Surgical Therapy for Carcinoid and PNETs

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Carcinoid Tumors

- Epidemiology
- 12,000 new cases per year
- 1% of GI cancer, 50% of intestinal cancer
- Small intestine – 40% of GI carcinoids
- Rectum – 25% of GI carcinoids
- Appendix – 25% of GI carcinoids
- 20%-30% of small bowel carcinoids are multiple
- Average age at diagnosis - mid-60's

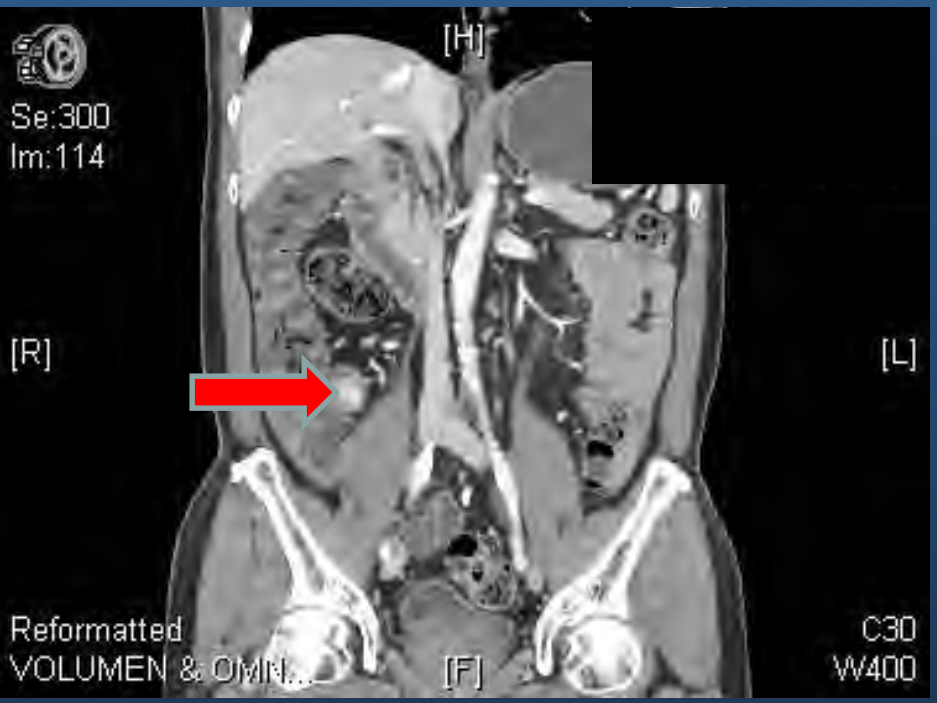
Clinical Presentation

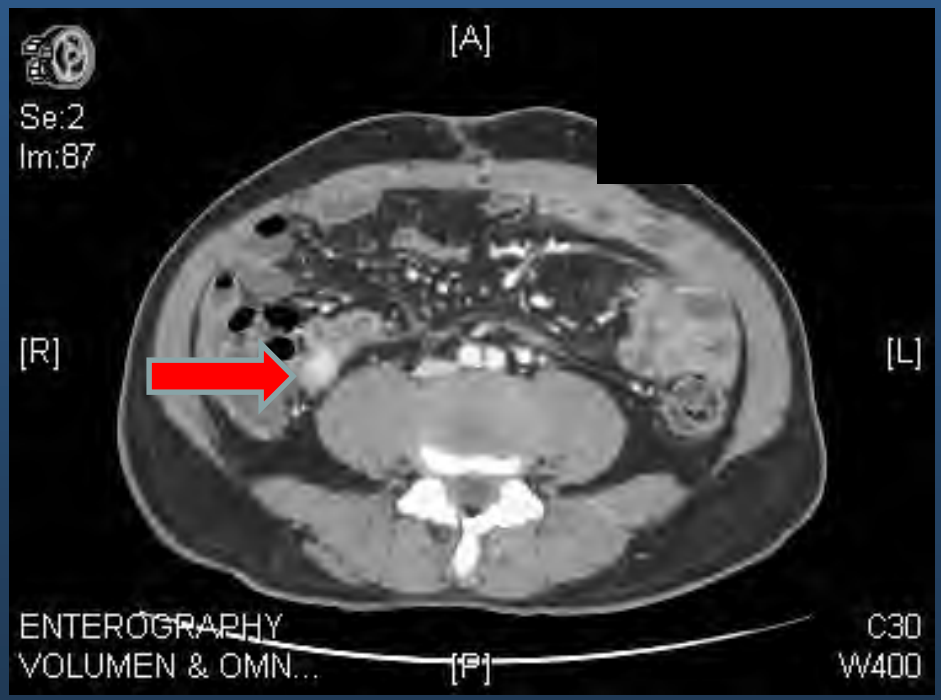
- Abdominal pain
- Weight loss
- Obstruction
- Diarrhea
- Intussusception
- Perforation
- GI bleeding
- Jaundice
- Pancreatitis

Work-up

- Enteroclysis
- CT enterography
- EGD
- Double balloon endoscopy
- Capsule endoscopy
- Octreotide scan
- MRI

CT Enterography





NETs are hypervascular on CT

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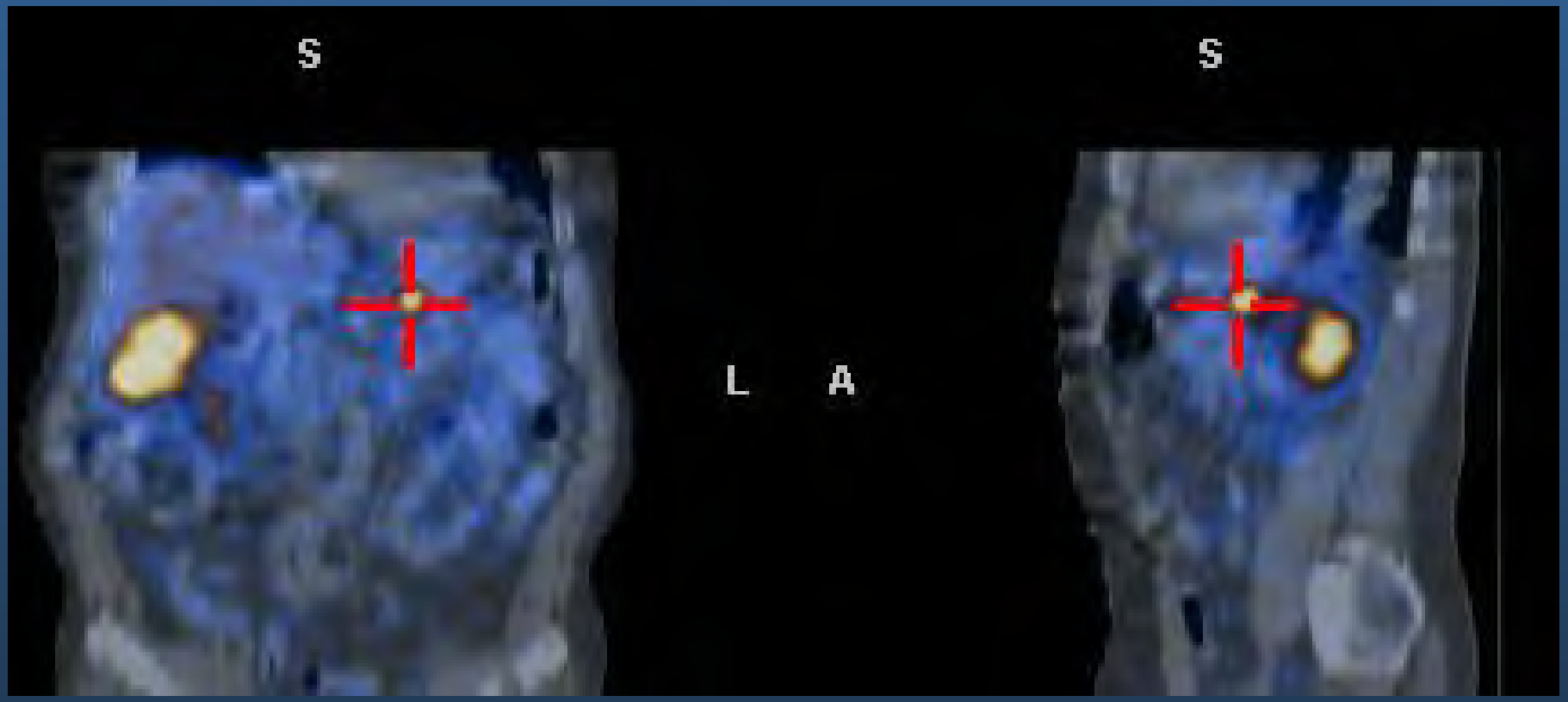
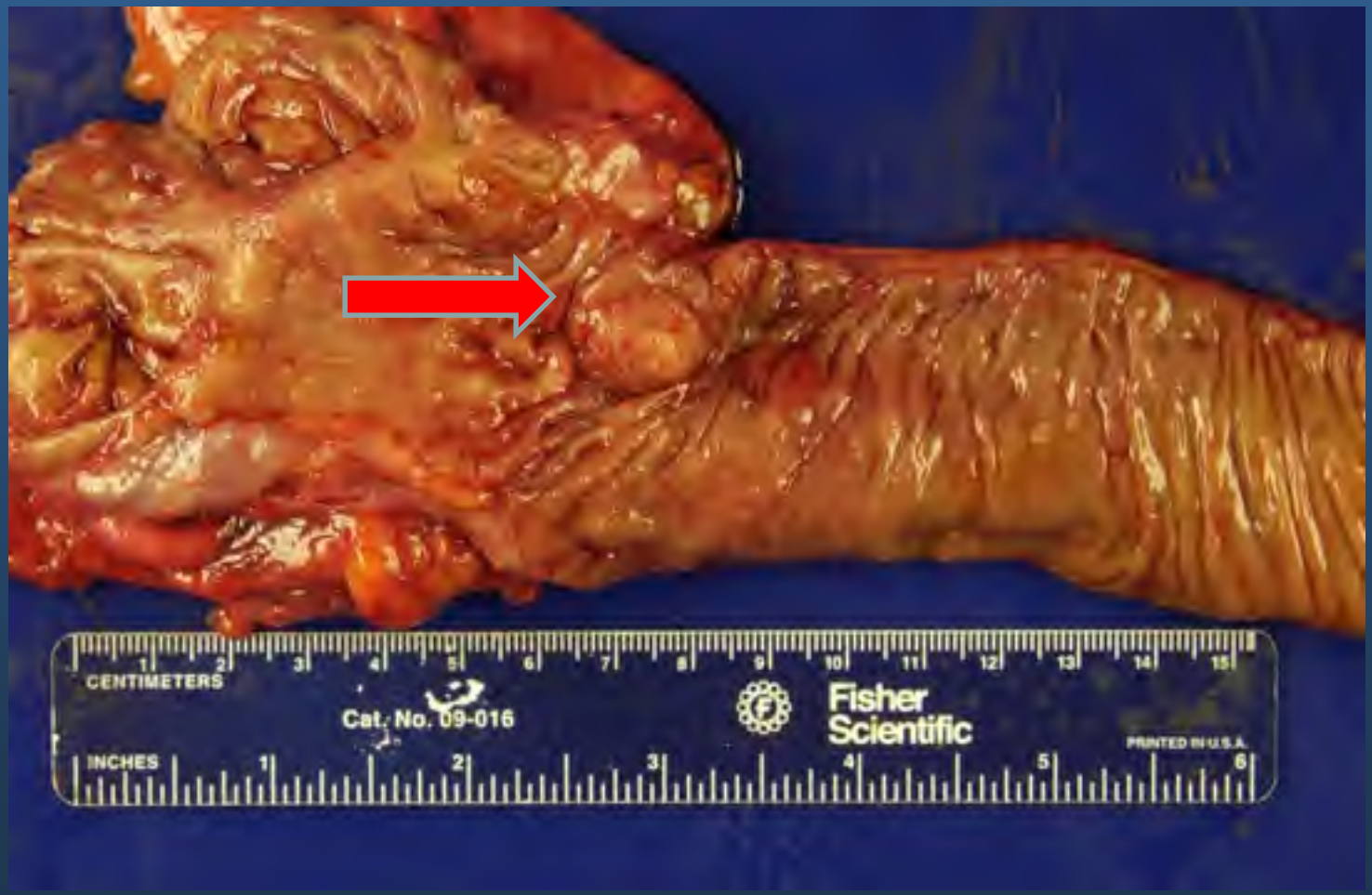
Nuclear Octreoscan



Pathology



Gastric Carcinoids

- 0.3% of all gastric neoplasms
- 3 types

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Gastric Carcinoids

- Type I
  - 75% of gastric carcinoids
  - Associated with chronic atrophic gastritis – check anti-parietal antibody
  - Associated with achlorhydria and hypergastrinemia – gastric pH probe not acidotic
  - 70-80 years old
  - Female > male
  - Tumors often < 1 cm
  - Metastasize in 10% of cases
  - Indolent – nearly 100% 5-yr survival
  - Not associated with carcinoid syndrome

Gastric Carcinoids

- Type II
  - 5% of gastric carcinoids
  - Associated with MEN1 and ZES
  - Gastric pH probe acidotic
  - Female = male
  - Tumors often < 1.5 cm
  - Metastasize in 25% of cases
  - Indolent course

Gastric Carcinoids

- Type III
  - 15-25% of gastric carcinoids
  - Sporadic carcinoids
  - Larger tumors
  - Metastasize to liver in 65% of cases
  - More aggressive course than types 1 and 2
  - 50% 5-yr survival
  - Develop atypical carcinoid syndrome
    - Pruritic patchy cutaneous flushes (due to histamine)

Small bowel and Colon

- Midgut carcinoid
  - 5-7% develop carcinoid syndrome (90% of all carcinoid syndrome)
  - Intense fibrosing reaction in mesentery and retroperitoneum (may cause small bowel or ureteral obstruction)
- Appendix
  - Often discovered incidentally
- Hindgut
  - Often found incidentally at colonoscopy

Treatment

- Gastric
- Types I and II
  - Endoscopic treatment if < 1 cm
  - Surgery (partial or total gastrectomy and lymphadenectomy) if > 2 cm
  - Local excision ± antrectomy (gastrin-producing cells) for 1-2 cm
- Type III
  - Surgery (partial or total gastrectomy and lymphadenectomy)

Treatment

- Duodenal
  - Endoscopic treatment if < 1 cm
  - Surgery (Whipple) if > 2 cm
  - Controversial for 1-2 cm
- Small Bowel
  - Segmental resection and lymphadenectomy
- Appendix
  - Appendectomy if < 2cm and tip location
  - Right colectomy if > 2 cm or location at base

Treatment

- Colon
  - Segmental resection and lymphadenectomy
- Rectal
  - Endoscopic treatment if < 1 cm
  - Surgery (LAR or APR) if > 2 cm
  - Controversial for 1-2 cm

Prognosis

- Indicators of aggressiveness
  - Lymphovascular invasion
  - Mitotic index
  - Grade
  - Size
  - Ki-67

Prognosis

5 year survival

	Locoregional	Nodal metastasis	Distant metastasis
Foregut	74%	40%	18%
Midgut	80%	75%	35%
Hindgut	76%	46%	19%
Appendix	94%	85%	34%

Carcinoid Syndrome

- 10-18% of all patients
- 40-50% of patients with advanced disease
- Serotonins, tachykinins, and histamine
- Mostly midgut
- Liver metastatses
  - Hepatic inactivation of active metabolite
- Flushing, diarrhea, wheezing, pellagra, right heart dysfunction

Carcinoid Syndrome

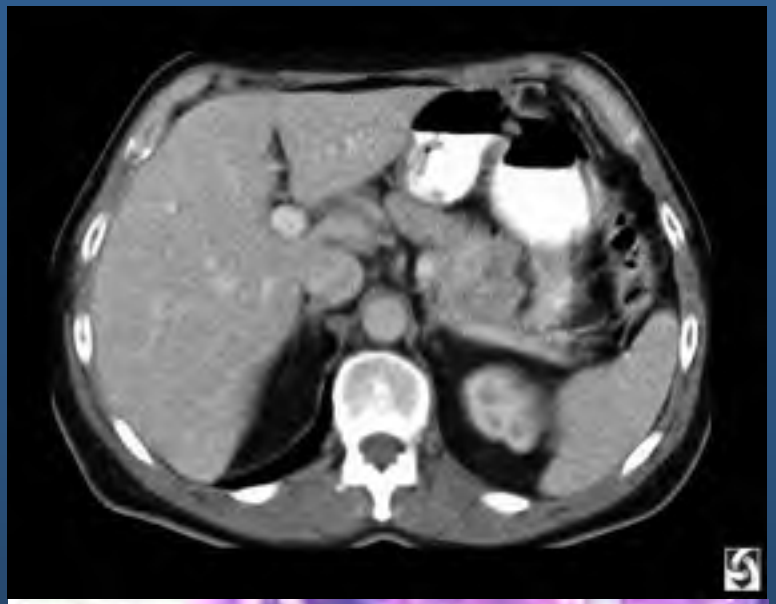
- Flushing
  - 85%, face most common, lasts 2-10 minutes
- Diarrhea
  - 80%, watery, non-bloody, most debilitating symptom
- Wheezing
  - 1-20%, often occurs with flushing episodes
- Right heart dysfunction
  - Valvular fibrosis
- Pellagra
  - Tryptophan deficiency, dermatitis, dementia

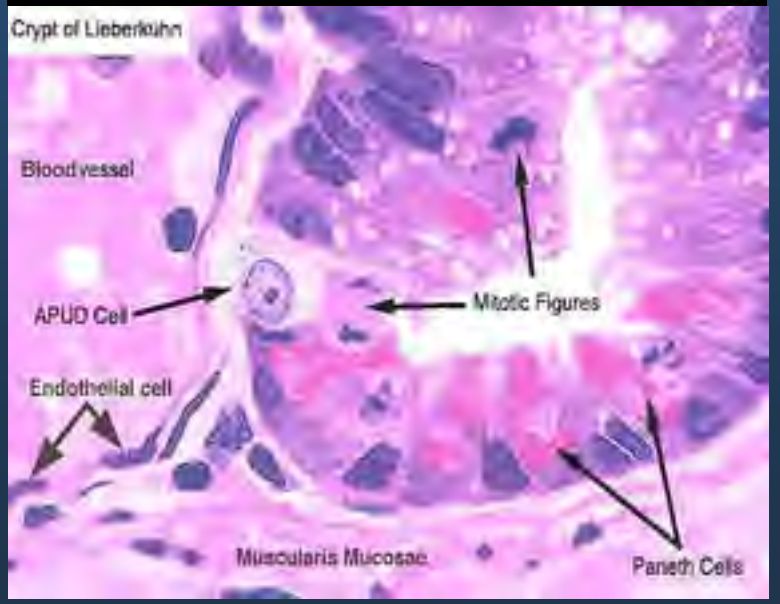
Liver Metastases

- Typically, patients live >5 years after development of metastases
- Liver Surgery
  - Resection for cure if possible
    - High recurrence rate
  - Resection for symptom palliation if 90% of tumor burden can be resected
    - Controversial
  - Hepatic artery embolization for symptom palliation
  - Ablation can be used alone or in combination

PNETs

- 1% of all pancreatic neoplasms
- Arise from amine precursor uptake decarboxylase (APUD) cells
- Produce aberrant physiology due to hormone secretion
- Nonfunctioning tumors represent up to 50% of cases
- Natural history and degree of malignancy variable
- Associated with MEN 1





Types of PNET

Table 1

Characteristics of Endocrine Tumors of the Pancreas

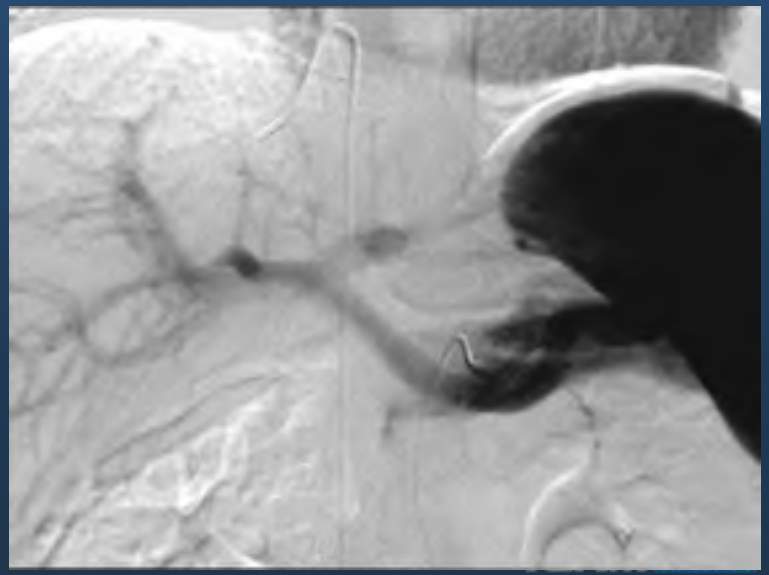
Tumor	Major Clinical Symptom	Predominant Hormone	Islet Cell Type	Malignant Potential	Other Clinical Features
Gastrinoma	Recurrent peptic ulcer	Gastrin	γ	Very high	Diarrhea/steatorrhea
Insulinoma	Hypoglycemia (fasting or nocturnal)	Insulin	β	Low	Catecholamine excess
Glucagonoma	Diabetes mellitus, Migratory necrolytic erythema	Glucagon	α	Very high	Panhypoaminoaciduria, Thromboembolism, Weight loss
VIPoma	Watery diarrhea, hypokalemia, achlorhydria (WDHA syndrome)	Vasoactive intestinal polypeptide (VIP)	δ	High	Metabolic acidosis, Hyperglycemia, Hypercalcemia, flushing
Somatostatinoma	Diabetes mellitus Diarrhea/steatorrhea	Somatostatin	δ	Very high	Hypochlorhydria, Weight loss, Gall bladder disease
PPoma	Hepatomegaly, Abdominal pain	Pancreatic polypeptide (PP)	PP cells	Very high	Occasional watery diarrhea

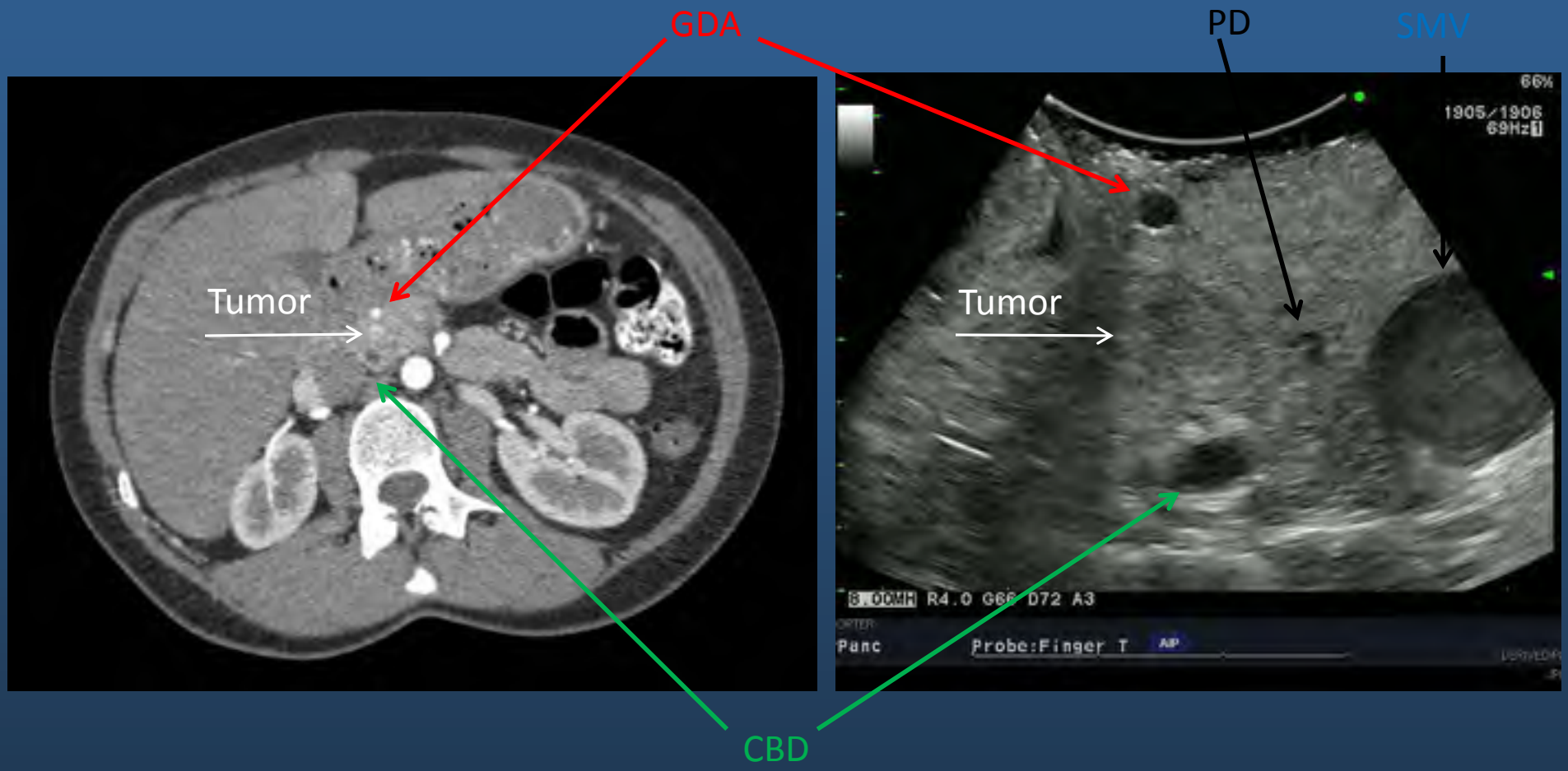
Staging principles

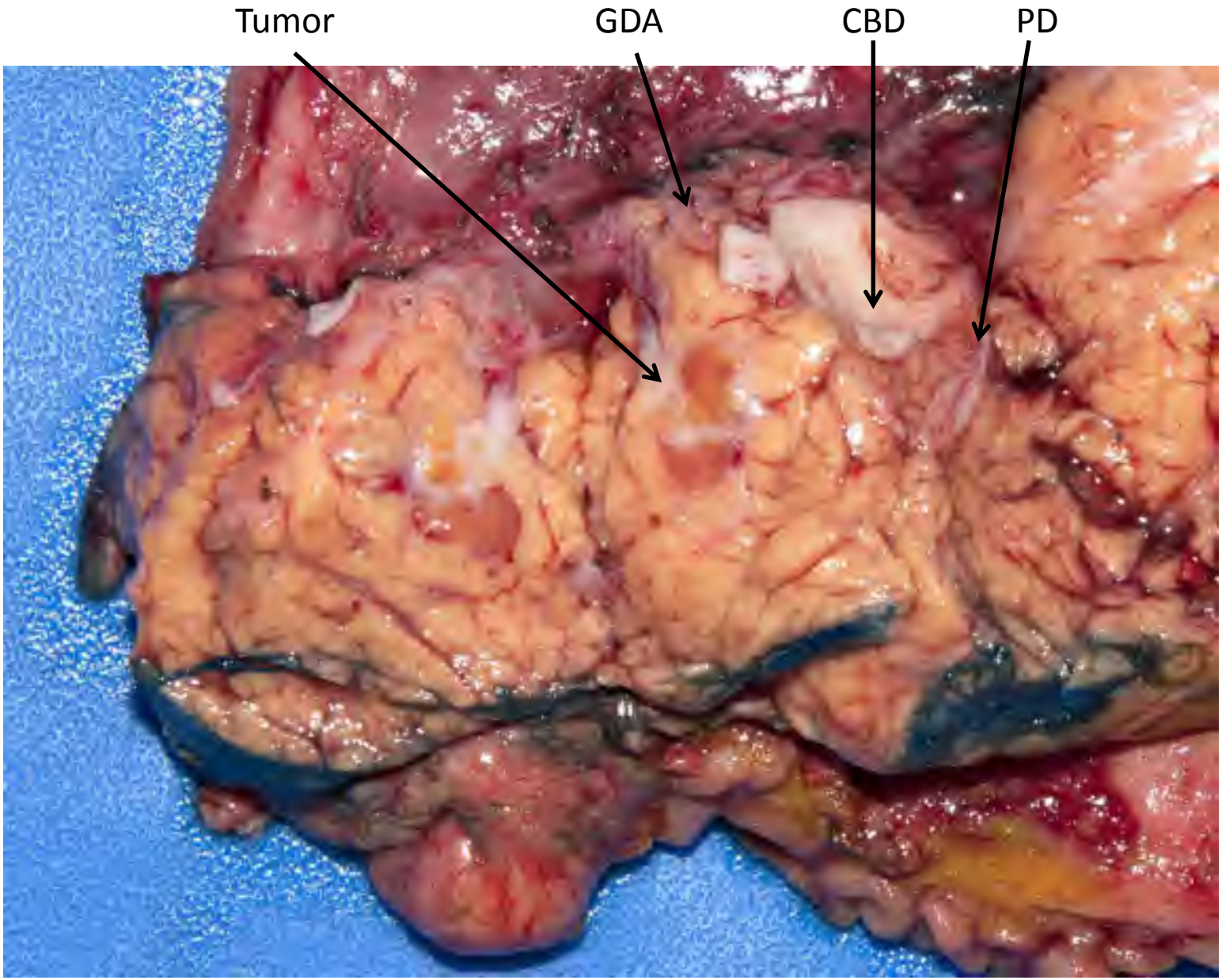
- H & Ps – watch out for signs of MEN I
- CT or MRI
- Octreotide Scan
- Elektrolytes, Chromogranin A levels
- Specific blood work see resp. chapters

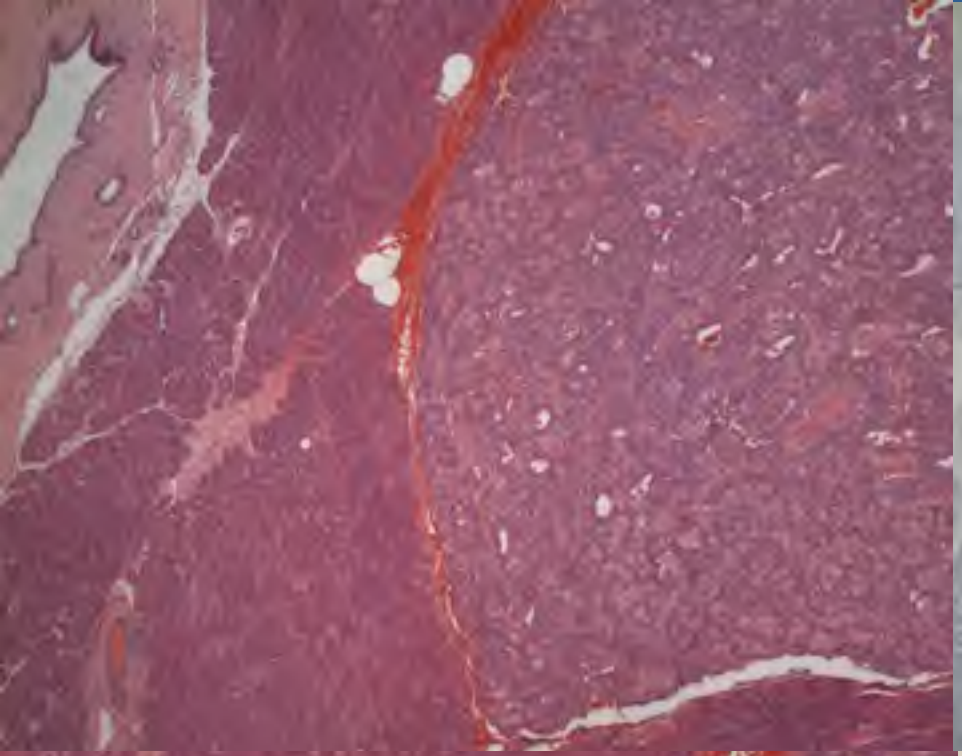
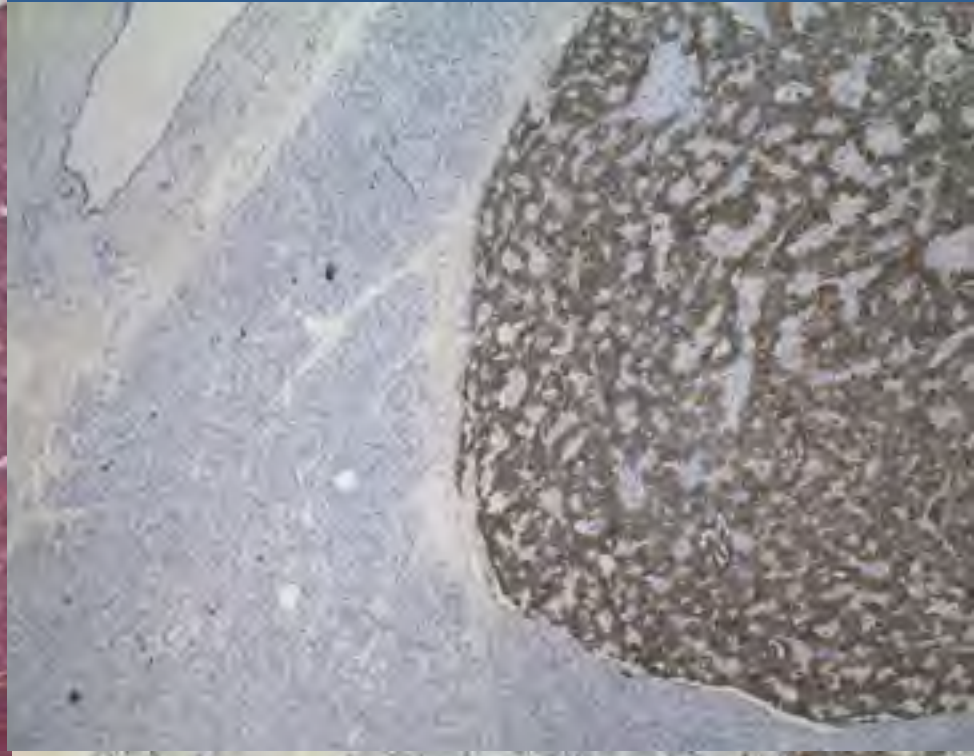
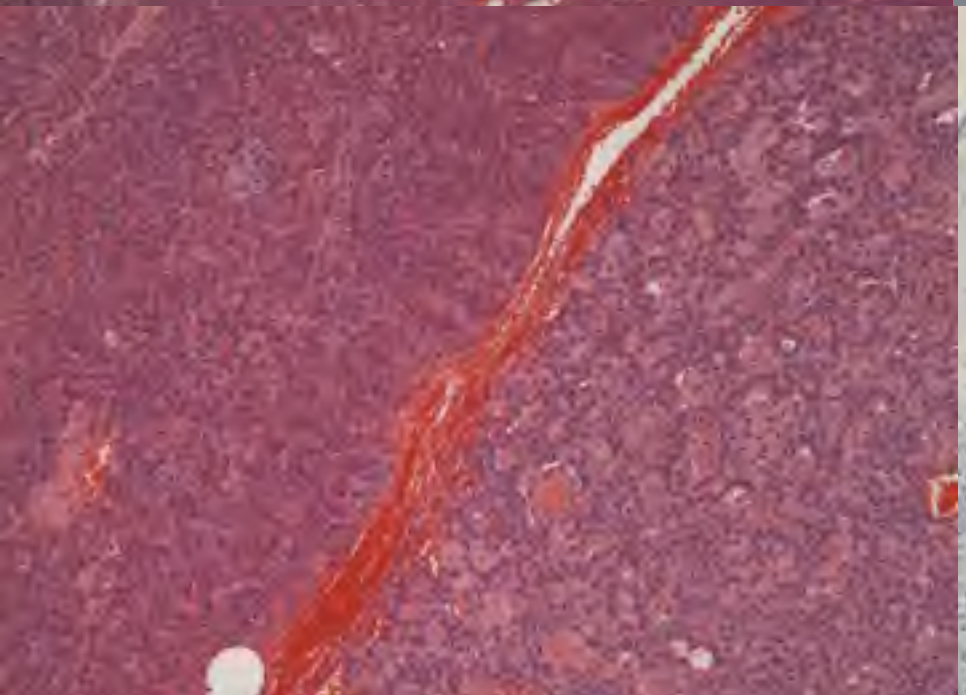
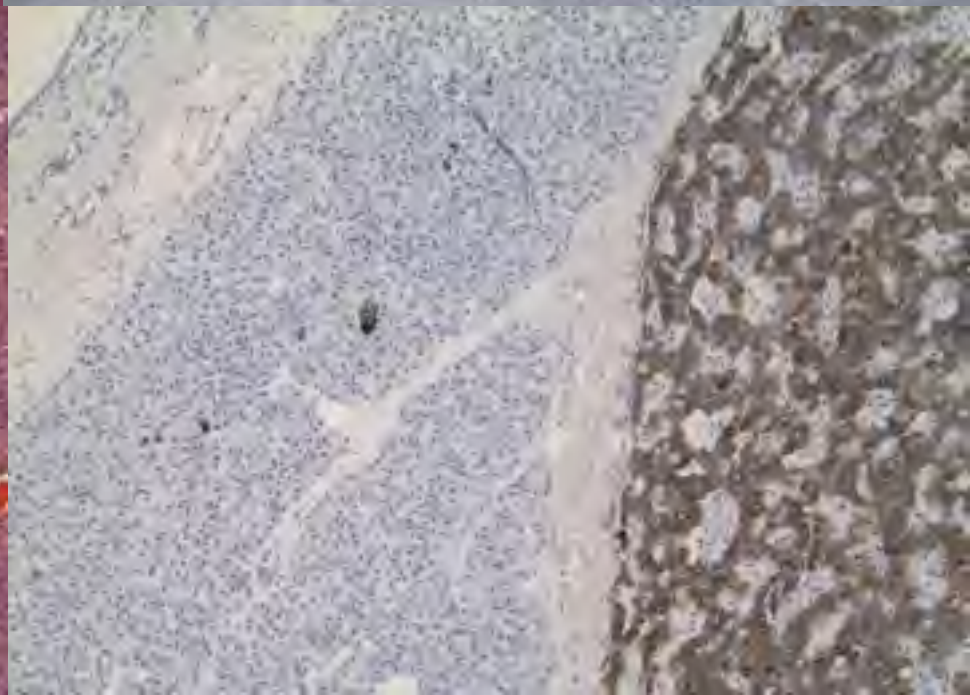
Insulinoma

- Most common (up to 50%), 90% benign
- Clinical: Whipple's triad
  - Symptoms of hypoglycemia with fasting/exercise
  - Plasma glucose less than 50 mg/dl
  - Relief of symptoms with oral/IV glucose
- Diagnosed by 72 hr fast
  - Elevated insulin (5mU/ml) in the presence of hypoglycemia (glucose < 40 mg/dl)
  - Insulin:Glucose ratio greater than 0.3
  - Elevated C-peptide
- Intraarterial calcium stimulation with portal venous sampling
- Transgastric ultrasound
- Treat symptoms with diazoxide



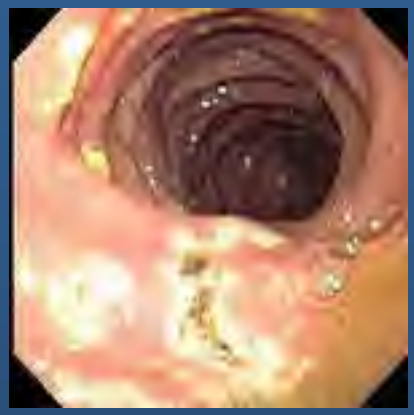

GDA
PD
SMV
Tumor
Tumor
CBD
66%
1905/1906
69Hz
Panc
Probe:Finger T

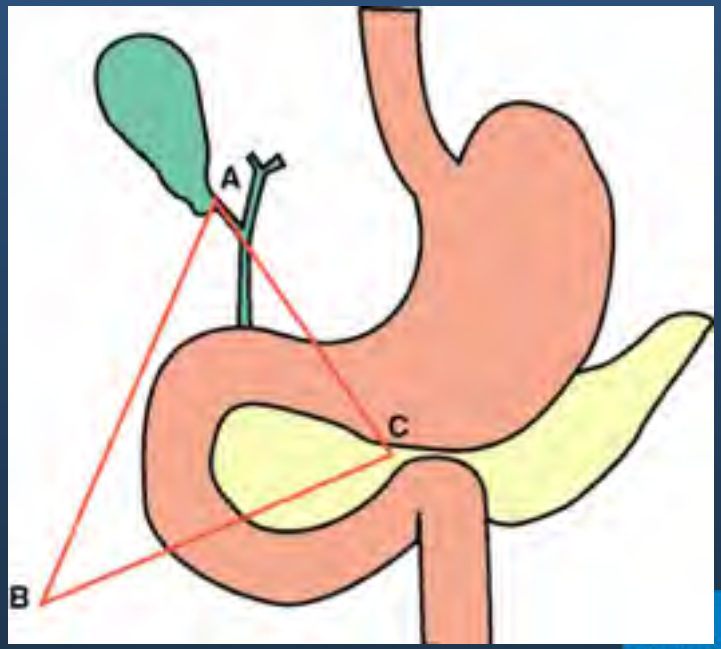

Tumor
GDA
CBD
PD

Gastrinoma

- Most common PET in MEN 1
  60-90% are malignant
  Sporadic worse than MEN1
- Zollinger-Ellison Syndrome
  - "ulcerogenic hormone factor"
  - Multiple and atypical locations
  - Fail or recur despite medical therapy
  - Ulcers with hyperparathyroidism
- Diagnosis
  - Serum gastrin >1000 pg/ml
  - Secretin stimulation test (gastrin>200)
  - PPIs, G-cell hyperplasia, atrophic gastritis, retained antrum, GOO, renal failure
- Localization
  - Gastrinoma (Passaro's) Triangle





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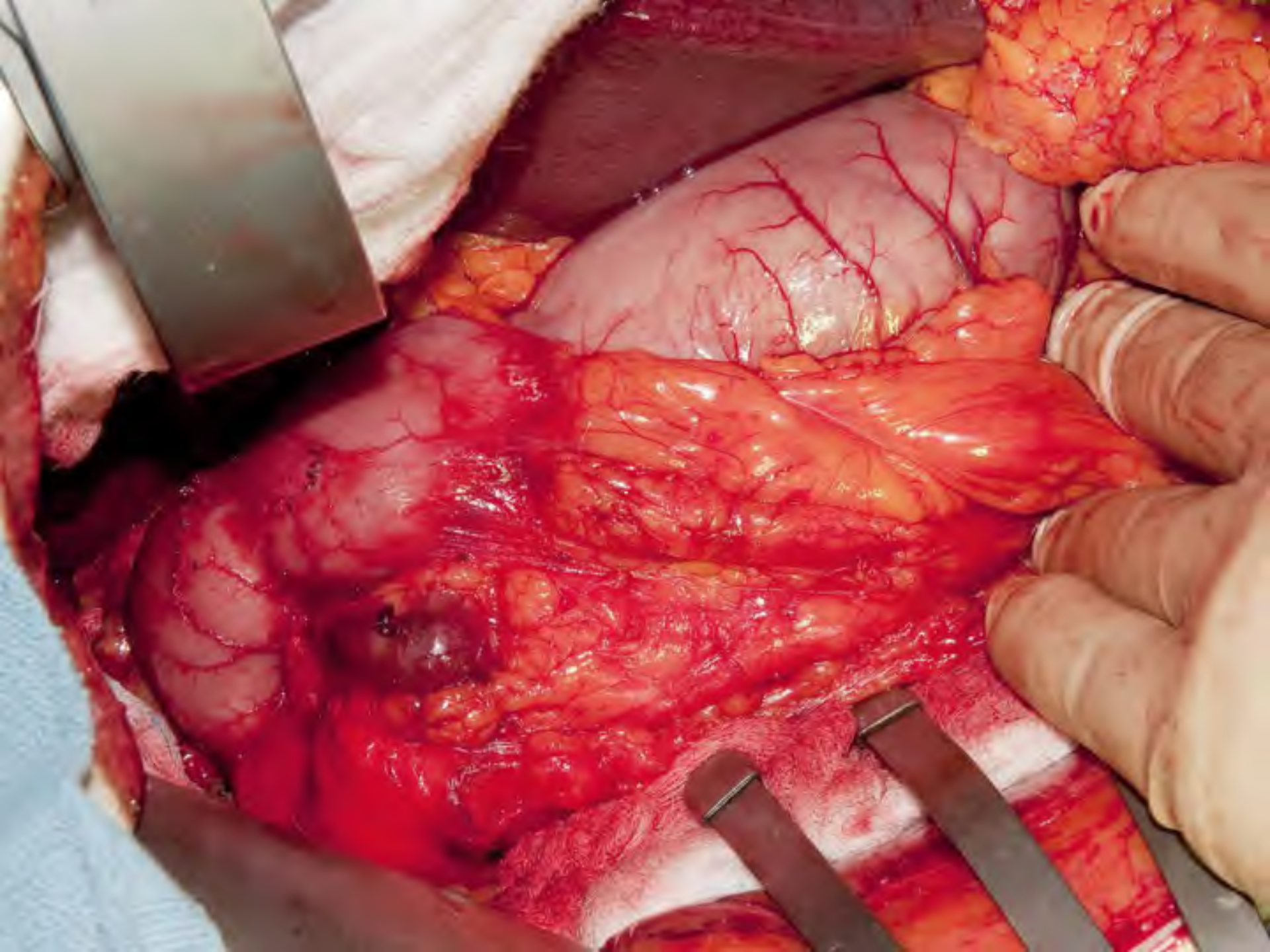
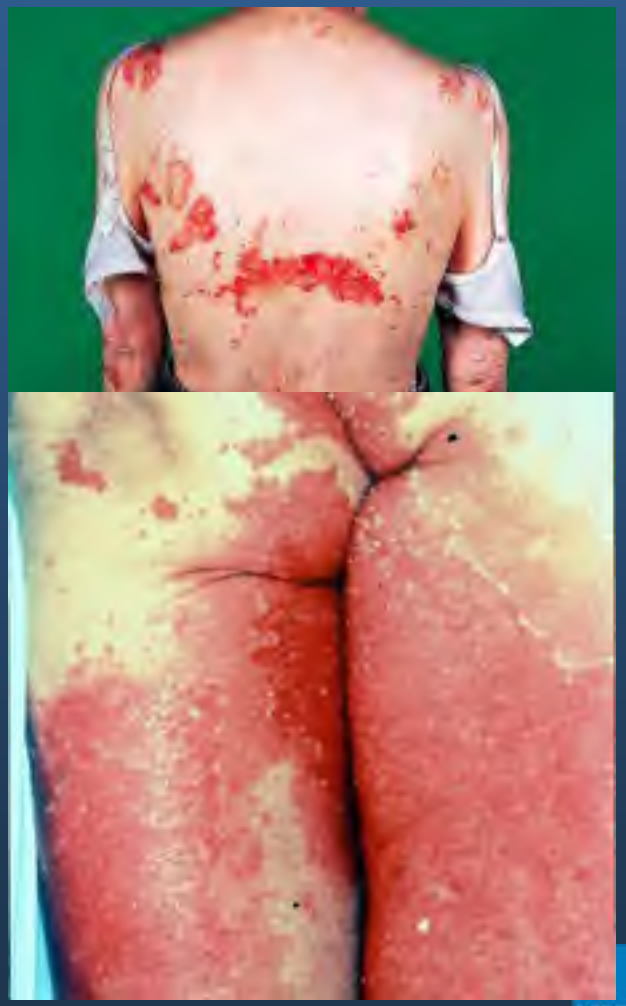


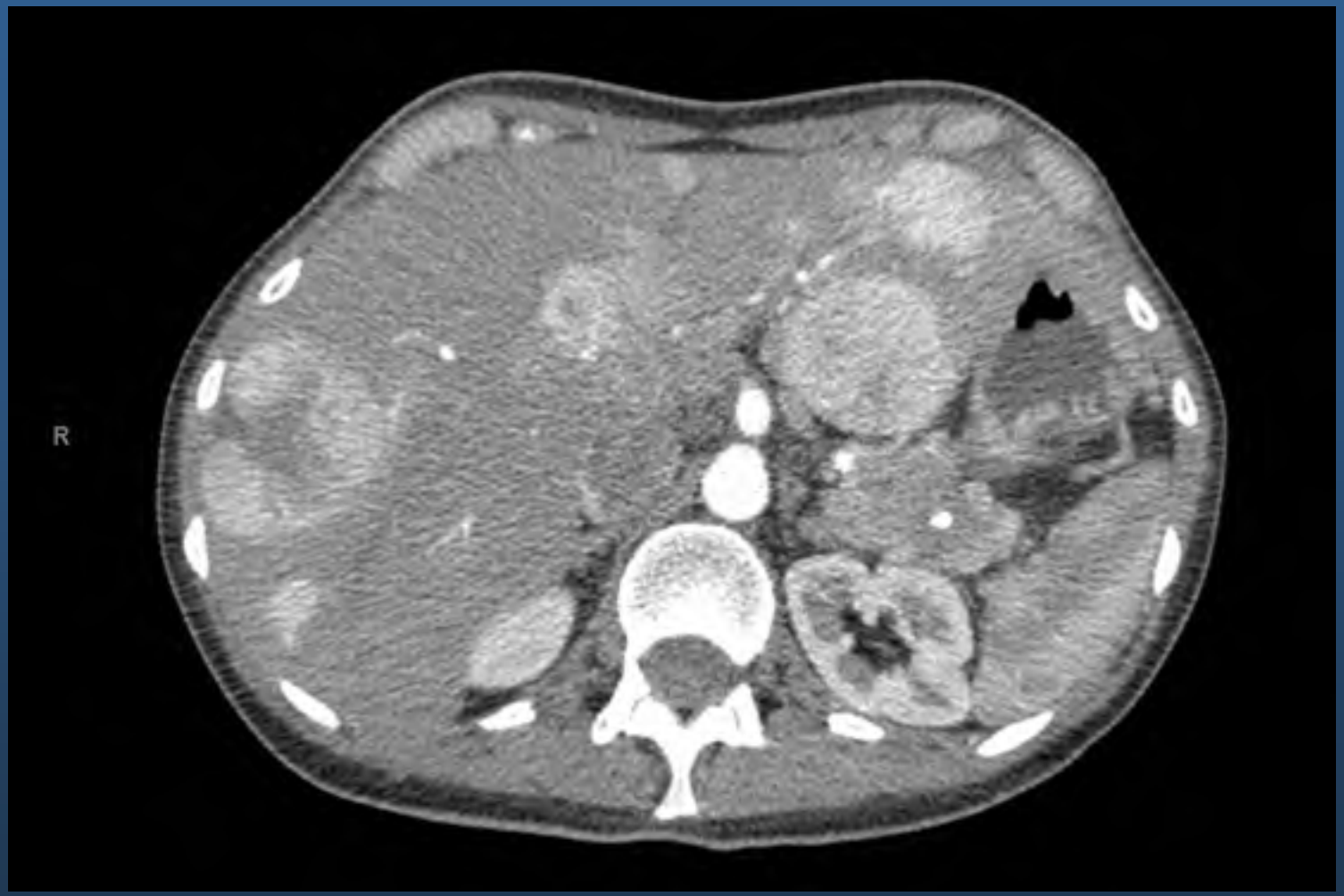
Multiple endocrine Neoplasia

Organ	Neoplasm	Patients Affected (%)
MEN1		
Parathyroid	Hyperplasia	98
Pituitary	Adenoma	35
Pancreas	Islet cell	50
Multiple	Carcinoid	3
Adrenal	Cortical adenoma	Uncommon
	Cortical carcinoma	rare
Thyroid	Adenoma	Uncommon
	Papillary	Uncommon
Adipocyte	Lipoma	Uncommon

Glucagonoma

- Clinical:
  - 3 Ds (Diabetes, Dermatitis, Depression)
  - Migratory necrolytic erythema
  - Predisposition to VTE (30%)
- Usually malignant and in tail of pancreas
- Lab:
  - Glucagon levels > 1000 pg/ml
  - Secretin stimulation
- Treat with high protein diet, zinc, and octreotide





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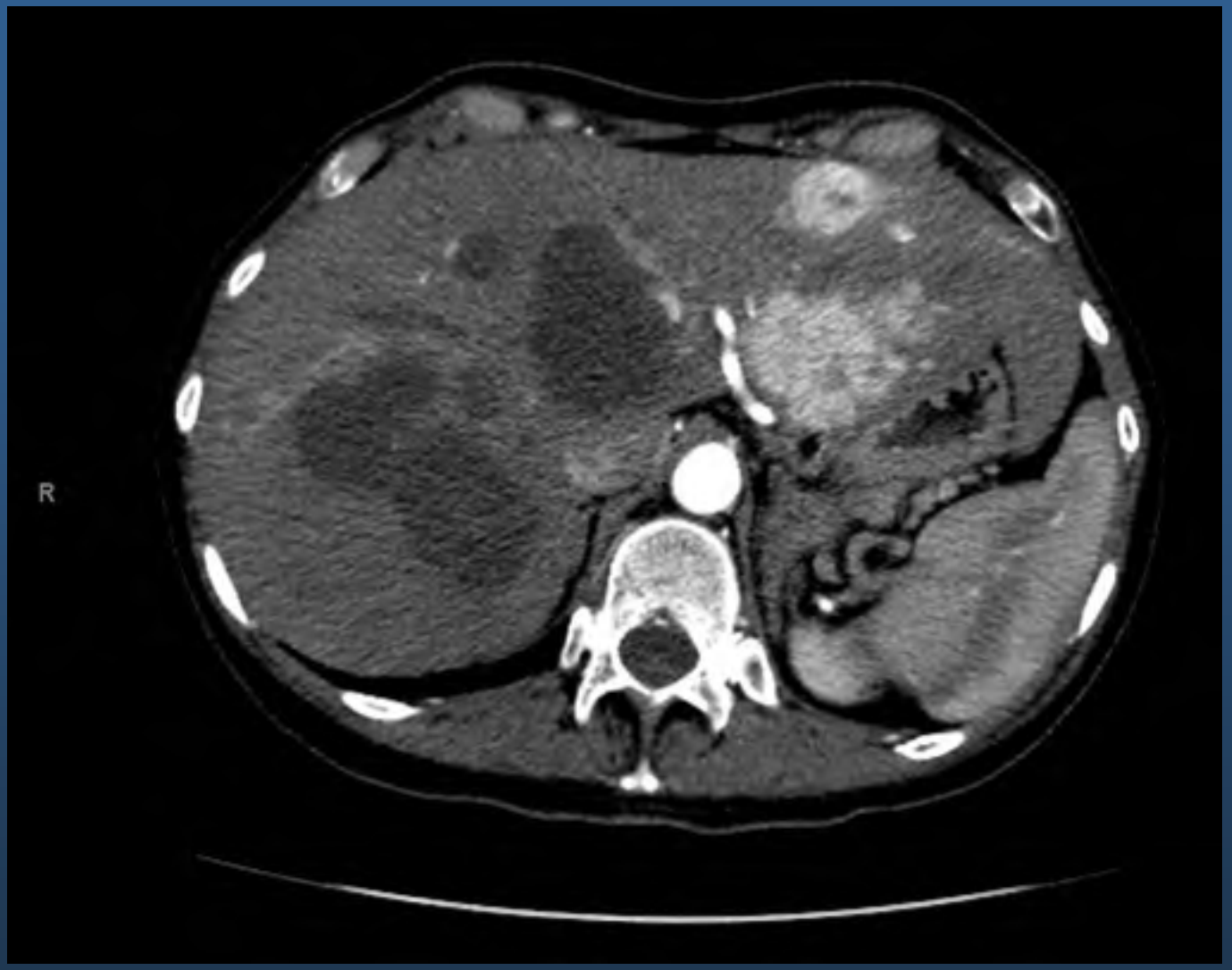
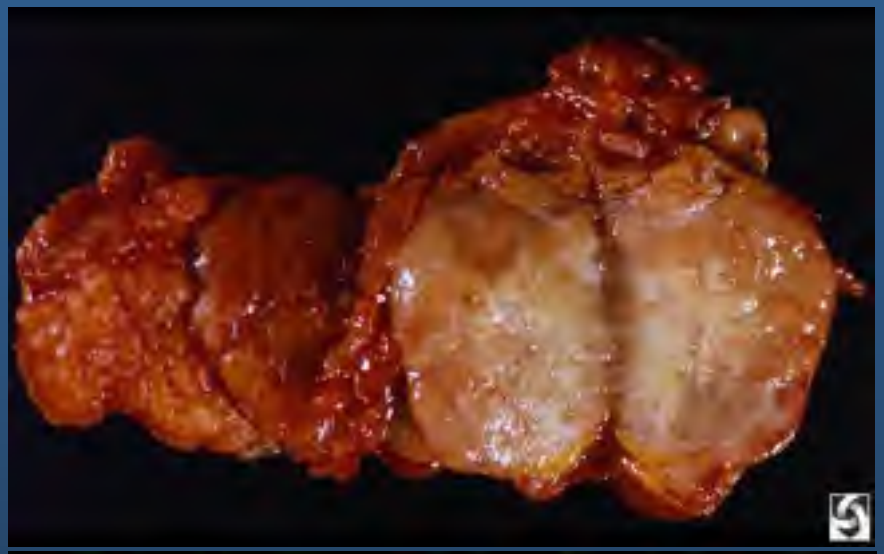


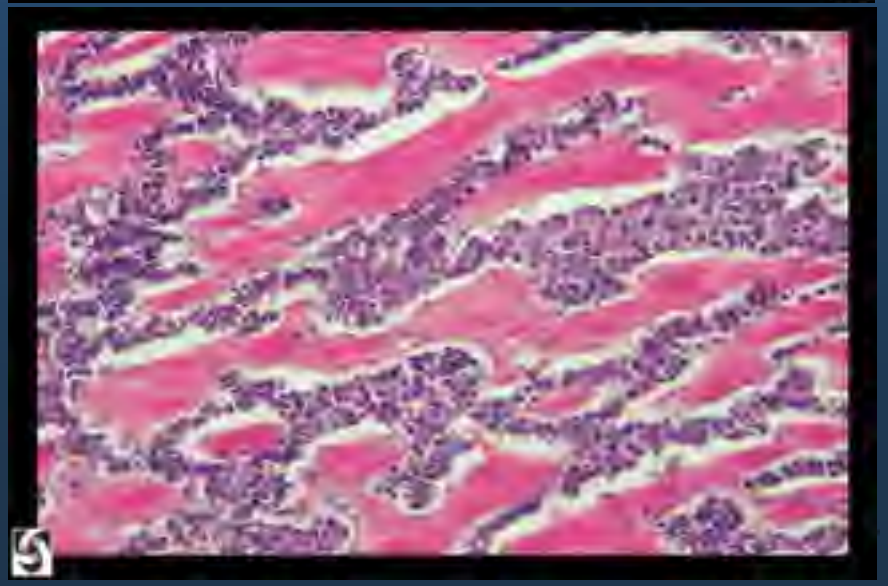
Others

- Somatostatinoma
  - Cholelithiasis, type 2 diabetes and steatorrhea
  - Difficult diagnosis due to nonspecific symptoms
  - Duodenal tumors associated with neurofibromas and asymptomatic
- VIPoma
  - Vasoactive intestinal peptide
  - WDHA syndrome (watery diarrhea, hypokalemia, achlorhydria)
  - VIP levels of >200 pg/ml
  - Octreotide scan
  - Requires electrolyte replacement, hydration and somatostatin
- PPoma
  - Pancreatic polypetide
  - Very rare

Nonfunctional tumors

- Typically present with mass effect of tumor (abdominal pain, weight loss, jaundice)
- Usually seen on CT, MRI, EUS
- Biochemical tests reveal hormone secretion but no clinical syndrome
- Can use chromogranin A levels to measure response
- Octreotide scan for localization





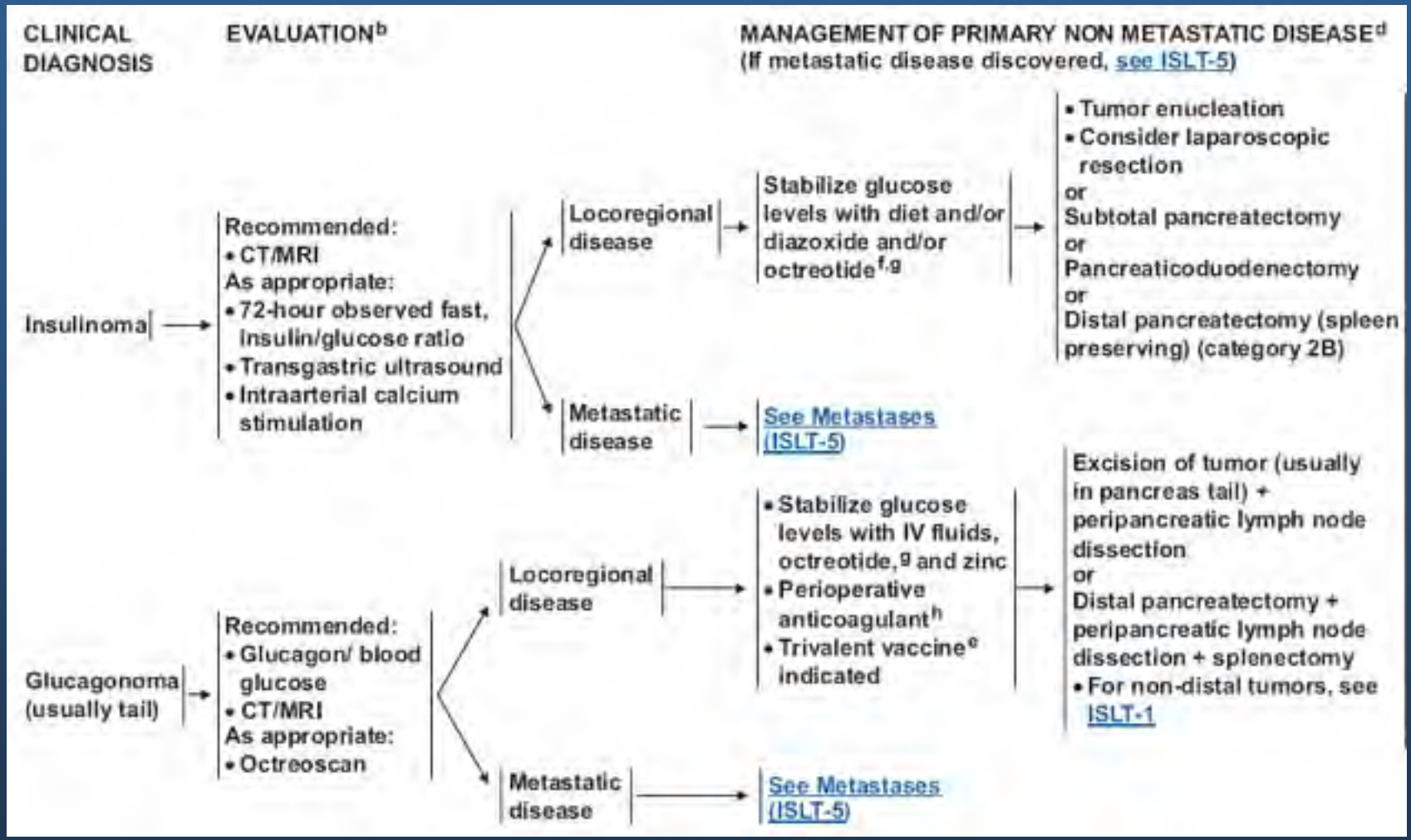
Surgical Principles

- Goal is to resect primary and localized metastases
- Reverse abnormal physiology and relieve symptoms
- Tumor localization when preoperative studies fail
- Midline or subcostal incision with careful inspection of liver, kocherization of duodenum (duodenotomy for gastrinomas), lymph node sampling (for gastrinomas) , palpation of gland
- Intraoperative endoscopy and ultrasound are useful adjuncts
- Enucleation preferred over resection if feasible

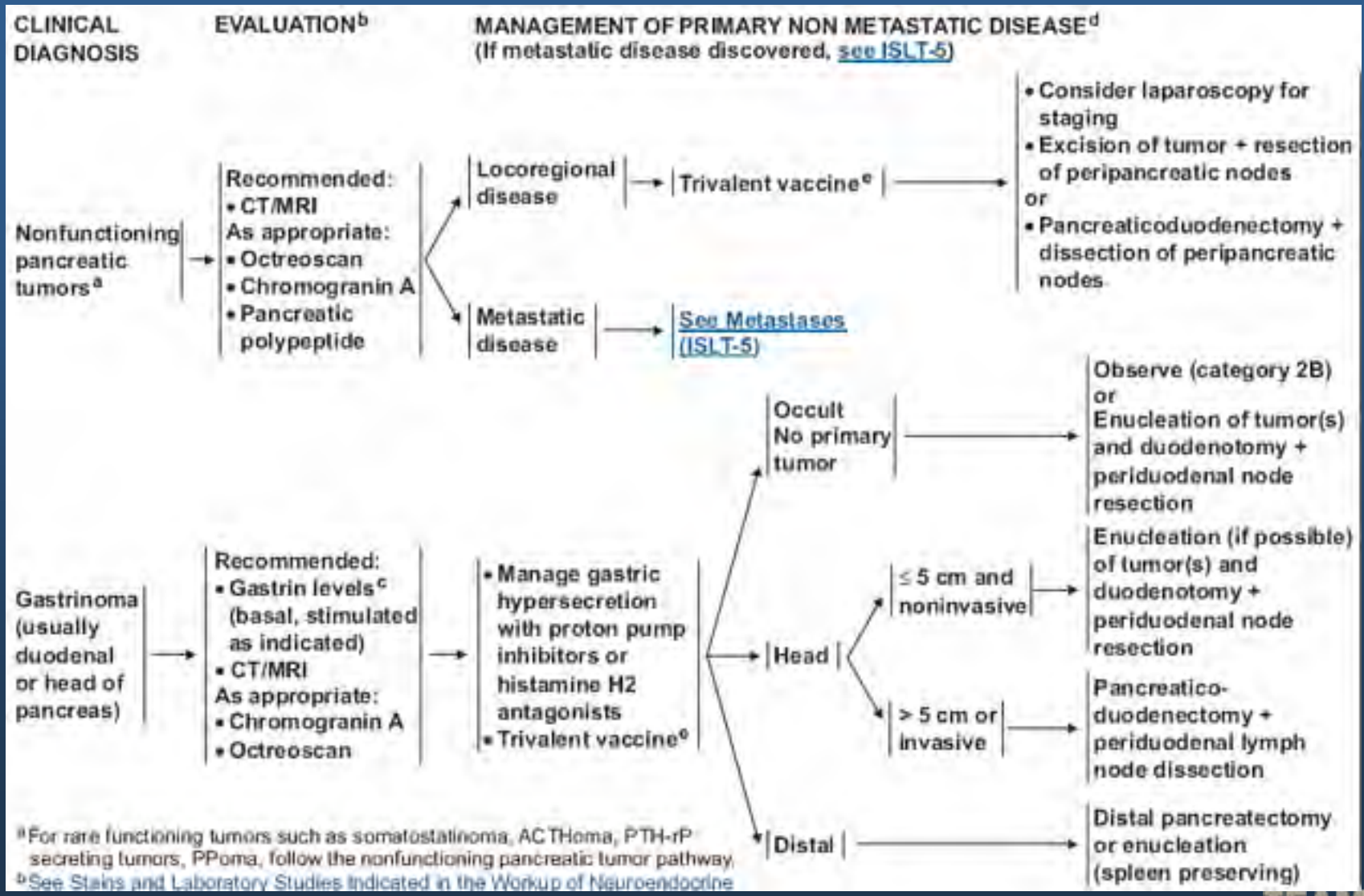
Treatment of Metastatic Disease

- Liver resection
  - <75% parenchyma
  - No evidence of extrahepatic disease
- Thermal Ablation
  - For lesions less than 3 cm
- Hepatic artery chemo and radioembolization
  - Palliative for symptomatic lesions
- Transplantation
  - Limited reports and role is controversial
- Hormonal (Octreotide) Therapy
- Targeted Therapy
  - Sunitib, Everoliums
- Cytotoxic chemotherapy
  - Streptozocin and doxorubicin
  - Dacarbazine
  - 5FU and capecitabine
  - Temozolomide

NCCN Guidelines



NCCN Guidelines



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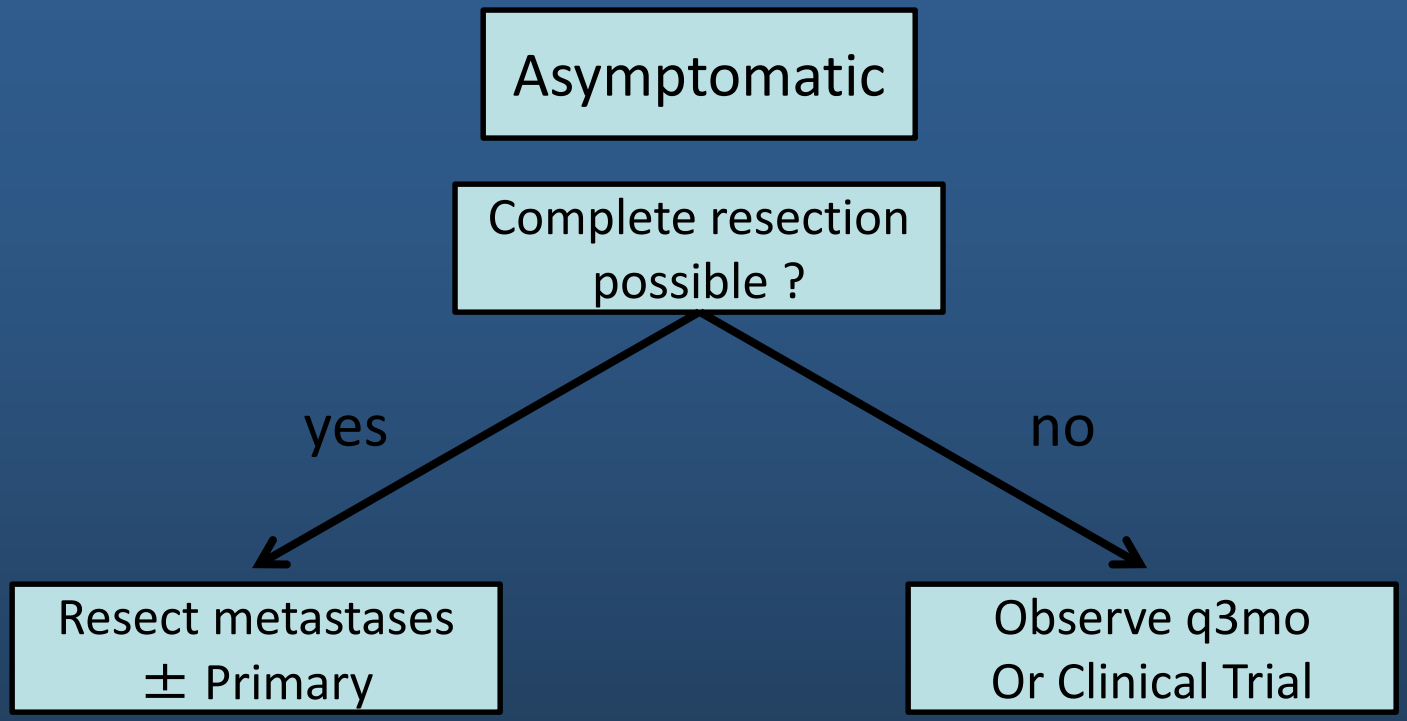
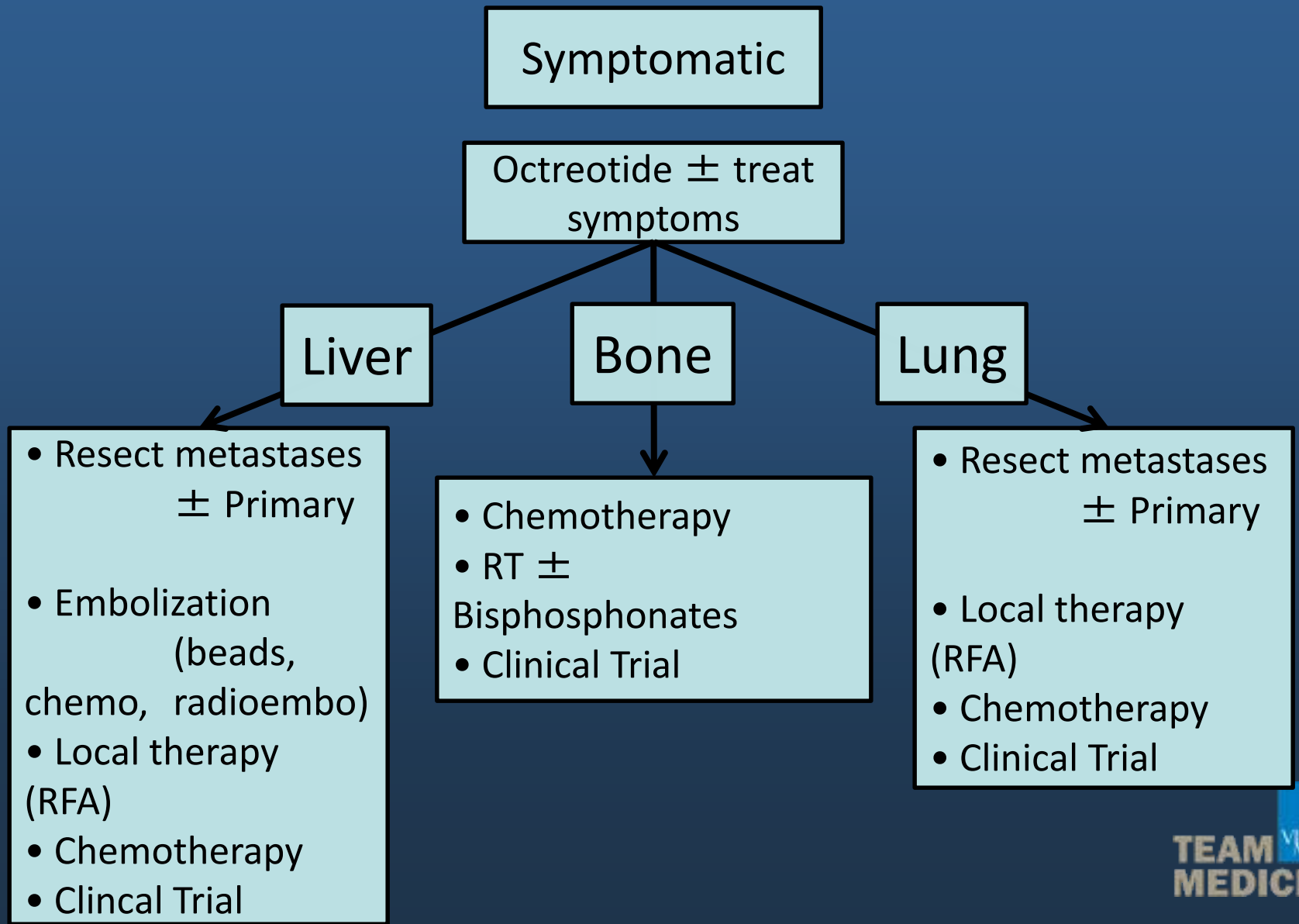
NCCN Guidelines – advanced or metastatic



NCCN Guidelines – advanced or metastatic



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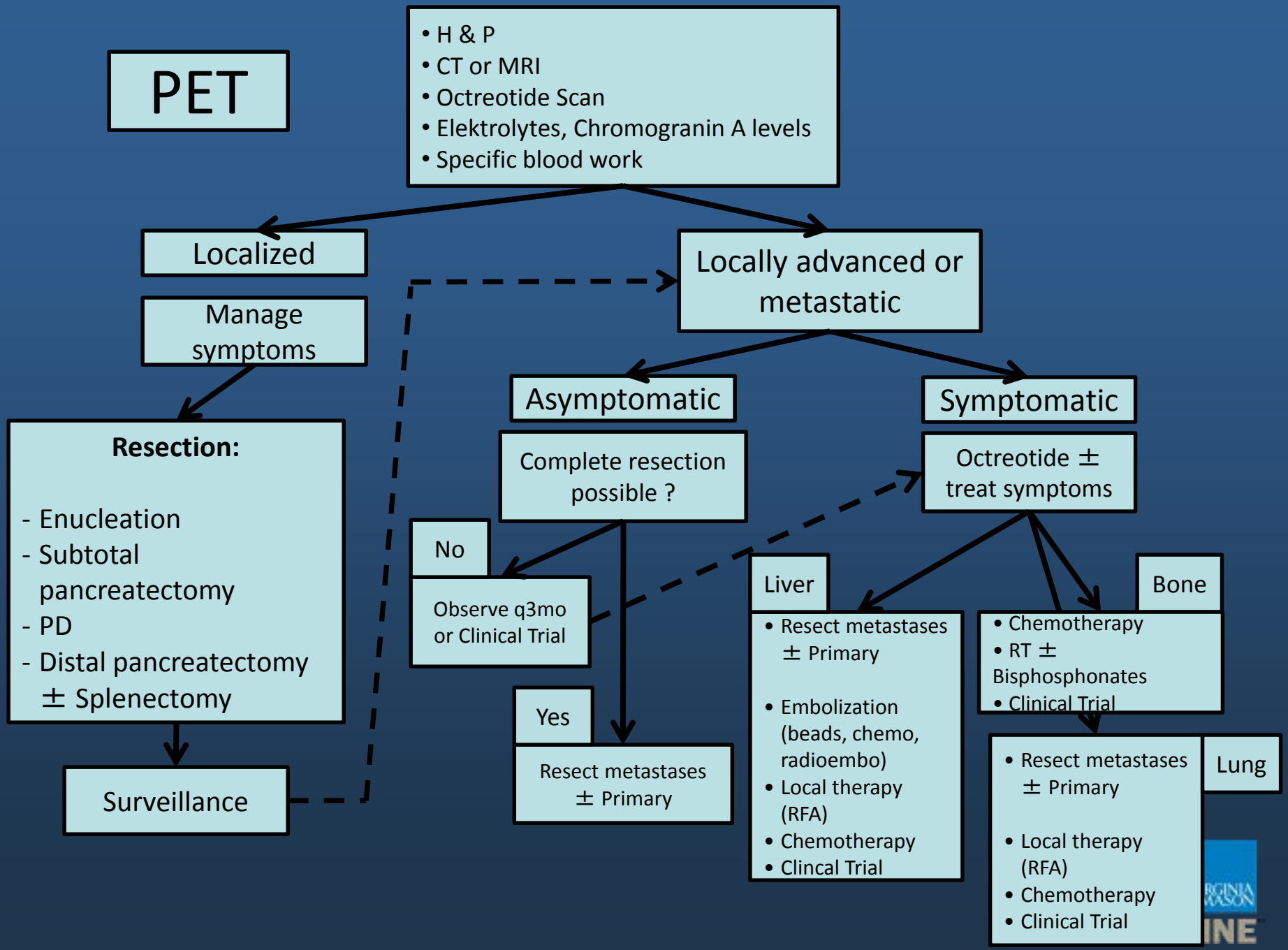
PET
• H & P
• CT or MRI
• Octreotide Scan
• Elektrolytes, Chromogranin A levels
• Specific blood work
Localized
Manage symptoms
Resection:
- Enucleation
- Subtotal pancreatectomy
- PD
- Distal pancreatectomy ± Splenectomy
Surveillance
Locally advanced or metastatic
Asymptomatic
Complete resection possible ?
No
Observe q3mo or Clinical Trial
Yes
Resect metastases ± Primary
Symptomatic
Octreotide ± treat symptoms
Liver
• Resect metastases ± Primary
• Embolization (beads, chemo, radioembo)
• Local therapy (RFA)
• Chemotherapy
• Clincal Trial
Bone
• Chemotherapy
• RT ± Bisphosphonates
• Clinical Trial
Lung
• Resect metastases ± Primary
• Local therapy (RFA)
• Chemotherapy
• Clinical Trial

Follow up

- First 3-12 months: - H & P, lab marker follow up
  - CT/MRI
- >12 months: - annual H & P, marker
  - CT/MRI as clinically indicated

Question

- What is the impact of aggressive surgical resection on survival in patients with asymptomatic metastatic carcinoid/PNET?

Medical therapy

- Somatostatin analogues: octreotide, lanreotide
  - *In vitro* studies demonstrate anti-angiogenic effects, apoptosis, inhibition of cell proliferation
  - *In vivo*, disease stabilization is more likely than disease regression
  - Median duration of disease stabilization is variable in literature (12-24mos)

Neuroendocrine metastases to the liver- considerations

- Completely different “natural history” of the disease (compared with other cancers)
- Inactivity of systemic chemotherapy
- Relative safety of hepatic resection

Concepts

- Although patients with NET met to liver “live longer”, they also “suffer longer”!
- Thus…
- If primary tumor is resectable/resected
- >90 % of the hepatic mets manageable with resection/ablation/embolization, we treat

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VM series

- 1998-2012
- N= 34 liver resections for NCRM
- N=22 non-neuroendocrine (ovarian, breast, pancreas, renal, testicular, sarcoma, gastric, anal)
- N=12 carcinoid/neuroendocrine

Comparison, Non-colorectal Mets to the Liver (VMMC)

Neuroendocrine/carcinoid

- N = 12
- 10/12 alive (83%) at ave 6.2 years
- Range 1-13 years
- Two deaths at 3, 8 yrs

Other (ovarian, breast…)

- N = 22
- N=18 (greater than 2 years f/u)
- 4 of these lost to f/u
- N=14
  - 7 alive (2-15 yrs)
  - 7 expired (3mos-13 yrs)
- 50% alive at 5 yrs

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Resection of Hepatic mets from Neuroendocrine Tumors– Sarmiento et al

- N= 170 patients over 20 years (1977-98)
- SB Carcinoid (90), Pancreas (52), lung (9), colon(5), rectum(1), unknown (8)
- Carcinoid (120), Functional NET (31), Nonfunctional NET (19)
- Complete resection 45%, “Palliative” resection 55% (>90 % hepatic tumor load)
- 64% had hormonal symptoms

Sarmiento et al, JACS 2003

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Sarmiento et al, cont'd

- Op mortality 1%
- 96% achieved symptomatic improvement
- But sx recurred in 59% at 5 years
- Recurrent tumor in 84% at 5 yrs
- Overall survival 61% at 5yrs, 35% at 10 yrs

Sarmiento et al, JACS 2003

Surgical Treatment of Neuroendocrine Metastases to the Liver: A Plea for Resection to Increase Survival

Juan M Sarmiento, MD, Glenroy Heywood, MD, Joseph Rubin, MD, Duane M Ilstrup, MS, David M Nagorney, MD, FACS, Florencia G Que, MD, FACS

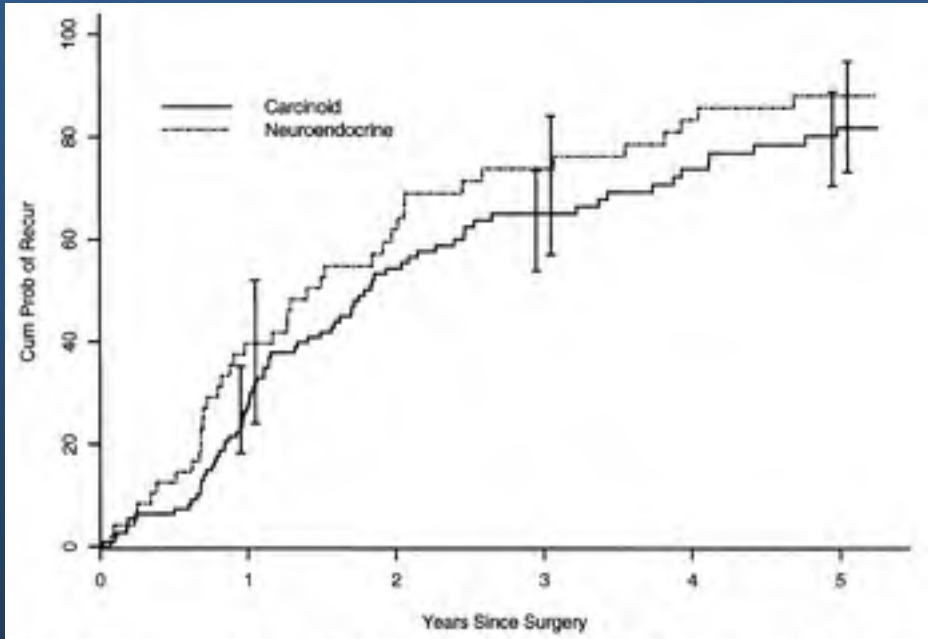

Figure 3. Recurrence rate was no different among patients with carcinoid versus islet cell tumors (82% versus 88%, respectively, at 5 years, p = 0.24 by the log-rank test). Cum Prob of Recur, cumulative probability of recurrence.

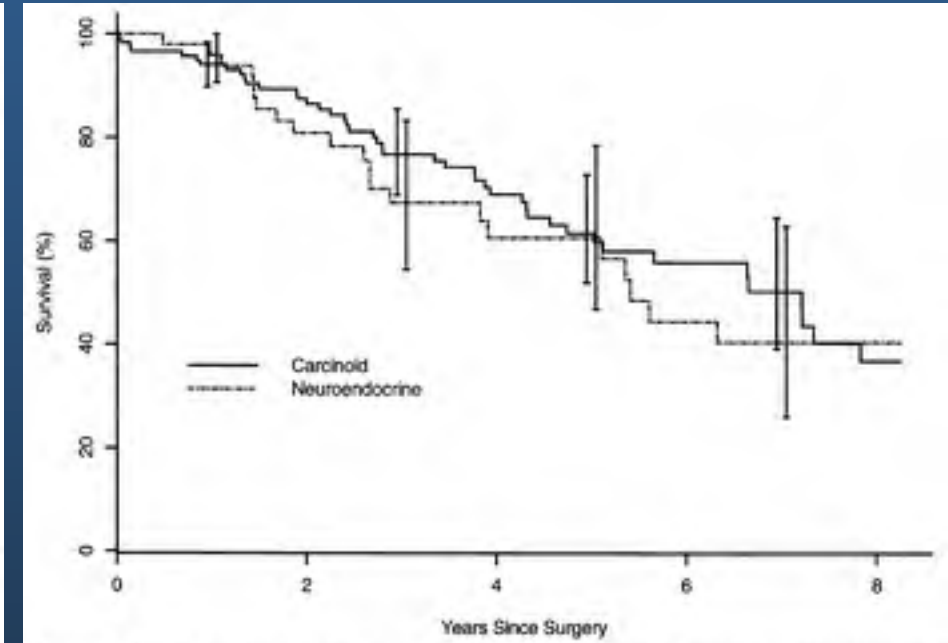

Figure 6. Overall survival rate was no different among patients with carcinoid tumors compared with patients with islet cell tumors (62% versus 61% at 5 years, median 87 months versus 66 months, respectively; p = 0.58 by the log-rank test).

Sarmiento et al, JACS 2003

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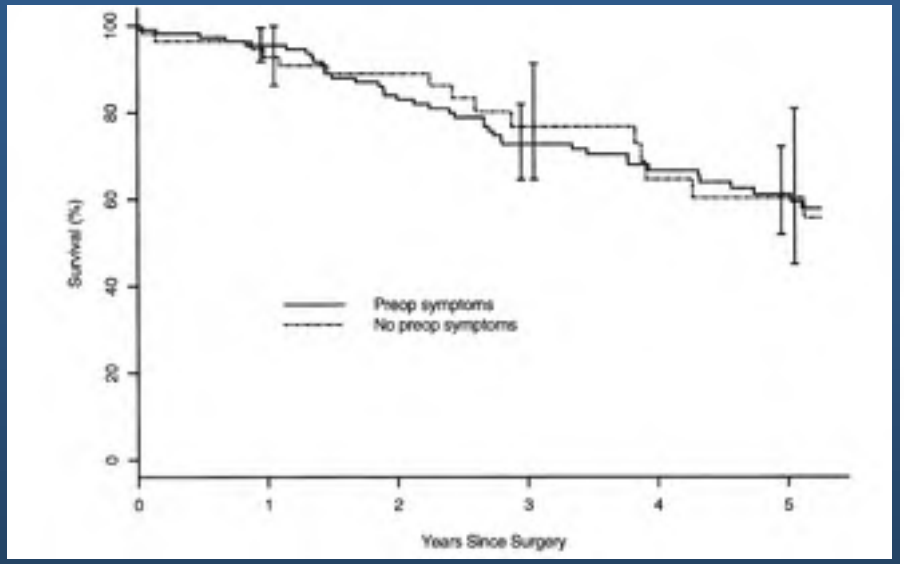
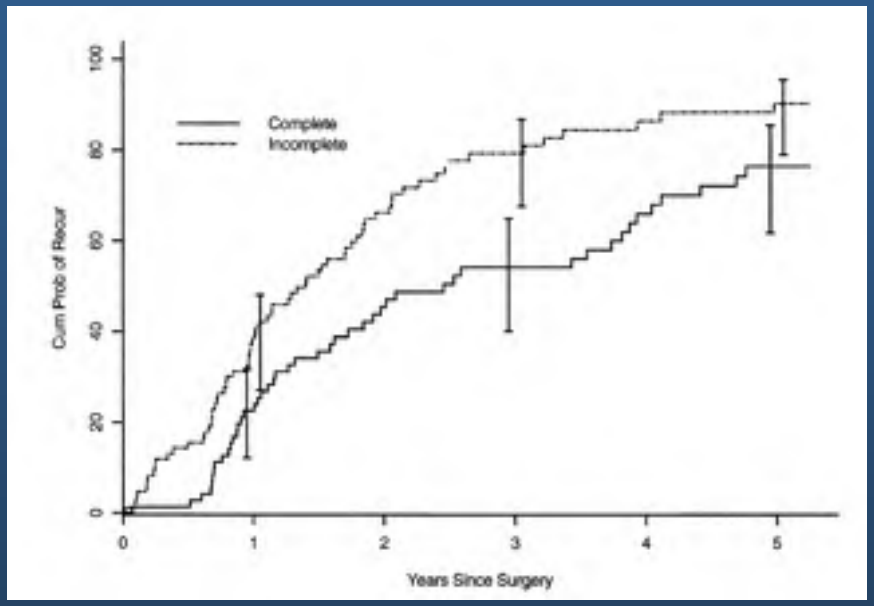
Outcomes after surgery:
Symptomatic vs. asymptomatic



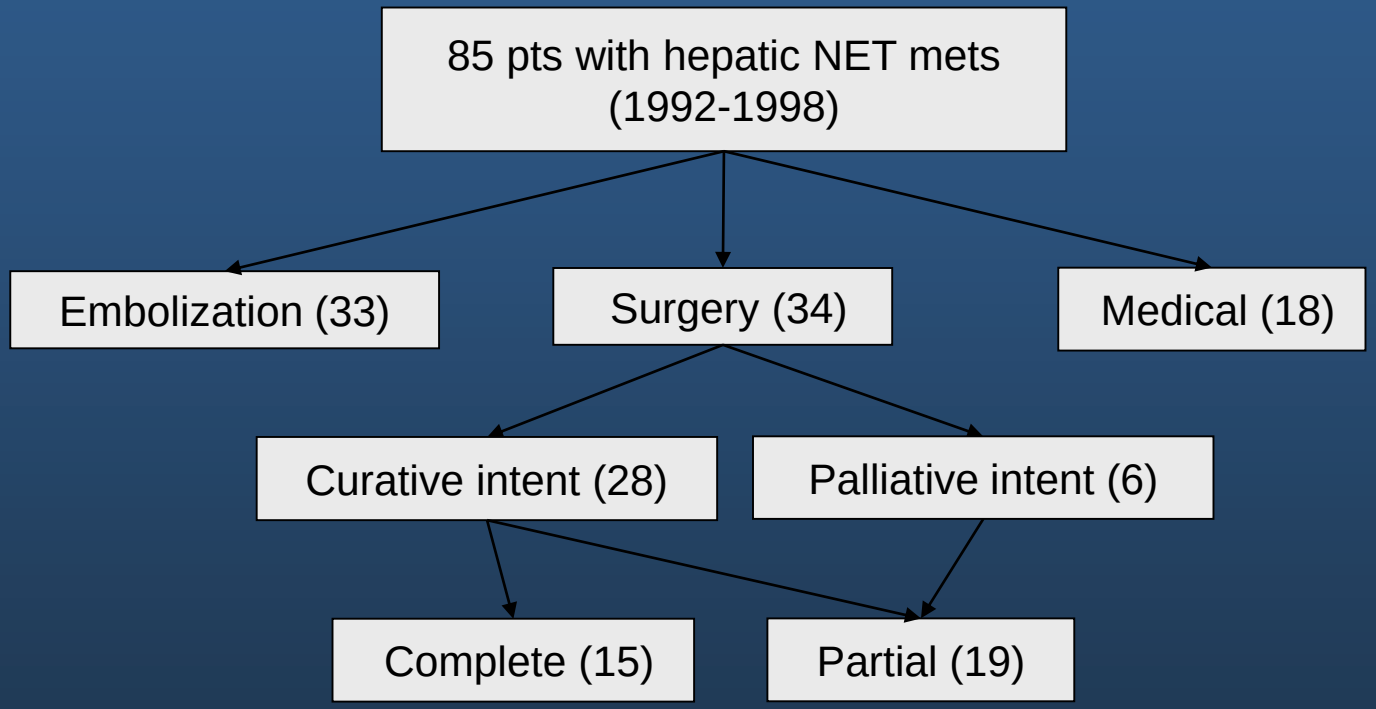


- No difference in survival between symptomatic and asymptomatic patients
- 76% 5-yr recurrence with complete resection

Sarmiento et al, JACS 2003

Outcomes after surgery

Comparison of treatment modalities

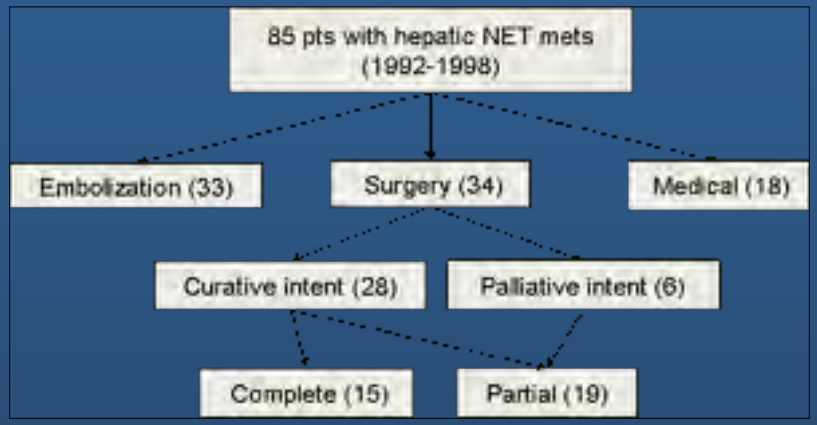


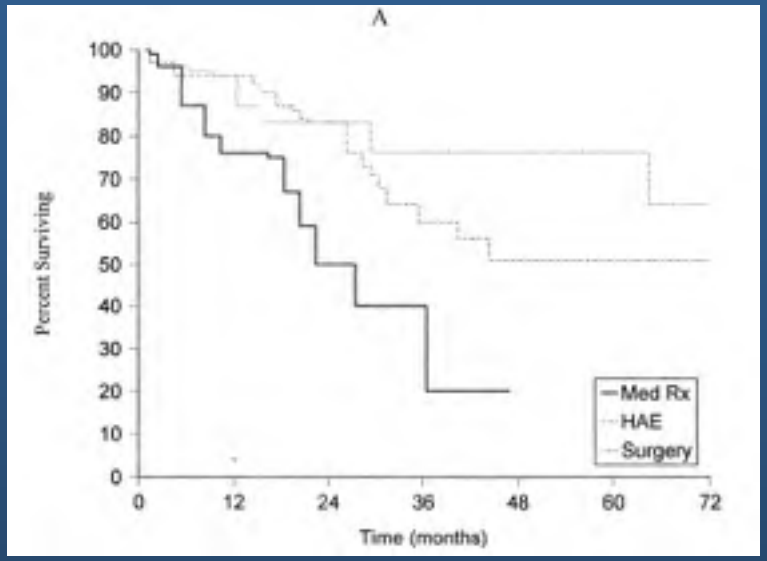
Median followup: 27 months

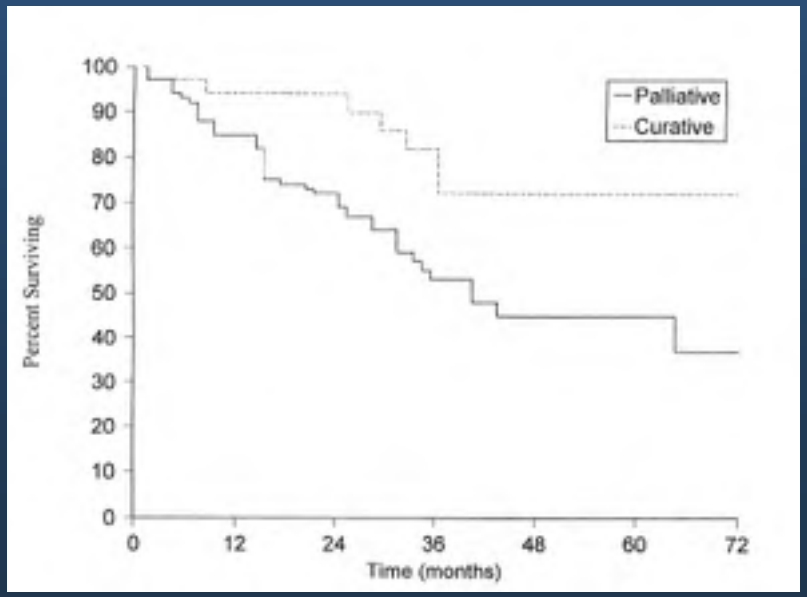
Chamberlain et al. JACS 190:432; 2000

Outcomes after surgery

Comparison of treatment modalities





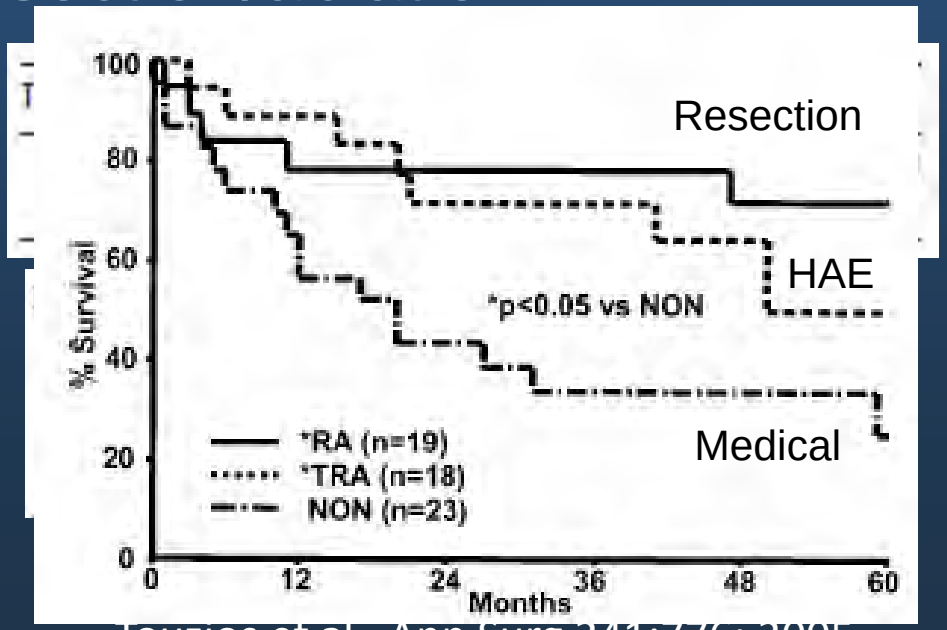


	5-yr survival (%)	Median survival (mo)
Complete	85	NR
Partial	63	66

Chamberlain et al. JACS 190:432; 2000

Impact of surgery on survival
Accounting for tumor burden

- N=60 patients with NET hepatic metastases
  - Treatments: medical, resection/ablation, HAE +/- resection/ablation



Touzios et al. Ann Surg 241:776; 2005

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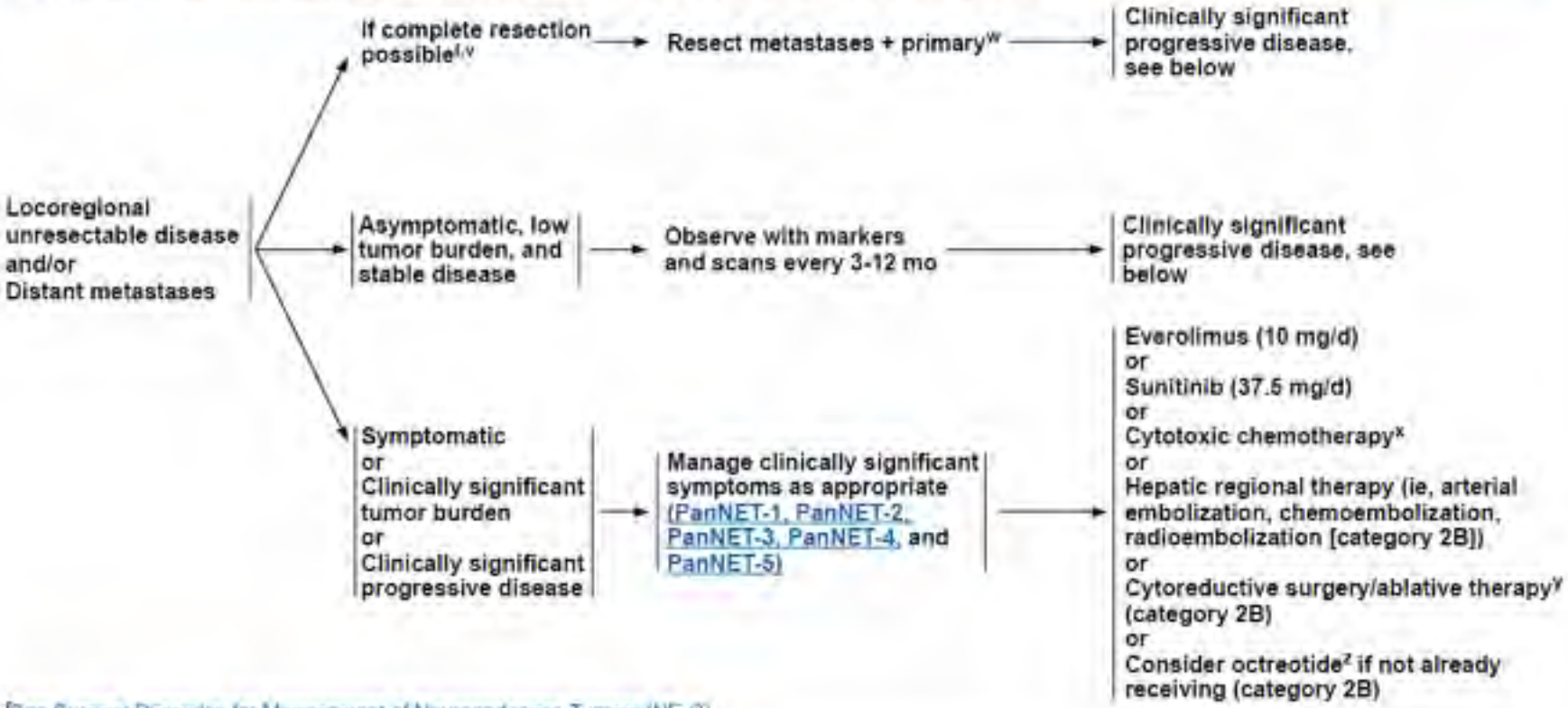
NCCN Guidelines Version 2.2014
Neuroendocrine Tumors of the Pancreas

MANAGEMENT OF LOCOREGIONAL UNRESECTABLE DISEASE AND/OR DISTANT METASTASES[f]



[f] See Surgical Principles for Management of Neuroendocrine Tumors (NE-C).

[v] Noncurative debulking surgery might be considered in select cases.

[w] Staged or synchronous resection when possible. When performing staged pancreatoduodenectomy and liver resection, consider hepatectomy prior to pancreatic resection in order to reduce risk of perihepatic sepsis. De Jong MC, Farnell MB, Sclabas G, et al. Liver-directed therapy for hepatic metastases in patients undergoing pancreaticoduodenectomy: A dual-center analysis. Ann Surg 2010;252:142-148.

[x] The following agents have been used: capecitabine, dacarbazine, doxorubicin, 5-FU, streptozocin, and temozolomide.

[y] Includes ablative techniques such as radiofrequency, microwave, and cryotherapy. There are no randomized clinical trials and prospective data for these interventions are limited, but data on their use are emerging.

[z] Octreotide should be used with caution in patients with insulinoma as it may transiently worsen hypoglycemia (See Discussion for details).

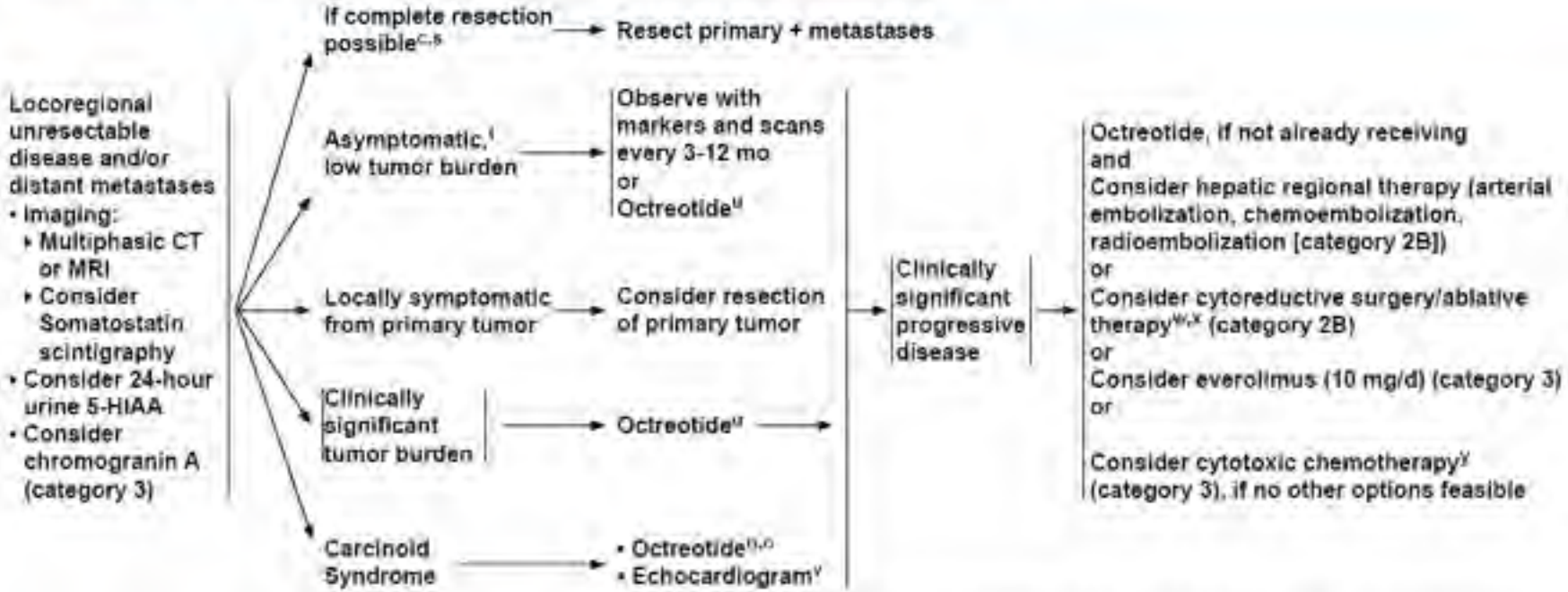
Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2014
Carcinoid Tumors

NCCN Guidelines Index
Neuroendocrine TOC
Discussion

MANAGEMENT OF LOCOREGIONAL UNRESECTABLE DISEASE AND/OR DISTANT METASTASES[C]



[C] See Surgical Principles for Management of Neuroendocrine Tumors (NE-C)

[I] For symptom control, octreotide 150-250 mcg SC TID or octreotide LAR 20-30 mg IM every 4 weeks. Dose and frequency may be further increased for symptom control as needed. Therapeutic levels of octreotide would not be expected to be reached for 10-14 d after LAR injection. Short-acting octreotide can be added to octreotide LAR for rapid relief of symptoms or for breakthrough symptoms.

[O] Lanreotide is approved for symptom control in Europe. Lanreotide has a similar mechanism of action as octreotide and may be preferable in patients who have difficulty tolerating an IM versus SC injection.

[S] Noncurative debulking surgery might be considered in select cases.

[I] Resection of a small asymptomatic (relatively stable) primary in the presence of unresectable metastatic disease is not indicated.

[U] For tumor control, the PROMID study (J Clin Oncol 2009;27:4656-4663) used octreotide LAR 30 mg IM every 4 weeks.

[V] If signs and symptoms of heart disease or planning major surgery.

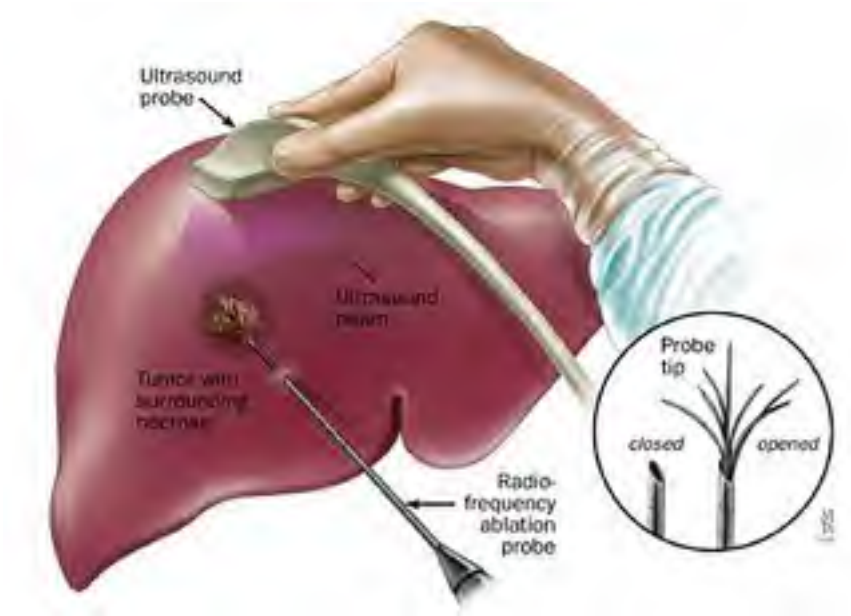
[W] Includes ablative techniques such as radiofrequency, microwave, and cryotherapy. There are no randomized clinical trials and prospective data for these interventions are limited. However, data on the use of these interventions are emerging.

[X] Only if near complete resection can be achieved.

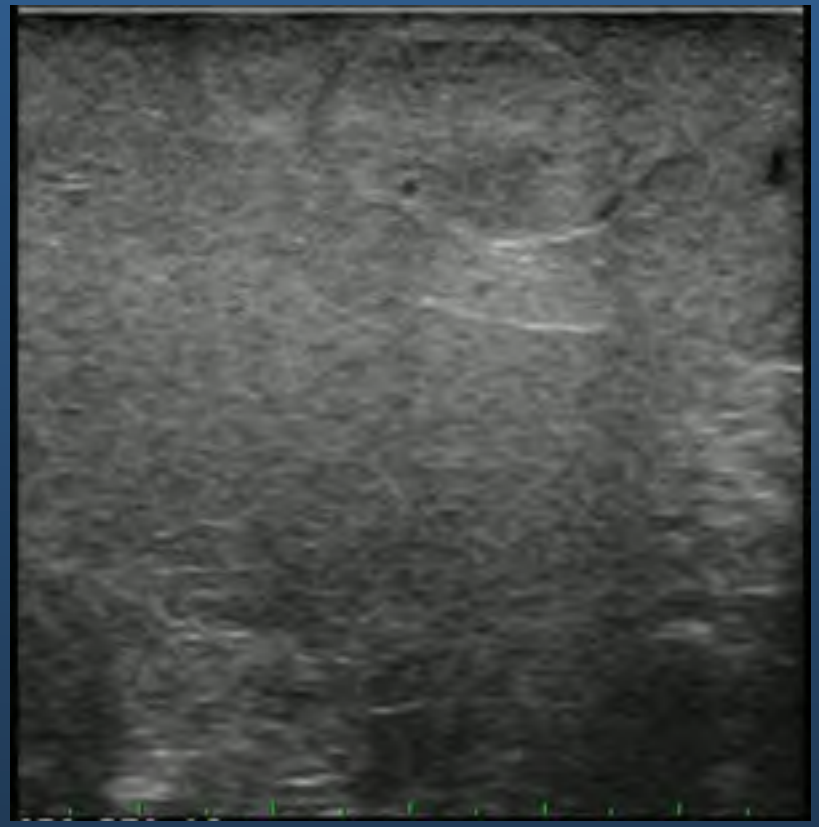
[Y] Anticancer agents such as capecitabine, dacarbazine, 5-FU, interferon, oxaliplatin, and temozolomide can be used in patients with progressive metastases for whom there are no other treatment options. See Discussion for details.

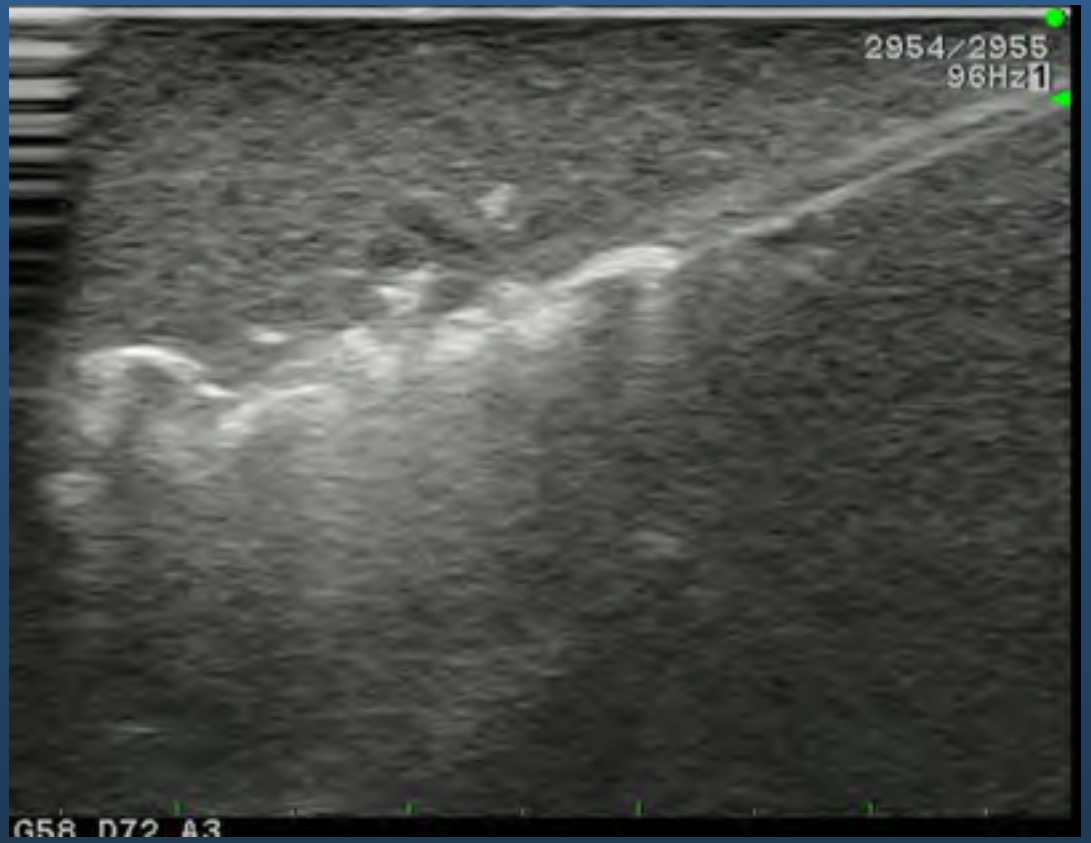
Ablation Techniques

- Cryoablation
- Radiofrequency Ablation
- Microwave Coagulation
- Irreversible Electroporation



Intraoperative US-guided MWA





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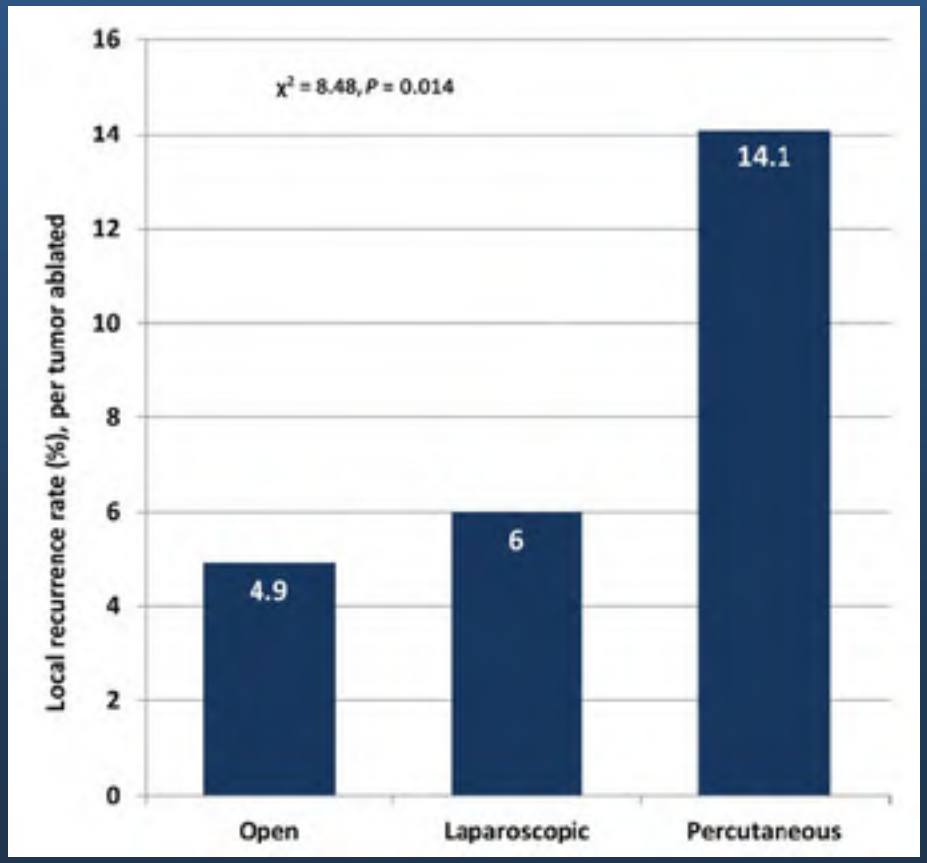
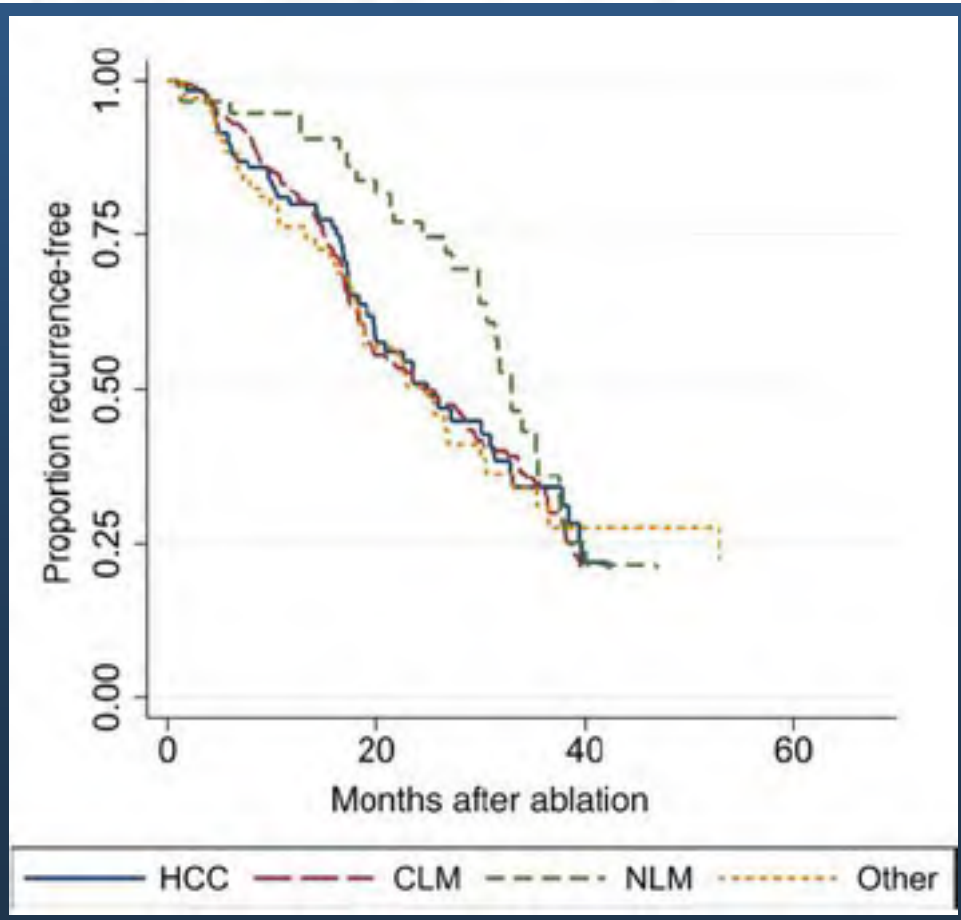
Microwave Ablation for Hepatic Malignancies

A Multiinstitutional Analysis

Ryan T. Groeschl, MD, Charles H. C. Pilgrim, MBBS (Hons), PhD,* Erin M. Hanna, MD,† Kerri A. Simo, MD,† Ryan Z. Swan, MD,† David Sindram, MD, PhD,† John B. Martinie, MD,† David A. Iannitti, MD,† Mark Bloomston, MD,‡ Carl Schmidt, MD,‡ Hooman Khabiri, MD,§ Lawrence A. Shirley, MD,‡ Robert C. G. Martin, MD, PhD,¶ Susan Tsai, MD, MHS,* Kiran K. Turaga, MD, MPH,* Kathleen K. Christians, MD,* William S. Rilling, MD,‖ and T. Clark Gamblin, MD, MS**





Liver Transplantation

- Controversial
- Available at limited centers on protocol
- Largest series of 85 pts with 14% mortality and 47% 5-year survival
- Proposed indications include:
  - Low-grade NET with resected primary
  - Must be drained by liver (no rectal/lung)
  - <50% liver involvement, stable disease x 6mo
  - Age 55 or less

Mayo et al, JACS 2013

ENETS Consensus Guidelines for the Standards of Care in Neuroendocrine Tumors: Peptide Receptor Radionuclide Therapy with Radiolabeled Somatostatin Analogs

Neuroendocrinology 2009;90:220–226

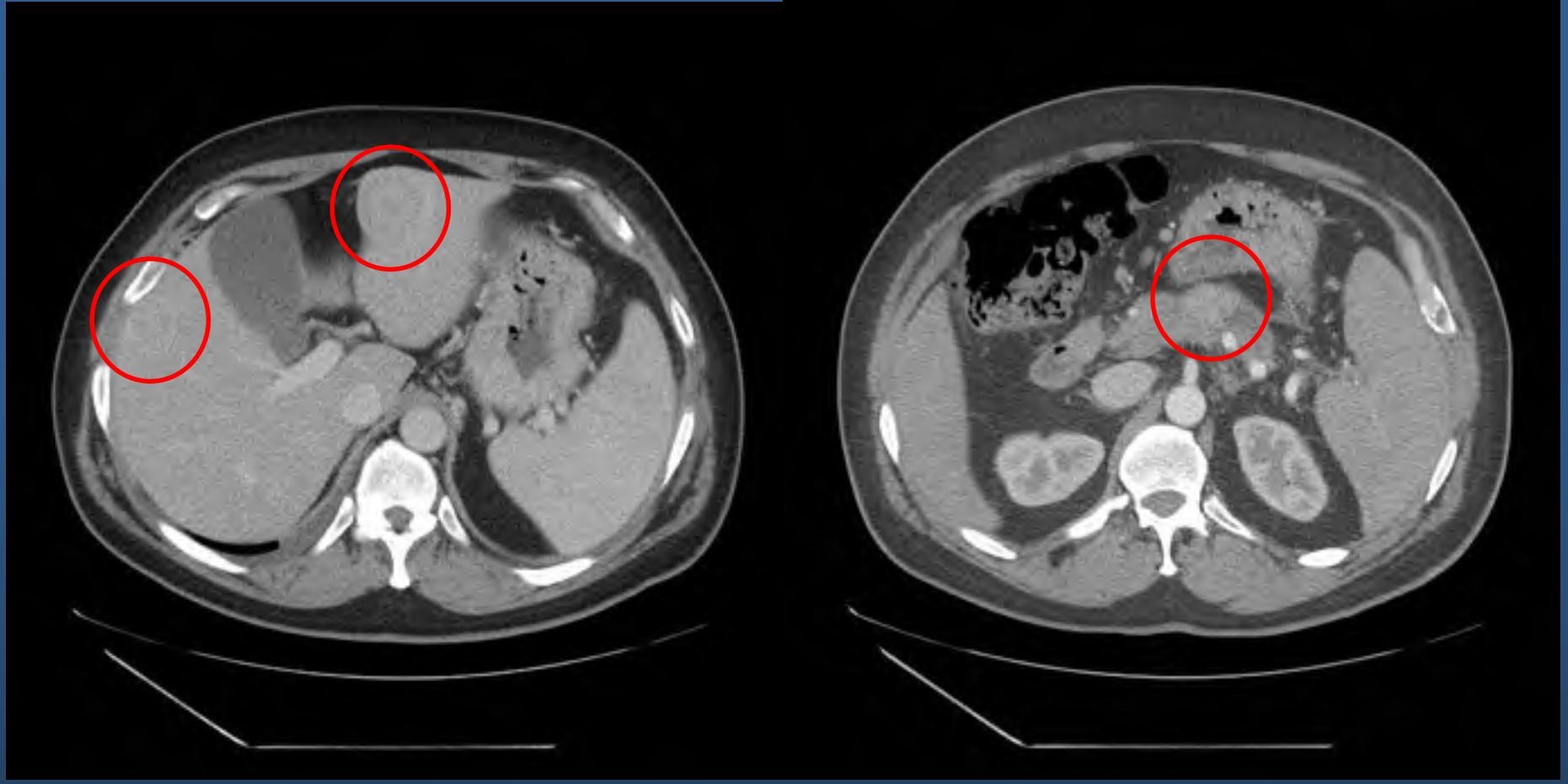
Eligibility Criteria

- Tumor uptake on the OctreoScan should be at least as high as normal liver uptake, as judged from planar images. Comparable uptake with other somatostatin receptor imaging modalities may apply, but direct correlations are not available
- Inoperable disease
- Life expectancy at least 3–6 months

Treatment with radiolabeled somatostatin analogs is a promising new tool in the management of patients with inoperable or metastasized neuroendocrine tumors. The results that were obtained with [^{90}Y-DOTA^{0},Tyr^{3}]octreotide and [^{177}Lu-DOTA^{0},Tyr^{3}]octreotate are very encouraging, although a direct, randomized comparison between the various treatments is lacking. Also, the re-

Case 1

- 47yM who presented with abd pain and reflux
- EGD with necrotizing esophagitis and duodenal ulcers
- Serological workup revealed a markedly elevated gastrin at 3,552 pg/ml
- Symptoms not relieved by high dose PPI/octreotide



- 2 large lesions (segs 3,5) 2 small lesions (segs 2, 8) splenomegaly with varices
- EUS with biopsy of liver/pancreas positive for NET
- Octreotide scan positive in pancreas and 2 liver lesions

Operation

- Distal pancreatectomy and splenectomy, cholecystectomy
- Segment 2, 3, 5, 8 wedge resections of known lesions plus multiple resections of all visible surface lesions > 1 cm
- 2 deeper lesions ablated by microwave, smaller <1cm lesions seen by IOUS, not treated
- >90% cytoreduction
- Pathology:
  - Pancreas: poorly differentiated NET, 0/14 LNs
  - Liver: metastatic NET, Ki67 30-40%

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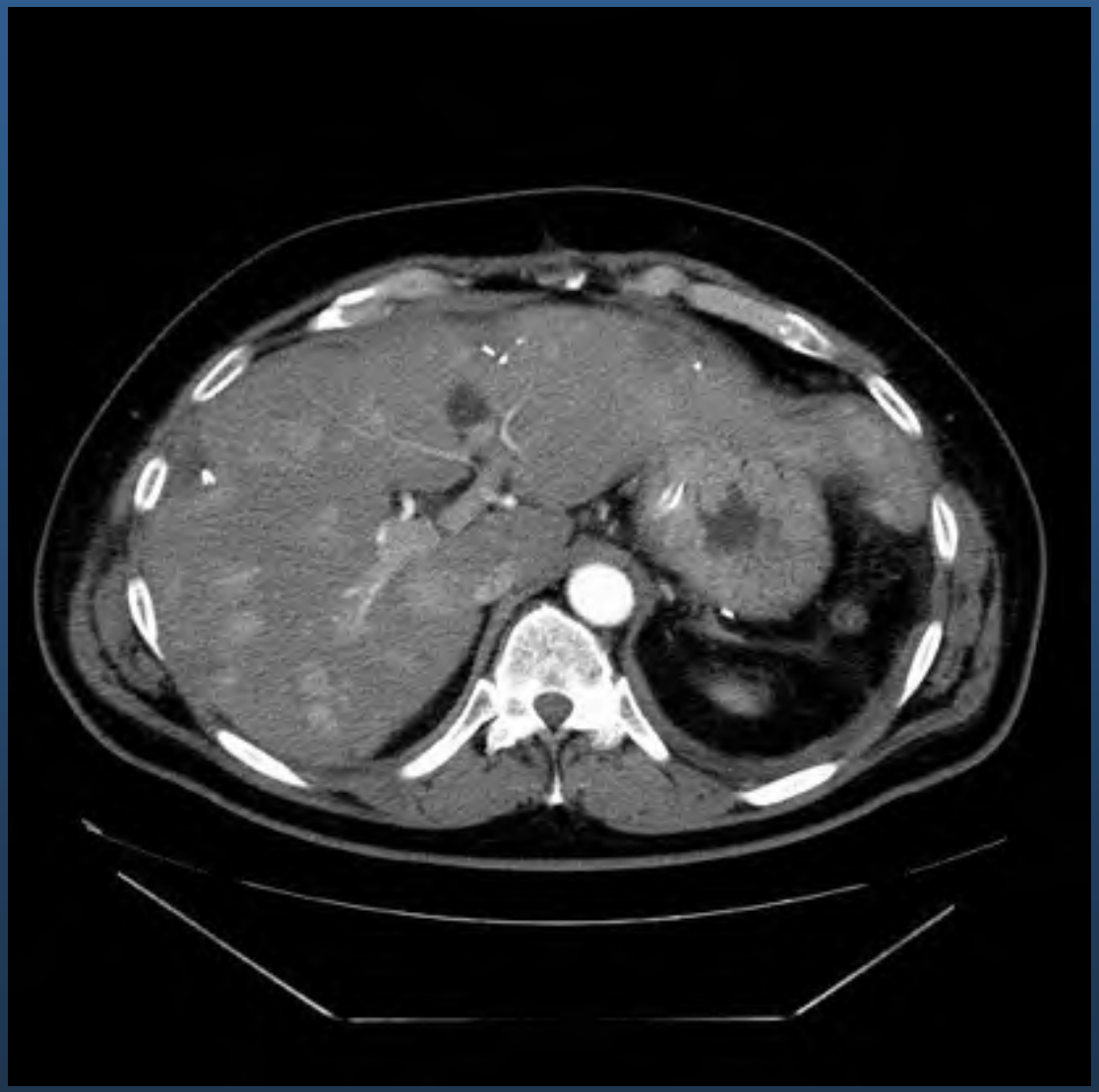
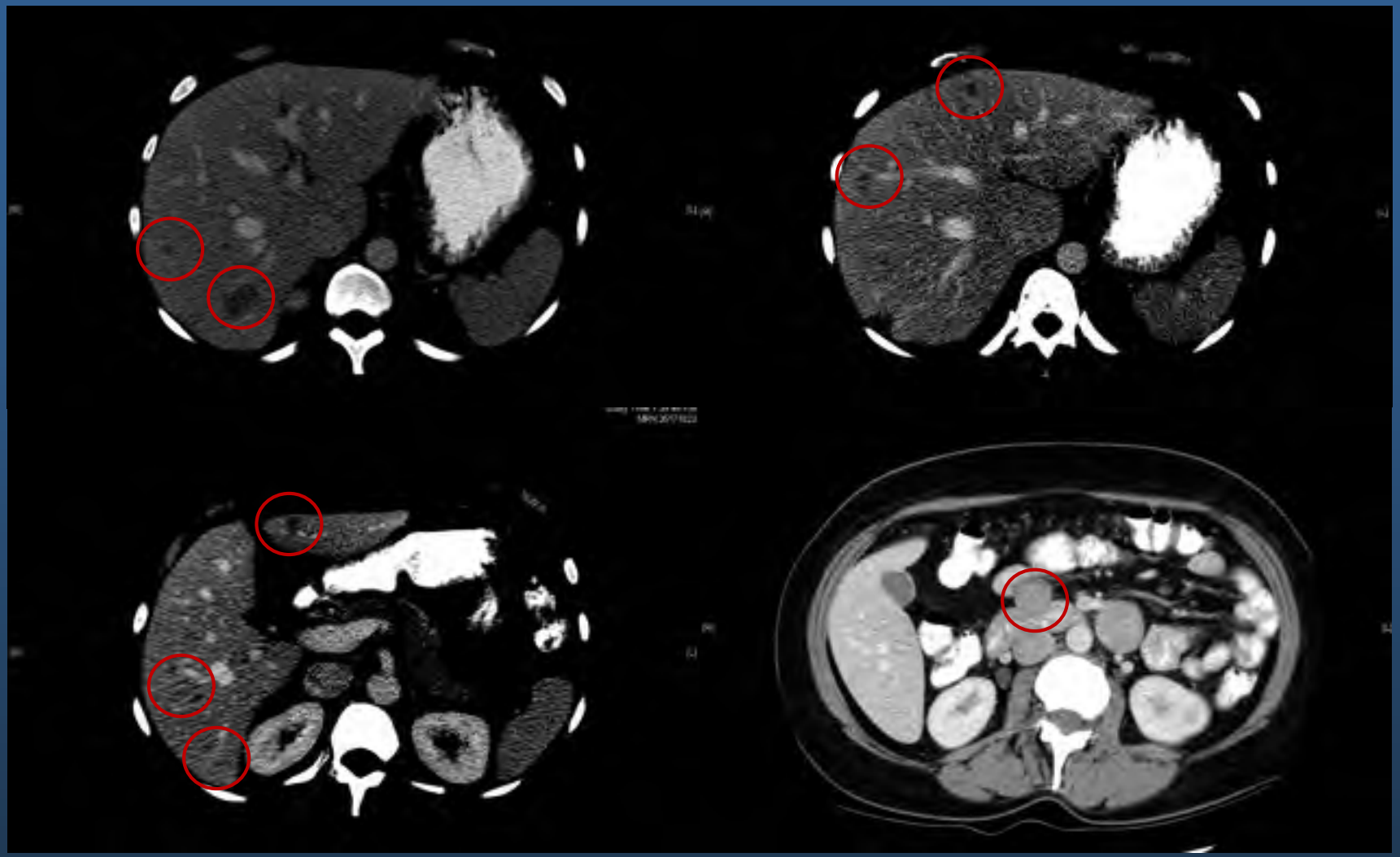
Recurrence in 6 months



Case 2

- 48yoF
- Found on routine labs to have elevated liver enzymes, which subsequently normalized
- Asymptomatic
- Imaging showed multiple liver lesions



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- Investigations:
  - CT: Multiple liver lesions, mesenteric mass anterior to pancreas
  - Liver bx: Consistent with neuroendocrine tumor
  - Bx of mesenteric masses: Inconclusive
  - Octreotide scan: Slightly increased uptake in tail of pancreas, liver

- Surgery:
  - Duodenal resection (primary tumor)
  - Liver: segment 7 resection, RFA x 2, Enucleation x 14
  - Lymphadenectomy
  - No lesion in pancreas
- Pathology:
  - Duodenum: 1.2cm carcinoid, well-differentiated, mitotic count <2/50hpf
  - Liver lesions: Metastatic carcinoid to liver
  - 6/7 LN positive

- Follow-up:
  - 2y post-resection
  - On long-term octreotide
  - No evidence of disease on imaging
  - Chromogranin A: 5.6

Summary

- Carcinoid/PNET is usually a slow-growing disease with survival measured in years, even if metastatic
- Somatostatin analogues are the mainstay of medical treatment, but they are unlikely to result in significant tumor regression, need better agents
- Even with complete surgical resection, vast majority of patients develop recurrent disease
- Regardless of symptomatology, surgical resection is associated with significant survival differences compared with medical or regional therapy alone
- Encourage multidisciplinary management with surgeons, oncologists and interventional radiologists