Liver transplantation for colorectal liver metastases

Prof Olivier Scatton

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FRANCE

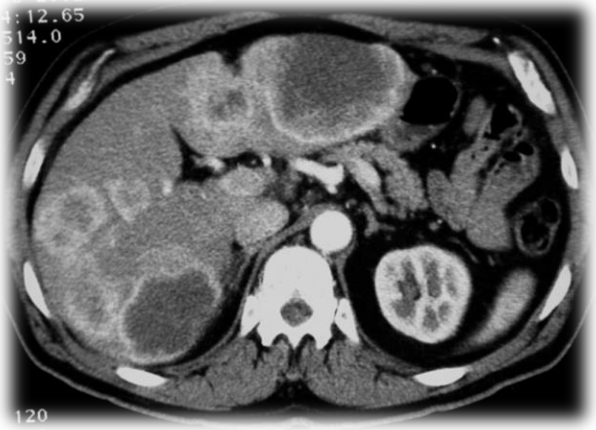
LIPS-S
Liver Institute of Pitié Salpêtriére-Sorbonne

Improvements in oncological management

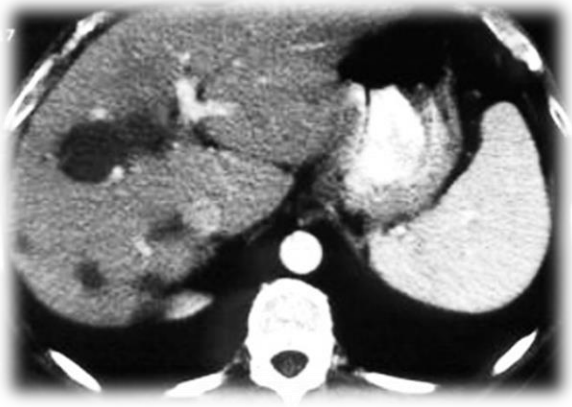
- Render “resectable” patients who were initially non-resectable: collaboration (chemo-radiotherapy) –surgical innovations
- Minimally invasive surgery
- transplant-oncology

Classification

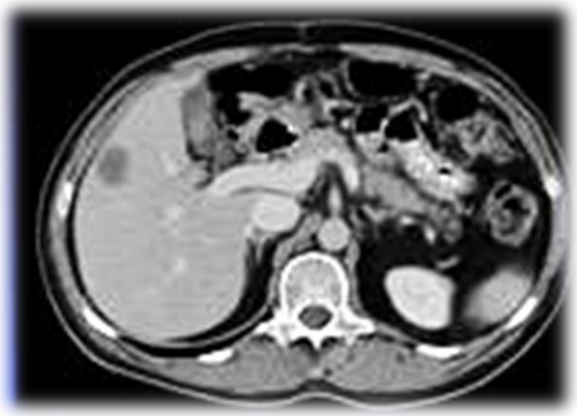
Classe III



Classe II



Classe I



Non-resectables | Resection POSSIBLE (borderline) | Easily resectable

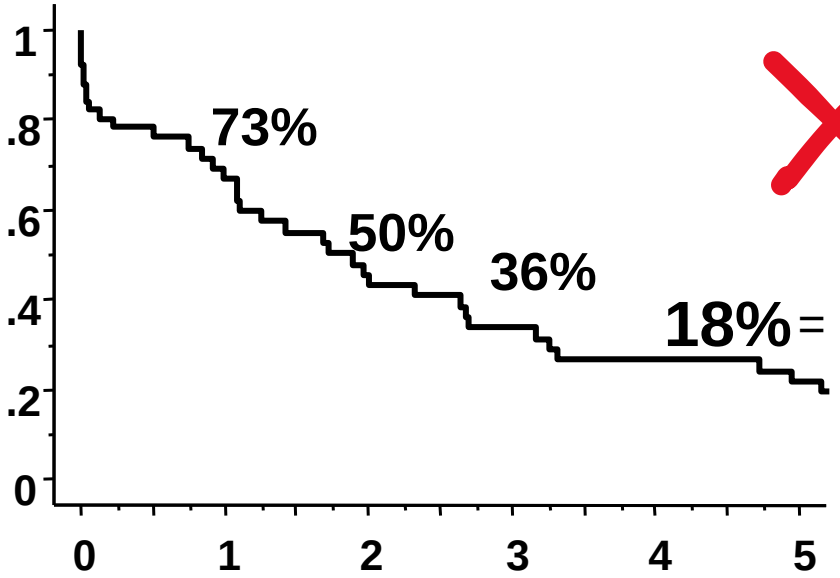
TRANSPLANTATION ?
“Transplant oncology”

HEPATECTOMY
- **Major FLR <40%**
- **“Staged”**
- **ALPSS**
- **Complex VVP**

FRL > 40%
Minor
Left hepatectomy

Patient Survival after LT for Colorectal Metastases

N=50, Feb. 1977 – Dec. 2004



= chemo in 2023

But 50% of deaths were not related to tumor recurrence

1995 = FUTILE

JAMA Surgery | Original Investigation

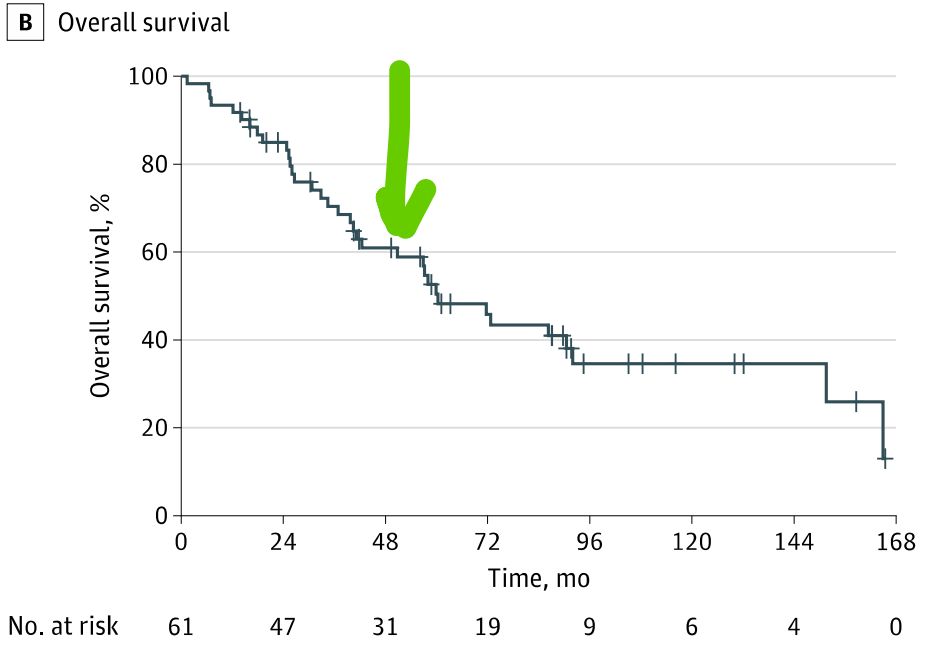
Long-Term Survival, Prognostic Factors, and Selection of Patients With Colorectal Cancer for Liver Transplant

A Nonrandomized Controlled Trial

Svein Dueland, MD, PhD; Tor Magnus Smedman, MD, PhD; Trygve Syversveen, MD, PhD; Harald Grut, MD, PhD; Morten Hagness, MD, PhD; Pål-Dag Line, MD, PhD

2023

e After Liver Transplant



Survival > 60 % at 5 years

Transplantation for non-resectable liver mets

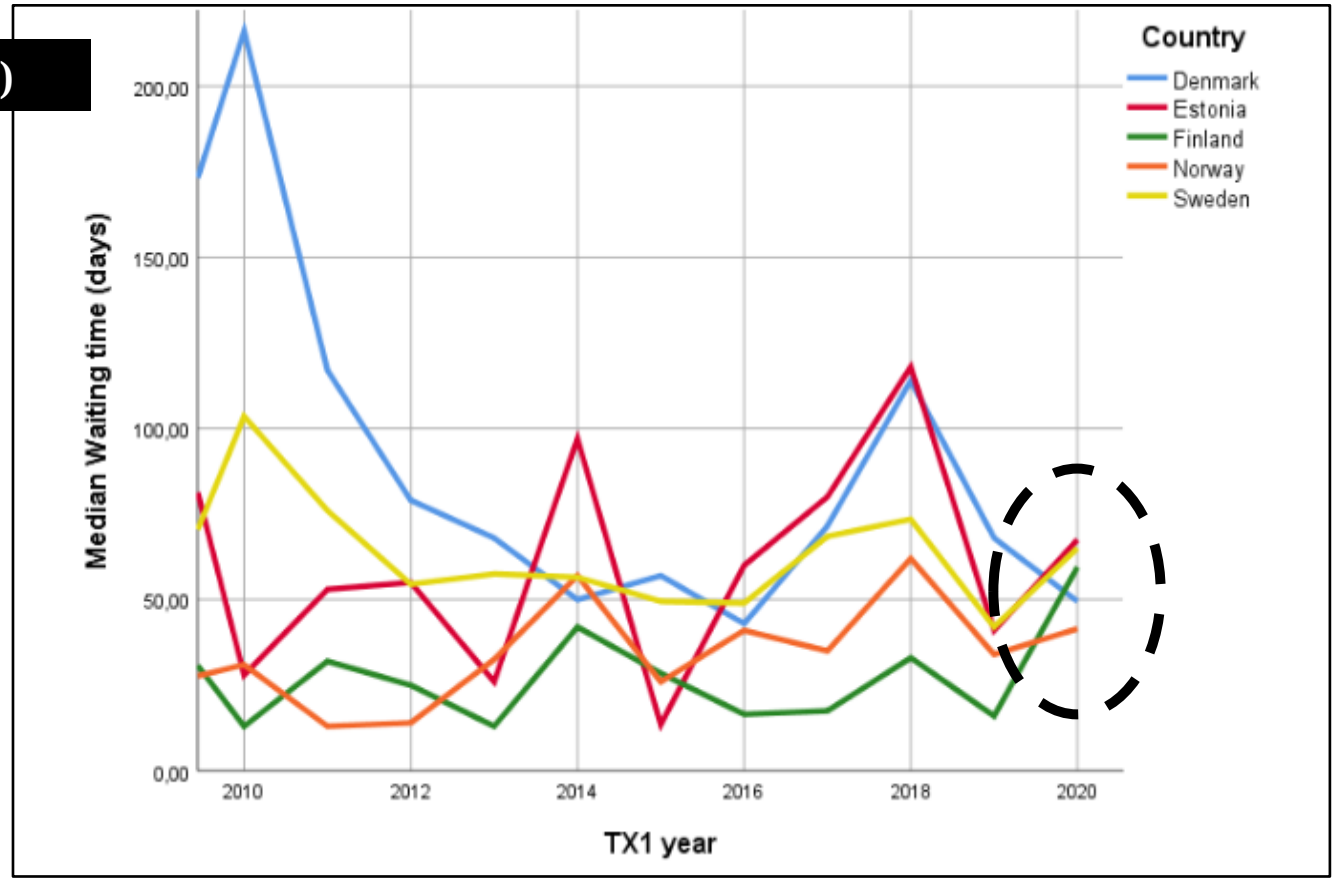
Rational

1. Better expertise in LT
2. Better knowledge of tumoral biology
3. Very efficient chemo
4. Immunosuppression adaptable
5. Better selection +++

The beginning of A new success story….

Remind | Very short waiting time before LT with cadaveric grafts in the Nordic countries

Mean delay (days)



Mean delay to obtain cadaveric graft shorter than 3 months

LT for non-resectable Mets

Liver Transplantation for Nonresectable Liver Metastases From Colorectal Cancer

SECA-1 2013 (2006-2011)

Critères d'inclusion

- Primitif réséqué
- ECOG 0-1
- Chimiothérapie
- Pas de maladie extra-hépatique
- Pas d'atteinte GG sur extempo
- ≤ 65 ans
- Pas de mutation BRAF

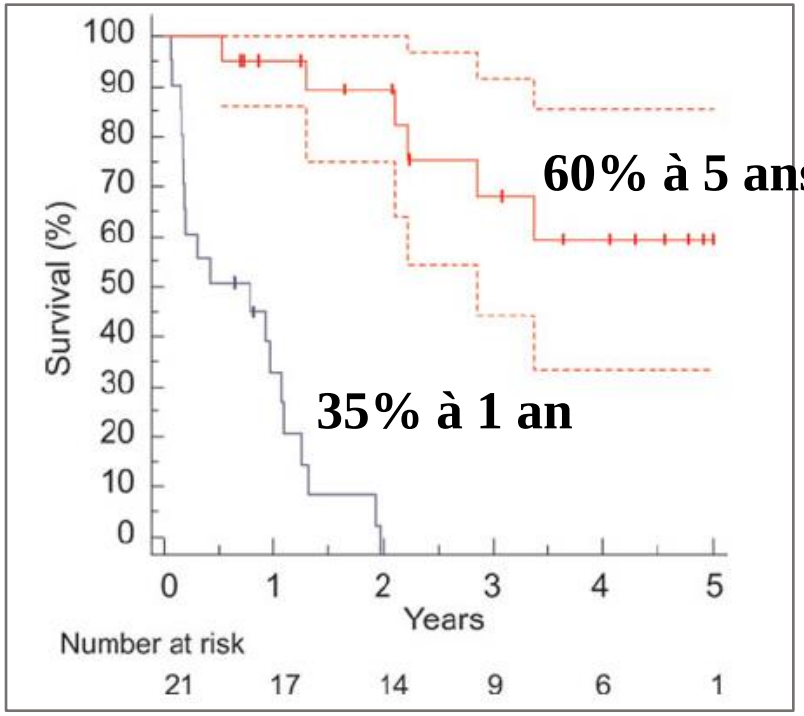
- N = **25** patients inscrits sur liste
- Exclus (n=3)
- ✓ Ascite et méta. pulmonaires, n = 1
- ✓ ADP métastatiques en per-TH, n = 2

Hagness et al. Ann Surg 2013

LT for non-resectable Mets

Liver Transplantation for Nonresectable Liver Metastases From Colorectal Cancer

SECA-1 2013 (2006-2011)



Time to recurrence,† median (range), mo	8 (2–24)
Metastases	
Lung, No. patients	17
Liver	7
Skeletal	5‡
Ovary	2
Para-aortal lymph nodes	2
Peritoneal	1
Adrenal	1
Recurrence of primary malignancy	
Rectal cancer, No. patients	2
New colonic cancer	1

Oslo score 0 to 4

1. **Colon – LT < 2 ans**
2. **ACE > 80**
3. **Size > 5,5cm**
4. **Progression on chemo**

- Overall 5 years Survival rate of **60%** (6 deaths / 21)
- DFS rate **35% at one year** (19 récidives)
- Fact pronostiques: **size > 55 mm**, **ACE > 80**, **progression on chemo**, **delay colectomy/LT < 2 years**

Hagness et al. Ann Surg 2013

LT versus chemotherapy alone

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

SECA-1 2015

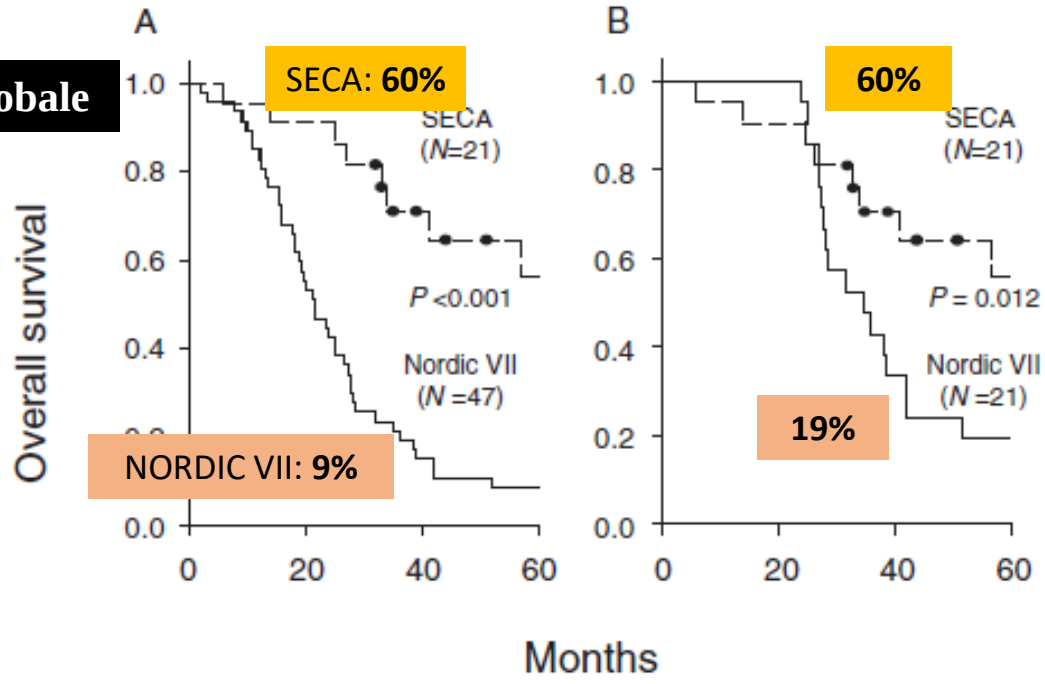
Critères d'inclusion

- MH non résécables
- Pas de maladie extra-hépatique
- ≤ 65 ans
- Pas de mutation BRAF

SECA
N = 21

NORDIC VII
N = 64

Survie globale



Survival is much better in LT group compare to Chemo group

Dueland et al. Ann Surg 2015

LT versus Chemo

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

SECA-1 2015

Critères d'inclusion

- MH non résécables
- Pas de maladie extra-hépatique
- ≤ 65 ans
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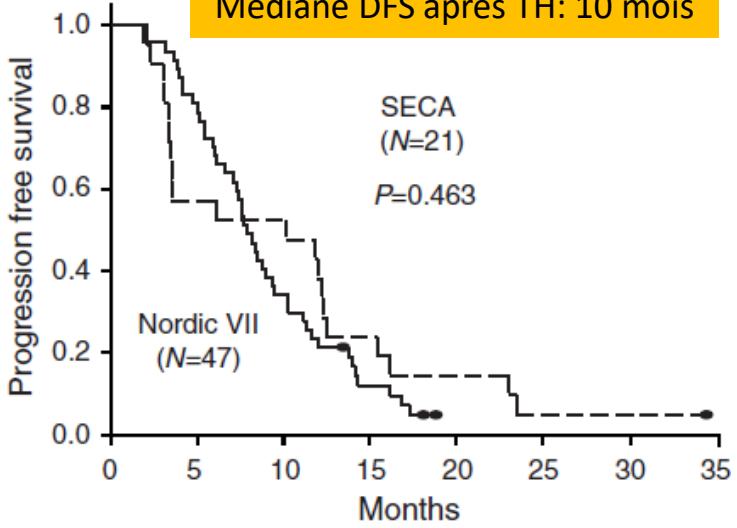
SECA
N = 21

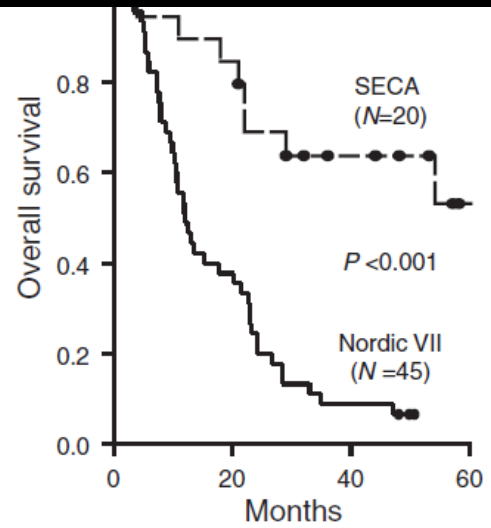
NORDIC VII
N = 64

Médiane DFS après TH: 10 mois



Médiane PFS après chimio: 8 mois

Survie globale à partir de la récidive ou progression



This difference in OS despite a comparable PFS is explained by the type of recurrence or progression: Isolated and treated pulmonary recurrence in the TH group vs. hepatic progression with cessation of chemo in the chemotherapy group

Dueland et al. Ann Surg 2015

Survie après TH

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

SECA-2 2020 (2012-2016)

Critères d'inclusion + sélectifs

- Primitif réséqué > 1 an
- 1 ligne de chimio avec 10% réponse RECIST
- TEP-TDM
- Lésion < 10 cm.
- Si > 30 nodules, taille < 5 cm avec 30% réponse RECIST
- Délai diagnostic-TH > 12 mois

- N = **15**
- yPT3: 73%
- Hepatectomy =/- RF: 4
- Waiting list: 29 days (Delay diagnostic- LT 24 months

	SECA-1	SECA-2	*P* *
Time from primary surgery to LT	16.8 (5.9–58.7) mo	22.6 (2.3–111.3) mo	0.526
Age, y	56 (45–65)	59 (35–71)	0.427
FCRS at LT	3 (1–5)	2 (1–3)	0.028
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
SUV_{max}	9.0 (2.3–21.5)	5.9 (2.4–11.2)	0.10
SUV_{peak}	7.3 (1.9–17.5)	4.3 (2.2–9.0)	0.09
SUV_{mean}	5.1 (1.6–13.3)	3.2 (2.0–6.4)	0.13
MTV, cm^3	98.5 (0–874)	21.3 (0–139)	0.08
TLG, g	302 (0–4437)	76 (0–405)	0.06
T/B ratio	5.3 (1.0–11.1)	2.6 (1.0–5.5)	0.03

Dueland et al. Ann Surg 2020

Survie après TH

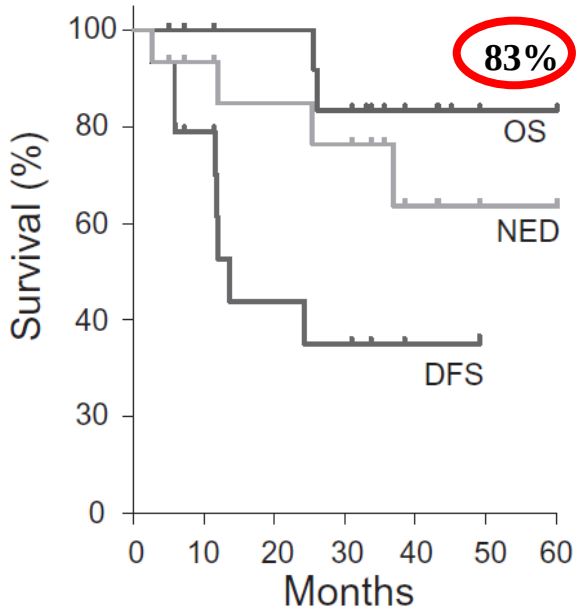
Survival Following Liver Transplantation for Patients With Nonresectable Liver-only Colorectal Metastases

SECA-2 2020 (2012-2016)

Critères d'inclusion + sélectifs

- Primitif réséqué > 1 an
- 1 ligne de chimio avec 10% réponse RECIST
- Pas de maladie extra-hépatique sur le TEP
- Lésion < 10 cm. Si > 30 nodules, taille < 5 cm avec 30% réponse RECIST
- Délai diagnostic-TH > 12 mois

- N = 15, yPT3: 73%
- Hépatectomie =/- RF: 4
- Durée d'attente sur liste: 29 jours (7-148)
- Délai diagnostic- TH: 24 mois
- Pas de chimio post-TH



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

75% des récidives sont pulmonaires (1ier site ou isolées)

TABLE 4. Treatment After Liver Transplantation

Pulmonary resection	5 patients
Number of pulmonary resections	6
Size diagnosed on CT-scans (median, range) n = 6	7.5 mm (5–10 mm)
Liver resection	1 patient
Lymph node resection and p.o. radiation therapy	2 patients, 2 Gy x 25
Palliative chemotherapy	2 patients
OS from start palliative chemotherapy	13 and 17 mo

With better selection, overall survival can reach 83% at 5 years because (mainly) pulmonary recurrences are treated. A hepatic recurrence, on the other hand, is catastrophic

Dueland et al. Ann Surg 2020

JAMA Surgery | Original Investigation

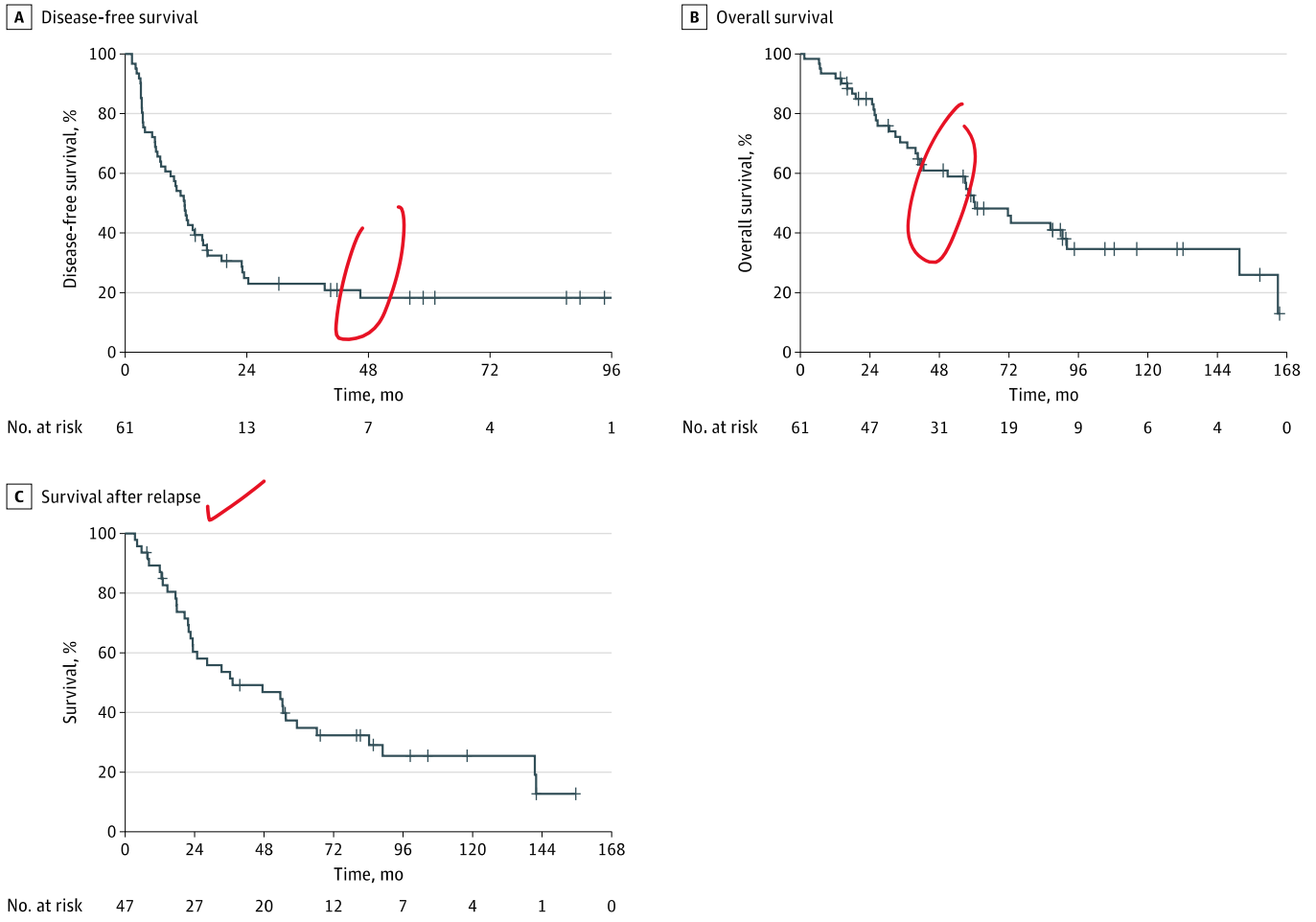
Long-Term Survival, Prognostic Factors, and Selection of Patients With Colorectal Cancer for Liver Transplant

A Nonrandomized Controlled Trial

Svein Dueland, MD, PhD; Tor Magnus Smedman, MD, PhD; Trygve Syversveen, MD, PhD; Harald Grut, MD, PhD; Morten Hagness, MD, PhD; Pål-Dag Line, MD, PhD

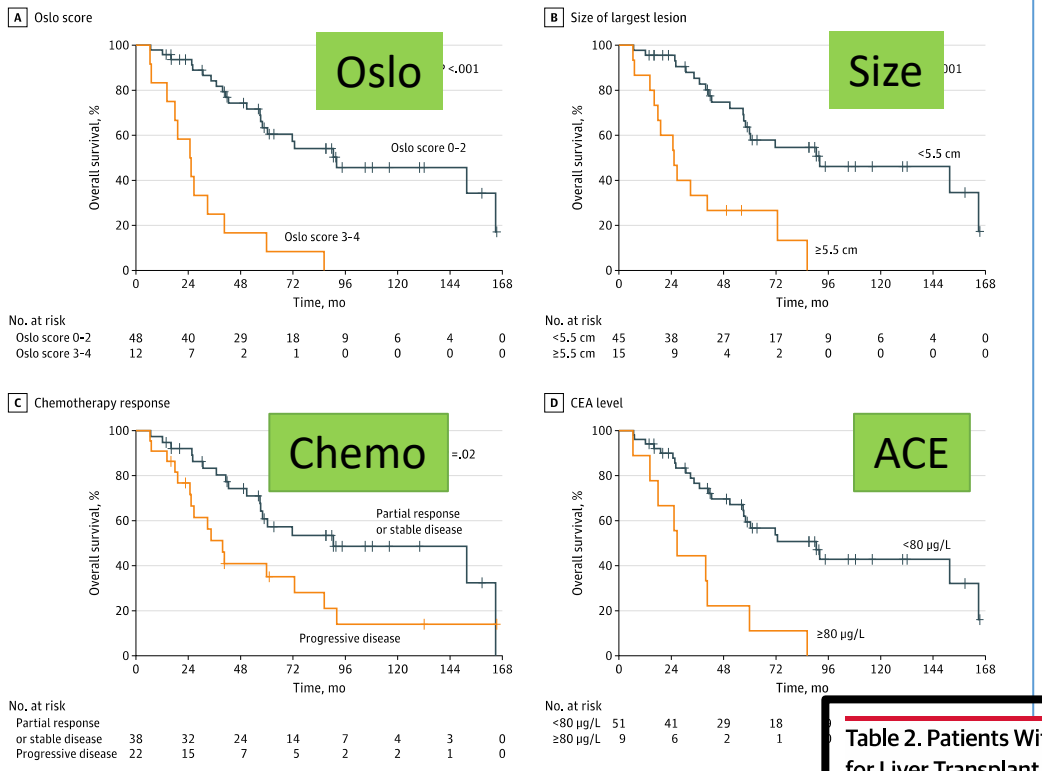
61 patients

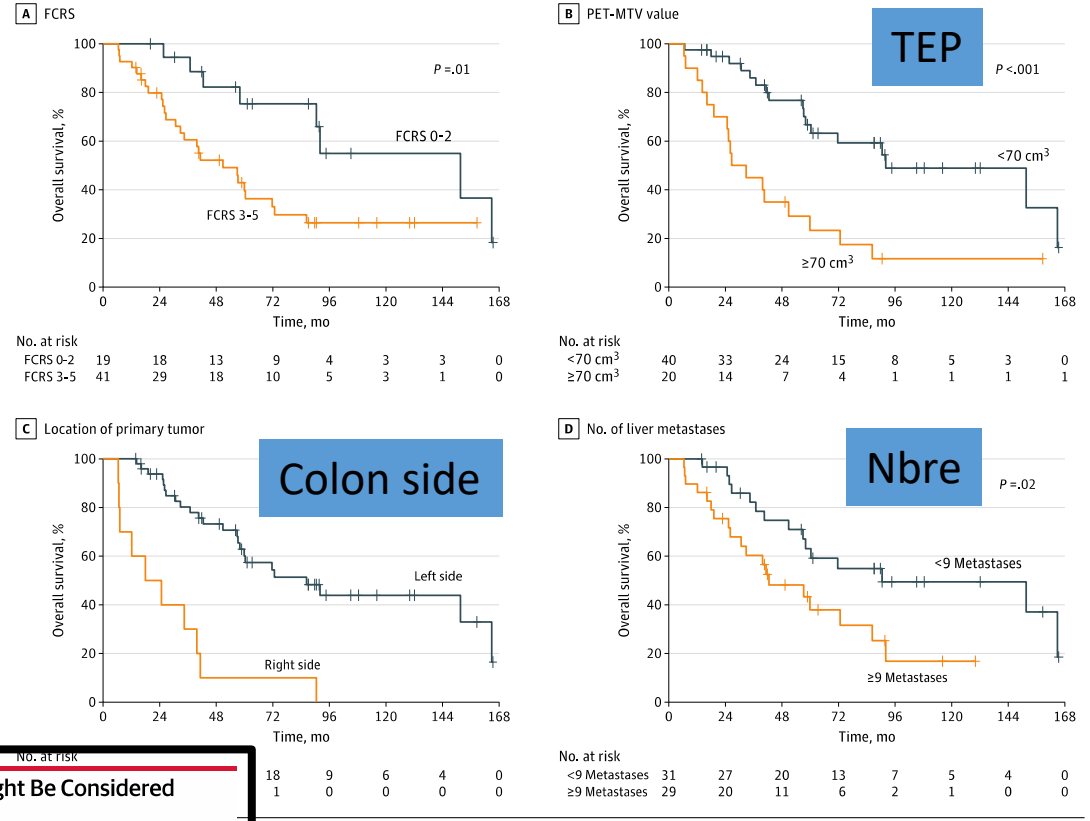
Figure 1. Disease-Free Survival, Overall Survival, and Survival After Relapse After Liver Transplant



A, Disease-free survival. B, Overall survival. C, Survival after relapse.

Figure 2. Association of Overall Survival After Liver Transplant With Oslo Score, Lesion Size, Treatment Response, Carcinoembryonic Antigen (CEA) Levels, and Time From Diagnosis





Oslo score 0 to 4

1. **Colon – TH < 2 ans**
2. **ACE > 80**
3. **Taille > 5,5cm**
4. **Progression sous chimio**

Table 2. Patients With Colorectal Cancer Who Might Be Considered for Liver Transplant (LT)

Very good prognosis after LT	No. of patients	Estimated 5-y survival
Metachronous disease (more than 12 mo from diagnosis of the primary tumor to detection of liver metastases)	5	100%
Time from diagnosis to LT >3 y	9	100%
Oslo score 0	10	88.9%
Fong Clinical Risk Score 1	5	100%
Good prognosis after liver transplant		
PET-MTV value <70 cm^3	40	66.7%
Oslo score 1	27	54.7%
Fong Clinical Risk Score 2	16	63.9%
Tumor Burden score, group 2 (score of 3-9)	25	72.3%

Abbreviations: MTV, metabolic tumor volume; PET, positron emission tomography.

Etudes randomisées TH + chimiothérapie vs. chimiothérapie seule

NIH U.S. National Library of Medicine

ClinicalTrials.gov

2023

Etude	**TRANSMET** *France* NCT02597348	**SECA 3** *Norvège* NCT03494946	**SOULMATE** *Suède* NCT04161092
Groupes	**TH+C vs C**	**TH+C vs C**	**TH+C vs C**
Greffon	**Cadavérique**	**Cadavérique**	**A critères élargis**
N	**94**	**30**	**45**
Inclusion	**Terminée**	**En cours**	**En cours**
Principal objectif	**Survie globale à 5 ans**	**Survie globale**	**Survie globale à 5 ans**

2024 ASCO ANNUAL MEETING

Liver Transplantation and Chemotherapy versus Chemotherapy alone in patients with definitively unresectable colorectal liver metastases : results from a prospective, multicentre, randomised trial (TransMet)

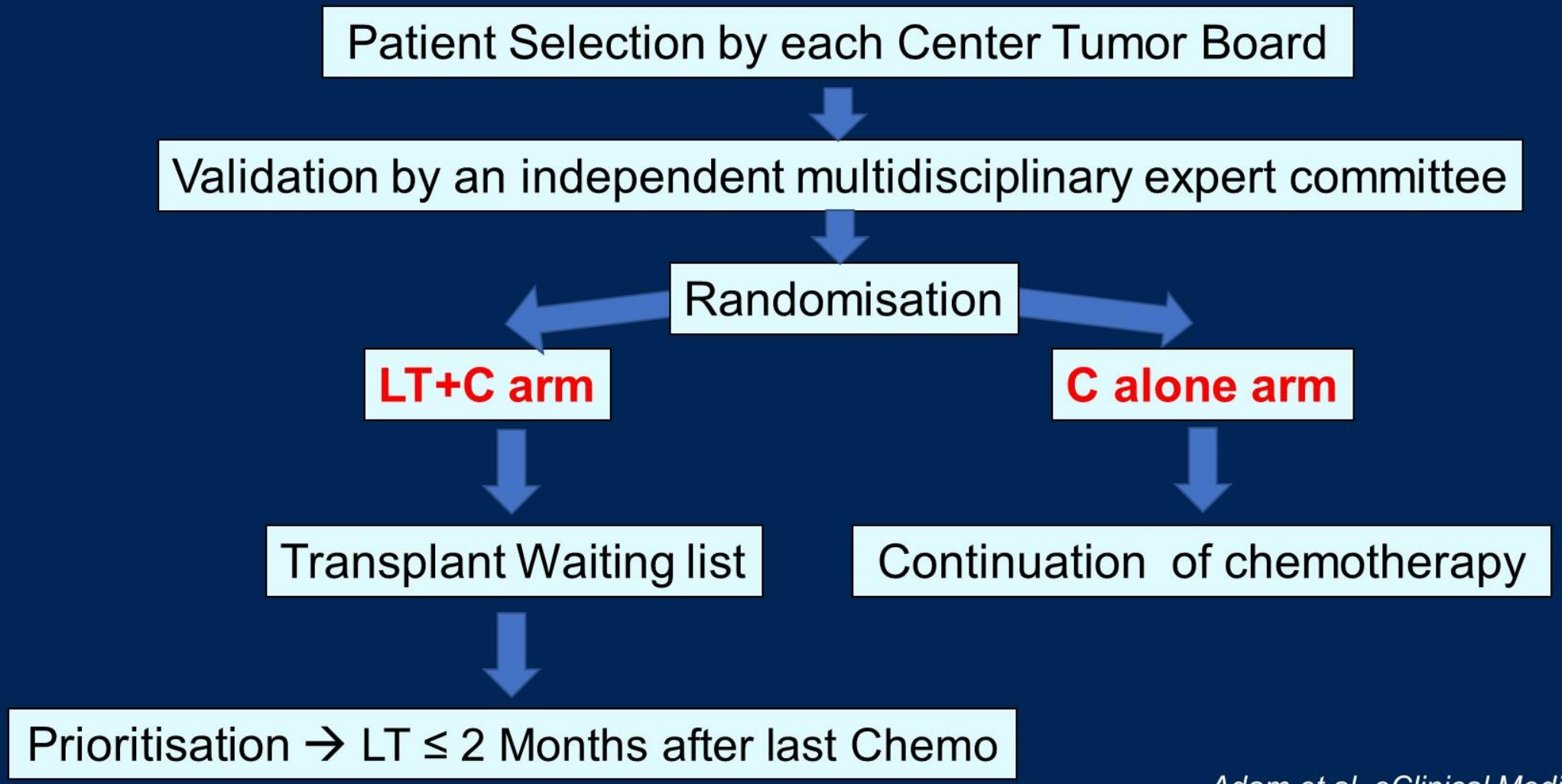
R Adam, C Piedvache, L Chiche, E Salamé, O Scatton, V Granger, M Ducreux, U Cillo, F Cauchy, JY Mabrut, C Verslype, L Coubeau, J Hardwigsen, E Boleslawski, F Muscari, J Lerut, L Grimaldi, F Levi, M Lewin, M Gelli

Paris-Saclay – Villejuif – Kremlin Bicêtre (France), Bordeaux (France), Tours (France), Paris (France), Grenoble (France), Villejuif (France), Padova (Italy), Clichy (France), Lyon (France), Leuven (Belgium), Louvain (Belgium), Marseille (France), Lille (France), Toulouse (France), Bruxelles (Belgium)

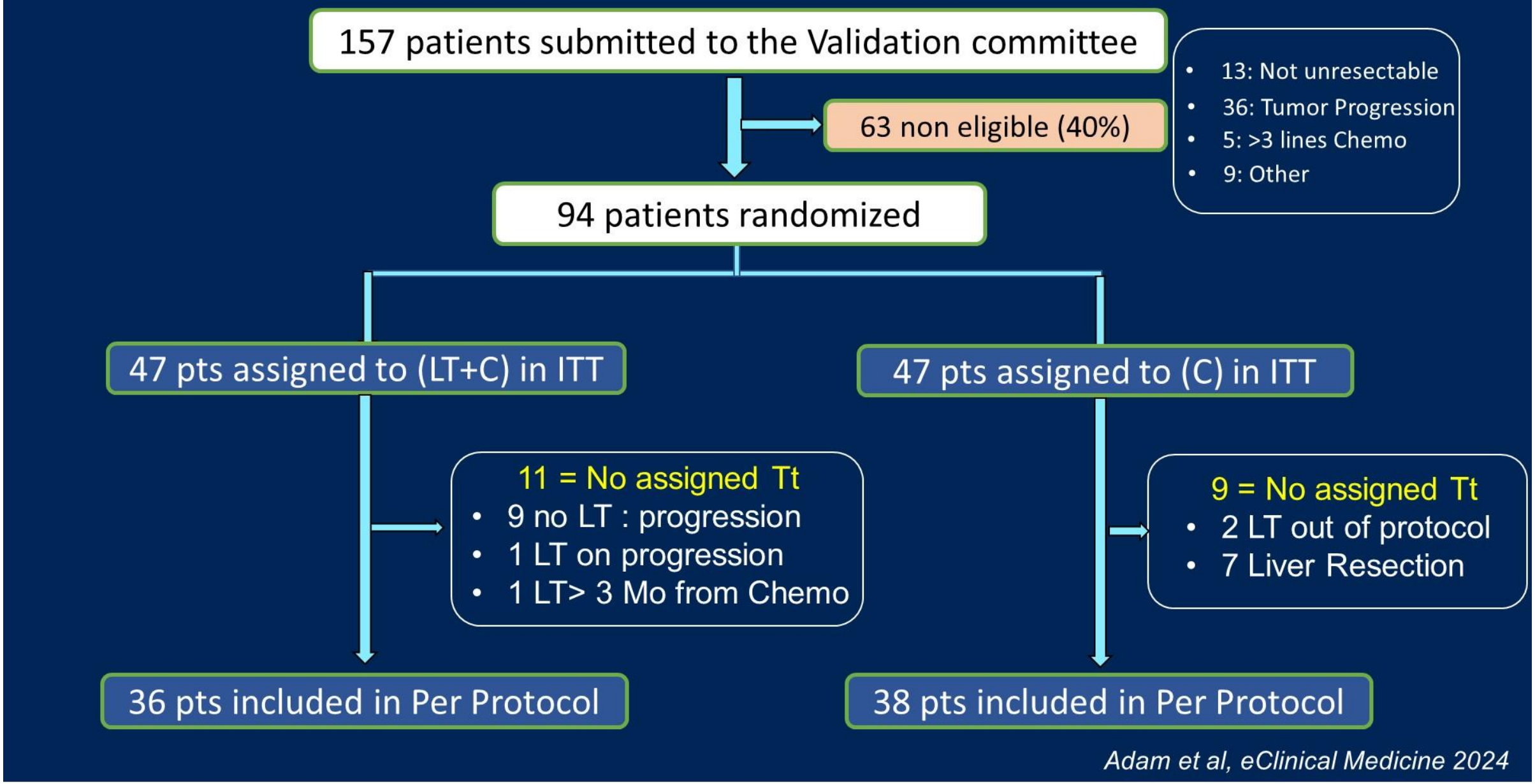
ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS

PRESENTED BY:

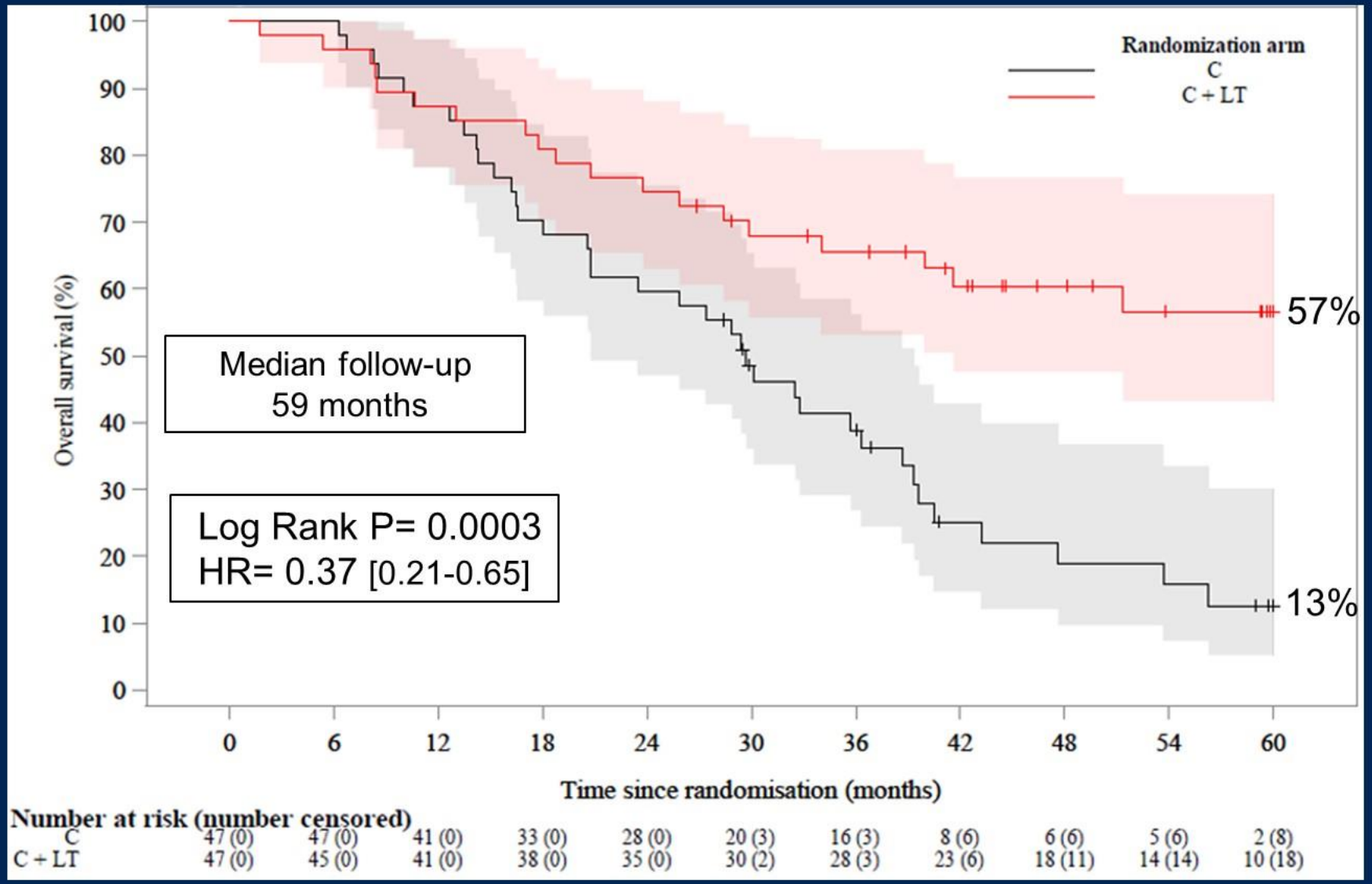
TransMet Trial : Study Design



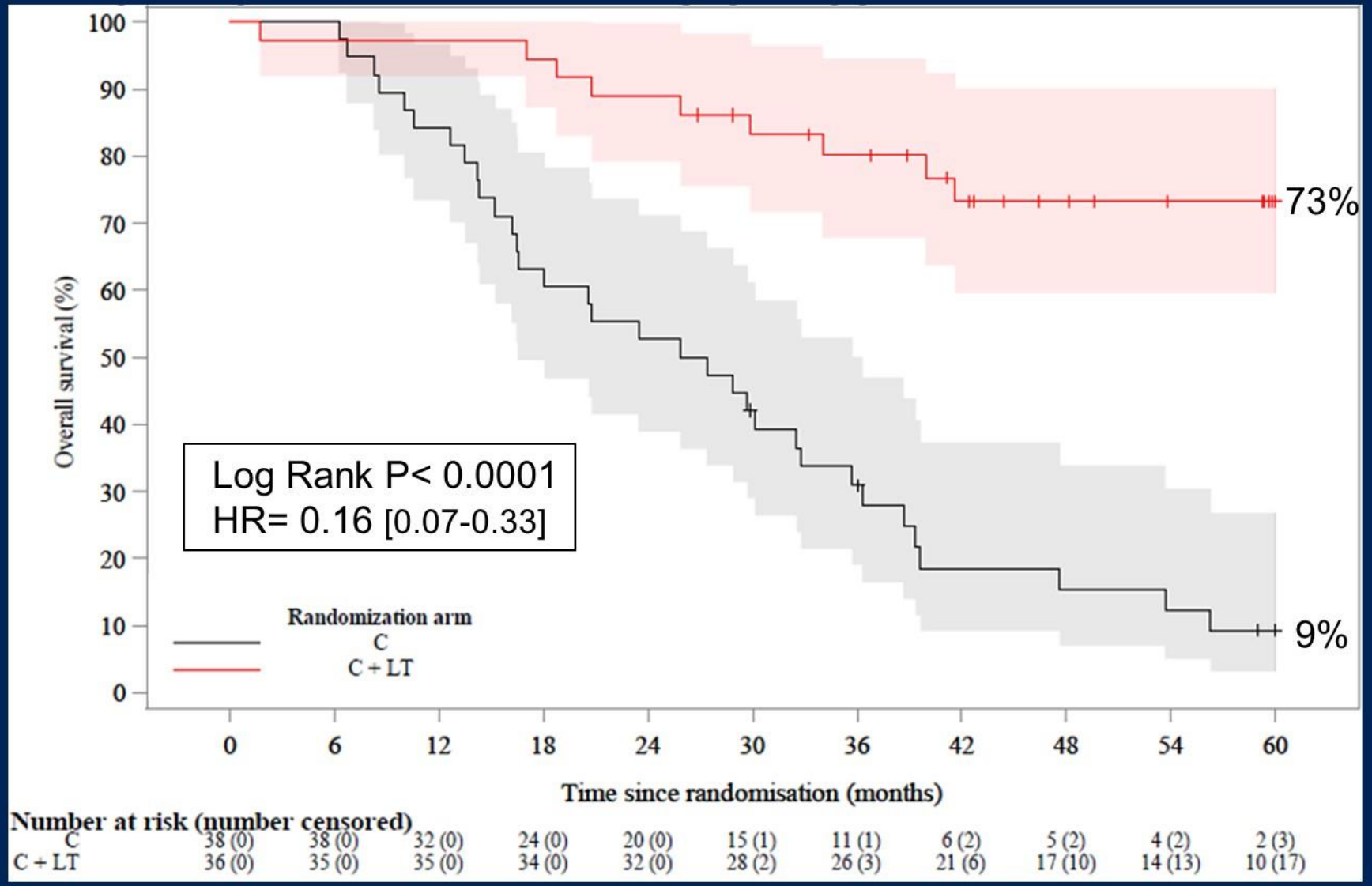
Adam et al, eClinical Medicine 2024



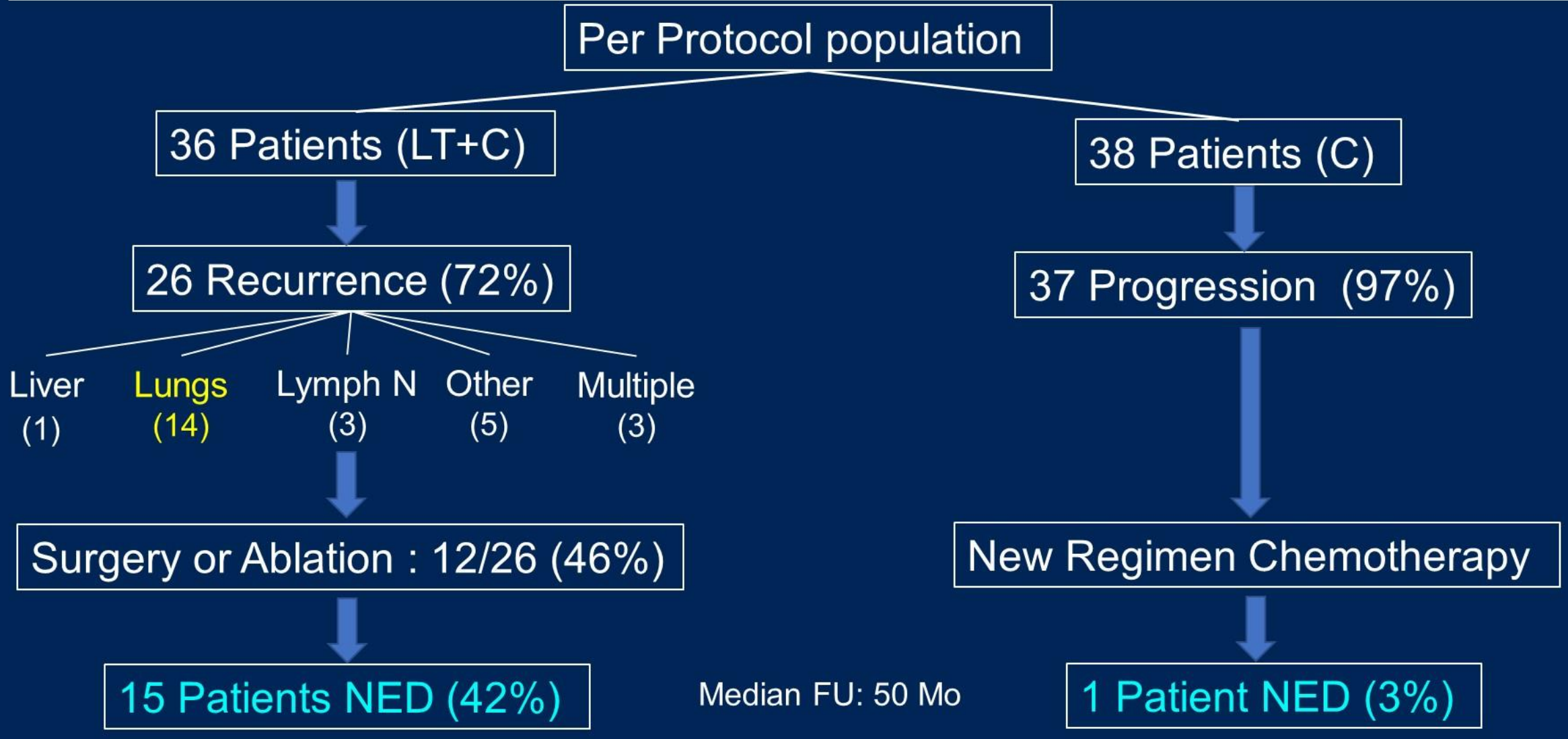
TransMet Trial : Primary Endpoint 5-Yr OS (ITT)



TransMet Trial : Primary Endpoint 5-Yr OS (Per Protocol)



TransMet Trial : Recurrence (LT+C) or Progression (C)



SURGICAL PERSPECTIVE

The Development of Transplant Oncology May Worsen the Liver Gap and Needs New Technical Options in Liver Transplantation

Olivier Soubrane, MD, PhD✉ and Olivier Scatton, MD, PhD†*

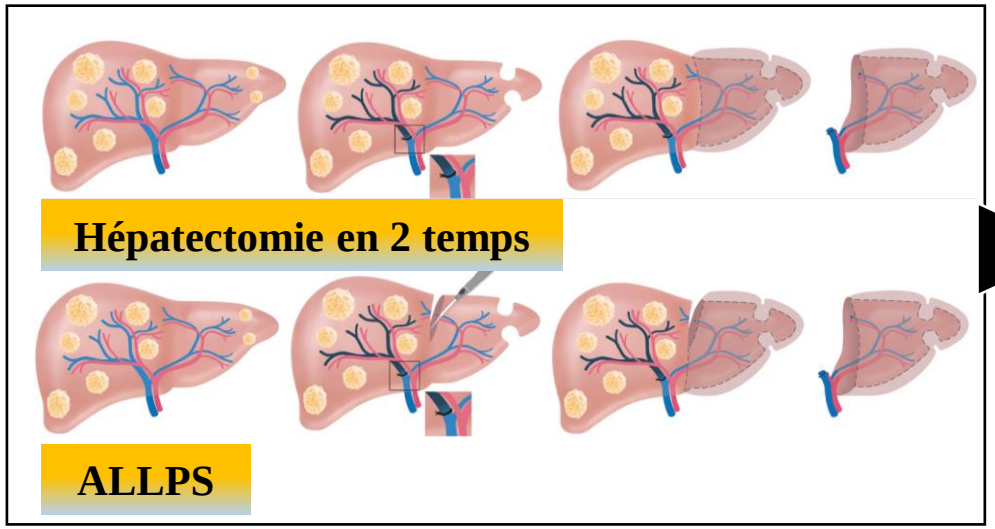
✓ We add a new indication
✓ While there is a lack of graft

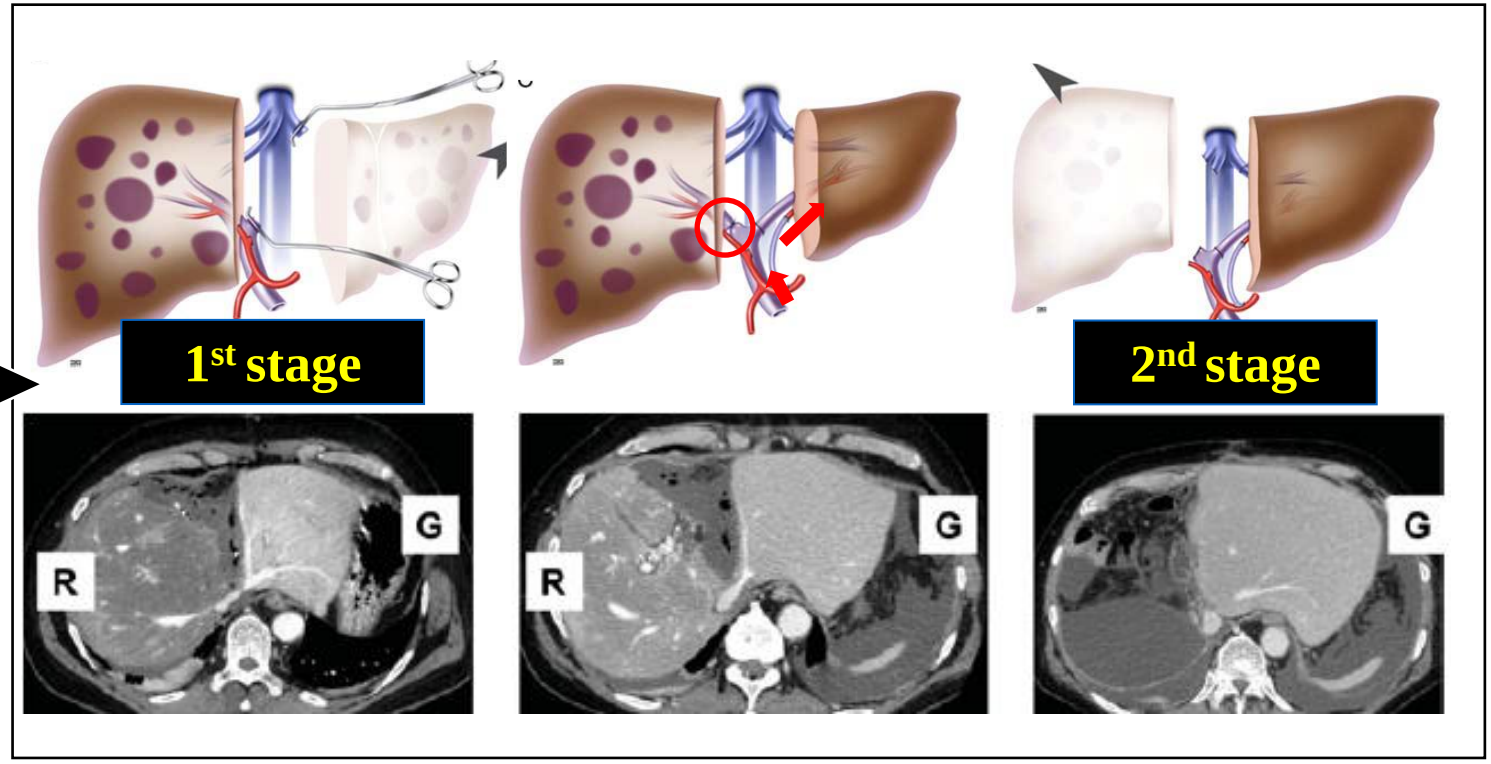
« RAPID » for liver mets

A Novel Concept for Partial Liver Transplantation in Nonresectable Colorectal Liver Metastases

The RAPID Concept

2015
Cadaveric LLS graft





« Deportalization » of the native liver in order to increase the graft regeneration

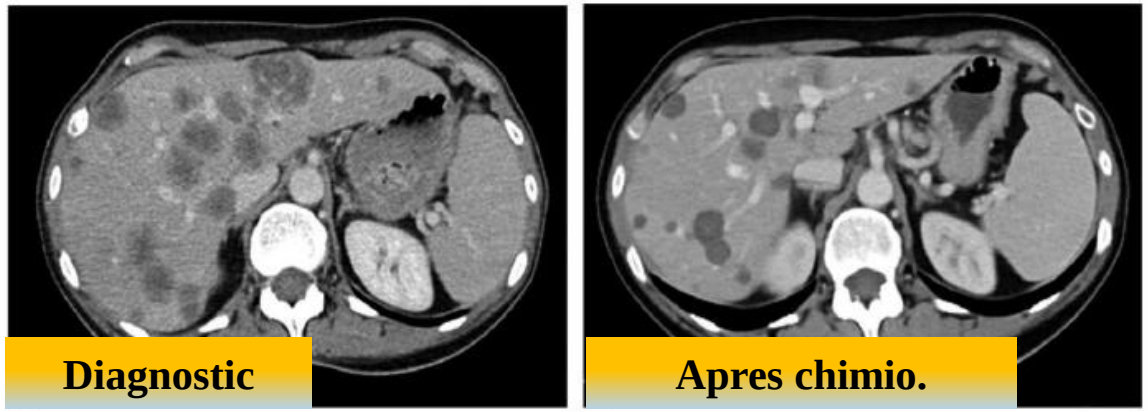
Line, Ann Surg 2015; Muller, Langenbecks Arch of Surg 2021: Settmacher, Ann Surg 2023

« RAPID » for Liver Mets

Paradigm Shift in the Management of Irresectable Colorectal Liver Metastases

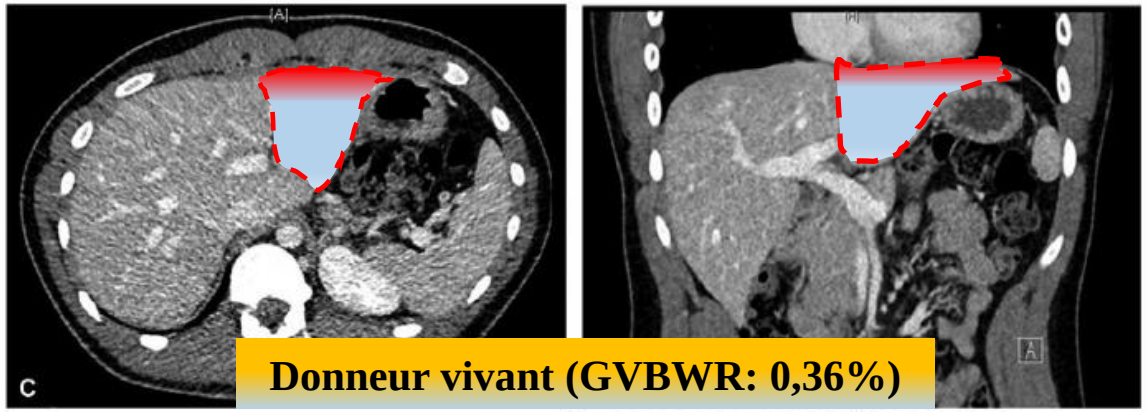
Living Donor Auxiliary Partial Orthotopic Liver Transplantation in Combination With Two-stage Hepatectomy (LD-RAPID)

2018
Living donor LLS

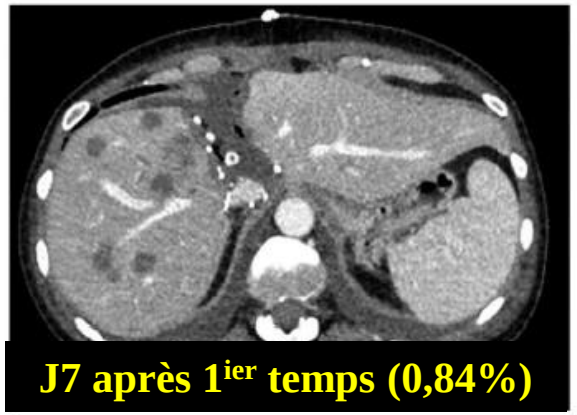


Diagnostic

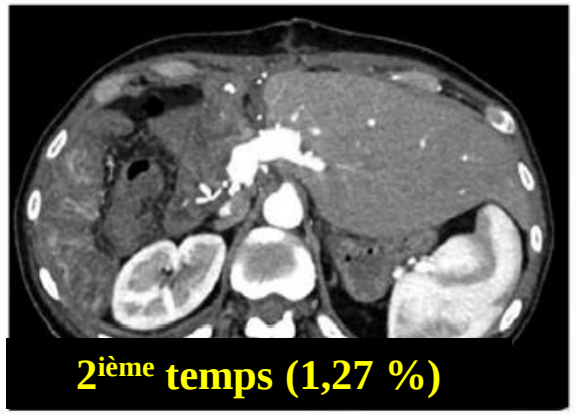
Apres chimio.



Donneur vivant (GVBWR: 0,36%)



J7 après 1ier temps (0,84%)



2ième temps (1,27 %)

LLS in the donor

Konisgrainer, Ann Surg 2018

« RAPID »

Auxilliary Liver Transplantation According to the RAPID Procedure in Noncirrhotic Patients

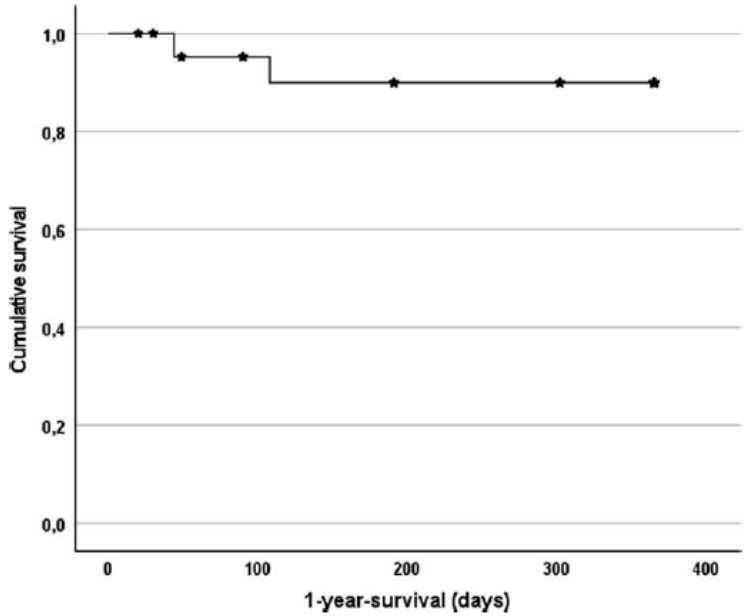
2023

RAPID sur foie non cirrhotique

- 6 centres, 2015-2022
- N = 23
- Laparotomy / living donor

- **Vivant, n=20,** cadav, n=3
- **Lobe gche, n=16;** F gche, n=7
- **MHCCR, n = 21**

Délai entre les 2 temps	**14 jours (10-60)**
Pas de 2ième temps	**4,3% (n=1)** **Thrombose porte**
Mortalité donneur	0%
Morbidité donneur	**4,3% (n=1)** **Plaie biliaire**
Mortalité	**4,3% (n=1)** **DMV après TAH J 44**
Morbidité sévère (≥IIIb)	**43,5% (n=10)** **Fistule biliaire++**



Settmacher, Ann Surg 2023

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

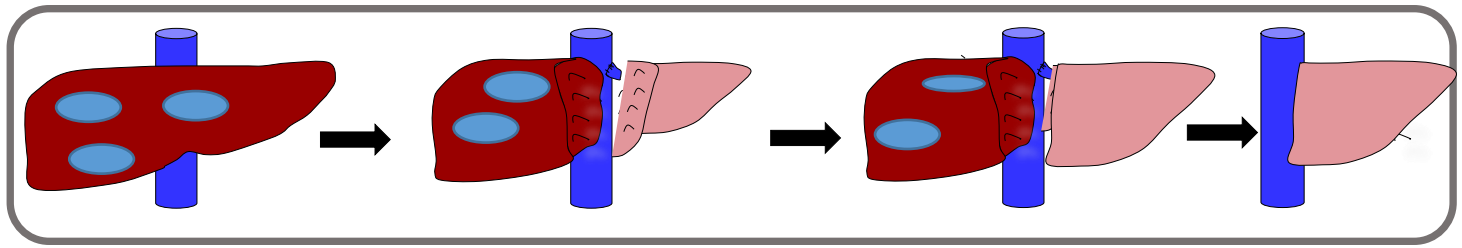
(3) Graft selection and allocation

Organ allocation and waitlist prioritisation	
Statement 30	The decision regarding the type of graft used for liver transplantation for non-colorectal liver metastases should be made ideally at the national organ allocation level or at least by the transplant centre. National organ availability, waiting list mortality, and centre-specific post-operative outcomes after liver transplantation should be considered
Expanding the deceased donor pool	
Statement 33	Novel surgical techniques, such as deceased donor RAPID and living donor RAPID, show promise for expansion of the donor pool; however, long-term oncological outcomes are unclear
	centres with experience in this technology, ideally within a prospective controlled trial
Statement 33	Novel surgical techniques, such as deceased donor RAPID and living donor RAPID, show promise for expansion of the donor pool; however, long-term oncological outcomes are unclear
Living donor liver transplantation for non-colorectal liver metastases	
Statement 34	Living donor liver transplantation in the setting of non-colorectal liver metastases should be done in centres with perioperative and long-term recipient and donor outcomes that are acceptable by international benchmarks, preferably within a prospective controlled trial. The morphology of the living donor graft (including graft-to-recipient weight ratio, vascular and biliary anatomy, steatosis, and future liver remnant) should meet the safe acceptable criteria of the transplanting centres
Organ allocation for re-transplantation	
Statement 35	Re-transplantation for early graft failure with standard donation after brain death grafts might be considered in accordance with national or centre-specific organ allocation criteria for liver transplantation. Where these criteria are not met, re-transplantation with extended criteria or living donor grafts might be considered on the basis of centre expertise. This practice might therefore vary between countries and regions worldwide

Bonnet GK et al. Lancet GastroHep 2021

ISLS 2023 ZURICH
RAPID.SURGERY
5TH CONGRESS OF INTERNATIONAL ADVANCED HBP SURGERY
October 18 (Wed) - 21 (Sat), 2023 | Kongresshaus Zurich, Switzerland

RAPID recommendations in the setting of no portal hypertension



NO- PORTAL HYPERTENSION
METASTATIC LIVER CANCER

Coordinator : Scatton O

Expert Panel: Daniel Azoulay, Deniz Balci, Albert Chan, Karim Halazun, Ki Hun Kim, Pal-Dag Line

Preoperative measures	Vote	QOE	GOR
4. What are the indications for RAPID? Which preoperative assessment modalities best identify patients suitable for RAPID in the setting of portal vs. no portal hypertension?			
4a. The indications of RAPID for Colorectal and Neuroendocrine Liver Metastases, should be according to the current recommendations of liver transplantation without expanding the indications based on easier access to a graft.	88.3%	Low	Strong
4b. Living donor RAPID, in the absence of recipient portal hypertension can be considered, when the only donor available would offer only a small for size graft.	83.3%	Very Low	Weak
4c. Given that the primary indication of RAPID is colorectal and neuroendocrine liver metastases, it is recommended to conduct a detailed transplant evaluation in conjunction with a comprehensive oncological assessment according to international guidelines.	86.5%	Very Low	Strong
4d. RAPID represents a treatment strategy for patients, irrespective of portal hypertension or the presence of hepatocellular carcinoma (HCC).	67.5%	Low	Weak
4e. The first stage of RAPID encompasses a left hepatectomy to create sufficient space for the graft. The functional volume of the native liver remnant should be adequate according to the current recommendations for liver resection.	81.4%	Low	Weak

APOLT and RAPID…

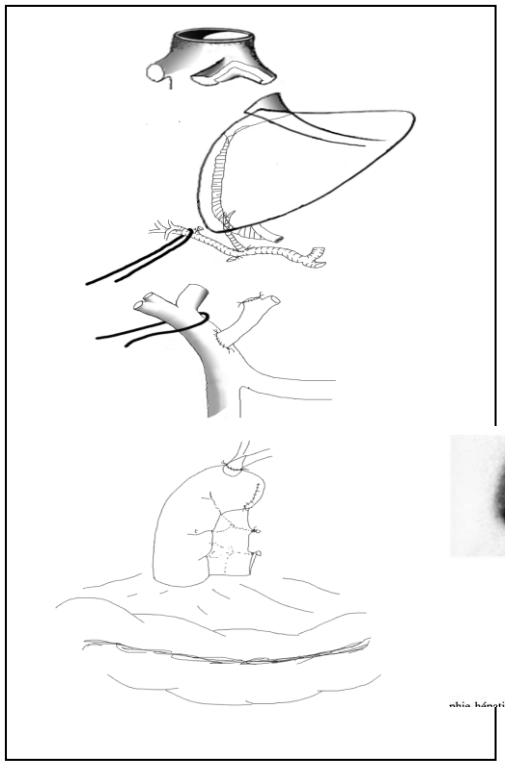
CAS CLINIQUE

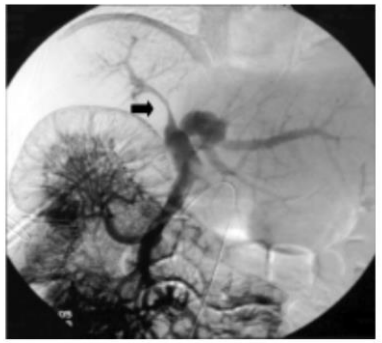
Transplantation auxiliaire pour cirrhose

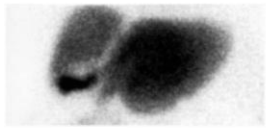
Une alternative possible pour l'utilisation de greffons de petit poids ?

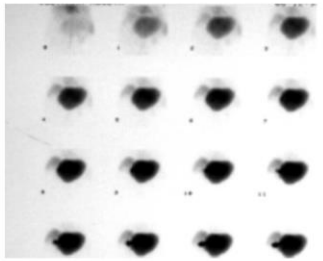
Olivier SCATTON, Daniel AZOULAY, Denis CASTAING, Antoinette LEMOINE, Philippe ICHAI, René ADAM, Didier SAMUEL, Henri BISMUTH

(1) Centre hépatobiliaire, (2) Service de biochimie, (3) Service de Réanimation, Hôpital Paul Brousse, Villejuif.









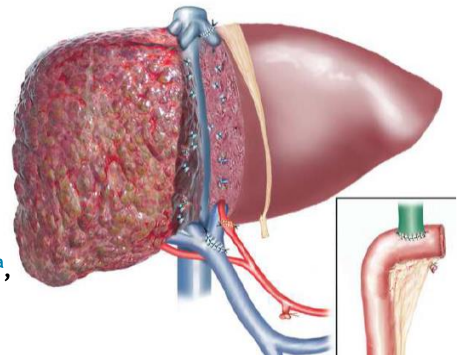
a | b

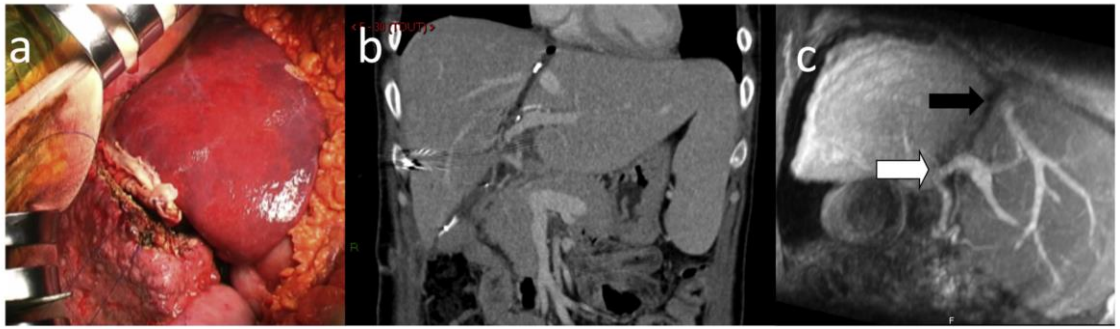
phie hépatique 99mTc-IDA montrant une accumulation du traceur dans le greffon gauche. Cette accumulation était de 75 %

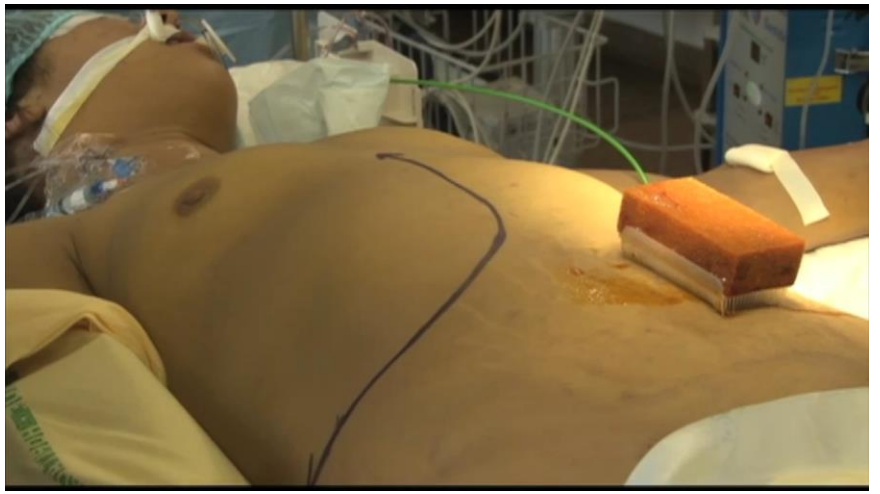
Dissection far from the Hilum
Lateral implantation PV
Open avenues for small graft from cadaver split

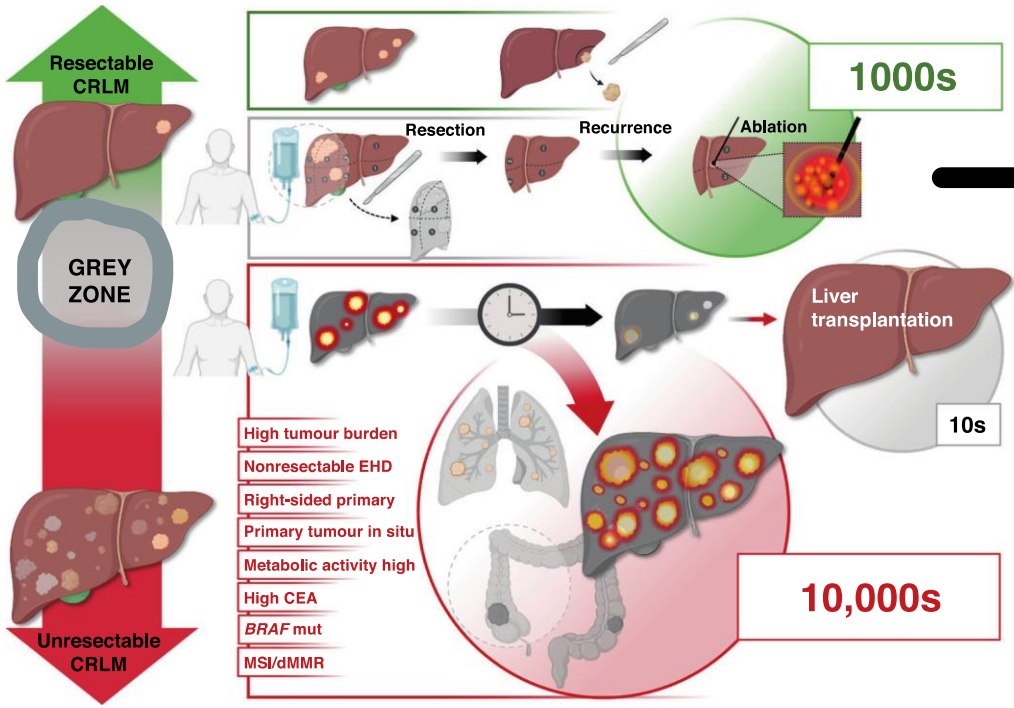
Two-stage liver transplantation using auxiliary laparoscopically harvested grafts in adults: Emphasizing the concept of ''hypersmall graft nursing''

Olivier Scatton[a,*], François Cauchy[b], Filomena Conti[a], Fabiano Perdigao[a], Pierre Philippe Massault[c], Claire Goumard[a], Olivier Soubrane[b]









British Journal of Cancer

Kjetil Søreide [1,2,3]

Oslo score 0 to 4

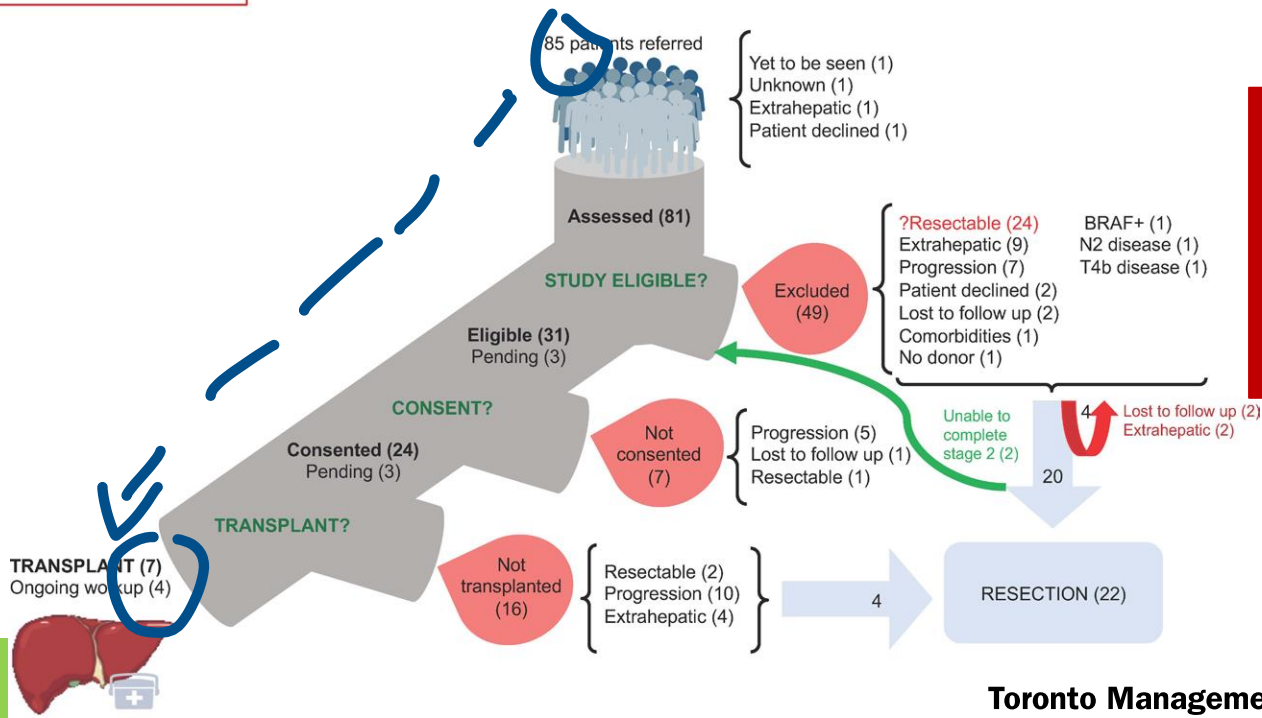
1. Colon – TH < 2 ans
2. ACE > 80
3. Taille > 5,5cm
4. Progression sous chimio

TEP scanner
Colon Gauche
BRAF neg
2 ligne de chimio

Donor pool !
LDLT
RAPID
DCD
DBD marginal machine

Grey zone

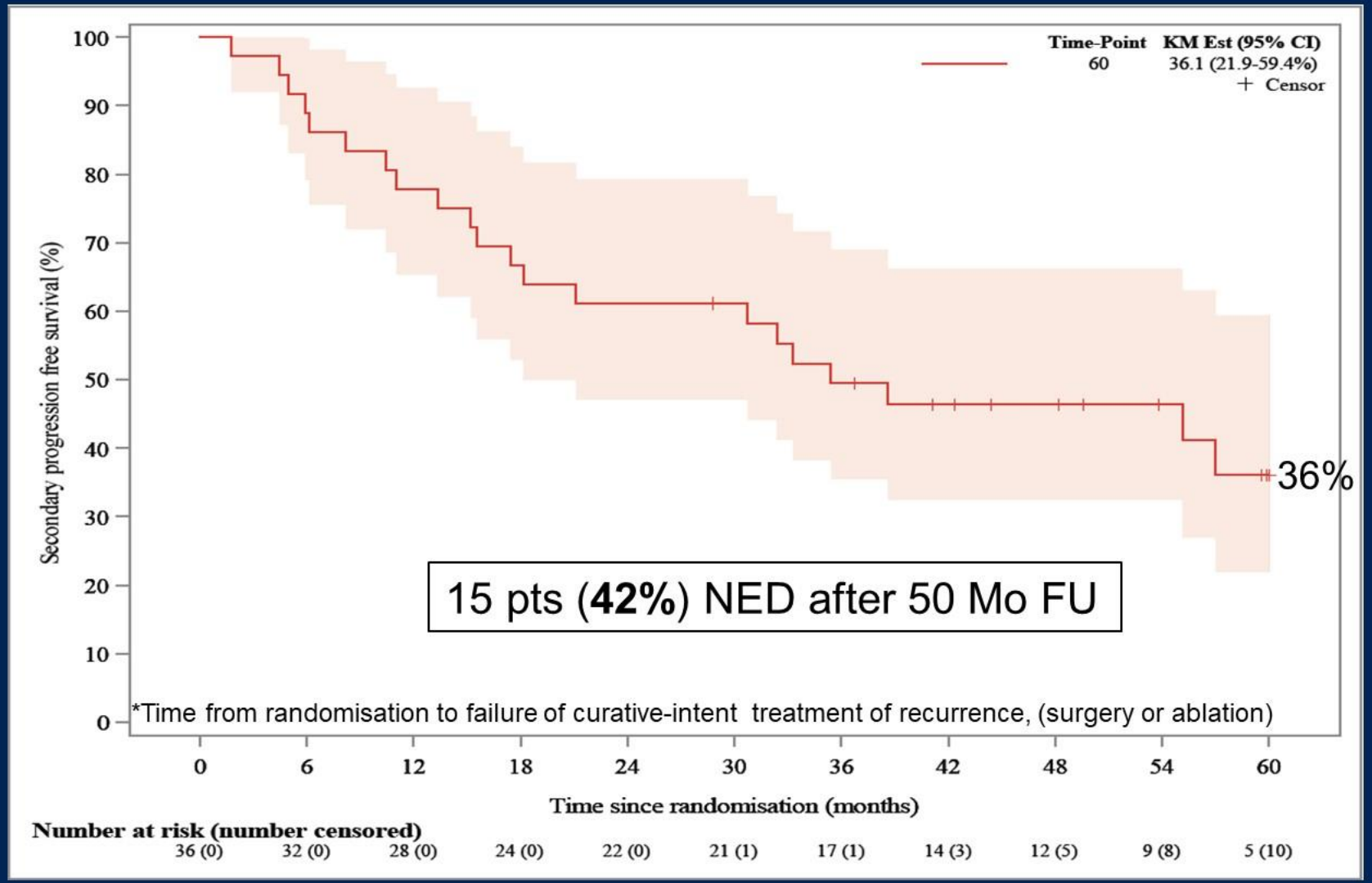
Small box



JACS 2023

Toronto Management of Initially Unresectable Liver Metastasis from Colorectal Cancer in a Living Donor Liver Transplant Program Luckshi Rajendran, MD, MEd,

TransMet Trial : 5-Yr PFS* after Rescue Surgery in LT+C group



Take Home messages from the TransMet trial

- Liver Transplantation + Chemotherapy significantly improves OS and PFS in selected patients with unresectable colorectal liver metastases compared to C alone
- These results were obtained through a rigorous patient selection and a prioritization for organ allocation
- Transplanted patients for CLM have similar survival (73% at 5 years) as those transplanted for established LT indications
- LT +C offers a potential of cure to cancer patients with otherwise poor long-term outcome

→ These results support LT as a new standard option that could change our practice in treating patients with liver-only, definitively unresectable CLM.

Etudes en cours sur le RAPID pour méta

NIH U.S. National Library of Medicine

ClinicalTrials.gov

2023

Etude	**RAPID PADOVA** *Italie* NCT04865471	**LIVER(W)OHEAL** *Allemagne* NCT03488953	*Norvege* NCT02215889	**LTLR-LC** *Chine* NCT05750329
Investigator	**Umberto Cillo**	**Falk Rauchfuss/Utz Settmacher/ Alfred Konigsrainer/Silvio Nadalin**	**Magnus Snedman**	**Renji Hospital**
Greffon	**Cadavérique ou donneur vivant**	**Donneur vivant**	**Donneur vivant**	**?**
N	**18**	**40**	**20**	**30**
Inclusion	**En cours**	**En cours**	**En cours**	**Pas encore**
Fin des inclusions	**Octobre 2025**	**Décembre 2023**	**Juin 2028**	**Décembre 2026**
Principal objectif	**% de patients ayant eu le temps 2 dans le mois qui suit le temps 1**	**Survie globale à 3 ans**	**% de patients ayant eu le temps 2 dans le mois qui suit le temps 1**	**Survie globale à 3 ans**