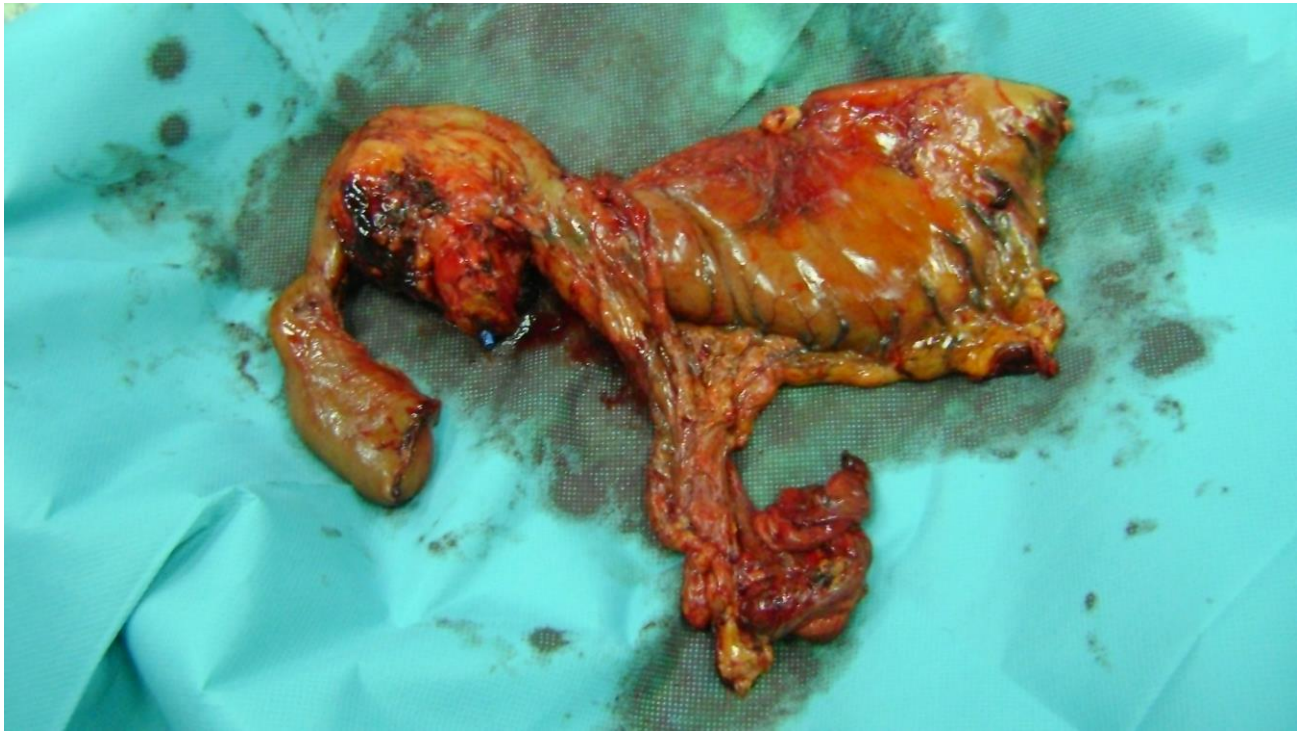
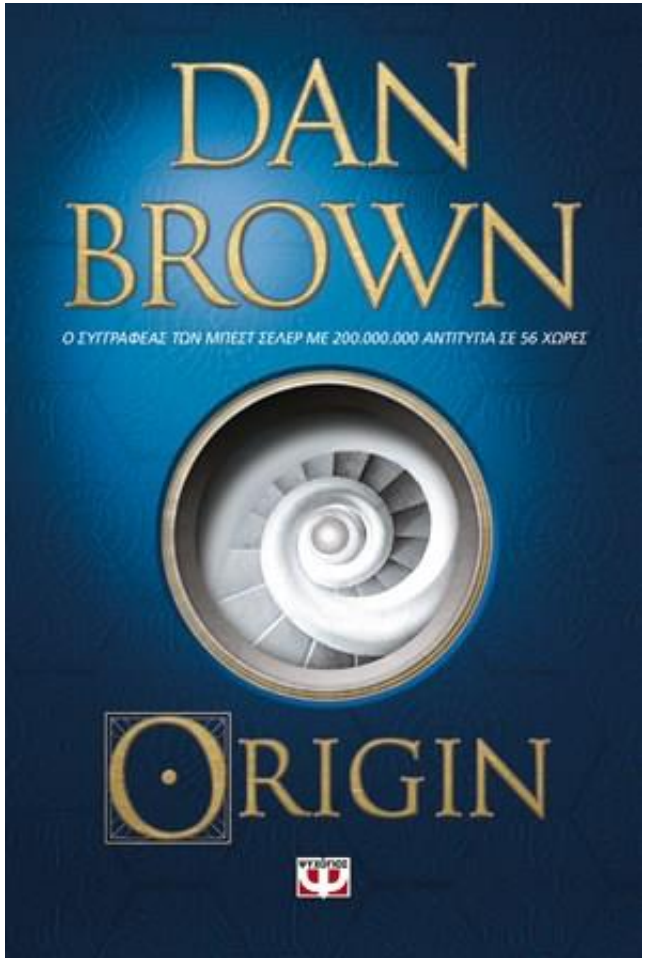
ΚΑΡΚΙΝΟΣ ΠΑΓΚΡΕΑΤΟΣ



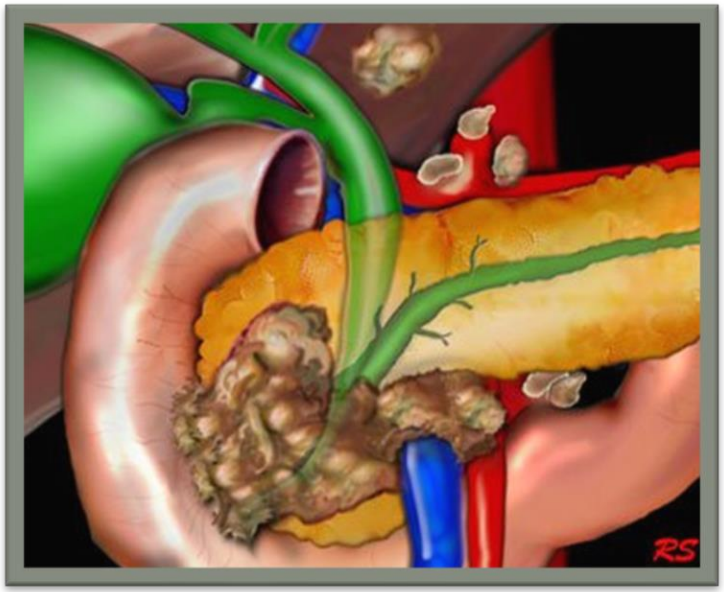
Κων/νος Γ. Τούτουζας

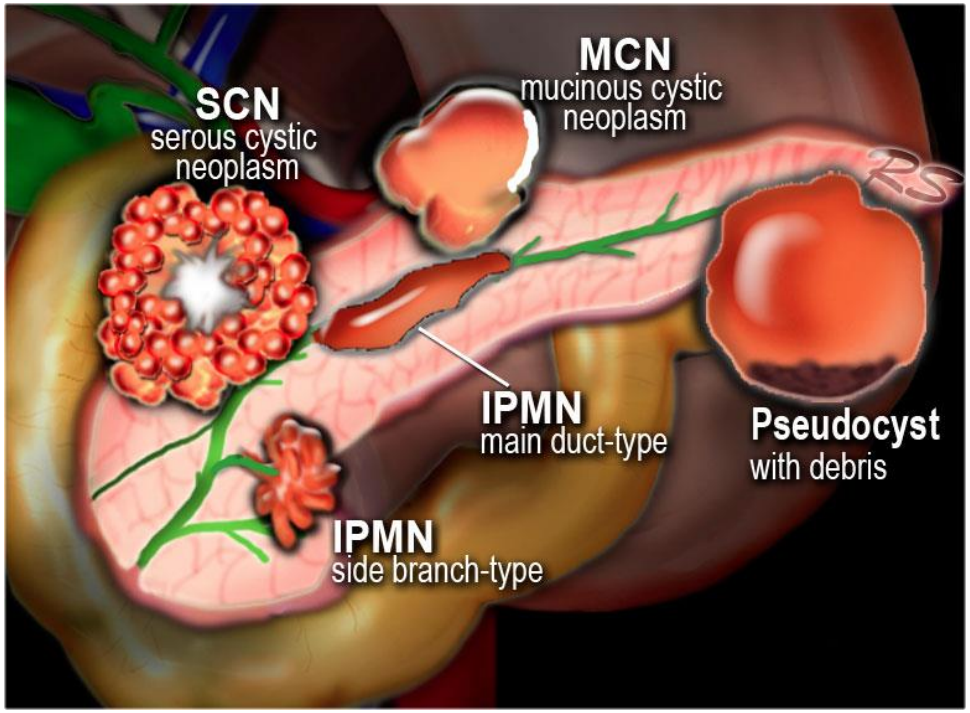
Καθηγητής Χειρουργικής

Trendy…disease

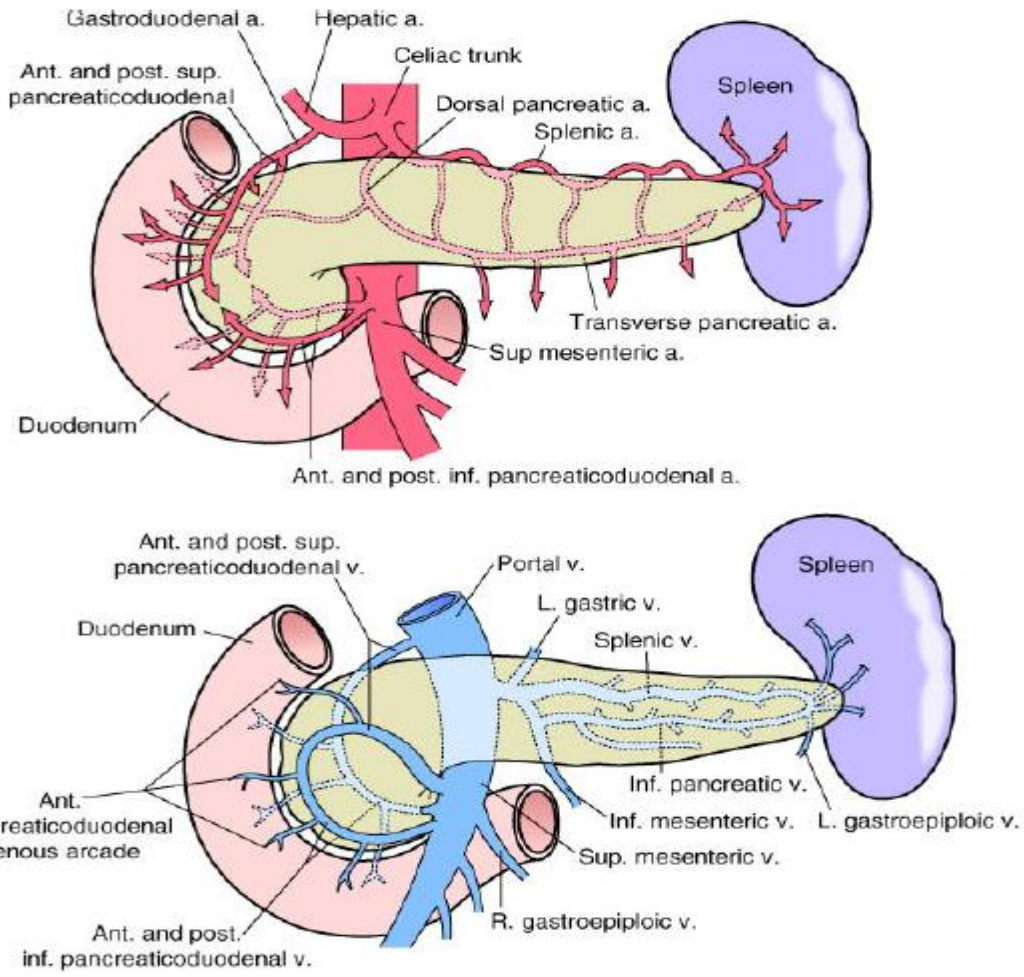


Καρκίνος παγκρέατος





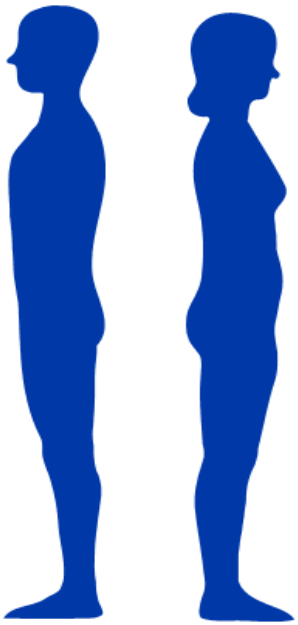
Ανατομία


Gastroduodenal a.
Hepatic a.
Celiac trunk
Ant. and post. sup. pancreaticoduodenal
Dorsal pancreatic a.
Splenic a.
Spleen
Transverse pancreatic a.
Sup mesenteric a.
Duodenum
Ant. and post. inf. pancreaticoduodenal a.
Ant. and post. sup. pancreaticoduodenal v.
Portal v.
L. gastric v.
Splenic v.
Spleen
Duodenum
Inf. pancreatic v.
Inf. mesenteric v.
L. gastroepiploic v.
Ant. pancreaticoduodenal venous arcade
Sup. mesenteric v.
R. gastroepiploic v.
Ant. and post. inf. pancreaticoduodenal v.

Επίπτωση

2012 Estimated US Cancer Cases*

Men 848,170		Women 790,740	
Prostate	29%	29%	Breast
Lung & bronchus	14%	14%	Lung & bronchus
Colon & rectum	9%	9%	Colon & rectum
Urinary bladder	7%	6%	Uterine corpus
Melanoma of skin	5%	5%	Thyroid
Kidney & renal pelvis	5%	4%	Melanoma of skin
Non-Hodgkin lymphoma	4%	4%	Non-Hodgkin lymphoma
Oral cavity	3%	3%	Kidney & renal pelvis
Leukemia	3%	3%	Ovary
Pancreas	3%	3%	Pancreas
All Other Sites	18%	20%	All Other Sites



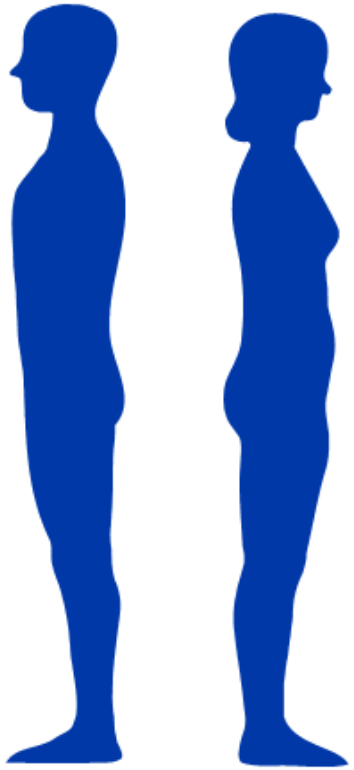
Source: American Cancer Society, 2012

Source: American Cancer Society, 2012.

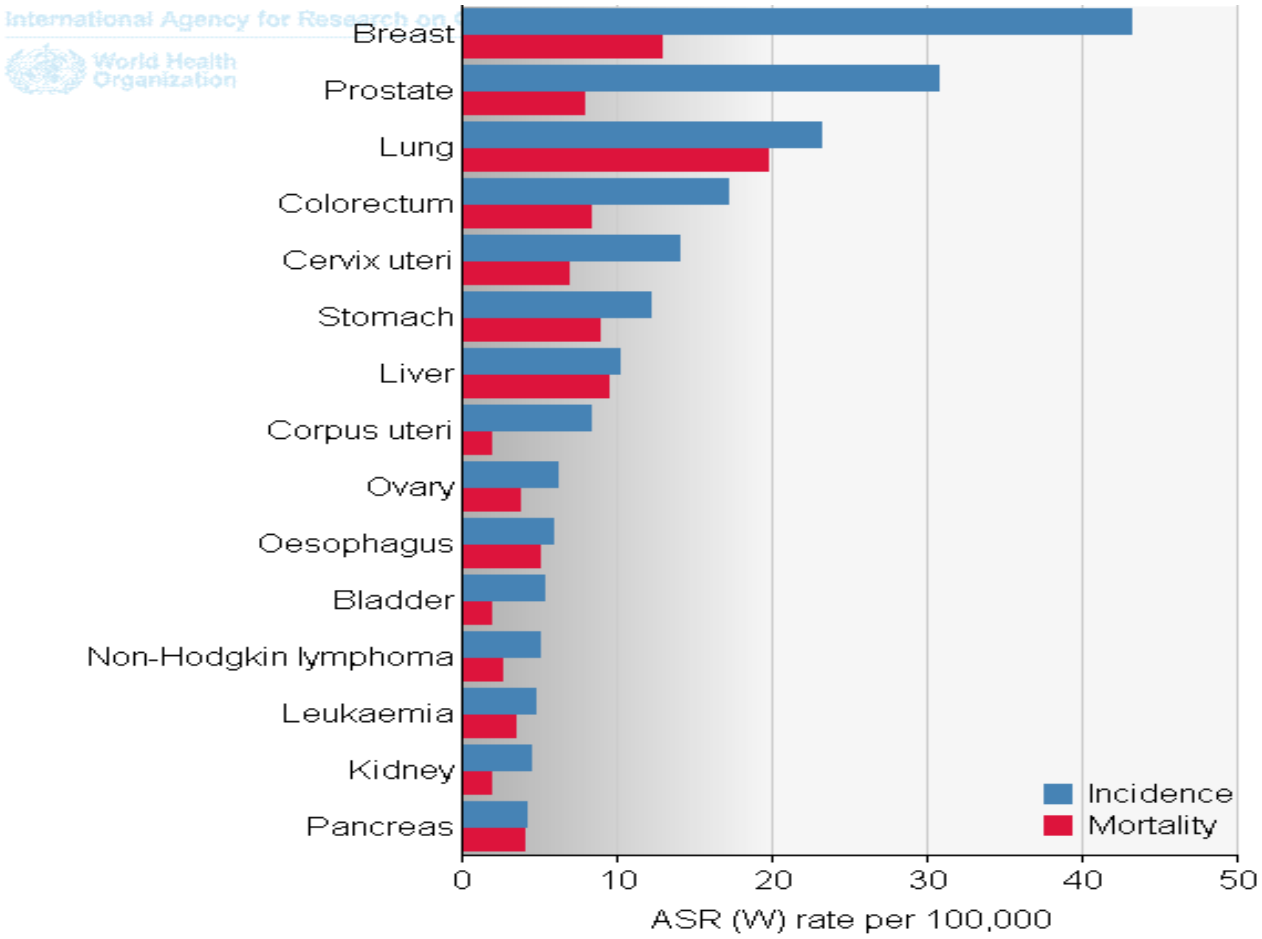
*Excludes basal and squamous cell skin cancers and in situ carcinomas except urinary bladder.

Θνησιμότητα

Men 301,820		Women 275,370	
Lung & bronchus	29%	26%	Lung & bronchus
Prostate	9%	14%	Breast
Colon & rectum	9%	9%	Colon & rectum
Pancreas	6%	7%	Pancreas
Liver & intrahepatic bile duct	5%	6%	Ovary
Leukemia	4%	4%	Leukemia
Esophagus	4%	3%	Non-Hodgkin lymphoma
Urinary bladder	3%	3%	Uterine corpus
Non-Hodgkin lymphoma	3%	2%	Liver & intrahepatic bile duct
Kidney & renal pelvis	3%	2%	Brain/other nervous system
All other sites	25%	24%	All other sites



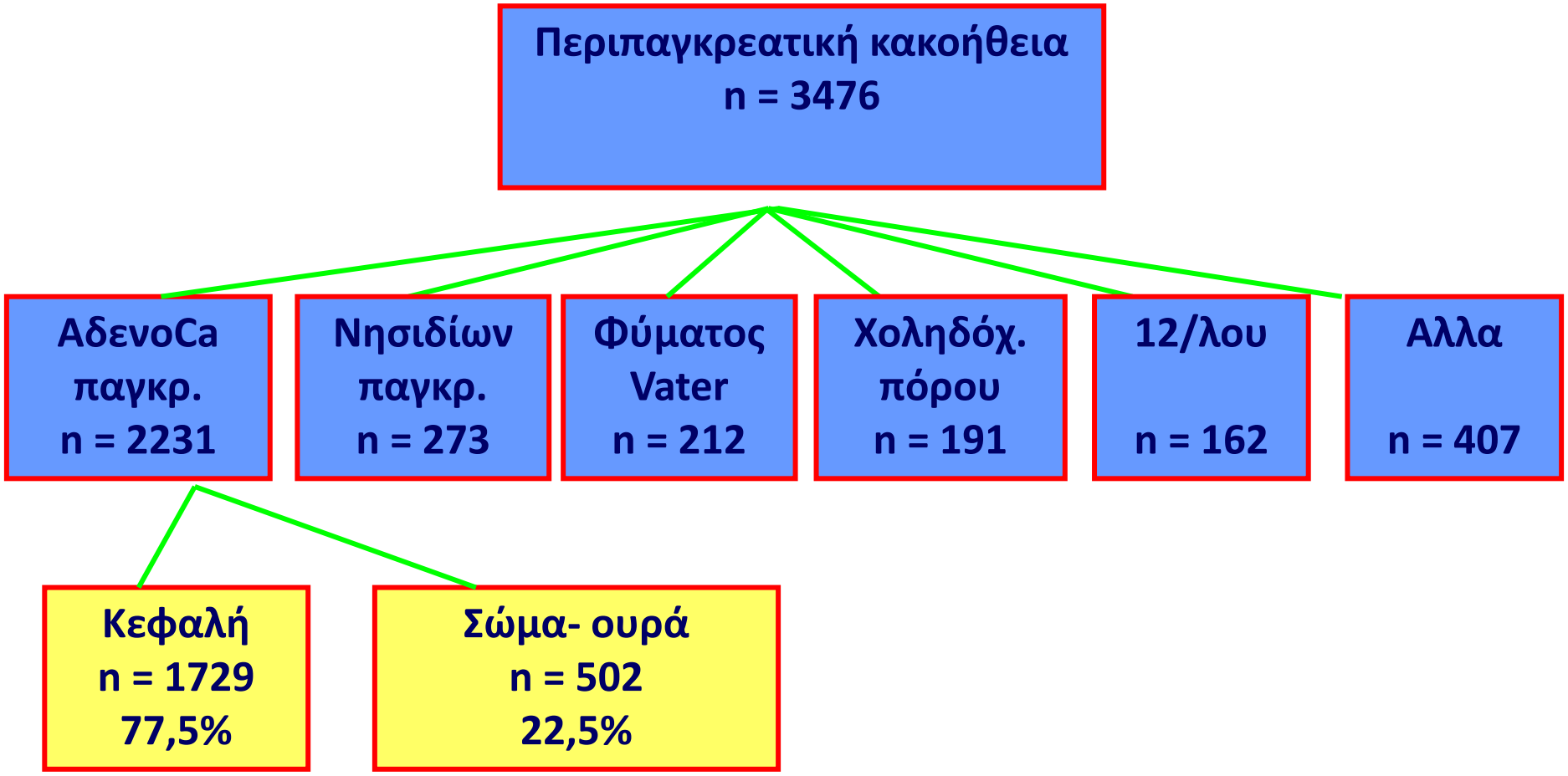
Επίπτωση/θνησιμότητα



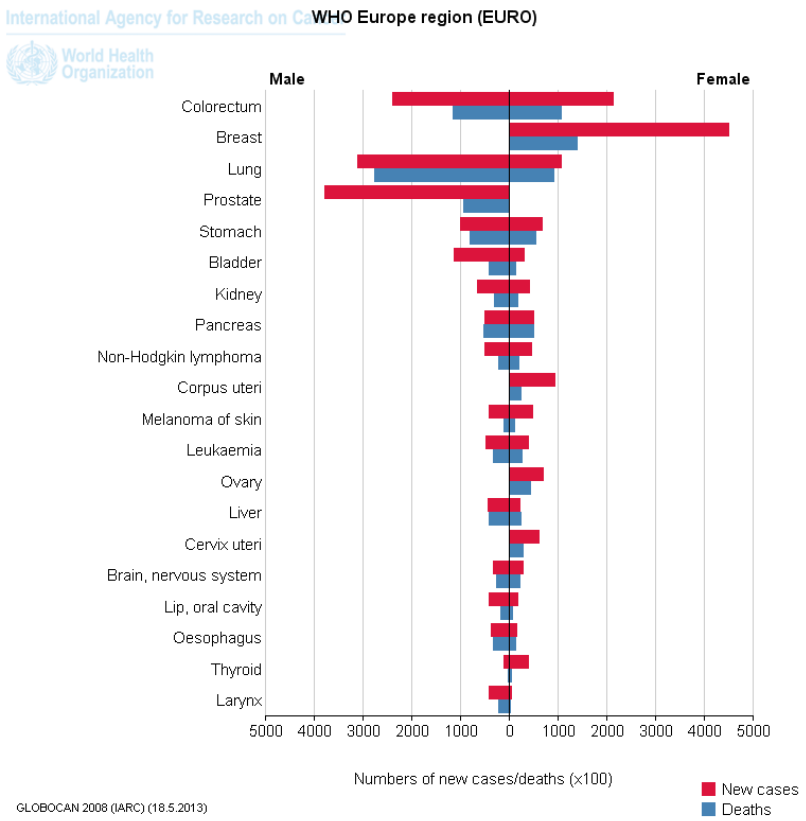
ΚΑΡΚΙΝΟΣ ΠΑΓΚΡΕΑΤΟΣ

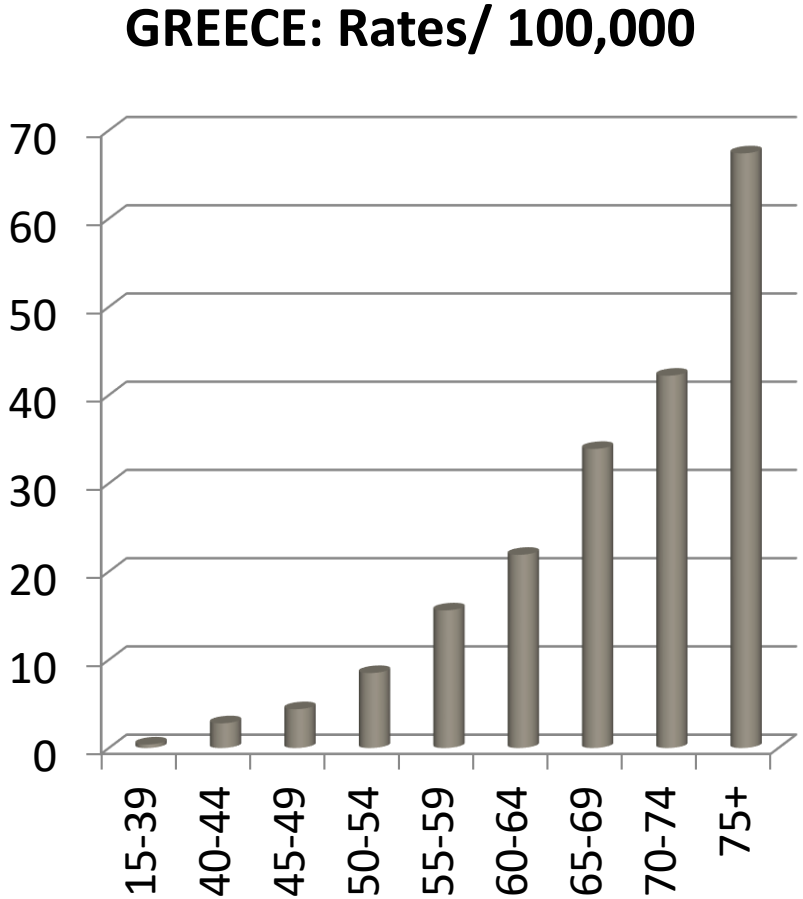
Επιδημιολογικά δεδομένα

(MSKCC 1983-2000)

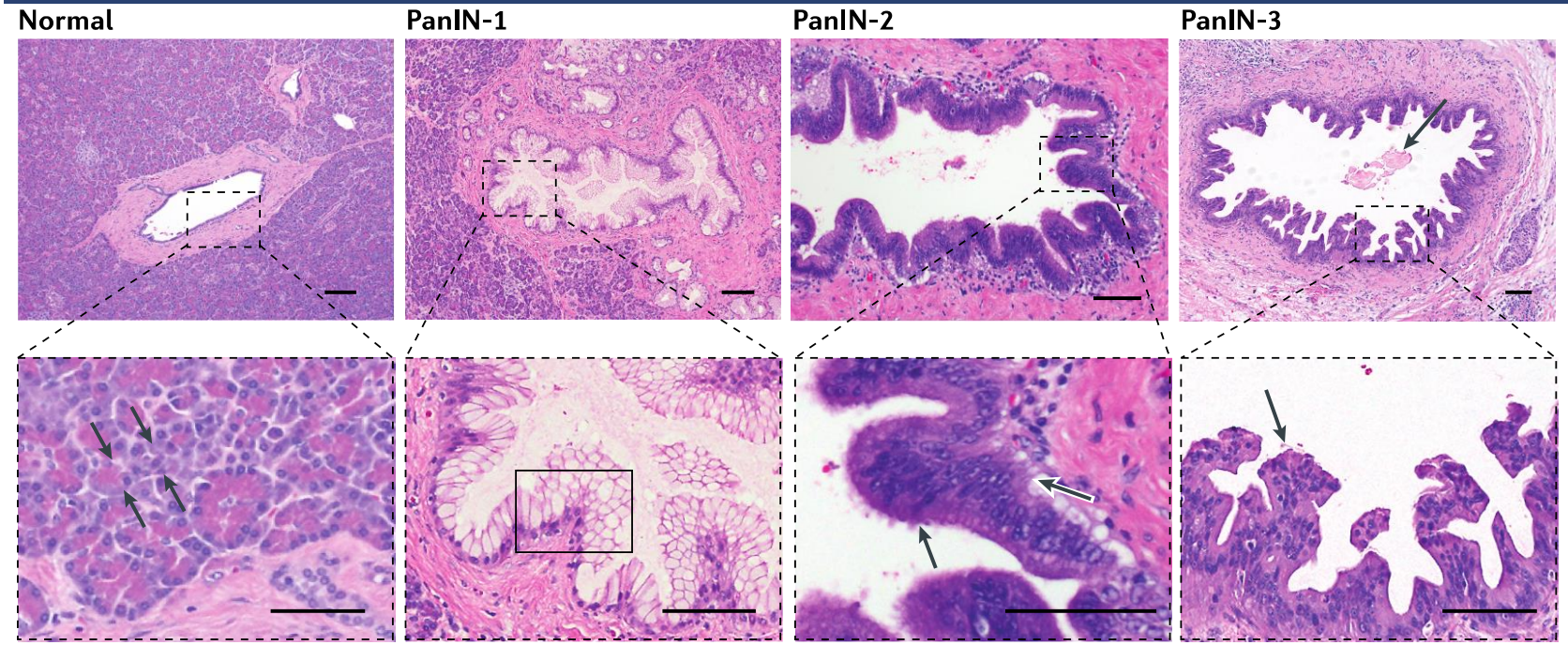


Φύλο - Ηλικία


International Agency for Research on Ca
World Health Organization
WHO Europe region (EURO)
Male
Female
Colorectum
Breast
Lung
Prostate
Stomach
Bladder
Kidney
Pancreas
Non-Hodgkin lymphoma
Corpus uteri
Melanoma of skin
Leukaemia
Ovary
Liver
Cervix uteri
Brain, nervous system
Lip, oral cavity
Oesophagus
Thyroid
Larynx
5000 4000 3000 2000 1000 0 1000 2000 3000 4000 5000
Numbers of new cases/deaths (x100)
New cases
Deaths
GLOBOCAN 2008 (IARC) (18.5.2013)


GREECE: Rates/ 100,000
70
60
50
40
30
20
10
0
15-39
40-44
45-49
50-54
55-59
60-64
65-69
70-74
75+

Nature, 2016



K-RAS (99%)

CDKN2A

TP 53

SMAD4

Παράγοντες κινδύνου

Major risk factor	Fold increased risk	% total pancreatic cancers
Smoking	x2	30%
Genetic factors	x5-10	10%
Chronic pancreatitis	x10-20	1%
Hereditary pancreatitis	x50-80	<1%
Age >70 years	x5	
Minor		
Diabetes mellitus type II	x1.5-2	-
Obesity	x1.7	-
High fat diet	x1.7	-
Previous gastric surgery	x1.8	-
Sclerosing cholangitis	x14	-
Helicobacter pylori	x1.8	-

Κληρονομικά σύνδρομα

Syndrome	Gene mutation
Peutz-Jeghers syndrome	STK11/LKB1
Familial breast and ovarian cancer syndromes	BRCA1 and BRCA2
Familial atypical multiple mole melanoma (FAMMM)	TP16
Familial pancreatic cancer	BRCA2 in up to 20%; 4q32-34 ?
Hereditary pancreatitis	PRSS1 in up to 80%
von Hippel-Lindau disease	VHL
Ataxia telangiectasia	ATM
Li-Fraumeni syndrome	TP53
Cystic fibrosis	CFTR
Familial adenomatous polyposis (FAP)	APC
Hereditary nonpolyposis colon cancer (HNPCC)	MLH1, MSH2, MSH6, PMS1, PMS2

Κληρονομικά σύνδρομα

Risk	Relative risk	Lifetime risk by age 70
No identifiable futures	1	0,5%
BRAC1	2x	1,2%
BRAC2	3.5-10x	2-5
HNPCC	8.6x	3.9
FAMMM	20-34x	10-17%
Familial PC	32x	16%
Hereditary pancreatitis	50-80x	25-40%
P-J syndrome	132x	66%

Σημεία & συμπτώματα *κεφαλή*

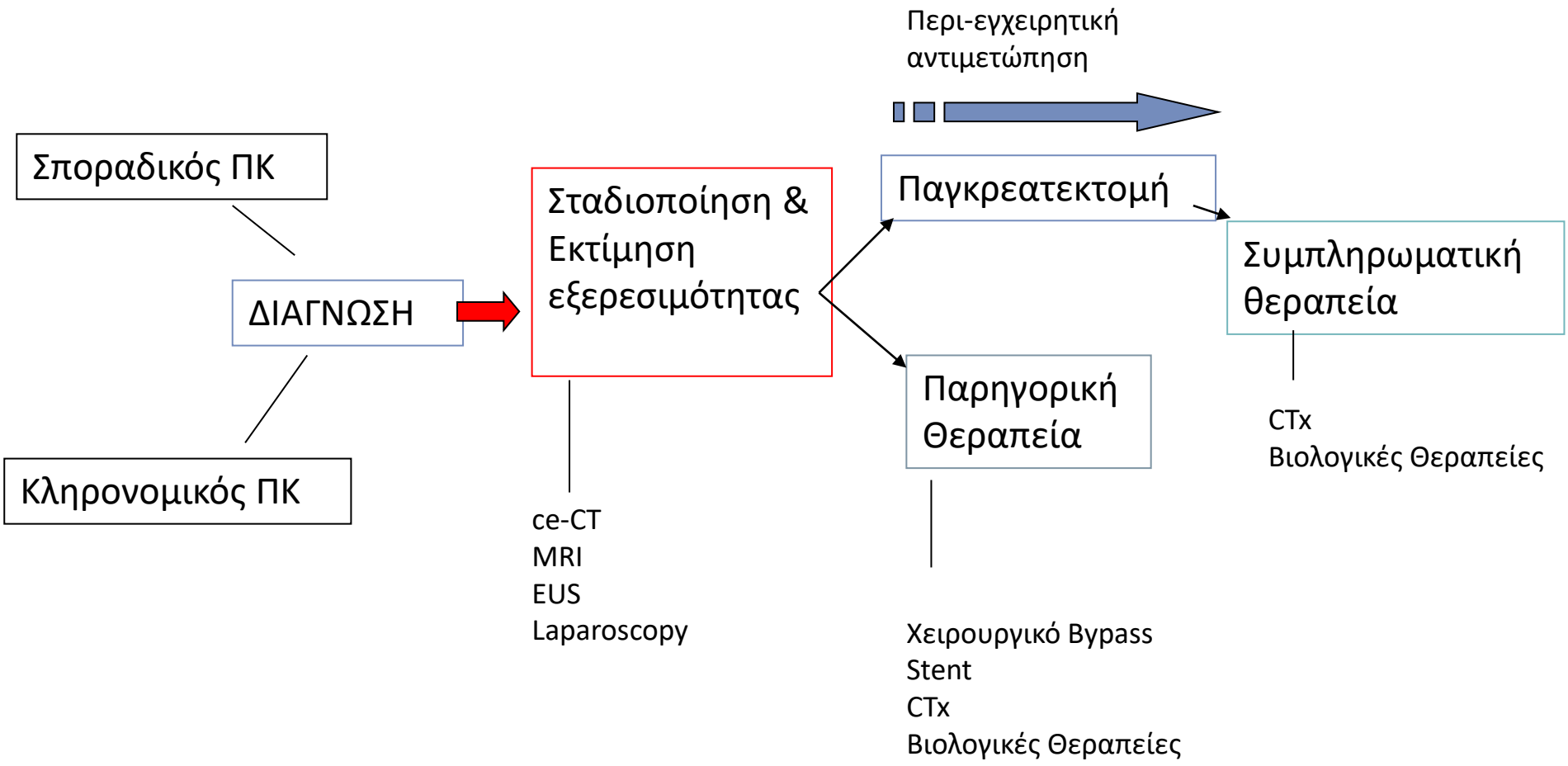
ίκτερος	**40-80%**
Κοιλιακό άλγος	60-80%
Απώλεια βάρους (συχνά μαζική και ταχεία)	50-80%
Ψηλαφητή χοληδόχος κύστη (σημείο Courvoisier)	20%
Κνησμός	25%
θρομβοφλεβίτιδα	15%
έμετος	15%
Οξεία παγκρεατίτιδα	15%

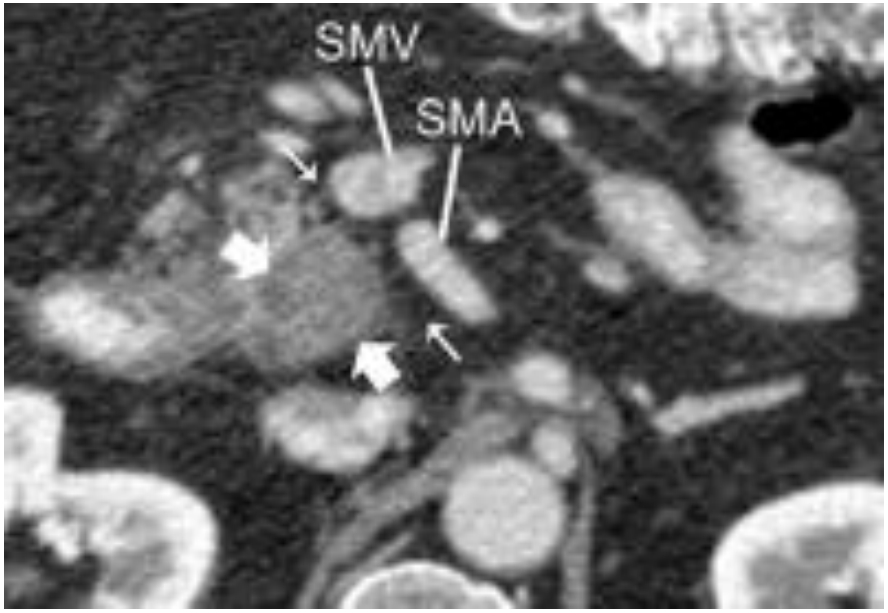
Σημεία & συμπτώματα
σώμα και ουρά

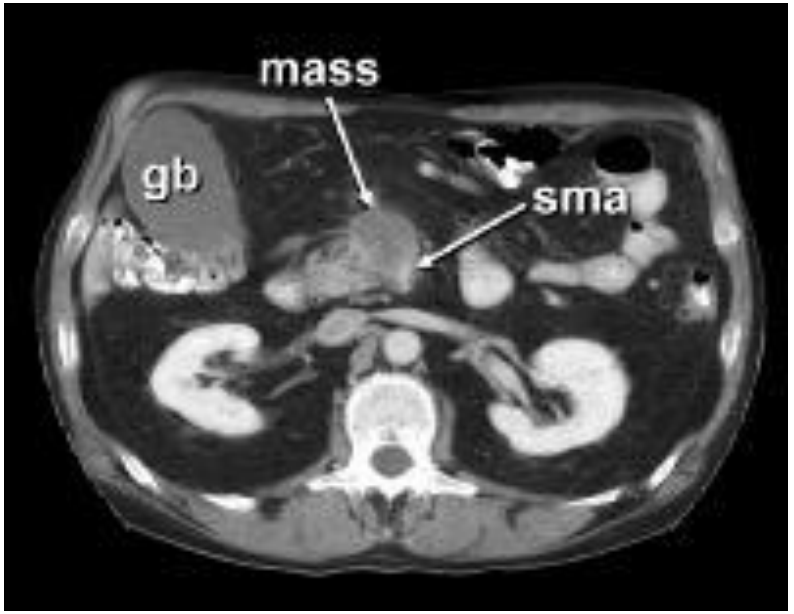
Απώλεια βάρους (συχνά μαζική και ταχεία)	**95%**
Κοιλιακό άλγος	90%
αδυναμία	50%
έμετοι	35%
Κοιλιακή μάζα	20%
Ασκίτης 20%	
ίκτερος	10%

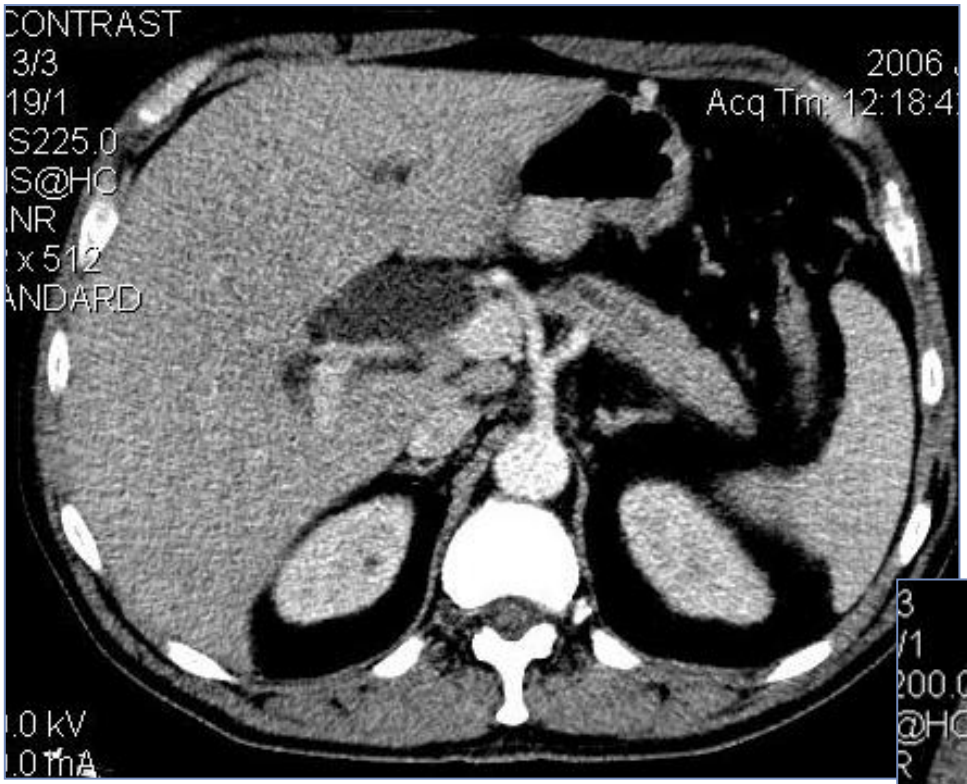
Σημεία & Συμπτώματα

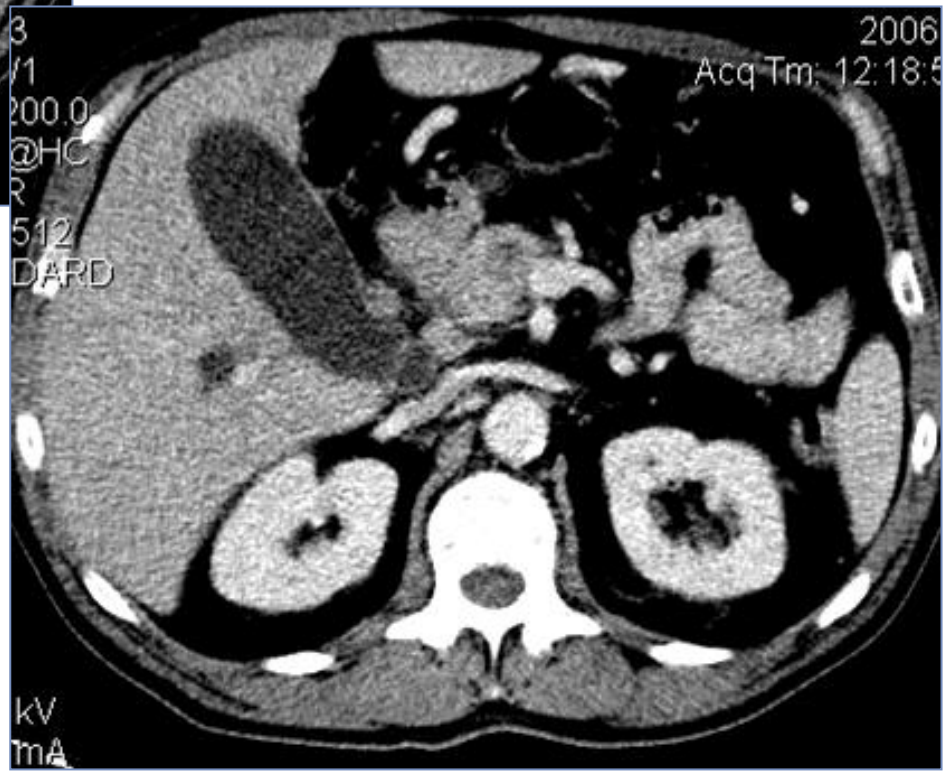
Η εμφάνιση ή η επιδείνωση διαβήτη, αρχικά μη-ινσουλινοεξαρτώμενου, θα πρέπει να μας βάζει σε υποψία ότι υπάρχει καρκίνος σε έναν άνθρωπο άνω των 40 ετών, ειδικά, εάν δεν υπάρχει προηγούμενο ιστορικό διαβήτη ή παχυσαρκίας

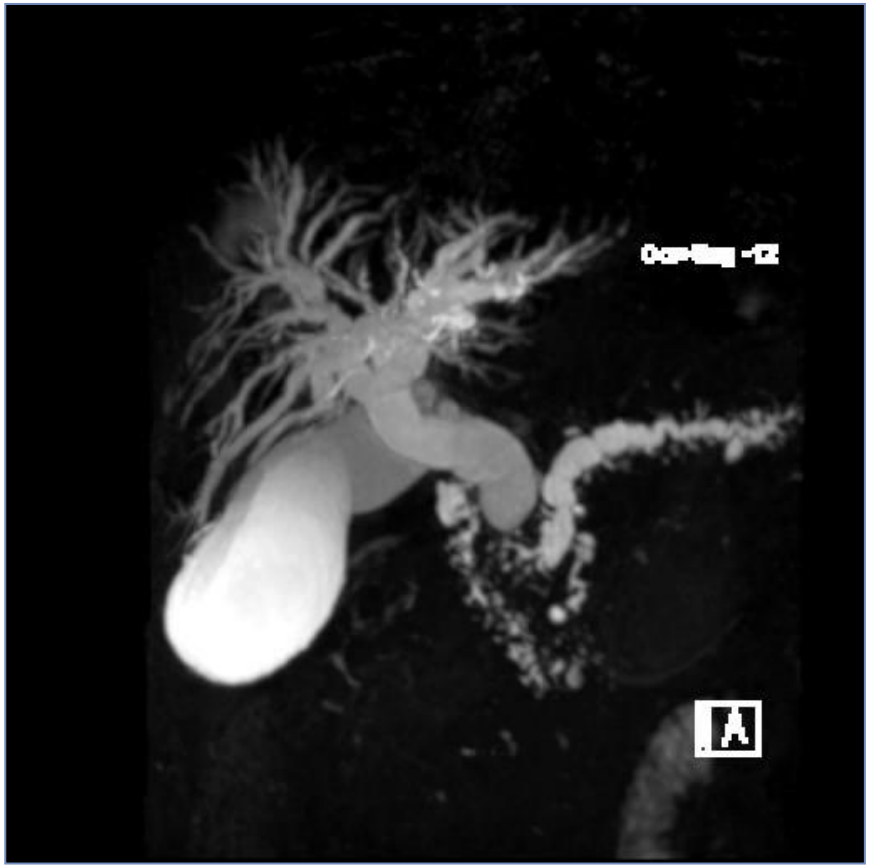

Περι-εγχειρητική αντιμετώπηση
Σποραδικός ΠΚ
ΔΙΑΓΝΩΣΗ
Κληρονομικός ΠΚ
Σταδιοποίηση & Εκτίμηση εξερεσιμότητας
ce-CT
MRI
EUS
Laparoscopy
Παγκρεατεκτομή
Παρηγορική Θεραπεία
Χειρουργικό Bypass
Stent
CTx
Βιολογικές Θεραπείες
Συμπληρωματική θεραπεία
CTx
Βιολογικές Θεραπείες

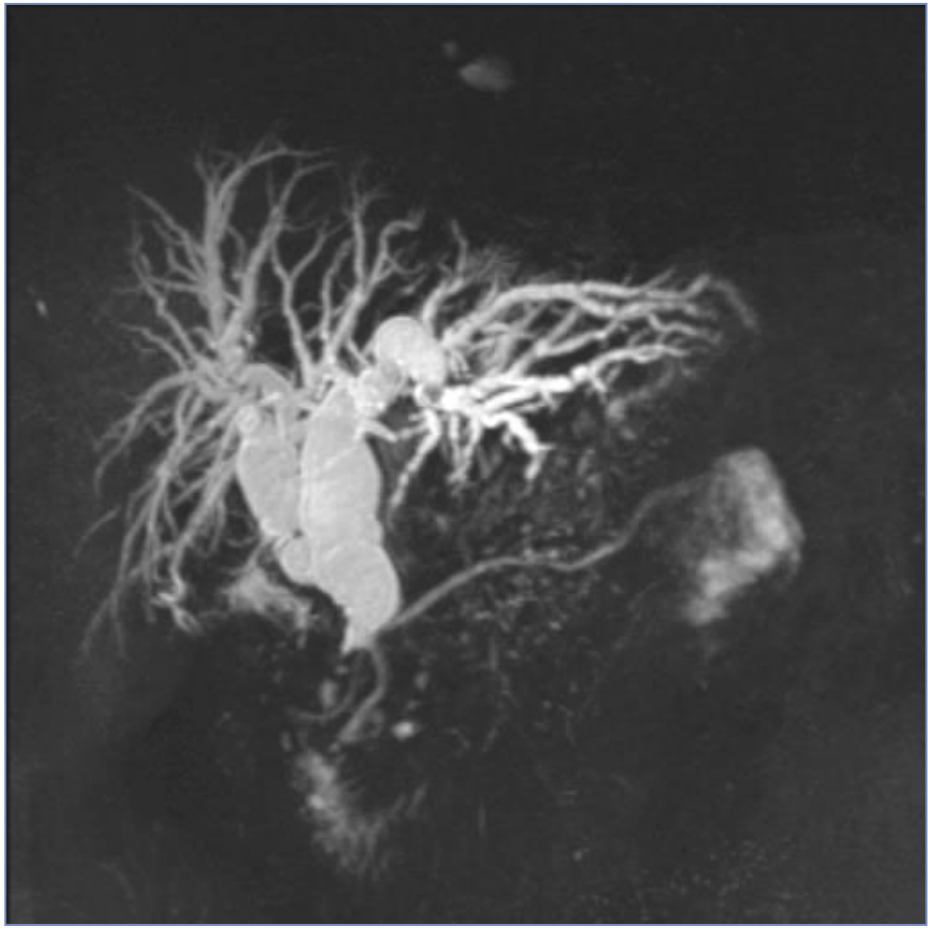

SMV
SMA

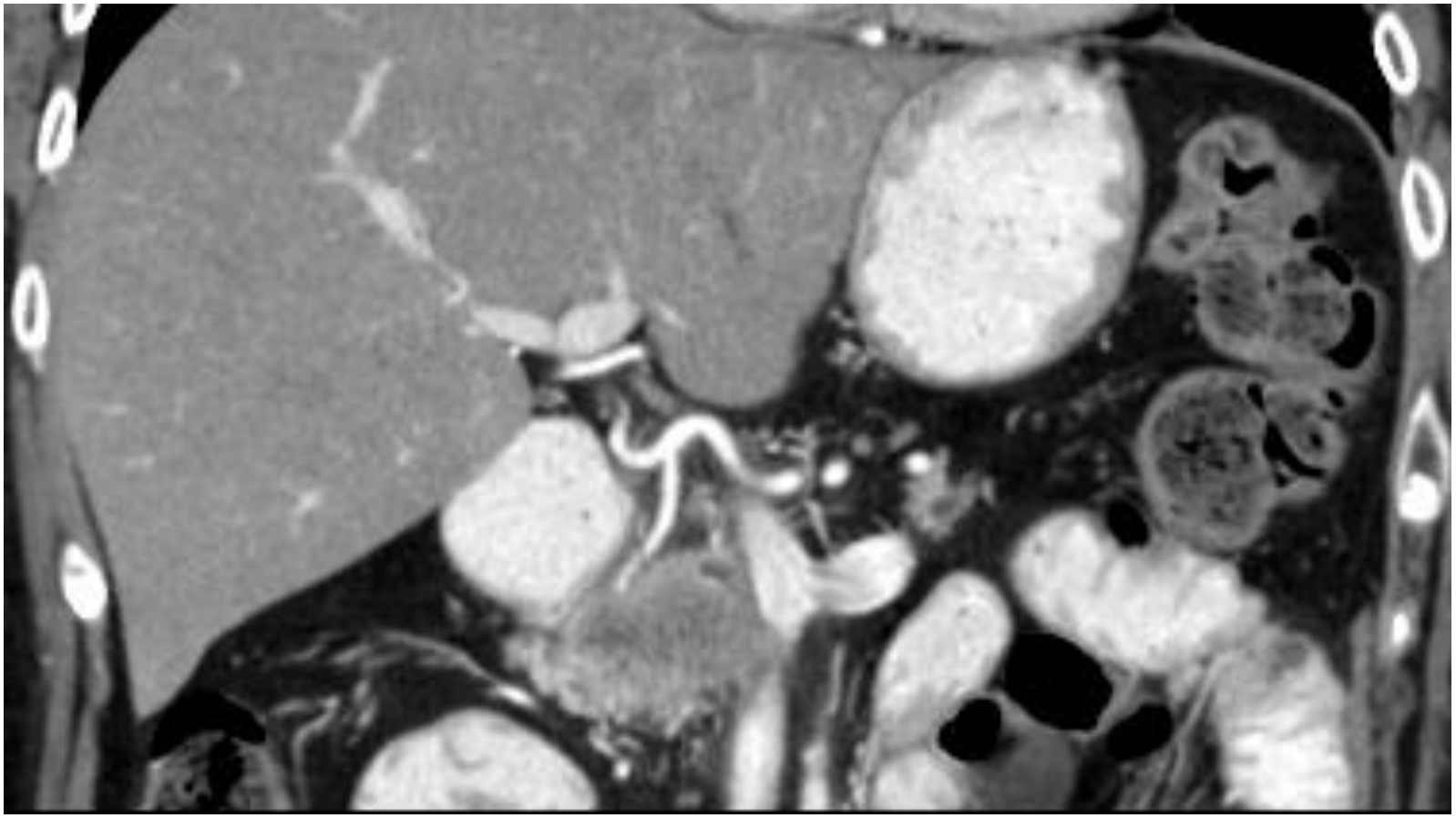

mass
gb
sma

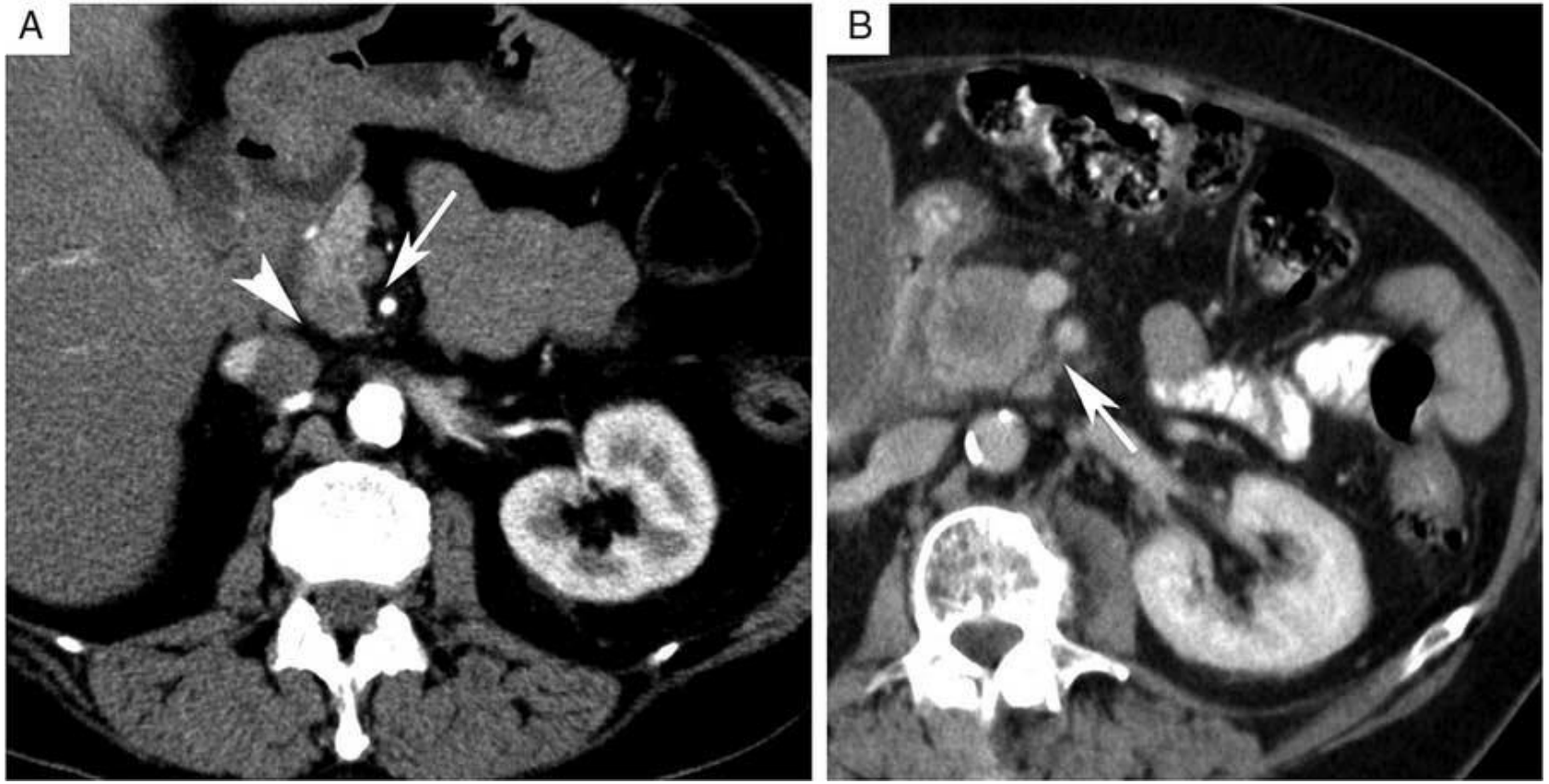

CONTRAST
3/3
19/1
S225.0
S@HC
NR
x 512
ANDARD
2006
Acq Tm: 12:18:4
.0 kV
.0 mA

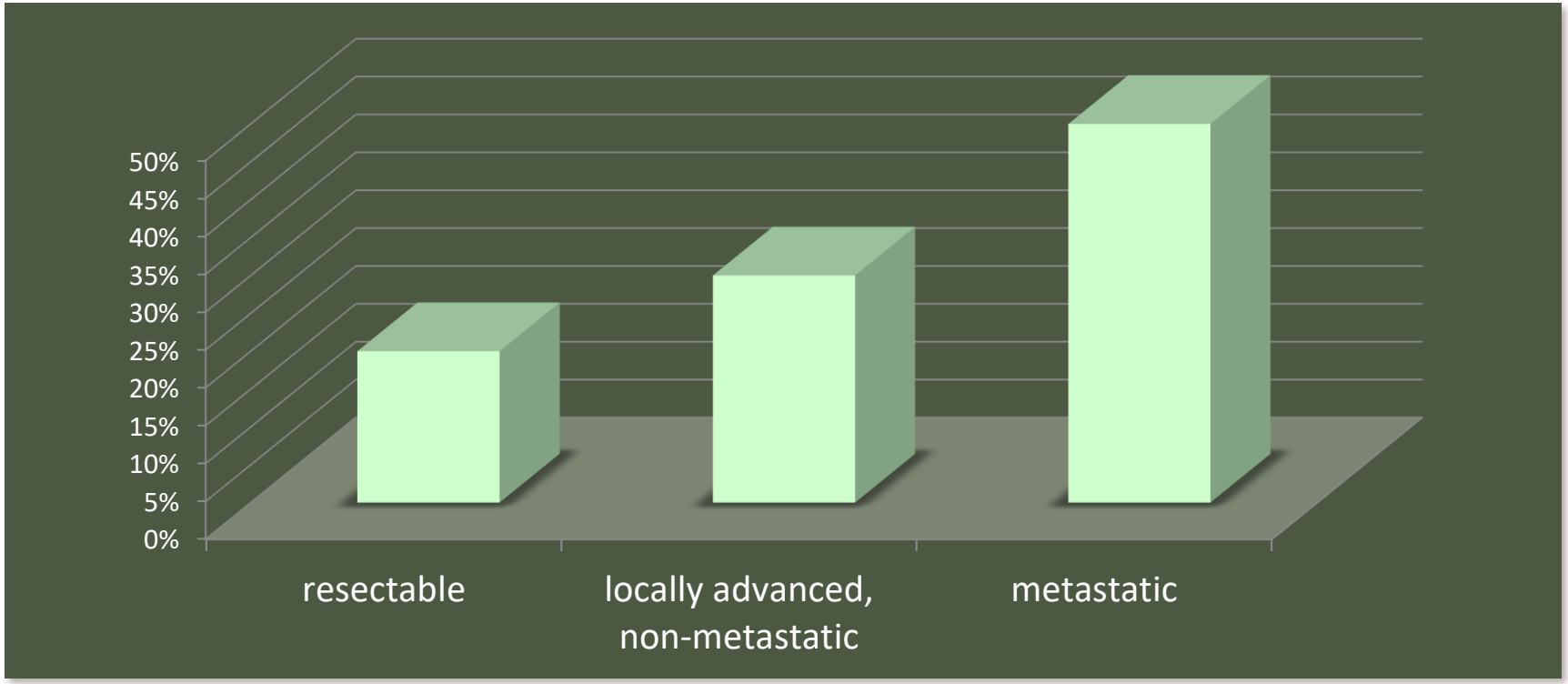

3
/1
200.0
@HC
512
DARD
2006
Acq Tm: 12:18:5
kV
mA


A

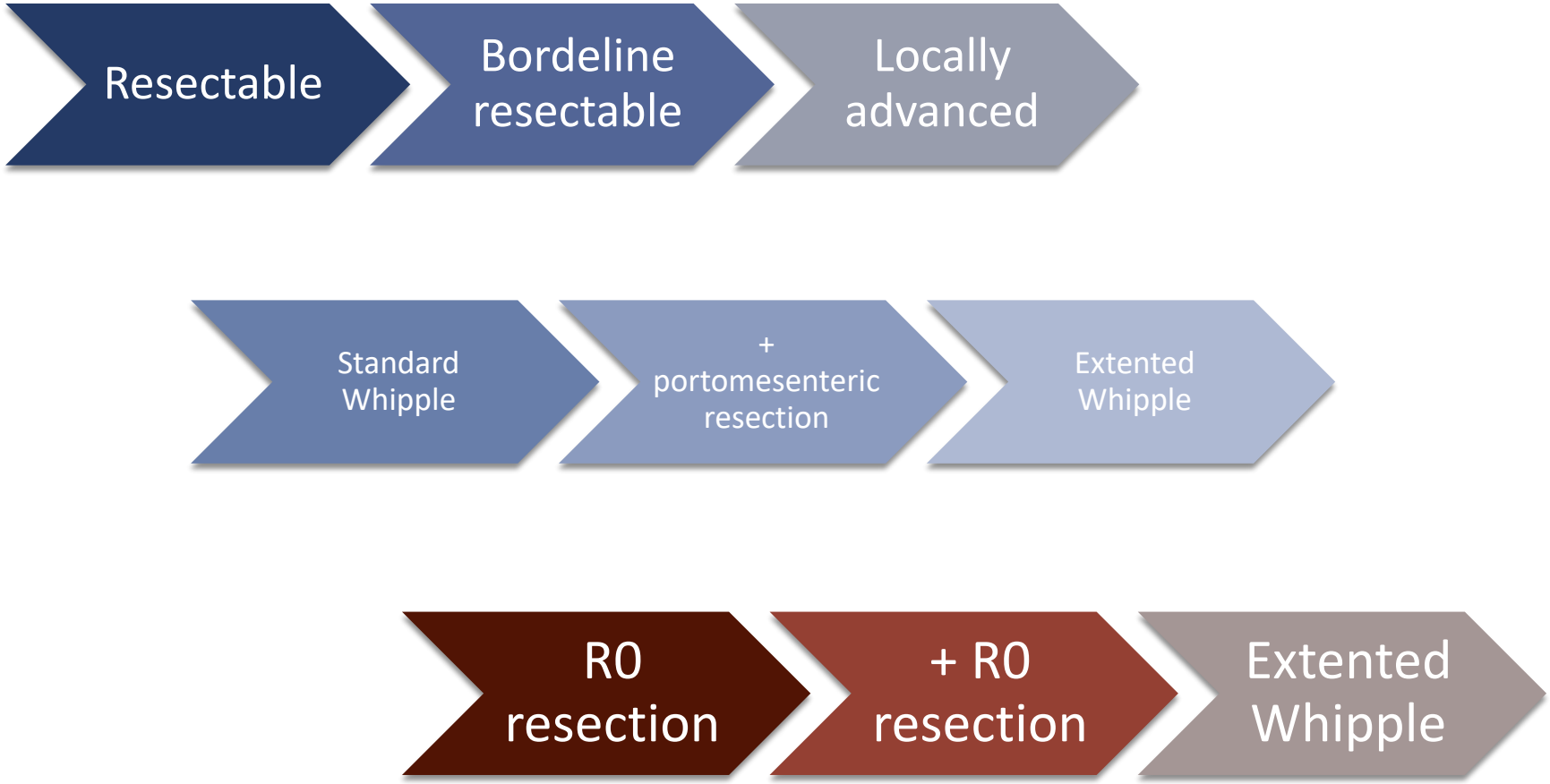





A
B

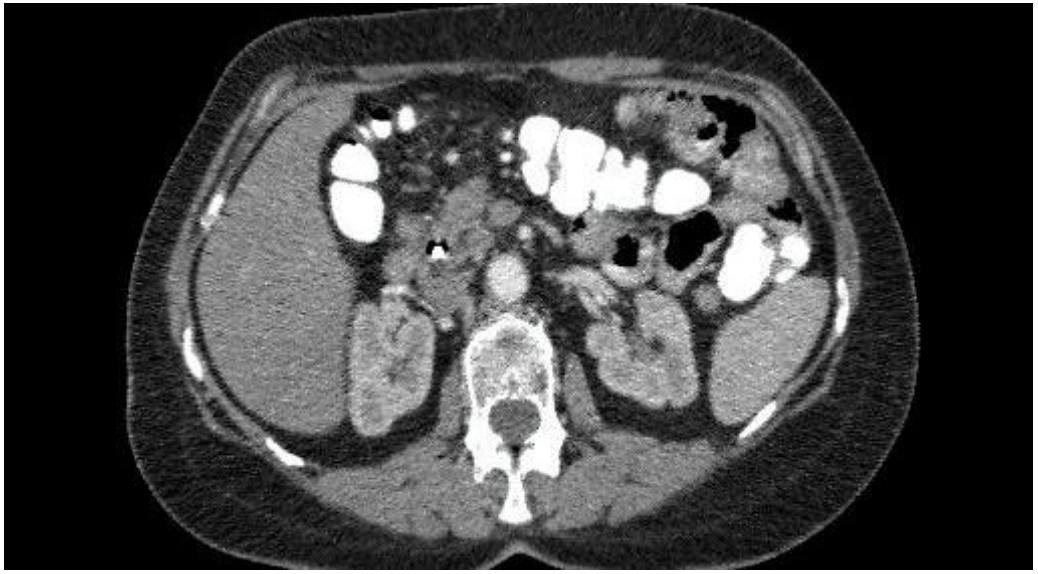

50%
45%
40%
35%
30%
25%
20%
15%
10%
5%
0%
resectable
locally advanced, non-metastatic
metastatic

The continuum of resectability



Resectable

Standard of care: surgery + adjuvant chemotherapy

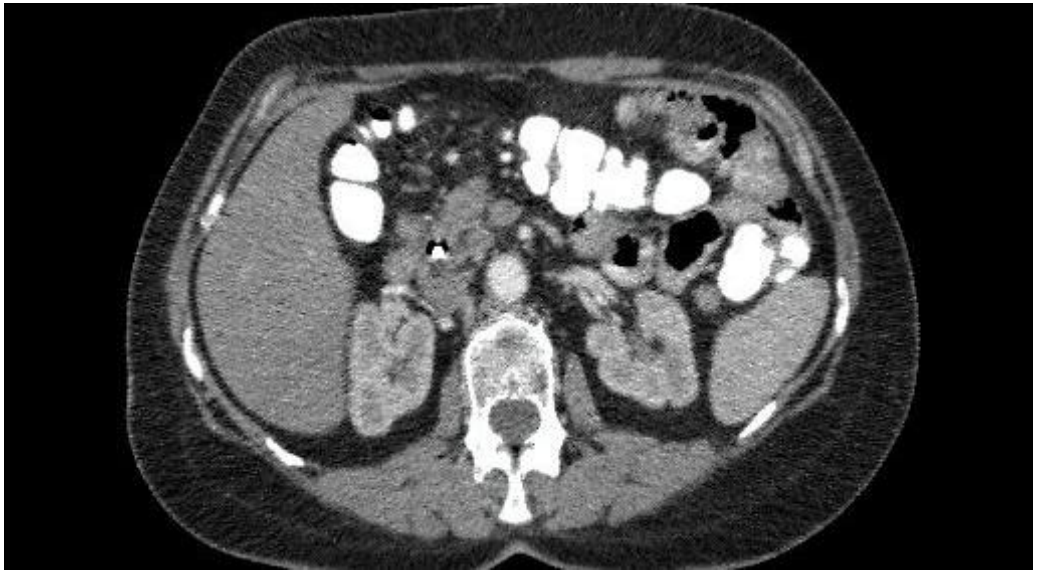


Median survival: 20 months
5-year survival: 20-25%

Hackert T. Cancer Letters 2016

Resectable – ‘the twenty disease’

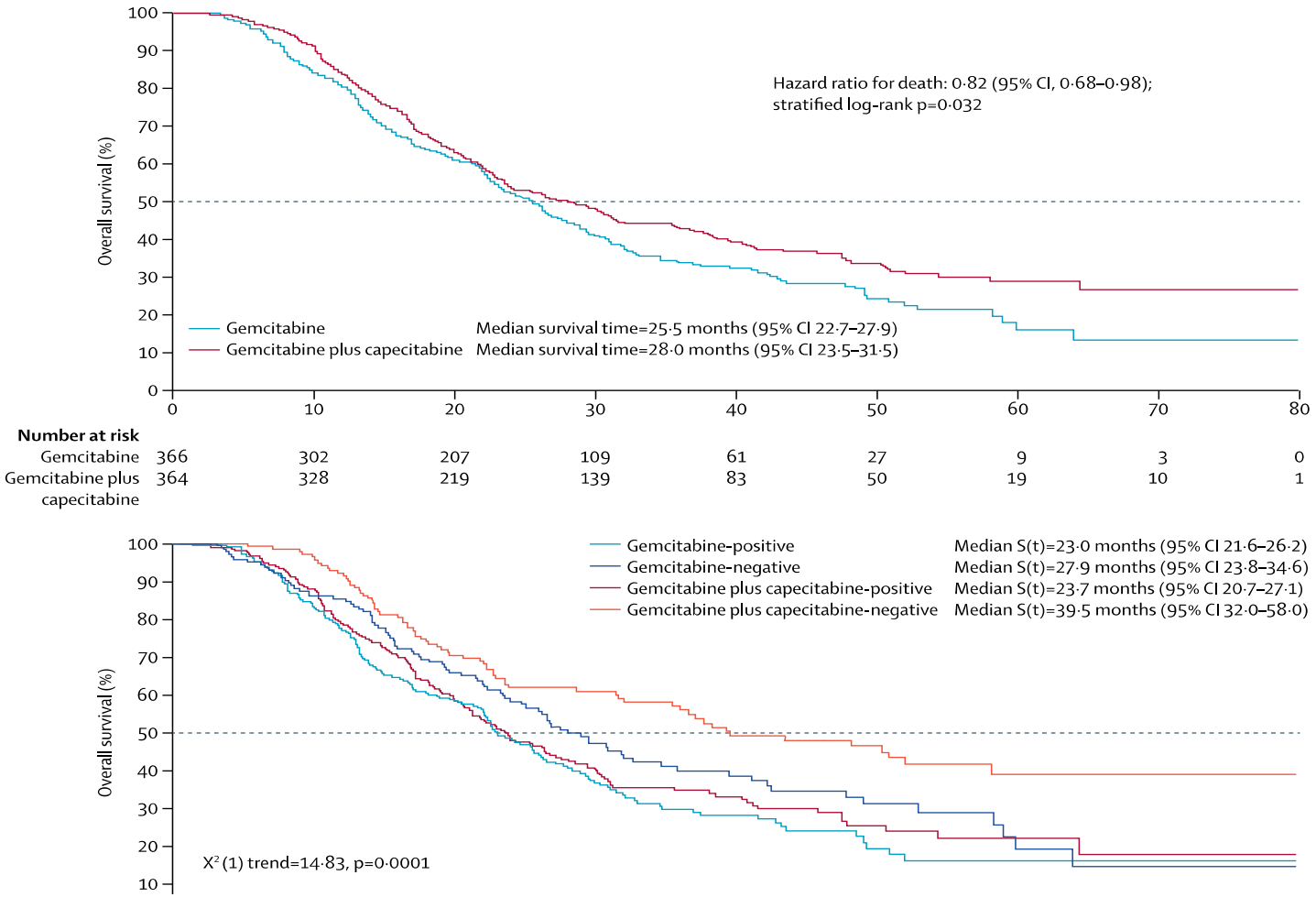
Standard of care: surgery + adjuvant chemotherapy



Median survival: 20 months
5-year survival: 20-25%

Hackert T. Cancer Letters 2016

Resectable- “the thirty disease”



ESPAC-4. Lancet 2017

Resectable - “the forty disease”

A contemporary analysis of survival for resected pancreatic ductal adenocarcinoma

Russell Lewis[1], Jeffrey A. Drebin,[1] Mark P. Callery[2], Douglas Fraker[1], Tara S. Kent[2], Jenna Gates[1] & Charles M. Vollmer Jr[1]

[1]Departments of Surgery, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, [2]Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA

Abstract

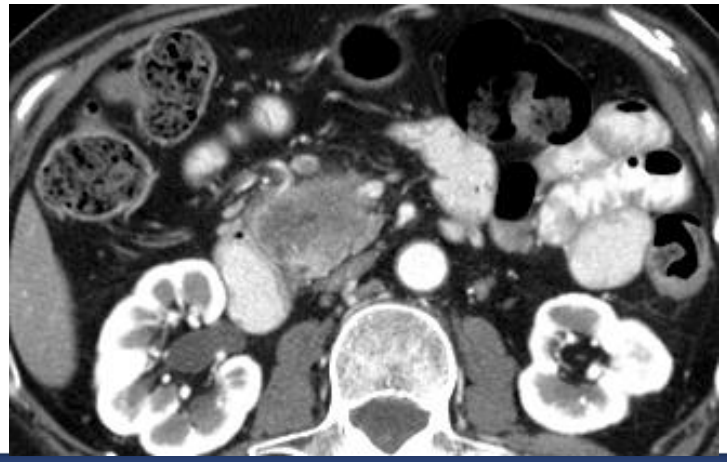
Introduction: Survival after a resected pancreatic ductal adenocarcinoma (PDAC) appears to be improving. Yet, in spite of advancements, prognosis remains disappointing. This study analyses a contemporary experience and identifies features associated with survival.

Methods: Kaplan–Meier analysis was conducted for 424 PDAC resections performed at two institutions (2001–2011). Multivariate analysis was performed to elicit characteristics independently associated with survival.

Results: The median, 1-, and 5-year survivals were 21.3 m, 76%, and 23%, with 30/90-day mortalities of 0.7%/1.7%. 76% of patients received adjuvant therapy. Patients with major complications (Clavien Grade IIIb-IV) survived equivalently to patients with no complications ($P = 0.33$). The median and 5-year survival for a total pancreatectomy was 32.2 m/49%; for 90 ‘favourable biology’ patients (R0/N0/M0) was 37.3 m/40%; and for IPMN (9% of series) was 21.2 m/46%. Elderly (>75 yo) and nonelderly patients had similar survival. Favorable prognostic features by multivariate analysis include lower POSSUM physiology score, R0 resection, absence of operative transfusion, G1/G2 grade, absence of lymphovascular invasion, T1/T2 stage, smaller tumor size, LN ratio <0.3, and receipt of adjuvant therapy.

Conclusion: This experience with resected PDAC shows decreasing morbidity and mortality rates along with modestly improving long-term survival, particularly for certain subgroups of patients. Survival is related to pathological features, pre-operative physiology, operative results and adjuvant therapy.

New classification



Locally advanced, non-metastatic

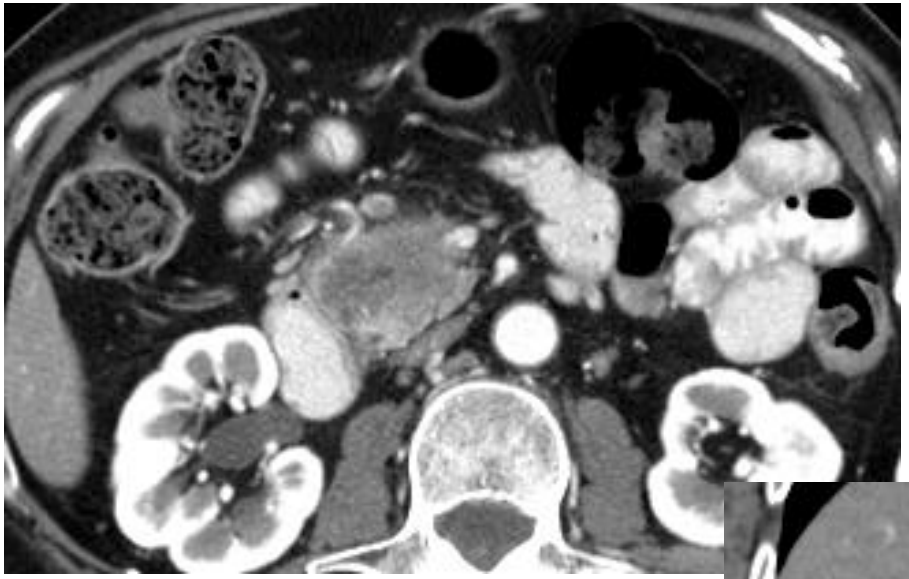
- Borderline resectable
- Borderline unresectable (Non-resectable)

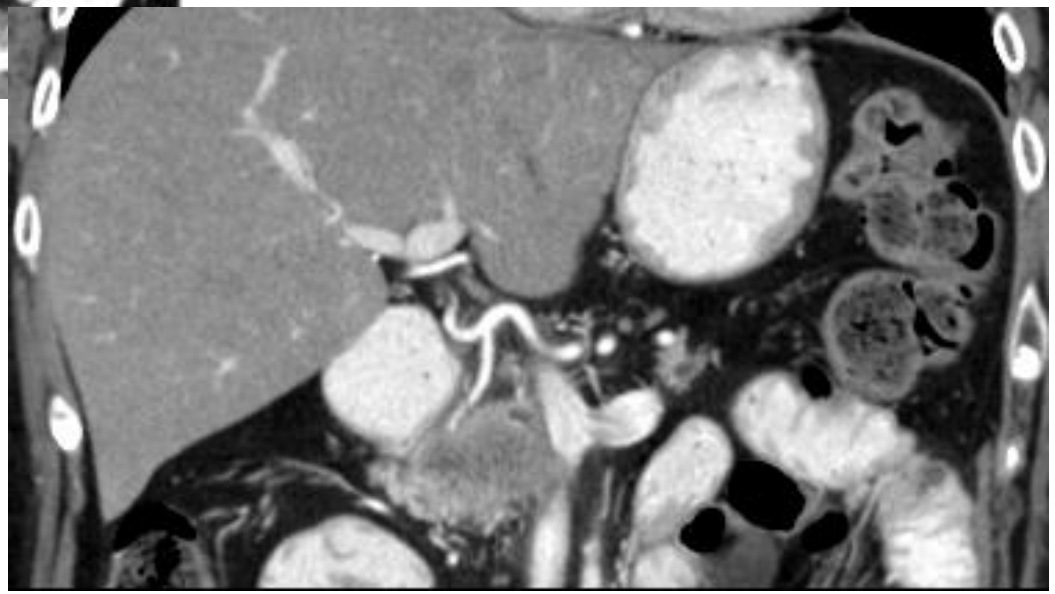
New classification

- Intermediate stage
- Between resectable and unresectable
- Involving
  - Mesenterico-portal axis
  - Arterial axis

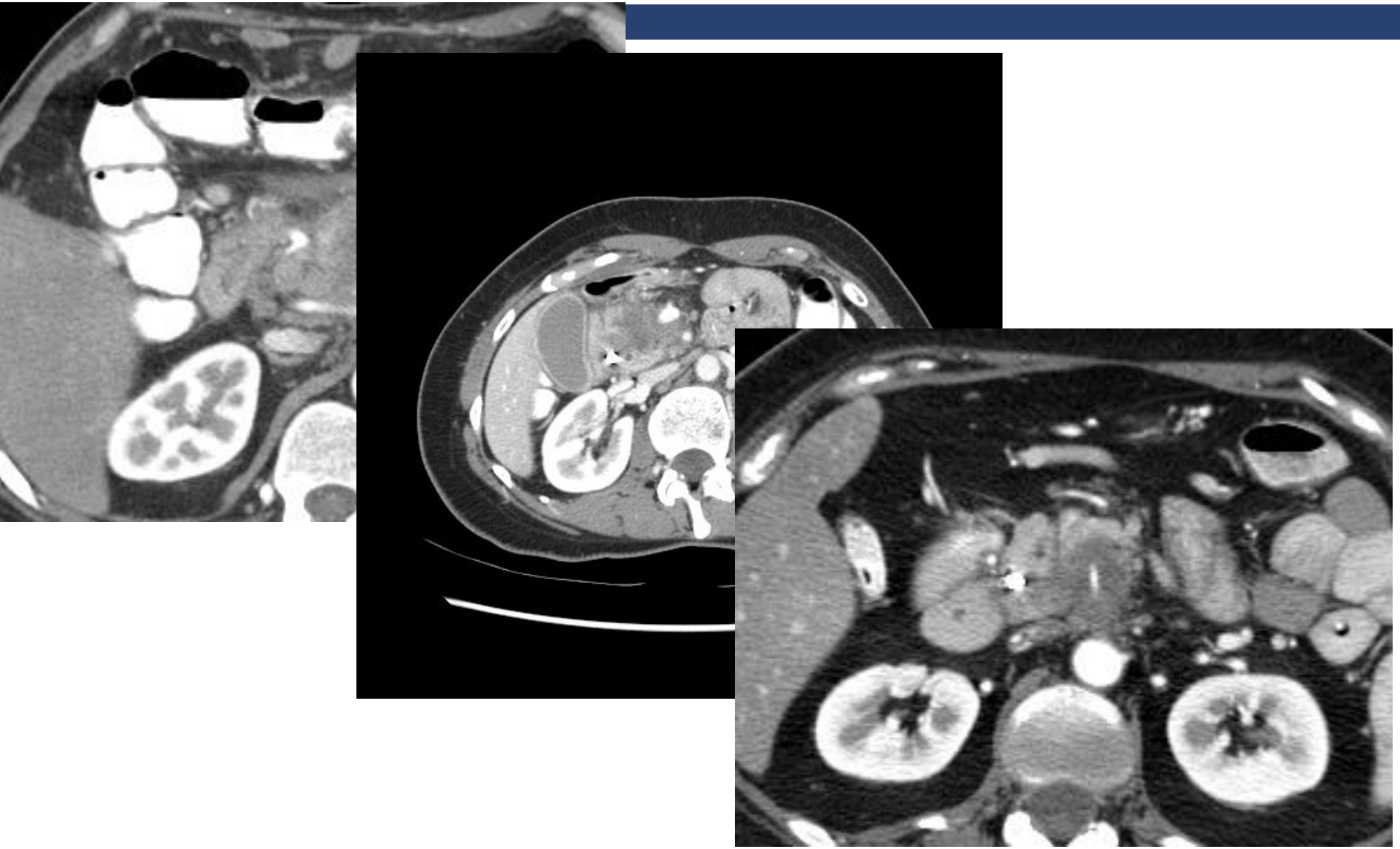
- CT based diagnosis
- Absence of adequate tools to differentiate
  - Non neoplastic inflammatory “infiltration”
  - True malignant infiltration

Portomesenterico vs arterial axis





Portomesenterico vs arterial axis



Neoadjuvant treatment for BL/LA pancreatic cancer

…any preoperative treatment aiming to convert unresectable to resectable tumor and to increase microscopic complete tumor resection rates.

- Chemotherapy alone
- Chemoradiation
- Upfront chemoradiation followed by chemotherapy
- Sequence of chemotherapy followed by chemoradiation

Heinemann H. Annals of Oncology 2013

What criteria should be met to proceed to operation?

RECIST criteria

- **Progressive disease (PD**) either the development of metastases or an increase 20% in the greatest dimension (with a mini- mum increase of at least 5mm) of the primary tumor — 23 (19%)
- **Partial response (PR)** decrease 30% in the greatest dimension of the primary tumor — 15 (12%)
- **Stable disease (SD**) was defined as neither sufficient shrinkage to qualify for PR nor sufficient growth to qualify for PD — 84 (69%)
- **Complete response (CR)** complete disappearance of the primary tumor — 1 (0,8%)

…proceed to pancreatectomy after initial therapy in the absence of metastases.

Katz et al. Cancer 2012

Concerns about…

- Assessment of resectability following neoadjuvant treatment
- Potential resectability even before neoadjuvant treatment - *functional imaging, other modalities*

- Pancreas is not rectum! – downstaging unclear

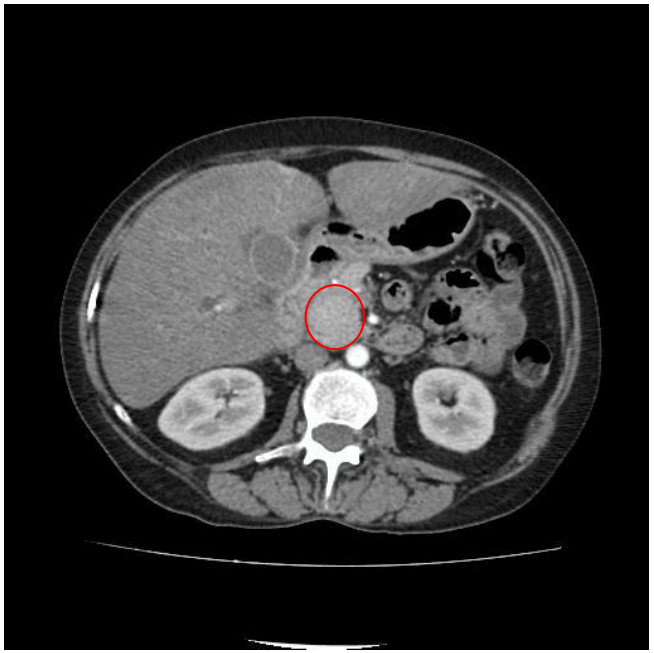
  new agents for better local control

Tosolini C. World j Gastrointest Surg 2013

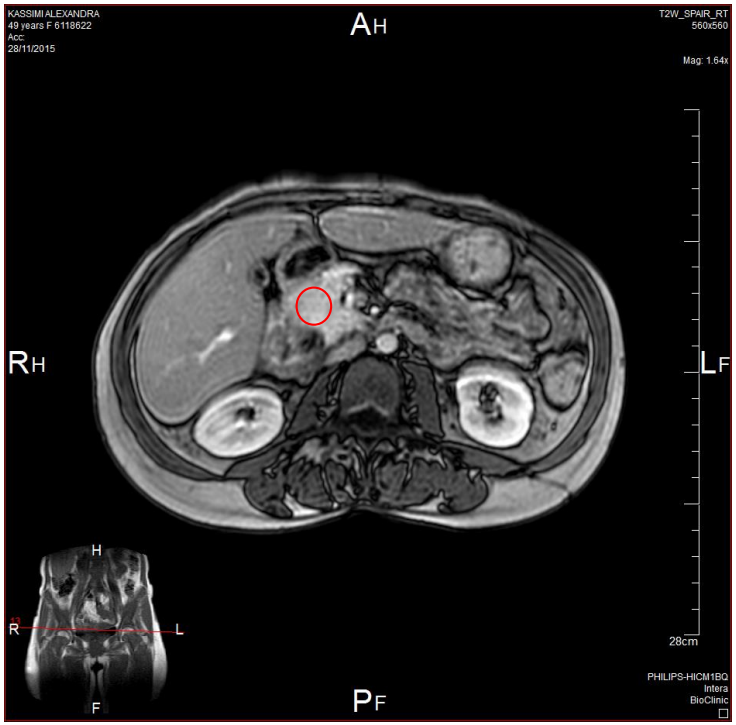
Neoadjuvant treatment for BL/LA pancreatic cancer

	Resection rate	R0	Vascular resections	Median survival (months)	18 month survival rate
Katz 2008	41%	94%	27%	40/13	
Alliance Trial, 2016	68%	93%	80%		67% vs43%
Buchler et al. Annals of Surgery 2016	**46%**	**41%**	**?**	**16**	**(23%)**
	61%		**?**	**16.5**	**(28%)**

61 yo female, 6 cycles FOLFIRINOX

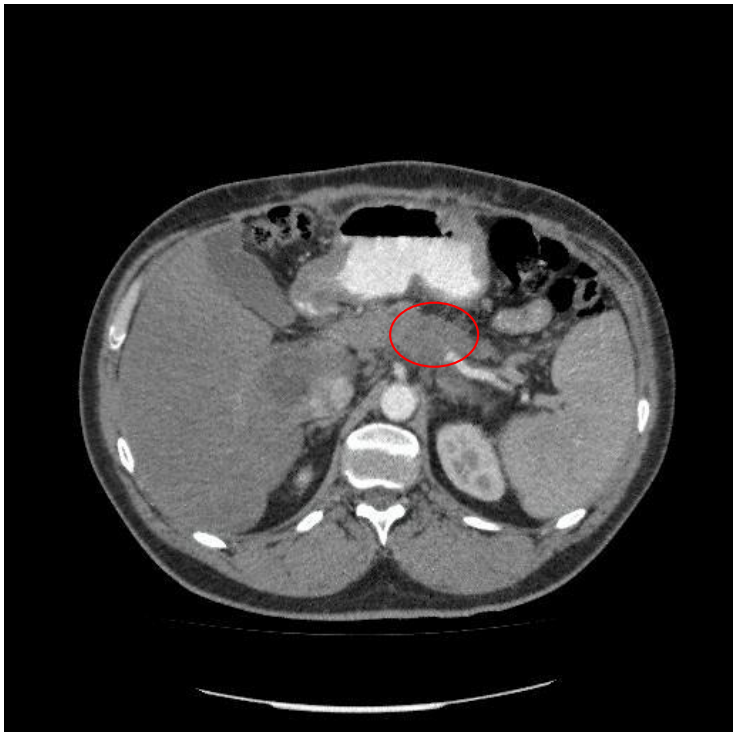


3 cm

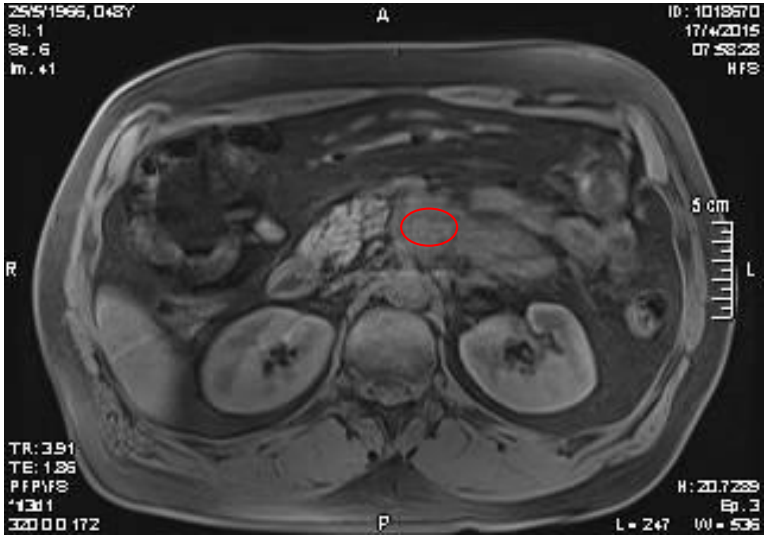


0.5 cm

48 yo male, 6 cycles FOLFIRINOX

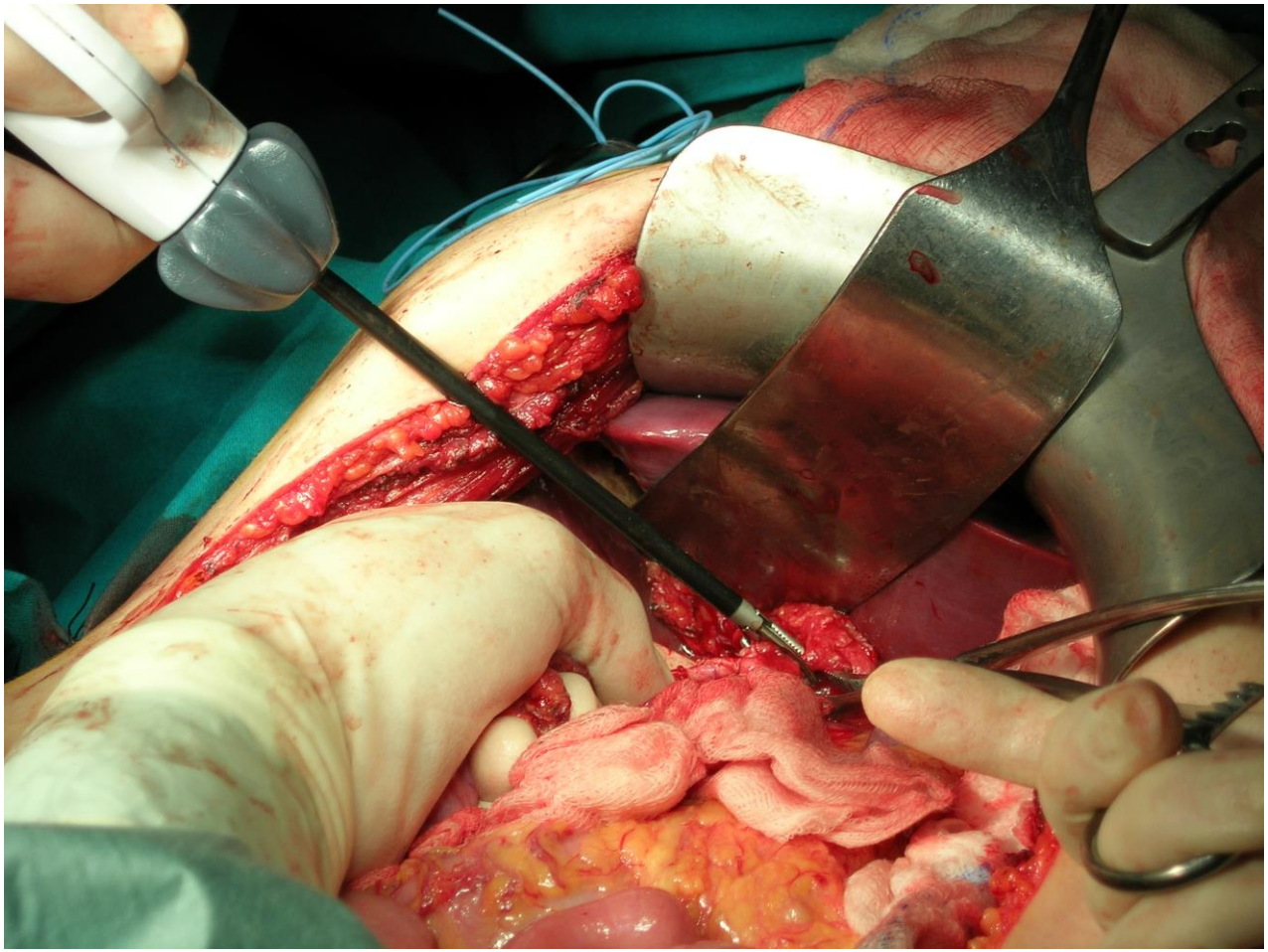


6.5 cm



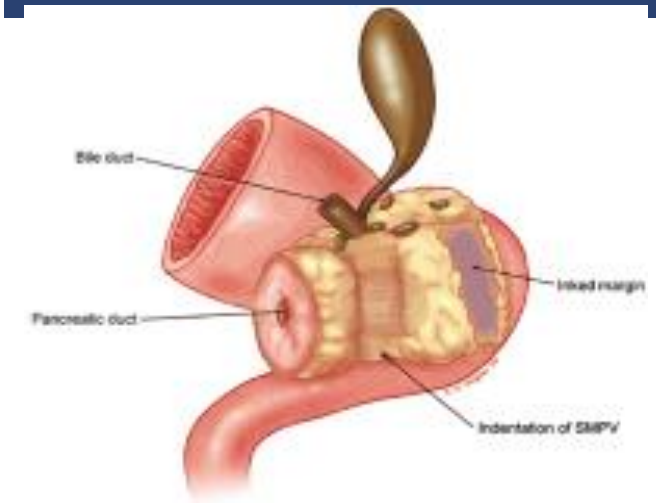
4.5 cm

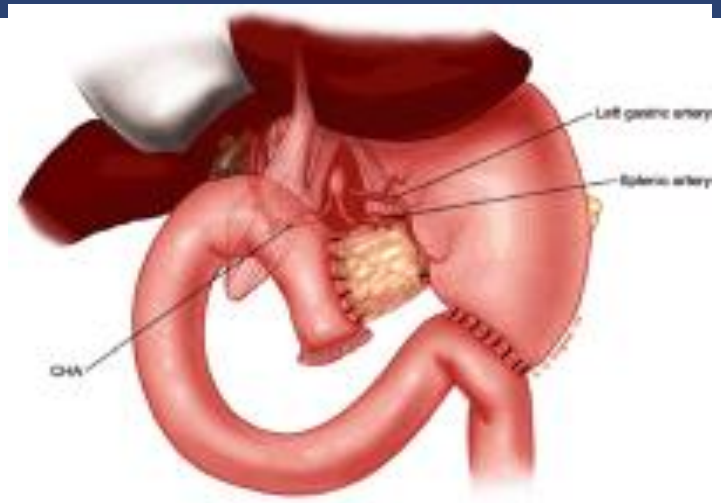
Παγκρεατοδωδεκαδακτυλεκτομή



Θνητότητα 1-4%, Νοσηρότητα 30-50%

The Whipple Procedure





Pancreaticoduodenectomy - Whipple

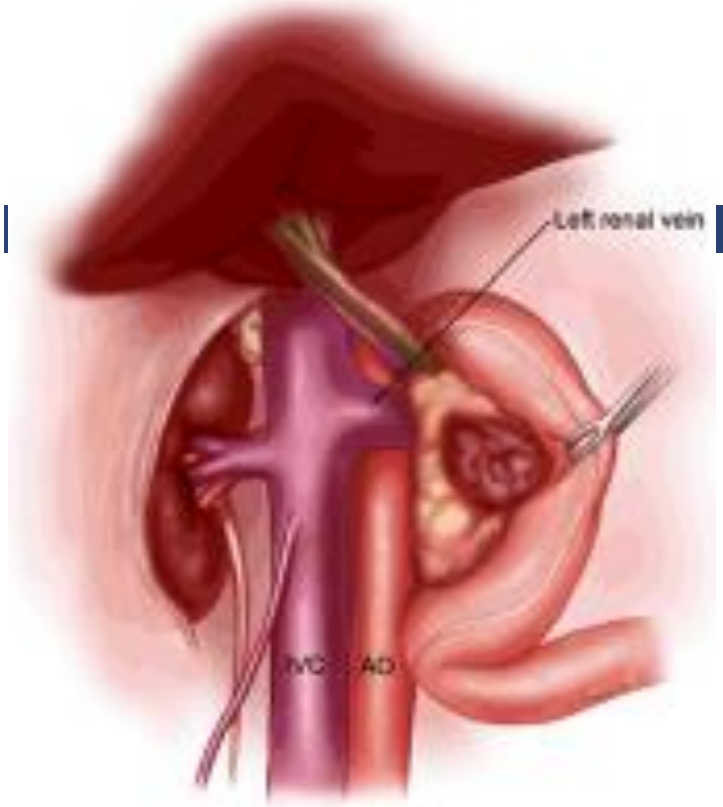
pancreatic head

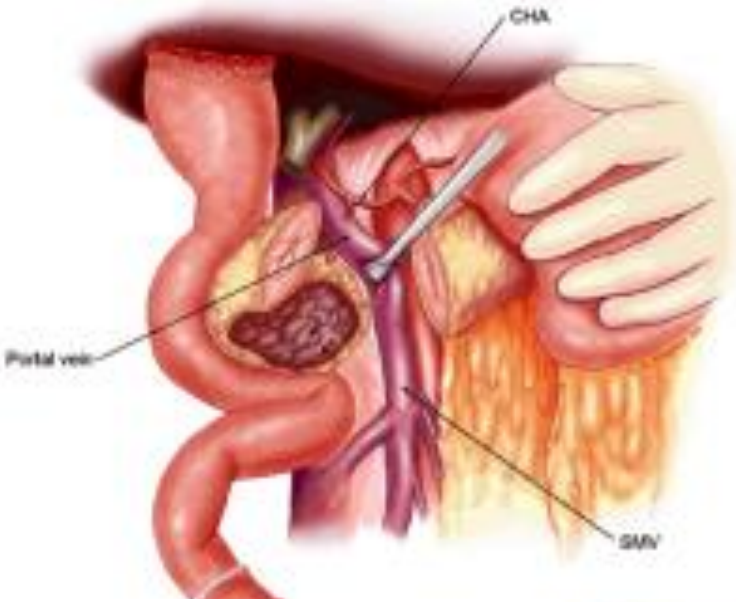
duodenum

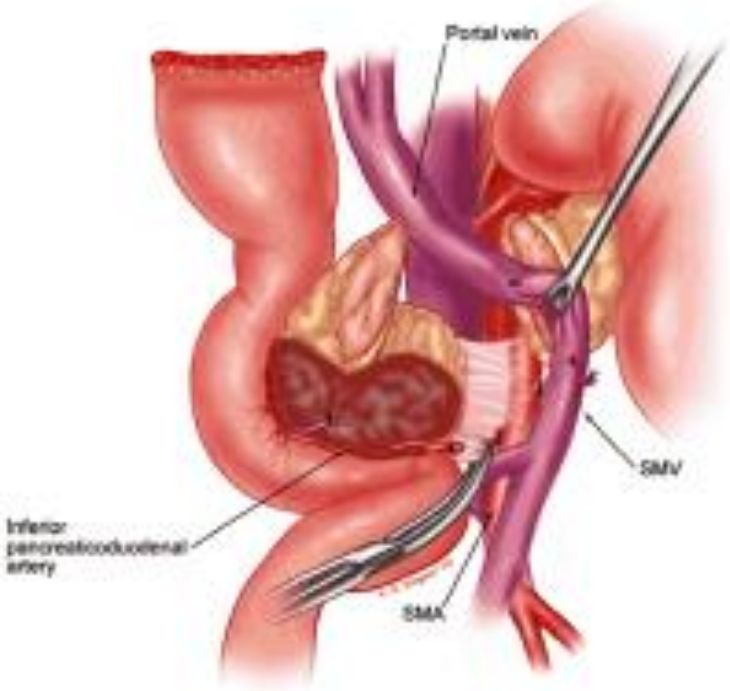
gallbladder

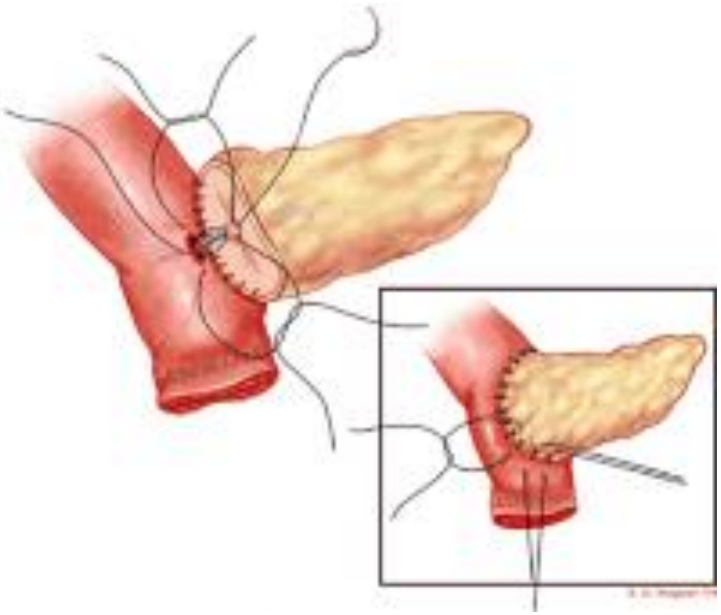
bile duct

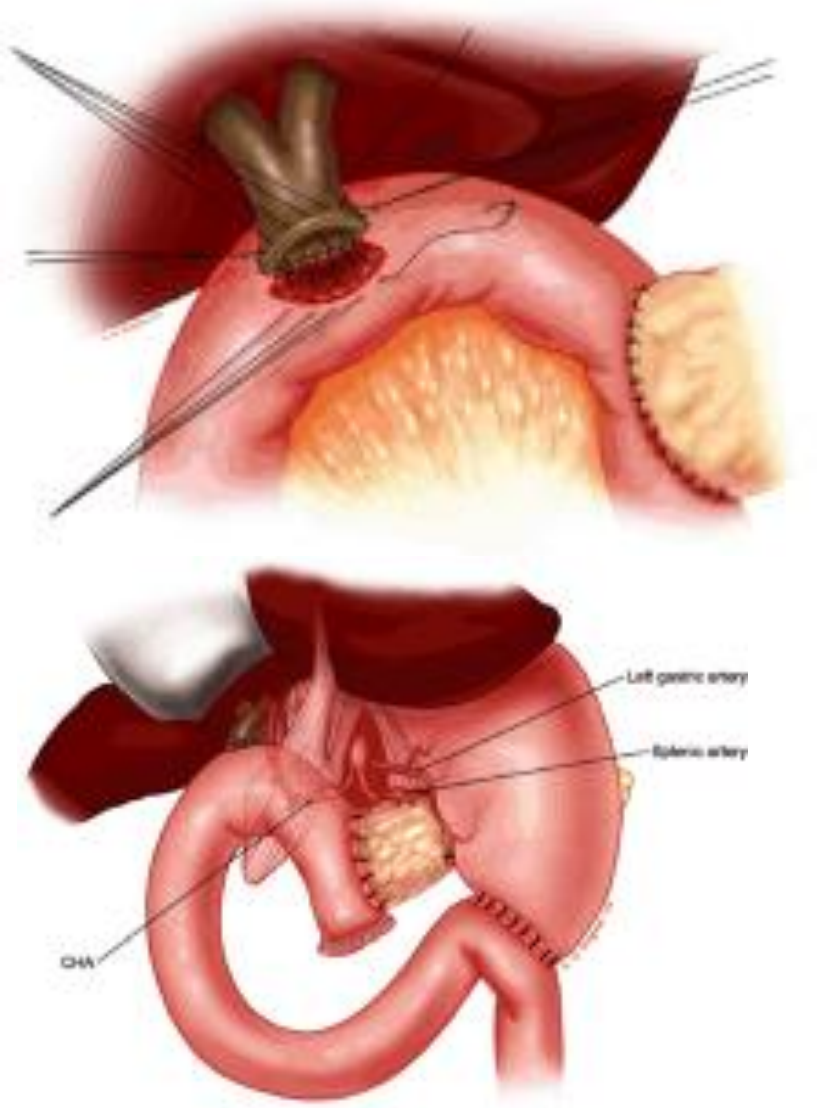
+/- gastric antrum


Left renal vein
IVC
AO


CHA
Portal vein
SMV


Portal vein
SMV
Inferior pancreaticoduodenal artery
SMA




Left gastric artery
Splenic artery
CHA

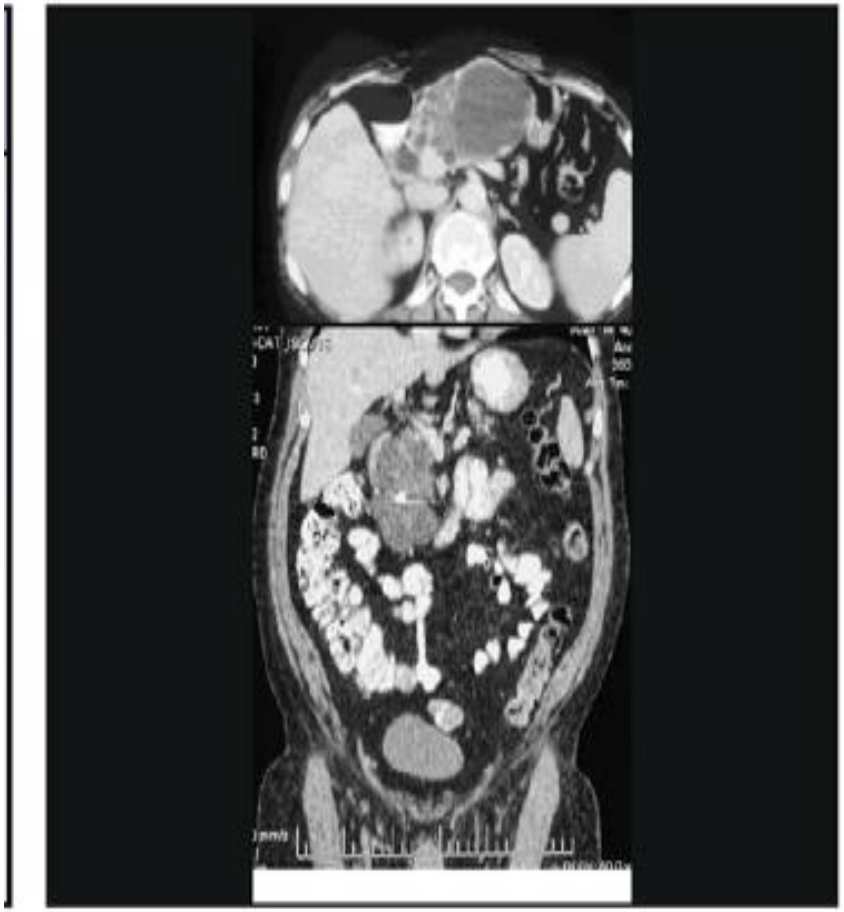
Cystic pancreatic tumors

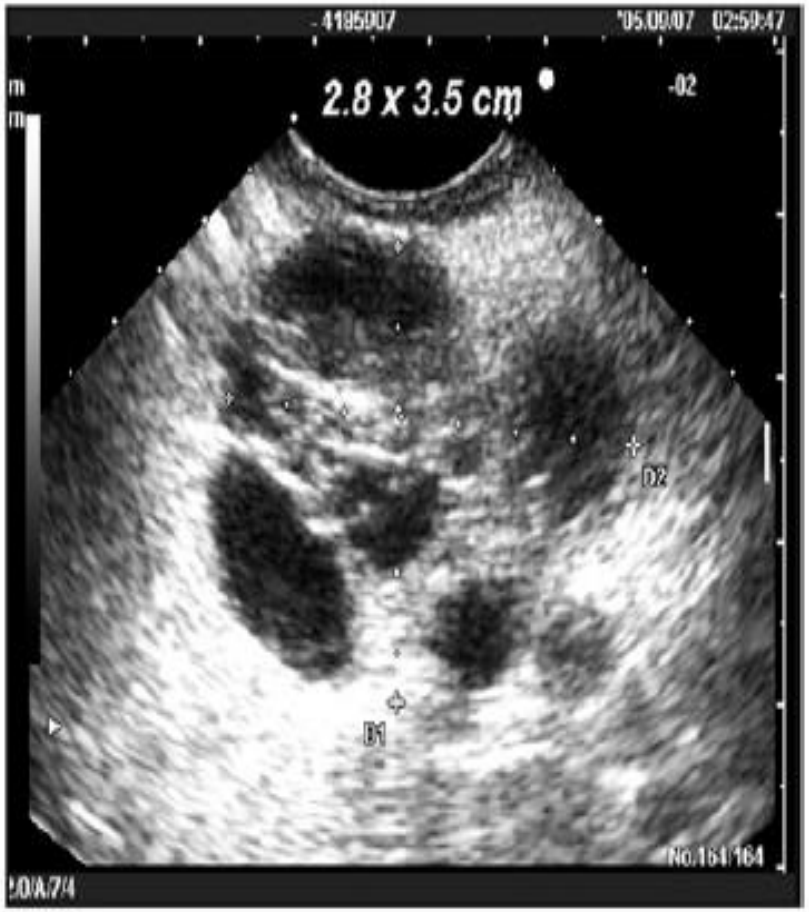
Epithelial neoplastic	Epithelial non-neoplastic
Intraductal papillary-mucinous neoplasm	Lymphoepithelial cyst
Mucinous cystic neoplasm	Mucinous non-neoplastic cyst
Serous cystic adenoma (microcystic, oligocystic/macrocystic)	Enterogeneous cyst
VHL associated serous cystic adenoma	Paraampullary duodenal wall cyst
Serous cystadenocarcinoma	Retention cyst
Cystic neuroendocrine tumour G1–2	Endometrial cyst
Acinar cell cystadenoma	Congenital cyst (in malformation syndromes)
Cystic acinar cell carcinoma	
Solid pseudopapillary neoplasm	
Accessory-splenic epidermoid cyst	
Cystic hamartoma	
Cystic teratoma (dermoid cyst)	
Cystic ductal adenocarcinoma	
Cystic pancreatoblastoma	
Cystic metastatic epithelial neoplasm	
Others	

Non-epithelial neoplastic	Non-epithelial non-neoplastic
Benign non-epithelial neoplasm (e.g. lymphangioma)	Pancreatitis-associated pseudocyst
Malignant non-epithelial neoplasms (e.g. sarcomas)	Parasitic cyst

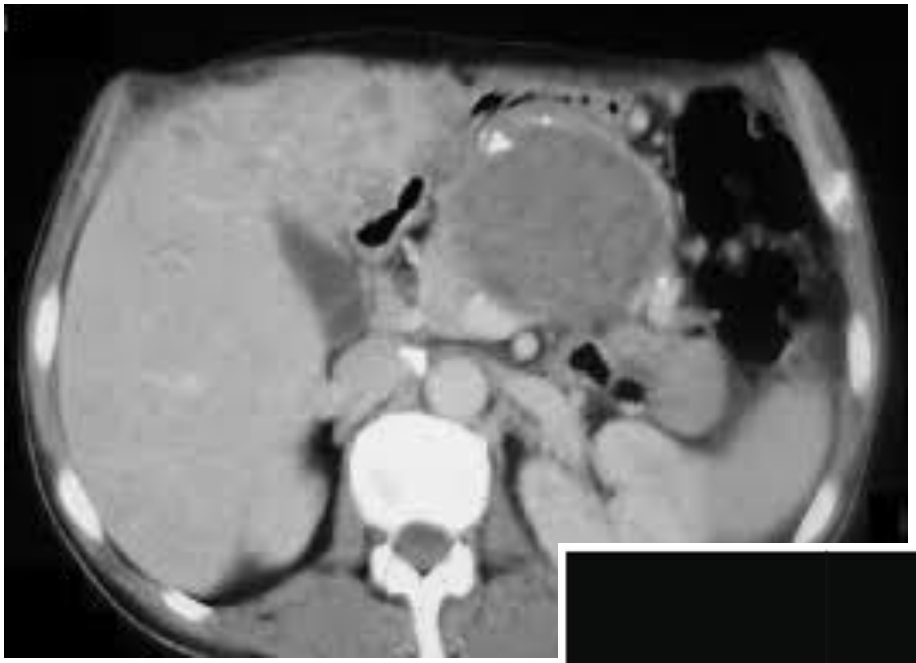
M. Del Chiaro, C. Verbeke et. Al M. Del Chiaro, C. Verbeke et. al. **European experts consensus statement on cystic tumors of the pancreas.**. Digestive and Liver Disease 2013

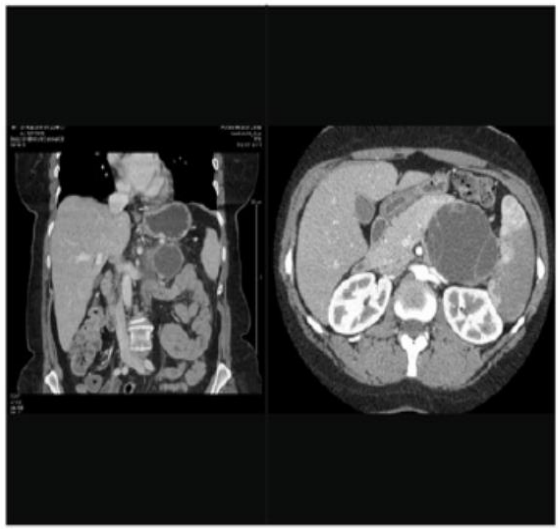
Ορώδης κυστική νεοπλασία

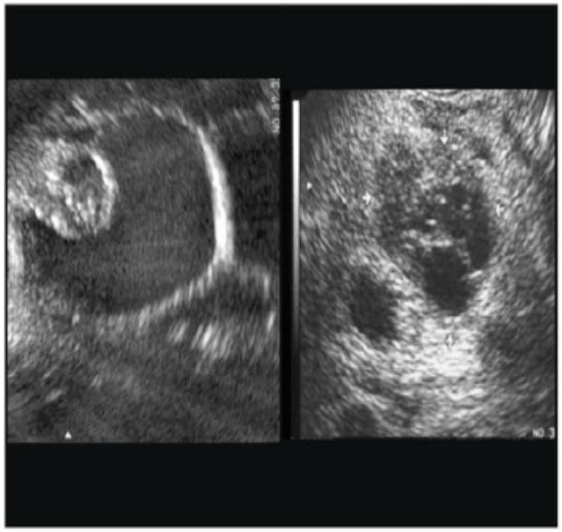




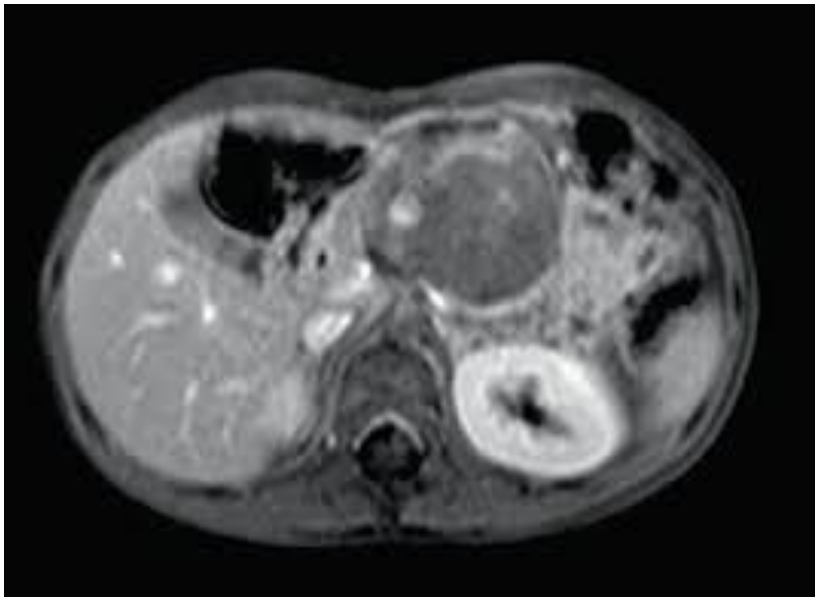
Βλεννώδης κυστική νεοπλασία

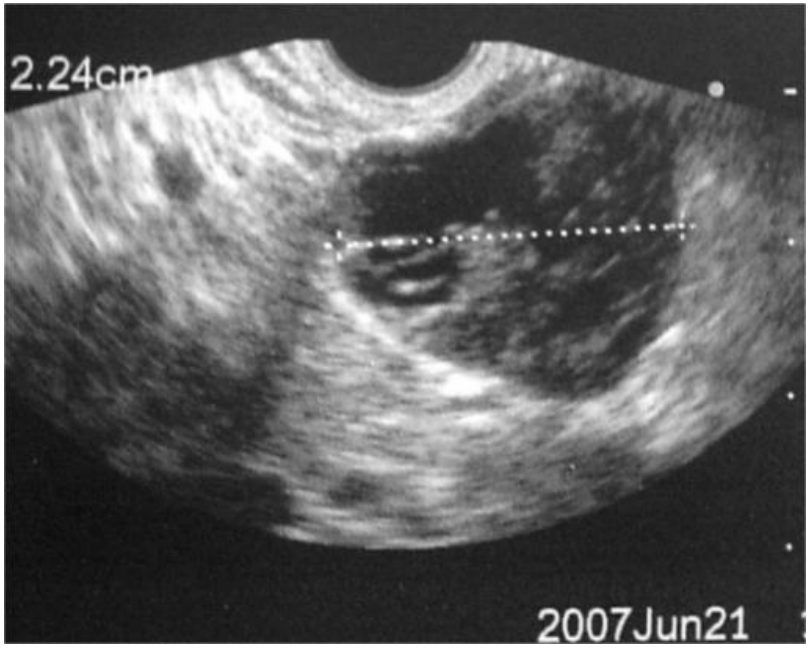






Συμπαγής ψευδοθηλώδης νεοπλασία





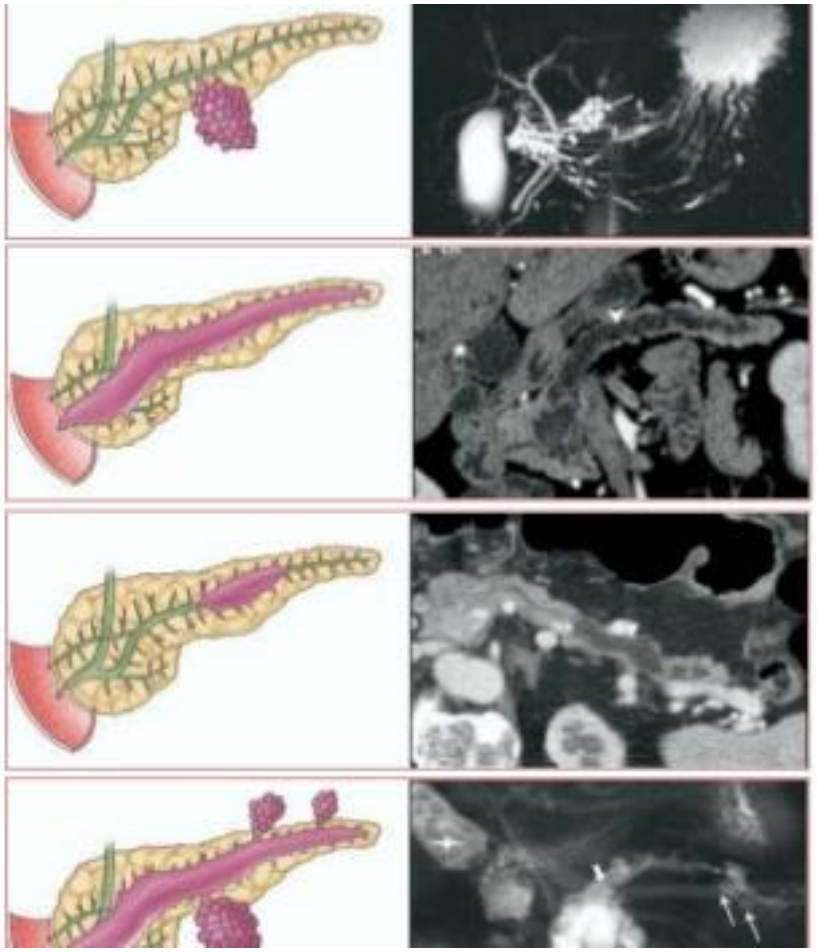
Intraductal Papillary Mucinous Neoplasia (IPMN)

Branch pancreatic duct

Diffuse main pancreatic duct

Segmental main pancreatic duct

Mixed (main & branch ducts)



Νευροενδοκρινικοί όγκοι παγκρέατος

Table 2 Tumor Syndromes of Gastrointestinal Neuroendocrine Tumors

Tumor type	Frequency of pancreatic NET tumors (%)	Malignancy (%)	Tumor location	% with MEN1	Syndrome
Insulinoma	70–75	< 10	Pancreas > 99%	4–5	Hypoglycemia Weight gain
Gastrinoma	20–25	> 50	Duodenum 70% Pancreas 25%	20–25	Abdominal pain Diarrhea Peptic ulceration
VIPoma	3–5	> 50	Pancreas 90%	6	Secretory diarrhea Hypokalemia Achlorhydria Metabolic acidosis Flushing
Glucagonoma	1–2	> 70	Pancreas 100%	1–20	Necrolytic migratory erythema Diabetes Cachexia Thromboembolic disease
PPoma	< 1	> 60	Pancreas 100%	18–44	Pain Weight loss Diarrhea
Somatostatinoma	< 1	> 50	Pancreas 55% Duodenum Jejunum 44%	45	Steatorrhea Diabetes Gallstones Weight loss
Carcinoid	< 1 mostly extrapancreatic	90	Midgut 75–87% Foregut 2–33% Hindgut 1–8% Unknown 2–15%	Rare	Classical carcinoid: Flushing Diarrhea Wheeze Cardiac fibrosis Pellagra dermatosis
ACTHoma CRFoma	< 1	> 99	Pancreas 4–14% (of all ectopic ACTH)	Rare	Cushing's syndrome Pigmentation
PTHrPoma	< 1	> 99	Pancreas	Rare	Hypercalcemia Nephrolithiasis Nephrocalcinosis Osteoporosis
Calcitoninoma	< 1	> 80	Pancreas	16	Diarrhea, flushing
GRFoma	< 1	50	Pancreas 30% Lung 54% Jejunum 7%	16	Acromegaly
Nonfunctioning	< 1	> 80	Pancreas + gastrointestinal tract	18–44	Symptoms of tumor bulk Weight loss