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METASTATIC INTESTINAL CARCINOID

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CASE

- 63 yr old male with PMH of prostate cancer, HTN, obesity, presented with complaints of abdominal pain, nausea and vomiting, no flatus or bowel movements for one day. He denied palpitations, hot flashes, diarrhea and wheezing.
- PSH: prostatectomy
- PE afebrile, VSS
- Gen: NAD
- CV:+s1, s2 no murmurs
- Abd: low infraumbilcal scar well healed, obese, no hernias, soft tender, distended
- Rectal: no masses, skin tags, no gross blood, guiac negative

CASE

- November 2012 admitted for small bowel obstruction. Ct showed stellate mesenteric lesion with calcification
- December 3.2012 Somatostatin PET scan which showed 3 lesions, anterior surface of liver, segment 5, lower pole of right kidney
- December 8, 2012 EGD- 3 lesions in ileum and one dominant lesion in terminal ileum extending into the Cecum
- December 14, 2012 MRI showed multiple liver lesions bilobar mostly on the right. Pericecal mass, mesenteric mass.

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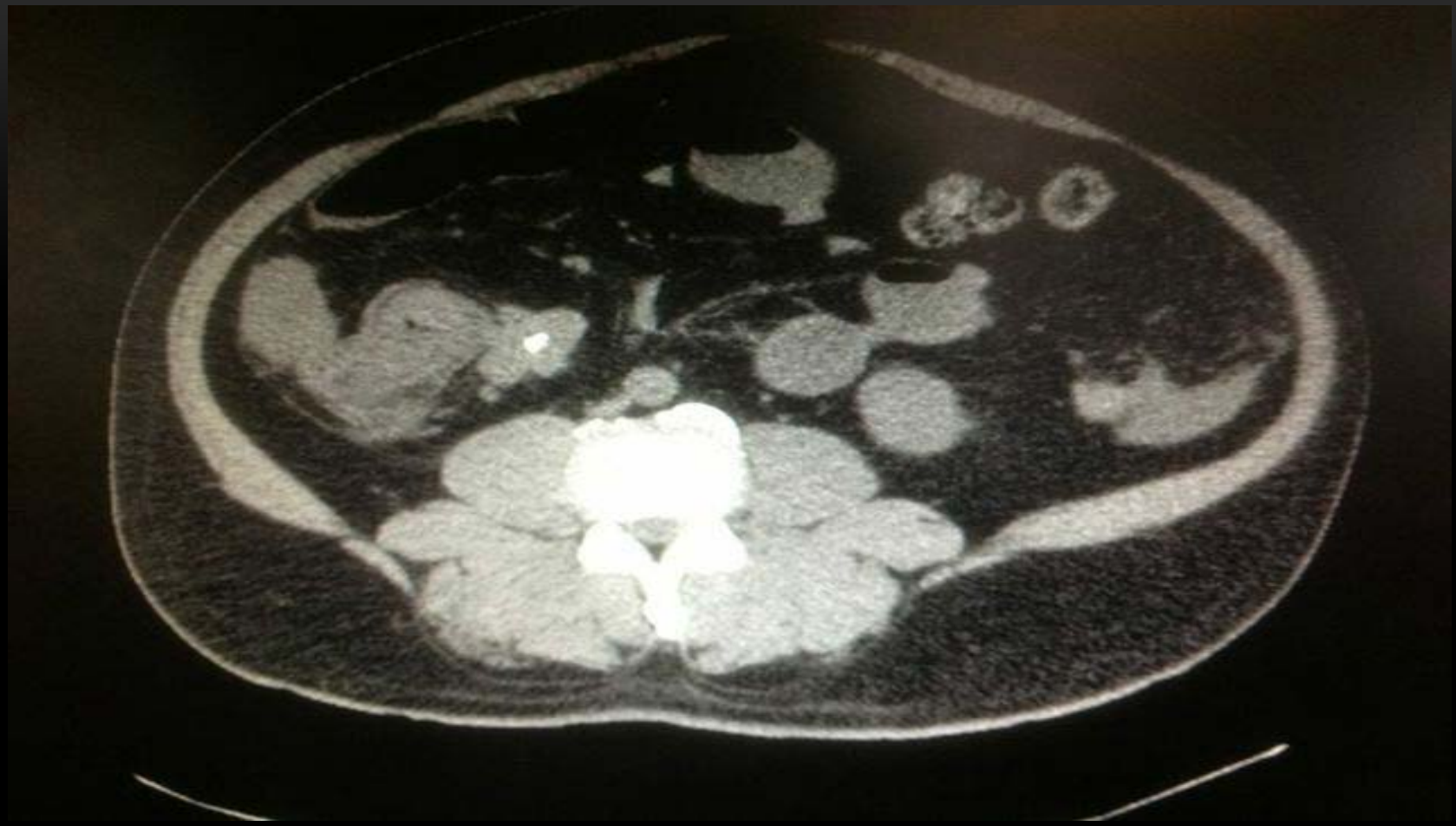


CASE

- December 23,2012 Tumor Board discussion:Heme/Onc, GI, Rad Onc, Surgery, Pulmonary. Plan for exploratory laparotomy
- December 30, 2012 Colonoscopy- Left sided diverticulosis and large cecal mass, biospy pathology: Carcinoid

- Urine 5 HIAA: 25, elevated
- Chromogranin A: 6.5 normal

- Pt was started on Octreotide 100mg sub cutaneous Q8hr 2 weeks pre-operatively, changed to Octreotide infusion 12 hours pre op.

CASE

- Pt was taken to the OR on 1/2/13 for Exploratory laparotomy, right hemicolectomy, right mesenteric mass excision, cholecystectomy, segement V liver resection, EGD, Intra operative US, cystoscopy and ureteral stent placement
- POD#1-8 Pt remained NPO awaiting bowel function, started on TPN
- POD#8-18 Pt started on diet, JP removed, treated for UTI, octreotide discontinued
- POD# 18-20 Pt still had intermittent fevers with leukocytosis, found to have hepatic abscess drained by IR
- POD# 27 Discharged home
- Repeat Octreoscan was negative for residual tumor, CT abdomen and pelvis showed resolution of hepatic abscess

HISTORY

- 1867 Theodor Langhans was the first to describe the histology of carcinoid tumor, Otto Lubrarsh is credited with the first report of two patients with ileal carcinoid
- 1907 Siegfried Obendorfer coined the term Karzinoide “carcinoma like”
- 1948 Rappaport discovered serotonin as the vasoactive substance
- 1952 the origin of the amine 5HIAA was the Kulchitsky cell
- 1968 Williams and Sandler proposed the classification into foregut, midgut and hindgut.

NEUROENDOCRINE CELLS

- GLANDULAR
- Pituitary
- Parathyroids
- Paraganglia
- Adrenal Medulla

- DIFFUSE
- Skin
- Thyroid
- Lung
- Thymus
- Pancreas,
- Gastrointestiinal **
- Biliary tree
- Urogenital

WHAT IS IN A NAME?

- Carcinoid
- Neuroendocrine
- Enteroendocrine
- APUD- amine precursor uptake and decarboxylation
- Gastorenteropancreatic neuroendocrine tumors (GEP-NETs)
- Seritoninomas

INCIDENCE

- 1.3 per 100,000 from 36 yr study in England
- Ranges 2.47-2.58 per 100,000 from 2008 SEER data depending on site
- 3-10% increase in incidence of neuroendocrine tumors over the past 30 yrs
- Jejunum, ileum, and cecum, stomach, and rectum have increasing incidence,while appendiceal has decreasing incidence
- Median age for midgut NET is 64, appendiceal subgroup was 47

TABLE 4
Distribution of 13,715 Carcinoid Tumors by Site: End Results Group, Third National Cancer Survey, and SEER Registries

	ERG (1950–1969)		TNCS (1969–1971)		Early SEER (1973–1991)		Late SEER (1992–1999)		Pan-SEER (1973–1999)		Total carcinoids (1950–1999)
Carcinoid site	No. of patients	%	No. of patients	%	No. of patients	%	No. of patients	%	No. of patients	%	No. of patients
All carcinoid sites	1867	—	970	—	5889	—	4989	—	10878	—	13,715
Digestive system	1635	87.57	545	56.19	3626	61.57	3370	67.55	6996	64.31	9176
Esophagus	—	—	—	—	3	0.05	3	0.06	6	0.06	6
Stomach	42	2.25	19	1.96	209	3.55	292	5.85	501	4.61	562
Small intestine	353	18.91	—	—	1697	28.82	1408	28.22	3105	28.54	3458
Duodenum	33	1.77	22	2.27	114	1.94	191	3.83	305	2.80	360
Jejunum	19	1.02	19	1.96	124	2.11	74	1.48	197	1.81	235
Ileum	202	10.82	134	13.81	956	16.23	666	13.35	1623	14.92	1959
Meckel diverticulum	—	—	—	—	25	0.42	27	0.54	52	0.48	52
Overlapping (ileocecum)	14	0.75	—	—	15	0.25	14	0.28	29	0.27	43
Small intestine, NOS	99	5.30	70	7.22	463	7.86	436	8.74	899	8.26	1068
Colon and rectum	1238	66.31	526	54.23	1592	27.03	1523	30.53	3115	28.64	4879
Colon, except appendix	72	3.86	65	6.70	558	9.48	380	7.62	938	8.62	1075
Cecum	50	2.68	29	2.99	271	4.60	173	3.47	444	4.08	523
Appendix	820	43.92	340	35.05	398	6.76	121	2.43	519	4.77	1679
Ascending colon	22	1.18	10	1.03	55	0.93	29	0.58	84	0.77	116
Hepatic flexure	—	—	—	—	13	0.22	7	0.14	20	0.18	20
Transverse colon	14	0.75	3	0.31	27	0.46	10	0.20	37	0.34	54
Splenic flexure	—	—	—	—	9	0.15	6	0.12	15	0.14	15
Descending colon	4	0.21	1	0.10	23	0.39	13	0.26	36	0.33	41
Sigmoid colon	23	1.23	13	1.34	101	1.72	106	2.12	207	1.90	243
Large intestine (colon), NOS	9	0.48	9	0.93	59	1.00	36	0.72	95	0.87	113
Rectosigmoid junction	15	0.80	2	0.21	80	1.36	97	1.94	177	1.63	194
Rectum	281	15.05	119	12.27	556	9.44	925	18.54	1481	13.61	1881
Anus, anal canal, and anorectum	—	—	—	—	9	0.15	9	0.18	18	0.17	18
Liver	—	—	—	—	14	0.24	31	0.62	45	0.41	45
Gallbladder	1	0.05	—	—	7	0.12	17	0.34	24	0.22	25
Other biliary	1	0.05	—	—	11	0.19	18	0.36	30	0.28	31
Pancreas	—	—	—	—	47	0.80	32	0.64	79	0.73	79
Digestive tract, NOS	27	1.45	8	0.82	171	2.90	174	3.49	346	3.18	381
Ovary	—	—	3	0.31	42	0.71	68	1.36	110	1.01	113
Testis	—	—	—	—	3	0.05	5	0.10	8	0.07	8
Other endocrine, including thymus	—	—	—	—	25	0.42	16	0.32	41	0.38	41
Trachea, bronchi, lung	191	10.23	137	14.12	1777	30.17	1260	25.26	3037	27.92	3365

TABLE 5
Distribution of 9421 Gastrointestinal Carcinoid Tumors by Site: End Results Group, Third National Cancer Survey, and SEER Registries

	ERG (1950–1969)		TNCS (1969–1971)		Early SEER (1973–1991)		Late SEER (1992–1999)		Pan-SEER (1973–1999)		Total carcinoids (1950–1999)
Carcinoid site	No. of patients	%	No. of patients	%	No. of patients	%	No. of patients	%	No. of patients	%	No. of patients
Digestive system	1635	—	790	—	3626	—	3370	—	6996	—	9421
Esophagus	—	—	—	—	3	0.08	3	0.09	6	0.09	6
Stomach	42	2.57	19	2.41	209	5.76	292	8.66	501	7.16	562
Small intestine	353	21.59	245	31.01	1697	46.80	1408	41.78	3105	44.38	3703
Duodenum	33	2.02	22	2.78	114	3.14	191	5.67	305	4.36	360
Jejunum	19	1.16	19	2.41	124	3.42	74	2.20	197	2.82	235
Ileum	202	12.35	134	16.96	956	26.37	666	19.76	1623	23.20	1959
Meckel diverticulum	—	—	—	—	25	0.69	27	0.80	52	0.74	52
Overlapping (lleocecum)	14	0.86	—	—	15	0.41	14	0.42	29	0.41	43
Small intestine, NOS	99	6.06	70	8.86	463	12.77	436	12.94	899	12.85	1068
Colon and rectum	1238	75.72	526	66.58	1592	43.91	1523	45.19	3115	44.53	4879
Colon, except appendix	72	4.40	65	8.23	558	15.39	380	11.28	938	13.41	1075
Colon, except rectum	942	57.61	405	51.27	956	26.37	501	14.87	1457	20.83	2804
Cecum	50	3.06	29	3.67	271	7.47	173	5.13	444	6.35	523
Appendix	820	50.15	340	43.04	398	10.98	121	3.59	519	7.42	1679
Ascending colon	22	1.35	10	1.27	55	1.52	29	0.86	84	1.20	116
Hepatic flexure	—	—	—	—	13	0.36	7	0.21	20	0.29	20
Transverse colon	14	0.86	3	0.38	27	0.74	10	0.30	37	0.53	54
Splenic flexure	—	—	—	—	9	0.25	6	0.18	15	0.21	15
Descending colon	4	0.24	1	0.13	23	0.63	13	0.39	36	0.51	41
Sigmoid colon	23	1.41	13	1.65	101	2.79	106	3.15	207	2.96	243
Large intestine (colon), NOS	9	0.55	9	1.14	59	1.63	36	1.07	95	1.36	113
Rectum and rectosigmoid junction	296	18.10	121	15.32	636	17.54	1022	30.33	1658	23.70	2075
Rectosigmoid junction	15	0.92	2	0.25	80	2.21	97	2.88	177	2.53	194
Rectum	281	17.19	119	15.06	556	15.33	925	27.45	1481	21.17	1881
Liver	—	—	—	—	14	0.39	31	0.92	45	0.64	45
Intrahepatic bile ducts	—	—	—	—	0	0.00	1	0.03	1	0.01	1
Gallbladder	1	0.06	—	—	7	0.19	17	0.50	24	0.34	25
Other billary	1	0.06	—	—	11	0.30	18	0.53	30	0.43	31
Pancreas	—	—	—	—	47	1.30	32	0.95	79	1.13	79
Digestive tract, NOS	27	1.65	8	1.01	171	4.72	174	5.16	346	4.95	381

RISK FACTORS

- Parent or sibling with history of carcinoid tumor
- Parent with history of brain, endocrine, breast, liver and urinary tract cancer
- Genetic disorders with pancreatic neuroendocrine tumors (PNET)
  - MEN I
  - von Hipple Lindau
  - von Recklinhausens
  - Tuberous sclerosis

DIAGNOSIS

- LABORATORY WORK UP
  - 24 hour urine 5HIAA
  - Serum Chromogranin A levels
  - Serum Serotonin levels
- SYMPTOMS
  - Flushing***Most common sx
  - Burning sensation of skin
  - Secretory diarrhea
  - Bronchospasm
  - Cramping abdominal pain

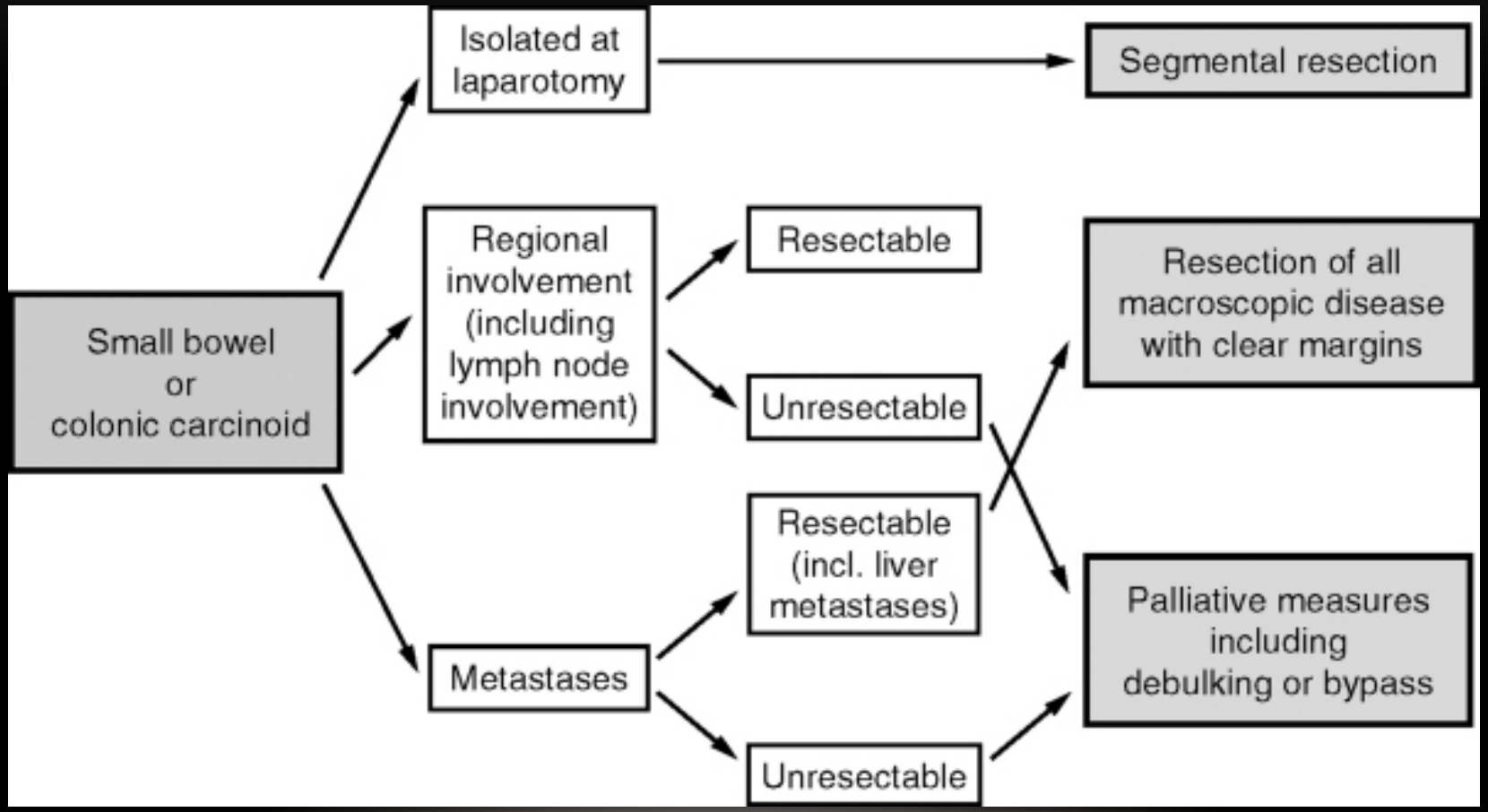
GASTRIC CARCINOID

- 4% of all GI NET, 1% of gastric neoplasms
- 4 subtypes
- Types 1-3 originate from enterochromaffin cells in the gastric mucosa.
- Types 1, 2 are gastrin dependent, multifocal, small (<2cm)
- Type 3 not associated with hypergastrinemia, usually solitary and large (>2cm)
- Type 4 is poorely differentiated, usually large (>5cm) ulcerated and unresectable, poor prognosis

SMALL INTESTINE

- Most common location of carcinoid tumor, usually in terminal ileum
- Multiple tumors in 1/3 of patients
- Carcinoid syndrome is common with liver metastasis
- Metastasis to liver in 50%, nodal spread in 70%
- Fibrosis around nodal metastases causes contraction of mesentery→occlusion of mesenteric vessels and ischemia→ chronic ischemia on antimesenteric border
- Size does NOT predict metastatic potential
- Small tumors less than 1cm can be segmentally resected, wide excision for tumors greater than 1cm. Right hemicolectomy for lesions of the terminal ileum
- 5 yr survival is fair (60%)

TREATMENT ALGORITHM



APPENDIX

- No longer the most common site of carcinoid tumor based on newer SEER data
- Is the most common neoplasm of the appendix
- Incidence is decreasing
- Most found incidentally
- Indications for right hemicolectomy for appendiceal carcinoids 1-2cm in size
  - Invasion into the mesoappendix
  - Lymphovascular invasion
  - Serosal involvement
  - Positive margins, positive LN on appendectomy specimen
  - HIGH KI67 Index
  - Goblet cell variant

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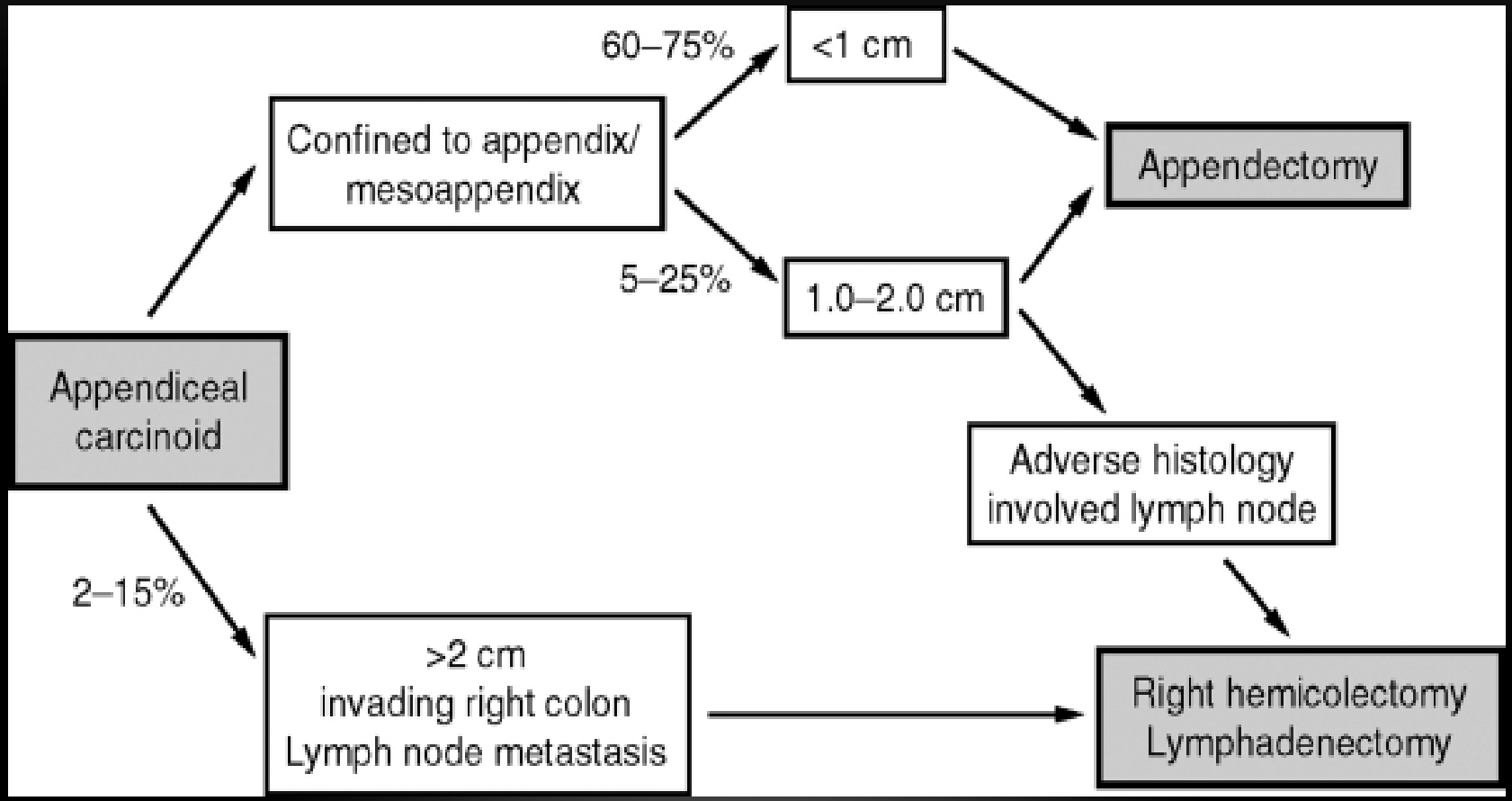
TREATMENT ALGORITHM



COLON

- Majority of tumors occur on the right side
- Rarely secrete serotonin, Carcinoid syndrome is RARE
- Usually present as large exophytic lesions
- Overall 5 yr survival is poor (33-37%)
- Worst prognosis among all patients with carcinoid of the GI tract

RECTUM

- More common in African Americans
- Most are small (<1cm)
- Most found incidentally
- Carcinoid syndrome is rare
- Prognosis is size dependent
- 5 yr survival is favorable (88%)

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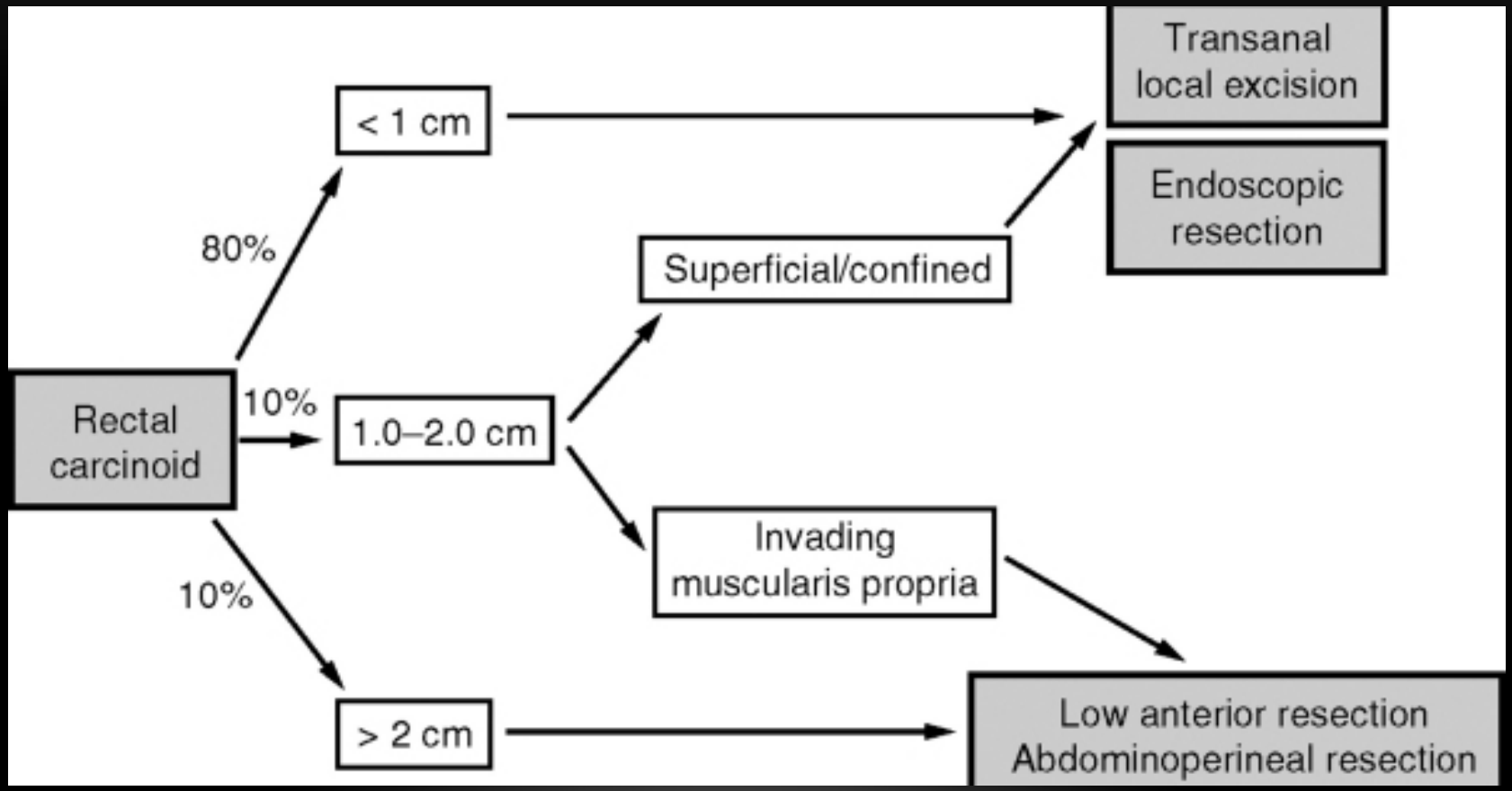
TREATMENT ALGORITHM



CHARACTERISTICS

Location	Non hormonal Symptoms	Carcinoid syndrome	Metastatic disease
Stomach	Pain pernicious anemia	Rare	uncommon type1-2 common type 3-4
Small Intestine	Pain, Intestinal Obstruction	5-18%	Common with liver metastasis
Appendix	Appendicitis, Incidental	Rare	Uncommon (less than 2cm)
Colon	Pain, Bleeding, Weight Loss	Rare	common
Rectum	Pain, Constipation, Bleeding, Incidental	Rare	uncommon

DIAGNOSIS-IMAGING

- Plain radiograph
- Cross sectional CT of the abdomen and pelvis
- Octreotide scintigraphy
  - Imaging should be performed at the end of dosing interval (3-6 wks after last dose) those on infusion pump should have stopped for 48 hrs.
  - Localizes primary, recurrent tumor and staging

TREATMENT- METASTATIC GI CARCINOID

- Surgical resection for well differentiated gastrointestinal NET- Curative
- Hepatic lobe resection, radio frequency ablation, microwave ablation and cryoablation for liver disease- Palliative
- Somatostatin analogs to manage carcinoid syndrome
- Novel Treatment for metastatic carcinoid
  - Radio labeled somatostatin analog
  - Recombinant human endostatin
  - Thalidomide
  - VEGF receptor inhibitors

CONCLUSIONS

- Symptom control
  - Somatostatin analogues control hypersecretion of neuropeptides in foregut and midgut carcinoids that express somatostatin receptors
- Biochemical control
  - Systemic chemotherapeutics like interferon alpha upregulate somatostatin receptors to act synergistcally
- Tumor control
  - Cytoreductive surgery is the mainstay of treatment and includes resection of primary tumor, ablative therapy or resection of hepatic metastasis

QUESTIONS

- A 54 yr old male reports a 2 month history of abdominal pain and significant weight loss. He had undergone upper endoscopy, lower endoscopy, and CT, all of which is normal. On a barium upper GI study with small bowel follow through, he was noted to have a mass in his mid ileum. A surgical exploration he is found to have carcinoid on frozen section. Which of the following is true?
- A. The prognosis is related to tumor size, location and histologic pattern
- B. The cell of origin is the Kupffer cell
- C. The rectum is the most common site of origin
- D. Carcinoid tumors are usually easily palpable on external physical examination of the bowel
- E. Resection is not indicated in patients with metastatic disease.

QUESTIONS

- On abdominal exploration for a suspected carcinoid tumor a 2cm mass is found at the terminal ileum. No liver lesions were detected on preoperative imagining or with intraoperative palpation. What is the best treatment option for this patient?
- A. Segmental resection
- B. Medical therapy with octreotide
- C. Resection of the terminal ileum with preservation of the ileocecal valve
- D Right hemicolectomy with wide resection of the terminal ileum
- E. Neoadjuvant therapy with streptozotocin and 5 FU.

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