TORONTO
Liver Transplant Program

COLOSOS
COLOrectal and Surgical Oncology Symposium

TORONTO
Liver and Pancreas Surgery

Unresectable Metastatic Disease
Considerations and Outcomes in Transplant Oncology

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What is Transplant Oncology?

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

In Toronto and other centers cancer indications represent 40-50% of Liver Transplants

Sapisochin G, et al. Ann Surg 2020

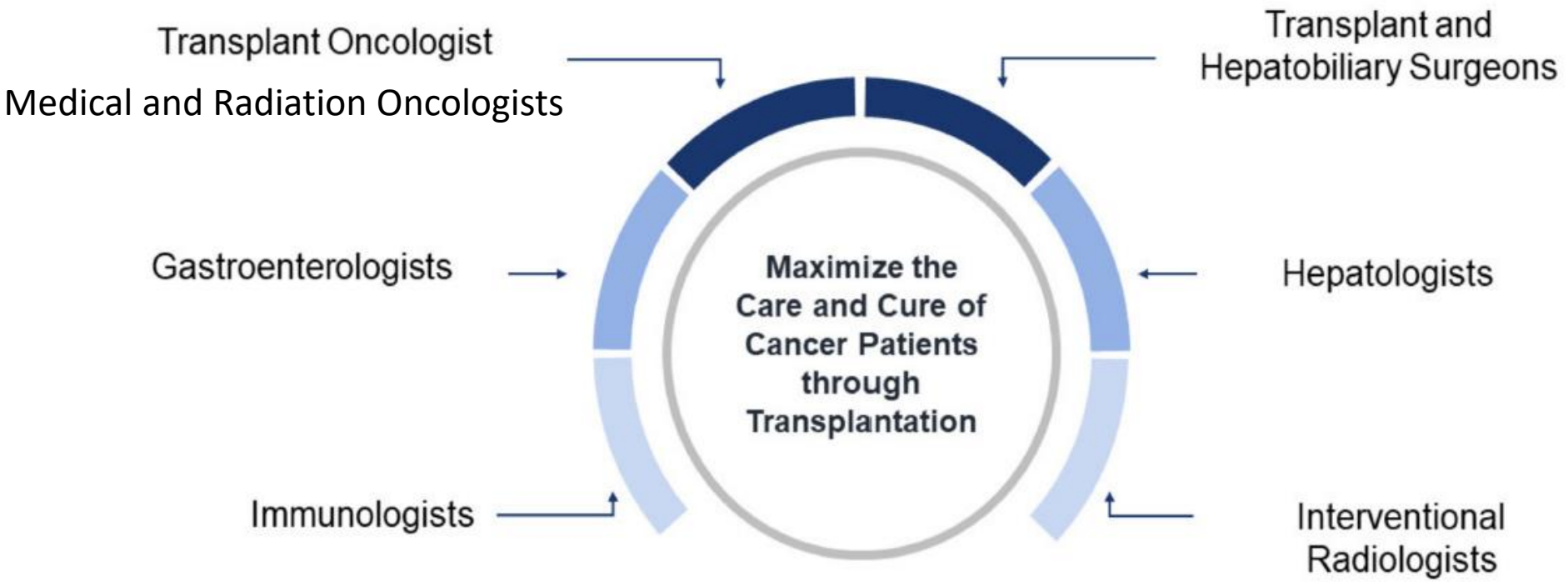
Principles and Controversies of Transplant Oncology

- 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

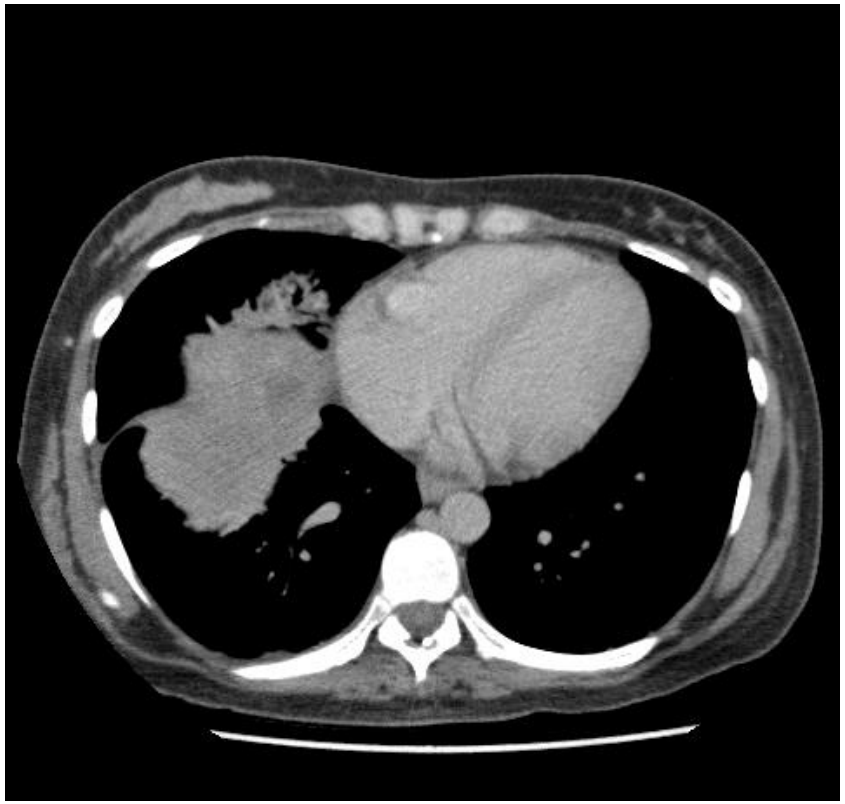
- Randomized controlled trials are impeded by the complexity and heterogeneity of transplant activities and waiting-list dynamics. The current framework of pharmacology-oriented clinical research poorly applies to transplant oncology: a field in need of **alternative methodologies to prove the associated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



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

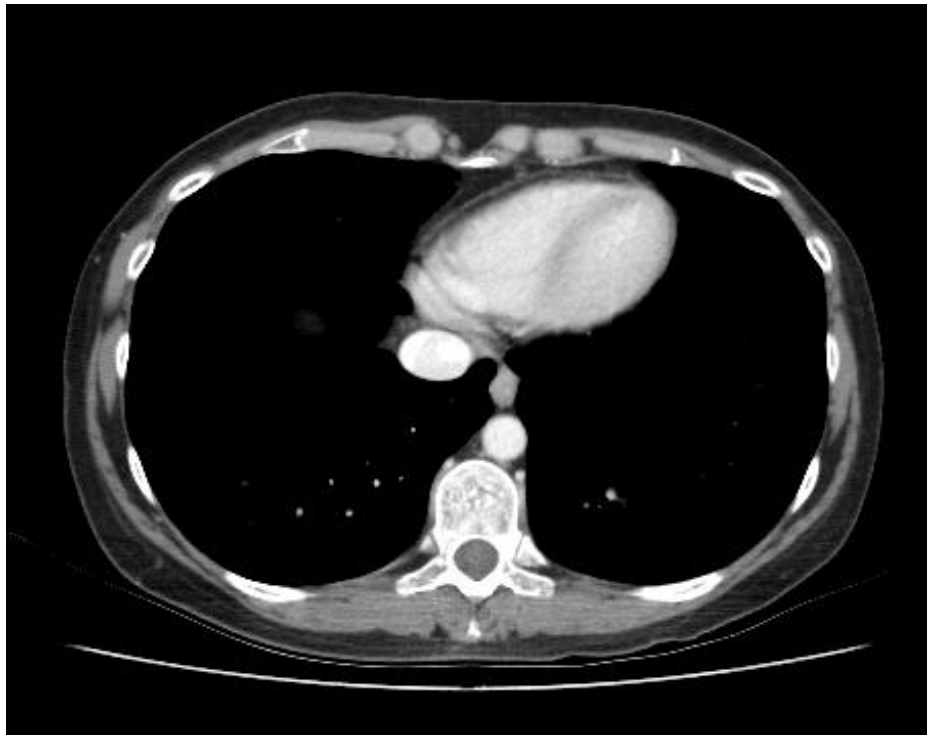
This is the Patient Population I will be Discussing

37 years old patient.
Sigmoid cancer (KRAS wt, BRAF wt, MSS) Synchronous liver metastasis
CEA: 3000 ng/mL



Folfirinox + Panitinumab
Hepatic Artery Infusion Pump
Colon Resection

20 months later
CEA 1.4 ng/mL

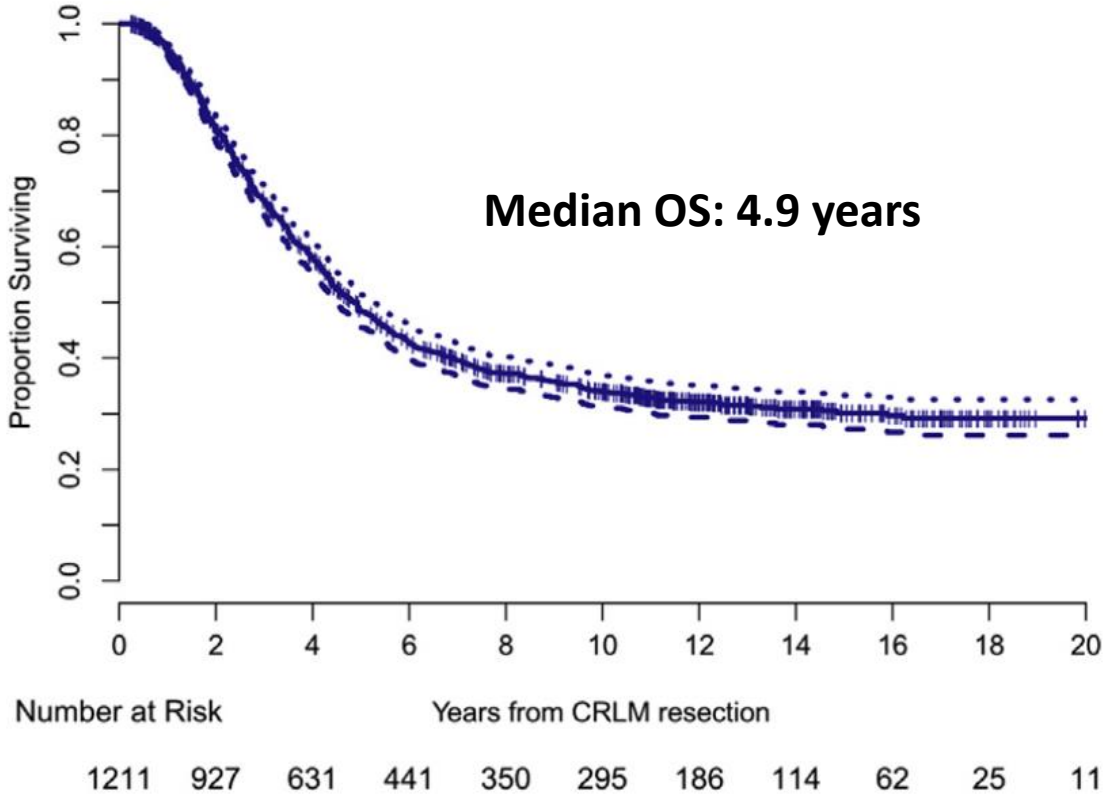


Outcomes after Liver resection for LM from CRC

50% of patients with CRC develop LM

Surgical resection of LM provides the highest chance of cure

Only a minority 20-40% are candidates for surgery

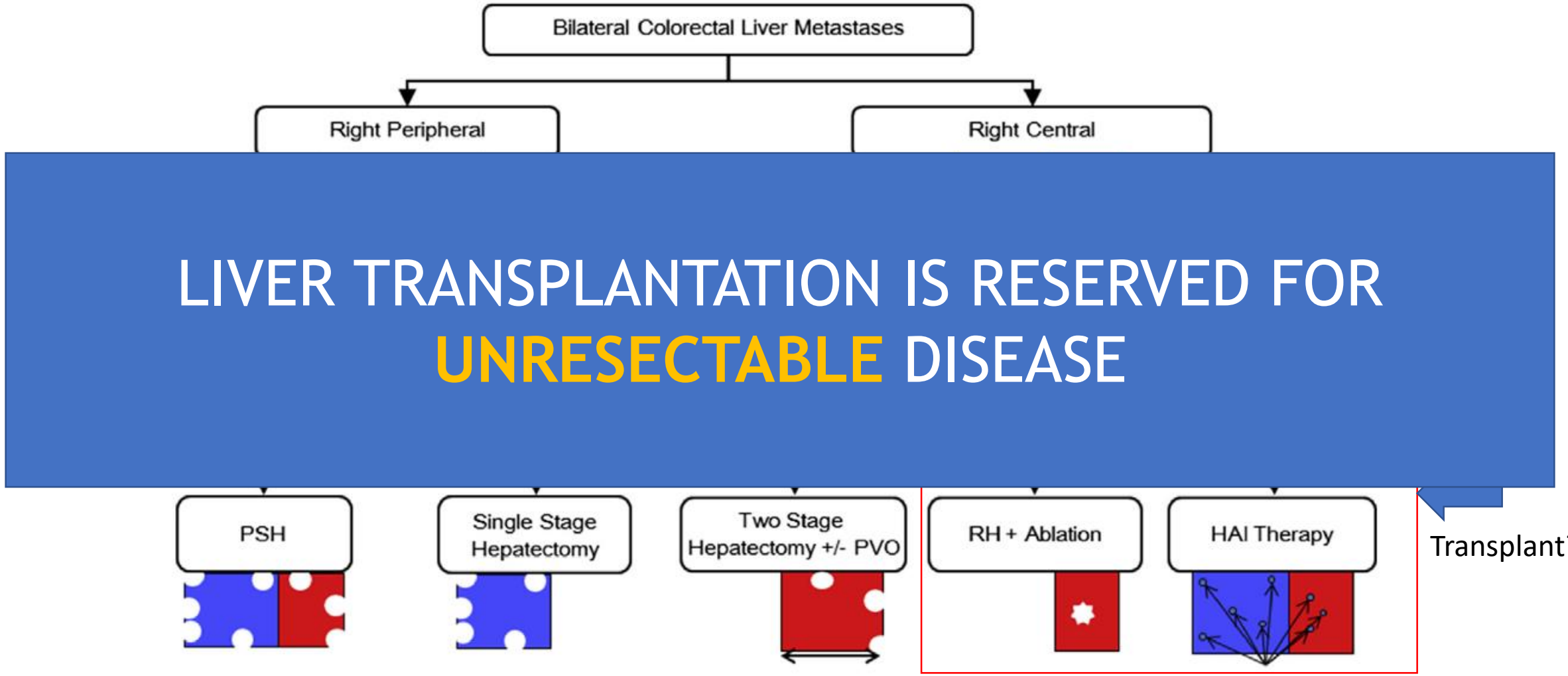


Median OS: 4.9 years

Author	Arm	n	5-Year Overall Survival (%)
Portier et al,[122] 2006	Surgery	85	42
	surgery → 5FU + leucovorin	86	51
Mitry et al,[123] 2008	Surgery	140	40
	surgery → 5FU + Leucovorin	138	53
Ychou et al,[124] 2009	Surgery → 5FU + leucovorin	153	72*
	surgery FOLFIRI	153	73*
Nordlinger et al	Surgery	182	48
	FOLFOX → surgery → FOLFOX	182	51

Lykoudis PM, et al. Br J Surg 2014
Manfredi S, et al. Ann Surg 20016
Adam R, et al. Cancer Treatment Reviews 2015
Padmanachan C, et al. Surg Oncol Clin N 2021

The combination of Chemotherapy & Resection Is the only potential for "cure"



Cloyd JM & Aloia T. Surgery 2017

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

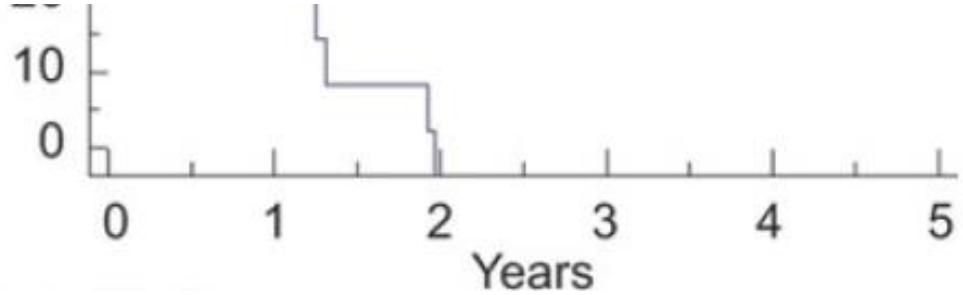
Oslo Trial:

Nov 2006 - Mar

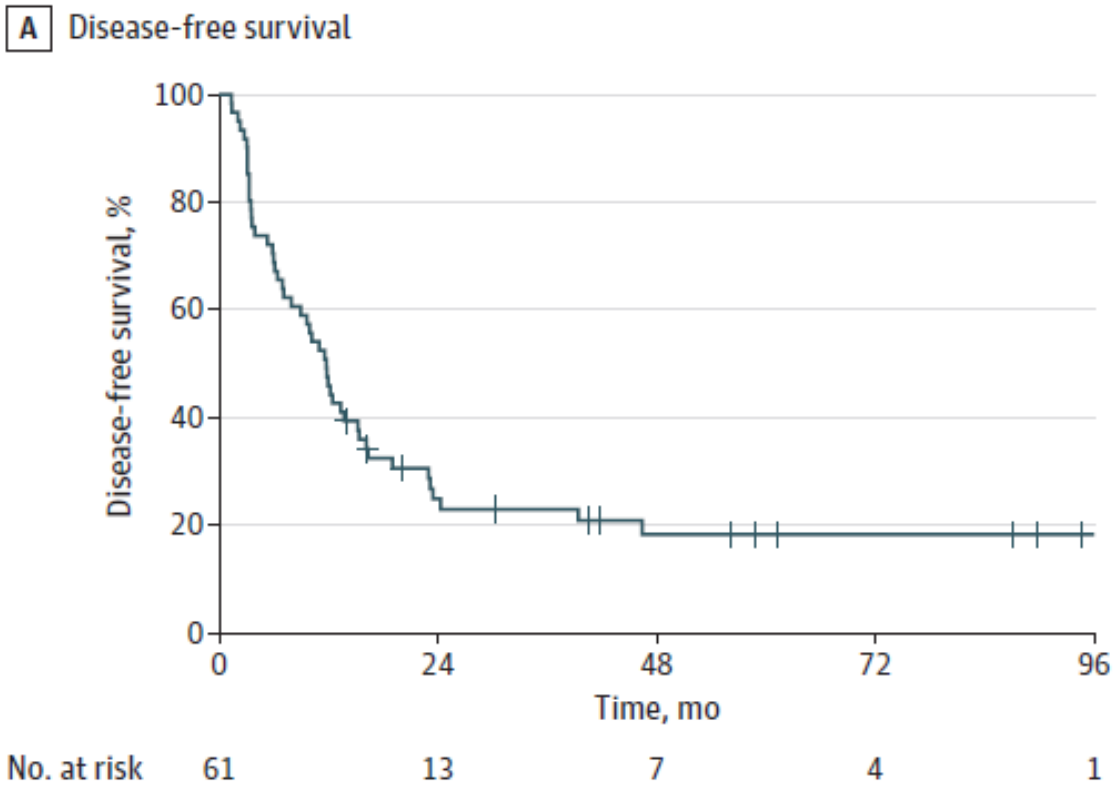
- **25 included i**
- **4 drop-outs**

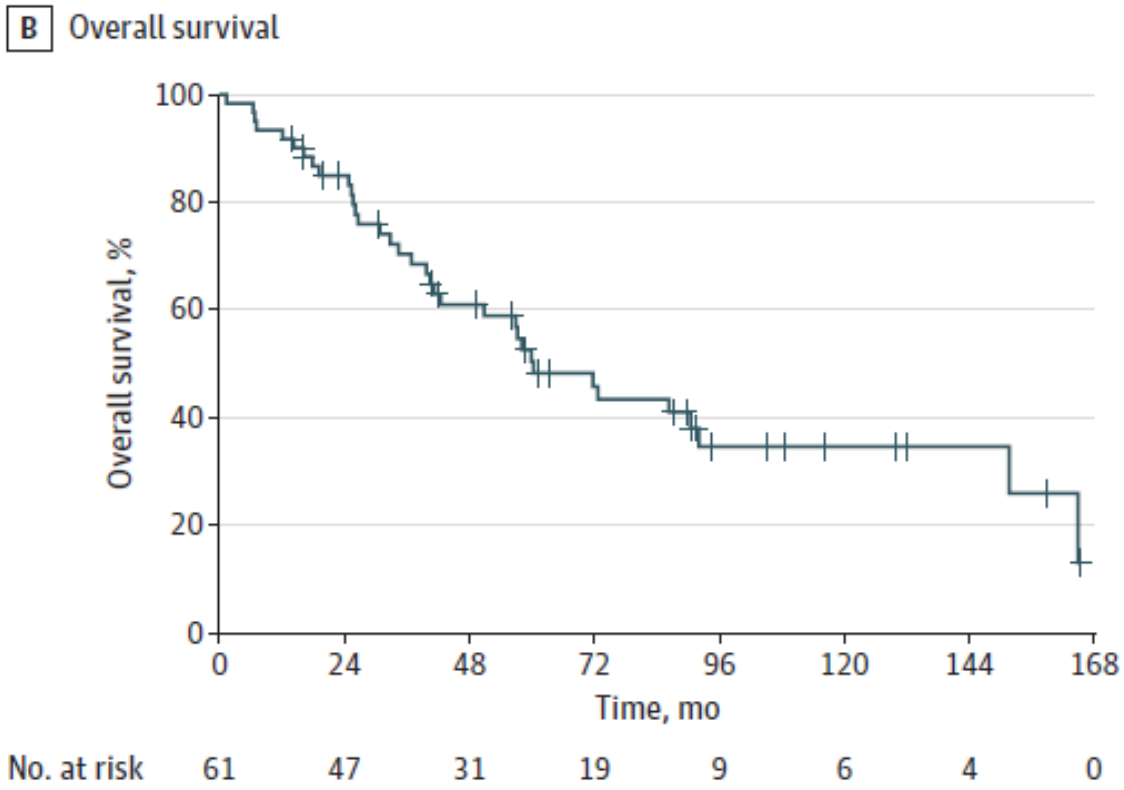
=21 patients tr

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



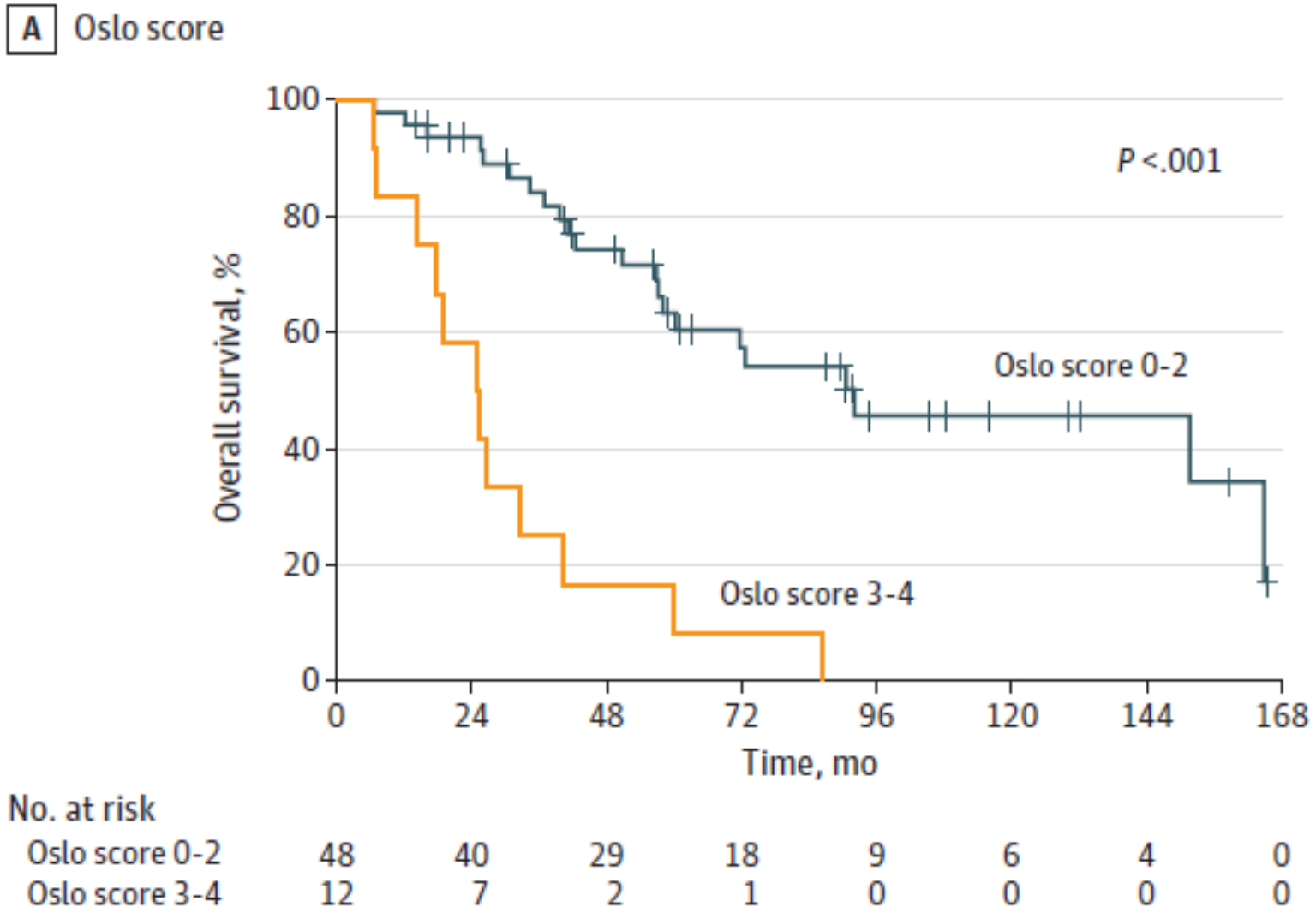
Long-term Outcomes of Oslo Patients





Dueland S, et al. JAMA Surgery 2023

Prognostic Factors



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

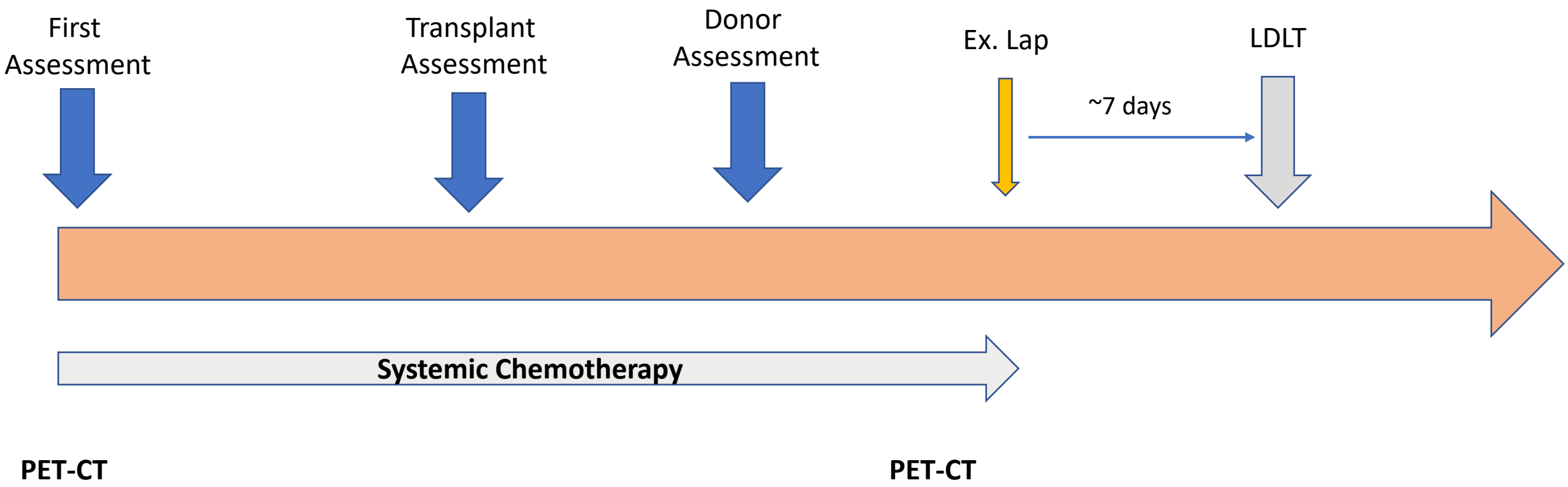
C — 2016 — French
NCT02597348
(TRANSMET)
RCT of LT versus CT for unresectable CRLM: - ARM LT þCadaveric LT þ standard chemotherapy - ARM C: standard chemotherapy

D — 2018 — Italian
NCT03803436
(COLT Trial)
Parallel trial:
- Study arm: LT for unresectable CRLM
- Control Arm: Triplete trial (triple regimen CT)

Abdelrahim M, et al. Cancers 2021

Toronto Protocol for LDLT CRC LM

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



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

University of Toronto Protocol – LDLT for CRC Mets

Main Inclusion Criteria

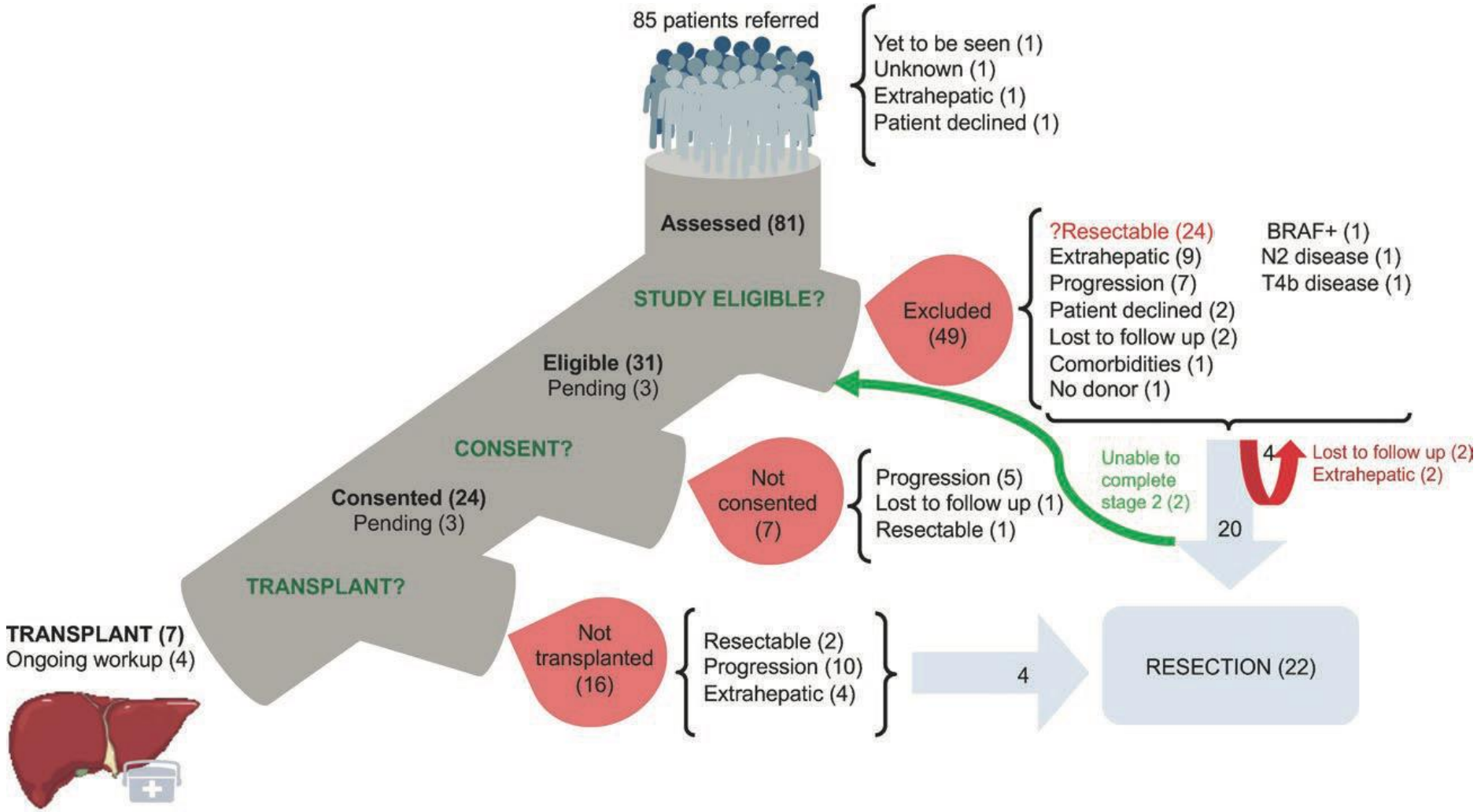
1. **Age 18-68**
2. **Non-resectable CRC LM. Liver ONLY disease**
3. **Primary CRC Resected >6 months**
4. **No major vascular invasion**
5. **Stable or responsive disease on SOC Chemotherapy (FOLFOX/FOLFIRI) for at least 6 months**
6. **Potential Living Donor Available**

Main Exclusion Criteria

1. **Metastatic disease outside the liver**
2. **BRAF V600E mutation**
3. **Progression on chemotherapy treatment**

Rajendran L, Sapisochin G et al. JACS 2023

Toronto Protocol for LDLT CRC LM



Rajendran L, Sapisochin G et al. JACS 2023

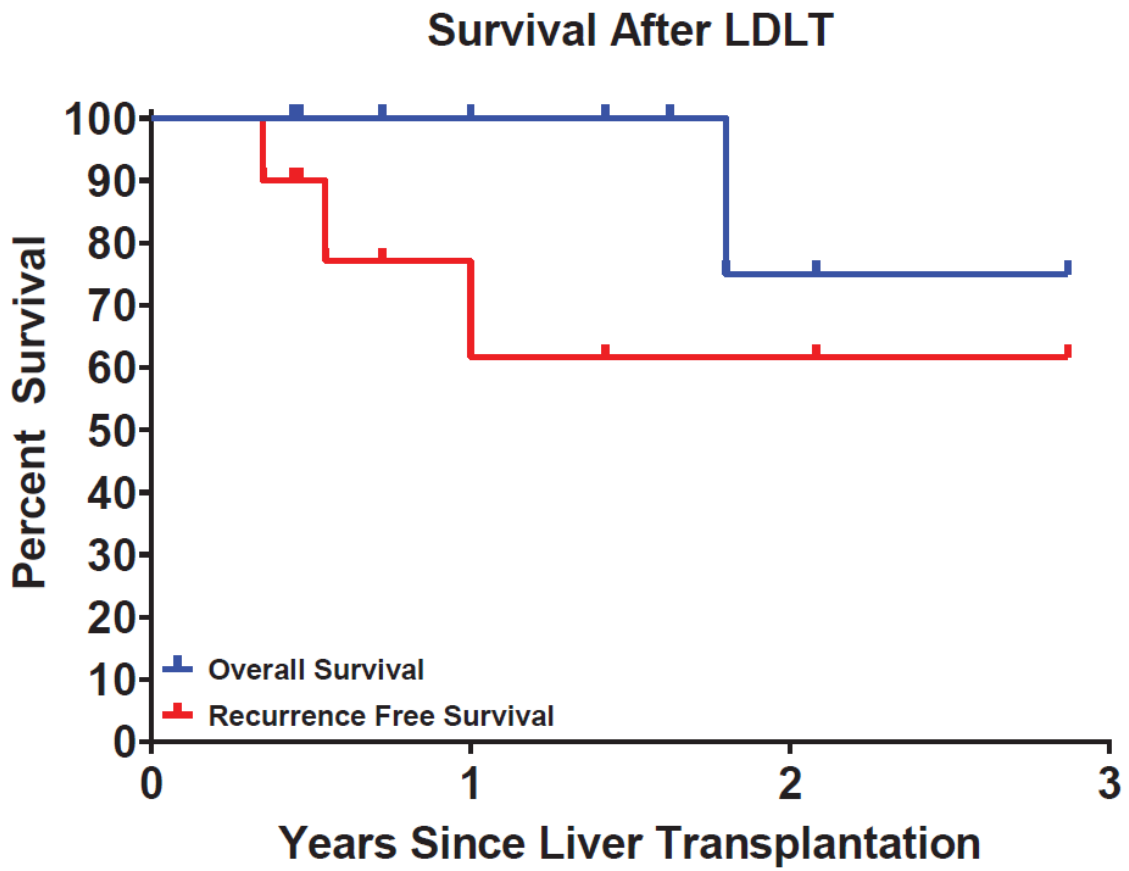
	Chemo type, line, # of cycles prior to initial assessment, total cycles pre-transplant	HAIP (Y/N), time from insertion to transplant	RAS mutation	Tumour type	Explant pathology	Recurrence (Y/N) site, time, treatment	Oslo Score	Post-transplant follow-up
1	FOLFIRI/Panitumumab, first, 10 cycles, total: 25 cycles	No	No	Left colon	3x foci with ~50% treatment effect	**Yes, intra-abdominal nodes, 12.4 months, chemo**	2	30.9
2	FOLFIRI/Bevacizumab, first, 18 cycles; total: ~60 cycles	**Yes, 25.0**	Yes	Left colon	6x foci with variable treatment effect	No	1	38.0
3	FOLFIRINOX/Panitumumab, first, 12 cycles, total: 21 cycles	**Yes, 14.6**	No	Left colon	6x foci + satellites, 95-100% necrosis/ fibrosis	No	1	30.2
4	FOLFIRI/Panitumumab, first, 12 cycles, total: ~20 cycles	No	No	Rectal	2x foci, one viable <50% treatment effect	No	0	34.5
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	53.7 **DECEASED**
7	FOLFOX, Second, 12 cycles, total: ~32 cycles	No	No	Left colon	1 foci, <50% necrosis	No	0	22.8
8	FOLFIRI/ Bevacizumab, Second, 3 cycles, total: ~16 cycles	No	No	Rectal	5x foci, 3 lesions >50% necrosis; 2 lesions <50% necrosis	No	1	19.3
9	FOLFIRI/Bevacizumab, first, 15 cycles; total: ~29 cycles	No		Left colon	2 foci, ~50% necrosis	**Yes, mediastinal mass, 11.0, surgery**	2	12.5
10	FOLFIRI/Panitumumab/Bevacizumab, first, 43 cycles, total: ~54 cycles	No	Yes	Left colon	8x foci, 6 lesions >50% treatment effect (3/6 + trans-capsular extension), 1 lesion >90% treatment effect, 1 lesions <50% treatment effect	**Yes, lung, 7.3 months, surgery**	0	14.1
11	FOLFIRI/Panitumumab, first, 8 cycles; total: ~31 cycles	**Yes, 20.9**	No	Left colon	5x foci, <50% necrosis and focal bile duct invasion	No	0	10.2
12	Capecitabine/Irinotecan/Bevacizumab, third, 23 cycles; total: ~30 cycles	**No**		Left colon	2 foci, complete necrosis; no viable tumour	No	0	8.0
13	FOLFIRI/Panitumumab, first, 20 cycles; total: ~30 cycles	**Yes, 18.5**	No	Left colon	Multiple foci, >85% necrosis	No	1	6.1
14	FOLFIRI/Panitumumab, first, 15 cycles; total: 27	**No**	No	Left colon	Single, <50% necrosis; MVI (LHV) and PNI	No	0	4.4
15	FOLFIRI/Panitumumab, first, 7 cycles; total: ~37cycles	**No**	No	Rectal	2 foci, <25% necrosis and bile duct invasion	No	0	1.0

JAMA Surgery | Original Investigation

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

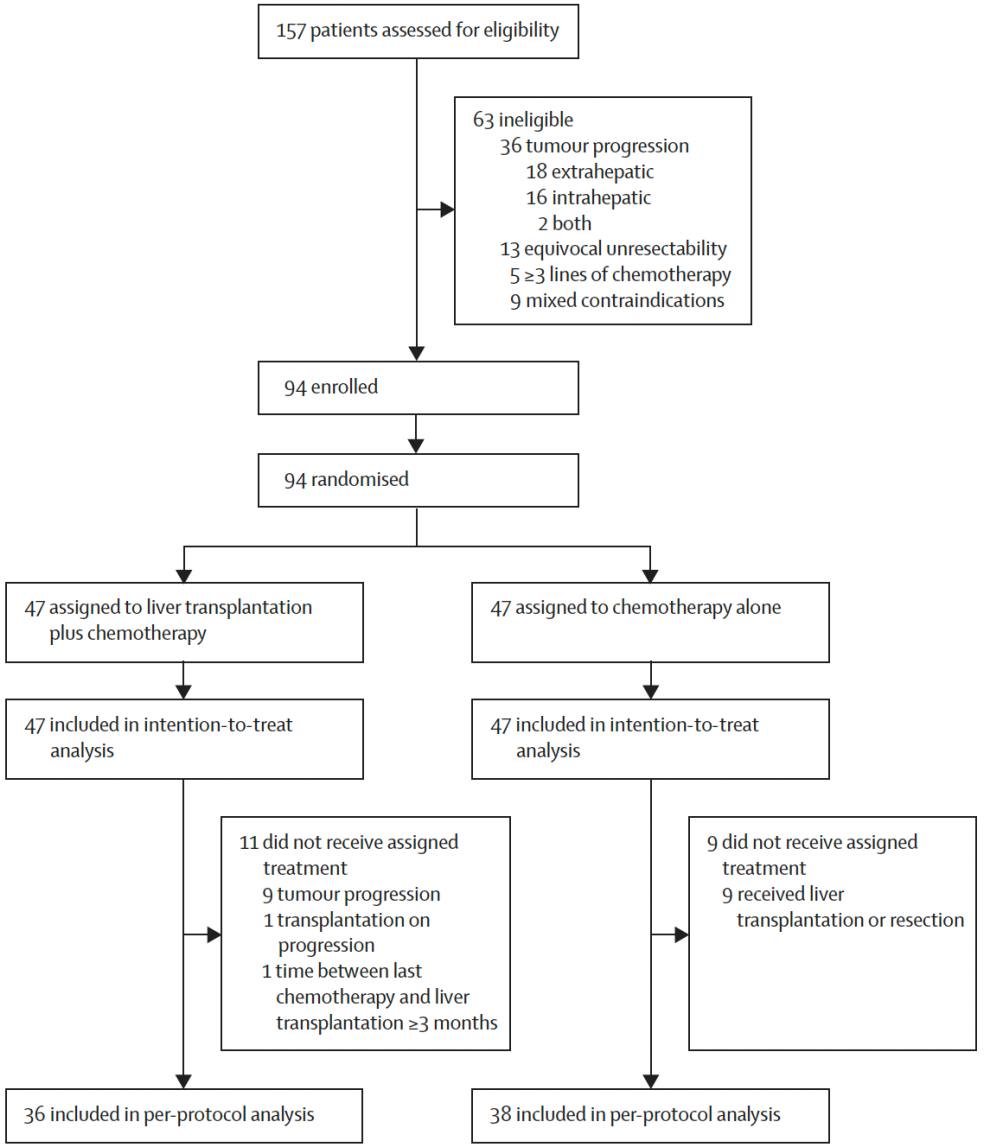
Roberto Hernandez-Alejandro, MD; Luis I. Ruffolo, MD; Kazunari Sasaki, MD; Koji Tomiyama, MD, PhD; Mark S. Orloff, MD; Karen Pineda-Solis, MD; Amit Nair, MD; Jennie Errigo, BS; M. Katherine Dokus, MPH; Mark Cattral, MD; Ian D. McGilvray, MD, PhD; Anand Ghanekar, MD, PhD; Steven Gallinger, MD, MSc; Nazia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

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

Liver transplantation plus chemotherapy versus chemotherapy alone in patients with permanently unresectable colorectal liver metastases (TransMet): results from a multicentre, open-label, prospective, randomised controlled trial

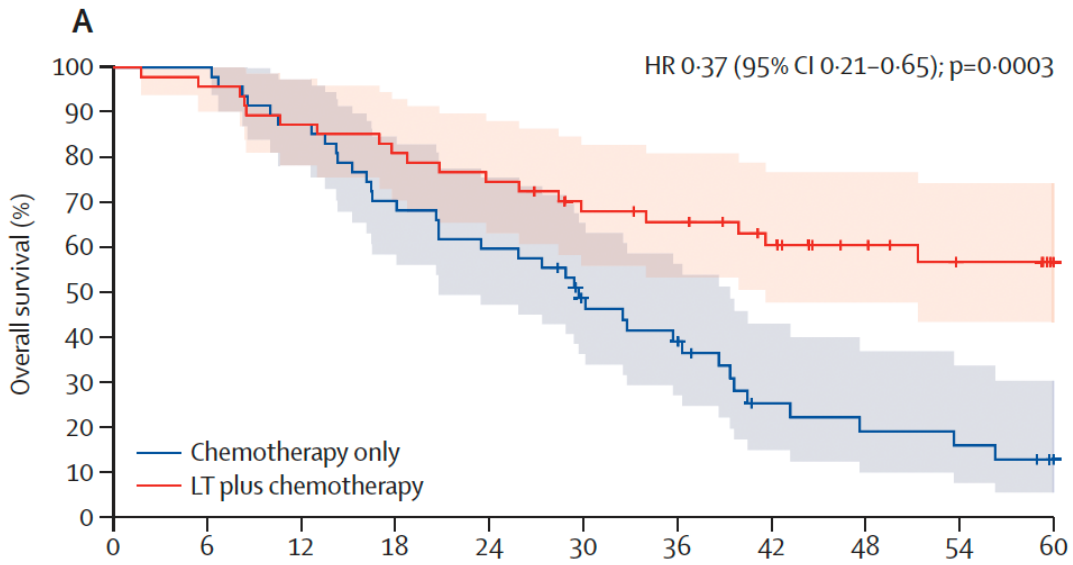


Adam R, et al. Lancet 2024

	Liver transplantation plus chemotherapy (n=47)	Chemotherapy alone (n=47)
Primary tumour		
Primary tumour site*		
Right	7 (15%)	7 (15%)
Left	25 (53%)	29 (62%)
Rectum	15 (32%)	11 (23%)
(y)pT3-T4		
Yes	37 (79%)	38 (81%)
No	9 (19%)	9 (19%)
Missing	1 (2%)	0
(y)pN status		
N0	21 (45%)	16 (34%)
N+	26 (55%)	31 (66%)
RAS mutation status		
Yes	17 (36%)	13 (28%)
No	29 (62%)	32 (69%)
Missing	1 (2%)	2 (4%)
Mismatch repair status		
Proficient mismatch repair	47 (100%)	46 (98%)
Deficient mismatch repair	0	1 (2%)
Liver metastases at diagnosis		
Timing of metastases		
Synchronous†	47 (100%)	45 (96%)
Metachronous	0	2 (4%)
Number of colorectal liver metastases	20·0 (14·0–25·0)	20·0 (12·0–25·0)
<10	5 (11%)	7 (15%)
10–20	19 (40%)	18 (38%)
>20	23 (49%)	22 (47%)
Diameter of largest colorectal liver metastases, mm	55·0 (43·0–76·0)	50·0 (27·0–83·0)
CEA level, ng/mL	305·0 (32·9–762·0)	81·0 (20·0, 530·0)
CA19–9 level, UI/mL	96·0 (19·7–800·0)	193·0 (20·9–1949·0)

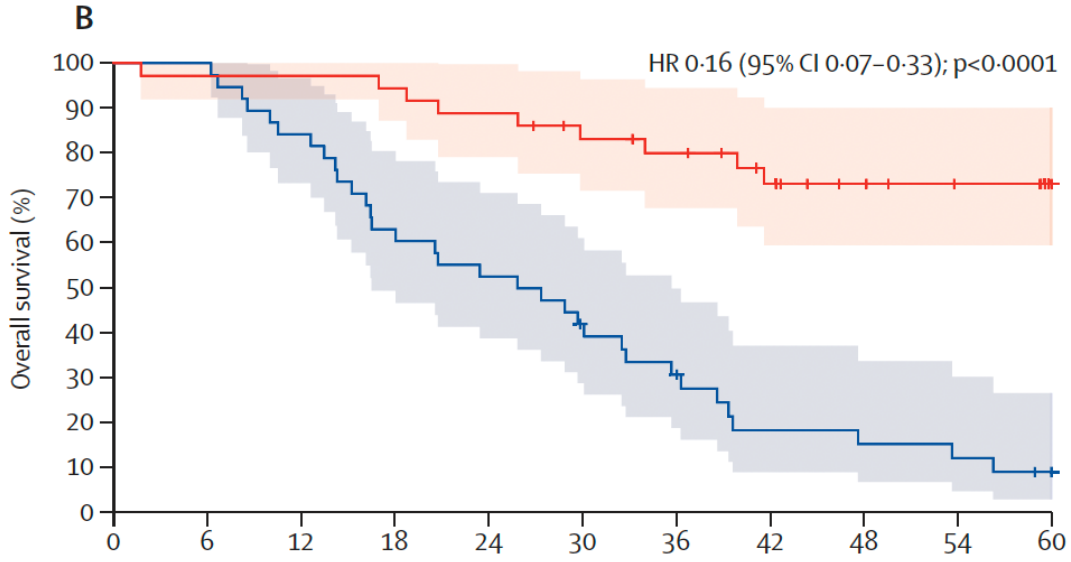
	Liver transplantation plus chemotherapy (n=47)	Chemotherapy alone (n=47)
Age, years	52·0 (47·0–59·0)	55·0 (47·0–59·0)
Sex		
Male	27 (57%)	28 (60%)
Female	20 (43%)	19 (40%)
ECOG performance status		
0	38 (81%)	37 (79%)
1	9 (19%)	10 (21%)
Number of colorectal liver metastases	14·0 (8·0–25·0)	15·0 (5·0–25·0)
<10	12 (26%)	16 (34%)
10–20	20 (43%)	17 (36%)
>20	15 (32%)	14 (30%)
Diameter of largest colorectal liver metastases, mm	27·0 (18·0–42·0)	27·0 (16·0–45·0)
CEA, ng/mL	3·6 (2·2–12·4)	3·6 (2·0–22·1)
CA19–9, IU/mL	11·4 (5·9–30·0)	15·0 (6·5–28·7)
Fong's clinical risk score*		
Low (0–2)	20 (43%)	13 (28%)
High (3–5)	27 (57%)	34 (72%)
Time between diagnosis and randomisation, months	15·9 (11·8–25·7)	13·5 (9·0–19·4)

Intention to Treat OS



Number at risk (number censored)											
Chemotherapy only	47 (0)	47 (0)	41 (0)	33 (0)	28 (0)	20 (3)	16 (3)	8 (6)	6 (6)	5 (6)	2 (8)
LT plus chemotherapy	47 (0)	45 (0)	41 (0)	38 (0)	35 (0)	30 (2)	28 (3)	23 (6)	18 (11)	14 (14)	10 (18

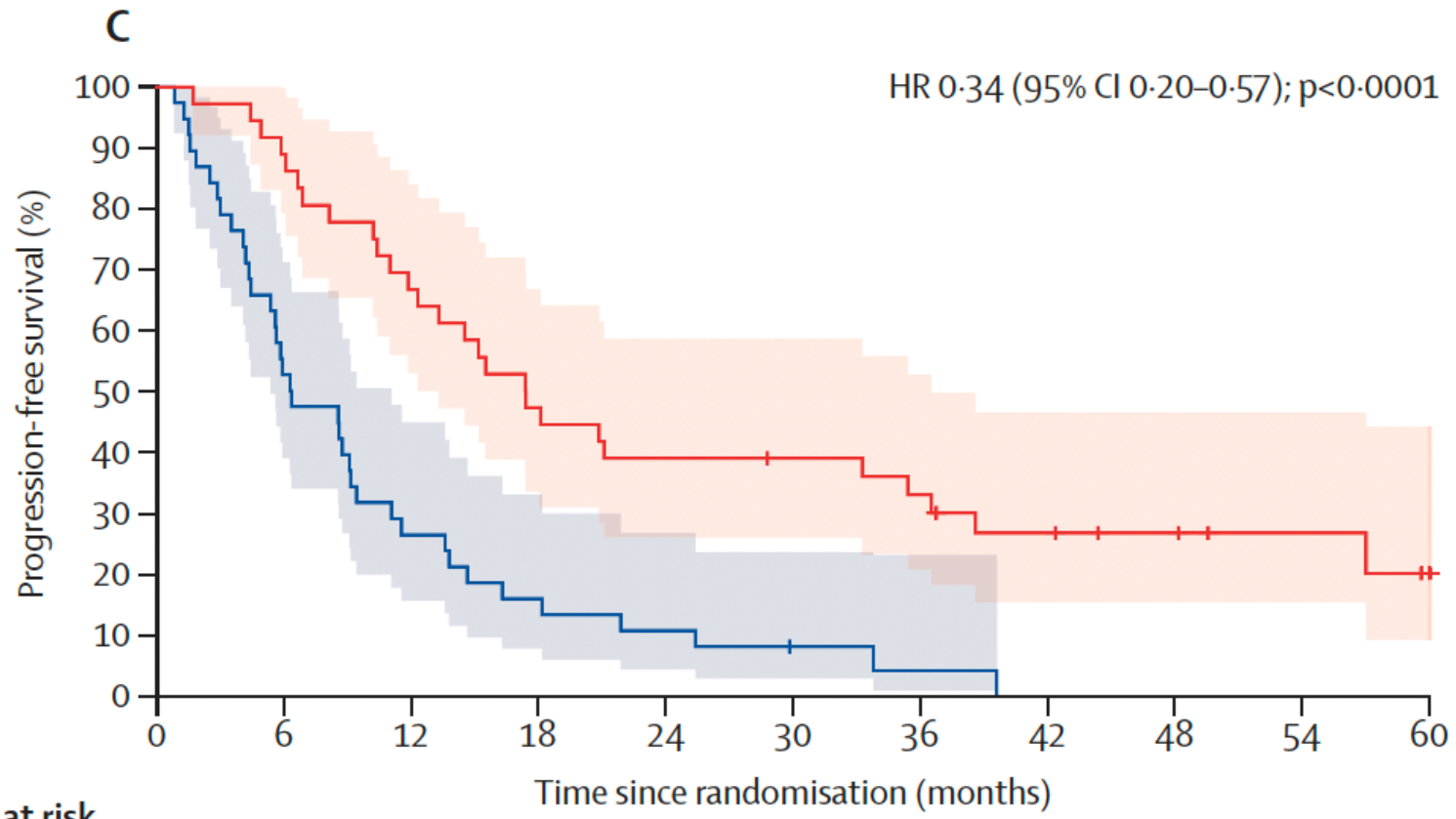
Per Protocol OS



Number at risk (number censored)											
Chemotherapy only	38 (0)	38 (0)	32 (0)	24 (0)	20 (0)	15 (1)	11 (1)	6 (2)	5 (2)	4 (2)	2 (3)
LT plus chemotherapy	36 (0)	35 (0)	35 (0)	34 (0)	32 (0)	28 (2)	26 (3)	21 (6)	17 (10)	14 (13)	10 (17)

Adam R, et al. Lancet 2024

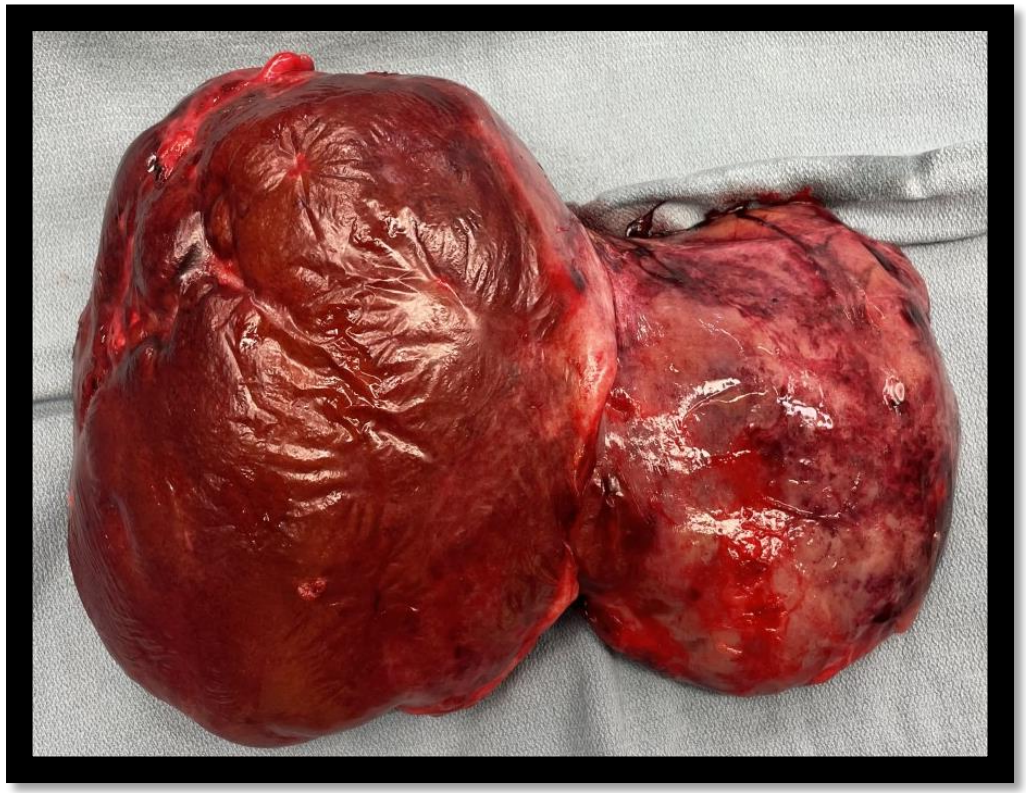
PFS

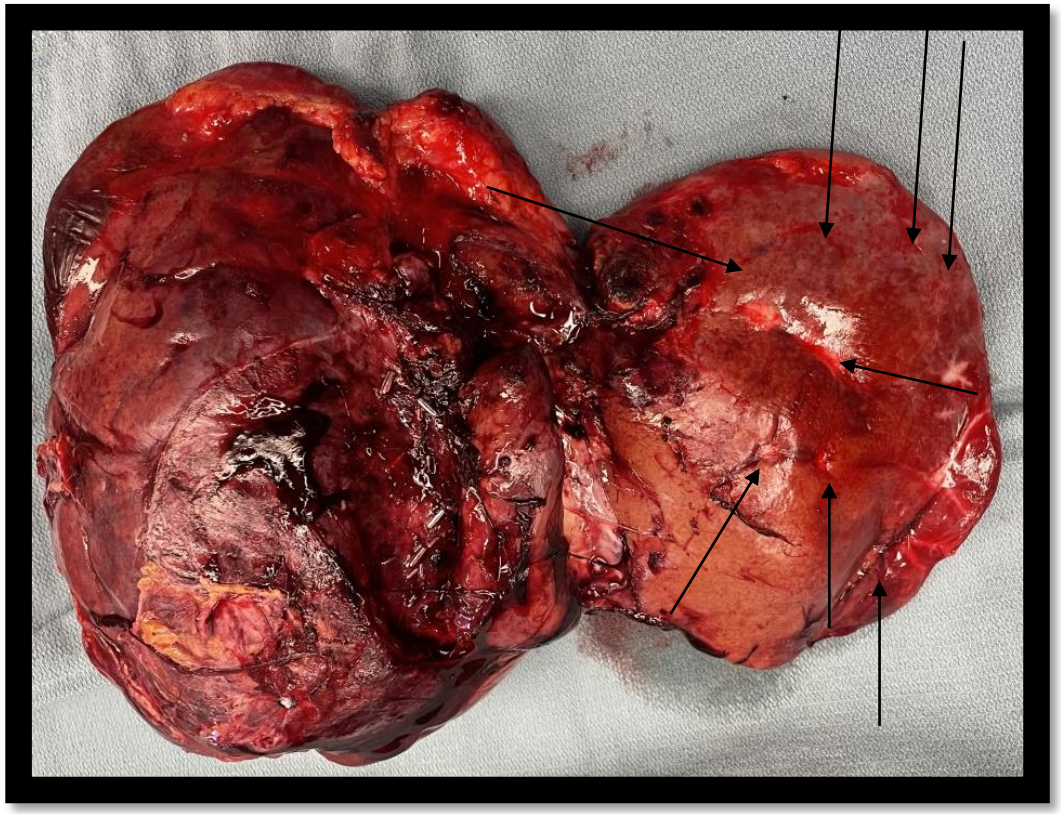


Number at risk (number censored)											
Chemotherapy only	38 (0)	20 (0)	10 (0)	6 (0)	4 (0)	2 (1)	1 (1)	0 (1)	..	..	..
LT plus chemotherapy	36 (0)	32 (0)	24 (0)	17 (0)	14 (0)	13 (1)	11 (1)	8 (2)	6 (4)	4 (6)	2 (7)

Adam R, et al. Lancet 2024

Our patient – LDLT 35 months ago
Doing well - No recurrence





Explant Pathology Assessment Demonstrated Extensive Tumor Necrosis but Viable Disease in Many Metastases

Challenges and Future Directions

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

Challenges and Future Directions

- Management of syncronous disease with complex colorectal surgeries. Timing? Indication?

- Utilization of HAIP in this setting.

- Expansion to a larger population – borderline resectable? >9 metastases?

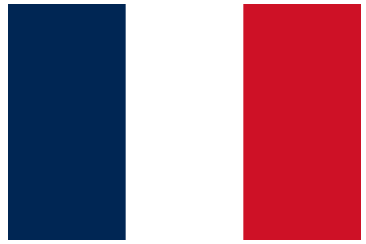
ASTS – AHPBA Recommendations White Paper – Oct 24, 2023

How to Prioritize in the List

Exception points
Median MELD at Transplant -20, minimum 15

Table 1. Proposed inclusion/exclusion criteria for MELD exception points

Inclusion criteria	Exclusion criteria
No progression of hepatic disease (need CT or MRI every 3 months)	Local relapse of the primary disease
No development of extrahepatic disease (need CT or MRI every 3 months)	Extra-hepatic disease after primary tumor resection
CEA Levels < 80 μg/l (Need testing every 3 months)	CEA Levels > 80 μg/l



34 points in Ontario
Similar in Quebec
France – top of the list

Transplant expected within 4 weeks of stopping the systemic chemotherapy

Withrock, J, et al. Curr Opin Transpl 2024

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