TORONTO
Liver Transplant Program

TORONTO
Liver and Pancreas Surgery

The Liver Transplant Symposium: Pushing Boundaries in Transplant Oncology
Singapore September 2023

Liver Transplantation for Cholangiocarcinoma

Gonzalo Sapisochin MD, PhD, MSc
Associate Professor of Surgery
University of Toronto
Abdominal Transplant & HPB Surgical Oncology
University Health Network, Toronto

UHN Ajmera Transplant Centre

TORONTO
Liver Transplant Program

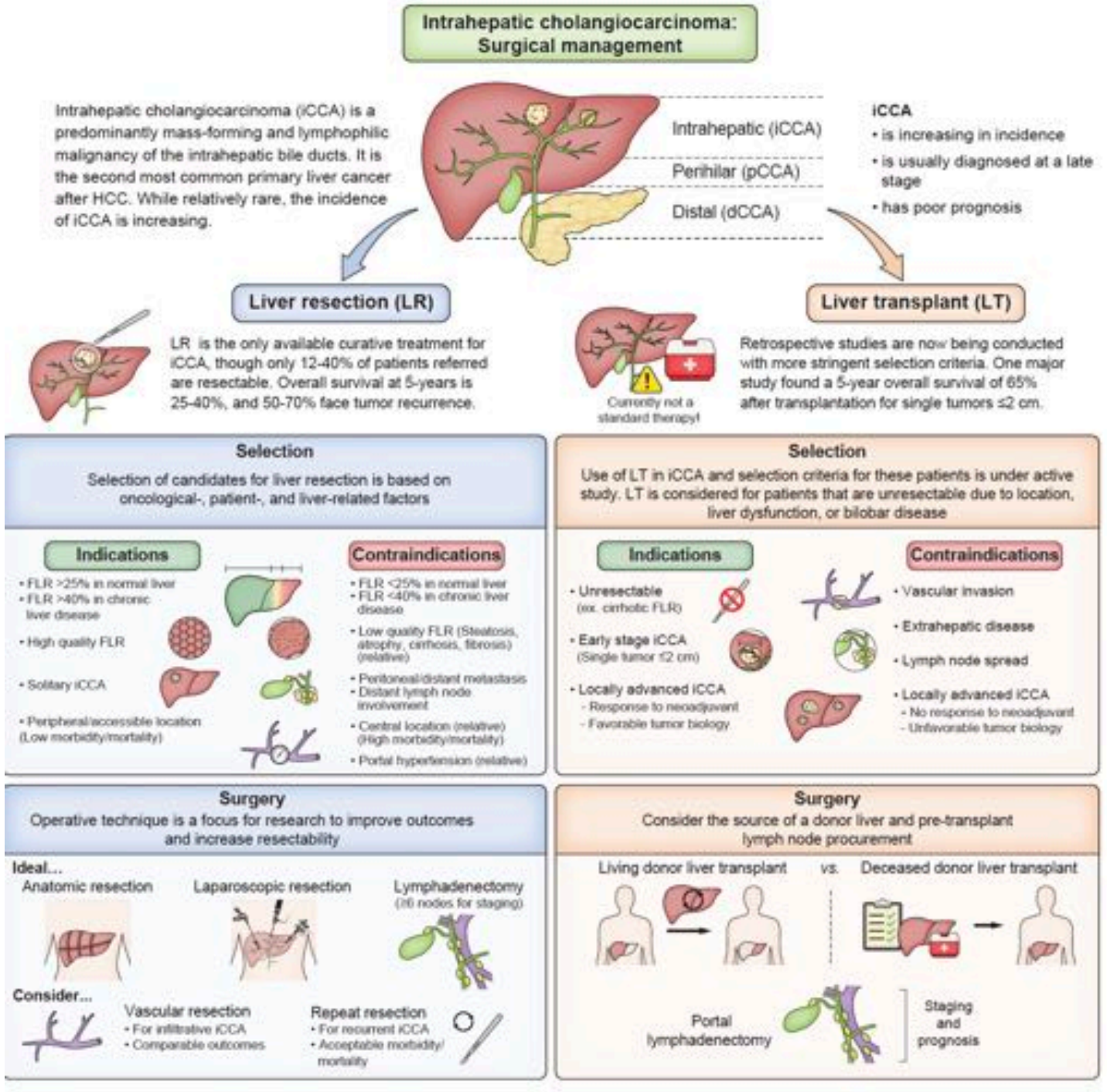
Disclosures

Grant Support from Bayer®, Roche®
Consultant for Novartis®, Integra®, Roche®, AstraZeneca®, Chiesi®, Eisai®, HepaRegeniX®.

First treatment option

Solitary iCCA

Hepatectomy plus lymphadenectomy



Cirrhotics single ≤3 cm

Experimental for larger and multifocal

Clinical trials

EASL-ILCA Guidelines
J hepatol 2023

Liver Resection for iCCA

- First treatment option for patients with single iCCA.
- However:
    - Most patients are NOT eligible for surgery (20-40%).
    - Cure rate is low 10-20%.
    - High risk of recurrence ~70%.
    - Most post-resection recurrences are intrahepatic.

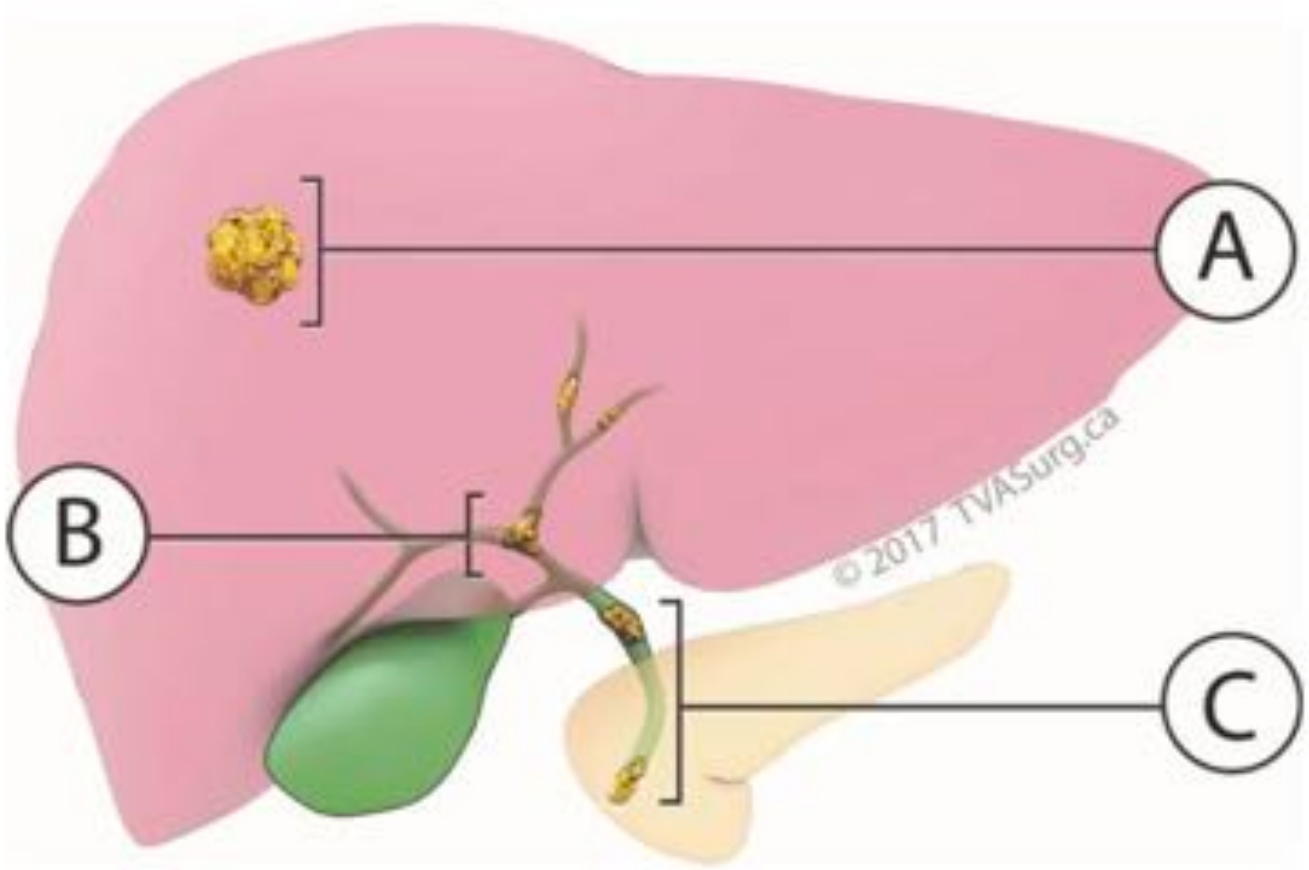


FIG. 1. CCA locations. (A) Intrahepatic (iCCA). (B) Hilar (hCCA). (C) Distal.

Treatment of choice is RESECTION

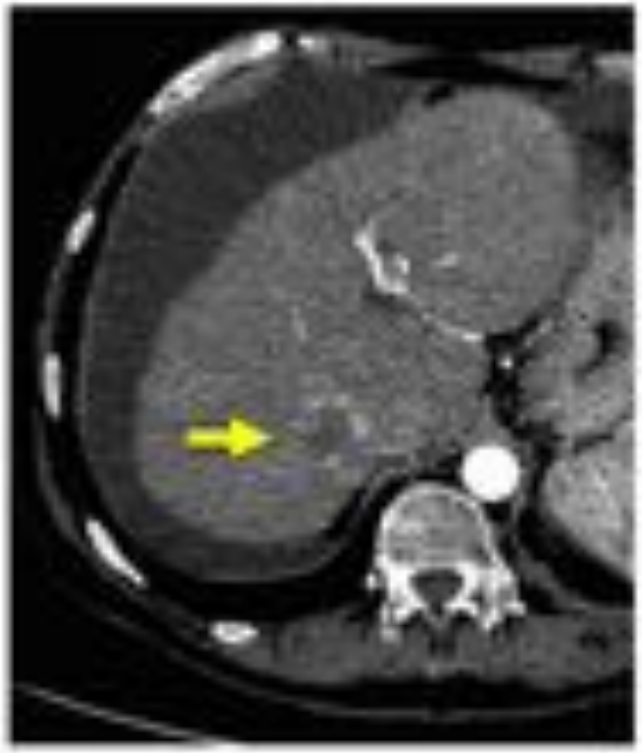
In cases that tumor is not-resectable, can liver transplantation be offered?

Goldaracena N & Sapisochin G, et al. Liver Transpl 2018

Are Patients Without EH disease or Vascular Invasion Candidates for Liver Transplantation? And if so, Who and How to select?

Liver Transplantation for iCCA

iCCa in Cirrhotics



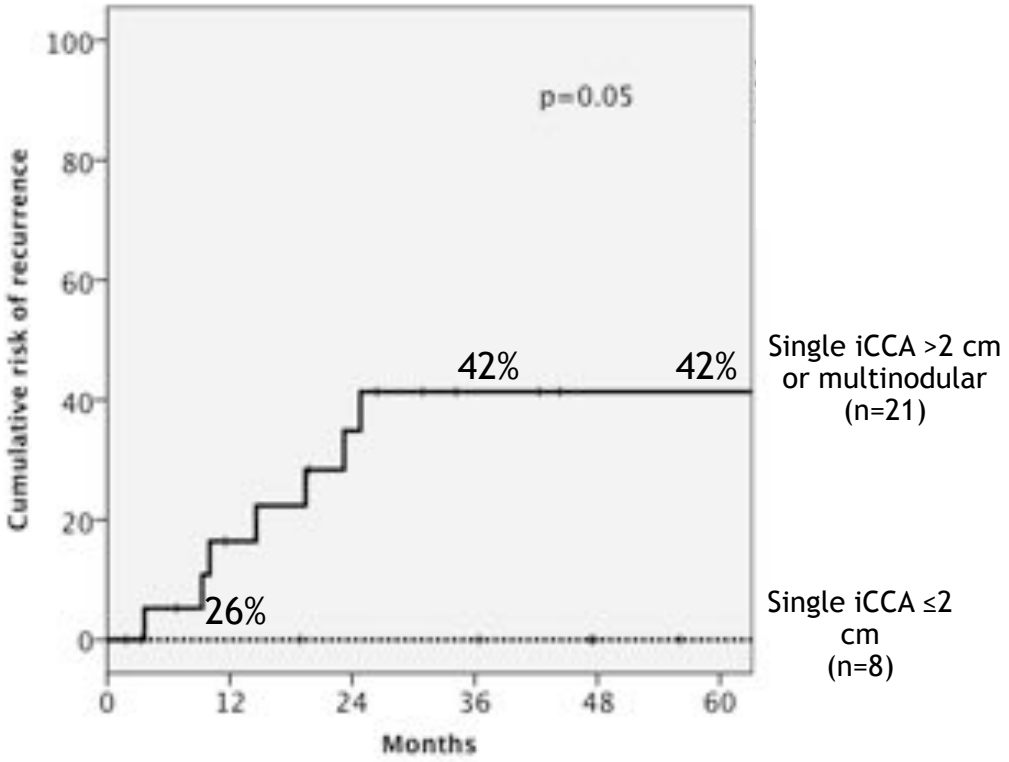
Large/Multifocal iCCa

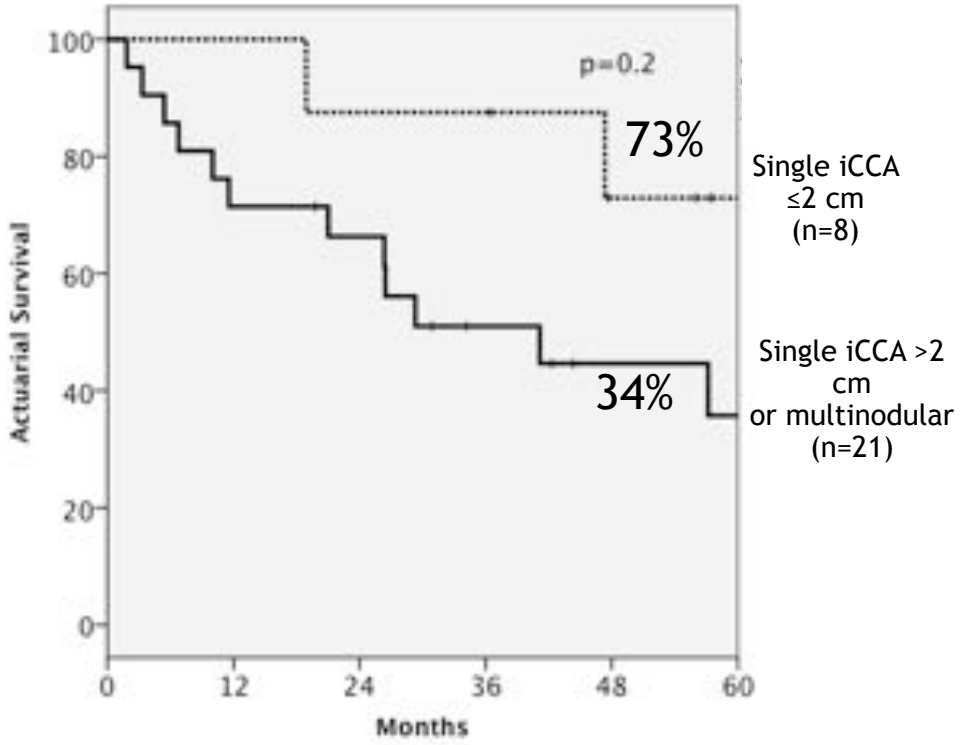
Liver Transplantation for iCCA

- LT is contraindicated in most centers due to poor results
- Studies are based on single center analysis with small number of patients
- Studies analyze patients with both iCCA and hilar cholangiocarcinoma
- Studies analyze patients with and without liver cirrhosis

Liver Transplantation for iCCa - Cirrhotics

"*Very Early*" Intrahepatic Cholangiocarcinoma in Cirrhotic Patients: Should Liver Transplantation Be Reconsidered in These Patients?



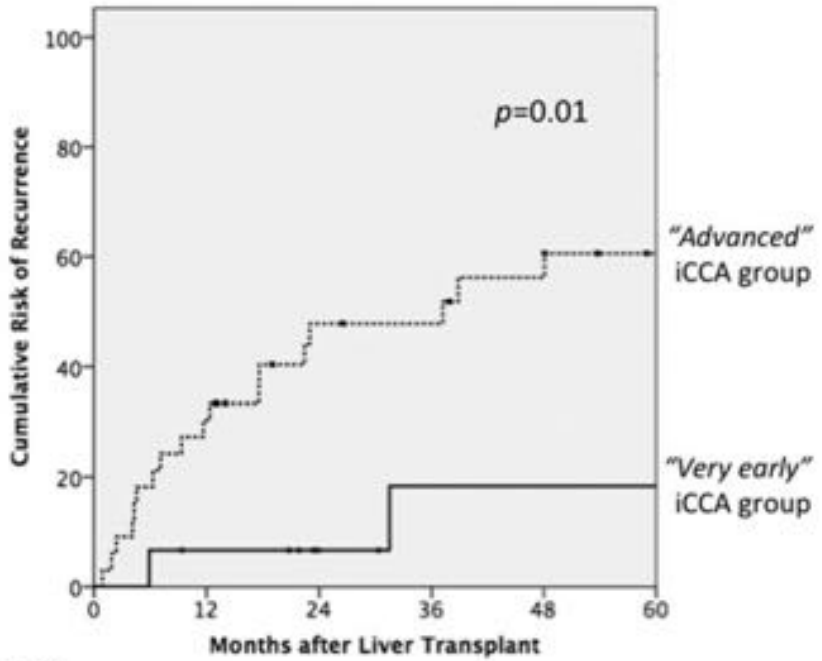


"Very Early" iCCa: Single tumor ≤2 cm

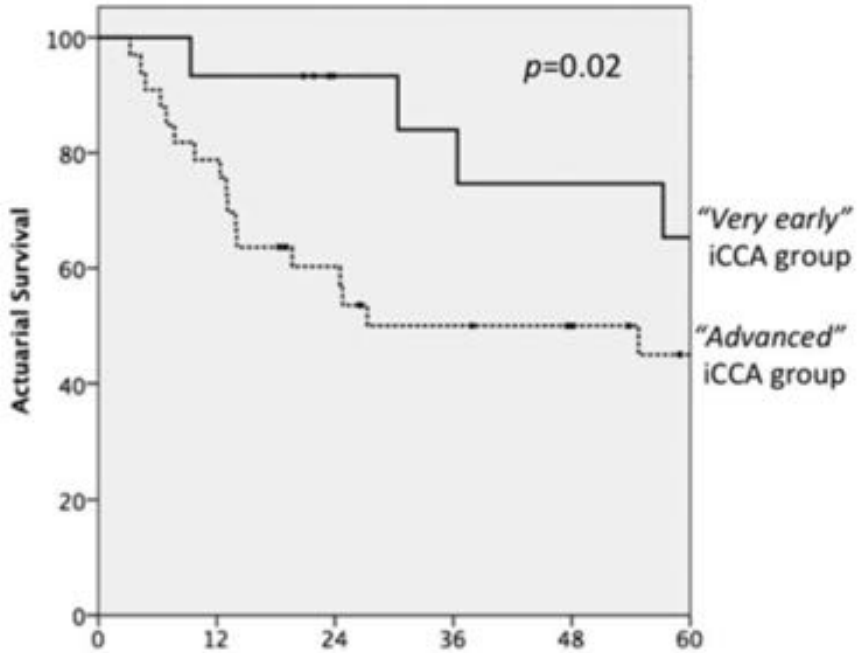
UHN Ajmera Transplant Centre

Sapisochin G, et al. Am J Transpl 2014

Liver Transplantation for "Very Early" Intrahepatic Cholangiocarcinoma: International Retrospective Study Supporting a Prospective Assessment



Patients at risk						
"Very Early"	15	13	9	7	7	7
"Advanced"	33	23	14	13	10	6



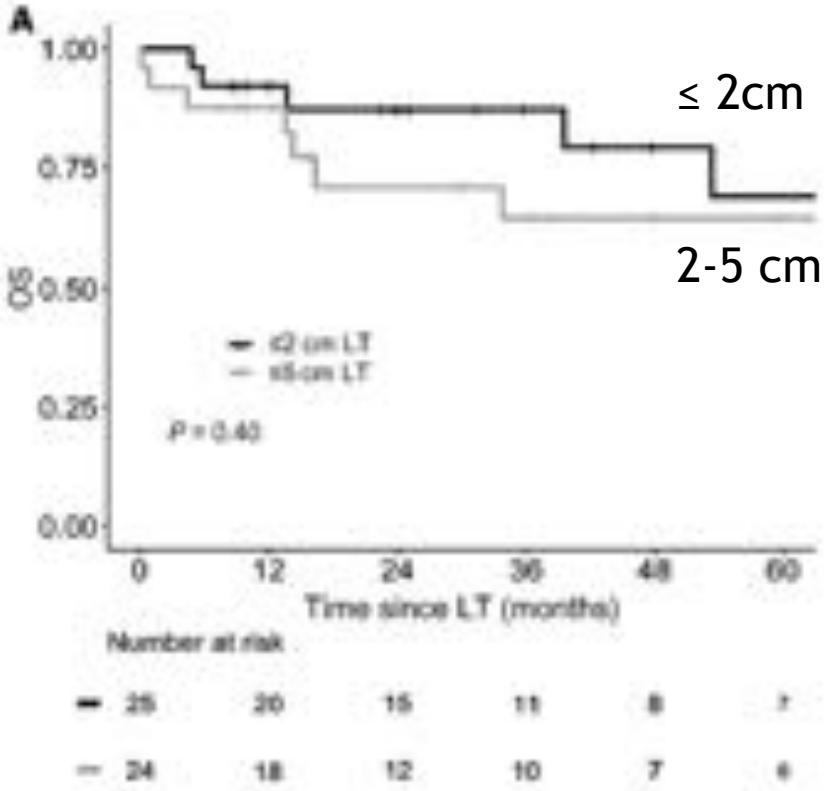
Patients at risk						
"Very Early"	15	14	10	9	8	7
"Advanced"	33	26	18	14	12	8

5-year recurrence 18%. 5-year survival 65%

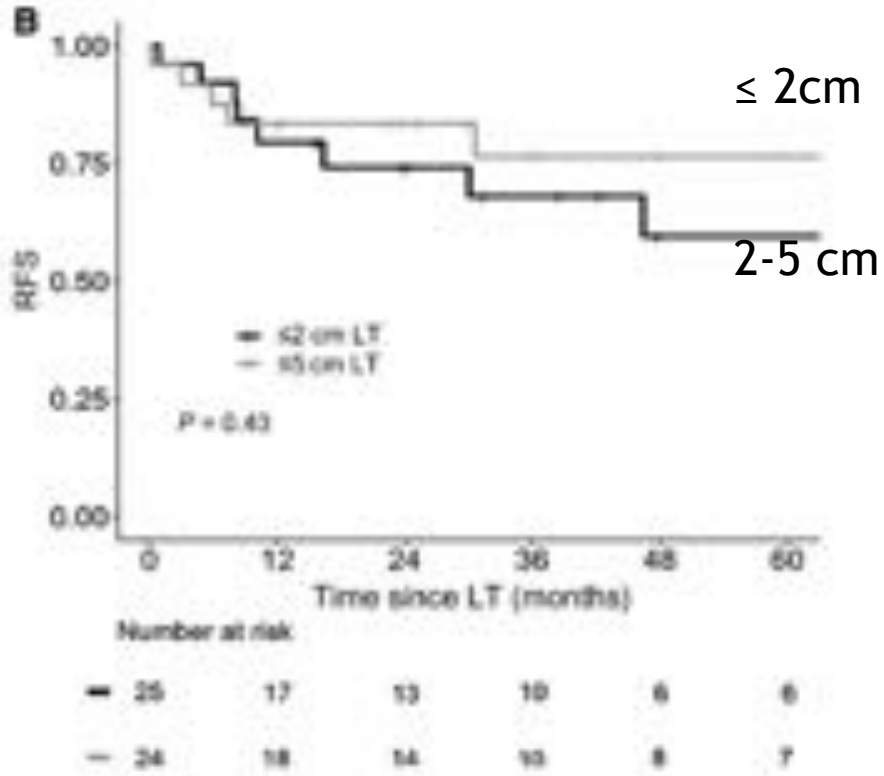
Sapisochin G et al. Hepatology 2016

Liver Transplantation ≤2 cm vs. 2-5 cm

Overall Survival



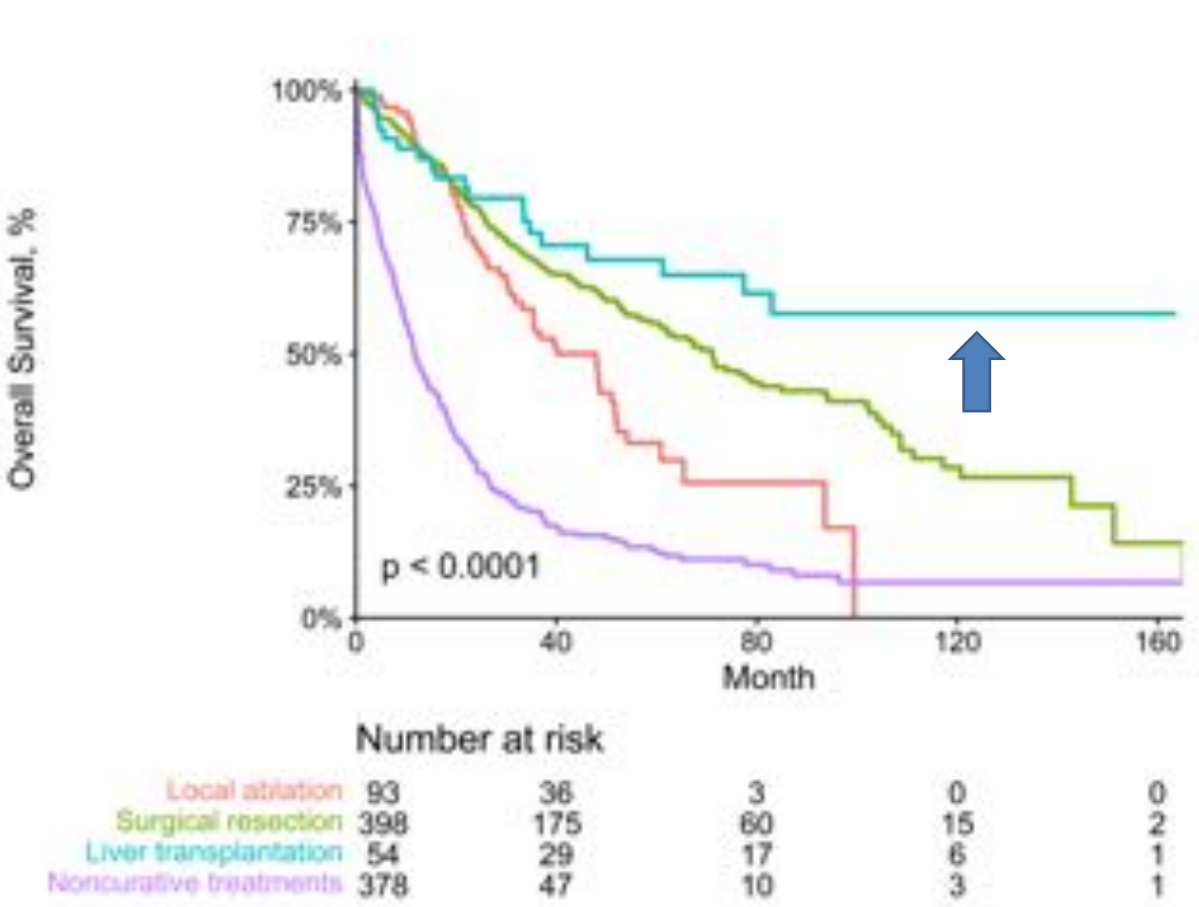
Disease-Free Survival

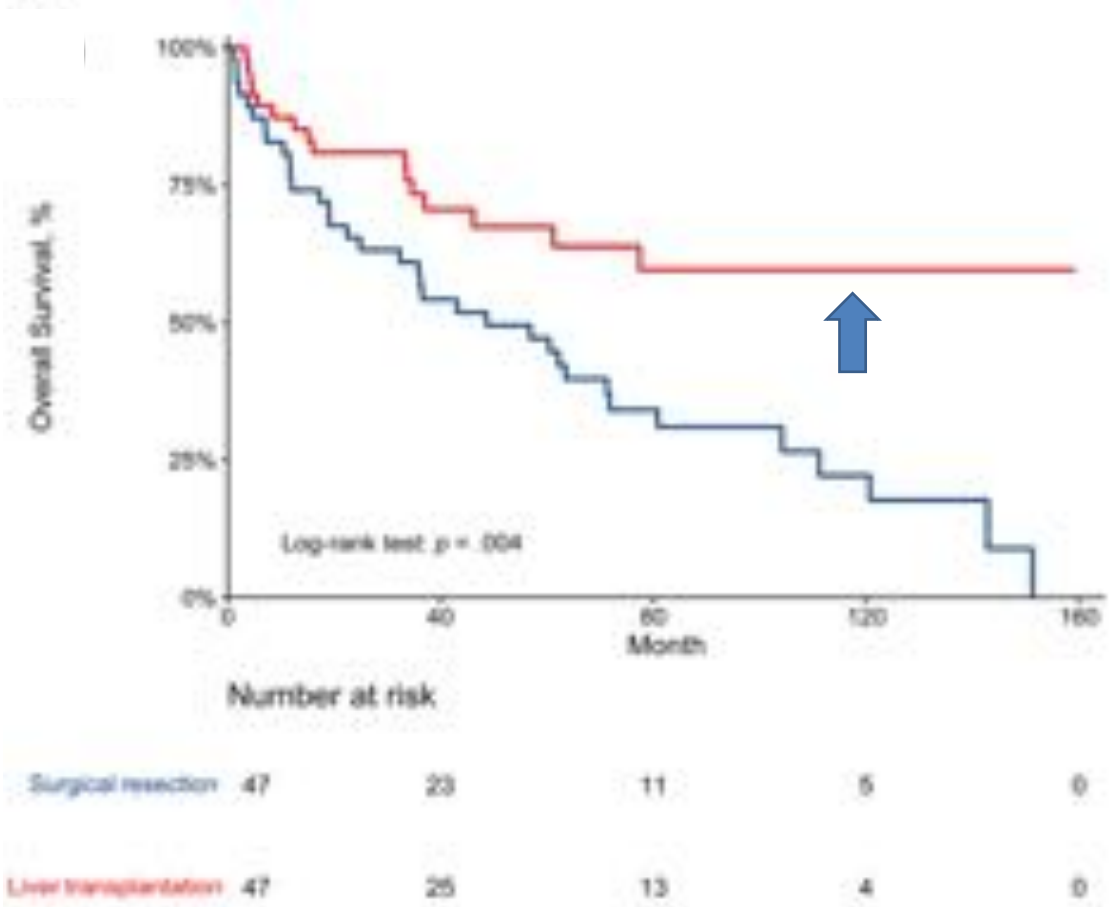


UHN Ajmera Transplant Centre

De Martin E, et al. Liver Transpl. 2020

US National Cancer Database
Treatments for early stage iCCA (single tumor < 3cm)

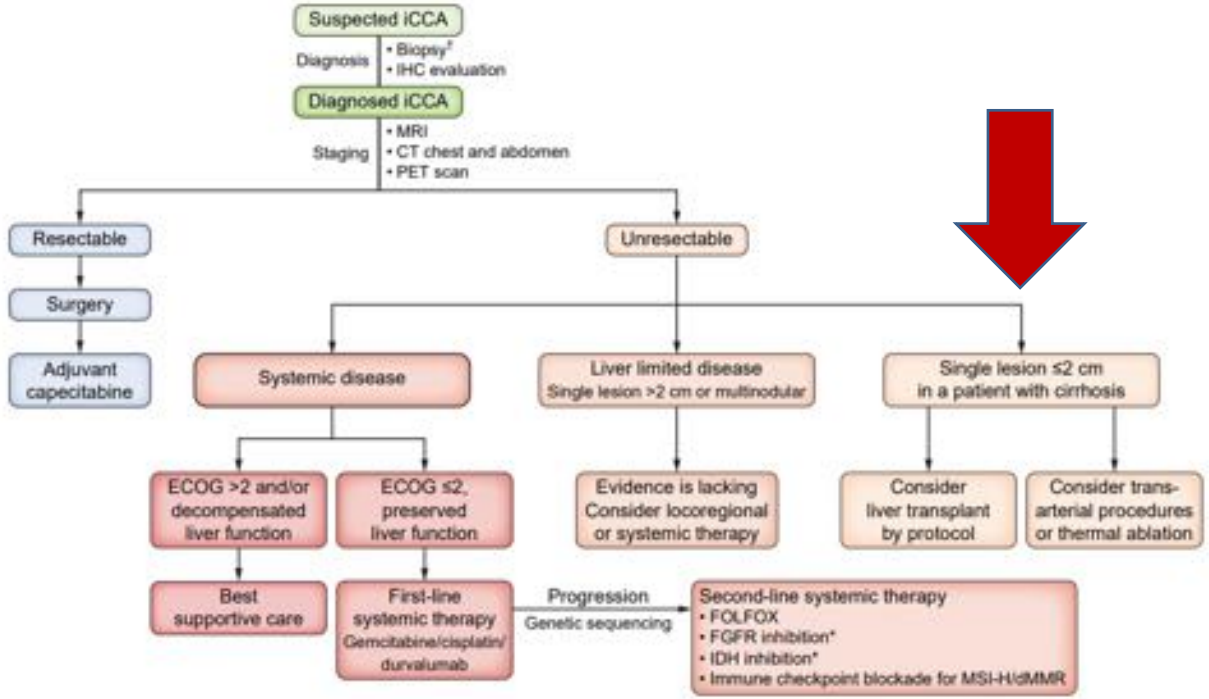


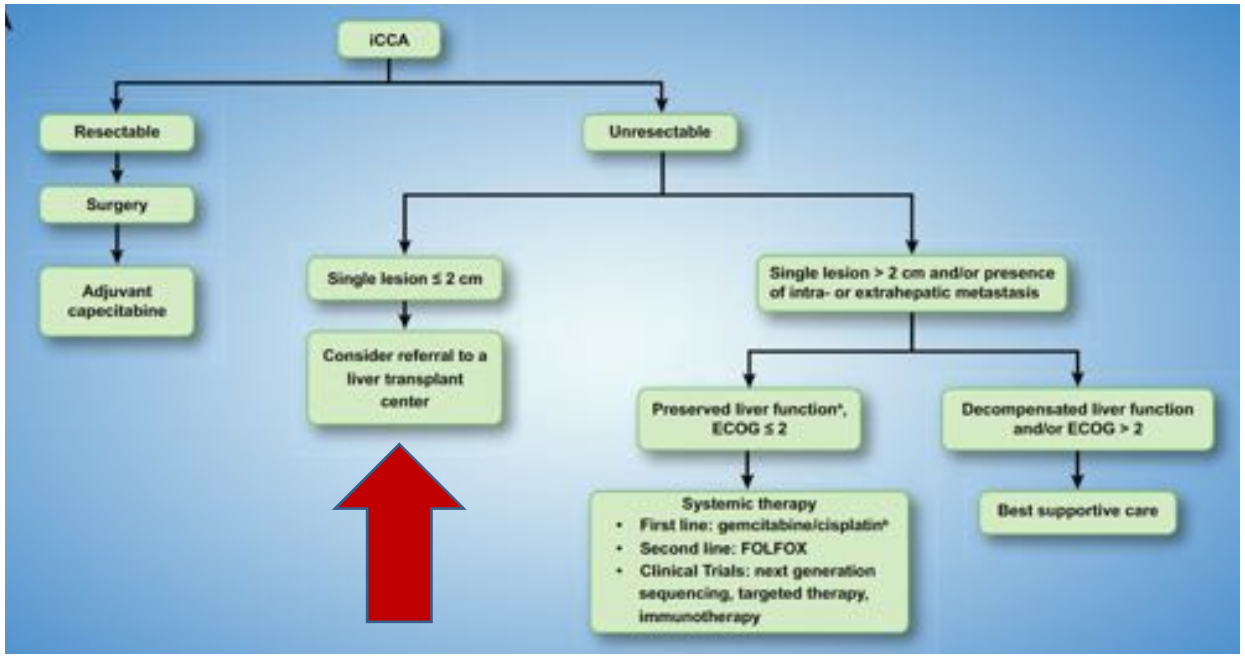


UHN Ajmera Transplant Centre

Lee Yi-Te, et al. Cancers 2022

American Association Study of the Liver CCA Guidelines
ILCA and EASL Guidelines





UHN Ajmera Transplant Centre

Bowlus CL, Sapisochin G et al. Hepatology 2022
EASL-ILCA Guidelines. J Hep 2023

Liver Transplantation for Early Intrahepatic Cholangiocarcinoma (LT for iCCA)

NCT02878473

PI Gonzalo Sapisochin, Toronto
Co-PI Jordi Bruix, BCLC, Barcelona

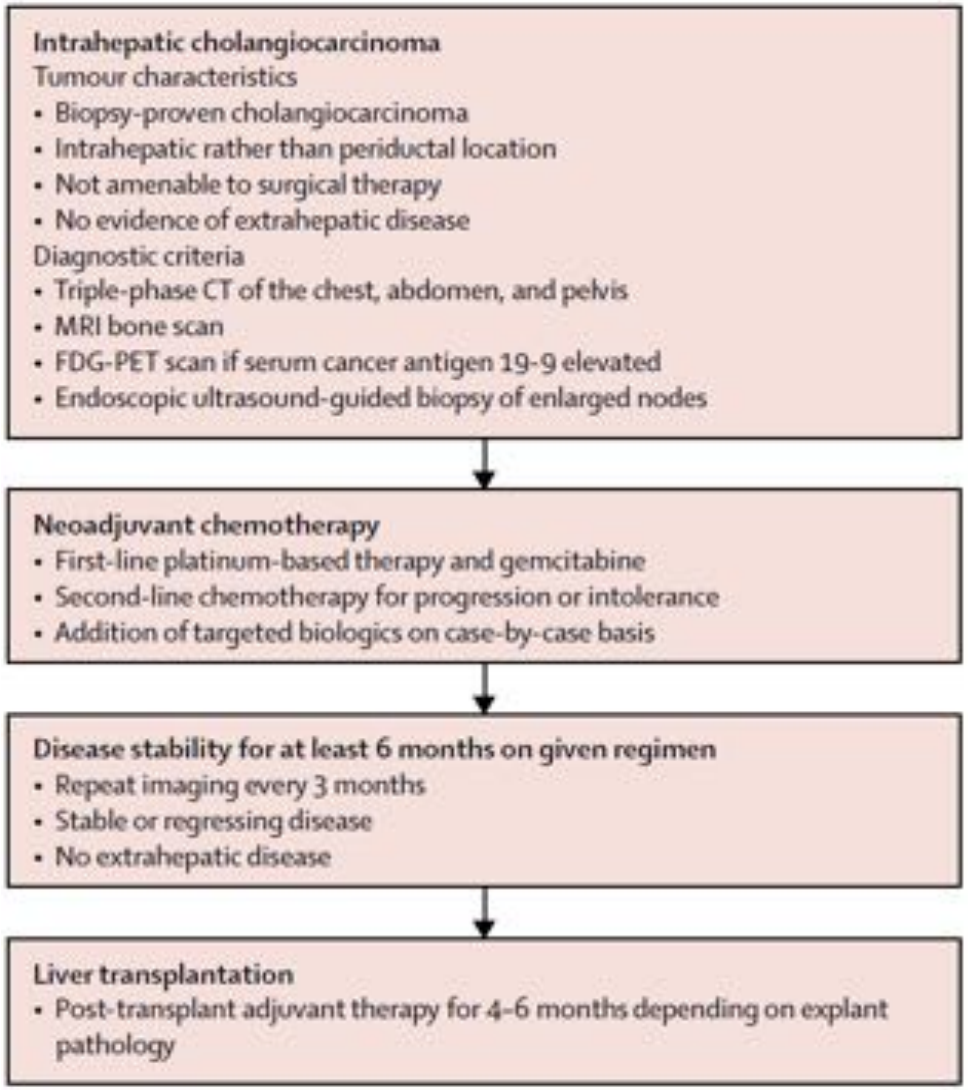
Sample Size **n=40**

Clinical Trial LT for “very early” iCCA

Limitations:

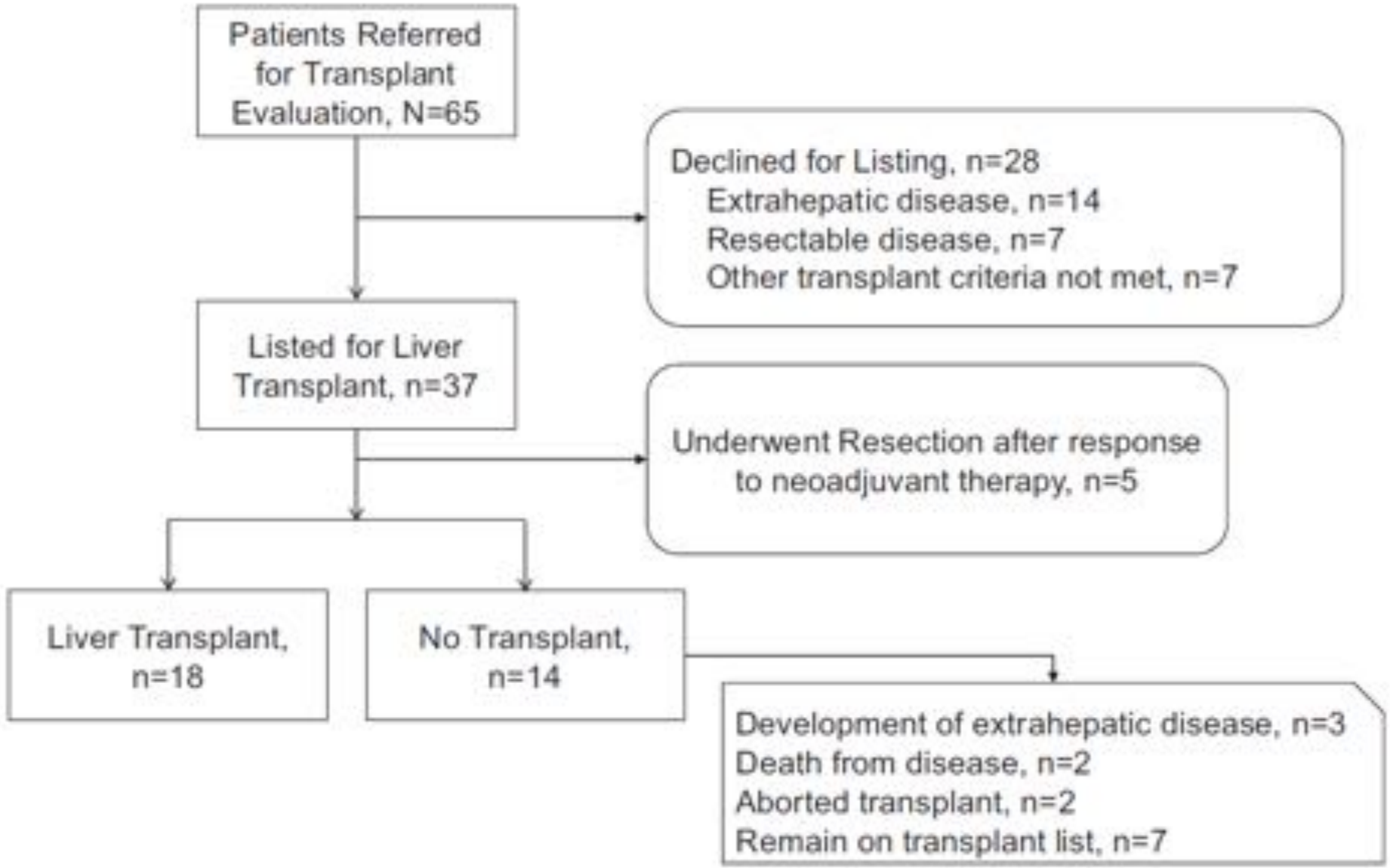
- Identification of patients (>2 cm?)
- Mandatory Biopsy
- Mixed HCC-CC
- Neoadjuvant therapies?
- Bridging?
- and a pandemic…

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



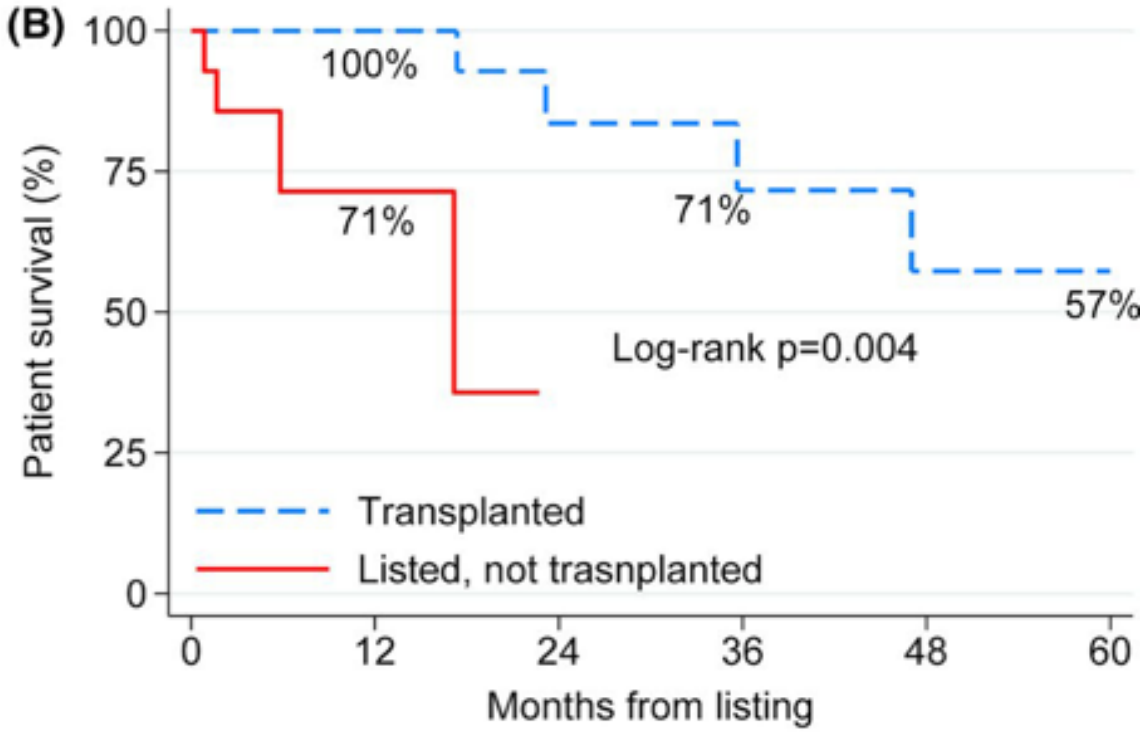
UHN Ajmera Transplant Centre

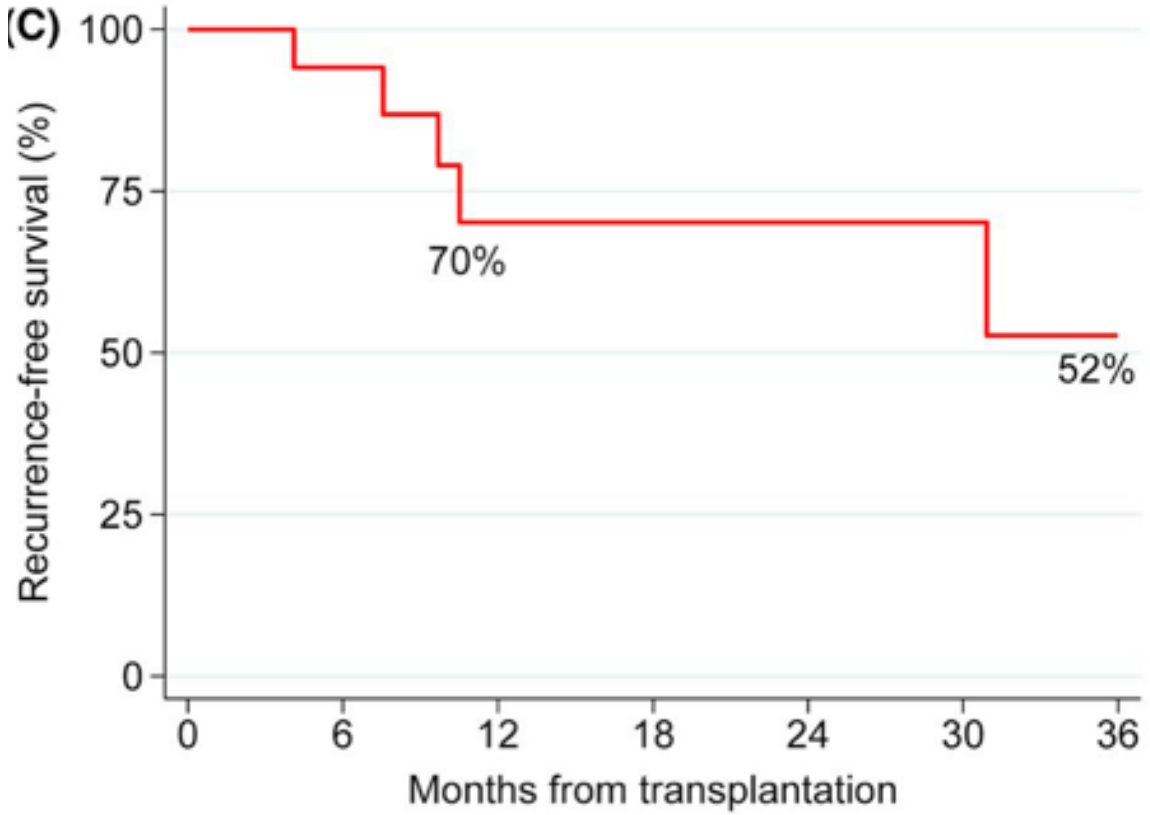
Lunsford KE, et al. Lancet Gastroenterol Hepatol 2018



McMillan R, et al. Am J Transplant 2021

Outcomes of LT for Large Multifocal iCCA





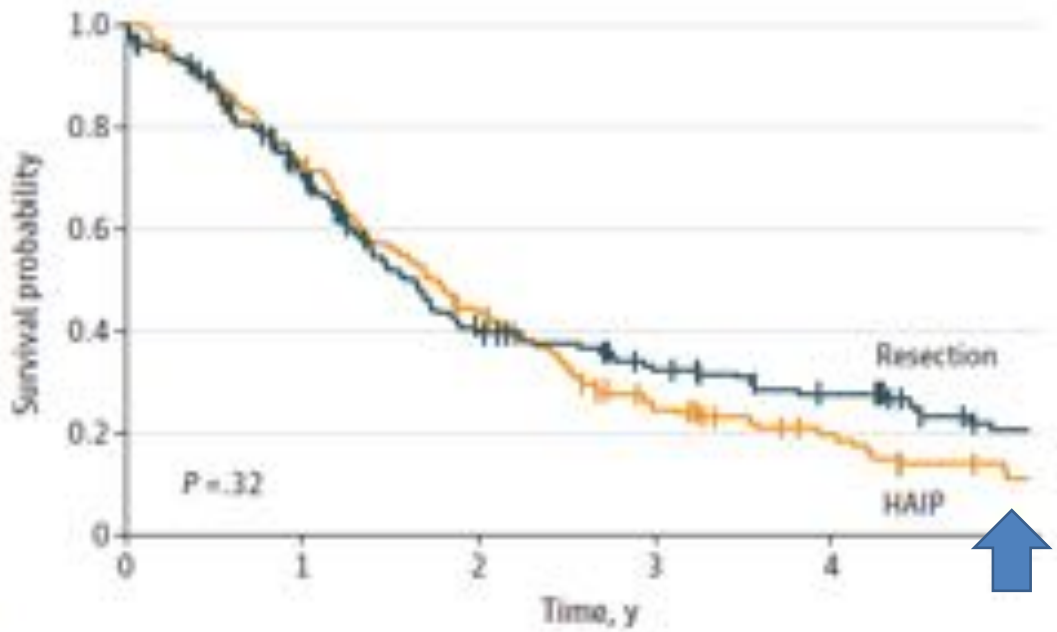
UHN Ajmera Transplant Centre

McMillan R, et al. Am J Transplant 2021

JAMA Surgery | Original Investigation

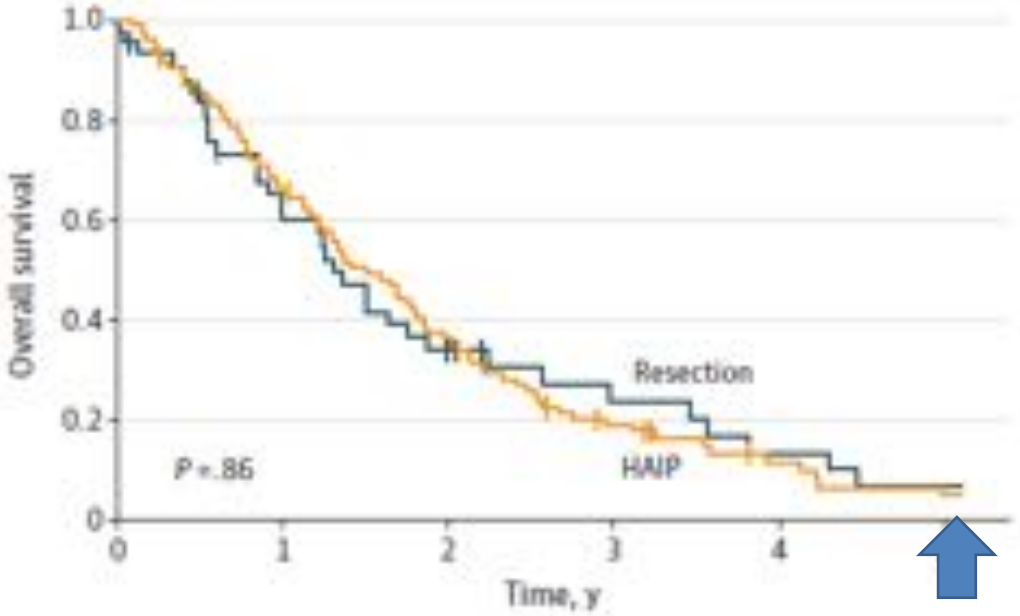
Comparison of Hepatic Arterial Infusion Pump Chemotherapy vs Resection for Patients With Multifocal Intrahepatic Cholangiocarcinoma

All-comers



No. at risk						
HAIP	141	102	60	30	17	7
Resection	178	111	57	39	29	1

4 lesions or more

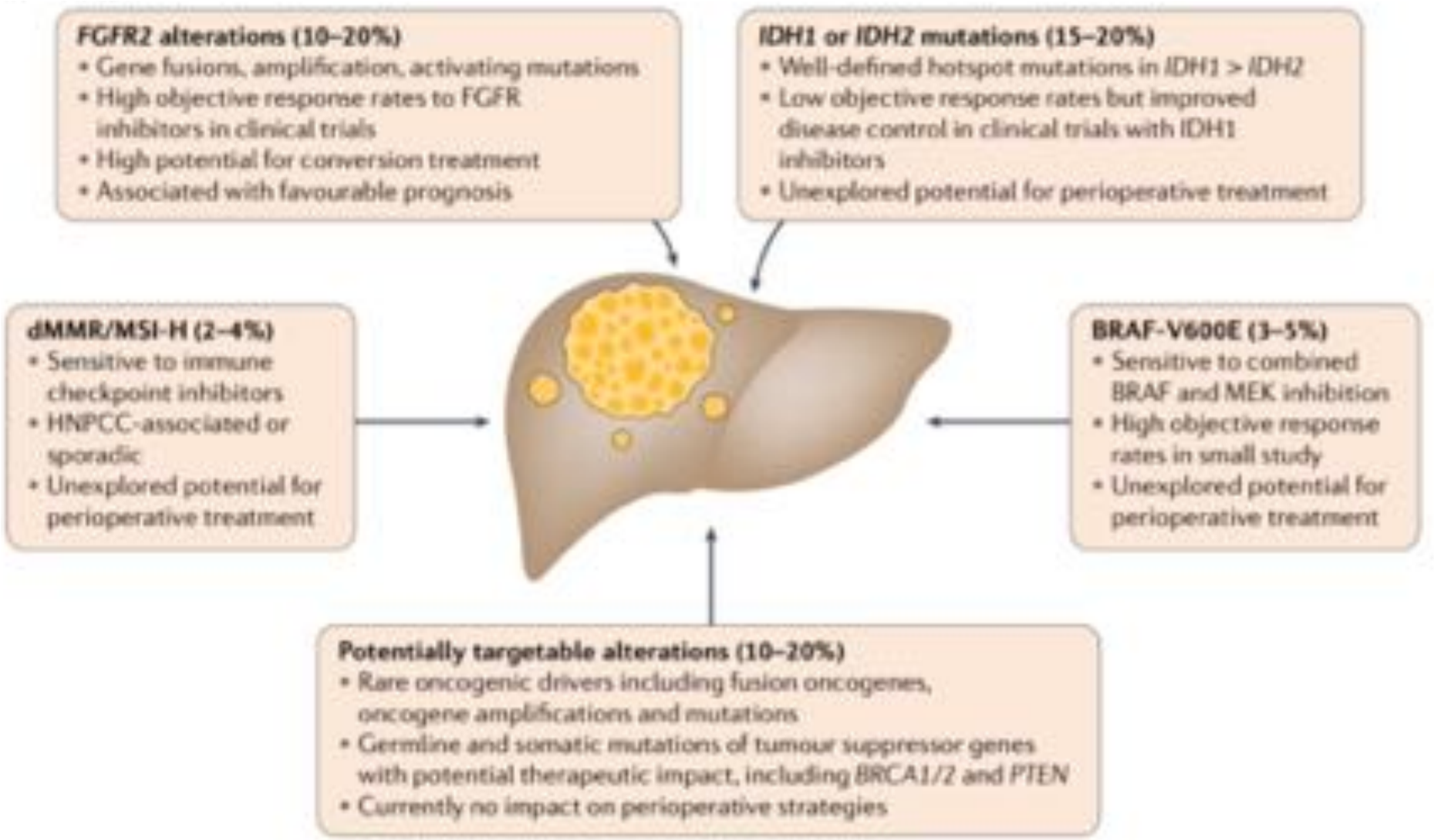


No. at risk						
HAIP	94	61	33	15	7	3
Resection	43	23	12	7	4	2

UHN Ajmera Transplant Centre

Franssen S, et al. JAMASurg 2022

Importance of Targetable Genetic Alterations in iCCA



UHN Ajmera Transplant Centre

Petrowsky H, et al. Nature Rev Gastro and Hep 2020

Genetic Alteration Analysis of Recipients

Pt	Genetic Mutation
1	Not Done
2	BLM, FANCF, FGFR2, KDR, MITF, MS6H6, NFKB1A, PDK1, PRKAR1A, SMARCA4, SPTA1
3	BAP1, FGFR2, MYC, MYST3
4	IDH1, KRAS
5	FGFR3, FRS2, MDM2, PTEN, SMAD4, SPTA1
6	BRAF
7	BRCA1, FGFR2, FGFR3, RAF1, MYC, ARID1A, CCND3, NOTCH1, SMAD4, TP53, VEGFA
8	IDH1, BRAF
9	ARID1A, EGFR, MYC, TP53

Limitations

EDITORIAL

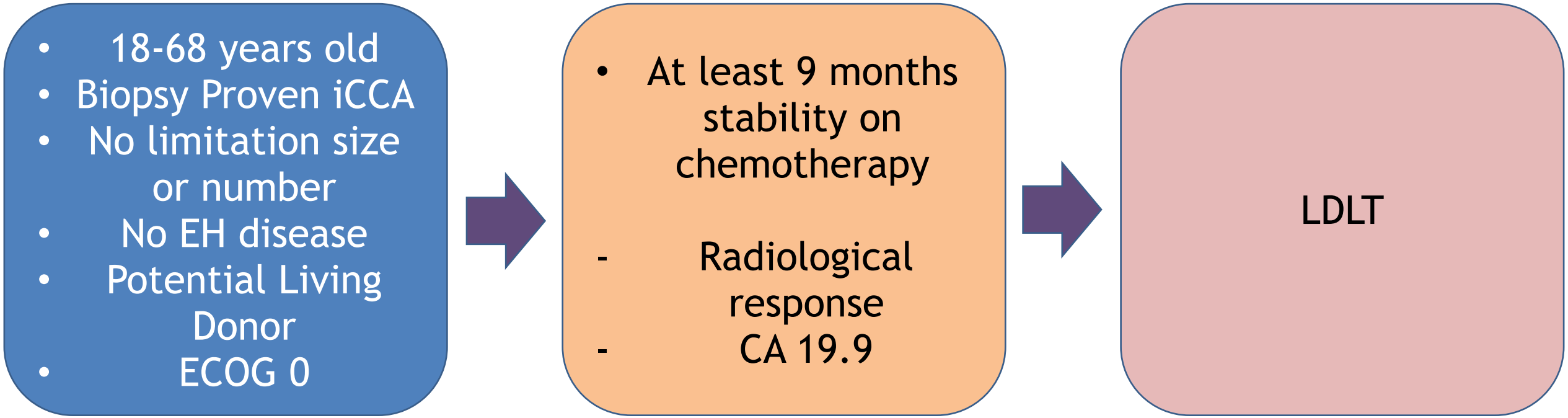
Transplant oncology in locally advanced intrahepatic cholangiocarcinoma: One more step on a long road

Strategy	Example
Identification of genetic determinants that portend a better or worse prognosis	- A recent bi-institutional study of unresectable iCCA patients identified specific genetic determinants, such as TP53, KRAS, and cyclin-dependent kinase inhibitor 2a (CDKN2A), to portend a worse prognosis.[6]
Clarifying the static and dynamic role of biomarkers such as CA 19-9	- Elevated CA19-9 is a risk factor for mortality in iCCA similar in impact to nodal metastases and positive resection margins.[7]
The use of new innovative technologies	- Radiomics, a field of imaging-based research that can extract data from imaging and be used as an imaging-based biomarker, can also possibly improve the characterization of more indolent disease. - Machine learning technology can be leveraged to identify favorable and unfavorable disease phenotypes based on all available clinical, genetic, and radiographic information.
Novel therapies	- Targeted therapies, such as FGFR-inhibition for iCCA with FGFR2 fusion.[8] - The addition of immune checkpoint inhibition to chemotherapy has shown early promise and potential benefit compared to standard-of-care chemotherapy (gemcitabine-cisplatin) and may help more patients reach the point of being considered for LT in the setting of ongoing and future trials.[9]

UHN Ajmera Transplant Centre

Ivanics T, Toso C, Ilyas SI, Sapisochin G et al. AJT 2021

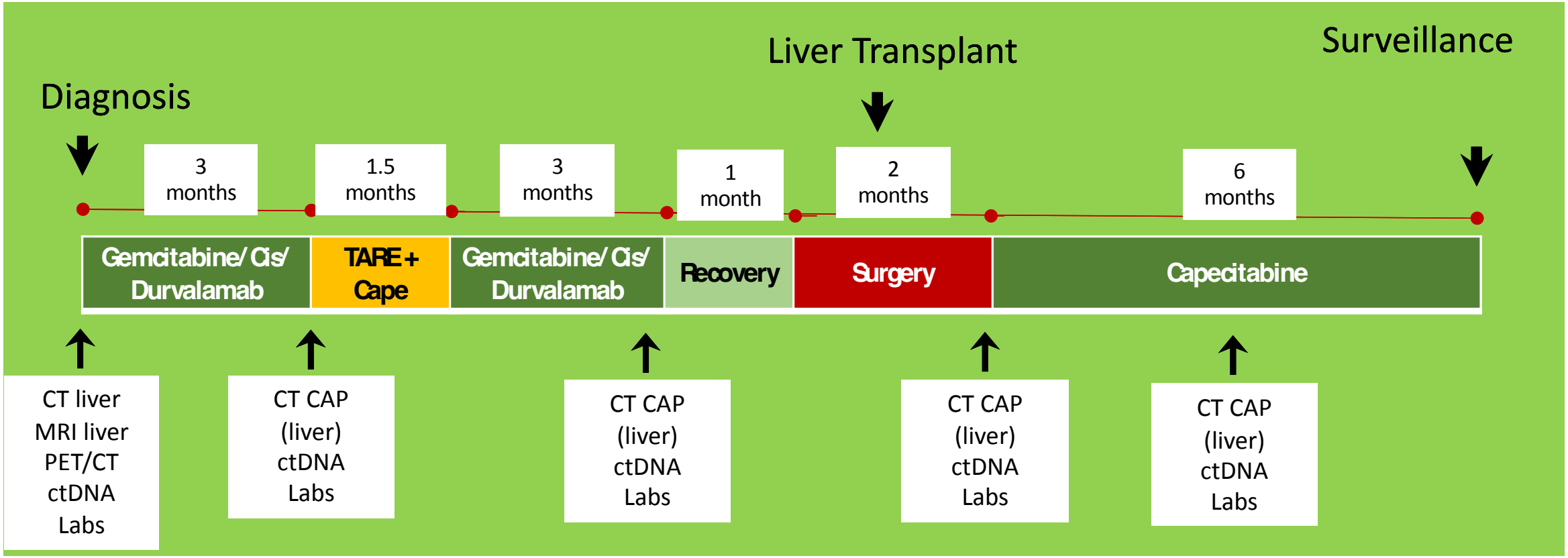
University of Toronto Trial - NCT04195503



TESLA Trial in Oslo NCT04556214

UHN Ajmera Transplant Centre

University of Utah Health / Huntsman Cancer Institute

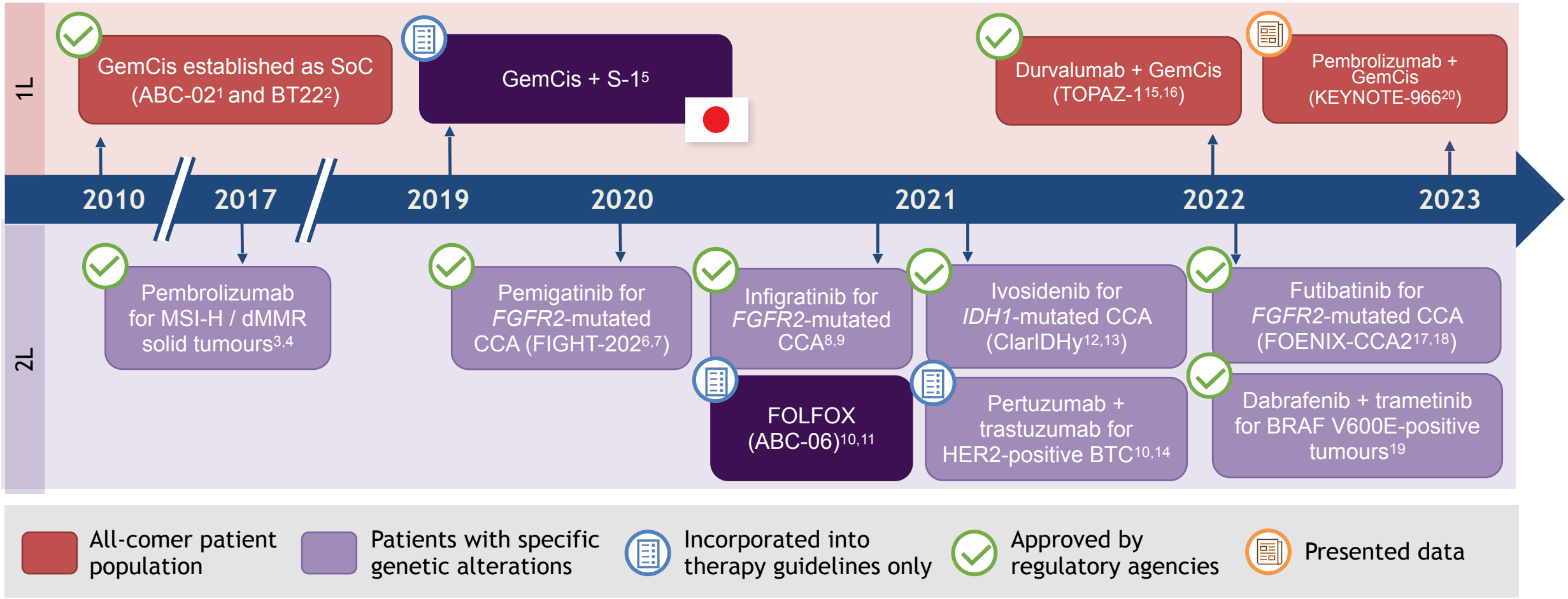


UHN Ajmera Transplant Centre

Courtesy of Dr. Talia Baker

How do we select best candidates?

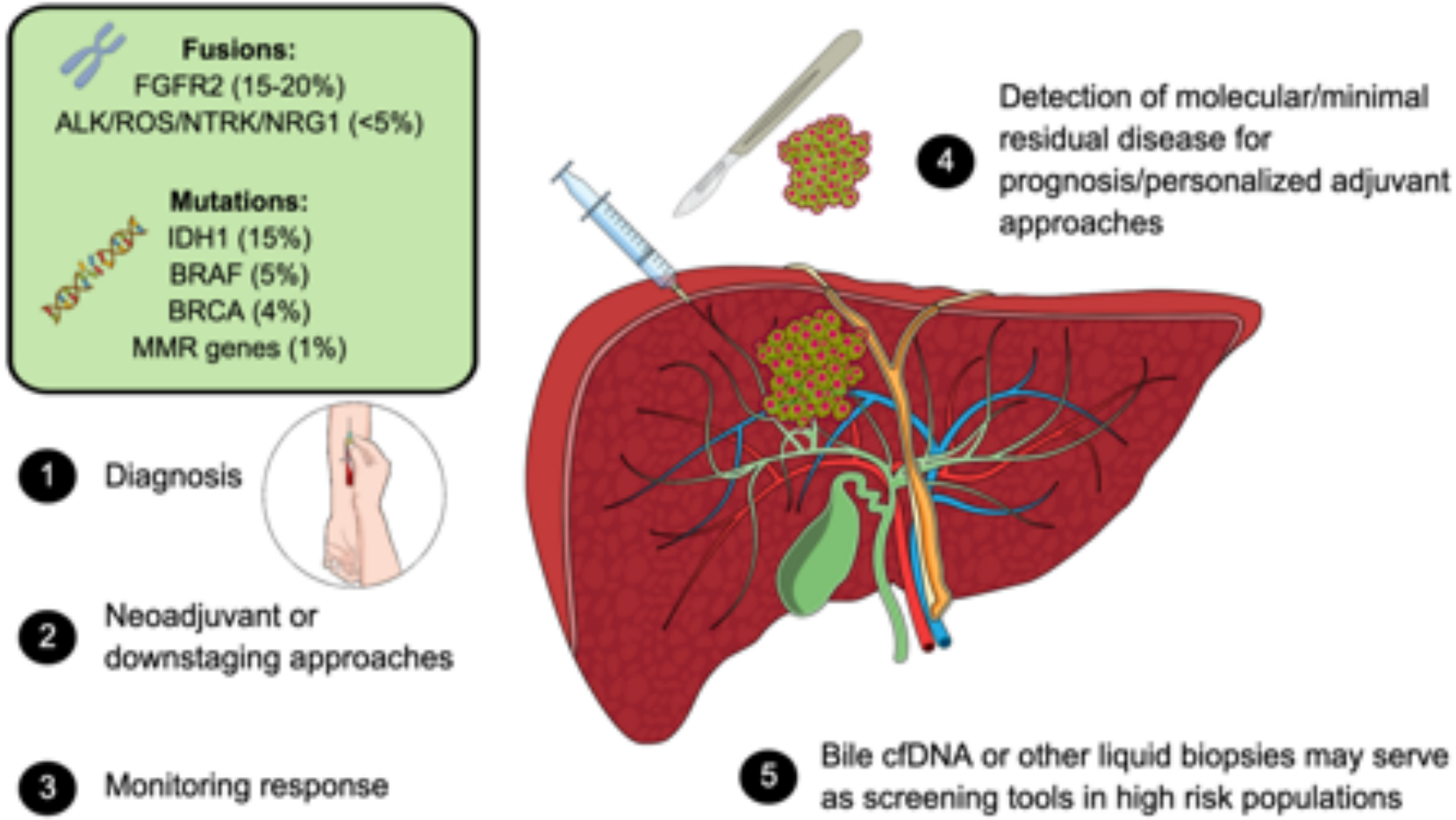
There have been a number of novel treatment options for advanced BTCs in recent years – Impact on Transplant?



UHN Ajmera Transplant Centre

1. Valle J, et al. *N Engl J Med* 2010;362:1273-1281. 2. Okusaka T, et al. *Br J Cancer* 2010;103:469-474. 3. Merck 4. European Medicines Agency. 5. Nagino M, et al. *J Hepatobiliary Pancreat Sci* 2021;28:26-54. 6. Abou-Alfa GK, et al. *Lancet Oncol* 2020;21:671-684. 7. US Food and Drug Administration. 8. Javle M, et al. *J Clin Oncol* 2018;36:276-282. 9. US Food and Drug Administration. 10. Vogel A, et al. *Ann Oncol* 2023;34:127-140. 11. Lamarca A, et al. *Lancet Oncol* 2021;22:690-701. 12. Abou-Alfa GK, et al. *Lancet Oncol* 2020;21:796-807. 13. US Food and Drug Administration. https://www. 14. Javle M, et al. *Lancet Oncol* 2021;22:1290-1300. 15. Oh D-Y, et al. *NEJM Evid* 2022;1:EVIDoa2200015. 16. US Food and Drug Administration. 17. Goyal L, et al. *J Clin Oncol* 40(16_suppl):4009-4009. 18. US Food and Drug Administration. 19. US Food and Drug Administration. 20. Kelley RK, et al. Presented at: AACR Annual Meeting

Future Tools for Selection Criteria and Response?



UHN Ajmera Transplant Centre

Choi WJ, Sapisochin G, O'Kane G et al. Ann Surg Oncol 2023

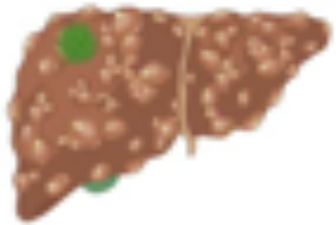
Upfront resection?
In situ cold perfusion and RHV Reconstruction

Biopsy and Sequence

Systemic Therapy +/- targeted?

- No response → Systemic/BSC
- Response → Downstaged Surgery? → Response → Not Downstaged → **Transplant**

WHO: Patients with **unresectable** intrahepatic cholangiocarcinoma



Decompensated cirrhosis with portal hypertension

- Single tumors ≥2cm (very early)
- No extrahepatic disease
- No vascular invasion

Locally advanced iCCA

- Large or multiple tumors
- No extrahepatic disease
- No vascular invasion
- No lymph node involvement
- ≥6mo stability with systemic chemotherapy and or LRT.

WHEN: Patient **selection strategies** to improve outcomes after LT

Systemic Chemotherapy ●●●

- Gemcitabine + cisplatin + durvalumab/pembrolizumab (1ºL)
- Gemcitabine + cisplatin (1ºL)
- FOLFOX (2ºL)

Ablation ●●○

- Radiofrequency, microwave, Cryoablation, Irreversible electroporation. (response rate 94%, OS 30 months)

Intra-arterial treatments ●○○

- TACE (26.3% RR, OS 15.9 months)
- TARE (23.4% RR, OS 14.9 months)
- HAI (41.3 % RR, OS 21.3 months)

External beam radiotherapy ●○○

(69.1% local control, OS 18.9 months)

Future treatments

- ctDNA guided
- Target therapies (2ºL)
- Molecular profile

HOW: Strategies to **increase liver grafts availability** for transplant oncology patients.

Living Donor Livers

- ▲ Excellent quality organs,
- ▲ Facilitates sequencing of treatment
- ▼ Donor risks.
- ▼ High technical complexity

Marginal Grafts

- ▲ Doesn't affect the waiting list mortality
- ▲ Whole livers
- ▼ Low-quality grafts, may increase complications
- ▼ Oncological risk?

RAPID Transplantation

- ▲ Doesn't affect the waiting list mortality
- ▼ Very high complexity
- ▼ Scarcity of split organs
- ▼ Increased biliary complications

Domino Transplantation

- ▲ Good quality organs
- ▲ Scarcity of domino organs
- ▼ May affect the waiting list mortality
- ▼ Risk of getting the donor's disease

Machine perfusion

- ▲ Reduces cold ischemia time
- ▲ Allows organ testing and selection
- ▲ Increased preservation time for staging
- ▼ High cost, low availability

RR: response rate; LT: Liver transplant; iCCA: intrahepatic cholangiocarcinoma; LRT: loco-regional therapies

●●● Level of evidence

▲▼ PROS and CONS

UHN Ajmera Transplant Centre

Achurra P, Sapisochin G, et al. Under Review

Hilar Cholangiocarcinoma

Liver Transplantation for hilar CCA – Selection Criteria – Mayo Clinic and Toronto

1. Malignant appearing stricture and at least one of the following:

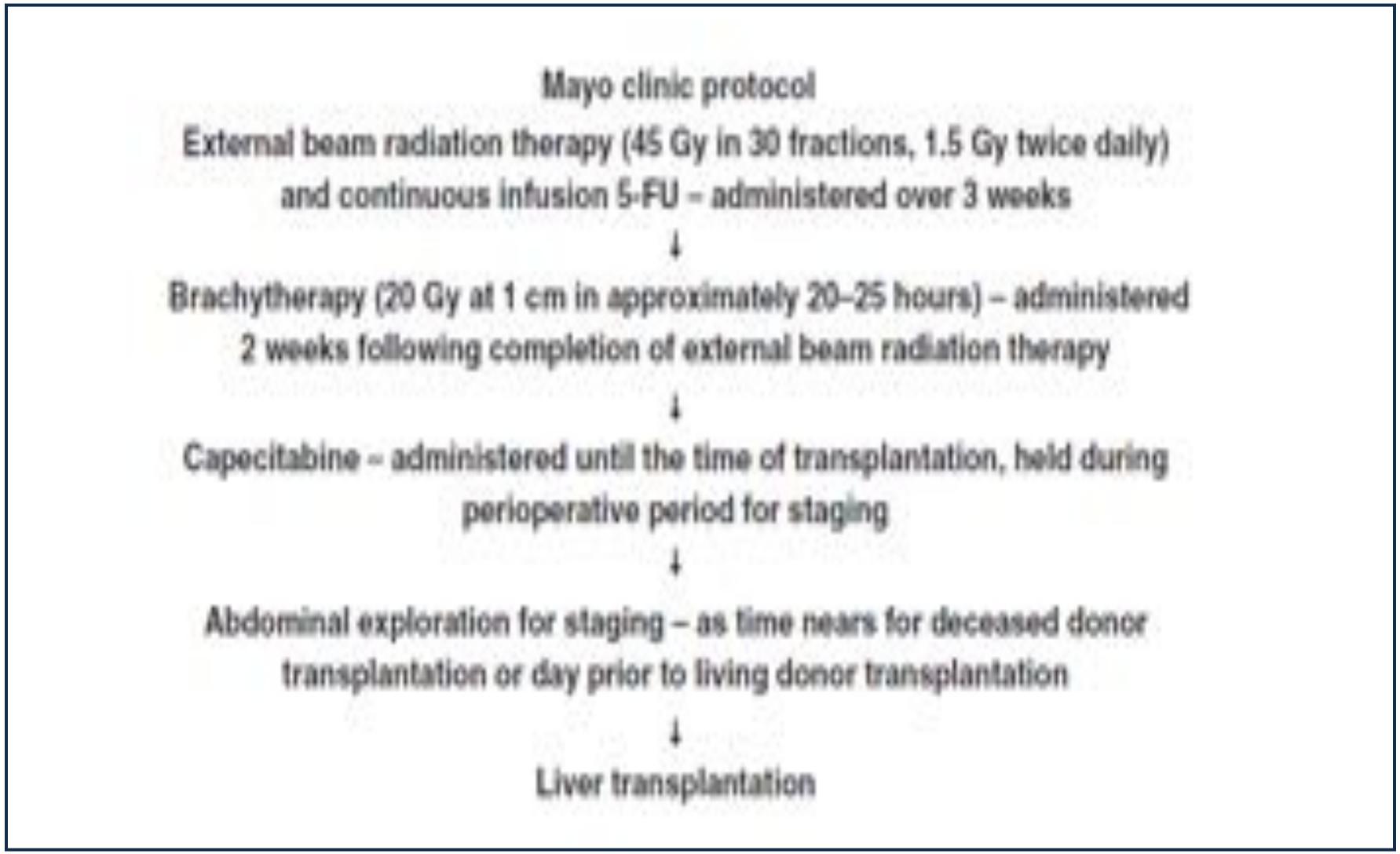
   - Malignant cytology or histology
   - CA-19.9 > 130 U/mL without cholangitis
   - Mass on cross-sectional imaging (radial diameter ≤3 cm)
   - No extrahepatic disease

2. Cancer located primarily above the cystic duct

3. Unresectable cancer (de novo CCA) or cancer arising in setting of PSC

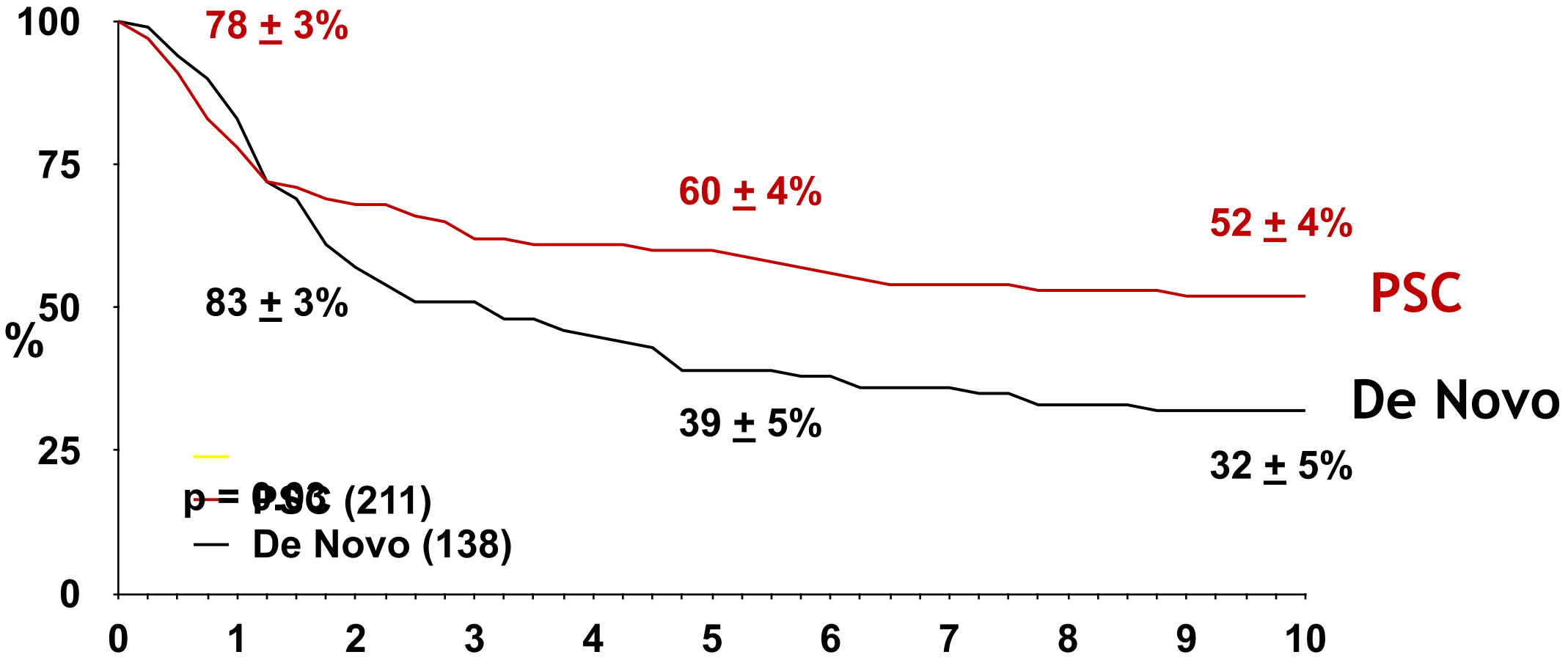
Courtesy of Julie Heimbach, Mayo Clinic

Liver Transplantation for pCCA
The Mayo Clinic Protocol



Rea DJ, et al. Ann Surg 2005

Mayo Clinic Experience
Intention to Treat

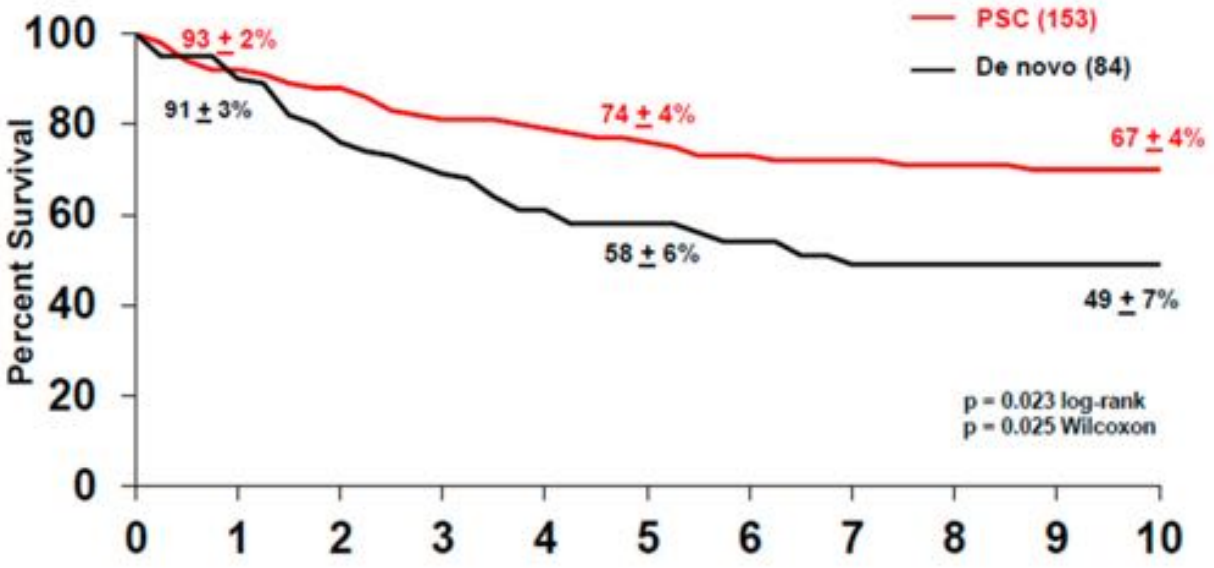


UHN Ajmera Transplant Centre

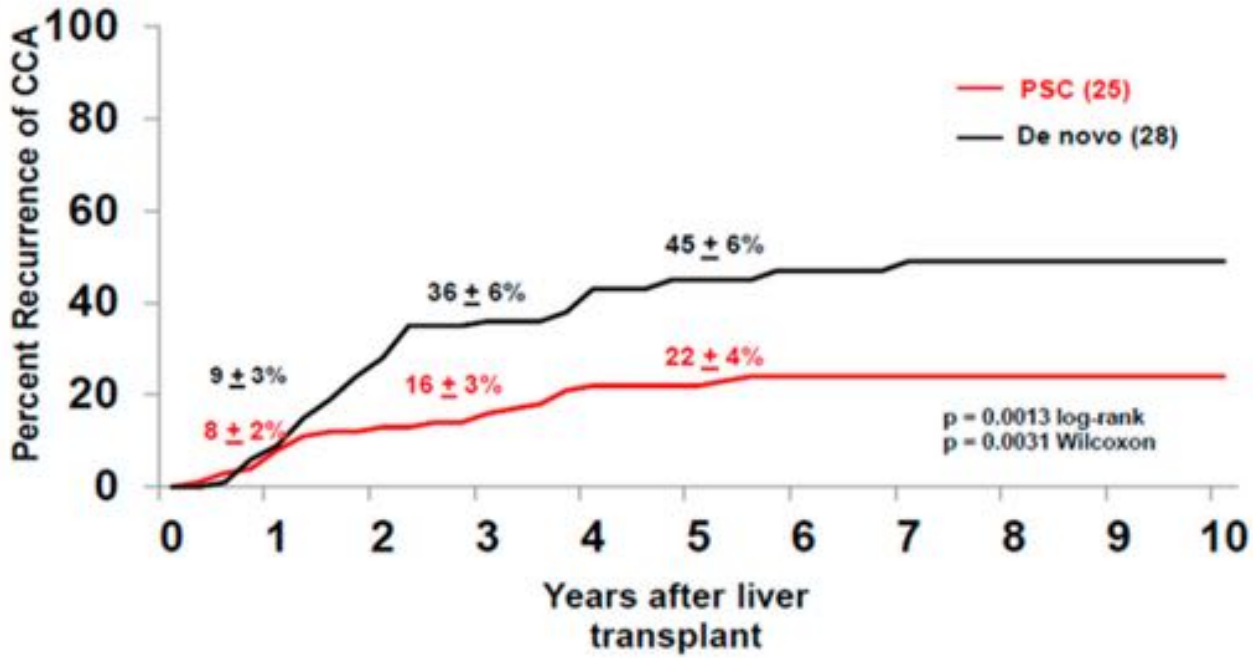
Azad AI, et al. Cancers 2020

Mayo Clinic Experience
Post-transplant Outcomes

Post-transplant Survival



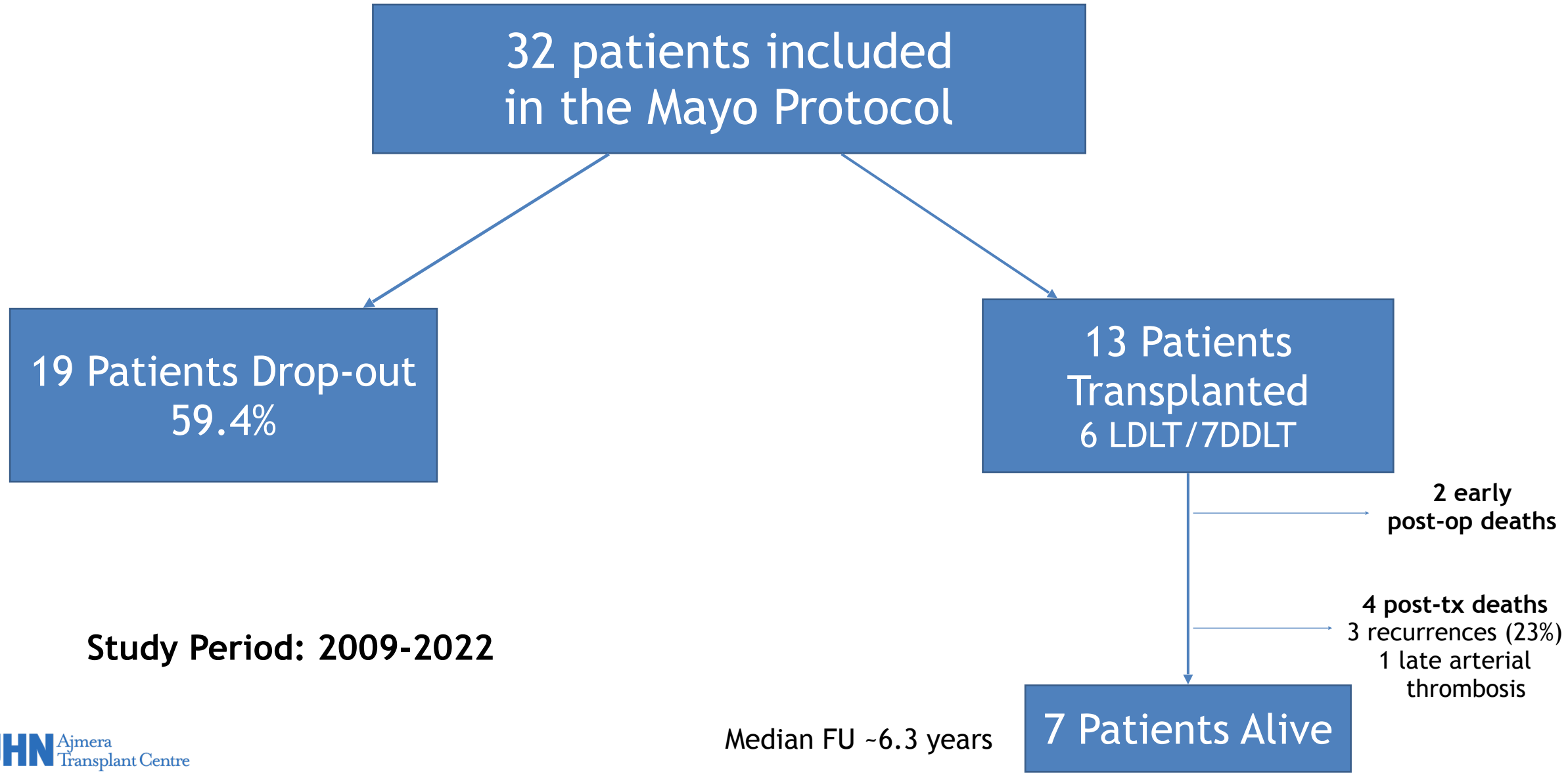
Post-transplant Risk of Recurrence



UHN Ajmera Transplant Centre

Azad Al, et al. Cancers 2020

Toronto Transplant Center Experience



Study Period: 2009-2022

Median FU ~6.3 years

UHN Ajmera Transplant Centre

Current Consensus for Liver Transplantation for "Transplant Oncology Consensus Conference"

INTERNATIONAL LIVER TRANSPLANTATION SOCIETY

ILTS CONSENSUS CONFERENCE 2019
ROTTERDAM | NETHERLANDS
FEBRUARY 7, 2019

1. Inclusion Criteria for LT based on Mayo Clinic Criteria.

2. Patients should undergo neoadjuvant chemoradiation prior to LT.

3. Due to organ allocation issues (US/Canada) LDLT is possibly the preferred option.

4. Surgical Technique:
   - Have available venous and arterial grafts both for LDLT and DDLT.

Take Home Message – Relevant Questions

- Liver Resection and portal lymphadenectomy should be the treatment of choice for single iCCA.

- Cirrhotic patients with unresectable single iCCA ≤3cm should be offered a LT.

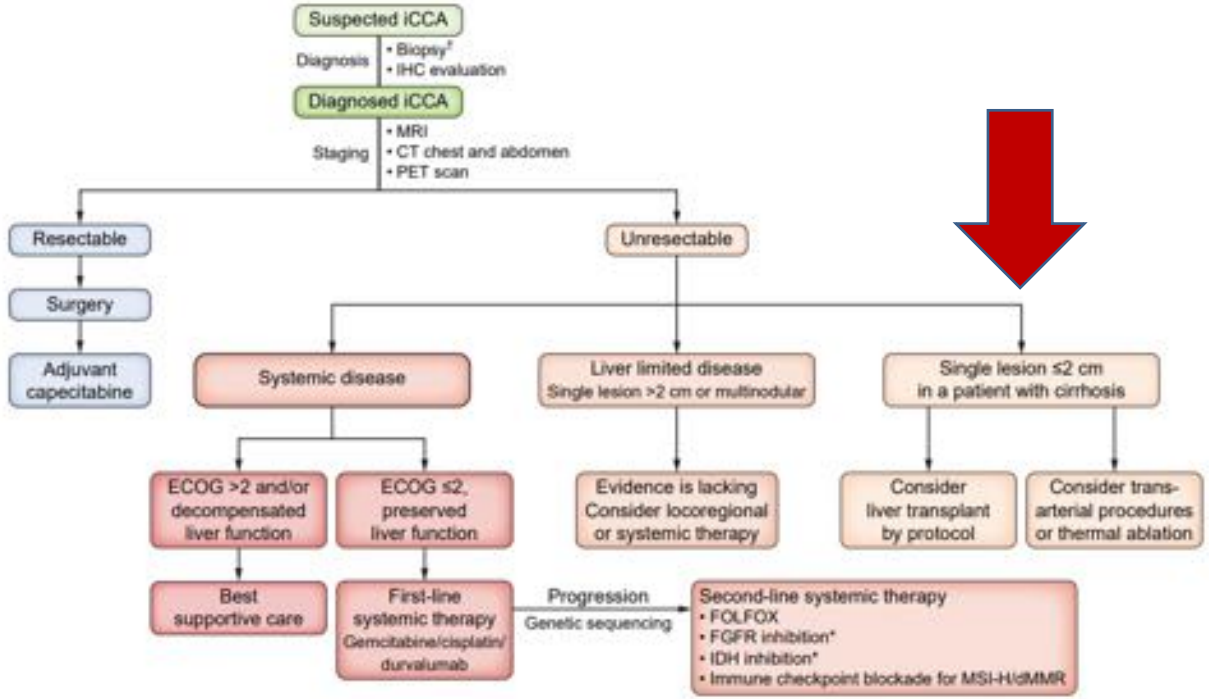
- Patients with larger and multifocal iCCA may benefit from LT but:
  - Better biomarkers needed
  - Enrich for favorable genetic alterations?
  - Neoadjuvant protocols?
  - Adjuvant treatment?

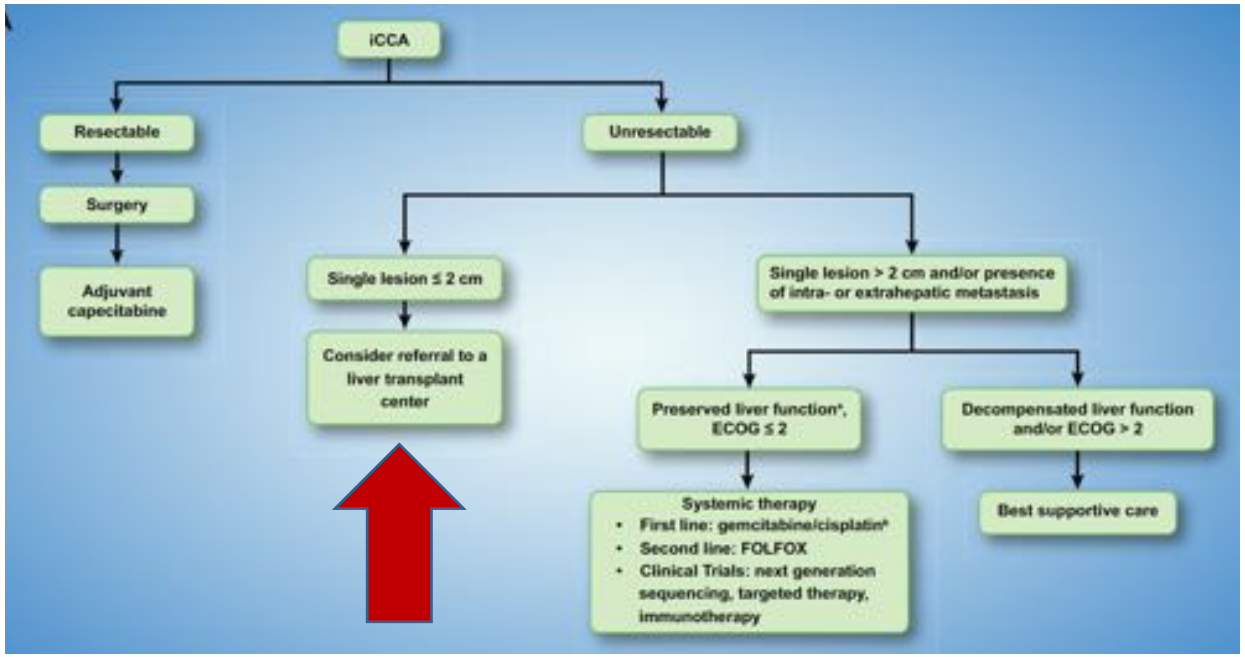
@sapisochin

Gonzalo.Sapisochin@uhn.ca

UHN Ajmera Transplant Centre

American Association Study of the Liver CCA Guidelines
ILCA and EASL Guidelines





UHN Ajmera Transplant Centre

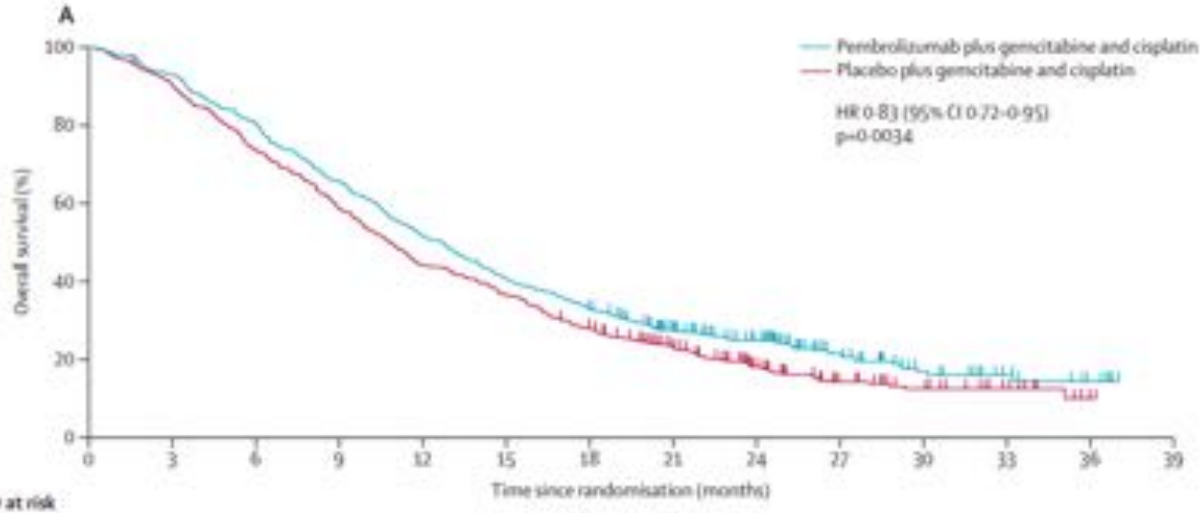
Bowlus CL, Sapisochin G et al. Hepatology 2022
EASL. J Hep 2023

Liver Transplantation for Early Intrahepatic Cholangiocarcinoma (LT for iCCA)

NCT02878473

PI Gonzalo Sapisochin, Toronto
Co-PI Jordi Bruix, BCLC, Barcelona

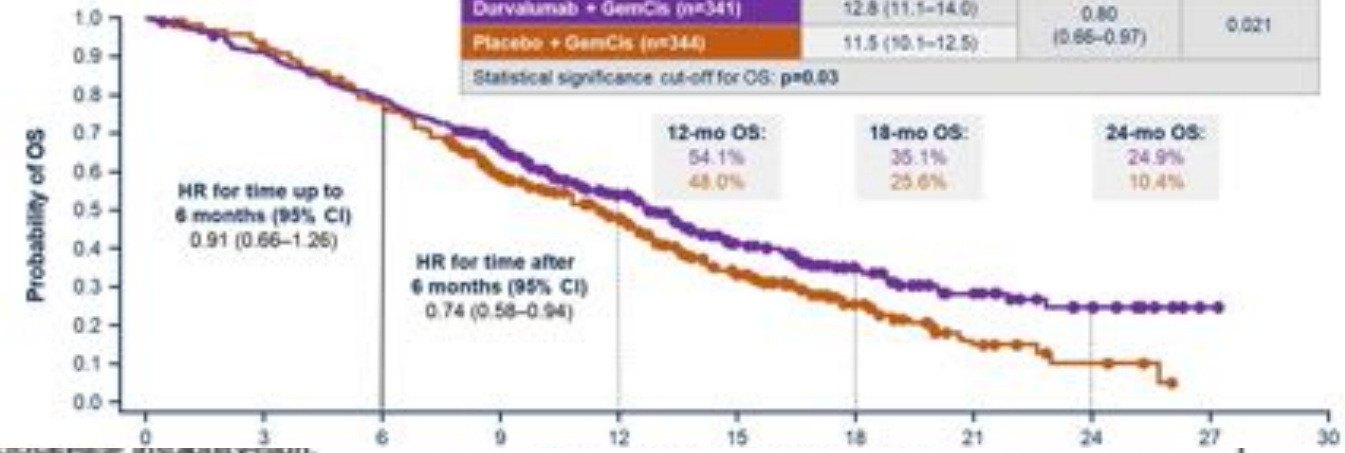
Sample Size **n=40**



Possible agents	ESCAT
Futibatinib (TAS-120),[30] Derazantinib (ARQ087),[30] Infigratinib (BJG398),[56] Erdafitinib[33] and Pemigatinib[35]	II-B
Ivosidenib[28] FT-1202	I-B
Pertuzumab–Trastuzumab[46]	–
Neratinib–Trastuzumab[46]	III-A
Pertuzumab–Trastuzumab[46] Durvalumab Pembrolizumab	II-B
Dabrafenib–trametinib[47]	III-A

*Experimental targets and drugs
BRCA2 m
EGRF mut amplifica
BRAF non mutation
c-MET am
BAP1/BRC DDR alte (SMARCA
EGFR amp
NTRK fusi
PIK3CA m

GBC gallbladder cancer, *ICCA* intrah
molecular Targets, *DDR* DNA-damage



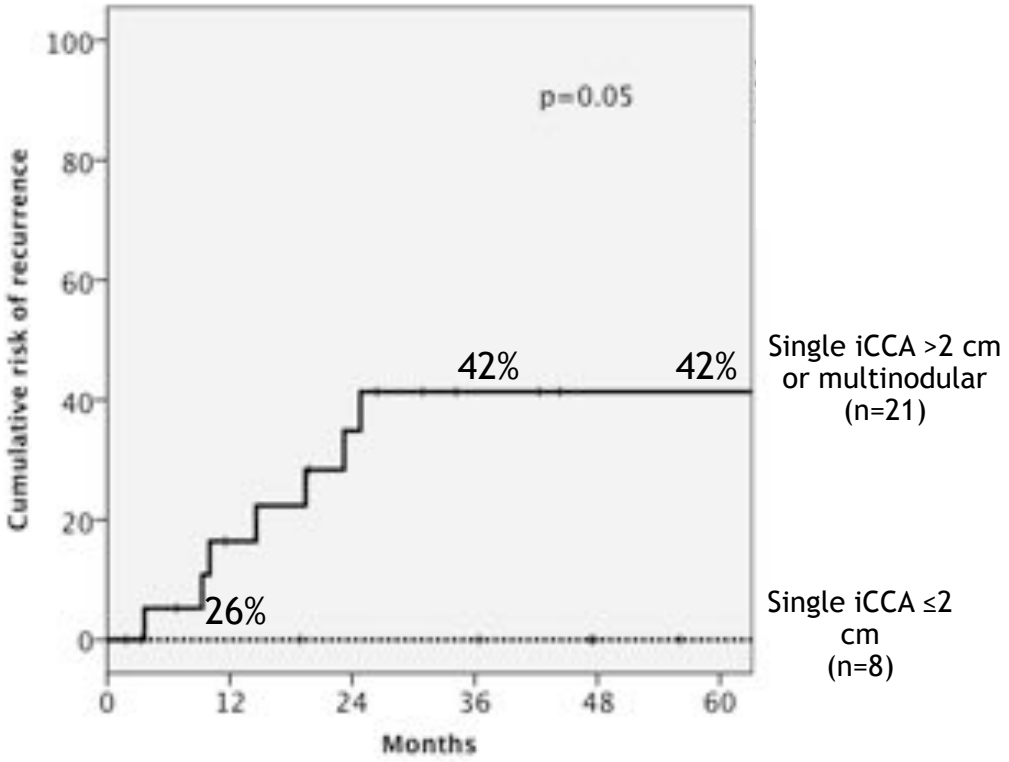
JJG Marin et al. British Journal of Cancer 2020
Oh DJ, et al. NEJM Evid 2022
Kelly K, et al. Lancet 2023

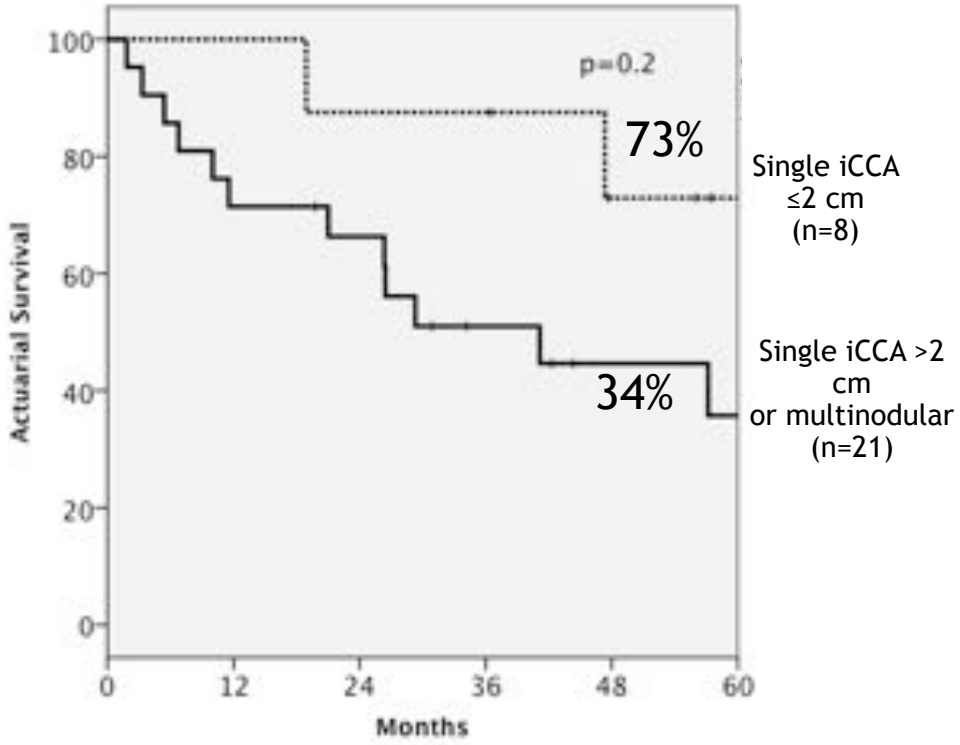
Liver Transplantation for iCCA

- LT is contraindicated in most centers due to poor results
- Studies are based on single center analysis with small number of patients
- Studies analyze patients with both iCCA and hilar cholangiocarcinoma
- Studies analyze patients with and without liver cirrhosis

Liver Transplantation for iCCa - Cirrhotics

"*Very Early*" Intrahepatic Cholangiocarcinoma in Cirrhotic Patients: Should Liver Transplantation Be Reconsidered in These Patients?



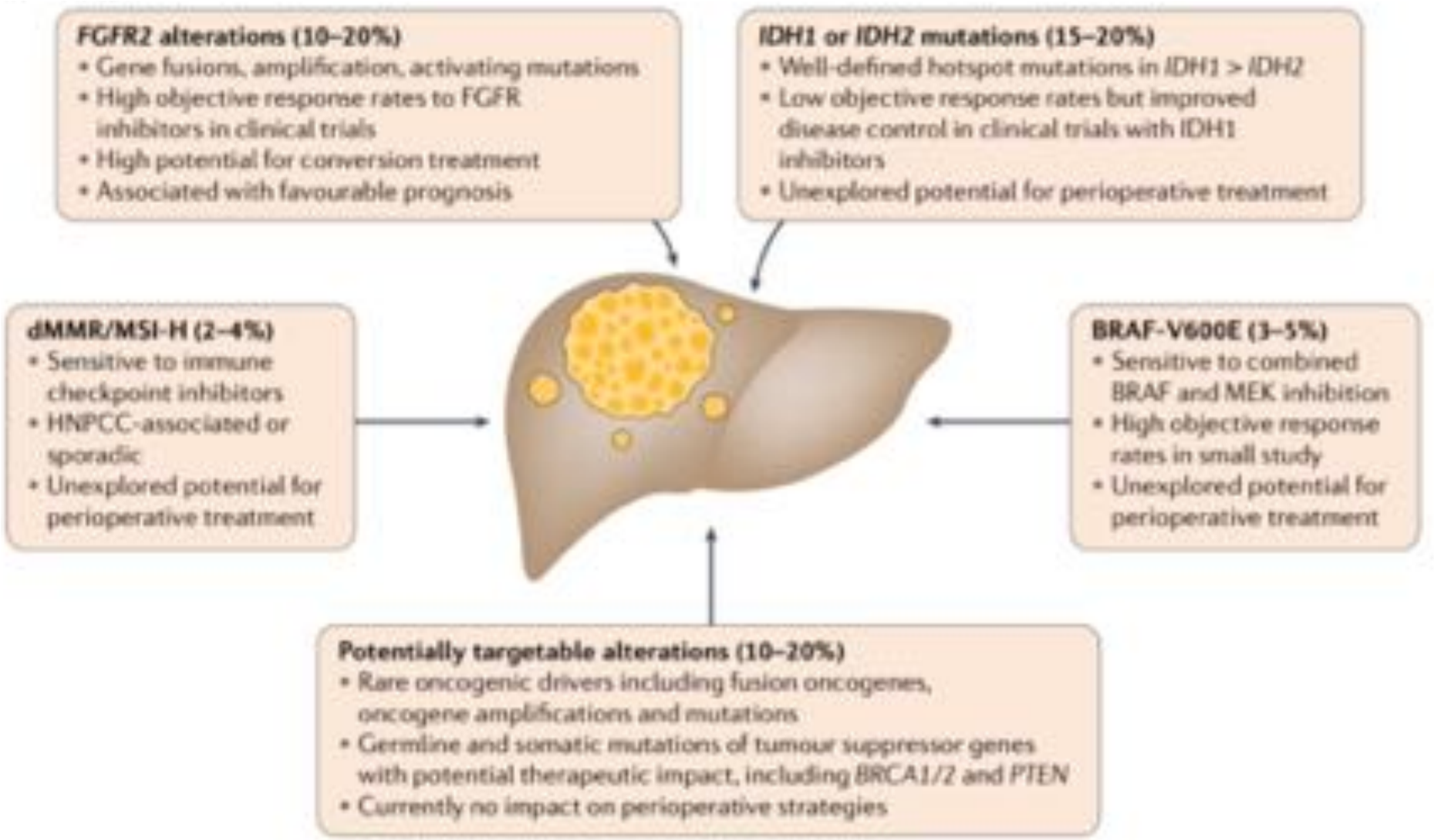


"Very Early" iCCa: Single tumor ≤2 cm

UHN Ajmera Transplant Centre

Sapisochin G, et al. Am J Transpl 2014

Importance of Targetable Genetic Alterations in iCCA



UHN Ajmera Transplant Centre

Petrowsky H, et al. Nature Rev Gastro and Hep 2020

Liver transplant for CCA

- Liver Transplantation for perihilar CCA is curative in selected patients under the Mayo Protocol.
- Liver Transplantation for patients with single iCCA <3cm (found at explant) can be curative.
- Liver Transplantation for patients with large or multifocal iCCA likely increases OS with a high recurrence rate.

Summary

- There is a new era of Transplant Oncology.

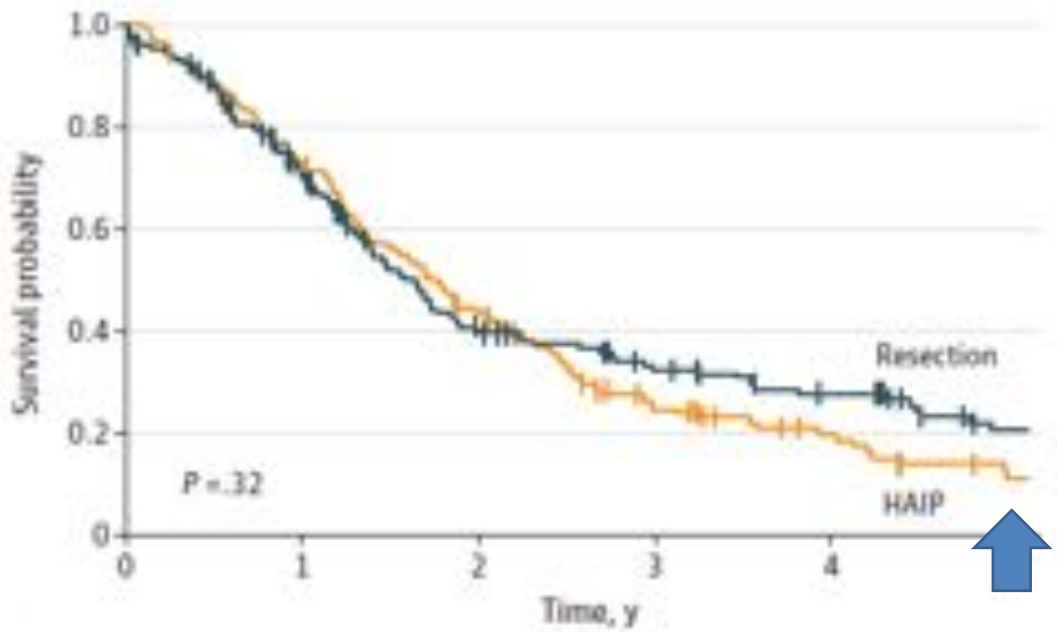
- Need further research in the 4Es.

- Collaboration between transplantation medicine, immunology and oncology will be crucial to move this field forward.

JAMA Surgery | Original Investigation

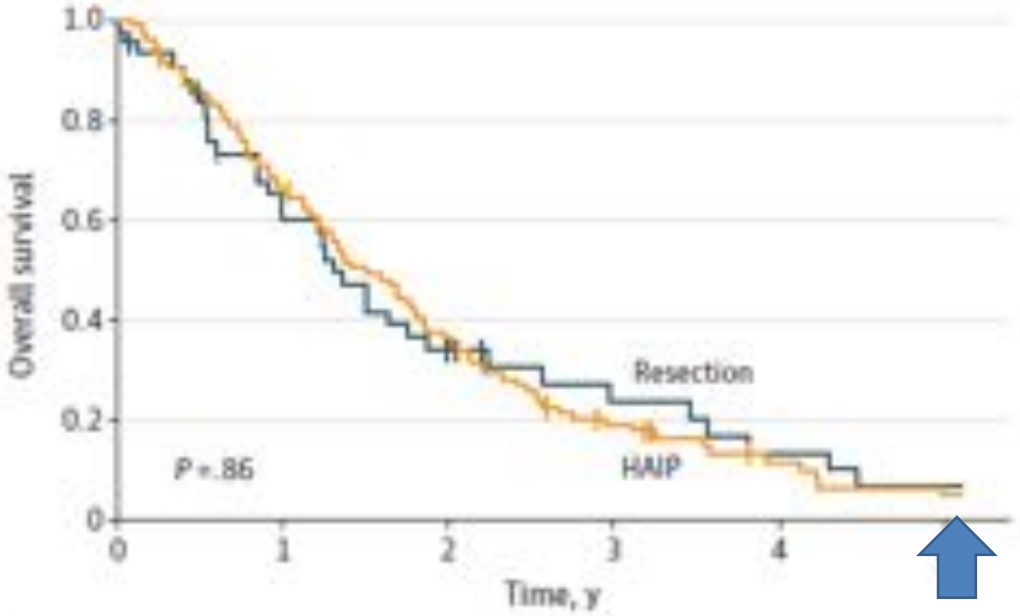
Comparison of Hepatic Arterial Infusion Pump Chemotherapy vs Resection for Patients With Multifocal Intrahepatic Cholangiocarcinoma

All-comers



No. at risk						
HAIP	141	102	60	30	17	7
Resection	178	111	57	39	29	1

4 lesions or more

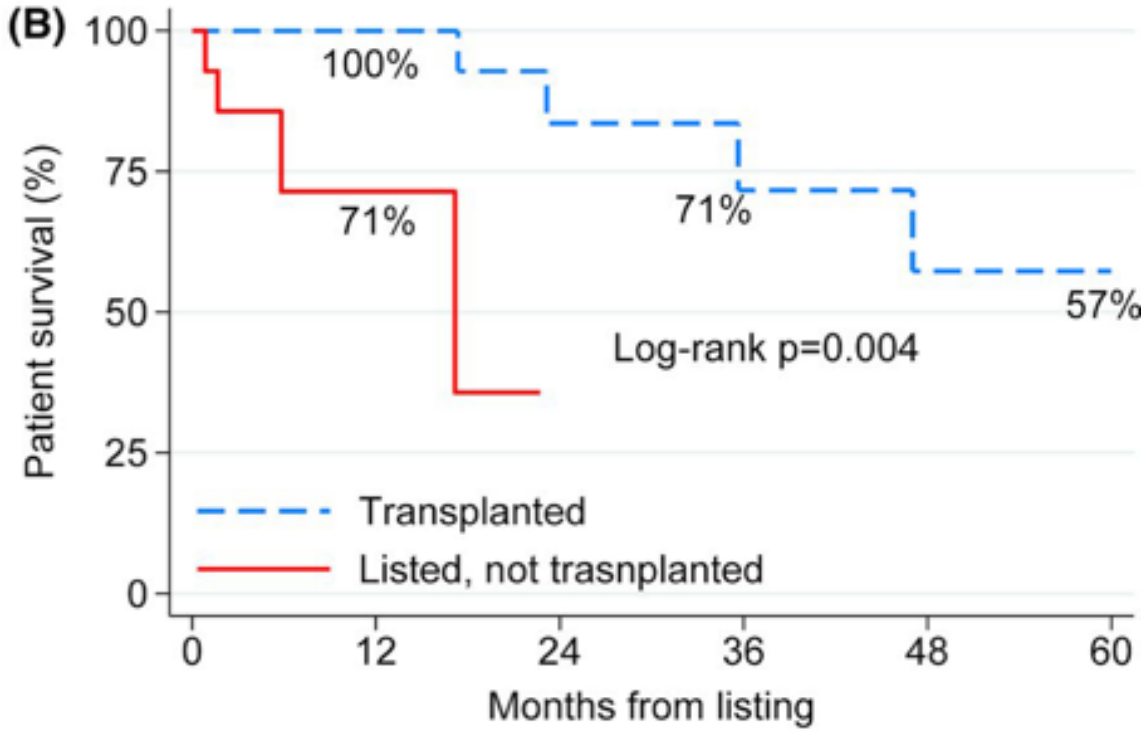


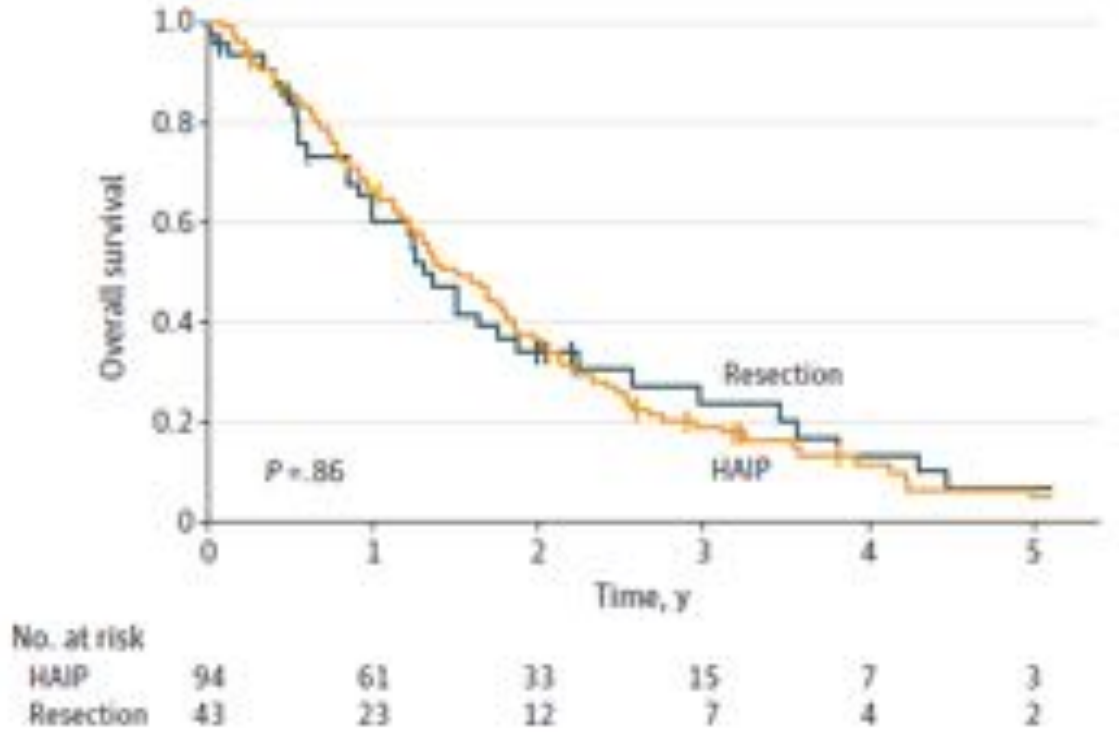
No. at risk						
HAIP	94	61	33	15	7	3
Resection	43	23	12	7	4	2

UHN Ajmera Transplant Centre

Franssen S, et al. JAMASurg 2022

Is HAIP a Good Strategy as a Bridge to Transplant?





McMillan R, et al. Am J Transplant 2021

Franssen S, et al. JAMASurg 2022

UHN Ajmera Transplant Centre

Take-home Messages

- LT is the BEST treatment option for HCC and should be offered to ALL patients (otherwise suitable) without EH disease and MVI.
- LT should be offered to patients with unresectable hCCA under the Mayo protocol.
- LT should be offered to cirrhotic patients with iCCA <3 cm.
- LT may be an option for patients with locally advanced iCCA and stable on systemic chemotherapy.
- LT is a treatment option for patients with liver-only metastases from CRC.

TAKE home

- Liver transplantation can be considered in selected patients with biliary tract cancer
  → Patients should be treated within clinical trials/transplant registries
- The benefit of transplantation must be weighted against the (high) risk of recurrence under immunosuppression

There are many open questions:

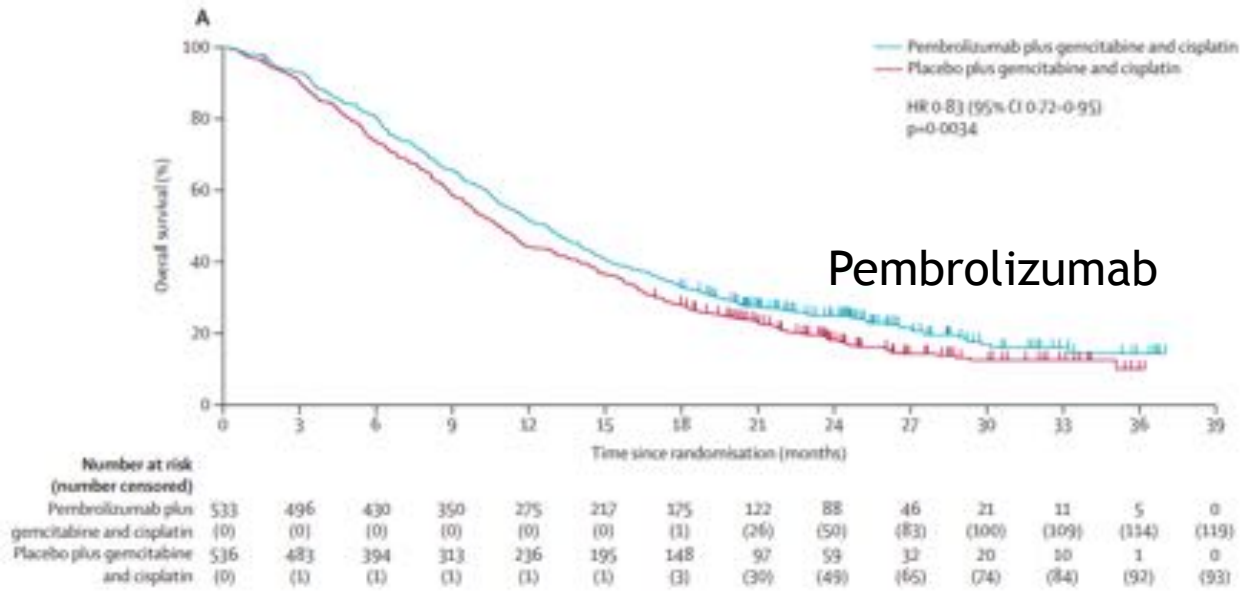
- **Who should be considered for transplantation?**
  → early CCCs (<2/ 5cm, unresectable, in cirrhotic livers, PSC?) -> early tumor with low risk of metastasis?
  → locally advanced CCCs after successful downstaging/-sizing -> test of „favourable“ biology > 6 months?
  -> CTx (+ICI) and targeted therapies may offer more oppertunities for deep response

- **How can we predict outcome prognosis?**
  → We need biomarkers
  → blood vs bile vs tissue

- **How can we prevent recurrence?**
  → So far, onlylimited evidence that adjuvant therapy improves outcome after liver resection -> Benefit in the transplant setting uncertain
  → Neoadjuvant strategies should be SOC -> CTx vs R-CTx? Role of ICI & targeted therapies?

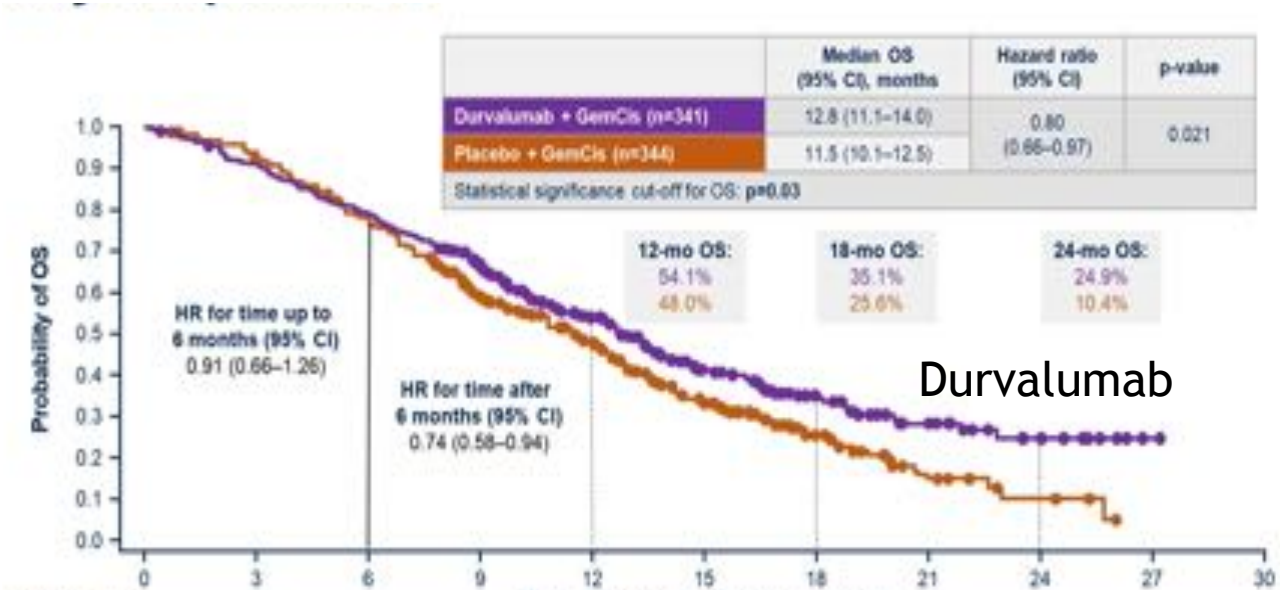
Positive Impact of Immunotherapy in Patients with Advanced BTC

Keynote 966



Pembrolizumab

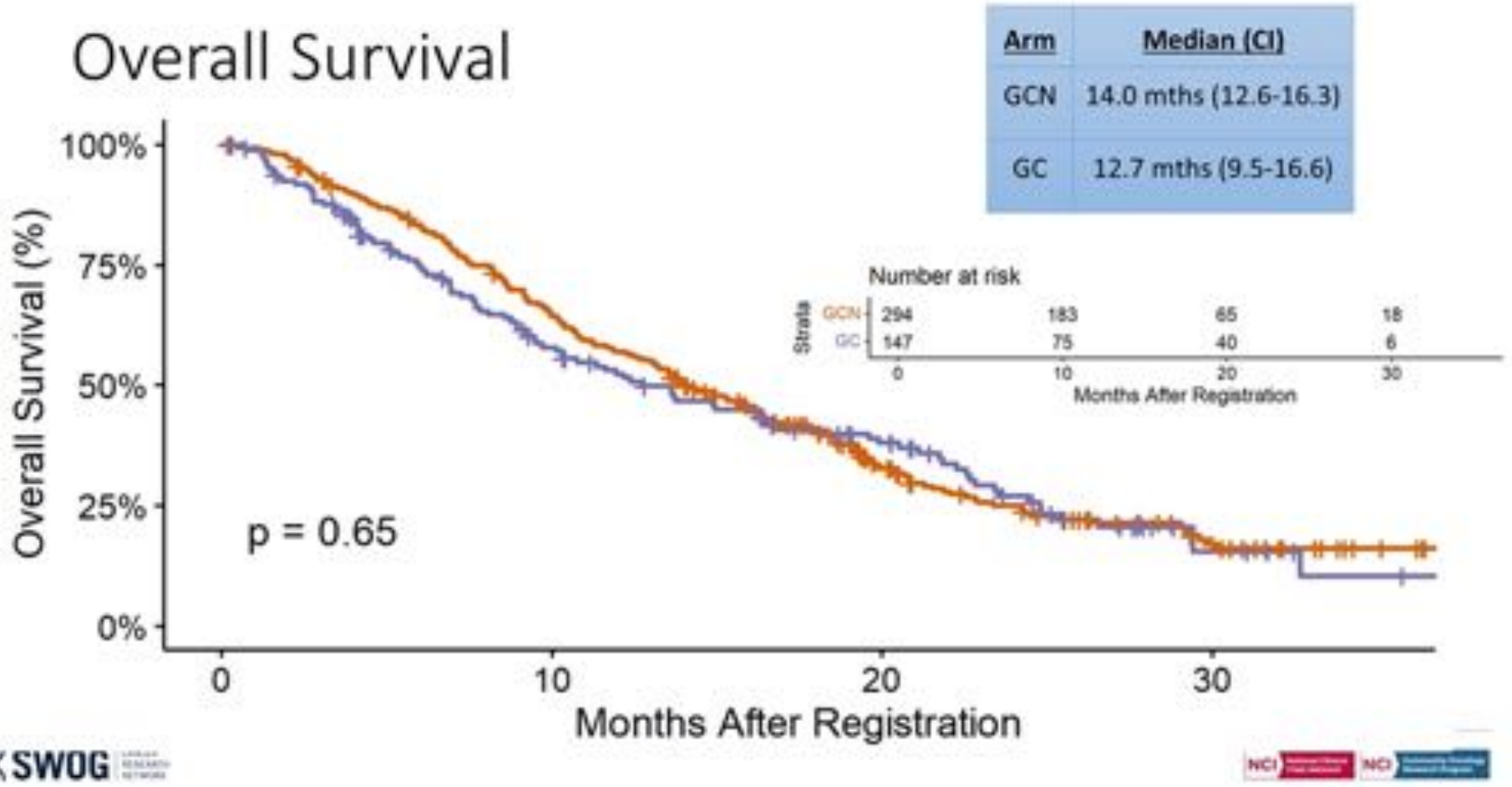
Topaz-1



Durvalumab

Oh DJ, et al. NEJM Evid 2022
Kelly K, et al. Lancet 2023

Gem-Cis Nab-Paclitaxel as Neoadjuvant?



Arm	Median (CI)
GCN	14.0 mths (12.6-16.3)
GC	12.7 mths (9.5-16.6)

iCCA

ORR
GC 22%
GCN 27%

UHN Ajmera Transplant Centre