Paris Hepatology Meeting 2021

Clinical management of cholangiocarcinoma

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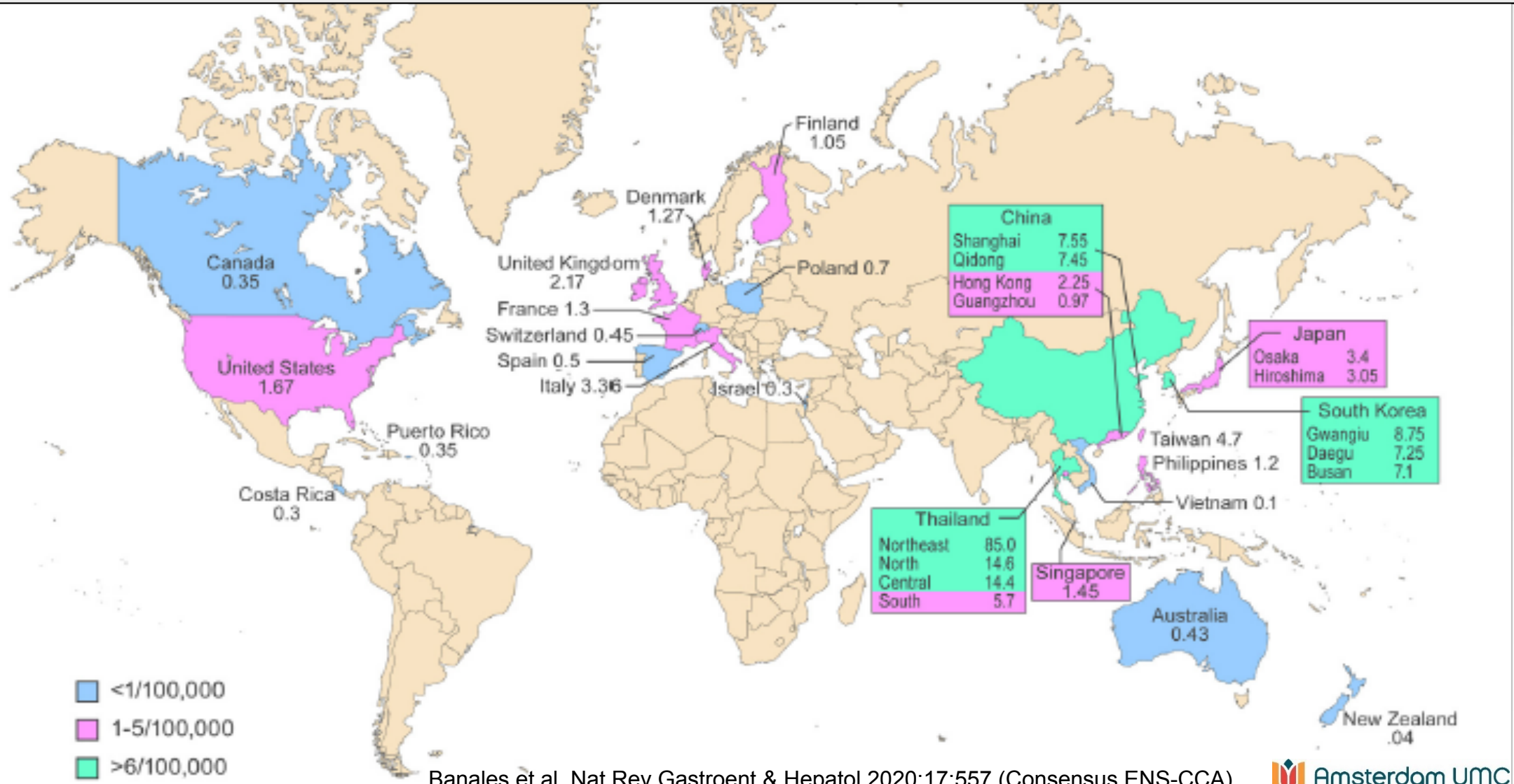
Cholangiocarcinoma

Challenges

- 2nd most common primary hepatic malignancy (~15%)
- Increasing incidence globally (highest in Asia)

Cholangiocarcinoma

Incidence



Banales et al. Nat Rev Gastroent & Hepatol 2020;17:557 (Consensus ENS-CCA)

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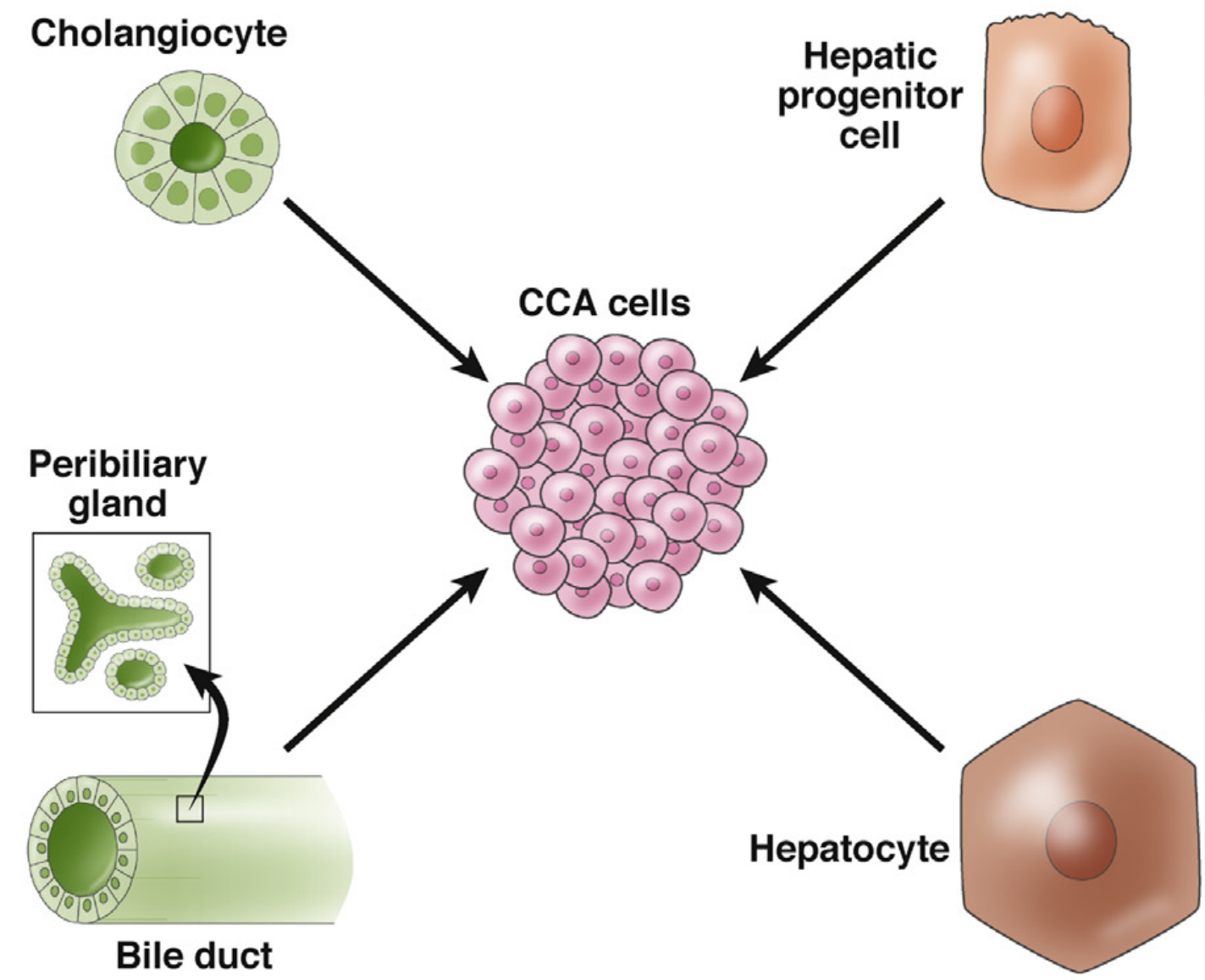
Cholangiocarcinoma

Challenges

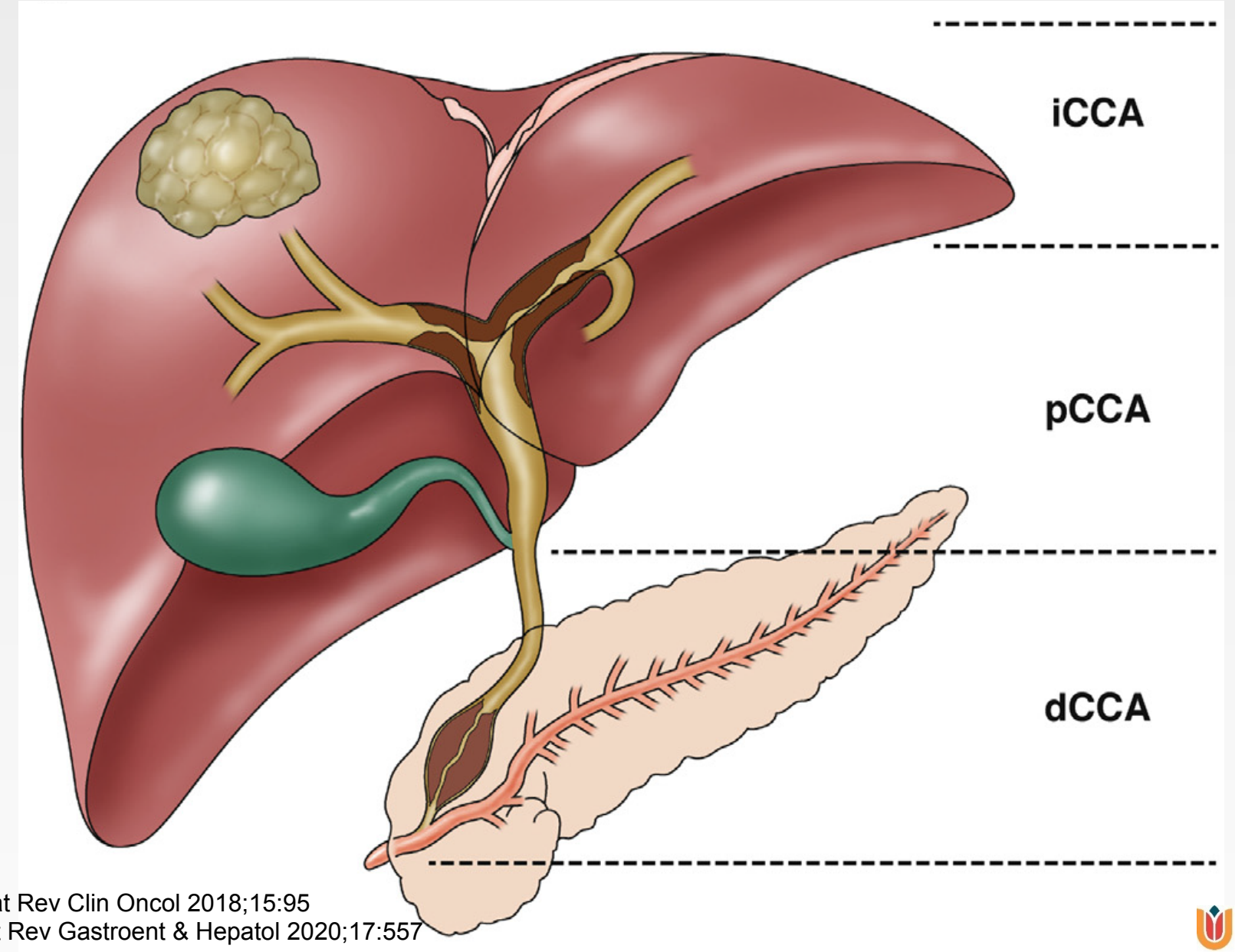
- 2nd most common primary hepatic malignancy (~15%)
- Increasing incidence globally (highest in Asia)
- **High heterogeneity**

Cells of origin in cholangiocarcinoma



Rizvi & Gores, Gastroenterology 2013;145:1215

Localization of cholangiocarcinoma



10-20%

50-60%

20-30%

Rizvi,…Gores, Nat Rev Clin Oncol 2018;15:95
Banales et al. Nat Rev Gastroent & Hepatol 2020;17:557

Cholangiocarcinoma

Challenges

- 2nd most common primary hepatic malignancy (~15%)
- Increasing incidence globally (highest in Asia)
- High heterogeneity
- **Silent growth → detection mostly at advanced stage**
- **Poor prognosis (5-yr survival 7-20%)**

Cholangiocarcinoma

Challenges

- 2nd most common primary hepatic malignancy (~15%)
- Increasing incidence globally (highest in Asia)
- High heterogeneity
- Silent growth, detection mostly at advanced stage
- Poor prognosis (5-yr survival 7-20%)
- **Multiple risk factors**, but most CCAs (~80%) develop spontaneously

Cholangiocarcinoma

Risk factors

Risk factor	Study type	OR or RR from selected studies
Choledochal cyst[30]	Meta-analysis	OR 26.71 for iCCA OR 34.94 for eCCA
Choledocholithiasis[30]	Meta-analysis	OR 10.08 for iCCA OR 18.58 for eCCA
Cholelithiasis[30]	Meta-analysis	OR 3.38 for iCCA OR 5.92 for eCCA
Cholecystolithiasis[30]	Meta-analysis	OR 1.75 for iCCA OR 2.94 for eCCA
Caroli disease[396]	Population-based study	OR 38 for iCCA OR 97 for eCCA
Primary sclerosing cholangitis[396]	Population-based study	OR 22 for iCCA OR 41 for eCCA
Cirrhosis[30]	Meta-analysis	OR 15.32 for iCCA OR 3.82 for eCCA
Chronic hepatitis B[30]	Meta-analysis	OR 4.57 for iCCA OR 2.11 for eCCA
Chronic hepatitis C[30]	Meta-analysis	OR 4.28 for iCCA OR 1.98 for eCCA

Banales et al. Nat Rev Gastroent & Hepatol 2020;17:557

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Cholangiocarcinoma

Risk factors

Chronic inflammation of the biliary epithelium

Cholangiocarcinoma

Risk factors

Risk factor	Study type	OR or RR from selected studies
Haemochromatosis[396]	Population-based study	OR 2.1 for iCCA
Inflammatory bowel disease[30]	Meta-analysis	OR 2.68 for iCCA OR 2.37 for eCCA
Chronic pancreatitis[396]	Population-based study	OR 2.7 for iCCA OR 6.6 for eCCA
Liver fluke (*Opisthorchis viverrini*, *Clonorchis sinensis*)[397]	Meta-analysis	OR 5 iCCA>eCCA
Type 2 diabetes mellitus[398]	Meta-analysis	OR 1.73 for iCCA OR 1.5 for eCCA
Nonalcoholic fatty liver disease[399]	Meta-analysis	OR 2.2 for iCCA OR 1.5 for eCCA
Obesity[30]	Meta-analysis	OR 1.14 for iCCA OR 1.2 for eCCA
Hypertension[30]	Meta-analysis	OR 1.10 for iCCA OR 1.21 for eCCA
Alcohol consumption[30]	Meta-analysis	OR 3.15 for iCCA OR 1.75 for eCCA
Cigarette smoking[30]	Meta-analysis	OR 1.25 for iCCA OR 1.69 for eCCA

Banales et al. Nat Rev Gastroent & Hepatol 2020;17:557

Cholangiocarcinoma

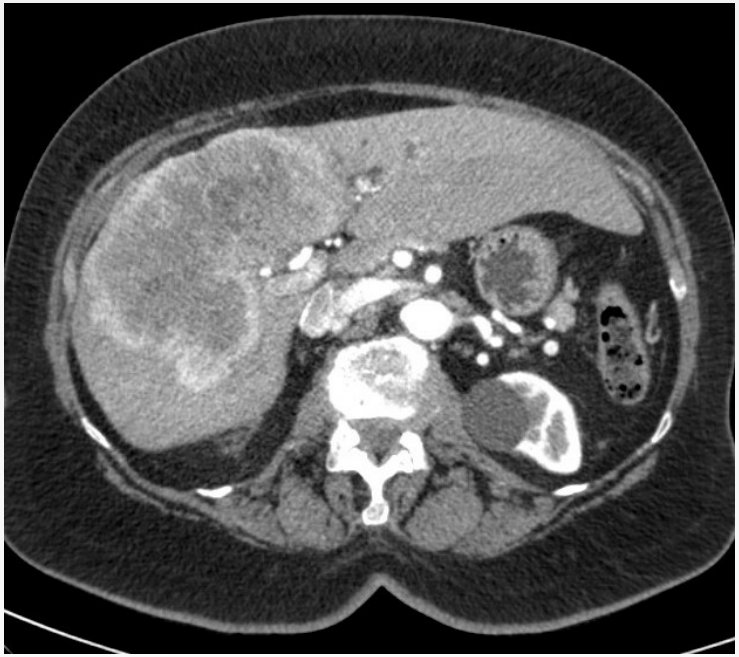
Diagnosis

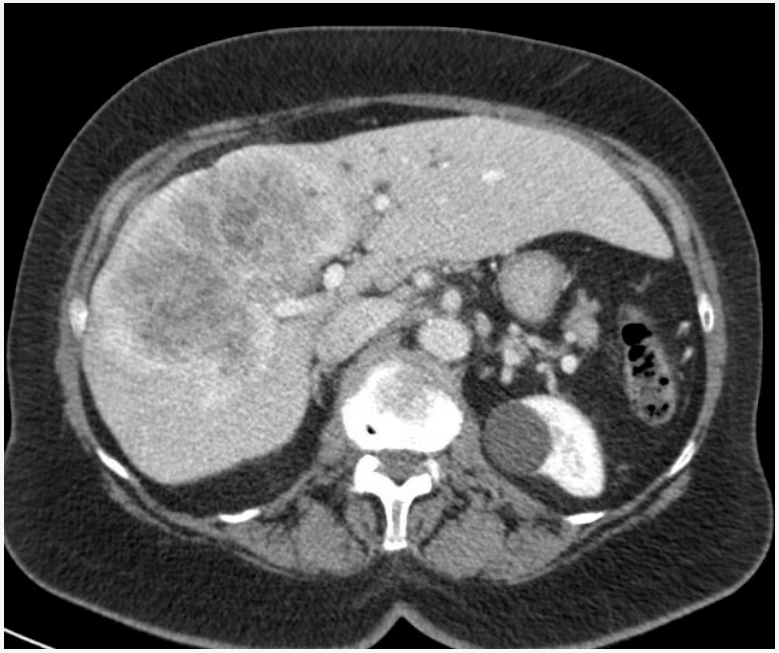
- **Clinical signs and symptoms often appear (too) late**

Cholangiocarcinoma

Diagnosis

- Clinical signs and symptoms often appear (too) late
- **CT is the standard imaging method for CCA**

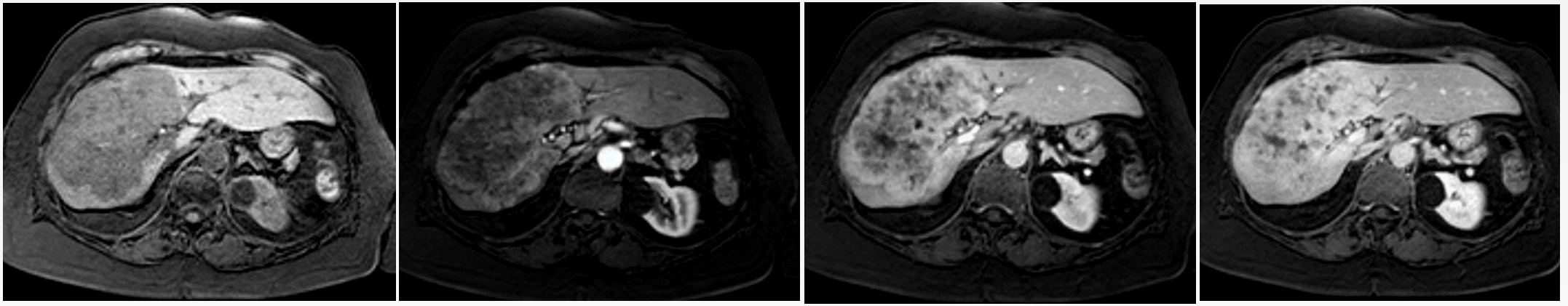




Cholangiocarcinoma

Diagnosis

- Clinical signs and symptoms often appear (too) late
- CT is the standard imaging method for CCA
- **MRI shows similar accuracy and may be of added va**



Cholangiocarcinoma

Diagnosis

- Clinical signs and symptoms often appear (too) late
- CT is the standard imaging method for CCA
- MRI shows similar accuracy and may be of added value (e.g. MRCP)
- **^{18}F- FDG PET has no evidence-based additional diagnostic value**

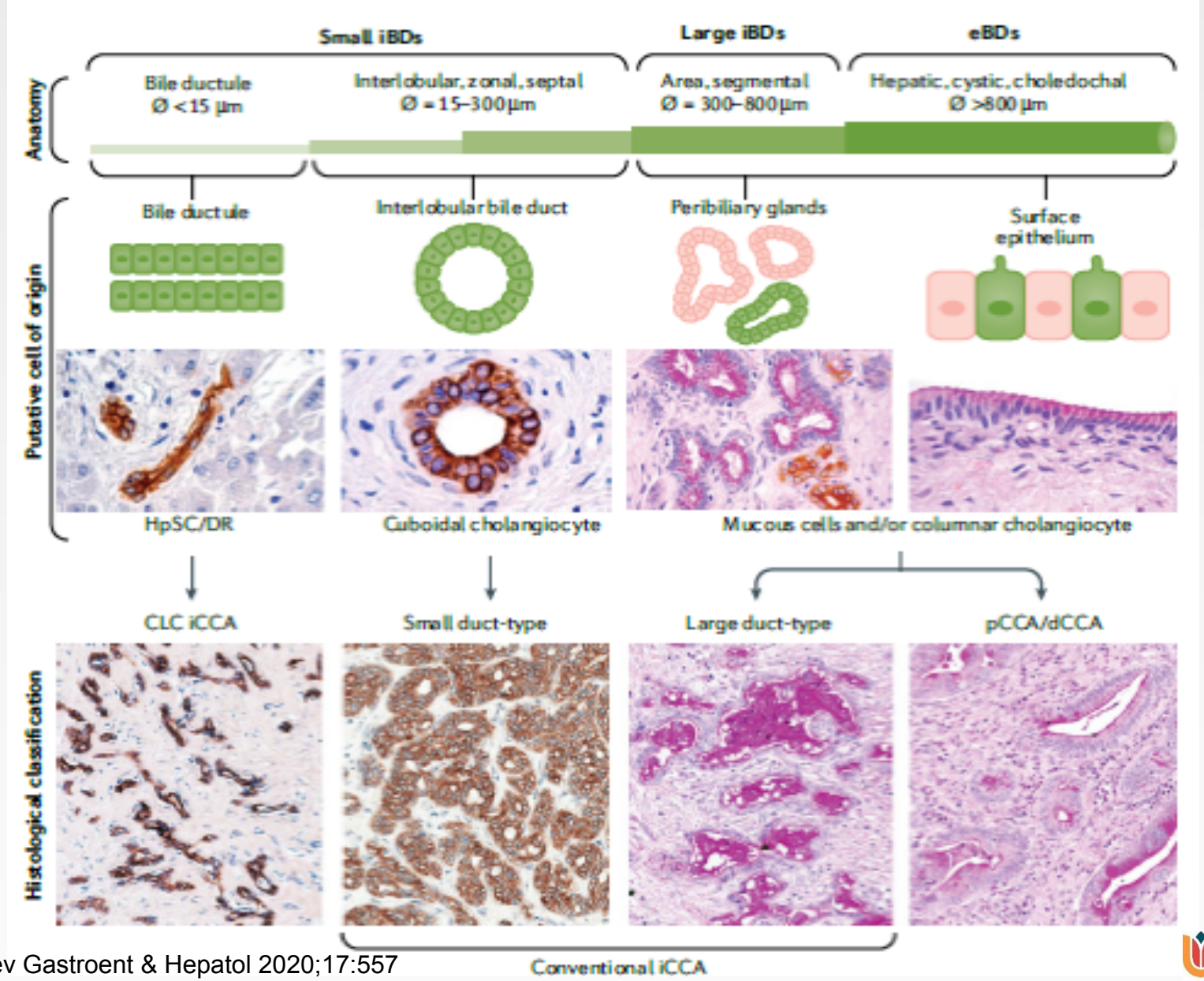
Cholangiocarcinoma

Diagnosis

- Clinical signs and symptoms often appear (too) late
- CT is the standard imaging method for CCA
- MRI shows similar accuracy and may be of added value by e.g. MRCP
- ^{18}F- FDG PET has no evidence-based additional diagnostic value
- **Histopathological / cytological analysis is mandatory for CCA**

  (e.g. by brush cytology, intraductal biopsy)

Cells of origin in cholangiocarcinoma



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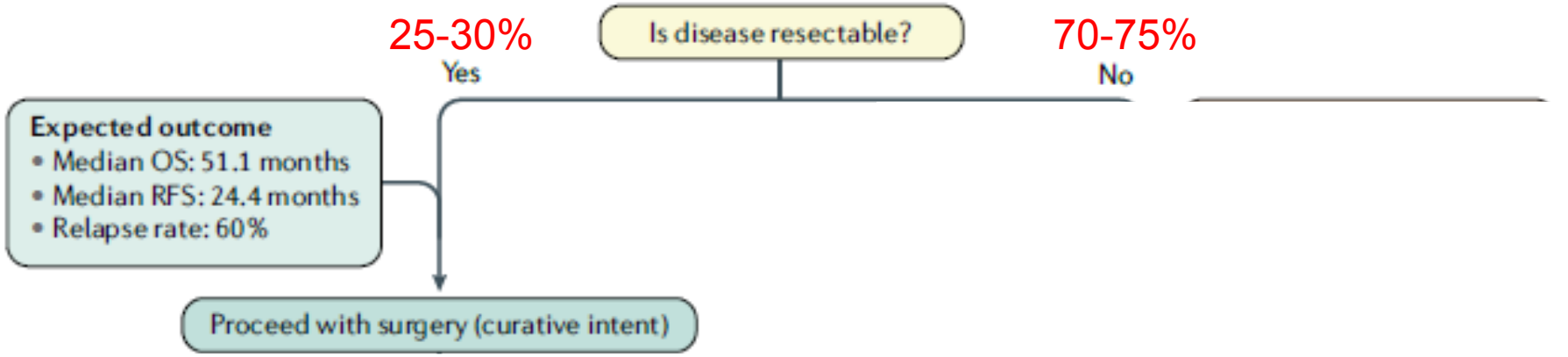
Cholangiocarcinoma

Diagnosis

- Clinical signs and symptoms often appear (too) late
- CT is the standard imaging method for CCA
- MRI shows similar accuracy and may be of added value by e.g. MRCP
- ^{18}F- FDG PET has no evidence-based additional diagnostic value
- Histopathological / cytological analysis is mandatory for CCA (e.g. by brush cytology, intraductal biopsy)
- Future approaches: e.g. biliary miRNAs, serum CYFRA 21-1, osteopontin…

Current management of patients with cholangiocarcinoma

Multidisciplinary approach



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Current management of patients with cholangiocarcinoma

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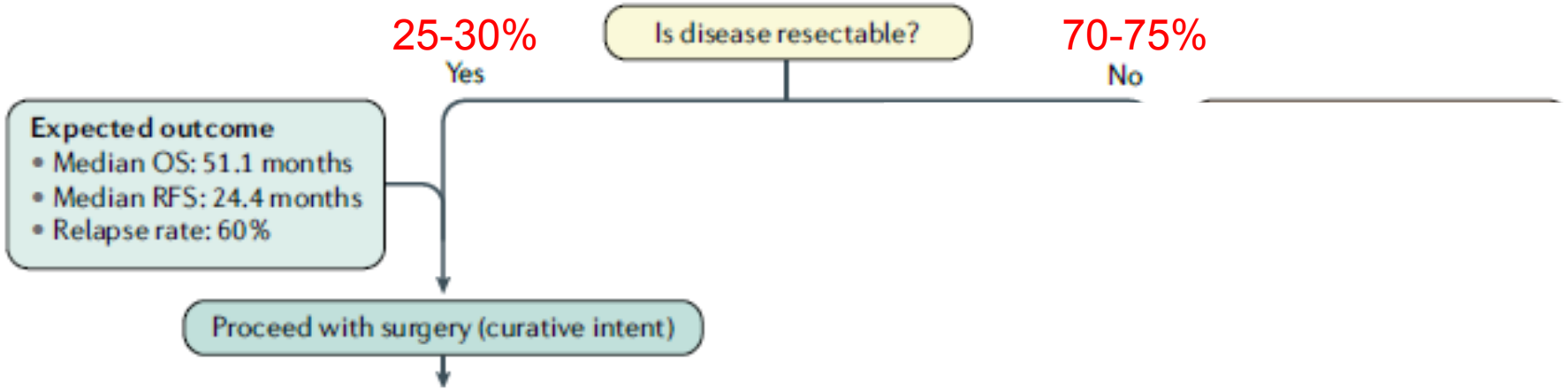


iCCA : (extended) hemihepatectomy, segmental resection

pCCA: (extended) hemihepatectomy

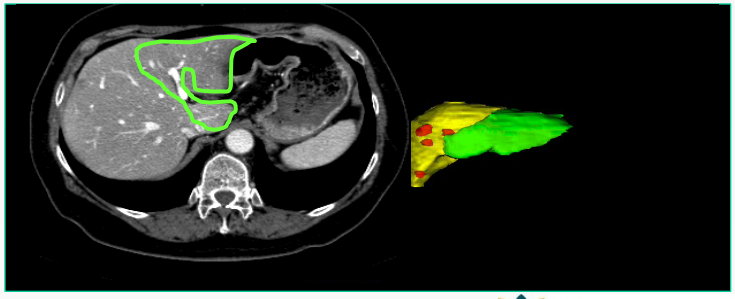
dCCA: pancreatoduodenectomy (Whipple's procedure)

Banales et al. Nat Rev Gastroent & Hepatol 2020;17:557 (Consensus ENS-CCA), modified

Cholangiocarcinoma

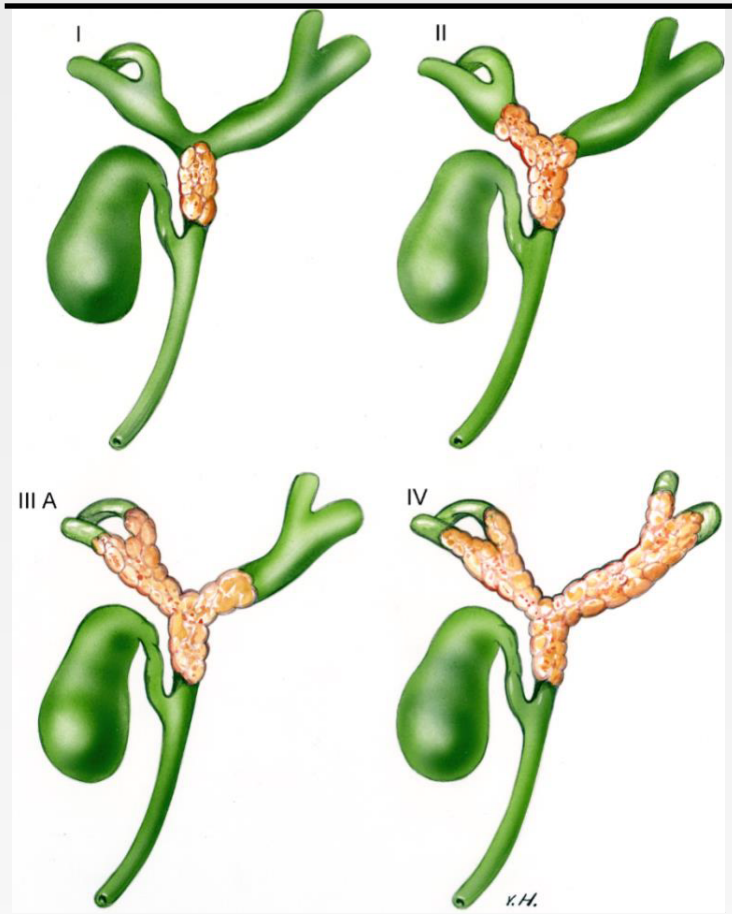
Criteria of resectability

- No (extra)hepatic metastases
- Lymph node metastases confined to hepatoduodenal ligament (N1)
- Possibility of achieving free ductal margins on future remnant liver
- Involvement of portal vein bifurcation possible
- Involvement of hepatic artery branch to future remnant liver : ?
- Volume of future remnant liver > 35-40%



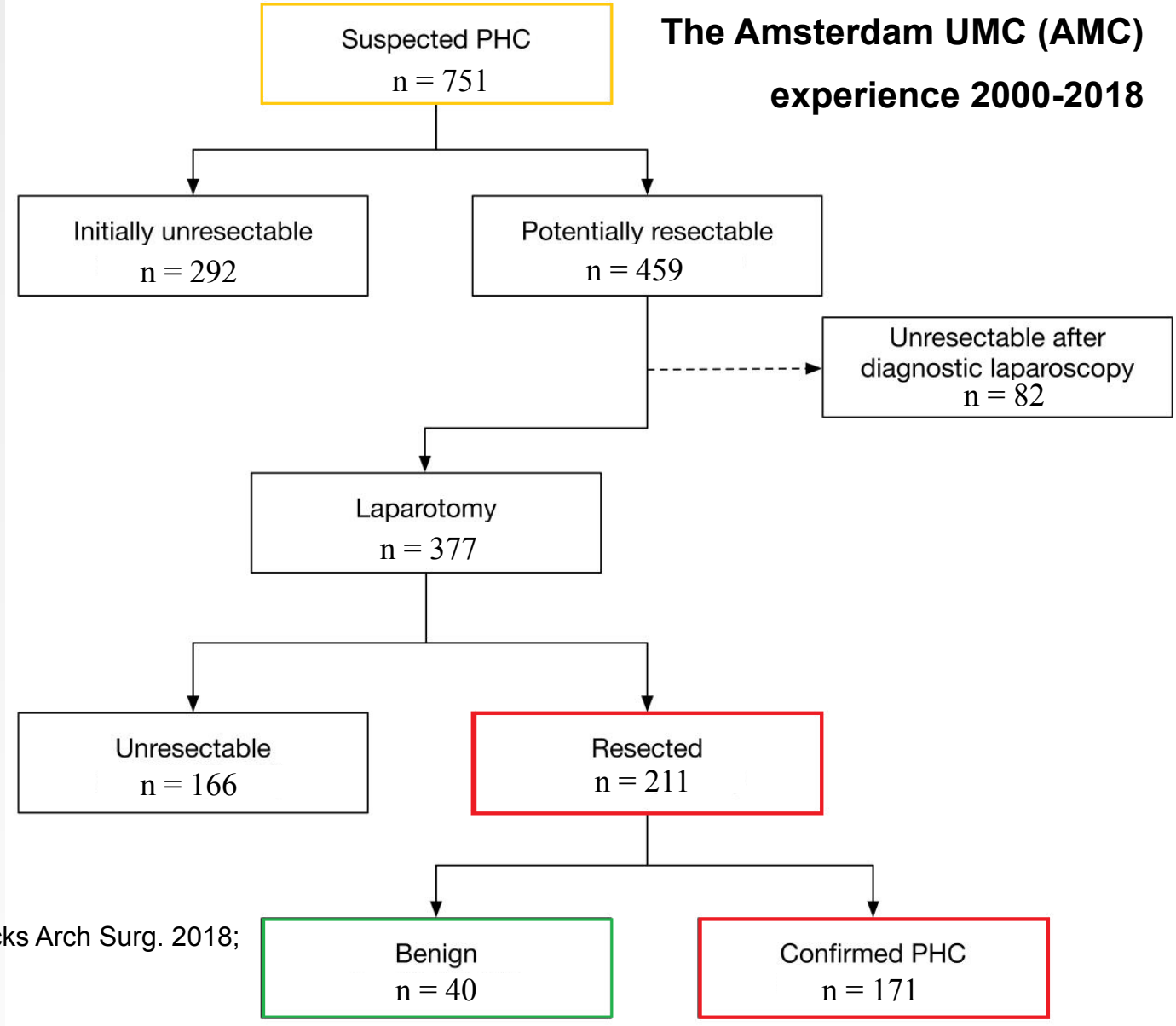
Perihilar Cholangiocarcinoma

Staging and Resectability



Staging according to Bismuth and Corlette

The Amsterdam UMC (AMC) experience 2000-2018



Rassam et al. Langenbecks Arch Surg. 2018; 403:289, updated

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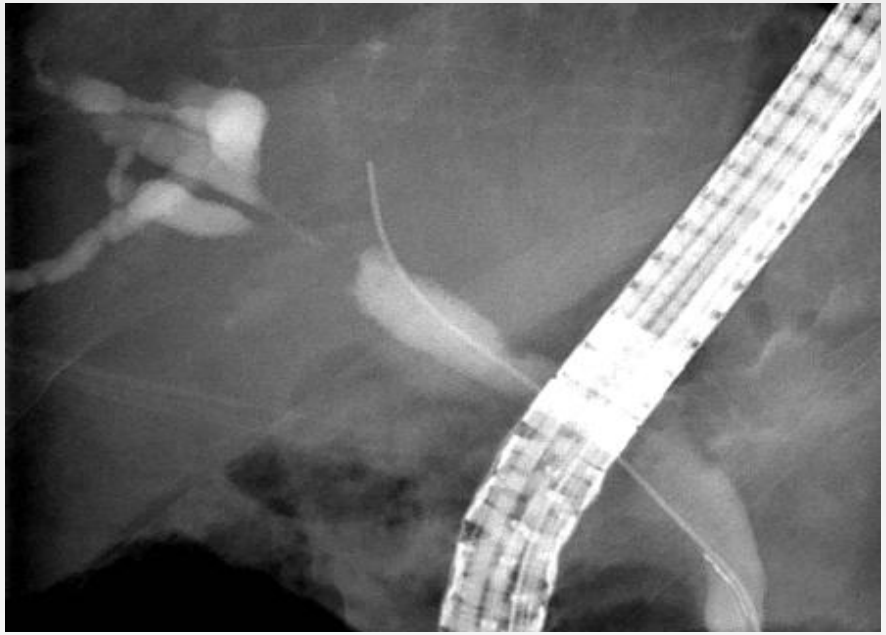
IgG4-related cholangitis mimics CCA

How to distinguish benign and malignant biliary stenosis?



Cholangiographic appearance mimicking cholangiocarcinoma (**CCA**)

Misdiagnosis is common!

Hubers & Beuers, Viszeralmedizin 2015;31:185

Cholangiocarcinoma mimicking lesion – a problem?

AMC 1984–2015: 323 resections under suspicion of cholangiocarcinoma

50 (15%) : benign

21/50 : IgG4-related cholangitis

29/50 : fibrosing cholangitis (undefined)

Roos et al. Am J Gastroenterol 2018;113:765

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Preoperative biliary drainage (PBD) in resectable CCA ?

pCCA

YES, at least when
- cholangitis
- <50% future liver remnant volume

Cholangitis
Pancreatitis

Improved liver remnant function and regeneration

<u>90-day mortality after PBD</u>

ERC	vs.	PTC
3/27		11/27

→ Endoscopic route prefered

Coelen et al. Lancet Gastroenterol Hepatol. 2018;3:681

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Preoperative biliary drainage (PBD) in resectable CCA ?

pCCA **vs.** **dCCA**

YES, at least when
- cholangitis
- <50% future liver remnant volume

NO

Cholangitis
Pancreatitis

Improved liver remnant function and regeneration

Cholangitis
Pancreatitis

Relief from jaundice

90-day mortality after PBD

ERC 3/27 vs. PTC 11/27

→ Endoscopic route prefered

Variable	Early Surgery (N=94)	PBD group (N=102)	RR	95% c.i.
Overall complications - n (%)*	37 (39)	76 (75)	0.53	0.40 - 0.70
PBD complications - n (%)	2 (2)	48 (47)	NA	
Surgery complications - n (%)	35 (37)	48 (47)	0.79	0.57 - 1.11
Other complications (not prot.) - n (%)	30 (32)	25 (25)	1.30	0.83 - 2.04
Mortality	4 (4)	9 (9)	0.48	0.15 - 1.51
Hospital readmisson - n (%)*	11 (12)	34 (33)	0.35	0.19 - 0.65
Hospital stay - days (median; IQR)	13 (10-20)	15 (11-22)	-	

Coelen et al. Lancet Gastroenterol Hepatol. 2018;3:681

Van der Gaag et al. N Engl J Med 2010;326:129

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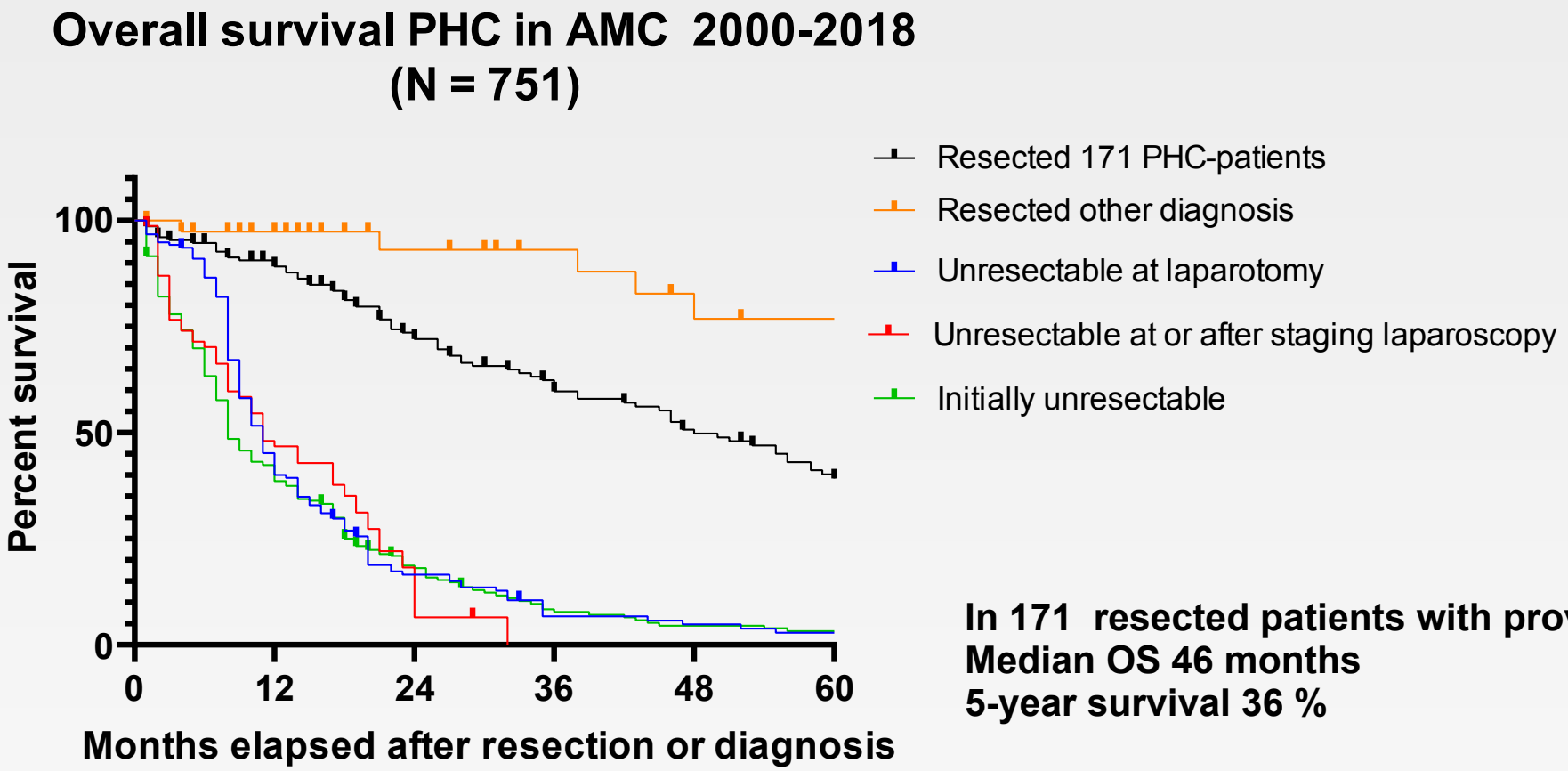
Overall survival of patients with pCCA 2000 - 2018



In 171 resected patients with proven pCCA:
Median OS 46 months
5-year survival 36 %

Rassam et al. Langenbecks Arch Surg. 2018;403:289, updated

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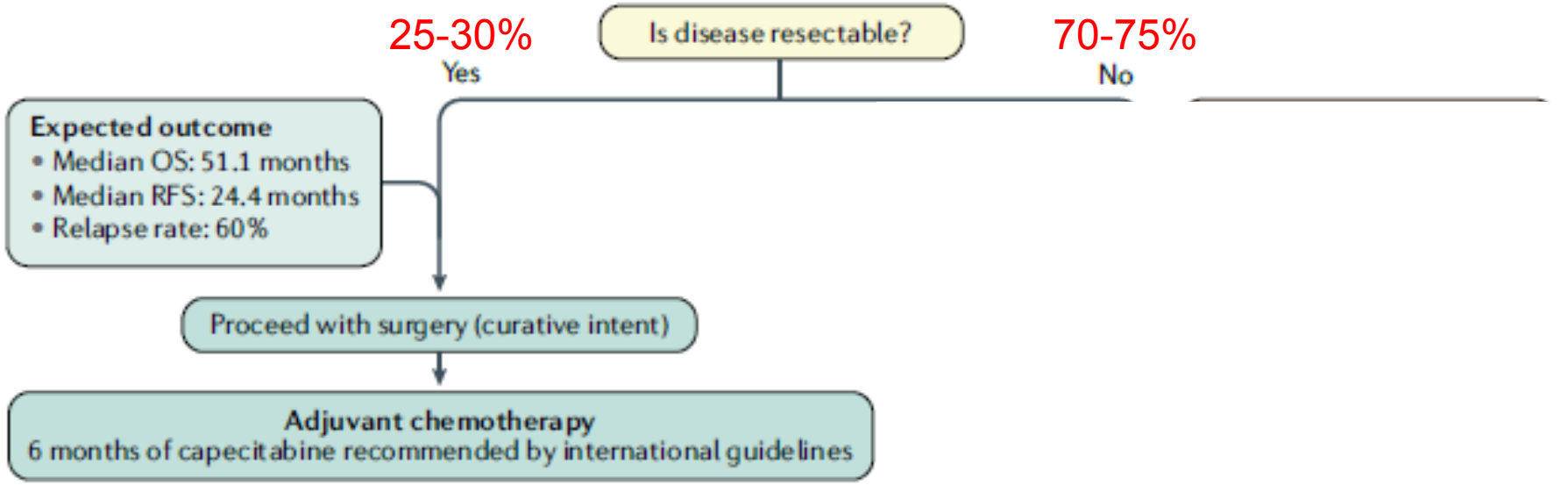
Current management of patients with cholangiocarcinoma

Multidisciplinary approach



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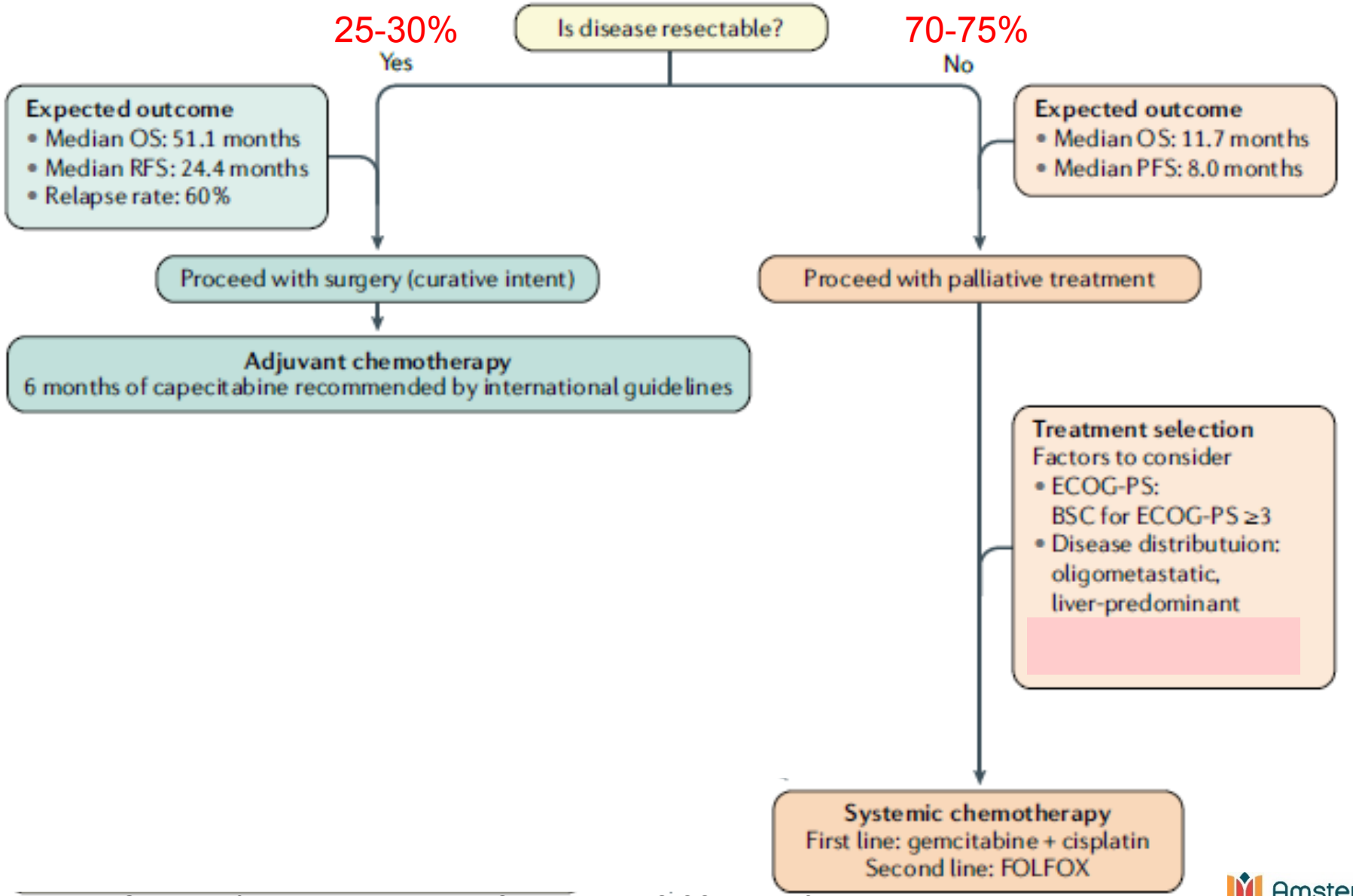

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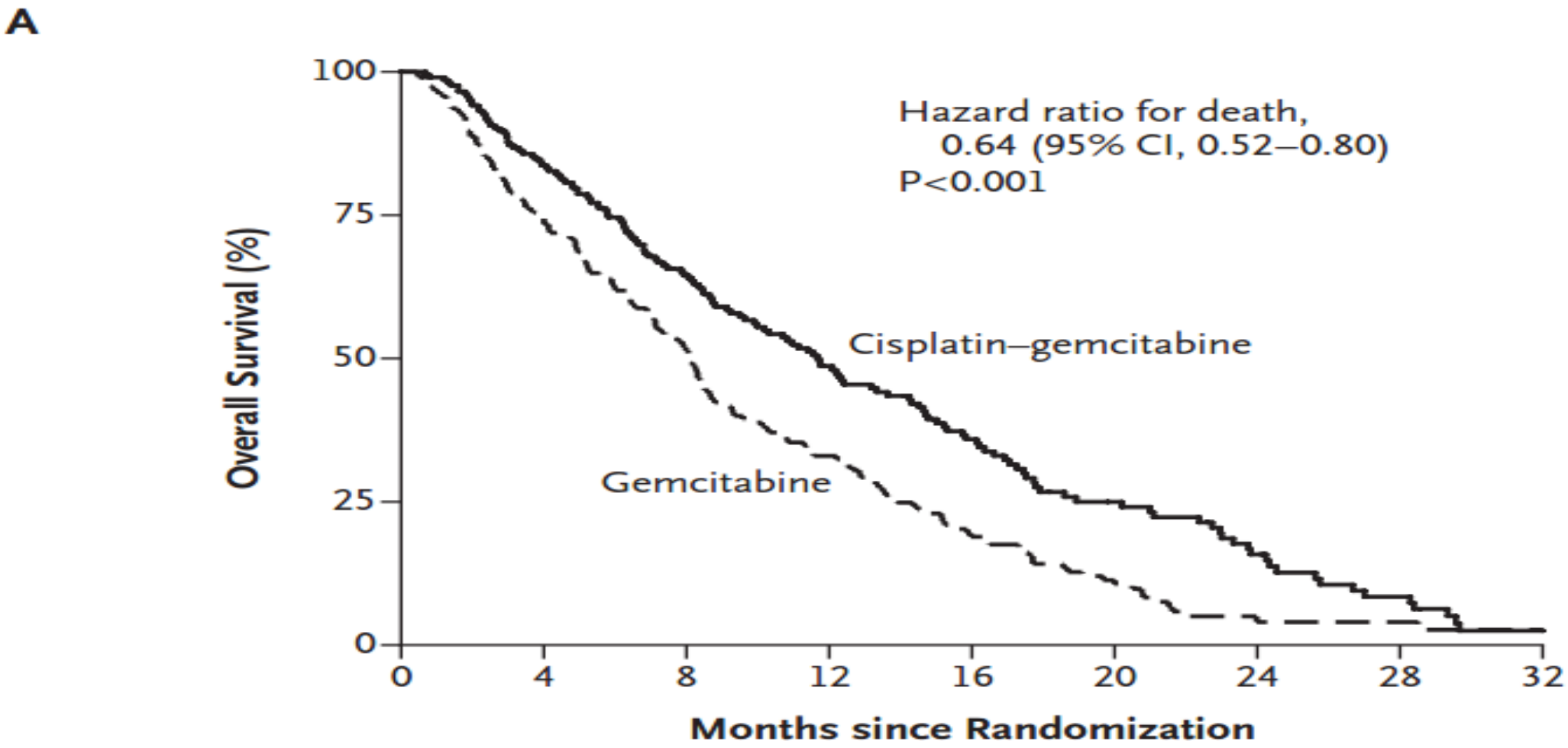
Systemic chemotherapy of cholangiocarcinoma

1st line: Cisplatin-Gemcitabine



No. at Risk									
Gemcitabine	206	151	97	53	28	15	4	3	2
Cisplatin–gem-citabine	204	167	120	76	51	28	17	8	2

Valle et al. N Engl J Med 2010; 362:1273

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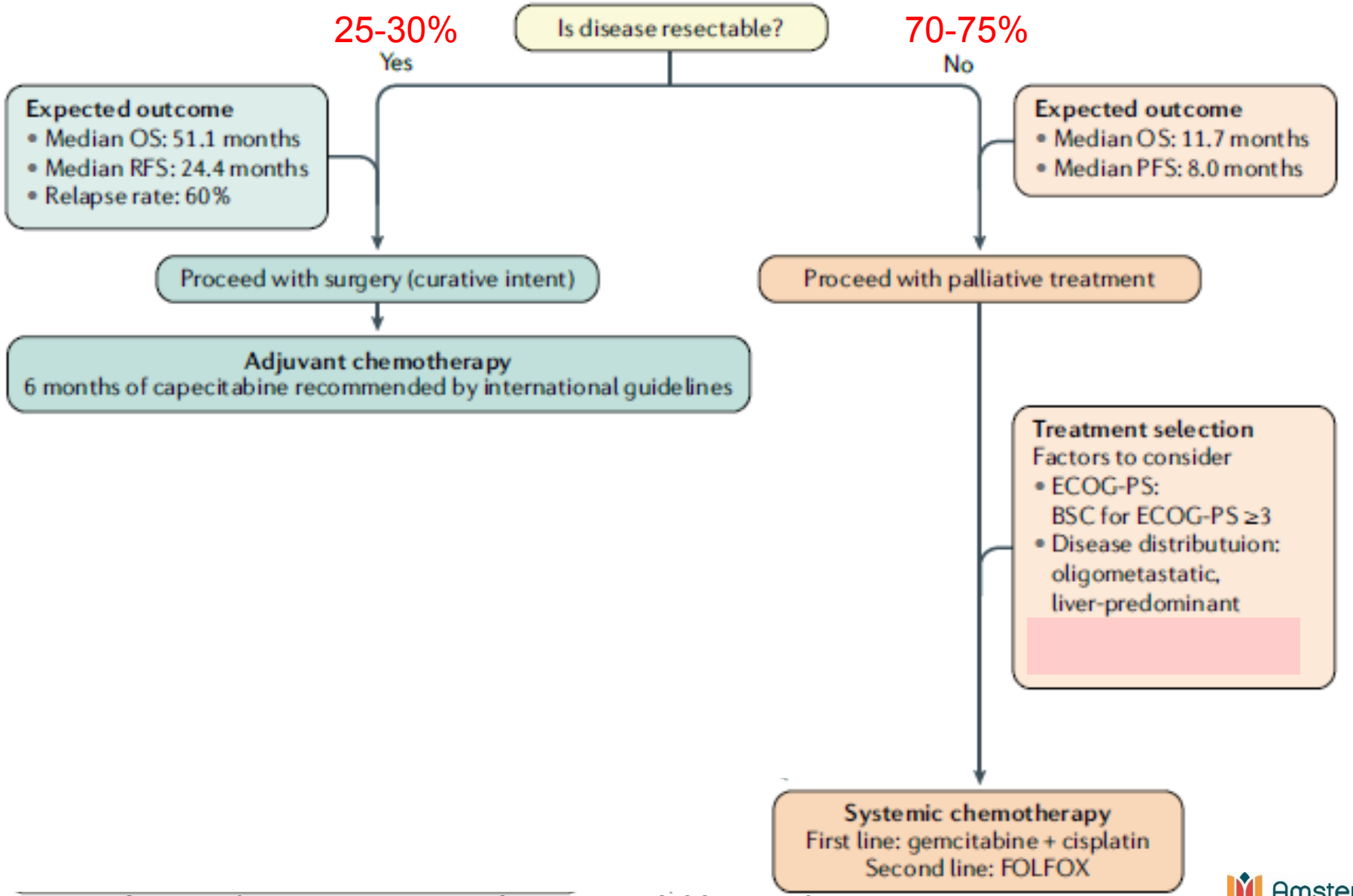
Current management of patients with cholangiocarcinoma

Multidisciplinary approach



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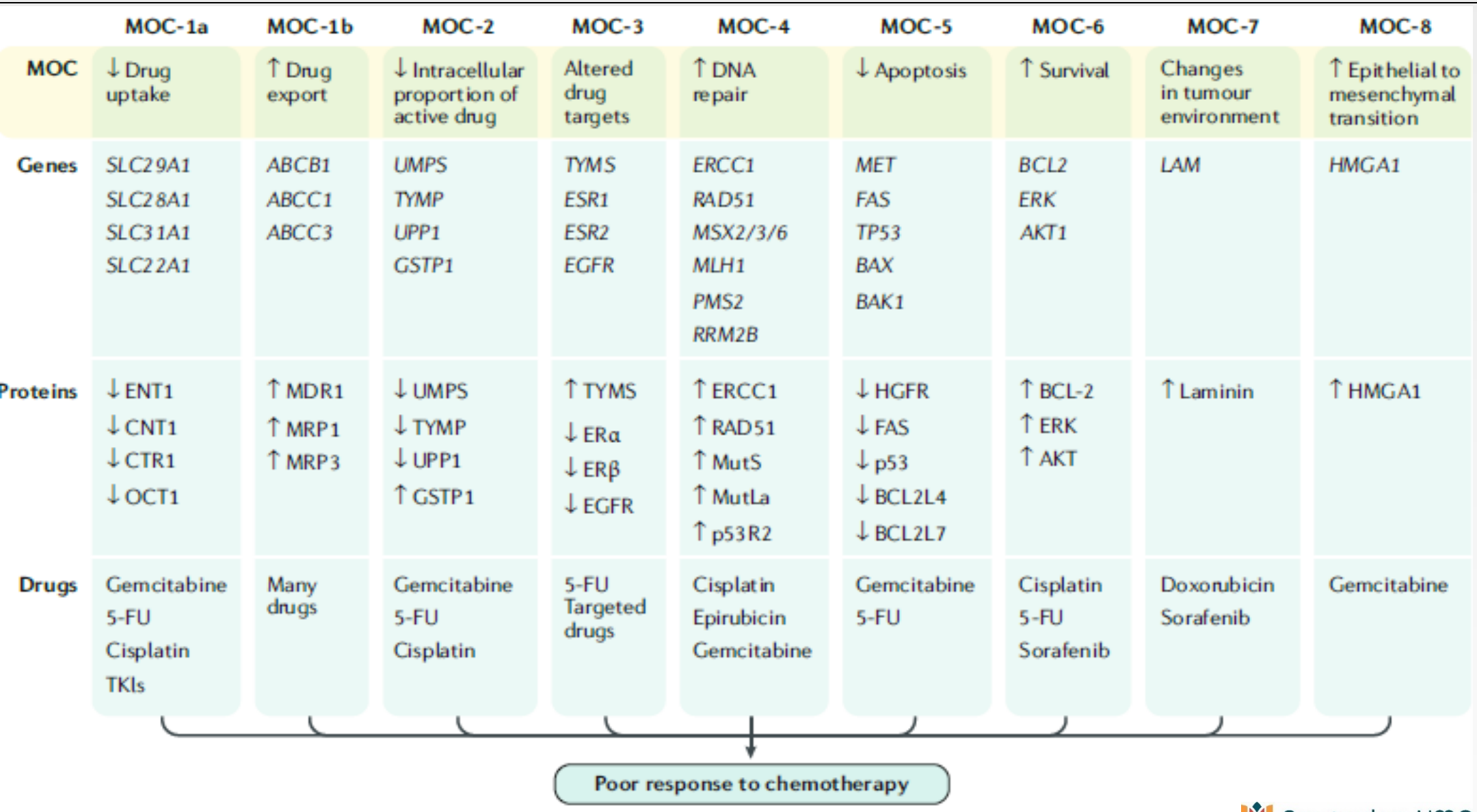
Systemic chemotherapy of cholangiocarcinoma

Mechanisms of chemoresistance



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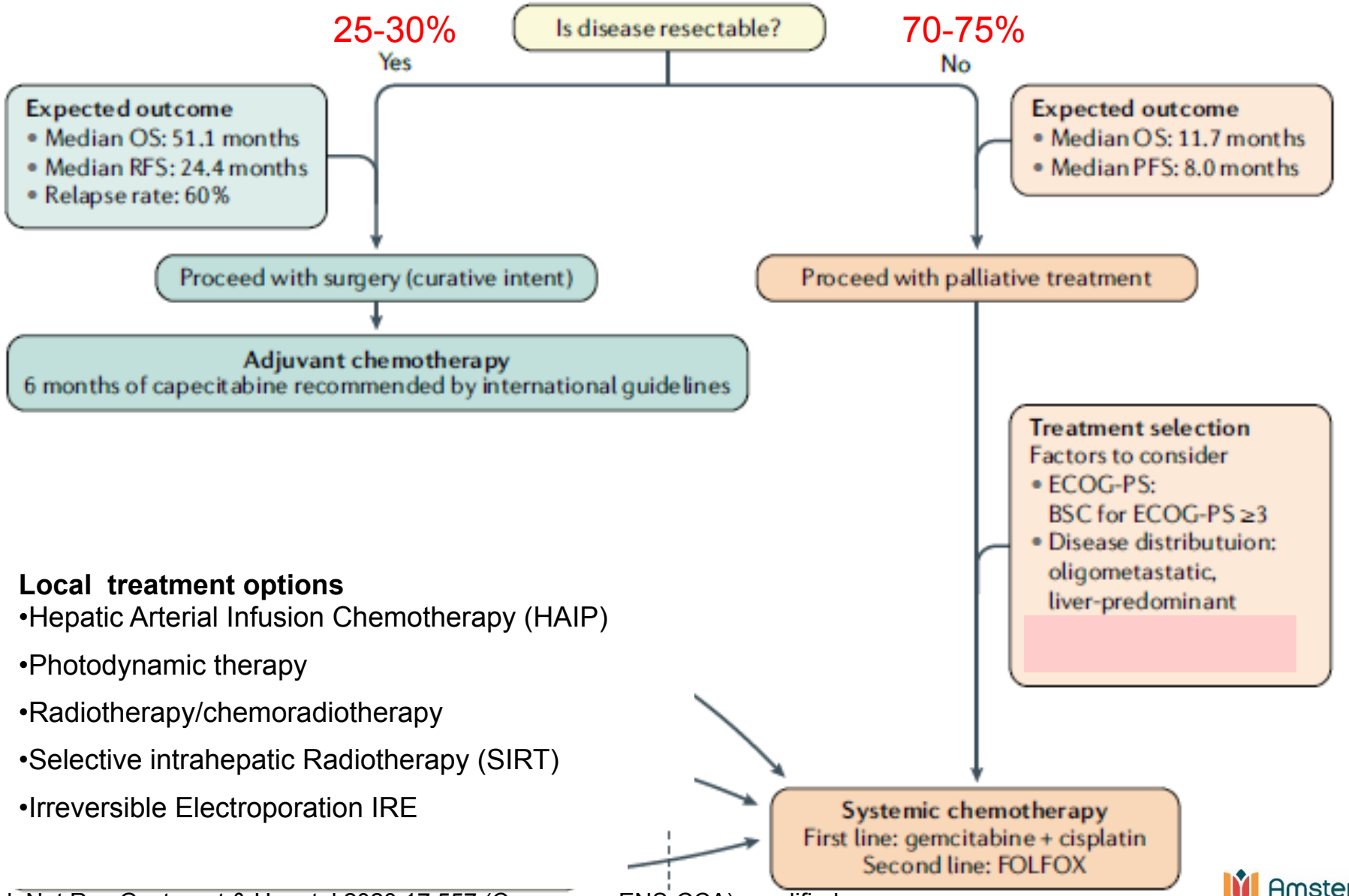
Current management of patients with cholangiocarcinoma

Multidisciplinary approach



Local treatment options

- Hepatic Arterial Infusion Chemotherapy (HAIP)
- Photodynamic therapy
- Radiotherapy/chemoradiotherapy
- Selective intrahepatic Radiotherapy (SIRT)
- Irreversible Electroporation IRE

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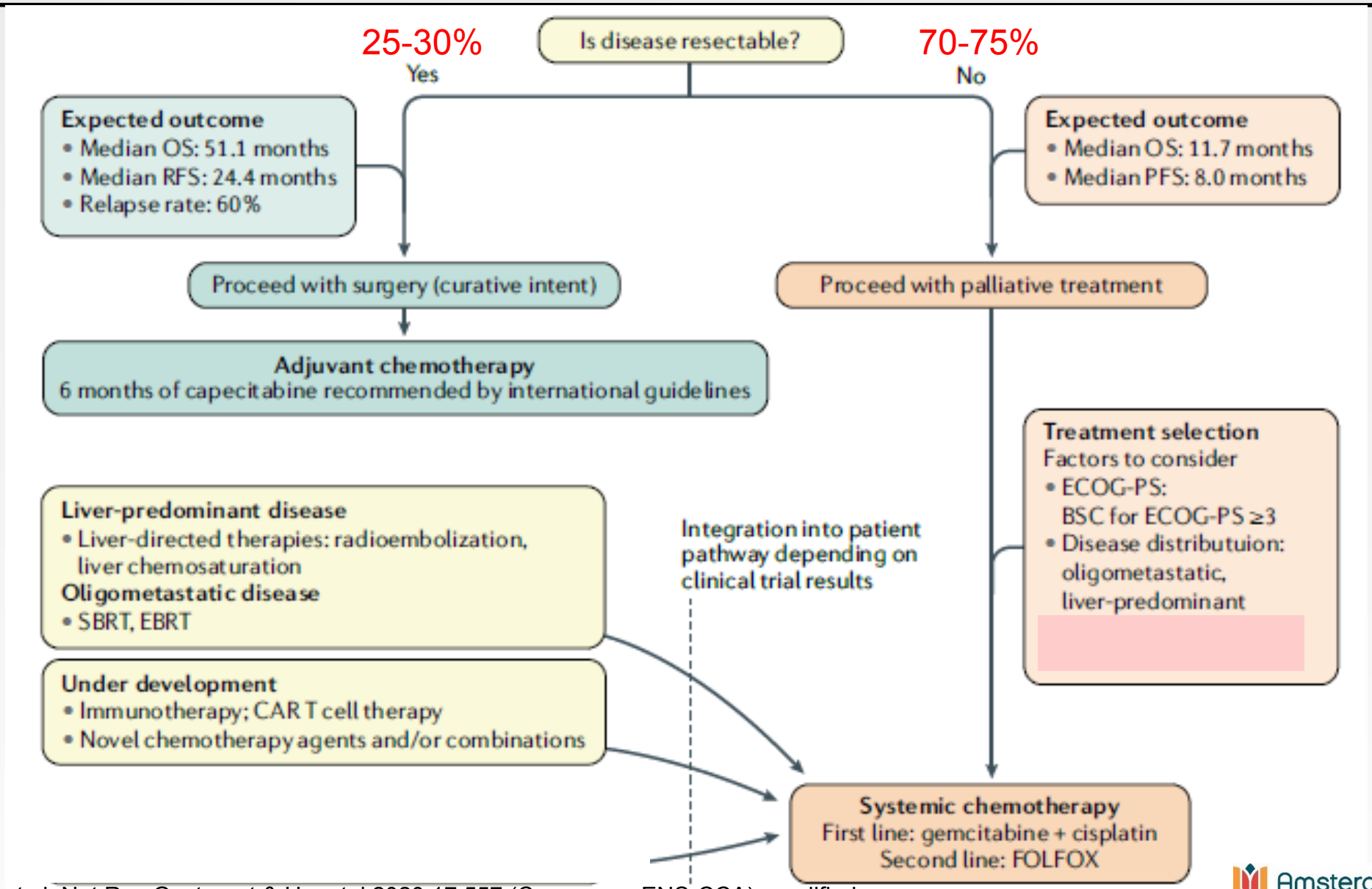
Current management of patients with cholangiocarcinoma

Multidisciplinary approach



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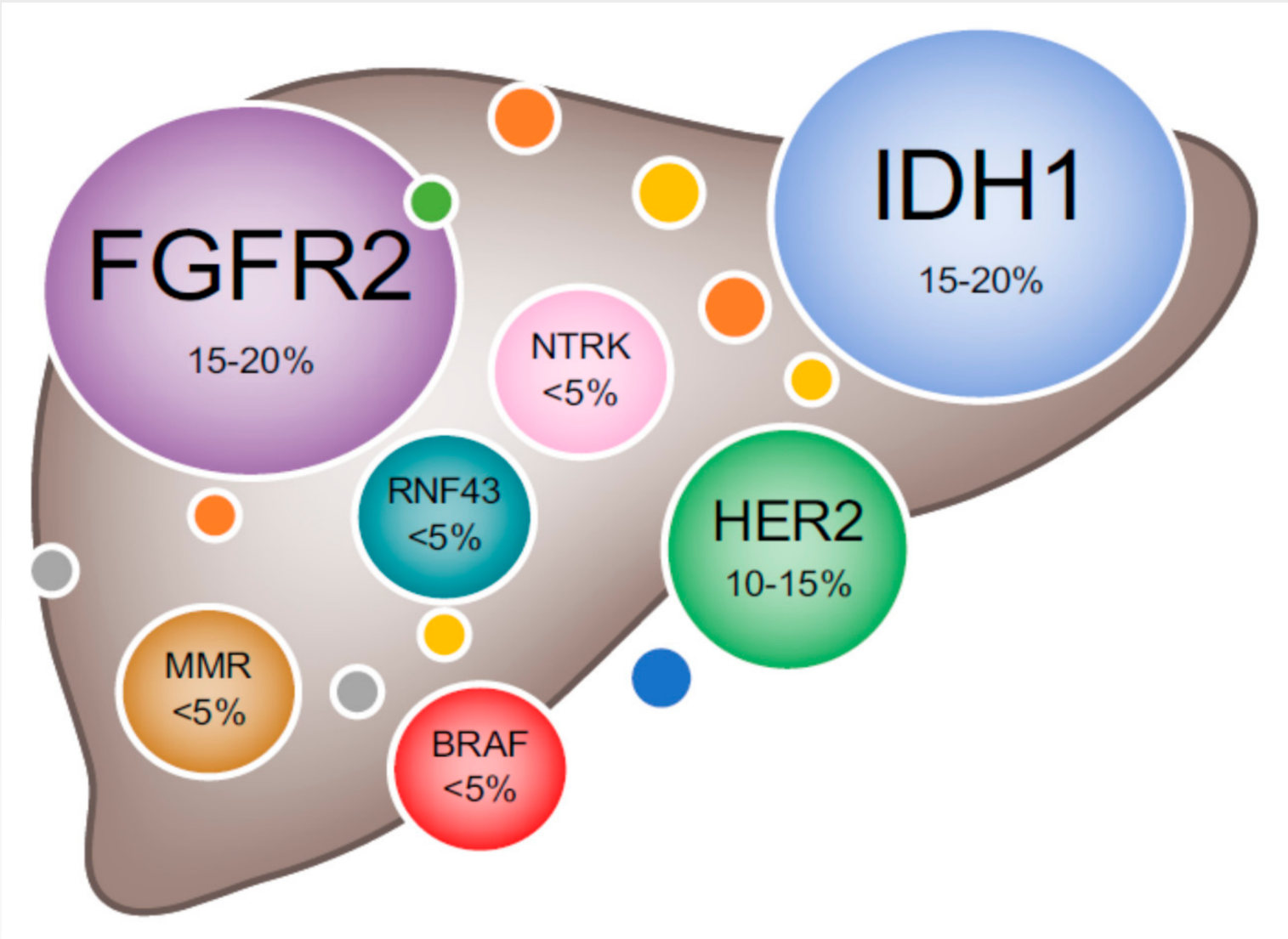
Chemotherapy of cholangiocarcinoma

Molecular profiling and targeting of actionable mutations/amplifications



Personeni et al. Cancers 2020;12:3370

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Current management of patients with cholangiocarcinoma

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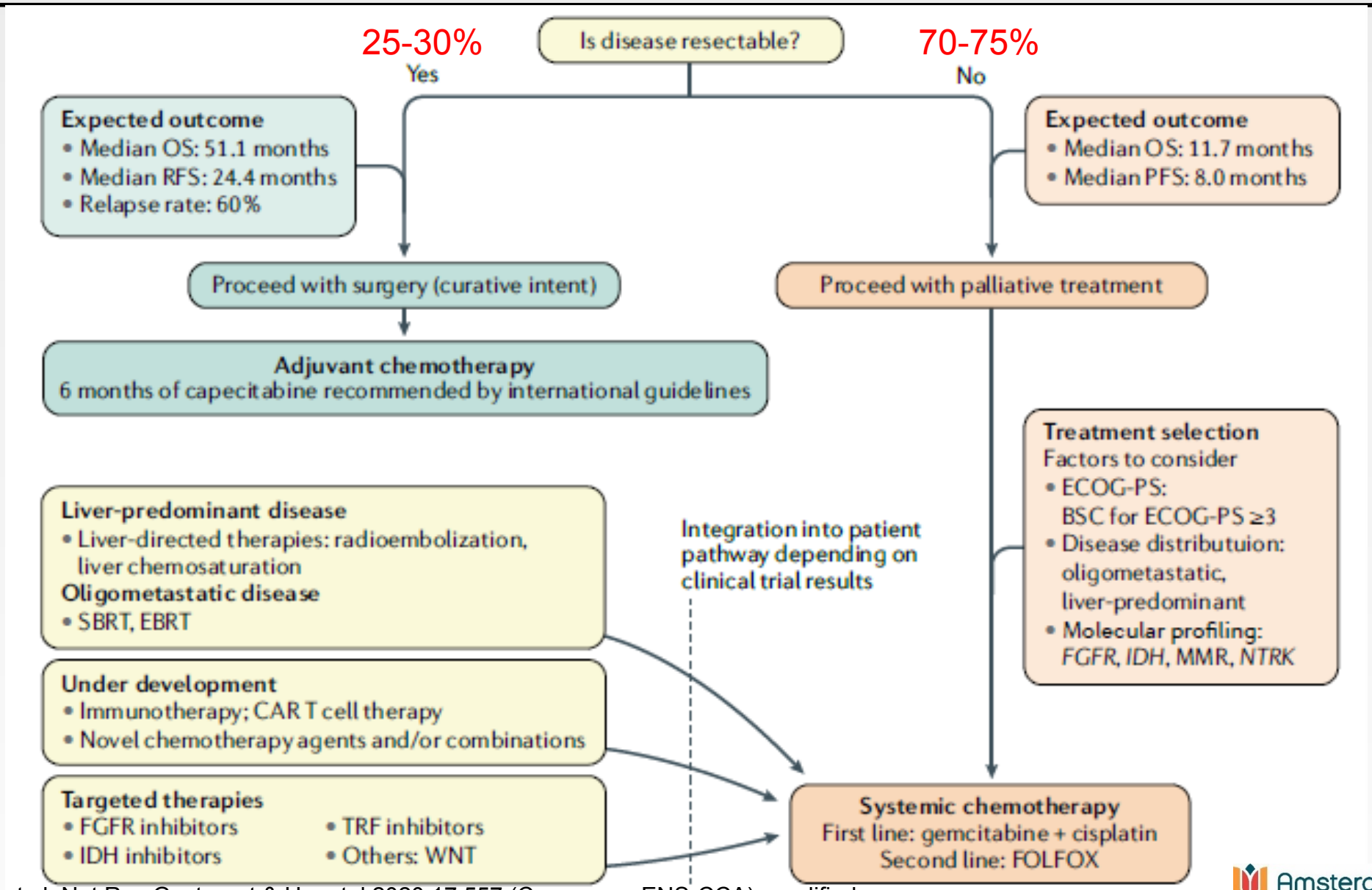

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Clinical management of cholangiocarcinoma

- Surgical resection is a potential curative option for CCA
- Adjuvant chemotherapy with Capecitabine for 6 months after surgical resection is recommended
- Liver transplantation is a potentially curative option for iCCA and pCCA under strict limitations following national protocols
- Cisplatin-Gemcitabine is the standard of palliative care chemotherapy for patients with unresectable CCA
- FOLFOX can be recommended as 2nd line standard of palliative care chemotherapy
- Promising local and systemic therapeutic approaches are under development

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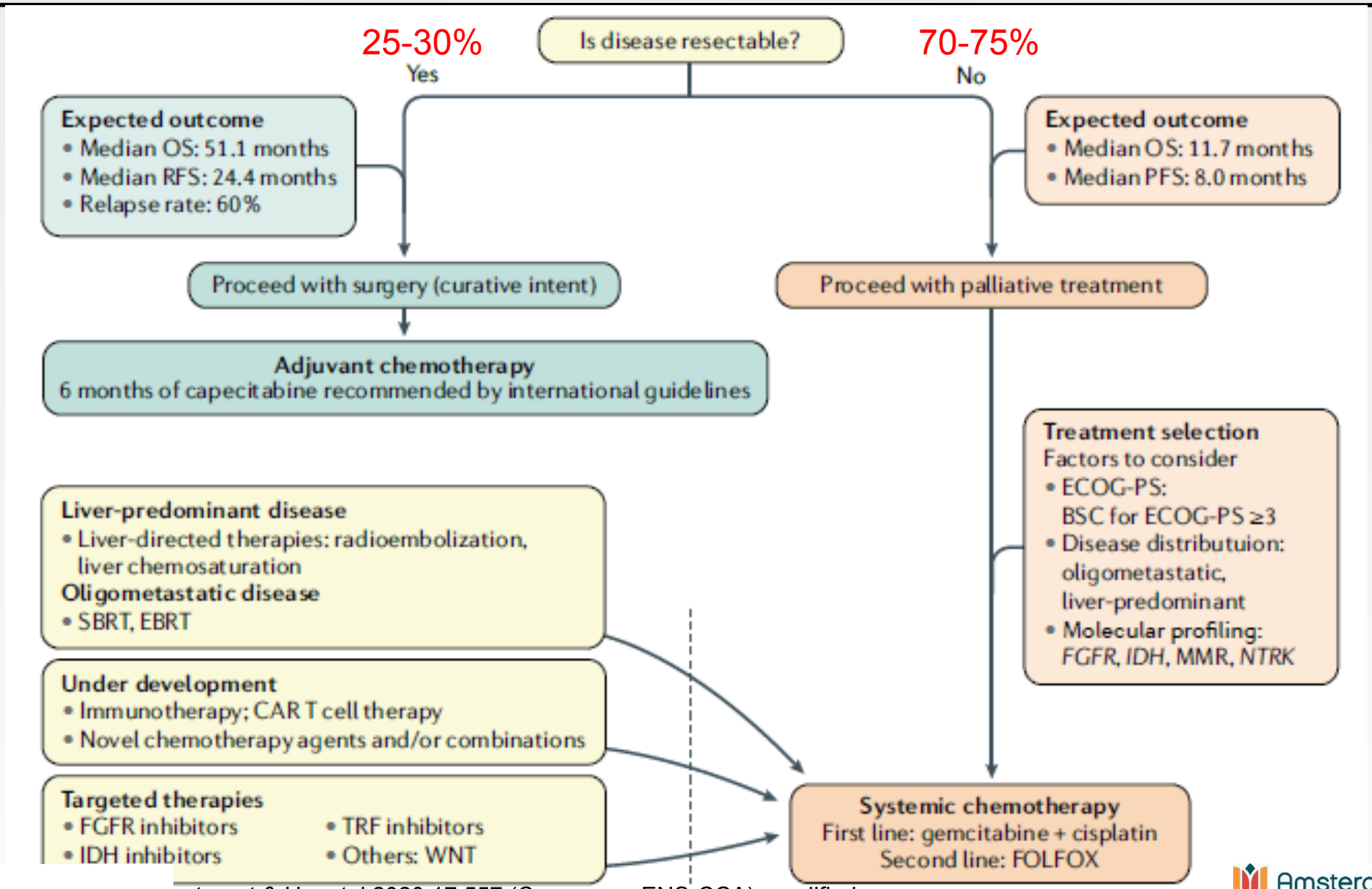

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