HCC:
update su epidemiologia e trapianto

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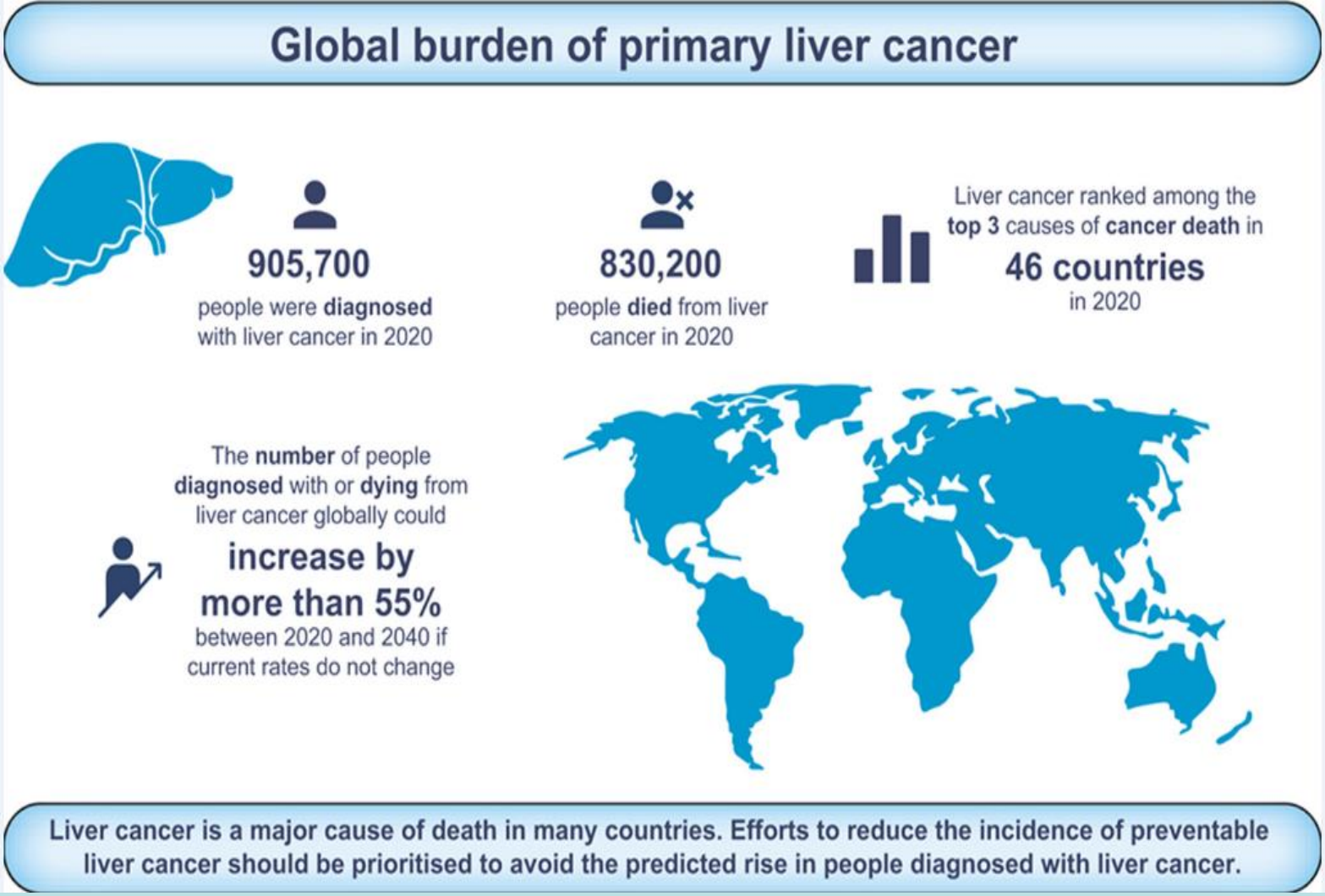


Nel 2018 in Italia sono stati stimanti 12800 nuovi casi, circa 3% di tutti i nuovi casi di tumore, con rapporto ♂:♀ 2,2:1.
E' terza causa di morte per tumore nella fascia 50-69 aa.
La sopravvivenza a 5 anni è del 20%.

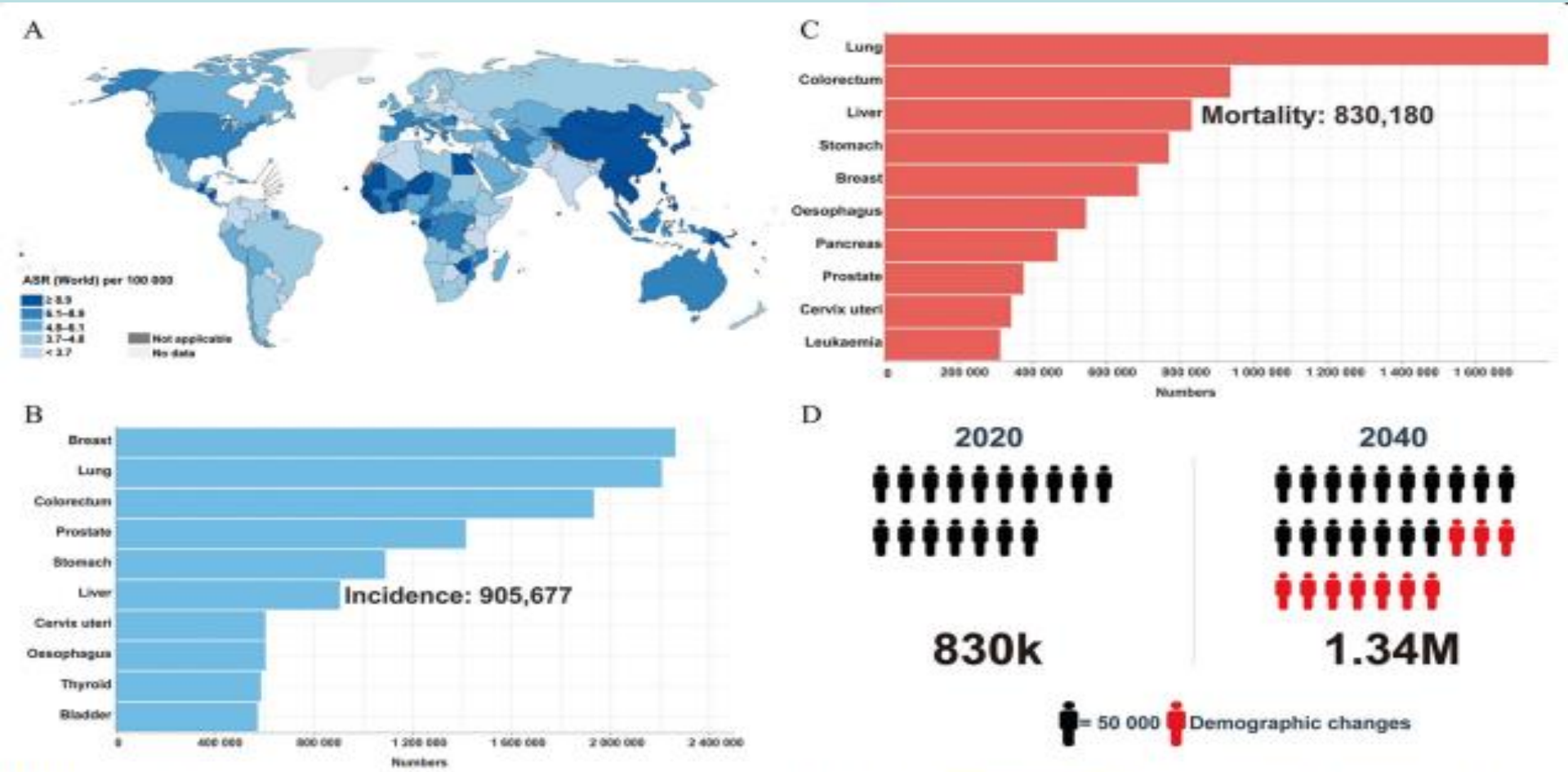
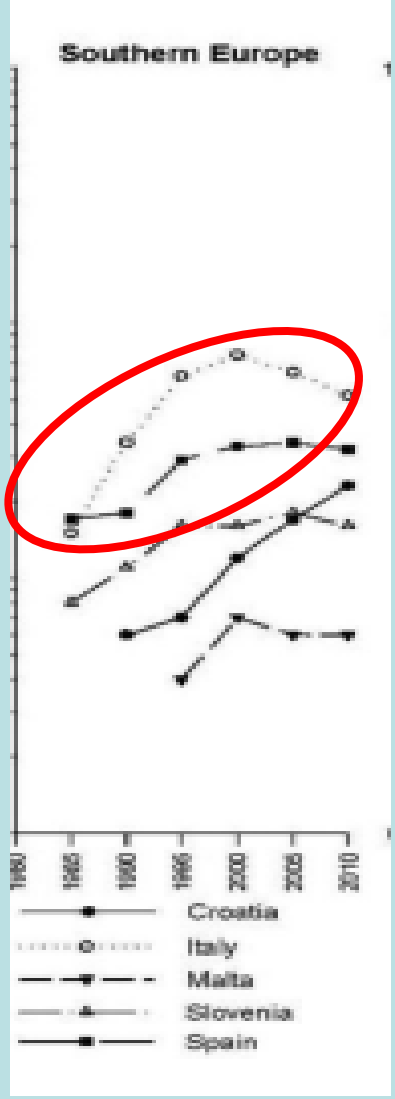
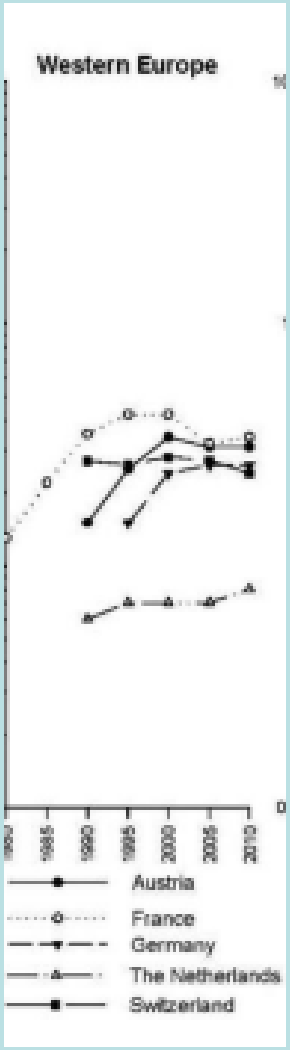


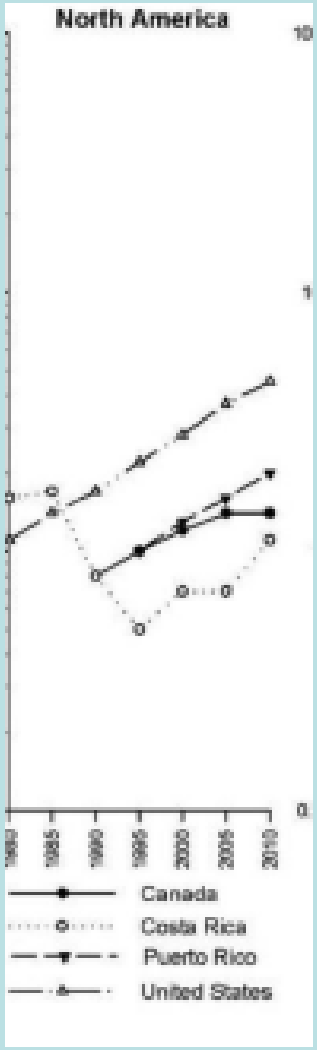
Fig. 1 Worldwide Epidemiology of Liver Cancer in 2020. Data source: GLOBOCAN 2020 (http://gco.iarc.fr/). (**A**) The estimated age-standardized incidences of liver cancer worldwide in 2020. (**B**) Bar charts of the estimated number of incident cases worldwide. (**C**) Bar charts of the estimated number of deaths worldwide. (**D**) WHO estimated the number of deaths from liver cancer from 2020 to 2040

Zhang et al. Biomarker Research (2022) 10:3 https://doi.org/10.1186/s40364-021-00350-4

Epidemiology of hepatocellular carcinoma







Trends in hepatocellular carcinoma incidence rates by country, 1978–1982 through 2008–2012. Rates are per 100,000 person-years and age-adjusted to the world standard population

K A Mc Glynn. Hepatology. 2021

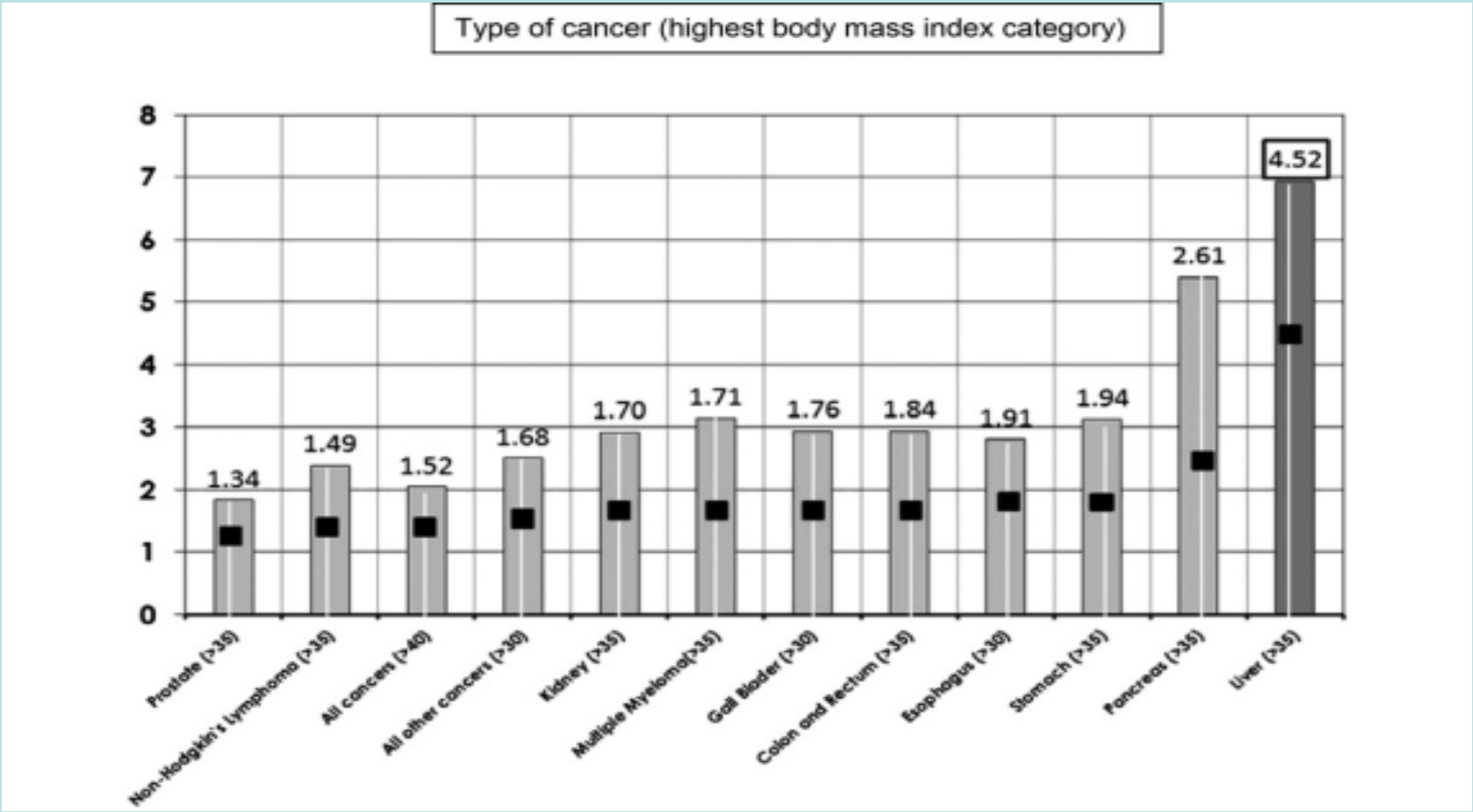
Main risk factors for primary liver cancer worldwide

- ~90% of HCCs are of known underlying aetiology1
  - Most frequently HCV, HBV, alcohol and aflatoxin exposure

	Alcohol (%)	HBV (%)	HCV (%)	Others (%)
Europe				
Western	32	13	44	10
Central	46	15	29	10
Eastern	53	15	24	8
North America	37	9	31	23
Andean Latin America	23	45	12	20
Asia				
East Asia	32	41	9	18
Asia-Pacific	18	22	55	6
South-East Asia	31	26	22	21
Africa				
North Africa, Middle East	13	27	44	16
Southern (sub-Saharan)	40	29	20	11
Western (sub-Saharan)	29	45	11	15

1- Akinyemiju T, et al. JAMA Oncol 2017;3:1683–91;
EASL CPG HCC. J Hepatol 2018; doi: 10.1016/j.jhep.2018.03.019

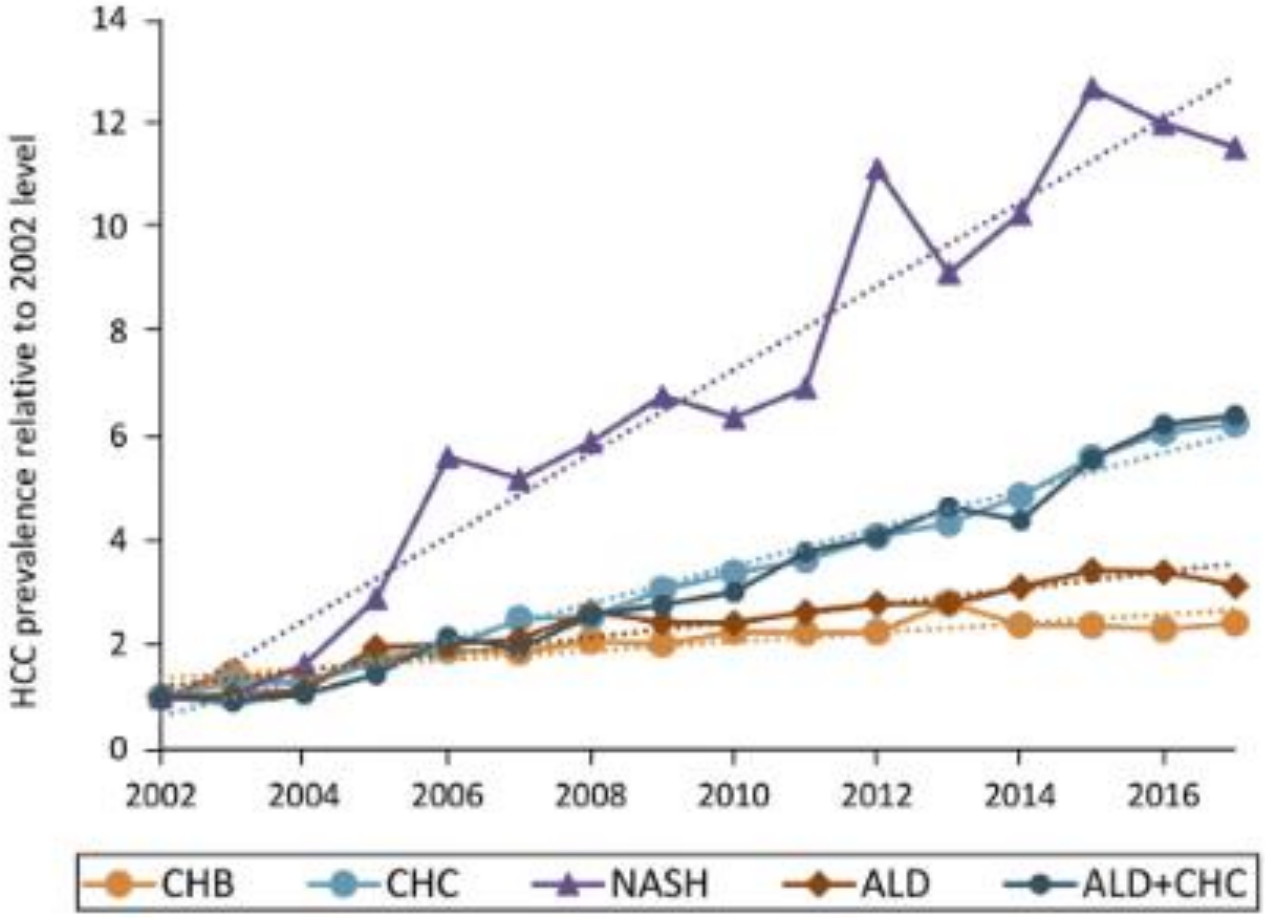
BMI and Mortality From Cancer Among U.S. Men



Global Epidemiology, Prevention, and Management of Hepatocellular Carcinoma.

MAK et Al . 2018 ASCO educational book

Prevalence of HCC in waitlisted candidates by etiology



Younossi Clin Gastroenterol Hepatol, 2018

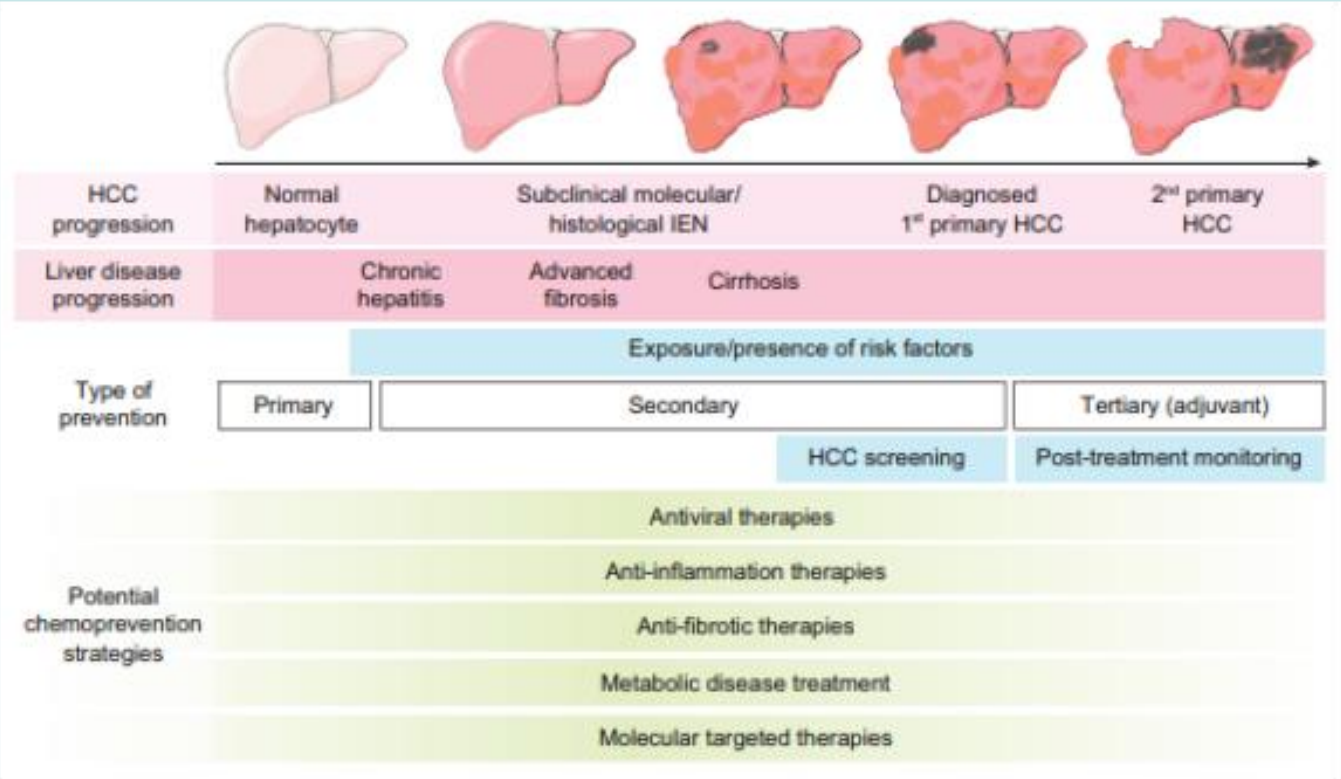
Dig Liver Dis. 2022 Dec;54(12):1664-1671. doi: 10.1016/j.dld.2022.08.033. Epub 2022 Sep 10.

Temporal trends of waitlistings for liver transplantation in Italy: The ECALITA (Evolution of IndiCAtion in LIver transplantation in ITAly) registry study

Tommaso Maria Manzia [1], Silvia Trapani [2], Alessandra Nardi [3], Andrea Ricci [2], Ilaria Lenci [4], Martina Milana [4], Roberta Angelico [1], Tullia Maria De Feo [5], Salvatore Agnes [6], Enzo Andorno [7], Umberto Baccarani [8], Amedeo Carraro [9], Matteo Cescon [10], Umberto Cillo [11], Michele Colledan [12], Luciano De Carlis [13], Paolo De Simone [14], Fabrizio Di Benedetto [15], Giuseppe Maria Ettorre [16], Salvatore Gruttadauria [17], Luigi Giovanni Lupo [18], Vincenzo Mazzaferro [19], Renato Romagnoli [20], Giorgio Rossi [21], Massimo Rossi [22], Marco Spada [23], Giovanni Vennarecci [24], Marco Vivarelli [25], Fausto Zamboni [26], Giuseppe Tisone [1], Massimo Cardillo [2], Mario Angelico [4]

Tra il **2004 e il 2020** sono stati rilevati i dati di 17.317 pazienti in lista di attesa in Italia. I pazienti sono stati suddivisi in tre ERE:1(2004-2011),2(2012-2014) and 3(2015-2020). Pazienti listati per **cirrosi sono diminuiti dal 65.9% in Era 1 al 46.1%** in Era 3, mentre quelli per **HCC sono aumentati dal 28.7% to 48.7%.** Confrontando le ERE 1 e 3, i listati per **cirrosi-HCV sono diminuiti dal 35.9% al 12.1%,**mentre coloro con **HCC –HCV** relato aumentati dal **8.5%al 26.7%.** Stabili i pazienti HBV (13.2% e 12.4%),mentre i casi di **HCC-HBV relati sono aumentati dal 4.0% al 11.6%.** Diminuiti i casi di malattia alcolica dal 16.9% al 12.9% mentre agli **HCC-alcool relati sono incrementati dal 1.9% al 3.9%.**

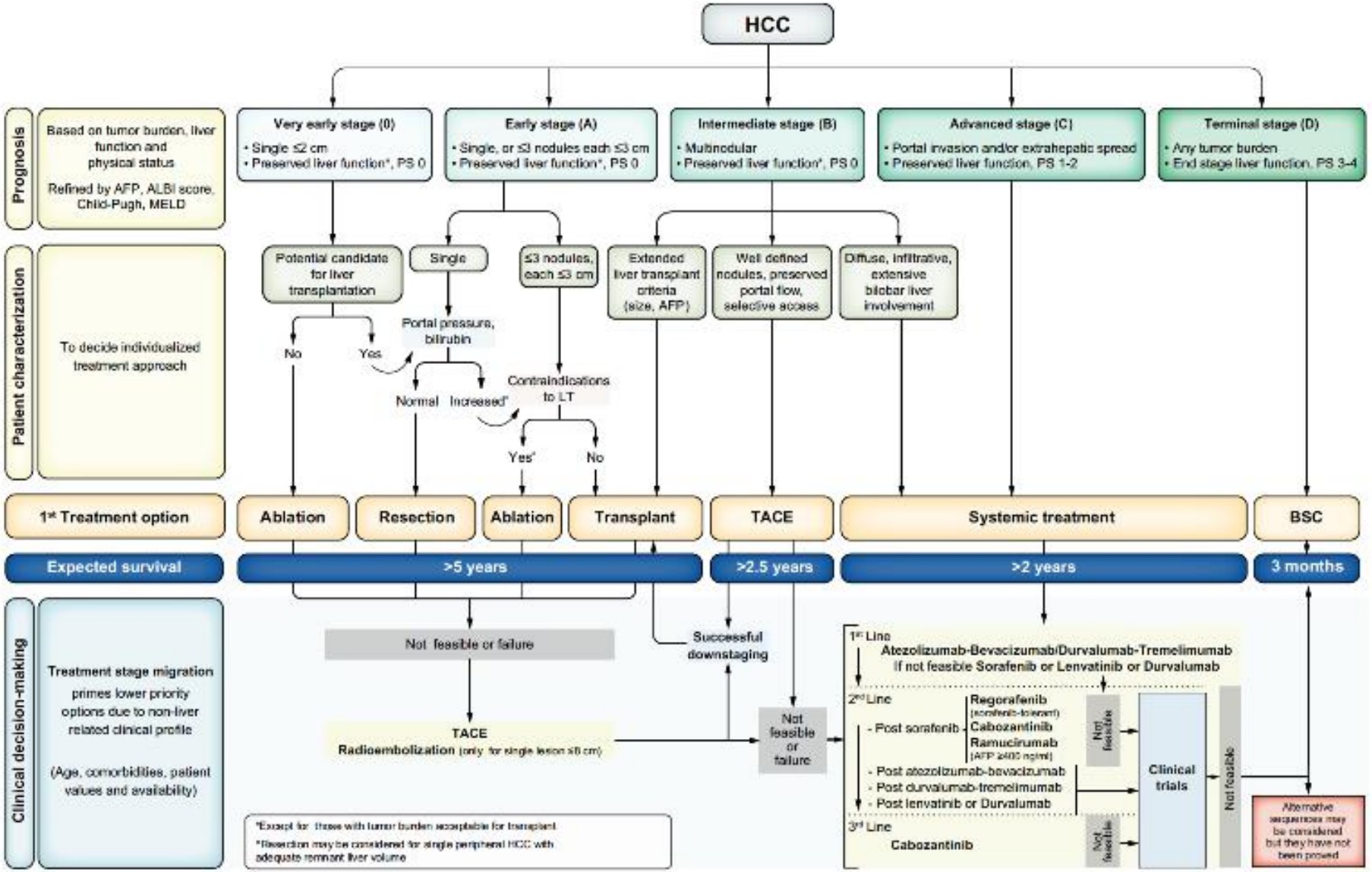
Raccomandazioni EASL



Fujiwara N, et al. J Hepatol 2018;68:526–49

EASL CPG HCC. J Hepatol 2018; doi: 10.1016/j.jhep.2018.03.019

BCLC strategy for prognosis and treatment recommendation: The 2022 update



Journal of Hepatology DOI: (10.1016/j.jhep.2021.11.018)

- **DOWNSTAGING**

- trattamento dell’ HCC per ridurre la massa tumorale (e riportarla in criteri di trapiantabilità) prima dell’inserimento in lista di attesa.

- **BRIDGE Therapy**

- trattamento dell’HCC durante il tempo di lista di attesa per ridurre il rischio di progressione del tumore e quindi il rischio di de-list.

ESOT | Transplant International

REVIEW
published: 21 April 2022
doi: 10.3389/ti.2022.10333

Patient Selection for Downstaging of Hepatocellular Carcinoma Prior to Liver Transplantation—Adjusting the Odds?

Daniel Seehofer[1], Henrik Petrowsky[2], Stefan Schneeberger[3], Eric Vibert[4], Jens Ricke[5], Gonzalo Sapisochin[6], Jean-Charles Nault[7,8] and Thomas Berg[9]*

TABLE 1 | Morphometric and combined (Toronto) selection criteria for LT.

	Solitary HCC	Multifocal HCC
Milan criteria (MC)	≤5 cm	Maximal 3 nodules ≤3 cm
Up-to-seven criteria (UT7)	≤7 cm	Sum of maximum tumor diameter (cm) and number of tumors ≤7
UCSF criteria	≤6.5 cm	HCC: largest nodule ≤4.5 cm and sum of the diameter of all nodules ≤8 cm
Extended Toronto criteria (eTC)	No limit in size Only G1 und G2 tumors (obligatory biopsy) No tumor-associated symptoms	No limits in size and number Only G1 und G2 tumors (obligatory biopsy) No tumor-associated symptoms

TABLE 2 | Molecular subclassification of HCC.

	"Proliferation class" (50%of HCC)	"Non-proliferation class" (50%of HCC)
G1-G6 classification	G1-G3	G4-G6
Histological/clinical characteristics	Poor differentiation High frequency of vascular invasion High AFP levels Frequent HBV etiology (G1-G2) G3: Macrotrabecular-massive histological subtypes (poor prognosis)	Well/moderate differentiation Low frequency of vascular invasion Low AFP levels Mainly HCV and alcohol G4: Contain the steatohepatitic subtypes of HCC, inflammatory infiltrates, and CRP expression
Molecular features	Chromosomal instability and TP53 mutations G1: Stem cell features, RPS6KA3 mutations G1-G2: AXIN1 mutations G3: Dysregulation of cell cycle genes, FGF19 amplification, and TSC1/2 mutations	Chromosomal stability G4: Retain hepatocyte-like features, IL-6/JAK/STAT activation, and rare CTNNB1 and TP53 mutations G5 and G6: Wnt/b-catenin pathway activation due to CTNNB1 mutations

ESOT | Transplant International

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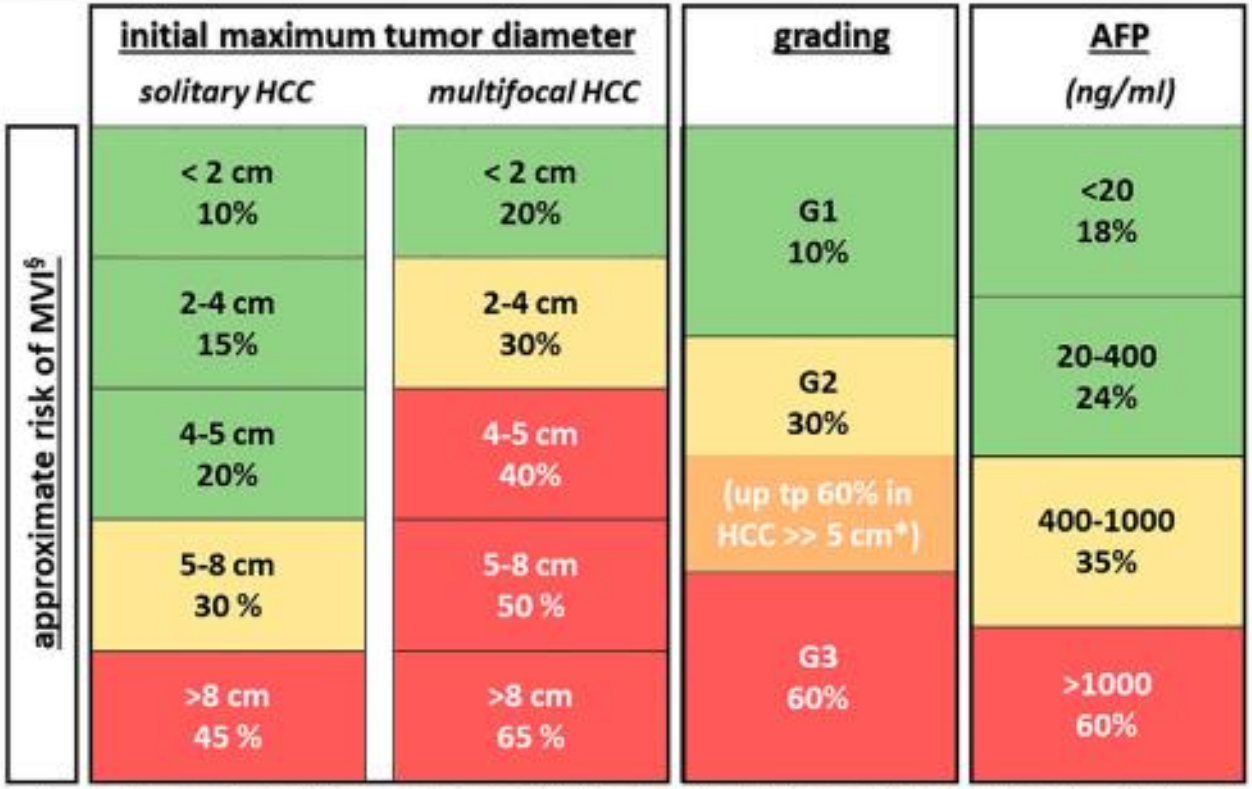

§ rough estimation of the approximate risk of microvascular invasion (MVI) by using pre-LT available parameter (data derived from different Western series, see suppl. table 1)

* especially G2 HCC represent an inhomogeneous group with significantly increasing risk of MVI in larger tumors but also concerning other tumor characteristics (e.g. PET poitivity, tumor heterogeneity (Pawlik)), and potentially also due to inter-observer heterogeneity in the pathological classification

FIGURE 1 | Rough estimation of the risk of microvascular invasion (mVI) by using pre-LT available parameters (data derived from different Western series, see **Supplementary Table S1**). * especially G2 HCC represents an inhomogeneous group with significantly increasing risk of mVI in larger tumors but also concerning other tumor characteristics (e.g., PET positivity, tumor heterogeneity [Pawlik]), and potentially also due to inter-observer heterogeneity in the pathological classification.

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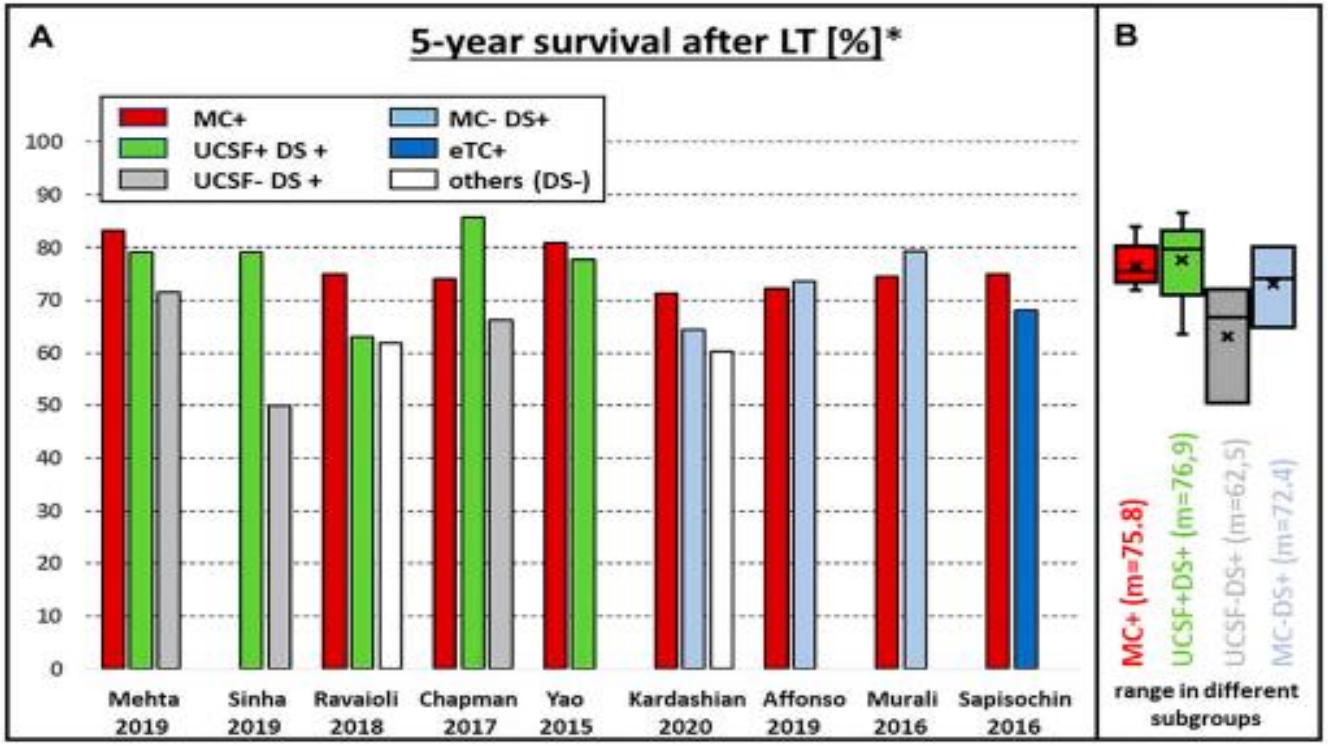
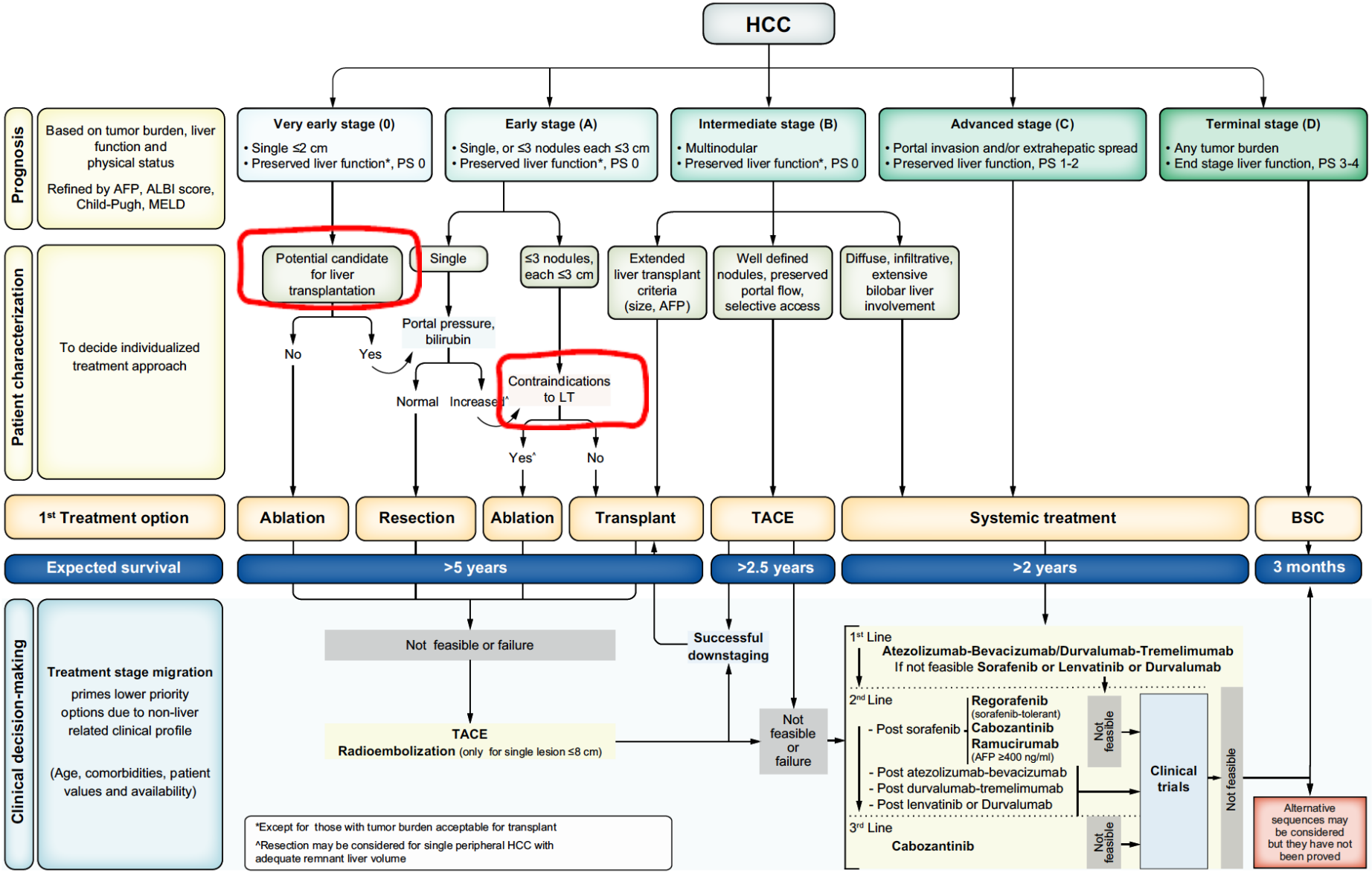


* publications within the last 5 years with indication of the 5-year recurrence rate are included
• detailed data are given in suppl. table 2
m = mean (x)

FIGURE 4 | (A) Actuarial 5-year survival after LT in recently published series of patients with subgroups outside the MC; **(B)** statistical summary of the different studies (box plot). & publications within the last 5 years with indication of the 5-year recurrence rate are included. * detailed data are given in **Supplementary Table S2**.

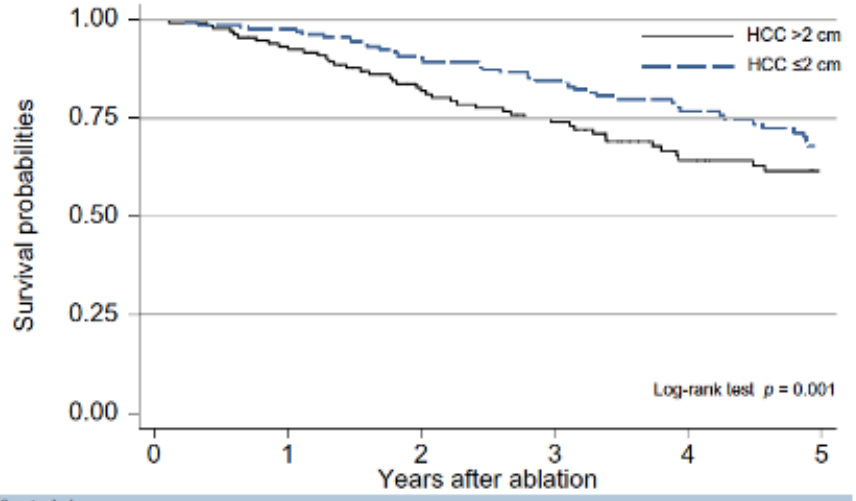
BCLC 2022 update: Keypoints

- Staging is linked to the 1st option to be considered according to scientific evidence
- **Personalized treatment indication is established according to an expert clinical decision-making process where all dimensions of the patients are taken into account.**
- Stage 0/Stage A management varies according to potential access to LT and specific profiles
- Resection to be preferred if LT is an option
- **When LT is not an option, ablation is considered equivalent to resection in stage 0 and stage A solitary lesion ≤ 3cm**
- **Because of less invasiveness and cost, ablation could be given priority**



»Stage 0 /Stage A management varies according to potential access to LT and specific profiles«

First-line RFA for HCC < 3cm in potentially transplantable patients



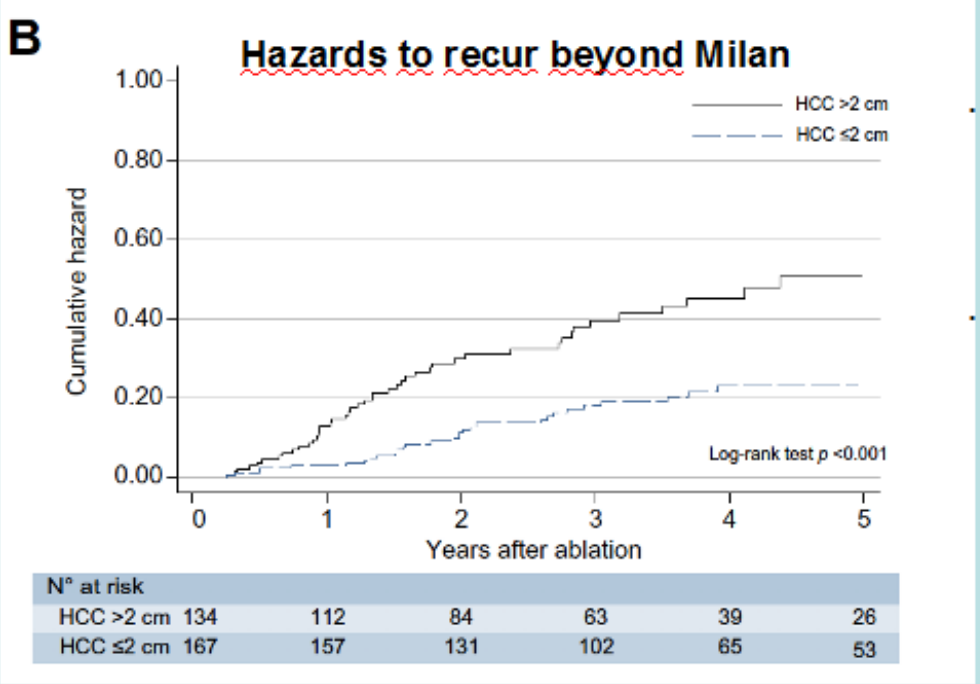
N° at risk						
HCC >2 cm	134	122	97	79	52	38
HCC ≤2 cm	167	160	140	116	73	58

Fig. 4. Survival probabilities between transplantable patients with HCC >2 cm and ≤2 cm after first-line ablation. HCC, hepatocellular carcinoma.

	Overall Survival		
	1 year	3-years	5-years
HCC ≤2 cm	98.2%	86.2%	79.0%
HCC >2 cm	93.3%	77.6%	70.9%

Doyle A, et al. J Hepatol 2019; 70(5):866-873

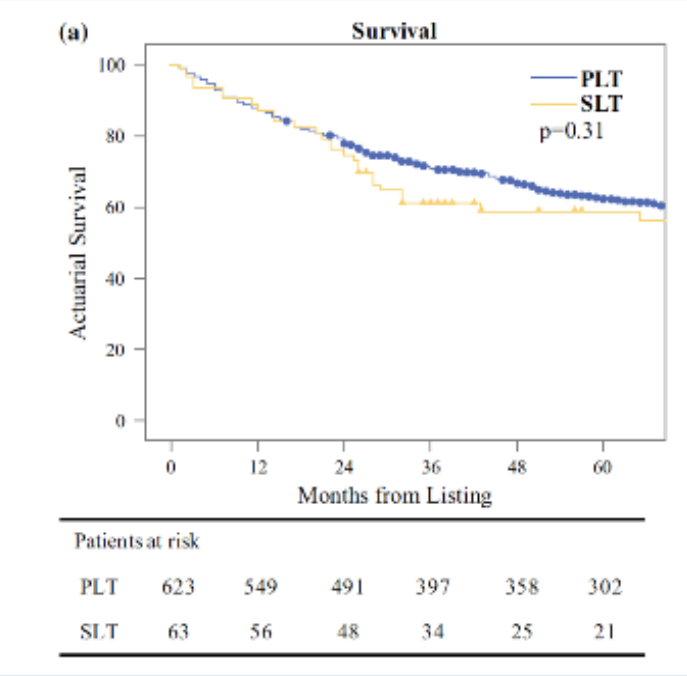
First-line RFA for HCC < 3cm in potentially transplantable patients

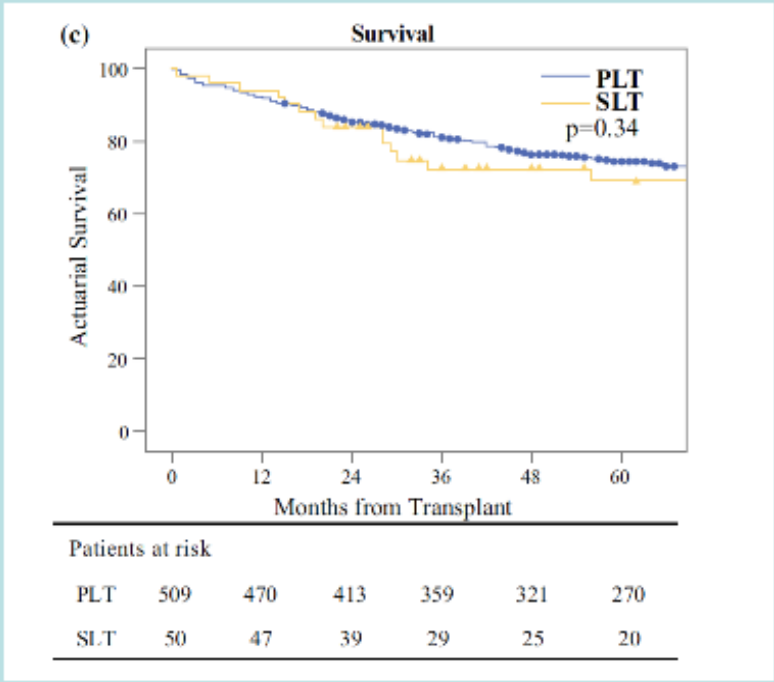


Patients with HCC >2 cm and AFP>100 ng/mL are at greater risk of recurrence beyond the transplant criteria.
Liver transplantation should be considered immediately after the first HCC recurrence for these patients

Doyle A, et al. J Hepatol 2019; 70(5):866-873

Liver transplantation is equally effective as a salvage therapy for patients with HCC recurrence following RFA or resection

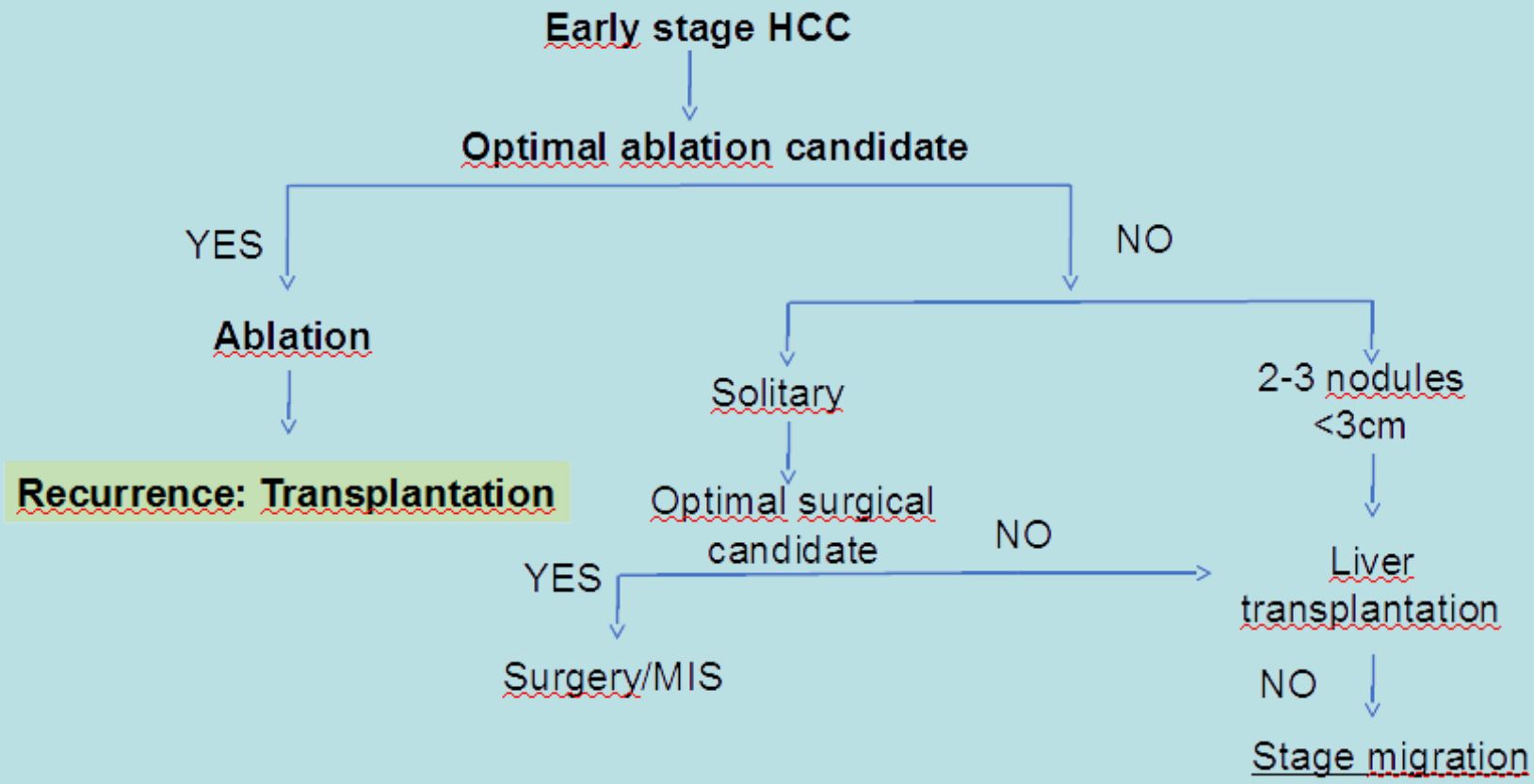




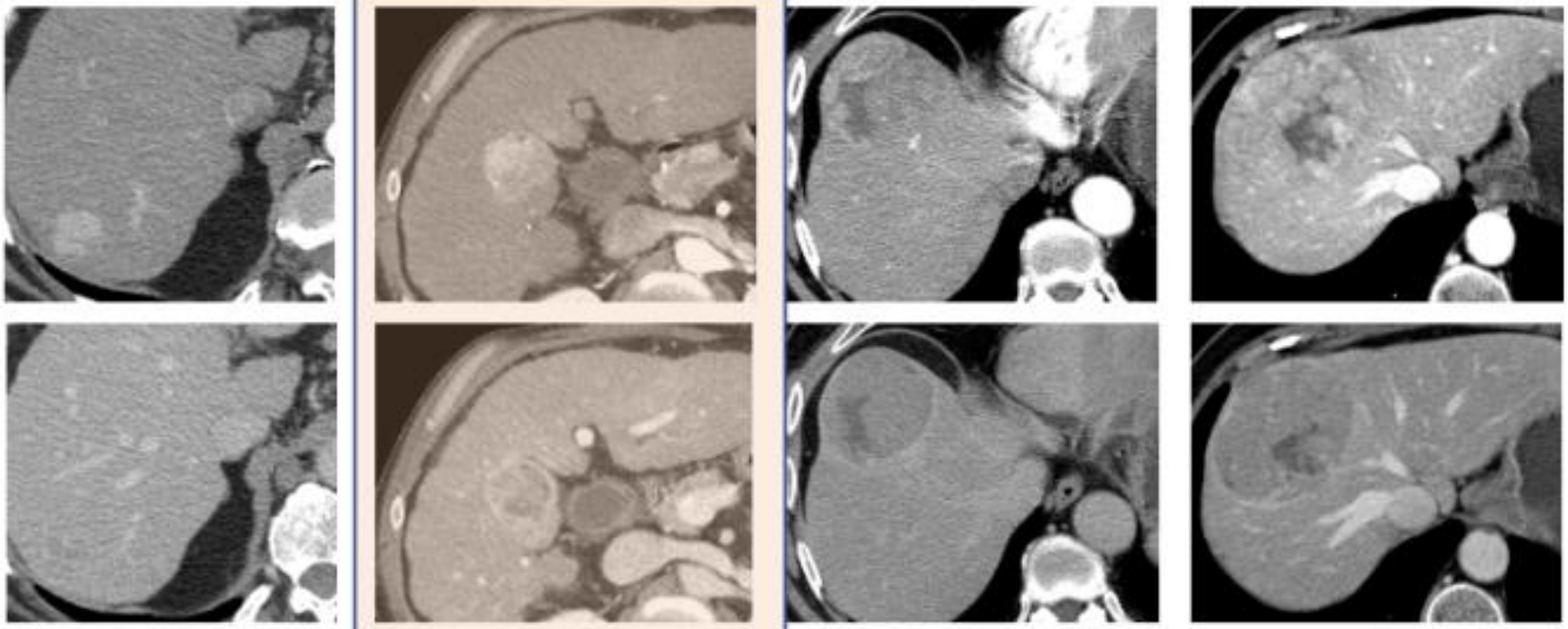
PLT: primary liver tranplantation - SLT: salvage liver transplantation

Muaddi H, et al. Ann Surg Oncol, 2018; 25:991-999

Early-stage HCC: central role of ablation



Early stage HCC

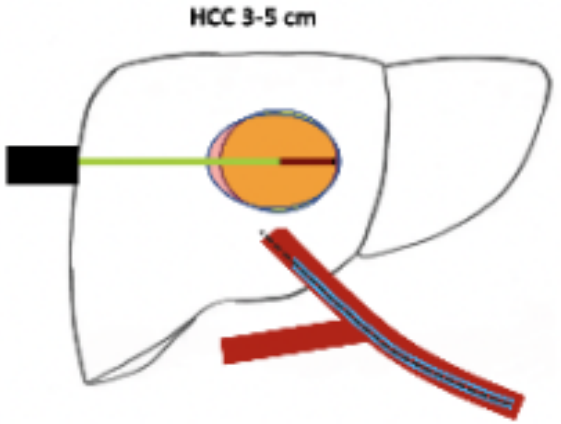


RESEARCH ARTICLE

Cancer Medicine WILEY

Hyperthermia ablation combined with transarterial chemoembolization versus monotherapy for hepatocellular carcinoma: A systematic review and meta-analysis

Zheng Li[1,2,3,4] | Qiang Li[1,2,3,5] | Xiaohu Wang[1,4] | Weiqiang Chen[1,2,3,5] | Xiaodong Jin[1,2,3,5] | Xinguo Liu[1,2,3,5] | Fei Ye[1,2,3,5] | Zhongying Dai[1,2,3,5] | Xiaogang Zheng[1,2,3,5] | Ping Li[1,2,3,5] | Chao Sun[1,2,3,5] | Xiongxiong Liu[1,2,3,5] | Qiuning Zhang[1,4] | Hongtao Luo[1,4] | Ruifeng Liu[1,4]



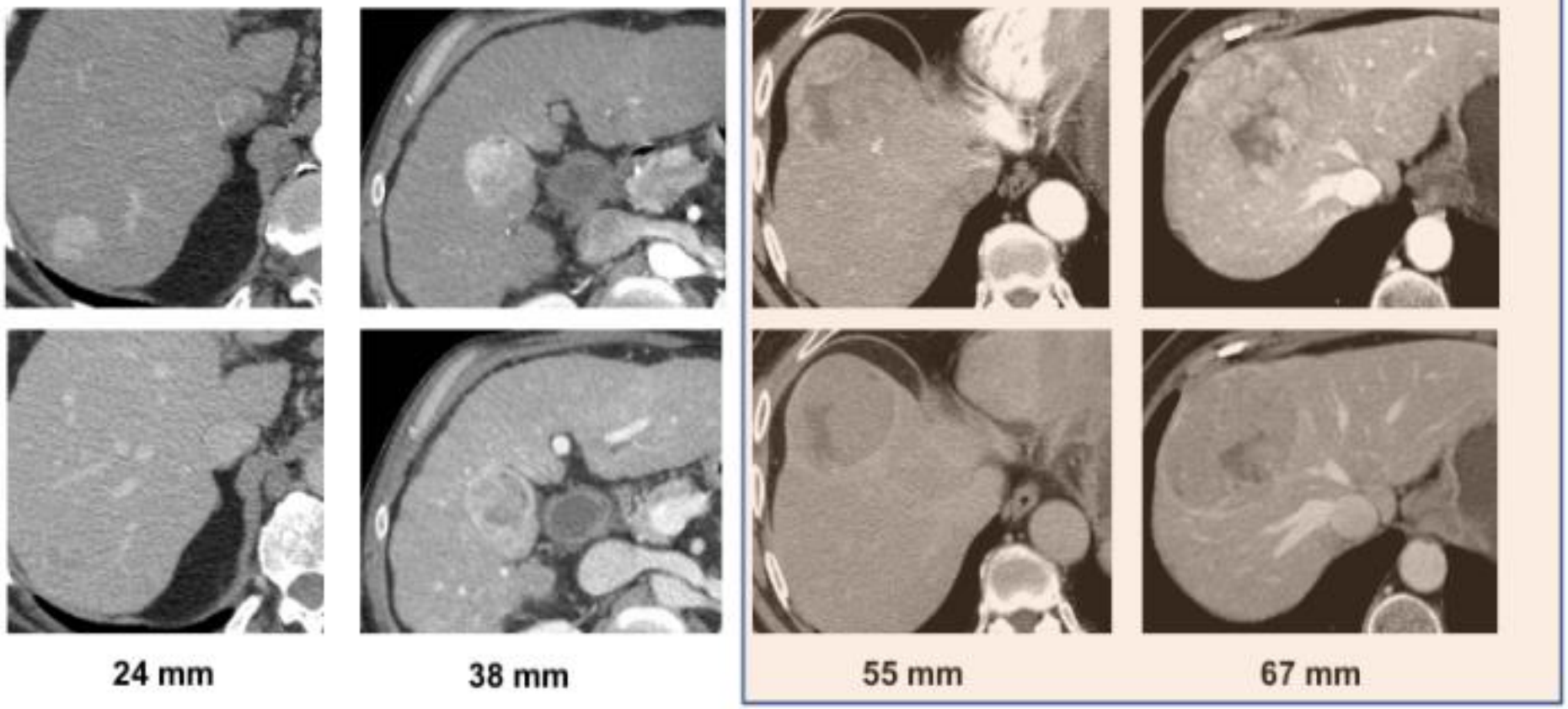
«In this study, we have demonstrated that HATACE for HCC is superior to TACE monotherapy with respect to either efficacy or safety.

HATACE is more effective than HA monotherapy with comparable safety for non-small-sized (>3 cm) HCC.

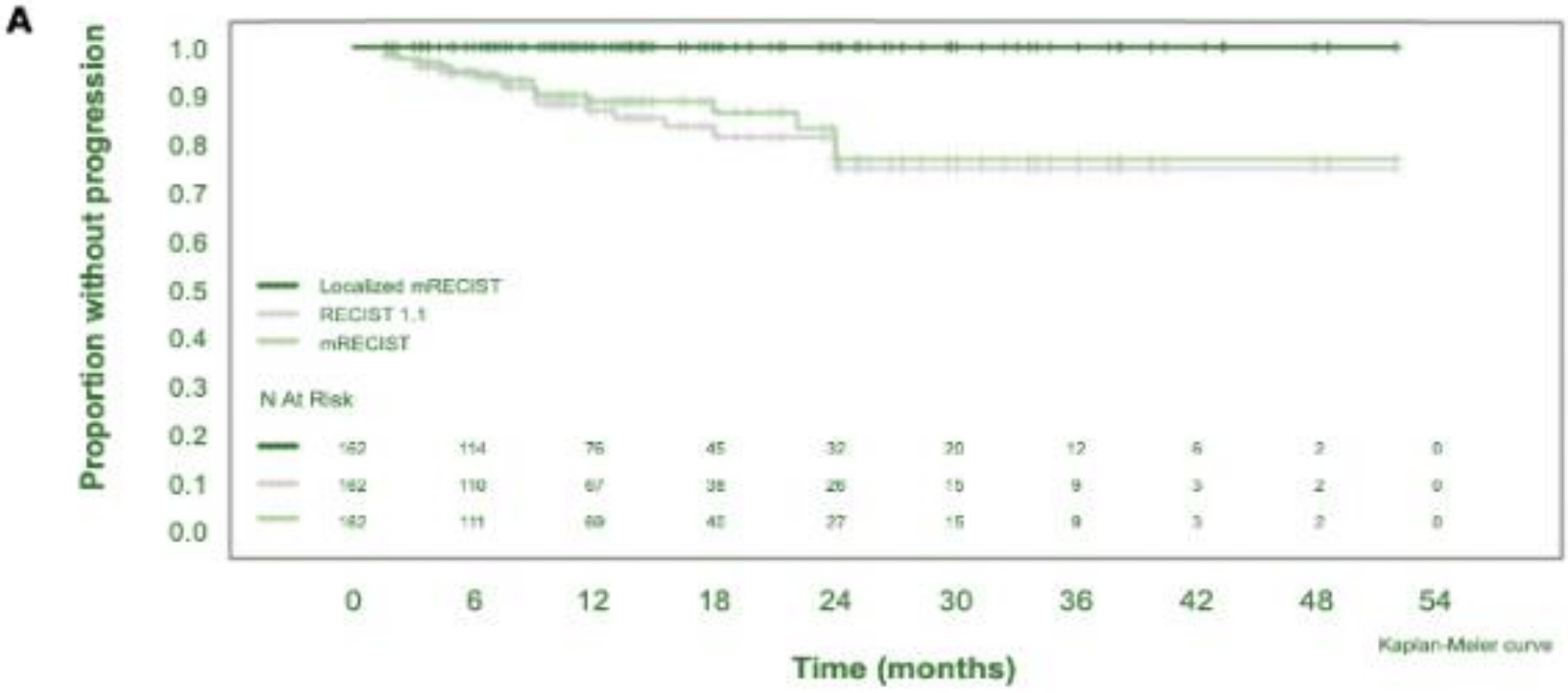
Compared with HATACE, HA monotherapy could provide comparable survival benefit for the patients with small (≤3 cm) HCC»

Cancer Medicine 2021;10:8432–8450

Early stage HCC

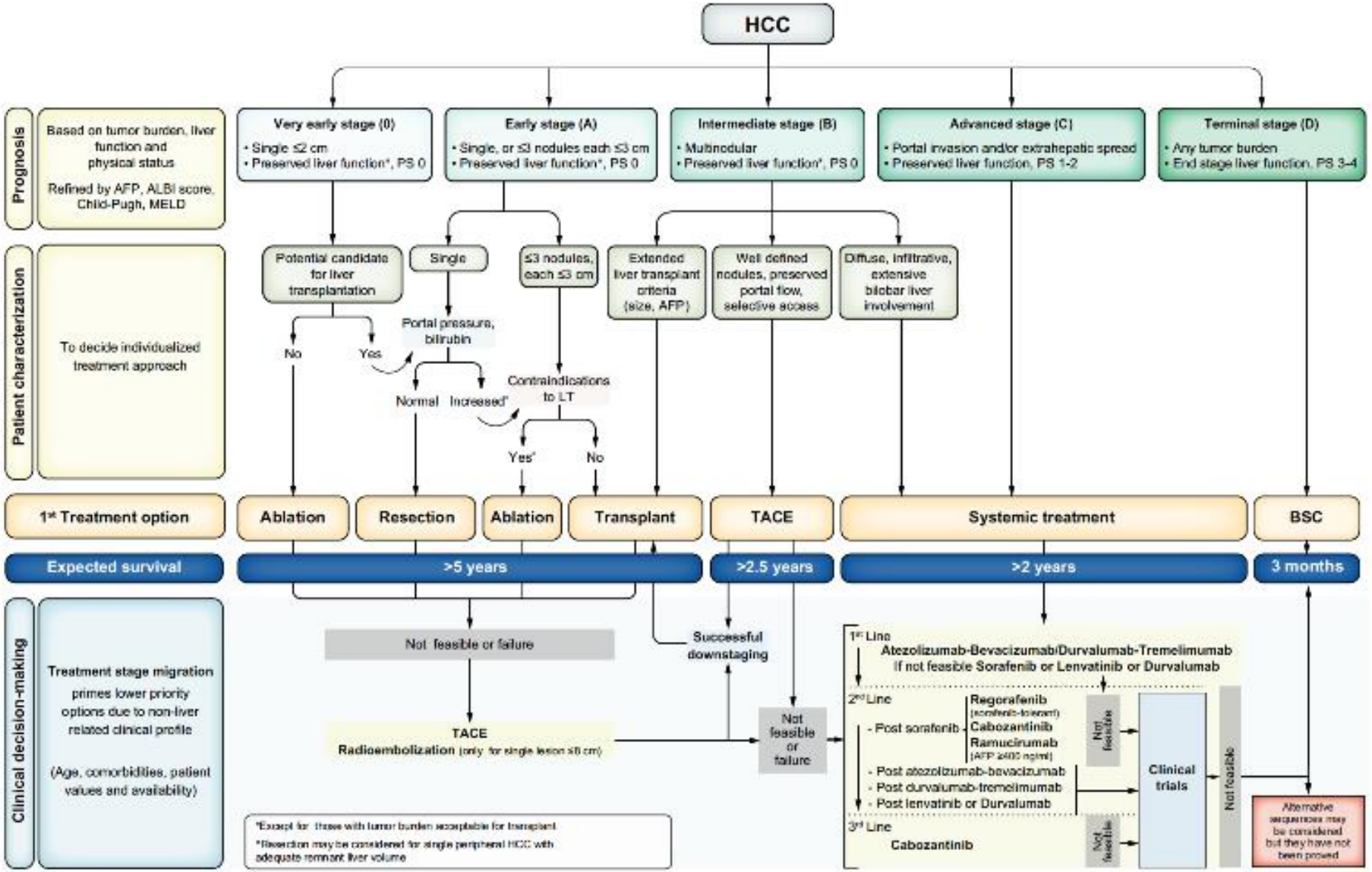


TARE for solitary HCC: the LEGACY study



Salem R, et al. Hepatology 2021;74(5):2342-2352.

BCLC strategy for prognosis and treatment recommendation: The 2022 update



Journal of Hepatology DOI: (10.1016/j.jhep.2021.11.018)

REVIEW Open Access

Recent advances in systemic therapy for hepatocellular carcinoma

Huajun Zhang[1], Wuyang Zhang[2], Longying Jiang[1,3*] and Yongheng Chen[1,4*]

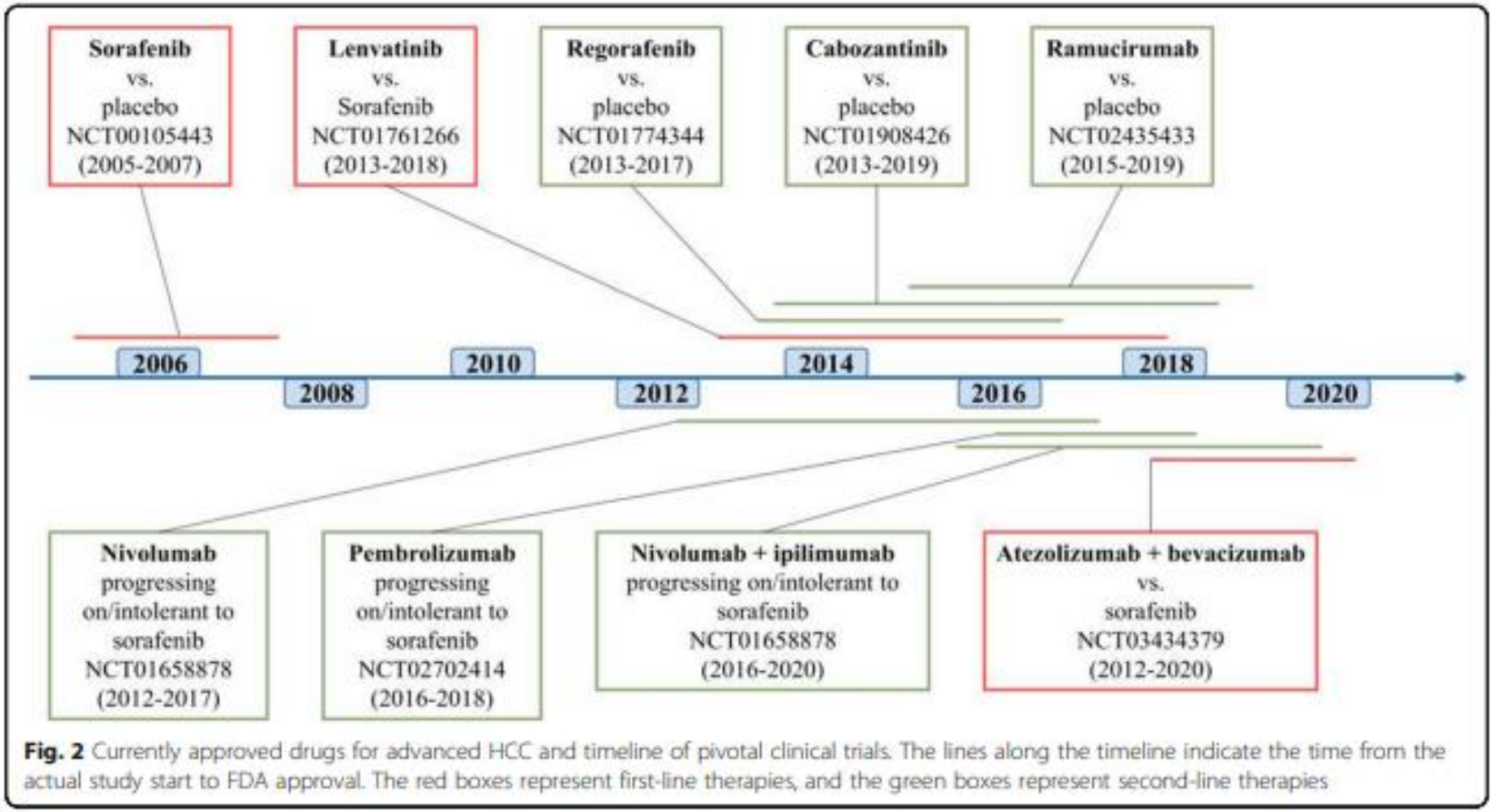


Fig. 2 Currently approved drugs for advanced HCC and timeline of pivotal clinical trials. The lines along the timeline indicate the time from the actual study start to FDA approval. The red boxes represent first-line therapies, and the green boxes represent second-line therapies

Zhang et al. Biomarker Research (2022) 10:3 https://doi.org/10.1186/s40364-021-00350-4

World Journal of Gastrointestinal Oncology

Submit a Manuscript: https://www.f6publishing.com

World J Gastrointest Oncol 2022 January 15; 14(1): 163-180

Immunotherapy in liver transplantation for hepatocellular carcinoma: Pros and cons

Yi Luo, Fei Teng, Hong Fu, Guo-Shan Ding

Efficacia nel downstaging e bridging al trapianto

Non definiti tempi di sospensione dopo il trapianto, l'entità del rischio di severo rigetto post trapianto, né il regime immunosoppressivo da seguire

Table 1 Characteristics of hepatocellular carcinoma patients receiving immunotherapy as a downstaging or bridging approach to liver transplantation

No.	Ref.	Age	Sex	Underlying liver disease	MTD (cm)	Pathology milan in/out	Cycles/duration	Immunotherapy	Days before LT	Post-LT follow-up (mo)	Initial immunosuppression	Rejection
1	Tabrizian *et al*[6]	69	M	None	10	Milan out within UCSF	21 cycles	Nivolumab	18	23	Tapering steroids + tacrolimus + MMF	No
2	Tabrizian *et al*[6]	56	F	HCV	5.4	Milan out within UCSF	8 cycles	Nivolumab	22	22	Tapering steroids + tacrolimus + MMF	No
3	Tabrizian *et al*[6]	58	M	HBV	21	Milan in	32 cycles	Nivolumab	1	22	Tapering steroids + tacrolimus + MMF	No
4	Tabrizian *et al*[6]	63	M	HCV, HIV	4.4	Milan in	4 cycles	Nivolumab	2	21	Tapering steroids + tacrolimus + MMF	No
5	Tabrizian *et al*[6]	30	M	HBV	3.2	Milan in	25 cycles	Nivolumab	22	16	Tapering steroids + tacrolimus + MMF	Mild
6	Tabrizian *et al*[6]	63	M	HBV	2	Milan in	4 cycles	Nivolumab	13	14	Tapering steroids + tacrolimus + MMF	No
7	Tabrizian *et al*[6]	66	M	HBV	2.5	Milan in	9 cycles	Nivolumab	253	14	Tapering steroids + tacrolimus + MMF	No
8	Tabrizian *et al*[6]	55	F	HBV	2.8	Milan in	12 cycles	Nivolumab	7	8	Tapering steroids + tacrolimus + MMF	No
9	Tabrizian *et al*[6]	53	F	NASH	8.7	Milan out within UCSF	2 cycles	Nivolumab	30	8	Tapering steroids + tacrolimus + MMF	No
10	Schwacha-Eipper *et al*[7]	66	M	Alcohol-associated liver cirrhosis	6.4	Milan out	34 cycles	Nivolumab	105	12	NA	No
11	Nordness *et al*[8]	65	M	HCV	5.5	Milan in	2 yr	Nivolumab	8	Death at day 10	Tacrolimus + MMF + steroids	Yes

Access to all therapies

Original Article

Centers with more therapeutic modalities are associated with improved outcomes for patients with hepatocellular carcinoma

Julie M. Jiang[1], Nitin Ohri[1], Justin Tang[1], Renee Moadel[2], Jacob Cynamon[3], Andreas Kaubisch[4], Milan Kinkhabwala[5], Madhur K. Garg[1], Chandan Guha[1], Rafi Kabarriti[1]

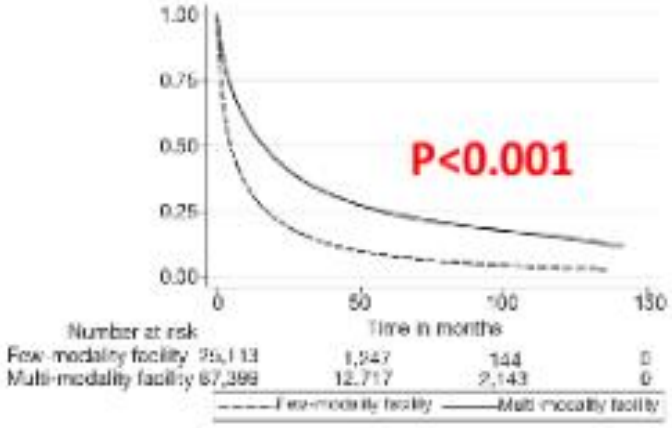


Figure 1 Unadjusted OS Kaplan-Meier curves. OS, overall survival.

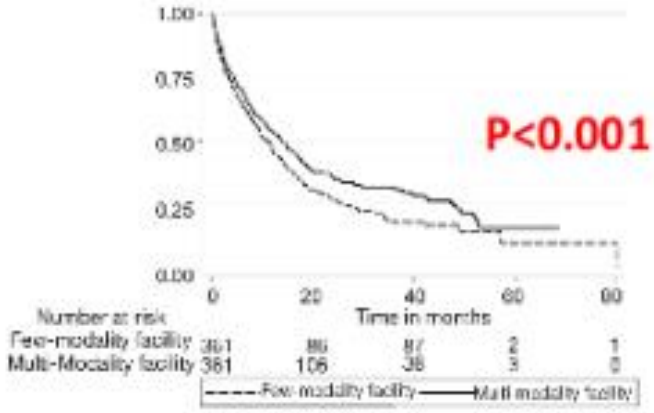


Figure 2 Propensity matched OS Kaplan-Meier curves. OS, overall survival.

Jiang JM, J Gastrointest Oncol 2019;10(3):546-553

Multidisciplinary care is key in management of HCC

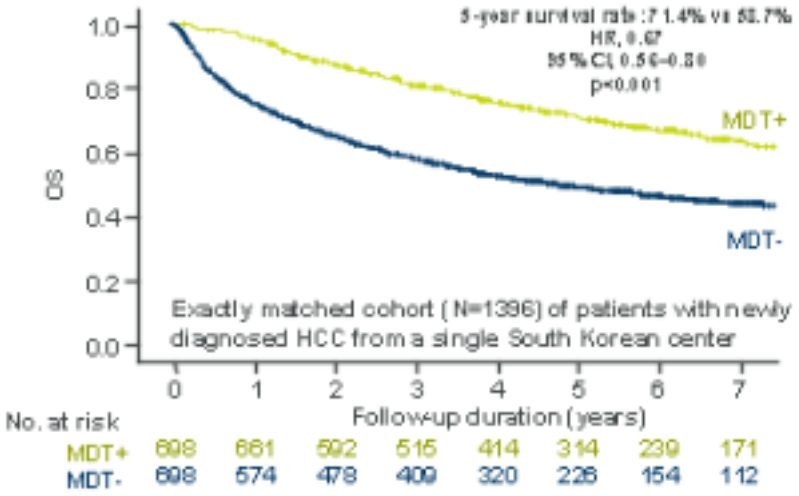
MDT care leads to individualised patient care and survival outcomes that can exceed general guideline expectations[1,2]

Expected and observed OS by BCLC Stage[1]

BCLC Stage	Treatments received	Expected OS, months[a]	Median OS, months
Early stage A (n=142)	Resection (n=21); transplant (n=3); RFA (n=24); TACE (n=22); TARE (n=71); palliative (n=1)	>60	NR (57% 10-year survival)
Intermediate stage B (n=28)	Resection (n=1); TACE (n=7); TARE (n=19); systemic (n=1)	20	51.0
Advanced stage C (n=100)	Resection (n=2); transplant (n=2); TACE (n=27); TARE (59); systemic (n=4); palliative (n=6)	11	25.4
Terminal stage D (n=51)	Transplant (n=9); RFA (n=1); TARE (n=19); systemic (n=4); palliative (n=18)	<3	13.4

In a real-world US study, MDT-directed care resulted in a 76% rate of BCLC-discordant first-line treatment, while still meeting or exceeding expected outcomes[1]

Survival of patients with HCC according to management through MDT tumour board[2]

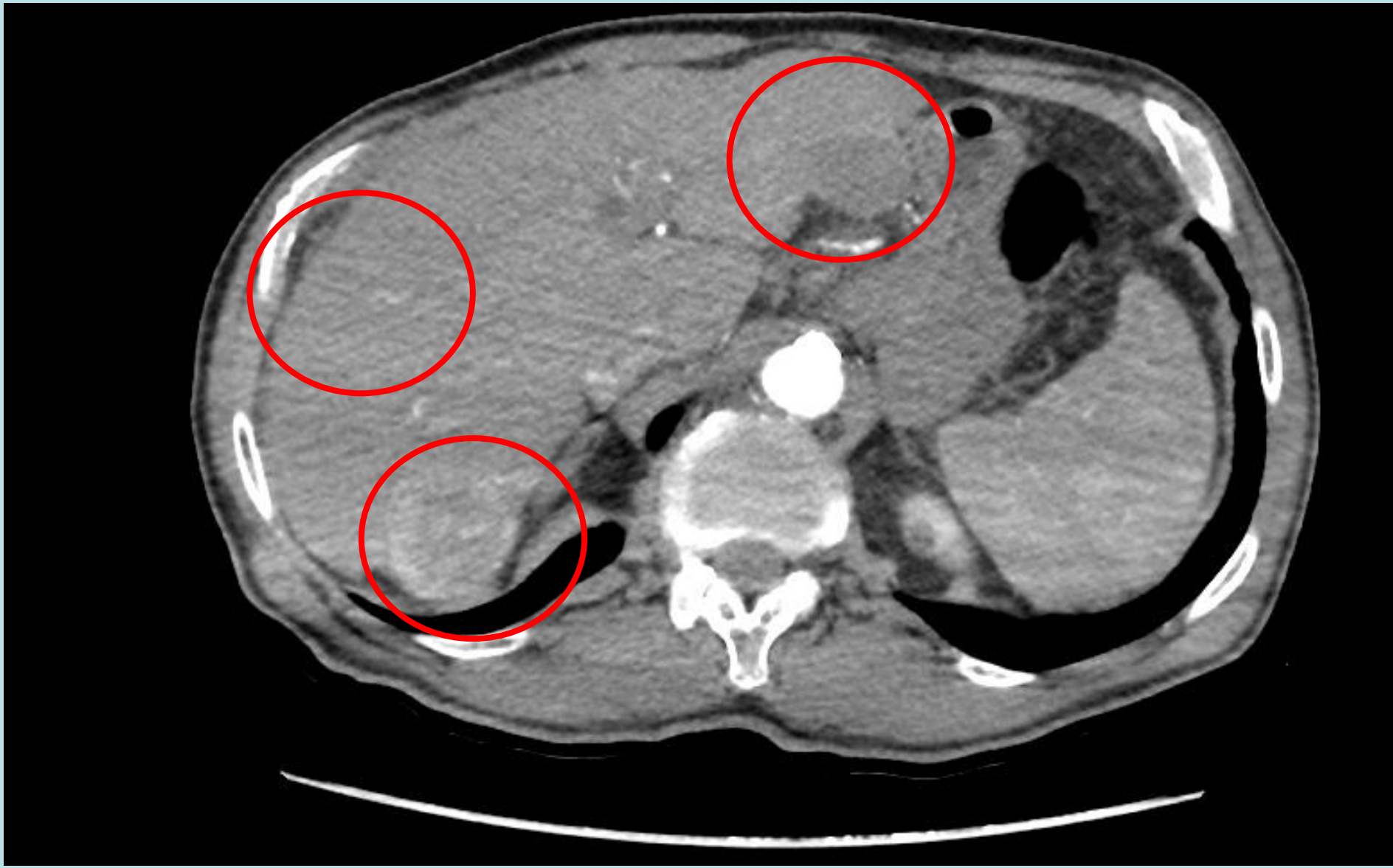


There was a significantly higher 5-year survival rate in patients managed via MDT versus those who were not[2]

1. Matsumoto MM, et al. Cardiovasc Intervent Radiol 2021;44:1070–1080;
2. Sinn DH, et al. PLoS One 2019;14:e0210730.

CASO CLINICO

- Dati anamnestici: uomo di 70 aa, altezza 173 cm, peso 62 Kg, emogruppo A+.
- Storia di obesità (ex 100 kg, moderato uso di vino ai pasti), fumatore corrente 10 sig/die. Non interventi chirurgici o patologie di rilievo in anamnesi.
- Nell'ultimo anno ha perso 20 Kg per cui si sottopone a controlli clinici e radiologici completi con prima diagnosi di cirrosi epatica e HCC multifocale (2 cm in S2, 2,7 mm in S5, 2,8 cm in S7e 2,4 cm in S8). Alfafetoproteina 3 µg/L, classe funzionale Child Pugh A6.
- Lo specialista epatologo lo avvia a trattamento di chemioembolizzazione di downstaging (TACE), ma complicata da successiva comparsa di ascite. La risposta alla TC dopo 1 mese non è completa (risposta completa in S2, parziale su altri segmenti).
- Il caso viene portato a discussione multidisciplinare e indicata la valutazione preliminare per eleggibilità al trapianto.
- La TC eseguita a 3 mesi dal trattamento evidenzia 2 focalità epatiche (4 cm in S7 e 3,8 cm S5), alfafetoproteina 5,1µg/L.
- La valutazione preliminare evidenzia pattern respiratorio moderatamente ostruttivo su enfisema polmonare centrolobulare. Una vasculopatia multidistrettuale priva di stenosi emodinamicamente significative (ostruzione del 60% della carotide interna sx e della femorale sx), non patologia coronarica significativa, né cerebrale.
- MELD 13 HCC MELD 21 ISOSCORE 21



- l paziente viene inserito in lista per trapianto di fegato nel maggio 2018 e trapiantato con organo ABO compatibile, donatore DBD, nel giugno 2018.
- Il decorso operatorio e l'immediato post operatorio sono stati regolari ed il paziente è stato dimesso in VII GPO.

- L'istologico del fegato nativo:
- Nodulo S2 (2,7 cm)nodulo in gran parte necrotico con minuto focolaio periferico di carcinoma epatocellulare con aspetti a cellule chiare GIII, non evidenza di angioinvasione.
- Nodulo S5(4,5 cm)carcinoma epatocellulare ad architettura trabecolare e solida GIII, estesamente necrotico, non evidenza di angioinvasione. Nodulo S7 (4 cm) carcinoma epatocellulare ad architettura trabecolare e pseudoghiandolare GI, non evidenzia di angioinvasione

- Il regime immunosoppressivo è stato minimizzato

- Il monitoraggio radiologico non evidenzia recidiva di HCC a tre anni dal trapianto

Conclusioni

- Ruolo chiave della prevenzione primaria, ma fondamentale è il ruolo della sorveglianza nella prevenzione secondaria e terziaria per la diagnosi precoce e la possibilità di poter offrire la scelta della miglior opzione terapeutica.
- I criteri di trapiantabilità dei pazienti sono stati progressivamente ampliati, anche grazie all'ottimizzazione delle opzioni terapeutiche: chirurgiche, locoregionali radiologiche e oncologiche sistemiche.
- Assolutamente necessario che il percorso del paziente sia gestito nell'ambito di Team multidisciplinare e che possa offrire tutte le tipologie di trattamento possibili, compresa quella trapiantologica, sin dai primi stadi della malattia.