Current Oncological Considerations in Liver Transplant

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Financial Disclosures

I have no financial relationships with commercial interests to disclose.

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Objectives

1. Understand the concept of transplant oncology.
2. Identify emerging indications for liver transplant in metastatic colorectal cancer and intrahepatic cholangiocarcinoma.
3. Identify future challenges and opportunities to improve the field.

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Is Transplant Oncology a New Concept?

No.	Location (ref.)	Age (yr)	Disease	Survival (days)	Main cause of death
1	Denver (1)	3	Extrahepatic biliary atresia	0	Hemorrhage
2	Denver (1)	48	Hepatocellular cancer, cirrhosis	22	Pulmonary emboli, sepsis
3	Denver (1)	68	Duct cell carcinoma	7½	Sepsis, pulmonary emboli, gastrointestinal bleeding
4	Denver (2)	52	Hepatocellular cancer, cirrhosis	6½	Pulmonary emboli, ? hepatic failure, pulmonary edema
5	Boston (3)	58	Metastatic colon carcinoma	11	Pneumonitis, liver abscesses, hepatic failure
6	Denver (2)	29	Hepatocellular cancer, cirrhosis	23	Sepsis, bile peritonitis, hepatic failure
7	Paris (4)	75	Metastatic colon carcinoma	0	Hemorrhage

Starzl et al, Hepatology, Sept. 1982

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journal homepage: www.elsevier.com/locate/surg

Clinical Review

What is transplant oncology?

Taizo Hibi, MD, PhD[a,*], Gonzalo Sapisochin, MD[b]

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[b] Multi-Organ Transplant and Hepato-Pancreato-Biliary Surgical Oncology, University Health Network, University of Toronto, Toronto, Canada

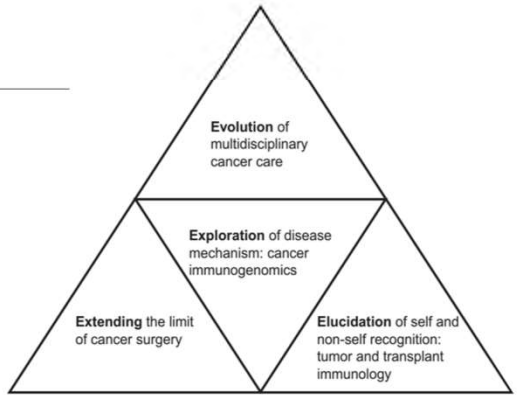

Fig. 1. The 4 Es of transplant oncology.

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Metastatic Colorectal Cancer

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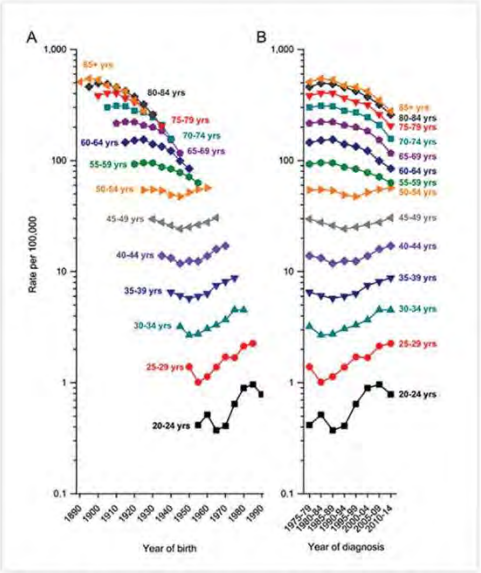
Background

- 151 030 new cases of CRC in 2021:
  50% have liver metastases at time of diagnosis or within 3 years of primary resection
- If metastases are resectable (20% of cases), 5-year survival is around 40%
- If metastases are unresectable, 5-year survival is around 5-10% with chemo

Figure 1. Trends in colorectal cancer incidence rates by age and year of birth, and by age and year of diagnosis, U.S., 1975 to 2014



Source: Wolf AMD, Fontham ETH, Church TR, et al. Colorectal screening for average-risk adults: 2018 guideline update from the American Cancer Society. CA Cancer J Clin. 2018;68(4):250-281.

Valderrama-Treviño et al, Euroasian J Hepatogastroenterol, Sept. 2017

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The First Prospective Pilot Study

SECA 1

Liver Transplantation for Nonresectable Liver Metastases From Colorectal Cancer

Hagness, Morten MD[*,†]; Foss, Aksel MD, PhD[*,†]; Line, Pål-Dag MD, PhD[*]; Scholz, Tim MD, PhD[*]; Jørgensen, Pål Foyn MD, PhD[*]; Fosby, Bjarte MD[*,†]; Boberg, Kirsten Muri MD, PhD[‡]; Mathisen, Øystein MD, PhD[§]; Gladhaug, Ivar P. MD, PhD[†,§]; Egge, Tor Skatvedt MD[¶]; Solberg, Steinar MD, PhD[‖]; Hausken, John MD[**]; Dueland, Svein MD, PhD[††]

N = 21

Main Inclusion Criteria:
- Complete radical excision of the primary tumor
- Absence of extrahepatic disease: assessed by total body CT, whole-body PET CT, and bone scan
- Good performance status (ECOG 0 - 1)
- Minimum 6 weeks of chemotherapy

Main Exclusion Criteria:
- Weight loss of more than 10%
- Standard contraindications for liver transplantation
- Other malignancies

At the time of admission for LT, a repeat chest CT scan and a perioperative staging laparotomy were performed.

Post LT, basiliximab was used for induction. Patients were maintained on an mTOR inhibitor + MMF.

Hagness et al, Annals of Surgery, May 2013

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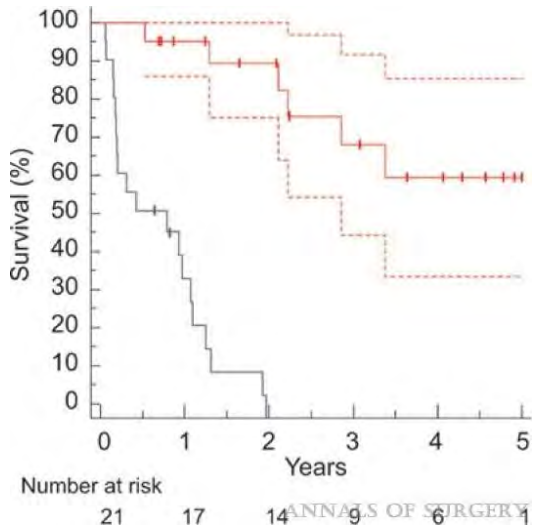

Median FU 27 months (8 – 60)

Red line: OS rate 95%, 68%, and 60% at 1, 3, and 5 years

Blue line: DFS rate 35% at 1 year, 0% at 3 years

Median time to recurrence was 8.0 months
- Lung 80%
- Liver 33%

Hagness et al, Annals of Surgery, May 2013

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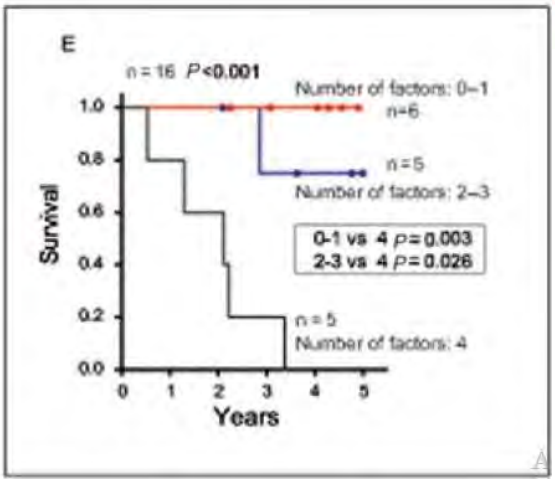
Factors Influencing Outcome

Oslo Score	Points
Maximal Tumor Diameter >5.5 cm	1
Pre-transplant CEA >80μg/dL	1
Progression on Chemotherapy	1
Time Interval Dx to Tx <2 years	1
SUMMARY SCORE	0-4



Hagness et al, Annals of Surgery, May 2013

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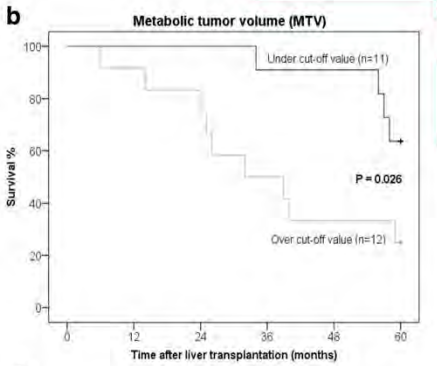
Eur J Nucl Med Mol Imaging (2018) 45:218–225
DOI 10.1007/s00259-017-3843-9

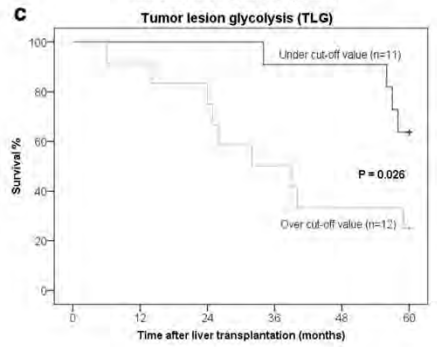
ORIGINAL ARTICLE

The prognostic value of ^{18}F–FDG PET/CT prior to liver transplantation for nonresectable colorectal liver metastases

Harald Grut[1,2] · Svein Dueland[3] · Pål Dag Line[2,4] · Mona Elisabeth Revheim[1,2]

Total Metabolic Tumor Volume (MTV) < 70 cm3 and
Total Lesion Glycolysis (TLG) < 257 g were significantly correlated with improved 3 and 5-year OS and DFS.





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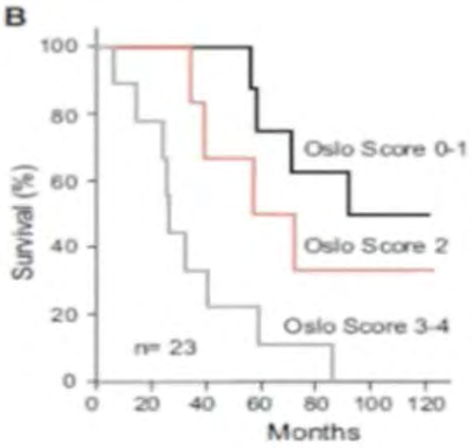
Long Term Follow- up of the First Prospective Pilot Study

10 year follow up

Oslo Score 0 - 1 (n= 6)
OS: 75% and 50 % at 5 and 10 years respectively

Oslo Score 2 (n=6)
OS: 50 and 33 % at 5 and 10 years respectively

All patients with Oslo Score 3 or 4 (n= 9) were deceased 86 months post-LT



Solheim et al, Annals of Surgery, August 2023

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Tailoring Prognostic Factors and Inclusion Criteria

Survival Following Liver Transplantation for Patients With Nonresectable Liver-only Colorectal Metastases

Svein Dueland, MD,✉ Trygve Syversveen, MD,† Jon Magnus Solheim, MD,‡ Steinar Solberg, MD,§ Harald Grut, MD,† Bjørn Atle Bjørnbeth, MD,¶ Morten Hagness, MD,‡ and Pål-Dag Line, MD‡||*

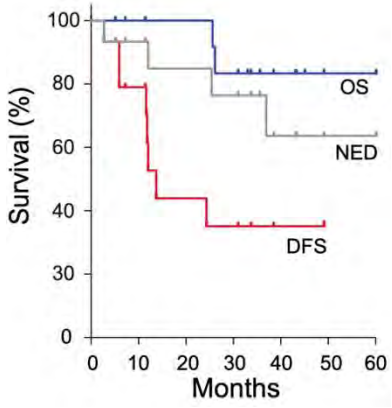
SECA 2

N = 15

Stricter inclusion criteria:

- 10% response to chemotherapy.
- CEA < 80 µg/L at the time of LT
- Interval from diagnosis to LT of at least 1 year.

The 4-year OS after recurrence remained at 73%



Duelan et al, Annals of Surgery, February 2020

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First North America Study

JAMA Surgery | Original Investigation

Recipient and Donor Outcomes After Living-Donor Liver Transplant for Unresectable Colorectal Liver Metastases

Roberto Hernandez-Alejandro, MD; Luis I. Ruffolo, MD; Kazunari Sasaki, MD; Koji Tomiyama, MD, PhD; Mark S. Orloff, MD; Karen Pineda-Solis, MD; Amit Nair, MD; Jennie Errigo, BS; M. Katherine Dokus, MPH; Mark Cattral, MD; Ian D. McGilvray, MD, PhD; Anand Ghanekar, MD, PhD; Steven Gallinger, MD, MSc; Nazia Selzner, MD, PhD; Marco P. A. W. Claasen, MD; Ron Burkes, MD; Koji Hashimoto, MD, PhD; Masato Fujiki, MD; Cristiano Quintini, MD; Bassam N. Estfan, MD; Choon Hyuck David Kwon, MD, PhD; K. V. Narayanan Menon, MD; Federico Aucejo, MD; Gonzalo Sapisochin, MD, PhD, MSc

DESIGN, SETTING, AND PARTICIPANTS This prospective cohort study included patients at 3 North American liver transplant centers with established LDLT programs, 2 in the US and 1 in Canada. Patients with liver-confined, unresectable CRLMs who had demonstrated sustained disease control on oncologic therapy met the inclusion criteria for LDLT. Patients included in this study underwent an LDLT between July 2017 and October 2020 and were followed up until May 1, 2021.

Of 91 evaluated patients, 10 (11%) underwent LDLT

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First North America Study

eTable. Inclusion and Exclusion Criteria of Participating LDLT Centers

University of Rochester

- Primary Tumor Removed
- Response to Chemotherapy ≥12 months
- No Evidence of Extrahepatic Disease
- CEA <80ng/dL
- Patient ECOG 0 or 1 and age ≤65
- Absence of synergistic tumor mutations (KRAS & TP53)
- Oslo Score ≤ 2

Cleveland Clinic

- > 12 Months From Primary Tumor Removal
- Response to Chemotherapy 6-12months
- No Evidence of Extrahepatic Disease
- CEA <100ng/dL
- Patient ECOG 0 or 1 and age ≤65
- Absence of tumor mutation (BRAF)

University Health Network

- Response to Chemotherapy at least 6 months
- Primary CRC resected > 6 months
- No Evidence of Extrahepatic Disease
- CEA stable or decreasing at all points prior to liver transplant
- Patient ECOG 0 or 1 and age 18-68
- Absence of tumor mutation (BRAF)

Hernandez-Alejandro et al, JAMA surgery, March 2022

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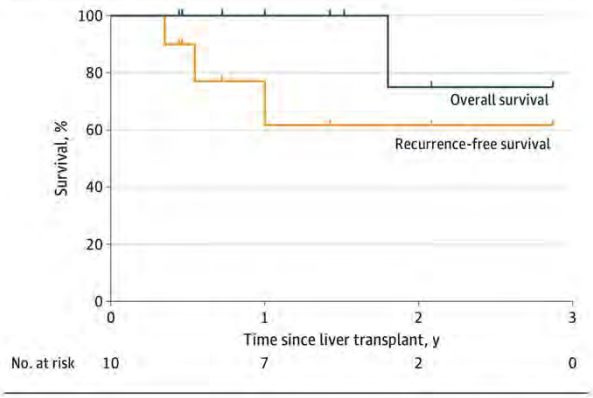
First North America Study

Perioperative morbidity for both donors and recipients was consistent with established standards.

"The results suggest that LDLT may be a viable treatment option for select patients with unresectable CRLMs with favorable tumor biology."

Figure. Kaplan-Meier Estimates of Overall and Recurrence-Free Survival in Patients Who Underwent Total Hepatectomy and Living-Donor Liver Transplant



Hernandez-Alejandro et al, JAMA surgery, March 2022

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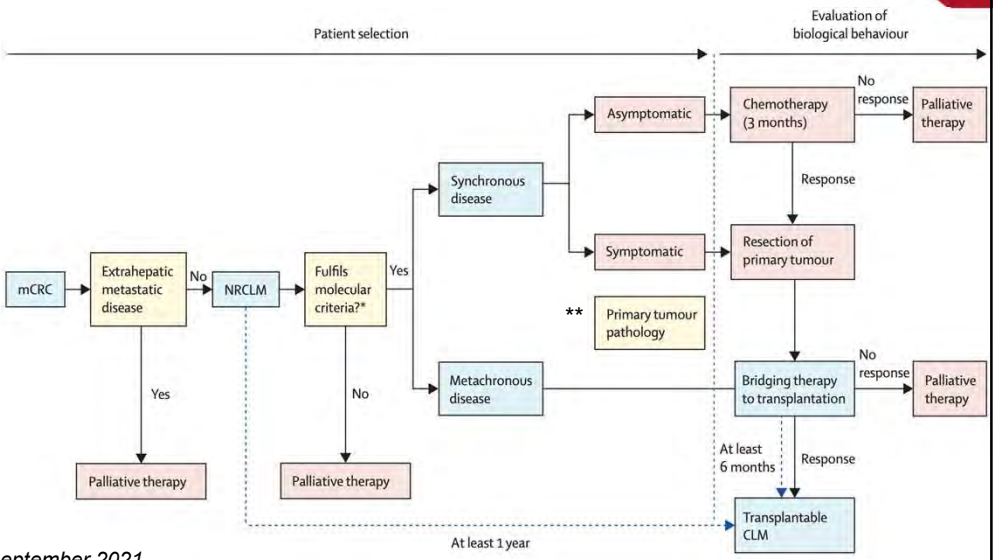
The International Hepato-Pancreato-Biliary Association consensus guidelines

*No BRAF V600E mutation, microsatellite stable, and mismatch repair proficient.

** Undifferentiated adenocarcinomas, signet ring-cell carcinomas,N2, metabolic tumors with a volume >70 cm^3 and total lesion glycolysis of >260 g should be excluded



Bonney et al, The Lancet, September 2021

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Intrahepatic Cholangiocarcinoma

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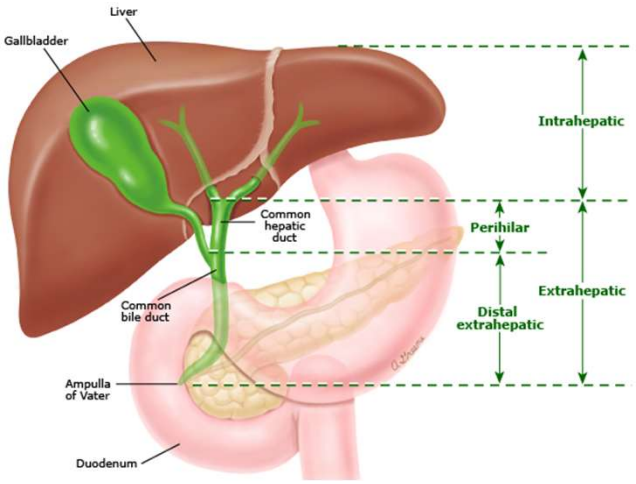
Background



Cholangiocarcinoma is the second most common primary hepatic malignancy.

Over the past 4 decades, the incidence of iCCA has increased by approximately 2.3% annually.

15 – 30% of iCCA are resectable.

5-year survival in resectable iCCA is 20 – 30%.

Previously poor outcomes resulted in liver transplantation being formally contraindicated for patients with iCCA.

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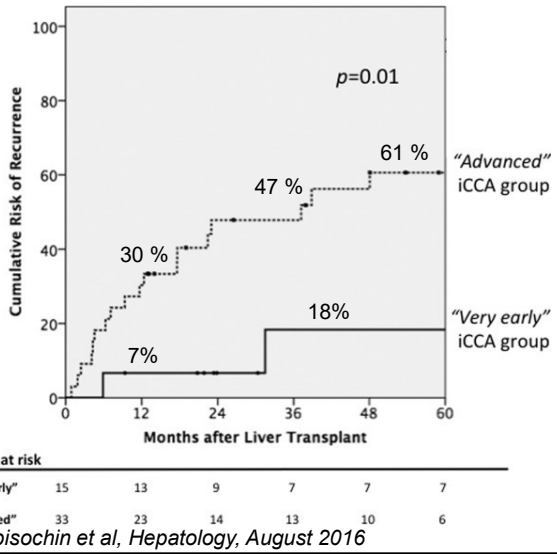
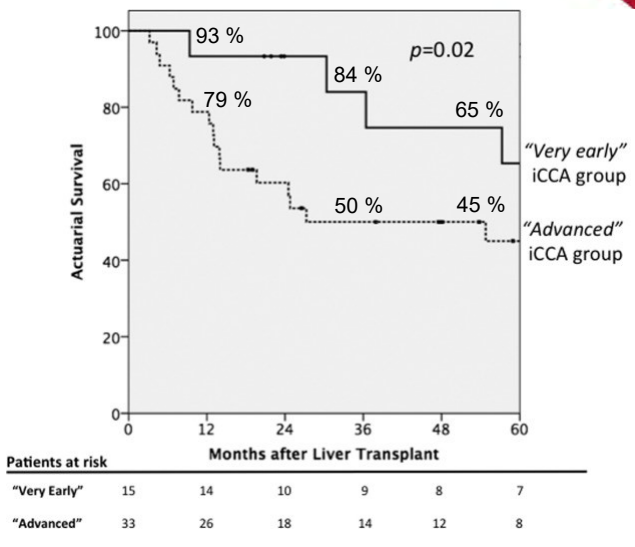
"Very Early" ≤ 2 cm vs "Advanced" > 2 cm or multifocal





Sapisochin et al, Hepatology, August 2016

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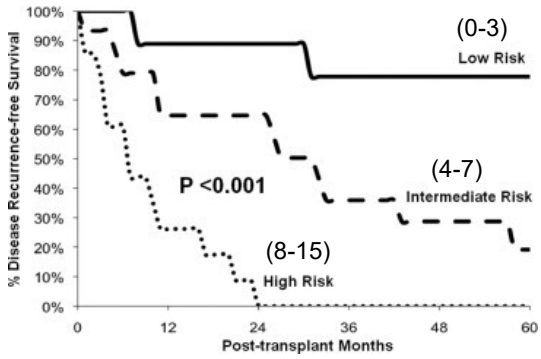
Predictive Index for Tumor Recurrence after LT for Locally Advanced iCCA

Table 3. Independent Predictors and Assigned Risk Score Points

Variable	Risk score points
Multifocality	4
Perineural invasion	4
Infiltrative tumor growth pattern	3
No neoadjuvant therapy	3
History of primary sclerosing cholangitis	2
Hilar cholangiocarcinoma	1
Lymphovascular invasion	1



Hong et al, JACS, April 2011

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LT for Locally Advanced iCAA Treated With Neoadjuvant Therapy

Intrahepatic cholangiocarcinoma
Tumour characteristics
- Biopsy-proven cholangiocarcinoma
- Intrahepatic rather than periductal location
- Not amenable to surgical therapy
- No evidence of extrahepatic disease

Diagnostic criteria
- Triple-phase CT of the chest, abdomen, and pelvis
- MRI bone scan
- FDG-PET scan if serum cancer antigen 19-9 elevated
- Endoscopic ultrasound-guided biopsy of enlarged nodes

↓

Neoadjuvant chemotherapy
- First-line platinum-based therapy and gemcitabine
- Second-line chemotherapy for progression or intolerance
- Addition of targeted biologics on case-by-case basis

↓

Disease stability for at least 6 months on given regimen
- Repeat imaging every 3 months
- Stable or regressing disease
- No extrahepatic disease

↓

Liver transplantation
- Post-transplant adjuvant therapy for 4–6 months depending on explant pathology

	Overall	Recipient 1	Recipient 2	Recipient 3	Recipient 4	Recipient 5	Recipient 6
Radiographic (pre-transplant)							
Stage	Stage II (T2bN0M0)	Stage II (T2bN0M0)	Stage II (T2aN0M0*)	Stage II (T2bN0M0*)	Stage IVB (T2bN1M0)	Stage I (T1N0M0)	Stage II (T2bN0M0)
Number of lesions	4·0 (3·0–5·8)†	3	5	>5	3	1	>5
Maximum size of largest lesion (cm)	7·0 (6·0–8·3)†	2·6	10·3	6·5	7·4	5·8	8·6
Cumulative diameter (cm)	10·5 (7·0–13·5)†	4·1	14·5	10·5	10·4	5·8	18·0
Explant							
Stage	Stage II (T2bN0M0)	Stage II (T2bN0M0)	Stage II (T2bN0M0*)	Stage II (T2bN0M0*)	Stage III (T3N0M0)	Stage I (T1N0M0)	Stage II (T2bN0M0)
Number of lesions	7 (2–10)†	8	6	10	1	1	10
Maximum size of largest lesion (cm)	5·9 (4·5–8·4)†	4·2	9·0	3·5	5·2	6·5	10·5
Cumulative diameter (cm)	14·2 (8·1–17·9)†	18·7	13·0	15·3	5·2	6·5	20
Location	NA	Bilobar	Bilobar	Bilobar	Left	Left	Bilobar
Differentiation	Moderate to poor	Poor	Well	Poor	Moderate	Moderate	Poor
Lymphovascular invasion	No	Yes	No	Yes	No	No	No
Perineural invasion	No	No	No	No	Yes	No	No
Microvascular invasion	No	Yes	No	Yes	No	No	No
Macrovascular invasion	No	No	No	No	No	No	No
Positive margins	No	No	No	No	Yes	No	No
Necrosis (%)	0%	0%	95%	0%	0%	0%	90%
Patient outcomes							
Post-transplant recurrence	NA	No	Yes	Yes	Yes	No	No
Post-transplant death	NA	No	No	Yes	No	No	No
Duration of follow-up (months)	36·3 (29·0–50·6)†	74·3	53·8	40·9	31·7	28·1	24·9

NA=not appropriate. *Retrospective radiographic analysis suggested that stable metastatic disease might have been present before liver transplantation. †Data are median (IQR).

Table 2: **Radiographic and explant tumour characteristics from liver transplant recipients with intrahepatic cholangiocarcinoma**

Lunsford et al, Lancet Gastroenterol Hepatol, May 2018

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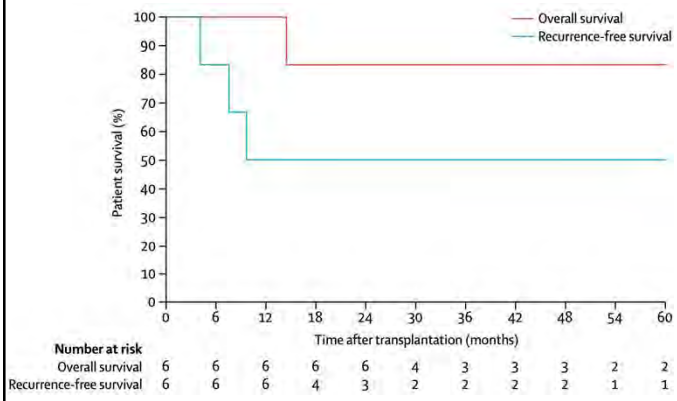

	Recipient 1*	Recipient 2	Recipient 3	Recipient 4	Recipient 5	Recipient 6
BAP1	..	0	Pro302fs*33	0	0	0
BLM	..	Arg15Cys	0	0	0	0
BRAF	..	0	0	0	0	Val600Glu
FANCF	..	Leu329Pro	0	0	0	0
FGFR2	..	Rearrangement intron 17	*PRKN* fusion	0	0	0
FGFR3	..	0	0	0	Amplification	0
FRS2	..	0	0	0	Amplification	0
IDH1	..	0	0	Arg132Cys	0	0
KDR	..	Asn141Asp	0	0	0	0
KRAS	0	0	0	Gly12Cys	0	0
MDM2	..	0	0	0	Amplification	0
MITF	..	Tyr18Cys	0	0	0	0
MSH6	..	Arg772Gln	0	0	0	0
MYC	..	0	Amplification	0	0	0
MYST3	..	0	Amplification	0	0	0
NFKBIA	..	Thr185Met	0	0	0	0
PDK1	..	Arg238Cys	0	0	0	0
PRKAR1A	..	Glu10Lys	0	0	0	0
PTEN	..	0	0	0	Tyr76fs*2	0
SMAD4	..	0	0	0	Pro218fs*16	0
SMARCA4	..	Pro674Leu	0	0	0	0
SPTA1	..	Gln255Arg	0	0	Arg891*subclonal	0

0 indicates no mutations. *This patient underwent *KRAS* mutation analysis only; all other patients underwent next-generation sequencing.

Table 4: Genetic mutation analysis of liver transplant recipients with intrahepatic cholangiocarcinoma

Lunsford et al, Lancet Gastroenterol Hepatol, May 2018

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Other Predictive Risk Factors for Tumor Recurrence after LT

Genetic profiling with next-generation sequencing/ whole genome sequencing:

- KRAS, BAP1, *CDKN2Adel and TP53mut* mutations have been associated with an aggressive phenotype and predicted worse outcomes in patients with unresectable iCCA.
- FGFR-2 mutations exhibit relatively indolent courses.
- Mutations such as IDH1, FGFR2, and BRCA somatic mutation offer potential therapeutic targets.

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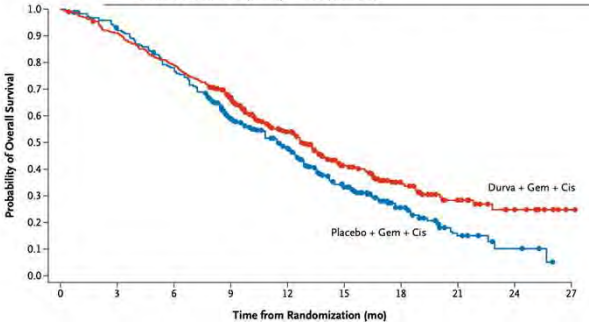
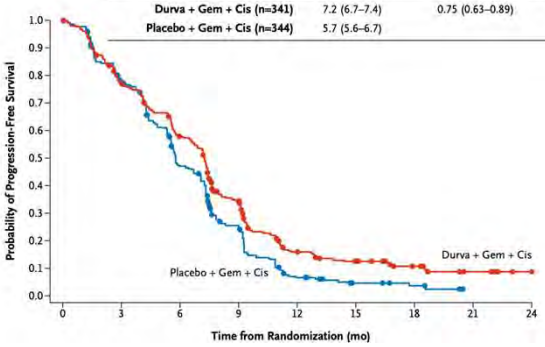
Durvalumab plus Gemcitabine and Cisplatin in Advanced Biliary Tract Cancer

	Median Overall Survival, mo (95% CI)	Hazard Ratio (95% CI)	Stratified Log-rank P Value
Durva + Gem + Cis (n=341)	12.8 (11.1–14.0)	0.80 (0.66–0.97)	0.021
Placebo + Gem + Cis (n=344)	11.5 (10.1–12.5)		



	Median Progression-free Survival, mo (95% CI)	Hazard Ratio (95% CI)	Stratified Log-rank P Value
Durva + Gem + Cis (n=341)	7.2 (6.7–7.4)	0.75 (0.63–0.89)	0.001
Placebo + Gem + Cis (n=344)	5.7 (5.6–6.7)		



Oh et al, NEJM, June 2022 (TOPAZ I)

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The Role of Immunosuppression for Recurrent CCA after LT

Immunosuppression Score

Immunosuppression units	Agents	Unit dose mg/day
1	Prednisone	5
1	Azathioprine	100
1	Cyclosporine	100
1	Tacrolimus	2
1	Mycophenolate mofetil	500
1	Sirolimus	2

Gul-Klein et al, Cancers, June 2022

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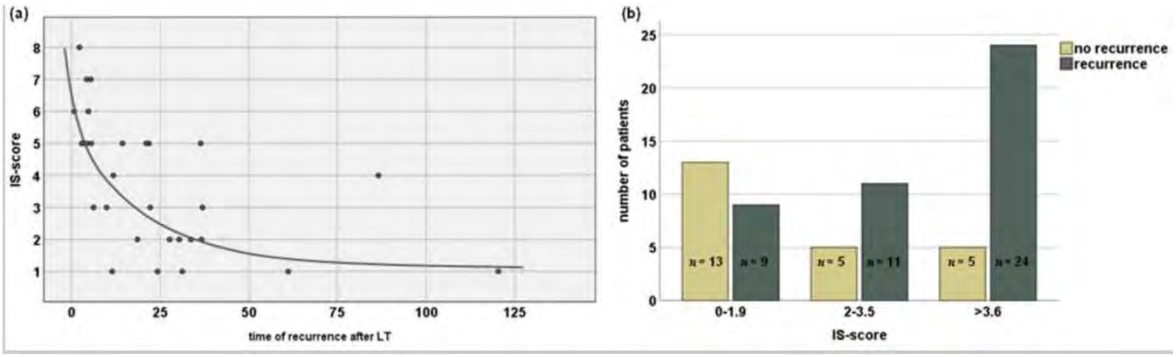
The Role of Immunosuppression for Recurrent CCA after LT



MTORI initiation before recurrence or after had no significant impact on survival.
Patients with recurrent CCA after LT benefit from a reduction in immunosuppression upon recurrence.

Gul-Klein et al, Cancers, June 2022

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Liver Transplantation for Intrahepatic Cholangiocarcinoma: Ready for Prime Time?

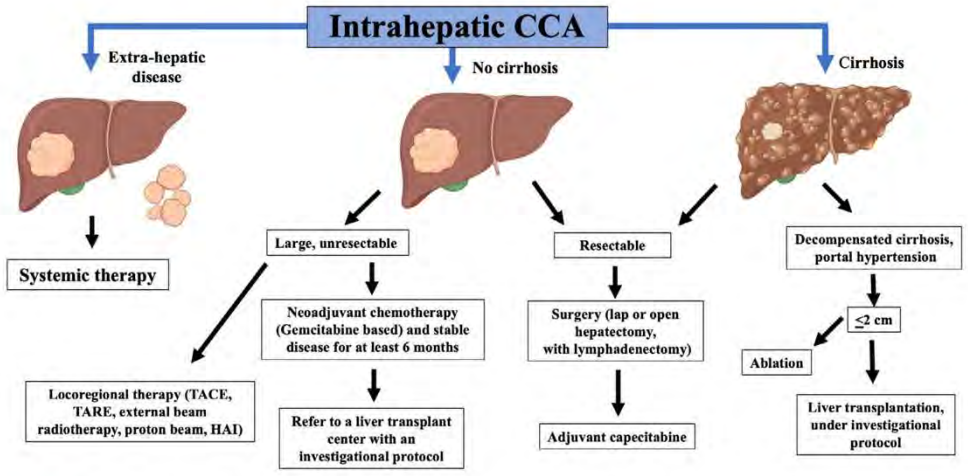

FIGURE 1 Proposed treatment approach to patients with iCCA and the role of LT (images created with BioRender.com)

Sapisochin et al, Hepatology, November 2021

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Future Challenges and Opportunities

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Future Perspectives in Transplant Oncology

Challenges

More data is needed to identify:

- Patients at risk of recurrence with a higher degree of accuracy.
- Optimal duration of chemotherapy.
- The role and safety of immunotherapy as a bridging and/ or down staging therapy before LT.
- The role of locoregional therapy and how they compare to one another.
- Optimal wait time between diagnosis and transplant.
- Optimal time for “drug holiday” before LT.
- Optimal immunosuppression regimen post LT.
- Optimal treatment of recurrence post LT.

Current UNOS policy and transplant center evaluation metrics limit centers’ consideration of “experimental” protocols, especially in lower volume centers.

- It is unclear if utilization of marginal grafts affects long-term outcomes.
- Some opponents argue that living donor livers should not be used for an indication not currently recognized by UNOS.

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Future Perspectives in Transplant Oncology

Opportunities

Build a world-wide tumor tissue repository and clinical database for future large-scale genomic studies.

Implement efforts to increase the donor pool: policies (opting in vs opting out), machine perfusion strategies, RAPID procedure, education campaigns to increase living donation.

Conduct multicenter, prospective studies/clinical trials to solve unanswered questions in integrating liver transplantation to the multidisciplinary treatment of hepatobiliary malignancies.

Build national and international registries of patients who undergo liver transplantation for emerging indications of hepatobiliary malignancies.

Set up joint meetings between major societies (e.g., EASL, AASLD, IHPBA, ILCA, SSO, ESMO, ASCO, etc.) and a Transplant Oncology Conference to advance and share knowledge.

Reproducible positive outcomes from multiple centers may set the groundwork for UNOS policies that will recognize iCCA and metastatic CRC as an indication for liver transplant and award MELD exception to these patients. New data may also redefine "successful outcome".

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