ΚΡΙΤΗΡΙΑ ΟΡΙΑΚΑ ΕΞΑΙΡΕΣΙΜΟΥ ΗΚΚ

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ΓΑΟΝΑ «Άγιος Σάββας»

ΗΚΚ

- Ο συχνότερος πρωτοπαθής καρκίνος του ήπατος
- Ηπατεκτομή: Πλέον αποτελεσματική θεραπευτική επιλογή
- Πρόοδος στη Συστηματική Θεραπεία
- Στροφή των Θεραπευτικών Αλγορίθμων
- TKIs, ICIs, TACE, TARE
- Ογκολογική Εξαιρεσιμότης ≠ Τεχνική Εξαιρεσιμότης
- Πρότυπο Καρκίνου Παγκρέατος – Μεταστατικού Καρκίνου Ήπατος
- Consensus!!!

ΟΡΙΣΜΟΣ

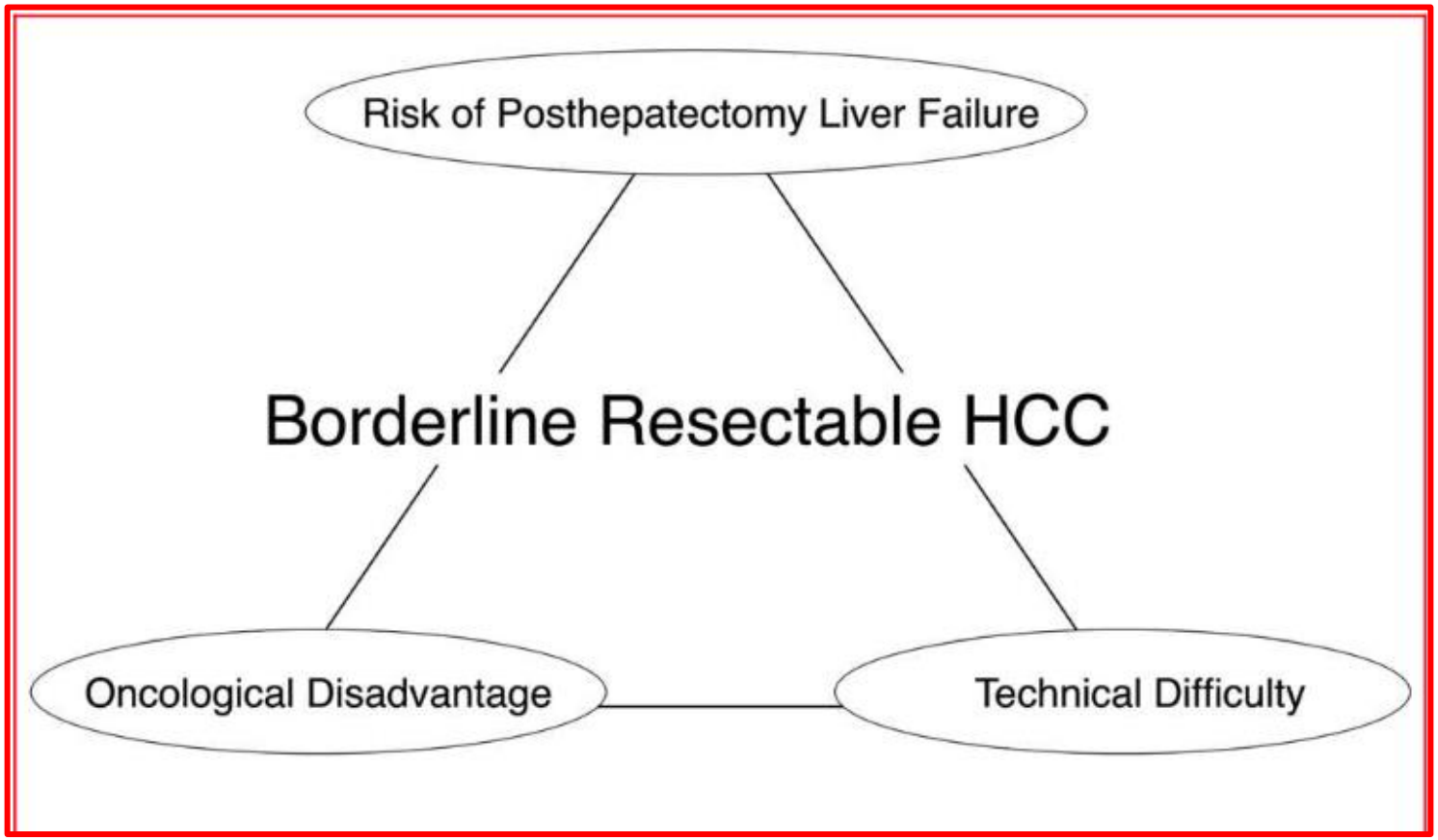
«Οριακά Εξαιρέσιμος ΗΚΚ είναι εκείνος που μπορεί, δυνητικά, να αφαιρεθεί χειρουργικά με σημαντικές, ωστόσο, τεχνικές δυσκολίες, πιθανά διηθημένα όρια, κίνδυνο μτχ ηπατικής ανεπάρκειας ή άλλων επιπλοκών, και φτωχή ογκολογική έκβαση.

Η προσθήκη νεώτερων θεραπευτικών επιλογών μπορεί να βελτιώσει σημαντικά τις μεταβλητές επιβίωσης.»

Κριτήρια Οριακά Εξαιρεσίμου ΗΚΚ

- Tumor size | >5-10 cm
- Tumor number | Limited multifocality, confined to one lobe
- Vascular involvement | Segmental/lobar portal vein or hepatic vein involvement; no main portal vein or IVC invasion
- Liver function (Child-Pugh) | Mostly A, selected B7
- MELD score | ≤10-12
- Future liver remnant (FLR) | ≥40% for cirrhosis; ≥20-30% non-cirrhotic
- ICG retention test (15 min) | ≤15-20%
- Portal hypertension | Absent or clinically insignificant
- Performance status | ECOG 0-1

A Conceptual Classification of Resectability for Hepatocellular Carcinoma



World J Surg 2023

A Conceptual Classification of Resectability for Hepatocellular Carcinoma

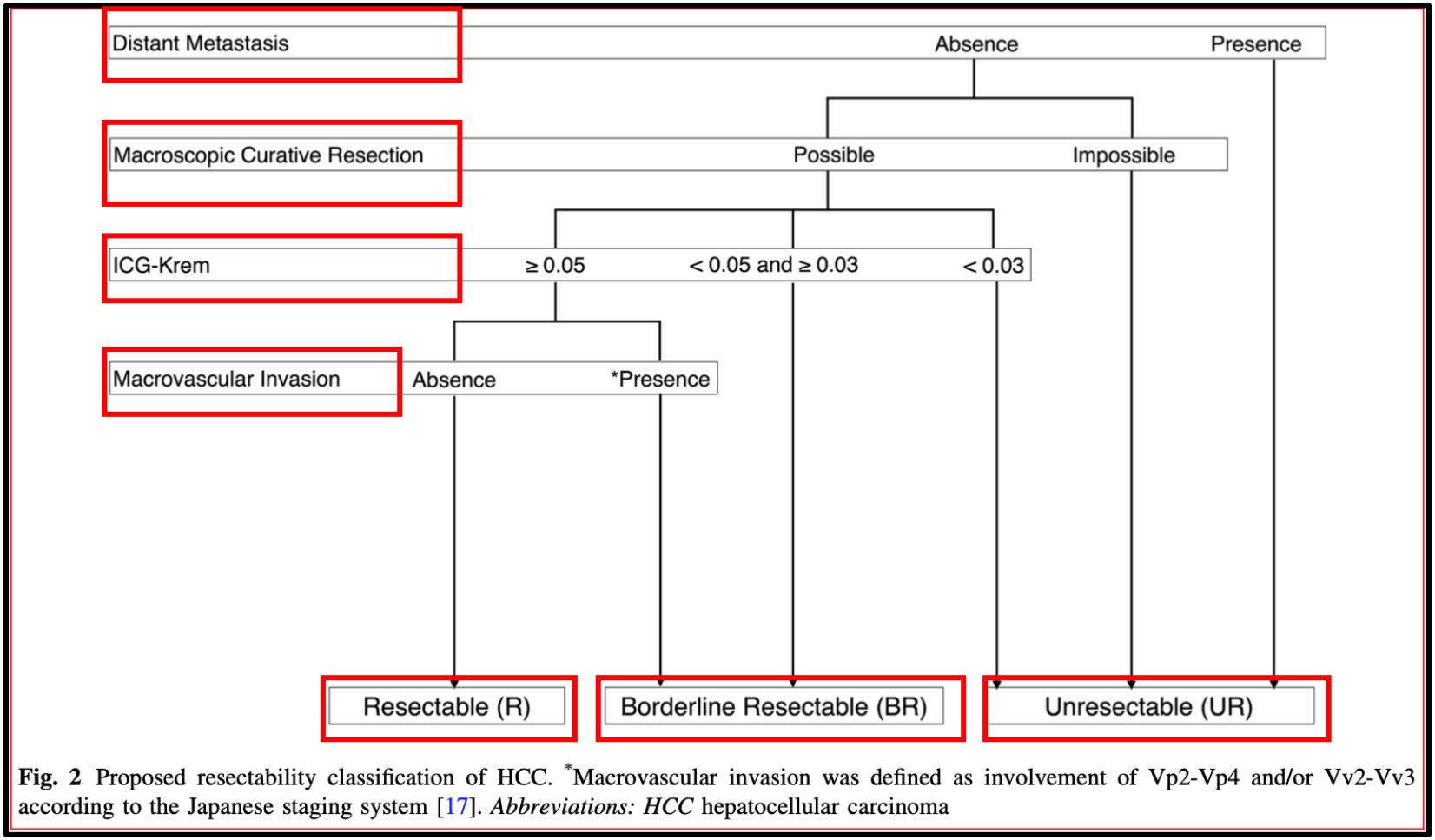


Fig. 2 Proposed resectability classification of HCC. *Macrovascular invasion was defined as involvement of Vp2-Vp4 and/or Vv2-Vv3 according to the Japanese staging system [17]. *Abbreviations: HCC* hepatocellular carcinoma

World J Surg 2023

A Conceptual Classification of Resectability for Hepatocellular Carcinoma

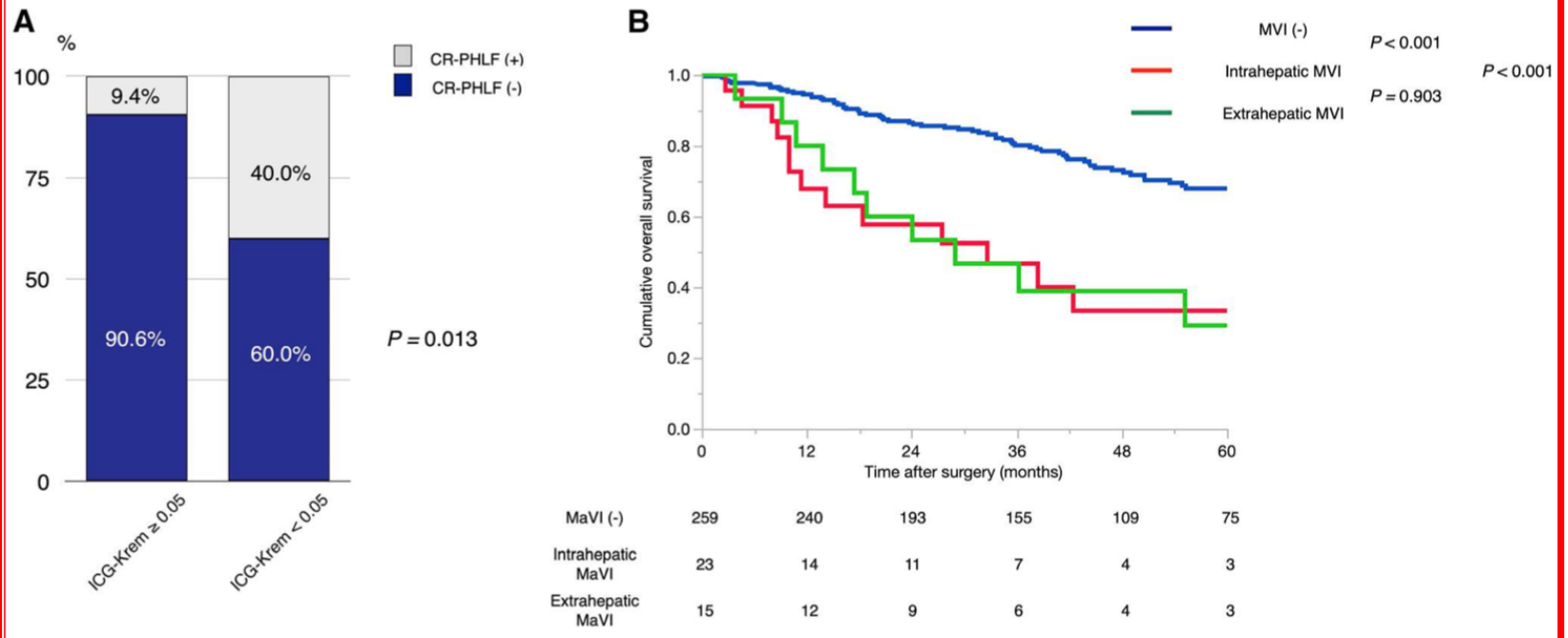


Fig. 4 Validity of using ICG-Krem and MVI for resectability classification. *Abbreviations: ICG-Krem* indocyanine green clearance of remnant liver, *MVI* macrovascular invasion, *CR-PHLF* clinically relevant posthepatectomy liver failure

World J Surg 2023

A Conceptual Classification of Resectability for Hepatocellular Carcinoma

Table 2 Risk factors of poorer overall survival in patients who underwent liver resection for HCC

Variables		Univariate *p* value	Multivariate analysis		*p* value
			HR	95% CI	
Age	Every 1 year increase	0.428			–
Gender	Female	0.638			–
	Male				
Child-Pugh classification	Grade A	0.140			–
	Grade B				
Serum AFP levels	Every 10 ng/ml increase	0.384			–
	Solitary	Reference			
Tumor number	2–3 tumors	0.276			–
	≥4 tumors	0.315			
Maximum tumor diameter	Every 1 cm increase	0.004*	1.029	0.971–1.086	0.313
Resectability classification	R-HCC	<0.001*	Reference		<0.001*
	BR-HCC		2.597	1.558–4.329	

World J Surg 2023

A Conceptual Classification of Resectability for Hepatocellular Carcinoma

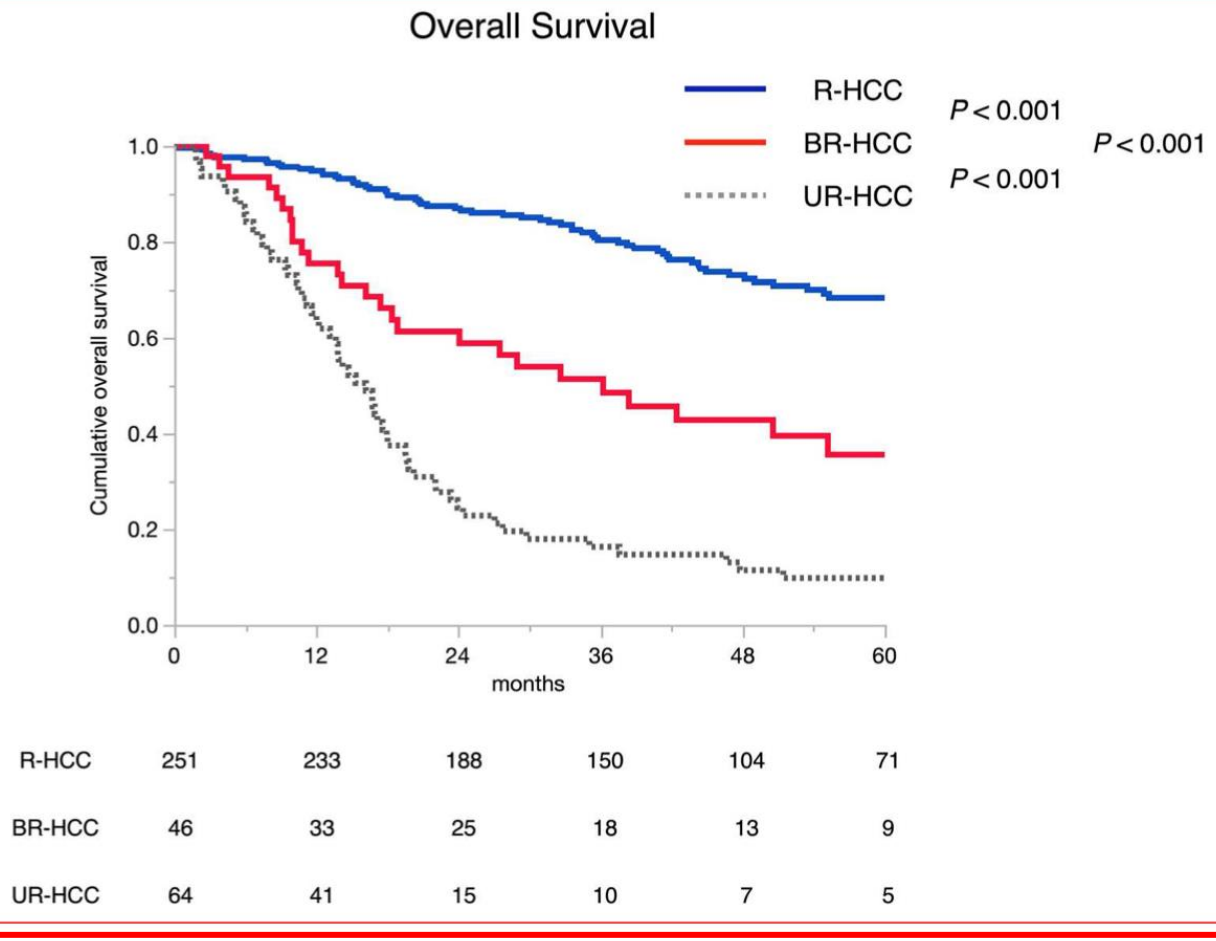


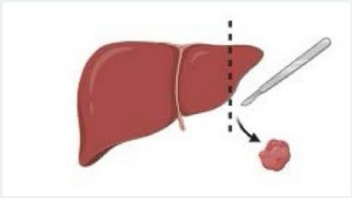
Fig. 5 Overall survival stratified by the proposed resectability classification. *Abbreviations: HCC* hepatocellular carcinoma, *R-HCC* resectable HCC, *BR-HCC* borderline resectable HCC, *UR-HCC* unresectable HCC

World J Surg 2023

Proposal for Prognosis-Oriented Definition of Borderline Resectable Hepatocellular Carcinoma

STUDY POPULATION

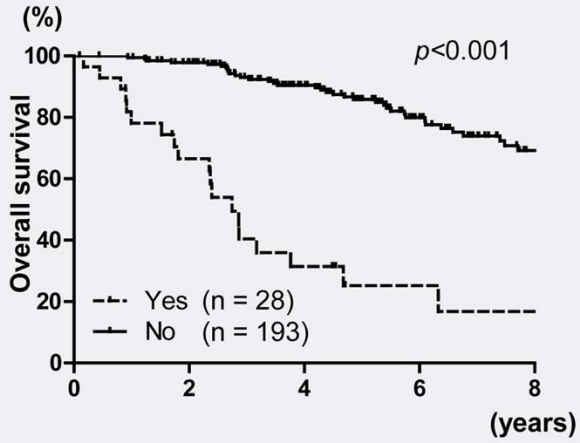
Patients who underwent hepatic resection for hepatocellular carcinoma



Original cohort
(n=221)

Validation cohort
(n=181)

Recurrence beyond the Milan criteria within 1 year after resection



Analysis for risk factors of early unresectable/unablatable recurrence

High-risk score

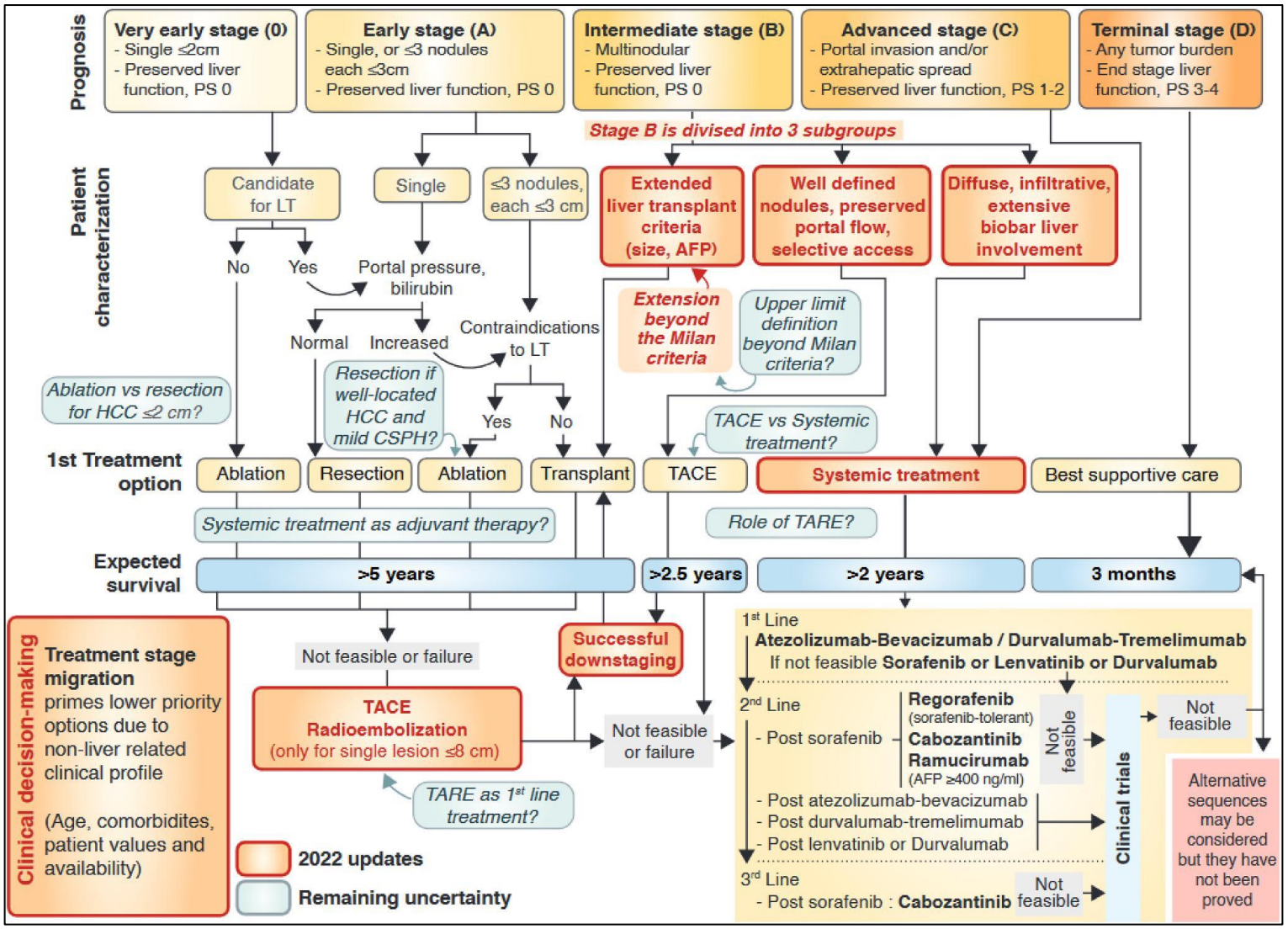
- Tumor diameter > 5 cm
- Tumor number ≥ 3
- Serum AFP ≥ 12 ng/mL
- Macrovascular invasion

Borderline resectable HCC
High-risk score ≥ 2

Haruki et al, *J Am Coll Surg*, June 2024

JACS JOURNAL OF THE AMERICAN COLLEGE OF SURGEONS
JOURNAL OF THE AMERICAN COLLEGE OF SURGEONS

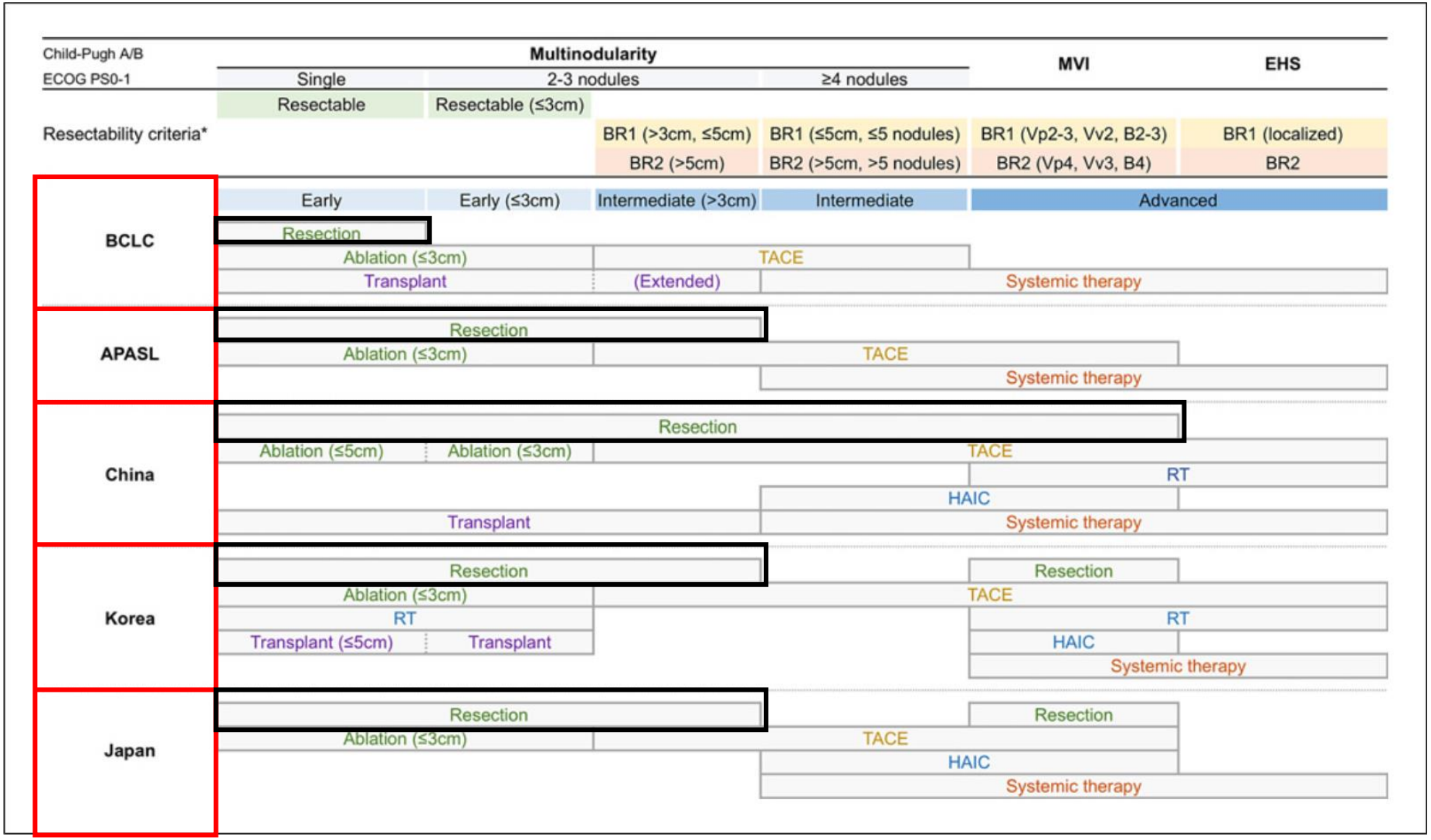
BCLC / EASL / ESMO



J Hepatol 2025

Current Perspectives on Perioperative Combination Therapy for Hepatocellular Carcinoma

Liver Cancer 2024



Oncological Resectability Criteria for HCC

Clinical question		Consensus statement
CQ1	What should be the basic structure for presenting the oncological resectability criteria for HCC?	The oncological resectability criteria for HCC can be classified into three groups **Group 1:** oncological status for which surgery alone may be expected to offer clearly better survival outcomes as compared with other treatments **Group 2:** oncological status for which surgical intervention as a part of multidisciplinary treatment may be expected to offer survival benefit **Group 3:** oncological status for which the efficacy of surgery is uncertain and the indication for surgery should be carefully determined under the standard multidisciplinary treatment
CQ2	What is the optimal terminology for the three groups of oncological resectability criteria?	The oncological resectability criteria classified into three groups shall be named R, BR1, and BR2
CQ3	What is the resectability status of single HCC?	Single HCC is classified as R, regardless of the tumor size
CQ4	What is the upper limit for "R" in the case of multinodular HCC?	Multinodular HCC with up to 3 nodules, each measuring ≤3 cm in diameter is the upper limit of R
CQ5	What is the lower limit for "BR2" in the case of multinodular HCC?	Multinodular HCC with more than 5 nodules and/or any nodule measuring >5 cm in diameter is the lower limit for BR2
CQ6	How should we classify the resectability of portal vein invasion?	Vp0–1 is classified as R, Vp2–3 as BR1, and Vp4 as BR2
CQ7	How should we classify the resectability of hepatic vein invasion?	Vv0–1 is classified as R, Vv2 as BR1, and Vv3 as BR2
CQ8	How should we classify the resectability of bile duct invasion?	B0–1 is classified as R, B2–3 as BR1, and B4 as BR2
CQ9	What is the resectability of cases with extrahepatic spread (EHS)?	EHS is basically BR2, while localized EHS could be classified as BR1

Liver Cancer 2024;13:579–589

Fundamental Definition of the Oncological Resectability Criteria for HCC

R: Resectable

Oncological status for which surgery alone may be expected to offer clearly better survival outcomes as compared with other treatments

BR1: Borderline resectable 1

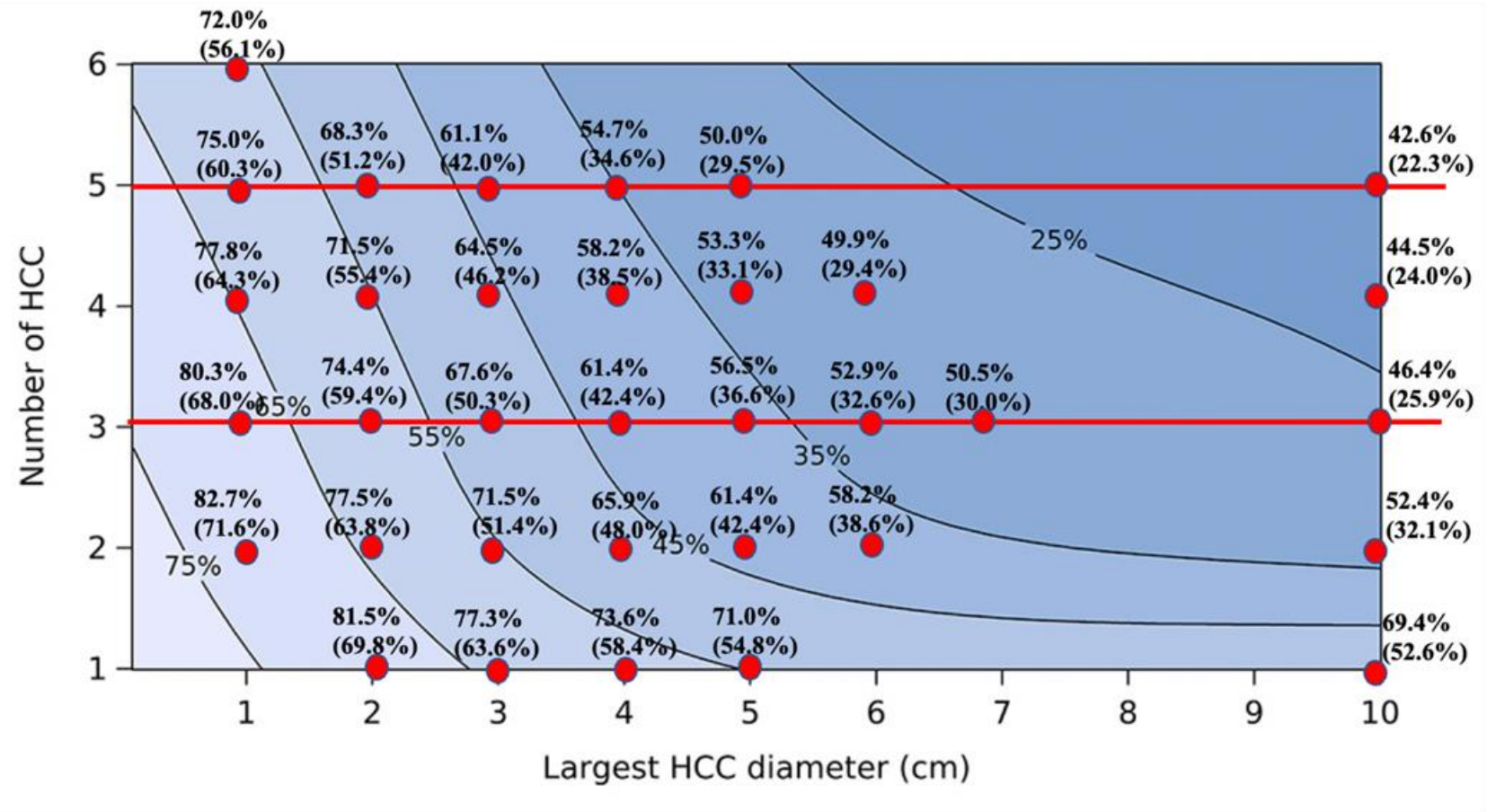
Oncological status for which surgical intervention as a part of multidisciplinary treatment may be expected to offer survival benefit

BR2: Borderline resectable 2
(initially unsuitable for resection)

Oncological status for which the efficacy of surgery is uncertain and the indication for surgery should be carefully determined under the standard multidisciplinary treatment

Liver Cancer 2024

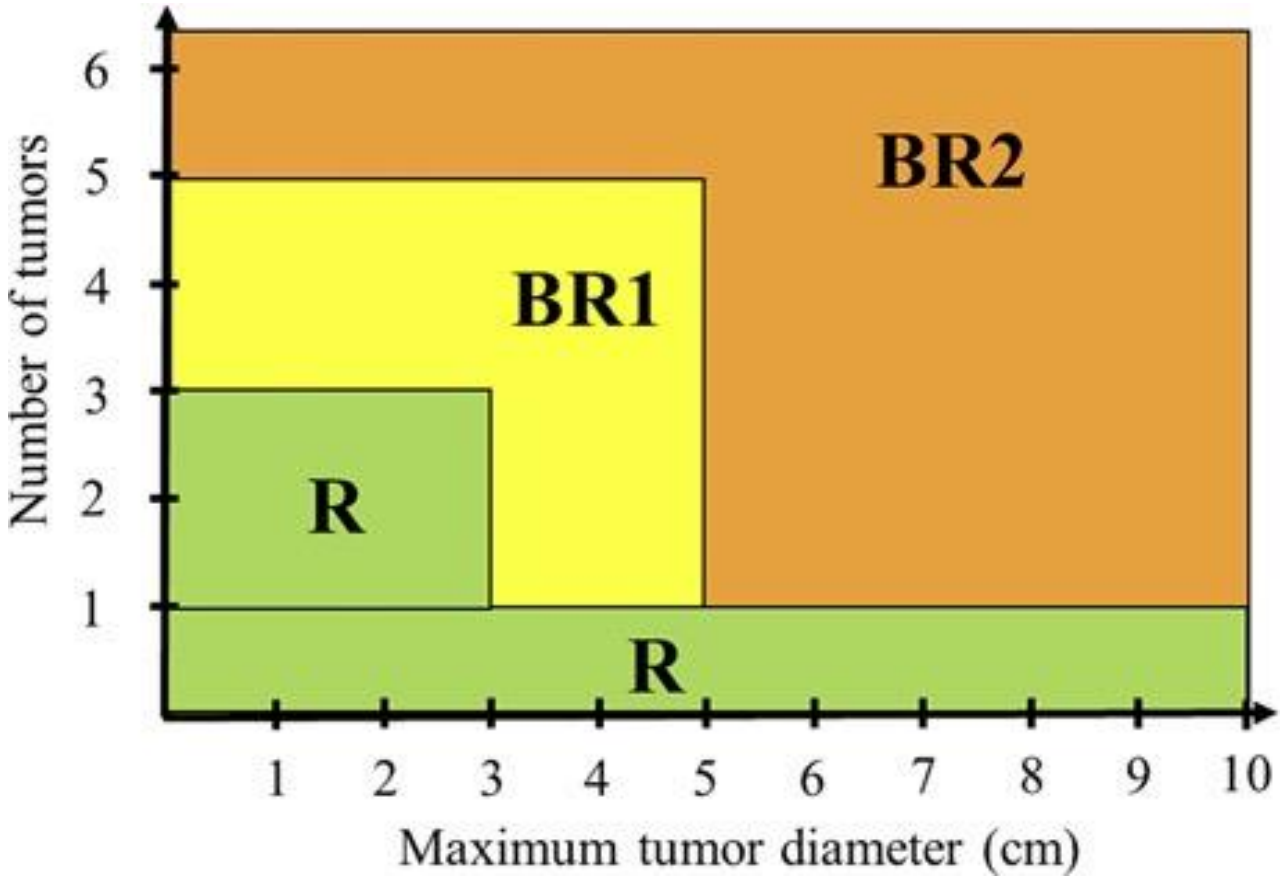
Oncological Resectability Criteria for Hepatocellular Carcinoma in the Era of Novel Systemic Therapies: the JLCA and JSHBPS Expert Consensus Statement 2023



Three- and five-year overall survival rates classified by the diameter of the largest HCC tumor diameter and number of HCC tumors in patients undergoing surgical resection.

Liver Cancer 2024

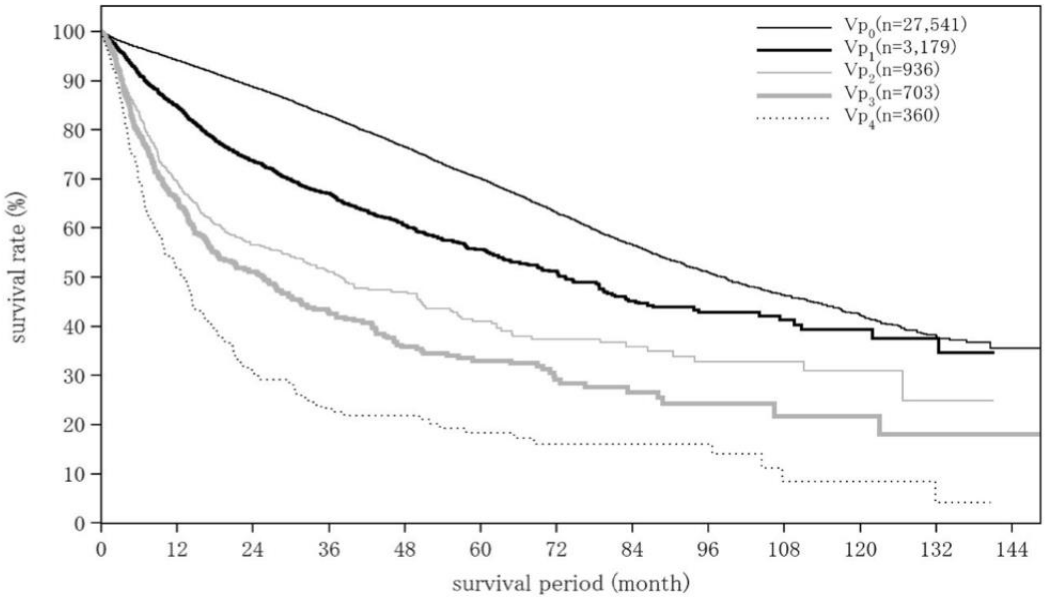
Fundamental Definition of the Oncological Resectability Criteria for HCC



Liver Cancer 2024

Report of the 22nd nationwide follow-up Survey of Primary Liver Cancer in Japan (2012–2013)

Title	Category name	*N*	Median OS (months)
Portal vein invasion	Vp_0	27 541	98.37
	Vp_1	3 179	73.36
	Vp_2	936	37.95
	Vp_3	703	25.46
	Vp_4	360	13.11



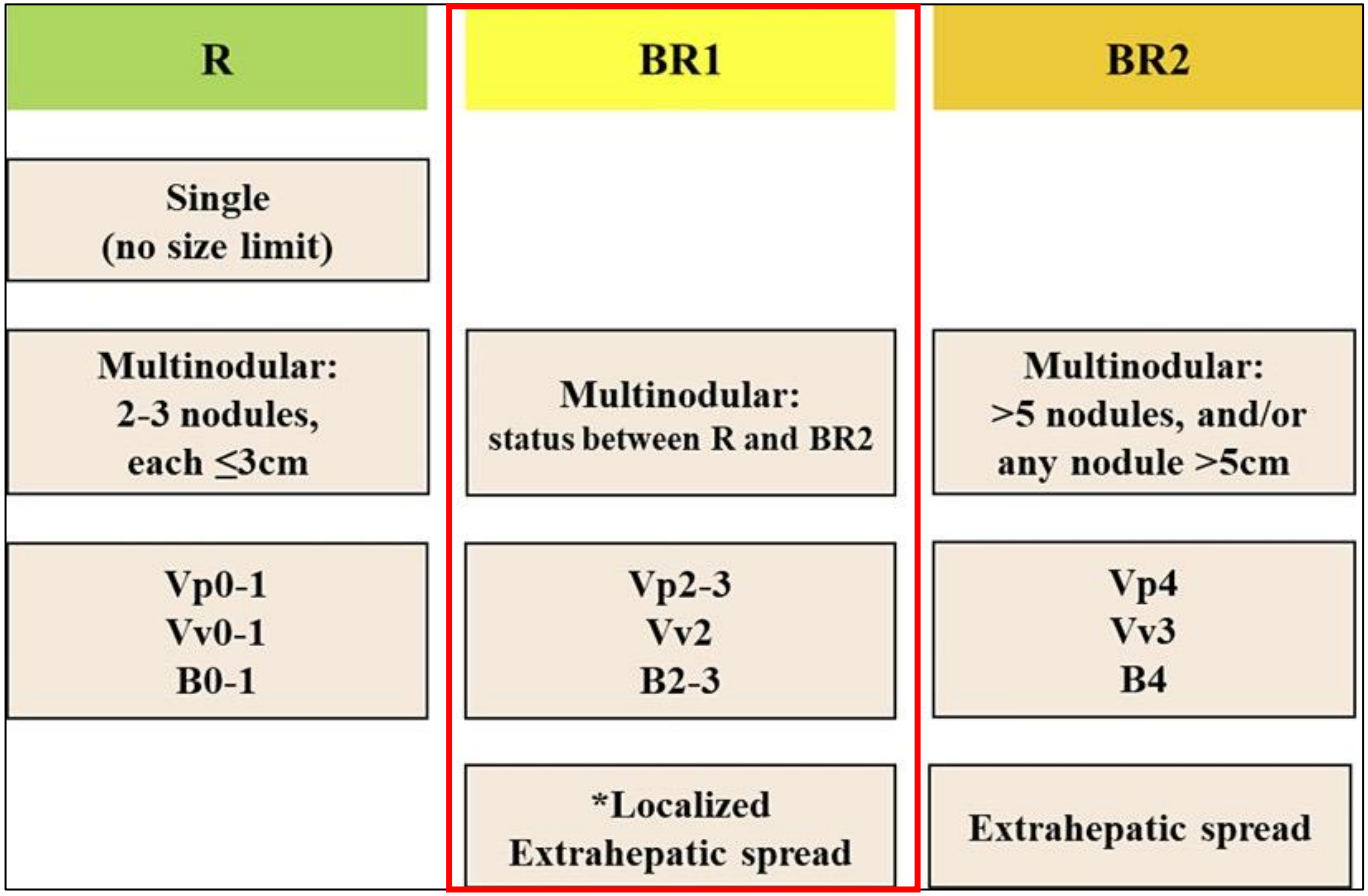
Hepatology Res 2022

Liver resection for hepatocellular carcinoma associated with hepatic vein invasion: A Japanese nationwide survey

	pHVTT (n = 305)*	mHVTT (n = 170)*	IVCTT (n = 71)*
Major hepatectomy§	175 (59.9)	124 (76.5)	51 (75.0)
Median survival time (y)	4.85 (95%CI 3.38-n.a.)	4.67 (95%CI 3.32-5.88)	1.37 (95%CI 1.07-4.21)
Recurrence-free survival (y)	2.36 (95%CI 1.38-3.17)	0.88 (95%CI 0.75-1.32)	0.82 (95%CI 0.42-1.10)
Site of the first recurrence			
Intrahepatic	92 (32.7)	60 (38.0)	17 (23.9)
Distant metastasis	14 (5.0)	18 (11.4)	9 (12.7)
Both	17 (6.0)	16 (10.1)	15 (21.1)
Median hospital stay (d)	21 (IQR 15-36)	23 (IQR 16-46)	26 (IQR 18-55)
90-day mortality	13 (4.3)	3 (1.8)	7 (9.9)

Hepatology 2017

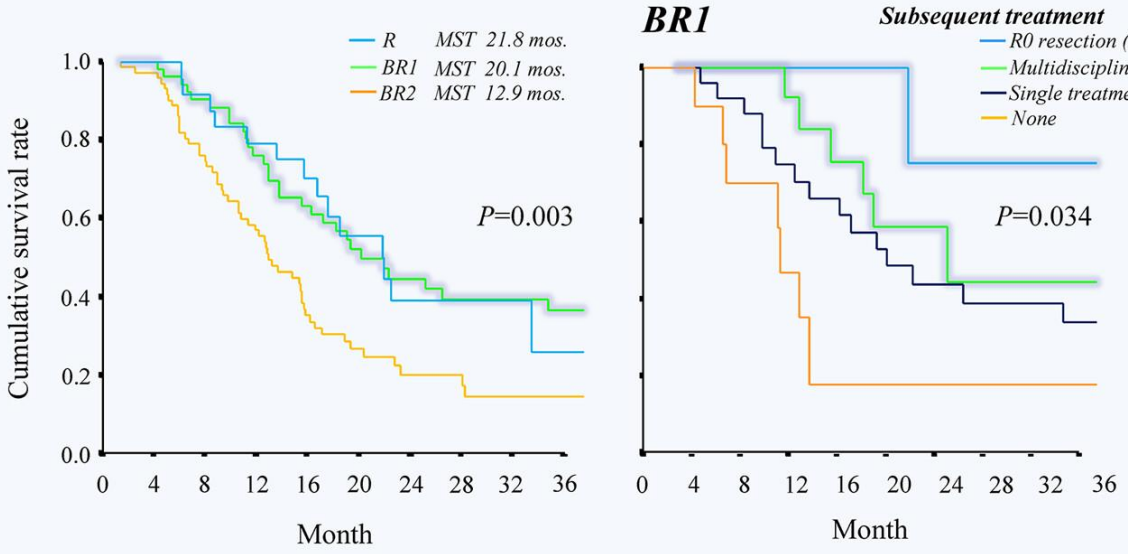
Fundamental Definition of the Oncological Resectability Criteria for HCC



*Solitary nodal involvement at no. 3, 8, or 12 lymph nodes
Localized peritoneal dissemination
Unilateral adrenal metastases
Oligometastasis to the lung

Liver Cancer 2024

Newly established borderline resectable 1 (BR1) category is one of the favorable candidates for selecting the use of multidisciplinary combination therapy in patients with advanced hepatocellular carcinoma treated with systemic therapy



R: resectable

Oncological status for which surgery alone may offer clearly better survival outcomes compared to the other treatment

BR1: borderline resectable 1

Oncological status for which surgical intervention as a part of multidisciplinary treatment may offer survival benefit

BR2: borderline resectable 2 (initially unsuitable for resection)

Oncological status for which efficacy of surgery is indeterminate and surgical indication should be carefully determined under the standard multidisciplinary management of HCC

※Oncological criteria of resectability should be determined independently from technical and/or functional criteria of resectability.

Oncological Criteria of Resectability for Hepatocellular Carcinoma (BR-HCC Expert Consensus 2023)

R	BR1	BR2
Solitary		
Multiple ≤3 nodules and ≤3cm	Multiple >3 nodules or >3cm ≤5 nodules or ≤5cm	Multiple >5 nodules or >5cm
Vp0-1 Vv0-1 B0-1	Vp2-3 Vv2 B2-3	Vp4 Vv3 B4
	*Localized Extrahepatic spreads	Extrahepatic spreads

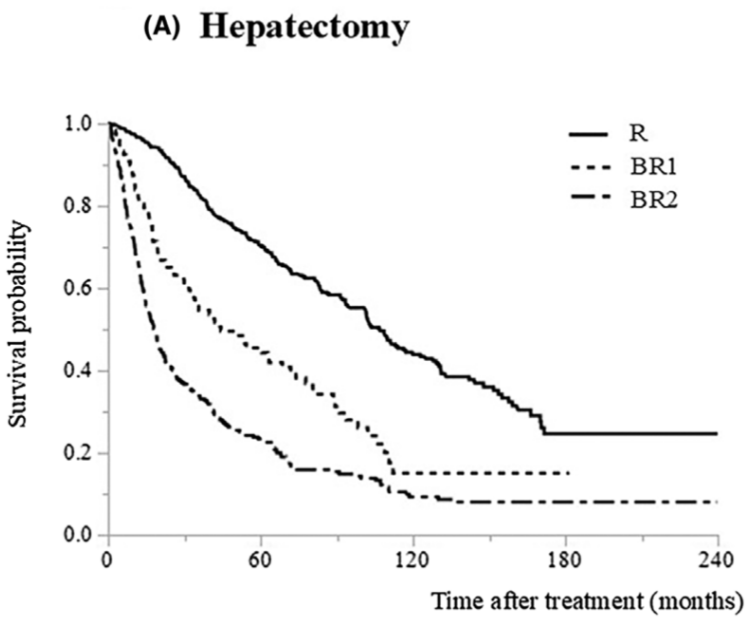
*Localized EHS

Solitary nodal involvement at No3, 8, or 12
Localized peritoneal mets
Unilateral adrenal mets
Oligometastases to the lung

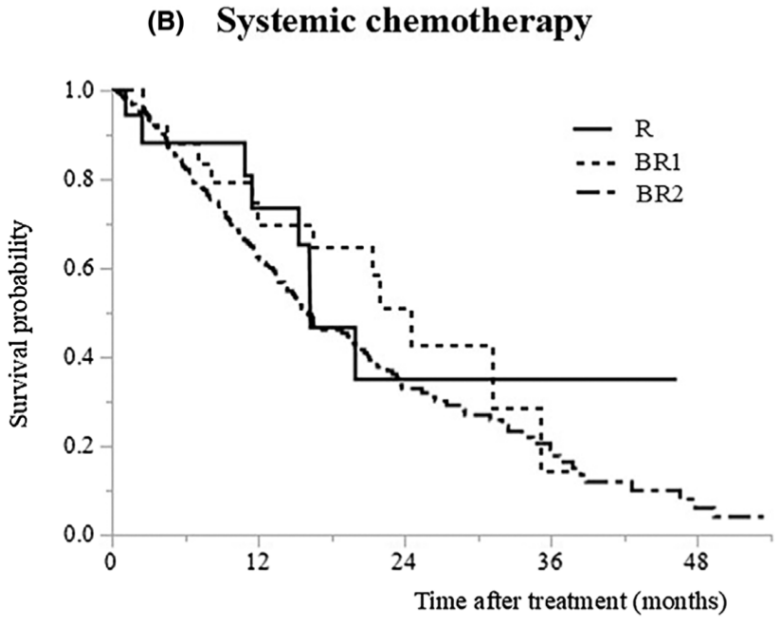
https://www.nihon-kangan.jp/files/2023_HCCExperConsensusStatement.pdf

Hepatology Res 2025

Treatment outcomes of hepatectomy and systemic chemotherapy based on oncological resectability criteria for hepatocellular carcinoma



R (n = 536) : 107.2 month
BR1 (n = 120) : 44.4 month
BR2 (n = 275) : 18.4 month
$p < 0.0001$

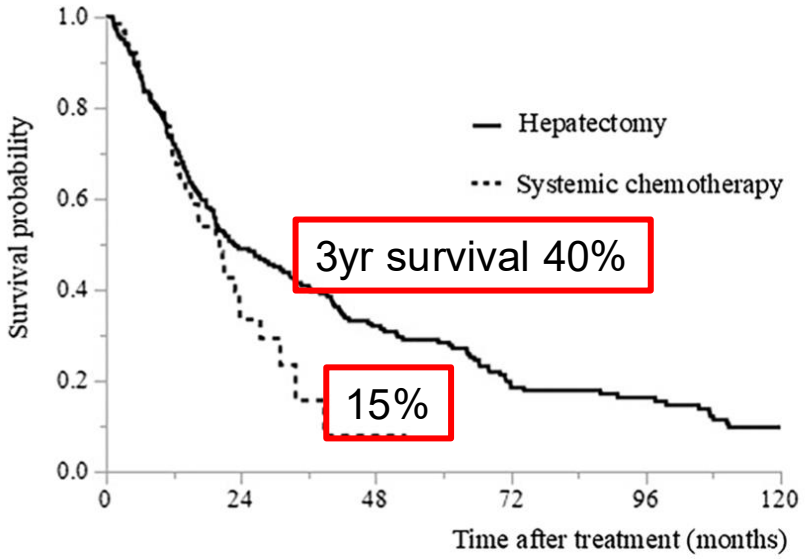


R (n = 19) : 16.3 month
BR1 (n = 29) : 24.5 month
BR2 (n = 225) : 16.1 month
$p = 0.3598$

Ann Gastroenterol Surg 2025

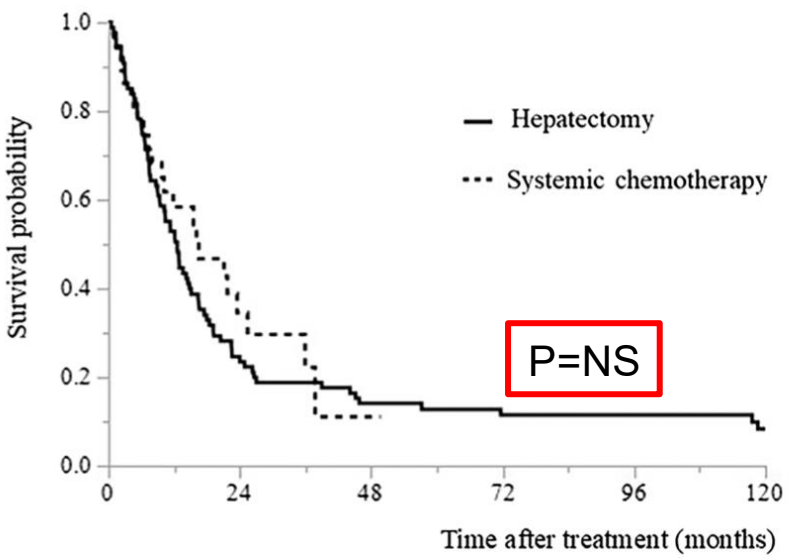
Treatment outcomes of hepatectomy and systemic chemotherapy based on oncological resectability criteria for hepatocellular carcinoma

(A) Patients with only one BR2-defining factor



Hepatectomy (n = 186)	: 22.9 month
Systemic chemotherapy (n = 67)	: 20.2 month
$p = 0.0977$	

(B) Patients with two or three BR2-defining factors

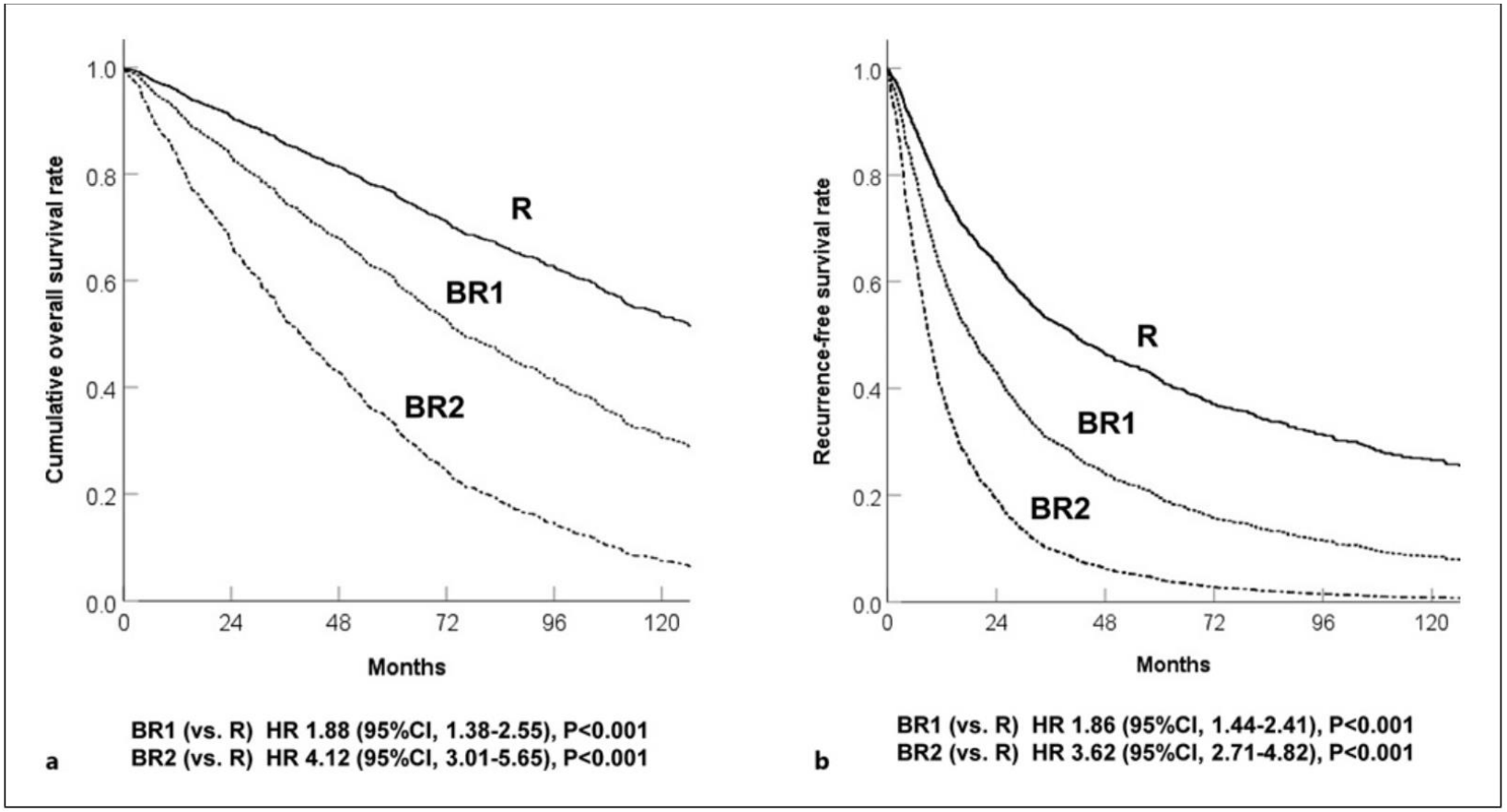


Hepatectomy (n = 87)	: 12.6 month
Systemic chemotherapy (n = 38)	: 16.5 month
$p = 0.4252$	

Ann Gastroenterol Surg 2025

Clinical Utility of the Novel Oncological Criteria of Resectability for Advanced Hepatocellular Carcinoma

Liver Resection



Liver Cancer 2024

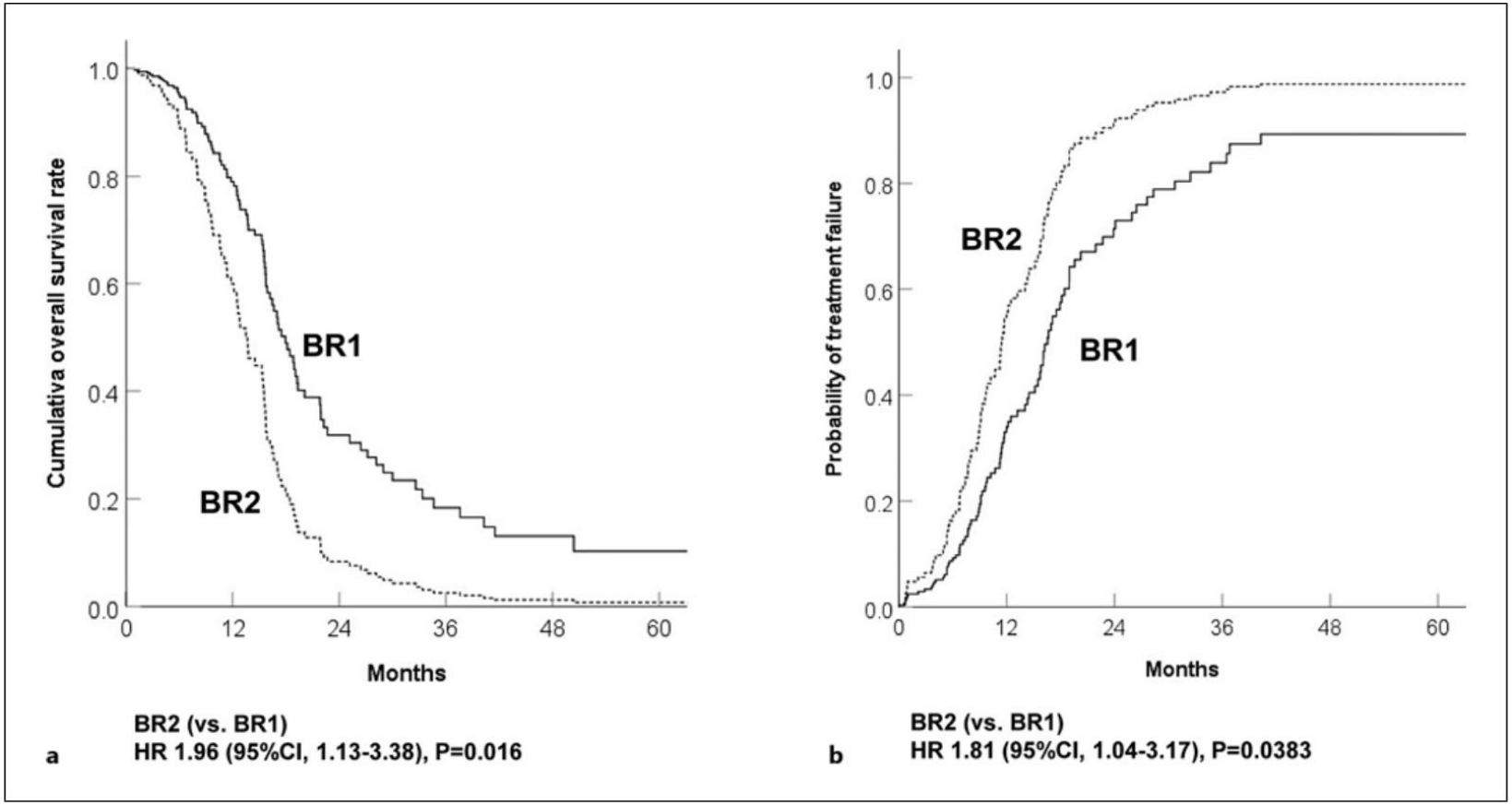
Clinical Utility of the Novel Oncological Criteria of Resectability for Advanced Hepatocellular Carcinoma

Predictive Factors of OS after Liver Resection

	p value[a]	Coefficient[b]	SE	Wald χ^2	HR	95% CI
Age	<0.001	0.026	0.004	35.55	1.03	1.02–1.04
Hepatitis C	0.001	0.273	0.083	10.88	1.31	1.12–1.55
Prior history of curative treatment	<0.001	0.622	0.109	32.63	1.86	1.51–2.31
Child-Pugh score +1	<0.001	0.354	0.052	45.80	1.43	1.29–1.58
Technical resectability (vs. R)						
MR	0.091	0.158	0.094	2.85	1.17	0.98–1.41
Oncological resectability (vs. R)						
BR1	<0.001	0.631	0.151	16.32	1.88	1.38–2.55
BR2	<0.001	1.417	0.161	77.29	4.12	3.01–5.65
AFP (+1 log ng/mL)	<0.001	0.186	0.038	23.93	1.20	1.12–1.30
DCP (+1 log mAu/mL)	<0.001	0.249	0.048	26.99	1.28	1.17–1.41
Era (vs. 1995–2008)						
2009–2017	<0.001	−0.307	0.088	12.28	0.74	0.62–0.87
2018–2023	<0.001	−0.554	0.145	14.65	0.58	0.43–0.76

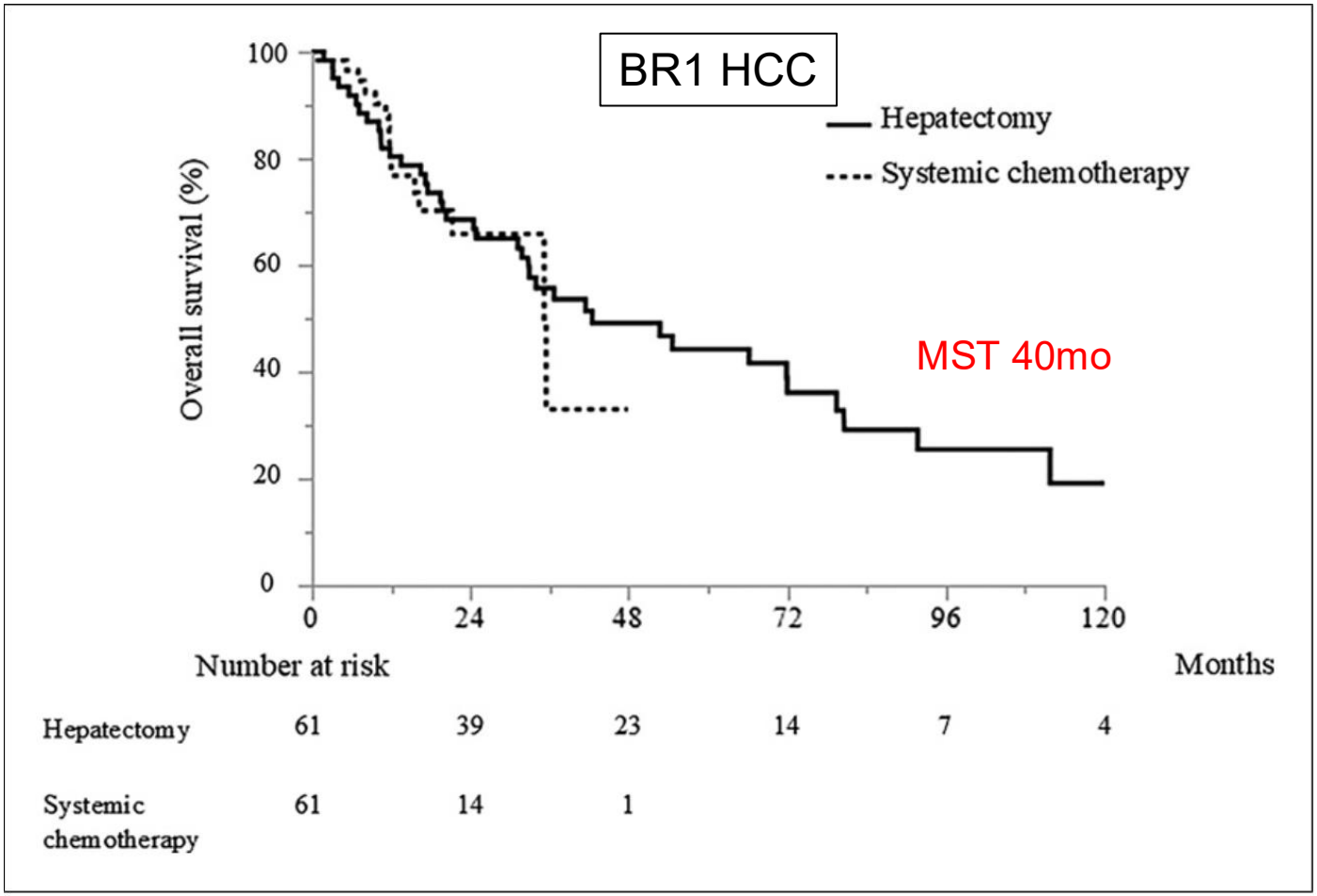
Clinical Utility of the Novel Oncological Criteria of Resectability for Advanced Hepatocellular Carcinoma

Lenvatinib



Liver Cancer 2024

Prognosis of Hepatectomy versus Systemic Chemotherapy Based on Oncological Resectability Criteria for Borderline Resectable Hepatocellular Carcinoma

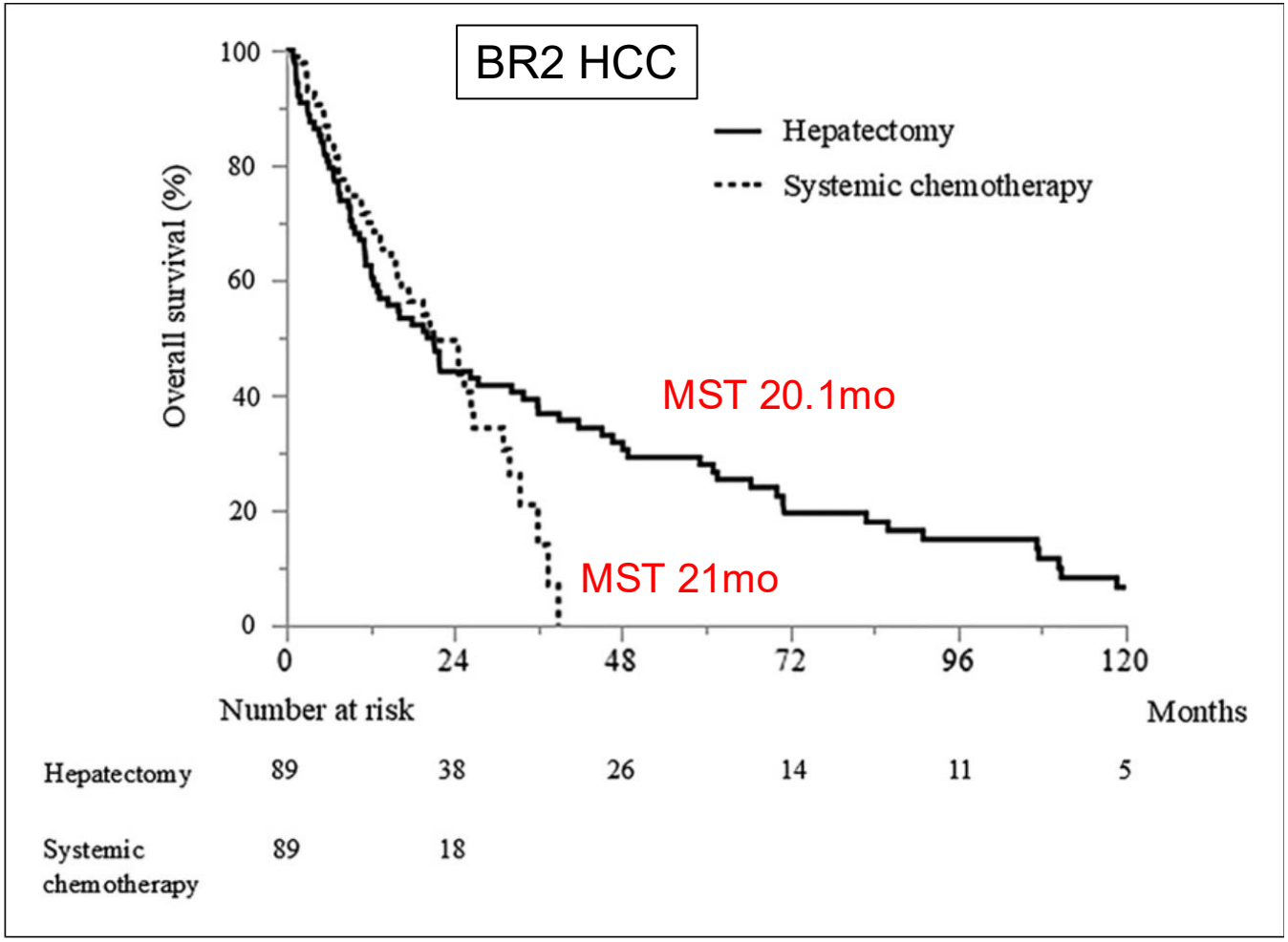


MVA for OS

HBV/HCV
mALBI 2+3
EHS

Liver Cancer 2025

Prognosis of Hepatectomy versus Systemic Chemotherapy Based on Oncological Resectability Criteria for Borderline Resectable Hepatocellular Carcinoma



Liver Cancer 2025

Treatment of Borderline Resectable HCC

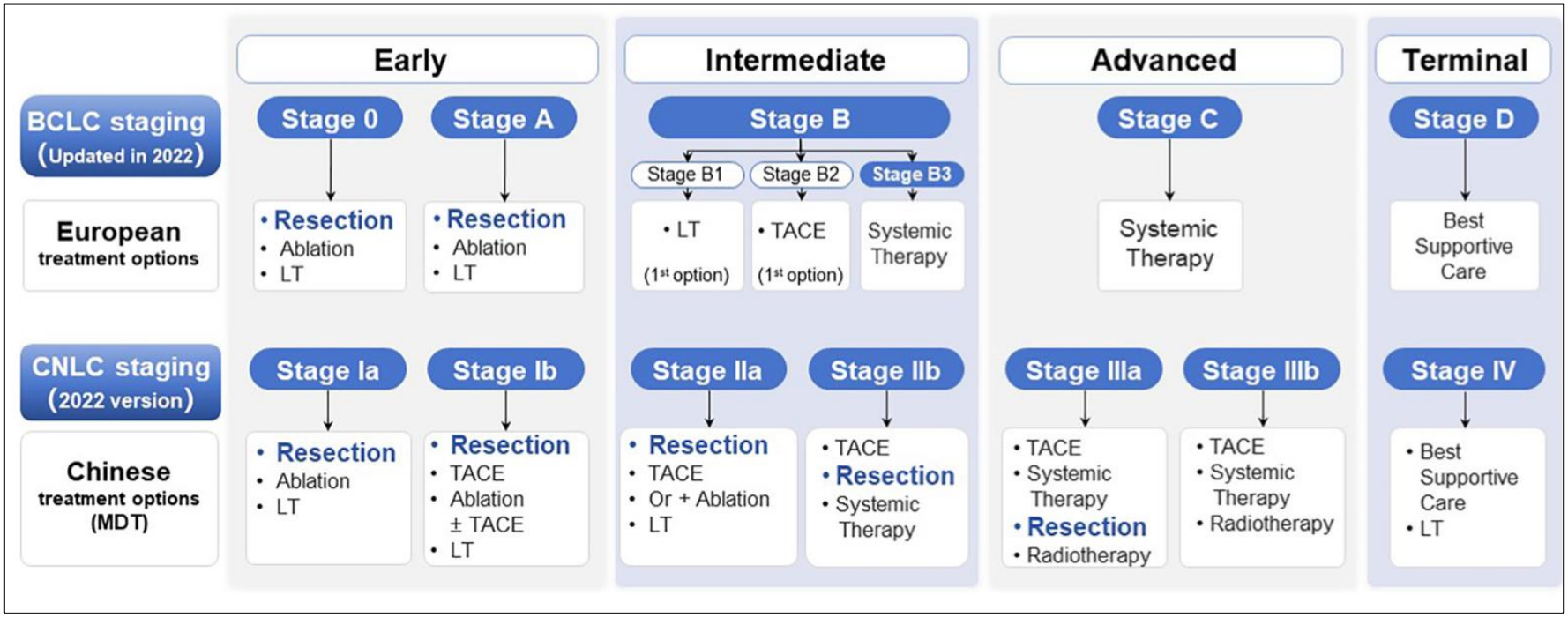
Preoperative strategies ("downstaging"):
TACE / HAIC
TARE
+TKIs, ICIs, bevacizumab to reduce tumor size or vascular invasion

Careful surgical planning:
Assessment of FLR and function
Possible PVE / ALPPS to increase FLR
Extended LR ± Vascular Reconstruction for R0

Postoperative care:
Close monitoring for PHLF or complications
Adjuvant therapies - AEs

Prognosis
Borderline resectable HCC has a guarded prognosis due to higher risks of incomplete resection, recurrence, and postoperative complications, but surgery might still offer the best chance for long-term survival compared to other treatments.

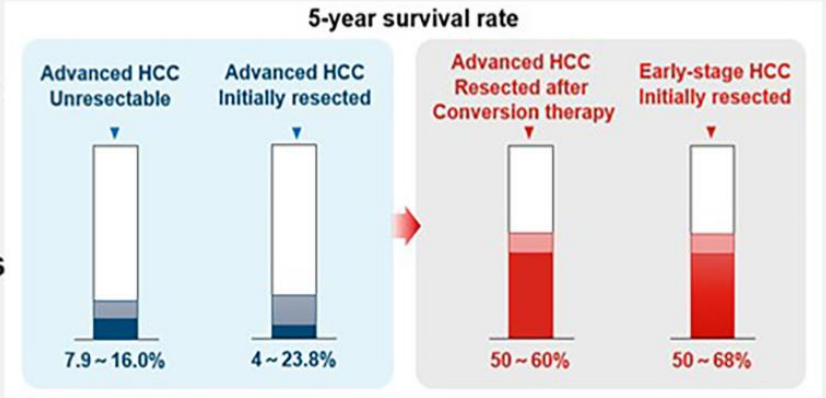
Conversion therapy for advanced hepatocellular carcinoma in the era of precision medicine: Current status, challenges and opportunities



Cancer Science. 2024;115:2159–2169.

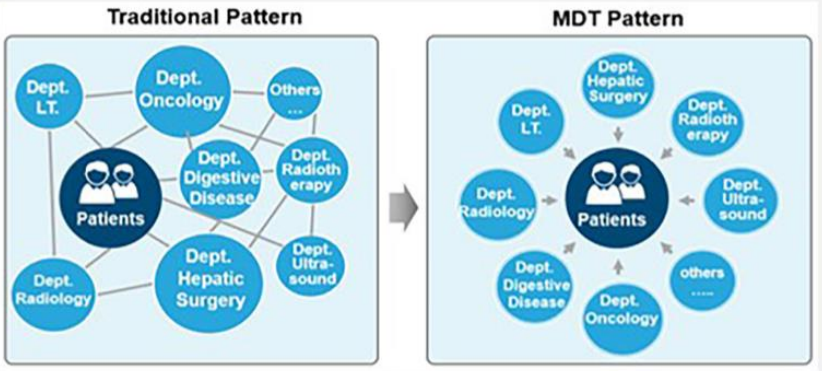
Current Status of Conversion Therapy

- Advanced HCC poses survival challenges
- Effective tumor downstaging brings surgical opportunities for uHCC patients
- Diverse combined conversion approaches show remarkable and promising results
- Lack of guidelines or standard protocols



Multi Disciplinary Team (MDT Model)

- Establishment of a stable MDT
- Convenient communication channels
- Comprehensively evaluation
- Timely decision-making or adjustment of treatment strategies



Short-term goal

Curative-intent Resection

Ultimate goal

High-quality Long-term Survival

Cancer Science 2024

Rationale of Borderline Resectability

- Improve Prognosis for BCLC Stages B and C
- Local treatment after systemic chemo
- “Stage migration – Conversion Therapy”
- Ate/Bev, LEN, Dur/Tre: High Response Rates
- 20% of cases: Progressive Disease
- Therapeutic window??????
- LR, TACE, TARE after neo-aduvant chemo
- Preserving liver function
- MDT

….Tumor Biology First….

"…Biology is the King,

Selection of Cases is Queen,

Technical Details of Surgical Procedures are Princes and Princesses who frequently try to overthrow the powerful forces of the King and Queen,

Usually to no long-term avail, although with some temporary apparent victories…"

Dr. Blake Cady
1930 - 2023