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# Epithelial-Myoepithelial Carcinoma

*Frequent Morphologic and Molecular Evidence of Preexisting Pleomorphic Adenoma, Common HRAS Mutations in PLAG1-intact and HMGA2-intact Cases, and Occasional TP53, FBXW7, and SMARCB1 Alterations in High-grade Cases*



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# 研究背景

# 关键词

EMCAs: Epithelial-myoepithelial carcinomas. 上皮-肌上皮癌

PA: Pleomorphic adenoma. 多形性腺瘤

*PLAG1*: Pleomorphic Adenoma Gene 1.

*HMGA2*: High Mobility Group A2.

# 上皮-肌上皮癌

## Epithelial-myoepithelial carcinomas

- 定义

- 一种恶性的涎腺肿瘤，由内层的腺腔导管上皮与外层的肌上皮组成。

- ICD-O编码：8562/3

- 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

# 上皮-肌上皮癌

## Epithelial-myoepithelial carcinomas

- 好发部位

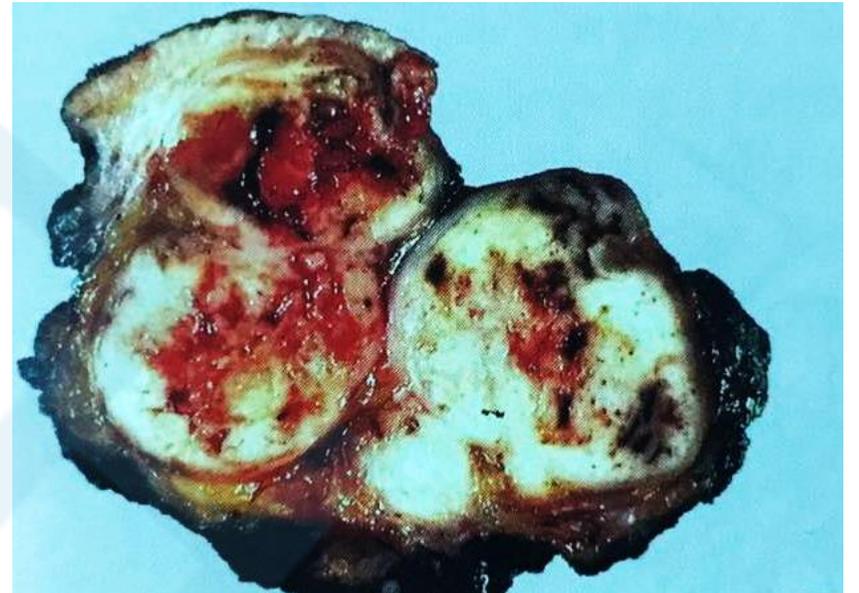
大部分发生于腮腺、下颌下腺，少部分发生于鼻腔、上腭

- 临床特征：缓慢生长的无痛性包块

- 大体特征

—分叶状，边界不清的质韧肿物

—部分包膜，小部分（30%）出现出血、囊性变



# 上皮-肌上皮癌

## Epithelial-myoepithelial carcinomas

- 组织病理学

- 分叶状生长方式

- 双层上皮：

- a.内层——小的腺腔导管细胞，胞浆嗜酸性；

- b.外层——多边形的肌上皮细胞，胞浆透亮。

- 可出现实性生长及坏死，神经侵犯常见，脉管侵犯少见

- 两种细胞都可出现嗜酸化生、梭形变、透明变、脂肪变

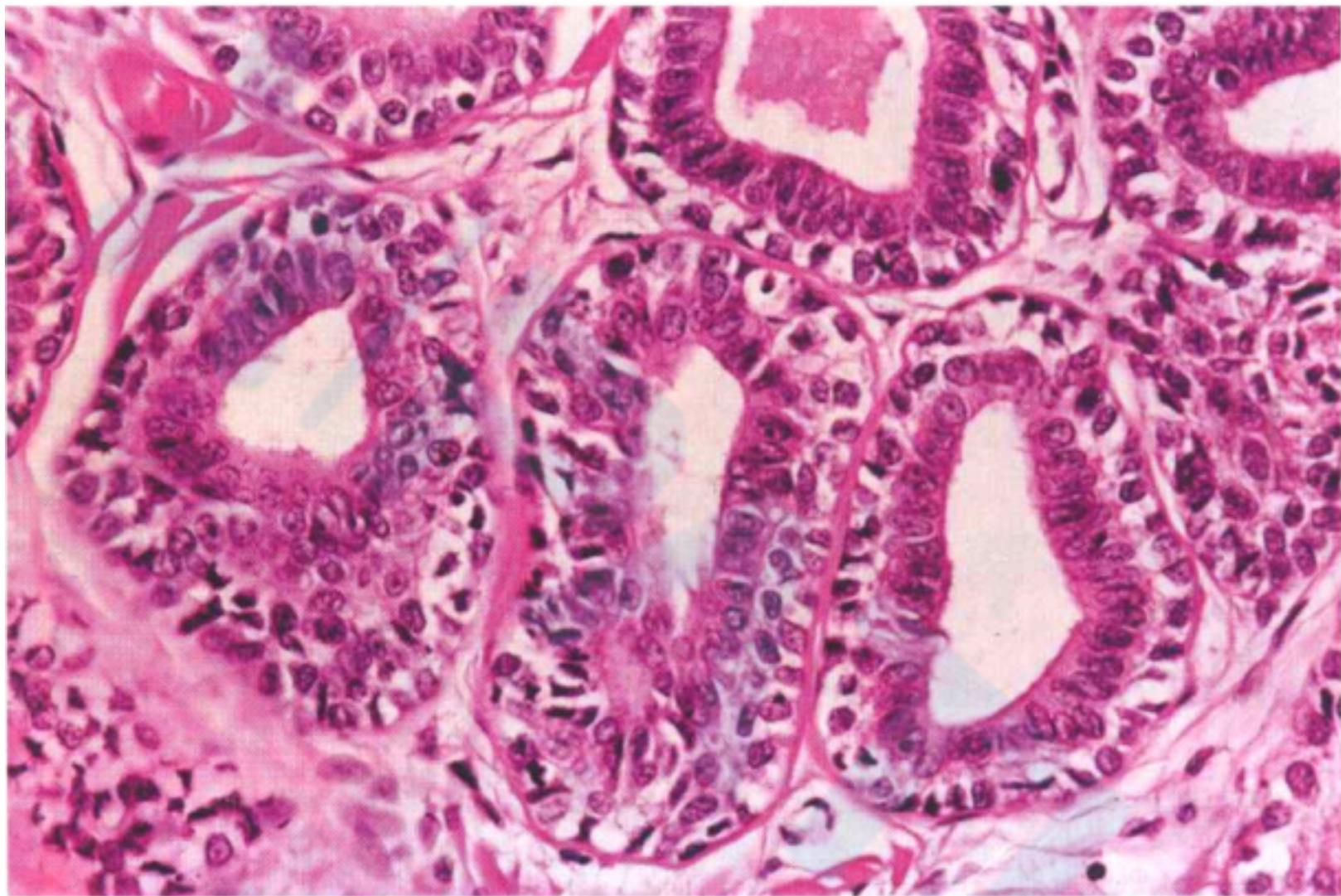
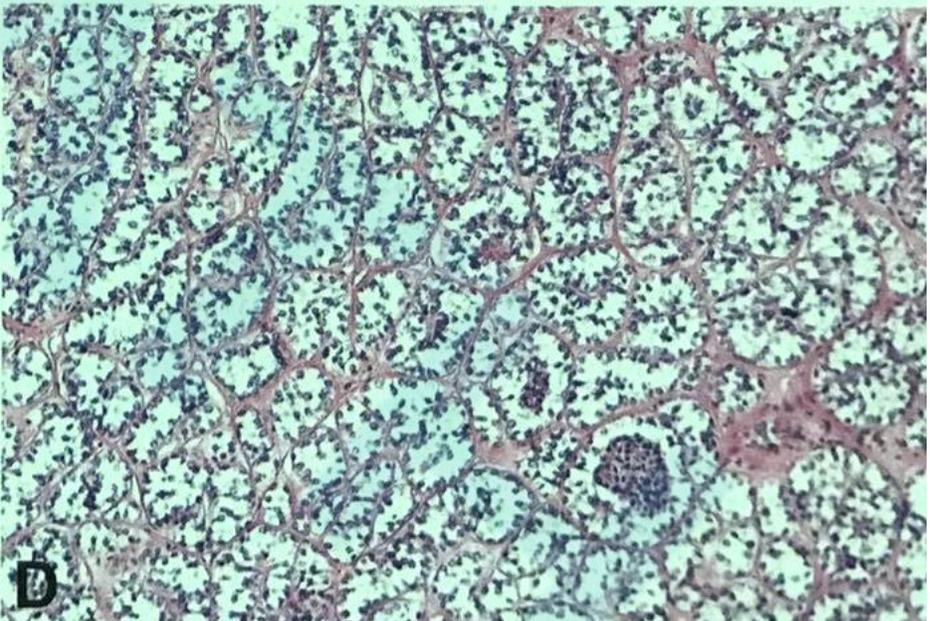
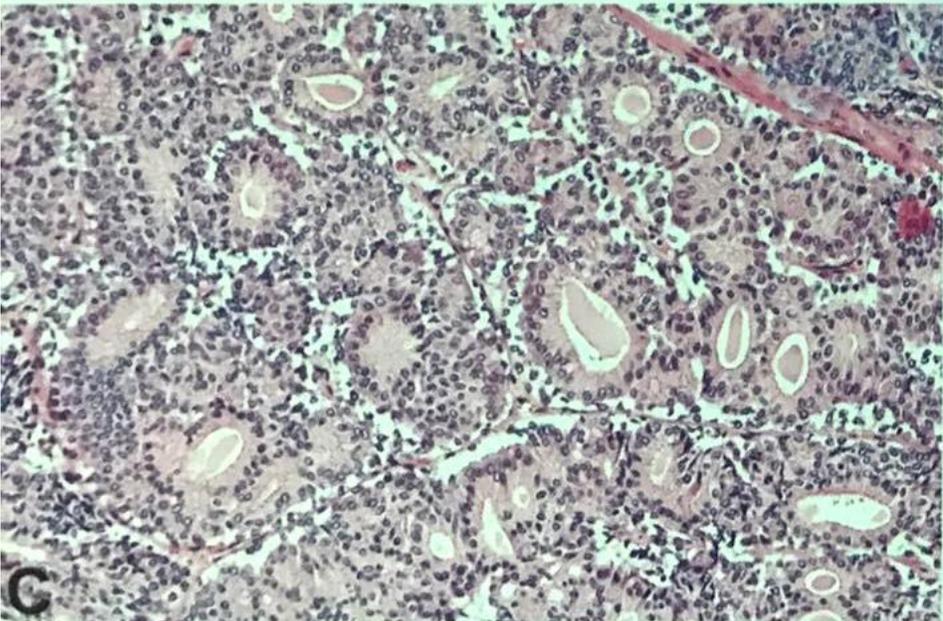
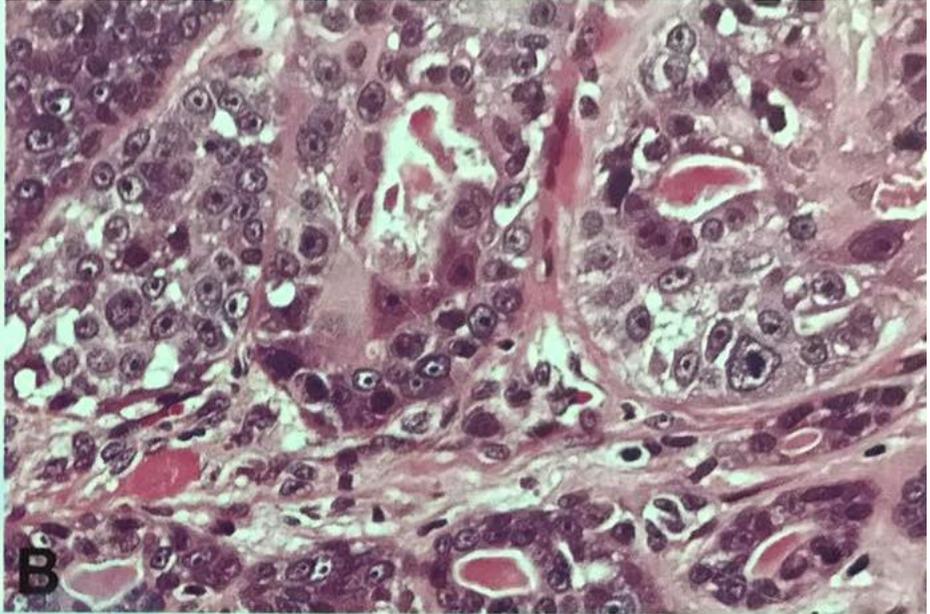
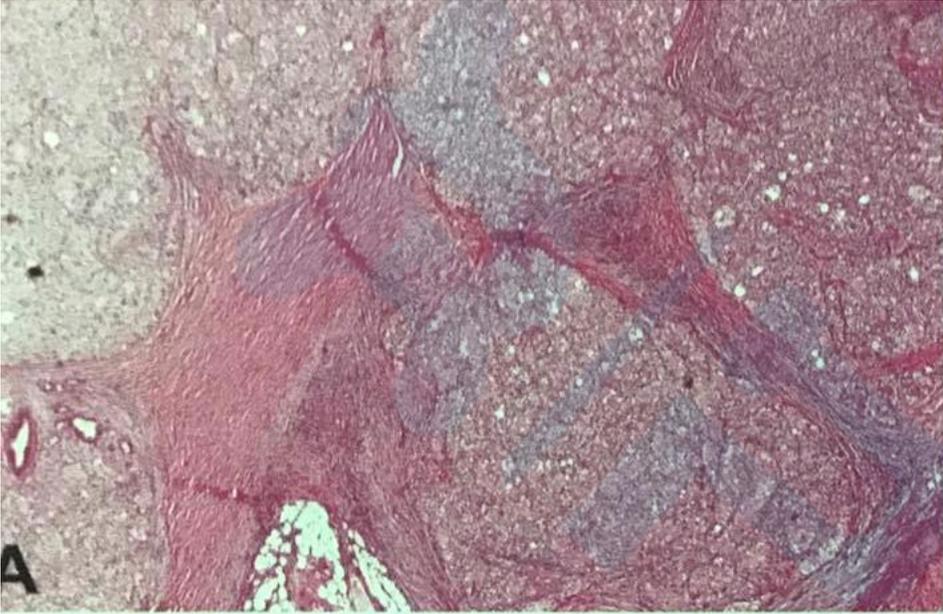


图 2-8 上皮-肌上皮癌

图示肿瘤由腺上皮细胞及肌上皮细胞构成,腺上皮细胞立方形或矮柱状,围成腺管。其外周有透明肌上皮细胞环绕



WHO Classification of Head and Neck Tumours 2017

# 上皮-肌上皮癌

## Epithelial-myoepithelial carcinomas

- 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

- 通常为惰性，少见局部复发；淋巴结与远处转移罕见
- 80%患者生存期达到180个月
- 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

- 鉴别诊断

- 大部分EMCAs为低级别，需要与多形性腺瘤鉴别
- 浸润性生长方式、与透明变基质分界清晰、导管上皮与肌上皮间隙
- 常常继发于多形性腺瘤

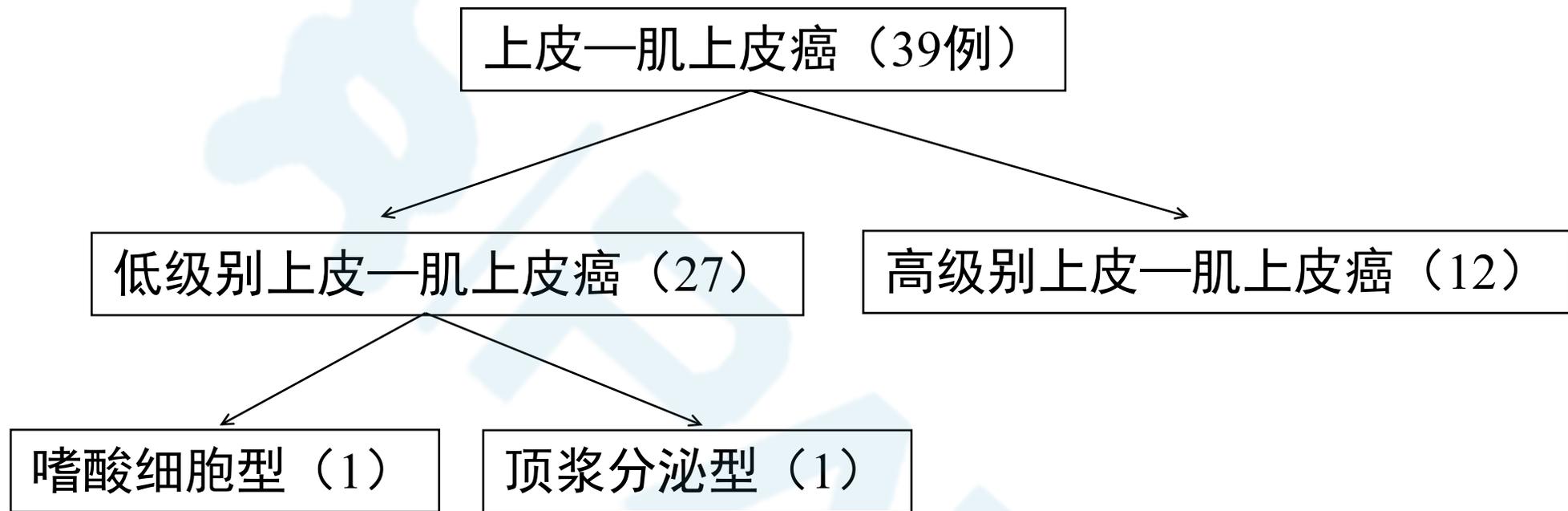
- 多形性腺瘤

- 良性的上皮型性肿瘤
- *PLAG1*、*HMGA2*重排，基因的重排状态结合形态学有助于鉴别EMCAs

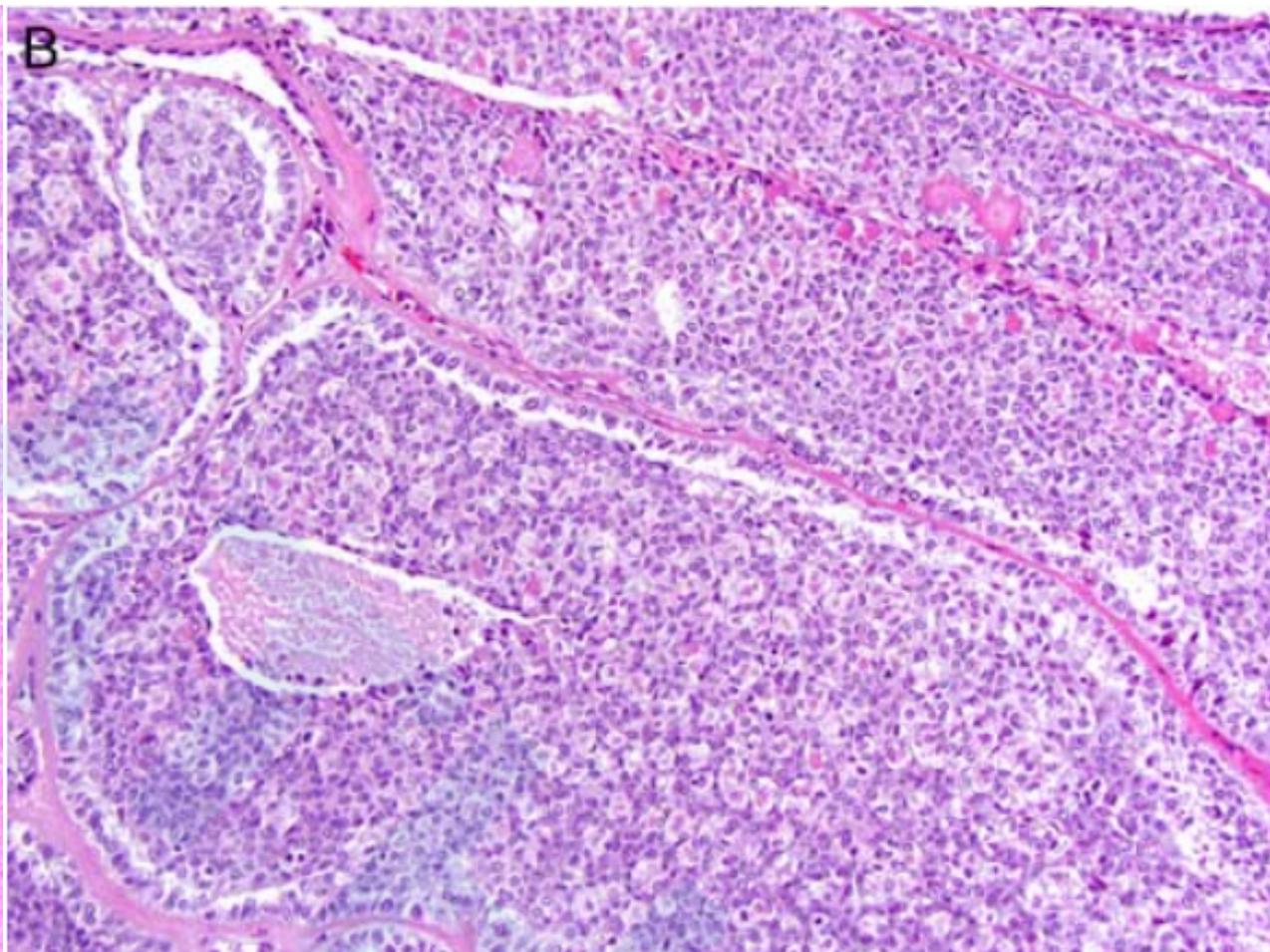
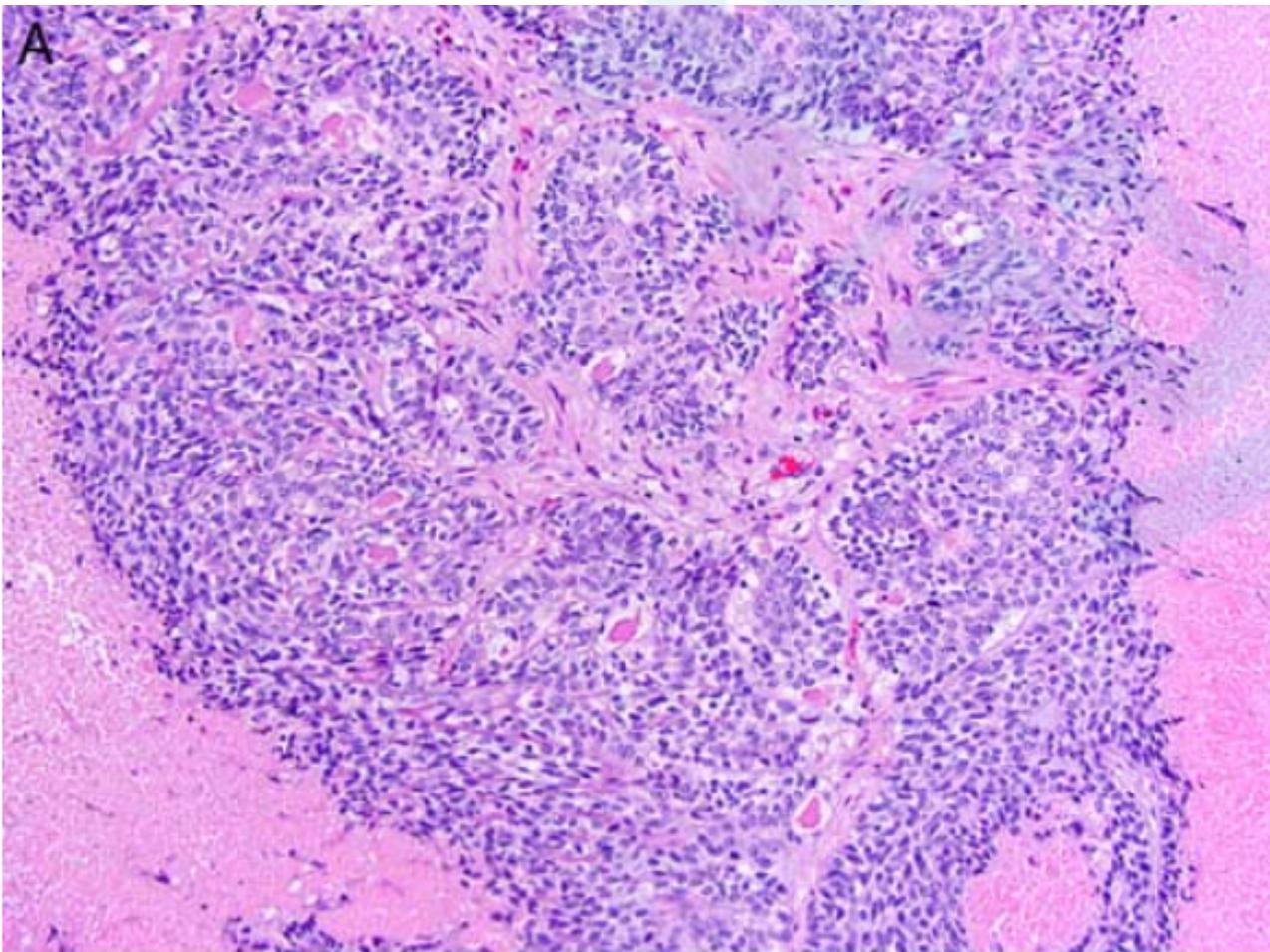
# 研究目的

- 确定由PA发展为EMCAs的发生率，显示*PLAG1*与*HMGA2*异常的频率，找出*PLAG1*、*HMGA2*的状态与临床病理学特征的相关性
- 找出PA的存在与50个癌症相关基因的突变及其拷贝数变异的关系

# 材料与amp;方法



- 1、低级别：具有双层上皮，肌上皮细胞：腺腔上皮细胞=1:1
- 2、高级别：腺上皮或肌上皮增生，伴有坏死及核多形性



# FISH、NGS

重排: *PLAG1*、*HMGGA2*

>2个信号肿瘤细胞超过75%

拷贝数变异: *SMARCB1* (*INI-1*)

NGS: 50-癌症相关基因

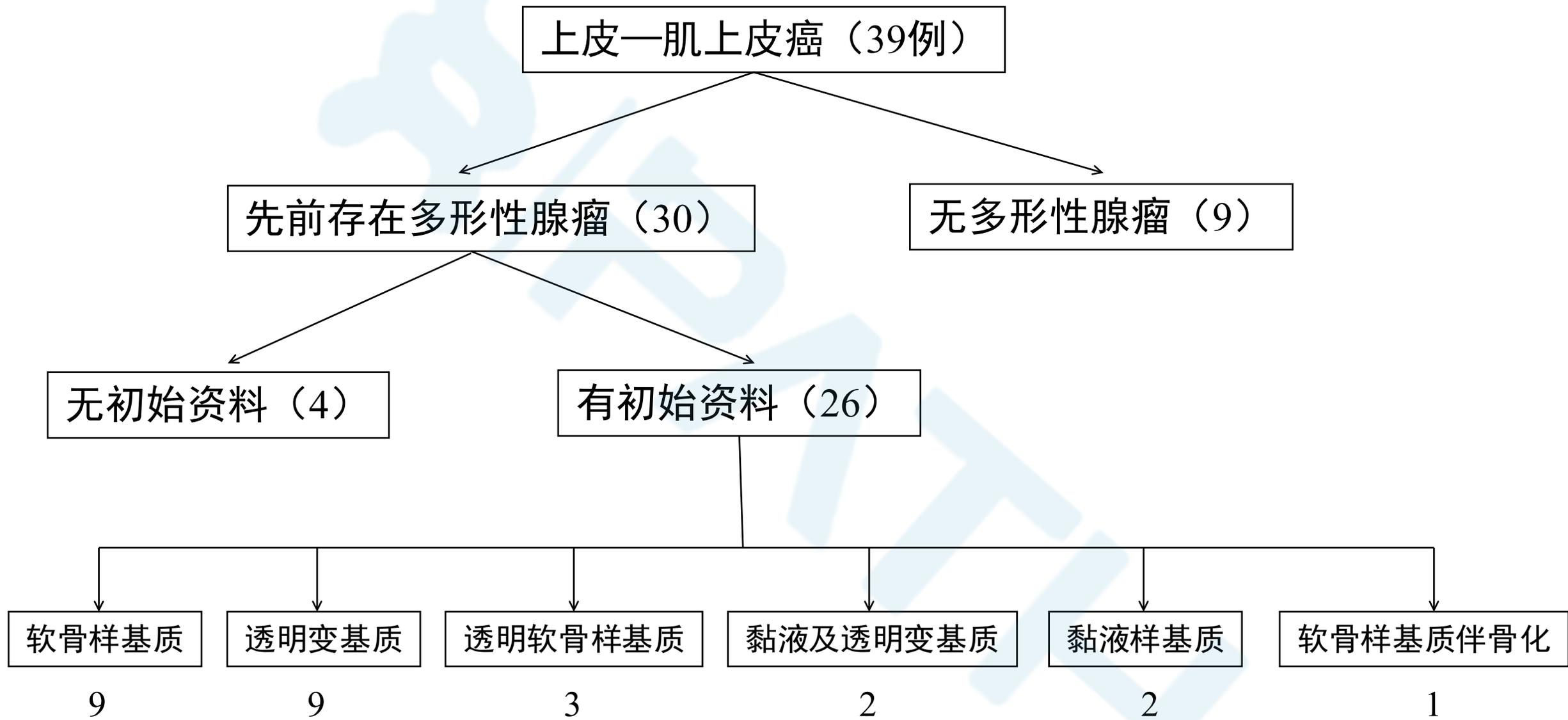
# 研究结果

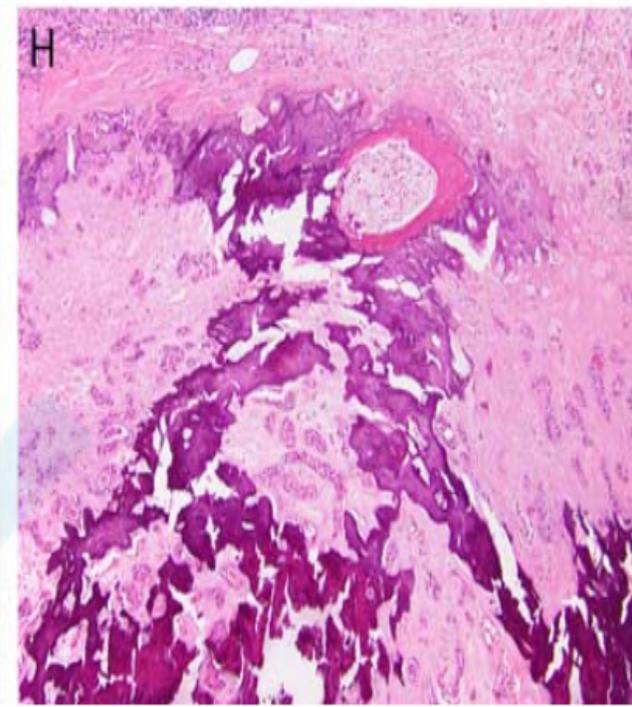
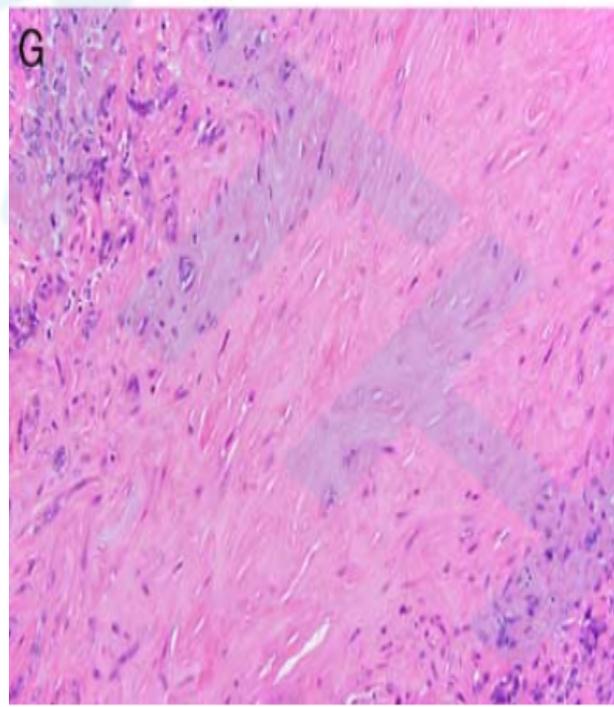
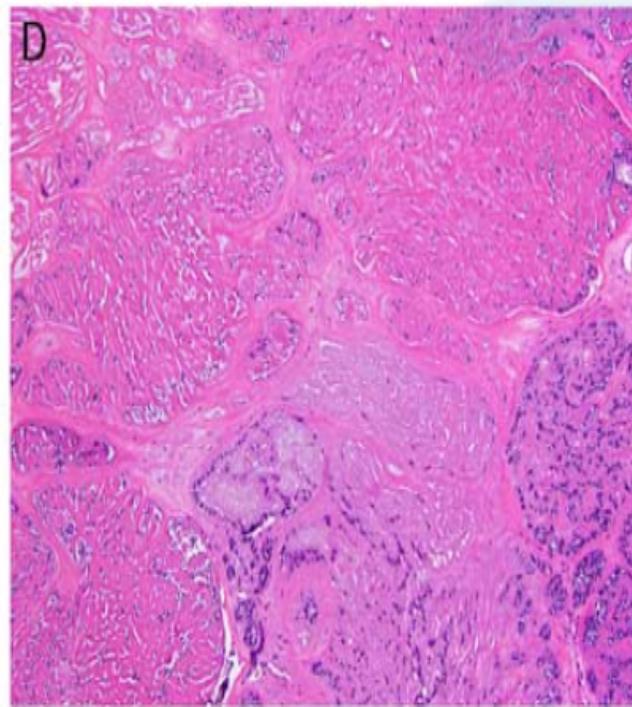
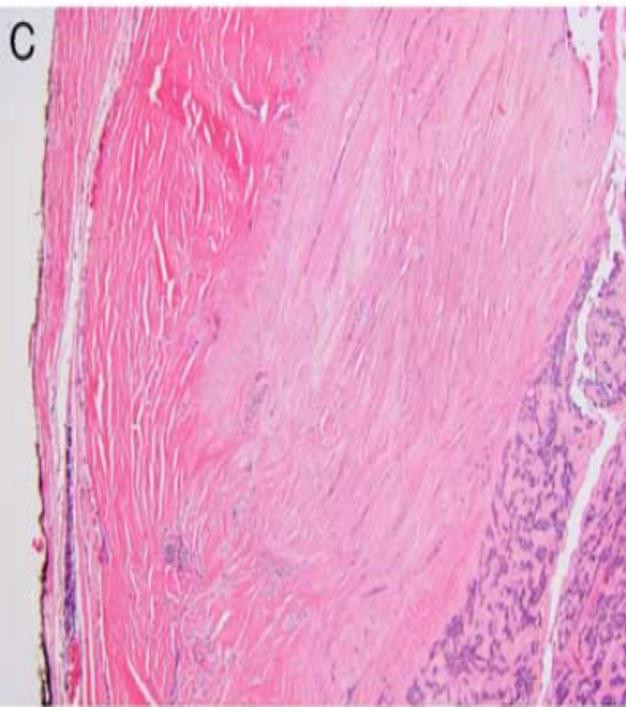
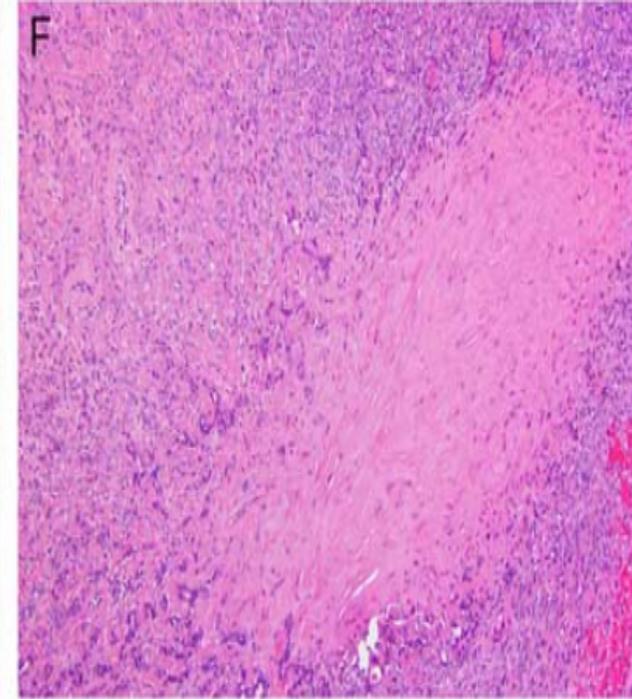
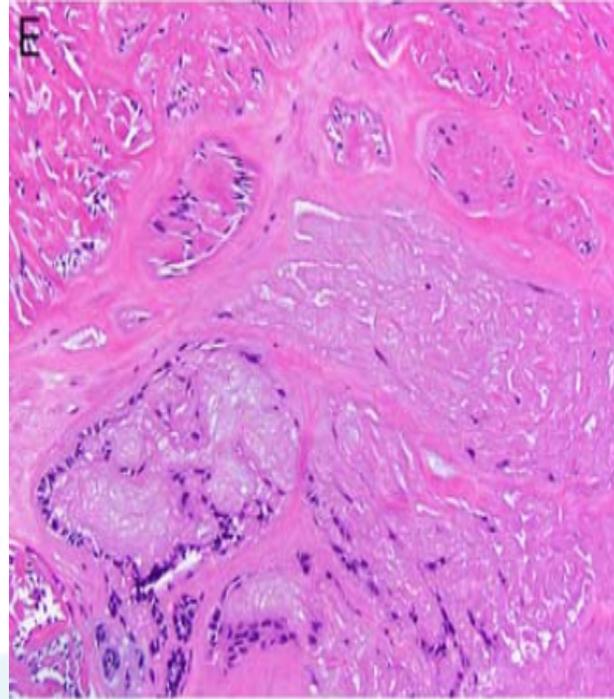
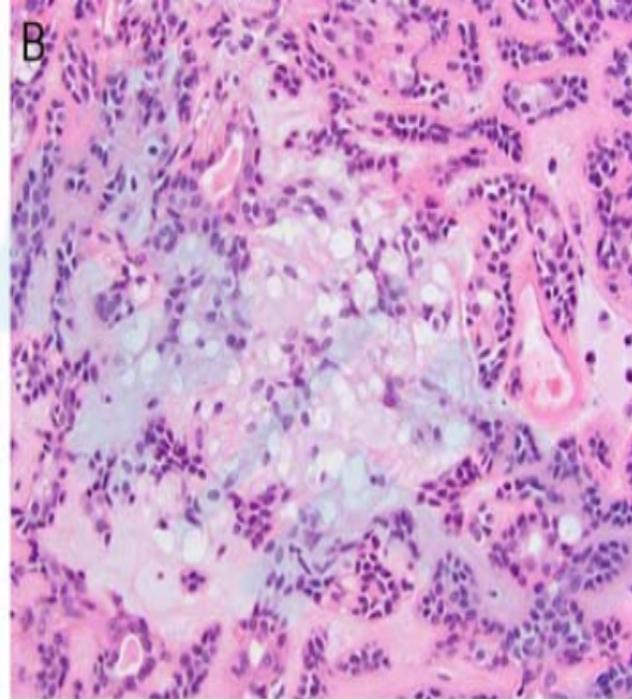
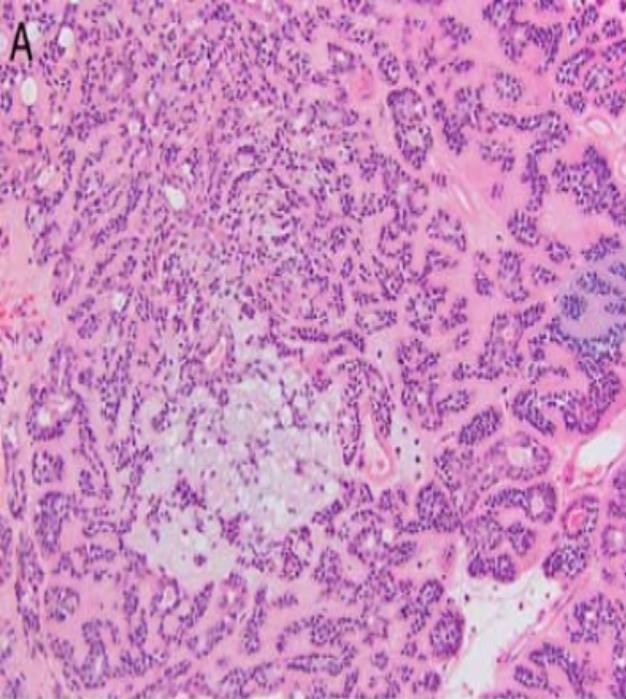
**TABLE 1. Clinicopathologic Features of Patients With EMCA**

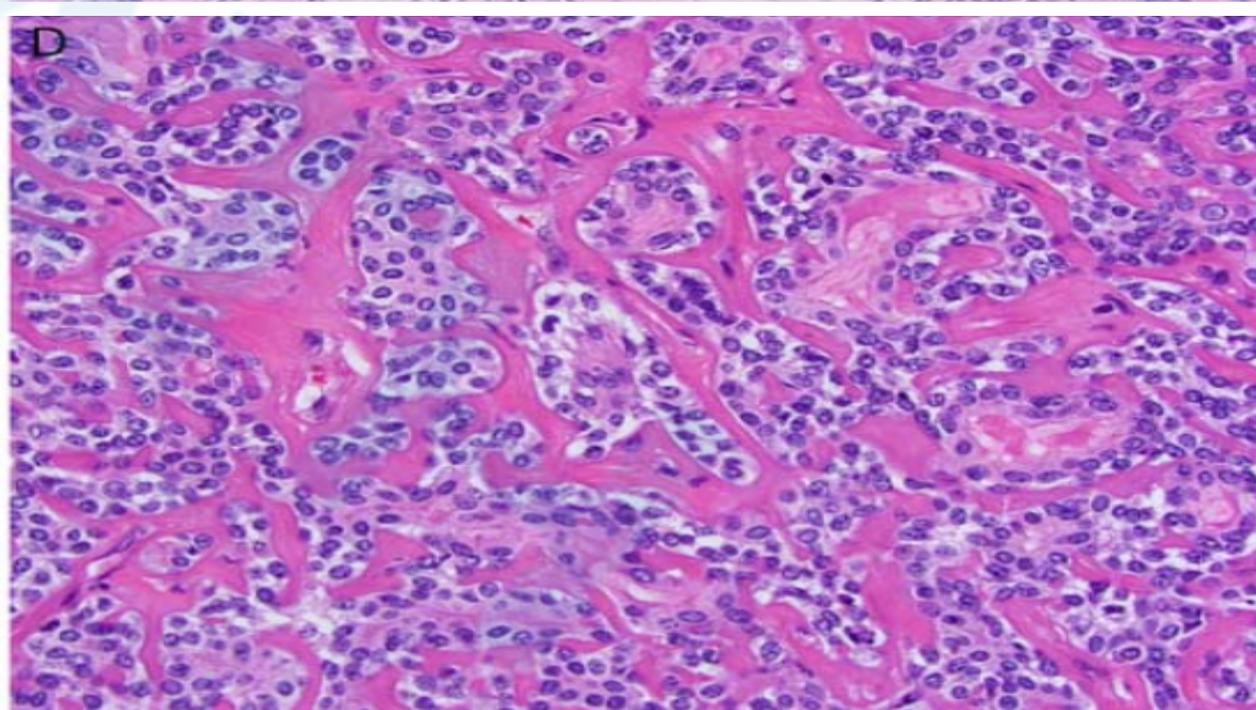
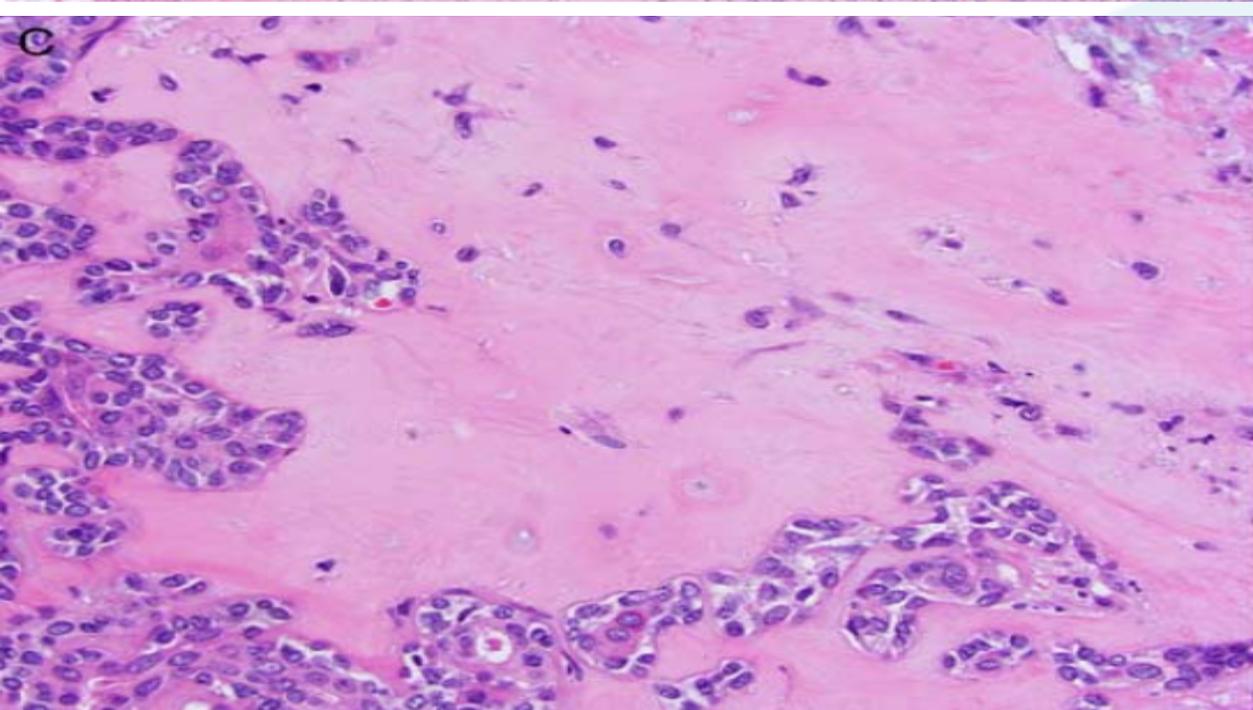
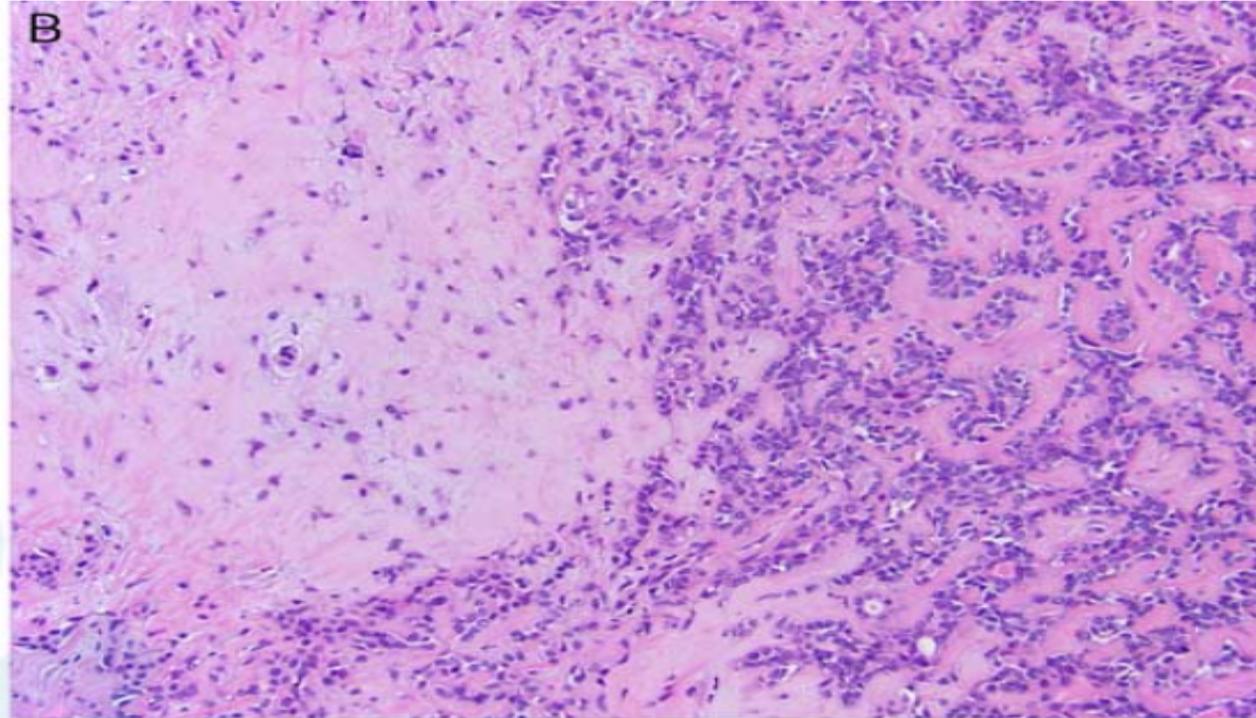
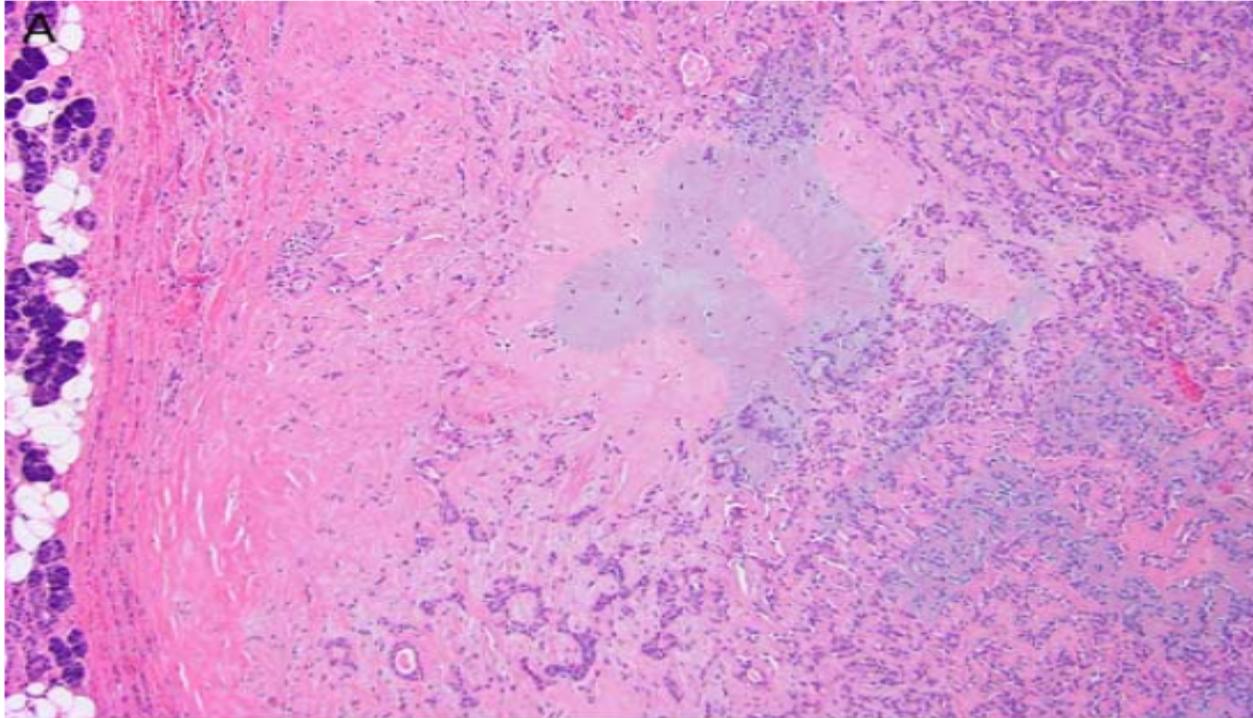
Sex, Female (n/N [%])	25/39 (64)
Age (mean [range]) (y)	66 (19-87)

- 1、女性多发（64%）
- 2、好发于腮腺（57%）
- 3、II期、III期患者占大多数（67%）

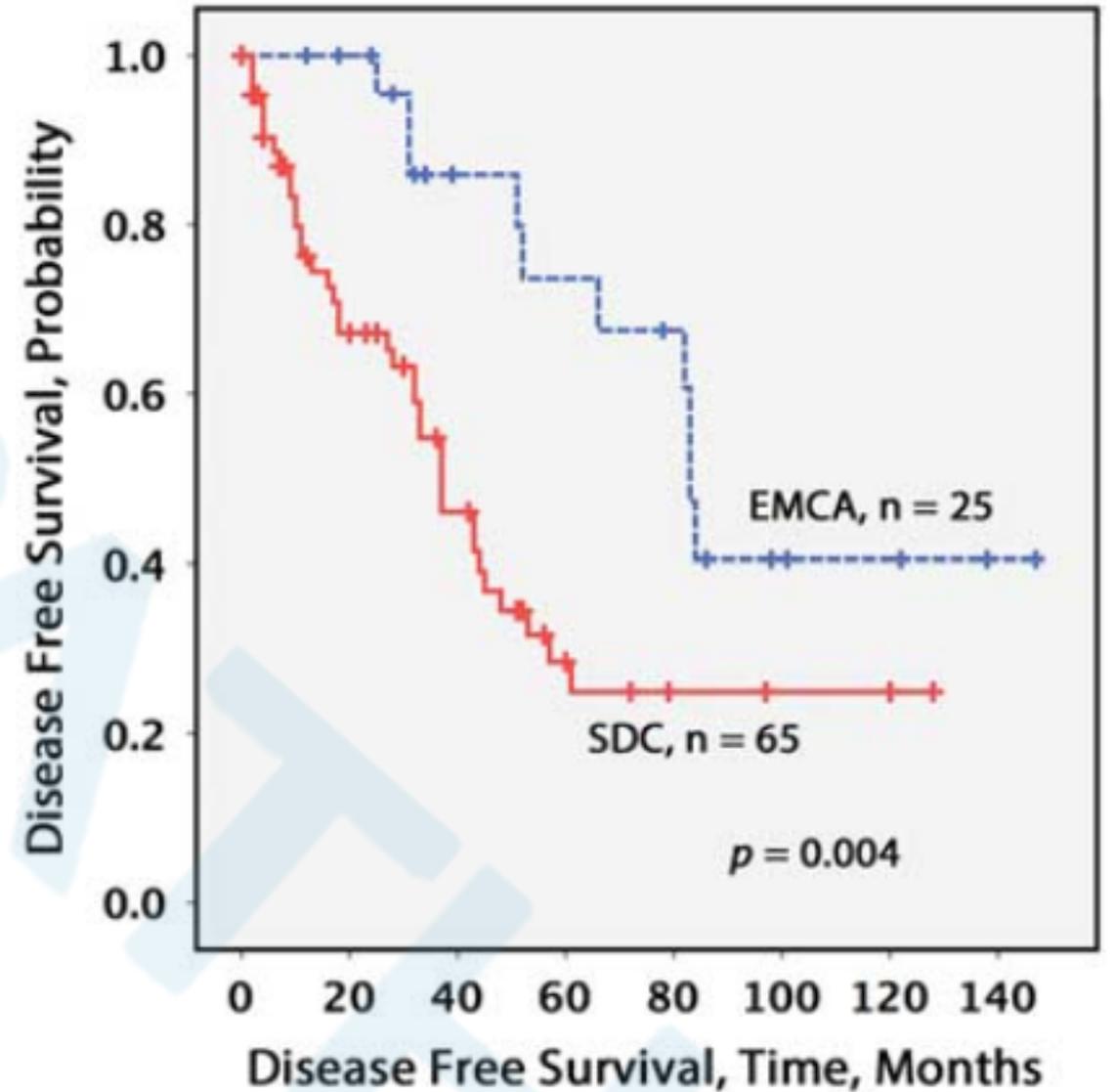
M (n [%])	
cM0	38 (98)
pM1	1 (2)







- 伴多形性腺瘤的EMCAs与不伴多形性腺瘤的EMCAs在临床病理参数（如年龄、性别、发生部位、分级、分期）及无病生存期无显著差异
- 平均无病生存期为80个月
- 4例患者于术后5年复发
- SDC：涎腺导管腺癌



**FIGURE 4.** Kaplan-Meier plot, estimated DFS of patients with EMCA, compared with patients with SDC (from Chiosea et al).<sup>13</sup>

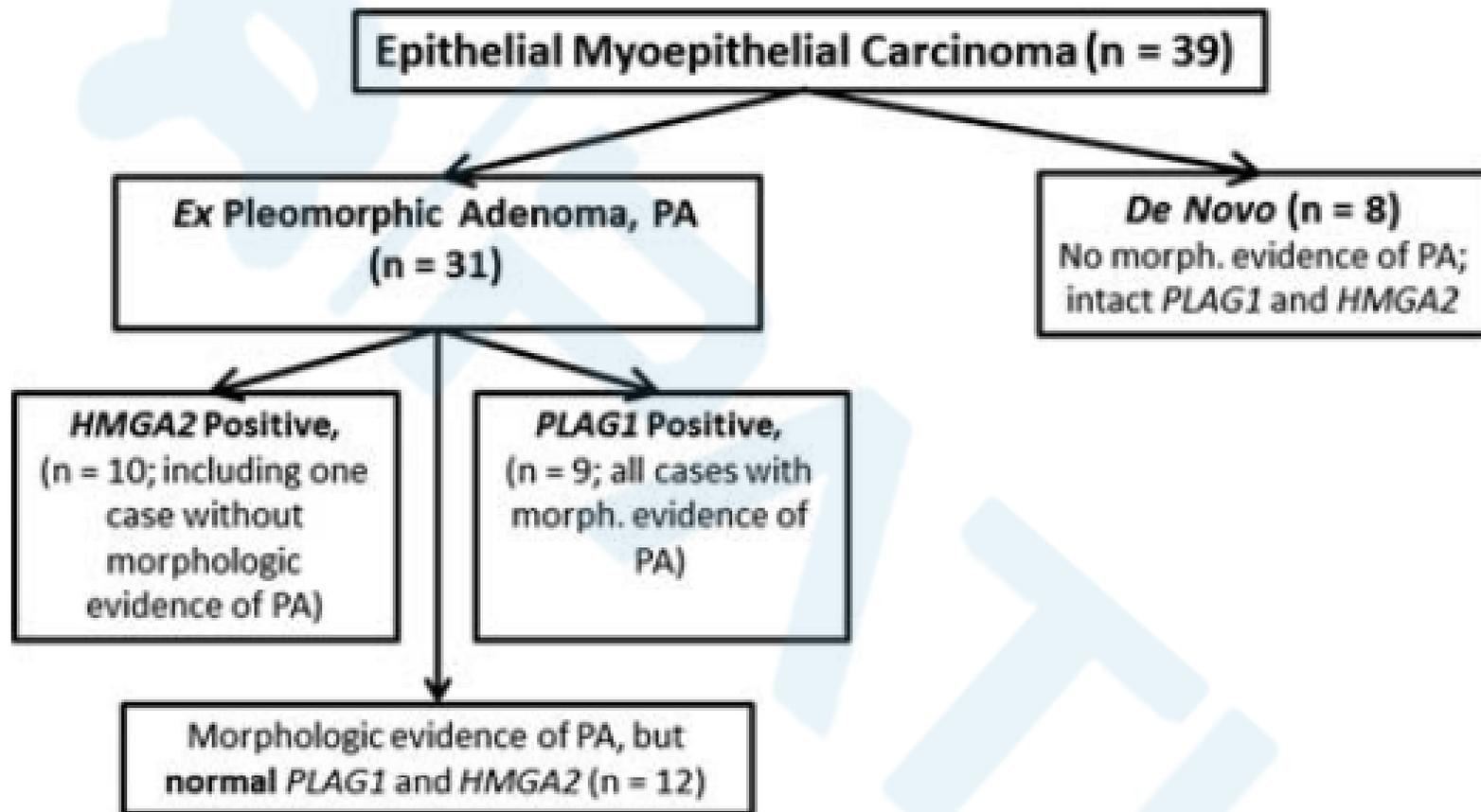
**TABLE 2.** Prevalence of *PLAG1* or *HMGA2* Alteration and Average Age of Patients With PA (Literature Review) and EMCA

	Patients' Age (Average [Range, for Patients in the Current Study]) (y)		Prevalence of Alterations (%)	
	PA*	EMCA	PA*	EMCA
Patients with tumors carrying <i>PLAG1</i> alteration	39	65 (47-81)	9/39 (23)	9/39 (23)
Patients with tumors carrying <i>HMGA2</i> alteration	45.9	69 (46-81)	10/39 (26)	10/39 (26)

\*The data on patients with PA are from Bullerdiek et al.<sup>9</sup>

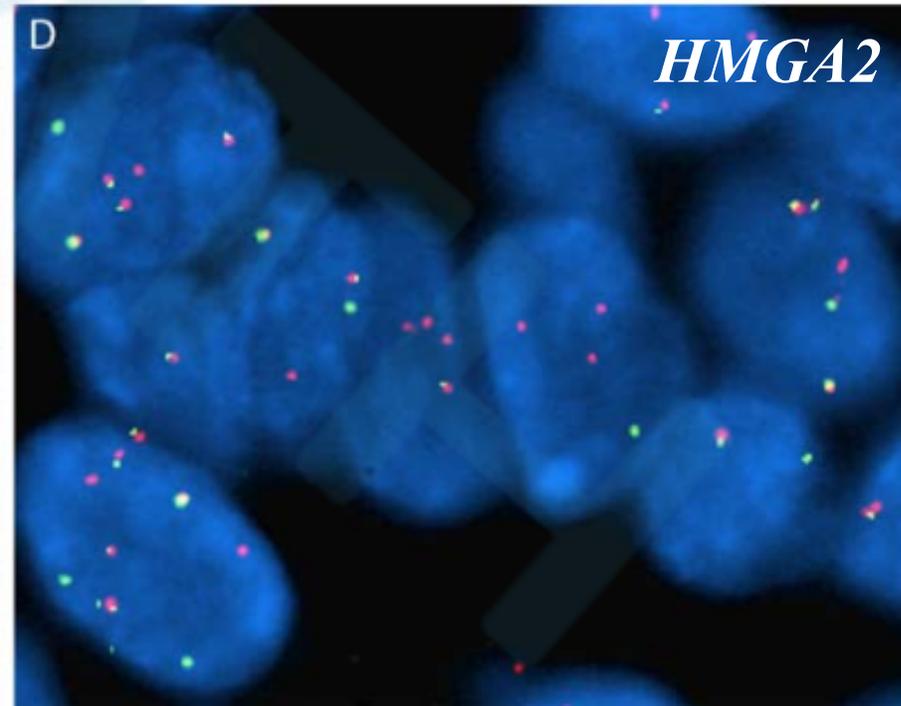
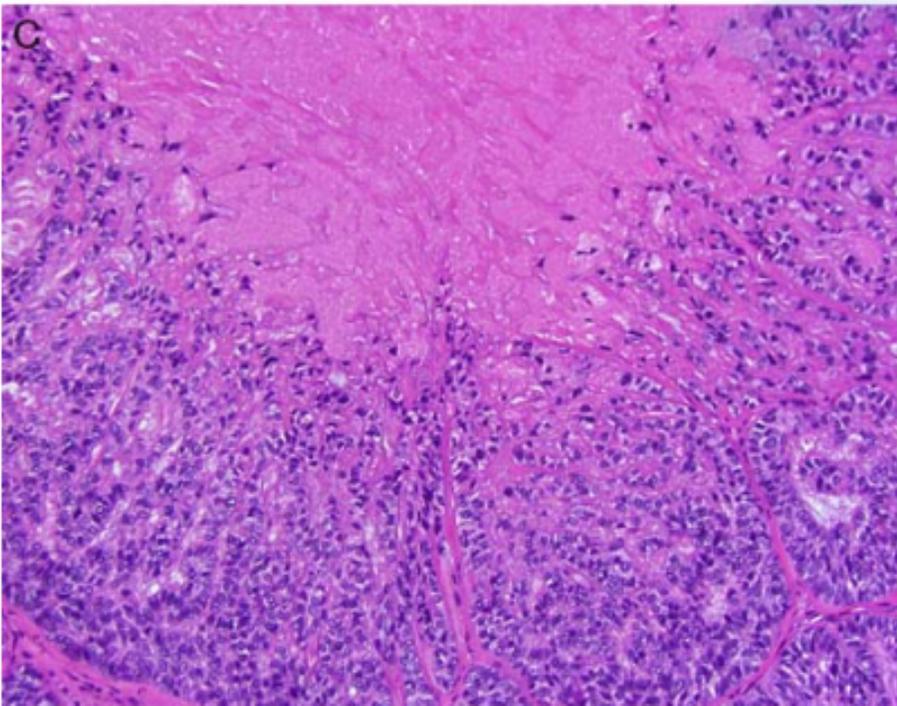
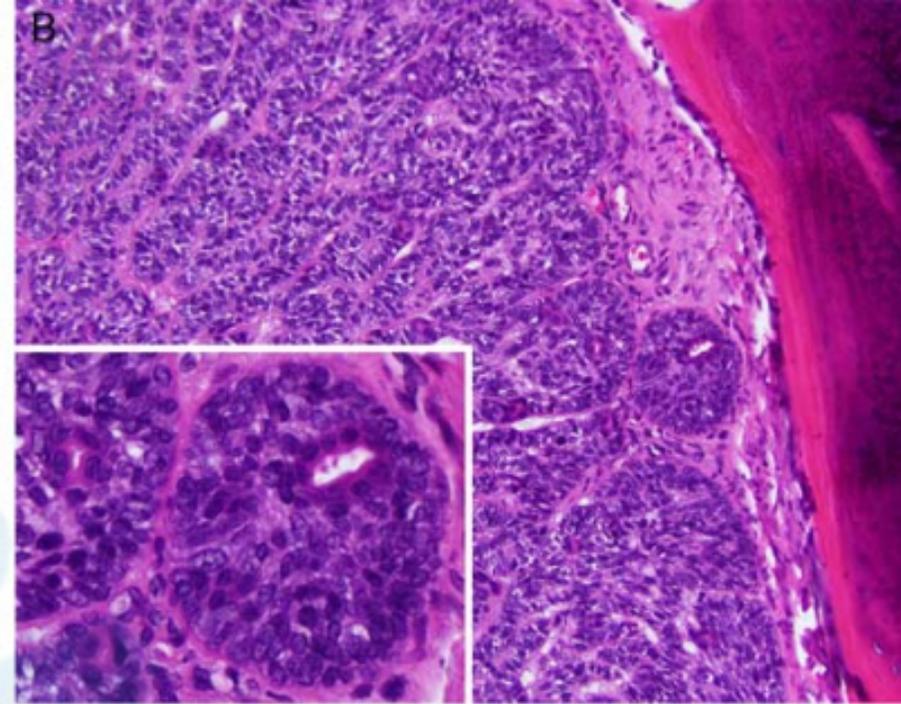
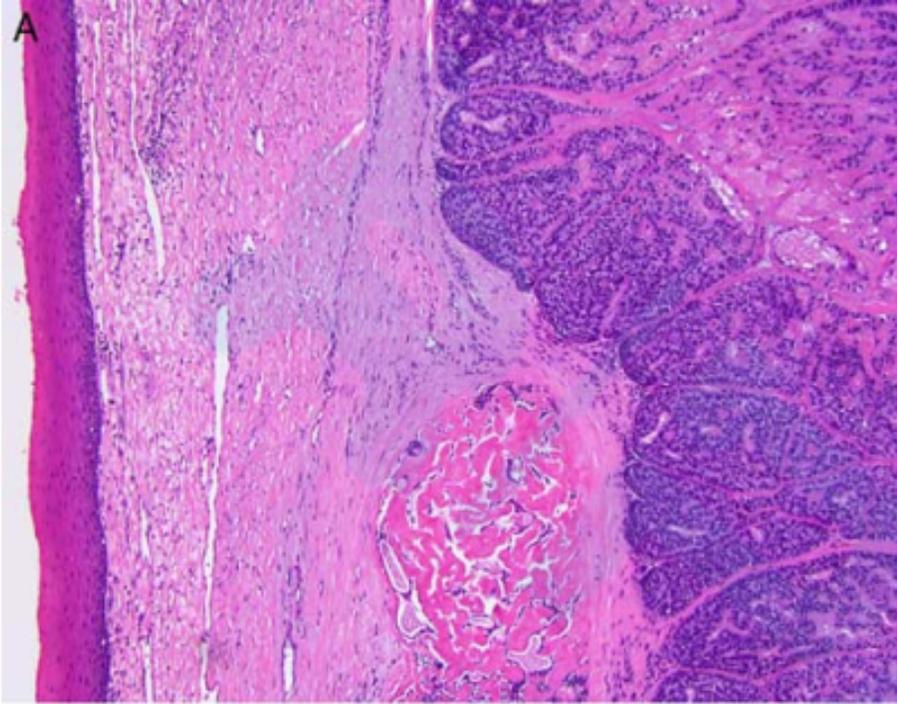
4例重排  
 3例重排+超倍体  
 3例超倍体  
 3例重排+超倍体

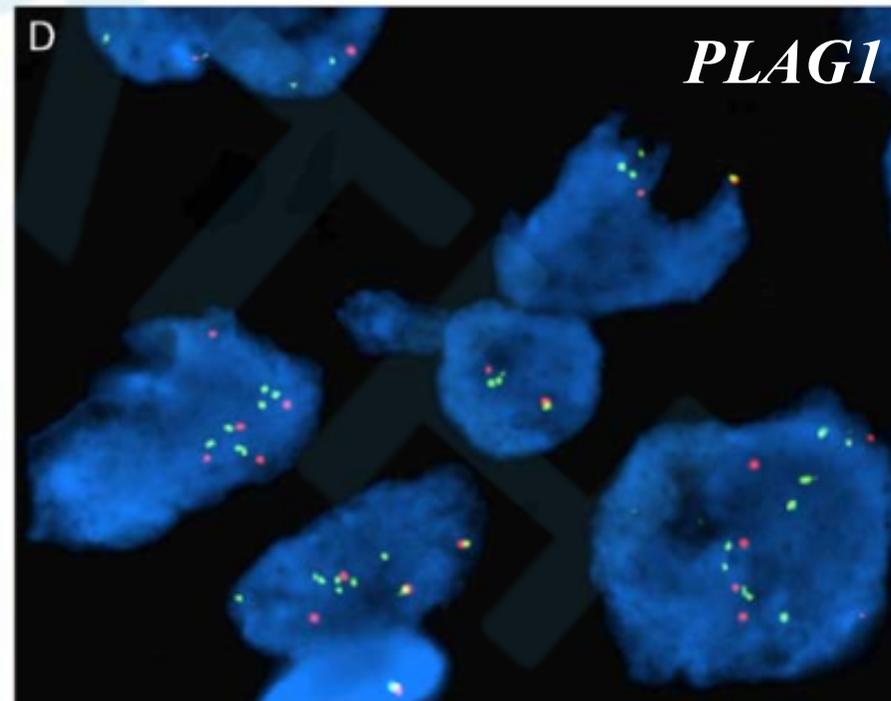
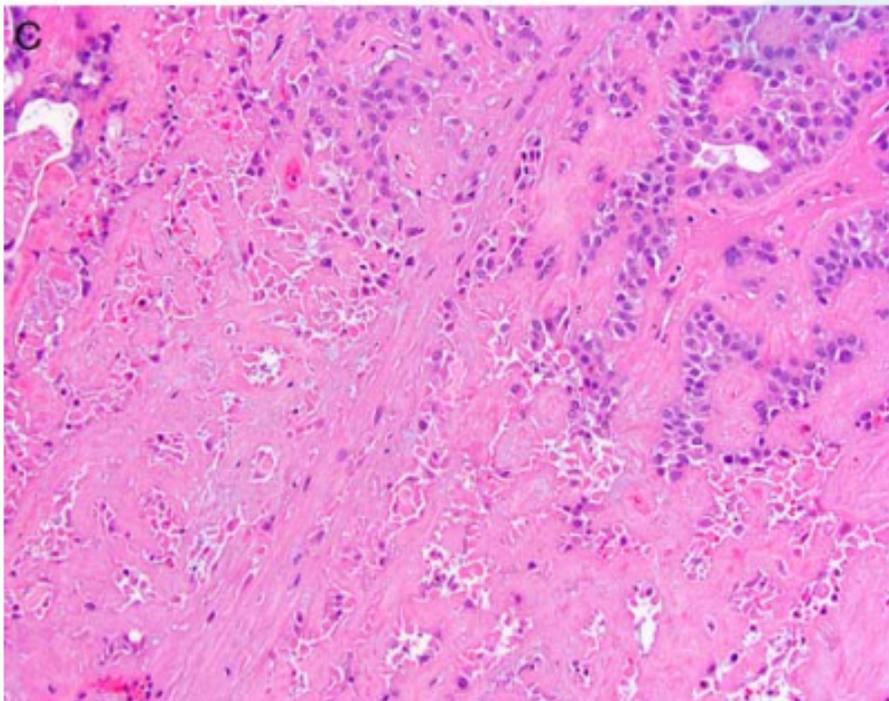
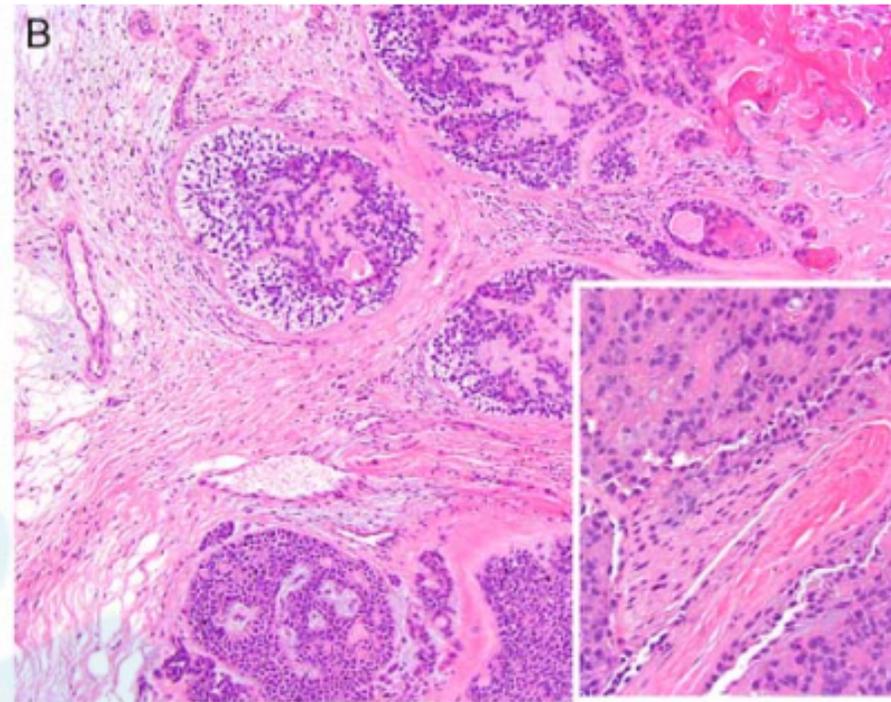
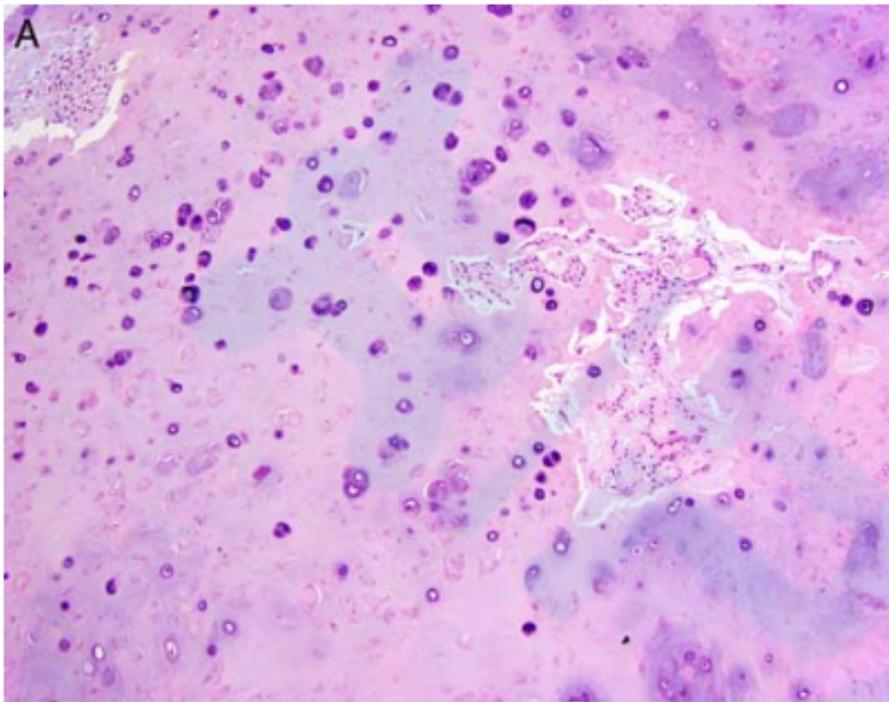
FISH检测为完整的*PLAG1*与*HMGA2*病例进行  
 NGS检测，其中2例检测到*FGFR1-PLAG1*融合

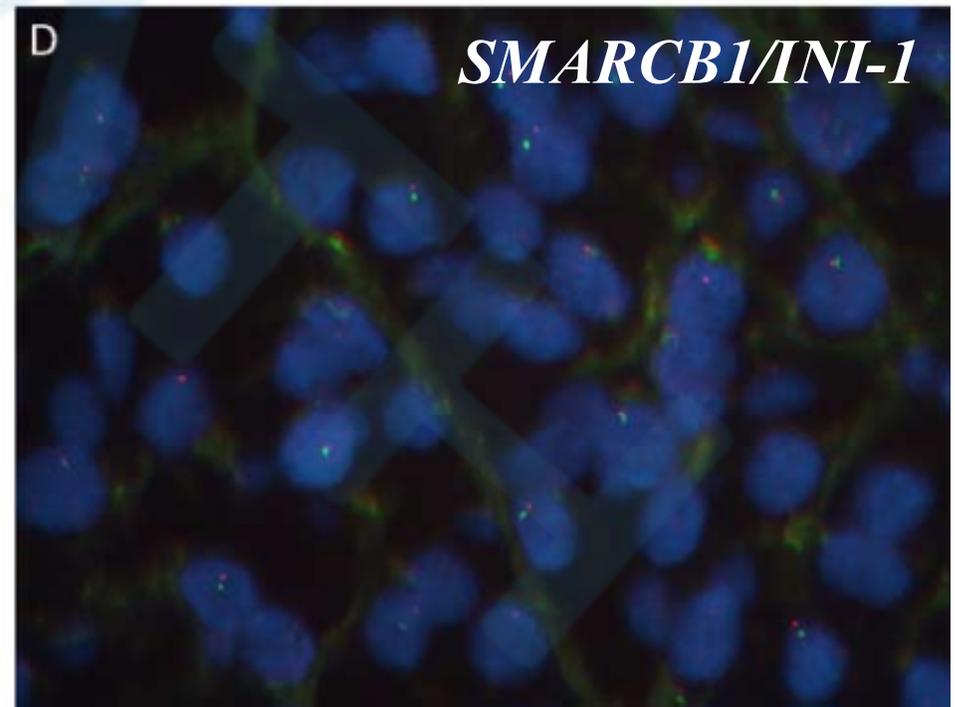
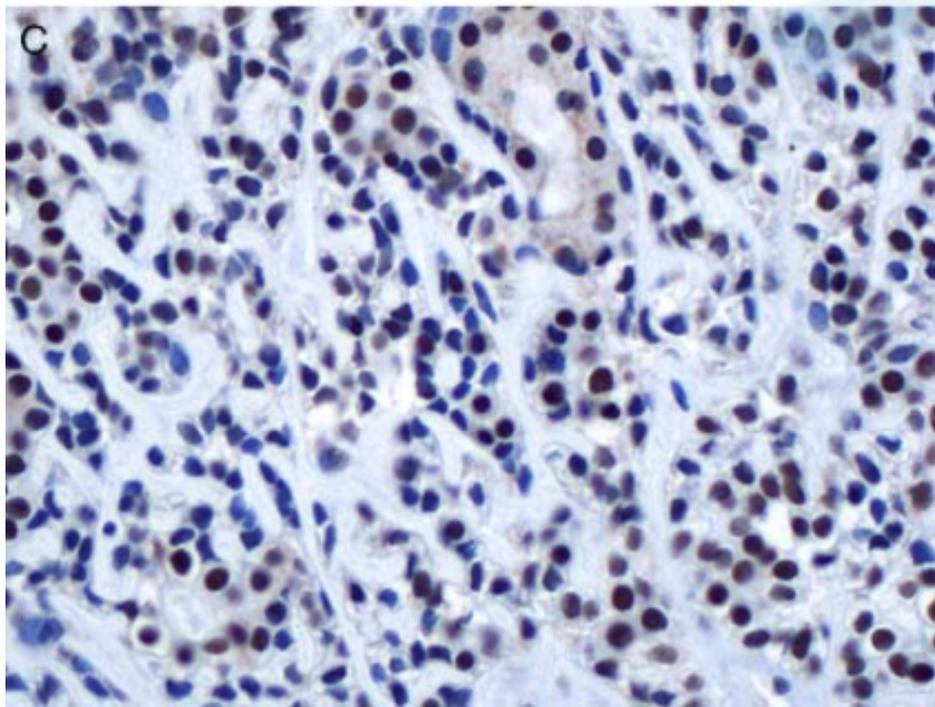
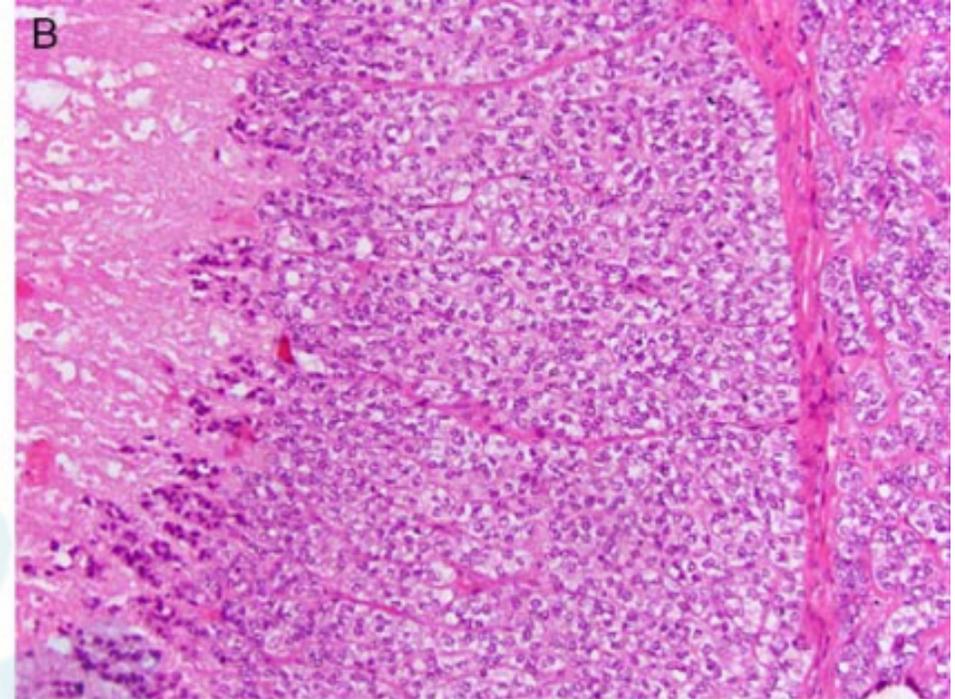
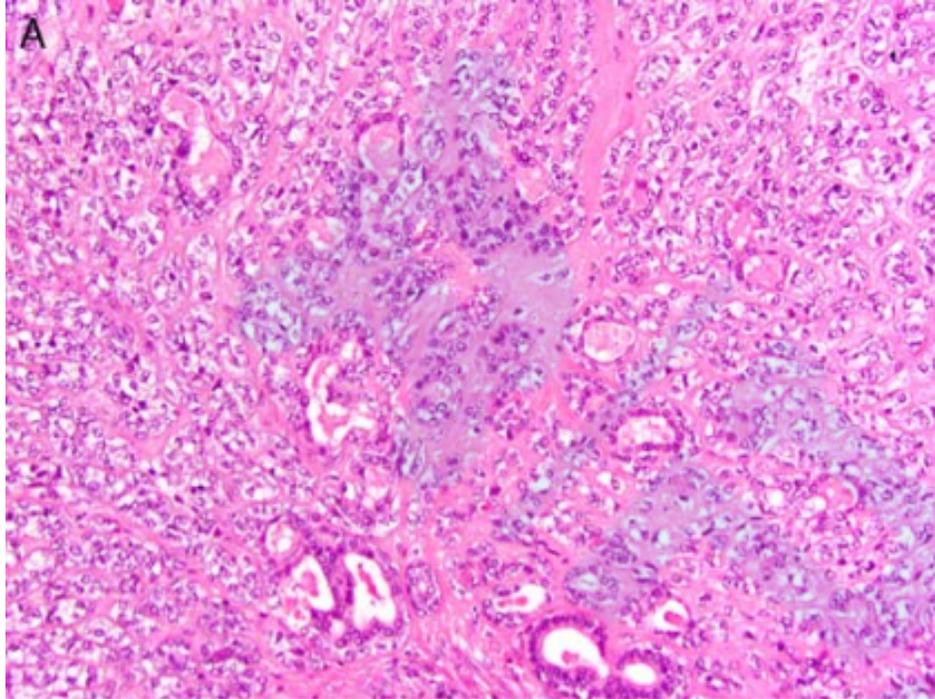


**FIGURE 7.** Subsets of EMCA: relationship between the morphologic evidence of PA and *PLAG1* or *HMGA2* status.









# 讨论

- *PLAG1*、*HMGA2*异常与存在多形性腺瘤的形态学证据关系密切
- 结合形态及分子检测，本研究中绝大部分EMCAs（31/39,80%）由多形性腺瘤发展而来

- *PLAG1*异常在多形性腺瘤与EMACs中的发生率相似，提示*PLAG1*异常与多形性腺瘤向EMCAs恶性转化无关。
- 与多形性腺瘤相比，*HMGA2*异常在EMCAs中更常见
- *HMGA2*阳性多形性腺瘤患者平均年龄为45.9岁，*HMGA2*阳性EMCAs患者平均年龄为69岁，提示*HMGA2*阳性多形性腺瘤患者需要24年发展为EMCAs

- *PLAG1*与*HMGGA2*完好的EMCAs病例中，*HRAS*突变率最高，随后是*TP53*, *FBXW7*, and *SMARCB1*
- 本研究中不同的组织学类型（如嗜酸性化生、顶浆分泌）病例数过少，因此无法确定这些组织学类型是否具有特定的分子特征

- 23例EMCAs中检测到1例*SMARCB1/INI-1*缺失，提示EMCAs可能与*SMARCB1/INI-1*缺失相关
- 该病例组织学为高级别，肌上皮增生过度，*INI-1*免疫组化显示肌上皮缺失*INI-1*，而导管上皮不缺失，提示*SMARCB1/INI-1*缺失可能是促使肌上皮成分向高级别转化的分子事件

# 局限性

- *PLAG1* FISH无法检测染色体内重排，如*FGFR1-PLAG1*
- FISH分离探针无法检测*PLAG1*或*HMGA2*的融合基因
- 导致多形性腺瘤向EMCAs转化的遗传事件仍然未知，本研究中NGS 所运用的50-癌症相关基因panel缺少能够促使*PLAG1*、*HMGA2*相关EMACs发展的基因

# 结 论

- 组织学与分子学证实，超过80%的EMCAs由多形性腺瘤发展而来，其中高级别EMCAs可占到30%
- EMCAs的基因特征与*PLAG1*及*HMGA2*的状态相关
- *PLAG1*及*HMGA2*无突变的EMCAs病例更可能发生*HRAS*突变，该突变在低级别EMCAs与高级别EMCAs中分布无差异
- *PLAG1*及*HMGA2*无突变的高级别EMCAs还可发生*TP53*, *SMARCB1*, 及*FBXW7*改变

■ THANK YOU

Any questions?

Q&A

