

MAML2 Rearrangements in Variant Forms of Mucoepidermoid Carcinoma

**Ancillary Diagnostic Testing for the Ciliated
and Warthin-like Variants**

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黏液表皮样癌

Mucoepidermoid Carcinoma , MEC

- 涎腺最常见的恶性肿瘤
- 好发部位：约53%发生在大涎腺，腮腺占45%，颌下腺7%，舌下腺1%
- ICDO编码：8430/3

黏液表皮样癌

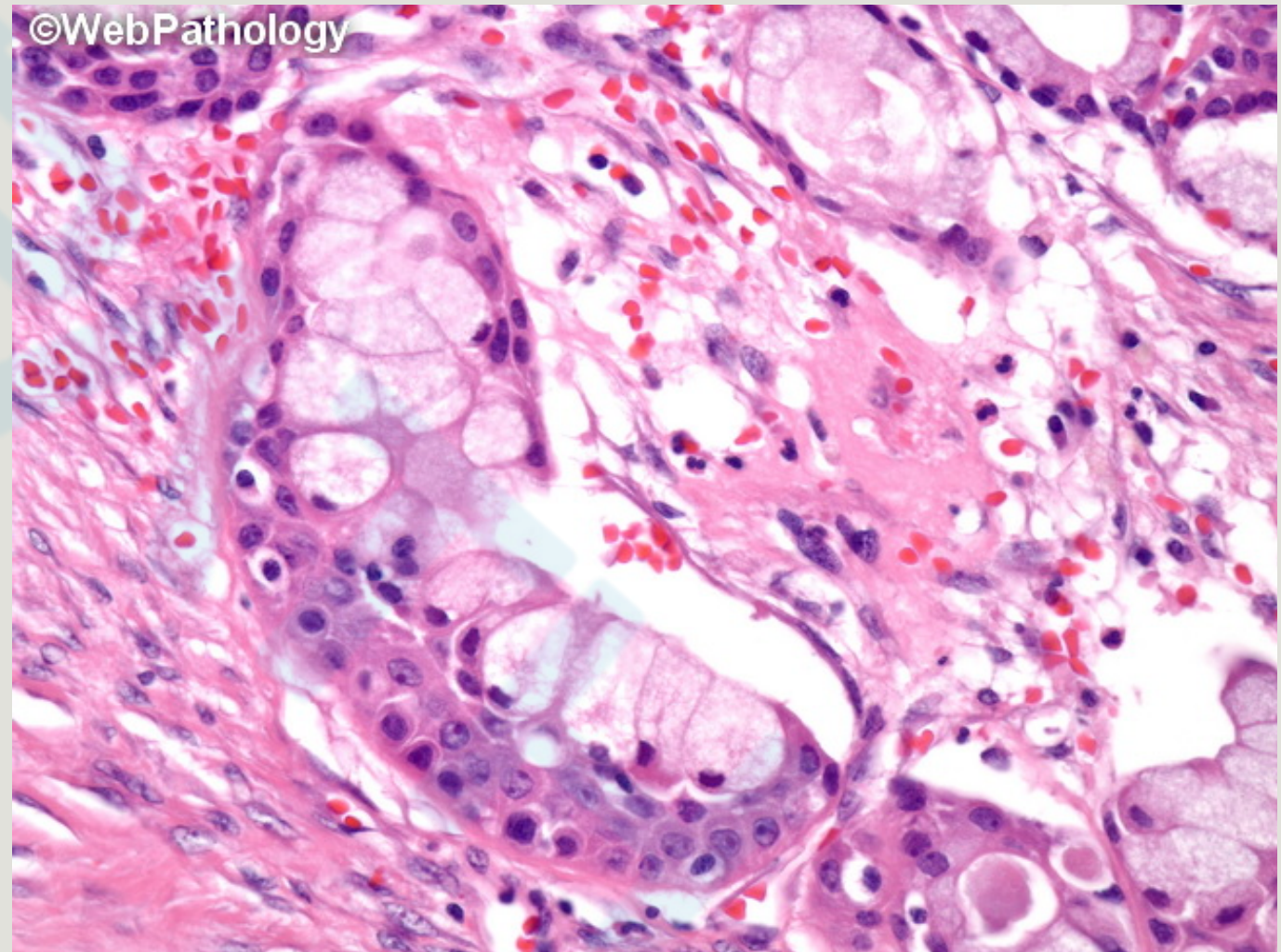
组织学形态：

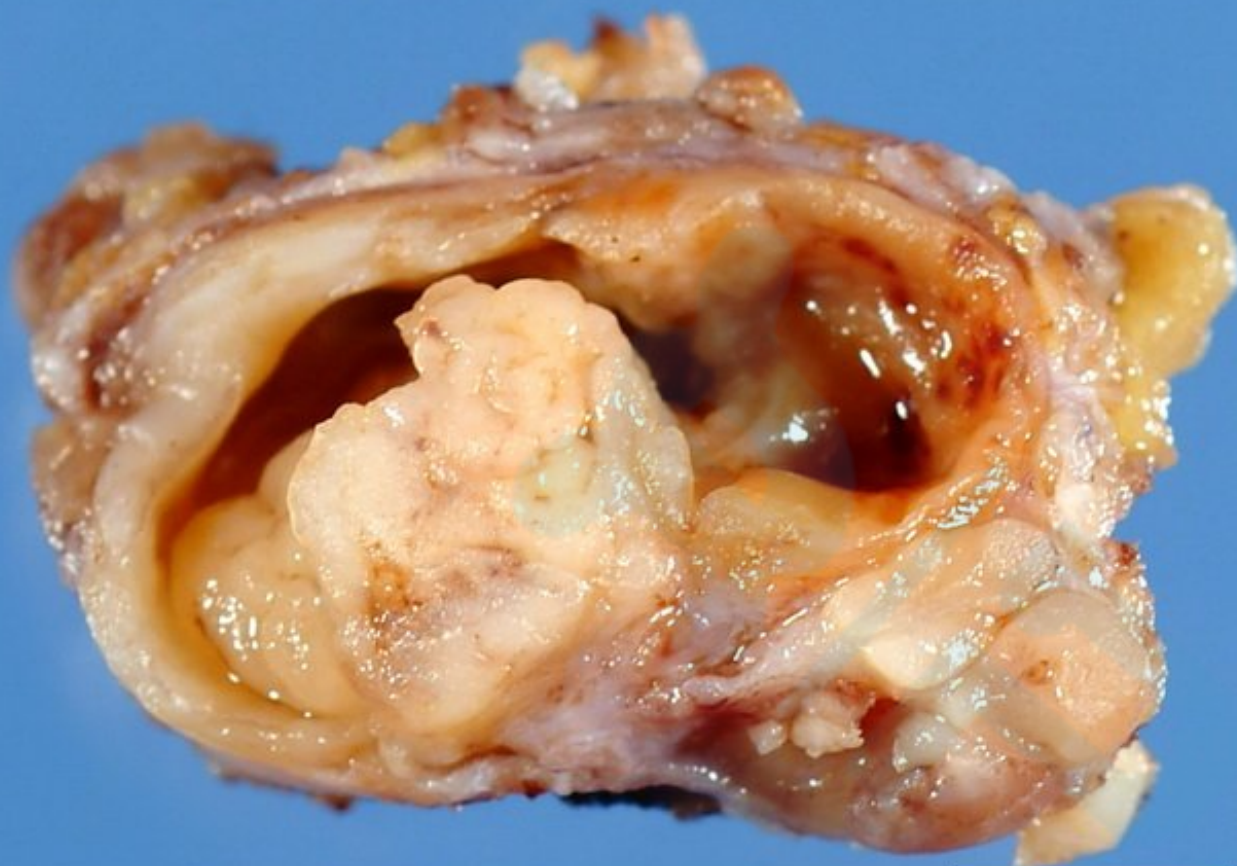
三种细胞

- 表皮样细胞
- 黏液细胞
- 中间型细胞

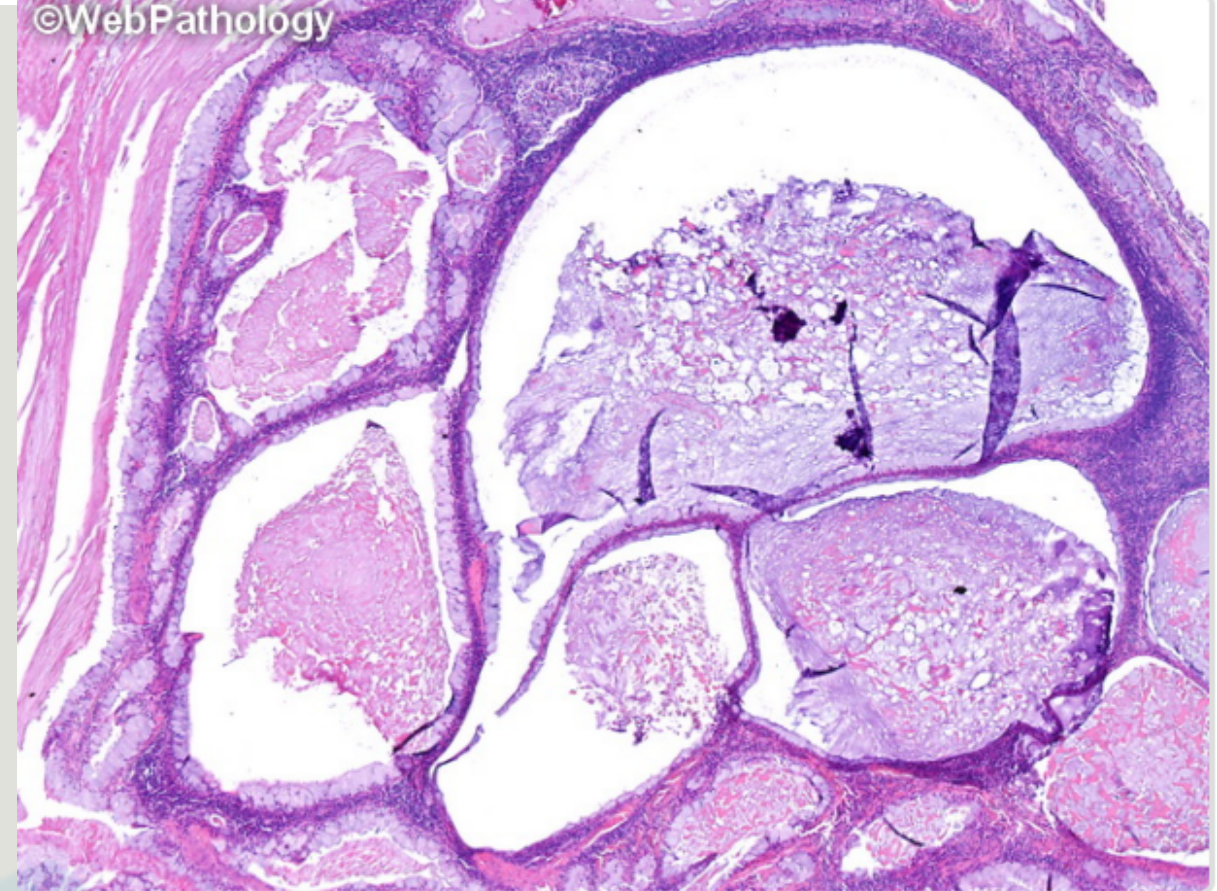
不同级别中，不同类型的细胞比例和所形成的结构不同

肿瘤通常为多囊性伴实性成分，有时以实性成分为主





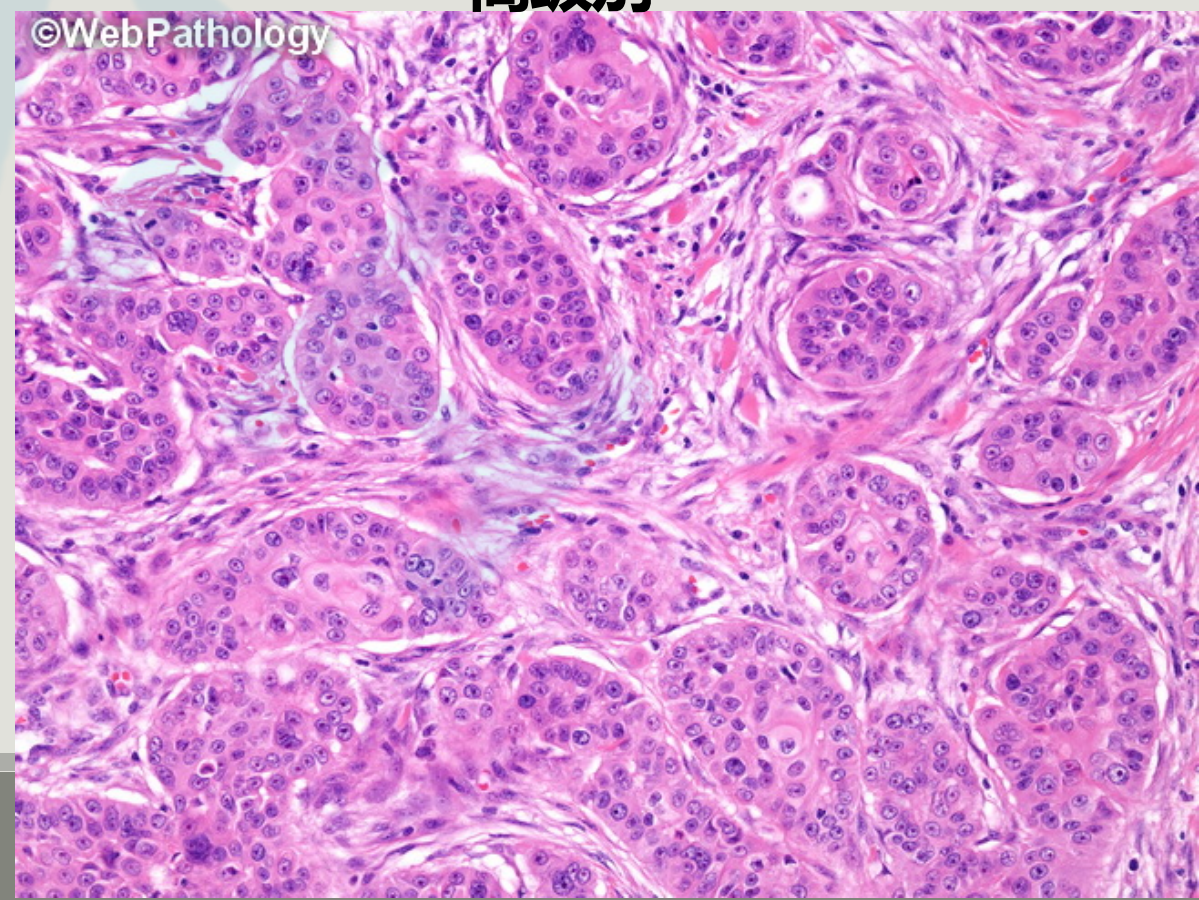
0.5 cm



低级别
高级别

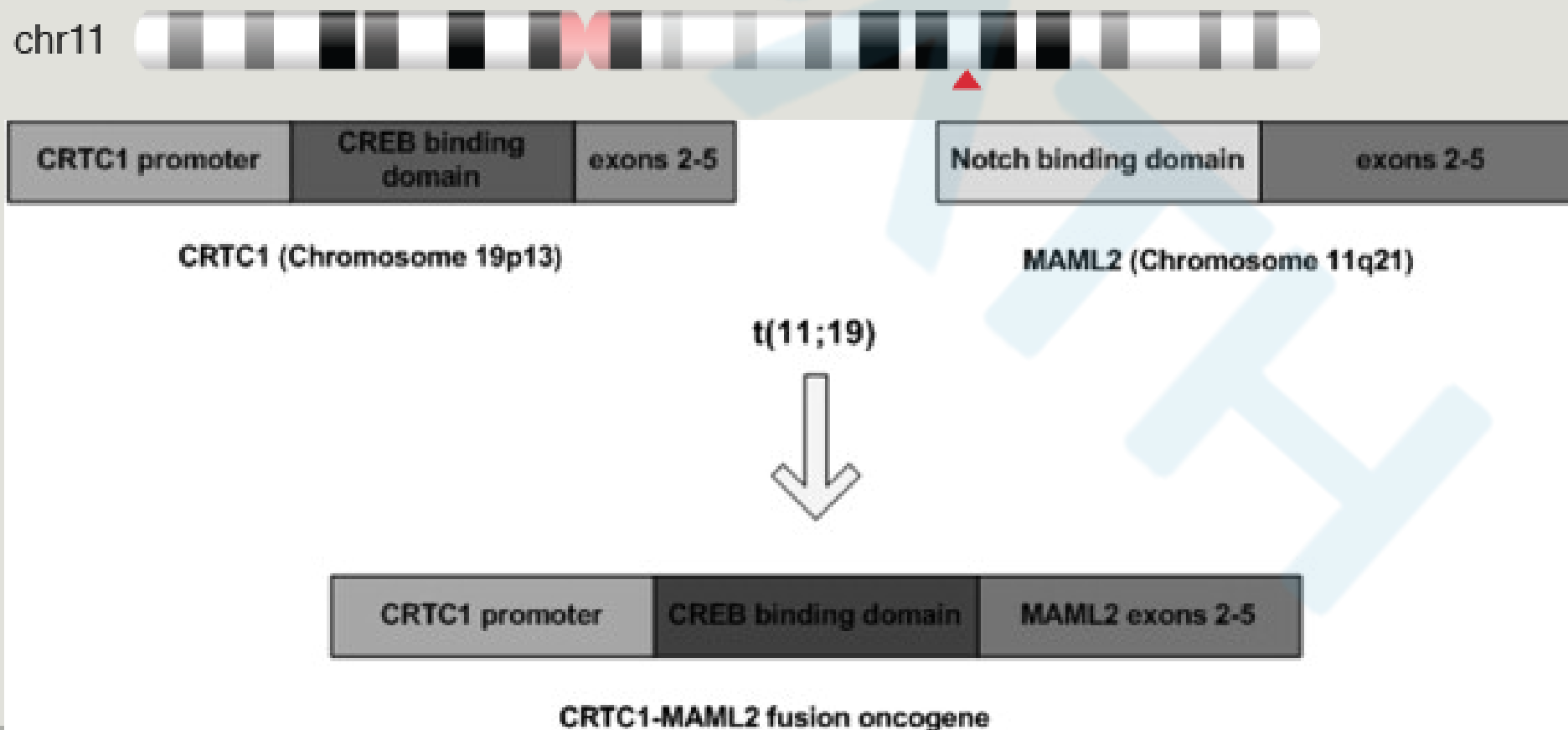


2.0 cm



黏液表皮样癌-遗传学改变

约75%-80%的MEC存在MAML2基因重排
MAML2 (mastermind-like 2)



MAML2基因重排检测的必要性

典型的MEC

- 单靠组织学形态就可诊断
- MAML2的检测是不必要的

组织学形态不典型的MEC

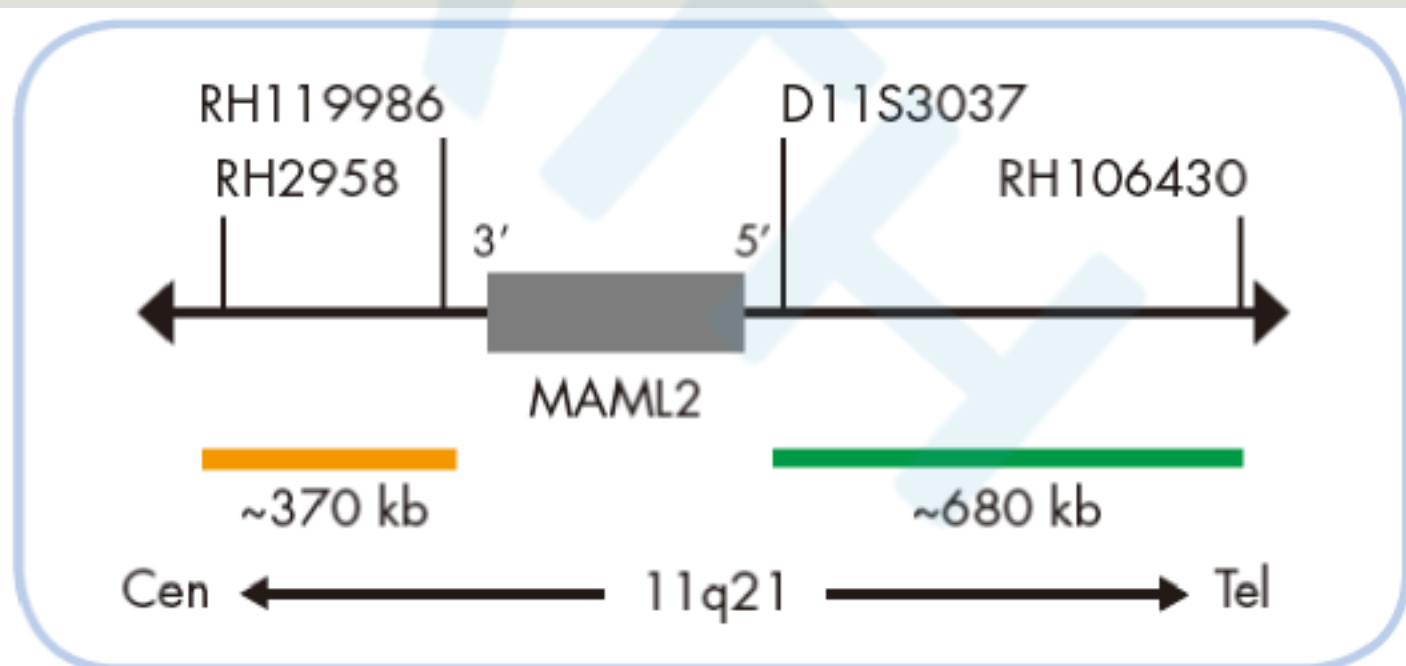
在纤毛样或Warthin样的MEC中，MAML2是否具有诊断价值，这就是本文作者的研究重点。

材料&方法

7例

高危HPV感染研究:以排除纤毛样HPV相关的癌

FISH: MAML2分离探针



SPEC MAML2 Probe map (not to scale).

结果

TABLE 1. Clinical and Pathologic Characteristics of Ciliated and Warthin-like Variants of Mucoepidermoid Carcinoma

Case	Variant	Age (y)	Sex	Presentation	Primary Tumor	Tumor Size (cm)	Submitted Preliminary Diagnosis	<i>MAML2</i> FISH
1	Ciliated	47	F	Cystic neck mass	Base of tongue	0.3	NA	+
2	Warthin-like	42	M	Parotid mass	Parotid gland	3.1	Lymphoepithelial cyst	+
3	Warthin-like	33	F	Parotid mass	Parotid gland	3.2	Warthin tumor	+
4	Warthin-like	53	F	Parotid mass	Parotid gland	3.3	NA	+
5	Warthin-like	51	M	Parotid mass	Parotid gland	NR	Warthin tumor	+
6	Warthin-like	51	F	Parotid mass	Parotid gland	1.2	N/A	+
7	Warthin-like	53	F	Parotid mass	Parotid gland	2.5	Warthin tumor	+

F indicates female; M, male; NA, not applicable; NR, not reported.

结果：Ciliated MEC病史

1例具有纤毛的黏液表皮样癌

- 女性，47岁
- 2013年发现右侧颈部一肿块，深达胸锁乳突肌，4年间，肿块从1.2cm增至4.2cm
- 手术切除后，病理显示为转移癌，建议查口咽部
- 后左侧舌根部发现直径约0.5cm-1cm肿块

结果：Ciliated MEC形态

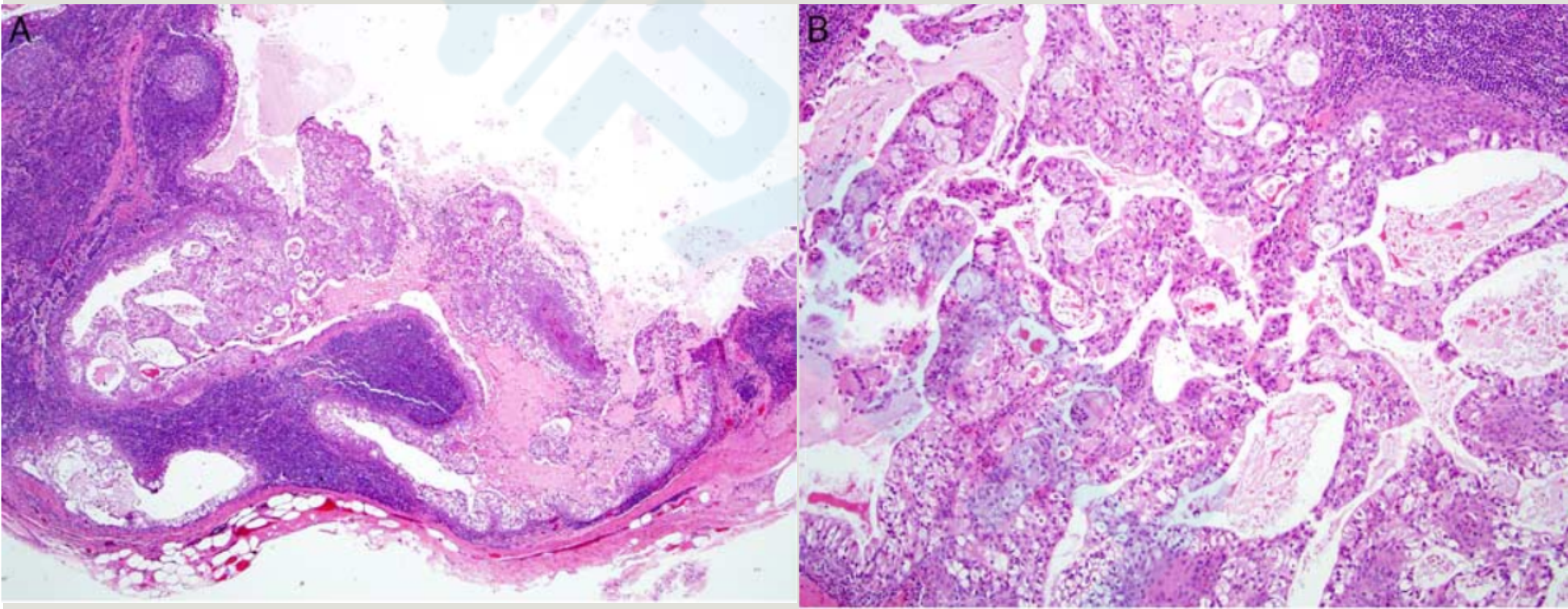


FIGURE 1. This ciliated mucoepidermoid carcinoma presented as a cystic metastasis to a lateral cervical lymph node (A). The cystic lining was comprised of variably proliferative papillae and glandular spaces (B). The tumor cells were predominantly intermediate cells with clear cytoplasm, admixed with squamoid and mucinous cells. The nuclei were very bland (C). Many of the tumor cells exhibited cilia (arrows) (D).

结果：Ciliated MEC形态

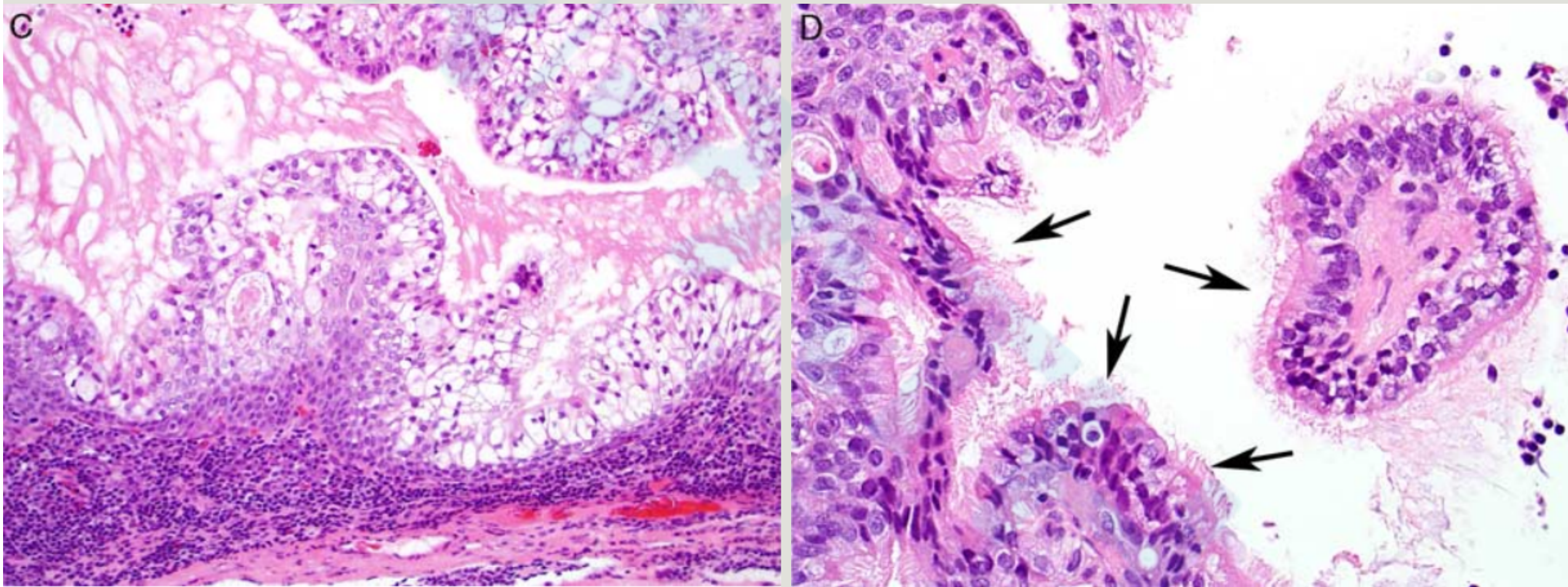


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结果：IHC及FISH

Ciliated MEC

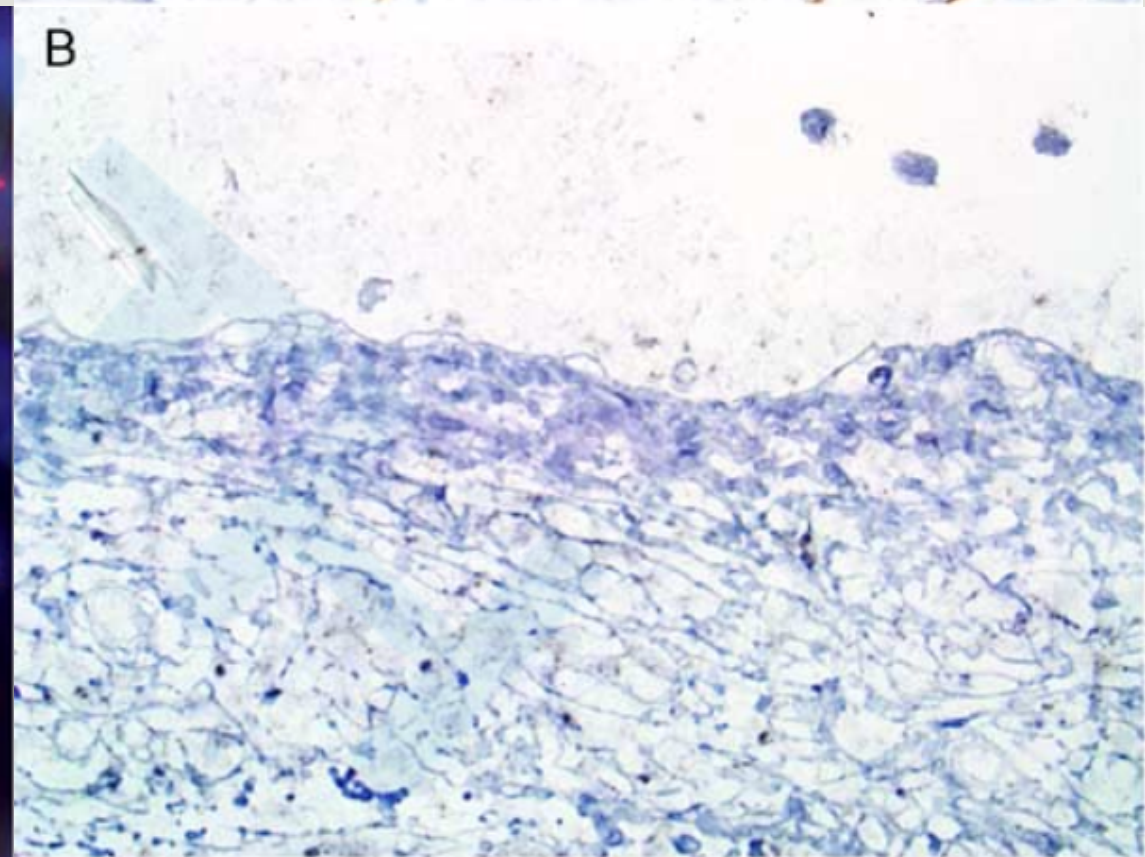
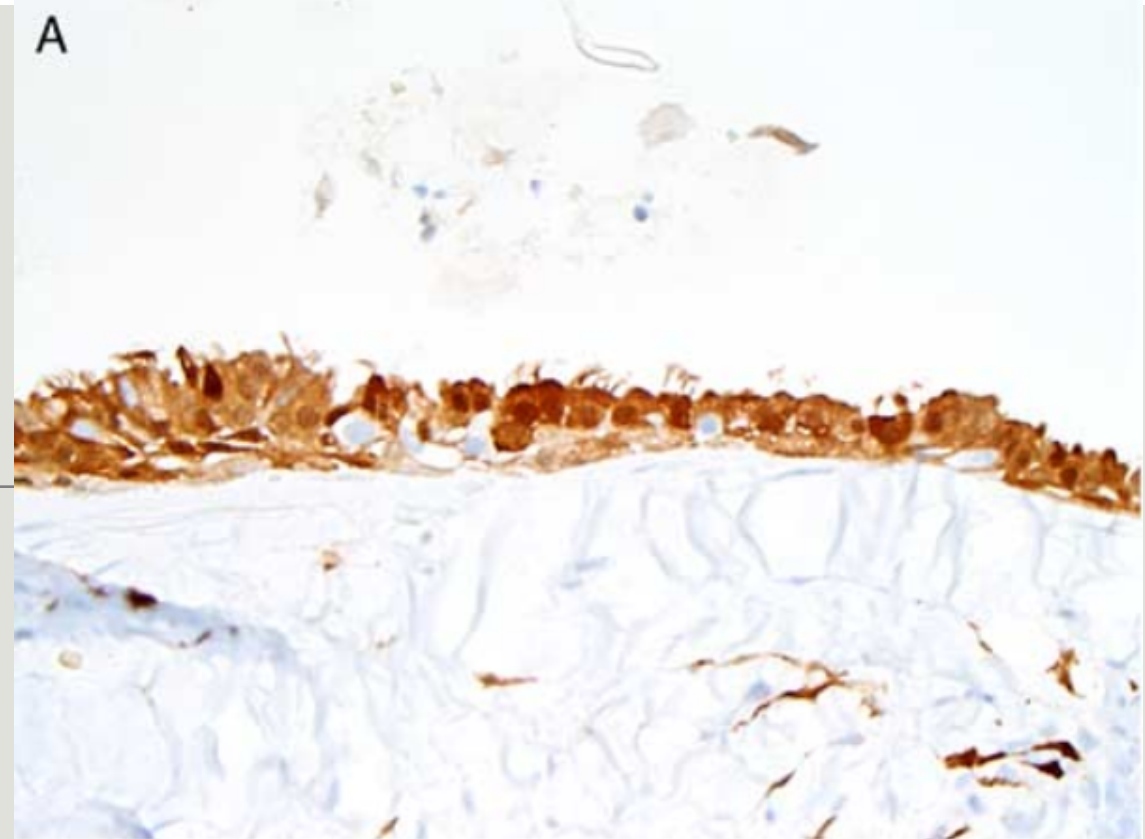
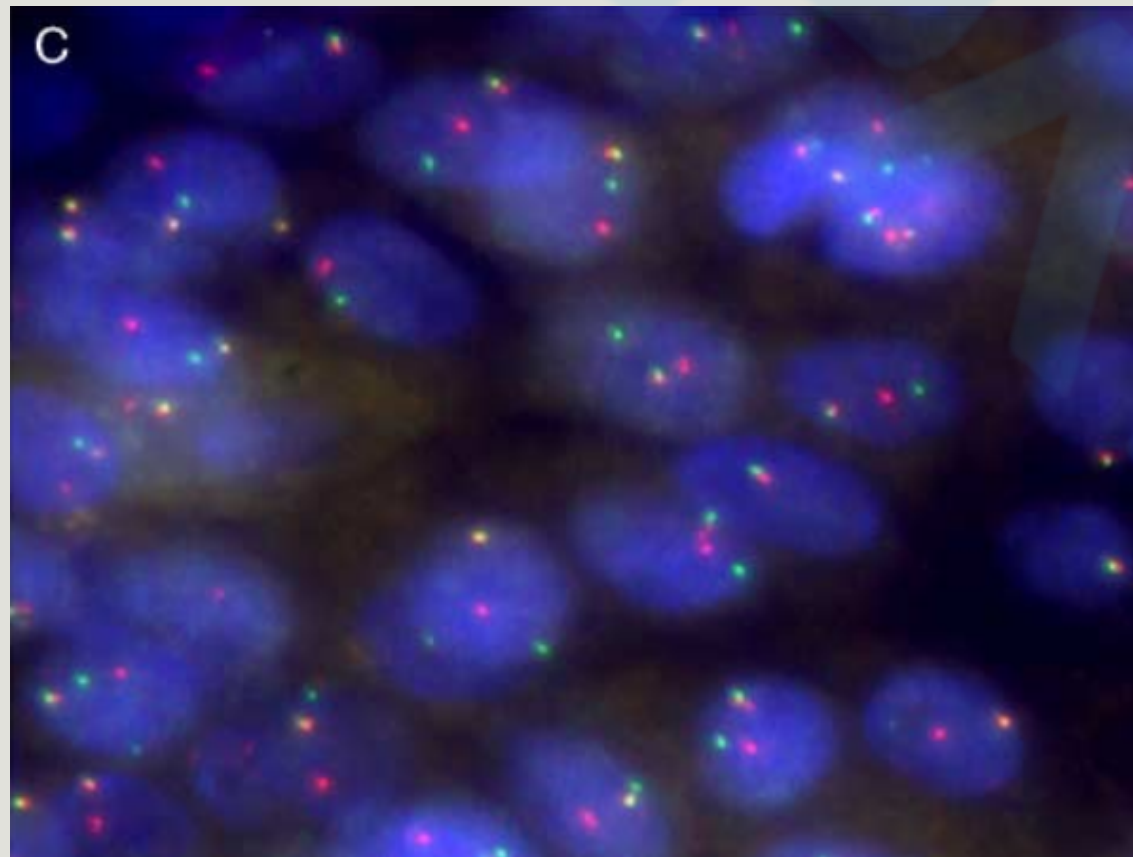


FIGURE 2. The ciliated mucoepidermoid carcinoma was positive for p16 by immunohistochemistry (A) but negative for high-risk HPV by RNA in situ hybridization (B). Break apart FISH for *MAML2* was positive, with one intact gene and one rearranged (C).

结果：Ciliated MEC的预后

病人做了舌根部肿瘤全切除，证实与颈部转移灶具有形同的组织学形态。

治疗后6个月随访，病人预后良好。

结果：Warthin-like MECs

6例类似腺淋巴瘤的黏液表皮样癌

- 均发生于腮腺
- 4名女性，2名男性
- 切除的5例病例中，肿瘤大小1.2cm-3.3cm（中位数，2.7cm）
- 4例被诊断为腺淋巴瘤，1例被诊断为淋巴上皮囊肿

结果：Warthin-like MECs形态

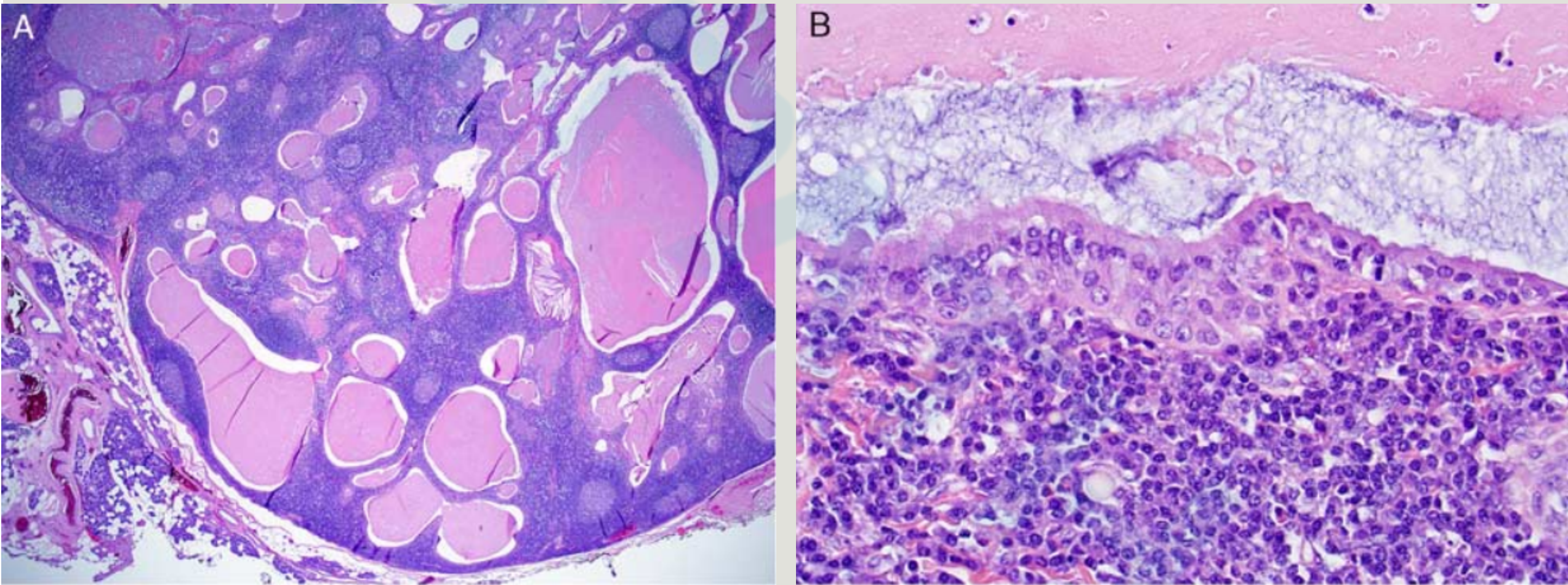


FIGURE 3. The Warthin-like mucoepidermoid carcinomas closely resemble Warthin tumor at low power. There are composed of cystically dilated glands and surrounded by a well-circumscribed cuff of chronic inflammation with germinal centers (A). The squamoid epithelial lining may be multilayered and eosinophilic, resembling that of Warthin tumor (B). Most cases had at least rare foci of more proliferative epithelium recognizable as conventional mucoepidermoid carcinoma (C). Break apart FISH for MAML2 was positive throughout the tumor (D).

结果：Warthin-like MECs形态及FISH

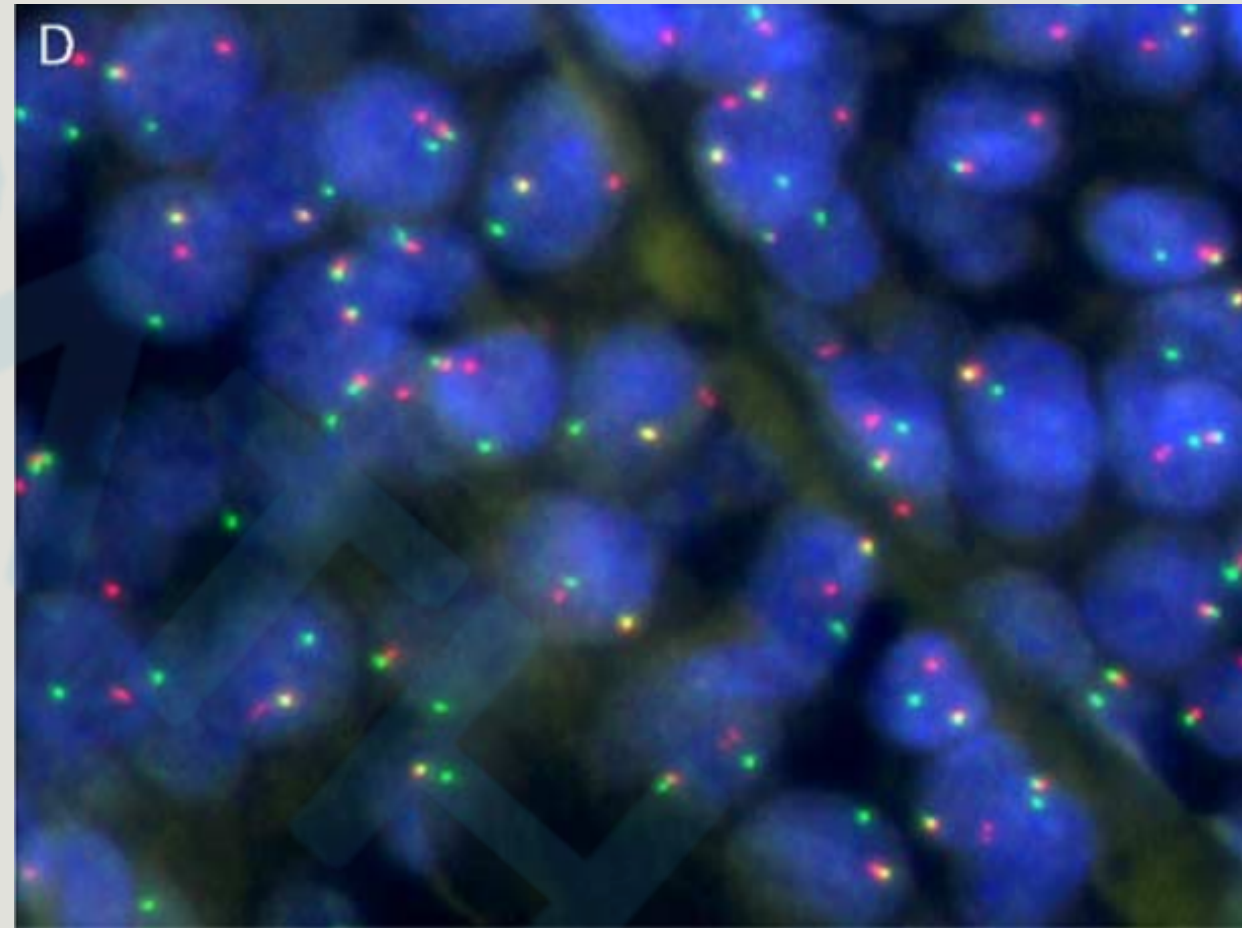
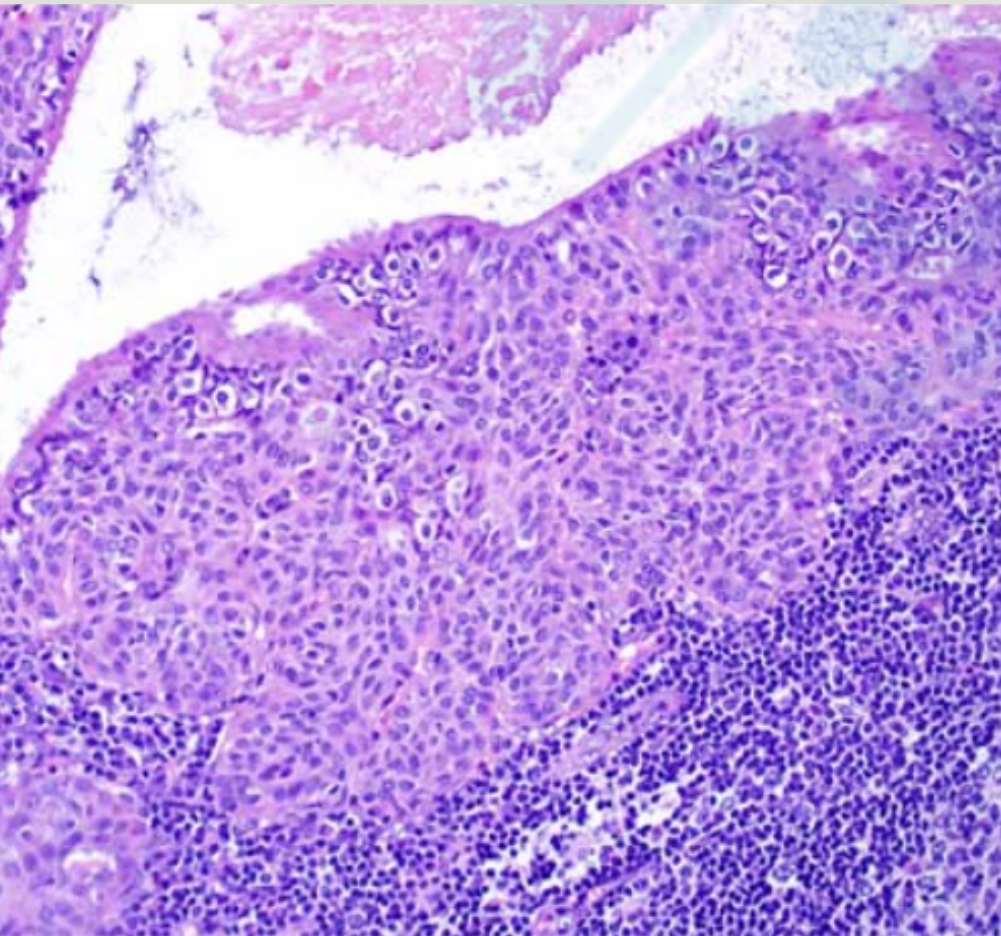


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结果：Warthin-like MECs预后

作者追查到2例内部病人的治疗随访信息

手术切除7个月和12个月随访，病人预后良好

讨论1

多种涎腺肿瘤具有遗传学改变

Salivary gland cancers	Fusion genes	Translocations
SC/MASC	<i>ETV6-NTRK3</i>	t(12;15)(p13;q25)
AdCC	<i>MYB-NFIB</i>	t(6;9)(q22-23;p23-24)
HCCC	<i>EWSR1-ATF1</i>	t(12;22)(q13;q12)
	<i>CRTC1-MAML2</i>	t(11;19)(q21;p13)
	<i>CRTC3-MAML2</i>	t(11;15)(q21;q26)
MEC	<i>EWSR1-POU5F1</i>	t(6;22)(p21;q12)

SC/MASC, secretory carcinoma/mammary analogue secretory carcinoma; AdCC, adenoid cystic carcinoma; HCCC, hyalinizing clear cell carcinoma; MEC, mucoepidermoid carcinoma.

讨论2

MEC组织学谱包括带有纤毛的变异种类，纤毛的出现增加了诊断的难度。

- 对于发生于颈部的具有纤毛结构的包块，低级别囊性MEC易与良性鳃裂囊肿相混淆，增加诊断难度。
- 具有纤毛的MEC易与同样具有纤毛结构的HPV相关的口咽癌相混淆

讨论2

具有纤毛的HPV相关性癌 v.s. MEC

相同之处

- 均易发生侧颈部淋巴结转移
- 免疫组化P16均阳性

鉴别点

- MAML2基因检测
- HPV直接检测（如原位杂交），而非p16免疫组化
- 在组织学水平，具有纤毛的HPV相关性癌，局灶具有纤毛及温和的囊性上皮，并且有明显的恶性非角化型鳞状细胞癌形态，而MEC罕见

讨论3：MEC&Warthin瘤

有报道，MEC有可能源自Warthin瘤，原因：

- Warthin瘤的内衬上皮通常发生鳞状上皮或/和黏液上皮化生，与MEC类似
- 早期报道，良性腺淋巴瘤存在MAML2转位，用于支持Warthin瘤是MEC前体这一观点

不同意见：在Warthin肿瘤中未检测到MAML2的转位，不支持腺淋巴瘤是MEC前体

Garcia 和Ishibashi发现，MAML2基因融合一直存在类似**Warthin**样MEC中，但与包含双层嗜酸性上皮的**Warthin**瘤不同，MEC没有双层嗜酸性上皮，并且存在典型的黏液表皮样癌成分，他们把这一类肿瘤成为“Warthin样的低级别MEC”

讨论3：MEC&Warthin瘤

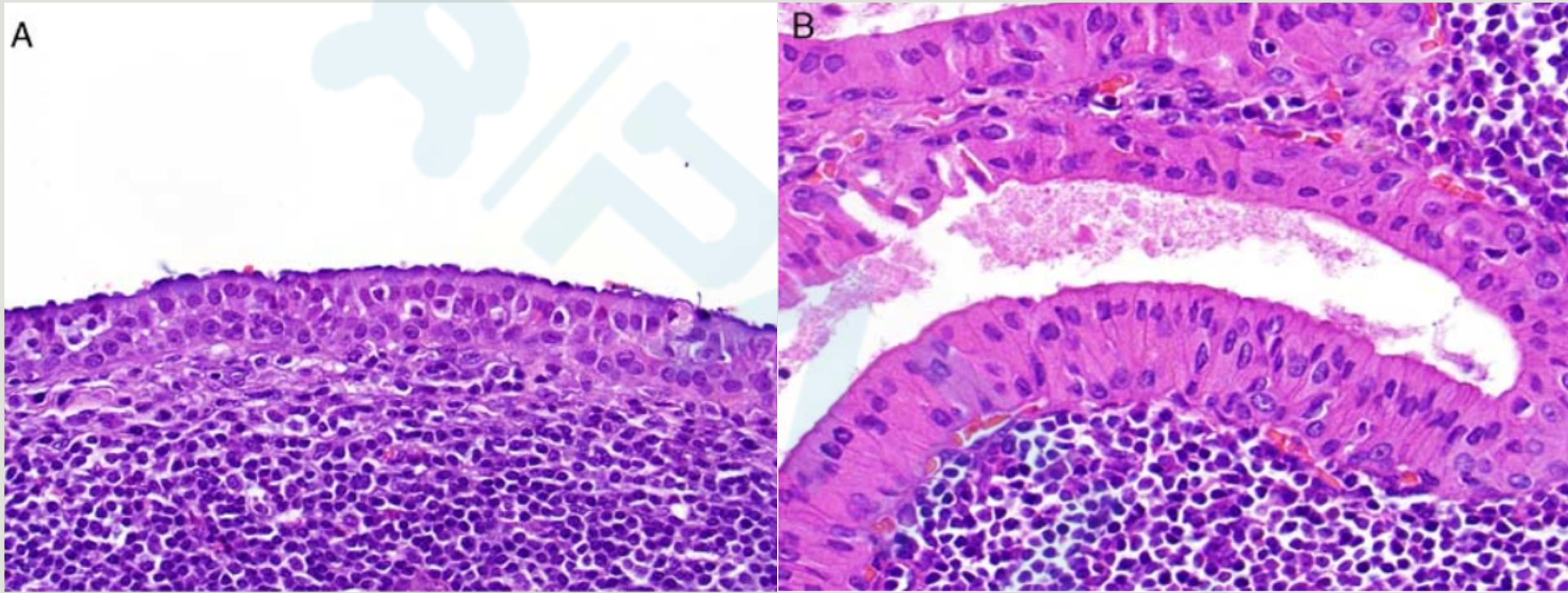


FIGURE 4. Comparison of the epithelial linings of Warthin-like mucoepidermoid carcinoma (A) and true Warthin tumor (B). The lining of Warthin-like mucoepidermoid carcinoma is more disorganized and less overtly oncocytic.

讨论3：MEC&Warthin瘤

- 在本文6例病例中，均有类似腺淋巴瘤的组织学形态，有大量扩张的腺腔结构及周围包绕的淋巴样间质。并且4例的最初诊断是良性肿瘤，其中3例是腺淋巴瘤。
- 但与腺淋巴瘤的双层肿瘤上皮相比，本文中病例内衬上皮通常是多层的。
- 6例病例中有5例存在典型的黏液表皮样癌形态，所有的上皮成分（典型和淋巴瘤样）均存在MAML2基因重排。

小结

- MAML2分子分析存在于所有的MEC组织学谱中，包括具有纤毛的和类似Warthin瘤的变异体。
- 对于颈部的具有纤毛的囊性病变，MAML2重排有助于MEC与发育囊肿及HPV相关性癌的鉴别。
- 对于Warthin样的MEC，MAML2重排有助于与具有黏液及鳞状上皮化生的真性Warthin瘤的鉴别。



THANKS