GOBLET CELL CARCINOID

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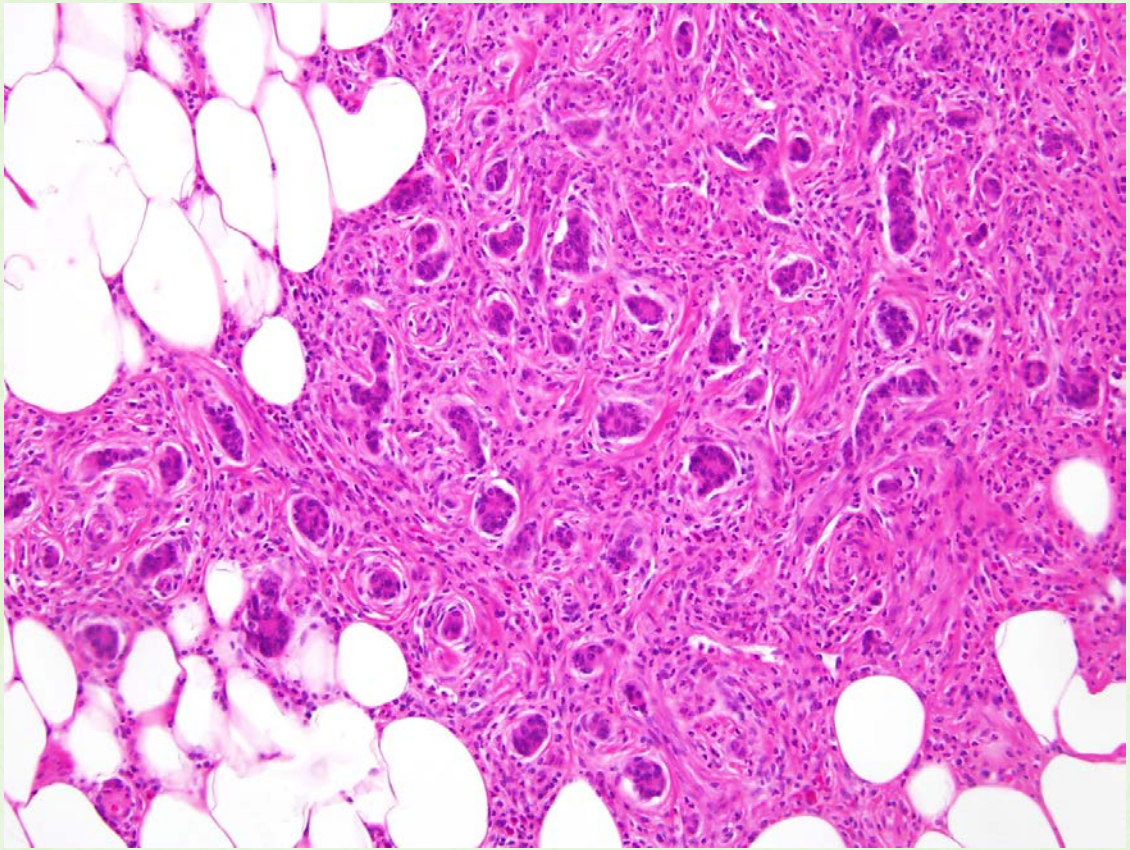
Dr. Hanlin Wang declares he has no conflict(s) of interest to disclose.

2010 WHO Classification of Neuroendocrine Neoplasms of the Appendix

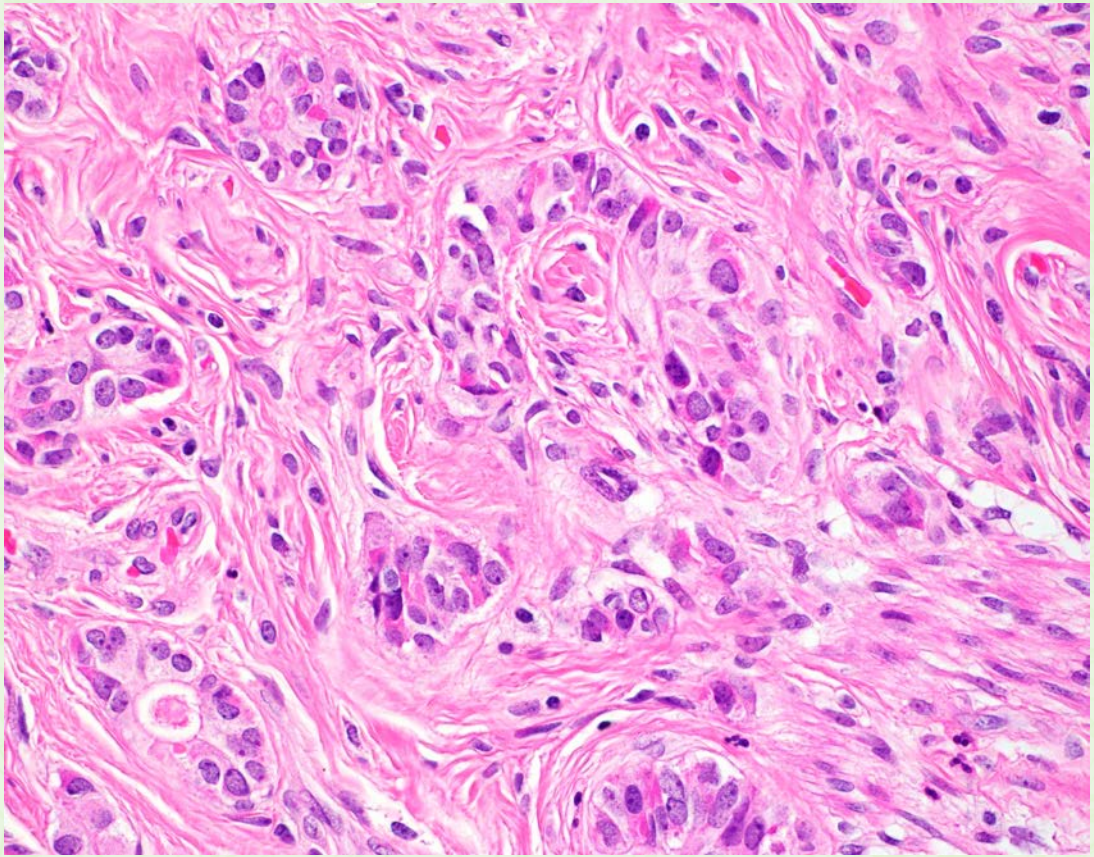
- Neuroendocrine tumor (NET)
  - NET G1 (carcinoid)
  - NET G2
- Neuroendocrine carcinoma (NEC)
  - Large cell NEC
  - Small cell NEC
- Mixed adenoneuroendocrine carcinoma
- EC cell, serotonin-producing NET
- L cell, glucagon-like peptide-producing and PP/PYY-producing NETs
- Goblet cell carcinoid (GCC)
- Tubular carcinoid

Tubular Carcinoid of the Appendix



- Always small (<1 cm)
- Found at the tip or distal half
- Primarily in the submucosa but may involve the muscularis propria, and rarely the subserosa
- Discrete small tubules and/or short solid cords
- Abundant fibrotic stroma

Tubular Carcinoid of the Appendix



- Cuboidal to low columnar cells with no cytologic atypia
- May have inspissated mucin in the lumens
- No mitotic figures
- Never recur or metastasize
- Not confused with metastatic adenocarcinoma

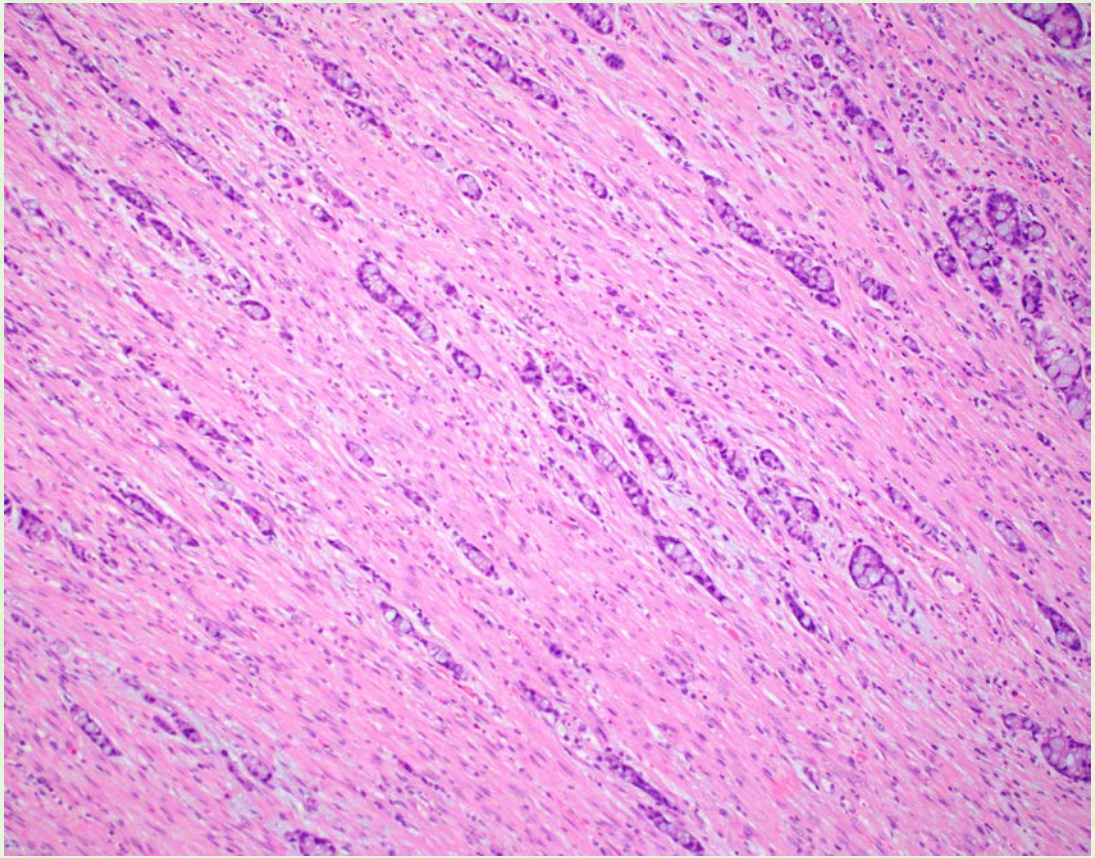
Goblet Cell Carcinoid

- A unique neoplasm with glandular and endocrine differentiation
- Almost exclusively seen in the appendix
  - Rarely seen in the stomach, small bowel and colon
- Synonyms
  - Adenocarcinoid
  - Mucinous carcinoid
  - Microglandular carcinoma
  - Crypt cell carcinoma
  - Amphicrine neoplasm
  - Mucin-producing neuroendocrine tumor/carcinoma

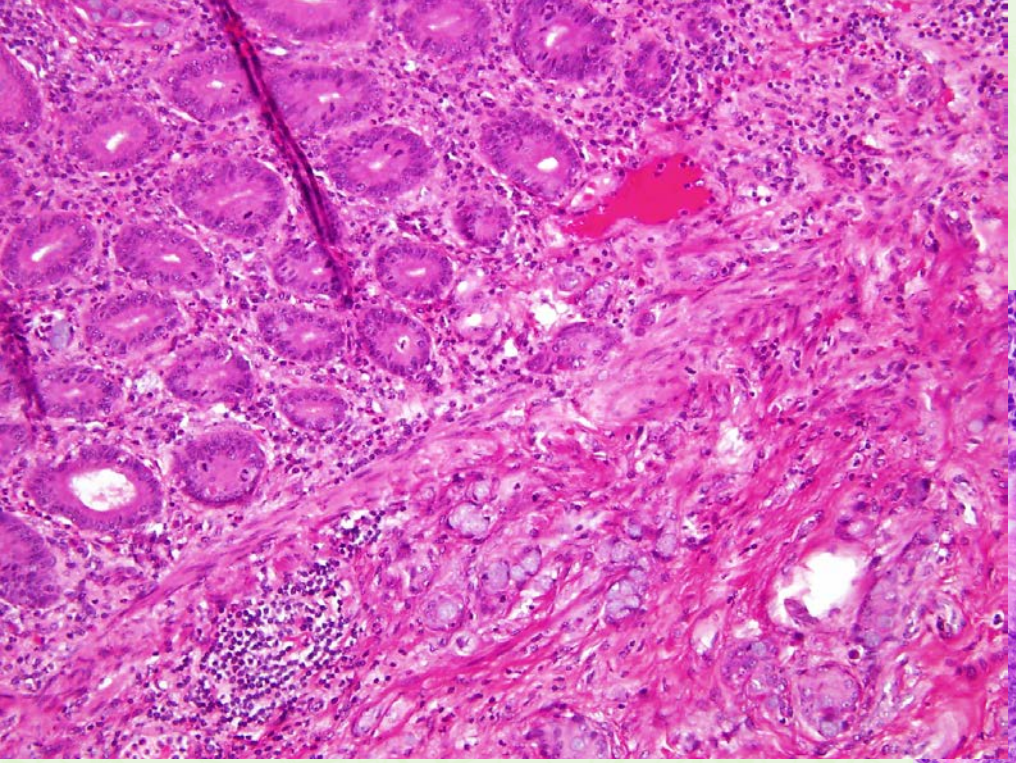
Goblet Cell Carcinoid

- Found in 0.3-0.9% of appendectomies
- Mean age: 59 years (18-89 years)
  - ~20 years older than that for classic carcinoid of the appendix
- Affecting males and females equally
- Initial presentation
  - Acute appendicitis in most cases
  - Lower abdominal palpable mass

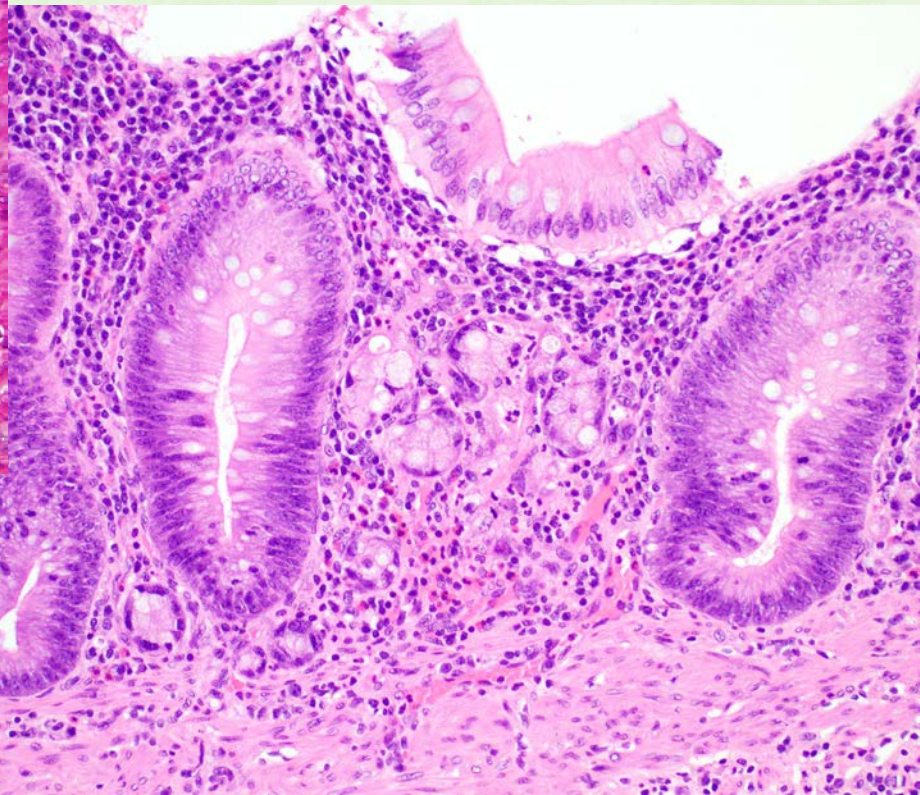
Goblet Cell Carcinoid



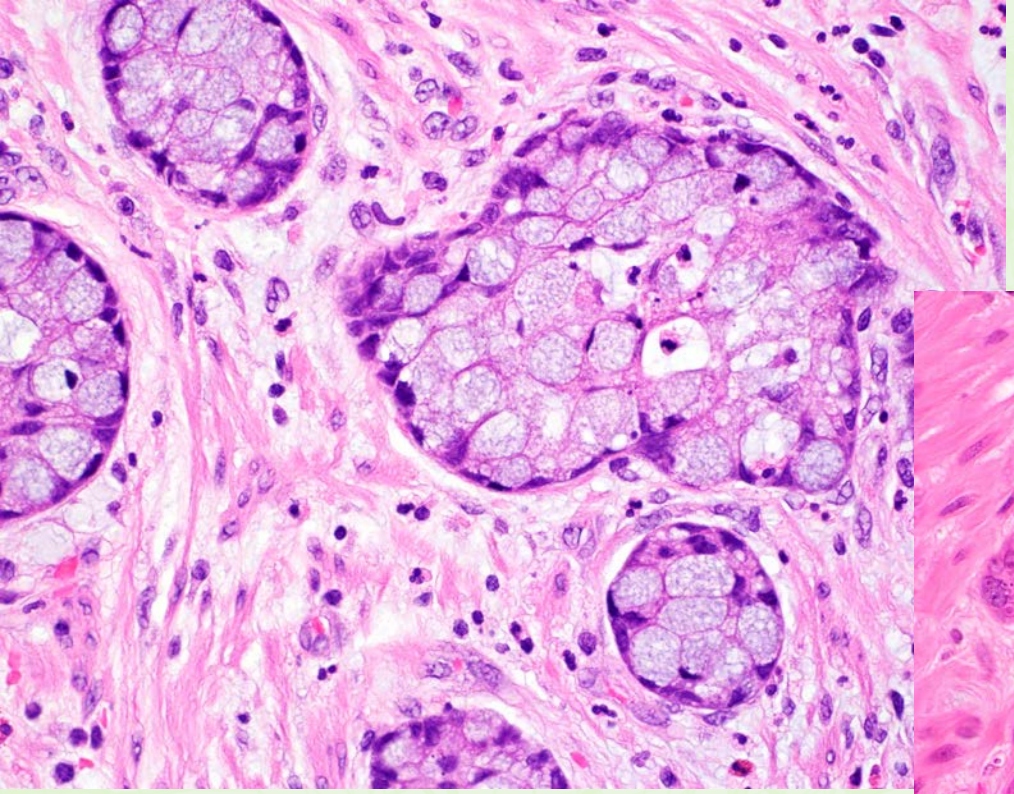
- Rarely forms a mass lesion
- Usually infiltrates the appendiceal wall circumferentially in a concentric manner
- Lacks desmoplastic reaction



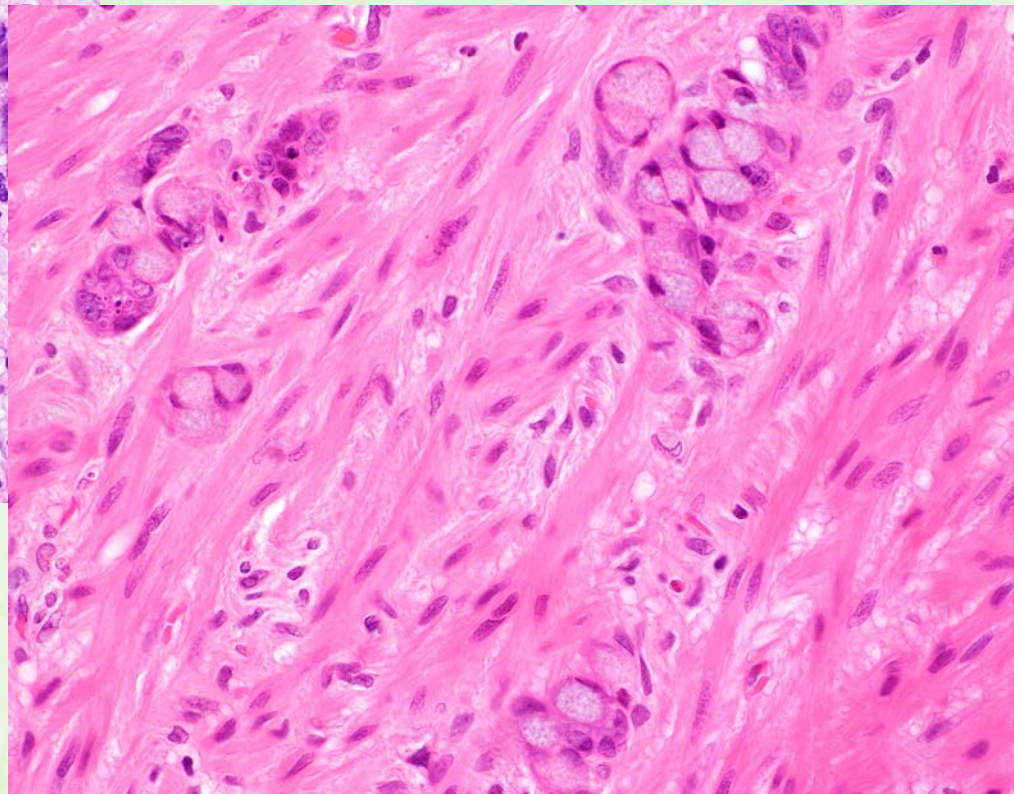
No adenomatous change in the mucosa



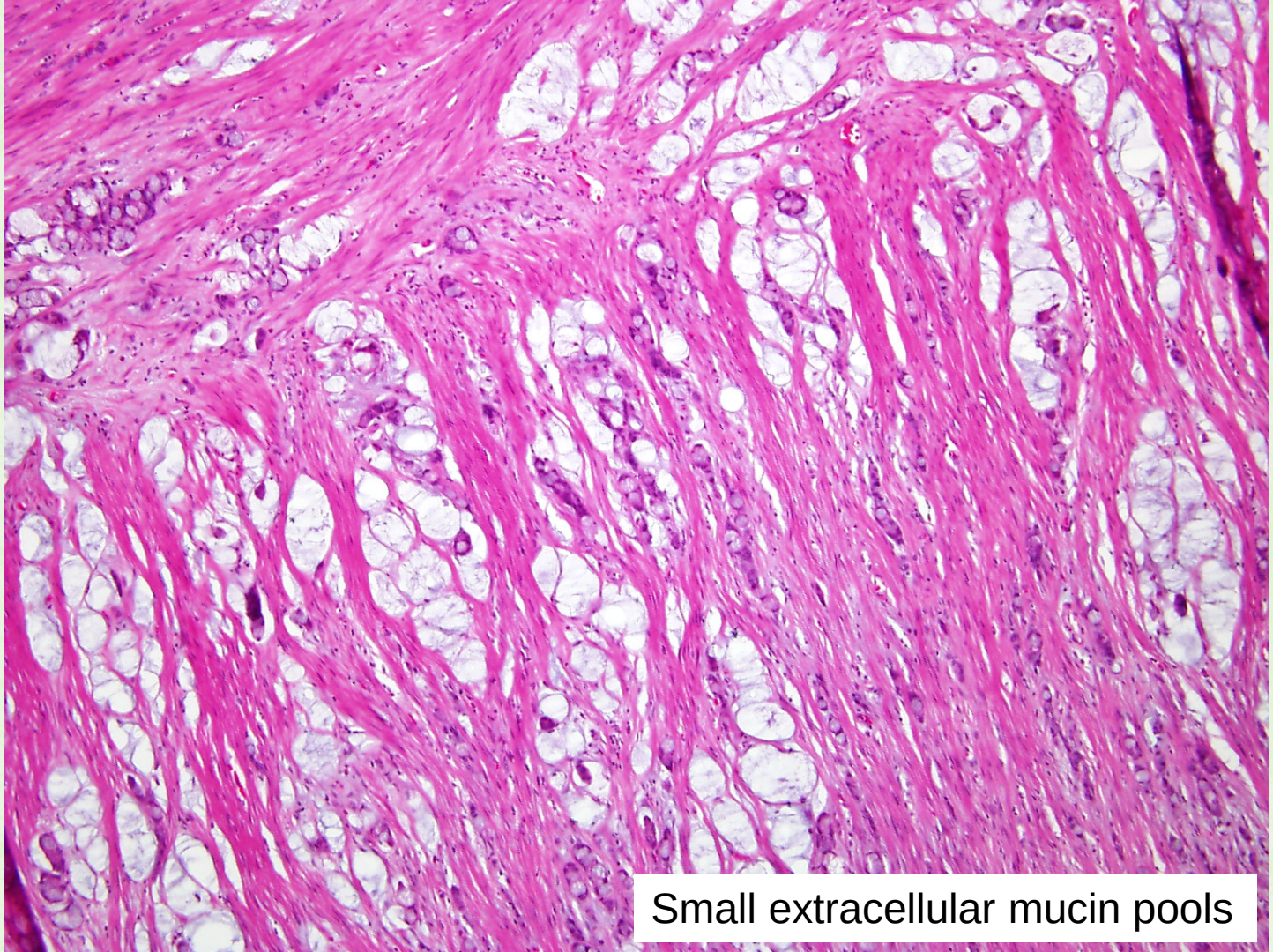
Typically spares the mucosa, but may show focal connection with the base of crypts

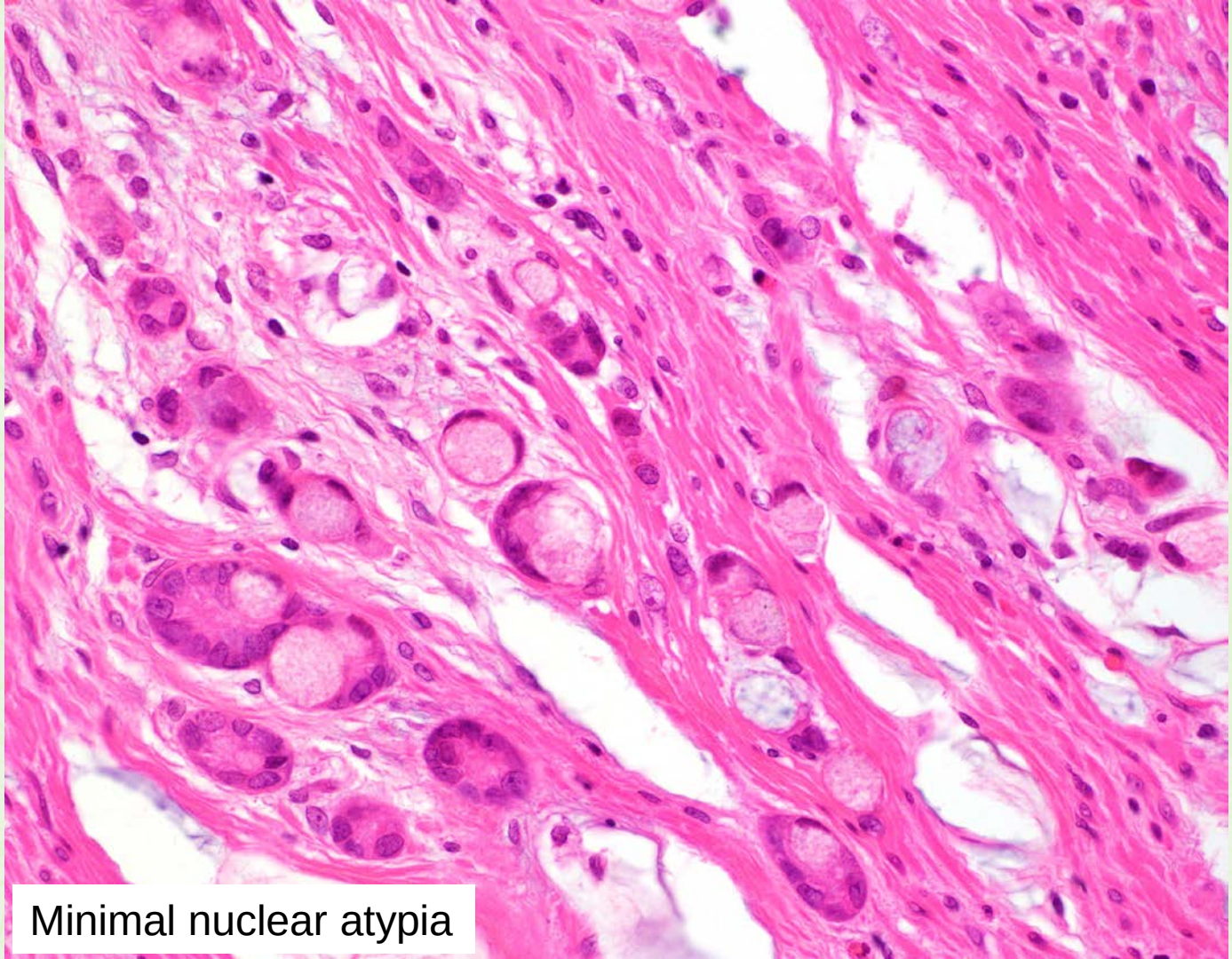


Small tight clusters, nests or cords of tumor cells, typically without overt luminal formation



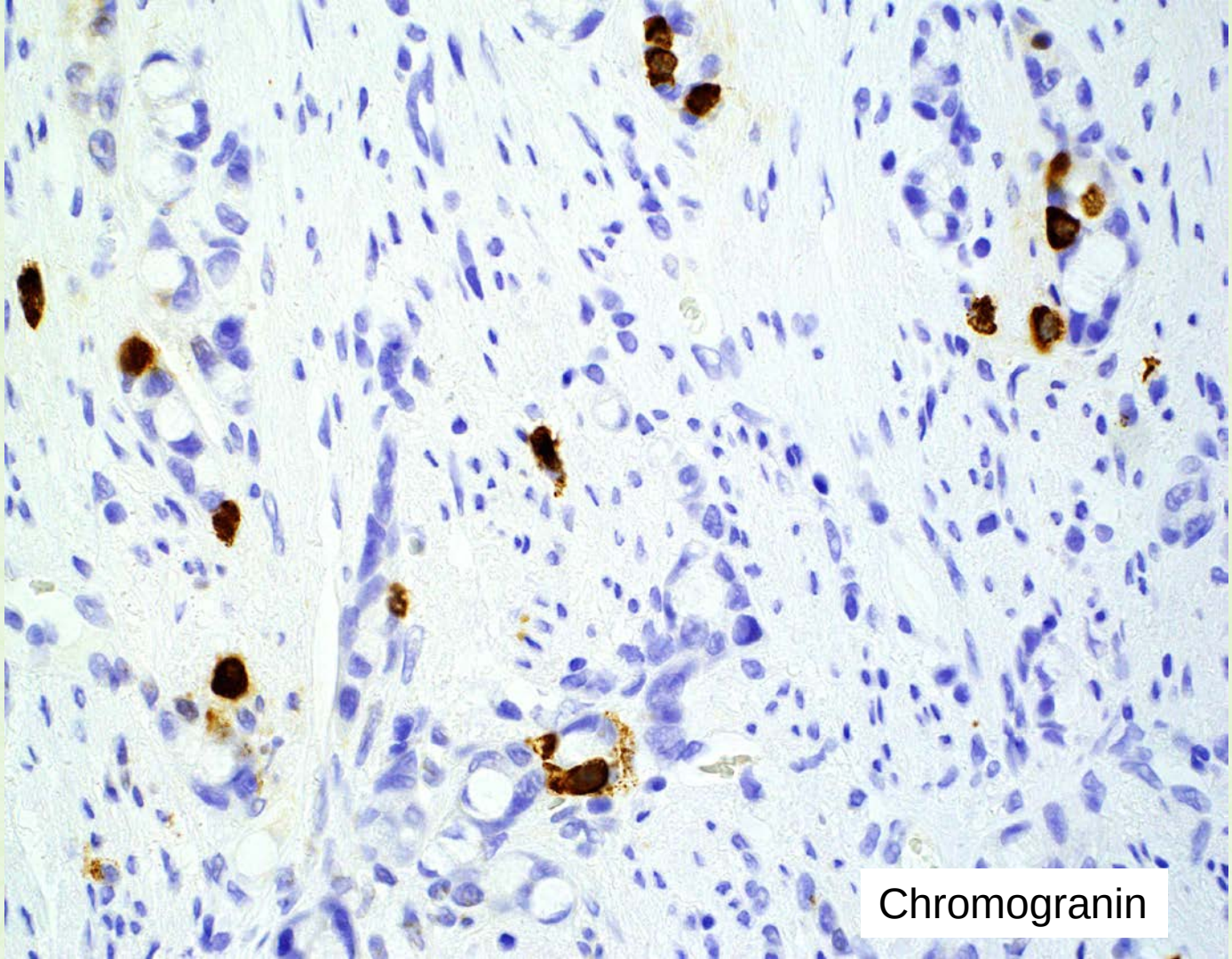
Goblet or signet-ring cell morphology


Small extracellular mucin pools


Minimal nuclear atypia

Immunophenotypical and Molecular Features of GCC in Comparison with Classic Carcinoid and Conventional Adenocarcinoma

Marker	GCC	Classic Carcinoid	Adenocarcinoma
CEA	+	-	+
CK7	+/-	-	+/-
CK20	+/-	-	+
CDX2	+	+/-	+
CD56	+/-	+	-
Synaptophysin	+/-	+	-
Chromogranin	+/-	+	-
Beta-catenin (nuclear)	-	-	+
p53	-	-	+
Ki67	intermediate	low	high
MUC1	-	-	+
MUC2	+	-	+/-
KRAS mutation	-	-	+/-
BRAF mutation	-	-	+/-
MSI	-	-	+/-


Chromogranin

GCC with A Component of Adenocarcinoma

- Mixed adenoneuroendocrine carcinoma
  - Mixed carcinoid-adenocarcinoma
  - Mixed goblet cell carcinoid-adenocarcinoma
- Adenocarcinoma ex goblet cell carcinoid
  - Signet-ring cell type
  - Poorly differentiated carcinoma type

Goblet Cell Carcinoids and Related Tumors of the Vermiform Appendix

Am J Clin Pathol 1990; 94:27-35

ALLEN P. BURKE, M.D. (MAJ, USAF, MC), LESLIE H. SOBIN, M.D., BIRGITTE H. FEDERSPIEL, M.D., KRIS M. SHEKITKA, M.D. (LTCOL, USAF, MC), AND ELSON B. HELWIG, M.D.

Goblet cell carcinoid

- N=25
- Negative appendectomy or right hemicolectomy margins
- Average follow-up: 19 months
- No metastasis or death

Mixed carcinoid-adenocarcinoma*

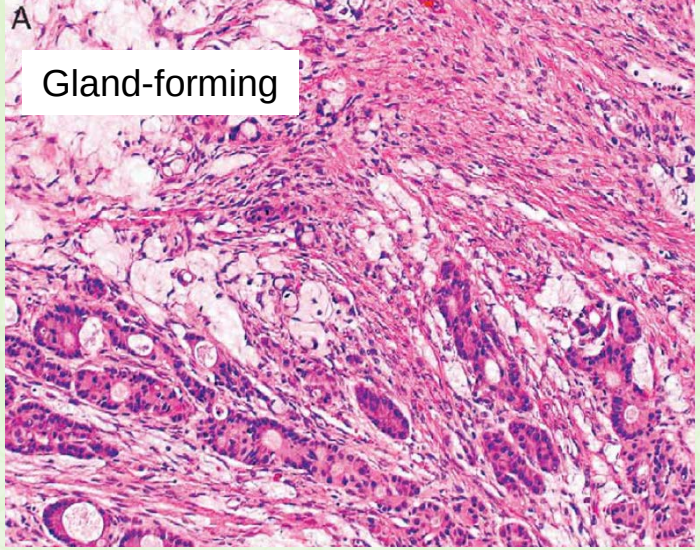
- N=10
- Average follow-up: 16 months
- 8 died of metastatic carcinoma
- 1 alive with disease
- 1 alive without disease following radiation therapy

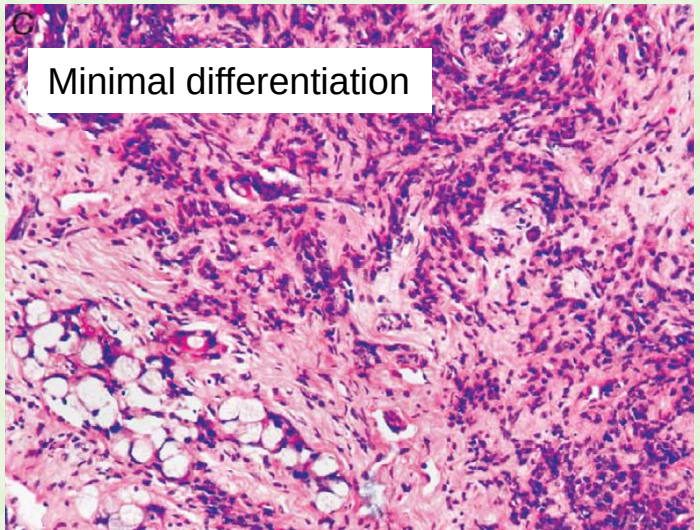
*Carcinomatous growth patterns included fused or cribriform glands, single file structures, infiltrating signet-ring cells or sheets of solid cells; accounting for >50% of the tumor volume

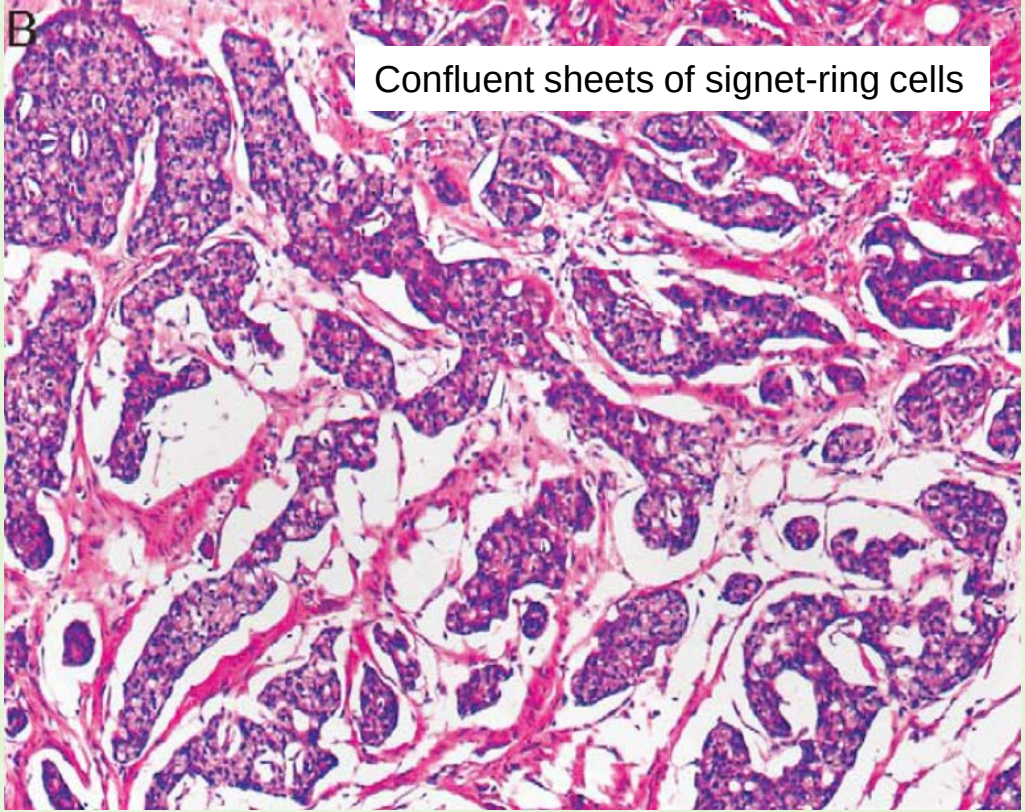
TABLE 4. Pathologic Classification of Goblet Cell Carcinoid Tumors

	Morphologic Criteria
Typical GCC (group A)	Well-defined goblet cells arranged in clusters or cohesive linear pattern Minimal cytologic atypia Minimal to no desmoplasia Minimal architectural distortion of the appendiceal wall Degenerative change with extracellular mucin is acceptable
Adenocarcinoma ex GCC, signet ring cell type (group B)	Goblet cells or signet ring cells arranged in irregular large clusters, but lack of confluent sheets of cells Discohesive single file or single cell infiltrating pattern Significant cytologic atypia Desmoplasia and associated destruction of the appendiceal wall
Adenocarcinoma ex GCC, poorly differentiated carcinoma type (group C)	At least focal evidence of goblet cell morphology A component (> 1 low power field or 1 mm^2) not otherwise distinguishable from a poorly differentiated adenocarcinoma, which may appear as either (a) gland forming, (b) confluent sheets of signet ring cells, or (c) undifferentiated carcinoma

Tang LH, et al. Am J Surg Pathol 2008; 32:1429-43

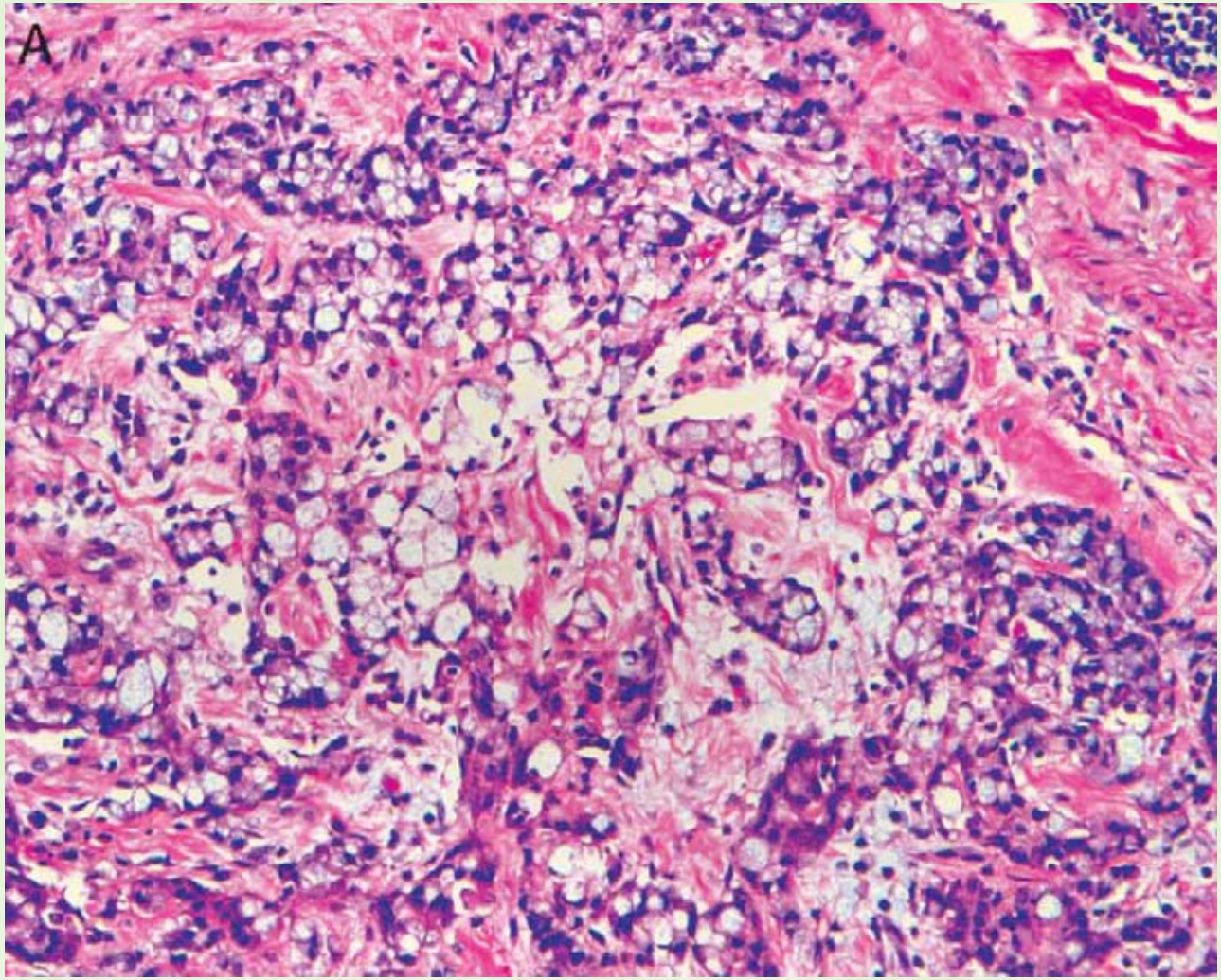






Adenocarcinoma ex GCC, poorly differentiated adenocarcinoma type

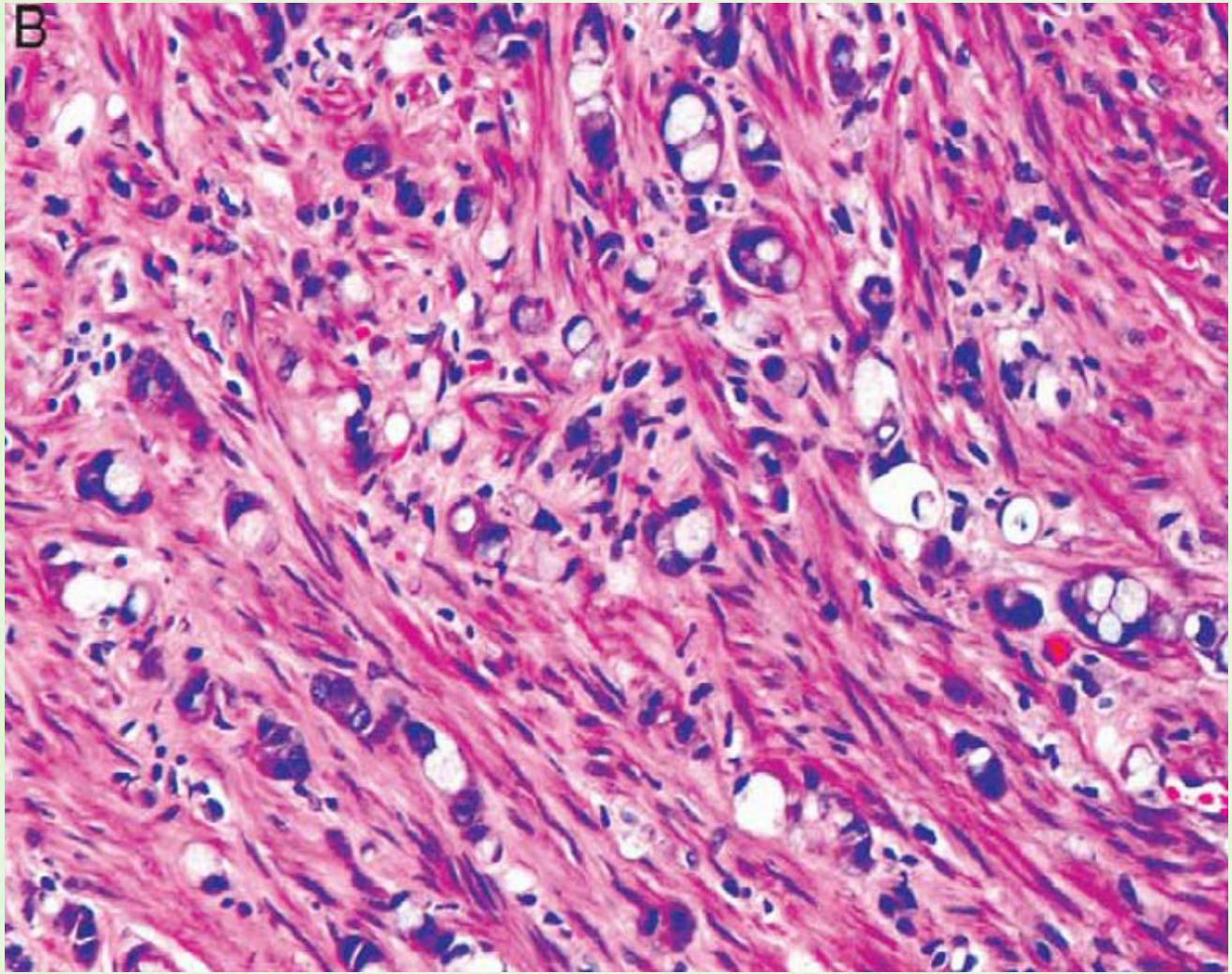
Tang LH, et al. Am J Surg Pathol 2008; 32:1429-43



Adenocarcinoma ex GCC
Signet-ring cell type

- Large irregular clusters
- Lack confluent sheets

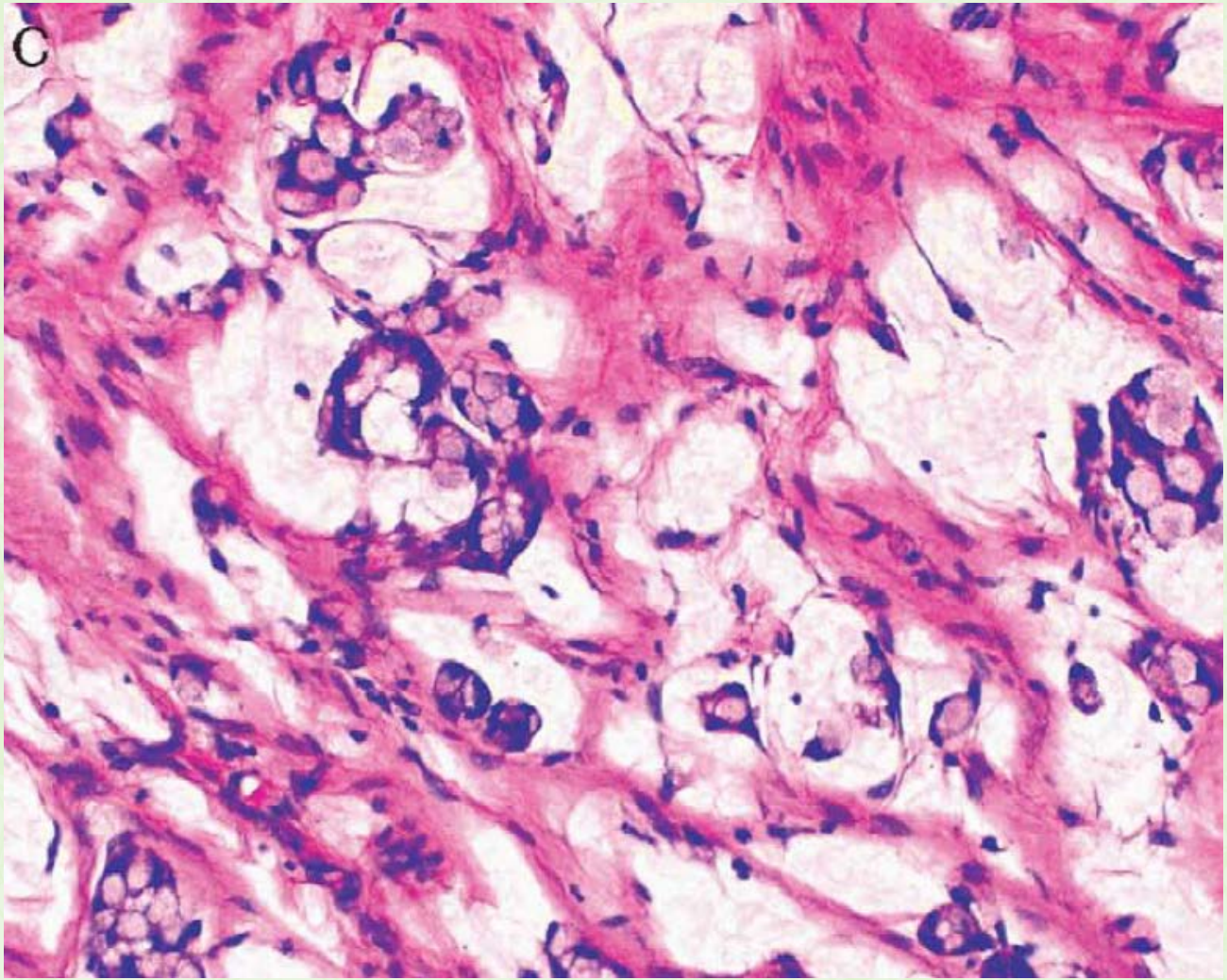
Tang LH, et al. Am J Surg Pathol 2008; 32:1429-43



Adenocarcinoma ex GCC Signet-ring cell type

- Discohesive single cell and single file infiltration
- Architectural distortion of the appendiceal wall and desmoplastic reaction

Tang LH, et al. Am J Surg Pathol 2008; 32:1429-43



Adenocarcinoma ex GCC
Signet-ring cell type

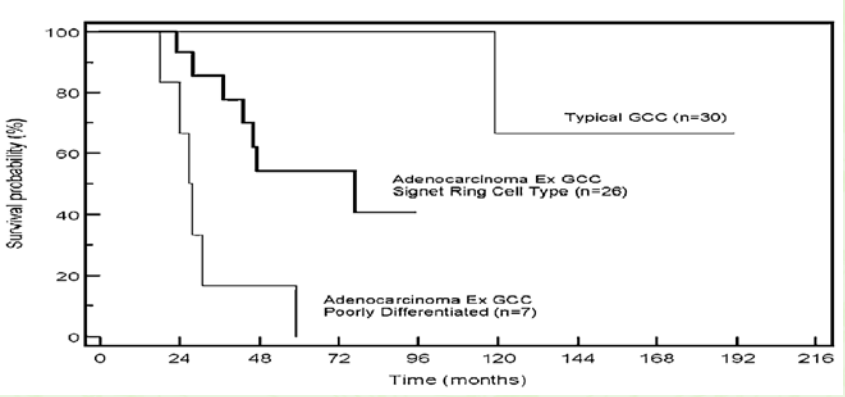
- Marked nuclear atypia with hyperchromatic nuclei

Tang LH, et al. Am J Surg Pathol 2008; 32:1429-43

TABLE 9. Mean Survival Time and Survival Status of All Cases of GCC by Subtype

	FU Months	Mean Survival*(mo)	NED (%)	AWD (%)	DOD (%)
All GCCs	49 ± 5 (8-191)	43 ± 7	28/61 (46)	19/61 (31)	14/61 (23)
Group A	66 ± 8 (13-191)	119 (1 case)	24/28 (86)	3/28 (11)	1/28 (4)
Group B	35 ± 5 (8-95)	43 ± 6	4/26 (15)	15/26 (58)	7/26 (27)
Group C	29 ± 5 (16-59)	31 ± 6	0 (0)	1/7 (14)	6/7 (86)

*Patients dying from disease only.
AWD indicates alive with disease; DOD, died of disease; FU, follow up; GCC, goblet cell carcinoid; NED, no evidence of disease.

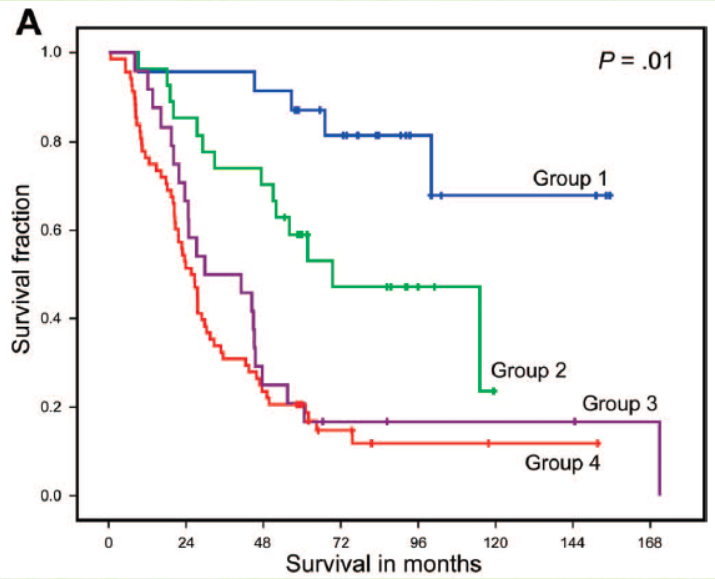


Tang LH, et al. Am J Surg Pathol 2008; 32:1429-43

TABLE 10. Prognosis of Stage IV GCCs Compared with Stage IV Primary Adenocarcinoma of the Appendix

	Stage IV			
Tumor Type	No. Cases (%)	DOD (%)	3-y DSS (%)	5-y DSS (%)
All GCCs	40/63 (63)	14/40 (35)	17/24 (71)	8/19 (42)
Group A	10/30 (33)	1/10 (10)	7/7 (100)	5/5 (100)
Group B	23/26 (88)	7/23 (30)	9/11 (82)	3/8 (38)
Group C	7/7 (100)	6/7 (86)	1/6 (17)	0/6 (0)
Adenocarcinoma	19/28 (68)	11/19 (61)	4/13 (31)	0/11 (0)

DOD indicates died of disease (stage IV only); DSS, disease-specific survival (stage IV only); GCC, goblet cell carcinoid.



Group 1: GCC or GCC with <25% adenocarcinoma
Group 2: GCC with 25-50% adenocarcinoma
Group 3: GCC with >50% adenocarcinoma
Group 4: Adenocarcinoma without GCC component

Taggart MW, et al. Arch Pathol Lab Med 2015;139:782-90

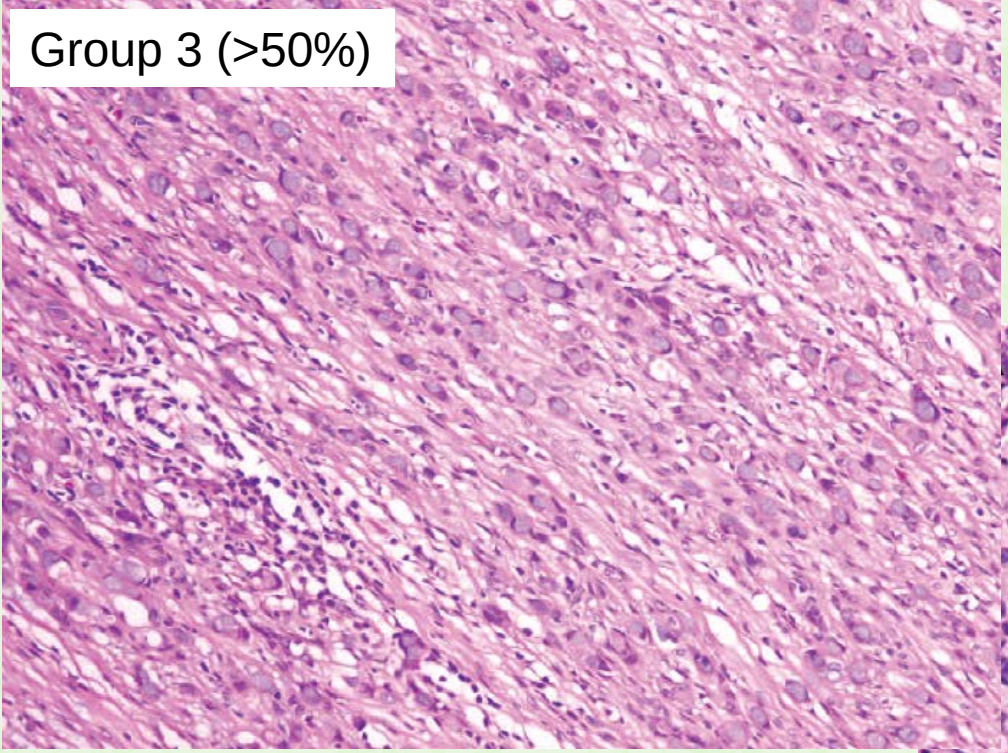
Group	Stage; N (%)				Overall Survival
	II	III	IV	Unknown	Mean (SD), mo
1 (n=23)	20 (87)	1 (4)	1 (4)	1 (4)	83.8 (34.6)
2 (n=27)	18 (67)	2 (7)	6 (22)	1 (4)	60.6 (30.3)
3 (n=24)	7 (29)	1 (4)	16 (67)	0	45.6 (39.7)
4 (n=68)	13 (19)	4 (6)	51 (75)	0	33.6 (27.6)

Definition of Adenocarcinoma

- Individual dyshesive cells
- Solid sheets of cells
- Infiltrative cords of cells (not within muscularis propria) or larger cords incompatible with GCC
- Complex glandular architecture (irregular, angulated, cribriform, tufting)
- Clusters of cells simulating GCC but with increased cytologic or architectural atypia beyond typical GCC nests (enlarged or irregular nests/glands, increased cytologic atypia, increased mitotic activity)
- Destructive invasion or desmoplasia

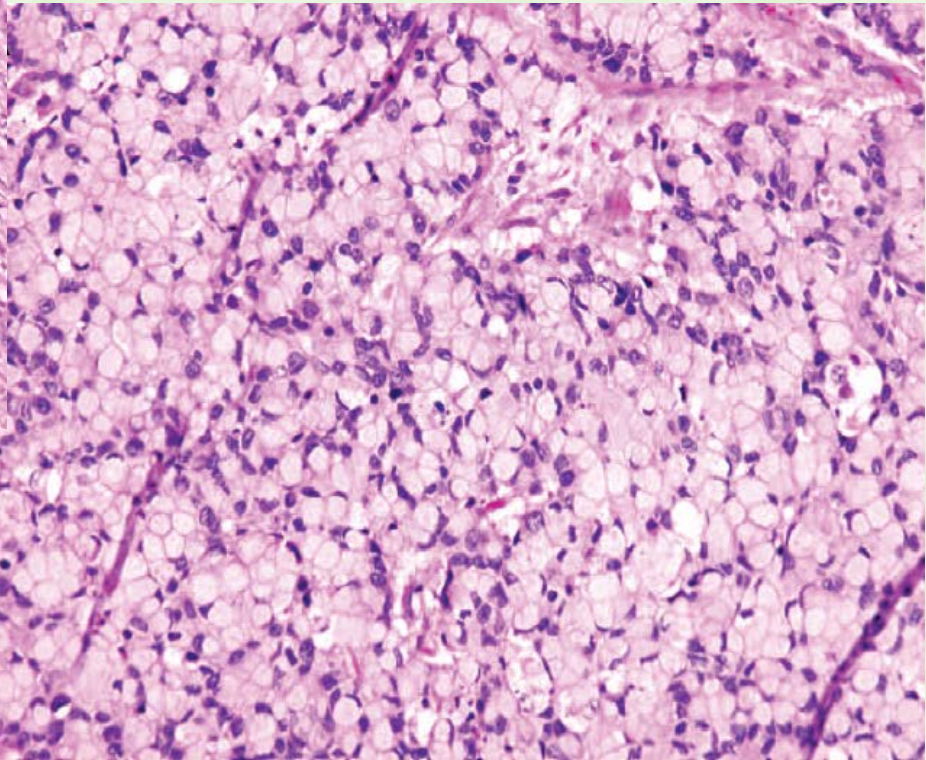
Taggart MW, et al. Arch Pathol Lab Med 2015;139:782-90

Group 3 (>50%)



Infiltrating single cells

Solid sheets of goblet/signet-ring cells



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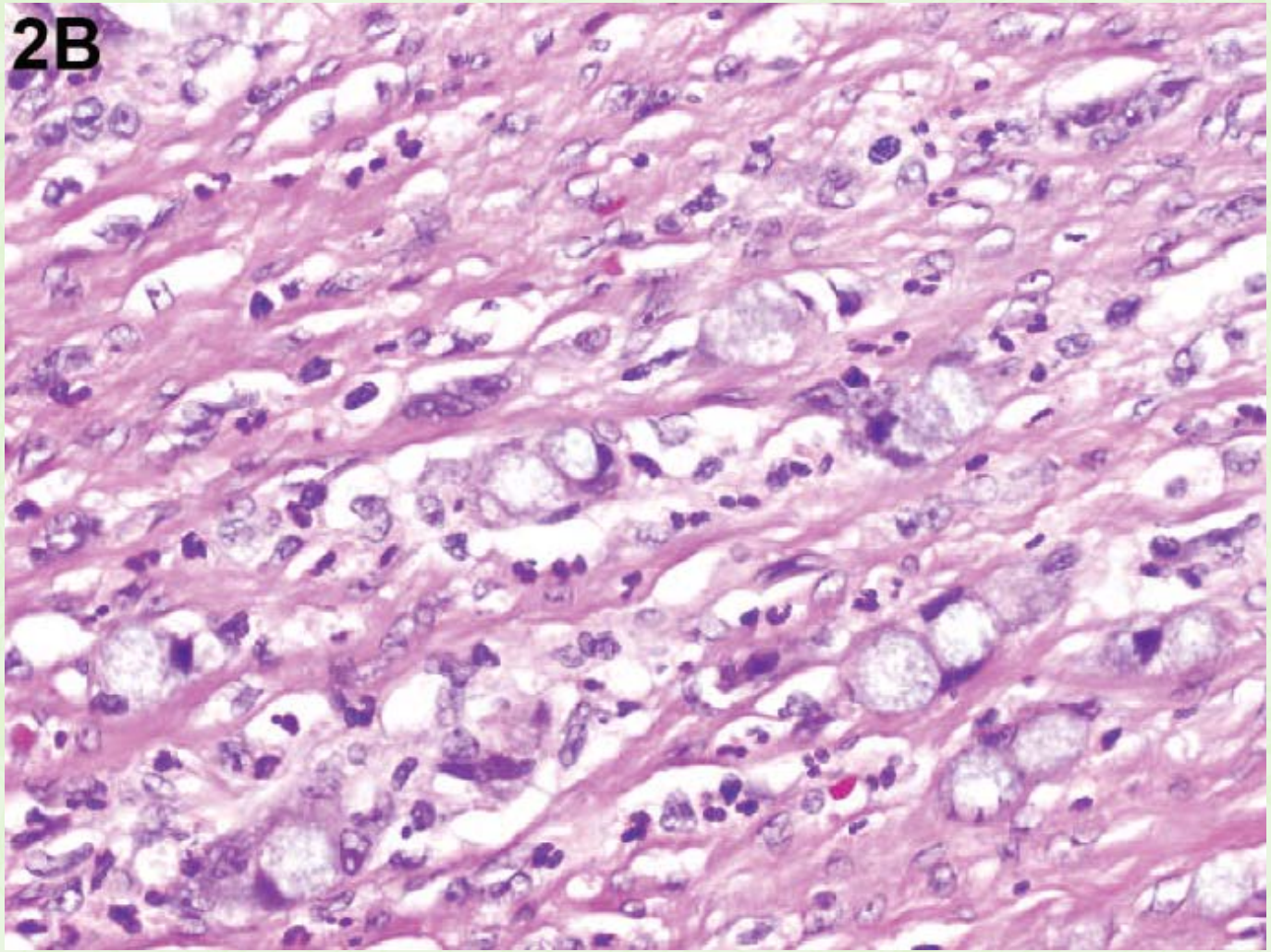
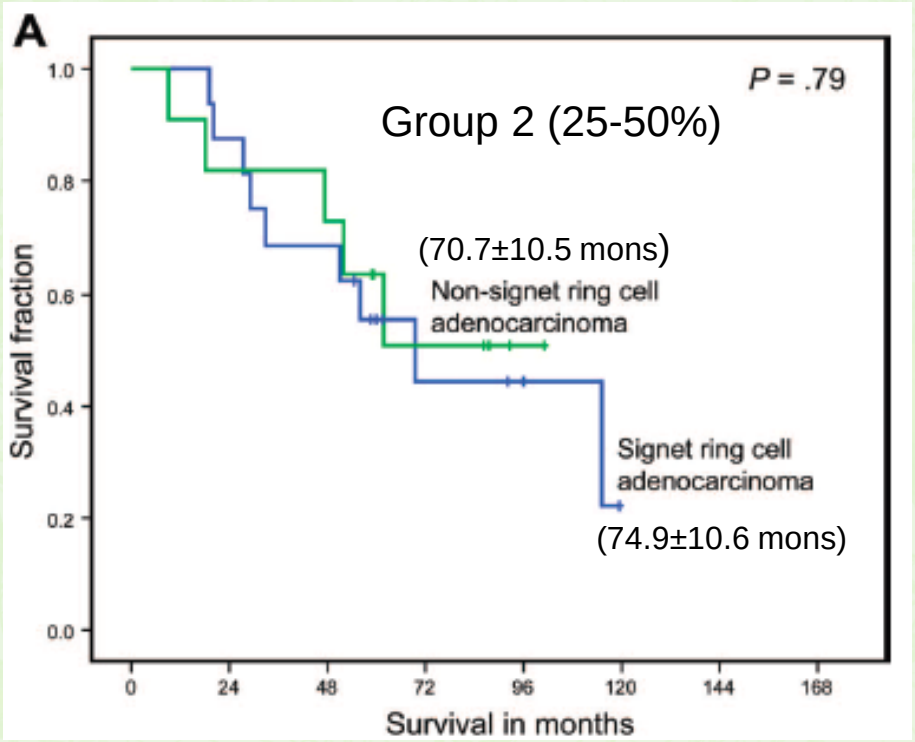
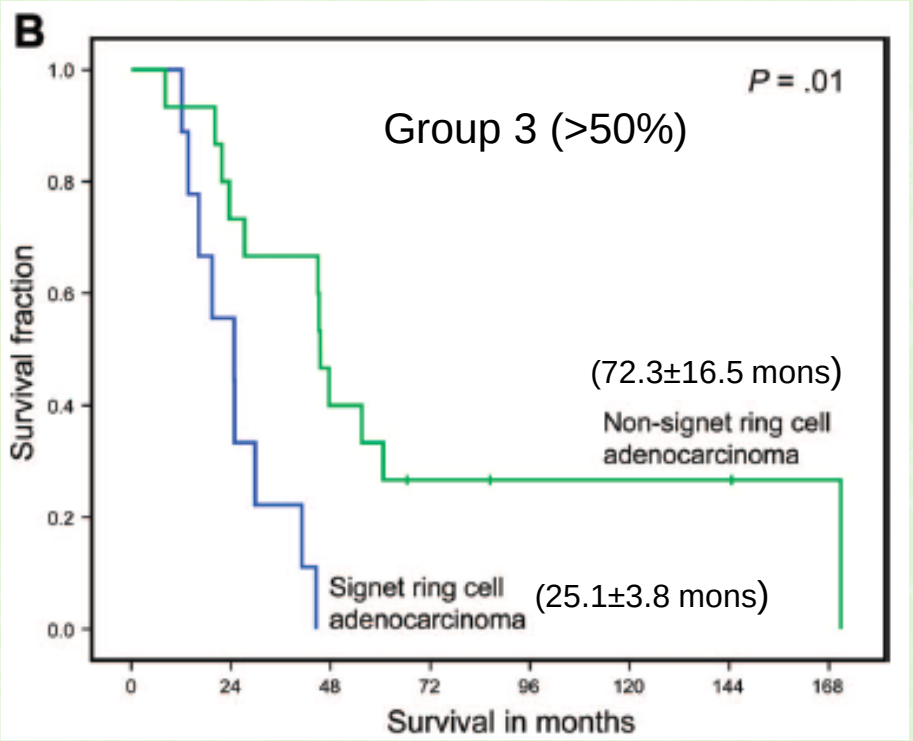


Group 2 (25-50%)

- An area of poorly differentiated signet-ring cell adenocarcinoma in a GCC

Taggart MW, et al. Arch Pathol Lab Med 2015;139:782-90





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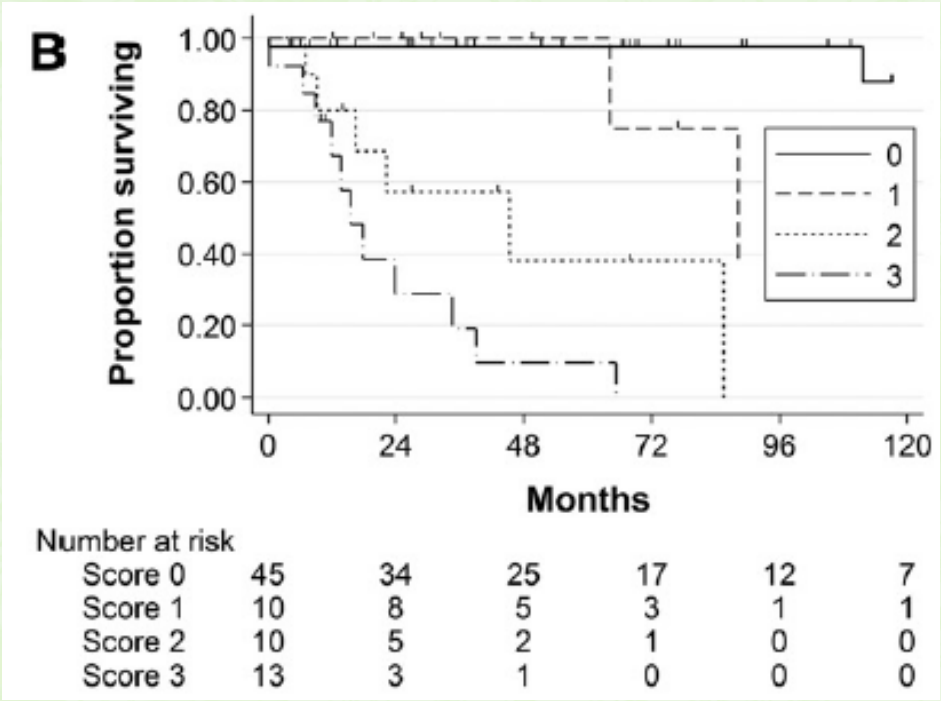
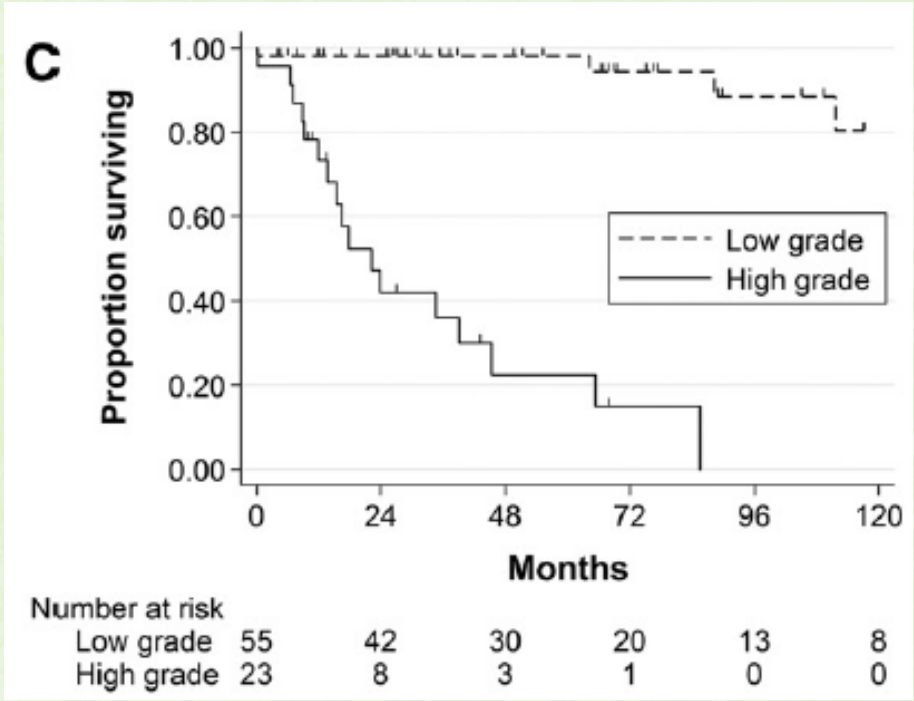
Simplified 2-Tier Histologic Grading System

Feature	Description	Scoring
Cytologic atypia [a]	At least 1 focus >1 mm^2 in size*	0: Absent
	High nuclear-to-cytoplasmic ratio with reduction in or loss of intracytoplasmic mucin	1: Present
	Nuclei are enlarged and hyperchromatic with irregular nuclear shape and contours	
Stromal desmoplasia	Dense fibrous connective tissue surrounding tumor cell clusters or individual tumor cells	0: Absent
	Replaces surrounding smooth muscle of the muscularis propria**	1: Present
	Results in distortion of the normal appendiceal architecture	
Solid growth pattern	At least 1 focus >1 mm^2 in size***	0: Absent
	Loss of distinct cell cluster architecture	1: Present
	Cells tightly packed together with no or minimal intervening stroma	
Total score	Sum of above points	/3
		Low grade: 0-1/3
		High grade: 2-3/3

*Four contiguous high power fields (x400) with a 0.55-mm field diameter are used to assess a 1 mm^2 area. At least one cytologically atypical tumor cell is required to be in each high power field.
**Desmoplasia of the submucosa or subserosal fat or serosal adhesions are insufficient.
***Spatially separate small foci of solid growth pattern, which aggregate to a total of 1 mm^2, are insufficient.

Lee LH, et al. Hum Pathol 2015; 46:1881-9





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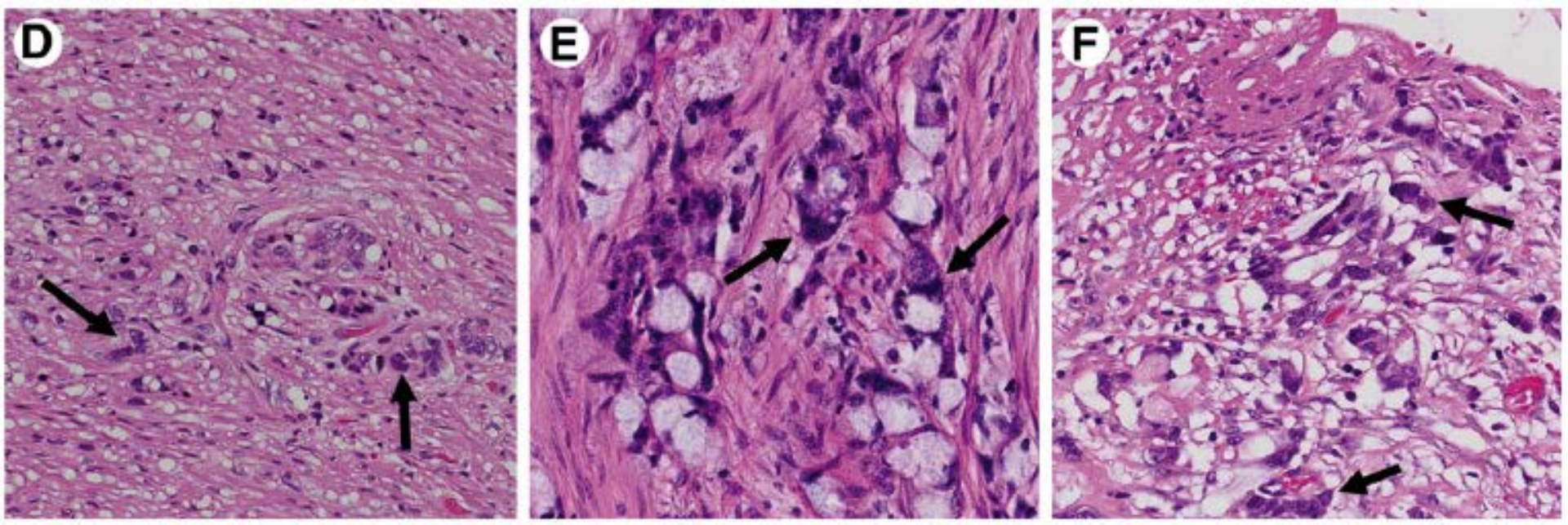
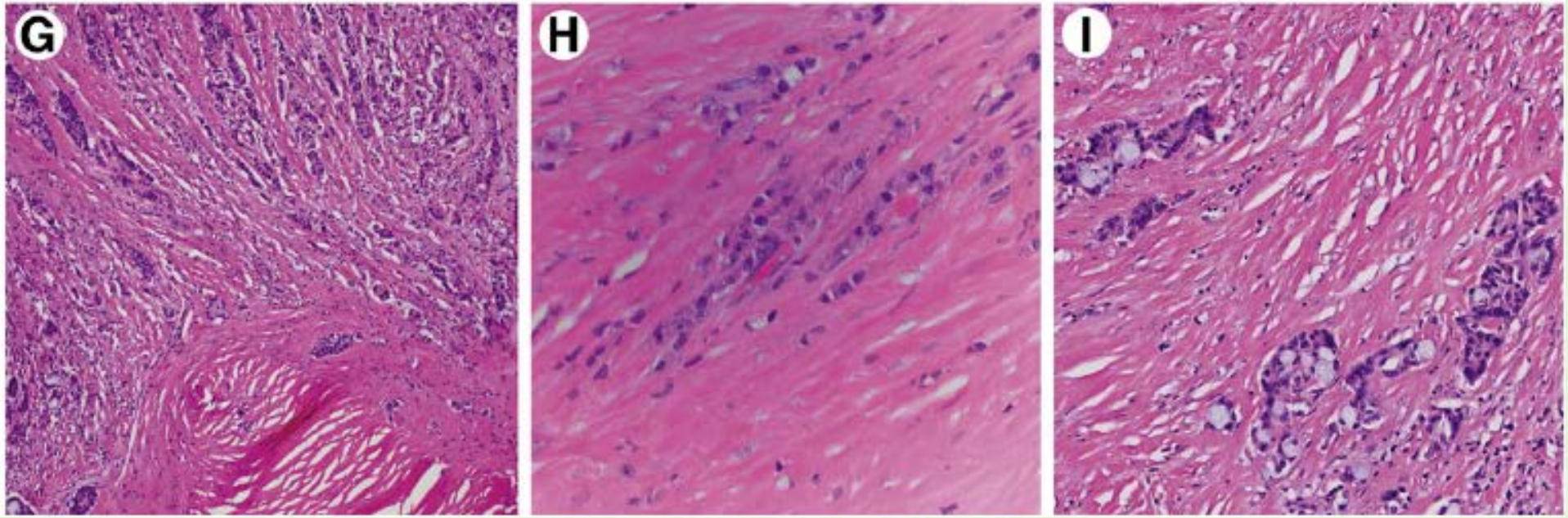


Cytologic atypia: enlarged hyperchromatic nuclei, irregular nuclear contour, variable loss of cytoplasmic mucin

Lee LH, et al. Hum Pathol 2015; 46:1881-9



Peritumoral stromal desmoplasia that replaces the smooth muscle of the appendiceal wall

Lee LH, et al. Hum Pathol 2015; 46:1881-9

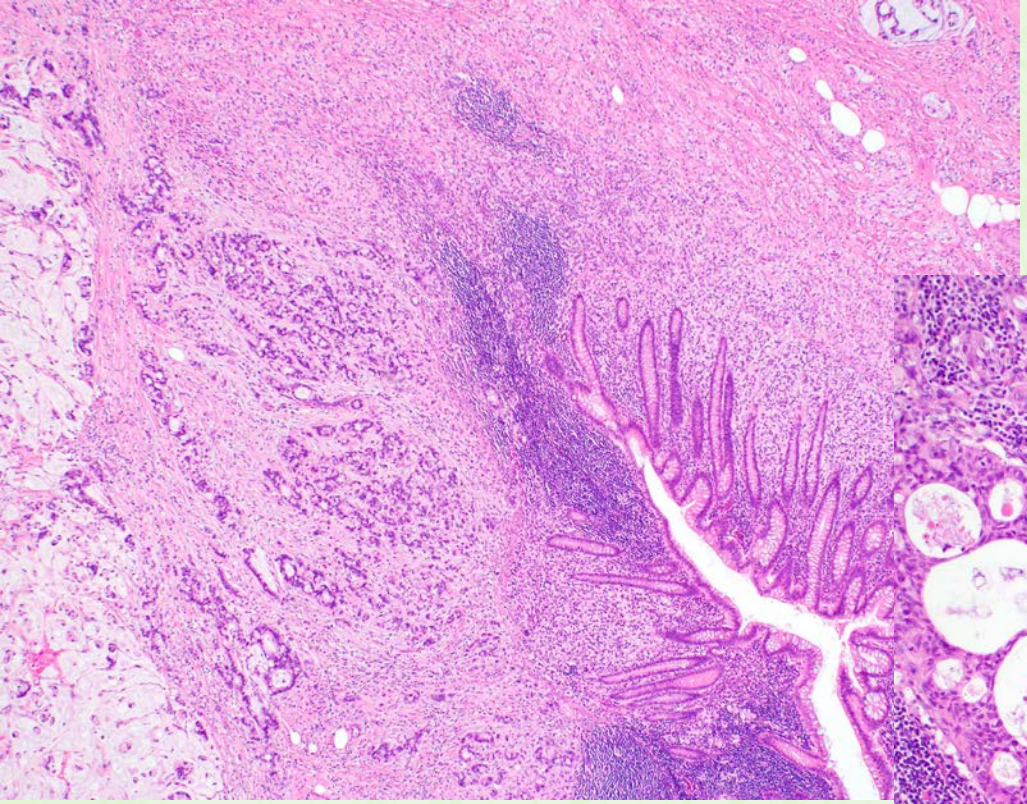
Recognition of Adenocarcinoma in GCC

Histologic Features

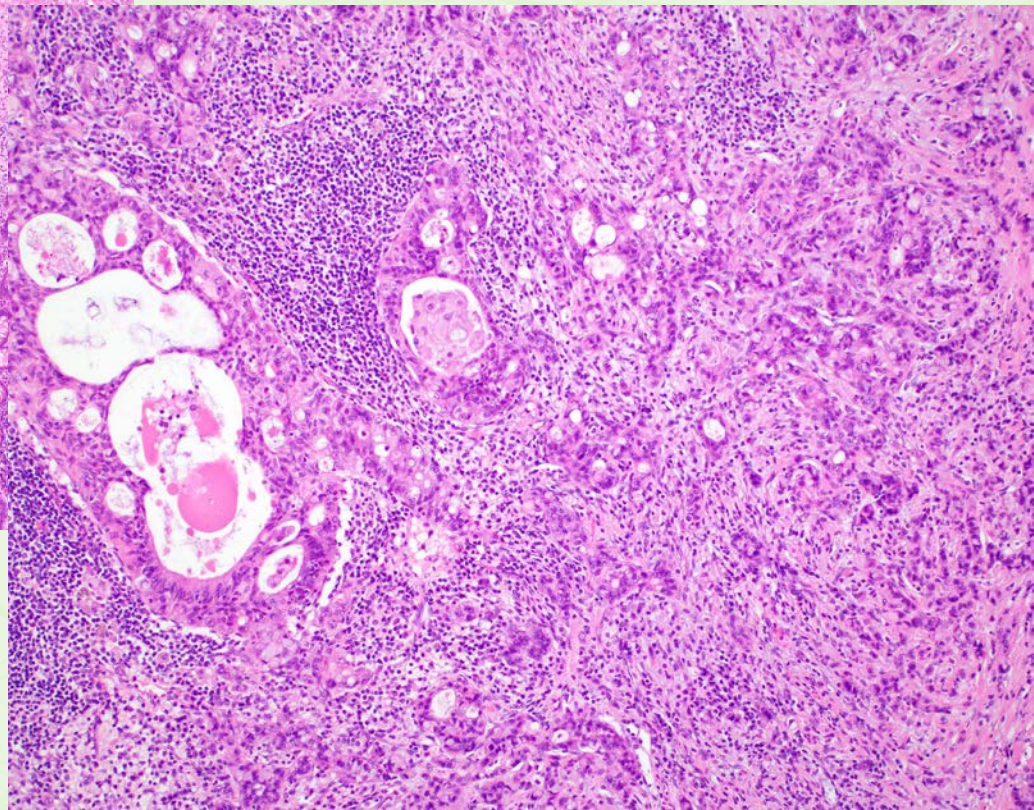
- Complex glandular architecture
- Loss of clustered architecture
  - Infiltrating individual discohesive cells
  - Solid sheets or irregular large clusters of cells
- Significant cytologic atypia
- Desmoplasia

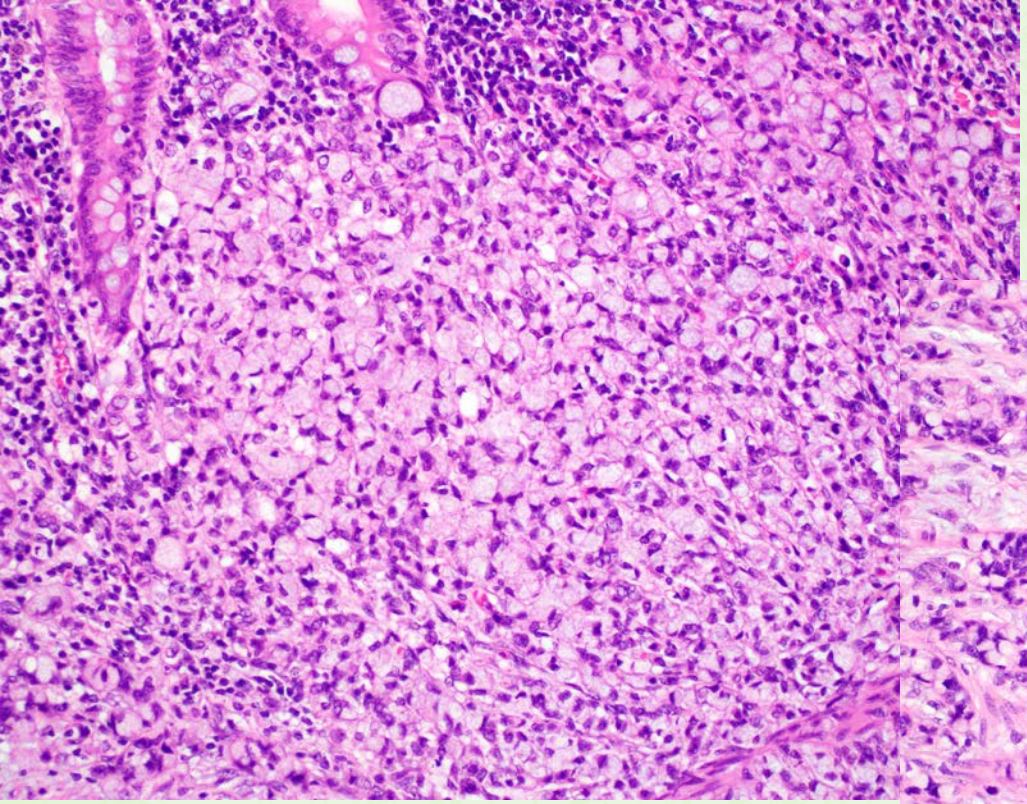
Tumor Volume

- >50% (Burke, 1990)
- >One low power field or 1 mm^2 for Tang's group C (2008)
- Partial or near complete loss of GCC clustered architecture for Tang's group B (2008)
- >30% (WHO, 2010)
- >25% and >50% (Taggart, 2015)
- > 1 mm^2 (Lee, 2015)



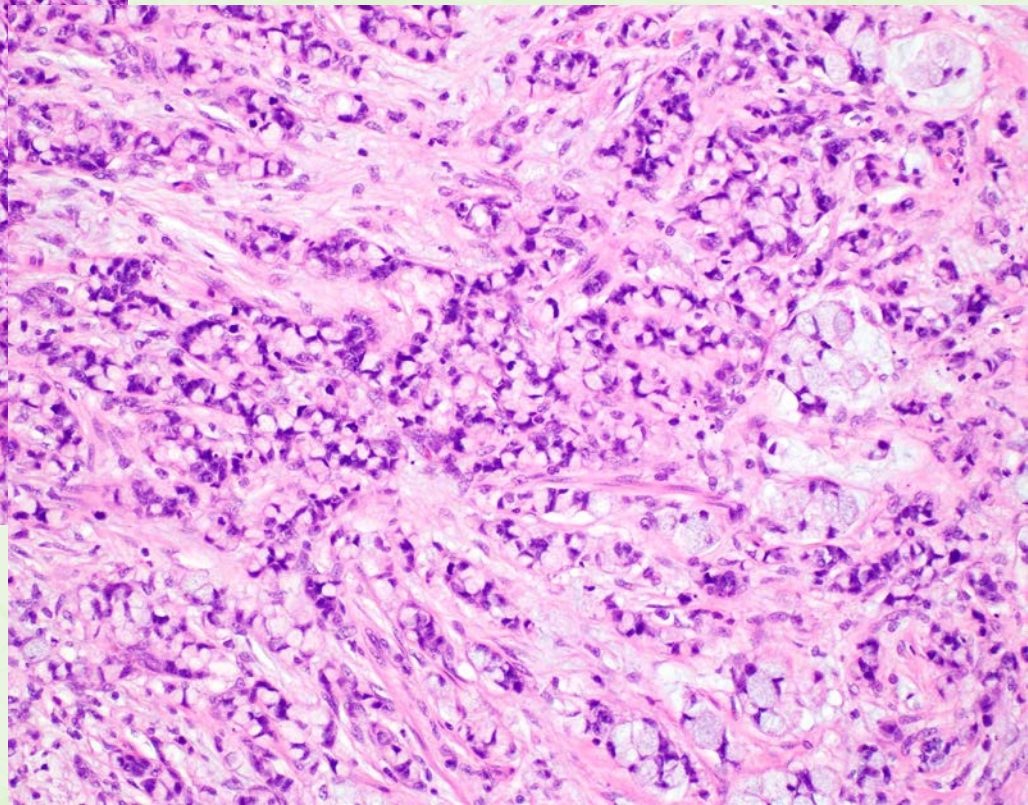
Poorly differentiated adenocarcinoma with focal glandular formation

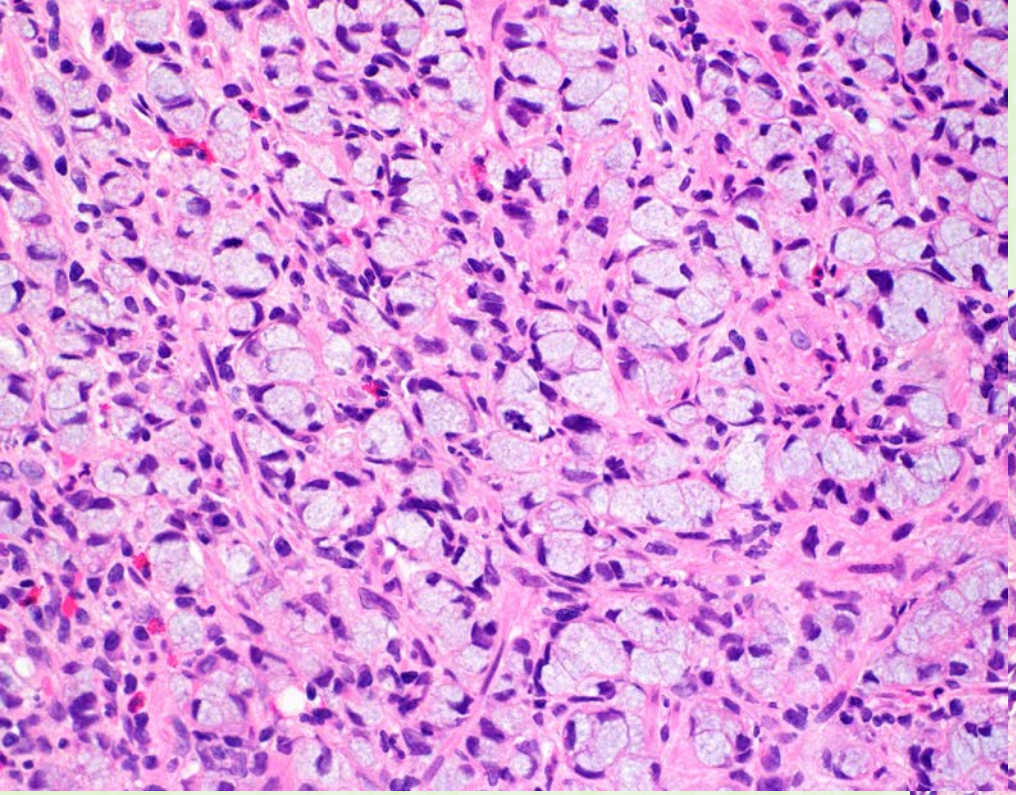




Solid sheets of goblet/signet-ring cells

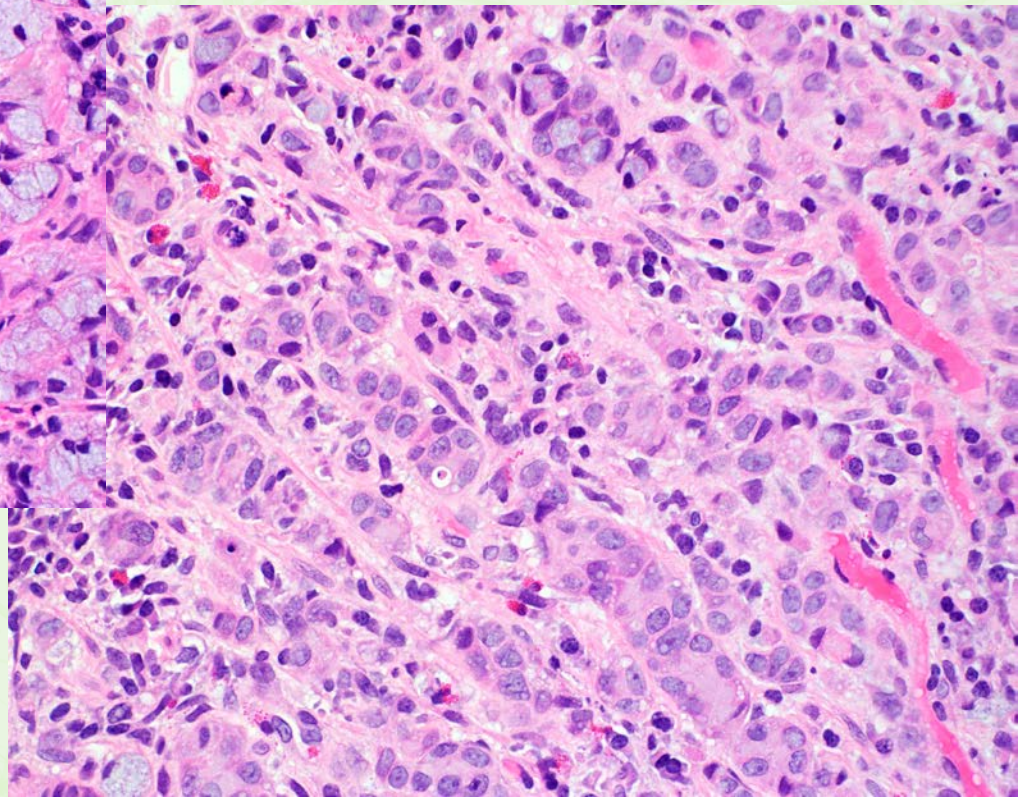
Irregular large clusters of goblet/signet-ring cells
Desmoplasia

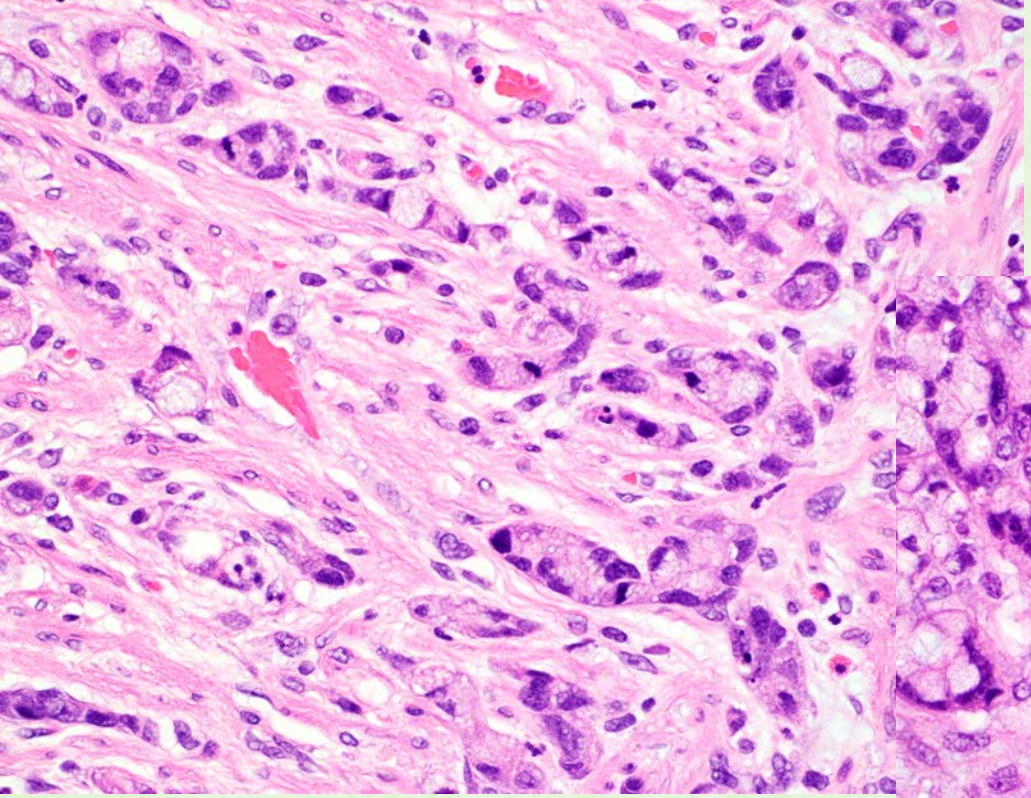




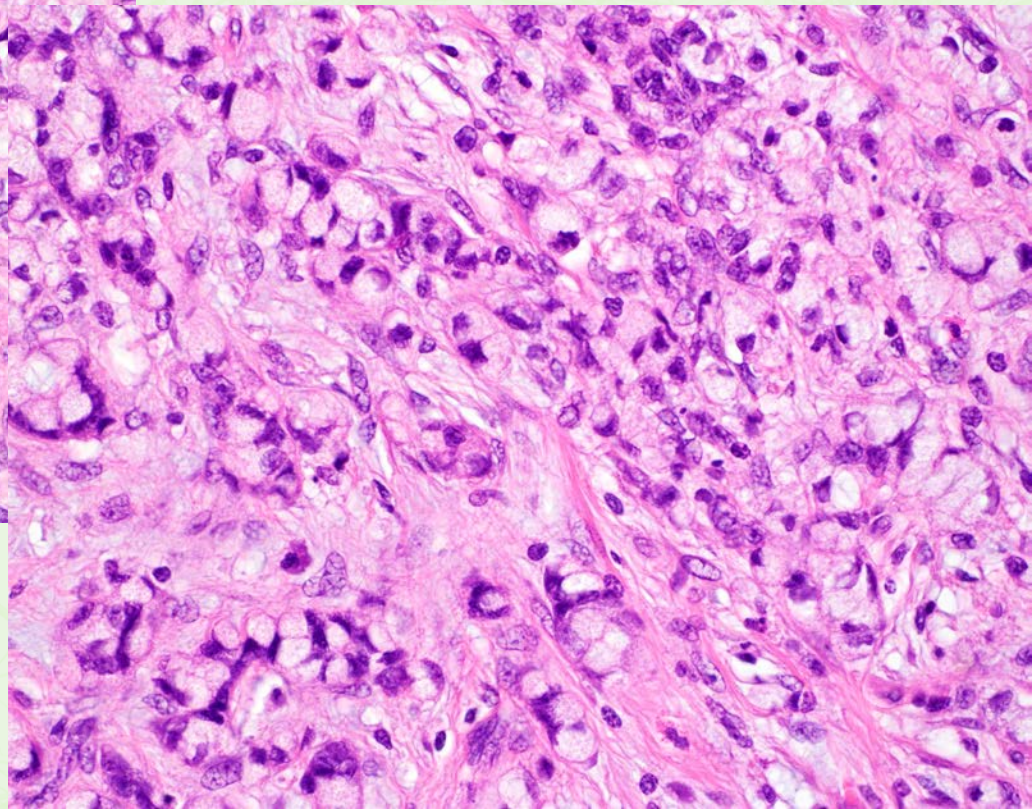
Infiltrating individual goblet/signet-ring cells with cytologic atypia

Solid cords with cytologic atypia and loss of intracytoplasmic mucin

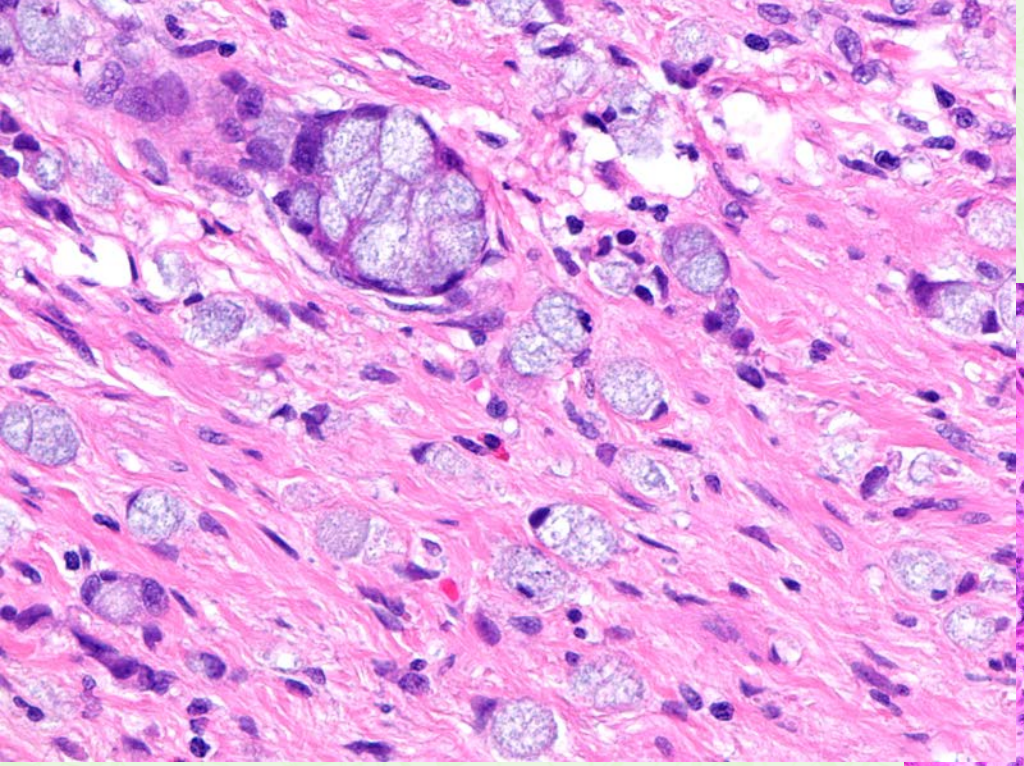




Desmoplasia

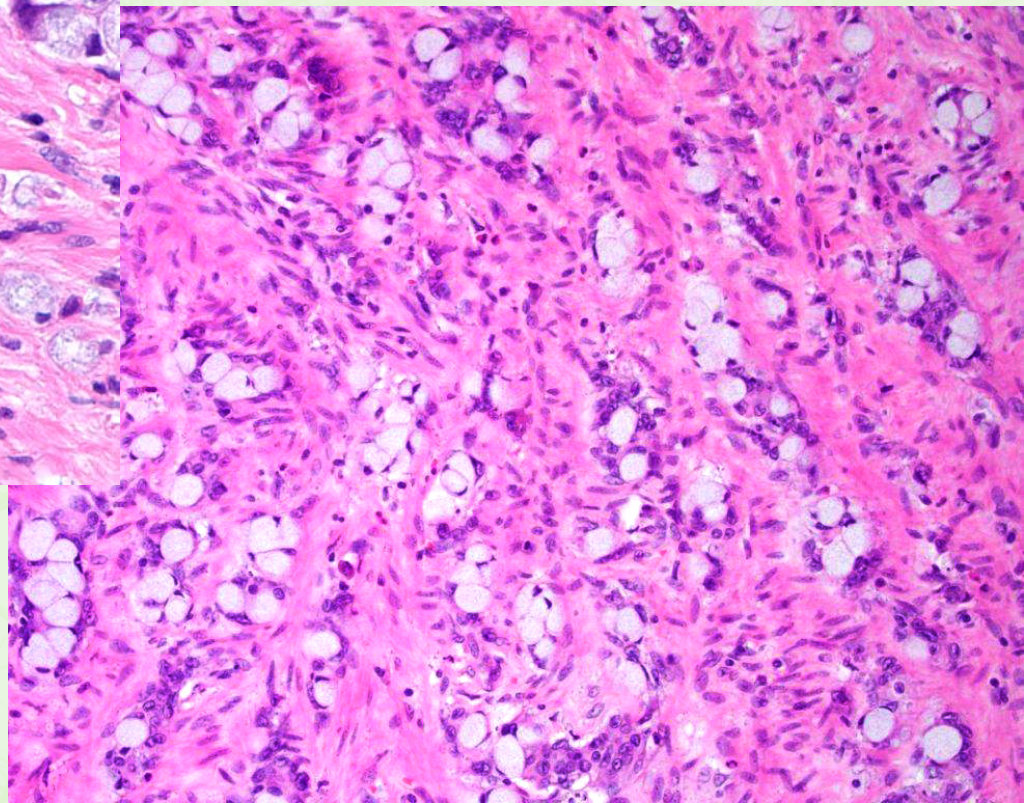


Cytologic atypia with mitoses



Goblet or Signet Ring Cells
That is the Question

Hanlin L. Wang, MD, PhD and Deepti Dhall, MD



Adv Anat Pathol 2009; 16:247-54

Goblet Cell Carcinoid
Staging and Management

- Staged as adenocarcinoma of the appendix
- Ki-67 labeling index is not required for grading
- Treatment options are primarily based on tumor stage and the presence or absence of adenocarcinoma

Management of Goblet Cell Carcinoid

- Appendectomy alone
  - Stage I (pT1 or pT2) pure GCC with negative margin
  - Comorbidities that do not allow further surgical intervention
  - Lifelong surveillance for metastasis
- Right hemicolectomy
  - Higher stage (pT3 or pT4) disease
  - Positive appendectomy margin
  - Presence of adenocarcinoma
  - Perforated appendix
- Cytoreductive surgery and intraperitoneal chemotherapy
  - Peritoneal spread
- Systemic chemotherapy
  - Stages III and IV disease
  - Recurrent disease
- Prophylactic oophorectomy, particularly for postmenopausal women
  - Candidates for right hemicolectomy and/or chemotherapy

Tang LH, et al. Am J Surg Pathol 2008;32:1429-43
Shenoy S. World J Gastrointest Surg 2016;8:660-9
Lamarca A, et al. Neuroendocrinology 2016;103:500-17

Summary

- GCC is a unique clinicopathologic entity that is frequently associated with adenocarcinoma
- Histologic identification and quantification of adenocarcinoma is important in determining prognosis and thus in guiding clinical management
- The entire appendectomy specimen should be histologically examined when a GCC case is encountered; and the margin status should be reported

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THANK YOU