The Big Picture: Comprehensive HCC Management in Japan

Masatoshi Kudo, MD, PhD
Dept. of Gastroenterology and Hepatology
Kindai University Faculty of Medicine

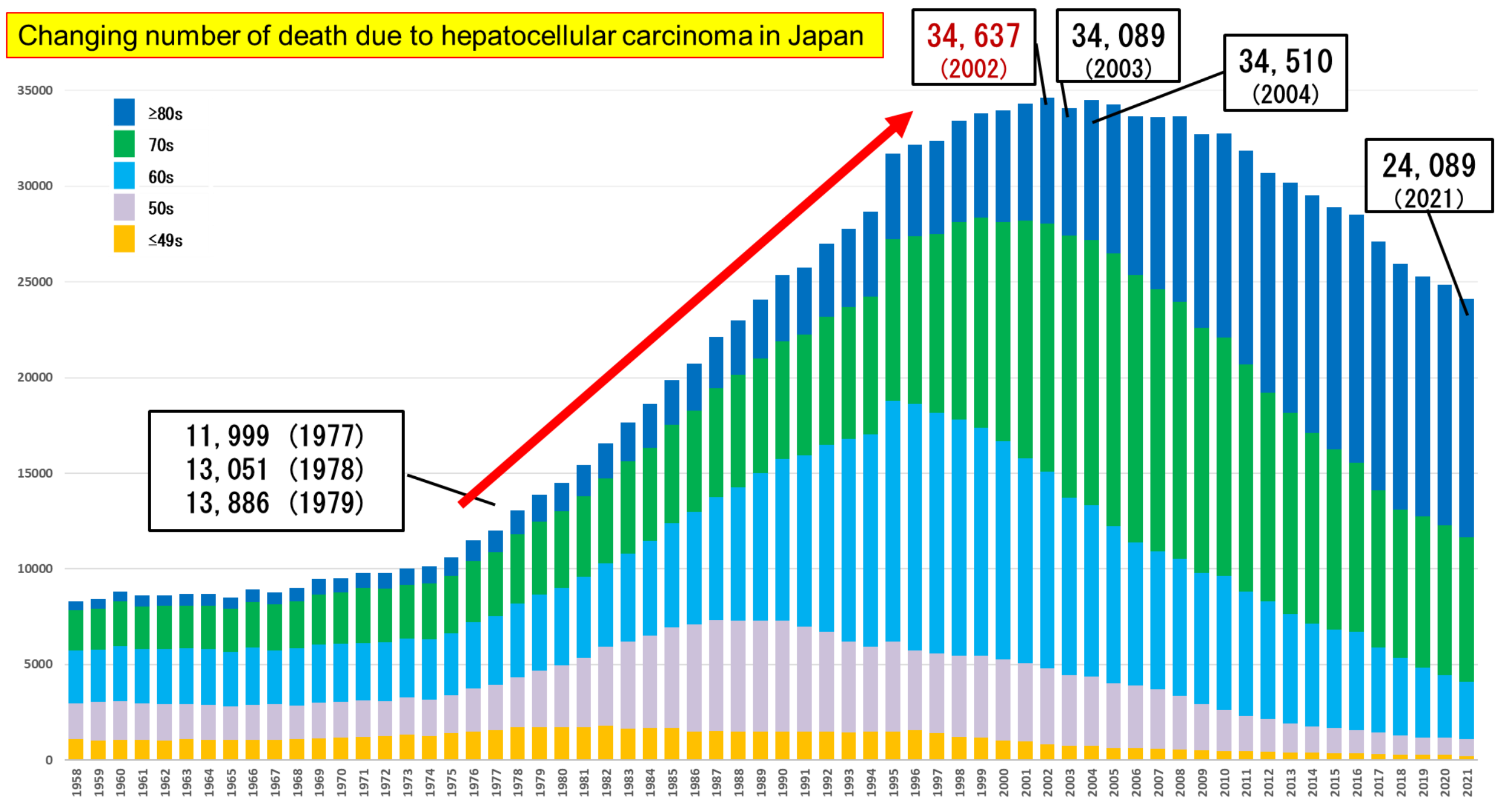
Outline

- Overview of HCC trend in Japan
- Overview of HCC outcome in Japan
- Overview of HCC surveillance in Japan
- Treatment strategy for Early-stage HCC
- Treatment strategy for Intermediate HCC
- Treatment strategy for Advanced stage HCC
- Summary and Conclusion

Outline

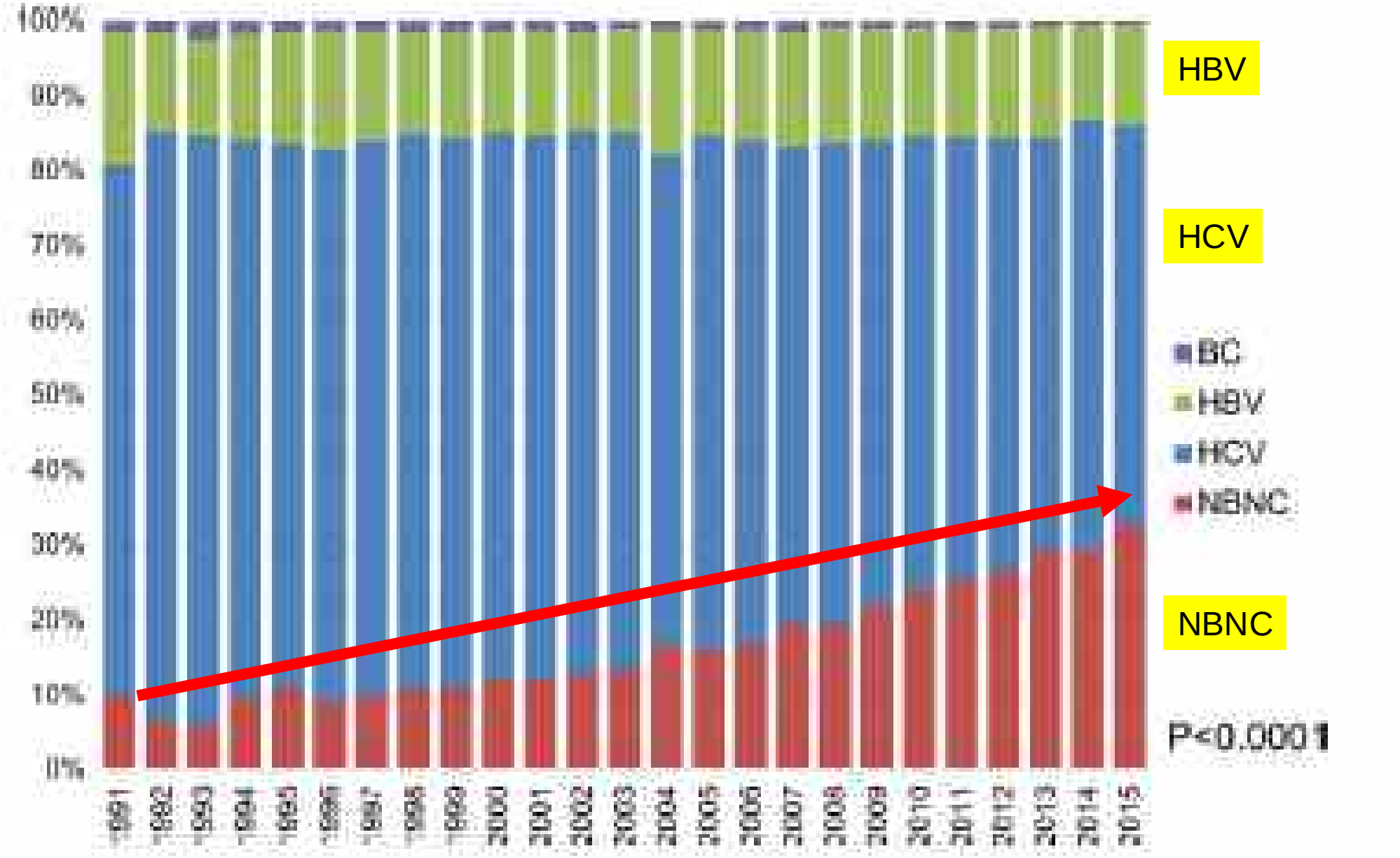
- Overview of HCC trend in Japan

Changing number of death due to hepatocellular carcinoma in Japan



Citation from [National Cancer Center Japan] (https://ganjoho.jp/reg_stat/statistics/stat/cancer/8_liver.html)

Changing Aetiology of HCC in Japan: Multicentre Study

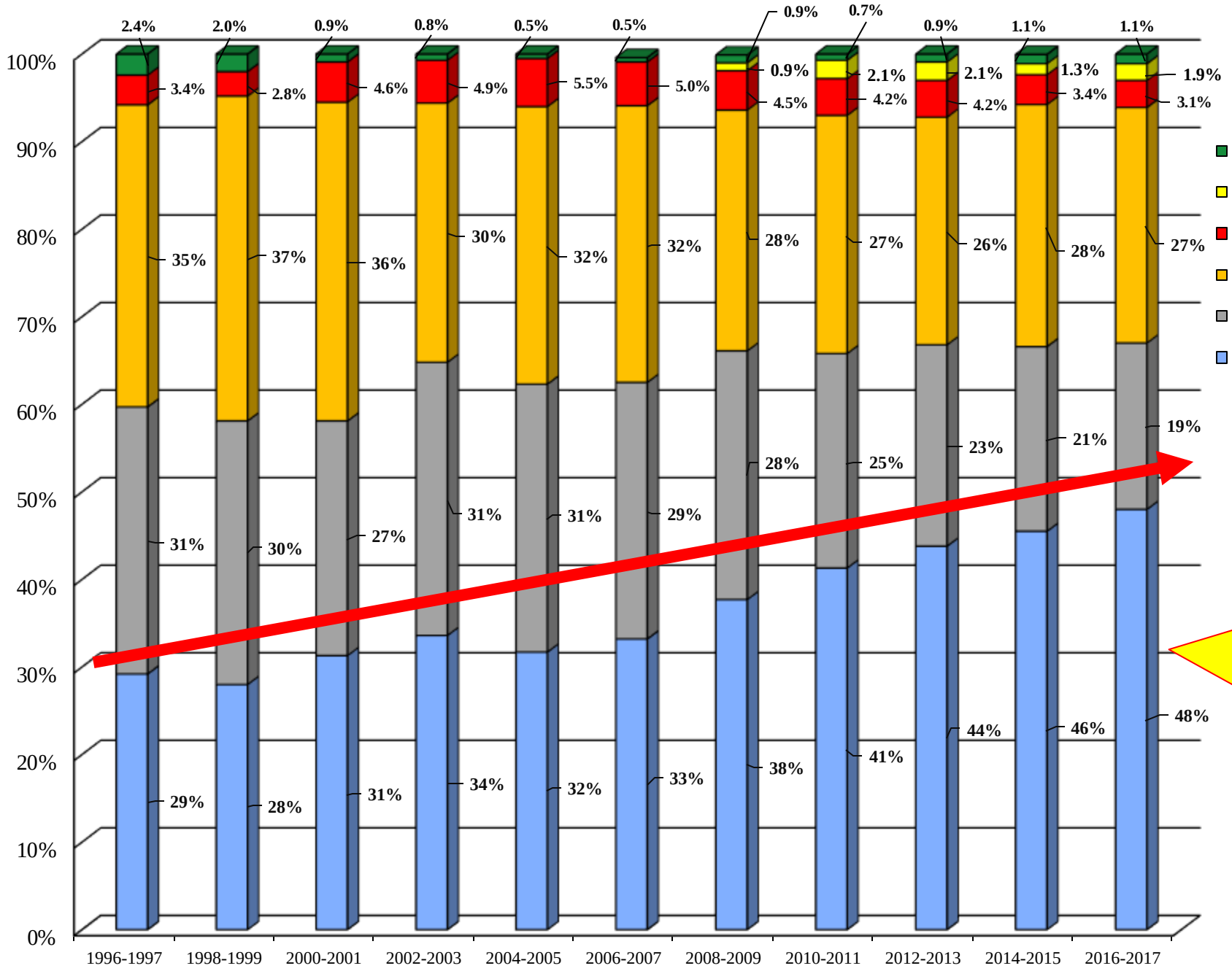


Tateishi R, et al. J Gastroenterol 2019

Changing Aetiology of HCC in Japan: JLCA Nationwide Follow-up Survey

Kudo M. Liver Cancer 2023

Initial Treatment Modality for Detected HCC: JLCA Nationwide Follow-up Survey



Resection rate is increasing.

In surgical department, 60-70% of surgical patients with HCC are MASH/MASLD etiology with mild fibrosis (**Huge tumor**)

Kudo M. Liver Cancer 2023

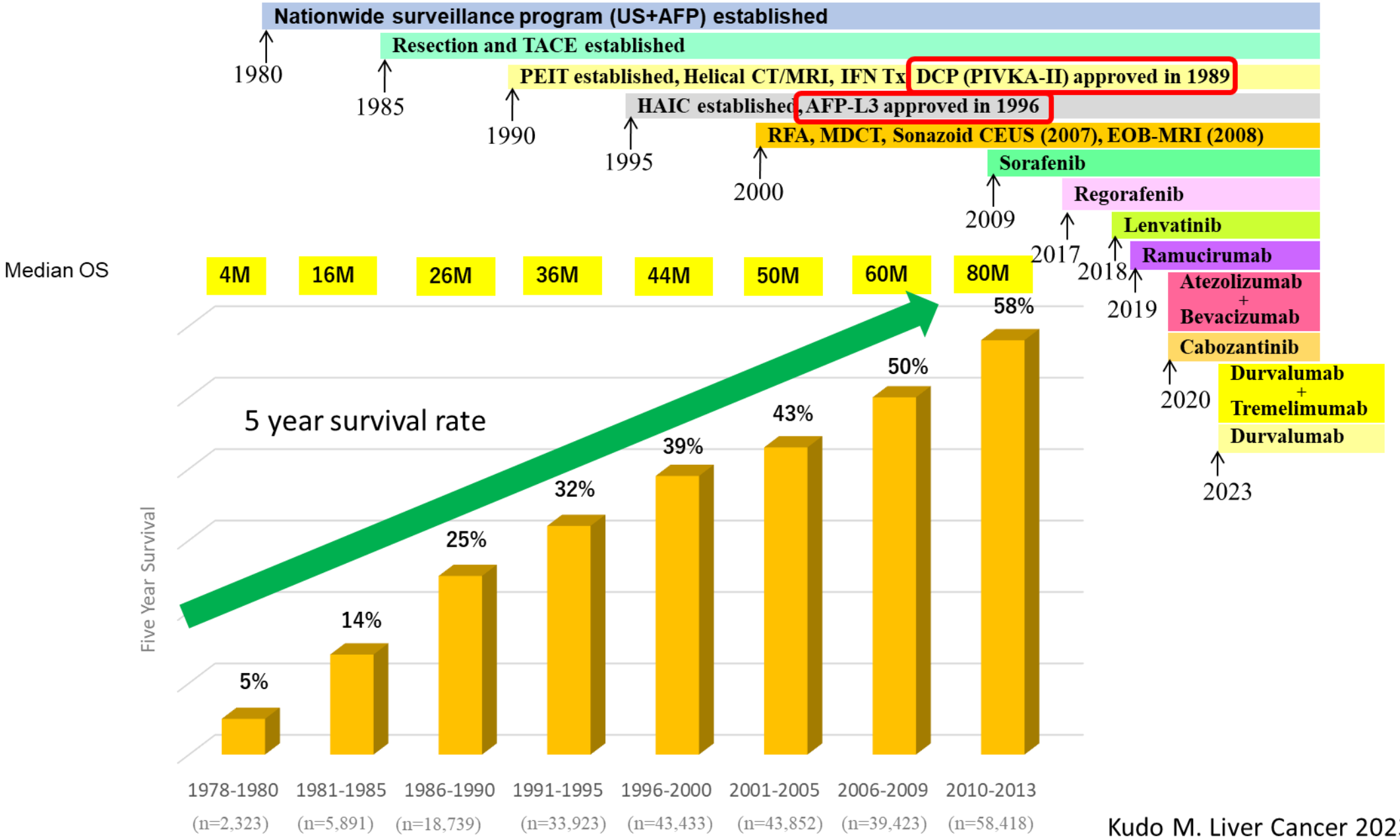
Outline

- Overview of HCC outcome in Japan

Surveillance: Japan as a successful model

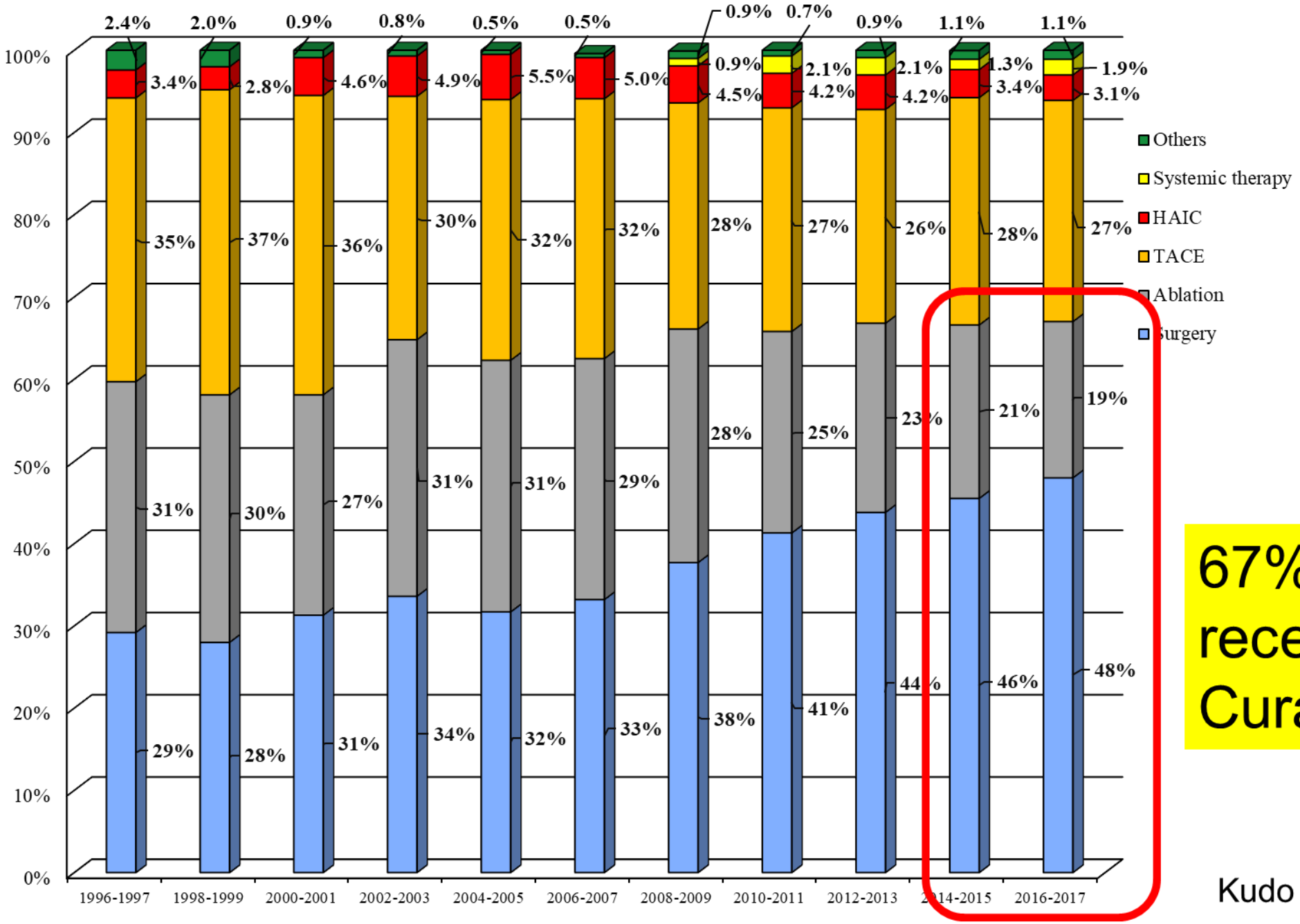
- Results of Nationwide Surveillance of HCC by JLCA
- Regional Difference of OS Results According to GIDEON, Non-interventional Study
- Treatment Outcome in Japan and Hong Kong: Effect of Nationwide Surveillance

Improvement 5-year survival rate and median OS in Japan in patients with all BCLC stage HCC



Kudo M. Liver Cancer 2023
24th Nation-wide Registry, JLCA

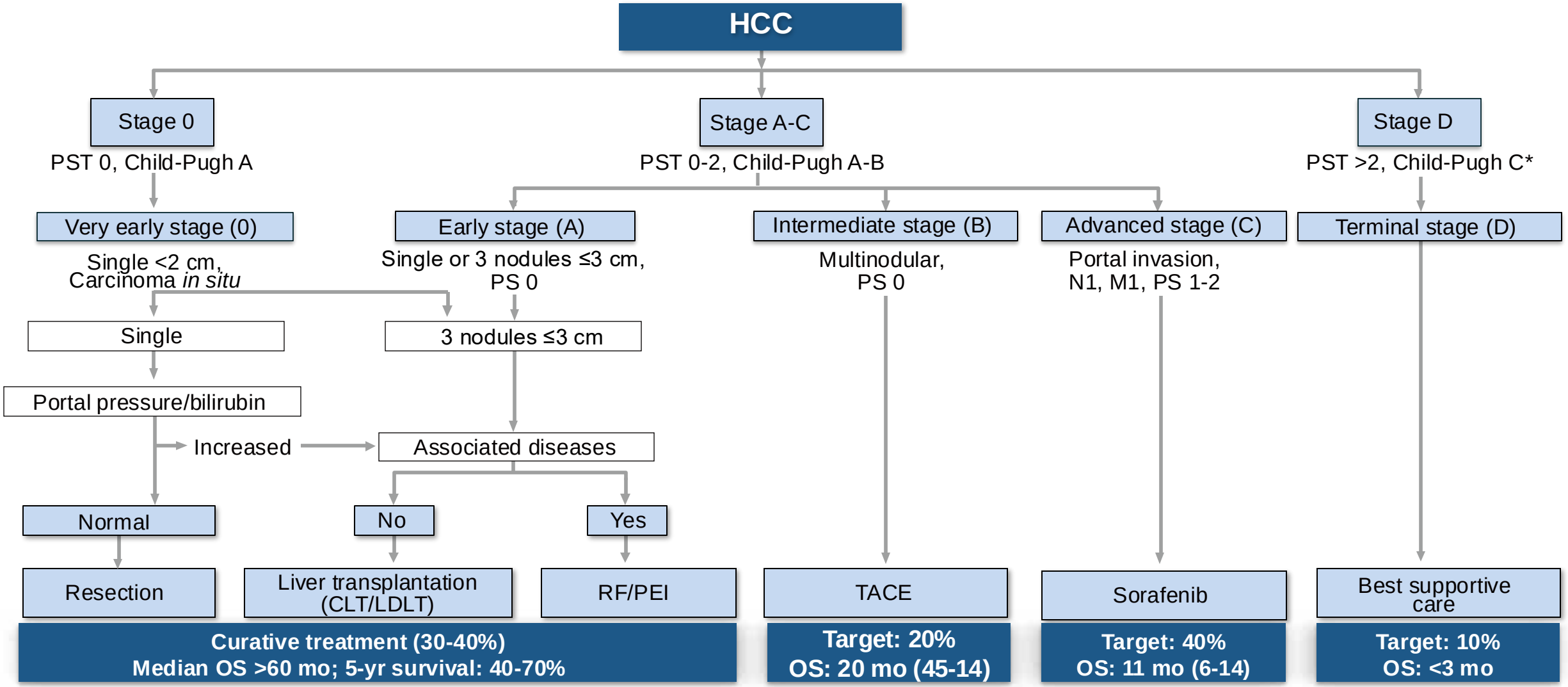
Initial Treatment Modality for Detected HCC: JLCA Nation-wide Registry Follow-up Survey



67% of patients received Curative therapy

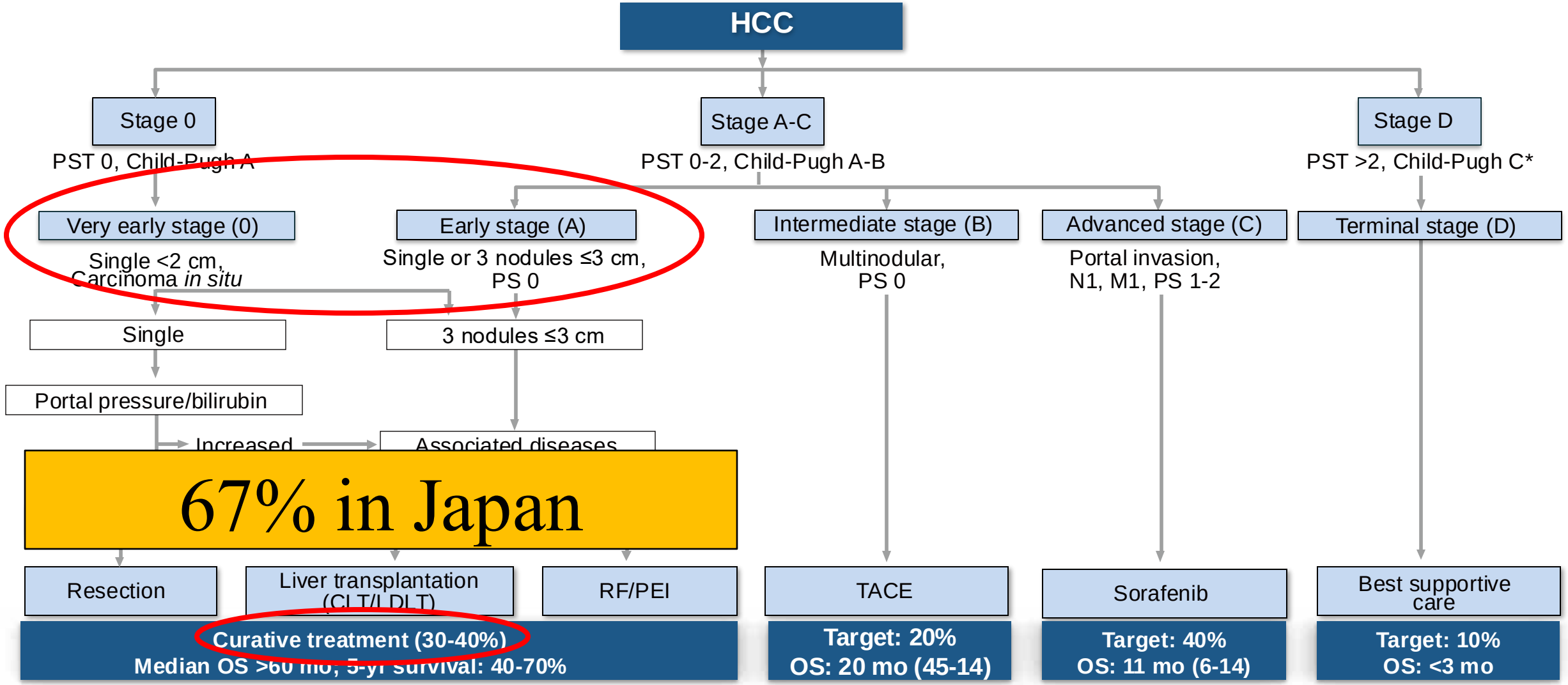
Kudo M. Liver Cancer 2023

BCLC/AASLD/EASL Staging and Treatment Algorithm



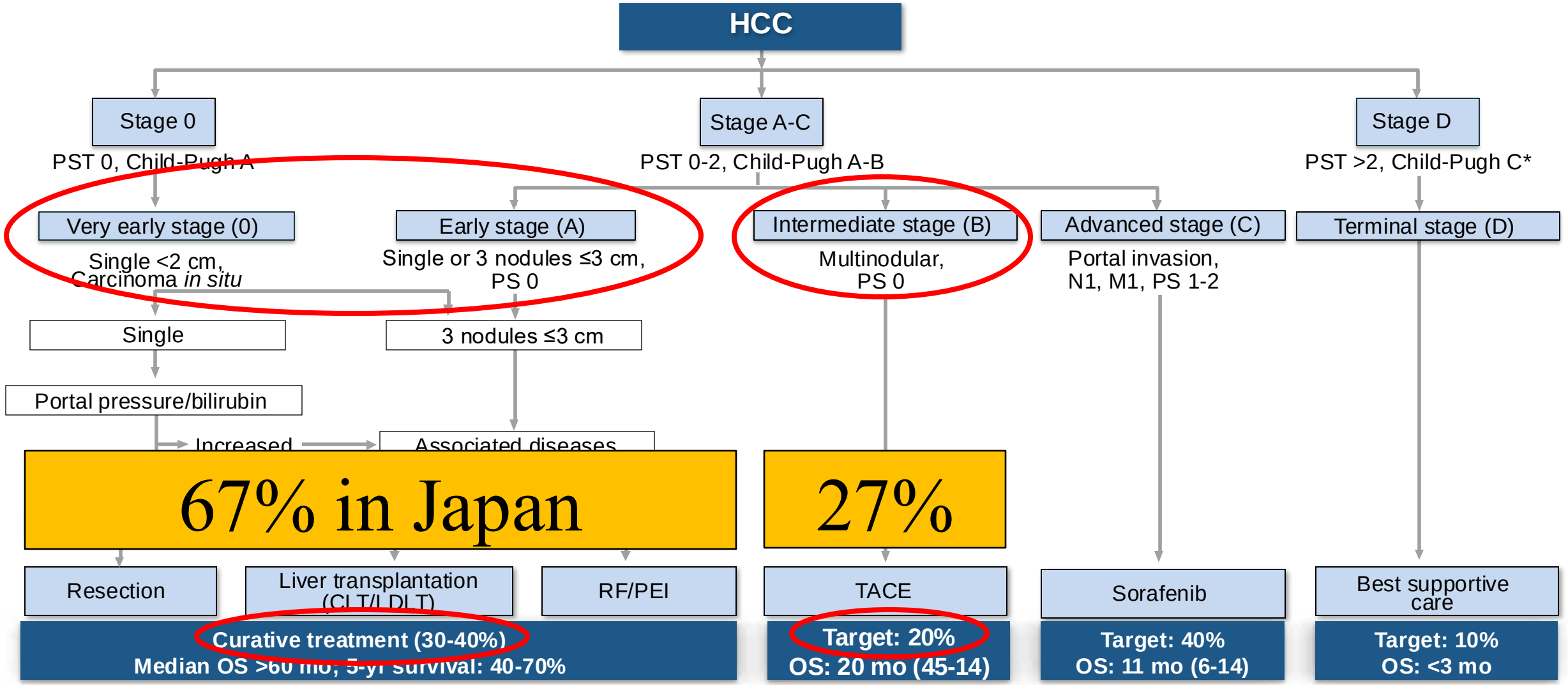
Bruix et al : Hepatology 2011 Mar;53(3):1020-2

BCLC/AASLD/EASL Staging and Treatment Algorithm



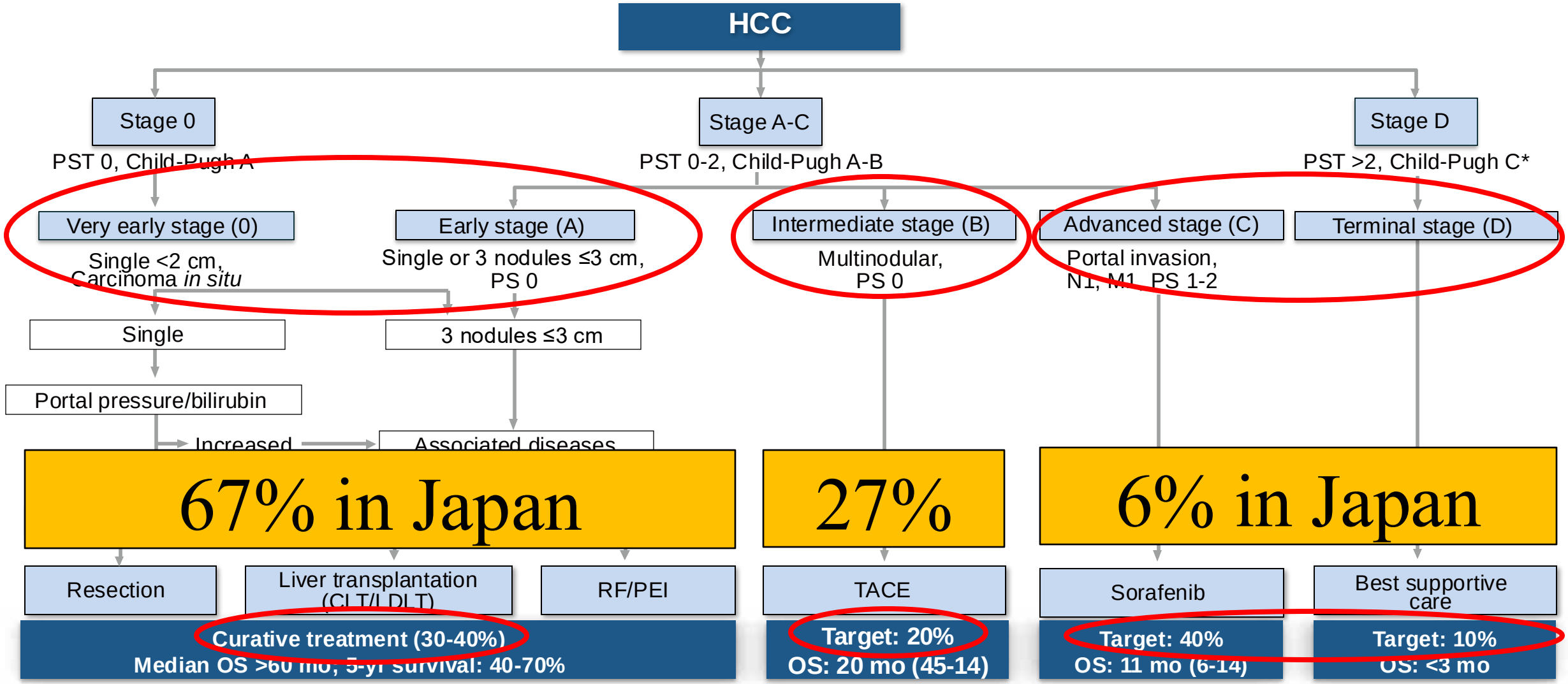
Bruix et al : Hepatology 2011 Mar;53(3):1020-2

BCLC/AASLD/EASL Staging and Treatment Algorithm



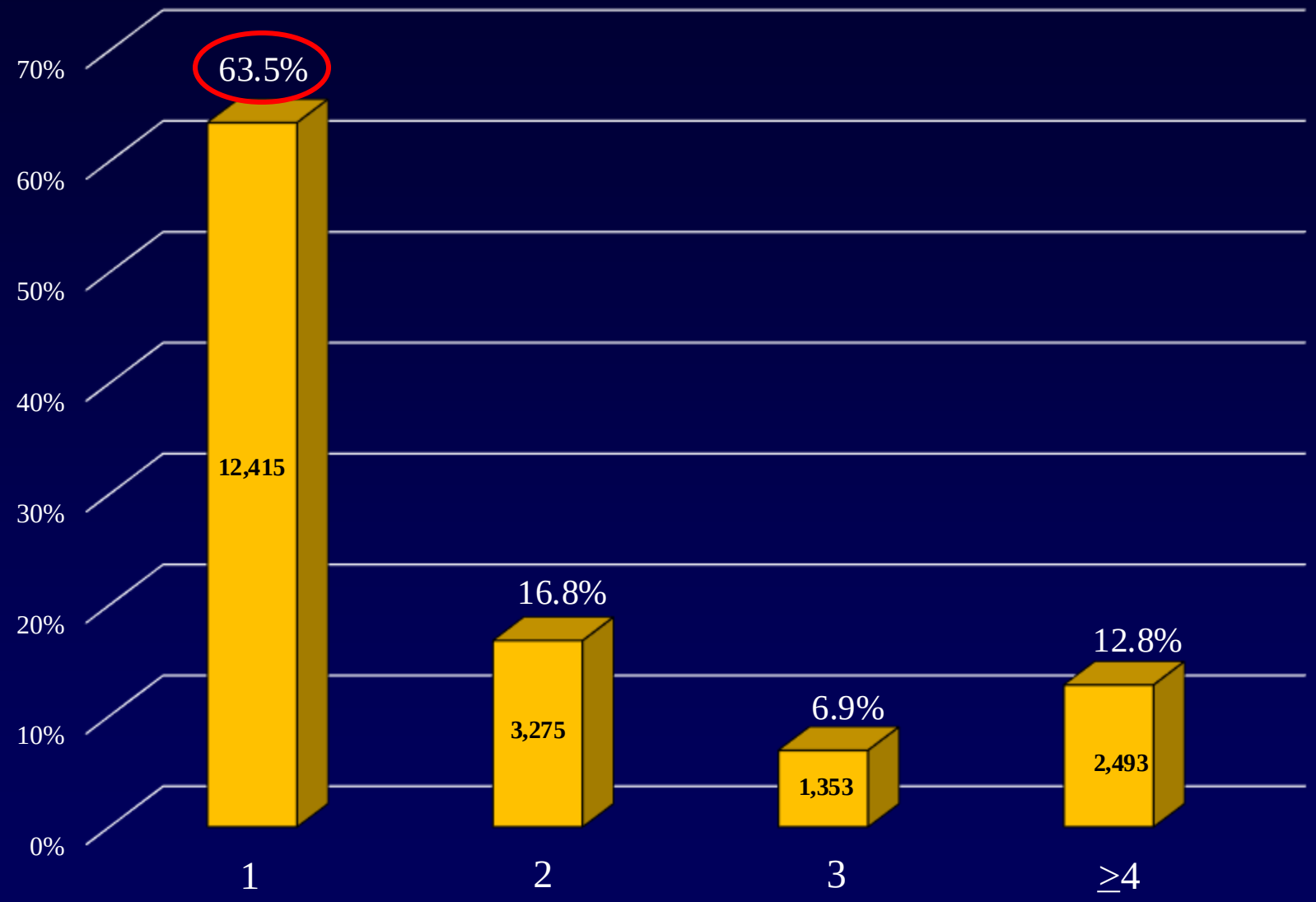
Bruix et al : Hepatology 2011 Mar;53(3):1020-2

BCLC/AASLD/EASL Staging and Treatment Algorithm



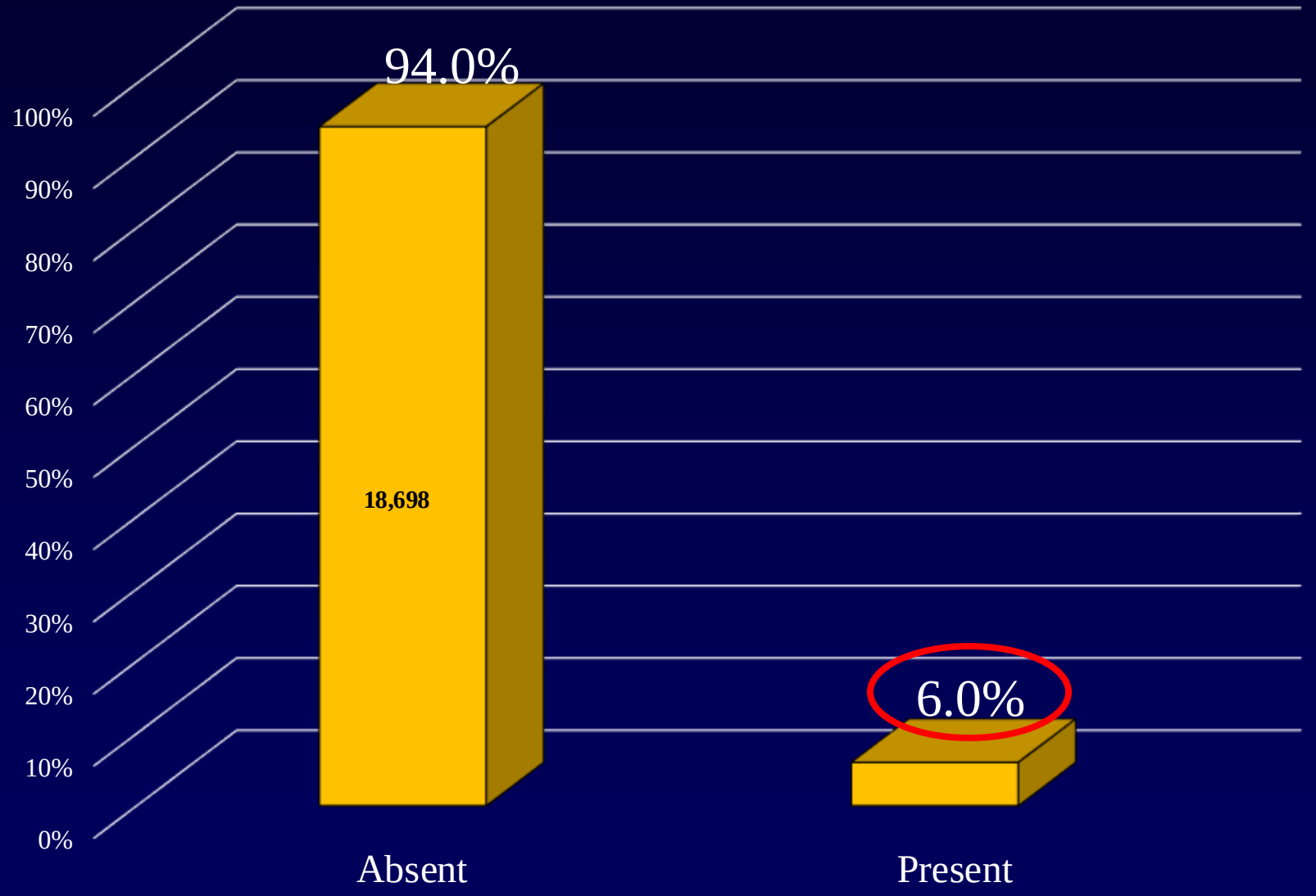
Bruix et al : Hepatology 2011 Mar;53(3):1020-2

Number of Nodules at the Time of Initial Detection (n=19,536)



21st Nation-wide Follow-up Survey, Japan Liver Cancer Association, 2020

Presence or Absence of Extrahepatic Spread at the Time of Initial Detection (n=19,887)

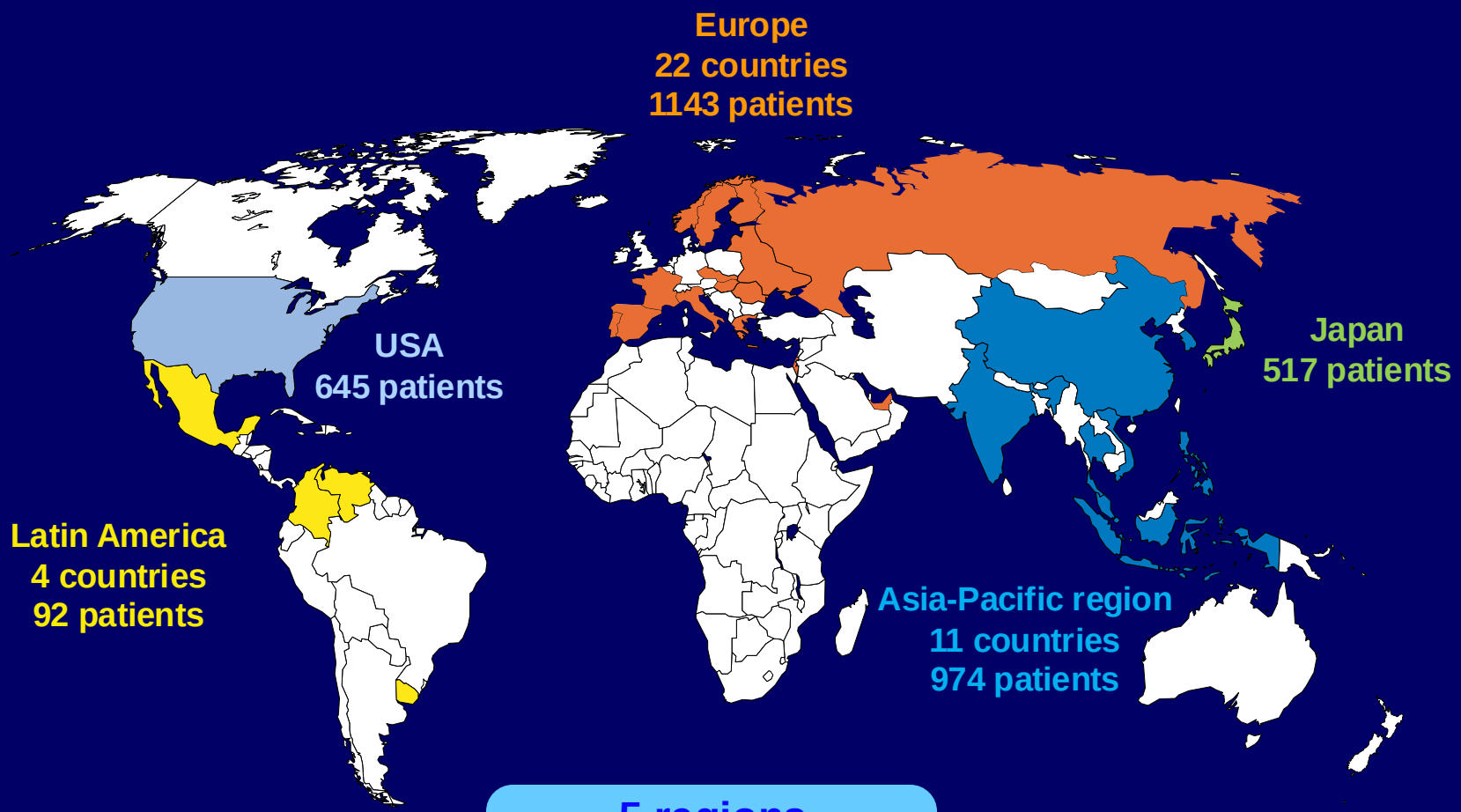


21st Nation-wide Follow-up Survey, Japan Liver Cancer Association, 2020

Surveillance: Japan as a successful model

- Regional Difference of OS Results According to GIDEON, Non-interventional Study

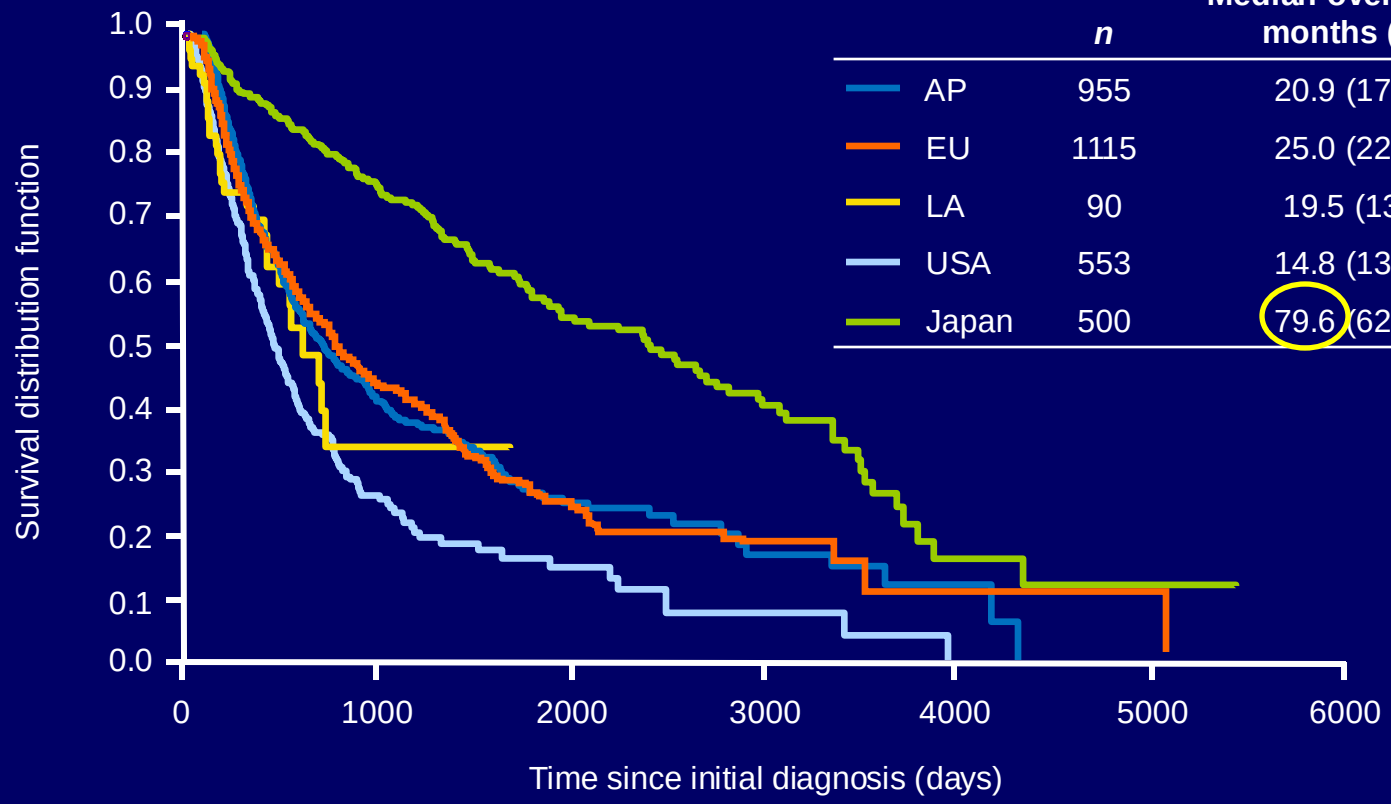
HCC Global Non-interventional Study: GIDEON



5 regions
39 countries
>3300 patients

Kudo M, et al. Liver Int 2016

Time from initial diagnosis to death by region



	n	Median overall survival, months (95% CI)
AP	955	20.9 (17.3-25.2)
EU	1115	25.0 (22.9-28.7)
LA	90	19.5 (13.5-NE)
USA	553	14.8 (13.1-17.0)
Japan	500	79.6 (62.1-96.0)

- Time from initial diagnosis to death was longest in Japan
- We also have to understand a caveat of lead-time bias

Kudo M, et al. Liver Int 2016

Time from initial diagnosis to death by BCLC stage at initial diagnosis

Median time from initial diagnosis to death, months (95% CI)	AP *n*=955	EU *n*=1115	LA *n*=90	USA *n*=553	Japan *n*=500	Overall *N*=3213[a]
BCLC stage A (*n*=686)	54.0 (10.3-NA)	49.3 (42.3-58.0)	23.3 (17.2-NA)	24.9 (18.4-53.5)	91.0 (76.6-113.1)	59.2 (51.9-67.5)
BCLC stage B (*n*=633)	31.0 (18.4-47.7)	27.3 (23.0-33.1)	22.2 (12.9-NA)	19.7 (11.1-36.8)	47.9 (40.9-86.2)	29.9 (25.6-39.0)
BCLC stage C (*n*=973)	10.3 (262-409)	11.0 (8.9-13.0)	11.2 (3.1-NA)	8.5 (6.2-10.2)	27.7 (16.6-40.8)	10.6 (9.4-12.4)
BCLC stage D (*n*=91)	8.9 (8.6-14.8)	11.0 (4.2-21.7)	NA	7.5 (4.5-12.8)	13.1 (NA-NA)	8.9 (6.2-13.1)
Overall	20.9 (17.3-25.2)	25.0 (22.9-28.7)	19.5 (13.5-NA)	14.8 (13.1-17.0)	79.6 (62.1-96.0)	25.5 (23.9-28.3)

- Time from initial diagnosis to death was longest in Japan, irrespective of BCLC stage

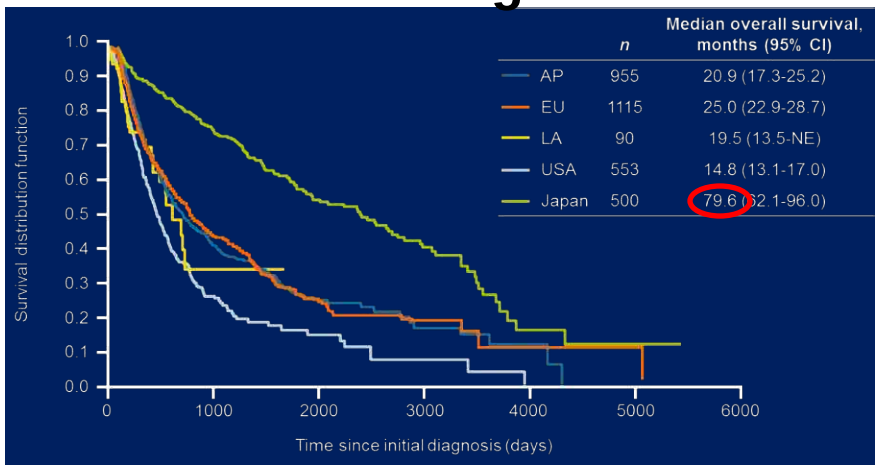
[a]Intention-to-treat population
NA, not available

Kudo M, et al. Liver Int 2016

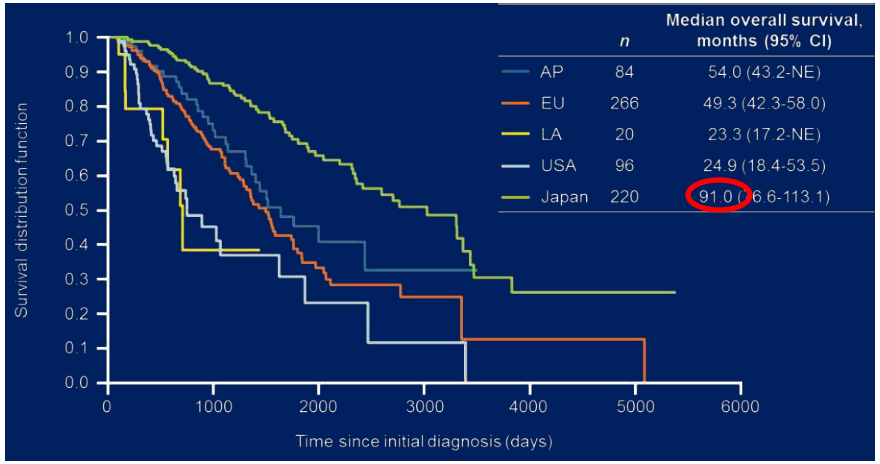
Global Non-Interventional Registry

Time from Initial Diagnosis to Death by BCLC stage

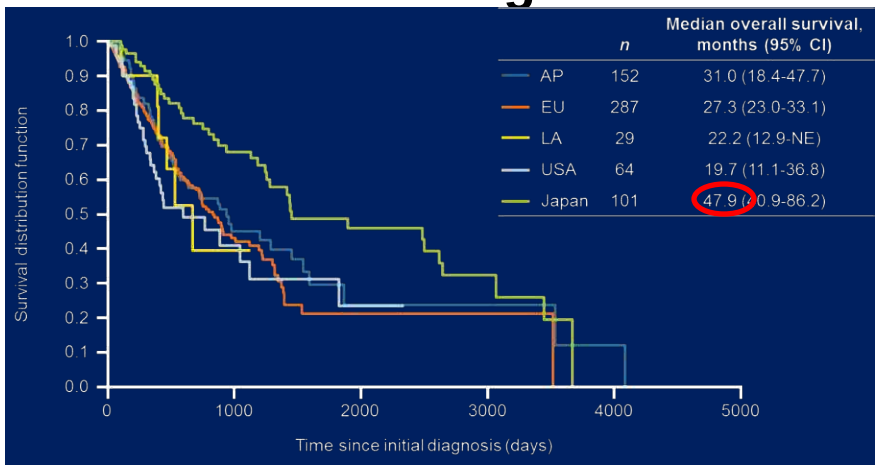
All stage



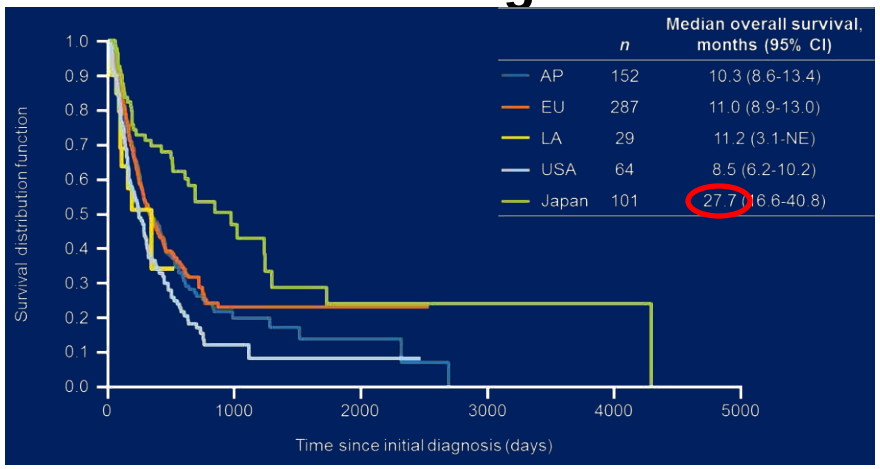
BCLC stage A



BCLC stage B



BCLC stage C



Kudo M et al. Liver Int. 2016;36(8):1196-205

Surveillance: Japan as a successful model

- Treatment Outcome in Japan and Hong Kong: Effect of Nationwide Surveillance

Screening/Surveillance For HCC

The clinical perception

- Advanced/terminal HCCs are incurable and fatal
- Small/early HCCs can be “cured” by surgery/Tp/RFA etc.
- If screening can deliver small/early HCC,
  the prognosis should be improved

The epidemiological perception

The aim of screening is to decrease the disease-specific mortality

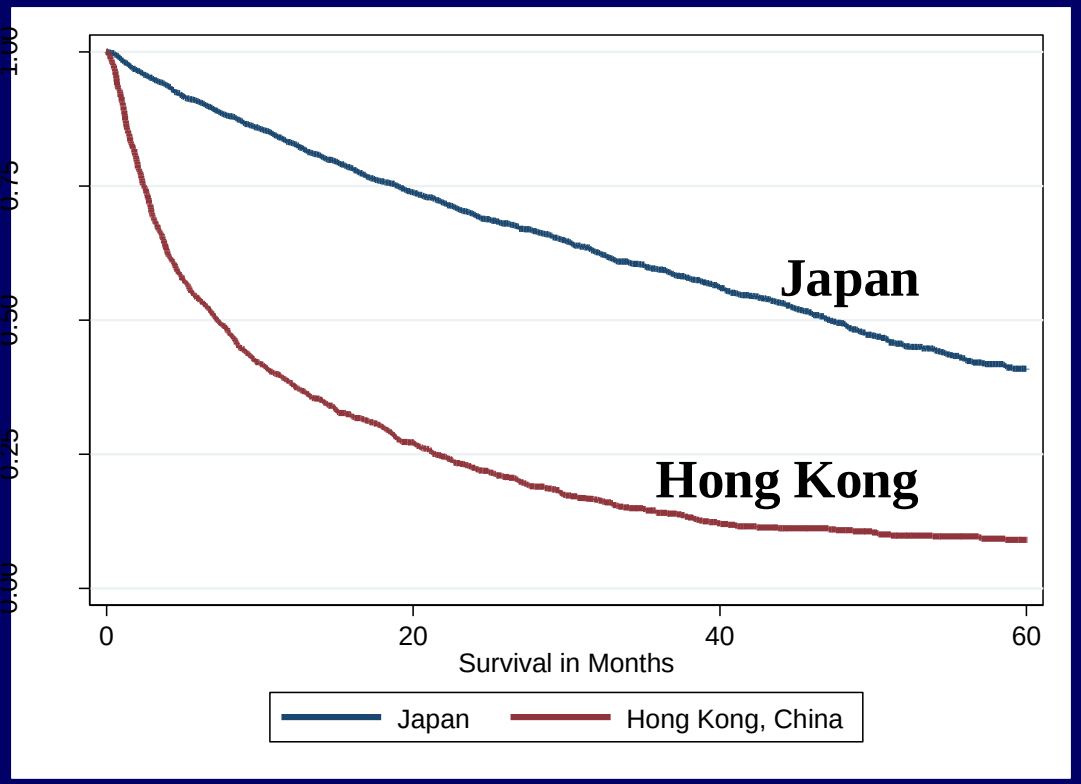
Comparison of Hong Kong & Japan Survival A Natural Experiment

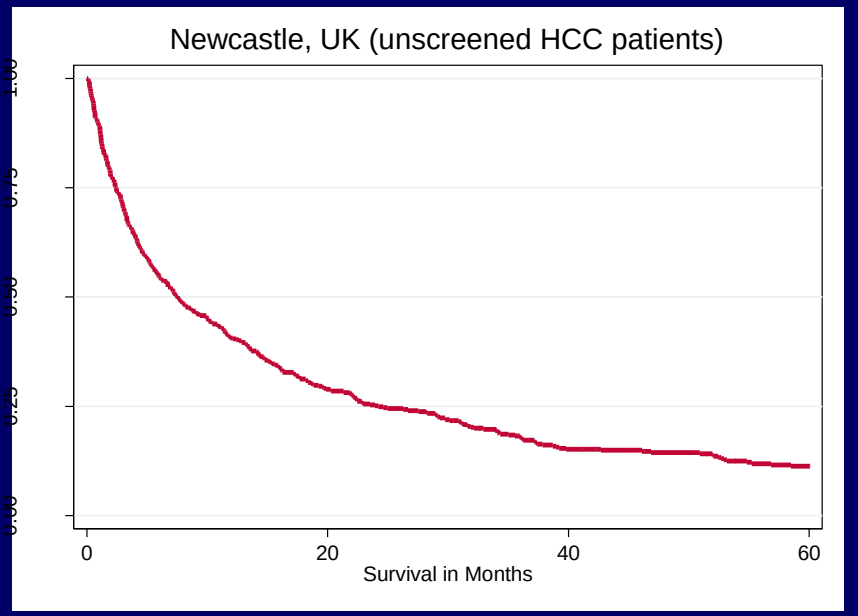
Country	Hong Kong*	Japan**
Healthcare system	Modern and sophisticated	Modern and sophisticated
Race	Oriental	Oriental
Transplant program	No	No
Incidence/aetiology	High - Mainly HBV	High - Mainly HCV
Screening programme	None	Mature, long-standing, intensive, national

*Profs Winnie Yeo, Paul Lai and Stephan China, Chinese University and Prince of Wales Hospital, Hong Kong
**Takashi Kumada, Hidenori Toyoda, Ogaki Municipal Hospital, Ogaki, Japan

Johnson P et al, EASL 2014
Johnson P et al, Br J Cancer 2017

Overall Survival in Japan and Hong Kong





Country	N	Median (months)
Newcastle, UK	470	7.5(6-9.9)

Region	N	Median survival (months), (95% CI)	5-year survival
Japan	2596	47.2 (44.6-49.5)	45-50%
Hong Kong, China	1108	7.2 (6.4-8.2)	10%

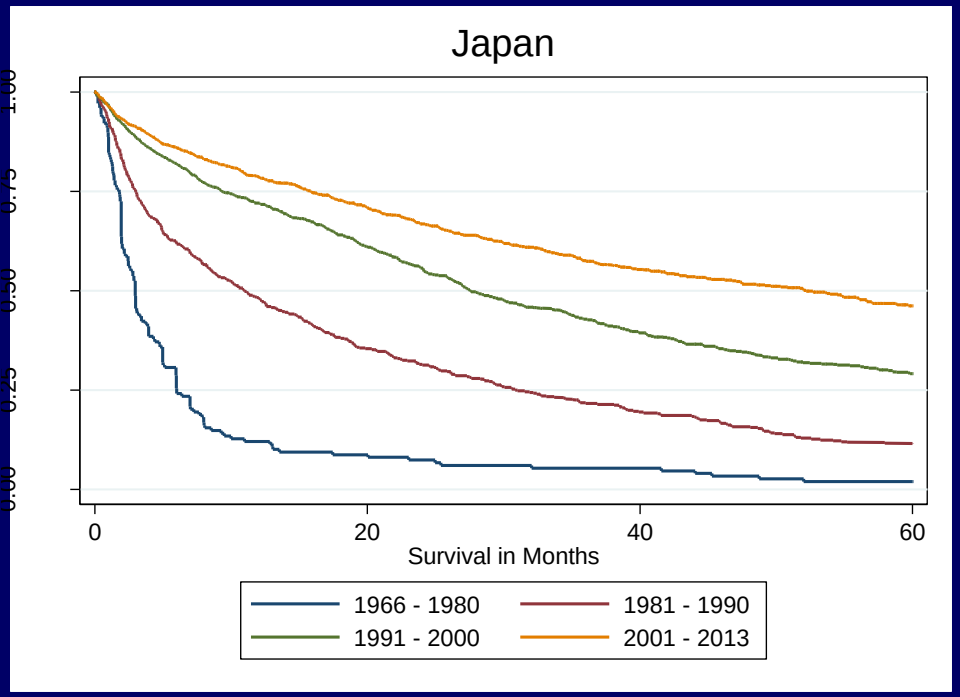
Johnson P et al, EASL 2014
Johnson P et al, Br J Cancer 2017

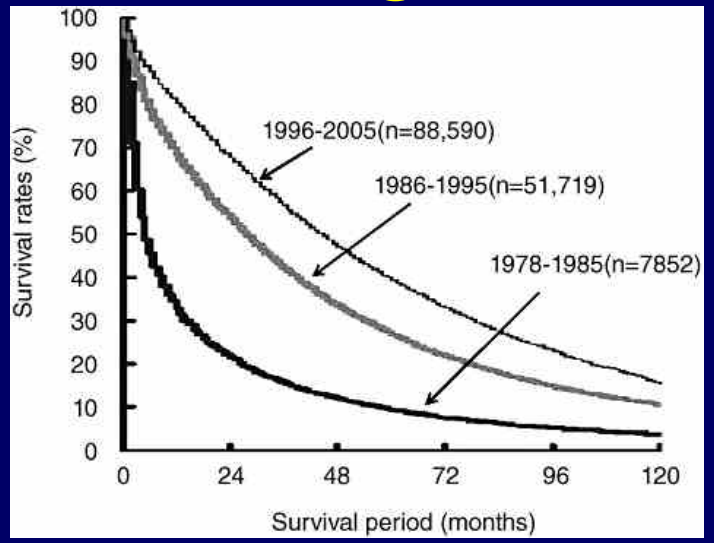
So, What Accounts For These Differences?

- ? Age & Gender – NO
- ? C-P status - NO
- ? Aetiology – Yes, but relatively minor
- ? Is HCC in Japan ‘just different’
- ? Disease stage
- ? Lead time bias

Johnson P et al, EASL 2014
Johnson P et al, Br J Cancer 2017

Changes In Survival In Japan Since Inception of Screening





Such Results Are Representative of Japan

From Ikai I et al, Hepatol Res. (2010)
Nation-wide data by LCSGJ

Pre-screening →

Period	N	Median survival in months	% screened	Median age (IQR)
1966 – 1980	178	2.96 (2.4 – 3.4)	15.23 (n=151)	60 (54 – 67)
1981 – 1990	509	10.99 (8.8 – 13.2)	55.26 (n=418)	61 (55 – 68)
1991 – 2000	812	27.5 (25.8 – 31.1)	72.41 (n=812)	64 (59 – 70)
2001 – 2013	1105	52.2 (44.1 – 59.7)	76.80 (n=1103)	70 (63 – 76)

Johnson P et al, EASL 2014
Johnson P et al, Br J Cancer 2017

So, What Accounts For These Differences?

Age & Gender ? – NO

C-P status ? - NO

Aetiology ? – Maybe Yes, but relatively minor

Is HCC in Japan ‘just different’ ? NO

Disease stage?

Lead-time bias ?

Johnson P et al, EASL 2014
Johnson P et al, Br J Cancer 2017

% Of Patients With Curative Treatments, Early Stage BCLC And Within Milan Criteria

Country	Curative Rx (%)	BCLC 0 and A (%)	Within Milan Criteria (%)
Japan	71.2 (n=2594)	65.7 (n=685)	58.9 (n=2473)
Hong Kong	15.7 (n=1112)	15.1 (n=517)	8.4 (n=1066)

1 year survival (%)		Japan	Hong Kong, China
HCV	BCLC early (0 and A)	92.6	83.3
HBV	BCLC early (0 and A)	94.8	89.9
2 year survival (%)		**Japan**	**Hong Kong, China**
HCV	BCLC early (0 and A)	81.9	75.0
HBV	BCLC early (0 and A)	74.2	76.9

Johnson P et al, EASL 2014
Johnson P et al, Br J Cancer 2017

So, What Accounts For These Differences?

Age & Gender ? – NO

C-P status ? - NO

Aetiology ? – Maybe Yes, but relatively minor

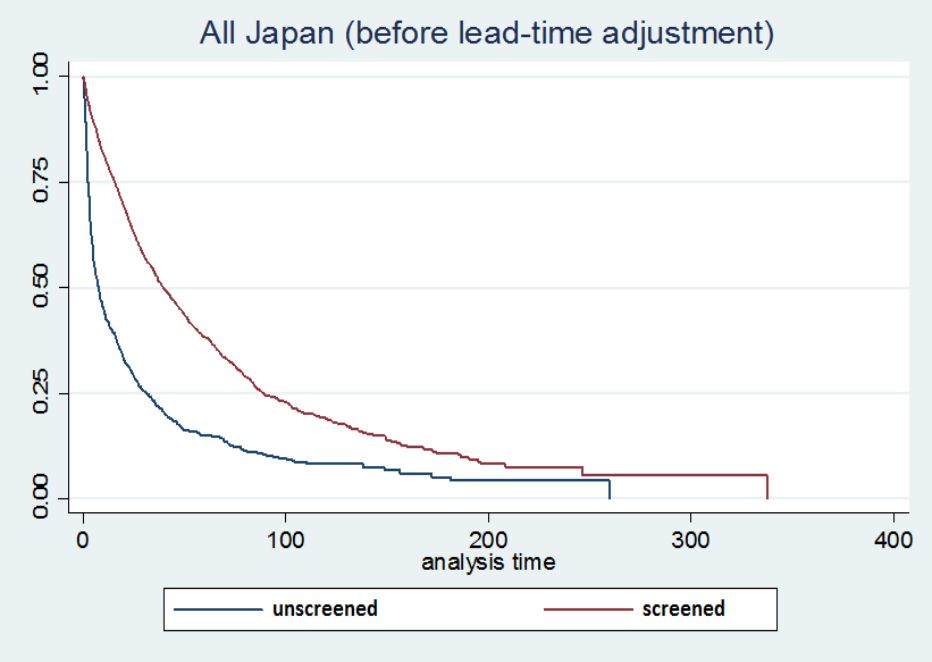
Is HCC in Japan ‘just different’ ? NO

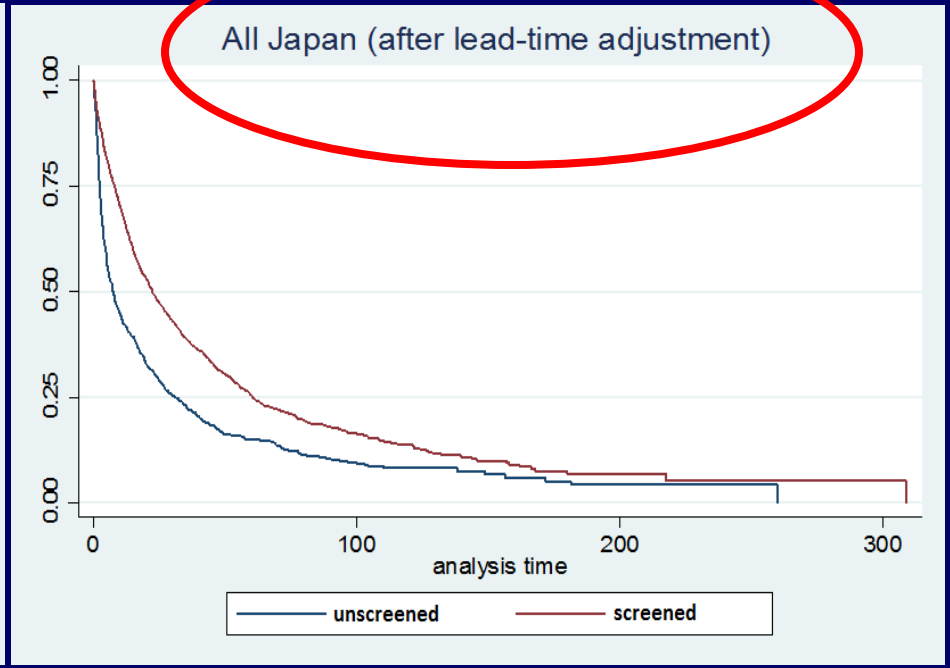
Disease stage? NO

Lead-time bias ?

Johnson P et al, EASL 2014
Johnson P et al, Br J Cancer 2017

Impact of Screening - Allowing For Lead Time Bias*





	Subjects N=	**Median in months(CI)**
Unscreened	794	**7.5 (6-9)**
Screened	1689	**39.4 (36-43)**

	Subjects N=	**Median in months(CI)**
Unscreened	794	**7.5 (6-9)**
Screened	1689	**22.3(21-25)**

*Method reference: Duffy SW, et al., Correcting for lead time bias in estimating the effect of screen detection on cancer survival. Am J Epidemiol. 2008

Johnson P et al, EASL 2014
Johnson P et al, Br J Cancer 2017

So, What Accounts For These Differences?

Age & Gender ? – NO

C-P status ? - NO

Aetiology ? – Maybe Yes, but relatively minor

Is HCC in Japan ‘just different’ ? NO

Disease stage? NO

Lead-time bias ? NO

Johnson P et al, EASL 2014
Johnson P et al, Br J Cancer 2017

Summary and Conclusion

Circumstantial evidence supports surveillance seems to increase likelihood of curative therapy and prolonged survival

Important issue

- Nationwide surveillance *DID* decrease the disease specific mortality in Japan
- Surveillance is easier/done better in Japan
- Treatment is just better in Japan

Johnson P et al, EASL 2014
Johnson P et al, Br J Cancer 2017

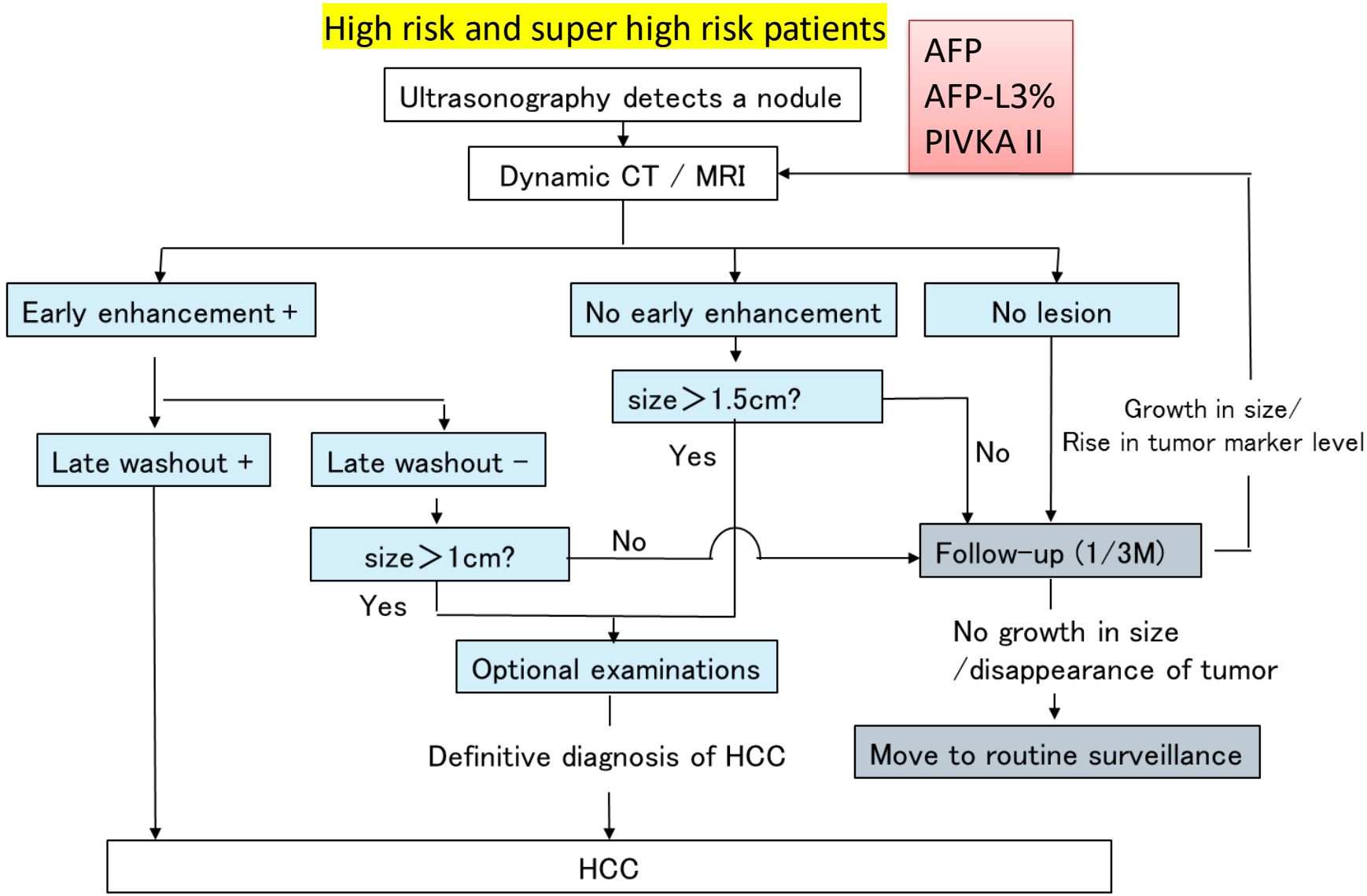
Outcome in Japanese patients with HCC seems to be the best in the world *in terms of nationwide survival rate* mainly due to early detection of HCC through established nation-wide surveillance program.

Johnson P et al, EASL 2014
Johnson P et al, Br J Cancer 2017

Outline

- Overview of HCC surveillance in Japan

JSH clinical practice guideline for surveillance and diagnosis of HCC



JSH HCC Clinical Practice Guideline 2005, 2009, 2013, 2017, 2021

Typical Nationwide Surveillance Methods: Definition of High-risk Group

High-risk
- Chronic hepatitis B
- Chronic hepatitis C
- Liver cirrhosis

Very-high-risk
- Hepatitis B cirrhosis
- Hepatitis C cirrhosis

In practice, non-cirrhotic MASH/MASLD patients are under surveillance as **medium risk patients**

This strategy is now under discussion in the currently ongoing revised guideline committee and may be included in the next version of JSH HCC Clinical Practice Guideline

JSH HCC Clinical Practice Guideline 2005, 2009, 2013, 2017, 2021

Tumor Markers for HCC in Japan

- AFP
- AFP-L3
  - Lectin-binding fraction of AFP
- PIVKA-II (DCP)
  - Prothrombin induced by Vit. K absence (des-γ -carboxy-prothrombin)

All are covered by social health insurance in Japan.

JSH HCC Clinical Practice Guideline 2005, 2009, 2013, 2017, 2021

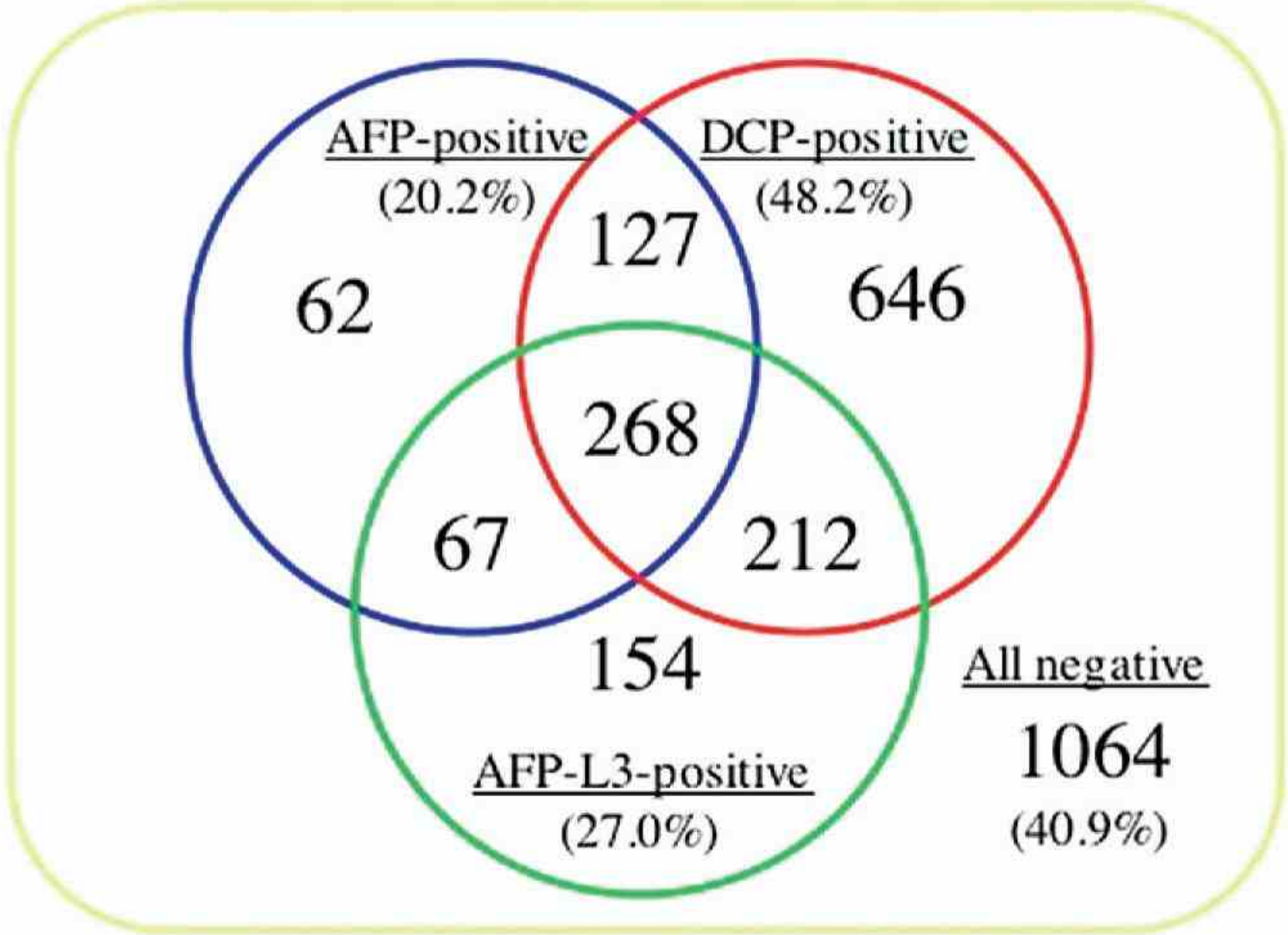
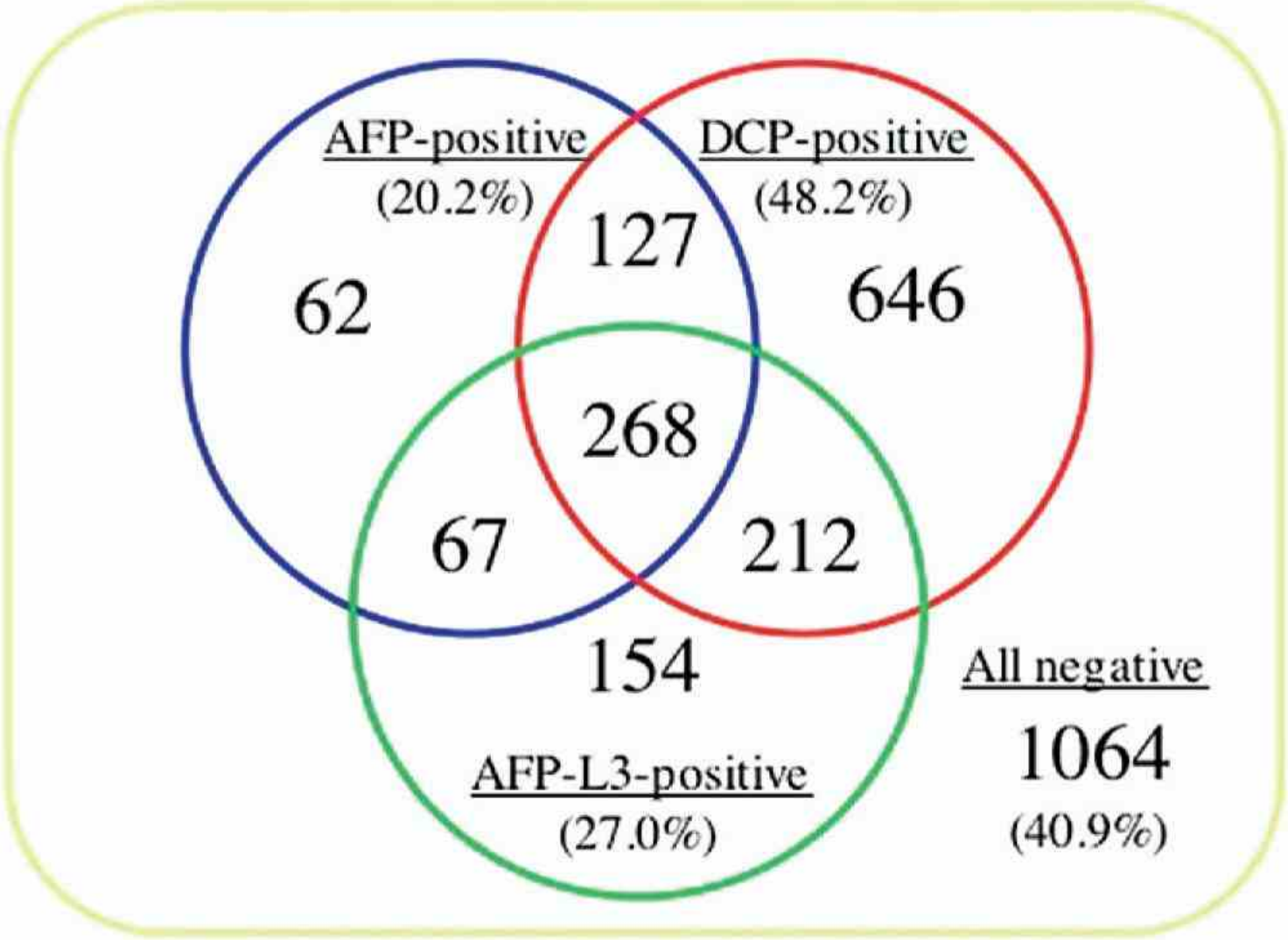


Figure 1. Distribution of patients with HCC according to tumor marker elevation. Cutoff values were set at 400 ng/mL for AFP, 15% for AFP-L3, and 100 mAU/mL for DCP.

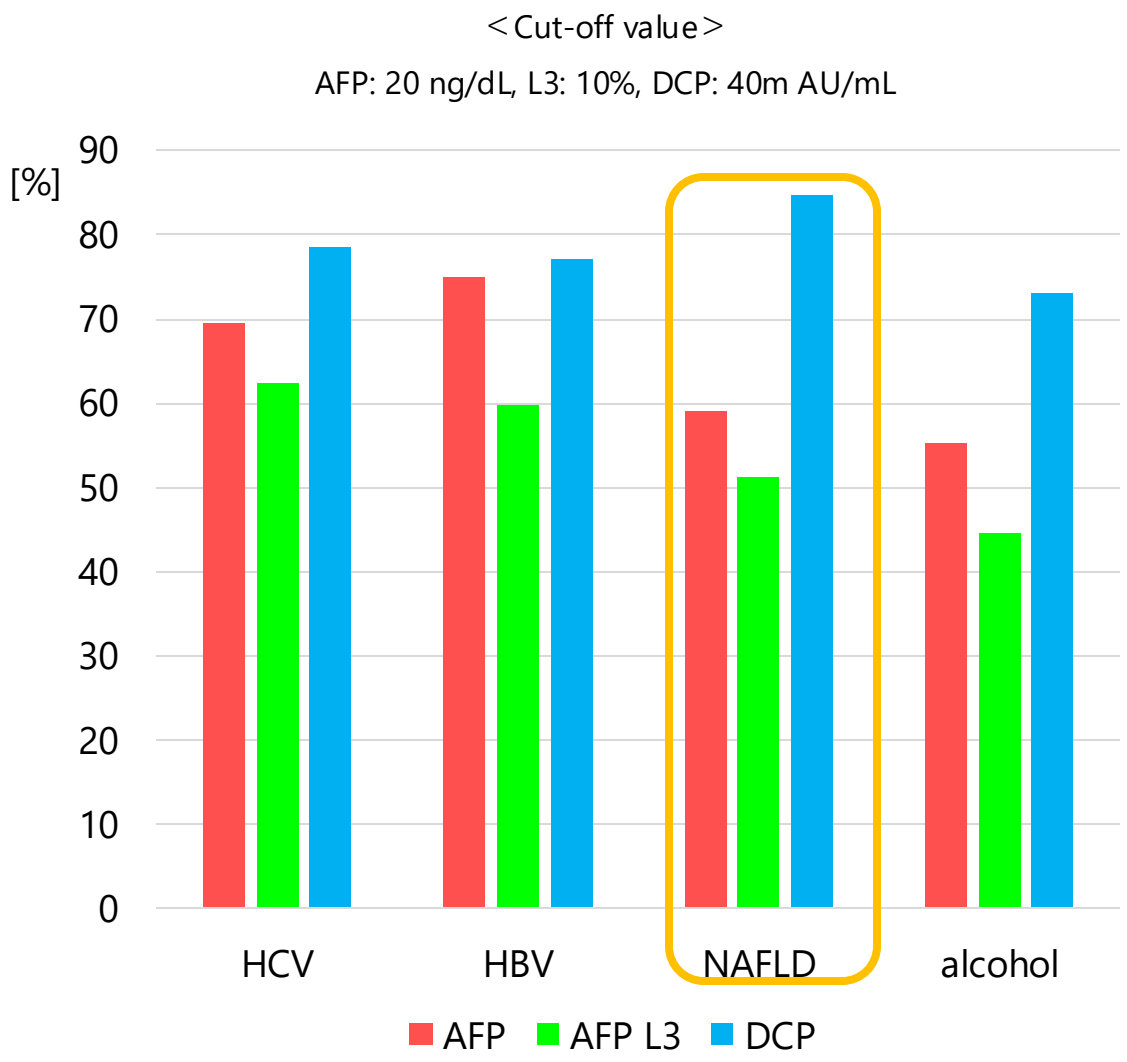
Toyoda H, et al Clinical Gastroenterol Hepatol 2006

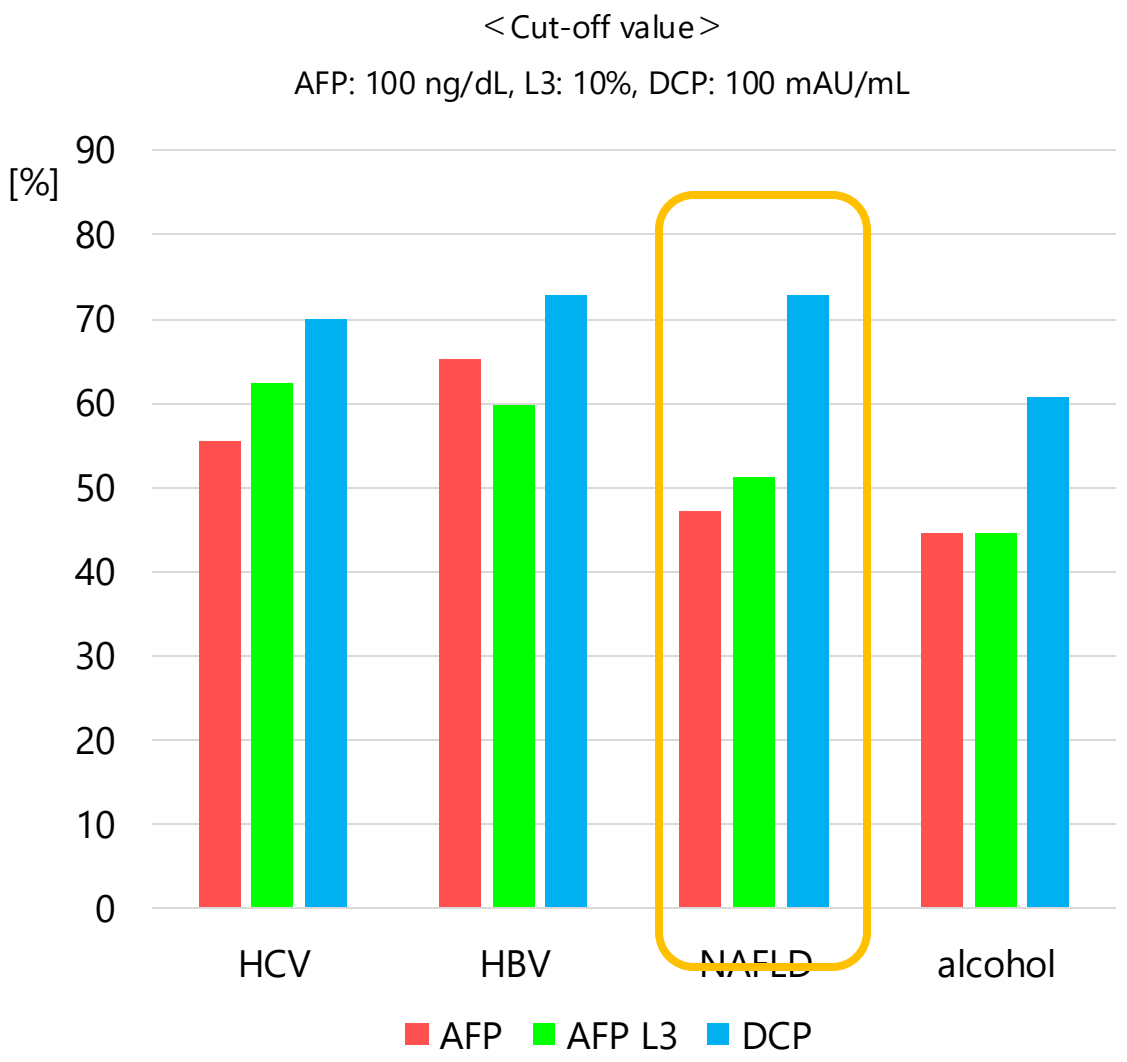


Since there is no correlation between these 3 tumour markers, AFP, DCP (PIVKA-II), and AFP-L3 play a complementary role.

Toyoda H, et al Clinical Gastroenterol Hepatol 2006

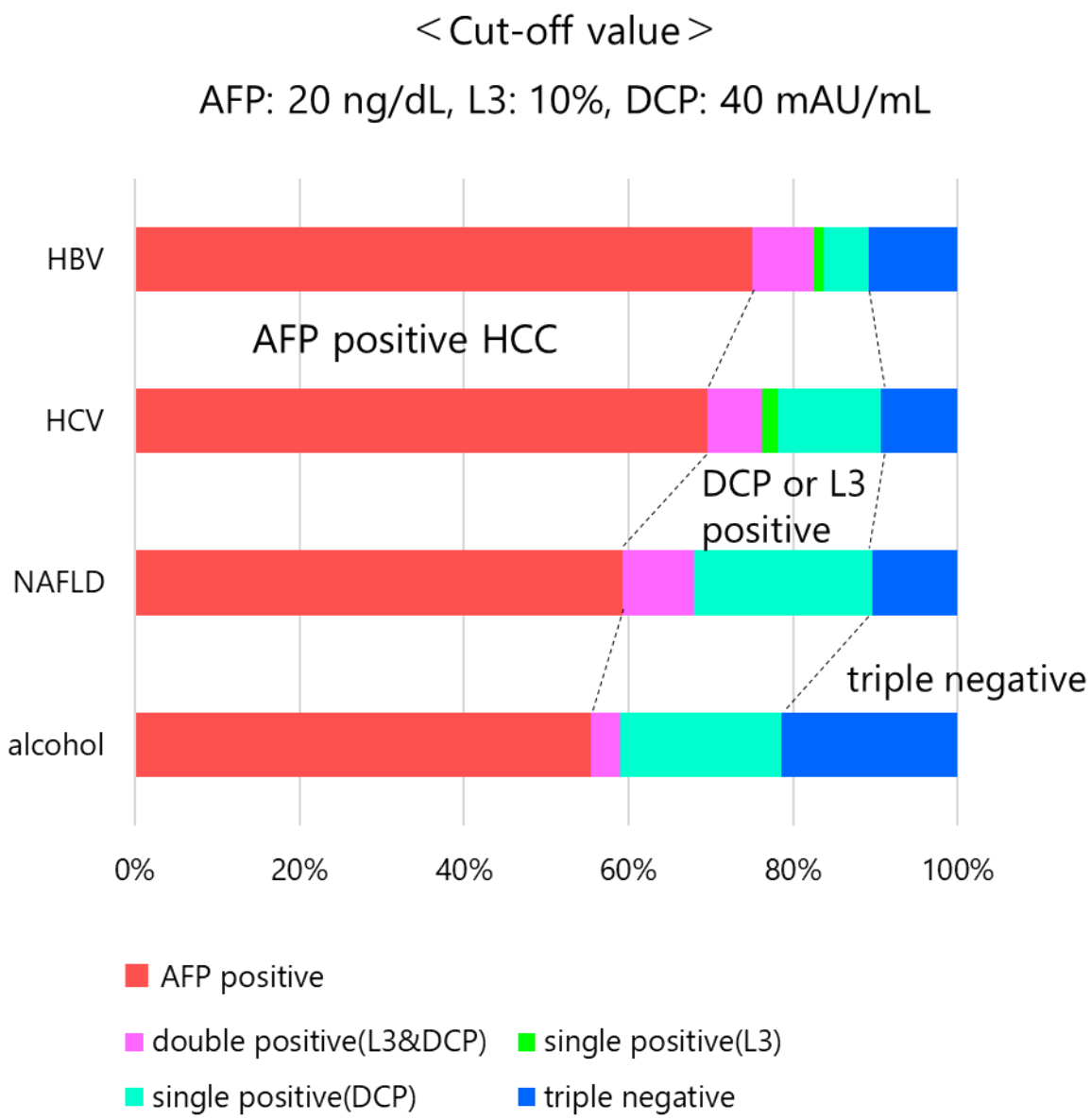
Comparison of TM Positive Rates by Etiology

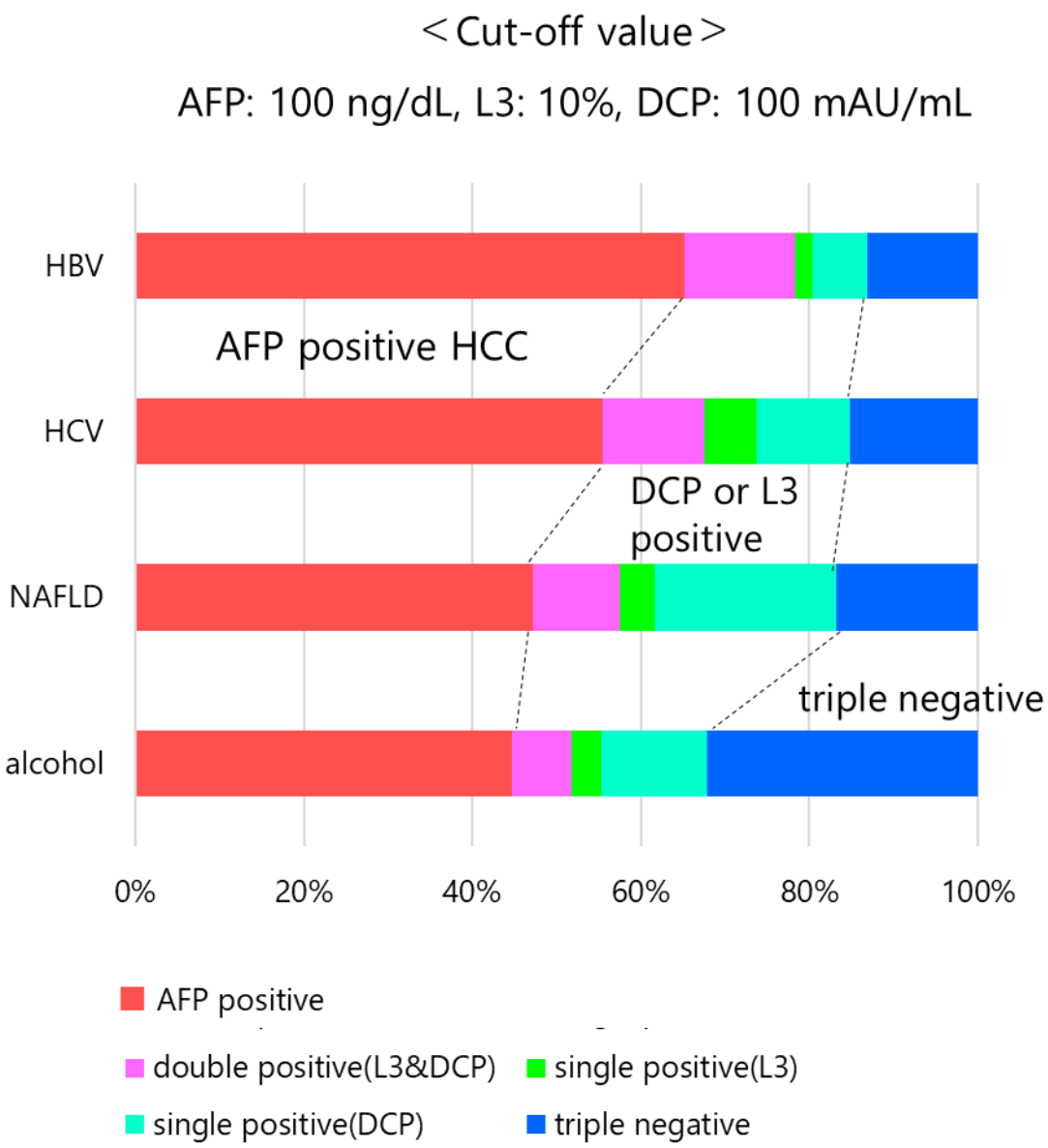




Kudo M. Liver Cancer 2023

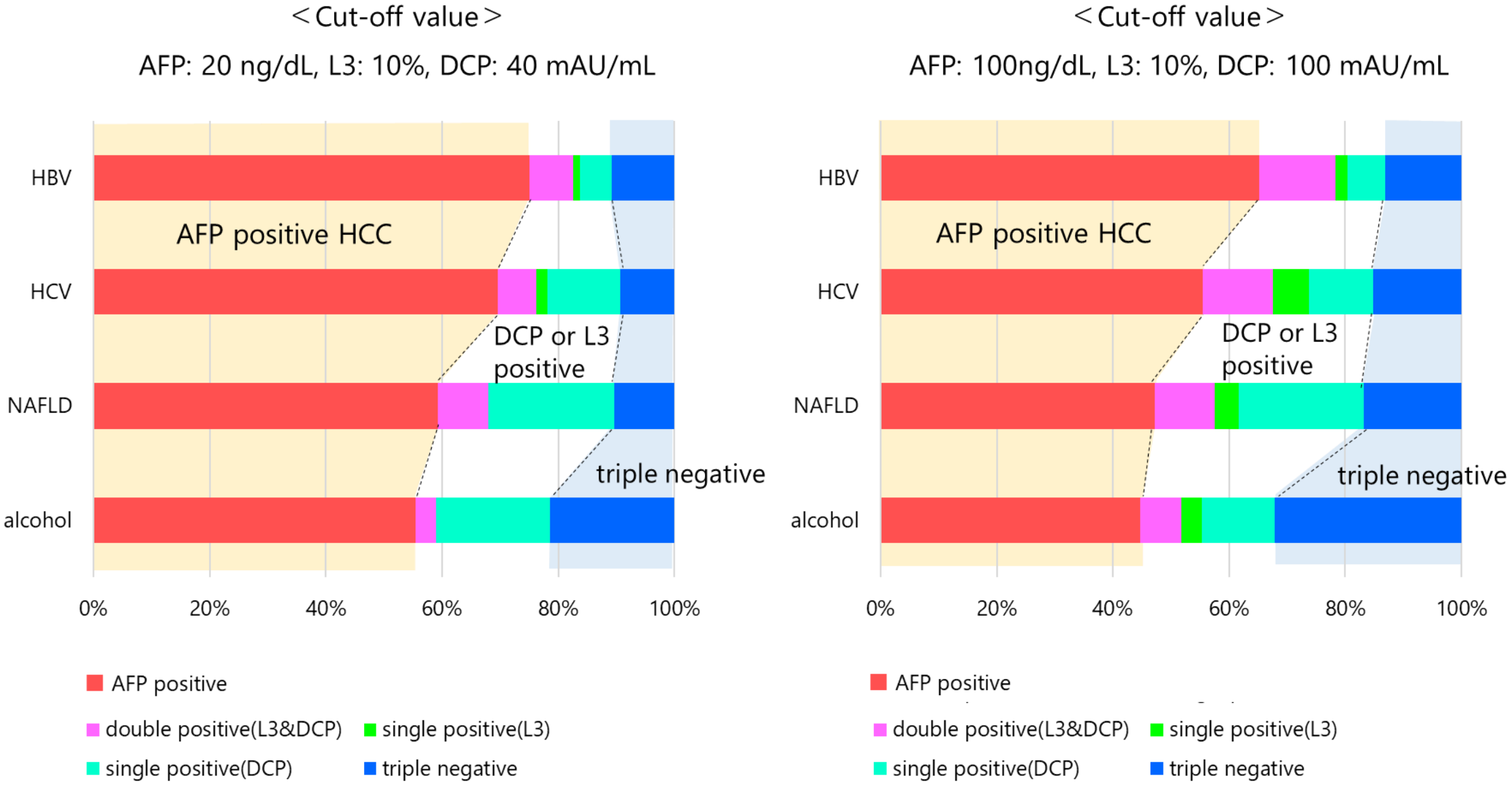
TM Positive Rates by Aetiology





Kudo M. Liver Cancer 2023

TM Positive Rates by Aetiology



Kudo M. Liver Cancer 2023

Clinical practice guideline

Recommendation

For the surveillance of small hepatocellular carcinoma, measurement of two or more tumor markers is recommended. (grade A)

JSH HCC Clinical Practice Guideline 2005, 2009, 2013, 2017, 2021

Follow up methods for high risk patients in all over Japan

- Medium Risk patients (??)
  - US at intervals of 12mo.
  - AFP/PIVKA-II/AFP-L3 every 12mo.
  - FIB4 index, PLT count every 12 mo.
- High Risk patients
  - US at intervals of 6mo.
  - AFP/PIVKA-II/AFP-L3 every 6mo.
- Very High Risk patients
  - US every 3-4 mo.
  - AFP/PIVKA-II/AFP-L3 every 3-4 mo.
  - Option: dynamic CT/EOB-MRI every 6-12 mo.

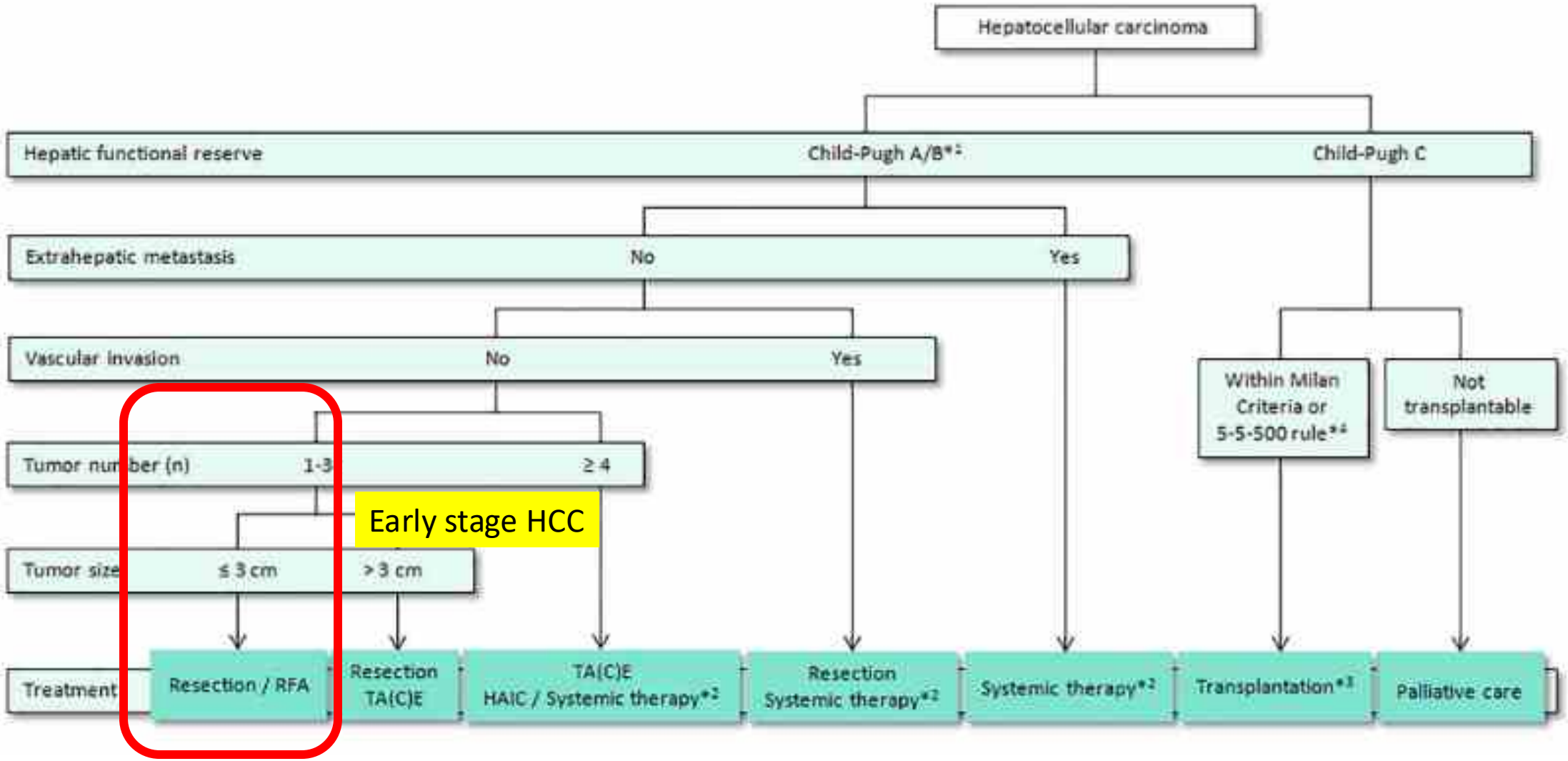
These HCC surveillance program has been well implemented throughout Japan since education to patients and private practitioner were established since 1980s.

JSH HCC Clinical Practice Guideline 2005, 2009, 2013, 2017, 2021

Outline

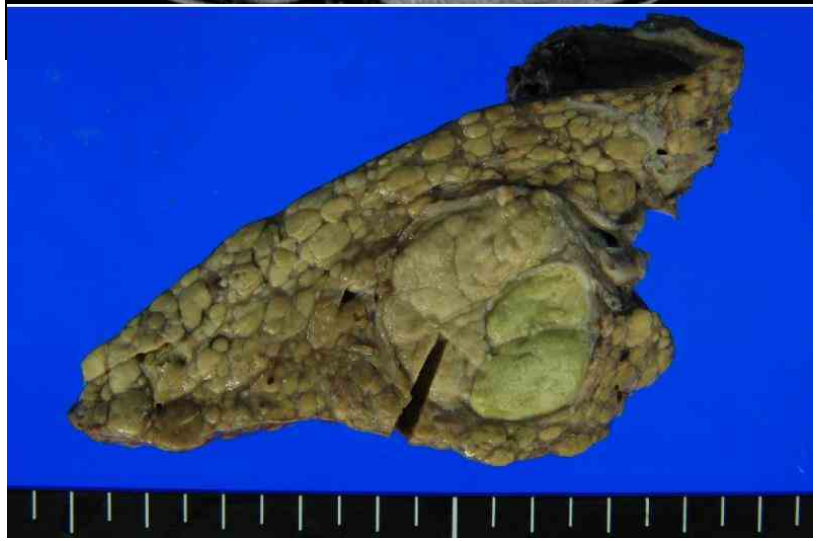
- Treatment strategy for Early-stage HCC

JSH HCC Guidelines 2021 Algorithm for Treatment

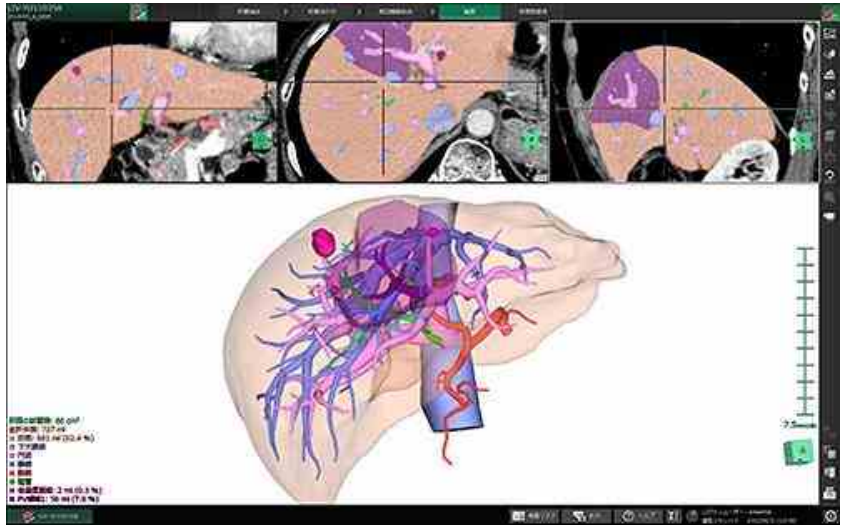


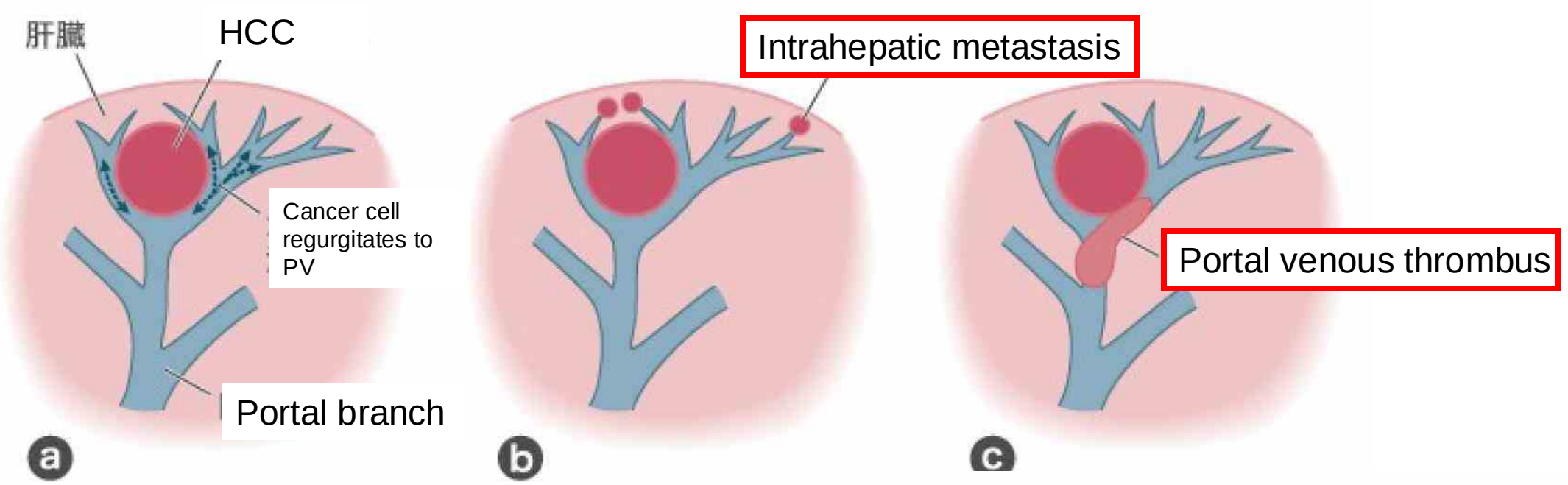
Hasegawa K, Tateishi R, Kudo M, et al. Hepatol Res. 2023

Resection

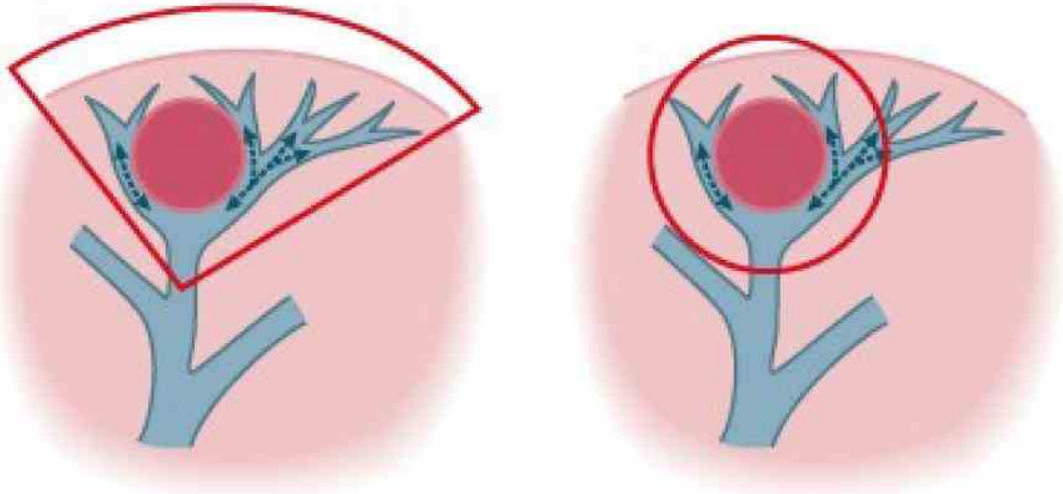


- Child-Pugh grade A
- Solitary tumour
- Laparoscopic and robotic surgery are reimbursed and frequently performed.





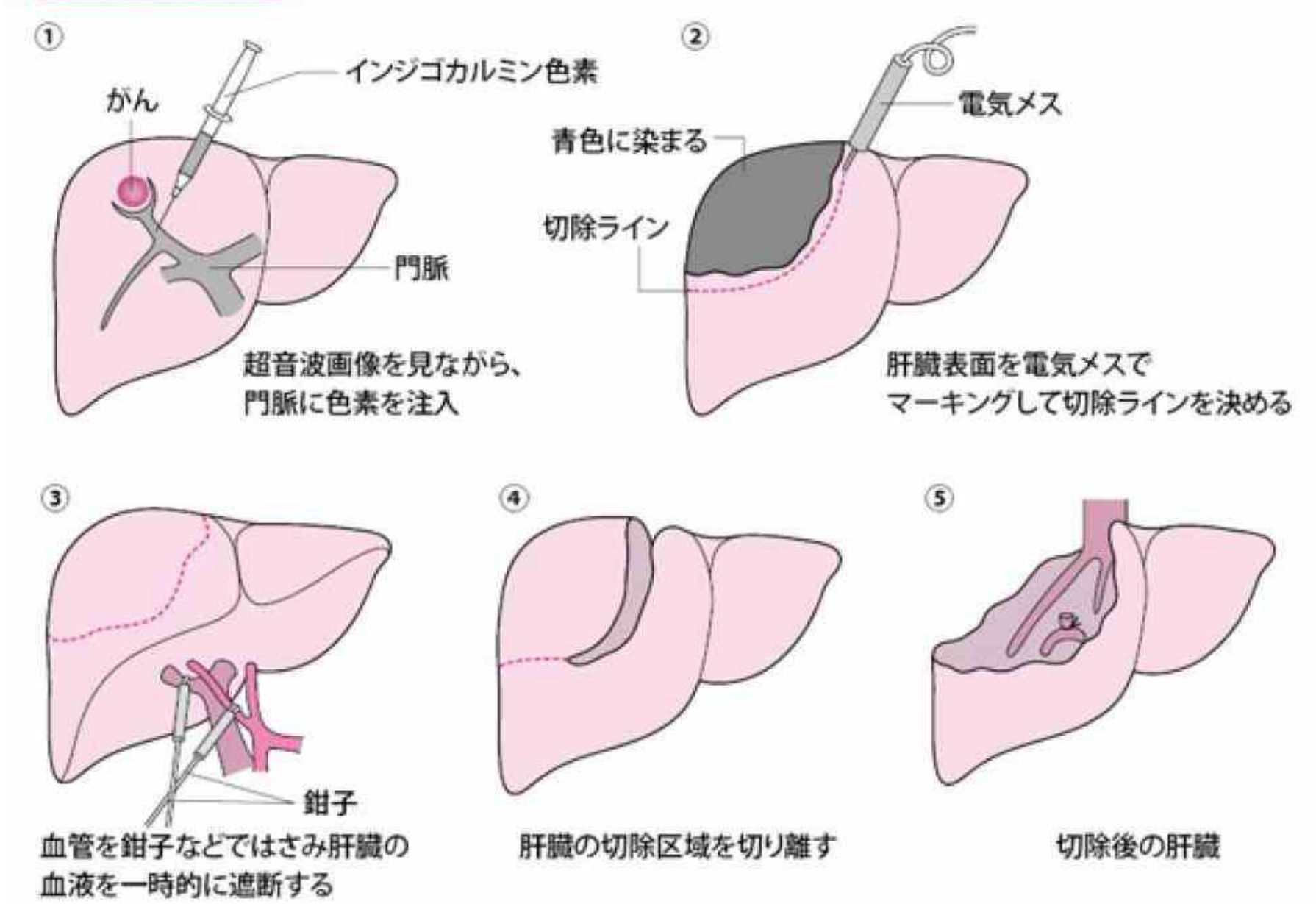
Subsegmental anatomical resection was invented in Japan by Prof. Makuuchi in 1980s, and spread to all over the world.



Anatomical resection

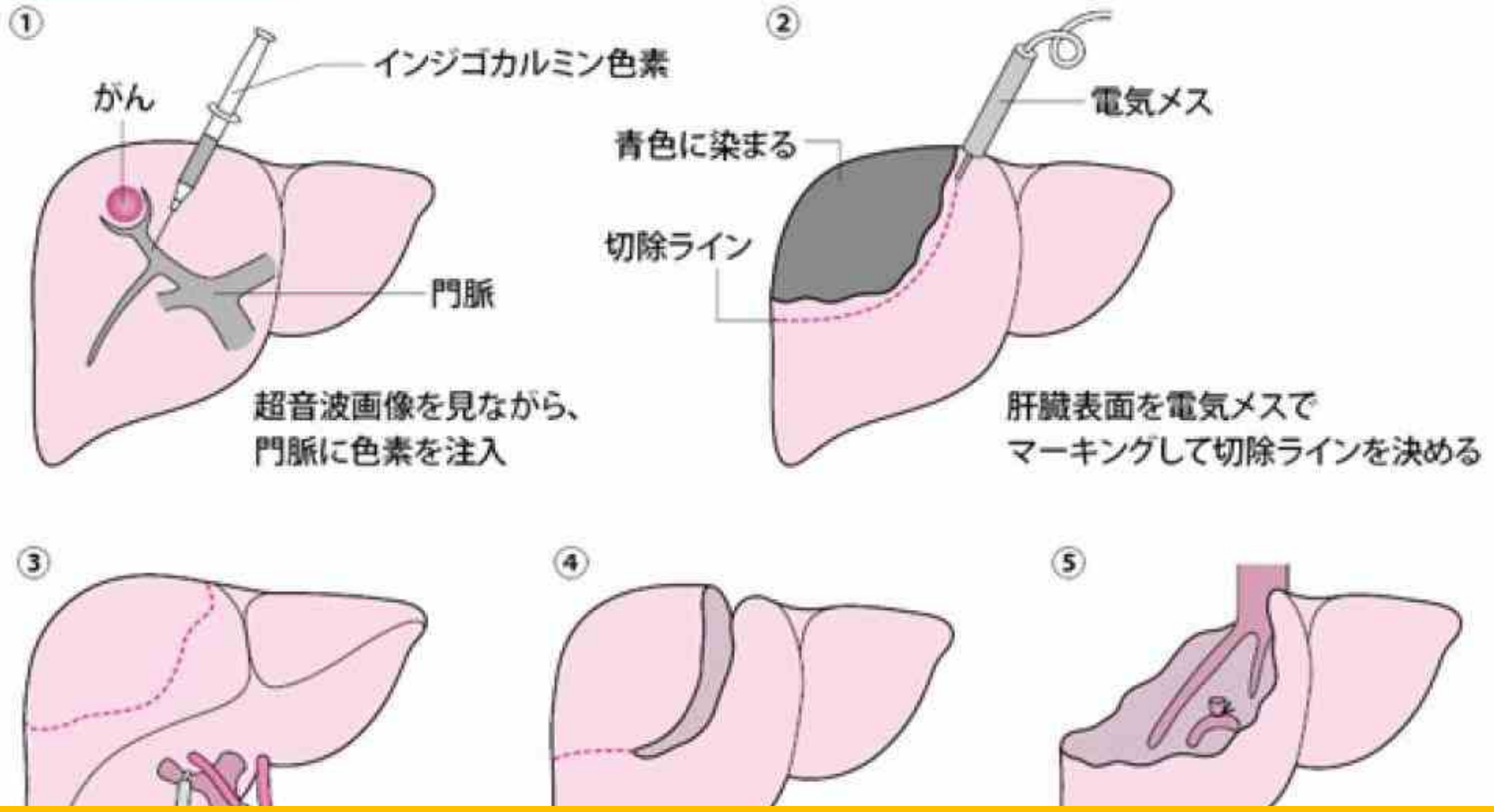
Radiofrequency ablation

Special technique (ICG injection into the portal branch) for anatomical resection



Makuuchi M, et al：Surg Gynecol Obstet 161：346-350, 1985より改変

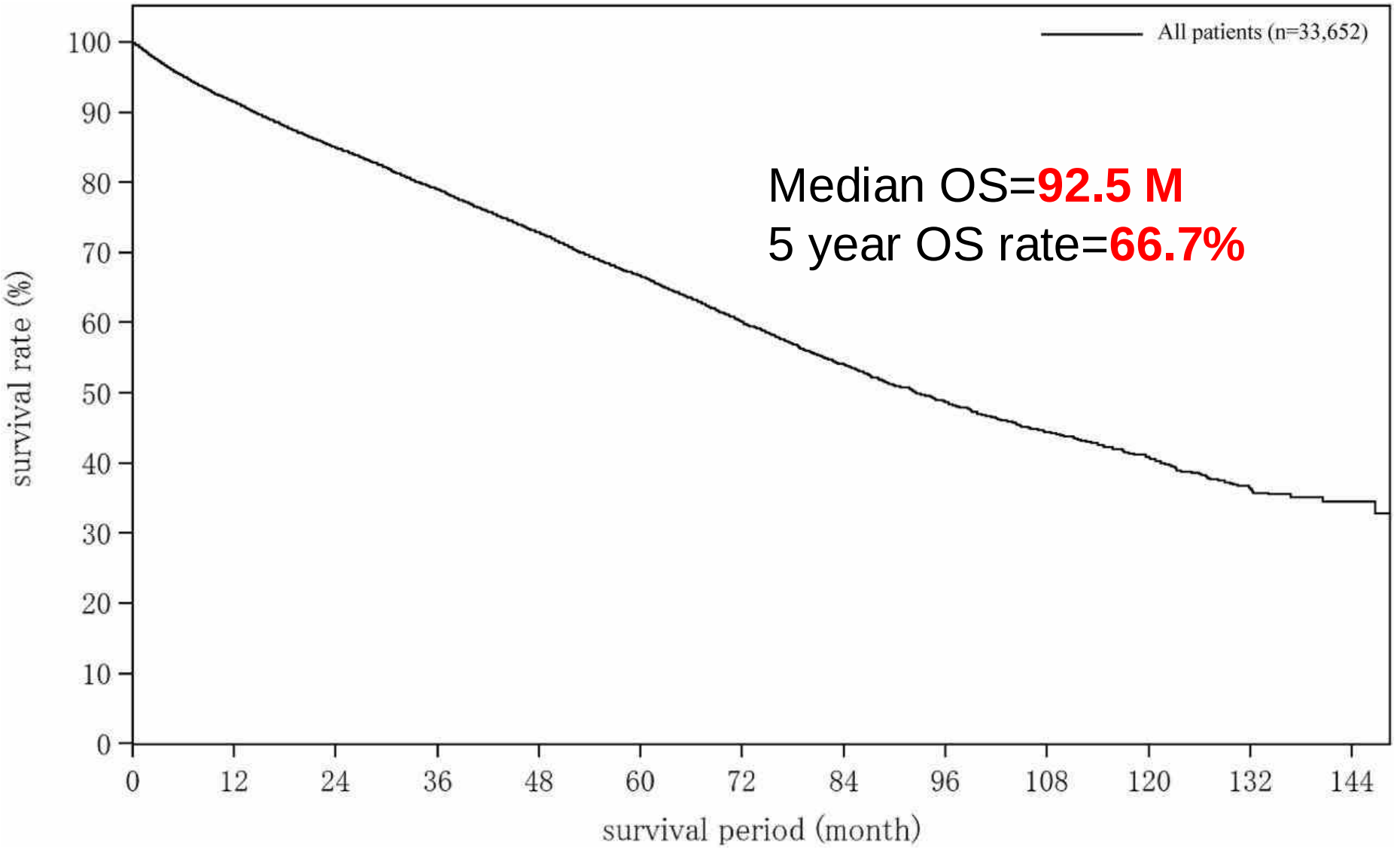
Special technique (ICG injection into the portal branch) for anatomical resection



This technique remove enough tumour, preventing recurrence, while preserving liver function

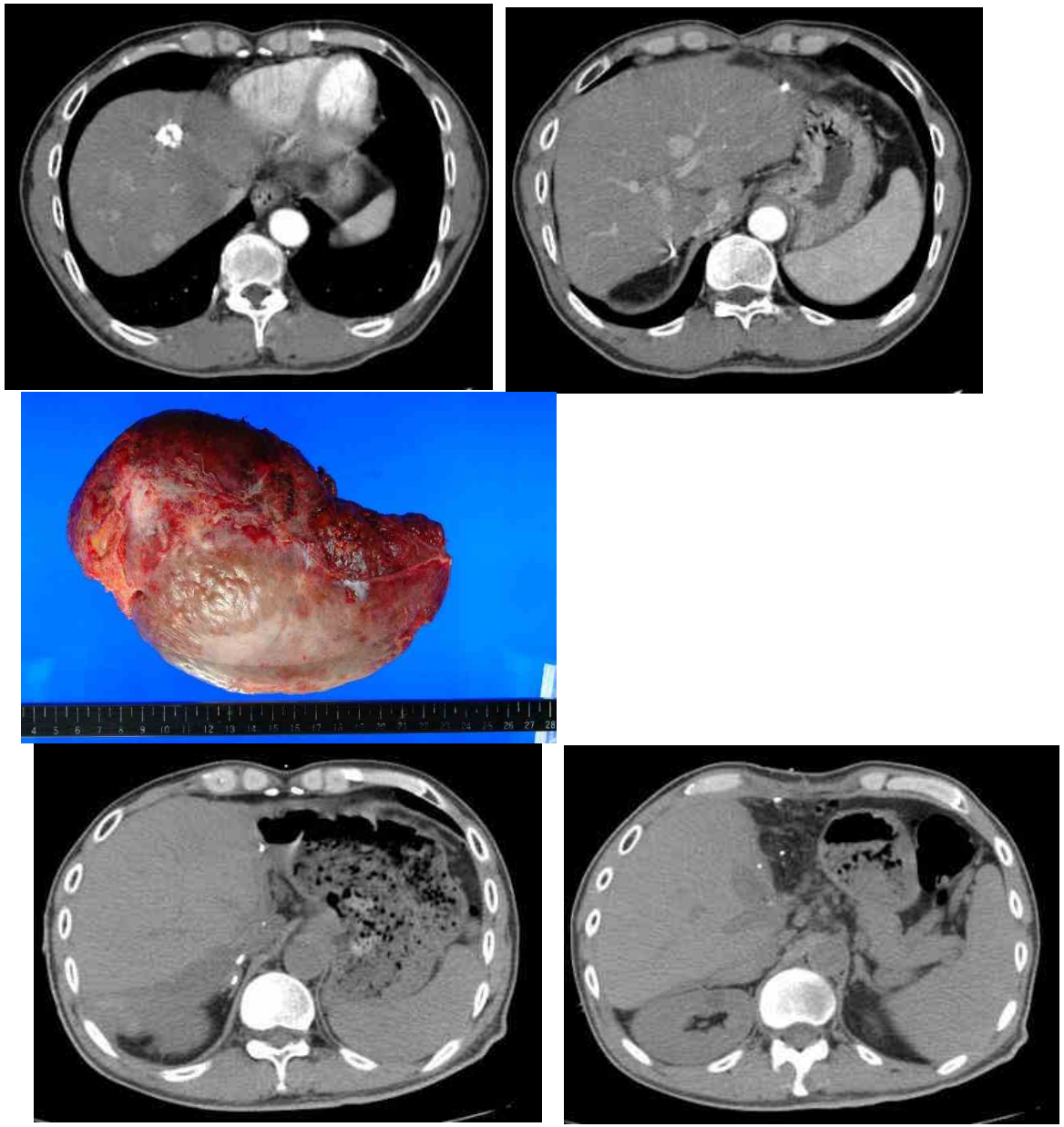
Makuuchi M, et al：Surg Gynecol Obstet 161：346-350, 1985より改変

Overall Survival by Surgical Resection (n=33,652)

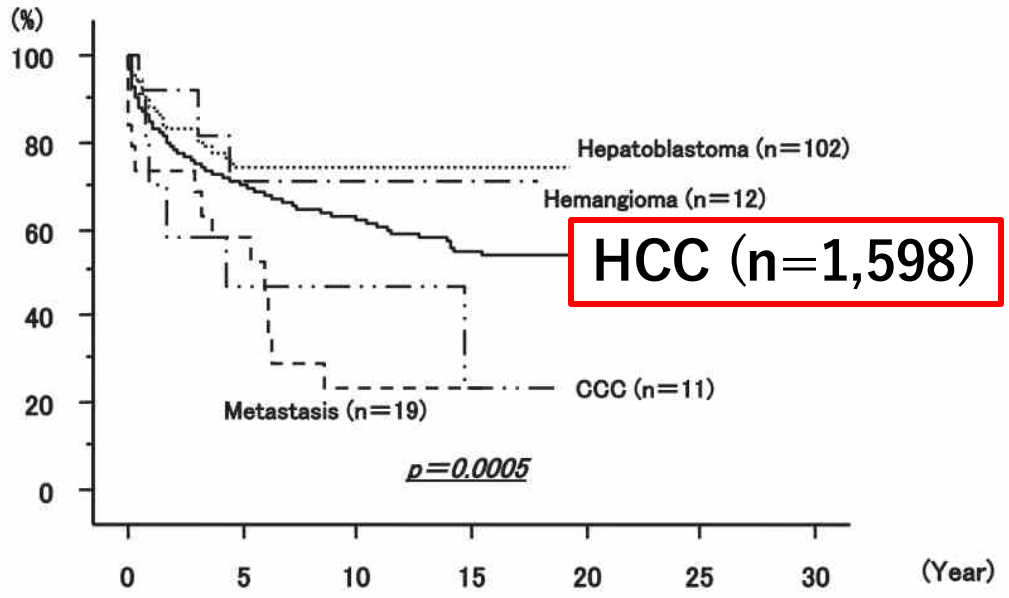


Kudo M, et al. 22nd Nation-wide follow-up survey by JLCA. Hepatol Res. 2022

Liver Transplantation



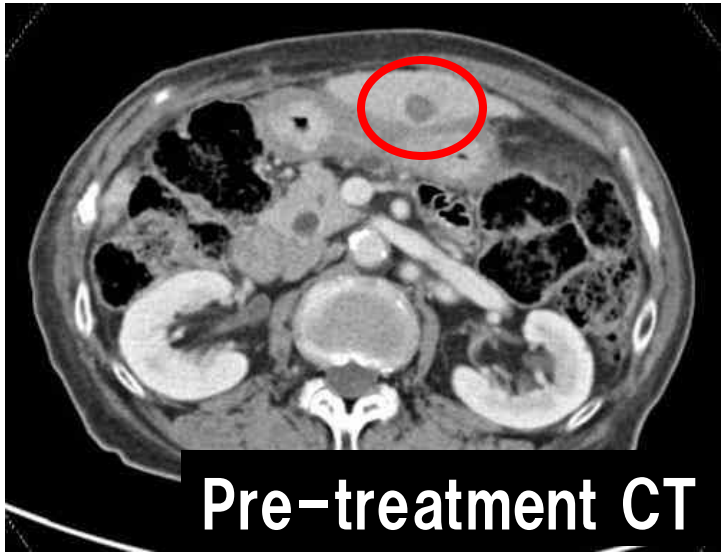
20 y survival rate: 60%

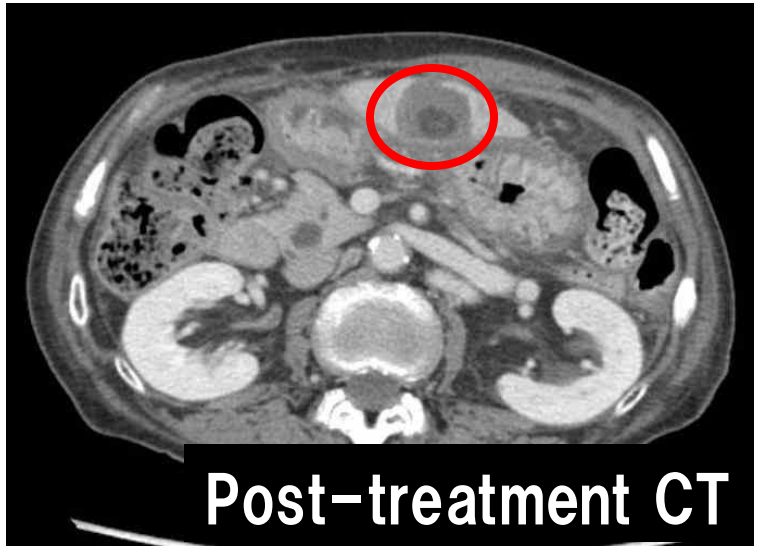


Japan Transplant Society；2017

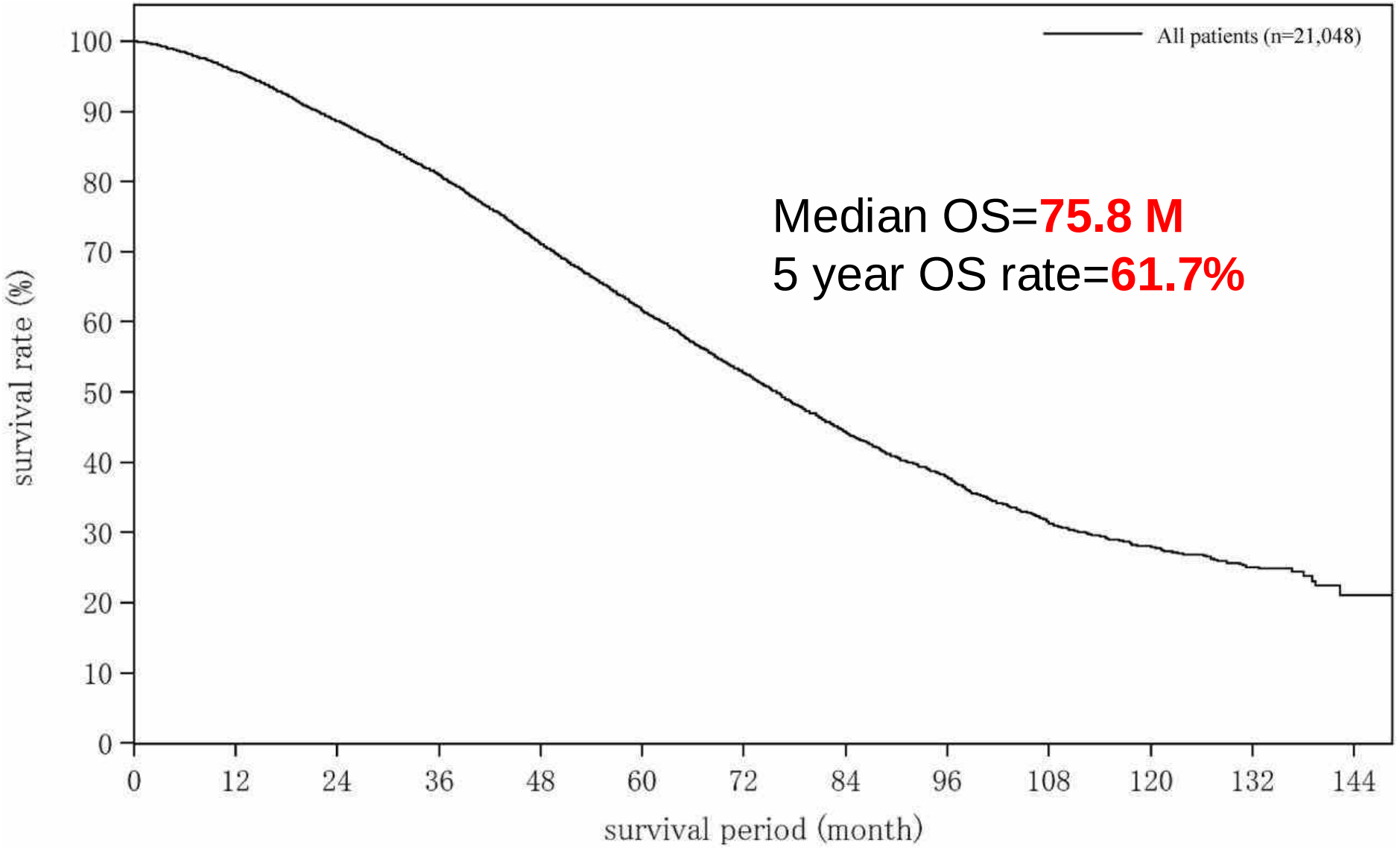
Ablation（Radiofrequency ablation，RFA）

Ablation with enough safety margin





Overall Survival by Radiofrequency Ablation (RFA) (n=21,048)



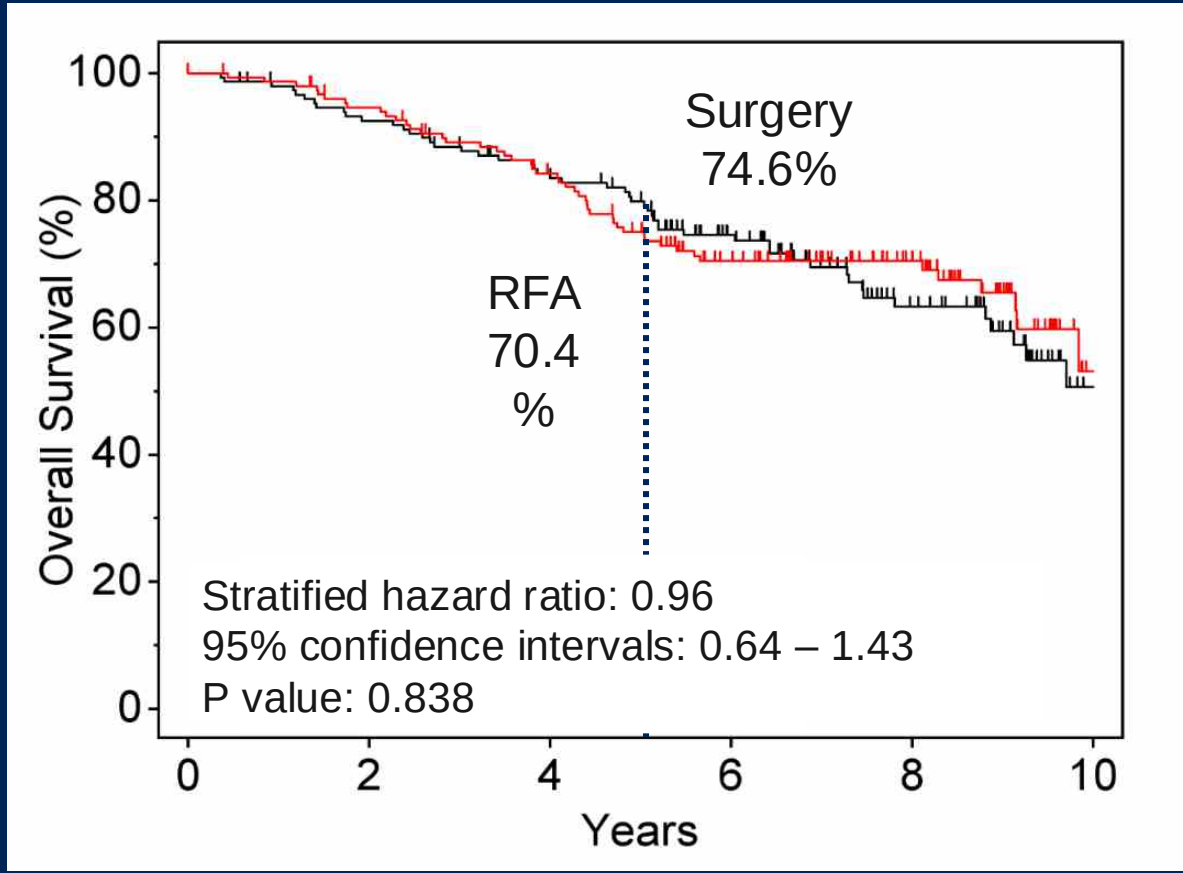
Median OS=**75.8 M**

5 year OS rate=**61.7%**

Kudo M, et al. 22nd Nation-wide follow-up survey by JLCA. Hepatol Res. 2022

SURF Trial: Prospective multicenter P3 trial

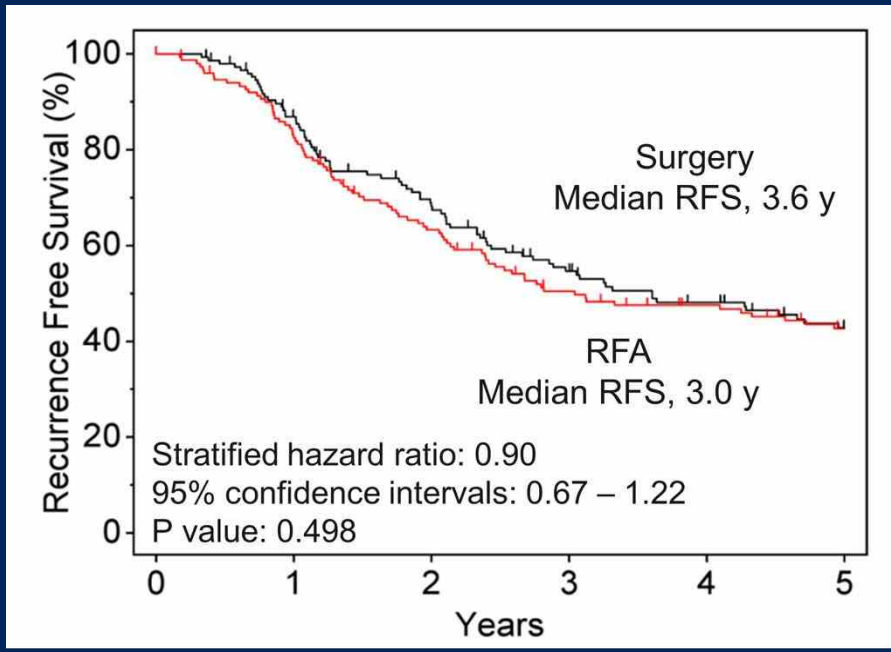
OS, Surgery vs. RFA



Number at risk

150	136	118	82	45	9
152	139	119	84	53	5

RFS Analysis Updates



Number at risk

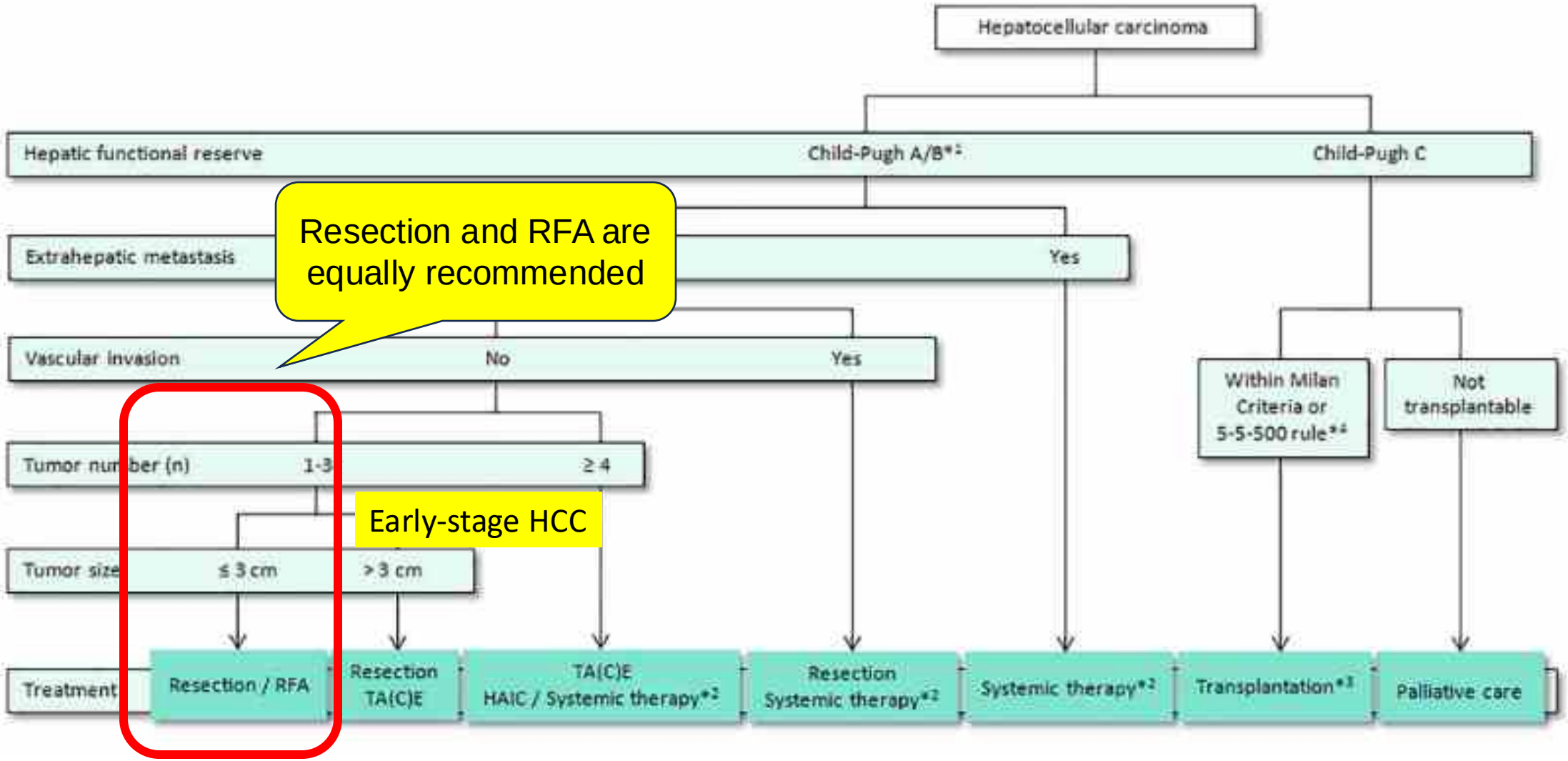
150	123	93	70	58	47
152	122	91	69	60	50

Median follow-up time

Surgery: 6.4 years

RFA: 6.6 years

JSH HCC Guidelines 2021 Algorithm for Treatment

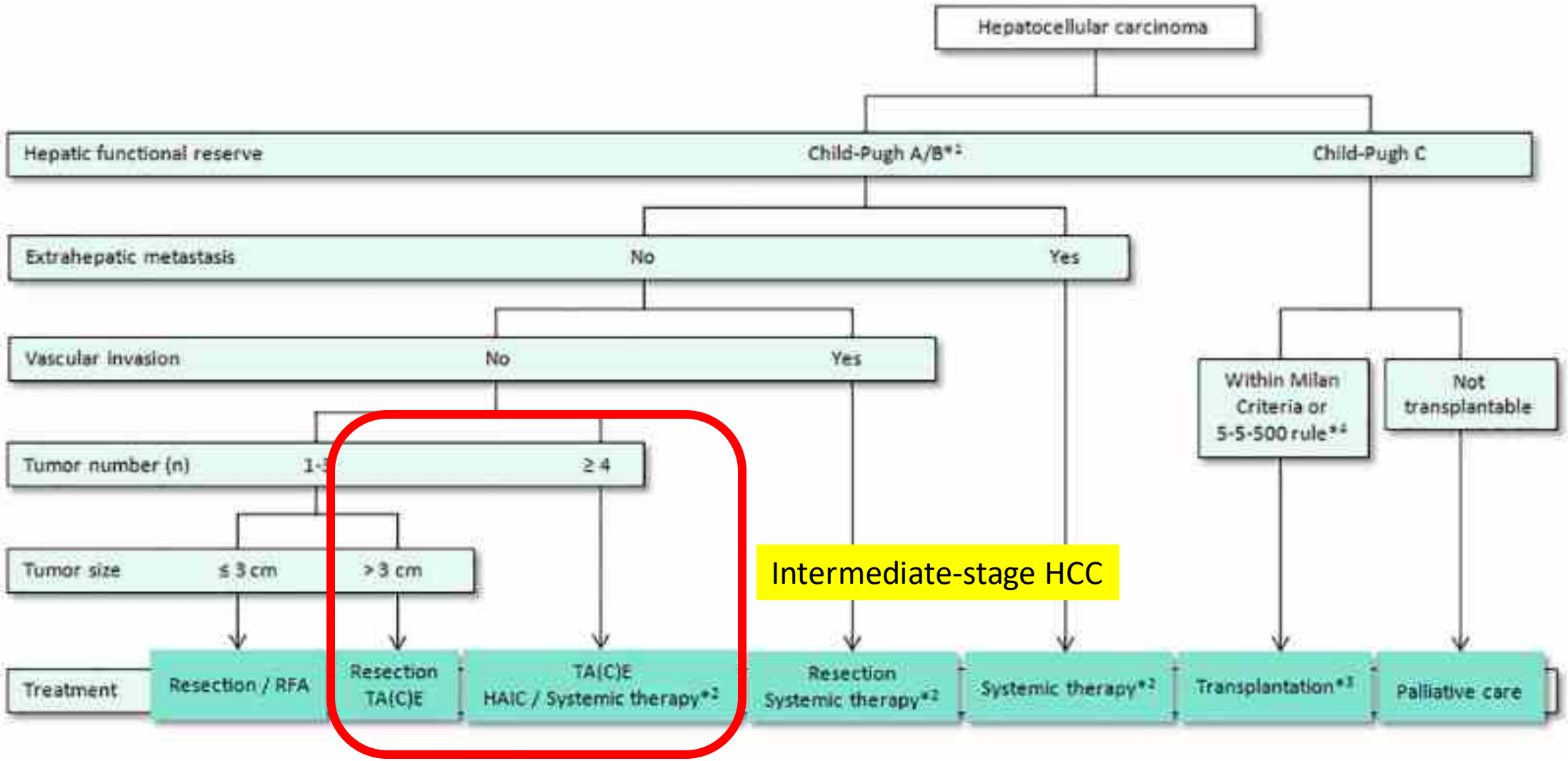


Hasegawa K, Tateishi R, Kudo M, et al. Hepatol Res. 2023

Outline

- Treatment strategy for Intermediate HCC

JSH HCC Guidelines 2021 Algorithm for Treatment



Hasegawa K, Tateishi R, Kudo M, et al. Hepatol Res. 2023

Ryusaku Yamada, M.D.
Morio Sato, M.D.
Mamoru Kawabata, M.D.
Haruki Nakatsuka, M.D.
Kenji Nakamura, M.D.
Sumio Takashima, M.D.

Hepatic Artery Embolization in 120 Patients with Unresectable Hepatoma[1]

Invention of TACE: first in the world in Japan in 1983 by Prof. Yamada

Transcatheter hepatic artery embolization was performed in 120 patients with unresectable hepatoma. The cumulative one-year survival rate was 44%. In most cases follow-up angiography revealed the selective disappearance of tumor vessels, and computed tomography demonstrated a marked decrease in tumor density without any changes in the surrounding liver parenchyma. Histologic examination in 14 cases confirmed these findings.

Index terms: Arteries, therapeutic blockade, 9.129 • (Hepatic artery, therapeutic embolization, 9[52].129) • (Liver, malignant hepatoma, 7[61].329) • Liver neoplasms, blood supply • Liver neoplasms, therapy

Radiology 148: 397–401, August 1983

HEPATOMA is a relatively common malignant tumor in Japan, and patients with this neoplasm have a poor prognosis. The first choice of treatment is hepatectomy, but most cases are considered inoperable due to extreme tumor extension at the time of diagnosis and accompanying advanced cirrhosis. According to the 1979 report of the Liver Cancer Study Group of Japan (1), only 9% of hepatoma patients underwent hepatectomy. The report also concluded that the one-year survival rate after surgery was only 28%. Chemotherapy produced even worse results: the survival rate one year after treatment was 7%, and the mean length of survival was 3 to 6 months.

Since 1977 we have performed transcatheter arterial embolization in 120 cases of unresectable hepatoma. This report describes our experience with embolization, which demonstrates far more satisfactory results than other existing treatments.

MATERIALS AND METHODS

Two hundred thirty-five embolization procedures were performed in 120 patients with unresectable hepatoma from June 1977 to May 1982. Repeat embolizations (2 to 7 procedures) were performed in 45%

Yamada R, et al. Radiology 1983

Changing Treatment Strategy of Intermediate Stage-HCC

TACE

- Matsui O (1993) Subseg Lip-TACE
- Ohishi H (1985) Lip-TACE
- Uchida H (1990) Seg Lip-TACE
- Llovet JM (2003) TACE vs BSC Meta-analysis
- Yamada R (1983) GS-TAE
- Miyayama S (2007) Ultraselective TACE
- PRESIDENT (2016) DEB-TACE vs cTACE

Concept of TACE Failure：
Kudo M, et al. JSH Guideline（2017）

Concept of TACE Unsuitable：
Kudo M, et al. JSH Consensus(2020)
Kudo M. APPLE Consensus（2020）

1983～ | 2016 | 2017 | 2018 | 2019 | 2020 | 2021 | 2022 | 2023

TACE+Systemic therapy

Because of the rapid advances of systemic therapy, TACE＋Systemic therapy has become a SOC in Japan

Japan P2
- TACTICS (2018) SOR + TACE vs TACE

Multicenter POC
- ABC Conversion (2023) Atezo/Bev + Op, RFA, TACE

Japan P2
- TACTICS-L (2022) LEN -TACE

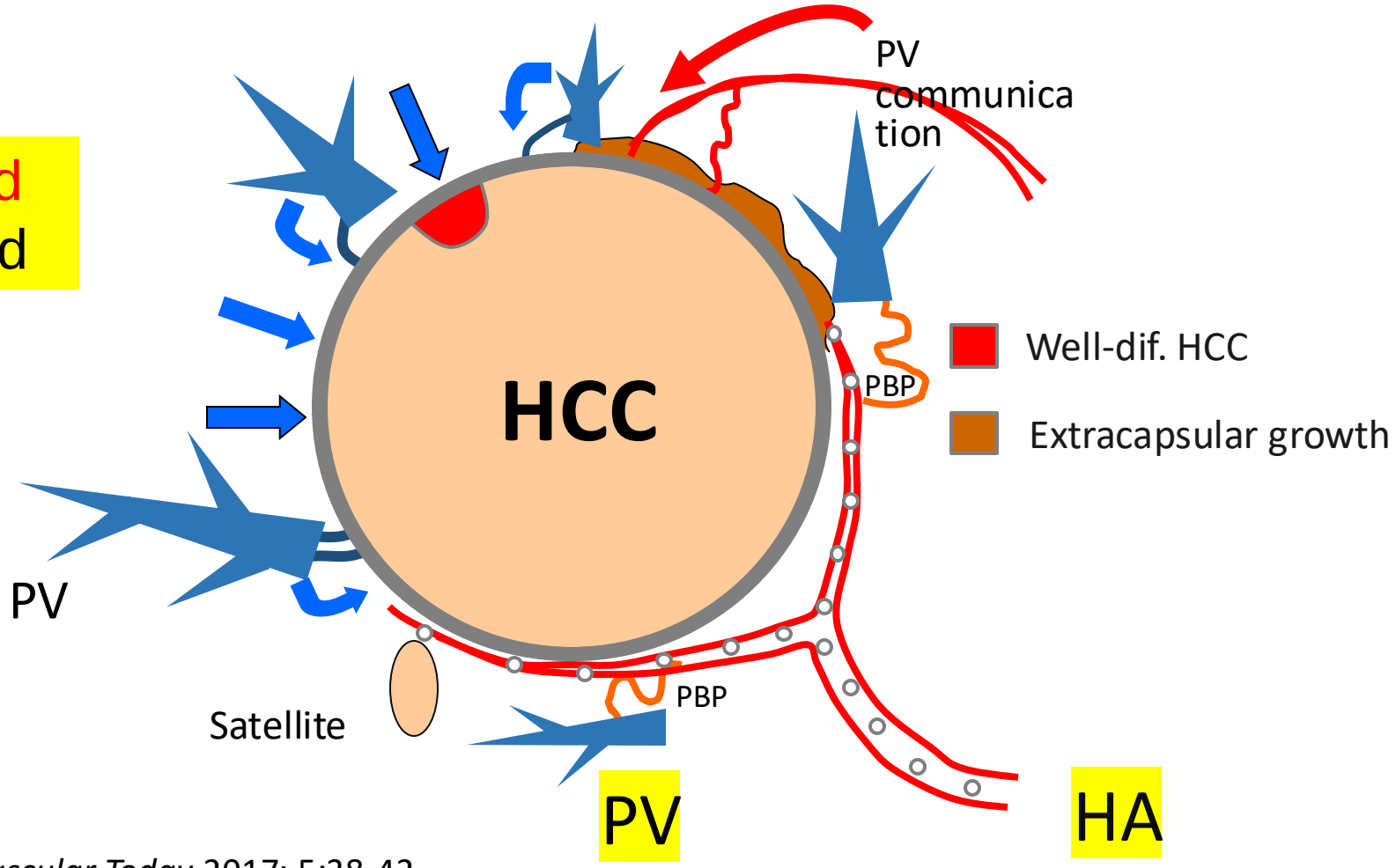
Global P3
- EMERALD-1 (2024) Durva±Bev TACE vs TACE

China P3
- LAUNCH (2022) LEN-TACE vs LEN BCLC-B+C

Global P3
- LEAP-012 (2024) LEN + PEM +TACE vs TACE

Non-selective TACE

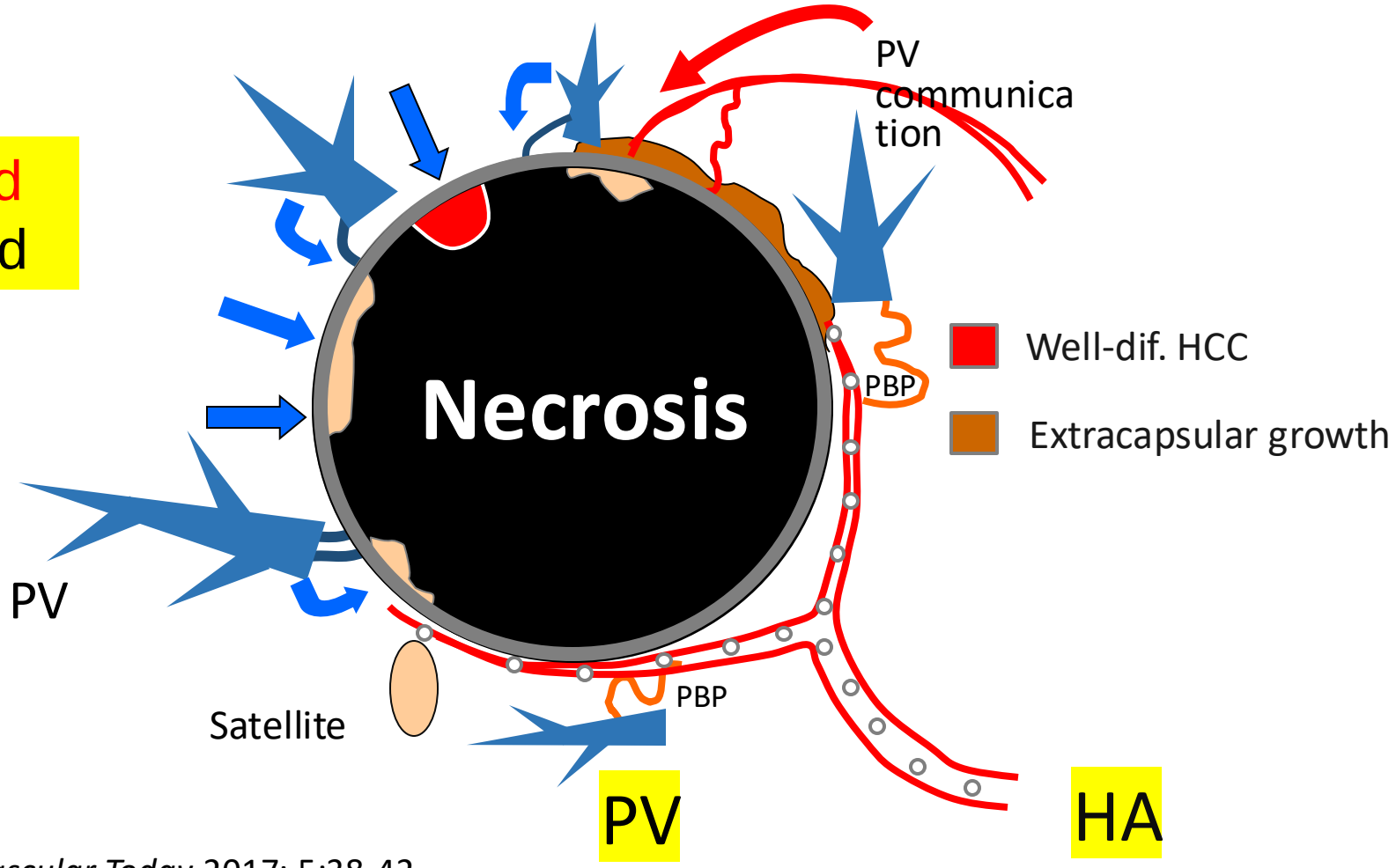
Inflow of portal blood when HA is occluded



Miyayama S and Matsui O. *Endovascular Today* 2017; 5:38-42.

Non-selective TACE

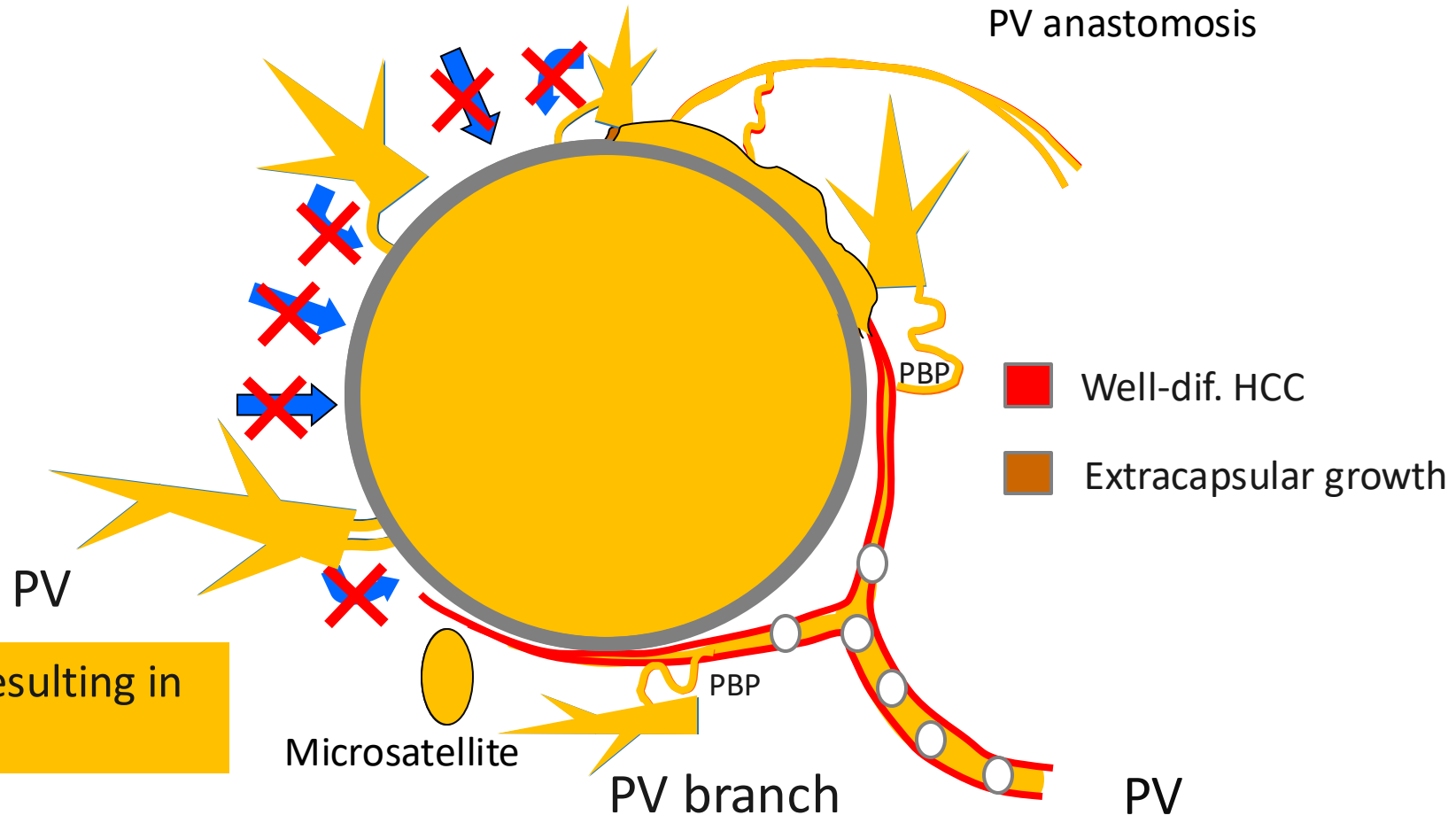
Inflow of portal blood when HA is occluded



Miyayama S and Matsui O. *Endovascular Today* 2017; 5:38-42.

Superselective cTACE

Intraarterial Lipiodol regurgitate to the PV, via PBP or drainage vessel

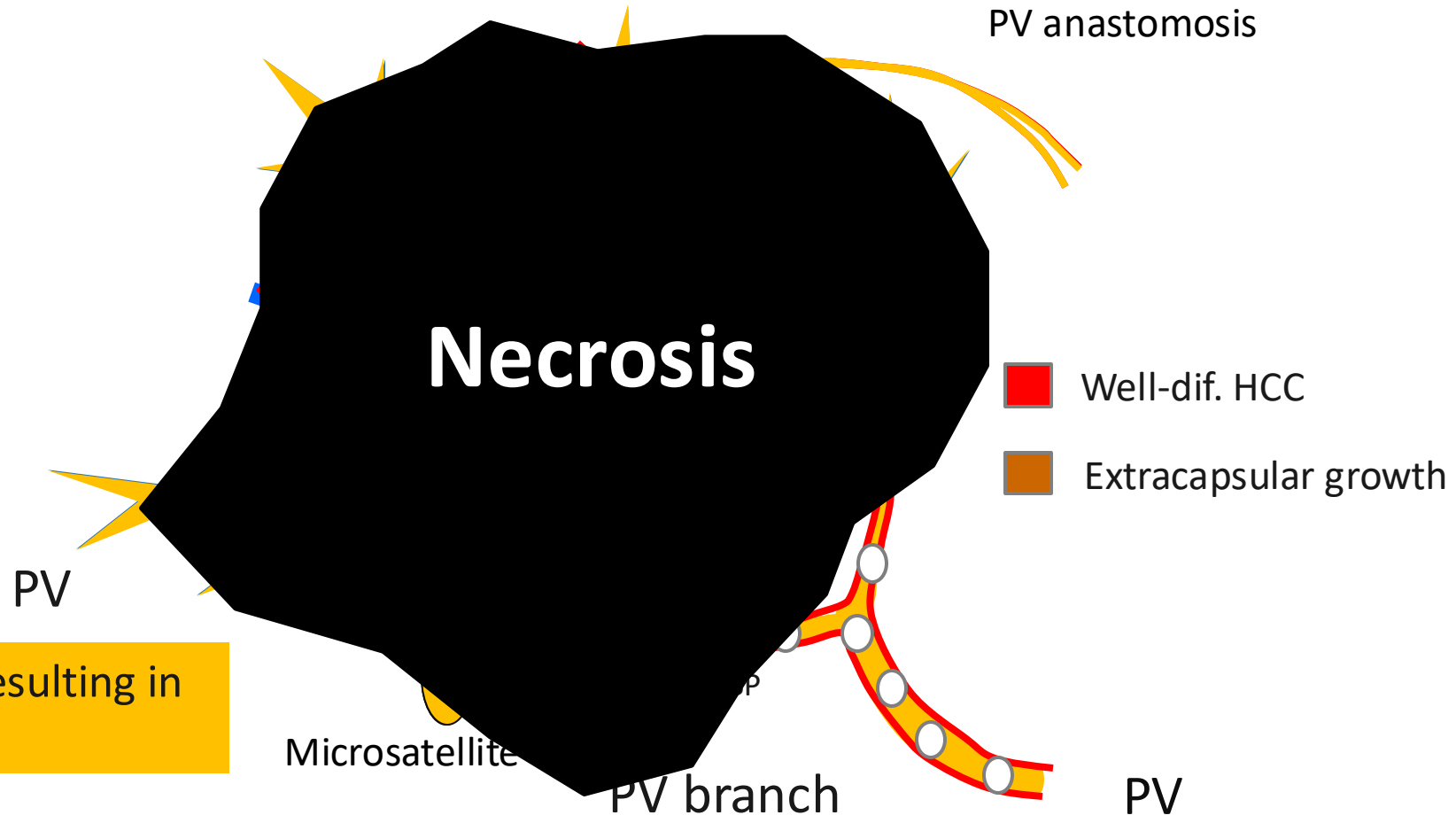


Lipiodol blocks PV flow, resulting in Complete necrosis

Miyayama S and Matsui O. *Endovascular Today* 2017; 5:38-42.

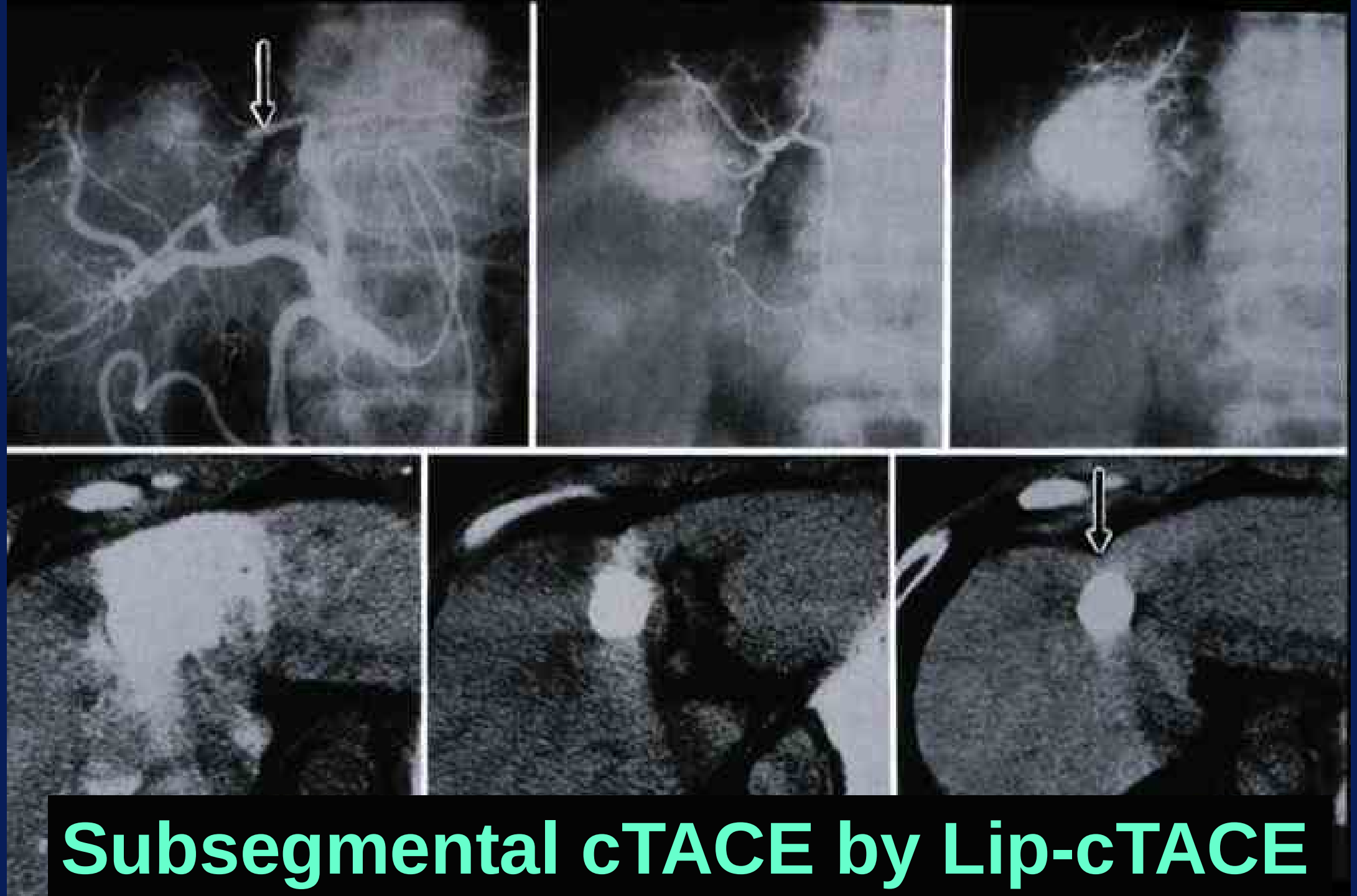
Superselective cTACE

Intraarterial Lipiodol regurgitate to the PV, via PBP or drainage vessel



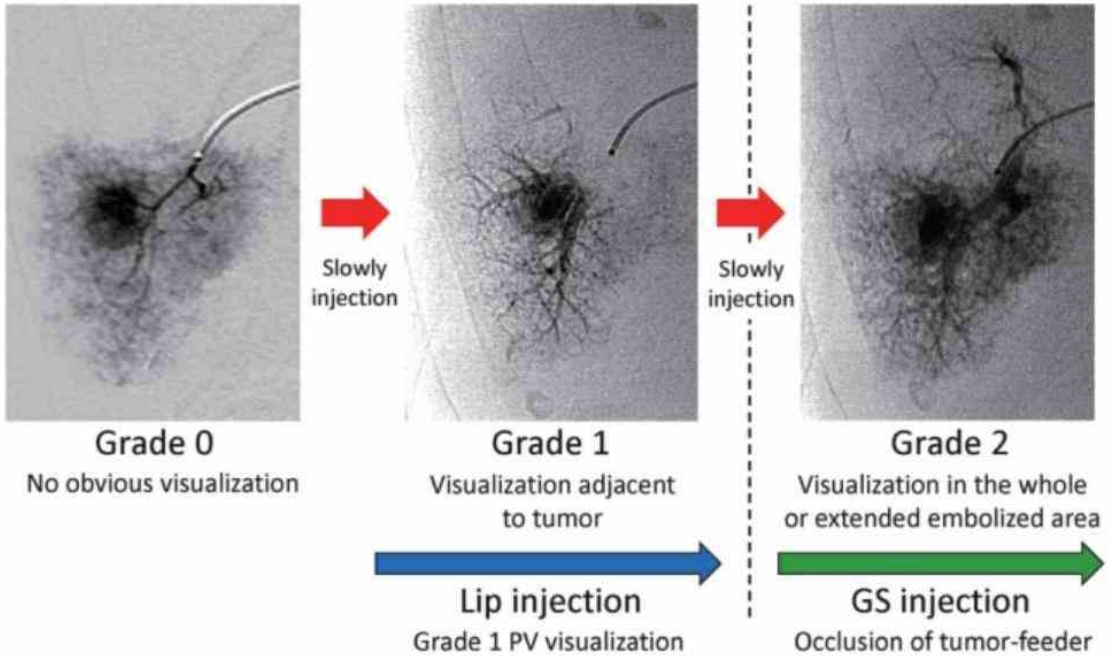
Lipiodol blocks PV flow, resulting in Complete necrosis

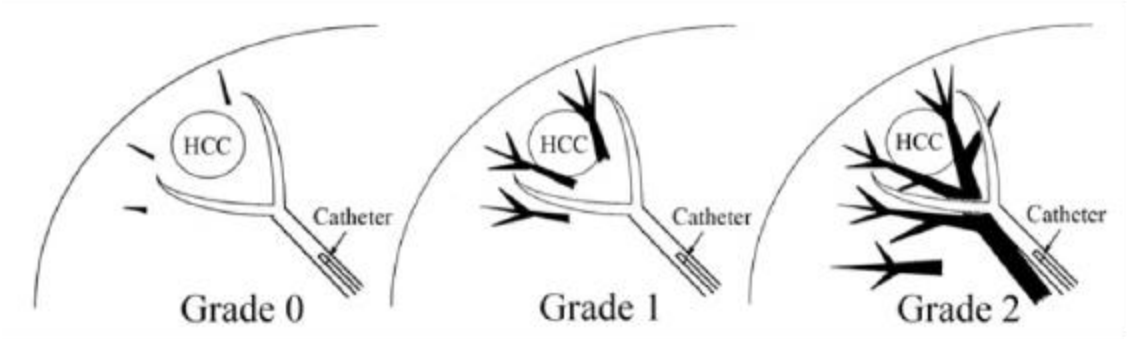
Miyayama S and Matsui O. *Endovascular Today* 2017; 5:38-42.

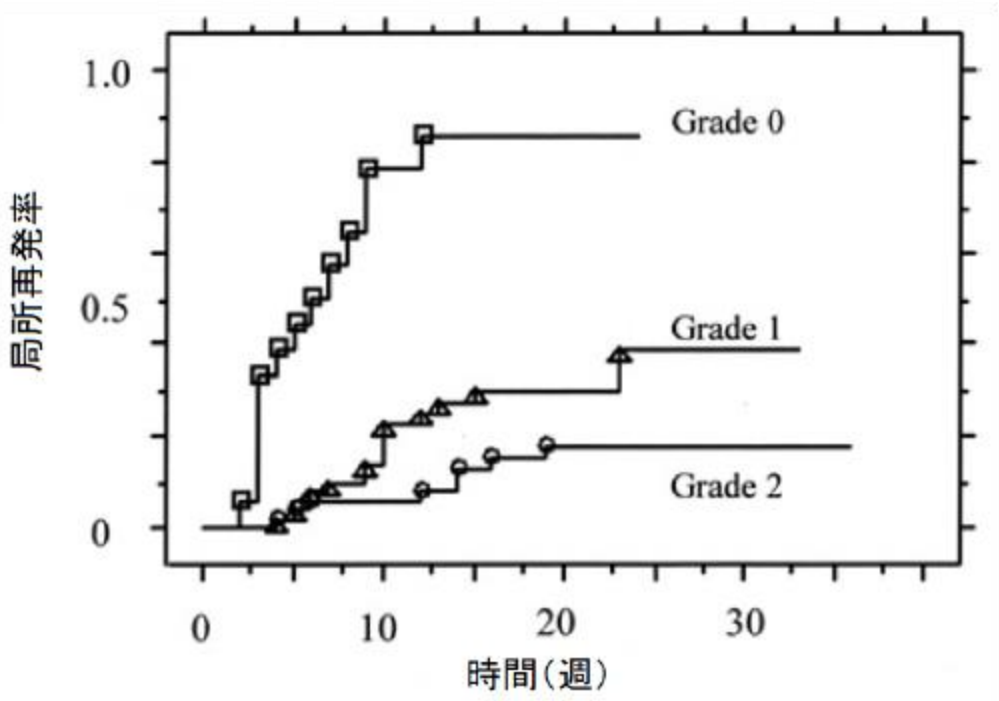


Subsegmental cTACE by Lip-cTACE

Grade of regurgitation of Lipiodol in the portal vein correlates to the local control rate.

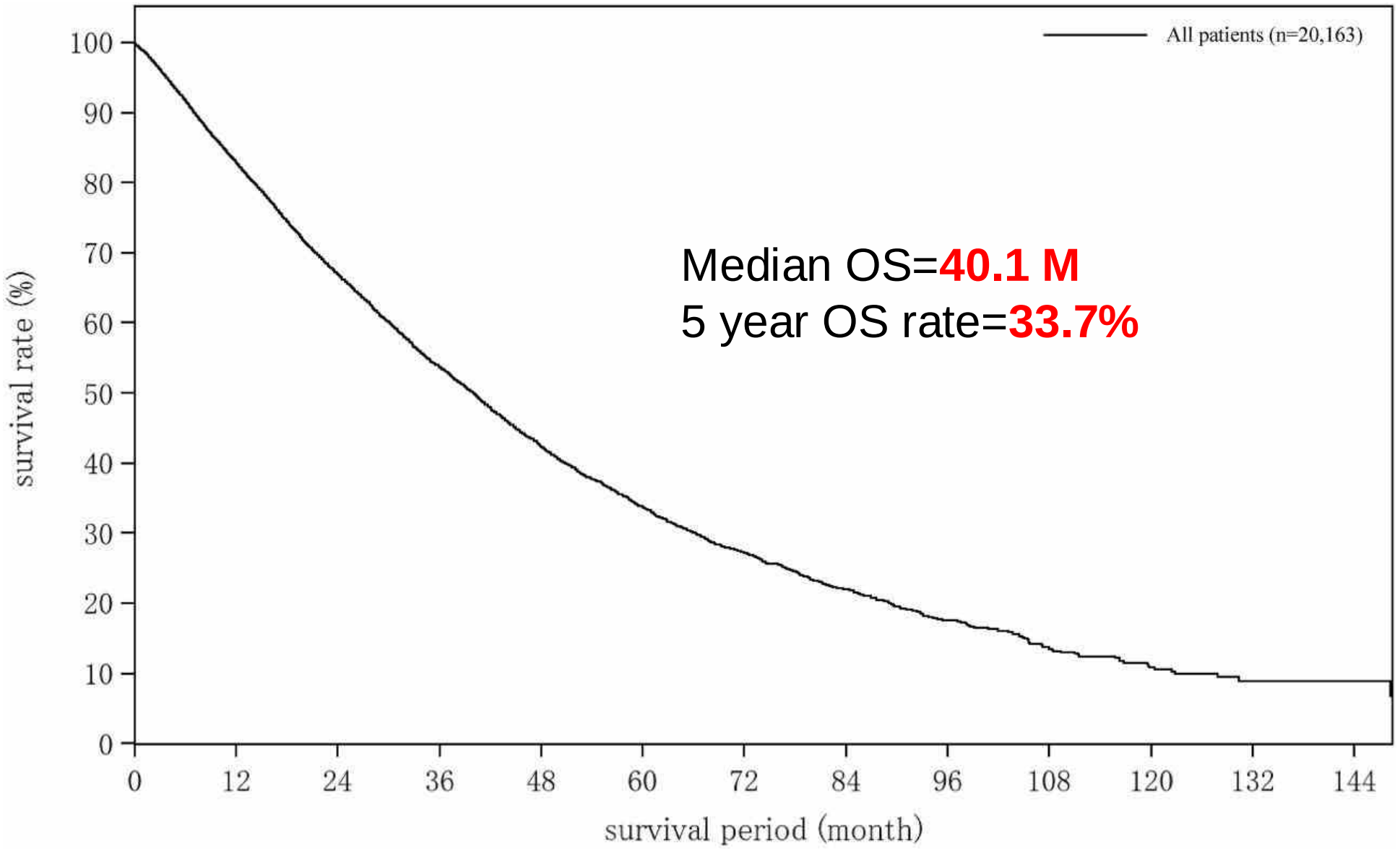






Miyayama S, Matsui O. 2016;27:1269–1278.
Miyayama S, et al. JVIR 2007;18:365-376

Overall Survival by TACE (n=20,163)



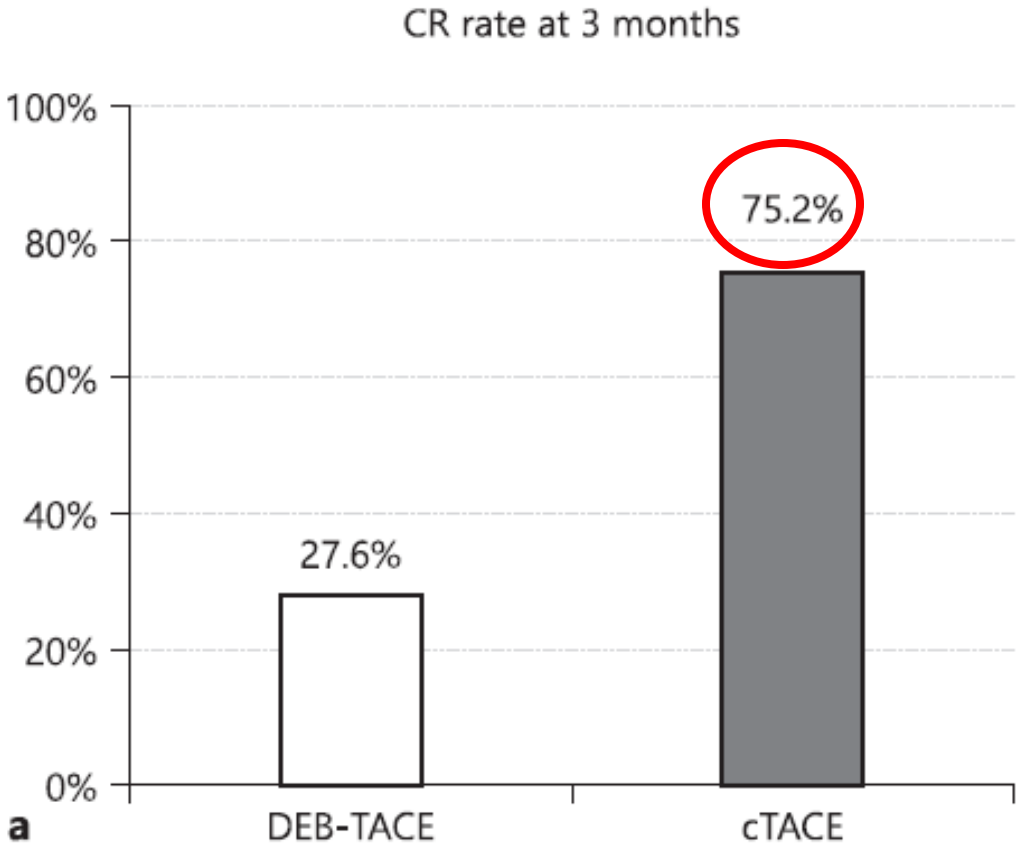
Median OS=**40.1 M**

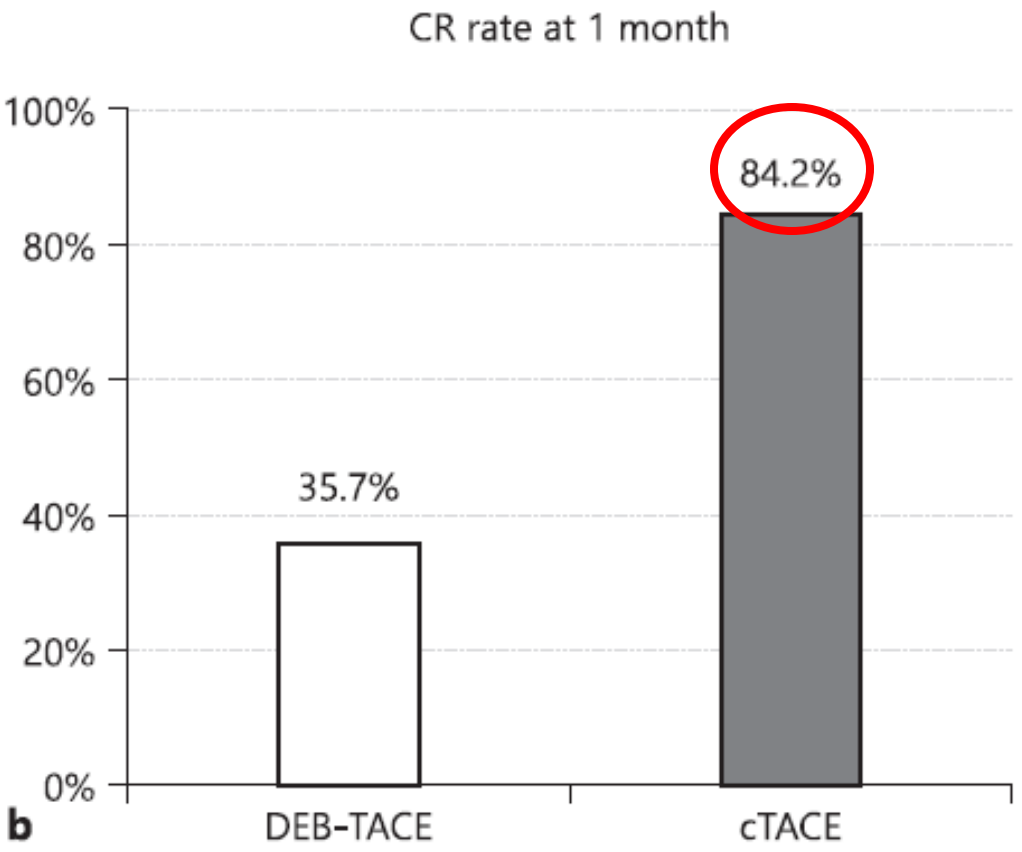
5 year OS rate=**33.7%**

Kudo M, et al. 22nd Nationwide follow-up survey by JLCA. Hepatol Res. 2022

President Study: Multicenter Prospective RCT

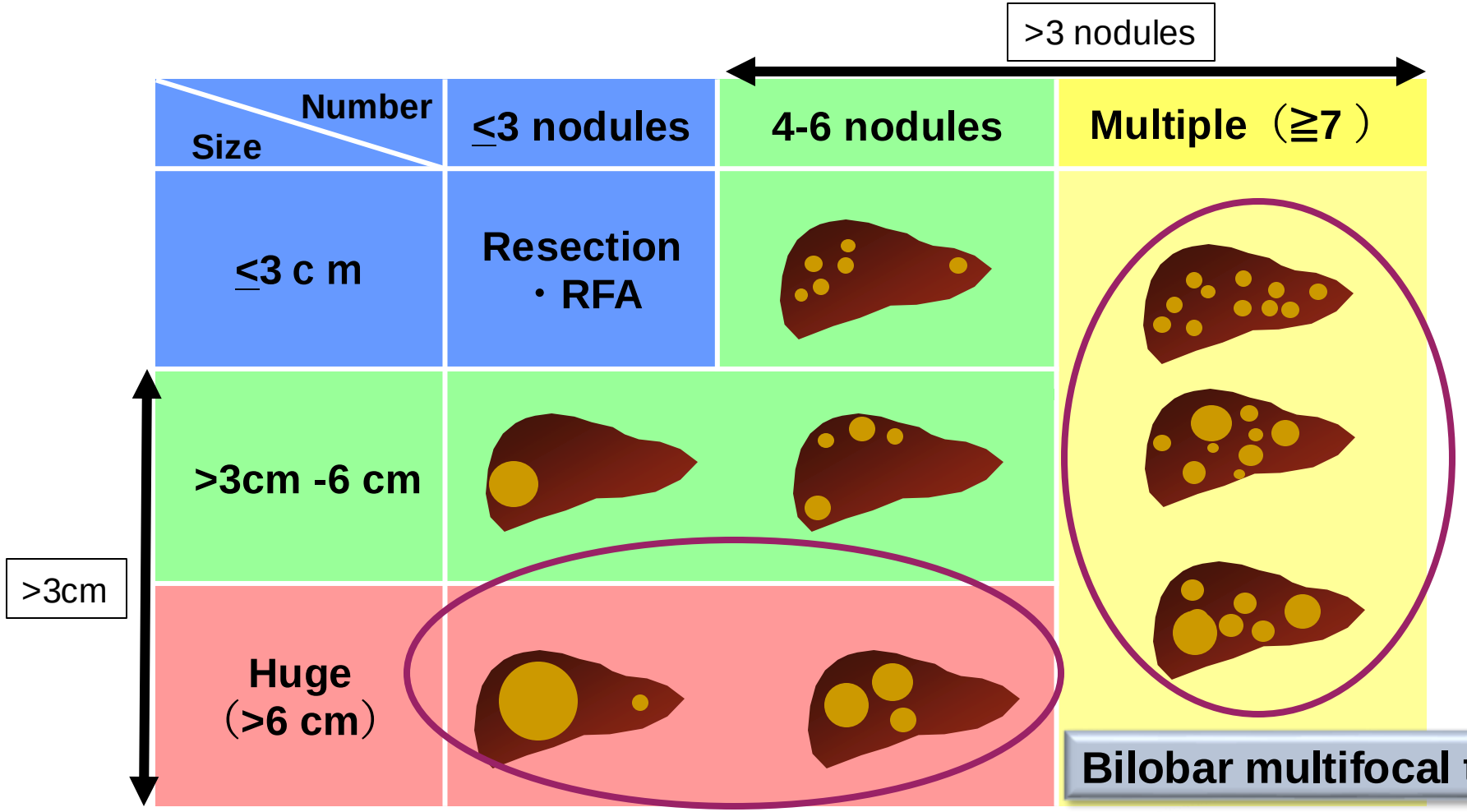
Selective cTACE achieves **higher CR rate**





Ikeda M, et al. Liver Cancer 2022

Heterogeneity and treatment strategy of intermediate stage HCC (Kinki Criteria)



N0
M0
VP0,Vv0

TACE unsuitable patients

green	good response subgroup to cTACE (within up-to-7 criteria)
pink	poor response subgroup to cTACE (beyond up-to-7 criteria)
yellow	poor response subgroup to cTACE (beyond up-to-7, Bilobar multifocal tumors)

Subgroup; easy to be TACE refractory

APPLE Consensus Statements

APPLE Consensus Members

Masatoshi Kudo
(Kindai University)

Chung-Kwe Wang
(Taipei City Hospital)

Kwang-Hyub Han
(Severance Hospital, Yonsei University)

Masafumi Ikeda
(National Cancer Hospital East)

Sheng-Long Ye
(Zhongshan Hospital, Fudan University)

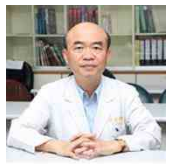
Stephen Lam Chan
(The Chinese University of Hong Kong)

Jian Zhou
(Zhongshan Hospital, Fudan University)

Su Pin Choo
(CURIE Oncology)

Yi-Hsiang Huang
(National Yang-Ming University)

Shiro Miyayama
(Fukui-ken Saiseikai Hospital)



Shi-Ming Lin
(Chang-Gung Memorial Hospital Linkou)

Ann Lii Cheng
(National Taiwan University)

Liver Cancer

Consensus Statement

A Changing Paradigm for the Treatment of Intermediate-Stage Hepatocellular Carcinoma: Asia-Pacific Primary Liver Cancer Expert Consensus Statements

Masatoshi Kudo[a] Kwang-Hyub Han[b] Sheng-Long Ye[c] Jian Zhou[d] Yi-Hsiang Huang[e, f] Shi-Ming Lin[g, h] Chung-Kwe Wang[i] Masafumi Ikeda[j] Stephen Lam Chan[k] Su Pin Choo[l] Shiro Miyayama[m] Ann Lii Cheng[n–p] on behalf of the APPLE Association

[a]Department of Gastroenterology and Hepatology, Kindai University Faculty of Medicine, Osaka-Sayama, Japan; [b]Department of Internal Medicine, Yonsei University College of Medicine, Seoul, South Korea; [c]Liver Cancer Institute, Zhongshan Hospital, Fudan University, Shanghai, China; [d]Department of Liver Surgery and Transplantation, Liver Cancer Institute, Zhongshan Hospital, Fudan University, Shanghai, China; [e]Division of Gastroenterology and Hepatology, Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan; [f]Institute of Clinical Medicine, National Yang-Ming University, Taipei, Taiwan; [g]Department of Gastroenterology and Hepatology, Chang Gung Memorial Hospital, Linkou, Taiwan; [h]College of Medicine, Chang Gung University, Taoyuan City, Taiwan; [i]Division of Gastroenterology and Hepatology, Department of Internal Medicine, Taipei City Hospital, Ren-Ai Branch and Kang Ning Hospital, Taipei, Taiwan; [j]Department of Hepatobiliary and Pancreatic Oncology, National Cancer Center Hospital East, Kashiwa-shi, Japan; [k]Department of Clinical Oncology, State Key Laboratory of Translation Oncology, The Chinese University of Hong Kong, Hong Kong, China; [l]Division of Medical Oncology, National Cancer Centre Singapore, Singapore, Singapore; [m]Department of Diagnostic Radiology, Fukui-ken Saiseikai Hospital, Fukui, Japan; [n]Department of Medical Oncology, National Taiwan University Cancer Center, Taipei, Taiwan; [o]Department of Oncology, National Taiwan University Hospital, Taipei, Taiwan; [p]Graduate Institute of Oncology, School of Medicine, National Taiwan University, Taipei, Taiwan

Kudo M et al, Liver Cancer 2020

Criteria for TACE unsuitability

APPLE Consensus Statement

CQ. 9 ：What is TACE-unsuitable?

(i) Unlikely to respond to TACE:
Confluent multinodular type, massive or infiltrative type, simple nodular type with extranodular growth, poorly differentiated type, intrahepatic multiple disseminated nodules, or sarcomatous changes after TACE

(ii) Likely to develop TACE failure/refractoriness:
up-to-7 criteria out nodules

(iii) Likely to become Child-Pugh B or C after TACE:
up-to-7 criteria out nodules (especially, bilobar multifocal HCC),
mALBI grade 2b

JSH Consensus Staement

Table 6-22：TACE-unsuitable patient population

①Likely to develop TACE failure/refractoriness
- up-to-7 criteria out nodules

②Likely to become Child-Pugh B after TACE
- up-to-7 criteria out nodules
（especially , bilobar multifocal HCC）
- ALBI grade 2（especially mALBI grade2B）

③Unlikely to respond to TACE
- Confluent multinodular type, massive or infiltrative type
- simple nodular type with extranodular growth
- poorly differentiated type
- intrahepatic multiple disseminated nodules
- sarcomatous changes after TACE

Kudo M et al :Treatment of Intermediate-Stage HCC: APPLE Consensus Statement. Liver Cancer 2020
Kudo M, et al. JSH Consensus Liver Cancer 2021. Kudo M, et al. JSH: Clinical practice manuals for hepatocellular carcinoma 4th edition, 2020.

TACTICS-L Study Schema

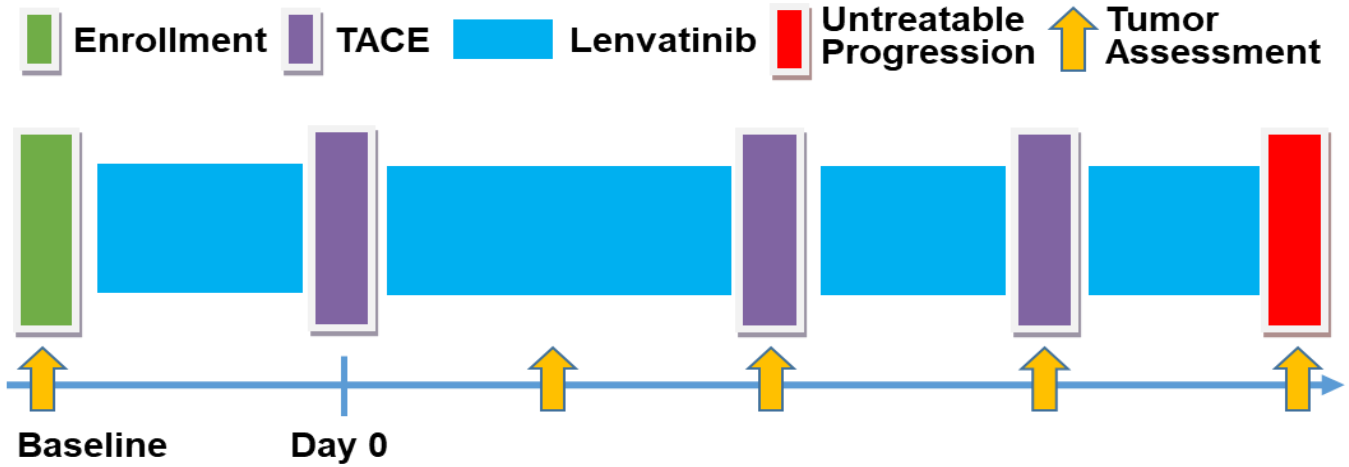
- A Phase 2, prospective, multicentre, single-arm study was conducted at 21 Japanese institutions between February 2019 and April 2021.
- Efficacy assessments were performed on the ITT population (All eligible subjects). Safety assessments were performed on subjects who received at least one dose of lenvatinib or TACE procedure

Study Schema

<Inclusion criteria>
- Unresectable HCC
- Child-Pugh ≤6
- Prior TACE 0-2
- Tumor size ≤10cm
- Tumor Number ≤10
- ECOG-PS: 0 or 1

<Exclusion criteria>
- Vascular invasion
- Extrahepatic spread

LEN+TACE Combination



<Primary Endpoint>
- Progression Free Survival (PFS) by RECICL

<Secondary Endpoints>
- TTUP (Time to untreatable progression)
- PFS by mRECIST
- ORR by RECICL
- OS
- Safety

- **The combination of TACE and lenvatinib (12 mg once daily ≥ 60 kg and 8 mg once daily < 60 kg) was applied and continued until the event specified in the PFS definition occurred.**
  - ✓ **TACE(cTACE) should be repeated on demand once the specified TACE criteria was met.**
  - ✓ **Tumor assessment should be done 4 weeks after first TACE and then every 8 weeks.**

［レンバチニブ添付文書抜粋］
4．効能または効果：切除不能な肝細胞癌
5．効能又は効果に関連する注意：5．3 局所療法（経皮的エタノール注入療法、ラジオ波焼灼療法、マイクロ波凝固療法、肝動脈塞栓療法／肝動脈化学塞栓療法、放射線療法等）の適応となる肝細胞癌患者に対する本剤の有効性及び安全性は確立していない。

Kudo M, et al. Liver Cancer 2023.

Tumor responses (per RECICL) in subjects

ORR of LEN+TACE

Tumor response (Patient N=62)	CR, n (%)	PR, n (%)	SD, n (%)	PD, n (%)	ORR, n (%) (90% CI)
4 weeks after first TACE [a]	33 (53.2)	16 (25.8)	4 (6.5)	2 (3.2)	49 (79.0) (68.7 – 87.1)
Best response [b]	42 (67.7)	13 (21.0)	1 (1.6)	2 (3.2)	55 (88.7) (79.8 – 94.6)

a: Not evaluable: n=7, b: Not evaluable: n=4

DoR rate

DoR rate (n=55)	Best Response (%) PR (n=13)	Best Response (%) CR (n=42)	Overall (%)
6 months (90% CI) [a]	61.5 (36.0, 79.4)	95.1 (85.0, 98.4)	87.0 (77.1, 92.8)
12 months (90% CI) [a]	28.8 (10.4, 50.6)	57.2 (42.5, 69.5)	50.5 (38.2, 61.6)

LEN-TACE achieved 68% CR (Best response)

Duration of response was >12M in more than 50 % of patients

Kudo M, et al. Liver Cancer 2023.

TACTICS-L ORR Sub-group analysis (4 weeks after first TACE)

Category		n	ORR, n	90% CI	CR, n
Performance status, n (%)	0	59	47 (79.7%)	69.1%-87.8%	32 (54.2%)
	1	3	2 (66.7%)	13.5%-98.3%	1 (33.3%)
Etiology, n (%)	Hepatitis B	8	6 (75.0%)	40.0%-95.4%	5 (62.5%)
	Hepatitis C	20	15 (75.0%)	54.4%-89.6%	9 (45.0%)
	Non-B Non-C	31	25 (80.6%)	65.3%-91.2%	16 (51.6%)
Child-Pugh score, n (%)	5	51	43 (84.3%)	73.5%-91.9%	30 (58.8%)
	6	11	6 (54.5%)	27.1%-80.0%	3 (27.3%)
AFP, n (%)	<200 ng/mL	52	42 (80.8%)	69.6%-89.2%	28 (53.8%)
	≥200 ng/mL	10	7 (70.0%)	39.3%-91.3%	5 (50.0%)
Milan criteria, n (%)	Within	28	22 (78.6%)	62.0%-90.2%	18 (64.3%)
	Outside	34	27 (79.4%)	64.8%-89.9%	15 (44.1%)
Up to 7 criteria, n (%)	Within	40	30 (75.0%)	61.3%-85.8%	22 (55.0%)
	Outside	22	19 (86.4%)	68.4%-96.2%	11 (50.0%)
BCLC stage, n (%)	A	25	18 (72.0%)	53.8%-86.1%	16 (64.0%)
	B1	15	12 (80.0%)	56.0%-94.3%	6 (40.0%)
	B2	22	19 (86.4%)	68.4%-96.2%	11 (50.0%)
Prior TACE, n (%)	0	35	29 (82.9%)	68.9%-92.3%	19 (54.3%)
	1-2	26	19 (73.1%)	55.3%-86.6%	14 (53.8%)

Etiology: unknown n=3, Prior TACE: unknown n=1

Kudo M, et al. Liver Cancer 2023.

TACTICS-L ORR Sub-group analysis (4 weeks after first TACE)

Category		n	ORR, n	90% CI	CR, n
Performance status, n (%)	0	59	47 (79.7%)	69.1%-87.8%	32 (54.2%)
	1	3	2 (66.7%)	13.5%-98.3%	1 (33.3%)
Etiology, n (%)	Hepatitis B	8	6 (75.0%)	40.0%-95.4%	5 (62.5%)
	Hepatitis C	20	15 (75.0%)	54.4%-89.6%	9 (45.0%)
	Non-B Non-C	31	25 (80.6%)	65.3%-91.2%	16 (51.6%)
Child-Pugh score, n (%)	5	51	43 (84.3%)	73.5%-91.9%	30 (58.8%)
	6	11	6 (54.5%)	27.1%-80.0%	3 (27.3%)
AFP, n (%)	<200 ng/mL	52	42 (80.8%)	69.6%-89.2%	28 (53.8%)
	≥200 ng/mL	10	7 (70.0%)	39.3%-91.3%	5 (50.0%)
Milan criteria, n (%)	Within	28	22 (78.6%)	62.0%-90.2%	18 (64.3%)
	Outside	34	27 (79.4%)	64.8%-89.9%	15 (44.1%)
Up to 7 criteria, n (%)	Within	40	30 (75.0%)	61.3%-85.8%	22 (55.0%)
	Outside	22	19 (86.4%)	68.4%-96.2%	11 (50.0%)
	A	25	18 (72.0%)	53.8%-86.1%	16 (64.0%)
	B2	22	19 (86.4%)	68.4%-96.2%	11 (50.0%)
Prior TACE, n (%)	0	35	29 (82.9%)	68.9%-92.3%	19 (54.3%)
	1-2	26	19 (73.1%)	55.3%-86.6%	14 (53.8%)

Regardless of Up-to-7 in/out, CR rate was >50%

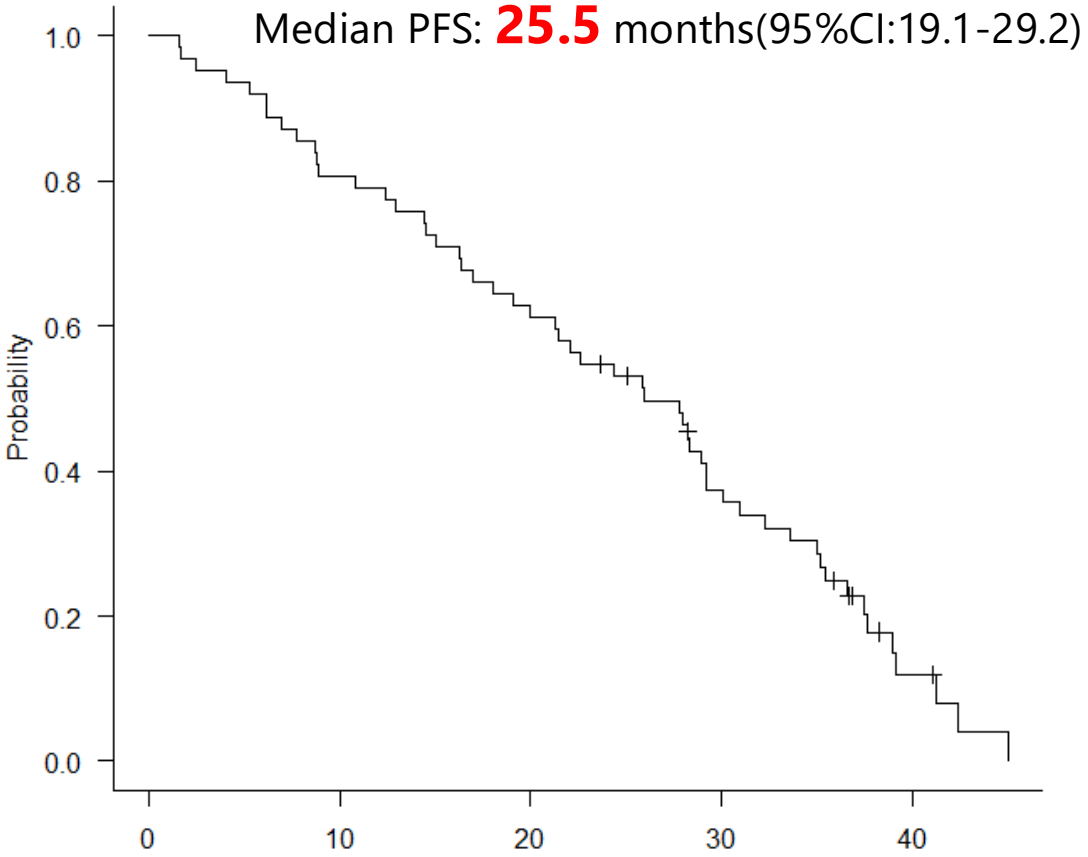
Etiology: unknown n=3, Prior TACE: unknown n=1

Kudo M, et al. Liver Cancer 2023.

Results of the interim follow-up analysis

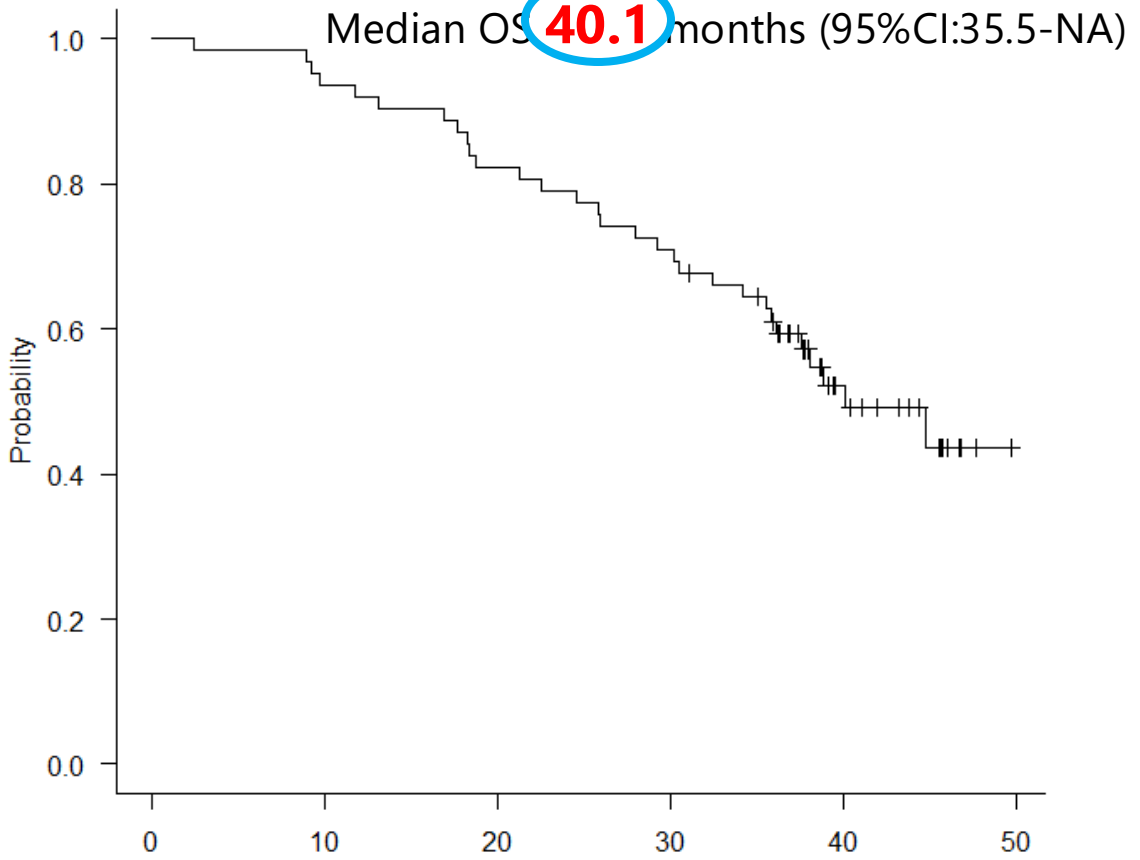
PFS

Median PFS: **25.5** months(95%CI:19.1-29.2)



OS

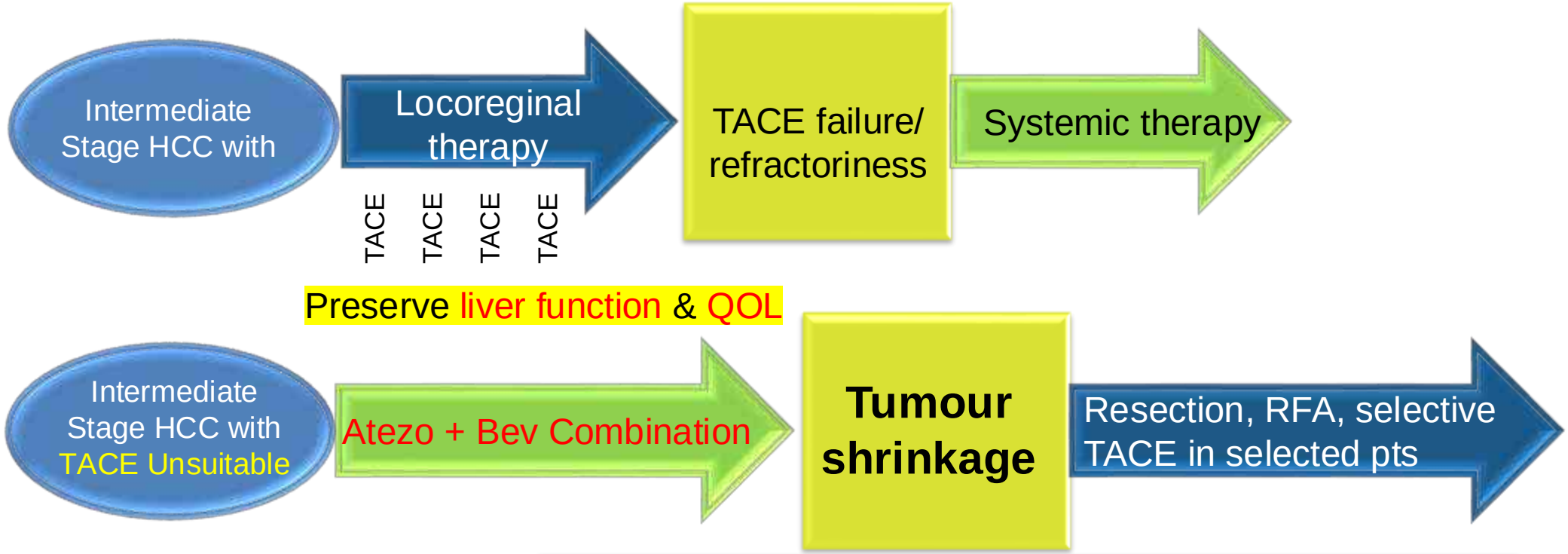
Median OS **40.1** months (95%CI:35.5-NA)



OS of 40.1 months in Intermediate-stage HCC is the longest in Prospective Trial.

Data cutoff, Apr 2023
Unpublished data

Atezo+Bev Curative Conversion Therapy



"ABC-Conversion therapy"

Cancer free with drug free

Kudo M et al, Liver Cancer 9: 367-377, 2020.

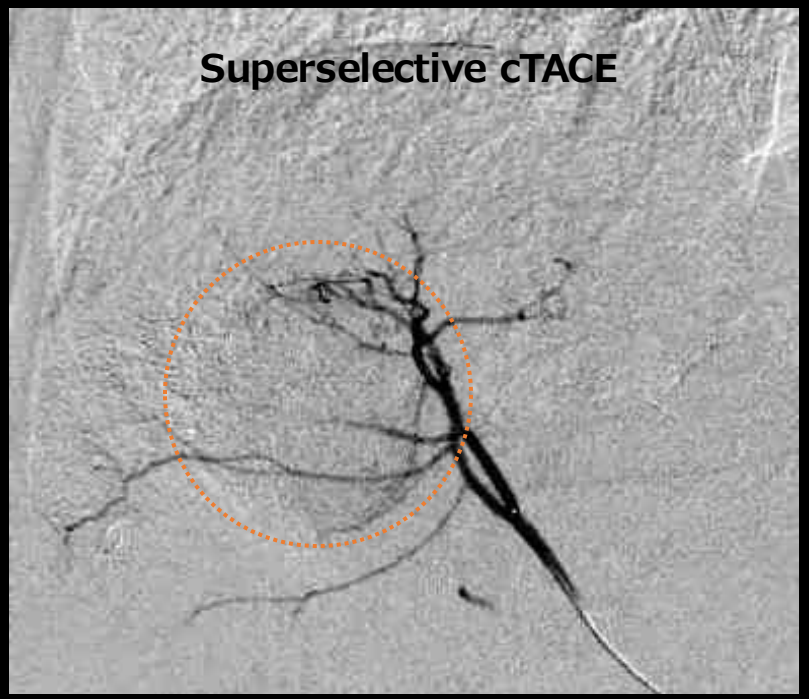
70s, NASH, BCLCB
S5: 45 mm, S7: 125 mm, Atz/Bev

Baseline	6 week	12 week
	mRECIST / RECIST v1.1	mRECIST / RECIST v1.1
S5: 45 mm	SD / SD	PR / SD
S7: 125 mm	Pseudoprogression like / SD	PR / PR

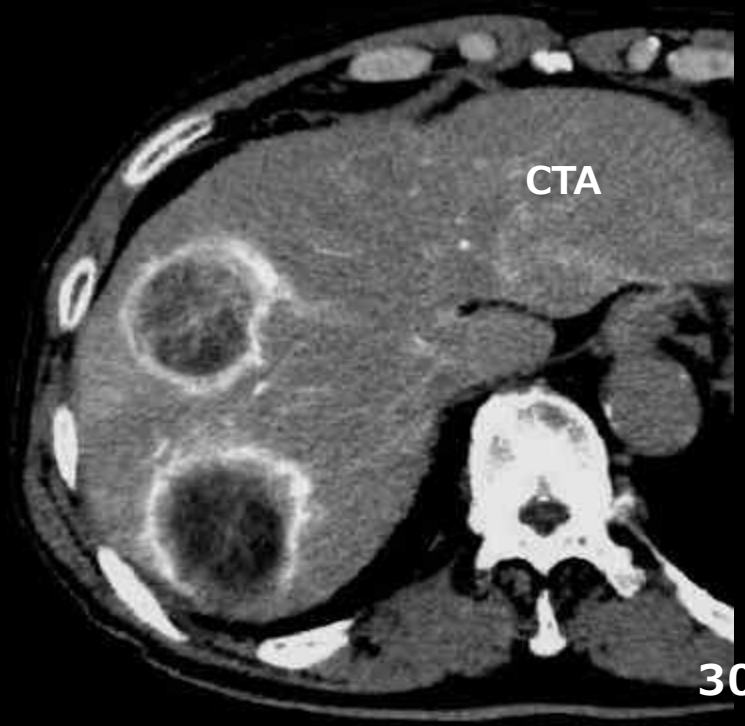
Courtesy: Dr. Abe and Kuroda, Iwate Medical University

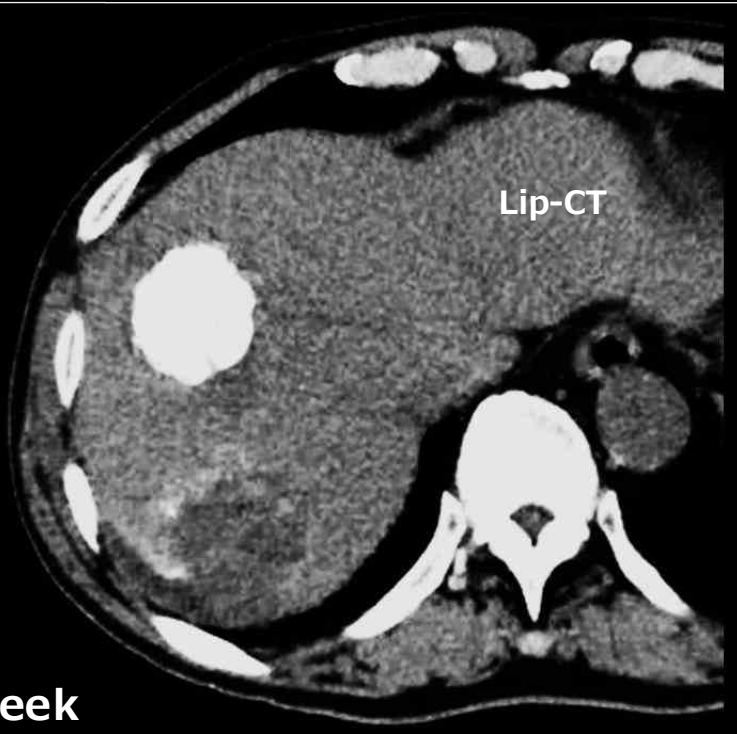
70s, NASH, BCLCB
S5: 45 mm, S7: 125 mm, Atz/Bev
conventional TACE

	6 week	12 week	30 week
	mRECIST / RECISTv1.1	mRECIST / RECISTv1.1	RECICL
S5: 45 mm	SD / SD	PR / SD	CR
S7: 125 mm	Pseudoprogression like / SD	PR / PR	PR



28 week



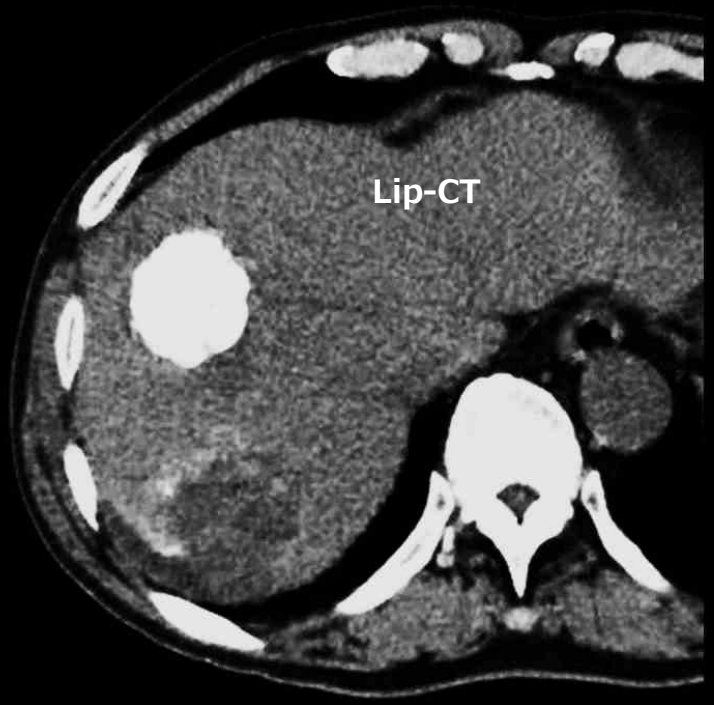


30 week

Courtesy: Dr. Abe and Kuroda, Iwate Medical University

70s, NASH, BCLCB
S5: 45 mm, S7: 125 mm, Atz/Bev
ABC conversion(MWA) → Drug free

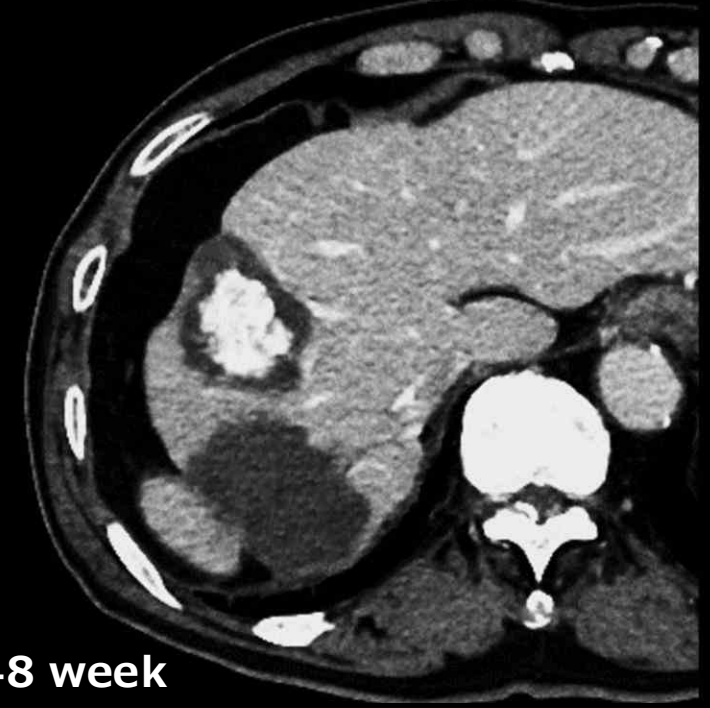
	6 week	12 week	30 week	48 week
	mRECIST / RECISTv1.1	mRECIST / RECISTv1.1	RECICL	RECICL
S5: 45 mm	SD / SD	PR / SD	CR	CR
S7: 125 mm	Pseudoprogression like / SD	PR / PR	PR	CR



30 week

Microwave Ablation

40 week



48 week

Courtesy: Dr. Abe and Kuroda, Iwate Medical University

Proof-of-Concept Study: ABC conversion therapy

Liver Cancer

Research Article

Liver Cancer
DOI: 10.1159/000529574

Received: August 15, 2022
Accepted: February 1, 2023
Published online: February 7, 2023

Achievement of Complete Response and Drug-Free Status by Atezolizumab plus Bevacizumab Combined with or without Curative Conversion in Patients with Transarterial Chemoembolization-Unsuitable, Intermediate-Stage Hepatocellular Carcinoma: A Multicenter Proof-Of-Concept Study

Masatoshi Kudo[a] Tomoko Aoki[a] Kazuomi Ueshima[a] Kaoru Tsuchiya[b]
Masahiro Morita[a] Hirokazu Chishina[a] Masahiro Takita[a] Satoru Hagiwara[a]
Yasunori Minami[a] Hiroshi Ida[a] Naoshi Nishida[a] Chikara Ogawa[c]
Tetsu Tomonari[d] Noriaki Nakamura[e] Hidekatsu Kuroda[f] Atsushi Takebe[g]
Yoshifumi Takeyama[g] Masaaki Hidaka[h] Susumu Eguchi[h] Stephen L Chan[i]
Masayuki Kurosaki[b] Namiki Izumi[b]

7 Multicentre study

Kindai U. [n=38], MRCH [n=36] , SGH [n=10], Tokushima U[n=13], TRCH [n=9], Nagasaki U [2], Iwate U [4]

TACE Unsuitable Intermediate-stage
Child-Pugh A
1st line Atezo+Bev
Consecutive cases [n=**110**]

↓

Curative Conversion

【Endpoints】CR rate, drug-free rate, time to CR, change in liver function, efficacy in PET-positive HCC, PFS, and

Kudo M, Aoki T, Ueshima, et al. Liver Cancer 2023.

ABC Conversion rate in Intermediate-stage HCC

TACE Unsuitable Intermediate-stage HCC
(1st line Atezo+Bev, Child-Pugh A, Consecutive cases [n=**110**])

Atezo + Bev → Curative Conversion +/- Locoregional Tx/Op

- Resection 7
- Ablation (TACE→RFA/MWA) 13
- TACE or LEN-TACE 15
- Atezo+Bev only 3

38

Cancer Free Rate 35% (38/110)

(Drug free rate **23%** [n=25/110])

7 Multicenter study (Kindai U. [n=38], MRCH [n=36] , SGH [n=10], Tokushima U[n=13], TRCH [n=9], Nagasaki U [2], Iwate U [4])

Kudo M, et al. Liver Cancer 2023, https://doi.org/10.1159/000529574

Drug-Off Criteria in Patients with Hepatocellular Carcinoma Who Achieved Clinical Complete Response after Combination Immunotherapy Combined with Locoregional Therapy

Masatoshi Kudo

Department of Gastroenterology and Hepatology, Kindai University Faculty of Medicine, Osaka-Sayama, Japan

Keywords
Hepatocellular carcinoma · Systemic therapy · Locoregional therapy · Clinical complete response · Drug-off criteria

Introduction

Hepatocellular carcinoma (HCC) is refractory to treatment under the following conditions: (A) a large number of

Prof. M. Kudo

Editor *Liver Cancer*

Kudo M. Liver Cancer 2023

Drug-off Criteria (Clinical CR [close to pCR])

Achievement of drug free status is highly suggestive of pCR

① CR (RECIST/mRECIST) on imaging (CT/MRI)

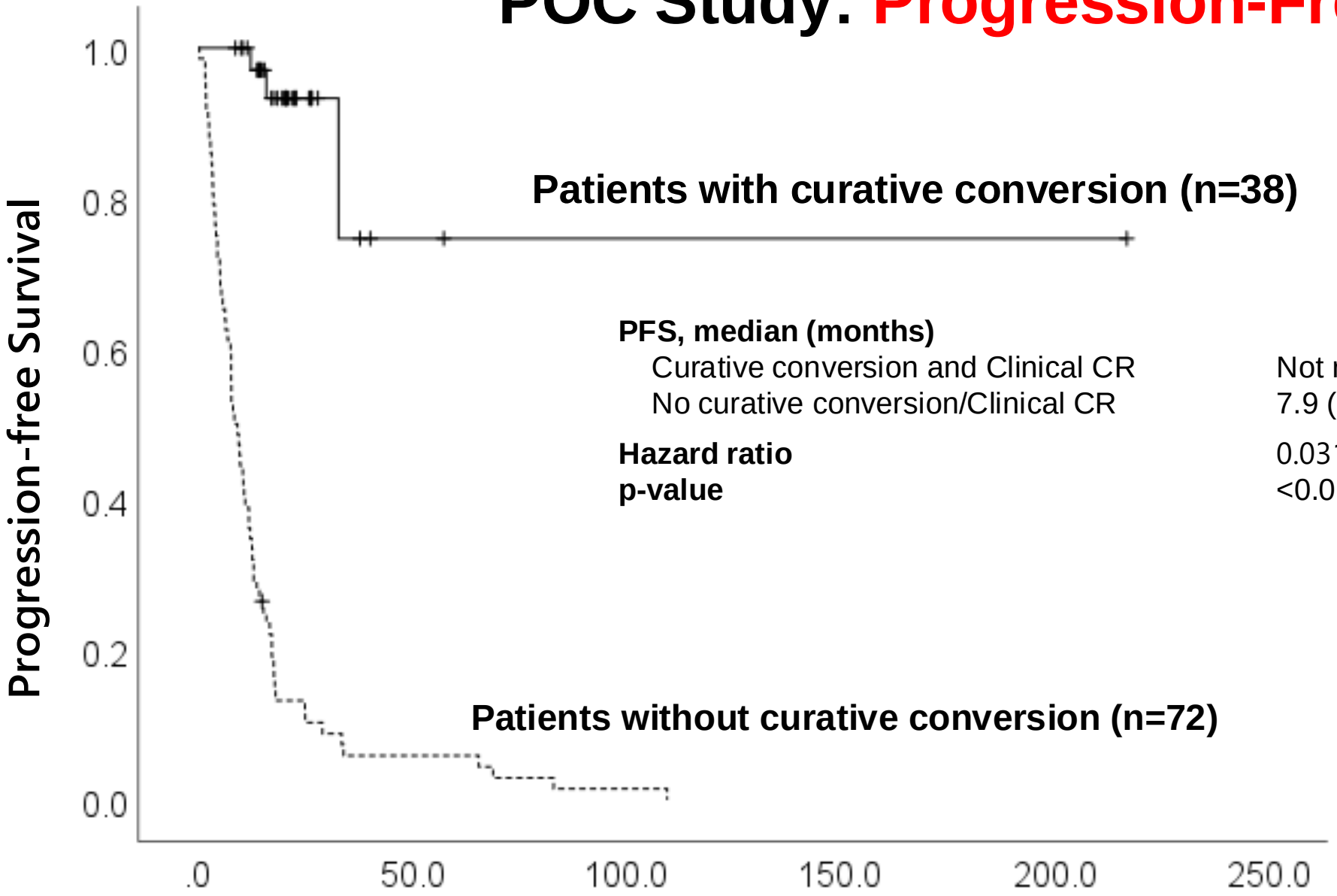
② Normalized all 3 TMs (AFP, DCP, AFP-L3) （>12–24 weeks）

③ No intratumoral arterial flow on Contrast-enhanced US (CEUS)

Consider Drug-off when all of 3 conditions are fulfilled.

Kudo M. Liver Cancer 2023

POC Study: Progression-Free Survival

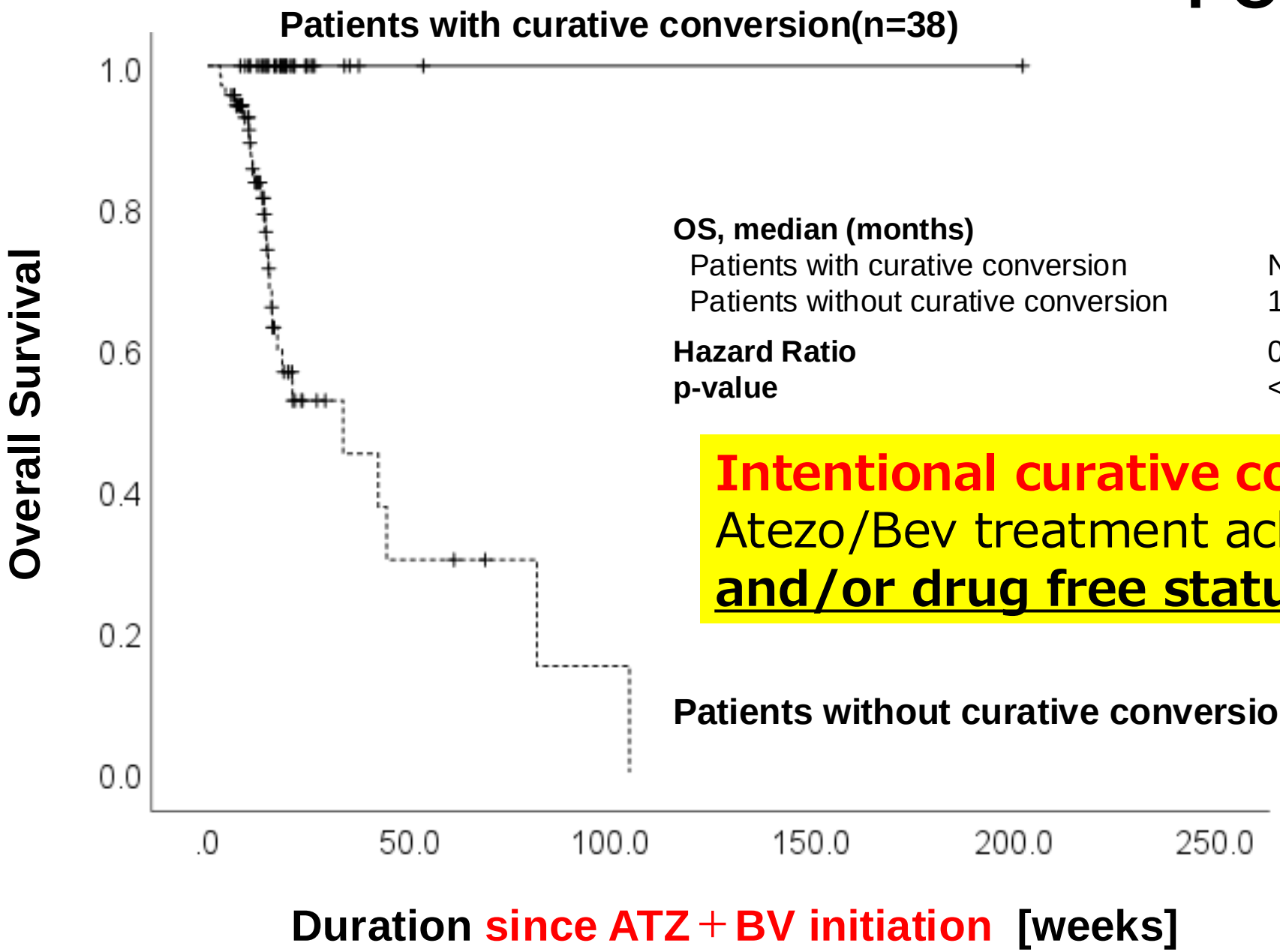


PFS, median (months)	
Curative conversion and Clinical CR	Not reached
No curative conversion/Clinical CR	7.9 (95%CI：6.3 – 10.7)
Hazard ratio	0.031 (95%CI：0.013 – 0.136)
p-value	<0.001

Duration of follow up: 21.2 months

Kudo M, et al. Liver Cancer 2023, https://doi.org/10.1159/000529574

POC Study: OS



OS, median (months)	
Patients with curative conversion	Not reached
Patients without curative conversion	18.5 (95%CI：13.4-23.7)
Hazard Ratio	0.016 (95%CI：0.001-0.391
p-value	<0.001

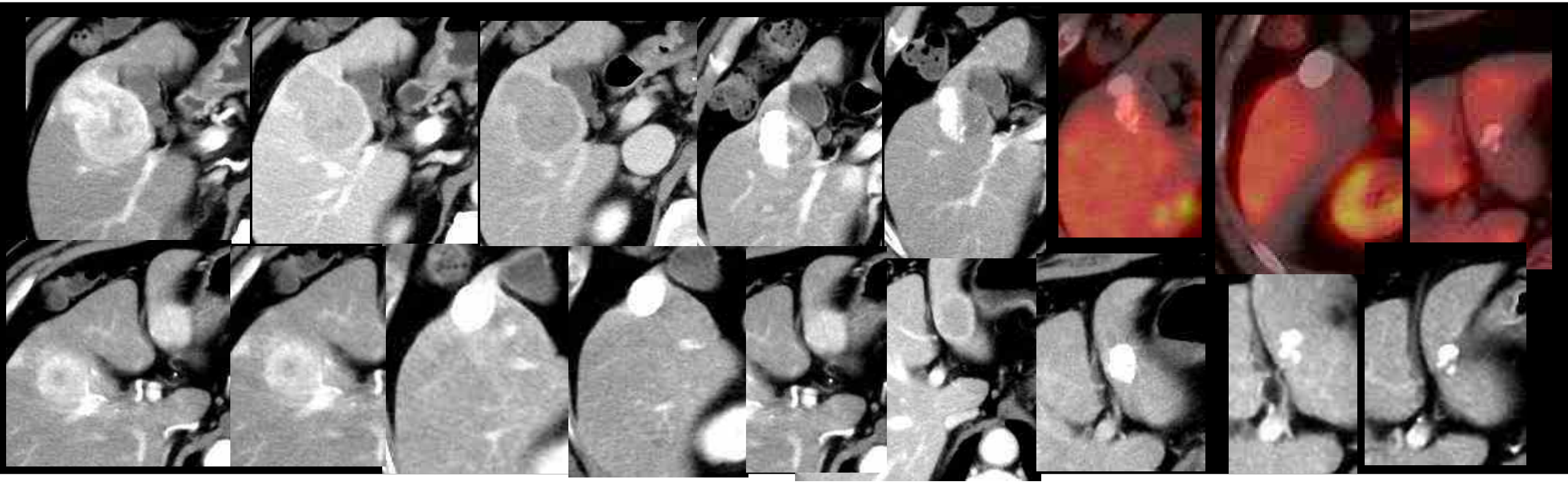
Intentional curative conversion during Atezo/Bev treatment achieves **Clinical CR and/or drug free status**

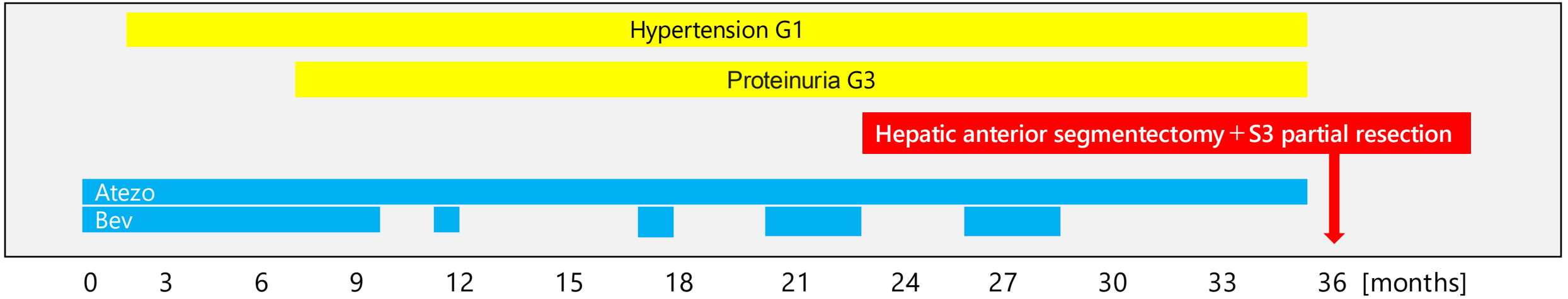
Patients without curative conversion (n=72)

Duration of follow up: 21.2 months

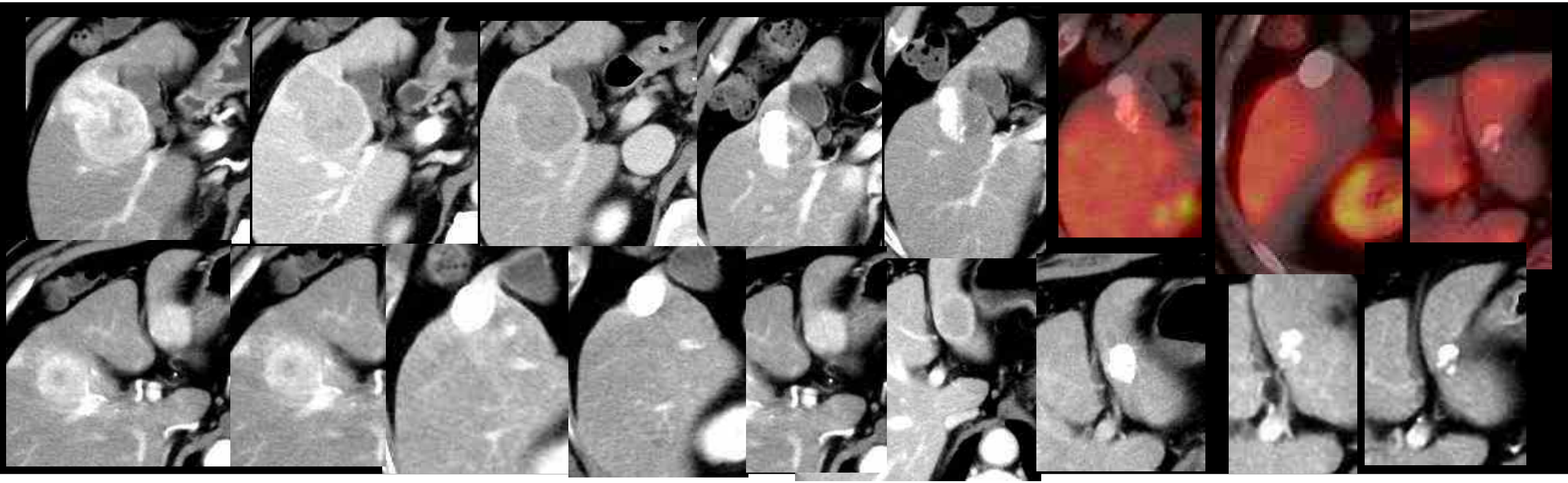
Kudo M, et al. Liver Cancer 2023, https://doi.org/10.1159/000529574

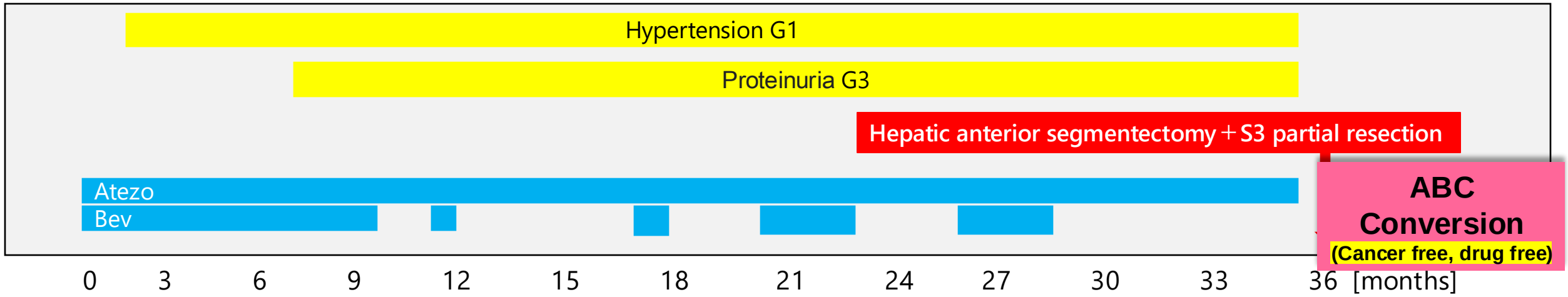
■60s, male　BCLC stage B (UT7-out) IO combination+ cTACE →Resection





■60s, male　BCLC stage B (UT7-out) IO combination+ cTACE →Resection

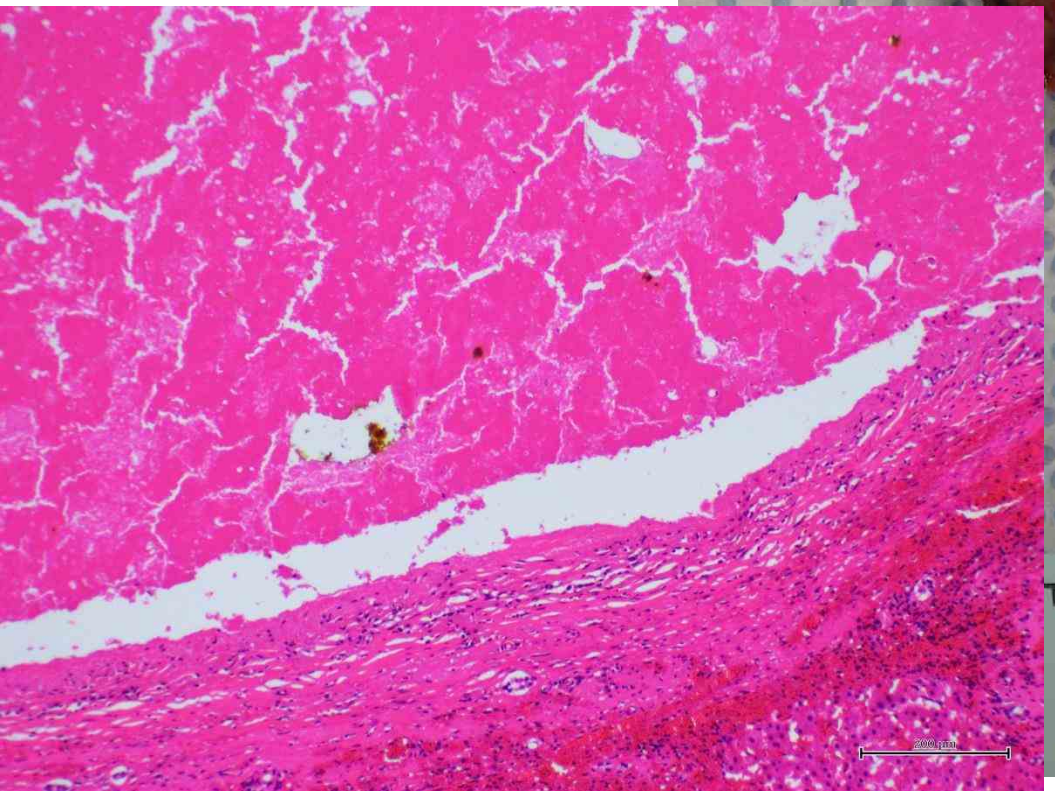




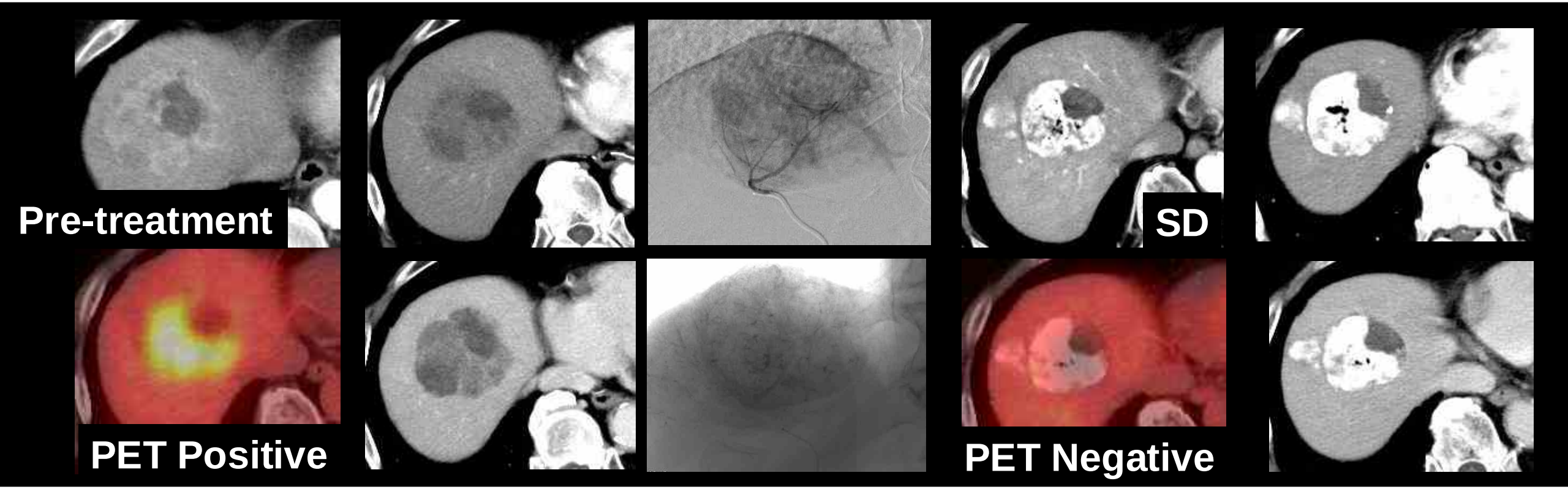
S3

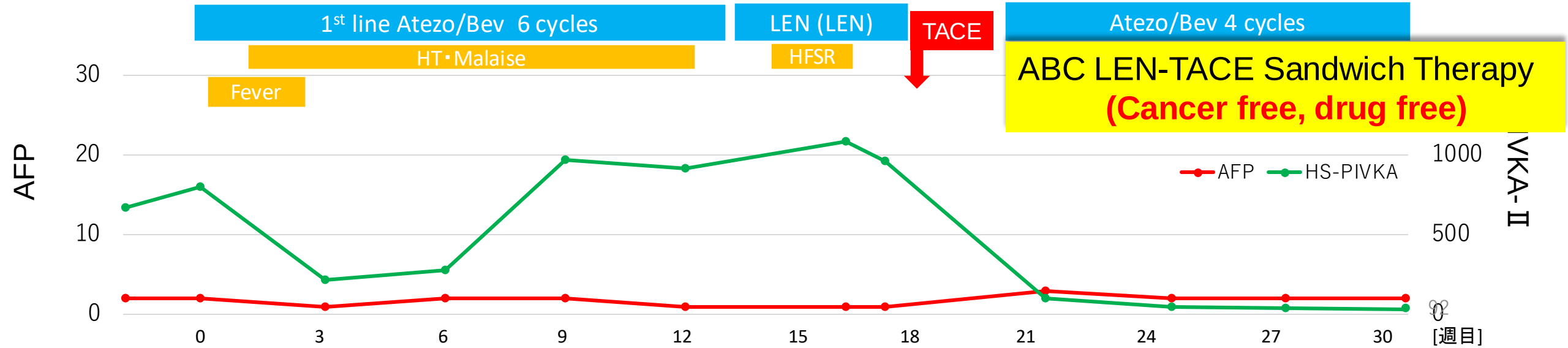
Ant seg.

Complete necrosis in all 3 nodules (Pathological CR)

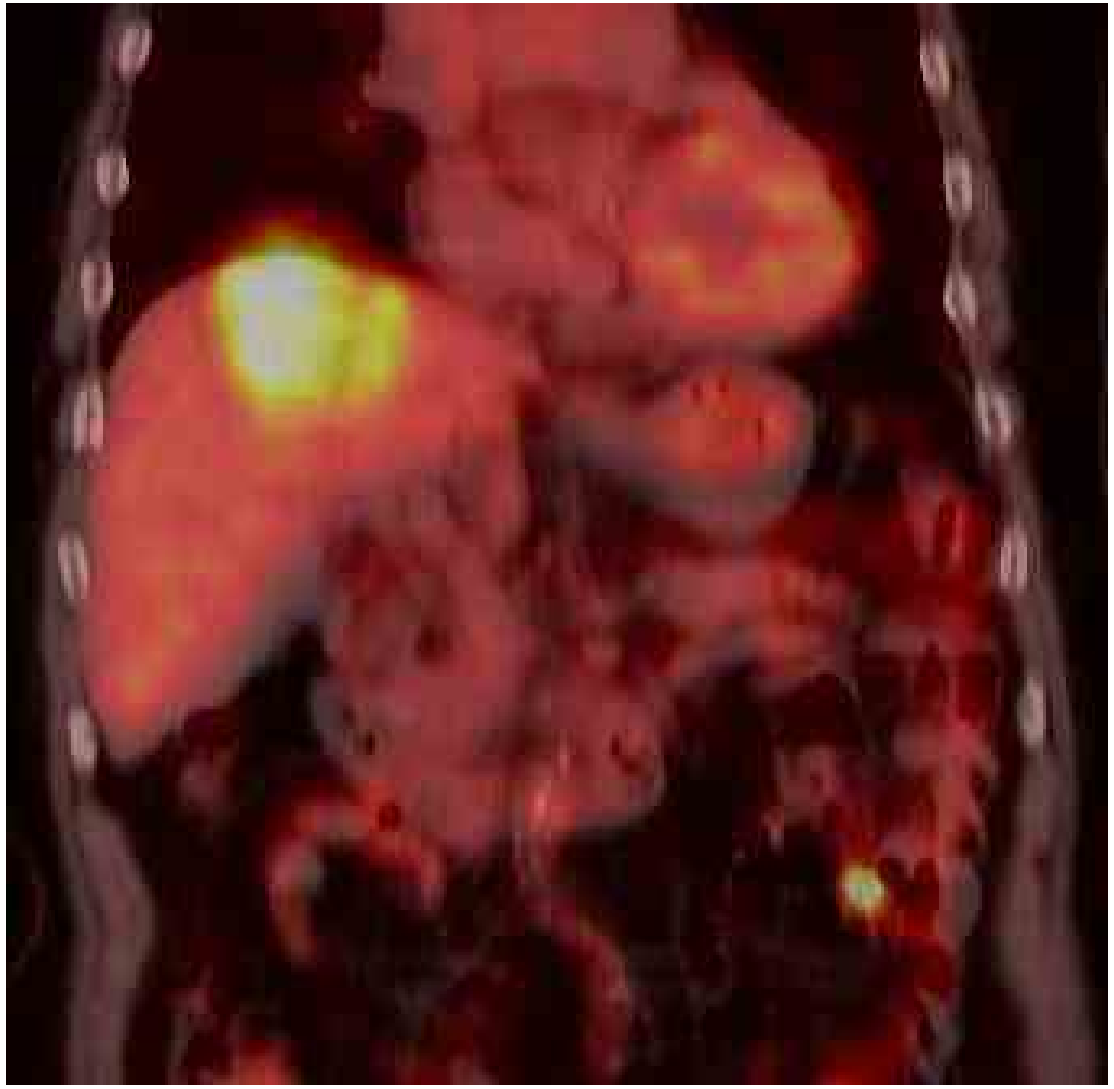


70s, Male, NBNC (alcohol), S8 63mm, solitary, BCLC stage B HCC

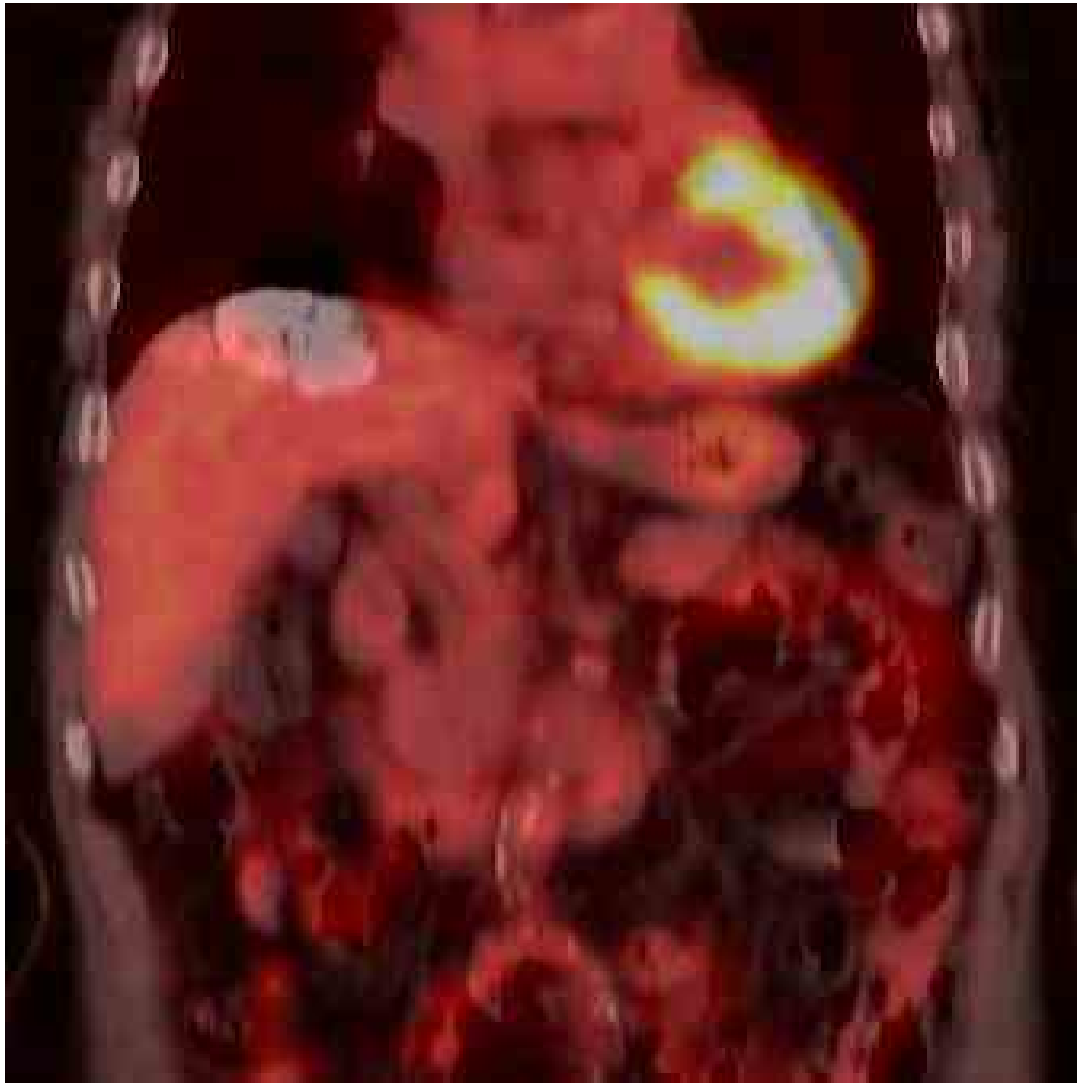




Before Treatment

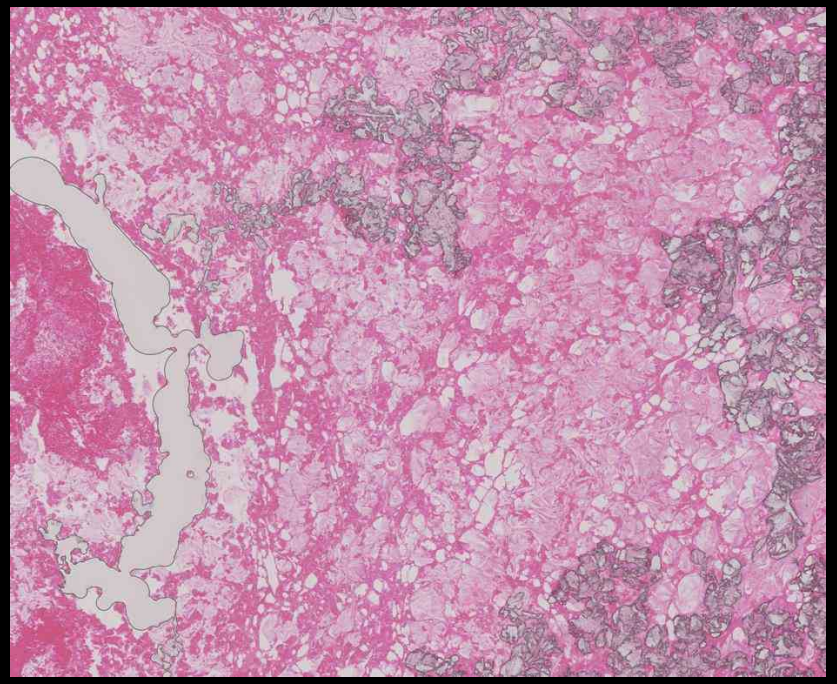


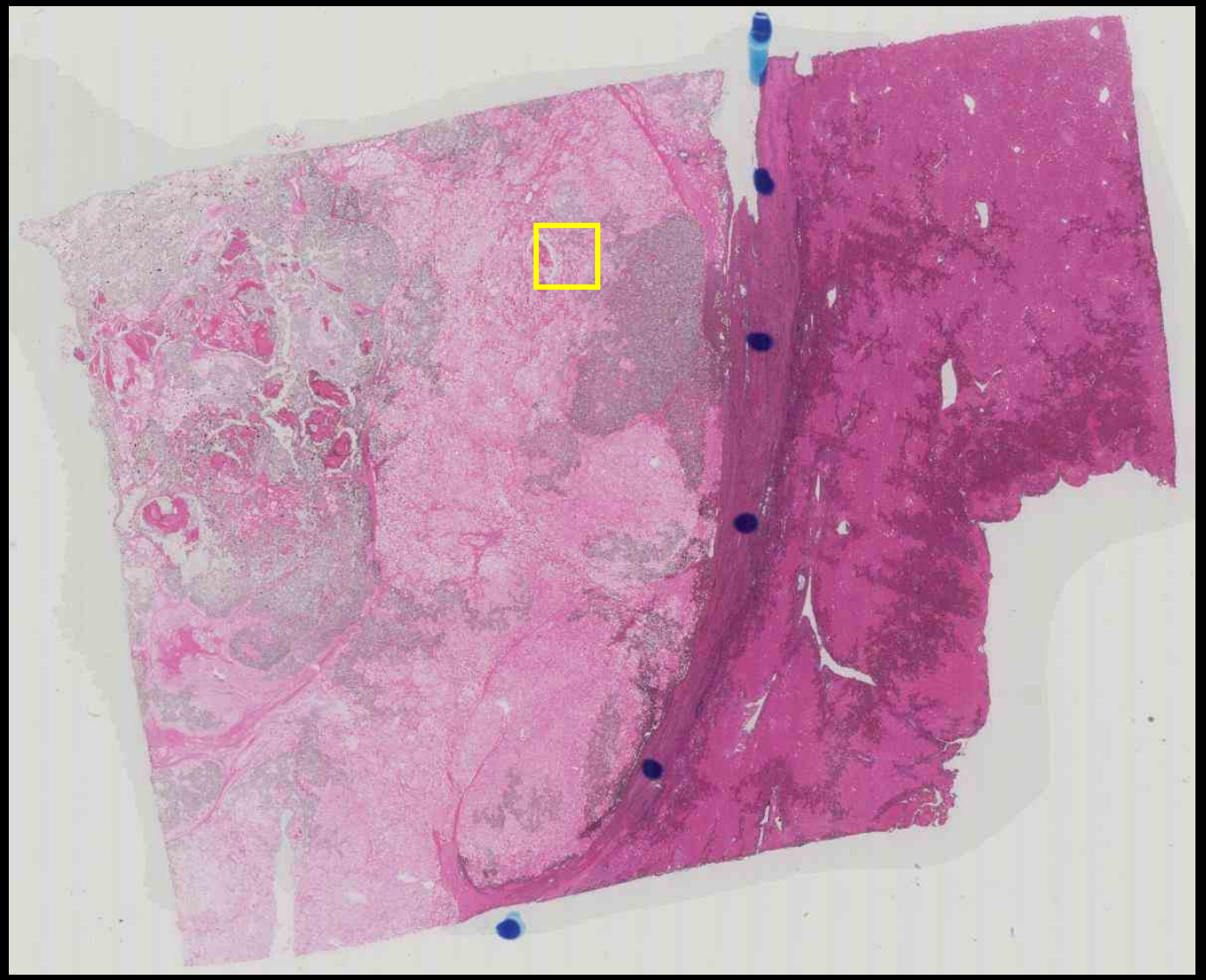
After ABC TACE Sandwich Therapy



Decreased FDG uptake
Tumor shrinkage

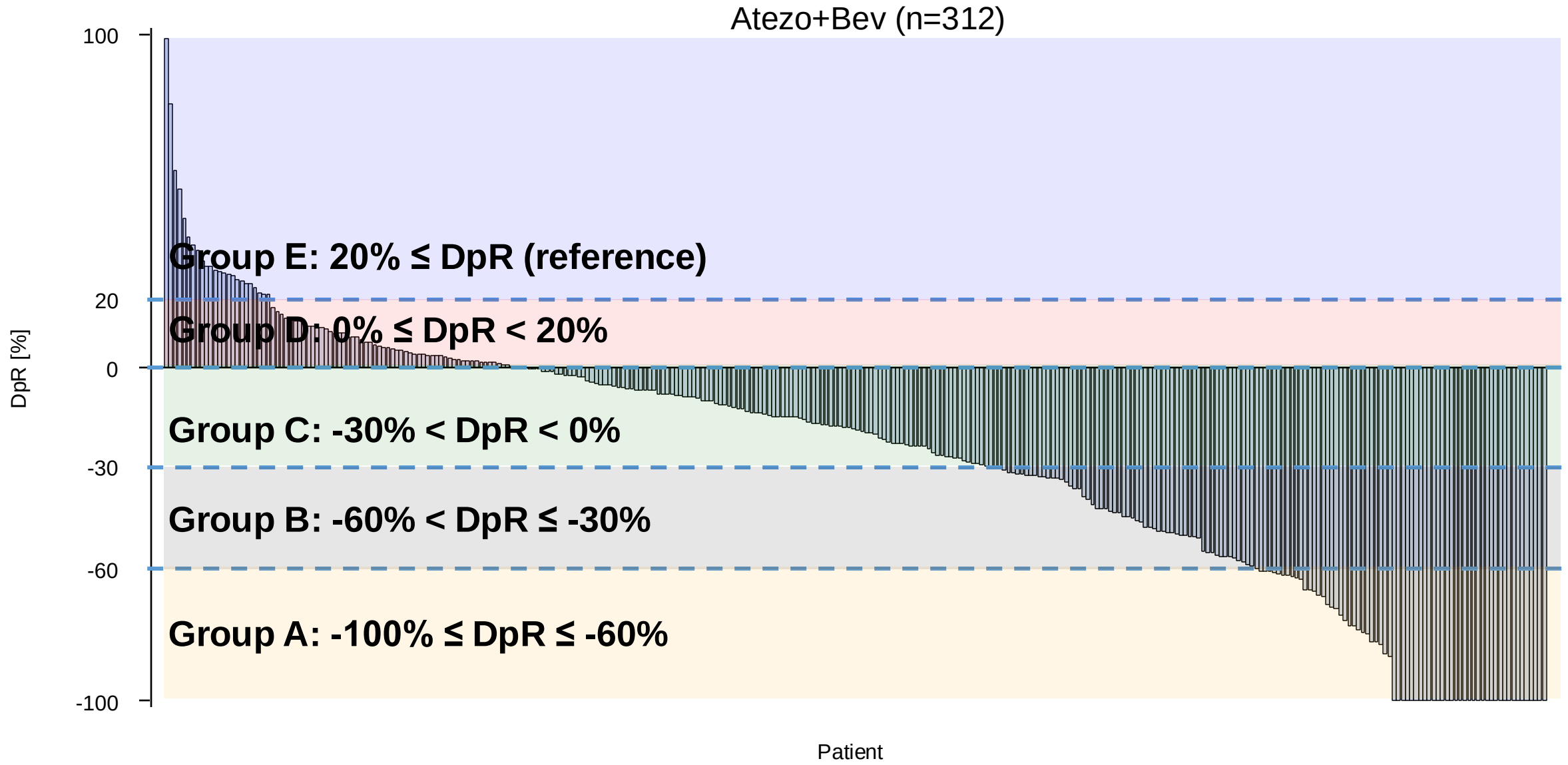
Laparoscopic subsegmentectomy





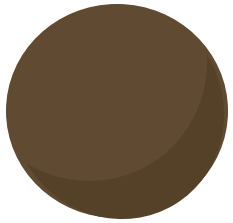
Pathological CR

IMbrave150: Survival analysis by DpR subgroups



Survival analysis by DpR subgroups

Baseline



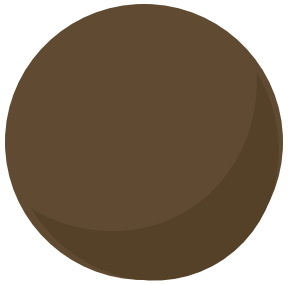
After Atezo+Bev administration

OS / PFS comparison in five DpR subgroups

PD

Group E

20% ≤ DpR (reference)



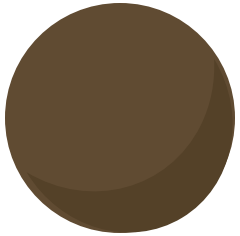
DpR +30%

vs

SD No-shrinkage

Group D

0% ≤ DpR < 20%



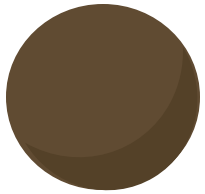
DpR +10%

vs

SD Shrinkage

Group C

-30% < DpR < 0%



DpR −10%

vs

Modest Response

Group B

-60% < DpR ≤ -30%

DpR −40%

vs

Deep Response

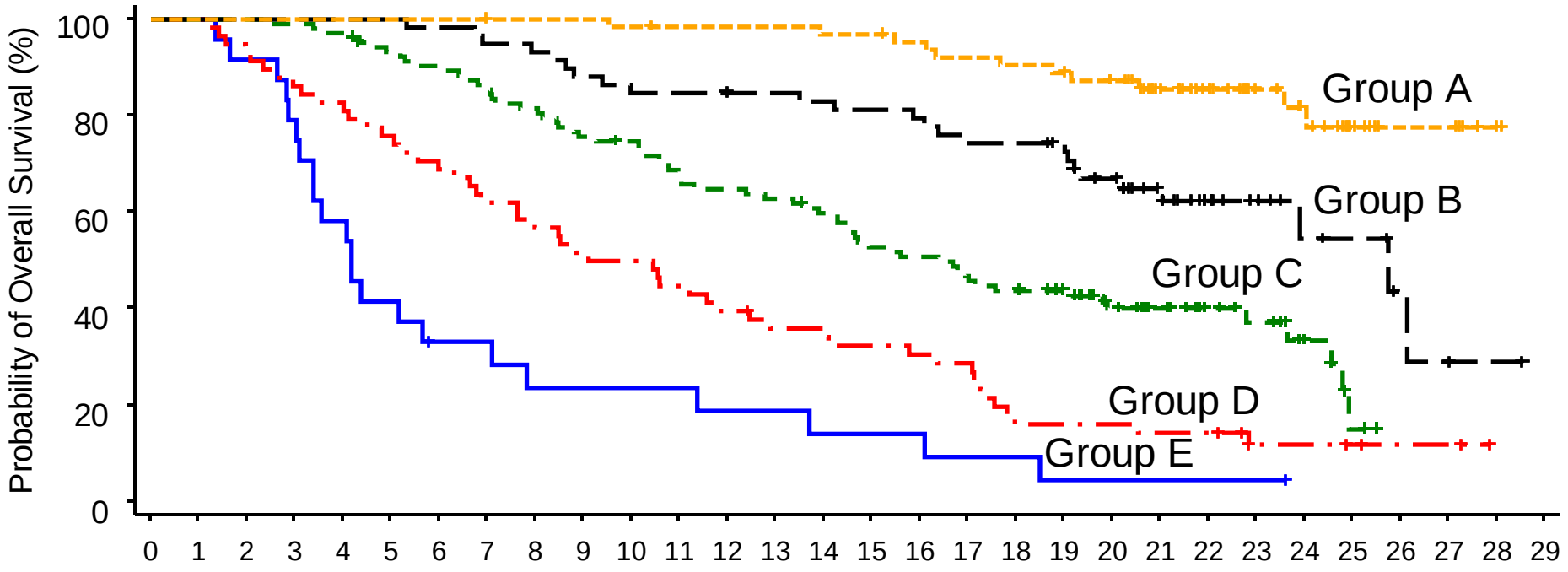
Group A

-100% ≤ DpR ≤ -60%

DpR −80%

Kaplan-Meier Plot of Overall Survival by Depth of Response based on IRF-Assessment per RECIST v1.1: IMbrave150 exploratory analysis

Protocol: YO40245
Analysis: Atezo + Bev arm, Measurable Disease at Baseline per IRF RECIST v1.1, Intent-to-Treat Population

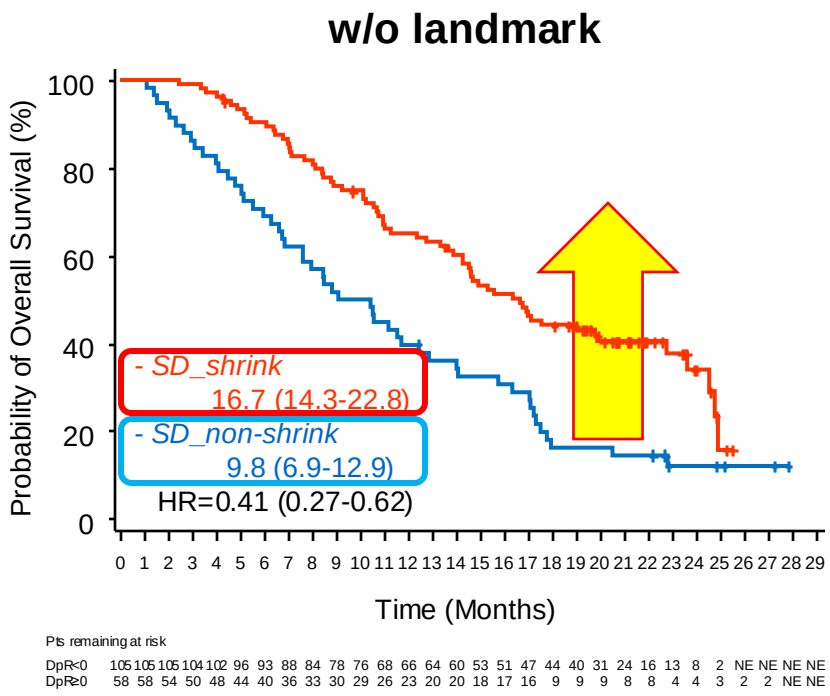


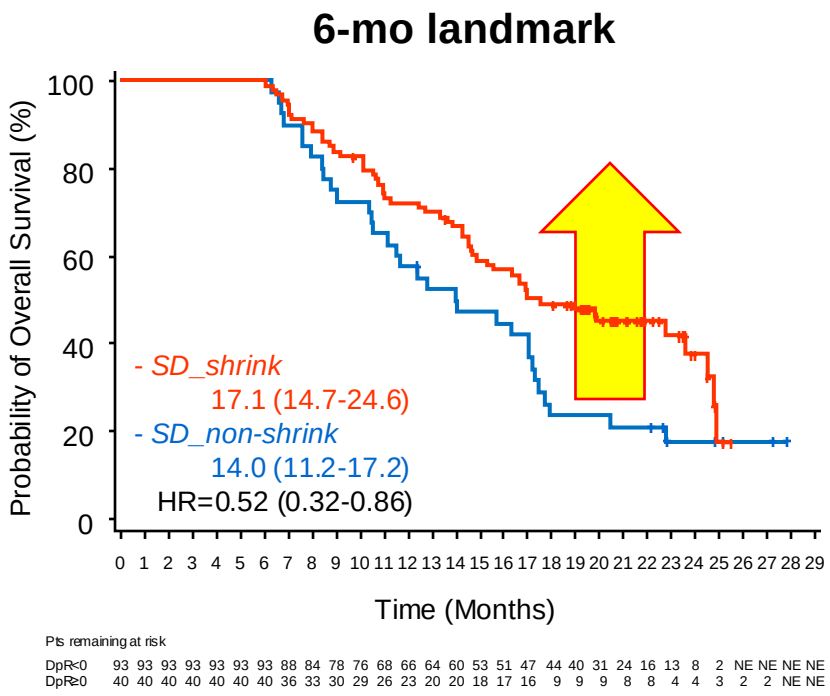
Pts remaining at risk																													
-100 ≤ DpR ≤ -60	66	66	66	66	66	66	66	65	65	65	64	63	63	63	62	62	60	58	57	56	52	41	34	24	20	12	7	7	1	NE
-60 < DpR ≤ -30	59	59	59	59	59	59	58	56	55	52	50	50	49	49	48	47	46	43	43	41	34	25	16	11	7	6	3	2	1	NE
-30 < DpR < 0	105	105	105	104	102	96	93	88	84	78	76	68	66	64	60	53	51	47	44	40	31	24	16	13	8	2	NE	NE	NE	NE
0 ≤ DpR < 20	58	58	54	50	48	44	40	36	33	30	29	26	23	20	20	18	17	16	9	9	9	8	8	4	4	3	2	2	NE	NE
DpR ≥ 20	24	24	22	19	14	10	7	7	5	5	5	5	4	4	3	3	3	2	2	1	1	1	1	1	NE	NE	NE	NE	NE	NE

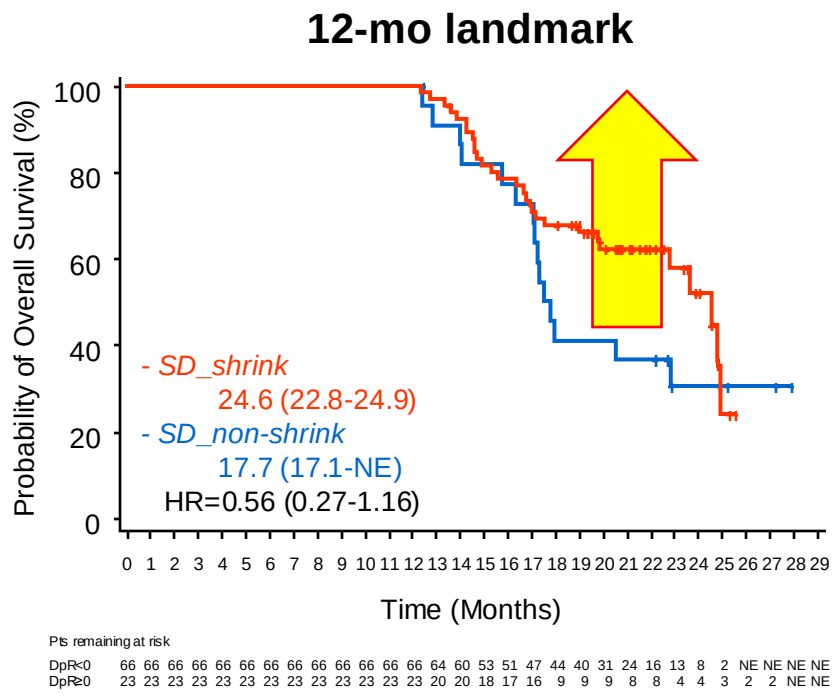
Kudo M, et al. Manuscript under review 2024

OS by DpR in pts receiving atezo+bev
SD shrink vs *SD* non-shrink population

SD patients with growing tumors have poor prognosis
⇒ These patients may require early LRT such as TACE.



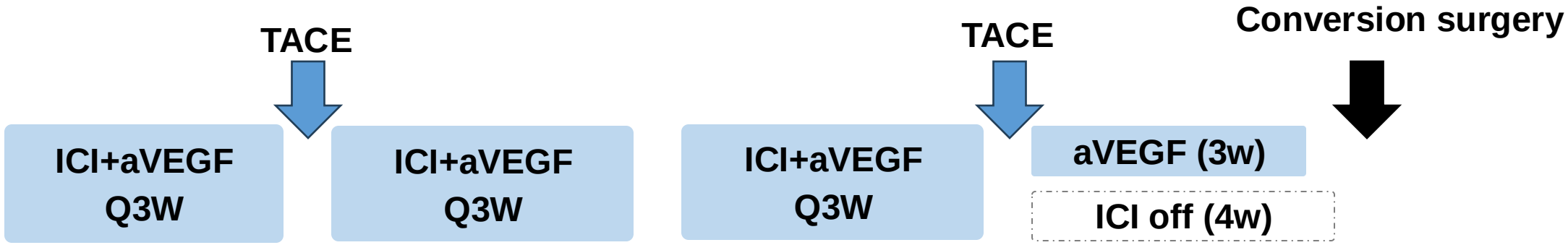




Kudo M, et al. ESMO Asia 2023; Kudo M, et al. Manuscript under review 2024.

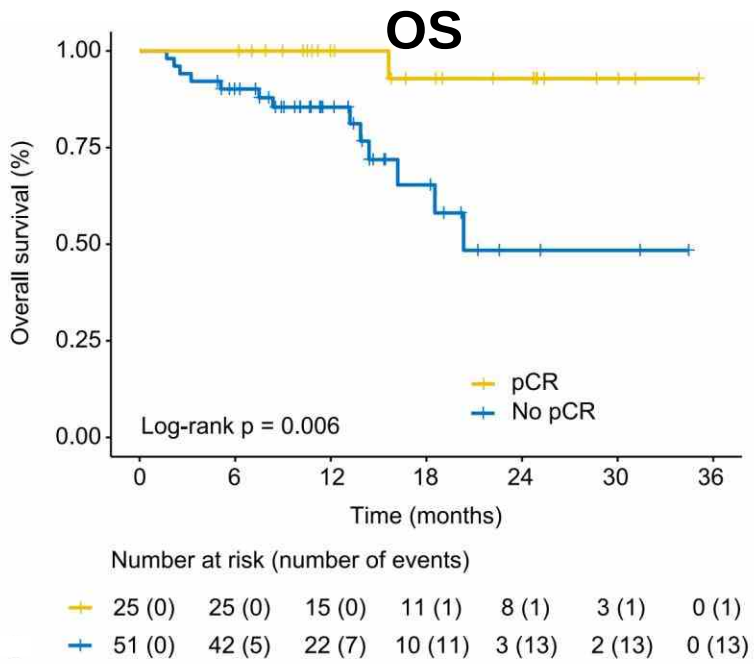
Conversion surgery after ICI+aVEGF+TACE

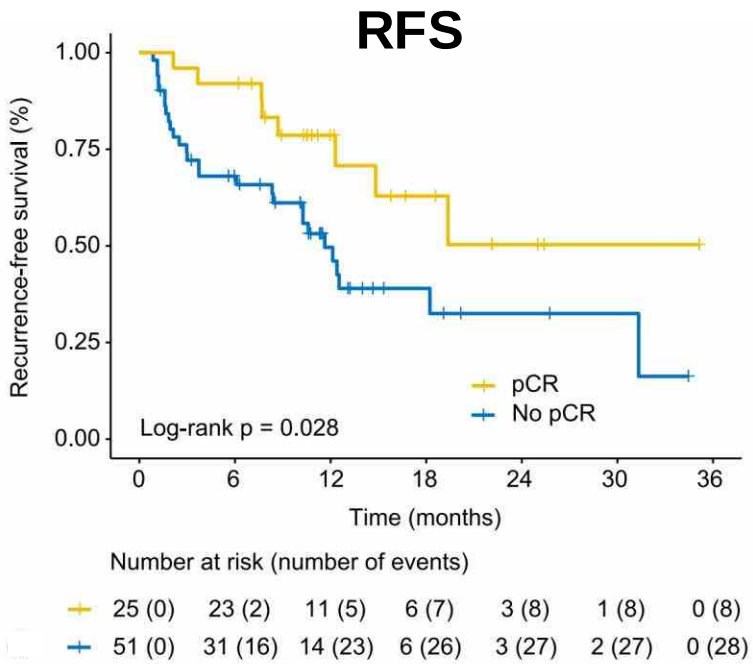
Treatment schedule



Characteristic	N=76
BCLC-C	52 (69%)
AFP ≥400ng/mL	46 (61%)
MVI, yes	52 (68%)
Maximum tumor size ≥ 10cm	33 (43%)

pCR rate : 32.9%

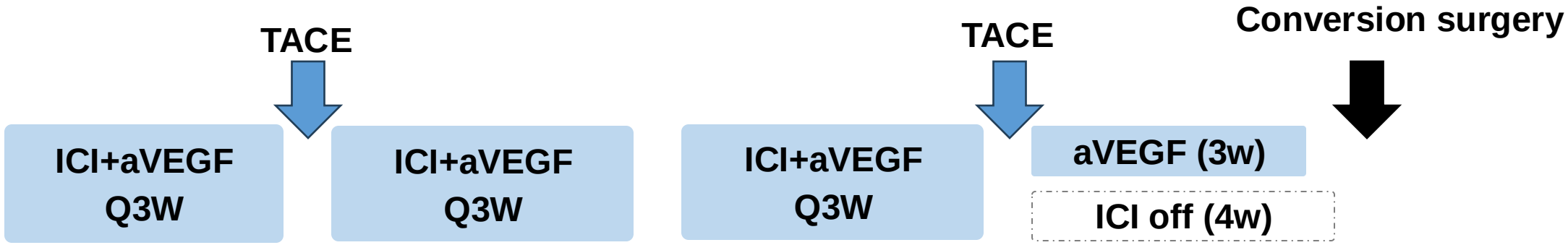




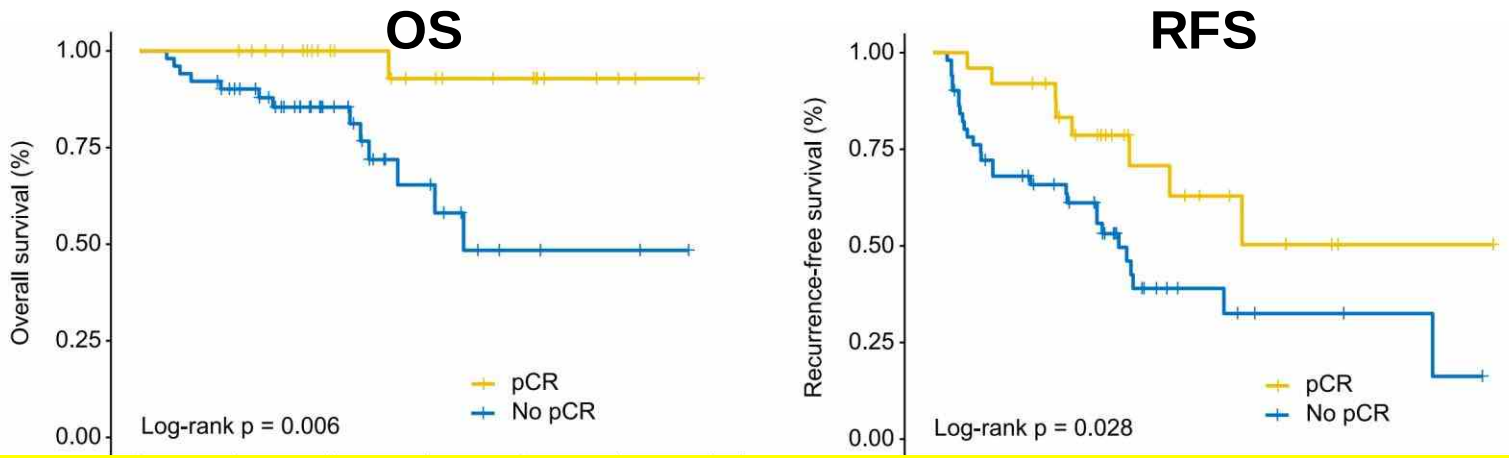
Zhen ZX, et al.: Liver Cancer 2024;13:498–508.

Conversion surgery after ICI+aVEGF+TACE

Treatment schedule



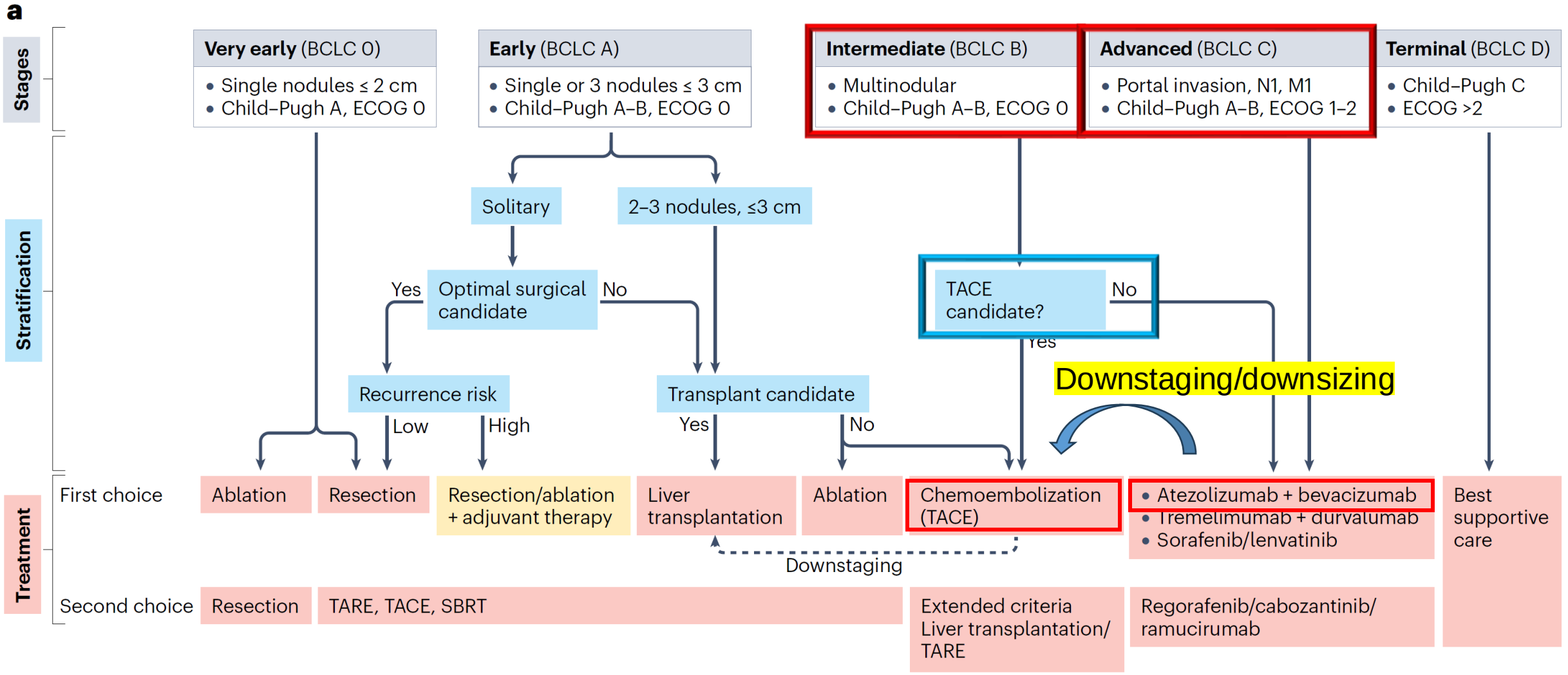
Characteristic	N=76
BCLC-C	52 (69%)
AFP ≥400ng/mL	46 (61%)
MVI, yes	52 (68%)
Maximum tumor size ≥ 10cm	33 (43%)



ICI+aVEGF⇒TACE⇒ICI+aVEGF before conversion surgery achieves high rate of pathological CR

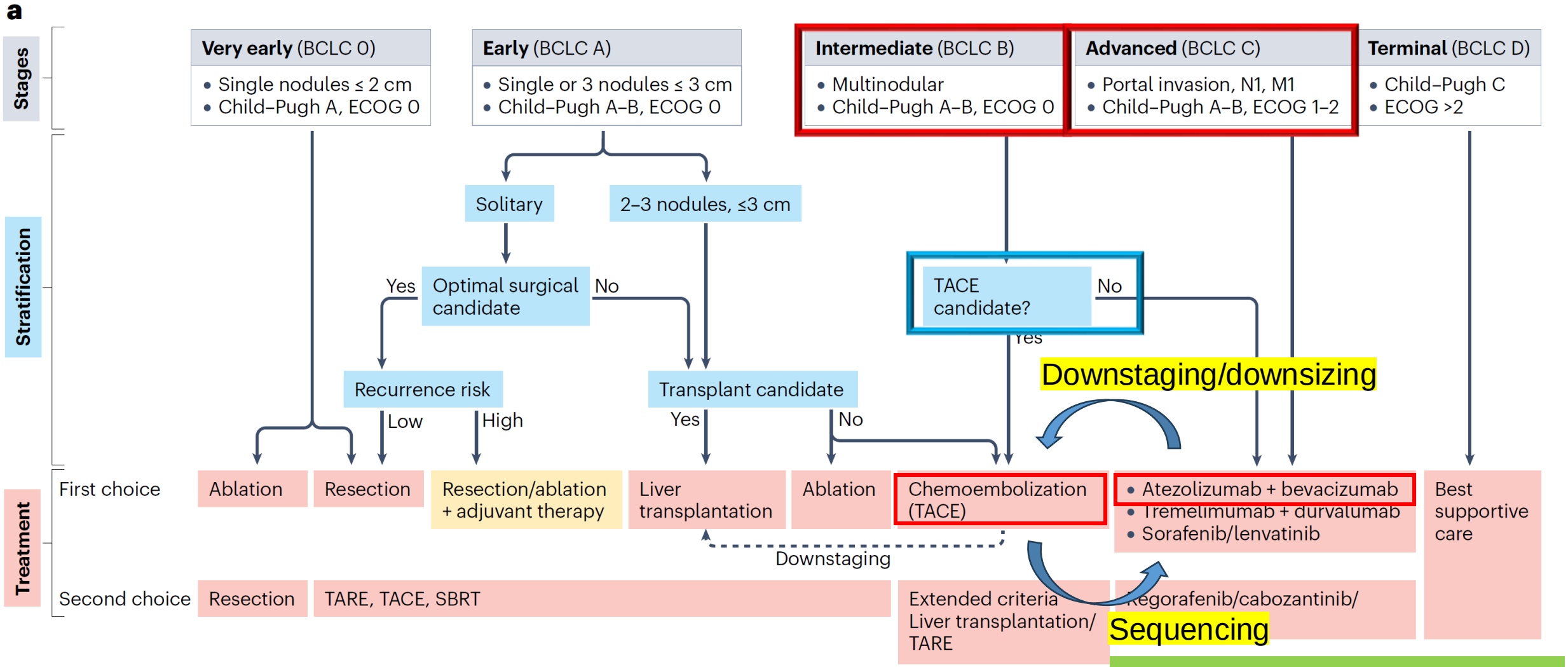
Zhen ZX, et al.. Liver Cancer 2024;13:498–508.

BCLC Staging (Modified) and Treatment Strategy



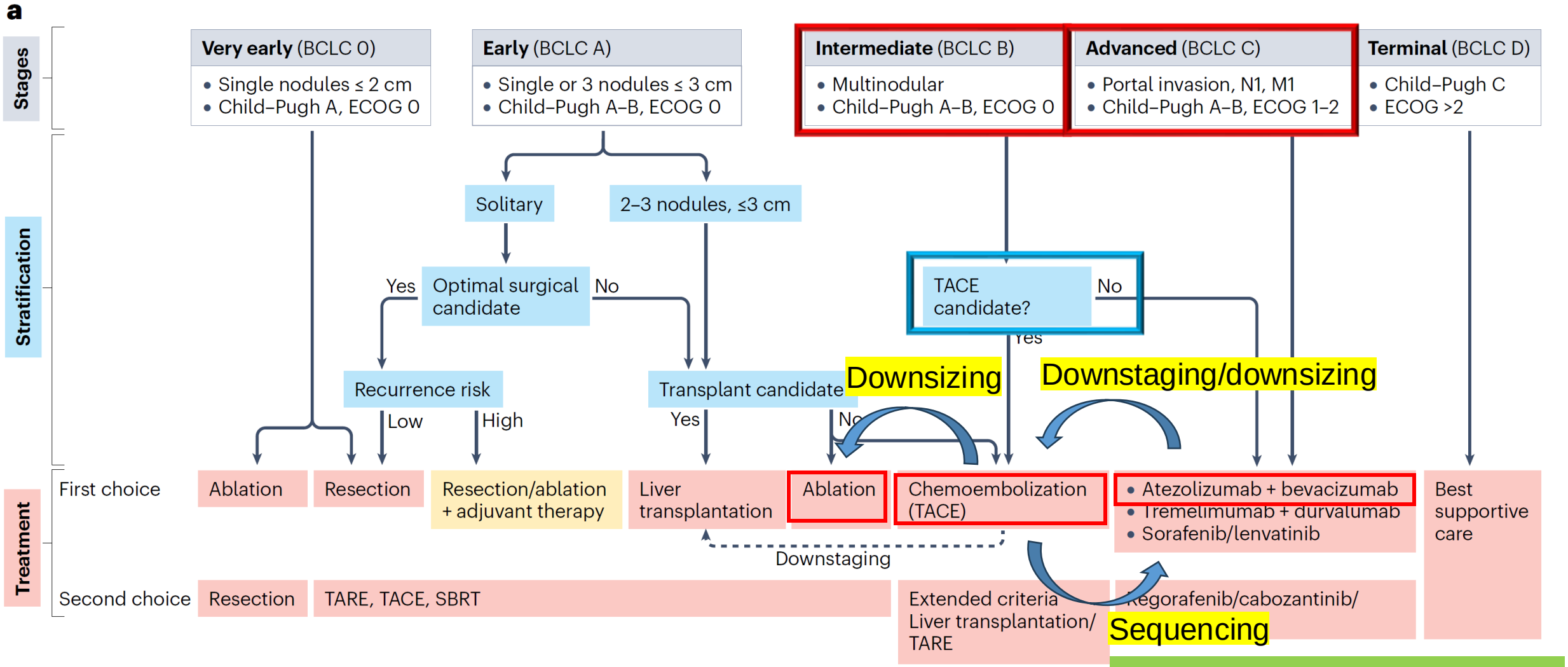
Llovet JM, Kudo M, et al. Nature Review Clin Oncol 2024

BCLC Staging (Modified) and Treatment Strategy



Llovet JM, Kudo M, et al. Nature Review Clin Oncol 2024

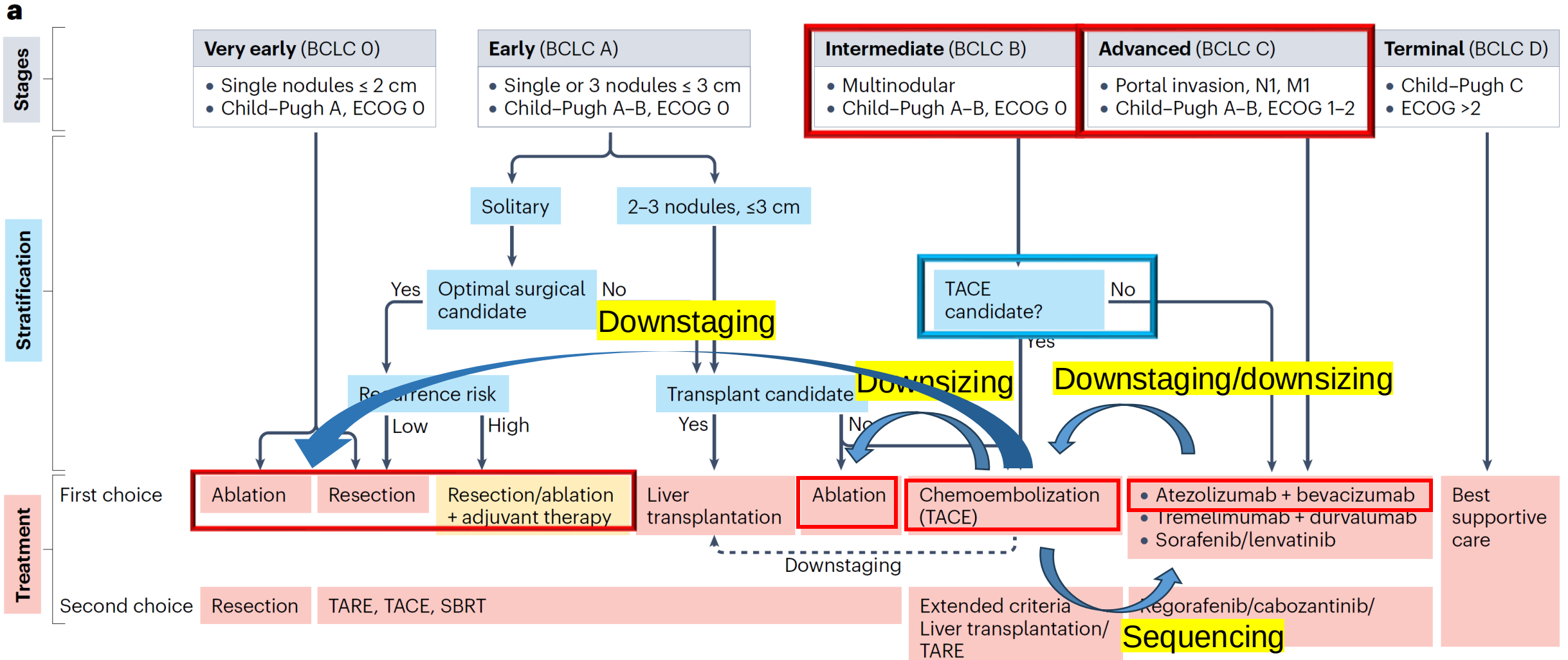
BCLC Staging (Modified) and Treatment Strategy



ABC Conversion,
ABC-TACE Sandwich therapy

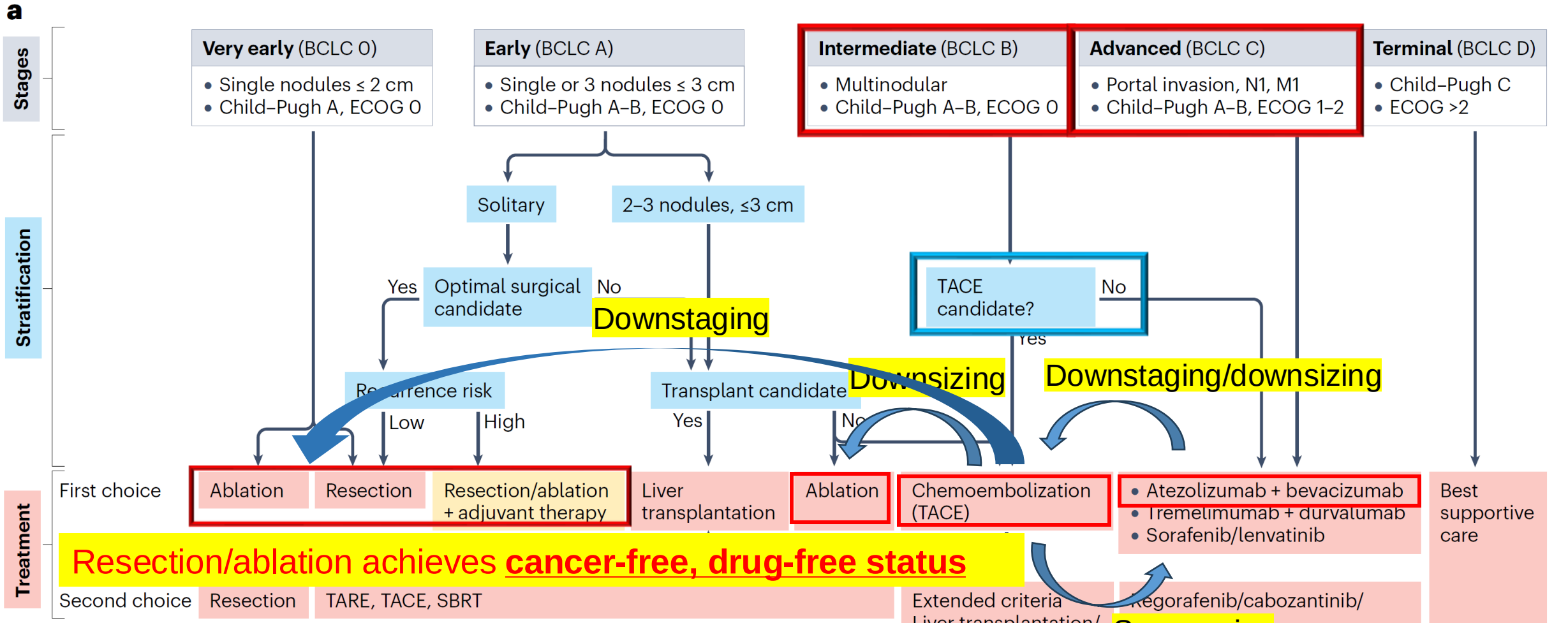
Llovet JM, Kudo M, et al. Nature Review Clin Oncol 2024

BCLC Staging (Modified) and Treatment Strategy



Llovet JM, Kudo M, et al. Nature Review Clin Oncol 2024

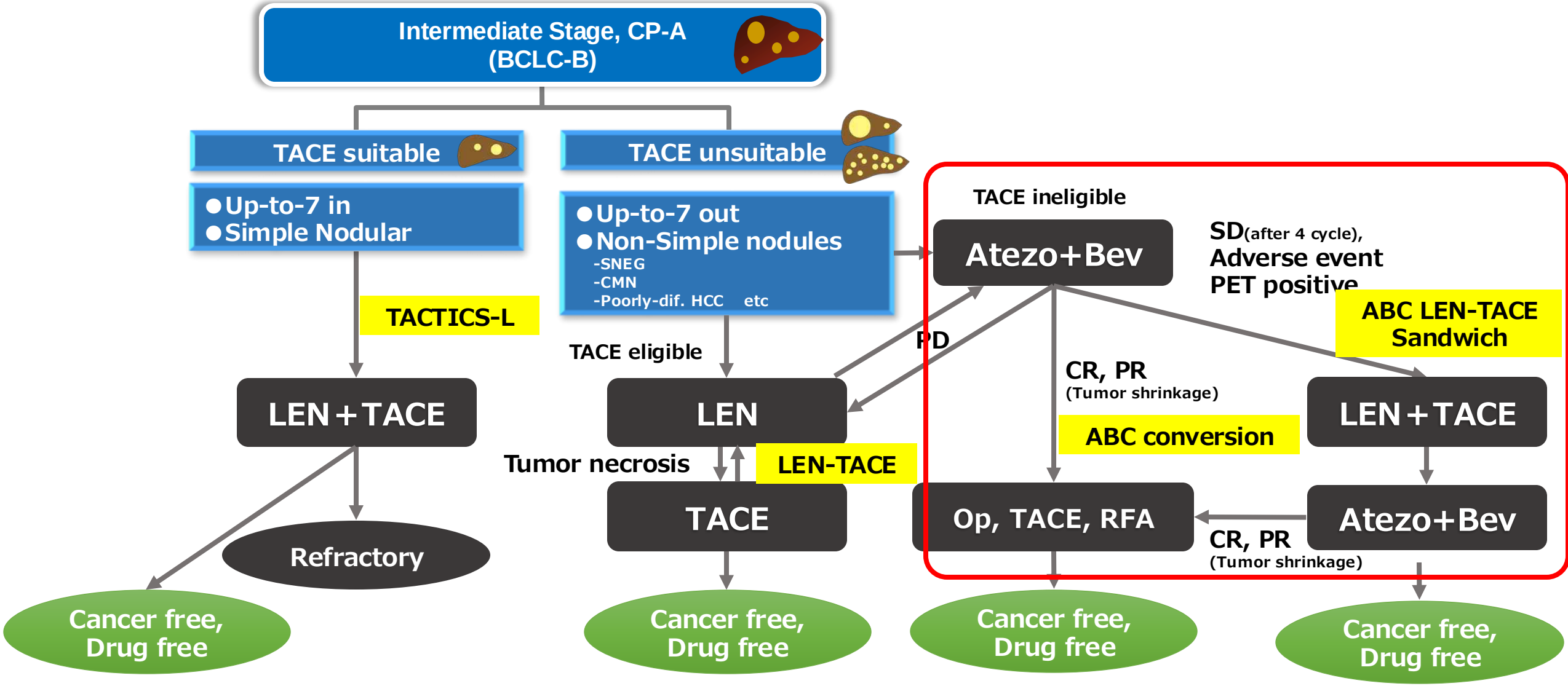
BCLC Staging (Modified) and Treatment Strategy



ABC Conversion,
ABC-TACE Sandwich therapy

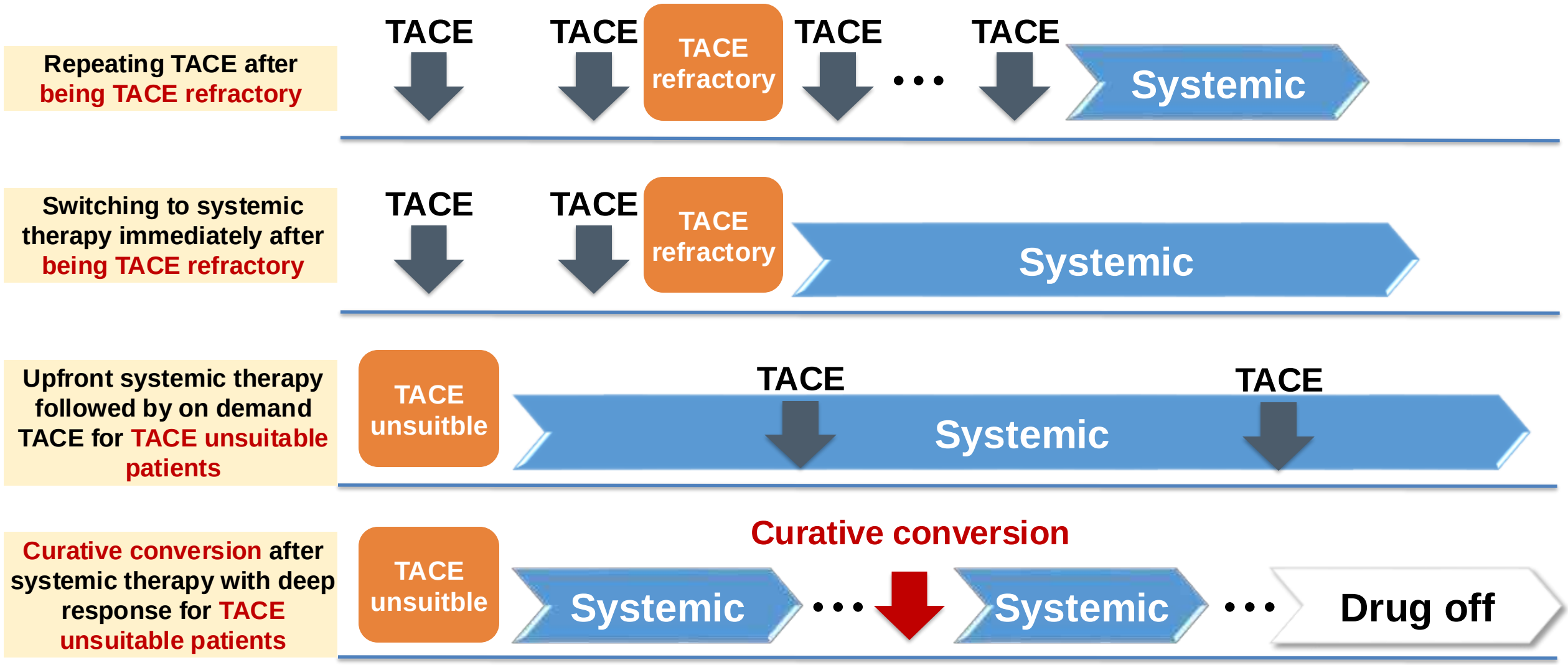
Llovet JM, Kudo M, et al. Nature Review Clin Oncol 2024

Treatment Strategy for Intermediate stage HCC



Kudo M. Int J Clin Oncol 2022.

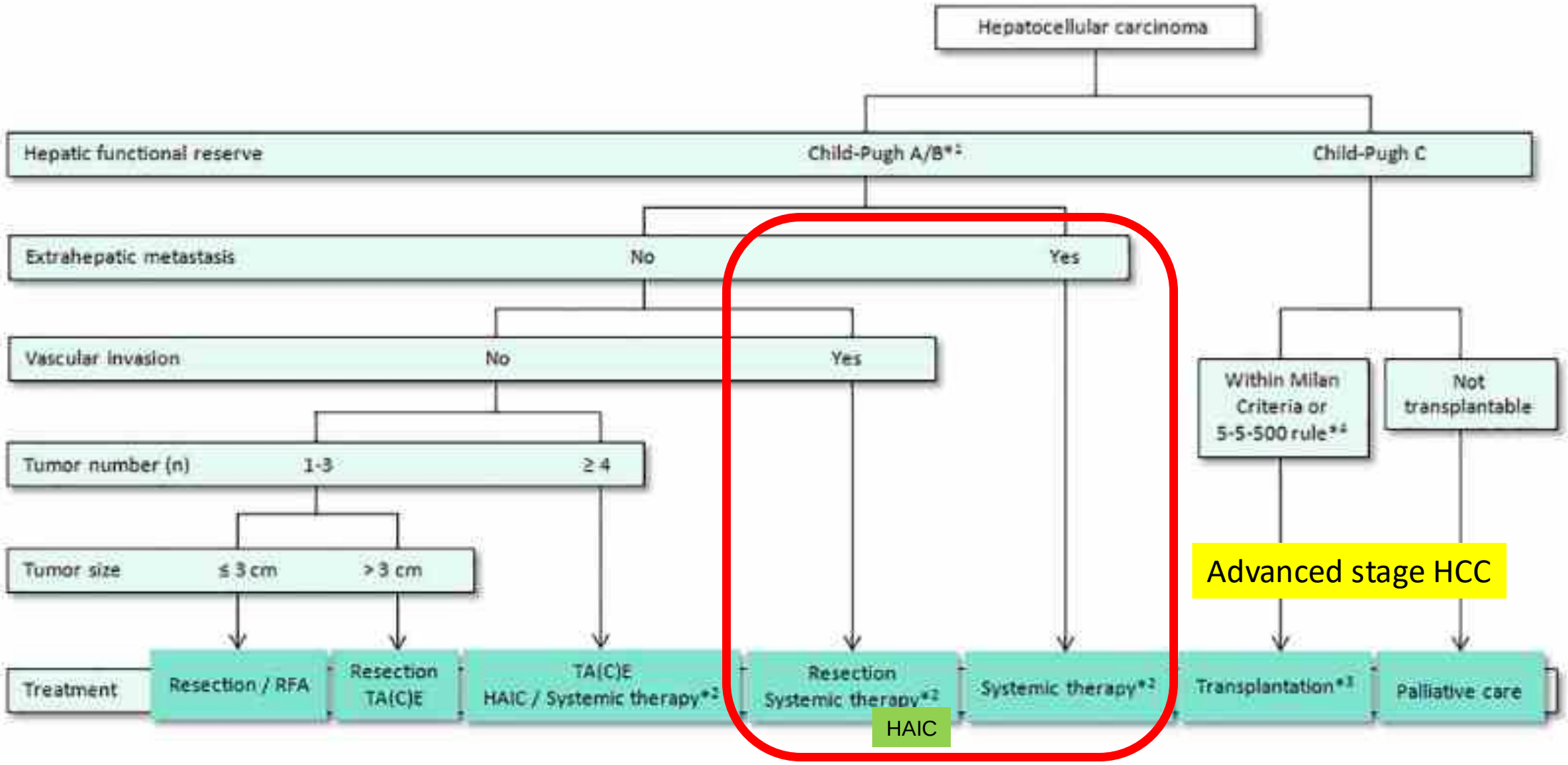
Evolving treatment landscape in intermediate-stage uHCC



Outline

- Treatment strategy for Advanced stage HCC

JSH HCC Guidelines 2021 Algorithm for Treatment



Hasegawa K, Tateishi R, Kudo M, et al. Hepatol Res. 2023

History of Drug Approval in HCC in Japan

1stLine

SHARP, Asia Pacific

Sorafenib

REFLECT

Lenvatinib

IMbrave150

Atezolizumab
+Bevacizumab

HIMALAYA

Durvalumab
+ Tremelimumab

Durvalumab

2009 2010 2011 2012 2013 2014 2015 2016 2017 2018 2019 2020 2021 2022 2023

2nd Line

Regorafenib

RESORCE

Ramucirumab

REACH-2

Cabozantinib

CELESTIAL

JSH-HCC Guidelines: Algorithm for systemic therapy

Hepatocellular carcinoma

Advanced HCC not indicated for resection, transplantation, RFA, TA(C)E, etc.
Good performance status and Child-Pugh A liver function

Indication for combination immunotherapy

Yes

1st line

- **Atezolizumab＋Bevacizumab**
- **Tremelimumab＋Durvalumab**

2nd line or later

- ・Sorafenib
  ・Lenvatinib
  ・Regorafenib
  ・Ramucirumab
  ・Cabozantinib
  ・Tremelimumab ＋Durvalumab
  ・Durvalumab
- ・Sorafenib
  ・Lenvatinib
  ・Regorafenib
  ・Ramucirumab
  ・Cabozantinib
  ・Atezolizumab＋Bevacizumab

No

1st line

- **Sorafenib**
- **Lenvatinib**
- **Durvalumab**

2nd line or later

- ・**Regorafenib**
  ・**Ramucirumab**
  ・**Cabozantinib**
  ・Lenvatinib
- ・Sorafenib
  ・Regorafenib
  ・Ramucirumab
  ・Cabozantinib
- ・Sorafenib
  ・Regorafenib
  ・Lenvatinib
  ・Ramucirumab
  ・Cabozantinib

Bold face with underline indicates the availability of evidence from randomized controlled trials.

JSH Clinical Practice Guideline for HCC 2023.

Positive phase III trials - Efficacy

Trial	IMbrave150 [1,2]	HIMALAYA [3]	REFLECT [4]
Treatment Arm	**Atezolizumab + Bevacizumab**	**Durvalumab + Tremelimumab**	**Lenvatinib**
mOS (months)	**19.2** (Sorafenib 13.4)	**16.4** (Sorafenib 13.8)	**13.6** (Sorafenib 12.3)
HR (95% CI)	**0.66** 95% CI (0.52-0.85)	**0.78** (0.65–0.93)	**0.92** (0.79-1.06)
mPFS (months)	**6.9** (Sorafenib 4.3)	**3.78** (Sorafenib 4.07)	**7.4** (Sorafenib 3.7)
HR (95% CI)	**0.65** (0.53-0.81)	**0.90** (0.77–1.05)	**0.66** (0.0.57-0.77)
ORR (%; RECIST 1.1 confirmed)	**30.0**	**20.1**	**24.1 per mRECIST**
PD (%, RECIST 1.1)	**19.0**	**40.0**	**15.0 per mRECIST**

1. Finn RS, Kudo M, et al. N Engl J Med 382: 1894-1905, 2020., 2. Cheng AL, Kudo M, et al. J Hepatol. 2022 Apr;76(4):862-873.,
3. Abou-Alfa GK, Kudo M, et al. NEJM Evid 2022 Aug;1(8):EVIDoa2100070., 4. Kudo M, Finn RS, Qin S, et al.. Lancet. 2018;391(10126):1163-1173.

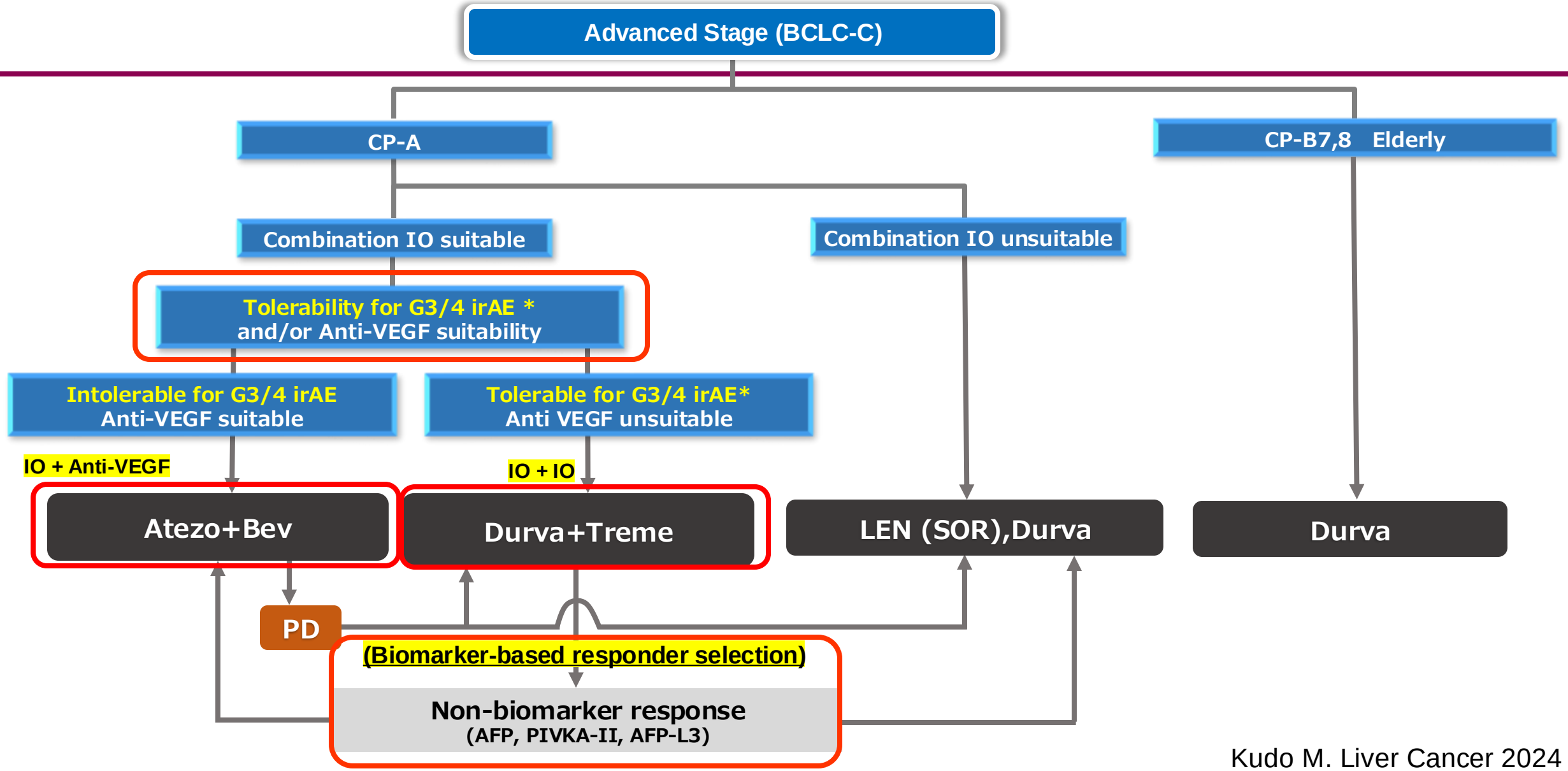
Positive phase III trials - Safety

Trial	IMbrave150 [1,2]	HIMALAYA [3]	REFLECT [4]
Treatment Arm	Atezolizumab + Bevacizumab	Durvalumab + Tremelimumab	Lenvatinib
Treatment Duration	8.4 mo (Atezo) 7.0 mo (Bev)	5.5 mo	5.7 mo
TRAE Rate	86%	76%	94%
G≥3 TRAE rate	43%	26%	57%
AEs leading to discontinuation	22%	14%	20%
irAEs requiring corticosteroid	12%	20%*	N.A.

*High-dose steroid only

1. Finn RS, Kudo M, et al. N Engl J Med 382: 1894-1905, 2020., 2. Cheng AL, Kudo M, et al. J Hepatol. 2022 Apr;76(4):862-873.,
3. Abou-Alfa GK, Kudo M, et al. NEJM Evid 2022 Aug;1(8):EVIDoa2100070., 4. Kudo M, Finn RS, Qin S, et al.. Lancet. 2018;391(10126):1163-1173.

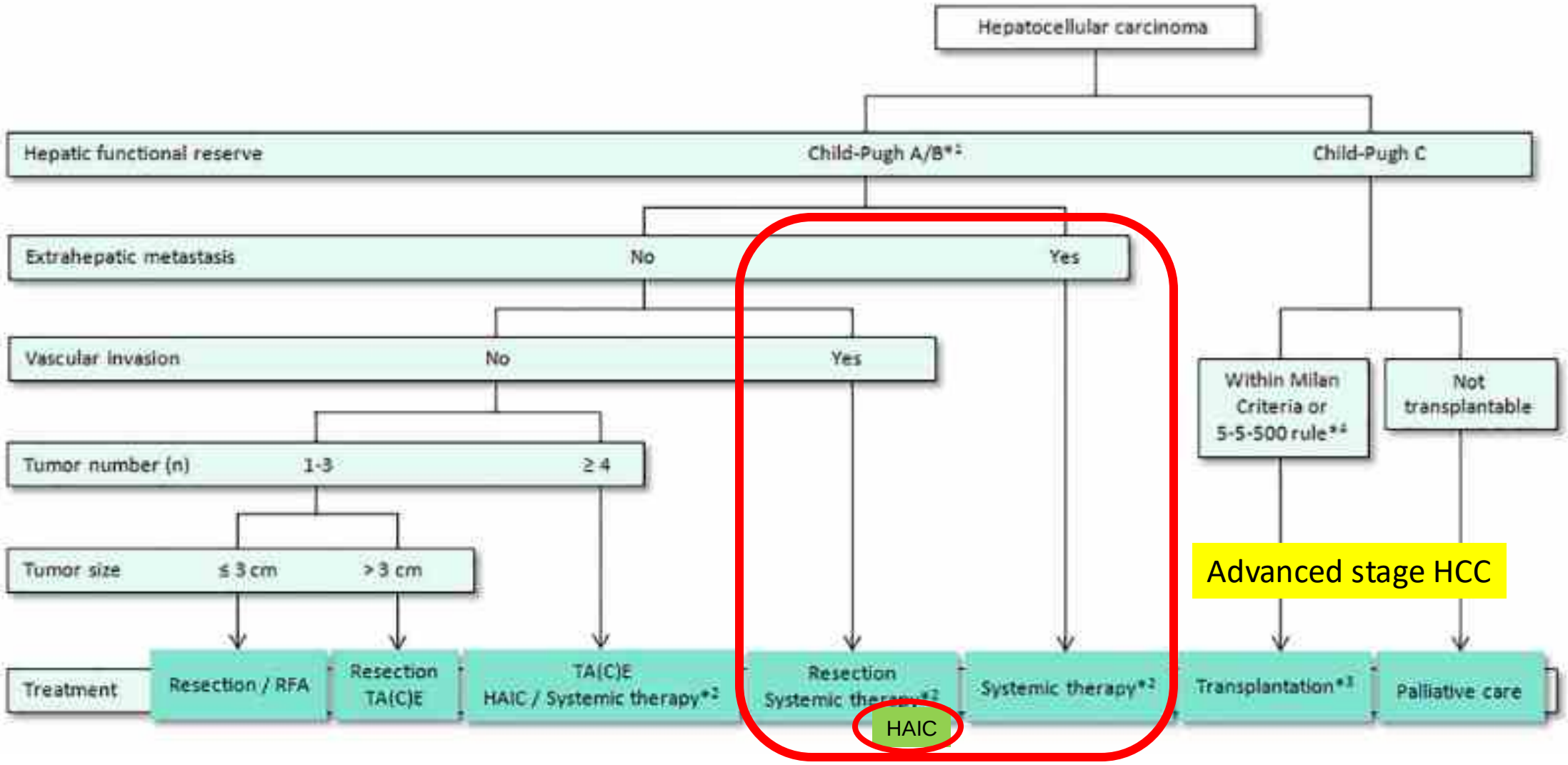
1st Line Treatment for Advanced HCC



Kudo M. Liver Cancer 2024

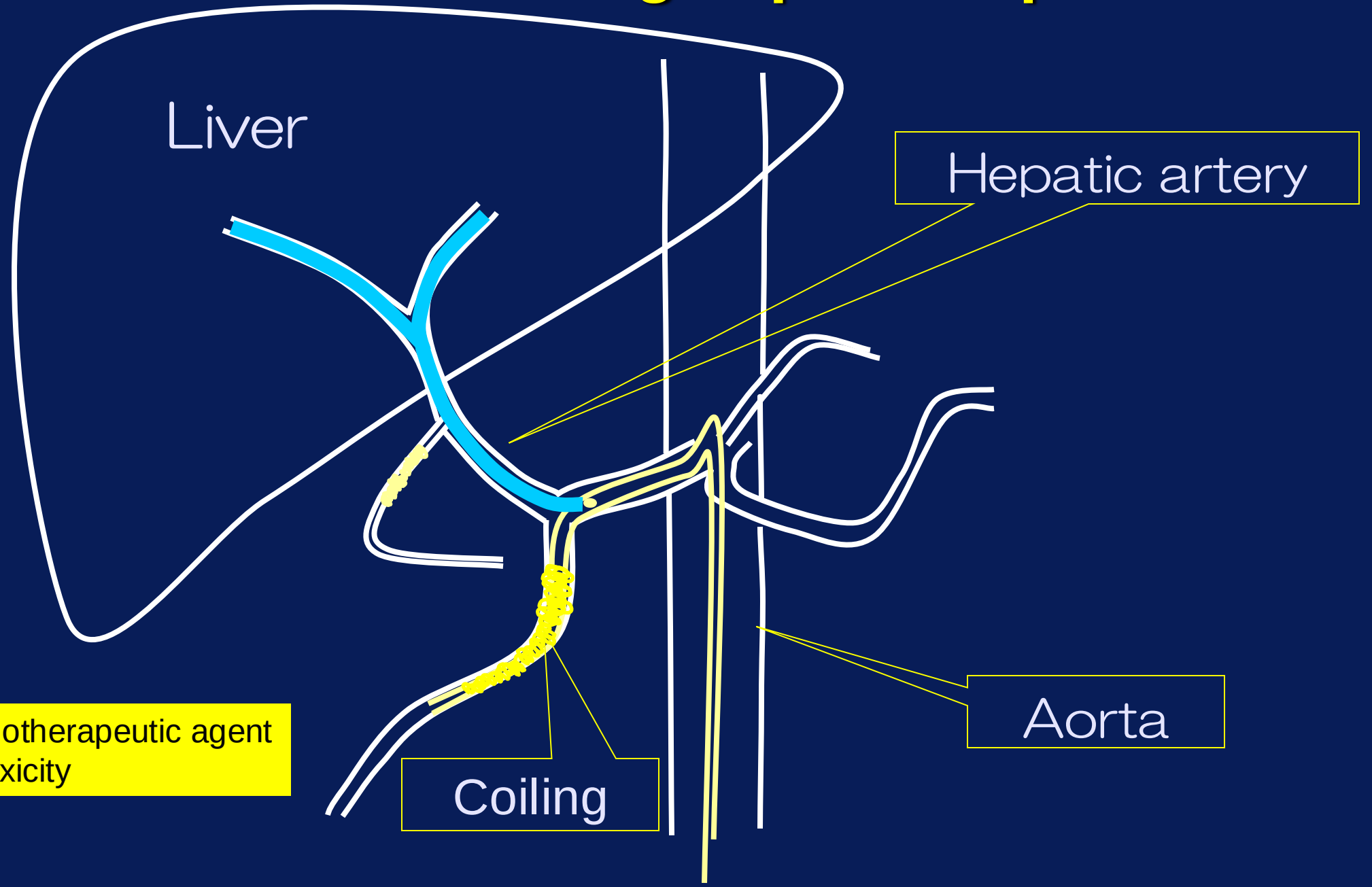
*Tolerable for G3/4 irAE: Pts with good PS, good liver function, younger age, no severe/active comorbidity (CVD, etc), No Vp3/4

JSH HCC Guidelines 2021 Algorithm for Treatment



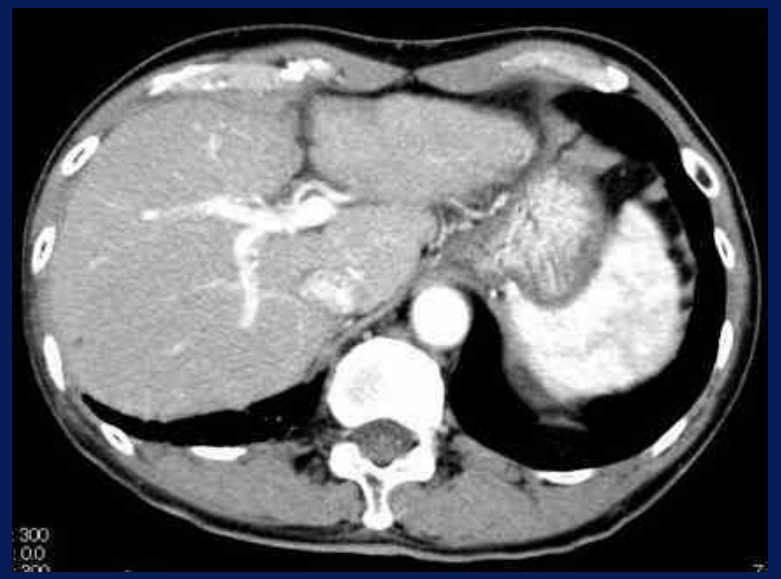
Hasegawa K, Tateishi R, Kudo M, et al. Hepatol Res. 2023

Continuous HAIC using implanted port



- ✓ High dose chemotherapeutic agent
- ✓ Low systemic toxicity

Continuous HAIC with implanted port

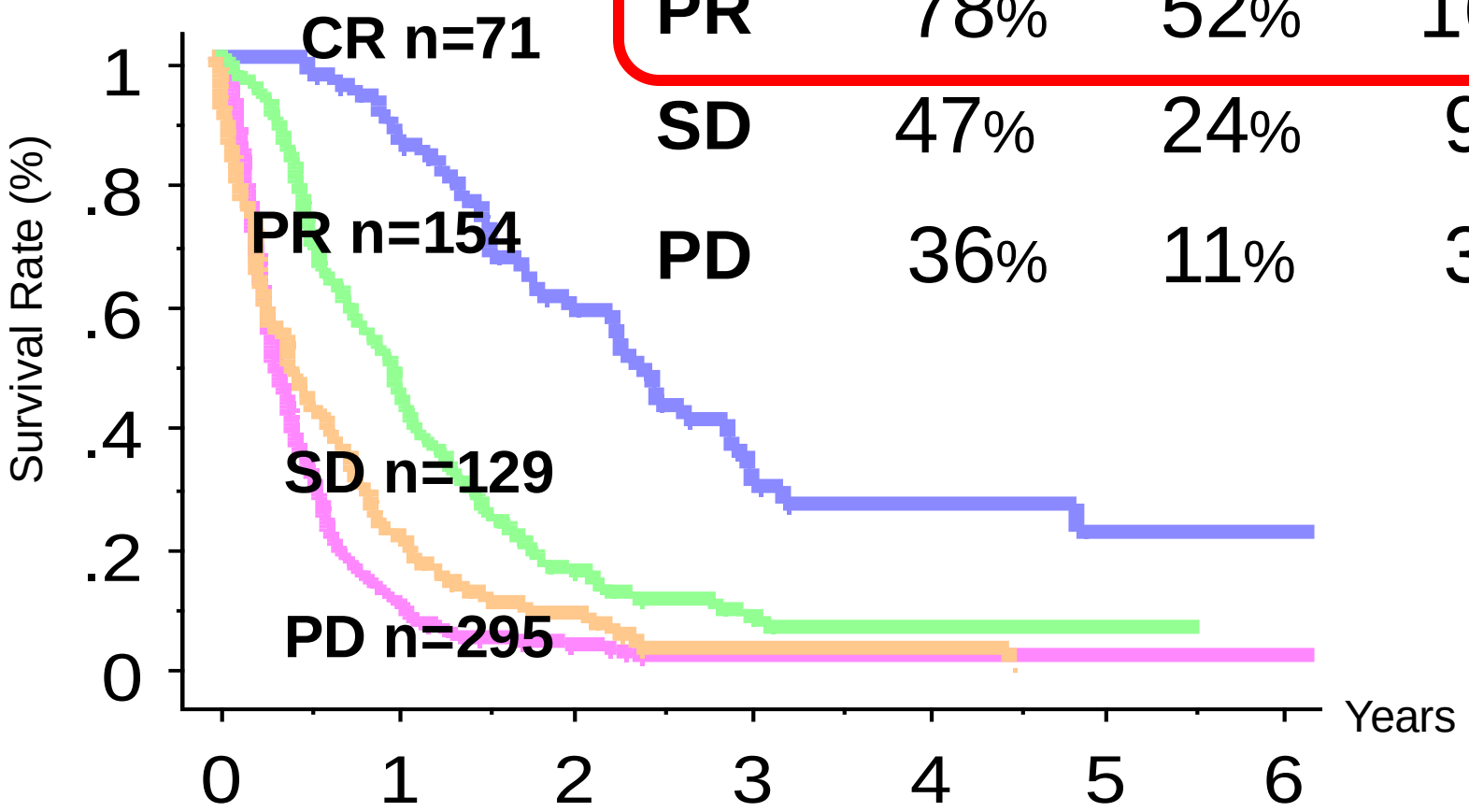


HAIC Efficacy

(n=649)

Effective for PVTT

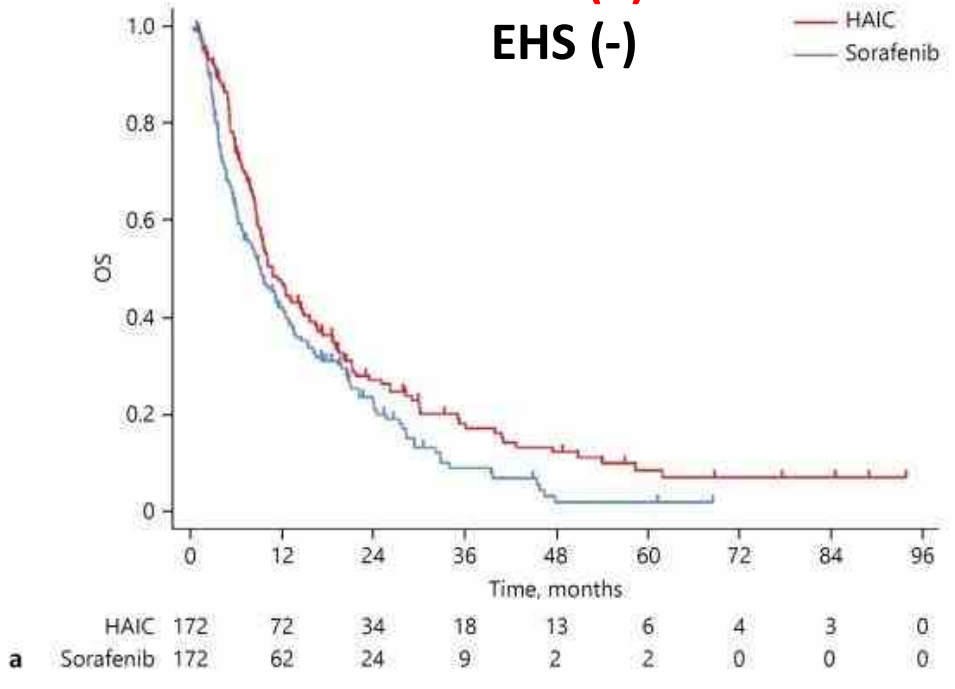
	0.5y	1y	2y	MST
CR	100%	91%	61%	**28.9 M**
PR	78%	52%	16%	**12.2 M**
SD	47%	24%	9%	**5.5 M**
PD	36%	11%	3%	**4.3 M**



HAICvs Sorafenib

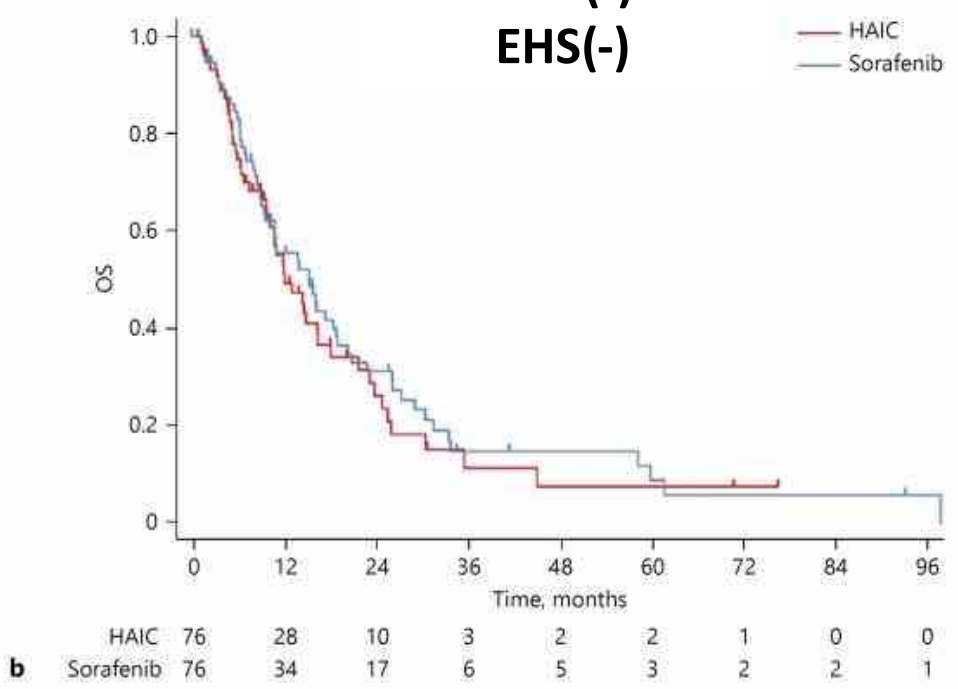
-PSM study-

MVI (+)
EHS (-)



HAIC: 10.6 months [95% CI 9.1–14.3]
Sorafenib: 9.1 months [95% CI 6.8–12.0]
HR: 0.667 [95% CI 0.475–0.935]
***p* = 0.018**

MVI(-)
EHS(-)



HAIC: 12.2 months [95% CI 9.9–16.5]
Sorafenib: 15.4 months [95% CI 9.7–19.1]
HR: 1.227 [95% CI 0.699–2.155]
***p* = 0.475**

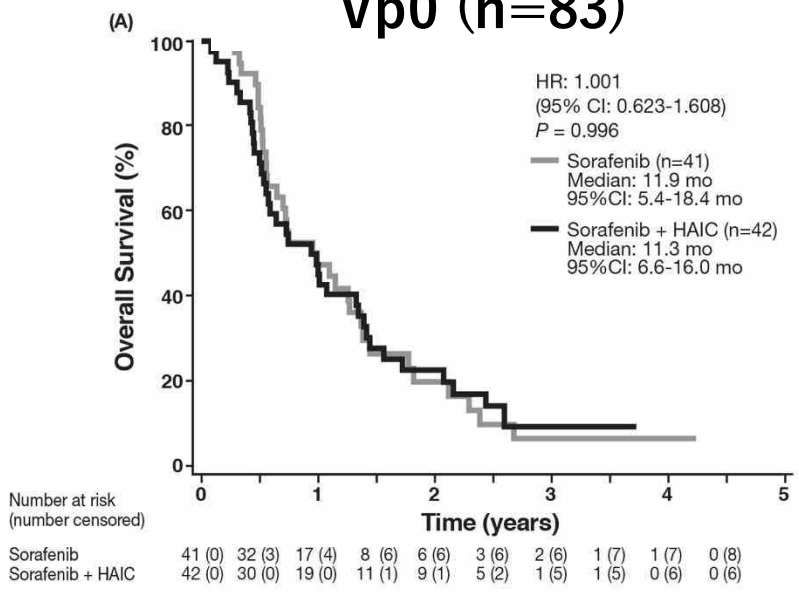
HAIC is effective for PVTT

Ueshima K, Kudo M et al. Liver Cancer. 2020;9(5):583-95.

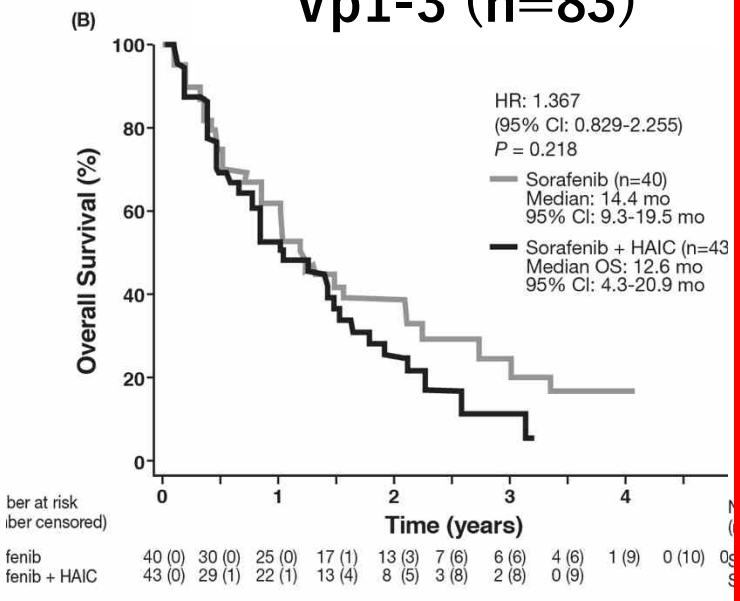
Phase 3 SILIUS Trial: OS sub-analysis

Sorafenib vs. Sorafenib plus HAIC (Low-dose FP)

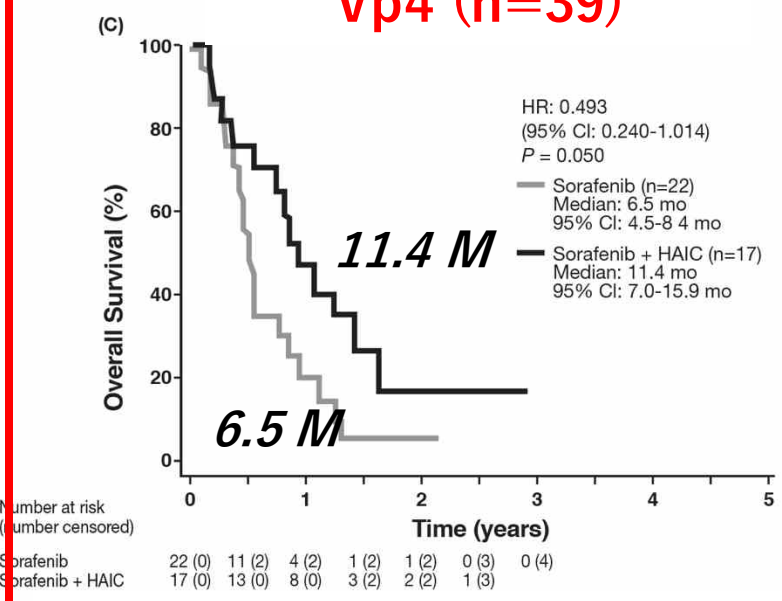
Vp0 (n=83)



Vp1-3 (n=83)



Vp4 (n=39)



HAIC is still performed in pts with MVI (Vp3/4) in Japan.

HAIC is effective for Vp4 patients

Kudo M, et al. Lancet Gastroenterol Hepatol 2018

In Japan,

All patients can **easily access these high quality, sophisticated treatments** including resection, transplantation, ablation, superselective TACE, combination of systemic and locoregional therapy and combination Immunotherapy at referral institute in all over Japan by fully covered insurance

Outline

- Summary and Conclusion

Conclusion

- Surveillance of HCC at high-risk patients can detect many small curable HCC, leading to receiving potentially curative therapy (Resection, Ablation, transplantation), providing patients a very long survival.
- Combination of systemic/IO and LRT, especially ABC conversion, has become a SOC in intermediate-stage HCC
- 3 tumor markers are essential from the surveillance to treatment monitoring/drug-free decision making.
- IO plus anti-VEGF/IO-IO regimen is the 1st choice of 1st line treatment in advanced HCC, however, HAIC is still a choice of treatment modality in aHCC with VP3/4

Thank you very much for your kind attention.

Kindai University, Japan