Trattamento chirurgico

dei
Tumori neuroendocrini gastroenteropancreatici

Oggi

giancarlo pansini

simona bonazza

di maestro in maestro

È con vivo compiacimento che prendo la parola nella cerimonia inaugurale di questo Convegno sulla fisiopatologia e sulla clinica della tiroide.

Compiacimento che deriva dal vedere realizzato qui a Ferrara – sede della mia cara Università – da cui vaggue motivazioni Anagrafiche risiedono a lontani lontani – un incontro scientifico, con contributi anche internazionali, nel campo della endocrinologia e cioè di una disciplina che, al pari della genetica applicata, della oncologia specie ematologica e della cardio-angiologia cito-iso-metabolica, galoppa – per così dire – sfrenata nel meraviglioso progresso continuo che contraddistingue tutta la scienza medica nell'era che stiamo vivendo.

Un compiacimento, altresì, nel sapere che il merito organizzativo di questo Congresso va alla mia Scuola ed in particolar modo al mio carissimo E. Degli Uberti che con i suoi Allievi ormai da molti anni si è reso artefice, in quella regione ferrarese, di un'Endocrinologia ad alto livello sia scientifico sia clinica sia didattico ed ha profuso nell'odierna iniziativa tutto il fervore della sua originalissima personalità – che ben conosco – fatta di entusiasmi latini congiunti ad una prudenza e ad una tenacia anglosassoni.

Un saluto cordiale ed affettuoso a tutti i Convenuti, fra i quali ho ritrovato anche cari amici di tempi lontani.

Ed un augurio che questo incontro raggiunga appieno le finalità che si è proposte, fornendo ai partecipanti un fruttifero scambio di conquiste e di idee.

G.

Affaire ai ringraziamenti

una introduzione

The Neuroendocrine System and Its Tumors

An Overview

Ronald A. De Lellis

Neuroendocrine tumors constitute an enigmatic family of neoplasms with a remarkably wide range of morphologic features, biologic behaviors, and functional capabilities. Currently, their diagnosis depends on the recognition of certain histologic and cytologic features together with the presence of markers indicative of neuroendocrine differentiation. During the past 3 decades, the use of increasingly more sophisticated immunohistochemical and molecular technologies has continued to broaden the scope of this family of tumors while also providing a source of continued controversy for cell biologists, pathologists, and oncologists interested in their pathobiology.

PRINCIPLES OF PATHOLOGY FOR DIAGNOSIS AND REPORTING OF NEUROENDOCRINE TUMORS

Required information:

- Anatomic site of tumor
- Diagnosis
- Grade (see Table 1)
- Mitotic rate
- Size of tumor
- Presence of multicentric disease
- Presence of vascular invasion
- Presence of perineural invasion
- Presence of other pathologic components (e.g., non-neuroendocrine components)
- Lymph node metastases to include the number of positive nodes and total number of nodes examined
- Margin status (report as positive or negative)
- Assign TNM stage per the AJCC TNM system (See Staging, in these guidelines, available online, at NCCN.org [ST-1–ST-4])

Table 1 Characteristics of Neuroendocrine Tumors of the Pancreas

Tumor	Major Clinical Symptom	Predominant Hormone	Islet Cell Type	Malignant Potential	Other Clinical Features
Gastrinoma	Recurrent peptic ulcer disease	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	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	PP	PP cells	Very high	Occasional watery diarrhea

Abbreviations: PP, pancreatic polypeptide; PPoma, pancreatic polypeptidoma; VIPoma, vasoactive intestinal polypeptide tumor.
Adapted with modifications from Skarin AT. Atlas of Diagnostic Oncology. Philadelphia: Elsevier Science; 2003. Copyright 2003, with permission from Elsevier.[77]

chirurgia dei net

- Strategia terapeutica
  - secondo stadiazione T|N|M, istotipo, profilo secretorio
- Finalità curativa
  - il principale obiettivo, quando possibile (minoranza dei casi)
- Finalità preventiva
  - discussa, comunque nelle sindromi poliendocrine
- Finalità palliativa sul T primitivo
  - non prolunga la sopravvivenza
- Finalità palliativa sulle M epatiche
  - prolunga la sopravvivenza (rimozione combinata del T + N)
- Finalità citoriduttiva
  - non prolunga la sopravvivenza, migliora le altre terapie e QdV

principi della chirurgia dei net

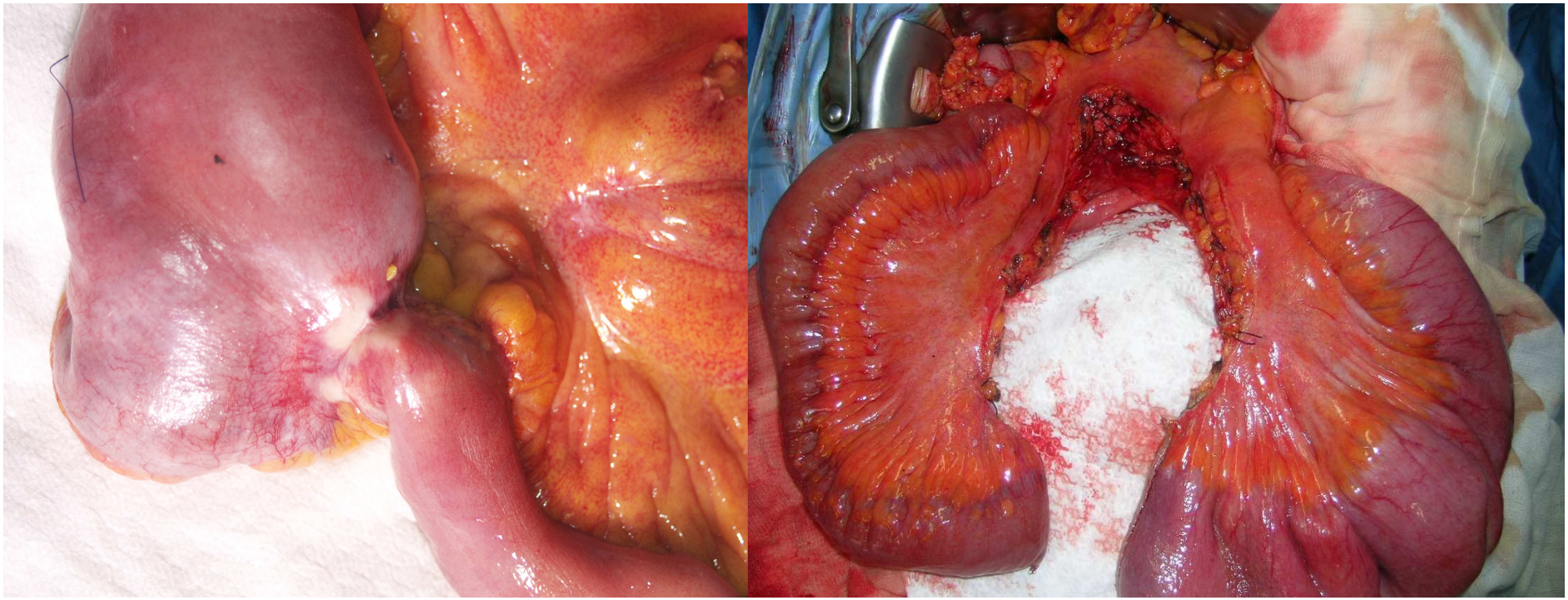
- Sicurezza diagnostica (biochimica/radiologica)
- Precisa localizzazione (forme ectopiche/sdr MEN)
- Chirurgia d'organo .. di una malattia sistemica
- Considerare cambi di strategia durante la procedura
- Mantenere l'obiettivo: miglioramento dei segni/sintomi
- Considerare gestione sequele postoperatorie
- Considerare possibilità di chirurgia reiterata

Stanley R. Friesen & Norman W. Thompson . "Surgical Endocrinology. Clinical Sindromes» 2nd Edition 1990

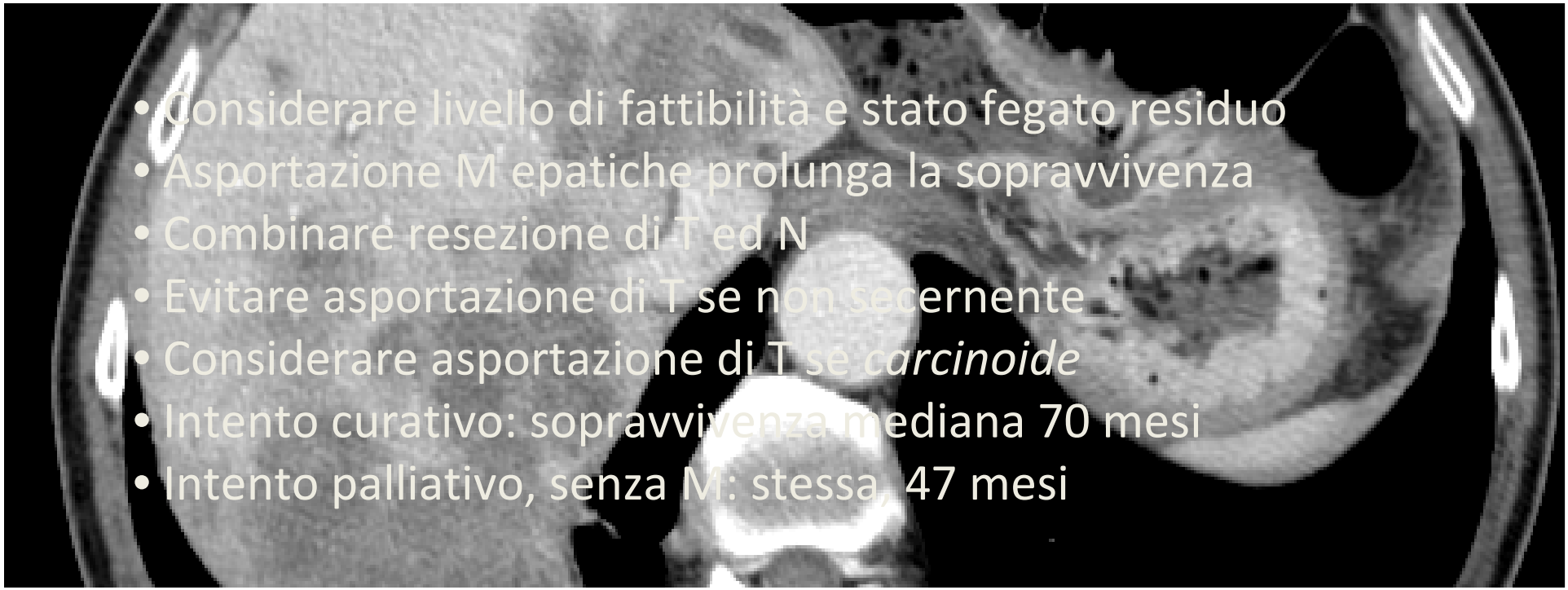
malattia localizzata & loco|regionale

- La resezione curativa resta l' obiettivo principale
- Attenersi ai medesimi criteri di radicalità delle altre patologie neoplastiche (margini, linfonodi regionali, asportazione altre localizzazioni sincrone (15%-30%)
- Ogni resezione incompleta è a rischio di recidiva e M
- Discriminanti nella scelta della tecnica chirurgica sono:
  - posizione e dimensioni del T
  - condizioni generali del paziente
- Sopravvivenza a 5 anni: dal 70 al 80%

malattia localizzata & loco|regionale



malattia metastatica

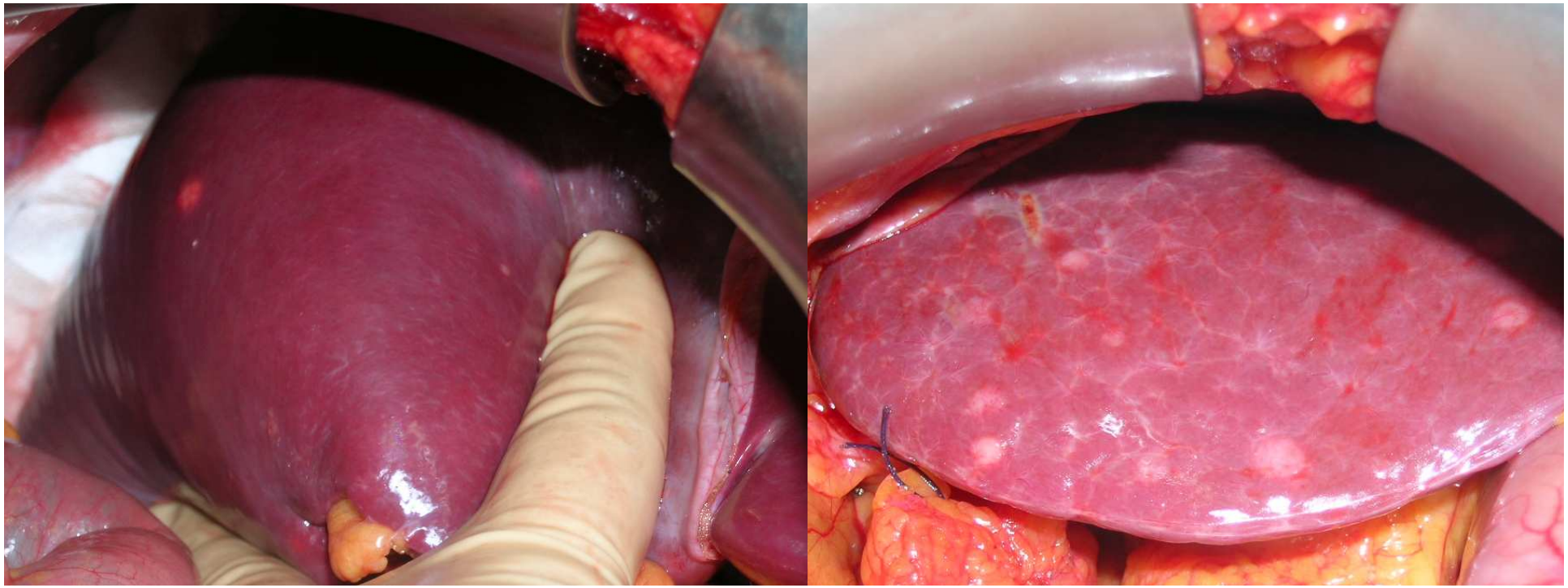


- Considerare livello di fattibilità e stato fegato residuo
- Asportazione M epatiche prolunga la sopravvivenza
- Combinare resezione di T ed N
- Evitare asportazione di T se non secernente
- Considerare asportazione di T se *carcinoide*
- Intento curativo: sopravvivenza mediana 70 mesi
- Intento palliativo, senza M: stessa, 47 mesi

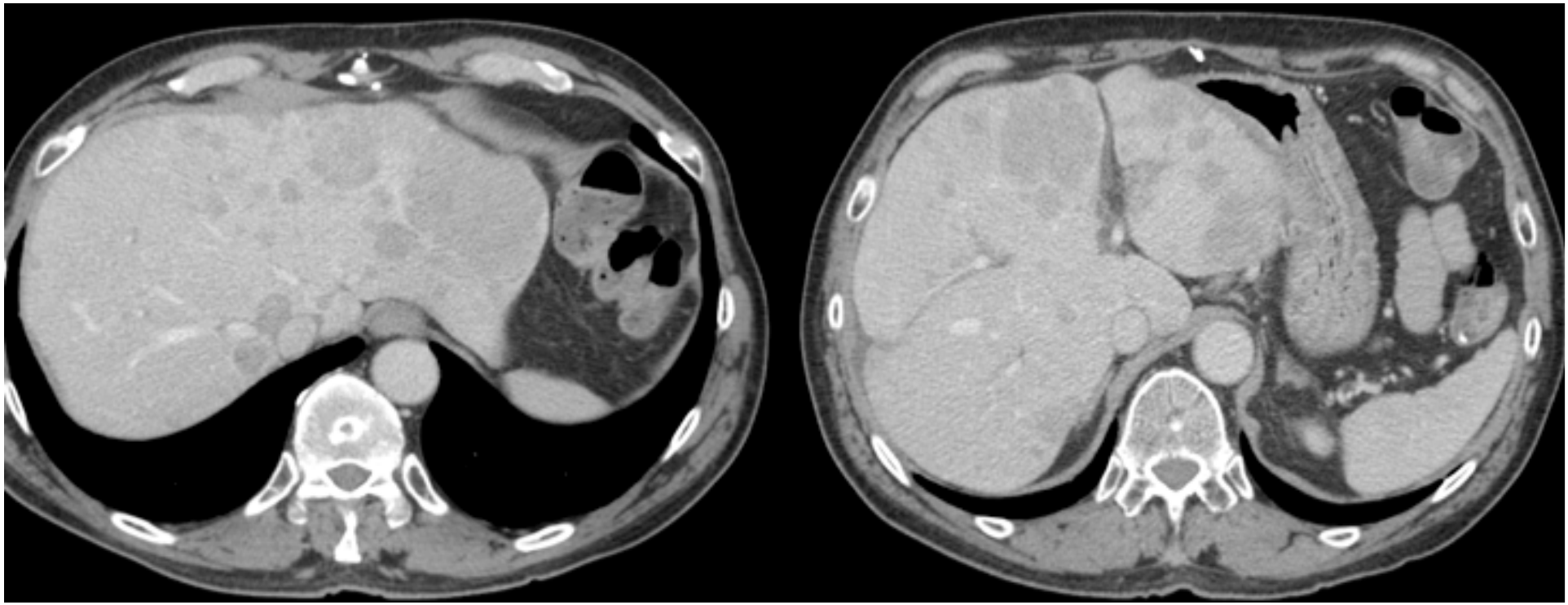
D Jaeck

World J Surgery, 2001

malattia metastatica



malattia metastatica



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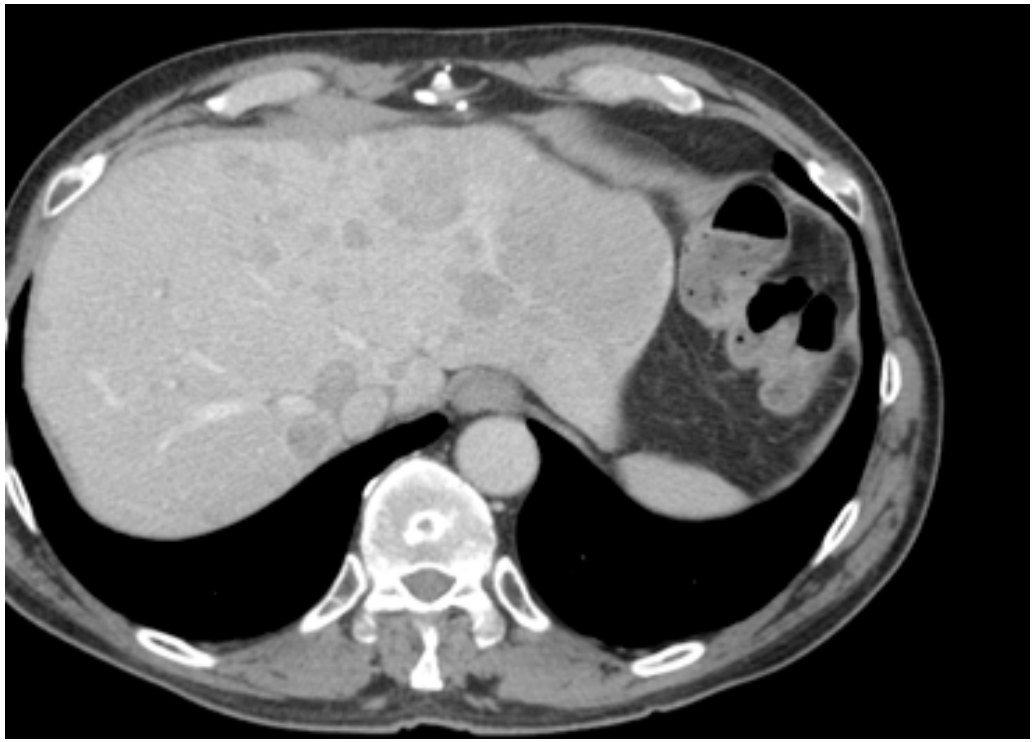
Neuroendocrine Tumors Version 1.2012

malattia metastatica



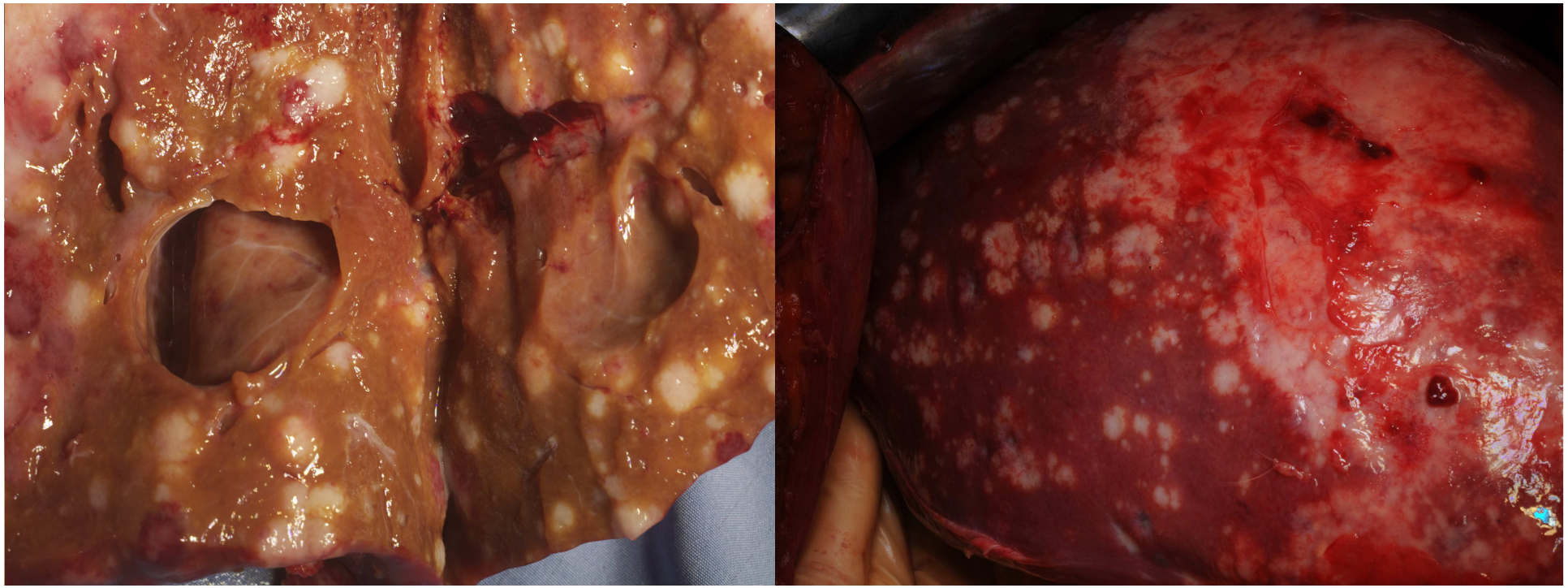
Liver Transplatation for Liver Metastases of Carcinoid Tumors.

Although some highly selected pastients have experienced long-term survival, the panel acknowledged the considerable associated risks and deemed liver transplantation to be investigational and not part of routine care at this time.

malattia locoregionale | M irresecabili

- La finalità palliativa resta l'obiettivo principale
- Procedure di asportazione completa del T primitivo
- Procedure di *debulking*: riduzione della taglia tumorale
- Possibile nel 90% dei NET sintomatici
- Si può ottenere la riduzione della sintomatologia
- Controversa nei NET non funzionanti, asintomatici
- Sopravvivenza bassa

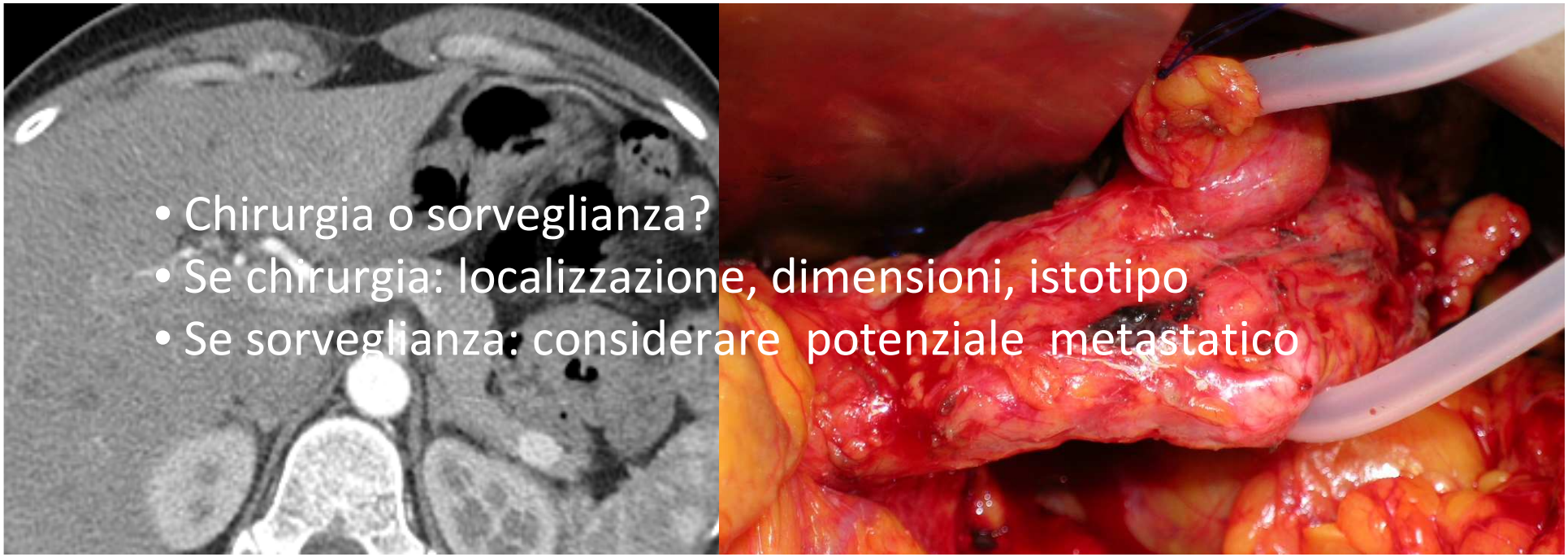
malattia locoregionale | M irresecabili



tumori asintomatici

aneurisma viscerale o net?

tumori asintomatici



- Chirurgia o sorveglianza?
- Se chirurgia: localizzazione, dimensioni, istotipo
- Se sorveglianza: considerare potenziale metastatico

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Do I
really need
a
SURGERY
for NET?

Guidelines for the management of gastroenteropancreatic neuroendocrine (including carcinoid) tumours (NETs)

John K Ramage,[1] A Ahmed,[2] J Ardill,[3] N Bax,[4] D J Breen,[5] M E Caplin,[6] P Corrie,[7]

Table 4 Sites and overall 5-year survival rates in patients with gastroenteropancreatic NETs in the USA (from the SEER Programme), Norway (from the NRC) and England and Wales[12–14 37]

	Percentage surviving				
	SEER data (n=17 312)			England and Wales	
Site	Black patients	White patients	NRC data (n=2013)	Well-differentiated tumours	Small cell tumours*
Lung	36	48	54	–	–
Stomach	56	64	45	52	18
Small intestine	64	70	59	59	27
Pancreas	27	35	43	39	17
Appendix	70	79	74	–	–
Colon	61	53	41	65	27
Rectum	85	88	74	–	–

*Data are for 1-year survival.
NET, neuroendocrine tumour; NRC, Norwegian Registry of Cancer; SEER, Surveillance, Epidemiology and End Results.

tumori pancreatici

tumori pancreatici

Evolving Diagnostic and Treatment Strategies for Pancreatic Neuroendocrine Tumors

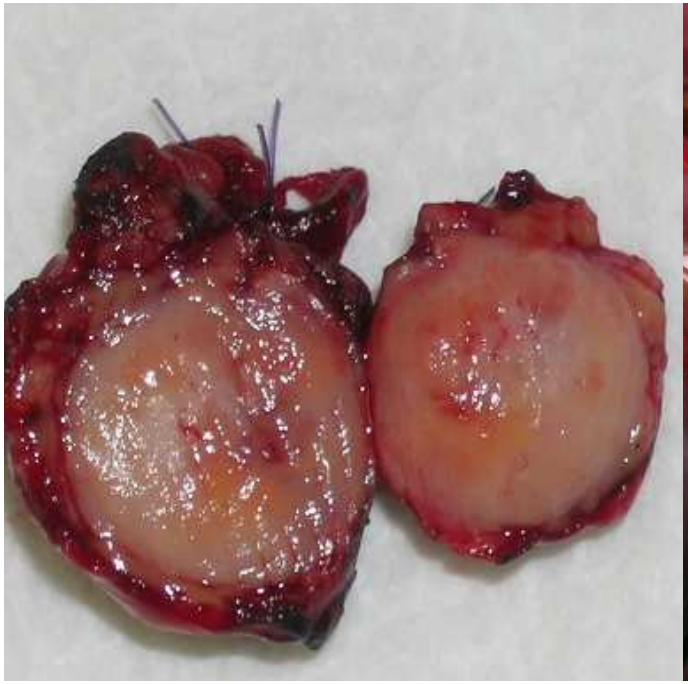
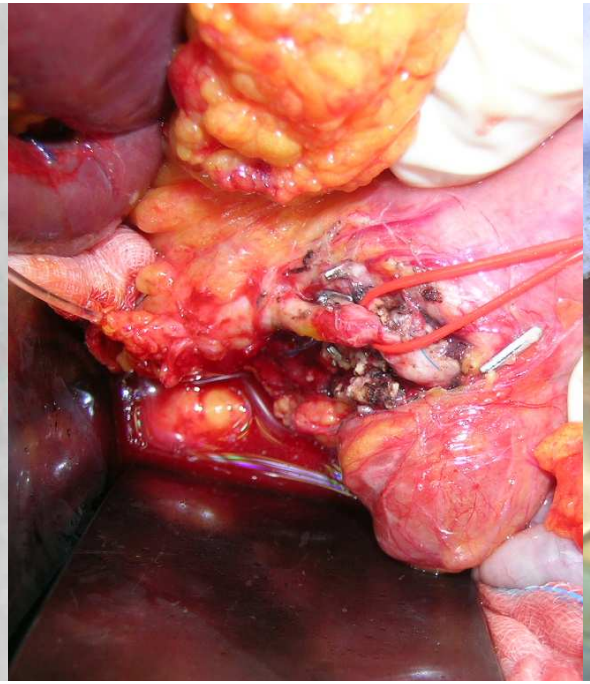
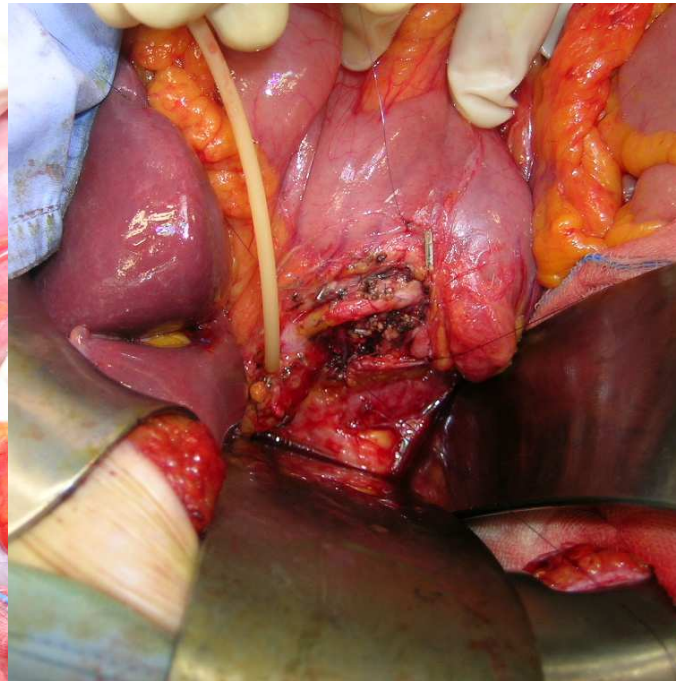
Matthew H Kulke
Dana-Farber Cancer Institute
Boston
2011

Patients with pancreatic NET present with diverse symptoms related to hormonal hypersecretion, tumor bulk, or both. Accurate diagnosis of this condition and differentiation of pancreatic NET from the more common pancreatic adenocarcinomas is a critical first step in developing an appropriate treatment plan. Similarly, pancreatic NET should be considered separately from carcinoid tumors, which arise in other sites. Surgical resection remains the mainstay of treatment for patients with localized disease.

tumori pancreatici

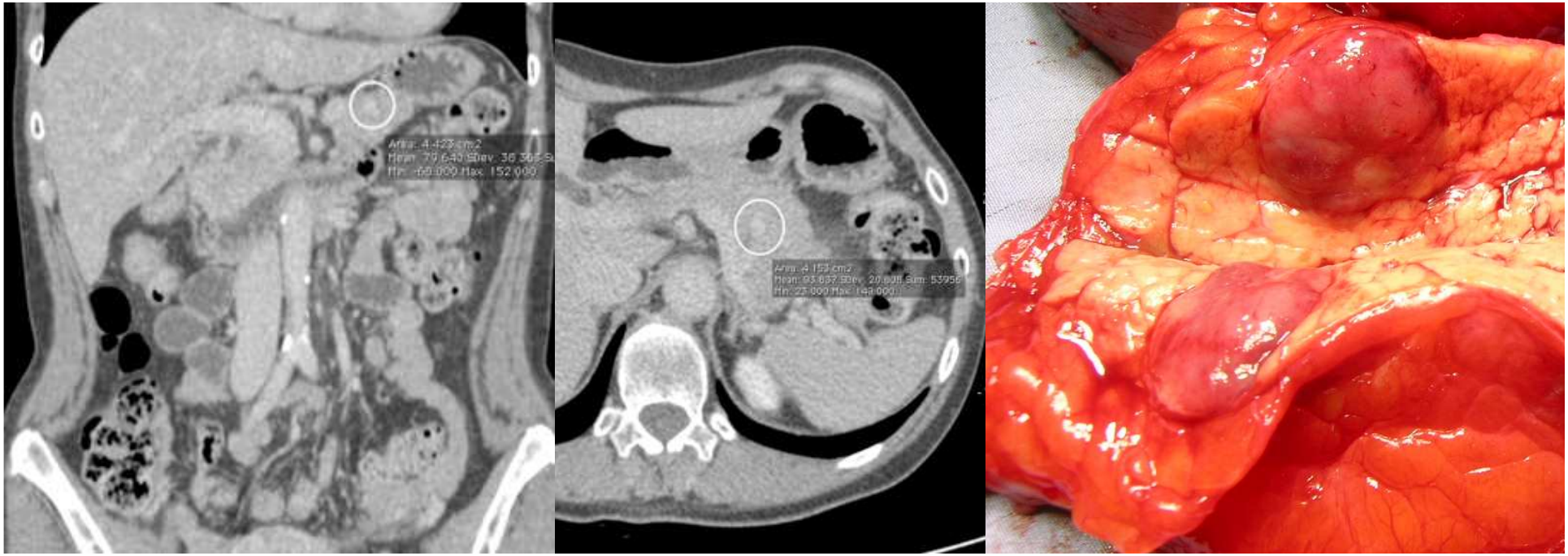
- Enucleazione : T<2cm
  - periferici
  - funzionanti, non funzionanti
- Pancreasectomia distale, per T >2cm
  - +/-splenectomia
  - chirurgia mini-invasiva (laparoscopia|robot)
- Duodenopancreasectomia: T >2cm, nella testa
- Pancreasectomia centrale
- MEN|1 con pancNETs

enucleazione

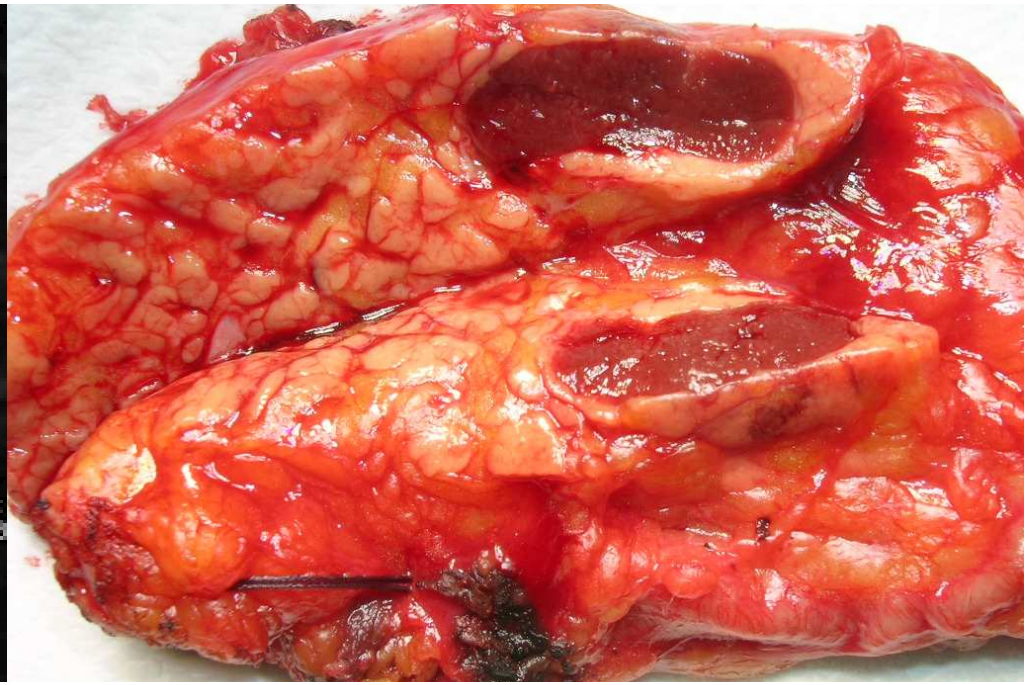




pancreasectomia

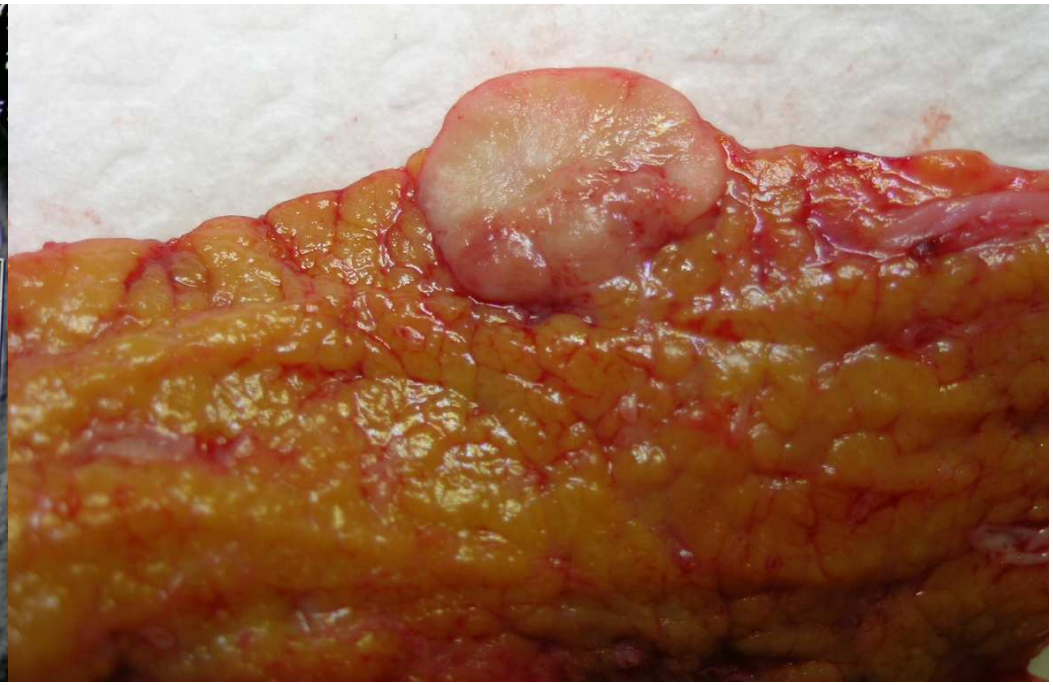
tumori pancreatici



tumori pancreatici



tumori pancreatici



Do you
really want
to remove
MY
PANCREAS?

Evolving Diagnostic and Treatment Strategies for Pancreatic Neuroendocrine Tumors

Matthew H Kulke[1*], Johanna Bendell[2], Larry Kvols[3], Joel Picus[4], Rodney Pommier[5] and James Yao[6]

Table 1 Clinical presentation of pancreatic neuroendocrine tumors (NET)

Tumor	Symptoms or signs	Incidence of metastases	Extrapancreatic location
Insulinoma	Hypoglycemia resulting in intermittent confusion, sweating, weakness, nausea; loss of consciousness may occur in severe cases	<15%	Rare
Glucagonoma	Rash (necrotizing migratory erythema), cachexia, diabetes, deep venous thrombosis	Majority	Rare
VIPoma, Verner-Morrison Syndrome, WDHA Syndrome	Profound secretory diarrhea, electrolyte disturbances	Majority	10%
Gastrinoma, Zollinger-Ellison Syndrome	Acid hypersecretion resulting in refractory peptic ulcer disease, abdominal pain, and diarrhea	<50%	Frequently in duodenum
Somatostatinoma	Diabetes, diarrhea, cholelithiasis	Majority	Rare
Non-functioning	May be first diagnosed due to mass effect	Majority	Rare

WDHA: Watery Diarrhea, Hypokalemia and Achlorhydria.

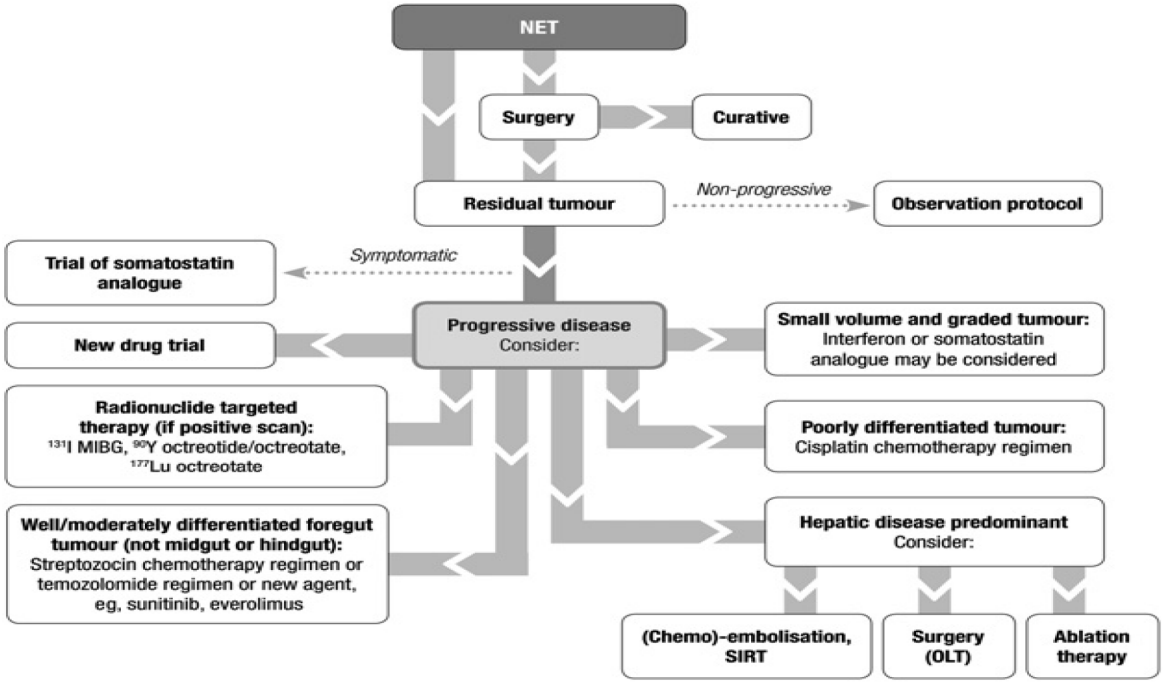
Role of Resection of the Primary Pancreatic Neuroendocrine Tumour Only in Patients with Unresectable Metastatic Liver Disease: A Systematic Review

Gabriele Capurso[a] Rossella Bettini[b] Maria Rinzivillo[a] Letizia Boninsegna[b, c]
Gianfranco Delle Fave[a] Massimo Falconi[b]

Table 3. Survival and symptomatic improvement in relation with the 'active' (resected) or 'not active' (unresected) group

Study (first author)	Median overall survival, months	5-Year survival, %	Median PFS months	Symptom improvement
Bettini [15]				
Resected	54.3 (95% CI 25–86)	40.4	7.6 (95% CI 0.5–14.7)	88%
Unresected	39.5 (95% CI 5.4–73.6)	41.8	12 (95% CI 3.7–20.3)	31%
Nguyen [18]				
Resected	not reported	60	not reported	not reported
Unresected	not reported	30	not reported	not reported
Solorzano [19]				
Resected	36 (95% CI 26.4–96)	49	not reported	not reported
Unresected	21.6 (95% CI 16.8–32.4)	16	not reported	not reported

conclusioni



" .. it is conceivable that the day is not far distant when it is quite probable that surgery will in the end come to play a less, rather than a more important role in ductless gland maladies."

H. Cushing, 1912

futuro

Future Trial Design

Recent successes have shown that large randomized controlled trials studying treatments for neuroendocrine tumors can provide practice-changing results. The NCI recently convened a task force to set priorities for future studies and to recommend appropriate standards for trials in this disease.[158] Among their recommendations are the following:

- Pancreatic neuroendocrine tumors should be studied separately from tumors in other locations.
- Well-differentiated and poorly differentiated neuroendocrine tumors should be studied in separate trials.
- Progression-free survival is an appropriate primary end point for phase III trials and many phase II trials.
- Trials studying treatment for hormonal symptoms are as critical as those assessing effects on tumor progression and should include quality-of-life end points.

Rigorous studies will allow continued progress in the development of improved treatments for patients with neuroendocrine tumors.