Liver Transplantation for Malignancy: Who, When, and Why?

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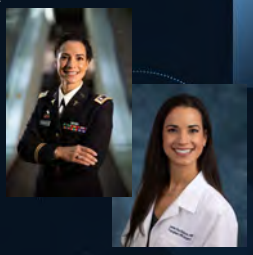

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Disclosures

- I have no financial relationships or disclosures.
- I have no conflicts of interest.

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Objectives

- Review the current indications and selection criteria for liver transplantation in hepatocellular carcinoma (HCC).
- Discuss emerging evidence supporting liver transplantation for colorectal liver metastases (CRLM), including trial data and patient selection.
- Discuss transplant pathways for Perihilar Cholangiocarcinoma
- Compare transplant with alternative therapies (resection, locoregional therapy, systemic chemotherapy) in malignant liver disease.
- Identify future directions and ongoing controversies in liver transplantation for oncologic indications.

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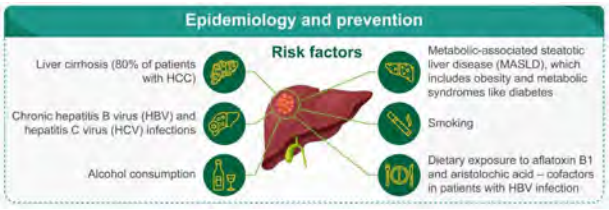

Hepatocellular Carcinoma (HCC) accounts for 75-85% of primary liver cancers, which is the 3rd leading cause of cancer deaths worldwide

- 2% annual risk in cirrhotic patients

AASLD

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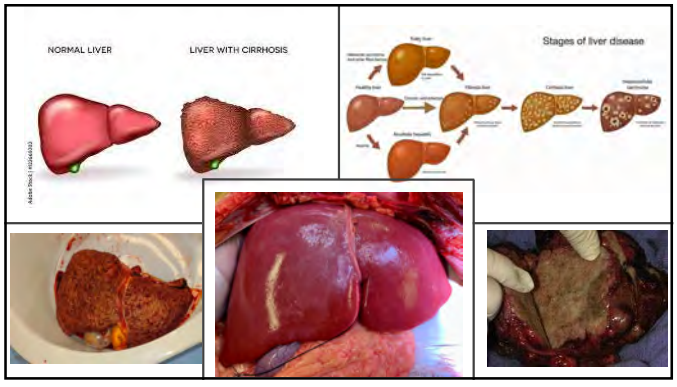

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Barcelona Clinic Liver Cancer (BCLC) Staging System (2022)[1]

***Table 1.* Definitions for Prognostic Groups**

Stage	Definition
Very early stage (0)	• Single ≤2 cm • Preserved liver function,* PS 0
Early stage (A)	• Single, or ≤3 nodules each ≤3 cm • Preserved liver function,* PS 0
Intermediate stage (B)	• Multinodular • Preserved liver function,* PS 0
Advanced stage (C)	• Portal invasion and/or extrahepatic spread • Preserved liver function, PS 1-2
Terminal stage (D)	• Any tumor burden • End stage liver function, PS 3-4

*Except for those with tumor burden acceptable for transplant.

NCCN Guidelines

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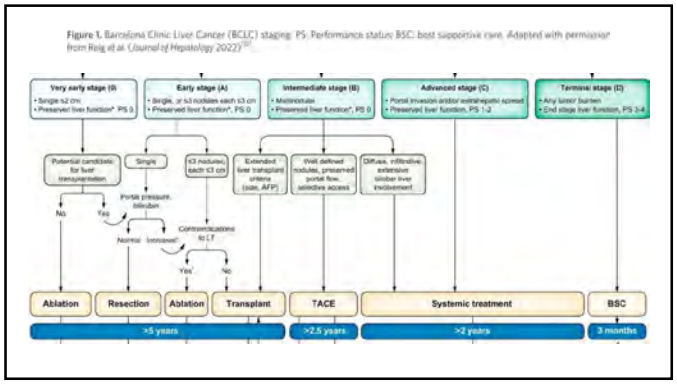

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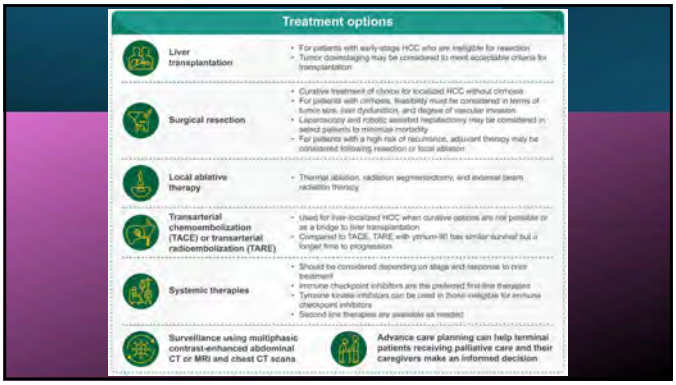

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Liver Resection

- Curative
- Reserved for:
  - Solitary tumor
  - Well-preserved liver function
  - No significant portal hypertension
- 5-year OS rates of 50-60%
- 5-year DFS is about 35%
- Recurrence rate approaches 70%

Changes of long-term survival of resection and liver transplantation in hepatocellular carcinoma throughout the years: A meta-analysis

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Child-Turcotte-Pugh Classification

	1 point	2 points	3 points
Encephalopathy	0	1-2	3-4
Ascites	none	slight	moderate
Bilirubin (mg/dL)	<2	2-3	>3
Albumin (g/dL)	>3.5	2.8-3.5	<2.8
PT prolonged (s)	1-4	5-6	>6
(INR)	<1.7	1.8-2.3	>2.3

Child's A = 5-6 points Child's B = 7-9 points Child's C = 10-15 points

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Liver Transplant

- Curative
- Tumor burden + cirrhosis
  - Not a resection candidate due to lack of preserved liver function
  - Meets Milan Criteria
- Better OS and DFS
  - 5-year OS 60-83%
  - 5-year DFS 70%
- Reduced rates of recurrence – 15%

AASLD Practice Guidance on prevention, diagnosis, and treatment of hepatocellular carcinoma

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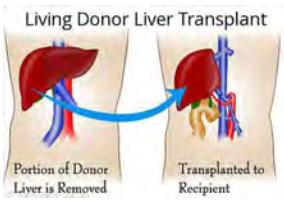
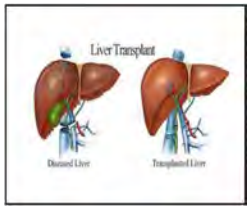
Liver Transplant Options

Living Donor



Deceased Donor



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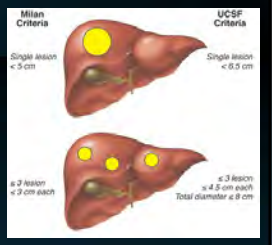
Criteria for Transplant Milan & Beyond…

	Milan Criteria	UCSF Criteria
Number and size of tumors	Solitary tumor with maximum diameter of 5 cm Up to three tumor nodules, each of which is <3 cm, with no vascular invasion or extrahepatic metastases	Solitary tumor with maximum diameter of 6.5 cm Up to three tumor nodules, with largest nodule <4.5 cm, or a total tumor diameter <8 cm, with no vascular invasion or extrahepatic metastases



UNOS Criteria
- **AFP ≤ 100ng/mL**
- **Tumor 2-5cm in diameter or 2-3 tumors 1-3cm in diameter**
- **No macrovascular involvement**
- **No Extrahepatic disease**

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Liver Allocation

- Sickest first/medical urgency
  - Not wait time
  - Not geography
- MELD-Na – Model for End Stage Liver Disease
  - Not inclusive for all medical urgency (cancer doesn't elevate MELD)
- Acuity circles around donor hospital
  - Median MELD to transplant
  - Higher numbers = more competitive
- Exception points
  - Increase the MELD to (Median MELD) - 3 to help patients compete for organs before progression/metastases

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OPTN/UNOS HCC Exception Policy

The American Association for the Study of Liver Diseases (AASLD) states that a patient with HCC within Milan criteria or down staged to within Milan are eligible for exception points after a 6-month waiting period.

- Prioritizes patients for a liver transplant by giving additional points
  - MMaT in DMV is 32
  - HCC exception points brings a patient up to 29
- 9 diagnoses in the policy that can apply for exception points to raise the score and increase competitive ability to get to transplant sooner
  1. HCC
  2. pCCA
  3. Hepatopulmonary Syndrome
  4. Portopulmonary Syndrome
  5. Familial Amyloidosis
  6. Primary Hyperoxaluria
  7. Cystic Fibrosis w/liver disease
  8. Neuroendocrine Metastases
  9. Polycystic Liver Disease

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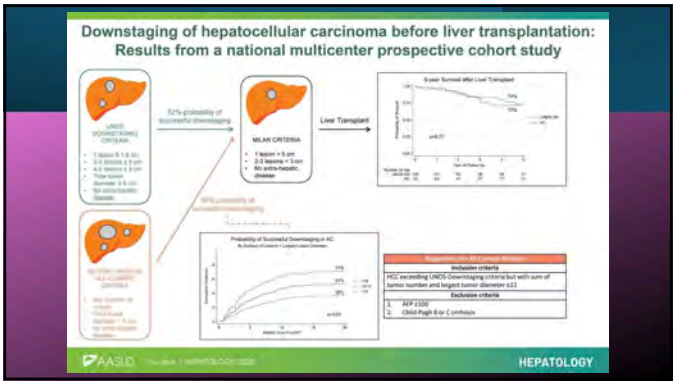

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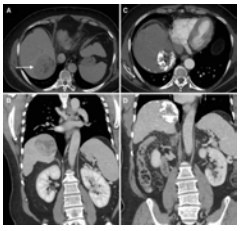
Downstaging

European Society of Organ Transplantation (ESOT) Consensus Report on Downstaging, Bridging and Immunotherapy in Liver Transplantation for Hepatocellular Carcinoma



Complete radiographic response, sustained radiographic response versus pathologic response…???

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Downstaging Options

TACE (CI in portal thrombosis)	TARE/SIRT	ABLATION	EBRT/SBRT	CHEMOTHERAPY	IMMUNOTHERAPY IMMUNE CHECKPOINT INHIBITORS
•Delivers chemo directly into tumor arterial supply + embolization for ischemia •Most used modality •cTACE and DEB-TACE •Multifocal, intermediate stage	•Intraarterial delivery of radioactive spheres to irradiate tumors •Y90 •Large tumors, portal vein invasion •Lower toxicity than TACE	•Thermal energy to destroy tumor tissue •Small localized tumors •RFA •MWA, larger lesions, less heat-sink	•Lesions near critical structure + poor liver function	•Not standard of care in the US •Doxorubicin, cisplatin, 5-FU	•Monoclonal Ab that block inhibitory pathways in T cells •Atezo + Bev •Rejection and Necrosis

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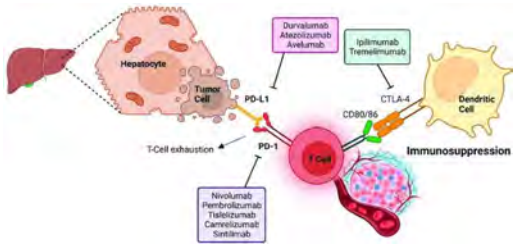
Where does immunotherapy fit in?



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Landmark Clinical Trials in the treatment of HCC

Study	Interventions	Molecular targets	Overall survival (months)
SHARP2007	Sorafenib vs. placebo	BRAF VEGFRs PDGFR KIT	Sorafenib 10.7 Placebo 7.9
CheckMate040	Nivolumab	PD-1	15.0
KEYNOTE224	Pembrolizumab	PD-1	12.9
CELESTIAL	Cabozantinib	VEGFRs KIT RET MET	8.0
REACH-2	Ramucirumab	VEGFR2	7.3
REFLECT	Lenvatinib vs. sorafenib	VEGFRs FGFRs PDGFRa KIT RET	Lenvatinib 13.6 Sorafenib 12.3
IMBrave150	Atezolizumab + bevacizumab	PD-L1, VEGF	12.0

PDGFR, platelet derived growth factor receptor; VEGFR, vascular endothelial growth factor receptor; FGFR, fibroblast growth factor receptor

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Biologics improving OS

Child-Pugh class A ONLY	Child-Pugh classes A and B	Child-Pugh class B	Child-Pugh class C
Atezolizumab + bevacizumab			
Sorafenib Lenvatinib nivolumab + ipilimumab pembrolizumab	Sorafenib		
Regorafenib Cabozantinib Ramcirumab Lenvatinib	Sorafenib		
	Nivolumab	Nivolumab FOLFOX	

Immune checkpoint inhibitor therapy for hepatocellular carcinoma

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Immunotherapy as a bridge to transplant

Intention-to-treat outcomes of patients with hepatocellular carcinoma receiving immunotherapy before liver transplant: The multicenter VITALITY study

- Developing
- First-line treatment
- Not amenable to curative or local regional therapy

Immunotherapy and transplantation for hepatocellular carcinoma

- 12week washout, hepatic necrosis or severe rejection
- Difficult to ascertain radiographic response versus pathologic response- explants with Beyond Milan findings

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Contraindication to UNOS Exception Points

- Macro-vascular invasion of main portal vein or hepatic vein*
- Extra-hepatic metastatic disease
- Ruptured HCC*
- T1 stage HCC – 2cm rule
  - LT candidate, decompensated cirrhosis, AFP <100 → wait
- AFP 1000 → >500 require a board review, Criteria is ≤100

- 6 month wait
- Recurrence after LR or LRT the **wait period is waived**
- Beyond Milan and went for LR and recurred - wait 6 months to assess biology

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Outcomes

- Equity in access to transplantation for HCC and non-HCC candidates, even in high-MELD regions like the DMV
- Comparable high-MELD survival
  - 5-year survival >70%
  - Recurrence 10-15% → RETREAT Microvascular invasion + AFP
- Benefit to HCC patients and preventing tumor progression

Management of Hepatocellular Carcinoma: A Review

Waitlist Outcomes for Exception and Non-exception Liver Transplant Candidates in the United States Following Implementation of the Median MELD at Transplant (MMaT)/250-mile Policy

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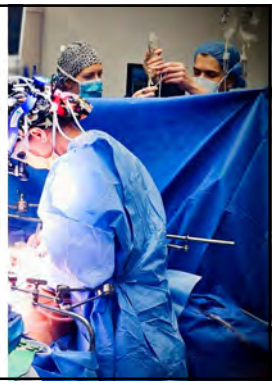
Colorectal Liver-only Metastases (CRLM)

- Unresectable, liver-only disease historically palliative; interest renewed by modern systemic therapy + transplant outcomes.



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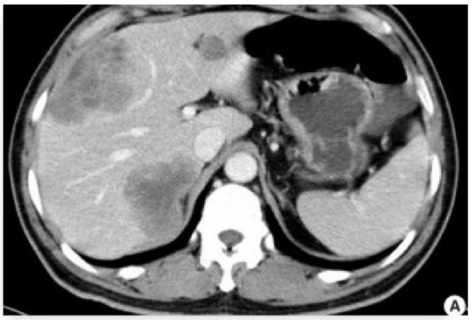

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Support from Landmark Prospective Trials

- 5-year overall survival of 73% for transplant plus chemotherapy versus 9% for chemotherapy alone in strictly selected patients

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TRANSMET randomized data (the pivot)

> ESMO Open. 2024 Sep;9(9):103669. doi: 10.1016/j.esmoop.2024.103669. Epub 2024 Aug 20.

Translating efficacy of liver transplantation in liver-limited metastatic colorectal cancer into clinical practice: the TransMet trial

M M Germani [1], N Raschzok [2], V Heinemann [3], D P Mudan [4]

Affiliations + expand

PMID: 39341649 PMCID: PMC11381977 DOI: 10.1016/j.esmoop.2024.103669

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SECA (Secondary Cancer) Trials

JOURNAL ARTICLE

Survival following liver transplantation for liver-only colorectal metastases compared with hepatocellular carcinoma

S Dueland, A Foss, J M Solheim, M Hagness, P-D Line

British Journal of Surgery, Volume 105, Issue 6, May 2018, Pages 736–742, https://doi.org/10.1002/bjs.10769

Published: 13 March 2018 **Article history**

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

Dueland, Svein MD[1]; Syversveen, Trygve MD[1]; Solheim, Jon Magnus MD[1]; Solberg, Steinar MD[1]; Grut, Harald MD[1]; Bjørnbeth, Bjørn Atle MD[1]; Hagness, Morten MD[1]; Line, Pål-Dag MD[1,2]

Author Information

Annals of Surgery 271(2):p 212-218, February 2020. | DOI: 10.1097/SLA.0000000000003494

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SECA Trials

- Prospective studies
- Establish modern eligibility criteria
- Demonstrate that LT can achieve long-term survival rates comparable to conventional indications for liver transplant
  - 60-83% compared to chemo alone at 9-14%
- Oslo and Fong were used to further risk stratify
- Limitations
  - Small sample size
  - Single-center design
  - Highly selective inclusion criteria
  - SECA I had heterogenous risk profiles
  - SECA II had stricter selection criteria

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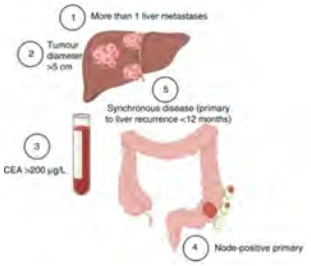
Fong Clinical Risk Score

- Initially developed for patients undergoing LR, but adapted for LT
- Assigns 1 point for each of the following:
  - Interval <12 months from primary tumor diagnosis to liver metastases
  - Largest lesion >5cm
  - >1 liver lesion
  - CEA >200µg/L
  - + LN in primary tumor
- Fong scores 0-2 show markedly improved OS after LT, 5-year survival rates approaching 80-100%



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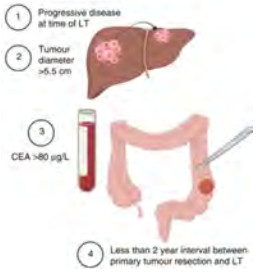
Oslo

- Developed for LT candidates with CRLM
- Assigns 1 point for each of the following:
  - Progressive disease on chemotherapy at the time of transplant
  - CEA >80µg/L
  - Largest liver lesion ≥5.5cm
  - Interval <2 years from primary tumor resection to transplant
- Oslo scores 0-2 have significantly better outcomes, 5-year OS of 63-89%
- Oslo scores 3-4 area associated with poor prognosis and are generally considered exclusionary for LT



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JAMA Network

From: **Long-Term Survival, Prognostic Factors, and Selection of Patients With Colorectal Cancer for Liver Transplant: A Nonrandomized Controlled Trial**

JAMA Surg. 2023;158(9):e232932. doi:10.1001/jamasurg.2023.2932

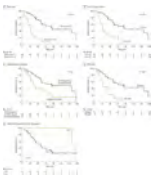

Figure Legend:

Association of Overall Survival After Liver Transplant With Oslo Score, Lesion Size, Treatment Response, Carcinoembryonic Antigen (CEA) Levels, and Time From DiagnosisAssociation of overall survival after liver transplant with Oslo score (A), size of largest lesion (B), response to chemotherapy at time of transplant (C), CEA levels at time of transplant (D), and time from diagnosis to liver transplant (E).

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Candidates for LT

Inclusion Criteria

- Liver-only, unresectable metastases
  - No extrahepatic disease on PET/CT
- Resected primary tumor
- Sustained response to at least 3 months of systemic chemotherapy

Key Selection Criteria

- Largest lesion <5.5cm
- CEA ≤80µg/L
- Metabolic tumor volume <70 cm^3 on PET
- Favorable clinical risk scores
  - Oslo ≤1
  - Fong ≤2

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Pathways to Transplant

- Multidisciplinary review
- Rigorous imaging
- Biomarker assessment
- Early referral

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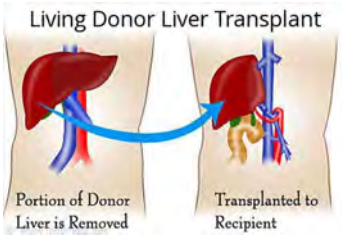
Transplant Options

- Living Donor Liver Transplant (mostly)
  - Donor ethical implications
  - Supported by survival for CRLM is comparable to other accepted indications
- UNOS does not grant exception points for CRLM
  - Policy is evolving

Policy Corner: Transplant oncology, colorectal liver metastases MELD nonstandard exception



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Contraindications

- Progression on chemotherapy, 6-12 months
- Extrahepatic disease
- Right-sided/ascending colon tumors*
  - Especially if RAS or BRAF mutation
  - 17.9mo survival
- Signet ring cell histology*

- BRAF mutations, V600E*
- ≥9 lesions or TB score*
- <2y interval from primary resection*

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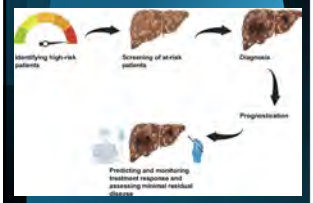
Biologic Marker Profiling



- RAS, KRAS and NRAS mutations are associated with poorer prognosis, higher recurrence risk and reduced OS after both resection and transplantation
  - RAS with right-sided tumors predict very poor prognosis
- BRAF mutations, V600E, are considered a biologic contraindication to liver transplant at many centers
  - Extremely poor outcomes
- ctDNA detected after surgery or chemotherapy is associated increased recurrence risk and shorter survival
- TP53, SMAD4, FBXW7 may confer worse prognosis
- APC mutation maybe associated with improved outcomes
- Microsatellite instability (MSI-H) and MMR deficiency are rare in CRLM but may predict responsiveness to immunotherapy

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Recurrence Patterns

- Common
- Median disease-free survival of 12 months
  - Slow growing, resectable pulmonary metastases
- Overall survival after relapse remains high
  - 5-year OS 60-83%
- Quality of life post-transplant is comparable to baseline

- **DFS is not a valid surrogate for OS as long-term survival is achievable even after recurrence

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Donor Ethics

- Double equipoise
  - Balancing recipient benefit with donor risk
- Real morbidity and rare mortality risk
- MultiD evaluation of both donor and recipient
  - Transplant surgeons, hepatologists, oncologists, psychosocial experts
- Robust informed consent
- Insurance approvals
- Technically investigational

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How does transplant compare to resection, LRT, systemic therapy?

- LT is reserved for highly selected patients with unresectable liver-only disease
  - Recurrence is common around 12 months, but overall 5-year survival is highest at 53-83%
- LR is that standard of care for resectable liver disease with the ability to achieve R0 resection
  - Recurrence is usually intrahepatic and repeat resection or ablation can improve outcomes
- Systemic therapy is for unresectable or extrahepatic disease and 5-year survival remains <15%

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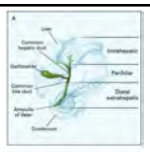
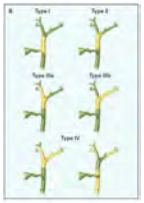
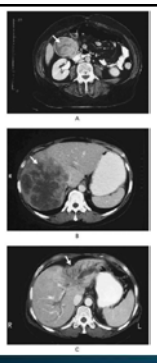
Cholangiocarcinoma-Perihilar (pCCA)

- LT is an acceptable indication for early-stage, unresectable pCCA
- Strict selection criteria
- Standardized neoadjuvant CRT protocol
- AASLD and the OPTN recognize this approach







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Eligibility

- Unresectable pCCA
  - Only 5% of patients meet criteria
  - Liver disease
  - Tumor location
- Tumor ≤3 cm in radial diameter
- No intrahepatic or extrahepatic metastases
- No LN involvement
- Diagnosis confirmed by biliary cytology, biopsy or in select cases imaging and tumor markers
  - Percutaneous or EUS-guided tumor biopsy and surgical violation of the tumor plane are CI due to risk of peritoneal seeding

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Neoadjuvant Therapy

- EBRT
- Concomitant 5-fluorouracil (5-FU)
- Brachytherapy
- Maintenance capecitabine until transplant
- Staging laparoscopy to exclude occult metastases

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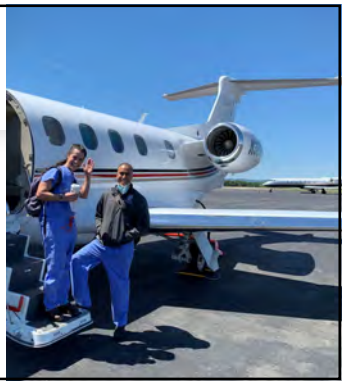
Allocation Policy

- UNOS grants MELD exception points for eligible pCCA patients treated under approved protocols
  - High risk of waitlist dropout
  - Curative potential



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Outcomes

- 5-year OS after transplant is 53-65%
  - LR 30-45% with recurrence rates up to 80% within 2 years mainly due to R1 resection and +LN
- Recurrence-free survival up to 78%
- Outcomes are superior in patients with PSC-associated pCCA
  - Earlier detection
- Mortality is similar to LR at 4-8%
- 41% rate of dropout on neoadjuvant


Meta-analysis and Meta-regression of Survival After Liver Transplantation for Unresectable Perihilar Cholangiocarcinoma

Journal of Gastrointestinal Surgery

Liver Transplantation for Peri-hilar Cholangiocarcinoma

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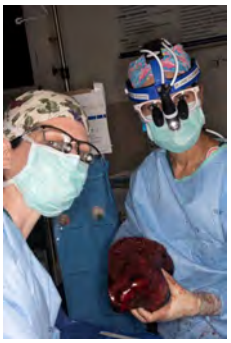
Intrahepatic CCA (iCCA)

- Historically a contraindication for liver transplant due to poor outcomes
- Recent data suggests select patients with small, solitary, unresectable (usually due to liver disease), liver-limited iCCA may benefit
  - 5-year OS up to 65% in highly selected cases
- The roll of LT remains controversial and is not standard of care



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Hepatic Artery Infusion Pump (HAIP)

- HCC
  - Well-established arterial-based LRT for unresectable disease
  - Demonstrated improved OS in RCT
  - Supported by NCCN as bridge to transplant
- CRLM
  - Facilitate conversion to LR or LT
- iCCA
  - Multifocal or unresectable disease
  - Leverages arterial delivery of high-dose chemo to the tumor
  - Evidence to support bridge to LT


Liver Transplantation After Hepatic Artery Infusion Pump Therapy: Single-Center Experience and Technical Considerations

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Indication	Transplant	Resection	LRT	Systemic Therapy
HCC (Milan)	5-yr OS 70–80%	Variable, high recurrence	Bridge, not curative	Median OS ~1–2 yrs
HCC (after DS)	Similar OS if stable biology	Often not feasible	Effective downstaging	Limited benefit
CRLM	5-yr OS ~56–73% (selected)	Feasible if resectable, OS up to 50%	Local control only	5-yr OS <15%
pCCA (Mayo)	5-yr OS 60–70% (protocolized)	Rarely feasible	Palliation	Poor outcomes

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Conclusions

- Early referral to specialized transplant centers (transplant oncology divisions)
- Robust MultiD collaboration
- Individualized management
  - Pathways, protocols, inclusion and exclusion criteria exist
  - No one-size-fits-all solution
- Treatment algorithms are increasingly dynamic, driven by evolving evidence, molecular profiling, and expanding therapeutic options
- Paradigm shifts: new transplant indications, targeted immune therapies, personalized, and adaptive treatment strategies

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