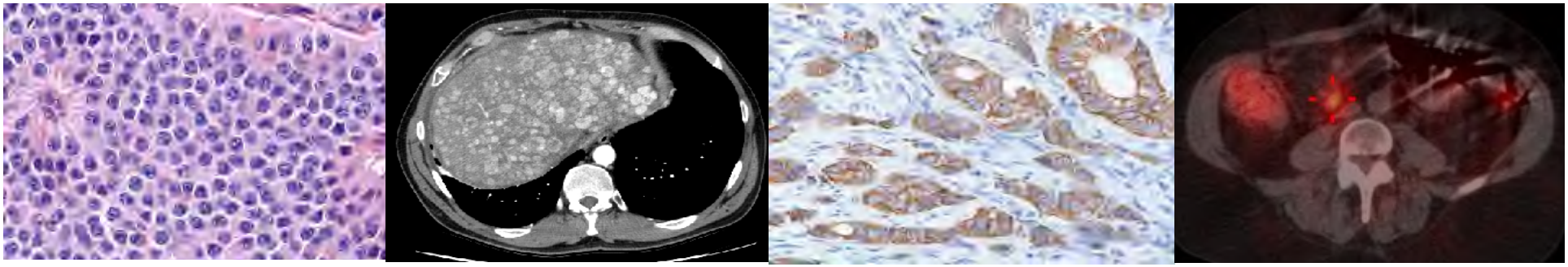
STANFORD
CANCER CENTER

Neuroendocrine Tumors: Just the Basics…

George Fisher, MD PhD



Topics that we will **not** discuss…

- Some types of lung cancer:
  - Small cell neuroendocrine lung cancer
  - Large cell neuroendocrine lung cancer
- Some types of colon cancer:
  - Adenocarcinoma with “neuroendocrine features”
- Rare type of appendiceal cancer:
  - Goblet cell “carcinoid”
- Rare type of skin cancer:
  - Merkel cell (neuroendocrine) tumor

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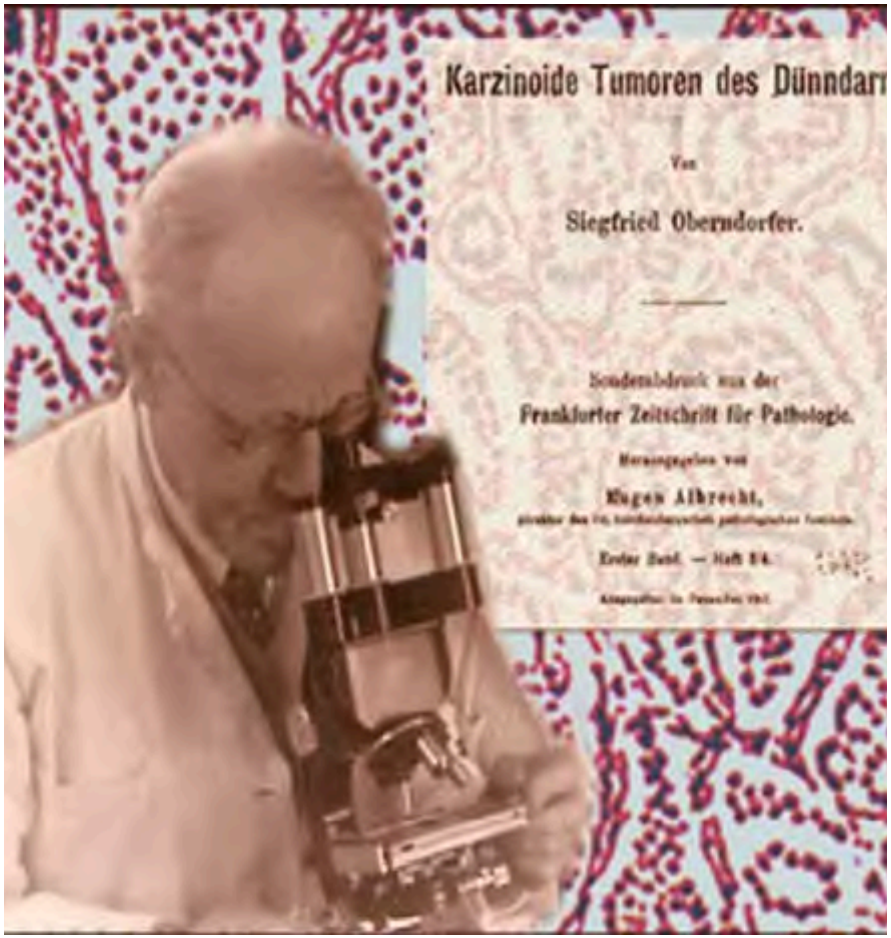
  - Merkel cell (neuroendocrine) tumor

If you have a poorly differentiated NET, meet us at the break

NET History

- 1907 Sigfried Oberndorfer uses term “karzinoid” to describe morphologically distinct class of intestinal tumors with less aggressive behavior than carcinomas



NET Basics: "You're (not quite) one in a million"

- Incidence is low

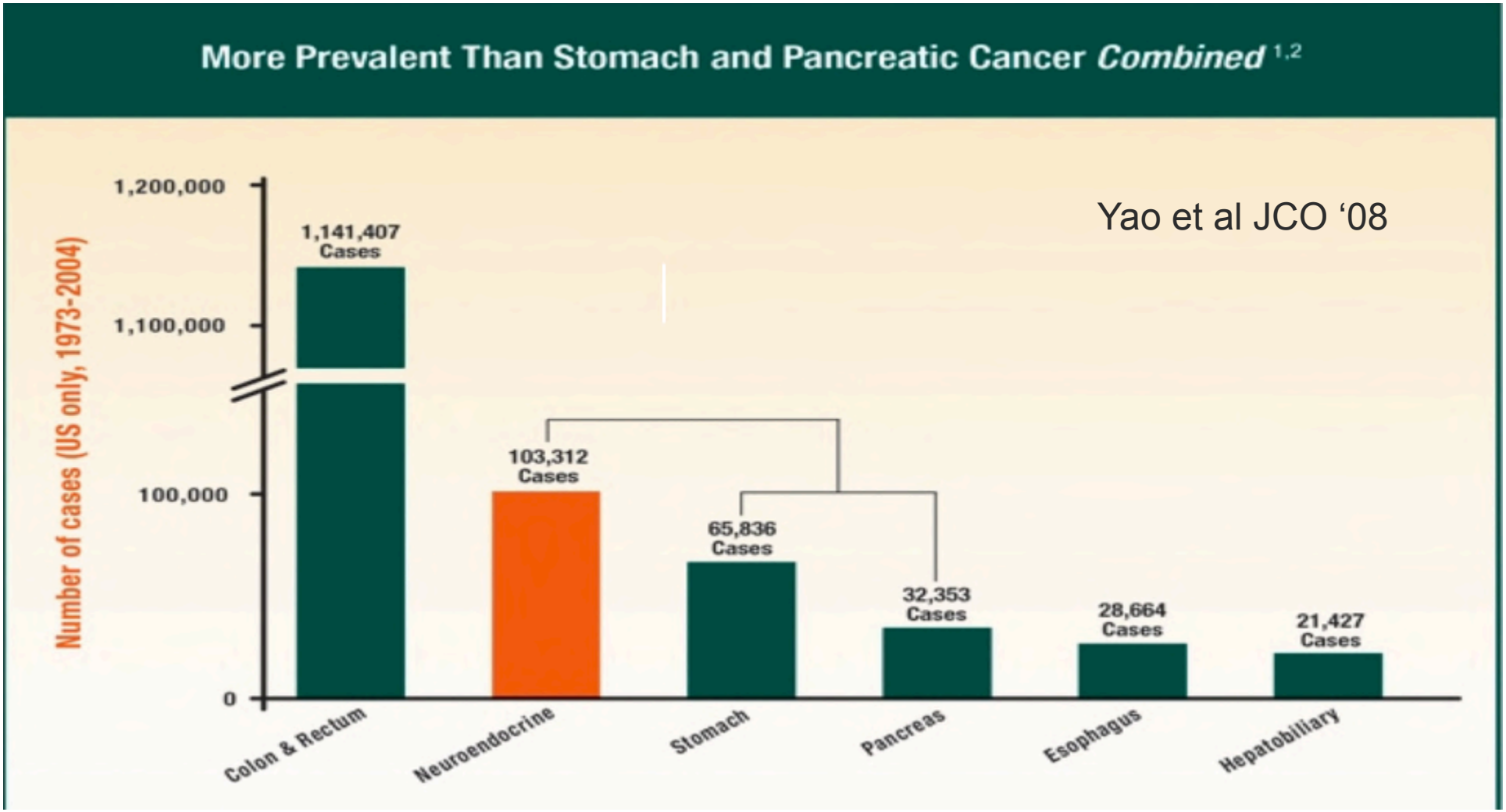
  # diagnosed per year per 100,000 people

Site	Incidence (per 100,000)
Lung	1.35
Thymus	0.02
Stomach	0.30
Small intestine	0.86
Colon	0.36
Appendix	0.15
Rectum	0.86
Pancreas	0.32
Liver	0.04
Other / unknown	0.74
Total	**5.00**

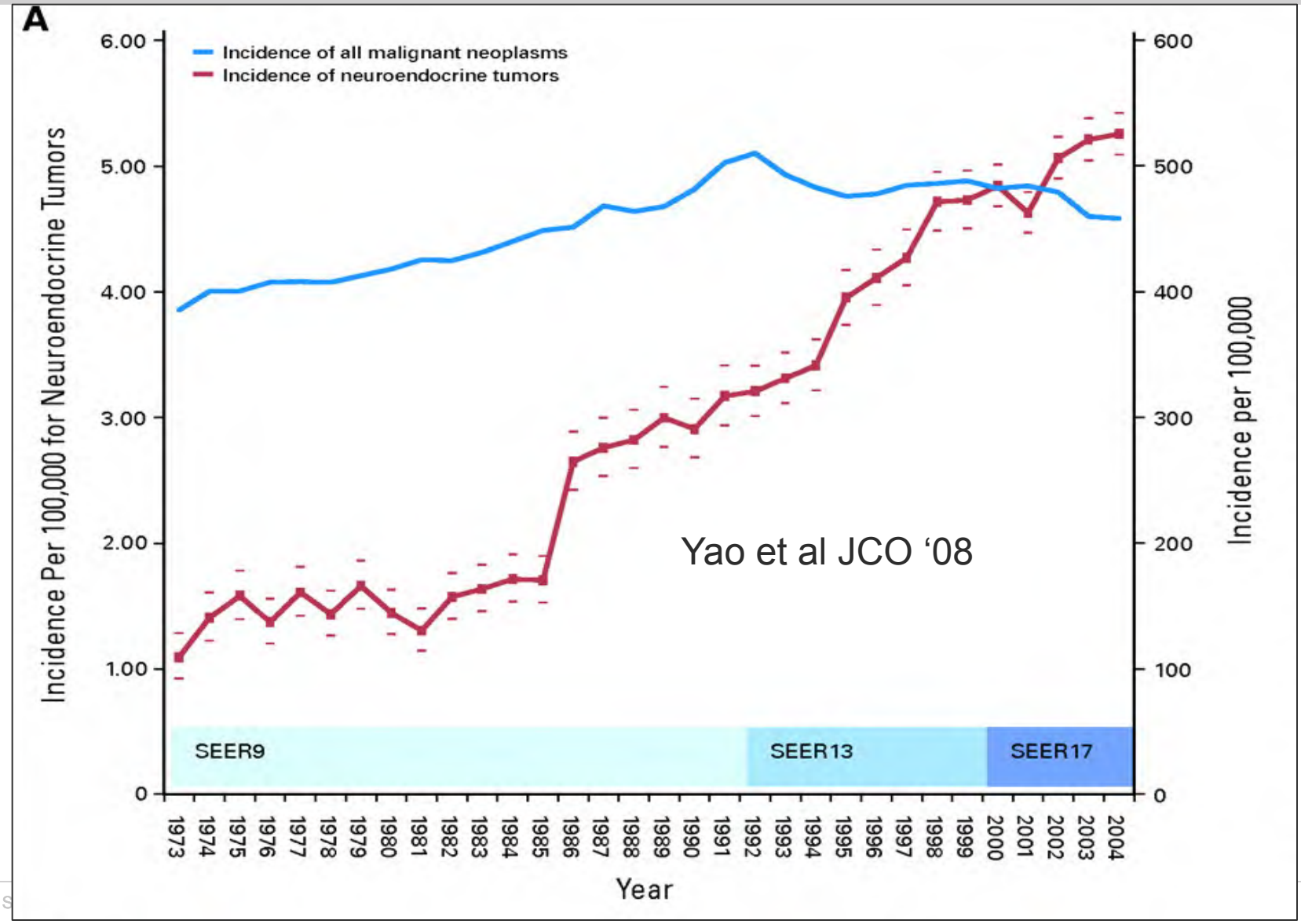
Yao et al JCO '08

NET Basics: Not really that “rare”

- Prevalence: # pts with the disease at any given time



NET Basics: Increasing Incidence



NET Basics: Historic nomenclature confusing

- APUDOMAS

  Amine precursor uptake and decarboxylation

- GEP NET

  gastro**e**ntero**p**ancreatic

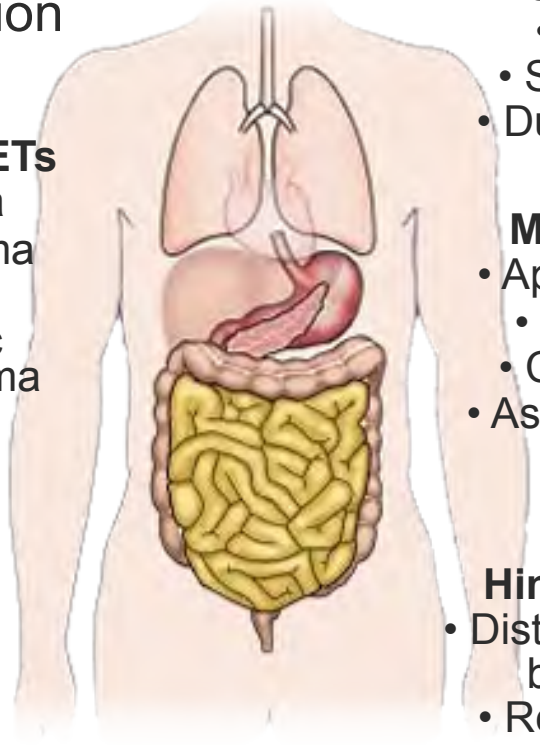
- ISLET CELL

- Carcinoid

- Bronchial: typical vs atypical

- Foregut / Midgut / Hindgut classification

Pancreatic NETs
- Insulinoma
- Glucagonoma
- VIPoma
- Pancreatic polypeptidoma



Foregut
- Thymus
- Esophagus
- Lung
- Stomach
- Duodenum

Midgut
- Appendix
- Ileum
- Cecum
- Ascending colon

Hindgut
- Distal large bowel
- Rectum

Modern NET Nomenclature

- **Organ of origin**
  - **e.g. ileal vs appendiceal vs pancreatic**

Modern NET Nomenclature

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  e.g. ileal vs appendiceal vs pancreatic

- **Secreting or not secreting**

  e.g. glucagon vs insulin vs pancreatic polypeptide vs serotonin

Modern NET Nomenclature

- Organ of origin

  e.g. ileal, appendiceal or pancreatic

- Secreting or not secreting

  e.g. glucagon, insulin, pancreatic polypeptide or serotonin

- **Syndrome vs no syndrome (functional or non-functional)**

  e.g. carcinoid syndrome from serotonin or hypoglycemia from insulin

Modern NET Nomenclature

- Organ of origin

  e.g. ileal vs appendiceal vs pancreatic

- Secreting or not secreting

  e.g. glucagon vs insulin vs pancreatic polypeptide vs serotonin

- Syndrome or no syndrome (“functional” or “non-functional”)

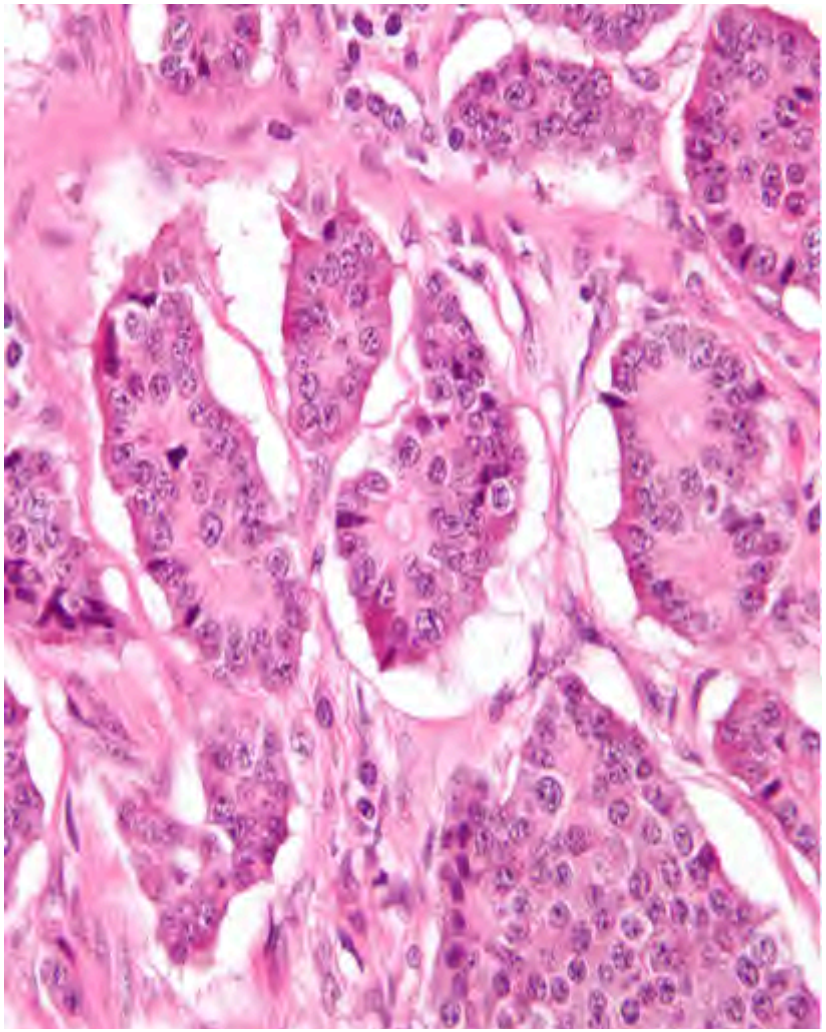
  e.g. carcinoid syndrome from serotonin vs hypoglycemia from insulin

- **Well differentiated or poorly differentiated**

  e.g. low grade (1 or 2) or high grade (3)

NET Biology

- Derived from neuroendocrine cells in the gut and elsewhere
  - -”endocrine” because they can release “hormones”
    - amines or small pieces of proteins called peptides
  - -”neuro” because they can be stimulated by nerves



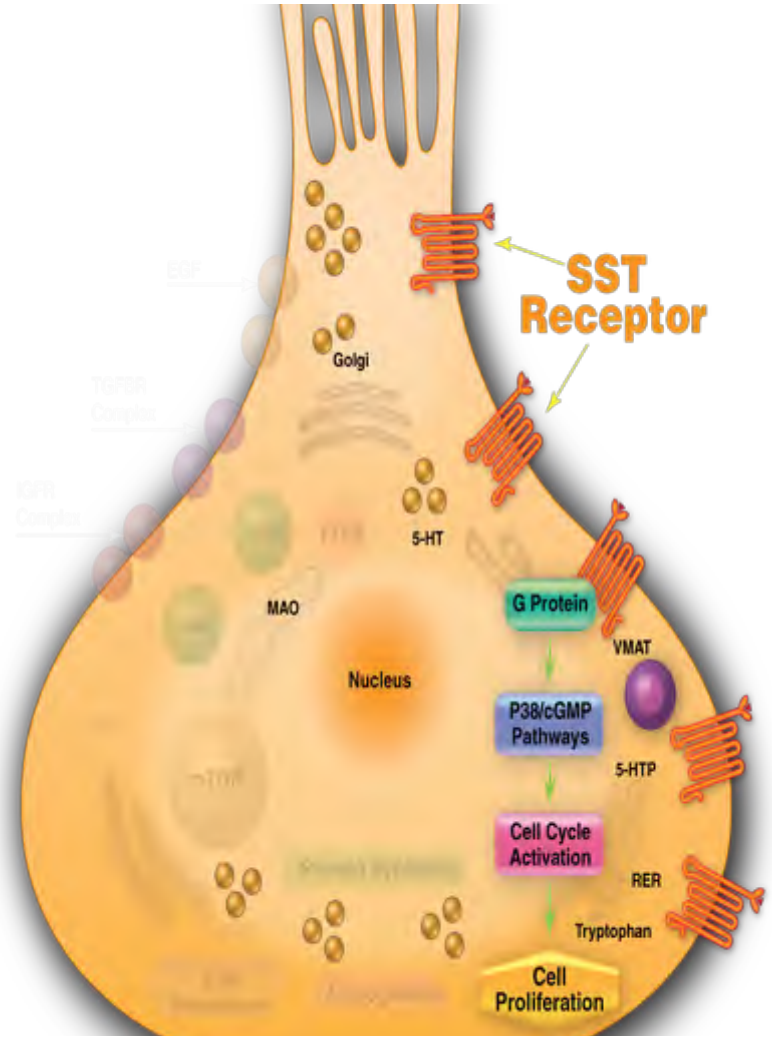
NET Biology

- Somatostatin receptors present on cell surface

  -5 somatostatin receptors (SSTR $_{1\text{-}5}$)

  -80% NETs over-express $SSTR_2$, followed by $SSTR_1$ and $SSTR_5$

  -Octreotide and lanreotide have high affinity for $SSTR_2$



NET Genetics

- Familial Genes
  - MEN-1 and MEN-2
  - Familial Paraganglioma
  - Carney Triad Syndrome
  - Von Hippel-Lindau disease
  - Neurofibromatosis Type 1
  - Tuberosclerosis
- Tumor Genes
  - Pancreatic NET
    - PTEN / TSC2
    - DAXX / ATRX
    - MEN-1
    - CDK 4/6 amplification
  - Midgut Carcinoid
    - CDKN2A in ~12%
    - others? - search continues

NET Clinical Tendencies

- **“slow growth” relative to all cancers**
  - **-hence the term “carcinoid” instead of carcinoma**
  - **-some grow so slowly that treatment is unnecessary**
  - **-exception: poorly differentiated NETs**

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- **Tumor cells release amines / peptides into blood**
  - **-hence can be used as "tumor markers"**
  - **-if causing symptoms then secretory syndromes or "functional"**

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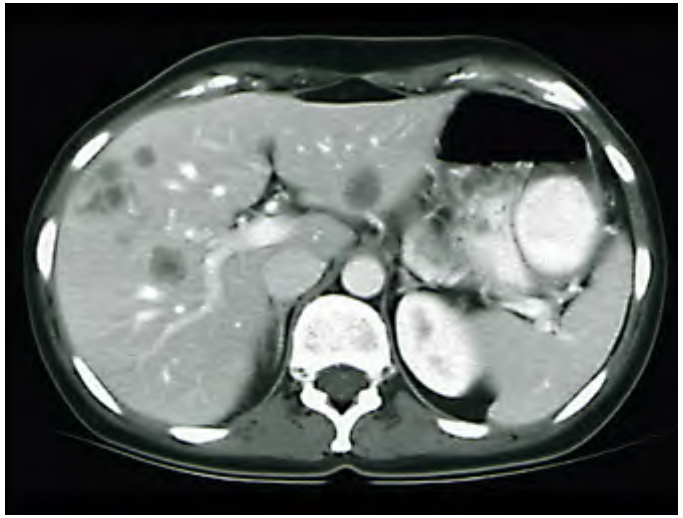
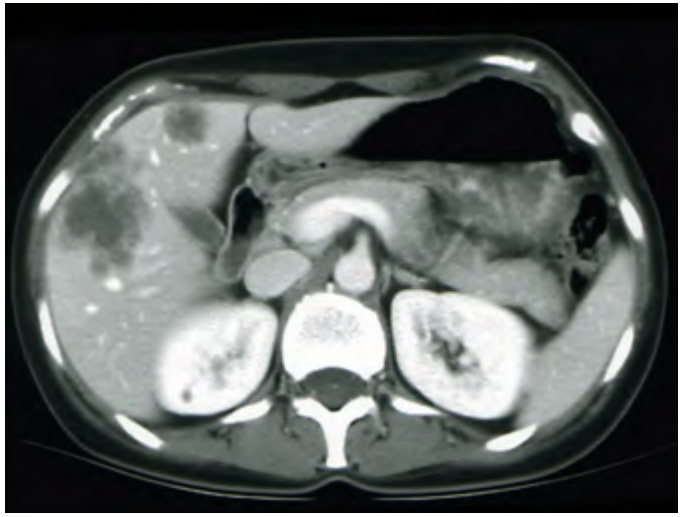
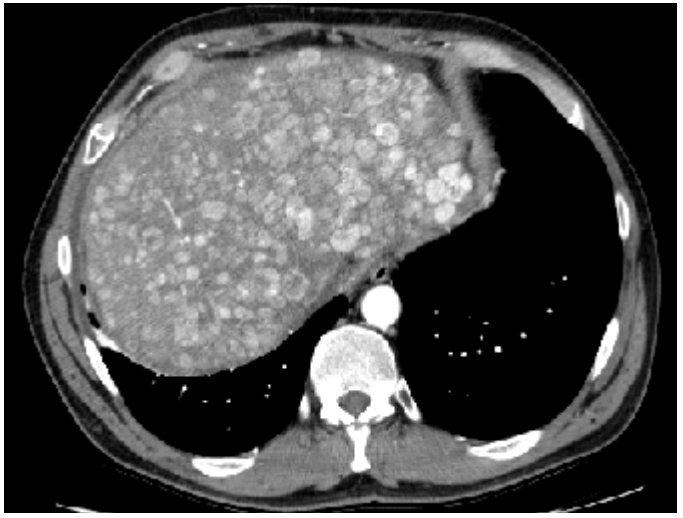
- **Hypervascular**
  - **-rich arterial blood supply compared with other cancers**

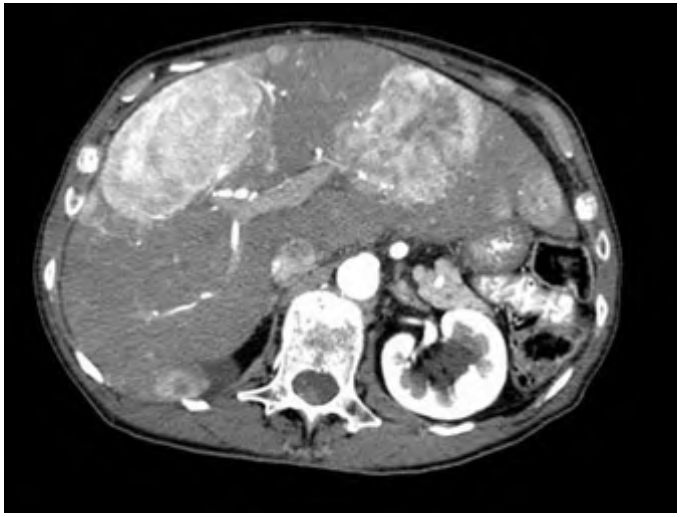
TYPICAL COLORECTAL CANCER METASTASES





TYPICAL NET METASTASES





NET: Staging and Grading

- **Stage**: defines the extent of disease at the time of diagnosis

  More importantly: where is it and can it be removed?

- **Grade**: defined by the pathologic characteristic of the tumor cells

  -how the cells look under the microscope

  -how many cells are in the process of dividing (i.e. growing)

  -% staining by Ki-67, a “proliferation” marker

Taking Advantage of NET Biology

- **Slow growth**
  - **Treat only those who need treatment**
    - **Tumor Grade and Ki-67**
    - **Extent of disease and symptoms**
    - **Rate of growth of disease**

Taking Advantage of NET Biology

- Slow growth

  Treat only those who need treatment

- **Somatostatin receptors on 80% of NETs**

  Somatostatin analogs: octreotide or lanreotide

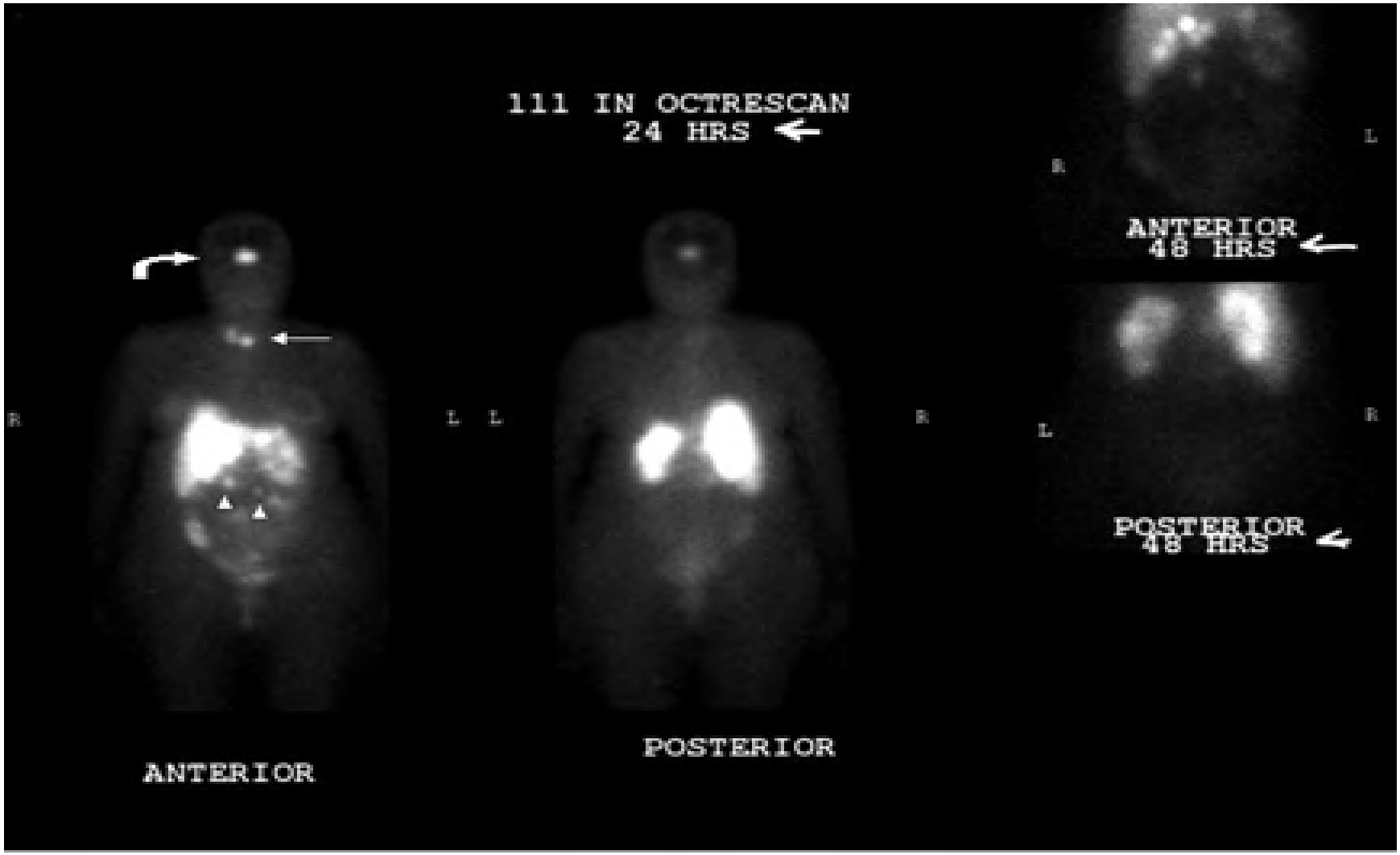
  -treats the syndrome by decreasing secretion of peptides

  -binds to receptors that might mediate growth

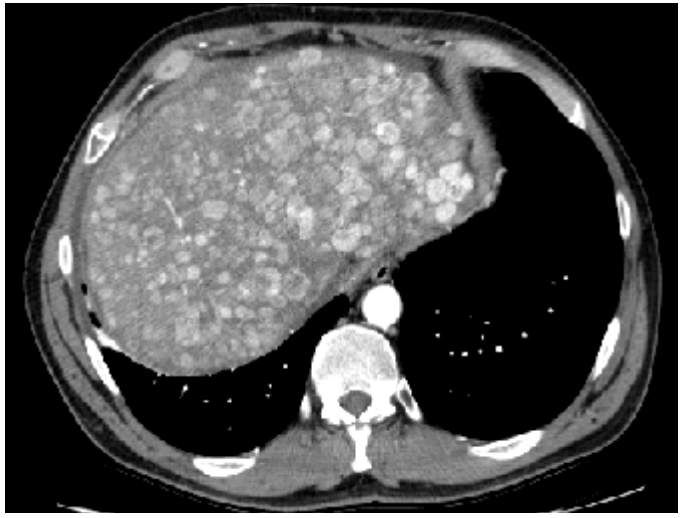
  -binds to the tumor so can be used as imaging agent

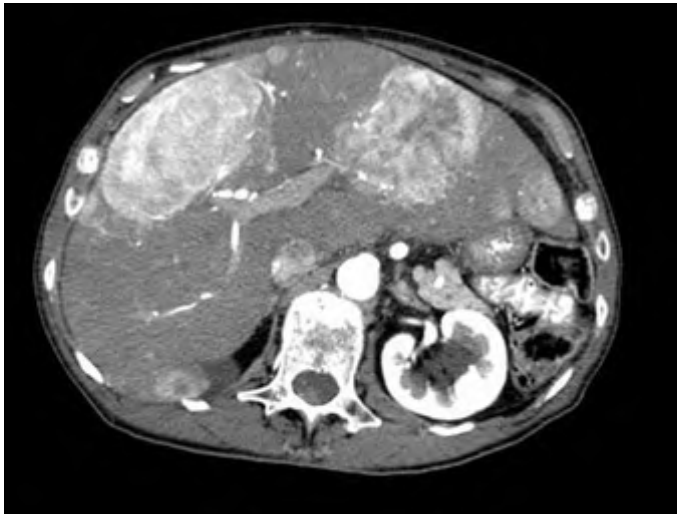
  -binds to the tumor so can be used as therapeutic delivery of high dose radiation (PRRT)

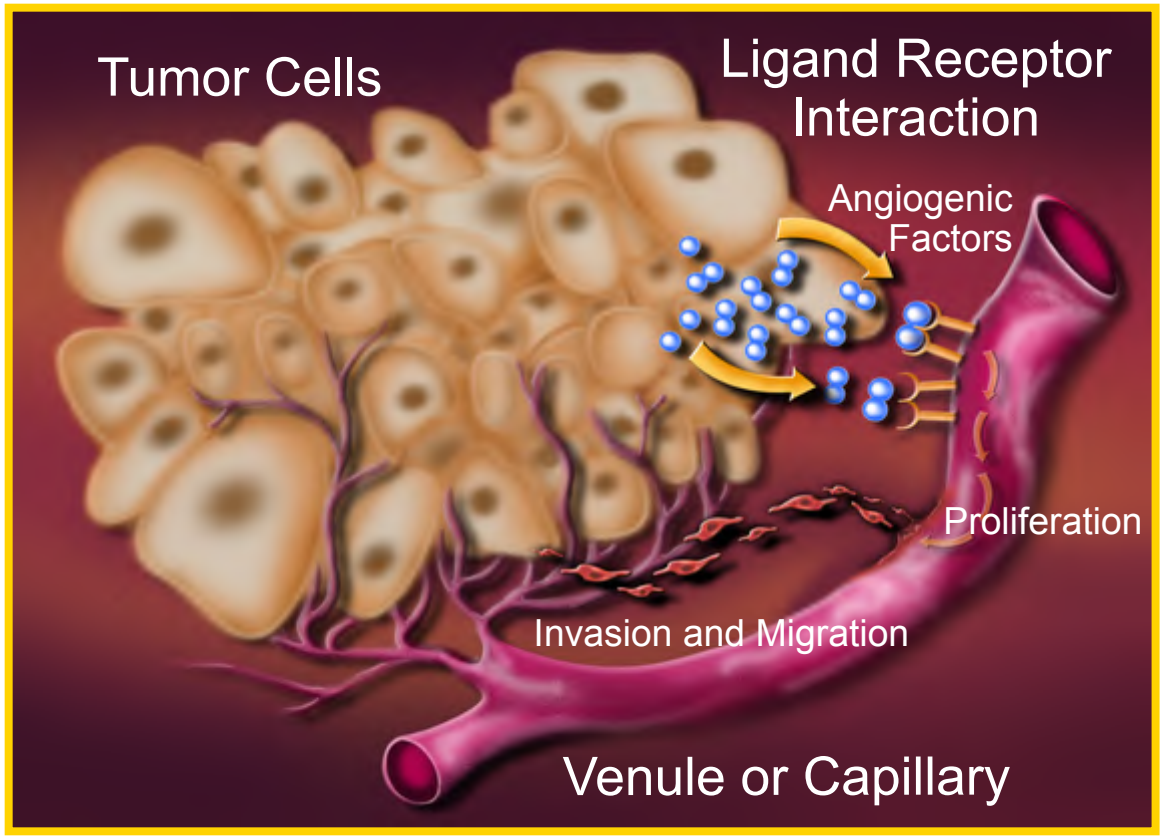
Somatostatin Receptors as Targets for Imaging (and treatment): patient with MEN-1



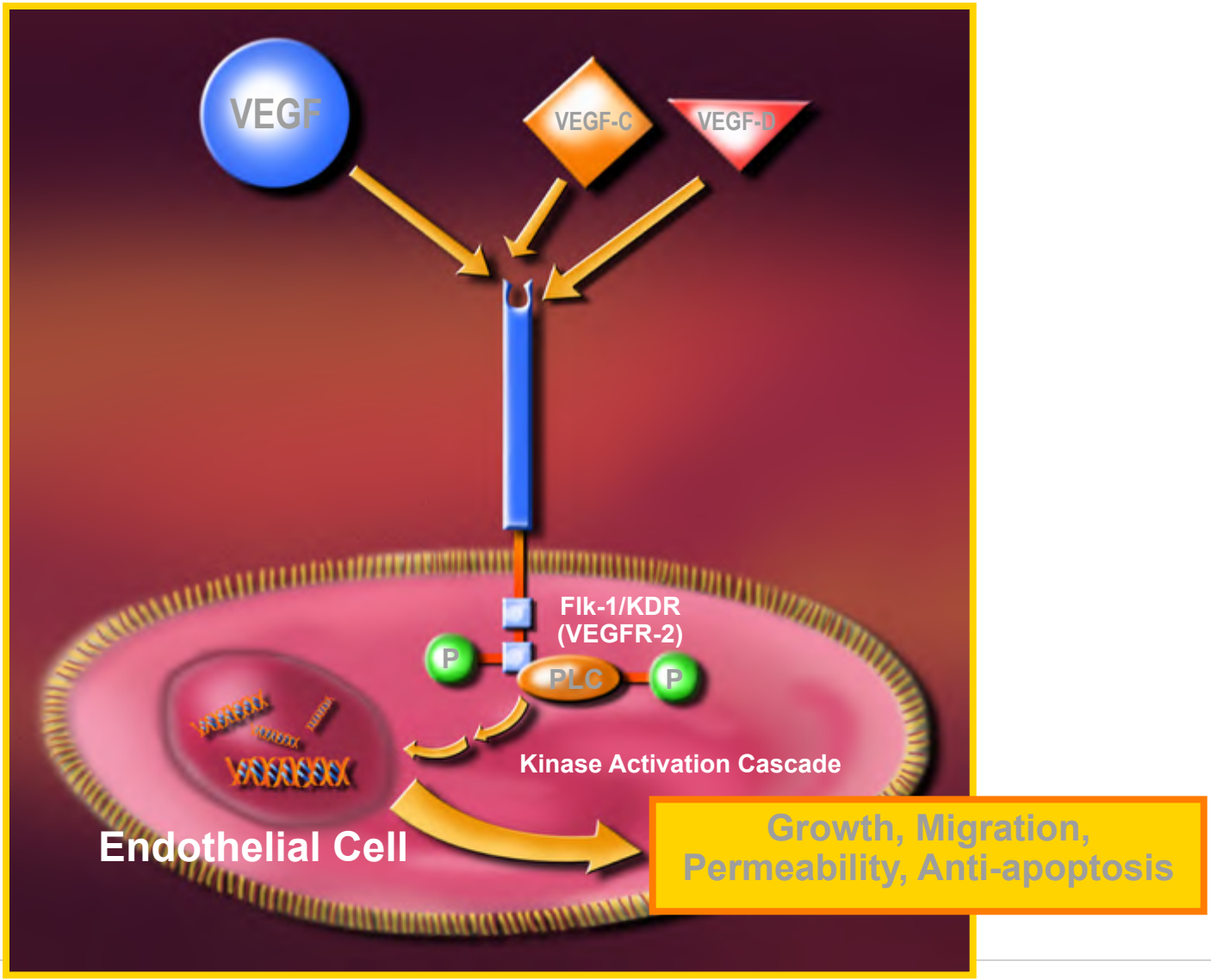
Taking Advantage of Hypervascular Features of NETs



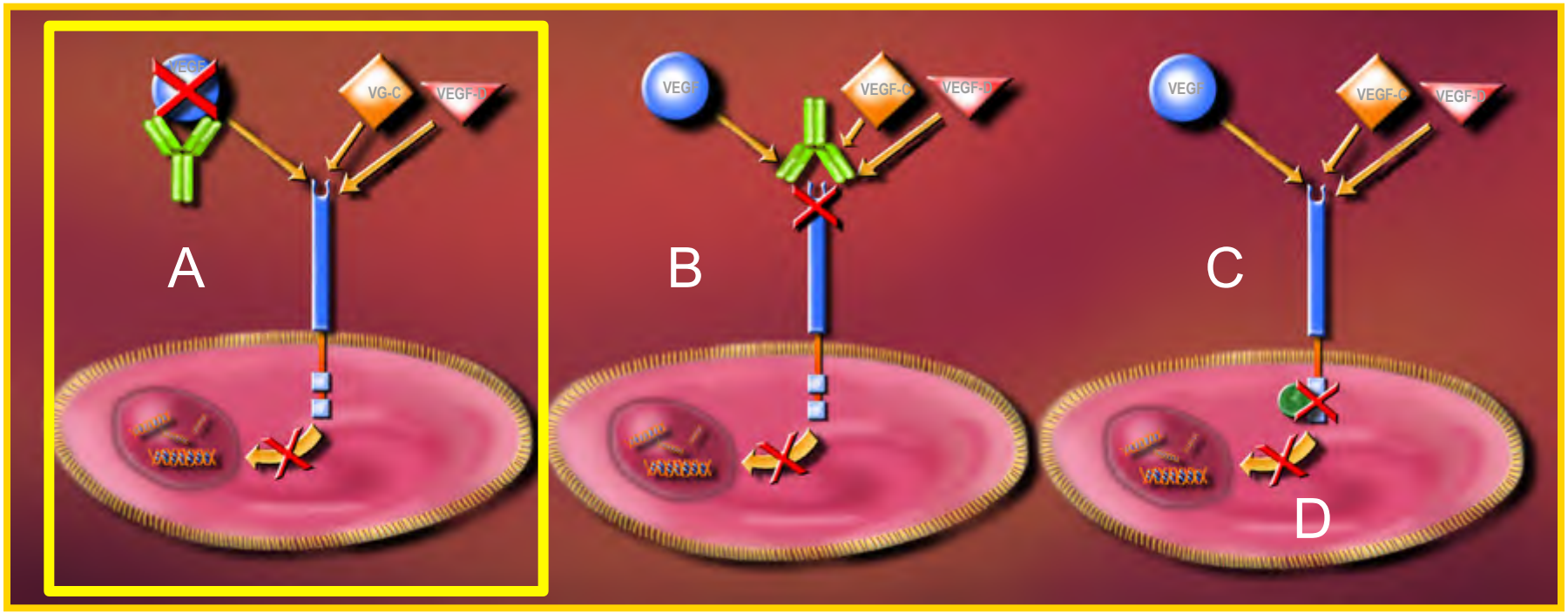




New blood vessels grow due to Receptor Mediated Signaling Pathway



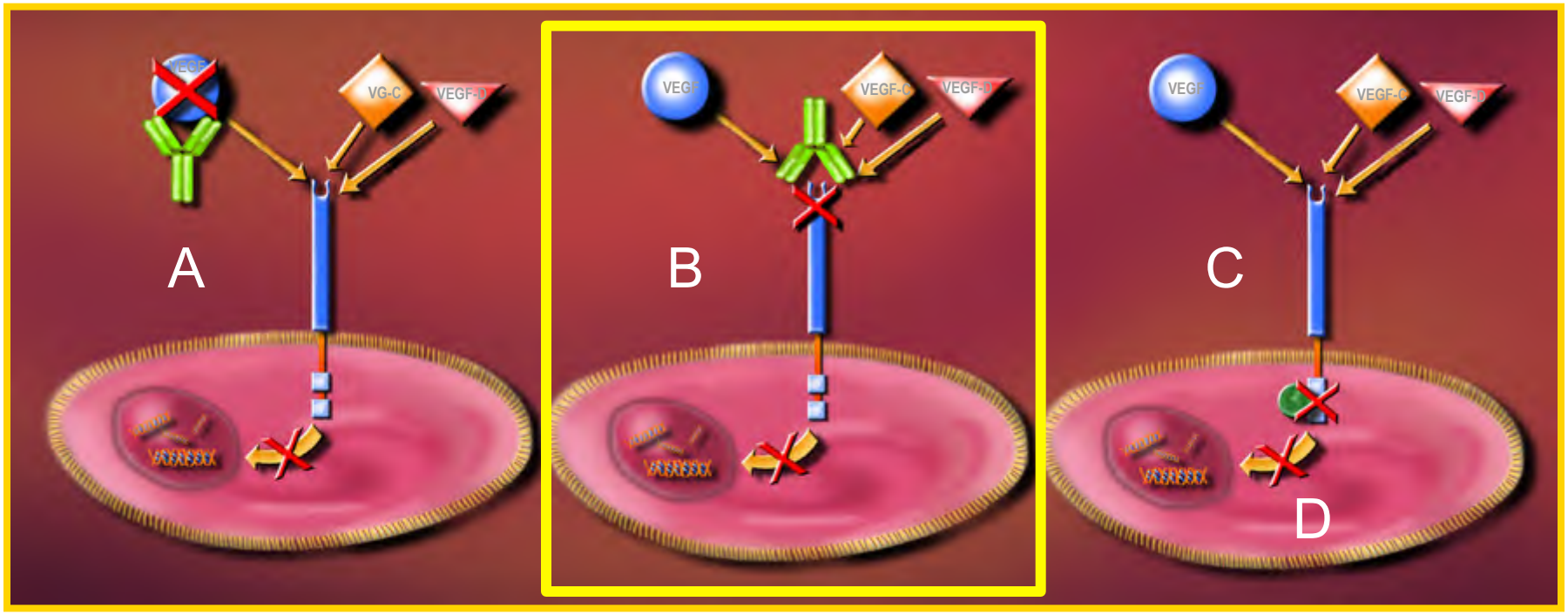
Four Strategies for Blocking Receptor-Ligand Mediated Signaling Pathways



A. Attacking the Ligand (growth factor)
   Bevacizumab and VEGF A
   Aflibercept and VEGF A, C, Placenta GF (PlGF)

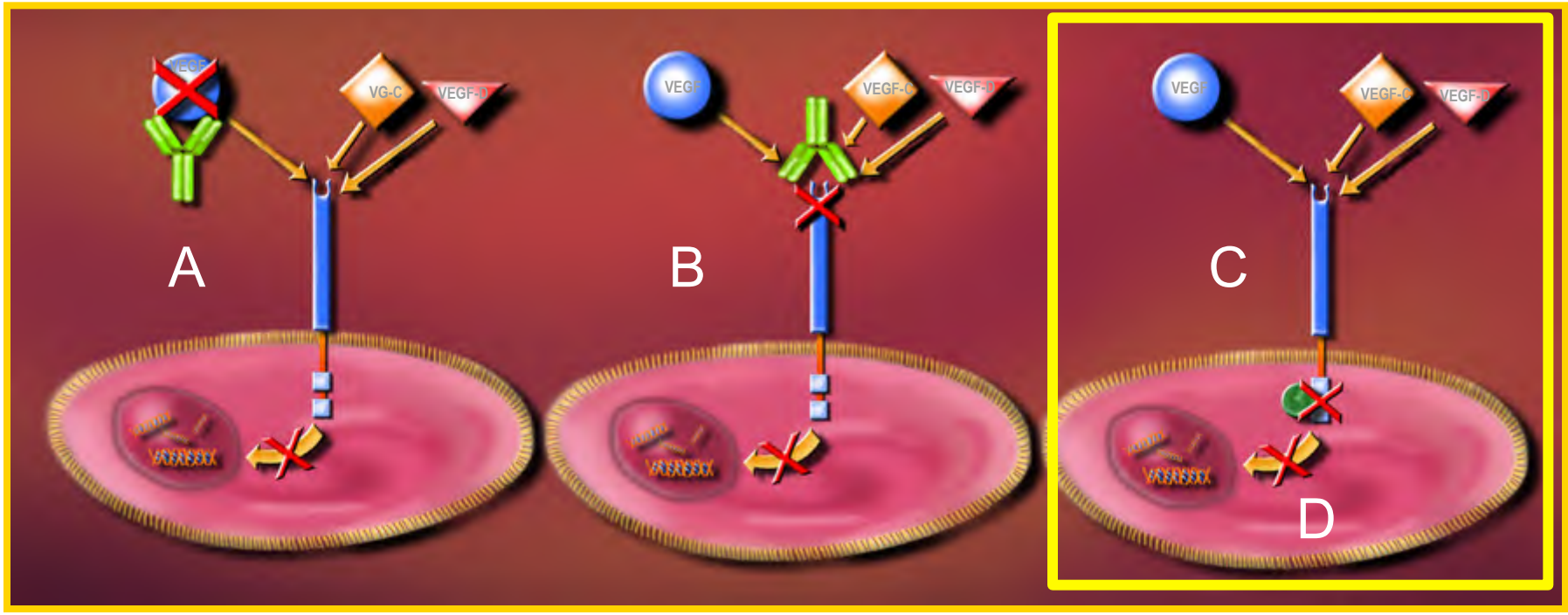
Results of Bevacizumab (Avastin) trials in PNET / carcinoid: June '15

Strategies for Blocking Receptor-Ligand Mediated Signaling Pathways



B. Attacking the Extracellular Domain of the Receptor
Ramicurumab (approved for gastric cancer in 2014)

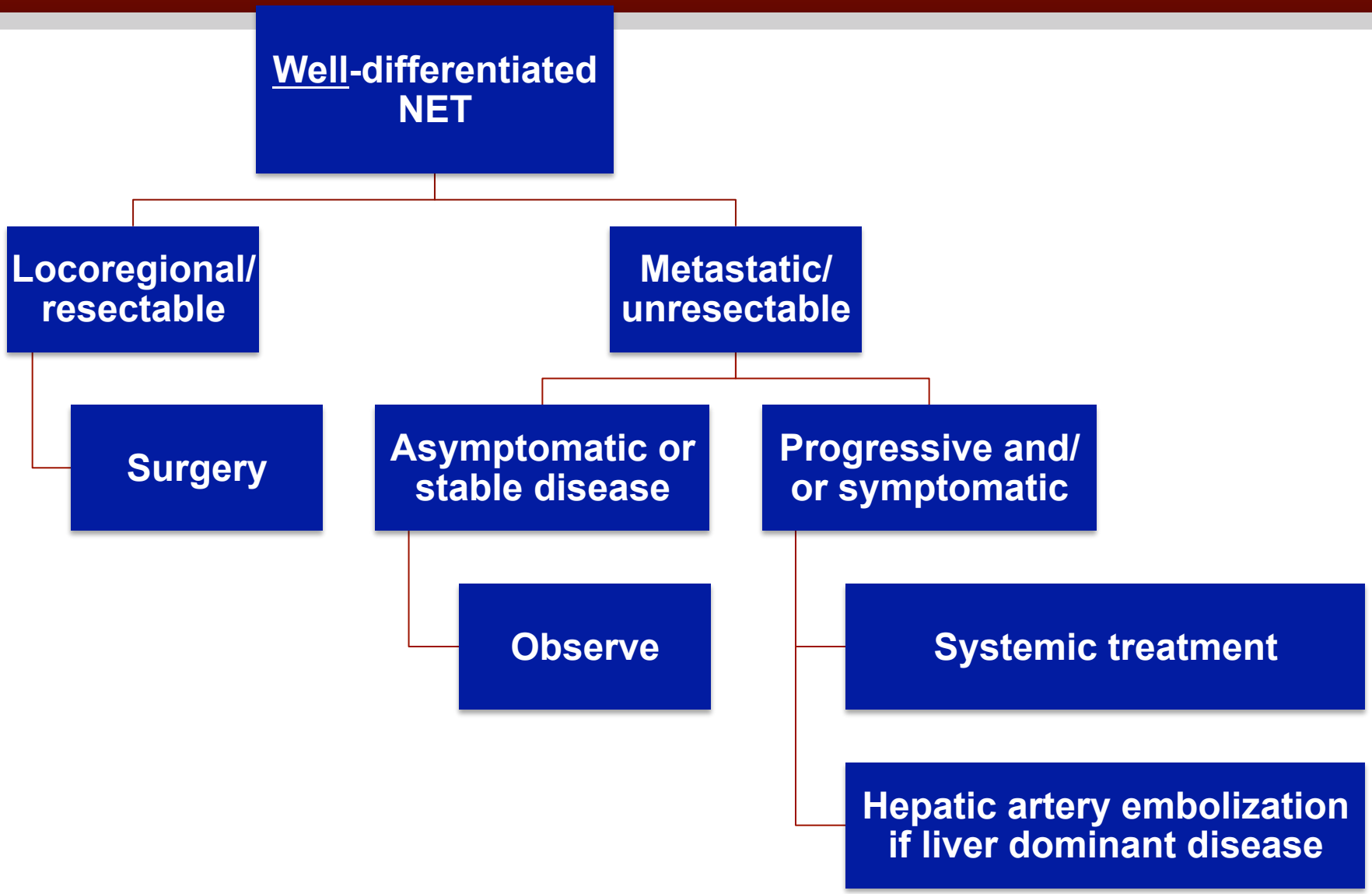
Strategies for Blocking Receptor-Ligand Mediated Signaling Pathways



C. Attacking the Kinase Domain of the Receptor
Sunitinib approved for pancreatic NETs
sorafenib, pazopanib, axitinib all approved in kidney cancers

Pazopanib in clinical trial right now for carcinoid patients

NET Treatment Algorithm



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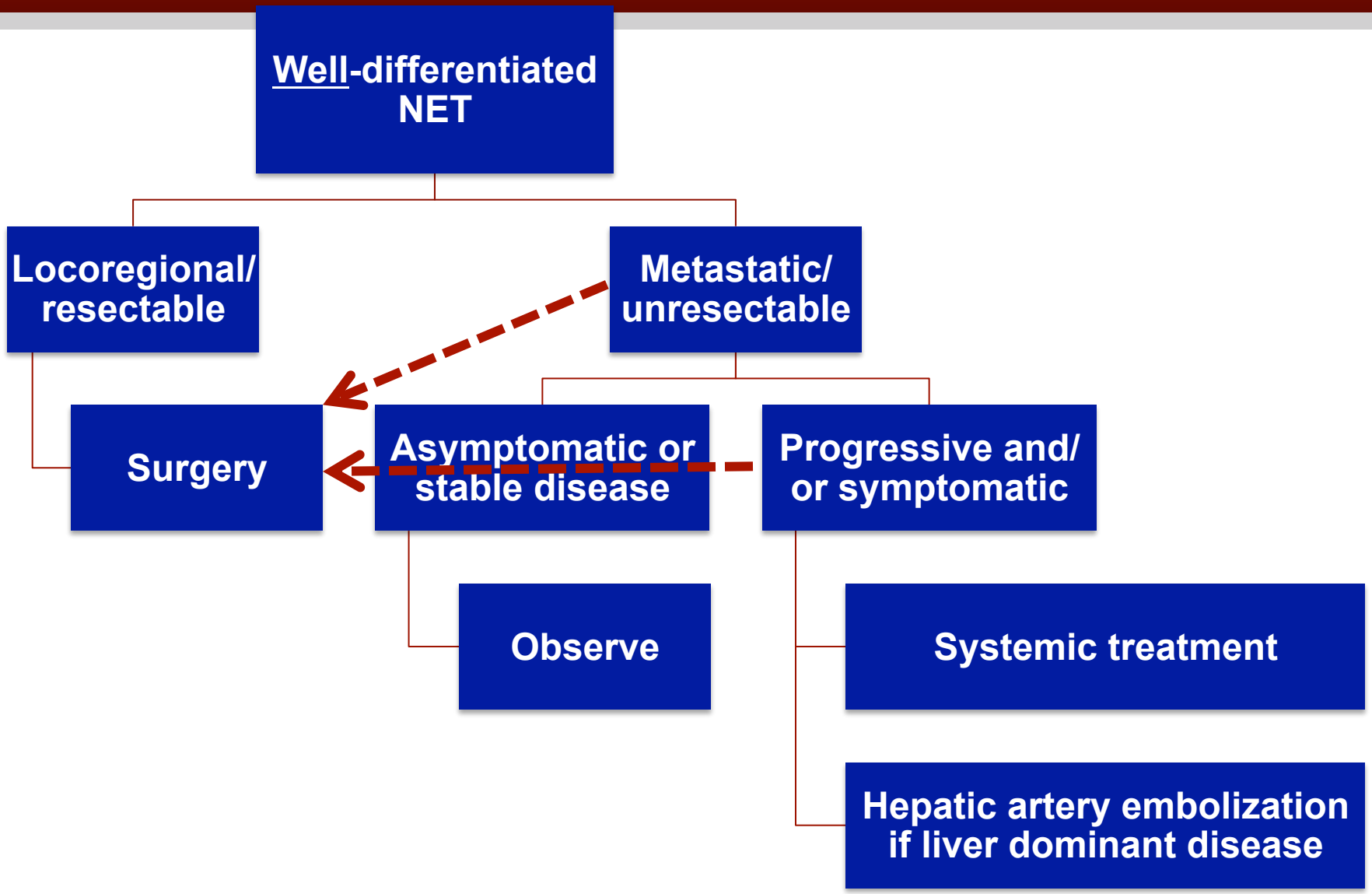

Impediments to Progress

- **Lack of adequate NET tumor models**
  - ***in vitro*** **(cells growing in petri dishes)**
  - ***in vivo*** **(tumors growing in animals)**
    - **mice that develop NETs**
    - **immune impaired mice for growth of human NETs**

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CFCF Prize to first lab to develop validated NET model for carcinoid and for pancreatic NET

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- **Lack of NET patient data base**
  - **EMR's don't talk to each other**
  - **Tissue scarce and often discarded**

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CFCF helped to initiate first NET tissue bank
(Dana Farber, MD Anderson, Memorial Sloan Kettering and Stanford)

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- Lack of NET patient data base
  - EMR's don't talk to each other
  - Tissue scarce and often discarded
- **Low accrual of patients in clinical trials**

Clinical Trials: Converting Discovery to Care

- **Preclinical: Works in mouse tumors…**
  - **Ideally, strong biological rationale**
  - **Effective in cells in culture and in tumors in mice**
  - **Deemed "safe" in larger animals (looking for major side effects)**

Clinical Trials: Converting Discovery to Care

- Preclinical: Works in mouse tumors…
- **Phase I = tests safety (hope for efficacy)**
  - **Often any type of tumor eligible**
  - **Usually 15-25 patients; defines sides effects; "best" dose**

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  - **Limited to specific type of tumor**
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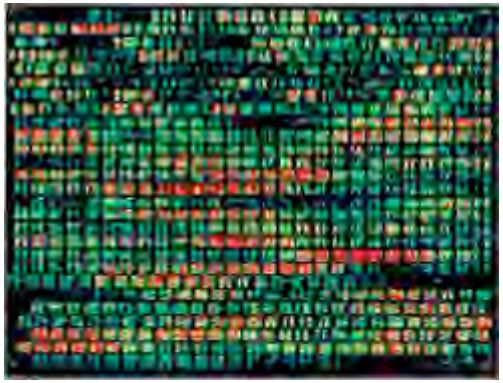
  - Usually 25-50 patients (sometimes randomized)
- **Phase III = tests efficacy compared with "standard"**
  - **Sometimes placebo "control"**
  - **Essential to assess survival differences**
  - **Usually 200-500 patients**

Design and interpretation of clinical trials

- Eligibility Criteria
  - Pathologic confirmation?
    - -tissue available?
  - Measurable disease?
  - Which NETs?
    - - well vs poorly differentiated?
    - - site of origin?
  - Growing? (or stable)
  - Functioning? (or not)
  - Prior treatment? (or not)
- Measures of Success
  - Response Rate
    - - complete or partial
    - - stable disease
    - - progressive disease
  - Delay in growth of tumor
    - -time until tumor starts to grow
    - -"progression free survival"
  - Overall Survival
  - Quality of life

Future directions

- The NET Registry will connect the tumor tissue bank, databases containing clinical and epidemiologic data, clinical outcome data, and archived blood specimens.
- Will enable the rapid examination of future hypotheses and allow studies using tissue and clinical data
- The NET Registry is a tool that will lead to improved understanding of neuroendocrine tumor prevention, pathogenesis, and treatment.



Take Home Points

- Research on NETS has been highly productive
  - New genes identified
  - New therapies approved
  - Many clinical trials in progress
  - Outcomes for patients improving…
- More to do
  - Better laboratory models to study
  - Understanding genes and gene regulation (epigenetics)
  - Build on success of clinical trials

Clinical trials are key to success in patient care…

Questions?