Taipei Veterans General Hospital Practice Guidelines Oncology

Hepatocellular carcinoma (HCC)

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大綱

Hepatocellular Carcinoma
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- Gastroenterology and Hepatology
- General Surgery
- Transplant Surgery
- Radiology
- Radiation Oncology
- Medical Oncology
- Pathology
- Family Medicine
- Specialized Nursing Care
- Social Workers
- Nutritional Support

Hepatocellular Carcinoma

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Hepatocellular Carcinoma
治療前檢查

- **Complete medical history and physical exam**
- **Blood tests**
  - CBC
  - Albumin, bilirubin
  - BUN/ creatinine
  - PT/ APTT
  - ALT/ AST
  - Alkaline phosphatase/ r-GT
  - *Indocyanine green (ICG) test
- **Tumor marker**
  - Alpha feto-protein (AFP)
  - *PIVKA-II (DCP)
- **Virological profiles**
  - HBsAg, anti-HBc, anti-HBs
  - *HBV-DNA, *HBsAg-HQ
  - Anti-HCV, *HCV-RNA
- **Radiological imaging**
  - Ultrasound, *contrast-enhanced ultrasound (CEUS)
  - Contrast-enhanced CT
  - *MRI (with primovist)
  - *PET/MRI
  - *Celiac angiography
- ***Gastroscopy**
- ***Liver biopsy**

* Optional

證據的強度及建議的等級

等級一：至少一個設計精良的隨機對照研究

等級二：設計精良的追蹤或病例對照研究

等級三：病例系列、病例報告或有瑕疵的臨床研究

等級四：專家的臨床經驗，記述型研究或專家會議的報告

肝癌定期偵監

Hepatocellular Carcinoma
肝癌定期偵監

建議一：

肝細胞癌之高危險性族群應定期接受肝癌定期偵監計畫（證據強度等級一）。

高危險群定義如下：

（1）慢性B型肝炎患者（2）慢性C型肝炎患者（3）原發性膽汁性硬變

（4）任何原因造成之肝硬化，包括：酒精性肝硬化、自體免疫性肝炎、非酒精性脂性肝炎、基因性鐵質沉積症，以及甲一型抗胰蛋白酶缺乏症等造成之肝硬化（證據強度等級四）。

建議二：

患者正在等待肝臟移植手術時，仍應定期接受肝癌偵監（證據強度等級四）。

建議三：

肝癌定期偵監應使用超音波檢查（證據強度等級二），

並合併血清甲型胎兒蛋白 (AFP) 檢測（證據強度等級四）。

經超音波發現大於 1 公分之結節、AFP異常之數值，進一步安排電腦斷層檢查或是磁振造影檢查。

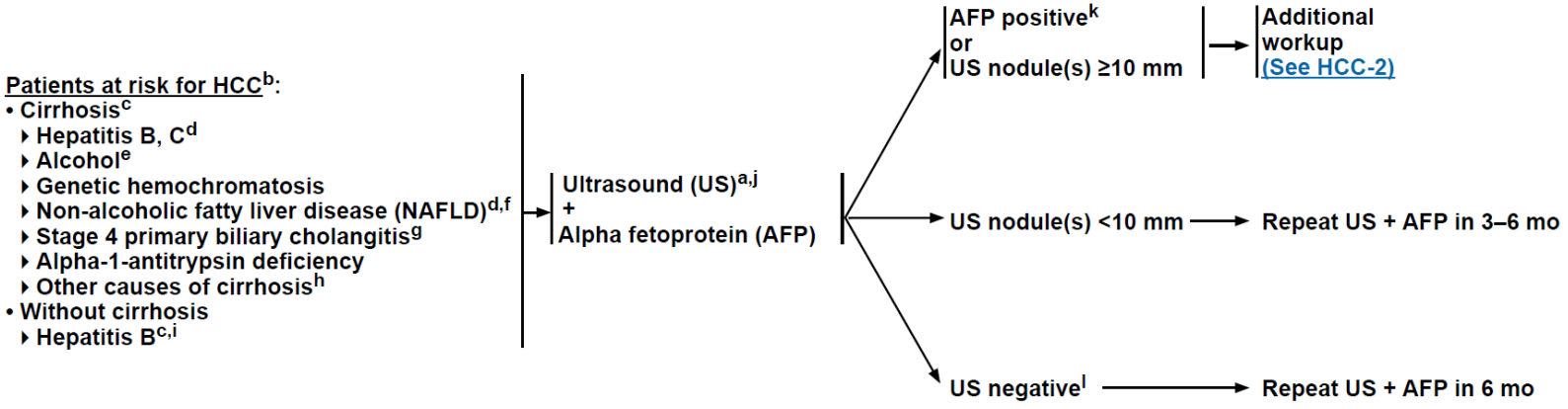
Hepatocellular Carcinoma
參考資料

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2022
Hepatocellular Carcinoma

2022 update

HEPATOCELLULAR CARCINOMA (HCC) SCREENING[a]



[a] See Principles of Imaging (HCC-A).
[b] Adapted with permission from Marrero JA, et al. Hepatology 2018;68:723-750.
[c] Patients with cirrhosis or chronic hepatitis B viral infection should be enrolled in an HCC screening program (See Discussion).
[d] There is evidence suggesting improved outcomes for patients with HCC in the setting of NAFLD/HBV/HCV cirrhosis when the NAFLD/HBV/HCV is successfully treated. Referral to a hepatologist should be considered for the management of these patients.
[e] Niazi SK, et al. J Natl Compr Canc Netw 2021;19:829-838.
[f] White DL, Clin Gastroenterol Hepatol 2012;10:1342-1359.
[g] Beuers U, et al. Am J Gastroenterol 2015;110:1536-1538.
[h] Schiff ER, Sorrell MF, and Maddrey WC. Schiff's Diseases of the Liver. Philadelphia: Lippincott Williams & Wilkins (LWW); 2007.
[i] Additional risk factors include HBV carrier with family history of HCC, Asian males ≥40 y, Asian females ≥50 y, and African/North American Blacks with hepatitis B.
[j] Most clinical practice guidelines recommend US for HCC screening. US exams should be done by qualified sonographers or physicians. Liver dynamic CT or dynamic MRI may be performed as an alternative to US if US fails to detect nodules or if visualization is poor. Korean Liver Cancer Association; National Cancer Center. Gut Liver 2019;13:227-299. (See Principles of Imaging, HCC-A).
[k] Positive or rising AFP should prompt CT or MRI regardless of US results.
[l] US negative means no observation or only definitely benign observation(s).

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Hepatocellular Carcinoma
肝癌定期偵監

建議四：

肝癌高危險群患者應每 6 個月實施定期偵監一次（證據強度等級一）；肝硬化患者依患者個別情況，可考慮每 3 至 6 個月實施定期偵監一次（證據強度等級四）；

肝癌患者經根除性治療後，依據國健局核心測量指標標準，修定為每 3 至 4 個月定期偵監一次，一年內追蹤至少3次（證據強度等級四）。

Hepatocellular Carcinoma

肝癌診斷

Hepatocellular Carcinoma
肝癌診斷

建議五：

肝癌之診斷可由以下兩種方法任一為之:

- 肝臟穿刺切片檢查。

  (外科切除術前不建議肝臟穿刺切片)

- 經超音波發現大於 1 公分之結節、AFP異常之數值，於電腦斷層檢查或是磁振造影檢查，呈現肝細胞癌之典型血管特徵（動脈相呈高血管性合併在門脈相及靜脈相有顯影劑早期消褪現象）（證據強度等級二）。

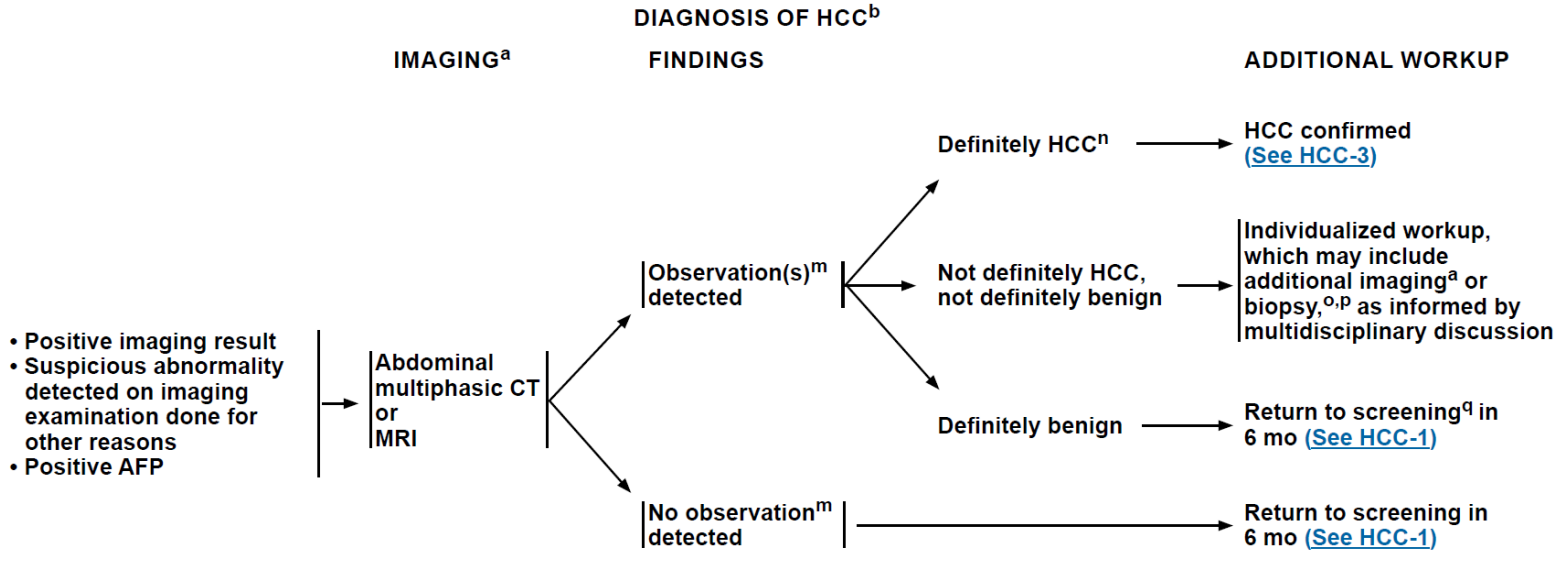
Hepatocellular Carcinoma
參考資料

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2022
Hepatocellular Carcinoma

2022 update

Discussion



[a] See Principles of Imaging (HCC-A).
[b] Adapted with permission from Marrero JA, et al. Hepatology 2018;68:723-750.
[m] An observation is an area identified at imaging that is distinctive from background liver. It may be a mass or a pseudo lesion.
[n] Criteria for observations that are definitely HCC have been proposed by LI-RADS and adopted by AASLD. These criteria apply only to patients at high risk for HCC. OPTN has proposed imaging criteria for HCC applicable in candidates for liver transplant. See Principles of Imaging (HCC-A).
[o] Before biopsy, evaluate if patient is a resection or transplant candidate. If patient is a potential transplant candidate, consider referral to transplant center before biopsy.
[p] The optimal diagnostic method is core needle biopsy. See Principles of Core Needle Biopsy (HCC-B).
[q] If no observations are detected at diagnostic imaging despite positive surveillance tests, then return to surveillance in 6 months if the most reasonable explanation is that surveillance tests were false positive. Consider imaging with an alternative method ± AFP if there is reasonable suspicion that the diagnostic imaging test was false negative.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

肝癌分期系統

Hepatocellular Carcinoma
肝癌分期系統

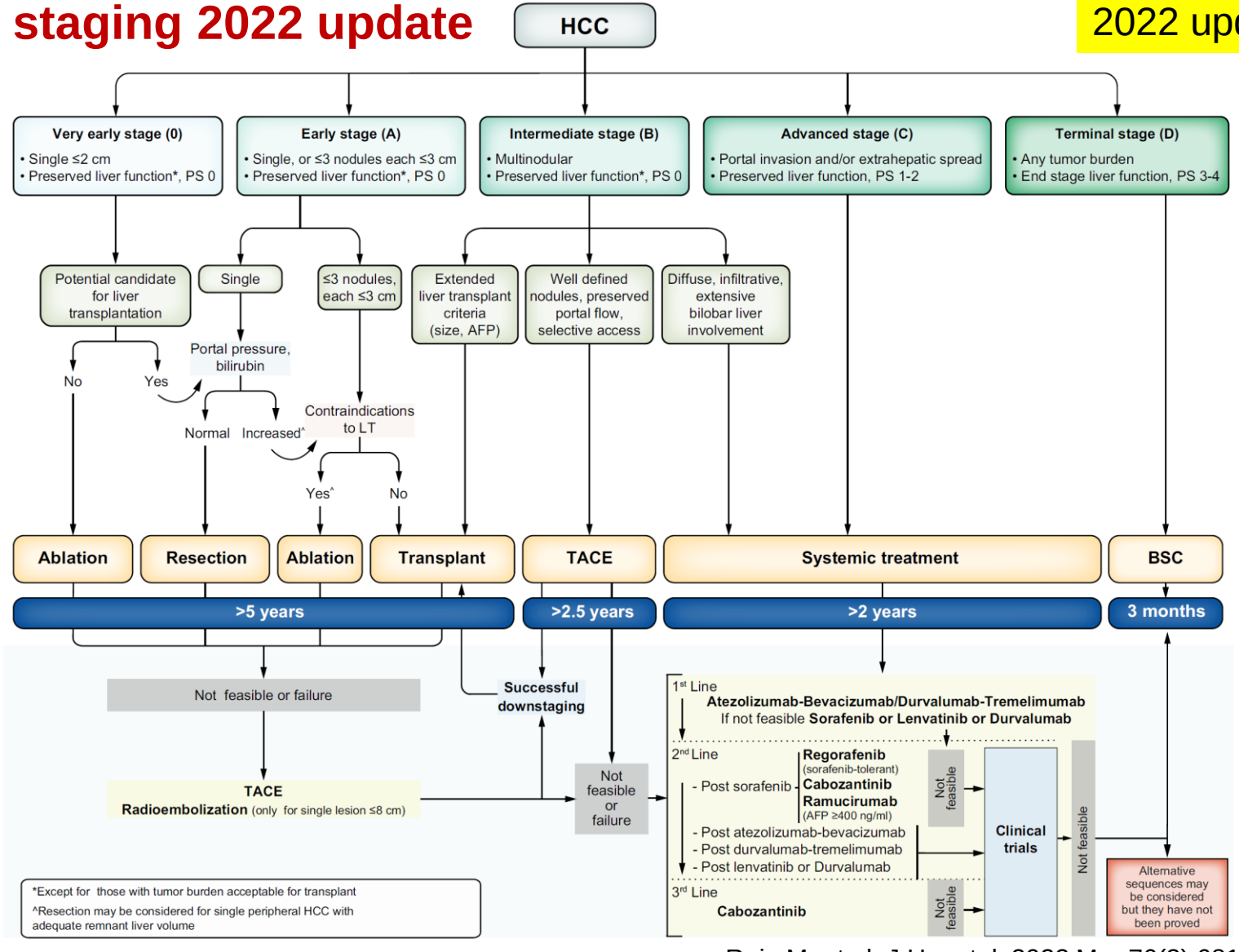
- **At least 11 systems have been raised**
  - **TNM classification/ AJCC (US)**
  - **BCLC (Barcelona clinic liver cancer, Spain)**
  - **CLIP (Cancer of the Liver Italian Program, Italy) CUPI (Chines University Prognostic Index, Hong Kong)**
  - **TIS (Taipei Integrated Scoring system, Taiwan)**
  - **Okuda (Japan)**
  - **LCSGJ (Liver Cancer Study Group of Japan)**
  - **GRETCH system (French)**
  - **JIS (Japan integrated staging, Japan)**
  - **Tokyo score**
  - **HKLC (Hong Kong Liver Cancer, Hong Kong)**

Kinoshita A, et al. World J Hepatol. 2015;7(3):406-424.

Hepatocellular Carcinoma
肝癌分期系統

BCLC staging 2022 update

2022 update



Reig M, et al. J Hepatol. 2022 Mar;76(3):681-693.

Hepatocellular Carcinoma
肝癌分期系統

TNM staging System: UICC/AJCC 2017 8th Edition

Definition of Primary Tumor (T)

T Category	T Criteria
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Solitary tumor ≤2 cm, or >2 cm without vascular invasion
T1a	Solitary tumor ≤2 cm
T1b	Solitary tumor >2 cm without vascular invasion
T2	Solitary tumor >2 cm with vascular invasion, or multiple tumors, none >5 cm
T3	Multiple tumors, at least one of which is >5 cm
T4	Single tumor or multiple tumors of any size involving a major branch of the portal vein or hepatic vein, or tumor(s) with direct invasion of adjacent organs other than the gallbladder or with perforation of visceral peritoneum

Definition of Regional Lymph Node (N)

N Category	N Criteria
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis

Definition of Distant Metastasis (M)

M Category	M Criteria
M0	No distant metastasis
M1	Distant metastasis

AJCC PROGNOSTIC STAGE GROUPS

When T is…	And N is…	And M is…	Then the stage group is…
T1a	N0	M0	IA
T1b	N0	M0	IB
T2	N0	M0	II
T3	N0	M0	IIIA
T4	N0	M0	IIIB
Any T	N1	M0	IVA
Any T	Any N	M1	IVB

Hepatocellular Carcinoma
肝癌分期系統

建議六：

評估肝癌之預後，腫瘤分期系統必須綜合考量腫瘤階段、肝功能及身體功能，治療方式之評估亦須考慮預期壽命。

目前BCLC系統為較理想之分期系統（證據強度等級二）。

目前本院治療以TNM系統及BCLC系統為主要之肝癌分期系統。

肝癌治療

Hepatocellular Carcinoma
Treatment Guidelines (8th Version)

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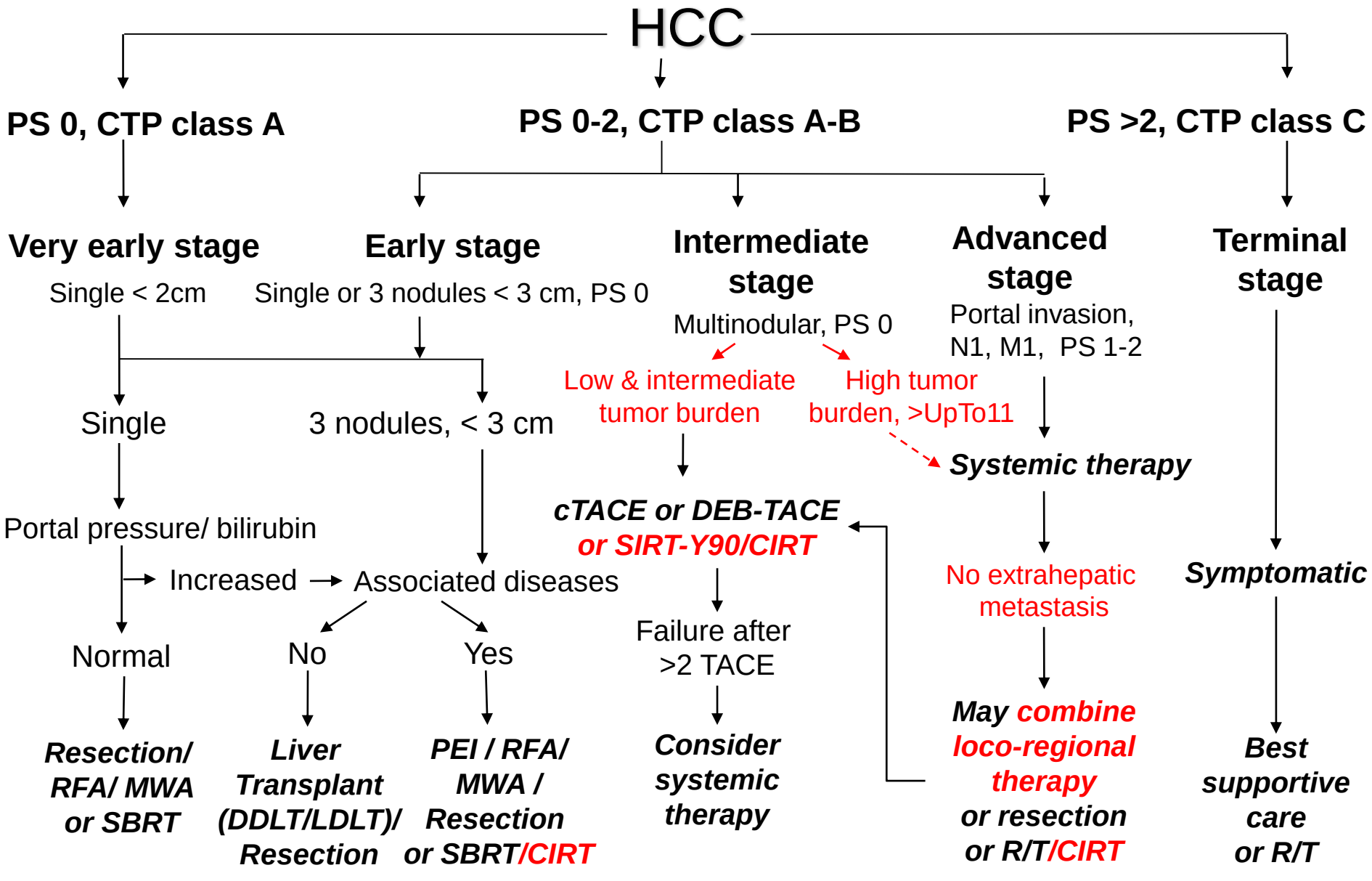

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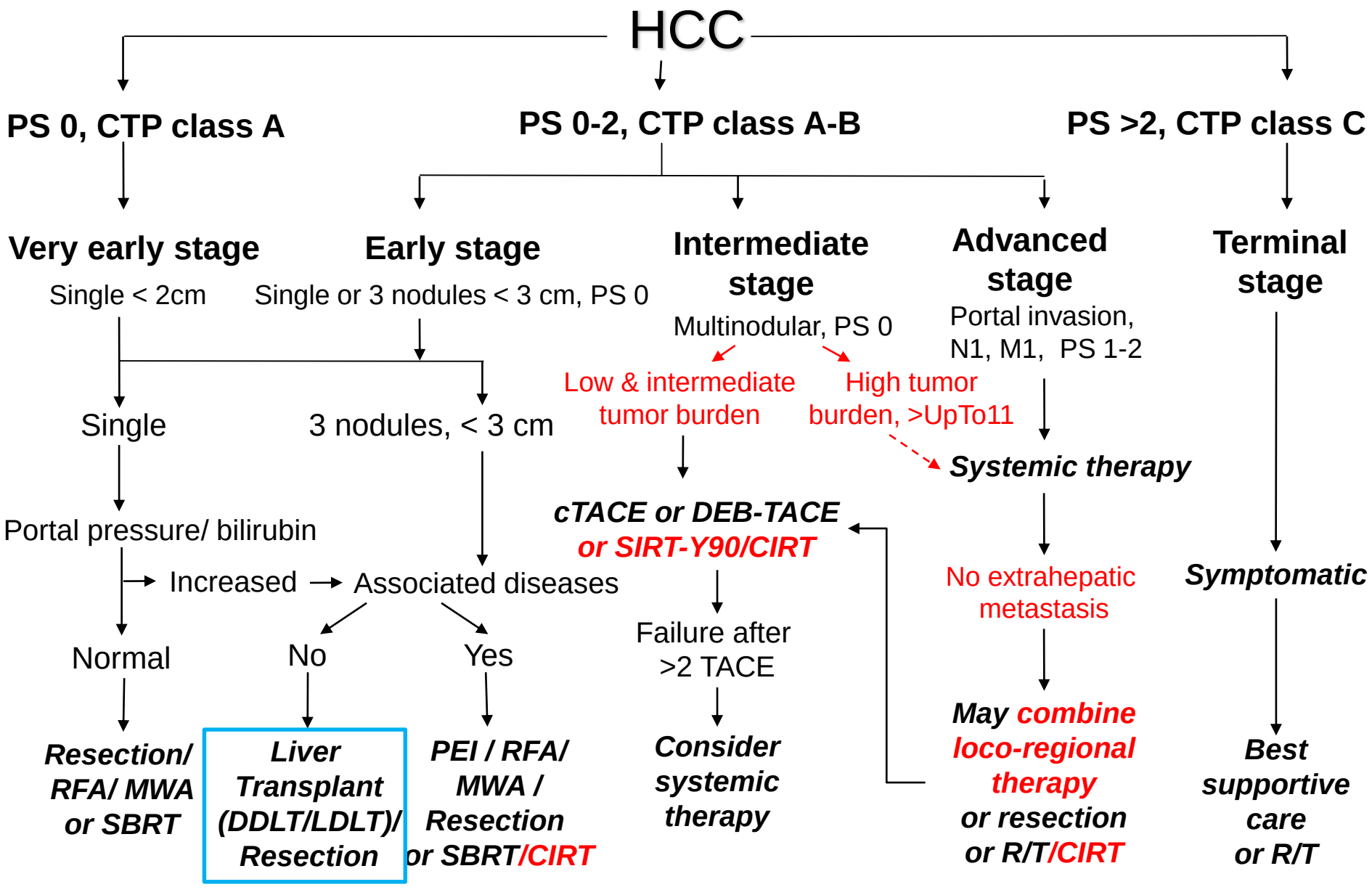

Hepatocellular Carcinoma
肝癌治療～肝臟移植

建議七：

若肝癌合乎米蘭規約（Milan criteria：單一腫瘤不大於5公分或2至3顆腫瘤且最大者小於3公分），肝臟移植手術能提供較佳之腫瘤無復發之存活率（證據強度等級二）。台灣外科醫師專家共識，若大小超過米蘭規約，但符合舊金山大學規約（University of San Francisco, UCSF criteria：單一腫瘤不大於6.5公分，或2至3顆腫瘤、最大者小於4.5公分且總直徑不大於8公分），臨床醫師可依患者狀況考慮是否接受肝臟移植手術（證據強度等級四）。

建議八：

若患者預期等待肝臟移植之時間超過六個月，應在手術前針對腫瘤先予過渡治療 (bridge therapy)（證據強度等級二），或是安排活體肝臟移植 (living donor liver transplantation)（證據強度等級二）。

建議九：

若患者腫瘤大小超過米蘭規約，且肝臟代償能力良好，可考慮先給予降階治療(down-staging therapy)，如栓塞治療術或是局部腫瘤消融治療術，之後至少觀察3個月確定腫瘤降階至合乎米蘭規約後，再安排患者進入移植等待名單（證據強度等級二）。 或是建議患者先接受切除手術若有腫瘤復發時再安排肝臟移植作為救援治療(salvage liver transplantation) (證據強度等級二）。

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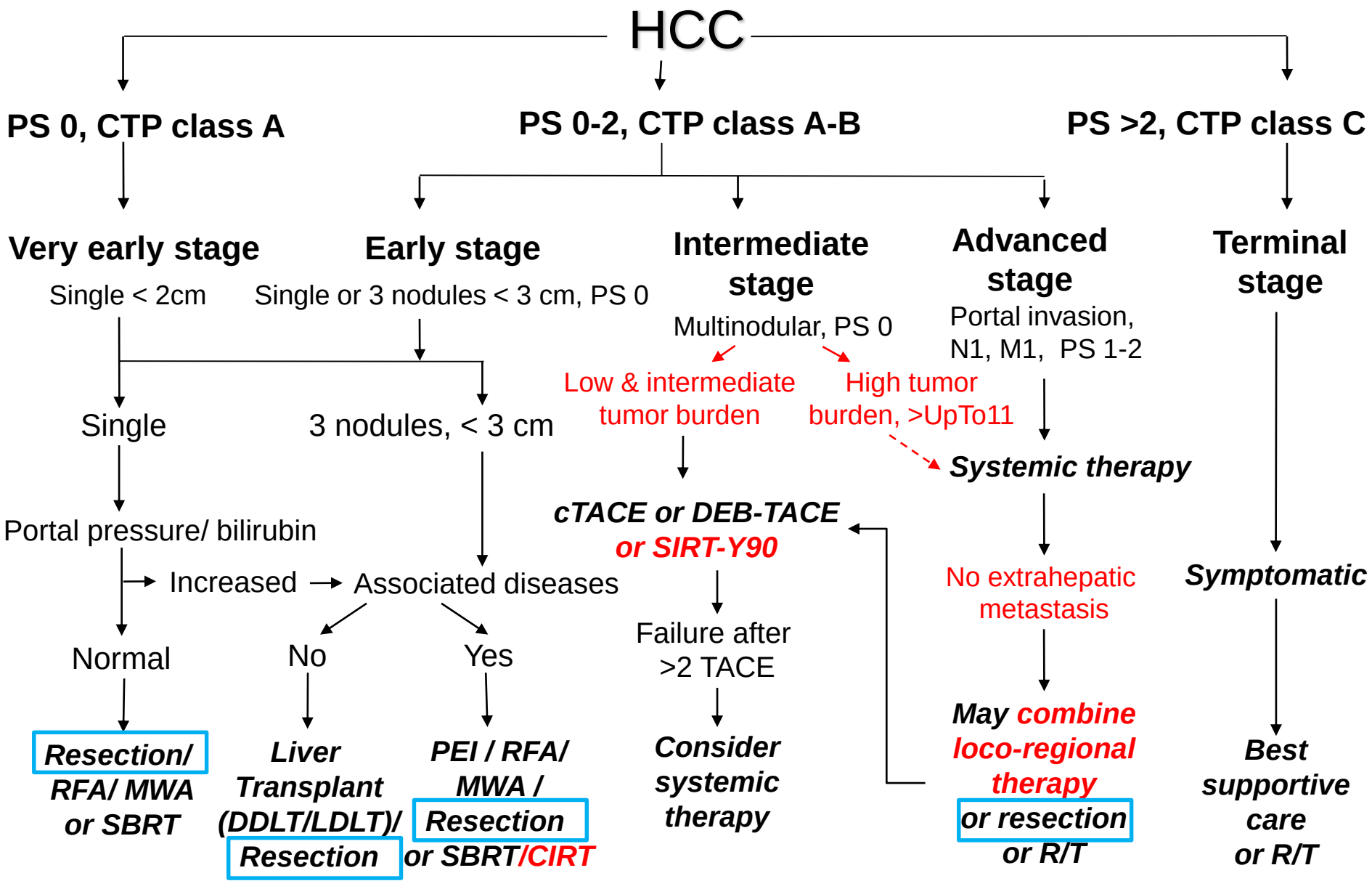


Hepatocellular Carcinoma
肝癌治療 ~ 手術

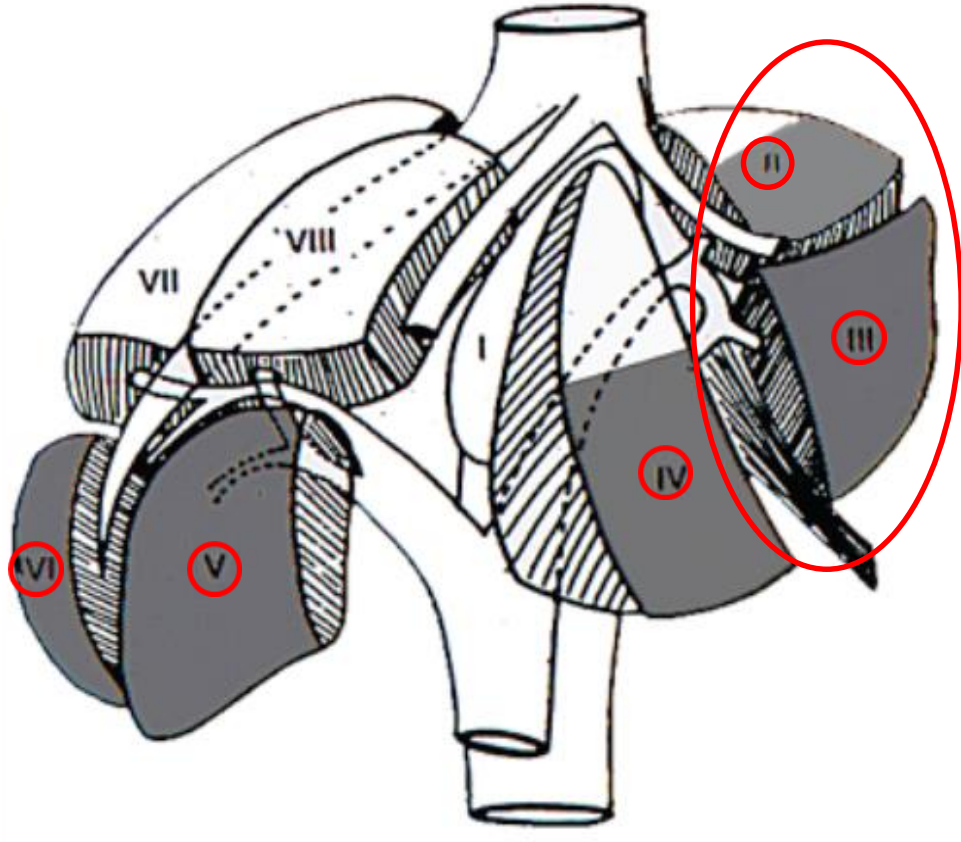
建議十：
在沒有肝硬化或是肝功能代償良好之肝硬化患者，單一肝臟腫瘤以手術切除治療為主（證據強度等級二）；

建議十一：
對於肝左葉第二節、第三節以及第四B節(不論大小)或是右葉第五、第六節單一腫瘤且不大於5公分之腫瘤可以考慮腹腔鏡微創肝葉切除術（證據強度等級三）。(參考資料)

建議十二：
在沒有肝硬化或是肝功能代償良好之肝硬化患者，雖然有大型、多顆或是局部血管侵犯，但僅限於肝葉之一側，且位置適合切除手術之患者臨床醫師可依患者狀況考慮是否接受切除手術（證據強度等級二）。

Selection of minimally invasive surgery

- **Solitary lesions, 5 cm or less, located in liver segments 2 to 6.**
- **Left lateral sectionectomy should be considered standard practice and regardless of tumor size.**
- **Major liver resections and difficult location (S7, S8 and S1) should be reserved for experienced surgeons**



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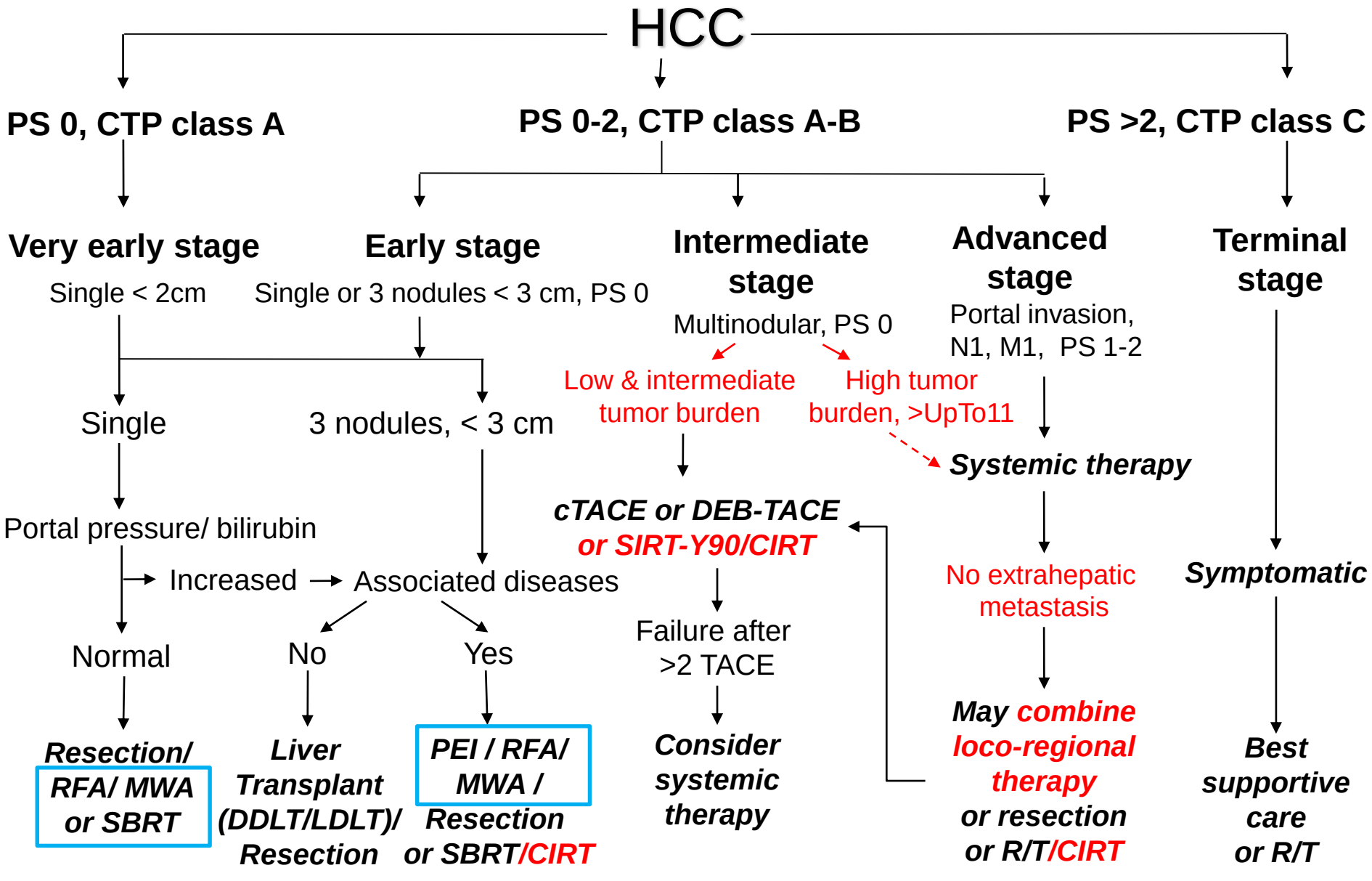

Hepatocellular Carcinoma
肝癌治療 ~局部腫瘤消除治療術

建議十三：

單一腫瘤不大於5公分、或2至3顆腫瘤且最大者小於3公分的狀況下，臨床醫師可依患者狀況考慮局部腫瘤消除治療術（包括：經皮酒精注射治療percutaneous ethanol injection therapy、經皮醋酸注射治療percutaneous acetic acid injection therapy、經皮微波熱凝治療percutaneous microwave coagulation therapy、射頻燒灼治療radiofrequency ablation therapy及微波燒灼治療microwave ablation therapy）（證據強度等級二）。

對於2公分以下之腫瘤，經皮酒精注射治療與射頻燒灼治療均同樣有效。但由於射頻燒灼治療對於造成腫瘤壞死之能力較經皮酒精注射治療為佳，對於超過兩公分之腫瘤，射頻燒灼治療之療效明顯優於經皮酒精注射治療（證據強度等級一）。

若因腫瘤位置所在位置無法進行射頻燒灼治療(radiofrequency ablation therapy)時，立體定位放射治療可為替代療法。
(分述於"肝癌治療~放射治療"章節)（證據強度等級二）。

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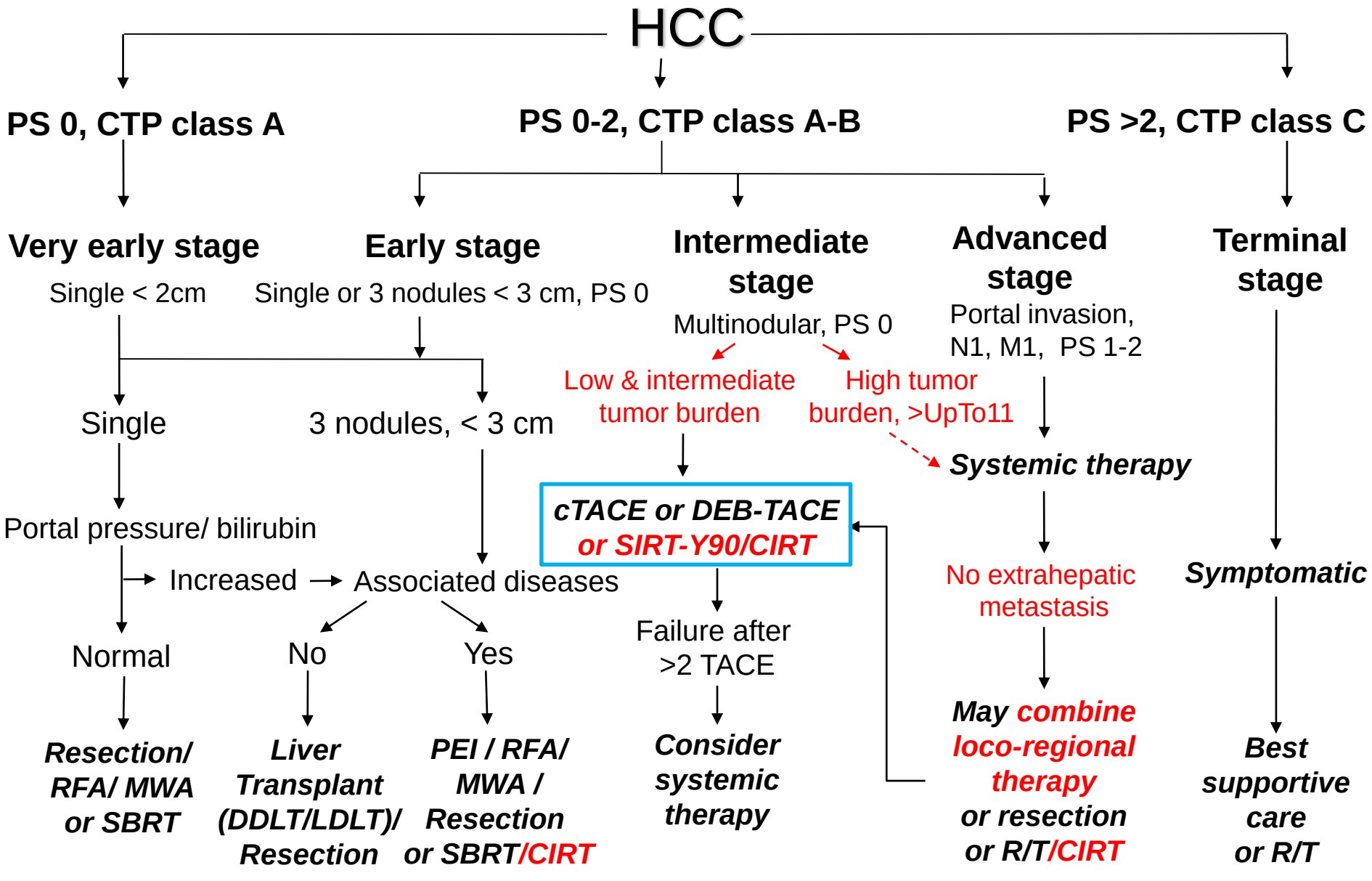


Hepatocellular Carcinoma
肝癌治療～動脈栓塞化學療法

建議十四：

動脈栓塞化學療法 (Transarterial chemoembolization)

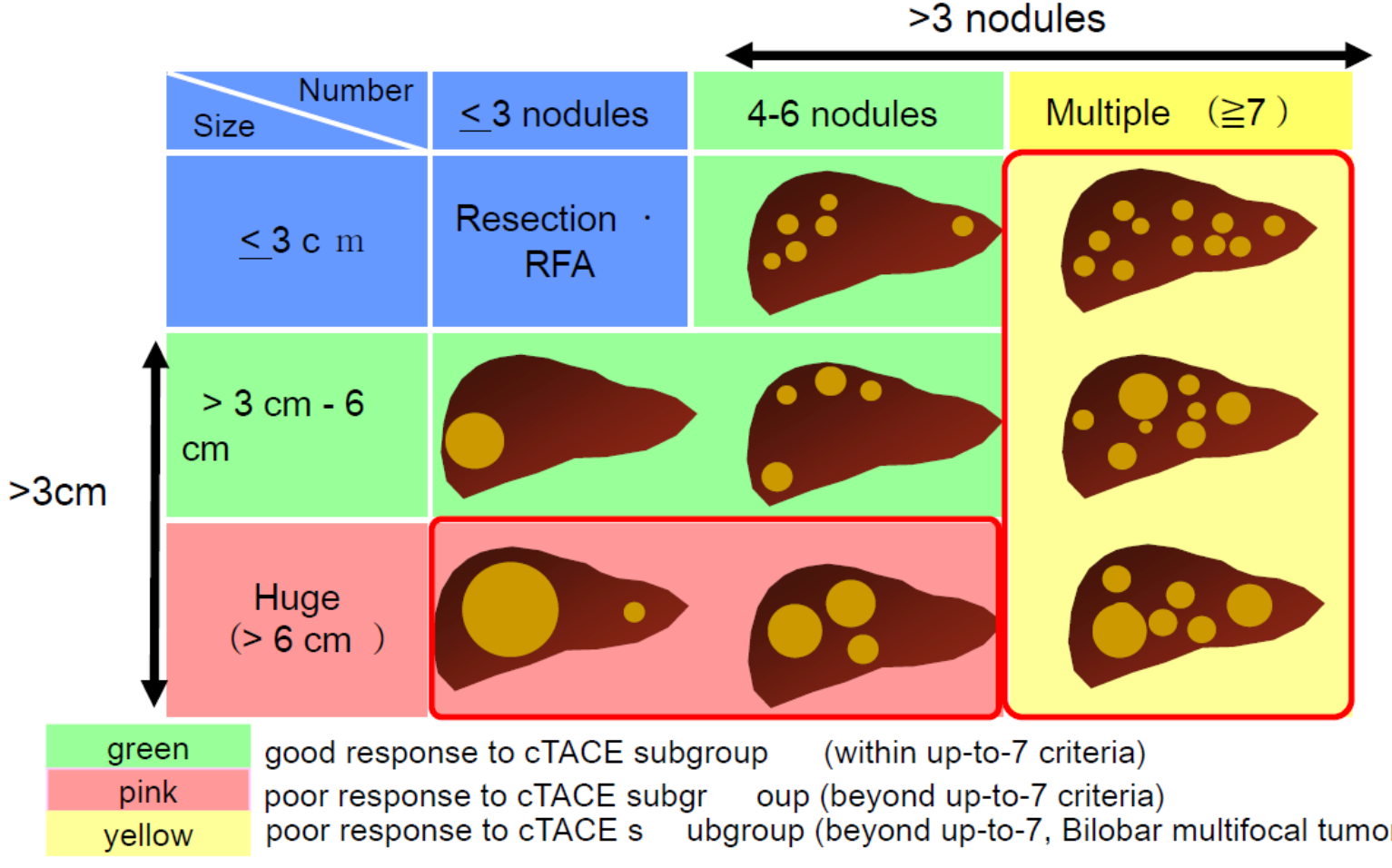
對於不適合手術治療或局部腫瘤消除治療術之大腫瘤或多發性腫瘤、~~或單側血管侵犯 VP3 or VP4、~~無肝外轉移及PV 侵犯時，為第一線之非治癒性療法（證據強度等級一）。

釔90放射栓塞術 (Y90 radioembolization) 對於此類患者可以考慮做為治療方式之選擇（證據強度等級三）。

(分述於"肝癌治療～動脈栓塞化學療法"章節)

Hepatocellular Carcinoma
肝癌治療～動脈栓塞化學療法

Heterogeneity of intermediate-stage HCC and grade of response to TACE



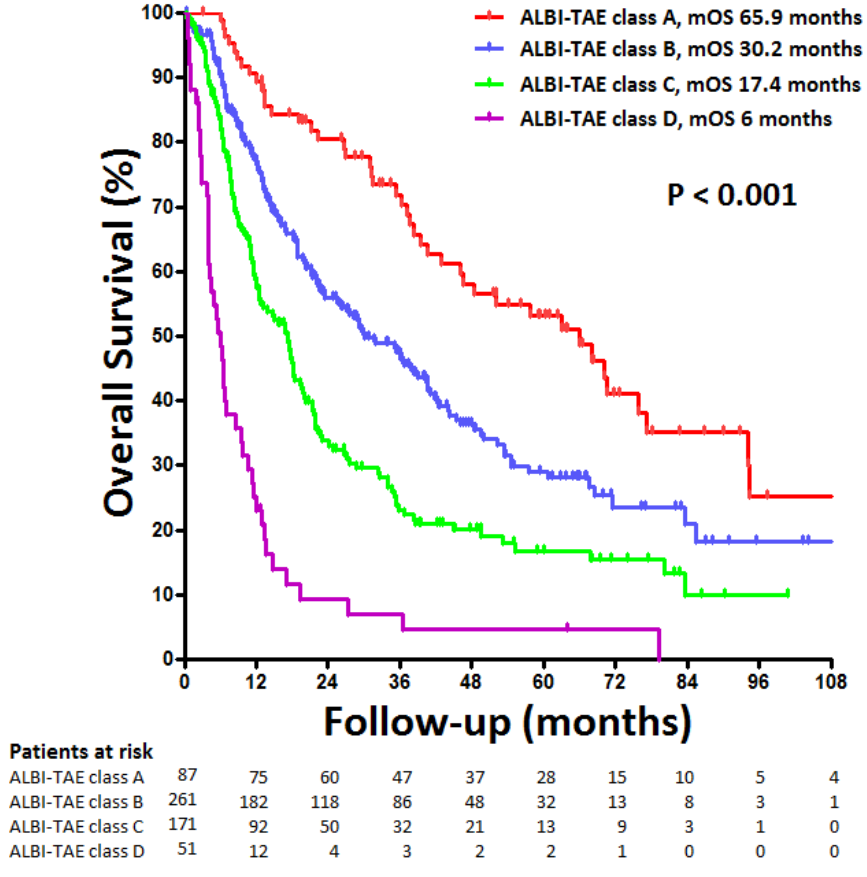
Kudo M, et al. Liver Cancer 2020;9(3):245-260.
Yasui Y, et al. Hepatol Res. 2018;48(6):442-450.

Hepatocellular Carcinoma
肝癌治療 ~ 動脈栓塞化學療法

VGH BCLC-B HCC sub-classification

ALBI-TAE model for BCLC-B HCC patients receiving TACE

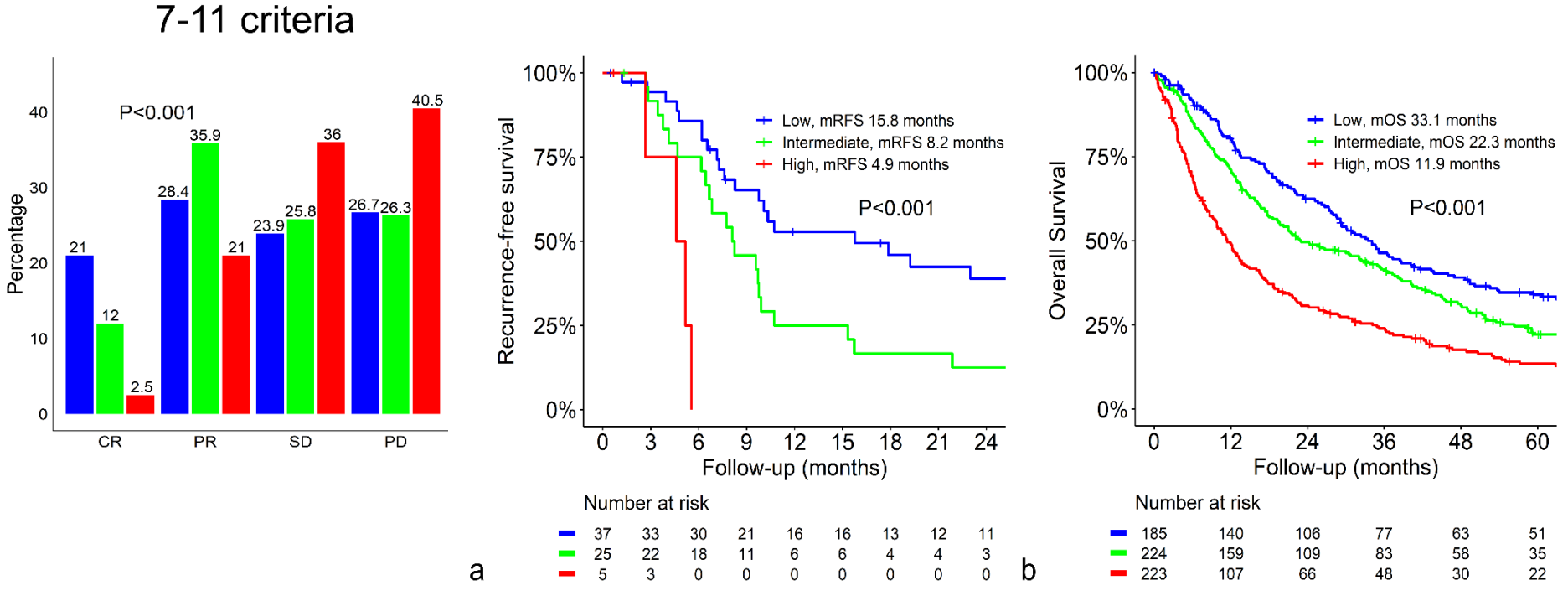
Points	0	1
ALBI grade	1	2-3
AFP (ng/mL)	≤200	>200
Up-to-11	In	Out
ALBI-TAE score:	**Class**	
0	A	
1	B	
2	C	
3	D	



Lee IC, et al. Liver Int 2019;39:1704-1712.

Hepatocellular Carcinoma
肝癌治療 ~ 動脈栓塞化學療法

VGH BCLC-B HCC 7-11 criteria



Hung YW, et al. Liver Cancer. 2021 Jul 22;10(6):629-640.

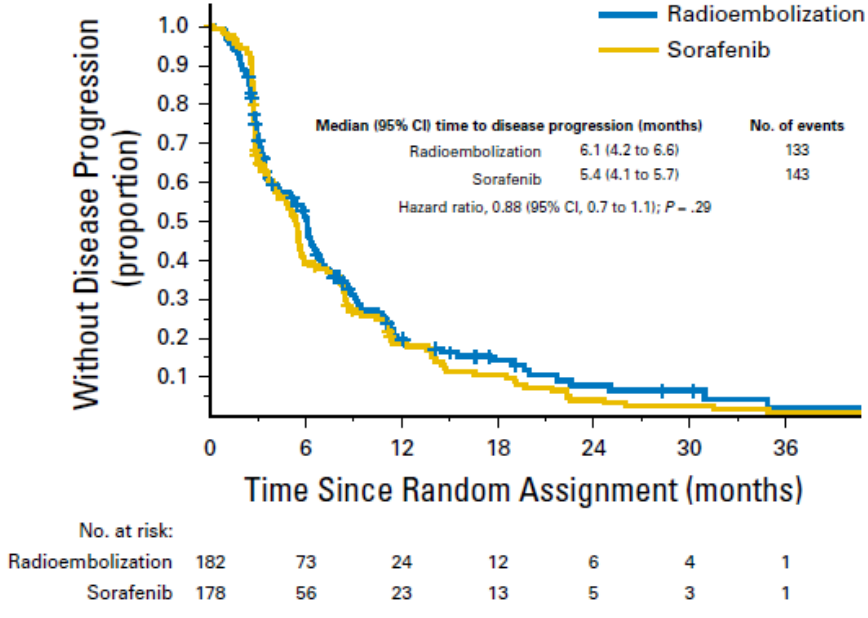
Hepatocellular Carcinoma
肝癌治療 ~ 選擇性體內放射療法

建議十五：

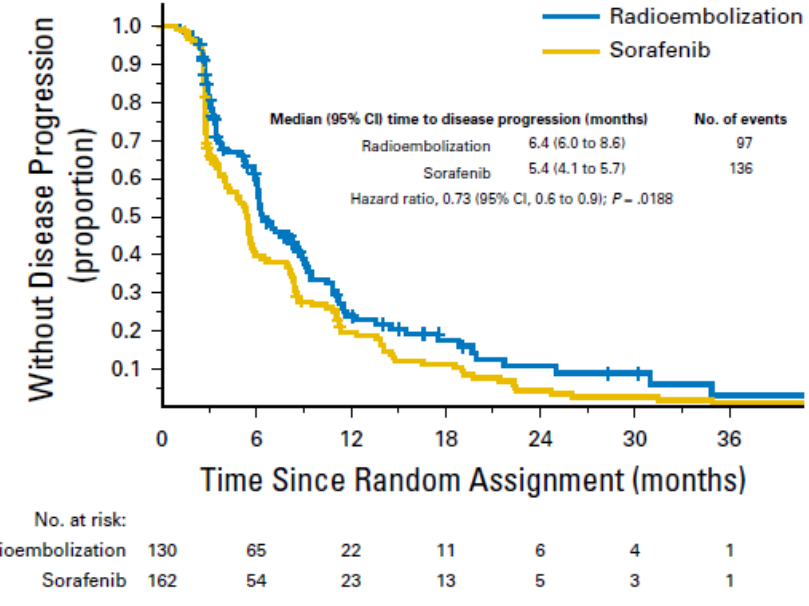
- ✓ 釔90放射栓塞術 (Y90 radioembolization)為選擇性體內放射療法 (selective internal radiation therapy) 之一種。
- ✓ 對於不適合手術治療或局部腫瘤消除治療術之大腫瘤或多發性腫瘤、或單側血管侵犯 VP3 or VP4 、無肝外轉移及MPV 侵犯時，~~或兩次動脈栓塞化學療法失敗之病人，~~ 可選擇使用釔90放射栓塞術（證據強度等級三）。
- ✓ 對於局部晚期(locally advanced stage)之病患，除了分子標靶治療之外，亦可以選擇釔90放射栓塞術 (Y90 radioembolization)，其存活數據與蕾莎瓦接近。 (根據SIRveNIB以及SARAH trial之結果)

Hepatocellular Carcinoma
肝癌治療 ~ 選擇性體內放射療法

SIRveNIB: Selective Internal Radiation Therapy Versus Sorafenib in Asia-Pacific Patients With Hepatocellular Carcinoma



Intention to treat population

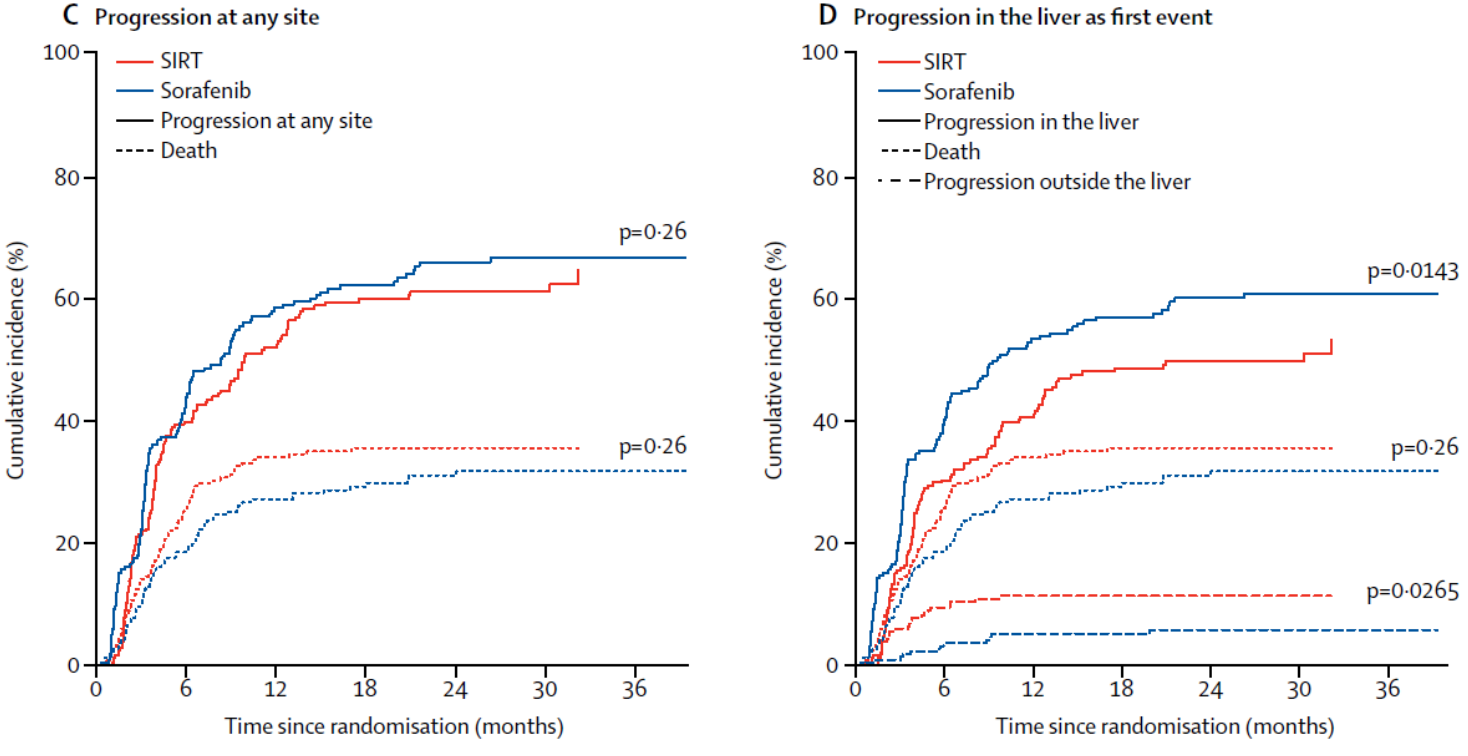


Treated population

Chow P KH, et al. J Clin Oncol. 2018;36(19):1913-1921.

Hepatocellular Carcinoma
肝癌治療 ~ 選擇性體內放射療法

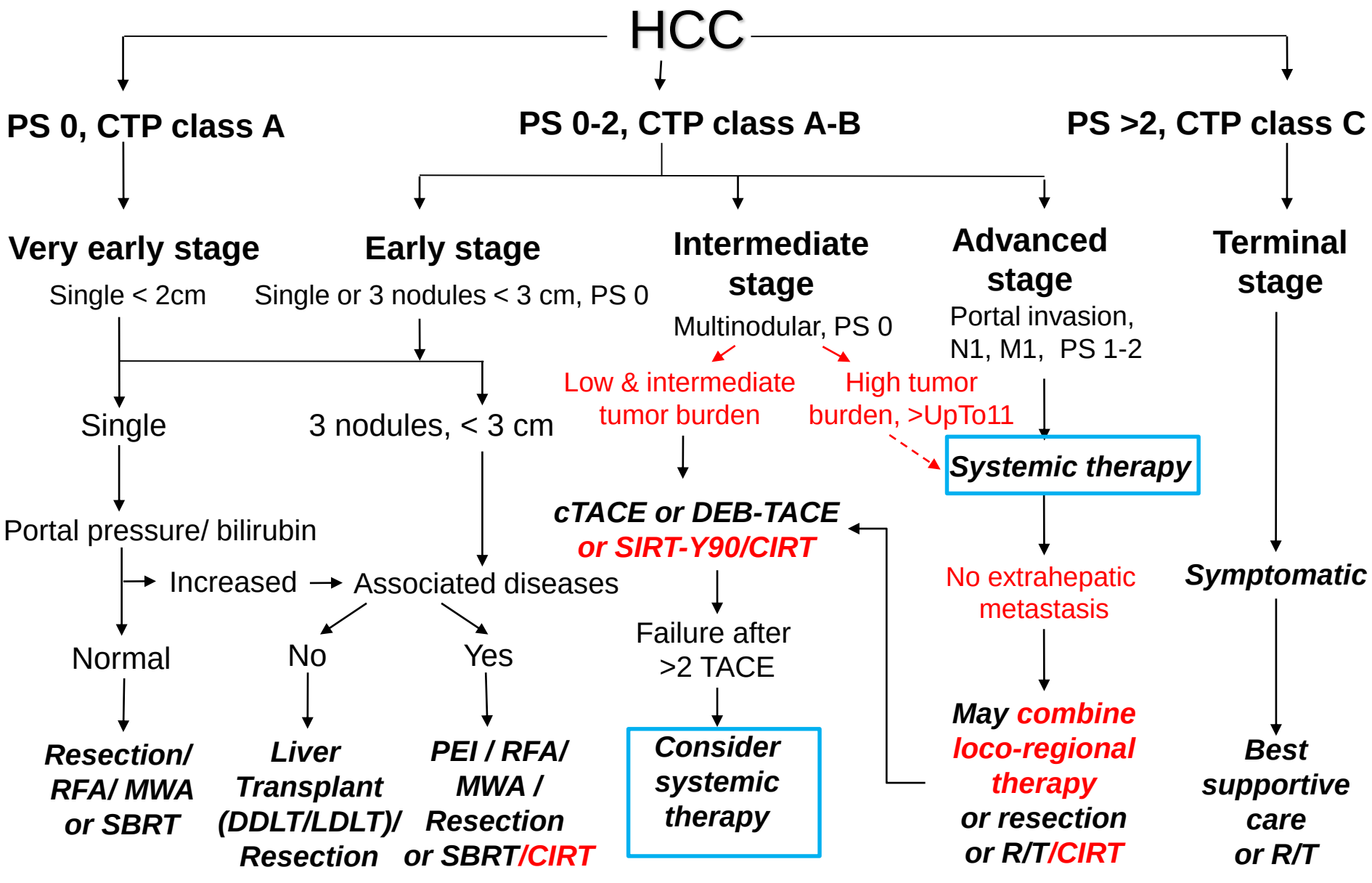
Efficacy and safety of selective internal radiotherapy with yttrium-90 resin microspheres compared with sorafenib in locally advanced and inoperable hepatocellular carcinoma (SARAH): an open-label randomised controlled phase 3 trial



Vilgrain V, et al. Lancet Oncol. 2017;18(12):1624-1636.

Hepatocellular Carcinoma
Treatment Guidelines (8th Version)

Table of Content
Staging, Manuscript



Hepatocellular Carcinoma
肝癌治療 ~ 全身性治療 (1)

建議十六：

- ✓ 單一藥物：分子標靶治療 (molecular target therapy) 如：sorafenib，對於已有血管侵犯或肝外轉移時，可有效延長患者之整體存活率，並延緩腫瘤進展（證據強度等級一），而 lenvatinib 在這類患者療效不亞於 sorafenib（證據強度等級一）。

- ✓ 合併治療：免疫藥物合併血管生長因子單株抗體 (atezolizumab + bevacizumab) 比起 sorafenib可有效延長患者之整體存活率（證據強度等級一）。

- ✓ Sorafenib 治療失敗後，可以選擇的藥物包括：regorafenib、cabozatinib、ramucirumab（證據強度等級一）、 nivolumab ± ipilimumab 或 pembrolizumab（證據強度等級二），惟 regorafenib 需使用在對sorafenib耐受性良好的患者， ramucirumab 需使用在 AFP 大於 400 ng/mL的患者。

Hepatocellular Carcinoma
肝癌治療 ~ 全身性治療 (2)

一線藥物：

Sorafenib 800mg po QD

Lenvatinib 12mg (BW > 60kg) or 8mg (BW < 60kg) po QD

Atezolizumab 1200mg + Bevacizumab 15mg/kg IV Q3W

二線藥物：

Regorafenib 160mg po QD for 3 weeks of every 4-week cycle

Ramucirumab 8mg/kg IV Q2W

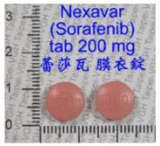
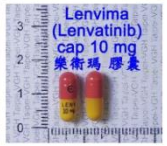
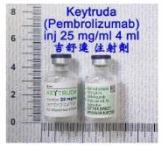
Cabozatinib 60mg po QD

Pembrolizumab 200mg IV Q3W

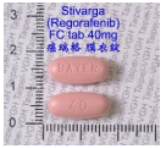
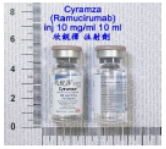
Nivolumab 3mg/kg IV Q2W

Nivolumab 1mg/kg + Ipilimumab 3mg/kg x IV Q3W 4 cycles followed by nivolumab 240mg Q2W

Hepatocellular Carcinoma
晚期肝癌醫病共享決策

	蕾莎瓦® NEXAVAR® Sorafenib	樂衛瑪® LENVIMA® Lenvatinib	樂衛瑪® + 吉舒達® LENVIMA® + KEYTRUDA® Lenvatinib + Pembrolizumab	癌自禦® + 癌思停® TECENTRIQ® + AVASTIN® Atezolizumab + Bevacizumab
藥物外觀				
藥物種類	口服標靶治療	口服標靶治療	靜脈免疫+口服標靶治療	靜脈免疫+標靶組合治療
適應症	晚期肝癌 第一線治療	晚期肝癌 第一線治療	晚期肝癌 第一線治療	晚期肝癌 第一線治療
平均存活	蕾莎瓦 10.7 月 安慰劑 7.9 月 延長 35%	樂衛瑪 13.6 月 蕾莎瓦 12.3 月 治療結果相當	樂衛瑪+吉舒達 22 月 (尚無對照組報告)	癌自禦+癌思停 19.2 月 蕾莎瓦 13.2 月 延長>21%
平均腫瘤控制	蕾莎瓦 5.5 月 安慰劑 2.8 月 延長 96%	樂衛瑪 7.4 月 蕾莎瓦 3.7 月 延長 100%	樂衛瑪+吉舒達 9.3 月 (尚無對照組報告)	癌自禦+癌思停 6.8 月 蕾莎瓦 4.3 月 延長 58%
腫瘤縮小率	蕾莎瓦 2% 安慰劑 1%	樂衛瑪 24% 蕾莎瓦 9%	樂衛瑪+吉舒達 46%	癌自禦+癌思停 33% 蕾莎瓦 13%
疾病控制率	蕾莎瓦 43% 安慰劑 32	樂衛瑪 76% 蕾莎瓦 61%	樂衛瑪+吉舒達 88%	癌自禦+癌思停 72% 蕾莎瓦 55%
生活品質保持	(無報告)	(無報告)	(無報告)	癌自禦+癌思停 11.2 月 蕾莎瓦 3.6 月 風險下降 37%
常見副作用	手足症(52%) 腹瀉(46%) 高血壓(30%) 疲倦(25%)	手足症(27%) 腹瀉(39%) 高血壓(42%) 疲倦(30%) 甲狀腺異常(16%)	高血壓(36%)、腹瀉(35%)、疲倦(30%)、甲狀腺異常(25%)	高血壓(30%)、疲倦(20%)、蛋白尿(20%)、肝指數上升(20%)

免疫治療可能有無法預期的全身免疫反應，須特別注意免疫致死性副作用，若有不適，請立即反應。

	癌瑞格® STIVARGA® Regorafenib	欣銳擇® CYRAMZA® Ramucirumab	癌必定® CABOMETYX® Cabozantinib
藥物外觀			
藥物種類	口服標靶治療	靜脈標靶治療	口服標靶治療
適應症	晚期肝癌第二線治療 能忍受蕾莎瓦副作用	晚期肝癌第二線治療 (AFP >400 ng/ml)	晚期肝癌第二線治療
存活延長(平均存活)	癌瑞格 10.6 月 安慰劑 7.8 月 (延長 36%)	欣銳擇 8.5 月 安慰劑 7.3 月 (延長 16%)	癌必定 10.2 月 安慰劑 8.0 月 (延長 28%)
腫瘤惡化風險(平均無惡化期)	癌瑞格 3.1 月 安慰劑 1.5 月 (延長 106%)	欣銳擇 2.8 月 安慰劑 1.6 月 (延長 75%)	癌必定 5.2 月 安慰劑 1.9 月 (延長 174%)
反應率(腫瘤縮小)	癌瑞格 7% 安慰劑 3%	欣銳擇 5% 安慰劑 1%	癌必定 4% 安慰劑 0.4%
疾病控制率(腫瘤無長大)	癌瑞格 66% 安慰劑 35%	欣銳擇 60% 安慰劑 39%	癌必定 64% 安慰劑 33%
常見副作用	手足症(53%)、腹瀉(41%)、疲倦(40%)	疲倦(14%)、高血壓(17%)、蛋白尿(14%)、出血(11%)	腹瀉(54%)、食慾不振(48%)、手足症(46%)
治療方式	每日口服 2-4 顆	每公斤 8 mg 每二週注射一次	每日口服 1 顆

Hepatocellular Carcinoma

VGH Sorafenib Real-world data

Outcome	**TPE-VGH (n=149)**	Asian-Pacific study	SHARP study
Overall survival (mo)			
Median (95% CI)	**8.0 (6.4-9.6)**	**6.5 (5.6-7.6)**	**10.7 (6.4-13.3)**
Estimated 6-mo survival rate (%)	59.3	53.3	NA
Estimated 1-yr survival rate (%)	36.1	NA	44
Progression-free survival (mo)			
Median (95% CI)	2.5 (1.7-3.3)	2.8 (2.6-3.6)	5.5 (4.1-6.9)
Post-progression survival (mo)			
Median (95% CI)	**4.6 (2.7-6.6)**	-	-
Level of response, n (%)			
Complete response	3 (2.0)	0	0
Partial response	5 (3.4)	3.3%	2%
Stable disease	59 (39.6)	54%	71%
Progressive disease	63 (42.3)	30.7%	NA
Not assessable	19 (12.8)	12%	NA

Llovet J, et al. N Engl J Med. 2008;359:378-390.
Cheng AL, et al. Lancet Oncol. 2009;10:25-34.
Lee IC, et al. Medicine 2015 ;94(14):e688

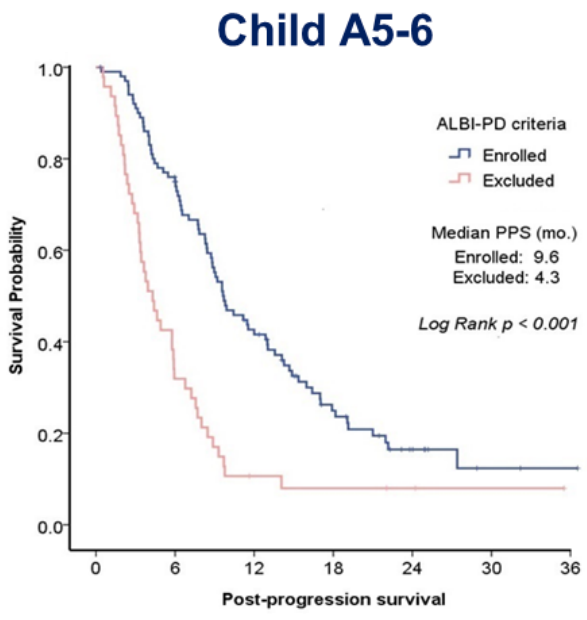
Hepatocellular Carcinoma
VGH Sorafenib Real-world data

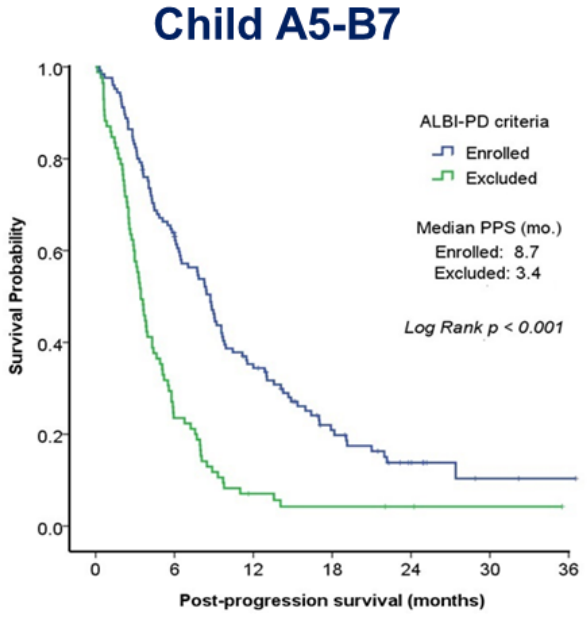
ALBI-PD Criteria differentiate Post-progression survival for Sorafenib-failed HCC

Scores of ALBI-PD criteria

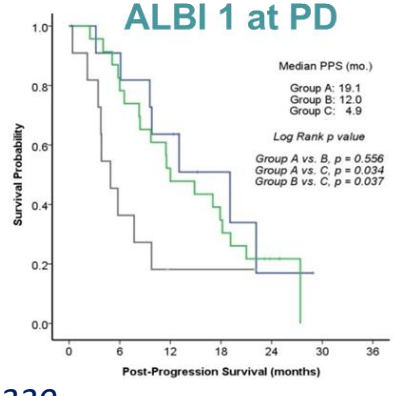
Factors	Score
ALBI grade at PD	
ALBI grade 1 or 2	2
ALBI grade 3	0
Early PD within 4 months	
No	0
Yes	-1
New extrahepatic metastasis	
No	0
Yes	-1

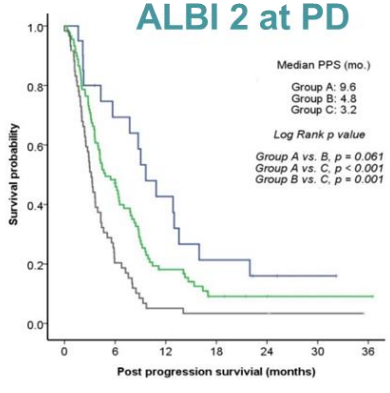
Total score > 0, enrolled

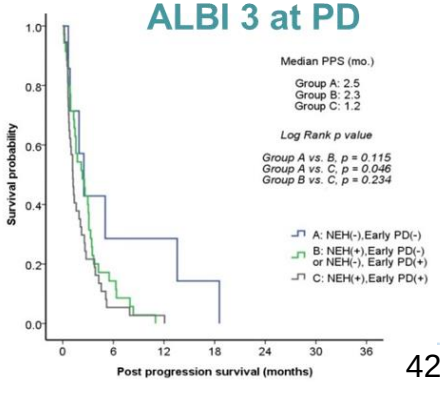




Modified figure
PPS according to
ALBI grade & PD patterns





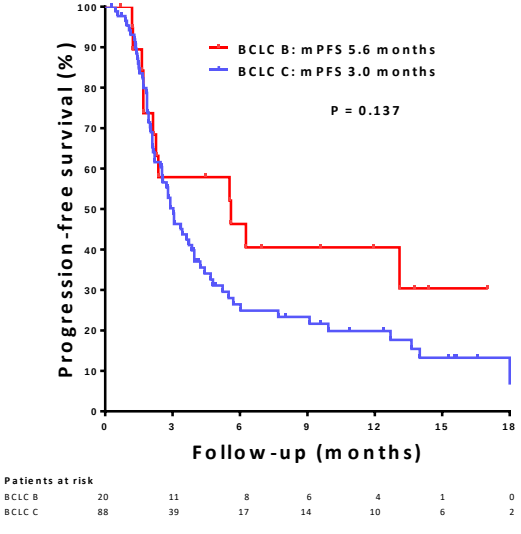


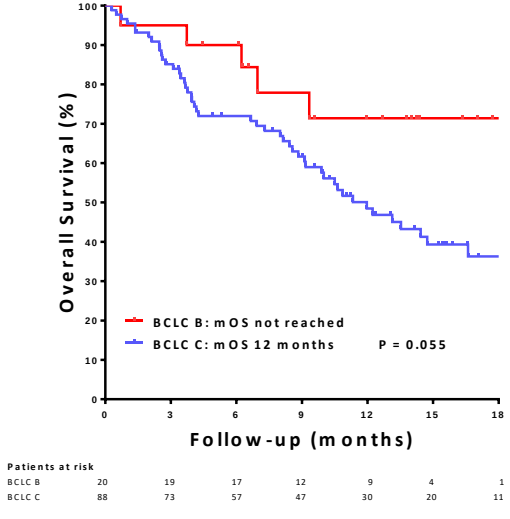
Lee PC, et al. Liver Int. 2018;38(2):321-330.

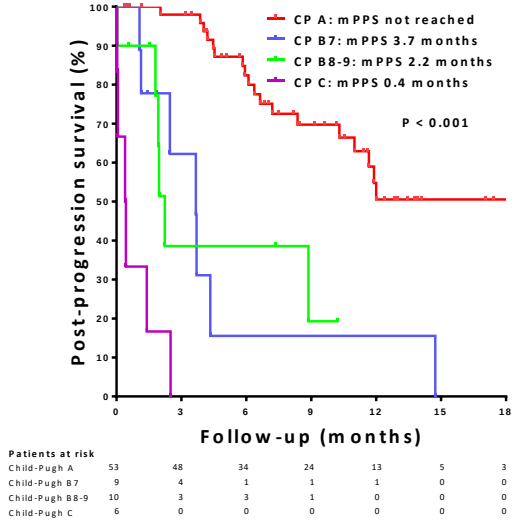
Determinants of Survival and Post-Progression Outcomes by Sorafenib-Regorafenib Sequencing for Unresectable HCC

2022 update

Radiologic response	CR	PR	SD	PD	ORR	DCR
Overall (n=96)	3 (2.9%)	8 (7.8%)	34 (33%)	58 (56.3%)	**11 (10.7%)**	**45 (43.7%)**
Line of therapy						
2L (n=77)	3 (3.6%)	6 (7.2%)	26 (31.3%)	48 (57.8%)	9 (10.8%)	35 (42.2%)
3-5L (n=19)	0 (0)	2 (10%)	8 (40%)	10 (50%)	2 (10%)	10 (50%)
P value				0.859	1.000	0.702







Lee IC, et al. Cancers (Basel). 2022 Apr 15;14(8):2014.

Hepatocellular Carcinoma

Lenvatinib versus sorafenib (REFLECT study)

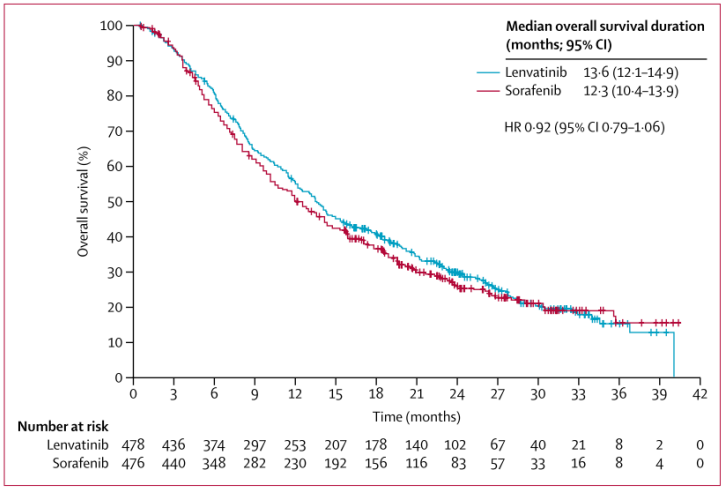


Figure 2: **Overall survival outcomes**
Kaplan-Meier estimates of overall survival by treatment group. HR=hazard ratio.

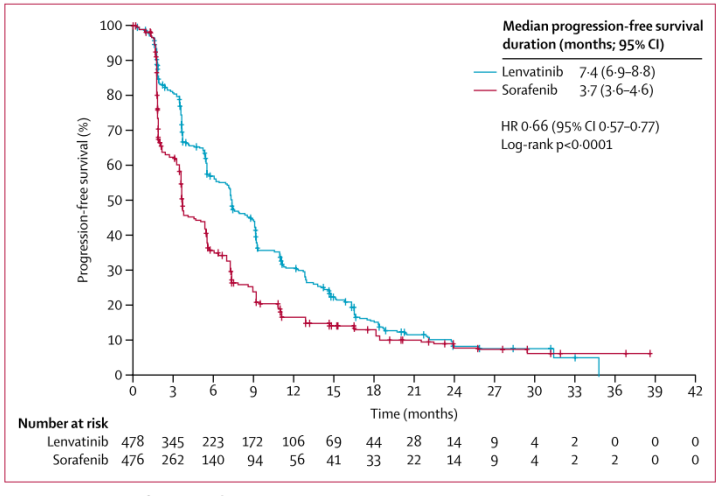


Figure 4: **Progression-free survival outcomes**
Kaplan-Meier estimates of progression-free survival by modified Response Evaluation Criteria in Solid Tumours. HR=hazard ratio.

	Lenvatinib (n=478)	Sorafenib (n=476)	Effect size (95% CI)	p value
Investigator review according to mRECIST				
Overall survival (months)	13·6 (12·1–14·9)	12·3 (10·4–13·9)	HR 0·92 (0·79–1·06)	..
Progression-free survival (months)	7·4 (6·9–8·8)	3·7 (3·6–4·6)	HR 0·66 (0·57–0·77)	<0·0001
Time to progression (months)	8·9 (7·4–9·2)	3·7 (3·6–5·4)	HR 0·63 (0·53–0·73)	<0·0001
Objective response (%, 95% CI)	115 (24·1%, 20·2–27·9)	44 (9·2%, 6·6–11·8)	OR 3·13 (2·15–4·56)	<0·0001
Complete response	6 (1%)	2 (<1%)	..	..
Partial response	109 (23%)	42 (9%)	..	..
Stable disease	246 (51%)	244 (51%)	..	..
Durable stable disease lasting ≥23 weeks	167 (35%)	139 (29%)	..	..
Progressive disease	71 (15%)	147 (31%)	..	..
Unknown or not evaluable	46 (10%)	41 (9%)	..	..
Disease control rate (%, 95% CI)	361 (75·5%, 71·7–79·4)	288 (60·5%, 56·1–64·9)	..	..

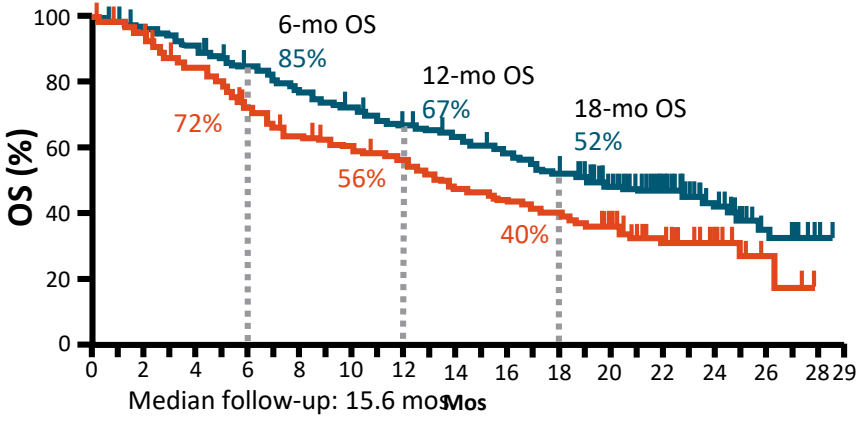
	Lenvatinib (n=476)	Sorafenib (n=475)
Total treatment-emergent adverse events	470 (99%)	472 (99%)
Total treatment-related treatment-emergent adverse events	447 (94%)	452 (95%)
Treatment-emergent adverse events of grade ≥3	357 (75%)	316 (67%)
Treatment-related treatment-emergent adverse events of grade ≥3	270 (57%)	231 (49%)
Serious treatment-emergent adverse events	205 (43%)	144 (30%)
Serious treatment-related treatment-emergent adverse events	84 (18%)	48 (10%)

Kudo M, et al. Lancet. 2018;391(10126):1163.

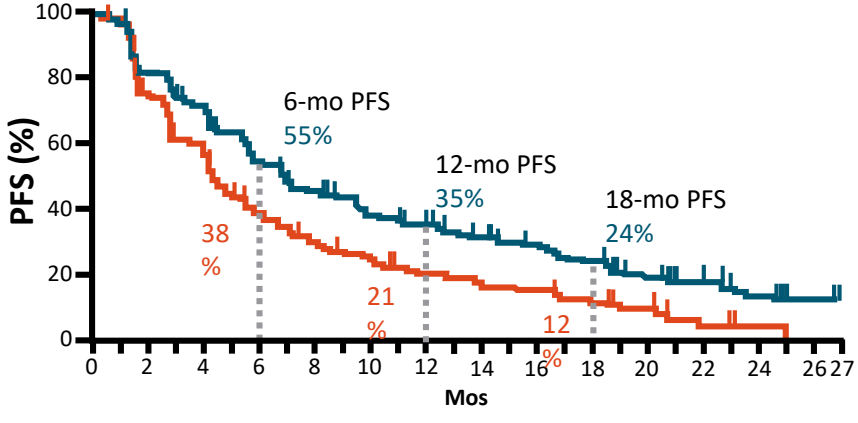
Hepatocellular Carcinoma

IMbrave150: Updated OS and PFS

	Atezo + Bev (n = 336)	Sorafenib (n = 165)
Median OS, mos	**19.2**	**13.4**
(95% CI)	(17.0-23.7)	(11.4-16.9)
Stratified HR (95% CI)	0.66 (0.52-0.85)	
	P = .0009	



	Atezo + Bev (n = 336)	Sorafenib (n = 165)
Median PFS, mos	**6.9**	**4.3**
(95% CI)	(5.7-8.6)	(4.0-5.6)
Stratified HR (95% CI)	0.65 (0.53-0.81)	
	P = .0001	



SINGAPORE 2019 ESMO ASIA

Response rate and duration of response

	IRF RECIST 1.1		IRF HCC mRECIST	
	Atezo + Bev (n = 326)	Sorafenib (n = 159)	Atezo + Bev (n = 325)[a]	Sorafenib (n = 158)
Confirmed ORR, n (%) (95% CI)	89 **(27)** (23, 33)	19 **(12)** (7, 18)	108 **(33)** (28, 39)	21 **(13)** (8, 20)
CR	18 (6)	0	33 (10)	3 (2)
PR	71 (22)	19 (12)	75 (23)	18 (11)
Stratified *P* value[b]	**< 0.0001**		**< 0.0001**	
SD, n (%)	151 (46)	69 (43)	127 (39)	66 (42)
PD, n (%)	64 (20)	39 (25)	66 (20)	40 (25)
DCR, n (%)	240 (74)	88 (55)	235 (72)	87 (55)
Ongoing response, n (%)[c]	77 (87)	13 (68)	84 (78)	13 (62)
Median DOR, months (95% CI)	NE	6.3 (4.7, NE)	NE	6.3 (4.9, NE)
Event-free rate at 6 months, n (%)	88	59	82	63

[a] IRF HCC mRECIST–evaluable population was based on patients who presented with measurable disease at baseline per HCC mRECIST criteria.
[b] Stratification factors included geographic region (Asia vs rest of world, including Japan), AFP level (< 400 vs ≥ 400 ng/mL) at baseline and MVI and/or EHS (yes vs no) per IxRS. [c] Denominator is patients with confirmed CR/PR. Data cutoff, 29 Aug 2019; median survival follow-up, 8.6 mo.

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Finn. ASCO GI 2021. Abstr 267.

Tremelimumab plus Durvalumab in Unresectable Hepatocellular Carcinoma

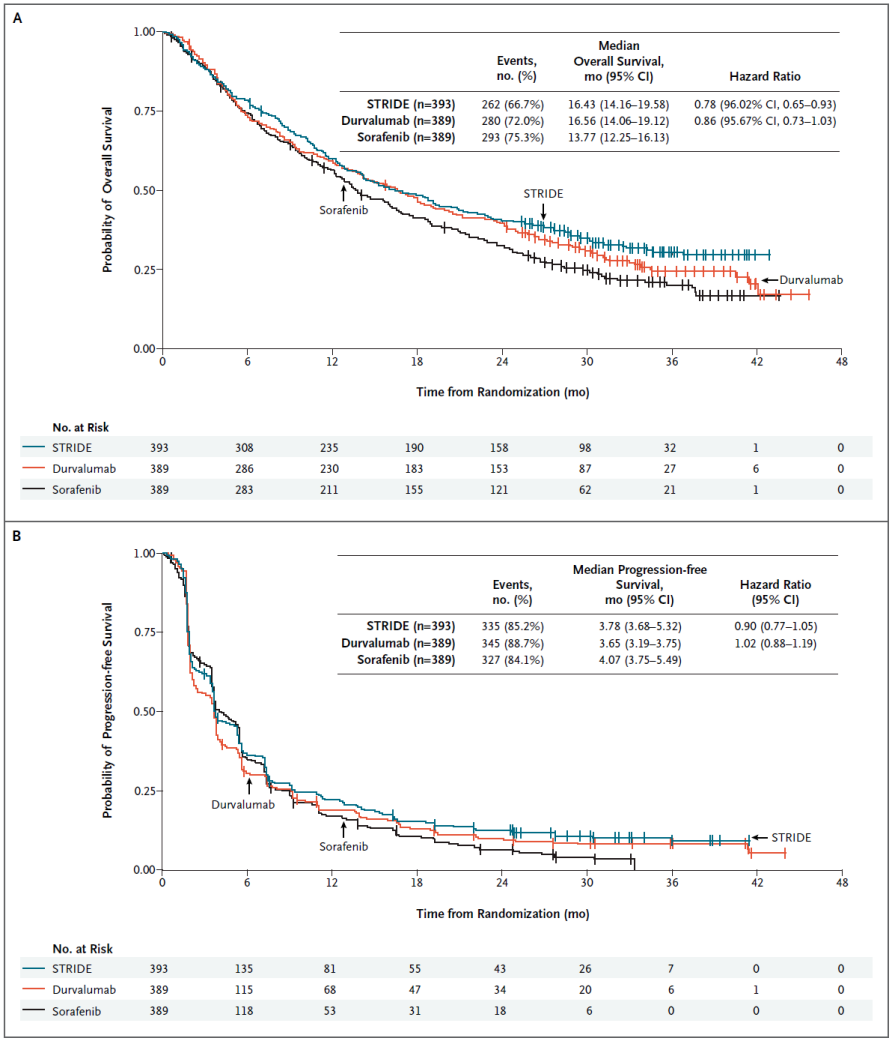
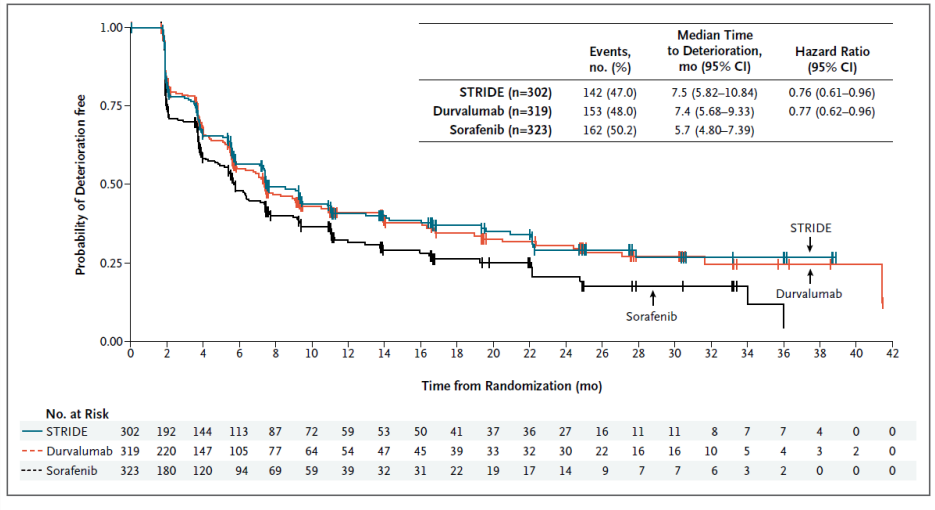


Table 2. Response Outcomes in the Intent-to-Treat Population (Confirmed).*

Parameter	STRIDE (n=393)	Durvalumab (n=389)	Sorafenib (n=389)
Response — no. (%)			
Objective†	79 (20.1)	66 (17.0)	20 (5.1)
Complete	12 (3.1)	6 (1.5)	0
Partial	67 (17.0)	60 (15.4)	20 (5.1)
Stable disease — no. (%)	157 (39.9)	147 (37.8)	216 (55.5)
Disease control rate — %	236 (60.1)	213 (54.8)	236 (60.7)
Duration of response — mo‡			
Median	22.34	16.82	18.43
IQR	8.54–NR	7.43–NR	6.51–25.99
Time to response — mo			
Median	2.17	2.09	3.78
95% CI	(1.84–3.98)	(1.87–3.98)	(1.89–8.44)



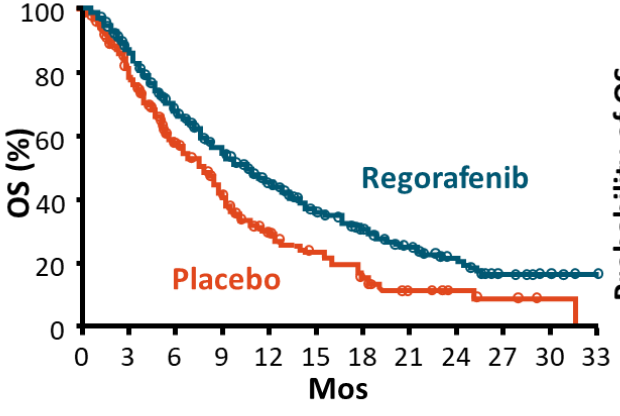
Abou-Alfa GK, et al. Tremelimumab plus Durvalumab in Unresectable Hepatocellular Carcinoma. NEJM Evid 2022; 1 (8)

Hepatocellular Carcinoma

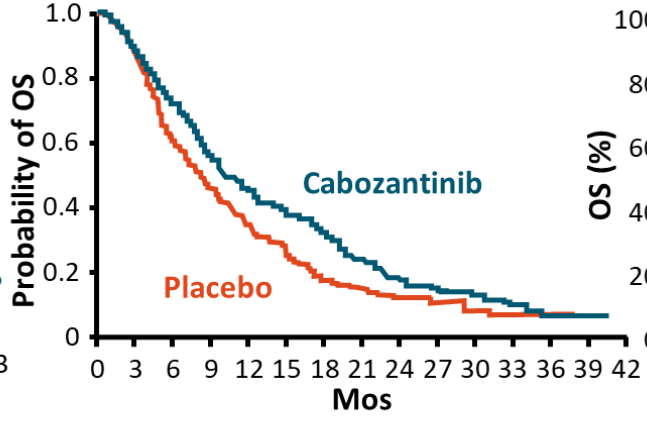
Post Sorafenib 2nd line MKI

Multiple VEGF-Targeted Therapies Have Activity After Sorafenib: Phase III Data

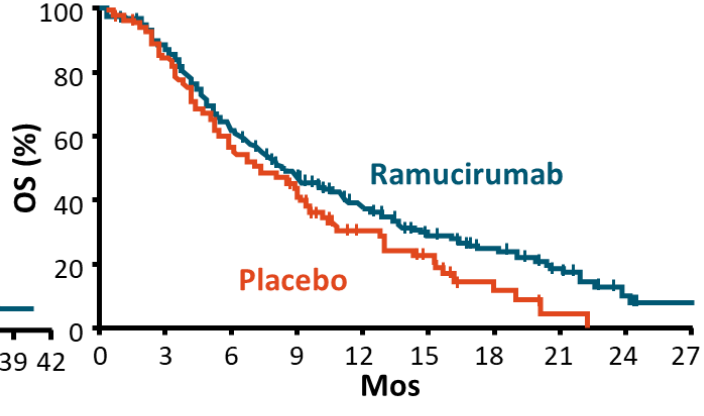
RESORCE	CELESTIAL	REACH-2
Regorafenib vs placebo	Cabozantinib vs placebo (N = 707)	Ramucirumab vs placebo
2L, sorafenib-tolerating pts only (N = 573)	2L or 3L (N = 707)	2L, AFP ≥ 400 ng/mL (N = 292)
Median OS: 10.6 vs 8.0 mos	Median OS: 10.2 vs 8.0 mos	Median OS: 8.5 vs 7.3 mos
HR: 0.63 (*P* < .0001)	HR: 0.76 (*P* = .005)	HR: 0.71 (P = .0199)



Regorafenib: multitargeted TKI



Cabozantinib: multitargeted TKI



Ramucirumab: anti-VEGFR2 Ab

Bruix J, et al. Lancet 2017; 389(10064): 56–66.
Abou-Alfa GK, et al. N Engl J Med 2018;379(1):54-63.
Zhu. Lancet Oncol. 2019;20(2):282-296.

Hepatocellular Carcinoma

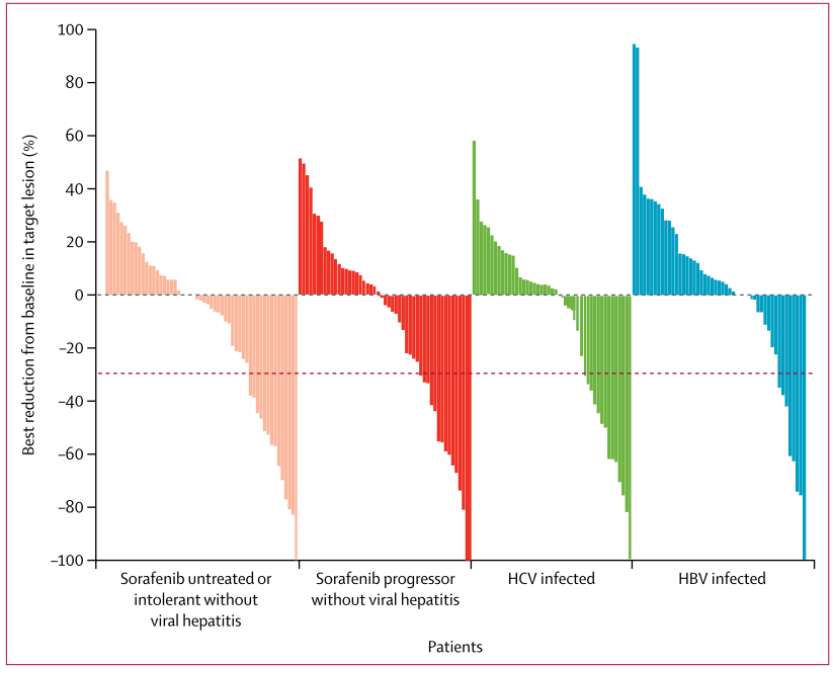
Nivolumab (CM-040)

	Escalation phase				Expansion phase				
	Uninfected (n=23)	HCV infected (n=10)	HBV infected (n=15)	All patients (n=48)	Uninfected untreated/ intolerant (n=56)	Uninfected progressor (n=57)	HCV infected (n=50)	HBV infected (n=51)	All patients (n=214)
Continuing treatment	1 (4%)	1 (10%)	0	2 (4%)	20 (36%)	10 (18%)	14 (28%)	14 (27%)	58 (27%)
Discontinued treatment	22 (96%)	9 (90%)	15 (100%)	46 (96%)	36 (64%)	47 (82%)	36 (72%)	37 (73%)	156 (73%)
Disease progression	18 (78%)	9 (90%)	15 (100%)	42 (88%)	29 (52%)	42 (74%)	24 (48%)	37 (73%)	132 (62%)
Study drug toxicity	1 (4%)	0	0	1 (2%)	4 (7%)	0	4 (8%)	0	8 (4%)
Unrelated adverse event	1 (4%)	0	0	1 (2%)	0	4 (7%)	4 (8%)	0	8 (4%)
Patient decision*	0	0	0	0	2 (4%)	1 (2%)	3 (6%)	0	6 (3%)
Complete response	2 (9%)	0	0	2 (4%)	0	0	0	0	0
Other/not reported	0	0	0	0	1 (2%)	0	1 (2%)	0	2 (1%)

Data are n (%). HCV=hepatitis C virus. HBV=hepatitis B virus. *Includes patients who withdrew consent.

***Table 2*: Patient disposition at data cutoff (Aug 8, 2016)**

	Uninfected untreated/ intolerant (n=56)	Uninfected progressor (n=57)	HCV infected (n=50)	HBV infected (n=51)	All patients (n=214)
Objective response*	13 (23%; 13 to 36)	12 (21%; 11 to 34)	10 (20%; 10 to 34)	7 (14%; 6 to 26)	42 (20%; 15 to 26)
Complete response	0	2 (4%)	0	1 (2%)	3 (1%)
Partial response	13 (23%)	10 (18%)	10 (20%)	6 (12%)	39 (18%)
Stable disease	29 (52%)	23 (40%)	23 (46%)	21 (41%)	96 (45%)
Progressive disease	13 (23%)	18 (32%)	14 (28%)	23 (45%)	68 (32%)
Not evaluable	1 (2%)	4 (7%)	3 (6%)	0	8 (4%)

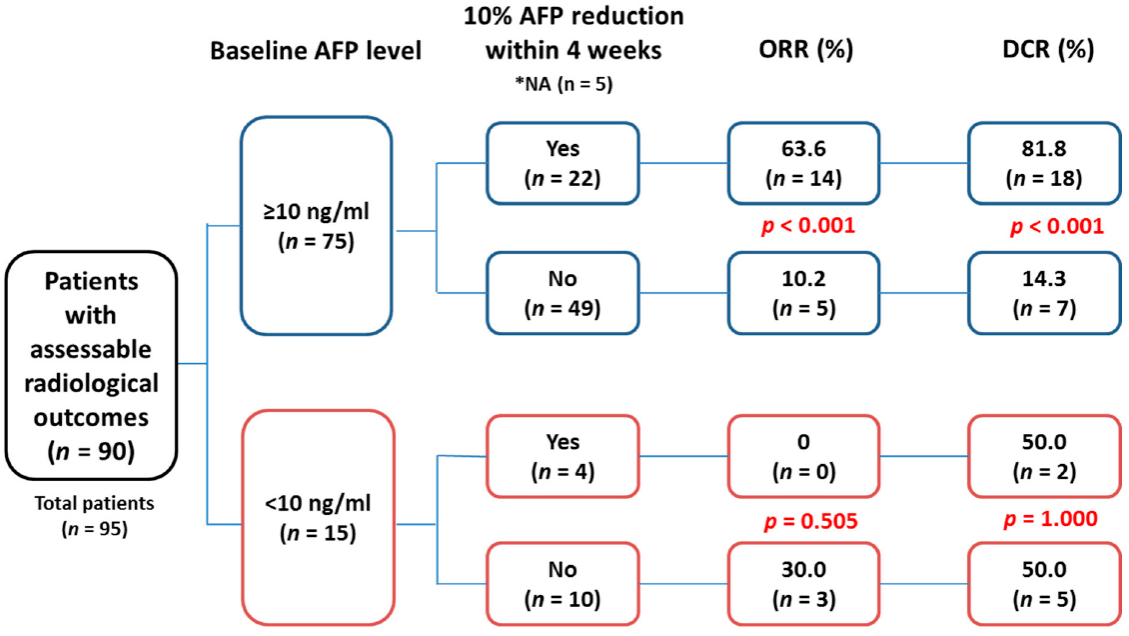


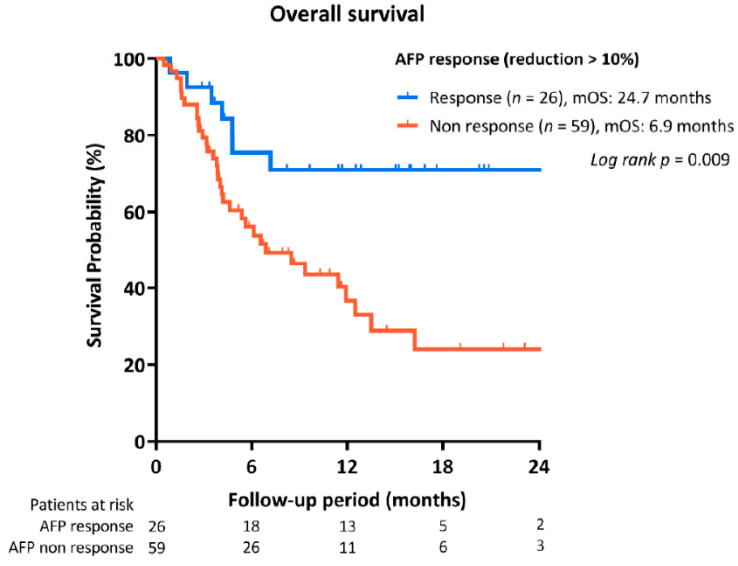
El Khoueiry AB, et al. Lancet. 2017;389(10088):2492.

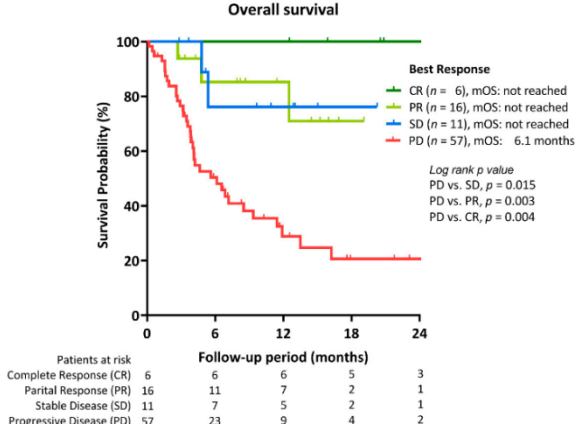
Hepatocellular Carcinoma

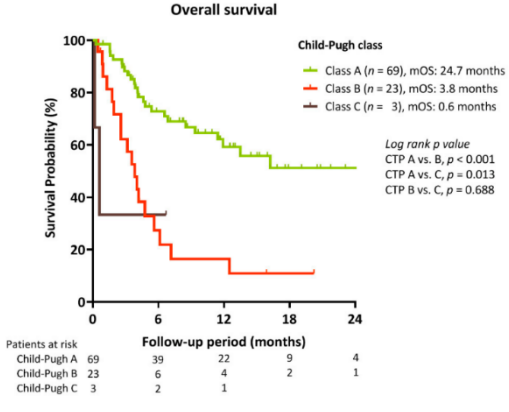
VGH Real-world data of ICI-treated HCC

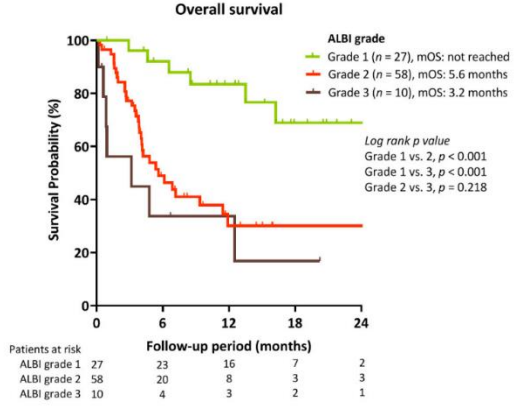
10-10 rule of AFP response to HCC immunotherapy









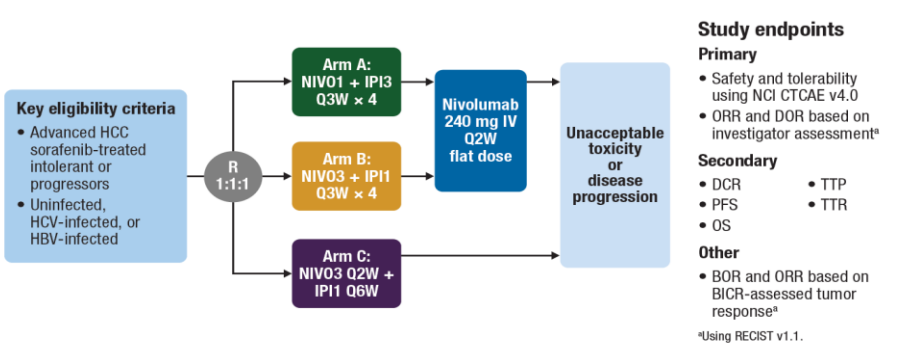


Lee PC, et al. Cancers (Basel). 2020;12(1):182.

Hepatocellular Carcinoma

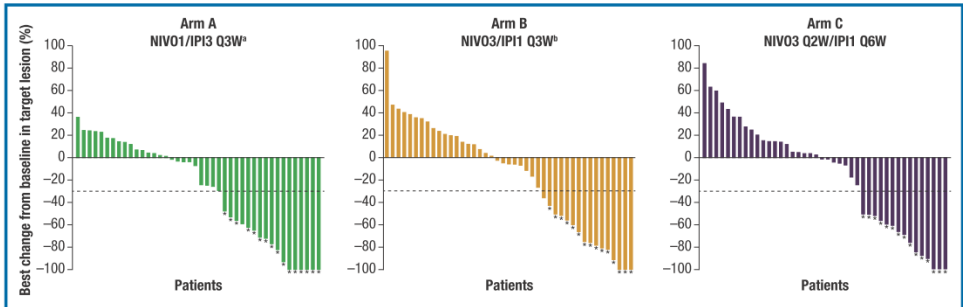
Nivolumab + ipilimumab (CM-040)

Figure 1. CheckMate 040 nivolumab plus ipilimumab combination cohort study design



Minimum follow-up at time of data cutoff: 28 months.
BICR, blinded independent central review; BOR, best overall response; DOR, duration of response; IPI1, ipilimumab 1 mg/kg; IPI3, ipilimumab 3 mg/kg; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; NIVO1, nivolumab 1 mg/kg; NIVO3, nivolumab 3 mg/kg; PFS, progression-free survival; R, randomization; TTP, time to progression; TTR, time to response.

Figure 2. Best change in target lesion by treatment arm



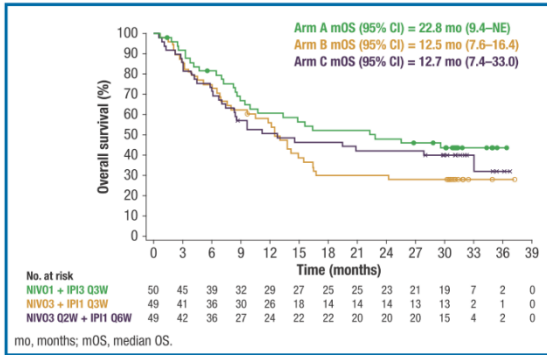
*Responders.
[a]NIVO1/IPI3 Q3W × 4 followed by nivolumab 240 mg IV Q2W flat dose; [b]NIVO3/IPI1 Q3W × 4 followed by nivolumab 240 mg IV Q2W flat dose.
Best change is based on evaluable target lesion measurements up to progression or start of subsequent therapy. Horizontal reference line indicates the 30% reduction consistent with a response per RECIST v1.1.

Table 4. Response, disease control, and durability

	Arm A NIVO1/IPI3 Q3W[a] n = 50	Arm B NIVO3/IPI1 Q3W[b] n = 49	Arm C NIVO3 Q2W/IPI1 Q6W n = 49
ORR by BICR using RECIST v1.1,[c] n (%)	16 (32)	15 (31)	15 (31)
BOR, n (%)			
CR	4 (8)	3 (6)	0
PR	12 (24)	12 (24)	15 (31)
SD[d]	9 (18)	5 (10)	9 (18)
PD	20 (40)	24 (49)	21 (43)
Unable to determine	3 (6)	4 (8)	4 (8)
DCR,[e] n (%)	27 (54)	21 (43)	24 (49)
Median TTR (range), months	2.0 (1.1–12.8)	2.6 (1.2–5.5)	2.7 (1.2–8.7)
Median DOR (range), months	17.5 (4.6 to 30.5+)	22.2 (4.2 to 29.9+)	16.6 (4.1+ to 32.0+)
ORR by investigator assessment using RECIST v1.1, n (%)	16 (32)	13 (27)	14 (29)

[a]NIVO1/IPI3 Q3W × 4 followed by nivolumab 240 mg IV Q2W flat dose; [b]NIVO3/IPI1 Q3W × 4 followed by nivolumab 240 mg IV Q2W flat dose; [c]Defined as CR + PR; [d]SD does not include 2 patients in Arm A and 1 patient in Arm B who were reported as non-CR/non-PD; [e]Defined as CR + PR + SD + non-CR/non-PD.
PR, partial response; SD, stable disease.

Figure 3. Overall survival



mo, months; mOS, median OS.

OS parameter	Arm A NIVO1/IPI3 Q3W[a] n = 50	Arm B NIVO3/IPI1 Q3W[b] n = 49	Arm C NIVO3 Q2W/IPI1 Q6W n = 49
12-mo OS rate, % (95% CI)	61 (46–73)	56 (41–69)	51 (36–64)
18-mo OS rate, % (95% CI)	52 (37.5–65)	30 (18–43.5)	47 (32–60)
24-mo OS rate, % (95% CI)	48 (34–61)	30 (18–43.5)	42 (28–56)
30-mo OS rate, % (95% CI)	44 (29.5–57)	28 (16–41)	40 (26.5–54)

[a]NIVO1/IPI3 Q3W × 4 followed by nivolumab 240 mg IV Q2W flat dose; [b]NIVO3/IPI1 Q3W × 4 followed by nivolumab 240 mg IV Q2W flat dose.

Yau T, et al. JAMA Oncol. 2020;6(11):e204564.

Hepatocellular Carcinoma

Pembrolizumab (Keynote-240)

	All treated participants (n=104)
Objective response*	18 (17%; 11–26)
Best overall response†	
Complete response	1 (1%)
Partial response	17 (16%)
Stable disease	46 (44%)
Progressive disease	34 (33%)
Not assessable‡	6 (6%)
Disease control§	64 (62%; 52–71)
Median time to response, months (IQR)¶	2·1 (2·1–4·1)
Median duration of response, months (range) ¶||	Not reached (3·1–14·6+**)
Duration of response ≥9 months¶||	12 (77%)

Data are n (%) or n (%; 95% CI), unless otherwise indicated. *Includes complete and partial responses. †Confirmed by independent central review with Response Evaluation Criteria in Solid Tumors. ‡These patients had a baseline assessment by investigator review or central radiology but no assessment after baseline on the data cutoff date, including discontinuation or death before the first scan after baseline. §Includes complete and partial responses and stable disease for at least 6 weeks. ¶Assessed in patients who had confirmed complete or partial responses as their best overall response. ||From product-limit (Kaplan-Meier) method for censored data. **No progressive disease by the time of last disease assessment.

Table 2: **Responses to pembrolizumab treatment**

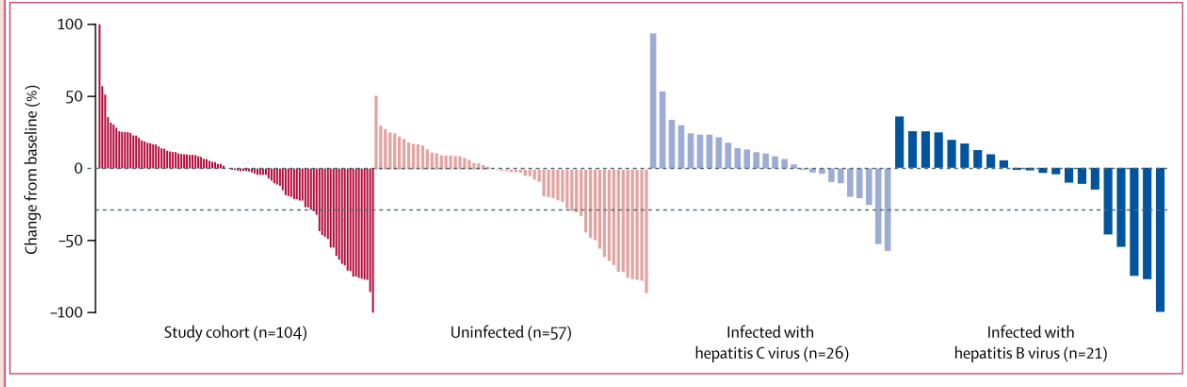


Figure 5: **Best percentage changes from baseline in size of target lesions**
Assessed with RECIST by central radiology review in patients with image measurements before and after treatment. The horizontal dashed line represents the threshold for response according to RECIST version 1.1.

Zhu AX, et al. Lancet Oncol. 2018;19(7):940-952.

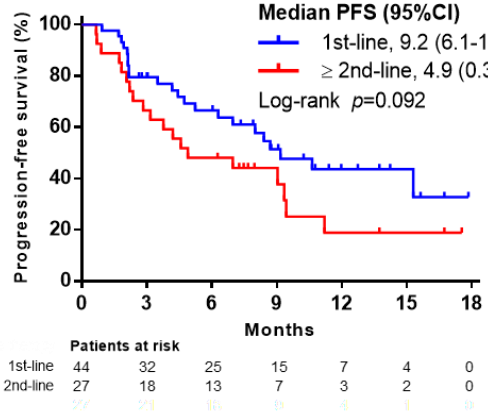
Hepatocellular Carcinoma

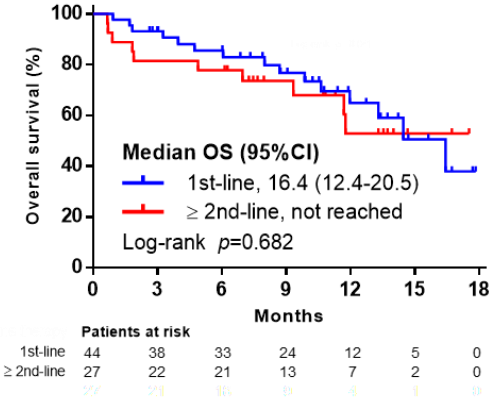
Pembrolizumab (Keynote-240)

Lenvatinib plus pembrolizumab for systemic therapy-naïve and -experienced unresectable HCC

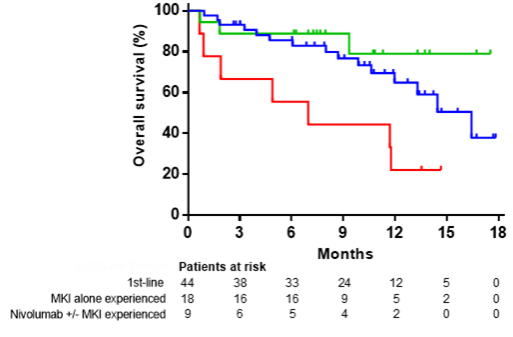
2022 update

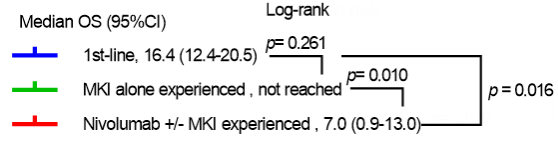
	Entire cohort (n=71)	
Radiologic response n (%)	RECIST v1.1	mRECIST
CR	1(1.5)	4(5.6)
PR	19(28.4)	37(52.1)
SD	36(53.7)	16(22.5)
PD	15(21.1)	14(19.7)
ORR	20(28.2)	41(57.7)
DCR	56(78.9)	57(80.3)





Predictor of OS		HR	p
Child–Pugh class	Class B vs. A	2.646	0.039
Nivolumab experience	Yes vs. No	3.340	0.014

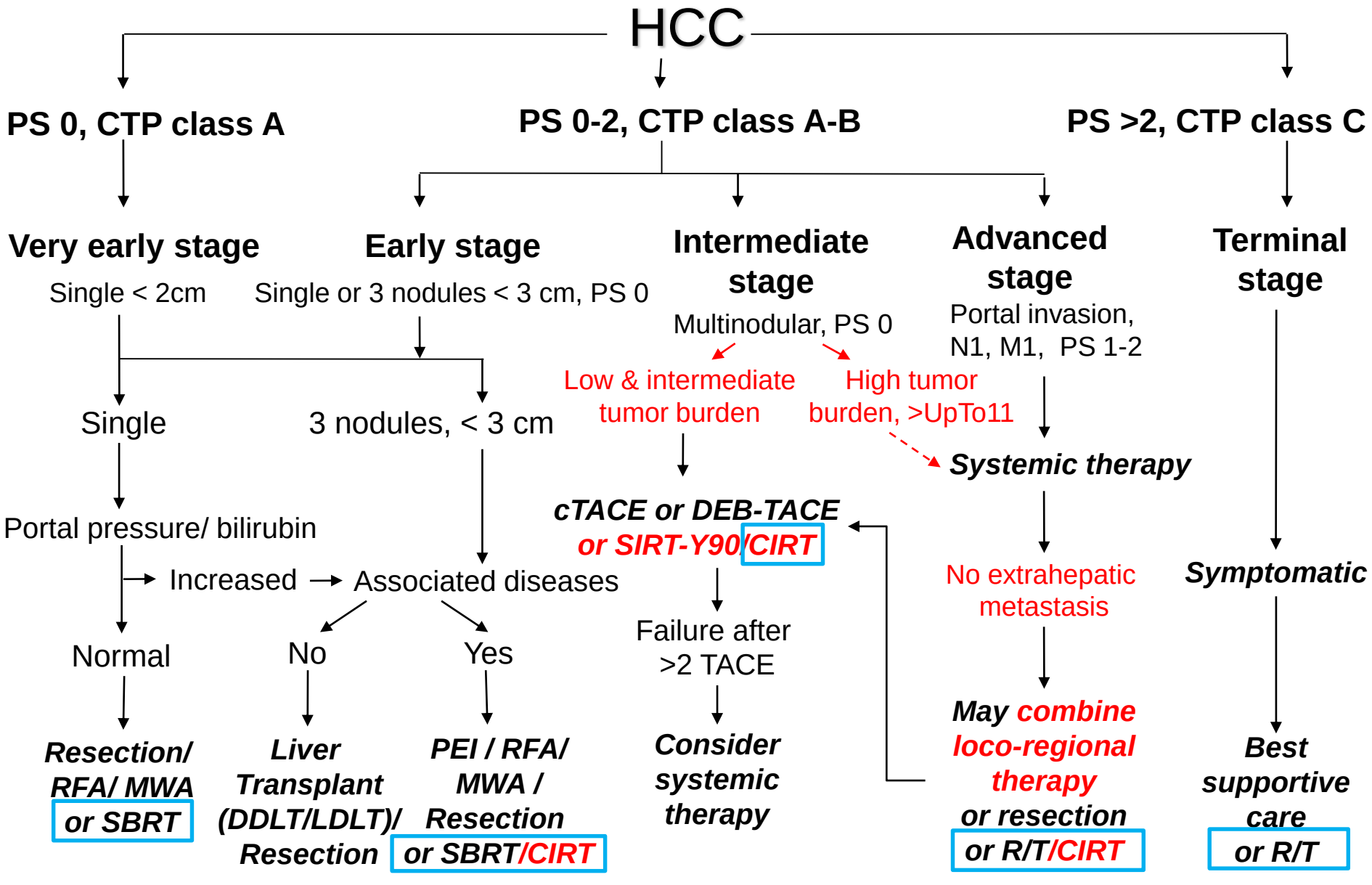




Wu CJ, al. Cancer Immunol Immunother. 2022 Mar 28. Online ahead of print.

Hepatocellular Carcinoma
Treatment Guidelines (8th Version)

Table of Content
Staging, Manuscript



Hepatocellular Carcinoma
肝癌治療 ~ 放射治療

建議十九：

立體定位放射治療(stereotactic ablative radiotherapy, SABR)可以做為肝癌初期 (PS 0; CTP score A)單一病灶患者，無法進行手術/電燒/動脈栓塞化學療法時之替代療法。腫瘤小於2cm之局部控制率與電燒相當（證據強度等級二）立體定位放射治療亦可作為銜接換肝之嫁接治療(bridging therapy) (證據強度等級二）

建議二十：

放射治療可做為局部晚期具有單獨肝門靜脈栓塞(portal vein thrombosis)無其他遠端轉移之患者打通靜脈栓塞，有利於動脈栓塞化學療法之進行。（證據強度等級二）

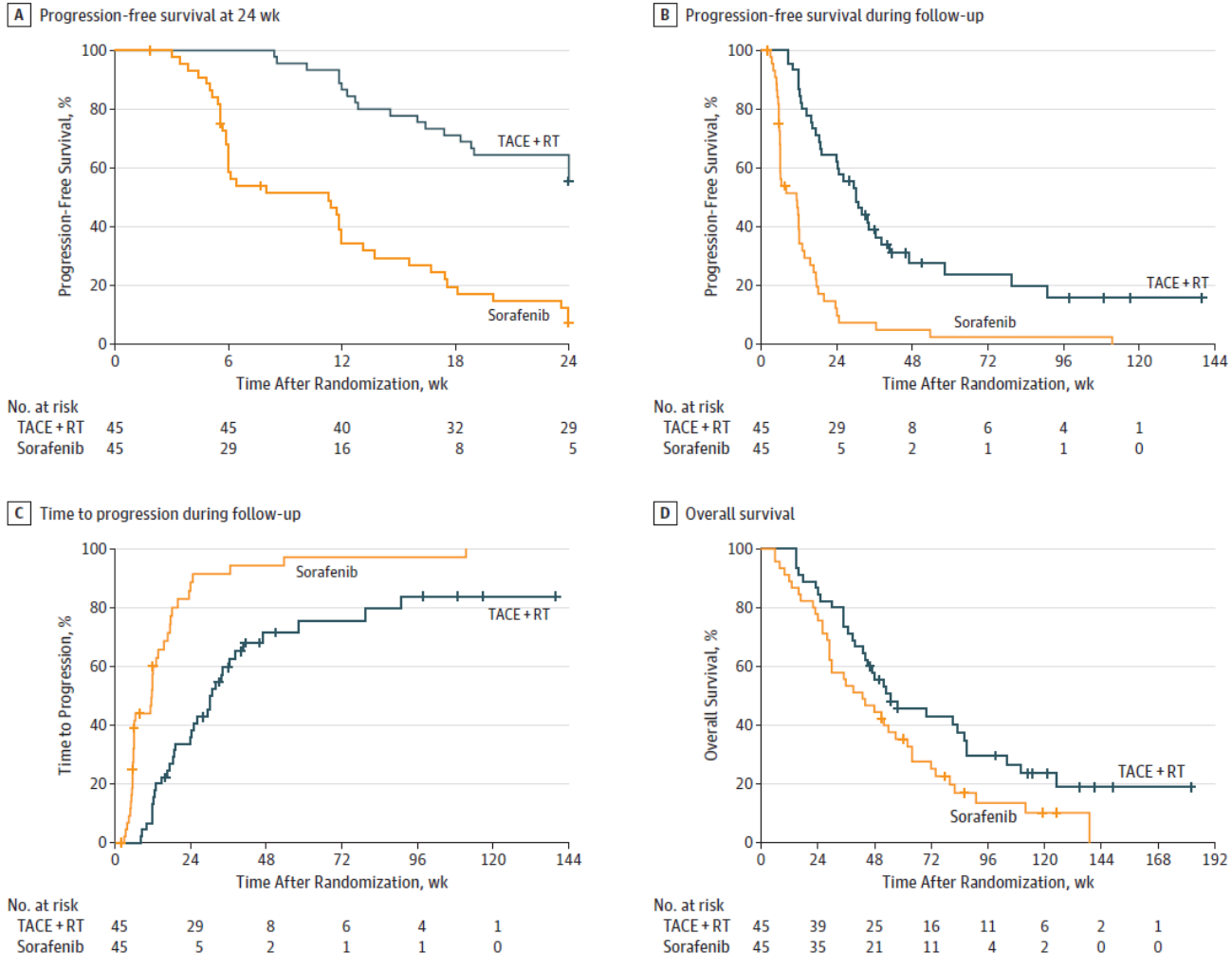
建議二十一：

放射治療可做為具有血管侵犯 (肝門靜脈或下腔靜脈)或是轉移 (腦、淋巴或是骨)且具有症狀(symptomatic)時之緩和治療選擇（證據強度等級三）。

Hepatocellular Carcinoma
肝癌治療～放射治療

建議二十二：

對局部晚期具有巨觀血管侵犯(macroscopic vascular invasion)，但無淋巴與遠端轉移之患者，於TACE後安排放射治療，疾病控制與存活皆優於僅使用sorafenib。（證據強度等級一）



Yoon SM, et al. JAMA Oncol. 2018;4(5):661-669.

Hepatocellular Carcinoma
參考資料

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2022
Hepatocellular Carcinoma

2022 update

Discussion

PRINCIPLES OF RADIATION THERAPY

External Beam Radiation Therapy:

- Treatment Modalities:[1]
  - EBRT is a treatment option for patients with unresectable disease, or for those who are medically inoperable due to comorbidity.
  - All tumors irrespective of the location may be amenable to radiation therapy (RT) (3D conformal RT (3D-CRT), intensity-modulated RT [IMRT], or stereotactic body RT [SBRT]). Image-guided RT (IGRT) is strongly recommended when using EBRT, IMRT, and SBRT to improve treatment accuracy and reduce treatment-related toxicity.
  - Hypofractionation with photons[2] or protons[2,3] is an acceptable option for intrahepatic tumors, although treatment at centers with experience is recommended.
  - SBRT is an advanced technique of hypofractionated EBRT with photons that delivers large ablative doses of radiation.
  - There is growing evidence for the usefulness of SBRT in the management of patients with HCC.[4,5] SBRT can be considered as an alternative to ablation/embolization techniques or when these therapies have failed or are contraindicated.
  - SBRT (typically 3–5 fractions) is often used for patients with 1 to 3 tumors. SBRT could be considered for larger lesions or more extensive disease, if there is sufficient uninvolved liver and liver radiation tolerance can be respected. There should be no extrahepatic disease or it should be minimal and addressed in a comprehensive management plan. The majority of data on radiation for HCC liver tumors arises from patients with Child-Pugh A liver disease; safety data are limited for patients with Child-Pugh B or poorer liver function. Those with Child-Pugh B cirrhosis can be safely treated, but they may require dose modifications and strict dose constraint adherence.[6] The safety of liver radiation for HCC in patients with Child-Pugh C cirrhosis has not been established, as there are not likely to be clinical trials available for these patients.[7,8]
  - Proton beam therapy (PBT) may be appropriate in specific situations.[9,10]
  - Palliative EBRT is appropriate for symptom control and/or prevention of complications from metastatic HCC lesions, such as bone or brain, and extensive liver tumor burden.[11]

- RT dosing,[1] depending on the ability to meet normal organ constraints and underlying liver function:
  - EBRT: SBRT or hypofractionation preferred
    - ◊ SBRT: 30–50 Gy (typically in 3–5 fractions)[12]
    - ◊ Hypofractionation[2]
      - – 37.5–72 Gy in 10–15 fractions
    - ◊ Conventional fractionation:[13,14]
      - – 50–66 Gy in 25–33 fractions

Hepatocellular Carcinoma

SBRT vs. RFA

Table 2. Univariate Analysis of Variables Predictive for Local Progression

Variable	All Lesions HR	All Lesions 95% CI	All Lesions P	RFA HR	RFA 95% CI	RFA P	SBRT HR	SBRT 95% CI	SBRT P
Treatment									
RFA *v* SBRT	2.63	1.20 to 5.75	.016	—	—	—	—	—	—
Age	1.02	0.98 to 1.06	.407	1.02	0.98 to 1.06	.439	1.01	0.91 to 1.11	.858
Tumor size	1.36	1.03 to 1.80	.029	1.54	1.13 to 2.09	.006	1.21	0.57 to 2.54	.617
Child-Pugh score	0.92	0.73 to 1.15	.452	0.92	0.75 to 1.15	.485	0.93	0.34 to 2.57	.898
AFP	1.14	0.98 to 1.32	.082	1.12	0.97 to 1.30	.116	1.23	0.86 to 1.76	.260
No. prior treatments	1.19	0.95 to 1.48	.124	1.04	0.83 to 1.31	.707	1.48	0.82 to 2.65	.190
SBRT dose	—	—	—	—	—	—	0.91	0.81 to 1.02	.110

NOTE. Age (per year), tumor size (per cm), Child-Pugh Score (per point), AFP (per doubling), No. prior treatments (per treatment), and SBRT dose (per Gy) were treated as continuous variables. Data in the All Lesions column has been corrected for treatment modality. Dashes indicate not applicable.
Abbreviations: RFA, radiofrequency ablation; SBRT, stereotactic body radiation therapy; HR, hazard ratio; AFP, alpha-fetoprotein.

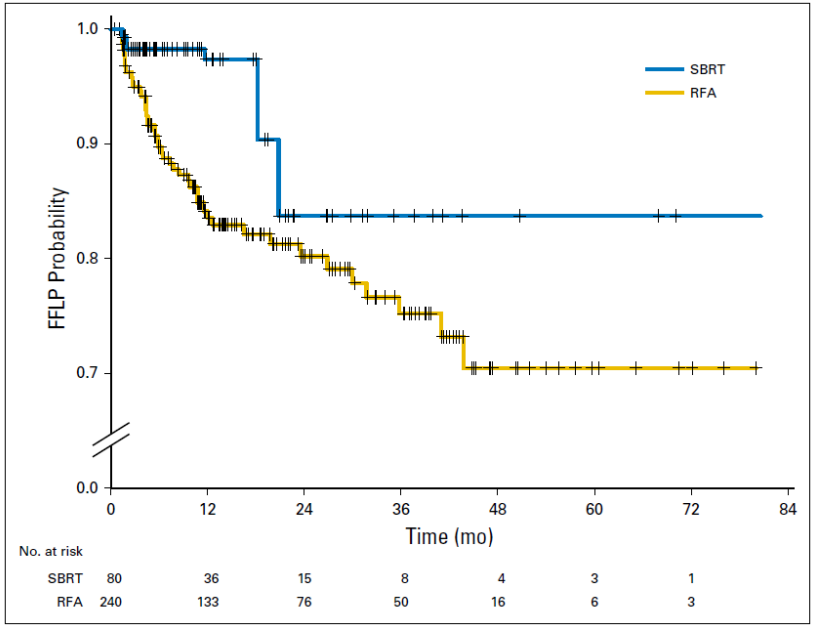


Table 3. Multivariate Cox Proportional Hazards Analysis of Factors Associated With Local Progression

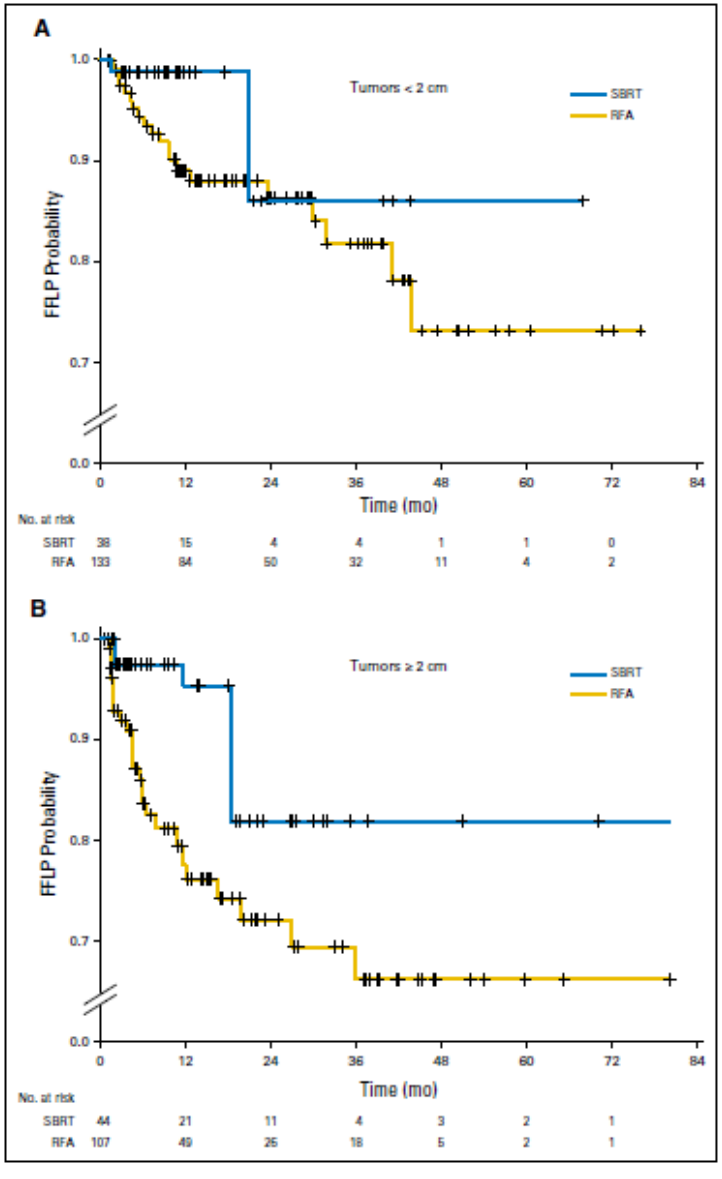
	HR	95% CI	P
Treatment			
RFA *v* SBRT	3.84	1.62 to 9.09	.002
Age	1.01	0.97 to 1.06	.514
Tumor size	1.35	0.99 to 1.84	.055
Child-Pugh score	0.95	0.74 to 1.22	.703
AFP	1.12	0.97 to 1.30	.130
No. prior treatments	1.25	1.00 to 1.56	.055

NOTE. Age (per year), tumor size (per cm), Child-Pugh score (per point), AFP (per doubling) and No. prior treatments (per treatment) were treated as continuous variables.

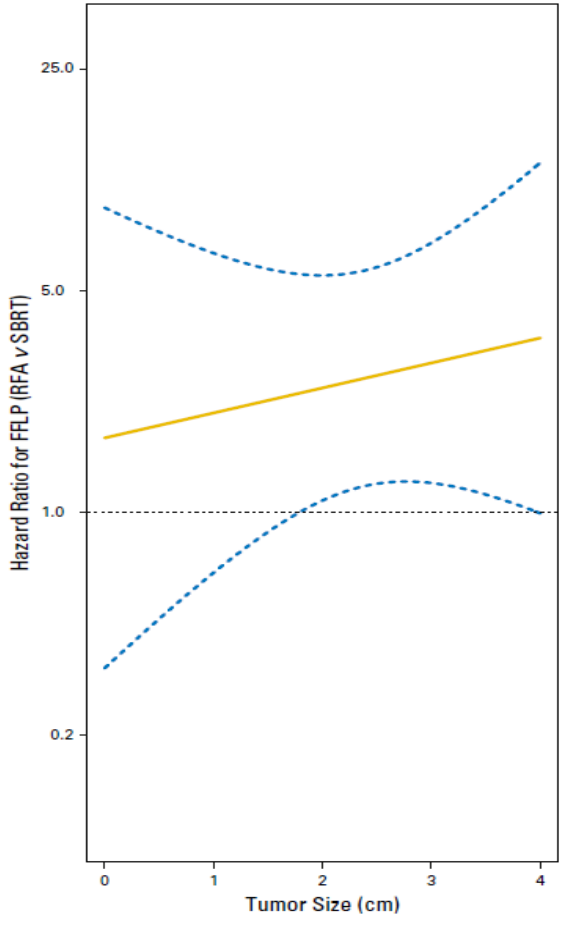
Wahi DR, et al. J Clin Oncol. 2016;34(5):452-459.

Hepatocellular Carcinoma

SBRT vs. RFA



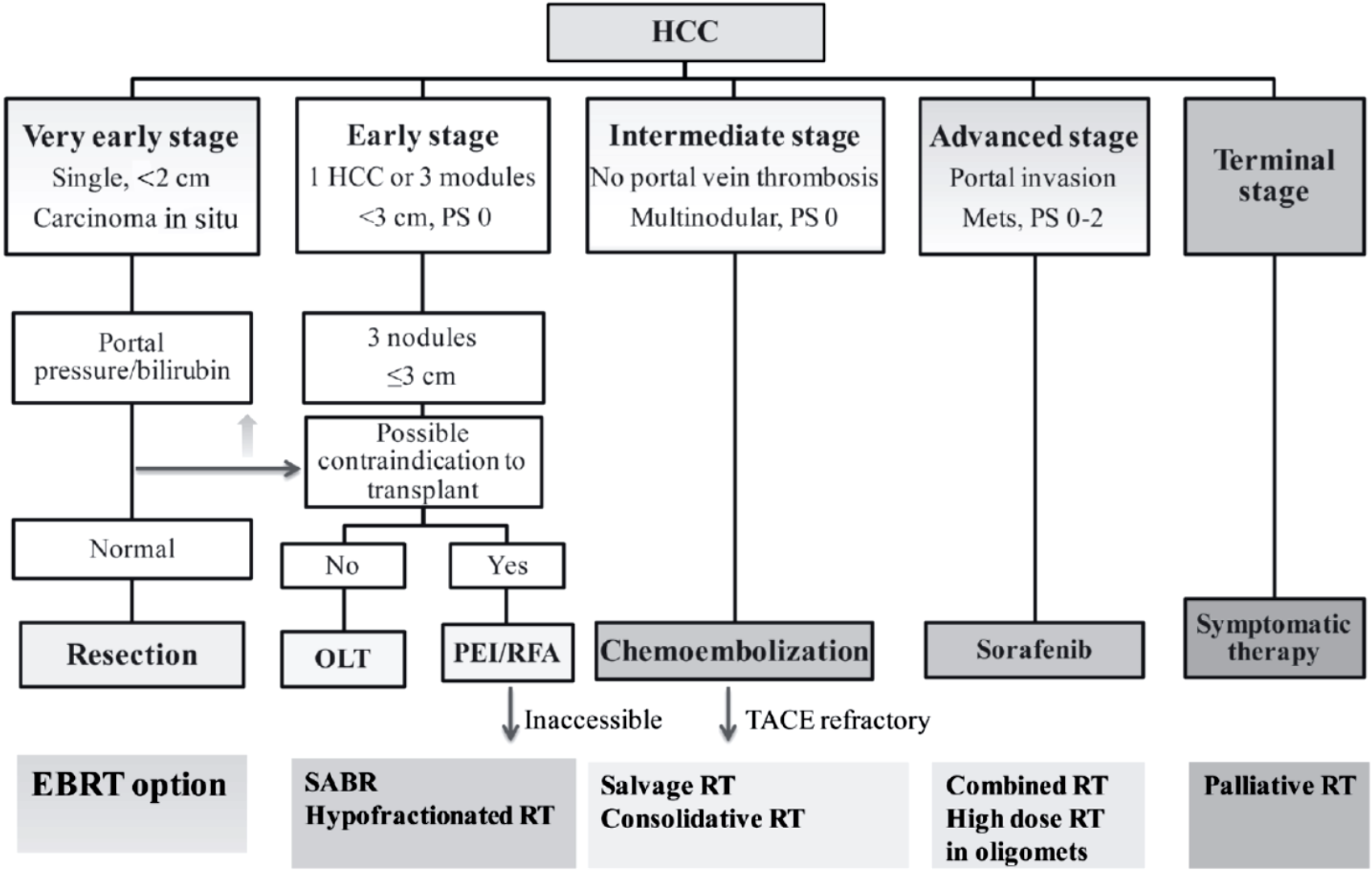
For tumors >2 cm, there was decreased FFLP for RFA compared with SBRT (HR, 3.35; *P* = .025)



Wahi DR, et al. J Clin Oncol. 2016;34(5):452-459.

Hepatocellular Carcinoma

Consensus for R/T in HCC (AAPLE 2014)



Park HC, et al. Liver Cancer. 2016;5(3):162-174.

Hepatocellular Carcinoma
肝癌治療 ~ 重粒子放射治療

建議二十三：

2022 update

重粒子放射治療(carbon ion radiotherapy, CIRT)可以做為早期/局部晚期肝癌病患無法進行手術/電燒/動脈栓塞化學療法時之替代療法。（證據強度等級二）。腫瘤單一顆大小在12公分以內，或是多顆相近的腫瘤，總治療體積最大徑不超過15公分者皆可治療。而腫瘤大小<3公分者，接受重粒子放射治療，局部控制率與電燒相當（證據強度等級二）。

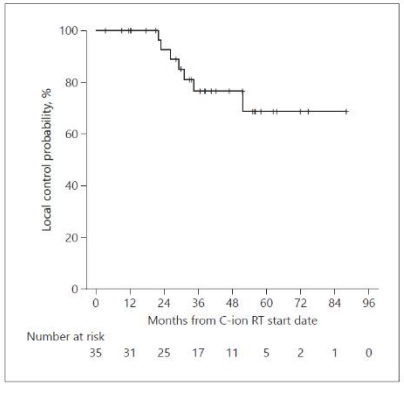


Fig. 1. LC rates of the overall cohort. LC, local control.

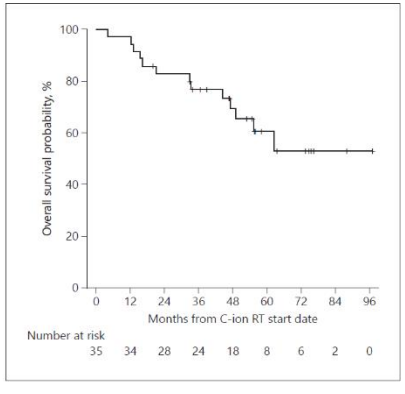


Fig. 2. OS rates of the overall cohort. OS, overall survival.

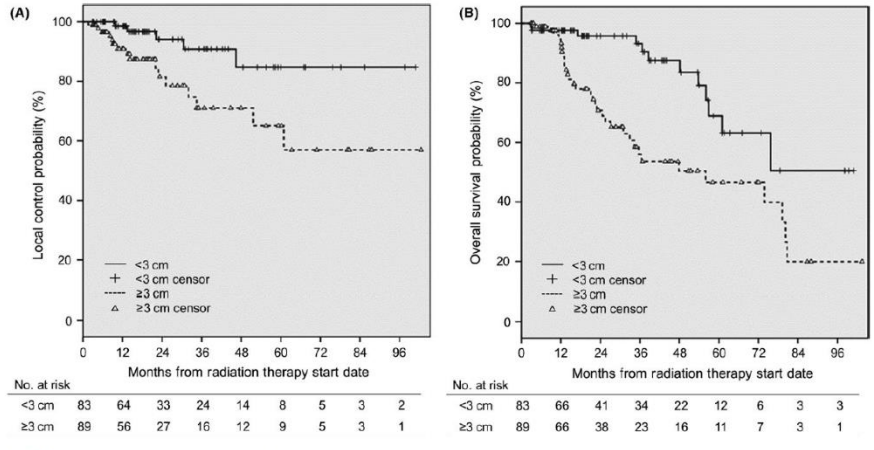


FIGURE 4 A, Local control and B, overall survival rates for the maximum tumour diameter (<3 or ≥3 cm)

Shibuya K, et al. Liver Cancer. 2021;11(1):61-74

Shibuya K, et al. Liver Int. 2018;38(12):2239-2247.

Hepatocellular Carcinoma
肝癌治療～其他治療

建議二十四：

- ✓ 其他治療，包括：tamoxifen、 anti-androgen（抗雄激素）、octreotide ，**不建議作為第一線之治療方式**（證據強度等級一）
- ✓ 系統性化學治療術(systemic chemotherapy)以及肝動脈灌注化學術(hepatic artery infusion chemotherapy)之療效，仍待進一步之臨床試驗來證實（證據強度等級二）。

Hepatocellular Carcinoma
肝癌治療 ~ 其他治療

建議二十五: 抗病毒治療

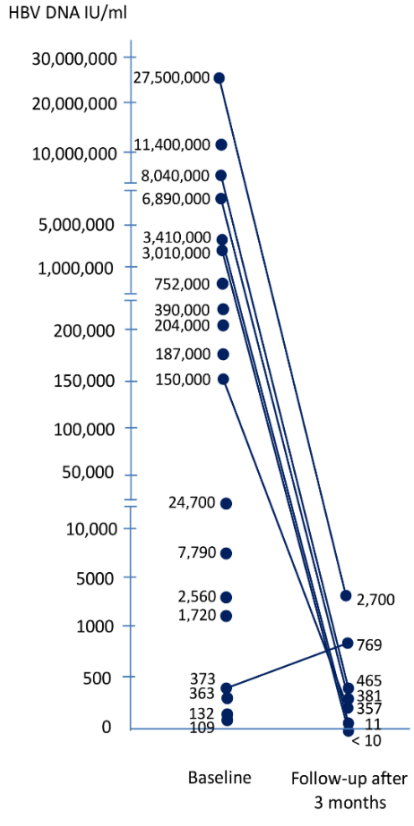
- ✓ 對於 B型肝炎高病毒量的肝癌患者，投予抗病毒藥物可以下降手術切除後的腫瘤復發率(尤其是在早期肝癌患者)。
- ✓ 對於慢性 C型肝炎合併肝癌患者，直接作用抗病毒藥物(DAA)可降低肝癌發生率，不會增加肝癌復發率。
- ✓ 全民健保於民國110年3月1日新增給付規定：
  確診肝癌並接受根除性治療且HBV-DNA可測得 (detectable)的病患，可長期使用抗病毒治療，直至肝癌復發且未能再次接受根除性治療為止。註：根除性治療包括：手術切除、肝臟移植、熱射頻消融術及局部酒精注射術。
- ✓ 對於B型肝炎的肝癌病患，無需等待其病毒量小於 100 IU/ml，在免疫治療開始時同時投予抗病毒藥物，可安全接受免疫治療，發生B型肝炎病毒的再活化風險低。

Hepatocellular Carcinoma

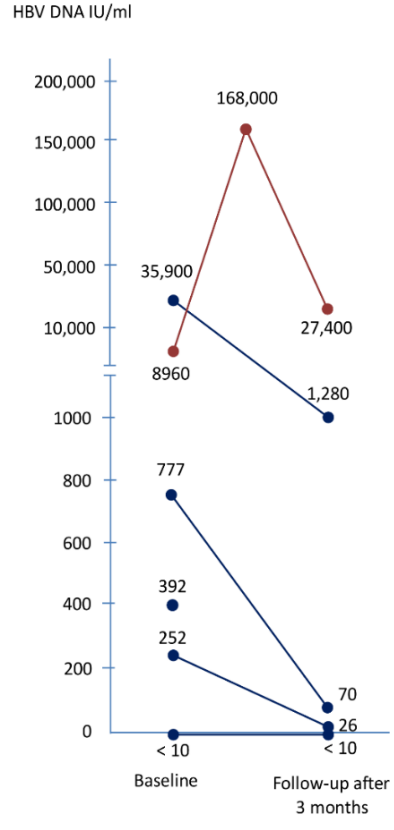
HBVr during HCC immunotherapy

n (%)	HBV DNA ≤100 IU/mL on NUCs (n = 35)	HBV DNA >100 IU/mL on NUCs (n = 19)	Patients with HBV without NUCs (n = 6)
Baseline HBV DNA			
Undetectable	31 (88.6)	0	1 (16.7)
Median (range) for detectable cases, IU/mL	41 (12 – 82)	187,000 (109 – 27,500,000)	777 (252 – 35,900)
HBV reactivation	0	0	1
HBV DNA during ICI treatment			
≥1 $\log_{10}$ elevation	0	0	1 (16.7)
≥2 $\log_{10}$ elevation	0	0	0
Undetectable to detectable	3 (8.6)	0	0
Undetectable to >1,000 IU/ml	0	0	0
Peak HBV DNA during ICI, IU/ml. median (range)	< 10 (< 10 – 1,130)	381 (< 10 – 2,700)	70 (< 10 – 168,000
Hepatitis flare			
ALT > 100 U/L	10 (28.6)	11 (57.9)	2 (33.3)
ALT > 5X ULN	5 (14.3)	4 (21.1)	1 (16.7)
ALT > 10X ULN	2 (5.7)	2 (10.5)	0 (0)
Icteric flare*	5 (14.3)	6 (31.6)	2 (33.3)
HBV DNA elevation & ALT > 100 U/L	0	0	1 (16.7)
iRAE hepatitis	1 (2.9)	1 (5.3)	0 (0)

A. HBV DNA >100 IU/mL on NUCs (n = 19)



B. HBV without NUCs (n = 6)



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