHO Classification of Head and Neck Tumours 4th Edition, 2017

BACKGROUND

多形性腺癌Polymorphous Adenocarcinoma (PAC)





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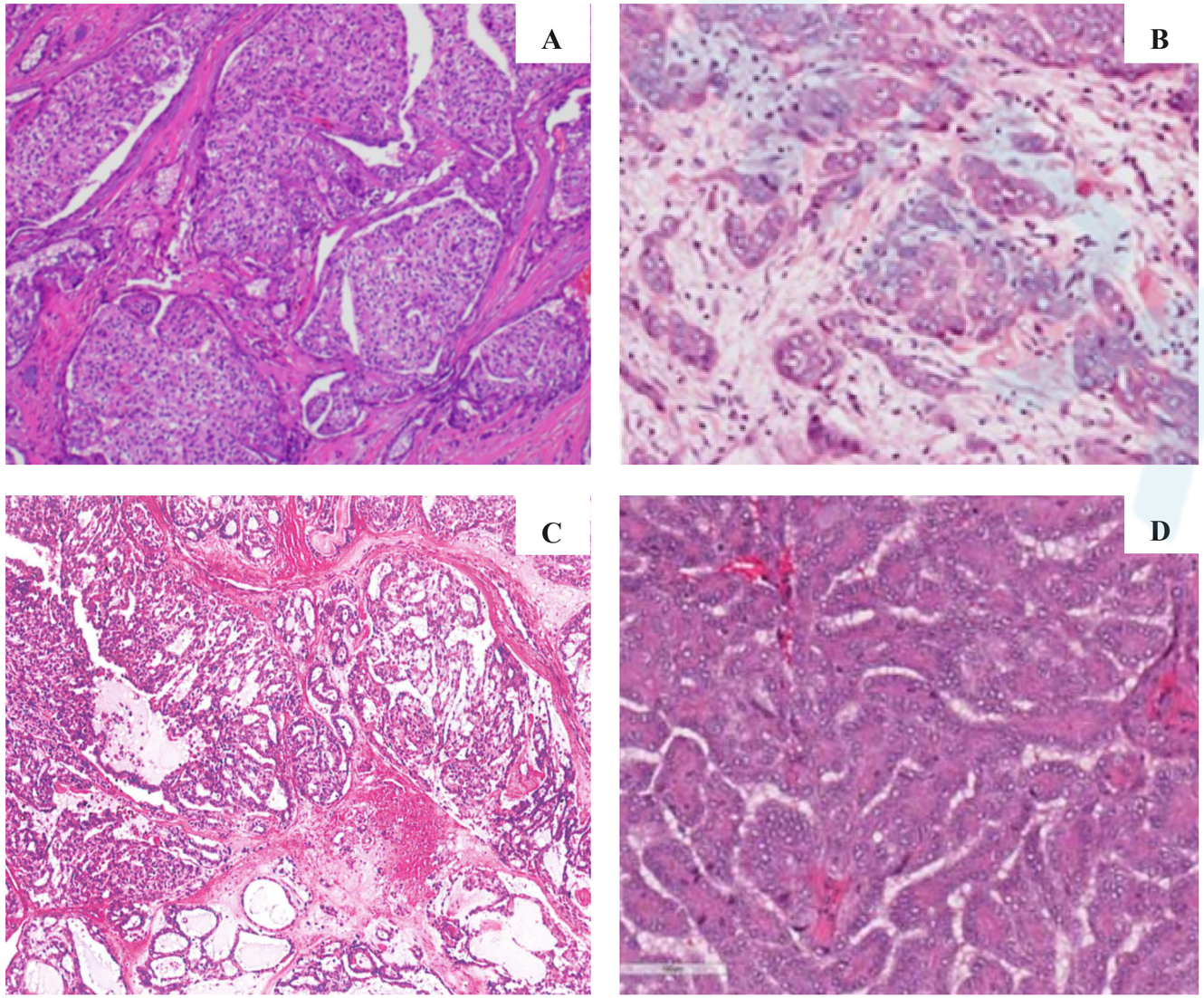
多形性腺癌Polymorphous Adenocarcinoma (PAC)



A：小叶状

B：小梁状

C：筛孔状

D：乳头状

WHO Classification of Head and Neck Tumours 4th Edition, 2017

Am J Surg Pathol 2020;44:545–552

Am J Surg Pathol. 2016 Nov; 40(11): 1526–1537.

BACKGROUND

多形性腺癌Polymorphous Adenocarcinoma (PAC)

【免疫组化】

阳性：CK7、CK8、S-100、CEA 、CD117 ，P63

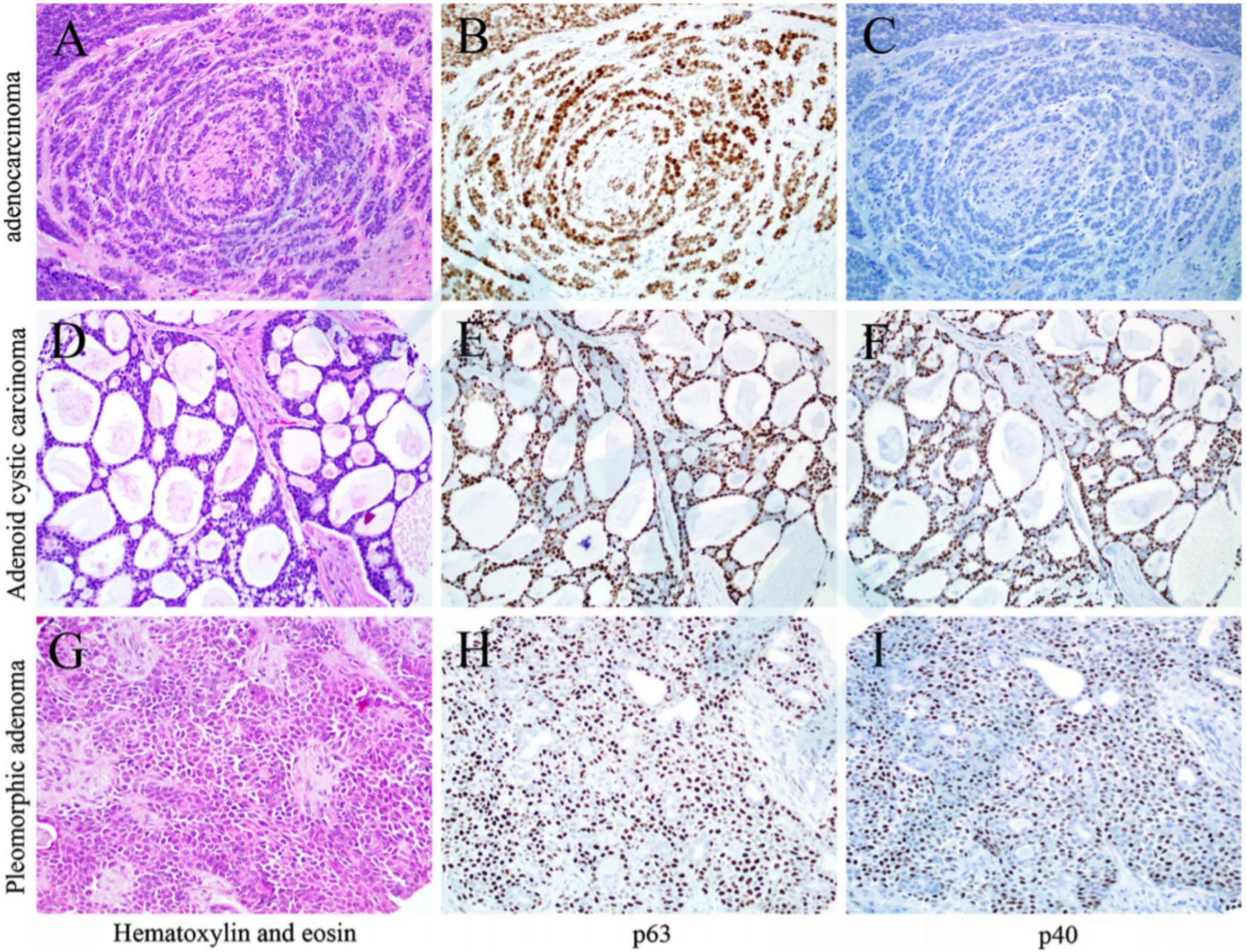
阴性：肌上皮标记、GFAP，P40

【分子遗传学】

点突变： *PRKD1*

重排/转位：*PRKD1*、*PRKD2*、*PRKD3*

WHO Classification of Head and Neck Tumours 4th Edition, 2017



Head Neck Pathol. 2015 Mar; 9(1): 79–84.

Histopathology 1999, **35**, 495–501

Cribriform adenocarcinoma of the tongue: a hitherto unrecognized type of adenocarcinoma characteristically occurring in the tongue

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Xu B, Aneja A, Ghossein R, et al. *Am J Surg Pathol* 2016;40:1526–1537

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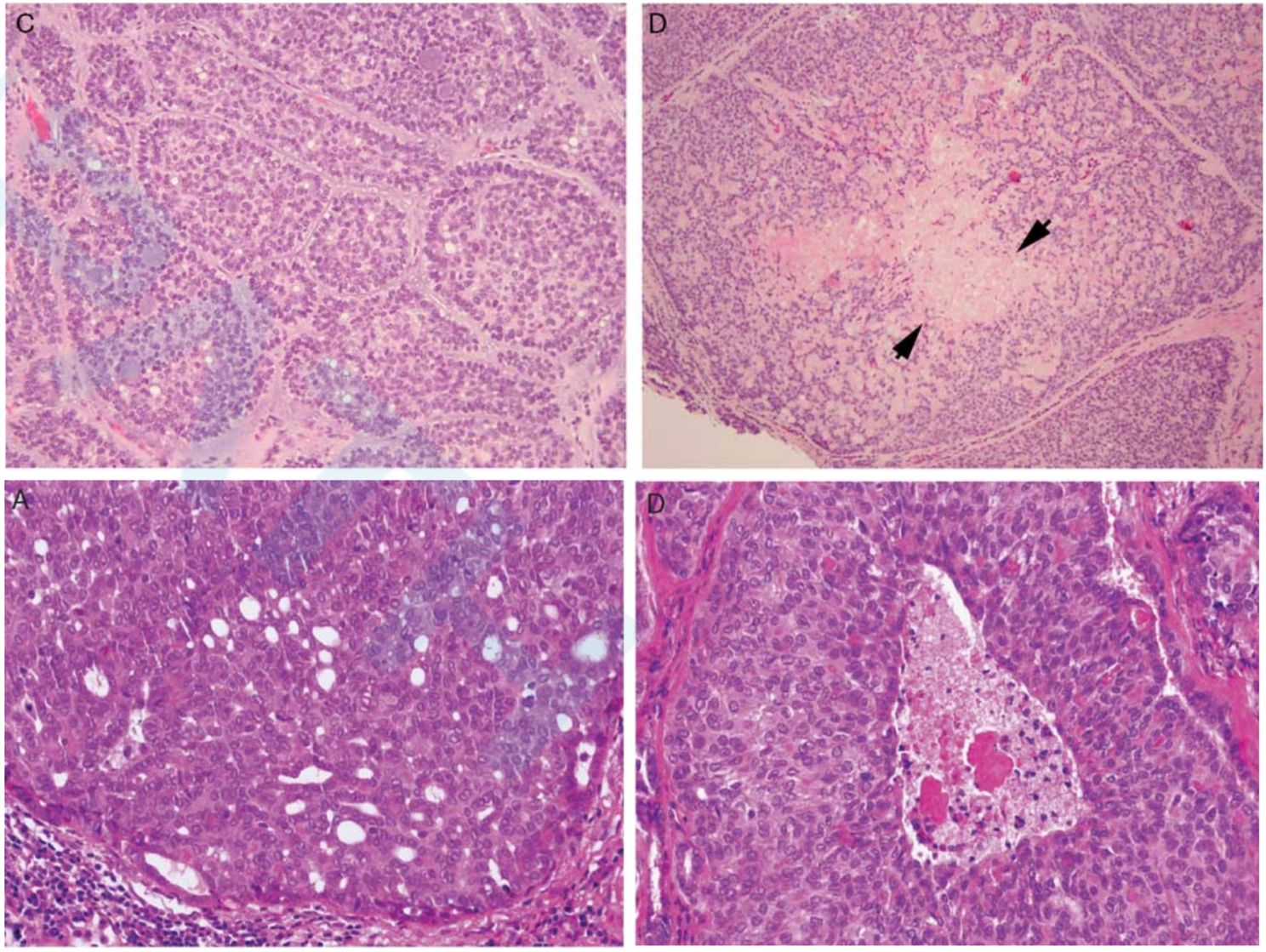
Cocek A, Hronkova K, Voldanova J, et al. *Oncol Lett*. 2011;2:135–138.

BACKGROUND

筛状腺癌Cribriform Adenocarcinoma of Salivary Gland (CASG)

- 多发于小涎腺，呈浸润性的小叶状的生长方式，排列呈筛状、实性或肾小球样；
- 大部分早期出现淋巴结转移，但不发生远处转移；
- 大部分具有*PRKD1*、*PRKD2*、*PRKD3*基因重排



Xu B, Aneja A, Ghossein R, et al. *Am J Surg Pathol* 2016;40:1526–1537

Skalova A, Sima R, Kaspirkova-Nemcova J, et al. *Am J Surg Pathol.* 2011;35:1168–1176.

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ORIGINAL ARTICLE

Predictors of ... Spectrum of Polymorphou... (PLGA) and Cribriform A... and (CASG)

Bin Xu, MD, Ph... Nora Katabi, MD

PLGA出现≥10% 乳头状区域或≥ 30%筛状区域提示预后不良；

CASG更常出现淋巴结转移，且预后更差；

两者形态学有重叠，分类困难；

均出现*PRKD*基因改变，但PLGA常出现*PRKD1*点突变，

CASG常出现*PRKD1*、*PRKD2*、*PRKD3*基因重排

BACKGROUND

研究目的

对比不同病理专家对PAC、CASG诊断的一致性及可靠性，阐述PAC、CASG是否为同一疾病的不同谱系

MATERIALS AND METHODS

MATERIALS AND METHODS

Case and Slide Selection

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, 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

MATERIALS AND METHODS

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;

(4) perception of CASG/PAC before the current study.

MATERIALS AND METHODS

Participants and Study Design

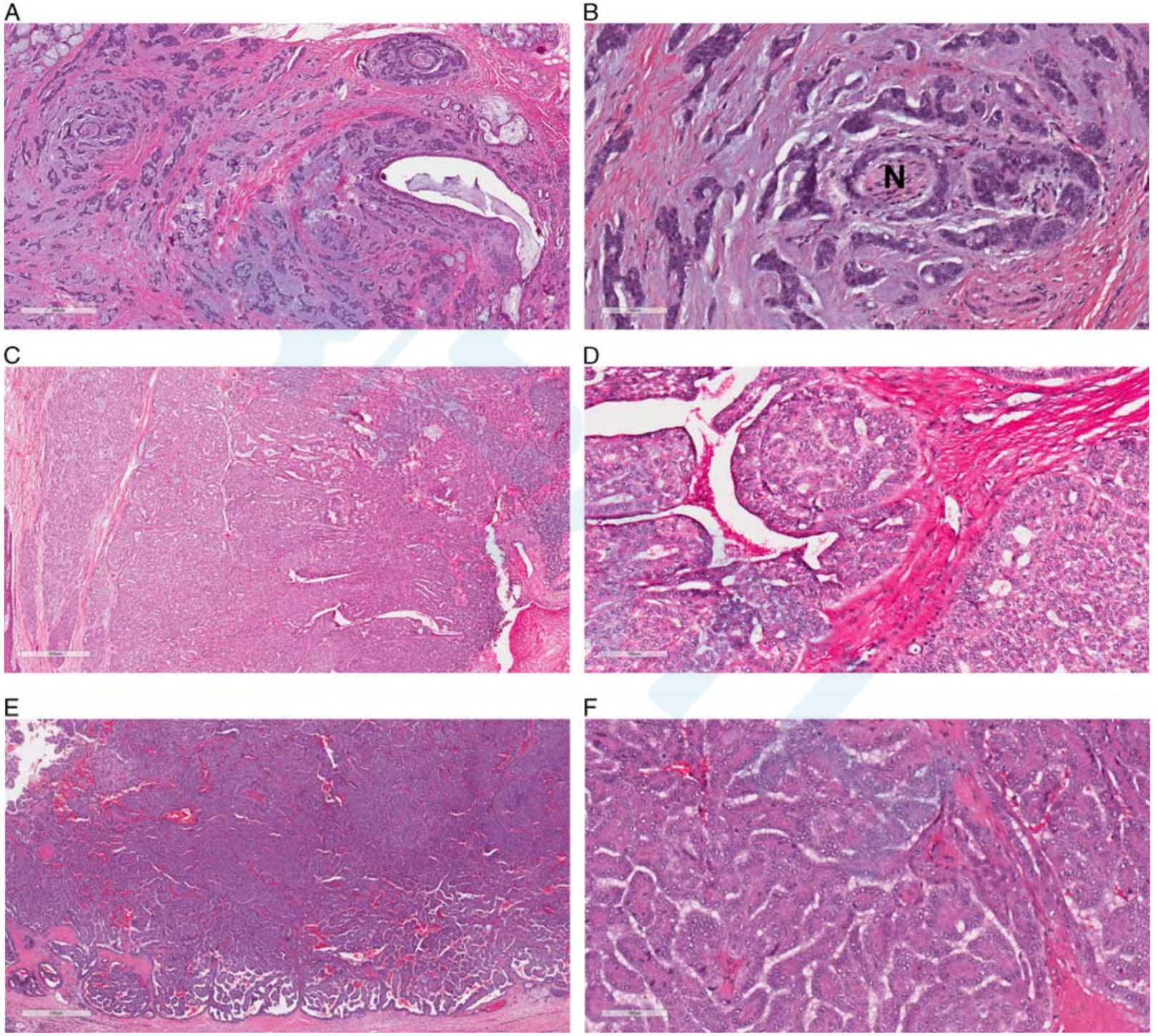
The cases were independently categorized into 1 of the 4 predefined categories:

(1) PAC: a carcinoma characterized by cytologic uniformity, architectural diversity and frequent swirling and targetoid arrangement of tumor cells;

(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 (≥ 50%) of papillary architecture;

(4) IND: tumors with indeterminate features defined as tumor within CASG/PAC spectrum but difficult to subclassify into any of the other 3 categories.


A
B
N
C
D
E
F

MATERIALS AND METHODS

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. Interobserver agreement among all participants followed by sub-stratification according to practice pattern and perception of CASG/PAC was calculated using Fleiss' κ analysis with κ values interpreted as follows:

1）0.01 to 0.20 slight agreement;

2）0.21 to 0.40 fair agreement,

3）0.41 to 0.60 moderate agreement,

4）0.61 to 0.80 substantial agreement,

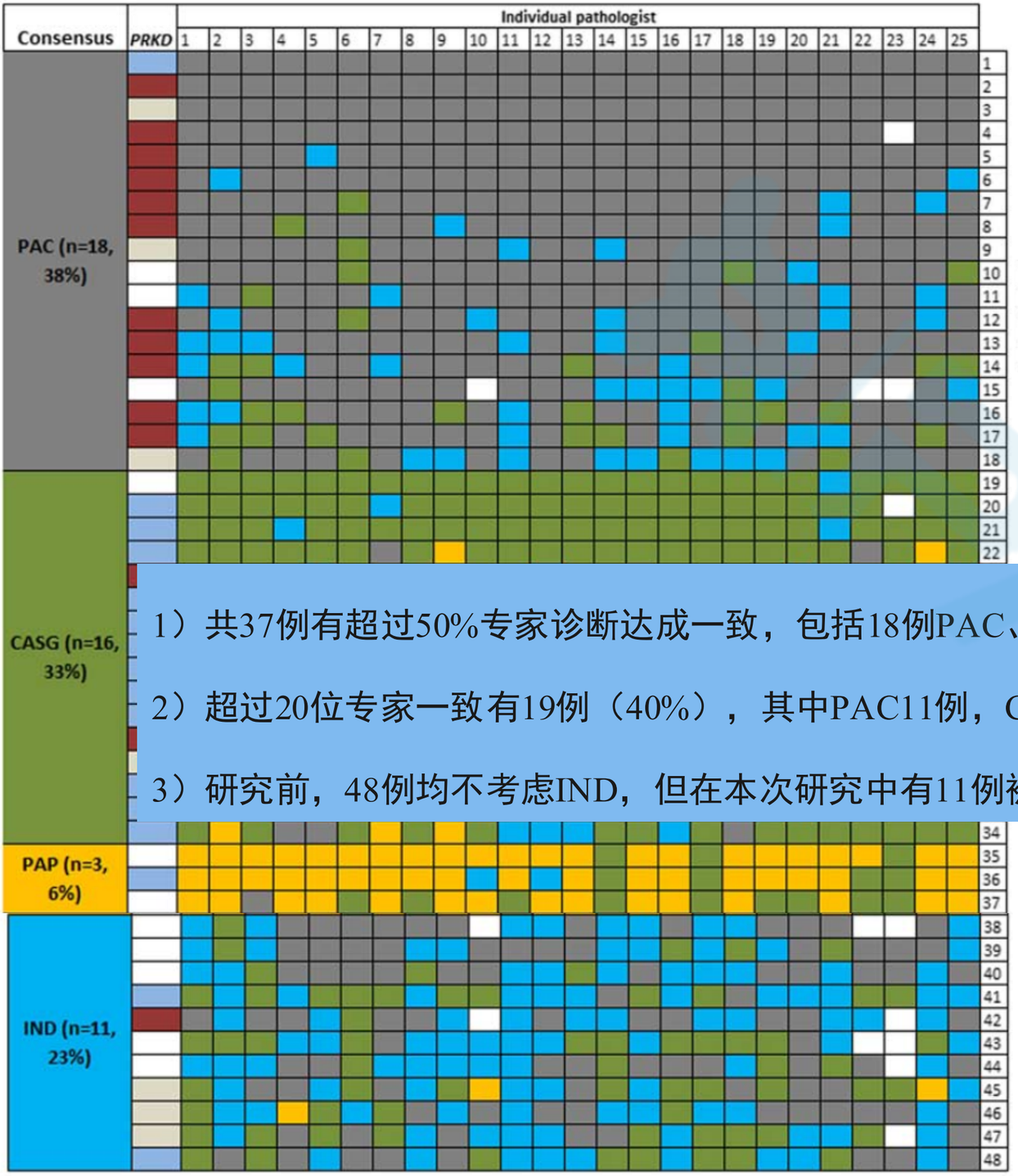
5）0.81 to 0.99 almost perfect agreement.

MATERIALS AND METHODS

Detection Mutation and Correlation With Consensus Classification

Thirty-seven cases with sufficient DNA retrieved from archived paraffin blocks were tested in our prior study 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



	Country	Practice	Experience	Perception of PAC/CASG
	USA	>50% HN	1-5 years	PAC and CASG are independent entities
	Canada	<50% HN	5-10 years	CASG is a variant of PAC
	Europe		>10 years	CASG does not exist

Classification
PAC
CASG
PAP

PRKD status
PRKD1 hotspot mutation
PRKD1, PRKD2, or PRKD3 fusion
Wild type
None

1）共37例有超过50%专家诊断达成一致，包括18例PAC、16例CASG、3例PAP，其余11例被归类为IND；

2）超过20位专家一致有19例（40%），其中PAC11例，CASG7例，PAP 1例；

3）研究前，48例均不考虑IND，但在本次研究中有11例被归类为IND，其中有3例由于组织破碎，无法评估，

...l diagnosis.

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 ($\kappa = 0.091$).

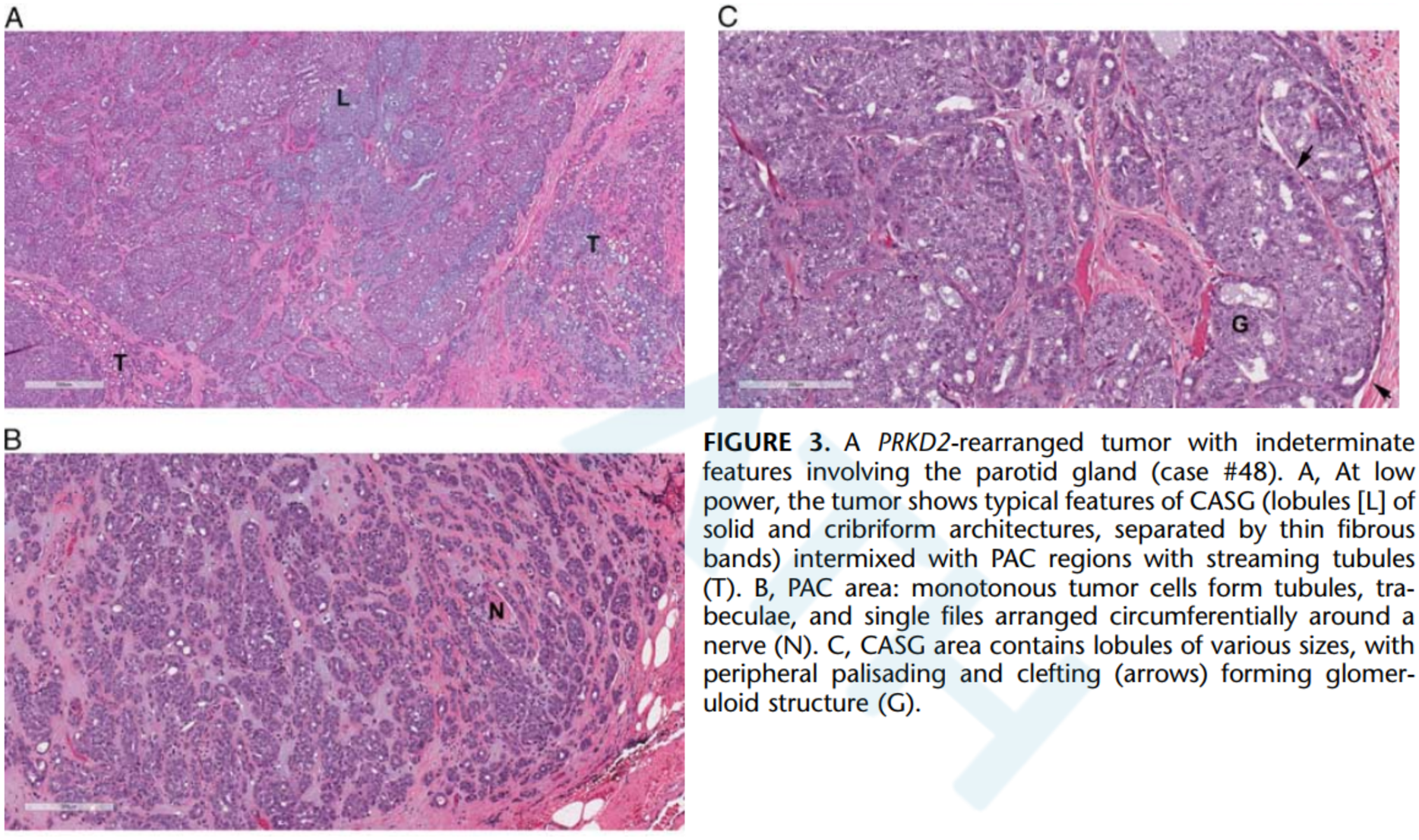


FIGURE 3. A *PRKD2*-rearranged tumor with indeterminate features involving the parotid gland (case #48). A, At low power, the tumor shows typical features of CASG (lobules [L] of solid and cribriform architectures, separated by thin fibrous bands) intermixed with PAC regions with streaming tubules (T). 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).

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).

DISCUSSION

DISCUSSION

1) This is the first study that examined the reproducibility of diagnosing the tumors within the PAC and CASG spectrum.

2) Several studies have shown that CASG is associated with a high rate (up to 72%) of lymph node metastasis, compared with 10% to 17% rate in classical PAC. It seems important to recognize typical CASG in daily practice.

3) 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.

DISCUSSION

In our study, PAC and PAP showed a higher level of concordance compared with CASG.

1) PAC is a well-recognized entity that has been described >30 years ago and included in several editions of WHO classification. In contrast, CASG described in 1999, is relatively rare and is not universally accepted even among expert HN pathologists, which may result in a relatively low diagnostic reproducibility for this tumor.

2) There is no well-accepted concise criteria for CASG.

3) Most of the prior series of CASG, including the very first report, have only provided a detailed histologic description results in significant diagnostic subjectivity.

DISCUSSION

1) 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.

2) However, we clearly demonstrated that the fusion or mutation was not exclusive for CASG or PAC.

3) Weinreb et al has previously reported *PRKD1, PRKD2, or PRKD3* fusion in a small percentage of classic PAC, which is confirmed by the current study.

4) Herein, we document 2 cases of CASG that harbored *PRKD1* hotspot mutation.

DISCUSSION

1) 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.

2) 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.

3) 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.

4) In our observation, PAP seems to be more closely related to CASG.

DISCUSSION

There were several potential weaknesses of this study.

1)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.

2)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).

3)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.

CONCLUSION

1) We have shown that a fair to moderate interobserver agreement can be achieved in classifying the morphologic spectrum of PAC/CASG.

2) A subset of these tumors (23%) showed indeterminate features and had a poor interobserver agreement and were difficult to classify.

3) 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.

4) The molecular analysis generally but not perfectly corroborated the histologic classification.

THANK YOU

感谢聆听