FONDAZIONE IRCCS ISTITUTO NAZIONALE DEI TUMORI

IL TRAPIANTO DI FEGATO OGGI IN ITALIA: QUALI INDICAZIONI?

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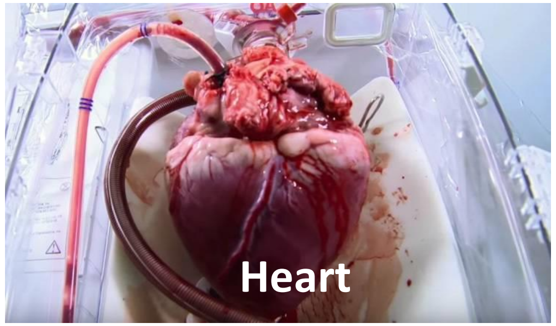
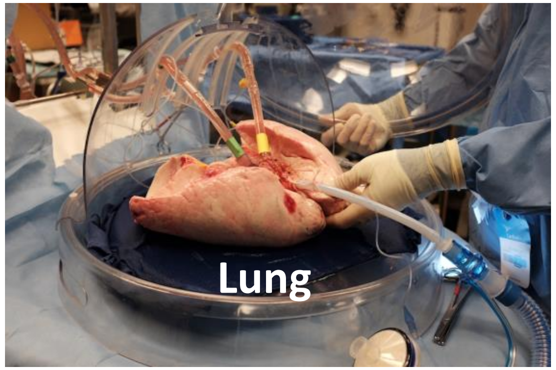
Direttore Prof Vincenzo Mazzaferro

How listing for life saving transplantation works in different organs?





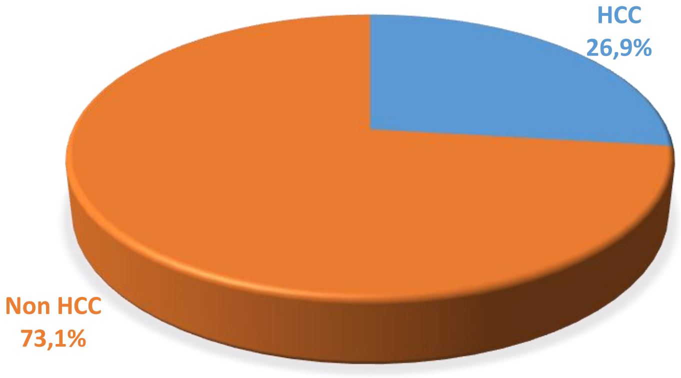
End stage function deterioration

Curative operation for oncologic indication

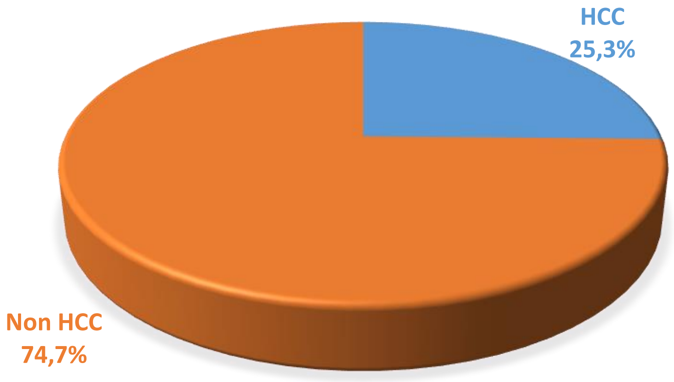
The liver is the only organ suitable for two distinguished transplant purposes:
end-stage functional disease and cancer

Current indication to Liver Transplantation

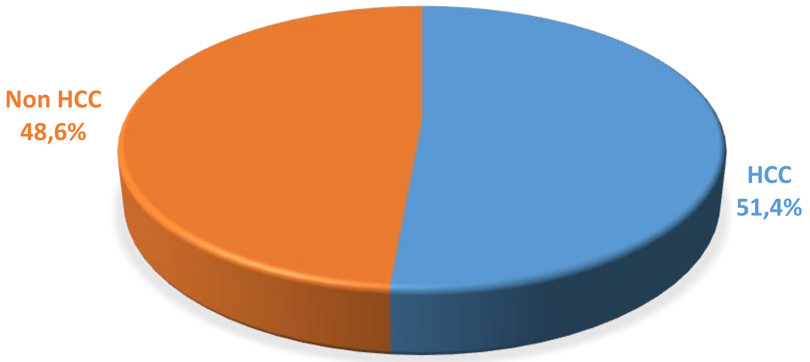
Indication to LT in Europe



Indication to LT in US



Indication to LT in China



[ELTR data 2022 ELTR Registry; SRTR data 2021, Haibo W, et al. China Liver Transplant Registry ILTS 2009]

Evolution of indication to Liver Transplantation

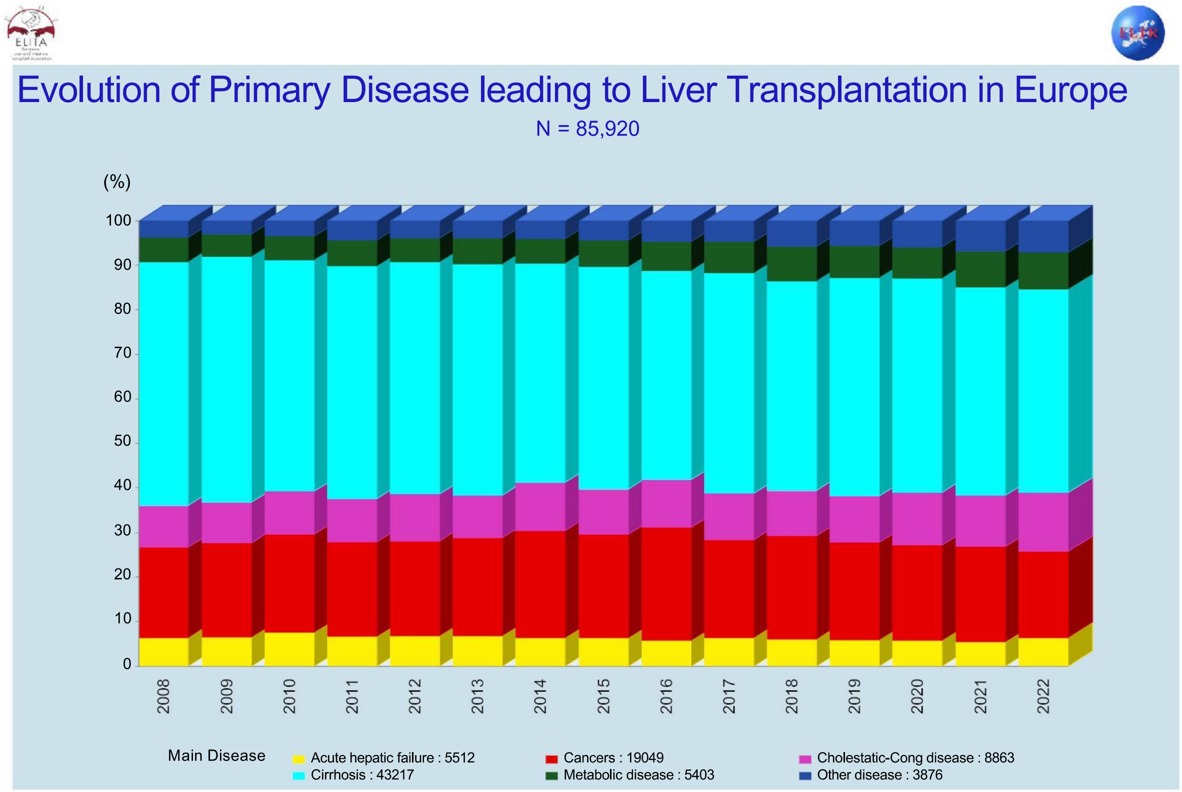
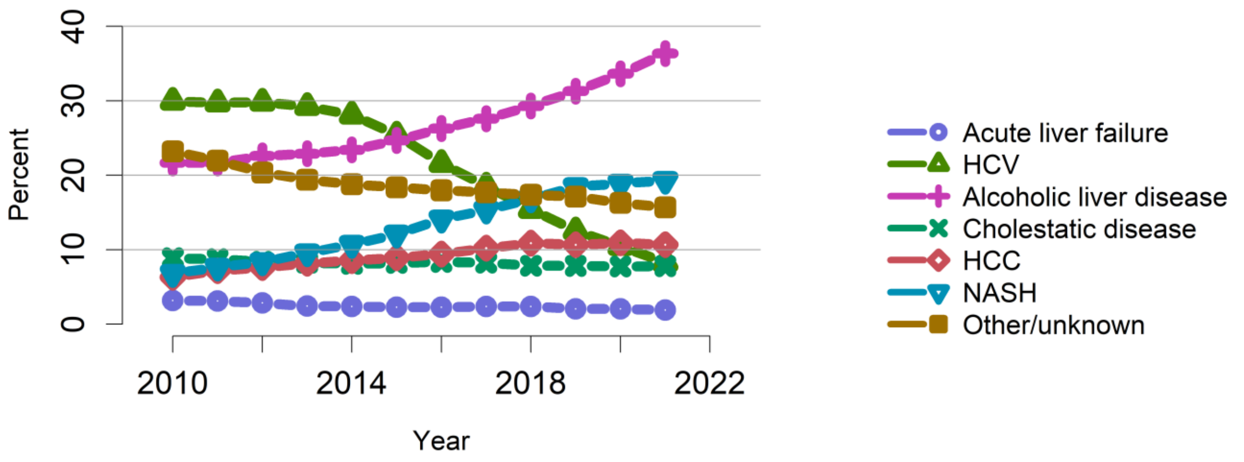


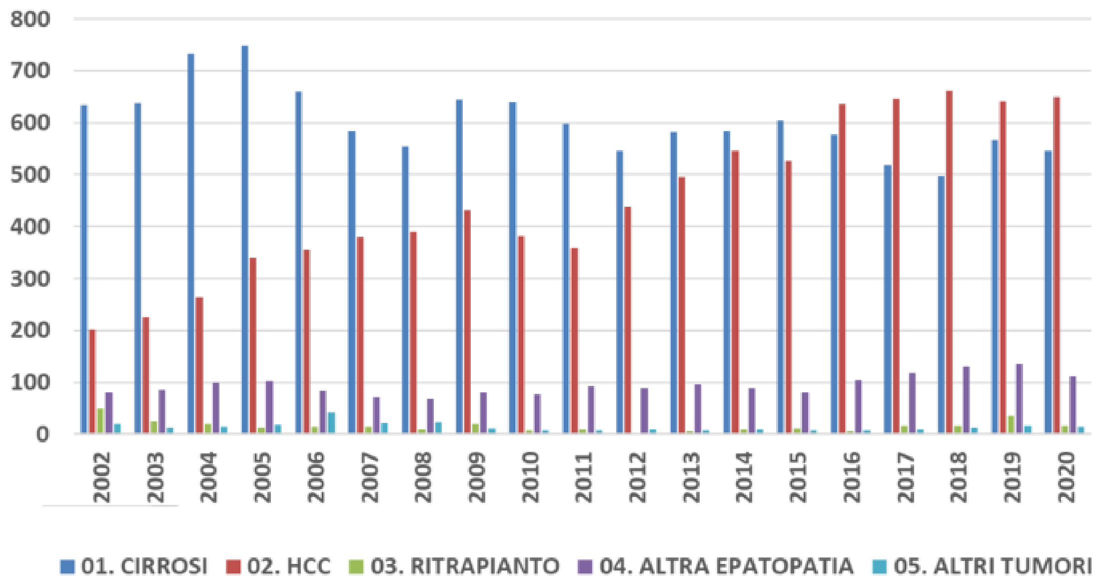
Figure LI 6: Distribution of adults waiting for liver transplant by diagnosis

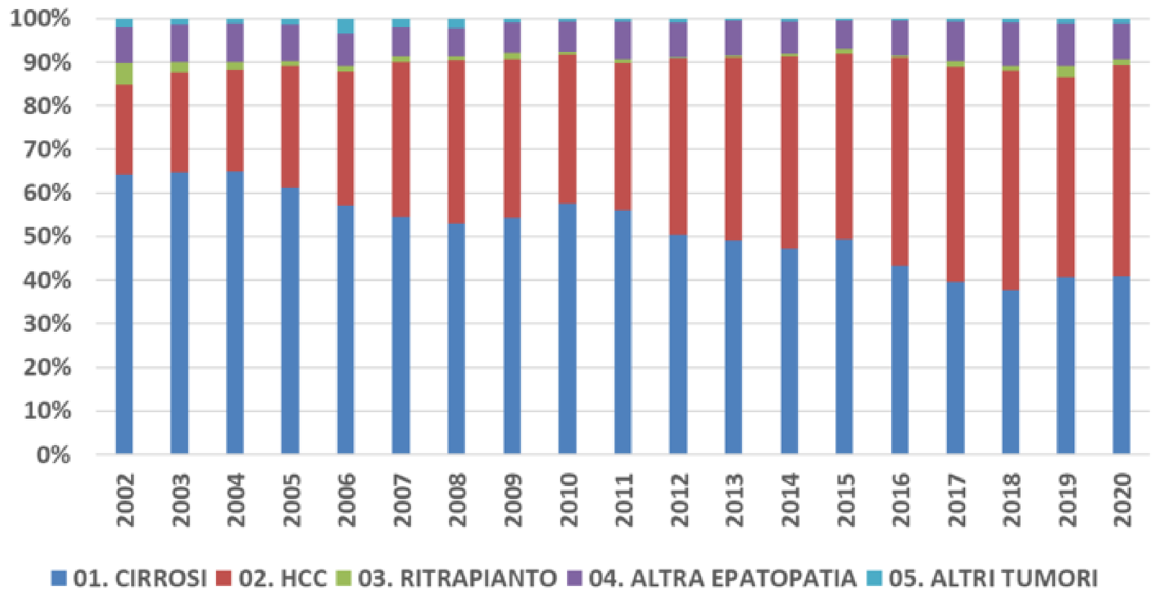


OPTN/SRTR 2021 Annual Data Report

[ELTR data 2022 ELTR Registry; SRTR data 2021,]

Evolution of indication to Liver Transplantation





[CNT data 2022]

The changing scenario of liver disease

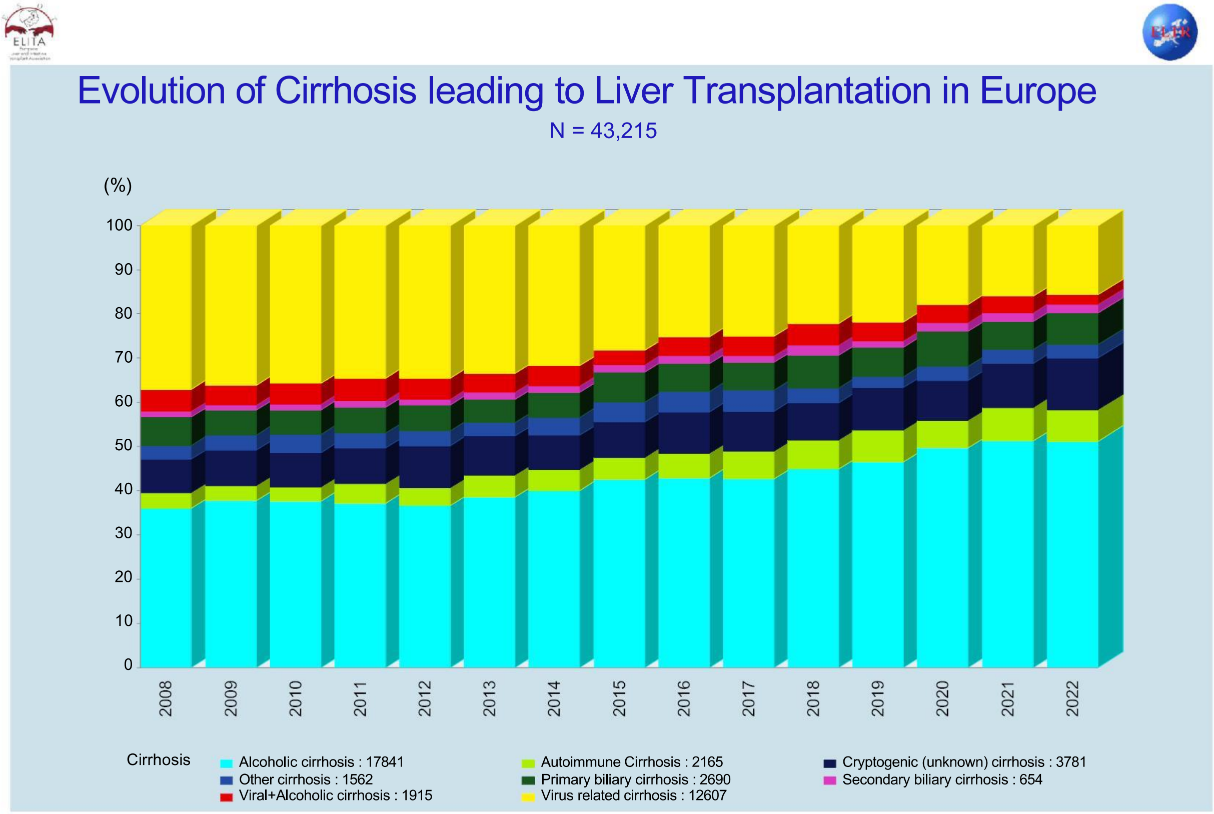
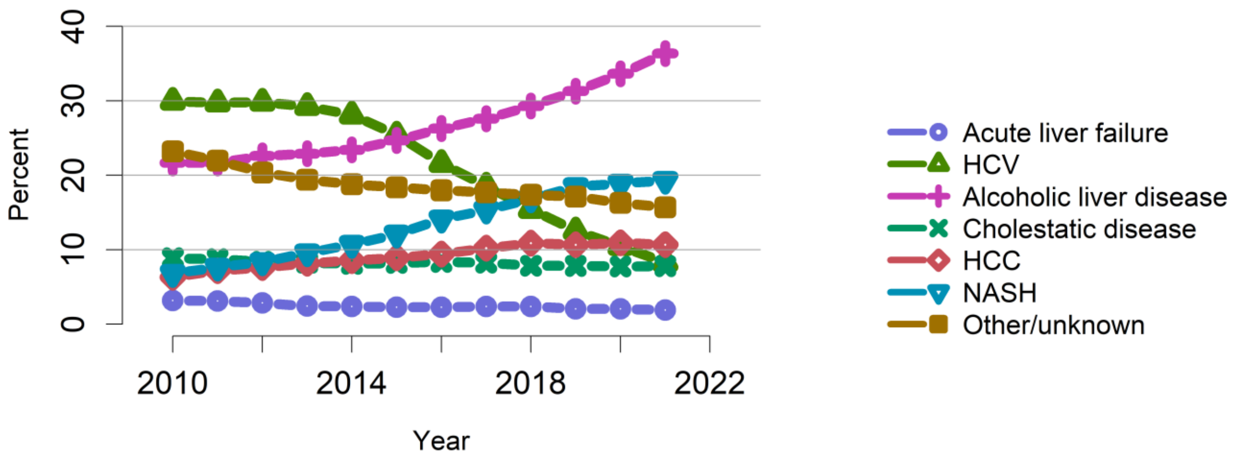


Figure LI 6: Distribution of adults waiting for liver transplant by diagnosis



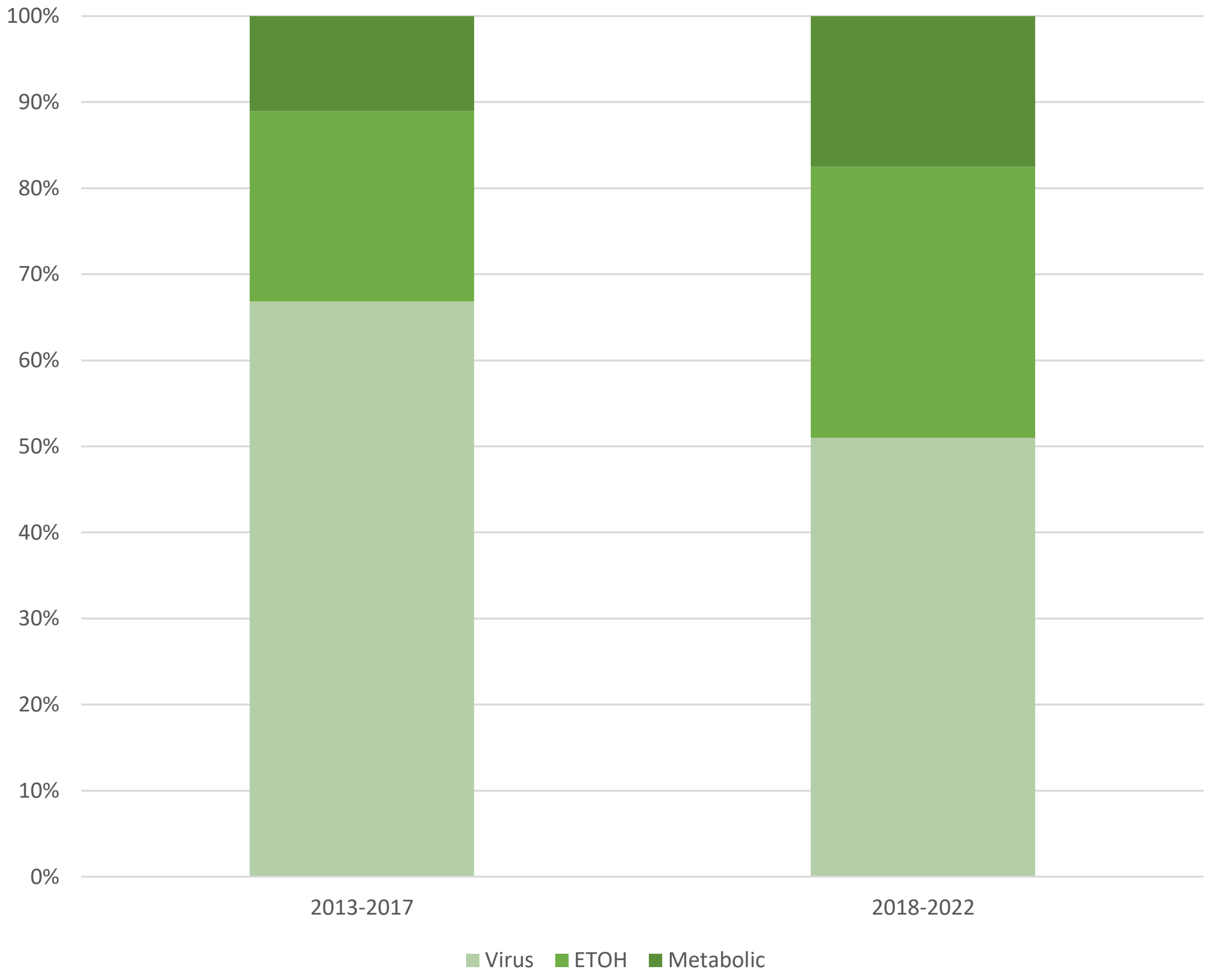
OPTN/SRTR 2021 Annual Data Report

[ELTR data 2022 ELTR Registry; SRTR data 2021,]

Epidemiology

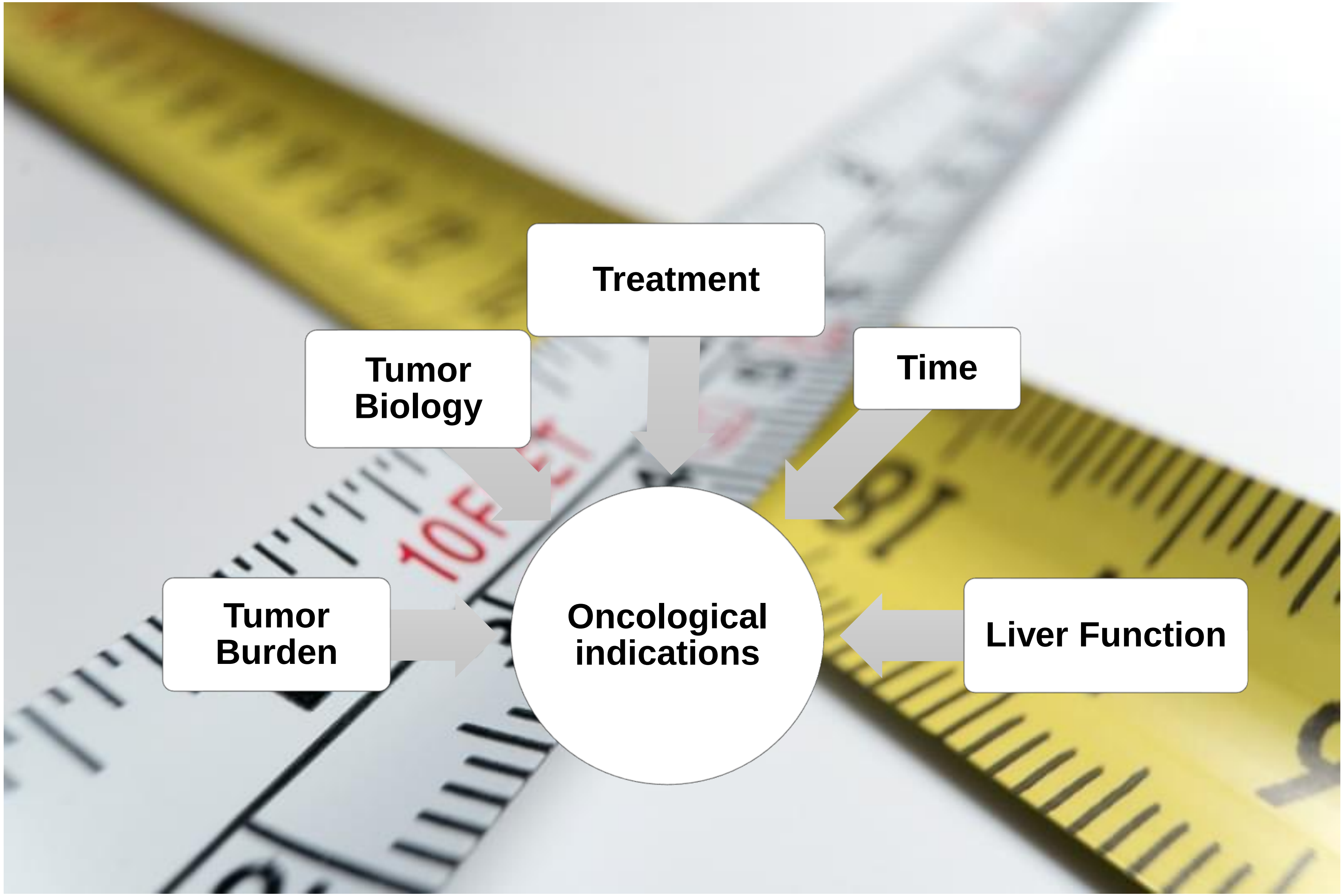
Alcohol related increased from 26% in 2013-2017 to **41,7%** in 2018-2022

Metabolic related increased from 12% in 2013-2017 to **22,5%** in 2018-2022

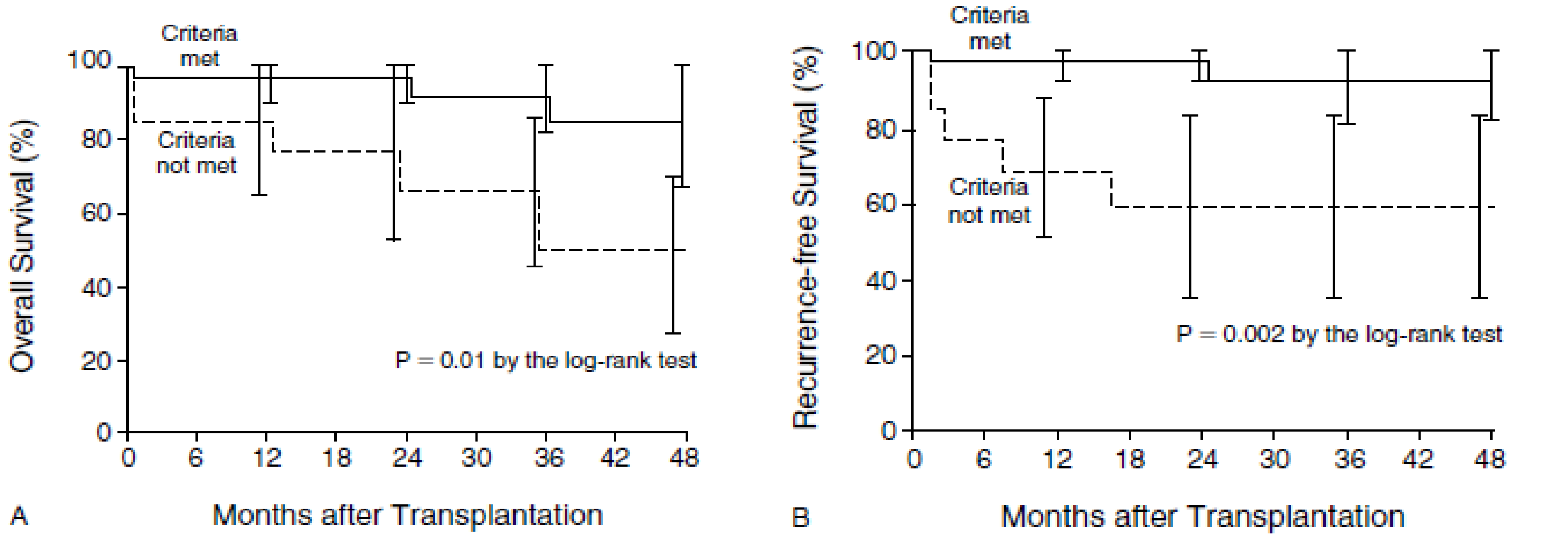


[INT Data presented at SITO 2023]

Factors influencing Drop-OUT and Liver Transplant Outcome



Milan Criteria

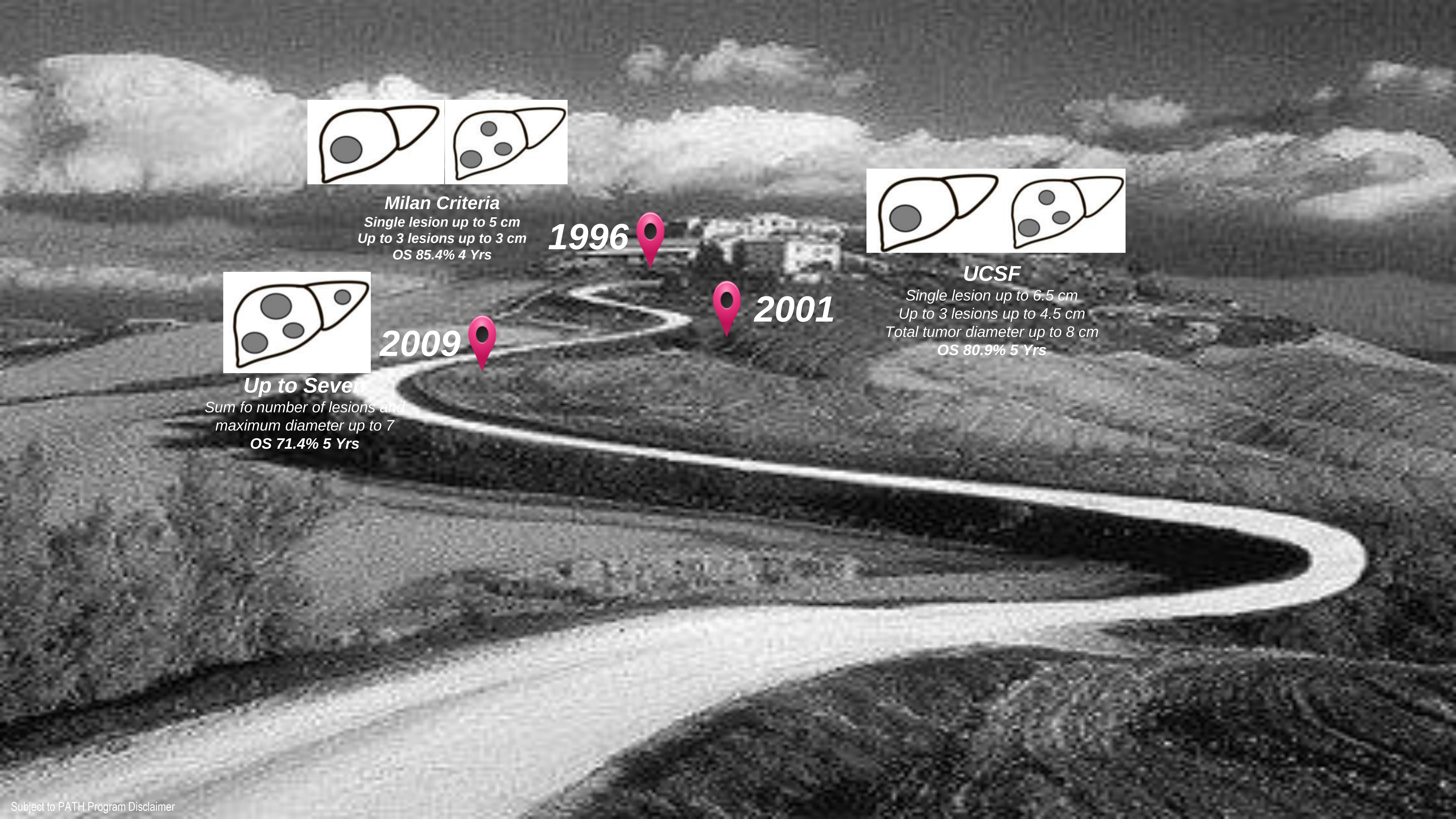


single HCC ≤ 5 cm or multiple HCC 3 nodules ≤ 3 cm

Liver Transplantation

- Liver transplantation is considered to be the first-line treatment option for patients with single tumors less than 5 cm or ≤3 nodules ≤3 cm (Milan criteria) not suitable for resection **(evidence 2A; recommendation 1A)**

[Mazzaferro V, et al NEJM 1996]


Milan Criteria
Single lesion up to 5 cm
Up to 3 lesions up to 3 cm
OS 85.4% 4 Yrs
1996
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Single lesion up to 6.5 cm
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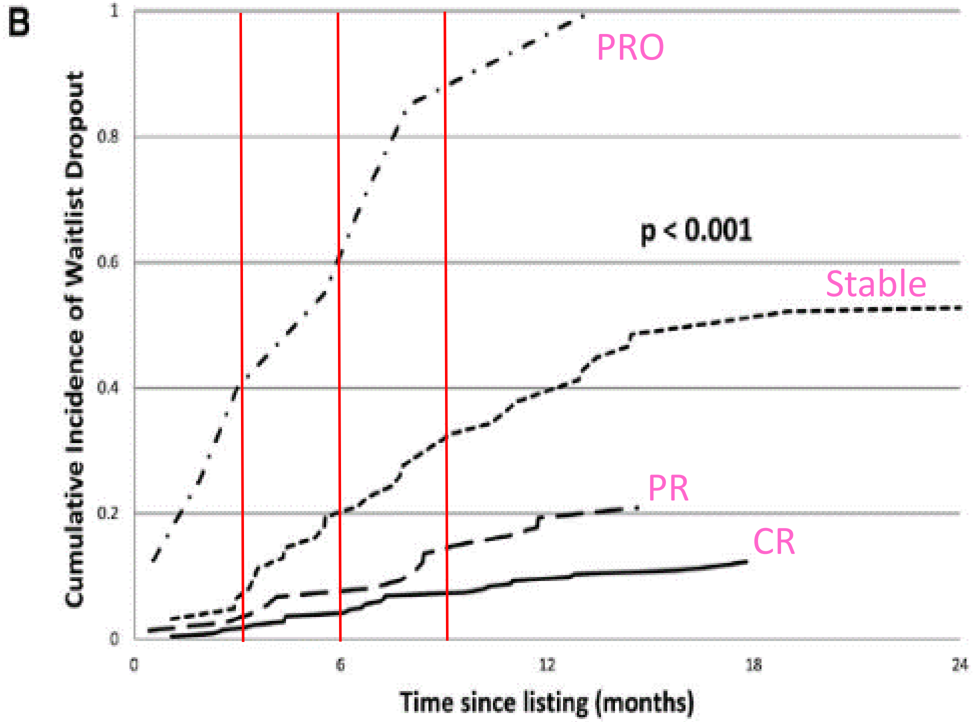
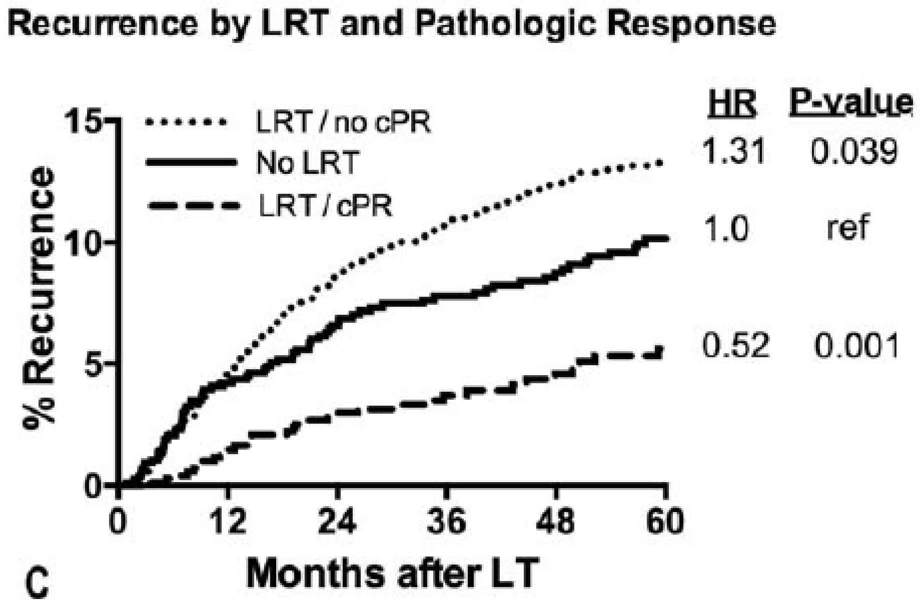
Total tumor diameter up to 8 cm
OS 80.9% 5 Yrs
2009
Up to Seven
Sum fo number of lesions and
maximum diameter up to 7
OS 71.4% 5 Yrs
Subject to PATH Program Disclaimer

Response to loco-regional therapy Bridiging

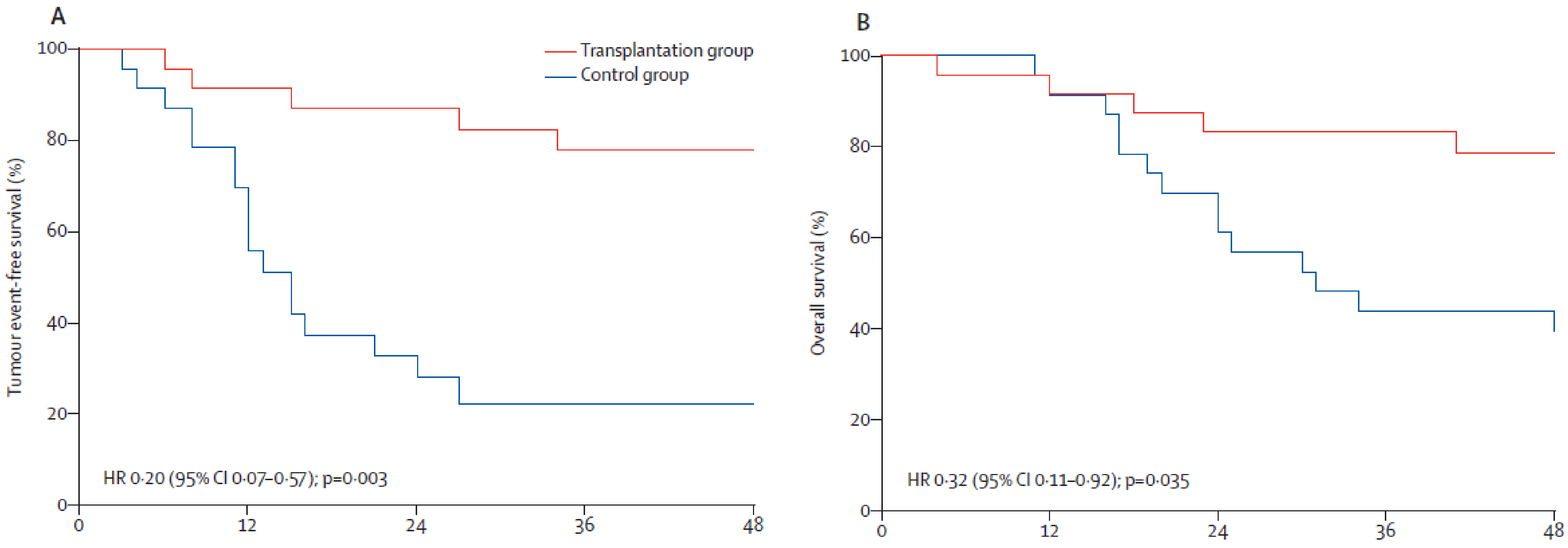
- **Bridging loco-regional therapy** in LT candidates with HCC can **reduce the risk of drop-OUT** from the waiting list, helps **asses tumor biology** according to response to treatment
- Bridging loco-regional therapy in LT candidates with HCC can **reduce post-LT recurrence** in case of a complete or partial response is achieved





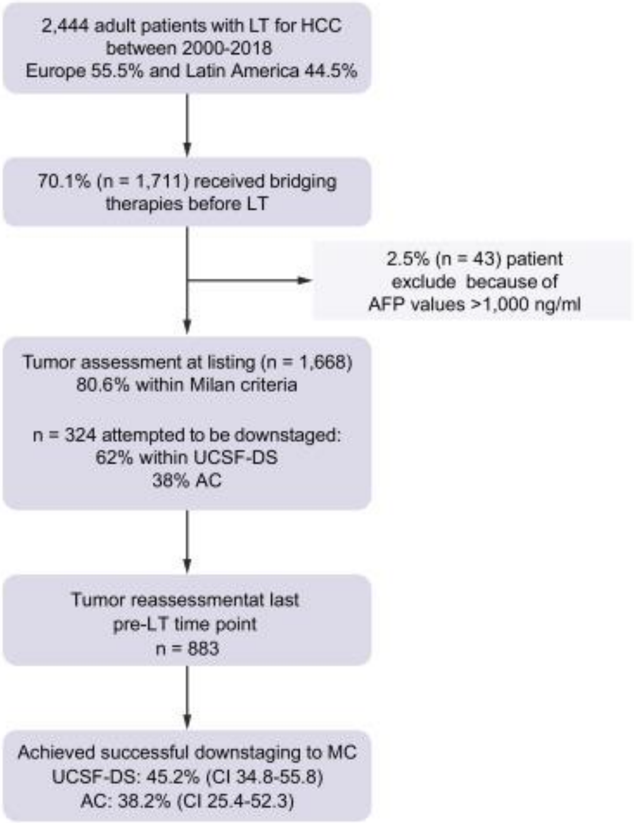
Liver transplantation in hepatocellular carcinoma after tumour downstaging (XXL): a randomised, controlled, phase 2b/3 trial

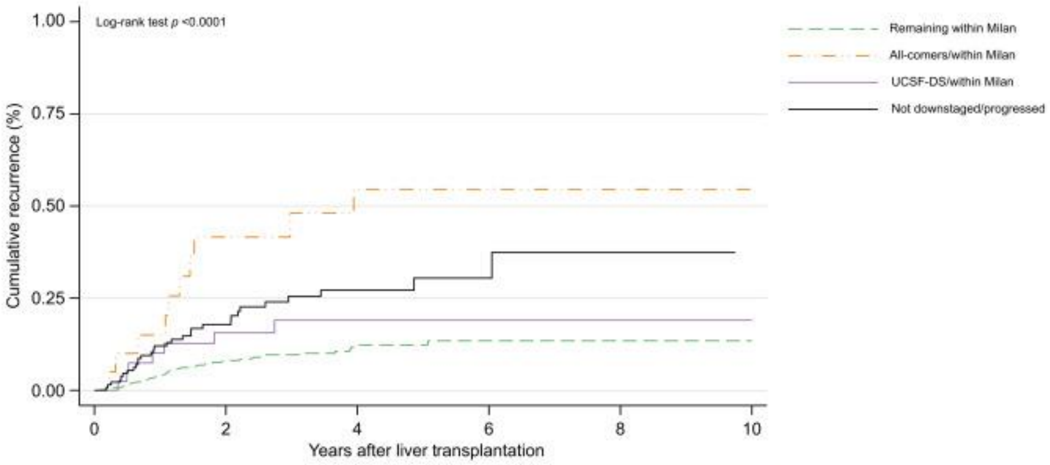
Mazzaferro V et al. Lancet Oncol 2020



- After downstaging of eligible HCC beyond the Milan criteria, liver transplantation improves tumour event-free survival and overall survival compared with non-transplantation therapies.
- Post-downstaging tumour response could contribute to the expansion of HCC transplantation criteria.

Response to loco-regional therapy downstaging





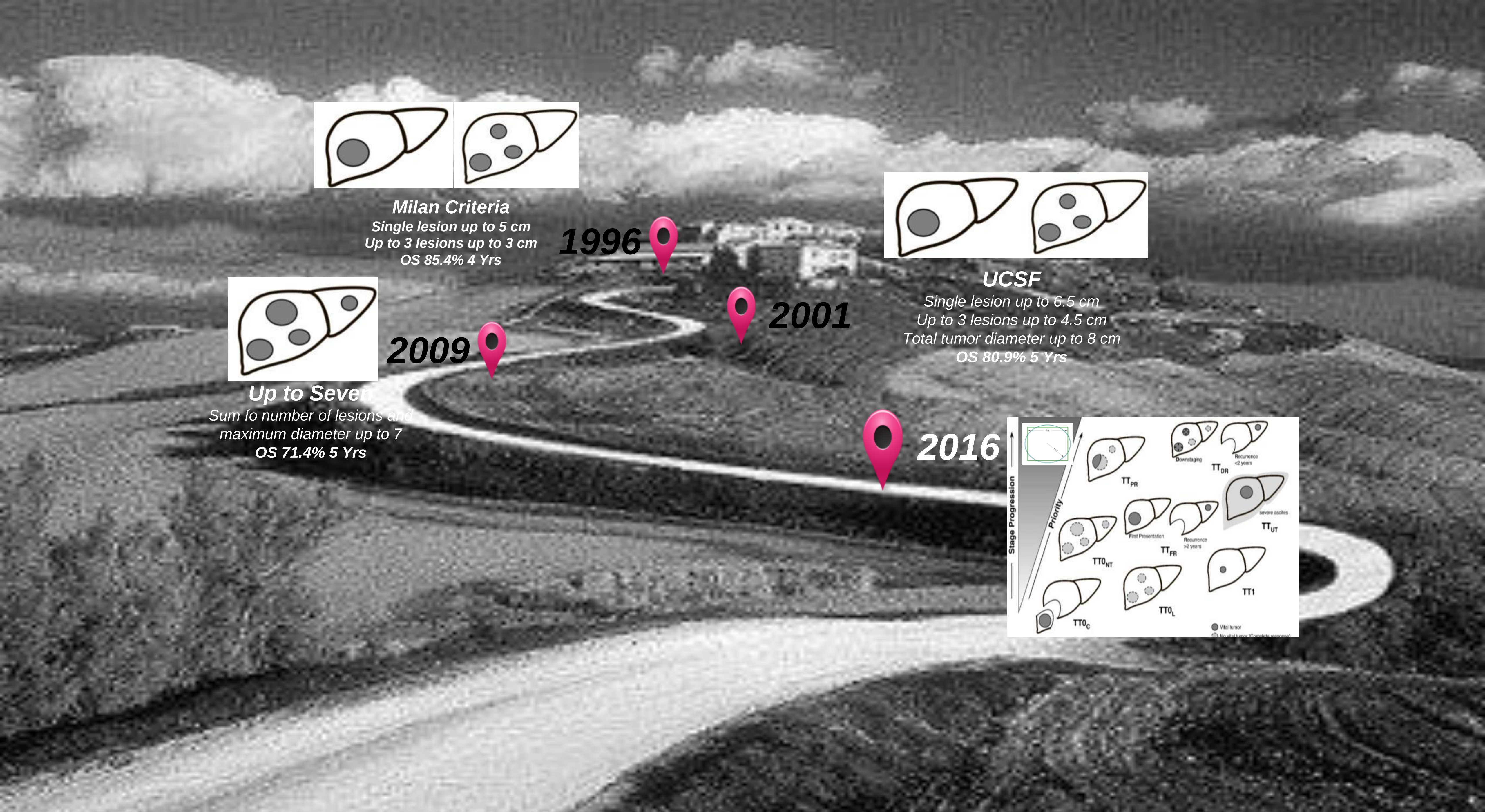
N° at risk						
Remaining within Milan	680	352	147	44	15	5
UCSF-DS/within Milan	42	29	10	3	2	2
All-comers/within Milan	21	9	7	4	2	1
Not downstaged/progressed	140	70	31	10	3	0

Patients within the UCSF-DS protocol at listing have similar post-transplant outcomes compared with those within Milan when successfully downstaged. All-comers have a higher recurrence and inferior survival irrespective of response to LRT.

Degroote H et al JHEP Rep 2021

LRT as an independent predictor of HCC recurrence in non–down-staged patients, suggesting that LRT itself may have a paradoxically aggravating role in a subset of patients who do not respond to treatment or, at the very least, that the lack of response to LRT is a surrogate for a more aggressive tumor biology that is not captured by other well-characterized tumor-related factors.

Kardashian A et al Hepatol 2020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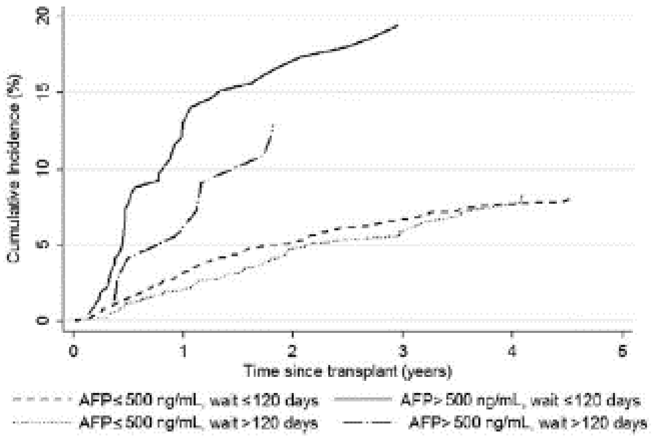
OS 80.9% 5 Yrs
2009
Up to Seven
Sum fo number of lesions and
maximum diameter up to 7
OS 71.4% 5 Yrs
2016
Stage Progression
Priority
TT$_{PR}$
Downstaging
Recurrence
<2 years
TT$_{DR}$
severe ascites
TT$_{UT}$
First Presentation
Recurrence
>2 years
TT$_{FR}$
TT0$_{NT}$
TT1
TT0$_{L}$
TT0$_{C}$
Vital tumor

Role of AFP serum level

5002 LT for HCC in UNOS Database (2006-2010)

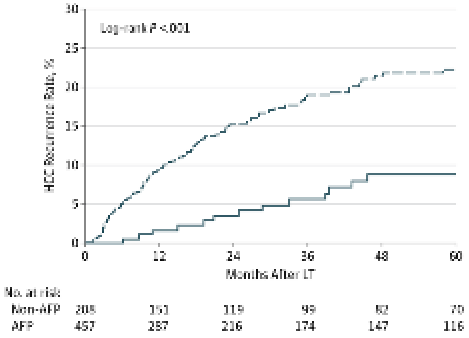
Higher risk of HCC recurrence at 1 year:
-Interval from listing to OLT <120days
-AFP > 500
Non significative at 2 years

[Samoylova ML, et al Liver Transpl 2014]



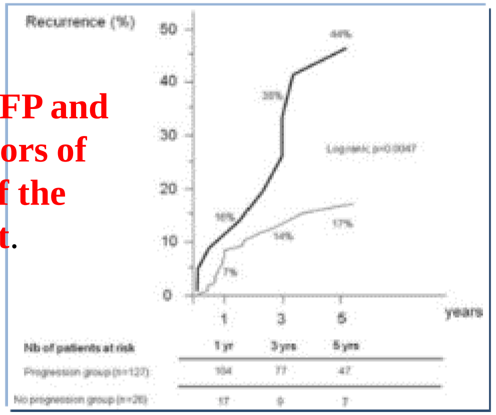
665 LT for HCC at UCLA (1989-2013)

Stratifying patients by AFP status in addition to radiological criteria improves the selection process for and the prioritization of transplant candidates



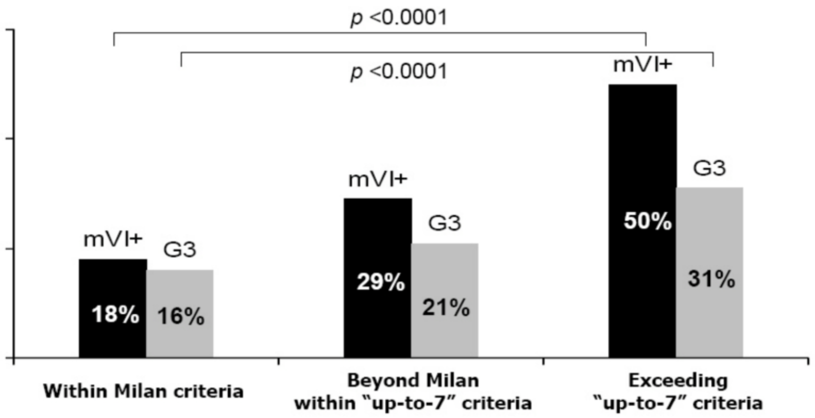
[Agopian VG, et Al JAMA Surg 2016]

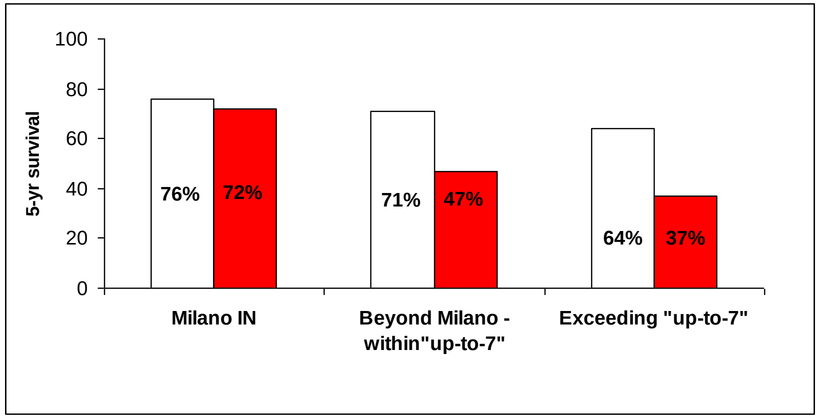
It could well be that **AFP and its variation are mirrors of the test of time and of the response to treatment**.

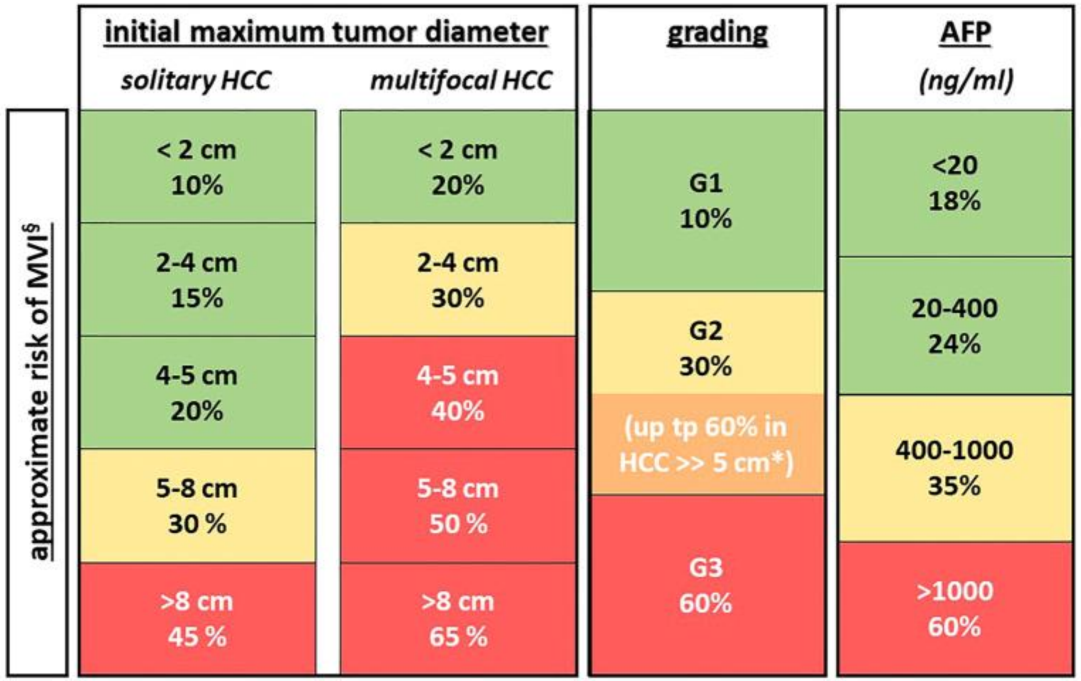


[Vibert E, Am J Transpl 2010]

Not Just a matter of size and number







Progressive increase in biological aggressiveness pattern incidence with disease beyond the conventional selection criteria

mVI, as one of the most relevant risk factors for HCC recurrence after LT and can only be detected in surgical specimens and not by imaging or in biopsy material.

Mazzaferro, Lancet Oncology 2009

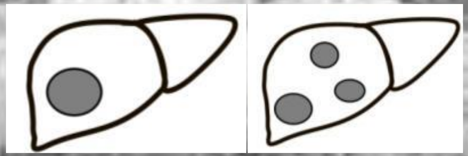
Seehofer, Transpl Int. 2022

Milan and beyond…

Selection Criteria for LT in HCC
cadaveric donor liver transplant (CDLT)

Center	Morphologic Criteria	Biomarker Criteria	Survival
Milan	1 lesion ≤ 5 cm, 2-3 lesions ≤ 3 cm each.	None	4 yr OS: 85%
UCSF	1 lesion ≤ 6.5 cm, 2-3 lesions ≤ 4.5 cm each. Total tumor diameter ≤ 8 cm	None	5 yr OS: 72.4%
Pamplona	1 lesion ≤ 6 cm, 2-3 lesions ≤ 5 cm each	None	5 yr OS: 79%
Edmonton	1 lesion < 7.5 cm, multiple lesions < 5 cm each	None	4 yr OS: 82.9% 4 yr RFS: 76.8%
Dallas	1 lesion ≤ 6 cm, 2-4 lesions ≤ 5 cm each	None	5 yr RFS: 1 lesion ≤ 6 cm: 63.9%/or 2-4 lesions 3.1 cm-5 cm each: 64.6%
Valencia	1-3 lesions ≤ 5 cm each. Total tumor diameter ≤ 10 cm	None	5 yr OS: 67%
Up to 7	The sum of the size and number of tumors not exceeding 7 in the absence of microvascular invasion	None	5 yr OS: 71.2%

Center	Morphologic Criteria	Biomarker Criteria	Survival
Hangzhou	Total tumor diameter ≤ 8 cm Total tumor diameter > 8 cm with histopathologic grade I or II	If total tumor diameter > 8 cm: AFP ≤ 400 ng/mL	5 yr OS: 70.7%, 5 yr DFS: 62.4%
Rome	Total tumor diameter ≤ 8 cm	AFP ≤ 400 ng/mL	5 yr DFS: 74.4%
Warsaw	UCSF or Up-to-7 criteria	AFP < 100 ng/mL	5 yr OS: 100%
Geneve (TTV)	Total tumor volume ≤ 115 cm^3	AFP ≤ 400 ng/mL	4 yr OS: 74.6%
Metroticket 2.0	Up-to-Seven Up-to-Five Up-to-Four	AFP ≤ 200 ng/mL AFP ≤ 400 ng/mL AFP ≤ 1000 ng/mL	5 yr Cancer Specific Survival: 75%,

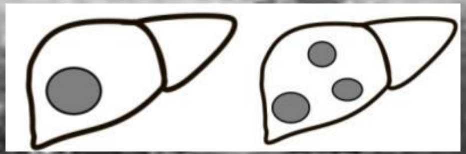


1996

Milan Criteria

Single lesion up to 5 cm
Up to 3 lesions up to 3 cm
OS 85.4% 4 Yrs

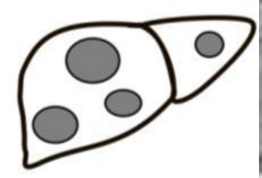
2001



UCSF

Single lesion up to 6.5 cm
Up to 3 lesions up to 4.5 cm
Total tumor diameter up to 8 cm
OS 80.9% 5 Yrs

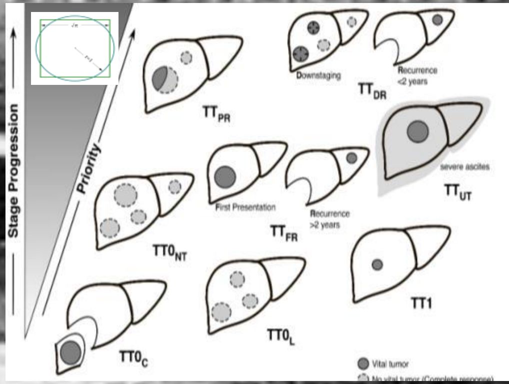
2009



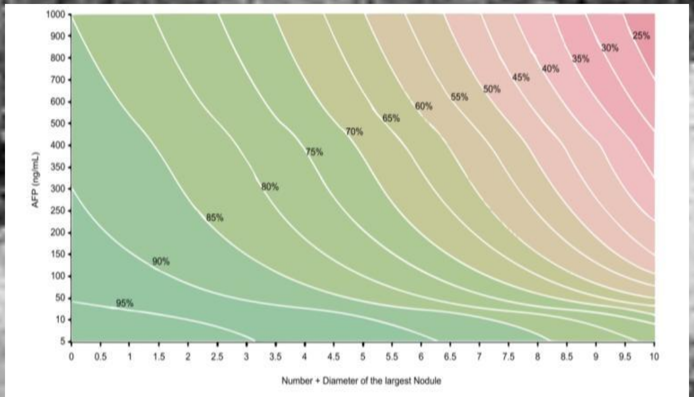
Up to Seven

Sum fo number of lesions and maximum diameter up to 7
OS 71.4% 5 Yrs

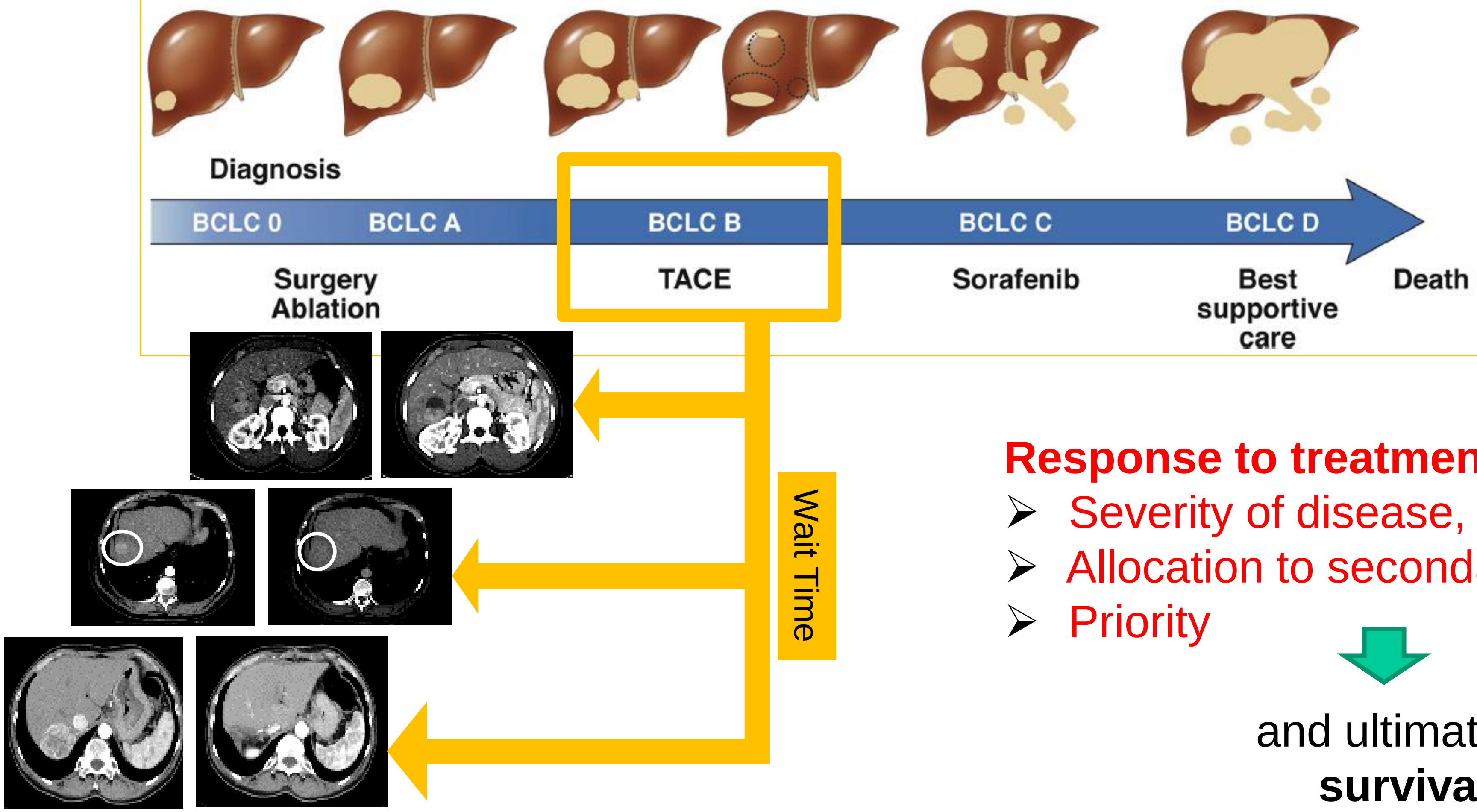
2016



2018



Innovative strategies can be more flexible
if based on quality of response to therapy

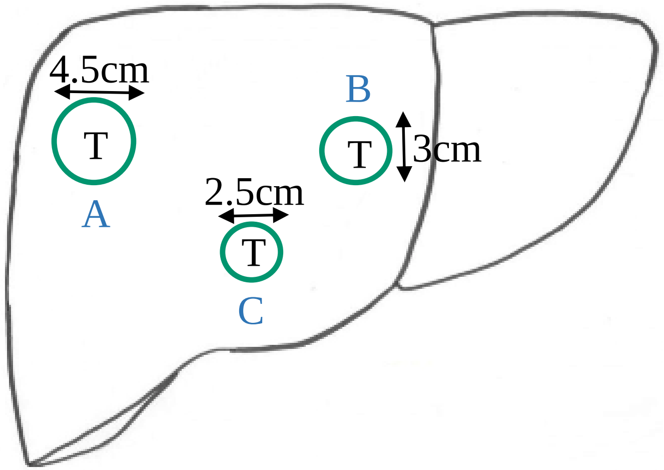


Response to treatment influences:

- ➢ Severity of disease,
- ➢ Allocation to secondary treatment
- ➢ Priority

and ultimately
survival

Through the metroticket calculator the **rate of «conversion to transplant» can be objectivized and measured** (even without the transplant)



AFP serum level
150 ng/mL

[EASL Guidelines J.Hepatol. 2018]

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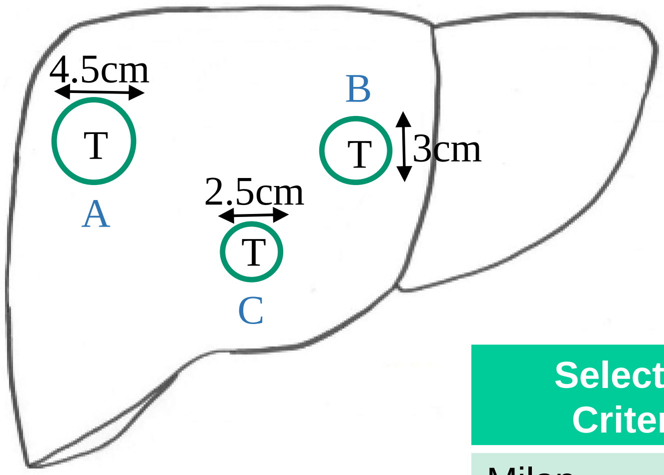
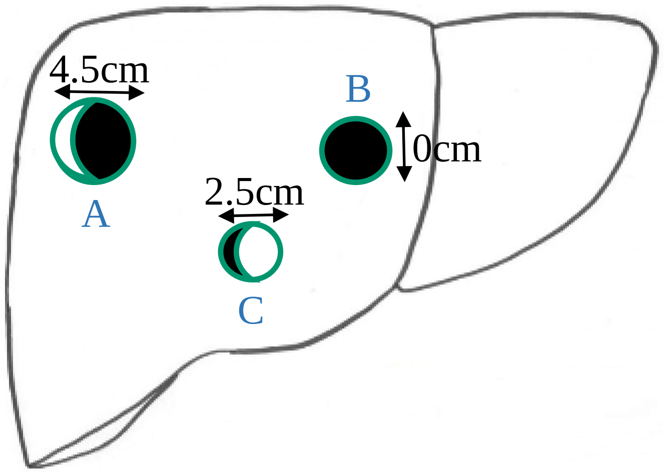


AFP serum level
150 ng/mL

Selection Criteria	Pre-treatment
Milan	OUT
UCSF	OUT
TTV+AFP	IN
Up-to-7	OUT
French Model	OUT (3 points)
HALT-HCC Score	High Risk (score 21)
Metroticket 2.0	55% at 5 yrs (if HCV-negative)

[EASL Guidelines J.Hepatol. 2018]

Through the metroticket calculator the **rate of «conversion to transplant» can be objectivized and measured** (even without the transplant)



AFP serum level
150 ng/mL
↓
45 ng/mL

[EASL Guidelines J.Hepatol. 2018]

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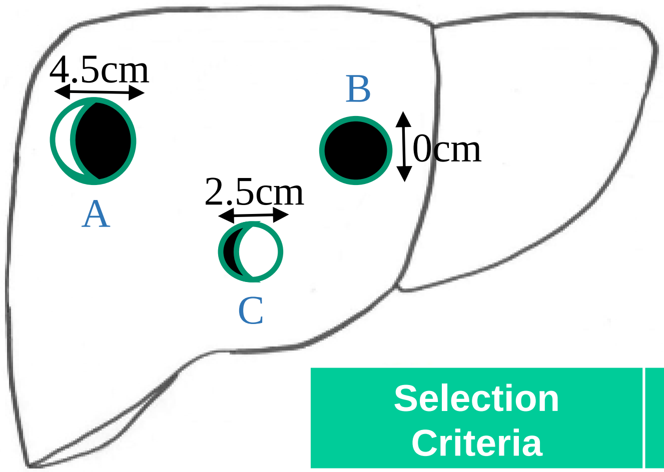
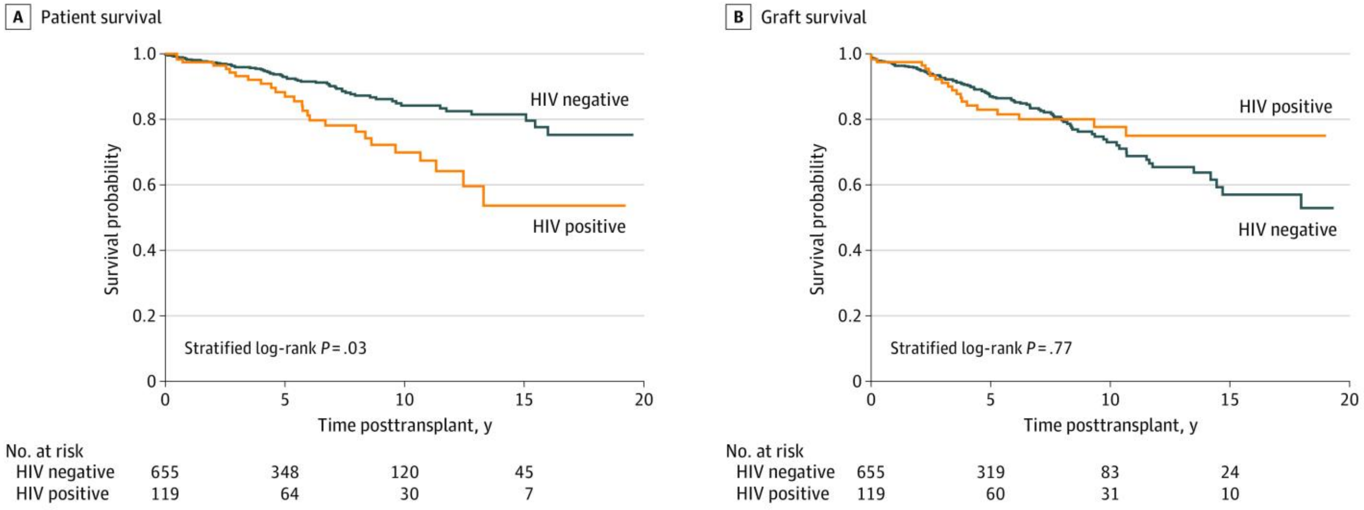


AFP serum level
150 ng/mL
↓
45 ng/mL

Selection Criteria	Pre-treatment	Post-treatment
Milan	OUT	OUT
UCSF	OUT	IN
TTV+AFP	IN	IN
Up-to-7	OUT	IN
French Model	OUT (3 points)	IN (1 point)
HALT-HCC Score	High Risk (score 21)	Low Risk (score 17)
Metroticket 2.0	55% at 5 yrs (if HCV-negative)	70% at 5yrs (if HCV-negative)

[EASL Guidelines J.Hepatol. 2018]

LT in HIV



LT in HIV-positive patients had comparable long-term outcomes with those in matched HIV-negative patients.
85 patient 2000 -2019 at UCSF
All indications

Arya Zarinsefat, JAMA Surg 2022

Liver transplantation for HCC in HIV patients. INT experience

30 patient 2010 - 2022 at INT
Only HCC patients

Inclusion criteria were:
unresectable HCC within Milan Criteria (MC),
CD4+ count > 200/mm3,
HIV-RNA undetectable,
absence of AIDS.

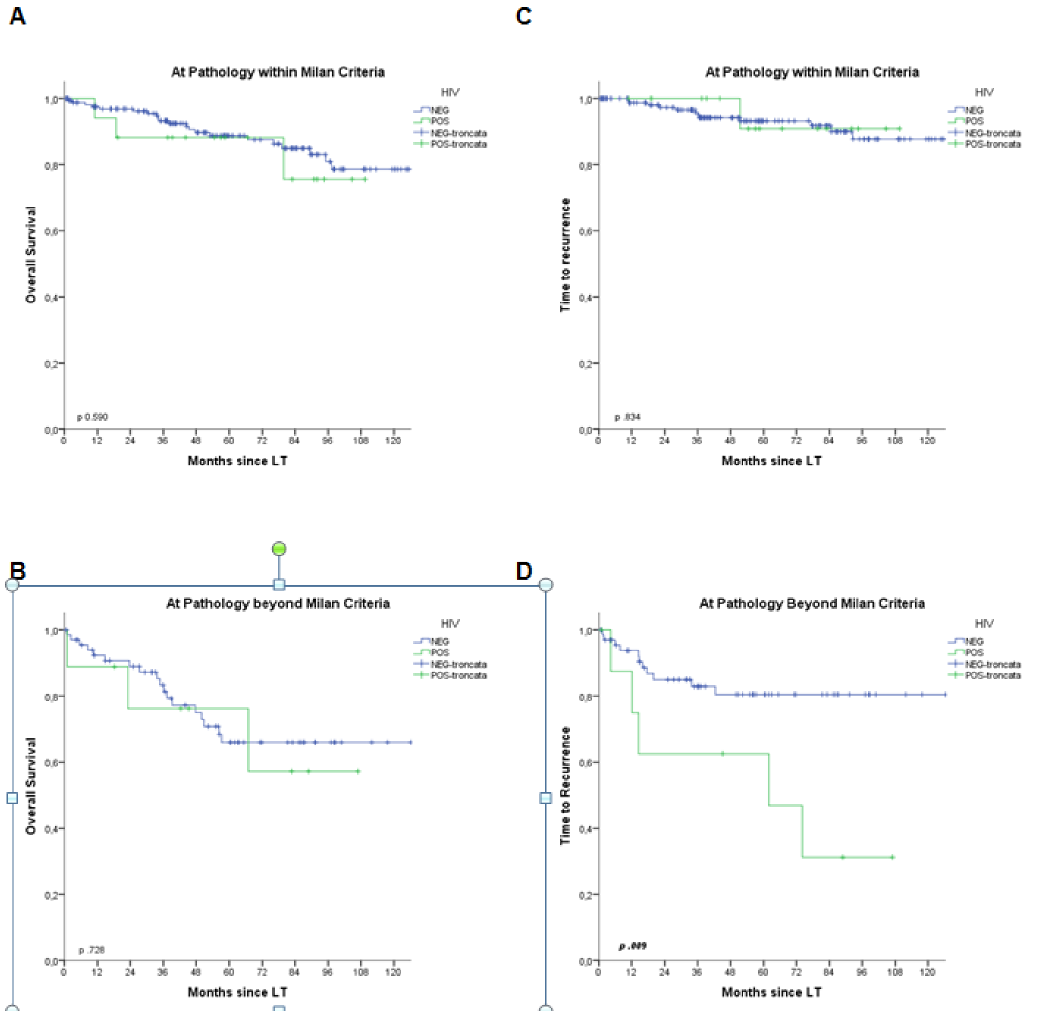
HIV patients were younger (median age 52 Vs 59 respectively p .005), more frequently HCV positive (92.6% Vs 52.4% respectively p .0001), and more frequently had an HBV-HCV co-infection (14.8% Vs 3.3% respectively p .005).

Liver function, median AFP and radiological presentation of HCC were similar between the two cohorts both at listing and at the last staging before LT.

	HIV Pos (n 30)	HIV Neg (n 285)	Sig.
General Characteristics			
Age	52 (44-62)	59 (28-71)	.005
HCV	28 (92.6%)	153 (52.4%)	.0001
HBV-HCV Co infection	5 (14.8%)	11 (3.3%)	.005
At listing for LT			
AFP	11.1 (1.0-140.7)	6.7 (1.0-2631)	.786
MELD	9 (6-18)	10 (6-24)	.503
Milan Criteria IN	30 (100%)	315 (100%)	NA
At last staging before LT			
AFP	9.34 (2.07-365.7)	6.0 (1-6805)	.953
MELD	10 (7-16)	9 (6-23)	.888
Milan Criteria IN	28 (92.6%)	265 (93.9%)	.731
At Pathology			
Milan Criteria IN	21 (69.2%)	203 (71.8%)	.750

Data are expressed as the median (range) or absolute number (%) as appropriate.

Liver transplantation for HCC in HIV patients. INT experience



After a **median follow-up of 62 months** (0.5-143), **5-year overall survival (OS) was similar** in HIV vs. non-HIV patients (**80.7% vs. 82.0%** respectively, **p .282**), while **5-year recurrence-free survival (RFS)** was significantly lower in HIV patients vs. non-HIV (**78.2% vs. 89.3%, p .018**).

5- year RFS was similar between the two cohorts with HCC within MC at pathology, while it was **62.5% vs. 81.2% in HIV vs. non-HIV patients beyond MC** (**p .009**).

CONCLUSIONS

Long-term survival after LT for HCC within Milan Criteria is similar in HIV and non-HIV patients, but HIV infected patients present a higher risk of HCC recurrence, particularly for tumors beyond Milan Criteria.

These data suggest that LT for HCC in HIV patients should preferably be performed within conventional MC

Take home message

Liver transplant patient changed over the last decade

Older patients and less virological background

Increase tumor burden beyond Milan Criteria doesn't seem to affect transplant outcomes in selected patients responding treatments and meeting combined morphological and biological criteria

HIV infected patients have similar post LT outcomes in case of tumor burden within Milan Criteria

Grazie!

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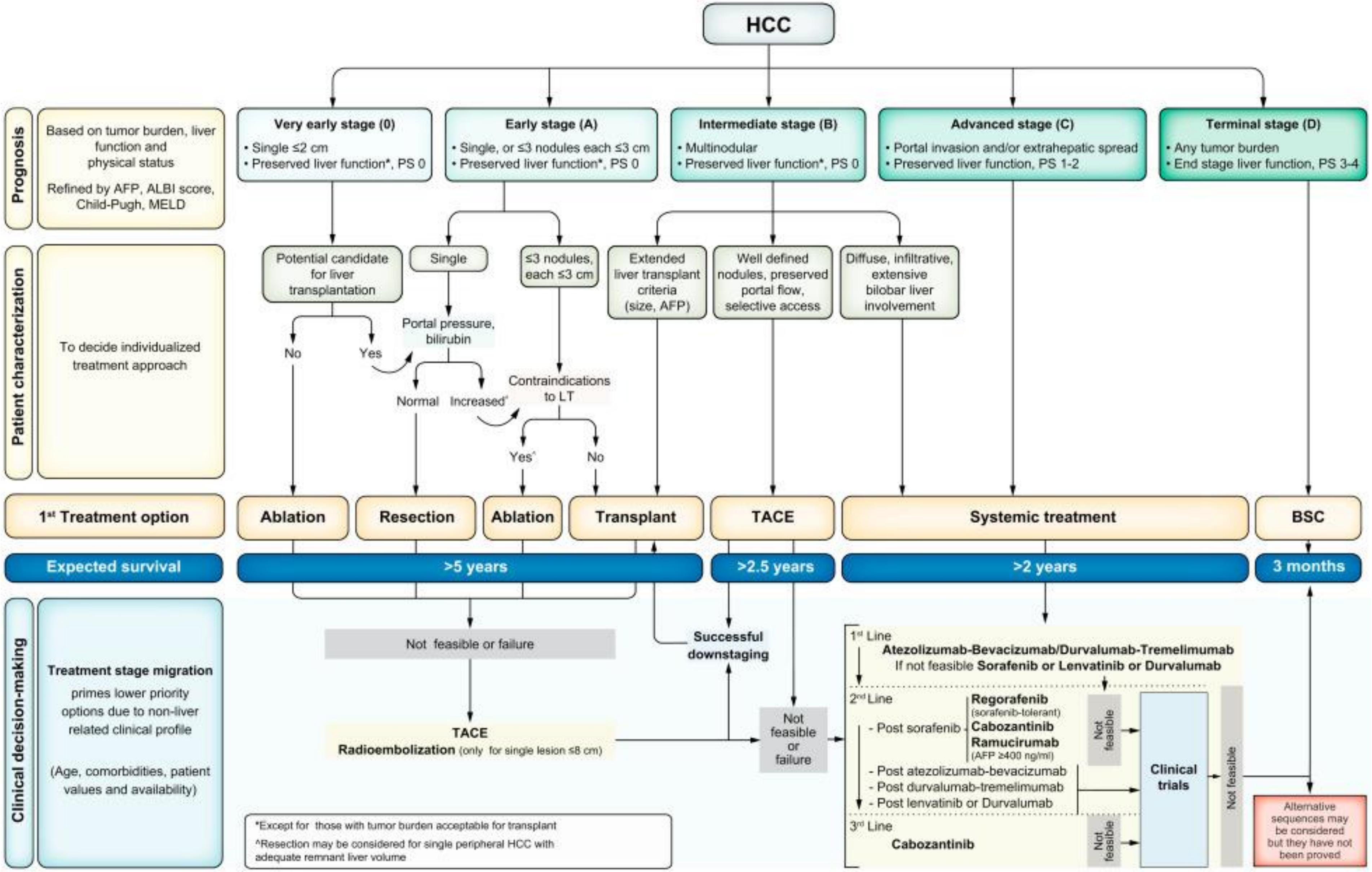
FONDAZIONE IRCCS
ISTITUTO NAZIONALE
DEI TUMORI

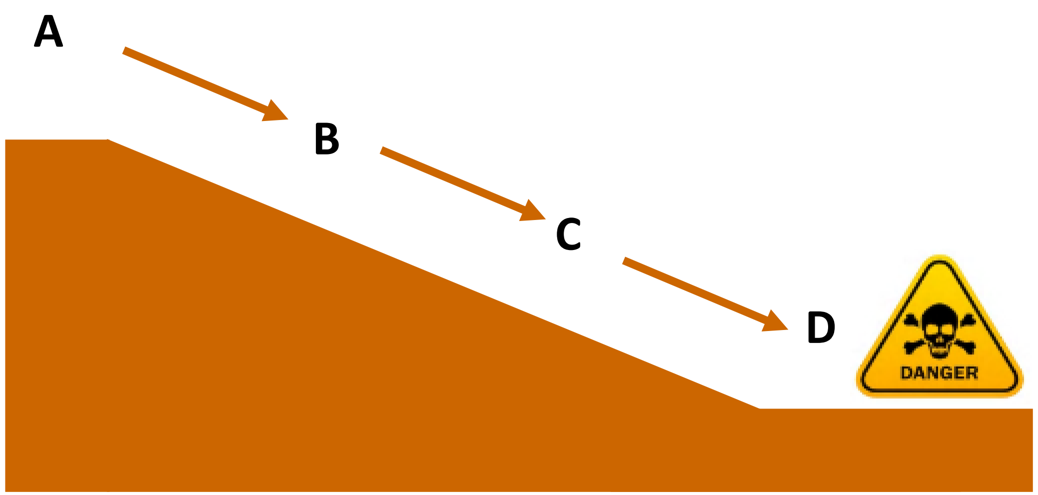
Sistema Sanitario Regione Lombardia

Evolution of indication to Liver Transplantation



Transplant Oncology : a slippery slope

The slippery slope in logic, critical thinking and caselaw, is a logical fallacy in which **a party asserts that a relatively small first step leads to a chain of related events culminating in some significant (usually negative) effect**.



1. If A then B
2. If B then C
3. If C then D
4. Not-D
Therefore, Not-A

Schematic representation of a slippery slope argument

Se ad A «succede» B (o si permette che succeda), C viene descritto come inevitabile passaggio a D, che però essendo ciò che andava evitato, porta a ridiscutere A, che pure era un accettato e stabile punto di partenza

Transplant Oncology : a slippery slope

The slippery slope in logic, critical thinking and caselaw, is a logical fallacy in which **a party asserts that a relatively small first step leads to a chain of related events culminating in some significant (usually negative) effect**.

Se ad A «succede» B (o si permette che succeda), C viene descritto come inevitabile passaggio a D, che però essendo ciò che andava evitato, porta a ridiscutere A, che pure era un accettato e stabile punto di partenza

Transplant Oncology in Primary and Metastatic Liver Tumor

Principles, Evidence, and Opportunities

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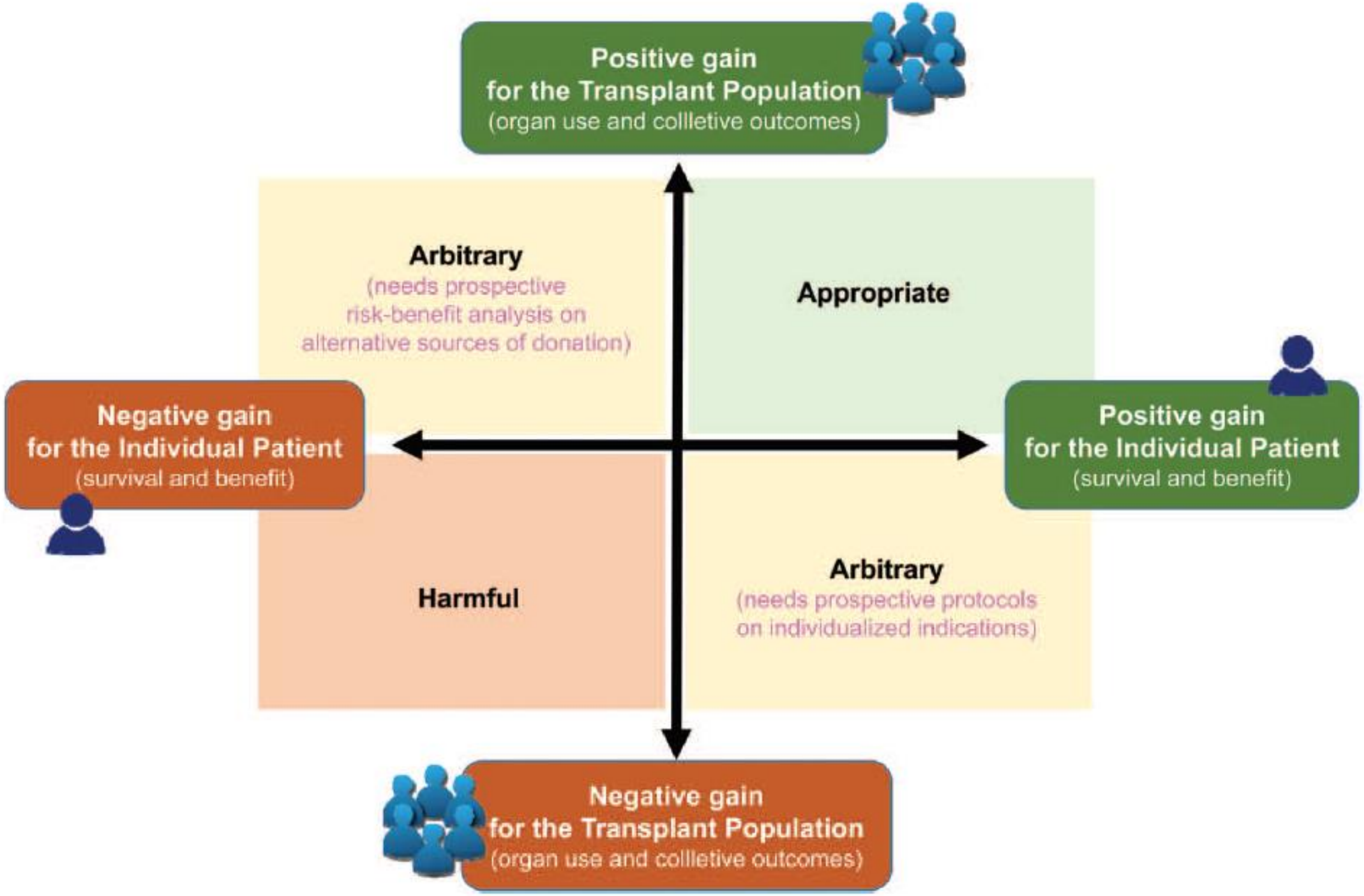
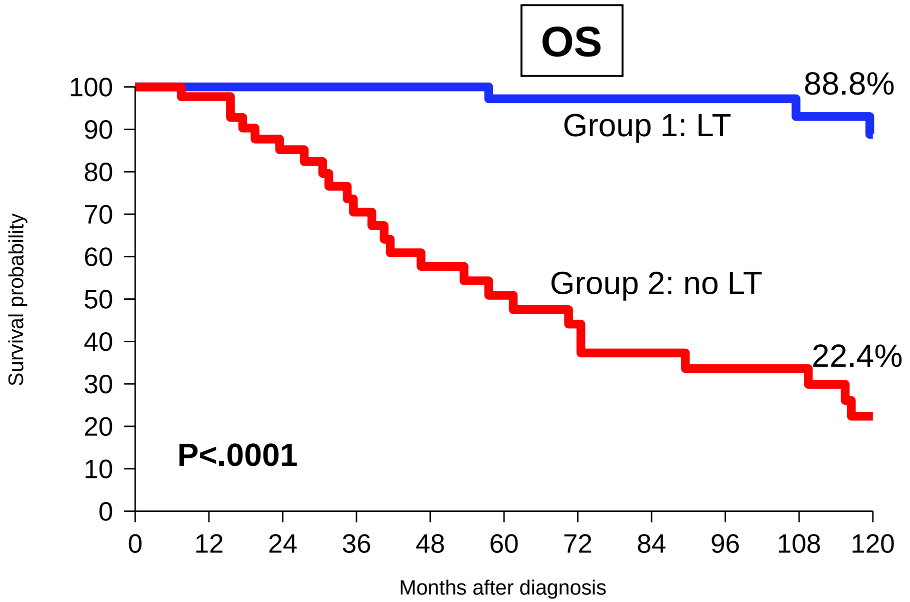


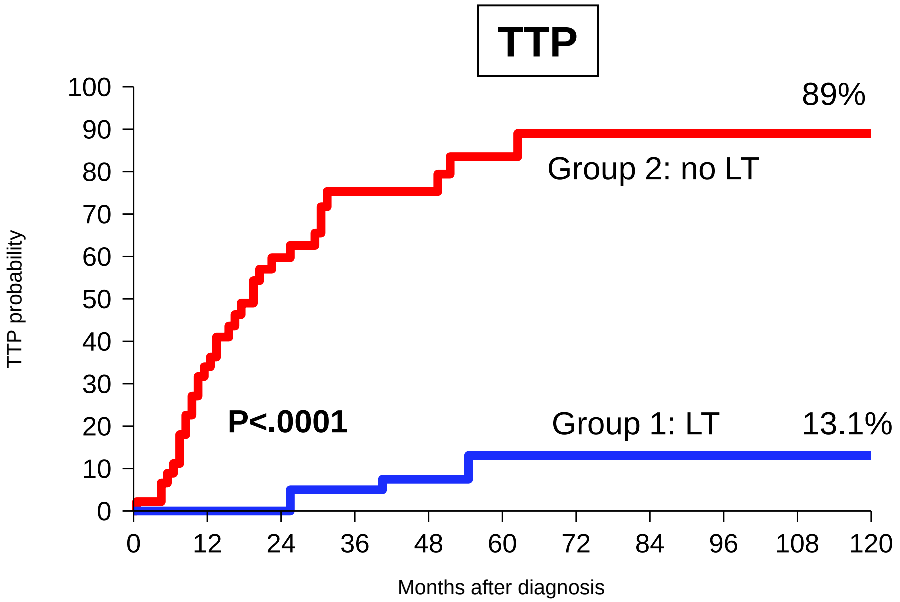
Balance of individual versus population-based perspective in transplantation applied to hepato-biliary cancer

Outcomes: Overall Survival and Time to Progression



Patients at risk

42	42	41	40	38	35	31	31	28	23	22
46	43	34	24	18	15	13	11	9	9	6



Patients at risk

42	42	41	38	35	32	27	27	25	20	20
46	30	15	6	6	3	2	2	2	2	2

	GROUP 1: LT	GROUP 2: no LT
5-yr OS	97.2%	50.9%
10-yr OS	88.8%	22.4%
Median OS	NR	62 months
Median TTP	NR	20 months

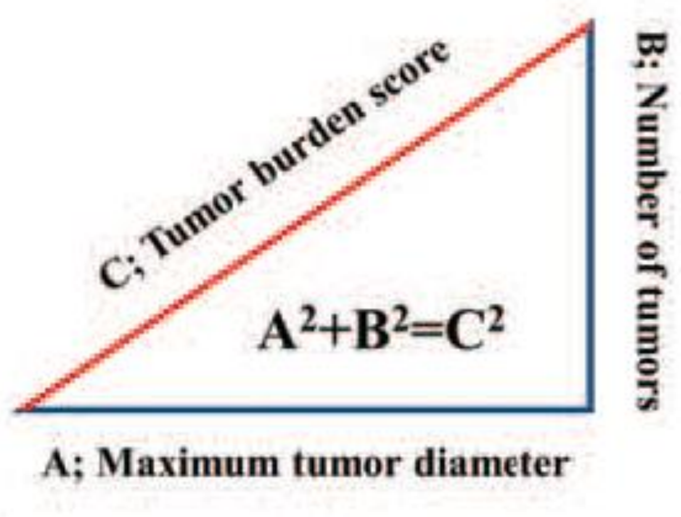
COLT trial
Improving outcome of selected patients with non-resectable hepatic metastases from colo-rectal cancer with liver transplantation: a prospective parallel trial

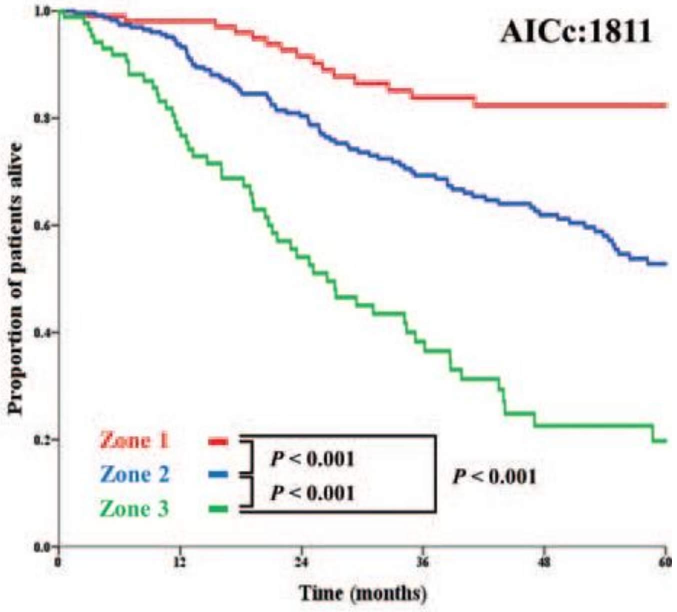
Criteria for non-resectability

Biologic/Functional non resectability: expected suboptimal outcome

- **Tumor burden score ≥ 9**

These patients, if resected, show 19.8-29.9% OS at 5 years, which is similar to that one achieved with hyper-intensive first-line chemotherapy regimens applied in non-resectable patients





Sasaki K et al. Ann Surg 2018