25e édition FORUM NATIONAL
28 ET 29 NOVEMBRE, LIMOGES
Engageons-nous tous, construisons et innovons avec un projet de santé publique ambitieux, concret et efficace !
SOS hépatites Fédération Hépatites & Maladies du foie

La greffe Hépatique en 2024

Dr Marilyne DEBETTE-GRATIEN
Limoges
FHU Limoges Tours Poitiers

Commençons par un cas clinique …

- Daniel 68 ans
- Diabétique de type 2
- Tabagique sevré
- 123 kgs, 1M 75 BMI 40
- Cirrhose métabolique sur MASH
- Antécédent d’alcool sevré depuis 1 an
- Apparition de 3 nodules de CHC , bifocal

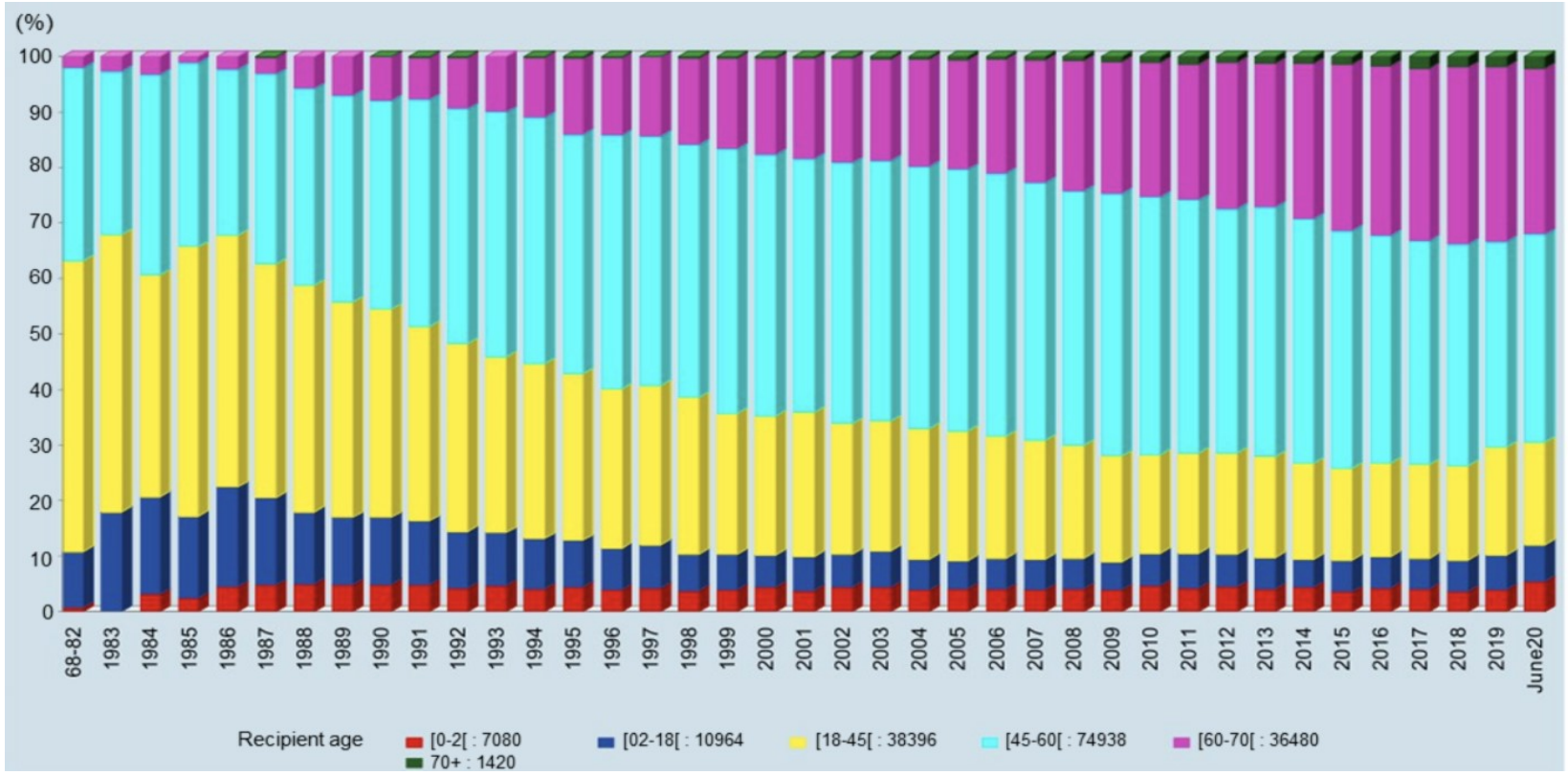
Quelle stratégie pour ce patient ?

- Trop âgé ?
- Trop de comorbidités ?
- Mauvais candidat à la TH ?
- Down staging du CHC et récidive du CHC en post TH ?

L’âge des receveurs de TH

Profils des Receveurs

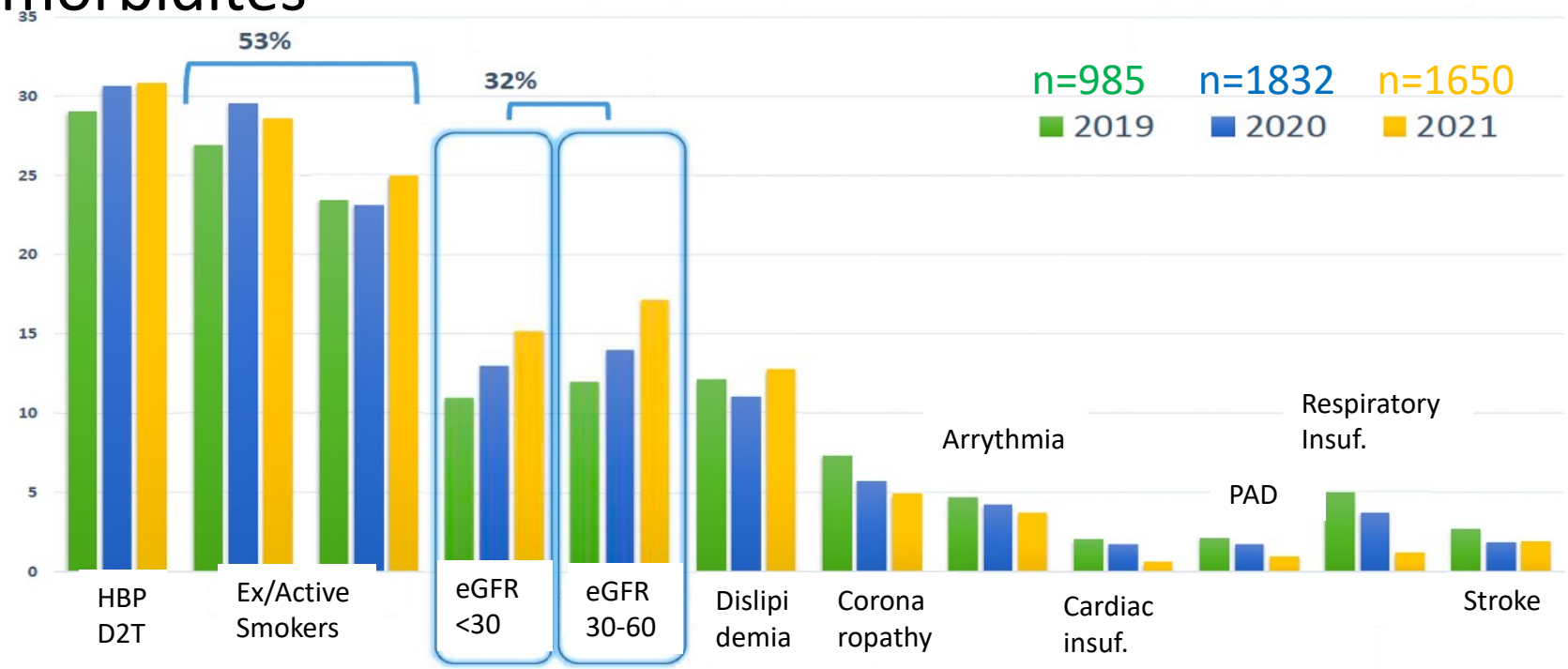
Evolution of recipient age (ELTR), n=169 278



Le receveur de TH a changé en 2024

1. Plus âgé
2. Plus de co morbidités

French LT registry (ABM), july 2019 – dec 2021



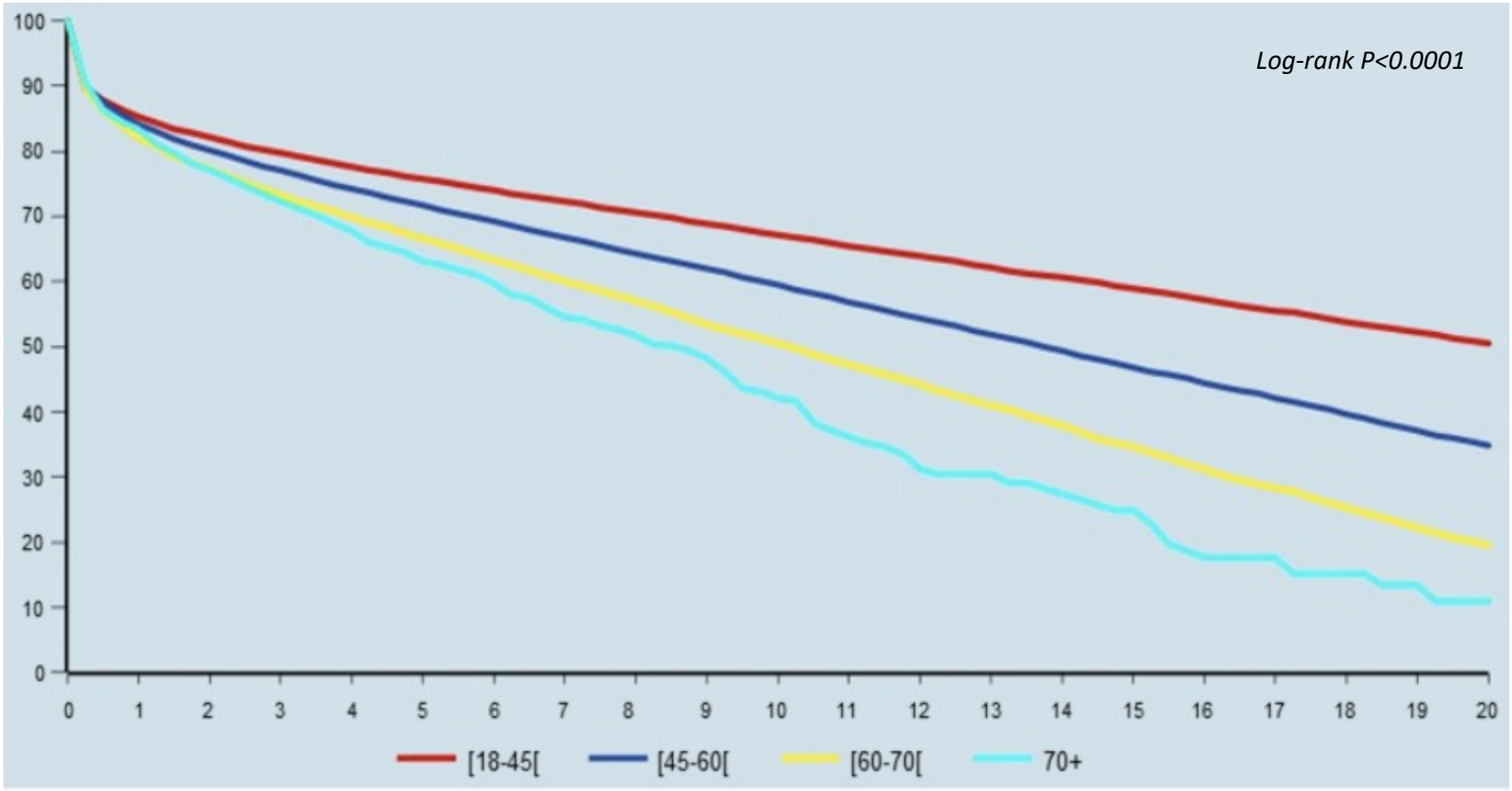
Younossi, ZM. Clinical Gastroenterology and Hepatology. 2021

Survie selon l'âge du receveur

Author	Year	Region	Age cut-off values (yr)	Patients	Follow-up (yr)	Post-transplant survival
Rudich S & Busuttil R.[138]	1999	US	≥70	30	6	57%
			<70	30		73%
Collins BH, *et al.*[5]	2000	US	≥60	91	5	52%
			<60	387		75%*
Garcia CE, *et al.*[26]	2001	Europe	≥60	174	5	69%
			<60	707		76%
Cross TJ, *et al.*[23]	2007	Europe	≥65	77	1	82%
			60–64	137		86%
			18–59	202		83%
Bilbao I, *et al.*[3]	2008	Europe	≥65	72	5	52%
			<65	313		75%*
Aloia TA, *et al.*[28]	2010	US	≥70	627	5	58%
			<70	7,325		68%*
Schwartz JJ, *et al.*[24]	2012	US	≥70	480	5	55%
			<70	22,296		73%*
Sonny A, *et al.*[29]	2015	US	≥60	223	5	89%
			<60	515		90%
Su F, *et al.*[10]	2016	US	≥70	581	5	62%
			65–69	1,738		68%
			60–64	2,663		72%
			50–59	6,801		73%*

Durand, F. J Hepatol. 2019

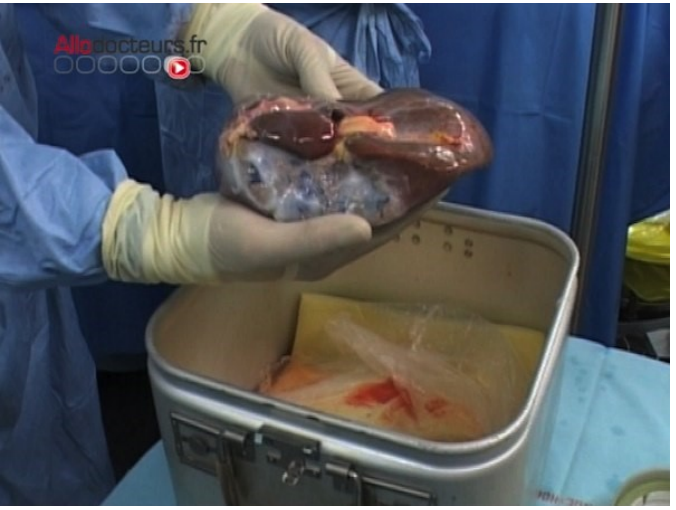
La survie post TH selon l'âge du receveur

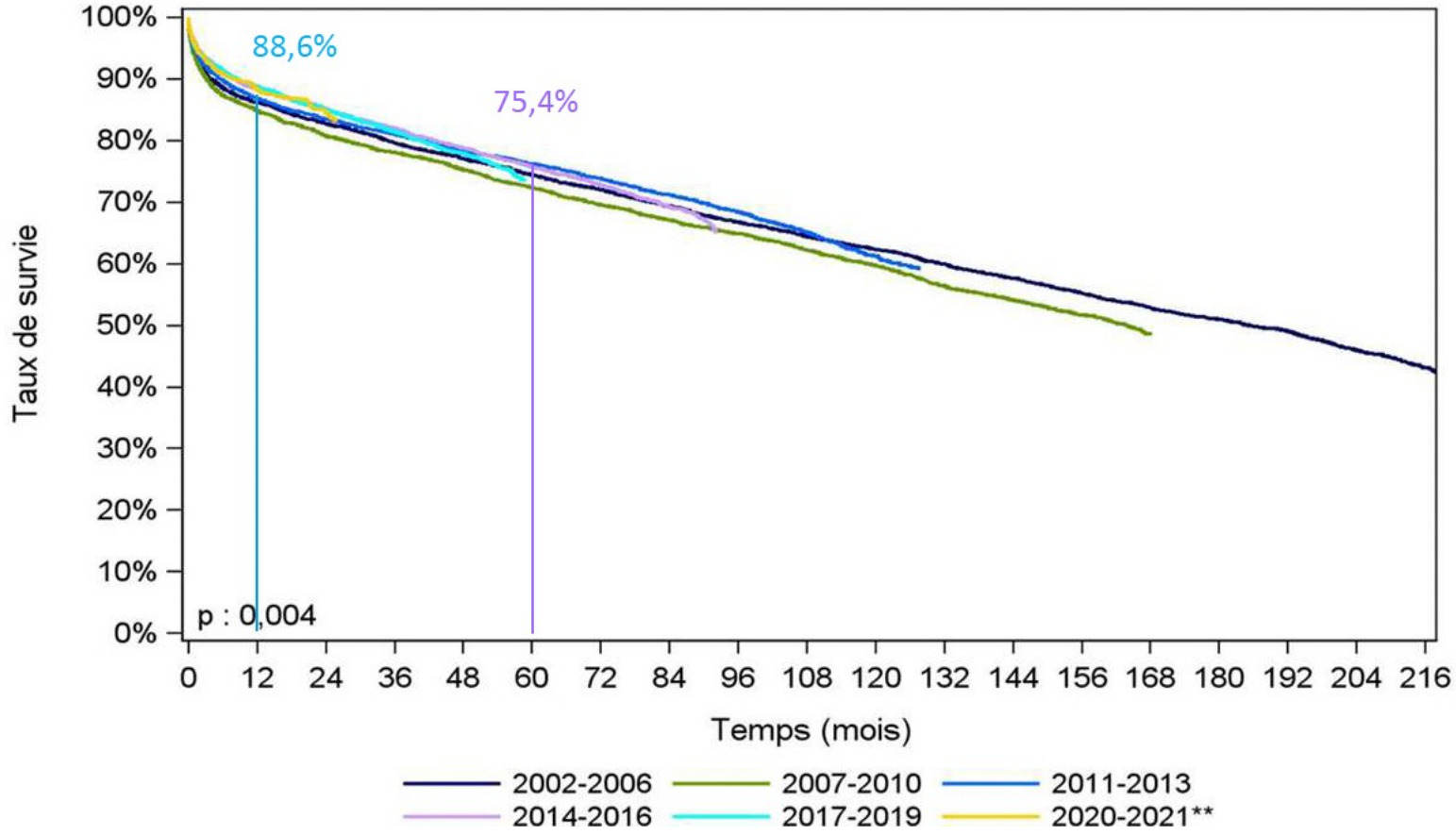


ELTR, 1988-2020, n=132,138

La greffe hépatique en 2024

Courbe de survie du receveur hépatique selon la période de greffe (2002-2020)

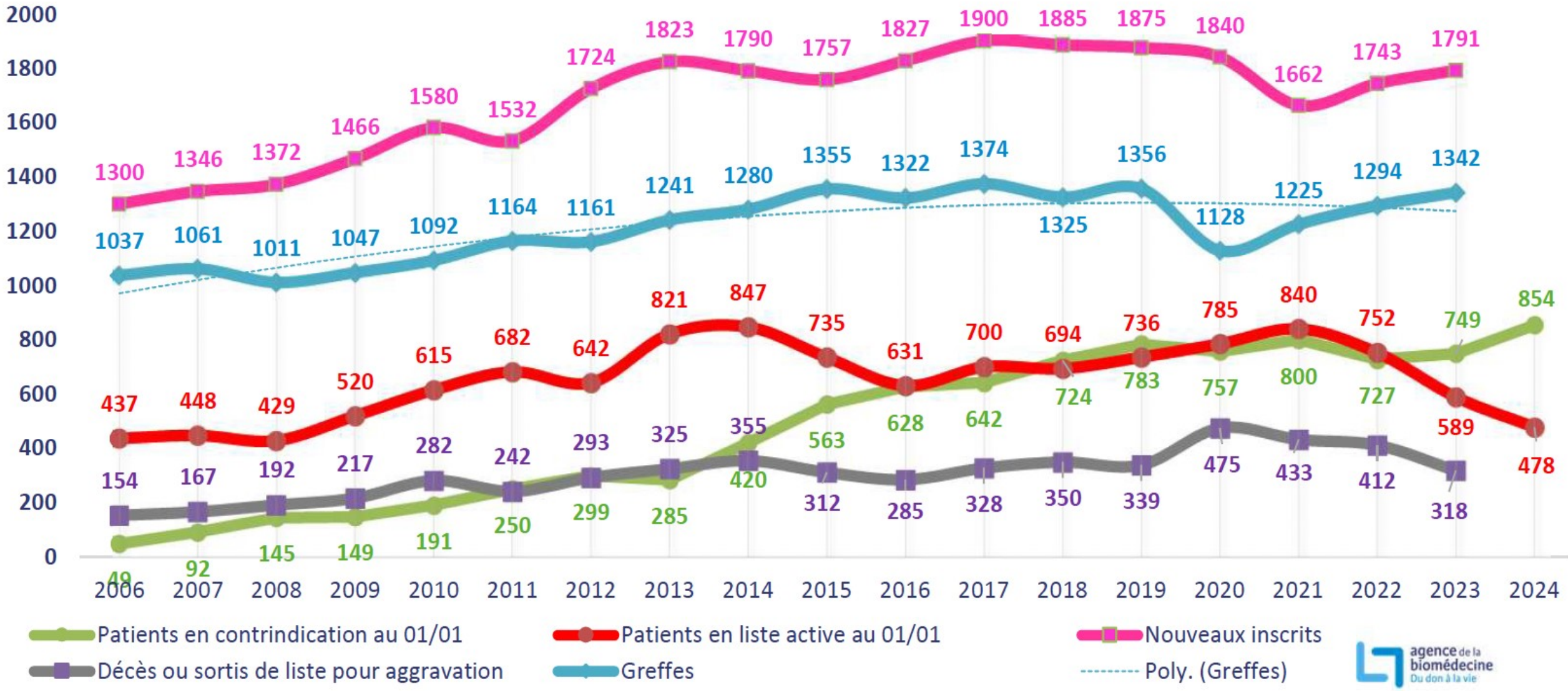




Données Agence de Biomédecine – nov 2023

La demande de greffon, l'offre de greffe :le foie

64% des inscrits en contrindication au 01/01/2024



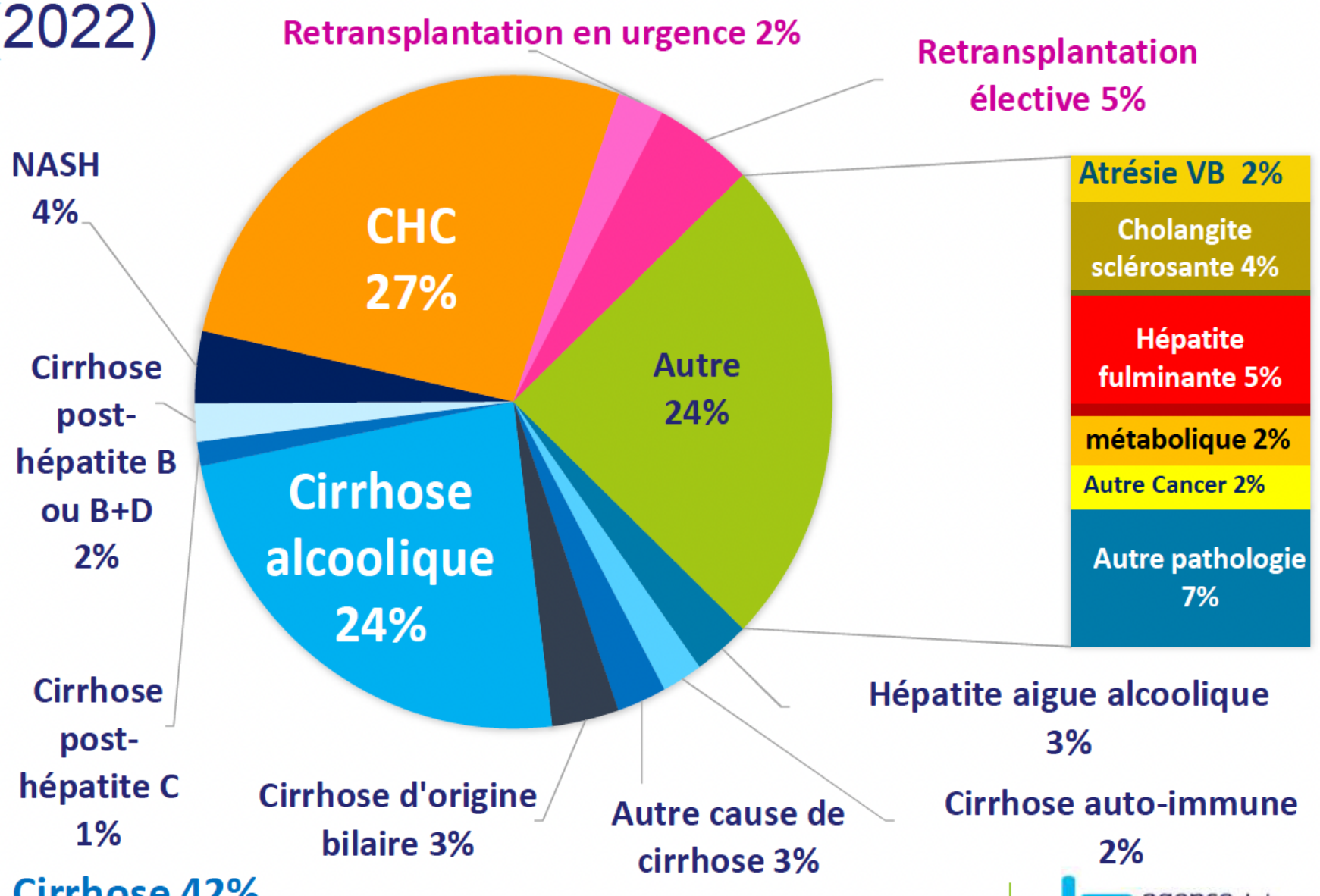
agence de la biomédecine
Du don à la vie

LES INDICATIONS DE GREFFE HÉPATIQUE (MALADIE INITIALE)

Nouveaux inscrits (2022)

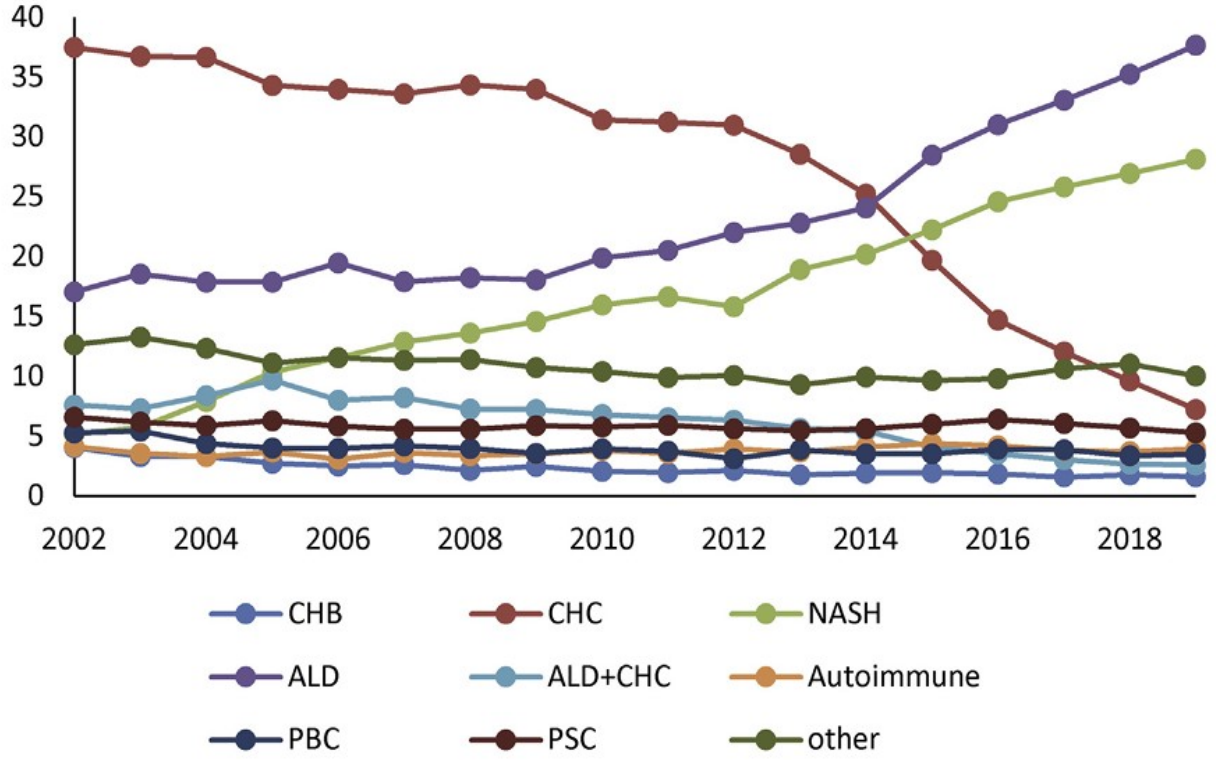
CHC 27%
Cirrhose 42% (OH 27%)
ReTH 7%
Fulminante 5%

	Hépatite aigue alcoolique	NASH
2018	20 (1,1%)	30 (1,6%)
2019	37 (2%)	55 (3%)
2020	34 (1,8%)	31 (1,7%)
2021	41 (2,5%)	55 (3,3%)
2022	50 (2,9%)	62 (3,5%)



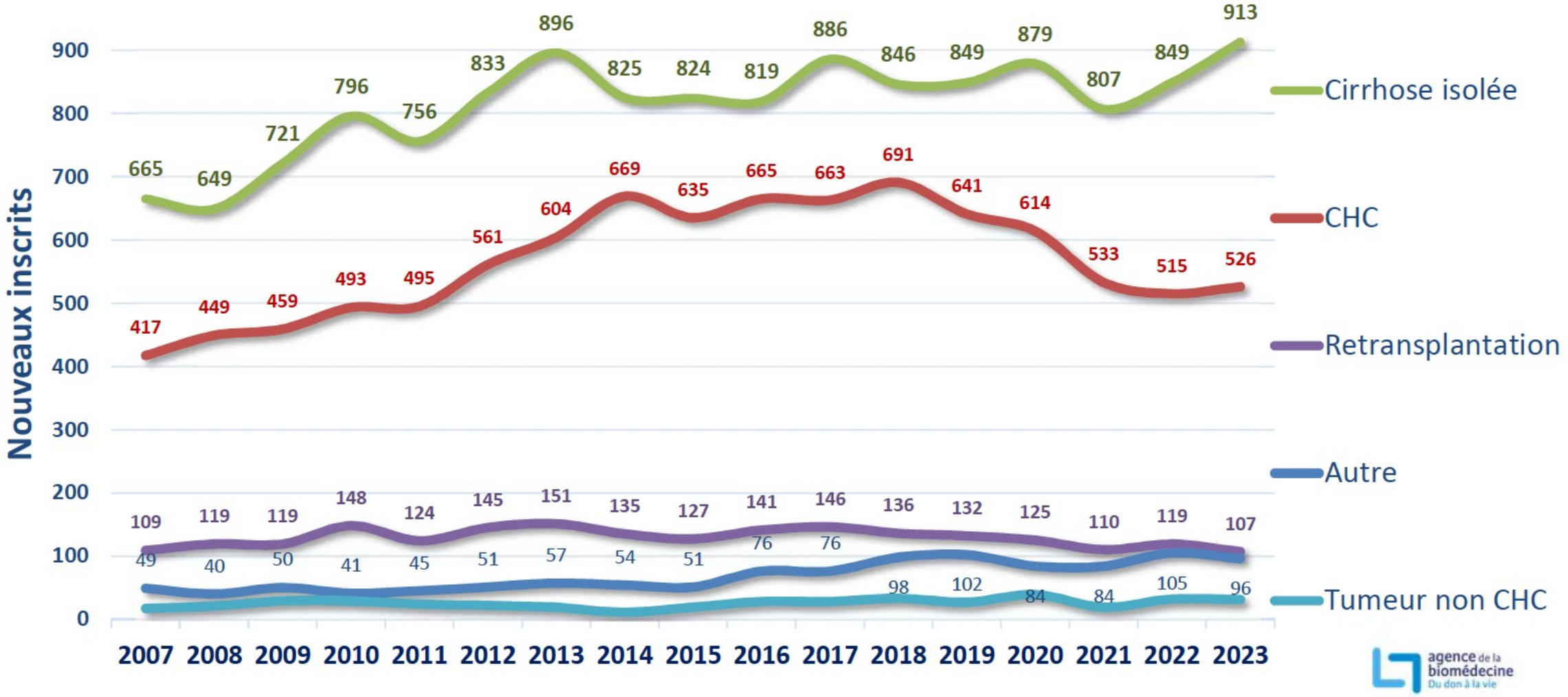
En 2024

1. Plus âgé
2. Plus de comorbidités
3. Les indications ont changé moins d'alcool plus de MASH

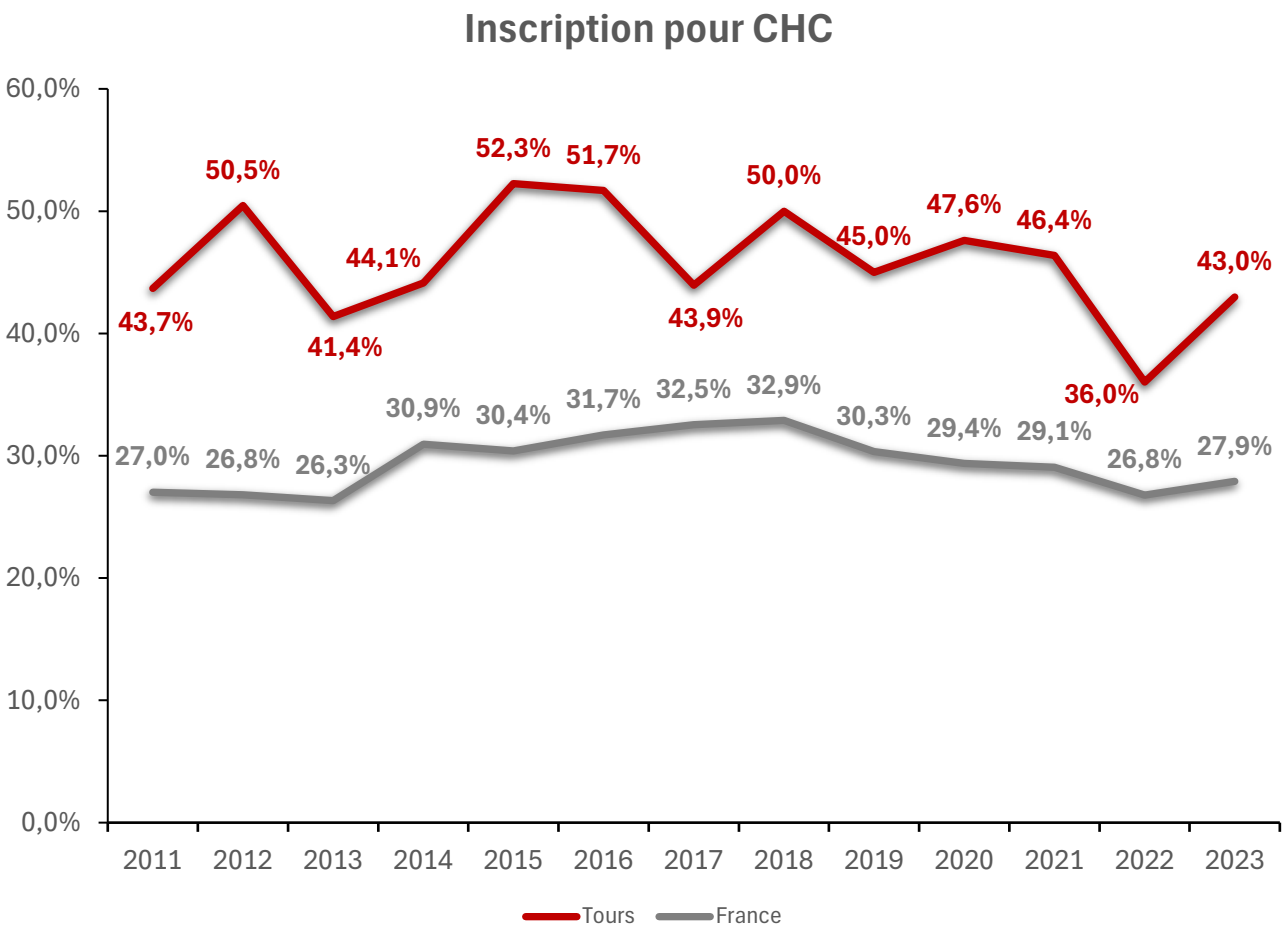


Scientific Registry of Transplant Recipients (2002-2019, n=168,441)

Evolution des composantes de greffe à l'inscription depuis la mise en place du score Foie (nombre nouveaux inscrits)

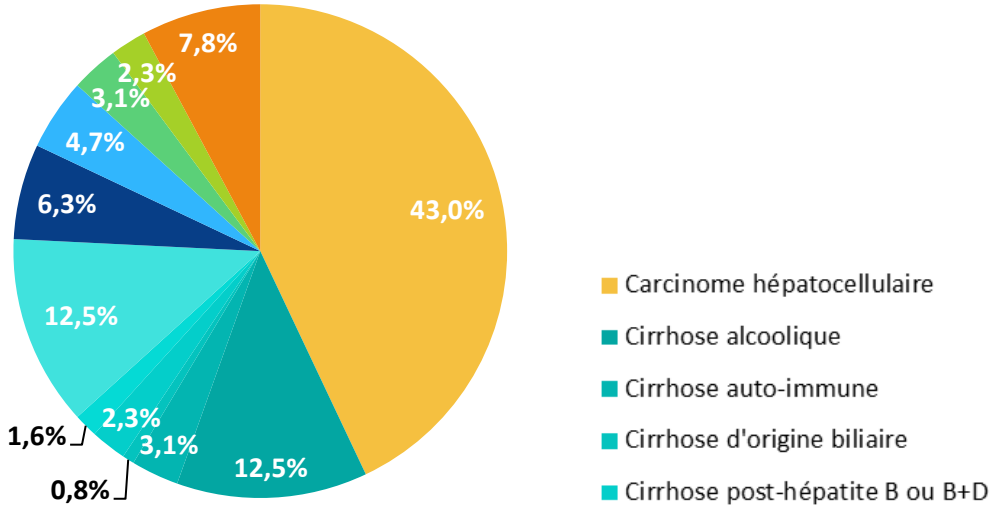


Indications d'inscription sur liste d'attente

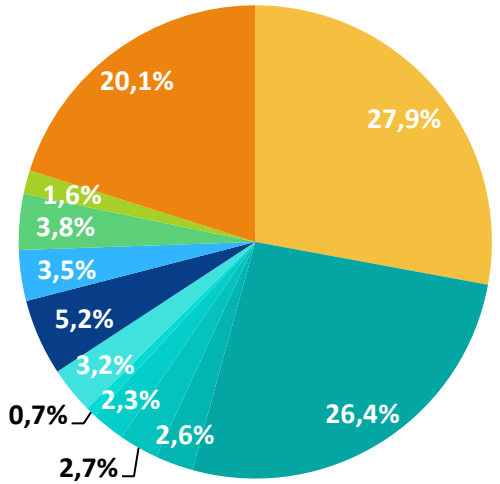


Délai moyen d'attente sur liste avec CHC à Tours : **302 jours**
versus Délai moyen d'attente pour les autres indications : **131 jours**

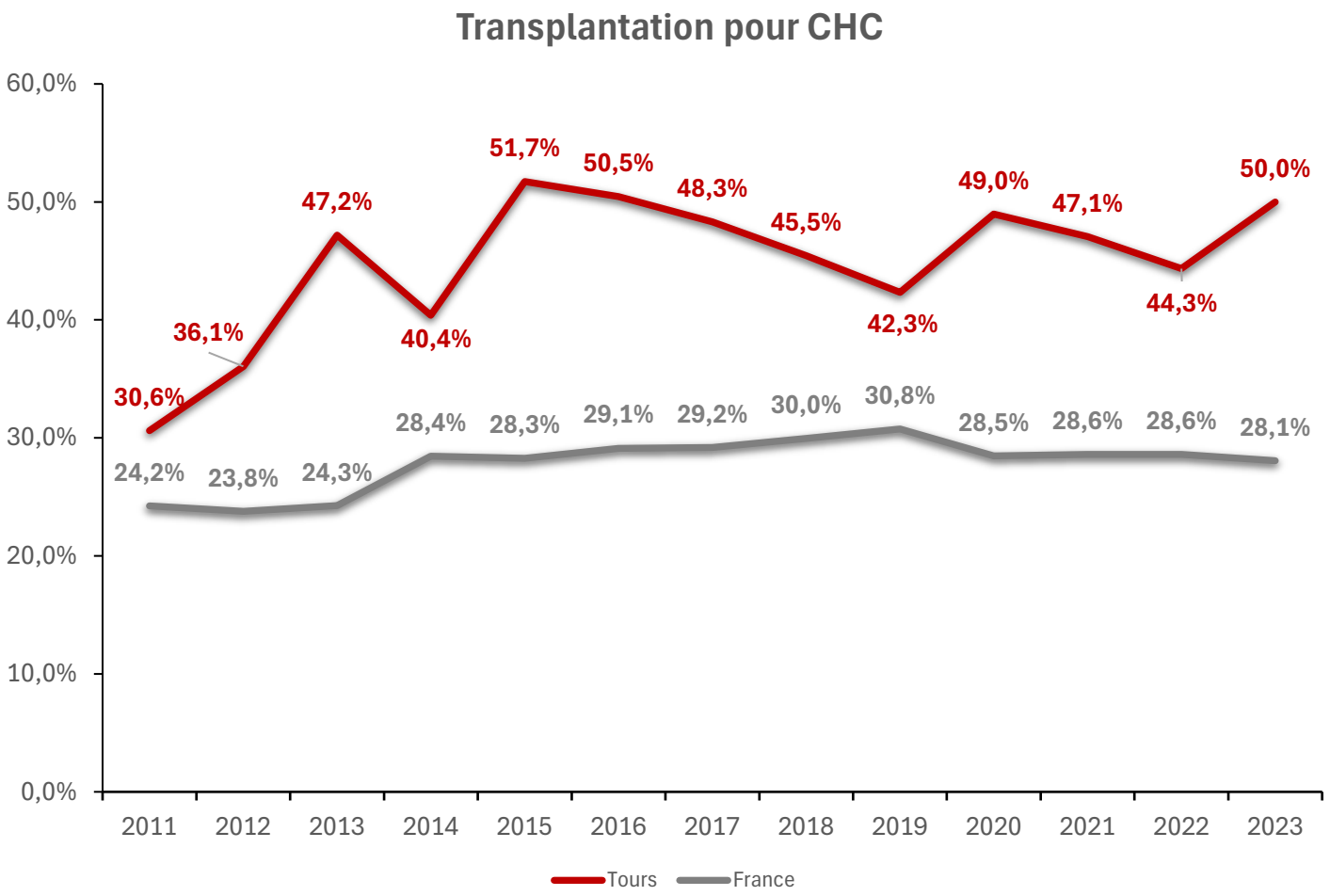
A Tours en 2023



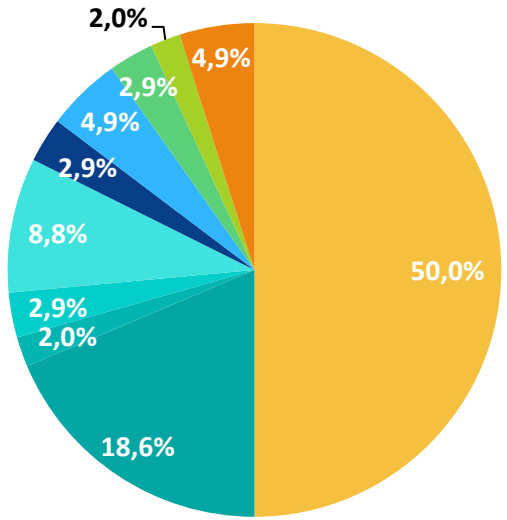
En France en 2023



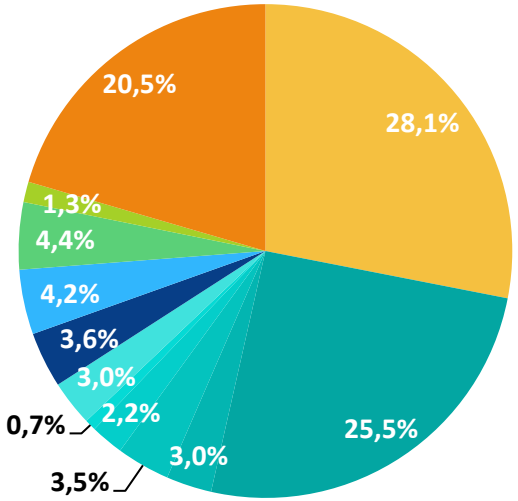
Indications de transplantation hépatique



A Tours en 2023

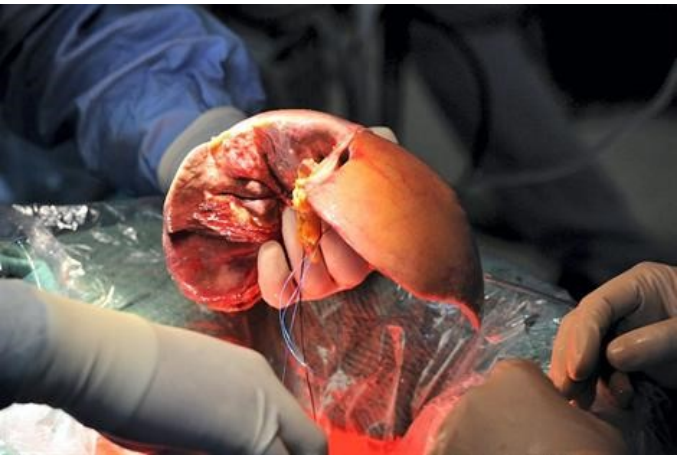


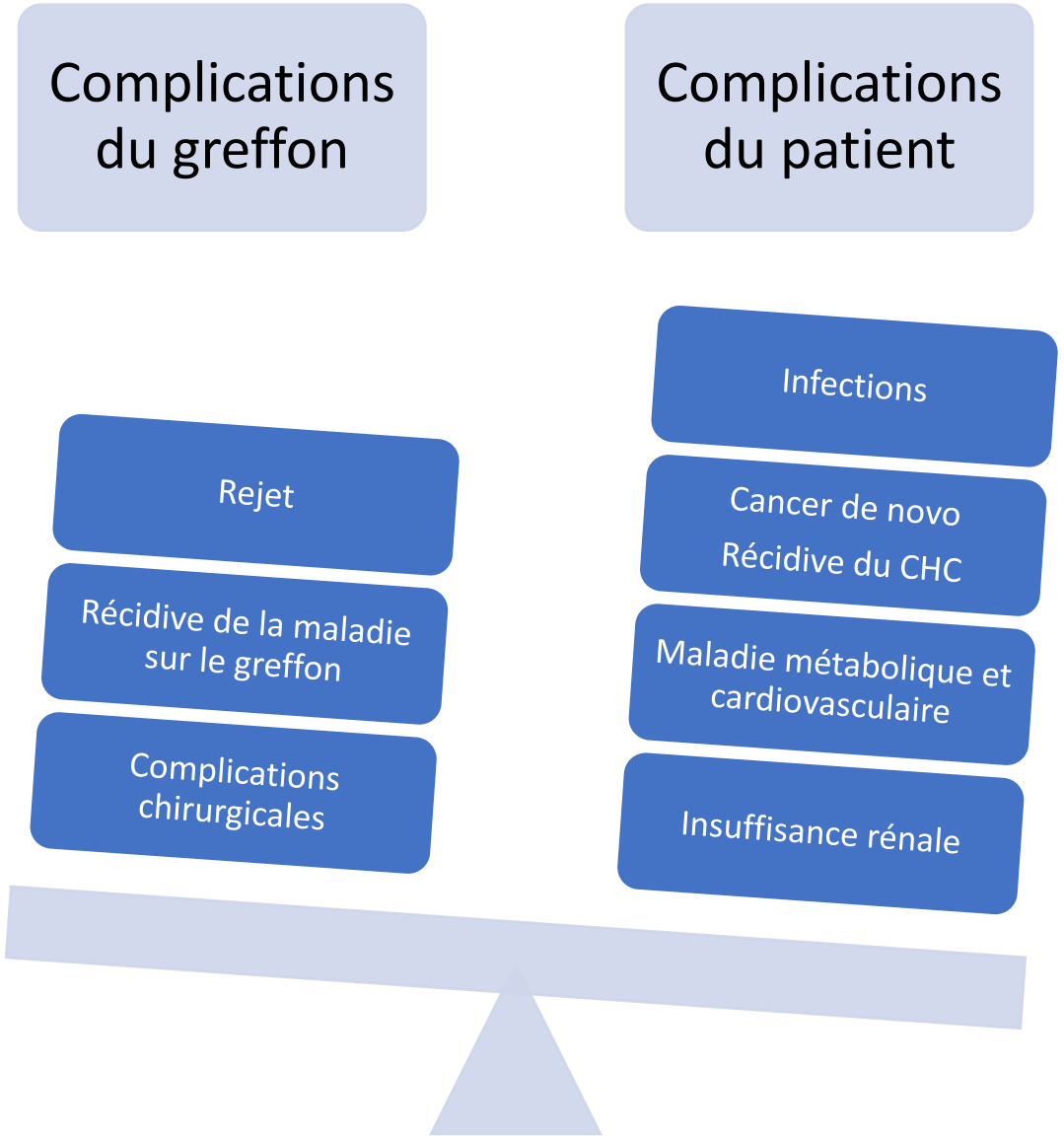
En France en 2023



- Carcinome hépatocellulaire
- Cirrhose alcoolique
- Cirrhose auto-immune
- Cirrhose d'origine biliaire
- Cirrhose post-hépatite B ou B+D
- Cirrhose post-hépatite C
- Autre cause de cirrhose
- Hépatite fulminante
- Cholangite sclérosante
- Retransplantation élective
- Retransplantation en urgence
- Autres pathologies

Les gardiens d'un jardin précieux et secret

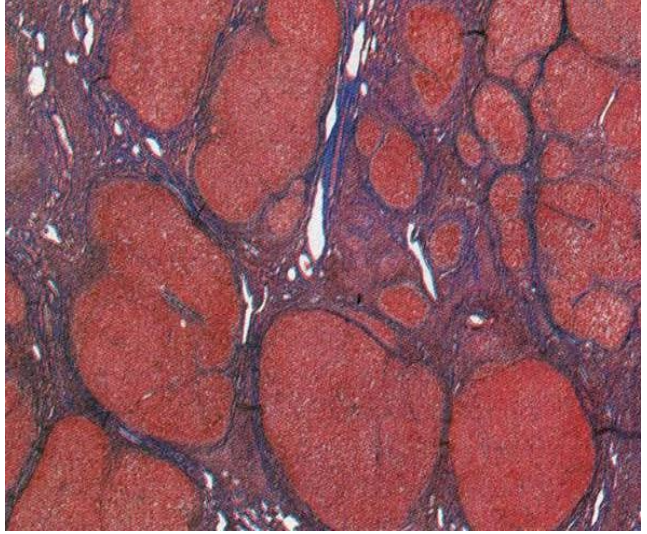


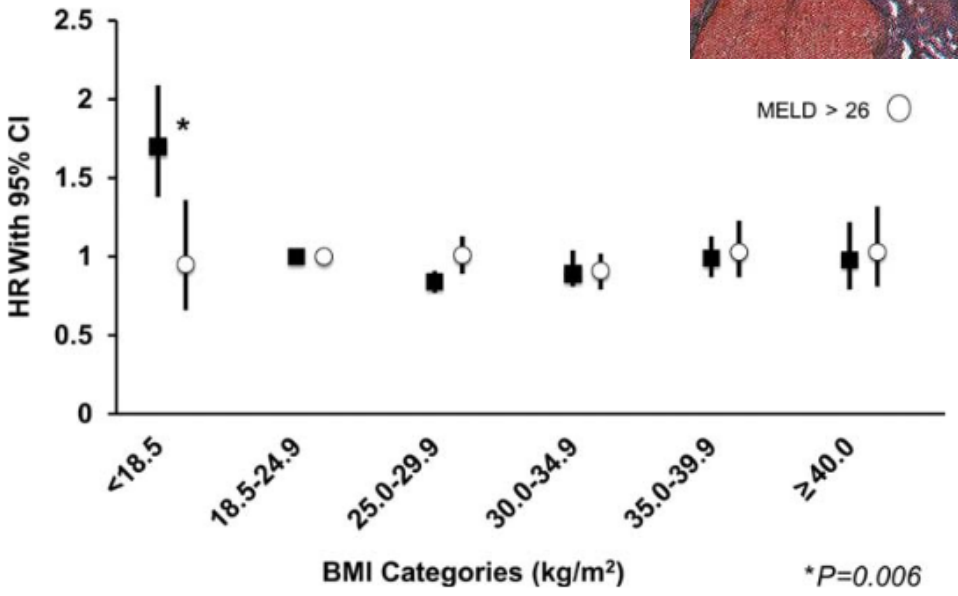


La MASH
Le CHC

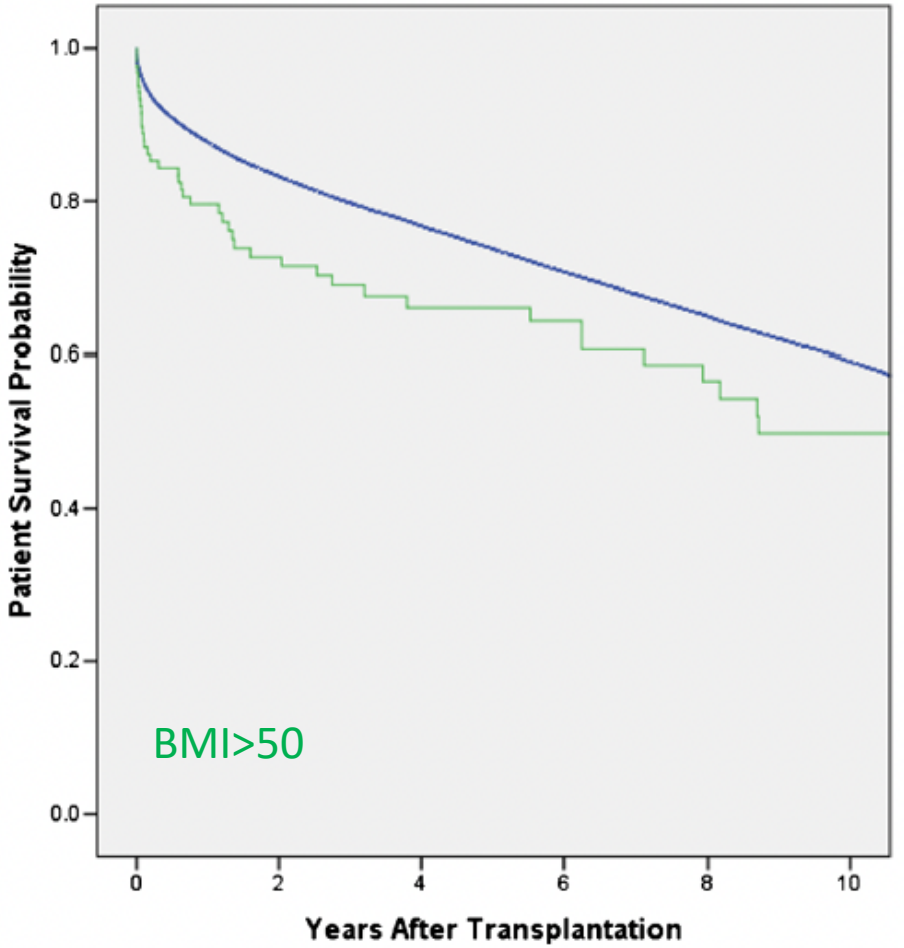
Scientific Registry of Transplant Recipients (2002-2019, n=168,441)

MASH et TH





Risk of patient death at 1 year after LT, stratified by BMI category and by the population 75th percentile for MELD score (MELD score = 26).



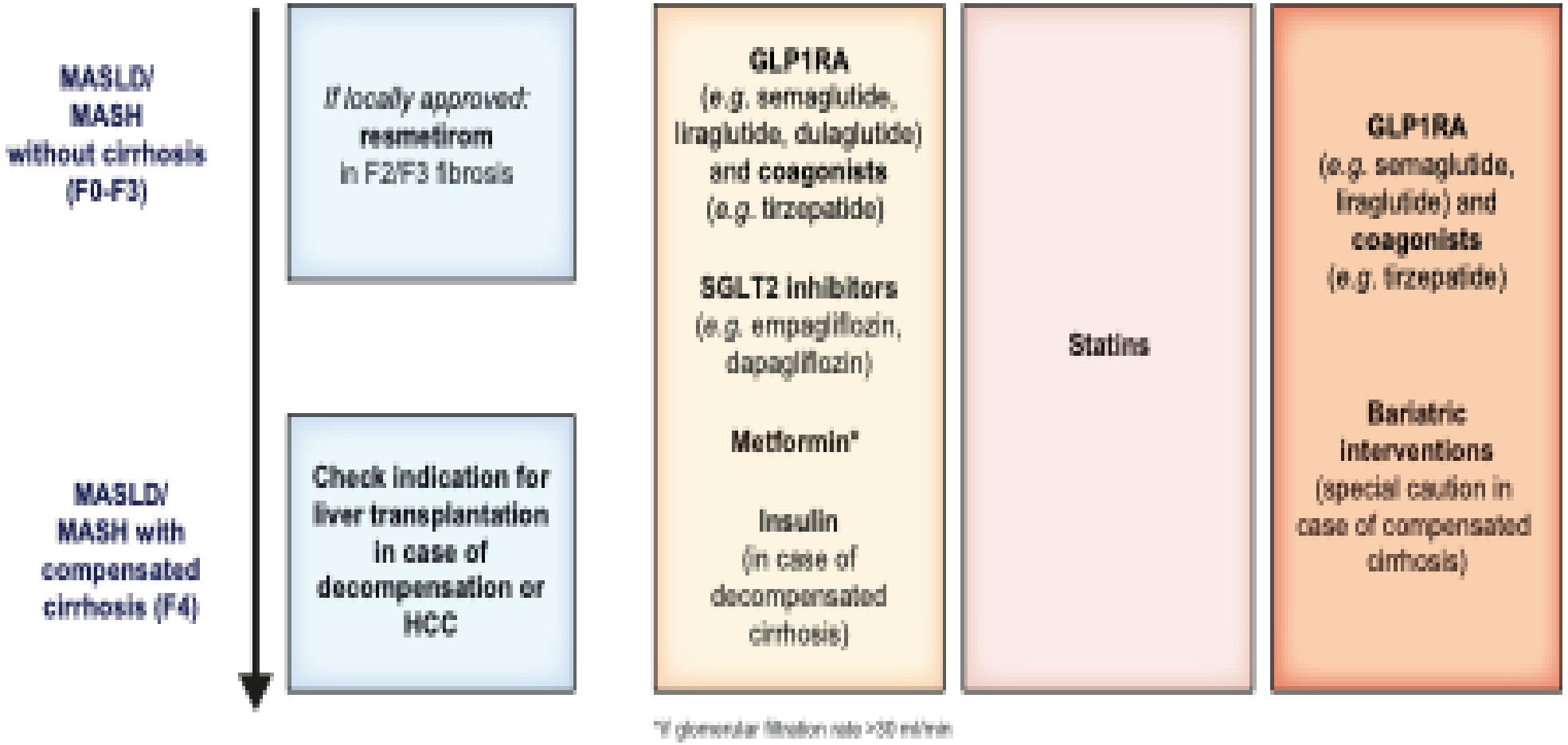
Bambha KM. Liver Transpl 2015. Alvarez, J. J Gastrointest Surg. 2016

JOURNAL OF HEPATOLOGY

EASL–EASD–EASO Clinical Practice Guidelines on the management of metabolic dysfunction-associated steatotic liver disease (MASLD)☆

2024

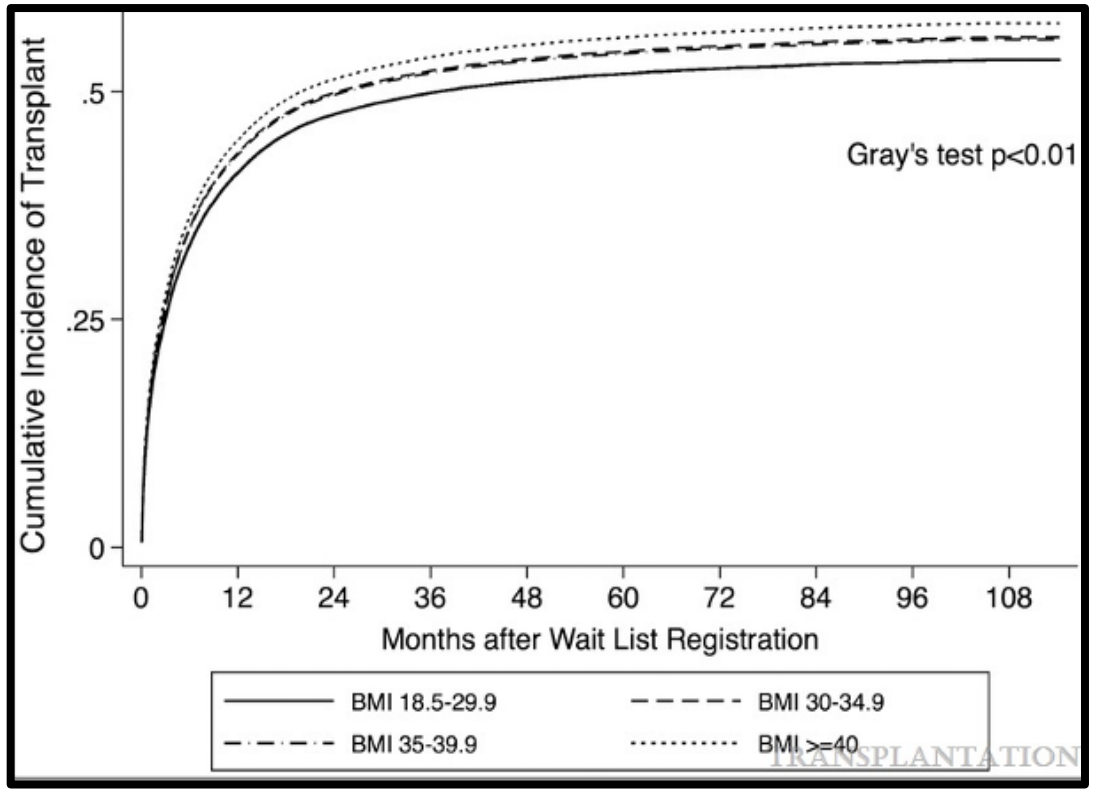
European Association for the Study of the Liver (EASL)*, European Association for the Study of Diabetes (EASD), European Association for the Study of Obesity (EASO)

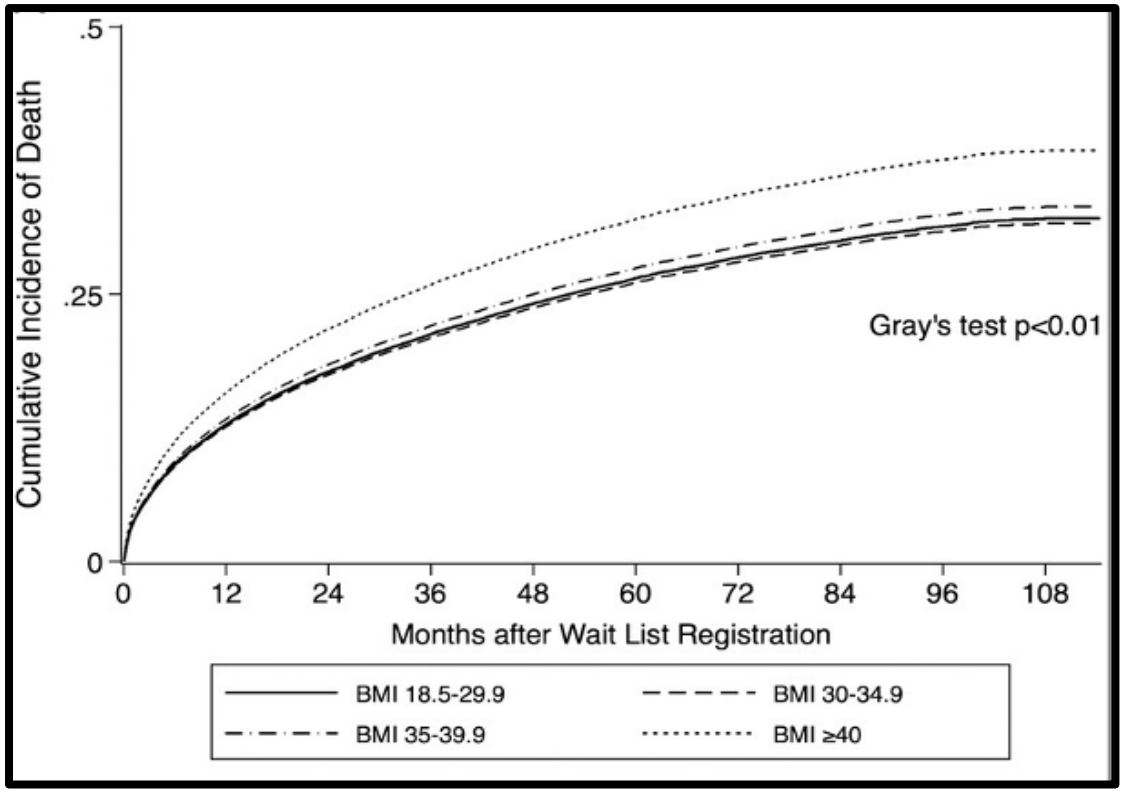


*If glomerular filtration rate >30 ml/min

Mais attente plus longue et TH moins fréquente

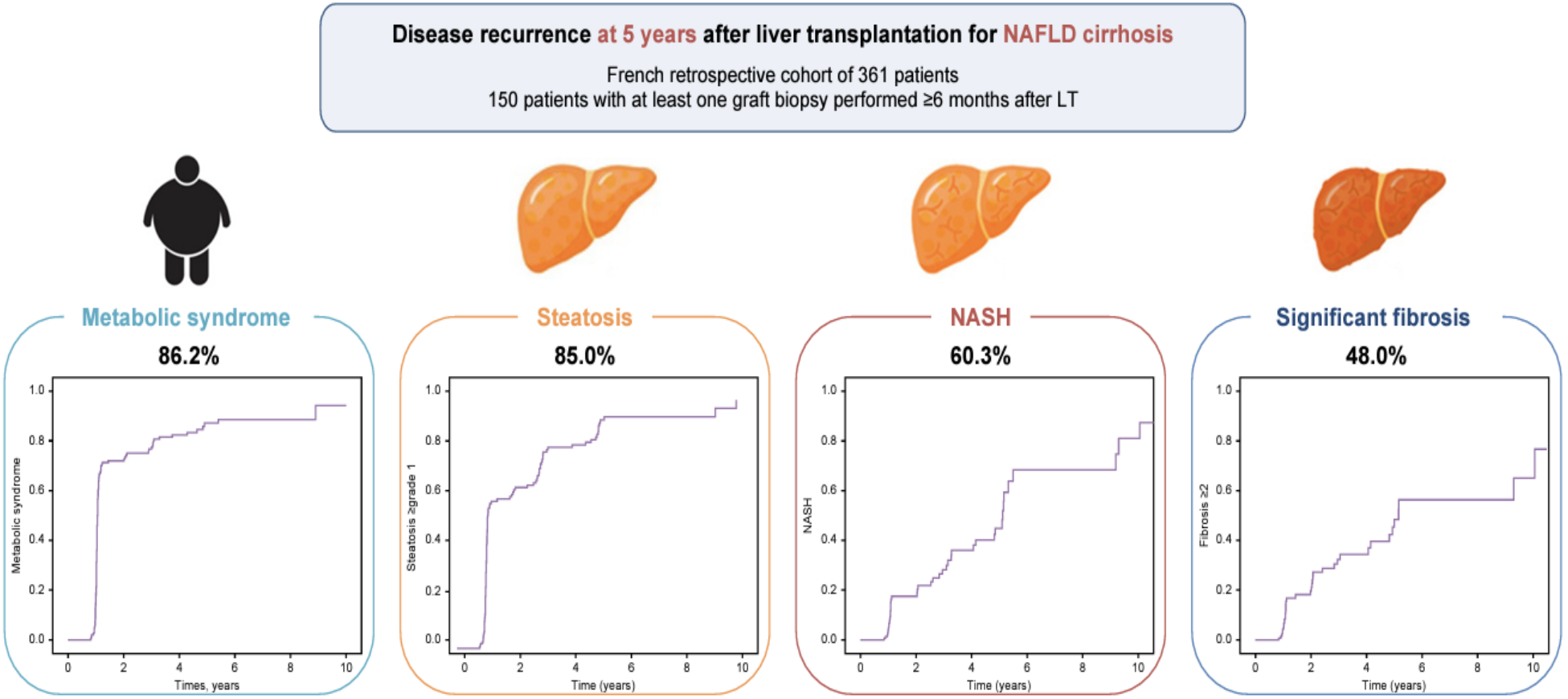
UNOS, March 2005 to Sept 2014, n=80,221





Schlansky, B. Transplantation 2016.

Récidive de la MASH post TH



Villeret, F. J Hep Reports 2023.

Traiter et prévenir la récidive de la MASH de Daniel

Life style

- Nutrition
- Exercise

Bariatric surgery

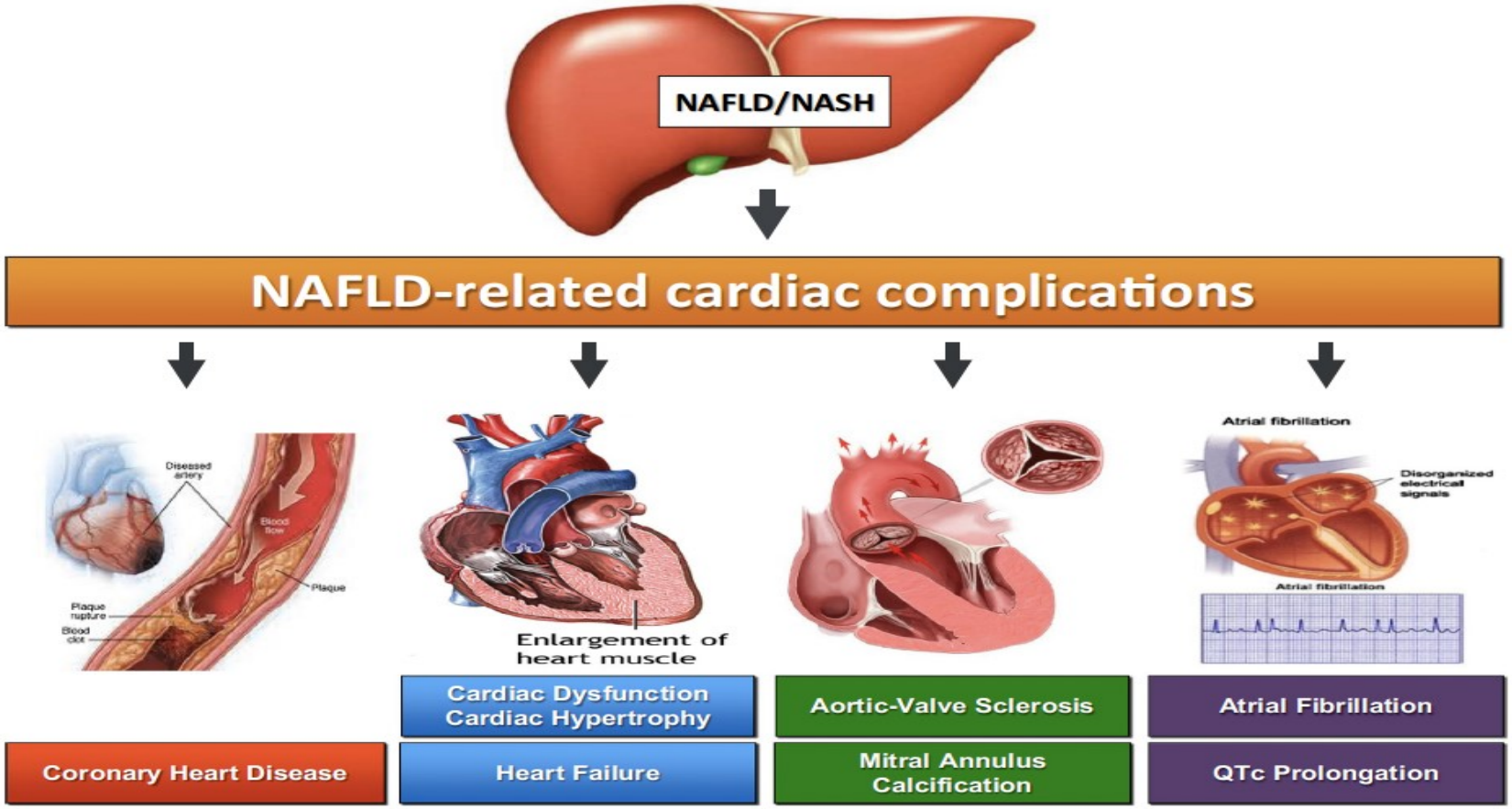
- TimLife style
  - Nutrition
  - Exercise
- Endoscopic alternatives

Pharmacotherapy

- GLP-1, GIP agonists

Terrault N. Liver Transplantation 2023.

Et le cœur de Daniel?



Mantovani, M. Dig Dis Sci. 2016

International Liver Transplantation Consensus Statement on End-stage Liver Disease Due to Nonalcoholic Steatohepatitis and Liver Transplantation

Tsochatzis, Emmanuel MD, PhD[1]; Coilly, Audrey MD[2,3]; Nadalin, Silvio MD, FEBS[4]; Levistky, Josh MD, MS[5]; Tokat, Yaman MD[6]; Ghobrial, Mark MD, PhD[7]; Klinck, John MD, FRCA, FRCPC[8]; Berenguer, Marina MD[9,10]

Author Information

Transplantation 103(1):p 45-56, January 2019. | *DOI:* 10.1097/TP.0000000000002433

3—HOW SHOULD CV RISK BE ASSESSED IN THE NASH-CANDIDATE FOR LT? SHOULD THE ASSESSMENT DIFFER FROM THAT DONE IN OTHER ETIOLOGIES?

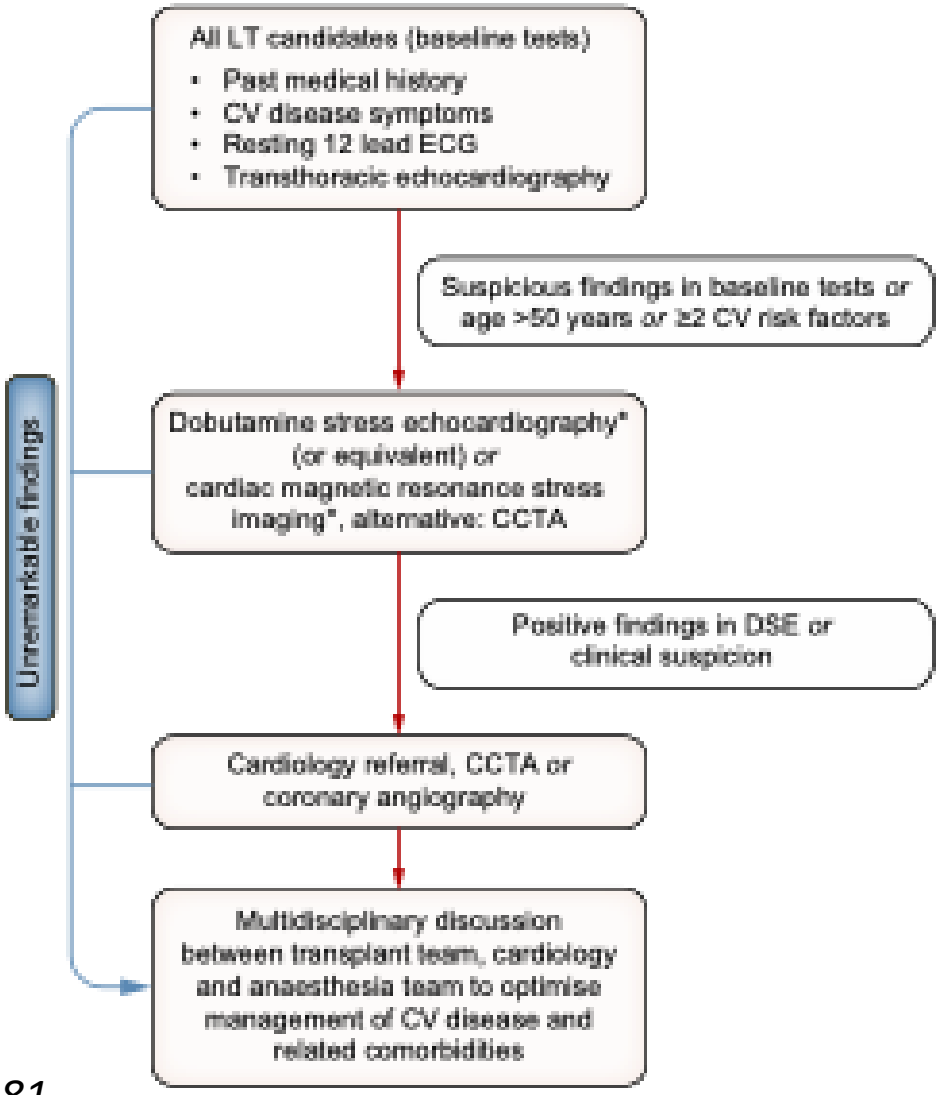
Recommendations

1- Liver transplant candidates with NASH should be considered at high risk of developing CV events before and after transplantation (quality of evidence, high; strength of recommendation, strong).

2- The accumulation of CV risk factors should be carefully assessed by a multidisciplinary team, which should include a cardiologist and anesthesiologist with special interest in transplantation (quality of evidence, low; strength of recommendation, strong).

3- Although NASH is considered an independent risk factor for CV events similar to other traditional risk factors, there is not enough evidence to support a different approach to the pre-LT CV assessment. (quality of evidence, moderate; strength of recommendation, strong).

4- There is insufficient evidence to recommend a specific CV risk algorithm for NASH patients undergoing liver transplantation evaluation. The algorithm, and particularly the place of stress tests, will be determined in part by local expertise (quality of evidence, moderate; strength of recommendation, moderate IIa)



J Hepatol, sept 2024, 81

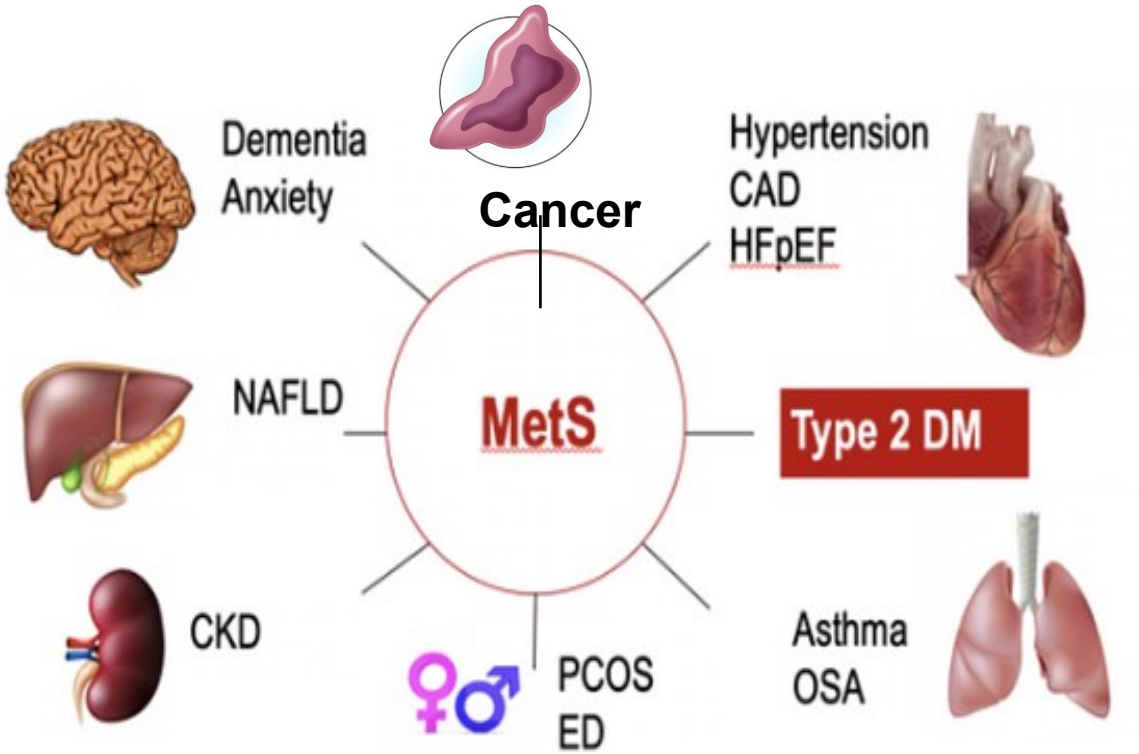
Frailty/Sarcopénie

Methods	Components	Clinical accessibility	Includes subjective variables	Cut-offs associated with clinical outcomes
Sarcopenia				
CT scan	Skeletal muscle index (SMI): total muscle area at the 3rd lumbar vertebrae/height^2	Easy though the analysis requires a dedicated software	No	SMI <50 cm^2/m^2 in male and <39 cm^2/m^2 in female
Frailty				
Activities of daily living	Questionnaire-based; assesses the individual's difficulty in performing daily self-care activities	Easy	Yes*	12
Karnofsky performance status	Incorporates activities of daily living + limitations one may experience with chronic diseases as well as cognitive decline.	Easy	Yes*	B
Clinical frailty scale	Same as Karnofsky performance status	Easy	Yes*	>4
Fried frailty phenotype°	Weight loss, self-reported exhaustion, weakness, slow walking speed, decreased physical activity levels	Moderate	Yes	≥3
Gait speed test	Measures gait speed (4 or 10 m walk)	Easy	No	≤0.8 m/s
6-minute walk test	Measure the distance an individual is capable of walking on a flat in 6 min.	Easy	No	<250 m
Cardiopulmonary exercise testing	Objectively assesses cardiovascular, pulmonary, and skeletal muscle systems capacity during exercise (maximal O_2 uptake).	Poor/very poor	No	<60%
Short physical performance battery	Assesses lower limb function via: standing balance, gait speed, continuous chair stands	Easy	No	<10
Liver frailty index^	Grip strength, chair stands, balance testing	Moderate	No	≥4.5

A multicentre US frailty cohort assessed the prevalence of physical frailty was similar in non-obese, class I obese, and class II obese candidates at 25.4%, 26.0%, and 29.2%, respectively (p=0.57)

Tandon P. J Hepatol. 2023. Haugen CE. Ann Surg. 2020.

MASH et TH : un couple infernal



Risque de décès par complications cardio Vx la première année et en péri opératoire

Obésité 21% à, 3 ans post TH

Pas de différence de survie du greffon et du receveur à long terme

Discuter la chirurgie bariatrique

Tsochatzis EA, Watt KD, VanWagner LB, et al. Evaluation of recipients with significant comorbidity - patients with cardiovascular disease. J Hepatol 2023;78(6):1089–1104.

Younossi, ZM. Hepatology. 2016

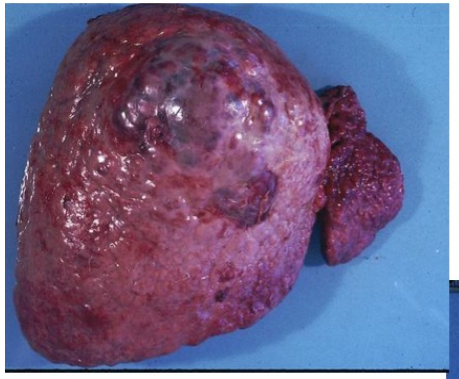
Table 11. Screening and management for comorbidities in individuals with MASLD before liver transplantation. Modified from.[488,500]

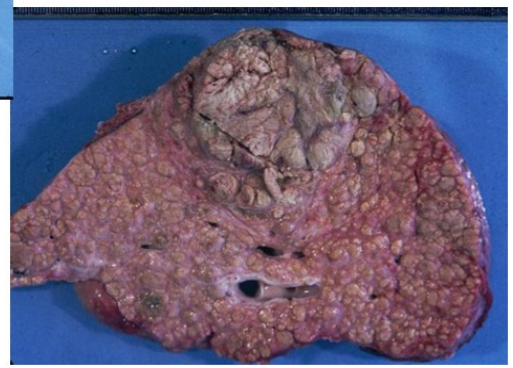
Condition	Recommendation
Type 2 diabetes	• Screen for impaired fasting glucose (IFG) or glucose tolerance (IGT) and/or T2D (OGTT, HbA1c) • Achieve good glycaemic control before LT • Preferentially use weight-lowering (e.g. SGLT2 inhibitors, GLP1RA) or weight-neutral (e.g. metformin) glucose-lowering medication, considering risk of other diabetes complications, if liver and/or renal function allow this
Nutrition	• Assess nutritional status before LT • Assess alcohol consumption • Healthy diet, physical exercise and lifestyle modification (including weight reduction in individuals with obesity) represent pillars in pre-LT management
Cardiovascular	• Pre-LT cardiovascular risk stratification is mandatory • Risk-adapted algorithm of cardiac work-up should be followed (see Fig. 5) • LT candidates with cardiovascular risk should be managed with goal-directed medical management (e.g. statins, anti-platelet agents, beta blockers, RAAS blockers), based on the stage of cirrhosis and renal function
Kidney	• Kidney function should be adequately monitored before LT • Comedications need to be adjusted (or replaced) dependent on kidney function
Malignancies	• Screening for pre-LT malignancies should follow the same protocols applied to individuals with non-MASLD related cirrhosis (including gastrointestinal and genital cancers)

GLP1RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated haemoglobin; LT, liver transplantation; MASLD, metabolic dysfunction-associated steatotic liver disease; OGTT, oral glucose tolerance test; RAAS, renin-angiotensin-aldosterone system; SGLT2, sodium-glucose cotransporter-2.

Et le CHC de Daniel?

- Downstaging pré TH
- Score Foie sur liste d'attente
- Penser à la sélection optimale du candidat





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

May 2023
Hepatology 78

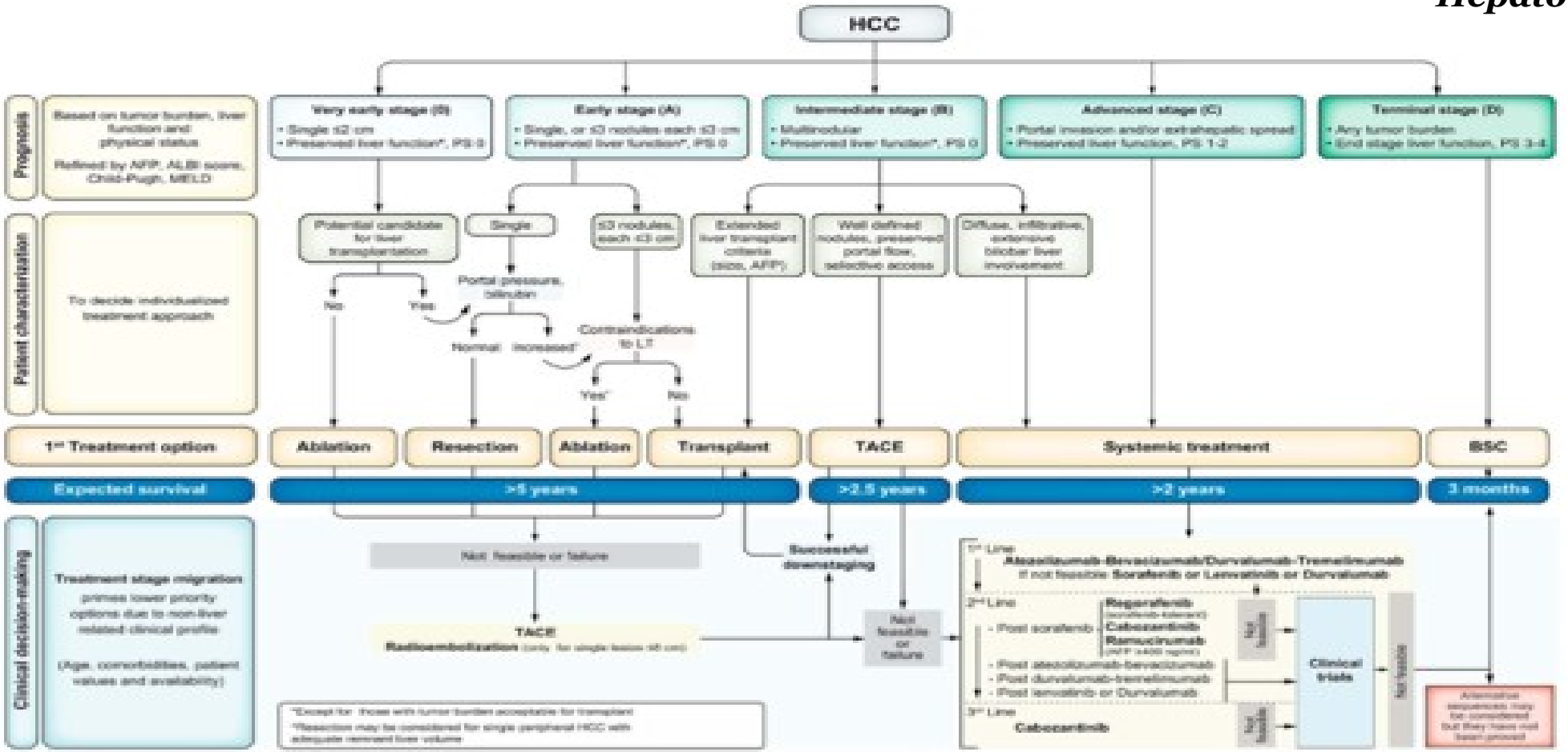
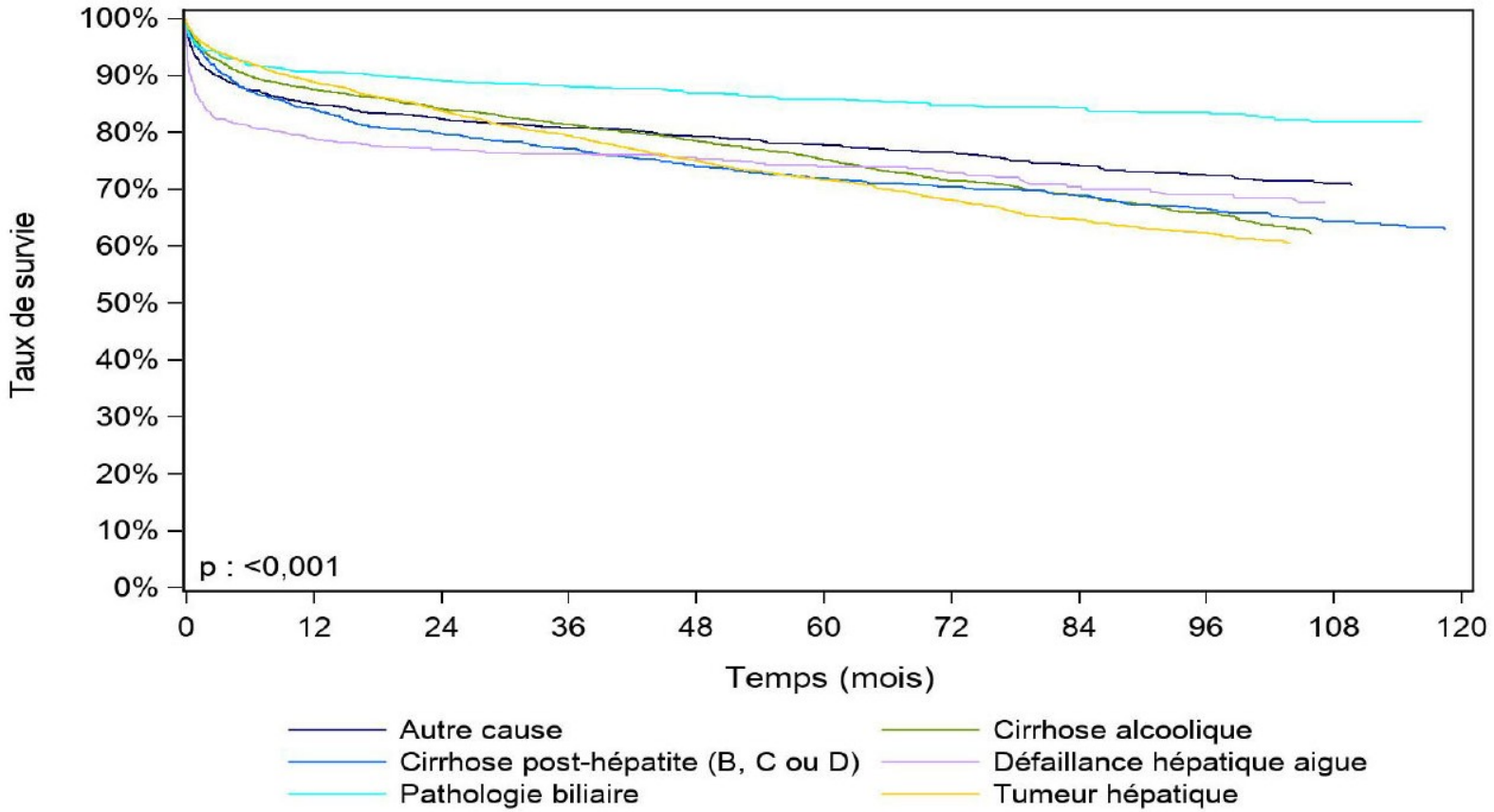


FIGURE 9 Updated Barcelona Clinic Liver Cancer Staging System 2022. Abbreviations: AFP, alpha fetoprotein; ALBI, albumin-bilirubin; BSC, best supportive care; ECOG-PS, Eastern Cooperative Oncology Group-performance status; HCC, hepatocellular carcinoma; LT, liver transplant; MELD, Model for End-Stage Liver Disease; TACE, transarterial chemoembolization. Reprinted with permission from Reig et al.[147]

Transplantation hépatique pour CHC



Survie à 5 ans
72,5%

Récidive du CHC
6 à 18%

Agence de la Biomédecine 2007-2018, Berenguer Transplantation 2018

GREFFE HEPATIQUE ET CHC

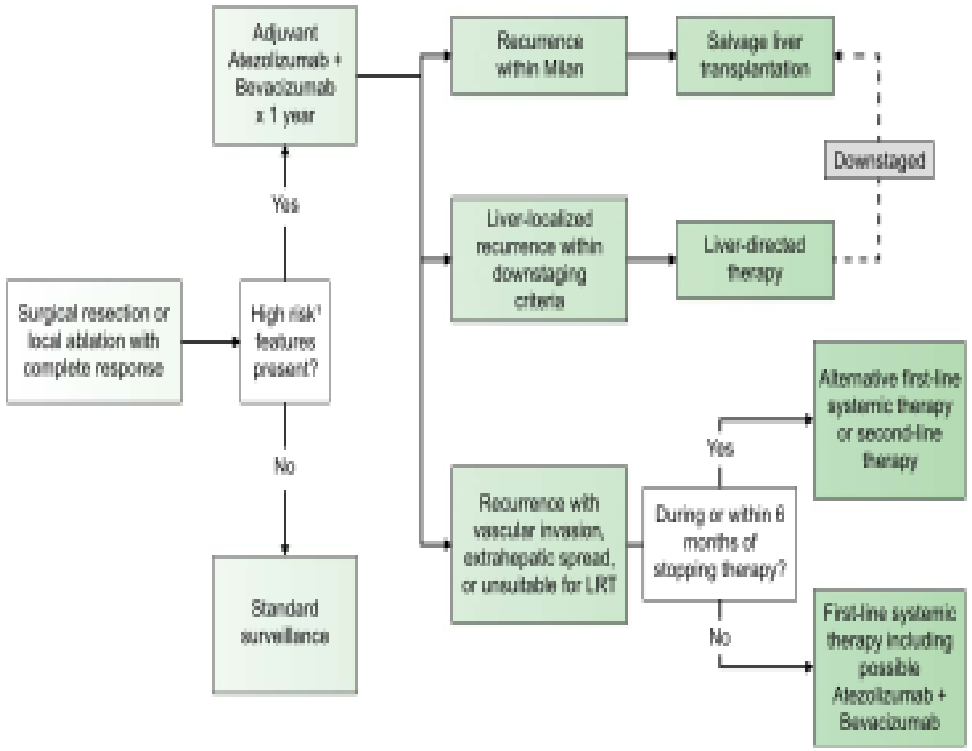


TABLE 3 Proposed expanded criteria for liver transplantation and associated outcomes

Examples of expanded criteria[a]		Post-transplant survival
UCSF criteria[207]	One tumor ≤ 6.5 cm or 2–3 tumors, each ≤ 4.5 cm, with total tumor volume ≤ 8 cm	81% 5-year survival
Total tumor volume < 115 cm[208]	Sum of volume for each tumor ≤ 115 cm^3	75% 4-year survival
Up-to-seven criteria[209]	Diameter or largest tumor (cm) + number of tumors ≤ 7	71% 5-year survival
Extended Toronto criteria[210]	Biopsy demonstrating well-to-moderate differentiation for patients beyond Milan criteria and ECOG performance status 0–1	68% 5-year survival
Kyoto criteria[211]	Number or tumors ≤ 10, maximum diameter of each tumor ≤ 5 cm, and serum DCP ≤ 400 mAU/ml	65% 5-year survival

Abbreviations: DCP, des-gamma carboxyprothrombin; ECOG, Eastern Cooperative Oncology Group; UCSF, University of California, San Francisco.
[a]All criteria include absence of vascular invasion and metastatic spread.

FIGURE 11 Management of patients with recurrence during or after adjuvant therapy. [1]High-risk features include tumor size > 5 cm, more than 3 tumors, microvascular or macrovascular invasion, and poor tumor differentiation.

TH et immunoTTT pré TH

Table 1. Utilization of ICPI in the pre-transplant setting of patients with HCC. Neoadjuvant intervention is primarily to "bridge" into designated transplant criteria. Abbreviations: M: male, F: female, UK: unknown, IST: immunosuppressive, ICPI: immune checkpoint inhibitor, HCC: hepatocellular carcinoma.

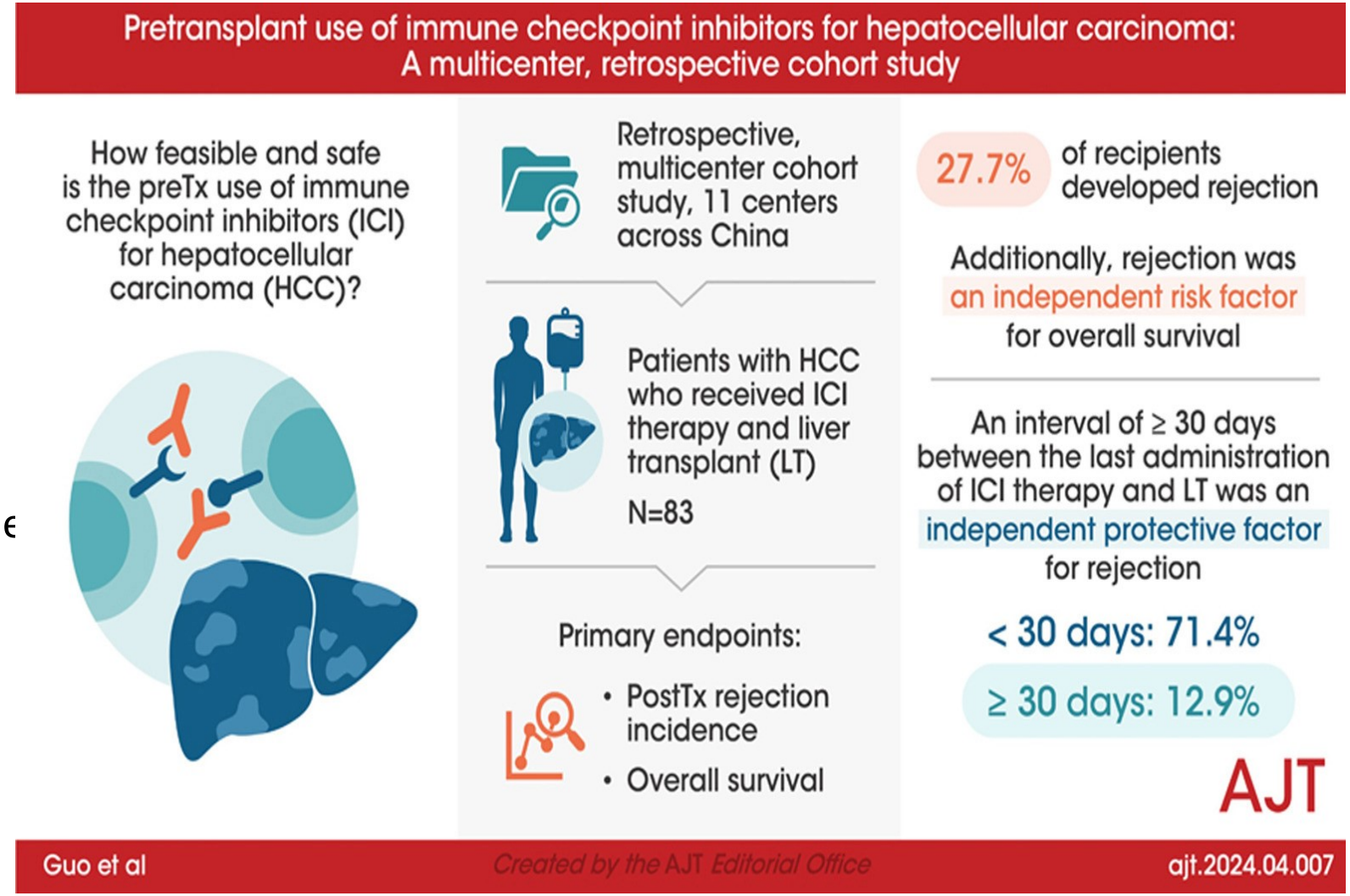
Age/Sex	ICPIs and Cycles	Timing Intervals btw ICPIs to LT	IST	Outcomes	Ref
14 M	Pembrolizumab 3	4.6 Months	Sirolimus Tacrolimus	No rejection	Kang et al. [7]
68 M	Nivolumab UK	10 Months	UK	No rejection	Peterson et al. [8]
60 M	Nivolumab 17	1.2 Months	Tacrolimus	No rejection	Dehghan et al. [9]
47 F	Nivolumab 1	4 Months	Tacrolimus Mycophenolate Steroid	Graft rejection	Chen, Z et al. [10]
39 M	Toripalimab 10 Lenvatinib UK	3.1 Months	Tacrolimus Methylprednisolone	Graft rejection	Chen, GH et al. [11]
64 M	Atezolizumab/Bevacizumab 6	4 months	Mycophenolate Tacrolimus	No rejection	Abdelrahim et al. [12]
61 M	Nivolumab 42	1 month	Mycophenolate Tacrolimus	No rejection	Abdelrahim et al. [12]
58 M	Lenvatinib 15 Atezolizumab/Bevacizumab 3	6 months	Mycophenolate Tacrolimus	No rejection	Abdelrahim et al. [12]
61 M	Nivolumab 1 Atezolizumab/Bevacizumab 3	2 months	Mycophenolate Tacrolimus Everolimus	No rejection	Abdelrahim et al. [12]
68 M	Atezolizumab/Bevacizumab 24 Lenvatinib 10	36 months	Mycophenolate Tacrolimus	No rejection	Abdelrahim et al. [12]
59 M	Nivolumab/Ipilimumab 1	41 months	Prednisone Tacrolimus Mycophenolate	No rejection	Abdelrahim et al. [12]

Mazzaferro et al, Current oncology 2024

Pretransplant use of immune checkpoint inhibitors for hepatocellular carcinoma: A multicenter, retrospective cohort study

Zhiyong Guo et al, Am J of Transplant, Oct 2024

- 83 patients
- Suivi médian post TH 8,1 mois
- rejet : FDR indépendant pour la survie



Prédiction de la récidive du CHC après TH

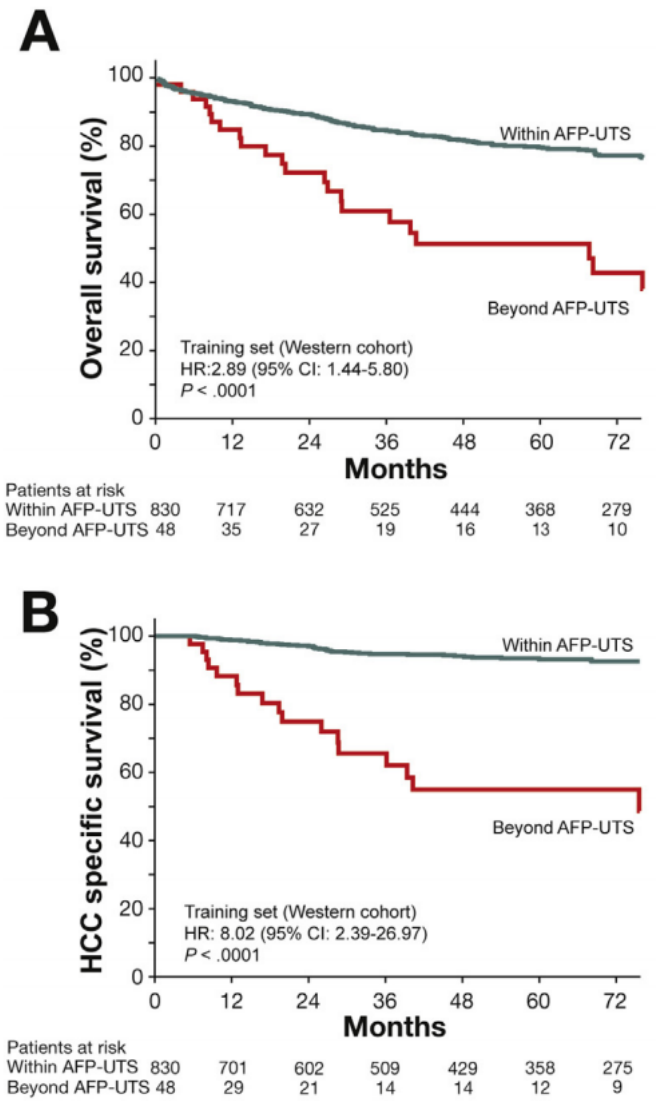
Facteurs pré-TH associés à la récidive de CHC	
Radiologie	**Taille de la plus grosse lésion** **Nombre de nodules**
Histologie	Différenciation Nodules satellites Invasion microvasculaire
Biologie	**AFP (100-1000 ng/ml)** Neutrophiles / lymphocytes (NLR)

Duvoux Gastroenterology 2012,Mazzafero Gastroenterology 2018, Mehta JAMA oncol 2017, Halazun Ann Surg 2017

Prédiction *de la survie* après TH pour CHC

Metroticket 2.0

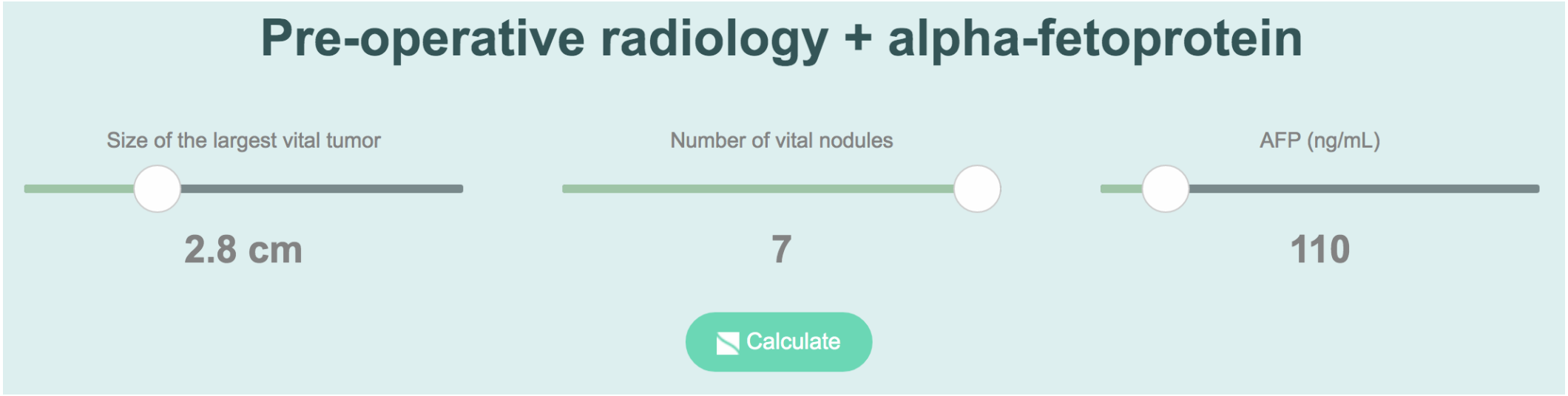
Dernière évaluation pré-TH		AFP avant la TH
Taille du plus gros nodule + nombre de nodules ≤7	Et	< 200 ng/ml
Taille du plus gros nodule + nombre de nodules≤ 5	Et	200-400 ng/ml
Taille du plus gros nodule + nombre de nodules ≤4	Et	400-1000 ng/ml



Mazzafero Gastroenterology 2018

Prédiction *de la survie* après TH pour CHC

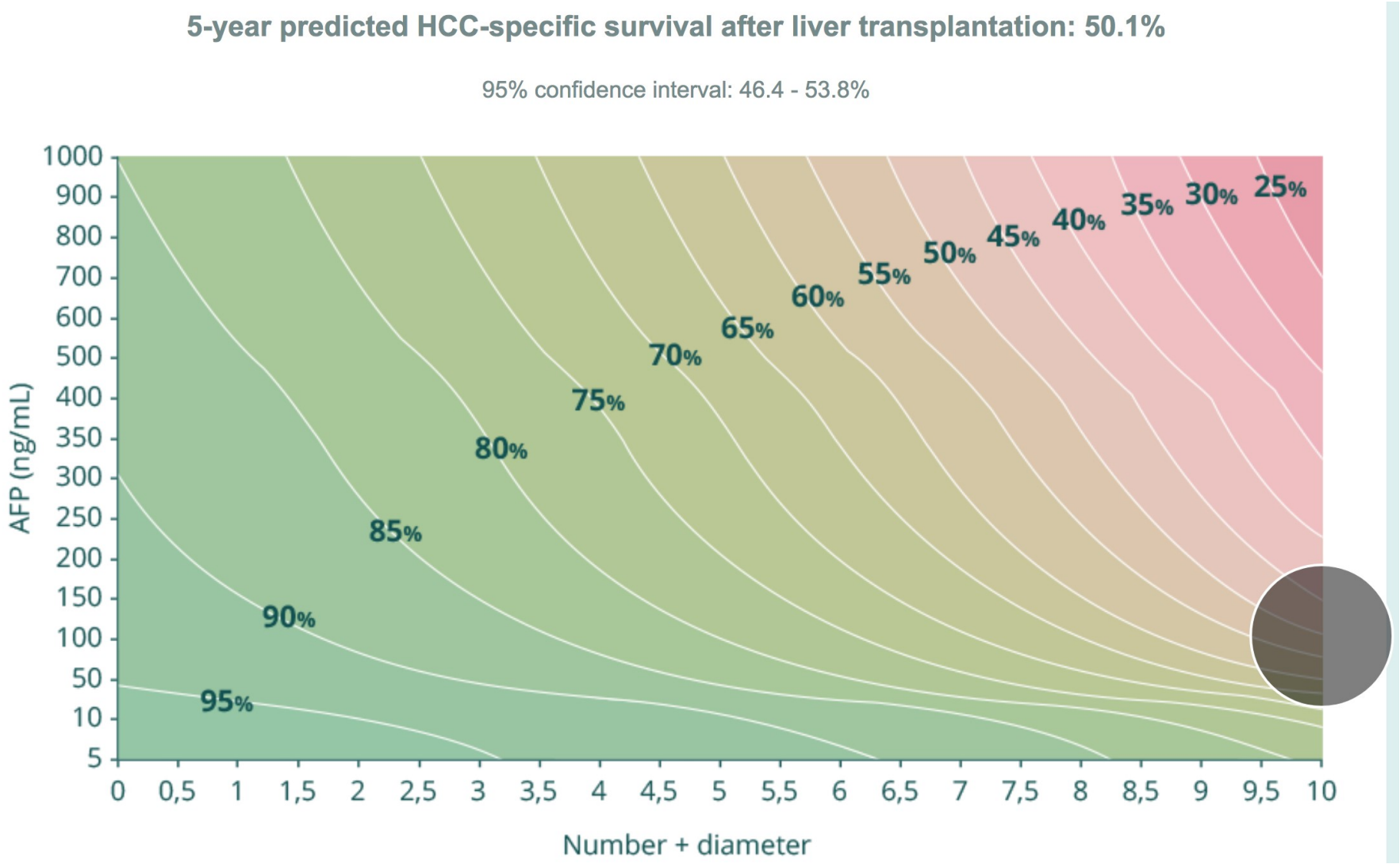
Metroticket Calculator www.hcc-olt-metroticket.org.



Mazzafero Gastroenterology 2018

Prédiction *de la survie* après TH pour CHC

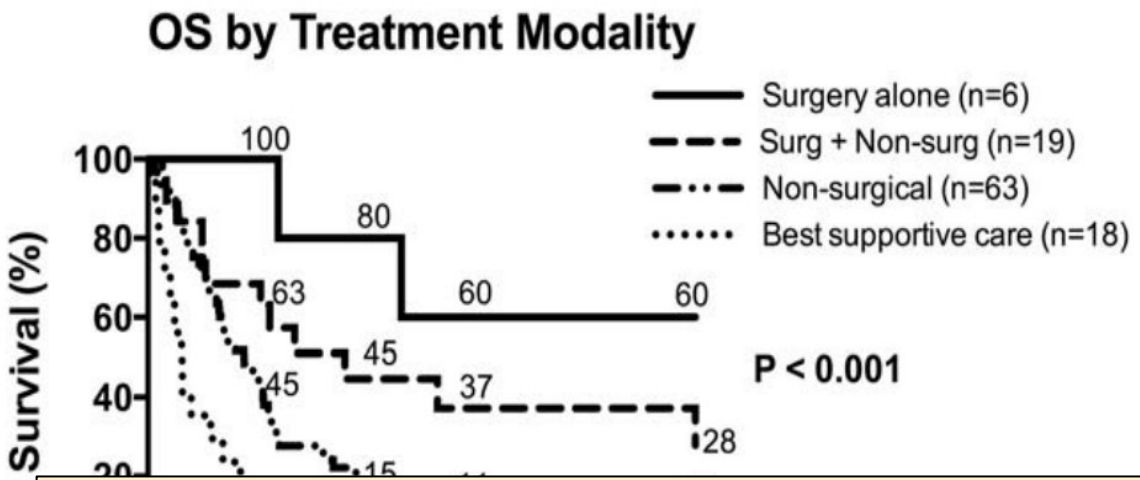
Metroticket Calculator www.hcc-olt-metroticket.org.



Mazzafero Gastroenterology 2018

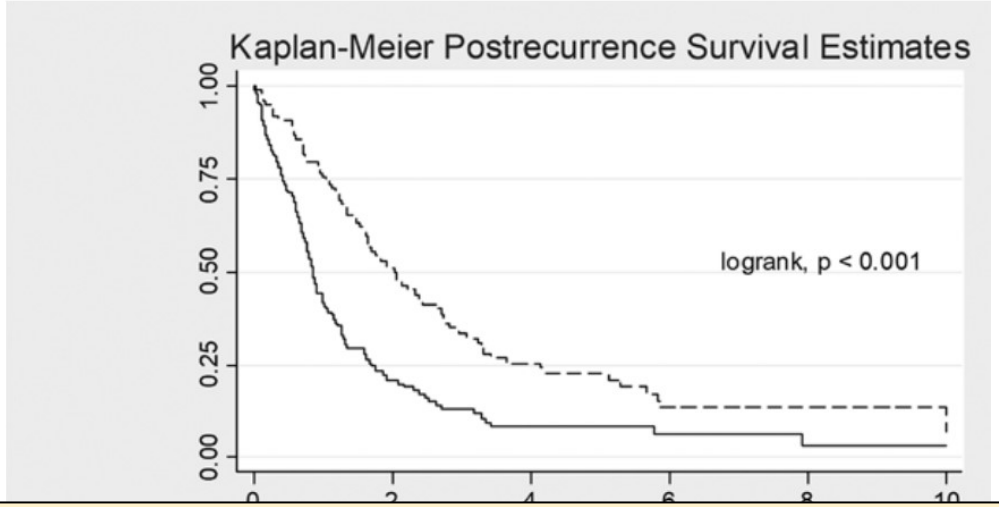
Pronostic de la récidive de CHC après TH

857 TH pour CHC (1984-2017), 106 récidives



Bodzin Annals of Surgery 2017

223 patients atteints de récidive de CHC post TH, Délai TH-récidive 13.3 mois



Lee Transplantation 2020

Un suivi rapproché après la TH est recommandé
pour détecter une récidive accessible à un traitement chirurgical / ablation
Scanner thoraco-abdominal + AFP tous les 6 mois pendant 3 ans post TH

Récidive CHC à l'ère du score AFP

Facteurs de risque de récidive	14,3%
Délai récidive-décès (mois)	10.6 (3.8–20.2)
Tabagisme actif Progression du CHC pré TH Nombre de traitements d'attente reçus Caractère progressif du CHC pré TH Taux maximal d'AFP en pré TH Nodules satellites Sous-type macro trabéculaire massif Tumeur mixte hépato cholangio K	

Paramètre	Nombre de points
Taille de la plus grosse tumeur (cm)	
≤ 3	0
]3 – 6]	1
> 6	4
Nombre de tumeurs	
≤ 3	0
> 4	2
Alpha-fœtoprotéine (ng/mL)	
≤ 100	0
]100 – 1000]	2
> 1000	3

Risque de récidive post-TH

≤ 2 : faible > 2 : élevé

Marjary et al, 2022

La récidive du CHC post TH : grave et fréquent

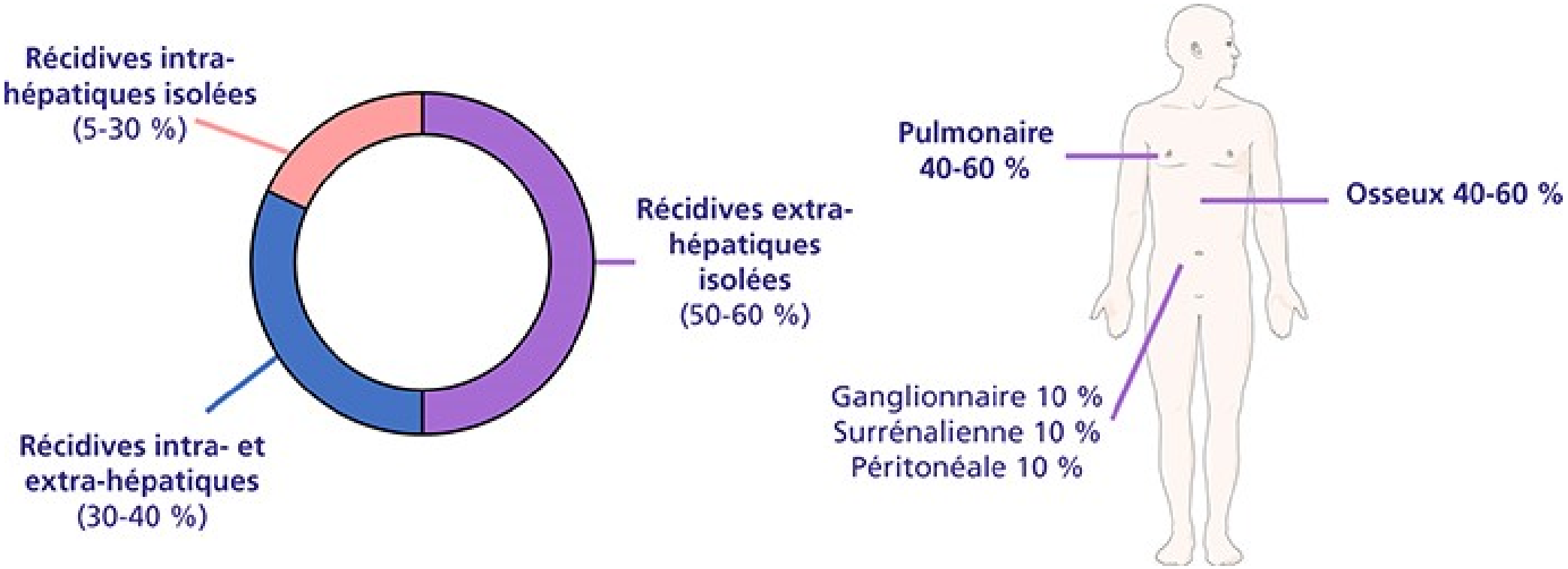
- 15%
- 255 patients étude rétrospective France 01/01/2018 -31/12/2021
  - Délai moyen 23 mois
  - Précoce < 6 mois: 12%
  - Tardive > 5 ans : 18%
- Extra hépatiques pures 60%, 59% unifocales
- SG à 10 ans 60% si TTT curatif et 6% si TTT palliatif
- Stratégie non curative
- Le type d'immunosuppression : aucun impact sur la survie
- Facteurs de SG
  - AFP > 100 ng/ml
  - Court délai de récidive
  - Site et nombre de sites tumoraux

- **Optimiser la surveillance post TH même tardive > 5 ans pour permettre un TTT curatif**

Ningarhari Massih, Lille, Natural history and management of recurrent hepatocellular carcinoma after liver transplantation: a multicenter nationwide study 2023

Récidives CHC post TH

Médiane de survie globale post récidive 12%
Récidive surtout extra hépatique
Délai TH récidive facteur majeur

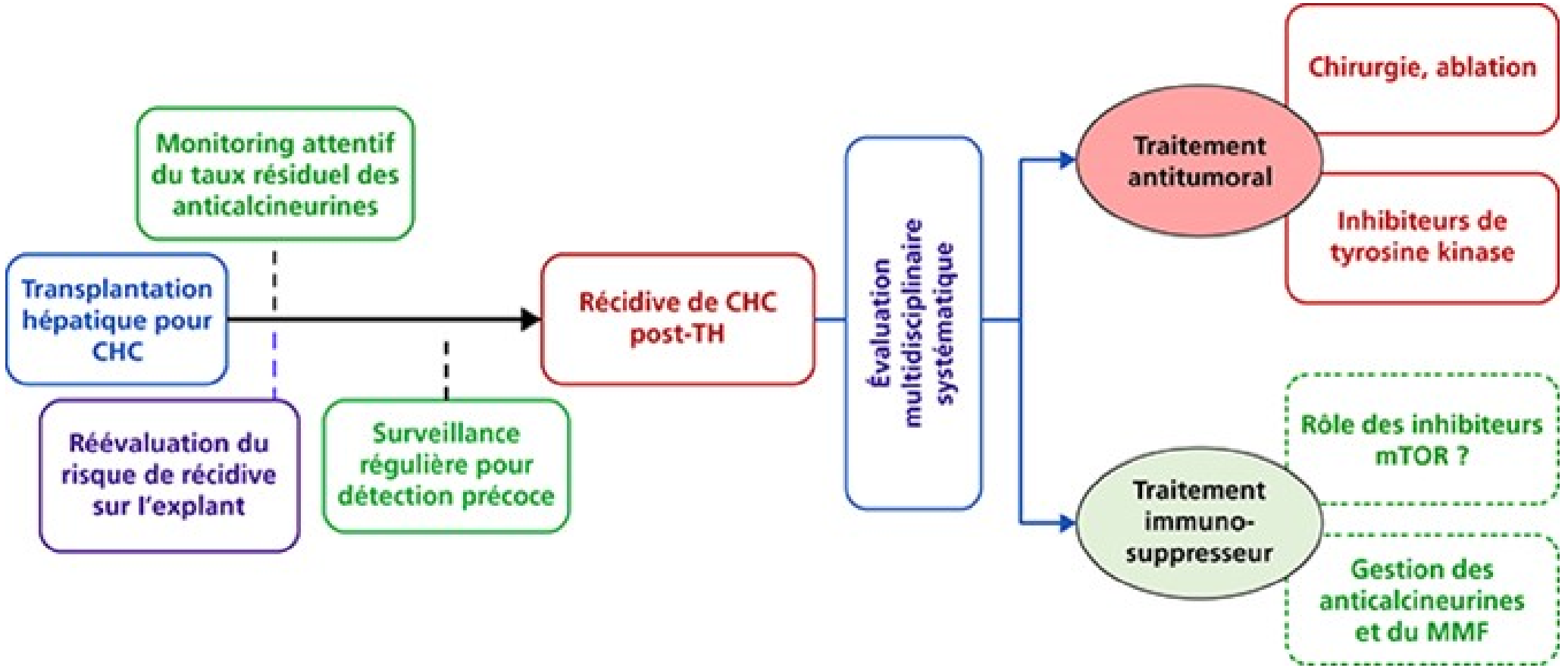


Récidives tardives > 5 ans : profil métabolique pré TH, récidive de l'hépatopathie, intra hépatiques, accessibles à un TTT curatif, meilleure survie

Figure 1
Localisations tumorales à la première récidive de carcinome hépatocellulaire après transplantation hépatique.

Ningarhari et al, 2023, JLE

Stratégies



Immunothérapie : risque de rejet et mortalité

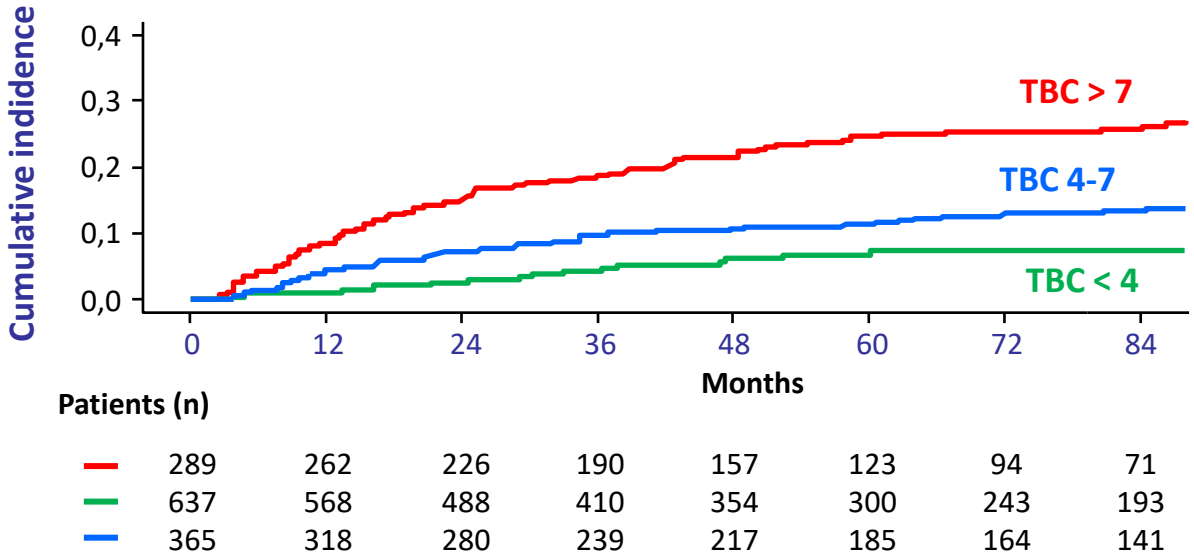
Figure 2
Points-clés de la surveillance et de la prise en charge de la récidive de carcinome hépatocellulaire après transplantation hépatique. (MMF : mycophénolate mofétil).

Ningarhari et al, 2023, JLE

Récidive du CHC : rôle des anticalcineurines

- In vitro
- Modèles animaux
- Etudes rétrospectives

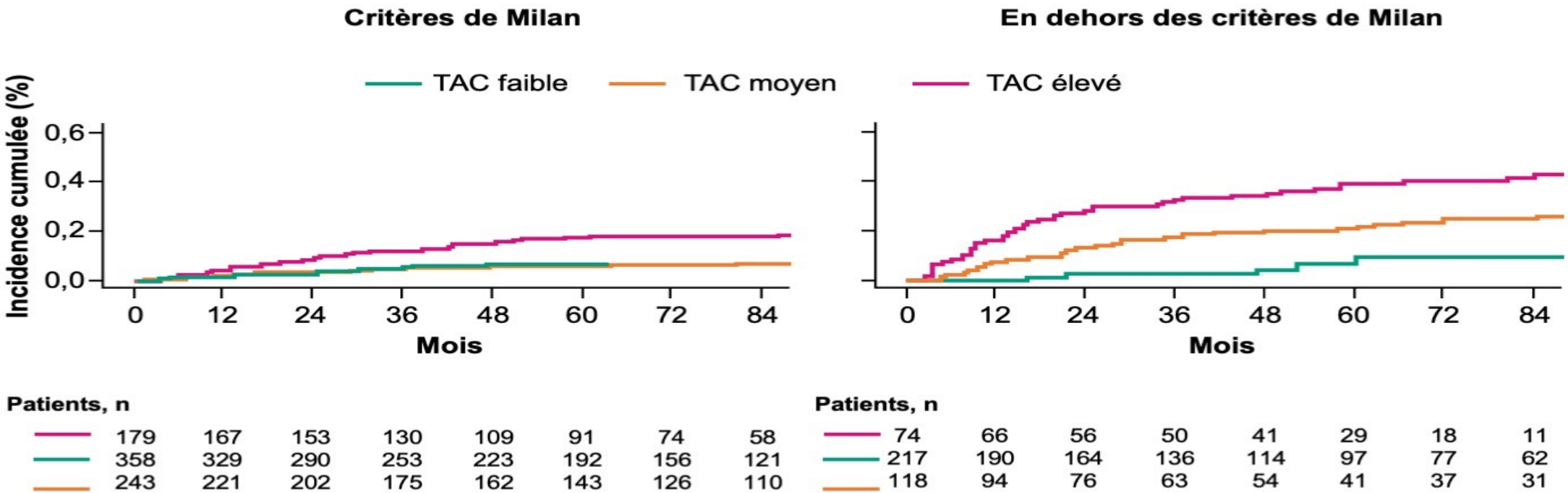
Incidence cumulée des récidives à 7 ans en fonction du niveau Tac moyen à 2 semaines



Hojo M. Nature 1999;397:530–534.
Freise CE. Transplantation 1999;67:510–513.
Rodriguez-Peralvarez M. J Hepatol 2013;59:1193–1199.
Vivarelli M. Transplantation 2002;74:1746–1751.
Kojima L, Etats-Unis, AASLD 2021, Abs. 57

Récidive de CHC après transplantation et tacrolimus (TAC) : les premières semaines sont cruciales ! *(2)*

- 4 centres américains
- 2002-2009



→ **La stratégie de minimisation du tacrolimus doit être mise en place très tôt pour les patients ayant un risque important de récidive**

AASLD 2021 - D'après Kojima L et al., abstr. 57, actualisé

Faut-il baisser l'immunosuppression?

OUI

219 patients greffés pour CHC (2000-2010), 36 récidives

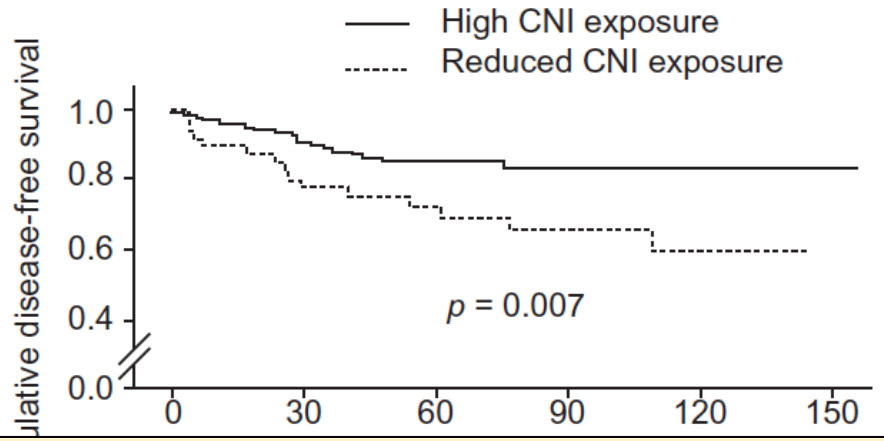


Table 3. Multiple Cox regression analysis showing independent associations with recurrence of hepatocellular carcinoma after liver transplantation in 219 patients.

Variables	RR	95% CI	*p* value
High exposure to calcineurin inhibitors*	2.82	1.4-5.8	0.005

Recommandations ILTS (Berenguer et al.Transplantation 2018)

Résiduel Tac <10ng/ml ou CsA < 300 ng/ml

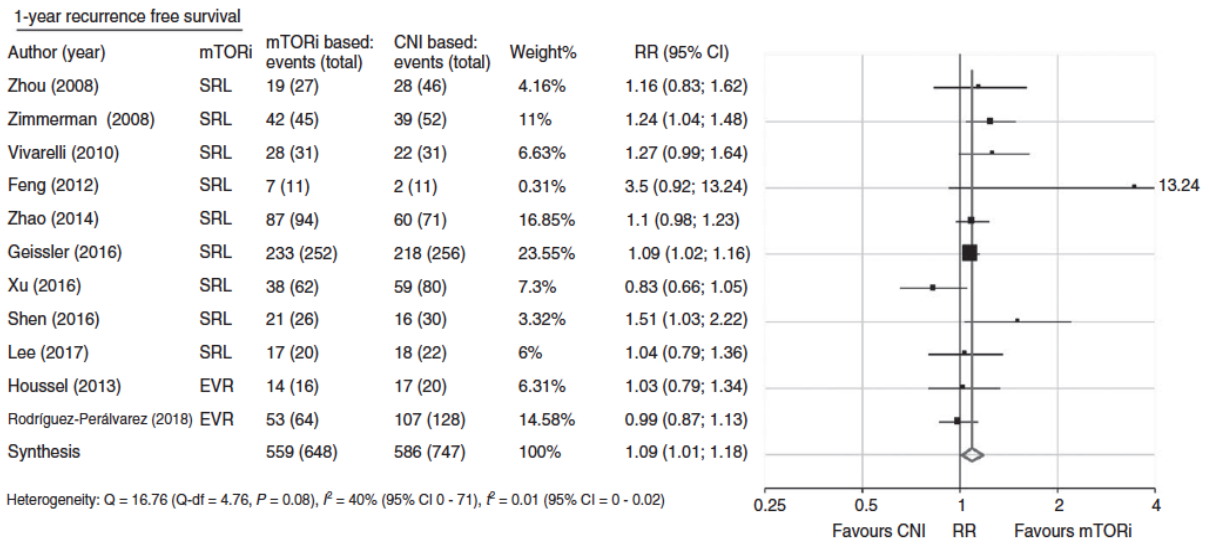
NB : pratiques actuelles Tac 4-7ng/ml dès le 1er mois (Lemaitre et al, Ther Drug Monit 2020)

Forte doses de CNI : résiduels de CsA > 300 ng/ml ou Tac > 10 ng/ml dans le 1er mois

Rodriguez-Peralvarez J Hepatology 2013

Faut-il traiter par inhibiteurs de mTor?

Survie sans récidive 1 an

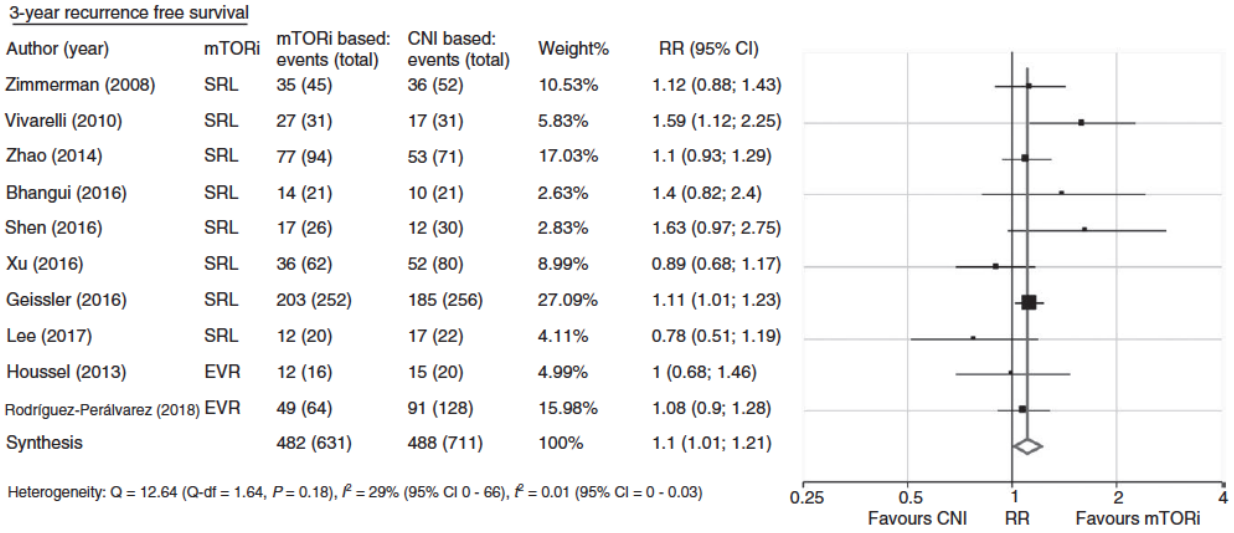


1-year recurrence free survival

Author (year)	mTORi	mTORi based: events (total)	CNI based: events (total)	Weight%	RR (95% CI)
Zhou (2008)	SRL	19 (27)	28 (46)	4.16%	1.16 (0.83; 1.62)
Zimmerman (2008)	SRL	42 (45)	39 (52)	11%	1.24 (1.04; 1.48)
Vivarelli (2010)	SRL	28 (31)	22 (31)	6.63%	1.27 (0.99; 1.64)
Feng (2012)	SRL	7 (11)	2 (11)	0.31%	3.5 (0.92; 13.24)
Zhao (2014)	SRL	87 (94)	60 (71)	16.85%	1.1 (0.98; 1.23)
Geissler (2016)	SRL	233 (252)	218 (256)	23.55%	1.09 (1.02; 1.16)
Xu (2016)	SRL	38 (62)	59 (80)	7.3%	0.83 (0.66; 1.05)
Shen (2016)	SRL	21 (26)	16 (30)	3.32%	1.51 (1.03; 2.22)
Lee (2017)	SRL	17 (20)	18 (22)	6%	1.04 (0.79; 1.36)
Houssel (2013)	EVR	14 (16)	17 (20)	6.31%	1.03 (0.79; 1.34)
Rodríguez-Perálvarez (2018)	EVR	53 (64)	107 (128)	14.58%	0.99 (0.87; 1.13)
Synthesis		559 (648)	586 (747)	100%	1.09 (1.01; 1.18)

Heterogeneity: Q = 16.76 (Q-df = 4.76, $P = 0.08$), $I^2 = 40\%$ (95% CI 0 - 71), $\hat{I}^2 = 0.01$ (95% CI = 0 - 0.02)

Survie sans récidive 3 ans



3-year recurrence free survival

Author (year)	mTORi	mTORi based: events (total)	CNI based: events (total)	Weight%	RR (95% CI)
Zimmerman (2008)	SRL	35 (45)	36 (52)	10.53%	1.12 (0.88; 1.43)
Vivarelli (2010)	SRL	27 (31)	17 (31)	5.83%	1.59 (1.12; 2.25)
Zhao (2014)	SRL	77 (94)	53 (71)	17.03%	1.1 (0.93; 1.29)
Bhangui (2016)	SRL	14 (21)	10 (21)	2.63%	1.4 (0.82; 2.4)
Shen (2016)	SRL	17 (26)	12 (30)	2.83%	1.63 (0.97; 2.75)
Xu (2016)	SRL	36 (62)	52 (80)	8.99%	0.89 (0.68; 1.17)
Geissler (2016)	SRL	203 (252)	185 (256)	27.09%	1.11 (1.01; 1.23)
Lee (2017)	SRL	12 (20)	17 (22)	4.11%	0.78 (0.51; 1.19)
Houssel (2013)	EVR	12 (16)	15 (20)	4.99%	1 (0.68; 1.46)
Rodríguez-Perálvarez (2018)	EVR	49 (64)	91 (128)	15.98%	1.08 (0.9; 1.28)
Synthesis		482 (631)	488 (711)	100%	1.1 (1.01; 1.21)

Heterogeneity: Q = 12.64 (Q-df = 1.64, $P = 0.18$), $I^2 = 29\%$ (95% CI 0 - 66), $\hat{I}^2 = 0.01$ (95% CI = 0 - 0.03)

	mTor	CNI	RR (95% CI)
In Milan	219/242	271/314	1.05 (0.98- 1.11)
Outside Milan	169/210	184/249	1.06 (0.94-1.19)

	mTor	CNI	RR (95% CI)
In Milan	202/242	231/314	1.13 (1.03- 1.23)
Outside Milan	116/172	137/192	0.95 (0.83-1.1)

Pas de sur-risque de rejet (association avec les CNI dose réduite)

Grigg et al, APT 2019

Récidive de CHC: mTOR inhibitors

- Les inhibiteurs de mTOR ont un effet anticancéreux potentiel

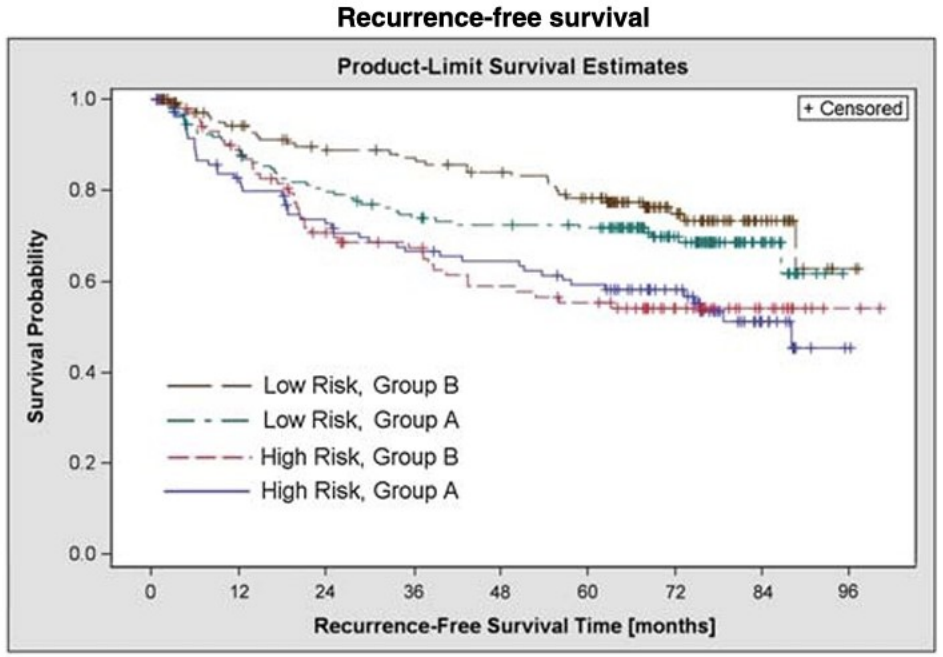
Inhibition de

Prolifération

Angiogénèse

Données SRL et EVR

- The Silver study
- Phase III, RCT, n=525



Améliore la survie sans récidive et la survie globale au cours des 3 à 5 premières années chez les patients à faible risque atteints de CHC selon les critères de Milan

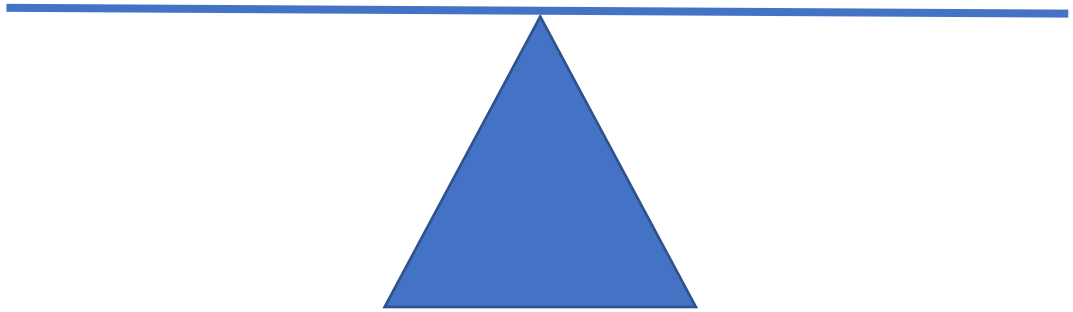
Geissler EK. Transplantation. 2016 Jan; 100(1): 116–125.

Faut-il traiter par inhibiteurs de mTor?

OUI

- néphroprotecteur
- ↓tumeurs cutanées
- Prévention récidive CHC

- Thrombose de l'artère hépatique
- Rejet cellulaire
- Retard de cicatrisation
- Tolérance



Traitement de la récidive de CHC : les options

Récidive locale	Traitements systémiques
Chirurgie Chimioembolisation Radiofréquence Radiothérapie	Sorafenib cabozantinib Regorafenib Lenvatinib Immunothérapie

+

Baisse de l'immunosuppression
Utilisation d'inhibiteurs mTor

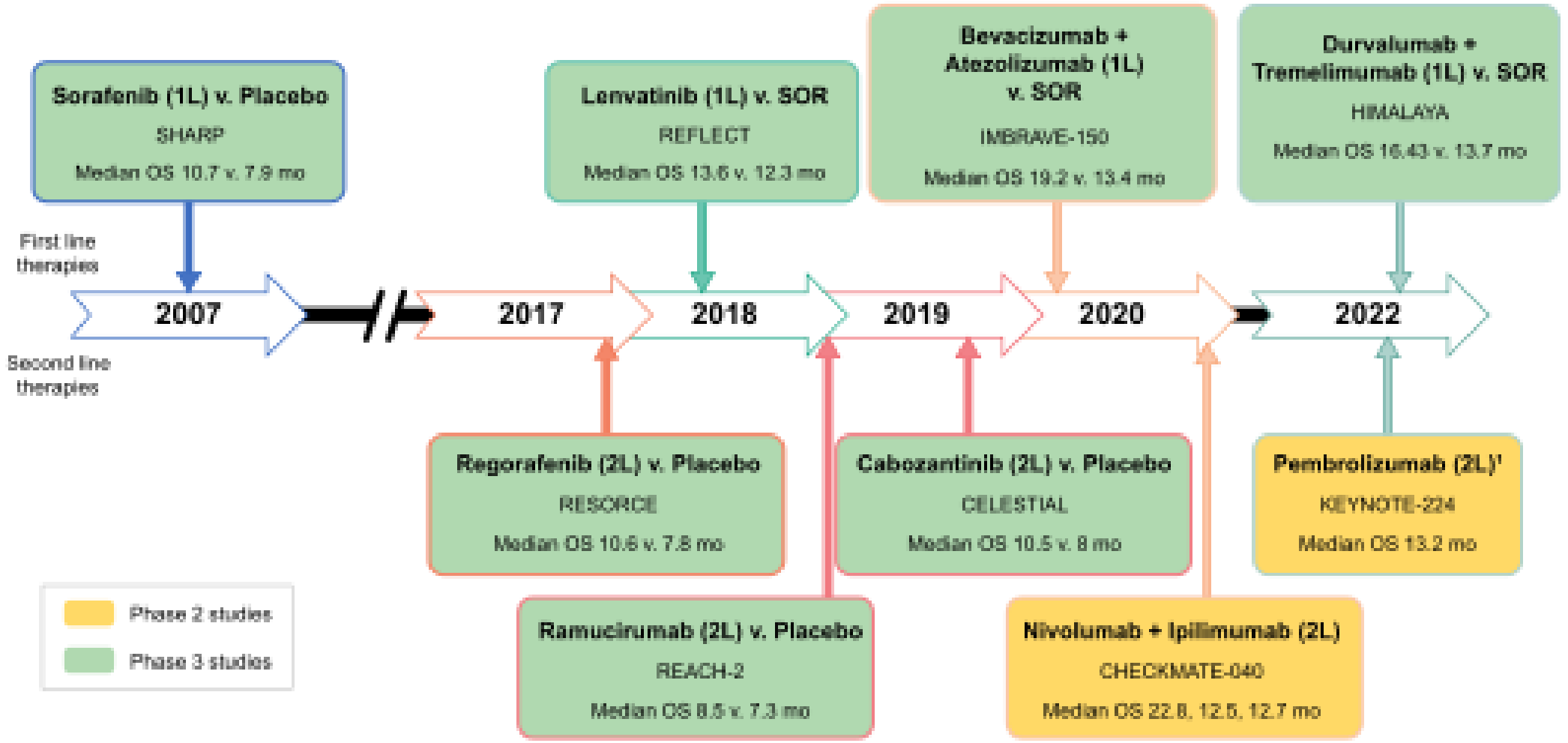


FIGURE 15 Timeline of systemic therapies for hepatocellular carcinoma (HCC) and resultant survival. (First line therapies are above the timeline; second line therapies are below the timeline.) [1]KEYNOTE 224 was a non-randomized phase 2 trial. Phase 3 studies of pembrolizumab versus sorafenib have had conflicting results, with improved median OS noted in an Asian population.

Traitement de la récidive de CHC : immunothérapie

NON

- Pas en dehors de protocoles +++
- Pitié salpétrière
- Cas colligés par Dr De Martin Paul Brousse

Au World J Gastroenterol 2018

Immunothérapie post TH I

TABLE 1 Case reports with the application of ICIs in HCC recurrence patients after LT.

No.	Age	Gender	Malignancy	TFTI	Treatment before ICIs	ICIs	Dose	Duration	IS therapy before ICIs	IS therapy during ICIs	Rejection	Outcome	Ref
1	41	M	HCC	1 yrs	TACE/MWA	Nivolumab	3 mg/kg/2 wks	15 cycles	TAC	TAC	NO	PD	(37)
2	20	M	HCC	4 yrs	Sorafenib/Capecitabine	Nivolumab	–	2 cycles	Sirolimus	Sirolimus	AMR/ TCMR	-	(38)
3	14	M	HCC	3 yrs	Gemcitabine/Oxaliplatin	Nivolumab	–	1 cycle	TAC	TAC	AMR/ TCMR	-	(38)
4	70	M	HCC	8 yrs	Sorafenib/Capecitabine/ External beam radiation	Pembrolizumab	3 mg/kg/2 wks	3 mths	TAC	TAC	NO	PD	(39)
5	56	M	HCC	5.5 yrs	Sorafenib	Nivolumab	–	–	TAC	–	NO	CR	(40)
6	55	M	HCC	1.8 yrs	Sorafenib	Nivolumab	–	–	Sirolimus/MMF	–	NO	PD	(40)
7	34	F	HCC	3.7 yrs	Sorafenib	Nivolumab	–	–	TAC	–	NO	PD	(40)
8	63	M	HCC	1.2 yrs	Sorafenib	Nivolumab	–	–	TAC	–	NO	-	(40)
9	68	M	HCC	1.1 yrs	Sorafenib	Nivolumab	–	–	Sirolimus	–	YES	-	(40)
10	53	F	HCC	3 yrs	Sorafenib	Nivolumab	200 mg/2 wks	1 cycle	Prednisone/MMF/ Everolimus	Everolimus/ MMF	TCMR	-	(41)
11	61	M	HCC	2 yrs	Sorafenib	Nivolumab	–	1 mth	–	–	TCMR	-	(42)
12	57	M	HCC	3 yrs	Sorafenib	Pembrolizumab	200 mg/3 wks	10 mths	TAC/MMF /Steroid	TAC/ Sirolimus	NO	CR	(43)
13	64	M	HCC	2 yrs	Sorafenib	Nivolumab	–	0.25 mths	–	–	TCMR	-	(44)
14	70	M	HCC	3 yrs	Sorafenib/Gemcitabine/Oxaliplatin	Nivolumab	240 mg/2 wks	4 cycles	TAC	TAC	NO	PD	(45)
15	62	F	HCC	2 yrs	Sorafenib/Regorafenib/5Fluorouracil/ Oxaliplatin	Nivolumab	240 mg/2 wks	5 cycles	TAC	TAC	NO	SD	(45)
16	66	M	HCC	2 yrs	Sorafenib/Regorafenib Gemcitabine/Oxaliplatin	Nivolumab	–	6 cycles	TAC	TAC	NO	PD	(45)
17	62	F	HCC	2 yrs	TACE	Nivolumab	–	16 mths	TAC/MMF	–	NO	CR	(46)

(Continued)

Jiang et al, Immunology 2023

Immunothérapie post TH II

26 % de patients avec maladie stable
22 rejets

TABLE 1 Continued

No.	Age	Gender	Malignancy	TFTI	Treatment before ICIs	ICIs	Dose	Duration	IS therapy before ICIs	IS therapy during ICIs	Rejection	Outcome	Ref
18	54	F	HCC	7 yrs	Sorafenib/Nanoknife /Ethanol ablation	Ipilimumab	3 mg/kg/3 wks	13 mths	Everolimus/TAC	Everolimus /TAC	NO	PR	(47)
19	54	M	HCC	4 yrs	Sorafenib/RFA /Lenvatinib	Camrelizumab	200 mg/3 wks	5 cycles	TAC	Sirolimus	NO	CR	(48)
20	54	M	HCC	2 yrs	Sorafenib/mFolfox-6/ Gemcitabine/TACE	Nivolumab	200 mg/2 wks	12 cycles	TAC	TAC	NO	PD	(49)
21	46	M	HCC	1 yrs	Sorafenib/Lenvatinib	Toripalimab	240 mg/3 wks	6 cycles	Sirolimus	Sirolimus	NO	PD	(50)
22	46	M	HCC	1 yrs	TACE/PEI/Resection /Sorafenib/Lenvatinib	Toripalimab	240 mg/3 wks	2 cycles	Sirolimus	Sirolimus	NO	SD	(50)
23	62	M	HCC	1 yrs	Sorafenib/Lenvatinib /TACE/PEI	Toripalimab	240 mg/3 wks	-	Sirolimus	Sirolimus	NO	-	(50)
24	66	M	HCC	1 yrs	Sorafenib/Lenvatinib /Regorafenib	Toripalimab	240 mg/3 wks	-	Sirolimus	Sirolimus	NO	-	(50)
25	35	M	HCC	4 yrs	Surgical/Gemcitabine/Oxaliplatin/ Fluorouracil/ IFN alfa-2b	Atezolizumab	-	6 mths	-	-	NO	PD	(51)
26	53	M	HCC	-	Sorafenib/Resection/ External radiotherapy	Nivolizumab/ Atezolizumab	-	7 cycles	-	-	NO	SD	(52)
27	55	M	HCC	1 yrs	Ablation/TACE/ External radiotherapy	Atezolizumab		2 cycles	-	-	NO	PD	(52)

TFTI, time from transplant to ICIs; ICI, immune checkpoint inhibitor; IS, immunosuppressive; Ref, references; M, male; F, female; HCC, hepatocellular carcinoma; TACE, transarterial chemoembolization; MWA, microwave ablation; TAC, tacrolimus; AMR, antibody-mediated rejection; TCMR, T cell-mediated rejection; IFN, interferon; PEI, percutaneous ethanol injection; MMF, mycophenolate mofetil; RFA, radiofrequency ablation; PD, progressive disease; CR, complete response; SD, stable disease; PR, partial response.

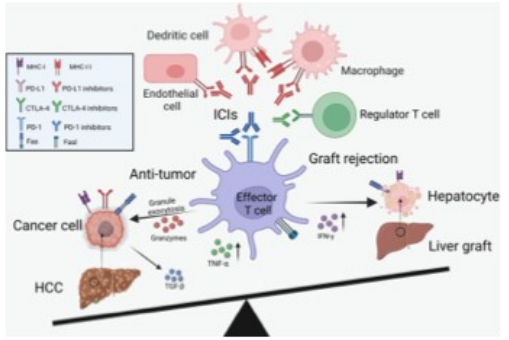


FIGURE 1
The balance between cancer immunology and transplant tolerance. Through the activation of effector T cells, the ICIs can not only reduce tumor burden but also increase the risk of graft rejection. IL-2, interleukin-2; IFN-γ, interferon-γ; TNF-α, tumor necrosis factor-α.

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TABLE 3 The efficiency and side effects of each drug based on the existing data.

Drugs		efficiency	side effects
mTOR's		The graft rejection rate in those treated with sirolimus is 22.2% (2/9).	Not mentioned.
		The graft rejection rate in those treated with everolimus is 50.0% (1/2).	
TKI's		81.5% (22/27) patients use TKI's and most of them change to ICI's due to disease progression.	Proteinuria (44); Nausea, Emesis (41)
ICI's	PD-1 inhibitors	28.5% (4/14) patients with disease control.	Graft rejection; Abnormal liver function (38)
	PD-L1 inhibitors	0% (0/2) patients with disease control.	
	CTLA-4 inhibitors	100% (1/1) patients with disease control.	
	combination therapy (PD-1 inhibitors +PD-L1 inhibitors)	100% (1/1) patients with disease control.	

mTOR, mammalian target of rapamycin; TKI, Tyrosine kinase inhibitors; ICI, immune checkpoint inhibitors; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1; CTLA-4, cytotoxic T lymphocyte antigen 4.

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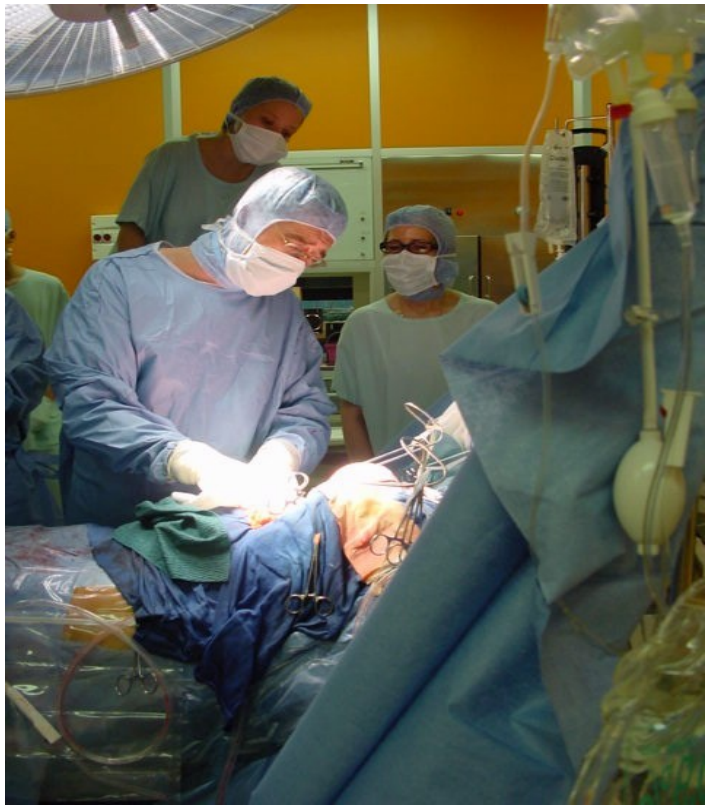
Privilégier sirolimus ou mTOR, pas de stéroides
Minimiser les anticalcineurines CNIs
Negative PDL 1 expression dans le foie et délai TH récidive : moins de rejet avec ITTT
PDL 1 moindre risque de rejet que PD-1 et CTL-4 inhibiteur
Monitorer CD4 CD8 et IFN gamma dans le sérum
Si rejet. Arrêt de l'ITTT, stéroides et thymoglobulines



Oui Daniel sera greffé mais …

Survie globale et du greffon

Effets secondaires

Optimiser le candidat en pré TH et en post TH
Immunosuppression
Récidive de la MASH et du CHC

FHU support une équipe de recherche : Merci