Liver Transplant for Cholangiocarcinoma: Ready for Prime Time?

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INEDSYS Hepatology Club and Video Library
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Disclosures

- Medical advisory board, AstraZeneca, 2022

INEDSYS

Acknowledgement

- Thank you to Sanjaya Satapathy for invitation

Objective

- Discuss current data on BTC and the role of liver transplantation

Case

- 64 year old healthy man
- Developed fatigue and painless jaundice in October 2009
- Laboratory evaluation revealed total bilirubin of 9.1 mg/dl
- RUQ ultrasound: decompressed gall bladder, no stones, intrahepatic ductal dilatation, extrahepatic bile duct 5 mm.

Courtesy of C. Sonnenday

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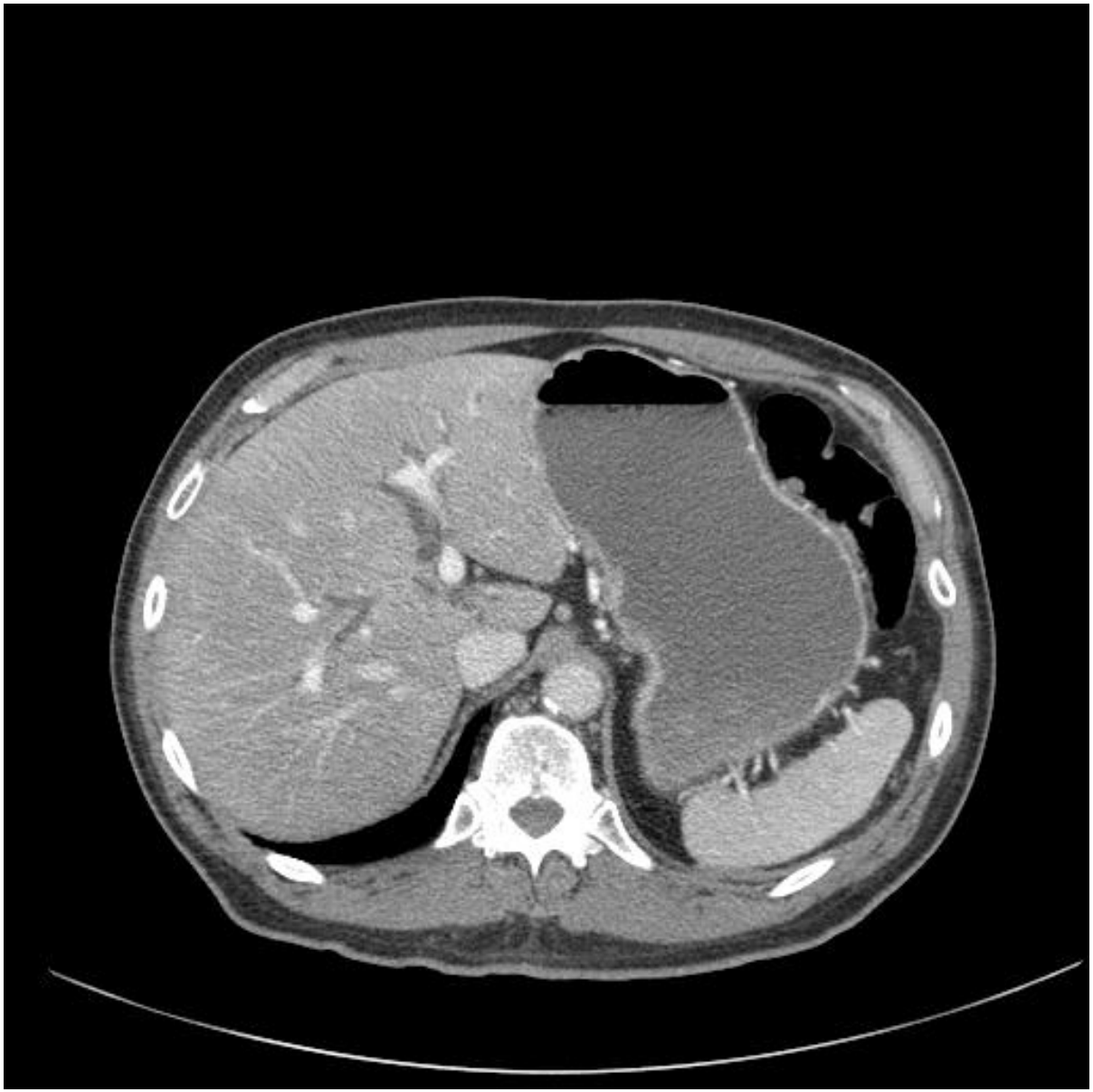

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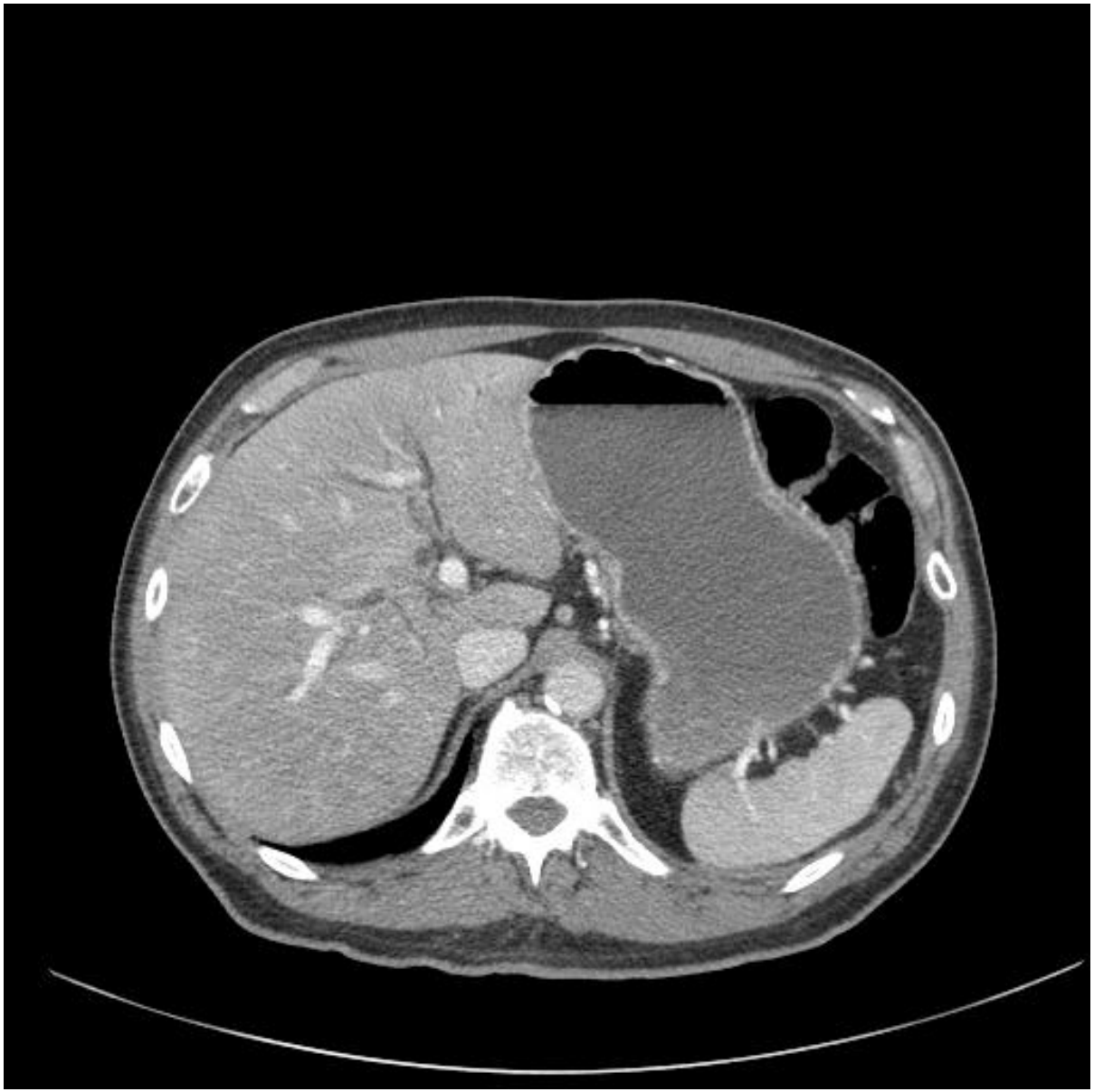

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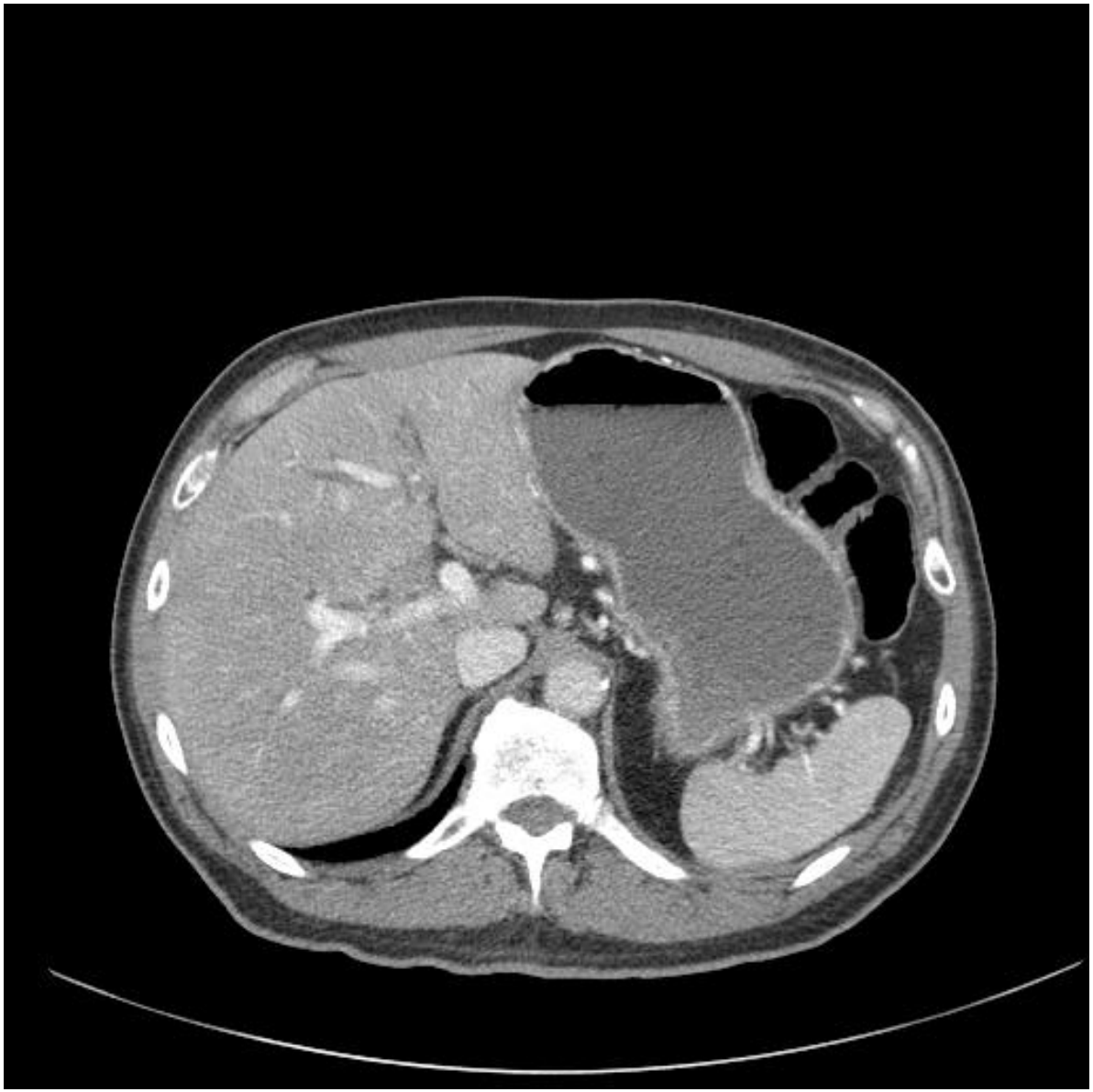

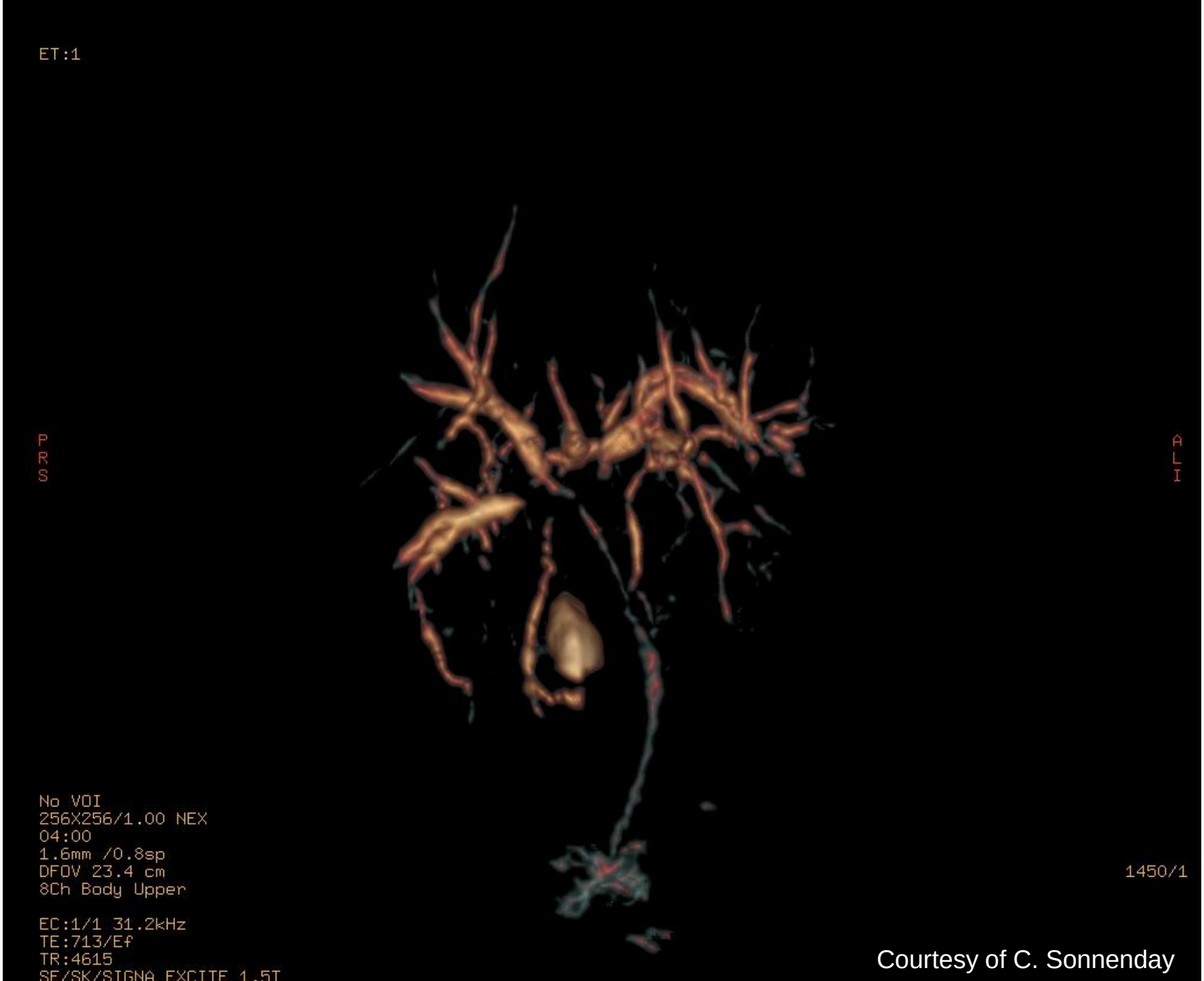

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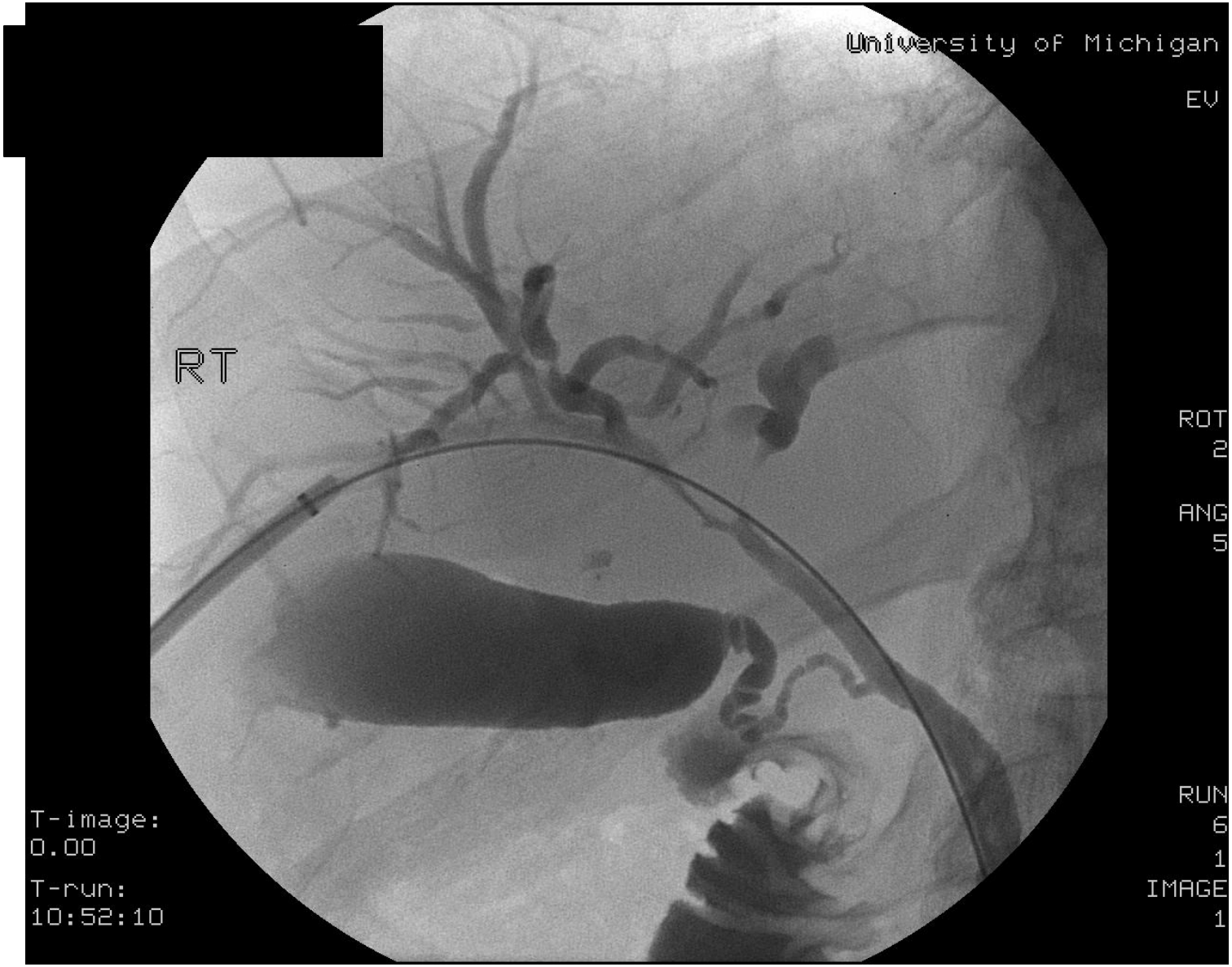

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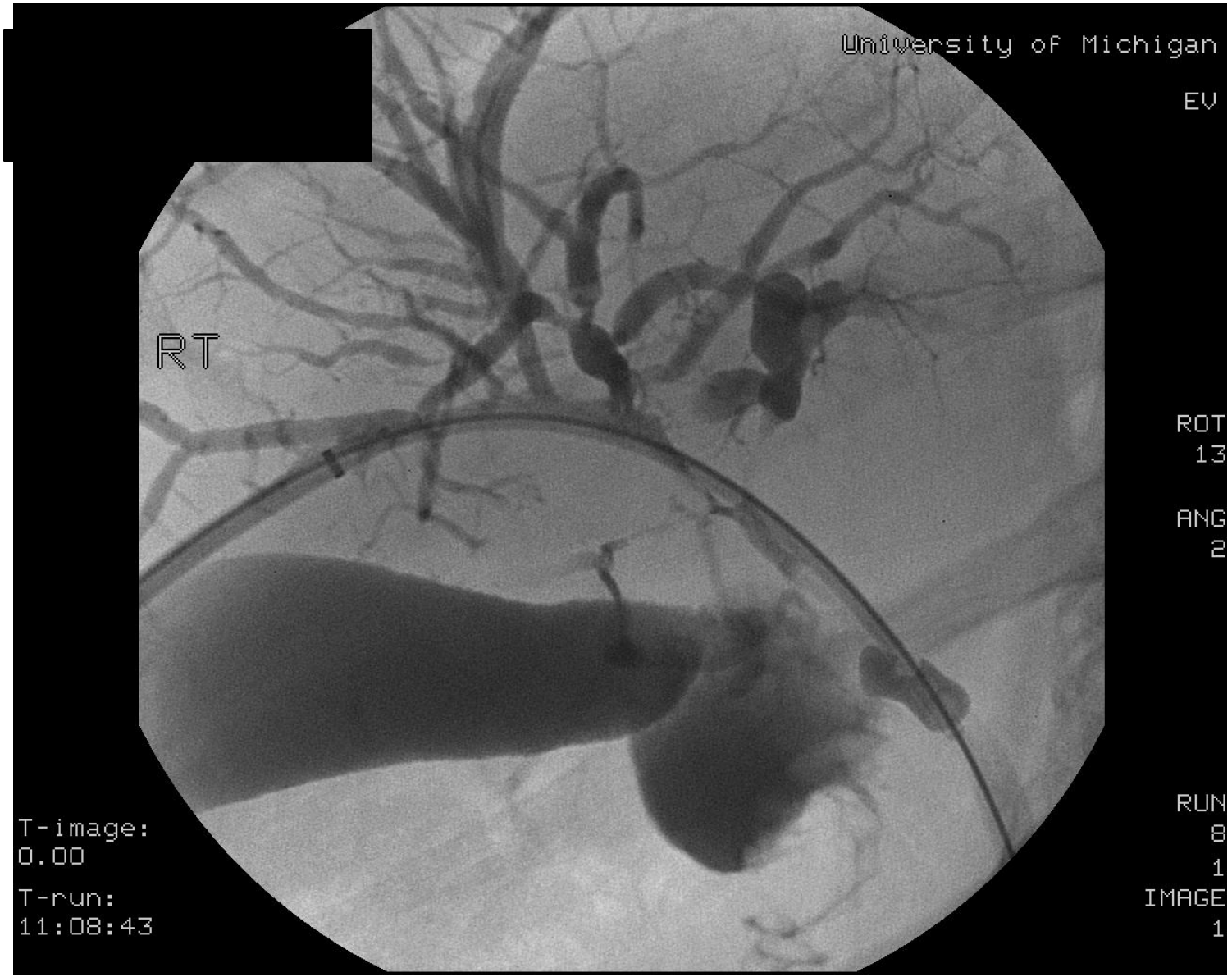

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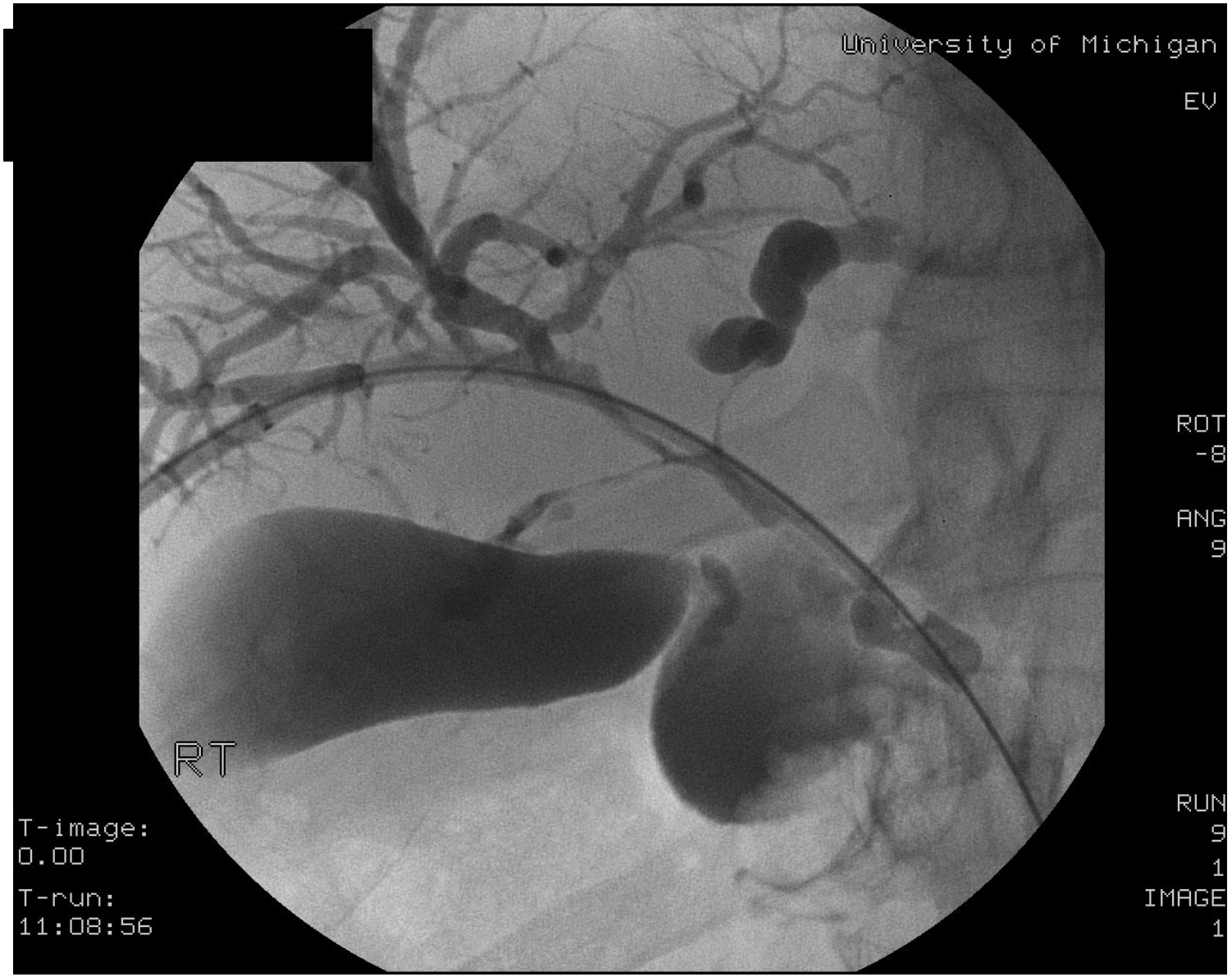


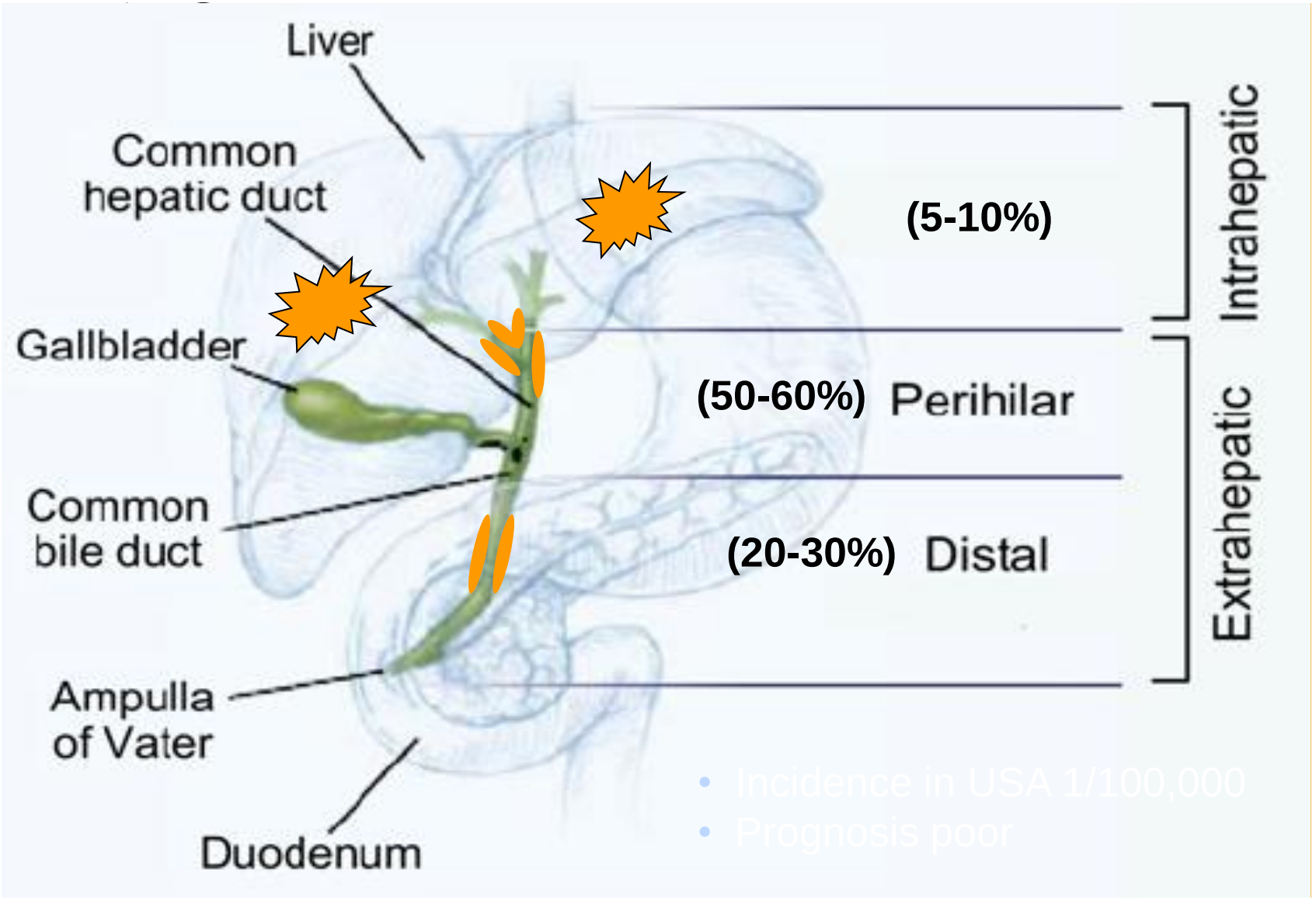
Adenocarcinoma of the Hepatic Duct at Its Bifurcation Within the Porta Hepatis*

An Unusual Tumor with Distinctive Clinical and Pathological Features

GERALD KLATSKIN, M.D.
New Haven, Connecticut

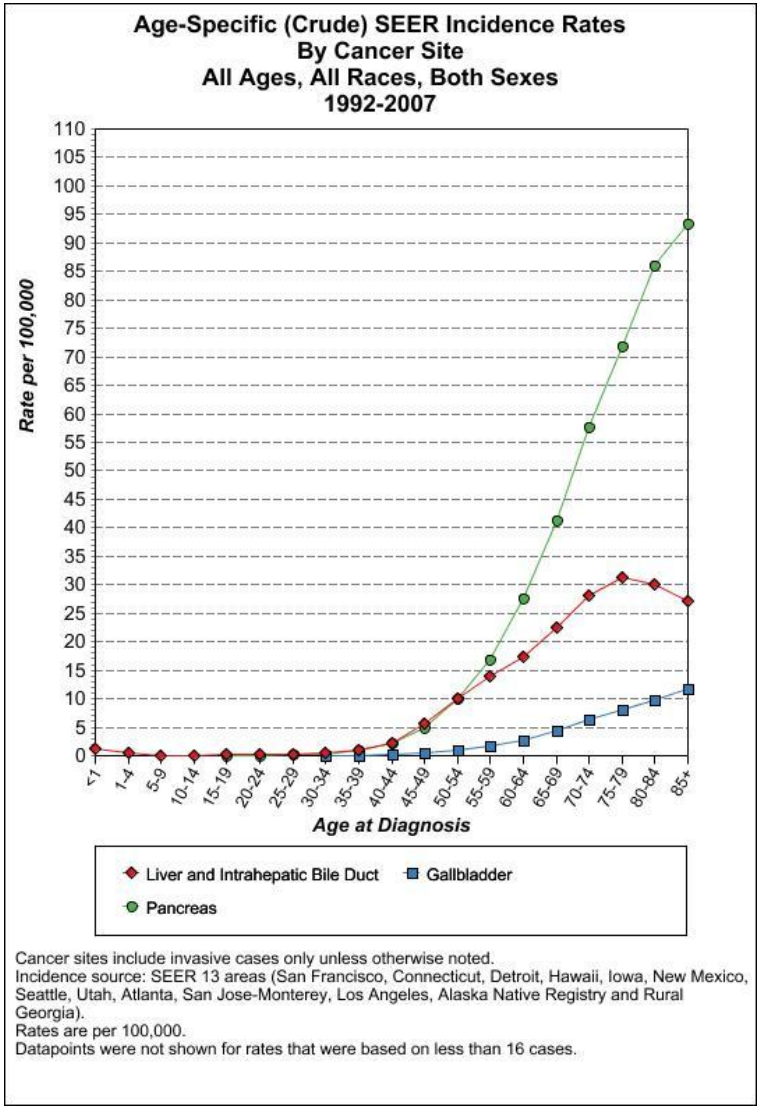
- "Based on a study of thirteen cases, the distinctive clinical and pathological features of adenocarcinomas of the hepatic duct at its bifurcation within the porta hepatis are described. It is concluded that (1) **tumors of this type are frequently overlooked during laparotomy because of failure to explore the hepatic duct bifurcation** and its tributaries by retrograde probing and cholangiography, (2) **death in this disease is usually attributable to hepatocellular failure and/or hepatobiliary infection secondary to unrelieved biliary obstruction rather than to massive invasion of the liver by tumor or to extrahepatic metastases**, (3) **palliative surgery aimed at relieving biliary obstruction may restore the patient to a good state of health for a remarkably long period of time**, and (4) **such palliation may be achieved by internal drainage of only one of the major intrahepatic bile ducts**."

***Amer J Med* 1965:241-256**



Courtesy of C. Rosen, G. Gores, & J. Heimbach

De-novo cholangiocarcinoma presents in older patients



Courtesy of C. Sonnenday

Risk factors for cholangiocarcinoma

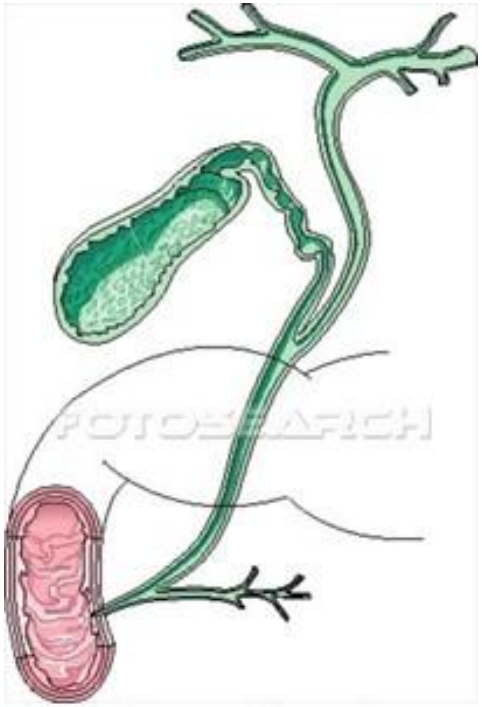
- Primary sclerosing cholangitis
  - 8-20% lifetime incidence
- Choledochal cyst
  - Best described with type I choledochal cysts
  - Risk if not excised is ~ 24% lifetime risk, increases w/ time
- Hepatolithiasis / choledocholithiasis
- Ulcerative colitis (even in absence of PSC)
- Liver flukes (*Clonorchis sinensis, Opisthorchis viverrini*)
  - Endemic areas: China, Cambodia, Laos, Vietnam, Korea
- Chronic liver disease
  - Increasing recognition of association with chronic hepatitis B & C infection

- Majority of patients have no identified risk factors
- Weak epidemiologic associations with obesity, smoking, pancreatitis, diabetes mellitus

Courtesy of C. Sonnenday

Presenting signs and symptoms: biliary tract malignancies

	Intrahepatic	Perihilar	Distal
Jaundice	Rare	Common	Typical
Weight loss	Rare	Common	Common
Abdominal pain	Common	Rare	Rare
Distended GB	No	Rare	Common
Cholangitis*	No	Rare	Rare



Nakeeb et al. *Ann Surg* 1996;224:463

Diagnosis of extrahepatic cholangiocarcinoma

- Identify cause of biliary obstruction
  - RUQ ultrasound – excellent sensitivity in calculous disease, assess level of obstruction
  - Liver CT – refine localization of level obstruction, assess for obvious metastatic disease, assess vascular involvement
    - Sensitivity 80-90%
    - Accuracy of assessment for resectability 60-85%
  - MRI/MRCP – highest sensitivity/specificity for CCA
    - PERFORM PRIOR TO INSTRUMENTING BILE DUCT
    - CCA PROTOCOL: three phase liver MRI + MRCP

Diagnosis of extrahepatic cholangiocarcinoma

- Cholangiography
  - ERCP – typically initial procedure
    - **Segmental decompression can often completely alleviate jaundice**
    - Biliary brushings have ~50% yield for malignant diagnosis
    - Yield of brushings may be increased by sending sample for fluorescence in-situ hybridization (FISH)
  - Percutaneous transhepatic cholangiography
    - Ideally should be coordinated with evaluating surgeon

- Tumor markers: Ca 19-9; AFP if mass lesion present in liver
  - Ca 19-9 > 100 in non-jaundiced patient favors diagnosis of CCA
  - Ca 19-9 > 100 predicts unresectability in ~70% of cases
  - Obtain after biliary decompression

Courtesy of C. Sonnenday

Key steps in the diagnosis of extrahepatic cholangiocarcinoma

- **Do NOT obtain percutaneous biopsies – high rate tumor seeding**
- A negative biliary brushing or biopsy does not mean the patient does not have cancer
- **A tissue diagnosis is often hard to establish, and is typically not necessary prior to treatment planning**
- Ca 19-9 should be drawn after biliary decompression, as spuriously high levels occur due to biliary obstruction
- **Involve the surgical consultant early!!**

Courtesy of C. Sonnenday

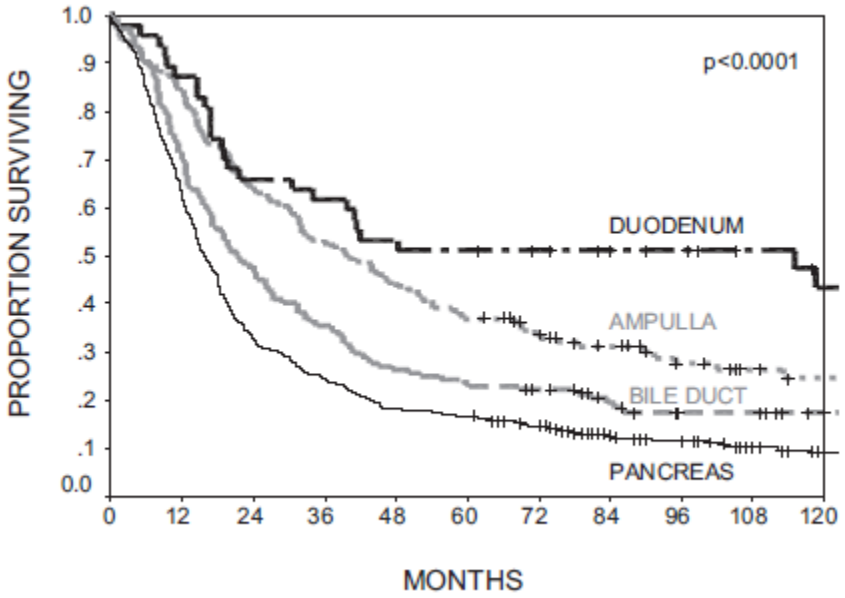
Additional diagnostic and staging modalities for cholangiocarcinoma

- Endoscopic ultrasound (EUS)
  - Most useful for sampling regional lymph nodes
  - Like percutaneous biopsy, EUS biopsy of primary tumor may be associated with tumor seeding
- Chest CT for staging
- PET
  - Poor specificity for primary tumor
  - Poor sensitivity for lymph node metastases (12%)
  - Reasonable sensitivity for extrahepatic disease (70-100%)

Courtesy of C. Sonnenday

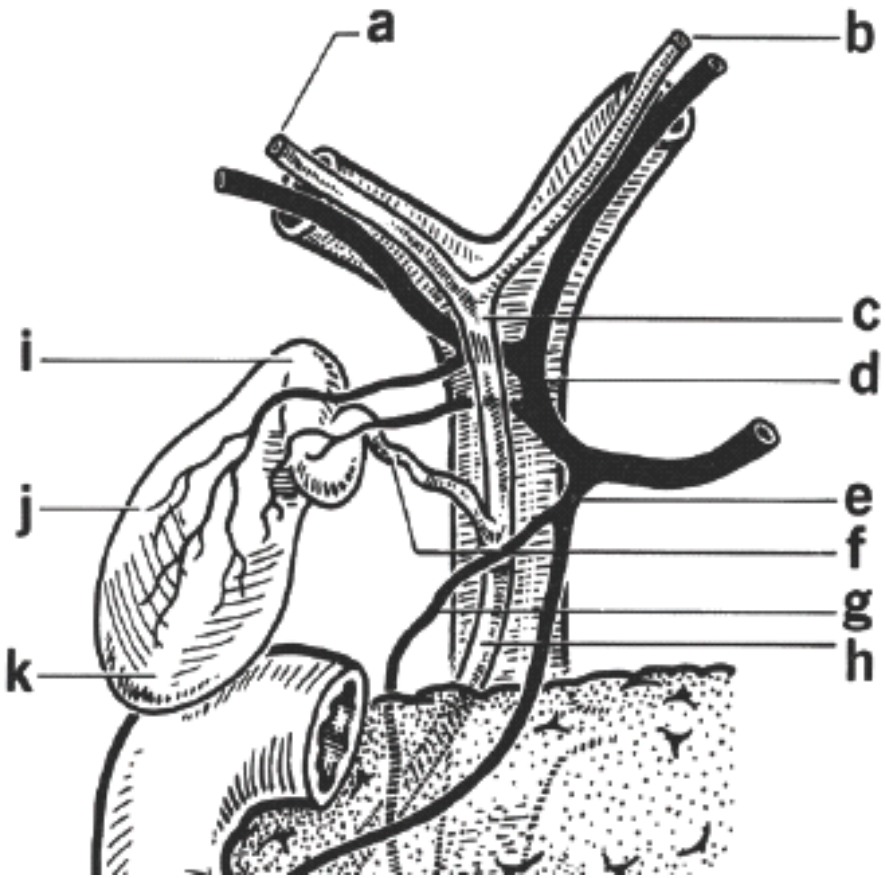
Distal cholangiocarcinoma

- Presentation similar to the other periampullary malignancies (pancreas, ampullary, duodenal)
- More favorable oncologic outcomes vs. pancreatic cancer
- Treatment for resectable disease is pancreaticoduodenectomy



Courtesy of C. Sonnenday

Anatomic considerations in extrahepatic cholangiocarcinoma



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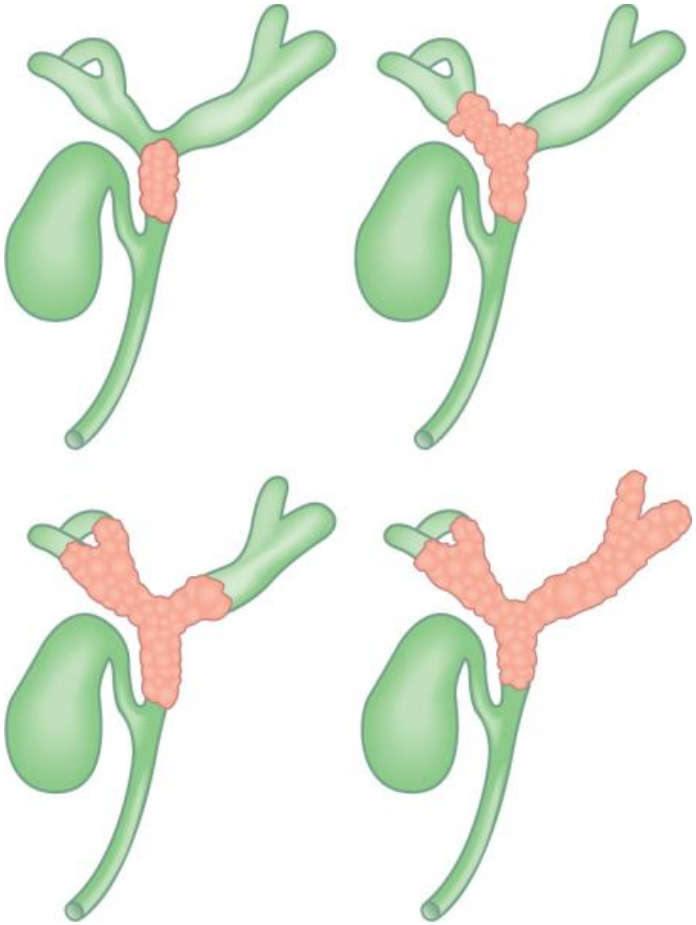
Bismuth-Corlette Classification of Extrahepatic CCA & Surgical Approach

Class I:
Excision of extrahepatic bile duct; hepaticojejunostomy



Class II:
Excision of extrahepatic bile duct +/- hepatic lobectomy; hepaticojejunostomy

Class III:
Excision of extrahepatic bile duct with hepatic lobectomy; hepaticojejunostomy

Class IV:
Unresectable disease

Courtesy of C. Sonnenday

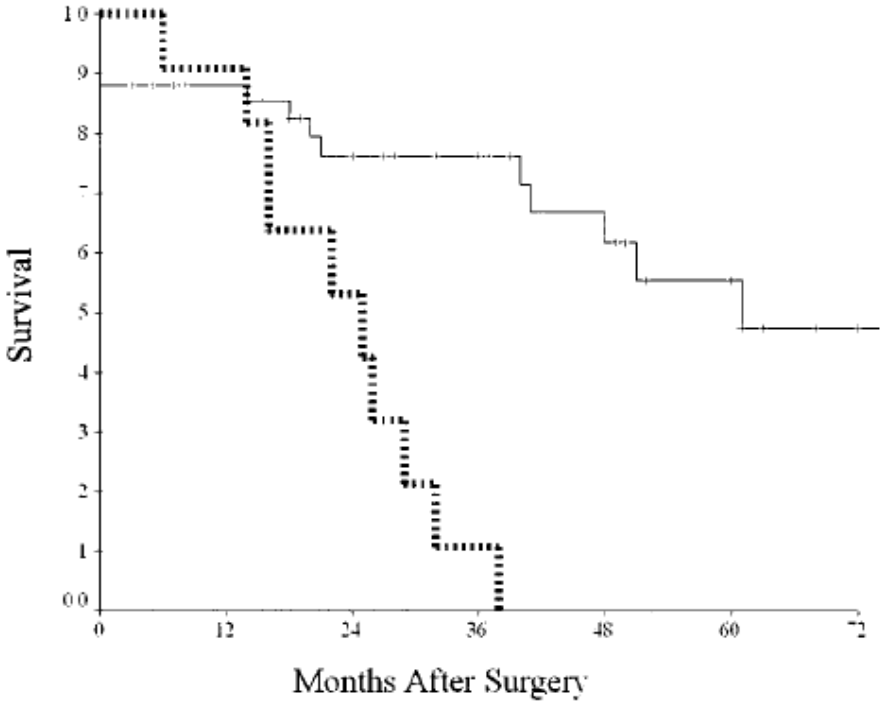
Surgical outcomes following resection for cholangiocarcinoma

TABLE 4. Results of Surgical Resection for Hilar Cholangiocarcinoma

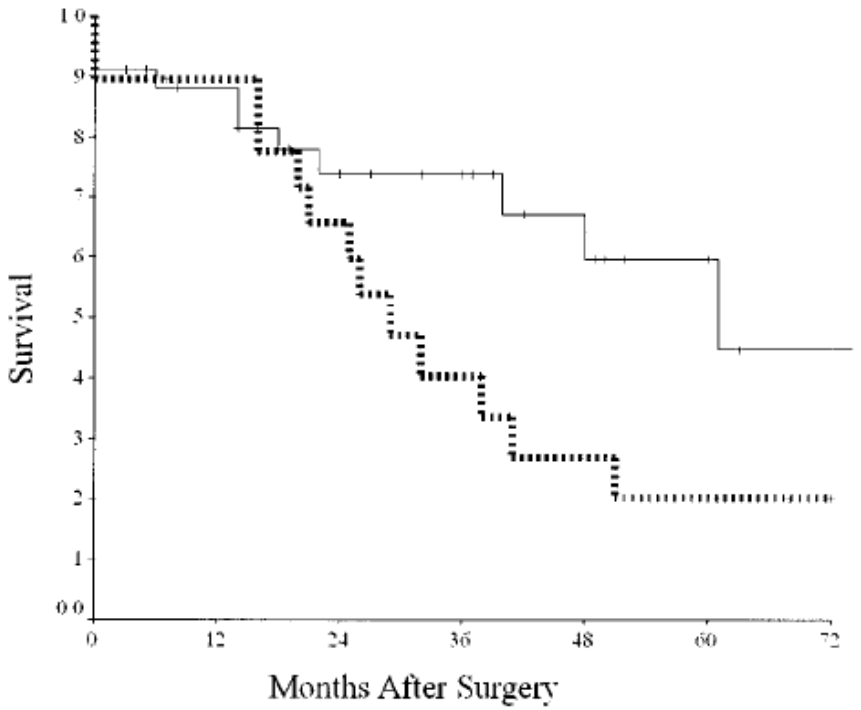
Authors	Published Year	Resections (n)	Resectability (%)	Negative Margin (%)	Liver Resection (%)	Morbidity (%)	Mortality (%)	5-yr Survival Rate (%)
Hadjis NS et al	1990	27	NA	56	60	NA	7	22
Nimura et al	1990	55	83	84	98	41	6	41*
Nakeeb et al	1996	109	56	26	14	47	4	11
Su et al	1996	49	28	49	57	47	10	15
Klempnauer et al	1997	151	45	77	77	NA	10	28
Miyazaki et al	1998	76	NA	71	86	33	13	26
Burke et al	1998	30	43	83	73	NA	6	45
Neuhaus et al	1999	80	NA	61	85	55	8	22
Kosuge et al	1999	65	73	52	80	37	9	33
Launois et al	2000	131	35	NA	37	NA	19	NA
Gerhards et al	2000	112	NA	14	29	65	18	NA
Nimura et al	2000	142	80	61	90	49	9	26†
Todoroki et al	2000	101	89	14	58	14	4	28
Jarnagin et al	2001	80	50	78	78	64	10	26
Kawarada et al	2002	65	89	64	75	28	2.3	26
Capussotti et at	2002	36	NA	89	83	47	3	27
Kawasaki et al	2003	79	75	68	87	14	1.3	22
Seyama et at	2003	87	94	64	67	43	0	40
Rea et al	2004	46	NA	80	100	52	9	26
Kondo et al	2004	40	95	95	65	48	0	NA
IJitsma et al	2004	42	NA	65	100	76	12	19
Hemming et al	2005	53	50	80	98	40	9	35
Jarnagin et al	2005	106	70	77	82	62	8	NA
Dinant et al	2006	99	NA	31	38	66	15	27
Ito et al	2008	38	55	63	53	32	0	33
			28-95%	**14-95%**	**14-100%**	**14-76%**	**0-19%**	**11-45%**

Courtesy of C. Sonnenday

Survival following resection for cholangiocarcinoma: margin & lymph node status



R1 vs. R0

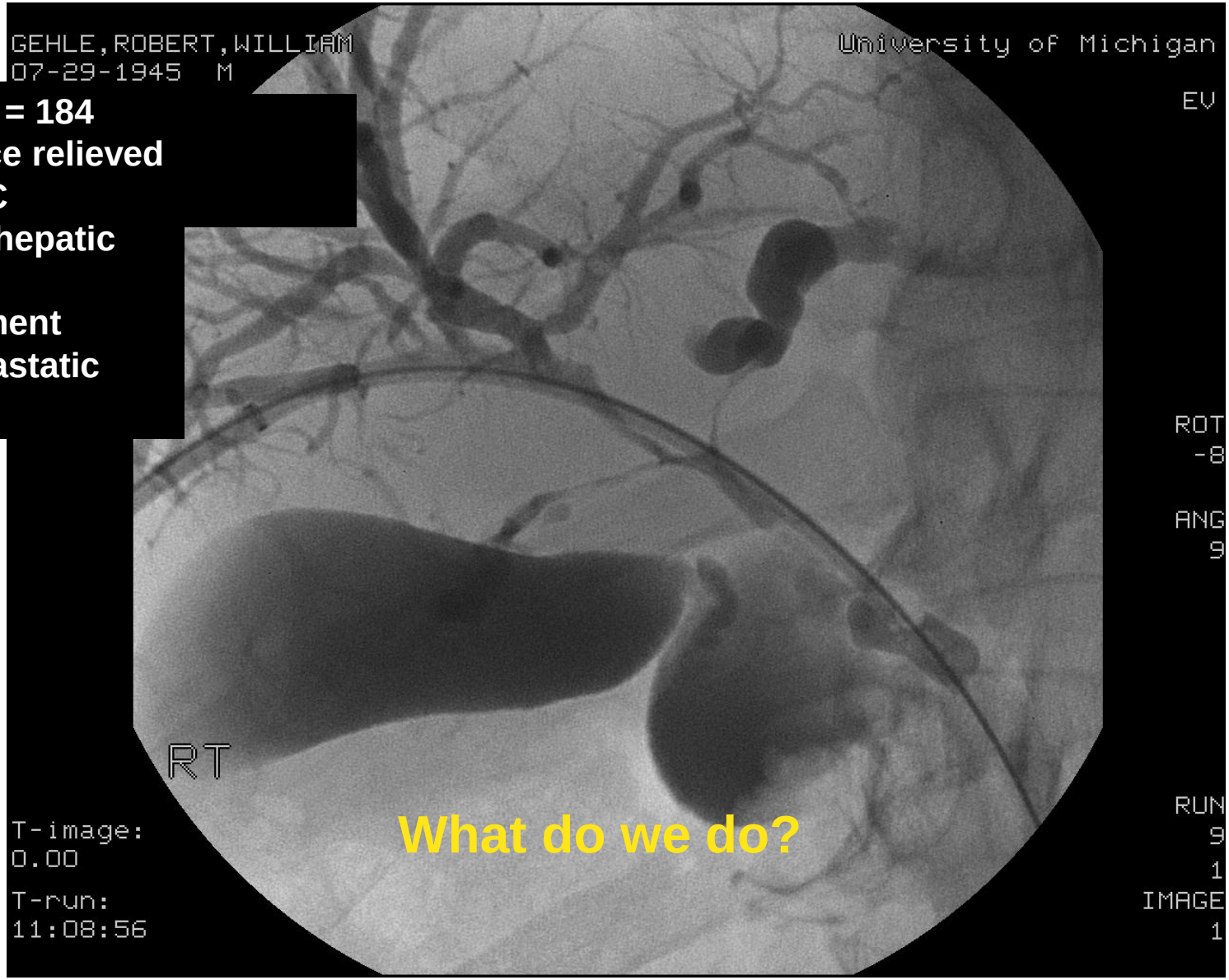


LN+ vs. LN-

Hemming et al, *Ann Surg*, 2005

Courtesy of C. Sonnenday

- **Ca 19-9 = 184**
- **Jaundice relieved with PTC**
- **Proper hepatic artery involvement**
- **No metastatic disease**



Courtesy of C. Sonnenday

Peri-Hilar Cholangiocarcinoma
Mayo Clinic Approach: 1993-Present

- Appears resectable
  - Resection with excision of extrahepatic bile duct, regional lymphadenectomy, and right or left hepatectomy (± caudate)
- Appears unresectable, or arising in setting of PSC
  - Neoadjuvant chemoradiation/chemotherapy and liver transplantation protocol

Courtesy of C. Rosen, G. Gores, & J. Heimbach

Selected Patients with Unresectable Hilar Cholangiocarcinoma: Mayo Clinic

- Neoadjuvant radiation and chemotherapy
  - External beam radiotherapy (4500), with 5-FU
  - Brachytherapy with protracted capecitabine or
  - Stereotactic beam radiation therapy (SBRT) with protracted capecitabine

↓

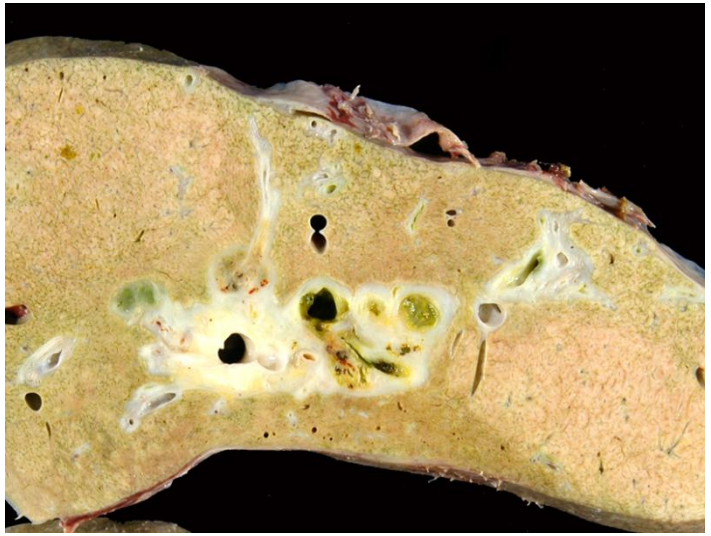
Staging laparoscopy to rule-out metastases or local extension of tumor precluding complete resection of tumor

↓

Liver transplantation

Courtesy of C. Rosen, G. Gores, & J. Heimbach

Marginally Resectable Hilar Cholangiocarcinoma: Important considerations



- Resection is not safe after high dose neoadjuvant chemoradiation
- Attempted resection compromises outcome of neoadjuvant therapy and liver transplantation
- Cross-over from one modality to the other is not possible
  - If in doubt for RO, transplant
  - If suspect nodal disease, resect

Courtesy of C. Rosen, G. Gores, & J. Heimbach

Hilar CCA-LT Protocol: Eligibility & Exclusions

Eligibility

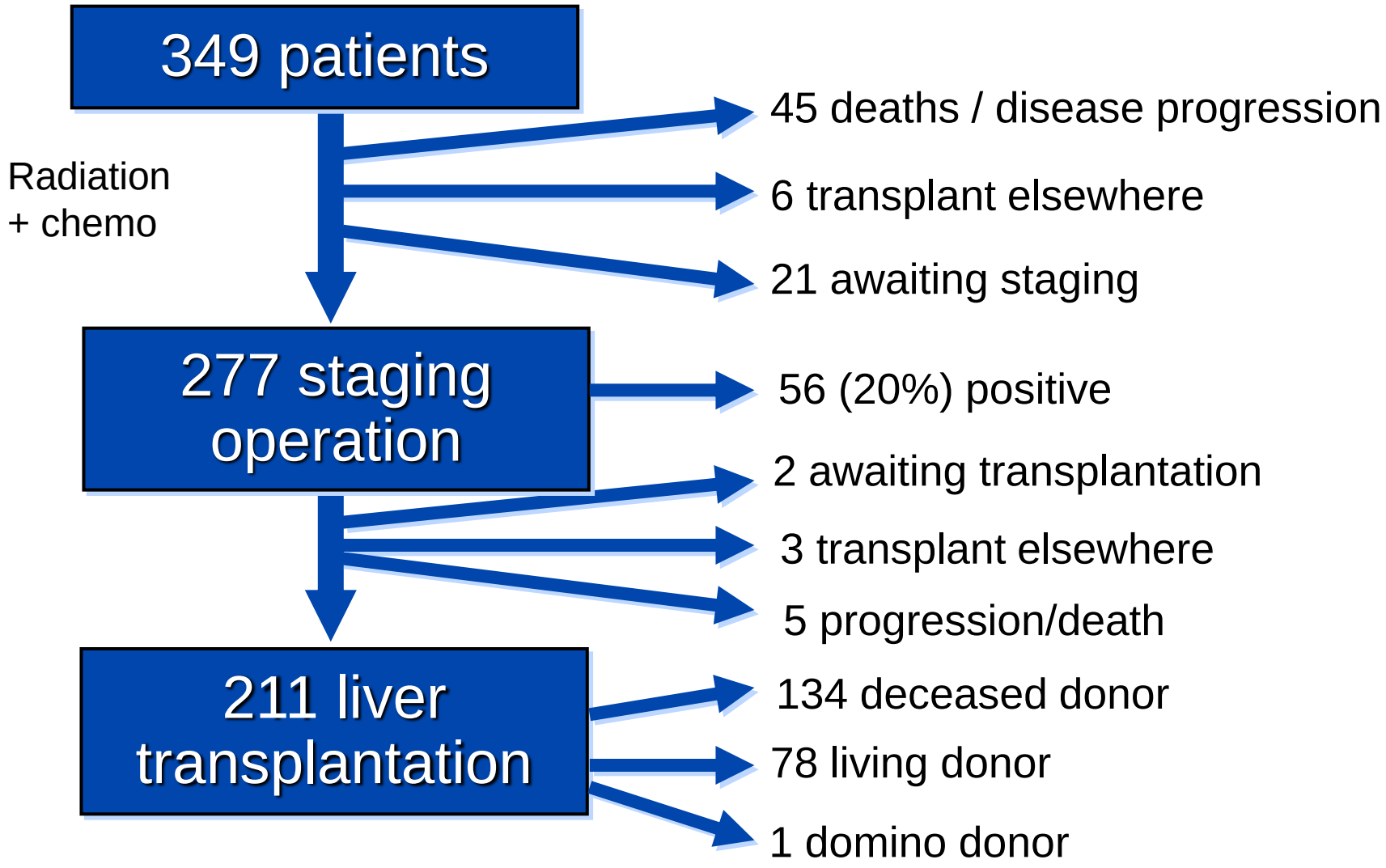
- Malignant appearing stricture **and** at least 1 of the following:
  - Malignant cytology or histology
  - CA-19.9 >100 U/mL
  - Polysomy on FISH
  - Mass on cross-sectional imaging
- Cancer located primarily above the cystic duct
- Unresectable cancer (de novo CCA) or cancer arising in setting of PSC

Exclusions

- Prior attempted resection with violation of tumor plane or **trans-peritoneal biopsy**
- Presence of mass lesion >3 cm radial margin (longitudinal margin not a contraindication)
- Intrahepatic or extrahepatic metastases, prior abdominal radiation that would preclude additional radiation, or other medical contraindication to surgery/transplant
- Nodal involvement

Courtesy of C. Rosen, G. Gores, & J. Heimbach

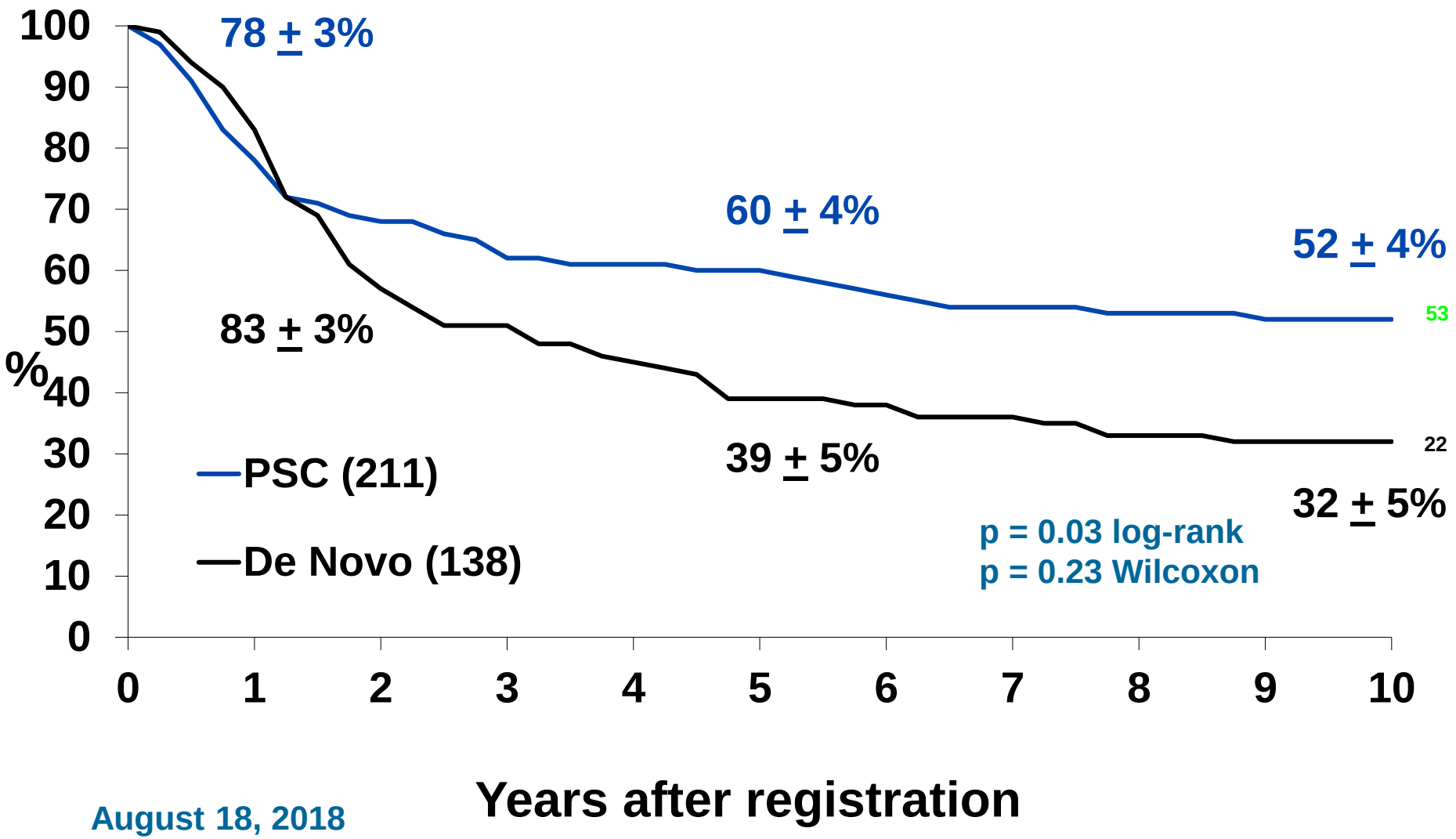
Cholangiocarcinoma Treatment Protocol
Results – Mayo Clinic Rochester (1993- 2018)



Courtesy of C. Rosen, G. Gores, & J. Heimbach

Patient Survival After Start of Therapy

1993 – 2018

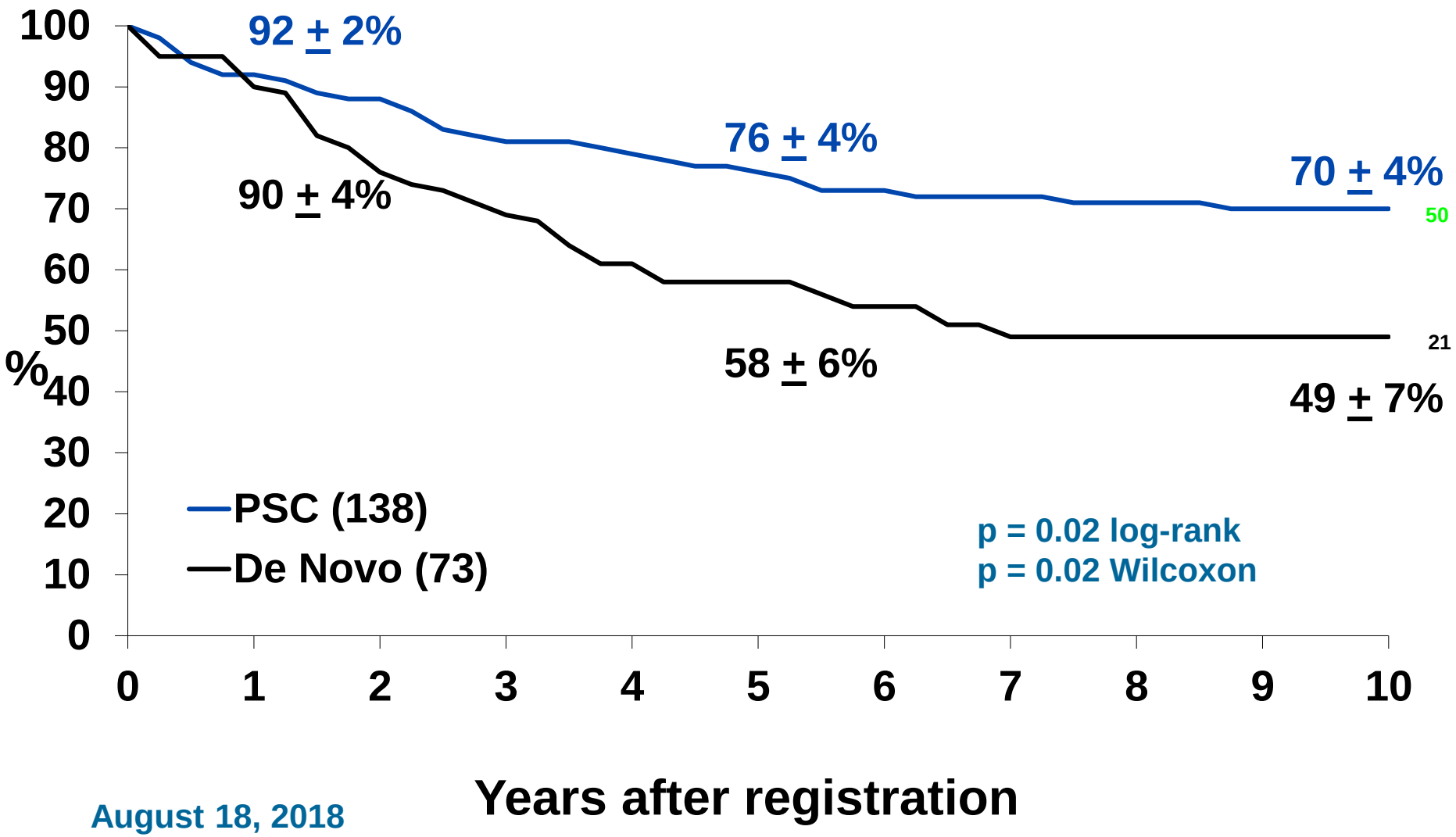


August 18, 2018

Courtesy of C. Rosen, G. Gores, & J. Heimbach

Patient Survival After Transplantation

1993 – 2018



August 18, 2018

Courtesy of C. Rosen, G. Gores, & J. Heimbach

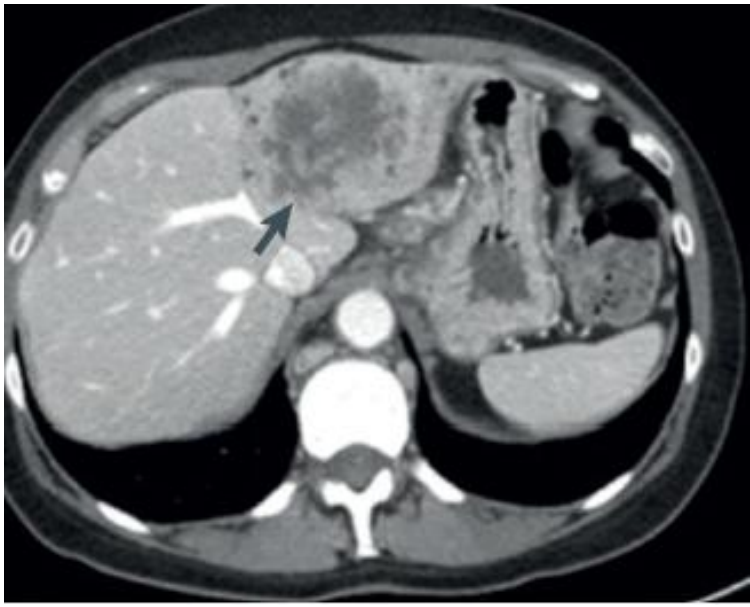
Case #1: RG

- Enrolled in protocol January 2010
- Liver transplantation April 2010
- Final pathology – no residual tumor, extensive treatment effect

Courtesy of C. Sonnenday

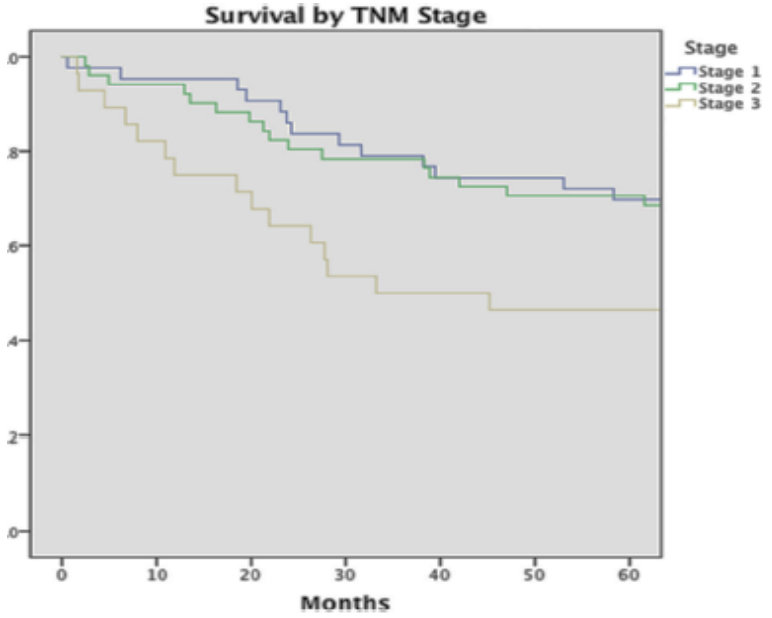
Diagnosis of intra-hepatic cholangiocarcinoma

- Typically presents as an incidental discovery on routine imaging done for other reasons (screening for HCC in cirrhosis, or abdominal pain evaluation, trauma, etc…)
- MRI and CT of iCCA: early initial rim or peripheral arterial phase-enhancement pattern followed by centripetal **enhancement** in the delayed phases
- Elevated Ca 19-9 (if Lewis antigen negative, will be normal: 7% of population)
- Biopsy is essential to differentiate from HCC



Courtesy of C. Rosen, G. Gores, & J. Heimbach

Treatment of intra-hepatic cholangiocarcinoma

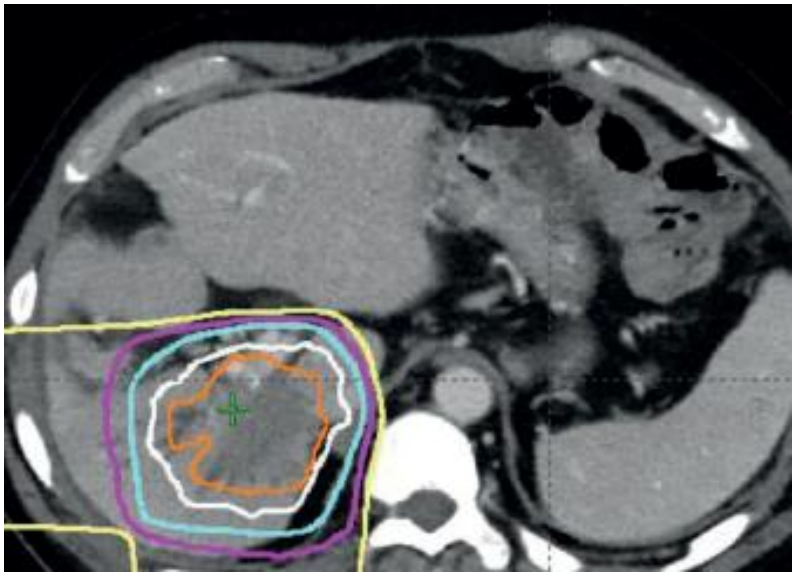


- Surgical resection is mainstay:

  Predictors of outcome include size (R0 resection), multiple lesions, nodal metastasis,

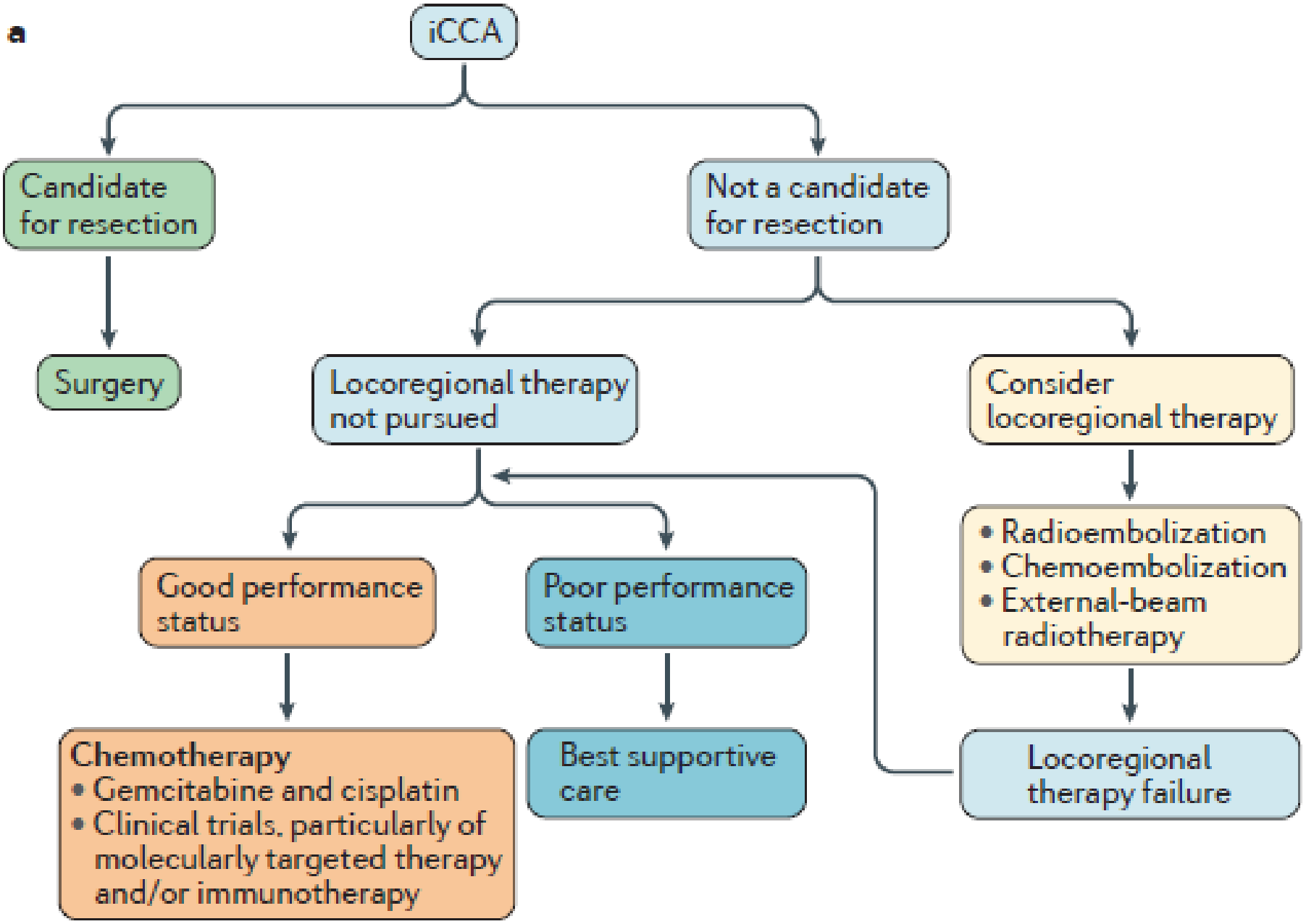
- <u>Transplant can be considered in early stage (<2 cm, iCCA)</u>
  - Retrospective multicenter reports 8 pts: **73% 5 year survival** (2014)
  - Follow-up: 15 patients **65% 5 year survival** (2016)

- TACE, TARE, and external beam radiation therapy are evolving strategies



Sapisochin Hepatology 64, 1178–1188 (2016).

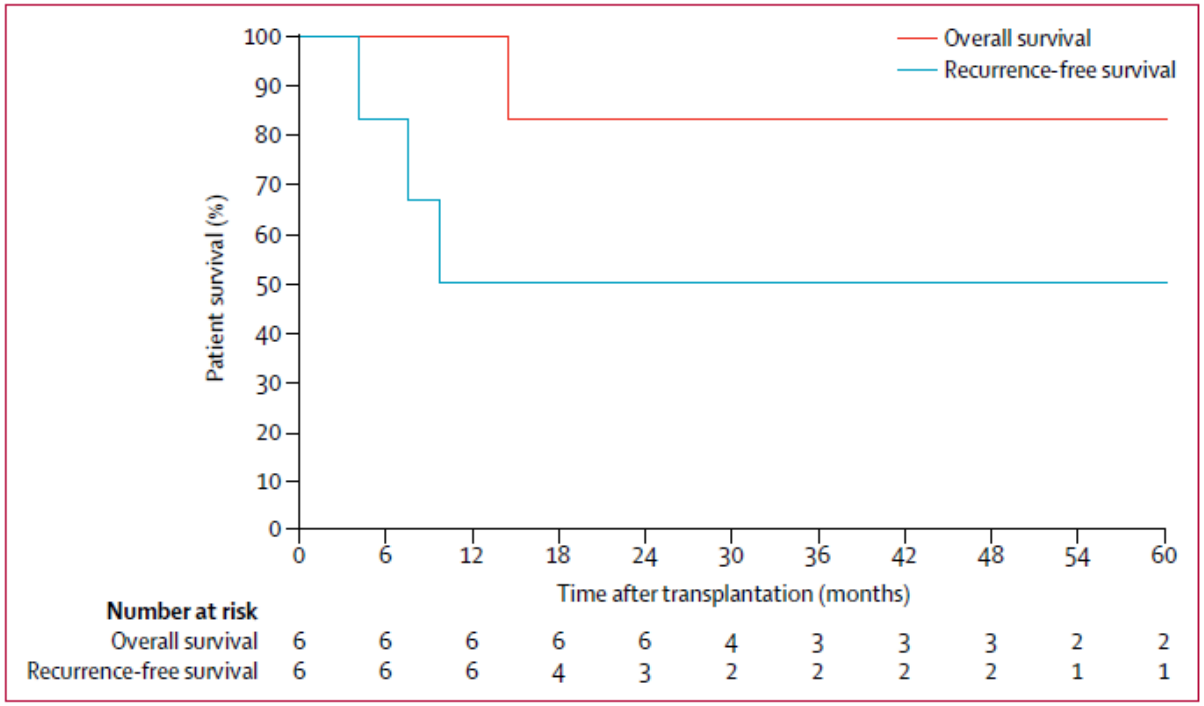
Courtesy of C. Rosen, G. Gores, & J. Heimbach



Rizvi et al Nature rev 2018

Liver transplantation for locally advanced intrahepatic cholangiocarcinoma treated with neoadjuvant therapy: a prospective case-series

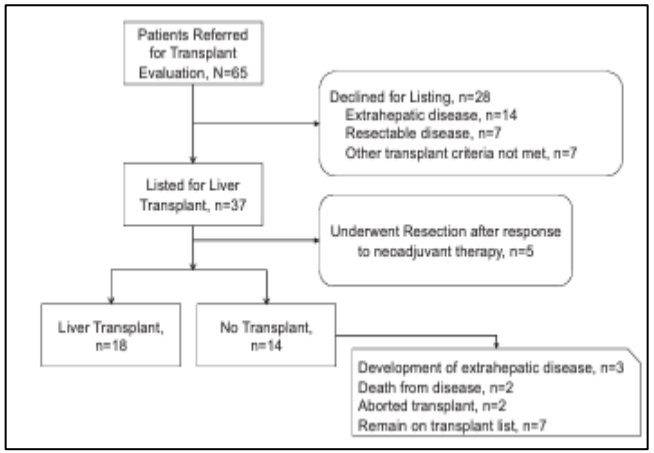
Lunsford et al Lancet Onc 2018;3: 337-48.



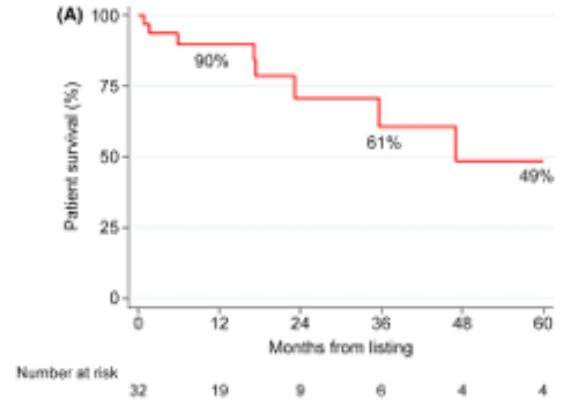
- Single-center, prospective analysis of 6 pts with iCCA treated with neoadjuvant chemotherapy then LT
- Average total tumor burden 10 cm, 4 lesions.
- Treated with Gem/Cis plus other agents

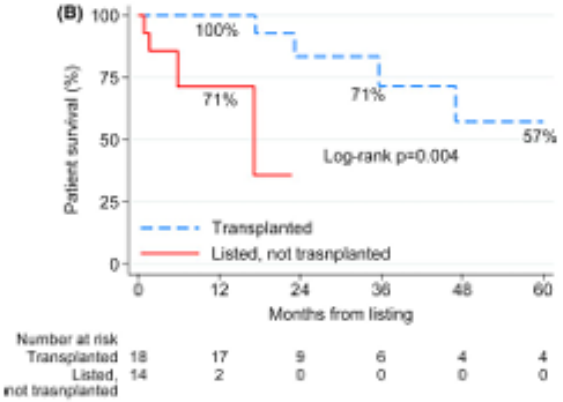
Survival following liver transplantation for locally advanced, unresectable intrahepatic cholangiocarcinoma

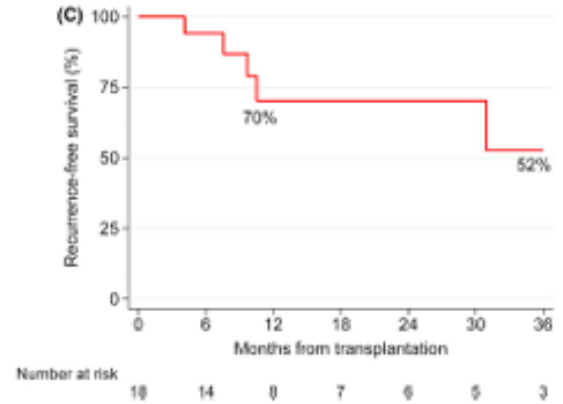
Robert R. McMillan[1] | Milind Javle[2] | Sudha Kodali[3] | Ashish Saharia[1] | Constance Mobley[1] | Kirk Heyne[4] | Mark J. Hobeika[1] | Keri E. Lunsford[5] | David W. Victor III[3] | Akshay Shetty[3] | Robert S. McFadden[3] | Maen Abdelrahim[4] | Ahmed Kaseb[2] | Mukul Divatia[6] | Nam Yu[7] | Joy Nolte Fong[1] | Linda W. Moore[1] | Duc T. Nguyen[6] | Edward A. Graviss[6] | A. Osama Gaber[1] | Jean-Nicolas Vauthey[8] | R. Mark Ghobrial[1]



- Unresectable disease, systemic therapy up-front, disease stability for 6 months with no metastatic disease
- 18 patients underwent LT
- 100%, 71%, 57% 1,3,5-year survival in transplanted patients







Transplanted patients

Median tumor number = 2

Median tumor diameter = 10.4cm

NGS in 26/32 listed patients and 16/18 LT patients

BAP1 35%, IDH1 35%, FGFR 27%, ARID1A 19%, BRAF 19%, TP53 19%

- ***Prospective protocol for locally advanced iCCA with neoadjuvant therapy, stability, and LT yields similar outcomes in other LT patients with oncological indications***

McMillan RR, et al AJT 2022

Key Points: iCCA-LT

- Standard treatment is resection: outcome depends on stage
- Very early unresectable small iCCA (<3cm) suitable for LT in select patients
  - Multidisciplinary-directed locoregional liver-directed therapy (TARE/ablation/SBRT) and stable disease for 6 months is necessary to demonstrate favorable tumor biology
- Potential role for LT in locally advanced iCCA with neoadjuvant therapy and observation
  - Further prospective multicenter data is needed
  - Locoregional control strategy has unknown significance
  - Role of tumor mutations on selection of up-front therapies may also assist in patient selection

Courtesy of C. Rosen, G. Gores, & J. Heimbach

Emergence of Immunotherapy: TOPAZ-1

NEJM Evidence

Published June 1, 2022
NEJM Evid 2022; 1 (8)
DOI: 10.1056/EVIDoa2200015

ORIGINAL ARTICLE

Durvalumab plus Gemcitabine and Cisplatin in Advanced Biliary Tract Cancer

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- N=685
- 341 Durva + Gem/Cis vs 344 Placebo + Gem/Cis

mPFS: Durva vs. Gem/Cis: 7.2mo vs 5.7mo

- HR (OS) = 0.80,95% CI(0.66-0.97), p=0.021
- HR (PFS) = 0.75, 95%CI 0.63-0.89, p<0.001
- Objective response rate: durva vs gem/cis: 26.7% vs. 18.7%
- Longer follow-up supported survival difference with no new safety concerns

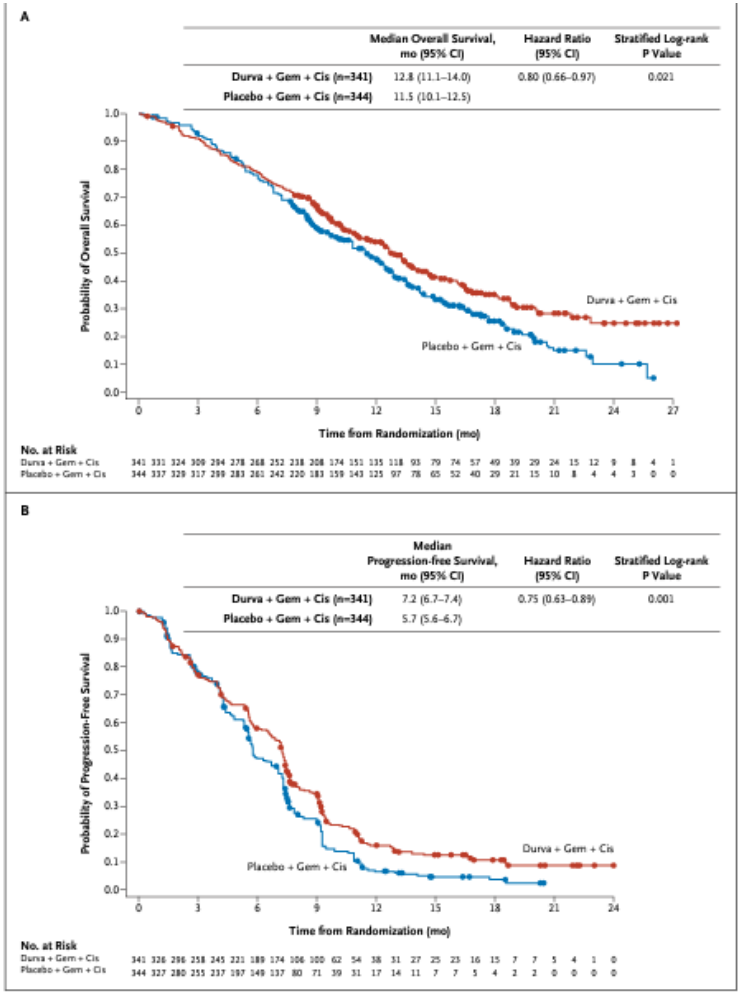
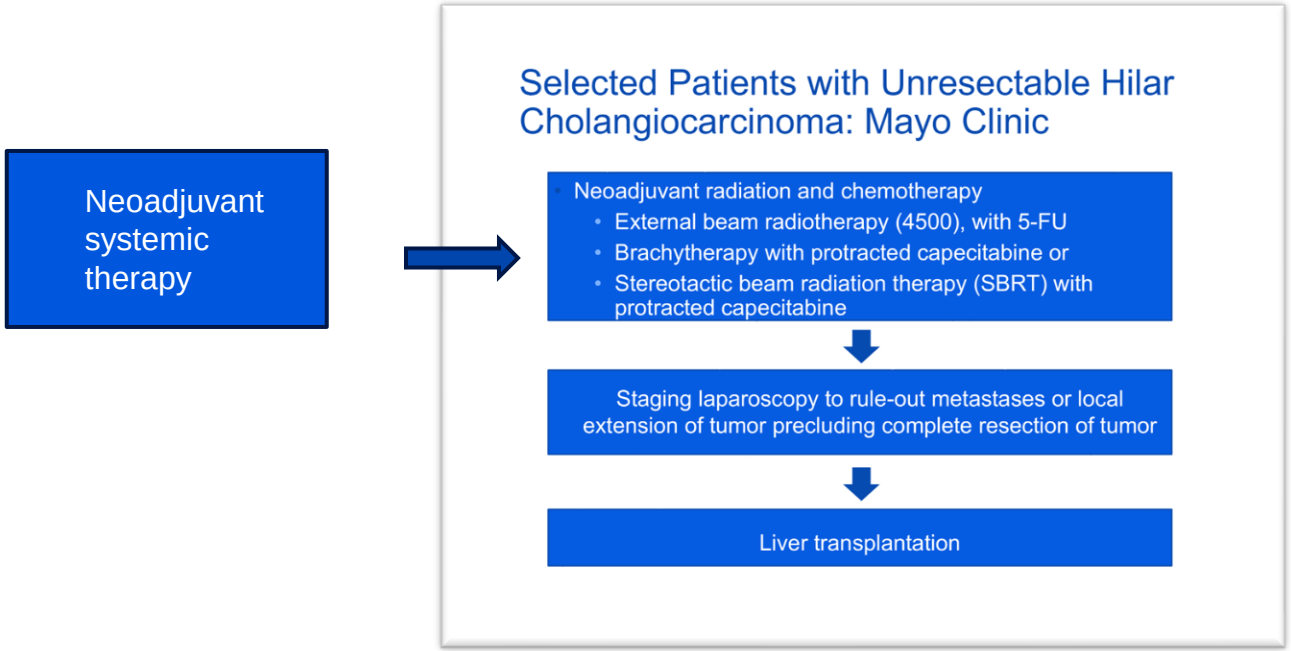


Figure 1. Kaplan–Meier Curves of Overall and Progression-Free Survival in the Full Analysis Set.
Kaplan–Meier curves are presented for overall survival (Panel A) and progression-free survival (Panel B). CI denotes confidence interval, Cis cisplatin, Durva durvalumab, and Gem gemcitabine.

The addition of durvalumab to gem/cis chemotherapy is the new standard of care in advanced BTC

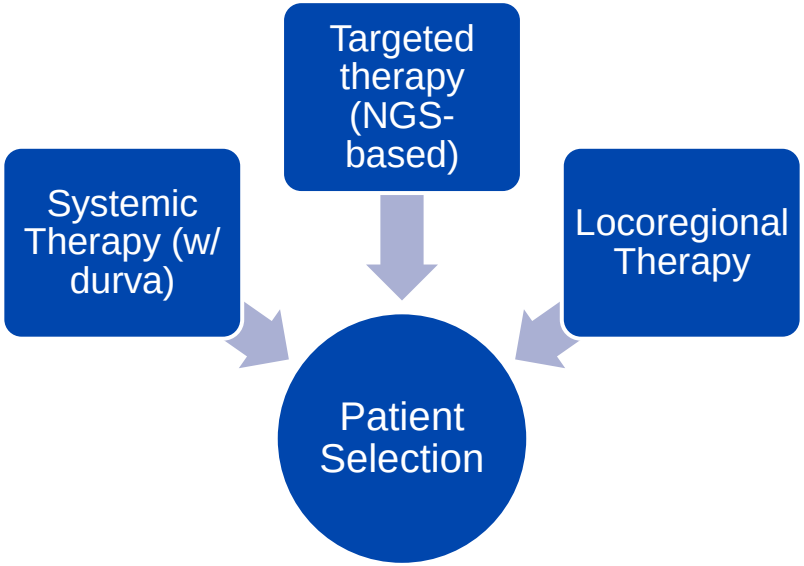
Implications of TOPAZ-1 on Mayo Clinic LT protocol for hilar CCA

- Patients referred to LT after diagnosis on durvalumab-based therapies
- Delays in pathological diagnosis lead to uncertainty of tumor behavior, challenges in CA19-9 interpretation with obstruction
- Durva + gem/cis may provide additional time to assess tumor biology



Implications of TOPAZ-1 on Mayo Clinic LT Protocol for iCCA

- Acceptable to place patients on systemic therapy including durvalumab and/or other biologics
  - Tumor mutations should be routinely assessed by NGS of tumor tissue or liquid biopsy to assist in systemic therapy selection
  - Medical oncology collaboration
- Locoregional therapy is required in small iCCA protocol (< 3cm)
- Observation for 6 months without progression
- <u>More data required</u>



<u>Future State</u>

Multidisciplinary approach to harness synergies of concurrent therapies to select LT candidates

Final Thoughts on Cholangiocarcinoma and LT: Prime Time is Now

- CCA is a family of disorders where treatment is determined by location of disease, underlying liver disease, and surgical fitness
- Resection is the mainstay if feasible
- In hilar CCA, resection is maintstay. R0 resection should be goal.
  - In PSC – transplant has proven benefit
  - De novo hilar CCA – facilitates excellent outcomes in node-negative patients, potentially better than resection
- Intrahepatic CCA, resection is mainstay.
  - Small iCCA in cirrhosis with 6 mo observation after LRT, LT is safe and successful
  - Multifocal, large unresectable disease = more data is needed, but promising current state with aggressive selection and upfront therapies


MAYO CLINIC

Questions & Discussion

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Liver Transplant for Cholangiocarcinoma: Ready for Prime Time?

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INEDSYS Hepatology Club and Video Library
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