

Diagnostic Significance of HRAS Mutations in Epithelial-Myoepithelial Carcinomas Exhibiting a Broad Histopathologic Spectrum



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Epithelial-myoepithelial carcinomas, EMC

❖ 定义

- 一种发生于涎腺的恶性肿瘤，由内层的腺腔导管上皮与外层的肌上皮两种细胞组成

❖ ICD-O编码：8562/3

❖ 好发部位

大部分发生于腮腺、下颌下腺，少部分发生于鼻腔鼻窦、上腭

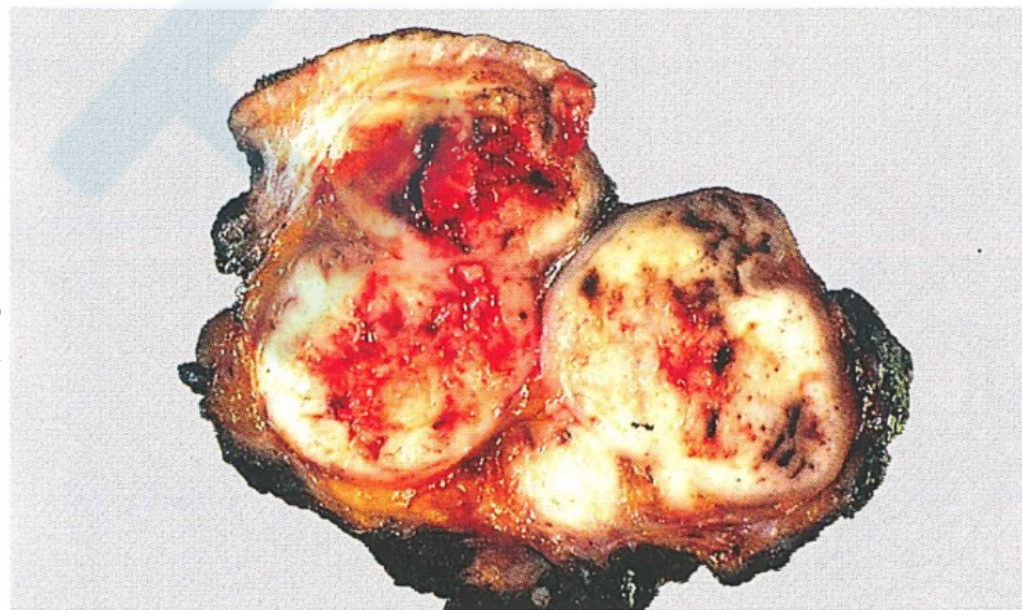
❖ 流行病学

- 少见的涎腺肿瘤，占涎腺恶性肿瘤 $<5\%$
- 好发于60-70岁女性

❖ 临床表现：缓慢生长的无痛性包块

❖ 大体特征

- 多结节状，质韧，呈推挤式边界
- 部分包膜，小部分（30%）出现囊性变



Epithelial-myoepithelial carcinomas, EMC

❖ 组织病理学

- 分叶状生长方式
- 双层上皮

❖ 经典型EMC

- 内层---小的腺腔导管细胞，胞浆嗜酸性
- 外层---多边形的肌上皮细胞，胞浆透亮

❖ 变异型EMC

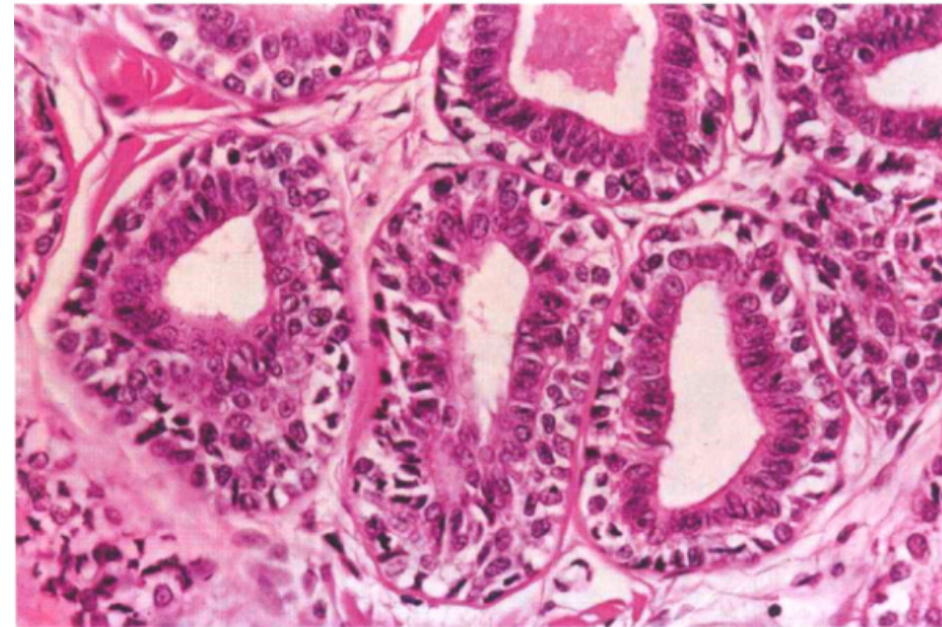
- 出现筛状、基底细胞样排列，Verocay样生长，乳头状/囊性结构
- 伴有皮脂腺分化、嗜酸细胞化生/顶浆分泌、双层细胞透明变、鳞化
- 高级别转化、砂粒体

❖ 免疫组化

- 低分子量角蛋白在腺腔导管上皮高表达，肌上皮成分低表达
- 肌上皮成分高表达肌上皮标记，如：SMA，HHF35，P63，calponin

❖ 预后

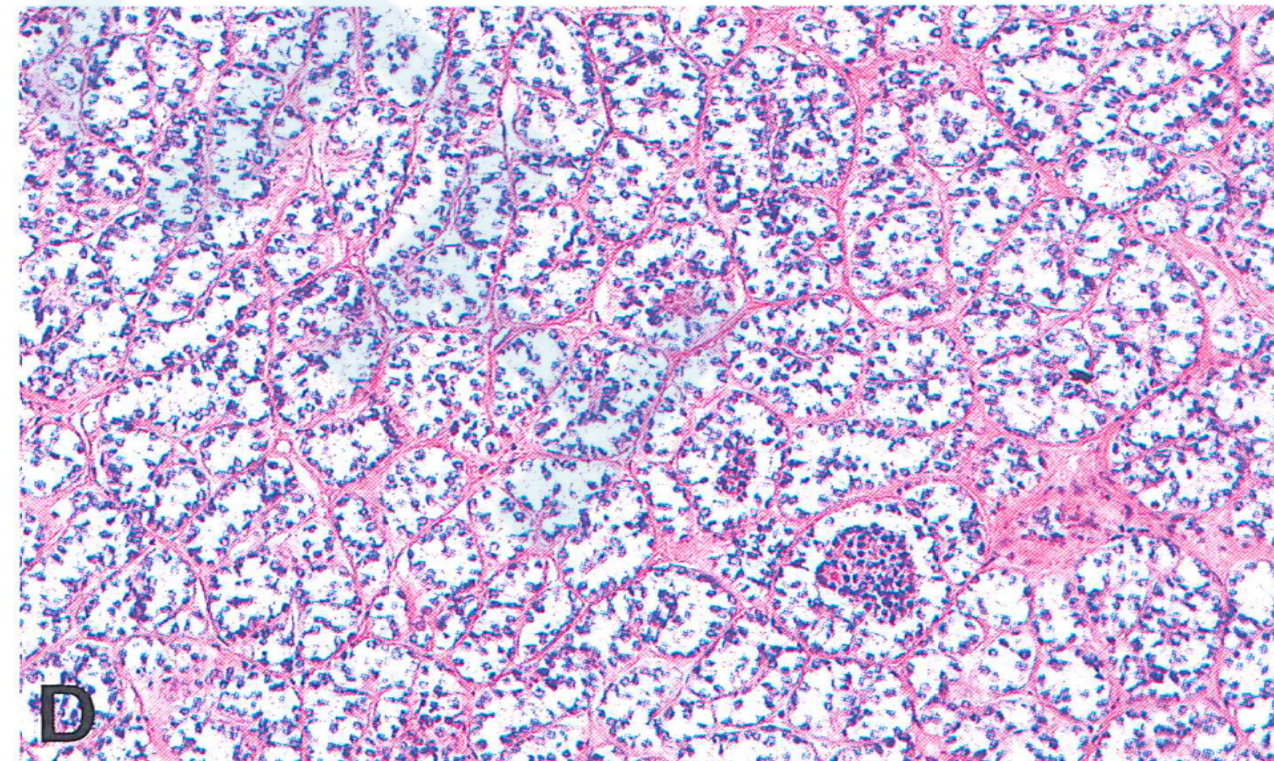
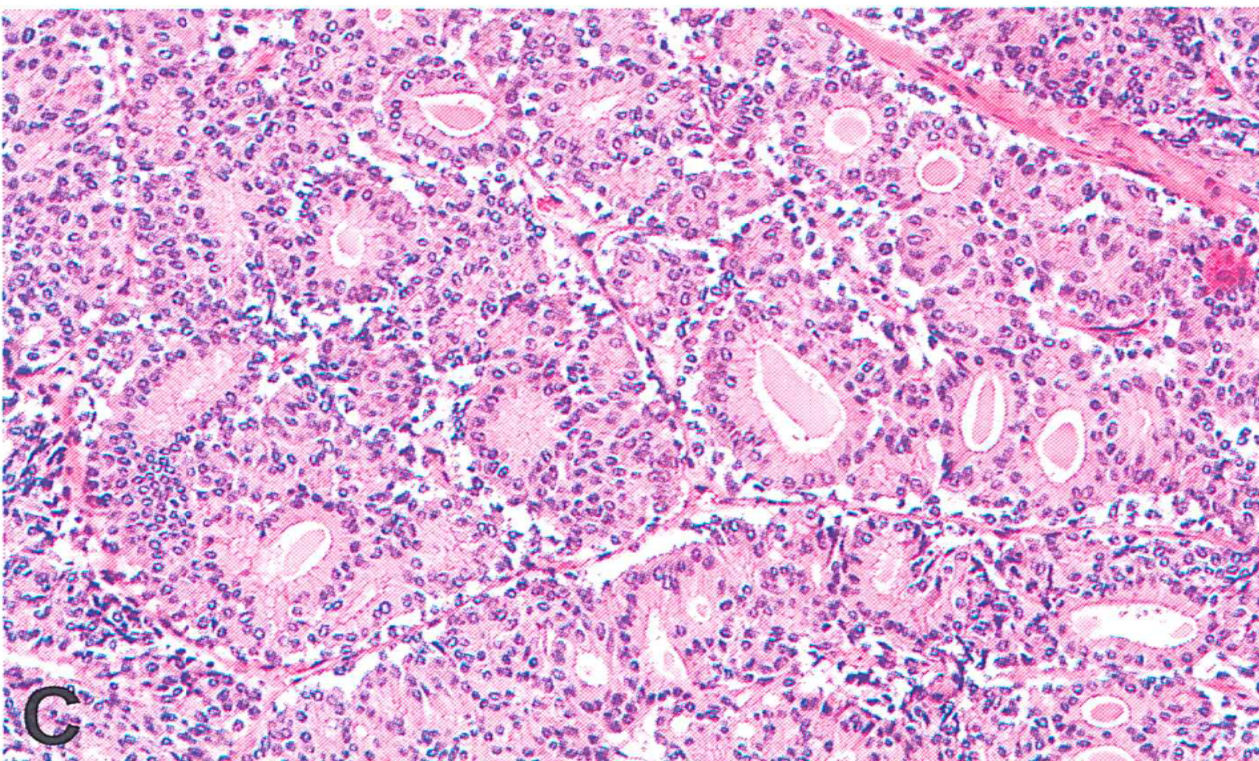
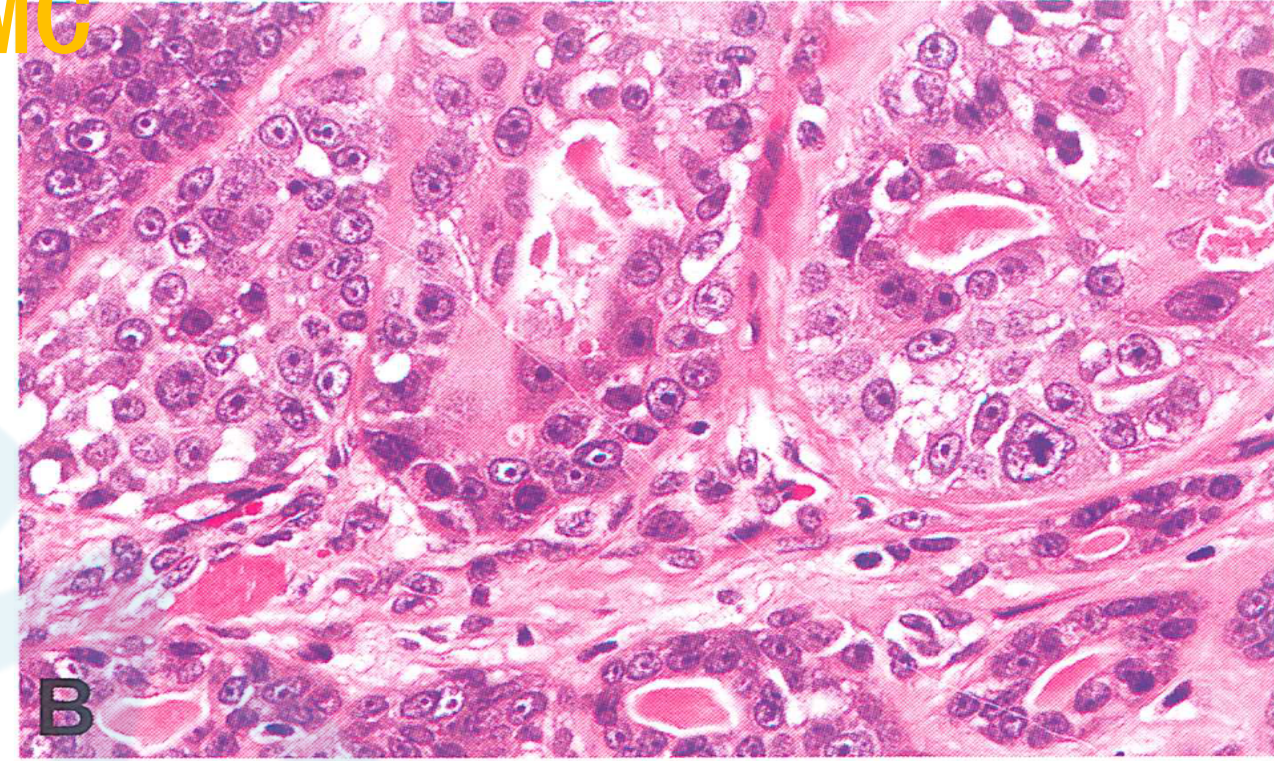
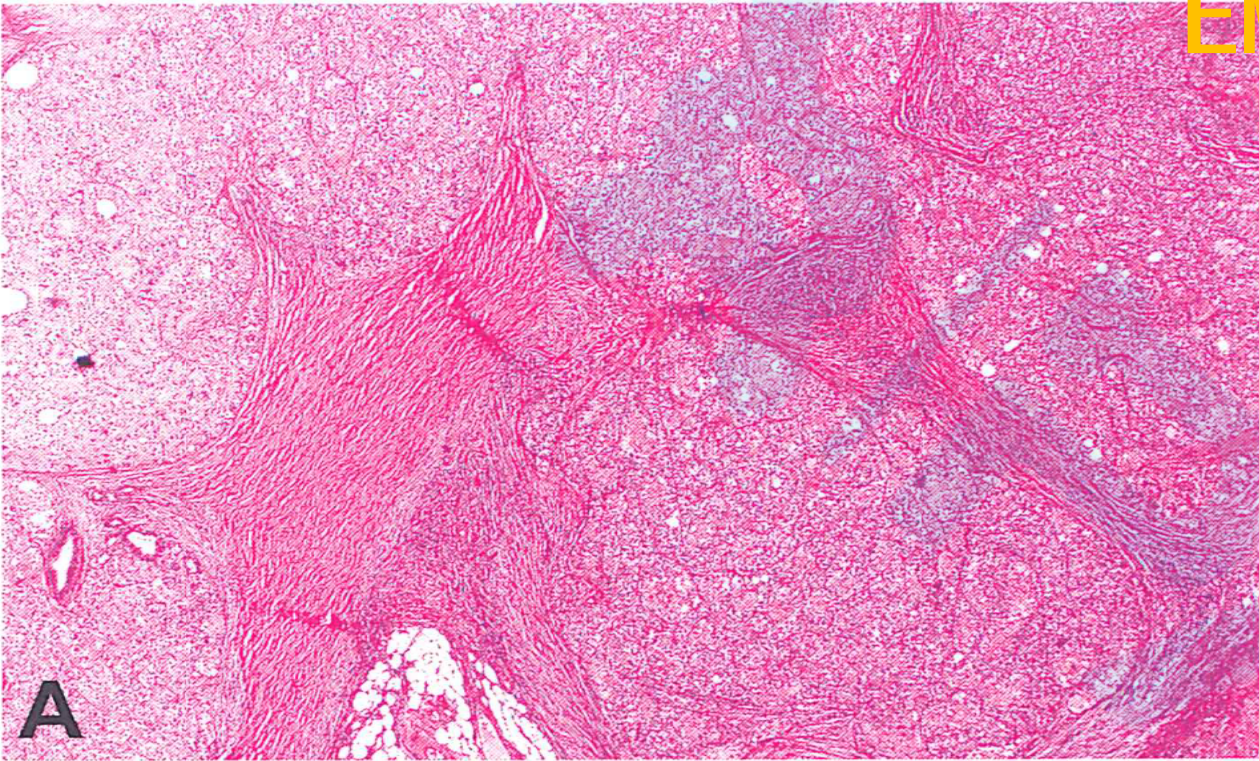
- 通常为低度恶性，局部复发率30-50%，淋巴结转移15-20%，远处转移罕见
- 5年生存率80-94%，10年生存率72-90%
- 预后因素包括肿瘤大小、边界情况、高级别转化、肌上皮间变、坏死、淋巴管侵犯



上皮-肌上皮癌

Epithelial-myoepithelial carcinomas,

EMC



鉴别诊断

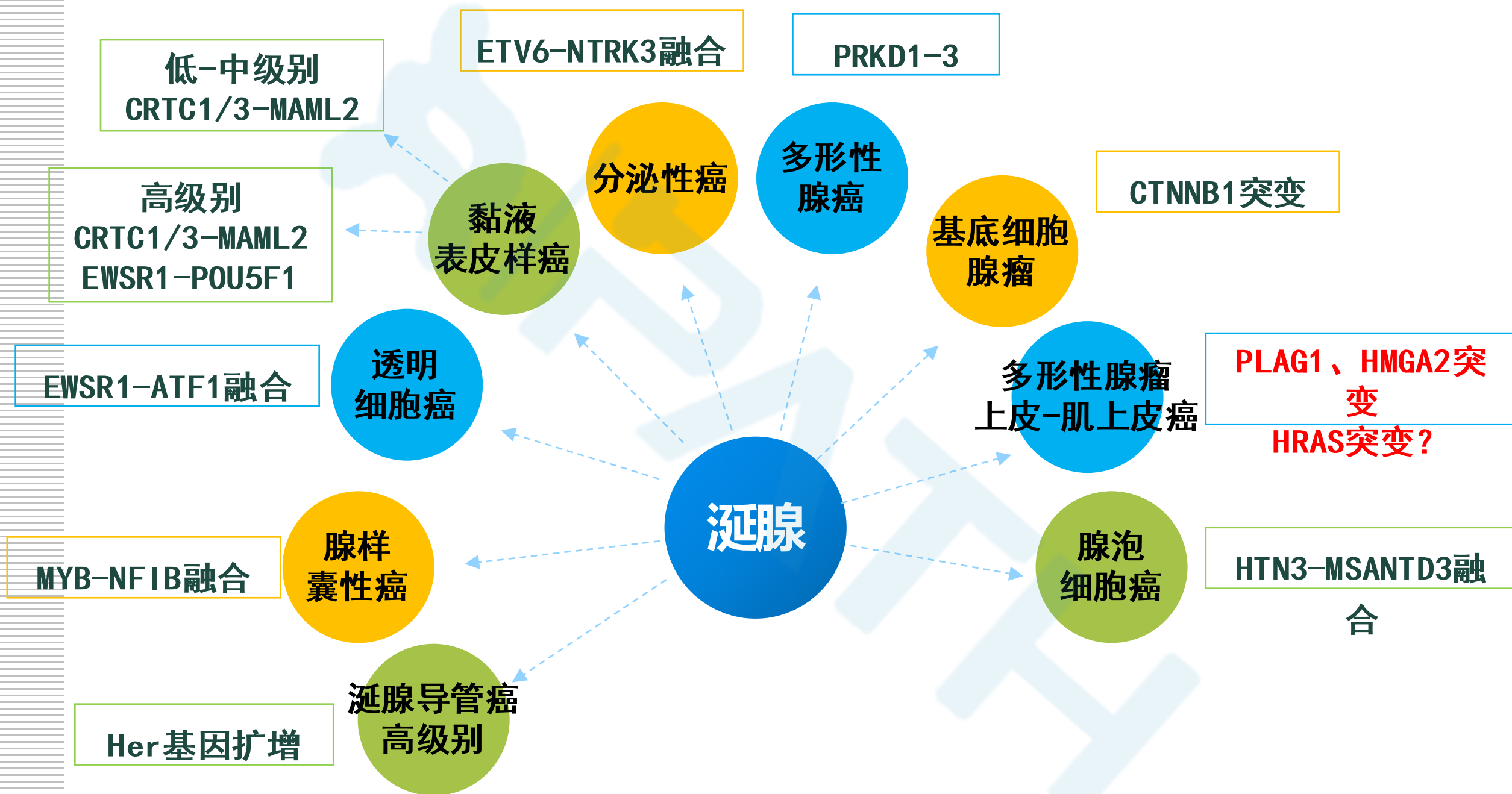
具有透明细胞涎腺肿瘤的鉴别诊断

肿 瘤	组织学特征	免疫组化特征	组织化学特征
腺泡细胞癌	圆形或卵圆形透明细胞，境界清楚，片状分布，“人工假像”，不存在“纯的”透明腺泡细胞癌	CK(+), p63(-), Calponin(-), SMA(-), S100(-)	PAS (-), AB (-) 黏液卡红 (-)
黏液表皮样癌	透明细胞常伴有经典黏液表皮样癌成份，可能不存在“纯的”透明细胞型黏液表皮样癌	CK(+), p63(+/-), Calponin(-), SMA(-), S100(-)	黏液卡红 (+) PAS-D (+)
玻璃样透明细胞癌	主要由透明细胞构成，伴分散的胞浆嗜酸的细胞，多数间质为粗大玻璃样胶原	CK (+) , p63 (+) , 肌上皮标记缺失	PAS-D (-) 黏液卡红 (-)
上皮-肌上皮癌	两种细胞成份：内层管腔上皮立方或柱状，胞浆嗜酸，外层肌上皮胞浆透明，境界清楚	上皮CK/EMA(+), S100(+/-), 肌上皮细胞均表达其标记	上皮/肌上皮/管腔内物质均 PAS-D(+),黏液卡红 (-)
嗜酸细胞腺瘤，透明细胞亚型	透明细胞部分或全部取代嗜酸性细胞，内含糖原，也有人工假象，	CK/EMA(+), 肌上皮标记(-)	透明细胞PAS-D(+) 嗜酸细胞PTAH(+)
透明细胞鳞状细胞癌	不同程度异型细胞形成团巢和条索结构，浸润生长，可见角化、细胞间桥等结构	CK, p63, CK5/6 阳性, 肌上皮标记均阴性	PAS-D (-) 黏液卡红 (-)

鉴别诊断

肿瘤境界清楚，无明确浸润

组织学特征	特殊染色	免疫组化	分子检测	诊断
丰富腺管和肌上皮成份，黏液软骨样间质	黏液样基质 AB+	上皮和肌上皮标记广泛+	PLAG1/HMG A2基因重排	多形性腺瘤
腺泡或囊性乳头结构，丰富嗜碱性酶原颗粒	PAS+, PASD+ 黏液卡红-	CK+/p63-/S100- /SMA-/DOG-1+ /Calponin-		腺泡细胞癌
囊状/微囊状，细胞形态一致，空泡状胞浆和嗜酸性分泌物	分泌物PAS+, PASD+, 黏液 卡红-	CK+/S100+/ MUC4+ Mamma+/ p63-/SMA-	ETV6- NTRK3融合 基因	乳腺样分泌性癌
浸润性边缘和细胞异型性，梭形/浆细胞样/上皮样和透明细胞	基底膜样物质 PAS+, PASD+ 黏液卡红-	CK+/p63+/SMA- S100-/Calponin-		肌上皮瘤/癌或 上皮-肌上皮癌
小涎腺发生,分叶状透明细胞,有玻璃样胶质分隔	PSA+, PASD-	CK+/p63+/SMA- S100-/Calponin-	EWSR1- ATF1融合 基因	玻璃样透明 细胞癌
小涎腺发生,细胞形态地致,结构多样		CK+, 无明确 肌上皮标记+		多形性低度恶性腺癌



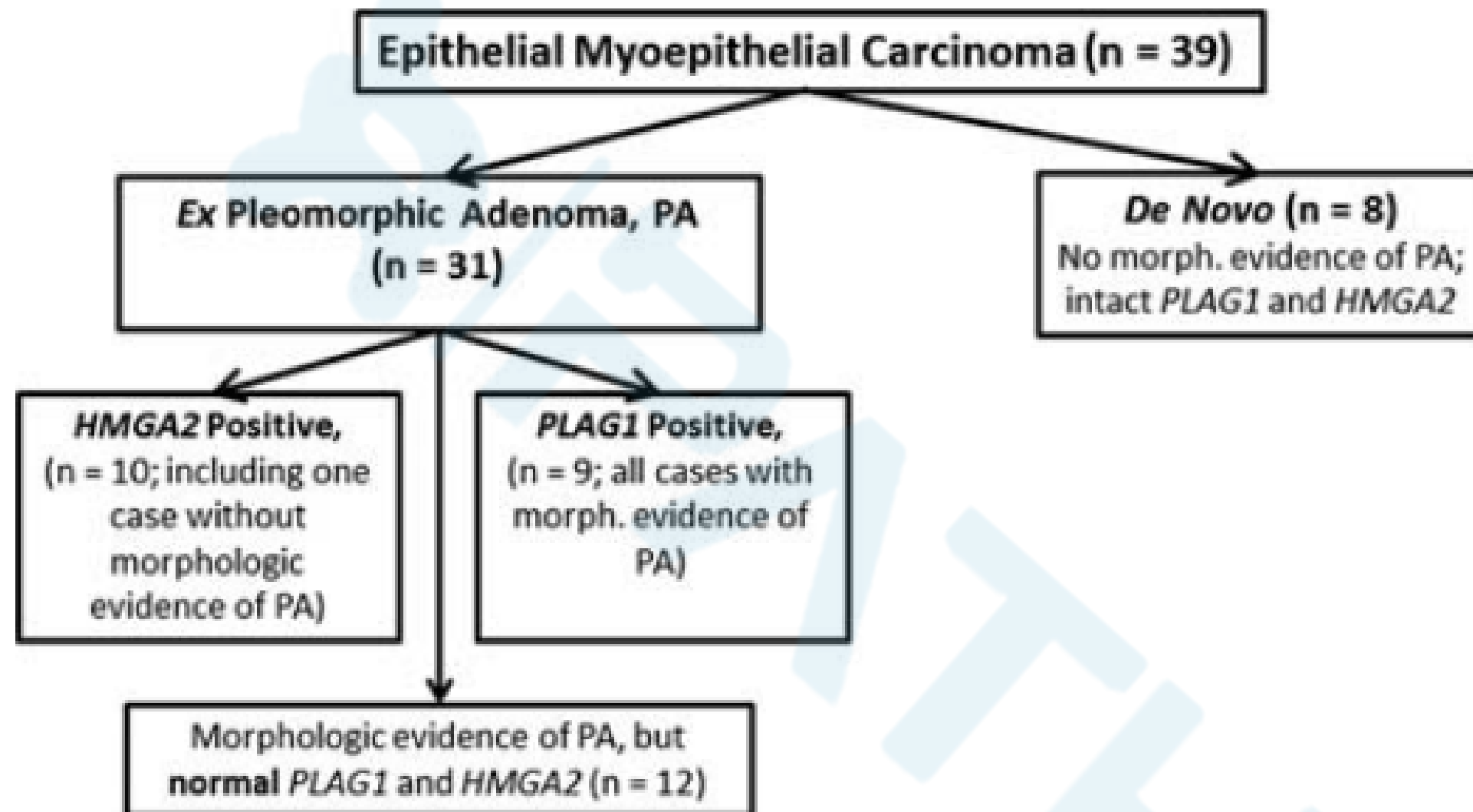


FIGURE 7. Subsets of EMCA: relationship between the morphologic evidence of PA and *PLAG1* or *HMGA2* status.

涎腺肿瘤的高级别转化

- ❖ 又称为肿瘤“去分化”，是指高分化的低级别肿瘤失去了原有的形态特征，转化为高级别肿瘤，在肿瘤中可见到低级别和高级别病变区域毗邻，但又截然分界的状态
- ❖ 可发生高级别转化的肿瘤：腺样囊性癌，黏液表皮样癌，腺泡细胞癌，肌上皮癌，上皮-肌上皮癌，多形性（低度恶性）腺癌，透明细胞癌，（乳腺样）分泌性癌
- ❖ 高级别转化区域：完全失去了低级别病变的结构特征，完全由间变肿瘤细胞伴大片坏死构成，形态上类似“低分化癌”或“未分化癌”，同时部分或完全丧失了原有的免疫组化表型和基因表型

HRAS 突变

- ❖ 上皮源性肿瘤常被激活的两个信号通路：RAS-RAF-MEK-MAPK 和PI3K-Akt，导致肿瘤的增殖、浸润、迁移和血管形成
- ❖ RAS基因家族主要包括KRAS、NRAS和HRAS 3个基因
- ❖ 多种肿瘤中均可发生RAS基因突变，常见的激活方式点突变、表达量升高以及插入/转位突变等
- ❖ KRAS突变主要发生在结直肠癌、胆管癌、胰腺癌、肺癌和子宫内膜癌中，NRAS突变常见于甲状腺滤泡性肿瘤、黑色素瘤和结直肠癌，HRAS突变多发于甲状腺乳头状癌和膀胱癌
- ❖ 有文献报道在涎腺EMC中存在HRAS基因突变，但其突变率和特异性及与不同组织学形态的关系还未见描述

MATERIALS AND METHODS

❖ Patients and Histologic Review

- 3 expert pathologists (M.U., M.N., and T.N.) 2017 WHO
- 87 EMC cases (institutional and consultation)
- Histomorphologic evaluation
 - specific histologic variants or features
 - histologic origin (de novo or ex PA)
 - necrosis, lymphovascular and perineural invasion,
 - nuclear grade, myoepithelial:ductal cell ratio, mitotic count, and Ki-67 labeling index
 - mild and moderate atypia as low-grade atypia and severe as high-grade atypia
- ACC (n=19), PA (n=12), BCA (n=14), BCAC (n=6), myoepithelial carcinoma (n=10), and myoepithelioma (n=1)

❖ Mutation Analysis

- HRAS (exons 2 and 3), AKT1 (exon 2), PIK3CA (exons 9 and 20), BRAF (exon 15), CTNNB1 (exon 3), and KRAS (exons 2 and 3)

❖ Statistical Analysis

RESULTS

❖ Clinicopathologic Findings

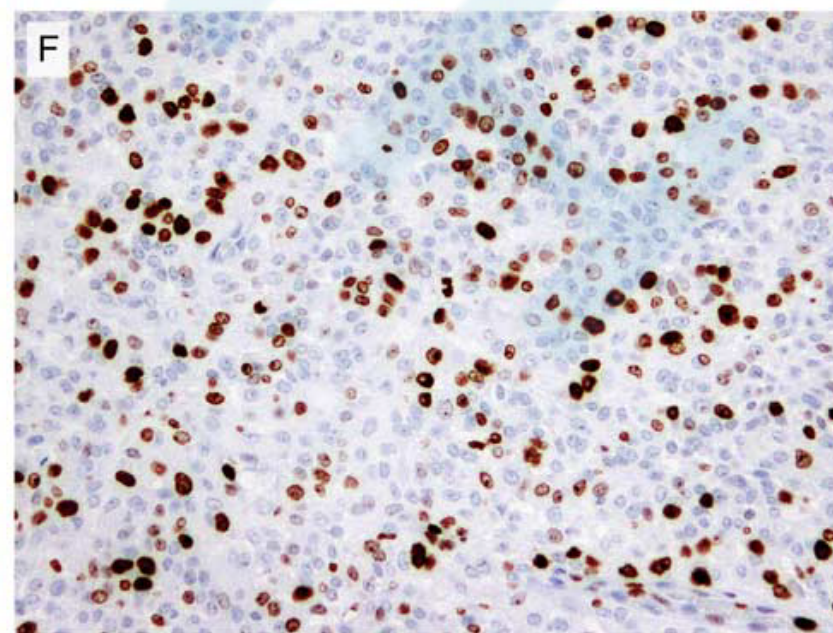
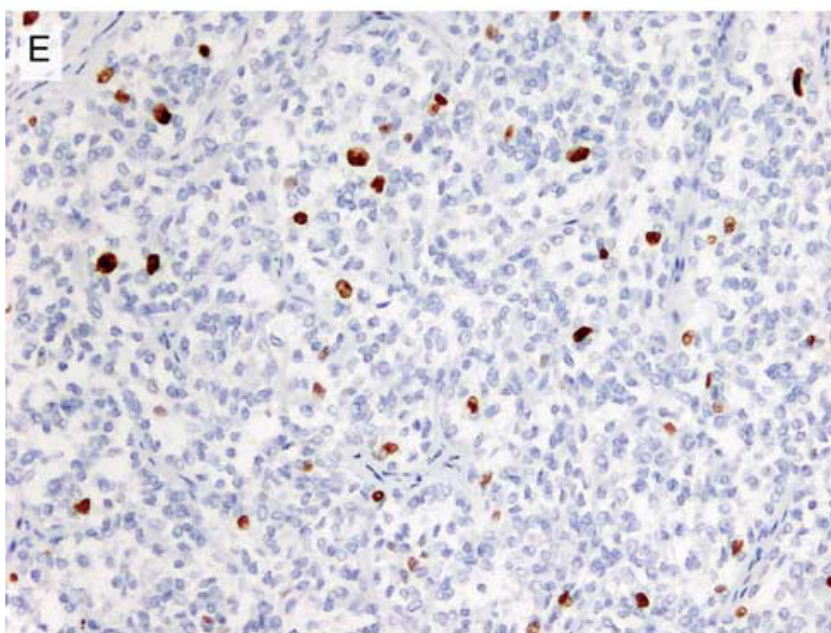
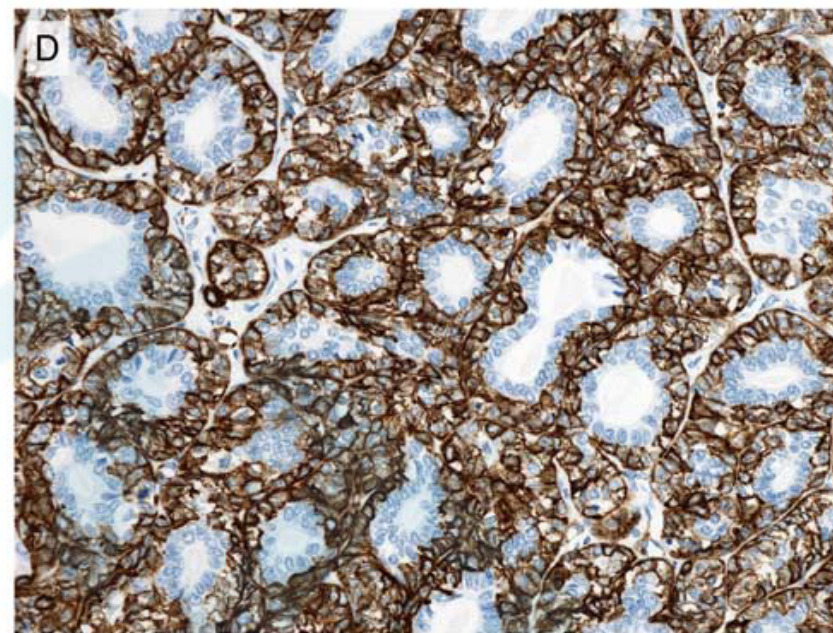
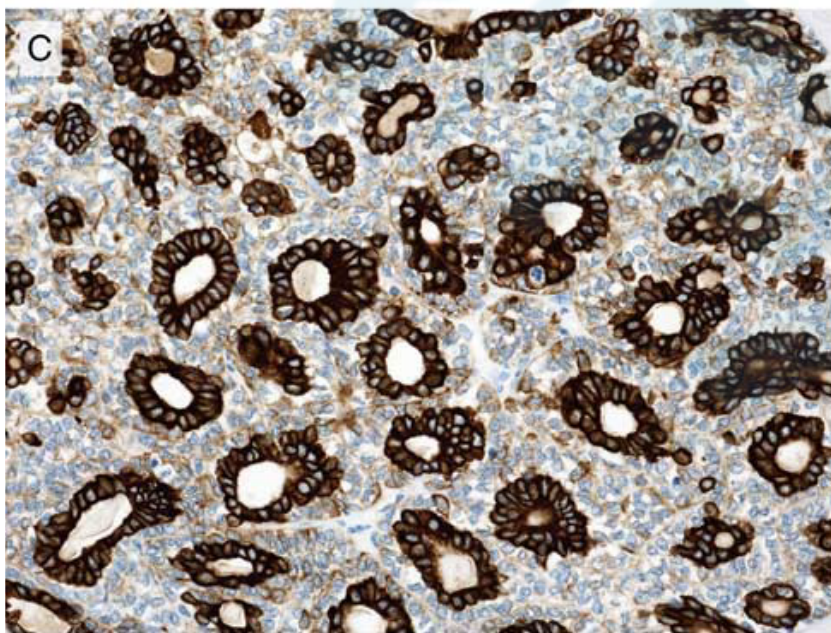
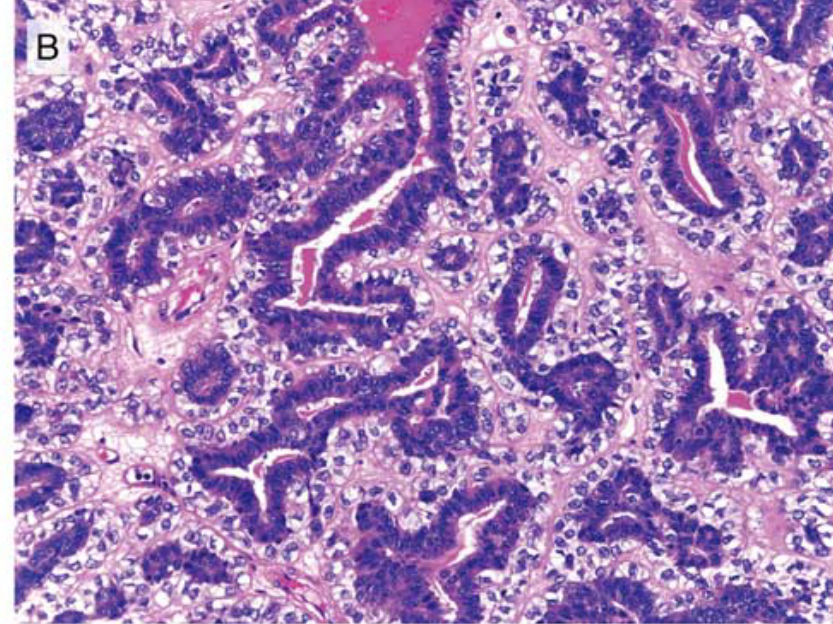
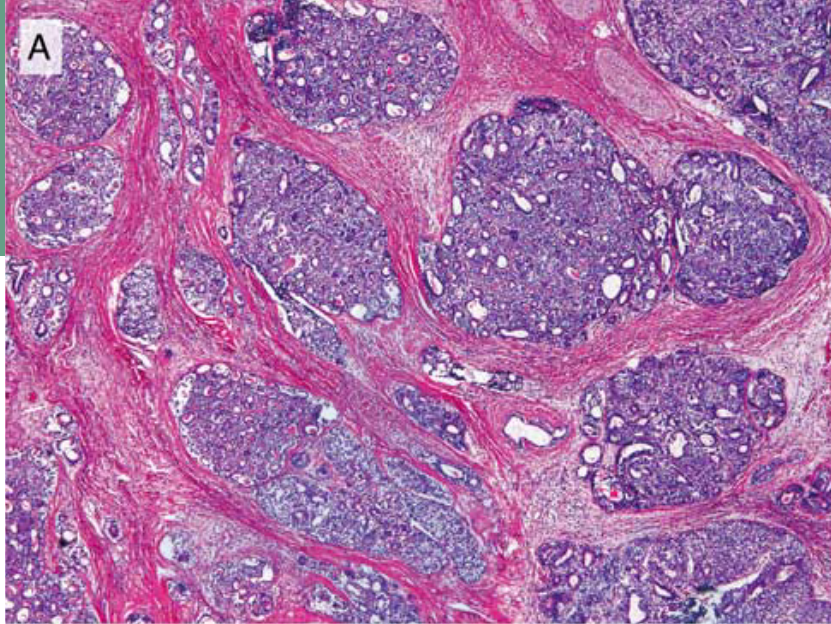
TABLE 1. Clinical Characteristics of Patients With Epithelial-Myoepithelial Carcinoma

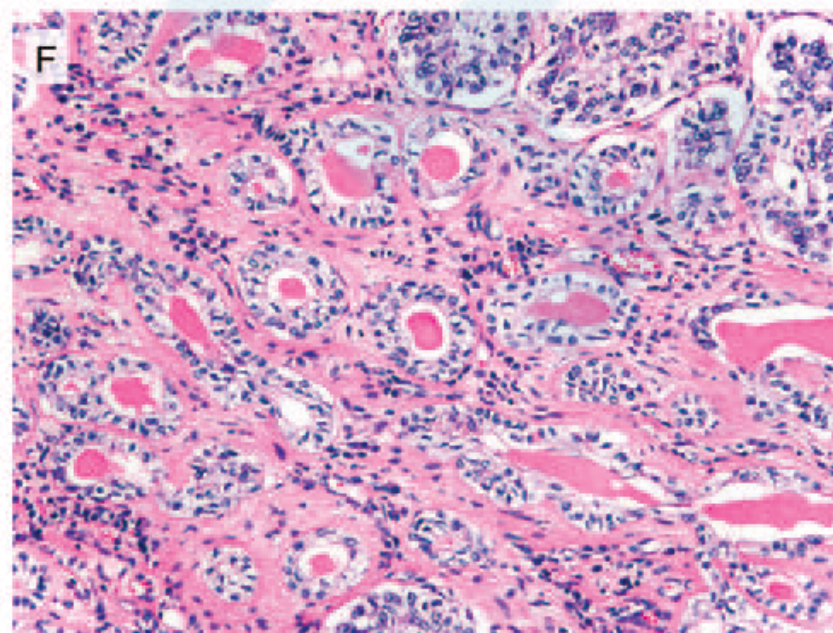
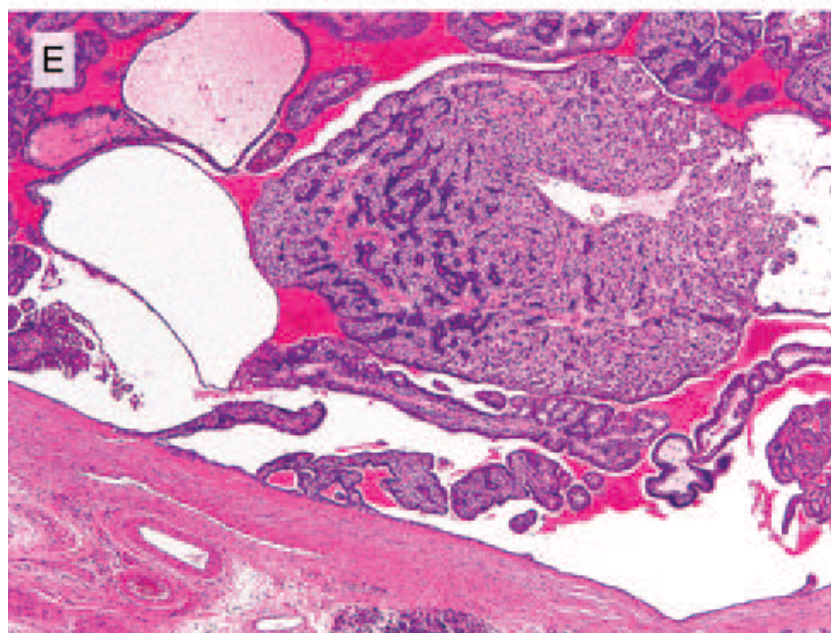
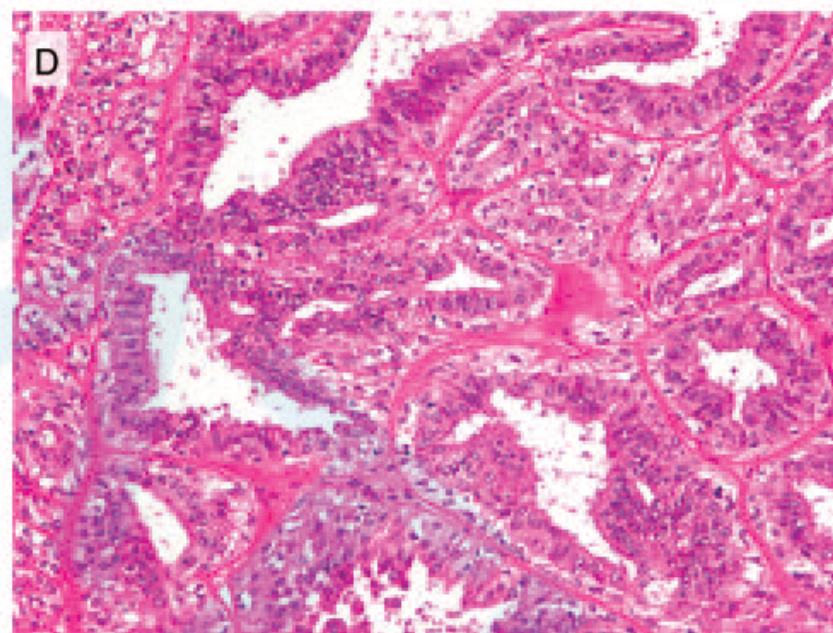
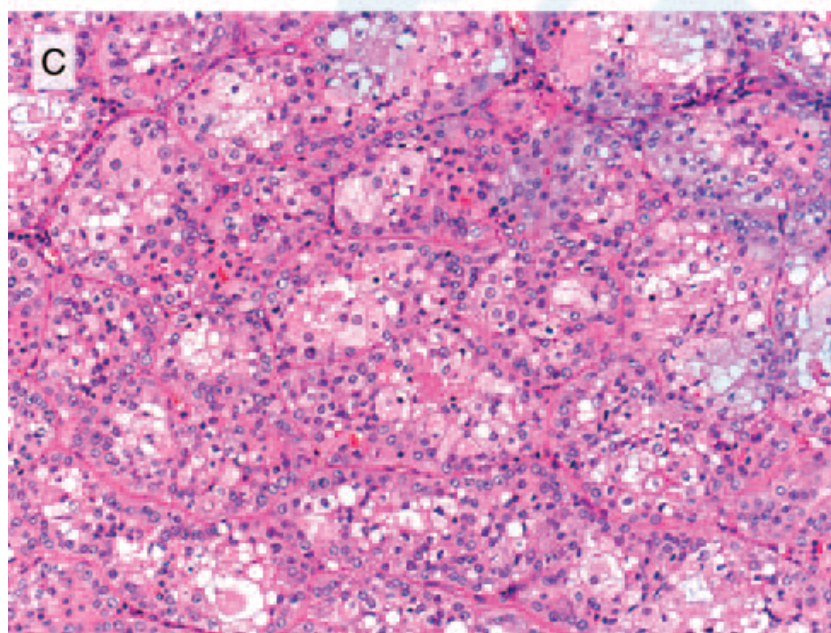
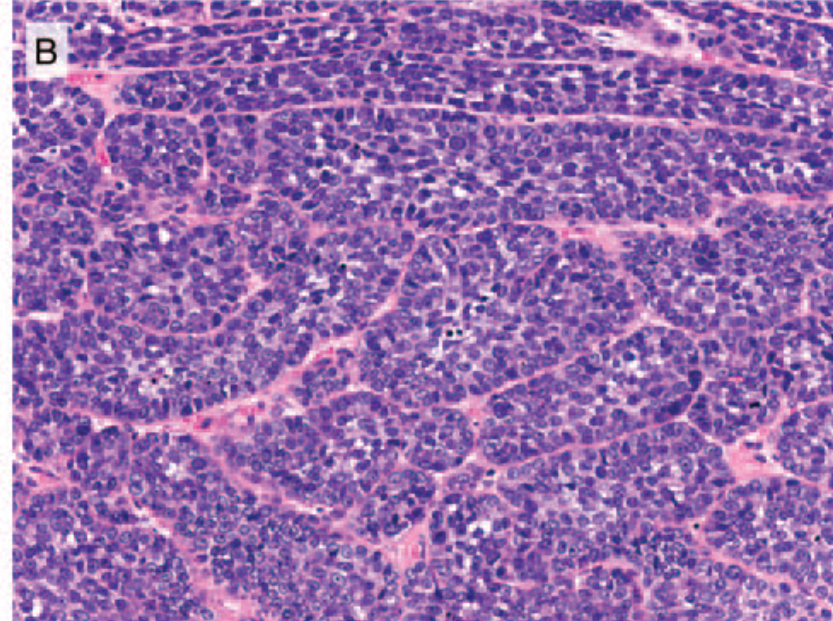
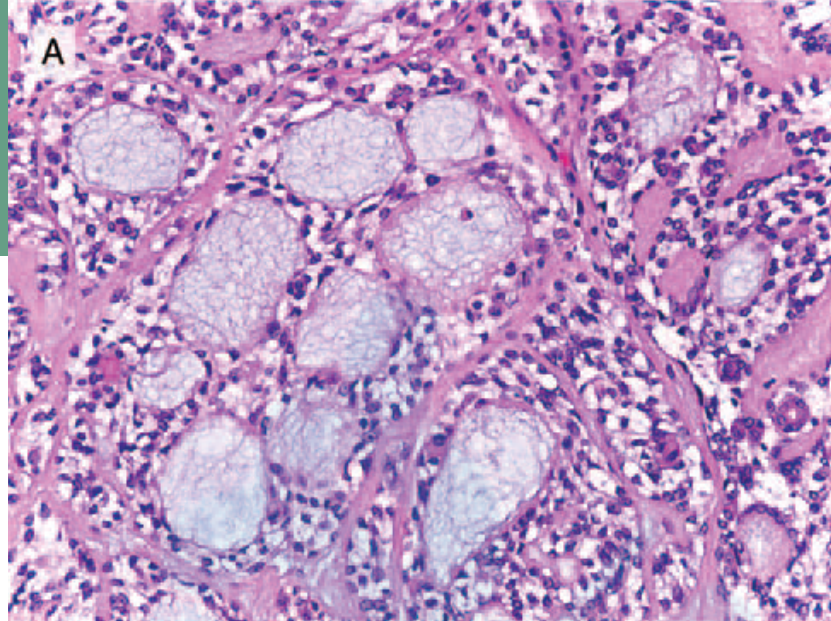
Age (mean [range]) (y)	69.6 (36-93)
Sex (n [%])	
Female	44 (50.6)
Male	42 (48.3)
Unknown	1 (1.1)
Anatomic site (n [%])	
Parotid gland	72 (82.8)
Submandibular gland	4 (4.6)
Nasal cavity	4 (4.6)
Bronchus	3 (3.4)
Oral cavity	3 (3.4)
Lacrimal gland	1 (1.1)
Size (mean [range]) (mm)	34.5 (8-75)

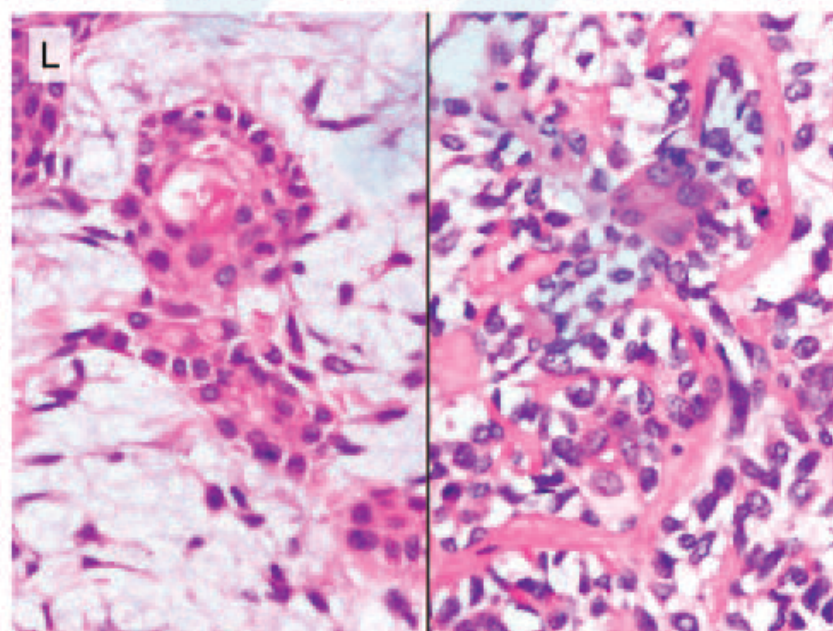
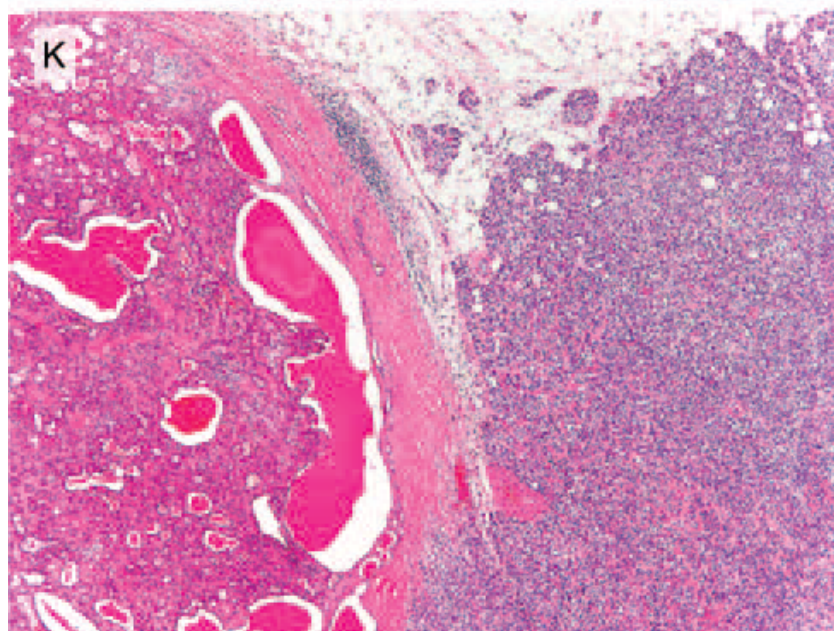
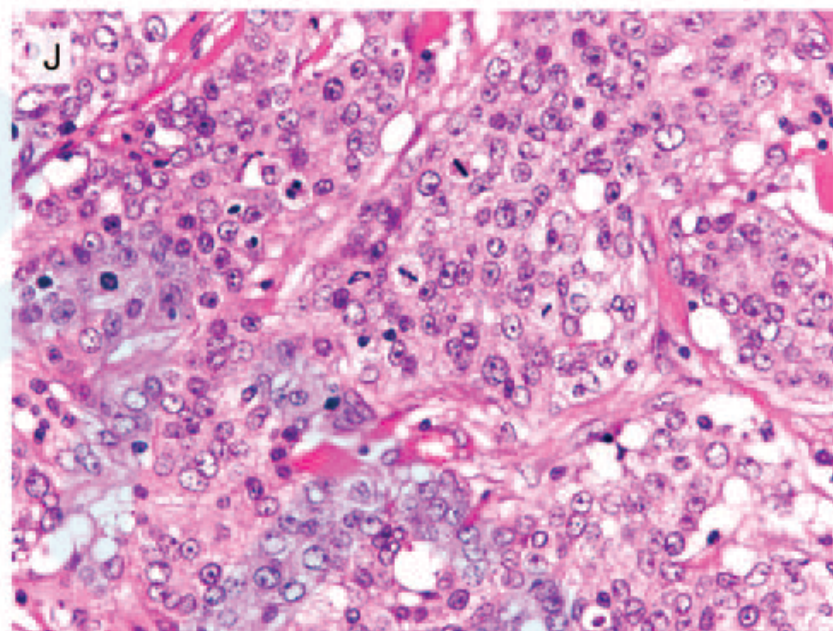
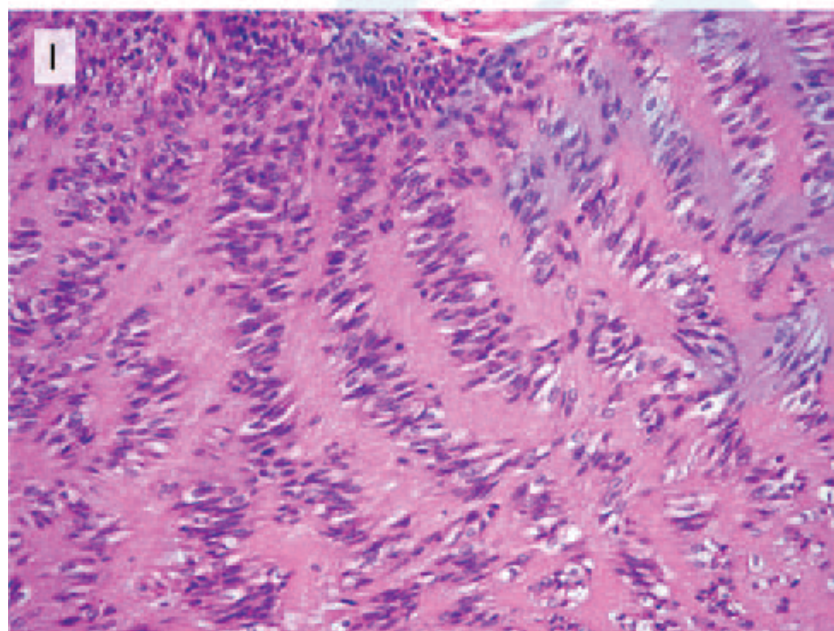
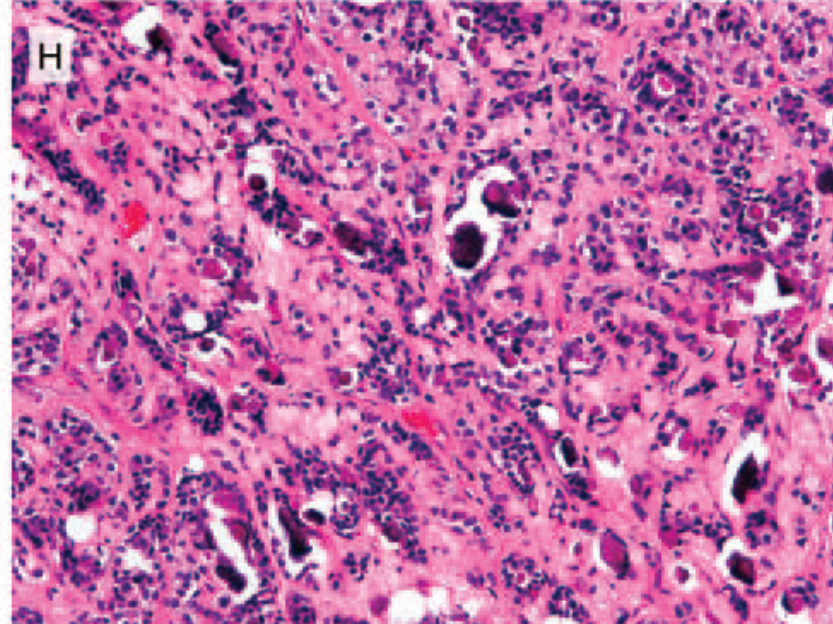
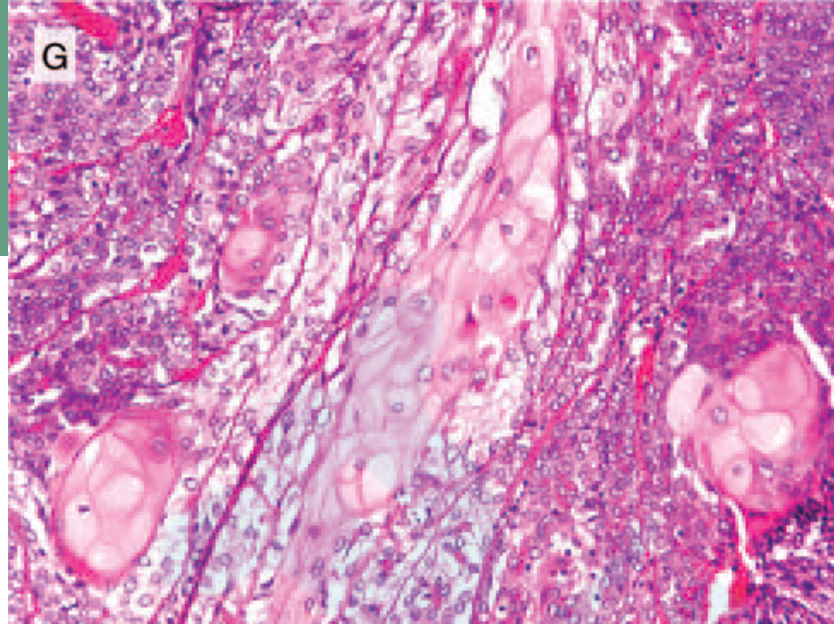
TABLE 2. Histologic Characteristics of Epithelial-Myoepithelial Carcinoma Cases

	n (%)
Histologic features	
Classic	35 (40.2)
Nonclassic	52 (59.8)
Variations	
Cribriform	16 (18.4)
Basaloid	16 (18.4)
Sebaceous	15 (17.2)
Oncocytic/apocrine	6 (6.9)
Papillary-cystic	5 (5.7)
Double-clear	3 (3.4)
Squamous	3 (3.4)
HG-T	3 (3.4)
Psammomatous	2 (2.3)
Verocay-like	1 (1.1)
Nuclear grade	
Low	79 (90.8)
High	8 (9.2)
Histologic origin	
<i>De novo</i>	83 (95.4)
Ex PA	4 (4.6)
Necrosis	
Present	17 (19.5)
Absent	70 (80.5)
Lymphovascular invasion	
Present	9 (10.3)
Absent	78 (89.7)
Perineural invasion	
Present	14 (16.1)
Absent	73 (83.9)
Myoepithelial:ductal cell ratio	
Mean (range)	4.3 (0.75-30)
< 5	60 (70.6)
≥ 5	25 (29.4)
Mitotic counts/10 HPF	
Mean (range)	3.6 (0-35)
Ki-67 labeling index	
Mean (range [%])	20.5 (4-70)
< 30%	49 (79.0)
≥ 30%	13 (21.0)

Ex PA indicates ex pleomorphic adenoma; HG-T, high-grade transformation; HPF, high-power field.



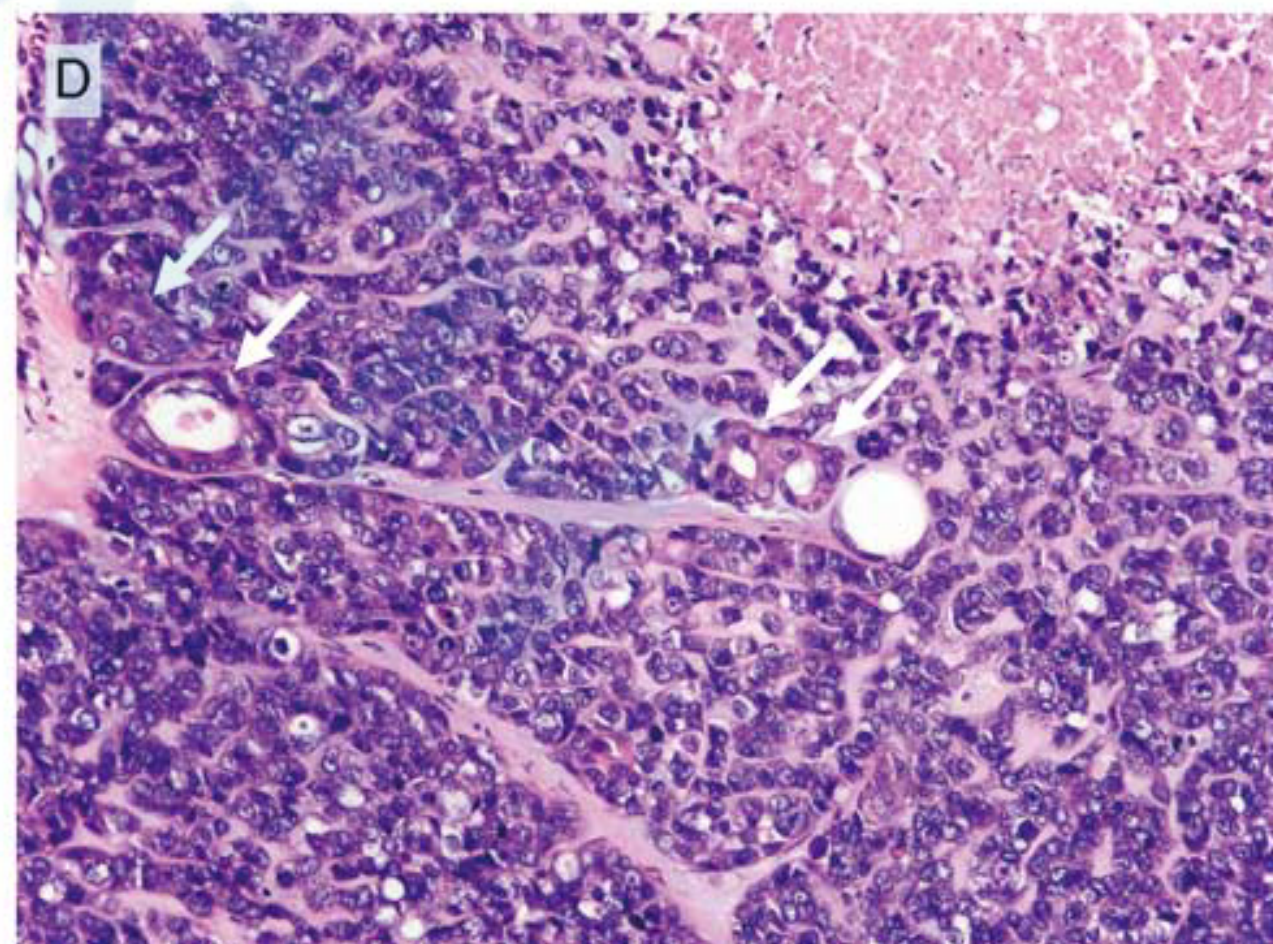
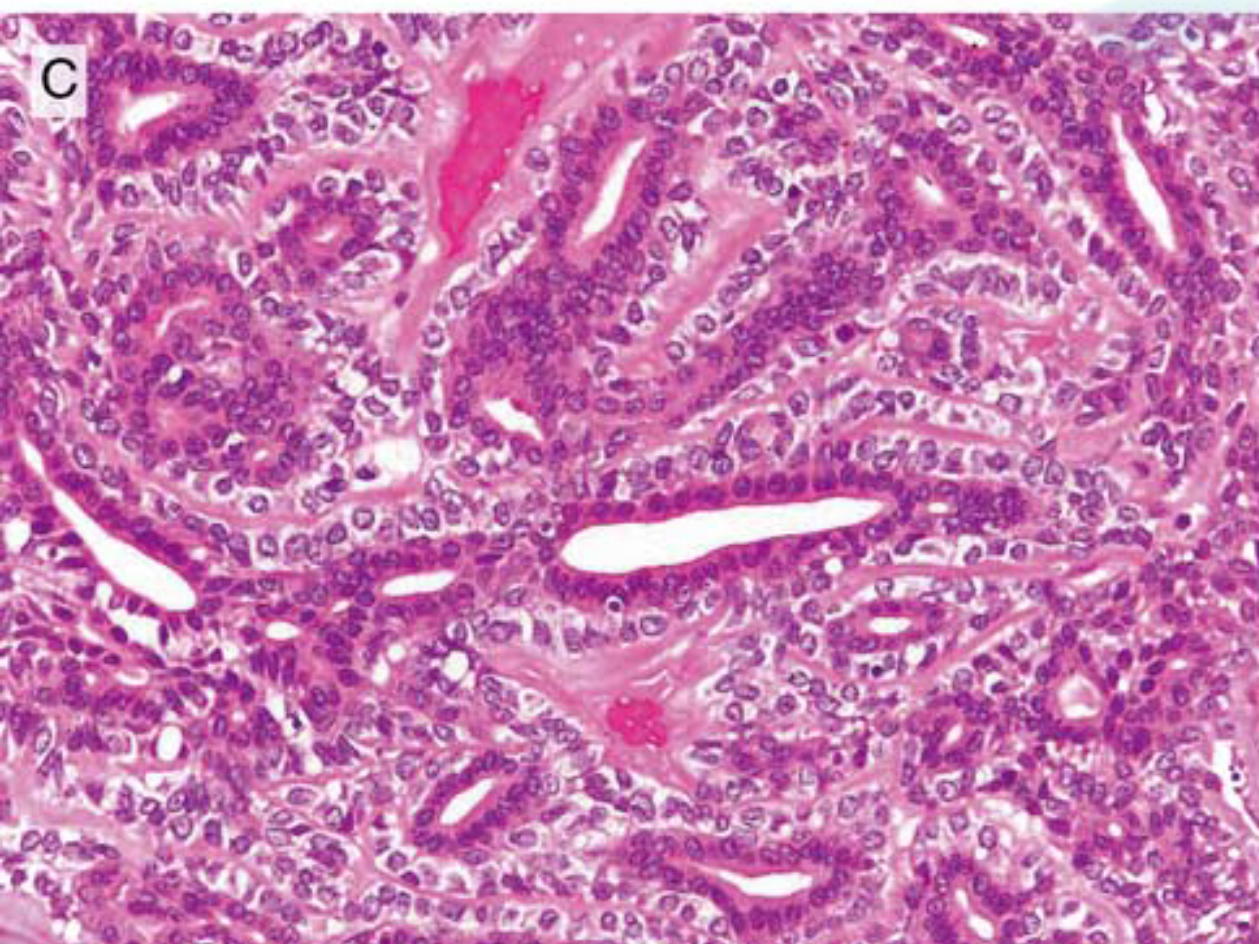
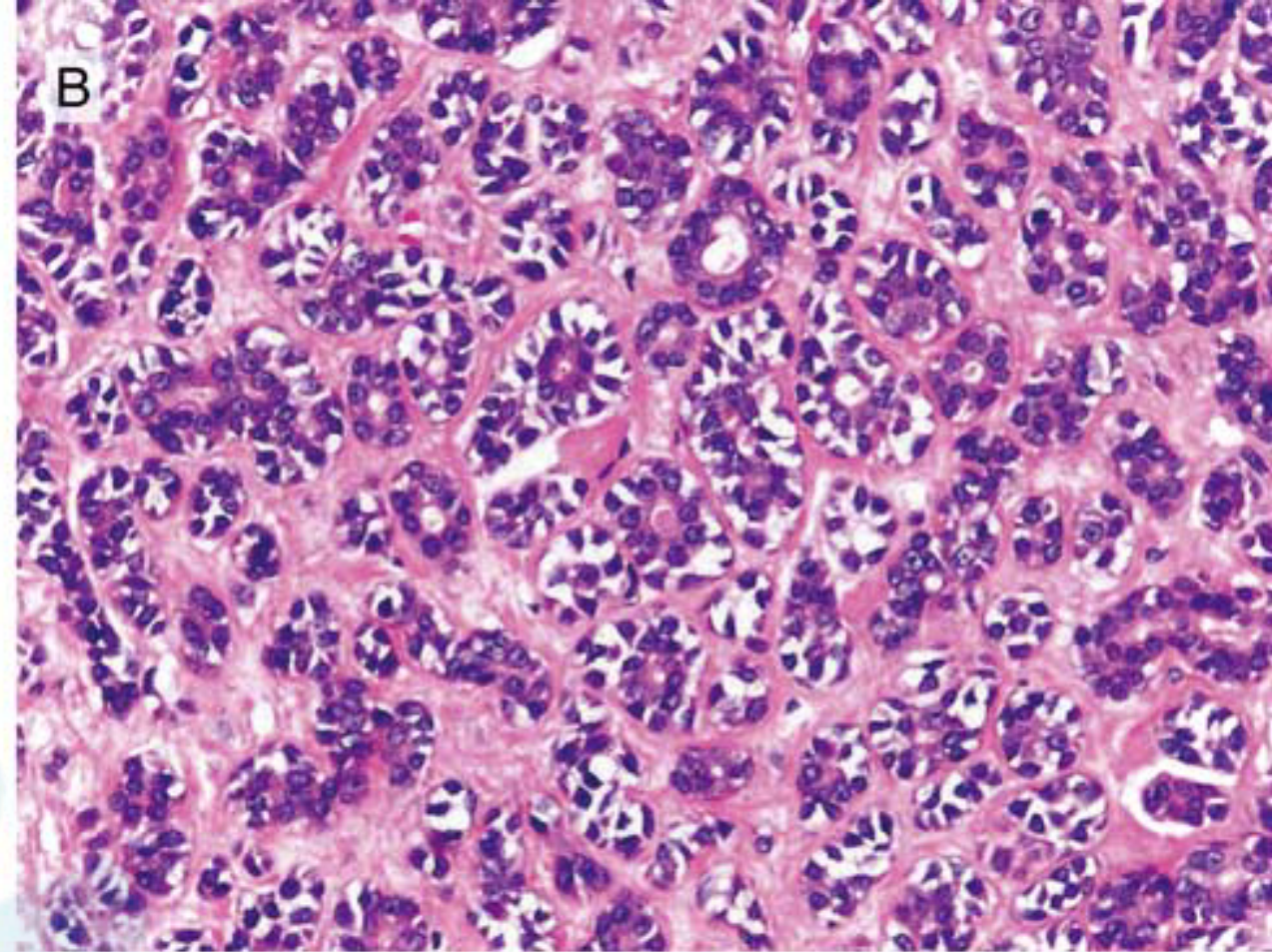
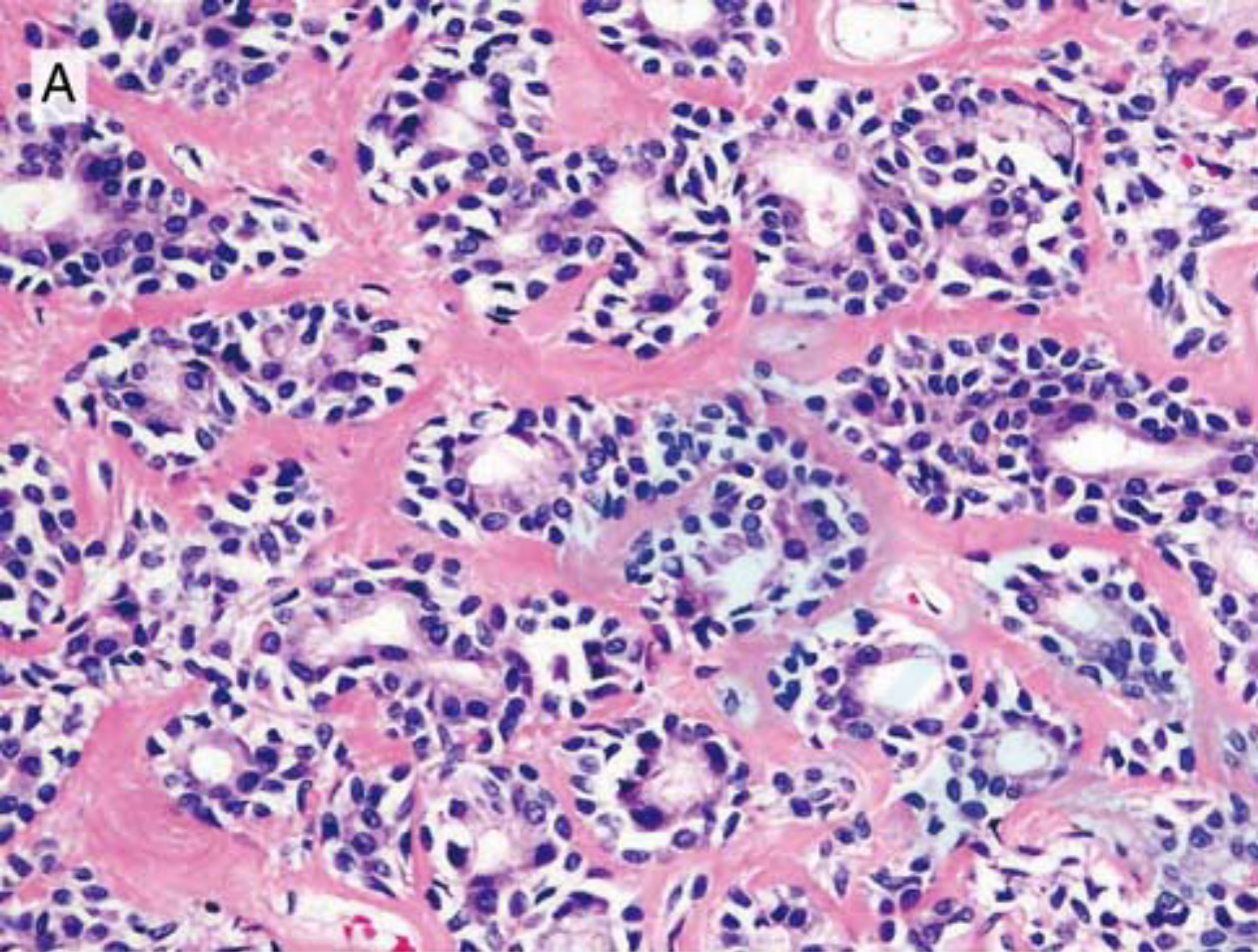




❖ Mutation Analysis

TABLE 3. Gene Mutations in Epithelial-Myoepithelial Carcinoma Cases

Gene	Mutation Site and Pattern		n/N (%)
<i>HRAS</i>			67/82 (81.7)
	Exon 2	G13R	6
	Exon 3	Q61R	55
		Q61K	5
		Q61 (stop)	1
<i>PIK3CA</i>			17/82 (20.7)
	Exon 9	E542K	1
		E545K	3
	Exon 20	H1047L	1
		H1047R	12
<i>AKT1</i>			5/77 (6.5)
	Exon 2	E17G	1
		E17K	4
<i>BRAF</i>	Exon 15	V600E	1/81 (1.2)
<i>CTNNB1</i>	Exon 3		0/82 (0)
<i>KRAS</i>	Exons 2, 3		0/81 (0)

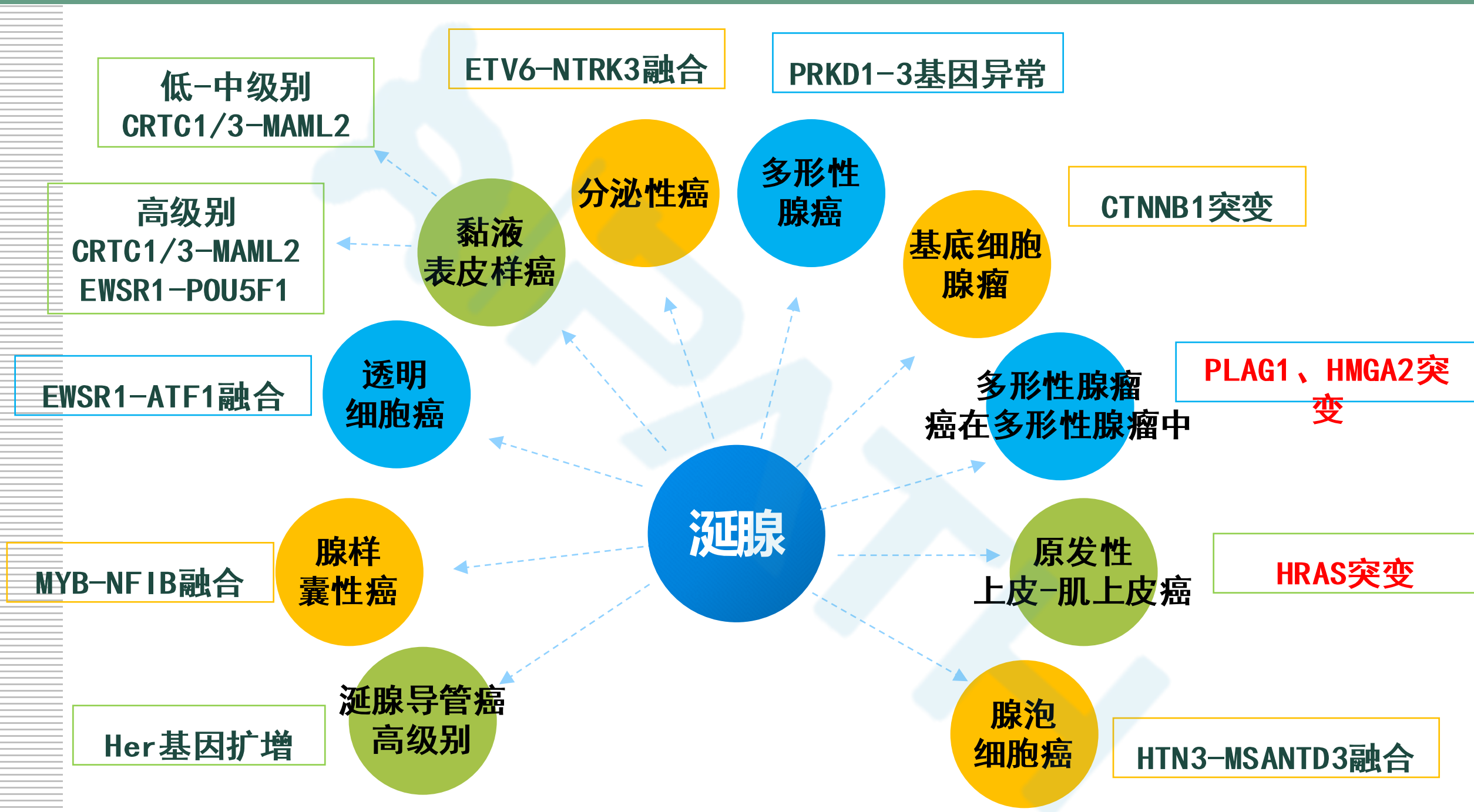


DISCUSSION

- ❖ Despite its wide histologic spectrum, EMC commonly harbors HRAS mutations
- ❖ HRAS mutation was not identified in any salivary gland tumor entities manifesting EMC-like features, including adenoid cystic carcinoma, pleomorphic adenoma, basal cell adenoma/adenocarcinoma, and myoepithelial carcinoma
- ❖ Further experiments with cell lines or animal models are required to clarify the functional roles of HRAS mutations in EMC tumorigenesis, differentiation, and development

CONCLUSION

- ❖ HRAS mutations are a frequent tumorigenic gene alteration in EMC, despite its histologic diversity
- ❖ The assessment of HRAS mutations will contribute to the correct diagnosis of EMC in challenging practical pathology settings
- ❖ This study provides further insight into strategies for diagnosing EMC and discriminating it from its mimics



Thank You !

