Downstaging/Bridging approaches and LT for HCC

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AOUI VERONA

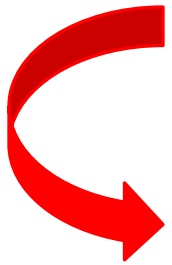
AGENDA

- Expanding criteria for LTx in HCC: Downstaging (DS)
- Bridging therapy for LTx
- Immunotherapy Pre-LTx: Expanding Horizons and Challenges
- Open questions ?

Tumor downstaging (DS): the concept

«Intent-to-cure treatments»

Tumor **downstaging (DS)** is defined as the approach with the aim of reducing tumor burden to select a subgroup of patients with favorable tumor biologies and prognoses that align with the accepted criteria for LT.



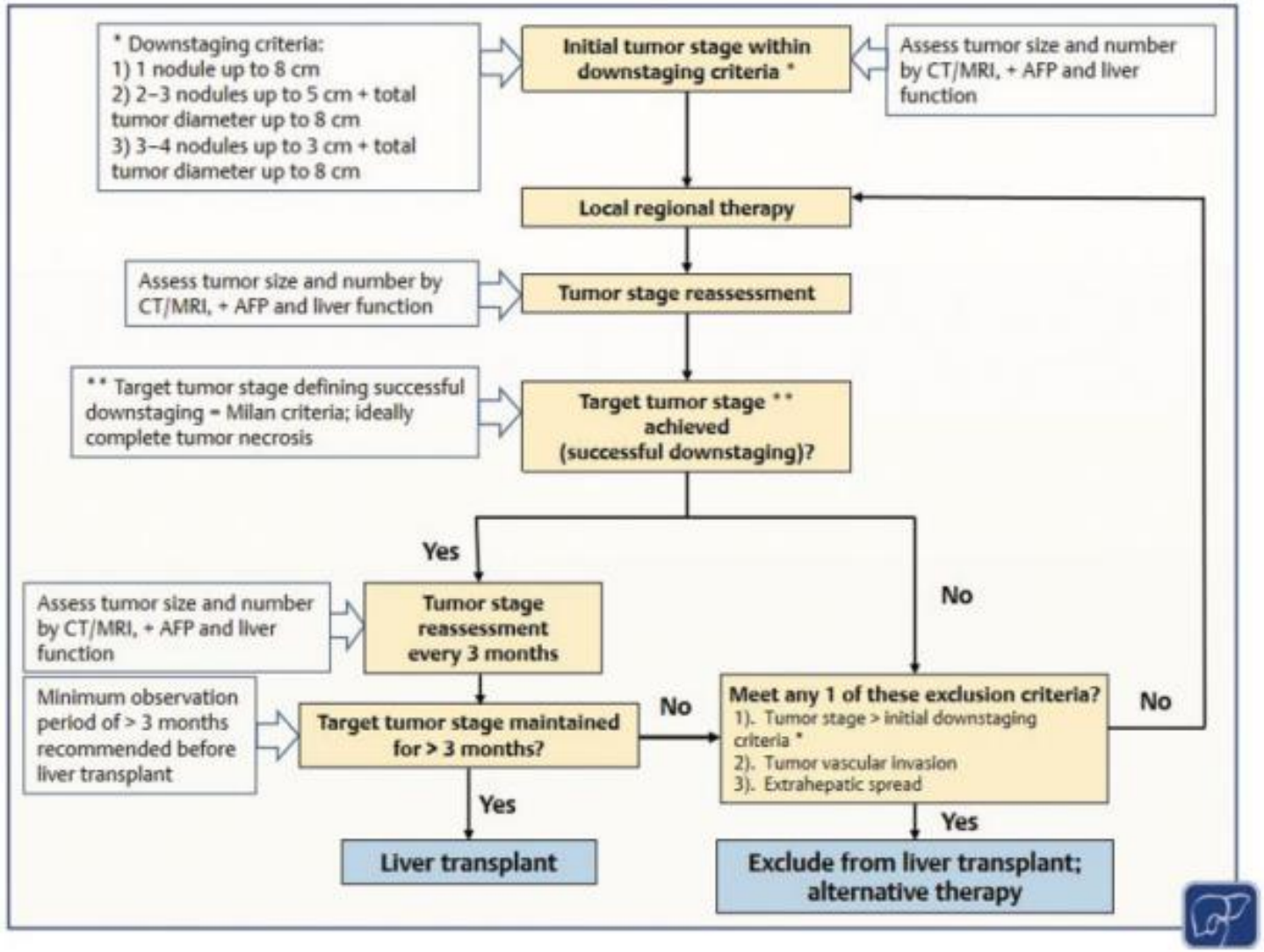
Equity: (a) applying equal treatment for equal needs, regardless of baseline disease or cause. (b) prioritize patients based on the "sickest-first" policy.

Utility: to obtain the greatest benefit post-transplant, overall survival and disease-free survival post-LT. (futility)

Benefit: survival gain from transplantation compared to the best alternative therapies.
5 to 10 y post-tx is considered the ideal time

Which downstaging criteria is the most reliable?

To standardize DS criteria, UNOS defined a national policy in the US in 2017 (UNOS-DS protocol)



UCSF downstaging criteria (UNOS/OPTN criteria)

(a) Single nodule 8 cm
(b) 2 or 3 nodules each 5 cm with the sum of the maximal diameters of all nodules 8 cm
(c) 3 or 4 nodules each 5 cm with the sum of the maximal diameters of all nodules 8 cm

Successful downstaging
1. Posttreatment tumor size and number within Milan criteria
2. Tumor burden must remain within Milan criteria for 6 months after downstaging to qualify for MELD exception points
3. Only viable tumors are included in measurement, necrosis from LRTs is not
4. If there are 2+ areas of enhancement in a tumor after treatment, the diameter of the entire lesion is counted toward the residual tumor burden

Semin Liver Dis 2021;41:117–127

UNOS Down-staging Criteria for Liver Transplantation of Hepatocellular Carcinoma: Systematic Review and Meta-Analysis of 25 Studies

1 Study Selection

Participants: Adult patients with HCC, that are deemed sutiable to undergo downstaging treatment.

Intervention: Patients with HCC who had undergone down-staging treatment by locoregional therapies, such as TACE or TARE, or a combination of therapies, for tumors initially beyond MC

Outcomes: Proportion of patients that were successfully down-staged to within MC, dropped out of the LT waitlist, underwent LT, HCC recurrence and overall survival .

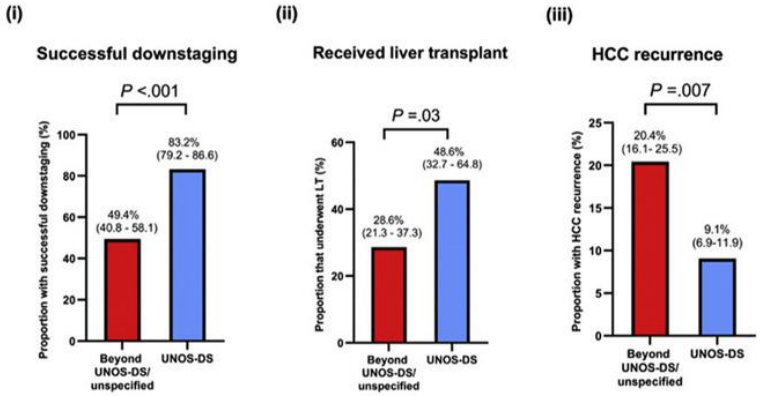
2 Findings

We screened 1,059 articles and included 25 articles involving 3,997 patients.

Patients from studies using UNOS-DS criteria had lower MELD score, lower AFP at listing, lower cumulative tumor diameter, and fewer HCC nodules compared to studies beyond UNOS-DS/ no specified tumor burden.

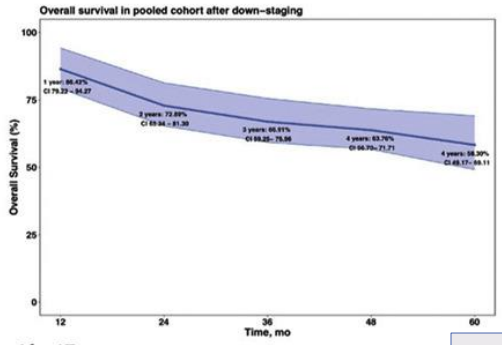
Overall, 51.82% underwent successful down-staging, 32.83% underwent LT and 16.08% developed HCC recurrence.

Summary of key outcomes of downstaging, by criteria used for baseline tumor burden

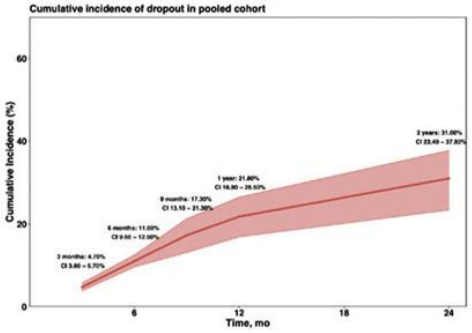


Overall pooled survival after Downstaging/LT

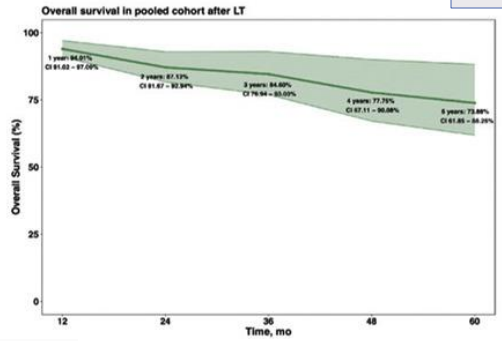
Intention-to-treat



Incidence of dropout



After LT



WL dropouts 36% vs 50%, P.007

3 Conclusion

Only half of all HCC patients underwent down-staging successfully and a third received LT.

Among studies that utilized the UNOS-DS criteria, downstaging was successful in four-fifths, half received LT and post-LT outcomes were excellent.

For patients within the UNOS-DS criteria, the intention-to-treat 1- and 5- year survival for was 86% and 58% respectively. 1- and 5- year post-LT survival was 94% and 74% respectively.

Keywords:LT, Liver Transplant; HCC, Hepatatocellular Carcinoma; UNOS-DS, United Network of Organ Sharing Down-staging; TACE, trans-arterial chemoembolization; TARE, trans-arterial radioembolization; MC, Milan Criteria

Clinical Gastroenterology and Hepatology

ITT (UNOS/DS)

1-, 3-, and 5-year OS after DS 86.420%, 66.91%, and 58.30%

1-, 3-, and 5-year OS **after LT** 94.01%, 84.60%, and 73.88%

AFP >100 ng/mL at diagnosis and at listing < odds of successful DS and < post-LT survival,

Clinical Gastroenterology and Hepatology 2023;21:1475–1484

Post-transplant outcome following downstaging

Author, year, institution (reference)	Initial tumor staging criteria	Study design	Post-transplant survival	p-Value
Yao 2015; San Francisco, CA	UCSF downstaging criteria	Prospective single-center study	Downstaged (n=64): 5y survival 78%; 5y recurrence-free probability 91% MC (no downstaging) (n = 332):	NS
Mehta 2018; Multicenter region 5 (3 centers)	UCSF downstaging criteria	Retrospective multicenter study	Downstaged (n	
Mehta 2020; UNOS database	UCSF downstaging criteria	Retrospective database analysis	Within UCSF MC Beyond UCSF dow	nd UCSF riteria vs n neeting UCSF staging criteria vs Milan
Tabrizian 2022; US multicenter study (5 centers)	10y post-LTx DS Criteria (5 centers)	Retrospective multicenter study	Downstaged MC (n=341): 10y ; 10y recurrence 20% MC (no downstaging) (n =2086): 1 vival 61%; 10y recurrence 14% Beyond MC not downstaged (n=110): 10y survival 44%; 10y recurrence 41%	p < 0.001 for beyond Milan (not downstaged) vs other groups
Ravaioli 2008; Bologna, Italy	Bologna criteria	Prospective single-center study	Downstaged (n=32): 3y tumor-free survival 71% MC (no downstaging) (n=88): 3y tumor-free survival 71%	NS

poor recurrence-free survival (RFS) in the DS: neutrophil-to-lymphocyte ratio (NLR) >5 at LT (*P*<0.001) and largest viable tumor >5 cm (*P*=0.002); **downstaging failure** included more than 3 tumors at diagnosis (*P*=0.01), tumor size >7 cm at diagnosis (*P*=0.02), and an AFP response (*P*=0.02).

From *Yao FY, Fidelman N, Mehta N. The Key Role of Staging Definitions for Assessment of Downstaging for Hepatocellular Carcinoma. Semin Liver Dis. 2021 May;41(2):117-127. doi: 10.1055/s-0040-1716565. Epub 2021 Jan 14. PMID: 33788207.*

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

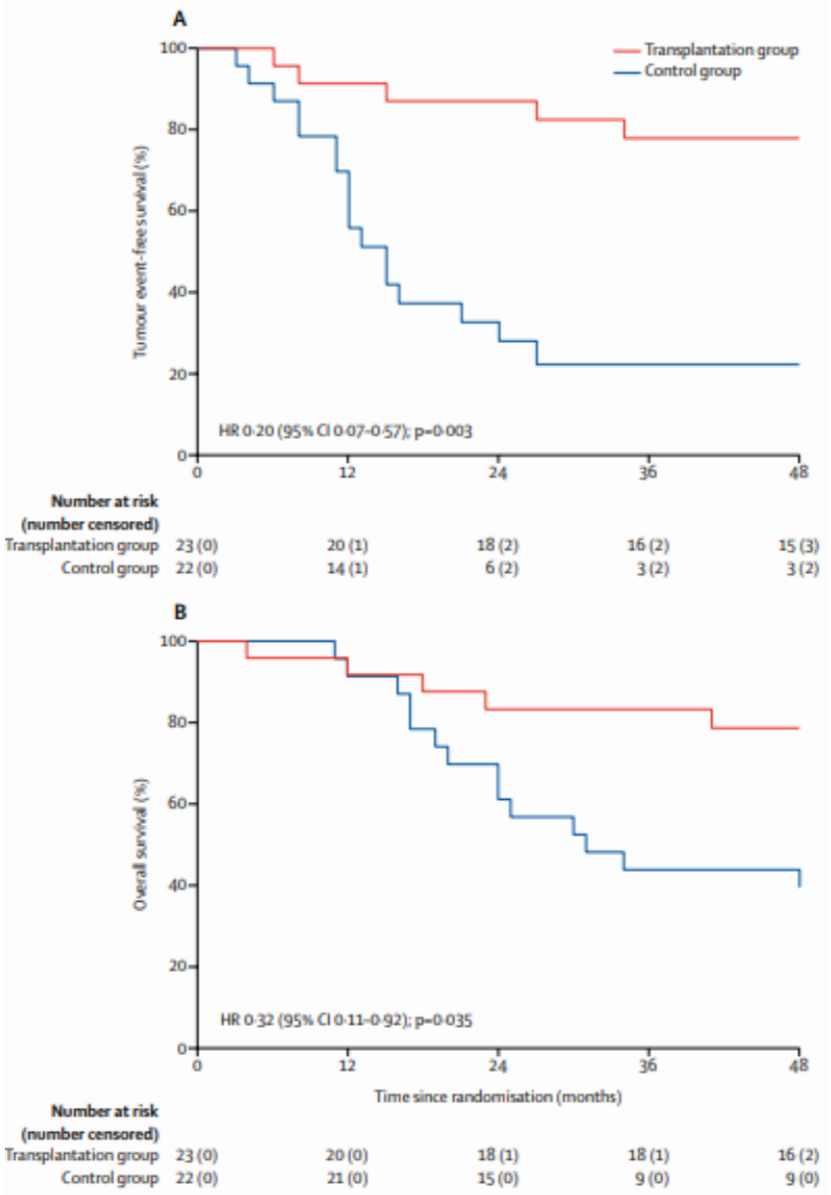
Open-label, multicentre, randomised, controlled trial (2b and 3), at 9 Italian centres.
Pts HCC beyond the Milan criteria, absence of macrovascular invasion or extrahepatic spread, 5-year estimated post-Tx survival of at least 50%, (Child-Pugh A-B7) and underwent tumour downstaging with locoregional, surgical, or systemic therapies.

1°: 5-year tumor event-free survival (phase 2b) and OS (phase 3).
Analyses were by intention to treat.

2011-2015, 74 pts (DS 6 months).
45 were randomly assigned: 23 to the transplantation group vs 22 to the control group.

5-year tumor event-free survival 76·8% in the tx group vs 18·3% in the control group (p=0·003).
5-year overall survival 77·5% in the tx group vs 31·2% in the control group (p=0·035).

→keeping the time to transplantation as short as possible.
→priority assignment to patients with HCC (partial or complete response to LRT).



Expansion of downstaging criteria

Are there upper limits in tumor burden for DS of HCC?

Is the "All Comers" Approach Worth It?

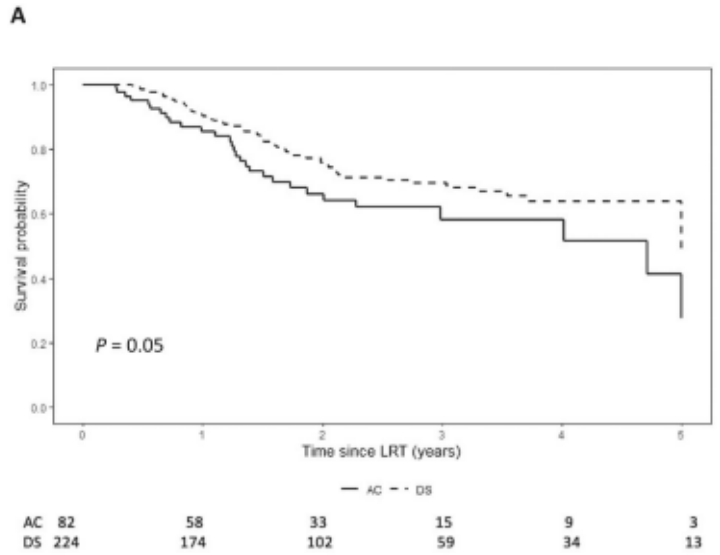
A multicenter analysis "all-comers" protocol (MERITS-LT) consortium

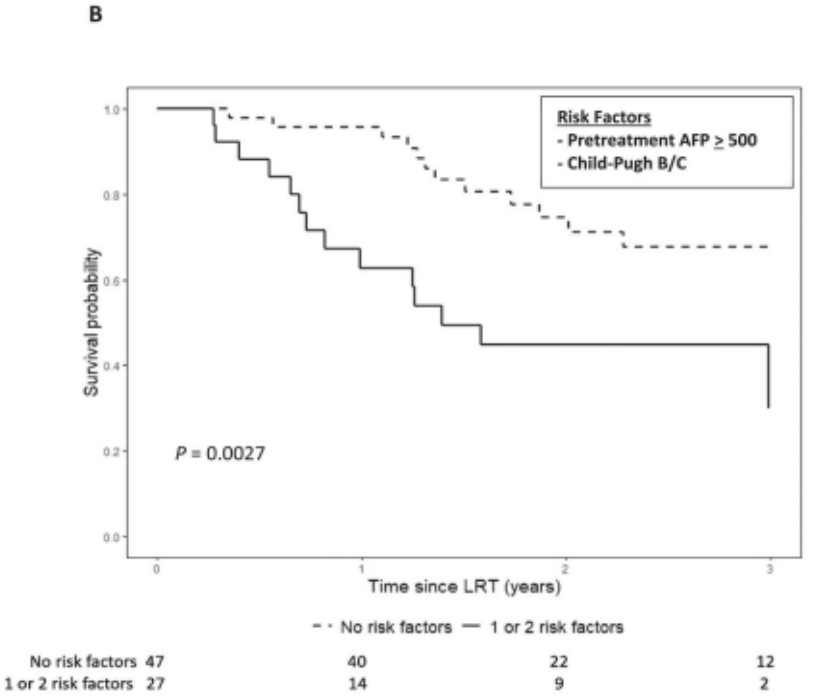
311 LT (229 in UNOS-DS, 82 in AC-DS)
3-year OS rate from LRT of 69% in the UNOS-DS group and 58% in the AC-DS group (*P*=0.05).
The 3-year post-LT OS rate not significantly different (91% vs. 81%; *P*=0.67).

3-year OS rate from LRT in AC-DS pts: no high-risk factors 67.7% vs 29.9% in AC-DS pts with high-risk (*P*=0.003).

LT could be considered for highly selected AC-DS patients with favorable tumor biology if successful downstaging is achieved.

B. Natarajan Am J Transplant. 2023; 23(11): 1771–1780

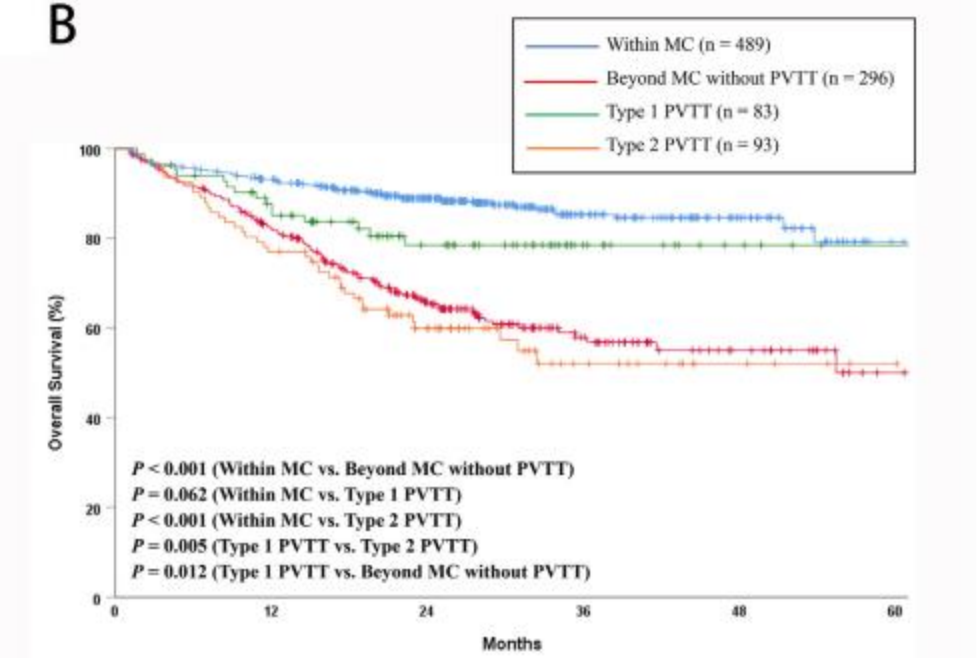




Long-term outcomes of deceased donor liver transplantation in hepatocellular carcinoma patients with portal vein tumor thrombus: A multicenter study

961 LT (489 within MC, 296 beyond MC but without PVTT, 83 with type 1 PVTT, and 93 with type 2 PVTT):
5-year OS rate for type 1 PVTT pts was not significantly different vs MC (78.3% vs. 79.1%; *P*=0.062) and was superior compared to patients beyond MC but without PVTT (78.3% vs. 50.0%; *P*=0.012).

OS and RFS rates for PVTT patients with AFP ≤100 ng/mL were significantly > vs pts beyond MC or PVTT patients with AFP >100 ng/mL (*P*<0.01).



Soin AS, Bhangui P, Kataria T, Baijal SS, Piplani T, Gautam D, et al. Experience with LDLT in patients with hepatocellular carcinoma and portal vein tumor thrombosis postdownstaging. Transplantation 2020;104:2334-2345.

Serenari M, Cappelli A, Cucchetti A, Mosconi C, Strigari L, Monari F, et al. Deceased donor liver transplantation after radioembolization for hepatocellular carcinoma and portal vein tumoral thrombosis: a pilot study. Liver Transpl 2021;27:1758-1766.

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

DS Patients, especially those meeting UNOS DS criteria, should be considered for LT following successful downstaging to within Milan criteria after a **3-to-6-month period of observation** (**Level 2, Strong Recommendation**).

a. Patients with AFP > 1000 ng/ml must be downstaged **to AFP < 500 ng/ml** to be considered downstaged (**Level 2, Strong Recommendation**).

Thermal ablation should be considered the treatment of choice for patients with early-stage HCC ≤ 3 cm who are ineligible for or decline surgery (Level 1, Strong Recommendation). (AASLD does not advise one thermal ablative modality over another)

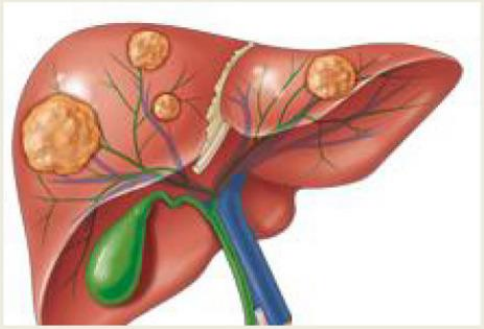
TARE or EBRT may be used as alternative therapies to thermal ablation for patients with BCLC stage A HCC not candidates for surgical resection (L**evel 3, Strong Recommendation**).

Patients with BCLC Stage B HCC should be treated with transarterial chemoembolization (Level 1, Strong Recommendation). AASLD advises TARE as an alternative therapy to TACE in BCLC Stage B HCC (**Level 3, Strong Recommendation**).

Hepatology. 2023 December 01; 78(6): 1922–1965

Down-staging Outcomes for HCC: Results from the Multicenter Evaluation of Reduction in Tumor Size before Liver Transplantation (MERITS-LT) Consortium

HCC meeting UNOS-DS criteria*

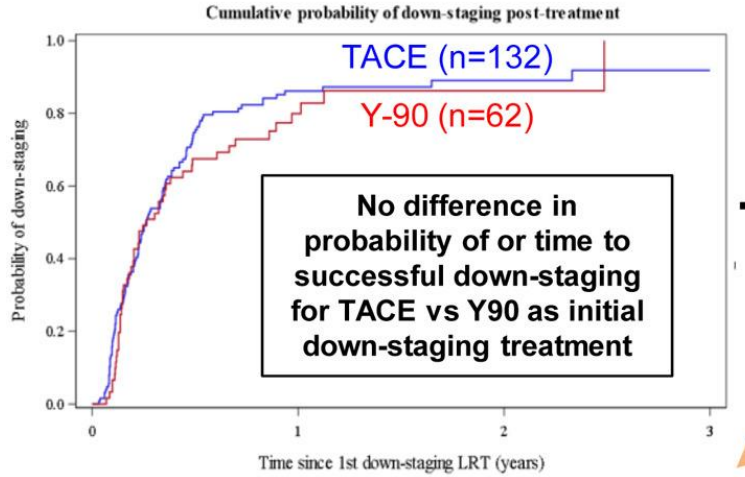


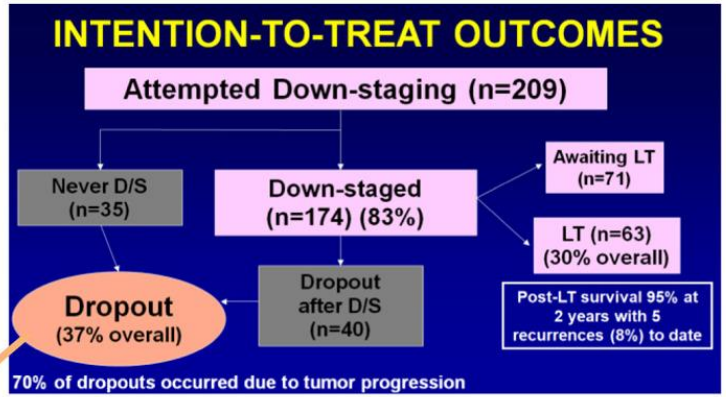
UNOS-DS inclusion criteria*

1 lesion > 5 cm and ≤ 8 cm
2 or 3 lesions ≤ 5 cm w/ total diameter ≤ 8 cm
4 or 5 lesions ≤ 3 cm w/ total diameter ≤ 8 cm
No vascular invasion or extrahepatic spread

Study Design

Consecutive pts from 7 LT centers in 4 UNOS regions enrolled from 2016-2019 and prospectively followed





Protocol Dropout

- No difference in dropout probability for TACE vs Y90 as 1st down-staging treatment
- Pre-tx AFP-L3 ≥10% (competing risks HR 3.7, p=0.02) only variable associated w/ dropout

Overall intention-to-treat survival

92% at 1 year and 72% at 3 years from 1st down-staging treatment

Gastroenterology

Mehta N et al Gastroenterology. 2021 November ; 161(5): 1502–1512.

AGENDA

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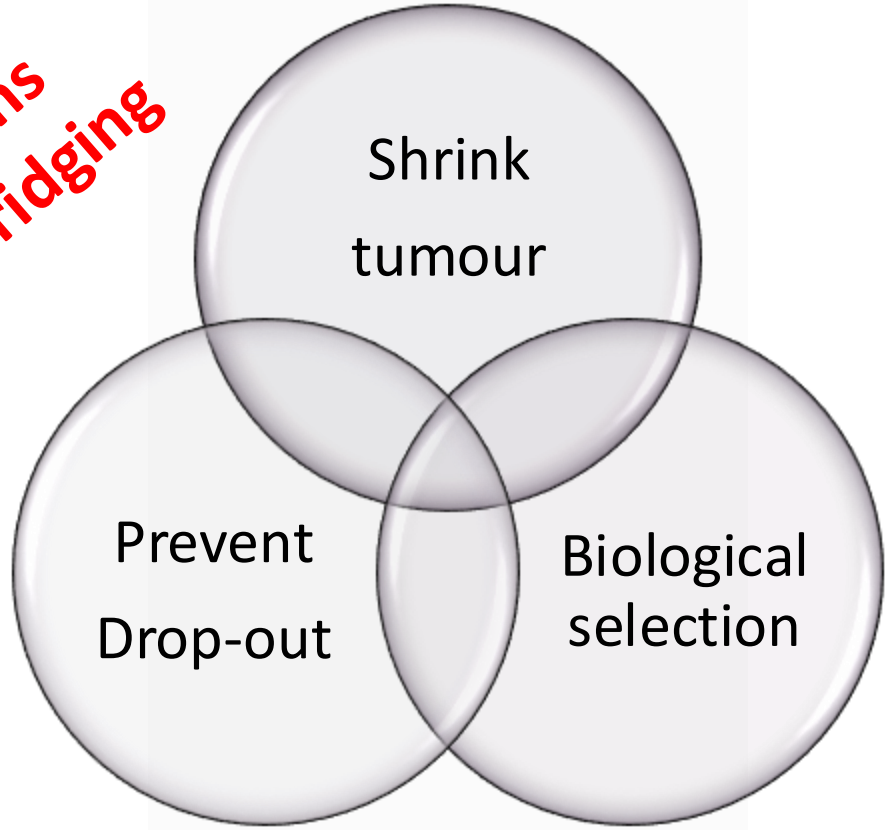
- Bridging therapy for LTx
- Immunotherapy Pre-LTx: Expanding Horizons and Challenges
- Open questions ?

Bridging Therapy(BT): the concept

Bridging therapy is commonly used to keep patients with HCC within established transplant criteria. However, it is uncertain whether this also results in improved post-transplant survival and should therefore be standard practice for every patient on the transplant waiting list.

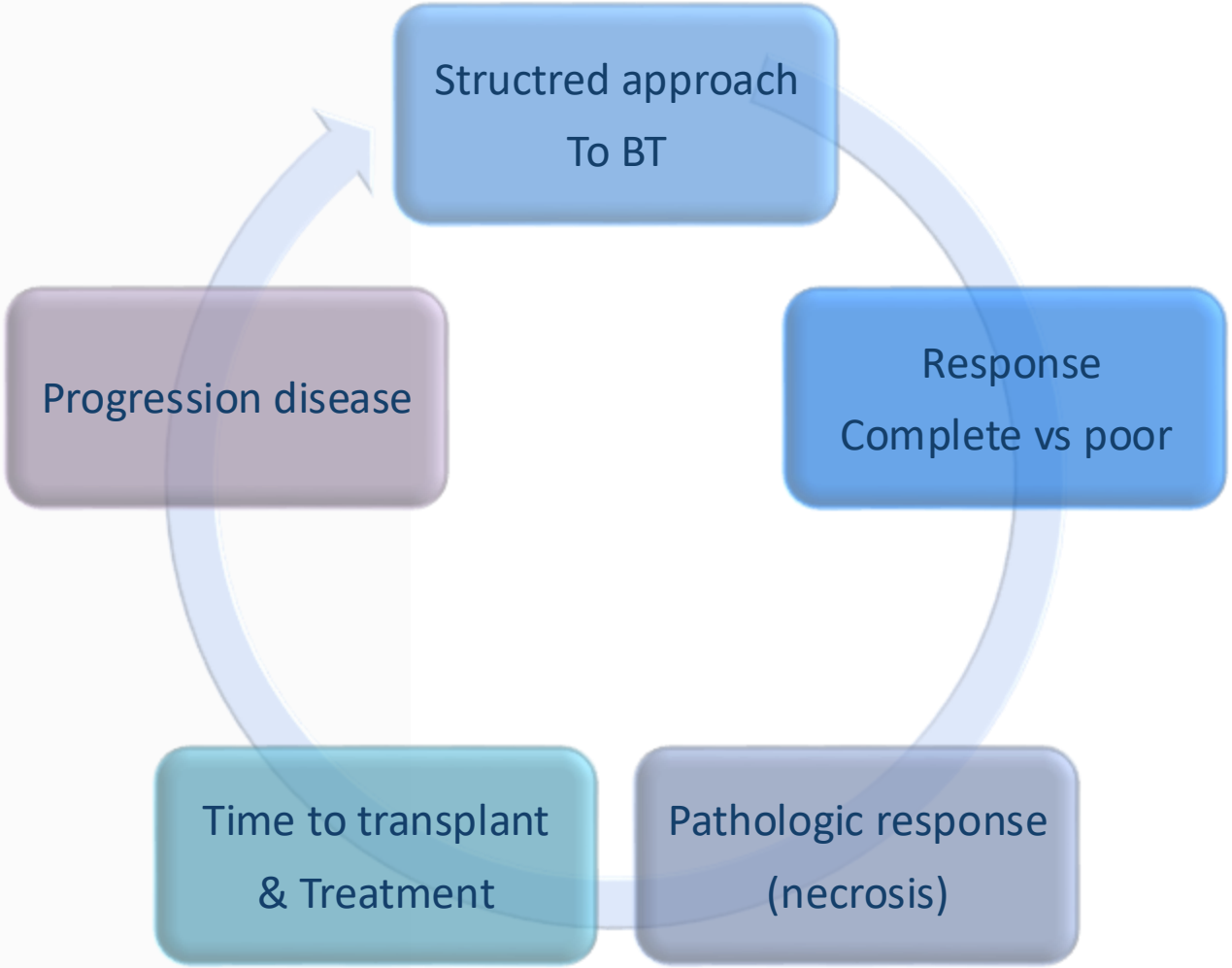
LTX: Tumor indications
Combined goals of bridging



Cancers 2021, 13, 5558.

Effect of Bridging Therapy on Hepatocellular Carcinoma Recurrence after Liver Transplantation

Patients with HCC progression from Milan in to Milan out < OS overall survival and recurrence-free survival *vs* controlled within the Milan criteria.



Renner, P. et al *BJS Open* **2021**, *5*, zrab005.

Agopian, V.G. et al. *Ann. Surg.* **2015**, *262*, 536–545.
Lai, Q. et al. *Liver Transplant.* **2019**, *25*, 1023–1033.
Rubinstein, M.M et al *J. Gastrointest. Oncol.* **2017**, *8*, 1051–1055.

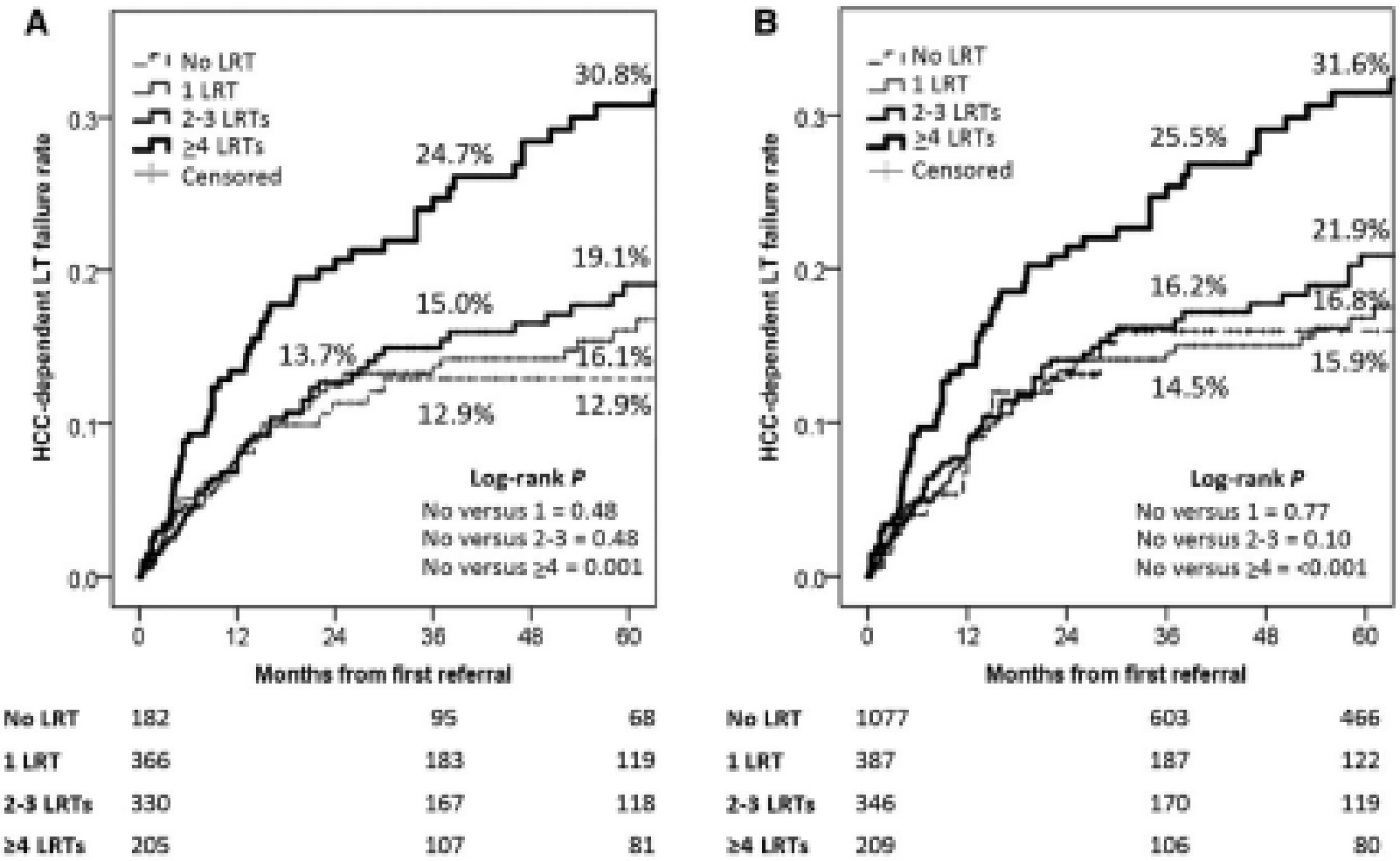
Role of Pretransplant Treatments for Patients with Hepatocellular Carcinoma Waiting for Liver Transplantation

Author	Country	Year	N. Of Patients	Selection Criteria	Time Period on Waiting List to LT	Treatment Modality	Drop-out Rate	OS,RR, DFS and RFS after LT
Lee	USA	2017	121	MC (within MC 90.1%)	10.2 months	RFA	1y 13.5%, 3y 37.2%, 5y 58.1%	RR 1y 2.5%, 3y 5.3%, 5y 7.2%
Tan						RFA	6m 18.7% 1y 33.3%	3y DFS 71%
Lee						RFA,RT, Resection	na	RFS T1 1y 97.8%, 3y 95.5%,5y 94% T2 1y 94.8%, 3y 92.1% 5y 90.7%
Na						RFA,PEI	Within→ beyond 24.5%	RFS 3y 78.3%, 5y 72.3%
Affonso						TACE	33.8%	RFS 3y 76.5%, 5y 72%
Xing	USA	2017	155	MC	5.92 (0.12-67.33) months	TAE,TACE,DEB-TACE,RE,RFA	28.3%	OS 3y 85%, 5y 72%
Agopian	USA	2017	2854	MC	NA	TACE,RE,RFA,PEI, Resection, MW	na	RFS 1y 89%, 3y 77% 5y 68%

Tan no difference in the frequency of drop-outs from the waiting list between the BT group and the non-BT group, but the waiting period tended to be longer in the BT group.

locoregional therapy for HCC should be given if the waiting period is 6 months or longer to prevent waiting list drop-out during the waiting period
EASL
Journal of Hepatology, February 2025. vol. 82 j 315–374

The Intention-to-Treat Effect of Bridging Treatments in the Setting of Milan Criteria–In Patients Waiting for Liver Transplantation



Liver Transplantation 25 1023–1033 2019 AASLD.

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

AASLD advises the use of pre-transplant locoregional bridging therapy for patients being evaluated or listed for liver transplantation, if they have adequate hepatic reserve, to reduce the risk of waitlist dropout in the context of anticipated prolonged wait times for transplant **(Level 3, Strong Recommendation).**

AASLD does not advise one LRT over another for bridging therapy. The choice of locoregional modality should be based on tumor size, location, and center expertise **(Level 3, Weak Recommendation).**

AASLD does not recommend the routine use of systemic therapy as bridging therapy for transplantation; however, its use does not preclude LT eligibility (Level 5, Weak Recommendation).

Hepatology. 2023 December 01; 78(6): 1922–1965

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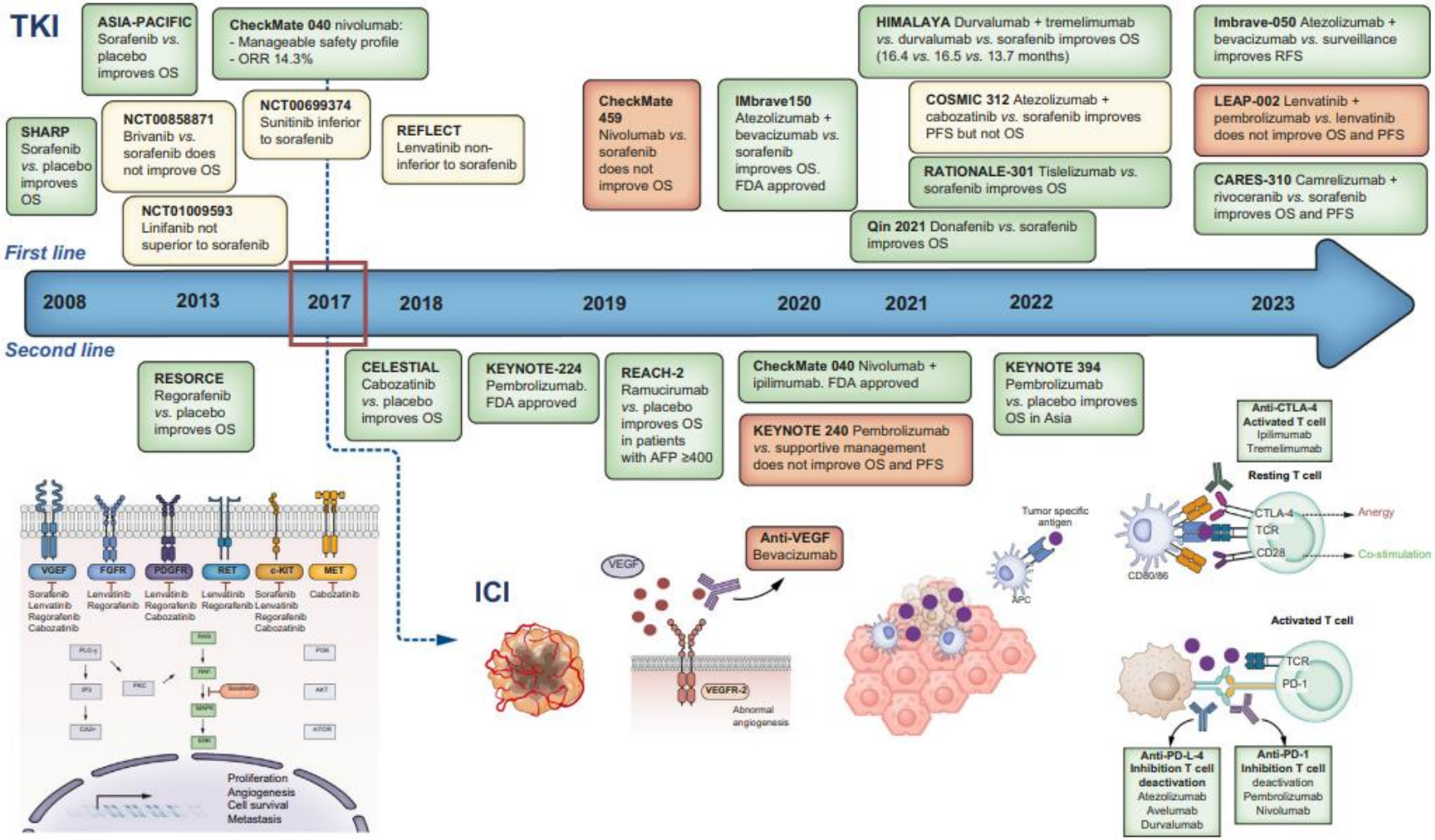
Chronological overview of all clinical trials investigating immunotherapy and immune checkpoint inhibitors in the treatment of HCC:

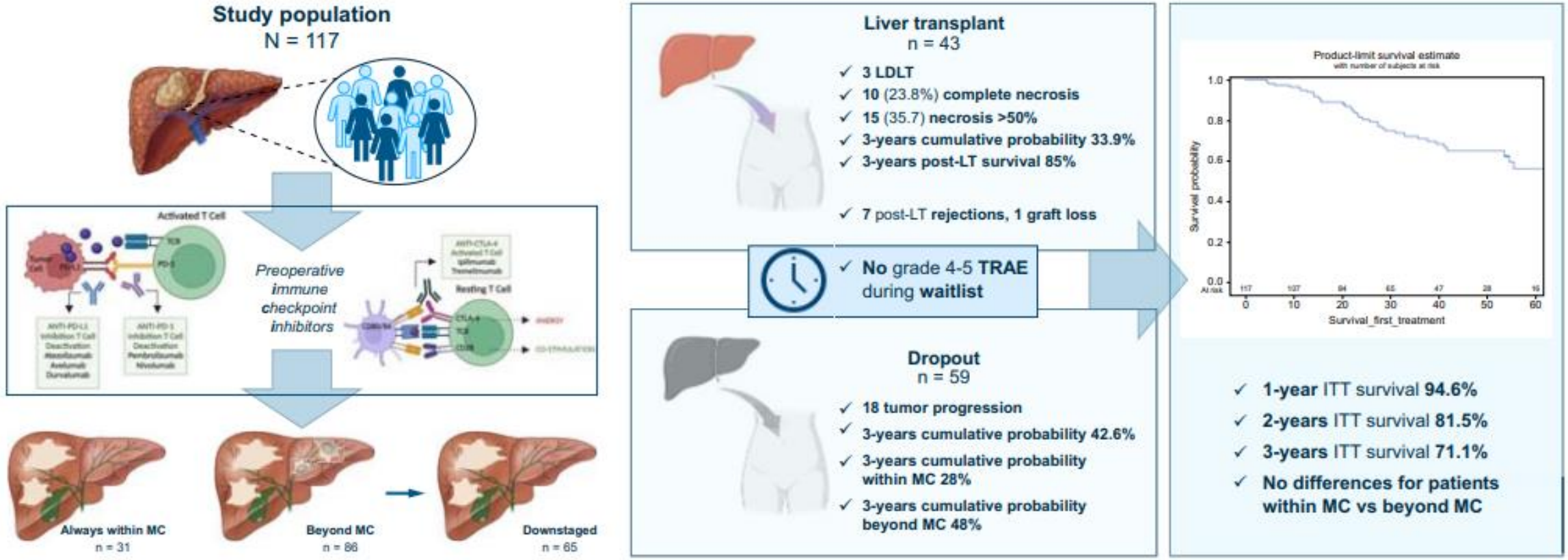
neoadjiuvant – coversion or DS intent?

BIOLOGICAL SELECTION Of HCC



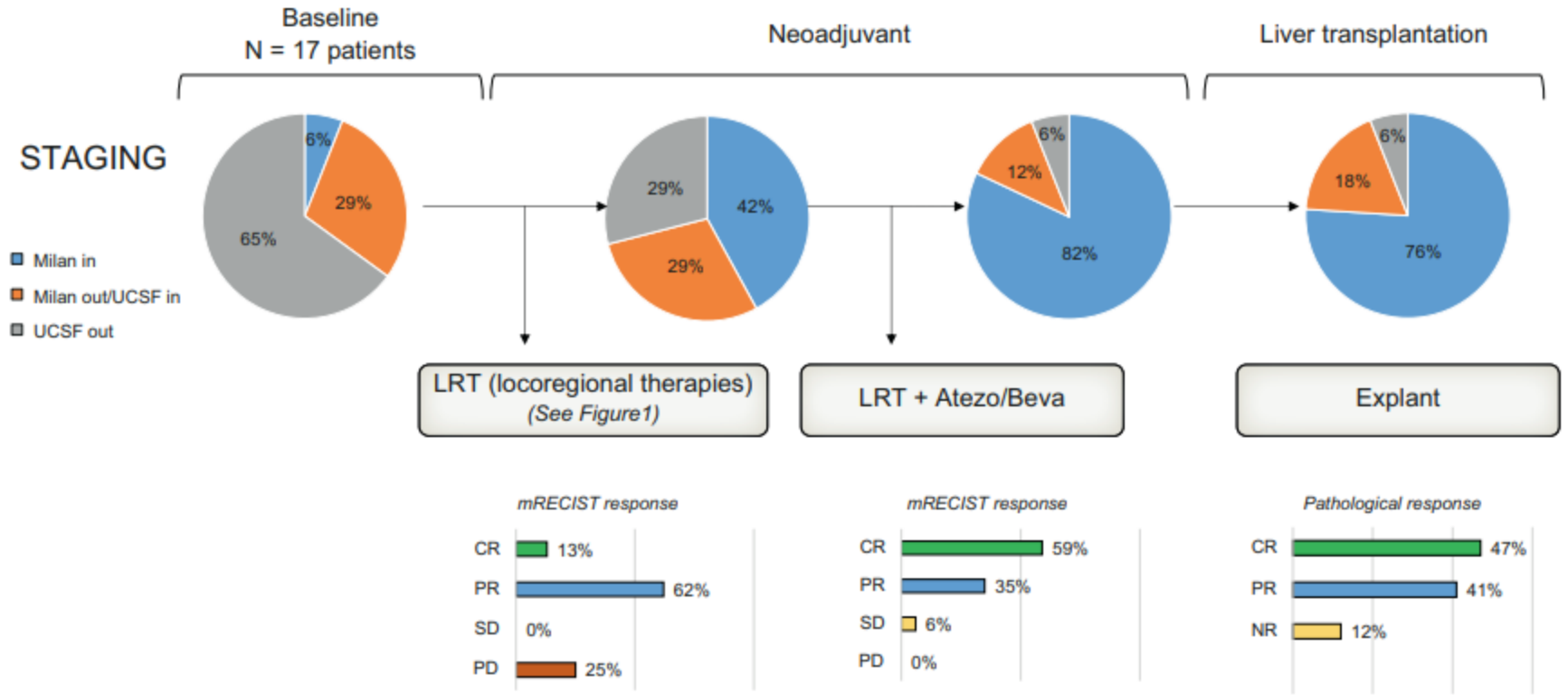
Tabrizian P. el at JHEP Reports, November 2024. vol. 6 ¡ 101181

Intention-to-treat outcomes of patients with hepatocellular carcinoma receiving immunotherapy before liver transplant: the multicenter VITALITY study.



Tabrizian P et al. J Hepatol 2025;82:512–522.

Neoadjuvant atezolizumab plus bevacizumab prior liver transplantation for hepato- cellular carcinoma.

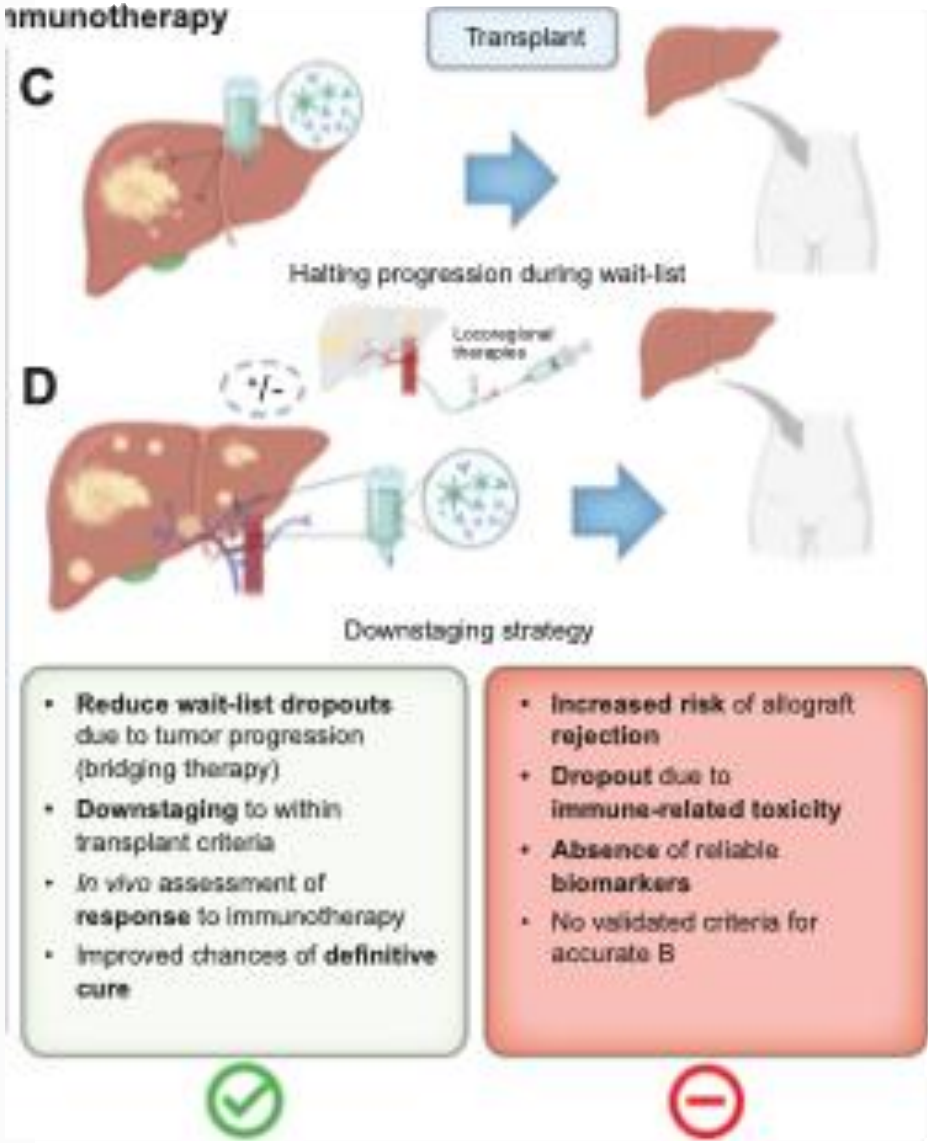


Tabrizian P et al. JHEP Rep 2025;7:101246.

Combined therapies

Sangro B et al. Durvalumab with or without bevacizumab with transarterial chemoembolisation in hepatocellular carcinoma (EMERALD-1): a multiregional, randomised, double-blind, placebo– controlled, phase 3 study. Lancet 2025;405:216–232.

Kudo M et al. Transarterial chemoembolisation combined with lenvatinib plus pembrolizumab versus dual placebo for unresectable, non-metastatic hepatocellular carcinoma (LEAP-012): a multicentre, randomised, double-blind, phase 3 study. Lancet 2025;405: 203–215.



Finally, combining ICIs with LRT may potentiate efficacy. LRT induces immunogenic cell death and neoantigen release, potentially synergizing with ICIs.

Interim analyses of EMERALD-1 and LEAP-012: improved progression-free survival for TACE + ICI versus TACE alone: median PFS was 9.2 vs. 8.2 months (HR = 0.77) in EMERALD-1, and 14.6 vs. 10.0 months (HR = 0.71) in LEAP-012

Downstaging Therapies for Patients with Hepatocellular Carcinoma Awaiting Liver Transplantation: A Systematic Review and Meta-Analysis on Intention-to-Treat Outcomes *11 papers (1874 pts)*

Outcomes: 1) drop-out rate; 2) time on the waiting list; 3) and 1, 3 and 5 year survival after LT (ITT analysis)

HCC beyond criteria and DS > drop-out rate vs HCC within criteria ($p < 0.001$).
1, 3 and 5 year survival post-LT not significant differences.

Patients with HCC beyond the listing criteria, successfully DS and then transplanted, had > 3 year ($p = 0.02$) and 5 year OS ($p = 0.02$) vs no Tx.

1) the rate of successful downstaging after LRT varies widely, from 87.5% to 35.9% → heterogeneity

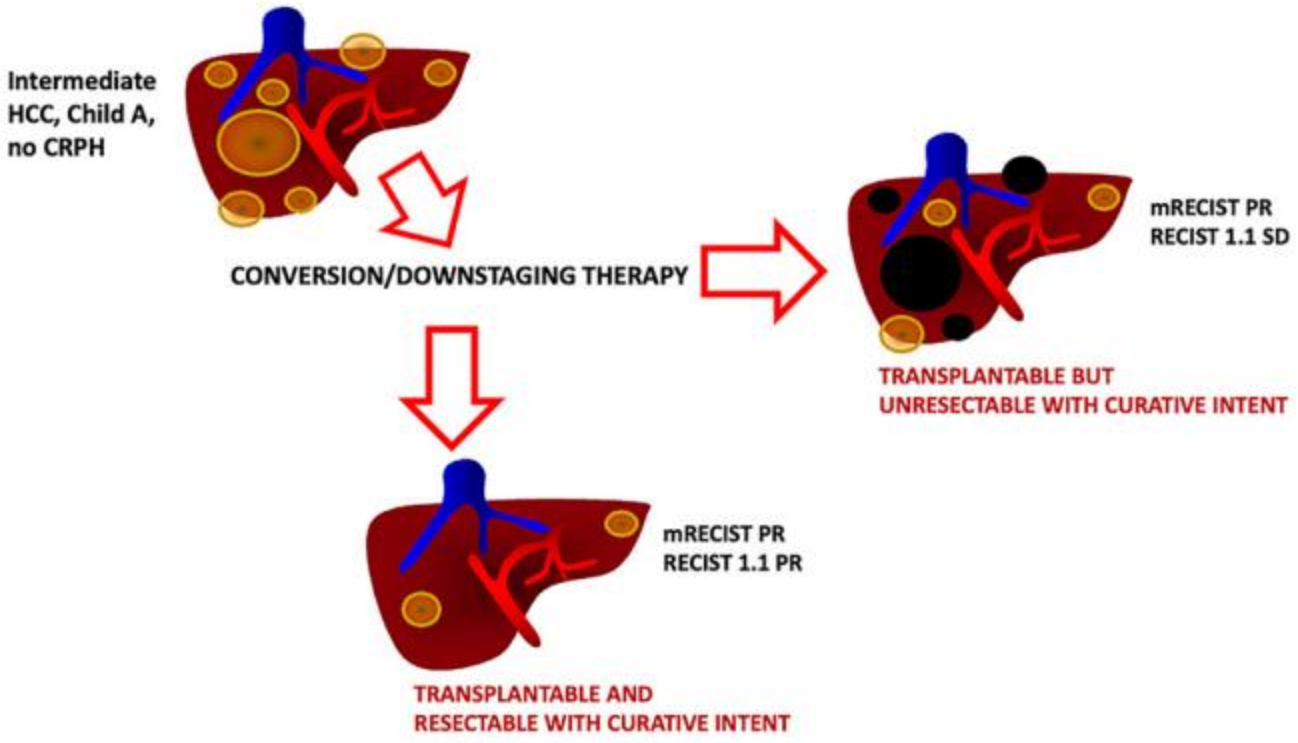
2) DS strategies and LT should be strongly encouraged HCC beyond the MC → the best chances of survival

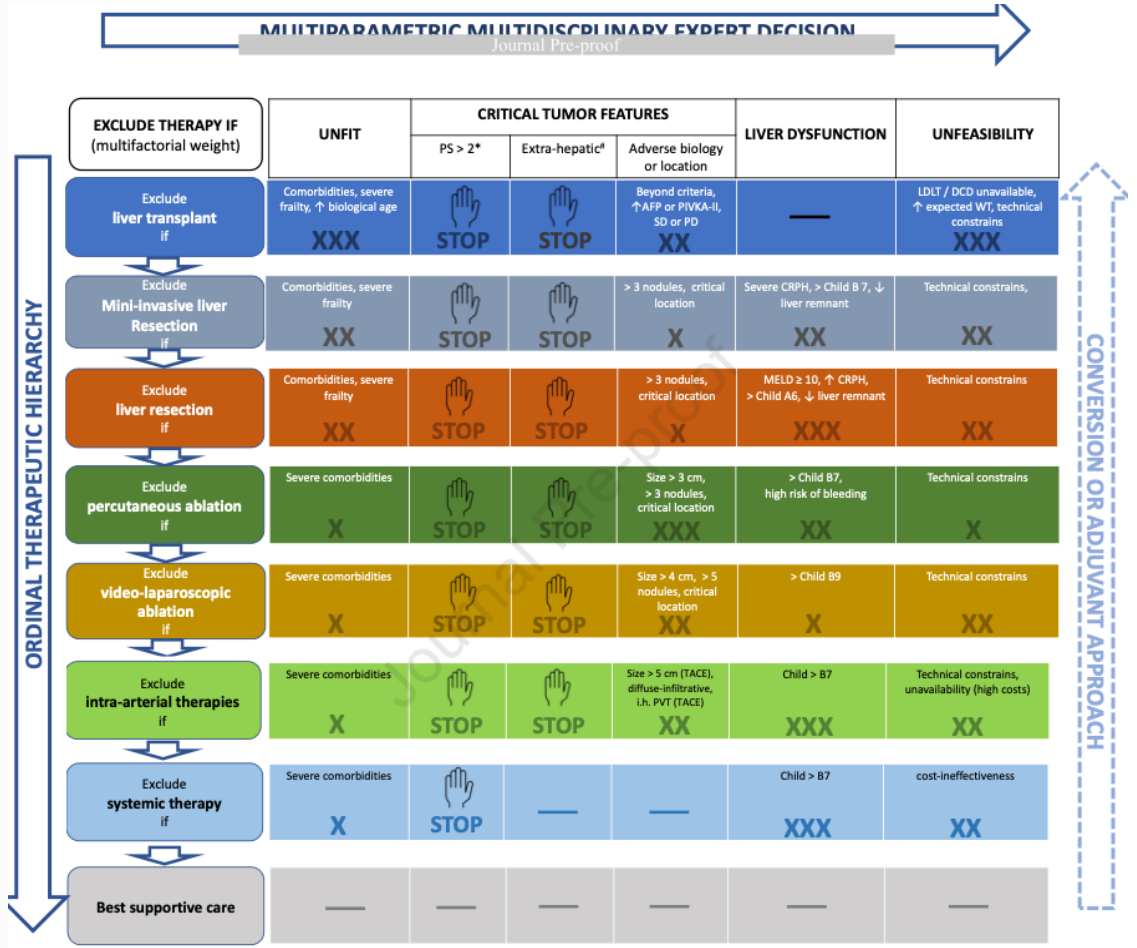
3) Principles of the treatment strategy migration and therapeutic hierarchy.
Despite the initial burden of the disease, DS and LTx pts presented comparable outcomes with patients with HCC within listing criteria

Cillo Vennarecci, Cancers 2022, 14, 5102

Complexity of Assessing the Response to Conversion, Downstaging/Downsizing, or Neoadjuvant Treatments in the multiparametric evaluation: "converse therapeutic hierarchy"

Curative conversion subgroup of pts



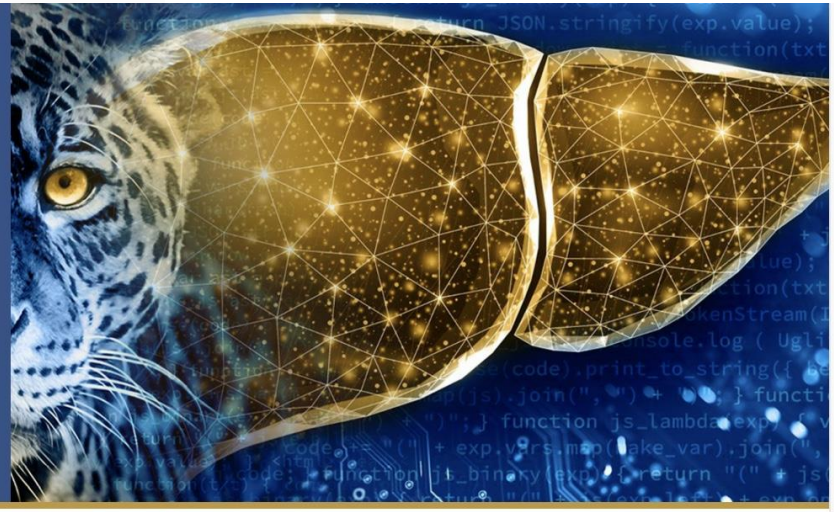


Journal of Hepatology (2024)
https:// doi.org/10.1016/j.jhep.2024.01.010.

Artificial intelligence will also offer new tools for researching and managing patients with HCC, particu- larly in complex clinical scenarios

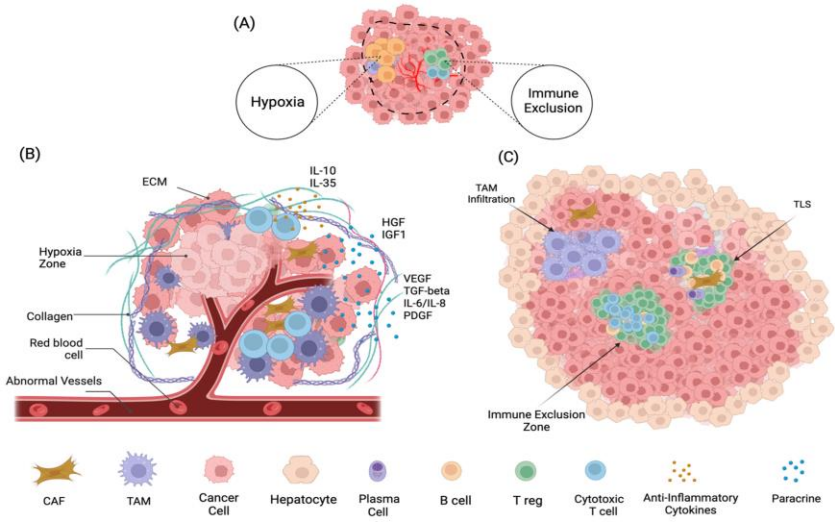
LEOPARD: **L**iver **E**lectronic **O**ffering **P**latform with **AR**tificial Intelligence-based **D**evices

A European commission-funded project



Artificial intelligence (AI) and biomarkers may provide the missing link between oncologic risk and transplant benefit

Harmonizing surrogate markers like radiologic versus pathologic response will also be key to guiding patient selection.

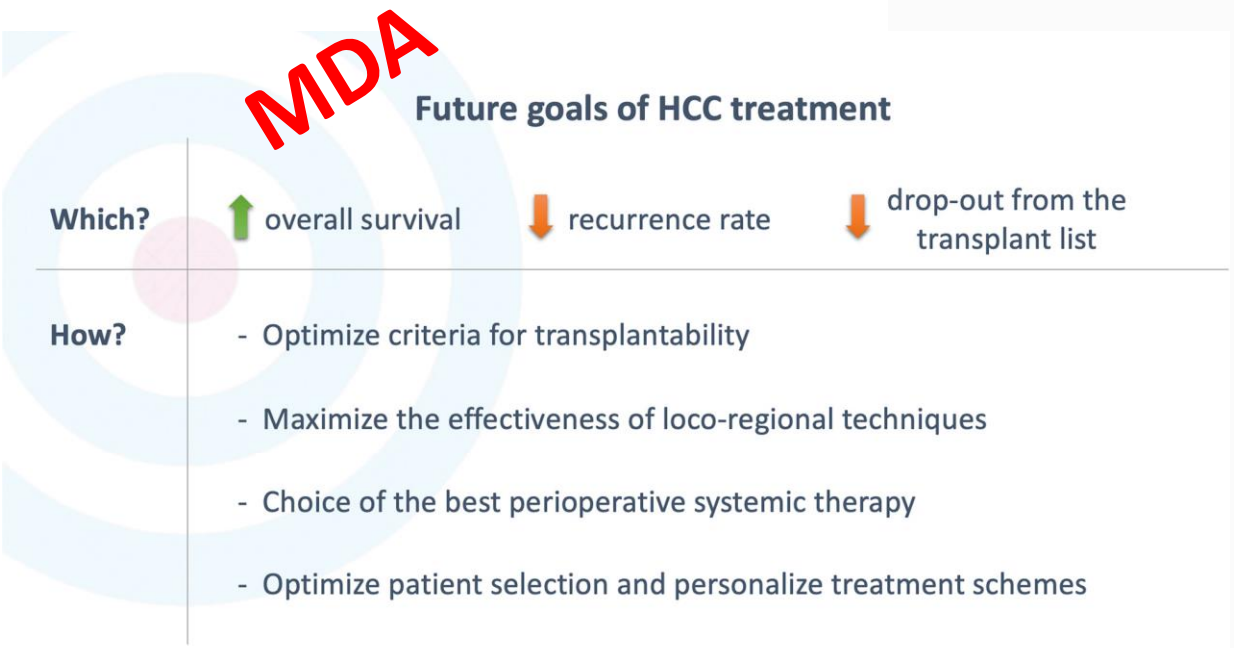


Multidisciplinary care for patients with HCC

The relevance of a multiparametric evaluation by an expert multidisciplinary tumour board has been endorsed by EASL ESMO guidelines

El Dahan et al.[19] conducted a meta-analysis of 12 studies encompassing 15,365 HCC patients and found that MDA was associated with improved overall survival (HR, 0.63; 95% CI, 0.45-0.88)

El Dahan Hepatol Commun 2023;7:e0143.



Finally, **equity of access and multidisciplinary management** is critical.

The concept of “curative conversion” deserves a multiparametric case-by-case assessment in the context of an expert MDA with a longitudinal re-evaluation of individual patient cases.

From this perspective, the possibility of “repetitive” expert tumour boards during each HCC patient history is of paramount clinical importance

Conclusion & open issues

Unresolved issues remain, such as defining the criteria for successful DS in terms of the extent and duration of tumor response (the best subgroup of pts)

It is crucial to consider expanding the downstaging criteria since it validates the principles of the treatment strategy migration and therapeutic hierarchy

Effective treatment strategies and homogenous protocol with significant tumor response are essential on successful tumor control and stabilization of tumor biology.

Based on a oncrete evidence of MDA's superiority for HCC downstaging, promising results from trials demonstrating the efficacy and safety of MDA for a tailored downstaging.

Clinical trial design must evolve. Randomized, prospective trials with clear endpoints (such as major pathologic response for neoadjuvant studies or recurrence-free survival in the adjuvant setting) are urgently needed.

Harmonizing surrogate markers like radiologic vs pathologic response will also be key to guiding patient selection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Thanks