Pleomorphic and Florid Lobular Carcinoma In Situ Variants of the Breast

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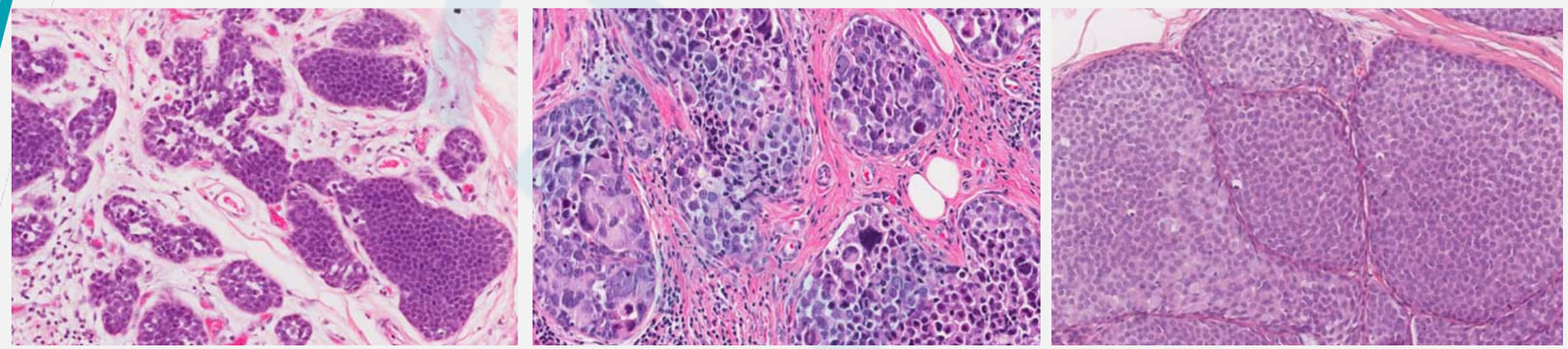


吴建锋

2019.04.10

目录

Part One
关键词

LCIS：小叶原位癌

CLCIS：经典型小叶原位癌

PLCIS：多形性小叶原位癌

FLCIS：旺炽性小叶原位癌

01 PART ONE
关键词——LCIS/CLCIS

1.定义：乳腺小叶（型）恶性上皮增生，癌细胞局限于小叶终末导管基底膜内，未突破基底膜，无镜下间质浸润的乳腺癌。

2.临床特征：常发生于绝经期前女性，50-60%多中心性，30-40%双侧发生。

3.形态学：

1）病变局限于终末导管小叶单位，小叶扩大变形，腺管（终末导管和腺泡）基膜完整；

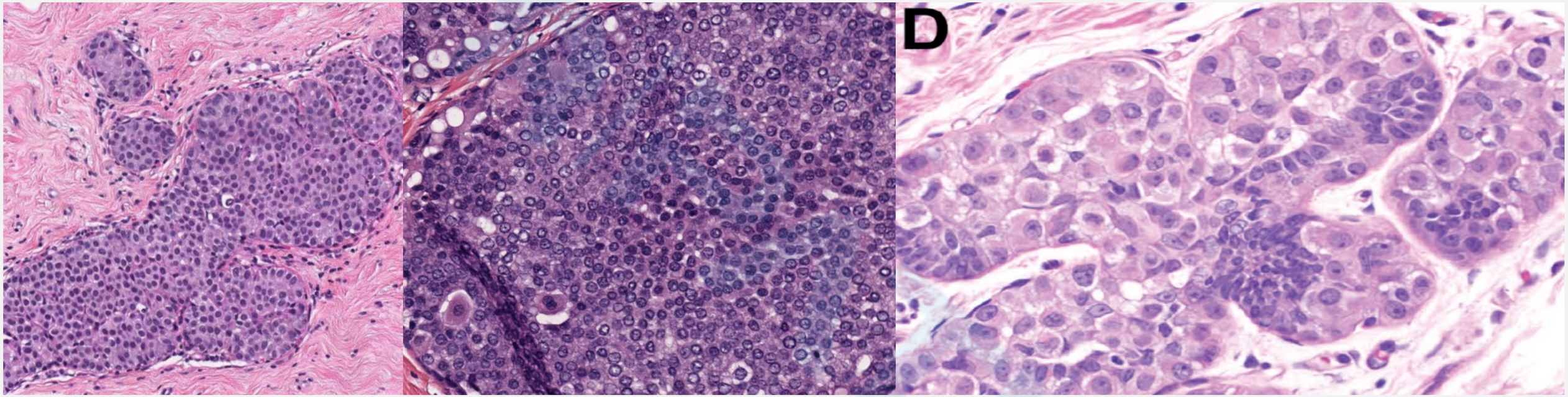
2）腺管明显膨大，充满均匀一致的瘤细胞，亦可呈腺样或筛状；

3）瘤细胞通常体小，形态温和，圆-多边形，核深染，无明显核仁，可有核沟。胞质较少，细胞界限不清，黏着性差；

4）常见胞质内空泡（其内可见嗜酸性小球）或印戒样细胞，黏液染色阳性；

5）核分裂象少见，坏死及钙化少见，增生细胞可比较大，有一定多形性和异型性。

01 PART ONE
关键词——LCIS/CLCIS

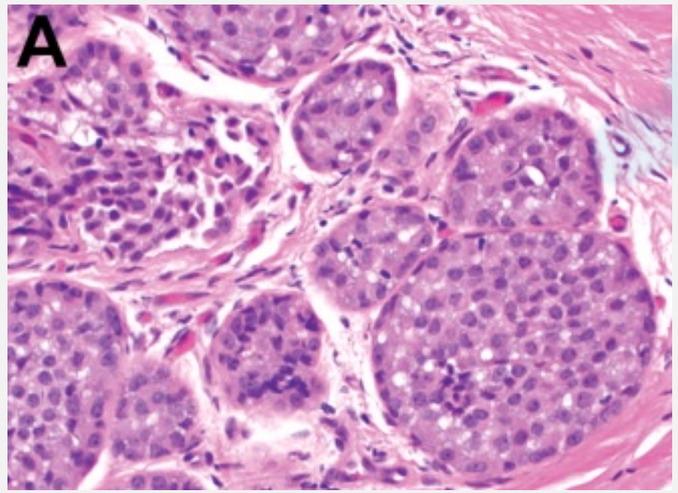


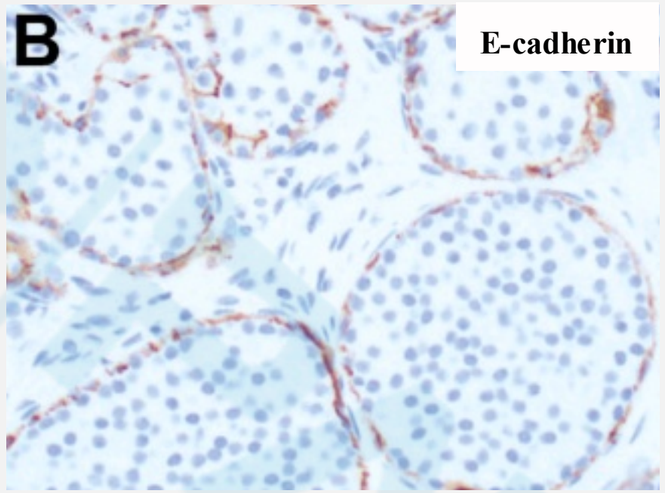
A型：肿瘤细胞胞质稀少，细胞核小、形态单一，呈圆形或卵圆形，无核仁

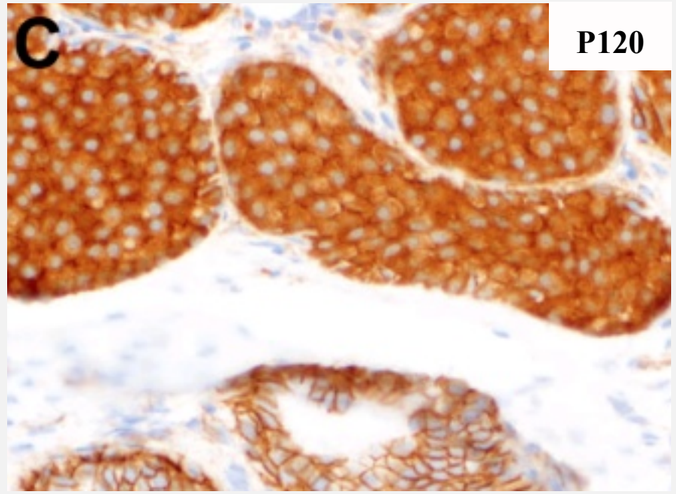
B型：细胞出现轻度多形性，即细胞核较大、可见核仁、胞质数量相对稍多

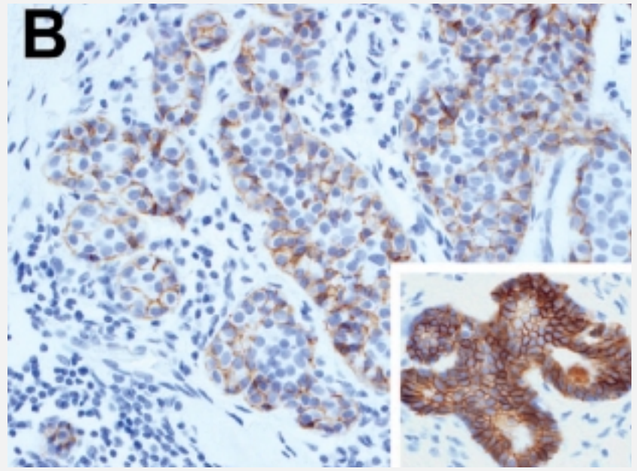
01 PART ONE

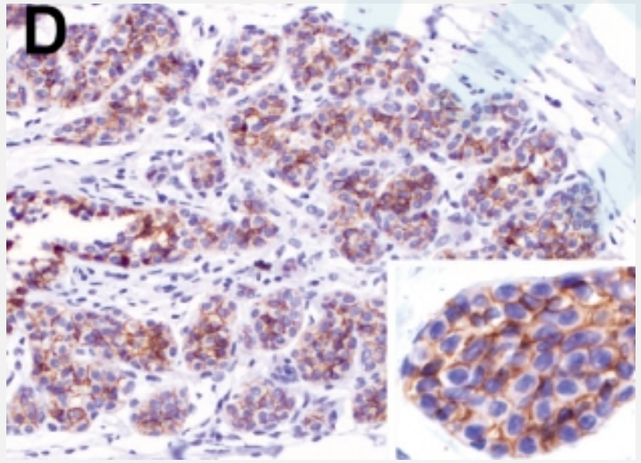
关键词——LCIS/CLCIS



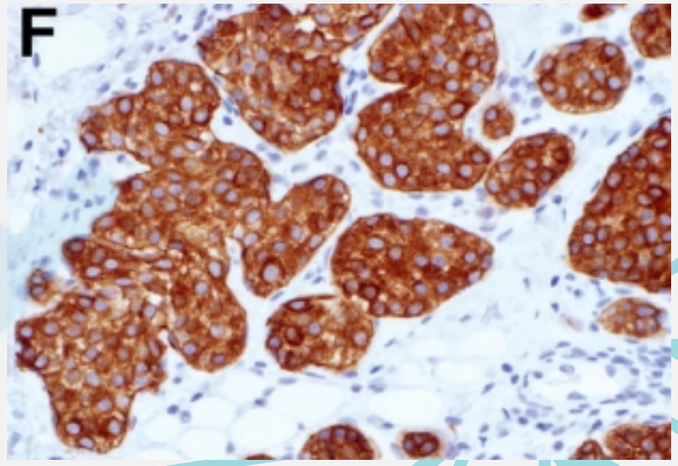






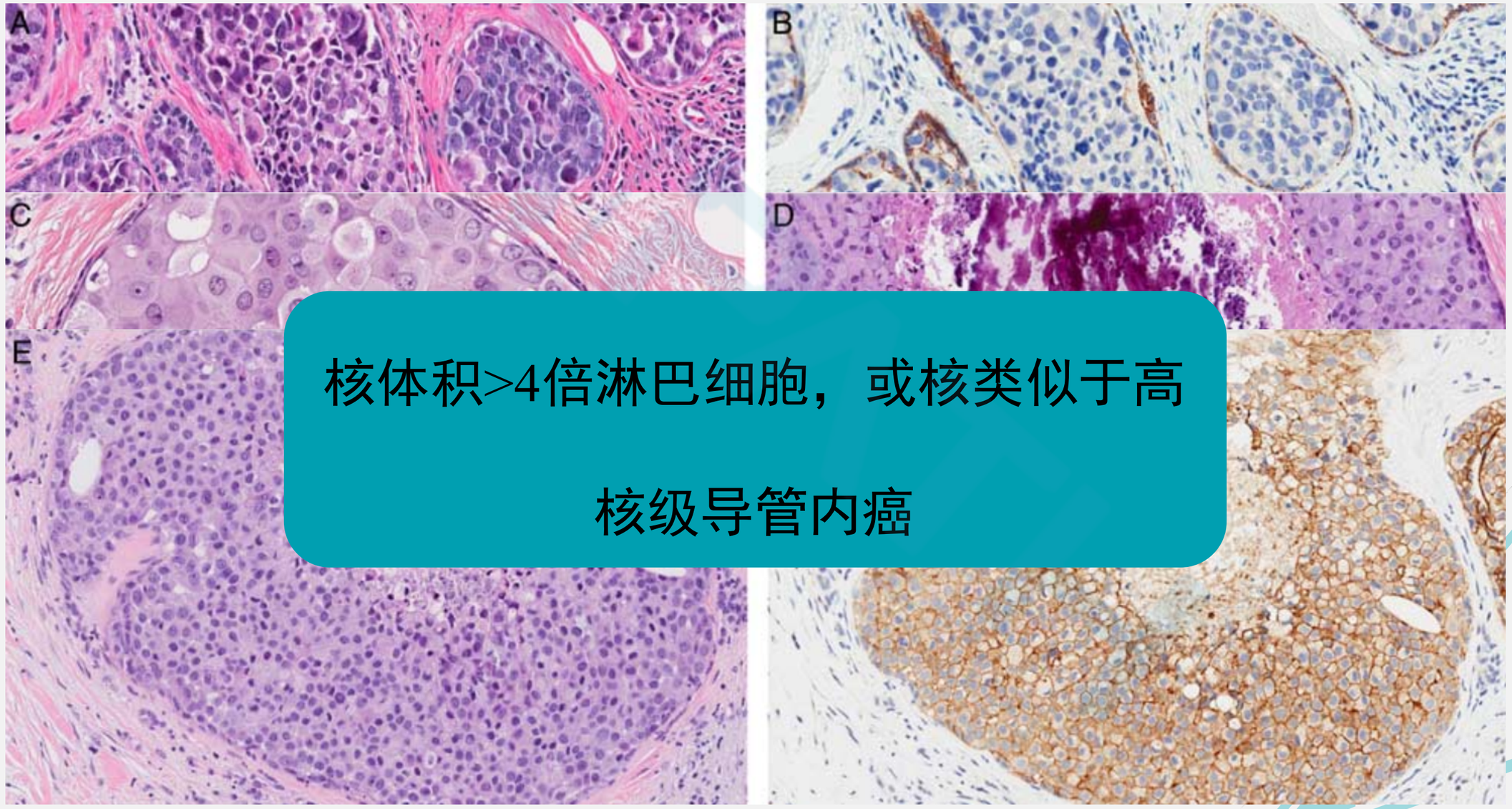


E-cadherin异常表达



01 PART ONE

关键词——PLCIS



核体积>4倍淋巴细胞，或核类似于高

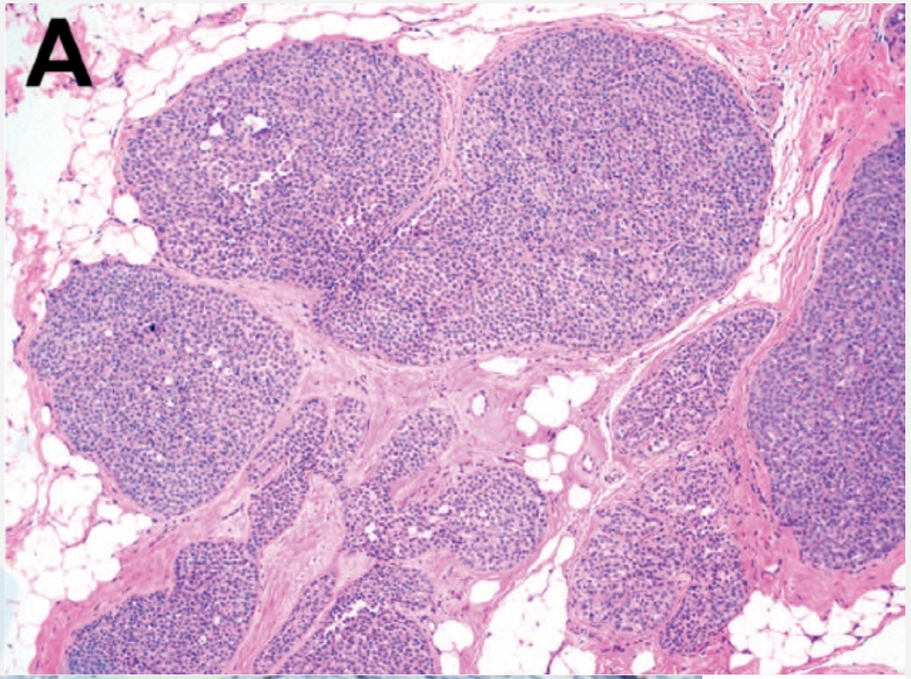
核级导管内癌

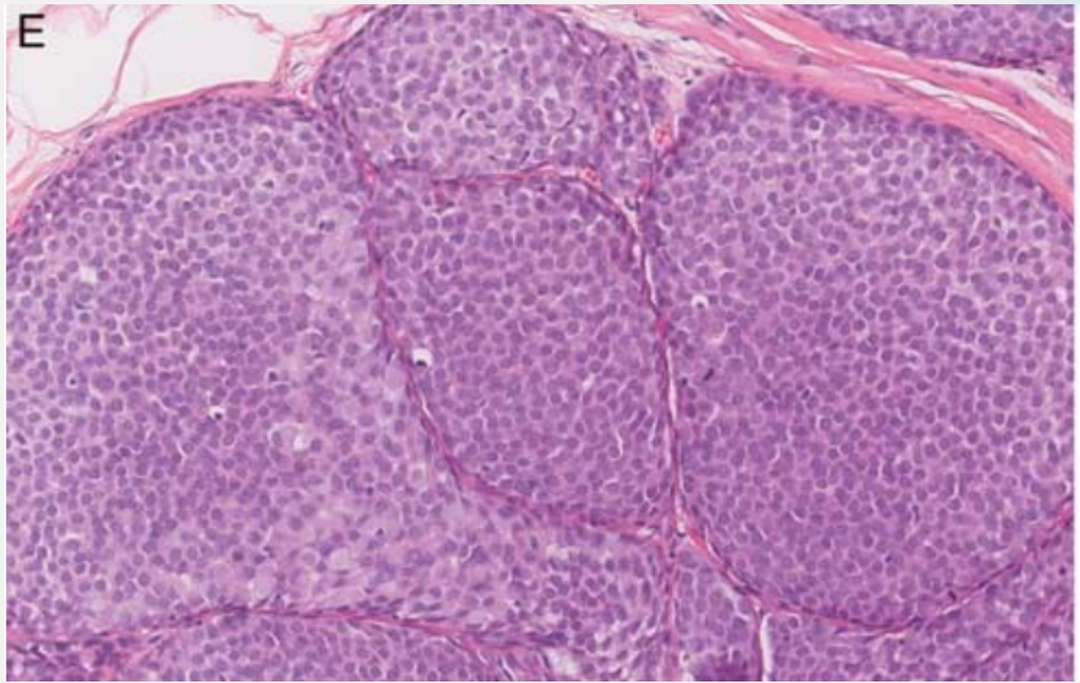
01 PART ONE

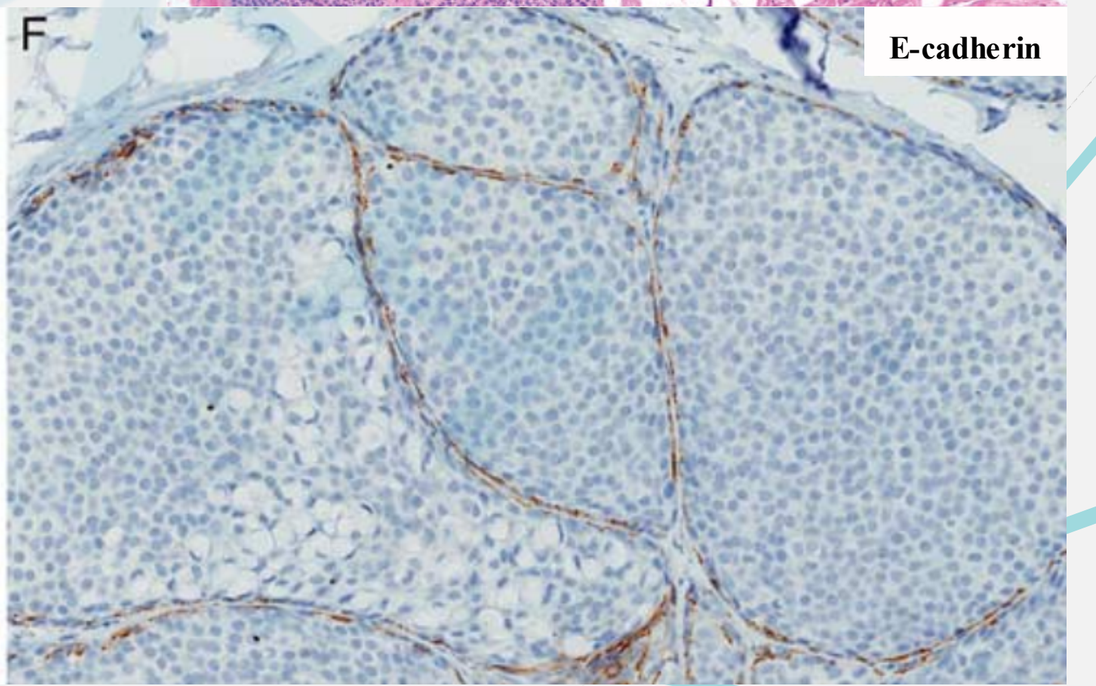
关键词——FLCIS

1）受累的终末小叶导管之间间质很少或消失；

2）单个腺泡至少占据一个高倍镜视野（直径大约40个细胞）。







01 PART ONE
关键词——CLCIS/PLCIS/FLCIS

TABLE 1. Histopathologic Features of Classic Lobular Carcinoma In Situ and Lobular Carcinoma In Situ Variants

	Classic LCIS	Florid LCIS	Pleomorphic LCIS
Loss of cohesion	Present	Present	Present
Cytologic features	Type A: small, uniform round nucleus (1-1.5× size of lymphocyte nucleus) with dense chromatin, scant cytoplasm Type B: larger nucleus (2× size of lymphocyte nucleus) with more variable shape, open chromatin, more abundant cytoplasm, +/− nucleoli	Type A, type B, or mixture of type A and B cells; often type B	Marked nuclear pleomorphism akin to high grade DCIS (~2-3-fold size variation) and/or at least some nuclei >4× size of lymphocyte nucleus
Architectural requirement	At least 50% of acini expanded (≥8 cells diameter)	(1) No or little intervening stroma between markedly expanded ductules of TDLU, and/or (2) expanded acinus/duct entirely fills one high-power field (~40 cells diameter)	None
Comedonecrosis	Absent	May be present	May be present
Distribution	Multifocal, discontinuous	Unifocal, continuous	Unifocal, continuous
E-cadherin	Negative or aberrant immunostaining	Negative or aberrant immunostaining	Negative or aberrant immunostaining

Part Two
研究目的

02 PART TWO
研究目的

1

CLCIS

是浸润性癌的危险因素（约1-4%），无需手术切除，仅长期随访

2

PLCIS

发展为浸润性癌的几率高（25-60%），切除后复发率（0-57%）

3

FLCIS

生物学行为及预后数据少

研究目的

通过回顾性研究，揭示PLCIS、FLCIS的临床、形态学特征及其与浸润性癌的关系，从而阐明其生物学行为及其最有效的治疗方案

Part Three
材料与方法

03 PART Three 材料与方法

病例收集

85 PLCIS and FLCIS diagnosed on core biopsy and/or surgical excision between 1997 and 2017 at UCSF Department of Pathology

1

- CLCIS
- PLCIS
  - PLCIS+/-necrosis
  - Apocrine PLCIS +/-necrosis
- FLCIS
  - FLCIS-necrosis
  - FLCIS+necrosis

2

评估组织学特征

① 是否存在粉刺样坏死；
② 肿瘤大小；
③ 组织学类型；
④ 分级；
⑤ 相关浸润性癌的分子标记特征

3

免疫组化及Spatial Mapping

✓ER、PR、Her-2、Ki-67、E-cadherin、P120

✓PLCIS/FLCIS与浸润性癌的大小； PLCIS/FLCIS单发或多发； PLCIS/FLCIS与浸润性癌是混合存在还是分离；CLCIS与PLCIS/FLCIS是否混合存在。

Part Four
研究结果

04 PART FOUR 研究结果

TABLE 2. Clinicopathologic Features of LCIS Variants

	n	Age, Mean (Range)	No. Pure LCIS Variant	No. LCIS Variant+DCIS	No. LCIS Variant+Invasive Carcinoma			
					ILC (mi)	PILC (mi)	IDC	ICDLF
PLCIS+/−necrosis	49	58 (42-83)	6*	3	7	25† (1)	1	5
Apocrine PLCIS +/−necrosis	12	70 (49-81)	3‡	1	3	2	0	0
PLCIS total	61	61 (42-83)	9	4	10	27 (1)	1	5
FLCIS−necrosis	9	54 (45-69)	4§	0	2 (1)	0	0	2
FLCIS+necrosis	15	57 (40-86)	1‖	1	7 (4)	0	1	1
FLCIS total	24	56 (40-86)	5	1	9 (5)	0	1	3
All cases	85	59 (40-86)	14¶	5	19 (5)	27 (1)	2	8

- ✓ 伴大汗腺化生的PLCIS患者年龄更大；
- ✓ 大部分PLCIS伴有浸润性癌（77%），都伴有明显的肿块或影像显示异常密度影。

PLCIS

- ✓ 大部分FLCIS伴有浸润性癌（75%）；
- ✓ 伴坏死的纯FLCIS在影像上可显示钙化灶；不伴坏死的病灶在影像上无明显改变。

FLCIS

TABLE 2. Clinicopathologic Features of LCIS Variants

	n	Age, Mean (Range)	No. Pure LCIS Variant	No. LCIS Variant+DCIS	No. LCIS Variant+Invasive Carcinoma			
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FLCIS total	24	56 (40-86)	5	1	9 (5)	0	1	3
All cases	85	59 (40-86)	14¶	5	19 (5)	27 (1)	2	8

- ✓ 大部分浸润性癌伴有小叶分化（97%）；
- ✓ PLCIS与FLCIS发生的浸润性癌无明显大小差异，但FLCIS发生的浸润性癌更常见微浸润

04 PART FOUR 研究结果

TABLE 3. Grades and Immunohistochemical Profiles of Invasive Carcinoma Associated With Lobular Carcinoma In Situ Variants

		mSBR Grade of Associated Invasive Carcinoma*			Biomarker Profile of Associated Invasive Carcinoma†			
	n	1 (%)	2 (%)	3 (%)	ER+ (%)	PR+ (%)	HER2+ (%)	TN (%)
PLCIS +/−necrosis	39	0	28 (78)	8 (22)	32 (84)	21 (55)	5 (13)	3 (8)
Apocrine PLCIS +/−necrosis	5	0	5 (100)	0	2 (40)	2 (40)	1 (20)	2 (40)
PLCIS total	44	0	33 (80)	8 (20)	34 (79)	23 (53)	6 (14)	5 (12)
FLCIS−necrosis	5	0	4 (100)	0	5 (100)	5 (100)	0	0
FLCIS+necrosis	13	2 (22)	7 (78)	0	11 (100)	9 (82)	1 (9)	0
FLCIS total	18	2 (15)	11 (85)	0	16 (100)	14 (88)	1 (6)	0

- ✓ 2级占80%、3级占20%；
- ✓ 大部分ER、PR阳性（分别为79%、53%），仅14%HER-2阳性，12%为三阴性；
- ✓ 6例HER-2阳性病例中5例为非大汗腺化生。

PLCIS

- ✓ 浸润性癌中无多形性成分；
- ✓ 1级占15%、2级占85%；
- ✓ 所有病例ER阳性，82%PR阳性，只有一例HER-2阳性。

FLCIS

04 PART FOUR 研究结果

TABLE 4. Management and Outcomes of Pure Lobular Carcinoma In Situ Variants on Core Biopsy

Biopsy Diagnosis	n	Surgery (%)	LE/M/M After LE	Final Margin Status for LCIS Variant	Upgrade Rate (%)	Upgrade Diagnosis (n)	Recurrence (Mean Follow-up, mo)	XRT* (%)	HT* (%)
PLCIS +/−necrosis	5	4/5 (80)†	1/2/1	Negative in 4/4	2/4 (50)	PILC (1), ILC (1)	0/5 (35)	0/3 (0)	1/3 (33)
Apocrine PLCIS +/−necrosis	7	6/6 (100)‡	3/1/2	Positive in 1/4§	1/4 (25)	ILC (1)	0/4 (28)	0/3 (0)	2/3 (67)
PLCIS total	12	10/11 (91)	4/3/3	Positive in 1/8	3/8 (38)	PILC (1), ILC (2)	0/9 (32)	0/6 (0)	3/6 (50)
FLCIS−necrosis	4	1/4 (25)	0/1/0	Negative in 1/1	0/1 (0)	—	0/4 (60)	0/4 (0)	2/4 (50)
FLCIS+necrosis‖	5	5/5 (100)	2/1/2	Negative in 5/5	2/5 (40)	ILC (1), DCIS (1)	0/4 (42)¶	0/2 (0)	2/2 (100)
FLCIS total	9	6/9 (67)	2/1/2	Negative in 6/6	2/6 (33)	ILC (1), DCIS (1)	0/8 (51)	0/6 (0)	4/6 (67)

- ✓ 8例手术标本中3例诊断升级；均无淋巴结转移；
- ✓ 3位患者进行二次手术；
- ✓ 半数患者接受激素治疗；
- ✓ 所有患者均无复发（平均随访时间32个月）

PLCIS

- ✓ 6例手术标本中2例诊断升级；均无淋巴结转移；
- ✓ 2位患者进行二次手术；
- ✓ 67%患者接受激素治疗；
- ✓ 所有患者均无复发（平均随访时间50个月）

FLCIS

TABLE 5. Biomarker Profiles of Pure Lobular Carcinoma In Situ Variants on Core Biopsy and Associated Classic Lobular Carcinoma In Situ/Upgraded Invasive Lobular Carcinoma

		Classic LCIS				LCIS Variant				Invasive Carcinoma (Excision)		
#	Biopsy Diagnosis	ER* % (H-score)	PR % (H-score)	HER2†	Ki-67%	ER % (H-score)	PR % (H-score)	HER2†	Ki-67%	ER % (H-score)	PR % (H-score)	HER2†
1	PLCIS										—	—
2	PLCIS										—	—
3	PLCIS										—	—
4	PLCIS										00 (290)	3+
5	PLCIS										0	2+‡
6	apo PLCIS										—	—
7	apo PLCIS										—	—
8	apo PLCIS										—	—
9	apo PLCIS										—	—
10	apo PLCIS										—	—
11	apo PLCIS										—	—
12	apo PLCIS										0	3+
13	FLCIS-nec										—	—
14	FLCIS-nec										—	—
15	FLCIS-nec										—	—
16	FLCIS-nec										—	—
17	FLCIS+nec	95 (250)	10 (17)	1+	3	95 (250)	2 (6)	2+	2	—	—	—
18	FLCIS+nec	NA	NA	NA	NA	NA	NA	NA	NA	—	—	—
19	FLCIS+nec	95 (255)	70 (100)	2+	<1	95 (255)	95 (135)	3+	21	—	—	—
20	FLCIS+nec	100 (250)	5 (7)	1+	<1	60 (135)	0	1+	3	—	—	—
21	FLCIS+nec	90 (225)	50 (125)	1+	1	90 (240)	1 (2)	1+	2	95 (230)	0	1+

- ✓ 在LCIS Variant中ER表达明显降低；PR表达无统计学差异；
- ✓ FLCIS与CLICS的ER、PR表达无统计学差异；
- ✓ 4例（20%）LCIS Variant病例HER-2 3+；CLCIS病例HER-2无3+；
- ✓ 在伴发浸润性癌的病例中，LCIS Variant与ILC成分的ER、HER-2表达一致；PR稍有区别；
- ✓ LCIS Variant病例KI-67较CLCIS高。

Part Five
讨论

发生

- ✓ 本研究首次分析PLCIS与FLCIS的发生率，PLCIS明显较FLCIS多（72%vs28%）；但PLCIS、FLCIS的判断标准主观性强，因此不能排除由于错误分类造成的差距；
- ✓ 单纯的PLCIS较少，大部分PLCIS病例均合并浸润性癌成分，需充分取材；

05 PART FIVE
讨论

诊断

- ✓ 实性生长的导管内癌形态与PLCIS、FLCIS相似，如E-cadherin出现异常表达，常常出现误诊；
- ✓ 提出FLCIS更客观的诊断标准：单个腺泡至少占据一个高倍镜视野（直径约40个肿瘤细胞）；
- ✓ PLCIS病例在影像学上总能见到钙化灶，而CLCIS出现钙化灶较少见；
- ✓ FLCIS病例在影像上也有变化，伴有坏死的表现为钙化灶，无坏死的表现为无明显肿块的增强影；
- ✓ 首次分析FLCIS的诊断升级率（33%），与先前报道的PLCIS的升级率一致（38%）；

05 PART FIVE
讨论

治疗、预后

- ✓ 本研究结果提示在穿刺活检诊断PLCIS、FLCIS的病例均应手术切除；
- ✓ 但4例FLCIS不伴坏死的患者有3例均未手术切除，目前随访时间56-73个月，均未复发，是否因为病例过少或不伴坏死的FLCIS的生物学行为不一样还需进一步的研究证实；
- ✓ 诊断为LCIS Variant的切除病例的最优化治疗目前仍不清楚，是否需要获得阴性切缘以及辅助性放疗？本研究结果显示应尽可能使切缘干净，但放疗无必要；

Pleomorphic lobular carcinoma in situ of the breast: clinicopathological review of 47 cases.

Khoury T[1], Karabakhtsian RG, Mattson D, Yan L, Syriac S, Habib F, Liu S, Desouki MM.

Clinical implications of margin involvement by pleomorphic lobular carcinoma in situ.

Downs-Kelly E[1], Bell D, Perkins GH, Sneige N, Middleton LP.

Pleomorphic lobular carcinoma in situ of the breast: a single institution experience with clinical follow-up and centralized pathology review.

De Brot M[1], Koslow Mautner S[2], Muhsen S[2], Andrade VP[1], Mamtani A[2], Murray M[3], Giri D[3], Sakr RA[2], Brogi E[3], King TA[4,5].

Clinical, histopathologic, and biologic features of pleomorphic lobular (ductal-lobular) carcinoma in situ of the breast: a report of 24 cases.

Sneige N[1], Wang J, Baker BA, Krishnamurthy S, Middleton LP.

Part Six
总结

06 PART SIX 总结

- ✓ PLCIS、FLCIS与浸润性小叶癌的发生相关，但二者的生物学行为有区别；
- ✓ LCIS Variant是浸润性小叶癌的前驱病变，ER、HER-2在LCIS Variant和小叶癌中的表达一致也支持该观点；
- ✓ 如果PLCIS具有以下免疫表型特征时，其生物学行为更具有侵袭性，HER-2过表达、KI67高表达、ER低表达；
- ✓ 关于PLCIS、FLCIS的更详尽的分子及遗传学研究（包括肿瘤发生的驱动基因）将更加深我们对这类疾病的认识。

THANK YOU

Any questions?

Q&A