TORONTO
Liver Transplant Program

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Liver and Pancreas Surgery

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

Paradigm Shift in Transplant Oncology – The Road Ahead

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UHN Ajmera Transplant Centre

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Disclosures:

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

What is Transplant Oncology?

- Revisited area of Transplantation Medicine
- Includes 4 E's (4 pillars)

Sapisochin G, et al. Ann Surg 2020

This is why this is being Revisited

TRANSPLANT ONCOLOGY

Historical Perspective: Transplantation for Liver Malignancies

"…the unequivocal indication for the operation of liver replacement was originally considered to be primary hepatic malignancy which could not be treated with conventional techniques of subtotal liver resection."

Thomas Starzl, MD, PhD - 1969

TRANSPLANT ONCOLOGY

Surgery, Gynecology & Obstetrics DECEMBER 1963 VOLUME 117 NUMBER 6

HOMOTRANSPLANTATION OF THE LIVER IN HUMANS

T. E. STARZL, M.D., F.A.C.S., T. L. MARCHIORO, M.D., K. N. VON KAULLA, M. D., G. HERMANN, M.D., R. S. BRITTAIN, M.D., and W. R. WADDELL, M.D., F.A.C.S.,

Age	Date	City	Diagnosis	Survival (Days)
3	03/63	Denver	Biliary Atresia	0
48	05/63	Denver	Hepatoma w/Cirrhosis	22
68	06/63	Denver	Duct Cell Carcinoma	7.5
52	07/63	Denver	Hepatoma w/Cirrhosis	6.5
58	09/63	Boston	Colon Metastases	11
29	10/63	Denver	Hepatoma	23
75	01/64	Paris	Colon Metastases	0

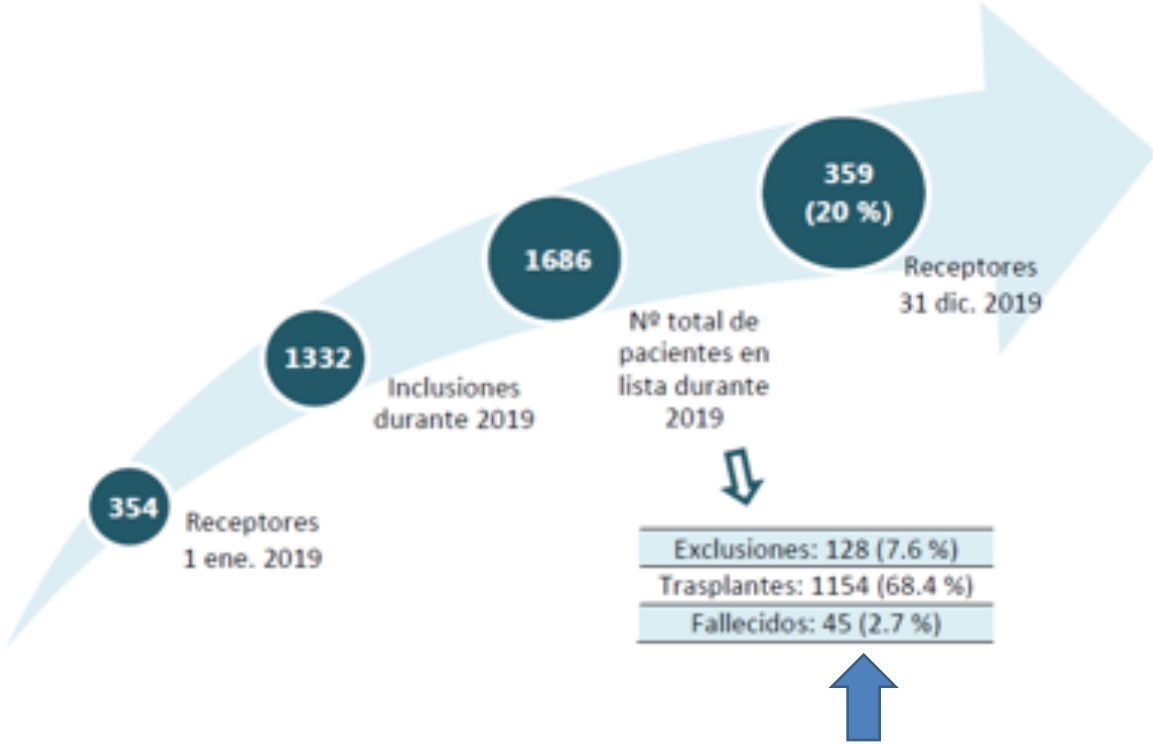
Courtesy of John Fung

Why is there a new era in Transplant Oncology?

- Optimization of surgical and perioperative management (~5% perioperative mortality, 90% 1-year survival)
- Increased availability of donor organ pool (DCD, split, LDLT)
- Minimization of post-LT immunosuppression in cancer patients
- Improvements of systemic therapies for abdominal cancers (colon, cholangio…) Immunotherapy?
- Impact of DAAs for HCV on organ availability
  - Both in US and EU decrease ~30% of decompensated HCV waiting a LT

Mazzaferro V, et al. Liver Transplant 2017
Mazzaferro V. Hepatology 2016
Belli LS, et al. J Hepatol 2016
Flemming JA, et al. Hepatology 2017

Decrease in wait list mortality?



Spanish National Transplant Organization

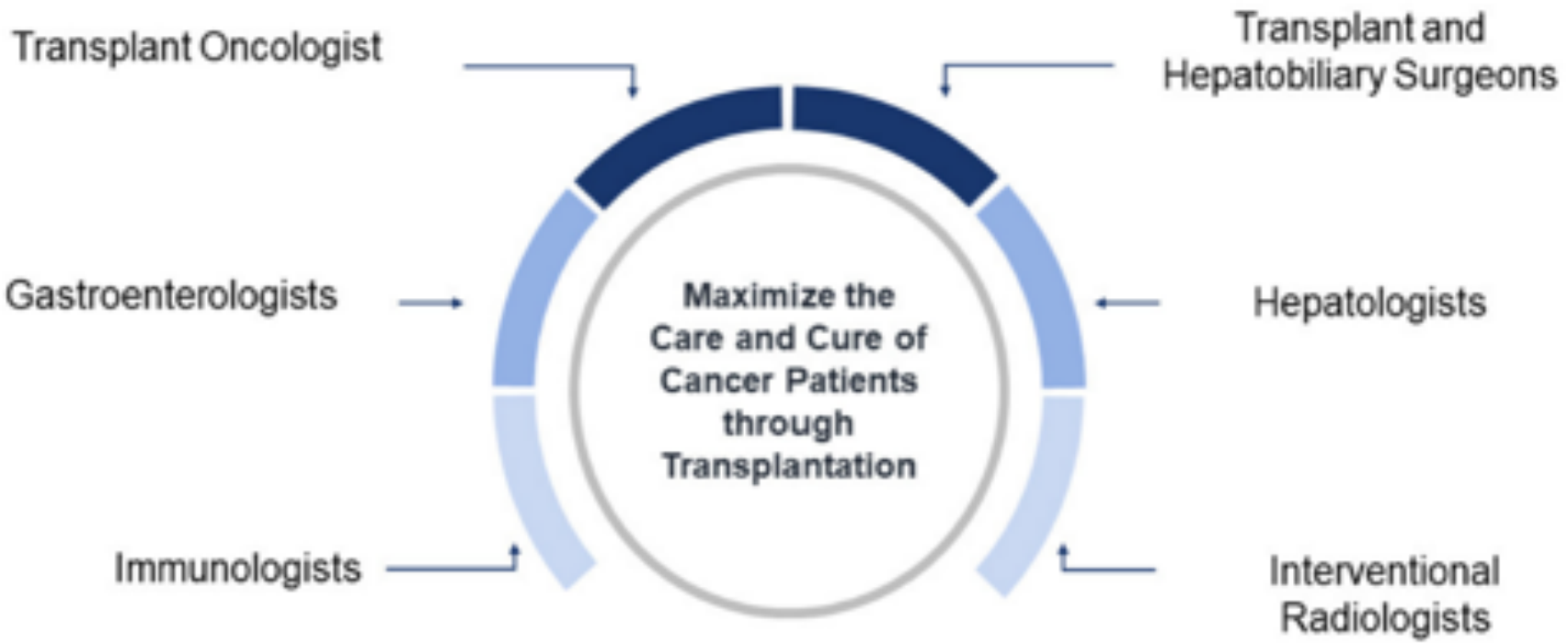
Principles and Controversies of Transplant Oncology

- LT contributes to cure liver tumors by **extending conventional margins of surgical oncology** and eliminating concurrent cancer progression-favoring conditions.
- Successful strategy of LT for cancer depends on reliable determination of the **exclusive liver-restricted** tumor location and growth.
- LT efficacy is increased in tumors with objective and sustained response to **neoadjuvant treatments.**
- In transplanting patients with cancer, **minimal inclusion/exclusion criteria** and achievable endpoints needs to be defined a-priori.

Sapisochin G et al. Ann Surg 2020

Principles and Controversies of Transplant Oncology

- Randomized controlled trials are impeded by the complexity and heterogeneity of transplant activities and waiting-list dynamics. The current framework of pharmacology-oriented clinical research poorly applies to transplant oncology: a field in need of **alternative methodologies to prove the associated benefits.**



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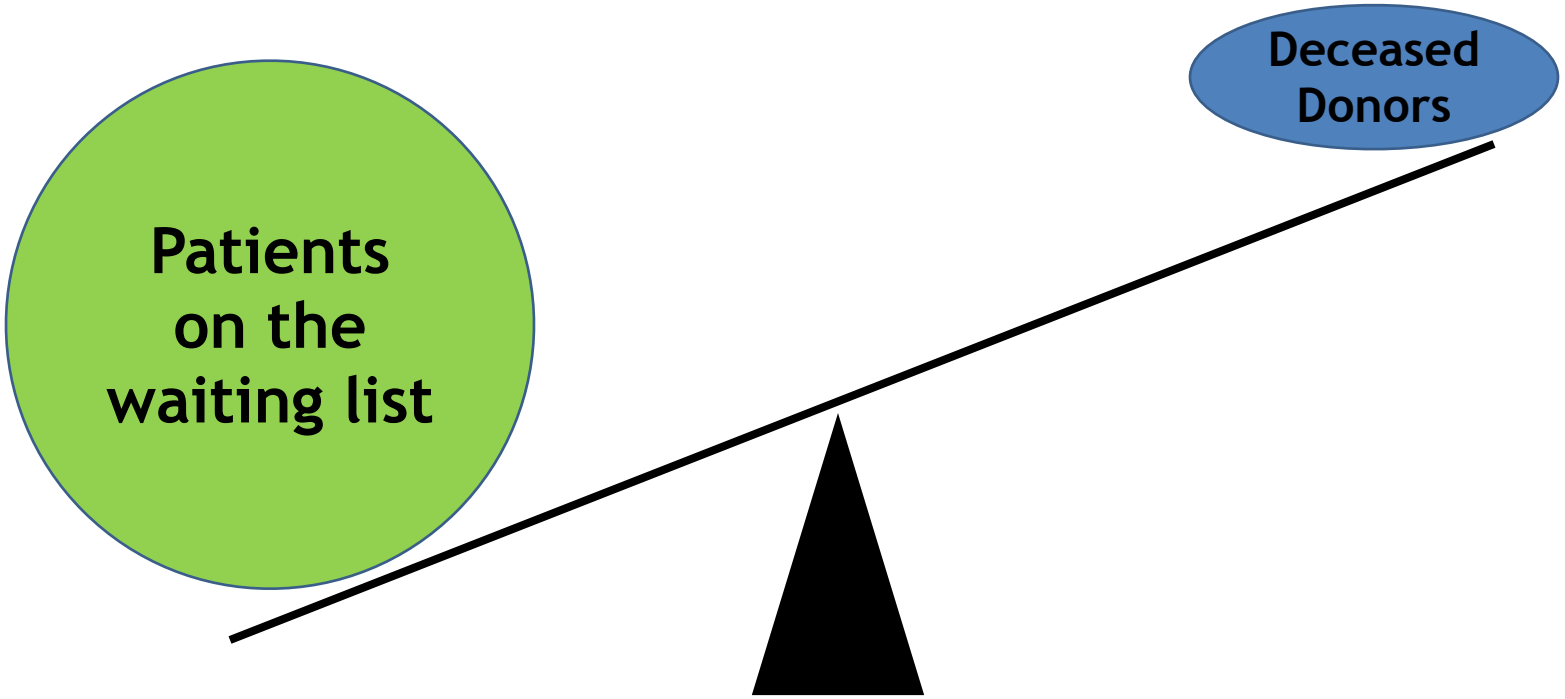
Sapisochin G et al. Ann Surg 2020
Abdelrahim M, et al. Cancers 2021

The Fundamental Problem is Organ Shortage

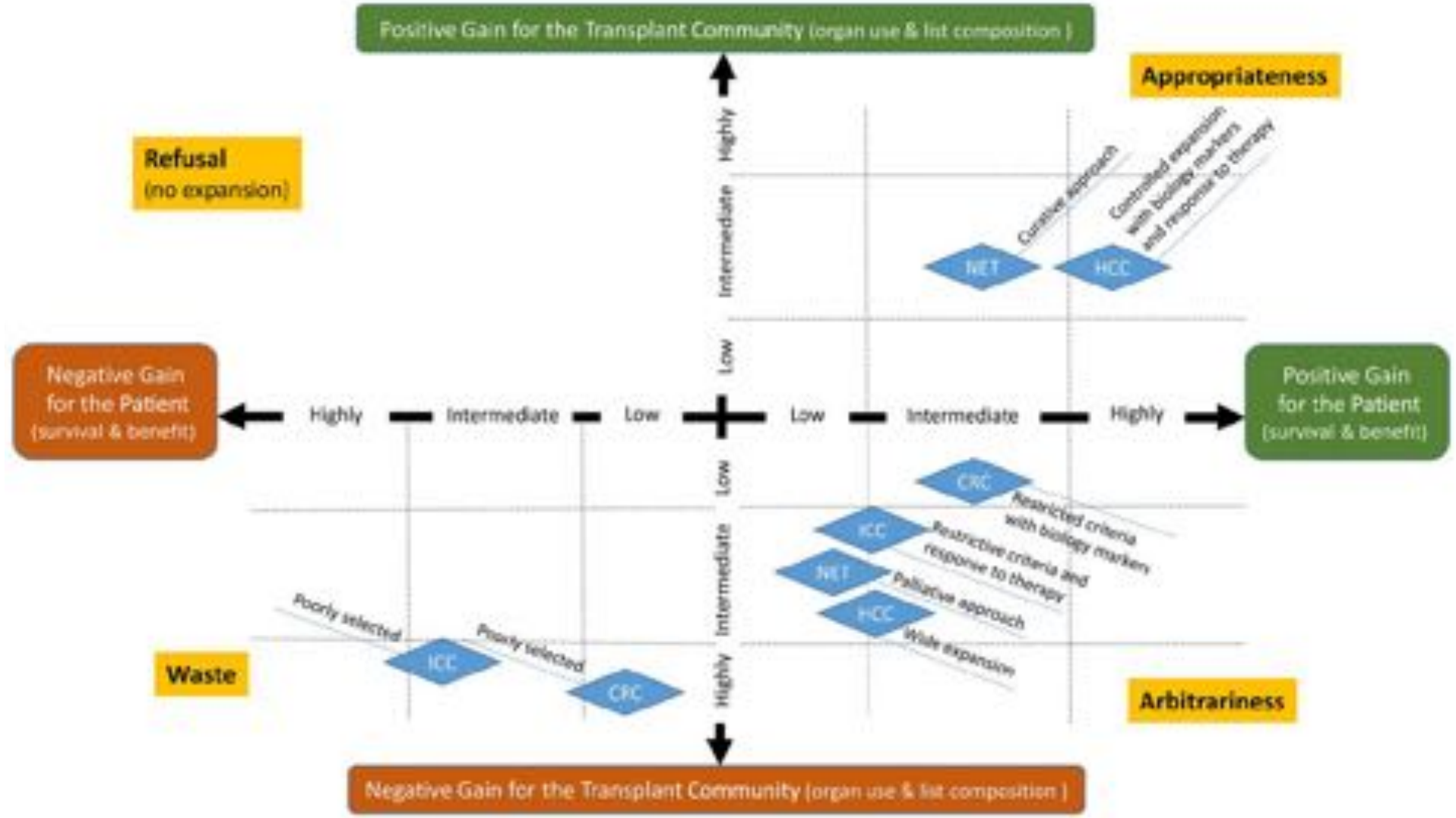
What is the minimum acceptable 5-year survival for patients transplanted with cancer?

50-60% 5-year survival
50% 10-year survival?



Bruix J, et al. Liver Transpl 2003
Navasa M & Bruix J. Hepatology 2009
Samuel D, et al. Liver Transpl 2011
Mazzaferro V. Hepatology 2015

Factors to take into account when expanding the Indications for LT for cancer



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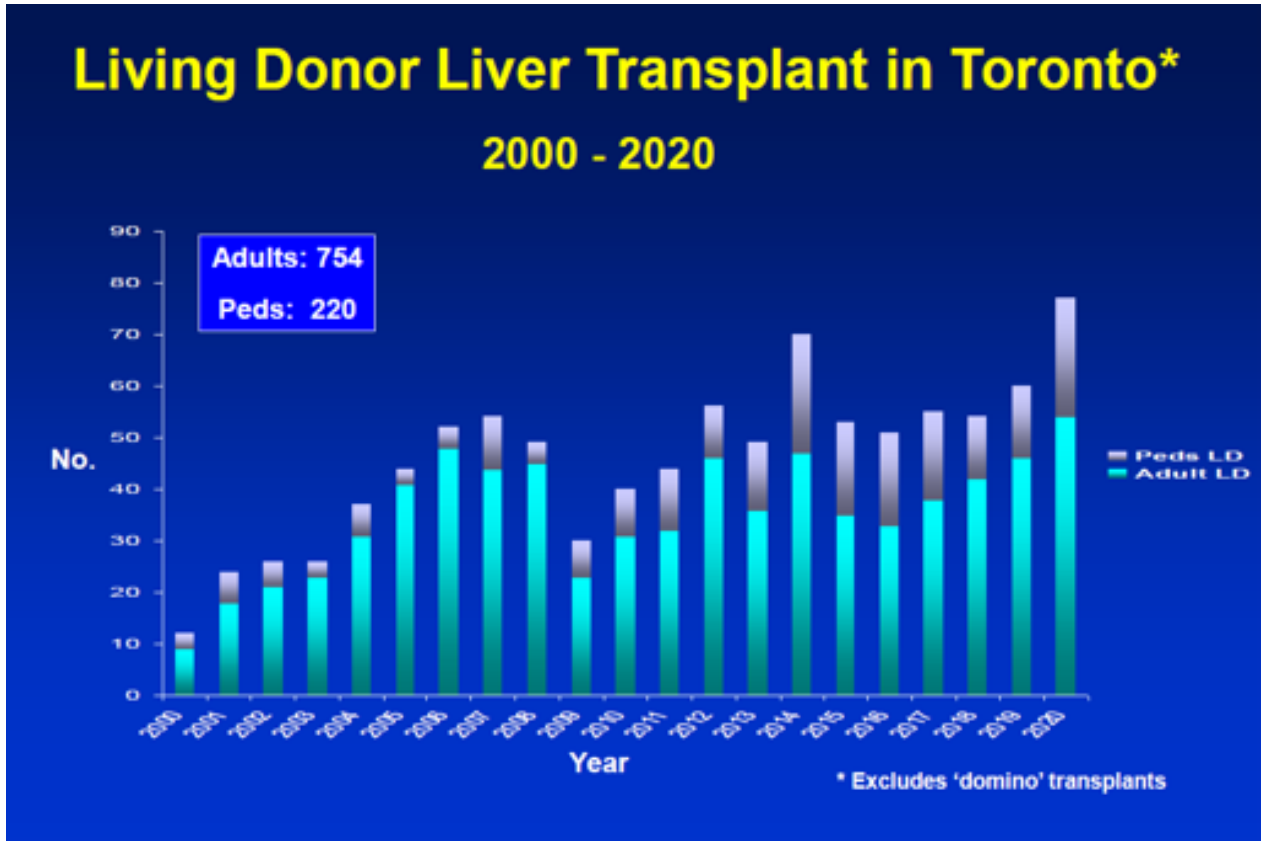
Mazzaferro V, et al. Liver Transplant 2017

Organ Shortage

Wait-list mortality for patients with HCC in Toronto is ~25-30%
Very similar for several jurisdictions in the World

Living donor Liver Transplant Program in Toronto

- **Largest LDLT program Western World >1500 to date**
- 25—35% of LT ~ 220-230 LT/year
- Mainly Right Lobes
- All patients listed are ”encouraged” LDLT



Sapisochin G, et al. Hepatobiliary Surgery and Nutrition 2016
Gorgen A & Sapisochin G, et al. Semin Liv Disease 2018

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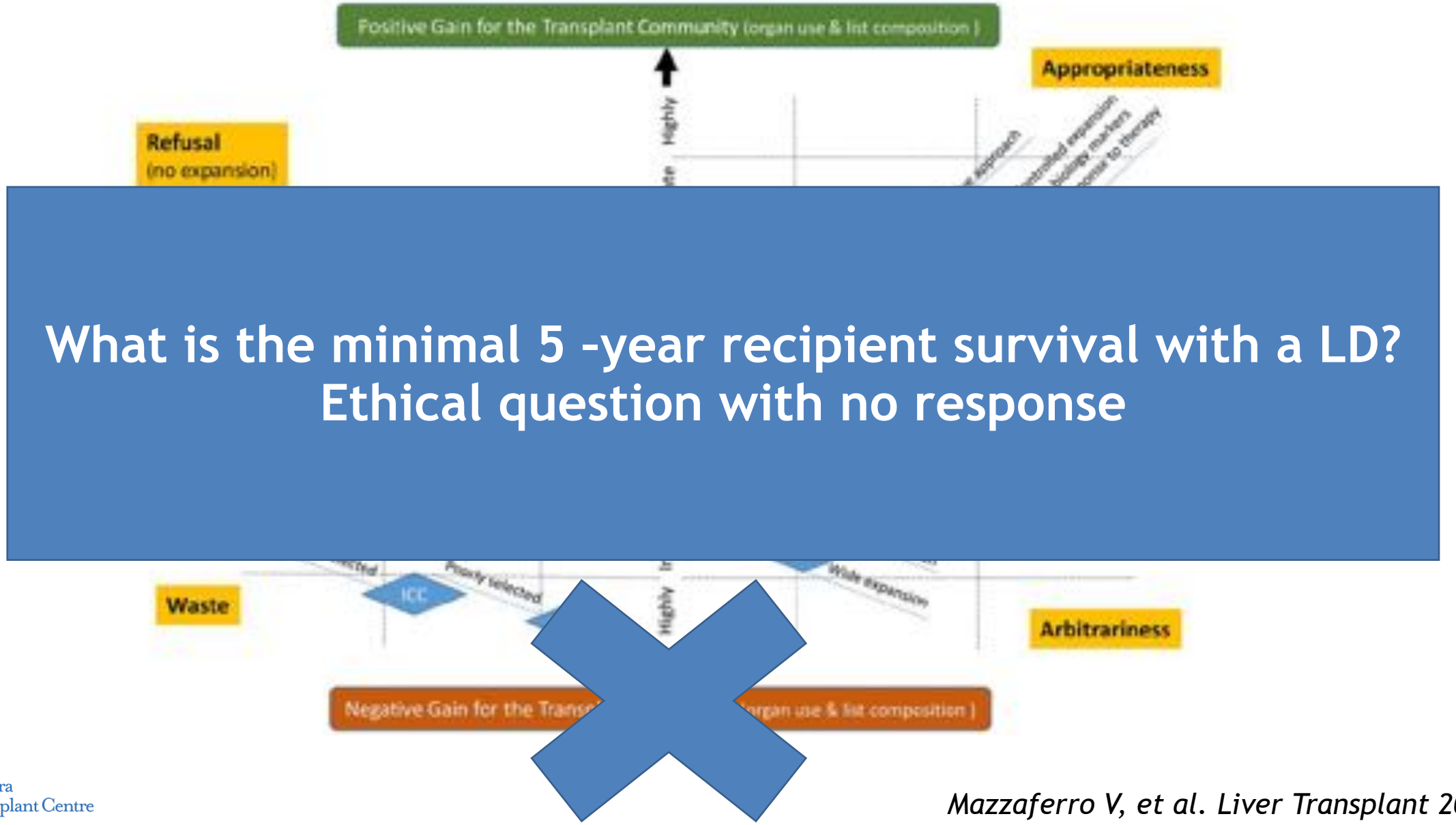
Unlimited Source of Grafts with LDLT



What is the minimal 5 -year recipient survival with a LD?
Ethical question with no response

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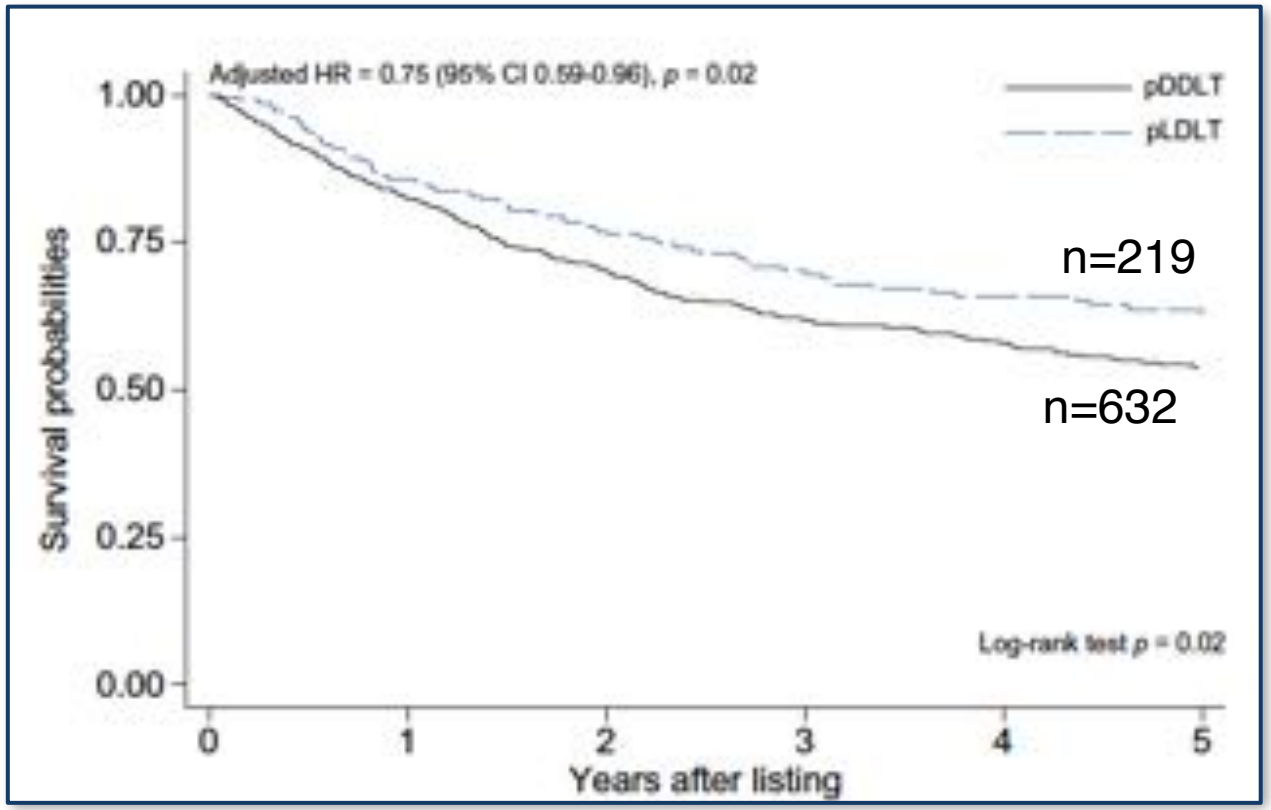
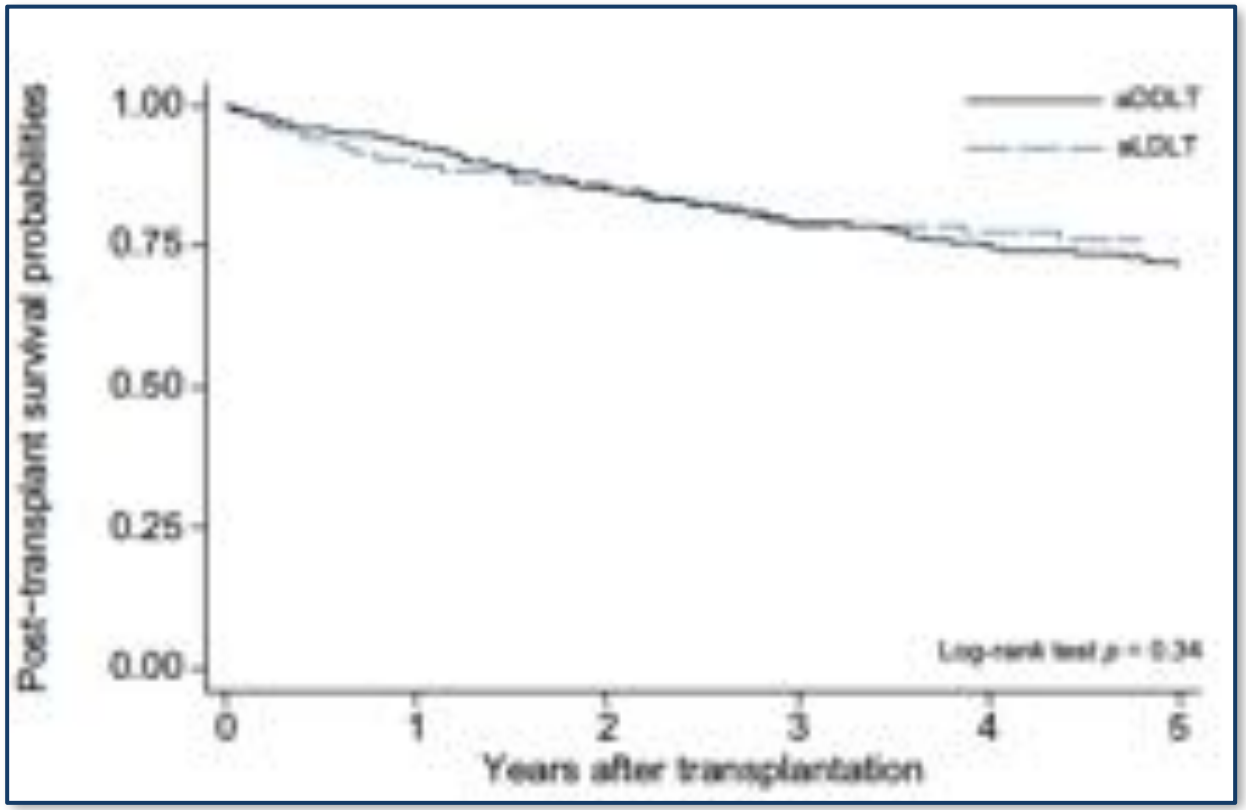
Mazzaferro V, et al. Liver Transplant 2017

Benefit of LDLT in Transplant Oncology

Intention-to-treat Survival



Post-Transplant Survival



Survival advantage of LD available for patients with HCC **HR 0.75 (0.59-0.96), p=0.02**

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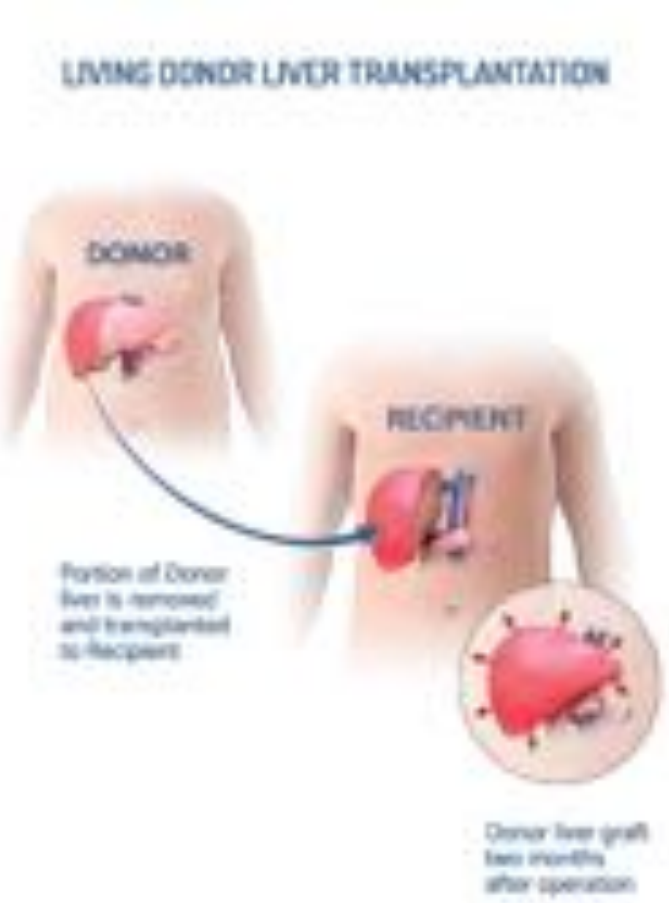
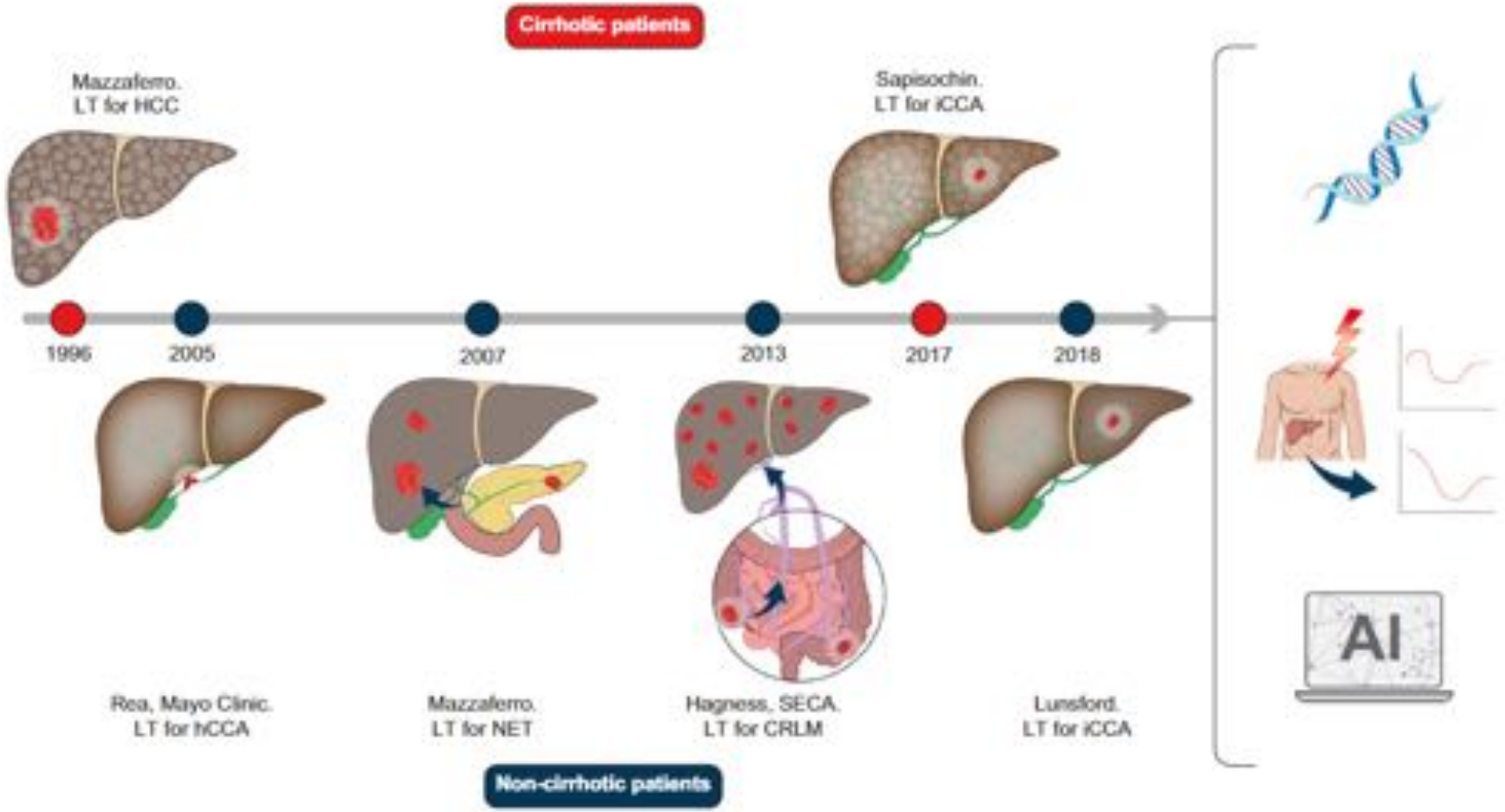
Goldaracena N & Sapisochin G et al. J Hepatol 2019

Advantages of LDLT for Patients with Cancer

- Decreased drop-out rates if graft is available
- Provides a healthy “perfect” graft
- Unlimited source of grafts
  - Extended Criteria
  - Palliative Transplant?
  - Adds another graft to the system



EVOLUTION of Multidisciplinary Care Including Advancements in Solid Organ Transplantation



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Abreu P, Sapisochin G, et al. J Hep Reports 2019

Transplanting patients within the Milan Criteria provides excellent outcomes but…

Milan Criteria

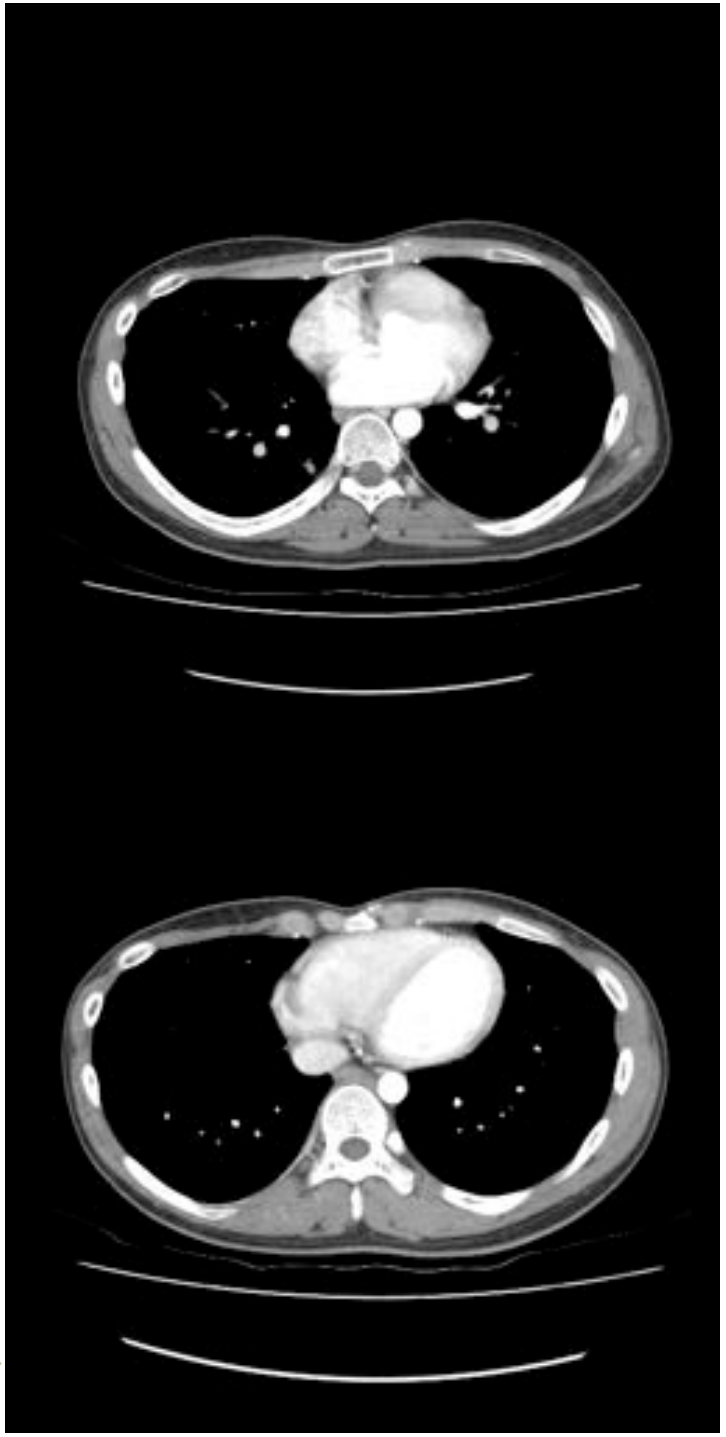
Size/Number Criteria
Single HCC <5 cm or 3 < 3cm

- Too restrictive
- Denies transplant to patients that will have excellent outcomes
- Alternative treatments?

Liver Transplantation for HCC

- Selection of patients is moving beyond size and number
  - Response to therapies (neoadjuvant)
  - Biomarkers (AFP, others)
  - Liquid biopsy, genomics

- Incorporating immunotherapy to the transplant for HCC field?
  - Neoadjuvant?
  - Adjuvant?
  - Treatment of recurrent cancer

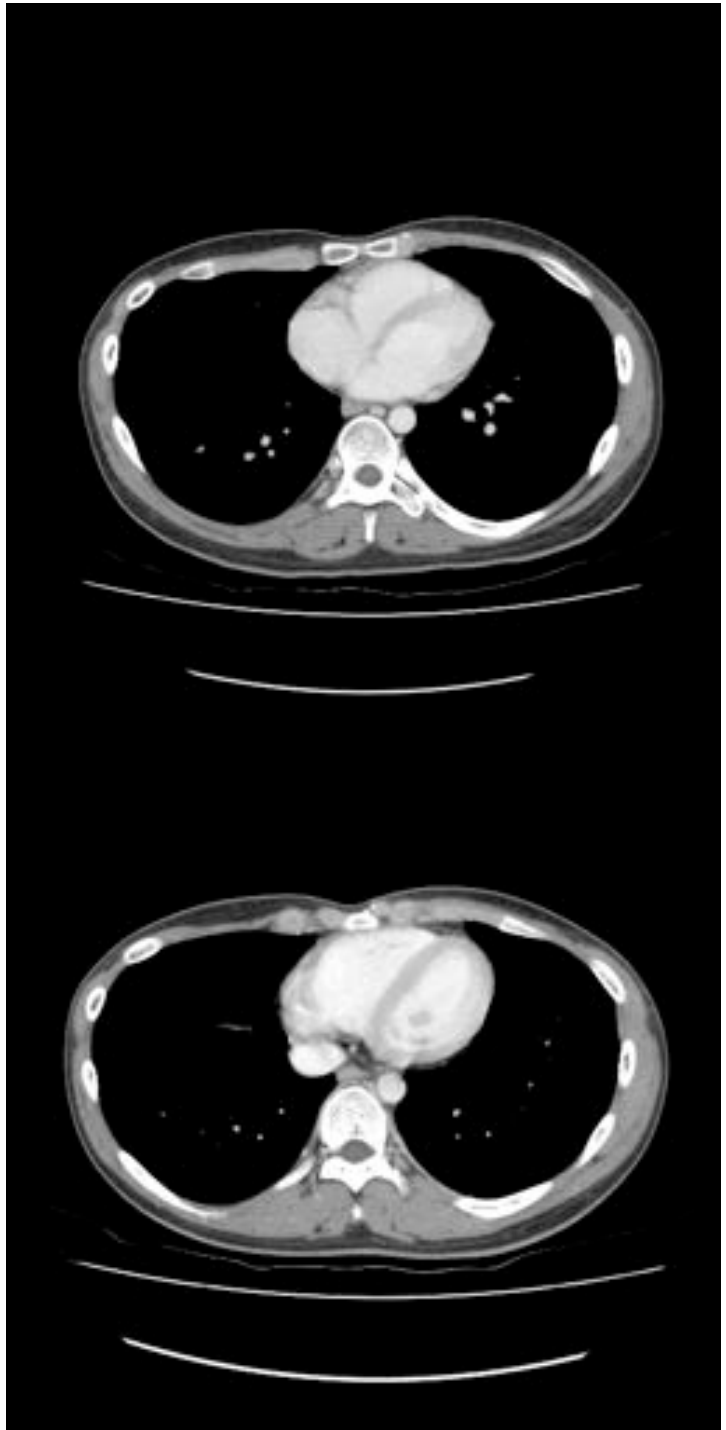


22 year old
No evidence of liver disease
AFP >40.000 µg/L

Atezo/Bev
6 cycles
plus TARE

PR close to CR
AFP 51 µg/L

Left Lobe LDLT
IVC resection

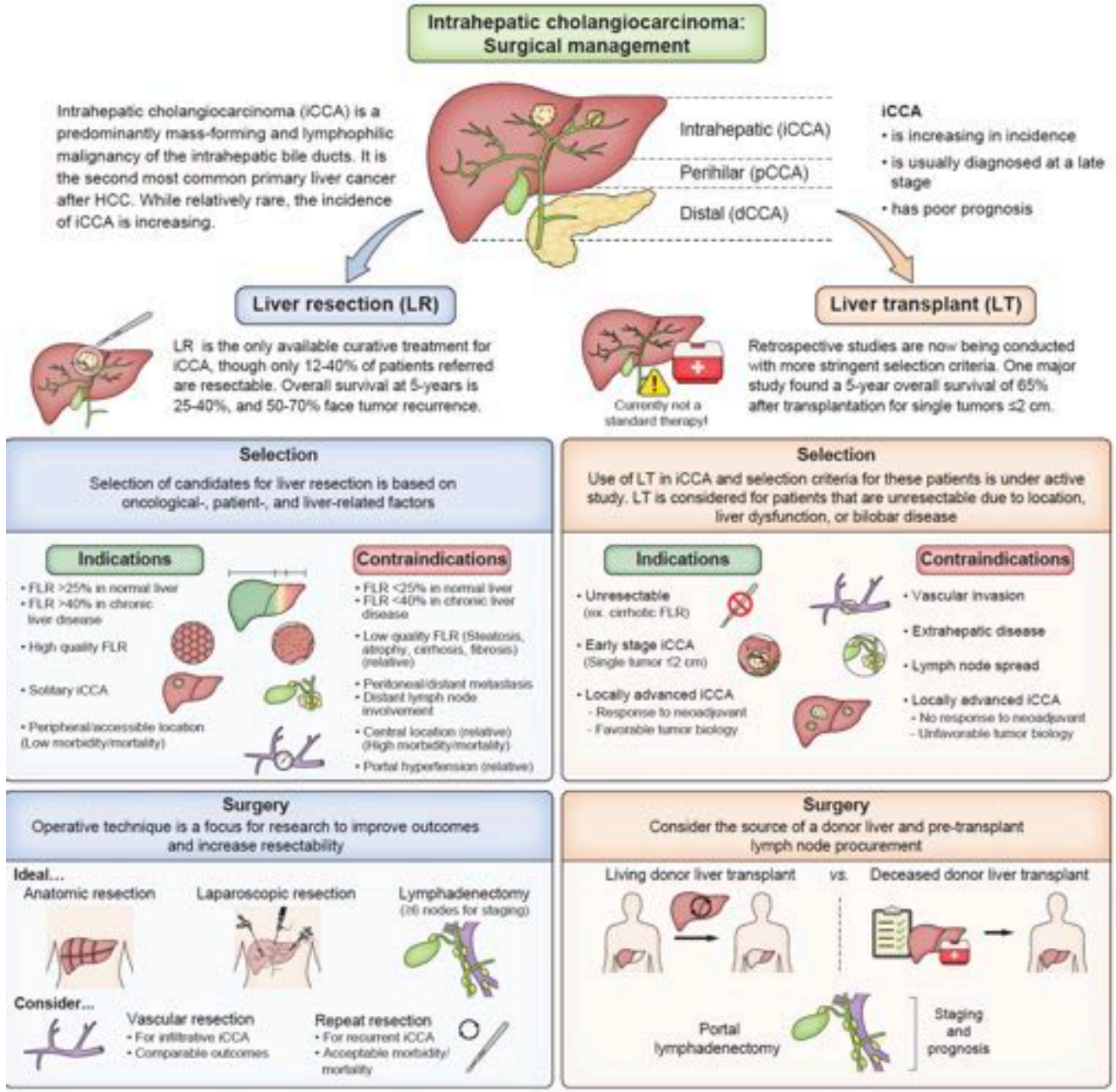


Liver Transplantation for CCA

First treatment option

Solitary iCCA

Hepatectomy plus lymphadenectomy



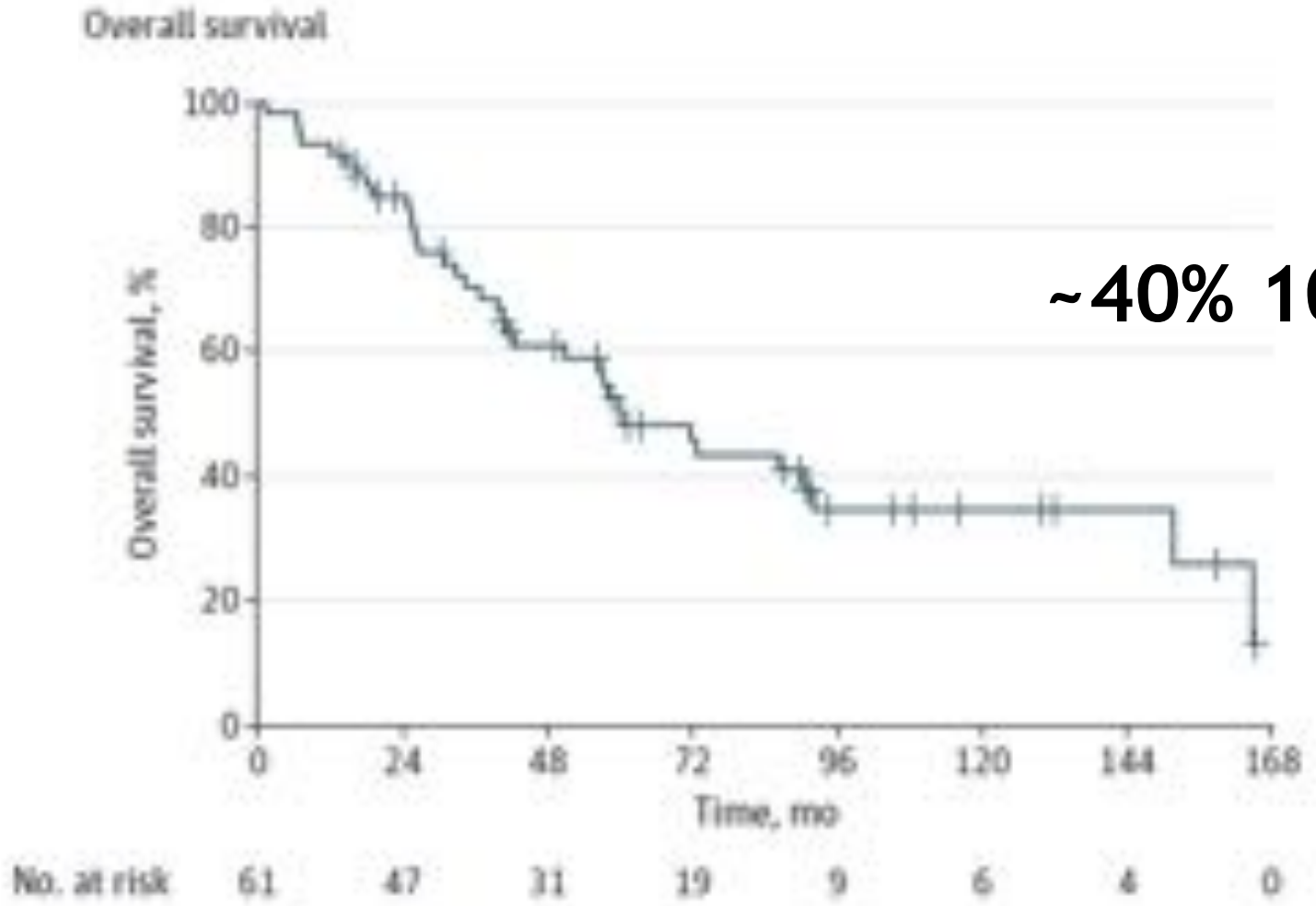
Cirrhotics single ≤3 cm

Experimental for larger and multifocal

Clinical trials

EASL-ILCA Guidelines
J hepatol 2023

Liver Transplantation for CRC Liver Metastases - Long-term Outcomes



~40% 10 year OS!!

Dueland S, et al. JAMA Surgery 2023

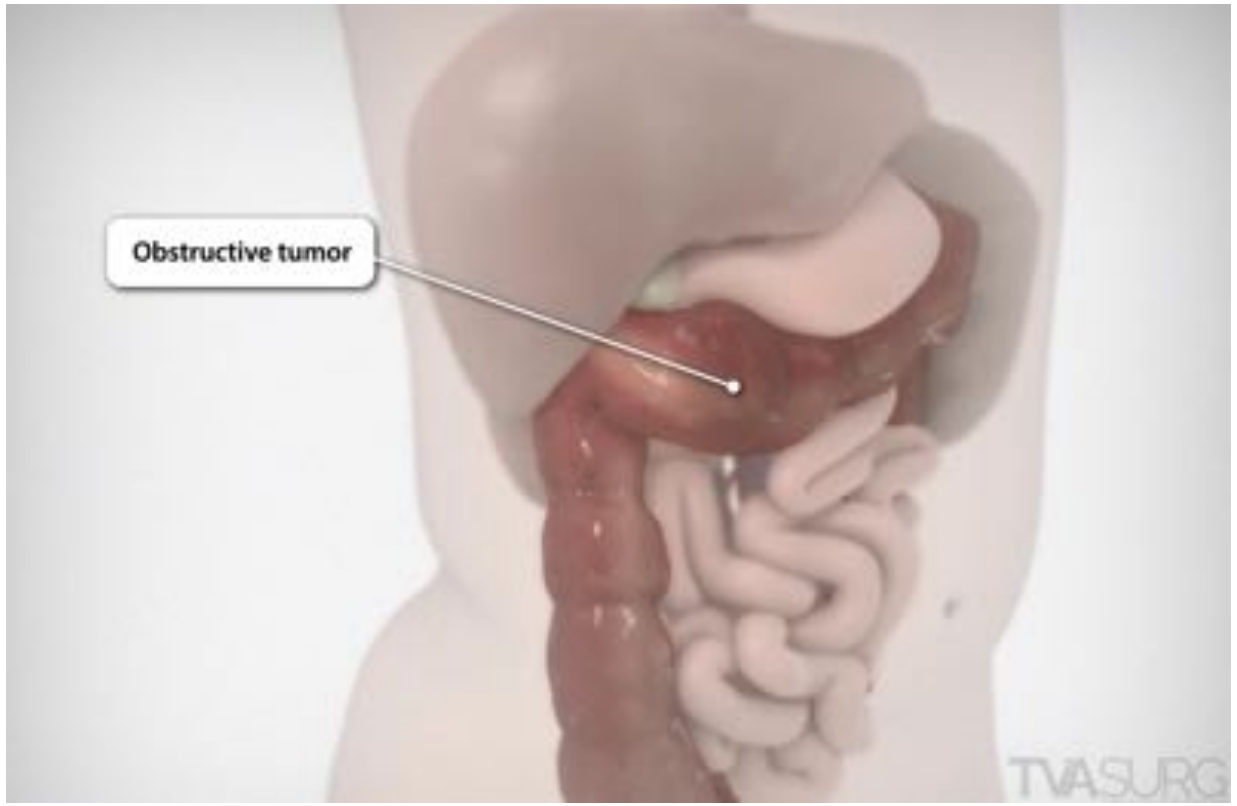
Toronto Protocol for LDLT CRC LM

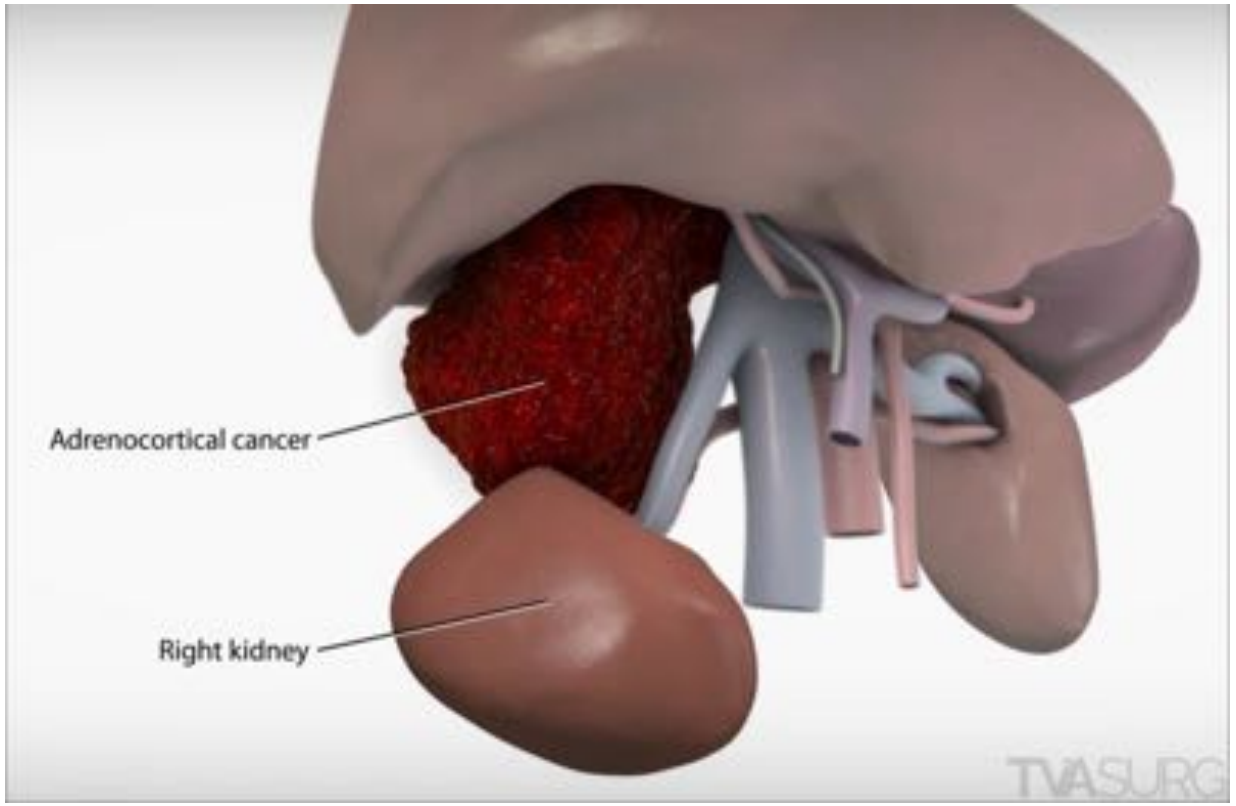
	Chemo type, line, # of cycles prior to initial assessment, total cycles pre-transplant	HAIP (Y/N), time from insertion to transplant	RAS mutation	Tumour type	Explant pathology	Recurrence (Y/N) site, time, treatment	Oslo Score	Post-transplant follow-up
1	FOLFIRI/ Panitumumab, first, 10 cycles, total: 25 cycles	No	No	Left colon	3x foci with ~50% treatment effect	**Yes, intra-abdominal nodes, 12.4 months, chemo**	2	18.9
2	FOLFIRI/ Bevacizumab, first, 18 cycles; total: ~60 cycles	**Yes, 25.0**	Yes	Left colon	6x foci with variable treatment effect	No	1	25.9
3	FOLFIRINOX/ Panitumumab, first, 12 cycles , total: 21 cycles	**Yes, 14.6**	No	Left colon	6x foci + satellites, 95-100% necrosis/ fibrosis	No	1	20.1
4	FOLFIRI/ Panitumumab, first, 12 cycles, total: ~20 cycles	No	No	Rectal	2x foci, one viable <50% treatment effect	No	0	20.5
5	FOLFIRI / Bevacizumab, first, 14 cycles, total: 30 cycles	No	No	Right colon	14x foci, 90-100% necrosis	**Yes, lung, 3.3 months, chemo**	1	39.4 DECEASED
6	FOLFIRI/ Bevacizumab, first, 19 cycles; total: 32 cycles	**Yes, 19.0**	No	Left colon	11x foci, rare viable cells	No	1	49.0
7	FOLFOX, Second, 12 cycles, total: ~32 cycles	No	No	Left colon	1 foci, <50% necrosis	No	0	8.0
8	FOLFIRI/ Bevacizumab, Second, 3 cycles, total: ~16 cycles	No	No	Rectal	5x foci; 3 lesions >50% necrosis; 2 lesions <50% necrosis	No	1	5.6
9	FOLFIRI/Panitumumab/ Bevacizumab, first, 43 cycles, total: ~54 cycles	No	Yes	Left colon	Pending	No	0	0.2

EVOLUTION of Multidisciplinary Care Including Advancements in Solid Organ Transplantation
The ROAD AHEAD

- Increase in patient referral – engagement from oncologists.
- More data from trials.
- More wide accceptance of certain indications (i.e CRC LM)

EXTENSION of the Traditional Margins of Surgical Oncology





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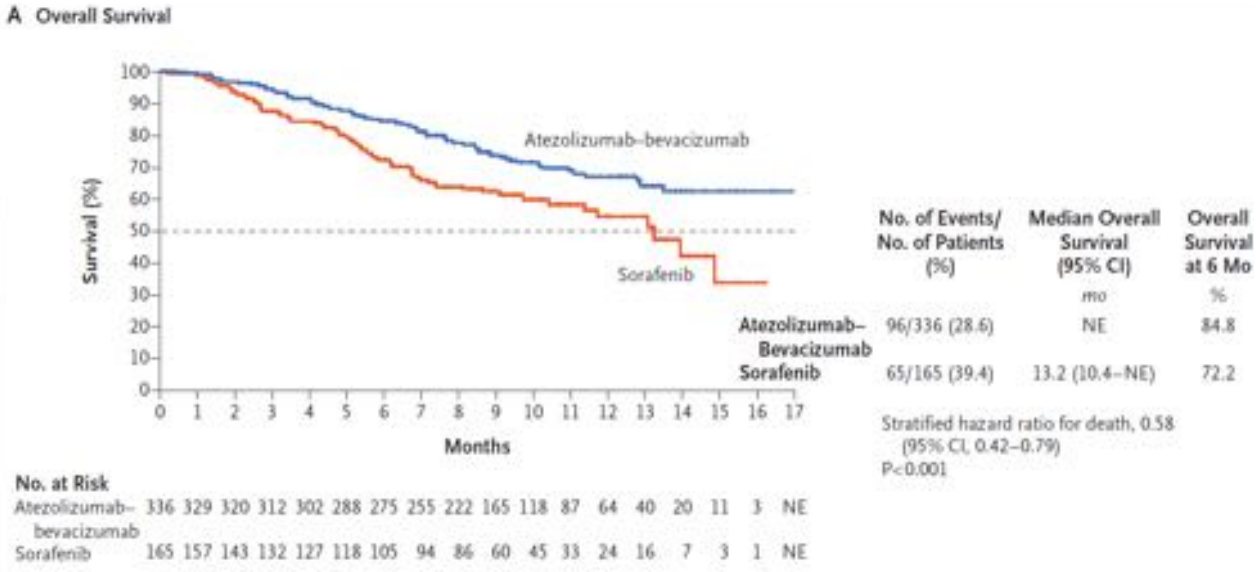
TVASurg.ca and Dr. Ian D. McGilvray

EXTENSION of the Traditional Margins of Surgical Oncology
The ROAD AHEAD

- Consolidation of HPB and Transplant Teams.
- Combined HPB and Transplant Training.
- Large international cohorts needed.

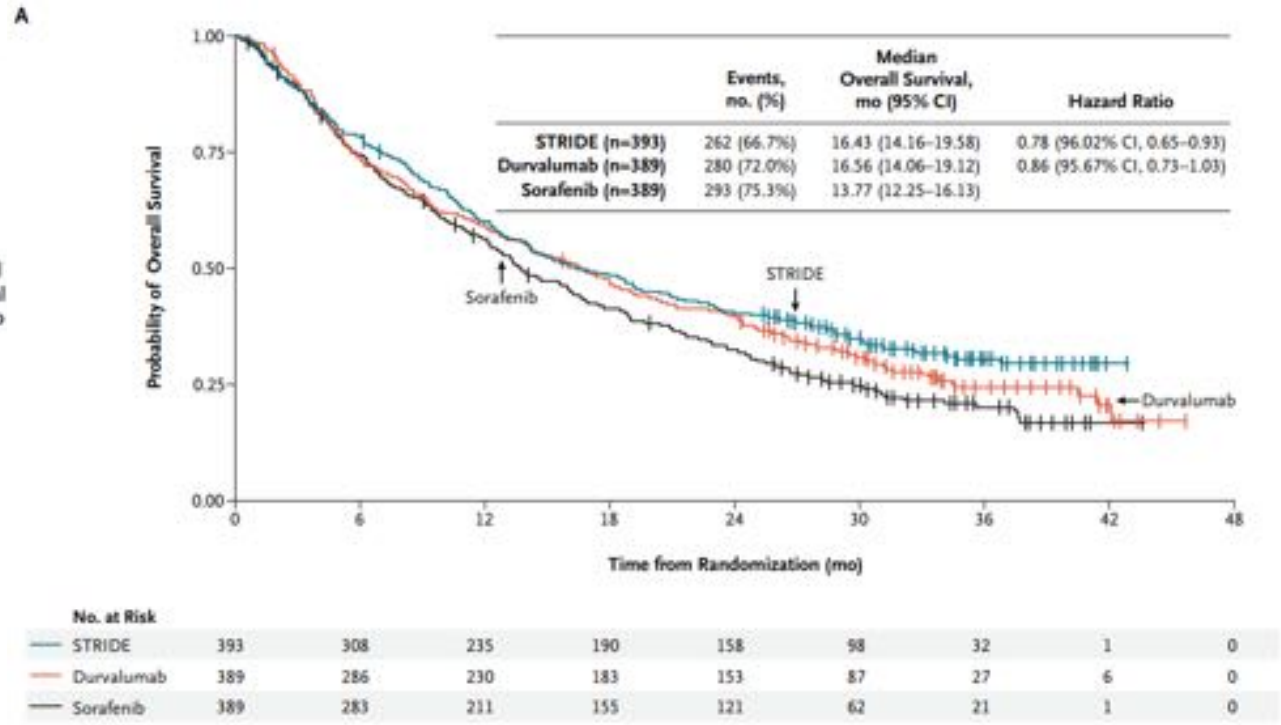
ELUCIDATION of Self and Non-Self Recognition: Tumor and Transplant Immunology Change Paradigm in HCC Treatment

Imbrave-150 Trial



Finn RS, et al. NEJM 2020

Himalaya Trial



Abou-Alfa GK, et al. NEJM Evid 2022

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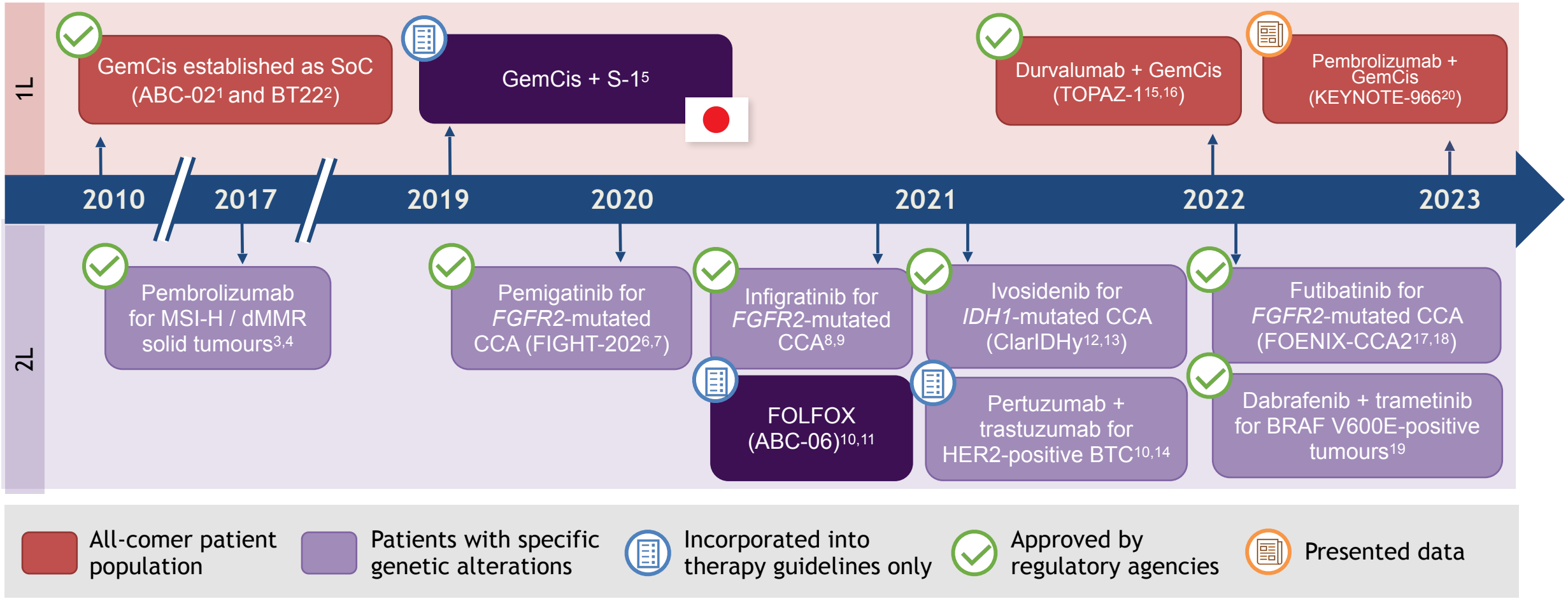
ELUCIDATION of Self and Non-Self Recognition: Tumor and Transplant Immunology

- Immunotherapy is becoming the standard of cancer therapy for many malignancies including HCC.

- The use of Immunotherapy in the transplant setting is under debate.

- Hot topic in transplantation and cancer medicine.

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



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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

ELUCIDATION of Self and Non-Self Recognition: Tumor and Transplant Immunology

Case Series of Patients Transplanted after Immunotherapy Treatment

Author, year	No. of patients	Study duration and setting	Intervention	Follow-up	Outcome
Abdelrahim, 2022[11]	1	Neoadjuvant	Downstaging using 6 cycles of atezolizumab; 1,200 mg given intravenously plus a total of 5 cycles of bevacizumab, 15 mg/kg; held 8 weeks before LT	1 year	Alive without severe allograft rejection or losses
Tabrizian, 2021[8]	9	2017-2020 Neoadjuvant	Received neoadjuvant nivolumab; 8/9 received last dose within 4 weeks of LT for HCC	16 months (range 8-23)	Alive without severe allograft rejection or losses
Lizaola-Mayo, 2021[12]	1	Neoadjuvant	Downstaging ipilimumab and nivolumab for 6 months after 3 months of sorafenib; stopped 9 weeks before LT	6 months	Alive without severe allograft rejection or losses
Nordness, 2020[9]	1	2017-2019 Neoadjuvant	HCC within Milan but high AFP; progressive disease not responsive to sorafenib; downstaging TACE plus nivolumab for 2 years until 8 days before LT; underwent LT (within Milan) in 2019	10 days	Acute hepatic necrosis leading to death
Schwacha-Eipper, 2020[13]	1	2015-2020 Neoadjuvant	Downstaging nivolumab for 34 cycles after nonresponse to 14 months of sorafenib for multifocal HCC; underwent LT 15 weeks after discontinuation of nivolumab	1 year	Alive without severe allograft rejection or losses

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Choi WJ, O'Kane G, Sapisochin G. ASCO Daily News 2023

ELUCIDATION of Self and Non-Self Recognition: Tumor and Transplant Immunology

Clinical Trials utilizing Immunotherapy Pre-transplant

Trial no., start year	Institution/location	Design	Estimated enrollment no.	Primary outcome
NCT05185505, 2022	Houston Methodist Research Institute; University Health Network, Toronto	Single-arm, LT for HCC beyond Milan criteria, neoadjuvant atezolizumab and bevacizumab	24	% of patients receiving LT experiencing acute rejection (within 1 year)
NCT05339581 (iPLENTY-pvtt), 2022	Renji Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai	Pilot, parallel, LT for HCC with Vp3 PVTT Arm A: neoadjuvant intensity-modulated radiotherapy plus PD-1 blockade plus lenvatinib Arm B: PD-1 blockade and lenvatinib; 42 days and 7 days off medications before LT for pembrolizumab and lenvatinib, respectively	78	1-year PVTT-related response and necrosis rate
NCT04425226 (PLENTY202001), 2020	Renji Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai	Parallel RCT, LT for beyond Milan criteria Arm A: neoadjuvant pembrolizumab plus lenvatinib Arm B: LT only; 42 days and 7 days off medications before LT for pembrolizumab and lenvatinib, respectively	192	4-year RFS

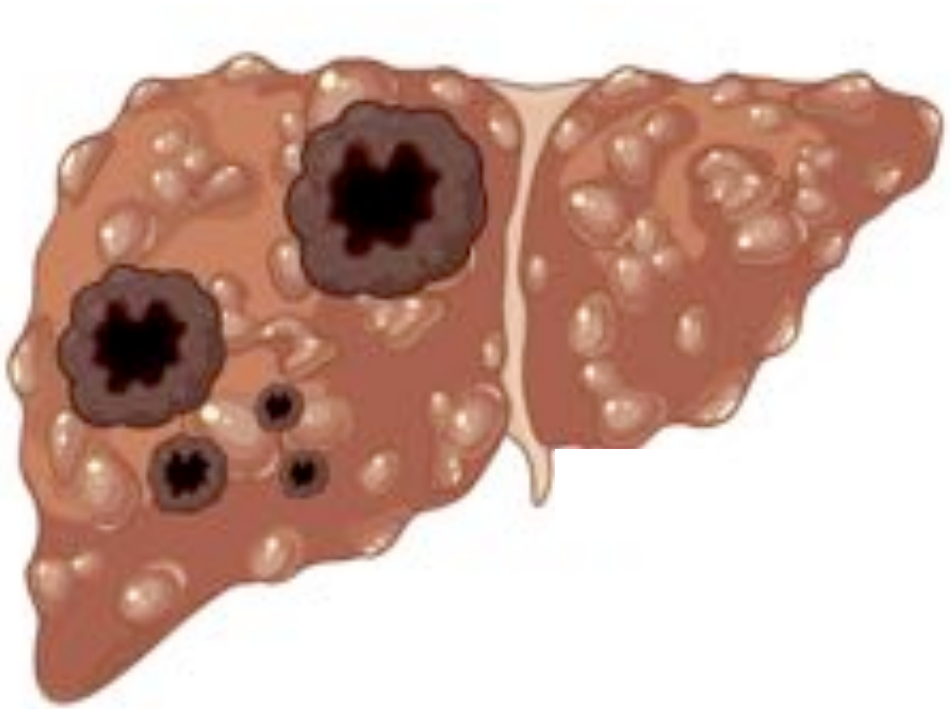
Choi WJ, O'Kane G, Sapisochin G. ASCO Daily News 2023

ELUCIDATION of Self and Non-Self Recognition: Tumor and Transplant Immunology The ROAD AHEAD

- Immunotherapy will be or is being incorporated in transplant oncology.
- Need better understanding on which check point inhibitors, when and combined with which immunosuppression.
- Identification of biomarkers of response.

EXPLORATION of Genomic Mechanisms of Carcinogenesis

Unique Source of Tumoral Material

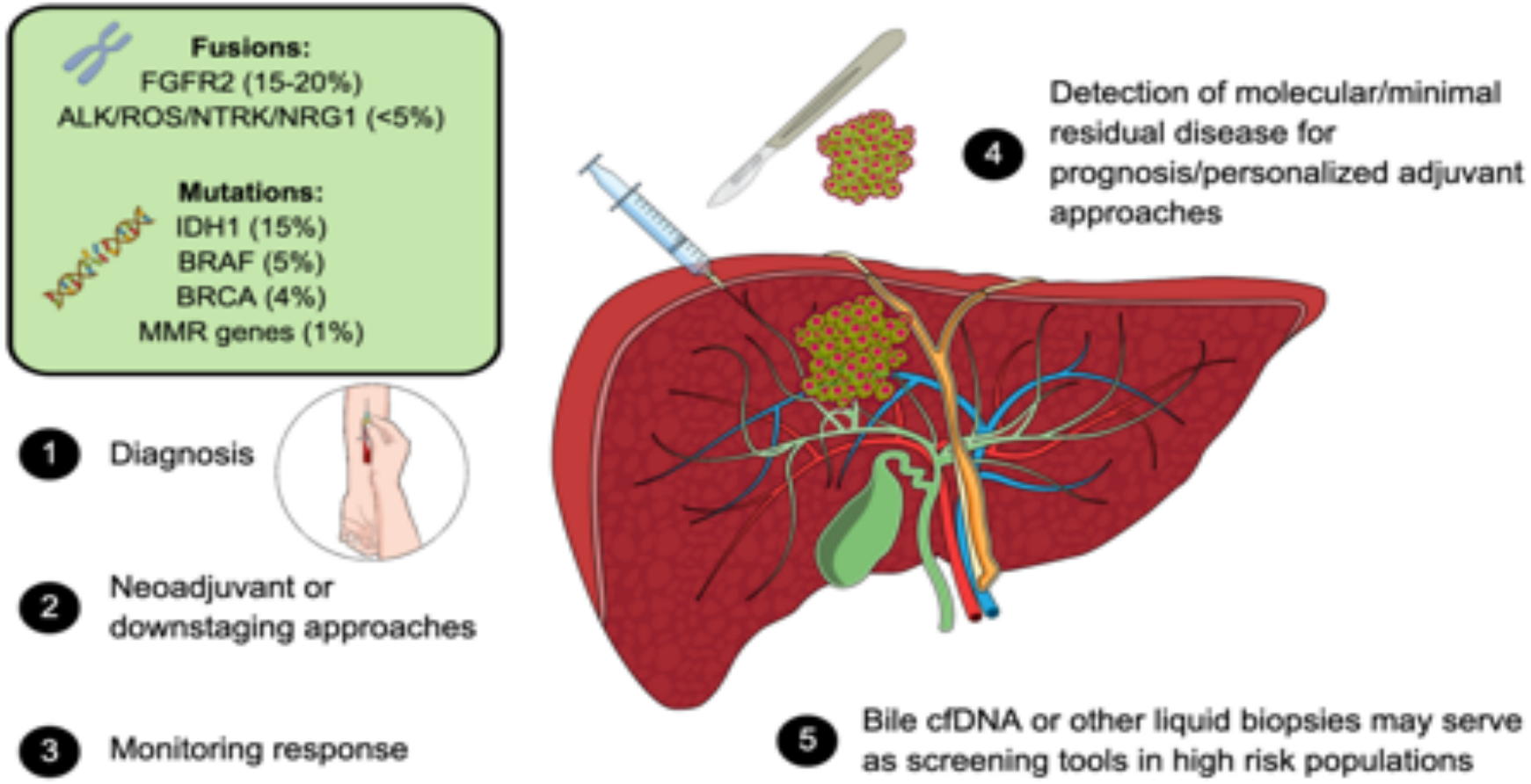


Biomarker Discovery

Tumor-Tumor Interactions

HCC; NETs; CCA; CRC LM

EXPLORATION of Genomic Mechanisms of Carcinogenesis



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

EXPLORATION of Genomic Mechanisms of Carcinogenesis
The ROAD AHEAD

- Application of better biomarkers for patients selection.
- Incorporation of liquid biopsy for treatment response and patient selection.
- Lots of very exciting research!

Transplant Oncology in Other Organs?

NORTH STAR study
Non-ablative Oligofractionated Radiation Therapy before Surgical Transplantation As Radiovaccination

Hypothesis

- Sub-ablative radiation delivered to the pulmonary malignancy followed by resection of the radiated tumor with the explanted lung at the time of transplant can act as an oncolytic radiovaccine to reduce the risk of cancer recurrence after transplantation.

Courtesy of Dr. Marc De Perrot

Paradigm Shift in Transplant Oncology Summary

- Transplant Oncology is here now and will only continue to evolve.
- Transplant Oncology will become the leading indication for LT in the next decade.
- Transplant Oncology provides a UNIQUE opportunity for cancer research.
- Engagement of local and global oncology community is key.

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Outline

- Liver Transplantation for Hepatocellular Carcinoma (HCC) New Insights
- Liver Transplantation for Hilar and Intrahepatic Cholangiocarcinoma
- Liver Transplantation for Unresectable Liver Metastases from colorectal cancer

Liver Transplantation for Hepatocellular Carcinoma
New Insights

Transplanting patients within the Milan Criteria provides excellent outcomes but…

Milan Criteria

Size/Number Criteria
Single HCC <5 cm or 3 < 3cm

- Too restrictive
- Denies transplant to patients that will have excellent outcomes
- Alternative treatments?

Liver Transplantation for HCC

- Selection of patients is moving beyond size and number
  - Response to therapies (neoadjuvant)
  - Biomarkers (AFP, others)
  - Liquid biopsy, genomics

- Incorporating immunotherapy to the transplant for HCC field?
  - Neoadjuvant?
  - Adjuvant?
  - Treatment of recurrent cancer

Liver Transplantation for Hilar and Intrahepatic Cholangiocarcinoma

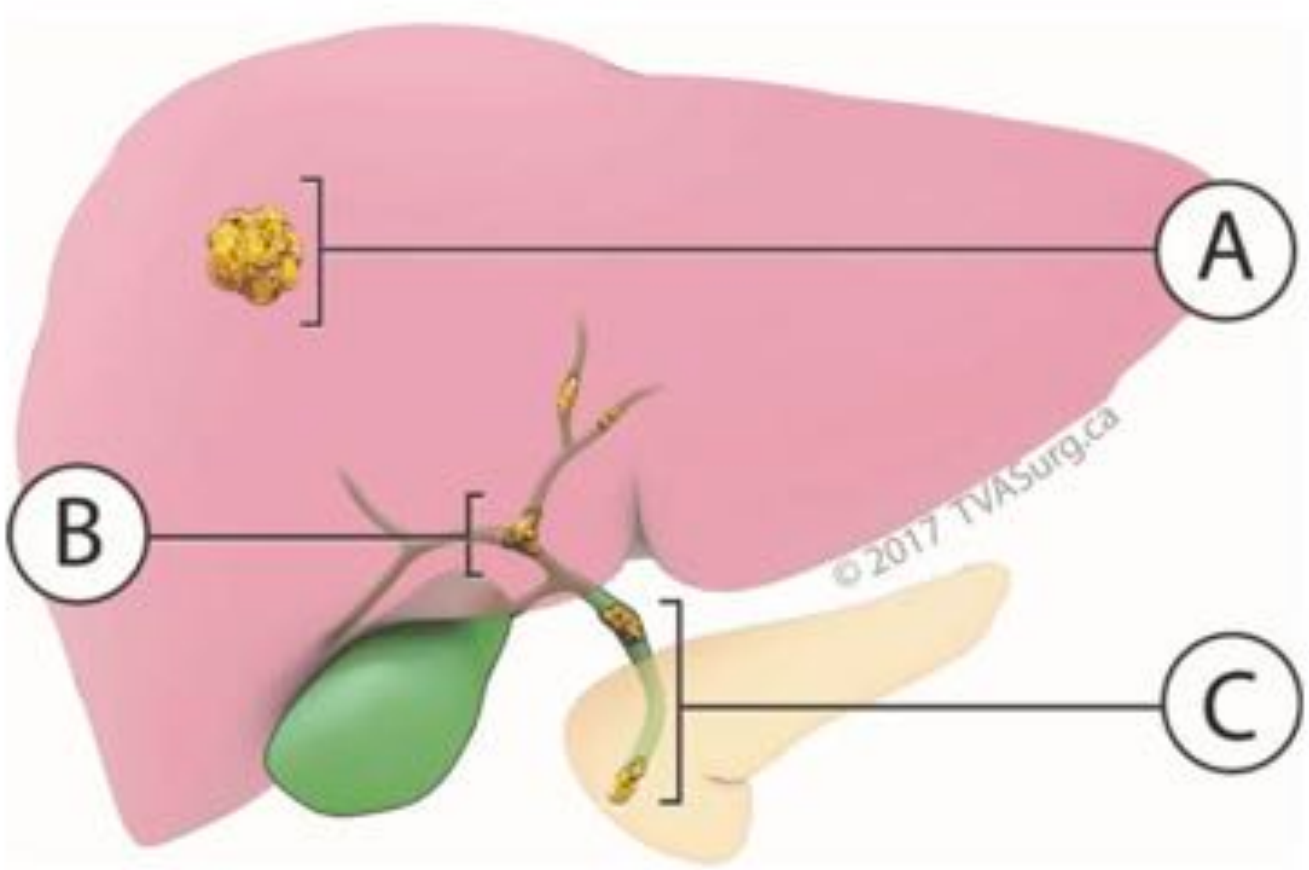


FIG. 1. CCA locations. (A) Intrahepatic (iCCA). (B) Hilar (hCCA). (C) Distal.

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

Hilar Cholangiocarcinoma

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

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

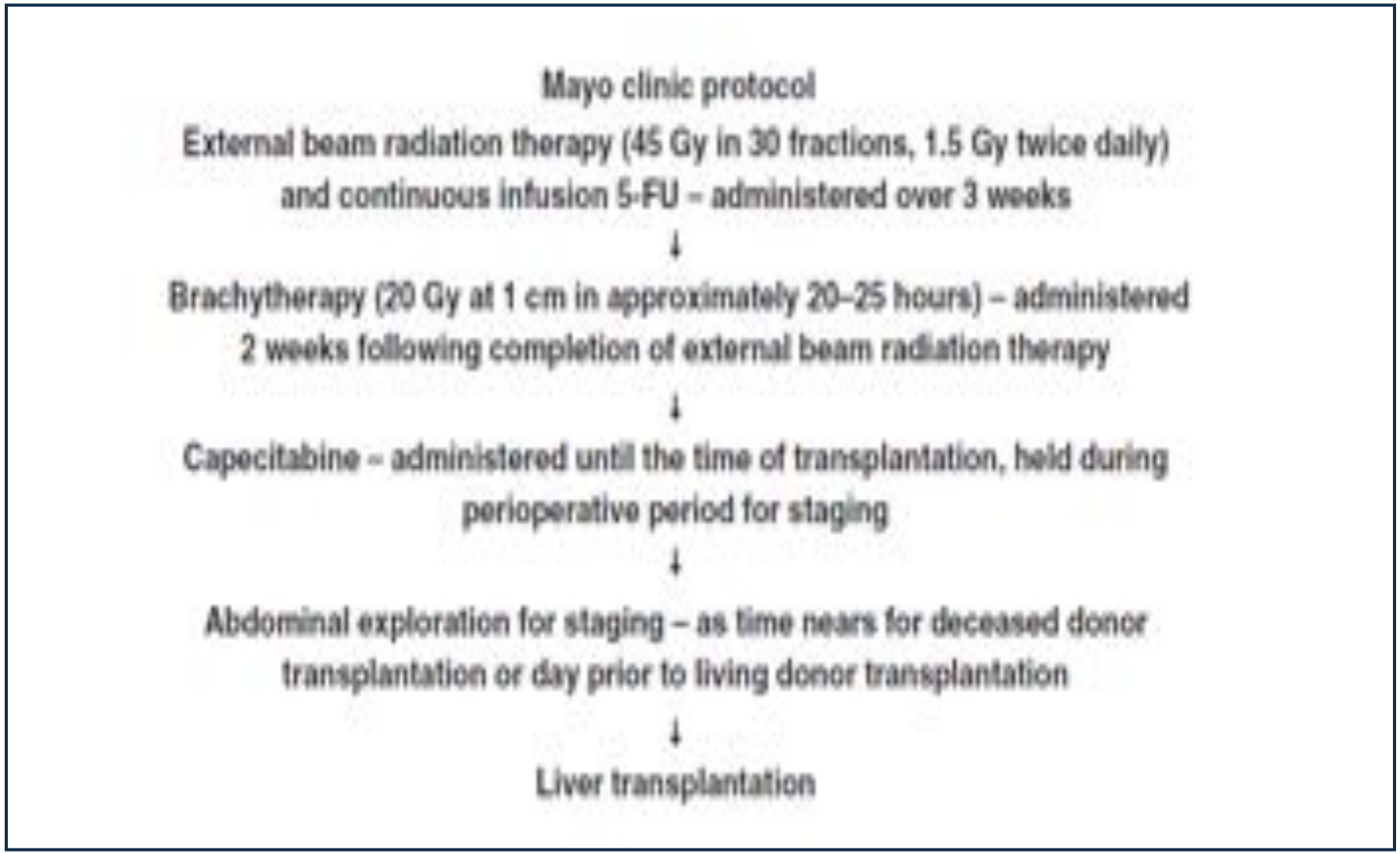
   - Malignant cytology or histology
   - CA-19.9 > 130 U/mL without cholangitis
   - Mass on cross-sectional imaging (radial diameter ≤3 cm)
   - No extrahepatic disease

2. Cancer located primarily above the cystic duct

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

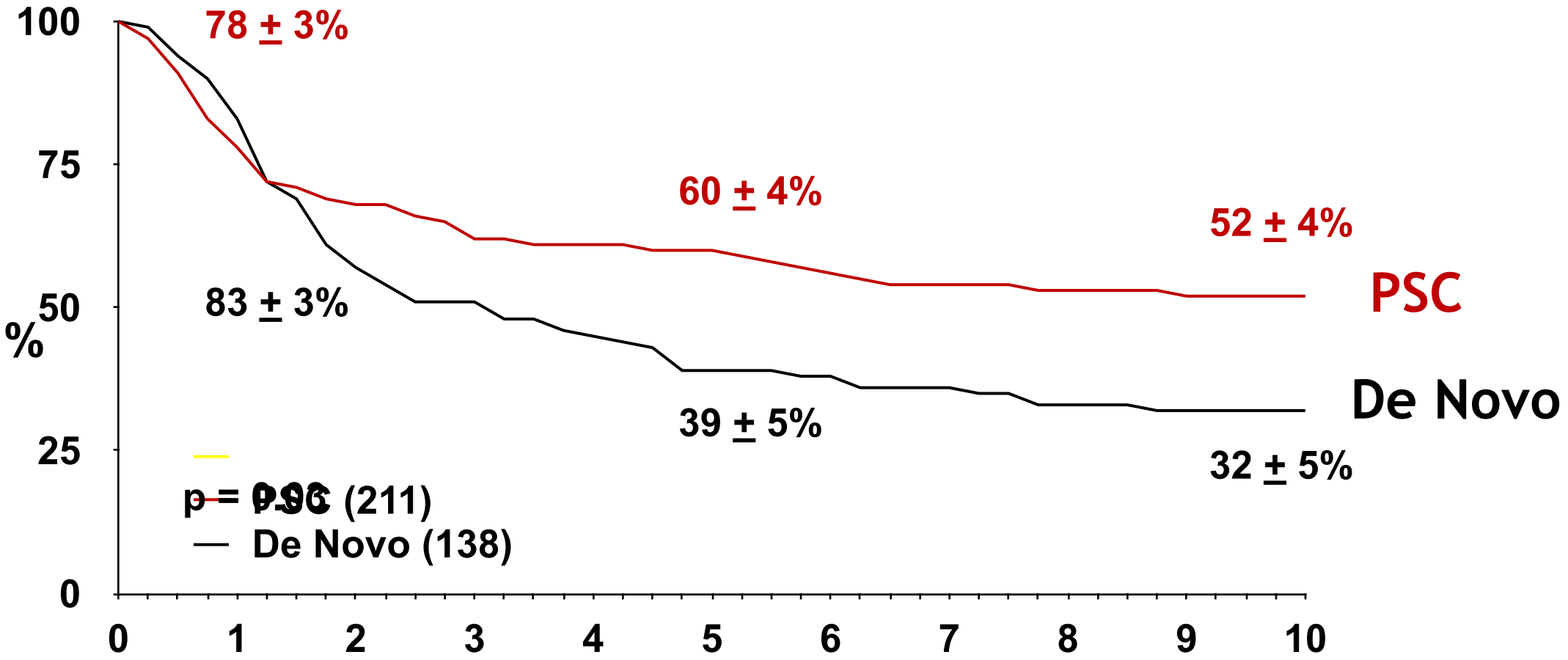
Courtesy of Julie Heimbach, Mayo Clinic

Liver Transplantation for pCCA
The Mayo Clinic Protocol



Rea DJ, et al. Ann Surg 2005

Mayo Clinic Experience
Intention to Treat



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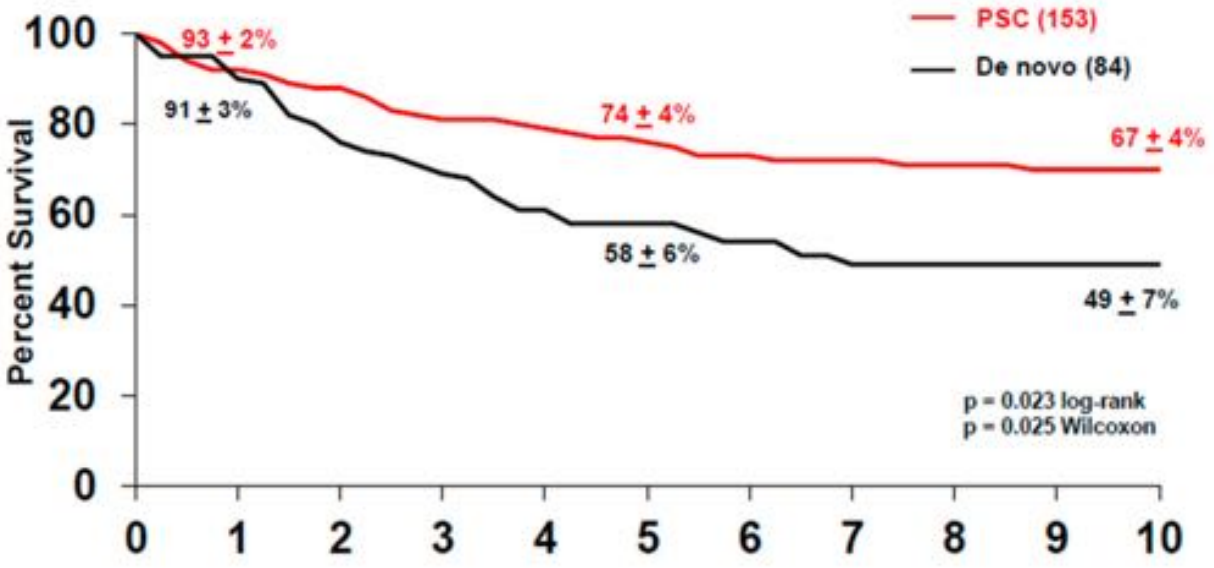
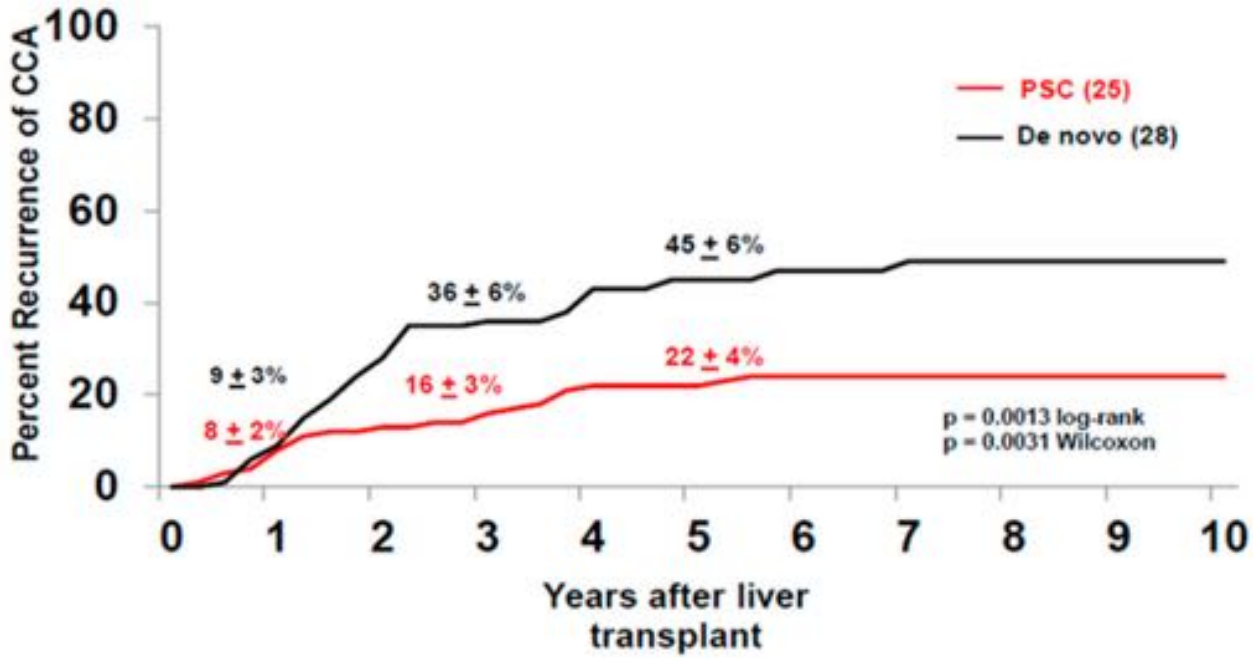
Azad AI, et al. Cancers 2020

Mayo Clinic Experience
Post-transplant Outcomes

Post-transplant Survival



Post-transplant Risk of Recurrence



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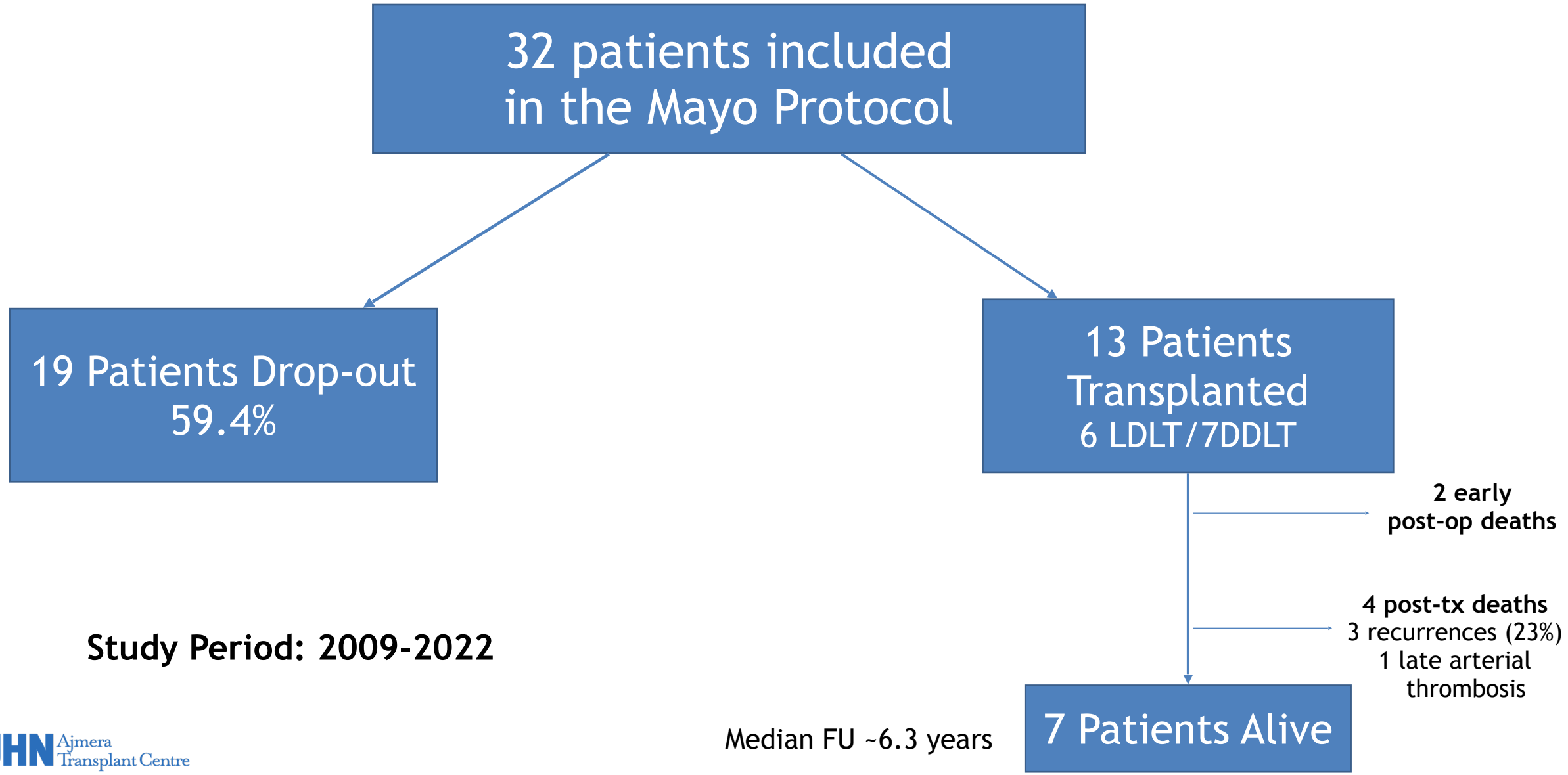
Azad Al, et al. Cancers 2020

Toronto Transplant Center Experience



Study Period: 2009-2022

Median FU ~6.3 years

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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.

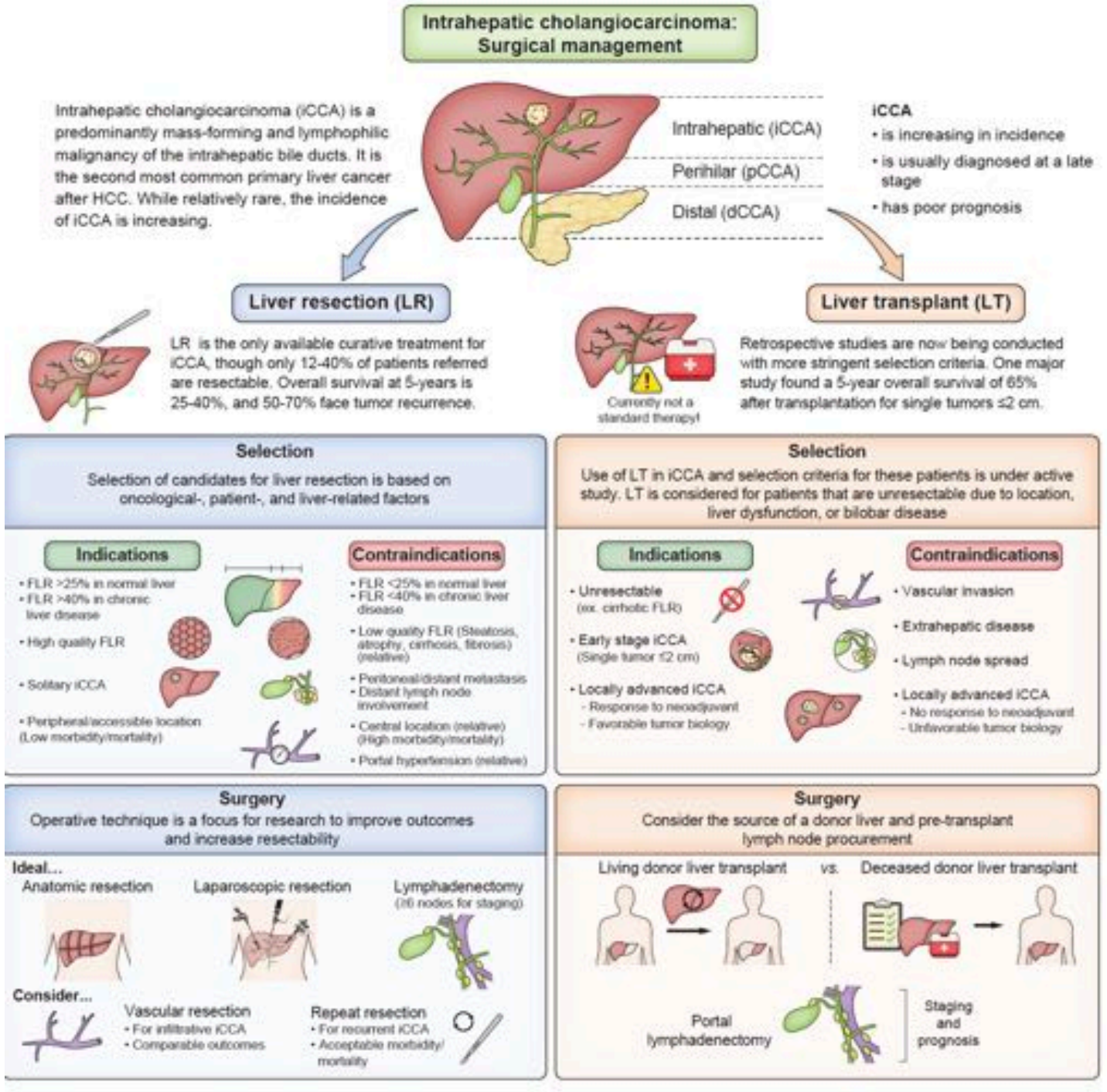
4. Surgical Technique:
   - Have available venous and arterial grafts both for LDLT and DDLT.

Intrahepatic Cholangiocarcinoma

First treatment option

Solitary iCCA

Hepatectomy plus lymphadenectomy



Cirrhotics single ≤3 cm

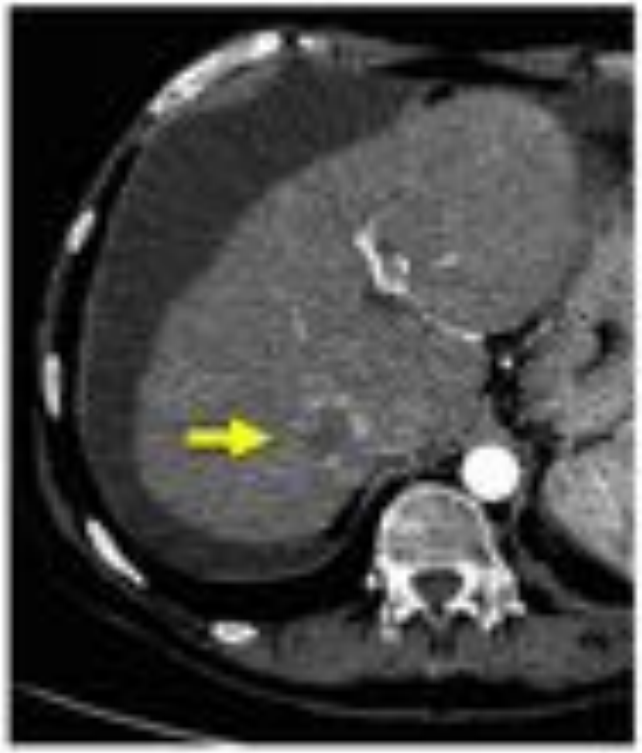
Experimental for larger and multifocal

Clinical trials

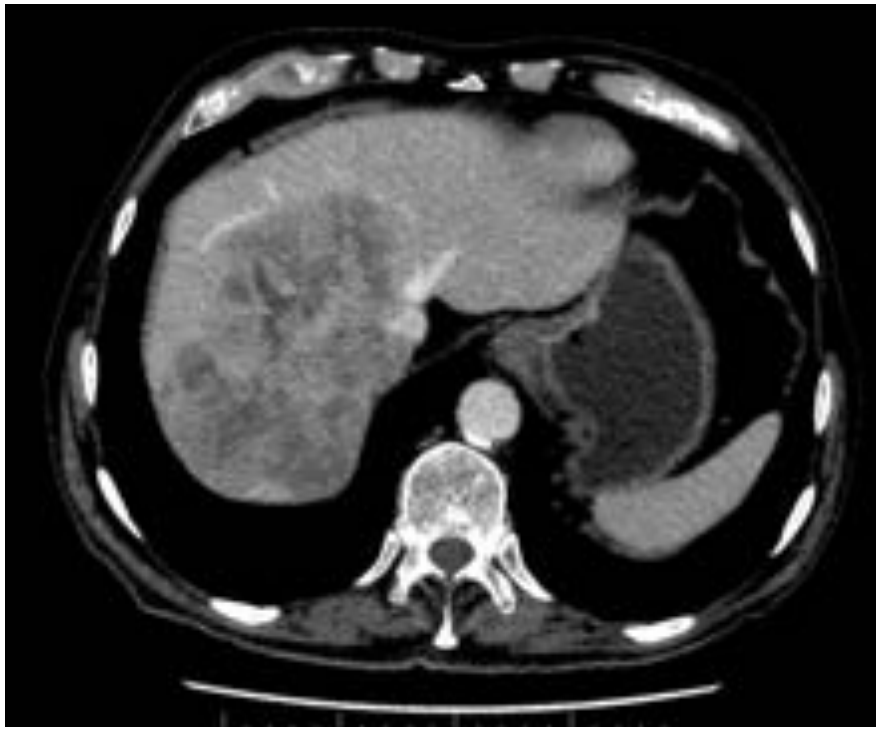
EASL-ILCA Guidelines
J hepatol 2023

Liver Transplantation for iCCA

iCCa in Cirrhotics

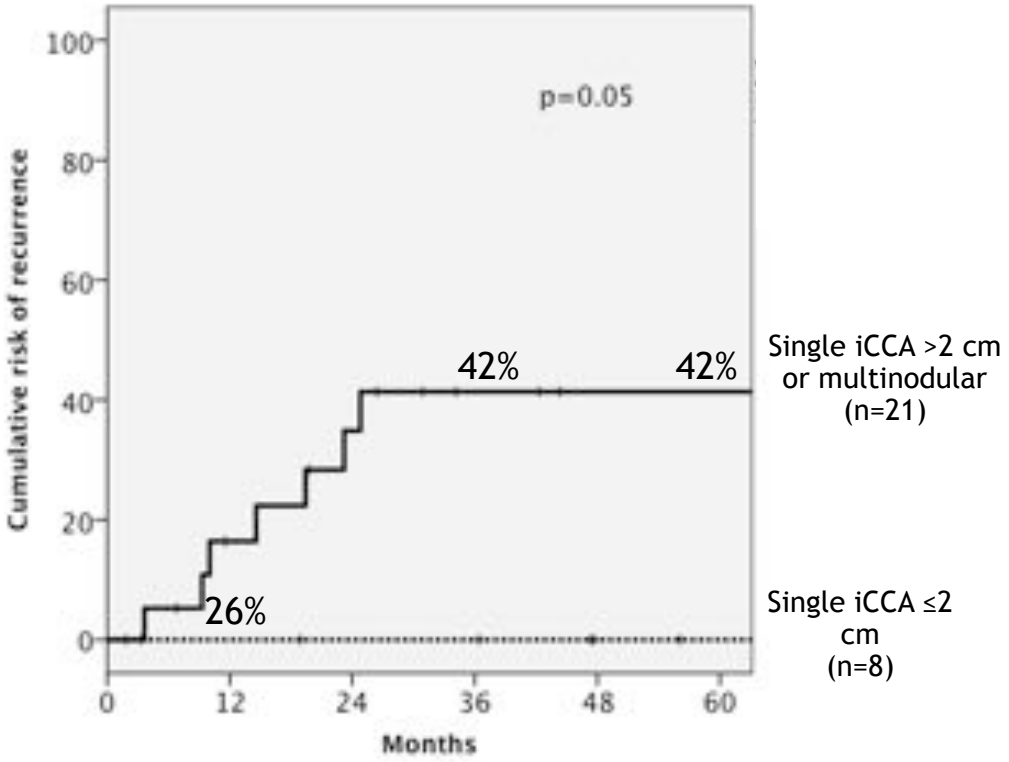


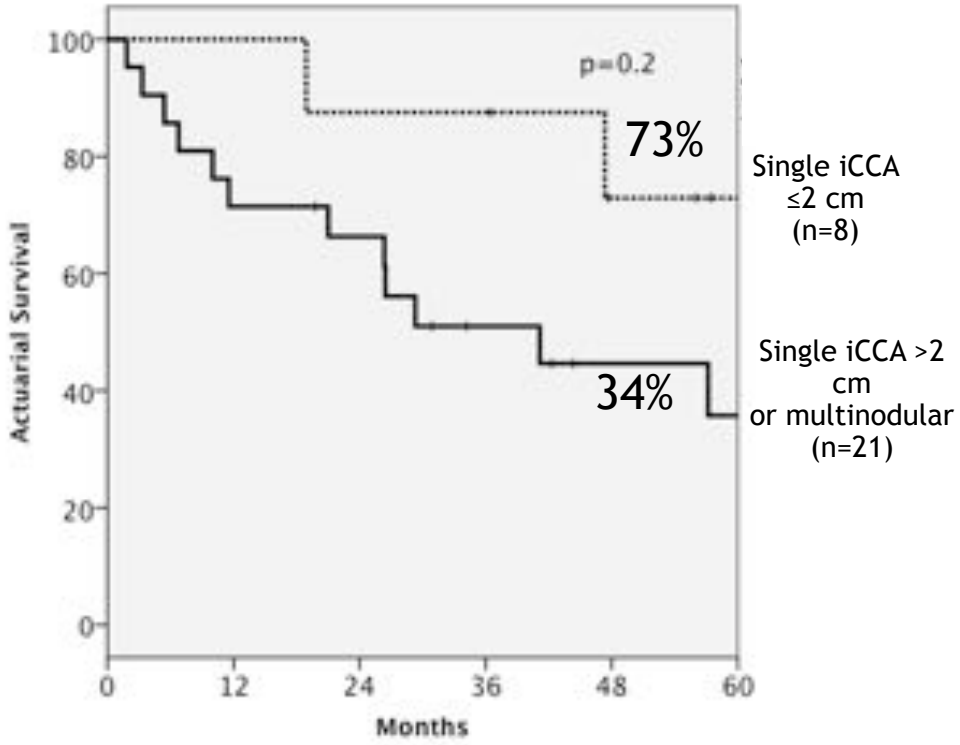
Large/Multifocal iCCa



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

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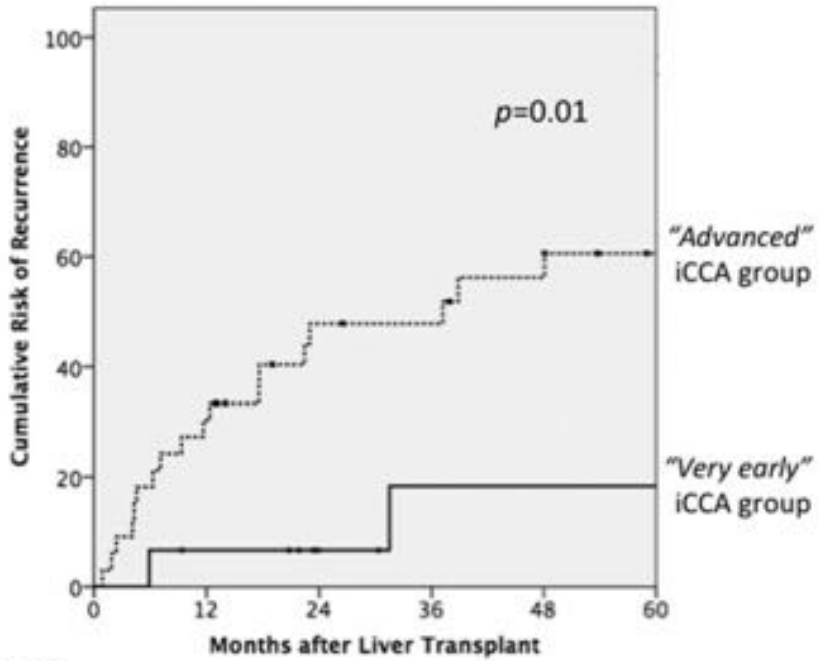
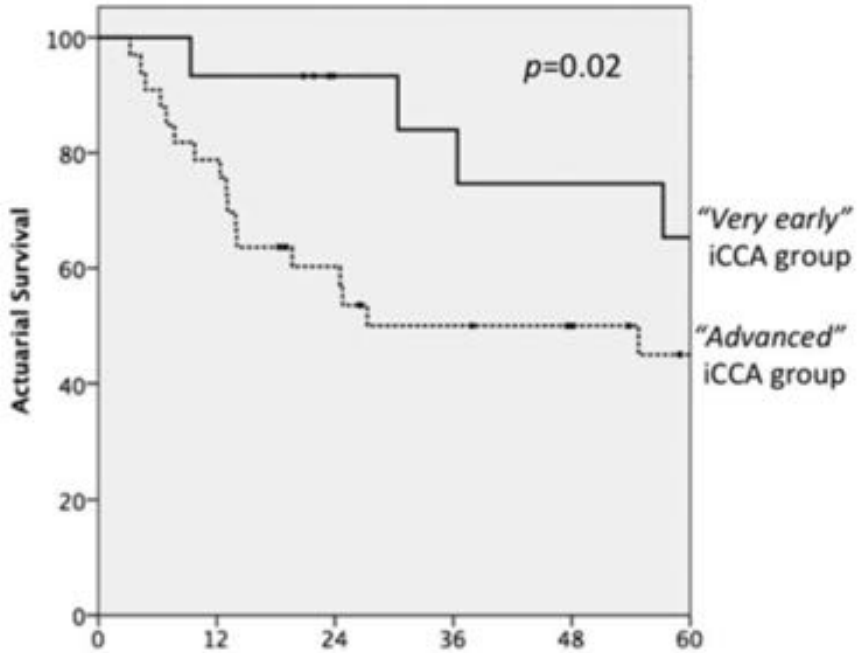
Sapisochin G, et al. Am J Transpl 2014

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



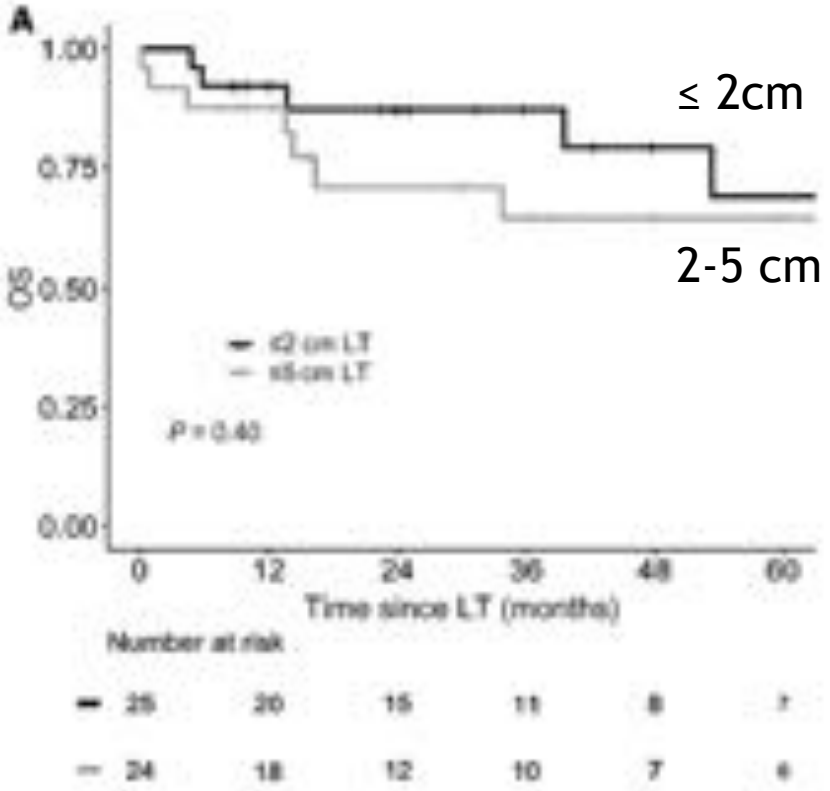
Patients at risk						
"Very Early"	15	14	10	9	8	7
"Advanced"	33	26	18	14	12	8

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

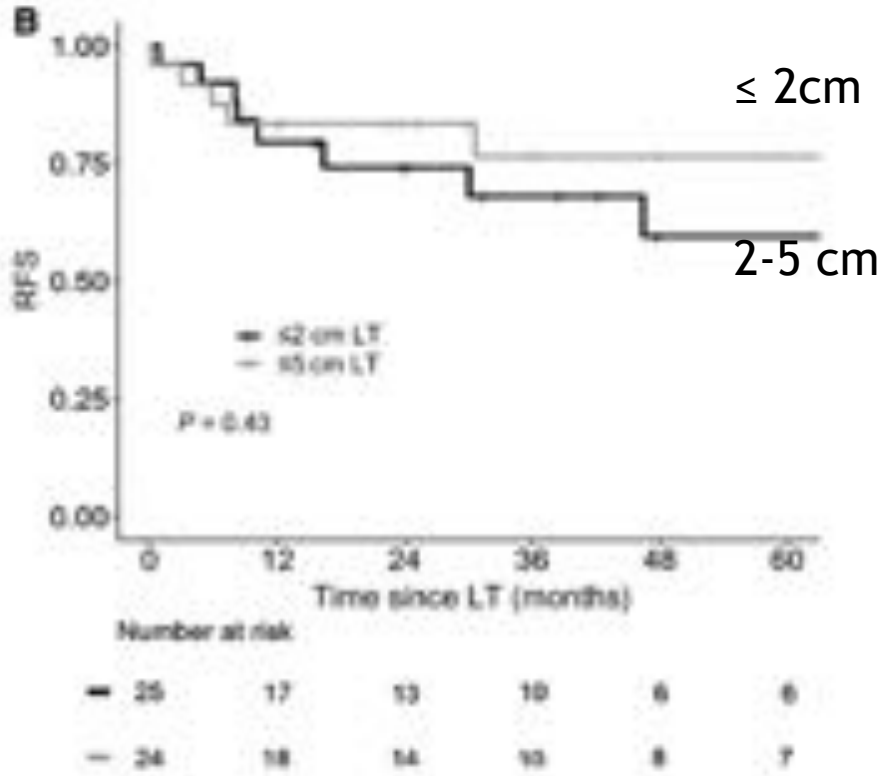
Sapisochin G et al. Hepatology 2016

Liver Transplantation ≤2 cm vs. 2-5 cm

Overall Survival



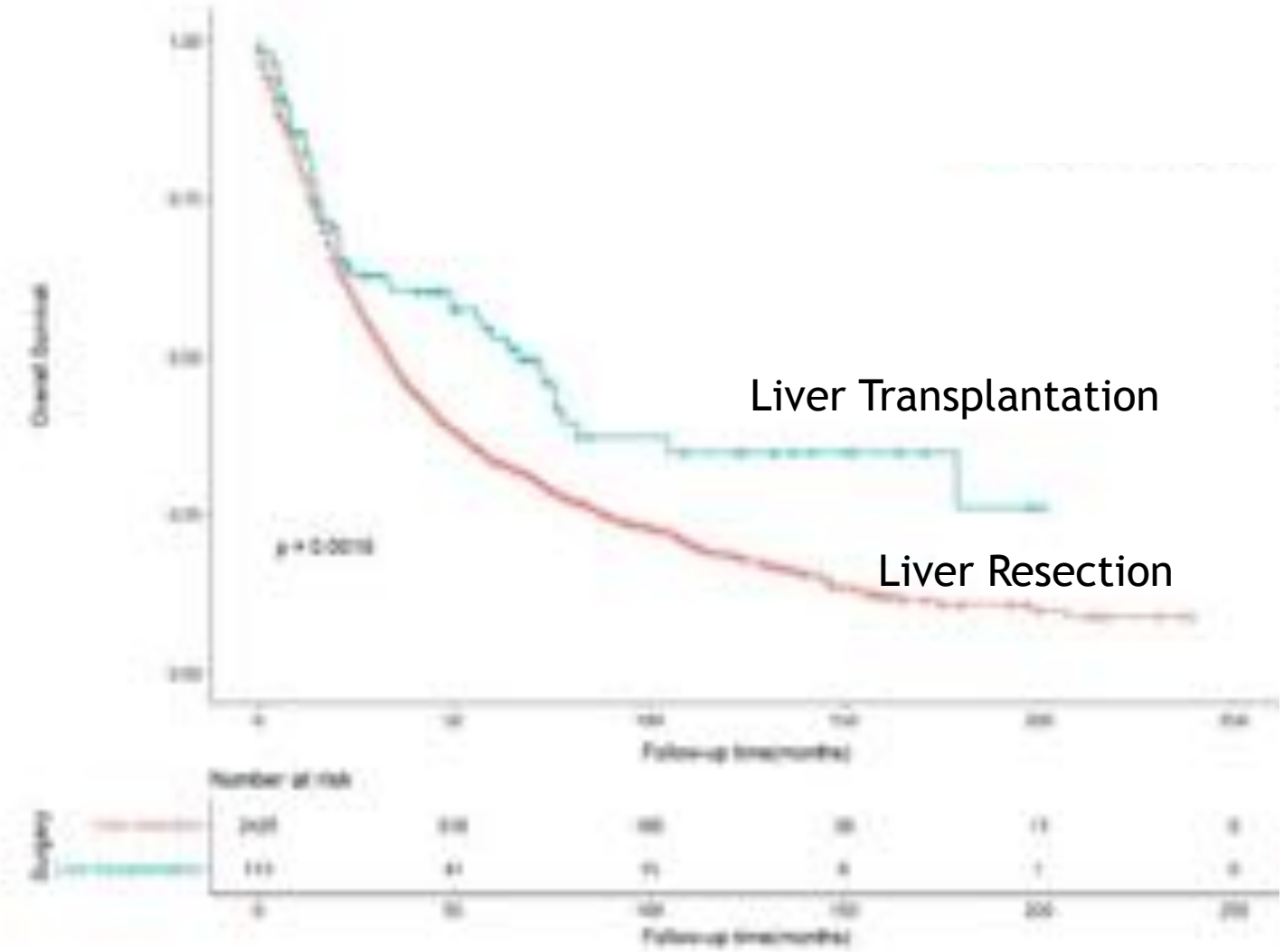
Disease-Free Survival



UHN Ajmera Transplant Centre

De Martin E, et al. Liver Transpl. 2020

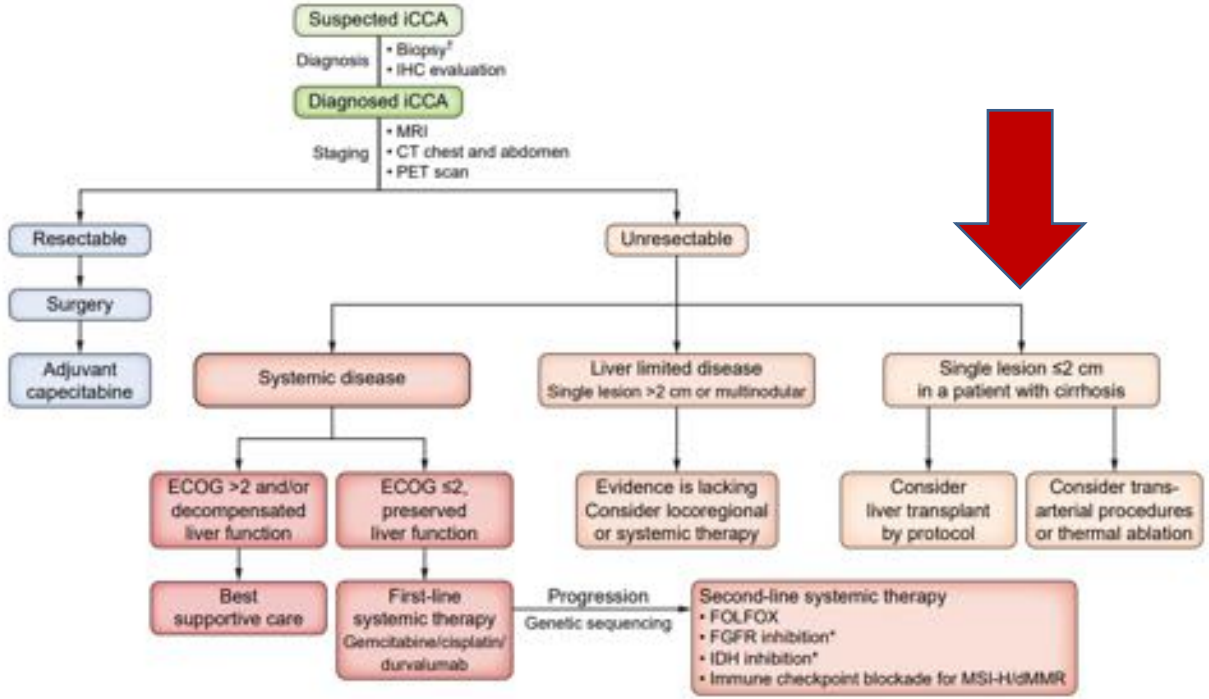
SEER Database Comparison LT and LR

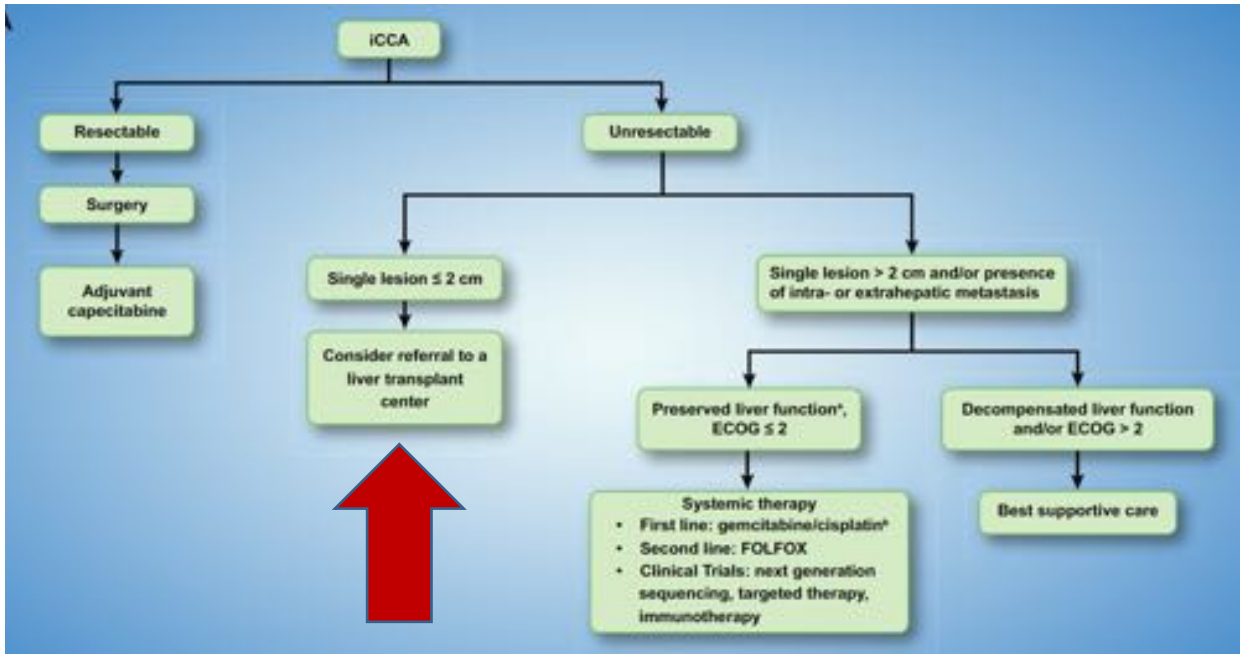


UHN Ajmera Transplant Centre

Huang G, et al. Sci Reports 2023

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



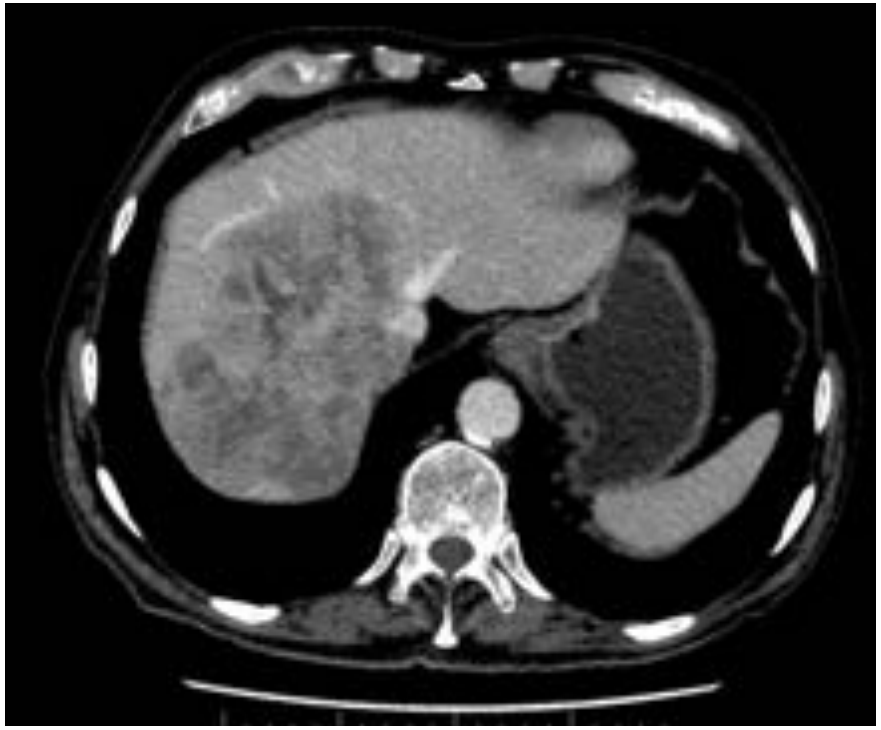


UHN Ajmera Transplant Centre

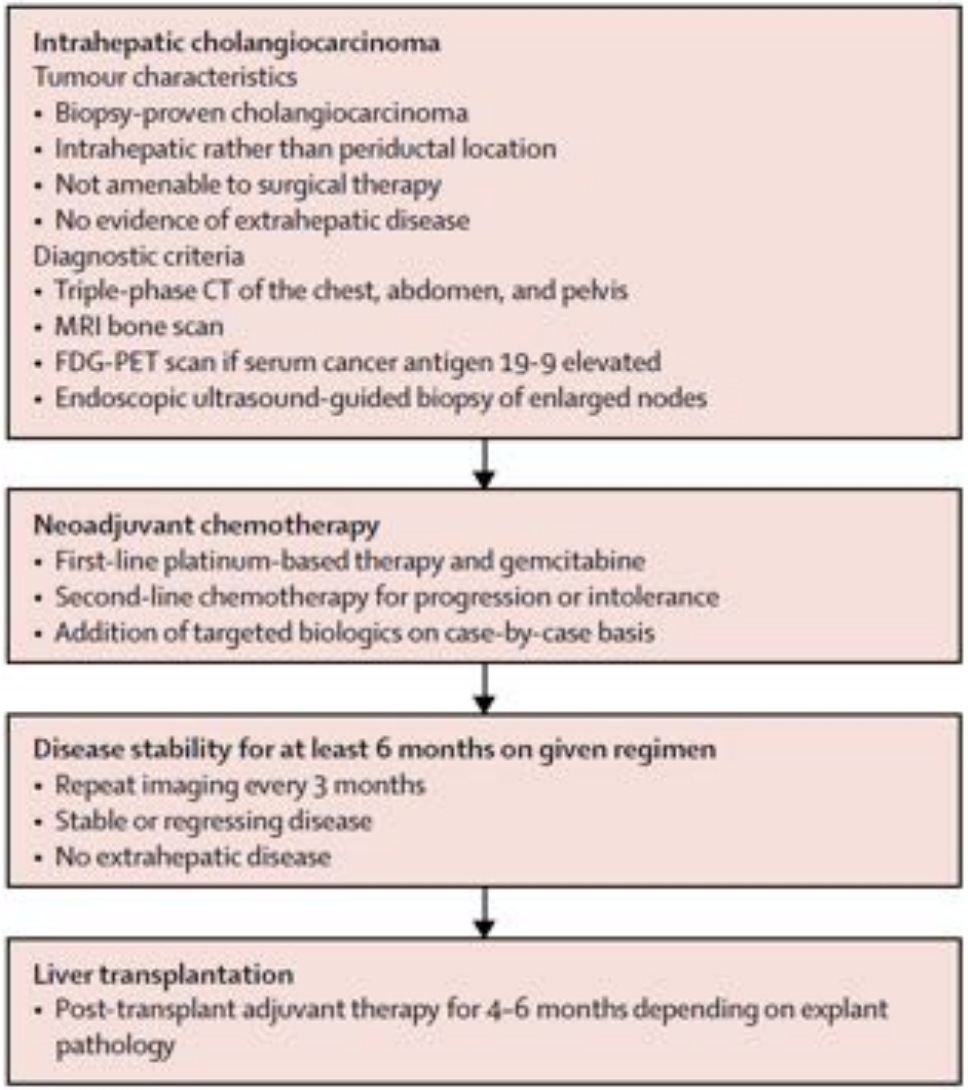
Bowlus CL, Sapisochin G et al. Hepatology 2022
EASL-ILCA Guidelines. J Hep 2023

Liver Transplantation for iCCA

Large/Multifocal iCCa

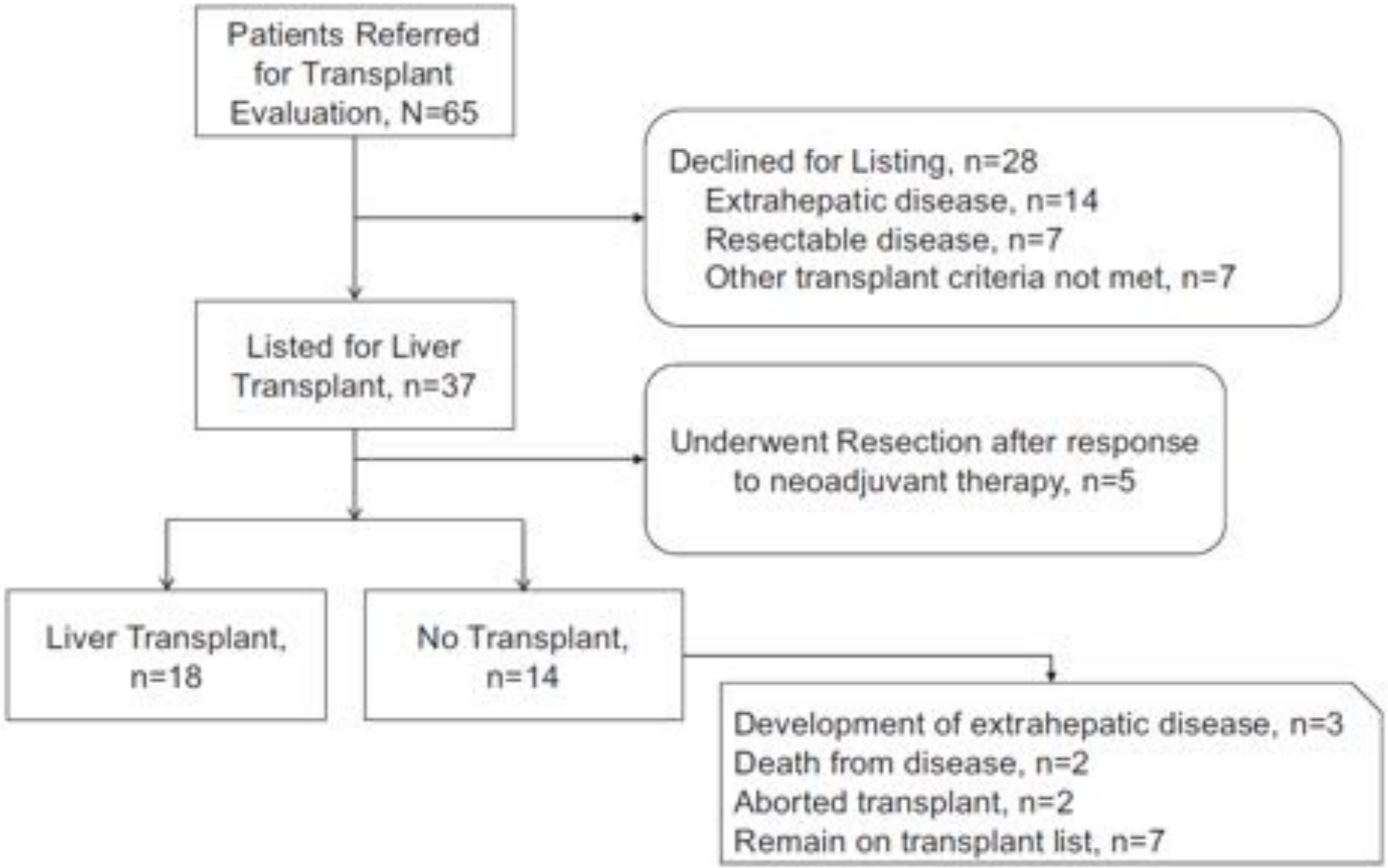


Liver transplantation for locally advanced intrahepatic cholangiocarcinoma treated with neoadjuvant therapy: a prospective case-series

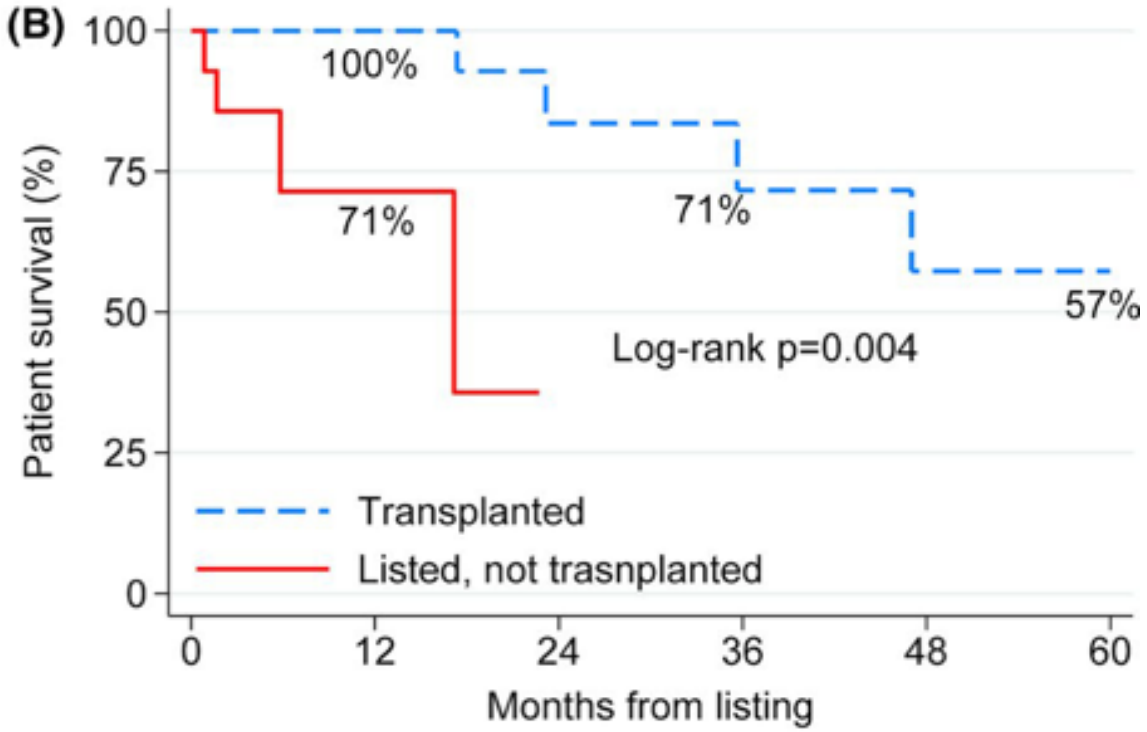


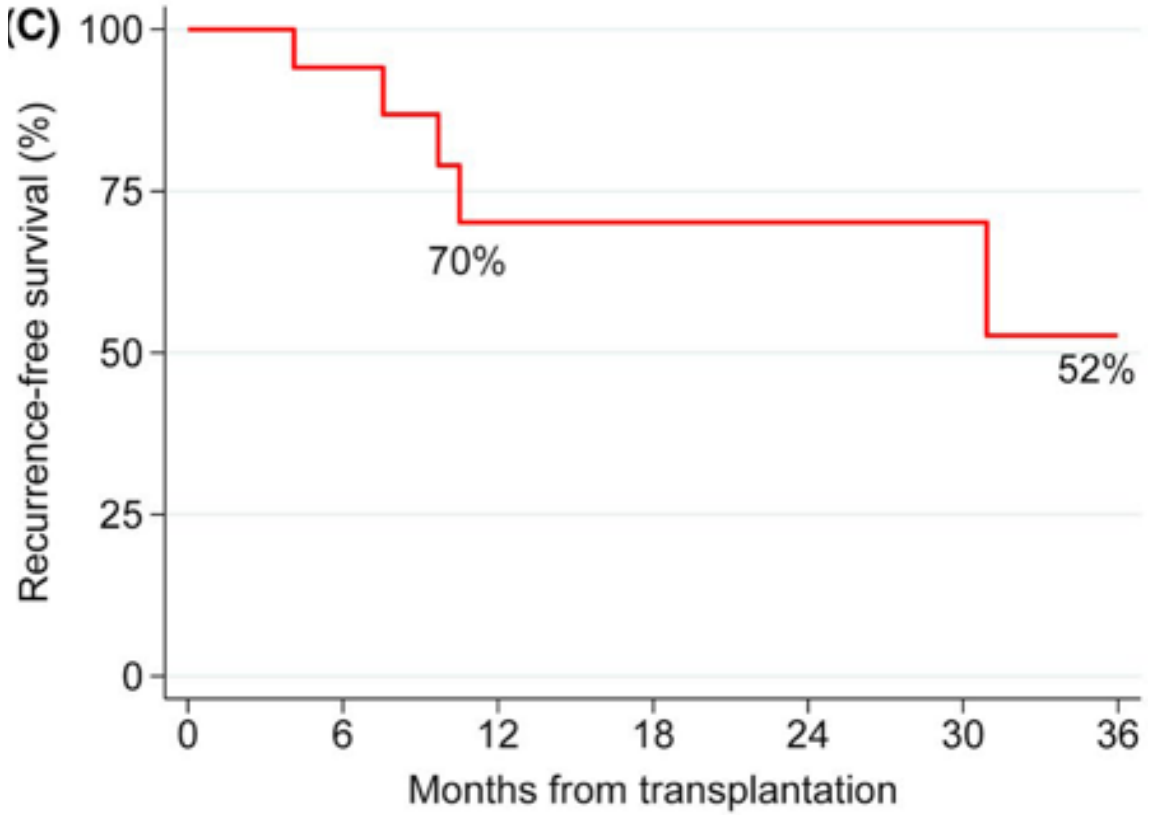
UHN Ajmera Transplant Centre

Lunsford KE, et al. Lancet Gastroenterol Hepatol 2018



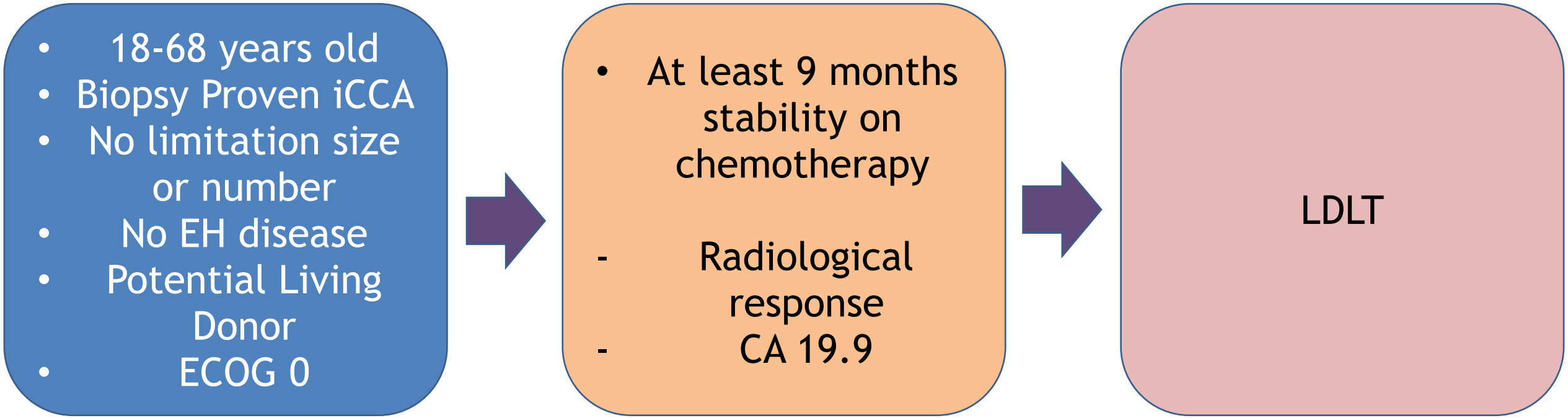
McMillan R, et al. Am J Transplant 2021





McMillan R, et al. Am J Transplant 2021

University of Toronto Trial - NCT04195503



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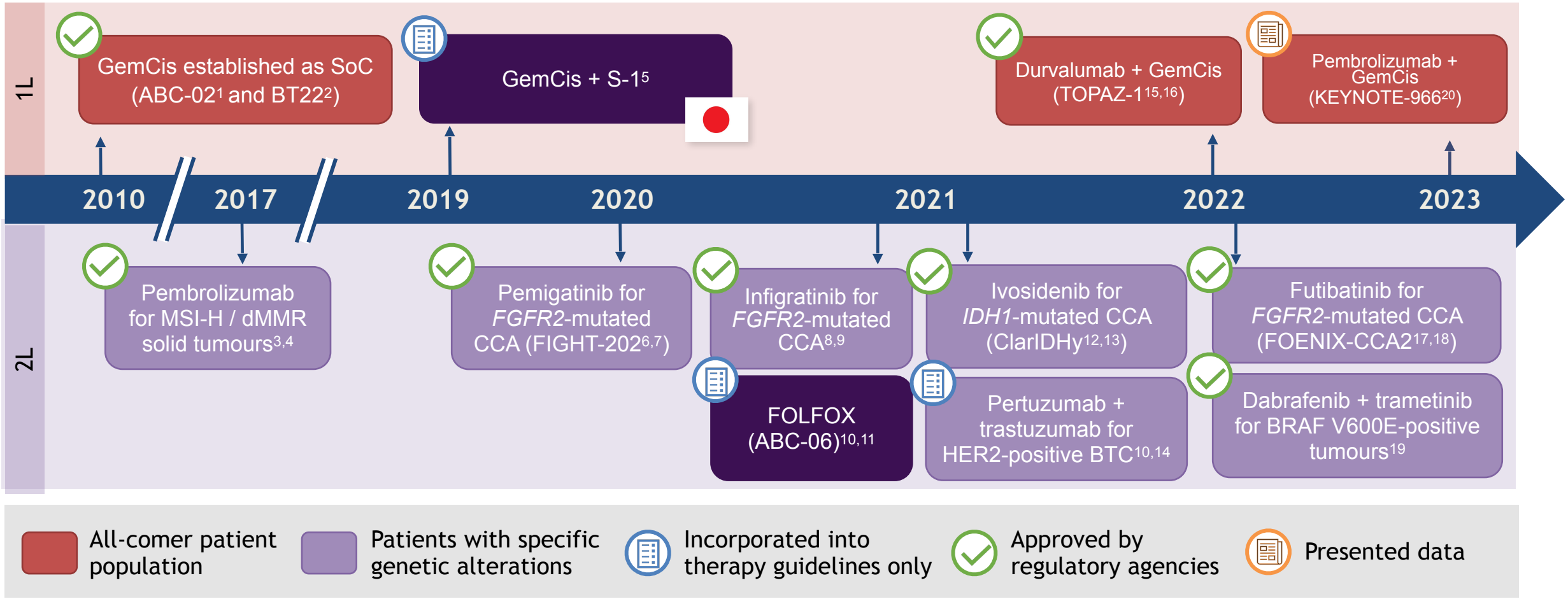
There have been a number of novel treatment options for advanced BTCs in recent years – Impact on Transplant?



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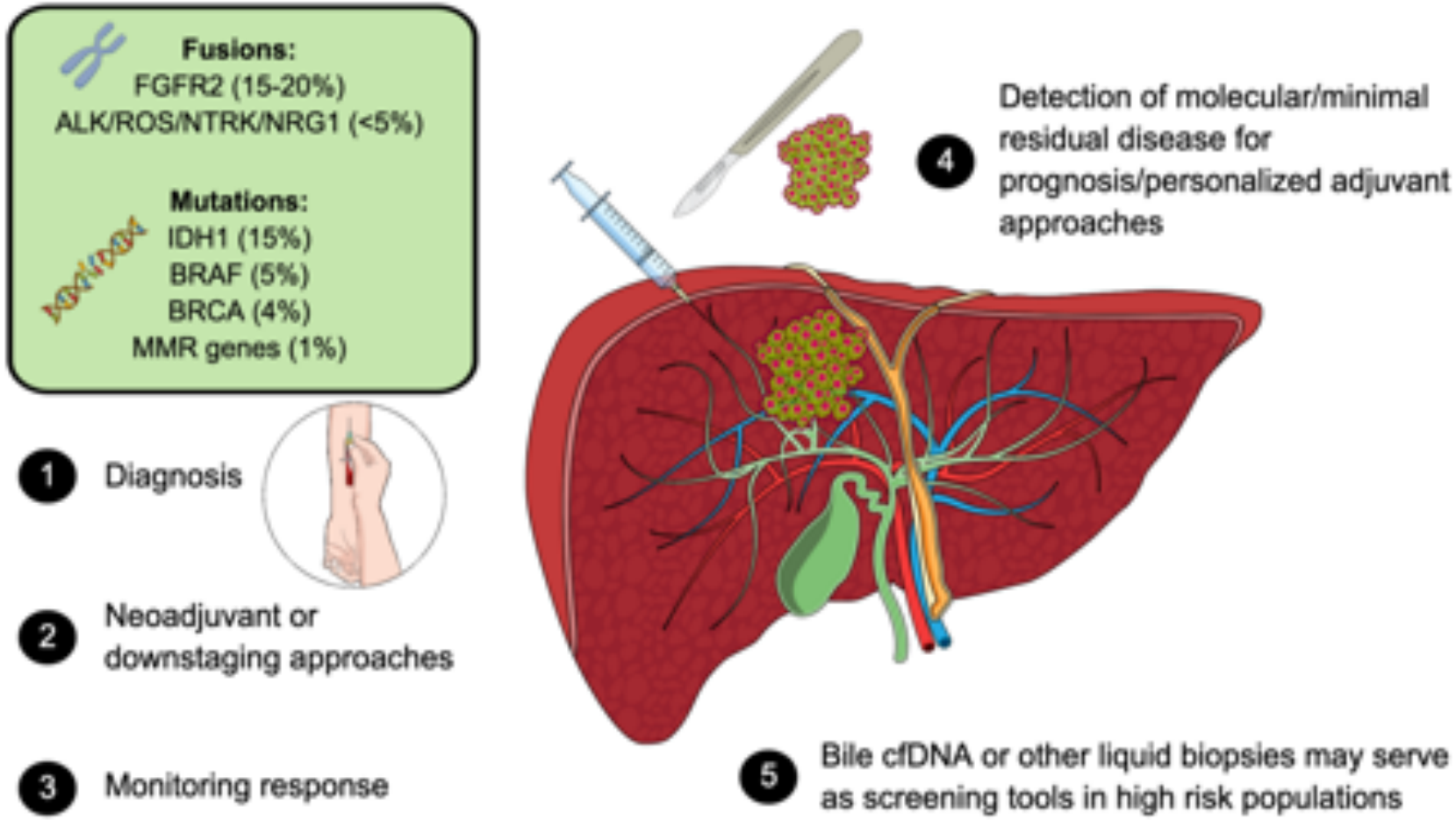
1. Valle J, et al. *N Engl J Med* 2010;362:1273-1281. 2. Okusaka T, et al. *Br J Cancer* 2010;103:469-474. 3. Merck 4. European Medicines Agency. 5. Nagino M, et al. *J Hepatobiliary Pancreat Sci* 2021;28:26-54. 6. Abou-Alfa GK, et al. *Lancet Oncol* 2020;21:671-684. 7. US Food and Drug Administration. 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?



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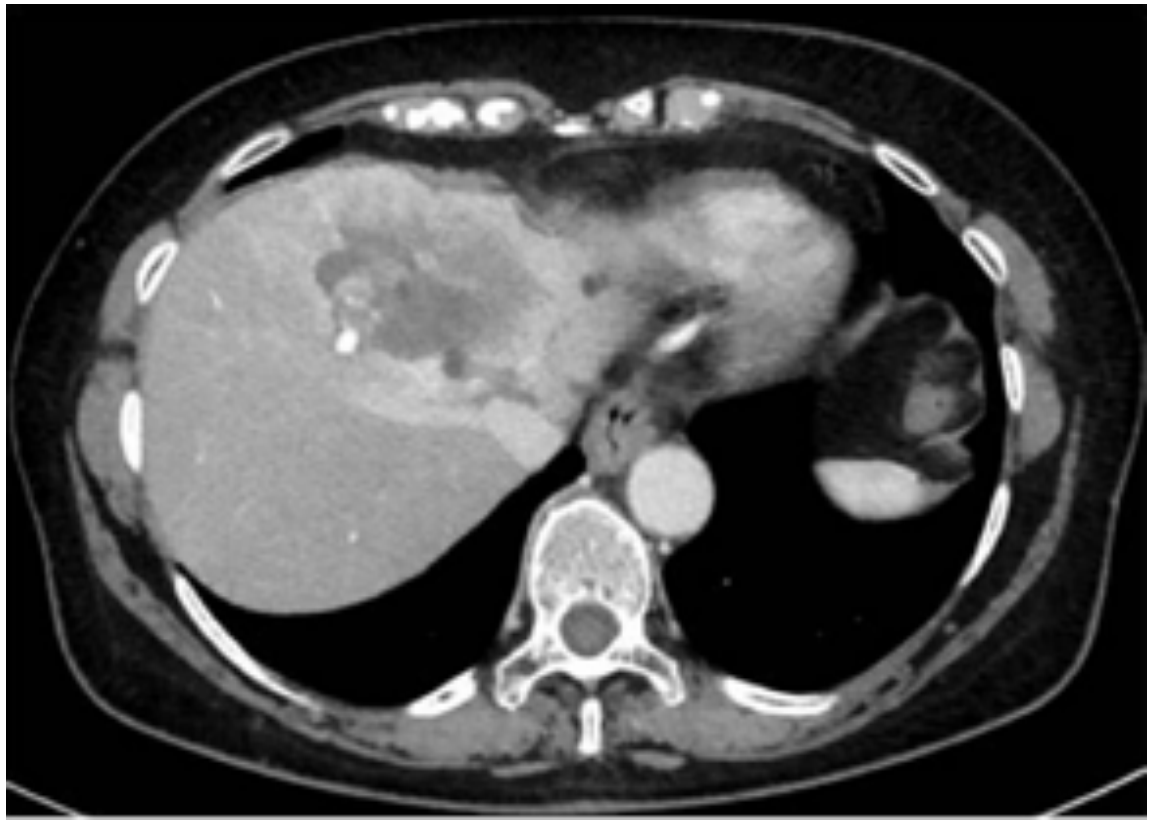
Choi WJ, Sapisochin G, O'Kane G et al. Ann Surg Oncol 2023



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**

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?

Liver Transplantation for Unresectable Liver Metastases from Colorectal Cancer

Liver Transplantation for Nonresectable Liver Metastases From Colorectal Cancer

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

urg 2013

Oslo Trial:

Nov 2006 – Mar

- **25 included i**
- **4 drop-outs**

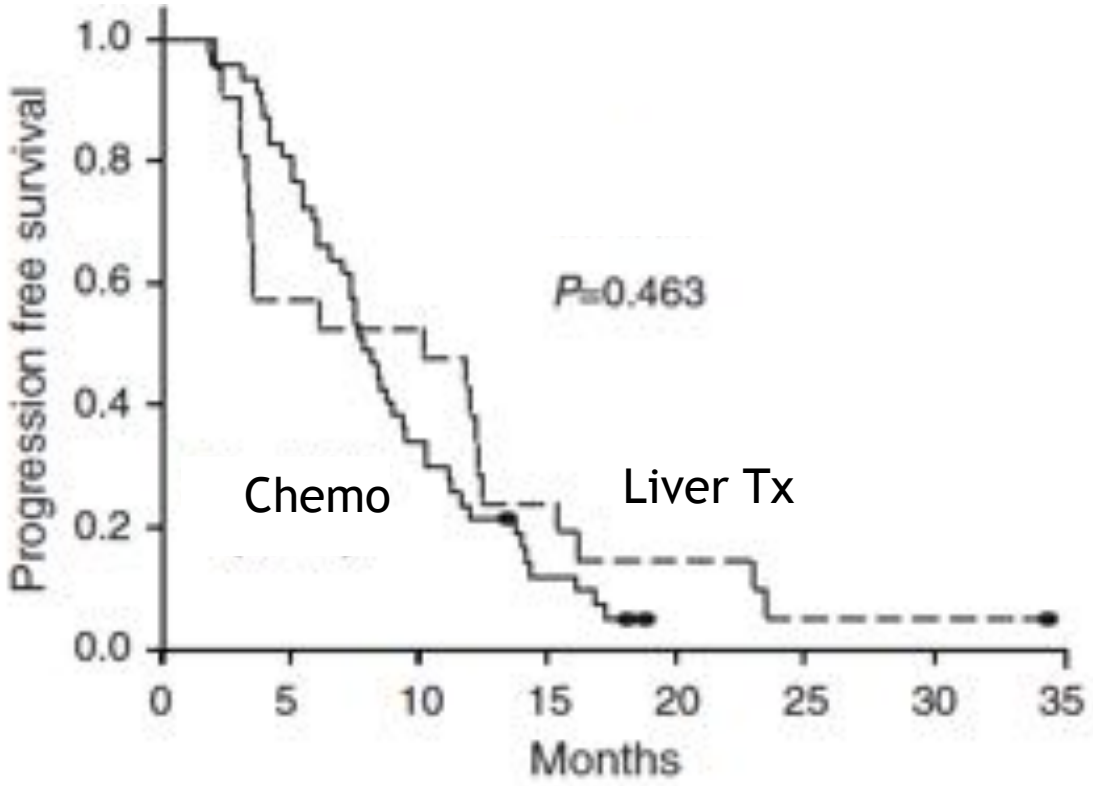
=21 patients tra

Oslo Score	
Maximal Tumor diameter > 5,5 cm	1
Pre transplant CEA > 80 µg/l	1
Progression on chemotherapy	1
Time interval: diagnosis to tx < 2 yrs	1
Summary score	0-4

60% 5-year Survival

Chemotherapy or Liver Transplantation for Nonresectable Liver Metastases From Colorectal Cancer?

Svein Dueland, MD, PhD, Tormod K. Guren, MD, PhD,* Morten Hagness, MD, PhD,†‡*
Bengt Glimelius, MD, PhD,§ Pål-Dag Line, MD, PhD,† Per Pfeiffer, MD, PhD,¶ Aksel Foss, MD, PhD,†‡
and Kjell M. Tveit, MD, PhD‡*



Ann Surg 2014

Chemotherapy or Liver Transplantation for Nonresectable Liver Metastases From Colorectal Cancer?

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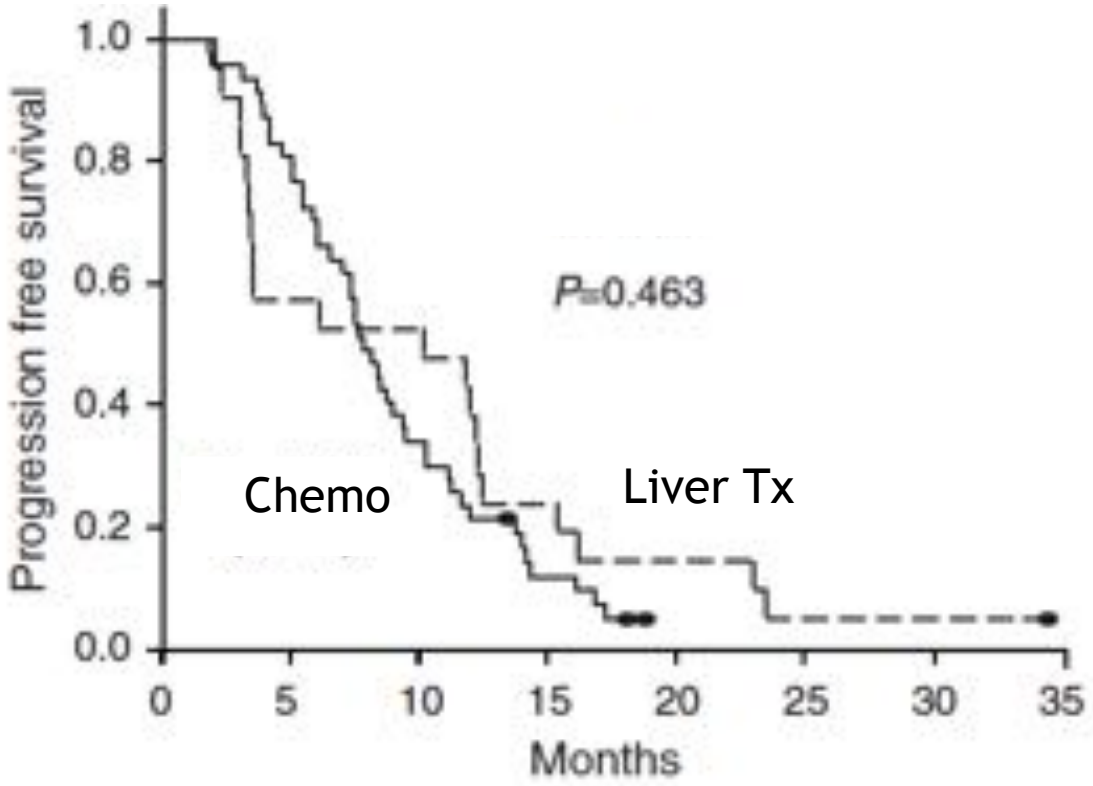

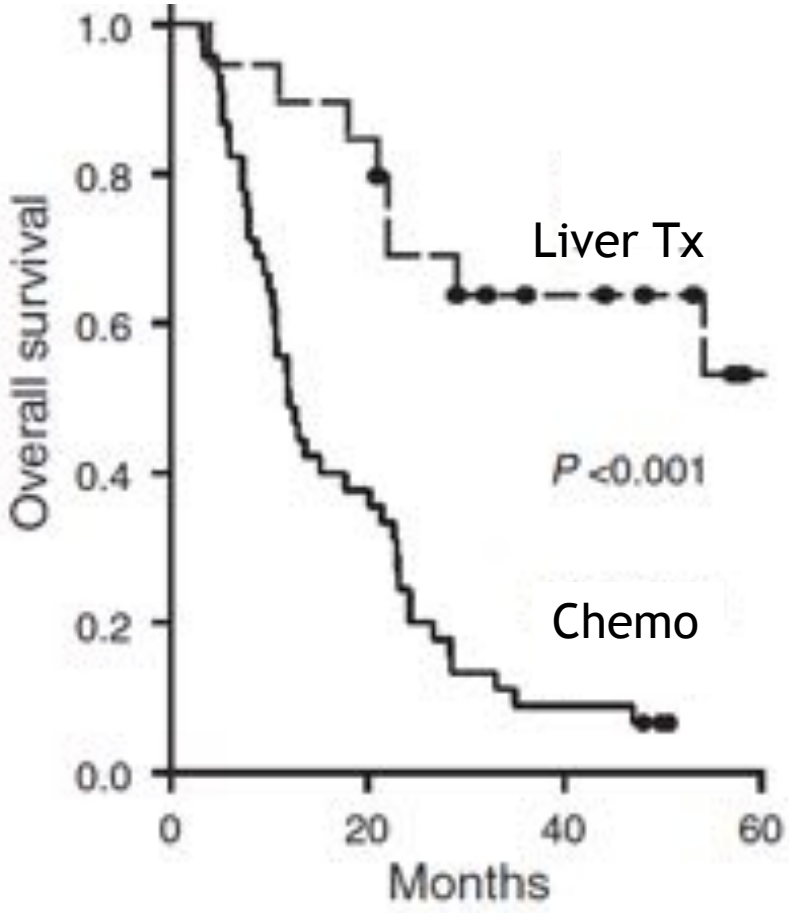

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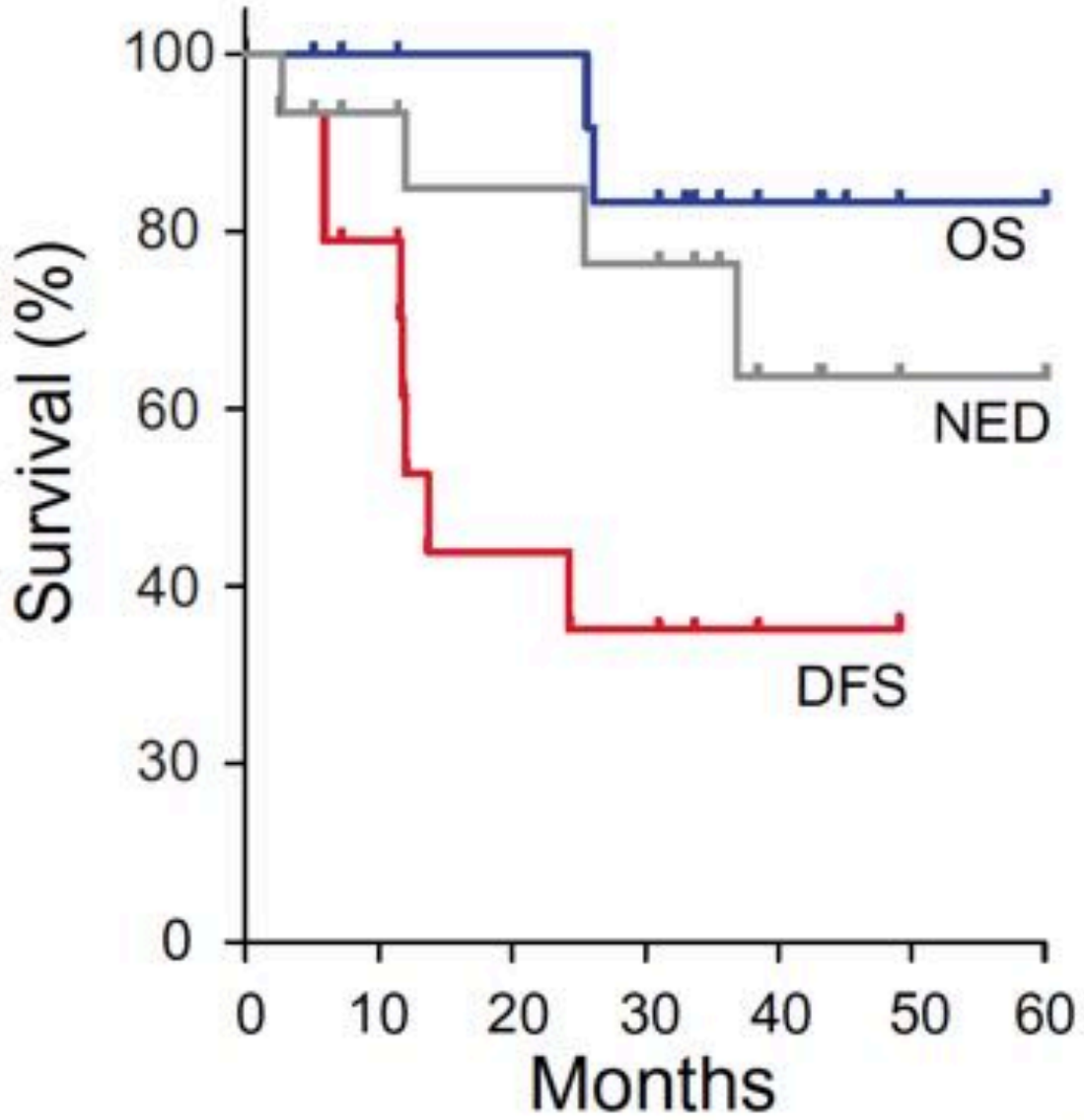
Ann Surg 2014

SECA-II Trial



Months	0	6	12	18	24	30	36	42	48	54	60
OS	15	14	12	12	12	10	6	5	2	1	2
DFS	15	11	6	5	5	4	2	1	1	0	0
NED	15	13	11	9	9	9	5	4	2	1	1

67% - 5-years

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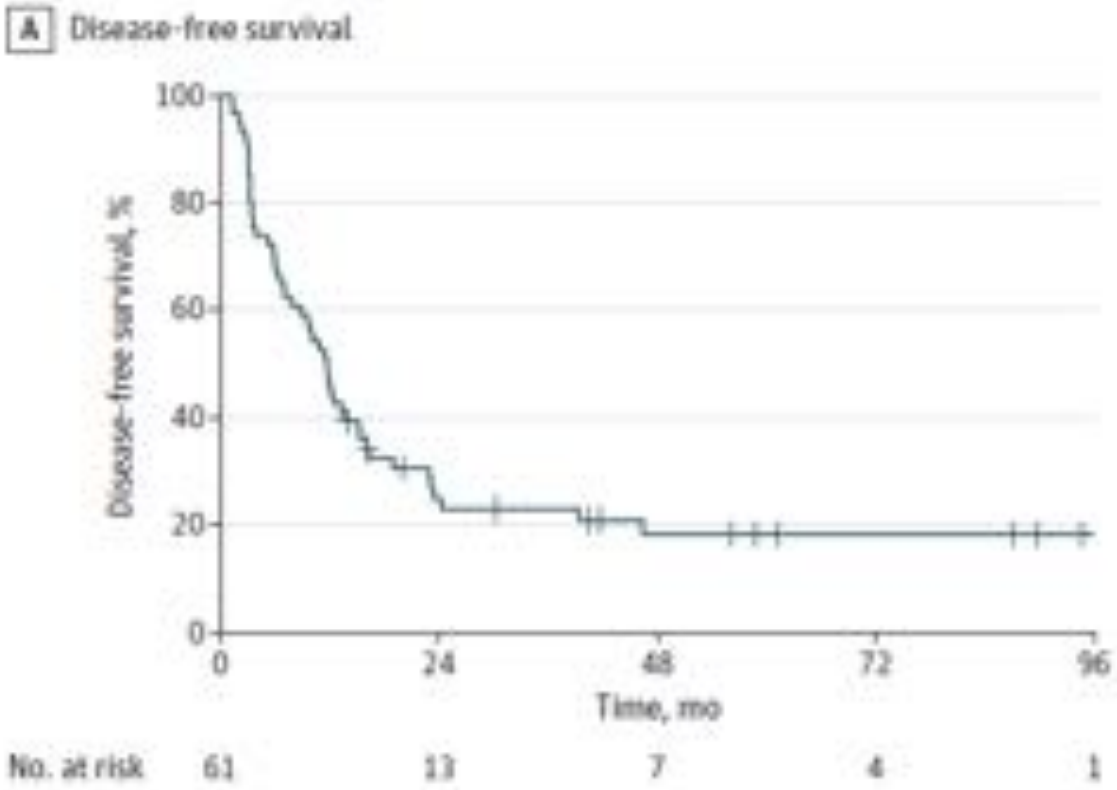
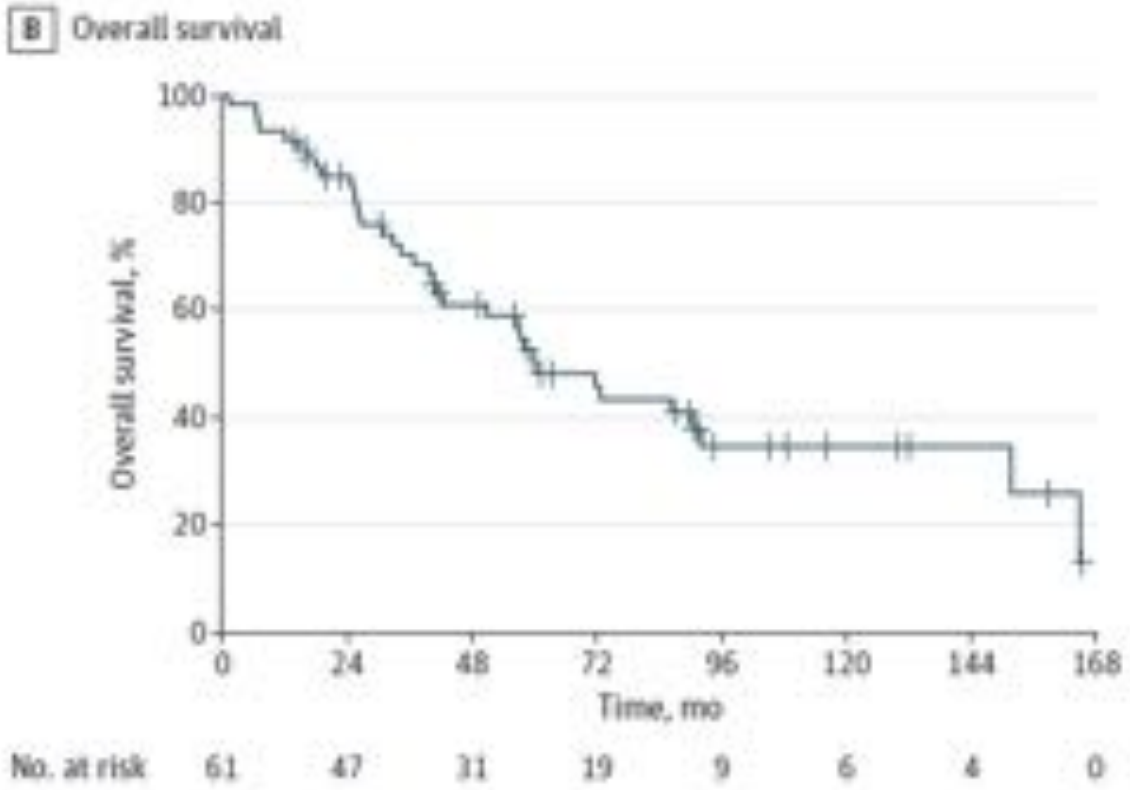
Dueland S, et al. Ann Surg 2019

SECA II Trial

Comparison between **SECA-I** and **SECA-II** at time of transplantation (median and range)			
	SECA-1	**SECA-2**	p-value+
Time from primary surgery to LT	16.8 (6.0-58.8) months	22.6 (2.3-111.3) months	
Age, years	56 (45-65)	59 (35-71)	NS
FCRS at LT	3 (1-5)	2 (1-3)	
Oslo Score at LT	2 (0-4)	1 (0-1)	<0.001
Liver lesions	8 (4-40)	5 (1-53)	0.049
Size	45 (28-130) mm	24 (3-47)mm	<0.001
CEA µg/L	15 (1-2002)	2 (1-30)	0.015

Long-term Outcomes of Oslo Patients





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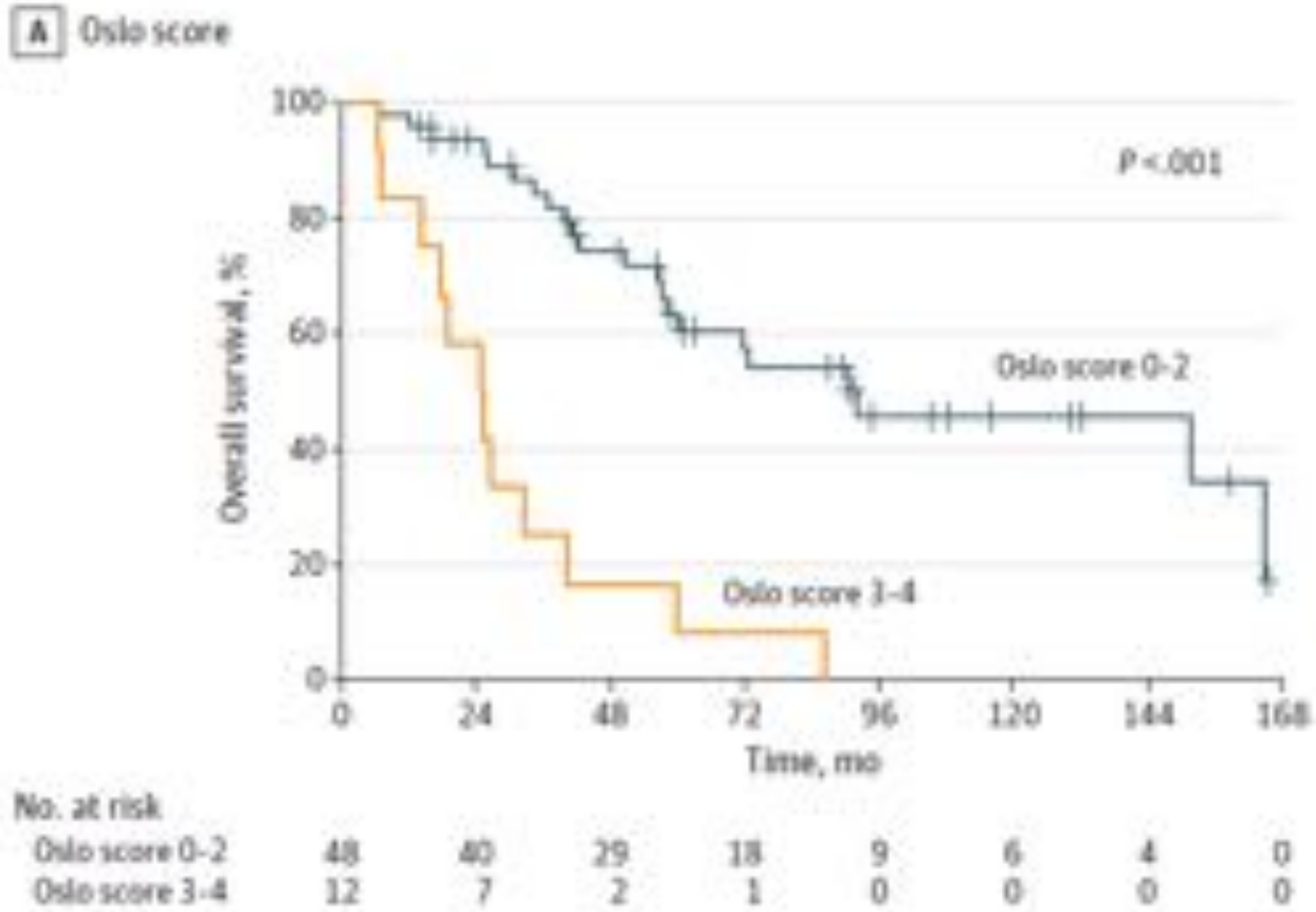
Dueland S, et al. JAMA Surgery 2023

Prognostic Factors



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Dueland S, et al. JAMA Surgery 2023

Current Active Trials

A — 2016

Canadian

NCT02864485
Single cohort of neo-adjuvant CT þ LDLT for unresectable CRLM

E — 2018

German

NCT03488953
(LIVERT(W)OHEAL)
Single cohort of LDLT (S3–2) þ RPVLþ -2stage hepatectomy for unresectable CRLM

B — 2011

Norwegian

NCT01479608
RCT of LR versus LT for resectable and unresectable CRLM: - ARM A: LT versus LR in pts with ≥ 6 resectable CRLM - ARM B: LT for unresectable metachronous CRLM - ARM C: LT for unresectable synchronous CRLM

B — 2014

Norwegian

NCT02215889
Single cohort of S3–2 LR þ partial S3–2 LT þ RPVL with delayed hepatectomy for unresectable CRLM

B — 2018

Norwegian

NCT03494946
(SECA III)
RCT of LT versus CT for unresectable CRLM - ARM A: LT - ARM B: Chemo, TACE, SIRT or any other available treatment

C — 2016

French

NCT02597348
(TRANSMET)
RCT of LT versus CT for unresectable CRLM: - ARM LT þCadaveric LT þ standard chemotherapy - ARM C: standard chemotherapy

D — 2018

Italian

NCT03803436
(COLT Trial)
Parallel trial:
- Study arm: LT for unresectable CRLM
- Control Arm: Triplete trial (triple regimen CT)

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Abdelrahim M, et al. Cancers 2021

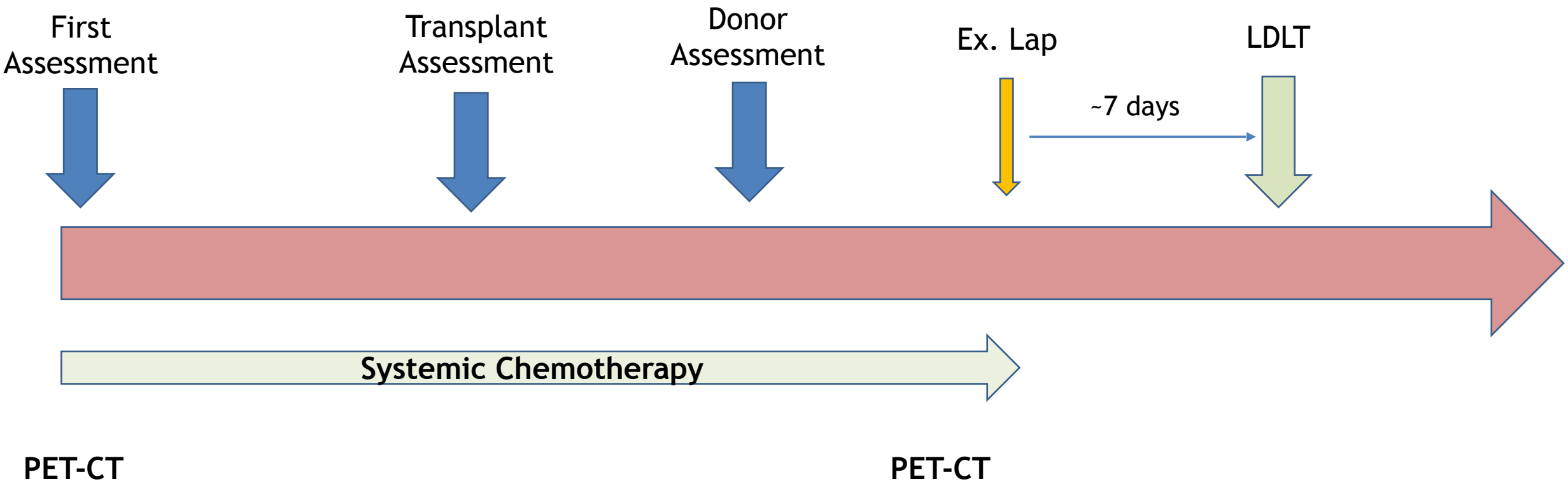
The Toronto Protocol

Assessment of a protocol using a combination of Neo-adjuvant chemotherapy plus Living Donor Liver Transplantation for Non-resectable Liver Metastases from Colorectal Cancer

(NCT02864485)

Toronto Protocol for LDLT CRC LM

Primary in situ – 3 m systemic primary resection if response
Primary resected



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https://clinicaltrials.gov/ct2/show/NCT02864485

University of Toronto Protocol – LDLT for CRC Mets

Main Inclusion Criteria

1. Age 18-68
2. Non-resectable CRC LM. Liver ONLY disease
3. Primary CRC Resected >6 months
4. No major vascular invasion
5. Stable or responsive disease on SOC Chemotherapy (FOLFOX/ FOLFIRI) for at least 6 months
6. Potential Living Donor Available

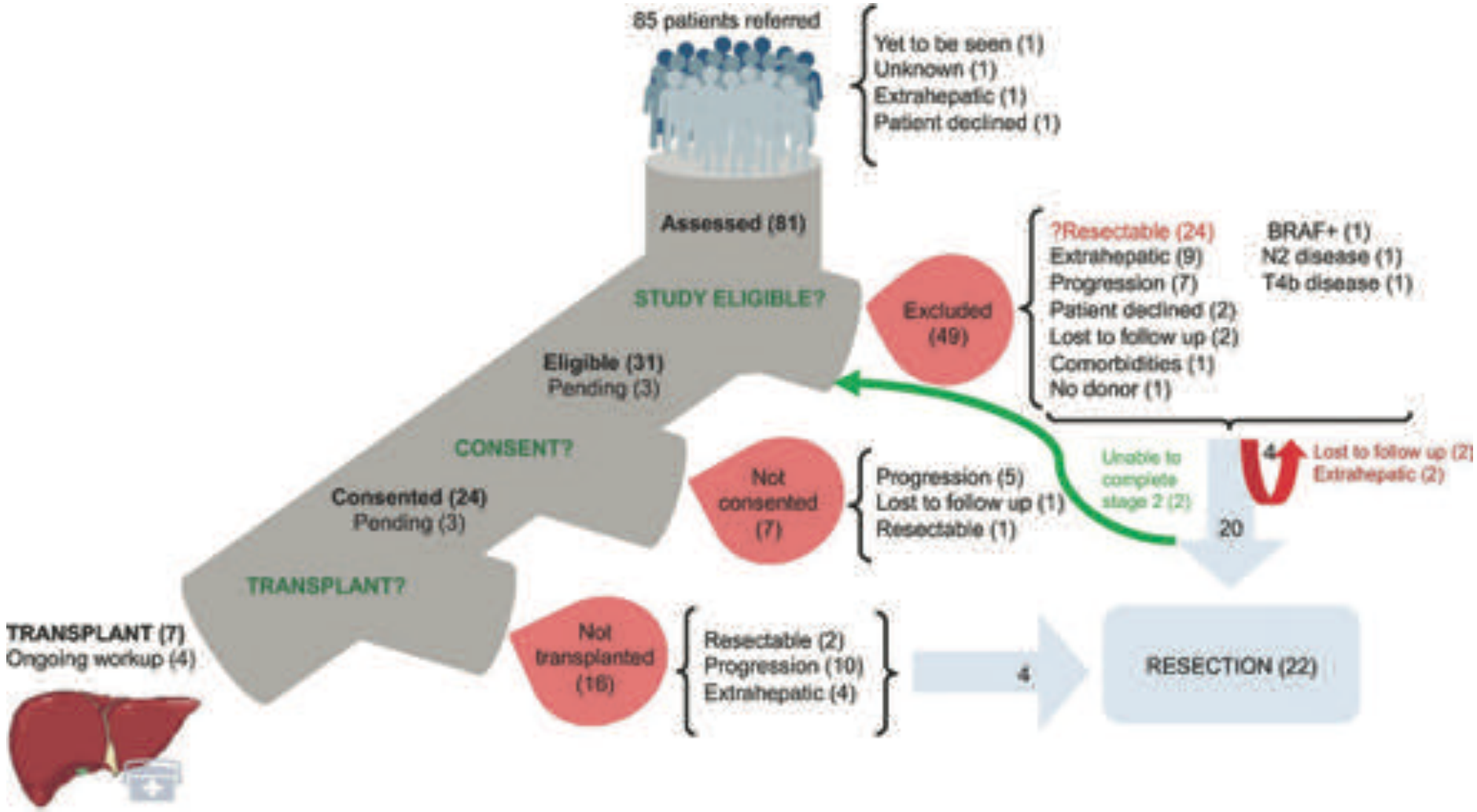
Main Exclusion Criteria

1. Metastatic disease outside the liver
2. BRAF mutation
3. Progression on chemotherapy treatment

UHN Ajmera Transplant Centre

Rajendran L, Sapisochin G et al. JACS 2023

Toronto Protocol for LDLT CRC LM



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Rajendran L, Sapisochin G et al. JACS 2023

Toronto Protocol for LDLT CRC LM

	Chemo type, line, # of cycles prior to initial assessment, total cycles pre-transplant	HAIP (Y/N), time from insertion to transplant	RAS mutation	Tumour type	Explant pathology	Recurrence (Y/N) site, time, treatment	Oslo Score	Post-transplant follow-up
1	FOLFIRI/ Panitumumab, first, 10 cycles, total: 25 cycles	No	No	Left colon	3x foci with ~50% treatment effect	**Yes, intra-abdominal nodes, 12.4 months, chemo**	2	18.9
2	FOLFIRI/ Bevacizumab, first, 18 cycles; total: ~60 cycles	**Yes, 25.0**	Yes	Left colon	6x foci with variable treatment effect	No	1	25.9
3	FOLFIRINOX/ Panitumumab, first, 12 cycles , total: 21 cycles	**Yes, 14.6**	No	Left colon	6x foci + satellites, 95-100% necrosis/ fibrosis	No	1	20.1
4	FOLFIRI/ Panitumumab, first, 12 cycles, total: ~20 cycles	No	No	Rectal	2x foci, one viable <50% treatment effect	No	0	20.5
5	FOLFIRI / Bevacizumab, first, 14 cycles, total: 30 cycles	No	No	Right colon	14x foci, 90-100% necrosis	**Yes, lung, 3.3 months, chemo**	1	39.4 DECEASED
6	FOLFIRI/ Bevacizumab, first, 19 cycles; total: 32 cycles	**Yes, 19.0**	No	Left colon	11x foci, rare viable cells	No	1	49.0
7	FOLFOX, Second, 12 cycles, total: ~32 cycles	No	No	Left colon	1 foci, <50% necrosis	No	0	8.0
8	FOLFIRI/ Bevacizumab, Second, 3 cycles, total: ~16 cycles	No	No	Rectal	5x foci; 3 lesions >50% necrosis; 2 lesions <50% necrosis	No	1	5.6
9	FOLFIRI/Panitumumab/ Bevacizumab, first, 43 cycles, total: ~54 cycles	No	Yes	Left colon	Pending	No	0	0.2

JAMA Surgery | Original Investigation

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

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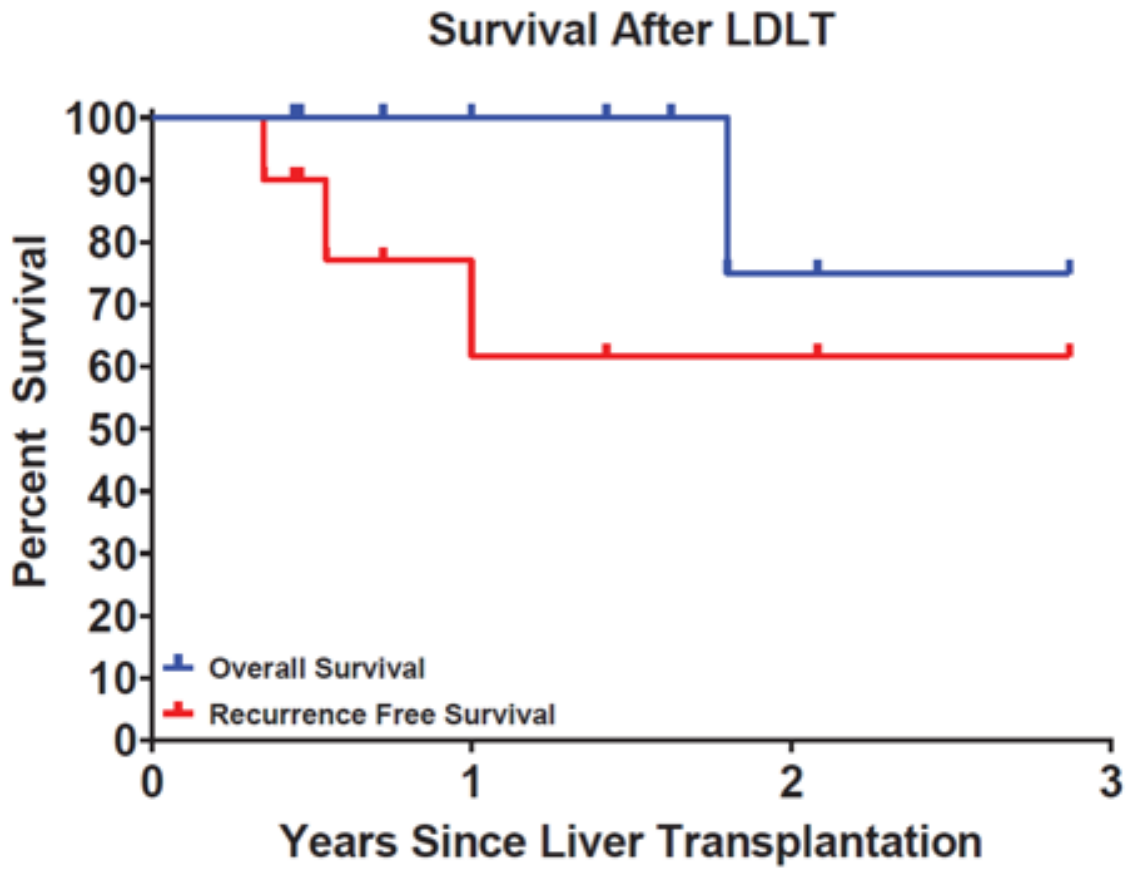
Pre-transplant Treatment and Tumor Characteristics	Unresectable CRLM (n=10)
Chemotherapy Cycles	22.5 (6-37)
Liver Resection	4 (40%)
HAI Pump	3 (30%)
Ablation	3 (30%)
Positive Mutation Status	
KRAS	3 (30%)
TP53	1 (10%)
SMAD4	1 (10%)
BRAF	1 (10%)
Clinical Risk Score	2.5 (1-4)
Oslo Score	1.5 (0-2)
CEA at time of LT (ng/ml)	7.7 (1.6-56.4)
Time from CRLM Dx to LT (years)	1.7 (1.1-7.8)
MELD-Na	6 (6-23)
Maximum Tumor Diameter (cm)	3.85 (1.4-5.9)
Distribution of CRLM	
Unilobar	2 (20%)
Bilobar	8 (80%)
Radiographic or Chemical Response to Treatment	10 (100%)



Hernandez-Alejandro, Sapisochin G, et al. JAMA Surg 2022

Challenges and Future Directions

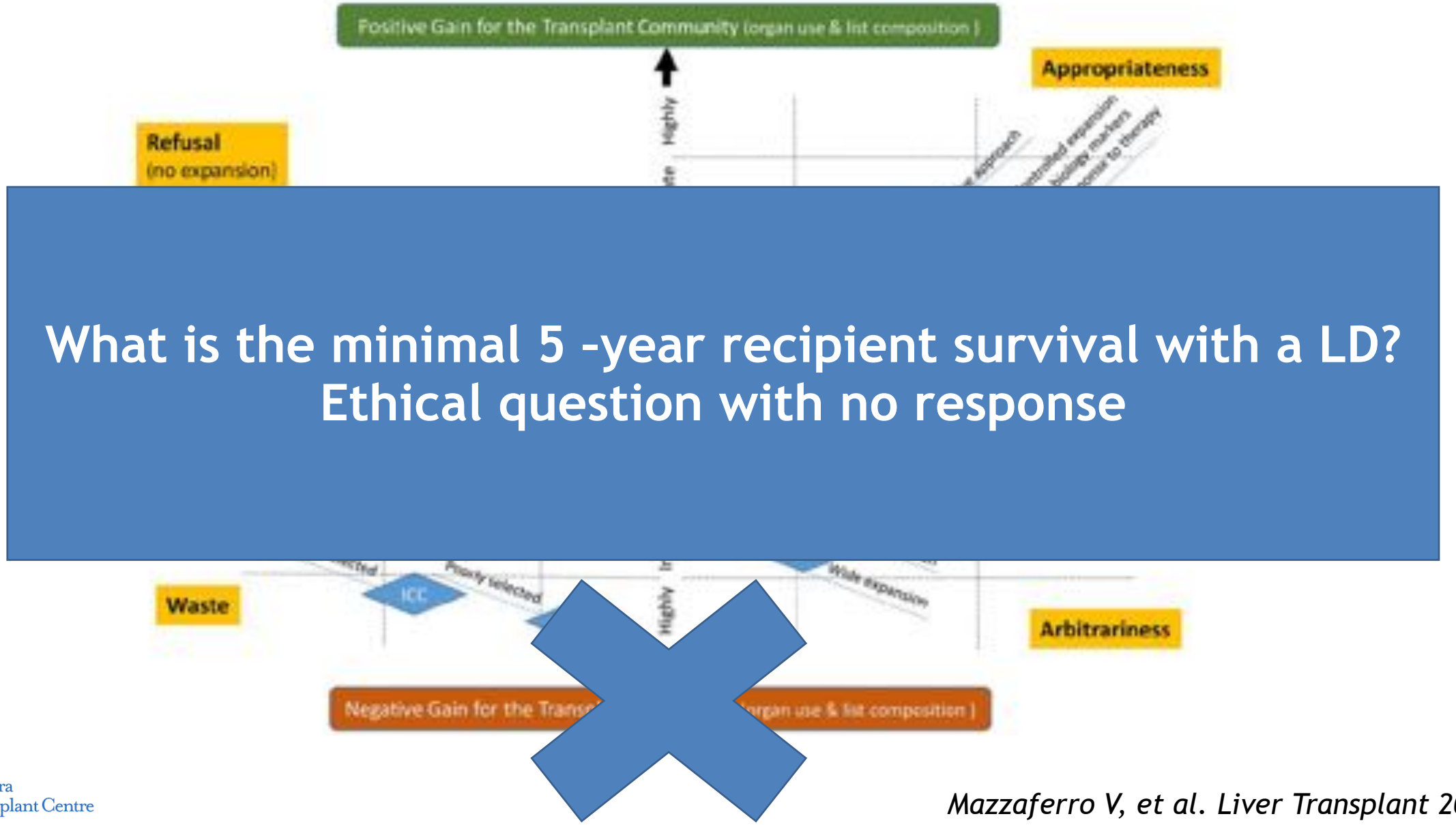
- Current approach not generalizable – need more data from trials
- Exception points vs. LDLT?
- Populations of resectable CRC LM that may benefit from LT?
- Better biomarkers – ctDNA?

The Fundamental Problem is Organ Shortage

Organ Shortage

Wait-list mortality for patients with HCC in Toronto is ~25-30%
Very similar for several jurisdictions in the World

Unlimited Source of Grafts with LDLT



What is the minimal 5 -year recipient survival with a LD?
Ethical question with no response

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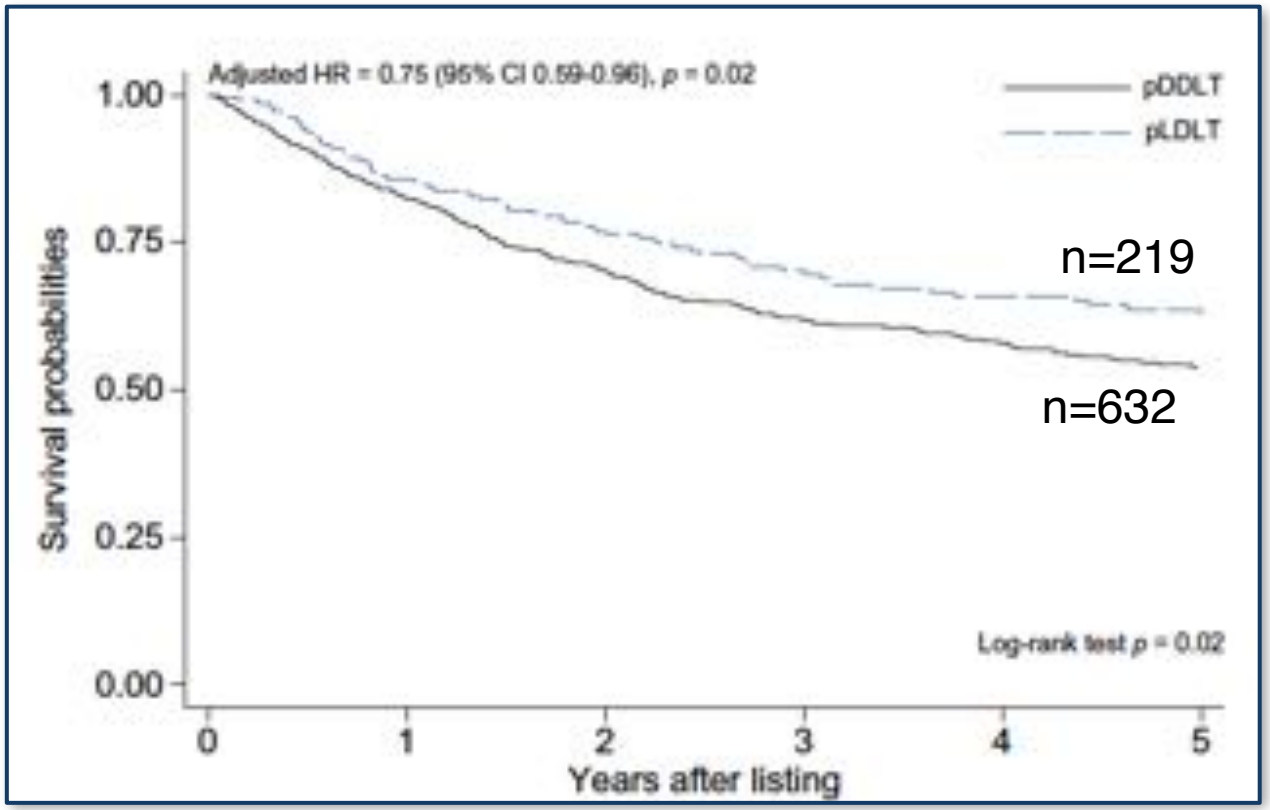
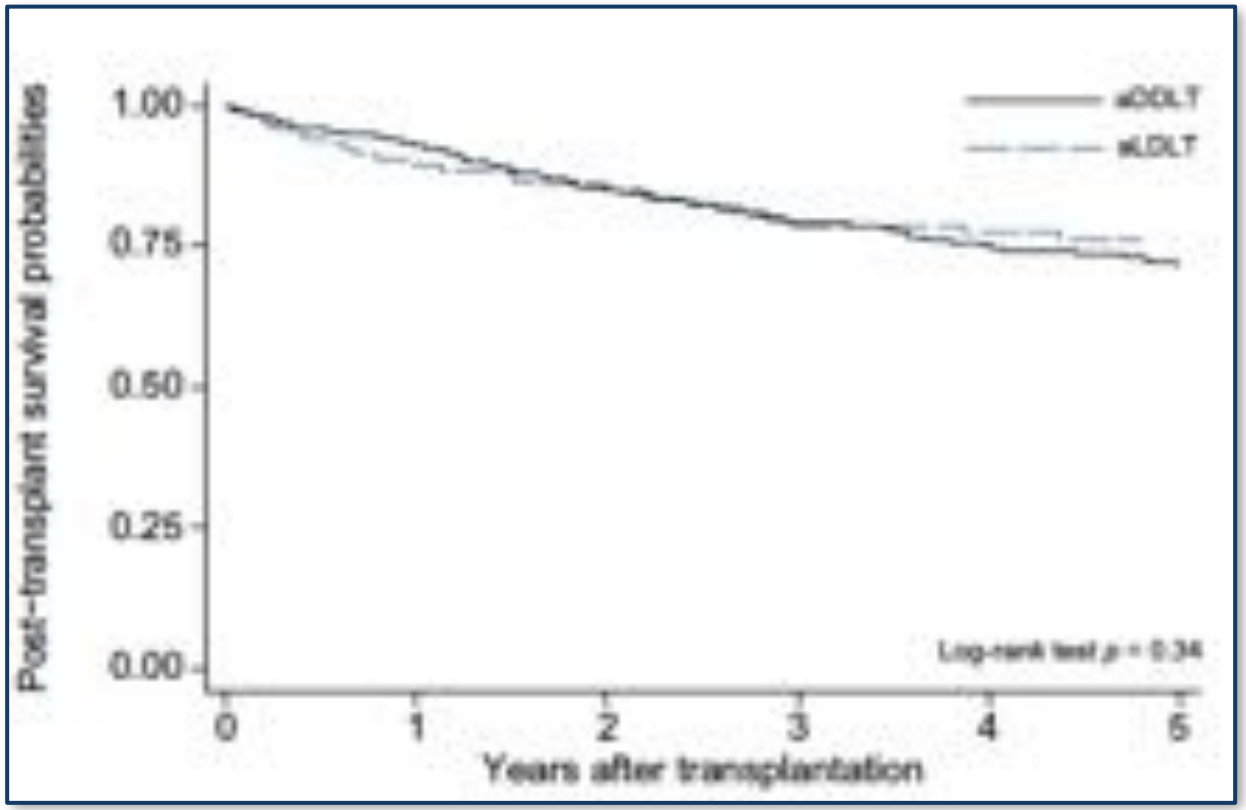
Mazzaferro V, et al. Liver Transplant 2017

Benefit of LDLT

Intention-to-treat Survival



Post-Transplant Survival



Survival advantage of LD available for patients with HCC **HR 0.75 (0.59-0.96), p=0.02**

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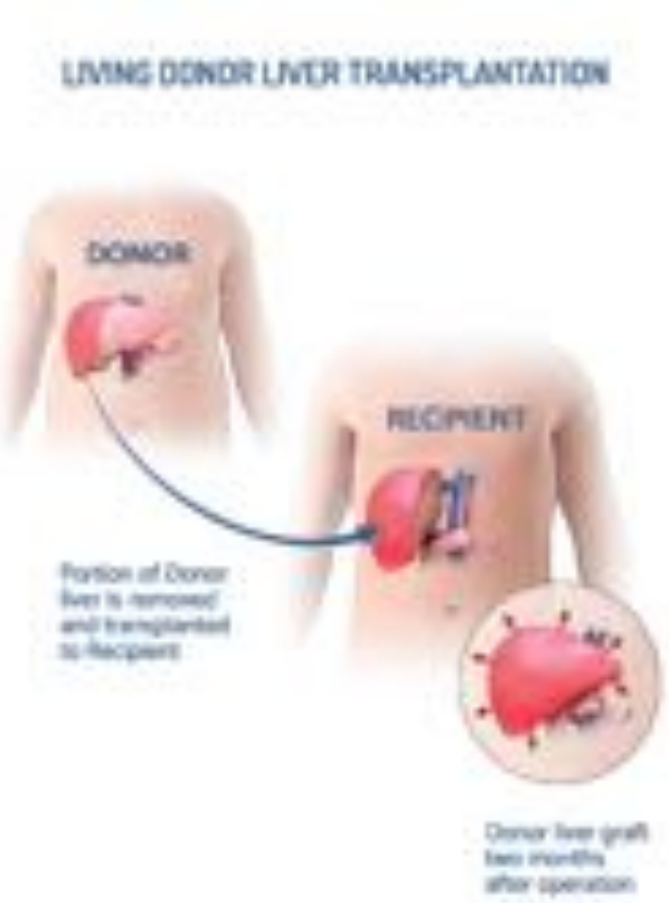
Goldaracena N & Sapisochin G et al. J Hepatol 2019

Advantages of LDLT for Patients with Cancer

- Decreased drop-out rates if graft is available
- Provides a healthy “perfect” graft
- Unlimited source of grafts
  - Extended Criteria
  - Palliative Transplant?
  - Adds another graft to the system



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.

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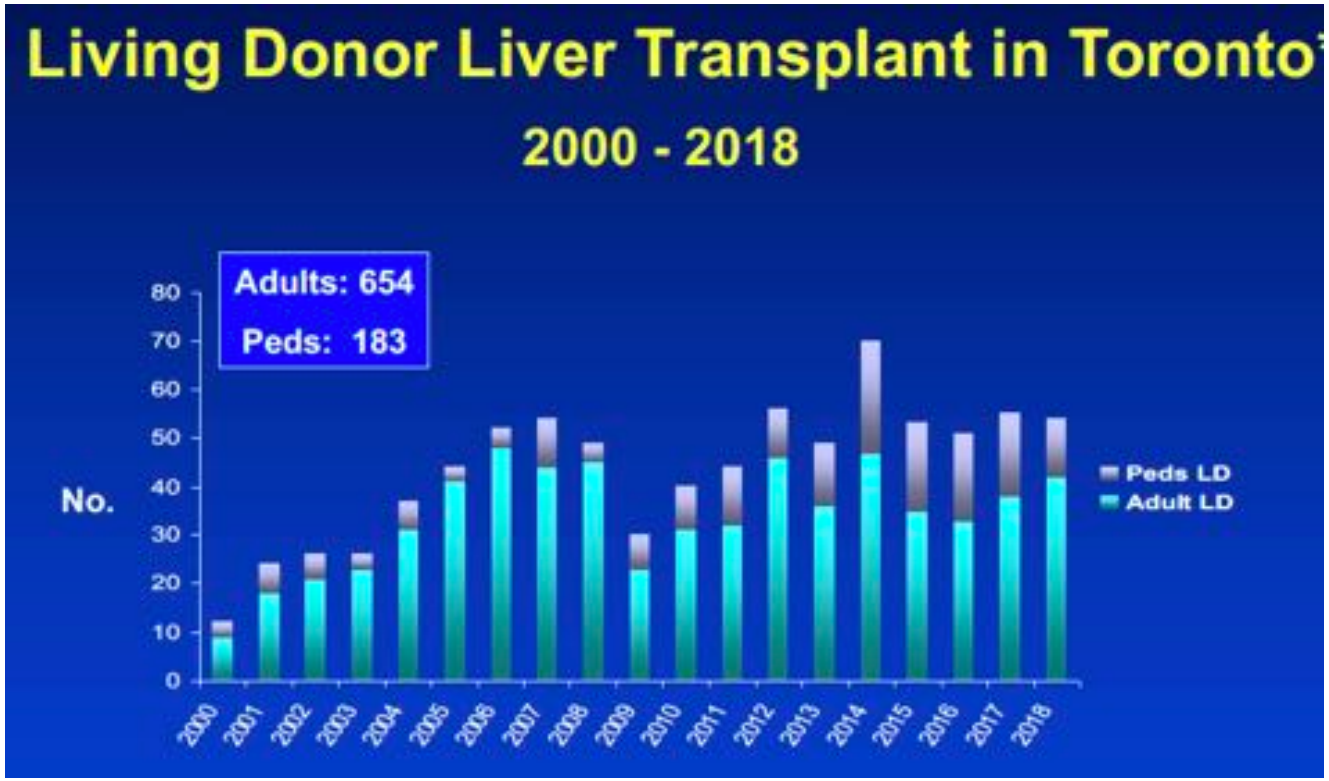
Summary

- There is a new era of **Transplant Oncology.**
- **Collaboration** between transplantation medicine, immuno and oncology will be crucial to move this field forward.
- Liver transplantation may be a **curative treatment for sele patients with liver-only stage IV colon cancer.**
  - Further research is on its way.
  - International Registry needed.

Living donor Liver Transplant Program UHN

- **Largest LDLT program Western World**
- 25—35% of LT
- Mainly Right Lobes
- 1 donor for every 3-4 work-ups
- 0 mortality, <5% major complications



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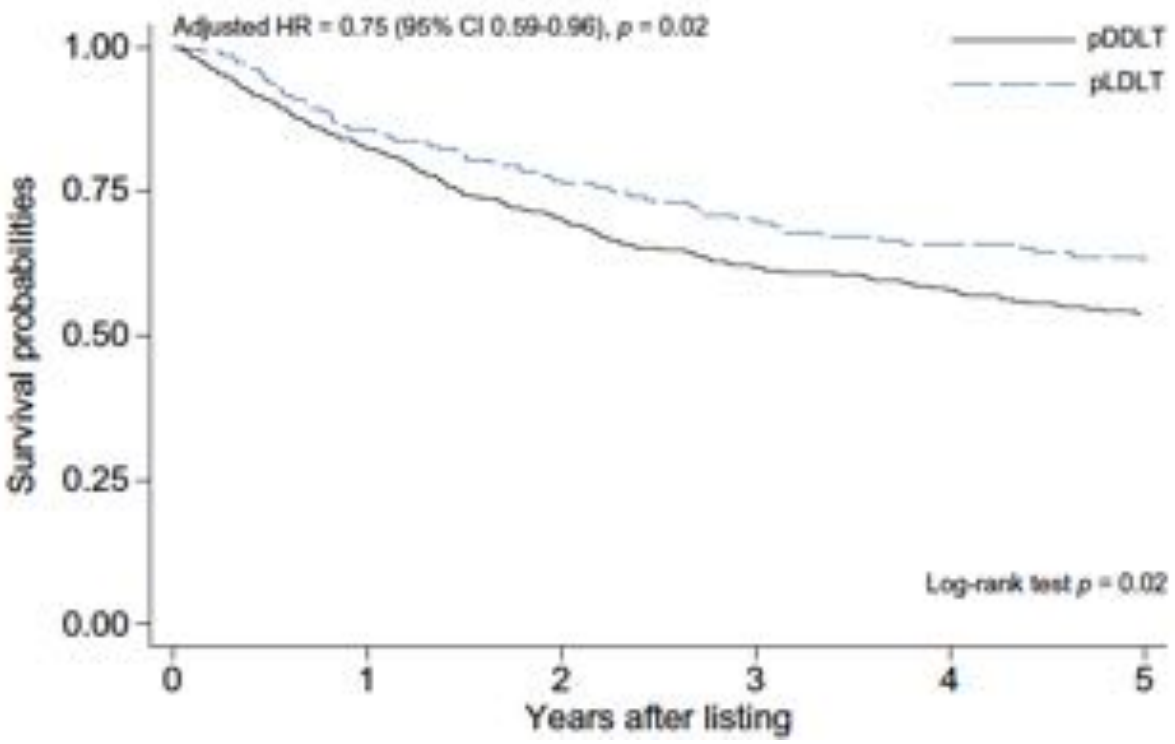
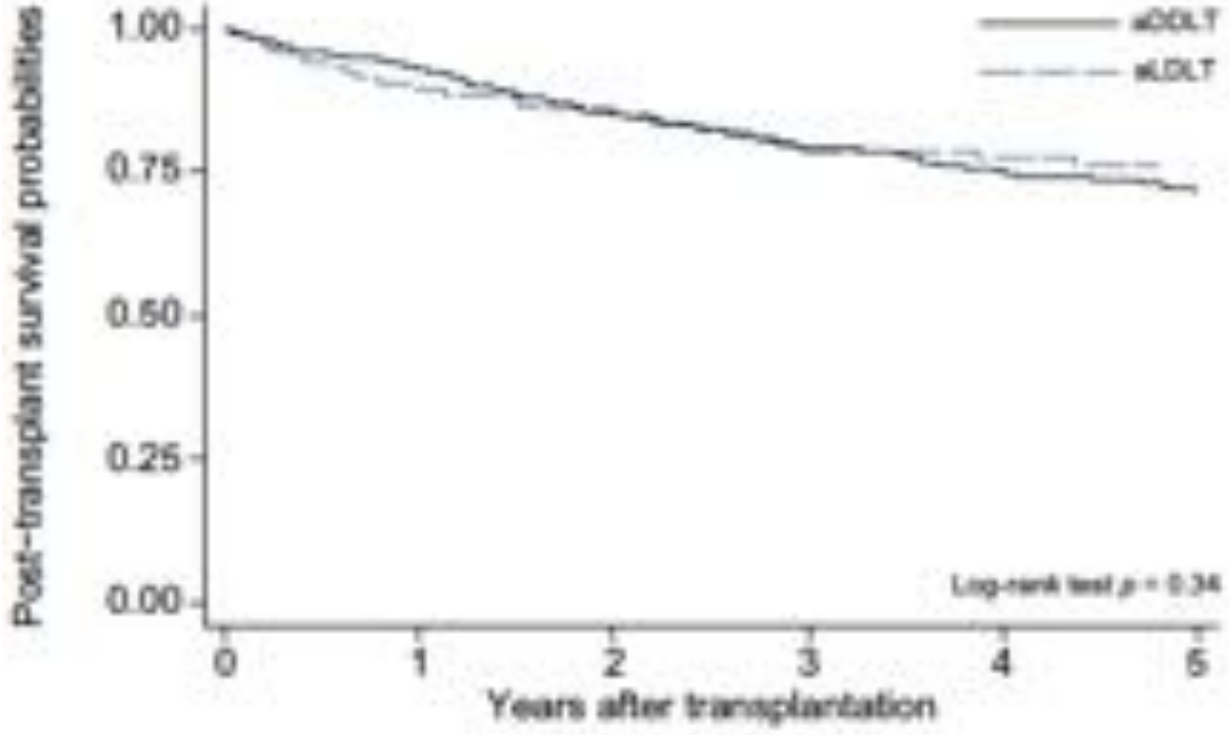
Sapisochin G, et al. Hepatobiliary Surgery and Nutrition 2016
Gorgen A & Sapisochin G, et al. Semin Liv Disease 2018

Benefit of LDLT

Intention-to-treat Survival



Post-Transplant Survival



Survival advantage of LD available for patients with HCC HR 0.75 (0.59-0.96), p=0.02

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Goldaracena N & Sapisochin G et al. J Hepatol 2019

Liver Transplantation for HCC

- **DDLT for HCC**
  - Composite criteria that considers surrogates of tumor biology (AFP) and response to neoadjuvant treatments, are likely to replace conventional morphological criteria (size and number) for defining transplant feasibility for DDLT
  - Tumor volume and tumor biology are good predictors of successful down-staging of HCC. Eligibility to downstaging should be defined upfront. In case of response, a no-treatment period to assess end-treatment sustainability is recommended.

Liver Transplantation for HCC

INTERNATIONAL LIVER TRANSPLANTATION SOCIETY

ILTS CONSENSUS CONFERENCE 2019
ROTTERDAM | NETHERLANDS
FEBRUARY 7, 2019

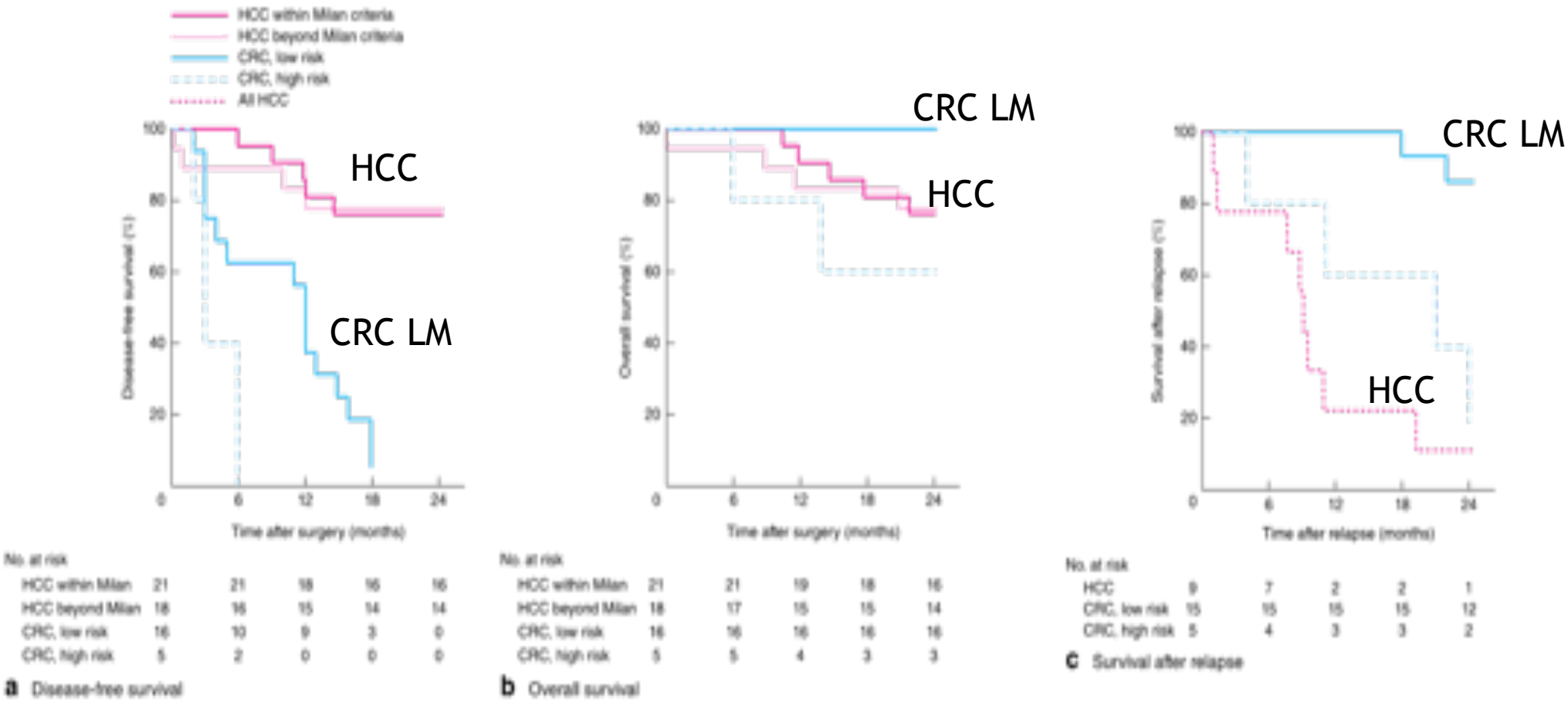
- **LDLT for HCC**
  - Aim for minimum recipient OS of 60% at 5 yrs. Selection criteria may be different than DDLT
  - With good biology with validated selection criteria based on AFP < 400, FDG 18 non-avid tumor, DCP< 400, response to LRT, eg., MoRAL, TRAIN, HALT) criteria may exceed UCSF size/no. provided there is no EHD, macrovascular invasion

Current Trials

Trial Protocol	Clinical trial Identifier	Country	Protocol Timeline	Design	Phase
SECA II	NCT01479608	Norway	2011–2027	LT vs. surgical Resection	Phase 3 Randomized
RAPID	NCT02215889	Norway	2014–2028	Liver resection and partial section 2-3 transplantation with two-stage hepatectomy	Phase 1-2
TRANSMET	NCT02597348	France	2015–2027	Chemo + LT vs. Chemo	Phase 3 Randomized
SECA III	NCT03494946	Norway	2016–2027	LT vs. chemo or ablation	Phase 3 Randomized
Toronto Protocol	NCT02864485	Canada	2016–2023	Chemo + LDLT vs. Chemo	Open Label
LIVERT(W) OHEAL	NCT03488953	Germany	2018–2023	LDLT with two-stage hepatectomy	Open Label
COLT	NCT03803436	Italy	2019–2024	Chemo + LT vs. Chemo	Open Label
SOULMATE	NCT04161092	Sweden	2020–2029	Chemo + LT with ECD vs. Chemo	Open Label Randomized

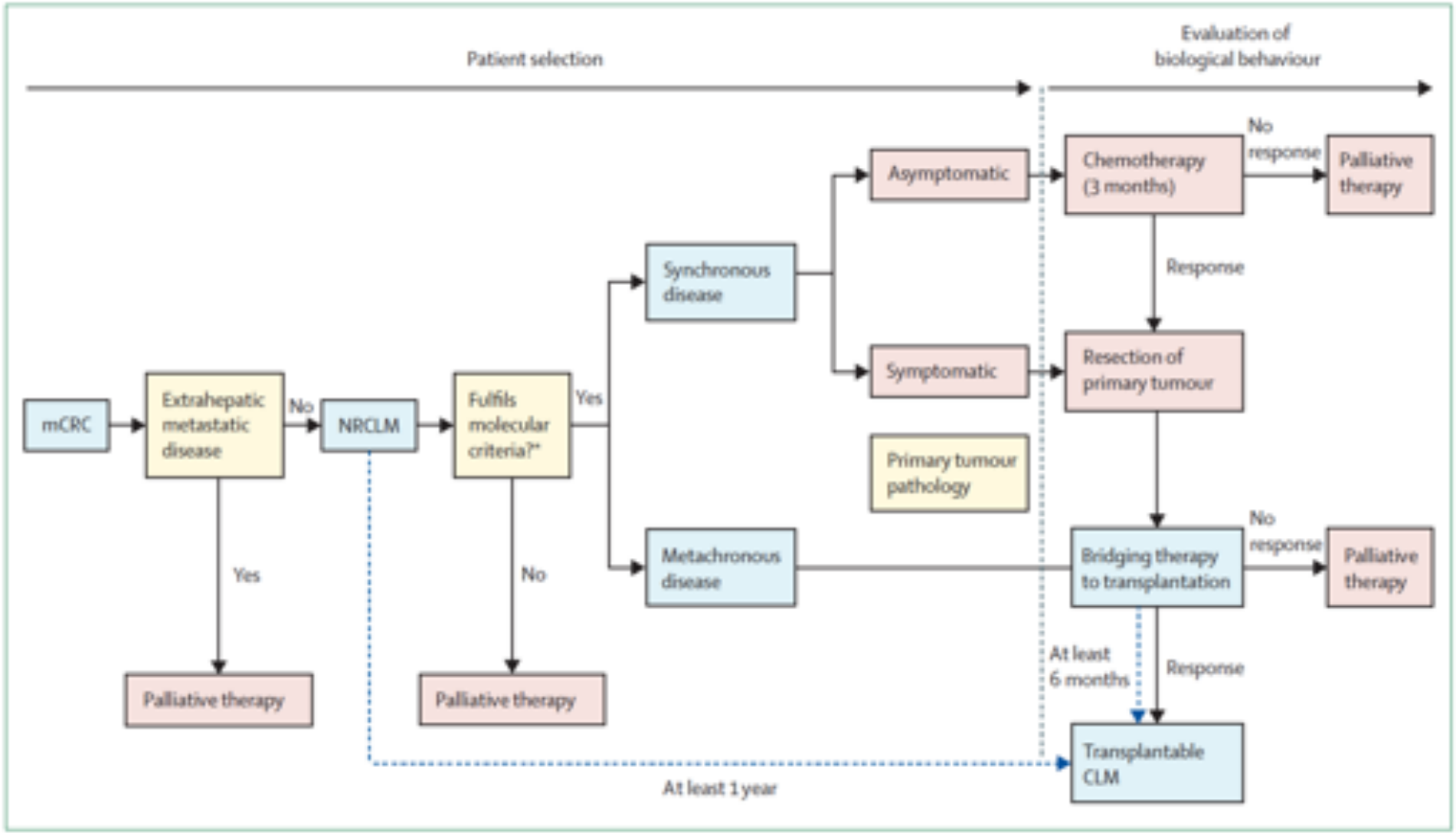
Line PD, et al. Int J Surgery 2020

Compared Outcomes with HCC



Dueland S, et al. BJS 2018

Management of CRC with LM



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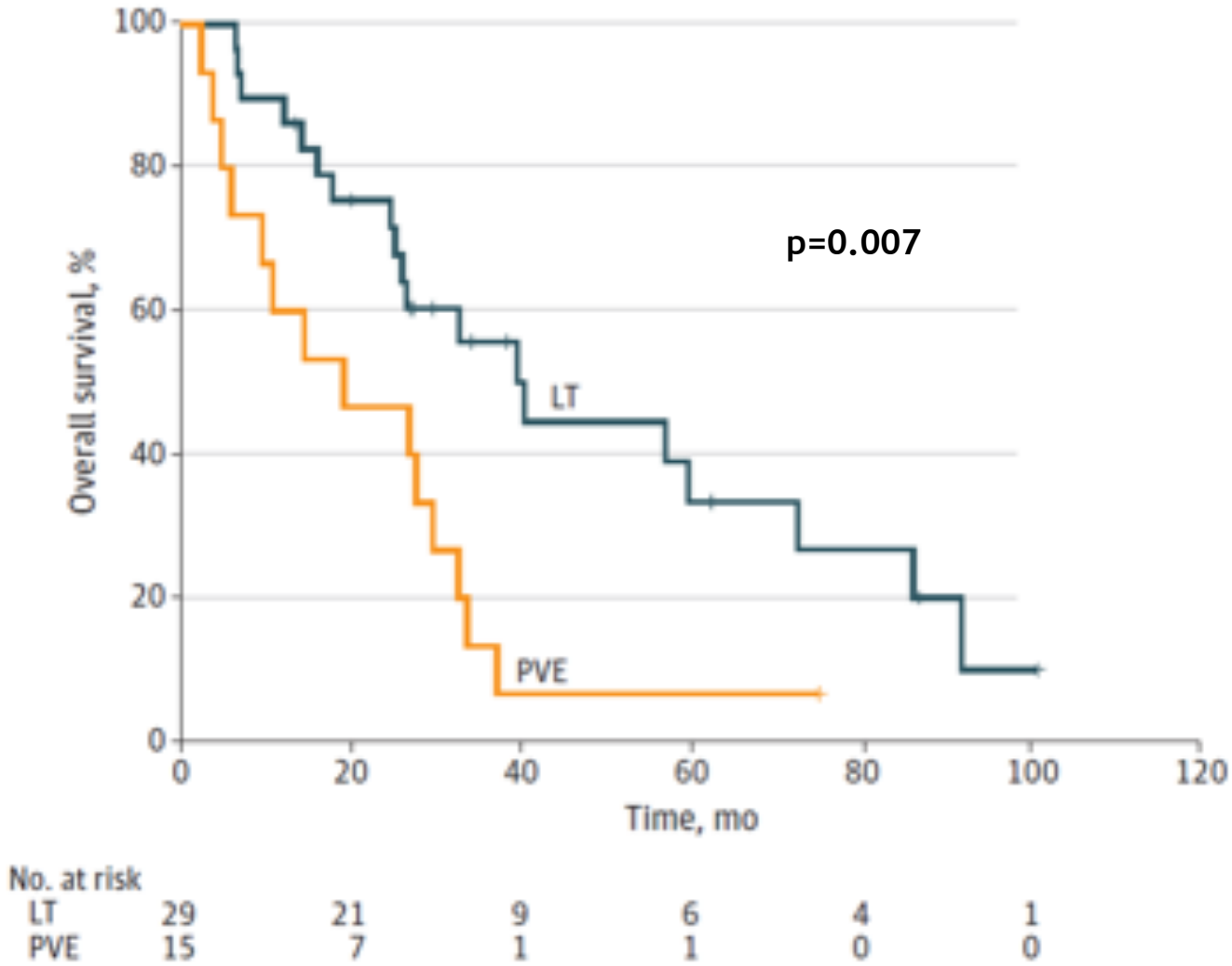
Bonney GK, el al. Lancet Gastroenterol Hepatol 2021

Is LT better than Liver Resection?



Dueland S, et al. JAMASurg 2021

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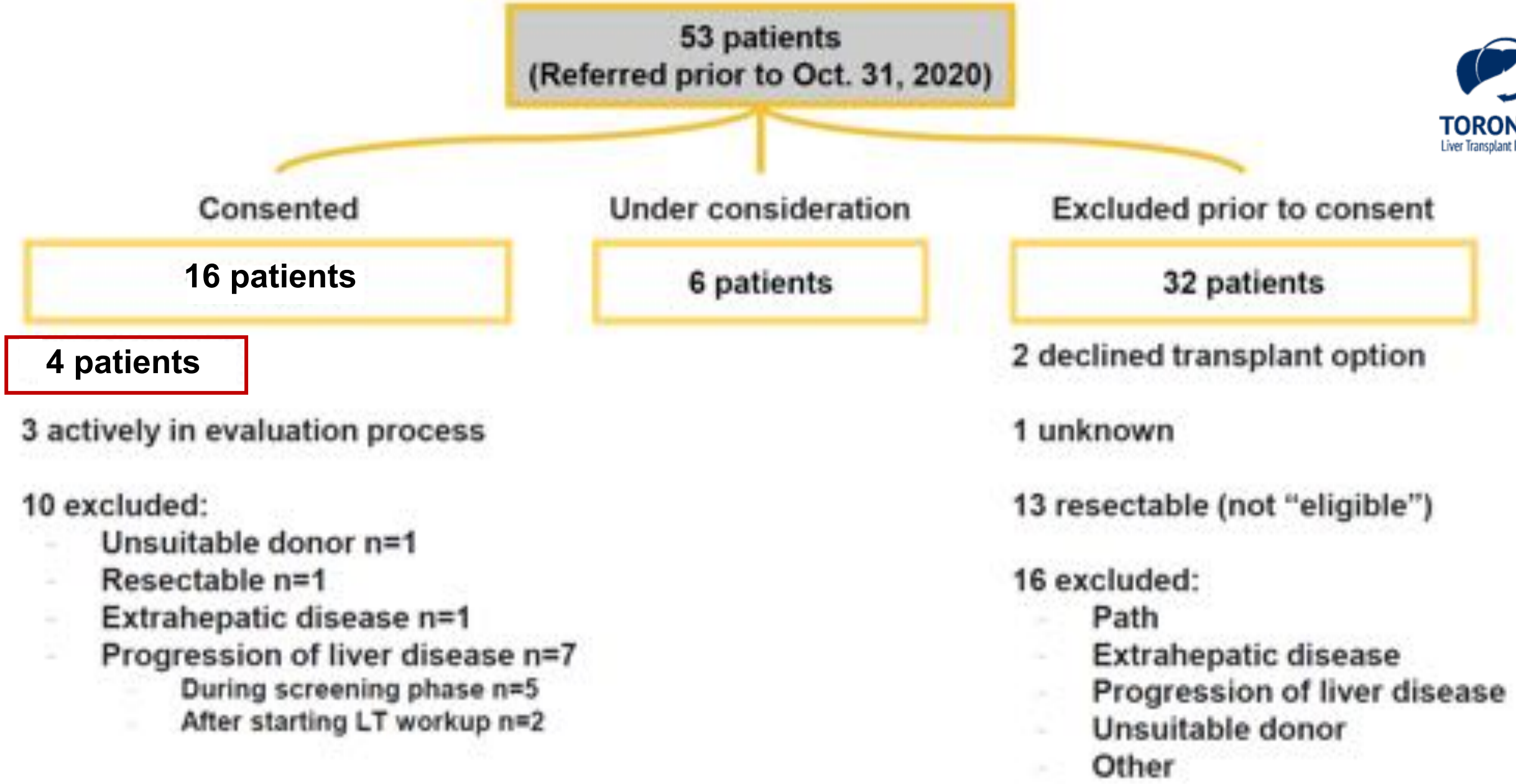
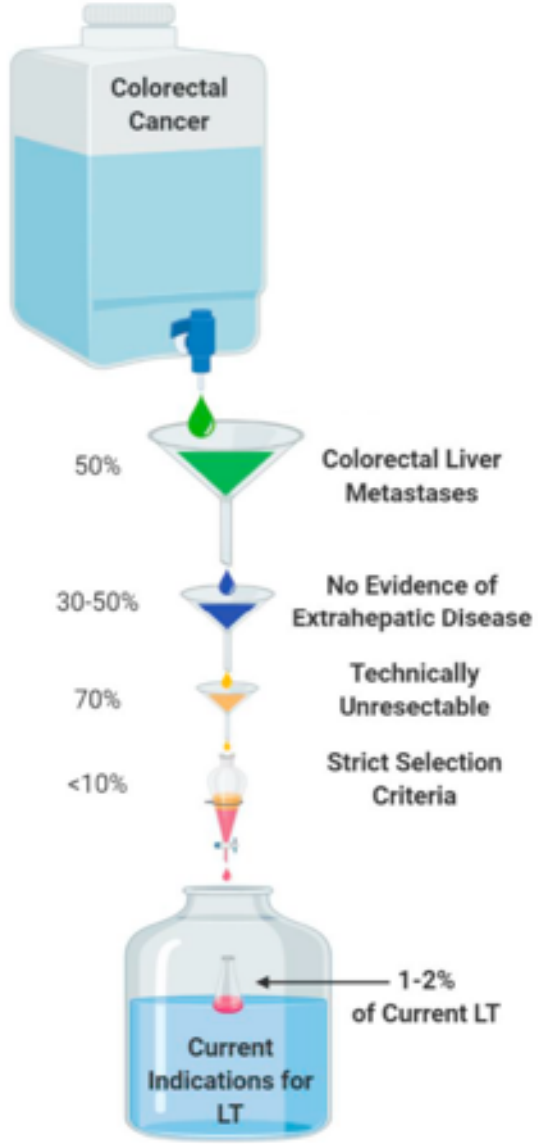


TORONTO Liver Transplant Program

UHN Ajmera Transplant Centre

https://clinicaltrials.gov/ct2/show/NCT02864485

Impact on the transplant list



Line PD, et al. Int J Surgery 2020

A MDT approach in HCC ensures patients receive optimal care based on best practice and evidence-based guidelines[1]

Implementation of a MDT has been shown to improve patient outcomes for this complex and heterogeneous disease[2]


Surgeon


Pathologist


Oncologist


Hepatologist or Gastroenterologist

Multidisciplinary Team


Nurse


Diagnostic Radiologist


Interventional Radiologist


Pharmacist

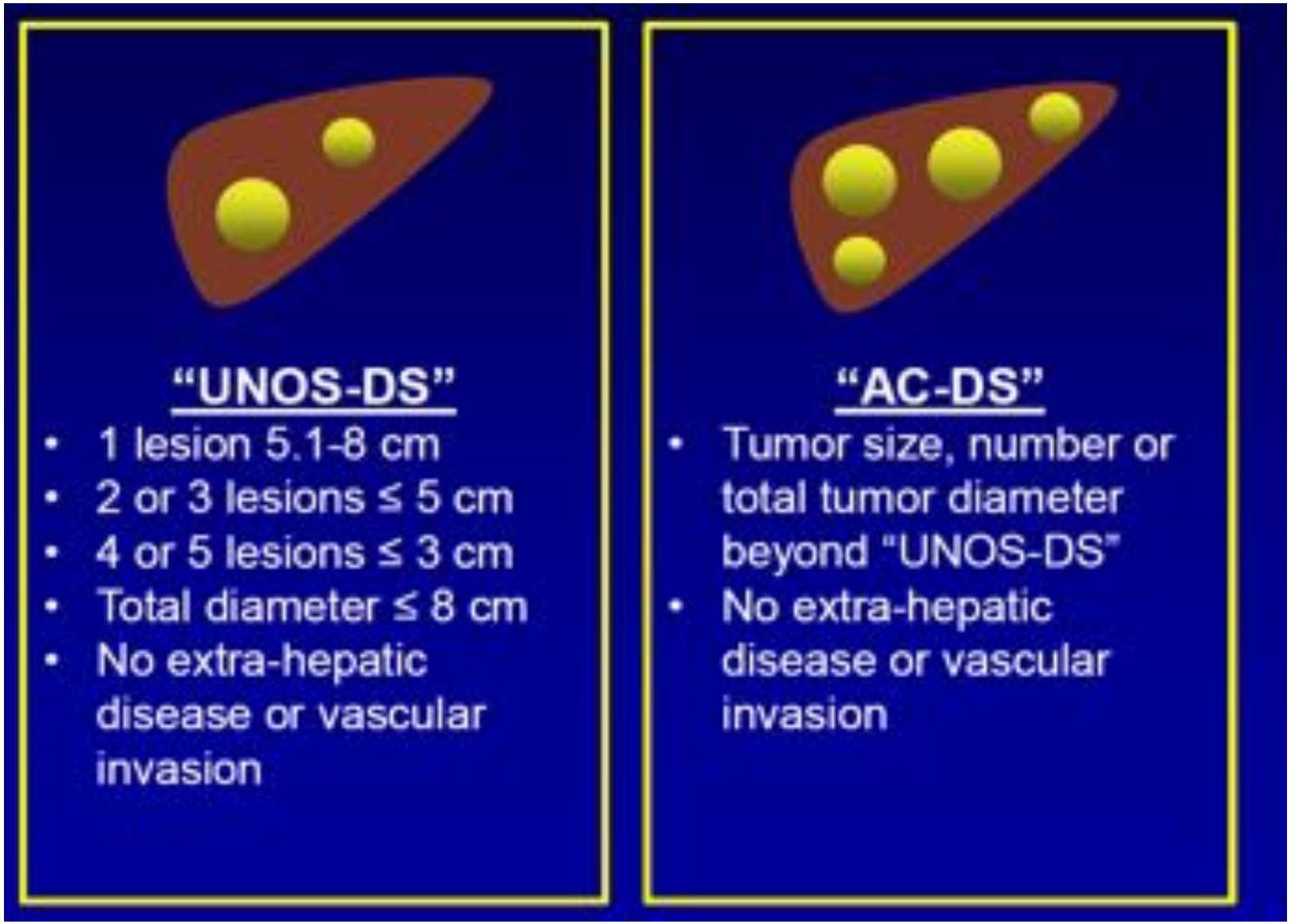
AE=adverse event; BCLC=Barcelona Clinic Liver Cancer; (i)(u)HCC=(intermediate)(unresectable)hepatocellular carcinoma; MDT=multidisciplinary team.

1. Barone C et al. *Ann Oncol*. 2013;24(suppl 2):ii15-ii23; 2. Chang TT et al. *HPB*. 2008;10(6):405-411; 3. Slotta JE et al. *World J Hepatol*. 2015; 7(9):1168-1183; 4. Kellock T et al. *Br J Radiol*. 202018; 91(1085):20170118

Can we Expand the Indications of Liver Transplantation for HCC by Tumor Downstaging?

Can response to LRT be integrated in the decision making of LT candidacy in patients with HCC?

Down-Staging Protocols – Inclusion Criteria



Courtesy of F. Yao and N. Mehta - UCSF

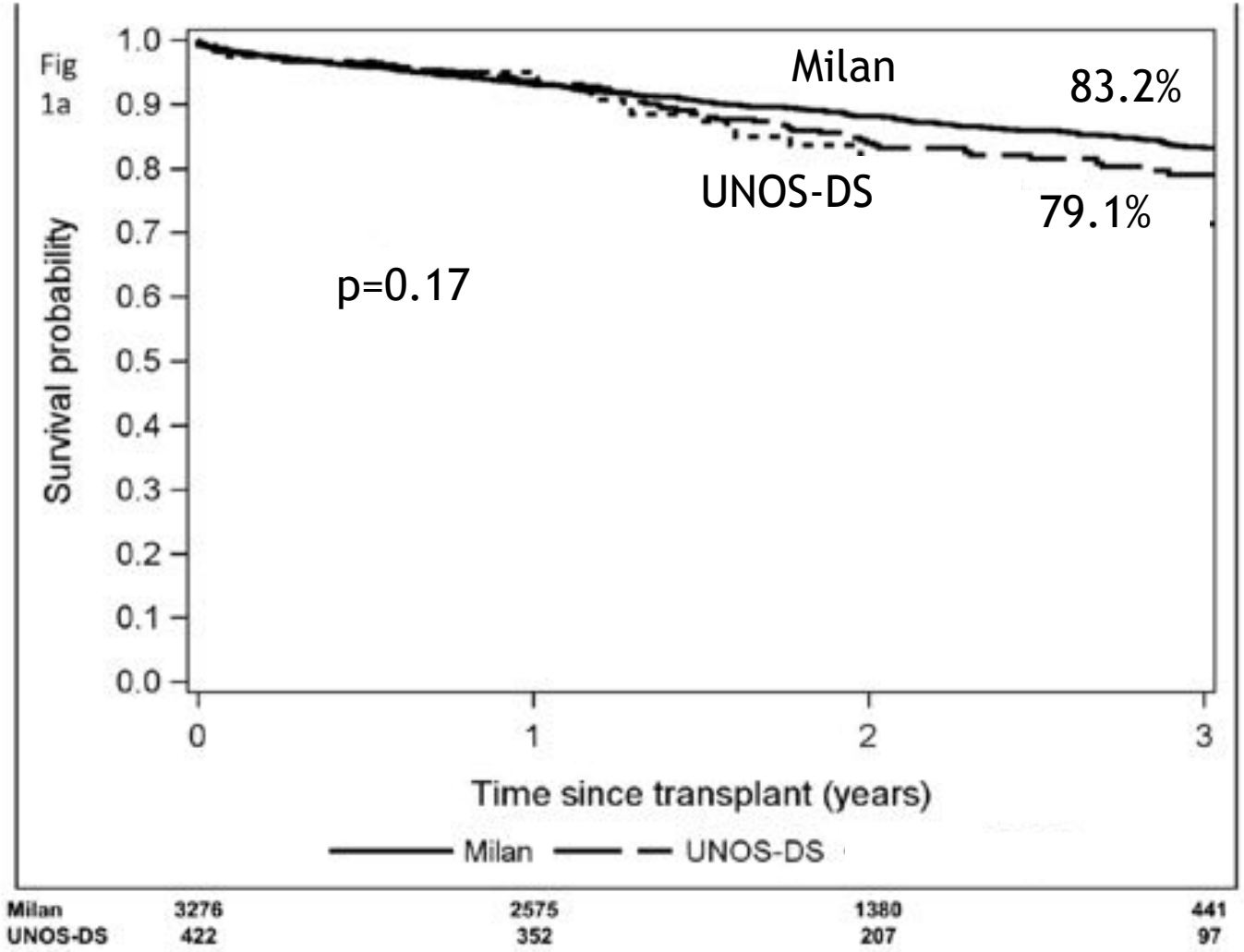
Outcomes of LT after Down-Staging

UNOS Database

3276 patients MILAN
422 DS to MILAN from UNOS-DS
Protocol

1 lesion 5-8 cm
2-3 lesions 3-5 cm with TTD <8 cm
4-5 lesions all <3 TTD <8

3-year Recurrence Probability
6.9% Milan vs. 12.8% UNOS-DS



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Mehta N et al. Hepatology 2019

Should there be an upper tumor burden to attempt Down-staging?

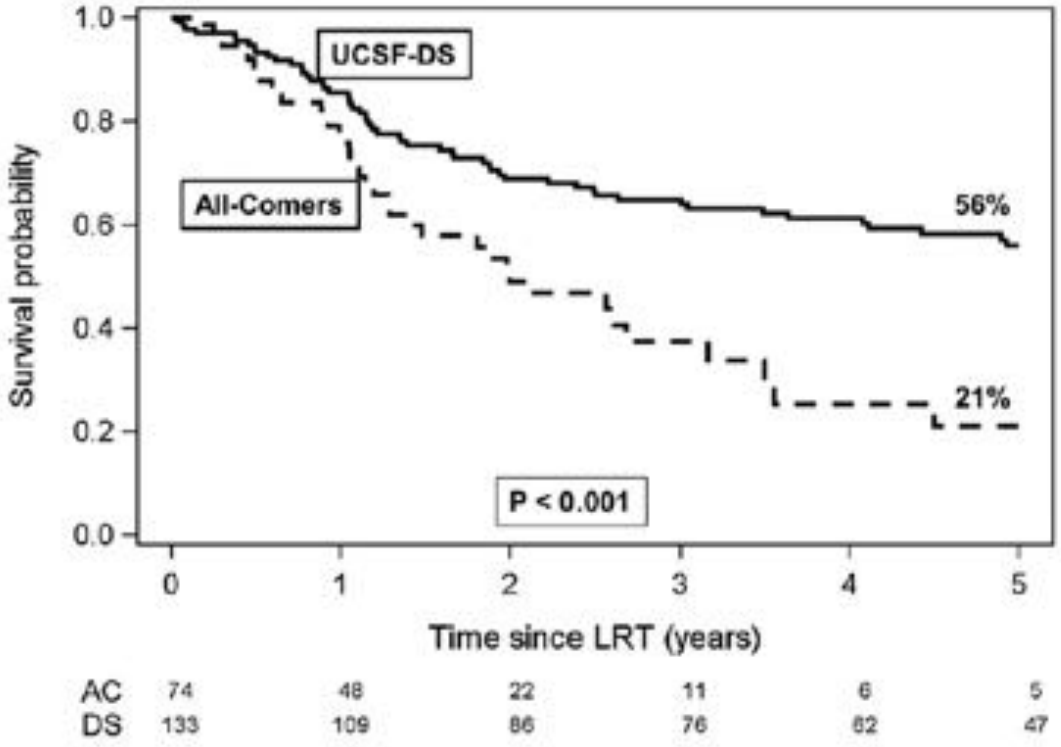
UCSF DS Criteria

Inclusion Criteria

HCC exceeding UNOS T2 criteria but meeting one of the following:

1. Single lesion ≤ 8 cm
2. 2 or 3 lesions each ≤ 5 cm with the sum of the largest tumor diameters ≤ 8 cm
3. 4 or 5 lesions each ≤ 3 cm with the sum of the largest tumor diameters ≤ 8 cm

Absence of vascular invasion based on cross-sectional imaging

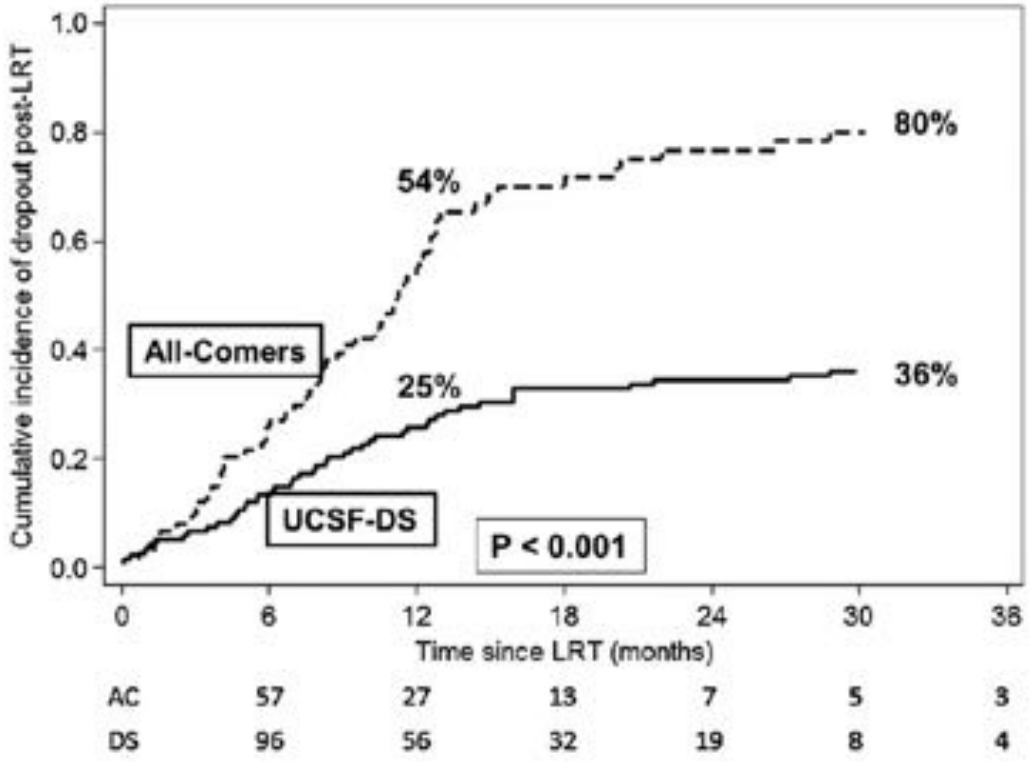


All-comers Criteria

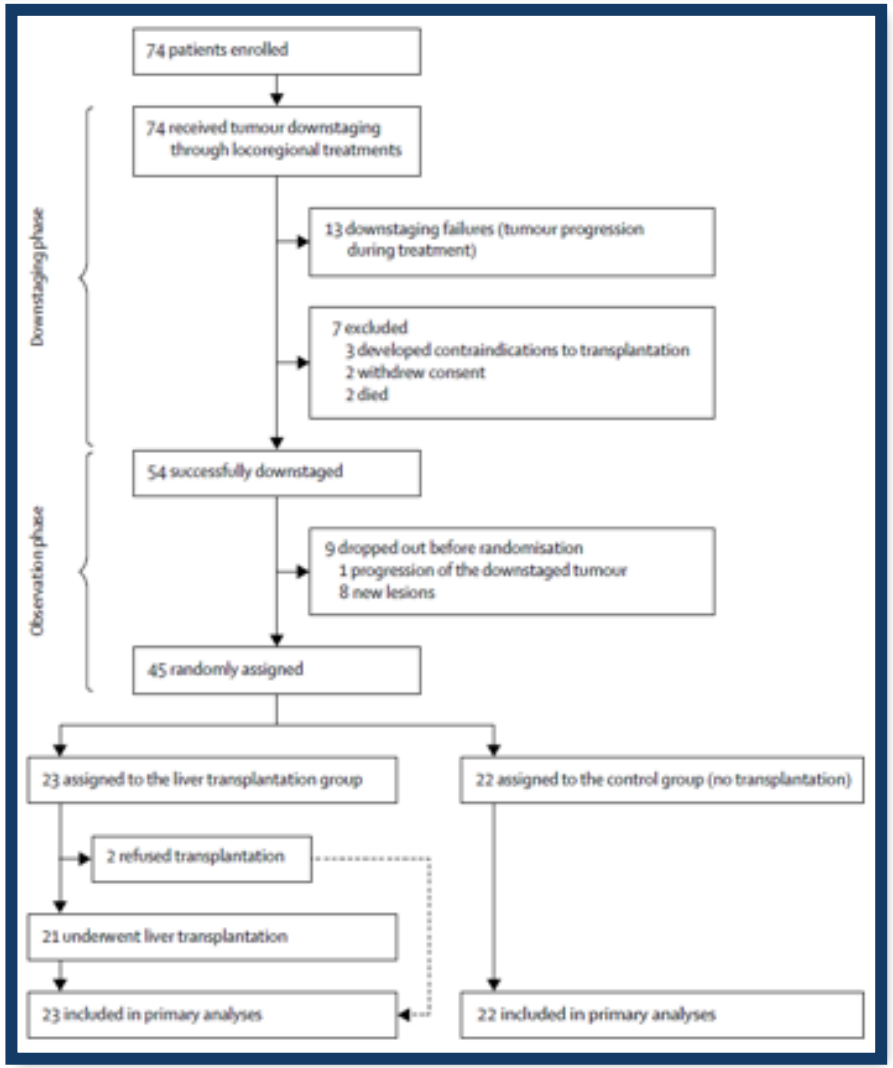
HCC exceeding UCSF-DS protocol by any of the following:

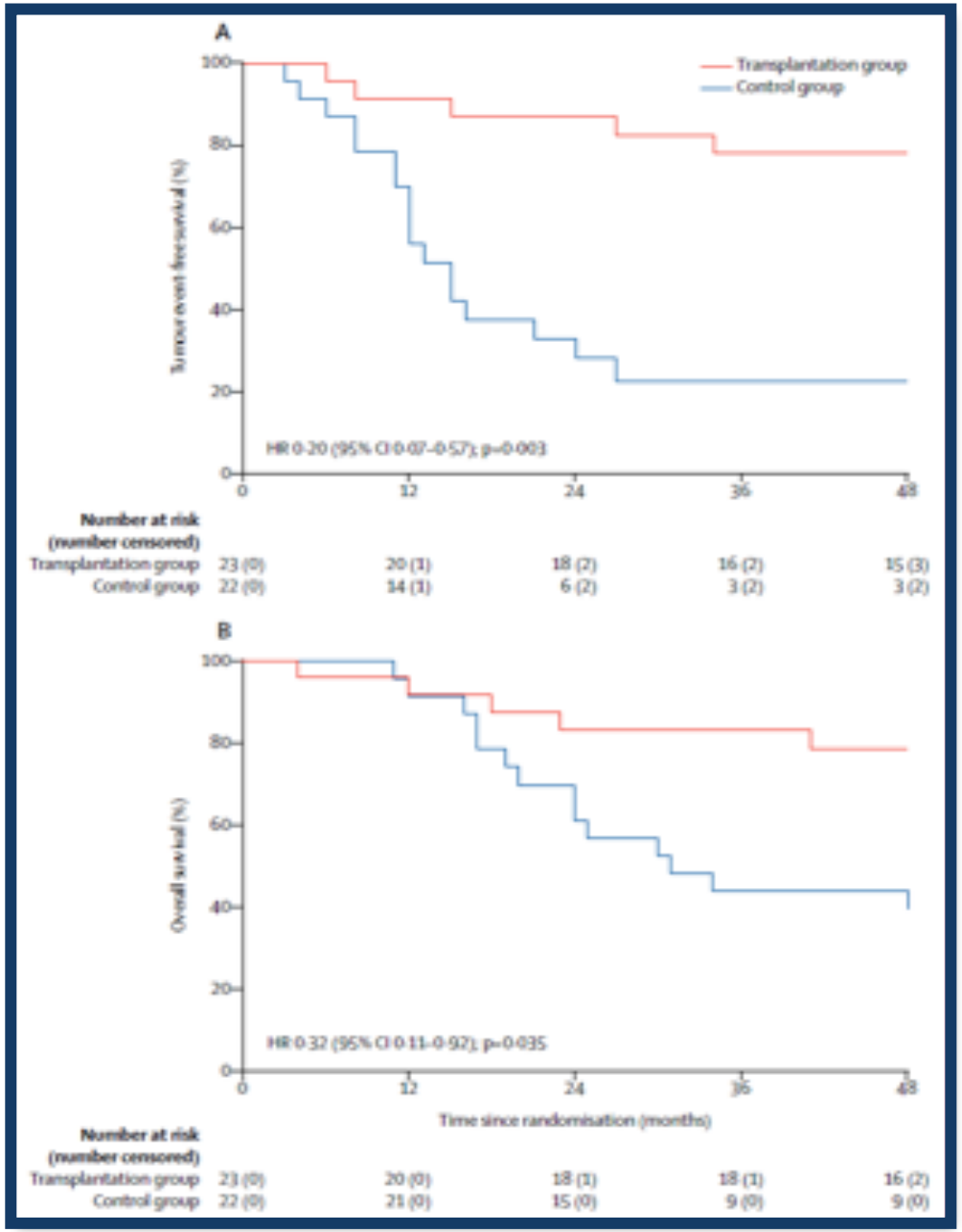
1. HCC tumor number
2. HCC tumor size
3. Total HCC tumor diameter

Absence of vascular invasion based on cross-sectional imaging



Liver transplantation in hepatocellular carcinoma after tumour downstaging (XXL): a randomised, controlled, phase 2b/3 trial





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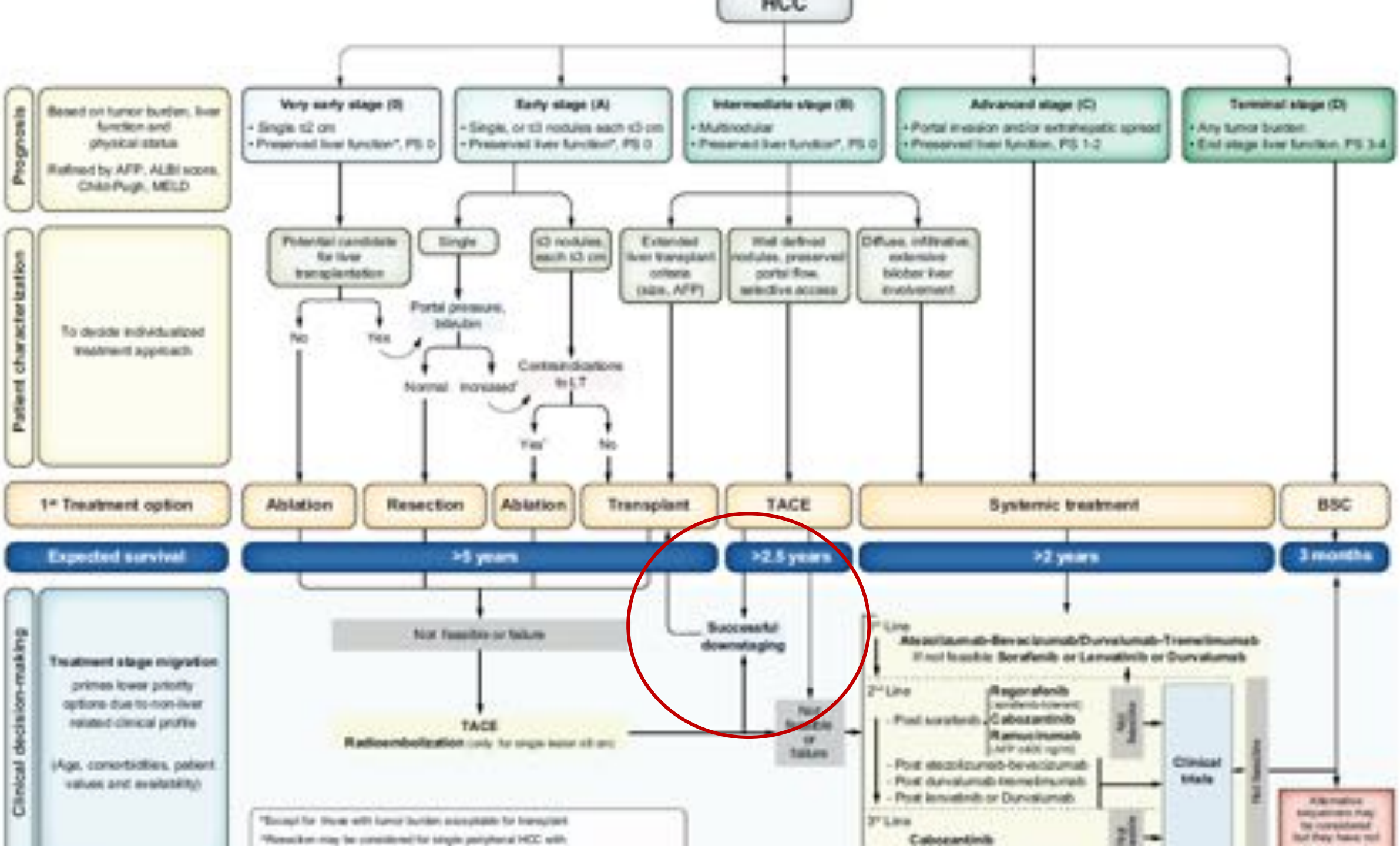
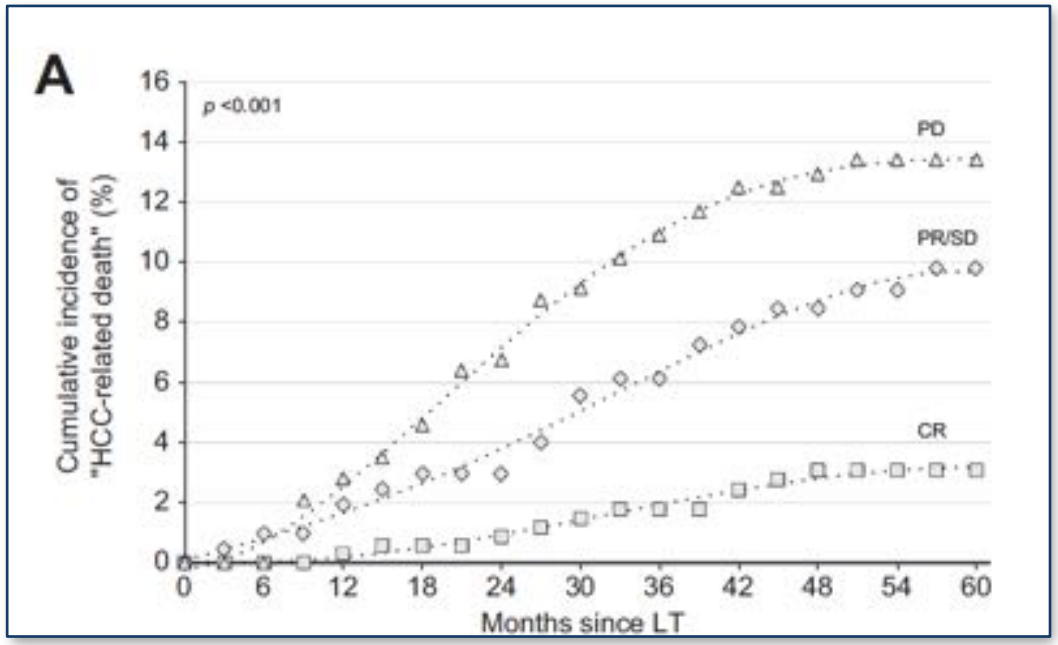
Mazzaferro V, et al. Lancet Oncol 2020

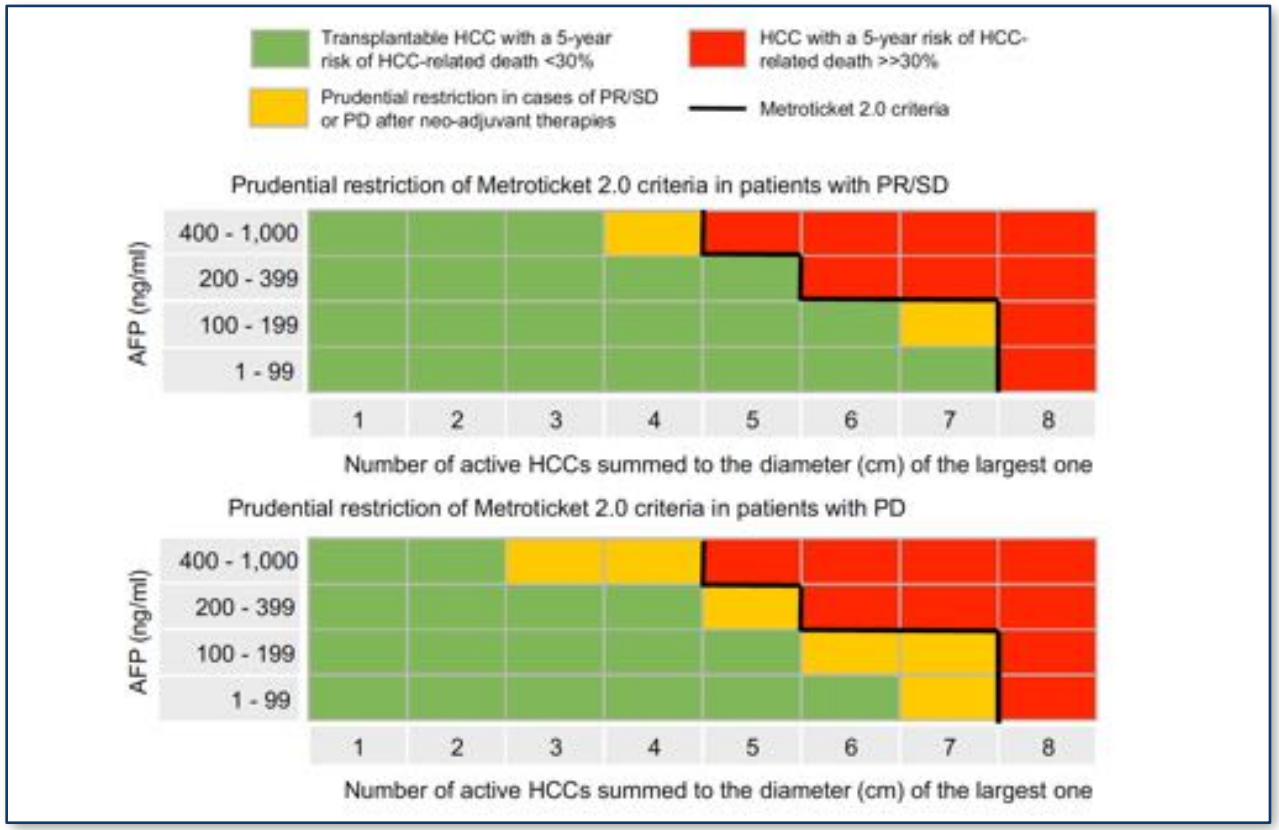

HCC
Prognosis
Based on tumor burden, liver function and physical status
Refined by AFP, ALBI score, Child-Pugh, MELD
Very early stage (0)
• Single ≤2 cm
• Preserved liver function*, PS 0
Early stage (A)
• Single, or ≤3 nodules each ≤3 cm
• Preserved liver function*, PS 0
Intermediate stage (B)
• Multinodular
• 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
Patient characterization
To decide individualized treatment approach
Potential candidate for liver transplantation
Single
>3 nodules, each ≤3 cm
Extended liver transplant criteria (size, AFP)
Well defined nodules, preserved portal flow, selective access
Diffuse, infiltrative, extensive bilobar liver involvement
No
Yes
Portal pressure, bilirubin
Normal
Increased
Contraindications to LT
Yes
No
1st Treatment option
Ablation
Resection
Ablation
Transplant
TACE
Systemic treatment
BSC
Expected survival
>5 years
>2.5 years
>2 years
3 months
Clinical decision-making
Treatment stage migration
primes lower priority options due to non-liver related clinical profile
(Age, comorbidities, patient values and availability)
Not feasible or failure
Successful downstaging
TACE
Radioembolization
1st Line
Atezolizumab-Bevacizumab/Durvalumab-Tremelimumab
If not feasible: Sorafenib or Lenvatinib or Durvalumab
2nd Line
Regorafenib
Cabozantinib
Ramucirumab
- Post sorafenib
- Post atezolizumab-bevacizumab
- Post durvalumab-tremelimumab
- Post lenvatinib or Durvalumab
3rd Line
Cabozantinib
Clinical trials
*Except for those with tumor burden acceptable for transplant

Bridging Therapy as a surrogate of tumor biology

Including mRECIST in the Metroticket 2.0 criteria improves prediction of hepatocellular carcinoma-related death after liver transplant



5-year "*HCC-related death*"
CR: 3.1%
PR/SD: 9.6%
PD: 13.4% (p<0.001)



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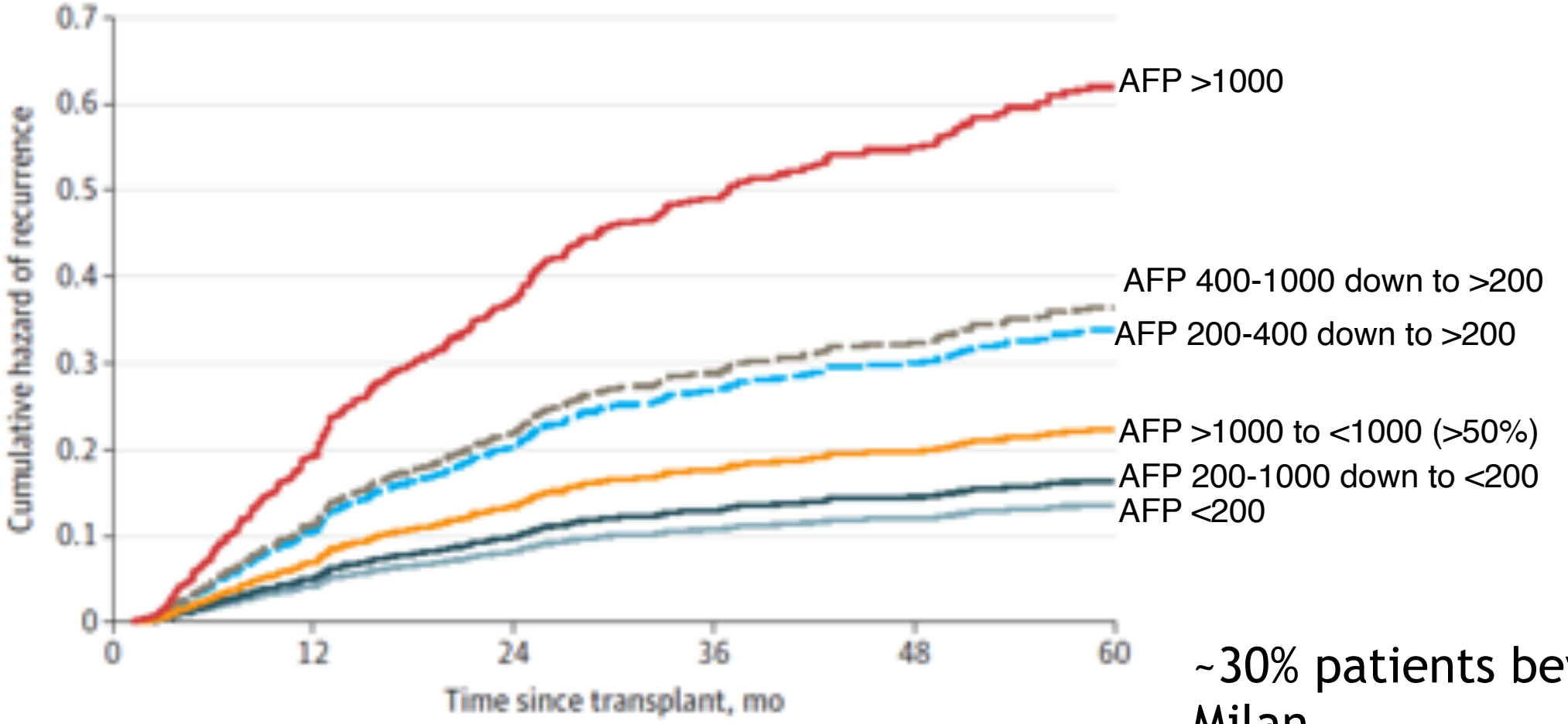
Cuchetti A, et al. J Hepatol 2020

Response to LRT by decrease in tumor markers (AFP)

JAMA Surgery | Original Investigation

Dynamic α-Fetoprotein Response and Outcomes After Liver Transplant for Hepatocellular Carcinoma



~30% patients beyond Milan

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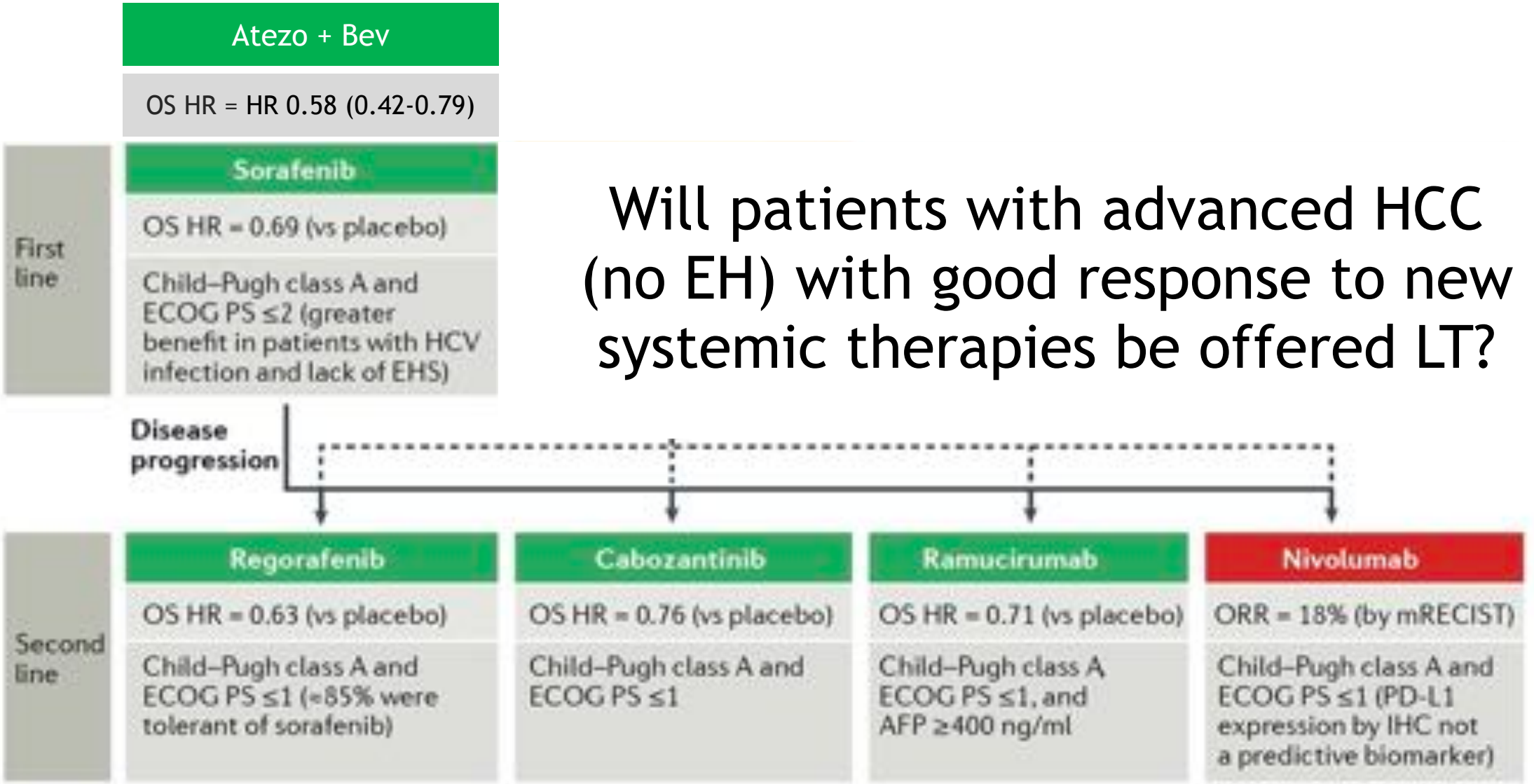
Halazun K, Sapisochin G et al. JAMA Surg 2021

Neoadjuvant systemic therapies and response?



Will patients with advanced HCC (no EH) with good response to new systemic therapies be offered LT?

Llovet et al. Nature Rev. 2018

Liver Transplantation for Metastatic Neuroendocrine Tumors

Liver Transplantation for Metastatic Neuroendocrine Tumors

- Liver Transplantation for NETs is an accepted indication in some centers
- Controversy on indications
- Controversy on best time for transplant
- Controversy on results

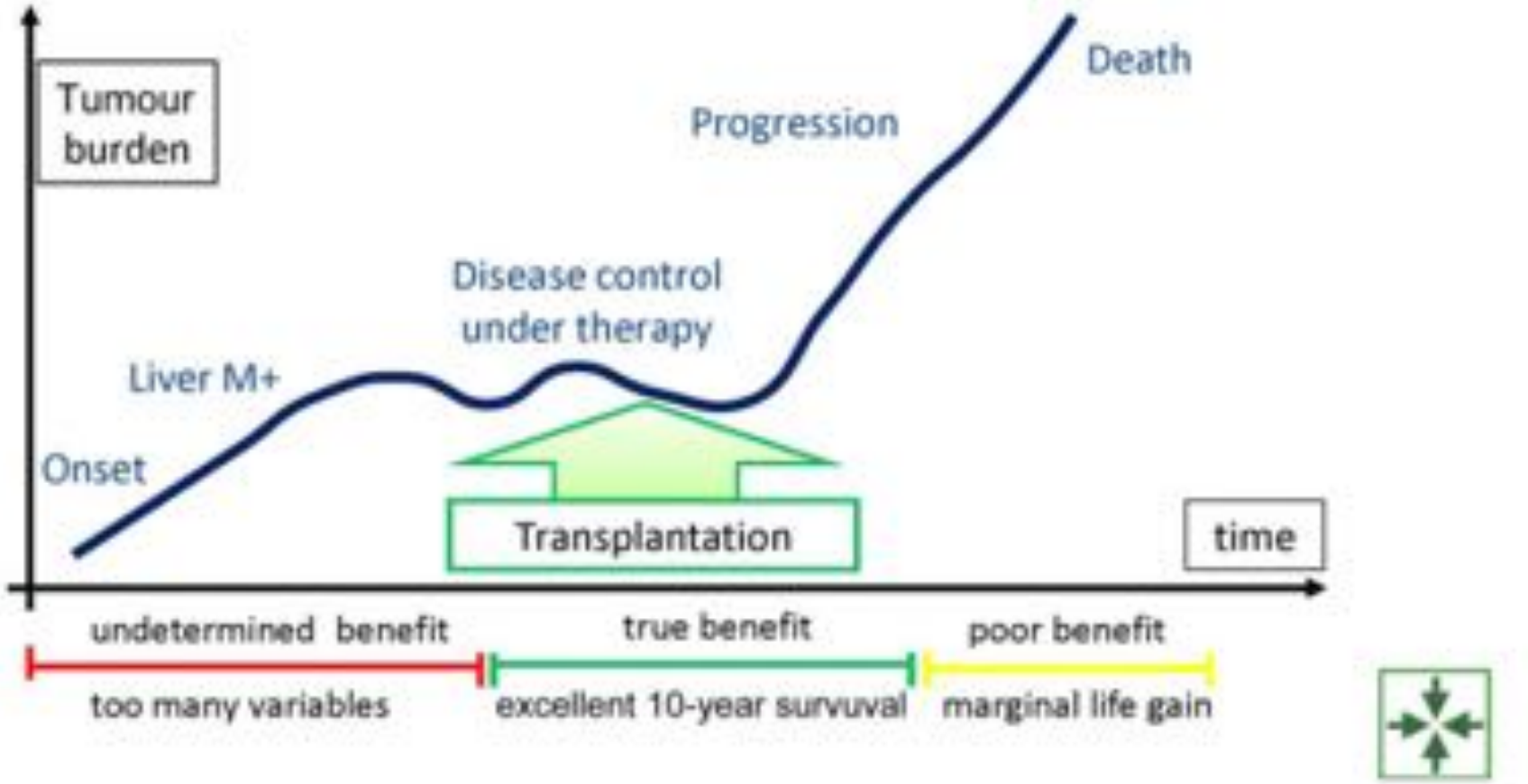
Liver Transplantation for Metastatic Neuroendocrine Tumors

Milan selection criteria for liver transplantation in patients with liver metastases from NET (6,15,35)
Confirmed histology of low-grade (G1-G2) NET
Primary tumor drained by the portal system and removed, with all extrahepatic deposits in a separate curative resection prior to transplant consideration
Metastatic diffusion to <50% of the total liver volume
Stable disease/response to therapies for at least 6 months prior to transplant consideration
Age < 60 (relative criteria)

Mazzaferro V, et al. AJT 2016

Liver Transplantation for Metastatic Neuroendocrine Tumors

Timing of transplantation should match the natural history of NET and target objective post-transplant benefit in survival with respect to alternative treatments



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Fan ST, et al. HPB 2014

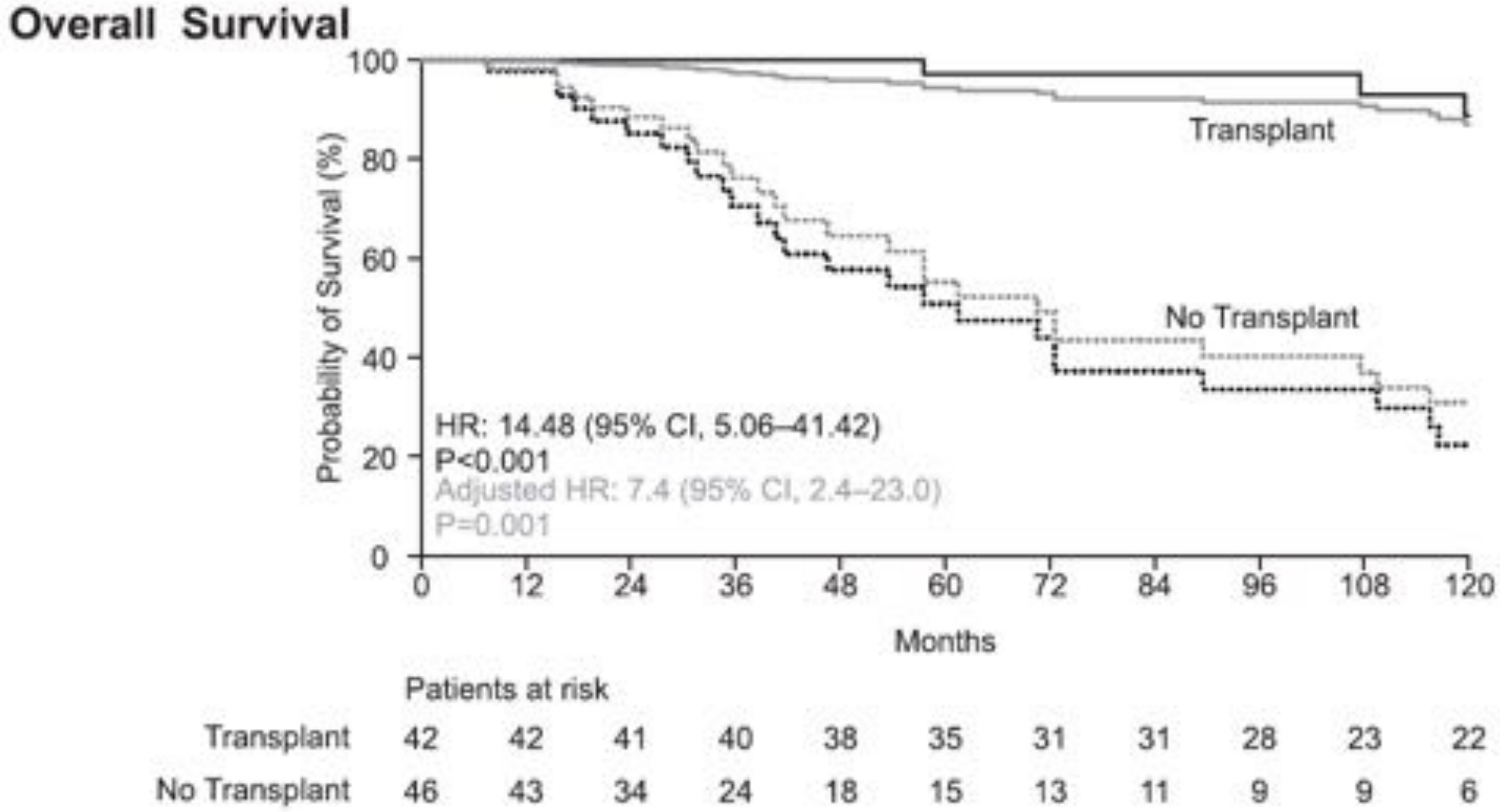
Liver Transplantation for Metastatic Neuroendocrine Tumors

	Rosenau *et al.* (2002)[12]	van Vilsteren *et al.* (2006)[14]	Olausson *et al.* (2007)[13]	Le Treut *et al.* (2008)[7]	Frilling *et al.* (2009)[5]	Mazzaferro *et al.* (2010)[18]	Gedaly *et al.* (2011)[1]	Nguyen *et al.* (2011)[4]	Le Treut *et al.* (2013)[8]
Number of patients	19	19	15	85	15	24	150	184	213
5-year post-transplant survival	80%	NR	90%	47%	67.2%	90%	49%	49.2%	52%

- Small single center series
- Some multicenter data
- Heterogeneity of patients and results

Fan ST, et al. HPB 2014

Liver Transplantation for Metastatic Neuroendocrine Tumors



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Mazzaferro V, et al. AJT 2016

Liver Transplantation for metastasic NETs Summary

- Liver transplantation can be an excellent option for selected patients with metastatic neuroendocrine tumors.

- The difficulty remains to find the optimal time for transplant

Less Common Tumors in Transplant Oncology

INTERNATIONAL LIVER TRANSPLANTATION SOCIETY

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- There is an urgent need for international registry of LT for colorectal and neuroendocrine liver metastases as well as pediatric liver tumors.

- Genomic studies are strongly recommended to explore carcinogenesis and mechanism of invasion and metastases

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Liver Transplantation for iCCA

- Liver Transplant for iCCA should ONLY be done under investigational protocols.

- Molecular profiling should be considered in patients with iCCA.

Sapisochin G, et al. Transplantation 2020