Notable Grand Rounds
of the
Michael & Marian Ilitch
Department of Surgery

Wayne State University
School of Medicine

Detroit, Michigan, USA

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Dr. Tmothy M. Pawlik

MANAGEMENT OF INTRAHEPATIC CHOLANGIOCARCINOMA

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October 5, 2022

About Notable Grand Rounds

These assembled papers are edited transcripts of didactic lectures given by mainly senior residents, but also some distinguished attending and guests, at the Grand Rounds of the Michael and Marian Ilitch Department of Surgery at the Wayne State University School of Medicine.

Every week, approximately 50 faculty attending surgeons and surgical residents meet to conduct postmortems on cases that did not go well. That “Mortality and Morbidity” conference is followed immediately by Grand Rounds.

This collection is not intended as a scholarly journal, but in a significant way it is a peer reviewed publication by virtue of the fact that every presentation is examined in great detail by those 50 or so surgeons.

It serves to honor the presenters for their effort, to potentially serve as first draft for an article for submission to a medical journal, to let residents and potential residents see the high standard achieved by their peers and expected of them, and by no means least, to contribute to better patient care.

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Management of Intrahepatic Cholangiocarcinoma

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October 5, 2022

The talk from which this paper was derived was delivered by Dr. Pawlik at the Wayne State University School of Medicine Surgical Grand Rounds on October 5, 2022.

Acknowledgement
I have been privileged and fortunate to be part of several consensus groups and guideline bodies. Much of the work described in this paper is from the International Liver Cancer Association (ILCA), whose guidelines I participate in setting.[1,2]

Organization
This paper discusses:

1. Epidemiology & Risk Factors,
2. Molecular Pathogenesis,
3. Clinical Diagnosis,
4. Surgical Resection,
5. Staging Systems,
6. The Future, and
7. Conclusions

with respect to the management of intrahepatic cholangiocarcinoma (iCCA)

1. **Epidemiology**.
iCCA is an under-studied malignancy. It is not too dissimilar from hepaticocellular carcinoma, which also has significant geographical variations (**slide 1**).

The incidence of iCCA in the United States is about 1 or 2 per 100,000, whereas the incidence in Asia and Eastern countries is markedly higher—in the range of about 7 to 8 per 100,000. In northern Thailand, the incidence of iCCA is as high as 90 per 100,000 because liver fluke—a major risk factor for iCCA—is endemic there.

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[1] Guidelines for the diagnosis and management of intrahepatic cholangiocarcinoma. Bridgewater J1, Galle PR?, Khan SA3, Llovet JM4, Park JW5, Patel T6, Pawlik TM7, Gores GJ8.

[2] Intrahepatic cholangiocarcinoma: expert consensus statement. Weber SM1. Ribero D2, O'Reillv EM3, Kokudo N4, Mivazaki M5, Pawlik TM6,

Cholangiocarcinomas (CCAs) are classified anatomically as intrahepatic (iCCA), perihilar (pCCA), and distal (dCCA). pCCA is the most common but there has been a marked increase in the incidence of iCCA over the last two-to-three decades (**slide 2**), in part perhaps because it was reclassified: Twenty years ago, pathologists would report adenocarcinoma in the liver as “adenocarcinoma, not otherwise specified". Today, hepatopathologies from immunohistochemical stainings are much more likely to report out the primary as iCCA.

The incidence of iCCA is probably also increasing as a result of significant geographic variations in the risk factors (**slide 3**). In Asia, the biggest risk factors are probably still hepatobillary flukes, hepatitis, and primary sclerosing cholangitis (PSC) which is much more predominant in Eastern countries. In the United States, the biggest risk factors right now are obesity, diabetes, non-alcoholic fatty liver disease, and non-alcoholic steatohepatitis (**slide 4**).

2. Molecular Pathogenesis

There has been much progress over the last 10 to 15 years in understanding the molecular underpinnings of iCCA (**slide 5**). The identification of a number of different molecular pathways is important not only prognostically, but also because they targetable.

A 2014 study in which I participated found that the most common genetic mutations included the KRAS and BRAF genes, as one would expect for GI cancers. But the interesting finding was that IDH1 genetic mutation (**slides 6-8, 10**) is much higher in iCCA than in pCCA and dCCA. This is important both prognostically and therapeutically. In about 20% of patients, the FGFR receptor plays a key role in iCCA. This is not the case in gallbladder cancer and extrahepatic CCA (**eCCA**).

It is not surprising that patients who have KRAS and BRAF mutations do significantly worse, with a median survival of only one year (**slide 9**). The 20% of patients who have the IDH mutation also have a worse prognosis—another study (in which I participated), published in *Nature Genetics*, about the whole exome sequencing of iCCA, showed that patients who had the IDH mutation had a median survival of only about 16 months (**slide 11**).

Immunotherapy is another hot topic in cancer. A small subset of patients with iCCA who stain for PD-1 or PD-L1 (**slide 12**) may be treatable with immunotherapy, but the big players are going to be FGFR2 and IDH1 and less than 5% will have other mutations such as mismatched repair genes or a BRAF mutation (**slide 13**).

Understanding the molecular underpinnings of this disease leads to advances in systemic therapy, adjuvant therapy, and even destination therapy for some patients who have advanced inoperable disease.

3. Clinical Diagnosis of iCCA

Early symptoms of iCCA tend to be elusive (**slide 14**) because this is a parenchymal lesion that gets quite sizable before symptoms appear. Not infrequently, the disease is found incidentally, when patients come in for other reasons. CT (**slide 15**) leads to biopsy and the pathologist’s identification of adenocarcinoma (**slide 16**).

The question then is: Is it a primary adenocarcinoma of the liver (*i.e.*, iCCA) or is it a secondary malignancy, a metastatic lesion arising from a colon or pancreatic cancer?

Signs of biliary dysplasia will call for immunohistochemical staining to rule out lung, colon, pancreatic, and other adenocarcinomas. IHC-positive staining with markers AE1, AE3, or CK are highly suggestive of a biliary epithelium (**slide 17**).

With this evidence of an adenocarcinoma highly suggestive of an hepatobillary primary tumor, it is very important next to check the tumor markers AFP, CA 19-9, and CEA, and vital to remember

that these markers are specific but not very sensitive (**slide 18**). A CA19-9 count of 100,000 is unlikely to be a false positive, but a normal CA19-9 does not rule out a cancer—so it does not rule out iCCA. A normal AFP does not rule out HCC. It is vitally important to consider the whole picture.

One should look for a primary adenocarcinoma, check that female patients have had an updated mammogram and gynecological exam, and that all patients have had a recent lower colonoscopy.

The workhorse for the workup of this disease is state-of-the-art cross-sectional imaging: CT, MRI, and PET. iCCA is FDG-avid with PET. Avid disease outside the liver will change how the patient is managed. Instead of immediate surgery, preoperative chemotherapy is probably called for because the prognosis may be prohibitive if the patient has a metastatic disease extending even to the nodal basins preoperatively.

There are three different morphologic iCCA subtypes: Panel A in **slide 19** shows the mass-forming lesion, which tend to be low-attenuating and homogenous. Capsular retraction and peripheral enhancement will be seen near the liver. Panel B in **slide 19** shows periductal infiltrating lesions with hyper-enhancement of the duct. Periductal thickening and enhancement are visible in the images. Panel C in **slide 19** shows the intraductal growth pattern, with a rather ratty looking duct. The papillary mass can sometimes be seen within the bile duct.

When surgeons speak of iCCA they are generally referring to the mass-forming lesion, not to the periductal, infiltrating, or papillary forms. Data from a liver cancer study group in Japan shows that over 80% of Japanese patients who have iCCA have a mass forming lesion (**slide 20**). Similar data have since been shown to apply in the United States also.

Most radiologists can very easily differentiate an iCCA from an hepatocellular carcinoma (HCC). The key phase for HCC is early arterial enhancement with late washout because in general the liver is hard and cirrhotic but the tumor is soft. In contrast, iCCA tumors tend to be very dense, stromal, and fibrinous. Early on, these lesions will be low-attenuating; only in later phases of the CT will they enhance. Very small lesions are occasionally can be hard to differentiate but a good hepatoradiologist typically would not confuse iCCA with HCC.

The classic things to look for are a large lesion, hypo-attenuating on early imaging; peritumoral ductal dilatation (tracking along the portal vein) and peritumoral dilatation (**slide 21**).

An image of an iCCA patient typically shows a large hypo-attenuating lesion (panel A in **slide 22**) with capsular retraction; enhancement and central necrosis in later imaging (panel B in **slide 22**); and peritumoral ductal dilatation (panel C in **slide 22**). Altogether, this amounts to the *sine qua non* for iCCA.

Because these lesions are so PET FDG-avid, the small amount of available literature suggests that PET will reveal occult disease in about 20 to 30% of patients (**slides 23 and 24**). Occasionally PET even shows that the occult primary that was thought to be an iCCA is in fact lighting up something in the rectum or the stomach. Even if it is an iCCA, if nodal disease is lighting up in the hepatoduodenal ligament or the celiac area I would generally treat those patients with preoperative neoadjuvant chemotherapy before taking them to surgery. Overall, PET is helpful preoperatively.

4. Surgical Resection

iCCA lesions can often be hard to resect because they present late. A large tumor in the central aspect of the liver (**slide 25)** is obliterating the anterior sectoral branch of the right portal vein and abuts the umbilical fissure and the right posterior sectoral branch. An extended right hemi hepatectomy was indicated with all of the

right liver and segment 4 having to be removed (**slide 26**, showing bile duct to segments 2 and 3, the portal vein, and the explant). It can sometimes be difficult to get wide negative margins on such large tumors in difficult locations.

Slide 27 is of a patient with a large left hemi liver mass abutting the middle and left hepatic vein, which was not readily visible on cross sectional imaging (**slide 28**). This was of concern since it was not certain that purchase above, on the common trunk, would be enough to take that structure at the time of surgery.

Slide 29 is an axial imaging. The patient was treated with some preoperative chemotherapy and Yttrium 90 (Y-90) radiotherapy but had very little response. An extended left hemi hepatectomy was performed and final pathology revealed 70% viable tumor. The patient is doing well a year later.

This was unfortunately not the case with a different patient who had a very large tumor in his right hemi liver, with biliary obstruction. **Slide 30** shows an endo stent and some atrophy of the right hemi liver with compensatory hypertrophy of the left liver. Segments 2 and 3 are quite big and ascites is visible on the outside of the liver. The patient had a very high CA19-9 of 100,000 and received a lot of chemotherapy preoperatively. His ascites resolved, his CA19-9 decreased by 50 or 70%, but six months after a right hepatectomy, the cancer recurred and he subsequently died.

The above two cases highlight the heterogeneity of the disease, the substantial size of the operations needed, and the complexity of the decisions involved.

There is much discussion in the operating room about whether anatomic resection is called for or whether getting a negative margin would suffice. For HCC, much literature reports oncologic benefit in anatomic resection; but for iCCA, some data—at least from our group—has not suggested any benefit from anatomic versus non-anatomic resection (**slide 33**).

Achieving a negative margin of 10 millimeters or more is the critical factor to achieving best chance at disease-free survival and overall survival (**slide 34**). If a vascular resection is needed to get that negative margin, the long term outcomes will be the same (**slide 35**) but it calls for great care: I usually call on transplant colleagues for assistance because even in the best of hands the morbidity associated with this procedure is significantly higher and perioperative mortality can be in the range of 5-10%. Again, these are big, complicated operations.

5. Staging Systems for iCCA

There was no staging for iCCA until the 7th edition of the AJCC Cancer Staging Manual. Prior to that, the manual had the single line: "Stage ICCA the same way as HCC." There simply were no data at that time, but it did not really make sense to combine ICC with HCC—they are two different diseases.

Two Japanese groups proposed new staging systems for iCCA (**slide 36**) but they did not receive much interest in the United States. In 2010, myself and Dr. Nathan, my research fellow at Hopkins at that time, proposed a novel staging system for iCCA based essentially on multifocality, tumor size, and vascular invasion (**slide 37**). It is a highlight of my career that our paper morphed into a chapter of the 7th edition of the AJCC manual. It has since been revised in the 8th edition. (The stages are summarized in **slides 38 and 39**.)

More recently, we have looked at other novel ways of assessing tumor burden in the liver and proposed a tumor burden score (TBS)—a single composite number using the Pythagorean theorem—that basically looks at the number and sizes of tumors in the liver (**slide 40**). We have shown that this is a powerful way to risk-stratify patients. Five-year survival in patients who have a high tumor burden is only 17% and their dis-

ease-free survival is only 7% (**slide 41**), suggesting that operating right away on patients who present with a very high TBS may not be advisable and that they might better be treated with preoperative chemotherapy to unveil their underlying tumor biology before operating on patients who do not have progressive disease or do not manifest disease outside the liver.

Using machine learning to identify different morphologic or phenotypic subtypes of iCCA (**slide 42**) resulted in identification of three different clusters (common ICC, proliferative, and inflammatory) of patients (**slide 43**). These categories are based on tumor size, CA 19-9, and lymphocyte-to-neutrophil ratio. Three-year survival for inflammatory iCCA patients is only about one year, suggesting some heterogeneity in this tumor, therefore we should not be treating everyone the same. Patients with a high TBS or with inflammatory iCCA should be given preoperative chemotherapy. Based on these data, up-front surgery should perhaps only be offered to patients with low TBS or who have common iCCA.

Lymph node disease and iCCA

Lymphadenectomy is not done for "garden variety" HCC. The liver is simply taken out. However, lymphadenectomy for fibrolamellar HCC is indicated because the incidence of lymph node disease is about 30%. Lymph node dissection is also done for gallbladder cancer. The question of whether lymphadenectomy is called for in iCCA remains controversial (**slide 44**).

Data from the iCCA consortium reveal that a lymphadenectomy is performed only about half the time, even at big centers, and that metastatic disease is noted in about 30% of patients. It might be argued that since half the patients are NX (never had any lymph node evaluated), the data are difficult to interpret; however, if one considers that even in the best-case scenario, all the patients who did not have a lymphadenectomy were N0, the incidence would still be 18-20% (**slide 45**).

Multiple studies have shown that the incidence of lymph node disease is about 20-30% for iCCA—similar to fibrolamellar. Why do we do lymphadenectomy for that disease but not for iCCA? Some people have proposed trying to predict who needs a lymph node dissection at the time of surgery, but it is incredibly difficult to predict the presence of lymph node metastasis preoperatively with extremely low AUC and ROC of most prediction tools (**slides 46 and 47**).

In general, it is very difficult to predict preoperatively, but it is important because lymph node metastasis is one of the most potent drivers of prognosis postoperatively. I would argue that it is not even worth staging the patient if the nodal basin is not assessed, because where there is nodal disease—N1 disease—the T categories, vascular invasion, and whether there is single or multiple disease no longer matter.

For patients with N0 disease, the prognosis is driven by whether the disease is multifocal and whether there is vascular disease. But among individuals with N1 disease, the horse is out of the barn and the presence or absence of single or multifocal disease or vascular invasion is no longer as prognostically important (**slides 48-50**).

Thus, nodal status is important for stratification, for prognosis, for discussing with patients their risk of recurrence, and also for identifying patients for clinical trials and highest-risk patients who may benefit from adjuvant therapy.

There is some laterality to performing a lymphadenectomy at the time of surgery. The liver has specific nodal basin drainage (**slide 51**). If a tumor is in the right side of the liver, nodal basin 12 (the perihilar hepatoduodenal ligament) should be dissected, as well as nodal basins 7, 8 and 13. However, if the lesion is in the left hemi liver, nodal basins 1 and 3 around the gastroesophageal junction should also be dissected because the nodal basin drainage areas are different.

In a paper published in the *Annals of Surgery* in December 2021[3] we showed that if there is a lymph node metastasis outside of station 12—the perihilar area—the prognosis is markedly worse. These are second-echelon lymph nodes. If it is in basin 8, 1, or 3, the prognosis is going to be worse.

The AJCC recommends lymphadenectomy in all cases and that at least six lymph nodes be evaluated (**slide 52**). Population-based data for the United States, however, show that currently only about 50% of patients will have even one lymph node evaluated at the time of surgery for iCCA, and only 15% of patients will have the AJCC recommended six lymph nodes evaluated (**slide 53**).

Patients with ICC often have a big tumor and need a big operation—but the probability of cure is only 10-15% (**slide 54**). This is a disease that generally has a very bad biology and prognosis. Five-year overall survival is about 30% (**slide 55**). The curve is reminiscent of pancreatic adenocarcinoma, another disease that has a bad overall biology.

The reason survival is so poor is because the cancers recur early, often, and systemically (**slide 56**). At a median follow up of less than two years, the data show that half of patients have recurred. In terms of pattern of recurrence, half of patients have an extra hepatic site as a component of their failure (**slide 57**). This is a systemic disease in many patients.

In a paper we published in 2020 in *JAMA Surgery,*[4] 22% had very early recurrence—defined as recurrence within six months of surgery (**slide 58**). With an extended right hepatectomy, even in the best of hands, the morbidity rate can be as high as 30% (**slide 59**). The patient may get through it but there will often be some bumps in the road, and then one in five patients will recur. It may be a decision both patient and doctor will come to regret.

We and others have tried to identify online calculators to try to risk stratify patients, because if patients present with multifocal disease or lymph node metastases, their risk of recurrence is prohibitively high (**slide 60**). For that reason patients should receive systemic chemotherapy first before going to the operating room. (I treat virtually all patients with pancreatic cancers with neoadjuvant therapy also.)

About a third of patients will recur in the lymph nodes—another reason to do a lymphadenectomy, because although there might not be a survival benefit, it is good loco-regional control to maintain quality of life and prevent biliary obstruction in some patients.

Because recurrence is such a problem, better systemic chemotherapy is necessary to make any meaningful change in this disease. Data from the ABC (Advanced Biliary Cancer) trial[5] found that patients treated with cisplatin-gemcitabine had a better outcome compared to gemcitabine alone (**slide 61**). More recent studies

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[3] Zhang XF, Xue F, Dong DH, Weiss M, Popescu I, Marques HP, Aldrighetti L, Maithel SK, Pulitano C, Bauer TW, Shen F, Poultsides GA, Soubrane O, Martel G, Koerkamp BG, Itaru E, Lv Y, Pawlik TM. Number and Station of Lymph Node Metastasis After Curative-intent Resection of Intrahepatic Cholangiocarcinoma Impact Prognosis. Ann Surg. 2021 Dec 1;274(6):e1187-e1195. doi: 10.1097/SLA.0000000000003788. PMID: 31972643.

[4] Tsilimigras DI, Sahara K, Wu L, Moris D, Bagante F, Guglielmi A, Aldrighetti L, Weiss M, Bauer TW, Alexandrescu S, Poultsides GA, Maithel SK, Marques HP, Martel G, Pulitano C, Shen F, Soubrane O, Koerkamp BG, Moro A, Sasaki K, Aucejo F, Zhang XF, Matsuyama R, Endo I, Pawlik TM. Very Early Recurrence After Liver Resection for Intrahepatic Cholangiocarcinoma: Considering Alternative Treatment Approaches. JAMA Surg. 2020 Sep 1;155(9):823-831. doi: 10.1001/jamasurg.2020.1973. PMID: 32639548; PMCID: PMC7344787.

[5] Valle J, Wasan H, Palmer DH, Cunningham D, Anthoney A, Maraveyas A, Madhusudan S, Iveson T, Hughes S, Pereira SP, Roughton M, Bridgewater J; ABC-02 Trial Investigators. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. N Engl J Med. 2010 Apr 8;362(14):1273-81. doi: 10.1056/NEJMoa0908721. PMID: 20375404.

looking at adjuvant therapy (so called "basket" trials—you throw things into the basket: some gallbladder, some cholangio, some distal cholangio) found a suggestion of an improvement in overall survival (at least in the BILCAP study) with capceitabene in the adjuvant setting (**slide 62**).

ASCO guidelines are that in general, patients who undergo resection for iCCA, especially those who are at high risk, with high tumor burden score and node positive disease, should be treated in the adjuvant setting, most often with capecitabine (**slide 63**).

6. The Future

The future lies in the molecular pathogenesis and classification of cholangiocarcinoma to help target some of molecular perturbations involving FGFR, IDH, and possibly BRAF. FGFR seems to be the major target with regard to mutations and deletions (**slide 64**).

The FIGHT-202 trial looked specifically at an FGFR inhibitor among patients who either had fusions or rearrangements, alterations, or no abnormalities in the FGFR receptor. A large number of patients treated with FGFR targeted therapy had a response, especially those who had fusions (not mutations) (**slides 65-69**). These patients had an improvement in progression free survival, as well as overall survival.

Thus, it is important to molecularly profile these patients, because some individuals who have FGFR fusions can have dramatic responses, like the patient whose response is captured in **slide 70**. The drugs used to treat him are now approved as second line therapy by the FDA.

As mentioned earlier, about 15-20% of patients also will have an alteration in IDH (IDH1 or IDH2) which is involved with ketogluterate synthesis in the liver (**slide 71**). A phase 3 trial looking at ivosidenib, an IDH1 inhibitor, in patients who have this mutation showed an improvement in progression-free survival (**slides 72-73**).

We are beginning to see that there is so much heterogeneity in this disease. If we can identify the subset of patients with FGFR fusions or IDH1 mutations we can begin to target them. Similarly, the ROAR trial (**slide 74-75**) showed that patients with a BRAF mutation can benefit from treatment with dabrafenib and trametinib combination therapy, although the BRAF mutation affects only about 5% of all cholangiocarcinoma patients.

Only about 5% of patients also will have mismatch repair gene alterations, and there has not been a lot of success using immunotherapy as monotherapy (**slides 76-77**), but there has been a lot of movement in combining cytotoxic chemotherapy with immunotherapy. **Slide 78** presents data recently revealed at ASCO GI 2022 showing that combining Gem/Cis (the backbone from the ABC trial) with an immunotherapy agent resulted in a 20% risk reduction and hazard of death. Combining immunotherapy with other agents holds promise for the future.

All that being said, it is important to stress that molecular testing is essential for this disease, and it should be done at the beginning, not at the end, because we know most of these patients are going to fail first line therapy and are going to recur. We need to know if they have the IDH1 mutation, the FGFR mutation, or the BRAF mutation, all of which are targetable today.

It is important also to be aware that molecular testing should be RNAseq-based because FGFR fusions are not mutations, so can be missed with DNA testing. Also, liquid biopsies that look for free DNA or circulating DNA will not suffice—tissue-based testing is necessary to identify potential targets.

7. Conclusion

First, the key take-aways:

- CCA is increasing in incidence. It is a very complex disease. It is a surgically challenging disease that requires—in many instances—very large and complex surgical operations.

- Lymphadenectomy provides important prognostic information. Margin negative surgical resection with lymphadenectomy is now the standard surgical approach.

- Genomic profiling should be standard of care for all iCCA patients. All iCCA patients need to be molecularly tested.

- We need to move towards a more personalized approach for these patients and enroll them in clinical trials.

As a student studying colorectal and pancreatic cancer, I remember being told that chemotherapy was getting so good that I would be put out of business as a surgeon. In fact, it is the exact opposite. As colorectal cancer chemotherapy improved, the indications for surgery broadened. Three lesions were once considered inoperable; today, we operate on ten! With pancreatic cancer, more effective chemotherapy is also emerging — and we are even beginning to talk about operating on oligo-metastatic disease of the liver. I believe the same thing will happen with iCCA: As the chemotherapy gets better, previously inoperable patients will become operable. There will be better control of systemic disease enabling us to focus our surgical techniques on the disease that is in the liver.

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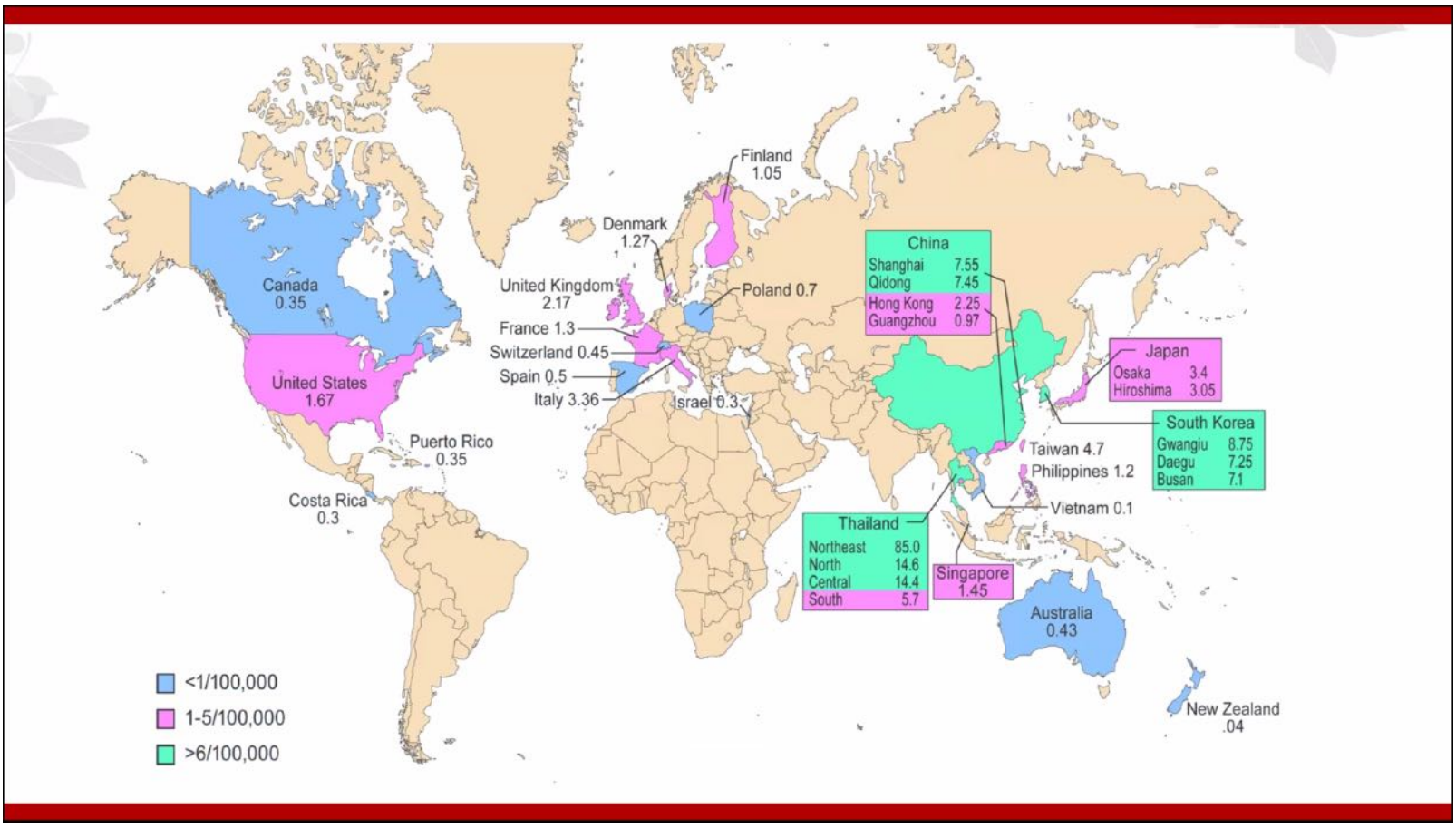
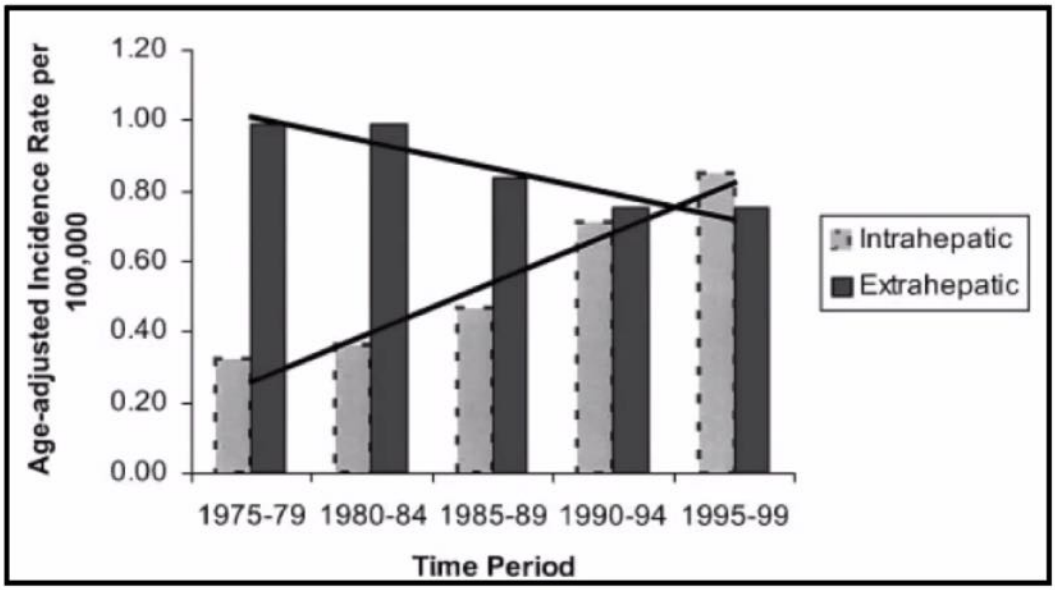


Slide 1

Epidemiology

Temporal Trends: Incidence of iCCA vs. pCCA/dCCA in US



El-Serag, Sem Liv Dis, 2004

Slide 2

iCCA
Risk Factors

Environmental Factors

- Hepatobiliary flukes
- PSC
- Choledochal cysts
- Hepatolithiasis
- Toxins
- Cirrhosis
- Chronic hepatitis B and C
- Obesity
- Diabetes

Host Factors

- Genetic polymorphisms

Slide 3

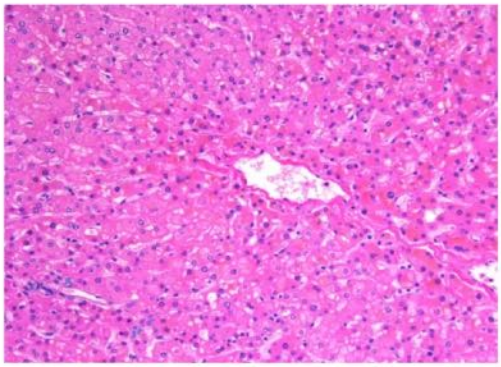
J Gastrointest Surg (2013) 17:748–755
DOI 10.1007/s11605-013-2149-x

ORIGINAL ARTICLE

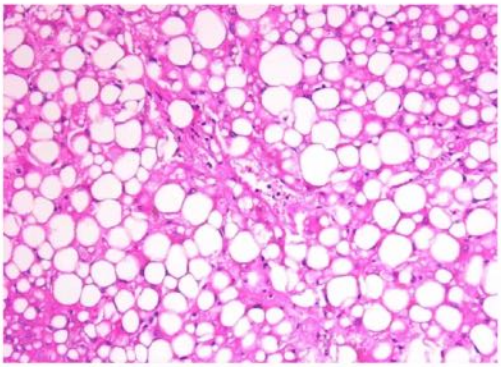
Prevalence of Nonalcoholic Steatohepatitis Among Patients with Resectable Intrahepatic Cholangiocarcinoma

Srinevas K. Reddy · Omar Hyder · J. Wallis Marsh · Georgios C. Sotiropoulos · Andreas Paul · Sorin Alexandrescu · Hugo Marques · Carlo Pulitano · Eduardo Barroso · Luca Aldrighetti · David A. Geller · Christine Sempoux · Vlad Herlea · Irinel Popescu · Robert Anders · Laura Rubbia-Brandt · Jean-Francois Gigot · Giles Mentha · Timothy M. Pawlik

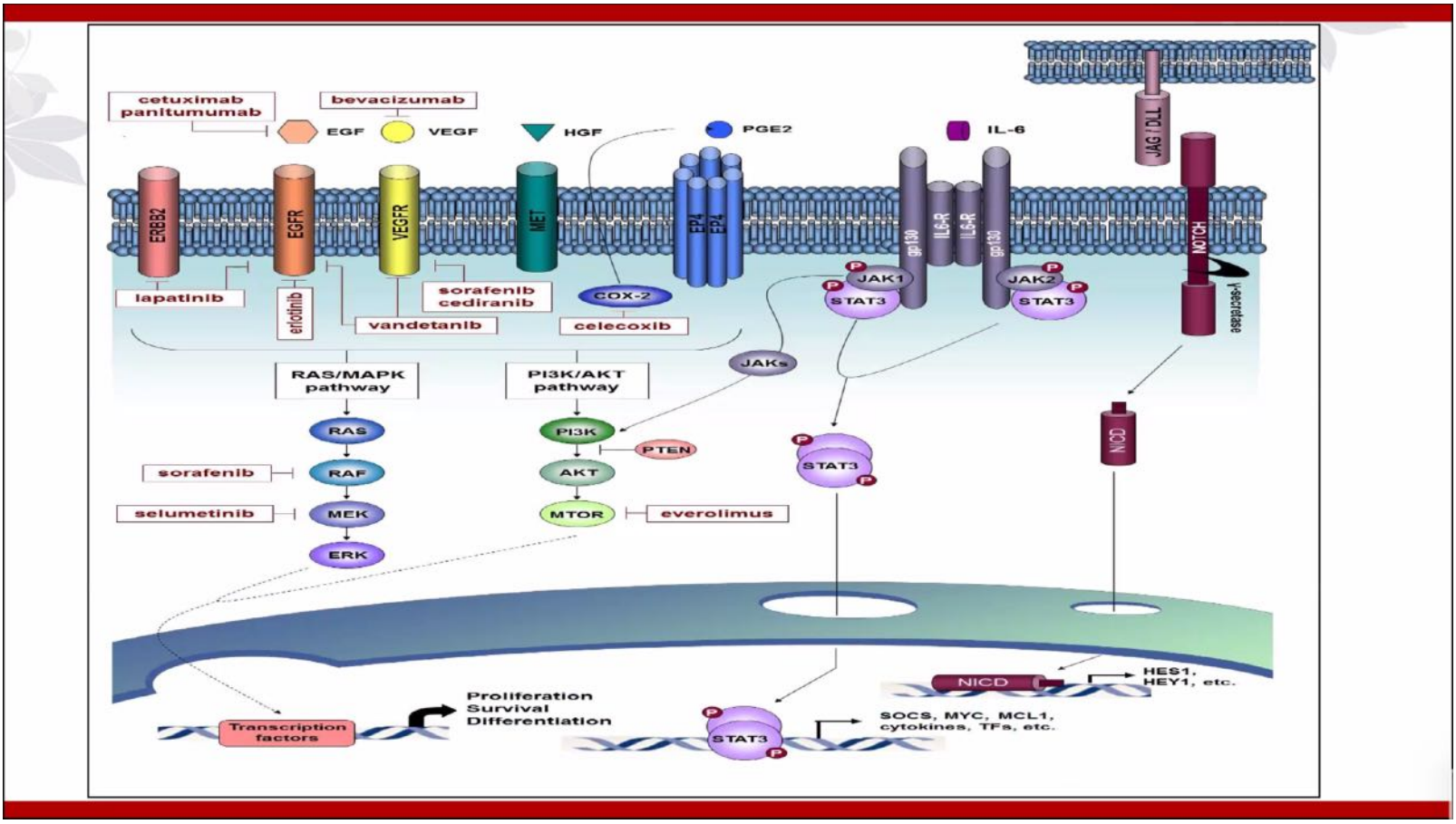
Normal Liver



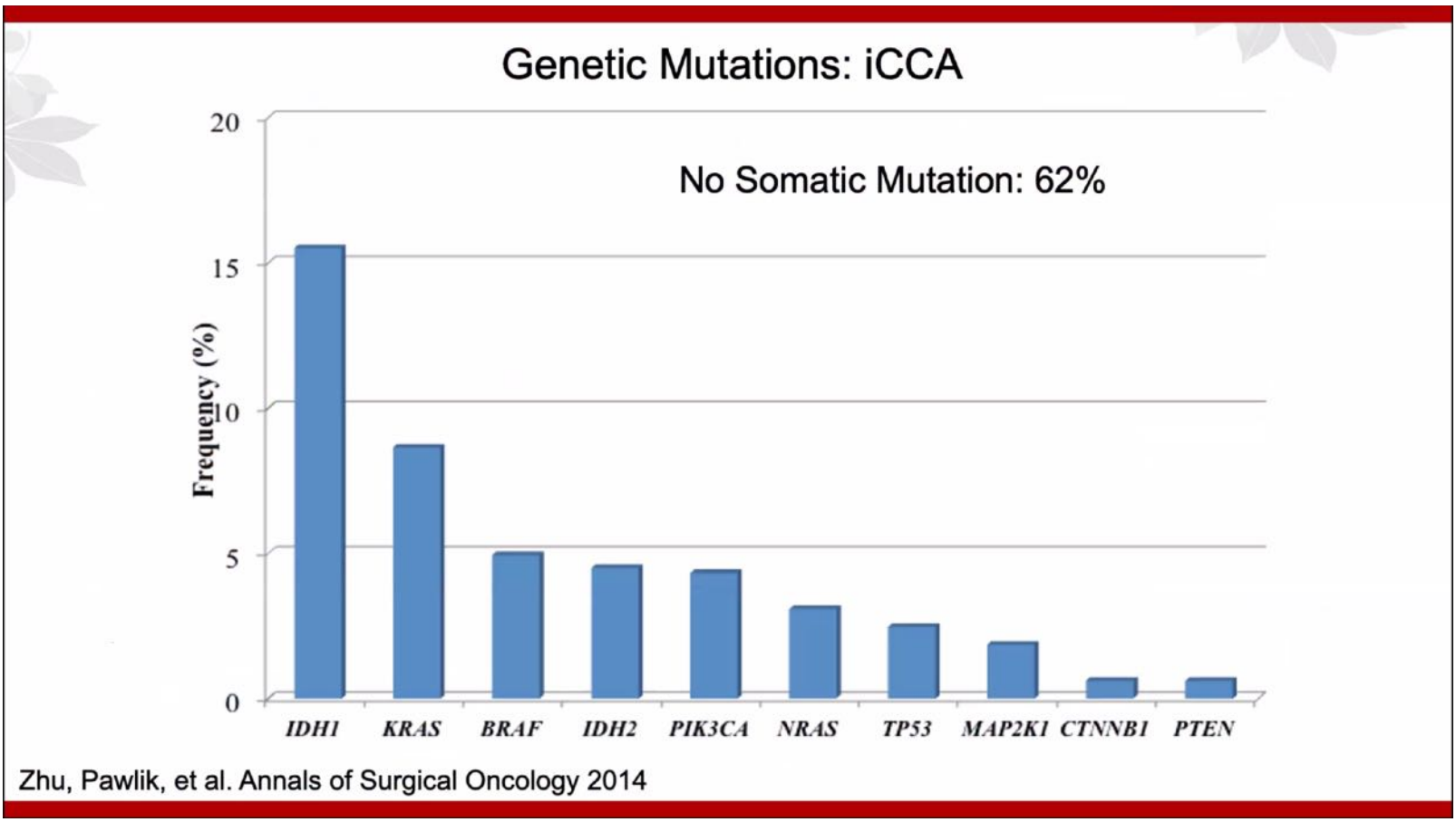
Steatosis



Slide 4

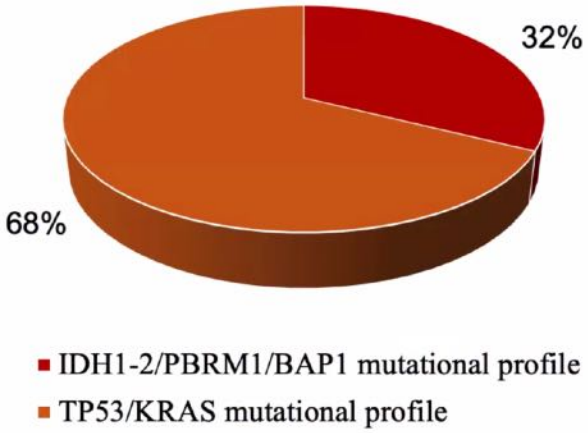


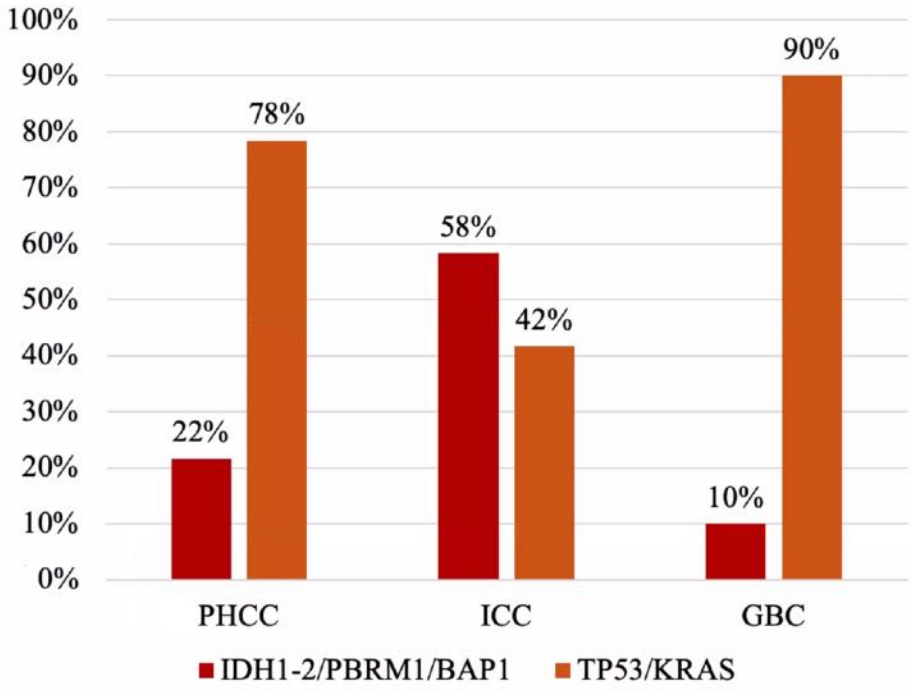
Slide 5



Slide 6

Genetic Classification





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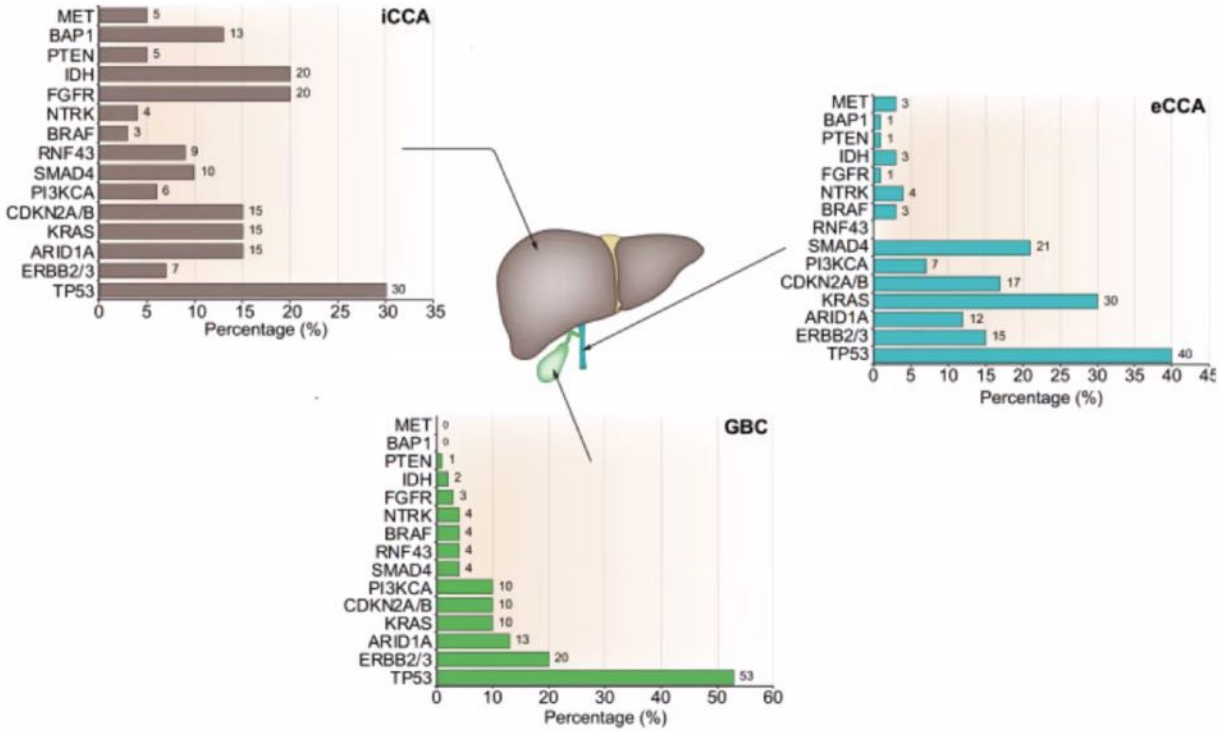
Slide 7

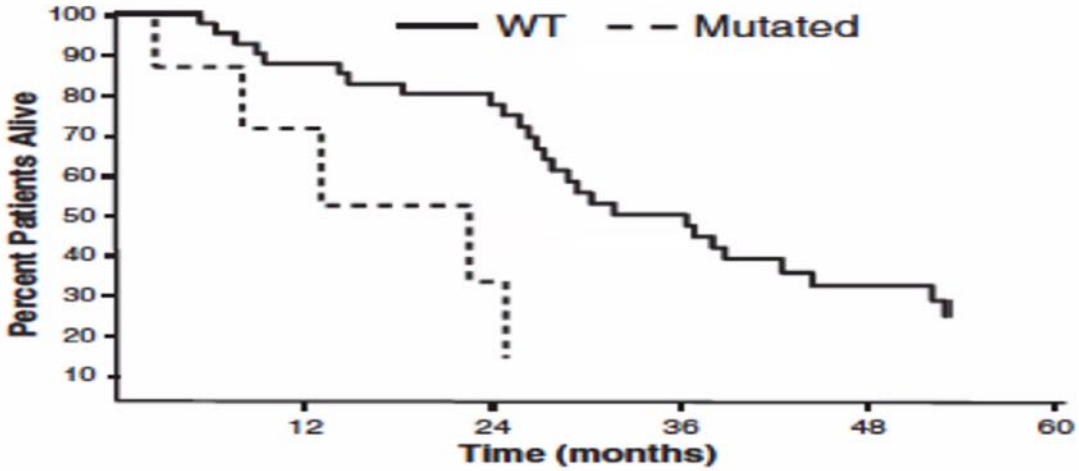


13

Slide 8

The frequency of *KRAS* and *BRAF* mutations in intrahepatic cholangiocarcinomas and their correlation with clinical outcome☆

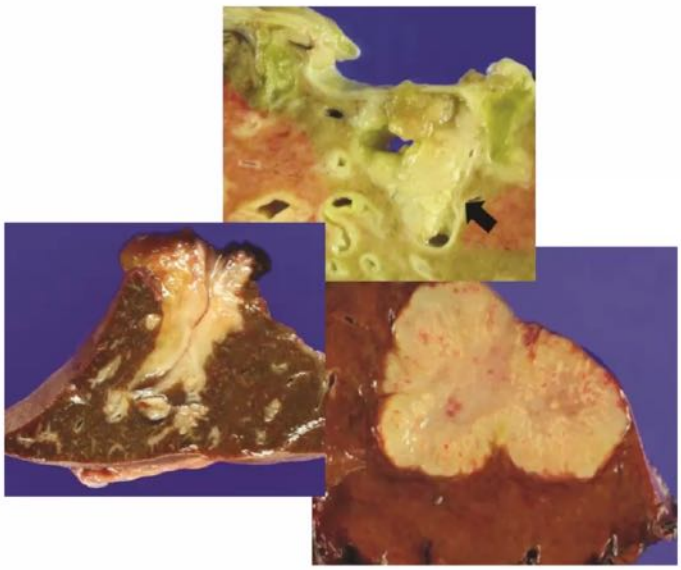
Scott Robertson MD, PhD[a], Omar Hyder MD, MS[b], Rebecca Dodson MD[b], Suresh K. Nayar[a], Justin Poling MD[a], Katie Beierl[a], James R. Eshleman MD, PhD[a,c], Ming-Tseh Lin MD, PhD[a], Timothy M. Pawlik MD, MPH, PhD[b,c], Robert A. Anders MD, PhD[a,c,*]

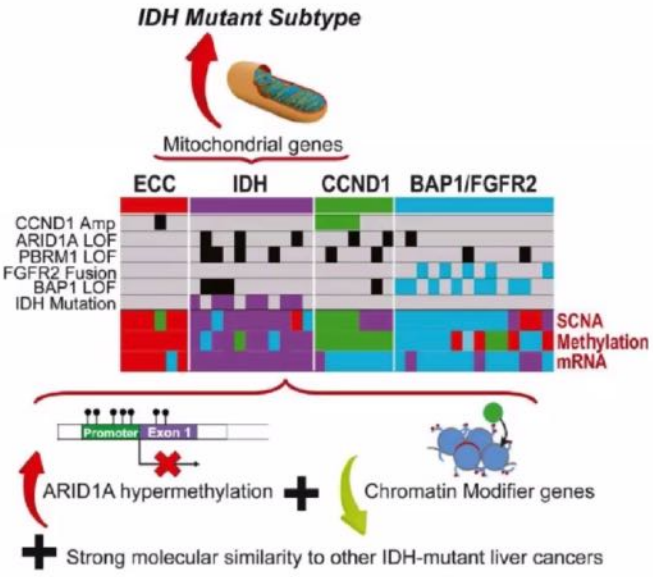


Slide 9

Integrative Genomic Analysis of Cholangiocarcinoma Identifies Distinct *IDH*-Mutant Molecular Profiles

Farshidfar et al.; Cell Reports: 18, 2780-2794, 2017



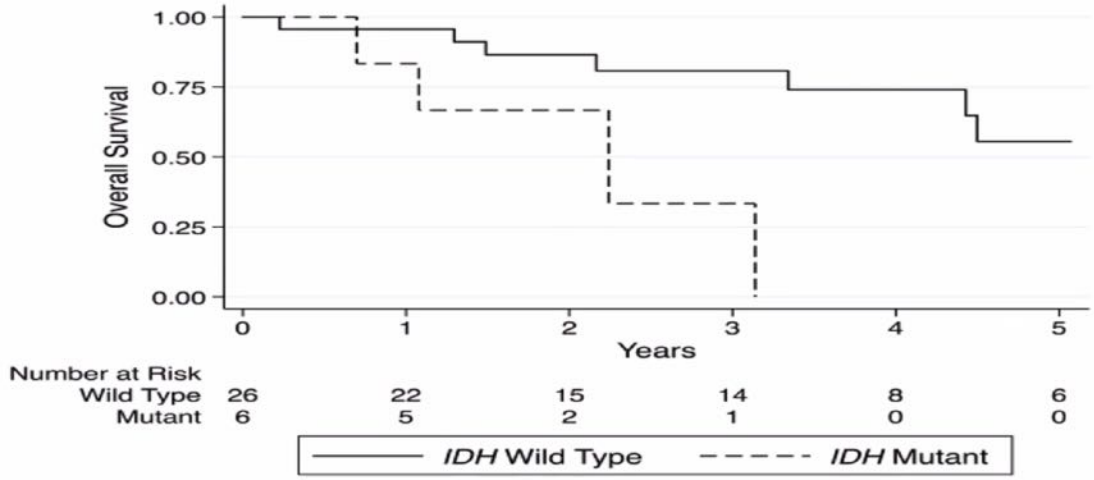


Slide 10

nature genetics

Exome sequencing identifies frequent inactivating mutations in *BAP1*, *ARID1A* and *PBRM1* in intrahepatic cholangiocarcinomas

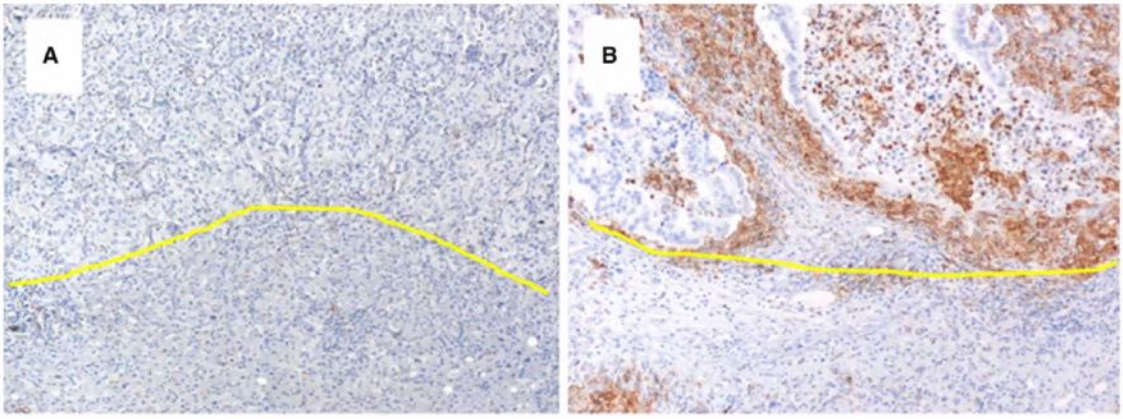
Yuchen Jiao, Timothy M Pawlik, Robert A Anders, Florin M Selaru, Mirte M Streppel, Donald J Lucas, Noushin Niknafs, Violeta Beleva Guthrie, Anirban Maitra, Pedram Argani, G Johan A Offerhaus, Juan Carlos Roa, Lewis R Roberts, Gregory J Gores, Irinel Popescu, Sorin T Alexandrescu, Simona Dima, Matteo Fassan, Michele Simbolo, Andrea Mafficini, Paola Capelli, Rita T Lawlor, Andrea Ruzzenente, Alfredo Guglielmi, Giampaolo Tortora + *et al.*



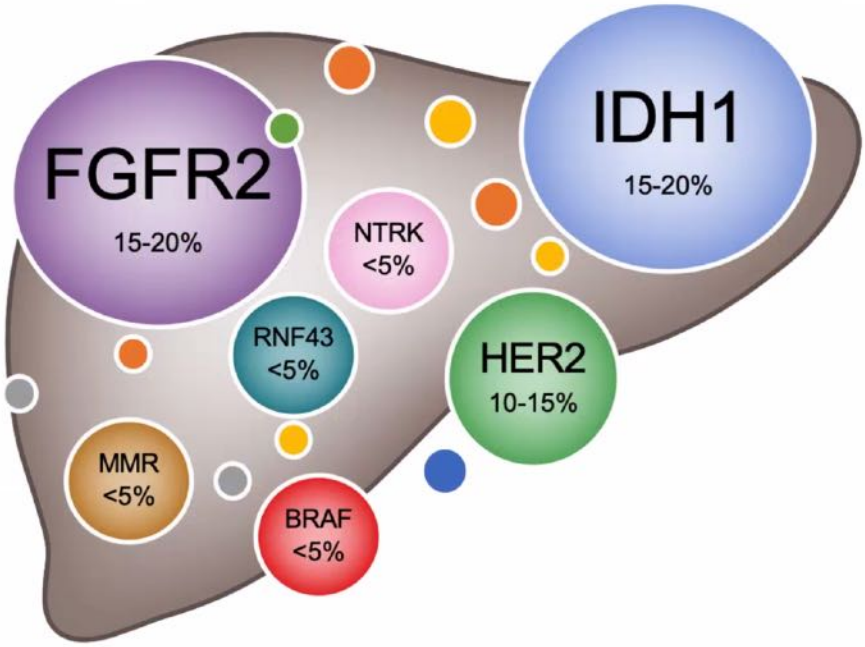
Slide 11

Program Death 1 Immune Checkpoint and Tumor Microenvironment: Implications for Patients With Intrahepatic Cholangiocarcinoma

Faiz Gani, MBBS[1], Neeraja Nagarajan, MD, MPH[1], Yuhree Kim, MD, MPH[1], Qingfeng Zhu, MD[2], Lan Luan, MD[2], Feriyl Bhaijjee, MD[2,3], Robert A. Anders, MD, PhD[2], and Timothy M. Pawlik, MD, MPH, PhD, FACS, FRACS (Hon.)[1,4]



Slide 12



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Clinical Presentation

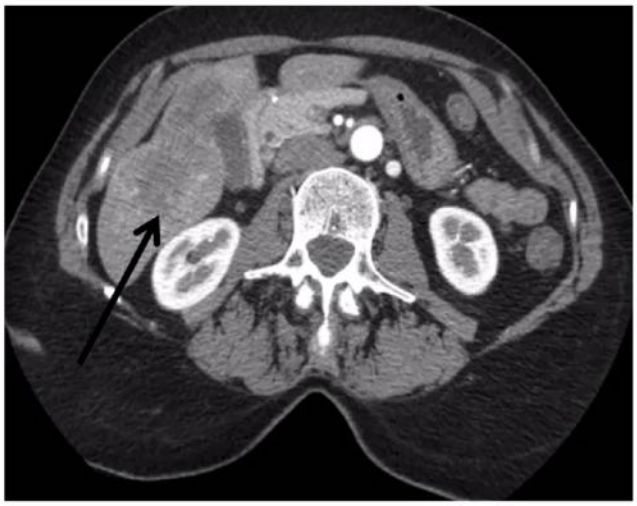
Cholangiocarcinoma

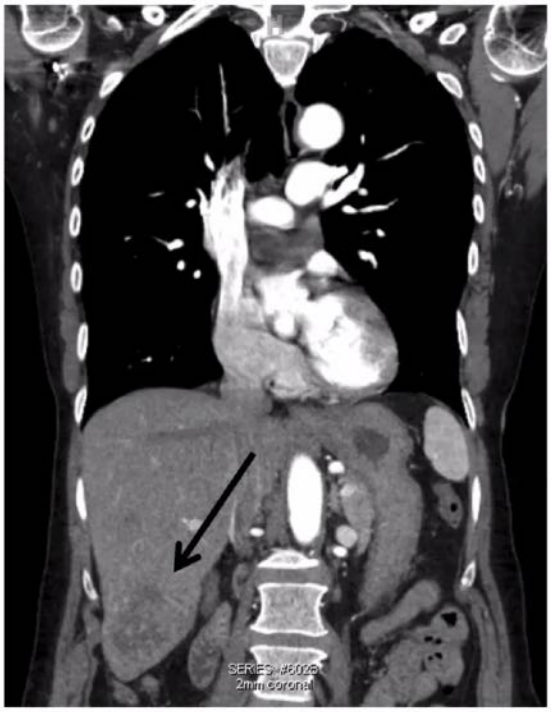
	Intrahepatic	Perihilar	Distal
Abdominal Pain	X	X	
Anorexia	X	X	X
Weight loss	X	X	X
Pruritus		X	X
Jaundice		X	X
Distended palpable GB			X
Asymptomatic	X		

Slide 14

Clinical Presentation

Intrahepatic Cholangiocarcinoma





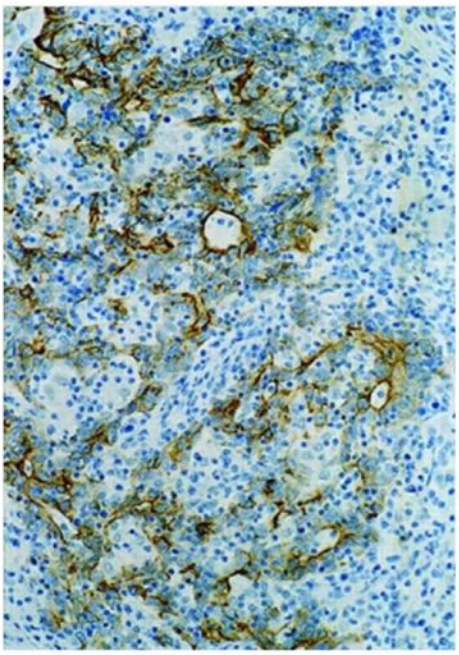
Slide 15

Pathology

Intrahepatic Cholangiocarcinoma

"Adenocarcinoma"

- No reliable markers to differentiate ICC from a metastasis
- Look for biliary dysplasia
- Diagnosis of exclusion



Slide 16

Pathology: Immunohistochemistry

Intrahepatic Cholangiocarcinoma

Negative: lung (TTF1), colon (CDX2), pancreas (DPC4)

Positive: biliary epithelium (AE1 / AE3; CK7+ and CK 20-)

Differentiation between iCCA and mixed HCC tumors may require evaluation of specific markers of hepatocellular or progenitor cell features:

Hep-Par-1
GPC3
HSP70
glutamine synthetase
EpCAM
K19

Slide 17

Pre-Operative Evaluation

Intrahepatic Cholangiocarcinoma

- CEA elevated in ~25% of cases
- CA 19-9 elevated in ~50% of cases
- AFP elevated in < 5% of cases
- CEA or CA 19-9 are not sensitive enough to diagnose cholangiocarcinoma (~50%)

Nehls, Sem Liv Dis, 2004

Slide 18

Radiographic Imaging

Intrahepatic Cholangiocarcinoma

Mass Forming

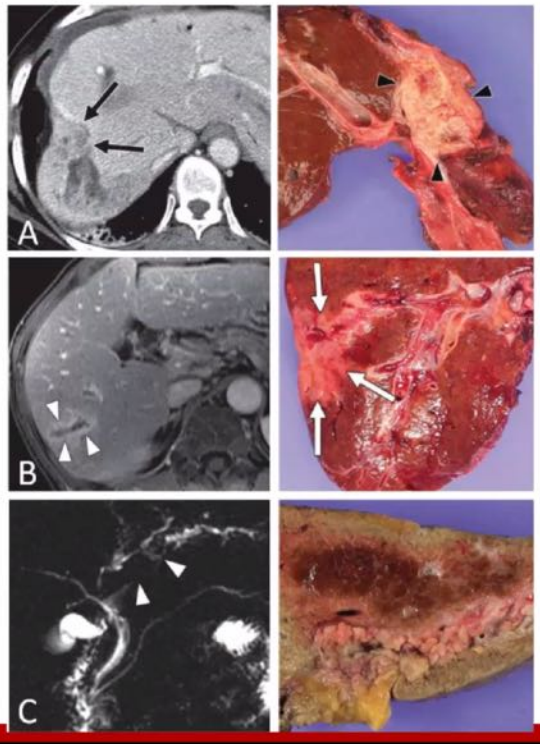
- homogenous
- low-attenuation mass
- capsular retraction
- peripheral irregular rim enhancement

Periductal Infiltrating

- periductal enhancement
- periductal thickening and enhancement
- irregularly dilated intrahepatic ducts

Intraductal-Growth

- diffuse and marked ductectasia
- with or without visible papillary mass
- intraductal cast-like lesion
- focal intrahepatic ductal stricture



Photos: Han, Radiographics, 2002

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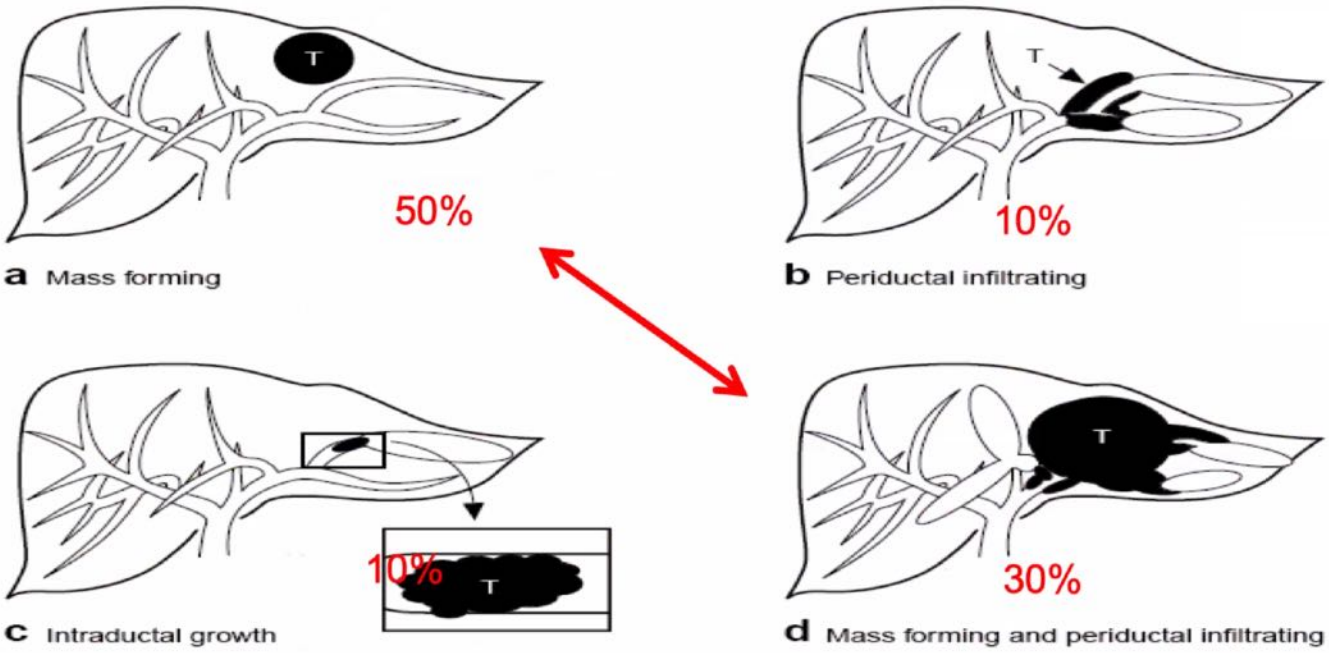
Gross Morphologic Classification System (LCSGJ)

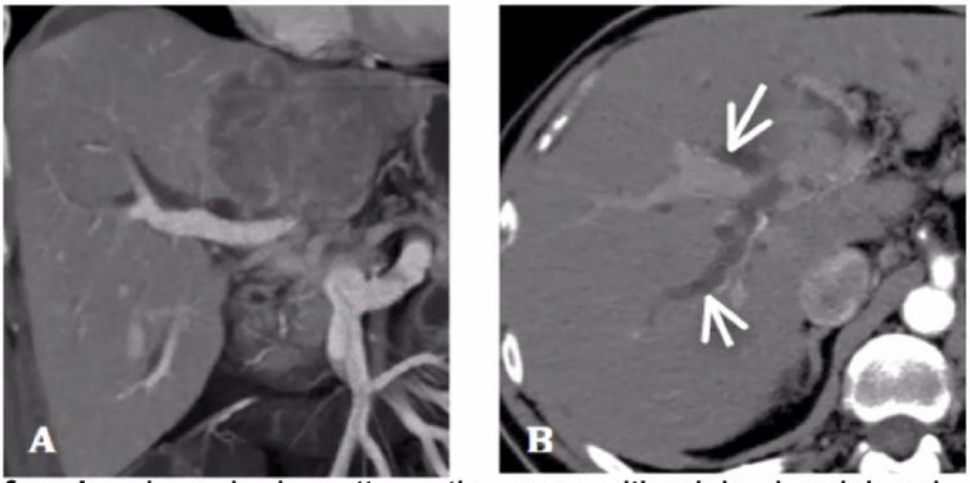
Intrahepatic Cholangiocarcinoma



Slide 20

iCCA

Contrast Enhanced CT



Mass forming: irregular low attenuation mass with minimal peripheral enhancement and focal dilatation of the intrahepatic ducts around the tumor

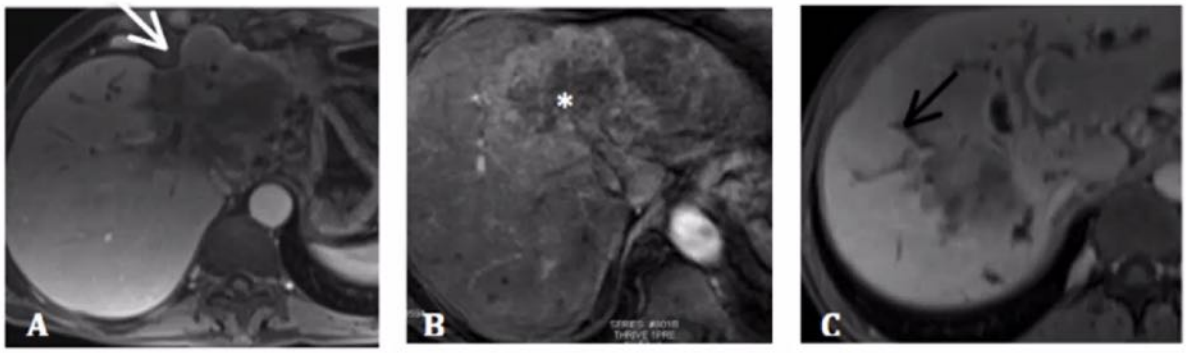
Periductal-infiltrating: homogeneous low-attenuation growth or enhancing periductal thickening along a dilated or narrowed bile duct

Intra-ductal: diffuse ductal dilatation with multifocal superficial spreading papillary or plaque-like masses

Slide 21

iCCA

Contrast Enhanced MRI



Mass forming ICC. MR-enhanced image demonstrates an ill-defined hypointense mass with peripheral rim enhancement associated with atrophy of the left hepatic lobe and capsular retraction.

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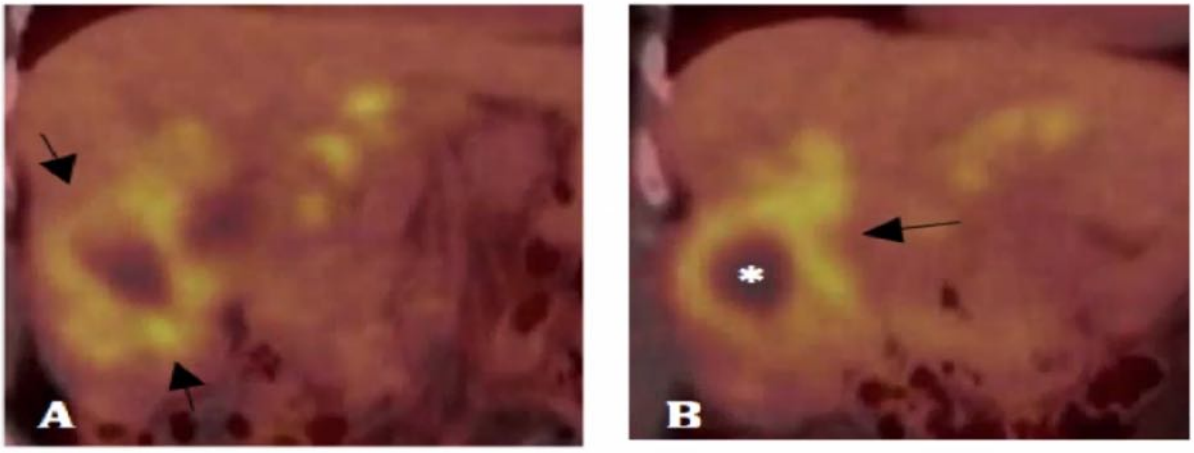
iCCA

PET Scan



Large mass within the right hepatic lobe showing peripheral hypermetabolism on FDG-PET (arrows), with a photopenic central area (*) suggesting necrosis.

Slide 23

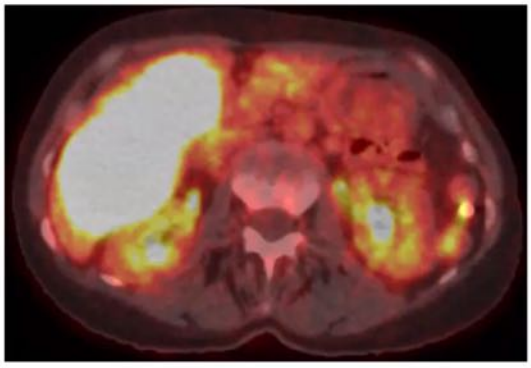
Radiographic Imaging: PET Scan

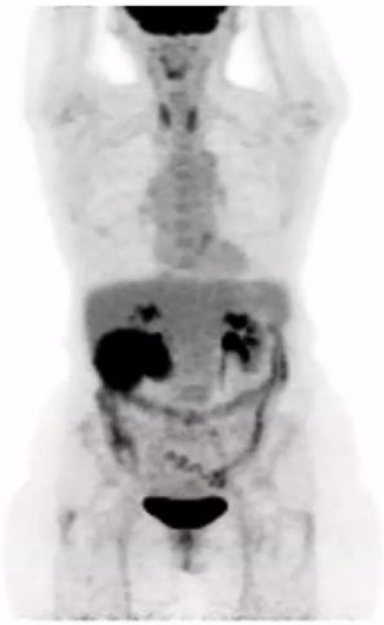
Intrahepatic Cholangiocarcinoma

PET Scan

85% of ICC cases FDG avid
Changed surgical management in 30%
Identified occult metastatic disease 20-30%

Helpful to rule out occult primary, but more so to identify other metastatic disease



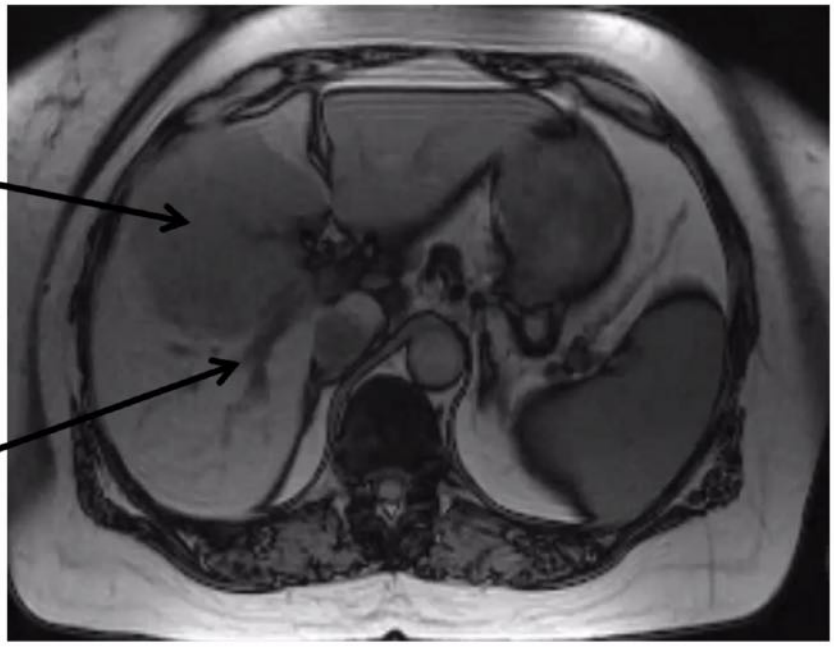


Anderson et al, JOGS 2004; Kim et al, Eur J Nuc Med 2003

Slide 24

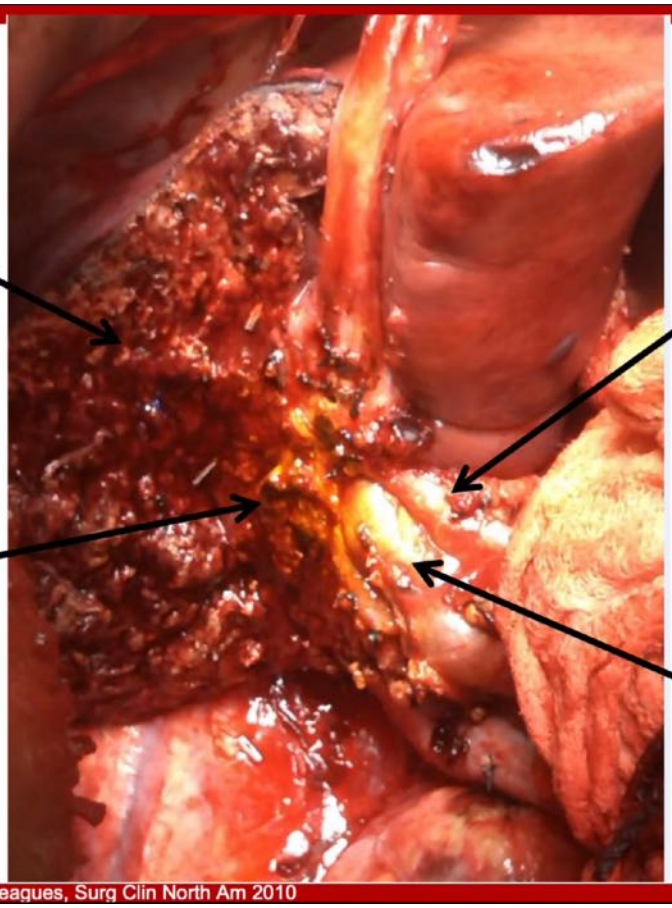
Surgical Procedure

Intrahepatic Cholangiocarcinoma



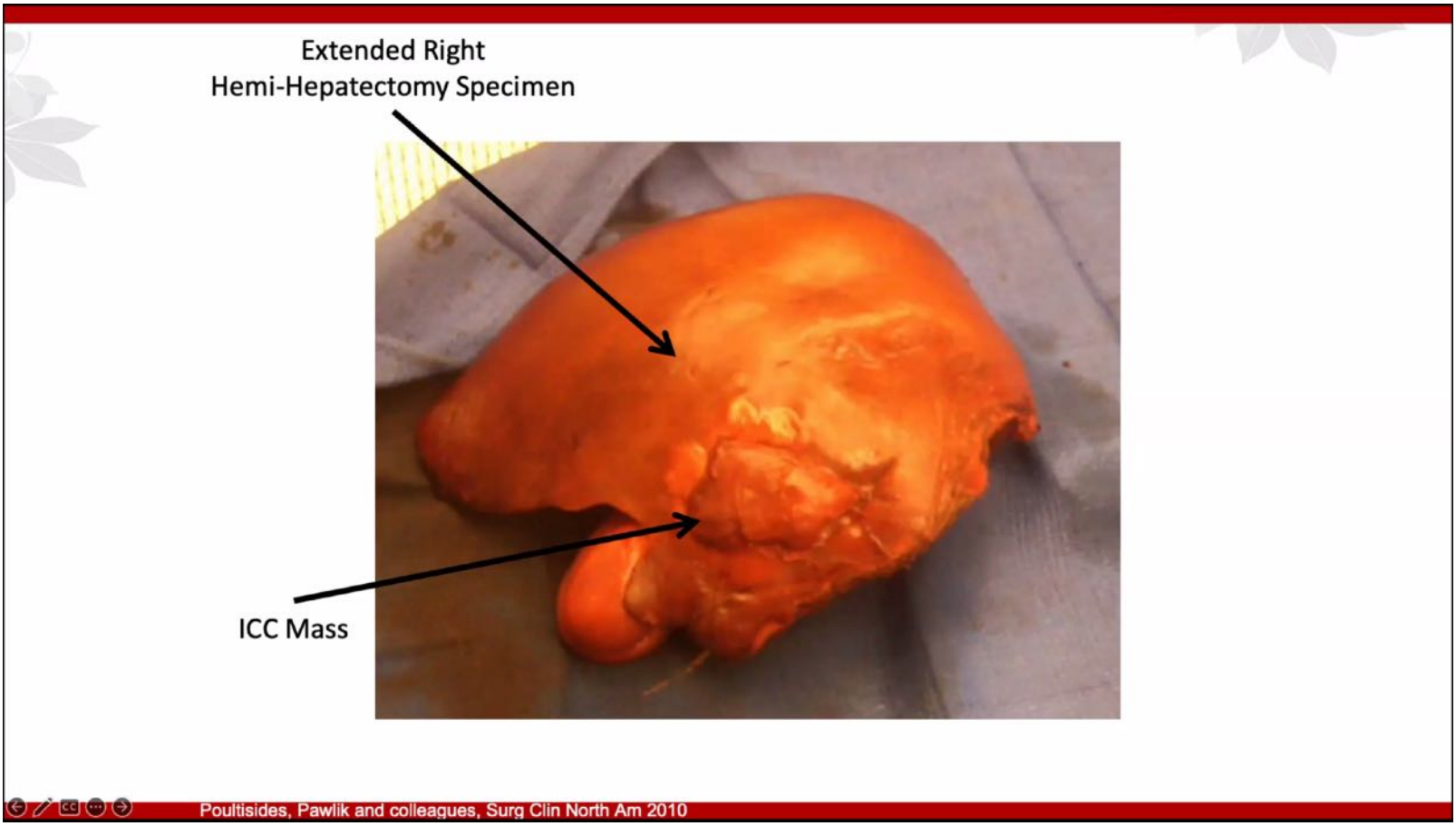
Poultisides, Pawlik and colleagues, Surg Clin North Am 2010

Slide 25

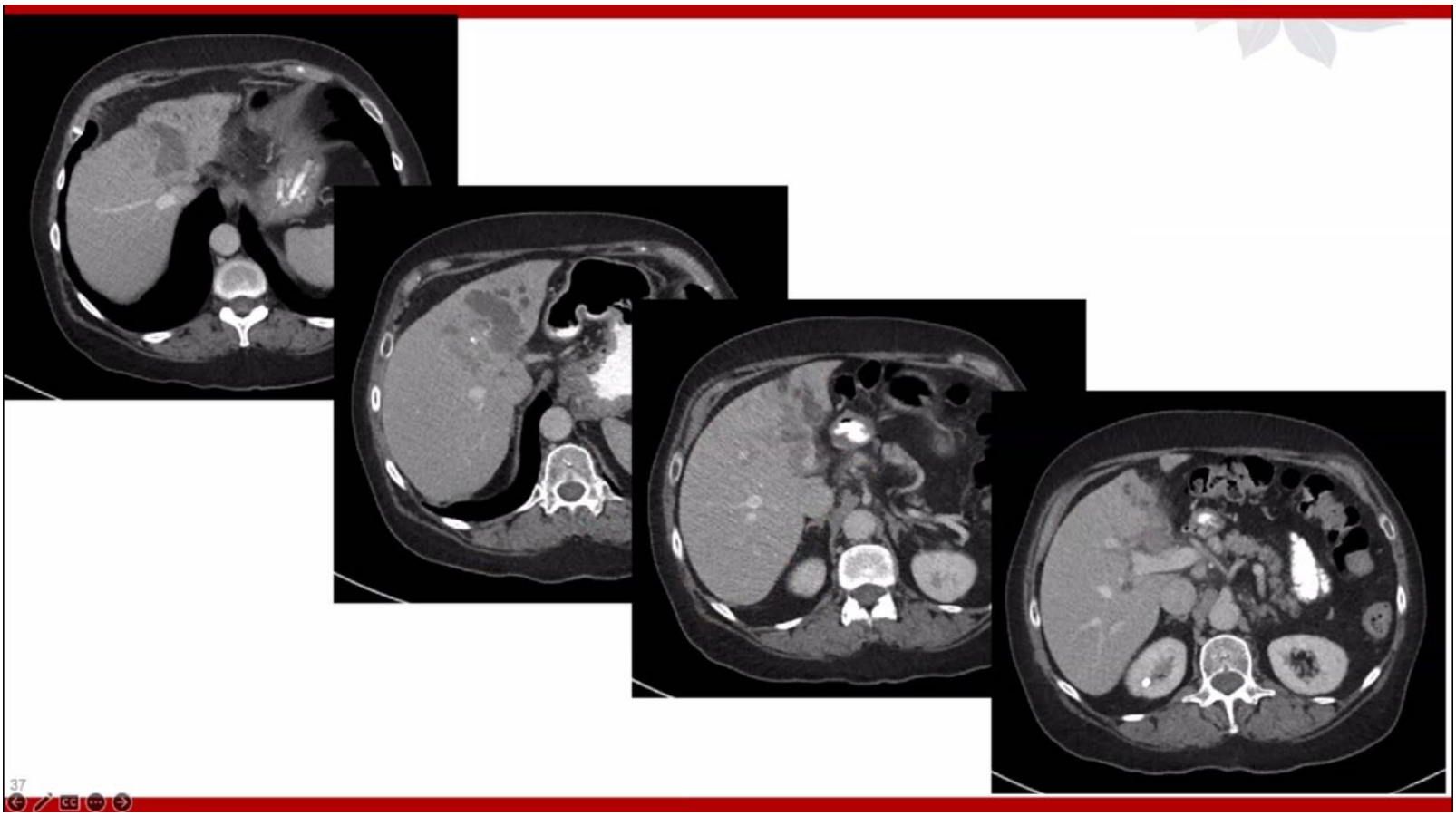


Poultisides, Pawlik and colleagues, Surg Clin North Am 2010

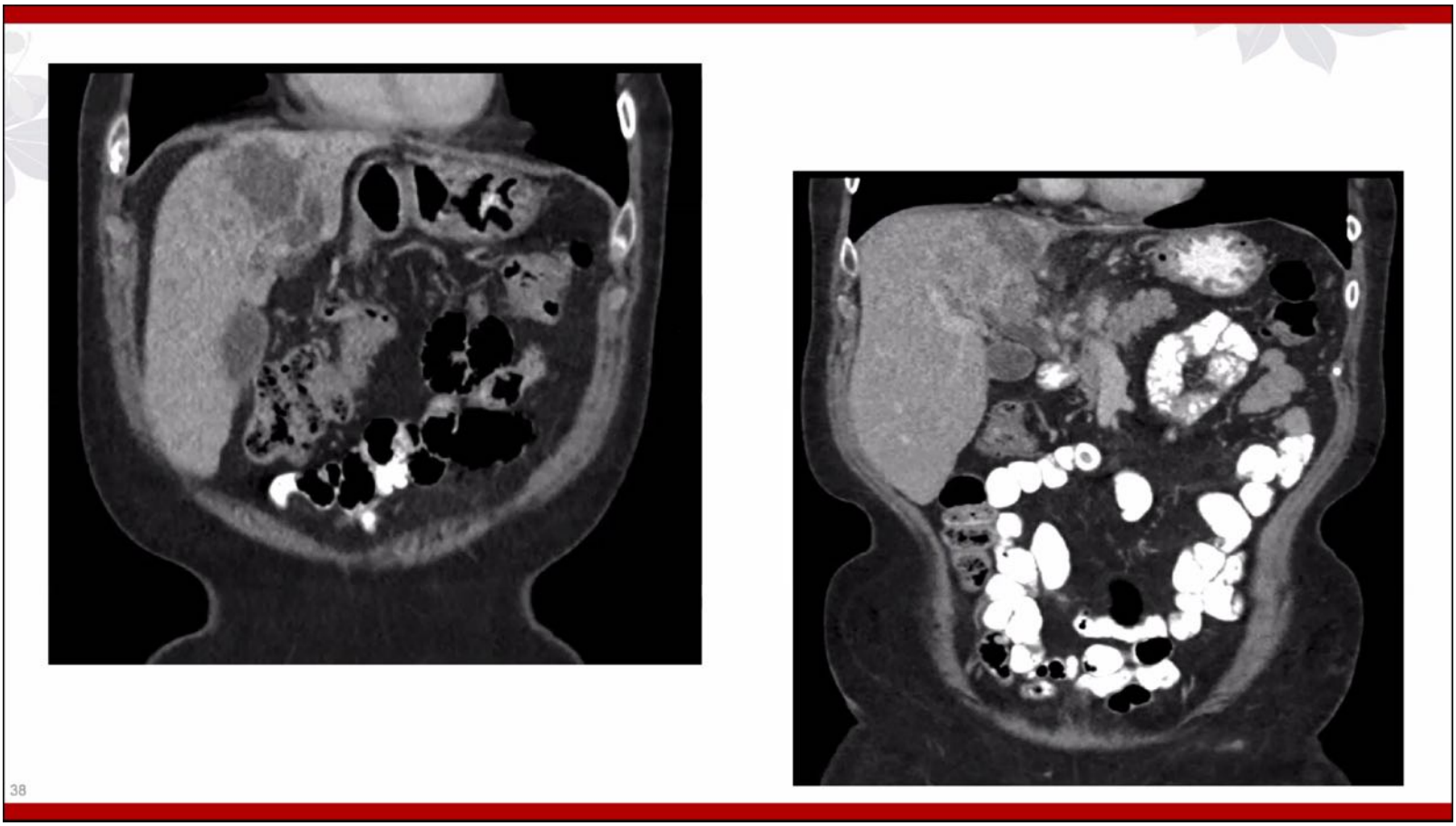
Slide 26



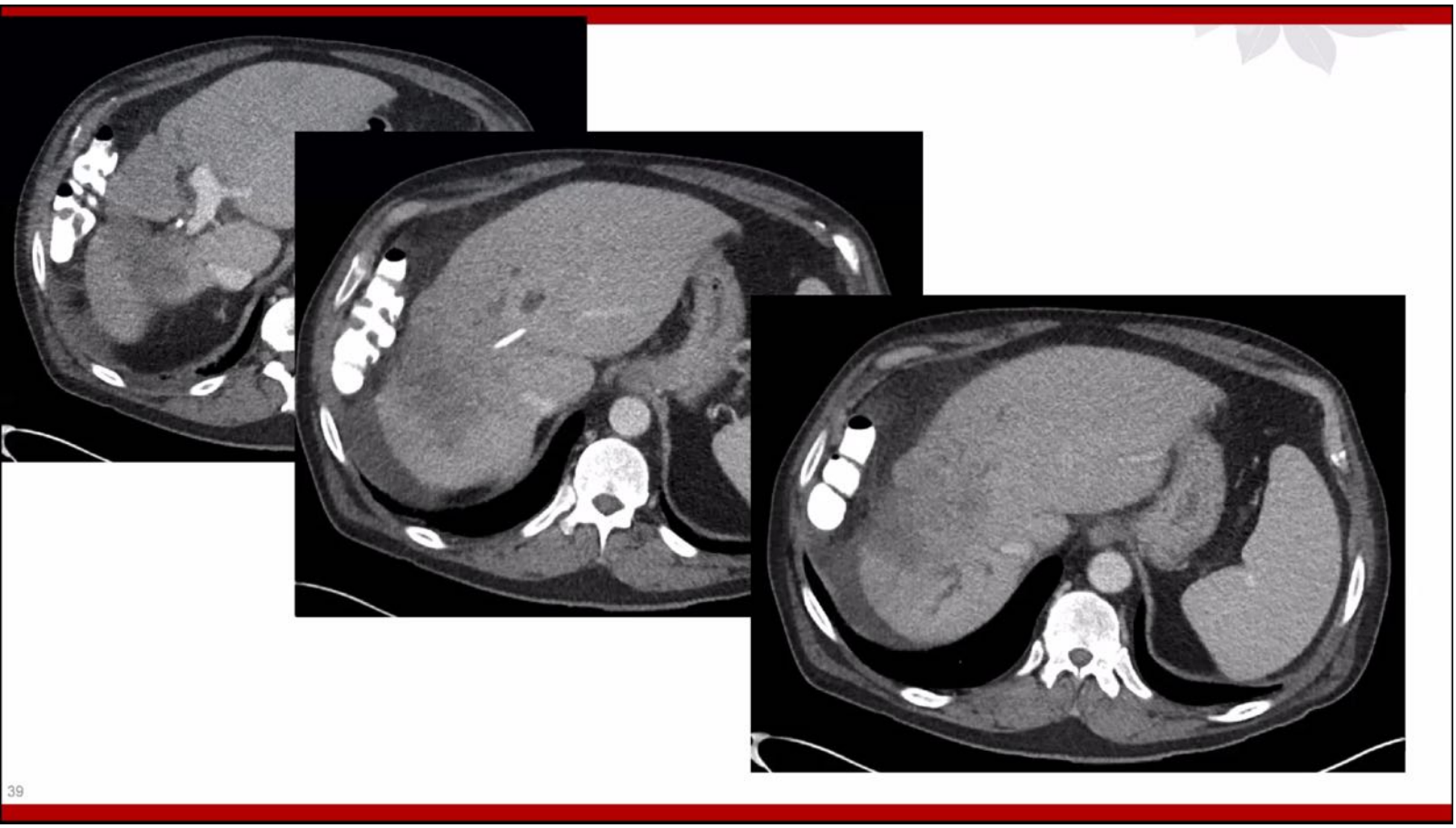
Slide 27



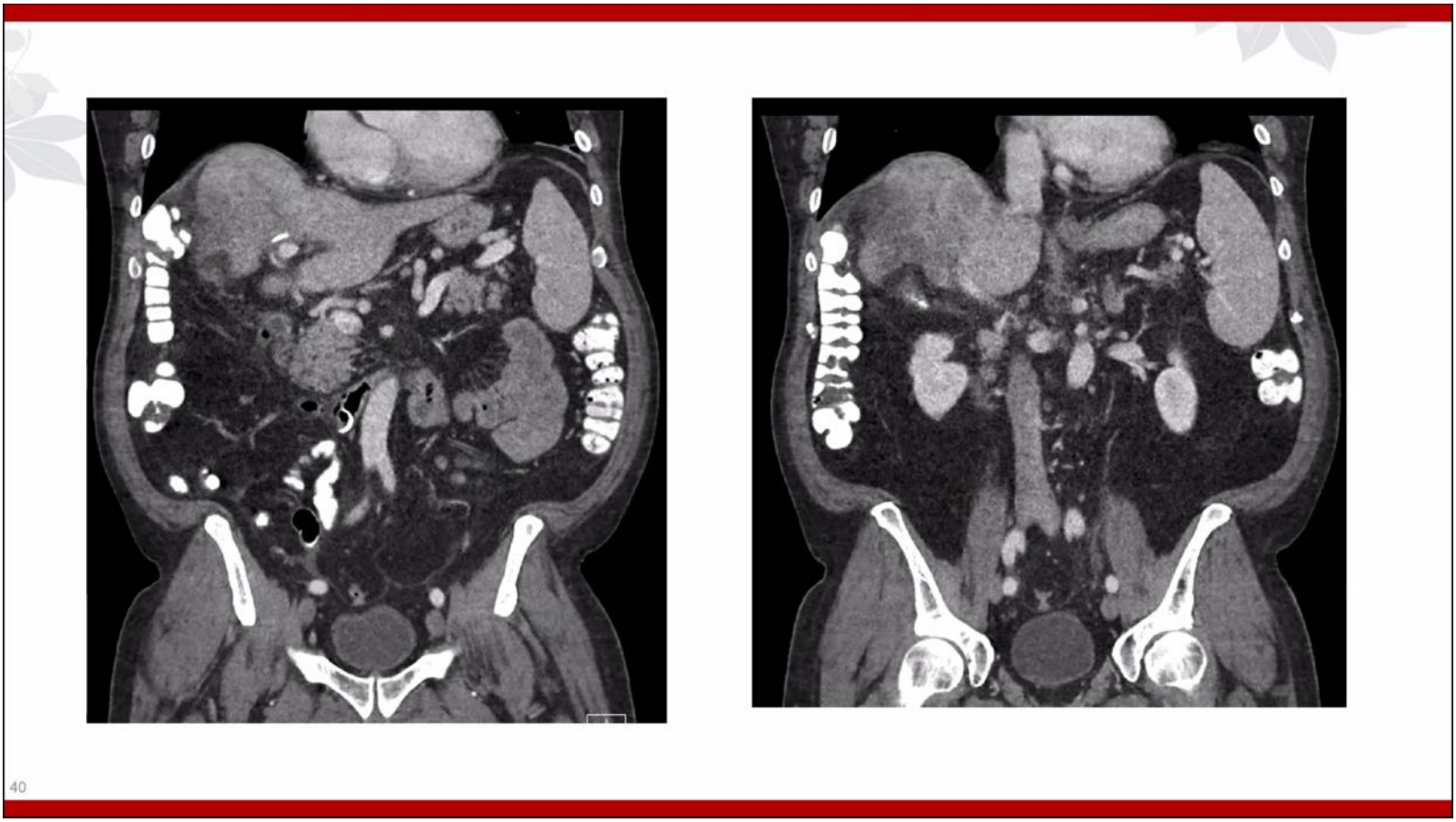
Slide 28



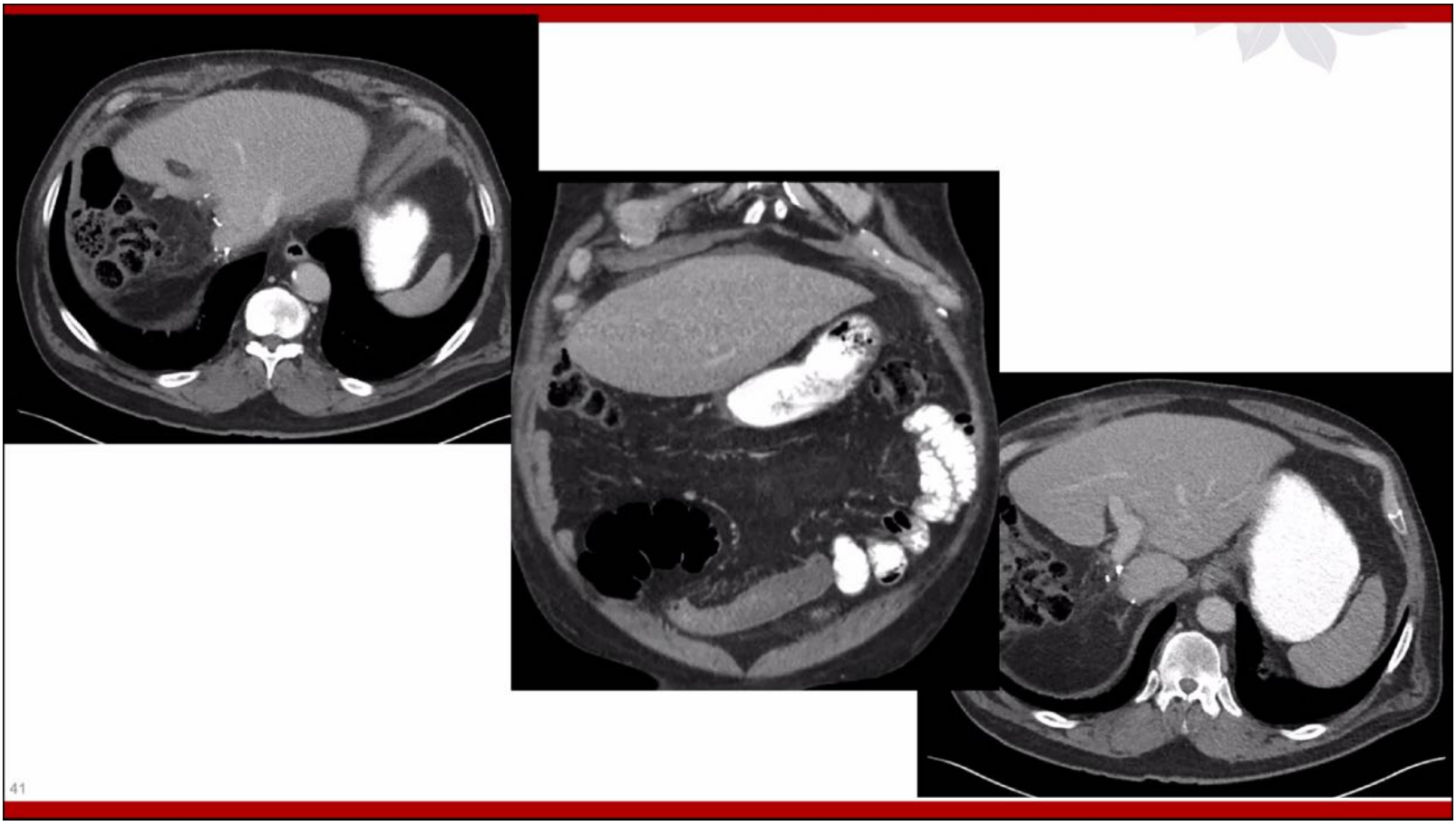
Slide 29



Slide 30



Slide 31



Slide 32

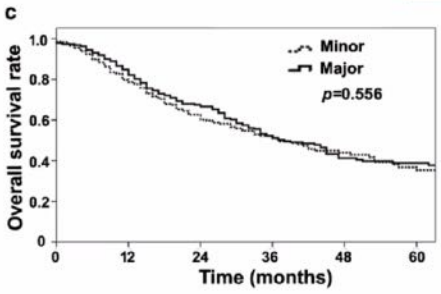
Anatomic versus Non-Anatomic Hepatectomy

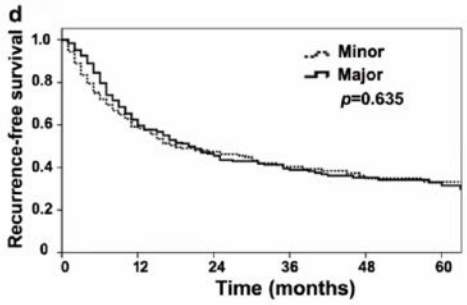
Patients with ICC undergoing hepatectomy
N = 1023

Anatomic
N = 608 (59.4%)

Propensity matching
N = 290 pairs

Non-Anatomic
N = 415 (40.6%)





Zhang, Pawlik, et al. JOGS 2017

median OS, 38 vs. 37 months, p = 0.556;
median RFS, 20 vs. 18 months, p = 0.635

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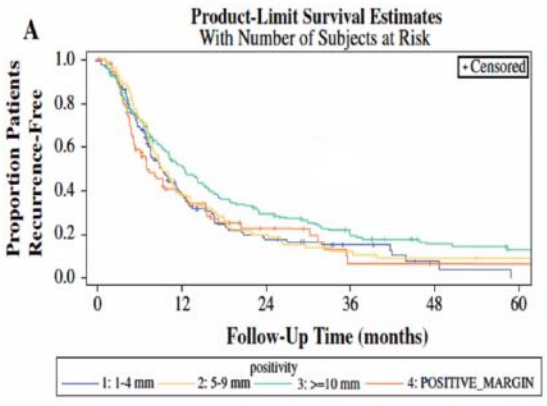
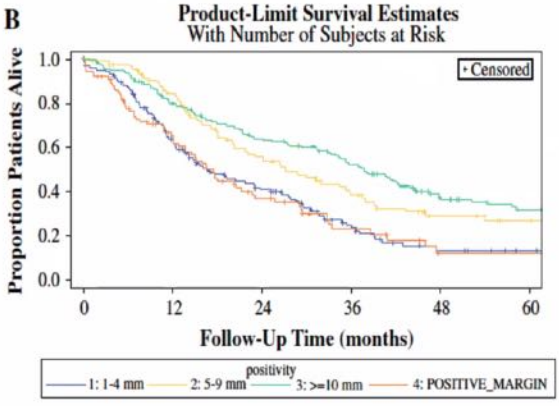
The Impact of Surgical Margin Status on Long-Term Outcome After Resection for Intrahepatic Cholangiocarcinoma

Gaya Spolverato, MD[1], Mohammad Y. Yakoob, MD, MS, PhD[1], Yuhree Kim, MD, MPH[1], Sorin Alexandrescu, MD[2], Hugo P. Marques, MD[3], Jorge Lamelas, MD[3], Luca Aldrighetti, MD[4], T. Clark Gamblin, MD[5], Shishir K. Maithel, MD[6], Carlo Pulitano, MD[7], Todd W. Bauer, MD[8], Feng Shen, MD[9], George A. Poultsides, MD[10], J. Wallis Marsh, MD[11], and Timothy M. Pawlik, MD, MPH, PhD, FACS[1,12]





Incremental worsening RFS and OS as margin width decreased from 1 cm → ≥ 1-cm margin to optimize long-term outcomes.

Spolverato, Pawlik, et al. Ann Surg Oncol 2015

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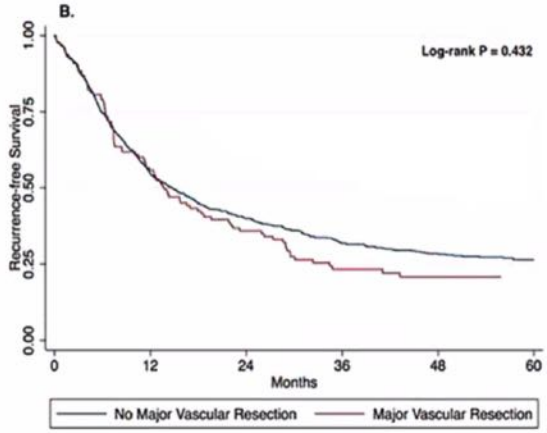
Impact of Vascular Resection on Outcomes (n=1,087)

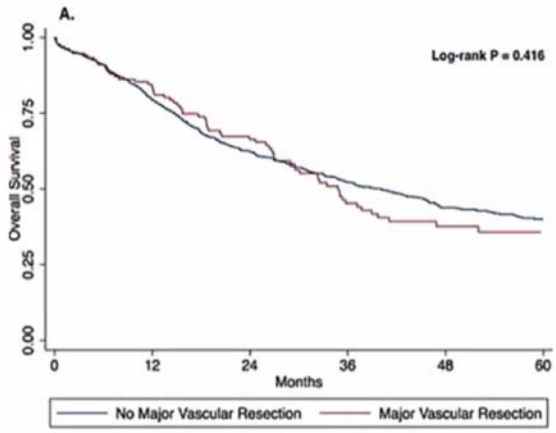
- No major vascular resection (n=959)
- Major vascular resection (n=128)

- ✓ IVC resections: 21 (16.4%)
- ✓ PV resections: 98 (76.6%)
- ✓ Combined resections: 9 (7%)

Disease-Free Survival



Overall Survival



Reames, Pawlik, et al. J Surg Oncol 2017

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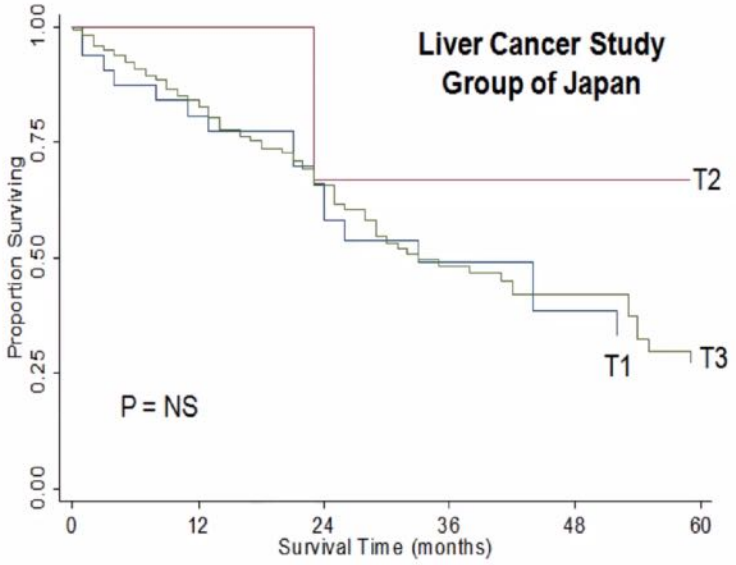
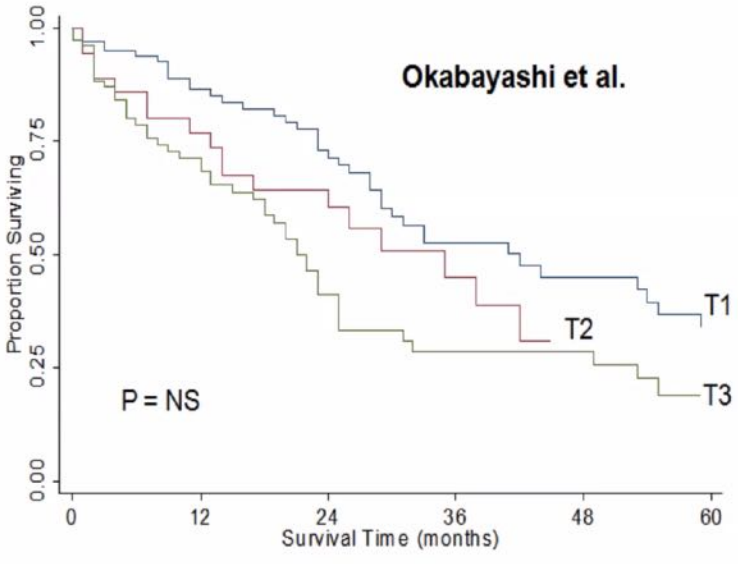
LCSGJ Staging of ICC



Okabayashi Staging of ICC



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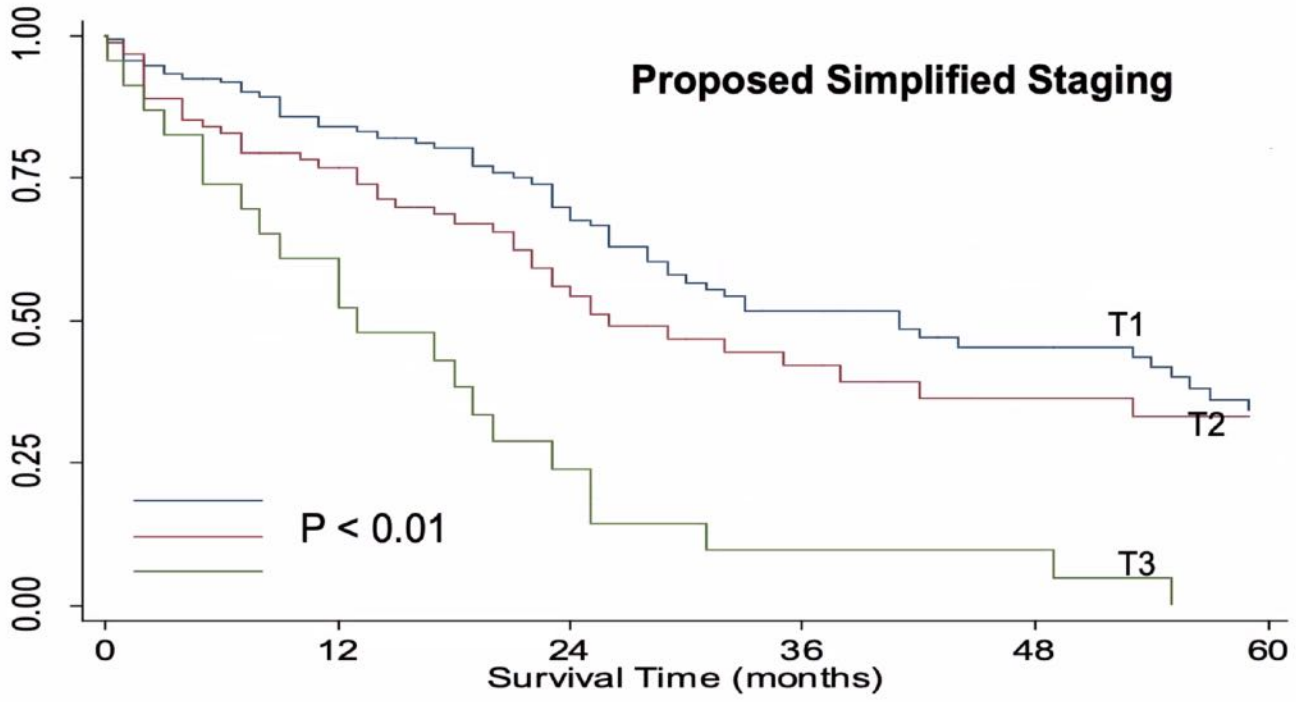
Results: Survival of N0M0 Patients



Nathan, Pawlik Annals of Surgical Oncology 2010

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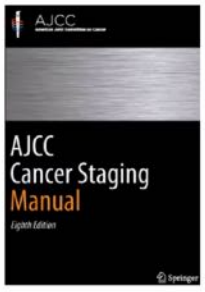
AJCC / UICC 8th Edition ICC Staging



Change	*Details of Change*	*Level of Evidence*
Note the heading, subheading or data element (TNM, Stage Group, prognostic factor) that contains the change.	Describe change	Note which of the 8th Edition levels of evidence support this change.
T1	The tumor category (T1) is revised to account for the prognostic impact of tumor size (T1a, ≤5 cm vs. T1b, >5cm)	II
T2	The tumor category (T2) is modified to reflect the equivalent prognostic value of vascular invasion and multifocal IHCC	II
T4	The AJCC 7th Ed. tumor category (T4), describing the tumor growth pattern is eliminated from staging, but remains recommended for data collection	III

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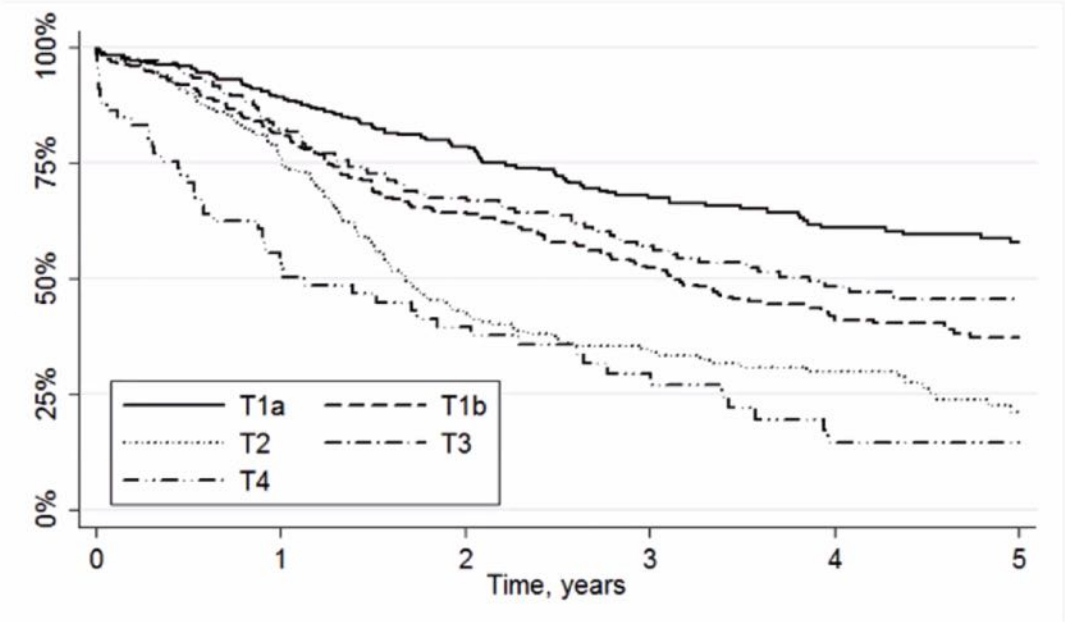
AJCC / UICC 8th Edition ICC Staging



Buettner, Pawlik, et al. Journal Surgical Oncology 2017

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Tumor Burden in ICC

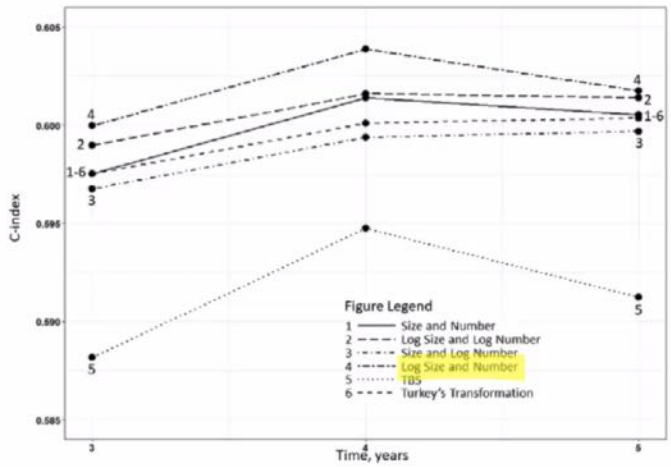
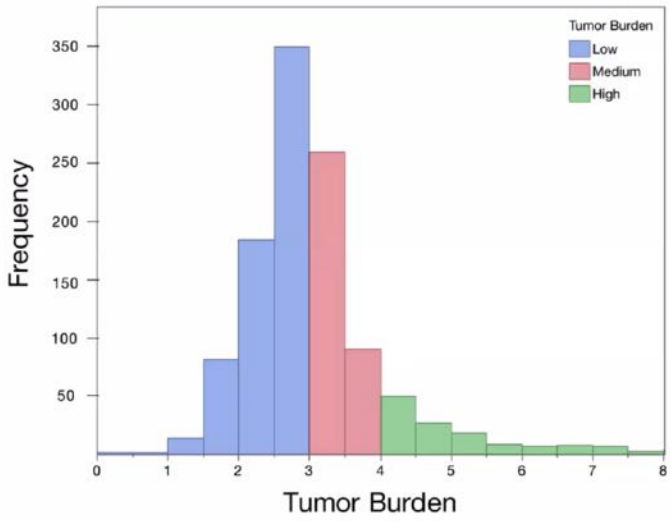


Fig 1. Trends of c-index values calculated for the different approaches to estim ICC tumor burden.



Low Tumor Burden [57%]
Medium Tumor Burden [31%]
High Tumor Burden [12%]

*Tsilimigras DI, TM Pawlik et al. *Ann Surg Oncol* 2020

*F Bagante, TM Pawlik et al. *Surgery* 2019

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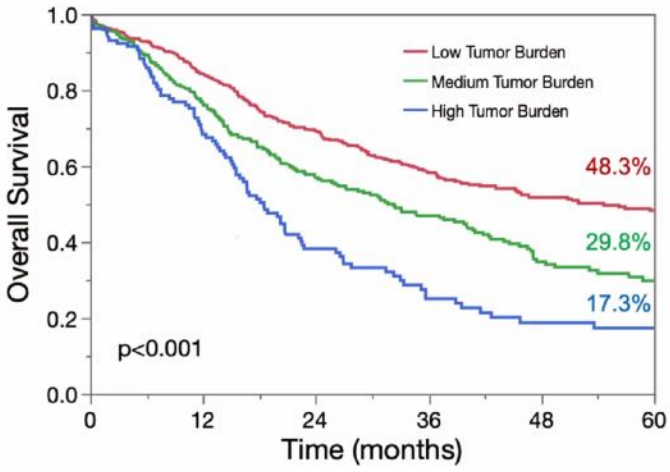
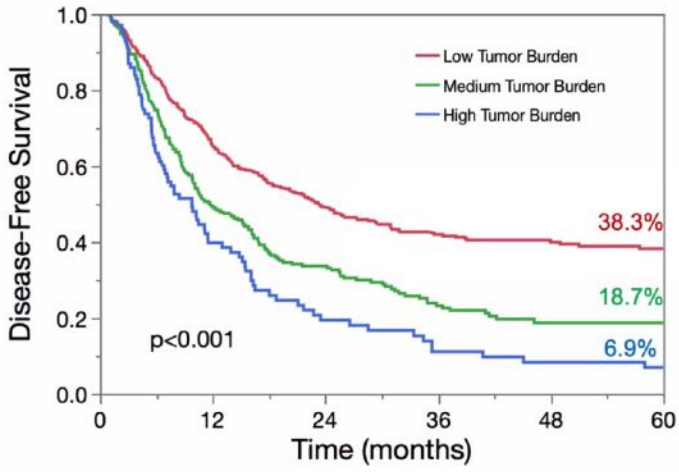
Tumor Burden Groups: Survival analysis

Multi-Institutional Cohort





*Tsilimigras DI, TM Pawlik et al. *Ann Surg Oncol* 2020

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Novel classification of ICC using machine learning

Common ICC	Proliferative ICC	Inflammatory ICC
59%	35%	6%
		
Size ↔ 4.6 cm	Size ↑ 9.0 cm	Size ↔ 6.2 cm
CA19-9 ↔ 40.3 UI/mL	CA19-9 ↑ 72.0 UI/mL	CA19-9 ↓ 26.2 UI/mL
NLR ↔ 2.6	NLR ↔ 2.7	NLR ↑ 13.5

*Tsilimigras DI, TM Pawlik et al. *Ann Surg Oncol. 2020 Dec;27(13):5224-5232*

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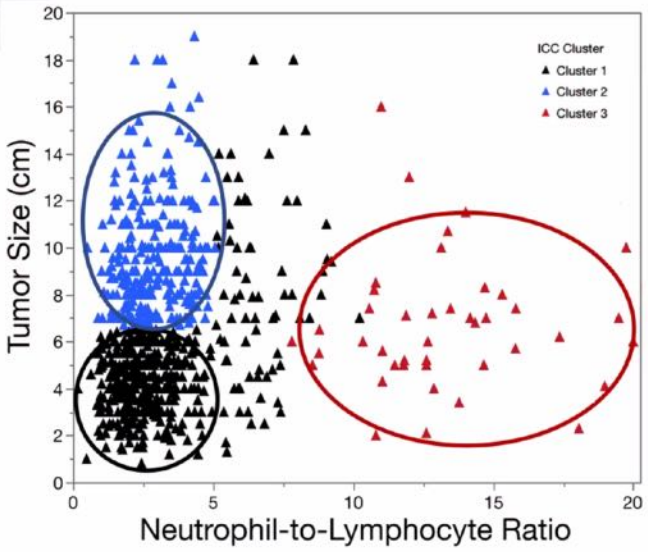
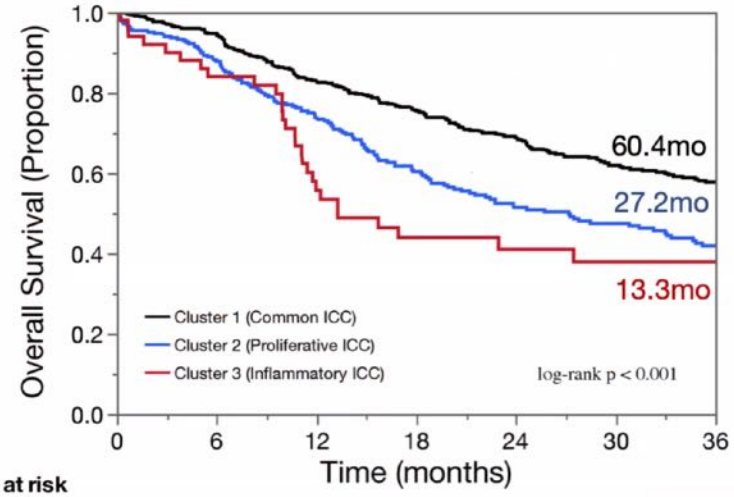
Unsupervised machine learning: ICC Clusters





No. at risk

Cluster 1	487	442	353	293	241	193	157
Cluster 2	288	235	184	129	98	80	67
Cluster 3	51	43	26	18	15	12	12

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*Tsilimigras DI, TM Pawlik et al. *Ann Surg Oncol. 2020 Dec;27(13):5224-5232*

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VOLUME 29 · NUMBER 23 · AUGUST 10 2011

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Intrahepatic Cholangiocarcinoma: An International Multi-Institutional Analysis of Prognostic Factors and Lymph Node Assessment

Mechteld C. de Jong, Hari Nathan, Georgios C. Sotiropoulos, Andreas Paul, Sorin Alexandrescu, Hugo Marques, Carlo Pulitano, Eduardo Barroso, Bryan M. Clary, Luca Aldrighetti, Cristina R. Ferrone, Andrew X. Zhu, Todd W. Bauer, Dustin M. Walters, T. Clark Gamblin, Kevin T. Nguyen, Ryan Turley, Irinel Popescu, Catherine Hubert, Stephanie Meyer, Richard D. Schulick, Michael A. Choti, Jean-Francois Gigot, Gilles Mentha, and Timothy M. Pawlik

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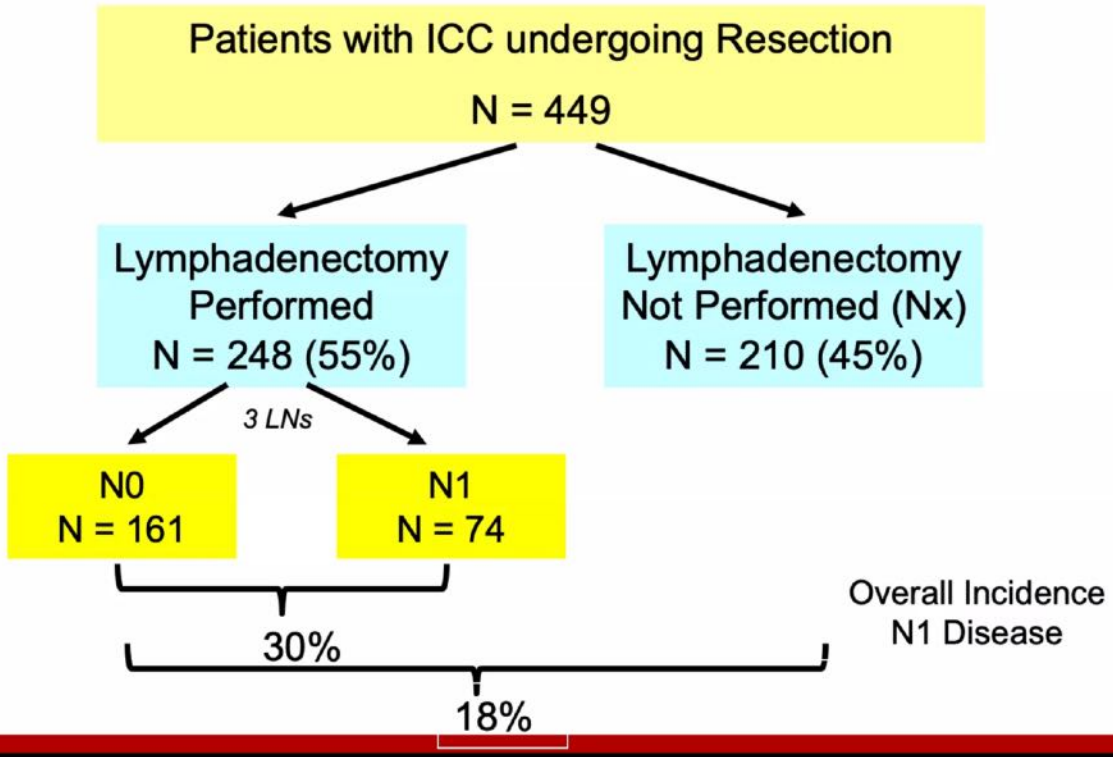
International iCCA Study Group

Lymphadenectomy



Slide 45

Enhanced Imaging Model to Predict LNM

	OR (95%CI)
Age	0.98 (0.96-0.99)
No of lesions	1.21 (1.01-1.45)
CA19-9 >200 UI/mL	2.02 (1.34-3.04)
ALBI grade 2/3	1.47 (1.01-2.15)
LN on imaging	1.99 (1.51-2.62)
Negative	Ref
Suspicious / Metastatic	3.44 (2.31-5.14)

*Tsilimigras DI, TM Pawlik et al. *J Gastrointest Surg* 2020

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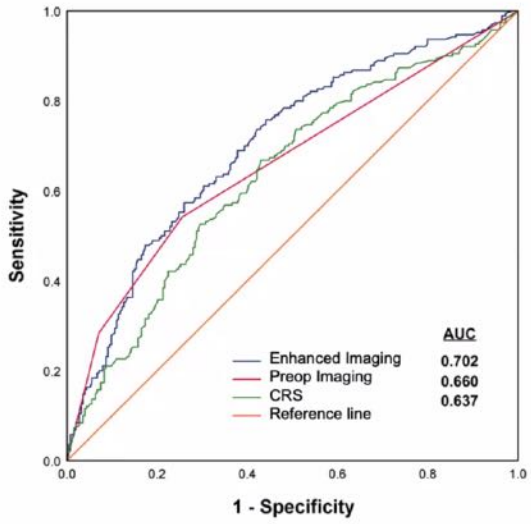
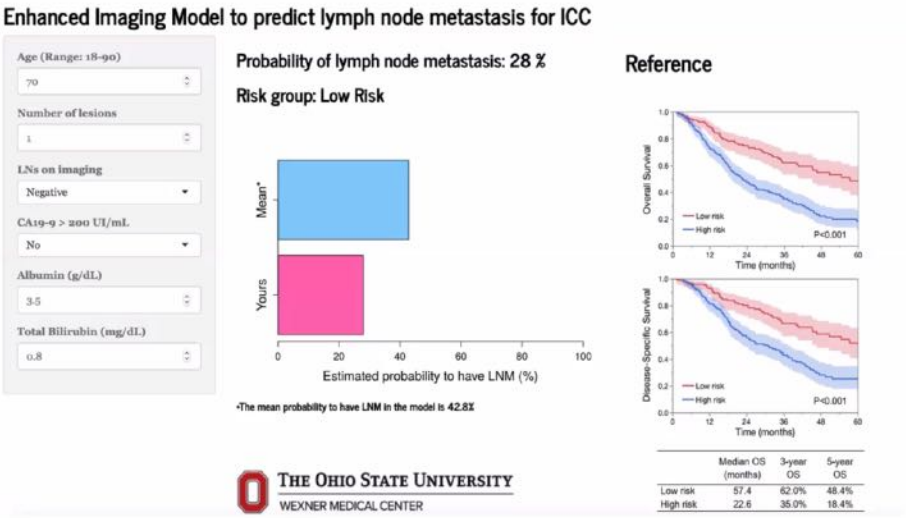
Prediction of LNM- Online calculator





https://k-sahara.shinyapps.io/ICC_imaging/

*Tsilimigras DI, TM Pawlik et al. *J Gastrointest Surg* 2020

THE OHIO STATE UNIVERSITY
WEXNER MEDICAL CENTER

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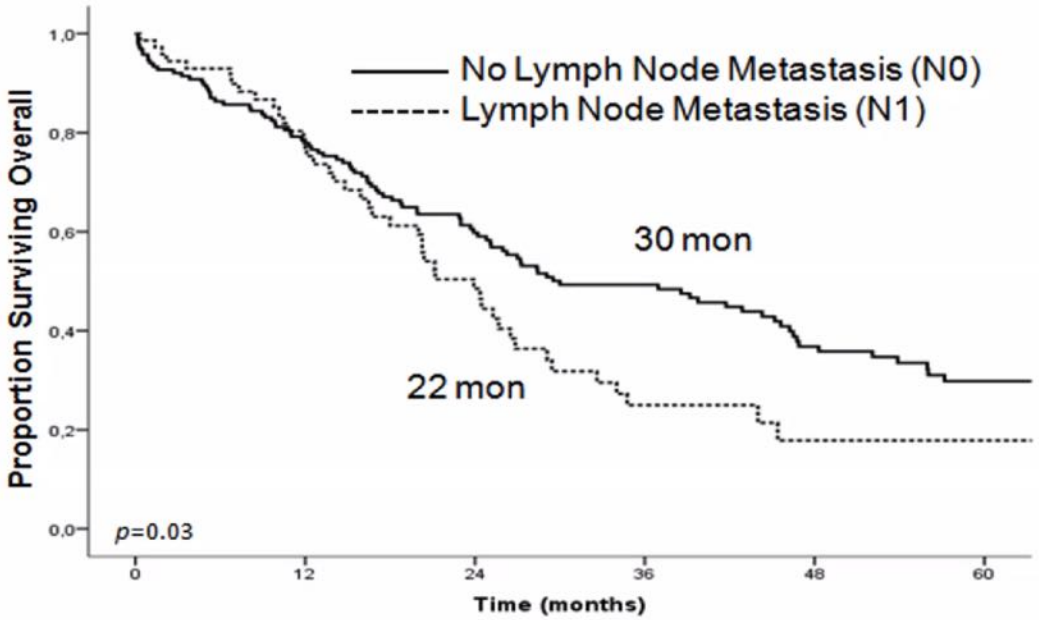
International iCCA Study Group

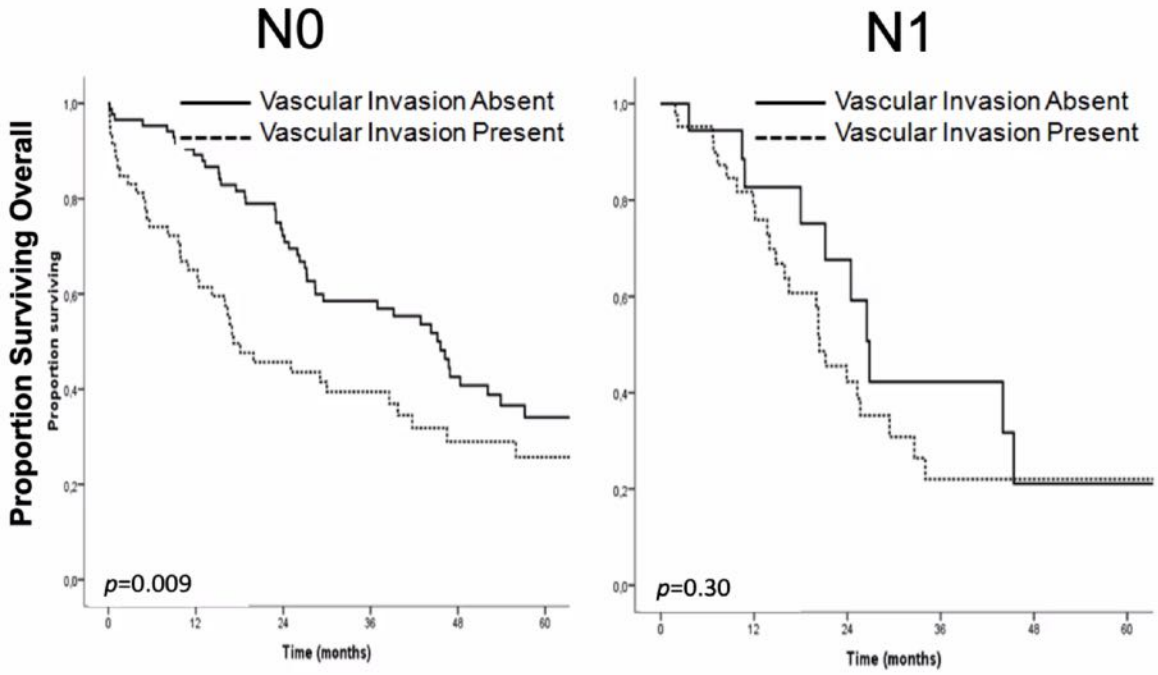
Survival Stratified by Lymph Node Status



de Jong, Pawlik, J Clin Oncol 29:3140-3145.

Slide 48

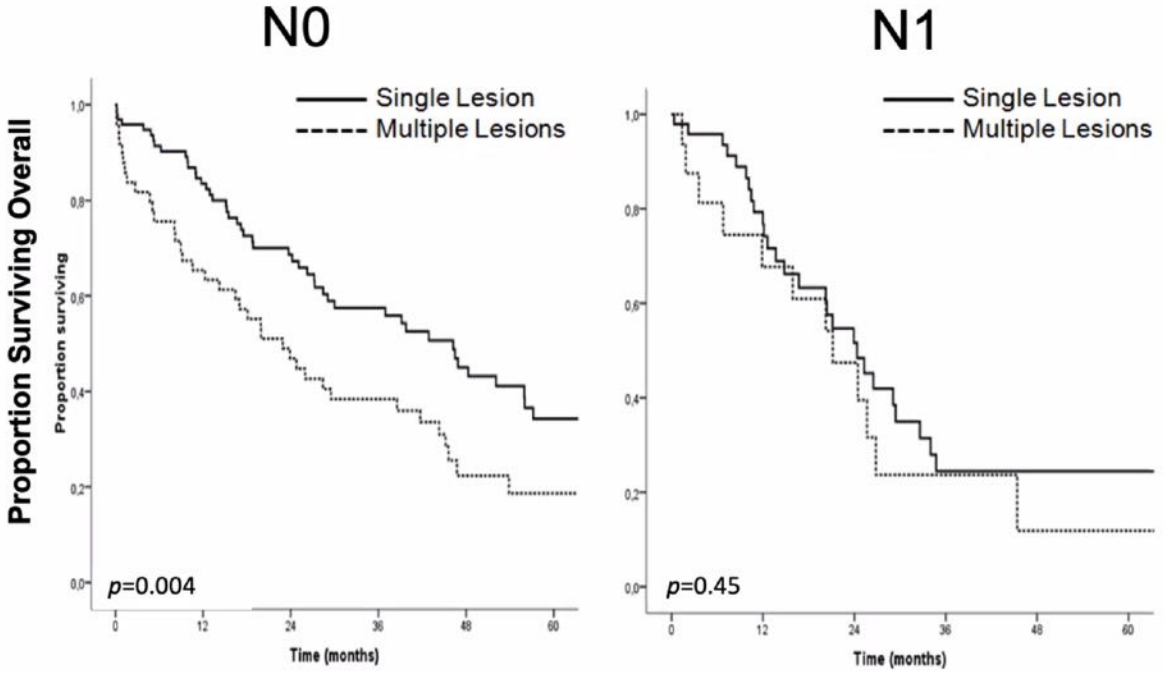
Impact of Vascular Invasion Stratified by Nodal Status



de Jong, Pawlik, J Clin Oncol 29:3140-3145.

Slide 49

Impact of Tumor Number Stratified by Nodal Status



de Jong, Pawlik, J Clin Oncol 29:3140-3145.

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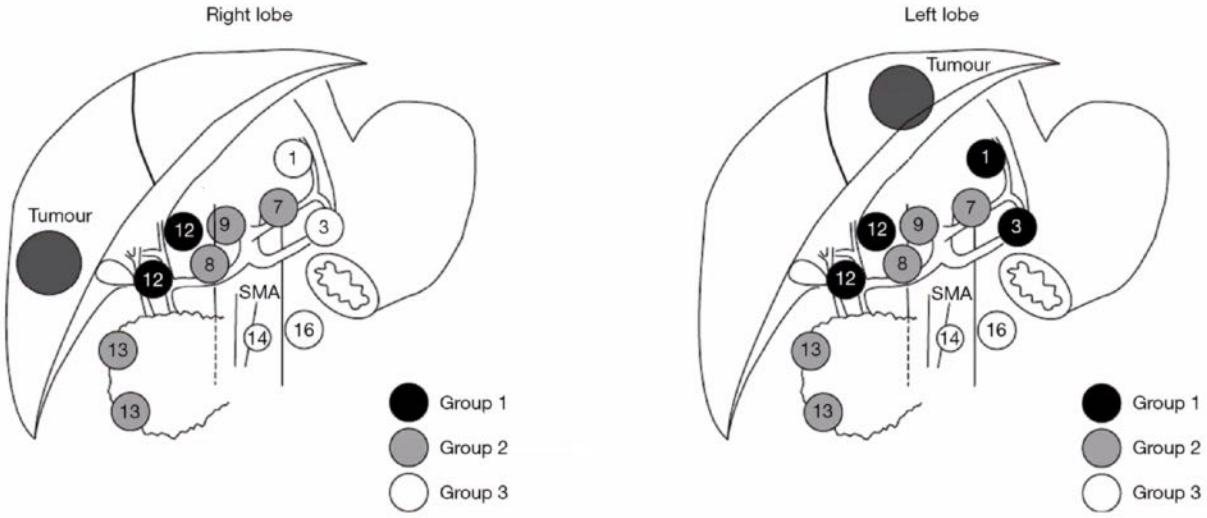
HBSN HEPATOBILIARY SURGERY AND NUTRITION
A RISING HIGH-QUALITY JOURNAL DEDICATED TO HEPATOBILIARY DISEASES AND NUTRITION
2017 IMPACT FACTOR 3.45

Staging of intrahepatic cholangiocarcinoma

Sean M. Ronnekleiv-Kelly[1], Timothy M. Pawlik[2]



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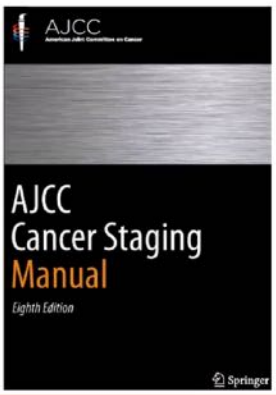
Intrahepatic Cholangiocarcinoma: expert consensus statement

Sharon M. Weber[1], Dario Ribero[2], Eileen M. O'Reilly[3], Norihiro Kokudo[4], Masaru Miyazaki[5] & Timothy M. Pawlik[6]

[1]Department of Surgery, University of Wisconsin, Madison, WI, USA, [2]Department of General Surgery and Surgical Oncology, Mauriziano 'Umberto I' Hospital, Turin, Italy, [3]Department of Medical Oncology, Memorial Sloan–Kettering Cancer Center, New York, NY, USA, [4]Hepato-Biliary-Pancreatic Surgery Division, Artificial Organ and Liver Transplantation Division, Department of Surgery, Graduate School of Medicine, University of Tokyo, Tokyo, Japan, [5]Department of Surgery, Chiba University Graduate School of Medicine, Chiba, Japan, and [6]Department of Surgery, Johns Hopkins Hospital, Baltimore, MD, USA

- Resectability for ICC is defined by the ability to completely remove the disease with curative intent (R0) while leaving an adequate liver remnant.
- Regional lymphadenectomy should be considered a standard part of surgical therapy for patients undergoing resection of ICC.



8th AJCC edition:
harvest ≥ 6 lymph nodes for accurate staging

66

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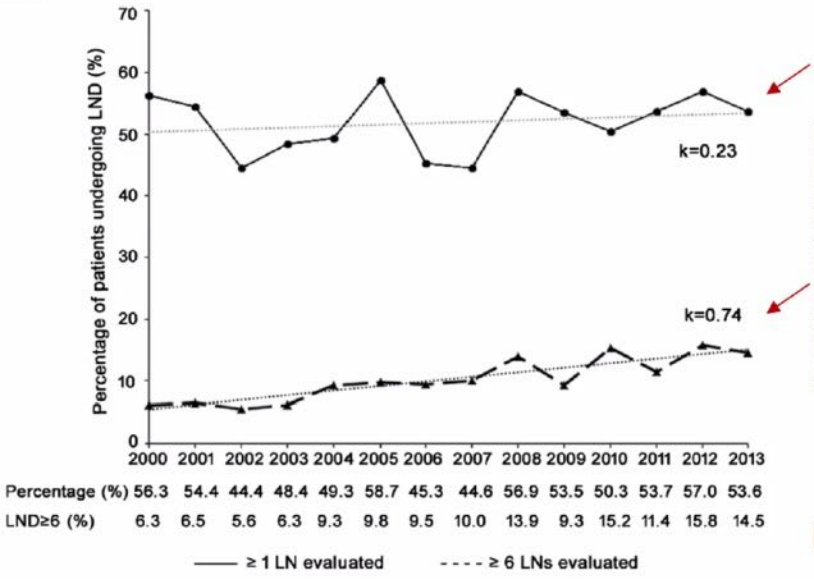
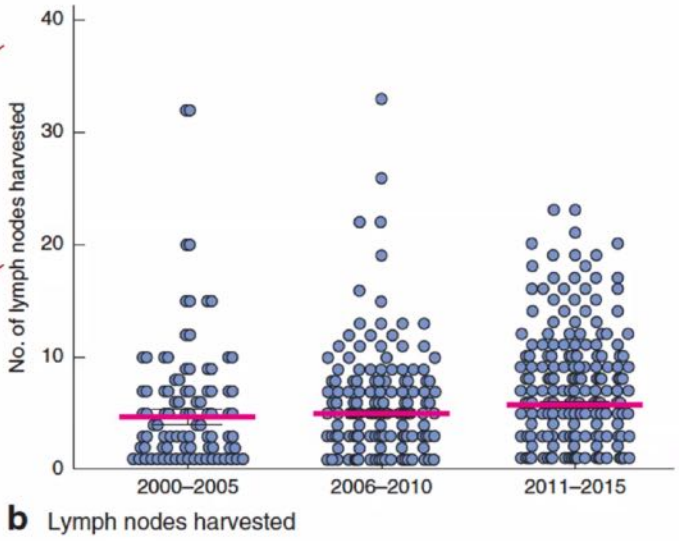
Lymphadenectomy at Time of Surgery for ICC





Zhang, Pawlik, et al. BJS 2018
Zhang, Pawlik, et al. JOGS 2018

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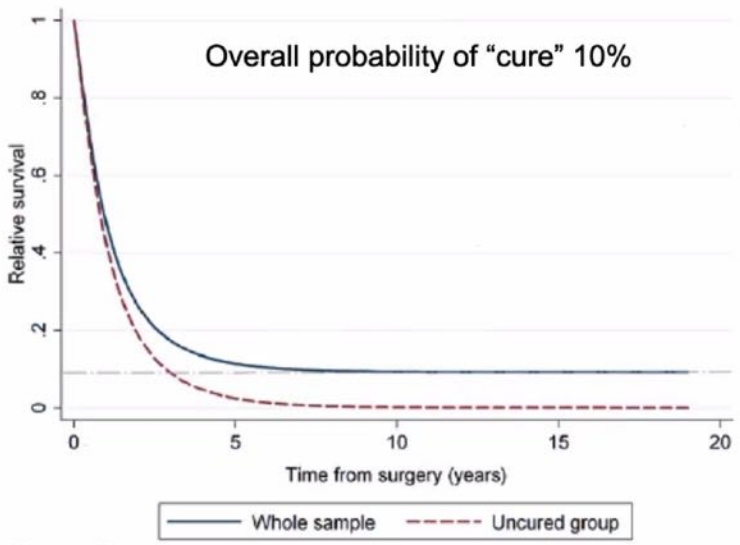
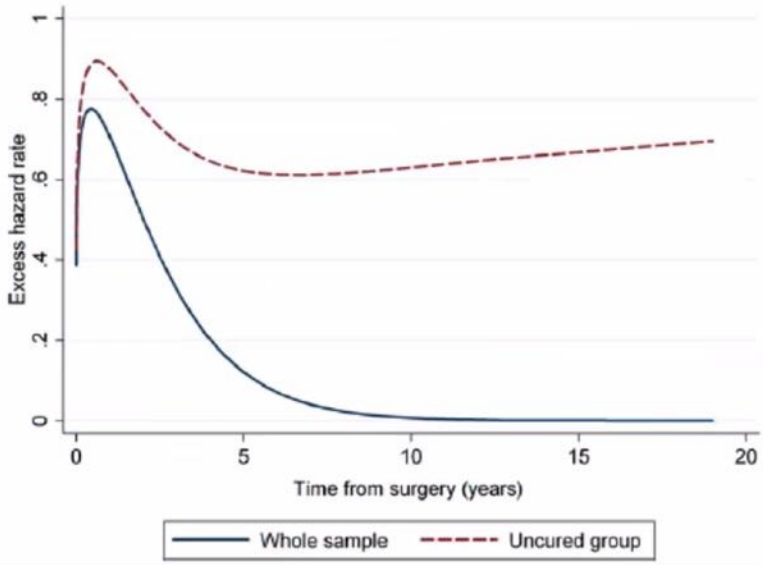
Can Hepatic Resection Provide a Long-Term Cure for Patients With Intrahepatic Cholangiocarcinoma?

Gaya Spolverato, MD[1]; Alessandro Vitale, MD, PhD[2]; Alessandro Cucchetti, MD[3]; Irinel Popescu, MD[4]; Hugo P. Marques, MD[5]; Luca Aldrighetti, MD[6]; T. Clark Gamblin, MD[7]; Shishir K. Maithel, MD[8]; Charbel Sandroussi, MD[9]; Todd W. Bauer, MD[10]; Feng Shen, MD[11]; George A. Poultsides, MD[12]; J. Wallis Marsh, MD[13]; and Timothy M. Pawlik, MD, MPH, PhD[1]





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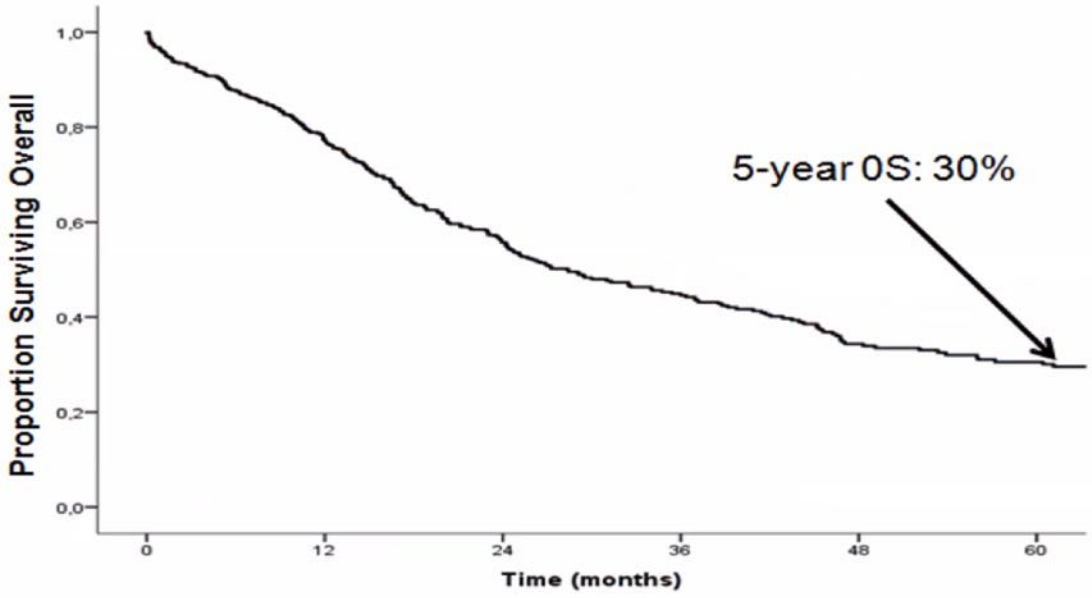
Overall Survival: International ICC Study Group

Intrahepatic Cholangiocarcinoma



de Jong, Pawlik, J Clin Oncol 29:3140-3145.

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Recurrence after operative management of intrahepatic cholangiocarcinoma

Omar Hyder, MD, MS,[a] Ioannis Hatzaras, MD,[a] Georgios C. Sotiropoulos, MD,[b] Andreas Paul, MD,[b] Sorin Alexandrescu, MD,[c] Hugo Marques, MD,[d] Carlo Pulitano, MD,[e] Eduardo Barroso, MD,[d] Bryan M. Clary, MD,[f] Luca Aldrighetti, MD,[e] Cristina R. Ferrone, MD,[g] Andrew X. Zhu, MD, PhD,[g] Todd W. Bauer, MD,[h] Dustin M. Walters, MD,[i] Ryan Groeschl, MD,[j] T. Clark Gamblin, MD, MS,[j] J. Wallis Marsh, MD, MBA,[k] Kevin T. Nguyen, MD, PhD,[k] Ryan Turley, MD,[f] Irinel Popescu, MD,[c] Catherine Hubert, MD,[k] Stephanie Meyer, MD,[l] Michael A. Choti, MD,[a] Jean-Francois Gigot, MD,[k] Gilles Mentha, MD,[l] *and* Timothy M. Pawlik, MD, MPH, PhD,[a] *Baltimore, MD, Essen, Germany, Bucharest, Romania, Lisbon, Portugal, Milan, Italy, Durham, NC, Boston, MA, Charlottesville, VA, Milwaukee, WI, Pittsburgh, PA, Brussels, Belgium, and Geneva, Switzerland*

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Results: Initial Pattern of Recurrence

Median Follow-Up 19 months

Patients with any site of recurrence
N = 252 (55%)

Intra-Hepatic Only	Intra- and Extra-Hepatic Only	Extra-Hepatic Only
N = 138 (55%)	N = 55 (23%)	N = 52 (22%)

18 months

15 months

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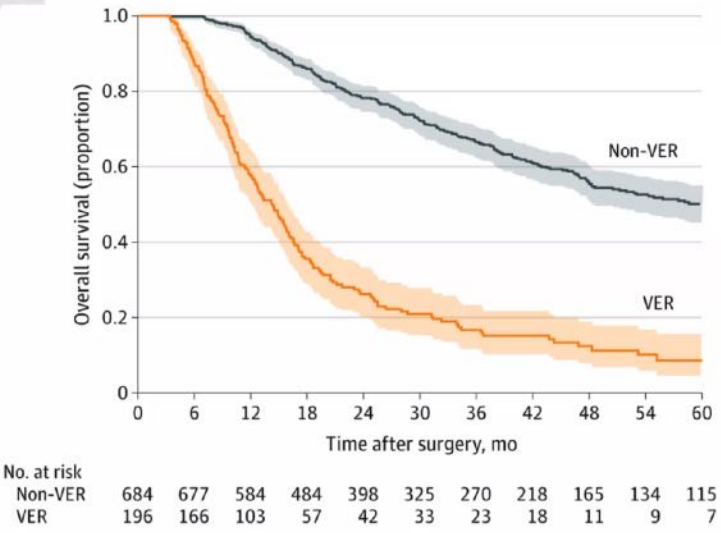
Very Early Recurrence after ICC resection



No. at risk

Non-VER	684	677	584	484	398	325	270	218	165	134	115
VER	196	166	103	57	42	33	23	18	11	9	7

22% Developed Very Early Recurrence (≤ 6 months)

*Tsilimigras DI, TM Pawlik et al. *JAMA Surgery* 2020

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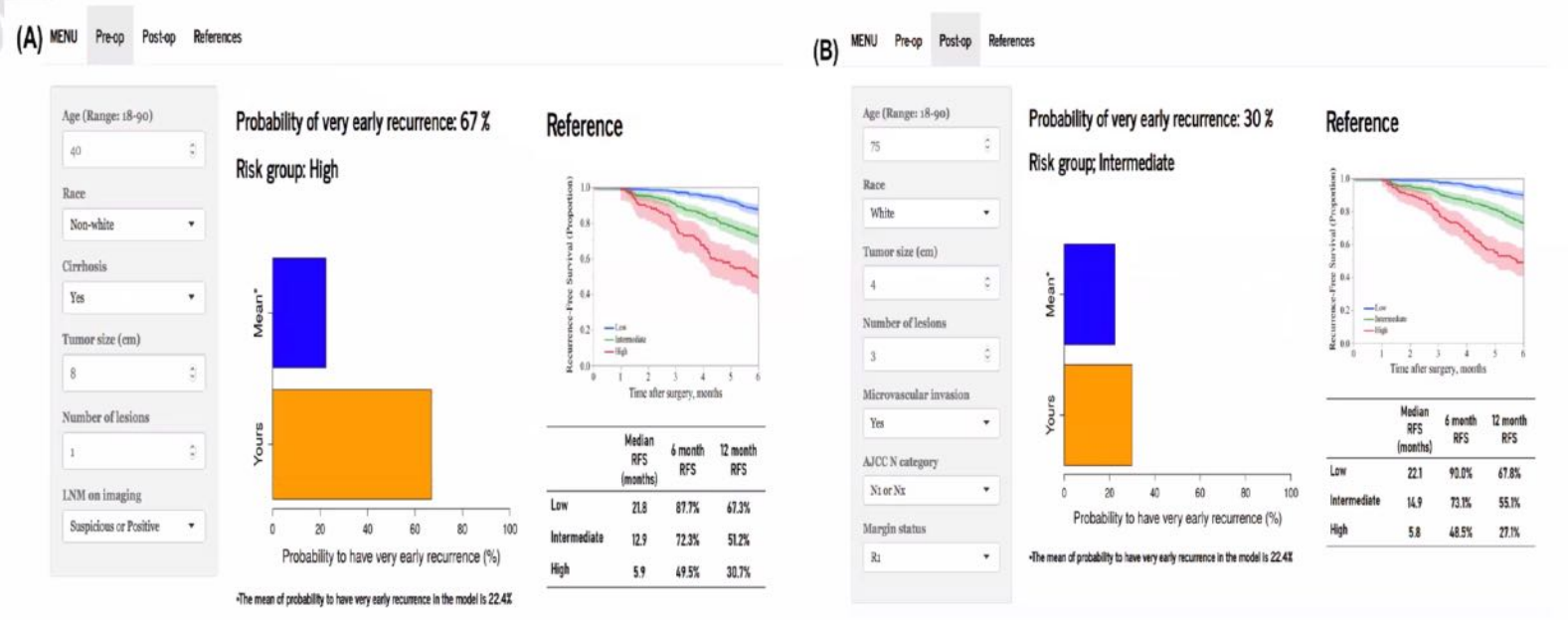
Very Early Recurrence after ICC resection



*Tsilimigras DI, TM Pawlik et al. *JAMA Surgery* 2020

https://k-sahara.shinyapps.io/Veryearly-recurrence/

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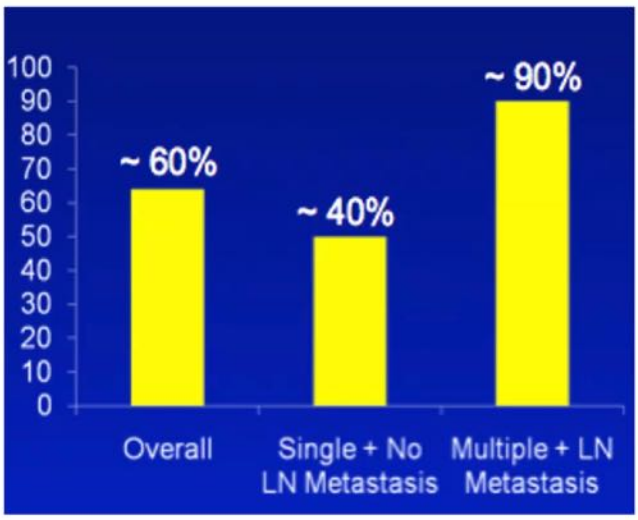
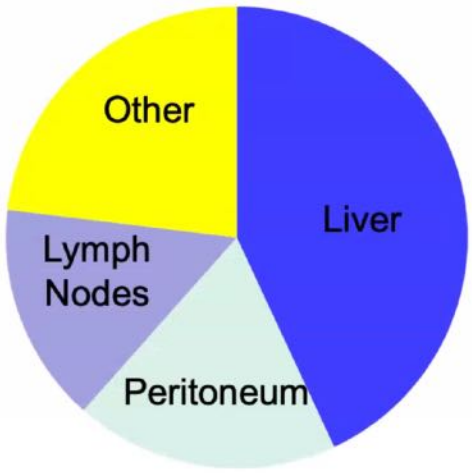
Risk of Recurrence

Intrahepatic Cholangiocarcinoma





Survival after recurrence 10 months

Endo et al. *Ann Surg* 2008
Choi et al. *Ann Surg Oncol* 2009
Yamamoto et al. *J Hepatobiliary Pancreat Surg* 2001

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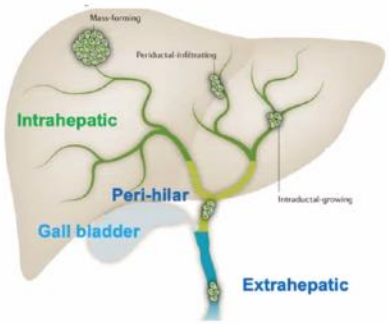
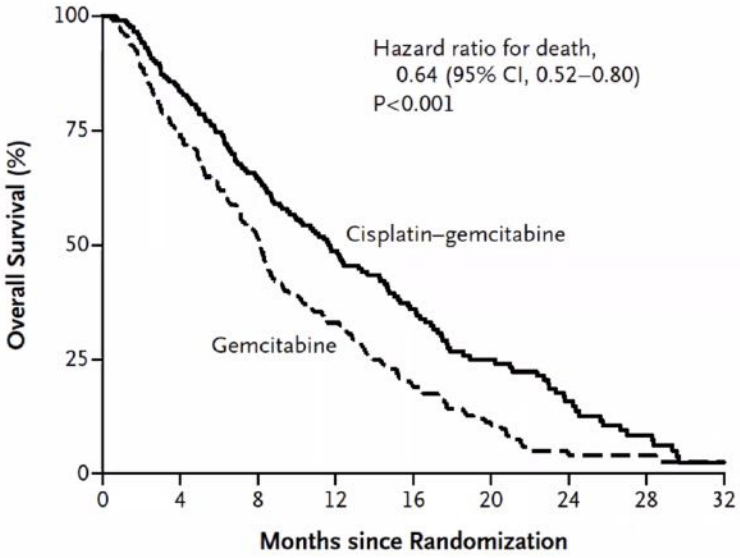
First-line therapy for metastatic cholangiocarcinoma

A





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

Valle et al NEJM 2008

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	SWOG S0809 (U.S.)	PRODIGE 12 (France)	BILCAP (U.K.)
Design	Single-arm phase 2	Randomized phase 3	Randomized phase 3
Treatment	Gemcitabine/capecitabine + capecitabine/XRT	Gemcitabine/oxaliplatin versus observation	Capecitabine versus observation
n	79	196	440
BTC tumor type	Gallbladder 32% Perihilar 48% Distal 20% Intrahepatic 0%	Gallbladder 19% Perihilar 8% Distal 28% Intrahepatic 45%	Gallbladder 18% Perihilar 28% Distal 35% Intrahepatic 19%
Positive margin (%)	32	15	38
Positive lymph nodes (%)	N/A	37	54
Endpoint/summary	• Two-year OS 65% • Treatment well tolerated • R0/R1 OS similar at 35 and 34 months	• RFS similar between treatment and control groups (p = 0.47) • Treatment well tolerated based on QOL	• ITT median OS 51 versus 36 months (p = 0.097) • Per protocol analysis median OS 53 versus 36 months (p = 0.028)

BTC = biliary tract cancer; XRT = external beam radiation therapy; OS = overall survival; RFS = recurrence free survival; QOL = quality of life; ITT = intention to treat

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ADJUVANT THERAPY FOR RESECTED BILIARY TRACT CANCER

6 MONTHS

Patients with resected biliary tract cancer should be offered adjuvant capecitabine chemotherapy for a duration of 6 months

Patients with extrahepatic cholangiocarcinoma or gallbladder cancer & microscopically positive surgical margins may be offered chemoradiotherapy

Shroff et al *J Clin Oncol* 2019
asco.org/gastrointestinal-cancer-guidelines

ASCO Guidelines

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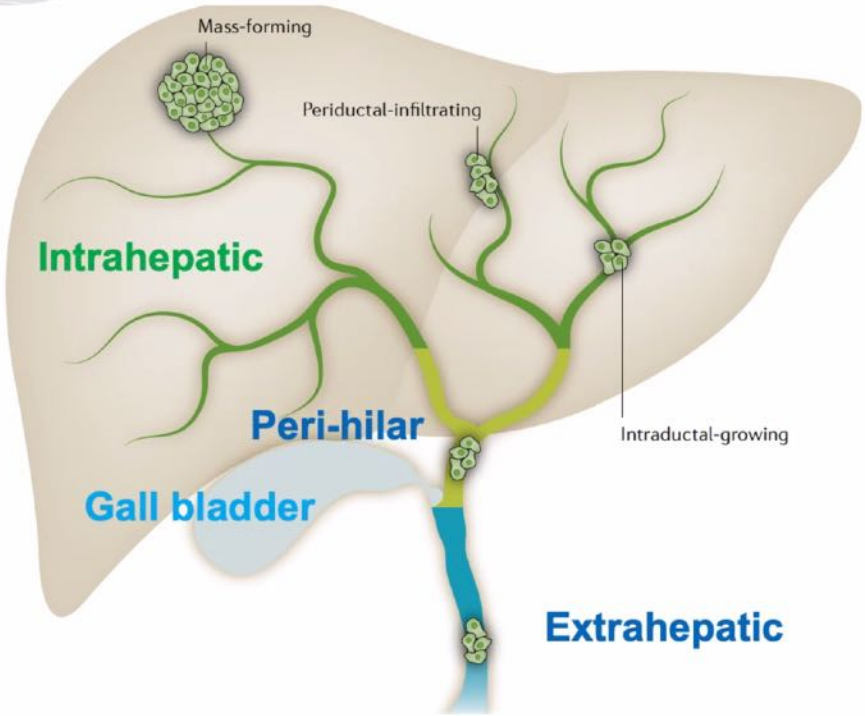
Molecular classification and therapy of cholangiocarcinoma



FGFR 15%
IDH 15%
BRAF 1%
ERBBx 1%
MSIH 1%*
EGFR<1%
NTRK <1%

~pancreas cancer
KRAS 99%

~ERBBx/EGFR

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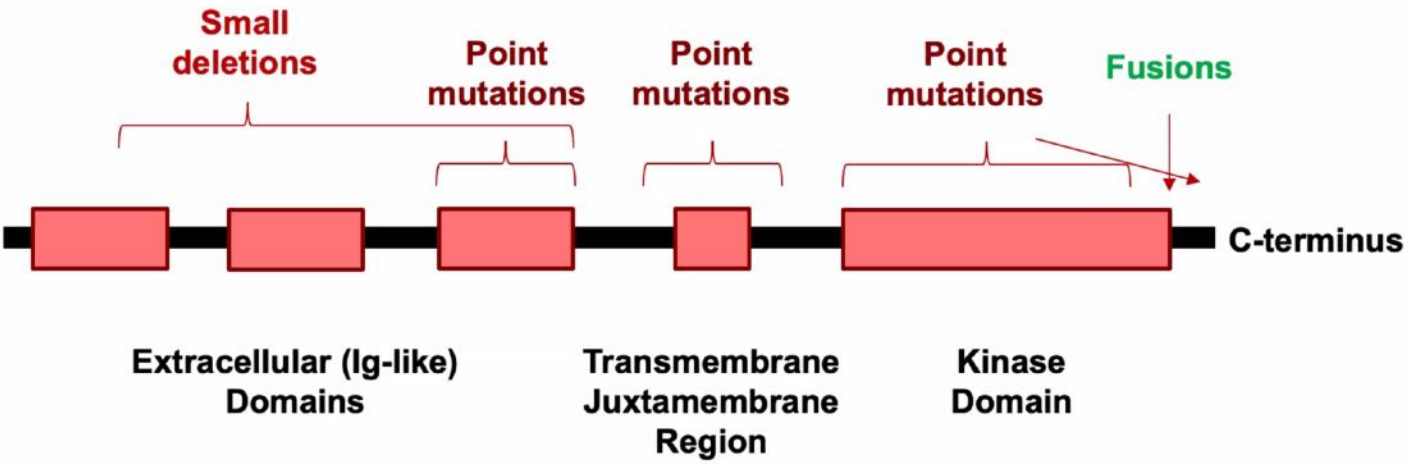
Different types of FGFR mutations may benefit from novel therapies



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Phase 2 FIGHT-202 Trial: Pemigatinib in Locally Advanced/Metastatic Cholangiocarcinoma[1]

- Pemigatinib is a selective oral inhibitor of FGFR1/2/3

Key Inclusion Criteria
- Adults with locally advanced or metastatic cholangiocarcinoma
- Known FGF/FGFR status
- Progression after ≥1 prior therapy
- ECOG PS ≤2
- Adequate hepatic/renal function

Cohort A (planned, N = 100) *FGFR2* fusions/rearrangements

Cohort B (planned, N = 20) Other *FGF/FGFR* genetics alterations

Cohort C (planned, N = 20) No *FGF/FGFR* genetics alterations

Oral pemigatinib 13.5 mg once daily (2 wk on, 1 wk off)

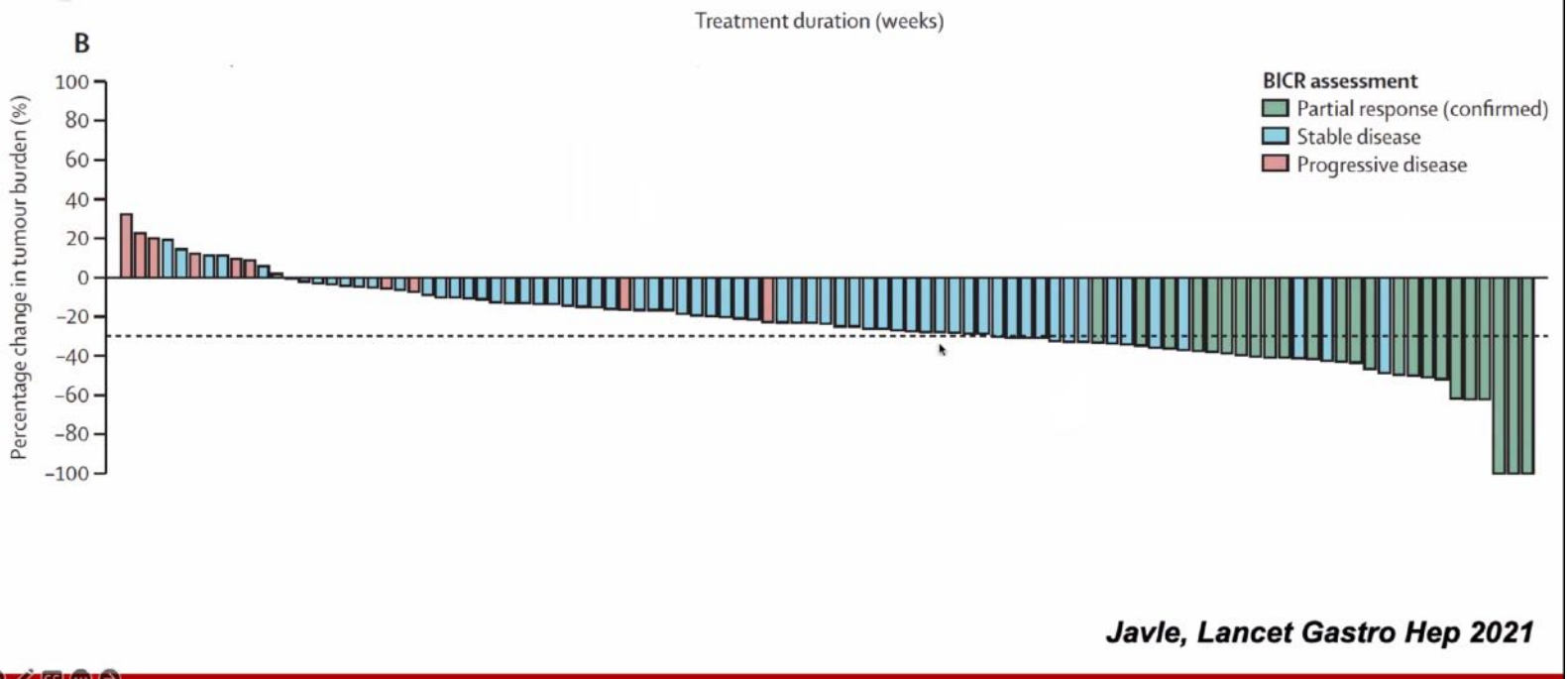
- **Primary endpoint:** confirmed ORR in cohort A by independent central review
- **Secondary endpoints:** ORR in cohorts B, A + B, and C; duration of response, disease control rate, PFS, OS, and safely in all cohorts

81

1. https://clinicaltrials.gov/ct2/show/NCT02924376. Accessed January 9, 2020.

Slide 66

FGFR targeted therapies benefit biliary cancer



Javle, Lancet Gastro Hep 2021

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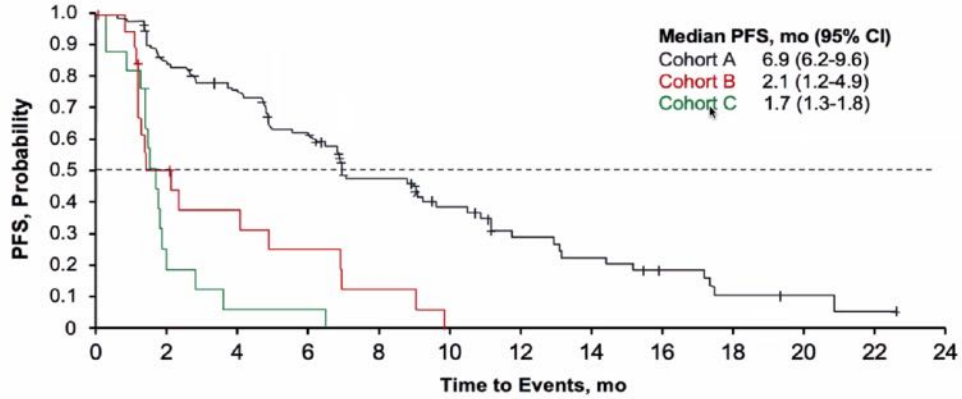
FIGHT-202: PFS[1]



Patients at Risk

Cohort A	107	88	76	61	37	22	14	11	7	4	2	1	0
Cohort B	20	9	6	4	2	0	0	0	0	0	0	0	0
Cohort C	18	3	1	1	0	0	0	0	0	0	0	0	0

1. Vogel A et al. ESMO 2019. Abstract LBA40.

83

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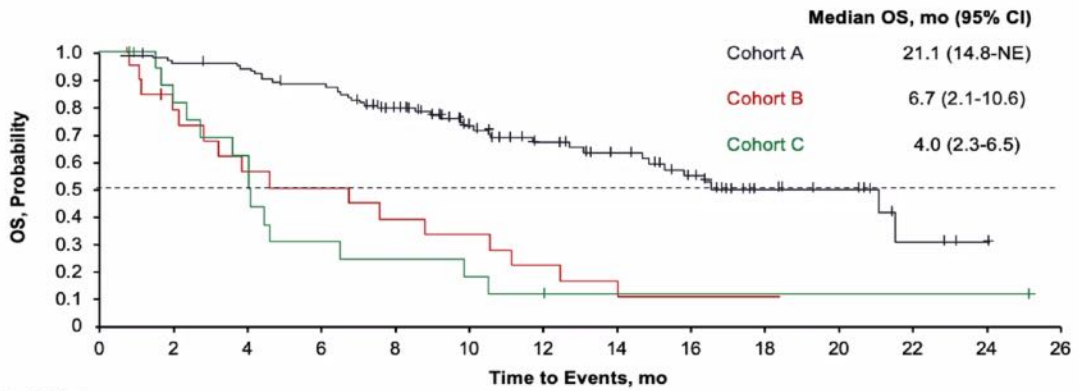
FIGHT-202: OS[1]



Patients at Risk

Cohort A	107	102	99	92	73	52	41	34	24	12	9	3	0	0
Cohort B	20	14	10	9	7	6	4	2	1	1	0	0	0	0
Cohort C														

	Cohort A	Cohort B	Cohort C
Median duration of follow-up, mo (range)	15.4 (7.0-24.7)	19.9 (16.2-23.5)	24.2 (22.0-26.1)
Median duration of treatment, mo (range)	7.2 (0.2-24.0)	1.4 (0.2-12.9)	1.3 (0.2-4.7)

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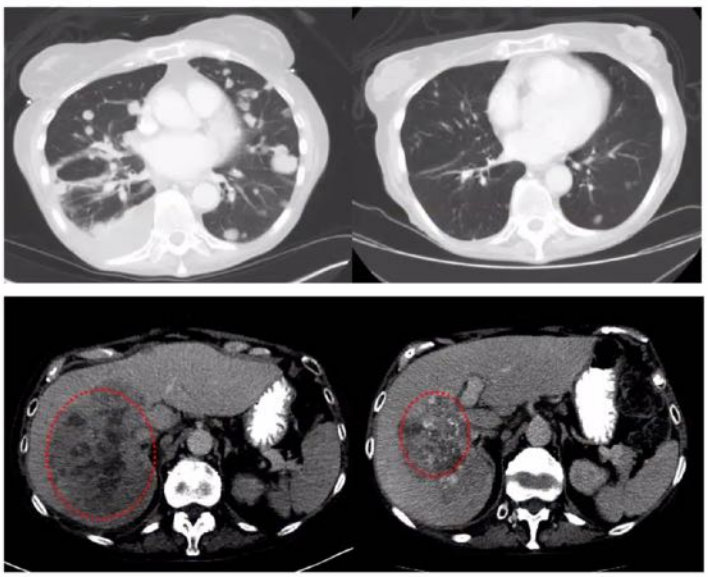
FGFR targeted therapies benefit biliary cancer



- **Pemigatinib** FDA-approved for 2nd line therapy
- **Infigratinib** FDA-approved for 2nd line therapy
- ~70-80% benefit rate
- Many more FGFR therapies in development

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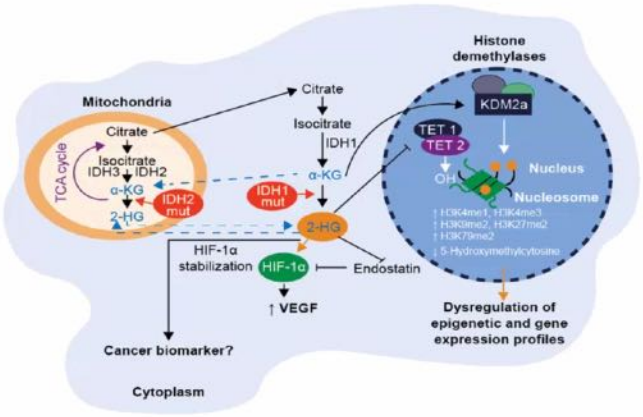
IDH Alterations[1]

- IDH catalyzes the interconversion of isocitrate to α-KG
- mDHD converts isocitrate to 2-HG
- High levels of 2-HG accumulate and inhibit α-KG dependent dioxygenases → epigenetic changes → gene expression changes
- How this process may predispose cells to specific types of cancer remains unclear



1. Ishii Y et al. 2018 American Association for Cancer Research-National Cancer Institute-European Organisation for Research and Treatment of Cancer International Conference (AACR-NCI-EORTC 2018). Abstract nr A071.

Slide 71

Phase 3 ClarIDHy Trial: IDH1 Inhibitor Ivosidenib Versus Placebo in Second-Line Setting[1]

Key eligibility criteria
- Aged ≥18 y
- Histologically confirmed cholangiocarcinoma diagnosis
- Centrally confirmed m*IDH1* status
- ECOG PS 0 or 1
- 1-2 prior therapies (≥1 regimen containing gemcitabine or 5-FU)
- Measurable lesion as defined by RECIST v1.1
- Adequate hematologic, hepatic, and renal function
- N = 185

R
2:1

Ivosidenib 500 mg once daily orally continuous 28-d (±2 d) cycles (n = 124)

Placebo (n = 61)

Crossover to ivosidenib at disease progression

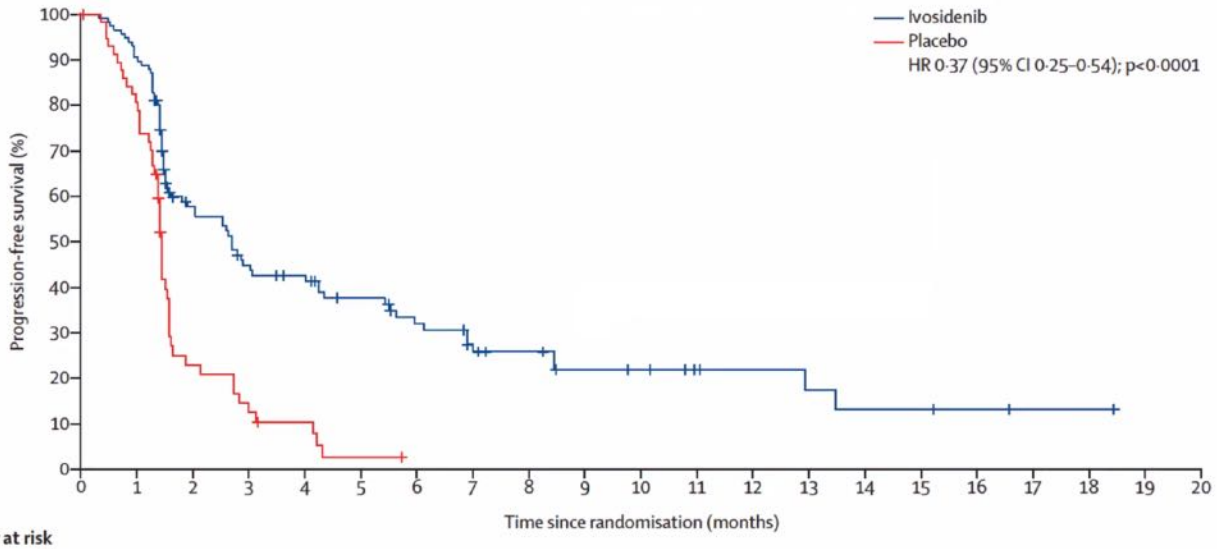
- **Stratification:** number of prior therapies
- **Primary endpoint:** PFS by blinded independent radiology center
- **Secondary endpoints:** safety and tolerability, PFS by local review, OS, ORR, QOL
- Sample size based on HR 0.5, 96% power, 1-sided alpha = .025.
- 846 patients screened for *IDH1* mutation across 49 sites and 6 countries

1. https://clinicaltrials.gov/ct2/show/NCT02989857. Accessed January 24, 2020.

Slide 72

Ivosidenib for IDH-mutant biliary cancer (ClarIDHy)

A

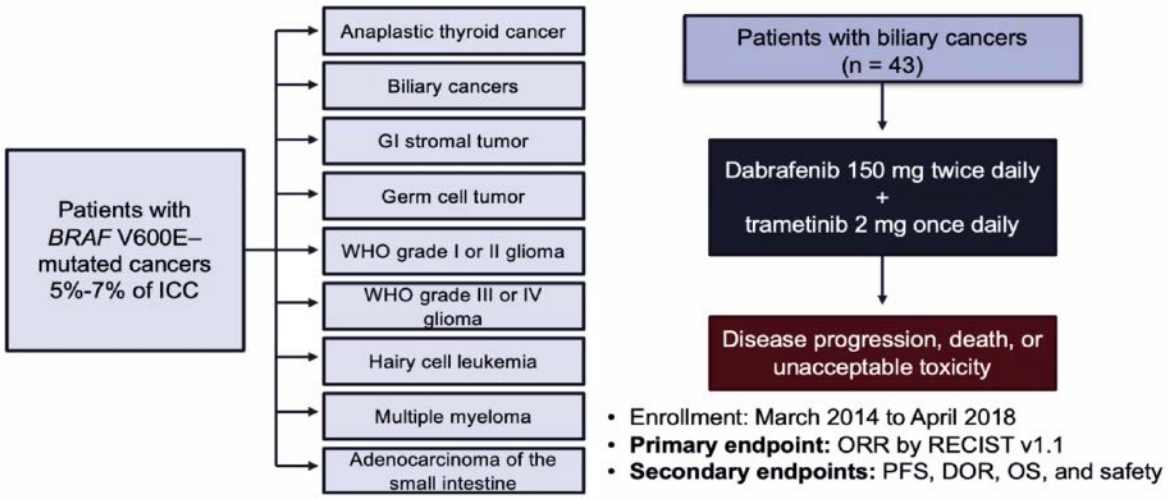


Number at risk (number censored)																					
Ivosidenib	124	105	54	40	36	28	22	16	14	10	9	6	5	4	3	3	2	1	1	0	..
	(0)	(8)	(24)	(26)	(28)	(32)	(34)	(36)	(38)	(40)	(41)	(44)	(45)	(45)	(45)	(45)	(46)	(47)	(47)	(48)	..
Placebo	61	46	11	6	4	1	0	..	..	..	..	..	..	..	..	..	..	..	..	..	..
	(0)	(4)	(9)	(9)	(10)	(10)	(11)	..	..	..	..	..	..	..	..	..	..	..	..	..	..

Abou-Alfa et al, Lancet 2020

Slide 73

Phase 2 ROAR Trial: Dabrafenib Plus Trametinib[1]

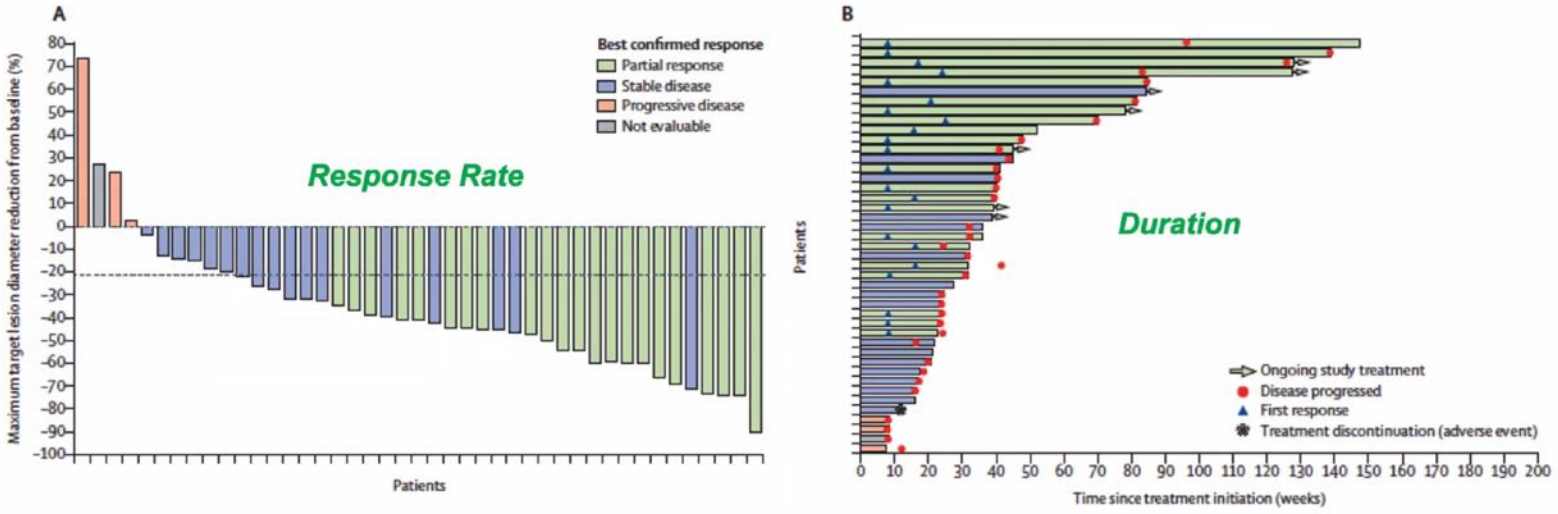


- Enrollment: March 2014 to April 2018
- **Primary endpoint:** ORR by RECIST v1.1
- **Secondary endpoints:** PFS, DOR, OS, and safety

1. Subbiah et al. Lancet Onc 2020.

Slide 74

Dabrafenib/Trametinib combination therapy for BRAF-mutant biliary cancer



Subbiah et al, Lancet 2020

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Immunotherapy trials in cholangiocarcinoma

5-15% for PD-1 response rates

	Drug	Setting	n	RR % (n)	Time to response (months)	Duration of response (months)	Median progression-free survival, months (95% CI)	Median overall survival, months (95% CI)
Bang Y-J et al, 2019[144] (KEYNOTE-028)	Pembrolizumab	Second-line or later-line therapy; PS 0–1; PD-L1+ (100%)	24	13% (3/23)	3·5	21·5, ≥51·4, and ≥53·2 months for each responder	1·8 (1·4–3·1)	5·7 (3·1–9·8)
Ueno et al, 2018[145] (KEYNOTE-158)	Pembrolizumab	Second-line or later-line therapy; PS 0–1; PD-L1 unselected	104; PD-L1+ 61; PD-L1- 43	5·8% (6/104); PD-L1+ 6·6% (4/61); PD-L1- 2·9% (1/34)	2·2	Not reached	2·0 (1·9–2·1); PD-L1+ 1·9 (1·8–2·0); PD-L1- 2·1 (1·9–2·6)	7·4 (5·5–9·6); PD-L1+ 7·2 (3·7–10·8); PD-L1- 9·3 (4·2–11·5)
Ueno et al, 2019[146]	Nivolumab	Post prior chemotherapy; PS 0–1; PD-L1 unselected	30	3% (1/30)	..	≥12·7	1·4 (1·4–1·4)*	5·2 (4·5–8·7)*
Ueno et al, 2019[146]	Nivolumab + CisGem	First-line; PS 0–1; PD-L1 unselected	30	37% (11/30)	..	5·1	4·2 (2·8–5·6)*	15·4 (11·8–not reached)*

RR=response rate. PS=performance status. PD-L1=programmed death ligand 1. CisGem=cisplatin and gemcitabine. *90% CIs.

Table 2: **Summary of reported studies of checkpoint inhibition in biliary tract cancer**

Biliary tract cancer

Juan W Valle, R Katie Kelley, Bruno Nervi, Do-Youn Oh, Andrew X Zhu

Lancet 2021; 397: 428–44

Biliary tract cancers, including intrahepatic, perihilar, an

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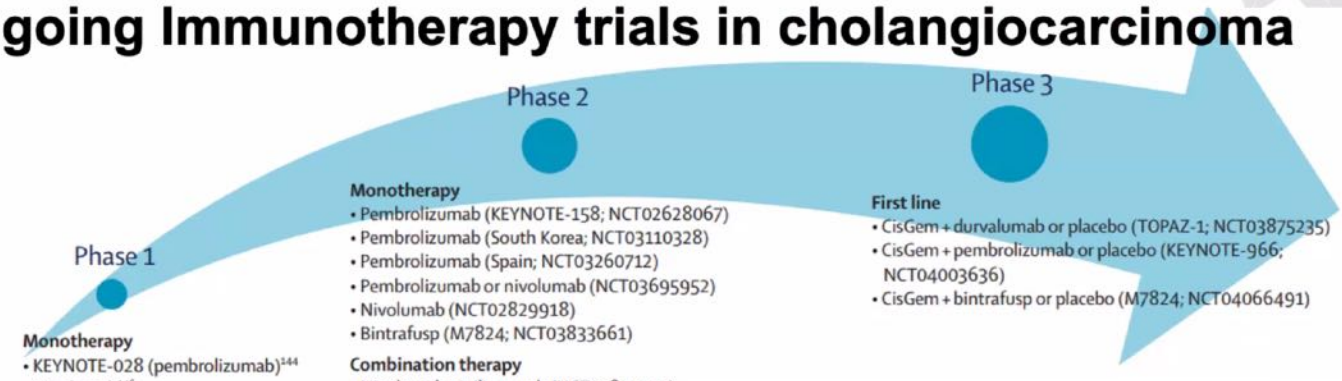
Ongoing Immunotherapy trials in cholangiocarcinoma



Phase 1

Monotherapy
- KEYNOTE-028 (pembrolizumab)[144]
- Nivolumab[146]
- Bintrafusp (M7824)[148]

Combination therapy
- Nivolumab + CisGem[146]
- Pembrolizumab + ramucirumab (NCT02443324)

Phase 2

Monotherapy
- Pembrolizumab (KEYNOTE-158; NCT02628067)
- Pembrolizumab (South Korea; NCT03110328)
- Pembrolizumab (Spain; NCT03260712)
- Pembrolizumab or nivolumab (NCT03695952)
- Nivolumab (NCT02829918)
- Bintrafusp (M7824; NCT03833661)

Combination therapy
- Nivolumab + ipilimumab (NCT02834013)
- Pembrolizumab + GM-CSF (NCT02703714)
- Pembrolizumab + Peg-interferon α2b (NCT02982720)
- Pembrolizumab + allogeneic natural killer cell (NCT03937895)
- Pembrolizumab + CisGem (EORTC-1607 ABC-09; NCT03260712)
- Pembrolizumab + capecitabine + oxaliplatin (NCT03111732)
- Pembrolizumab + ramucirumab (NCT03260712)
- Pembrolizumab + lenvatinib (LEAP-005; NCT03695952)
- Durvalumab + tremelimumab + TACE/RFA/ablation (NCT02821754)
- Durvalumab + tremelimumab + SIRT (NCT04238637)
- Durvalumab + tremelimumab + radiotherapy (NCT03482102)
- Durvalumab + tremelimumab + CisGem (NCT03046862)
- Durvalumab + tremelimumab +/− paclitaxel (NCT03704480)
- Durvalumab + AZD6738 (NCT04298008)
- Camrelizumab + GemOx (NCT03486678)
- Nivolumab + etinostat (NCT03250273)
- Atezolizumab +/− cobimetinib (NCT03201458)
- Neoadjuvant CisGem +/− durvalumab (DEBATE; NCT04308174)

Phase 3

First line
- CisGem + durvalumab or placebo (TOPAZ-1; NCT03875235)
- CisGem + pembrolizumab or placebo (KEYNOTE-966; NCT04003636)
- CisGem + bintrafusp or placebo (M7824; NCT04066491)

Variety of PD-1 and CTLA-4 trials

Biliary tract cancer

Juan W Valle, R Katie Kelley, Bruno Nervi, Do-Youn Oh, Andrew X Zhu

Lancet 2021; 397: 428–44 Biliary tract cancers, including intrahepatic, perihilar, an

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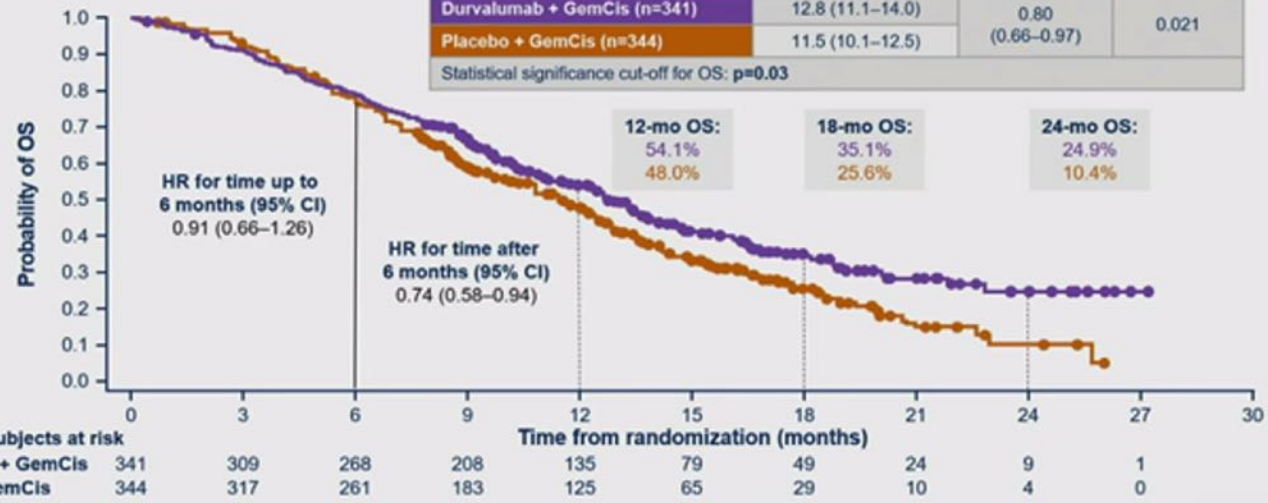
Phase 3: Gem/Cis + Durvalumab (vs Gem/Cis)

Primary endpoint: OS

	Median OS (95% CI), months	Hazard ratio (95% CI)	p-value
Durvalumab + GemCis (n=341)	12.8 (11.1–14.0)	0.80 (0.66–0.97)	0.021
Placebo + GemCis (n=344)	11.5 (10.1–12.5)		
Statistical significance cut-off for OS: **p=0.03**			



Number of subjects at risk										
Durvalumab + GemCis	341	309	268	208	135	79	49	24	9	1
Placebo + GemCis	344	317	261	183	125	65	29	10	4	0

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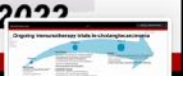

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