

# Incidental Appendiceal Tumors

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SUNY - Downstate

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# Case Presentation

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- 32 year old female presents to the ED in August 2011 with one week history of right lower quadrant pain. She describes the pain as intermittent, sharp, radiating to suprapubic region, associated with nausea and diarrhea. She has history of intermittent RLQ pain since May 2011, which she was evaluated for in the ED and dx with PID. She was worked up as outpatient for GYN pathology, workup was negative.
- PMH: asthma
- PSH: none
- Meds: Albuterol PRN
- NKDA
- Social: ex-smoker, 5pk yr history

- Vitals:

- T 98.6 BP 100/68 HR 95 R 18 100%
- 5'3, 184lbs
- Abdomen soft, nondistended, +RLQ tenderness, no mass palpable

- Labs

- Cbc 10/11/34/500

# CT scan

Contrast: CONTRAST

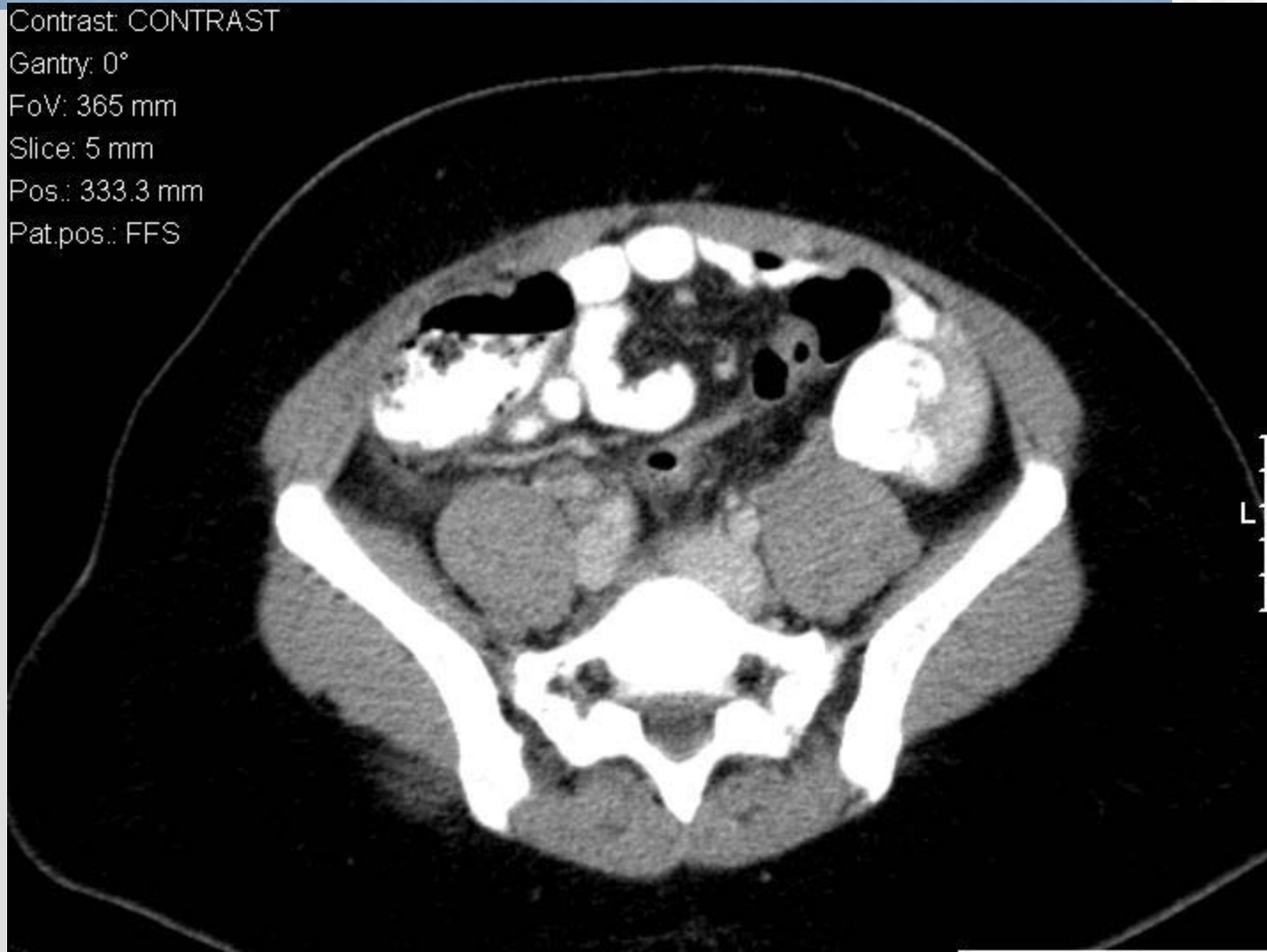
Gantry: 0°

FoV: 365 mm

Slice: 5 mm

Pos.: 333.3 mm

Pat.pos.: FFS



Contrast: CONTRAST

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Pos.: 318.3 mm

Pat.pos.: FFS



Contrast: CONTRAST

Gantry: 0°

FoV: 365 mm

Slice: 5 mm

Pos.: 328.3 mm

Pat.pos.: FFS



Contrast: CONTRAST

Gantry: 0°

FoV: 365 mm

Slice: 5 mm

Pos.: 353.3 mm

Pat.pos.: FFS



Contrast: CONTRAST

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FoV: 365 mm

Slice: 5 mm

Pos.: 363.3 mm

Pat.pos.: FFS



Contrast: CONTRAST

Gantry: 0°

FoV: 365 mm

Slice: 5 mm

Pos.: 368.3 mm

Pat.pos.: FFS



Contrast: CONTRAST

Gantry: 0°

FoV: 365 mm

Slice: 5 mm

Pos.: 378.3 mm

Pat.pos.: FFS



Contrast: CONTRAST

Gantry: 0°

FoV: 365 mm

Slice: 5 mm

Pos.: 388.3 mm

Pat.pos.: FFS



Contrast: CONTRAST

Gantry: 0°

FoV: 365 mm

Slice: 5 mm

Pos.: 393.3 mm

Pat.pos.: FFS



Contrast: CONTRAST

Gantry: 0°

FoV: 365 mm

Slice: 5 mm

Pos.: 398.3 mm

Pat.pos.: FFS



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Gantry: 0°

FoV: 365 mm

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Pos.: 408.3 mm

Pat.pos.: FFS



Contrast: CONTRAST

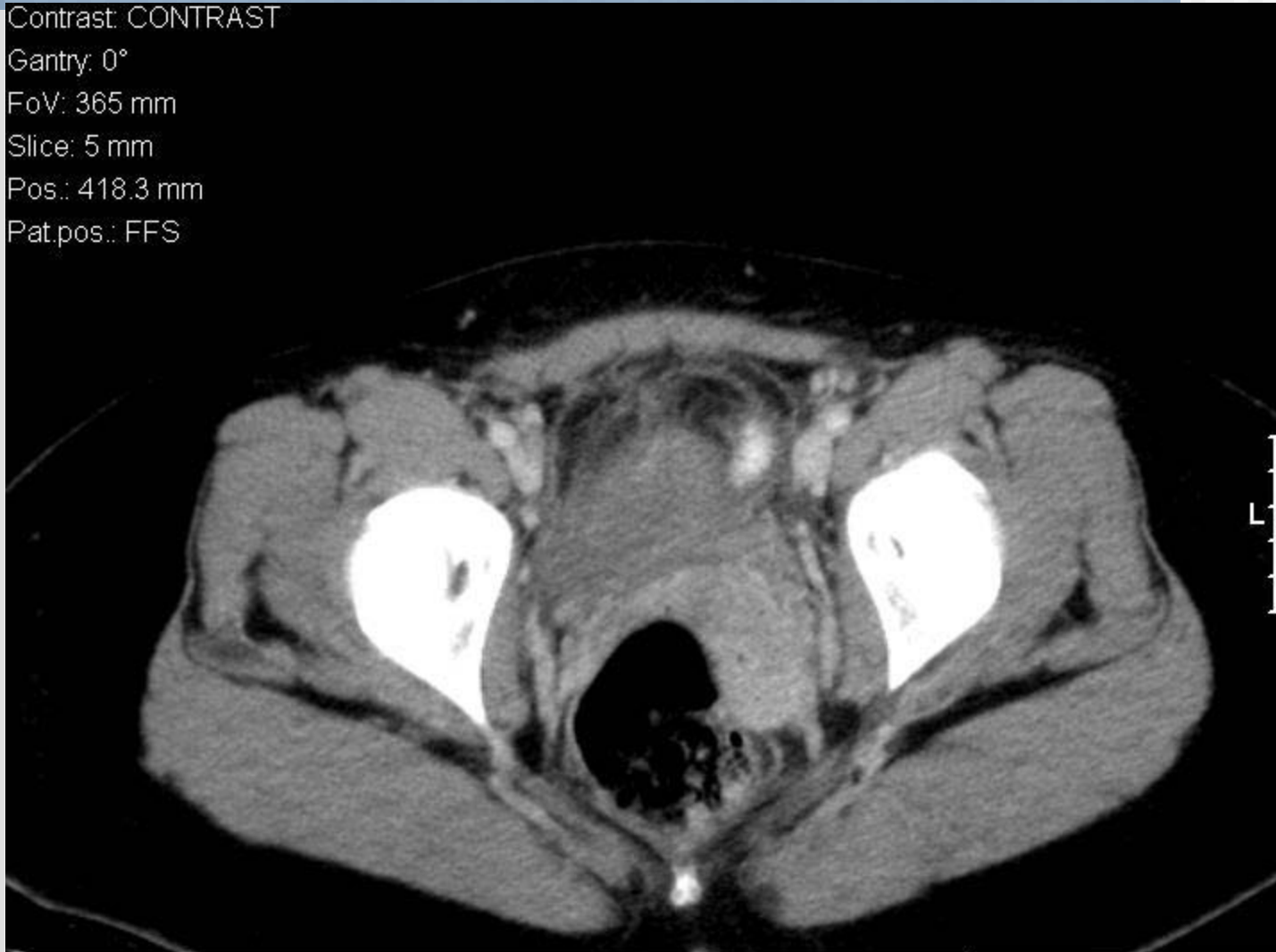
Gantry: 0°

FoV: 365 mm

Slice: 5 mm

Pos.: 418.3 mm

Pat.pos.: FFS



- CT scan: Nonfilling, dilated appendix containing multiple appendicoliths with surrounding inflammatory changes

- OR for laparoscopic appendectomy
- Hospital course
  - POD#1 – clears diet
  - POD#2 – diet advanced, discharged home

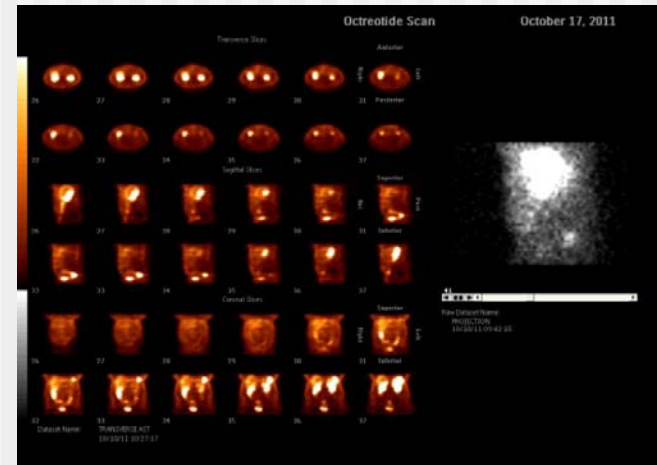
# Pathology

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- 2.8cm well differentiated neuroendocrine carcinoma, grade 1
- No lymphovascular or perineural invasion
- Chronic periappendicitis
- Immunohistochemistry stain
  - Positive for synaptophysin and chromogranin
- pT2 pNx PMx

# Outpatient workup

- Upper Endoscopy
- Colonoscopy
- Octreotide scan
- Chromogranin A level – 5 nmol/L
- Scheduled for Right hemicolectomy in October 2011



# Pathology

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- Right ileocelectomy
  - Negative for tumor
  - 0/20 Lymph nodes

# Questions?

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# Appendiceal Tumors

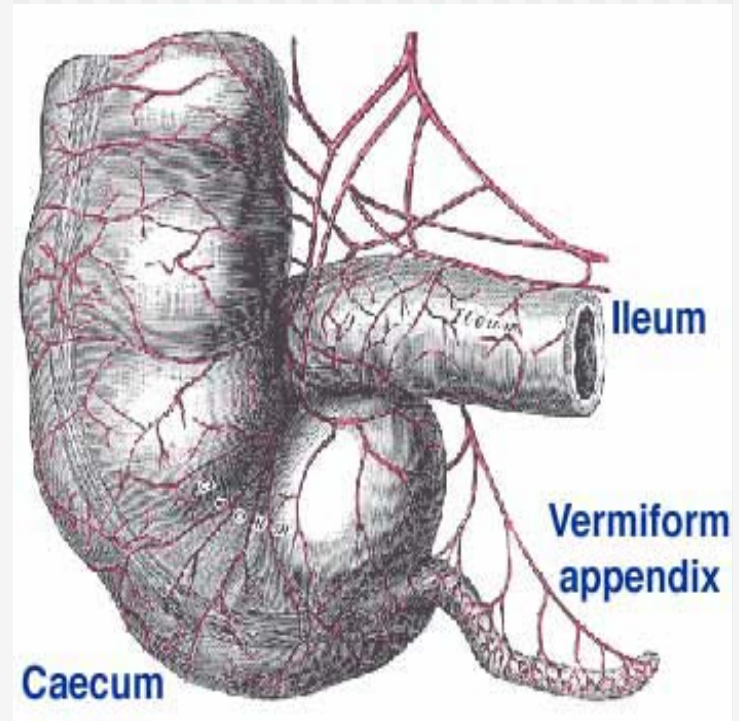
# Appendiceal Carcinoma Epidemiology

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- Incidence:
  - 0.12 per million
  - 1% of appendectomies
  - 1 in 300 appendectomies
- Most commonly present as acute appendicitis, followed by chronic abdominal pain and RLQ mass
- Preop diagnosis is usually associated with advanced disease

# The Appendix

- Derived from midgut
- Appears at 8<sup>th</sup> week gestation as outpouching of cecum
- Base located at convergence of taeniae
- Length varies 2-20cm, average 9cm
- Blood supply: appendiceal artery, branch of ileocolic artery
- Lymphatic drainage – anterior ileocolic lymph nodes



# Primary Appendiceal Carcinoma

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- Neuroendocrine tumors (carcinoid)
- Goblet cell carcinoid
- Adenocarcinomas
  - Mucinous – cystadenocarcinomas (Pseudomyxoma peritonei)
  - Colonic
  - Signet-ring

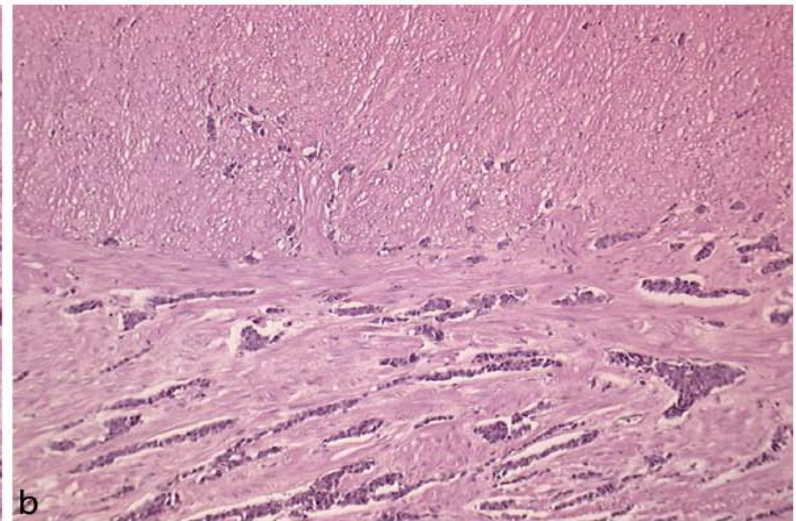
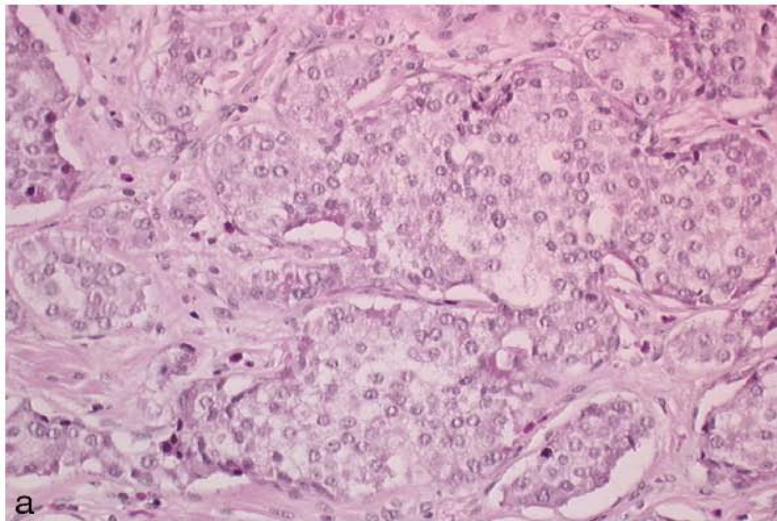
# Appendiceal Carcinoid Tumors

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- Mean Age and Gender: 38yo, 2.6:1 Female: Male
- Neuroendocrine tumor (Enterochromaffin cell)
- 24% carcinoids in appendix
  - 3<sup>rd</sup> most common location for carcinoid tumors following small bowel and rectum
- 2<sup>nd</sup> primary tumor – 18.2%
- Location
  - 60-75% tip of appendix
  - 5-21% mid appendix
  - 7-10% base of appendix
- Size
  - 60-76% <1cm
  - 4-27% 1-2cm
  - 2-17% >2cm

# Histology

- Originate from subepithelial neuroendocrine cells
- Immunohistochemistry:
  - Chromogranin A
  - Synaptophysin antibodies
- Proliferation rate
  - Ki-67 marker



# World Health Organization Classification

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- **Well-differentiated endocrine tumor**
  - **Benign behavior**
    - Nonfunctioning
    - Confined to appendiceal wall
    - <2cm
    - Nonangioinvasive
    - Ki-67 index <2%
    - Mitoses of <2cells/high powerfields x40
  - **Uncertain behavior**
    - Nonfunctioning
    - Confined to subserosa
    - >2cm
    - Angioinvasive
- **Malignant well-differentiated endocrine carcinoma – low grade**
  - Invading mesoappendix or beyond
  - Or metastases
  - +/- carcinoid syndrome
- **Mixed exocrine-endocrine carcinoma**
  - Goblet cell carcinoids

# TNM Classification

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- European Neuroendocrine Tumor Society (2007)
  - T1 - <1cm, submucosa or muscularis propria
  - T2 - <2cm, <3mm invasion of mesoappendix
  - T3 - >2cm, >3mm invasion of mesoappendix
  - T4 - peritoneum or other organs
  - G1 – Mitotic count <2, Ki-67 index <2%
  - G2 – Mitotic count 2-20, Ki-67 index 3-20%
  - G3 – Mitotic count >20, Ki-67 index >20%
- American Joint Committee on Cancer (2009)
  - T1a - <1cm
  - T1b - 1-2cm
  - T2 - 2-4cm or extension to cecum
  - T3 - >4cm or extension to ileum
  - N0 – no regional lymph node metastasis
  - N1 – regional lymph nodes metastasis
  - M0 – no distant metastasis
  - M1 – distant metastasis

# Staging (AJCC)

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- Stage I
  - T1 N0 M0
- Stage II
  - T1 N1 M0
  - T2 N0 M0
  - T3 N0 M0
- Stage III
  - T4 N0 M0
  - Any T N1 M0
- Stage IV
  - Any I Any N M1

# Workup

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- Chromogranin A – blood marker found elevated in 80-100% of patients with neuroendocrine tumors
  - Corresponds to tumor load
  - >5000 ug/L predict poor outcome
- Octreotide scan – most sensitive in diagnosis and staging of metastatic disease
- CT Scan
- Endoscopy – high incidence of metachronous and synchronous GI neoplasms (18-33%)

# Prognosis

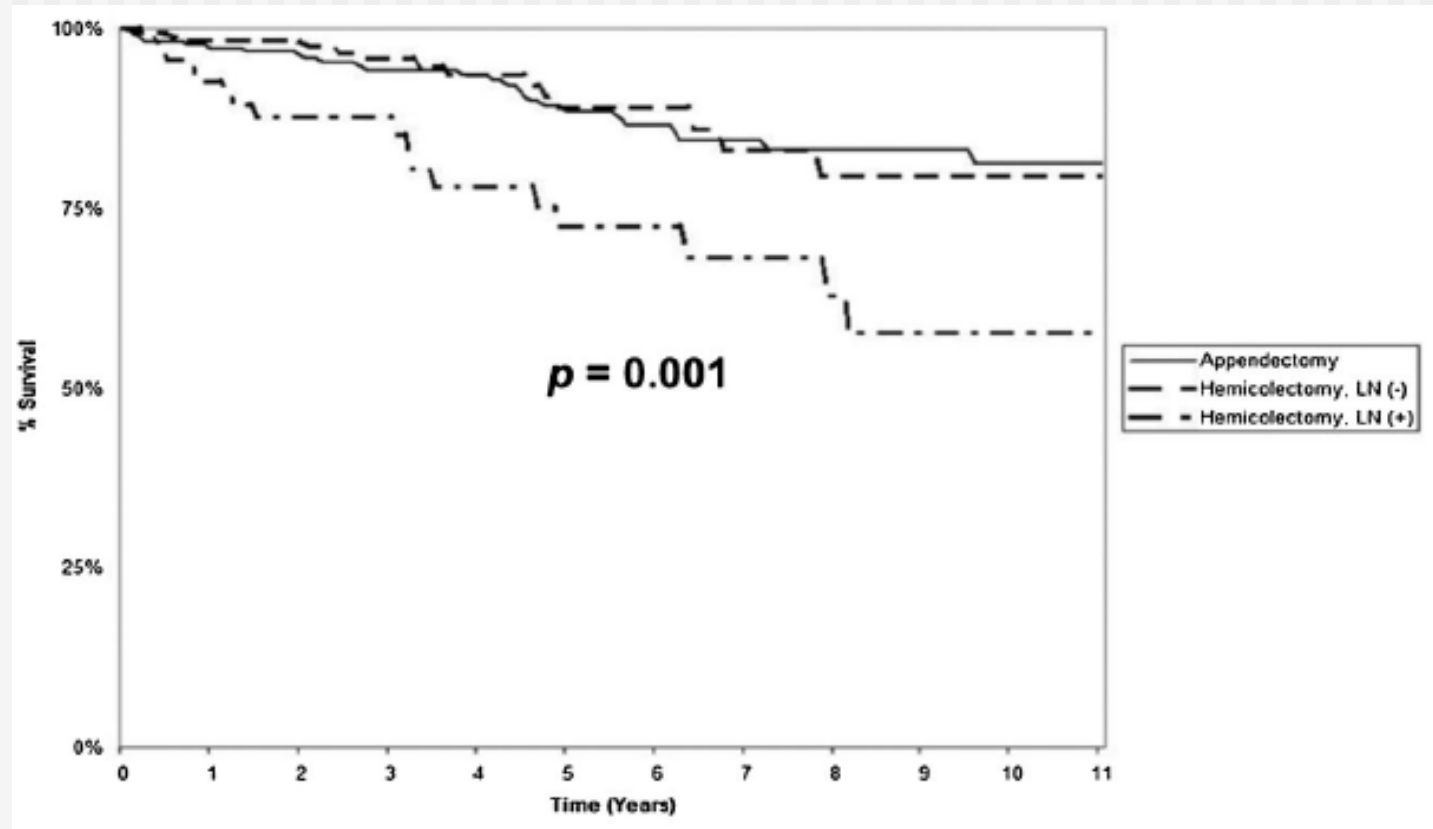
- Prognosis is directly related to size of tumor
- High incidence of lymph node metastasis in tumors >2cm

**Table 1.** Prognosis of appendiceal endocrine tumours according to size

Author	Median follow-up	All patients	Metas-tases	Patients	<2 cm	<2 cm + mesoappendiceal invasion	>2 cm + mesoappendiceal invasion	
Stinner and Rothmund [16]	n.i.	493	neg	476	361	75	40	
			pos	17	0 (0%)	5 (6.7%)	12 (30%)	
					<1 cm	>1 and <2 cm	>2 and <3 cm	≥3 cm
Moertel et al. [15]	26 years	150	neg	143	104	23	11	5
			pos	7	0 (0%)	0 (0%)	3 (21%)	4 (44%)

Plockinger et al. Consensus Guidelines for the Management of Patients with Digestive Neuroendocrine Tumors: Well-differentiated tumor/carcinoma of the Appendix and Goblet Cell Carcinoma. Neuroendocrinology 2008; 87:20-30

# Lymph Node Metastasis and Survival



Groth et al. Appendiceal Carcinoid Tumors: Predictors of Lymph Node Metastasis and the Impact of Right Hemicolectomy on Survival. *Journal of Surgical Oncology*. 2011; 103:39-45

# Prognosis

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- Impact of survival with mesoappendix infiltration is controversial
  - Found in 33-57% of cases
  - Studies from Rossi et al and Moertel et al found no recurrent or metastatic disease in pt with mesoappendiceal invasion
  - MacGillivray et al found tumors >2cm and mesoappendiceal invasion related to metastatic disease

# Survival based on Staging

TABLE 4. 5-Year Survival Rates by Carcinoid Location (1973–1997)

Site	All Stages	Local Stage	Regional Stage	Distant Stage
Stomach	75.1%/55.3%	90.2%/69.6%	40.4%/27.2%	18.0%/9.0%
Small bowel	76.1%/54.6%	94.5%/70.4%	84.4%/64.1%	51.2%/32.4%
Appendix	76.3%/65.0%	95.6%/87.8%	80.0%/67.6%	37.5%/26.8%
Colon	69.5%/41.8%	94.1%/77.1%	72.5%/35.3%	27.8%/4.1%
Rectum	87.5%/77.8%	94.9%/86.2%	53.7%/42.1%	14.6%/13.1%

\*Cancer-specific survival/relative overall survival.

Survival rates are all age-adjusted to standard 2000 population.

# Management

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- < 1cm – appendectomy
- > 2cm – right hemicolectomy
- 1 – 2 cm - ???
  - Mesoappendiceal infiltration
  - Positive or unclear margins
  - Vascular invasion
  - Tumor involving base of appendix
- Two-step approach
  - Timing of hemicolectomy should be performed within 3 months after appendectomy
  - Can be performed by laparoscopic or open approach
  - No data to support two-step approach to have negative impact on prognosis

# Follow-up

## ENETS Guidelines

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- For well-differentiated tumors <1cm and R0 resection, no follow-up is required after surgery
- For tumors 1-2cm and R0 resection, insufficient data regarding follow-up. Recommend follow-up investigations for high proliferation marker, vascular invasion, deep mesoappendiceal invasion, involvement of base of appendix
- For well-differentiated tumors >2cm, at all locations of the appendix, imaging followup is recommended
  - CT scan
  - Octreotide scintigraphy
  - Colonoscopy
  - Tumor markers – chromogranin A level, 5-HIAA (carcinoid syndrome)

**Table 1.** Summary of follow-up recommendations in patients with benign and malignant neuroendocrine tumors

	Follow-up				
	yes/no	endoscopy	US/CT/MRI	Octreoscan	CgA
Benign insulinoma	no				
Type 1 gastric carcinoid	yes	yearly			
Rectal carcinoid	no (if completely resected)				
Appendiceal carcinoid T1	no				
Appendiceal carcinoid T2	? (see text)				
Resectable tumor (uncertain behavior)					
G1	every 6–12 months	yes (gastric carc.)	yes	every 2 years <sup>2</sup>	yes <sup>1</sup>
Resectable malignant tumor with/without nodal involvement					
G1	every 6–12 months		yes	every 2 years <sup>2</sup>	yes <sup>1</sup>
G2	every 6 months		yes	yearly <sup>2</sup>	yes <sup>1</sup>
G3	every 3 months		yes	yearly <sup>2</sup>	yes <sup>3</sup>
Non-resectable malignant tumor with/without nodal involvement and/or liver and other metastases					
G1	every 6–12 months		yes	every 2 years <sup>2</sup>	yes
G2	every 6 months		yes	yearly <sup>2</sup>	yes
G3	every 3 months		yes	yearly <sup>2</sup>	yes <sup>3</sup>

<sup>1</sup> Only in the presence of a visible tumor.

<sup>2</sup> Recommendations regarding the time frames of Octreoscan should be adjusted to the individual situation.

<sup>3</sup> In poorly differentiated tumors and negative CgA NSE may act as a suitable marker.

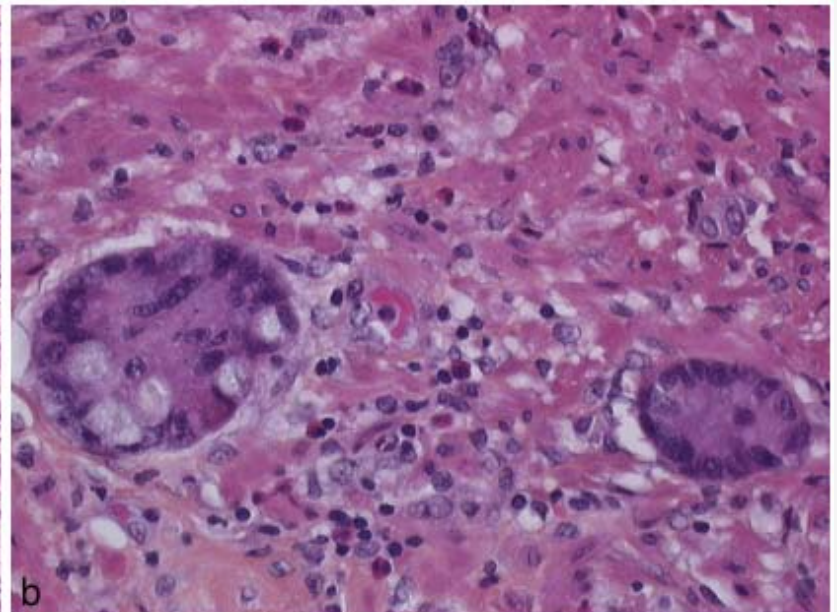
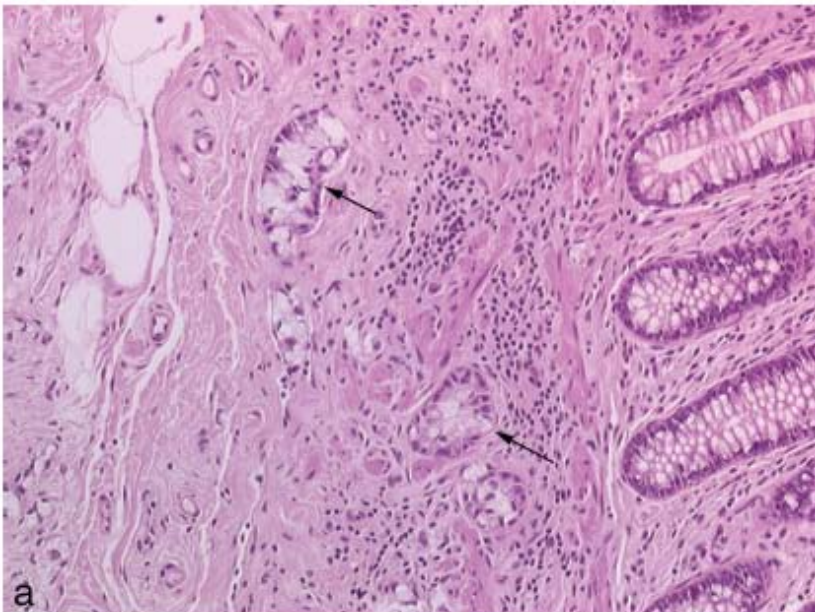
# Goblet Cell Carcinoids

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- Adenocarcinoid, mucinous carcinoid, goblet cell tumors
- Introduced in 1970s as a separate entity with mixed histological features that differed from carcinoid and adenocarcinoma
- Distinct prognostic group intermediate between carcinoid tumor and adenocarcinoma
- 5% of all primary appendiceal malignancies
- 1:1 Male:Female ratio
- Median age 58, second peak at 70
- 63% metastases (ovaries, right colon, peritoneum) present at diagnosis
- Commonly presents as acute appendicitis, followed by abdominal pain/mass, bowel obstruction, intussusception, bleeding

# Histology

- Mixed phenotype – partial neuroendocrine cell and intestinal type goblet cell
- Mucin-containing, goblet-shaped epithelial cells
- Submucosal growth pattern with sparing of mucosa
- Focal positive immunoreactivity for neuroendocrine markers (chromogranin or synaptophysin)



# Workup

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- Chest CT
- Abd/pelvis CT
- Octreotide scan
- Endoscopy
- Tumor markers: CEA, CA19-9, CA-125

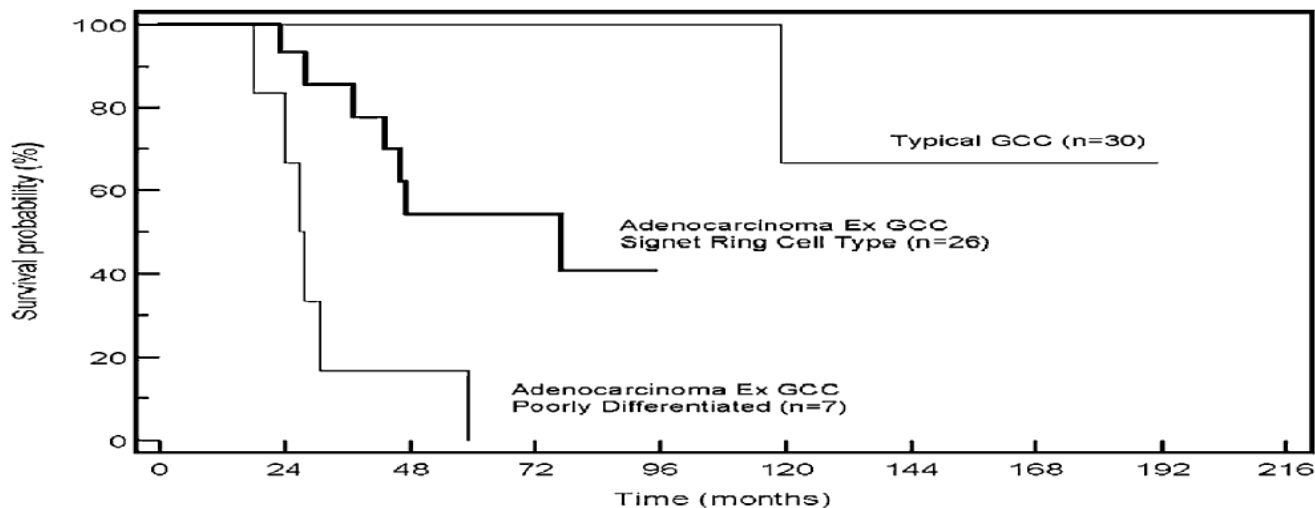
# Prognosis

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- Prognosis is dependent on:
  - Size
  - Serosal involvement
  - Mesoappendiceal invasion
  - Histology
  - Stage

# Prognosis

- Survival is dependent on histological subtype
  - Typical GCC
  - Adenocarcinoma ex GCC, signet ring cell type
  - Adenocarcinoma ex GCC, poorly differentiated adenocarcinoma cell type



# Survival

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- SEER data (1973-2001)
- 5 year overall survival 76%
  - Localized 86%
  - Regional 74%
  - Distant 18%

# Management

**TABLE 11.** Recommended Management of Goblet Cell Carcinoid Tumors of the Appendix

Tumor Presentation	Management
Tumor localized and confined to appendix (pT1 or pT2) and Typical GCC histology (group A) and Negative appendectomy resection margin	Insufficient data to recommend
Tumor spread beyond appendiceal wall (pT3 or pT4) or Histology of an adenocarcinoma (group B or C) or Localized perforation (secondary to inflammation) or Positive appendectomy resection margin	Right hemicolectomy Consider oophorectomy Chemotherapy in stage III and IV
Intraperitoneal spread (stage IV) or Presence of poorly differentiated adenocarcinoma component	Debulking surgery Consider oophorectomy  Systemic and intraperitoneal chemotherapy

# Appendiceal Adenocarcinoma

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- Mucinous adenocarcinoma
- Colonic type adenocarcinoma
- Signet ring cell adenocarcinoma

# Appendiceal Adenocarcinoma

Demographic and Clinical Data for the Most Common Appendiceal Cancer Histologies

	Mucinous	Adeno	Carcinoid	Goblet	Signet
No. of cases	951 (38)	646 (26)	435 (17)	369 (15)	113 (4)
Incidence rate <sup>a,b</sup>	1.3	0.95	0.63	0.5	0.15
Age (yr)	60 ± 15	63 ± 16	41 ± 19	52 ± 16	59 ± 14
Male	47	58	29	51	49
Race					
White	78	75	86	82	83
Black	7	13	8	10	4
Hispanic	8	5	3	2	4
Asian	4	5	2	5	5
Tumor size (cm) <sup>c</sup>	5.2 ± 3.8	3.9 ± 2.5	2.5 ± 2.1	2.4 ± 2.2	4.2 ± 2.5
Size (cm)					
≤1	6	8	13	19	6
>1 to ≤2	17	20	32	32	20
>2	77	72	55	49	74
Overall stage					
Localized	28	45	60	64	14
Regional	21	28	28	24	26
Distant	51	27	12	12	60

Data are percentages or means ± standard deviations unless otherwise indicated.

<sup>a</sup>Incidence rate per 1,000,000 population from 1973 to 2001.

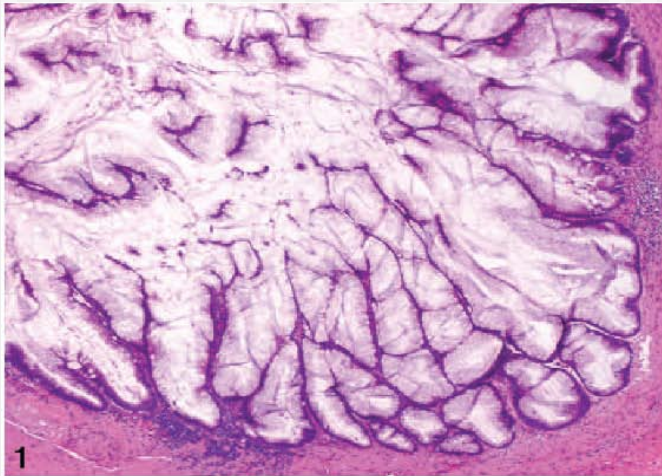
<sup>b</sup>Age-adjusted.

<sup>c</sup>Data available only for patients from 1988 to 2001.

McGory et al. Malignancies of the appendix: beyond case series. Dis Colon Rectum. 2005;48: 2264-2271

# Mucinous adenocarcinoma

- Malignant mucocele, cystadenocarcinoma
- Rarely spread via lymphatics or hematologically
- Noninvasive characteristic – spreads along serosal surfaces of the viscera
- Half present with disseminated disease - Pseudomyxoma peritonei
- Stephenson et al. (1985) 10 yr survival
  - 37% appendectomy
  - 65% right hemicolectomy
- Surgical debulking, omentectomy for metastatic disease
  - Chemotherapy and radiotherapy have not been found to be effective



# Appendiceal adenocarcinoma

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- Colonic type adenocarcinoma
  - Presents in older patients
  - Localized to base of appendix
  - Lymphatic and hematogenous spread
  - Anderson et al. 5 yr survival
    - 46% appendectomy alone
    - 60% right hemicolectomy
- Signet ring cell type adenocarcinoma
  - Worst prognosis
- Management: Right hemicolectomy +/- chemotherapy

# AJCC TNM Staging

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- Tis – carcinoma in situ
  - T1 – invades submucosa
  - T2 – invades muscularis propria
  - T3 – invades subserosa or mesoappendix
  - T4a – invades beyond visceral peritoneum
  - T4b – invade adjacent organs
  
  - N0 – no lymph nodes
  - N1 – 1-3 lymph nodes
  - N2 – 4+ lymph nodes
  
  - M1a – intraperitoneal mets
  - M1b – nonperitoneal distant metastasis
- Stage 0 – carcinoma insitu
  - Stage I
    - T1 N0 M0
    - T2 N0 M0
  - Stage IIa T3 N0 M0
  - Stage IIb T4a N0 M0
  - Stage IIc T4b N0 M0
  - Stage IIIa T1/T2 N1 M0
  - Stage IIIb T3/T4 N1 M0
  - Stage IIIc any T N2 M0
  - Stage IVa any T N0 M1a
  - Stage IVb
    - Any T, N0, M1a, G2/G3
    - Any T, N1, M1a, any G
    - Any T, N2, M1a, any G
  - Stage IVc any T, any N, M1b, any G

# Survival

Overall Five-Year Survival Outcomes for the Most Common Appendiceal Cancer Histologies

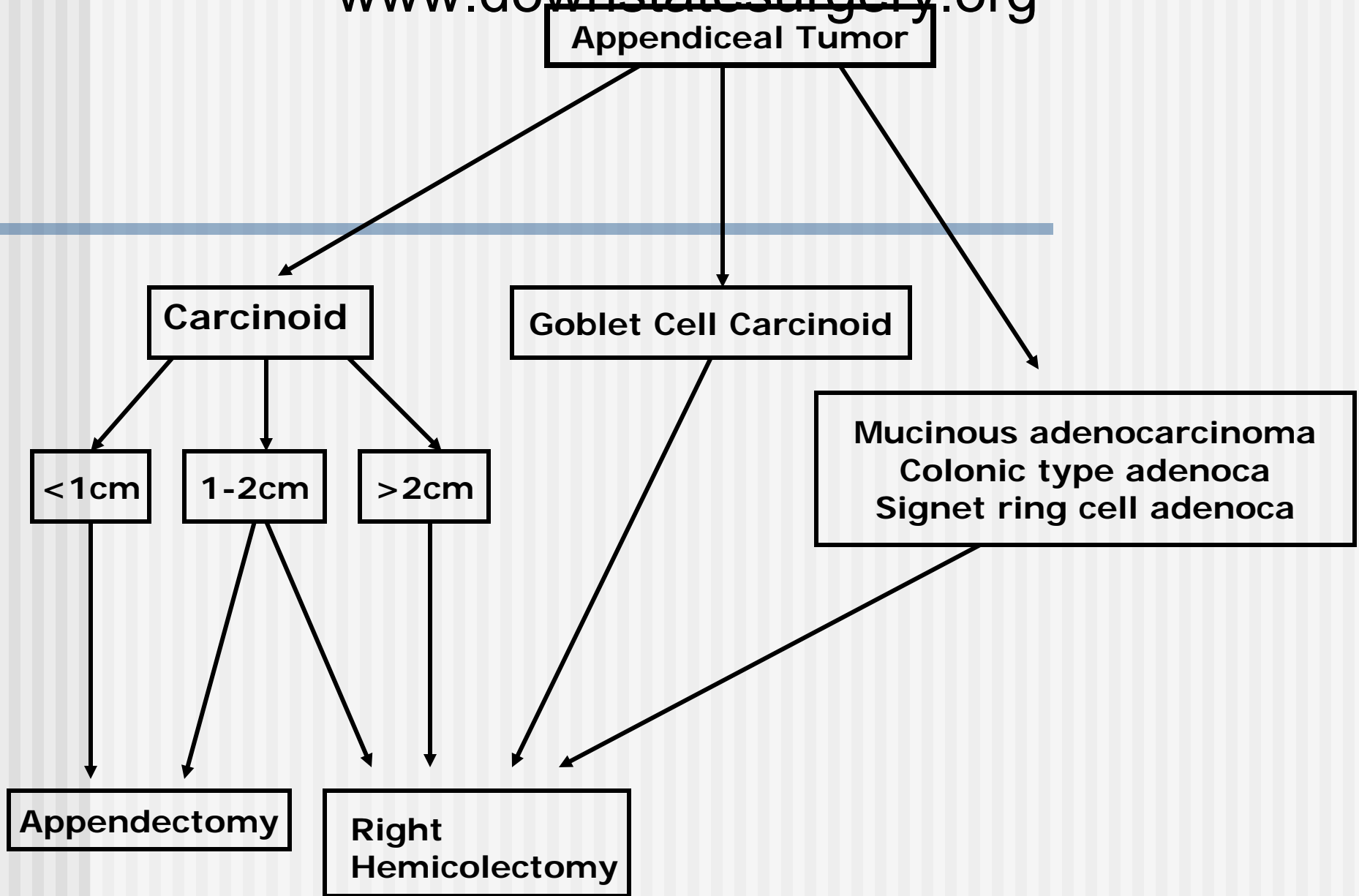
	Mucinous	Adeno	Carcinoid	Goblet	Signet
All stages	46	42	83 <sup>a</sup>	76 <sup>a</sup>	18 <sup>a</sup>
Localized	64	64	94 <sup>a</sup>	86 <sup>a</sup>	55
Regional	54 <sup>b</sup>	37	83 <sup>a</sup>	74 <sup>a</sup>	21
Distant	32 <sup>a</sup>	11	31 <sup>b</sup>	18 <sup>b</sup>	7

Data are percentages.

*P* values based on comparison with adenocarcinoma (*P* = not significant unless otherwise noted).

<sup>a</sup>*P* < 0.0001 compared with adenocarcinoma five-year survival.

<sup>b</sup>*P* < 0.05 compared with adenocarcinoma five-year survival.



# Summary

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- Appendiceal tumors are rarely diagnosed preoperatively
- Most present as acute appendicitis, followed by chronic abdominal pain or RLQ mass
- Carcinoid tumors < 1cm in size may be managed with appendectomy alone
- All others should be managed with right hemicolectomy
- Two stage surgery is an acceptable approach to management of appendiceal tumors
- Carcinoid tumors have the best prognosis while adenocarcinoma (signet ring cell type) has the worst prognosis

# References

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- Yoon et al. Primary signet ring cell carcinoma of the appendix: A rare case report and our 18-year experience. *World J Gastroenterology.* 2008;14: 5763-5768

# Carcinoid tumors

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- 67% of all carcinoid tumors found in GI tract
- 25% found in tracheobronchopulmonary complex (most common extradigestive site), other sites: ovaries, testus, liver, GB, pancreas
- Within GI tract
  - 42% in small bowel, half in ileum
  - 27% rectum
  - 24% appendix
  - Goodwin 1973 – gold standard paper – showed appendix most common – not true anymore
- Overall incidence 38.4/million