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28th ANNUAL CONGRESS • 17-19 JUNE 2026
Perth Convention and Exhibition Centre

The Evolving Role of Liver Transplantation in Cancer

Arul Suthananthan

Hepatopancreaticobiliary and Liver Transplant Surgeon

WA Liver & Kidney Transplant Unit
Sir Charles Gairdner Hospital

Disclosures

None

Transplant Oncology - Why This Matters Now

Historically

- Transplantation reserved for:
  - End-stage liver disease
  - Selected HCC

Today

- Transplant oncology is expanding into:
  - HCC
  - Perihilar cholangiocarcinoma
  - Intrahepatic cholangiocarcinoma
  - Colorectal liver metastases
  - Neuroendocrine liver metastases

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Key question:

Can transplantation provide cure where conventional surgery cannot?

Transplant Oncology - Relevance

DISCLAIMER:

- Not for all kinds of cancer in the liver
- Not Experimental
- Evidence based medicine
- Standard indication now globally

Concept of Transplant Oncology

Goals:

- Remove tumour
- Remove underlying diseased liver

Concept of Transplant Oncology

Goals:

- Remove tumour
- Remove underlying diseased liver
- Reduce recurrence
- Improve long-term survival

When is a liver cancer a transplant indication rather than a contraindication?

When is a liver cancer a transplant indication rather than a contraindication?

The indication is favourable biology, demonstrated over time, in a patient for whom no better therapy exists — and a graft that the system can ethically spare

HCC: The Original Success Story

Before Milan

- 5-year survival: 20–30%
- Recurrence: Extremely high

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Milan Criteria

- Single lesion ≤5 cm OR Up to 3 lesions ≤3 cm
- Result:
  - 5-year survival >70%
  - Recurrence <15%
- Changed global practice

Beyond Milan – Sized based criteria

Expansion of selection criteria

- UCSF
- Up-to-Seven

Beyond Milan – Size + Biology based criteria

Expansion of selection criteria

- UCSF
- Up-to-Seven
- Metroticket 2.0
  - Size of largest nodule
  - Number of nodules
  - **AFP**

Criteria	Typical 5-year Overall Survival
Milan	70–85%
UCSF	70–80%
Up-to-7	65–75%
MetroTicket 2.0	70–80%

MT2 allows more patients to be transplanted while maintaining acceptable survival outcomes.

Modern HCC Selection

Shift from:

- "How big is the tumour?"

To

- "How aggressive is the tumour?"

Morphology vs Biology

MORPHOLOGY

What the tumour looks like

- Size, number, location, vascular invasion on imaging.
- Static — captured at the moment of staging.
- Milan 1996 was a morphology contract, validated by 4-year OS 75%.

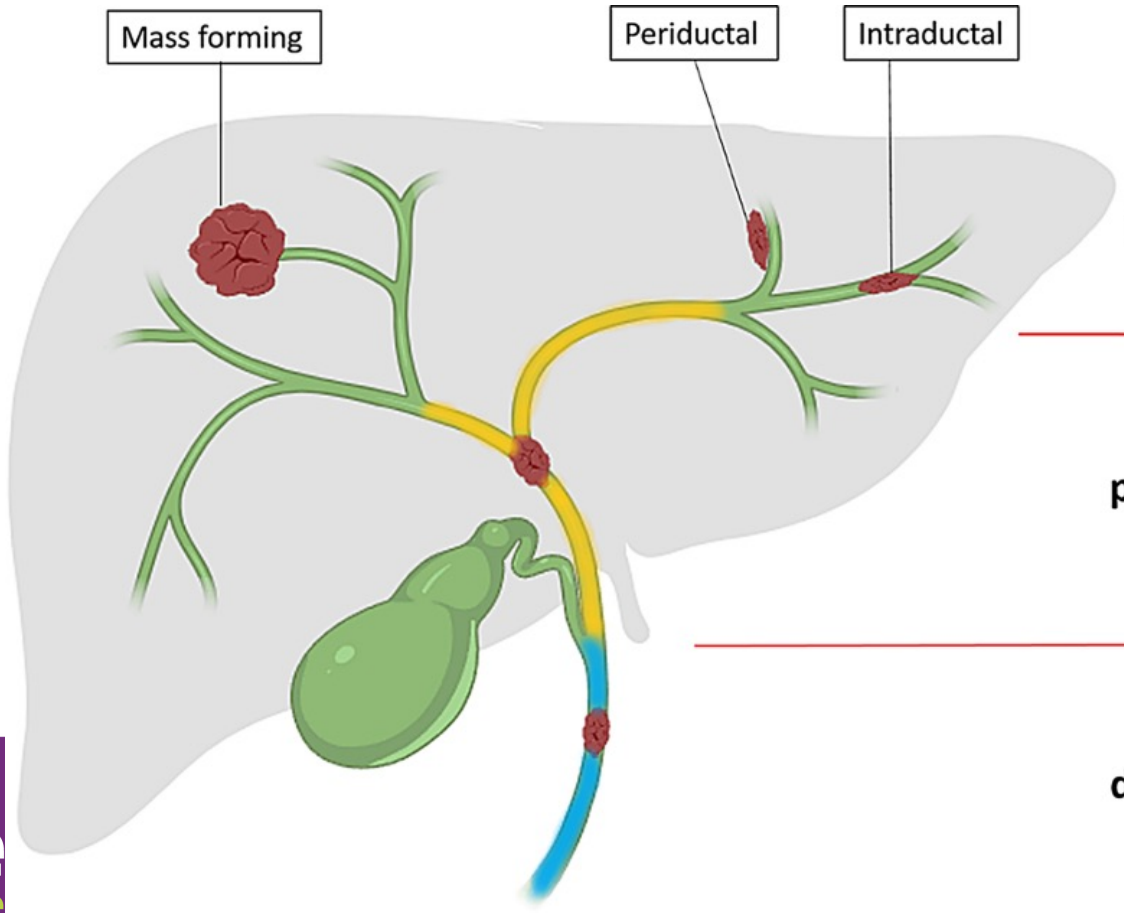
BIOLOGY

How the tumour behaves

- Grade, differentiation, molecular profile, AFP / CEA / CgA / Ki-67.
- Response to neoadjuvant therapy and stability on imaging over time.
- Macrovascular invasion, nodal status, extrahepatic disease.
- Metroticket 2.0, AFP model, Mayo pCCA protocol, SECA / TransMet — every modern selection rule is fundamentally biological.

PERIHILAR CHOLANGIOCARCINOMA

Perihilar Cholangiocarcinoma

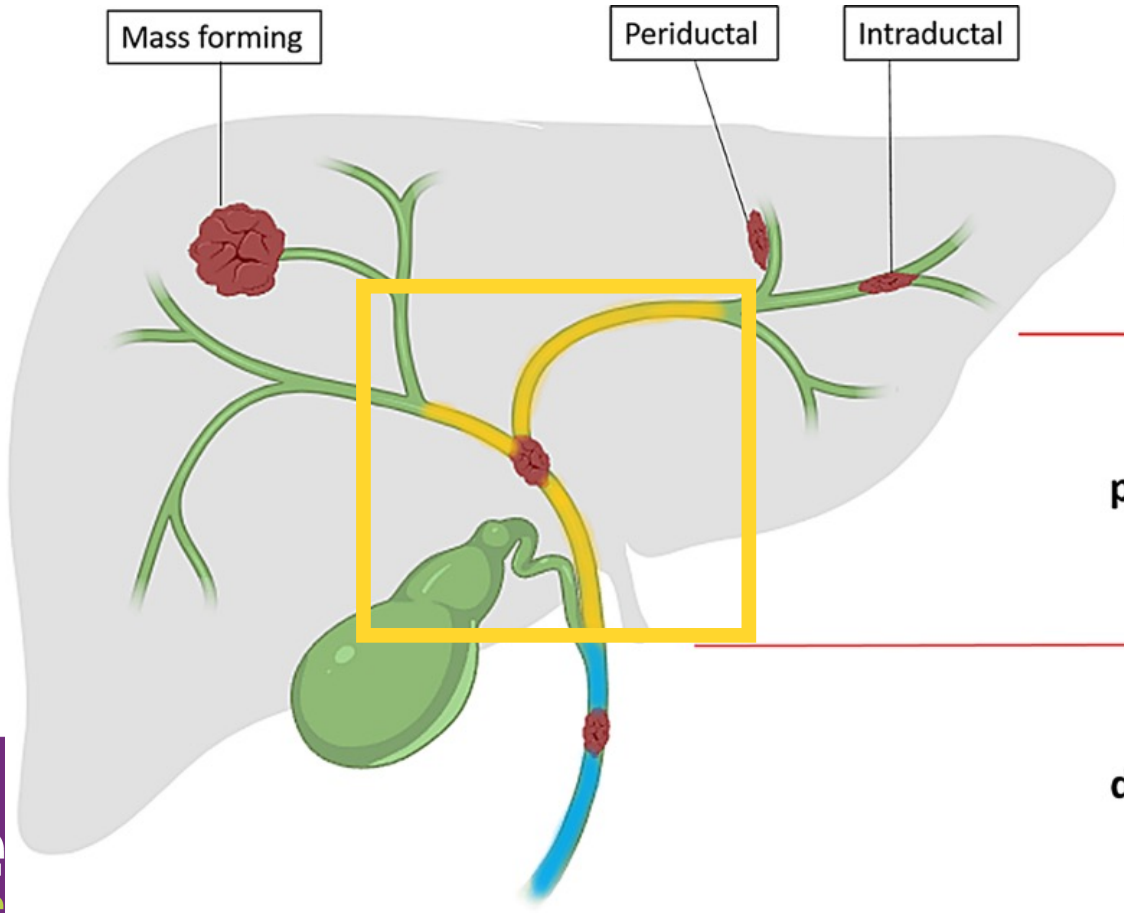


iCCA (10%) — Bile ductules ↕ Segmental bile ducts

pCCA (70%) — Right, left and common hepatic ducts

dCCA (20%) — Common Bile duct

Perihilar Cholangiocarcinoma



iCCA (10%) — Bile ductules ↕ Segmental bile ducts

pCCA (70%) — Right, left and common hepatic ducts

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Perihilar Cholangiocarcinoma

- pCCA accounts for ~50–60% of all cholangiocarcinomas.

- Very aggressive disease
  - Most patients present with locally advanced disease.
  - Complete surgical resection (R0) is challenging.
  - Even after R0 resection: 5-year survival typically 20–40%.
  - Recurrence rates remain high

Perihilar Cholangiocarcinoma

- Transplant advantages:
  - Removes the entire biliary tree (no residual disase)
  - Removes occult multifocal disease.
  - Treats underlying PSC simultaneously.

Perihilar Cholangiocarcinoma

- Historical Outcomes
  - Early liver transplantation for pCCA performed poorly:
    - 5-year survival <30%.
    - High recurrence rates.
  - No patient selection
  - No neoadjuvant therapy.

Perihilar Cholangiocarcinoma – Mayo Protocol

Selection Criteria

- Unresectable pCCA OR pCCA in PSC.
- Tumour <3 cm.
- No metastases.
- No nodal disease.

Liver transplantation for unresectable perihilar cholangiocarcinoma

Julie K Heimbach [1], Gregory J Gores, Michael G Haddock, Steven R Alberts, Scott L Nyberg, Michael B Ishitani, Charles B Rosen

Affiliations + expand

Perihilar Cholangiocarcinoma – Mayo Protocol

Selection Criteria

- Unresectable pCCA OR pCCA in PSC.
- Tumour <3 cm.
- No metastases.
- No nodal disease.

Treatment Pathway

- External beam radiotherapy
- Brachytherapy
- Capecitabine maintenance
- Operative staging
- Liver transplantation

Perihilar Cholangiocarcinoma

- Outcomes of the Mayo Protocol:
  - 5-year overall survival ≈60-80%.
  - reproducible outcomes when adopted in other centres

Heimbach et al. Semin Liver Dis 2004
Rea et al. Ann Surg 2005
Murad et al. Gastroenterology 2012

Perihilar Cholangiocarcinoma

- Outcomes of the Mayo Protocol:
  - 5-year overall survival ≈70–75%.
  - reproducible outcomes when adopted in other centres

Treatment	5-year survival
Resection	20–40%
Transplantation	60–80%

TSANZ Guidelines

- Inclusion:
  - Unresectable (or resectable with PSC)
  - Mass <3cm
  - Biopsy proven (or clinical suspicion with 2x failed biopsies)

- Exclusion:
  - Metastatic disease (including nodal)
  - Trans-peritoneal biopsy
  - Do not fulfill general tx indications

TSANZ Guidelines

Staging (laparoscopy + EUS nodal sampling)

↓

Chemo (Gemcitabine + Cisplatin) + Radiotherapy (CK)

↓ Stability

Repeat staging

↓

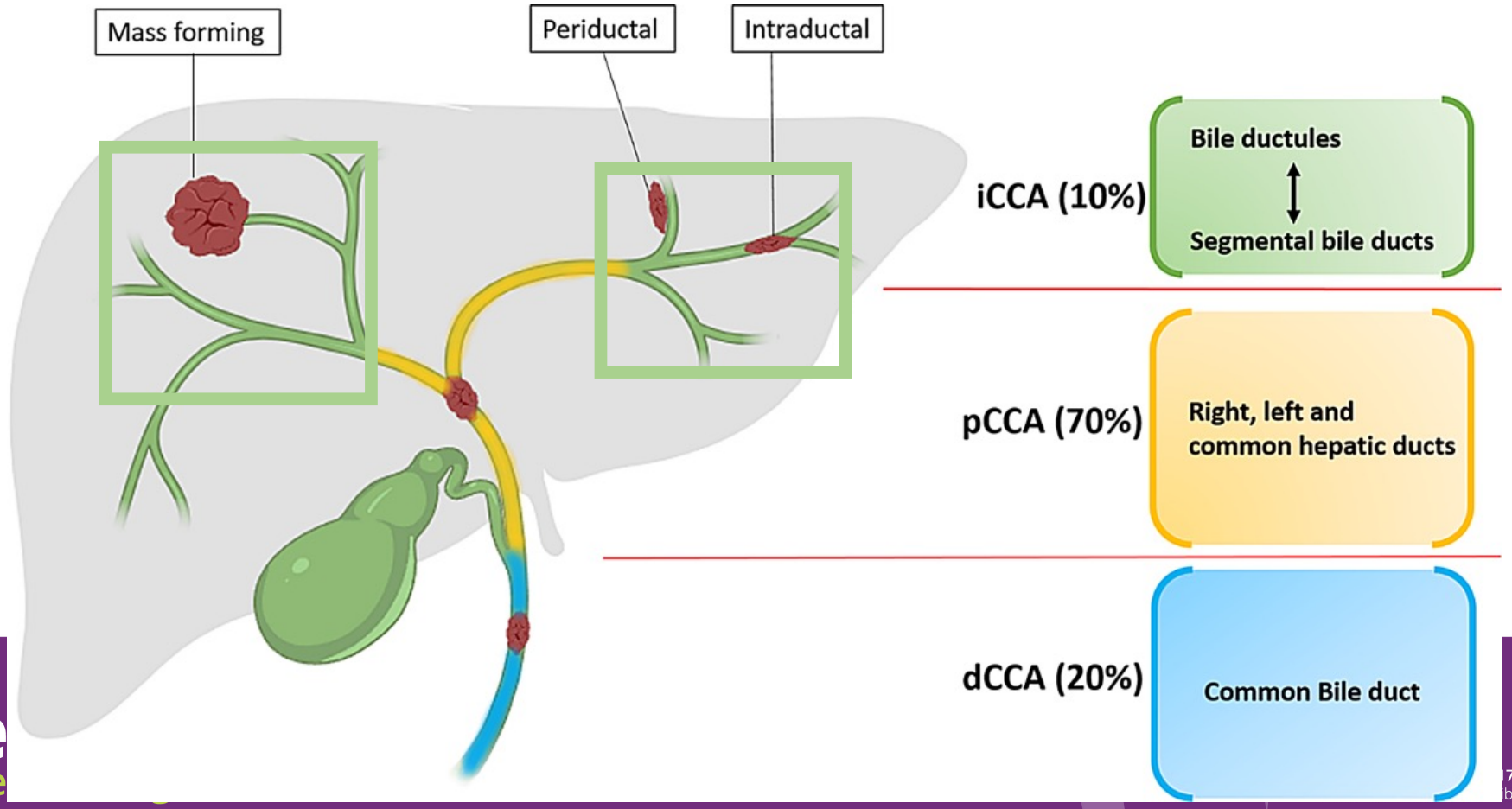
Transplant Assessment + Waitlisting

↓ Maintenance chemo

Transplant

INTRAHEPATIC CHOLANGIOCARCINOMA

Intrahepatic Cholangiocarcinoma



Transplantation in Intrahepatic CCA (iCCA)

- Historical Perspective
  - Poor outcomes → contraindicated
  - 5-year survival <25%

- Emerging Indications
  - Very Early iCCA (≤2 cm, +/- cirrhosis)
    - Often incidental
    - 5-year survival: ~65–70% (Comparable to HCC)

Transplantation in Intrahepatic CCA (iCCA)

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

G. Sapisochin[1,*], C. Rodríguez de Lope[2], M. Gastaca[3], J. Ortiz de Urbina[3], M. A. Suarez[4], J. Santoyo[4], J. F. Castroagudín[5], E. Varo[5], R. López-Andujar[6], F. Palacios[6], G. Sanchez Antolín[7], B. Perez[8], A. Guiberteau[9], G. Blanco[9], M. L. González-Diéguez[10], M. Rodriguez[10], M. A. Varona[11], M. A. Barrera[11], Y. Fundora[12], J. A. Ferron[12], E. Ramos[13], J. Fabregat[13], R. Ciria[14], S. Rufian[14], A. Otero[15], M. A. Vazquez[15], J. A. Pons[16], P. Parrilla[17], G. Zozaya[18], J. I. Herrero[19], R. Charco[1] and J. Bruix[20,*]

Hepáticas y Digestivas (CIBERehd), Hospital Universitario Virgen de la Arrixaca, Murcia, Spain
[17]Liver Transplant and Hepatology Unit, Department of Surgery, Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBERehd), Hospital Universitario Virgen de la Arrixaca, Murcia, Spain
[18]Department of General Surgery, Clínica Universidad de Navarra, Pamplona, Spain
[19]Liver Unit, Clínica Universidad de Navarra, Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBERehd), Pamplona, Spain
[20]Barcelona Clinic Liver Cancer (BCLC) Group, Liver Unit, ICMDM, Hospital Clínic, IDIBAPS, University of Barcelona, Centro de Investigación Biomédica en Red de

- N= 29
- 8 patients with tumour <2cm
- 5YS 73%

Transplantation in Intrahepatic CCA (iCCA)

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

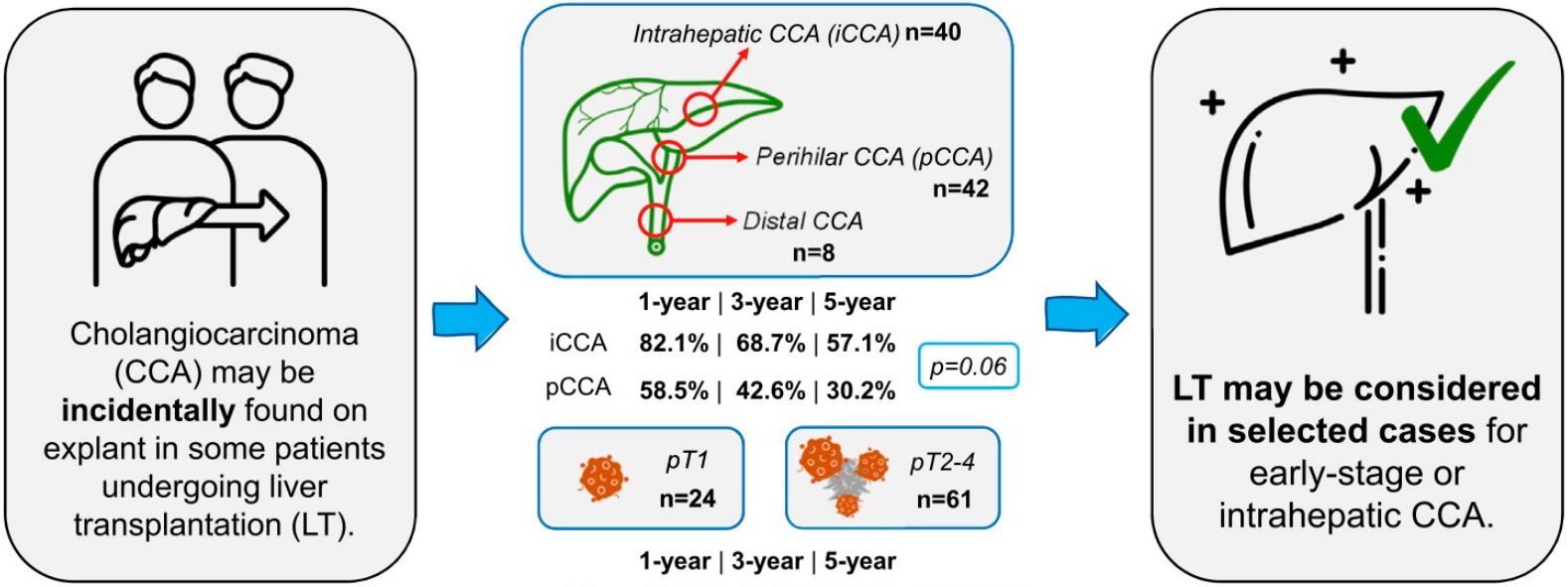
G. Sapisochin,[1] M. Facciuto,[2] L. Rubbia-Brandt,[3] J. Marti,[2] N. Mehta,[4] F.Y. Yao,[4] E. Vibert,[5] D. Cherqui,[5] D.R. Grant,[1] R. Hernandez-Alejandro,[6] C.H. Dale,[6] A. Cucchetti,[7] A. Pinna,[7] S. Hwang,[8] S.G. Lee,[8] V.G. Agopian,[9] R.W. Busuttil,[9] S. Rizvi,[10] J.K. Heimbach,[10] M. Montenovo,[11] J. Reyes,[11] M. Cesaretti,[12] O. Soubrane,[12] T. Reichman,[13] J. Seal,[13] P.T.W. Kim,[14] G. Klintmalm,[14] C. Sposito,[15] V. Mazzaferro,[15] P. Dutkowski,[16] P.A. Clavien,[16] C. Toso,[17] P. Majno,[17] N. Kneteman,[18] C. Saunders,[18] and J. Bruix[19]; on behalf of the iCCA International Consortium

Explants with incidental iCCA

- n=48
- 15/48 (31%) <2cm
- 33/48 (69%) >2cm

5YS 65% vs 45%

Outcomes after liver transplantation with incidental cholangiocarcinoma



Nawaz Safdar, et al. *Transpl. Int.* 2022
doi: 10.3389/ti.2022.10802

GRAPHICAL ABSTRACT |

Transplantation in Intrahepatic CCA (iCCA)

- Historical Perspective
  - Poor outcomes → contraindicated
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- Emerging Indications
  - Very Early iCCA (≤2 cm + cirrhosis)
    - Often incidental
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- Inclusion:
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  - Mass <2cm
  - + Cirrhosis

- Exclusion:
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TSANZ - WA Guidelines

- Inclusion:
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  - Mass <2cm
  - + Cirrhosis

- Exclusion:
  - Metastatic disease (including nodal)
  - Do not fulfill general tx indications

Summary

- Liver transplantation for unresectable liver cancer can provide a survival advantage in a well selected cohort
- Selection criteria will continue to evolve – molecular profiling, role of ctDNA
- Utilitarian argument: Organ scarcity
- High volume workup load for low volume transplantation
  - Low threshold for referrals
  - High threshold for elegibility
  - Stricter criteria during learning curve