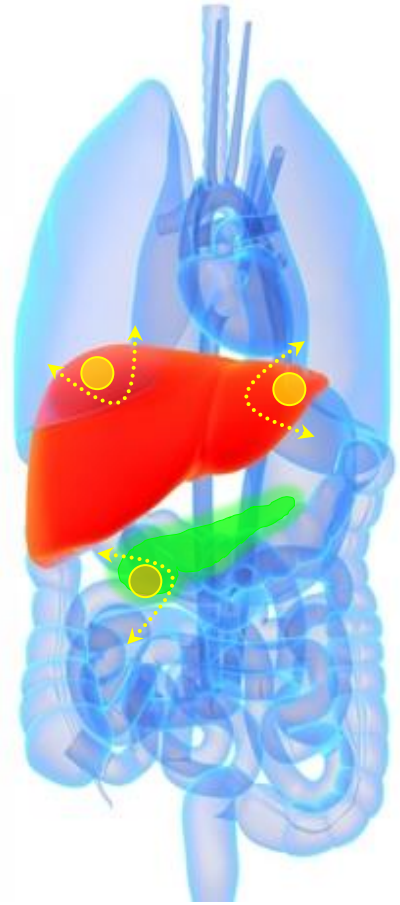
# Role of Surgical Resection in Advanced Neuroendocrine Tumors

## Surgical Management of Neuroendocrine ~~Tumors~~ Neoplasms

City of Hope

## NENs >> NETs = Carcinoids

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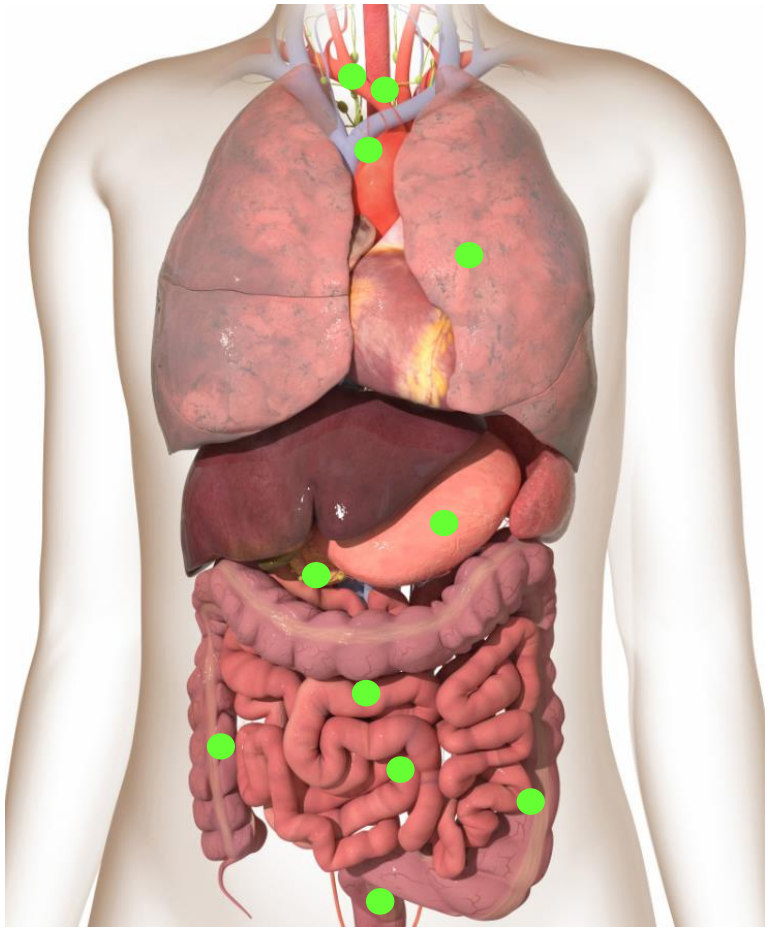
Professor, Clinical Surgery
City of Hope, Comprehensive Cancer Center

# Disclosures

I have nothing to disclose.

# Neuroendocrine Tumors

**NECK**
- Thyroid
- Parathyroid



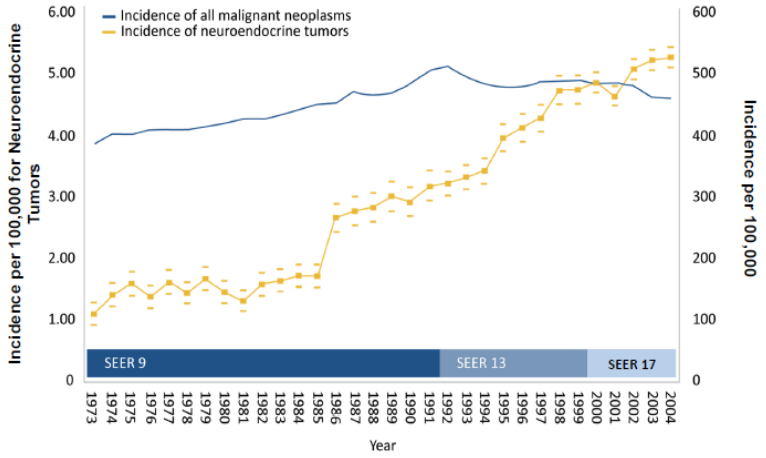
**CHEST**
- Thymus
- Lungs

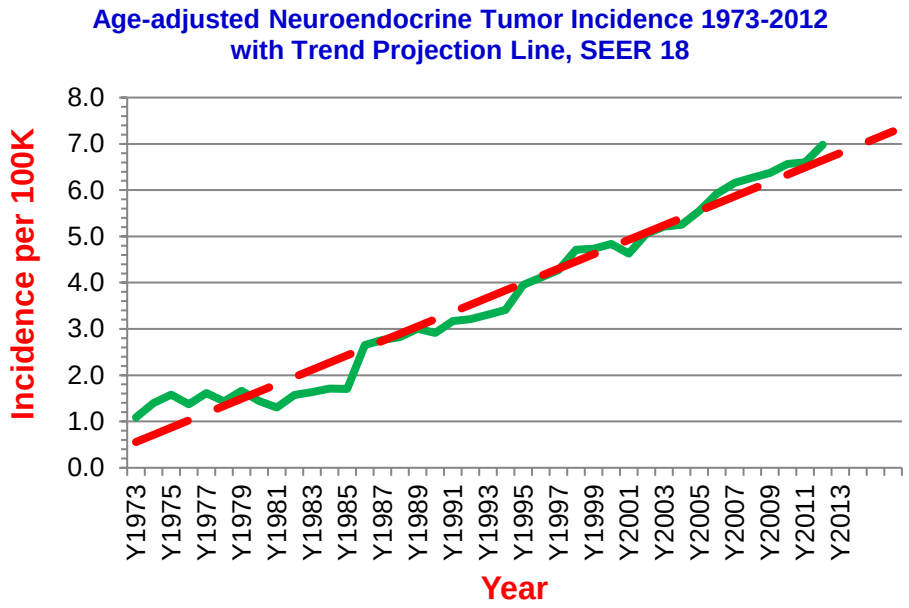
**ABDOMEN**
- Adrenals
- Pancreas
  - Gastrinoma
  - Insulinoma
  - Glucagonoma
  - VIPoma
  - Somatostatinoma
  - VIPoma

**ABDOMEN**
- Stomach
- Small Intestine
- Colon
- Rectum

# 5-fold Increase in NETs over the past 30 years

**7-fold Increase in the past 40 years**



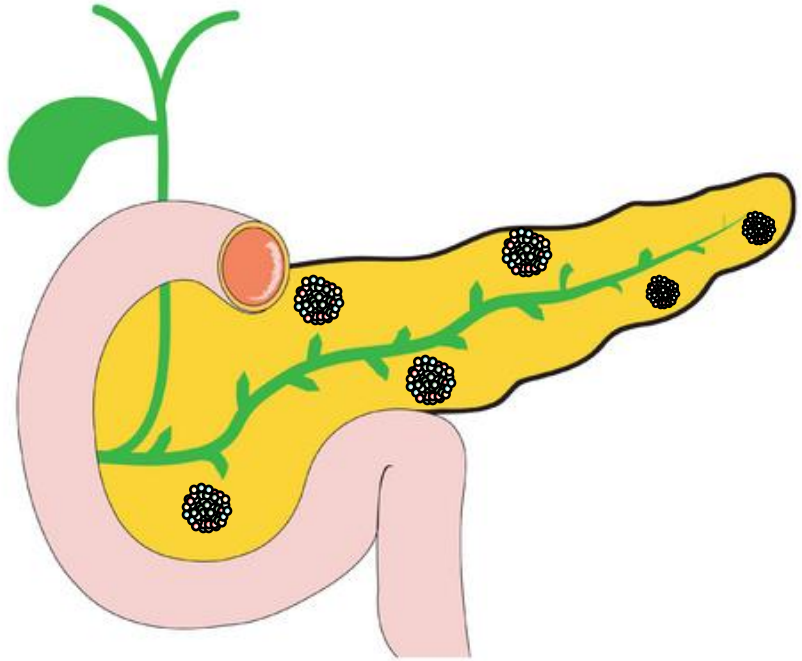




Yao et al. *J Clin Oncol 2008; 26: 3063-3072*

# Cell Type & Cancer

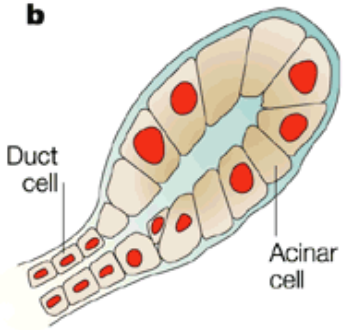
## EXOCRINE: ≅ 93%

- Acinar Cells
- Duct Cells

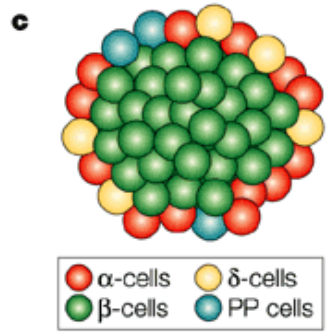


**Digestive Enzymes**

- Trypsin: Digests Proteins
- Lipases: Digests Fats
- Amylase: Digest Carbohydrates




**Adenocarcinoma**




**Neuroendocrine Ca**

## ENDOCRINE: ≅ 5%

- Alpha Cells
- Beta Cells
- Delta Cells
- Others

**Hormones**

- Glucagon
- Insulin
- Somatostatin
- Gastrin, VIP

# NEN = NET (G1, G2 & G3) + NEC (G3)

chromogranin A, chromogranin B, and synaptophysin

Surgery

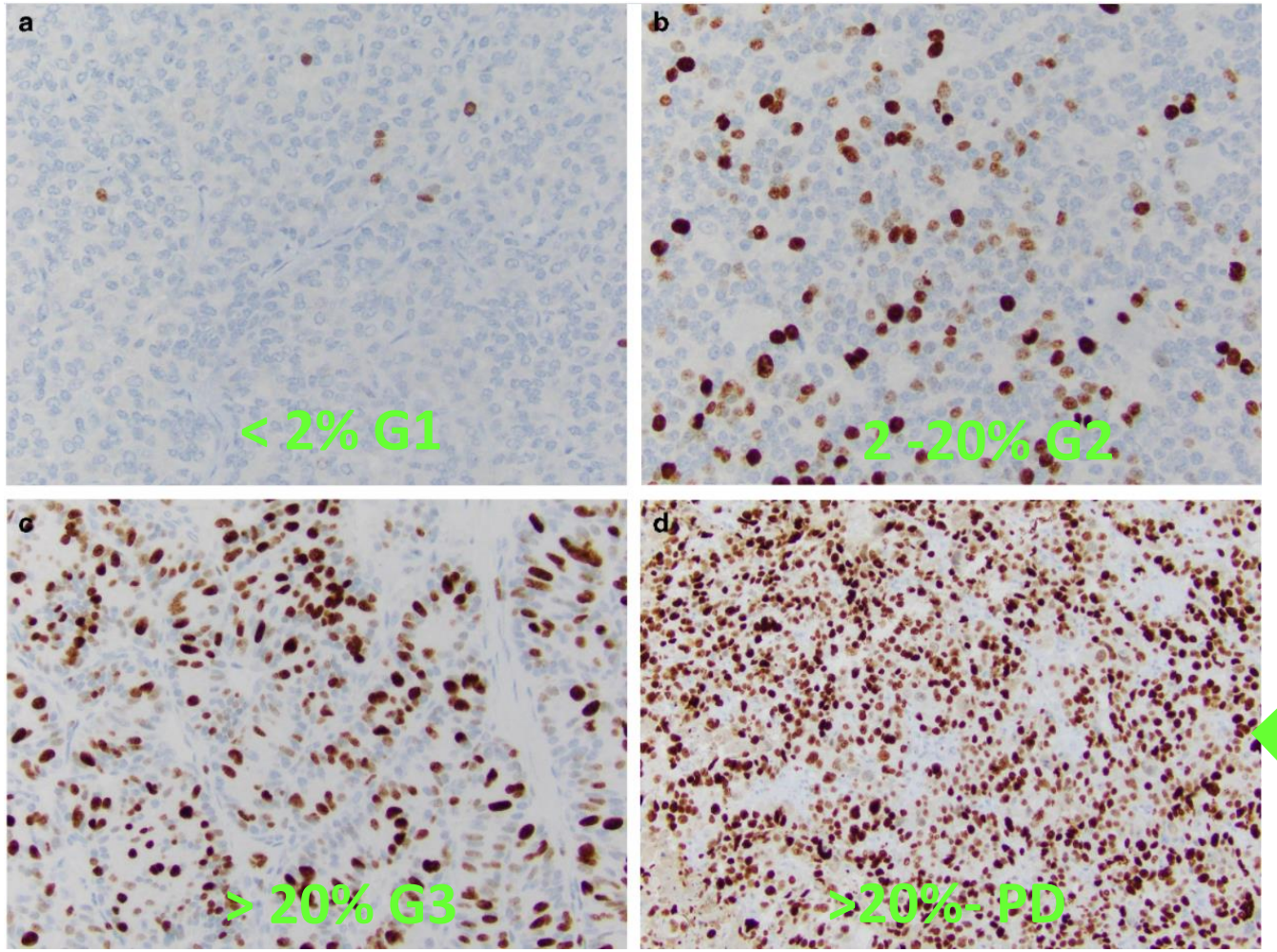
Chemo

| | Morphological differentiation | Mitotic count/2mm$^2$ | Ki67 index |
|---|---|---|---|
| NET G1 | well-differentiated | <2 | <3% |
| NET G2 | well-differentiated | 2–20 | 3–20% |
| NET G3 | well-differentiated | >20 | >20% |
| NEC | poorly differentiated | >20 | >20% |
| MiNENs | well or poorly differentiated | variable | variable |

Necrosis

MiNEN: mixed neuroendocrine/non-neuroendocrine neoplasm

# Ki 67

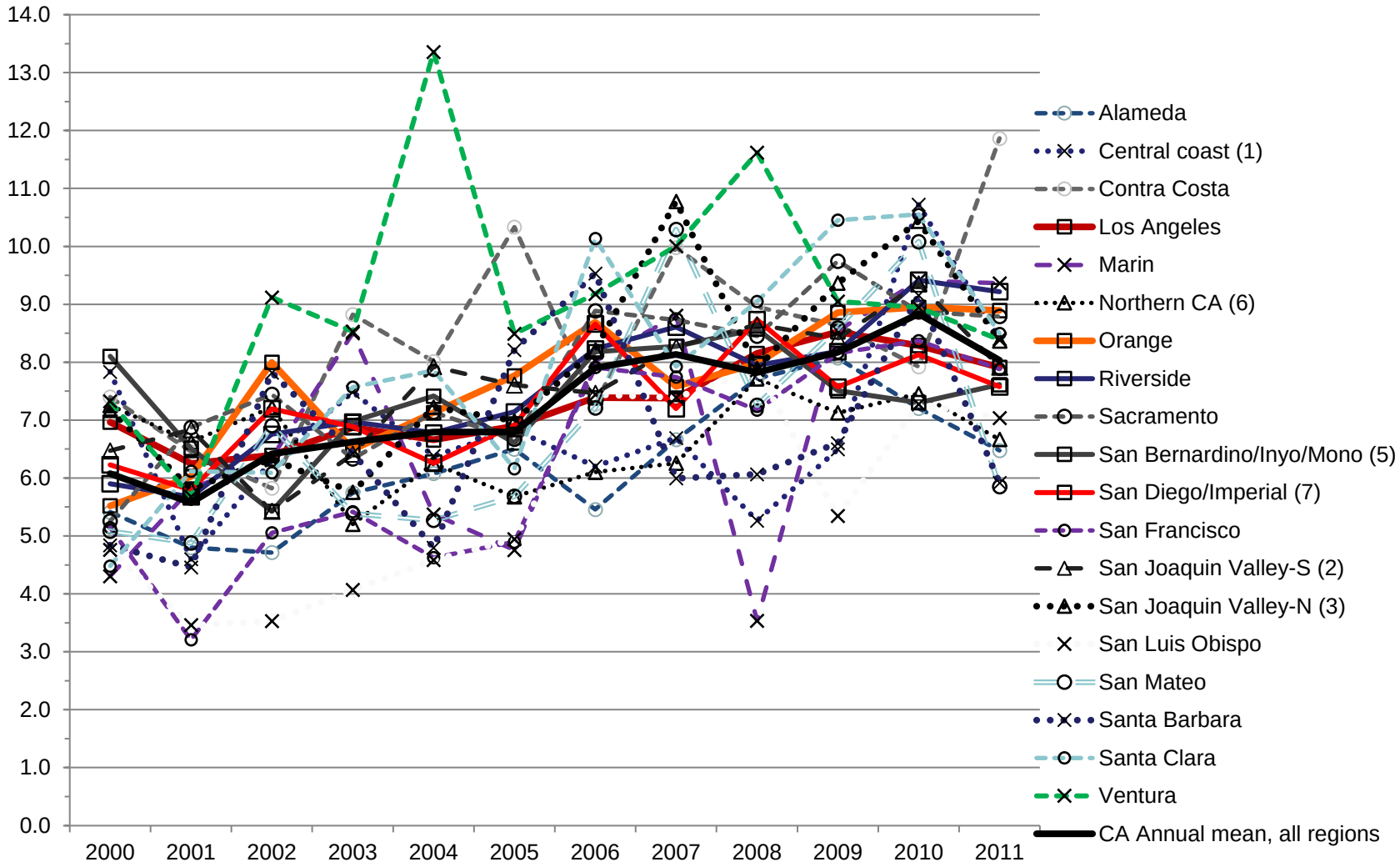



Small Cell

Large Cell

*Modern Pathology* **volume 31**, pages1770–1786 (2018)

# California Cancer Registry- Doubled in the last 10 years



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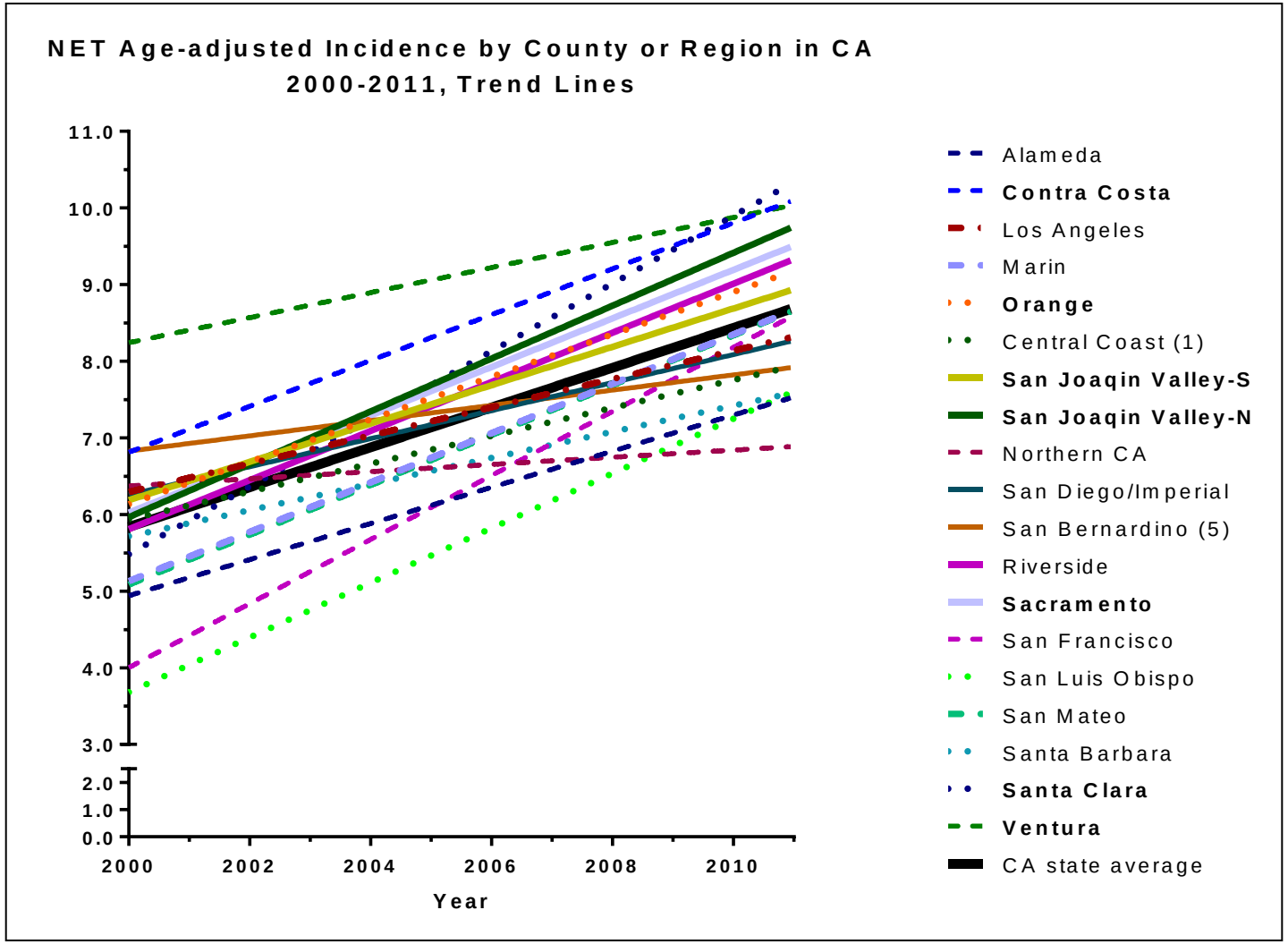
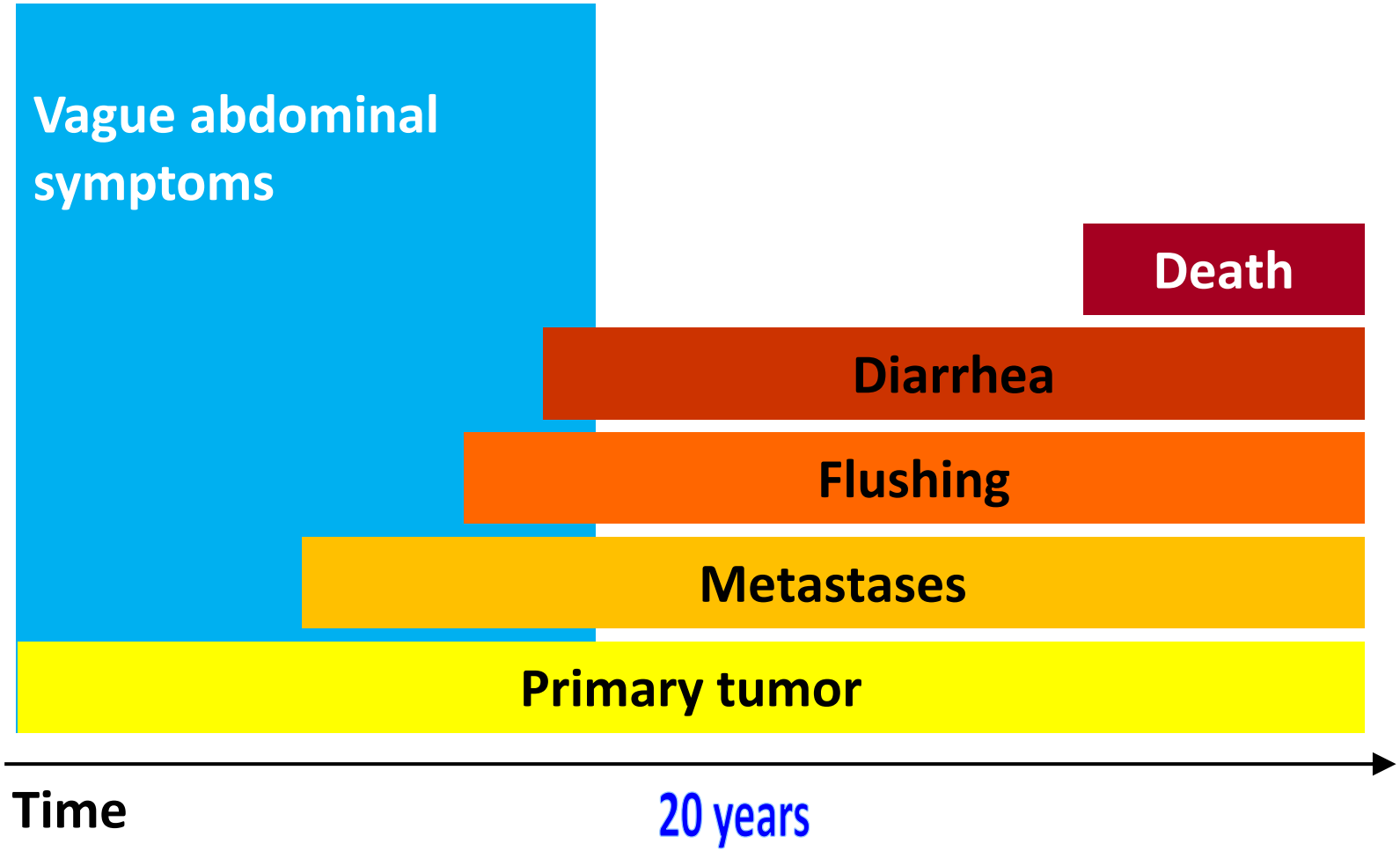


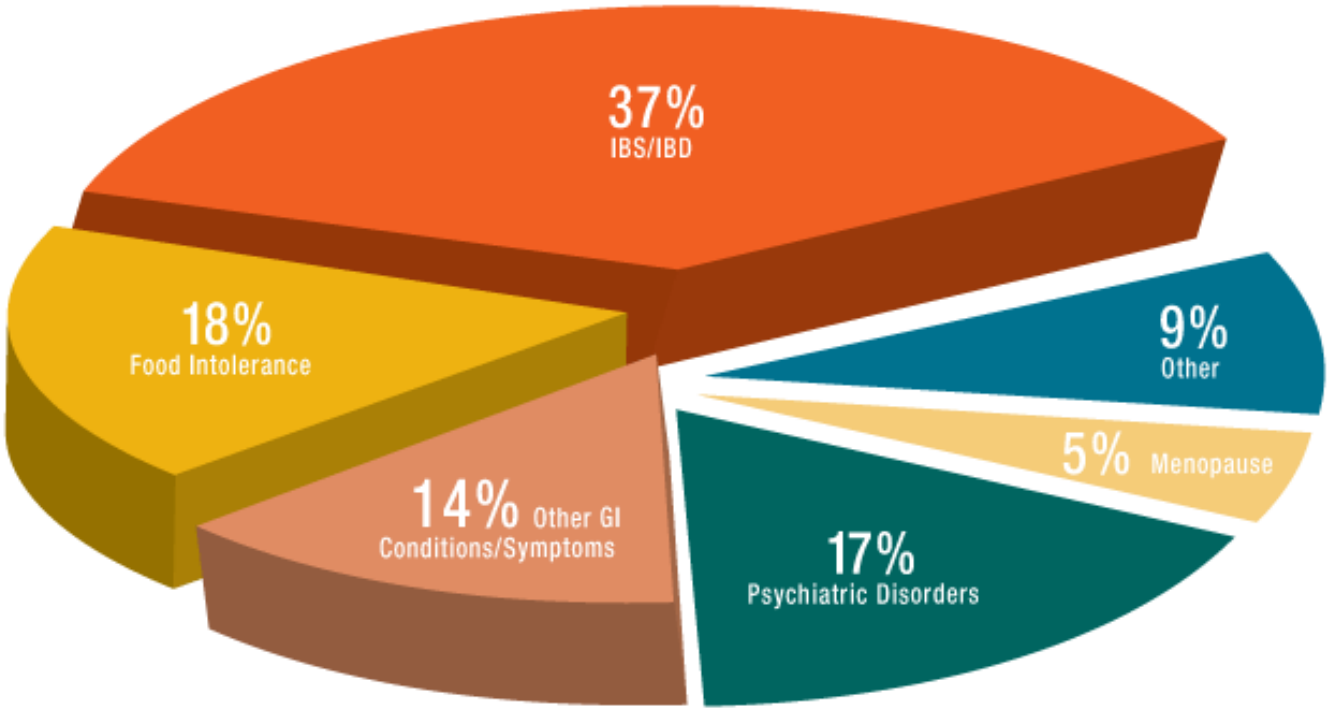
# NETs- Natural History




Vinik A, Moattari AR. *Dig Dis Sci*. 1989;34[Suppl]:14S-27S.

# NETs- Misdiagnoses

## Common Misdiagnoses for Abdominal NETs[2]

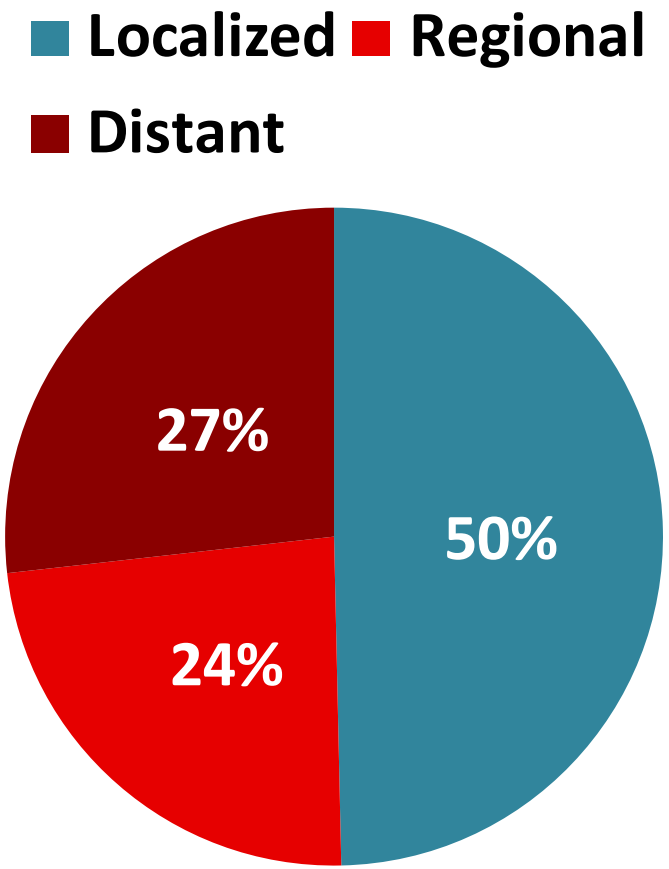



n=101*

* Data based on 147 misdiagnoses. Some patients were given more than 1 incorrect diagnosis.

2. Toth-Fejel S, Pommier RF. Relationships among delay of diagnosis, extent of disease, and survival in patients with abdominal carcinoid tumors. Am J Surg. 2004;187(5):575-579.

# Missed Symptoms & Late Diagnosis

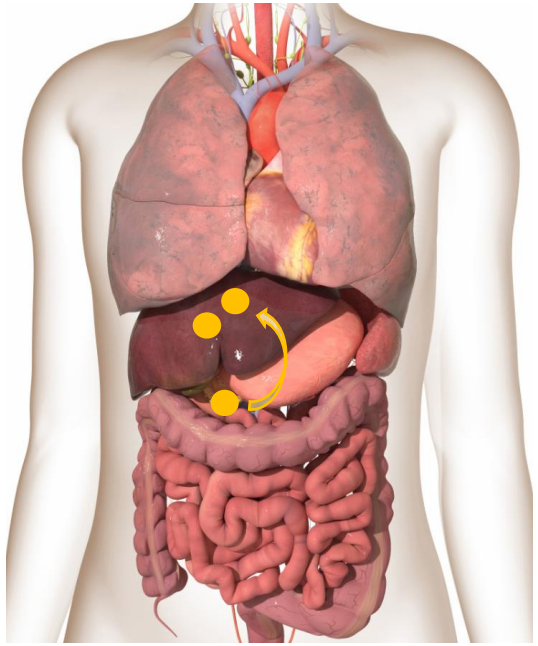



- Flushing
  - ✓ No sweating
  - ✓ First sip of alcohol
- Diarrhea
  - ✓ Especially nocturnal
- Wheezing
- Irritable bowel syndrome
- Bloating

Yao JC et al. *J Clin Oncol*. 2008;26:3063-3072

# Liver Mets from NETs

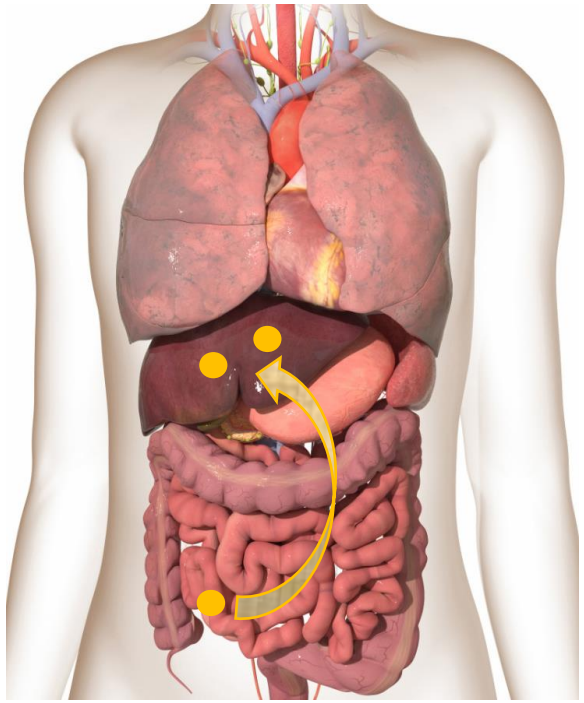
## Neuroendocrine Tumors- Pancreatic



30%

60% → Non Functional
40% → Functional

## Carcinoid Tumors- Stomach, Small Bowel, Colon, Rectum

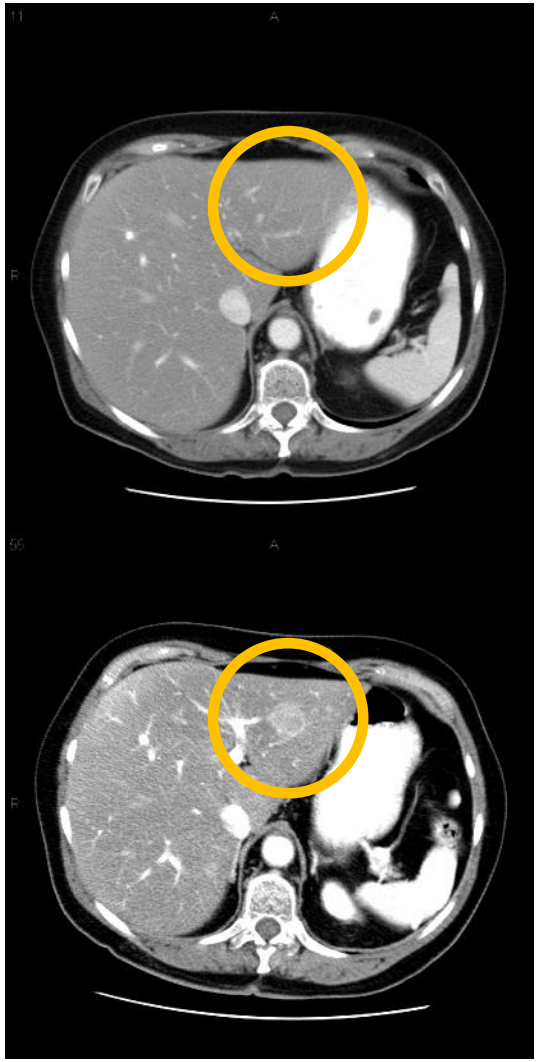


70%

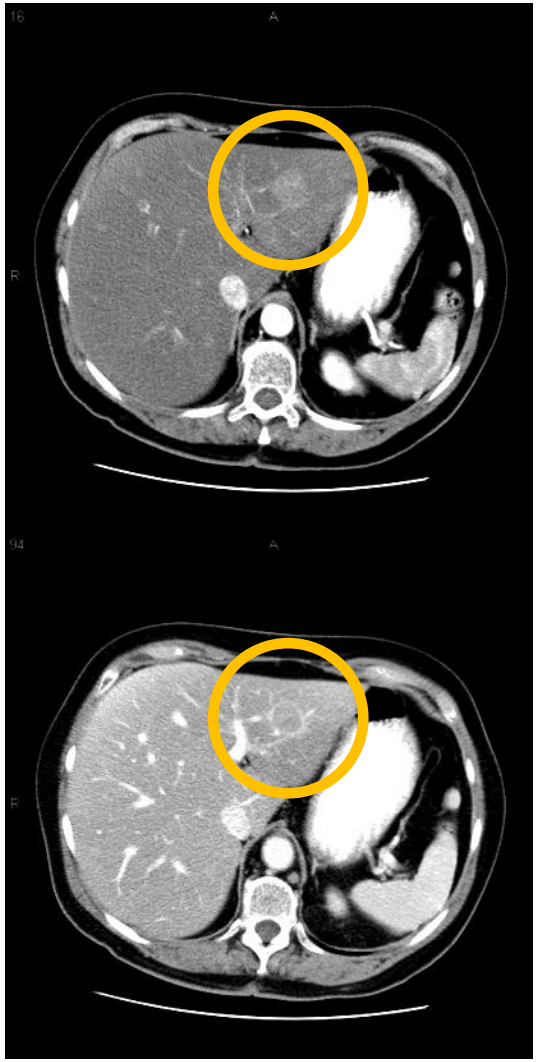
90% → Asymptomatic
10% → Symptomatic

# Anatomic Imaging- CT scan Vs MRI

Std



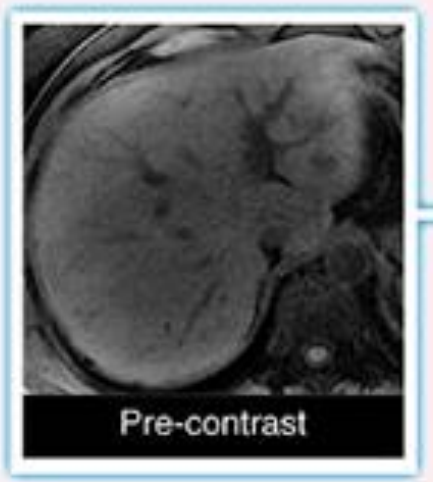
Arterial



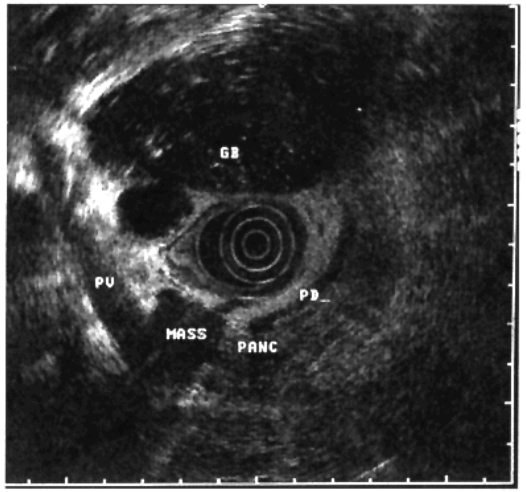
Venous

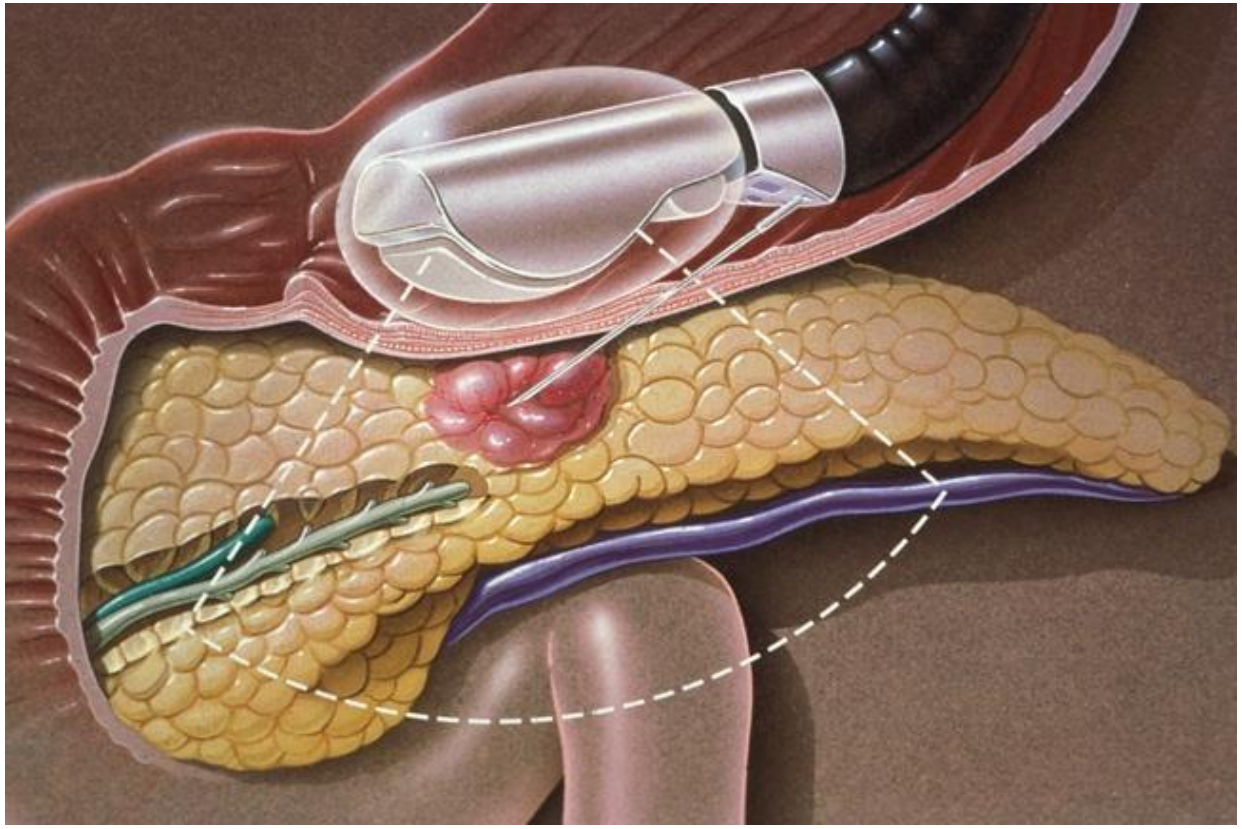
Delayed

# Liver MRI with Eovist



# ERCP and Endoscopic Ultrasound

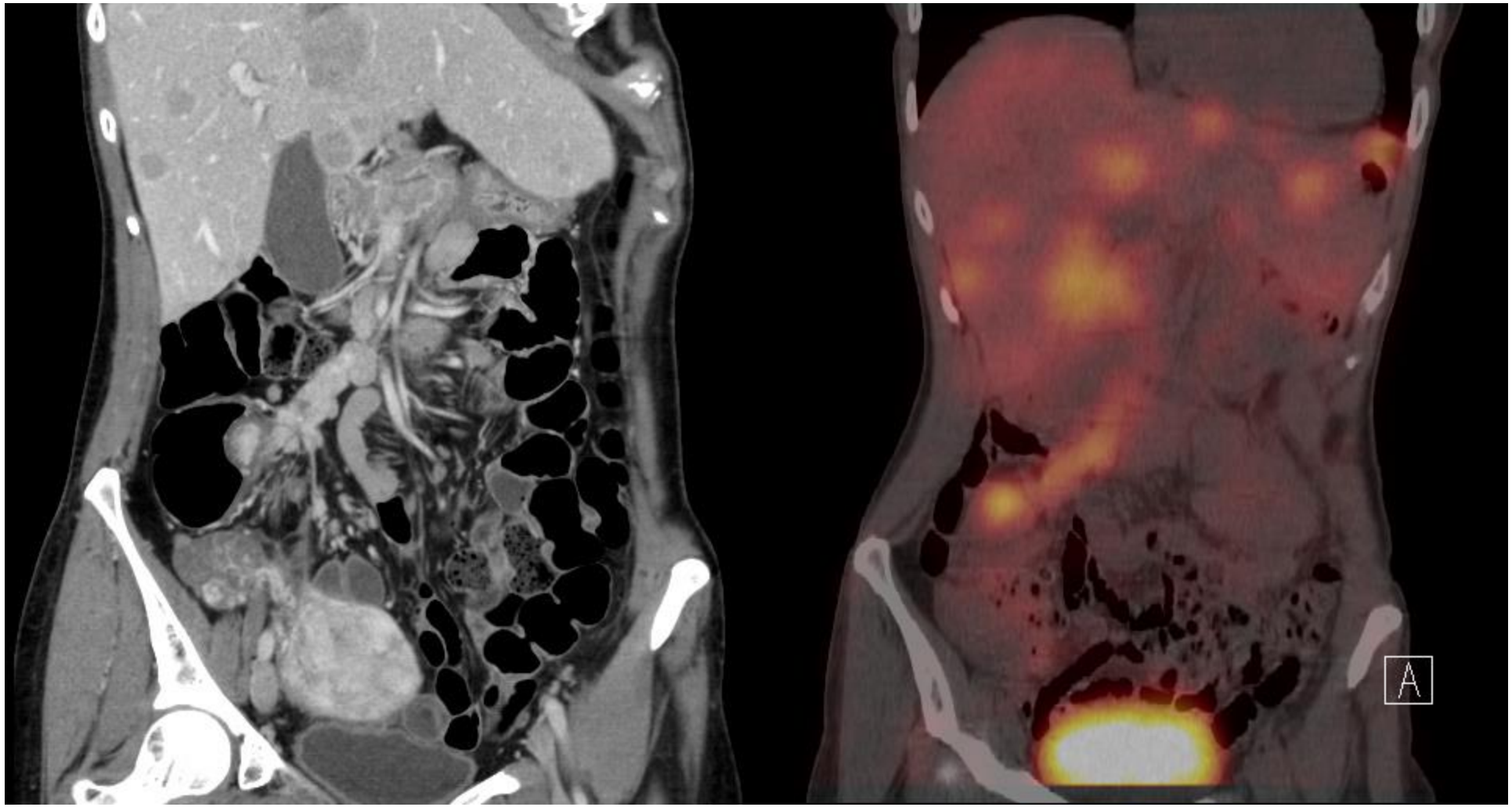


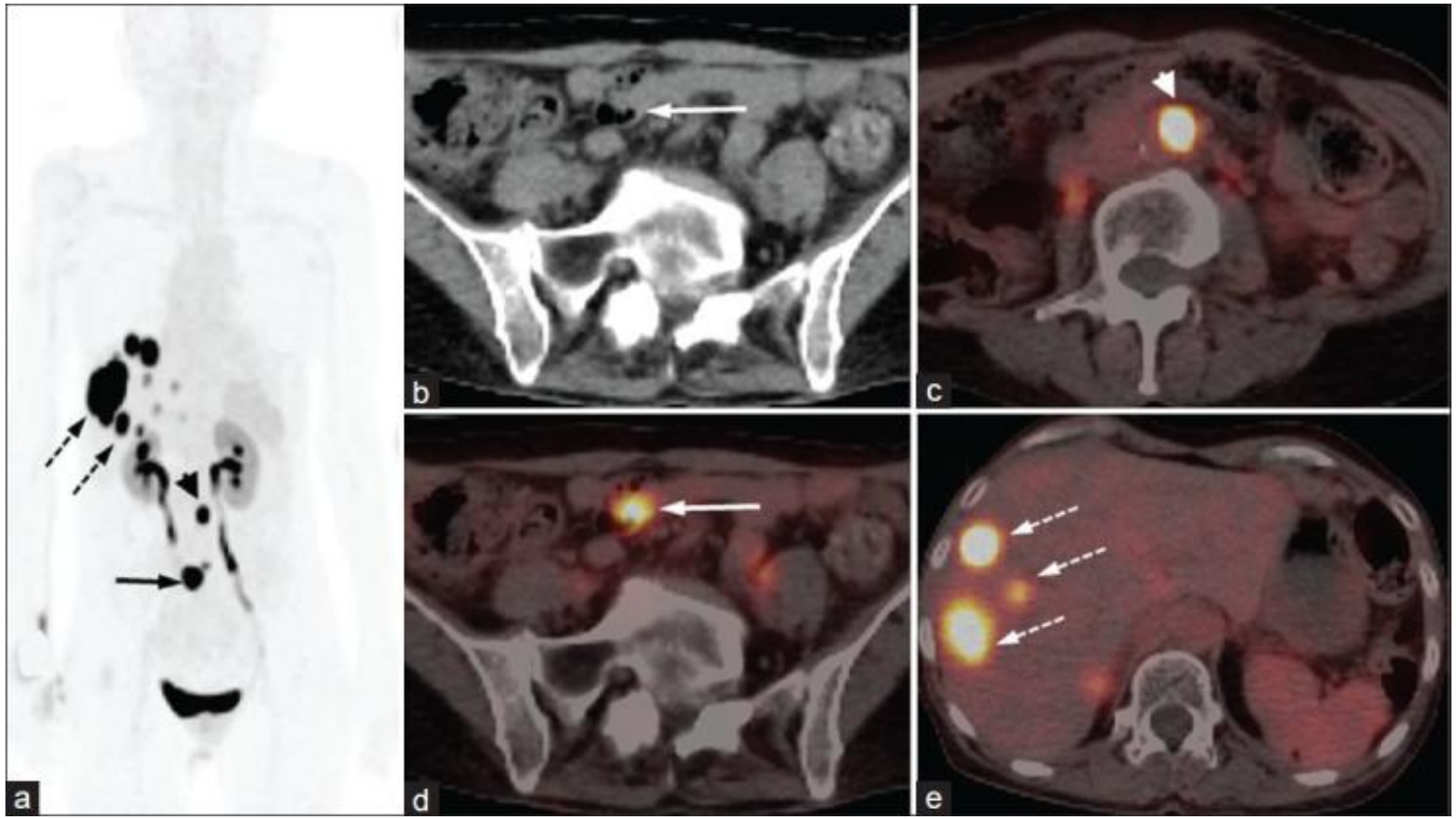
**CT & MRI**

**The ability to pick up extrapancreatic Dz**

# Anatomic CT scan & $^{111}$ Indium Pentetreotide/ Octreotide Scintigraphy

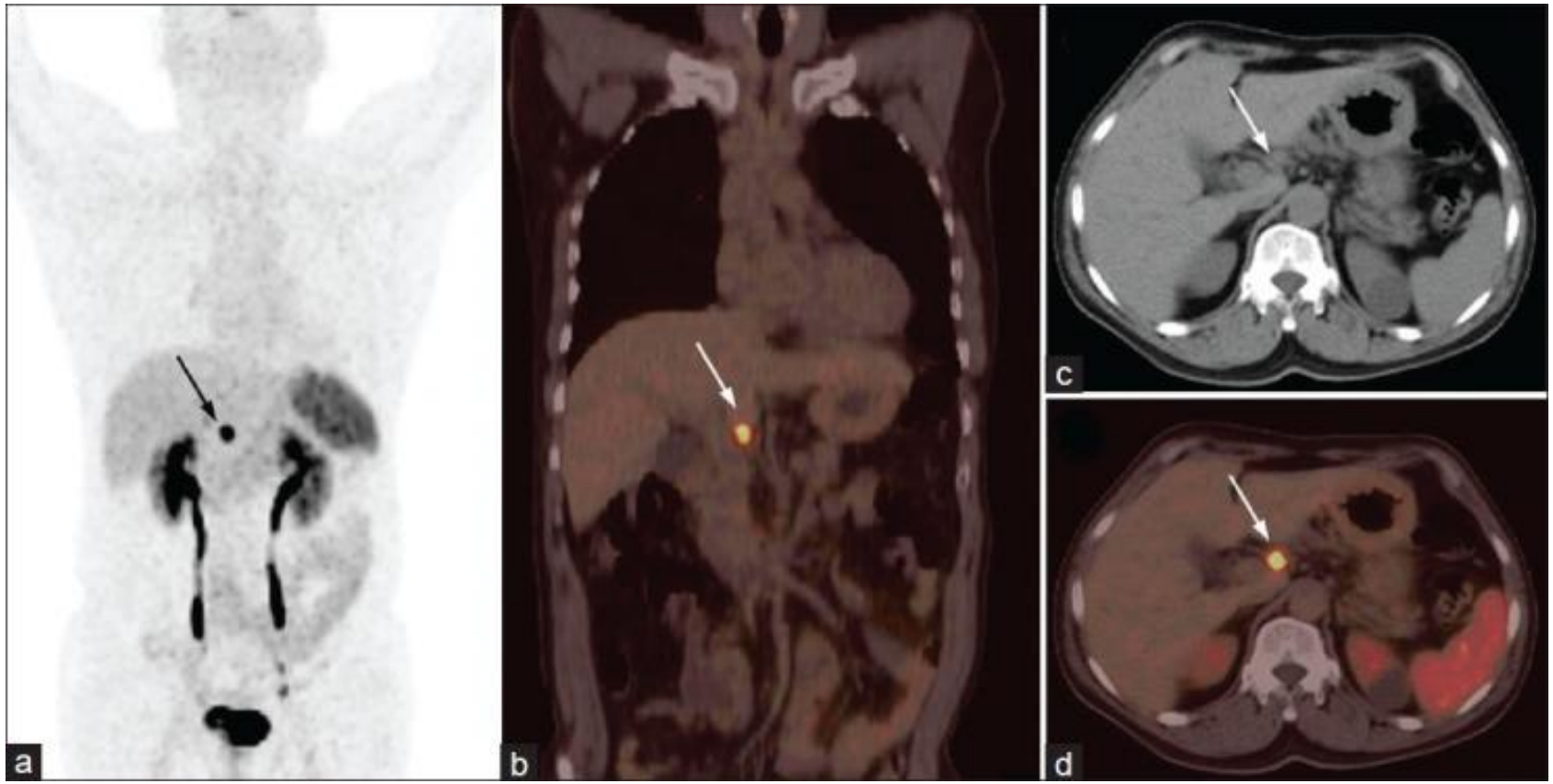


# $^{68}$Gallium- labelled PET/CT



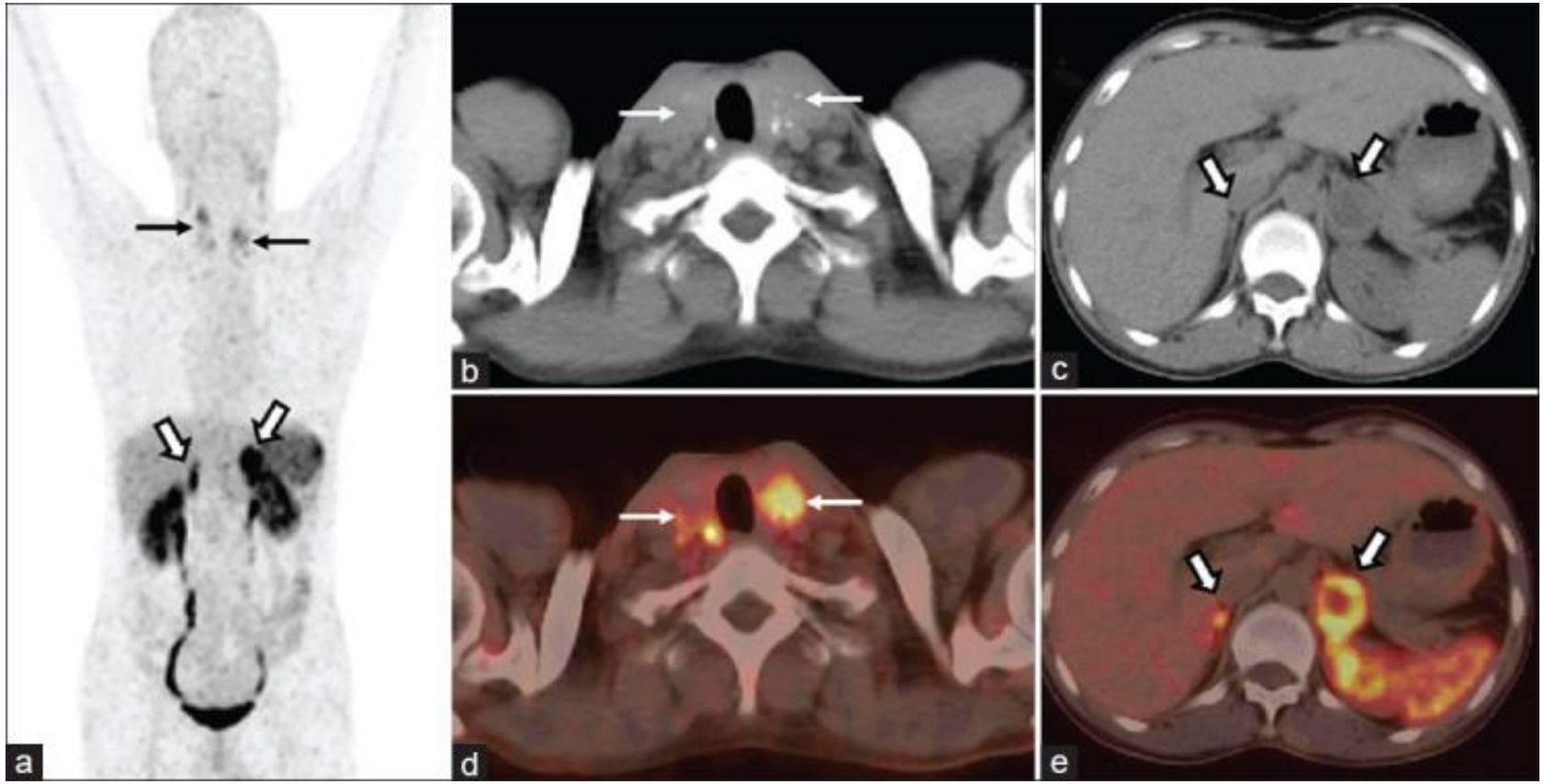

Potential as first-line imaging for GEP-NETs.
SB Tumor, R/P LN, Liver Mets

# $^{68}$Gallium- labelled PET/CT




Gastric Carcinoid (Thickening) with Portal LN

# $^{68}$Gallium- labelled PET/CT




MEN 2A

B/L Cervical masses- Medullary Ca Thyroid

B/L Adrenal masses

Also good for: Phaeo, Paraganglionoma, VHL Syndrome, MEN 1 (Functional NETs)

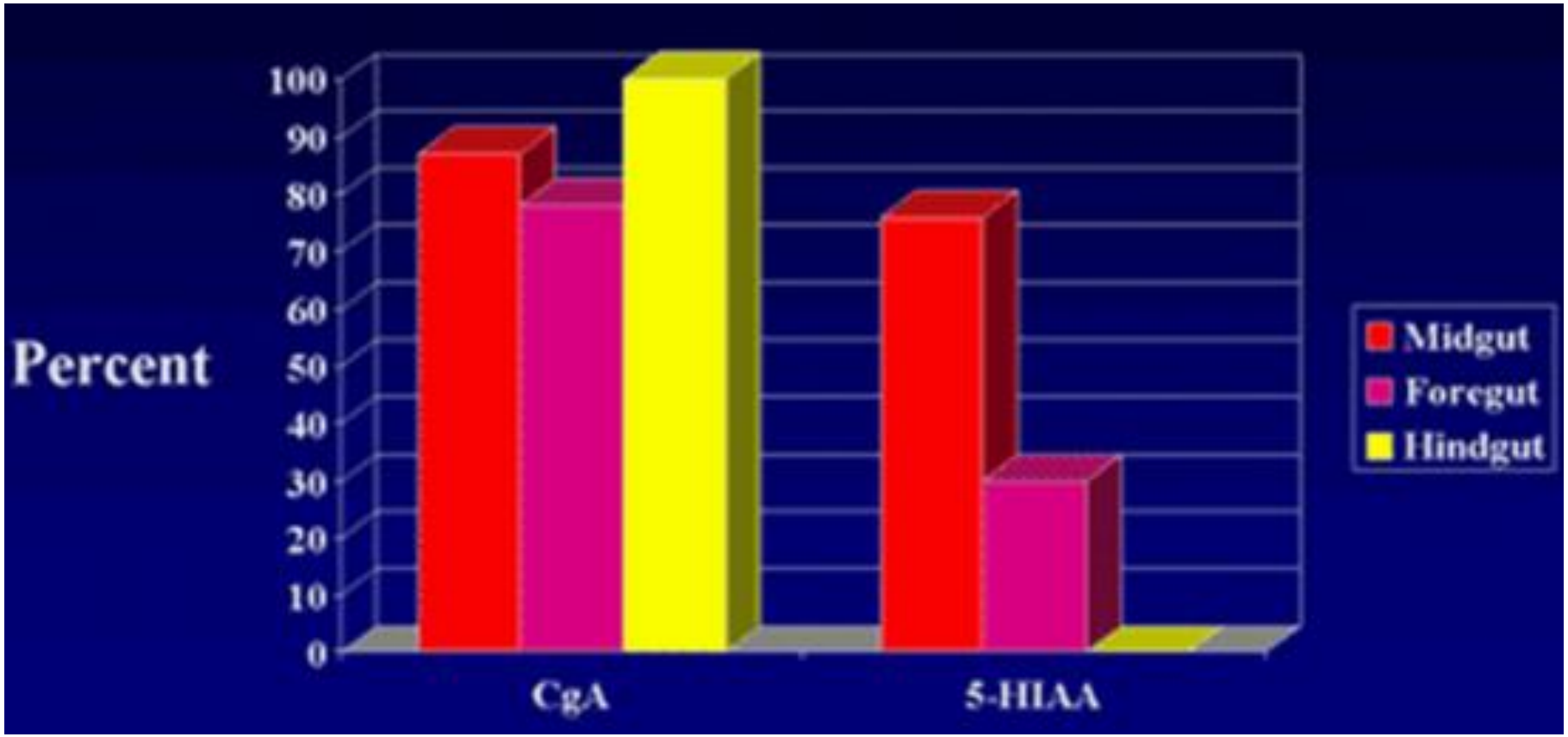
# Tumor Markers

- General NET markers
  - Chromogranin A
    - Affected by somatostatin analogues, proton pump inhibitors, kidney function, liver function
  - Neuron-specific enolase

- Midgut (small bowel, appendix, cecum)
  - 5 HIAA (24-hr urine collection)
  - Serotonin (blood, more variable)

*5-HIAA = 5-hydroxyindoleacetic acid*

# Chromogranin A vs 5HIAA




5HIAA is more important if the Chromogranin A levels are negative

# Functional Tumors- PNETs

## Fasting measurements when possible

| Gastrinoma | Glucagonoma | Insulinoma | VIPoma |
| --- | --- | --- | --- |
| Gastrin | Glucagon | Insulin | Vasoactive intestinal peptide |
| | | Pro-insulin | |
| | | C-peptide | |

# Principles of Marker Assessment

- **Lots of markers; expression can change over time**
  - Chromogranin B and C, pancreastatin, substance P, neurotensin, neurokinin A, pancreatic polypeptide
- **Take large panel of markers at key points**
  - Diagnosis or relapse
- **Follow a few elevated markers over time**
- **Not necessary to check every marker at each visit**

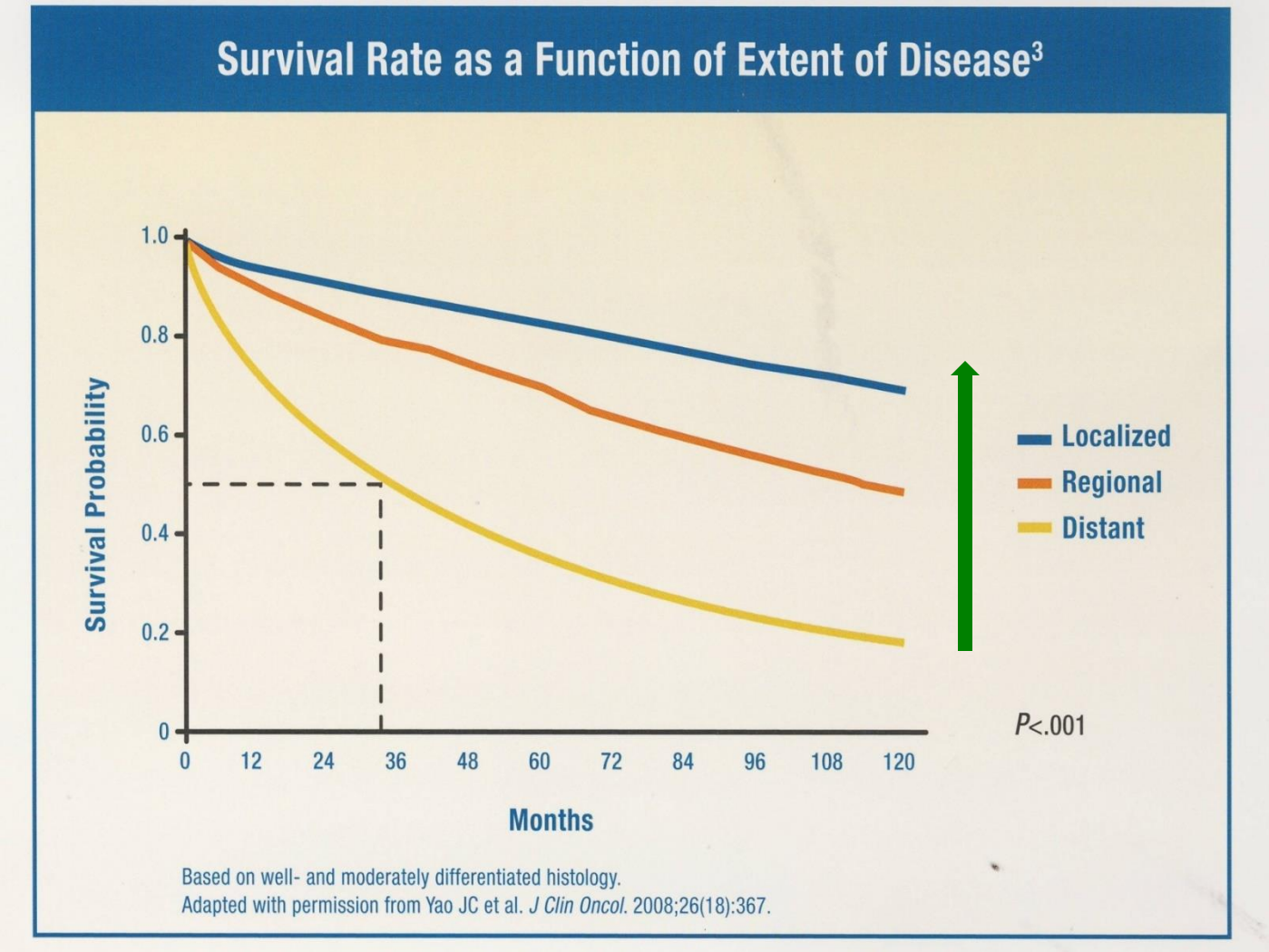
# Current Treatment Approaches

*" The first question we ask ourselves is- are the tumors surgically resectable?"*

## SURGERY IS THE GOLD STANDARD

### WHEN POSSIBLE

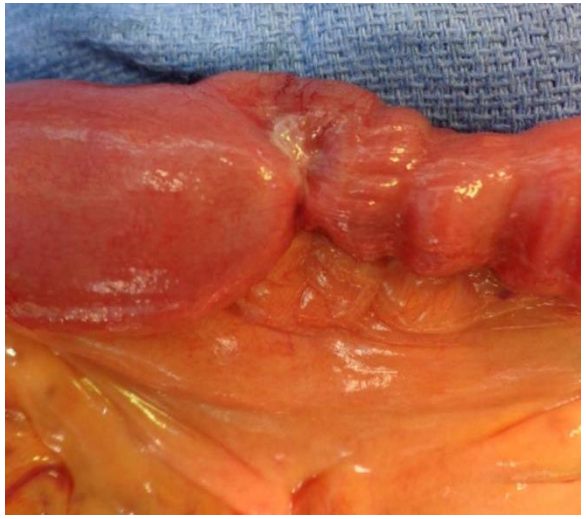
# Neuroendocrine Tumors

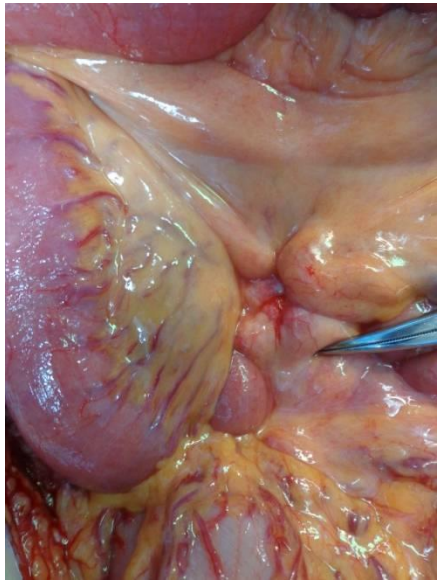


# Principles of NET Surgery

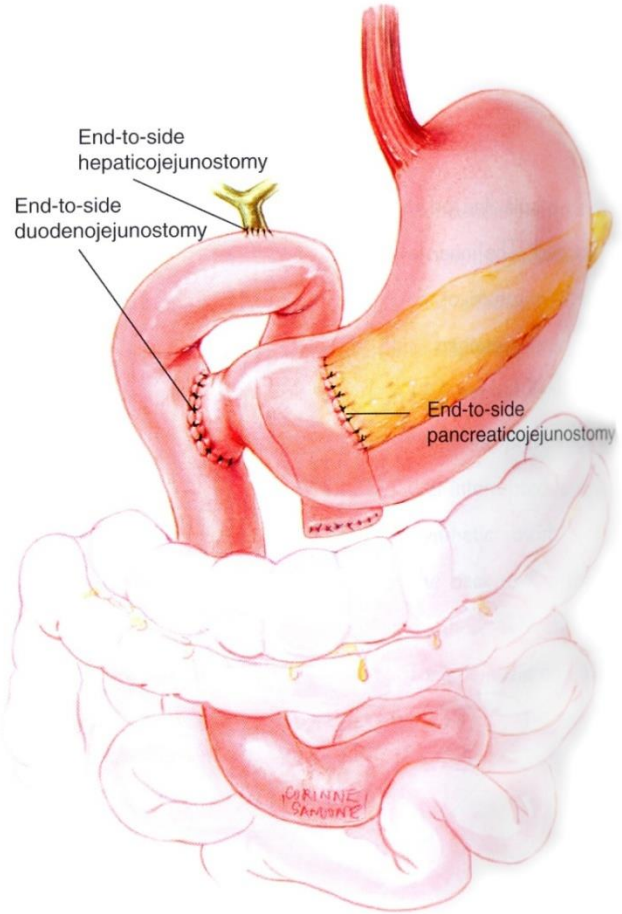
- **Locate and resect primary PNET or Small Bowel NET/Carcinoid**
  - Imaging & Tumor Markers
- **Resect Mesenteric Nodal Masses**
- **Resecting Liver Metastases**
- **Remove the Gall Bladder (If needs SSA)**
- **Be prepared for Carcinoid Crisis**

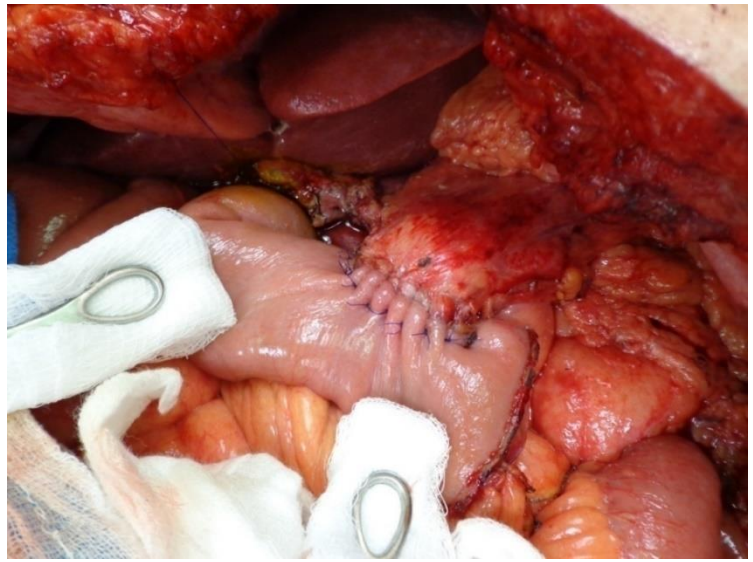
# Small Bowel NETs

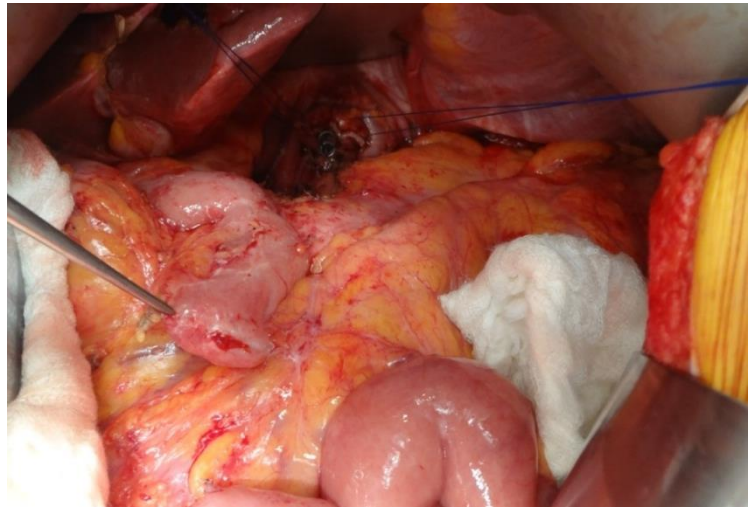




# Pancreato-Jejunostomy

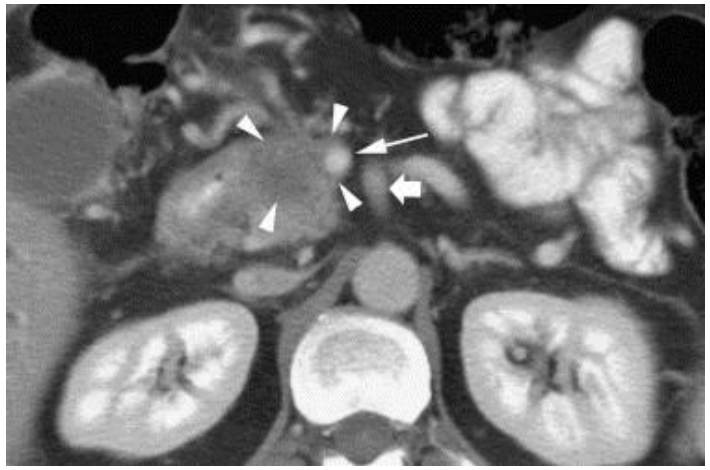


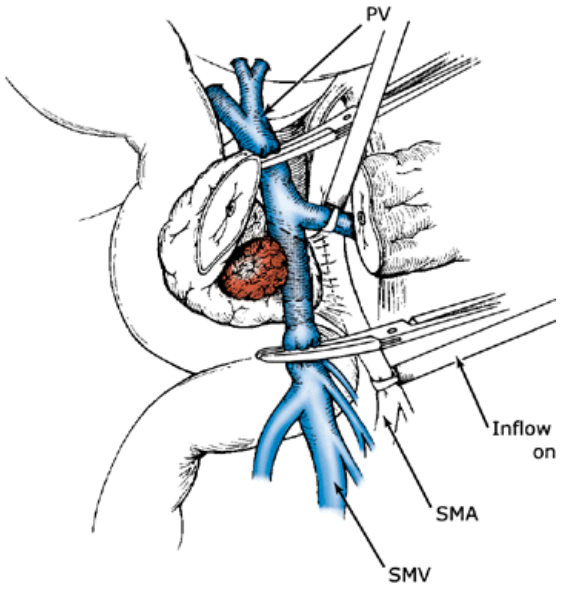



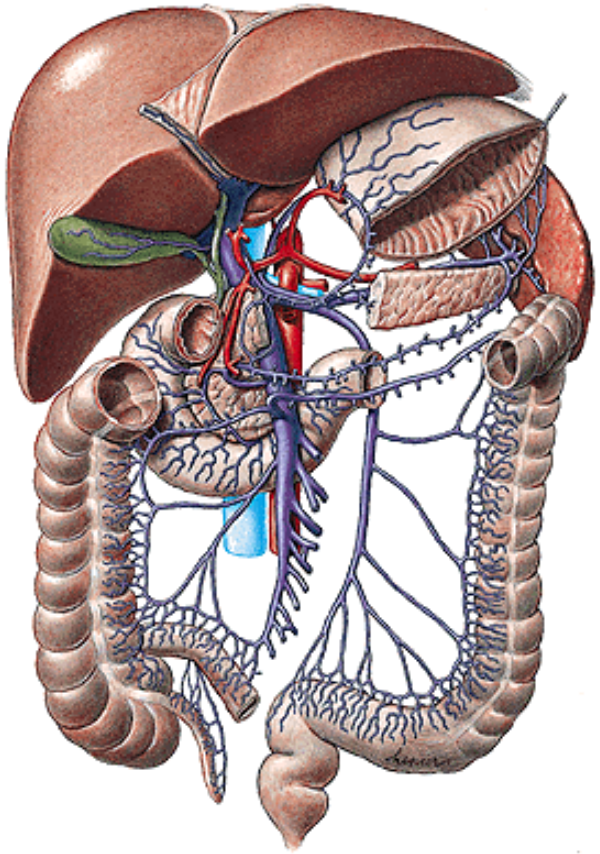


# JG Fortner: 1973- Regional Pancreatectomy

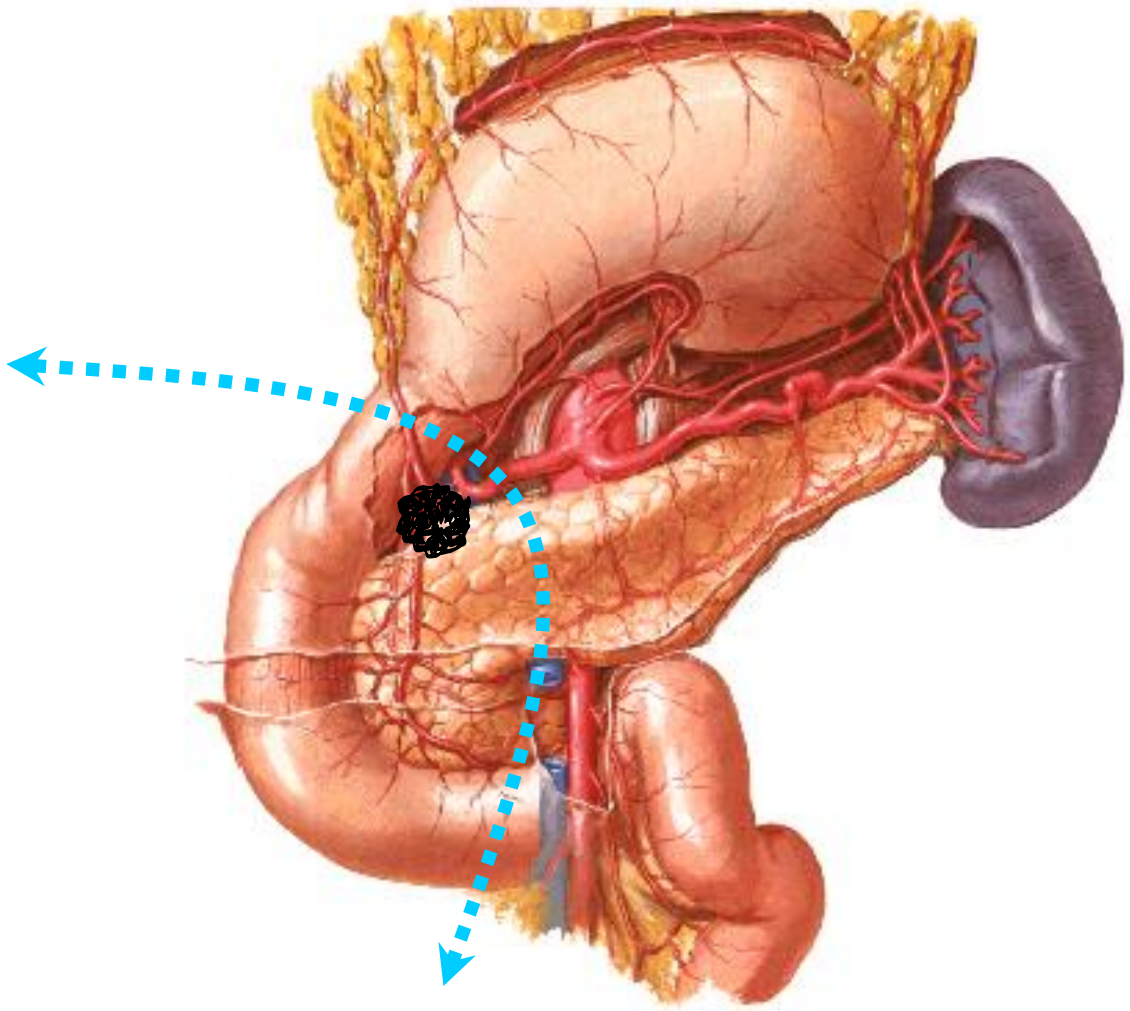
## Extended Pancreatectomy

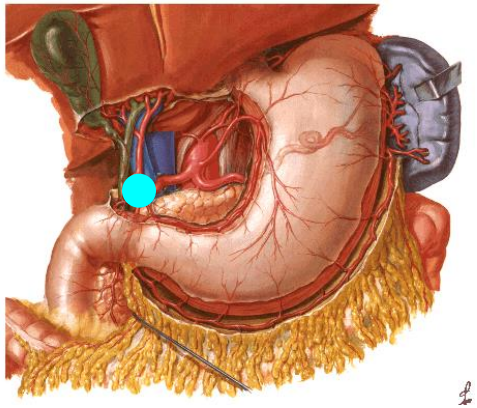


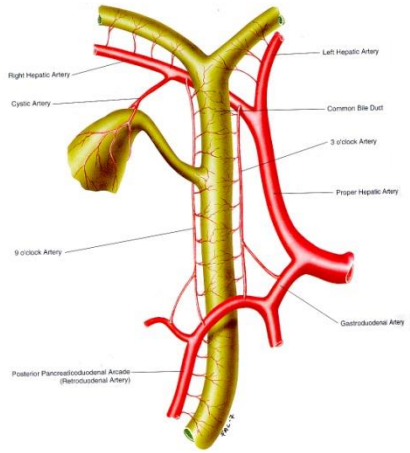


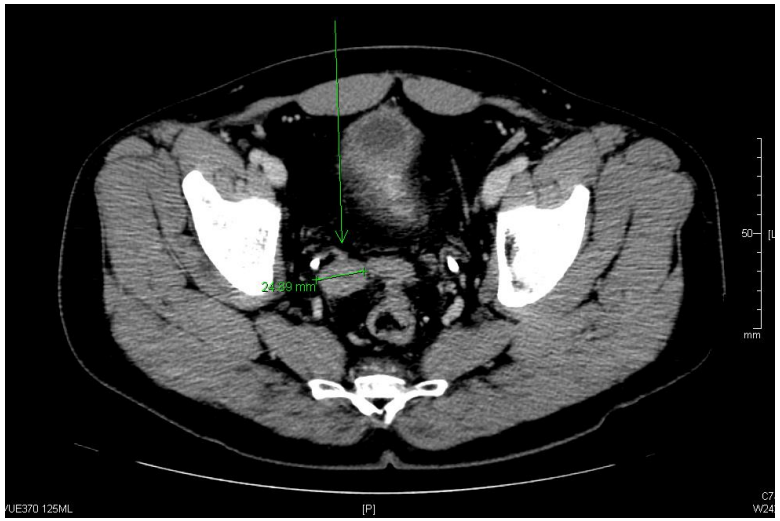
# Arterial Resections- Hepatic Artery

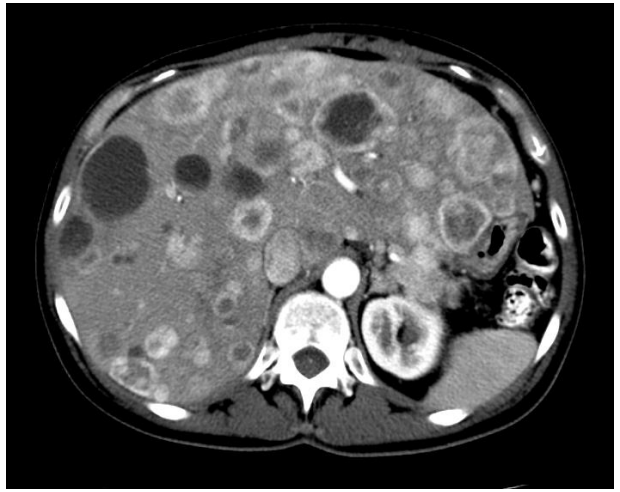


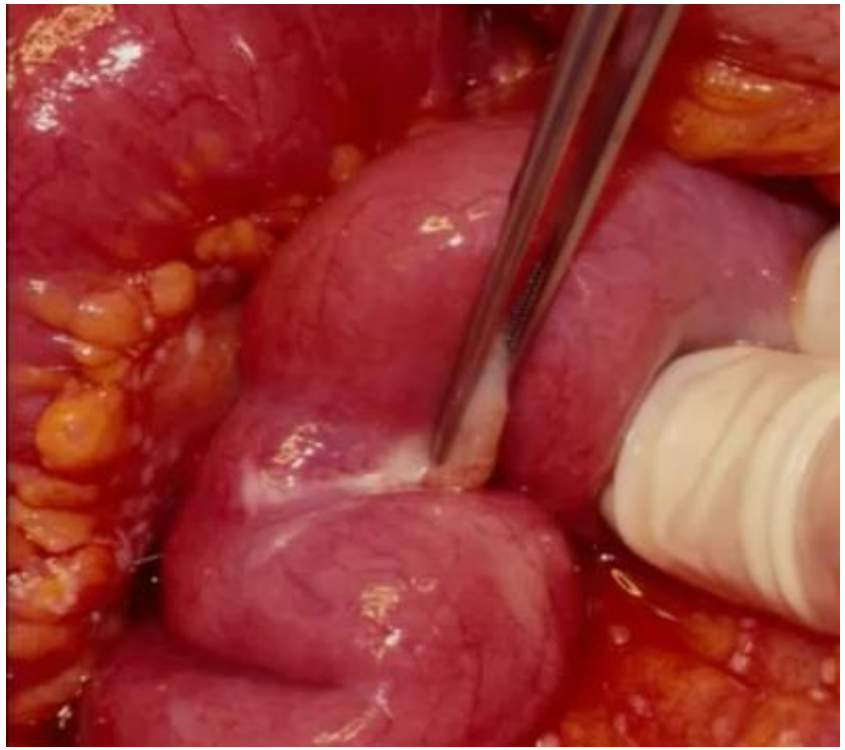




# Primary NET of the Small Bowel



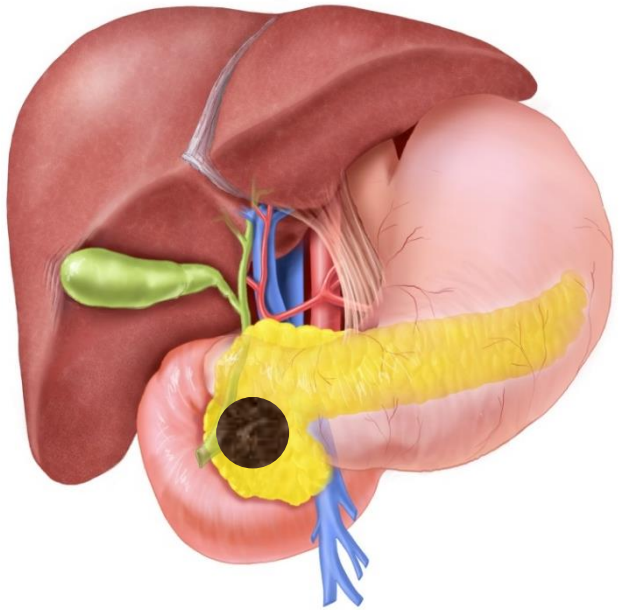





# PNETs

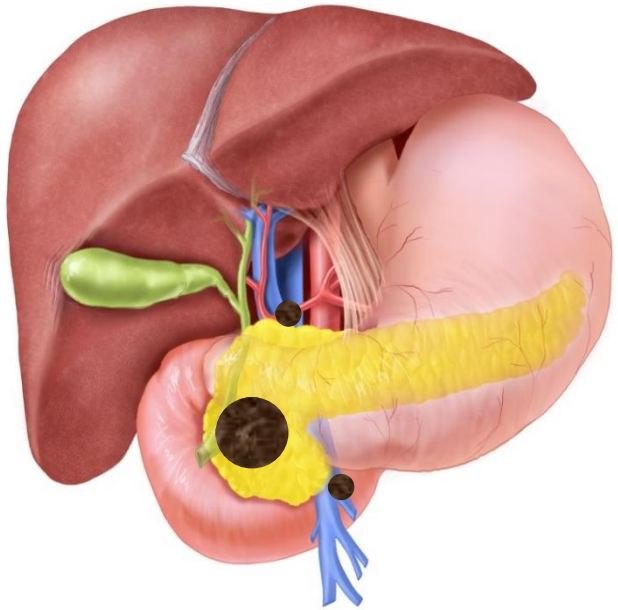
## Median Survival: Overall= 42 m

### pNET alone



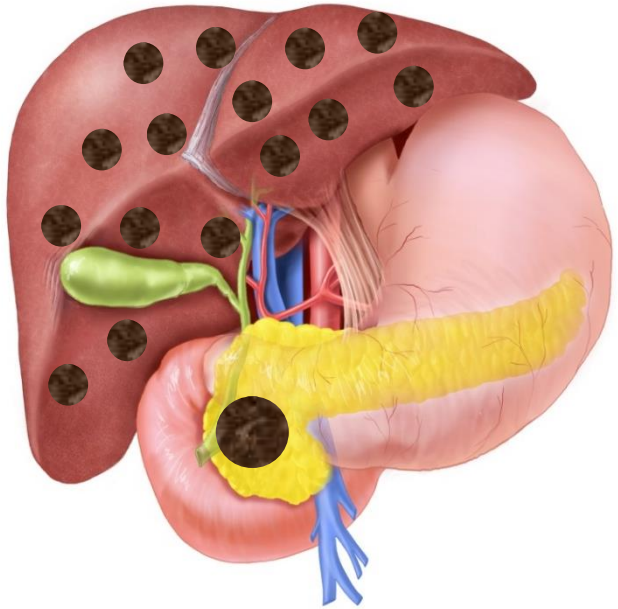
Median Survival 136 m

### pNET, LN+



77 m

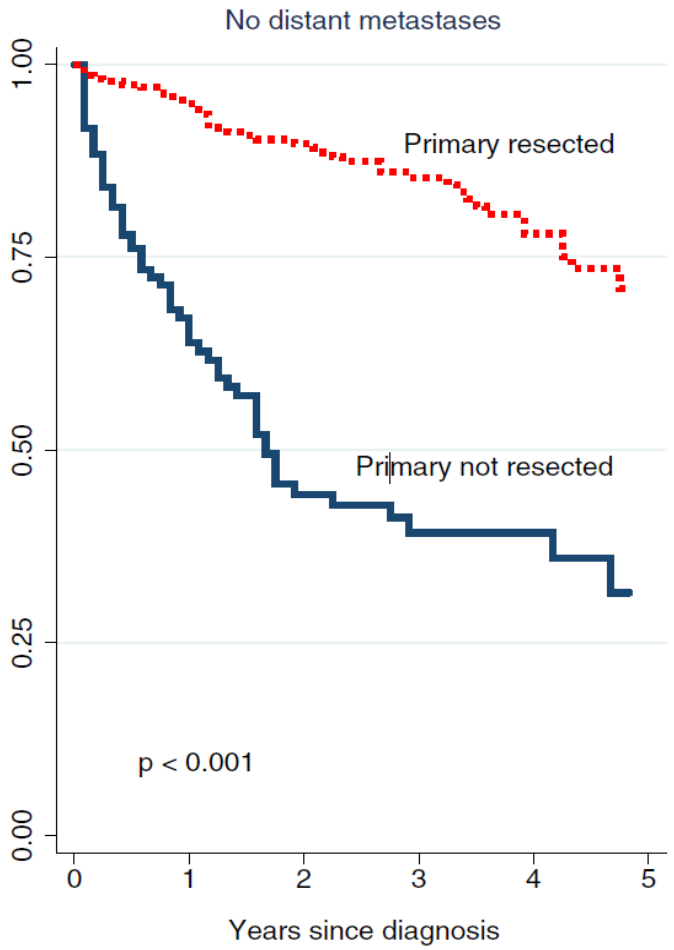
### pNET, LN+, LM

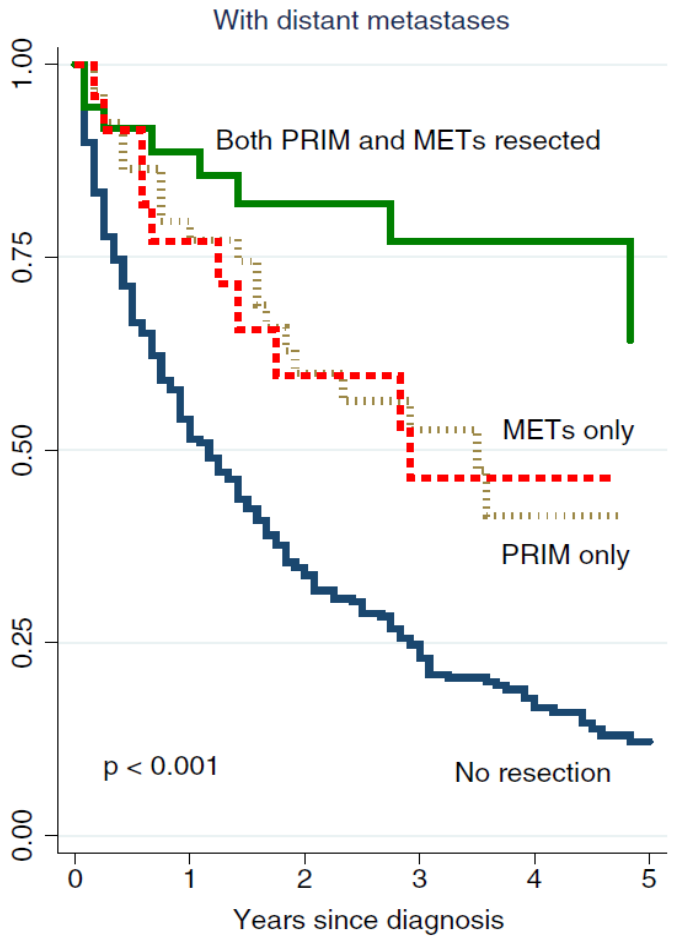


24 m

Pancreas. 2020 Jan;49(1):1-33. Consensus. Howe.....Singh.....Pommier.

# Resection of the Primary vs No Resection

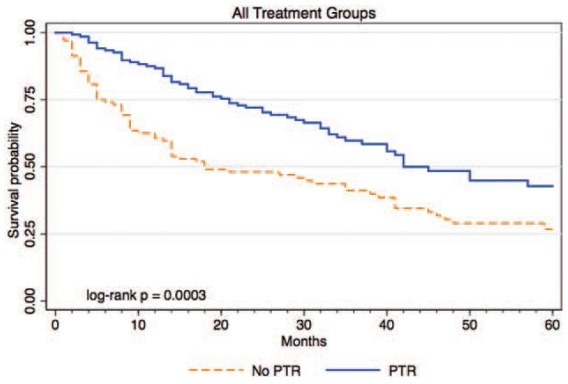



J Gastrointest Surg (2010) 14:541–548

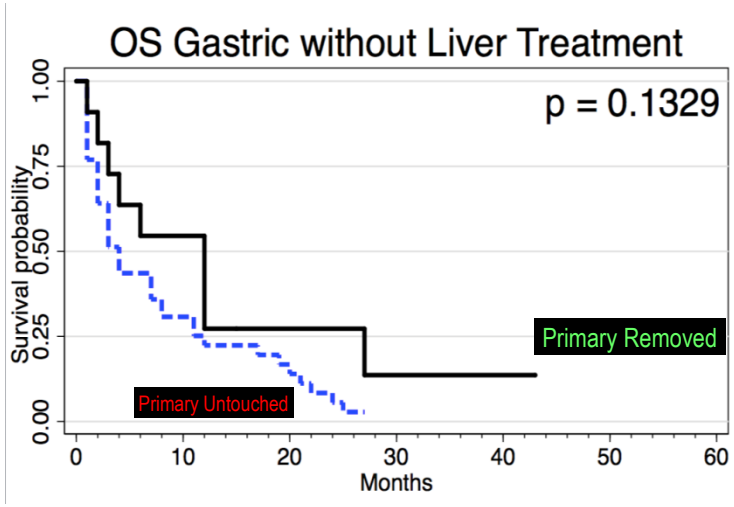
# Resection of the Primary NET- Without Liver Treatment

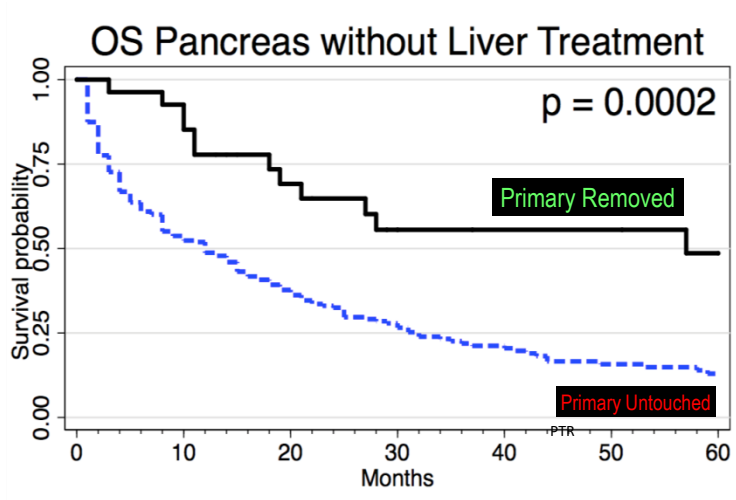
Presented at Society of Surgical Oncology 2016

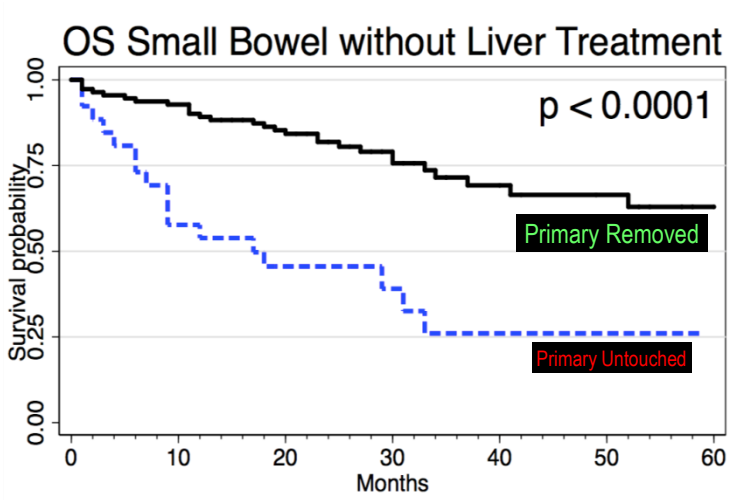


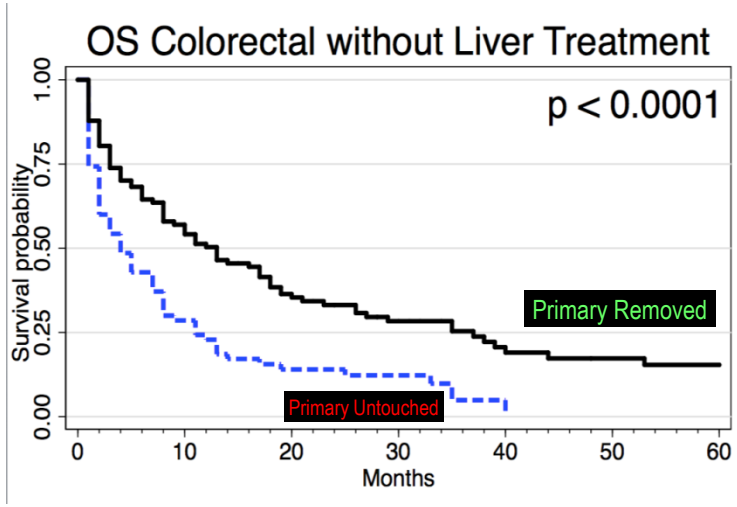

## Improves Survival EVEN WITHOUT Liver Treatment

**n= 864 Stage 4**
**California Cancer Registry**



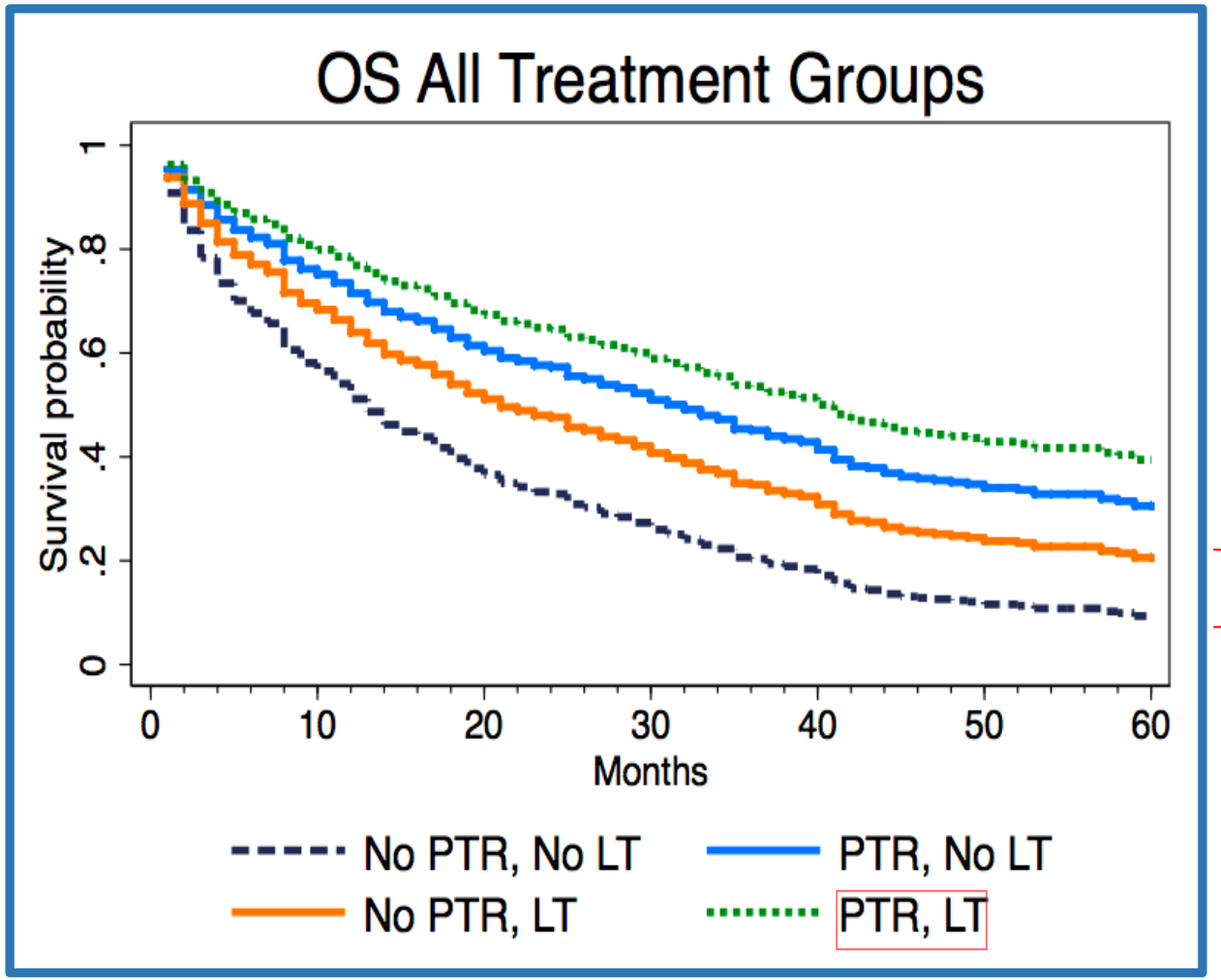

A Lewis.....G Singh. Ann Surg. *2019 Dec; 270(6):1131-1137. PMID: 29746336*

# Resection of the Primary NET & Liver treatment

Presented at Society of Surgical Oncology 2016

## Improves Survival even MORE with Liver Treatment

**n= 864 Stage 4**
**California Cancer Registry**




Primary Removed with Liver Rx

Primary Removed

Primary Untouched

A Lewis.....G Singh. Ann Surg. 2019 Dec; 270(6):1131-1137. PMID: 29746336

# Management Modalities for NET Liver Metastases

1. Surgery
2. SSA/Immunotherapy/ Targeted therapy/ Chemotherapy
3. PRRT
4. Microwave Ablation/ ~~Radiofrequency Ablation~~
5. Irreversible Electroporation (NanoKnife)
6. Chemoembolization/ Bland Embolization
7. Radiation/ Radioembolization (SIRT)
8. Bland Embolization
9. ~~Cryotherapy~~
10. ~~Ethanol Injection~~
11. ~~Transplant (limited donor pool)~~
12. ~~Gene Therapy~~

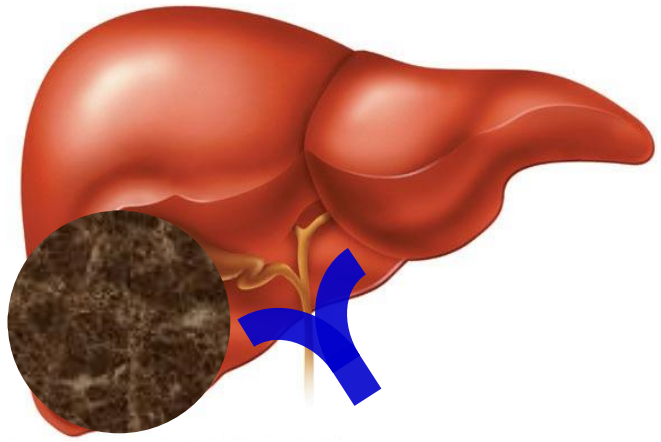
# The QUESTION?

**The MOST important question is**

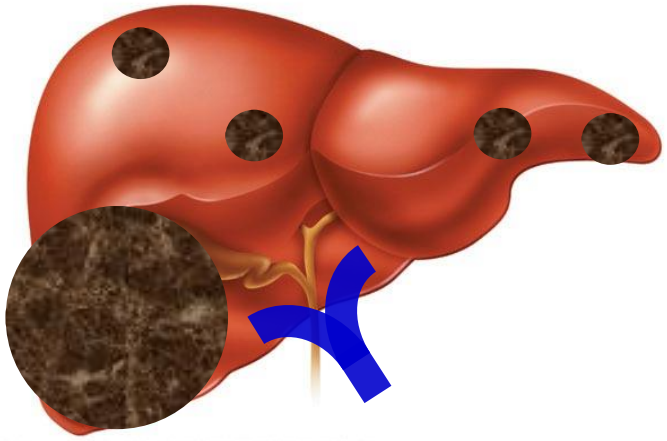
**WHAT IS THE BURDEN (status) OF THE LIVER DISEASE?**

# Liver Mets in NETs

Type 1



Type 2



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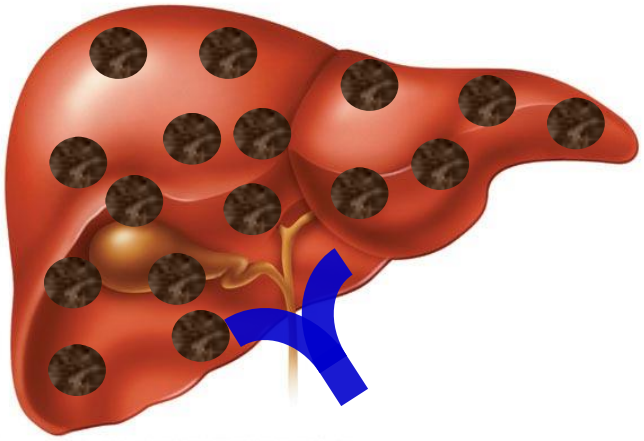

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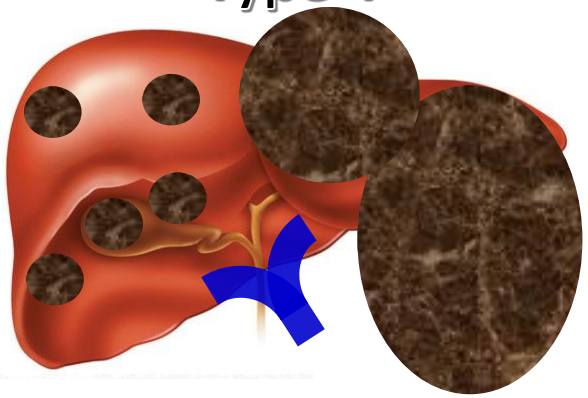
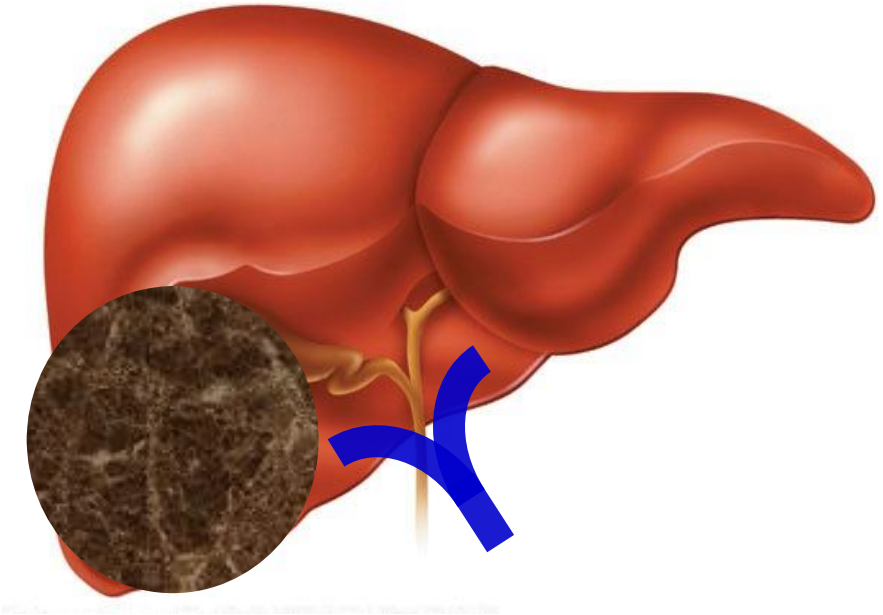
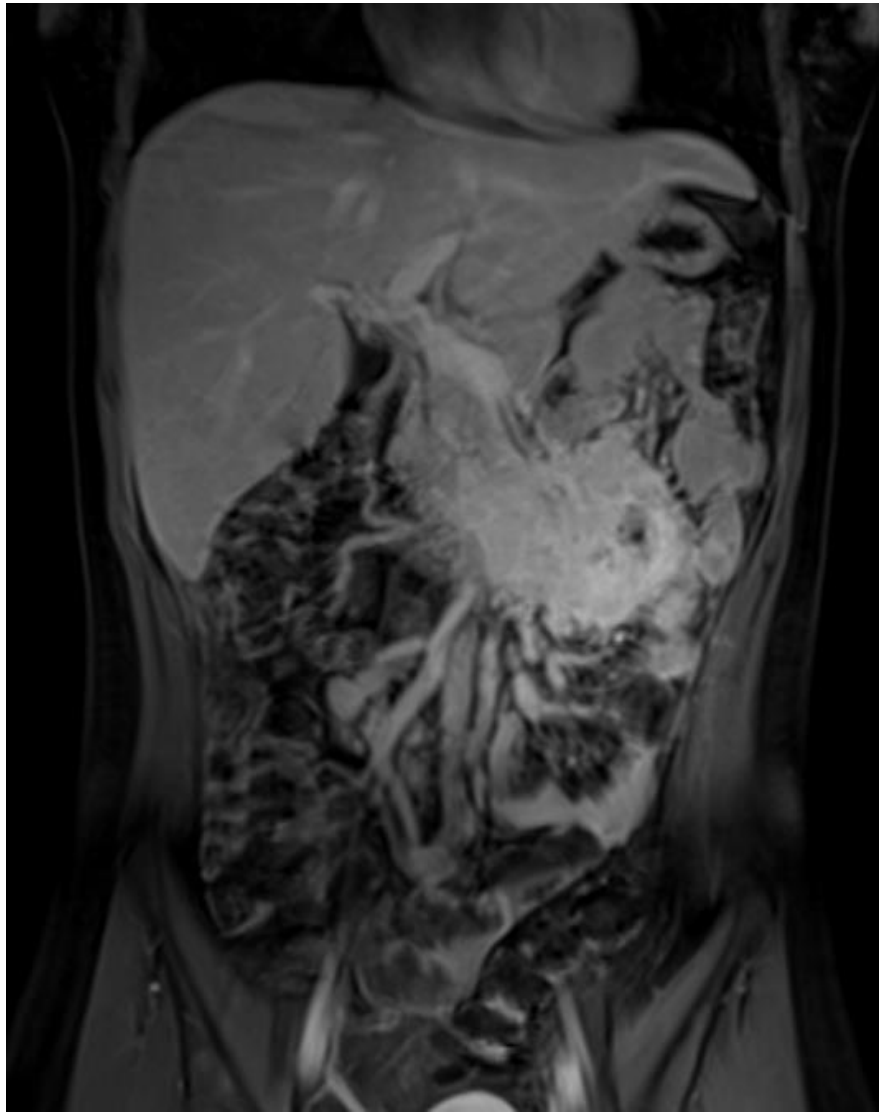


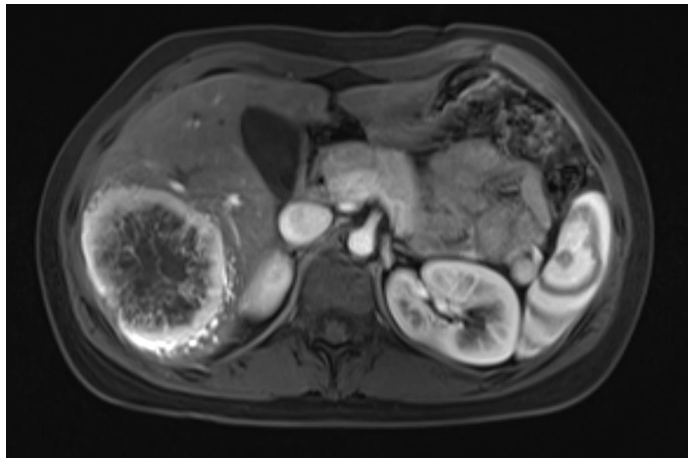
# Liver Mets in NETs

Type 1



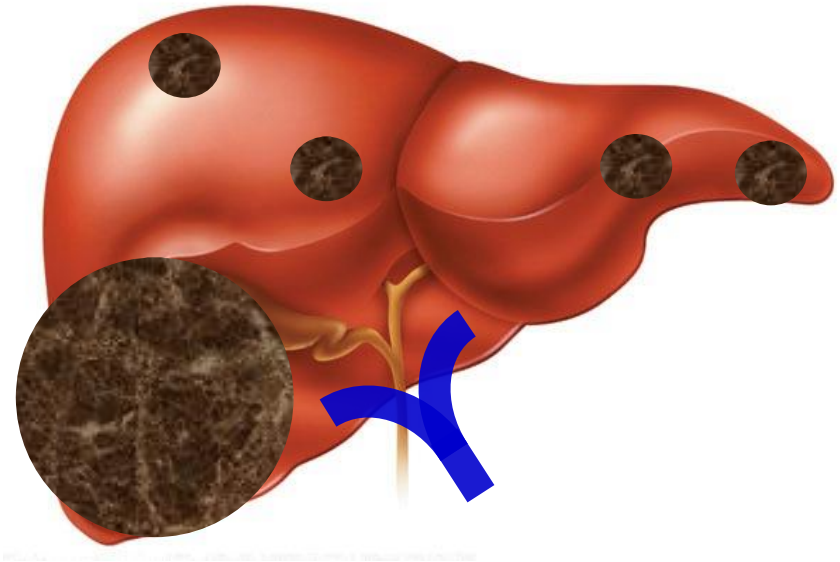
# NET LIVER Mets- Type 1





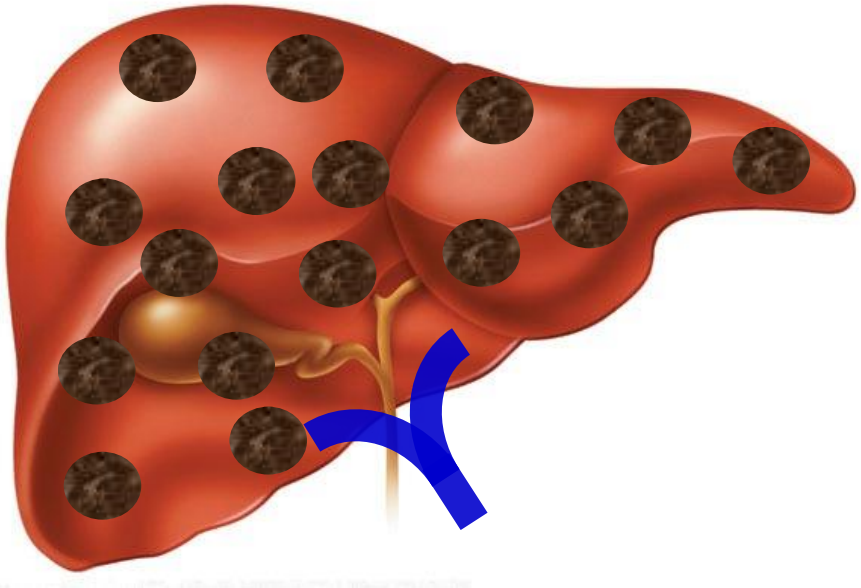
# Liver Mets in NETs

Type 2

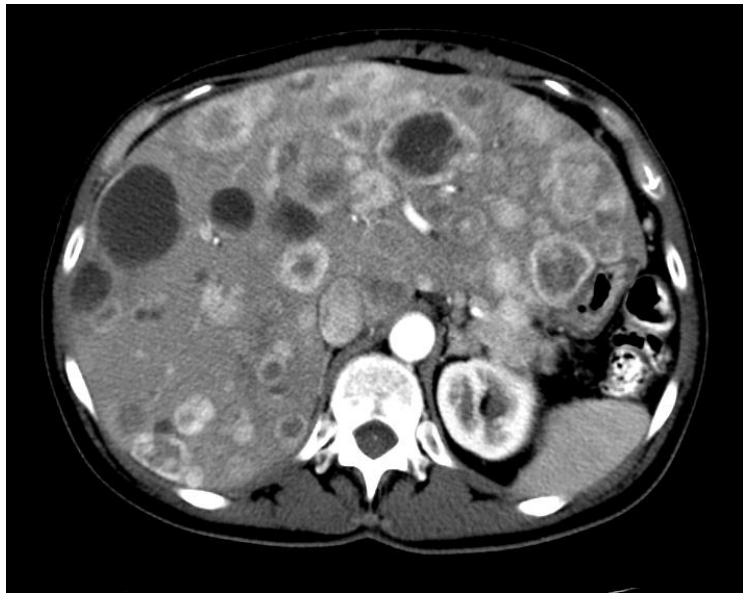


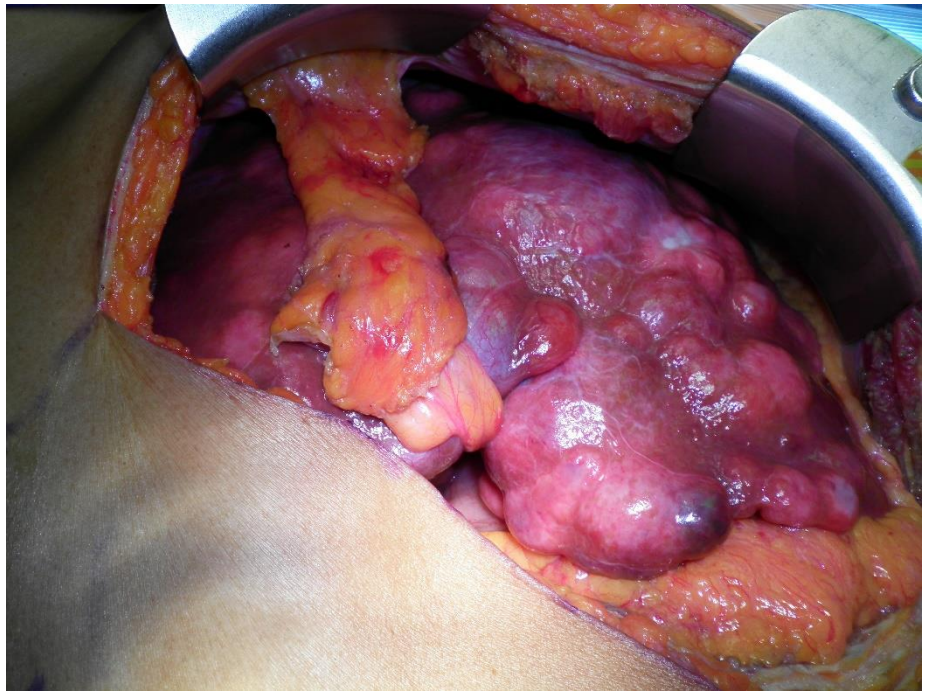
# Liver Mets in NETs

Type 3



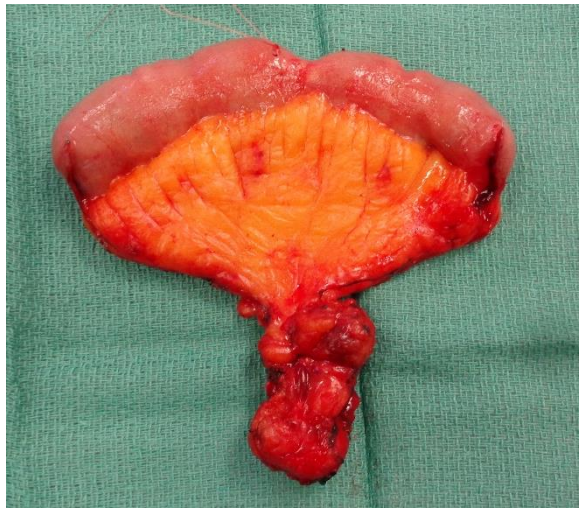
# NET LIVER Mets- Type 3

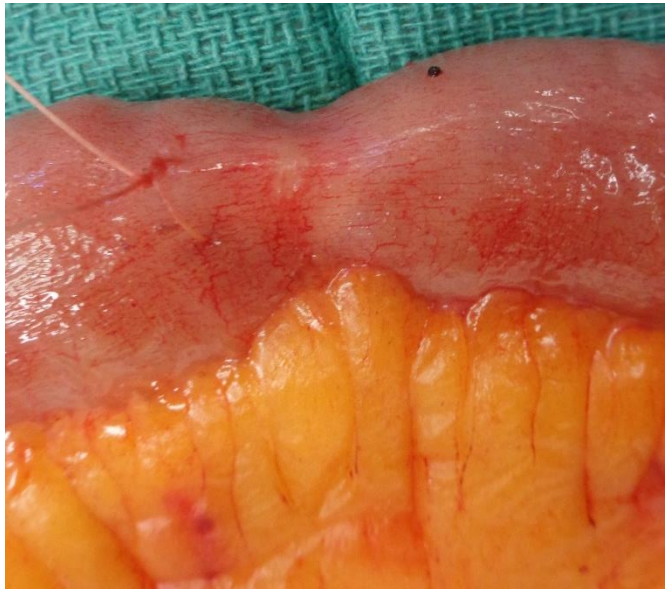


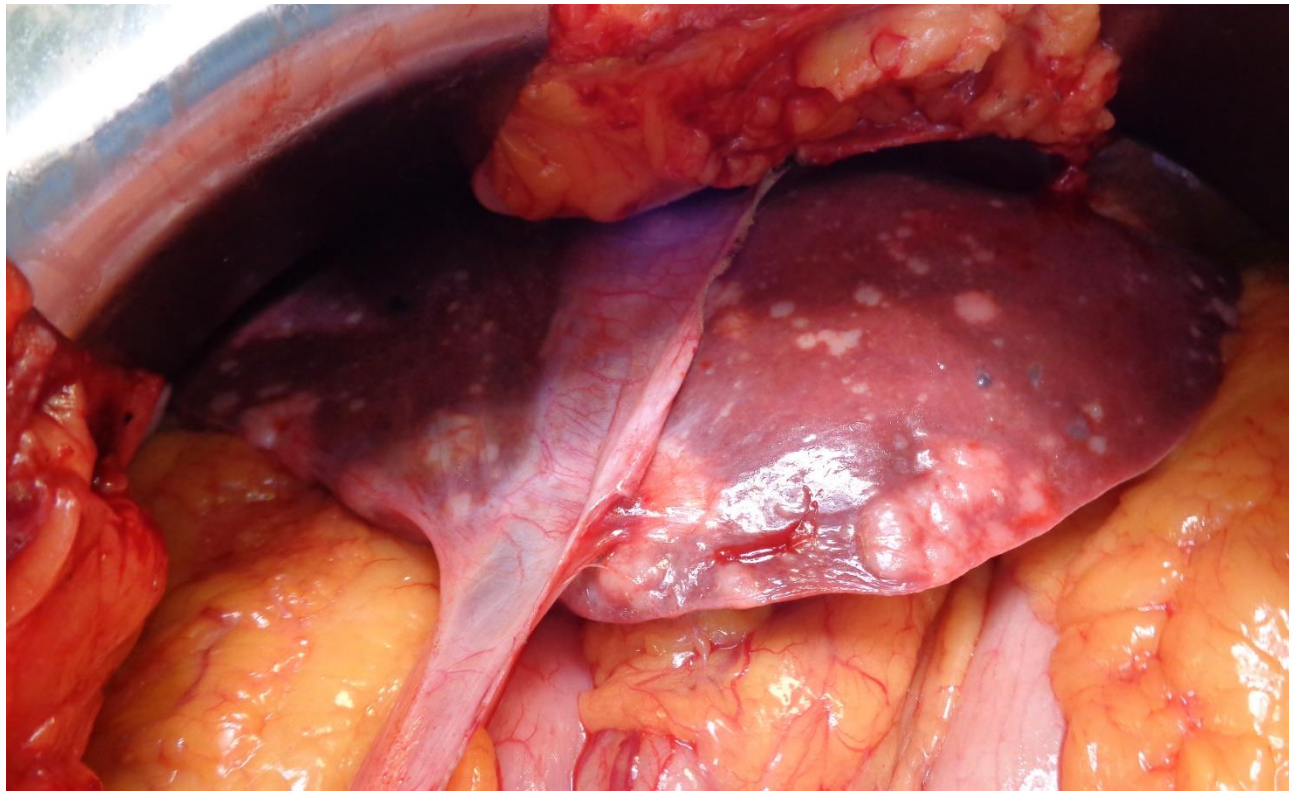



- ✓ 7 years later
- ✓ s/p Distal Pancreatectomy
- ✓ Radioembolization x2

# NET LIVER Mets- Type 3



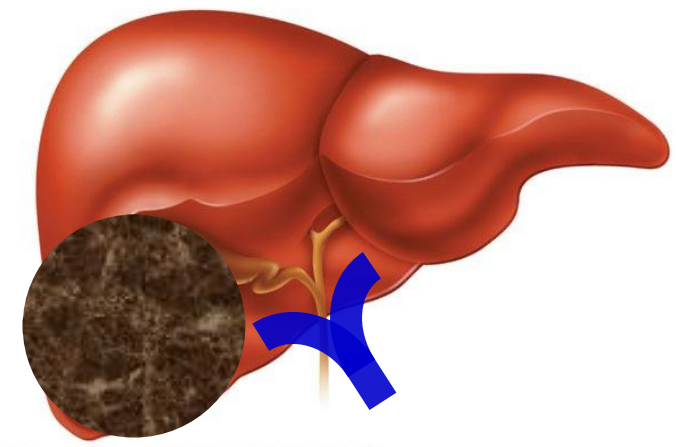




✓ **Primary is almost undetectable**

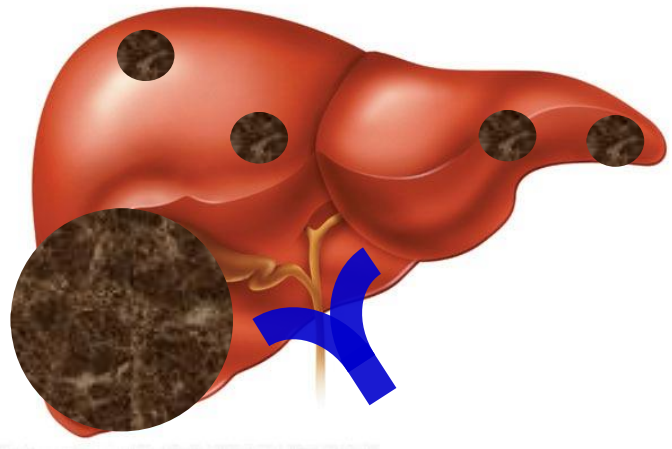
# Liver Mets in NETs

## Type 1



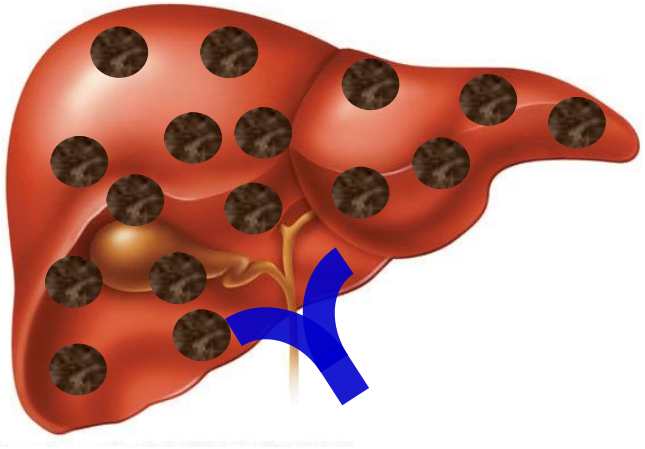
Resection
±
Ablation (<3 cm)

## Type 2



Multiple Resections
±
Multiple Ablations (<3 cm)

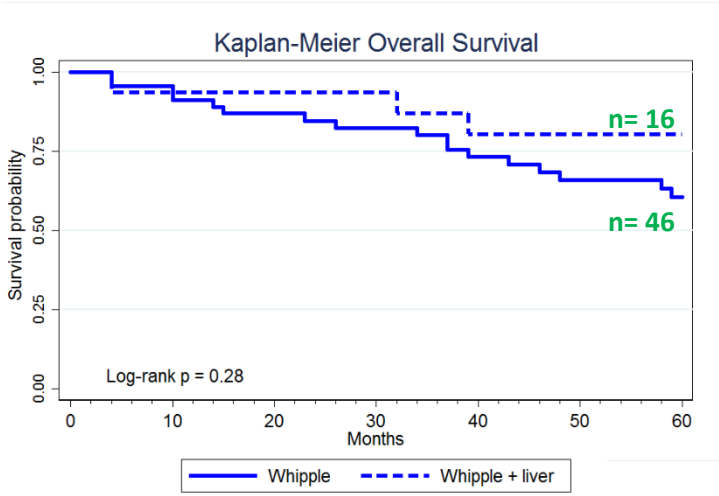
## Type 3

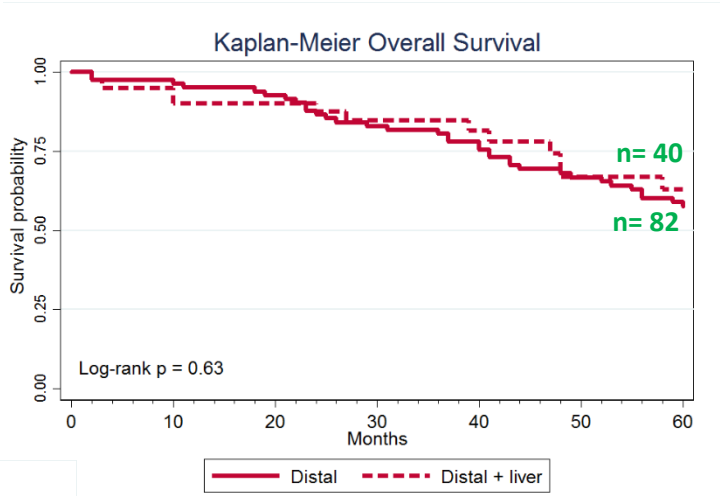


**Unresectable**
Surveillance
±
Alternate Therapies

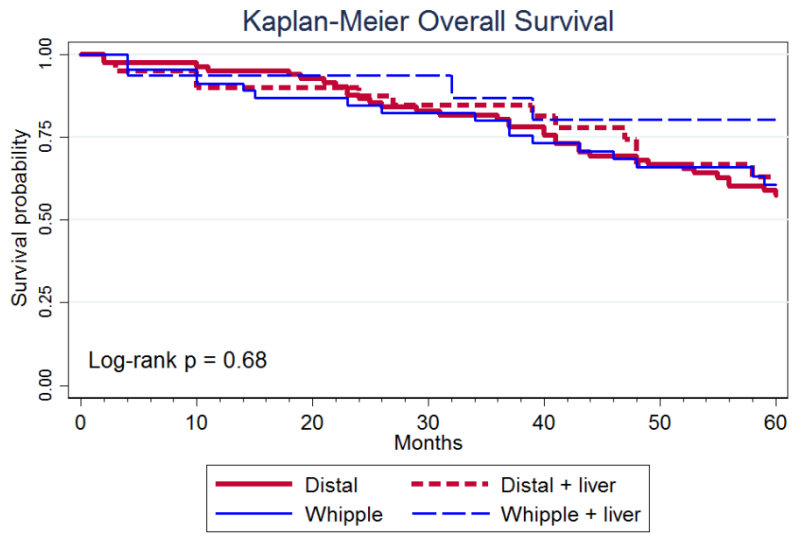
# California Cancer Registry- Whipple & Distal with Liver Resections

2000-2012




| | |
|---|---|
| Hemorrhage: | NS |
| Abscess: | NS |
| POPF: | NS |
| Respiratory: | NS |
| Wound: | NS |
| Stroke: | NS |
| DVT: | NS |
| PE: | NS |
| CV: | NS |
| DGE: | NS |




| | |
|---|---|
| Hemorrhage: | NS |
| Abscess: | 0.004 |
| POPF: | 0.04 |
| Respiratory: | NS |
| Wound: | NS |
| Stroke: | NS |
| DVT: | NS |
| PE: | NS |
| CV: | NS |
| DGE: | NS |


**Lafaro K**, Blakely AM, Kessler J, Li D, Ituarte PHG, Lee B, **Singh G**. Resection of primary pancreatic neuroendocrine tumors with concomitant liver resection: reasonable and safe. AHPBA, Miami, FL, March 22, 2019.

# Synchronous resection of the primary & Difficult Liver mets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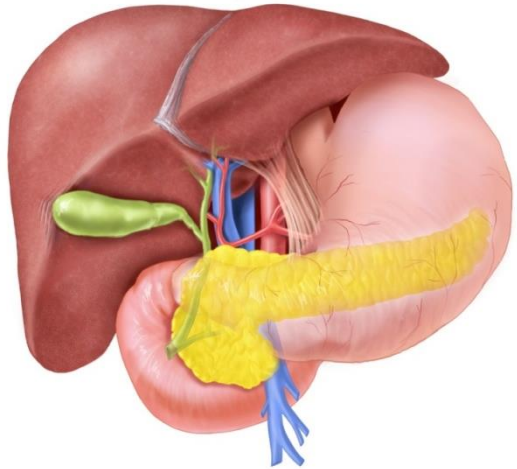

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Aram Lee, MD
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## Radiation Oncology

**YJ Chen, MD**
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**Heather McGee, MD**

# Conclusion

## SURGERY IS THE GOLD STANDARD

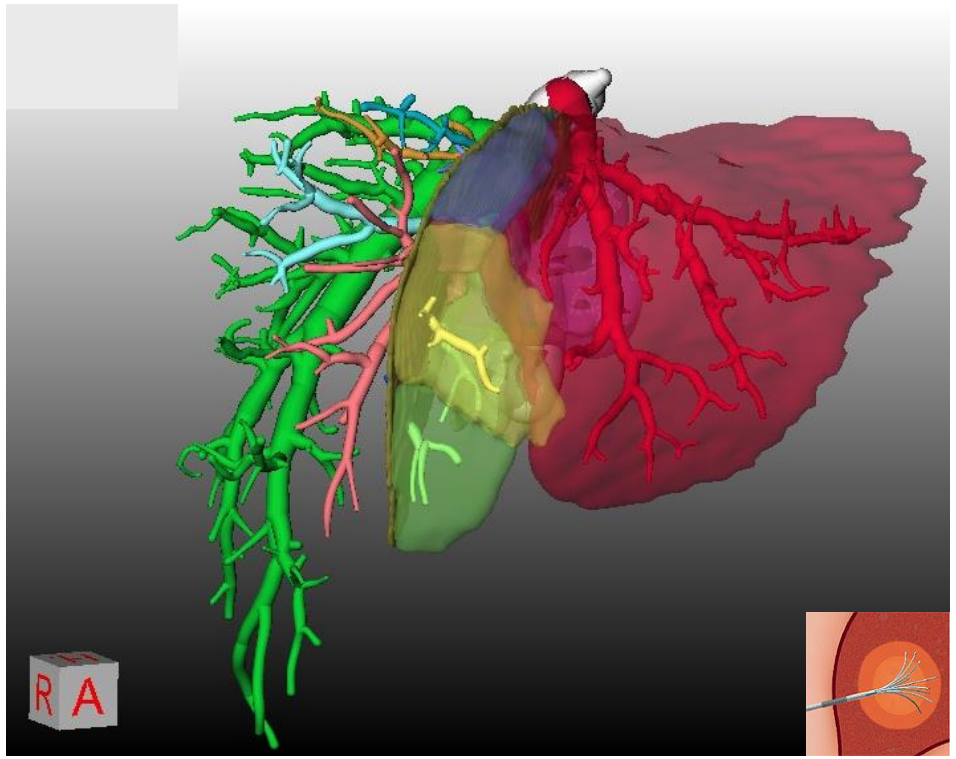
### DEBULK WHEN POSSIBLE- Definite Survival Advantage

- ✓ Somatostatin analogs effective in controlling hormonal syndrome
- ✓ Several new drugs and immunotherapy in trials
- ✓ The rise of PRRT very encouraging
- ✓ THE FUTURE IS REALLY BRIGHT & PROMISING

# Summary: Resection the Gold Standard

## Paradigm Shift

**What is Removed** **BUT** **What is Left Behind**




- Future Liver Remnant of 20% (30%)
- Adequate Inflow and Outflow
- At least 2 Contiguous Segments
- Capability of Resecting all visible Dz
- MWA/ IRE/ RFA/ Nanoknife is an Adjunct or Compliment
- Ablation for <3 cm masses acceptable

Question is no longer 'WHO IS RESECTABLE' but rather 'WHO IS NOT RESECTABLE'