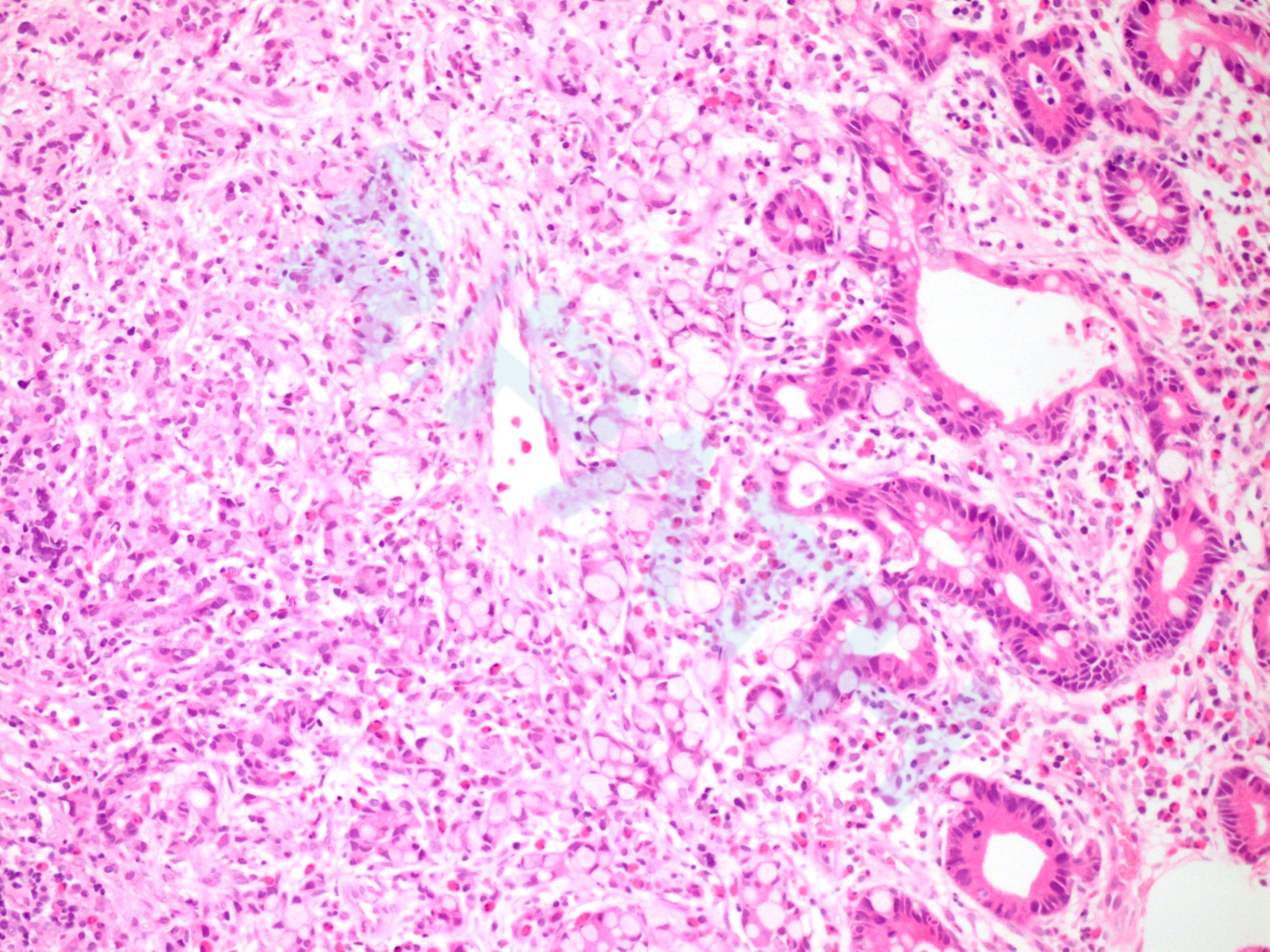
Am J Surg Pathol， Volume 42, Number 7, July 2018

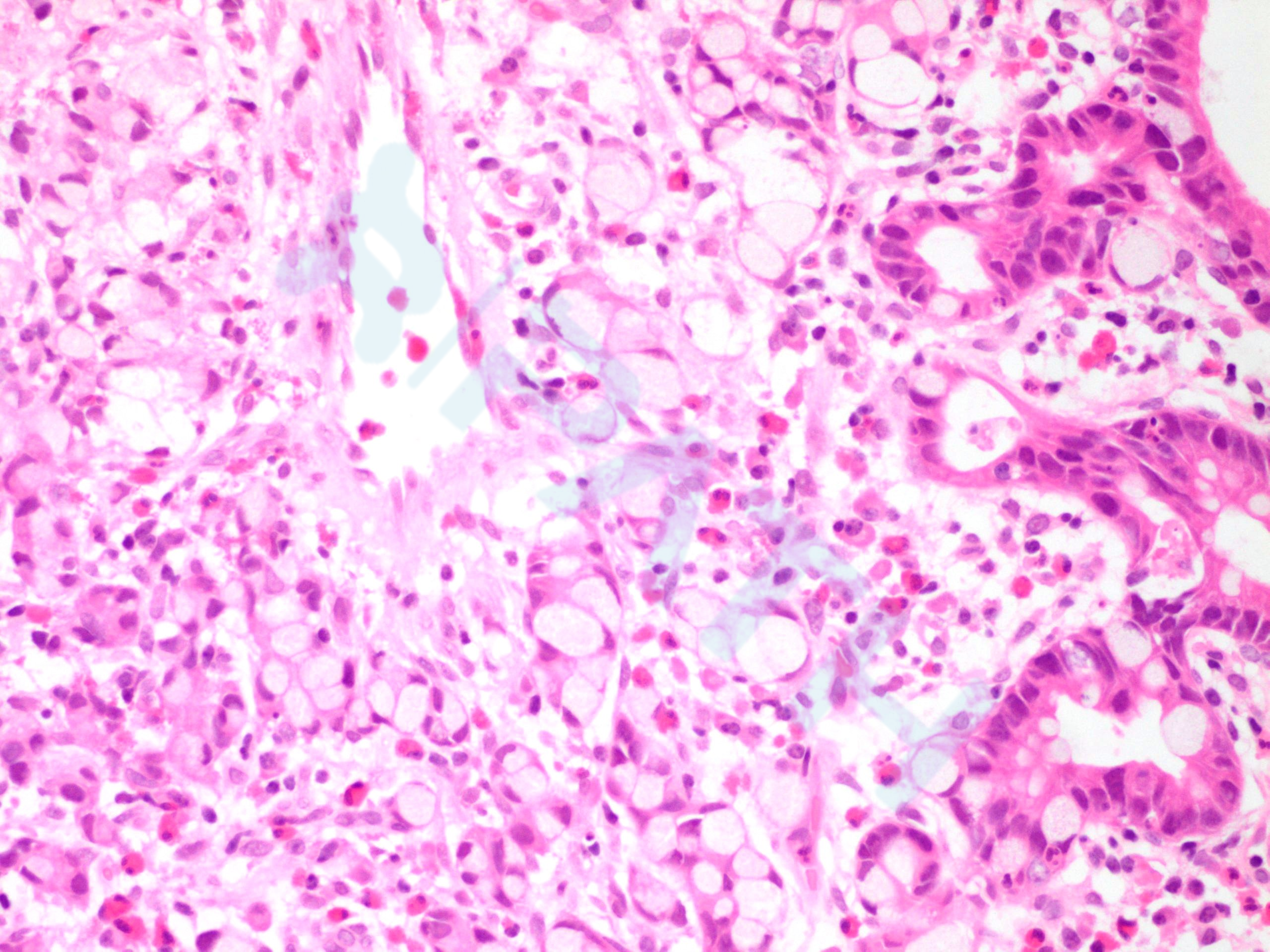
Histologic and Outcome Study Supports Reclassifying Appendiceal Goblet Cell Carcinoids as Goblet Cell Adenocarcinomas, and Grading and Staging Similarly to Colonic Adenocarcinomas

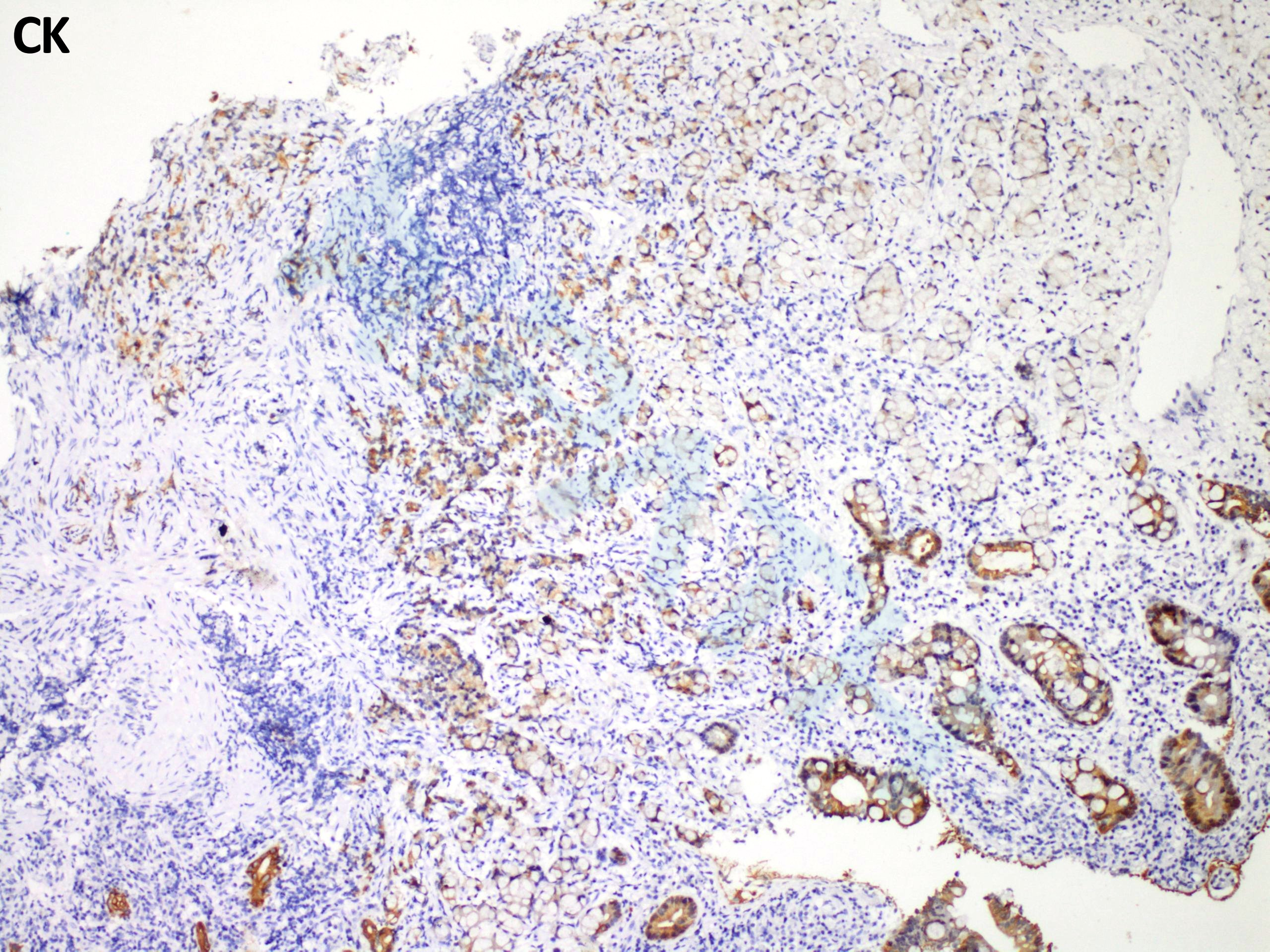
汇报人：许秀丽
指导教授：张丽英

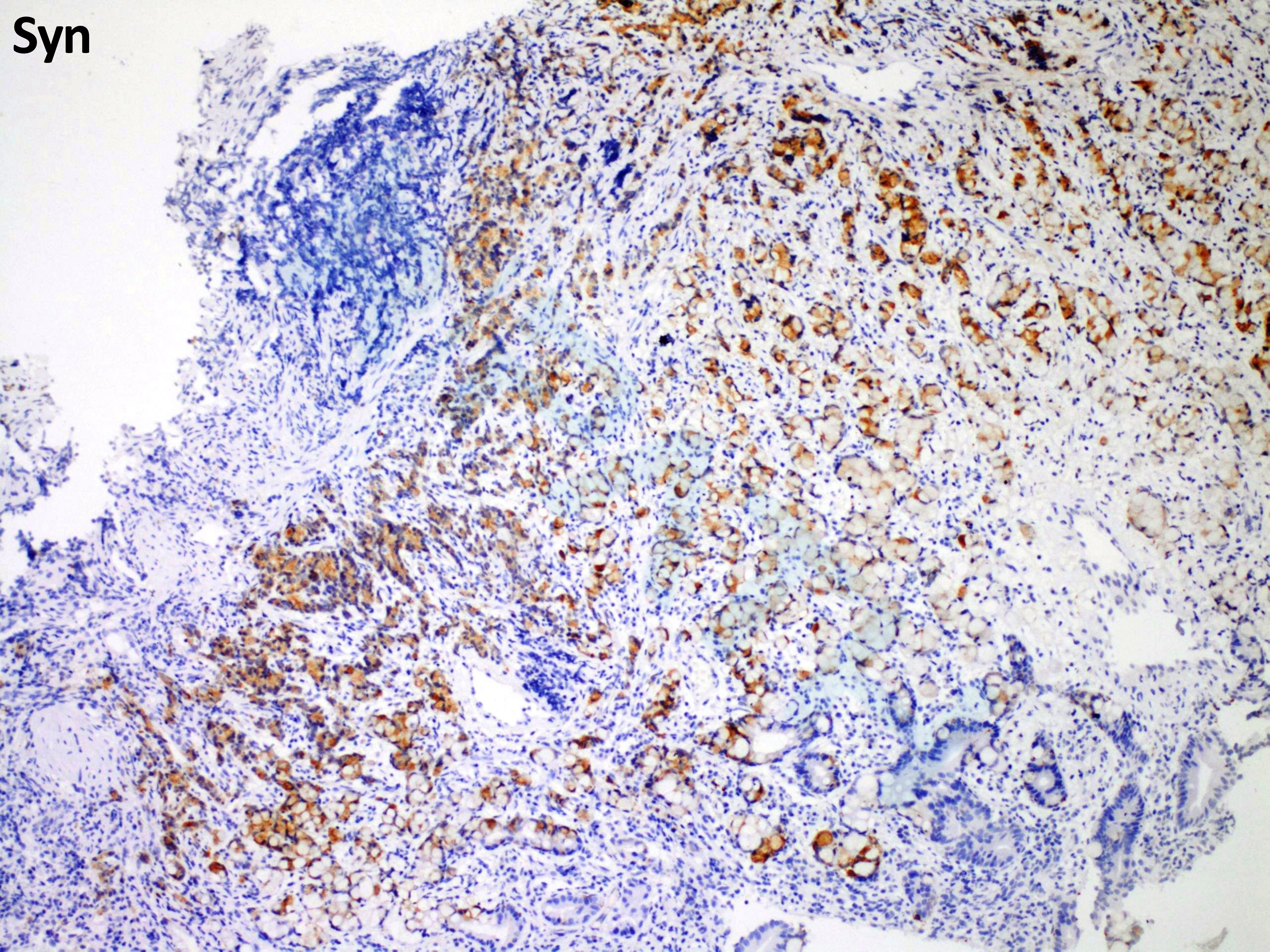
病例

- 男性 42岁
- 间断右下腹痛6年，逐渐加重
- 门诊结肠镜：阑尾开口处结节状隆起样改变，表面充血，取材质软






CK


Syn

- CK、Syn、CD56、CK8/18阳性
- KI67增值指数约5%
- 诊断：（阑尾）杯状细胞类癌

杯状细胞类癌

- 杯状细胞类癌（goblet cell carcinoid,GCC ）
- 具有杯状细胞特征，可分泌黏液
- 具有典型神经内分泌肿瘤（NET）免疫表型
- 1974年首次命名
- 大部发生于阑尾
- 少见，占阑尾肿瘤5%

- 发病：50-60岁
- 早于阑尾腺癌，晚于NET
- 男女比例报道不一
- 2010年WHO归于混合性腺神经内分泌癌
- 起源：阑尾隐窝上皮底部的多潜能干细胞

- 最常见：阑尾尖部，其次基底部、体部
- 沿纵轴呈圆周状生长，明显肿块少见
- 大部因阑尾壁增厚导致狭窄，诱发阑尾炎就诊
- 含黏液的杯状细胞呈圆形、椭圆形、巢状排列
- 至少散在瘤细胞神经内分泌SYN或CGA阳性

- The first significant grading system for goblet cell tumors was published in 1990 by Burke et al.

goblet cell carcinoid:

tumors with<25% carcinomatous growth .

mixed carcinoid-adenocarcinomas:

tumors>50% carcinomatous growth.

- Carcinomatous growth patterns included fused or cribriform glands, single file structures, diffusely infiltrating signet ring cells, or sheets of solid cells.

➢Grading of Tumors

Low-grade Histologic Features in Goblet Cell

Adenocarcinoma： Tumors with >75% tubular or clustered growth.

intermediate-grade goblet cell adenocarcinoma: Tumors with 50% to 75% tubular growth.

High-grade goblet cell adenocarcinoma: tumors with <50% tubular growth

MATERIALS AND METHODS

- 126 tumors were included over the period from 1981 to 2017.
- Low-grade Goblet Cell Adenocarcinoma (n=47)
- Intermediate-grade and high-grade tumors (n=79)

TABLE 1. Architectural Patterns in the Assessment of Goblet Cell Tumors

Low-grade Histologic Feature	Common High-grade Histologic Features
Tubular growth with round to oval discrete tumor clusters comprising a mixture of goblet cells, cuboidal cells, and Paneth-like cells, with or without lumens	Single cells, including nonmucinous single cells and signet ring-like cells, often admixed with abortive tubules
Simple trabecular growth consistent with tubules sectioned longitudinally	Single file growth or sheets of tumor cells, often admixed with abortive tubules
Limited tubule fusion or crowding	Fusion of goblet cell clusters to form anastomosing complex growth of goblet cell clusters or tubules
Mucin pools with discrete tubules or clusters, including ectatic tubules	Very large aggregates of goblet cells or drifts of goblet cells in extracellular mucin
Tubular nonmucinous glands including oncocytic tubules	Mucin-poor tumor cells in nests or clusters with high N:C ratio and jagged outlines
	Glands lined by cuboidal or columnar cells with high cytologic grade that resemble conventional adenocarcinoma
	Glands floating in mucin lined by columnar cells with high cytologic grade

Grade 1 (low-grade) tumors consist of <75% low-grade features and < 25% high-grade features. Grade 2 (intermediate-grade) tumors consist of 50% to 75% low-grade features, with the balance being any combination of high-grade features. Grade 3 (high-grade) tumors have <50% low-grade components, with the balance being any combination of high-grade features.

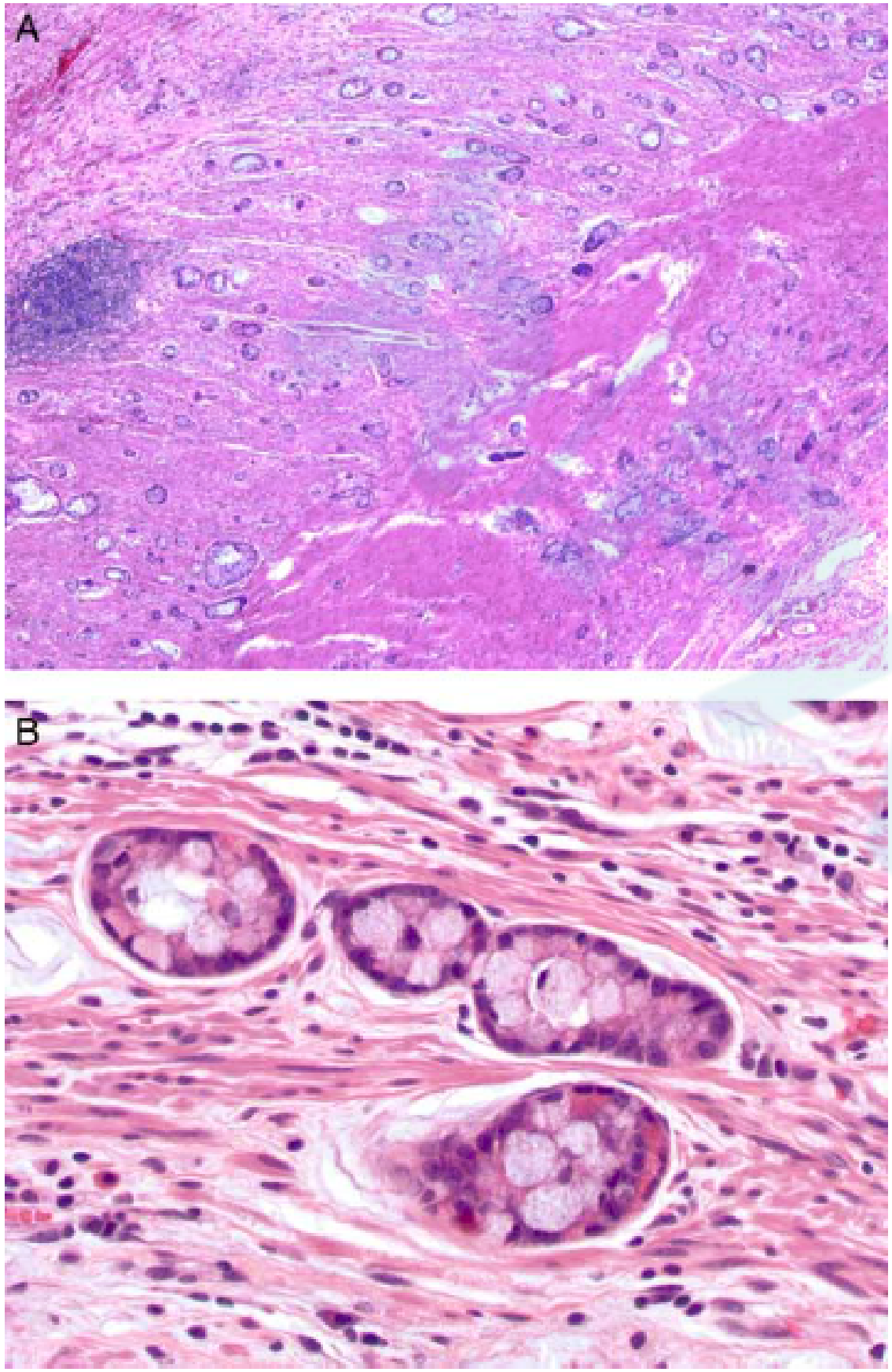


FIGURE 1. Low-grade pattern in goblet cell adenocarcinoma. Grade 1 goblet cell adenocarcinoma was defined as having>75% low-grade patterns. A, Low-power view showing round to oval, small tumor clusters infiltrating the appendix. Many of the groups have lumens and a few (lower left) are slightly dilated. B, High-power view of tumor clusters show that they comprise goblet-like mucinous cells and Paneth-like cells with cytoplasmic granules.

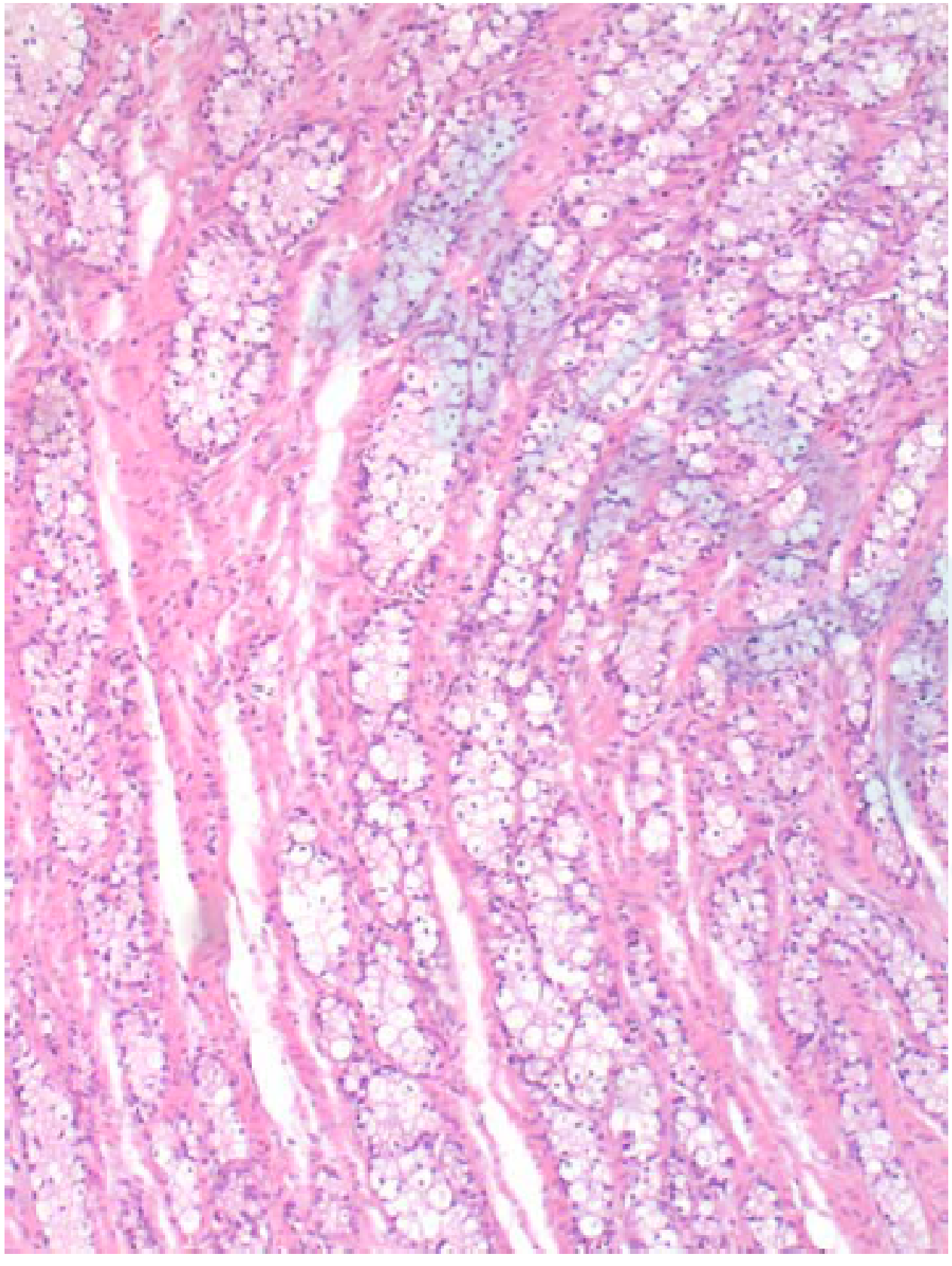


FIGURE 2. Low-grade pattern in goblet cell adenocarcinoma showing elongate tubular appearance. Longitudinal sectioning of elongate tubules creates a pattern of thickened trabecular structures, with peripheral localization of nuclei.

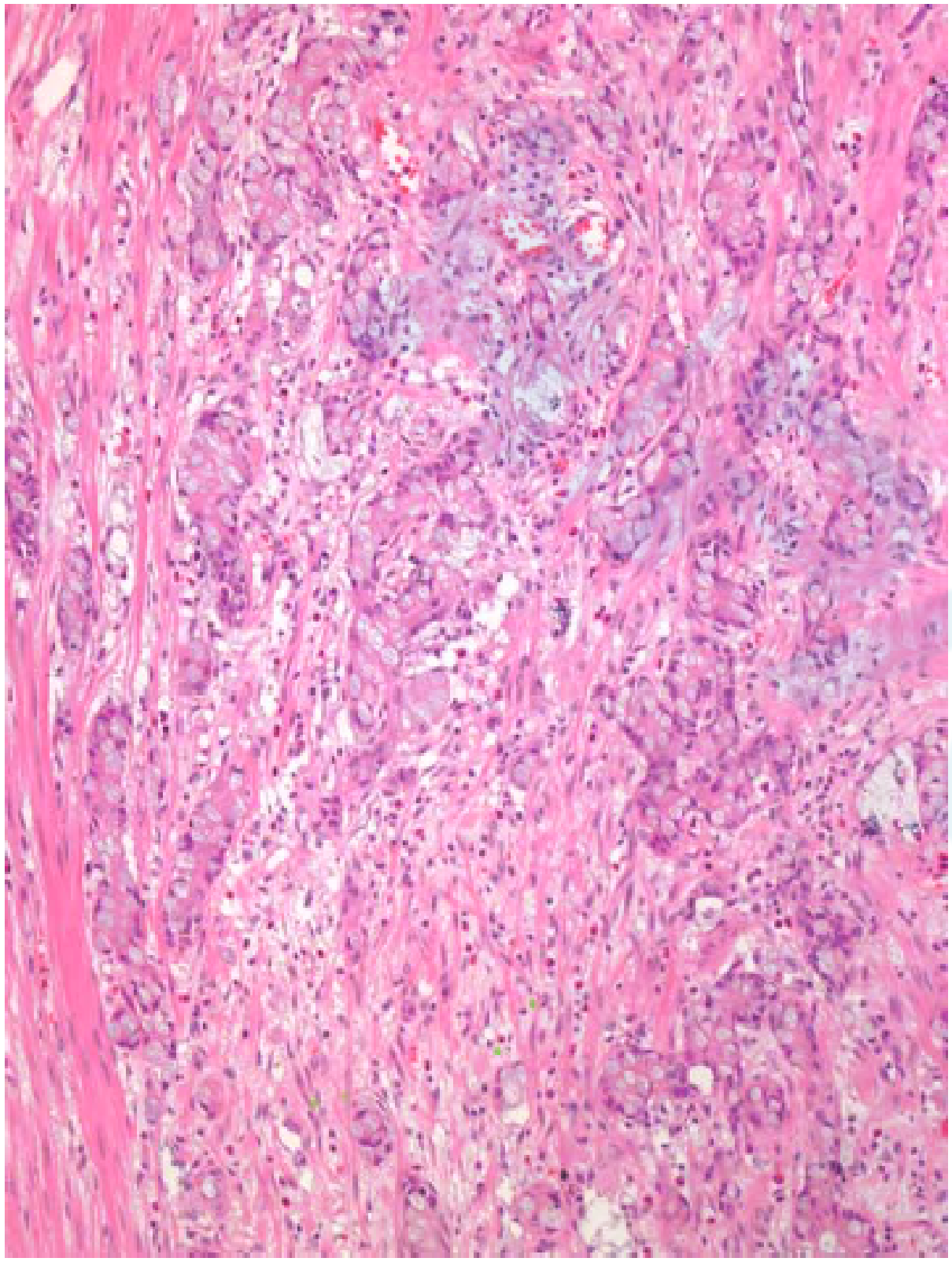


FIGURE 3. Low-grade pattern in goblet cell adenocarcinoma showing focal limited tubular fusion. The tubules show some degree of fusion and disorganized growth, although the basic
tubular and clustered architecture is maintained.

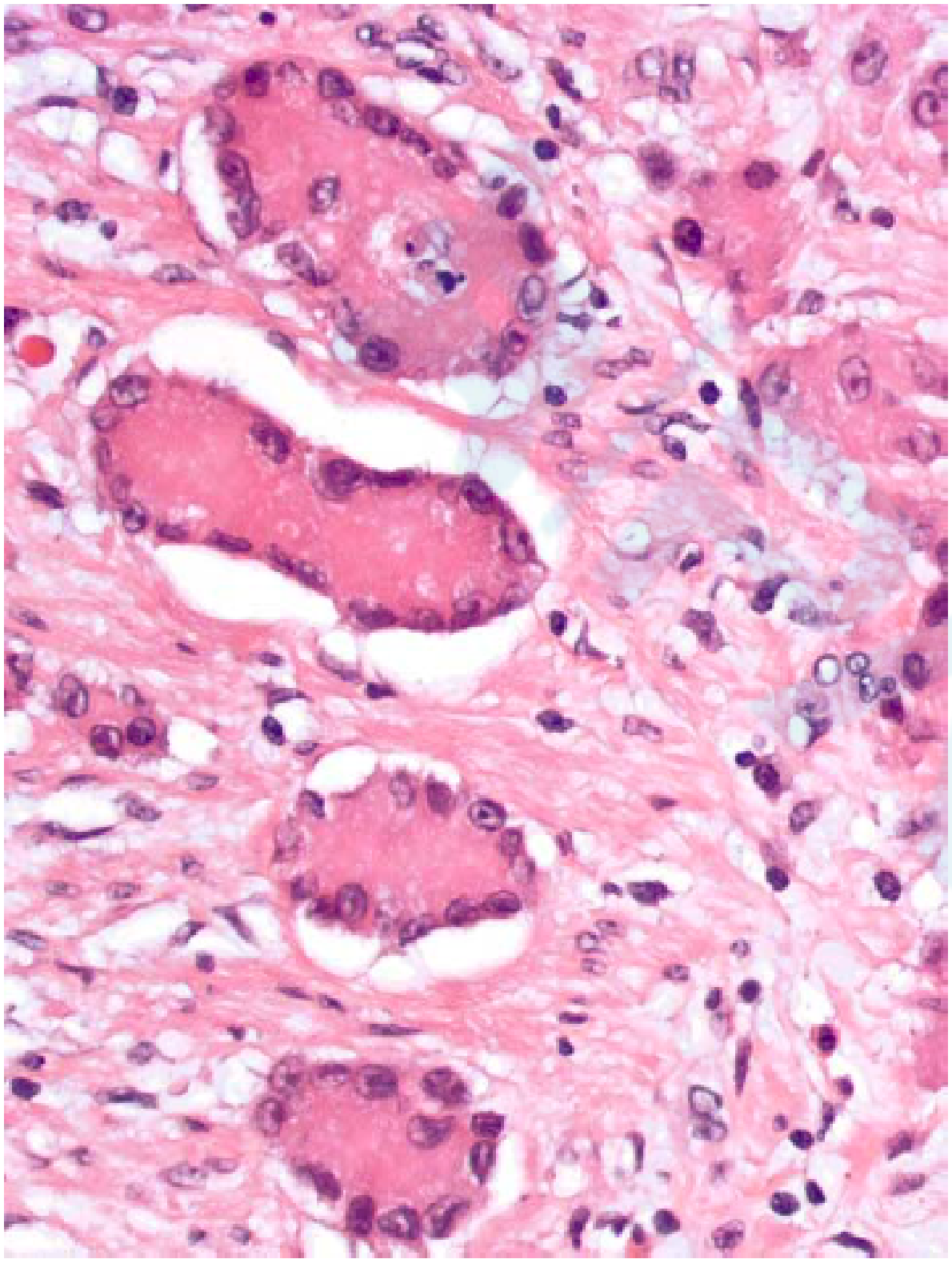


FIGURE 4. Low-grade pattern in goblet cell adenocarcinoma. In this example, the tubules are well formed and discrete with oncocytic cytoplasm. Although goblet cells are absent, the tumor clusters are oval with a small lumen.

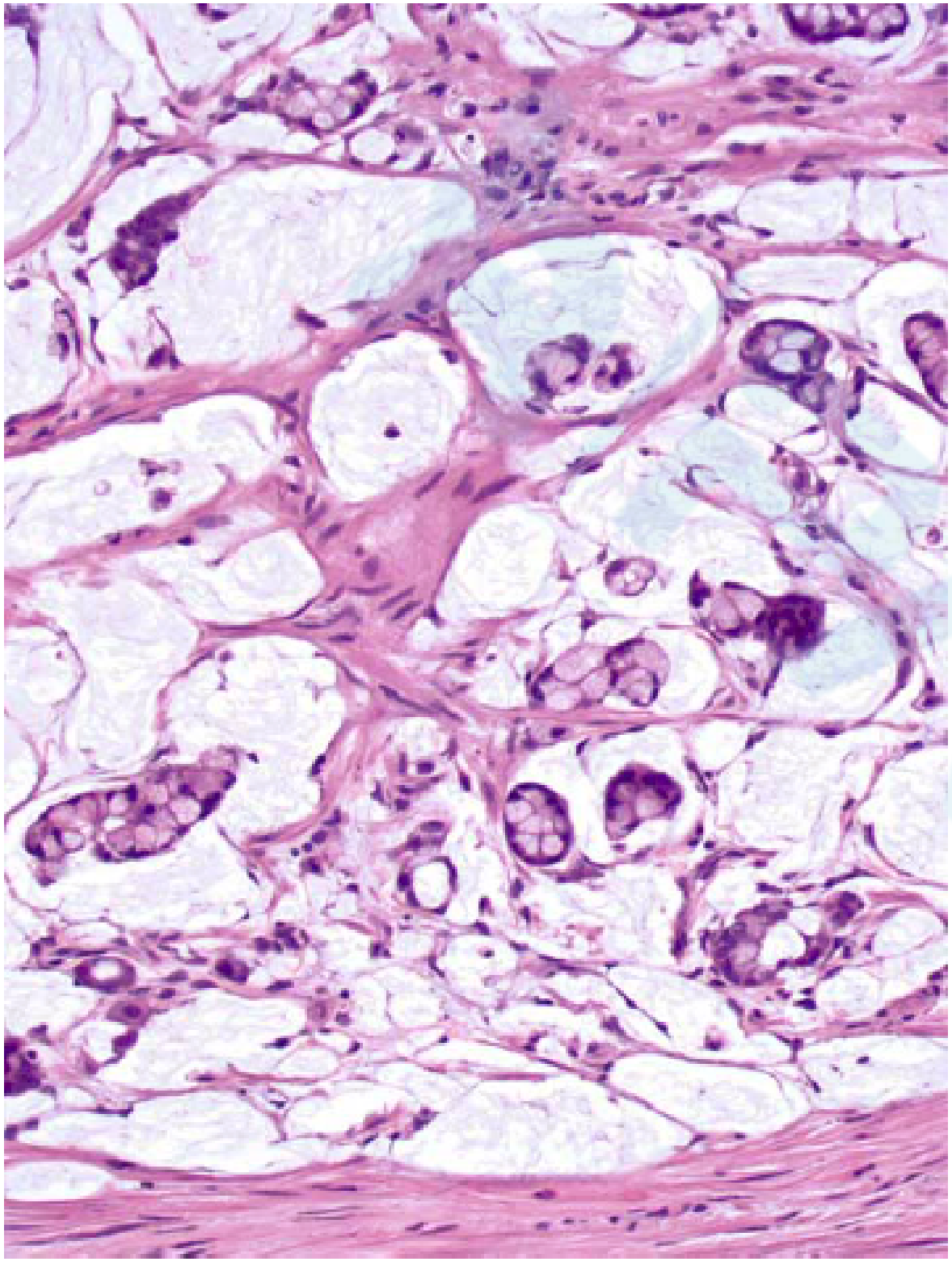


FIGURE 5. Low-grade pattern in goblet cell adenocarcinoma. In tumors with abundant extracellular mucin, the tumor clusters maintain their cohesive, uniform appearance, and resemble floating intestinal crypts.

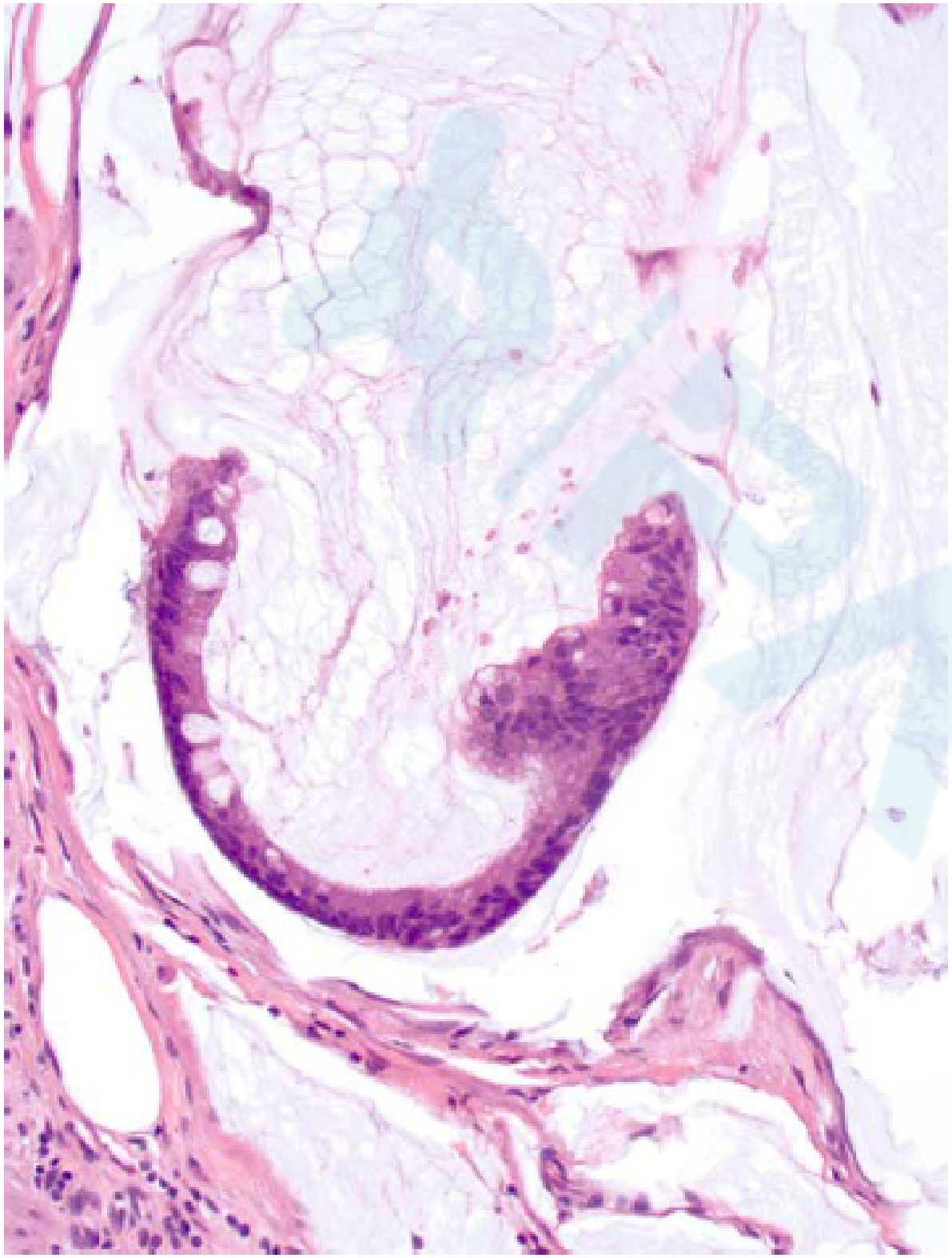


FIGURE 6. Low-grade pattern in goblet cell adenocarcinoma. In tumors with abundant extracellular mucin, ectatic, or disrupted low-grade floating tubules can resemble C-shaped structure. This pattern is reminiscent of well-differentiated mucinous adenocarcinoma, but in the context of otherwise low-grade goblet cell patterns, was considered a low-grade feature. Note the low-grade cytologic features and resemblance to a dilated disrupted intestinal crypt.

TABLE 1. Architectural Patterns in the Assessment of Goblet Cell Tumors

Low-grade Histologic Feature	Common High-grade Histologic Features
Tubular growth with round to oval discrete tumor clusters comprising a mixture of goblet cells, cuboidal cells, and Paneth-like cells, with or without lumens	Single cells, including nonmucinous single cells and signet ring-like cells, often admixed with abortive tubules
Simple trabecular growth consistent with tubules sectioned longitudinally	Single file growth or sheets of tumor cells, often admixed with abortive tubules
Limited tubule fusion or crowding	Fusion of goblet cell clusters to form anastomosing complex growth of goblet cell clusters or tubules
Mucin pools with discrete tubules or clusters, including ectatic tubules	Very large aggregates of goblet cells or drifts of goblet cells in extracellular mucin
Tubular nonmucinous glands including oncocytic tubules	Mucin-poor tumor cells in nests or clusters with high N:C ratio and jagged outlines
	Glands lined by cuboidal or columnar cells with high cytologic grade that resemble conventional adenocarcinoma
	Glands floating in mucin lined by columnar cells with high cytologic grade

Grade 1 (low-grade) tumors consist of <75% low-grade features and < 25% high-grade features. Grade 2 (intermediate-grade) tumors consist of 50% to 75% low-grade features, with the balance being any combination of high-grade features. Grade 3 (high-grade) tumors have <50% low-grade components, with the balance being any combination of high-grade features.

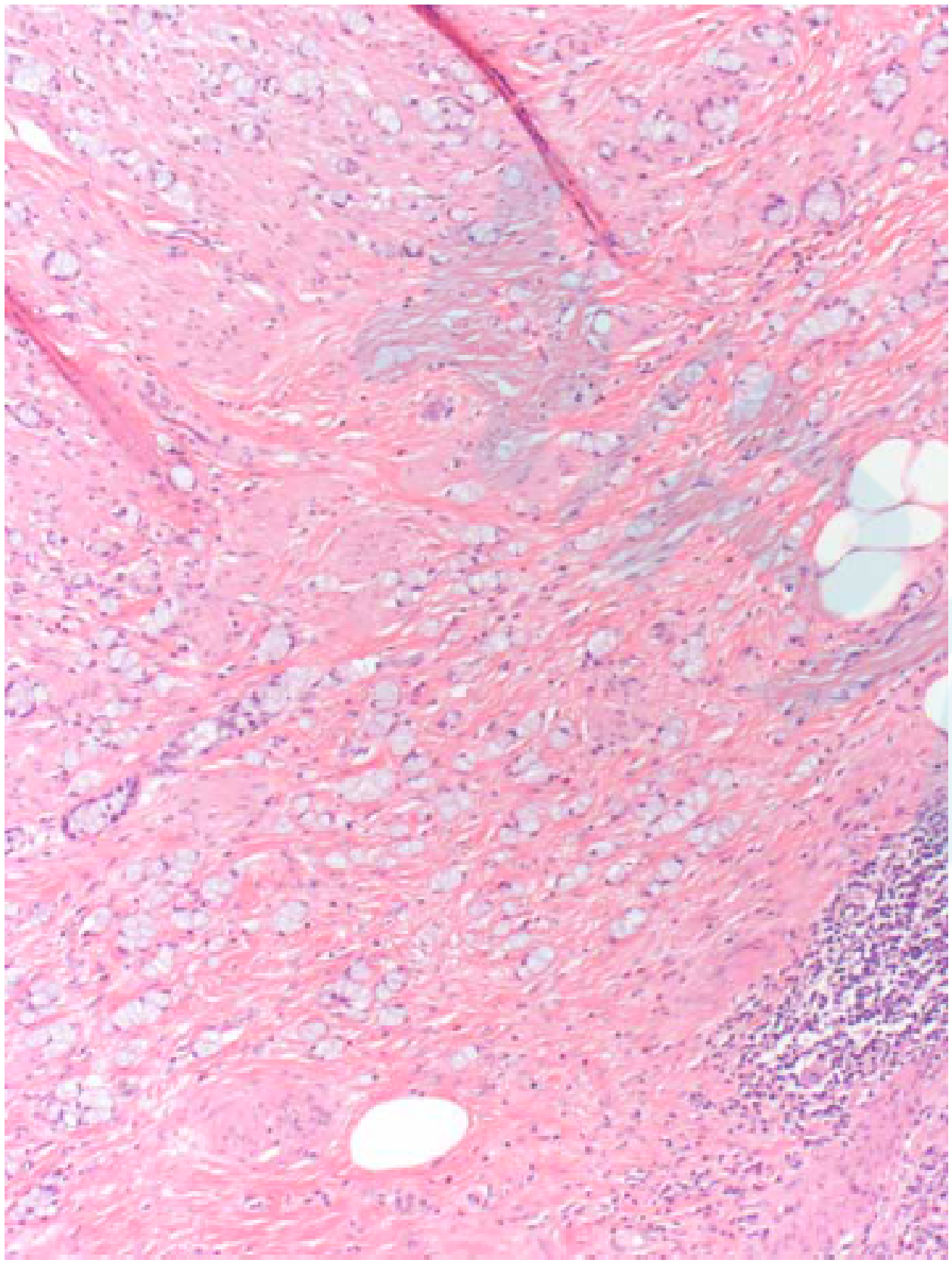


FIGURE 7. **High-grade histologic pattern** in goblet cell adenocarcinoma: **single cells**. Any of the high-grade patterns, singly or in combination, were used to assess grade. This mediumpower view of a goblet cell adenocarcinoma demonstrates bland single cells interspersed among clustered groups. At least some degree of single cell growth is common in goblet cell adenocarcinomas, even low-grade tumors. However, in low-grade tumors, the total amount of nontubular growth (including single cell growth, alone or in combination with other patterns) comprises <25% of the tumor.

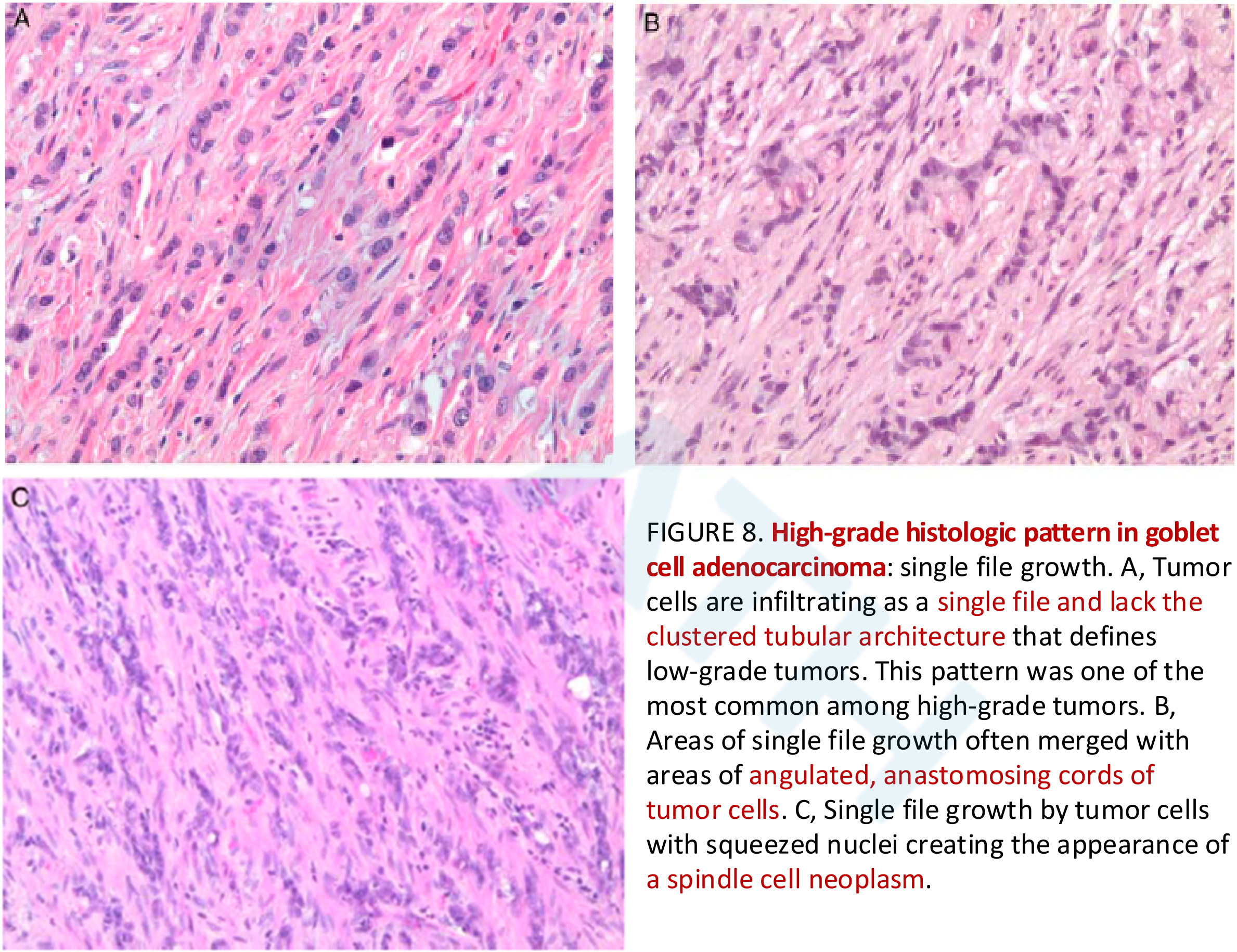


FIGURE 8. **High-grade histologic pattern in goblet cell adenocarcinoma**: single file growth. A, Tumor cells are infiltrating as a single file and lack the clustered tubular architecture that defines low-grade tumors. This pattern was one of the most common among high-grade tumors. B, Areas of single file growth often merged with areas of angulated, anastomosing cords of tumor cells. C, Single file growth by tumor cells with squeezed nuclei creating the appearance of a spindle cell neoplasm.

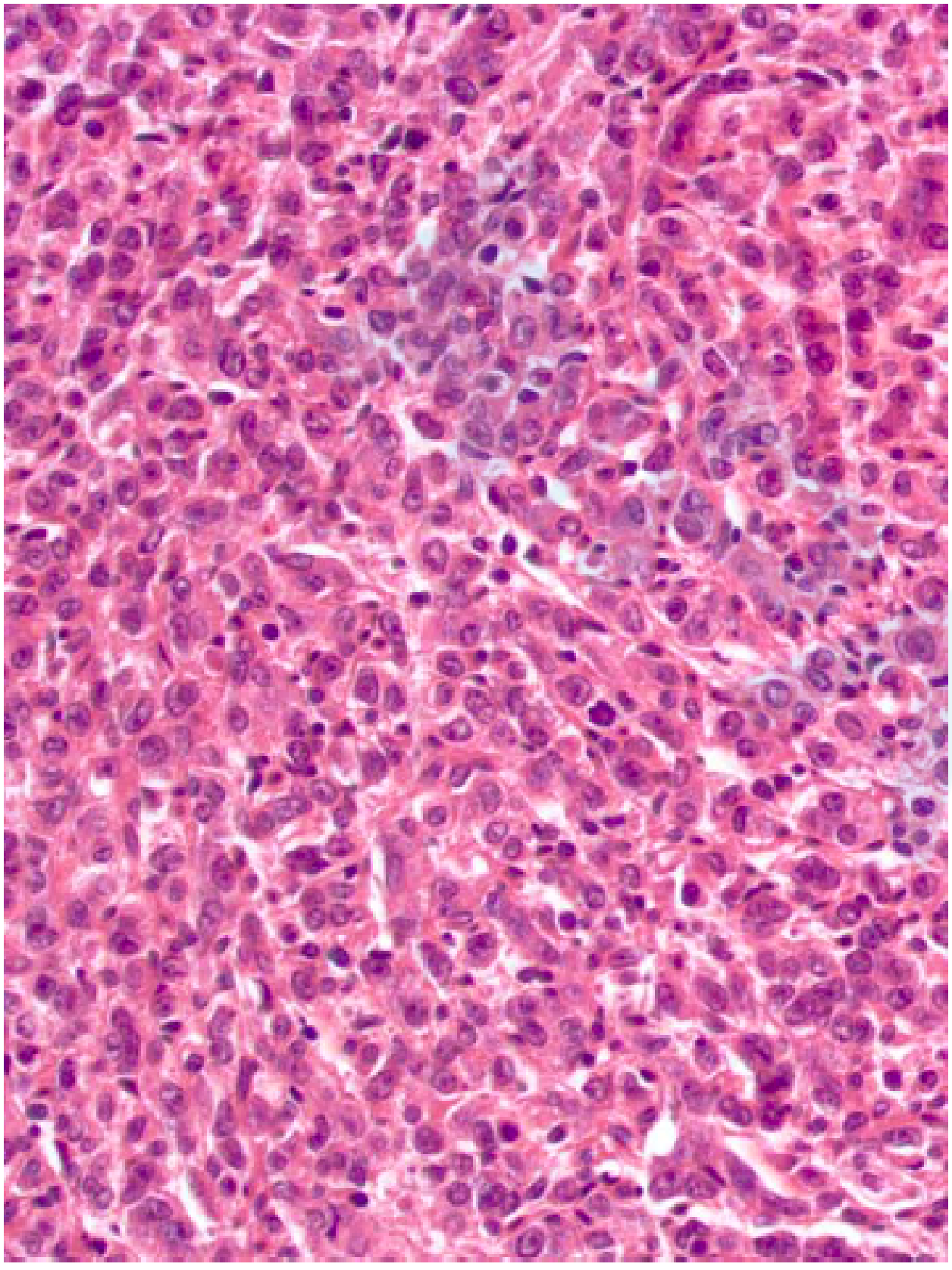
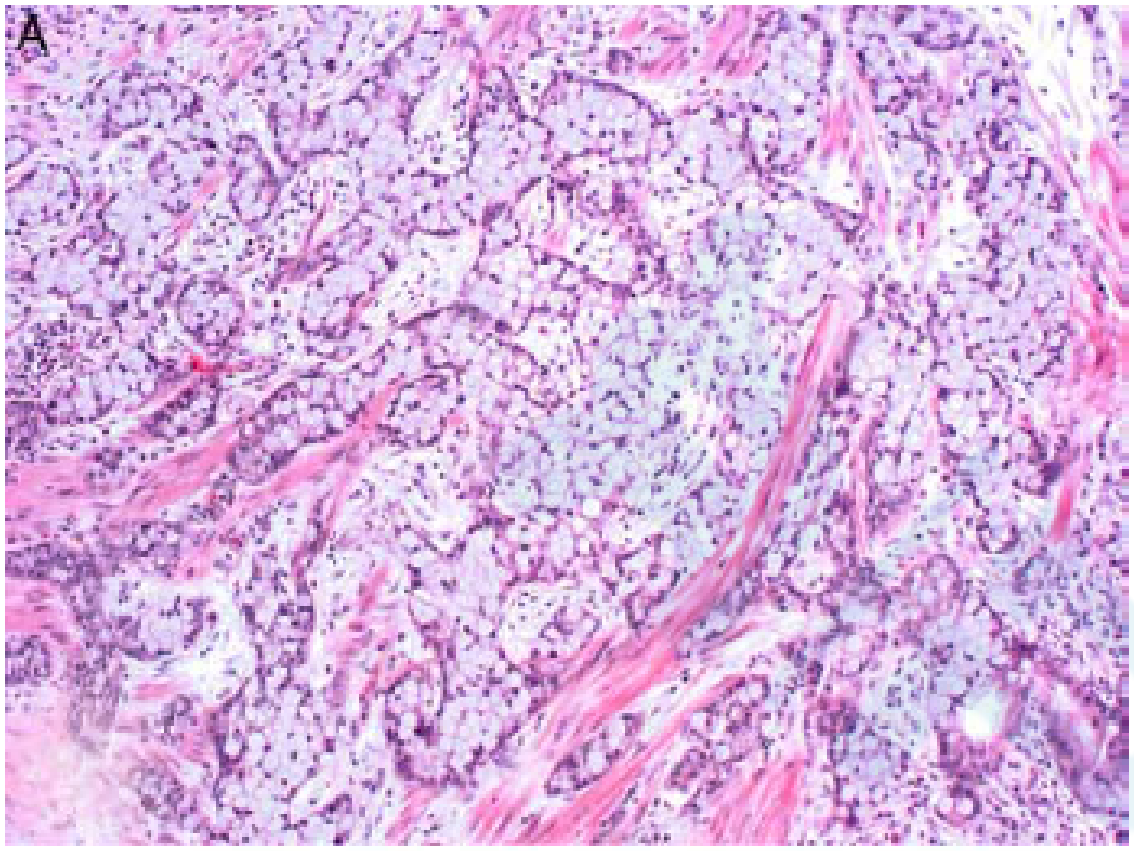
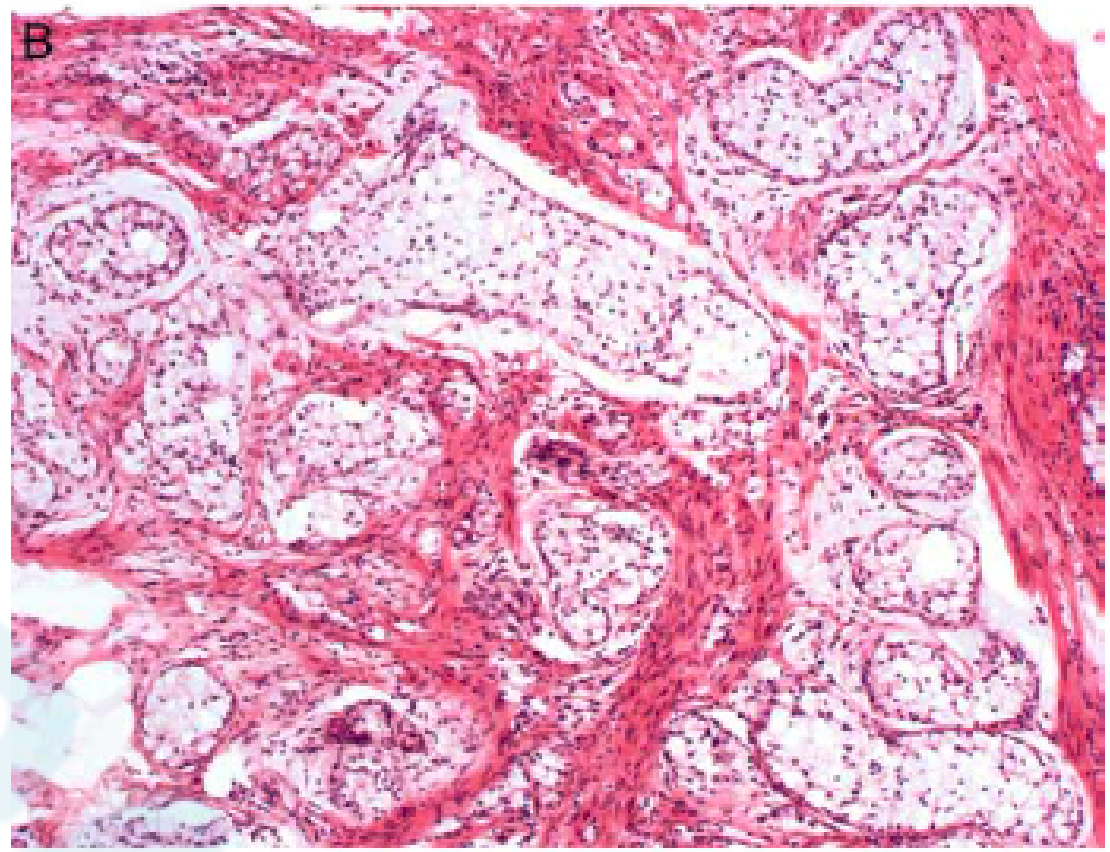


FIGURE 9. **High-grade histologic pattern** in goblet cell adenocarcinoma: sheet-like growth. In this example, crowded tumor cells are present that lack discrete clustered growth.





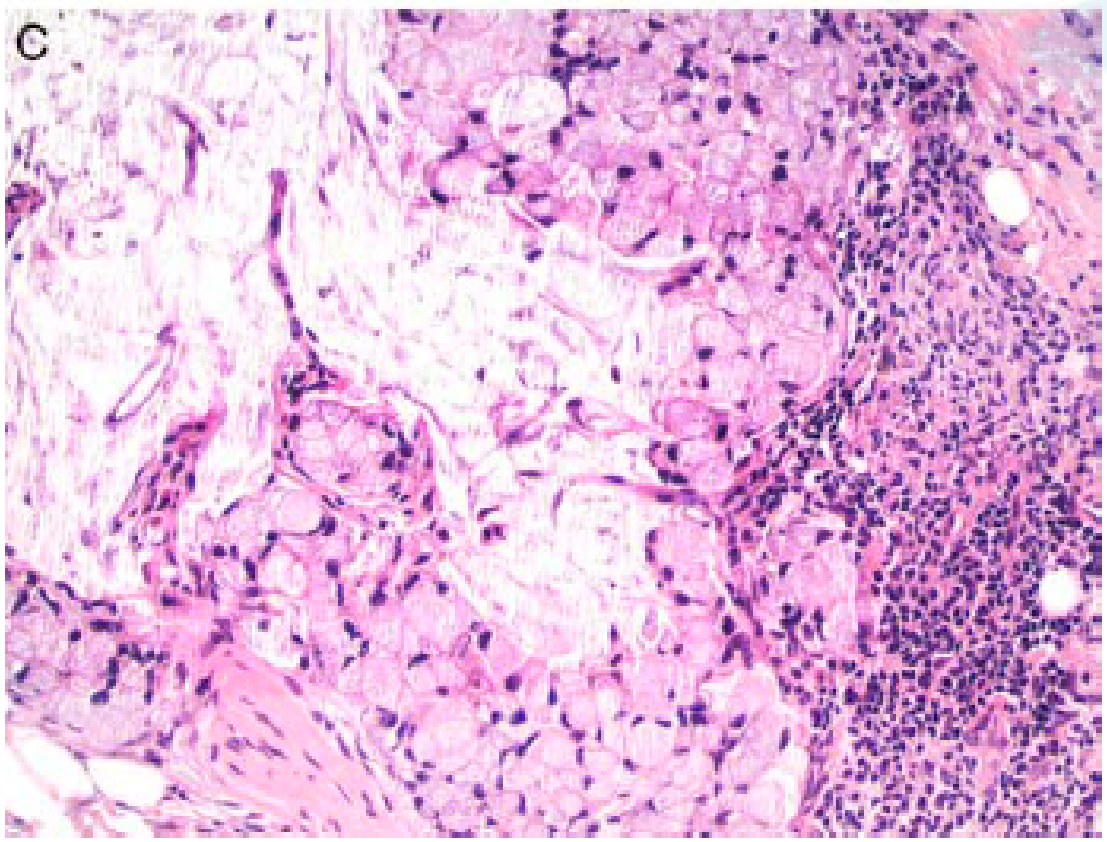


FIGURE 10. **High-grade histologic pattern** in goblet cell adenocarcinoma: large aggregates of goblet cells in goblet cell adenocarcinomas. A, Goblet cells in thick trabecular arrangements forming complex anastomosing structures. B, Cloud-like formations of goblet cells that are considerably larger than a normal intestinal crypt and lack the ordered architecture of low-grade tumors. C, Extracellular mucin pool with drifts of goblet cells in loose aggregates without clustered or tubular architecture. Despite the low-grade cytology, these patterns were considered deviations from the classic low-grade pattern.

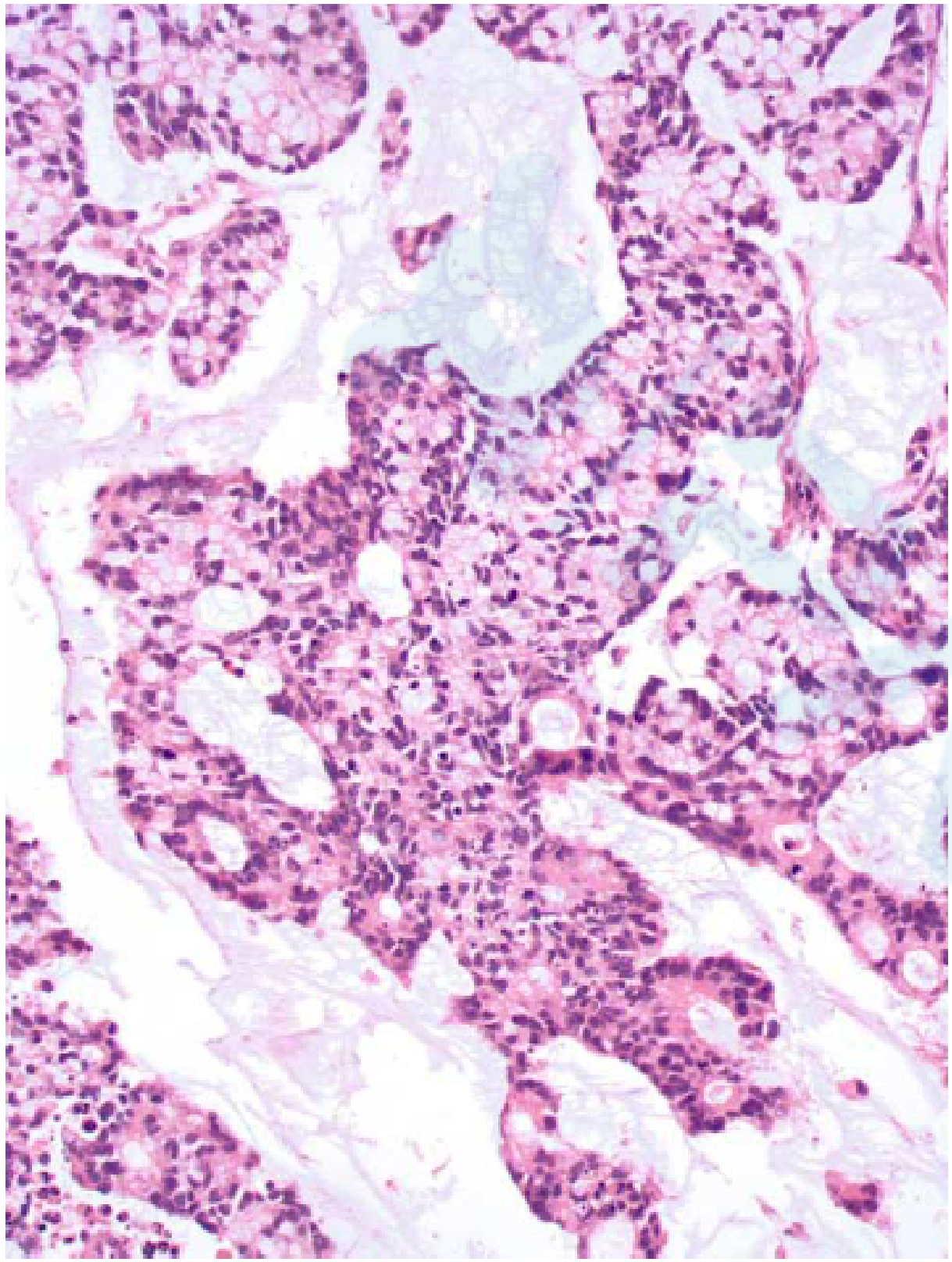


FIGURE 11. **High-grade histologic pattern** in goblet cell adenocarcinoma: fusion of goblet cell clusters. The tumor tubules are fused, forming a complex mass that is considered a deviation from the low-grade pattern of discrete tubules.

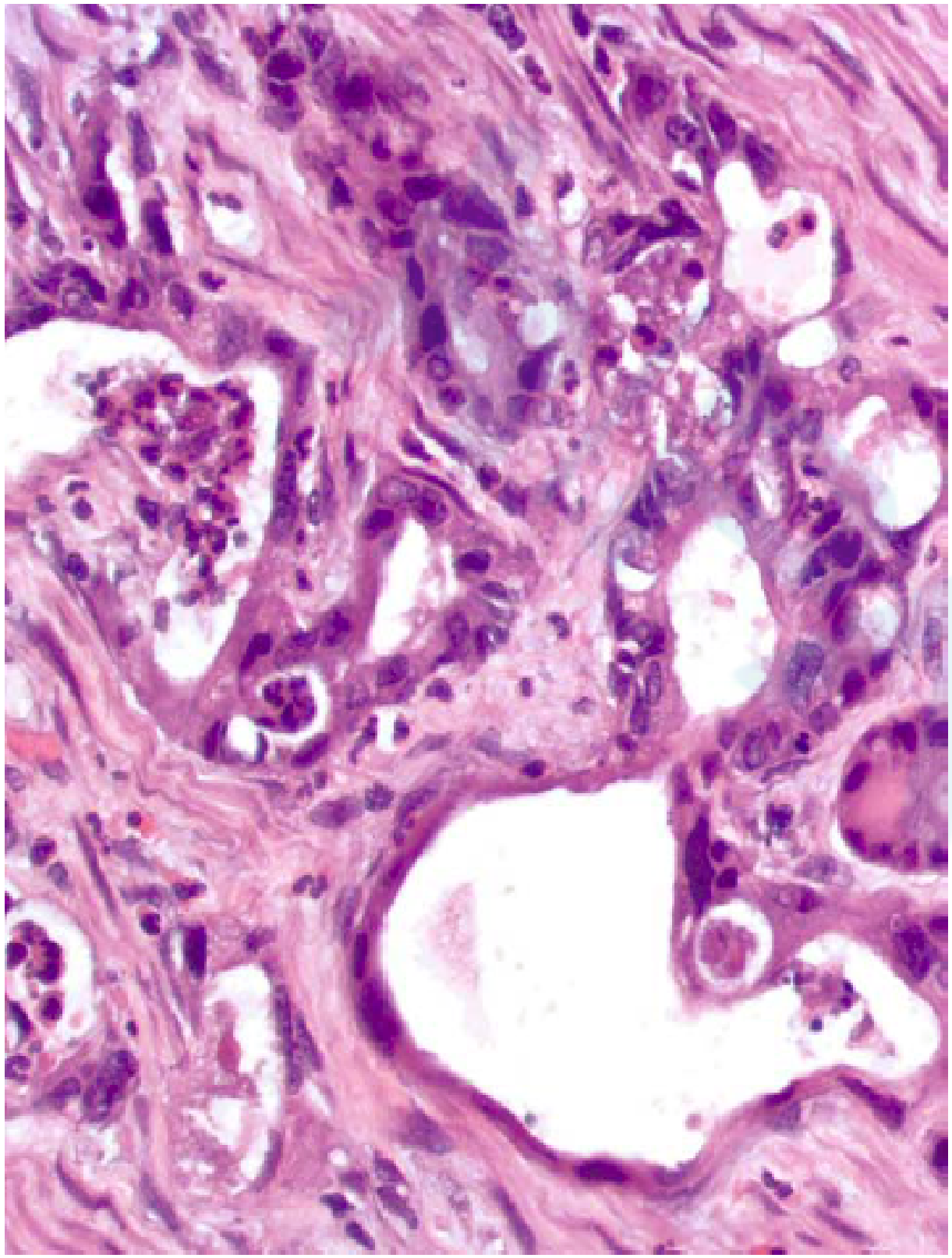


FIGURE 12. **High-grade histologic pattern** in goblet cell adenocarcinoma: jagged glands lined by cuboidal cells with high-grade cytologic features resembling conventional adenocarcinoma. This tumor had other areas that resemble goblet cell adenocarcinoma.

RESULTS

- 126 tumors were included over the period from 1981 to 2017.

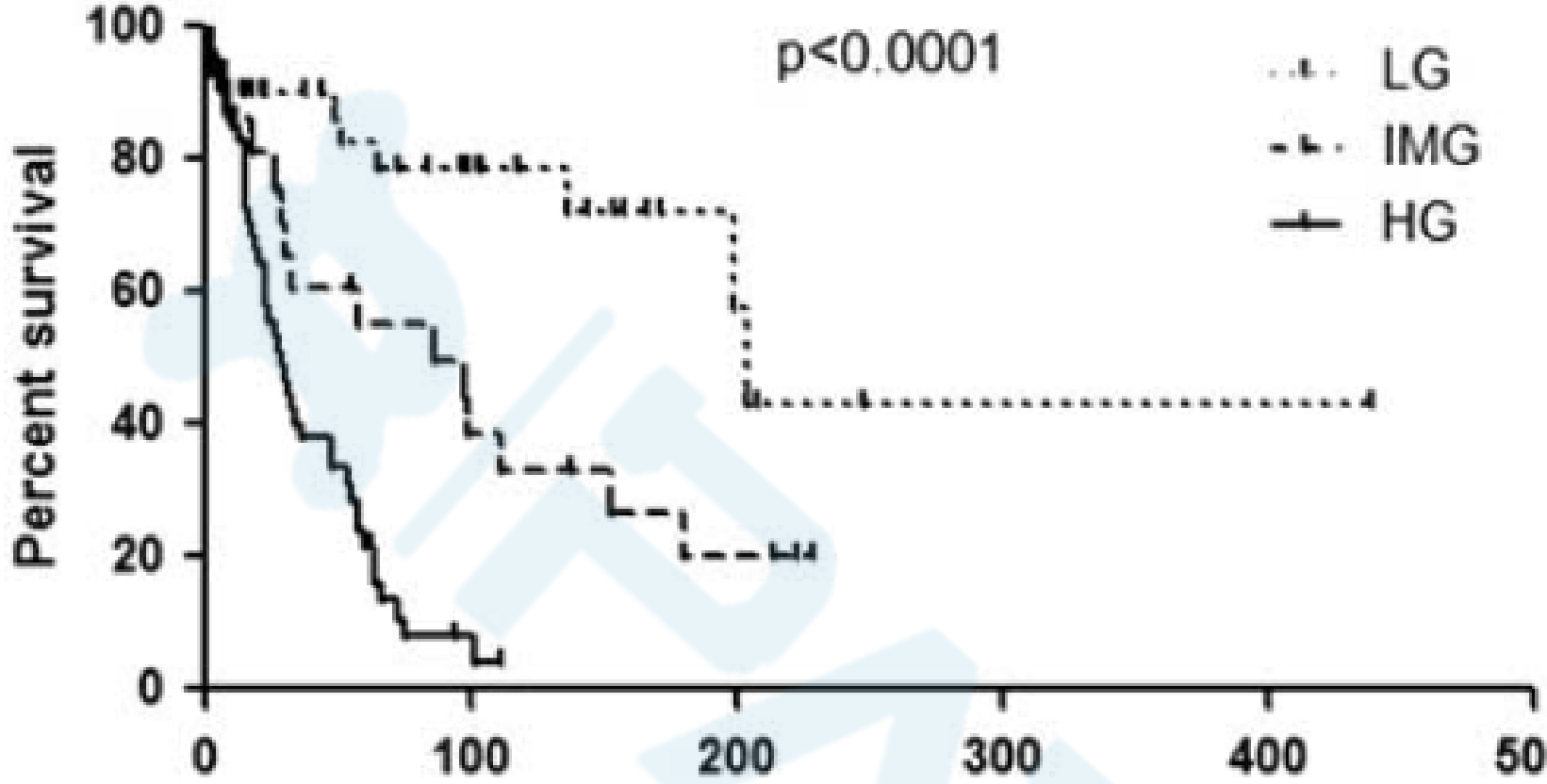
TABLE 2. Clinicopathologic Characteristics of Appendiceal Goblet Cell Adenocarcinoma (n = 126)

Characteristics	N (%)
Age (mean [range])	57 (33-86)
Sex	
Female	61 (48)
Male	65 (52)
Surgical resection (n = 117)	
Appendectomy alone	35 (30)
Appendectomy and right colectomy	82 (70)
Grade	
Low	47 (37)
Intermediate	22 (18)
High	57 (45)
Anatomic stage	
I	5 (4)
II	74 (59)
III	16 (13)
IV	31 (24)
Overall survival, median (mo)	58

TABLE 3. Histologic Characteristics of Goblet Cell Adenocarcinoma According to Tumor Grade

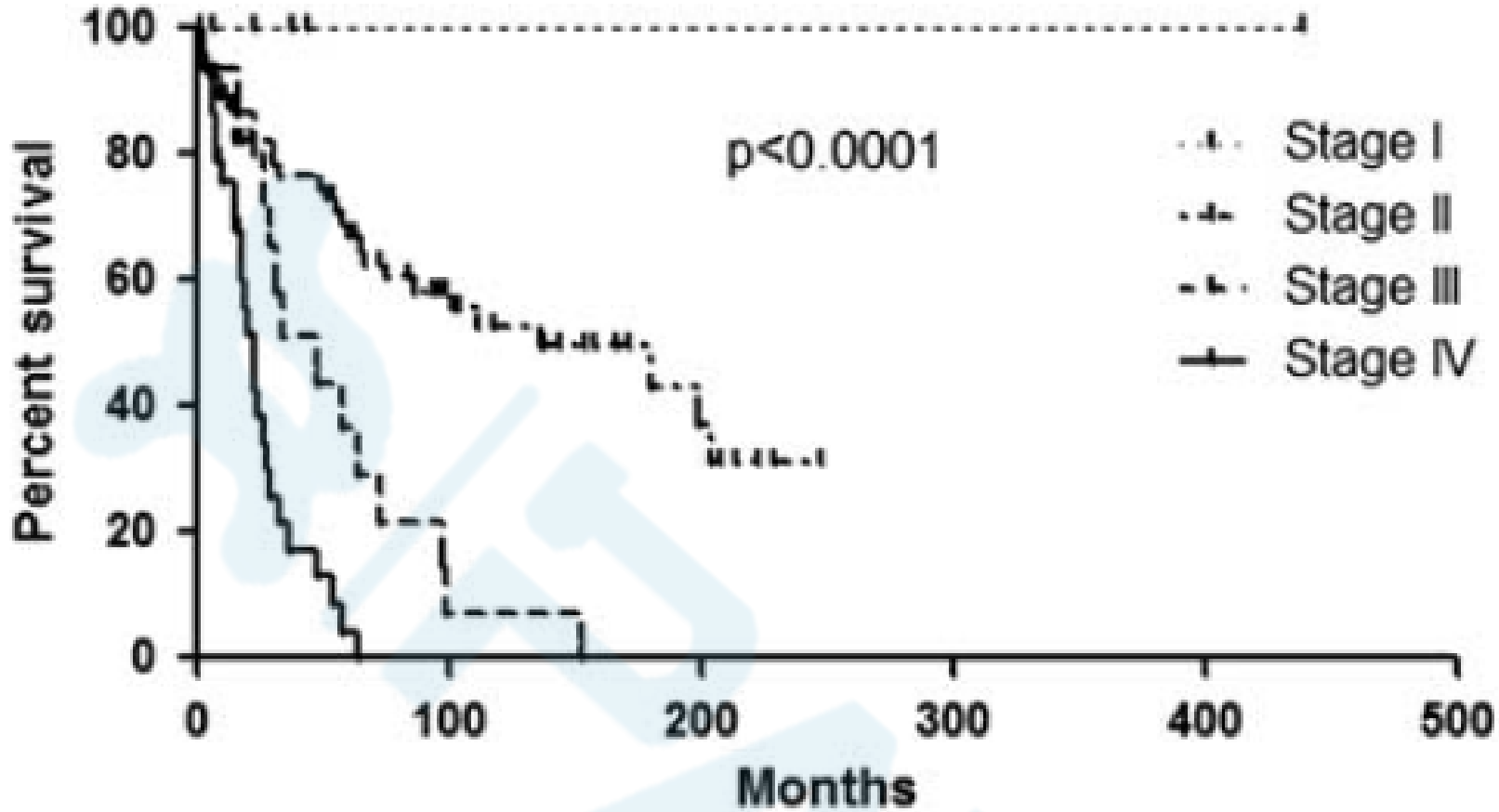
	Low Grade (n = 47) (N [%])	Intermediate Grade (n = 22) (N [%])	High Grade (n = 57) (N [%])	Statistical Significance (*P*)
pT				
T1	2 (4)	0	0	< 0.0001
T2	3 (6)	0	0	
T3	37 (79)	18 (82)	24 (42)	
T4	5 (11)	4 (18)	33 (58)	
pN				
N0	47 (100)	17 (77)	35 (61)	< 0.0001
N1	0	4 (18)	10 (18)	
N2	0	1 (5)	12 (21)	
pM				
M0	47 (100)	19 (86)	29 (51)	< 0.0001
M1a	0	1 (5)	7 (12)	
M1b	0	2 (9)	21 (37)	
Stage				
I	5 (11)	0	0	< 0.0001
II	42 (89)	15 (68)	17 (30)	
III	0	4 (18)	12 (21)	
IV	0	3 (14)	28 (49)	
Other histologic findings				
Perineural invasion	43 (91)	21 (95)	54 (95)	NS (0.74)
Lymphovascular invasion	1 (2)	6 (27)	27 (47)	< 0.0001
Acute appendicitis	30 (64)	10 (45)	9 (16)	< 0.0001
Perforation	14 (30)	5 (23)	4 (7)	< 0.01

NS indicates not significant.



	Median survival (month)	5 year survival (%)	10 year survival (%)
LG (n=42)	204	82	78
IMG (n=22)	86	55	33
HG (n=56)	29	22	4

FIGURE 13. Kaplan-Meier survival curves for the cohort based on tumor grade, using our proposed grading system.



	Median survival (month)	5 year survival (%)	10 year survival (%)
Stage I (n=5)	n/a	100	100
Stage II (n=69)	136	67	43
Stage III (n=16)	48	36	0
Stage IV (n=30)	22	4.2	0

FIGURE 14. Kaplan-Meier survival curves for the cohort based on tumor stage.

TABLE 4. Univariate Analysis of Variables to Assess the Effect on Overall Survival

	HR	95% CI	Statistical Significance
Sex	1.37	0.85-2.21	NS (0.20)
Age	1.03	1.01-1.05	$P < 0.01$
Right colectomy	0.84	0.52-1.37	NS (0.49)
Grade	2.72	1.90-3.89	$P < 0.001$
Stage	2.72	2.00-3.69	$P < 0.001$
Perineural invasion	0.61	0.22-1.70	NS (0.35)
Lymphovascular invasion	2.27	1.35-3.79	$P < 0.01$
Acute appendicitis	0.31	0.17-0.55	$P < 0.001$
Perforation	0.46	0.22-0.97	$P < 0.05$

CI indicates confidence interval; HR, hazard ratio; NS, not significant.

TABLE 5. Multivariate Analysis of Variables to Assess the Effect on Overall Survival

	HR	95% CI	Statistical Significance (*P*)
Age	1.03	1.00-1.05	0.016
Grade	1.77	1.16-2.71	0.009
Stage	1.88	1.32-2.73	0.001
Lymphovascular invasion	1.37	0.78-2.42	NS (0.28)
Acute appendicitis	0.60	0.30-1.19	NS (0.14)
Perforation	1.14	0.48-2.73	NS (0.76)

CI indicates confidence interval; HR, hazard ratio; NS, not significant.

Validation of Tang's and Lee's System

➢ Tang's System

- Goblet cell carcinoids were designated group A
- 2 forms of adenocarcinoma ex goblet cell carcinoid were described, an intermediate signet ring cell type (type B),
- a poorly differentiated carcinoma type (type C).

➢ Seven cases were discordant between our grading system and Tang's system (concordance rate of 94.4%). All 7 cases were low grade by our criteria but high grade by Tang's criteria (group B) (Fig. 15).

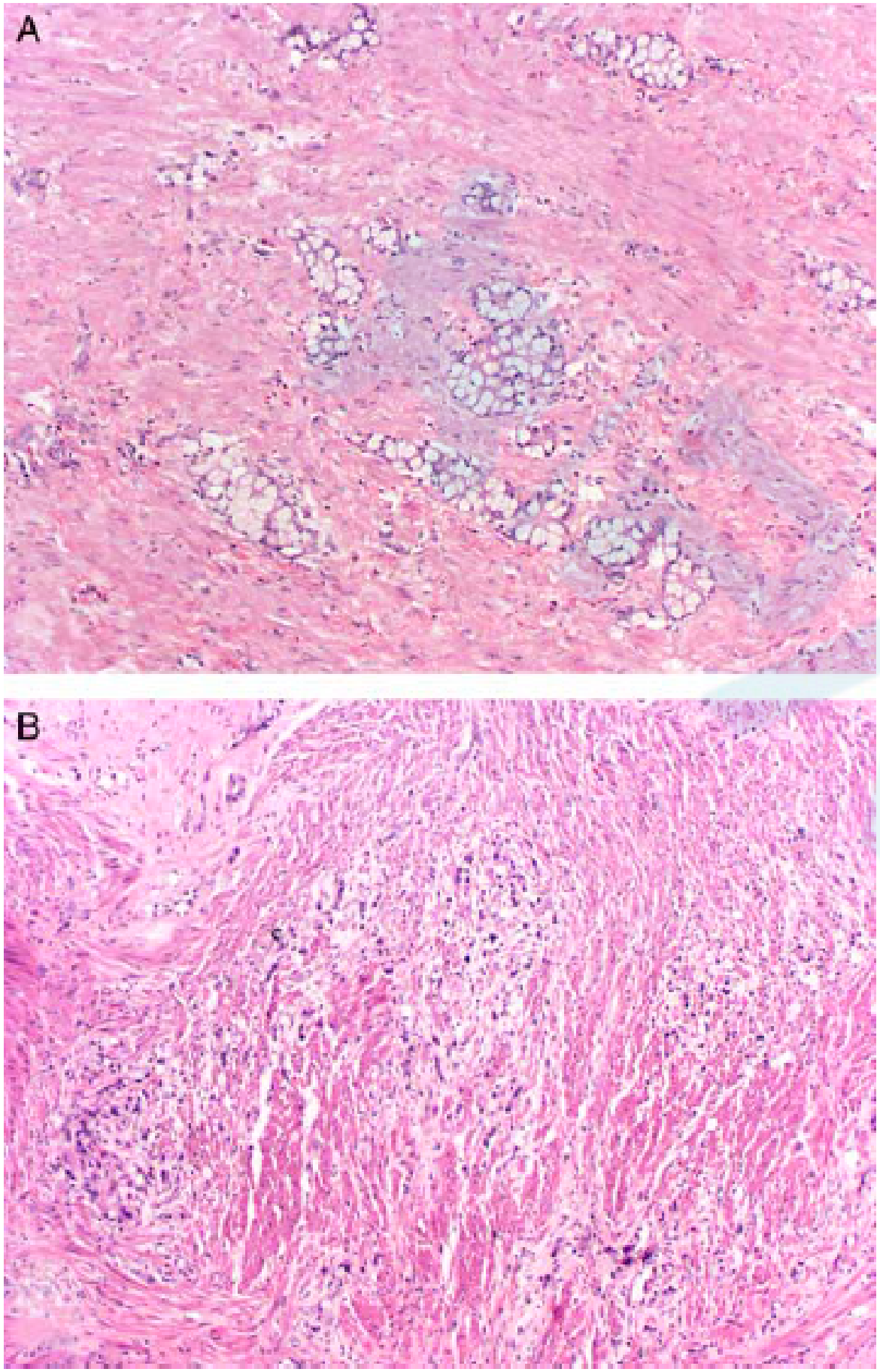


FIGURE 15. Example of goblet cell adenocarcinoma that qualifies as high grade in the Tang system (adenocarcinoma ex goblet cell carcinoma, signet ring cell type) but does not meet criteria for high grade in our system. A, Representative view of 90% of the tumor, showing uniform clusters of goblet cells. B, View of an area that accounts for ~10% of the tumor, in which the tumor cells infiltrate singly and in disorganizes abortive clusters. In Tang's system, discohesive single cell infiltrating pattern qualifies as group B, but in our system, this pattern would have to account for 25% to 50% of the tumor to qualify as intermediate grade.

- Lee's System

  a 2-tier grading system that required scoring tumors on the presence of 3 variables: cytologic atypia, stromal desmoplasia, and solid growth. Tumors with at most 1 of these variables were low grade whereas tumors with 2 or 3 of these variables were high grade.

- 31 cases were discordant between our grading system and Lee's system (concordance rate of 75.4%).

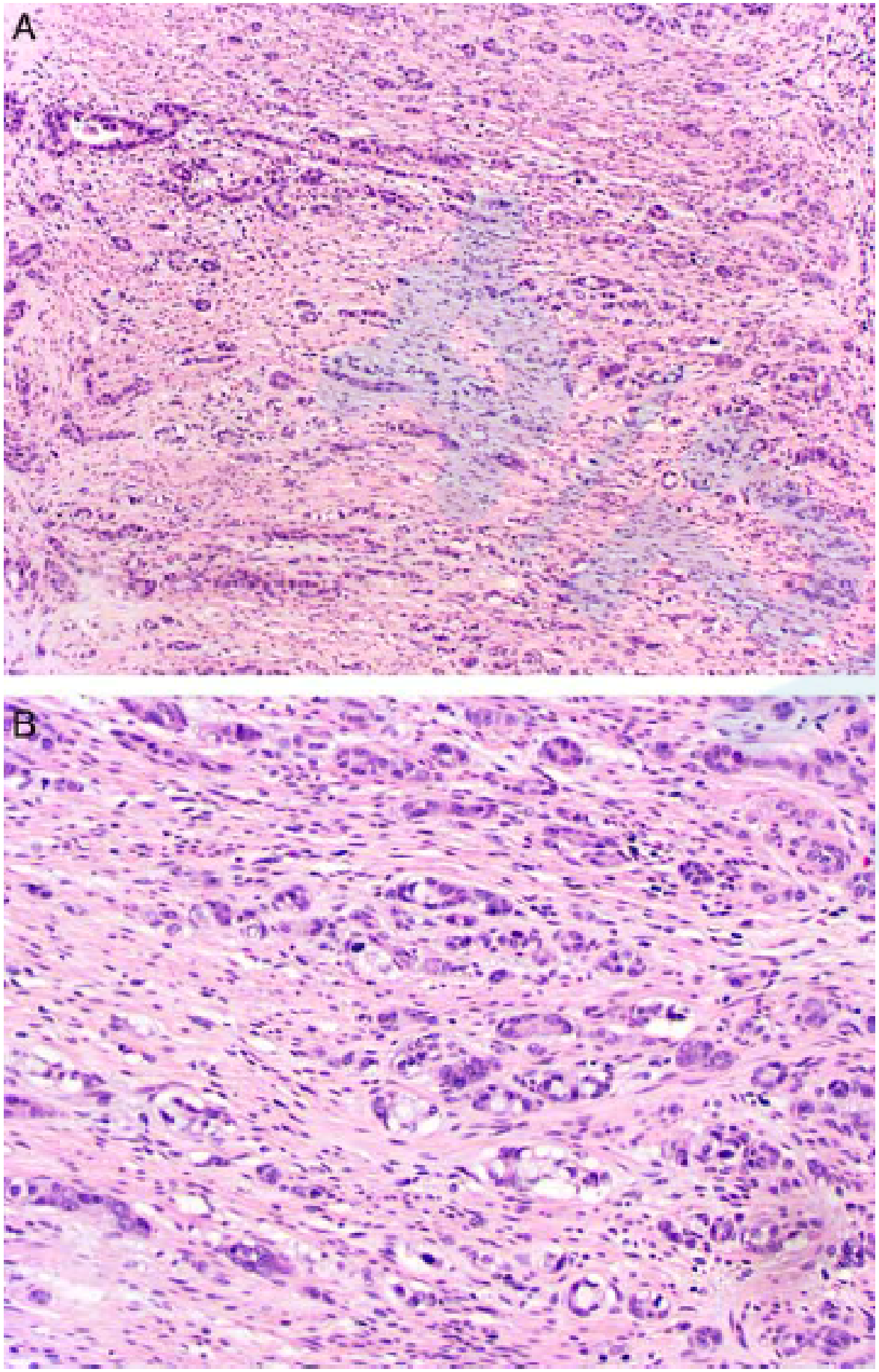
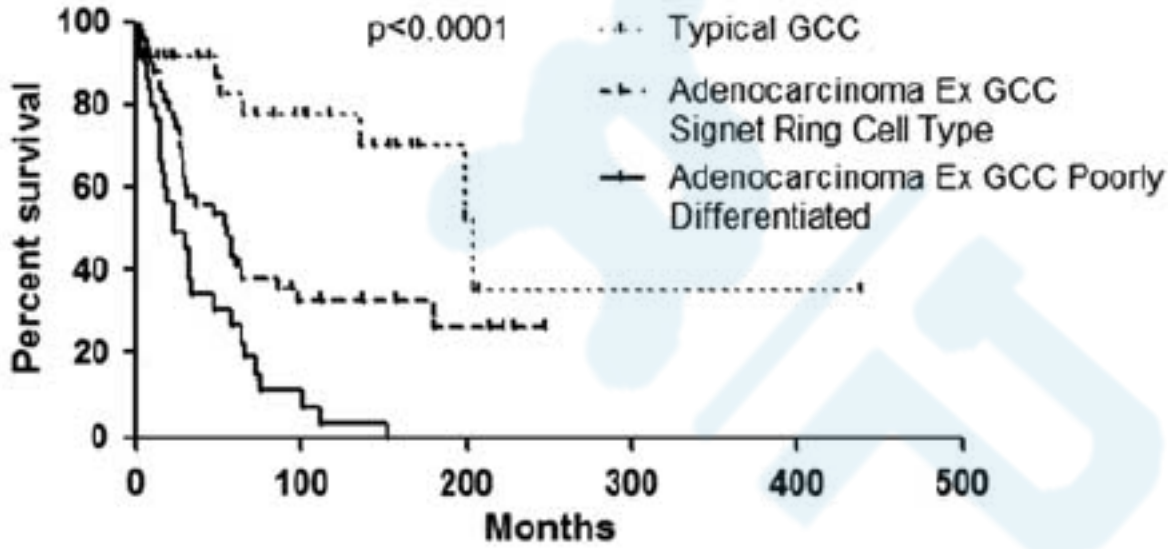
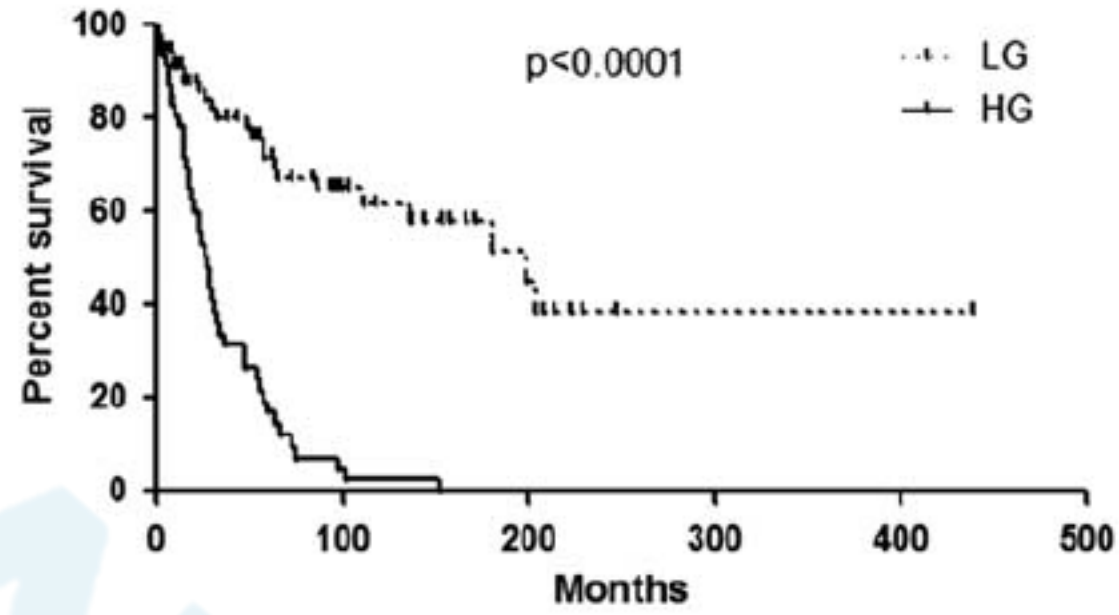


FIGURE 16. Low-power (A) and high-power (B) views of a goblet cell adenocarcinoma that qualifies as high grade in our system, but does not meet criteria for high grade in Lee's system. This tumor was almost entirely composed of single file structures, single cells, and small abortive type tubules that infiltrated the appendix. In our system, <50% of the tumor shows uniform tubular or clustered pattern, qualifying as high grade. In Lee's system, tumors must have 2 of 3 features to be classified as high grade: cytologic atypia, desmoplasia replacing the muscle, and sheet-like growth. This case scores a point for cytologic atypia, but desmoplasia is not striking and, while the tumor is crowded, it is not sheet like.



	Median survival (month)	5 year survival (%)	10 year survival (%)
Typical GCC (n=36)	204	83	77
Adenocarcinoma Ex GCC Signet Ring Cell Type (n=53)	55	41	32
Adenocarcinoma Ex GCC Poorly Differentiated (n=31)	22	27	3.7



	Median survival (month)	5 year survival (%)	10 year survival (%)
LG (n=72)	199	72	61
HG (n=48)	28	17	2.4

FIGURE 17. Kaplan-Meier survival curves for the cohort when graded according to Tang's system(left) and when graded according to Lee's system(right) .

DISCUSSION

- The pathologic evaluation of goblet cell tumors has been complicated by inconsistent terminology and grading systems. This has led to confusion among both pathologists and clinicians about the true nature of these tumors and their management.
- We propose that goblet cell tumors be classified as goblet cell adenocarcinoma, and staged and graded in a manner analogs with other gastrointestinal adenocarcinomas.

- We found that overall survival was significantly different between the 3 groups, with median overall survival of 204, 86, and 29 months, respectively.
- Other than histologic grade and tage, none of these other factors was significant on multivariate analysis.

- Our histologic tumor grade and tumor stage were independent prognostic indicators that together guide decisions regarding additional surgical or chemotherapeutic interventions.

谢谢！