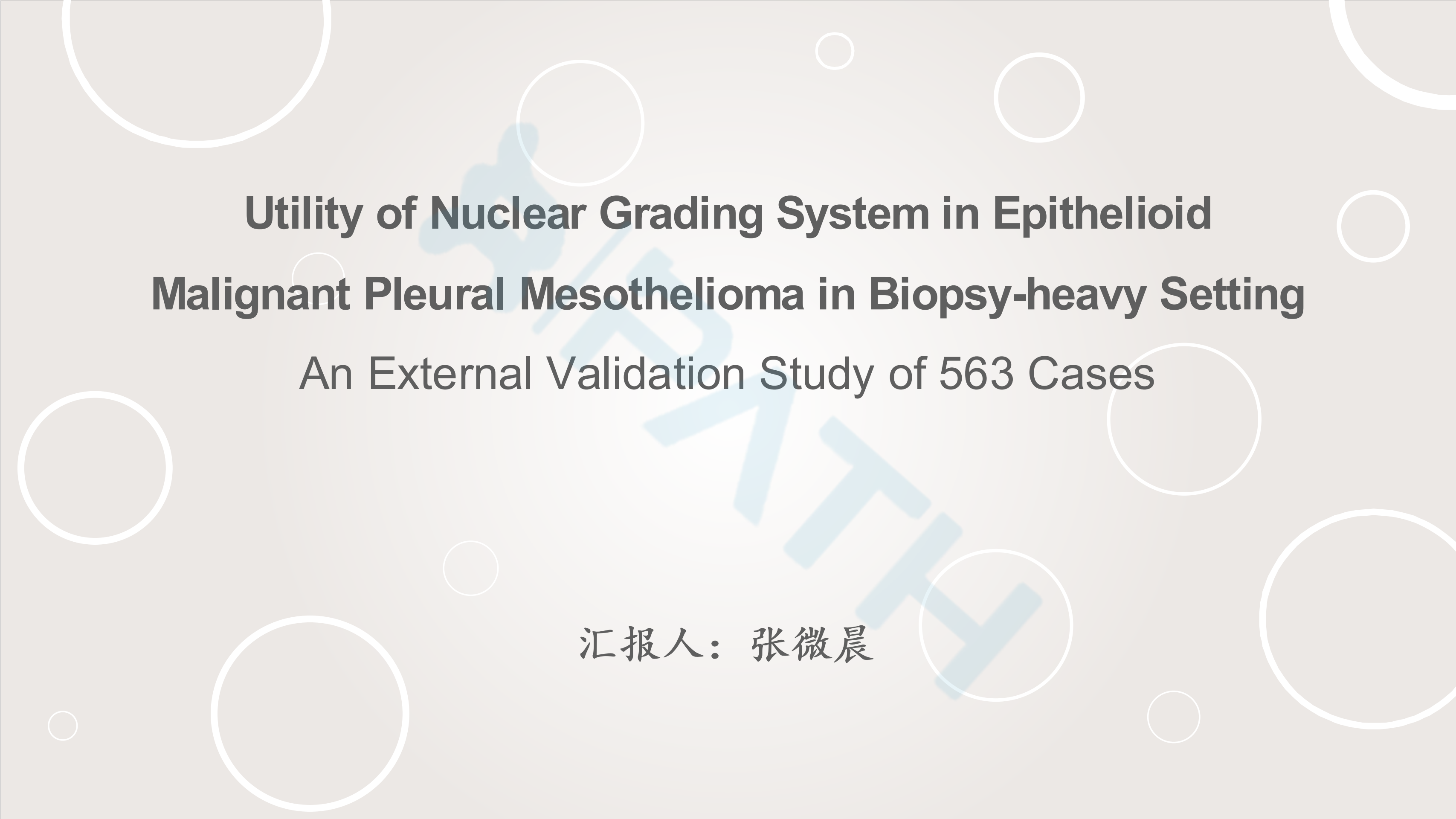




Utility of Nuclear Grading System in Epithelioid Malignant Pleural Mesothelioma in Biopsy-heavy Setting

An External Validation Study of 563 Cases

汇报人：张微晨

恶性胸膜间皮瘤 (Malignant Pleural Mesothelioma , MPM)

概述： 原发于胸膜间皮表面罕见、恶性程度高的恶性肿瘤，约占胸膜恶性肿瘤的**5%**，占全部恶性肿瘤的**0.04%**。临床上分为局限型和弥漫型两种，前者多为良性或低度恶性，后者多为高度恶性。

流行病学： **MPM**发病率不断上升，过去**10**年每年上升**50%**，我国发病率为**0.02/10万-0.03/10万**。好发年龄**40-70**岁，男性多于女性。

致病因素： 石棉、矿物、放射线、病毒 (**SV40**)、家族遗传 (常染色体显性遗传) 等。

恶性胸膜间皮瘤（MPM）

临床表现：（1）常见症状：胸痛、呼吸困难、消瘦等。

（2）其他症状：咳嗽、声嘶、发热、盗汗。

95%的病例可有胸腔积液。

预后：中位生存期**4-9个月**。**2年生存率0%-10%，5年生存率<5%。**

病理诊断（大体）

病变发生于壁层或膈胸膜，呈弥漫性生长，胸膜增厚，形成多发的融合结节或肿块，常见坏死和出血。



Fig. 7.72 Classical pattern of spread of advanced pleural mesothelioma. (Courtesy of Dr. RA Cooke, Brisbane, Australia; from Cooke RA, Stewart B: Colour Atlas of Anatomical Pathology. Edinburgh, Churchill Livingstone, 2004).

病理诊断（镜下）

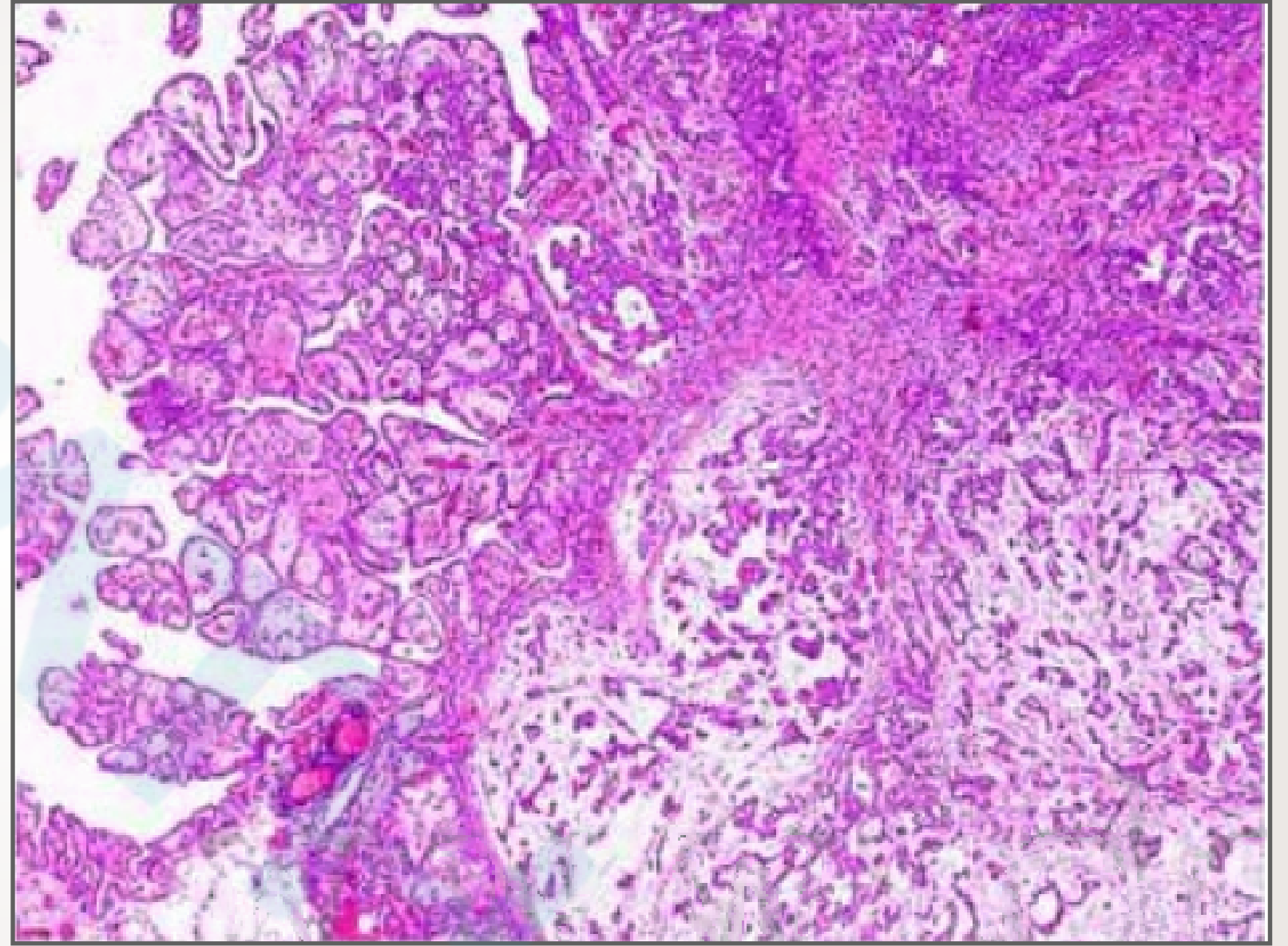
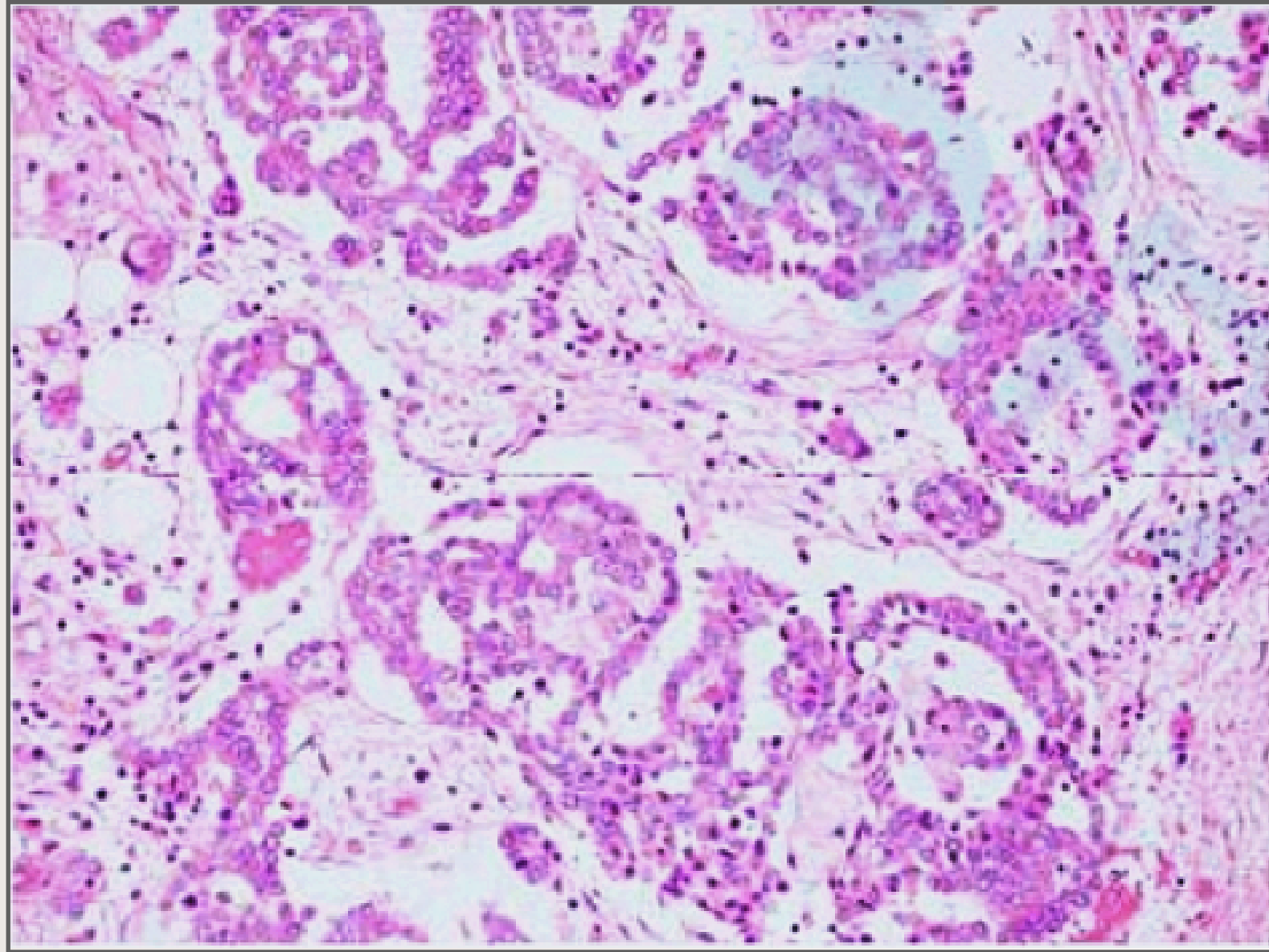
上皮样（50%，预后较好）

肉瘤样（35%，侵袭性强，生存<6个月）

双相性/混合性

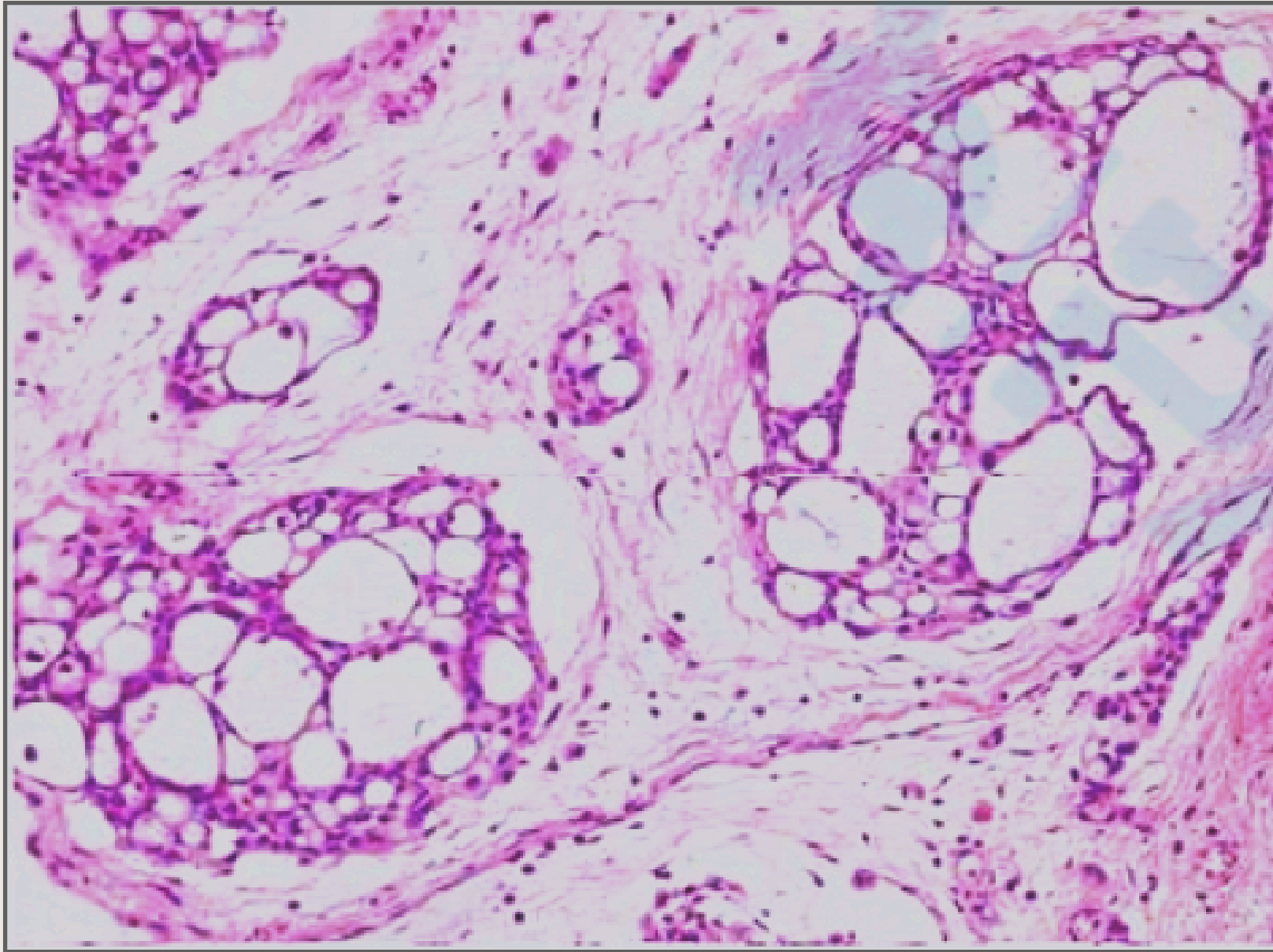
- 上皮样间皮瘤
 - 管状乳头状(tubulopapillary)
 - 微乳头状(micropapillary)
 - 梁状(trabecular)
 - 小腺泡状/腺样(acinar/glandular)
 - 腺瘤样/微腺样(adenomatoid/microglandular)
 - 腺样囊性(adenoid cystic)
 - 实性(solid)
 - 小细胞(small cell)
 - 透明细胞(clear cell)
 - 蜕膜样(deciduoid)
 - 印戒细胞样(signet ring cell-like)
 - 横纹肌样(rhabdoid)
 - 多形性(pleomorphic)
 - 淋巴组织细胞样(lymphohistiocytoid) *
 - 黏液样(myxoid)
- 肉瘤样间皮瘤
 - 梭形细胞型(spindle cell)
 - 促结缔组织增生性(desmoplastic)
 - 伴有异源性分化(with heterologous differentiation)
- 双相性间皮瘤
 - 弥漫性肺内间皮瘤(diffuse intrapulmonary)

病理诊断（镜下）

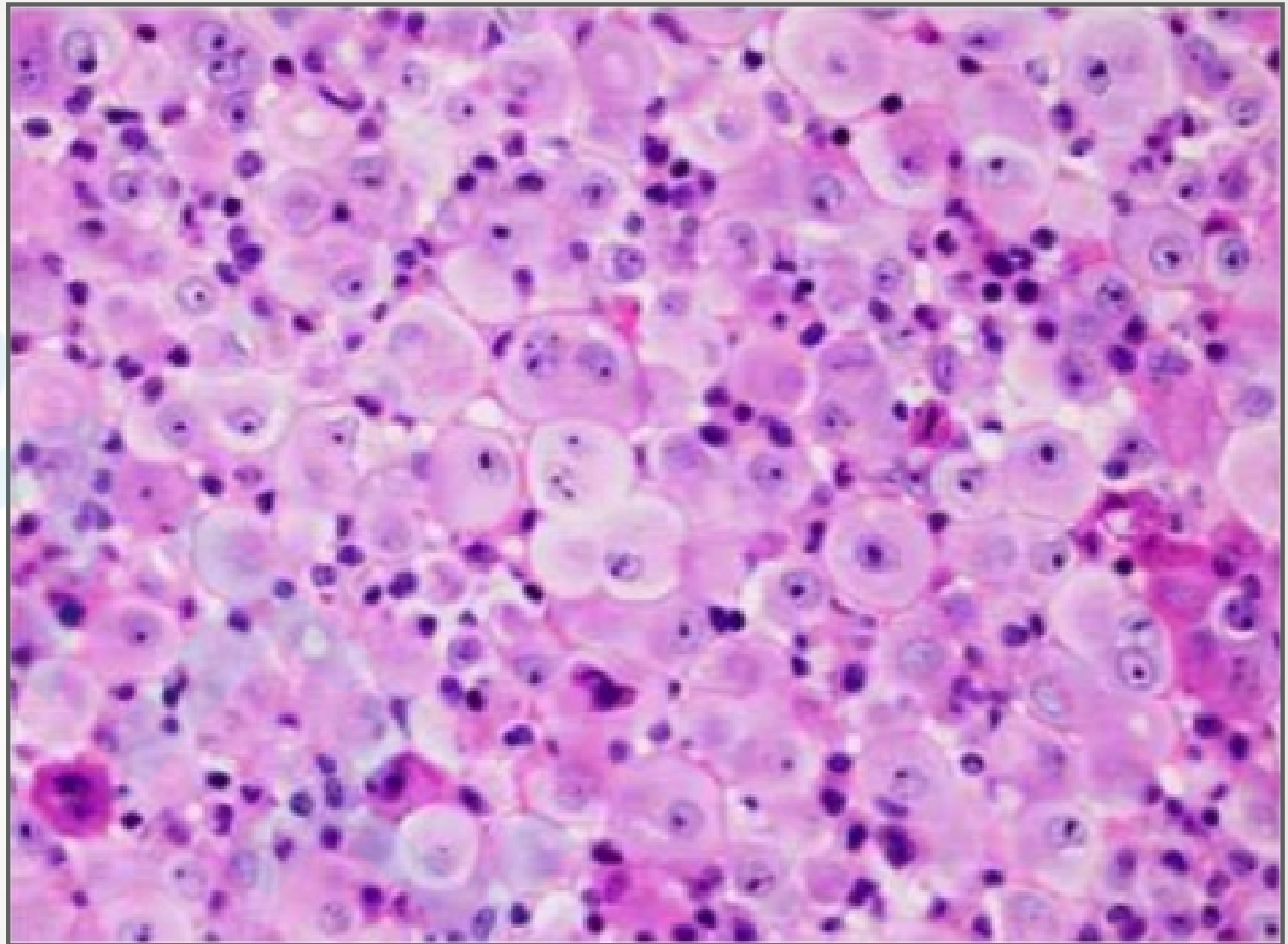


管状乳头状型：最常见，以瘤细胞呈管状、乳头状结构排列为特征。少数病例中，瘤细胞可沿着胸膜的表面呈乳头状生长，类似高分化乳头状间皮瘤，但在其他区域可见明显的间质性浸润。

病理诊断（镜下）

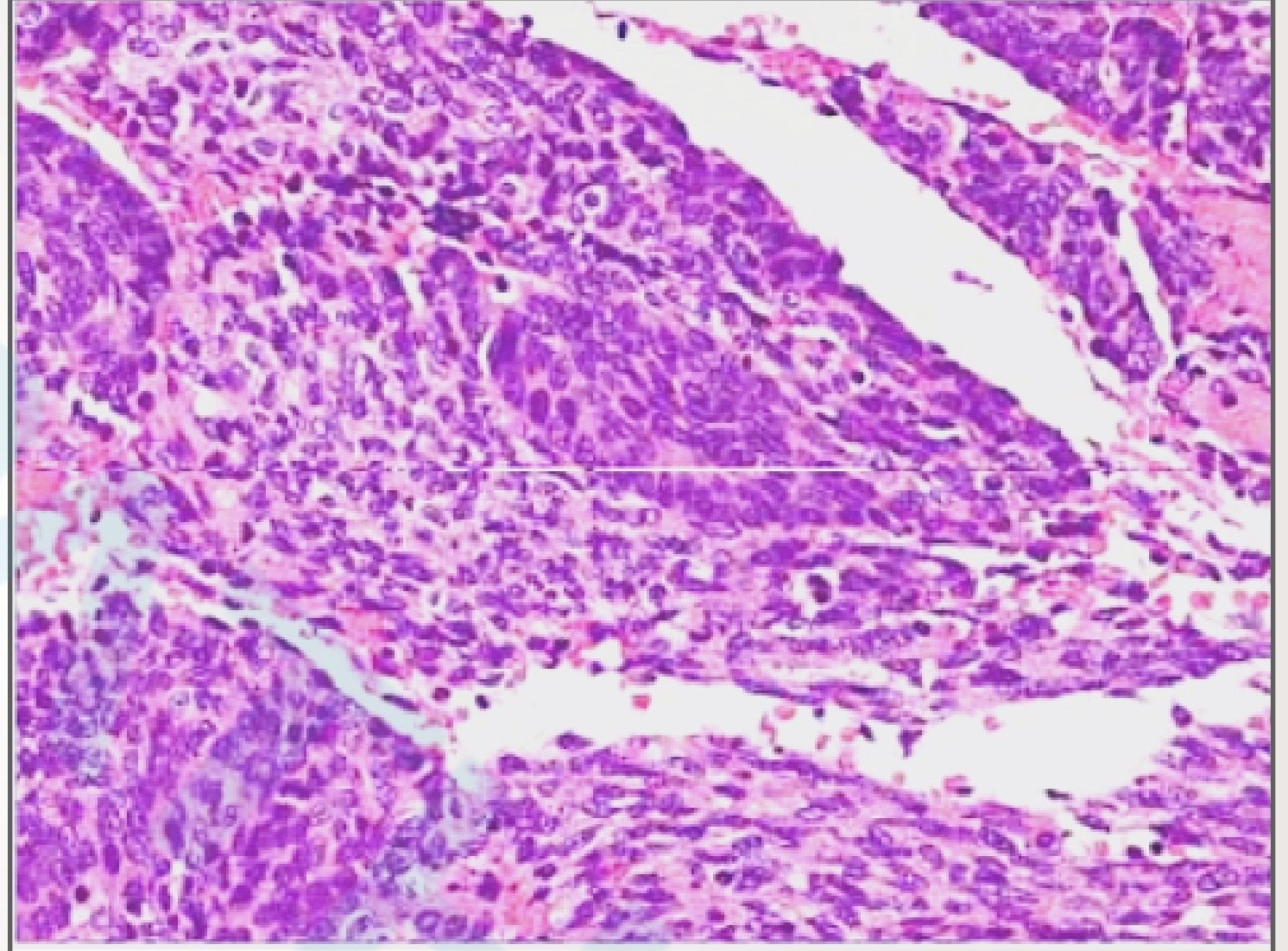
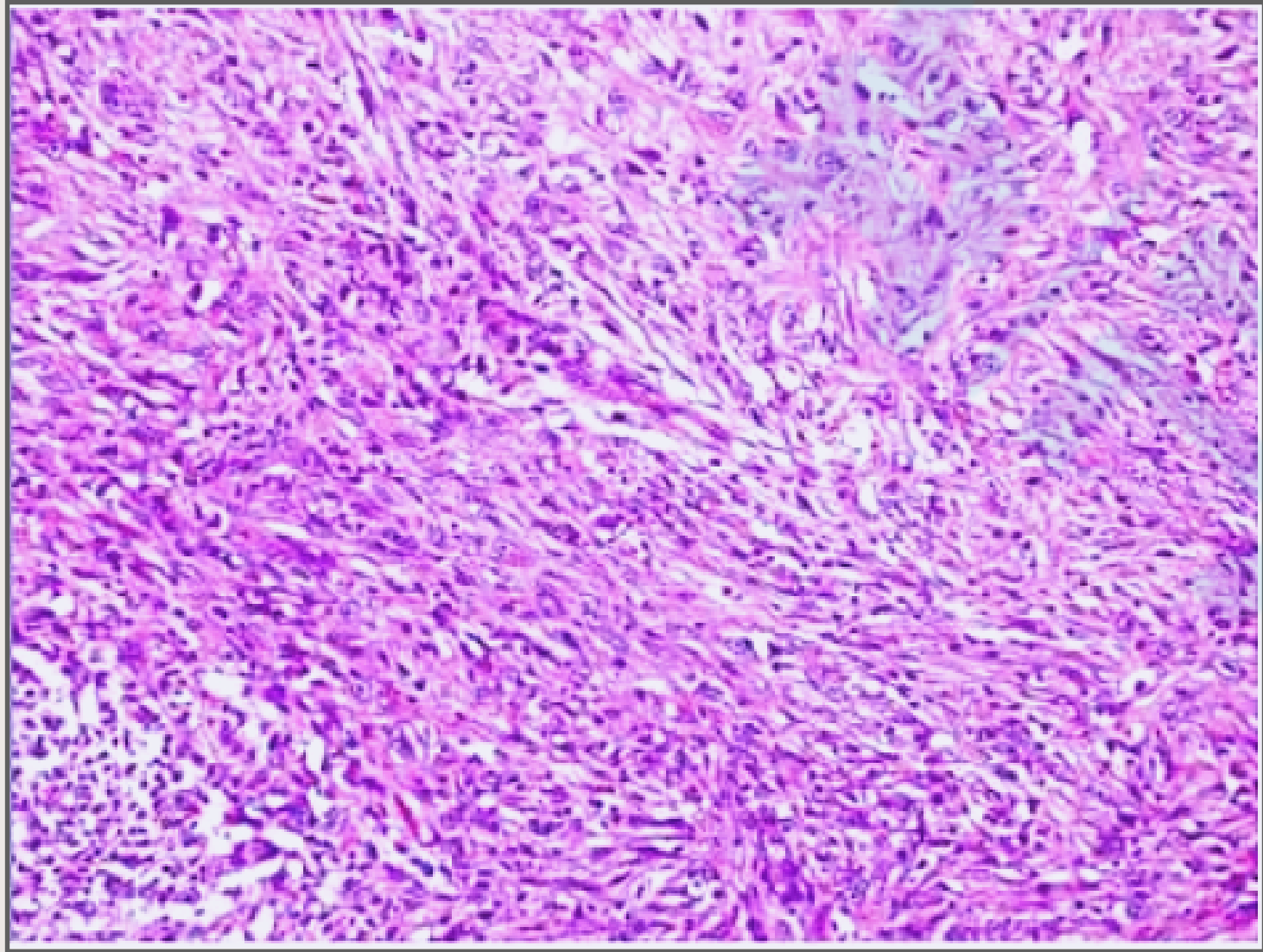


腺样囊性型：瘤细胞呈管状和筛孔状排列，类似腺样囊性癌。



实体型：由实性片状或巢状排列的圆形细胞和多边形细胞组成，类似铺路砖。

病理诊断（镜下）

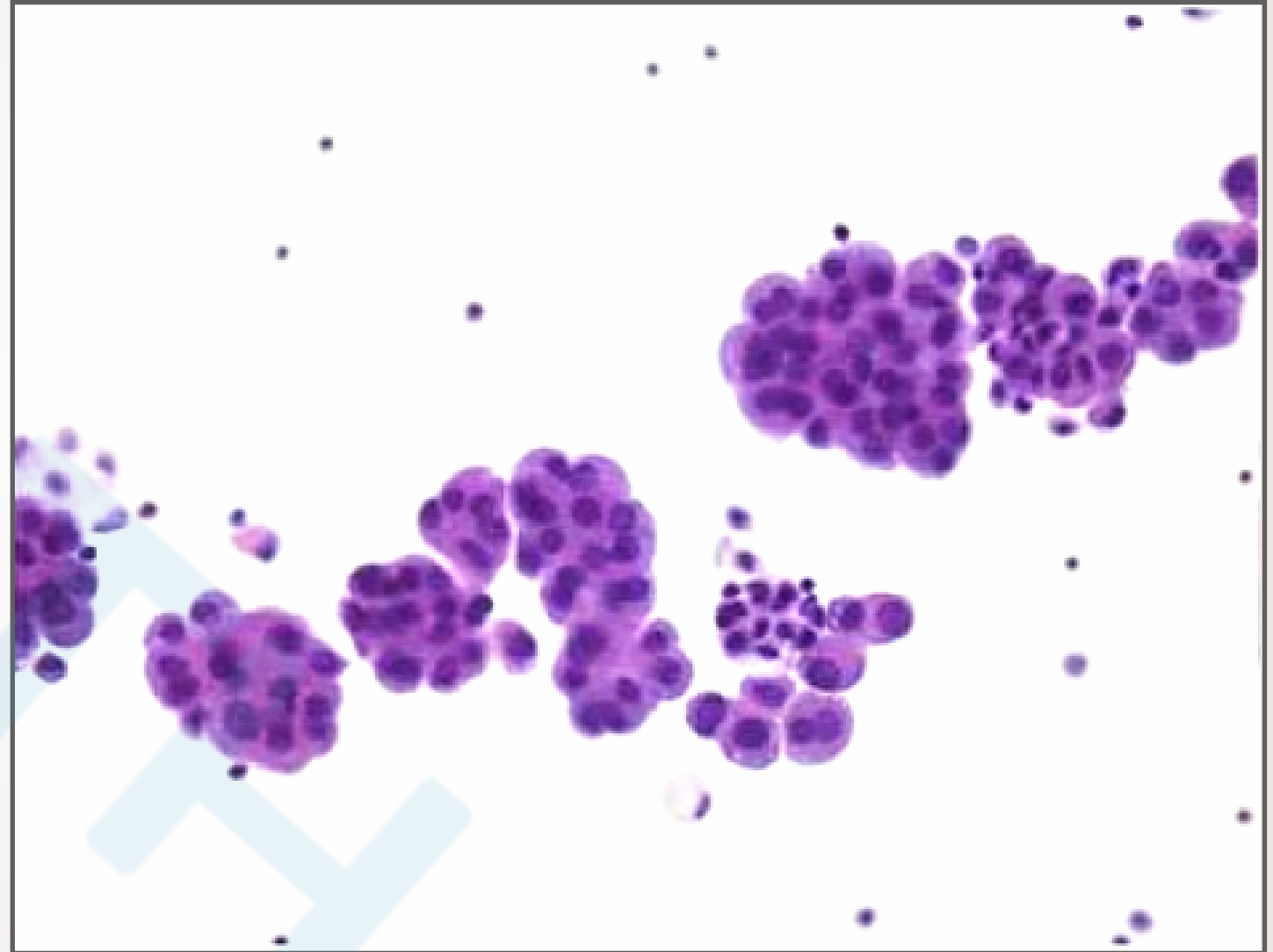


梭形细胞型：由条束装或杂乱排列的纤维母细胞样梭形细胞组成，瘤细胞异型性明显，核分裂象易见，类似纤维肉瘤或未分化多形性肉瘤。

病理诊断（镜下）

细胞学提示恶性间皮瘤的形态特征包括：出现大的细胞团；细胞团轮廓呈浆果样

（berry-like），细胞增大，核增大，可见双核细胞，但核质比仍较低；核多居中，核轮廓不规则，可见明显的大核仁。



病理诊断（免疫组化）

一线间皮标记物：**CR、D2-40、CK5/6、WT-1。**

二线间皮标记物：**HBME-1、TM、MSLN。**

肉瘤样间皮瘤表达AE1/AE3, CR等间皮性标记常为灶阳，另D2-40多为胞质染色，与上皮样间皮瘤胞膜染色有所不同。

病理诊断（免疫组化）

上皮样MPM .VS. 癌

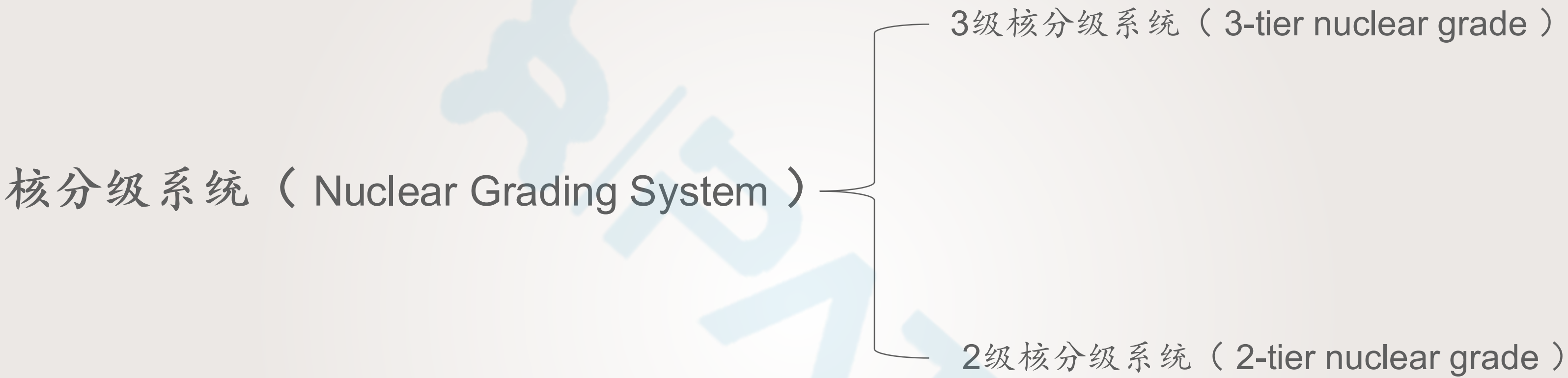
国际间皮瘤学会建议任何标记物应至少包括2个间皮瘤标记和2个其他癌标记。

反应性间皮增生.VS. 恶性间皮瘤

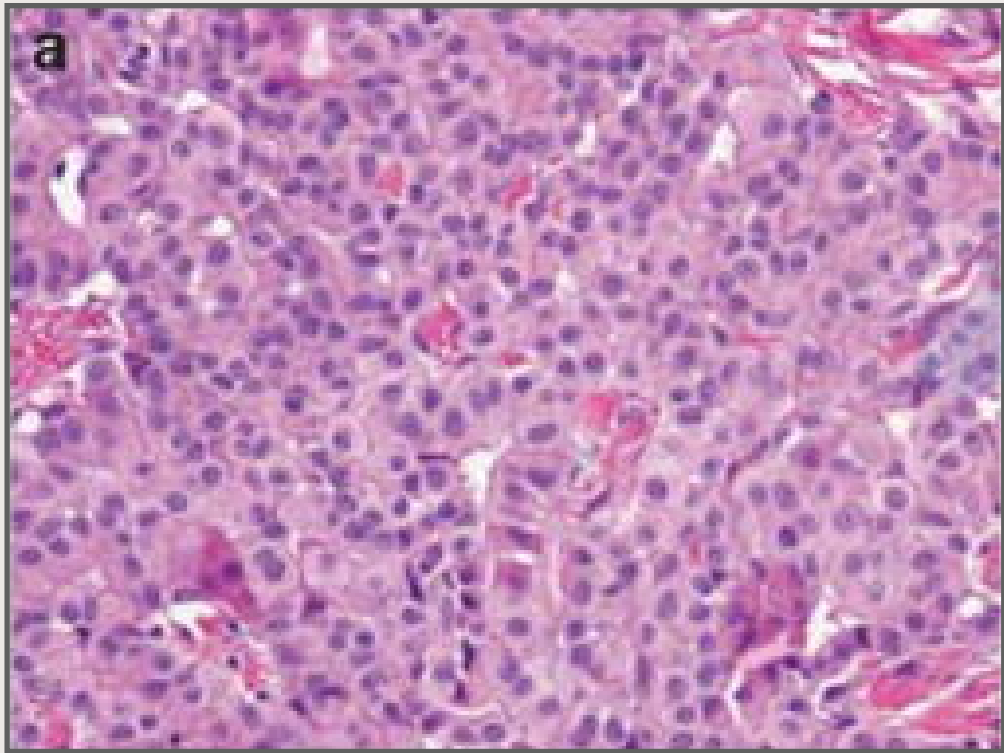
抗体	反应性间皮细胞增生 (%)	恶性间皮瘤 (%)
Desmin	85	10
EMA	20	80
P53	0	45
GLUT-1	3	67
IMP3	0	73

分子病理改变

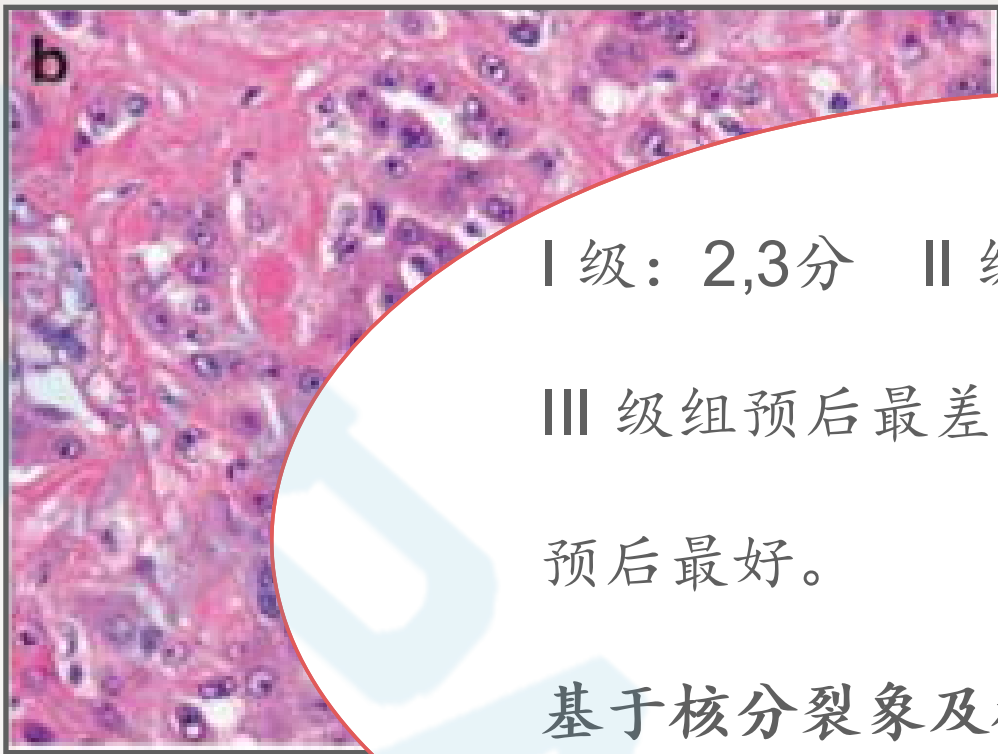
有研究报道胸膜间皮瘤内P16/CDKN2A缺失率达80%，而P16/CDKN2A缺失仅发生于恶性间皮瘤，因此，基因缺失的检测是鉴别恶性间皮瘤和良性反应性增生的有效办法，但不能帮助恶性间皮瘤与其他类型恶性肿瘤之间的鉴别。



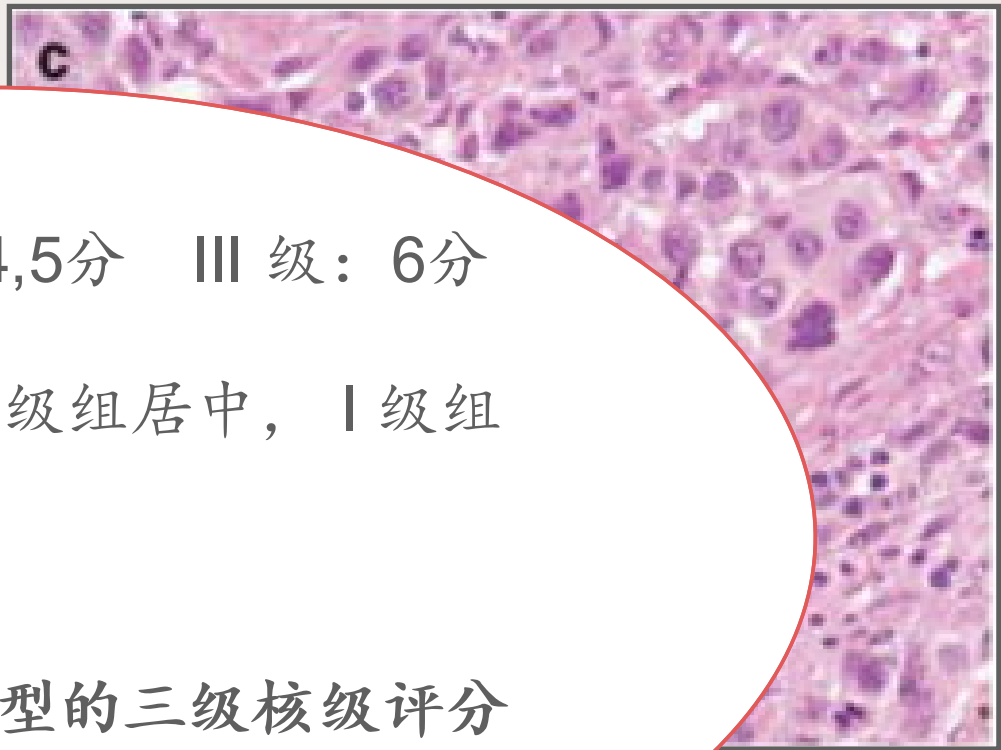
核异型性



Mild (1)



Mod



(3)

I 级：2,3分 II 级：4,5分 III 级：6分

III 级组预后最差，II 级组居中，I 级组
预后最好。

基于核分裂象及核异型的三级核级评分
具有评估**MPM**的预后意义。

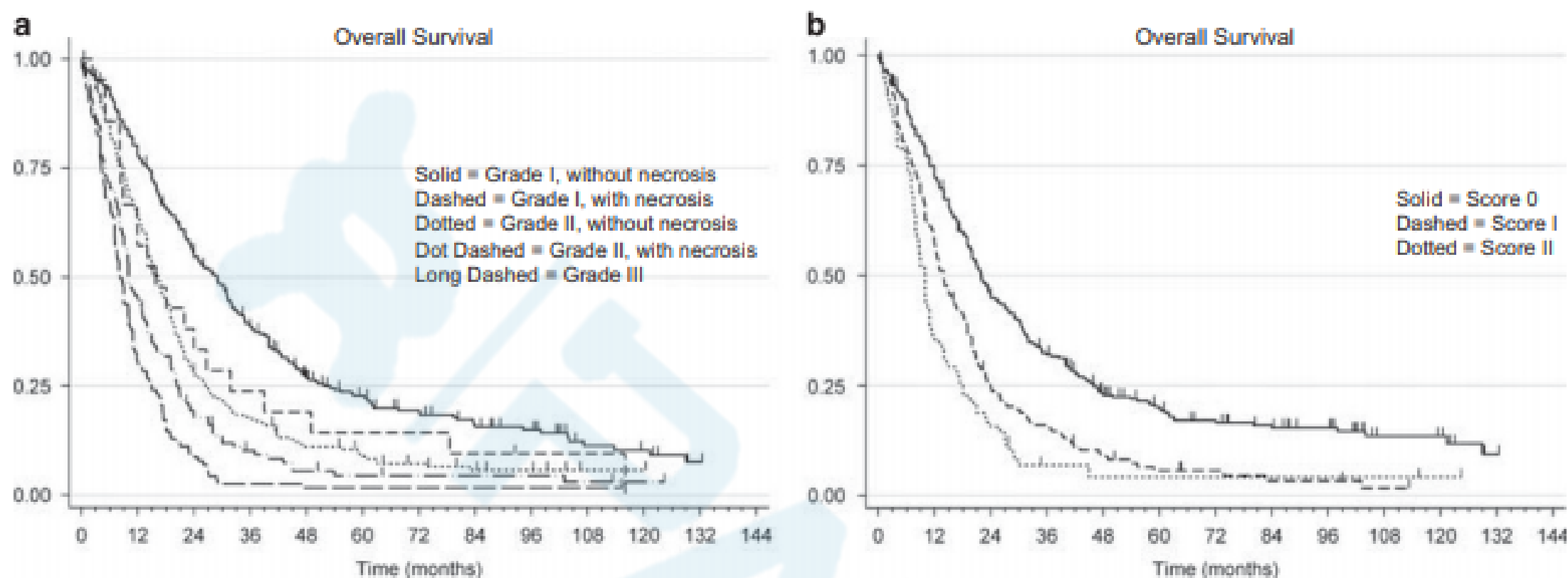
核分裂象

Low (1) 0-1 10/HPF

Intermediate (2) 2-4 10/HPF

High (3) 5-10 10/HPF

A nuclear grading system is a strong predictor of survival in epitheloid diffuse malignant pleural mesothelioma



Grade & Necrosis	Median OS
Grade I, without necrosis	29 months
Grade I, with necrosis	16 months
Grade II, without necrosis	16 months
Grade II, with necrosis	10 months
Grade III	8 months

Mitosis - Necrosis Score	Median OS
Score 0	22 months
Score I	14 months
Score II	10 months

核分裂 < 5 10/HPF 0分
 核分裂 ≥ 5 10/HPF 1分
 无坏死 0分
 有坏死 1分

Figure 5 Overall survival by nuclear grade and necrosis, and mitosis–necrosis score. (a) Patients with nuclear grade I tumors without necrosis had the best overall survival. Patients with nuclear grade I tumors with necrosis and nuclear grade II tumors without necrosis had similar overall survival. Patients with nuclear grade II tumors with necrosis and nuclear grade III tumors had the worst overall survival. (b) Patients with tumors with a mitosis–necrosis score of 0 had a better overall survival than patients with scores of I and II.

Nuclear grade and necrosis predict prognosis in malignant epithelioid pleural mesothelioma: a multi-institutional study

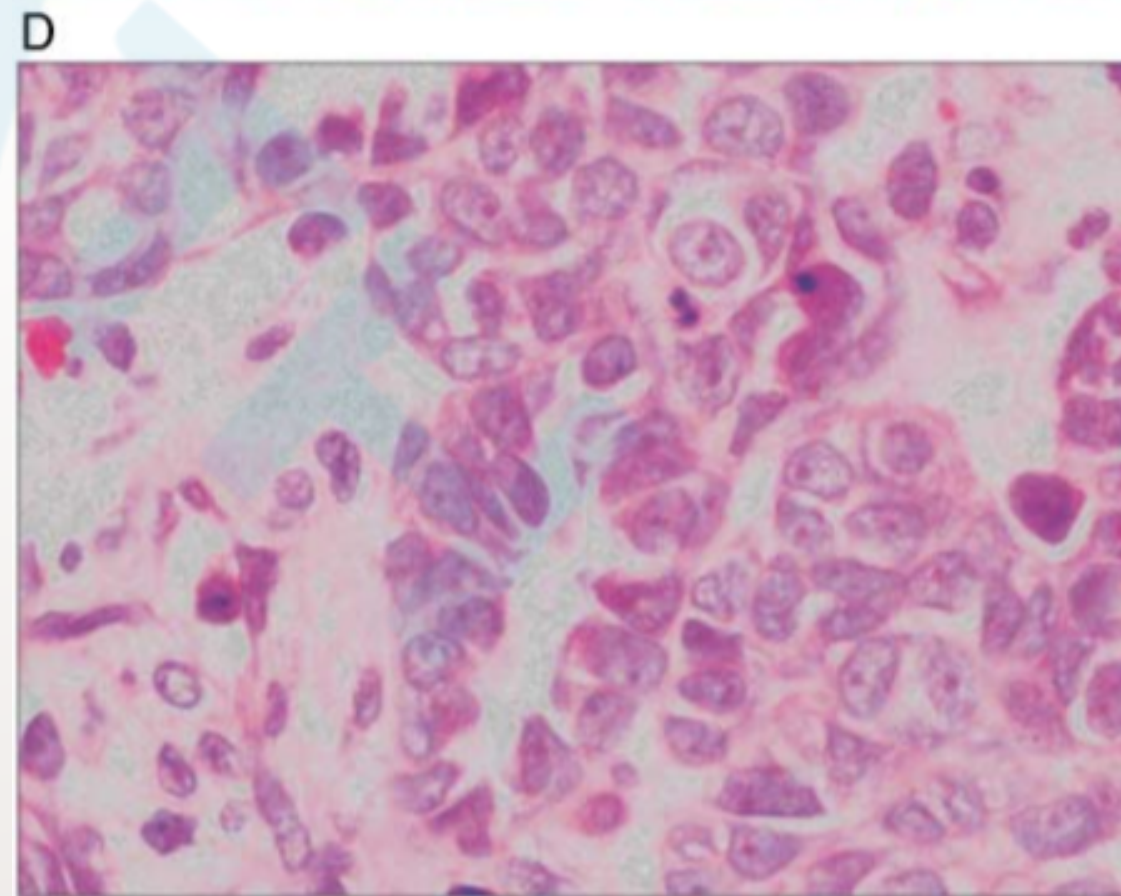
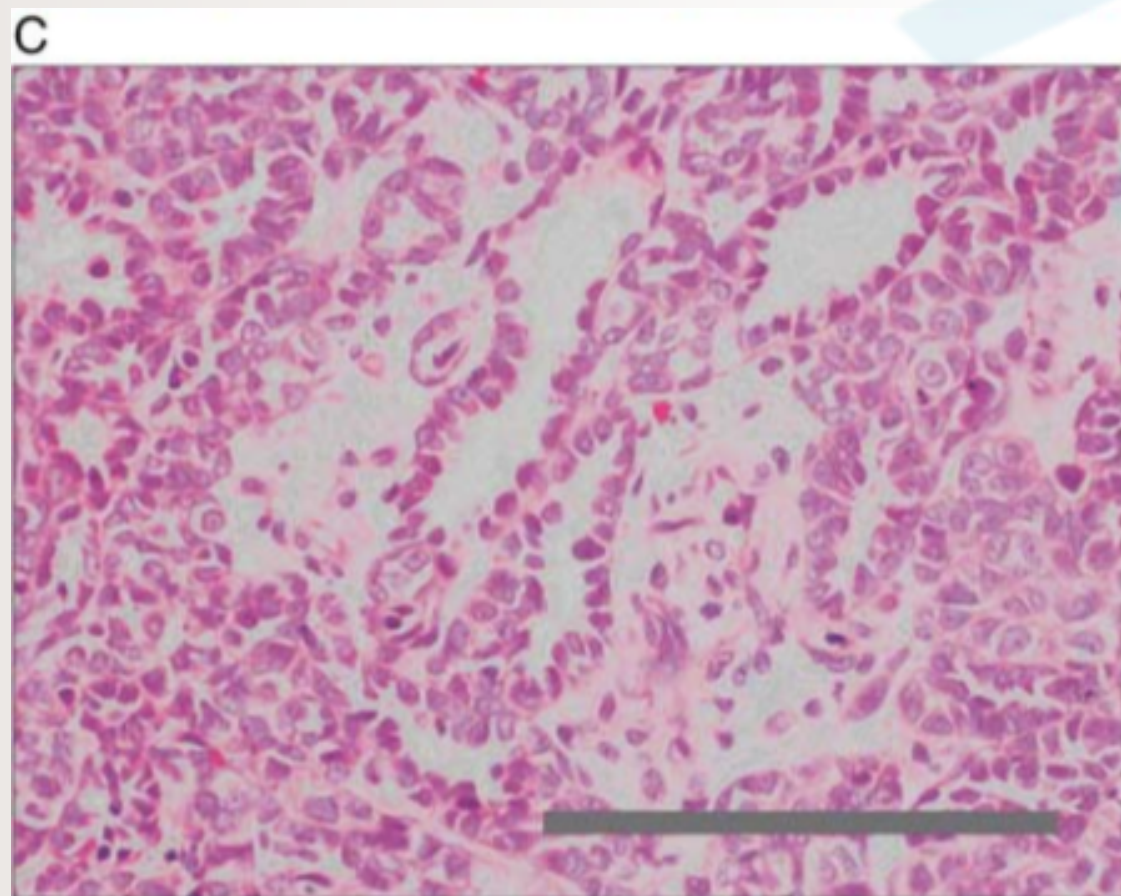
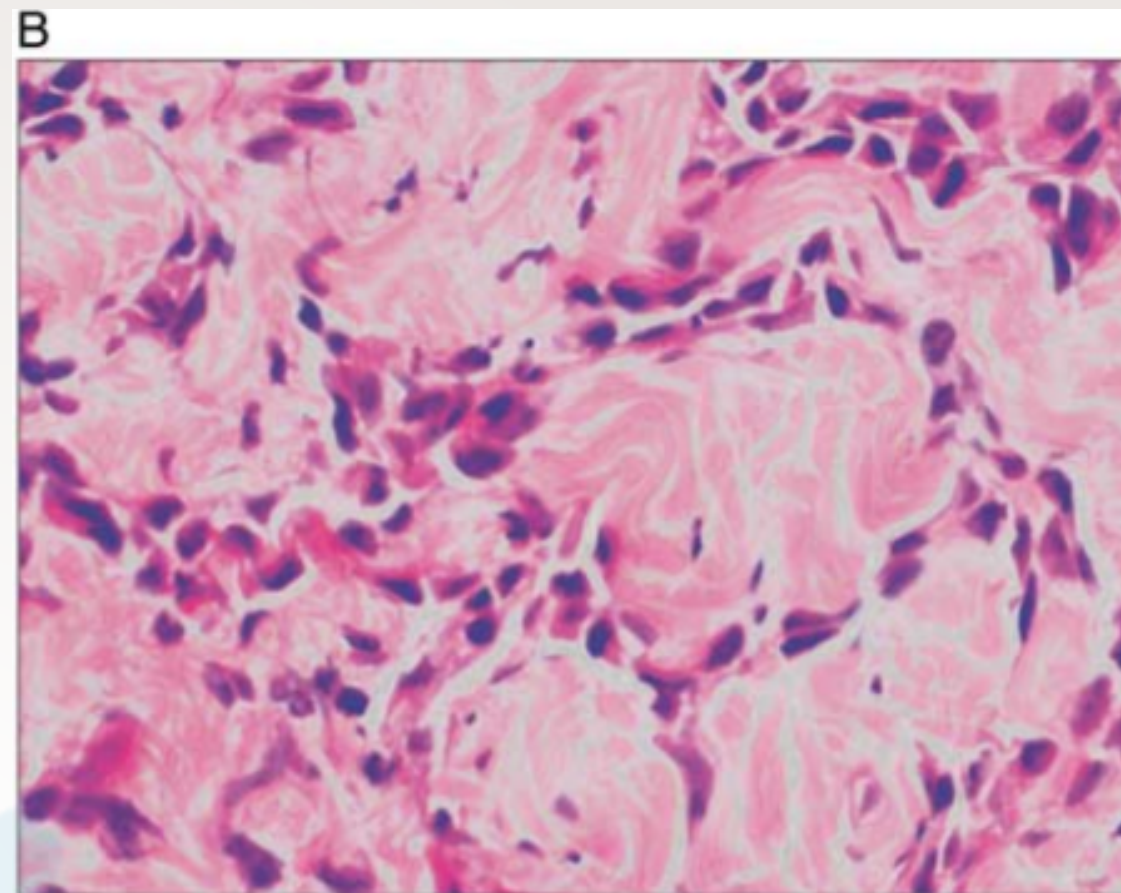
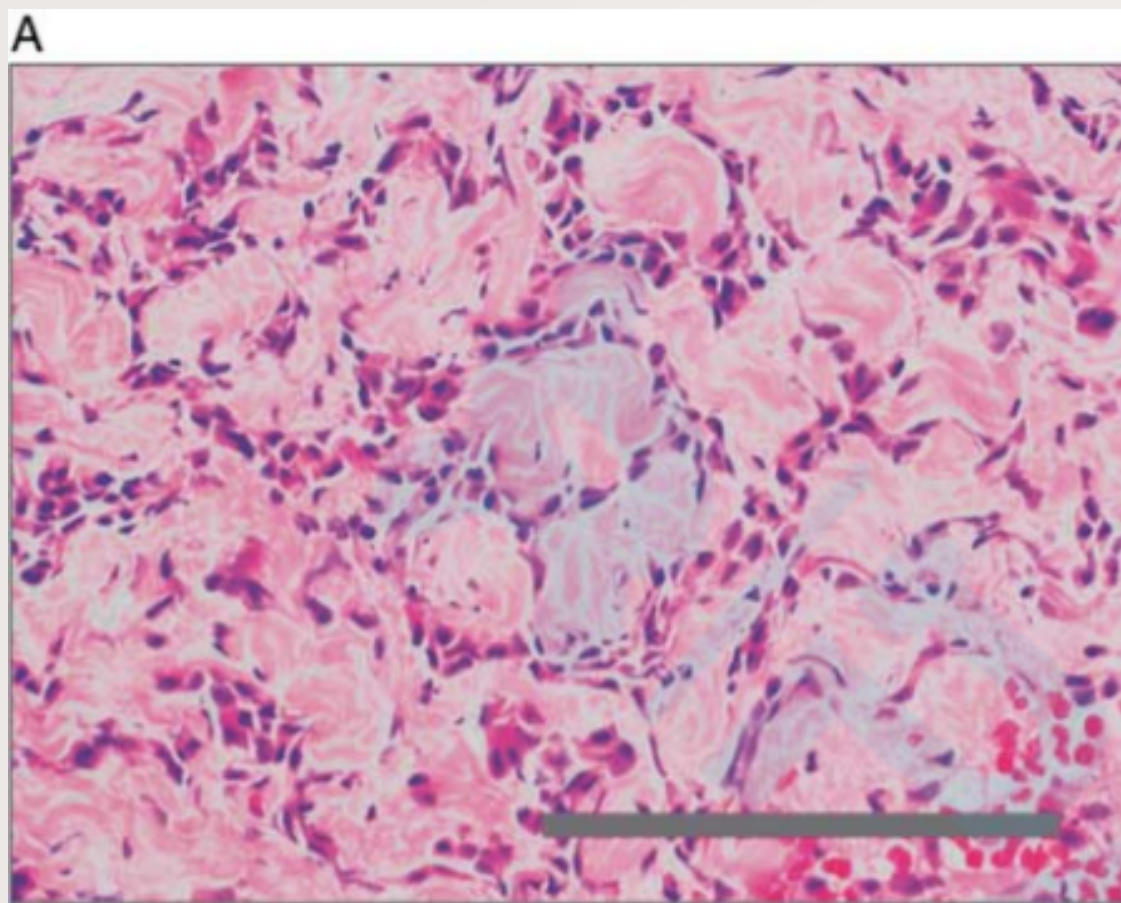
材料 & 方法

病例选择：选取2003-2017年共563例上皮型MPM病例，中位年龄69.1岁，其中423例为男性，65例为女性。87%的病例仅做了胸膜活检。另有51例多形性MPM病例作为参照。

方 法：三级核分级（The 3-tier nuclear grade）& 二级核分级（The 2-tier nuclear grade）

统计学分析（SPSS 24）

结果



结果

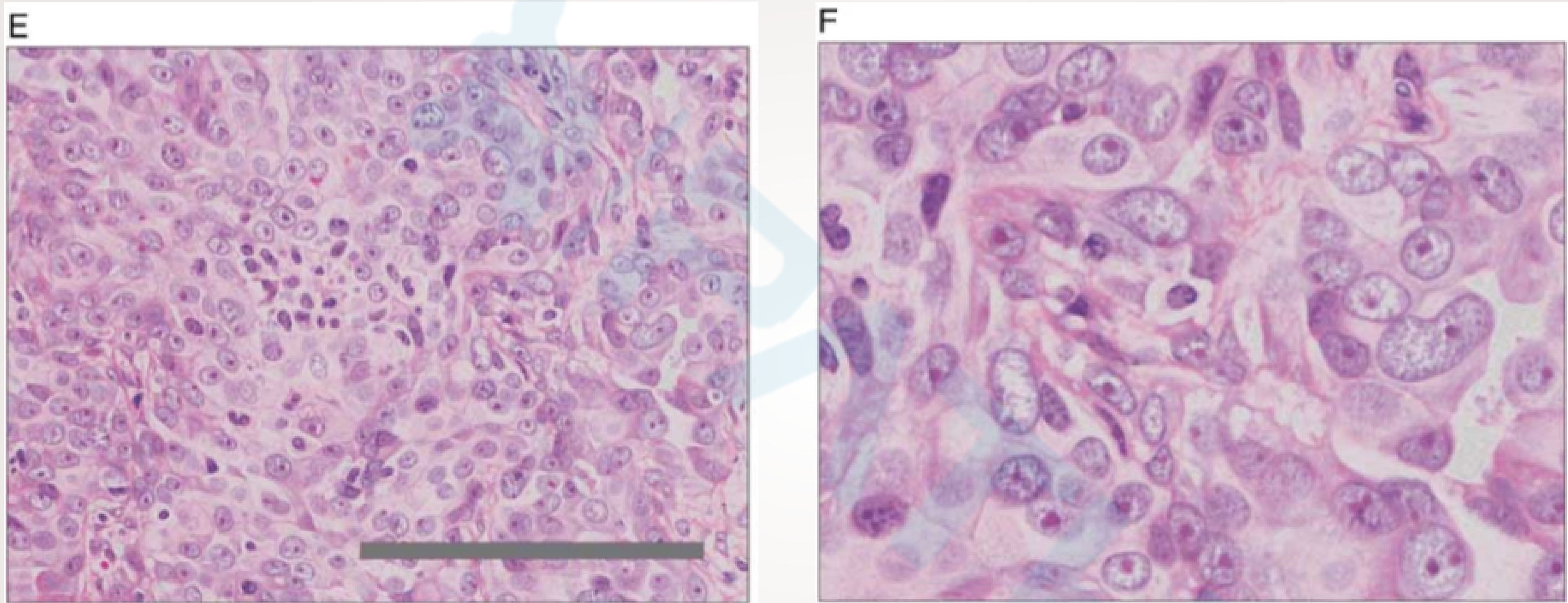


FIGURE 1. Nuclear features of epithelioid MPM (hematoxylin and eosin stain). A, Nuclear grade I tumor with trabecular growth pattern. B, Tumor cells show features of mild nuclear atypia: small, uniform nuclei with fine chromatin pattern and no nucleoli are seen. C, Nuclear grade II tumor with predominantly tubulopapillary growth pattern. D, Tumor cells show features of moderate nuclear atypia: enlarged and moderately pleomorphic nuclei with small but conspicuous nucleoli. E, Nuclear grade III tumor with a predominantly solid growth pattern. F, Tumor cells show features of severe nuclear atypia: large and pleomorphic nuclei with prominent nucleoli and occasionally multiple nucleoli. Tumor giant cells are seen. A minor transitional component is also present. Scale bar=100 μ m.

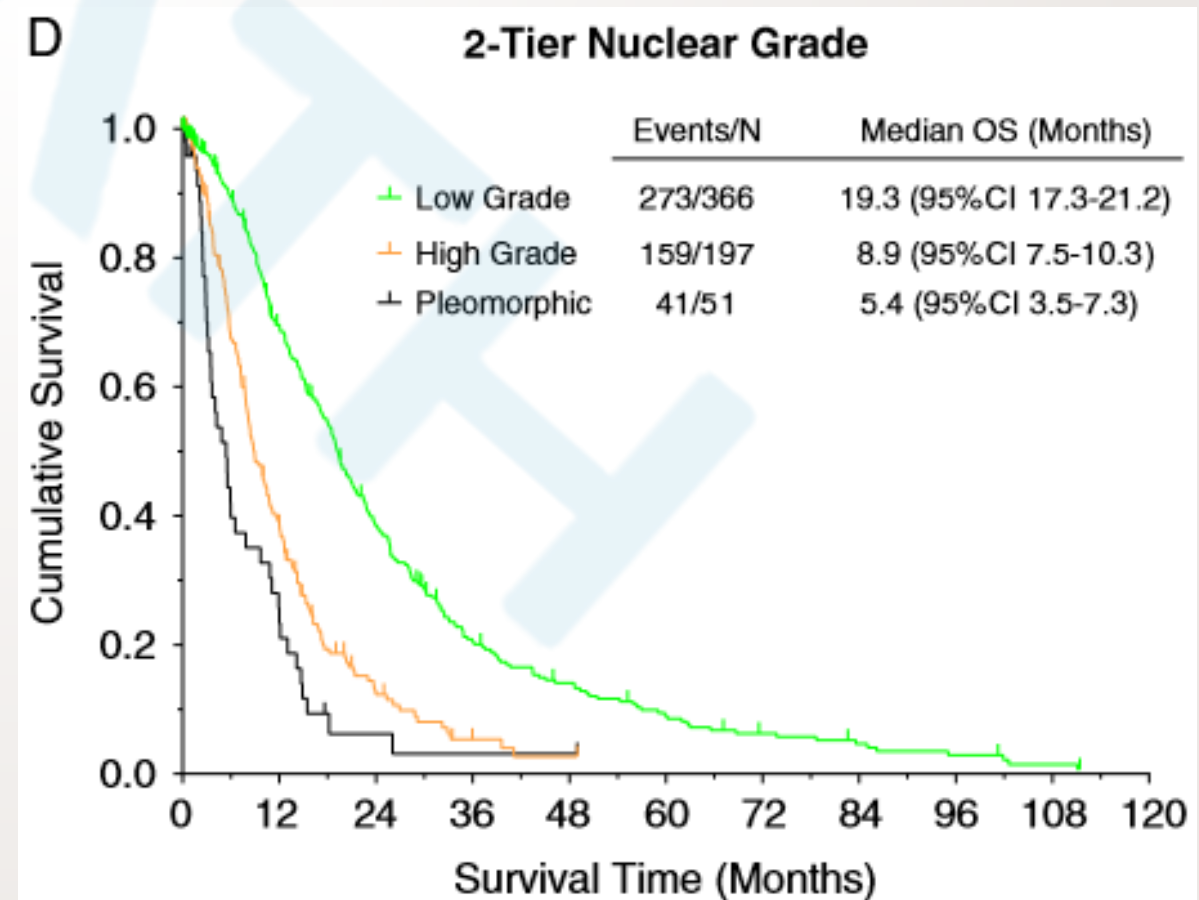
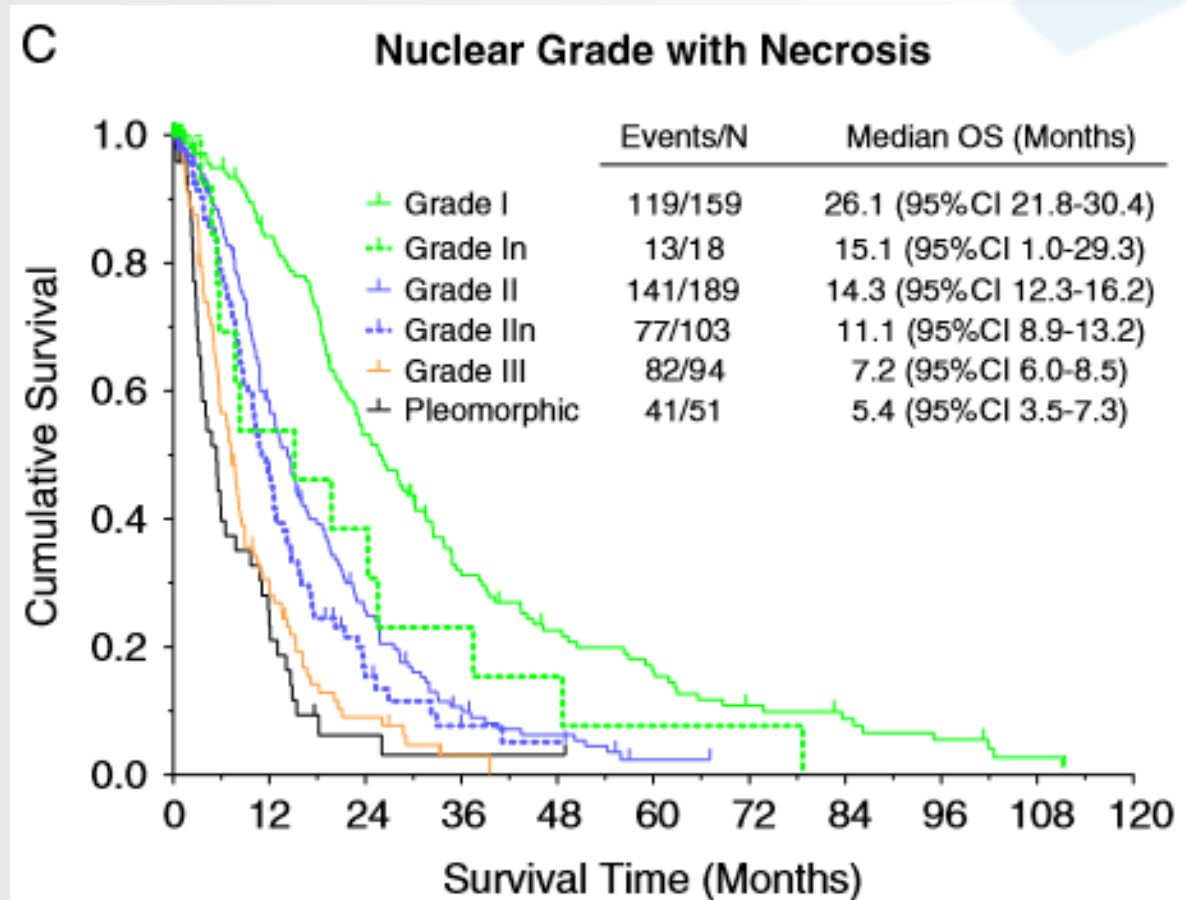
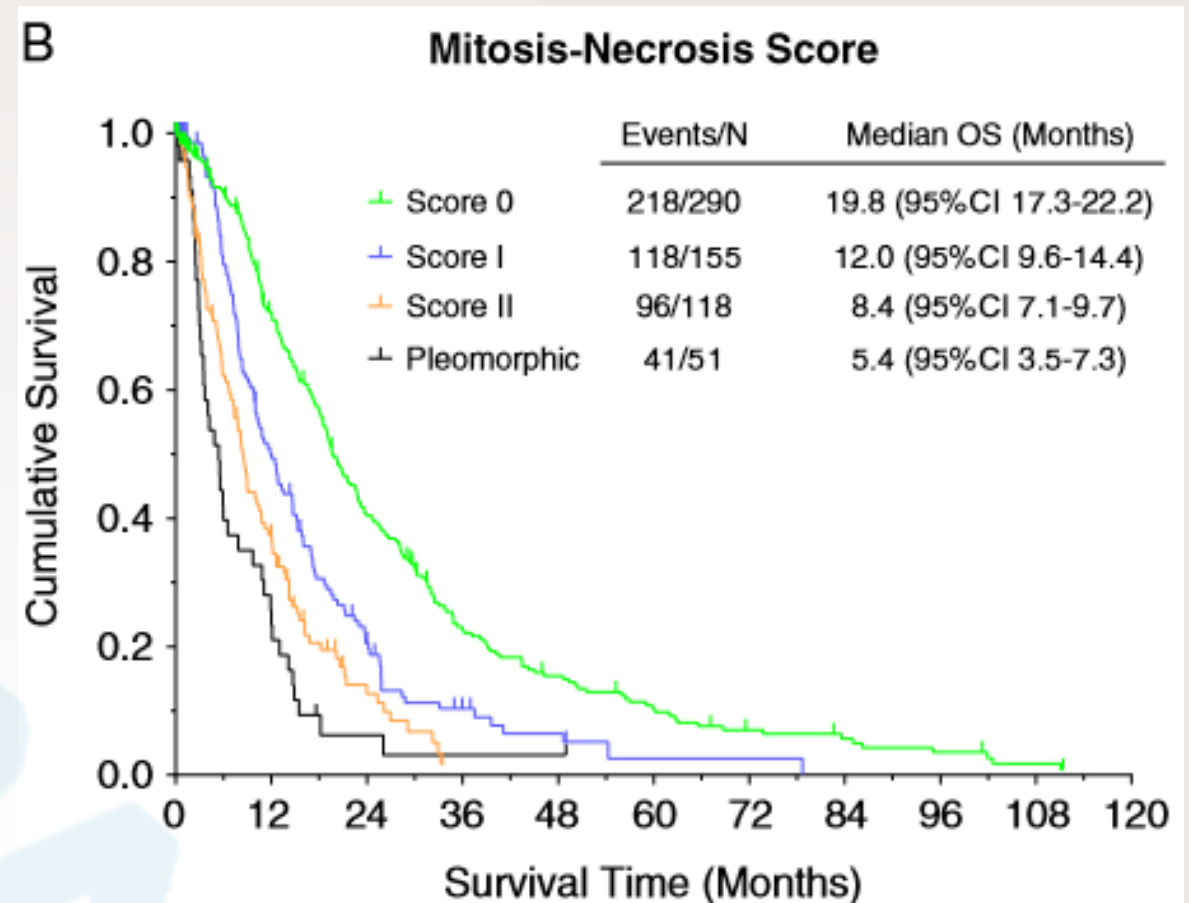
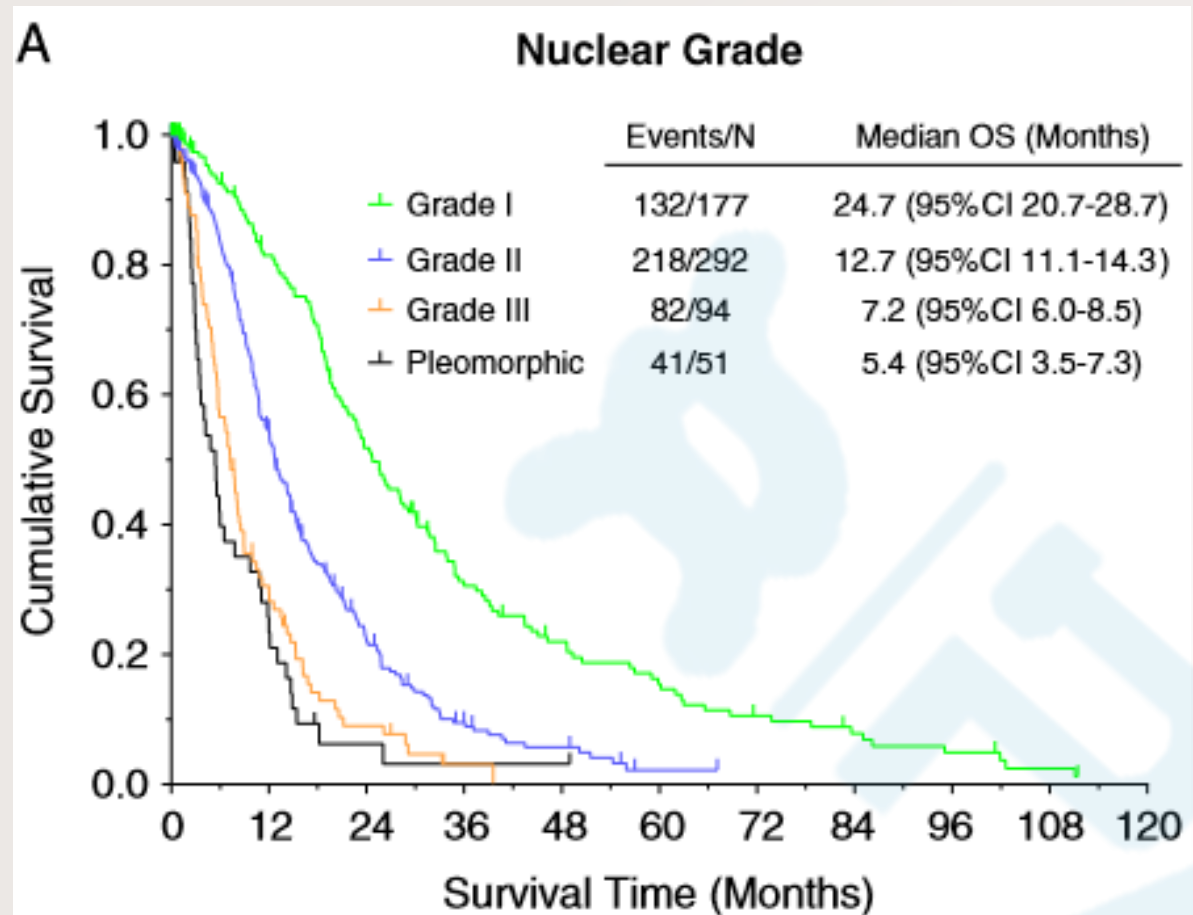
结果

TABLE 4. Distribution of Clinicopathologic Variables by Nuclear Grade

Variables	n (%)				<i>P</i>
	All Patients	Grade I	Grade II	Grade III	
All patients	563 (100.0)	177 (31.4)	292 (51.9)	94 (16.7)	—
Age (y)					
Median	70	71	69.5	70	0.600
Range	32-91	41-88	37-90	32-91	
Sex					
Male	423 (75.1)	137 (77.4)	209 (71.6)	77 (81.9)	0.092
Female	140 (24.9)	40 (22.6)	83 (28.4)	17 (18.1)	
Laterality					
Left	227 (40.3)	80 (45.7)	117 (40.3)	30 (32.3)	0.101
Right	331 (58.8)	95 (54.3)	173 (59.7)	63 (67.7)	
Not documented	5 (0.9)	—	—	—	—
Procedure					
Biopsy	490 (87.0)	169 (95.5)	242 (82.9)	79 (84.0)	0.003
PD or EPD	65 (11.6)	7 (4.0)	43 (14.7)	15 (16.0)	
EPP	5 (0.9)	1 (0.5)	4 (1.4)	0 (0.0)	
Other procedures	3 (0.5)	0 (0.0)	3 (1.0)	0 (0.0)	
Solid-predominant growth pattern					
Yes	213 (37.8)	32 (18.1)	120 (41.1)	61 (64.9)	< 0.001
No	350 (62.2)	145 (81.9)	172 (58.9)	33 (35.1)	
Necrosis					
Present	189 (33.6)	18 (10.2)	103 (35.3)	69 (73.4)	< 0.001
Absent	374 (66.4)	159 (89.8)	189 (64.7)	25 (26.6)	
Lymphatic invasion					
Present	47 (8.3)	1 (0.6)	30 (10.3)	16 (17.0)	< 0.001
Absent	516 (91.7)	176 (99.4)	262 (89.7)	78 (83.0)	
Vascular invasion					
Present	42 (7.5)	3 (1.7)	24 (8.2)	15 (16.0)	< 0.001
Absent	521 (92.5)	174 (98.3)	268 (91.8)	79 (84.0)	
Atypical mitosis					
Present	398 (70.7)	41 (23.2)	265 (90.8)	92 (97.9)	< 0.001
Absent	165 (29.3)	136 (76.8)	27 (9.2)	2 (2.1)	

EPD indicates extended pleurectomy and decortication.

结果



结果

TABLE 1. Univariate Analysis in Predicting OS by Clinicopathologic Factors

Variables	Patients, n (%)	Median OS (mo)	<i>P</i>
All patients	563 (100.0)	14.7	—
Age (y)			
≤ 65	193 (34.3)	18.2	< 0.001
> 65	370 (65.7)	12.7	
Sex			
Male	423 (75.1)	14.7	0.469
Female	140 (24.9)	14.7	
Laterality			
Left	227 (40.3)	15.6	0.053 (left vs. right)
Right	331 (58.8)	13.8	
Not documented	5 (0.9)	—	
Procedure			
Biopsy	490 (87.0)	13.2	< 0.001 (biopsy vs. resection)
PD or EPD	65 (11.6)	25.3	
EPP	5 (0.9)	28.4	
Other procedures	3 (0.5)	32.9	
Solid-predominant growth pattern			
Yes	213 (37.8)	10.5	< 0.001
No	350 (62.2)	18.0	
Necrosis			
Present	190 (33.7)	9.3	< 0.001
Absent	373 (66.3)	18.5	
Lymphatic invasion			
Present	47 (8.3)	16.8	0.169
Absent	516 (91.7)	14.6	
Vascular invasion			
Present	42 (7.5)	15.6	0.303
Absent	521 (92.5)	14.6	

EPD indicates extended pleurectomy and decortication.

结果

TABLE 2. Univariate Analysis in Predicting OS by Nuclear Features			
Variables	Patients, n (%)	Median OS (mo)	P
Nuclear atypia			
Score 1 (mild)	71 (12.6)	24.3	Reference
Score 2 (moderate)	378 (67.1)	15.5	0.002
Score 3 (severe)	114 (20.3)	7.8	<0.001 (3 vs. 2: <0.001)
Mitotic count			
Score 1 (0-1)	178 (31.6)	23.7	Reference
Score 2 (2-4)	182 (32.3)	12.8	<0.001
Score 3 (≥ 5)	203 (36.1)	10.0	<0.001 (3 vs. 2: 0.002)
Atypical mitosis			
Yes	398 (70.7)	12.0	<0.001
No	165 (29.3)	20.3	
Nuclear grade			
I	177 (31.4)	24.7	Reference
II	292 (51.9)	12.7	<0.001
III	94 (16.7)	7.2	<0.001 (III vs. II: <0.001)
M-N score			
Score 0	290 (51.5)	19.8	Reference
Score I	155 (27.5)	12.0	<0.001
Score II	118 (21.0)	8.4	<0.001 (II vs. I: 0.003)
2-tier nuclear grade			
Low grade	366 (65.0)	19.3	Reference
Grade I	159 (28.2)	26.1	—
Grade I with necrosis	18 (3.2)	15.1	—
Grade II	189 (33.6)	14.3	—
High grade	197 (35.0)	8.9	<0.001
Grade II with necrosis	103 (18.3)	11.1	—
Grade III	94 (16.7)	7.2	—

核异型性越大，预后越差

核分裂象越多，预后越差

核级评分越高，预后越差

核分裂-坏死评分越高，预后越差

高级别组，预后较差

结果

TABLE 3. Multivariate Analysis in Predicting OS

Variable	Hazard Ratio	95% CI	P
Age (y)			
> 65 vs. ≤65	1.46	1.19-1.81	< 0.001
Procedure			
Resection vs. biopsy only	0.30	0.21-0.43	< 0.001
Predominant growth pattern			
Solid vs. nonsolid	1.03	0.83-1.27	0.799
Necrosis			
Present vs. absent	1.72	1.35-2.20	< 0.001
Nuclear atypia			
Score 2 vs. 1	1.43	1.04-1.95	0.027
Score 3 vs. 1	2.29	1.56-3.38	< 0.001
Mitotic count			
Score 2 vs. 1	2.19	1.55-3.09	< 0.001
Score 3 vs. 1	3.00	2.07-4.34	< 0.001
Atypical mitosis			
Present vs. absent	0.95	0.71-1.27	0.713
Nuclear grade			
II vs. I	2.56	1.87-3.49	< 0.001
III vs. I	3.77	2.52-5.63	< 0.001
M-N score			
I vs. 0	1.65	1.22-2.23	0.001
II vs. 0	2.38	1.49-3.78	< 0.001
2-tier nuclear grade			
High grade vs. low grade	2.02	1.33-3.07	0.001

CI indicates confidence interval.

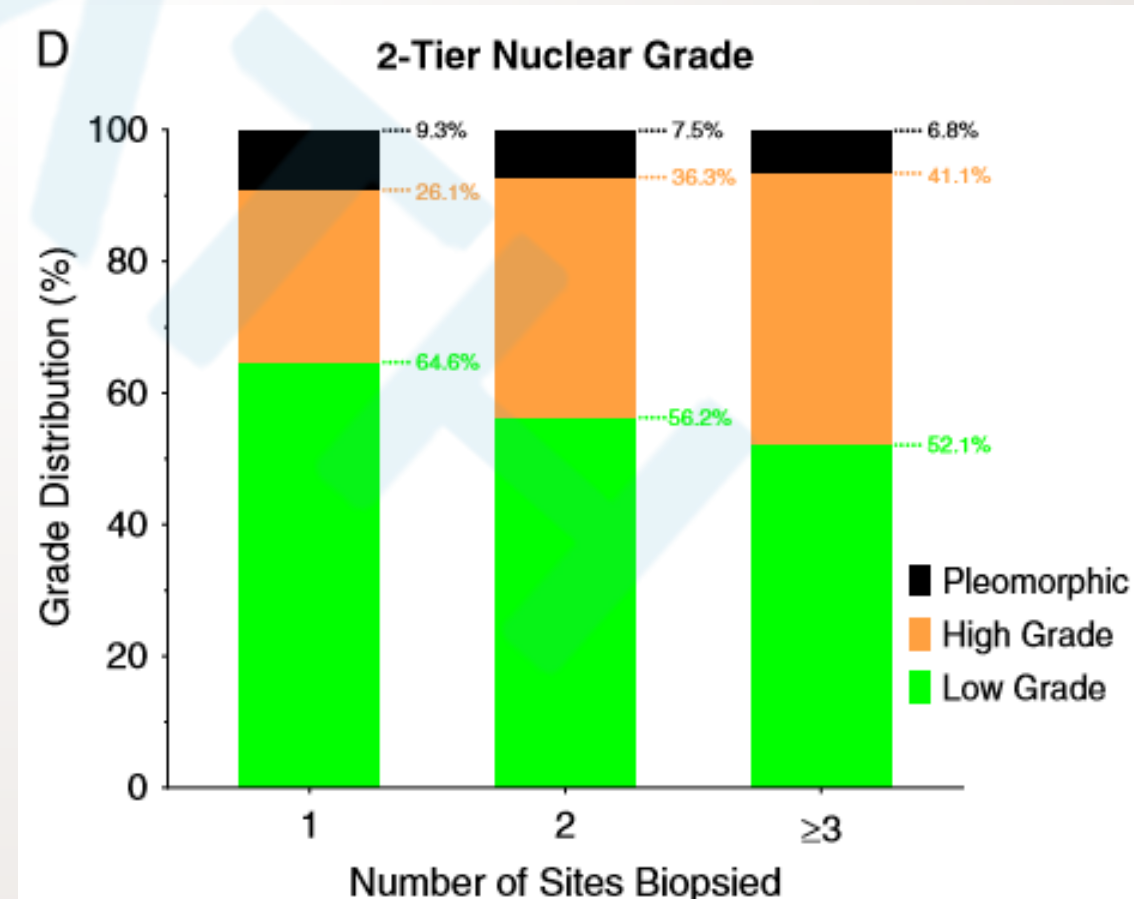
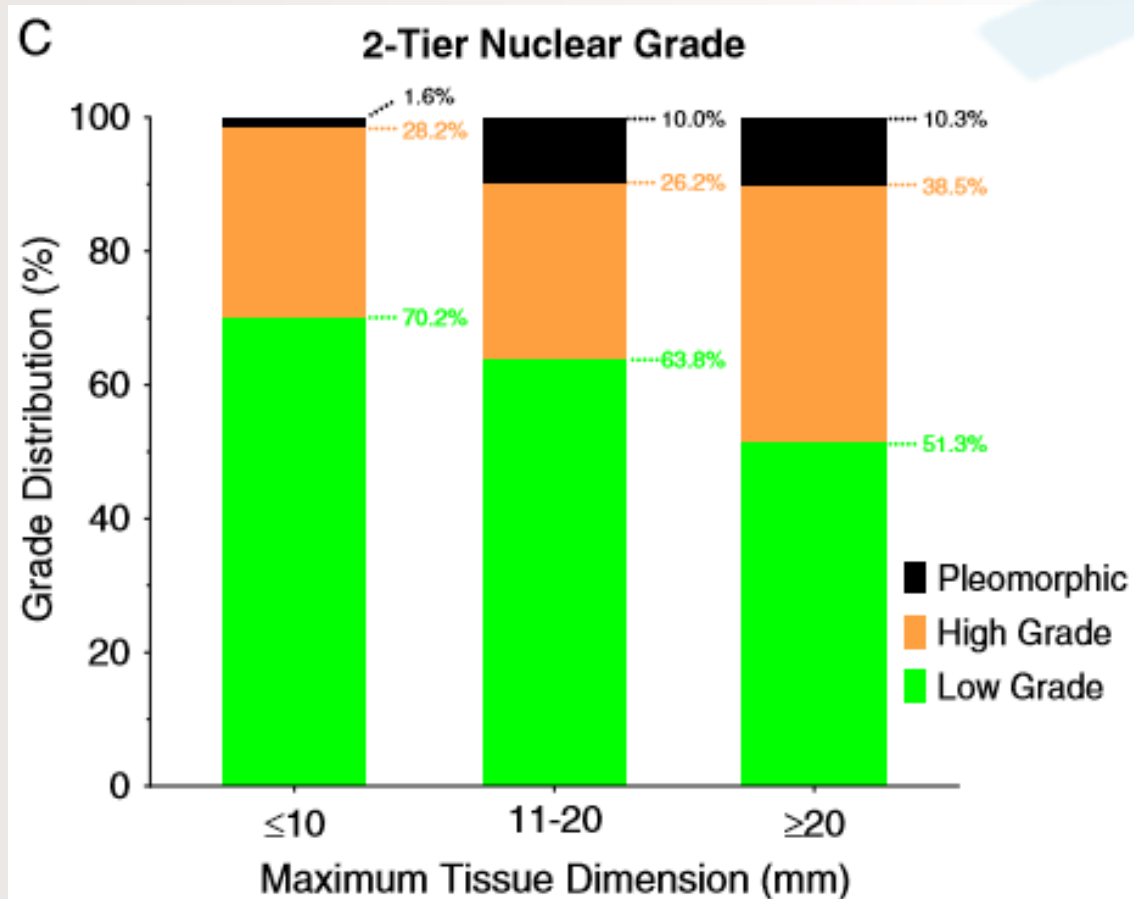
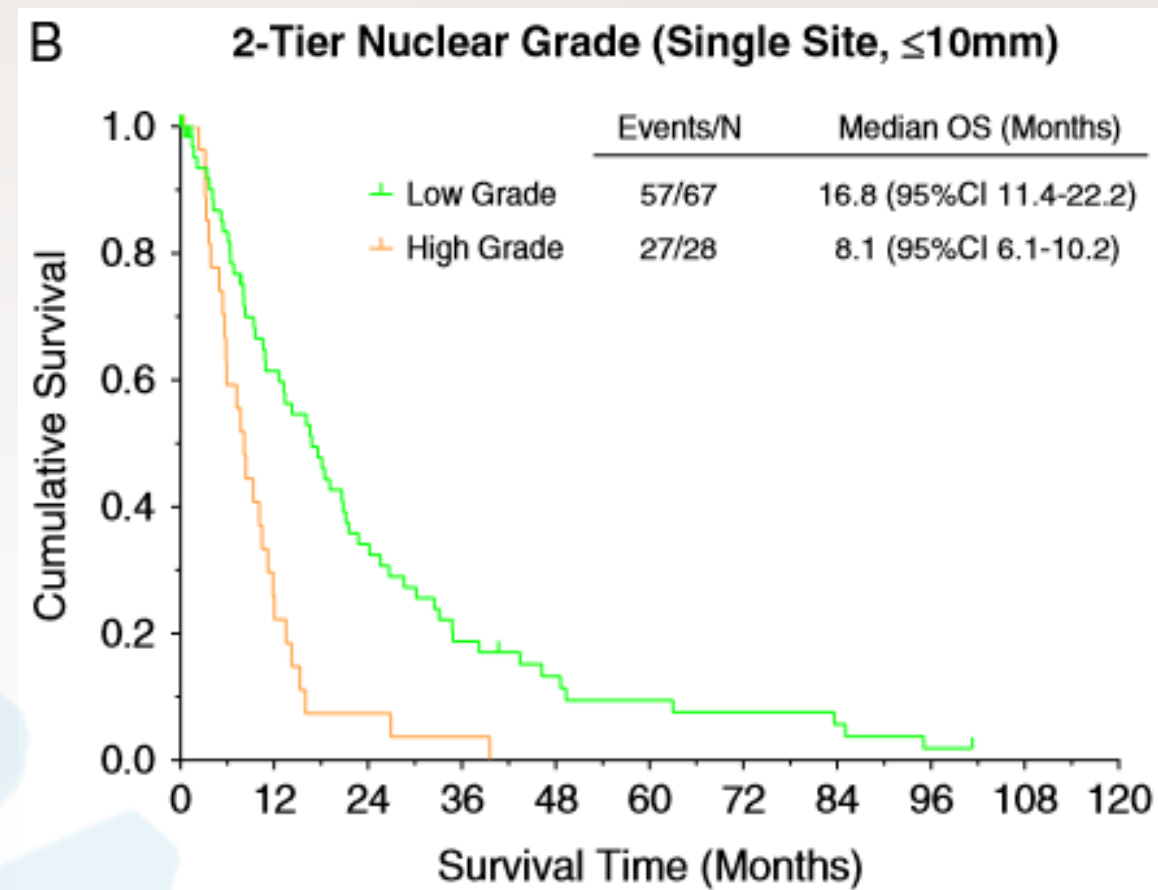
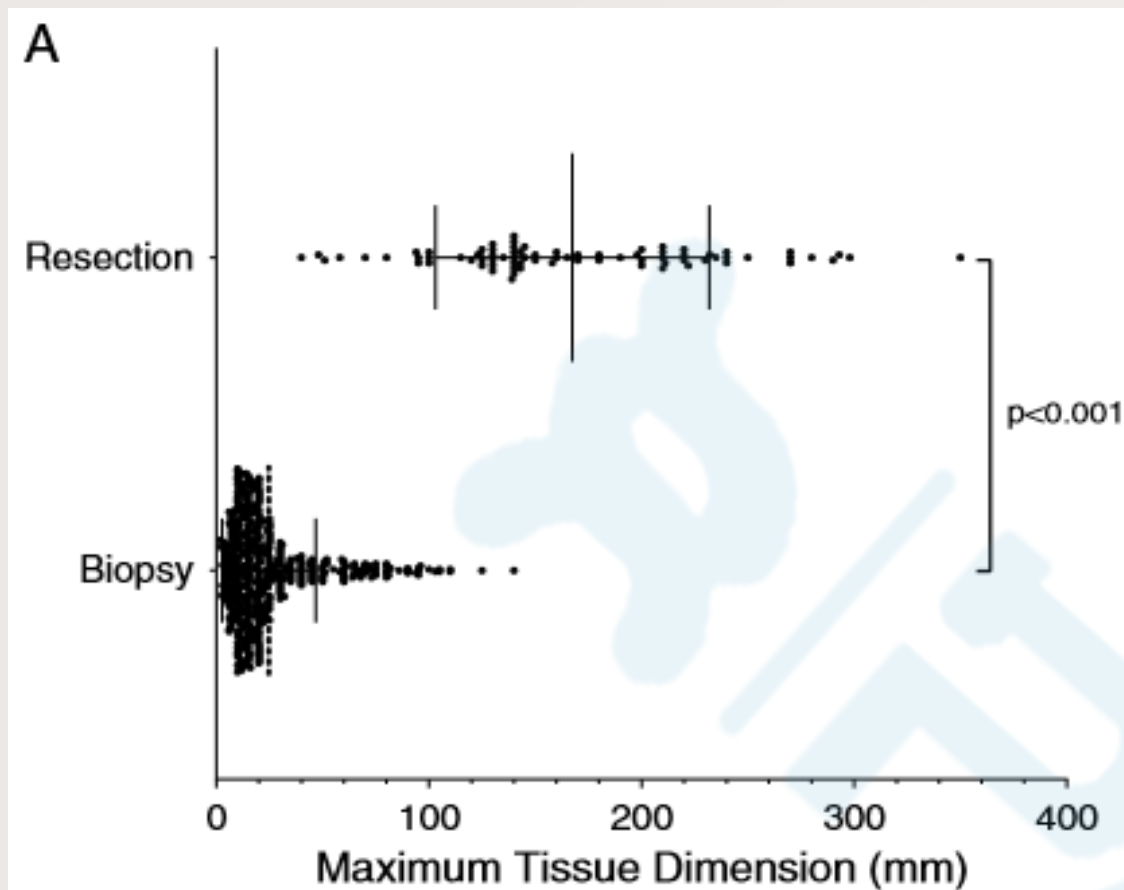
结果

TABLE 5. Multivariate Analysis in Predicting OS (Single-site Biopsy)

Variables	Hazard Ratio	95% CI	<i>P</i>
Age (y)			
> 65 vs. ≤ 65	1.31	0.97-1.77	0.074
Predominant growth pattern			
Solid vs. nonsolid	1.17	0.88-1.55	0.290
Necrosis			
Present vs. absent	2.13	1.51-3.01	< 0.001
Nuclear atypia			
Score 2 vs. 1	1.55	1.01-2.40	0.046
Score 3 vs. 1	2.23	1.31-3.81	0.003
Mitotic count			
Score 2 vs. 1	2.09	1.31-3.32	0.002
Score 3 vs. 1	2.80	1.67-4.67	< 0.001
Atypical mitosis			
Present vs. absent	0.83	0.57-1.21	0.333
Nuclear grade			
II vs. I	2.26	1.52-3.37	< 0.001
III vs. I	3.04	1.77-5.20	< 0.001
M-N score			
I vs. 0	2.04	1.36-3.04	0.001
II vs. 0	2.08	1.10-3.95	0.025
2-tier nuclear grade			
High grade vs. low grade	1.87	1.11-3.14	0.019

CI indicates confidence interval.

结果



结果

TABLE 6. Multivariate Analysis in Predicting OS (Single-site Biopsy, Maximum Dimension ≤ 10 mm)

Variables	Hazard Ratio	95% CI	<i>P</i>
Age (y)			
> 65 vs. ≤ 65	2.30	1.34-3.94	0.002
Predominant growth pattern			
Solid vs. nonsolid	1.34	0.80-2.25	0.267
Necrosis			
Present vs. absent	1.55	0.67-3.55	0.303
Nuclear atypia			
Score 2 vs. 1	1.62	0.80-3.27	0.182
Score 3 vs. 1	2.99	1.23-7.27	0.015
Atypical mitosis			
Present vs. absent	1.31	0.76-2.26	0.339
2-tier nuclear grade			
High grade vs. low grade	1.27	0.55-2.92	0.572

CI indicates confidence interval.

结论

(1) 三级核级评分系统：Ⅰ级占**31%**，Ⅱ级占**52%**，Ⅲ级占**17%**。Ⅰ级预后最好（中位生存期：**24.7**个月），Ⅱ级居中（中位生存期：**12.7**个月），Ⅲ级预后最差（中位生存期：**7.2**个月）。

(2) 二级评分系统：低级别中位生存期（**19.3**个月），高级别生存期（**8.9**个月）。在多因素分析中，三级核级评分系统、二级评分系统以及**M-N**评分均可作为上皮型**MPM**的独立预后因素。

(3) 活检部位**≥3**个，或者单个活检组织标本直径**≥20mm**，对于评估核分级有明显优势。

本文的不足

(1) 临床资料不完整，没有**TNM**分期及治疗方法。

(2) 由于临床资料不完整，所以无法对三级/二级分级系统与**TNM**分期比对，不能判断哪一种能更准确的判断预后。

谢谢！