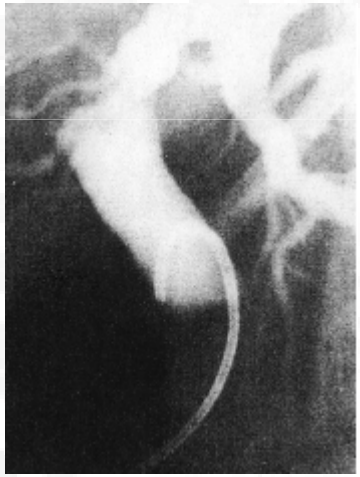
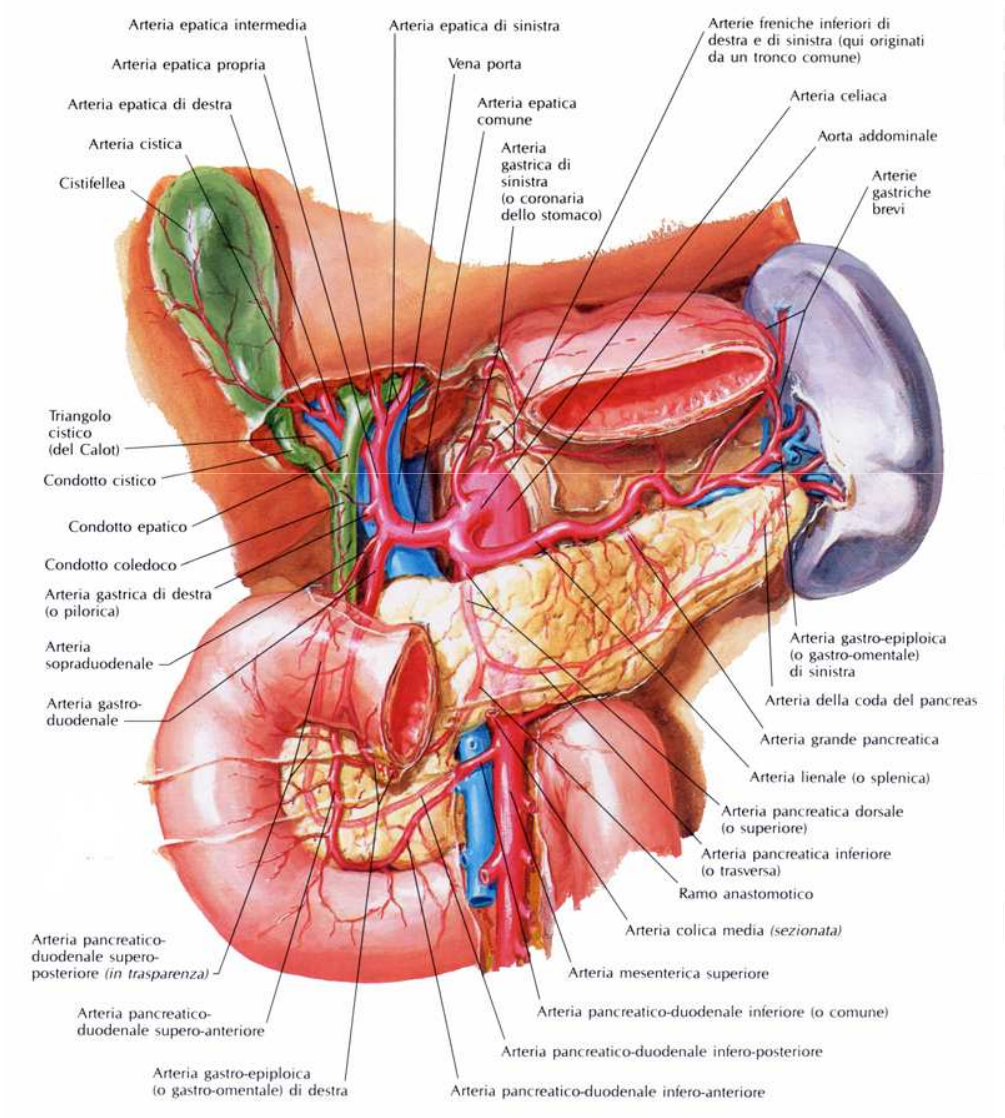
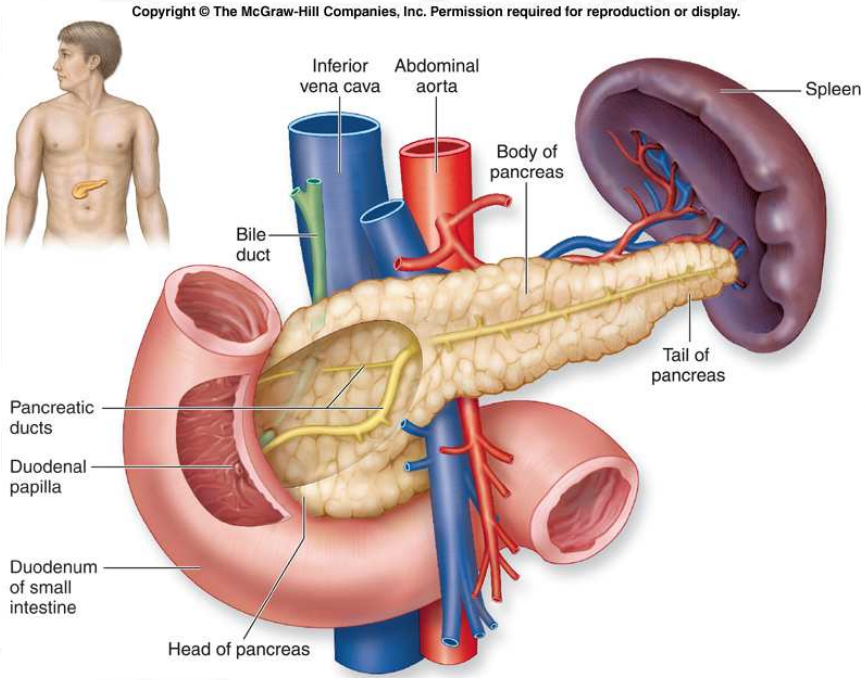
Diagnosi e trattamento dei tumori del pancreas e delle vie biliari

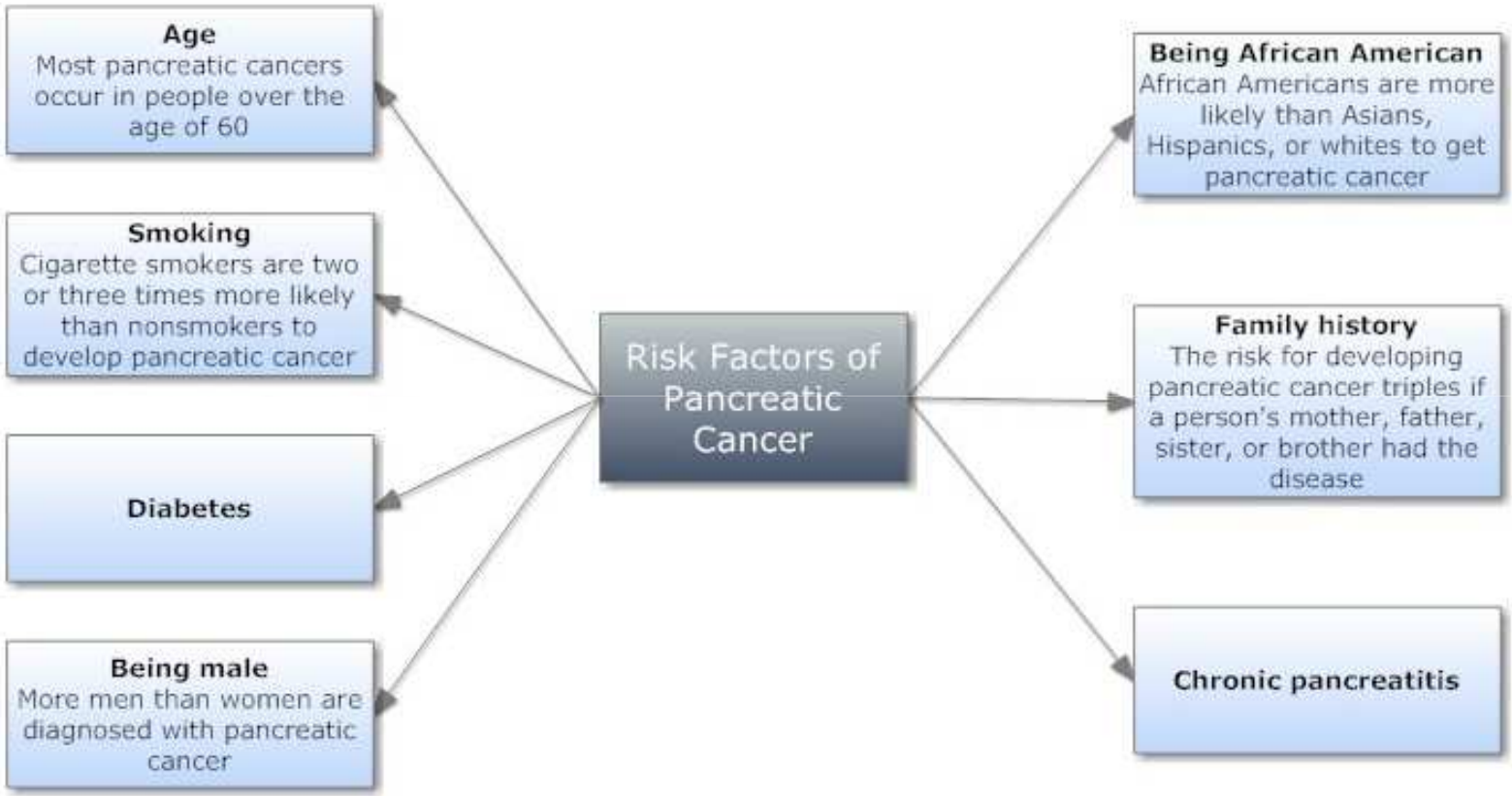


Dott. Romano Sassatelli
Gastroenterologia ASMN RE

Pancreas

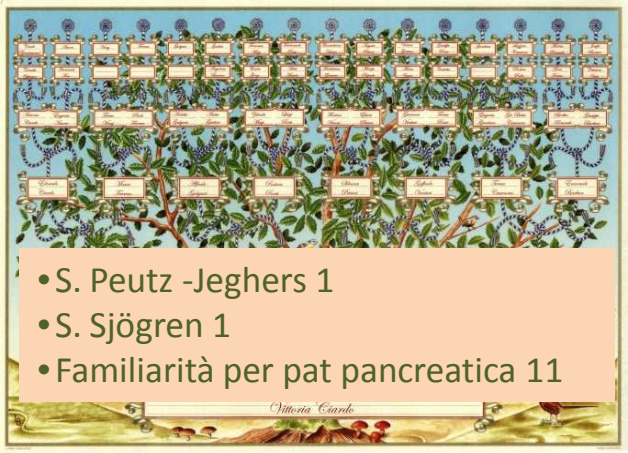

Arteria epatica intermedia
Arteria epatica di sinistra
Arterie freniche inferiori di destra e di sinistra (qui originati da un tronco comune)
Arteria epatica propria
Vena porta
Arteria epatica di destra
Arteria epatica comune
Arteria celiaca
Arteria cistica
Arteria gastrica di sinistra (o coronaria dello stomaco)
Aorta addominale
Cistifellea
Arterie gastriche brevi
Triangolo cistico (del Calot)
Condotto cistico
Condotto epatico
Condotto coledoco
Arteria gastrica di destra (o pilorica)
Arteria sopraduodenale
Arteria gastro-duodenale
Arteria gastro-epiploica (o gastro-omentale) di sinistra
Arteria della coda del pancreas
Arteria grande pancreatica
Arteria lienale (o splenica)
Arteria pancreatica dorsale (o superiore)
Arteria pancreatica inferiore (o trasversa)
Ramo anastomotico
Arteria colica media (sezionata)
Arteria pancreatico-duodenale supero-posteriore (in trasparenza)
Arteria mesenterica superiore
Arteria pancreatico-duodenale inferiore (o comune)
Arteria pancreatico-duodenale supero-anteriore
Arteria pancreatico-duodenale infero-posteriore
Arteria gastro-epiploica (o gastro-omentale) di destra
Arteria pancreatico-duodenale infero-anteriore


Copyright © The McGraw-Hill Companies, Inc. Permission required for reproduction or display.
Inferior vena cava
Abdominal aorta
Spleen
Body of pancreas
Bile duct
Tail of pancreas
Pancreatic ducts
Duodenal papilla
Duodenum of small intestine
Head of pancreas

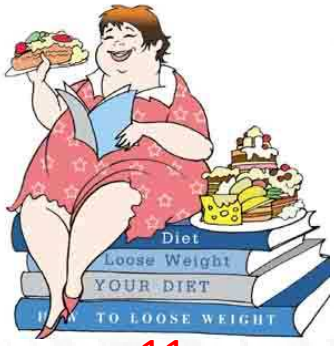

Risk Factors of Pancreatic Cancer
Age
Most pancreatic cancers occur in people over the age of 60
Smoking
Cigarette smokers are two or three times more likely than nonsmokers to develop pancreatic cancer
Diabetes
Being male
More men than women are diagnosed with pancreatic cancer
Being African American
African Americans are more likely than Asians, Hispanics, or whites to get pancreatic cancer
Family history
The risk for developing pancreatic cancer triples if a person's mother, father, sister, or brother had the disease
Chronic pancreatitis

RTSP: fattori di rischio

casi incidenti 2008-2010



- S. Peutz -Jeghers 1
- S. Sjögren 1
- Familiarità per pat pancreatica 11

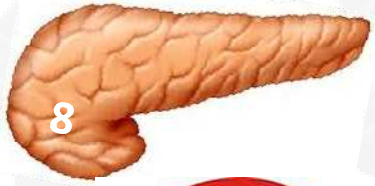


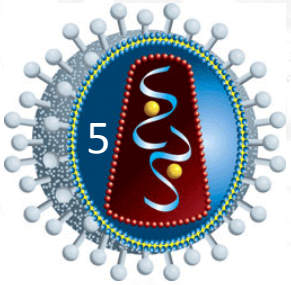
11

(1 ch. bariatrica)

- Fattori genetici
- Fumo
- Obesità
- Sindrome metabolica, Diabete, Dislipidemia
- Pancreatite cronica
- HBV
- Alcool
- Dieta e caffè
- **Attività lavorativa**

- S. Metabolica 8
- Diabete 93
- Dislipidemia 5
- Ipertensione 148





Fattori genetici

Gene	Sindrome	Rischio	Frequenza
BRCA-1	Hereditary Breast-Ovarian Cancer Syndrome (HBOC)	2.8%	1/500 pop gen
BRCA-2		5-7%	
ATM	Ataxia Telangiectasia (AT)		2.4-4.6% di FPC
CDKN2a/p16	Familial Atypical Multiple Mole Melanoma Syndrome	58%	3.3% dei FPC
APC	Familial Adenomatous Polyposis (FAP)	Slightly higher	
MEN1; MLH1; MSH2; MSH6; PMS2	Lynch Syndrome (Hereditary Non-Polyposis Colorectal Cancer)	1.3-4%; RR 30 per ca <50yy	
PALB2	Fanconi Anemia DNA repair pathway	RR 6	3-4% dei FPC
PRSS1	Hereditary Pancreatitis (HP)	18-53%	Rare
STK11	Peutz-Jeghers Syndrome (PJS)	RR 130	Rare

Solomon et al Cancer J, 2013

SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Unità Sanitaria Locale di Reggio Emilia

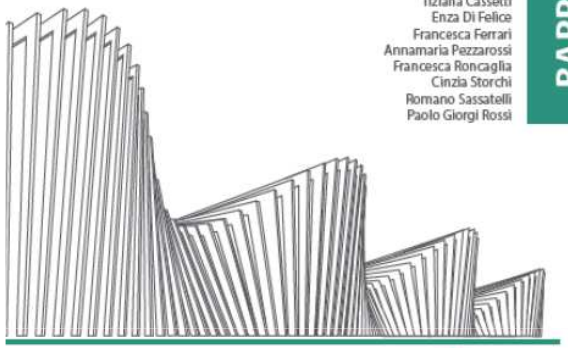
SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Ospedaliero di Reggio Emilia
Arcispedale S. Maria Nuova

REGISTRO TUMORI REGGIANO

I TUMORI IN PROVINCIA DI REGGIO EMILIA
ANNI 2009-2010

RAPPORTO 2014

Lucia Mangone
Massimo Vicentini
Simonetta Piana
Stefania Caroli
Tiziana Cassetti
Enza Di Felice
Francesca Ferrari
Annamaria Pezzarossi
Francesca Roncaglia
Cinzia Storchi
Romano Sassatelli
Paolo Giorgi Rossi



LILT

Tabella 1. Sintesi dei risultati.
Anni 2009-2010.

	INCIDENZA			MORTALITÀ		
	M+F	M	F	M+F	M	F
Numero casi	205	104	101	201	102	99
Percentuale sul totale	3,3	3,1	3,4	7	6,4	7,8
Tasso grezzo[1]	19,4	20	18,8	19	19,6	18,5
Tasso standardizzato[1] (pop. europea)	11,1	13,6	8,7	10,6	12,9	8,4
Rischio cumulativo 0-74 anni (%)	0,8	1,2	0,5	0,8	1	0,5

[1] per 100.000 abitanti

Tabella 2. Cambiamento percentuale annuo (APC) del tasso standardizzato (pop. europea). *Anni 1996-2010*

◆▶ Trend stabile ▲ Trend in aumento - APC significativamente>0 ▼ Trend in diminuzione - APC significativamente<0

	INCIDENZA		MORTALITÀ	
	M	F	M	F
1.	◆▶ +2,33% (1996-2010)	▲ +10,56% (1996-2004)	◆▶ +0,60% (1996-2010)	▲ +6,74% (1996-2006)
2.		◆▶ -7,29% (2004-2010)		◆▶ -11,46% (2006-2010)

Figura 1. Tassi di incidenza per età in provincia di Reggio Emilia e confronti nazionali. *Anni 2006-2010.*

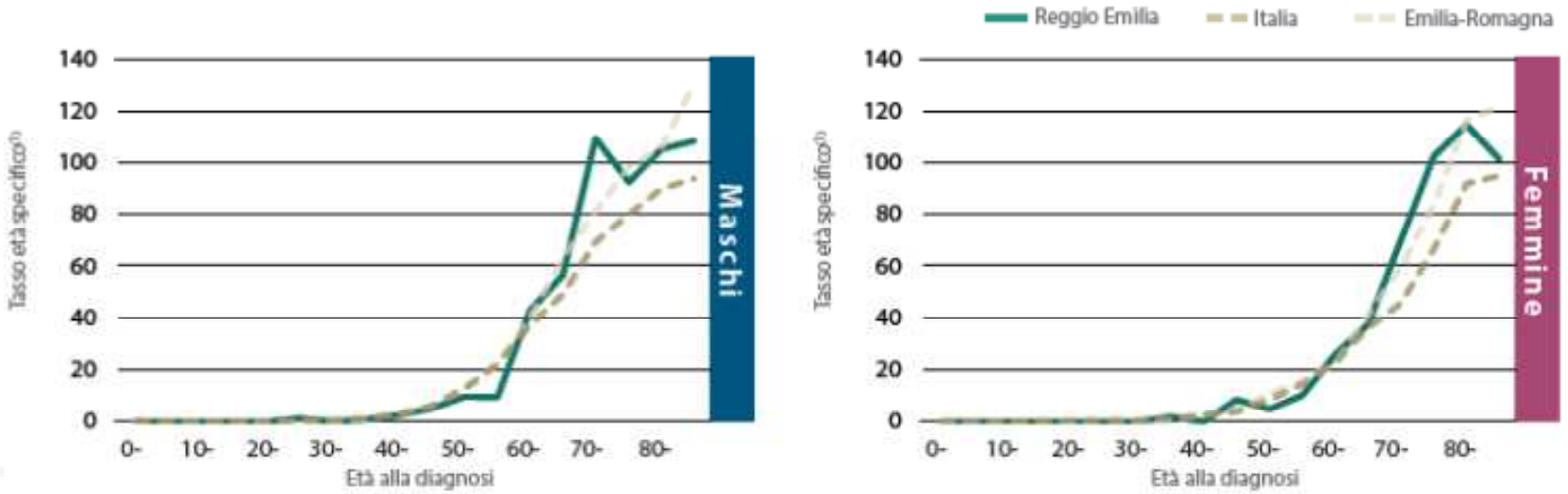


Figura 2. Tassi standardizzati in provincia di Reggio Emilia e confronti nazionali. *Anni 2006-2010.*

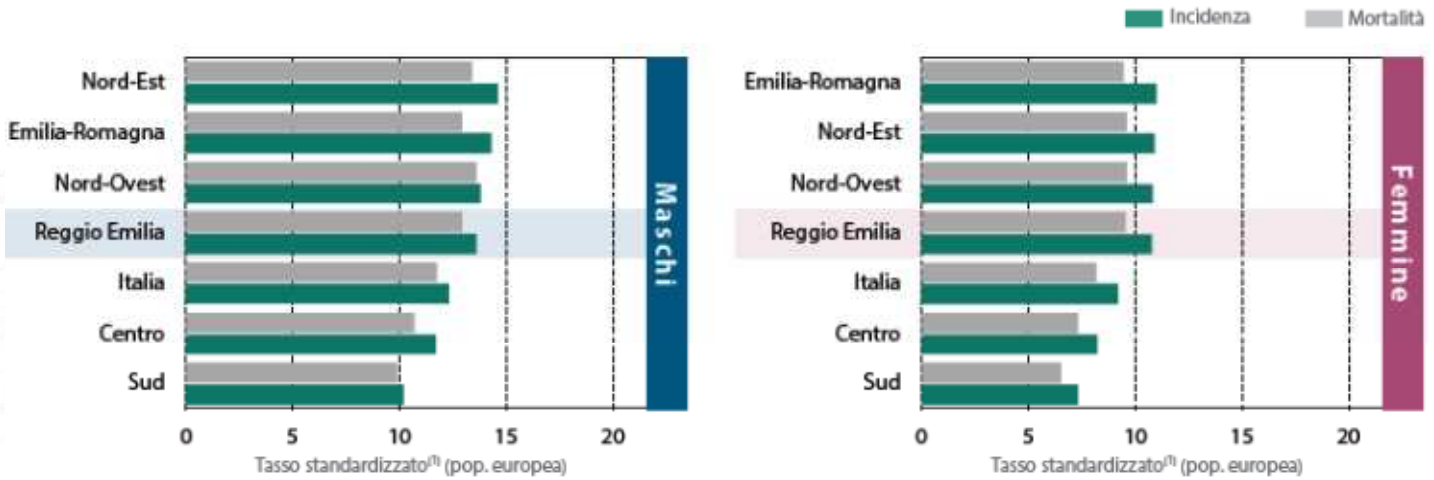


Figura 3. Andamento temporale dei tassi standardizzati per anno. *Anni 1996-2010.*

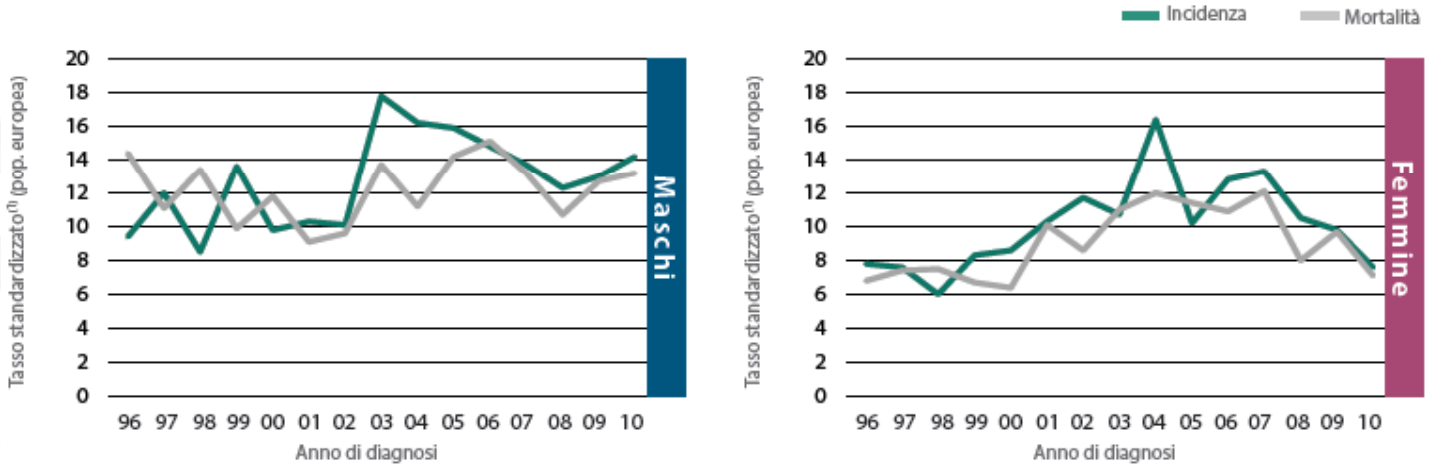


Tabella 3. Distribuzione dei casi per modalità di diagnosi e sesso. *Anni 2006-2010*

	M+F		M		F	
Modalità di diagnosi	N	%	N	%	N	%
Istologica	201	37,6	107	42,6	94	33,1
Citologica	86	16,1	48	19,1	38	13,4
Clinica	244	45,6	95	37,8	149	52,5
Altro	0	0	0	0	0	0
Certificato di decesso	4	0,7	1	0,4	3	1,1

Tabella 4. Distribuzione dei casi per gruppo morfologico e sesso. *Anni 2006-2010*

	M+F		M		F	
Gruppo morfologico	N	%	N	%	N	%
Adenocarcinoma	231	80,5	129	83,2	102	77,3
Altre morfologie	16	5,6	8	5,2	8	6,1
Carcinoma NAS	18	6,3	8	5,2	10	7,6
Non specificato	22	7,7	10	6,5	12	9,1

Lucia Mangone
Massimo Vicentini
Simonetta Piana
Stefania Caroli
Tiziana Cassetti
Enza Di Felice
Francesca Ferrari
Annamaria Pezzarossi
Francesca Roncaglia
Cinzia Storchi
Romano Sassatelli
Paolo Giorgi Rossi

Figura 4. Sopravvivenza relativa cumulata (standardizzata per età) per periodo di diagnosi. *Anni 1996-2010.*

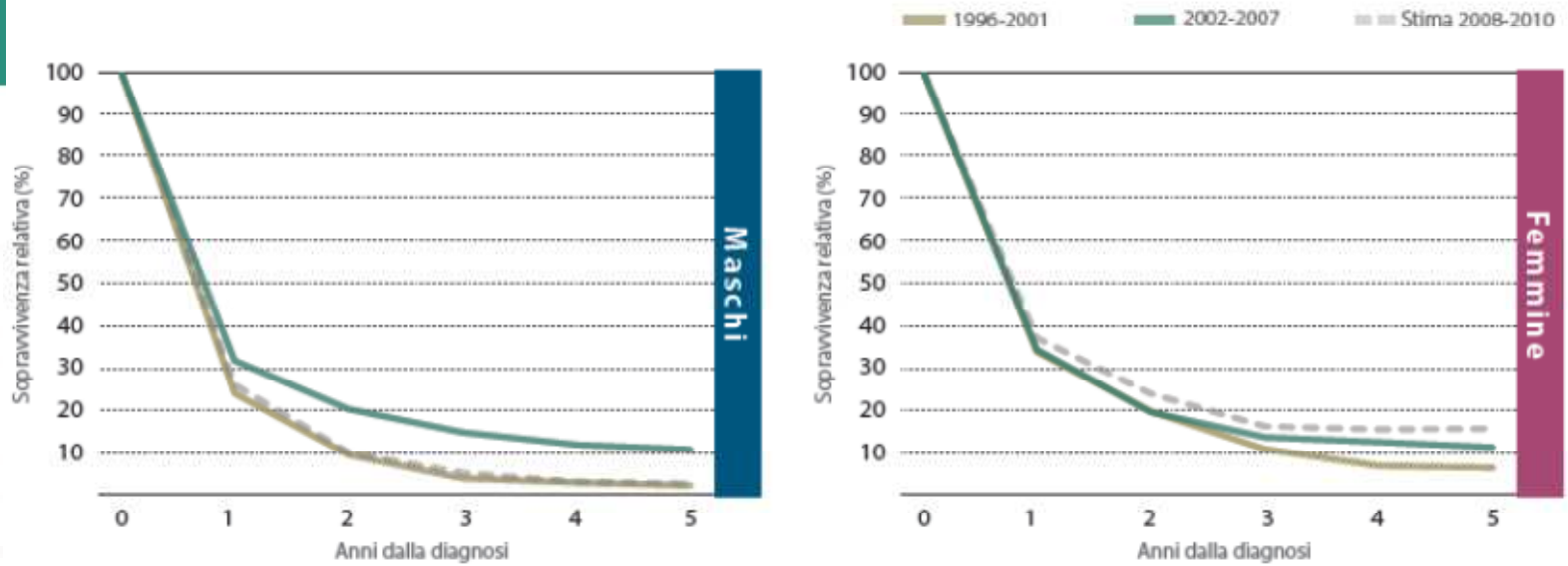
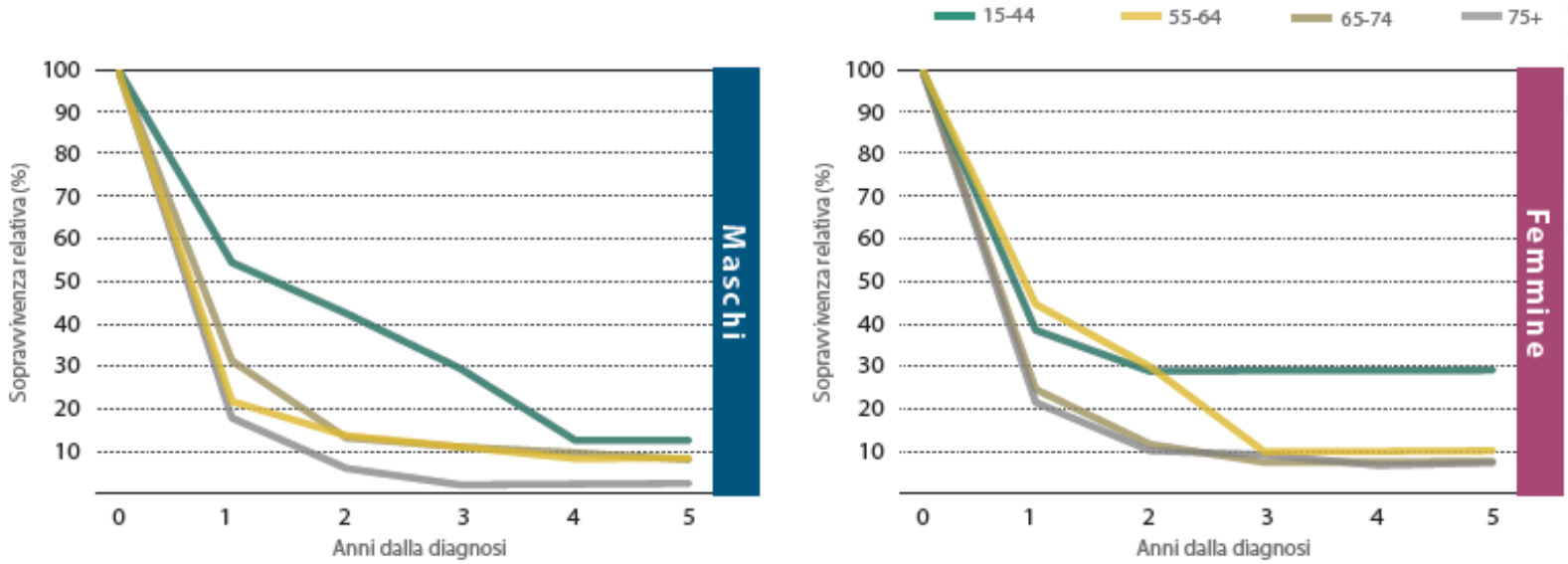
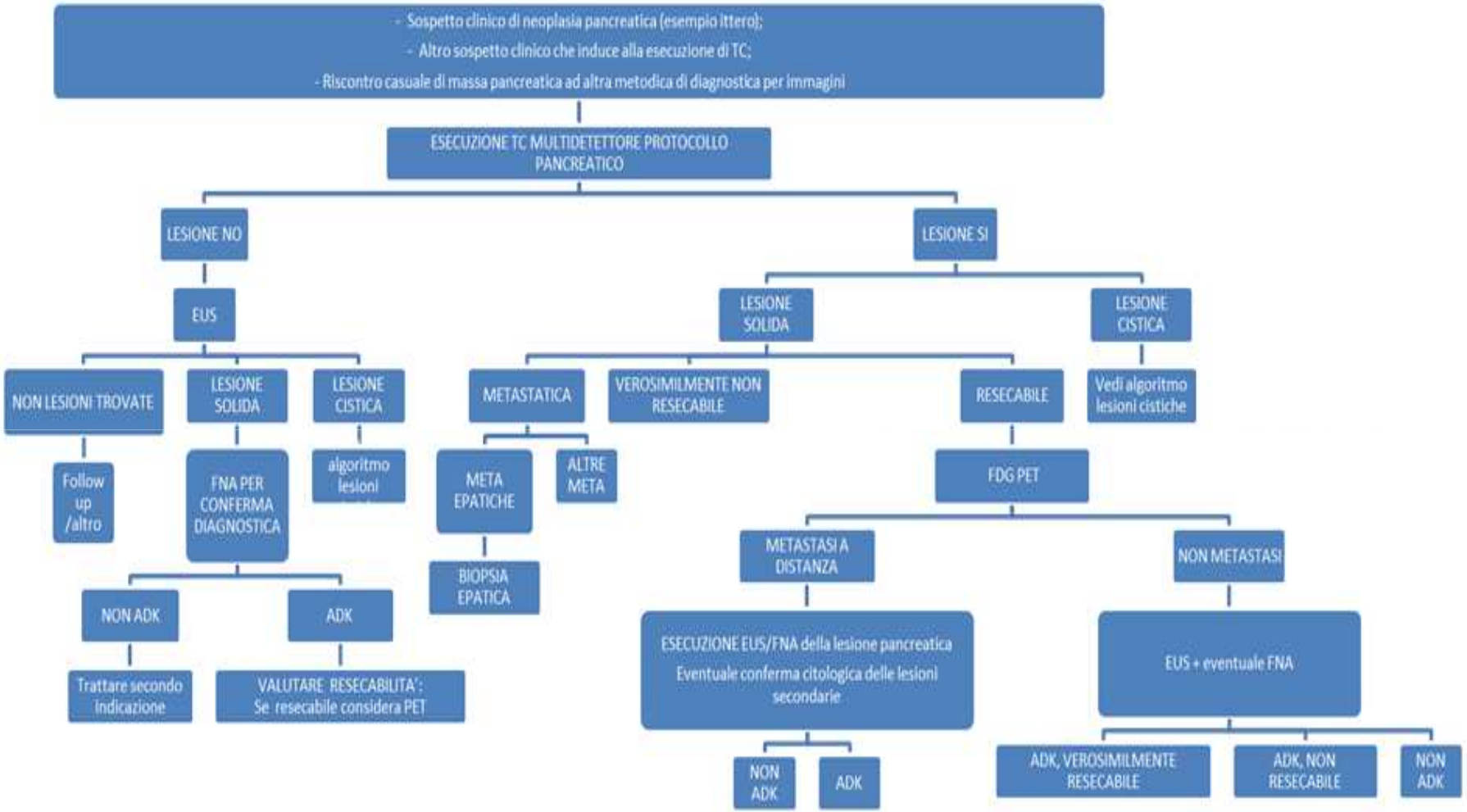
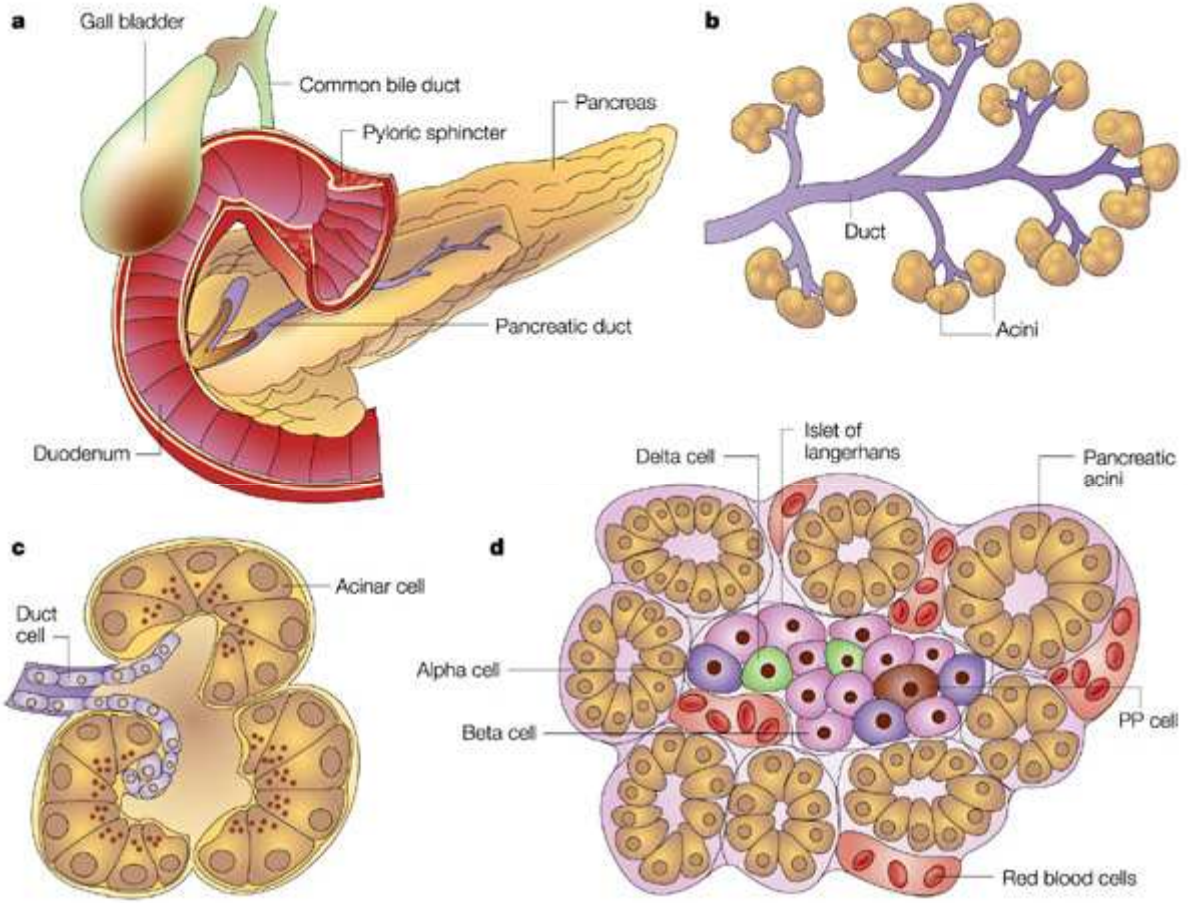


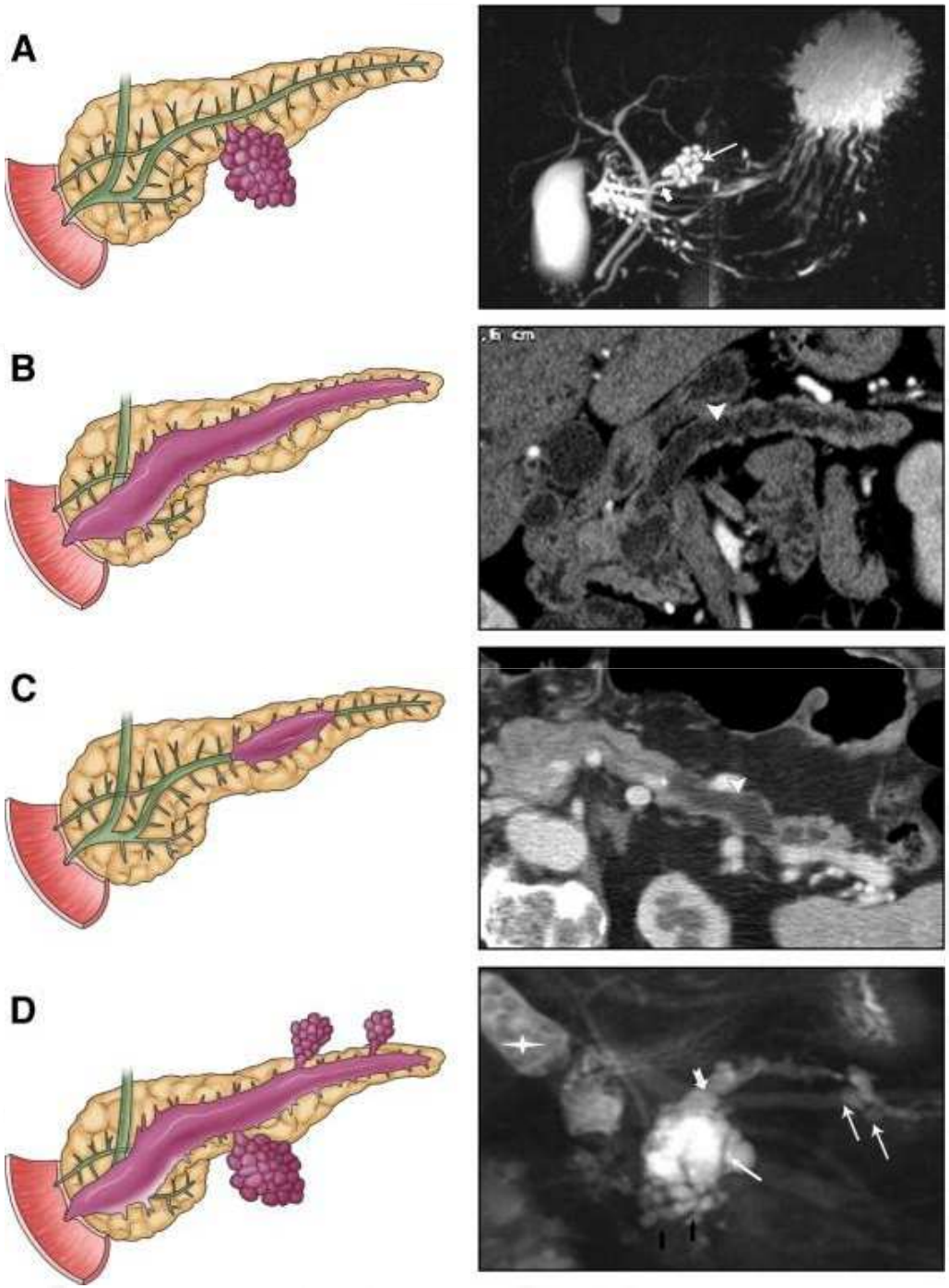
Figura 5. Sopravvivenza relativa cumulata per fascia di età. *Anni 2006-2010.*




- Sospetto clinico di neoplasia pancreatica (esempio ittero);
- Altro sospetto clinico che induce alla esecuzione di TC;
- Riscontro casuale di massa pancreatica ad altra metodica di diagnostica per immagini
ESECUZIONE TC MULTIDETETTORE PROTOCOLLO PANCREATICO
LESIONE NO
LESIONE SI
EUS
LESIONE SOLIDA
LESIONE CISTICA
NON LESIONI TROVATE
LESIONE SOLIDA
LESIONE CISTICA
METASTATICA
VEROSIMILMENTE NON RESECABILE
RESECABILE
Vedi algoritmo lesioni cistiche
Follow up /altro
FNA PER CONFERMA DIAGNOSTICA
algoritmo lesioni
META EPATICHE
ALTRE META
FDG PET
BIOPSIA EPATICA
METASTASI A DISTANZA
NON METASTASI
NON ADK
ADK
ESECUZIONE EUS/FNA della lesione pancreatica
Eventuale conferma citologica delle lesioni secondarie
EUS + eventuale FNA
Trattare secondo indicazione
VALUTARE RESECABILITA':
Se resecabile considera PET
NON ADK
ADK
ADK, VEROSIMILMENTE RESECABILE
ADK, NON RESECABILE
NON ADK



Nature Reviews | Cancer



IPMN

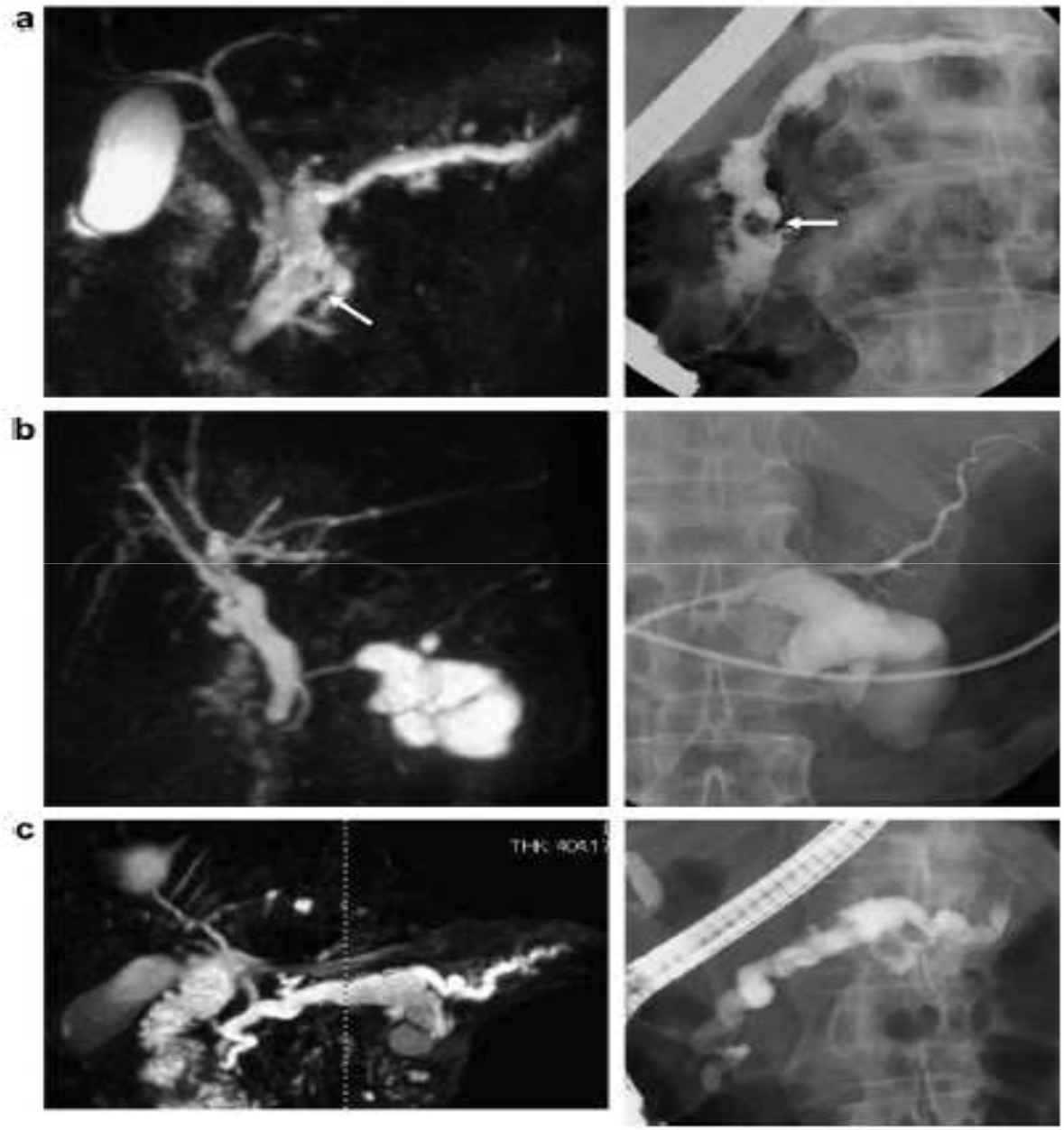


Fig. 1. MRCP (left panels) and ERCP (right panels) demonstrating the three morphological types of IPMN. a. Main duct type with a mural nodule (arrows). b. Branch duct type. c. Mixed type.

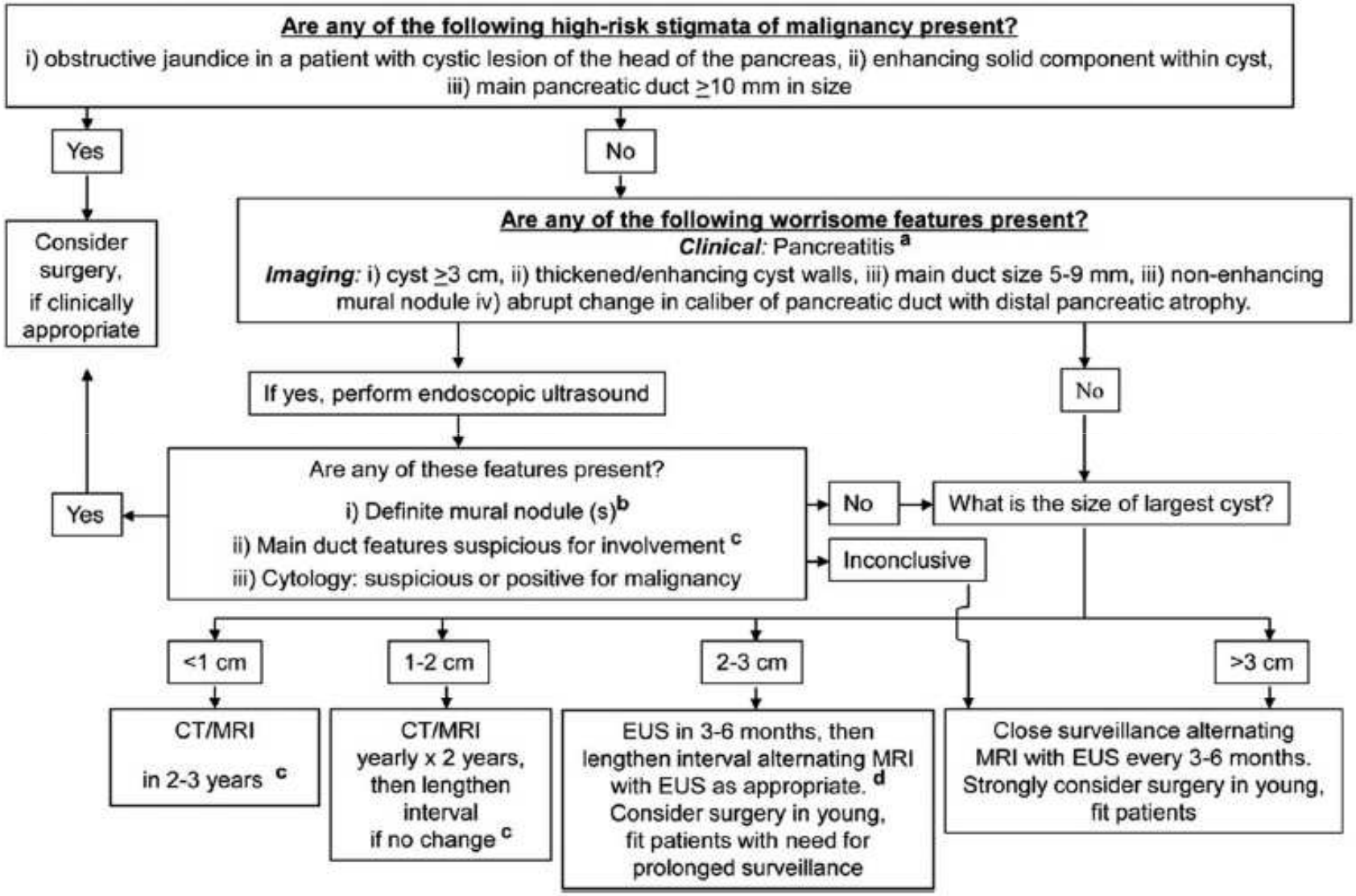
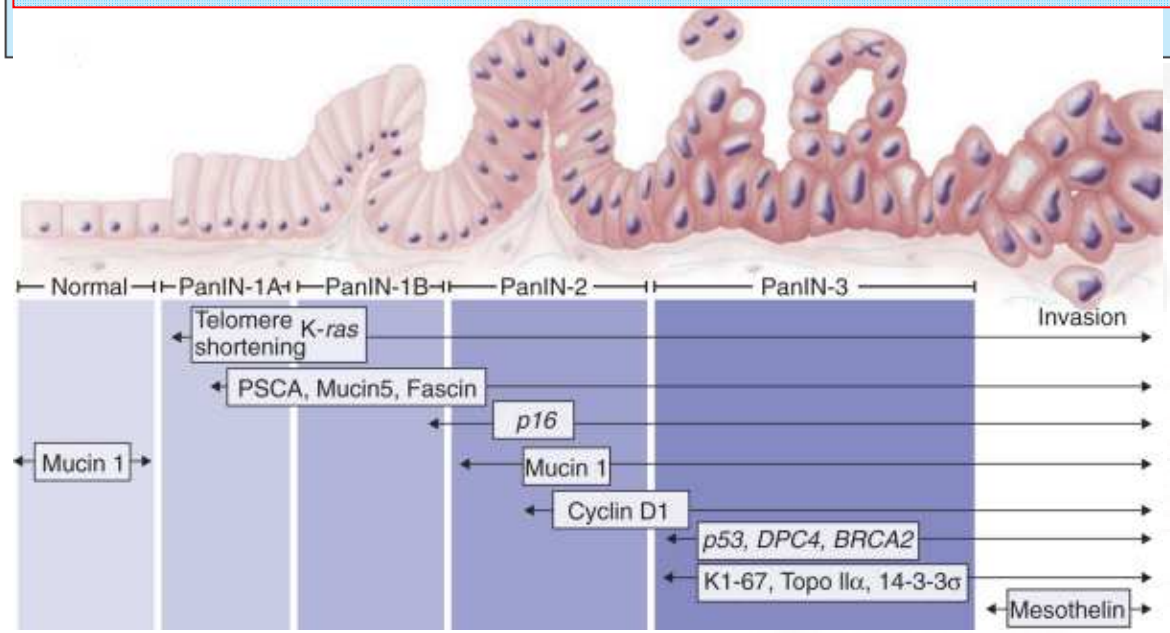


Figure 1. Management algorithm for suspected branch-duct IPMN. (Reproduced with permission from Tanaka et al.[20])

List of recommended terms with synonyms for focal hyperplastic and metaplastic duct lesions in the human exocrine pancreas.

Recommended WHO term	Previous WHO classification {947}	Other synonyms
Squamous metaplasia Incomplete squamous metaplasia	Squamous metaplasia Incomplete squamous metaplasia	Epidermoid metaplasia, multilayered metaplasia focal epithelial hyperplasia, focal atypical epithelial hyperplasia, multilayered metaplasia
PanIN-IA	Mucinous cell hypertrophy	Mucinous cell hyperplasia, mucinous ductal hyperplasia, mucoid transformation, simple hyperplasia, flat ductal hyperplasia, mucous hypertrophy, hyperplasia with pyloric gland metaplasia, ductal hyperplasia grade 1, non-papillary epithelial hypertrophy, nonpapillary ductal hyperplasia
PanIN-IB	Ductal papillary hyperplasia Adenomatoid ductal hyperplasia	Papillary ductal hyperplasia, ductal hyperplasia grade 2 Adenomatous hyperplasia, ductular cell hyperplasia
PanIN-II	Any PanIN-I lesion with moderate dysplasia as defined in the text	
PanIN-III	Severe ductal dysplasia	Ductal hyperplasia grade 3, atypical hyperplasia Carcinoma in situ



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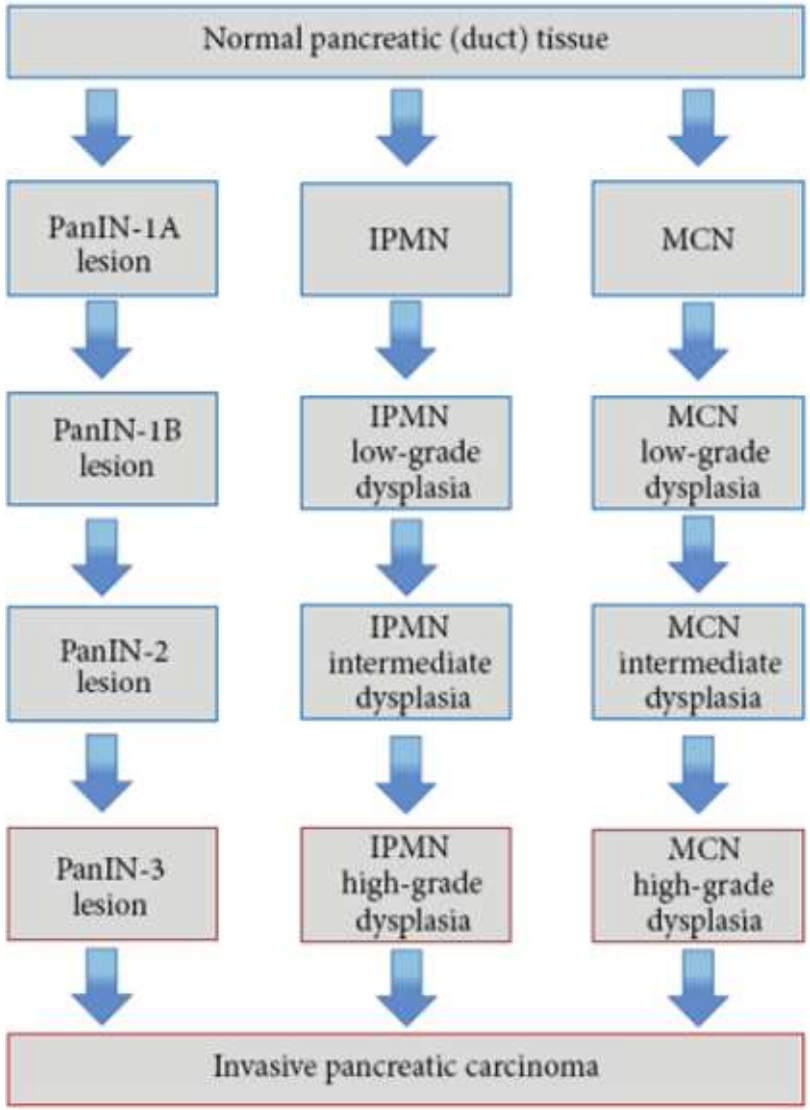
BioMed Research International
Volume 2014, Article ID 474905, 11 pages
http://dx.doi.org/10.1155/2014/474905

Review Article

Precursor Lesions for Sporadic Pancreatic Cancer: PanIN, IPMN, and MCN

M. Distler,[1] D. Aust,[2] J. Weitz,[1] C. Pilarsky,[1] and Robert Grützmann[1]



Model of three distinct morphological pathways to invasive pancreatic carcinoma: OPTIMIZE FOLLOW-UP

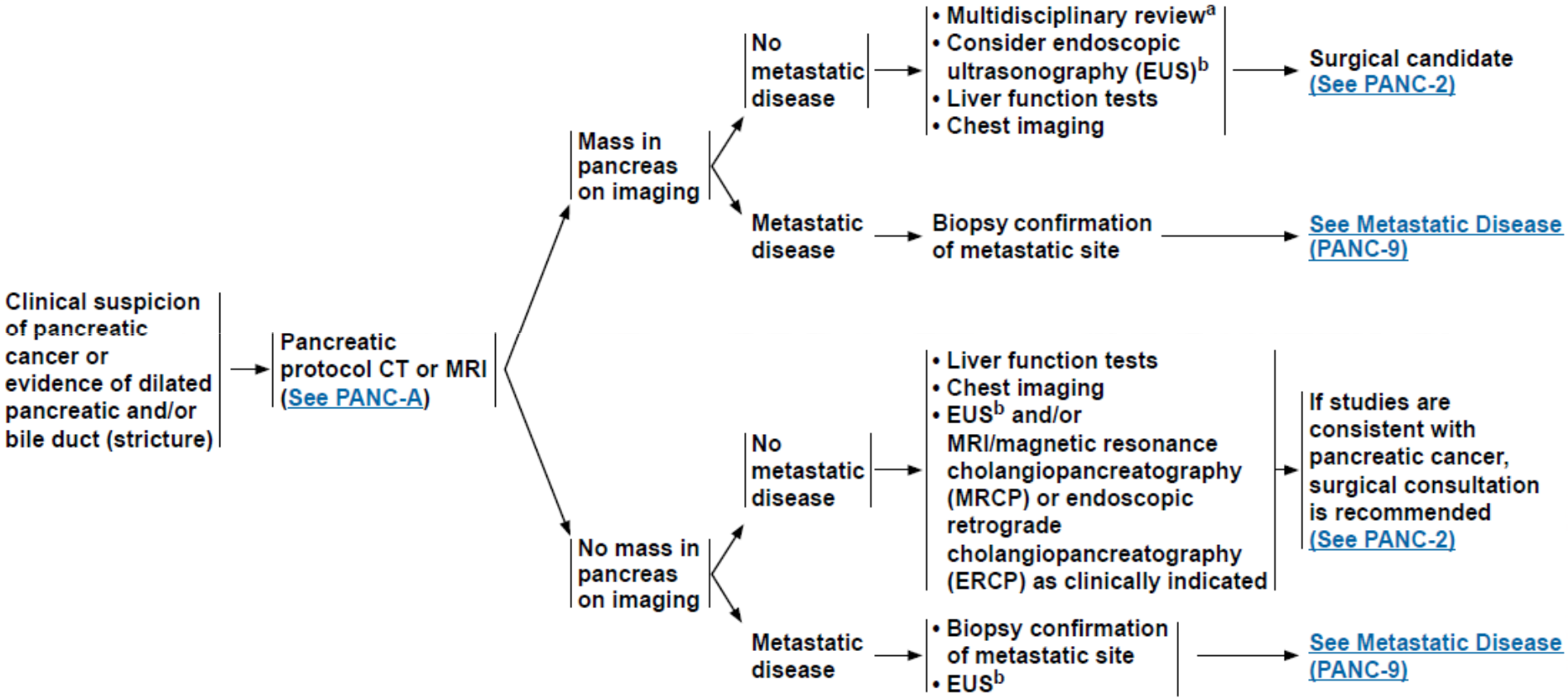
INTRODUCTION

Decisions about diagnostic management and resecability should involve multidisciplinary consultation at a high-volume center with reference to appropriate imaging studies

NCCN Guidelines Version 2.2014
Pancreatic Adenocarcinoma

NCCN Guidelines Index
Pancreatic Table of Contents
Discussion

CLINICAL PRESENTATION | **WORKUP**



[a]Multidisciplinary review should ideally involve expertise from surgery, diagnostic imaging, interventional endoscopy, medical oncology, radiation oncology, surgery, and pathology.
[b]EUS-FNA if clinically indicated.

PRINCIPLES OF DIAGNOSIS AND STAGING

#1 Decisions about diagnostic management and resectability should involve multidisciplinary consultation at a high-volume center with reference to appropriate high-quality imaging studies to evaluate the extent of disease. Resections should be done at institutions that perform a large number (at least 15-20) of pancreatic resections annually.

#2 Imaging should include specialized pancreatic CT or MRI. CT should be performed according to a defined pancreas protocol such as triphasic cross-sectional imaging and thin slices. Optimal multi-phase imaging technique includes a non-contrast phase plus arterial, pancreatic parenchymal and portal venous phases of contrast enhancement with thin cuts (3 mm or less) through the abdomen. Multiplanar reconstruction is preferred. This technique allows precise visualization of the relationship of the primary tumor to the mesenteric vasculature as well as detection of metastatic deposits as small as 3-5 mm. Pancreas protocol MRI is emerging as an alternative to CT for patients.

#3 The role of PET/CT scan remains unclear. PET/CT scan may be considered after formal pancreatic CT protocol in high-risk* patients to detect extra pancreatic metastases. It is not a substitute for high-quality, contrast enhanced CT.

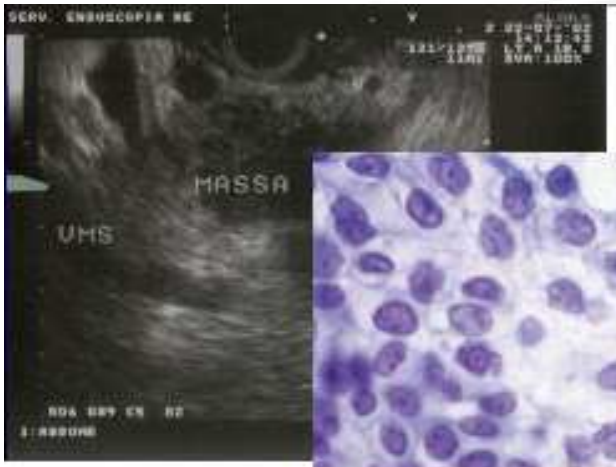
#4 EUS may be complementary to CT for staging.

#5 EUS-FNA is preferable to a CT-guided FNA in patients with resectable disease because of better diagnostic yield, safety, and potentially lower risk of peritoneal seeding with EUS-FNA when compared with the percutaneous approach. Biopsy proof of malignancy is not required before surgical resection, and a non-diagnostic biopsy should not delay surgical resection when the clinical suspicion for pancreatic cancer is high.

#6 Diagnostic staging laparoscopy to rule out subradiologic metastases (especially for body and tail lesions) is used in some institutions prior to surgery or chemoradiation, or selectively in patients who are at higher risk* for disseminated disease.

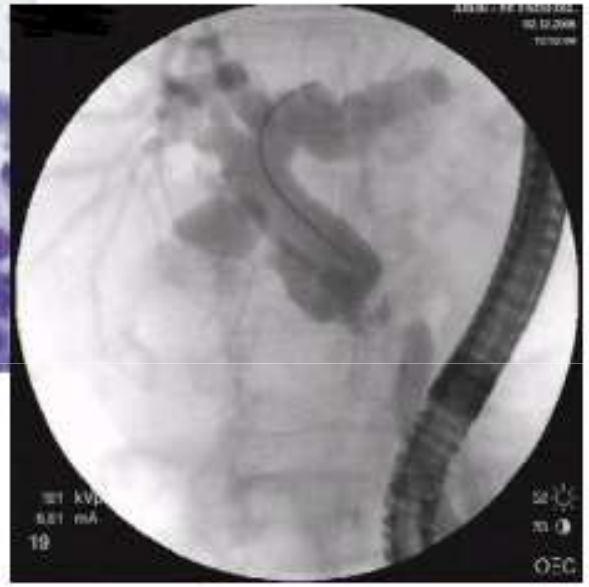
#7 Positive cytology from washings obtained at laparoscopy or laparotomy is equivalent to M1 disease. If resection has been done for such a patient, he or she should be treated for M1 disease.

*Indicators of high-risk patients may include borderline resectable disease, markedly elevated CA 19-9, large primary tumors, or large regional lymph nodes.



Completamento diagnosi/stadiazione

Conferma con citologia



Trattamento con ERC…

Tentativo di integrare in un'unica seduta le manovre endoscopiche ritenute utili per il paziente.

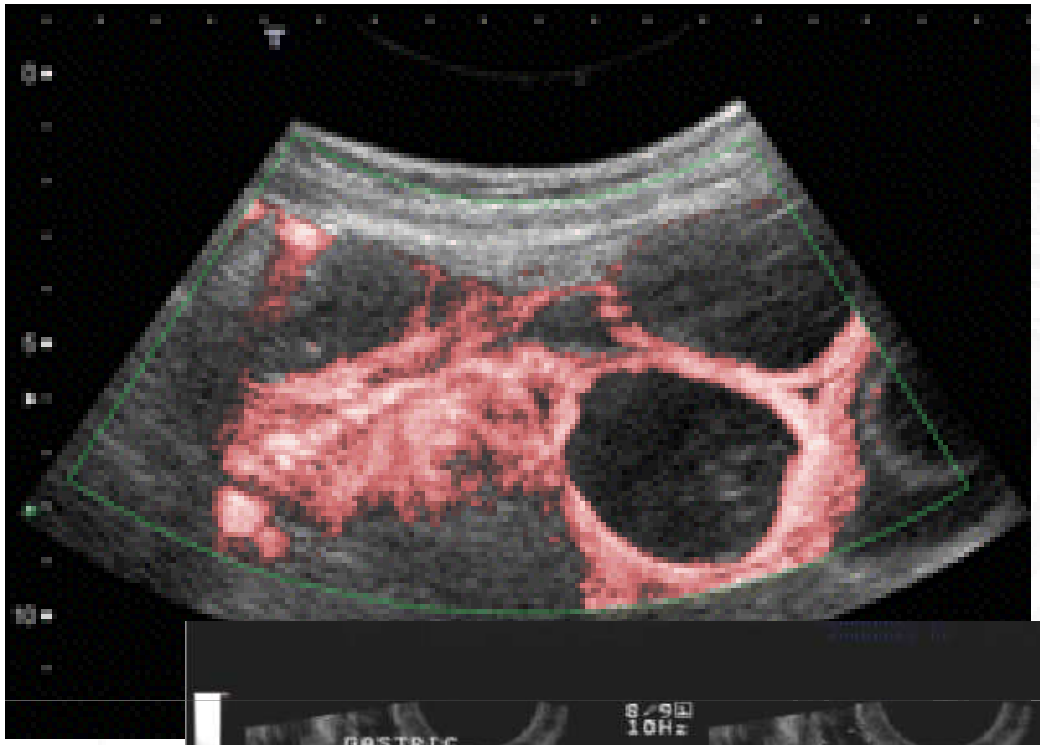
mission **accomplished**…

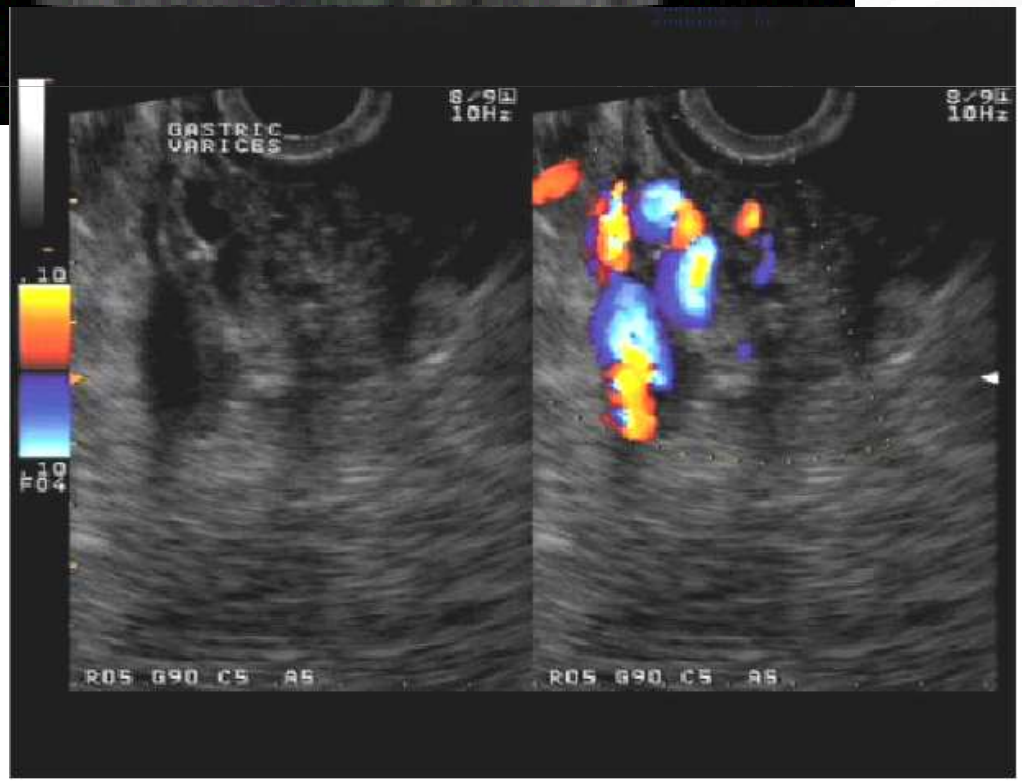
Questo richiede

Competenze

Organizzazione

Informazione




GASTRIC
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Volume 2012, Article ID 317167, 17 pages
doi:10.1155/2012/317167

Review Article

Endoscopic-Ultrasound-Guided Fine-Needle Aspiration and the Role of the Cytopathologist in Solid Pancreatic Lesion Diagnosis

Shahzad Iqbal,[1] David Friedel,[1] Mala Gupta,[2] Lorna Ogden,[2] and Stavros N. Stavropoulos[1]

[1] *Division of Gastroenterology, Department of Medicine, Winthrop-University Hospital, Mineola, NY 1150, USA*
[2] *Department of Pathology, Winthrop-University Hospital, Mineola, NY 1150, USA*

- ✓ EUS is the most sensitive imaging modality for solid pancreatic lesions.
- ✓ It is an outpatient safe procedure
- ✓ High accuracy of
  - ✓ 78–94% for T (local tumor) stage
  - ✓ 64–82% for N (lymph node) stage
- ✓ Specificity is low (about 75%), but can be increased to 100% with an accuracy of 95% with the addition of fine needle aspiration.
- ✓ The diagnostic yield of EUS-FNA for solid pancreatic lesion is
  - ✓ cytologic 86.8–98.5%
  - ✓ histologic examinations 68.9–89%
  - ✓ lymph nodes 65–100%

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Review Article

Endoscopic-Ultrasound-Guided Fine-Needle Aspiration and the Role of the Cytopathologist in Solid Pancreatic Lesion Diagnosis

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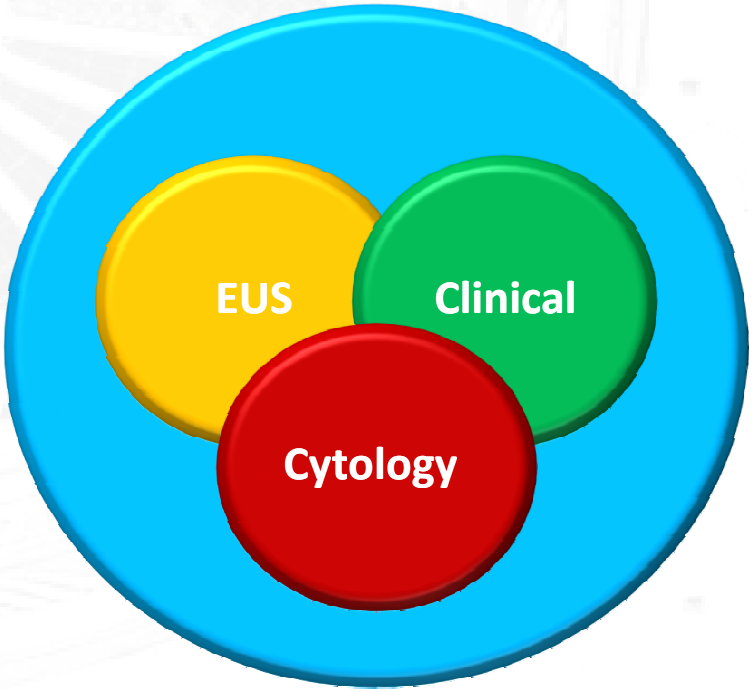
[2] *Department of Pathology, Winthrop-University Hospital, Mineola, NY 1150, USA*

Factors related to either endoscopist or cytopathologist affect the diagnostic yield of EUS-FNA.

A close interaction with cytopathologist is vital in improving the diagnostic yield.

The final diagnosis is based upon correlation of clinical, EUS, and cytologic features.



SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Ospedaliera di Reggio Emilia
Istituto in tecnologie avanzate e modelli assistenziali in oncologia
Istituto di Ricovero e Cura a Carattere Scientifico
Arcispedale S. Maria Nuova
Dipartimento Oncologico e Tecnologie Avanzate
Gastroenterologia - Endoscopia Digestiva
Dott. Romano Sassatelli - Direttore

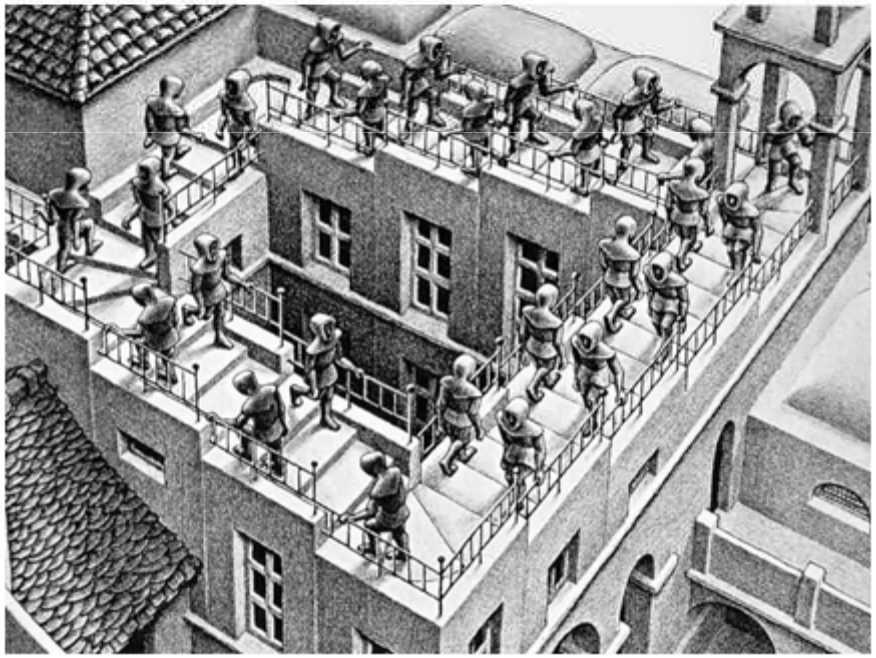
SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Unità Sanitaria Locale di Reggio Emilia
Servizio di Epidemiologia e Comunicazione, Direzione Sanitaria AUSL, Reggio Emilia 3, ASMN- IRCCS e Azienda Unità Sanitaria Locale, Reggio Emilia
Dott. Giorgi Rossi Paolo - Direttore

Registro Tumori Specialistico del Pancreas

della provincia di Reggio Emilia

i primi 3 anni di registrazione

2008-2010



A cura di:
Dott. Romano Sassatelli: Direttore del Registro Tumori Specialistico del Pancreas
Dott.ssa Tiziana Cassetti: Coordinatrice del Registro Tumori Specialistico del Pancreas
Dott. Lorenzo Camellini: Coordinatore del gruppo multidisciplinare del Pancreas
Dott. Paolo Giorgi Rossi: Direttore del Servizio di Epidemiologia AUSL Reggio Emilia

TNM staging system for exocrine and endocrine tumors of the pancreas

Primary tumor (T)			
TX	Primary tumor cannot be assessed		
T0	No evidence of primary tumor		
Tis	Carcinoma in situ*		
T1	Tumor limited to the pancreas, 2 cm or less in greatest dimension		
T2	Tumor limited to the pancreas, more than 2 cm in greatest dimension		
T3	Tumor extends beyond the pancreas but without involvement of the celiac axis or the superior mesenteric artery		
T4	Tumor involves the celiac axis or the superior mesenteric artery (unresectable primary tumor)		
Regional lymph nodes (N)			
NX	Regional lymph nodes cannot be assessed		
N0	No regional lymph node metastasis		
N1	Regional lymph node metastasis		
Distant metastasis (M)			
M0	No distant metastasis		
M1	Distant metastasis		
Anatomic stage/prognostic groups			
Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
Stage IIA	T3	N0	M0
	T1	N1	M0
Stage IIB	T2	N1	M0
	T3	N1	M0
Stage III	T4	Any N	M0
Stage IV	Any T	Any N	M1

* This includes lesions classified as PanInIII classification.

AJCC Cancer Staging Manual, Seventh Edition (2010)

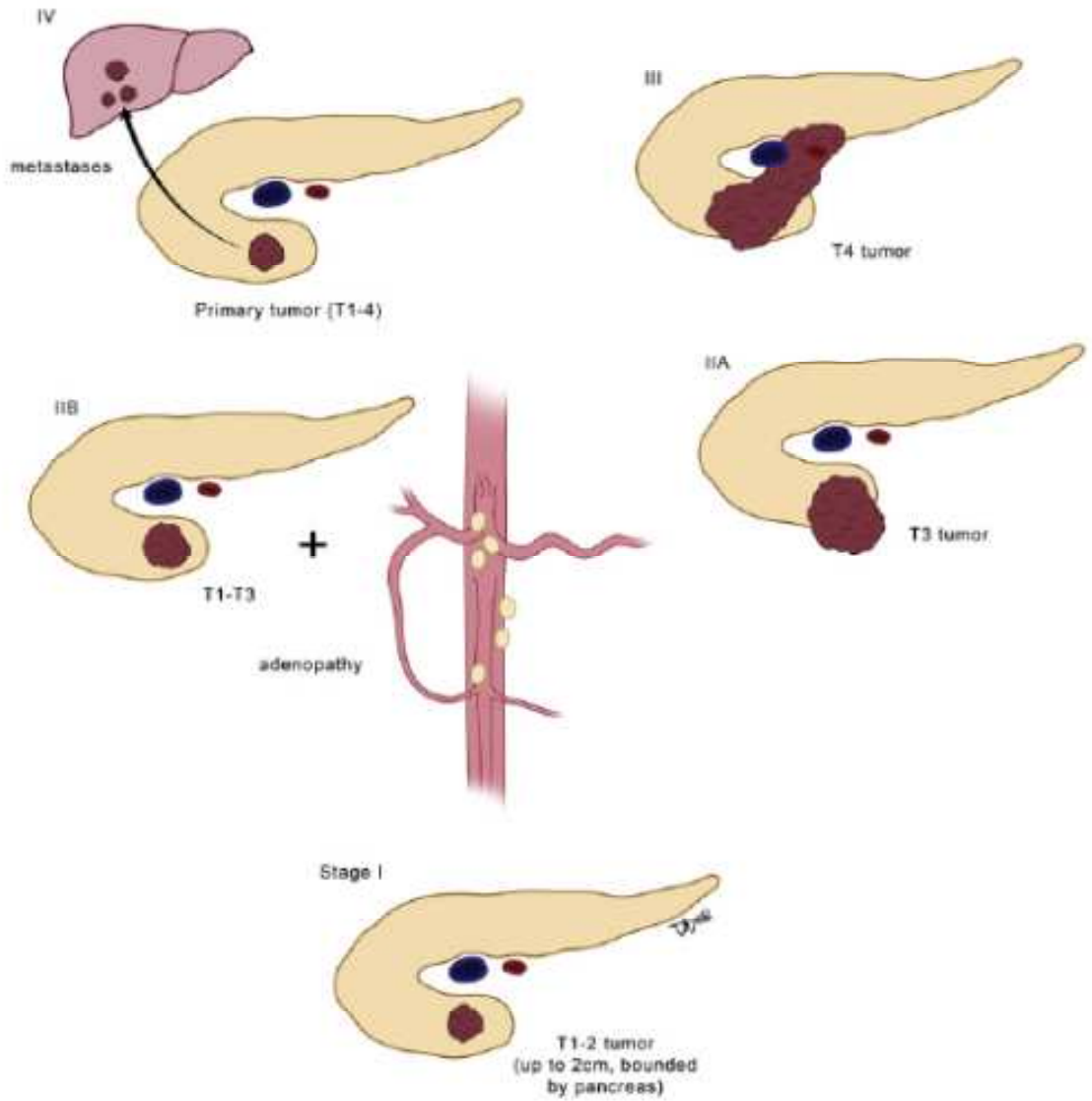
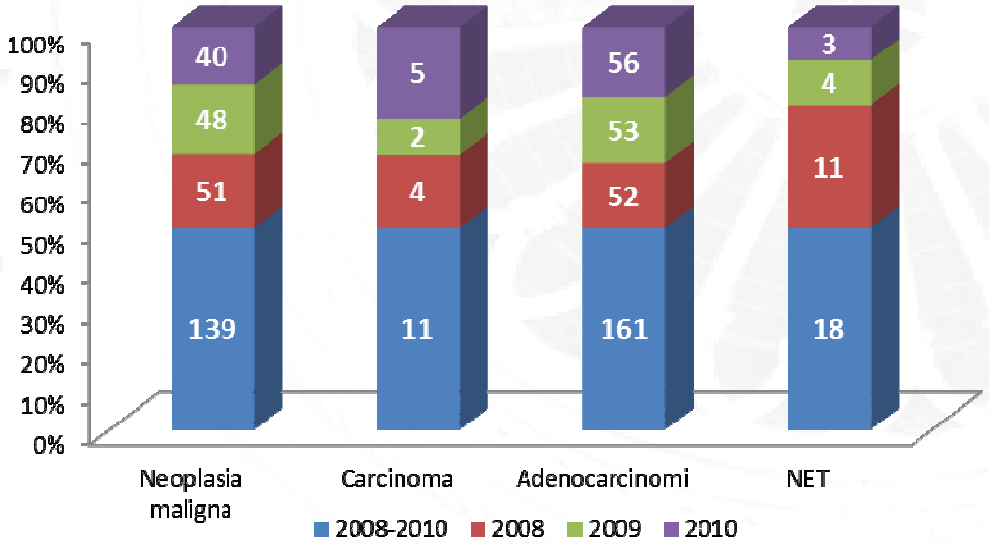
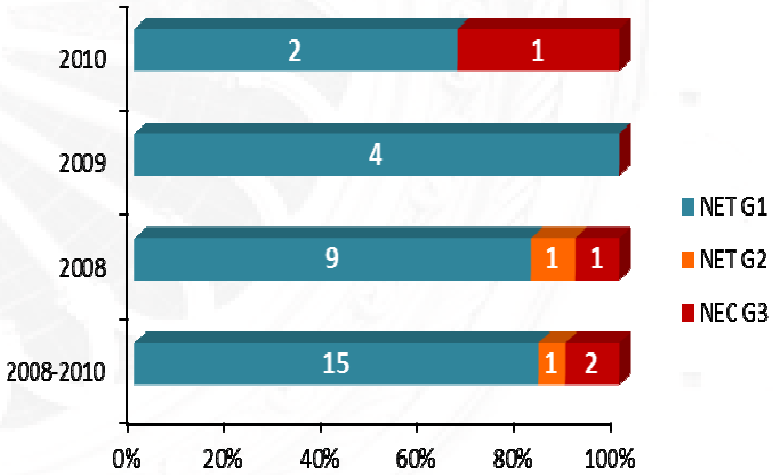


Fig. 10. Current staging of pancreatic cancer. Stage IV disease is the presence of distant metastases. Stage III disease is any other disease in which tumor involves the celiac or superior mesenteric arteries. Stage IIB disease is any other disease with adenopathy, and T1 to T3. Stage IIA is T3 disease (extending beyond the pancreas but without superior mesenteric or celiac artery involvement) without adenopathy or distant metastases. Stage I disease is any other disease (no metastases, no adenopathy) with primary tumor confined to the pancreas (T1–T2).

	Totali		2008		2009		2010	
	N	%	N	%	N	%	N	%
Totale	369	*100*	142	*38*	113	*31*	114	31
Benigni	39	*11*	24	*17*	6	*5*	9	8
In situ	1*	*0*	0	*0*	0	*0*	1*	1*
Maligni	329	*89*	118	*83*	107	*95*	104	91

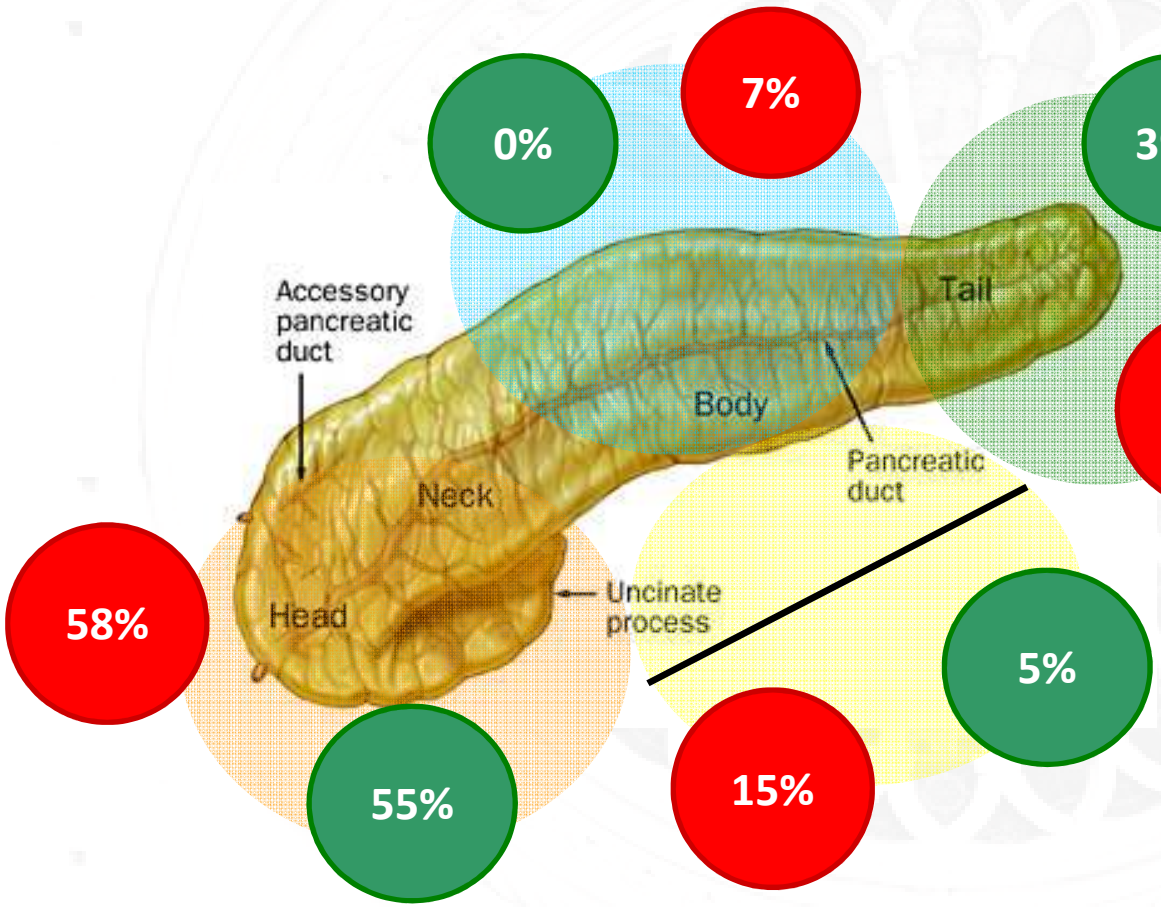




Sottosede

XY% Neoplasie solide

XY% NET



NAS

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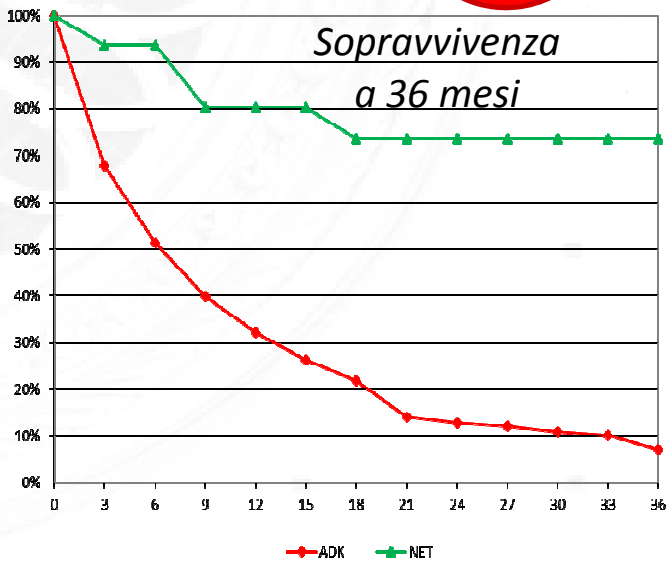
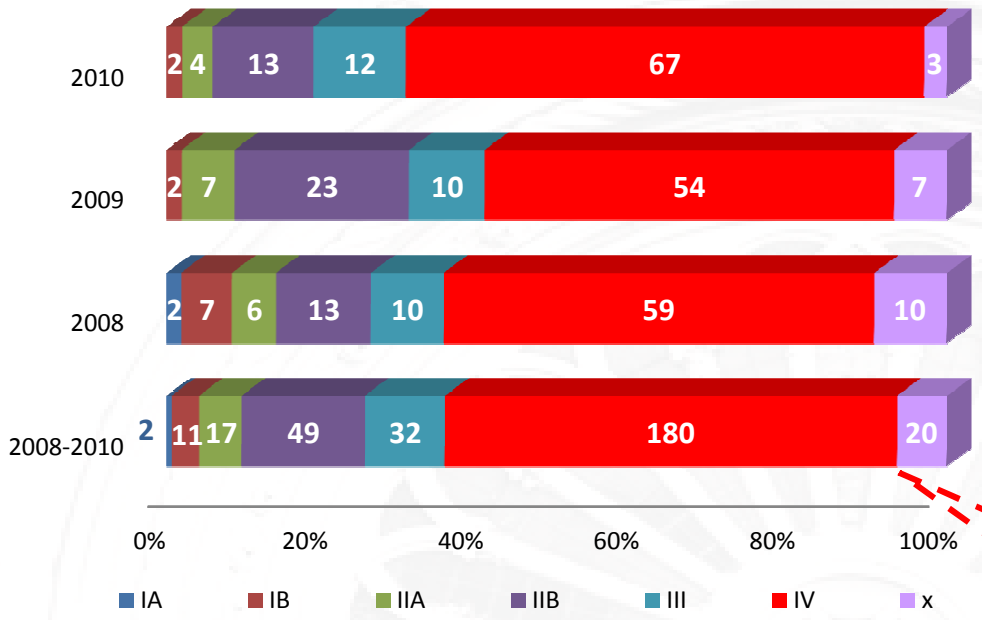


Neoplasie solide

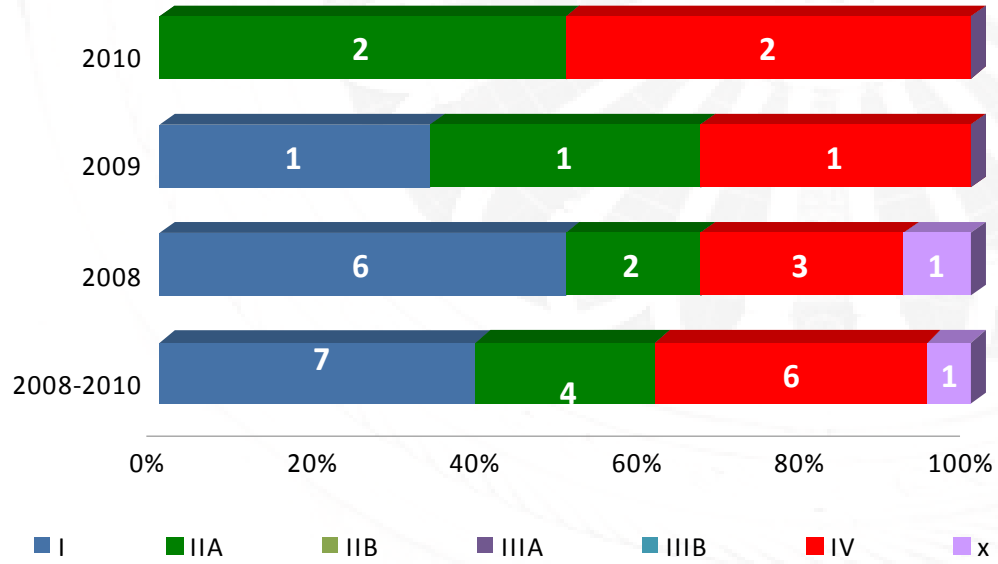


Il 32% dei pazienti sono plurimetastatici al momento della diagnosi.

4% T1*
17% T2

Bilimoria KY et al
Validation of the 6th edition AJCC Pancreatic Cancer Staging System
Cancer. 2007; 110(4):738-44

NET



Seminar

Pancreatic cancer

Audrey Vincent, Joseph Herman, Rich Schulick, Ralph H Hruban, Michael Goggins

Lancet 2011; 378: 607–20

Clinical staging[88]

Local or resectable (about 10%, median survival 17–23 months)

- Stage 0 (Tis, N0, M0)
- Stage IA (T1, N0, M0)
- Stage IB (T2, N0, M0)
- Stage IIA (T3, N0, M0)
- Stage IIB (T1, N1, M0; T2, N1, M0; T3, N1, M0)

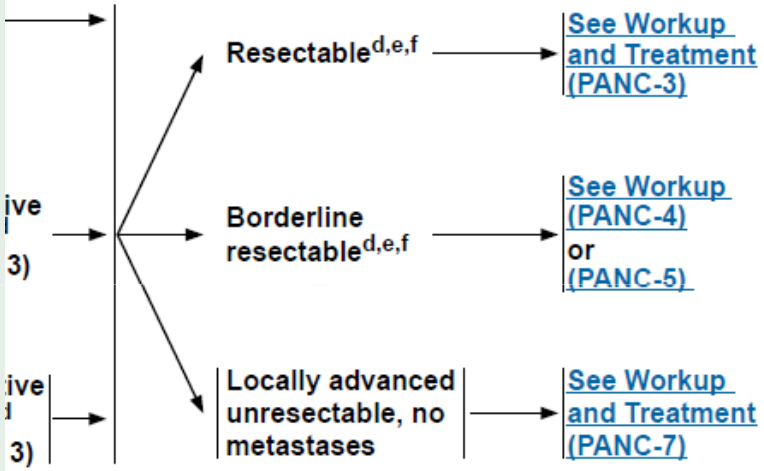
Borderline resectable (10%, median survival up to 20 months)

Stage 3 disease with tumour abutment or <180° circumference of the superior mesenteric artery or coeliac arteries, or a short segment of hepatic artery or the superior mesenteric vein, pulmonary vein, or confluence of these veins

Locally advanced or unresectable (about 30%, median survival 8–14 months)

- Stage III (T4, any N, M0)

Tumour encasement >180° circumference of the superior mesenteric artery or coeliac arteries, any unreconstructable venous involvement



[c]Elevated CA 19-9 does not necessarily indicate cancer or advanced disease. CA 19-9 may be elevated as a result of biliary infection (cholangitis), inflammation, or obstruction, benign or malignant. In addition, CA 19-9 may be undetectable in Lewis antigen-negative individuals. (See Discussion)

[d]See Principles of Diagnosis and Staging (PANC-A).

[e]See Criteria Defining Resectability Status (PANC-B).

[f]See Principles of Surgical Technique (PANC-C) and Pathologic Analysis: Specimen Orientation, Histologic Sections, and Reporting (PANC-D).

Imaging of Pancreatic Adenocarcinoma: Update on Staging/ Resectability

Eric P. Tamm, MD[a,*], Aparna Balachandran, MD[a], Priya R. Bhosale, MD[a], Matthew H. Katz, MD[b], Jason B. Fleming, MD[b], Jeffrey H. Lee, MD[c], Gauri R. Varadhachary, MD[d]

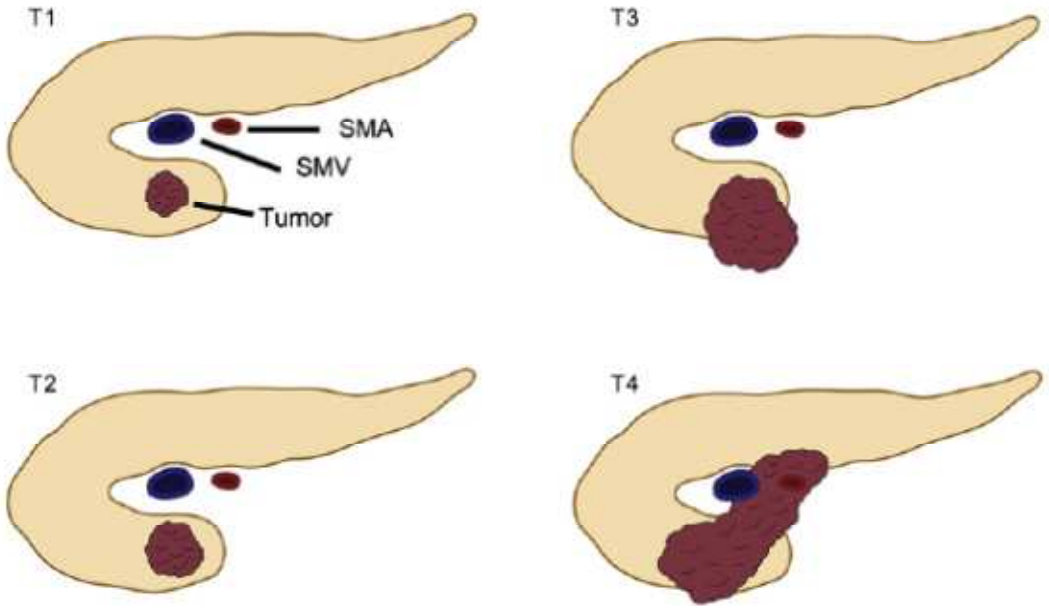


Fig. 9. T1 (<2-cm tumor, bounded by pancreas), T2 (tumor ≥2 cm, but bounded by pancreas), T3 (tumor extending beyond pancreas but not involving the celiac or superior mesenteric arteries), and T4 disease (tumor involving the celiac or superior mesenteric arteries). SMV, superior mesenteric vein; SMA, superior mesenteric artery.

Radiol Clin N Am 50 (2012) 407–428

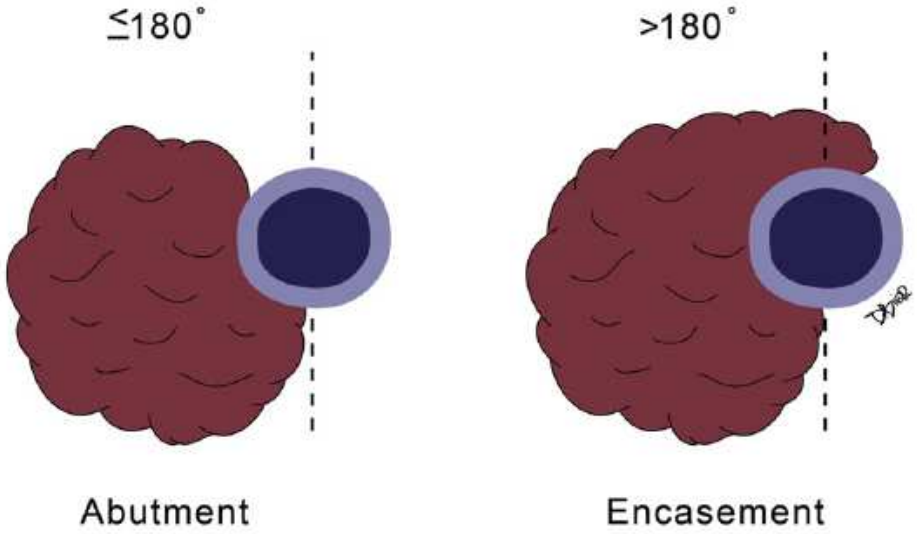


Fig. 12. The terms abutment (defined as ≤180° of tumor involvement of a vessel's circumference) and encasement (>180° of tumor involvement of a vessel's circumference). Either the terms abutment/encasement or degrees of circumferential involvement should be used to describe vascular involvement to facilitate communication with specialties outside radiology.

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Pancreatic Adenocarcinoma

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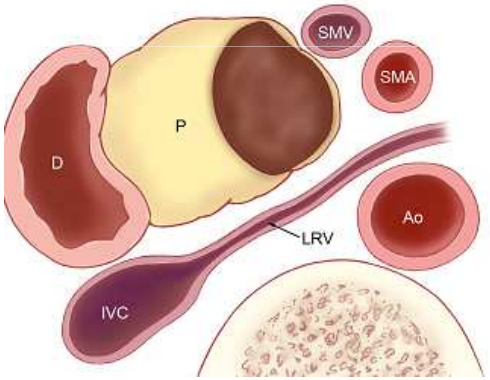
RESECTABLE **WORKUP** **TREATMENT**

15-20%

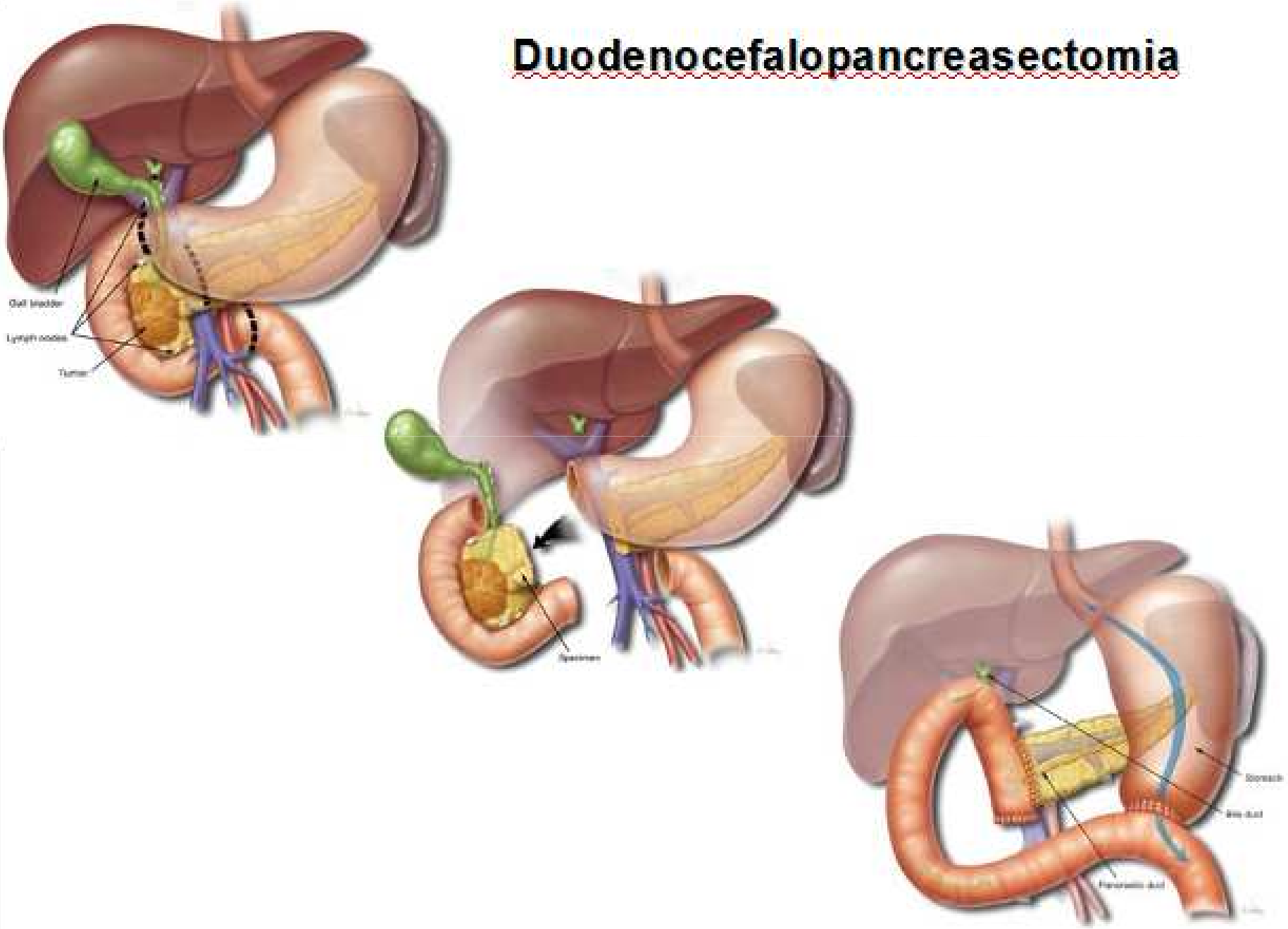
Resectable[e,f,g,h] → Consider staging laparoscopy[i] in high-risk patients or as clinically indicated → Laparotomy

- Surgical resection[f] → See Adjuvant Treatment and Surveillance (PANC-6)
- Unresectable at surgery[j] → Biopsy confirmation of adenocarcinoma, if not performed previously
  - No jaundice → If appropriate, consider duodenal bypass (category 2B for prophylactic duodenal bypass) ± open ethanol celiac plexus block (category 2B) → See Locally Advanced Unresectable (PANC-7)
  - Jaundice → Stenting or biliary bypass ± duodenal bypass (category 2B for prophylactic duodenal bypass) ± open ethanol celiac plexus block when indicated by pain → See Metastatic Disease (PANC-9)

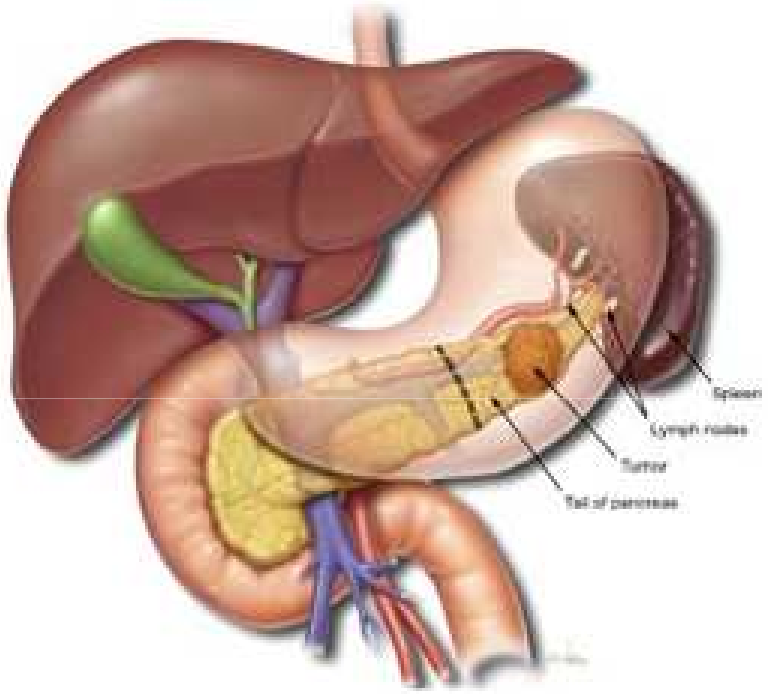


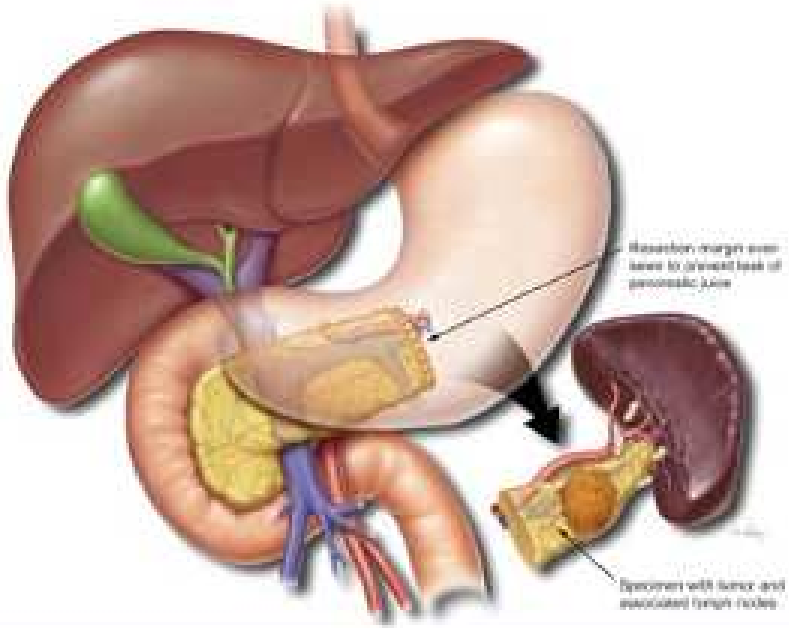
[e] See Criteria Defining Resectability Status (PANC-B).
[f] See Principles of Surgical Technique (PANC-C) and Pathologic Analysis: Specimen Orientation, Histologic Sections, and Reporting (PANC-D).
[g] In selected patients who appear technically resectable but have poor prognostic features (ie, very highly elevated CA 19-9, large primary tumors, large regional lymph nodes, excessive weight loss, or extreme pain) consider neoadjuvant therapy (clinical trial preferred), which requires biopsy confirmation of adenocarcinoma (see PANC-4). For patients with biliary obstruction, durable biliary decompression is required.
[h] There is limited evidence to recommend specific neoadjuvant regimens off-study, and practices vary with regard to the use of chemotherapy and chemoradiation. Most NCCN Member Institutions prefer neoadjuvant therapy at a high-volume center. Performing surgery with a high likelihood of a positive margin is not recommended.
[i] See Principles of Diagnosis and Staging #6 (PANC-A).
[j] See Principles of Palliation and Supportive Care (PANC-E).

Duodenocefalopancreasectomia

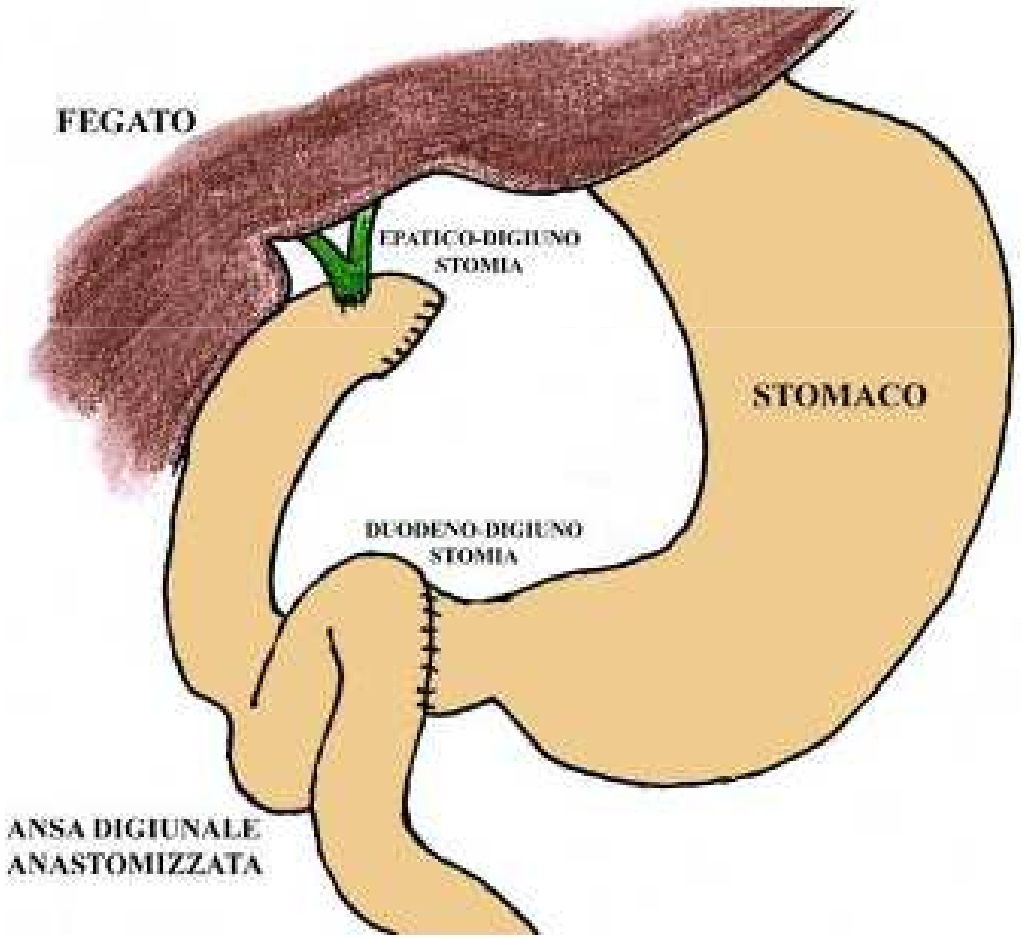


Pancreasectomia distale

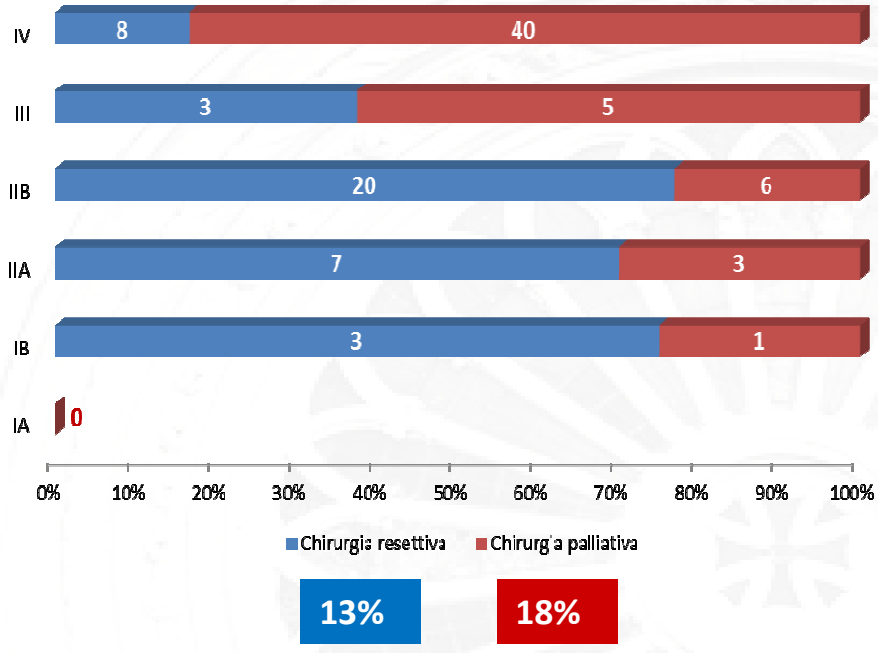




Pancreasectomia totale



Trattamenti chirurgici



13%

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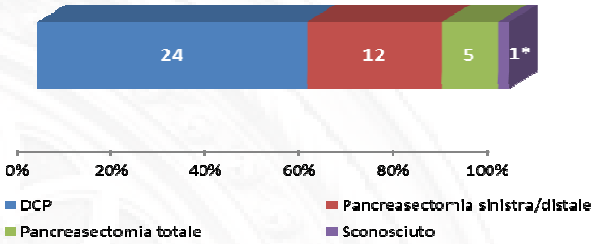

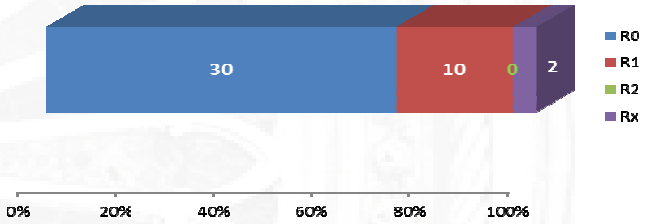

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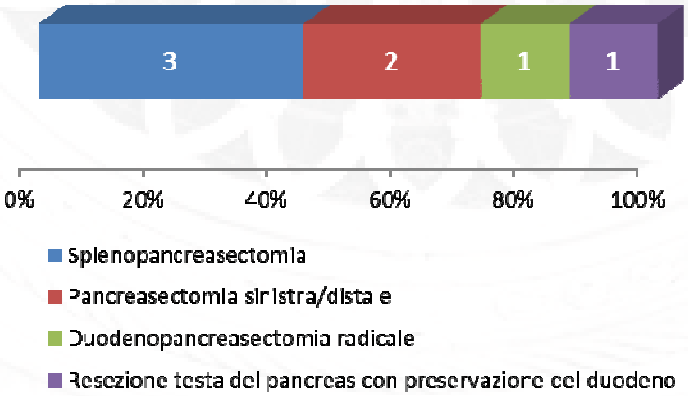
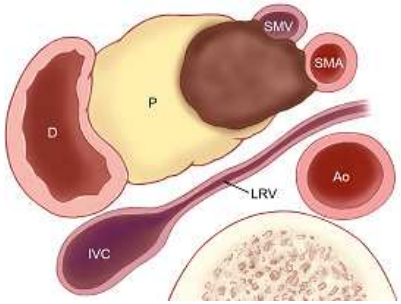


39% interventi

BORDERLINE RESECTABLE[d,e] NO METASTASES, PLANNED NEOADJUVANT THERAPY



WORKUP

Planned neoadjuvant therapy[h]

- Biopsy, EUS-FNA preferred[k]
- Consider staging laparoscopy[i]
- Placement of stent (preferably a short metal stent) if biliary ductal obstruction is present

Biopsy positive → Neoadjuvant therapy → Abdominal (pancreas protocol), pelvic, and chest imaging

Cancer not confirmed → Repeat biopsy

- Biopsy positive → Neoadjuvant therapy (follow pathway above)[j]
- Cancer not confirmed (exclude autoimmune pancreatitis [AIP]) → See Planned Resection (PANC-5)

TREATMENT

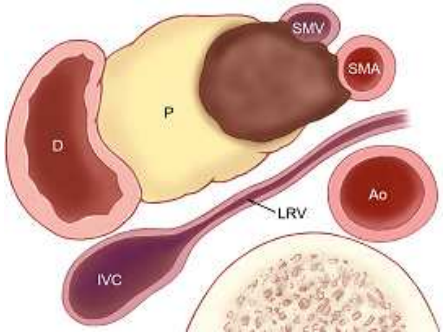
Consider staging laparoscopy if not previously performed

- Surgical resection[f] → See Adjuvant Treatment and Surveillance (PANC-6)
- Unresectable at surgery[f,j]
  - No jaundice → See Locally Advanced Unresectable (PANC-7) or Metastatic Disease (PANC-9)
  - Jaundice → Stenting or biliary bypass ± duodenal bypass (category 2B for prophylactic duodenal bypass) ± open ethanol celiac plexus block (category 2B)

Disease progression precluding surgery[j] → See Locally Advanced Unresectable (PANC-7) or Metastatic Disease (PANC-9)

[d] See Principles of Diagnosis and Staging (PANC-A).
[e] See Criteria Defining Resectability Status (PANC-B).
[f] See Principles of Surgical Technique (PANC-C) and Pathologic Analysis: Specimen Orientation, Histologic Sections, and Reporting (PANC-D).
[h] There is limited evidence to recommend specific neoadjuvant regimens off-study, and practices vary with regard to the use of chemotherapy and chemoradiation. Most NCCN Member Institutions prefer neoadjuvant therapy at a high-volume center. Performing surgery with a high likelihood of a positive margin is not recommended.
[i] See Principles of Diagnosis and Staging #6 (PANC-A).
[j] See Principles of Palliation and Supportive Care (PANC-E).
[k] See Principles of Diagnosis and Staging #1 and #5 (PANC-A).

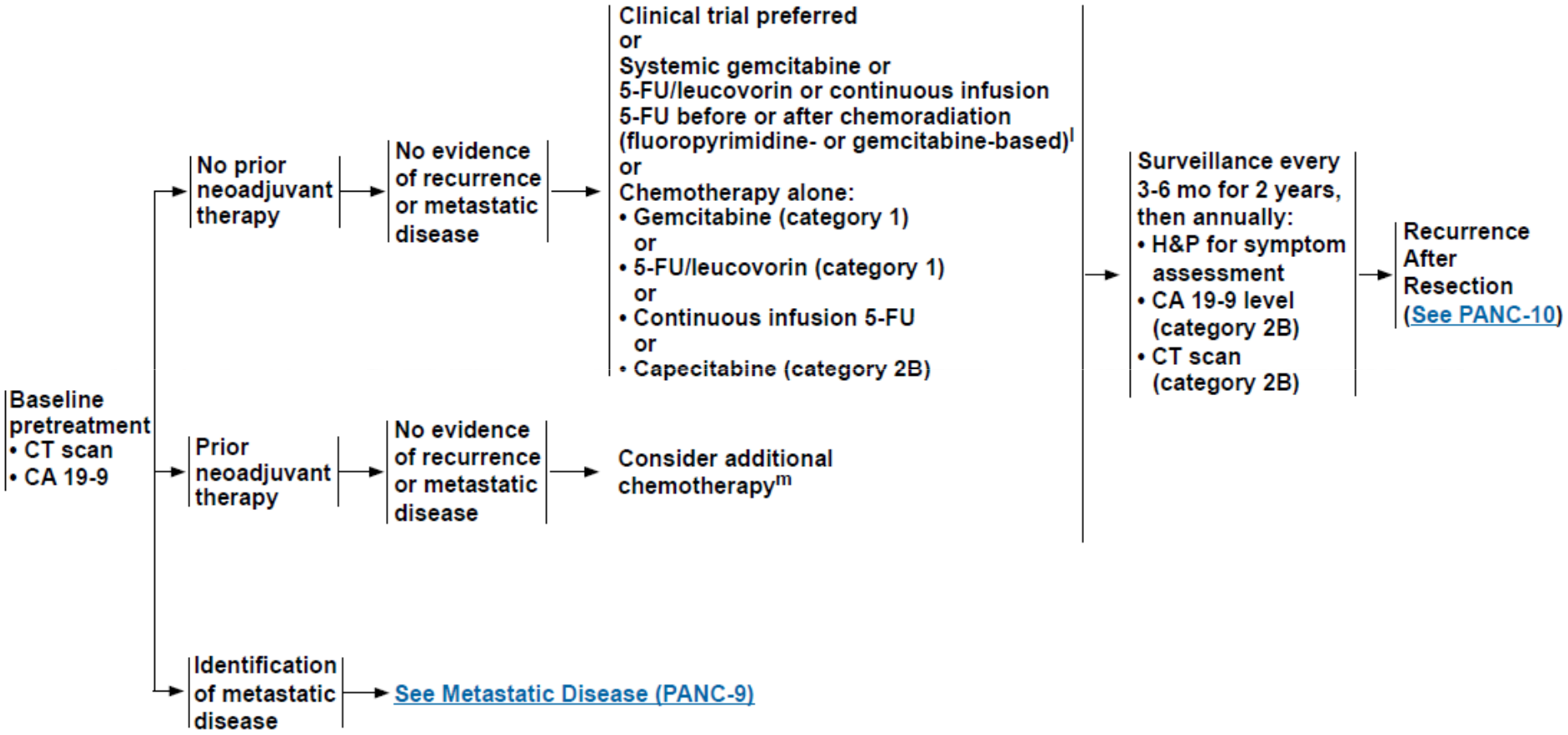
BORDERLINE RESECTABLE[d,e] NO METASTASES, PLANNED RESECTION WORKUP



Planned Resection[f] (category 2B) → Laparotomy

- Surgical resection[f] → See Adjuvant Treatment and Surveillance (PANC-6)
- Unresectable at surgery[f,j] → Biopsy confirmation of adenocarcinoma if not performed previously
  - No jaundice → If appropriate, consider duodenal bypass (category 2B for prophylactic duodenal bypass) ± open ethanol celiac plexus block (category 2B) → See Locally Advanced Unresectable (PANC-7)
  - Jaundice → Stenting or biliary bypass ± duodenal bypass (category 2B for prophylactic duodenal bypass) ± open ethanol celiac plexus block when indicated by pain → See Metastatic Disease (PANC-9)

[d] See Principles of Diagnosis and Staging (PANC-A).
[e] See Criteria Defining Resectability Status (PANC-B).
[f] See Principles of Surgical Technique (PANC-C) and Pathologic Analysis: Specimen Orientation, Histologic Sections, and Reporting (PANC-D).
[j] See Principles of Palliation and Supportive Care (PANC-E).



[l] See Principles of Radiation Therapy (PANC-F).

[m] Patients who have received neoadjuvant chemoradiation or chemotherapy may be candidates for additional chemotherapy following surgery and multidisciplinary review. Adjuvant treatment should be administered to patients who have not had neoadjuvant chemotherapy and who have adequately recovered from surgery; treatment should be initiated within 4-8 weeks. If systemic chemotherapy precedes chemoradiation, restaging with imaging should be done after each treatment modality.

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Pancreatic Adenocarcinoma

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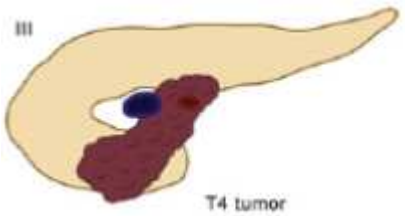
LOCALLY ADVANCED UNRESECTABLE

WORKUP



Locally advanced unresectable → Biopsy if not previously done[k]

- Adenocarcinoma confirmed → If jaundice: placement of stent (expandable metal stent preferred)[n] → See Treatment (PANC-8)
- Cancer not confirmed → If jaundice: placement of stent (preferably a short metal stent) with brushings → Repeat biopsy[o]
  - Adenocarcinoma confirmed → Follow pathway above
  - Cancer not confirmed → Repeat biopsy[o]
  - Other cancer confirmed → Treat with appropriate NCCN Guideline
- Other cancer confirmed → Treat with appropriate NCCN Guideline

[k] See Principles of Diagnosis and Staging #1 and #5 (PANC-A).
[n] Unless biliary bypass performed at time of laparoscopy or laparotomy.
[o] EUS-FNA ± core biopsy at a center with multidisciplinary expertise is preferred.

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Pancreatic Adenocarcinoma

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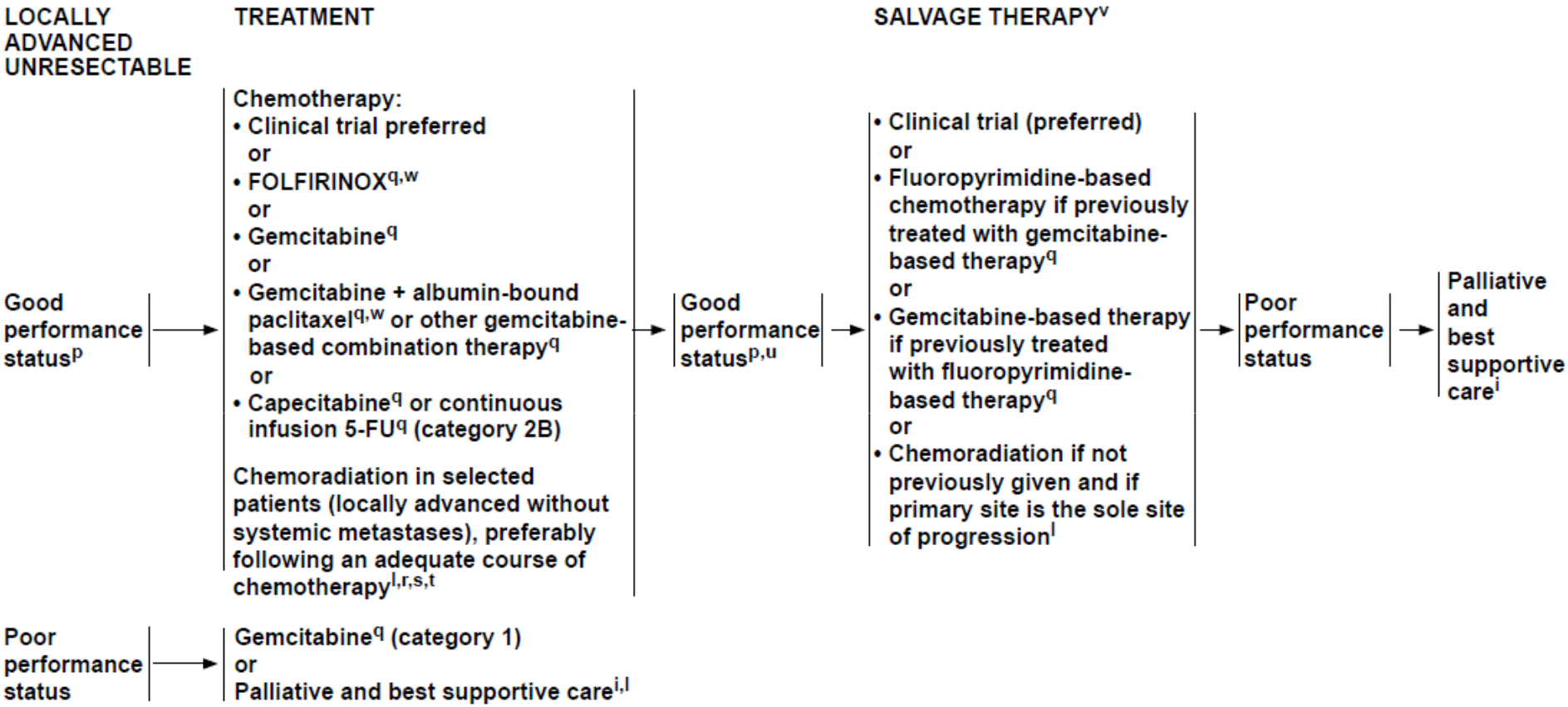

[i] See Principles of Palliation and Supportive Care (PANC-E).
[l] See Principles of Radiation Therapy (PANC-F).
[p] Defined as ECOG 0-1 with good pain management, patent biliary stent, and adequate nutritional intake.
[q] See Principles of Chemotherapy (PANC-G).
[r] Laparoscopy as indicated to evaluate distant disease.
[s] Chemoradiation should be reserved for patients who do not develop metastatic disease while receiving systemic chemotherapy.
[t] Based on preliminary data from the LAP-07 trial, there is no clear survival benefit with the addition of conventional chemoradiation following gemcitabine monotherapy. (Hammel P, Huguet F, van Laethem J-L, et al: Comparison of chemoradiotherapy and chemotherapy in patients with a locally advanced pancreatic cancer controlled after 4 months of gemcitabine with or without erlotinib: Final results of the international phase III LAP 07 study. 2013 ASCO Annual Meeting. Abstract LBA4003.)
[u] Patients with a significant response to therapy may be considered for surgical resection.
[v] Best reserved for patients who maintain a good performance status.
[w] The recommendations for FOLFIRINOX and gemcitabine + albumin-bound paclitaxel in patients with locally advanced disease are based on extrapolations from randomized trials in patients with metastatic disease.

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METASTATIC DISEASE | **TREATMENT** | **SALVAGE THERAPY[v]**

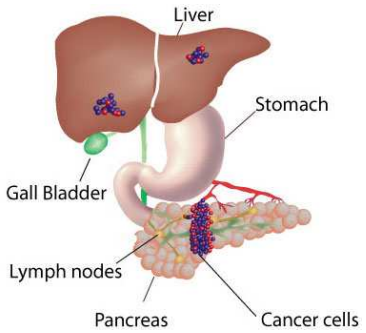
Metastatic disease → If jaundice placement of stent (permanent stent preferred)[n]

Good performance status[p] →
- Clinical trial preferred
- or
- FOLFIRINOX[q] (category 1)
- or
- Gemcitabine + albumin-bound paclitaxel[q] (category 1)
- or
- Gemcitabine + erlotinib[q,x] (category 1)
- or
- Gemcitabine-based combination therapy[q]
- or
- Gemcitabine[q] (category 1)
- or
- Capecitabine[q] or continuous infusion 5-FU[q] (category 2B)

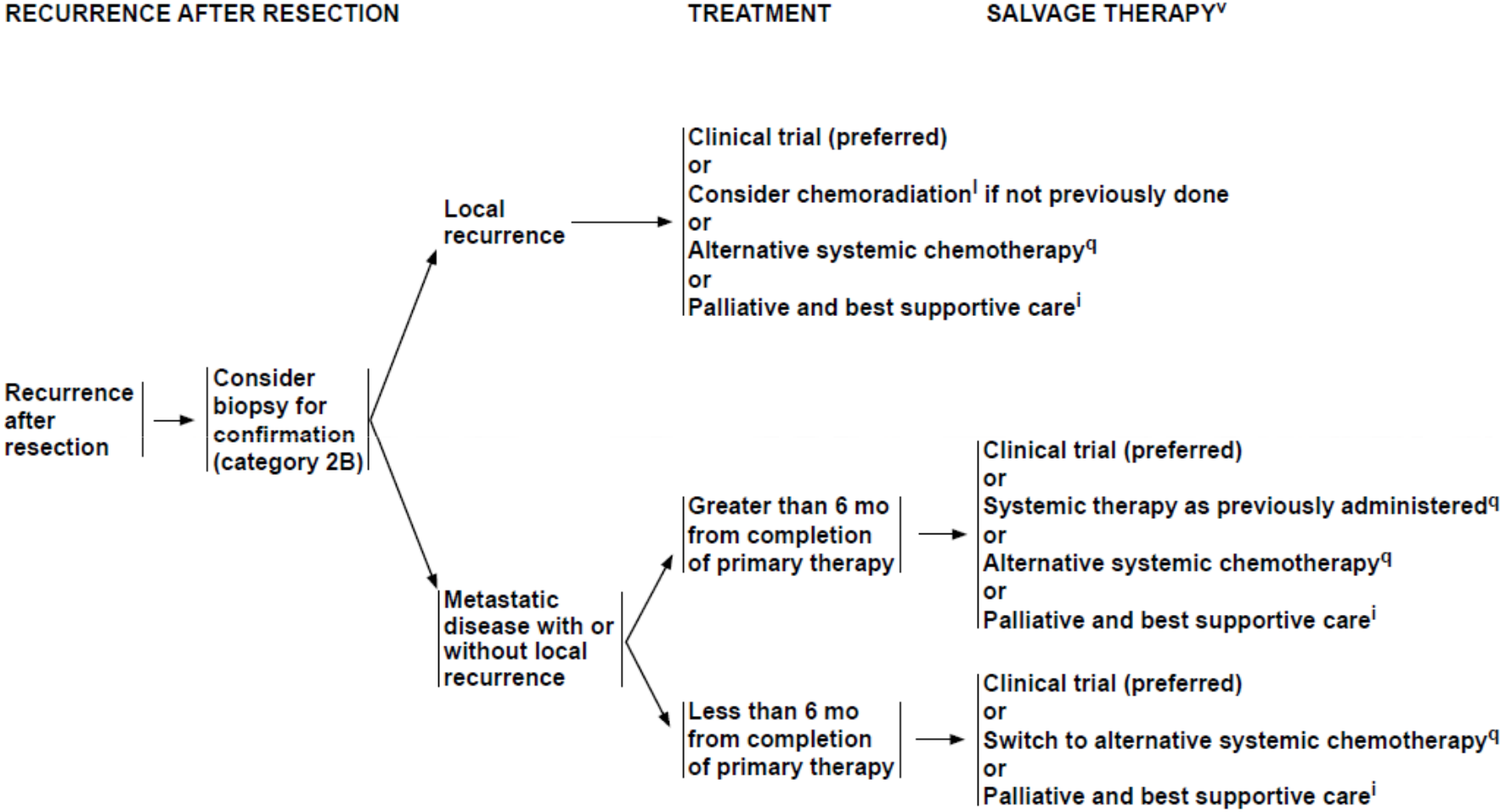
→ Clinical trial (preferred)
- or
- Fluoropyrimidine-based chemotherapy if previously treated with gemcitabine-based therapy[q]
- or
- Gemcitabine-based therapy if previously treated with fluoropyrimidine-based therapy[q]
- or
- RT for severe pain refractory to narcotic therapy[l]

→ Palliative and best supportive[i] care or Clinical trial

Poor performance status →
- Gemcitabine[q] (category 1)
- or
- Palliative and best supportive care[i]



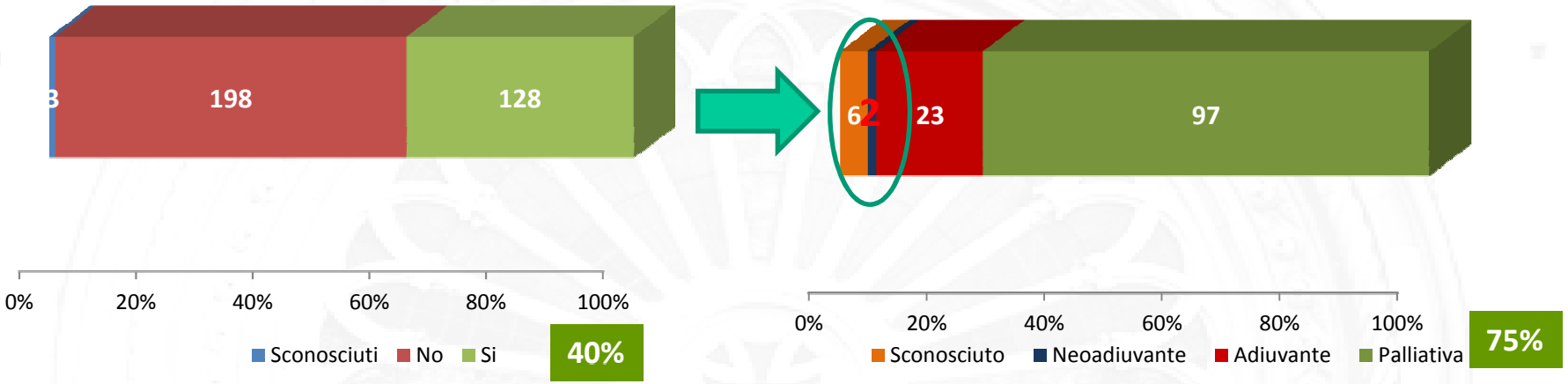
[i] See Principles of Palliation and Supportive Care (PANC-E).
[l] See Principles of Radiation Therapy (PANC-F).
[n] Unless biliary bypass performed at time of laparoscopy or laparotomy.
[p] Defined as ECOG 0-1 with good pain management, patent biliary stent, and adequate nutritional intake.
[q] See Principles of Chemotherapy (PANC-G).
[v] Best reserved for patients who maintain a good performance status.
[x] Although this combination significantly improved survival, the actual benefit was small, suggesting that only a small subset of patients benefit.



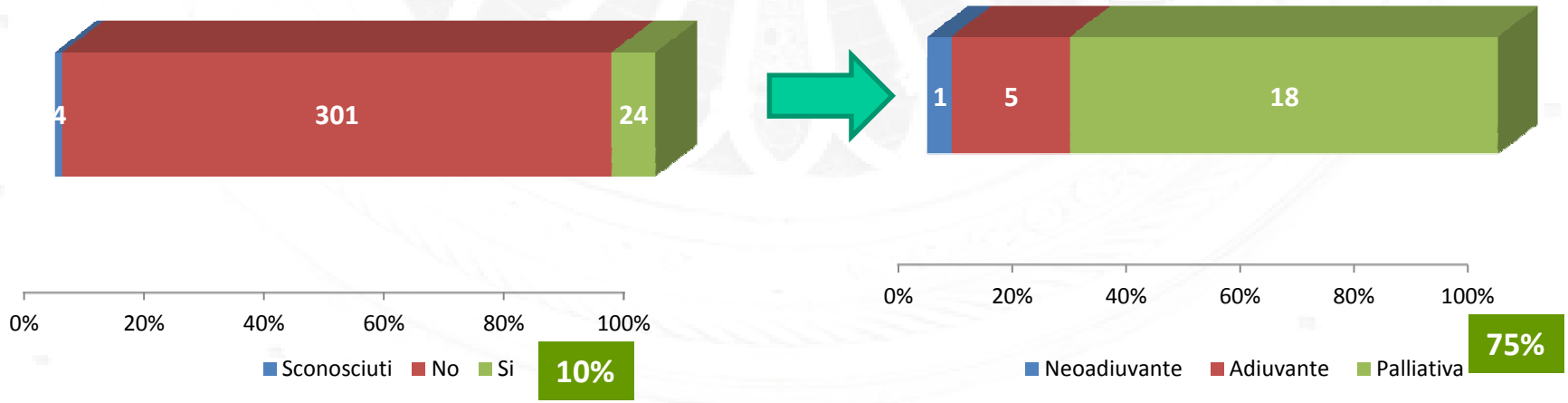
[i]See Principles of Palliation and Supportive Care (PANC-E).
[l]See Principles of Radiation Therapy (PANC-F).
[q]See Principles of Chemotherapy (PANC-G).
[v]Best reserved for patients who maintain a good performance status.

Trattamenti oncoradioterapici

Chemioterapia



Radioterapia



PRINCIPLES OF PALLIATION AND SUPPORTIVE CARE[2]

Objectives: Prevent and ameliorate suffering, while ensuring optimal quality of life

- Biliary obstruction
  - Endoscopic biliary metal stent (preferred method)
  - Percutaneous biliary drainage with subsequent internalization
  - Open biliary-enteric bypass

- Gastric outlet obstruction
  - Good performance status
    - Gastrojejunostomy (open or laparoscopic) ± J-tube
    - Consider enteral stent[1]
  - Poor performance status
    - Enteral stent[1]
    - Percutaneous endoscopic gastrostomy (PEG) tube

- Severe tumor-associated abdominal pain
  - EUS-guided celiac plexus neurolysis (fluoroscopic- or CT-guided if unavailable)
  - Consider palliative radiation with or without chemotherapy if not already given as part of primary therapy regimen

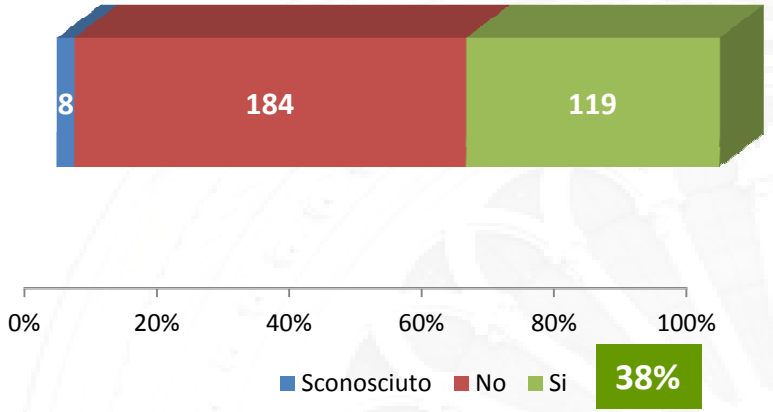
- Depression, pain, and malnutrition
  - Formal Palliative Medicine Service evaluation when appropriate (See NCCN Guidelines for Supportive Care)
  - Nutritional evaluation when appropriate.

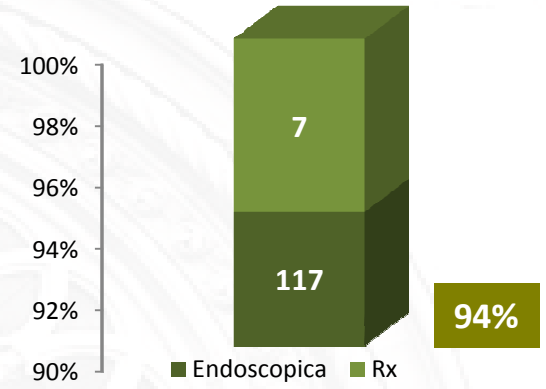
- Pancreatic insufficiency (inadequate production of digestive enzymes)
  - Pancreatic enzyme replacement

- Thrombembolic disease
  - Low-molecular-weight heparin preferred over warfarin

[1]Placement of an enteral stent is particularly important for patients with poor performance status and should be done after biliary drainage is assured.
[2]Palliative surgical procedures are best reserved for patients with a longer life expectancy.

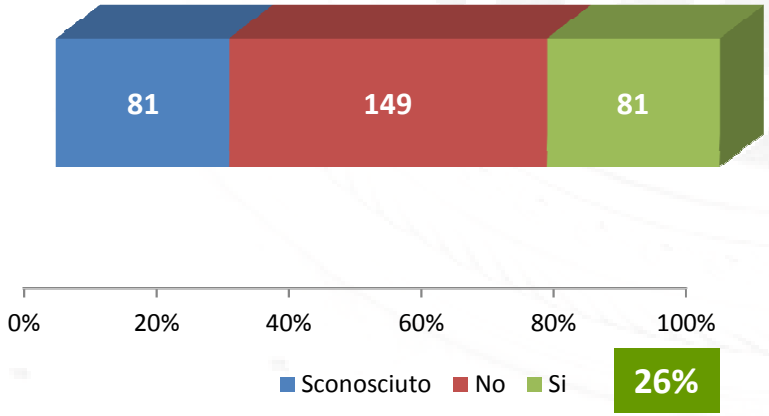
Ittero

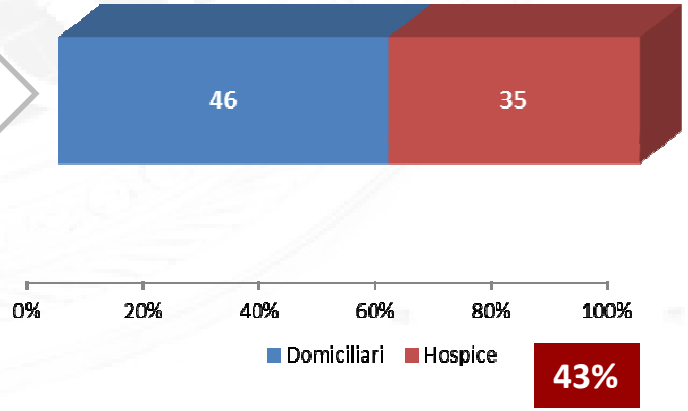




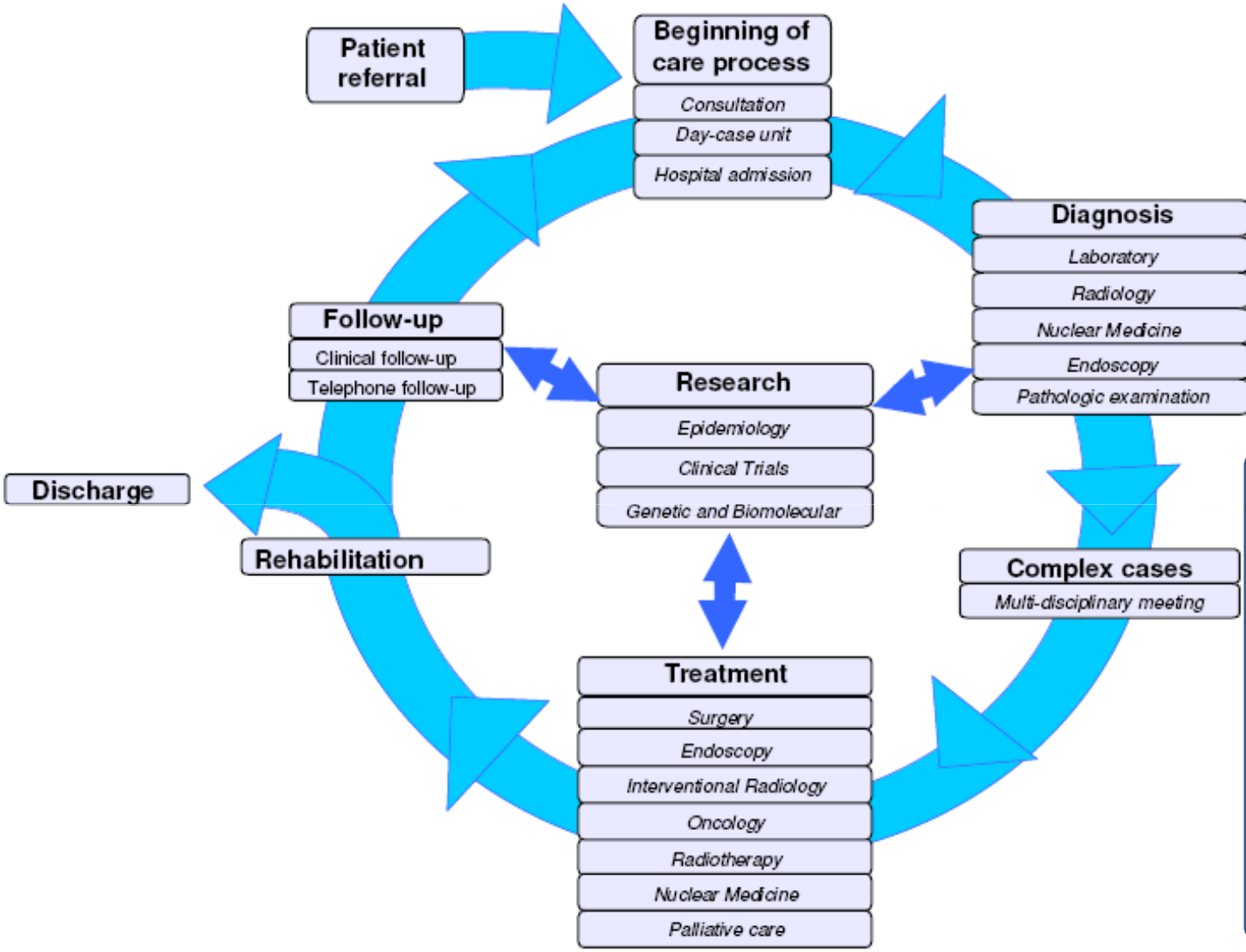
- ✓ Fra i pazienti con diagnosi di PNET, la palliazione dell'ittero è stata eseguita solo in 1 caso (NECG3 della testa del pancreas).
- ✓ Per nessun paziente con PNET è stato attivato il percorso delle cure palliative.

Cure palliative

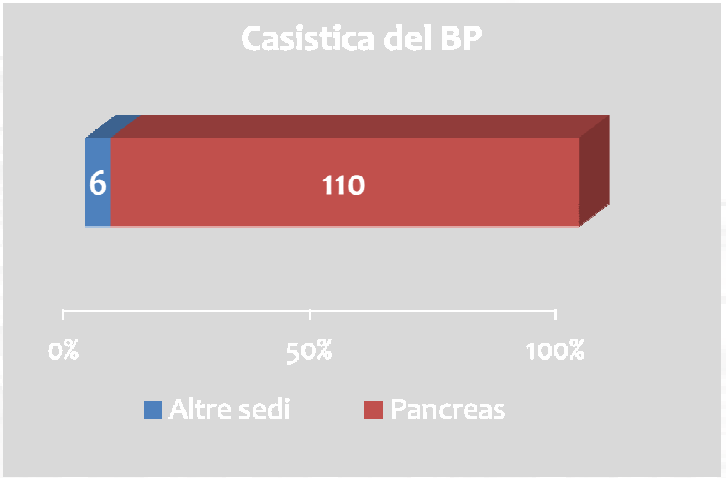




I tumori del pancreas: un circolo complesso!!!!!!!!



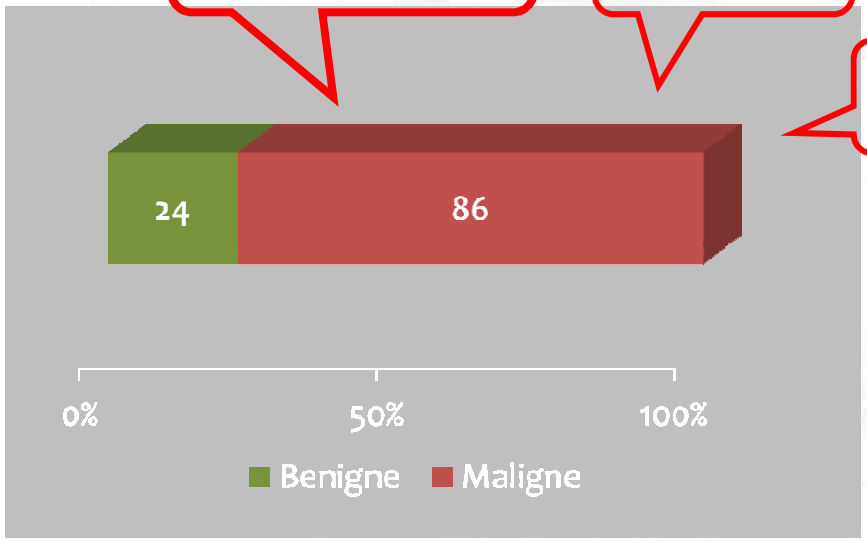
2011-2012

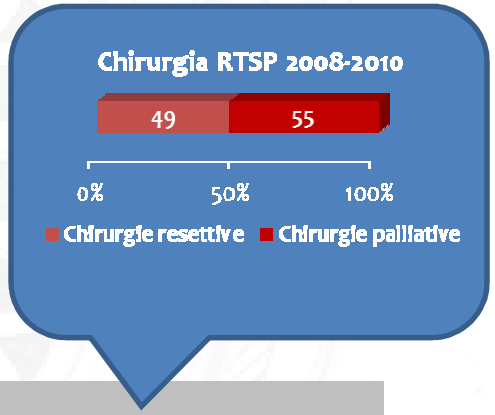


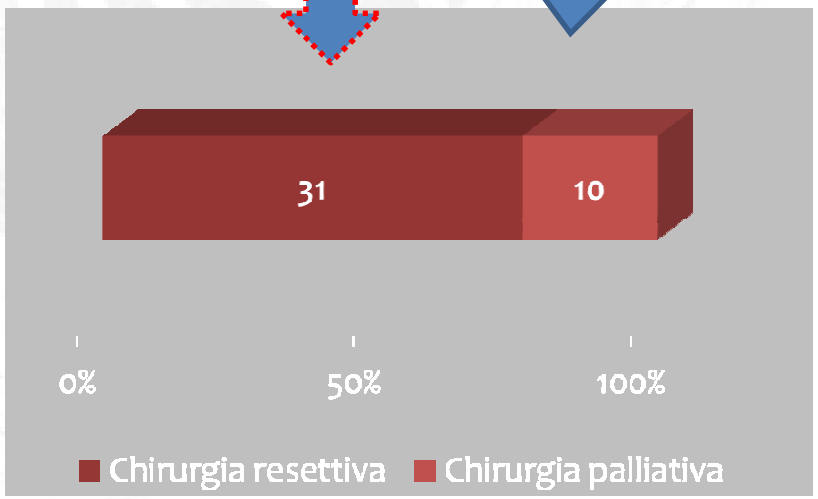
Terapia del dolore: 20%

Non operati: 52,3%

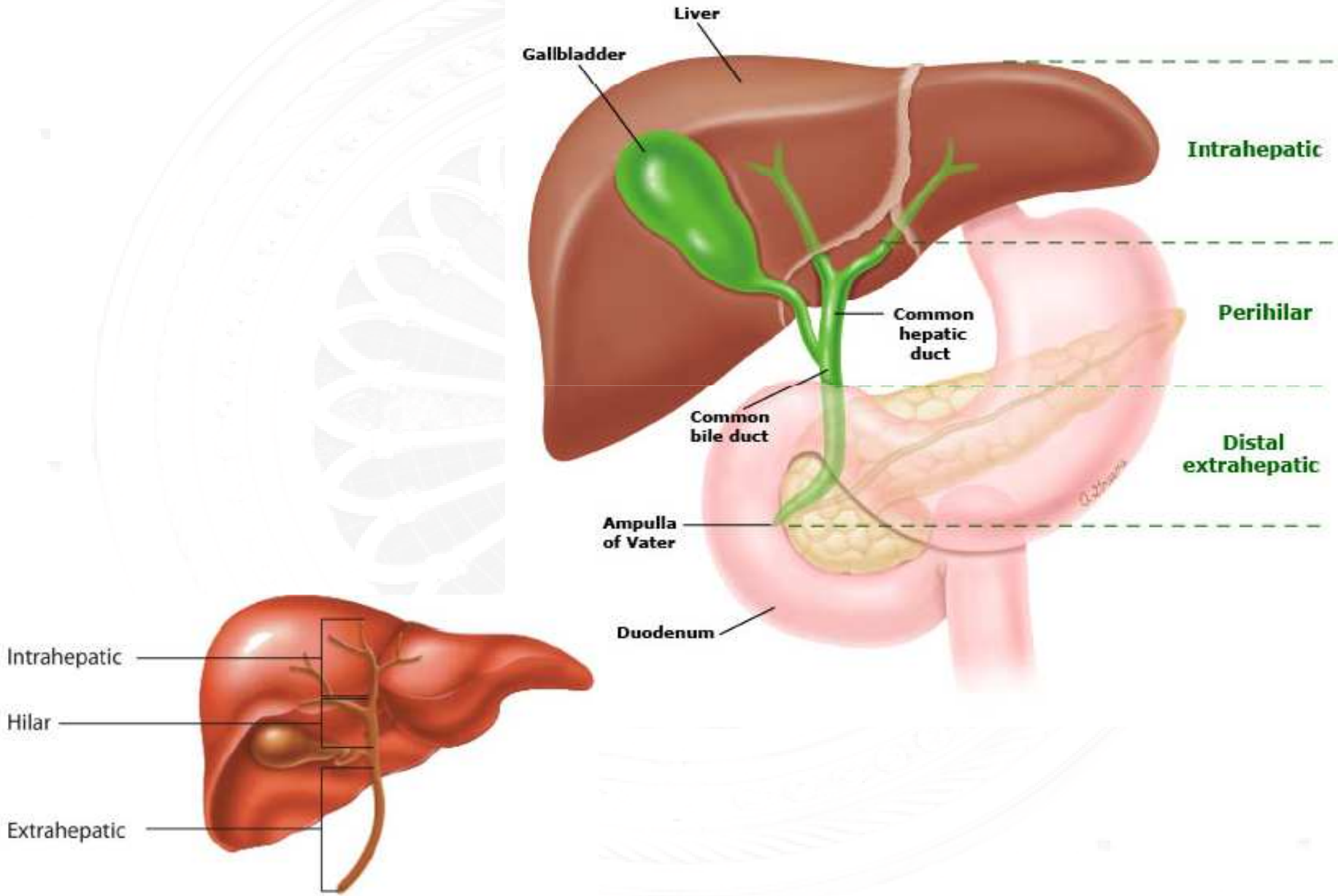
Operati: 47,7%

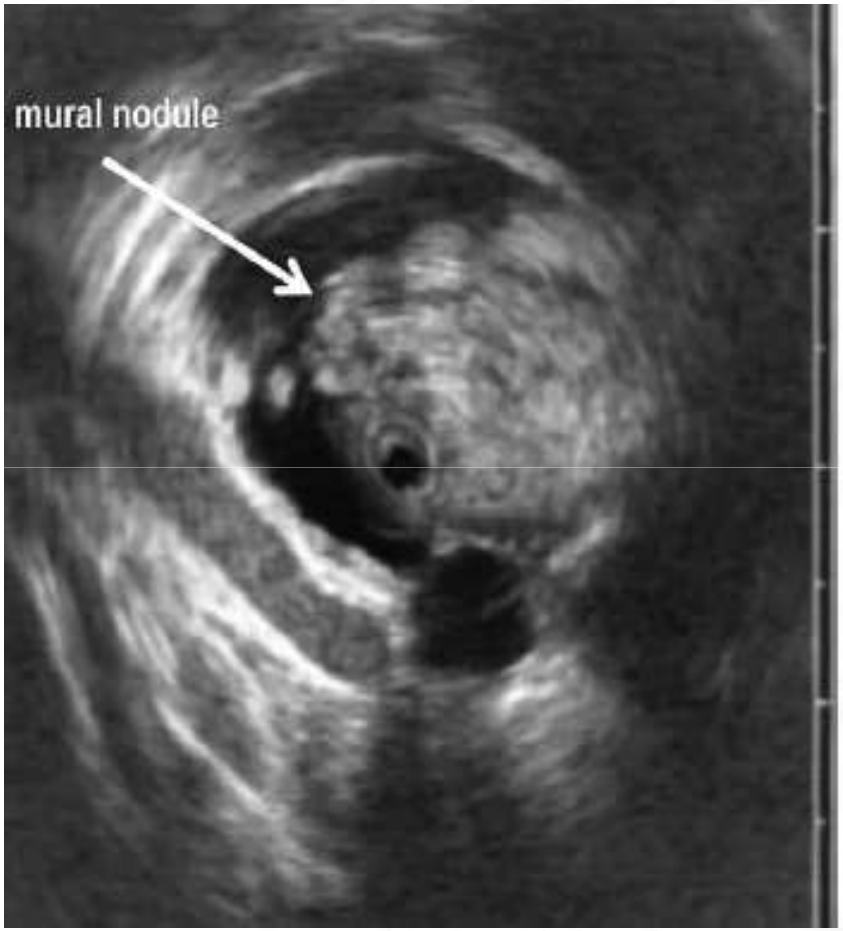


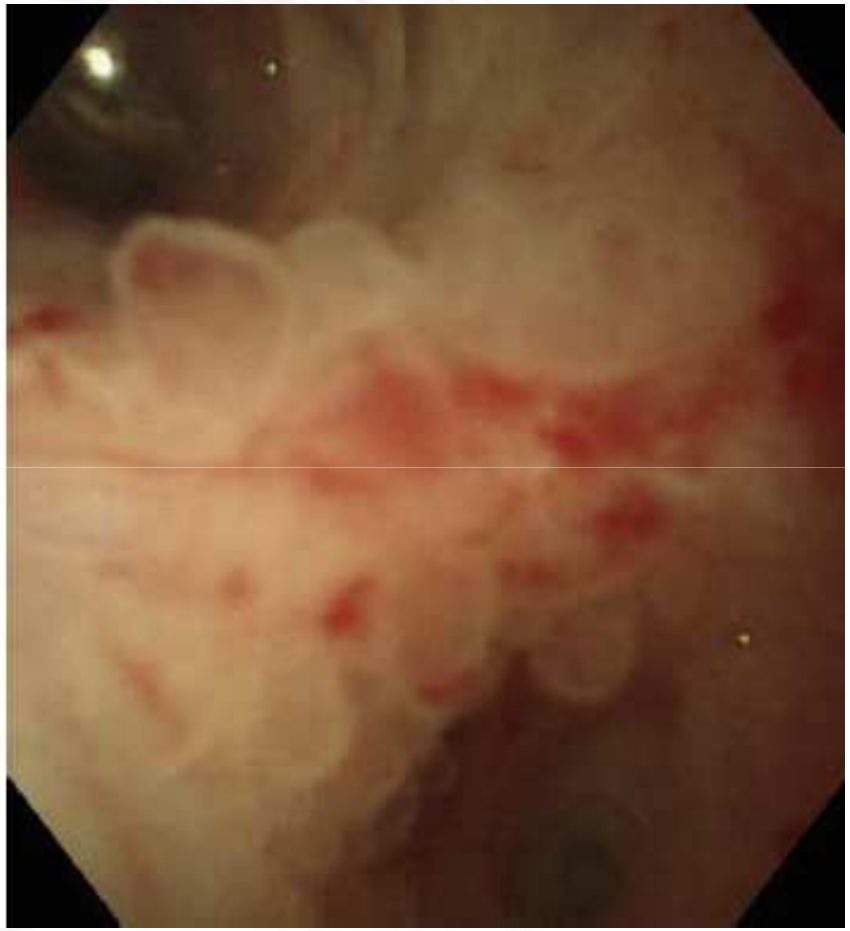




Anatomic classification of cancers of the human biliary tract




mural nodule



Seminar

Cholangiocarcinoma

Nataliya Razumilava, Gregory J Gores

Lancet 2014; 383: 2168-79

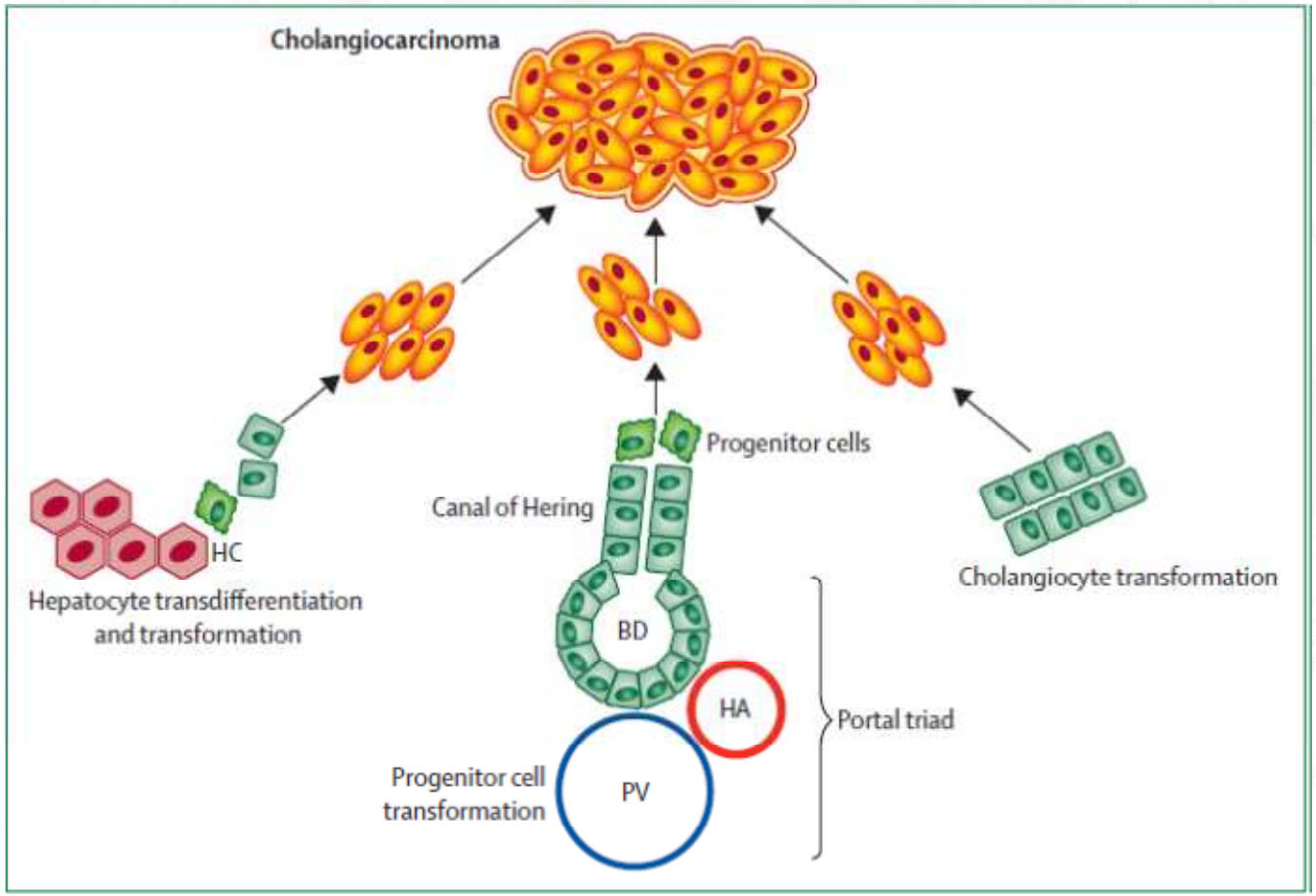


Figure 2: **Potential cells of origin in intrahepatic cholangiocarcinoma**
PV=portal vein. HA=hepatic artery. BD=bile duct. HC=hepatic cell.

SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Unità Sanitaria Locale di Reggio Emilia

SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Ospedaliera di Reggio Emilia
Arcispedale S. Maria Nuova

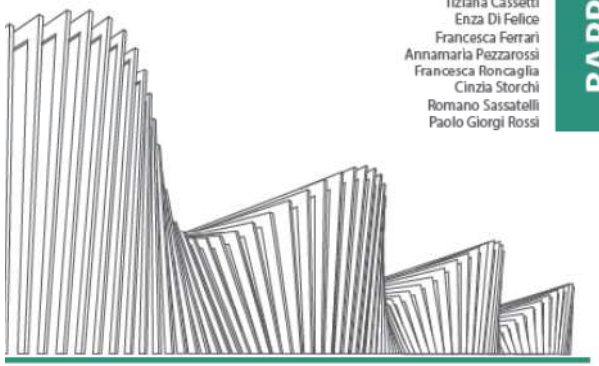
REGISTRO TUMORI REGGIANO

I TUMORI IN PROVINCIA DI REGGIO EMILIA

ANNI 2009-2010

RAPPORTO 2014

Lucia Mangone
Massimo Vicentini
Simonetta Piana
Stefania Caroli
Tiziana Cassetti
Enza Di Felice
Francesca Ferrari
Annamaria Pezzarossi
Francesca Roncaglia
Cinzia Storchi
Romano Sassatelli
Paolo Giorgi Rossi



LILT

Tabella 1. Sintesi dei risultati.
Anni 2009-2010.

	INCIDENZA			MORTALITÀ		
	M+F	M	F	M+F	M	F
Numero casi	63	33	30	49	22	27
Percentuale sul totale	1	1	1	1,7	1,4	2,1
Tasso grezzo[1]	6	6,4	5,6	4,6	4,2	5
Tasso standardizzato[1] (pop. europea)	3,3	4	2,8	2,3	2,4	2,4
Rischio cumulativo 0-74 anni (%)	0,2	0,3	0,2	0,1	0,1	0,1

[1] per 100.000 abitanti

Tabella 2. Cambiamento percentuale annuo (APC) del tasso standardizzato (pop. europea). *Anni 1996-2010*

◆▶ Trend stabile ▲ Trend in aumento - APC significativamente>0 ▼ Trend in diminuzione - APC significativamente<0

	INCIDENZA		MORTALITÀ	
	M	F	M	F
1.	◆▶ +1,67% (1996-2010)	◆▶ -3,16% (1996-2010)	◆▶ -0,63% (1996-2010)	◆▶ -3,59% (1996-2010)

Figura 1. Tassi di incidenza per età in provincia di Reggio Emilia e confronti nazionali. *Anni 2006-2010.*

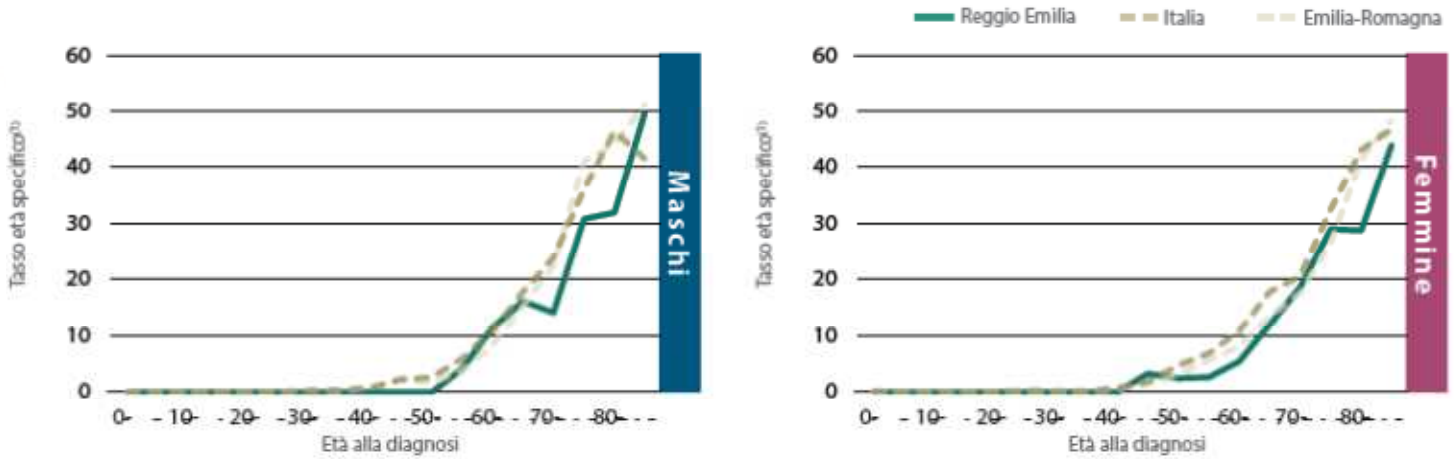


Figura 2. Tassi standardizzati in provincia di Reggio Emilia e confronti nazionali. *Anni 2006-2010.*

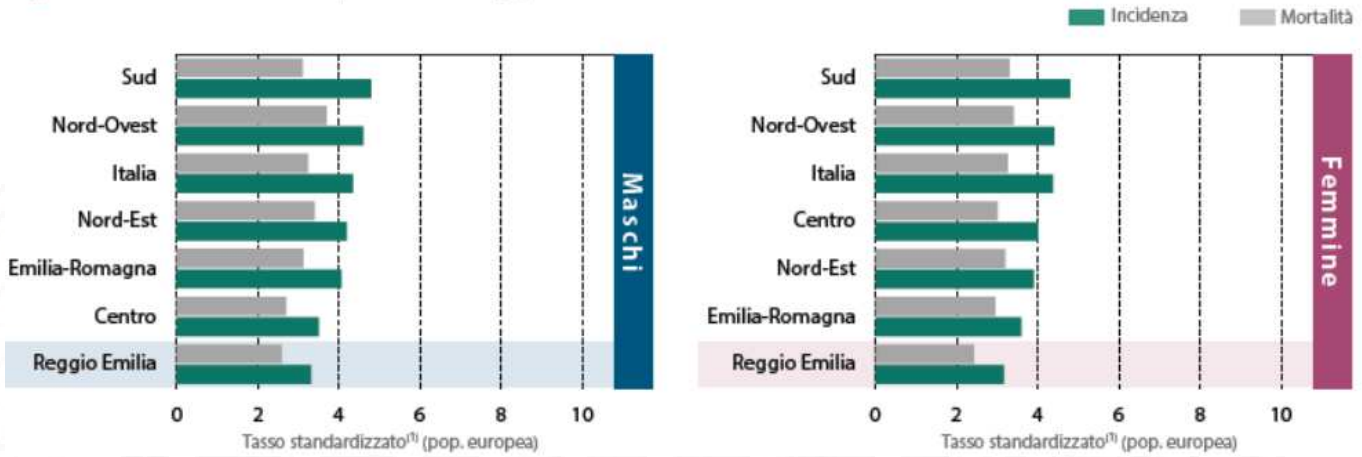


Figura 3. Andamento temporale dei tassi standardizzati per anno. *Anni 1996-2010.*

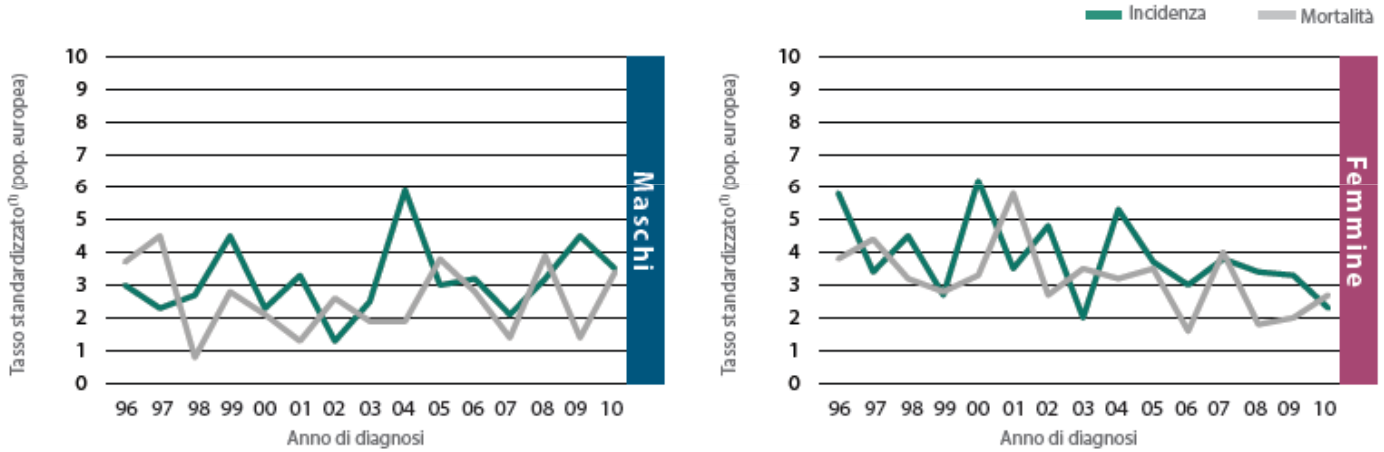


Tabella 3. Distribuzione dei casi per modalità di diagnosi e sesso. *Anni 2006-2010*

	M+F		M		F	
Modalità di diagnosi	N	%	N	%	N	%
Istologica	82	54,7	33	51,6	49	57
Citologica	3	2	0	0	3	3,5
Clinica	65	43,3	31	48,4	34	39,5
Altro	0	0	0	0	0	0
Certificato di decesso	0	0	0	0	0	0

Tabella 4. Distribuzione dei casi per gruppo morfologico e sesso. *Anni 2006-2010*

	M+F		M		F	
Gruppo morfologico	N	%	N	%	N	%
Colangiocarcinoma	75	88,2	31	93,9	44	84,6
Carcinoma NAS	5	5,9	2	6,1	3	5,8
Altre morfologie	3	3,5	0	0	3	5,8
Non specificato	2	2,4	0	0	2	3,8

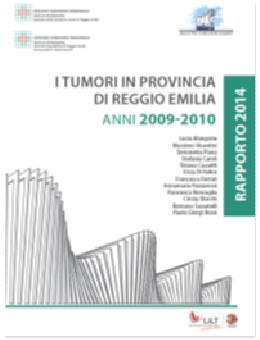


Figura 4. Sopravvivenza relativa cumulata (standardizzata per età) per periodo di diagnosi. *Anni 1996-2010.*

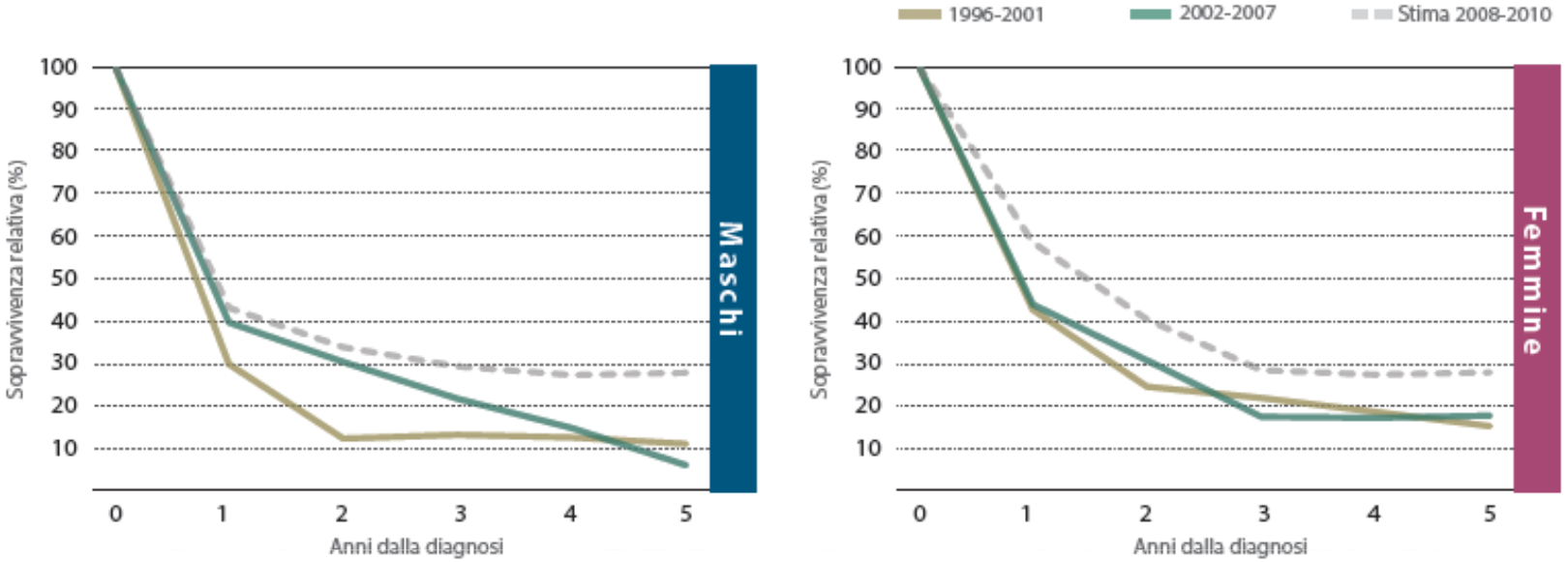
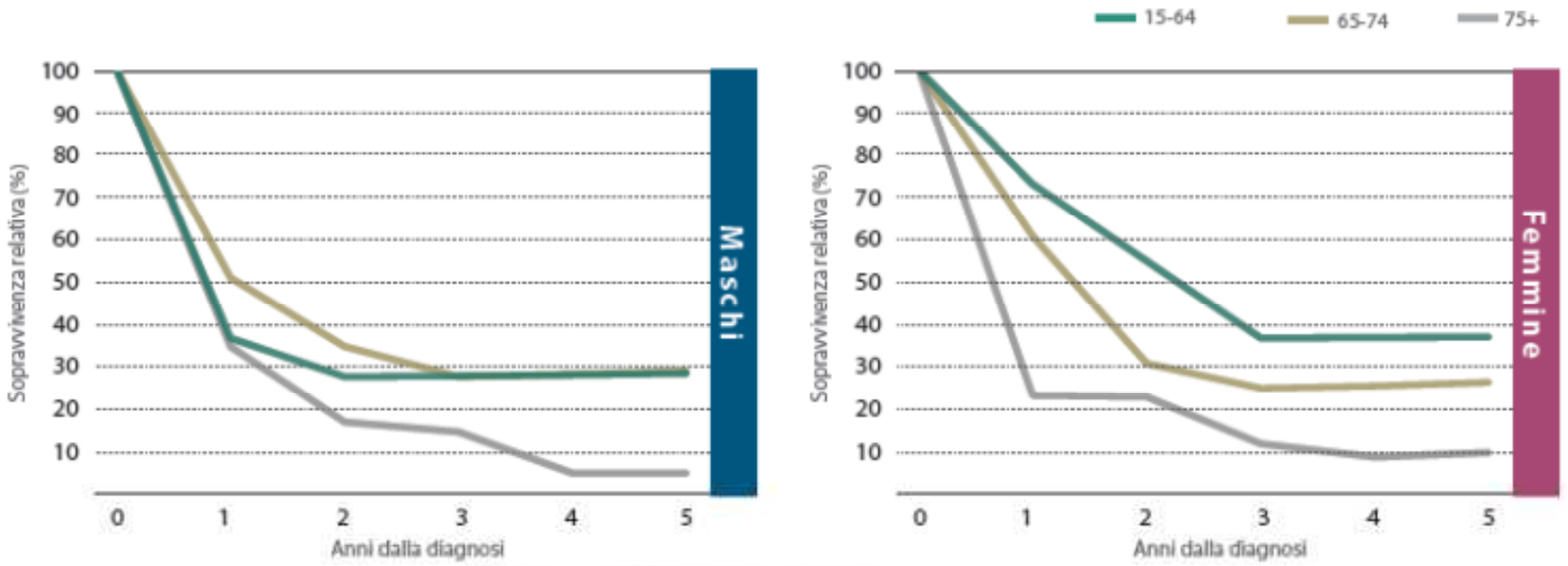
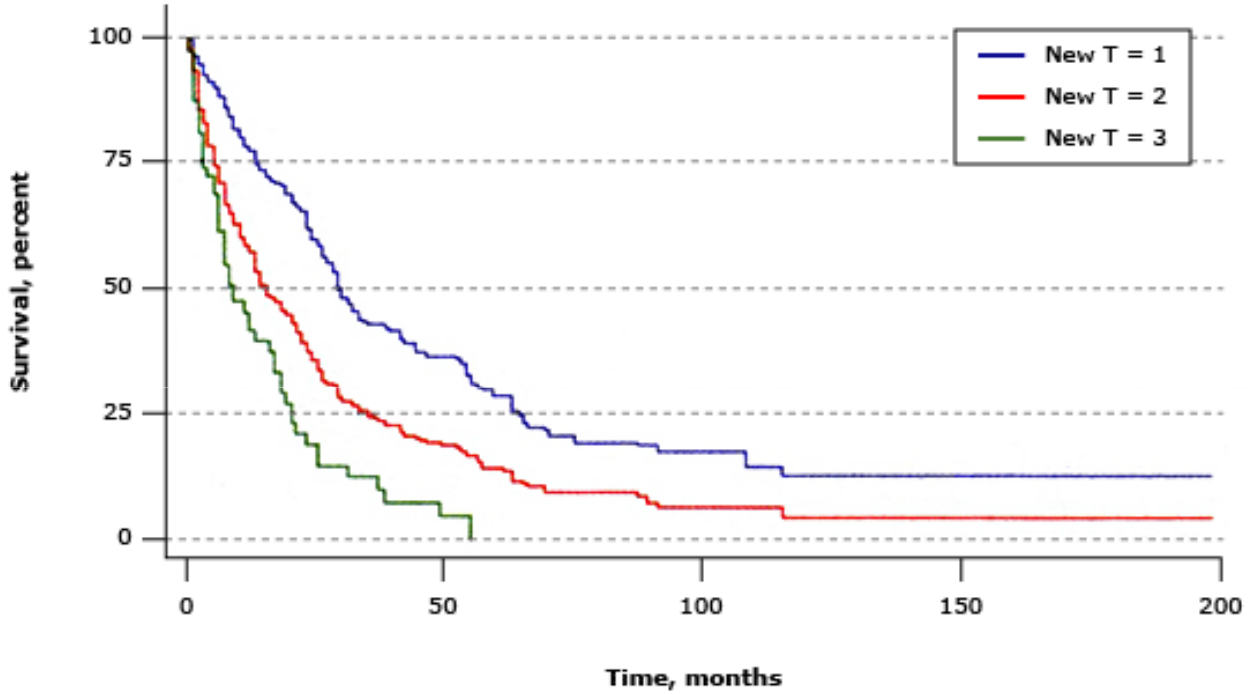


Figura 5. Sopravvivenza relativa cumulata per fascia di età. *Anni 2006-2010.*



Stratification of survival for 647 patients with confirmed intrahepatic cholangiocarcinoma based on new T category classification using Surveillance, Epidemiology and End Results (SEER) registry data



T1: solitary tumor without vascular invasion;
T2: solitary tumor with vascular invasion or multiple tumors;
T3: tumor perforating the visceral peritoneum or involving the local extra hepatic structures by direct invasion.

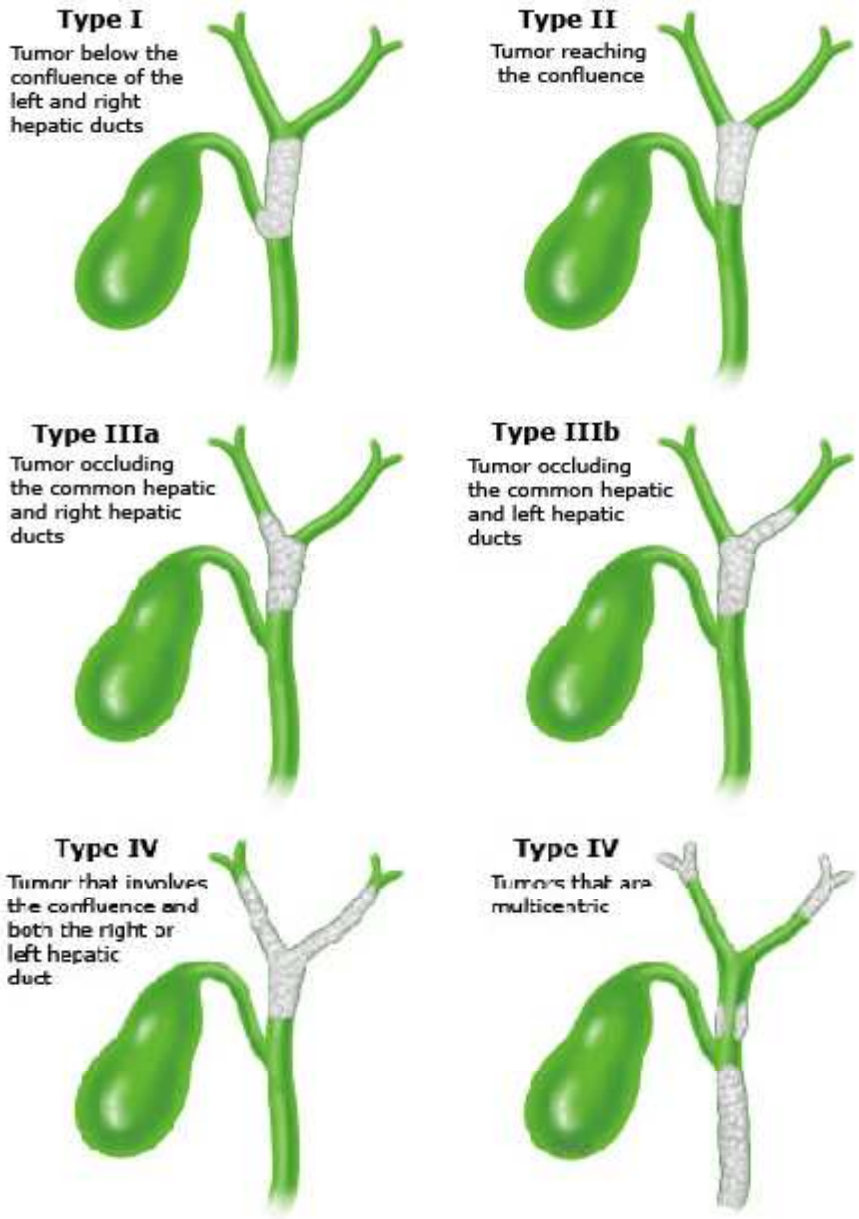
AJCC Cancer Staging Manual, Seventh Edition (2010)

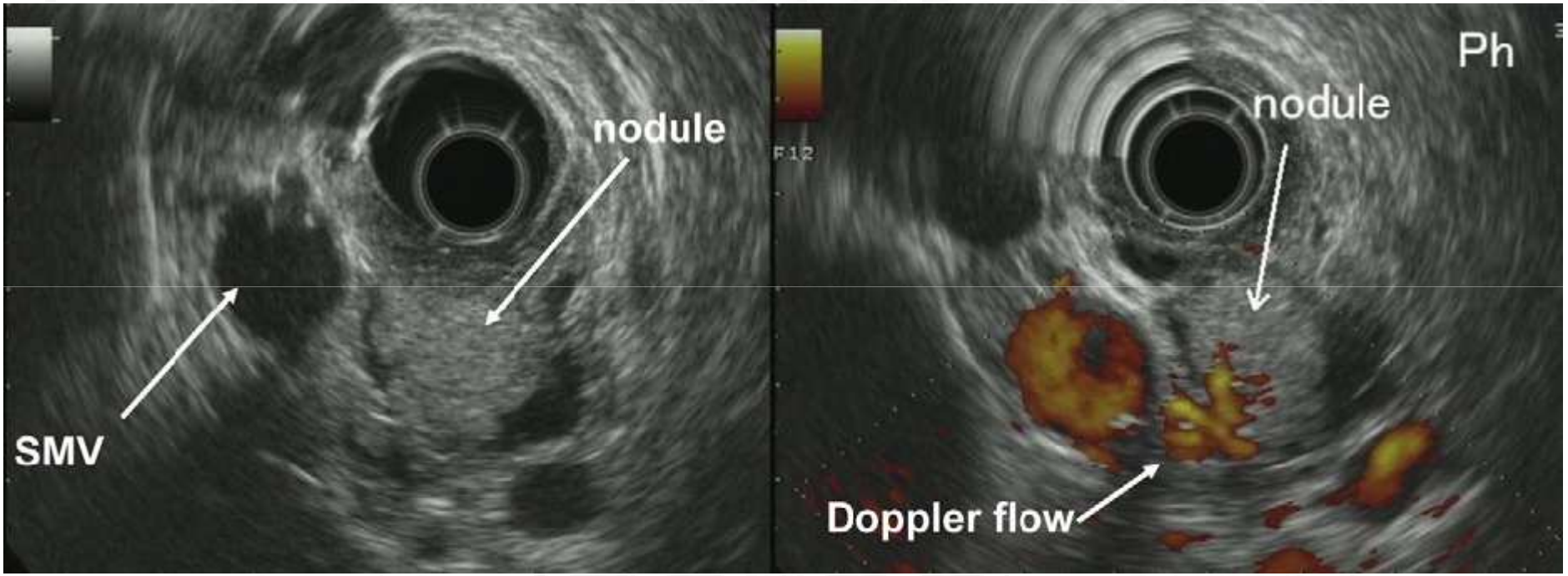
Risk factors for Cholangiocarcinoma (CCA).		
Definitively estabilished risk factors	Intrahepatic	Extrahepatic
Liver flukes (*Clonorchis Sinensis, Opisthorchis viverrinii*)		
Primary Sclerosing Colangitis		
Choledochal cysts		
Toxins (Thorotrast, dioxins)		
Pancreaticobiliary maljunction with bile duct dilatation		X
Hepatolithiasis	X	
Hepatitis C virus infection	X	
Probable risk factors	**Intrahepatic**	**Extrahepatic**
Diabetes, Obesity, Alcohol, Tobacco Smoking		
Genetic Polymorphisms		
Caroli's Disease		
Inflammatory bowel disease		
Cholangitis and choledocolitiasis		
Surgical biliary-enteric drainage		
Cholecystectomy		X
Cholelithiasis		X
Hepatic Schistosomiasis	X	
Liver cirrhosis	X	
Hepatitis B virus infection	X	

X=risk factors exclusive for intrahepatic-CCA or extrahepatic-CCA ; others factors are common for both CCA types

Transl Gastrointest Cancer 2012;1:21-32.

Bismuth-Corlette classification of biliary tract cancers




nodule
SMV
Ph
nodule
Doppler flow

TNM staging for intrahepatic cholangiocarcinomas

Primary tumor (T)			
TX	Primary tumor cannot be assessed		
T0	No evidence of primary tumor		
Tis	Carcinoma in situ (intraductal tumor)		
T1	Solitary tumor without vascular invasion		
T2a	Solitary tumor with vascular invasion		
T2b	Multiple tumors, with or without vascular invasion		
T3	Tumor perforating the visceral peritoneum or involving the local extra hepatic structures by direct invasion		
T4	Tumor with periductal invasion*		
Regional lymph nodes (N)			
NX	Regional lymph nodes cannot be assessed		
N0	No regional lymph node metastasis		
N1	Regional lymph node metastasis present		
Distant metastasis (M)			
M0	No distant metastasis		
M1	Distant metastasis present		
Anatomic stage/prognostic groups			
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
Stage IVA	T4	N0	M0
	Any T	N1	M0
Stage IVB	Any T	Any N	M1

* The pathologic definition of periductal invasion is the finding of a longitudinal growth pattern along the intrahepatic bile ducts on both gross and microscopic examination.

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TNM staging system for perihilar cholangiocarcinoma

Primary tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor confined to the bile duct, with extension up to the muscle layer or fibrous tissue
T2a	Tumor invades beyond the wall of the bile duct to surrounding adipose tissue
T2b	Tumor invades adjacent hepatic parenchyma
T3	Tumor invades unilateral branches of the portal vein or hepatic artery
T4	Tumor invades main portal vein or its branches bilaterally; or the common hepatic artery; or the second-order biliary radicals bilaterally; or unilateral second-order biliary radicals with contralateral portal vein or hepatic artery involvement
Regional lymph nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis (including nodes along the cystic duct, common bile duct, hepatic artery, and portal vein)
N2	Metastasis to periaortic, pericaval, superior mesenteric artery, and/or celiac artery lymph nodes
Distant metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis

Anatomic stage/prognostic groups			
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2a-b	N0	M0
Stage IIIA	T3	N0	M0
Stage IIIB	T1-3	N1	M0
Stage IVA	T4	N0-1	M0
Stage IVB	Any T	N2	M0
	Any T	Any N	M1

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TNM staging system for distal cholangiocarcinoma

Primary tumor (T)			
TX	Primary tumor cannot be assessed		
T0	No evidence of primary tumor		
Tis	Carcinoma in situ		
T1	Tumor confined to the bile duct histologically		
T2	Tumor invades beyond the wall of the bile duct		
T3	Tumor invades the gallbladder, pancreas, duodenum, or other adjacent organs without involvement of the celiac axis, or the superior mesenteric artery		
T4	Tumor involves the celiac axis, or the superior mesenteric artery		
Regional lymph nodes (N)			
NX	Regional lymph nodes cannot be assessed		
N0	No regional lymph node metastasis		
N1	Regional lymph node metastasis		
Distant metastasis (M)			
M0	No distant metastasis		
M1	Distant metastasis		
Anatomic stage/prognostic groups			
Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
Stage IIA	T3	N0	M0
	T1	N1	M0
Stage IIB	T2	N1	M0
	T3	N1	M0
Stage III	T4	Any N	M0
Stage IV	Any T	Any N	M1

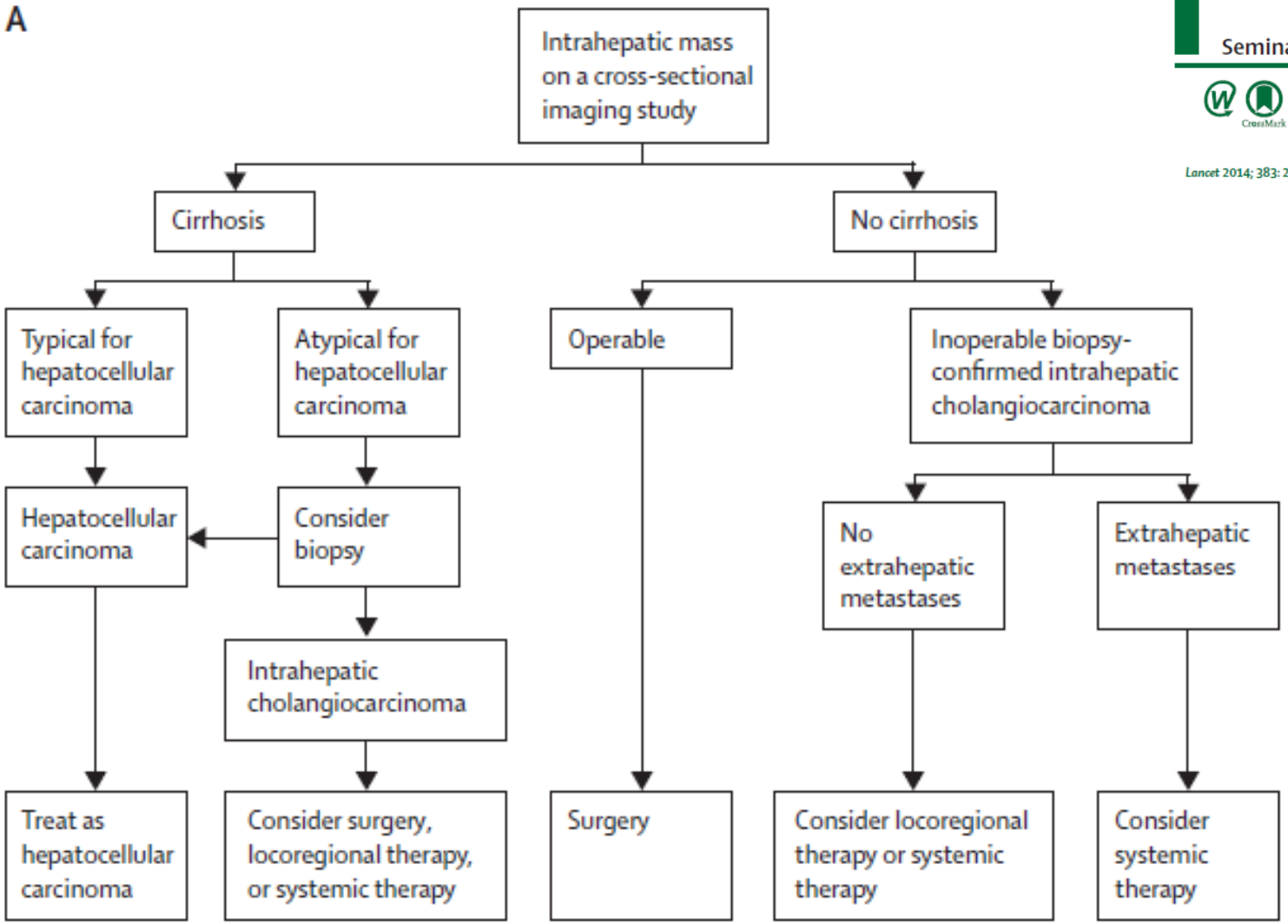
AJCC Cancer Staging Manual, Seventh Edition (2010)

Seminar

Cholangiocarcinoma

Nataliya Razumilava, Gregory J Gores

Lancet 2014; 383: 2168–79



Approach to management of Intrahepatic CC

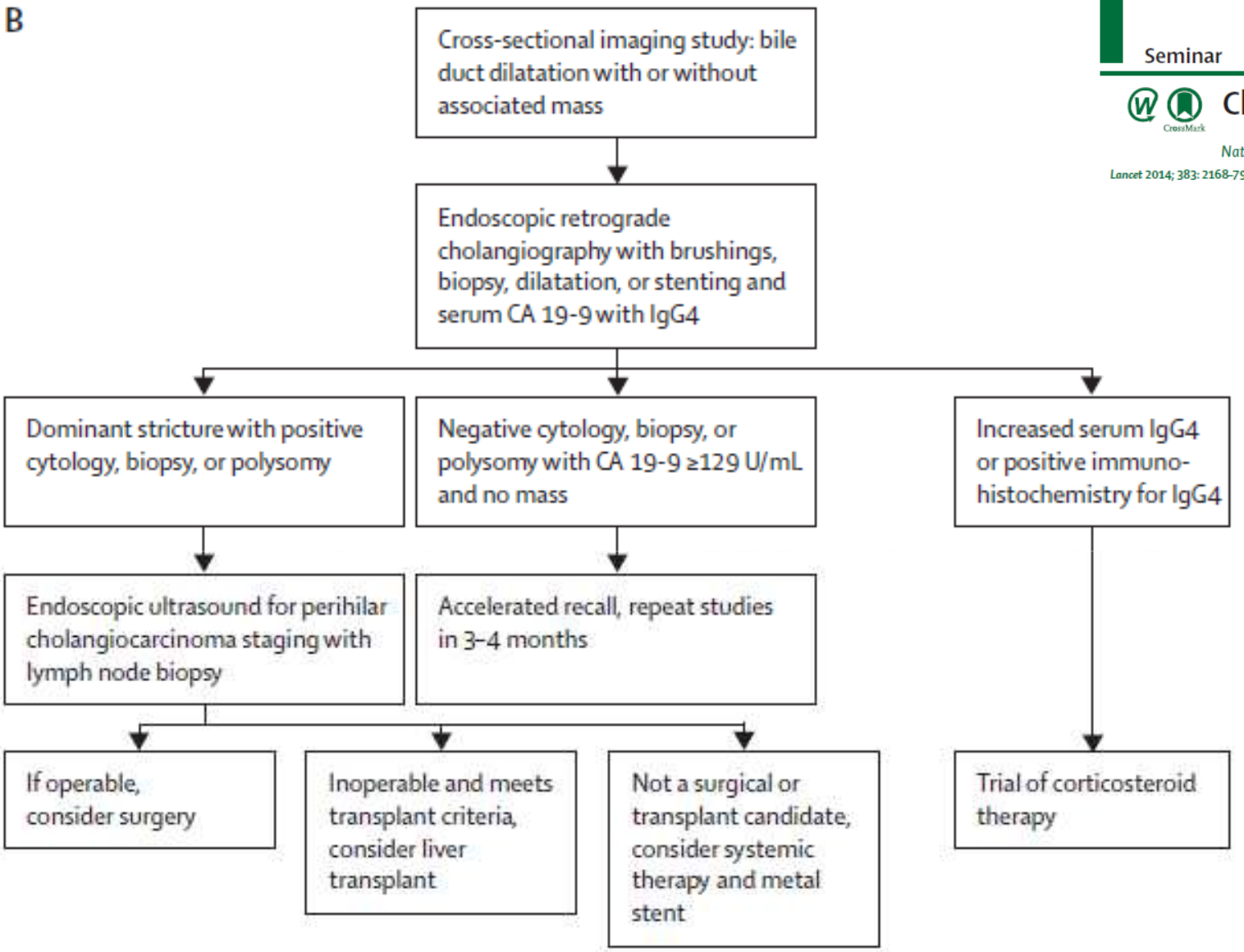
HCC: hepatocellular carcinoma
Ca19.9: carbohydrate antigen 19.9

Seminar

Cholangiocarcinoma

Nataliya Razumilava, Gregory J Gores

Lancet 2014; 383: 2168–79



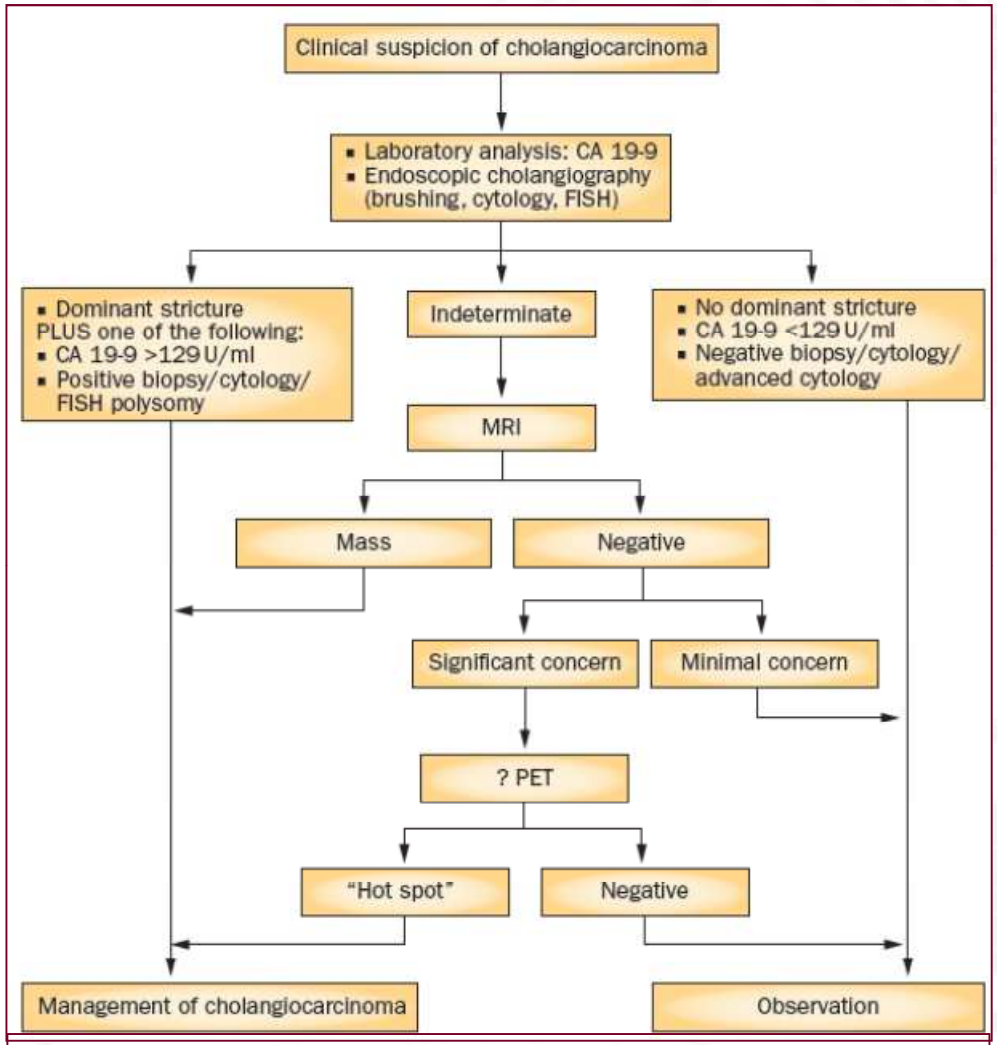
Approach to management of perihilar cholangiocarcinoma

HCC: hepatocellular carcinoma
Ca19.9: carbohydrate antigen 19.9

REVIEWS

Clinical diagnosis and staging of cholangiocarcinoma

Blechacz, B. *et al. Nat. Rev. Gastroenterol. Hepatol.* 8, 512–522 (2011); published online 2 August 2011



Diagnosti criteria for perihilar and distal extrahepatic cholangiocarcinoma

Box 2 | Histologic type of cholangiocarcinomas

- Adenocarcinoma
- Clear cell adenocarcinoma
- Mucinous carcinoma
- Signet ring cell carcinoma
- Squamous cell carcinoma
- Adenosquamous carcinoma
- Small cell carcinoma
  - Undifferentiated carcinoma
  - Spindle and giant cell types
- Small cell types
- Papillomatosis
- Papillary carcinoma, noninvasive
- Papillary carcinoma, invase
- Carcinoma

NCCN Guidelines Version 2.2014
Intrahepatic Cholangiocarcinoma

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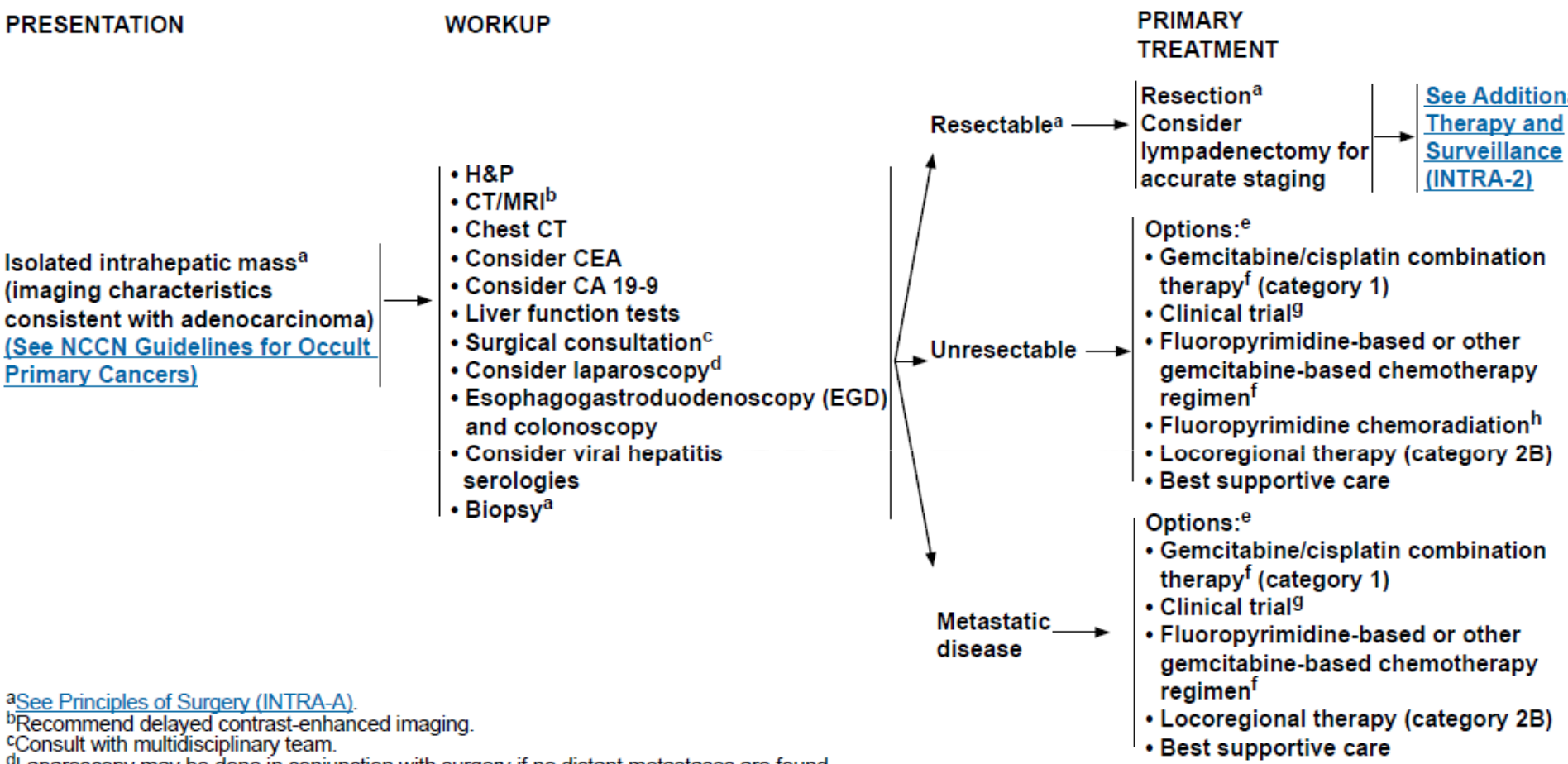

[a] See Principles of Surgery (INTRA-A).
[b] Recommend delayed contrast-enhanced imaging.
[c] Consult with multidisciplinary team.
[d] Laparoscopy may be done in conjunction with surgery if no distant metastases are found.
[e] Order does not indicate preference. The choice of treatment modality may depend on extent/location of disease and institutional capabilites.
[f] A phase III trial supporting gemcitabine/cisplatin has been reported for patients with advanced or metastatic billiary tract cancer. (Valle JW, Wasan HS, Palmer DD, et al. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. N Eng J Med 2010;362:1273-1281.) Clinical trial participation is encouraged. There are phase II trials that support the following combinations: gemcitabine/oxaliplatin, gemcitabine/capecitabine, capecitabine/cisplatin, capecitabine/oxaliplatin, 5-fluorouracil/oxaliplatin, 5-fluorouracil/cisplatin, and the single agents gemcitabine, capecitabine, and 5-fluorouracil in the unresectable or metastatic setting. (Hezel AF and Zhu AX. Systemic therapy for biliary tract cancers. The Oncologist 2008;13:415-423).
[g] Systemic or intra-arterial chemotherapy may be used in a clinical trial or at experienced centers.
[h] There are limited clinical trial data to define a standard regimen or definitive benefit. Participation in clinical trials is encouraged. (Macdonald OK, Crane CH. Palliative and postoperative radiotherapy in biliary tract cancer. Surg Oncol Clin N Am 2002;11:941-954)

NCCN Guidelines Version 2.2014
Intrahepatic Cholangiocarcinoma

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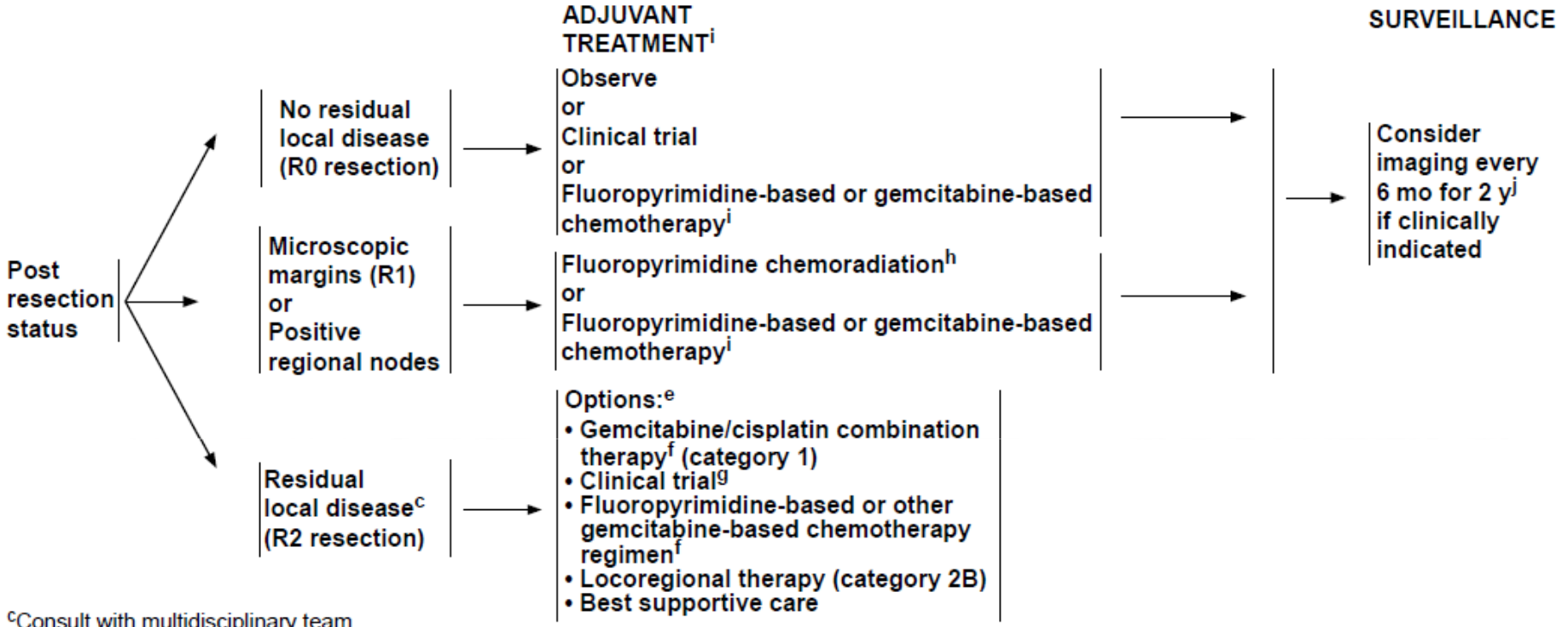
Discussion



[c]Consult with multidisciplinary team.
[e]Order does not indicate preference. The choice of treatment modality may depend on extent/location of disease and institutional capabilites.
[f]A phase III trial supporting gemcitabine/cisplatin has been reported for patients with advanced or metastatic billiary tract cancer. (Valle JW, Wasan HS, Palmer DD, et al. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. N Eng J Med 2010;362:1273-1281.) Clinical trial participation is encouraged. There are phase II trials that support the following combinations: gemcitabine/oxaliplatin, gemcitabine/capecitabine, capecitabine/cisplatin, capecitabine/oxaliplatin, 5-fluorouracil/oxaliplatin, 5-fluorouracil/cisplatin, and the single agents gemcitabine, capecitabine, and 5-fluorouracil in the unresectable or metastatic setting. Hezel AF and Zhu AX. Systemic therapy for biliary tract cancers. The Oncologist 2008;13:415-423).
[g]Systemic or intra-arterial chemotherapy may be used in a clinical trial or at experienced centers.
[h]There are limited clinical trial data to define a standard regimen or definitive benefit. Participation in clinical trials is encouraged. (Macdonald OK, Crane CH. Palliative and postoperative radiotherapy in biliary tract cancer. Surg Oncol Clin N Am 2002;11:941-954)
[i]Adjuvant chemotherapy or chemoradiation has been associated with survival benefit, in patients with biliary tract cancers, especially in patients with lymph node-positive disease. (Horgan AM, Amir E, Walter T, Knox JJ. Adjuvant Therapy of Biliary Tract Cancer: A Systemic Review and Meta-Analysis. J Clin Oncol 2012;30:1934-1940). However, this meta-analysis included only a few patients with intrahepatic cholangiocarcinoma. There are no randomized phase III clinical trial data to support a standard adjuvant regimen. Clinical trial participation is encouraged. There are phase II trials that support the following combinations: gemcitabine/cisplatin, gemcitabine/oxaliplatin, gemcitabine/capecitabine, capecitabine/cisplatin, capecitabine/ oxaliplatin, 5-fluorouracil/oxaliplatin, 5-fluorouracil/cisplatin and the single agents gemcitabine, capecitabine, and 5-fluorouracil in the unresectable or metastatic setting. (Hezel AF and Zhu AX. Systemic therapy for biliary tract cancers. The Oncologist 2008;13:415-423).
[j]There are no data to support aggressive surveillance. There should be a patient/physician discussion regarding appropriate follow-up schedules/imaging.

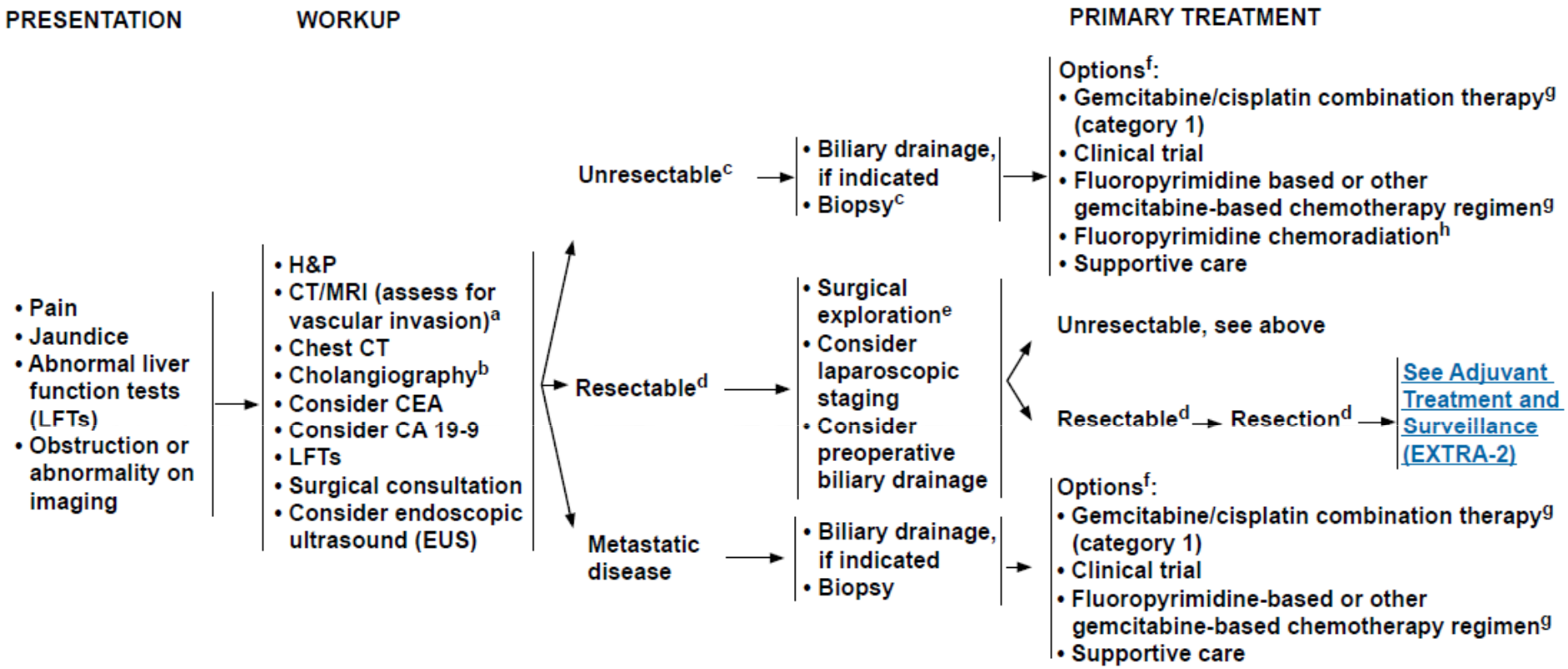
PRINCIPLES OF SURGERY[1,2]

- **A preoperative biopsy is not always necessary before proceeding with a definitive, potentially curative resection. A suspicious mass on imaging in the proper clinical setting should be treated as malignant.**
- **Diagnostic laparoscopy to rule out unresectable disseminated disease should be considered**
- **Initial exploration should assess for multifocal hepatic disease, lymph node metastases, and distant metastases. Lymph node metastases beyond the porta hepatis and distant metastatic disease contraindicate resection.**
- **Hepatic resection with negative margins is the goal of surgical therapy. While major resections are often necessary, wedge resections and segmental resections are all appropriate given that a negative margin can be achieved.**
- **A portal lymphadenectomy is reasonable as this provides relevant staging information.**
- **Multifocal liver disease is generally representative of metastatic disease and is a contraindication to resection. In highly selected cases with limited multifocal disease resection can be considered.**
- **Gross lymph node metastases to the porta hepatis portend a poor prognosis and resection should only be considered in highly selected cases.**

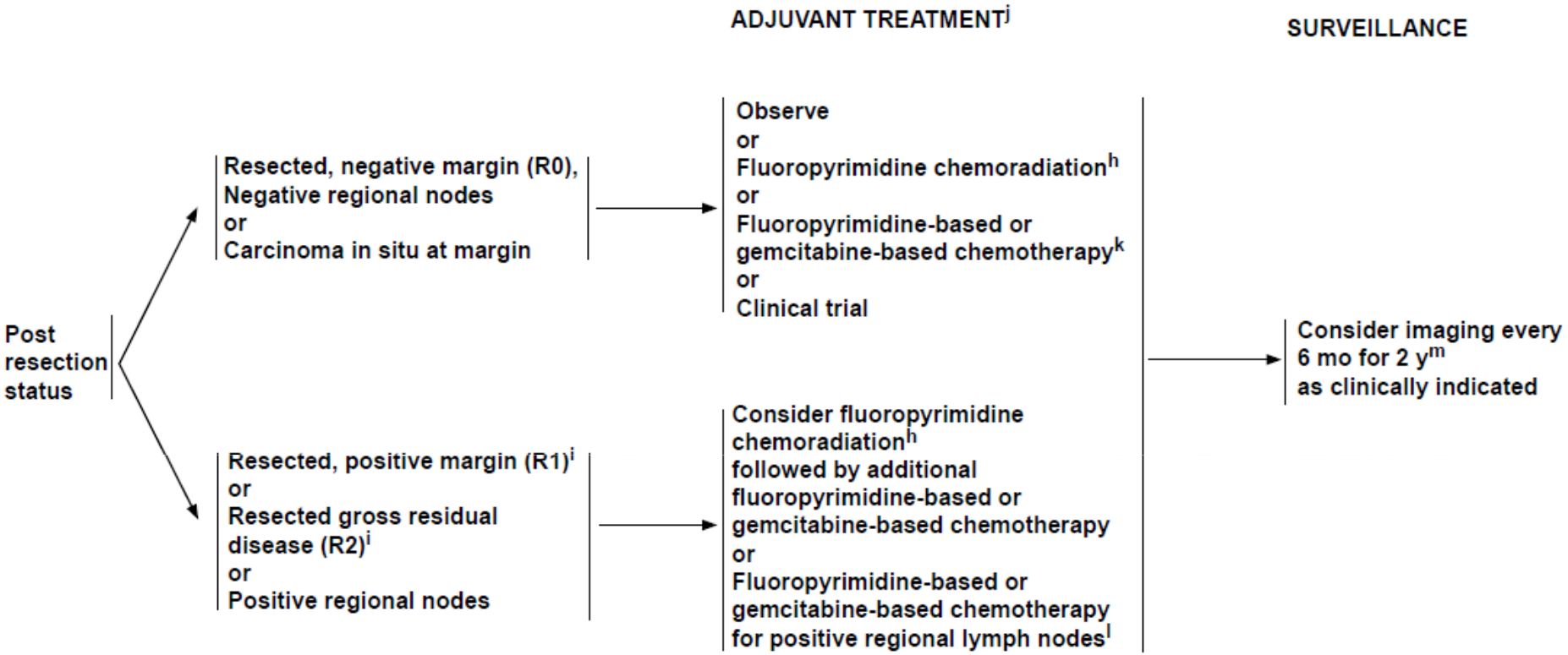
[1]Endo I, Gonen M, Yopp A. Intraheptic cholangiocarcinoma: rising frequency, improved survival and determinants of outcome after resection. Ann Surg 2008;248:84-96
[2]de Jong MC, Nathan H, Sotiropoulos GC. Intrahepatic cholangiocarcinoma: an international multi-institutional analysis of prognostic factors. J Clin Oncol 2011;29:3140-3145.

NCCN Guidelines Version 2.2014
Extrahepatic Cholangiocarcinoma

NCCN Guidelines Index
Hepatobiliary Cancers Table of Contents
Discussion



[a]Recommend delayed contrast-enhanced imaging.
[b] Noninvasive cholangiography with cross-sectional imaging.
[c]Before biopsy, evaluate if patient is a surgical or transplant candidate. If patient is a potential transplant candidate, consider referral to transplant center before biopsy.
[d]See Principles of Surgery (EXTRA-A).
[e]Surgery may be performed when index of suspicion is high; biopsy not required.
[f]Order does not indicate preference. The choice of treatment modality may depend on extent/location of disease and institutional capabilites.
[g]A recent phase III trial supporting gemcitabine/cisplatin has been reported for patients with advanced or metastatic biliary tract cancer. (Valle JW, Wasan HS, Palmer DD, et al. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. N Eng J Med 2010;362:1273-1281) Clinical trial participation is encouraged. There are phase II trials that support the following combinations: gemcitabine/oxaliplatin, gemcitabine/capecitabine, capecitabine/cisplatin, capecitabine/oxaliplatin, 5-fluorouracil/oxaliplatin, 5-fluorouracil/cisplatin and the single agents gemcitabine, capecitabine, and 5-fluorouracil in the unresectable or metastatic setting. (Hezel AF and Zhu AX. Systemic therapy for biliary tract cancers. The Oncologist 2008;13:415-423)
[h]There are limited clinical trial data to define a standard regimen or definitive benefit. Clinical trial participation is encouraged. (Macdonald OK, Crane CH. Palliative and postoperative radiotherapy in biliary tract cancer. Surg Oncol Clin N Am 2002; 11:941-954)



[h]There are limited clinical trial data to define a standard regimen or definitive benefit. Clinical trial participation is encouraged. (Macdonald OK, Crane CH. Palliative and postoperative radiotherapy in biliary tract cancer. Surg Oncol Clin N Am 2002;11:941-954).
[i]R1 or R2 resections should be evaluated by a multidisciplinary team.
[j]Adjuvant chemotherapy or chemoradiation has been associated with survival benefit in patients with biliary tract cancers, especially in patients with lymph node-positive disease (Horgan AM, Amir E, Walter T, Knox JJ. Adjuvant Therapy of Biliary Tract Cancer: A Systemic Review and Meta-Analysis. J Clin Oncol 2012;30:1934-1940).
[k]There are limited clinical trial data to define a standard regimen. Clinical trial participation is encouraged.
[l]There are no randomized phase III clinical trial data to support a standard adjuvant regimen. Clinical trial participation is encouraged. There are phase II trials that support the following combinations: gemcitabine/cisplatin, gemcitabine/oxaliplatin, gemcitabine/capecitabine, capecitabine/cisplatin, capecitabine/oxaliplatin, 5-fluorouracil/oxaliplatin, 5-fluorouracil/cisplatin and the single agents gemcitabine, capecitabine, and 5-fluorouracil in the unresectable or metastatic setting. (Hezel AF and Zhu AX. Systemic therapy for biliary tract cancers. The Oncologist 2008;13:415-423).
[m]There are no data to support aggressive surveillance. There should be a patient/physician discussion regarding appropriate follow-up schedules/imaging.

PRINCIPLES OF SURGERY

- The basic principle is a complete resection with negative margins and regional lymphadenectomy. This generally requires a pancreaticoduodenectomy for distal bile duct tumors and a major hepatic resection for hilar tumors. Rarely, a mid bile duct tumor can be resected with a bile duct resection and regional lymphadenectomy.
- Diagnostic laparoscopy should be considered.
- Occasionally a bile duct tumor will involve the biliary tree over a long distance such that a hepatic resection and pancreaticoduodenectomy will be necessary. These are relatively morbid procedures and should only be carried out in very healthy patients without significant comorbidity. Nonetheless, these can be potentially curative procedures and should be considered in the proper clinical setting. Combined liver and pancreatic resections performed to clear distant nodal disease are not recommended.

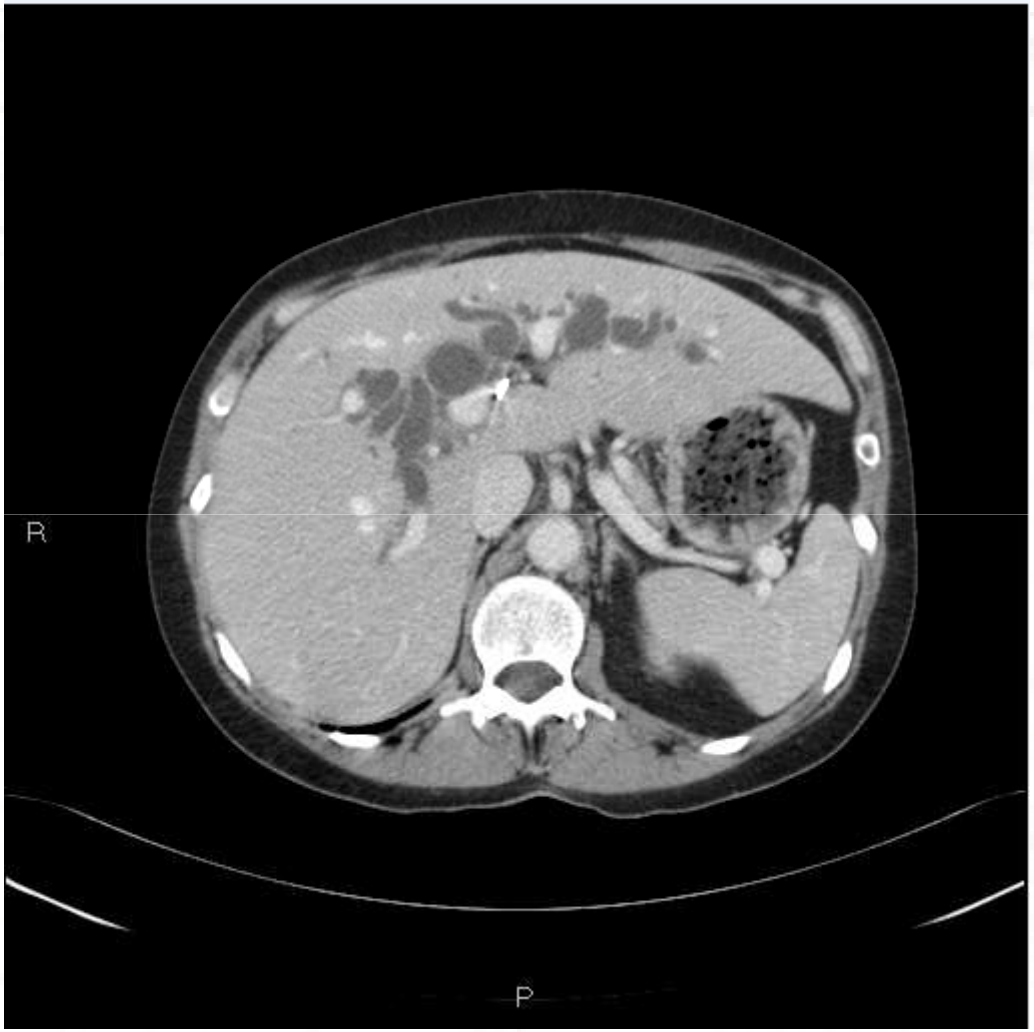
Hilar cholangiocarcinoma

- Detailed descriptions of imaging assessment of resectability are beyond the scope of this outline. The basic principle is that the tumor will need to be resected along with the involved biliary tree and the involved hemi-liver with a reasonable chance of a margin negative resection. The contra-lateral liver requires intact arterial and portal inflow as well as biliary drainage.[1,2,3]
- Detailed descriptions of preoperative surgical planning are beyond the scope of this outline but require an assessment of the future liver remnant (FLR). This requires an assessment of biliary drainage and volumetrics of the FLR. While not necessary in all cases, the use of preoperative biliary drainage of the FLR and contralateral portal vein embolization should be considered in cases of a small future liver remnant.[4,5]
- Initial exploration rules out distant metastatic disease to the liver, peritoneum, or distant lymph nodes beyond the porta hepatis as these findings contraindicate resection. Further exploration must confirm local resectability.
- Since hilar tumors, by definition, abut or invade the central portion of the liver they require major hepatic resections on the involved side to encompass the biliary confluence and generally require a caudate resection.
- Resection and reconstruction of the portal vein and/or hepatic artery may be necessary for complete resection and require expertise in these procedures.
- Biliary reconstruction is generally through a Roux-en-Y hepaticojejunostomy.
- A regional lymphadenectomy of the porta hepatis is carried out.
- Frozen section assessment of proximal and distal bile duct margins are recommended if further resection can be carried out.

Distal cholangiocarcinoma

- Initial assessment to rule out distant metastatic disease and local resectability.
- The operation generally requires a pancreaticoduodenectomy with typical reconstruction.

[1]Nishio H, Nagino M, Nimura Y. Surgical management of hilar cholangiocarcinoma: the Nagoya experience. HPB 2005;7:259-262.
[2]Matsuo K, Rocha FG, Ito K, et al. The Blumgart preoperative staging system for hilar cholangiocarcinoma: analysis of resectability and outcomes in 380 patients. J Am Coll Surg 2012;215:343-355.
[3]Jarnagin WR, Fong Y, DeMatteo RP, et al. Staging, resectability and outcomes in 225 patients with hilar cholangiocarcinoma. Ann Surg 2001;234:507-517.
[4]Nimura Y. Preoperative biliary drainage before resection for cholangiocarcinoma. HPB 2008;10:130-133.
[5]Kennedy TJ, Yopp A, Qin Y, et al. Role of preoparative biliary drainage of live remnant prior to extended liver resection of hilar cholangiocarcinoma. HPB 2009;11:445-451.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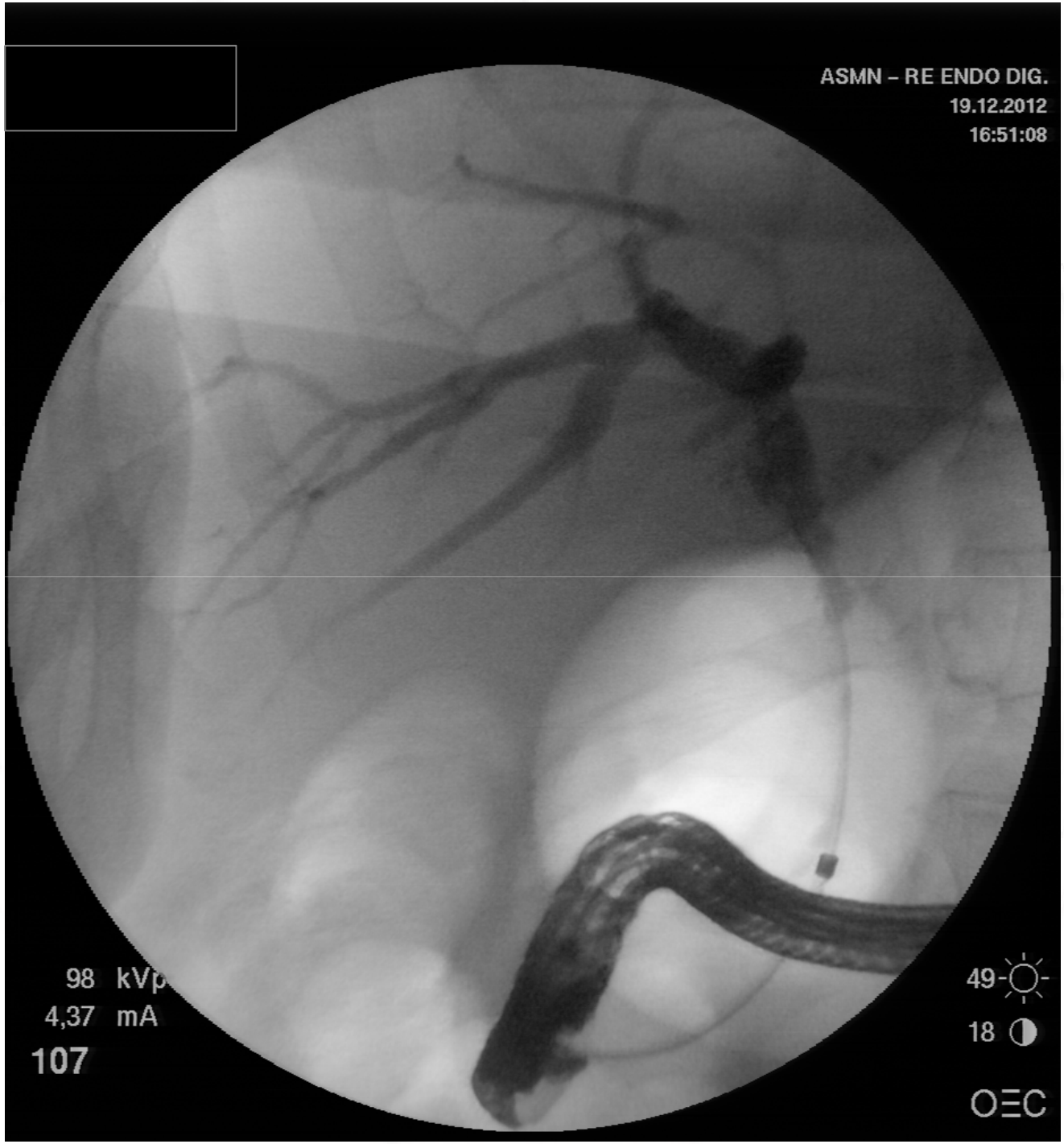
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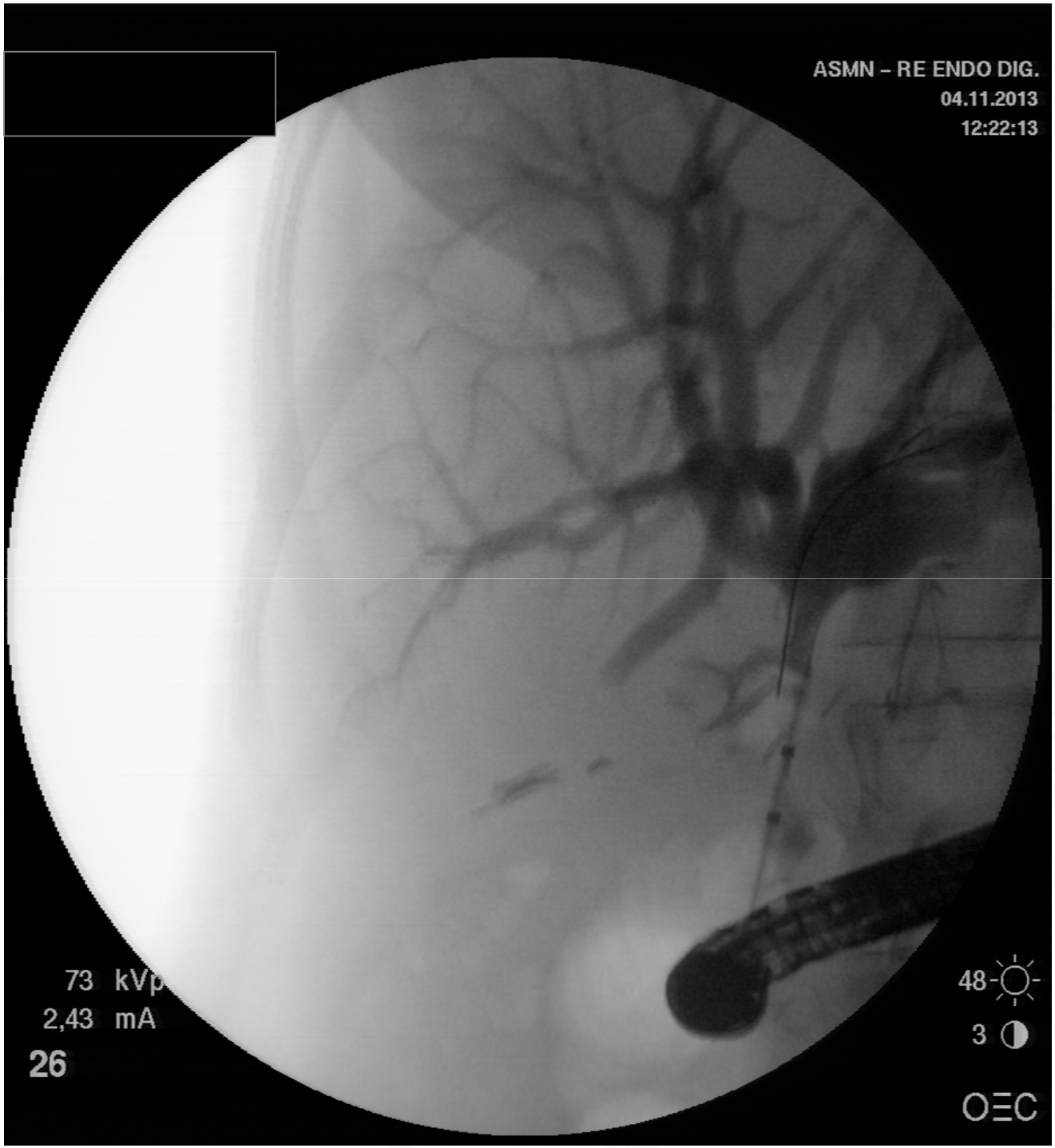
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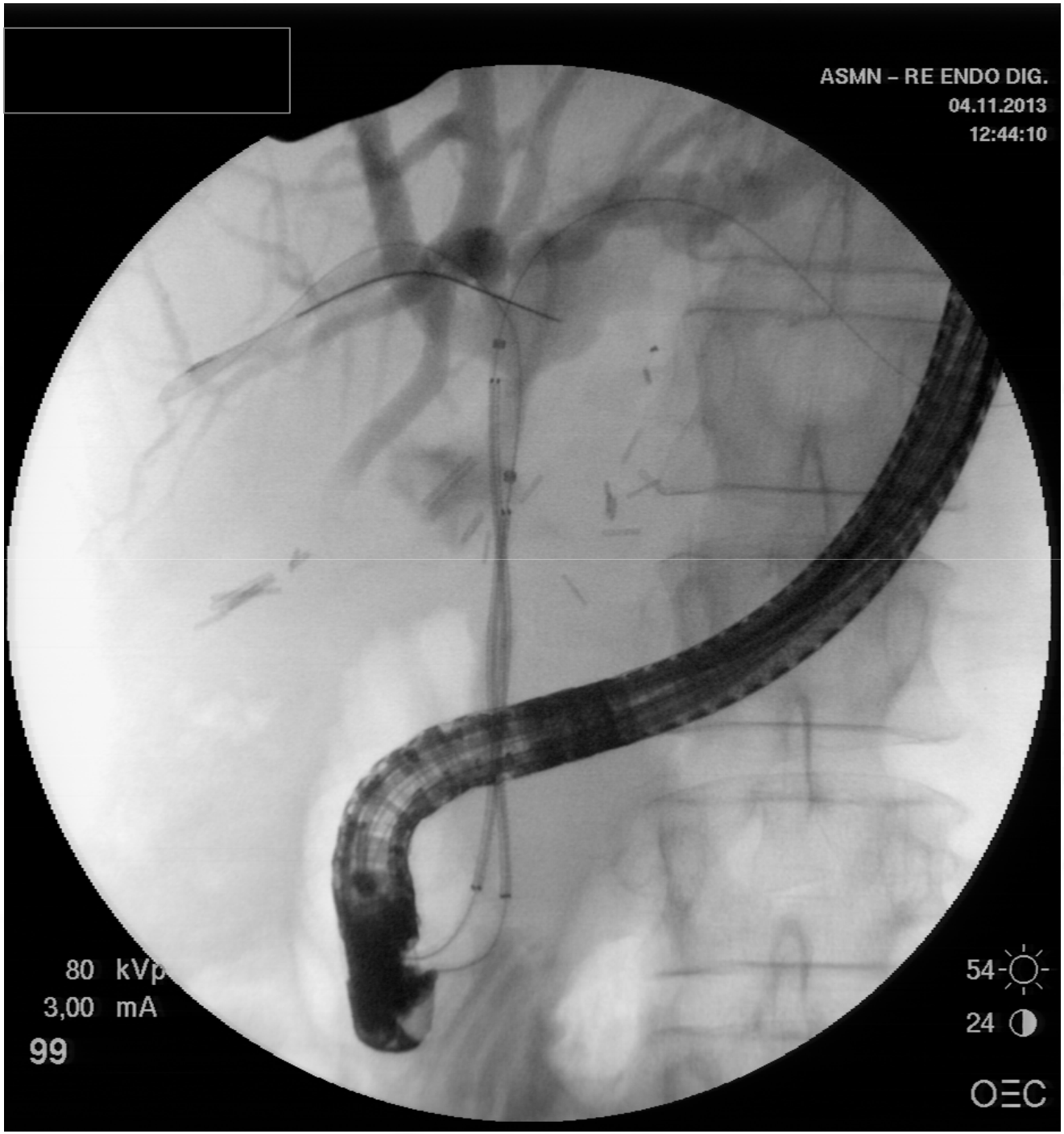
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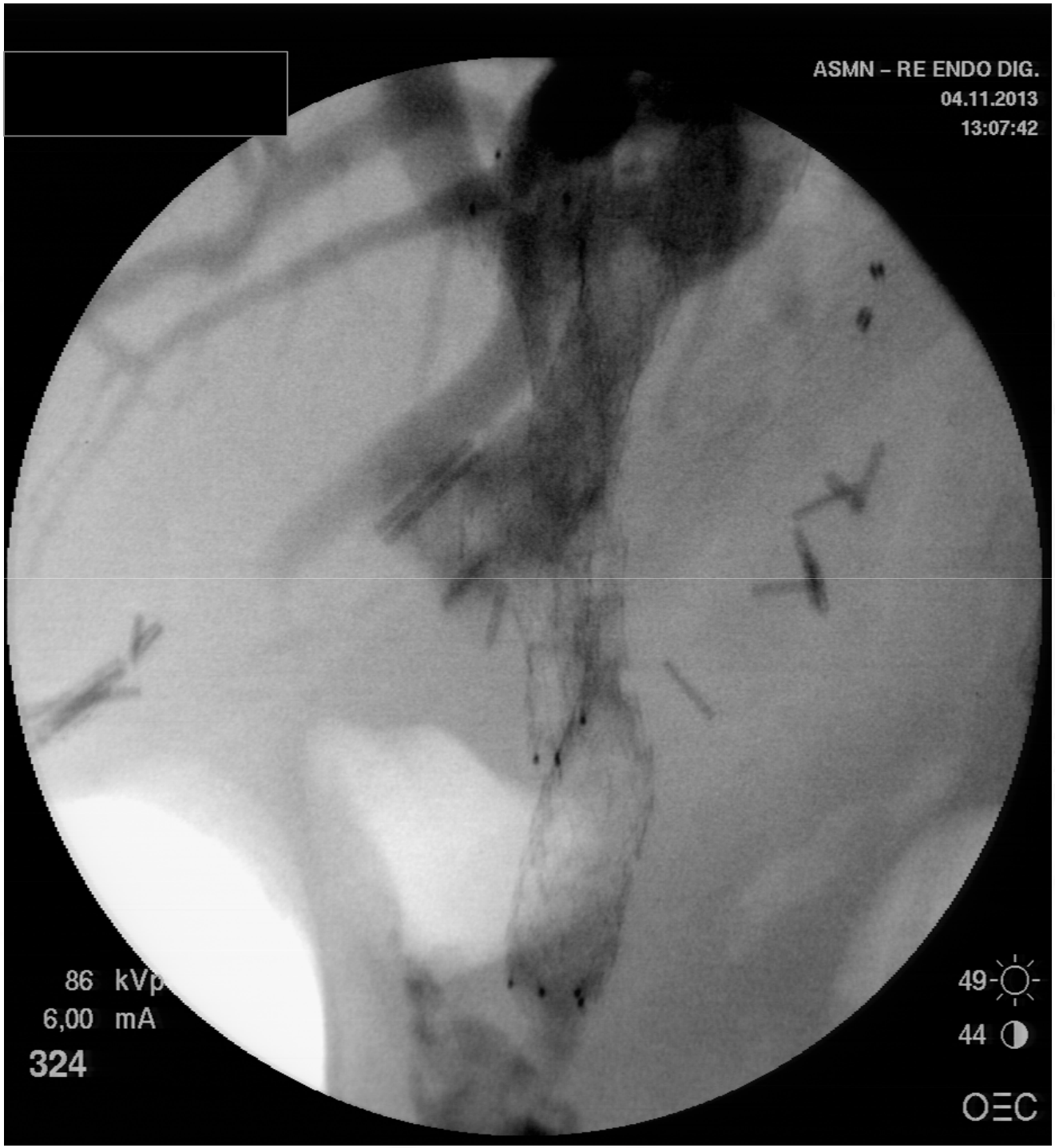
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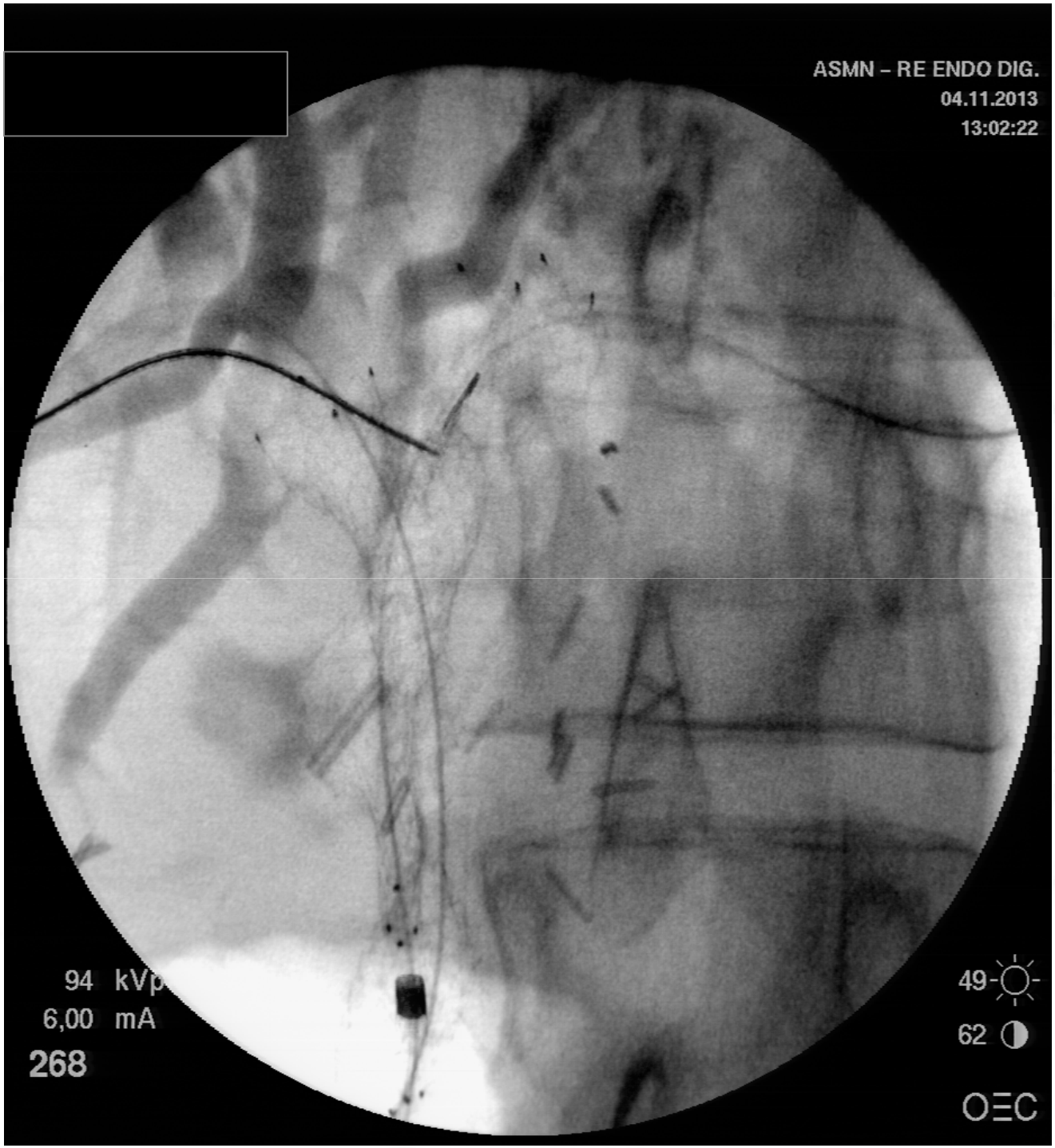
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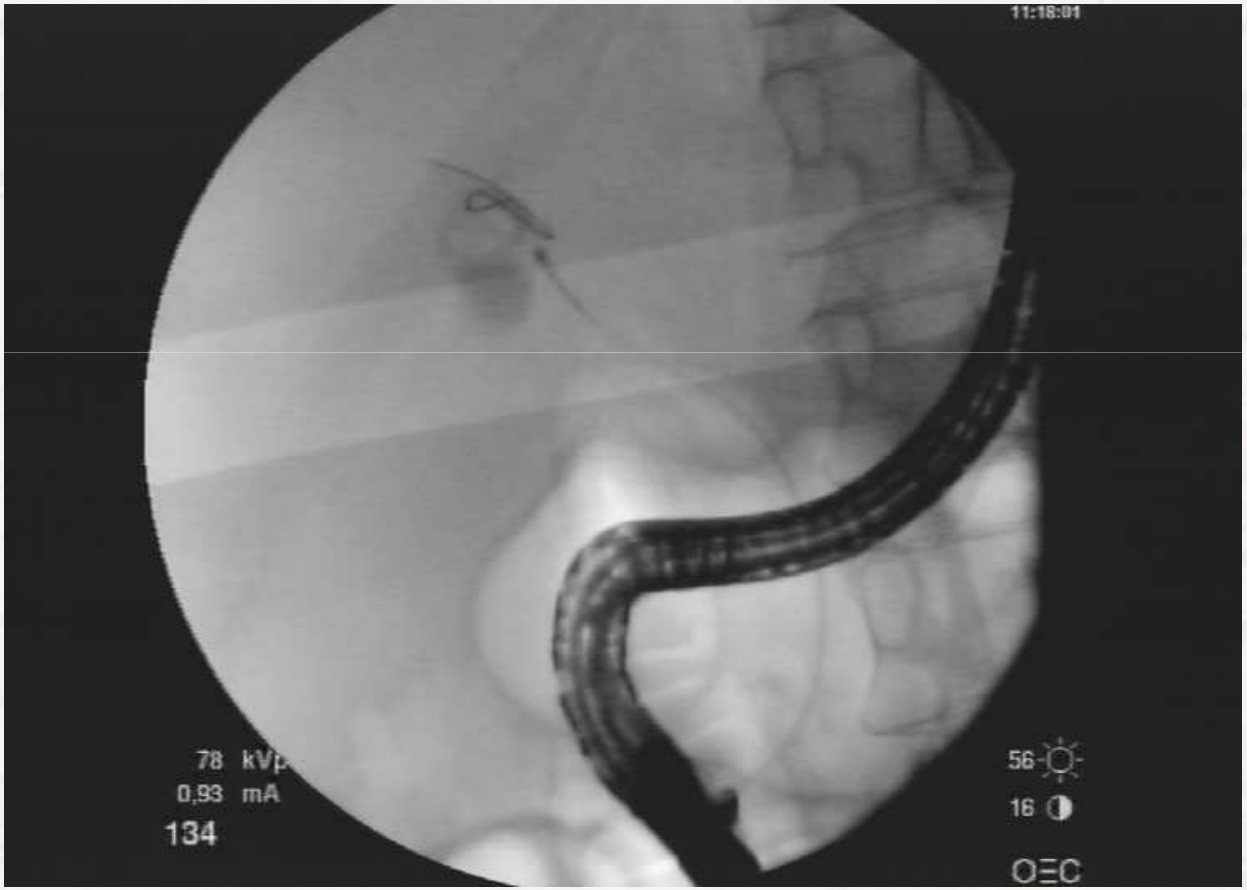
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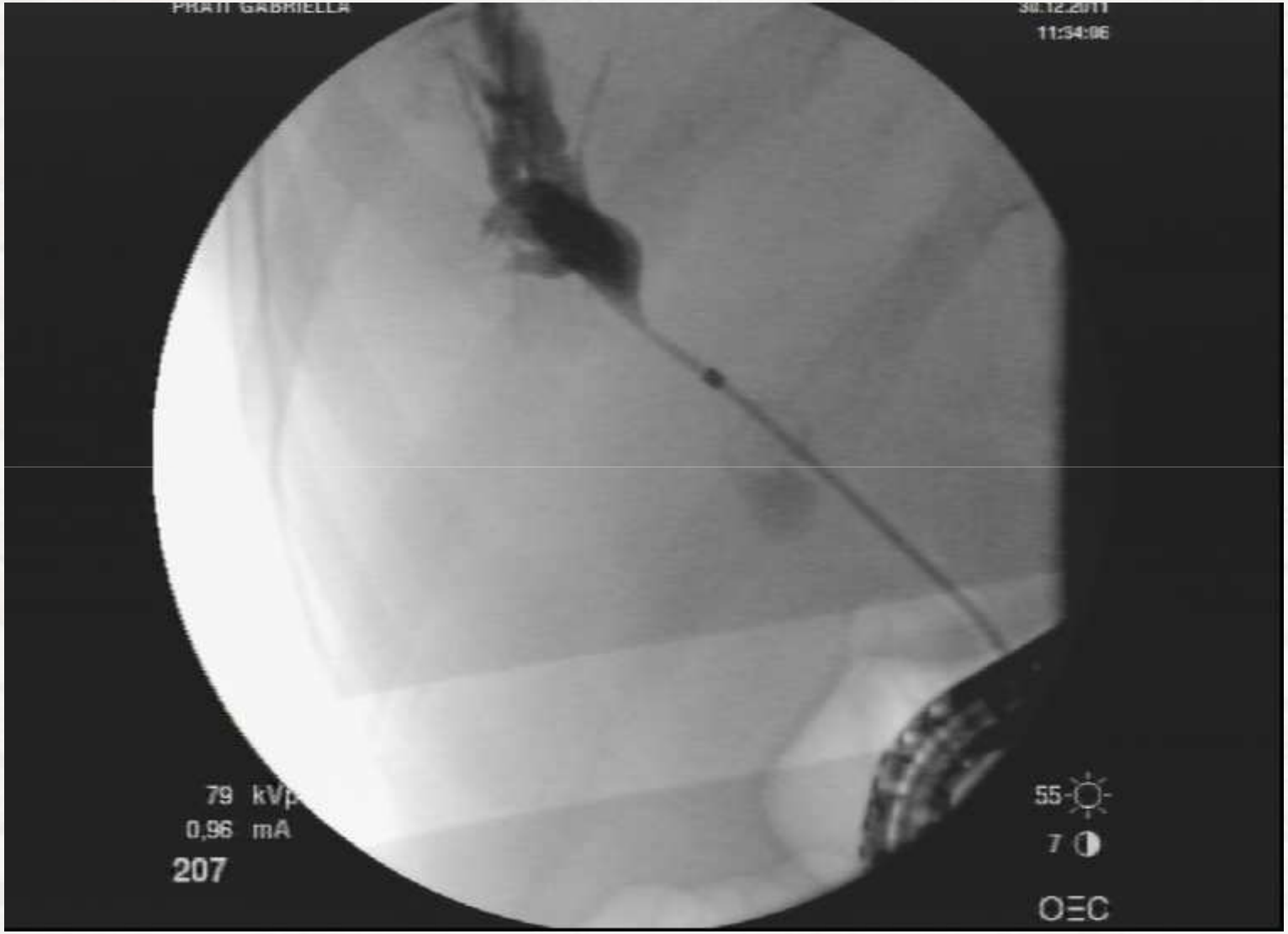
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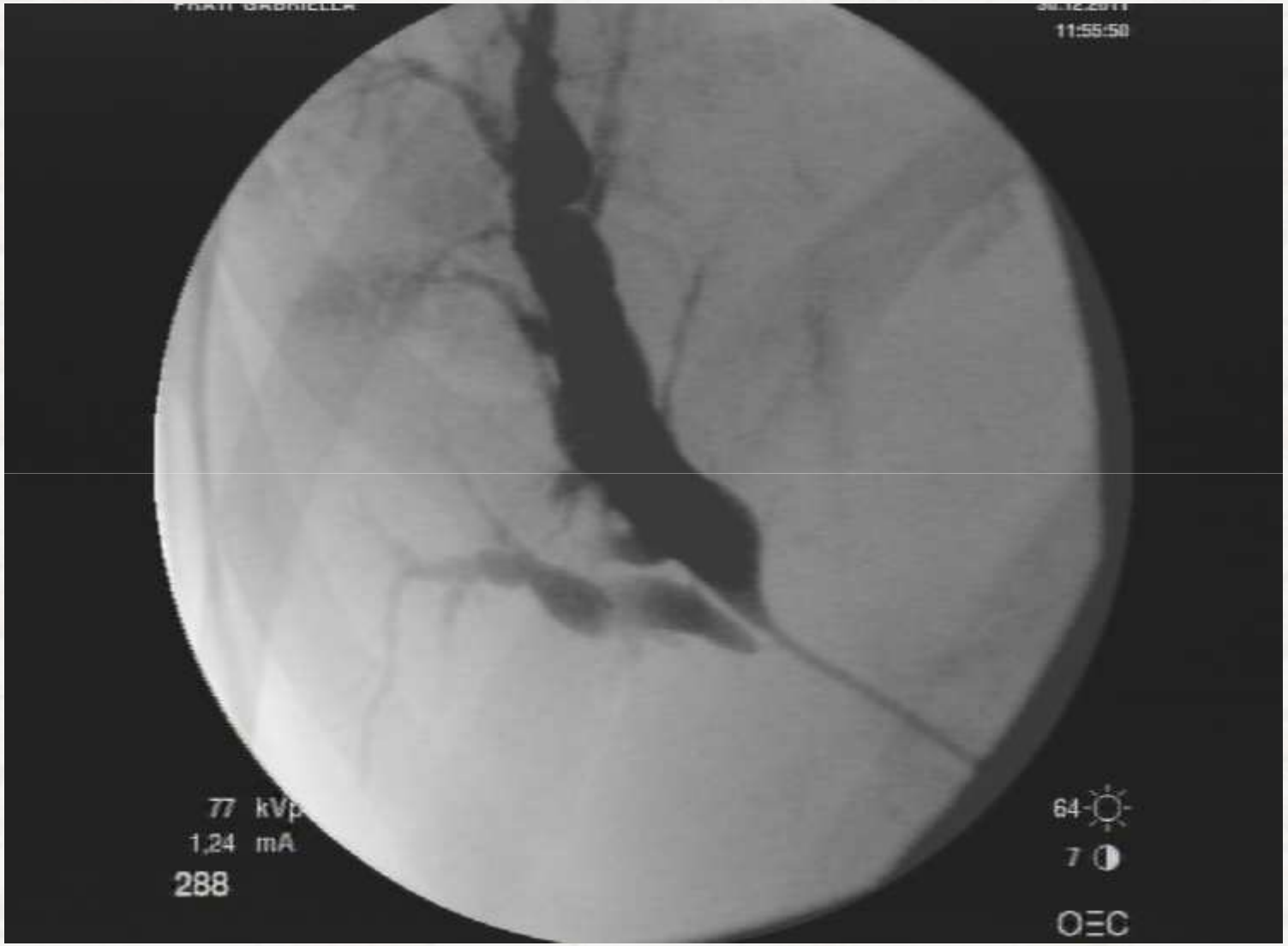
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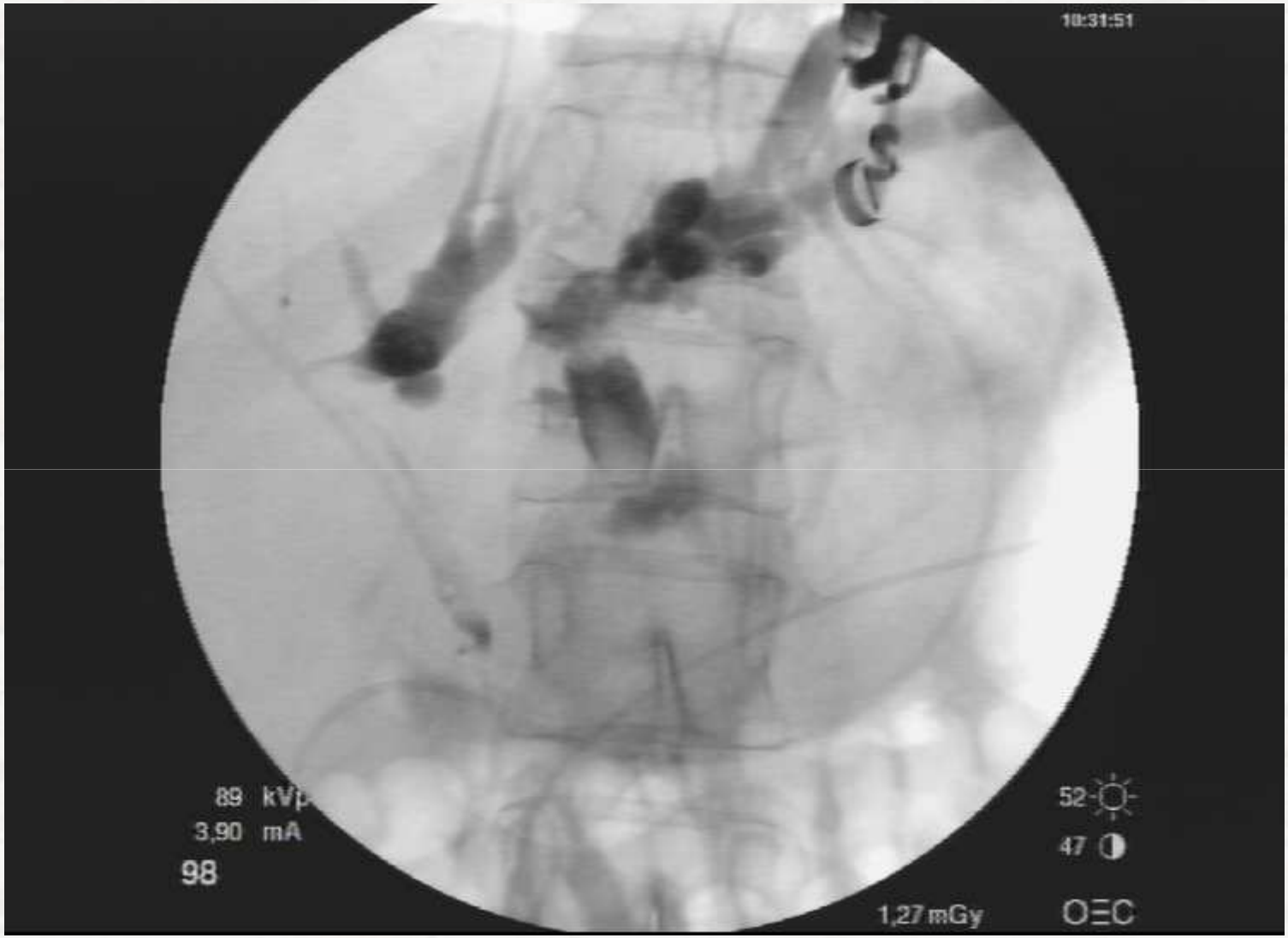
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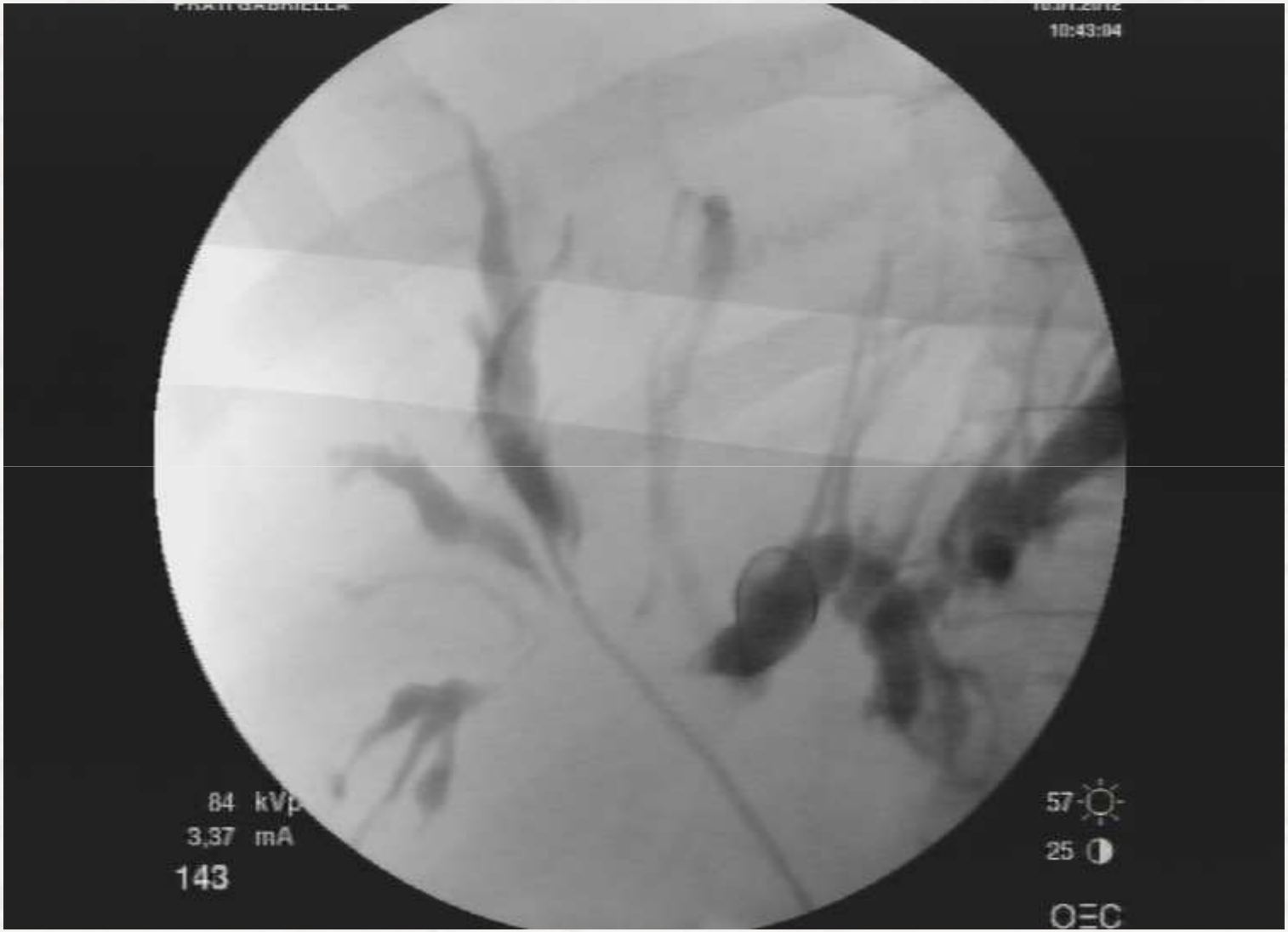
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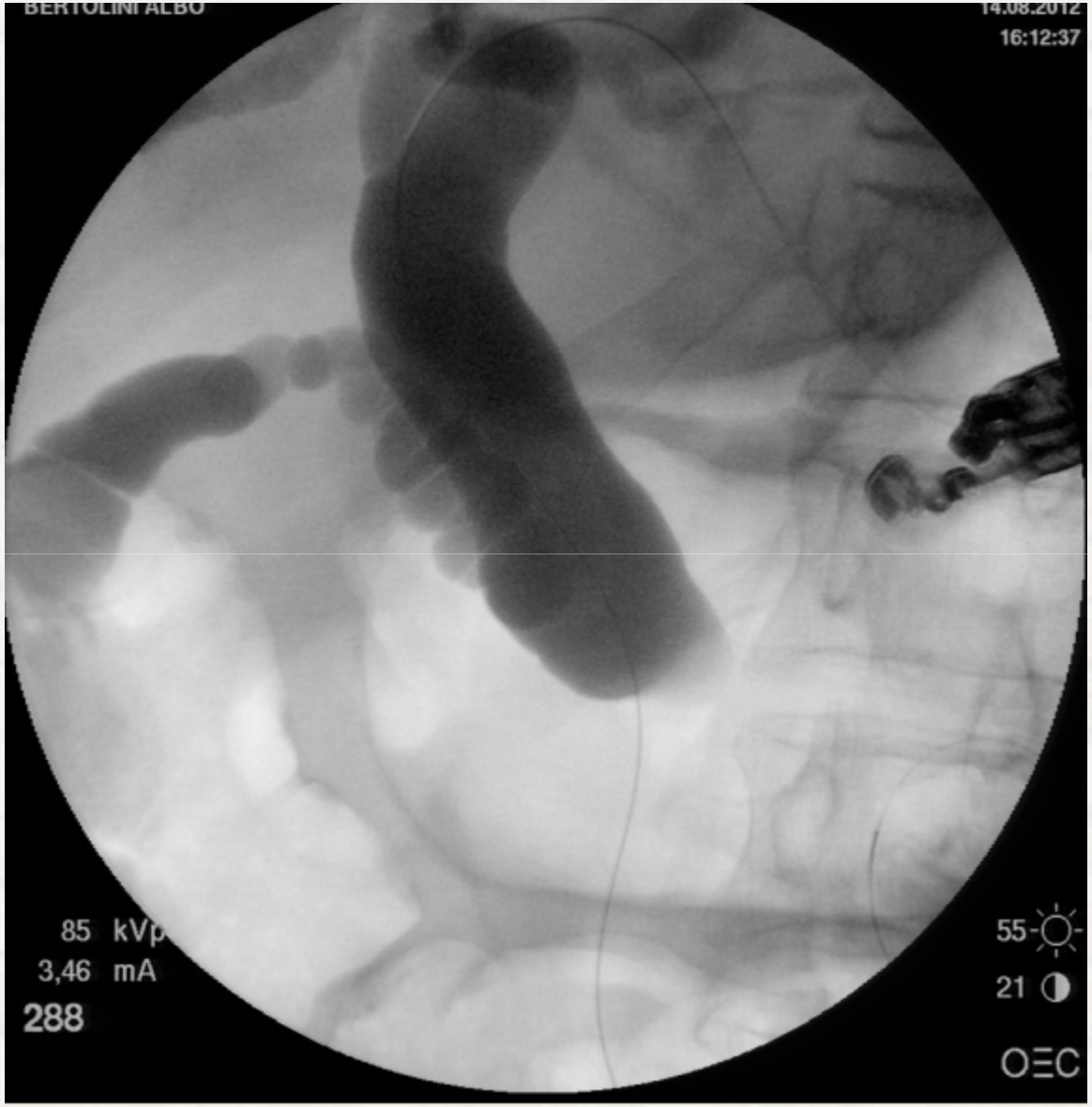
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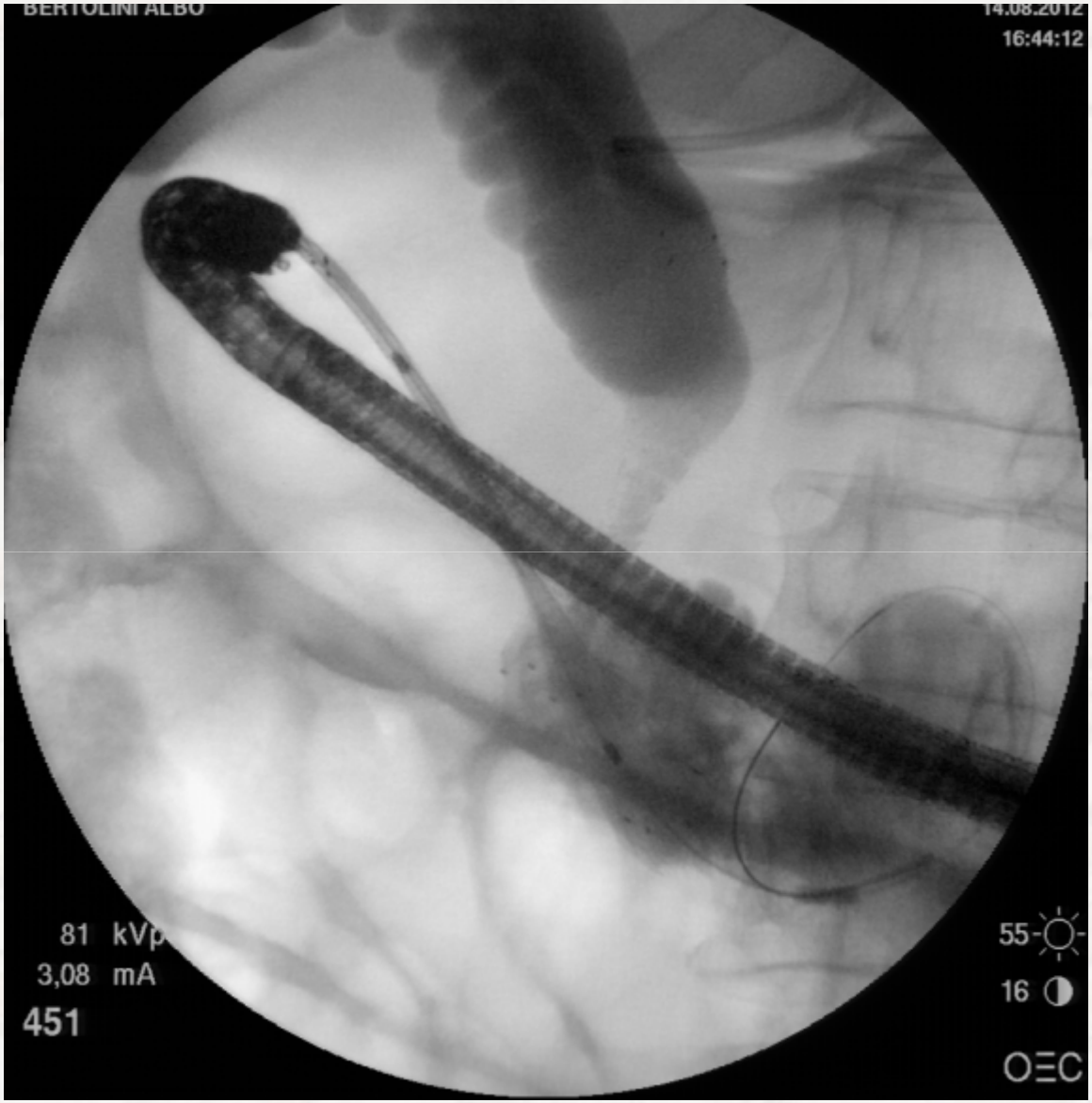
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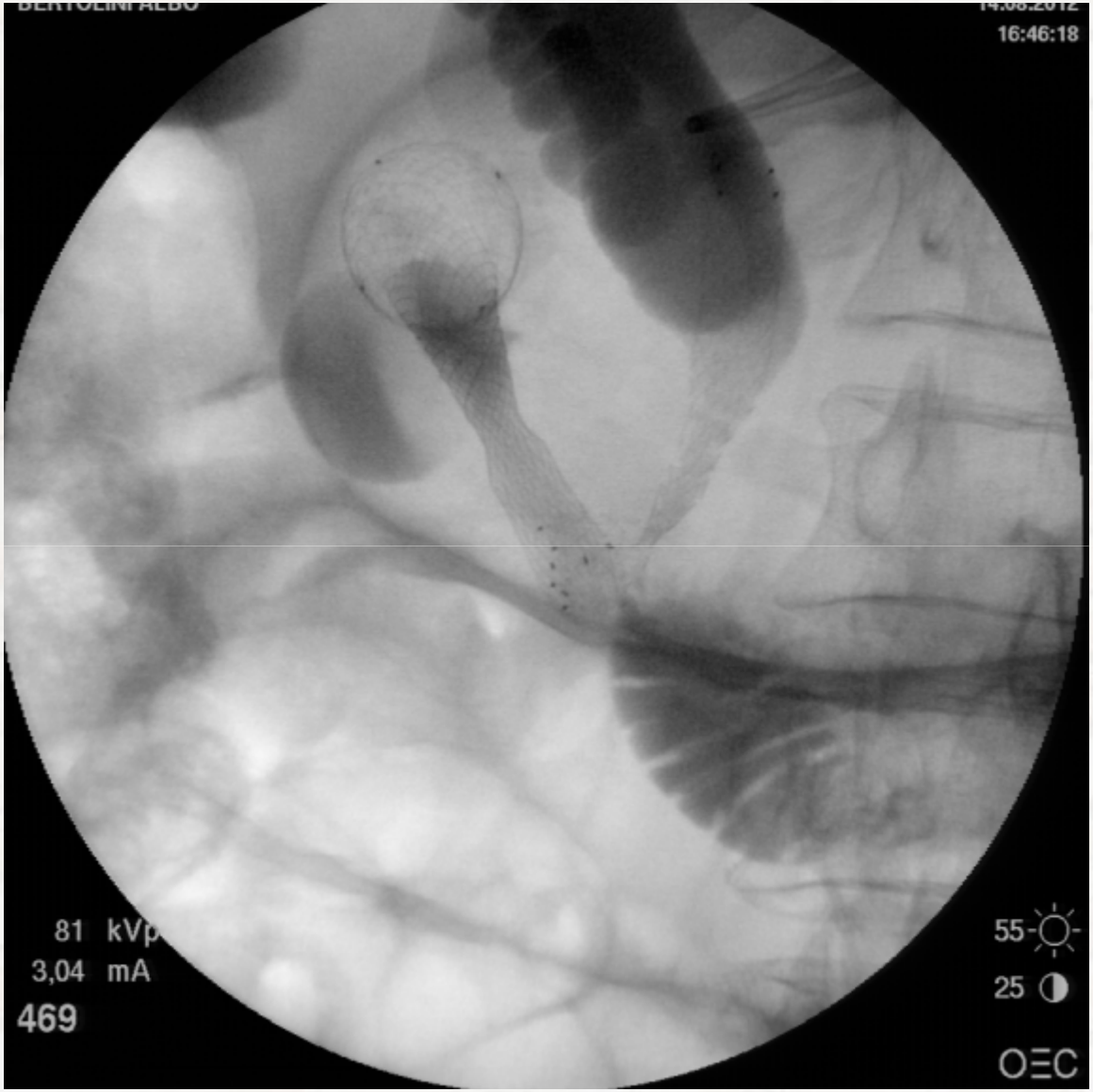
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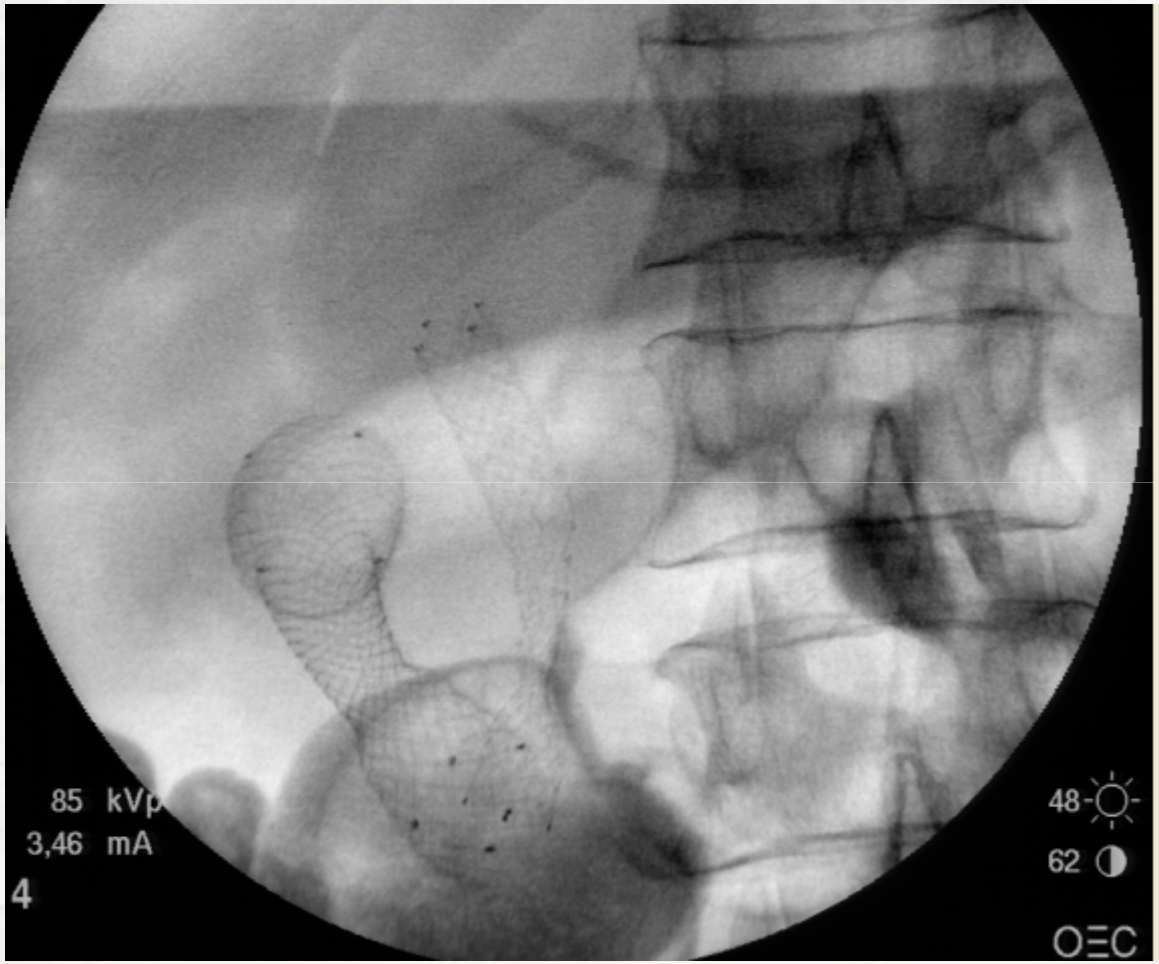
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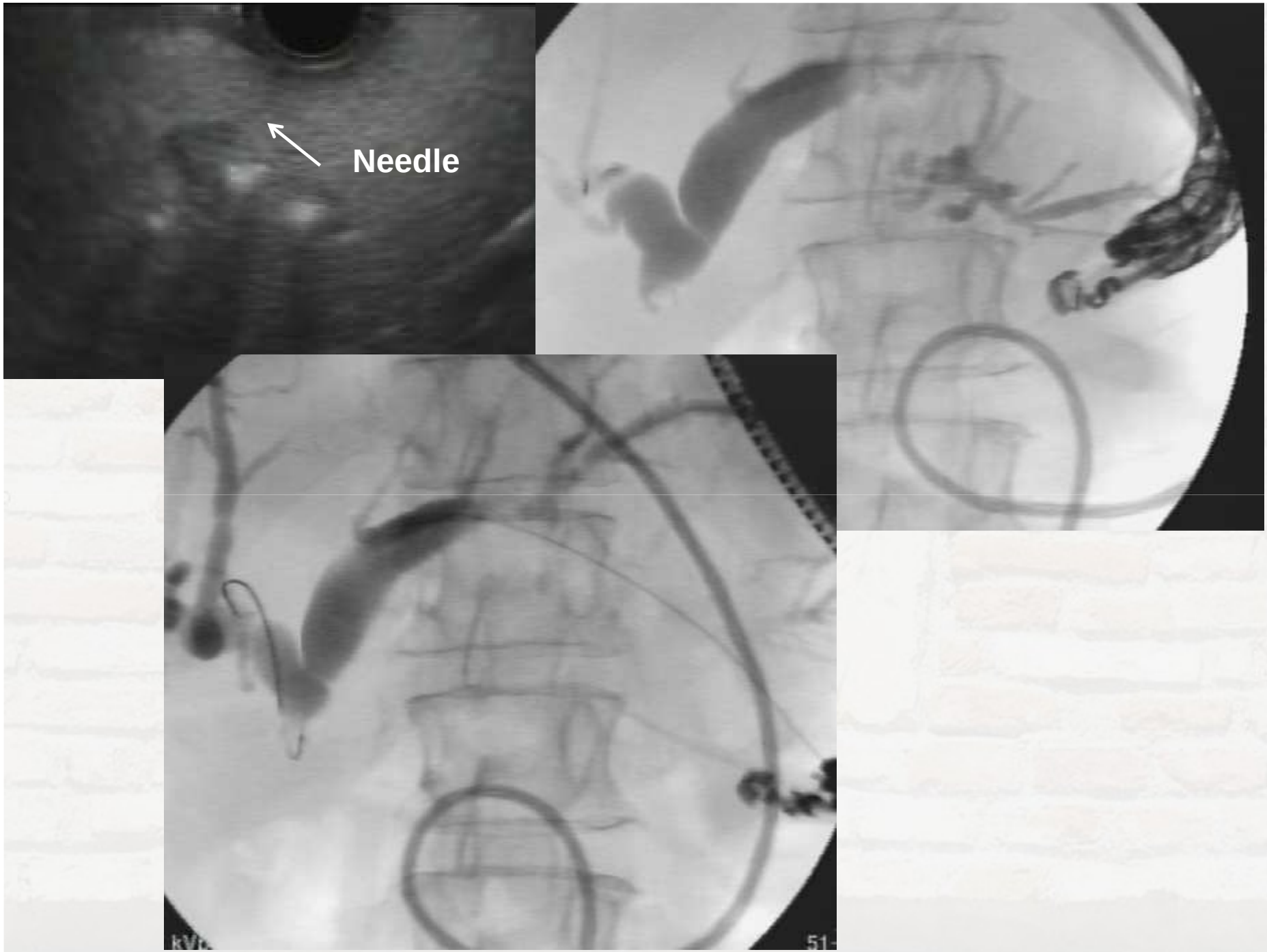
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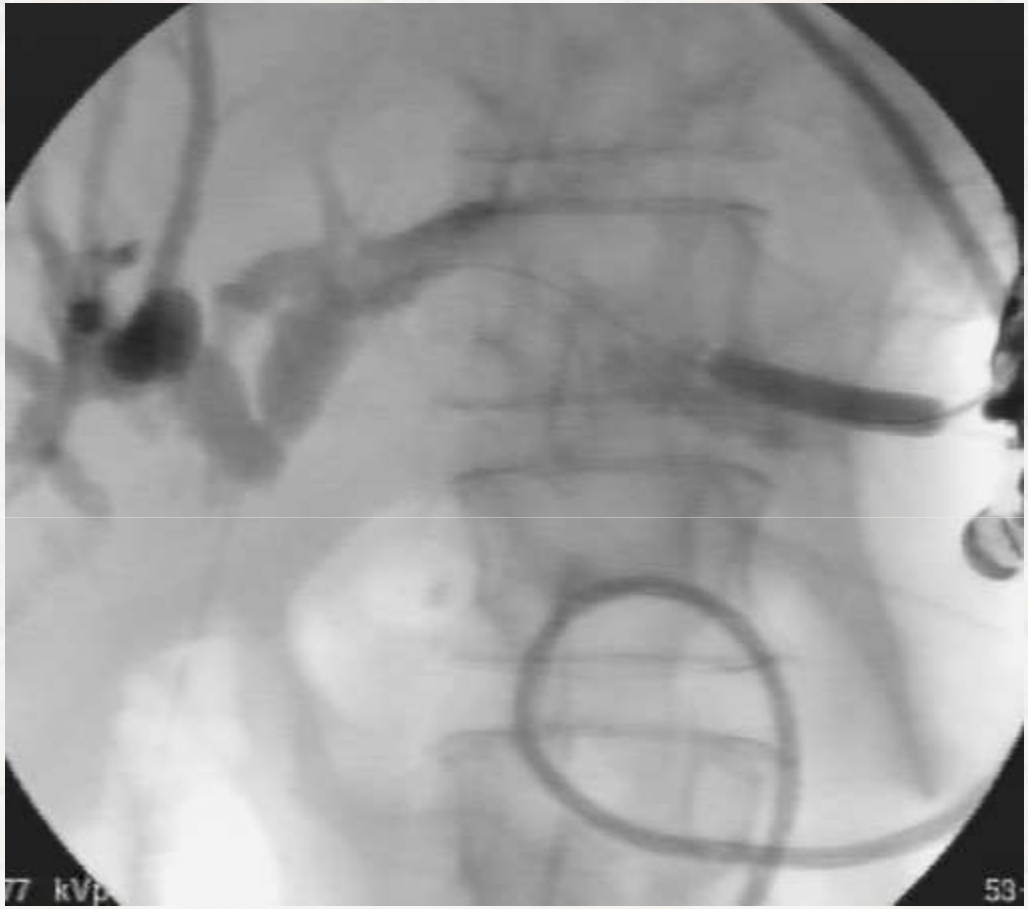

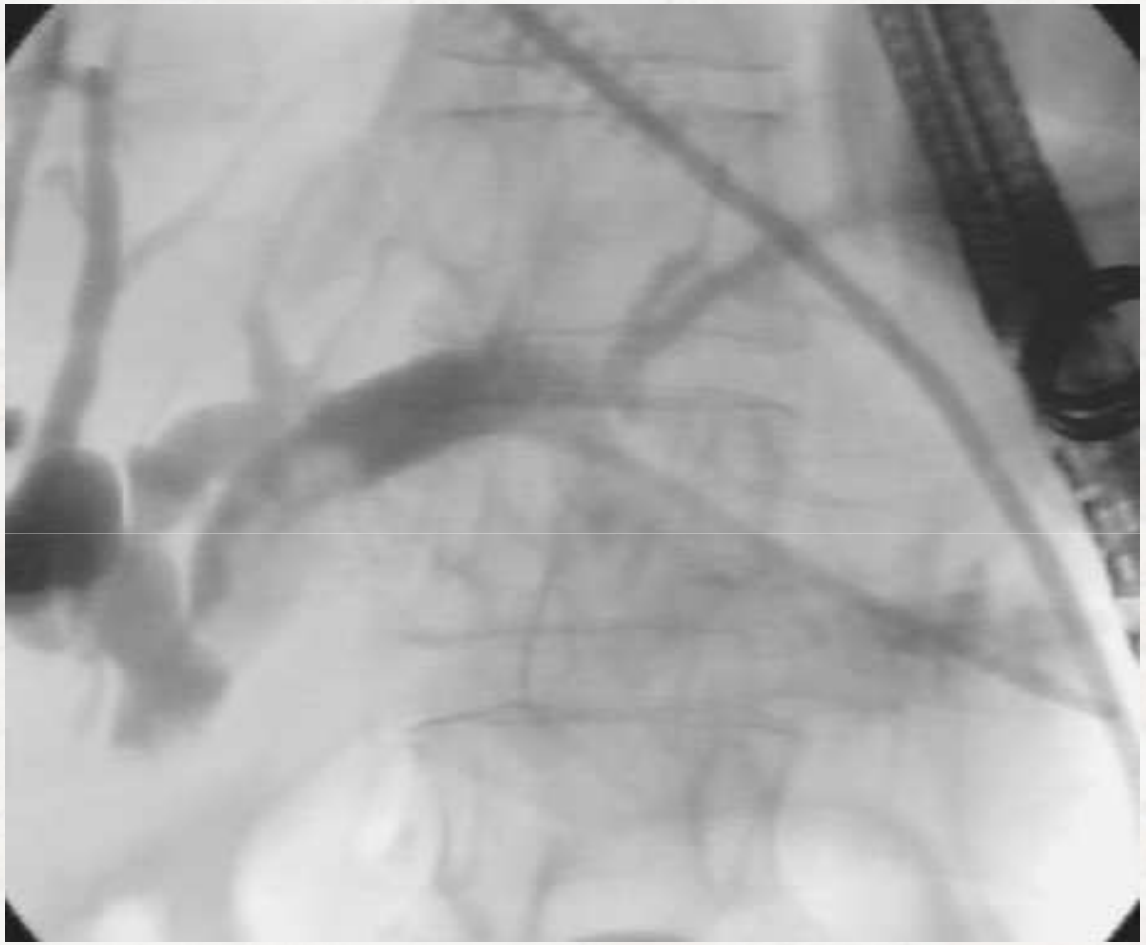

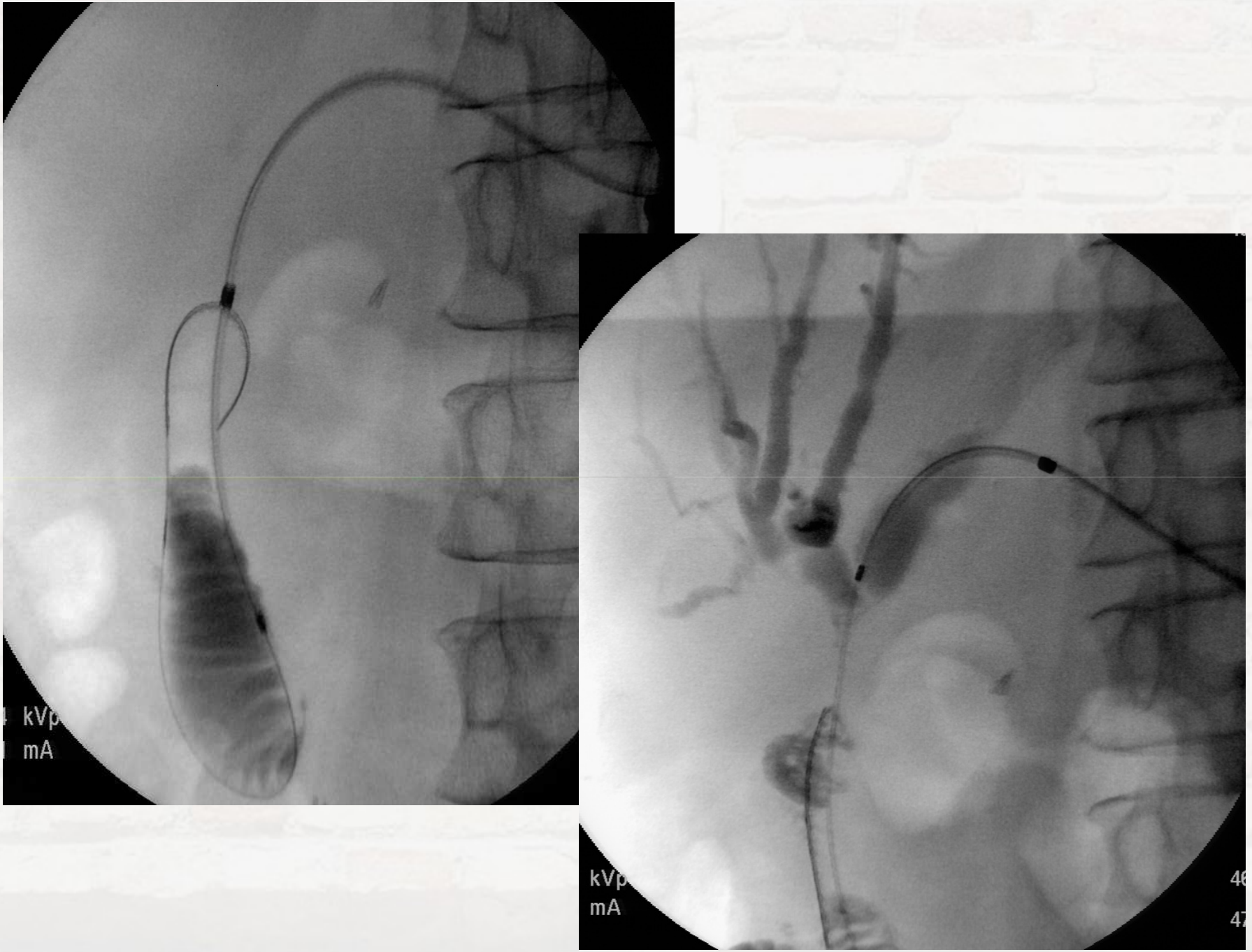
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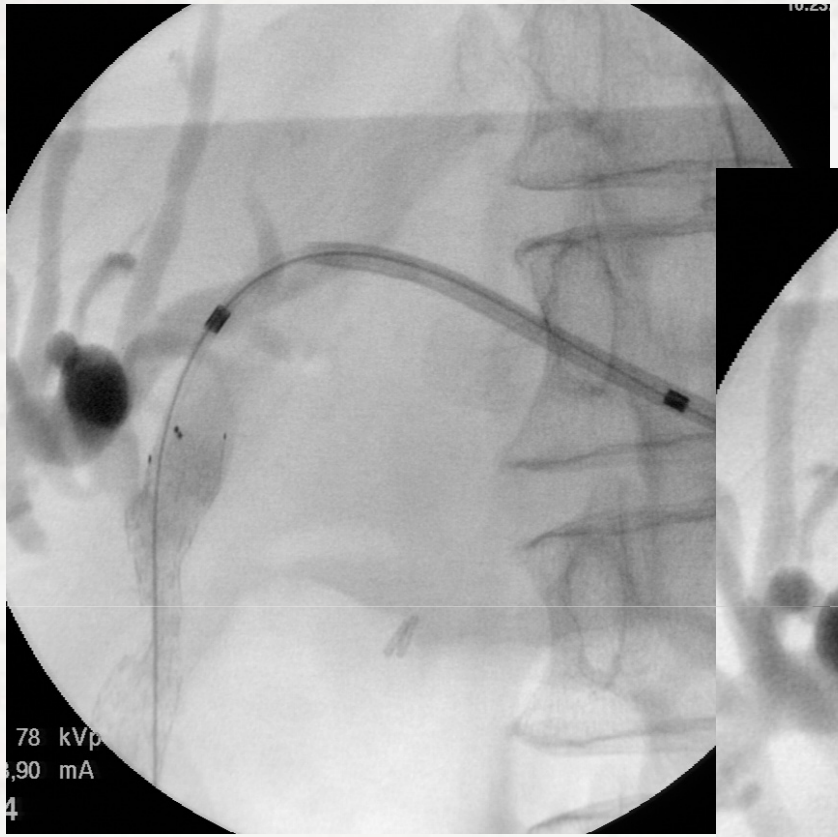
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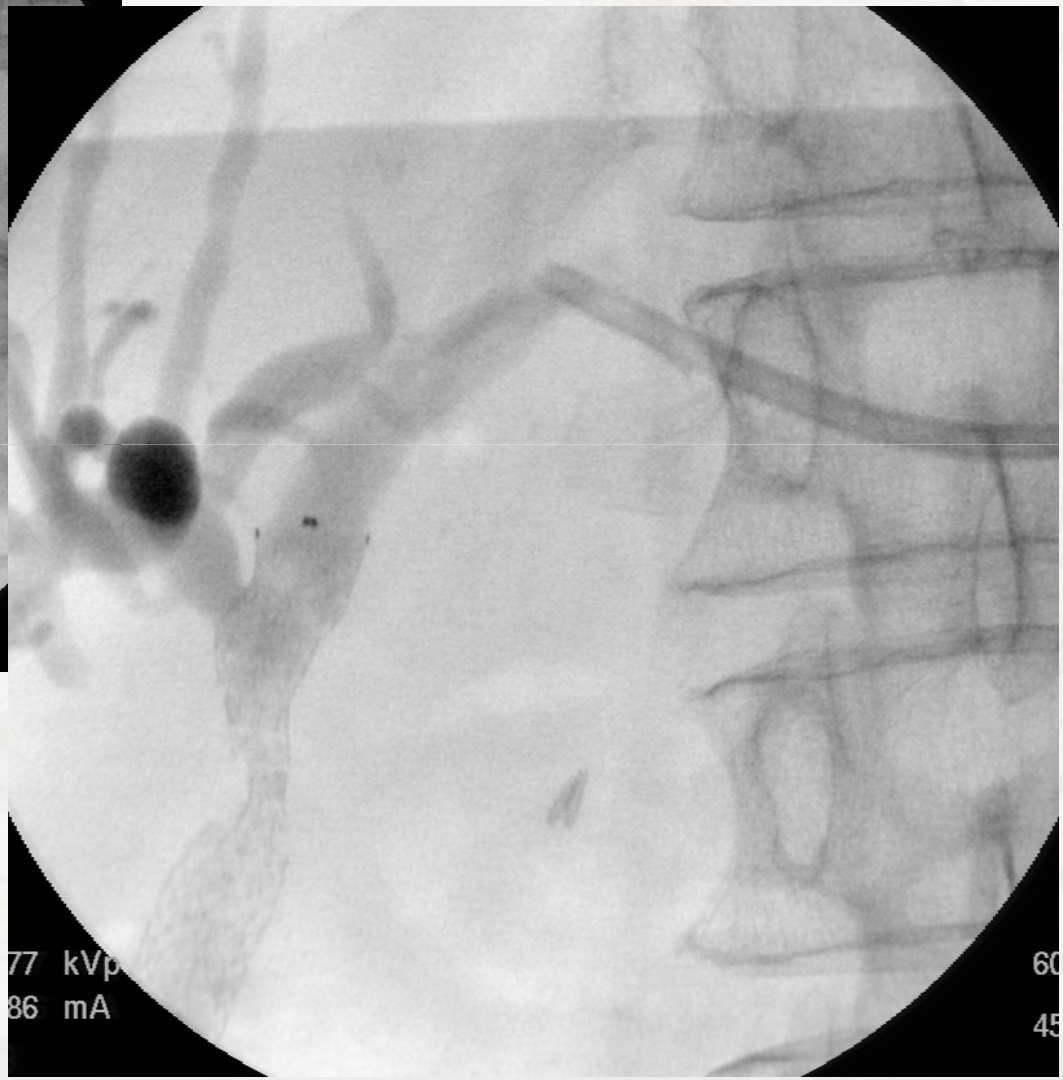
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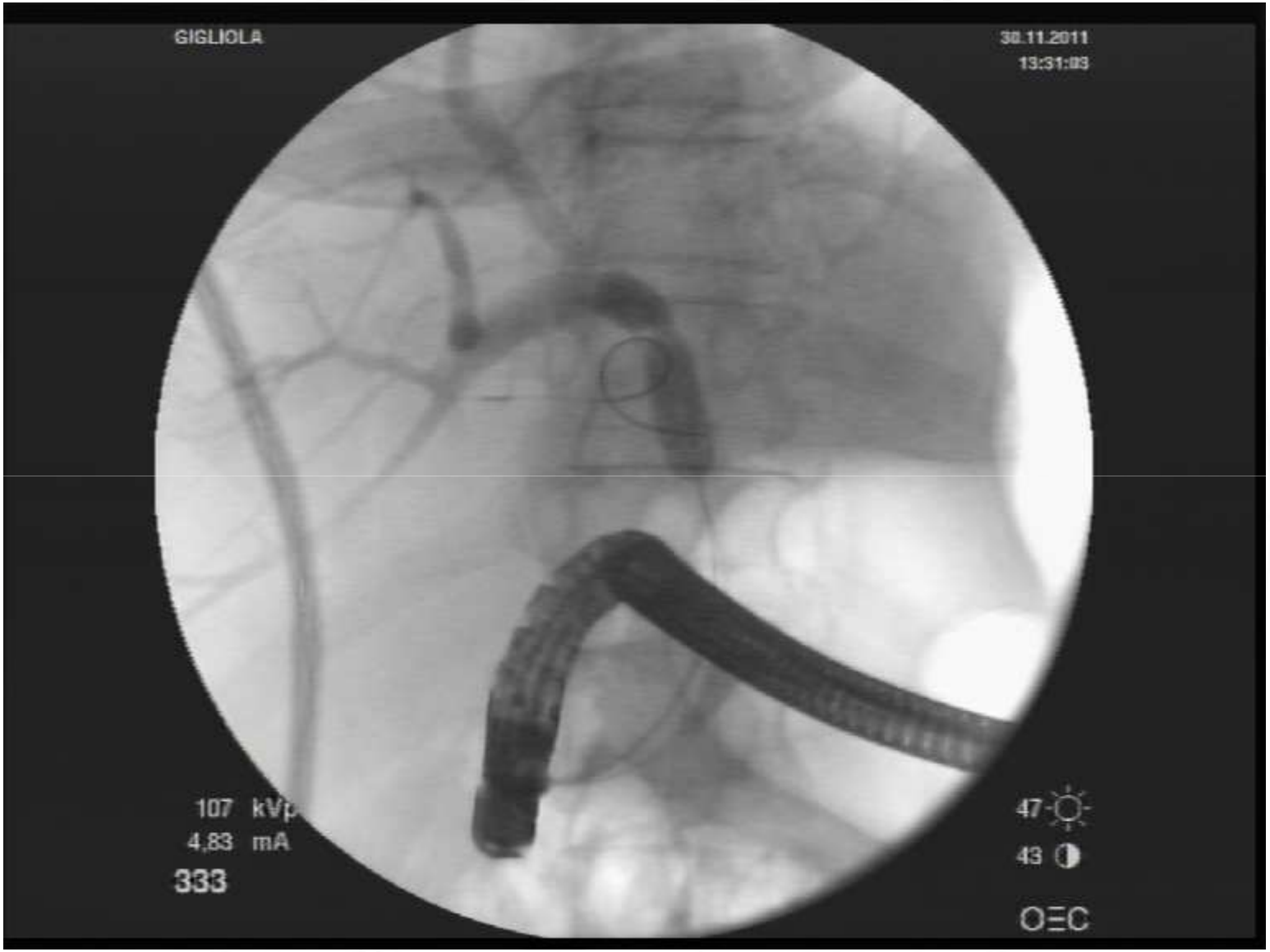
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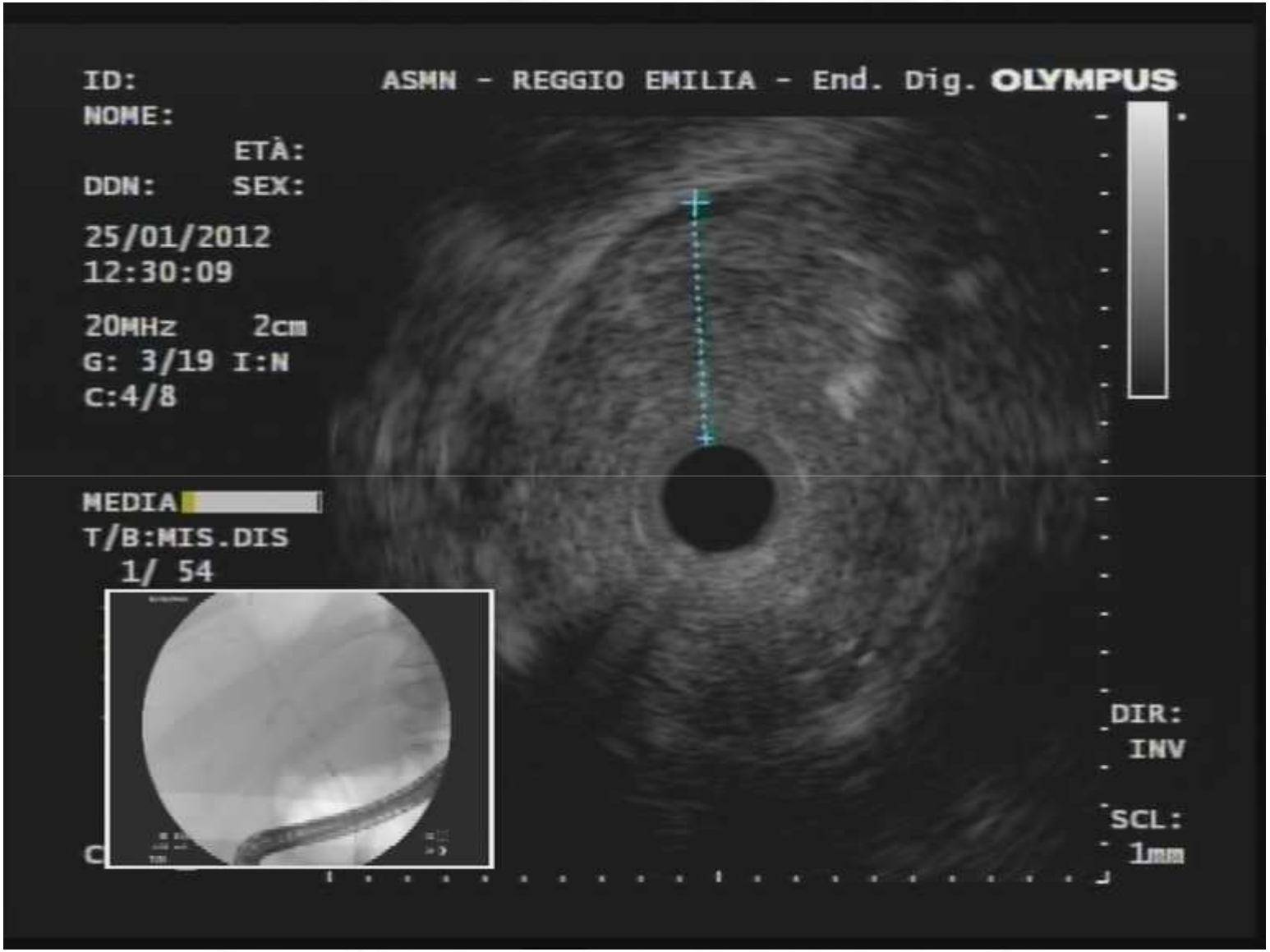
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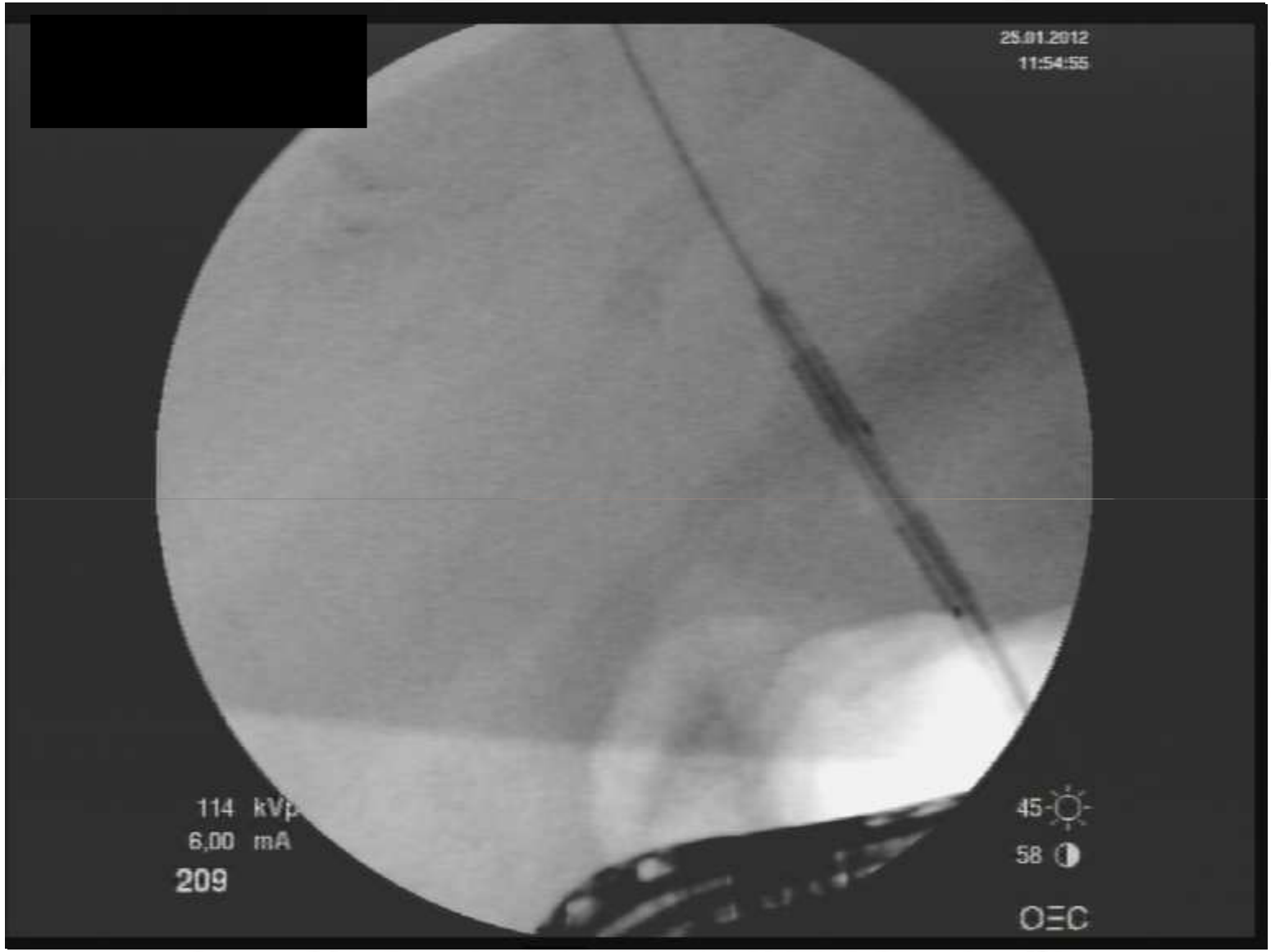
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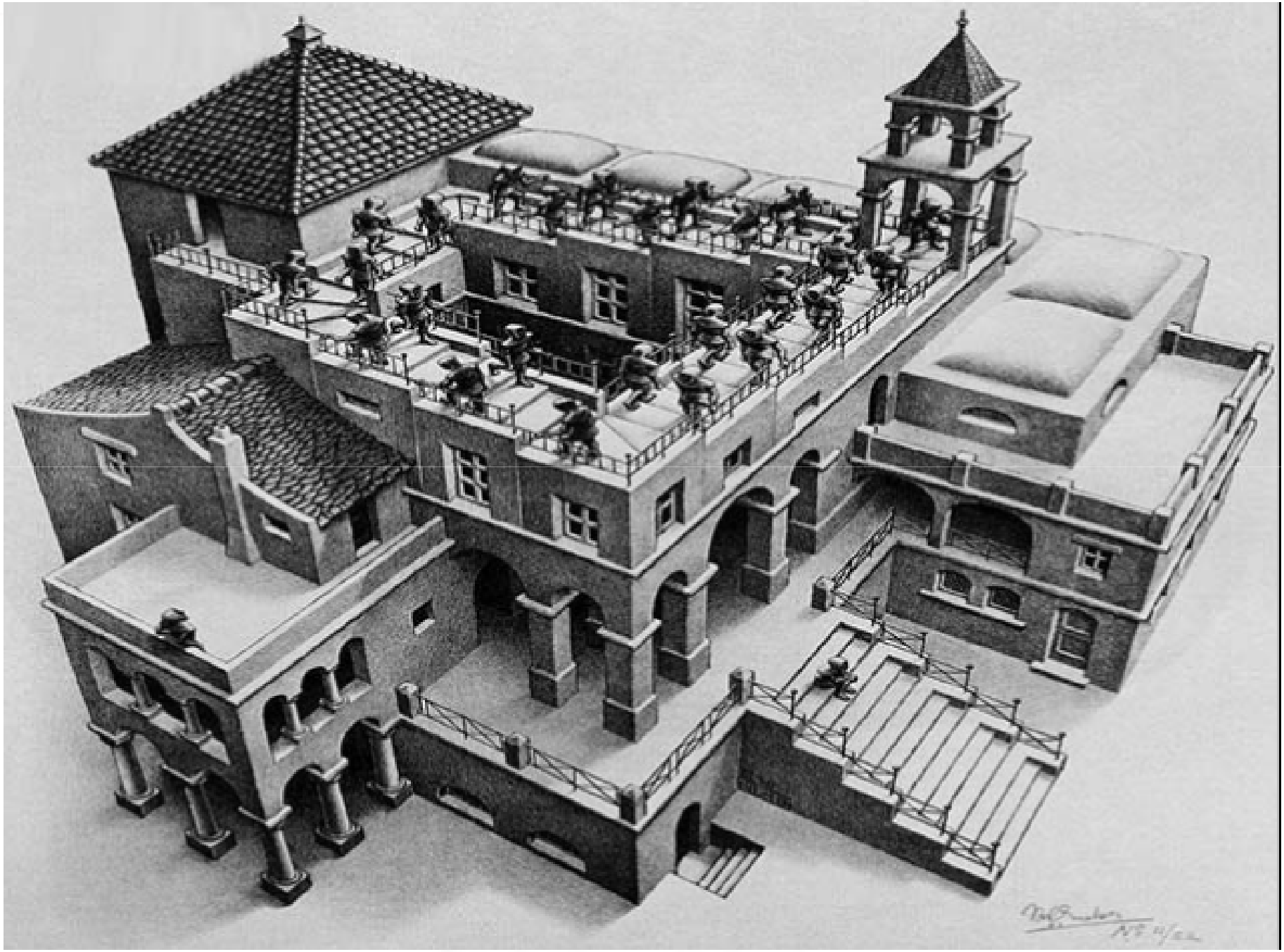


... Dopo aver scalato una montagna, ci si accorge
solo che ce ne sono tante altre da scalare
Nelson Mandela