ANNUAL

Advances and Innovations in Endoscopic Oncology and Multidisciplinary Gastrointestinal Cancer Care

Should Liver Transplantation be a Standard Treatment Option for Metastatic Colorectal Cancer?

Maarouf A. Hoteit, MD

Professor of Clinical Medicine

Medical Director of Liver Transplant

Director, Liver Tumor Clinic

University of Pennsylvania

Disclosures

- I do not have any relevant financial relationships.

This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content

Cultural Linguistic Competency (CLC) & Implicit Bias (IB)

STATE LAW:

The California legislature has passed Assembly Bill (AB) 1195, which states that as of July 1, 2006, all Category 1 CME activities that relate to patient care must include a cultural diversity/linguistics component. It has also passed AB 241, which states that as of January 1, 2022, all continuing education courses for a physician and surgeon **must** contain curriculum that includes specified instruction in the understanding of implicit bias in medical treatment.

The cultural and linguistic competency (CLC) and implicit bias (IB) definitions reiterate how patients' diverse backgrounds may impact their access to care.

EXEMPTION:

Business and Professions Code 2190.1 exempts activities which are dedicated solely to research or other issues that do not contain a direct patient care component.

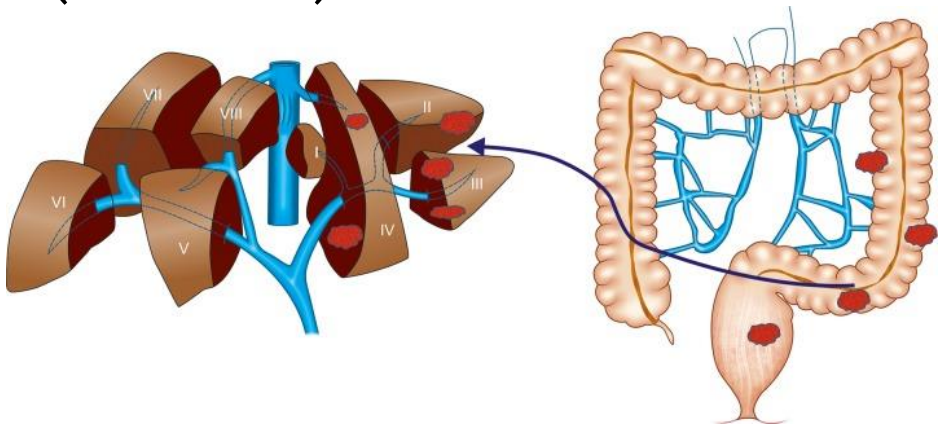
The following CLC & IB components will be addressed in this presentation:

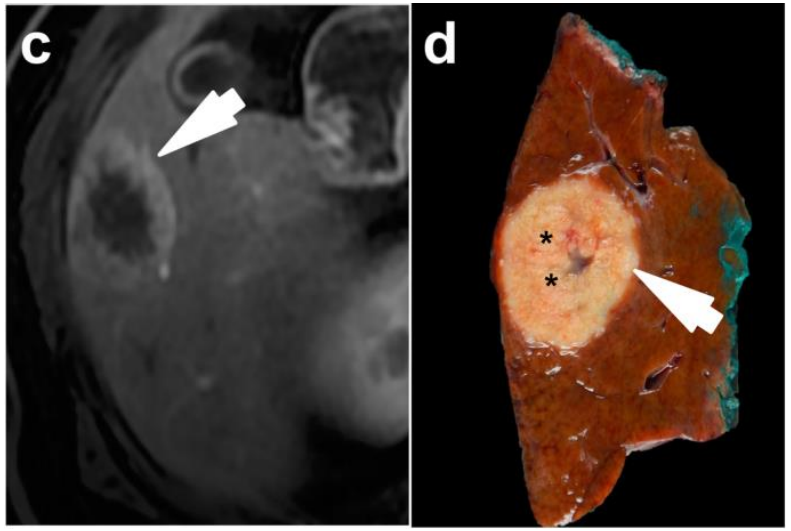
- Catering to the needs of a diverse patient population in transplant care.
- Economic and cultural barriers to liver transplantation.

Colorectal cancer liver metastasis (CRLM)

- Colorectal cancer (CRC) is the 3rd most common cancer and 2nd leading cause of cancer-related mortality worldwide.

- Liver is the most common site of metastasis:
  - 50-70% of patients will have metastatic disease during their illness, of which 30-40% will be confined to liver.





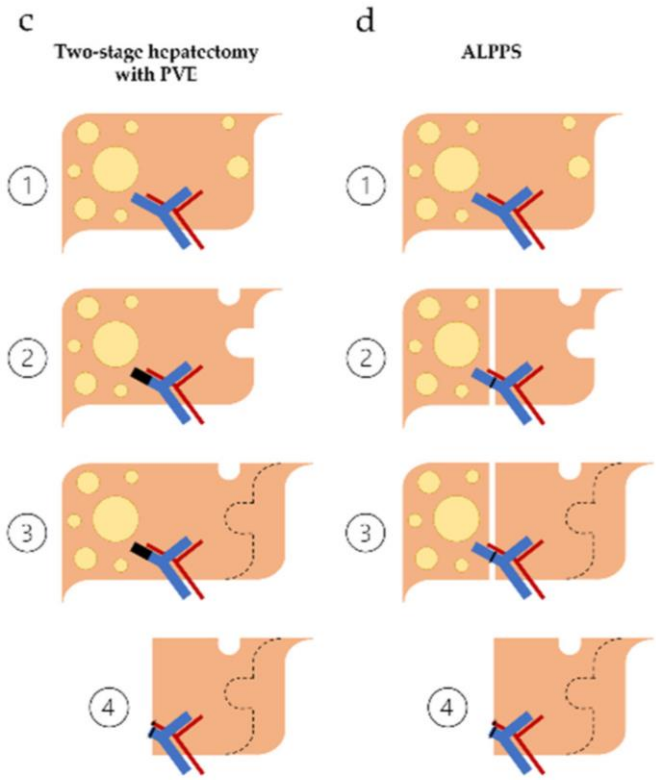
GLOBOCAN 2020; Finotti et al *Front* Surg 2021;Paulatto et al. *Insights into Imaging* 2020.

CRLM – Management

- Resection of CRLM:
  - Only 10-20% of patients on initial evaluation
    - Parenchyma-sparing hepatectomy, staged resections, PV embolization, ALPPS (Associating Liver Partition and Portal vein Ligation for Staged hepatectomy)
  - Neoadjuvant chemotherapy: up to 40% can be downstaged

- Even as liver resections are associated with a high recurrence rate (60-80%) they have a major impact on survival

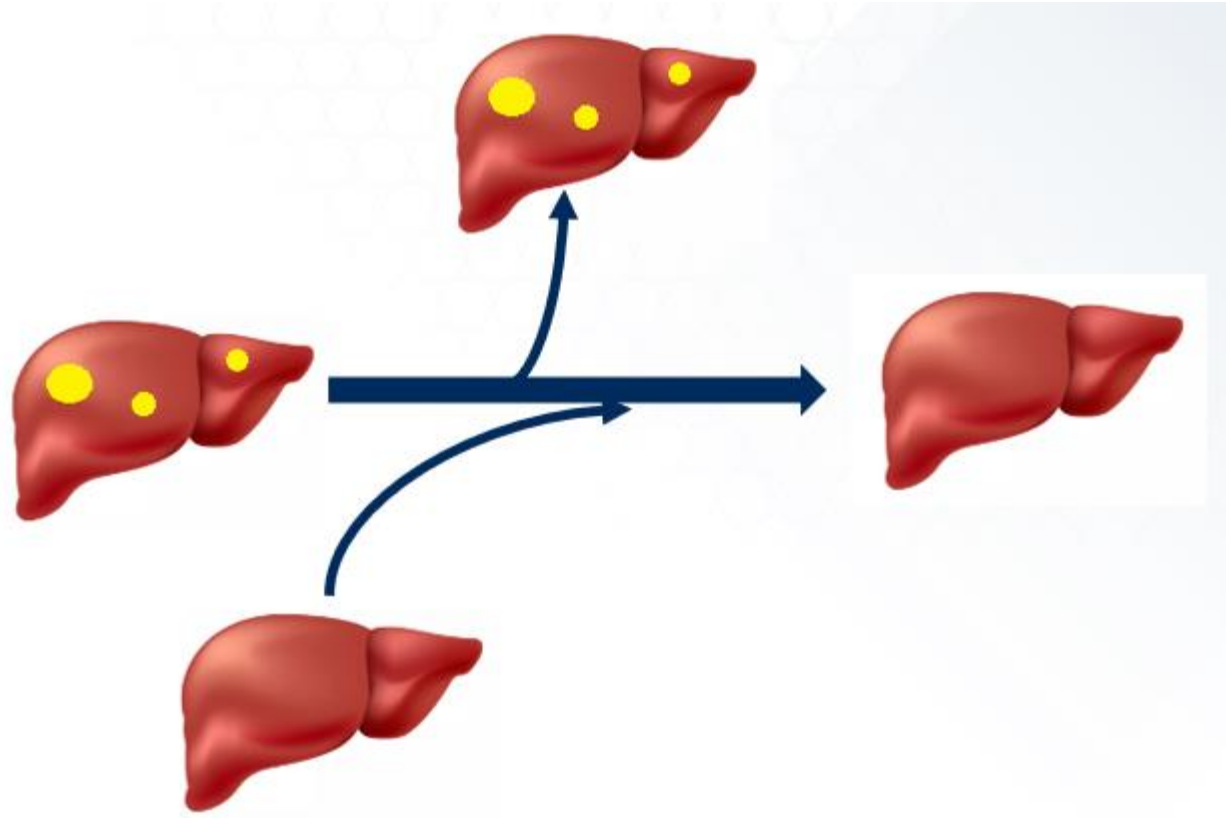
- 5-year survival:
  - Resection ~ 40-60%
  - Resection after downstaging with chemo ~ 33%
  - Chemotherapy alone 10-15 %



NCCN Guidelines 2021; Fernandez et al *Ann Gastroenterol Surg* 2019; Adam et al *Ann of* Surgery 2004; Liu et al *Oncotarget* 2016

Liver Transplantation as Treatment for Cancer

- Malignant disease limited to the liver
- Not amenable to a surgical resection or alternative curative therapy
- Liver Transplantation amounts to a ‘radical resection’ of the malignant disease



Early Experience in Transplant for Cancer had poor outcomes

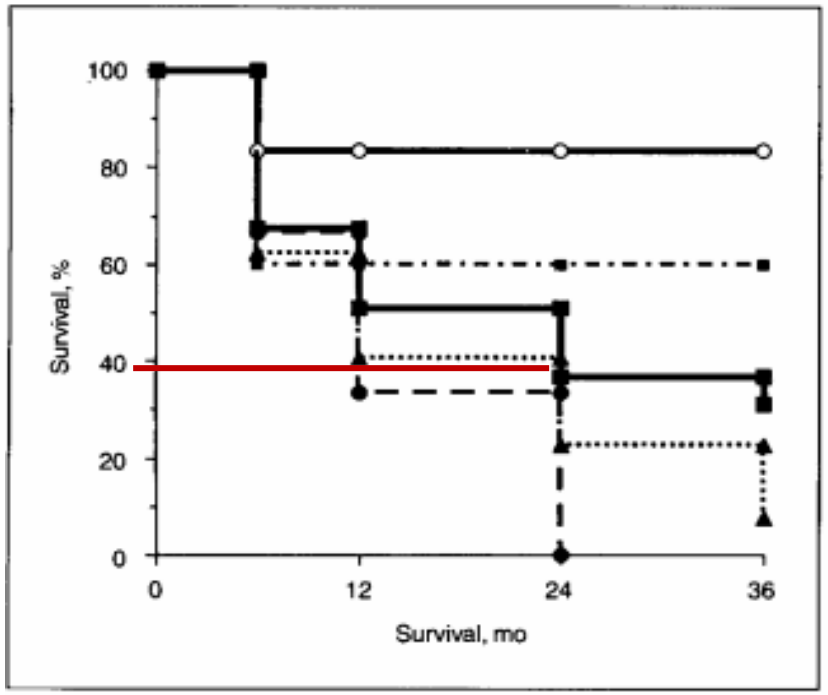
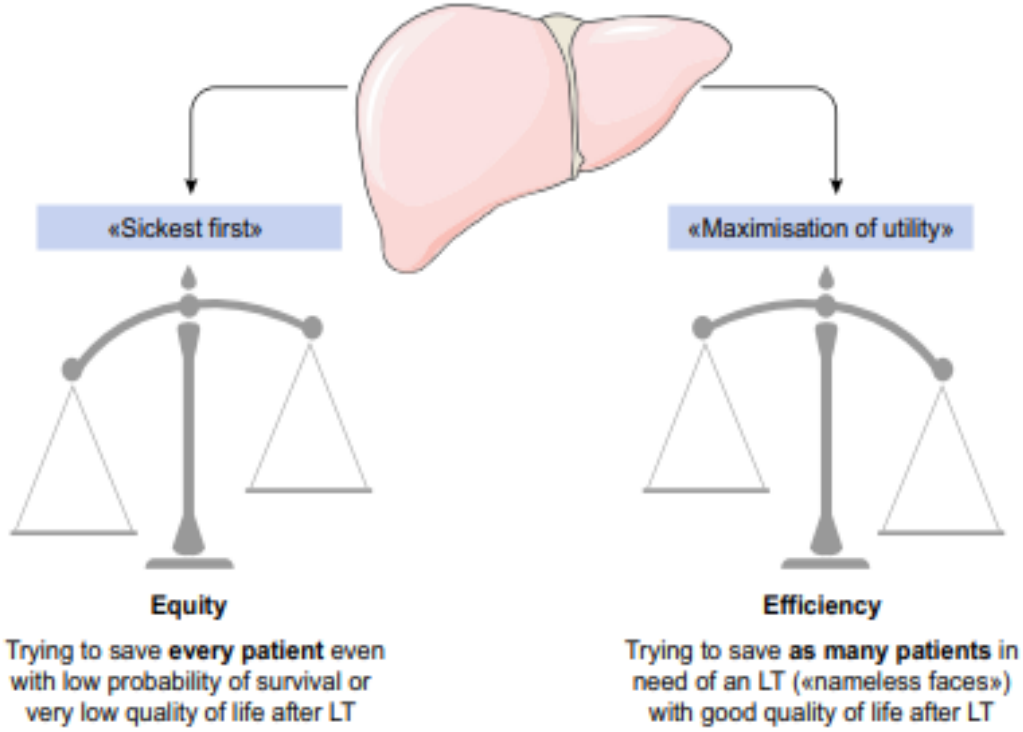


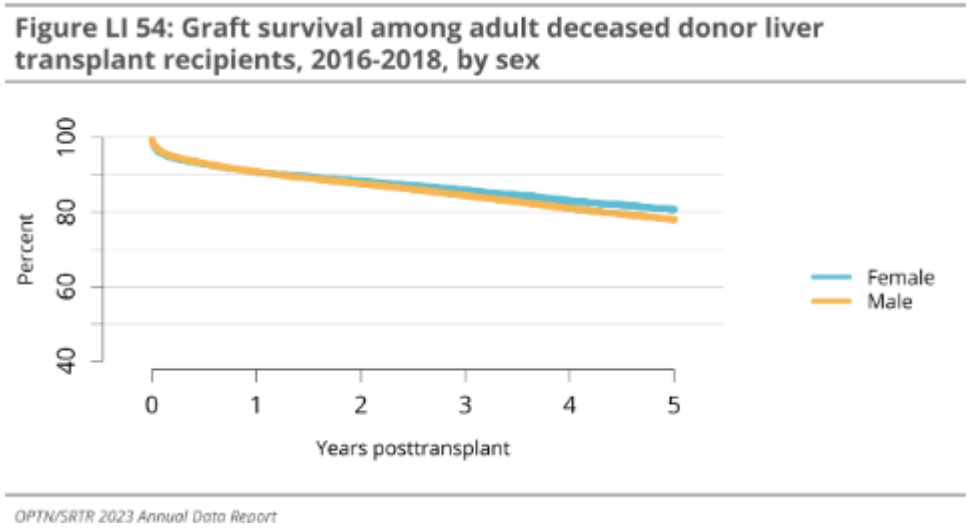
Fig 1.—Actuarial survival time vs percent after orthotopic liver transplantation for malignancy (UCLA, 1984-1989). Squares with solid line indicate overall malignancies; triangles, hepatocellular carcinoma; solid circles, cholangiocarcinoma; open circles, other primary cancers; and squares with broken line, metastatic disease.

Olthoff KM, et al. *Ann Surg* 1990;125:1261-68

General concepts – Liver Transplant Allocation Ethics

- Transplantation is a special type of medical treatment requiring allocation of a limited resource (donor organs)

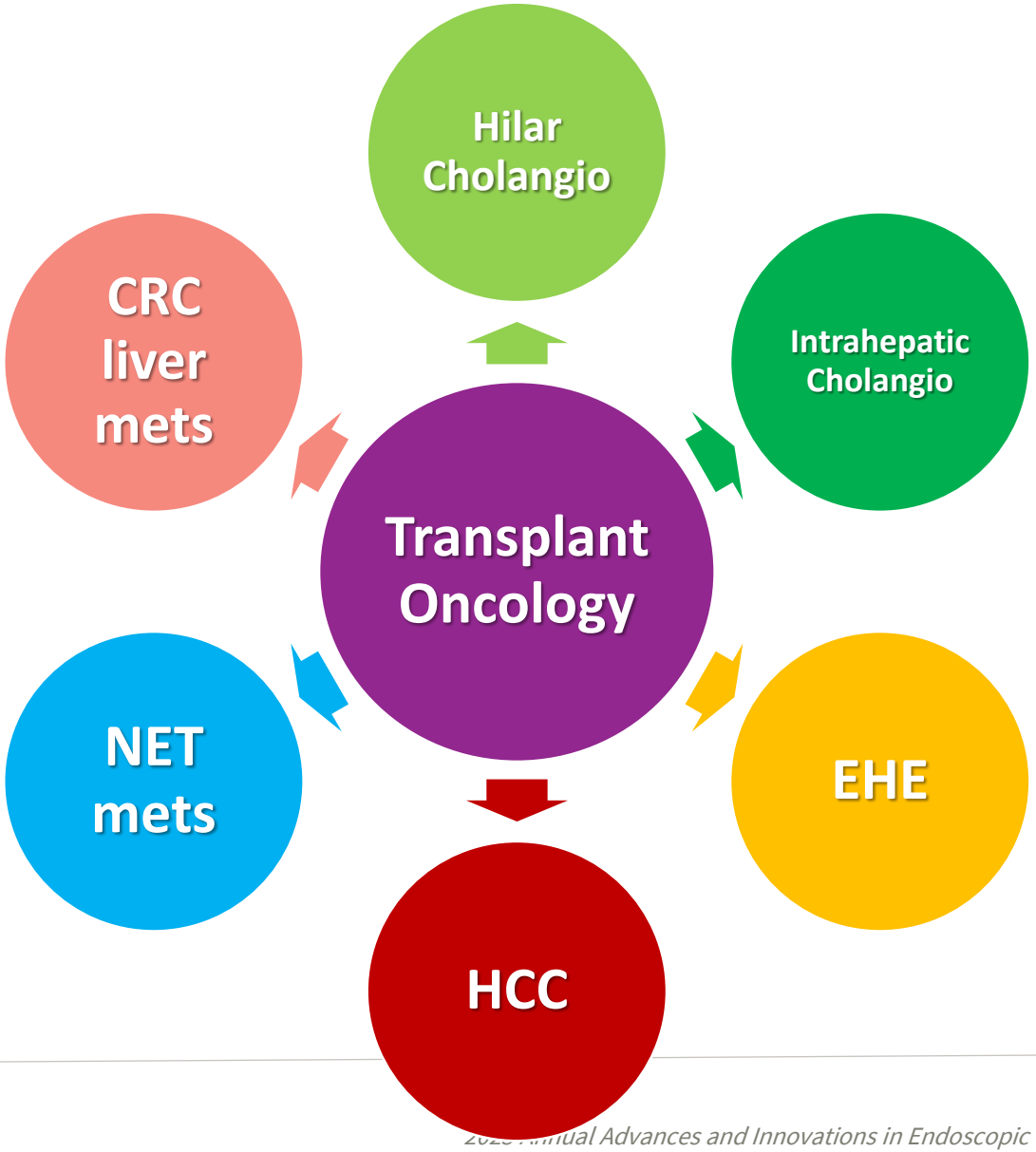




Linecker M, et al. J of Hepatology 2018

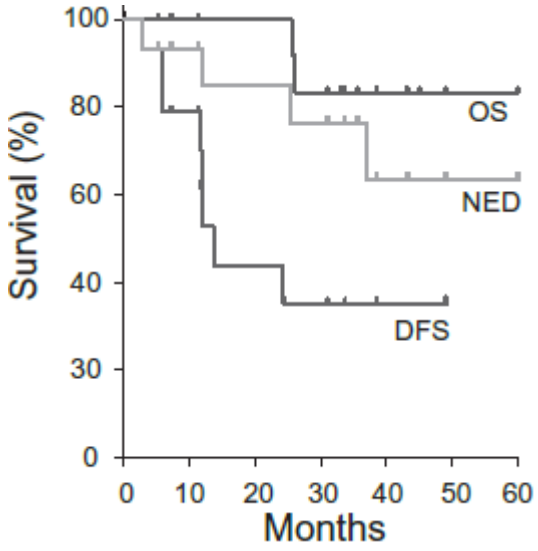
Liver Transplant for Cancer – general principles for optimizing outcome

- Patient selection – defining the subgroup that derives substantial benefit from transplantation
- This subgroup is not static:
  - Refinement of selection criteria
  - Improvement of neoadjuvant (before transplant) and adjuvant (after transplant) cancer Rx
- In most cases, **controlling the tumor before LT** is important in improving the outcome.
- Conversely, **tumor progression prior to LT**, even if limited to the liver, is generally associated with poor outcomes.


Hilar Cholangio
CRC liver mets
Intrahepatic Cholangio
Transplant Oncology
NET mets
EHE
HCC

Liver transplant (LT) for uCLRM – The Norwegian experience

- Norway has a unique situation: more liver donors than recipients in need
- The historic experience (1980s-1990s): adverse outcomes potentially preventable with improved transplant care, and improved CRC chemotherapy
- 1st prospective, single arm pilot 2013 (SECA-I):
  21 pts: unresectable, resected primary, >6 weeks of chemotherapy
  - Although ~ 90% recurred, post LT OS = 60% at 5 y
- 2nd prospective single arm (SECA-II):
  15 pts: > 1 y since primary, >=10% RECIST response
  OS = 83%, DFS = 35% at 3 y



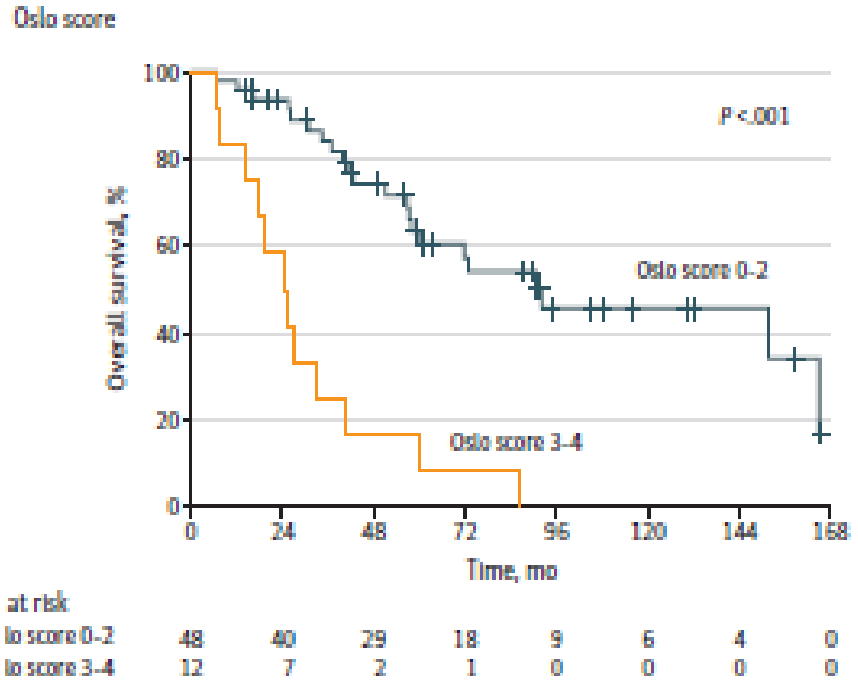
Hagness N, *Ann Surg* 2013
Dueland S, *Ann Surg* 2020

Liver Transplant for uCLRM – The Oslo Score

- Overall Norwegian experience in 2023:
  61 pts: OS = 50% at 5y

- Oslo Score major predictor of post LT outcome:
  - Lesion > 5.5 cm
  - CEA > 80
  - Dx CRC to LT < 2 yr
  - Tumor Progression Immediately prior to LT

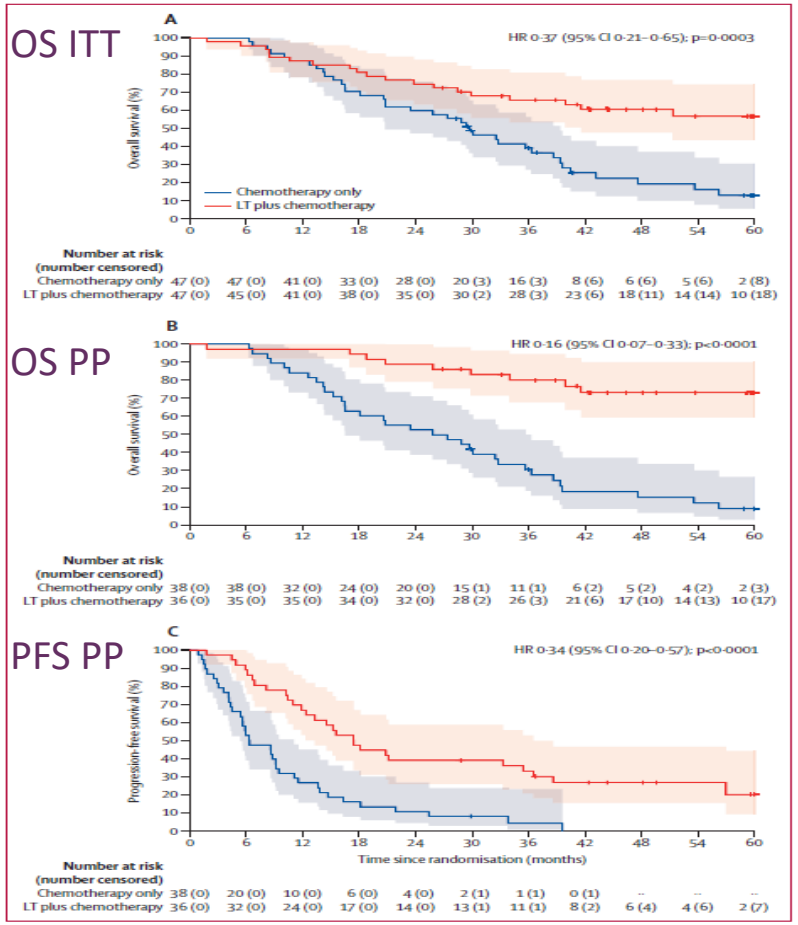
- Oslo 0-2: **OS = 70% at 5 y**



Dueland S, *Ann Surg* 2023

RCT evidence of LT benefit: the TRANSMET Trial

- RCT 94 pts, multicenter in France
- 1:1 randomized Chemo alone vs OLT+chemo (neoadj+/- adj)
- **OLT group**: 36/47 pts actually transplanted (drop out due to progression or intraop findings)
  Chemo group: 38/47 remained on chemo alone (7 resections, 2 transplants)
- OS ITT: 5y survival 56.6% vs 12.6% (P<0.0001)
  OS PP: **5 y survival 73.2%** vs 9.3% (P<0.0001)



Adam R, *Lancet* 2024

Notice of OPTN Policy and Guidance Changes

National Liver Review Board (NLRB) Updates Related to Transplant Oncology

Public Comment: January 23, 2024 – March 19, 2024
Board Approved: June 17-18, 2024

Colorectal Liver Metastases

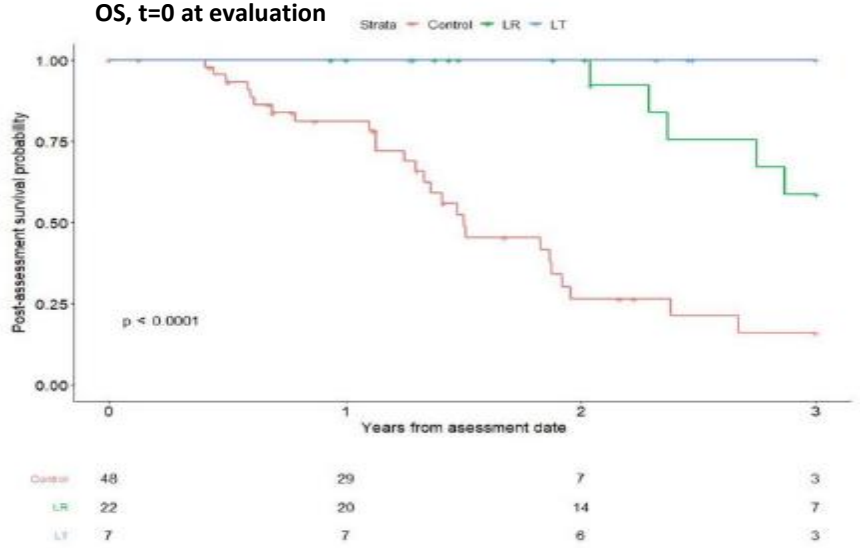
The diagnosis of unresectable colorectal liver metastases (CRLM) has a poor prognosis despite improved local and systemic treatments. Published studies support liver transplantation in highly selected patients and has demonstrated a survival benefit in initial prospective clinical trials.[12, 13, 14, 15]

Candidates meeting the criteria described should be considered for a MELD exception score equal to MMaT-20. If MMaT-20 results in an exception score below 15, the candidate's exception score **will automatically be set to a MELD score of 15** per OPTN Policy 9.4.E: *MELD or PELD Exception Scores Relative to Median MELD or PELD at Transplant*.

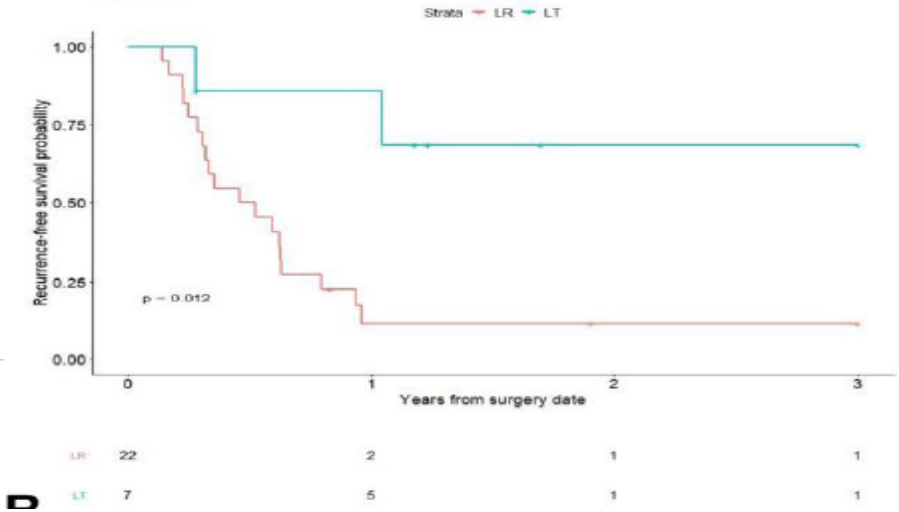
https://optn.transplant.hrsa.gov

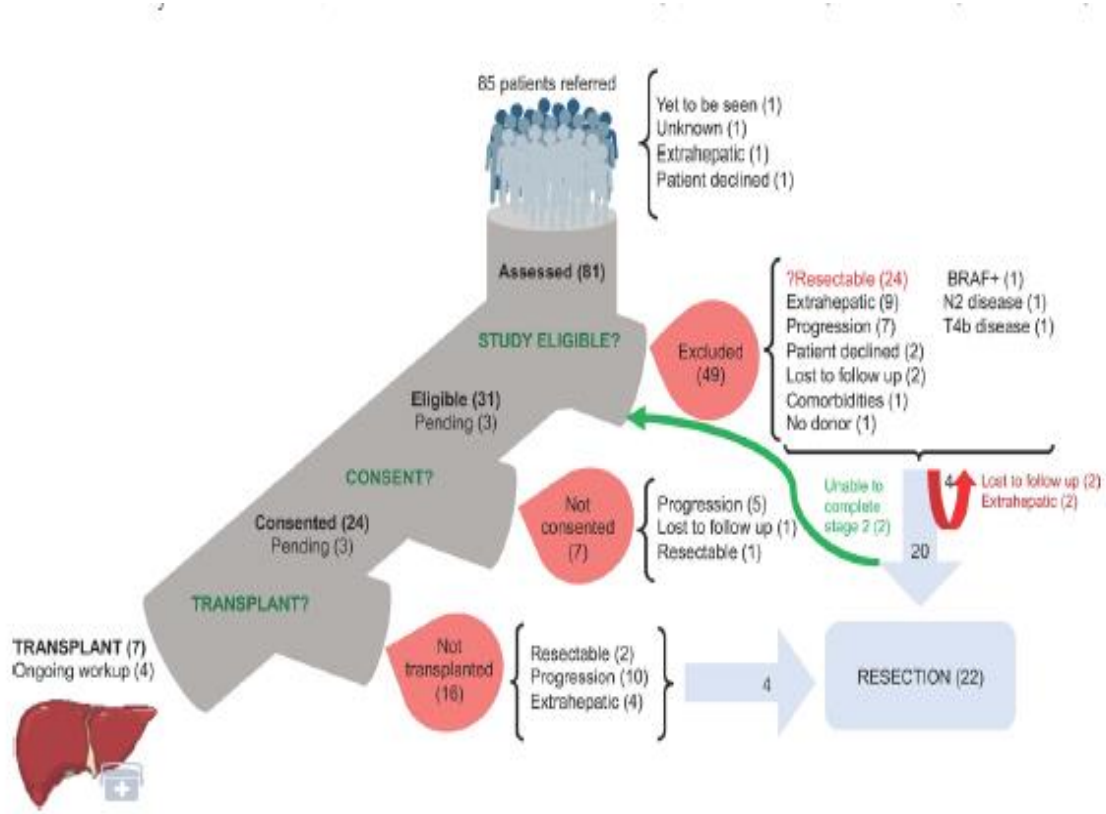
LT for uCLRM – Living Donor LT, Toronto Experience

OS, t=0 at evaluation



DFS, t=0 at surgery





Rajendran L, *J Am Coll Surg* 2023

Liver transplantation for non-resectable colorectal liver metastases: the International Hepato-Pancreato-Biliary Association consensus guidelines

Glenn K Bonney, Claire Alexandra Chew, Peter Lodge, Joleen Hubbard, Karim J Halazun, Pavel Trunecka, Paolo Muiesan, Darius F Mirza, John Isaac, Richard W Laing, Shridhar Ganpathi Iyer, Cheng Ean Chee, Wei Peng Yong, Mark Dhinesh Muthiah, Fabrizio Panaro, Juan Sanabria, Axel Grothey, Keymanthri Moodley, Ian Chau, Albert C Y Chan, Chih Chi Wang, Krishna Menon, Gonzalo Sapisochin, Morten Hagness, Svein Dueland, Pål-Dag Line, René Adam

Lancet Gastroenterol Hepatol
2021; 6: 933–46

Which CLRM pts are good candidates?

- **Unresectable** both before and after chemotherapy (LT outcomes are close to resection)
- Primary tumor is resected
- No extrahepatic disease (other than N1 and ?N2 disease)
- Long term observation on therapy without the development of extrahepatic disease (>1 yr)
- Response to chemotherapy / no progression
- BRAF mutations are a contraindication (aggressive), MSI relative contraindication (response to ICI)
- Pt in good health, no end organ disease, candidate for liver transplant. Preferably living donor

Should Liver Transplantation be a Standard Treatment Option for Metastatic Colorectal Cancer?

- **Yes !**

- Caveats:

  - Complex, multidisciplinary discussions and engagement
  (med onc, surg onc, transplant surg, transplant hepatology, Radiology, IR, etc…)

  - 150,000 CRC/y in the US
  → 30,000 w CLRM.
  Assuming 10% are unresectable and good candidates for transplant
  → 3,000 candidates: **~ 1/3 of all deceased liver donors available.** All living donor liver in the US ~ 600

  - Attention needed to avoiding exacerbating existing barriers to transplantation:
  URM have lower access to LT because of access to insurance, language/cultural barriers, support structure/resources available, all exacerbated further in cases where there is a need to identify a living donor

Thank you!