中 山 醫 學 大 學 附 設 醫 院

肝 癌 診 療 指 引

本臨床指引參考AASLD、APASL、JSH、EASL與美國NCCN版本

再依據中山醫學大學附設醫院肝癌小組經驗作編修

肝癌多專科醫療團隊編修

2017/11/22 Version11.0
2016/12/14 Version10.0
2015/11/25 Version9.0
2014/12/10 Version8.0
2013/12/25 Version7.0
2012/12/12 Version6.0
2011/12/14 Version5.1
2011/03/22 Version5.0
2010/02/11 Version4.0
2009/12/17 Version3.0
2008/11/14 Version2.0
2007/10/11 Version1.0

癌症委員會主任委員	癌症委員會執行長	癌症中心主任	團隊負責人

修訂內容

<table>
<tr><th>頁數</th><th>原文</th><th>修訂/新增</th></tr>
<tr><td>第 1 頁</td><td>根據衛生福利部2015年死因統計年報：肝癌為國人主要癌症死因第二位，標準化死亡率為每十萬人口有35.2人。男性肝癌標準化死亡率為每十萬人口47.7人，女性肝癌標準化死亡率為每十萬人口22.7人。</td><td>修訂根據衛生福利部2016年死因統計年報：肝癌為國人主要癌症死因第二位，標準化死亡率為每十萬人口有35.5人。男性肝癌標準化死亡率為每十萬人口48.0人，女性肝癌標準化死亡率為每十萬人口23.2人。</td></tr>
<tr><td>第 4 頁</td><td>
<table>
<tr><th>points</th><th>1</th><th>2</th><th>3</th></tr>
<tr><td>Encephalopathy (grade)</td><td>None</td><td>1-2</td><td>3-4</td></tr>
<tr><td>Ascites</td><td>None</td><td>Slight</td><td>Moderate</td></tr>
<tr><td>Bilirubin-T (mg/dL)</td><td>＜2.0</td><td>2.0~3.0</td><td>＞3.0</td></tr>
<tr><td>Albumin(g/dL)</td><td>＞3.5</td><td>2.8~3.5</td><td>＜2.8</td></tr>
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INR</td><td>＜4.0
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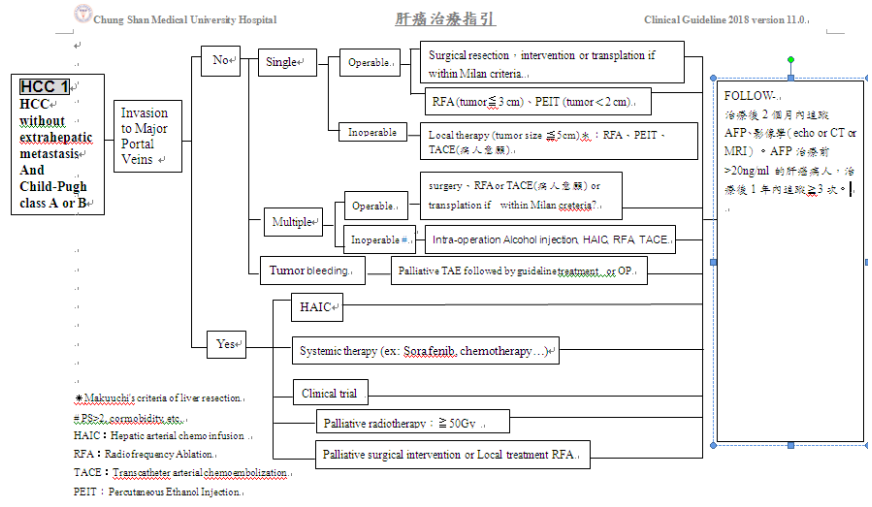
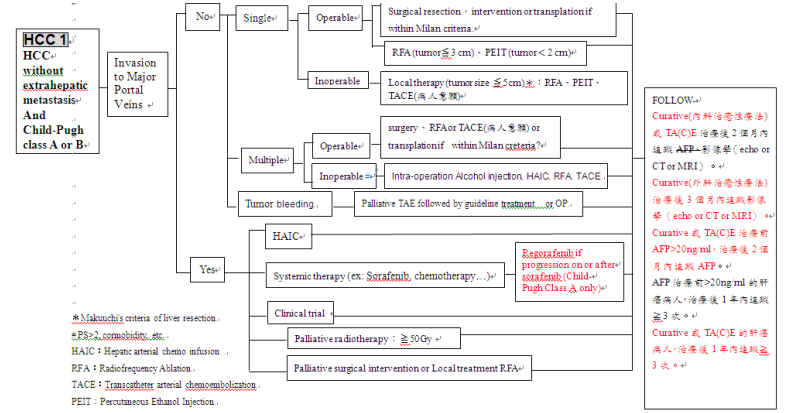
</table>
</td></tr>
<tr><td>第 6 頁</td><td></td><td>修訂</td></tr>
</table>

Primary Tumor(T)	
TX	Primary tumor cancer be assessed（主要腫瘤無法評估）
T0	No evidence of primary tumor(沒有腫瘤之證據)
T1	Solitary tumor without vascular invasion（單顆腫瘤沒有侵犯）
T2	Solitary tumor with vascular invasion or multiple tumors none more than 5cm (單顆腫瘤有血管侵犯，或多顆腫瘤沒有一顆超過 5 公分)
T3a	multiple tumors more than 5cm(多顆腫瘤且任一顆超過 5 公分)
T3b	Single tumor or multiple tumors of size involving a major branch of the portal vein or hepatic vein(單顆或多顆腫瘤侵犯門靜脈或肝靜脈主要分枝）
T4	Tumor(s) with direct invasion of adjacent organs other than the gallbladder or with perforation of visceral peritonem (腫瘤直接侵犯膽囊以外的鄰近器官或穿透臟壁腹膜)

T-N-M	Stage Grouping		
I	T1	N0	M0
II	T2	N0	M0
IIIA	T3a	N0	M0
IIIB	T3b	N0	M0
IIIC	T4	N0	M0
IVA	Any T	N1	M0
IVB	Any T	Any N	M1

Primary Tumor(T)	
TX	Primary tumor cancer be assessed
T0	No evidence of primary tumor
T1	Solitary tumor ≦2cm，or >2cm without vascular invasion
T1a	Solitary tumor ≦2cm
T1b	Solitary tumor ＞2cm without vascular invasion
T2	Solitary tumor ＞2cm with vascular invasion，or multiple tumors，none>5cm
T3	Multiple tumors，at least one of which is ＞5cm
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 peritonem

T-N-M	Stage Grouping		
IA	T1a	N0	M0
IB	T1b	N0	M0
II	T2	N0	M0
IIIA	T3	N0	M0
IIIB	T4	N0	M0
IVA	Any T	N1	M0
IVB	Any T	Any N	M1

第 9 頁	7.Enrolled onto clinical trial as indication and patients' preference： Targeted agents, immune therapy, gene therapy....	**新增** Enrolled onto clinical trial as indication and patients' preference：Targeted agents, immune therapy(Nivolumab), gene therapy....
第 11 頁	AFP＞200ng/ml	**修訂** **AFP＞100ng/ml**
第 12 頁		**新增及修訂** 
第 14 頁	**HCC3HCC with extrahepatic metastasis** **Child-Pugh class** A/B Systemic therapy (ex: Sorafenib, chemotherapy…)	**新增** Regorafenib if progression on or after sorafenib (Child-Pugh Class A only)

第 16 頁	無	**新增**標靶藥物治療健保申請規範 Sorafenib（如 Nexavar）：(98/10/1、100/6/1、101/8/1、104/6/1、105/11/1、106/1/1) 晚期肝細胞癌部分：(101/8/1、105/11/1) (1)轉移性或無法手術切除且不適合局部治療或局部治療失敗之晚期肝細胞癌，並符合下列條件之一： Ⅰ.肝外轉移（遠端轉移或肝外淋巴結侵犯）的 Child-Pugh A class 患者。 Ⅱ.大血管侵犯（腫瘤侵犯主門靜脈或侵犯左/右靜脈第一分支）的 Child-Pugh A class 患者。 III.經導管動脈化學藥物栓塞治療（Transcatheter arterial chemoembolization, T.A.C.E.）失敗之晚期肝細胞癌的 Child-Pugh A class 患者，需提供患者於六個月內 >=3 次局部治療之記錄。 (2)需經事前審查核准後使用，每次申請之療程以 2 個月為限，送審時需檢送影像資料，每 2 個月評估一次。
第 20 頁	**完治率定義** 1.確診後或是治療中接受安寧緩和照護。 2.執行 TAE 或 TACE 1 次。 3.開立 Nexavar 使用。 4.肝內膽管 palliative C/T 以做 3 個 cycle，只要是姑息性治療，治療中接受安寧緩和照護。	**修訂** **完治率定義** 1.治療中接受安寧緩和照護。確診後不列入分母計算需排除依據評鑑條文 2.執行 TAE 或 TACE 1 次。 3.開立 Nexavar 使用。 4.肝內膽管 palliative C/T 以做 3 個 cycle，只要是姑息性治療，治療中接受安寧緩和照護。

目錄

一、前言

- 根據衛生福利部2016年死因統計年報：肝癌為國人主要癌症死因第二位，標準化死亡率為每十萬人口有35.5人。男性肝癌標準化死亡率為每十萬人口48人，女性肝癌標準化死亡率為每十萬人口23.2人。
- 本院肝癌診斷流程的建立，係參考2010年AASLD，期以提高肝癌診斷證實率與準確性。
- 本院肝癌分期採用美國TNM與歐洲BCLC二大癌症分期系統並行,後者除了考慮腫瘤大小因素外，亦加入肝功能指標，以符合臨床科的需求。
- 本院肝癌治療指引係多專科醫療團隊的整合，治療流程以實證醫學並參考國內外醫學中心治療指引，期以提高肝癌病人生活品質。

二、組織病理分期與分化

肝癌以肝細胞癌(hepatocellular carcinoma)為主，本指引對本院較為常見臨床肝癌加以論述。

肝癌的病理組織分化分為：

分化良好	(grade 1)
分化中度	(grade 2)
分化不良或未分化	(grade 3)
分化無法評估	(grade 4)

三、肝癌分期

(1)Barcelona Clinic Liver Cancer (BCLC)分期

Stage		PST	Tumor Status Tumor Stage	Liver Function Status
Stage 0： Very early	0	0	Single,≦2cm	Serum bilirubin (WNL) or Child A
Stage A： Early	A	0	Single,≦5cm 3 tumors and ＜3 cm	Serum bilirubin (WNL) or Child A~B
Stage B：Intermediate		0	Large, multinodular	Child-Pugh A~B
Stage C：Advanced		1-2	Vascular invasion or extrahepatic spread	Child-Pugh A~B
Stage D：End stage		3-4	Any	Child-Pugh C

Stage 0, A and B：all criteria should be fulfilled

Stage C and D：all least one criteria should be fulfilled

(2)Child-Pugh Score

points	1	2	3
Encephalopathy (grade)	None	1-2	3-4
Ascites	None	Moderate	Severe
Bilirubin-T (mg/dL)	＜2.0	2.0~3.0	＞3.0
Albumin(g/dL)	＞3.5	2.8~3.5	＜2.8
PT(sec) prolong	＜4.0	4.0~6.0	＞6.0
INR	＜1.7	1.7-2.3	＞2.3

***Child-Phug Score is the sum of 5 items.**

Class Ａ：5~6 points, good operative risk

Class B：7~9 points, moderate operative risk

Class Ｃ：10~15 points, poor operative risk

(3) Okuda staging system

Stage	肝臟被腫瘤取代的比率		腹水		血清白蛋白		血清總膽紅素	
	+ (>50%)	- (<50%)	+	-	+ (<3g/dL)	- (>3g/dL)	+ (>3mg/dL)	- (<3mg/dL)
I	四項都沒有出現							
II	四項中出現1~2項							
III	四項中出現3~4項							

(4)8th AJCC T-N-M 分期

Primary Tumor(T)	
TX	Primary tumor cancer be assessed
T0	No evidence of primary tumor
T1	Solitary tumor ≦2cm，or >2cm without vascular invasion
T1a	Solitary tumor ≦2cm
T1b	Solitary tumor ＞2cm without vascular invasion
T2	Solitary tumor ＞2cm with vascular invasion，or multiple tumors，none>5cm
T3	Multiple tumors，at least one of which is ＞5cm
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Regional Lymph Nodes(N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph nodes metastasis

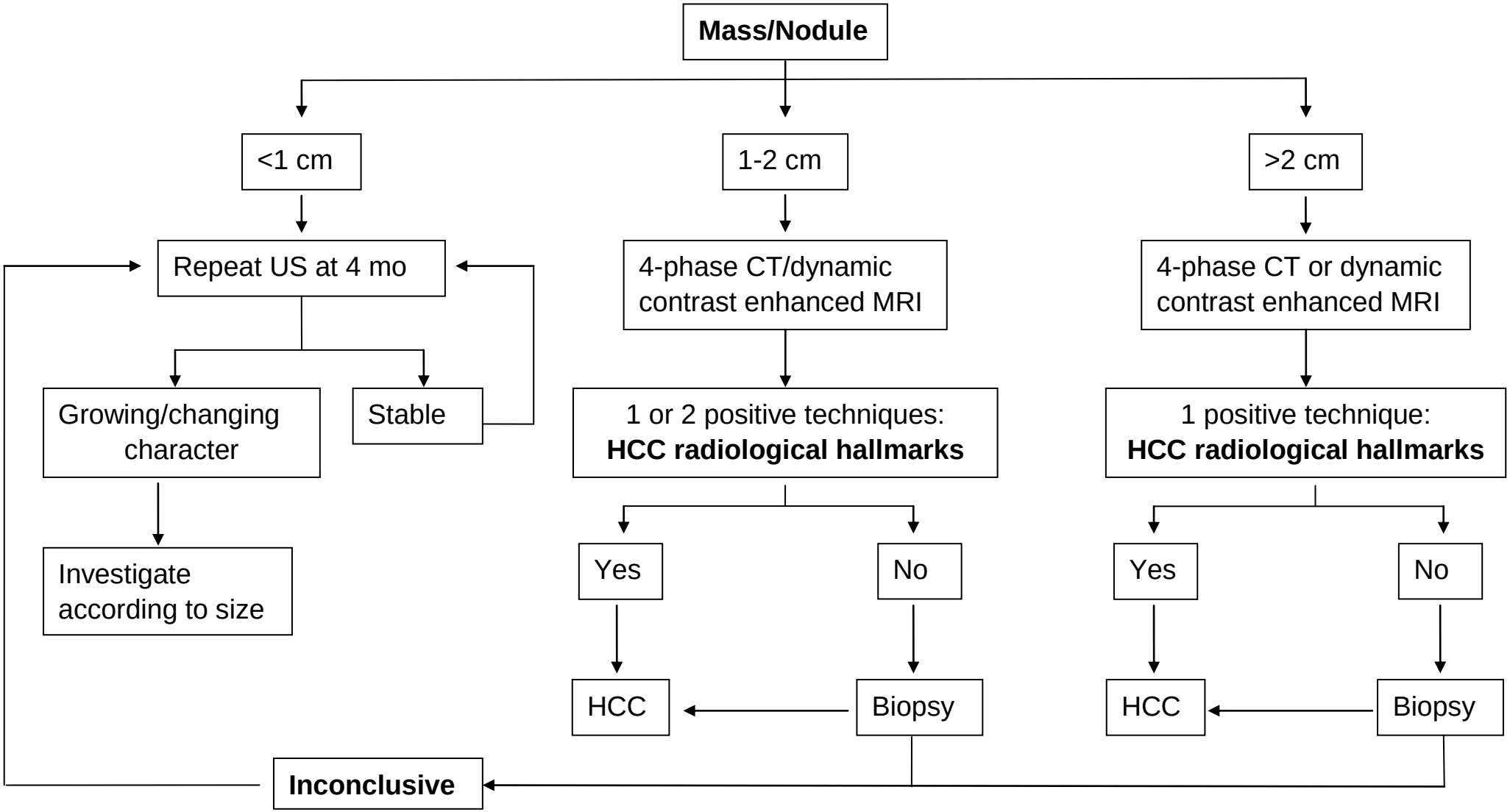
Distant Metastasis(M)	
M0	No distant metastasis
M1	Distant metastasis

T-N-M Stage Grouping			
IA	T1a	N0	M0
IB	T1b	N0	M0
II	T2	N0	M0
IIIA	T3	N0	M0
IIIB	T4	N0	M0
IVA	Any T	N1	M0
IVB	Any T	Any N	M1

Histologic Grade(G)	
GX	Grade cannot be assessed
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated
G4	Undifferentiated

Fibrosis Score(F)	
F0	Fibrosis score 0-4 (no to moderate fibrosis)
F1	Fibrosis score 5-6 (severe fibrosis or cirrhosis)

四、肝癌診斷 EASL 2012 年 Diagnosis Guide



五、肝癌治療

1. Liver transplantation.
   1.1 親屬捐肝之活體肝臟移植條件:成年人或十八歲以上之未成年人已結婚者，得捐贈部分肝臟予其五親等以內之親屬；十八歲以上之未成年人，經其法定代理人之書面同意，得捐贈部分肝臟予其五親等以內之血親。五等親範圍:1.配偶(應與捐贈者生有子女或結婚二年以上) 2.直系血親卑親屬。3.父母。4.兄弟姊妹。5.祖父母。6.曾祖父母或三親等旁系血親。7. 一親等直系姻親。
   1.2 若要接受屍體捐肝則條件從嚴(單一腫瘤小於或等於 5 公分，或多發生性腫瘤小於或等於 3 顆，且每一顆大小小於或等於 3 公分)
   活肝移植：單一腫瘤≦6.5cm；或多發腫瘤≦3個，最大直徑≦4.5cm，全部腫瘤直徑和≦8cm。
2. 外科手術治療
   2.1 None or controlled ascites
   2.2 Bilirubin小於2
   2.3 Child A與ICG≦15可行大範圍的肝切除Child B與ICG＞15%時應視病人整體情況，由病人與手術醫師討論之後決定

3. Local therapy(PEIT or RFA)，relative contraindication：
   3.1 Tumor numbers：多於3個
   3.2 Tumor size：> 5 cm；（≦3 cm，則可考慮取代Surgery）
   3.3 Ascites(massive or uncontrollable)
   3.4 Bleeding tendency (platelet＜80000 or prolonged PT＞5 seconds)
   3.5 PEIT > 2 cm，則不建議,除非RFA無法執行.

4.Contraindication to TACE
   4.1 Thrombus in the main portal vein (severe)
   4.2 Encephalopathy .
   4.3 Biliary obstruction .
   4.4 Child-Pugh C cirrhosis：lobar or main portal vein thrombus poor candidates for TACE.

5.Relative contraindication to TACE ::

5.1 Serum bilirubin > 3mg/dL.

5.2 Lactate dehydrogenase >425 units/L.

5.3 Aspartate aminotransferase >100 units/L .

5.4 Tumor burden involving >50 percent of the liver .

5.5 Cardiac or renal insufficiency.

5.6 Ascites, recent variceal bleed, or significant thrombocytopenia.

6.依病人performance status and liver reserve，由醫師針對實際狀況考量與病患討論後決定，不建議作為常規之治療方式：

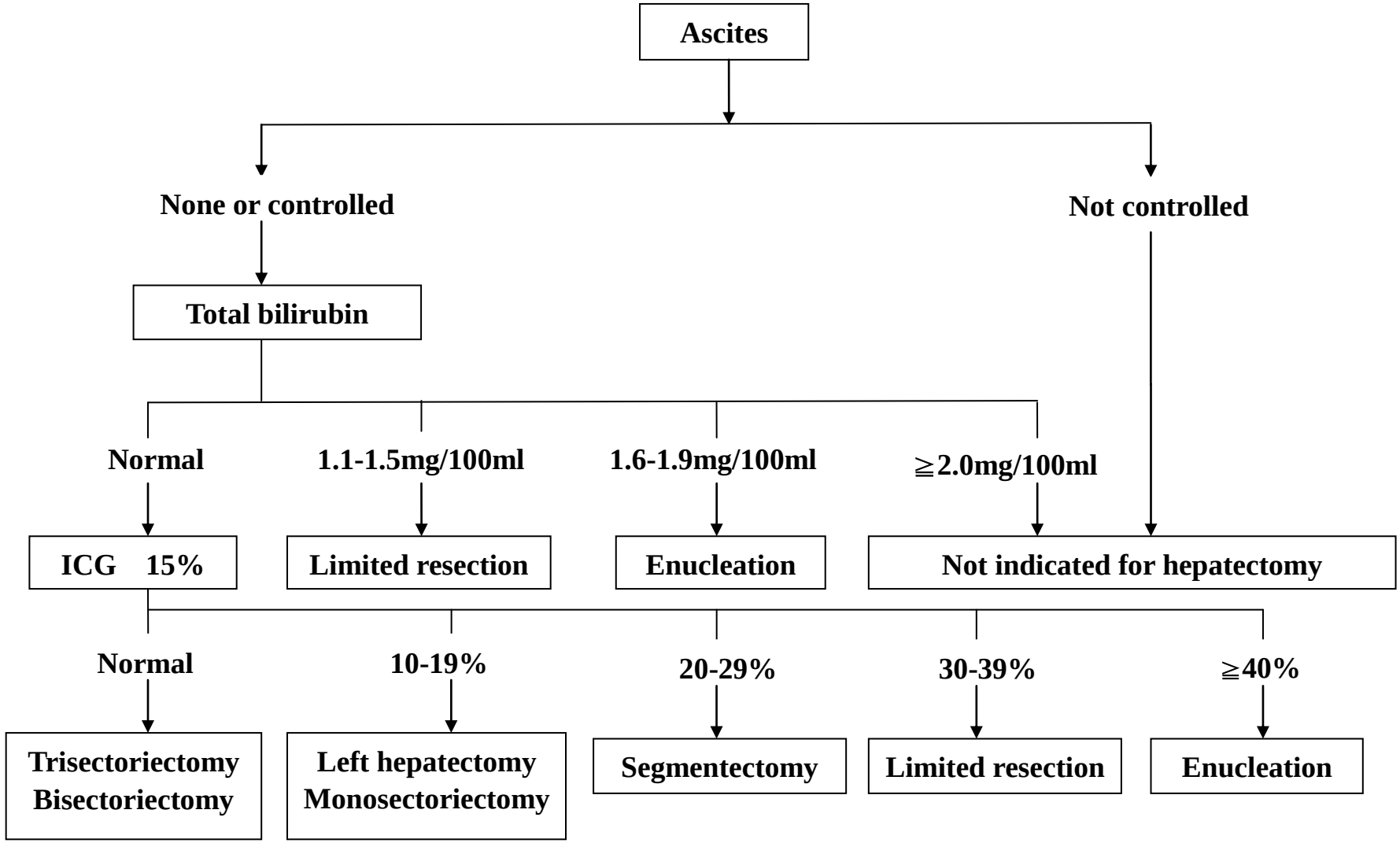
6.1Chemotherapy agents such as doxorubicin(Epirubicin, Mitoxantrone), 5-FU,cisplatin,Etoposide,Gemcitabine(自費)等

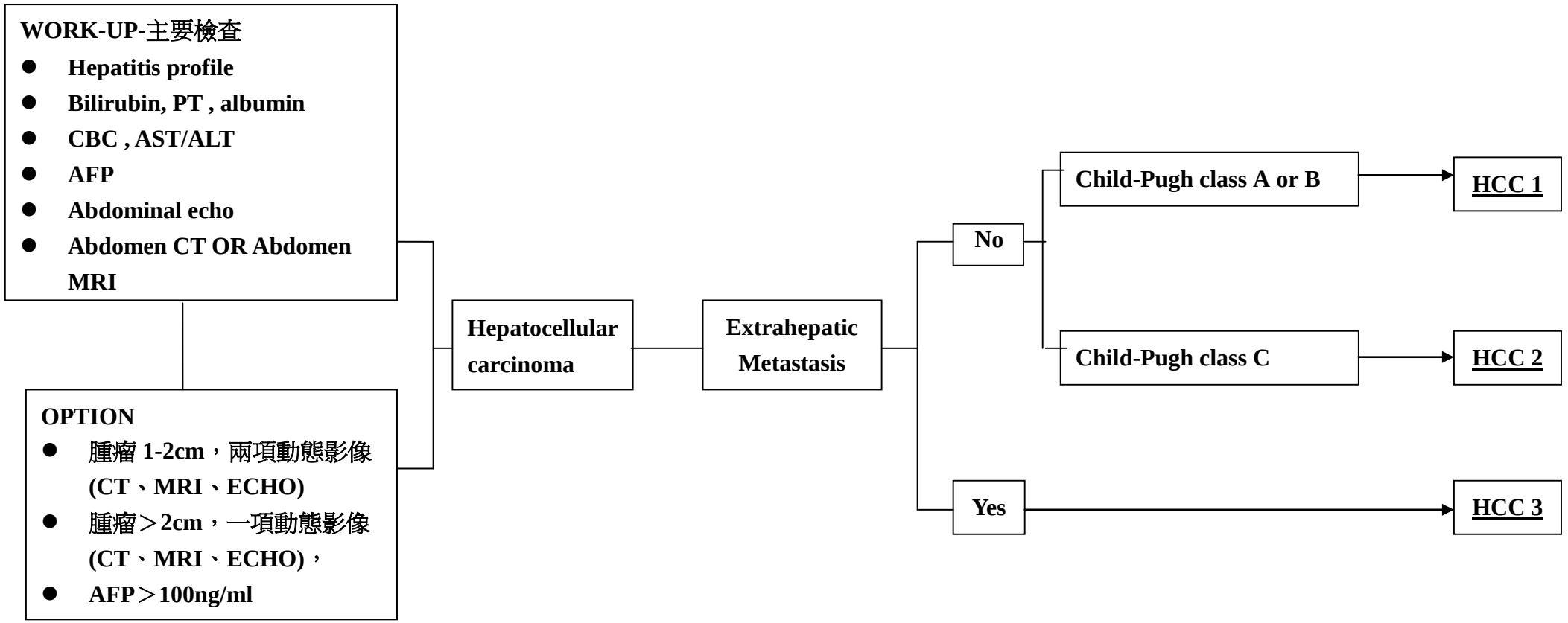
6.2Oral Agents(自費) such as Thalidomide, UFT....

7.Enrolled onto clinical trial as indication and patients' preference：Targeted agents, immune therapy(Nivolumab), gene therapy....

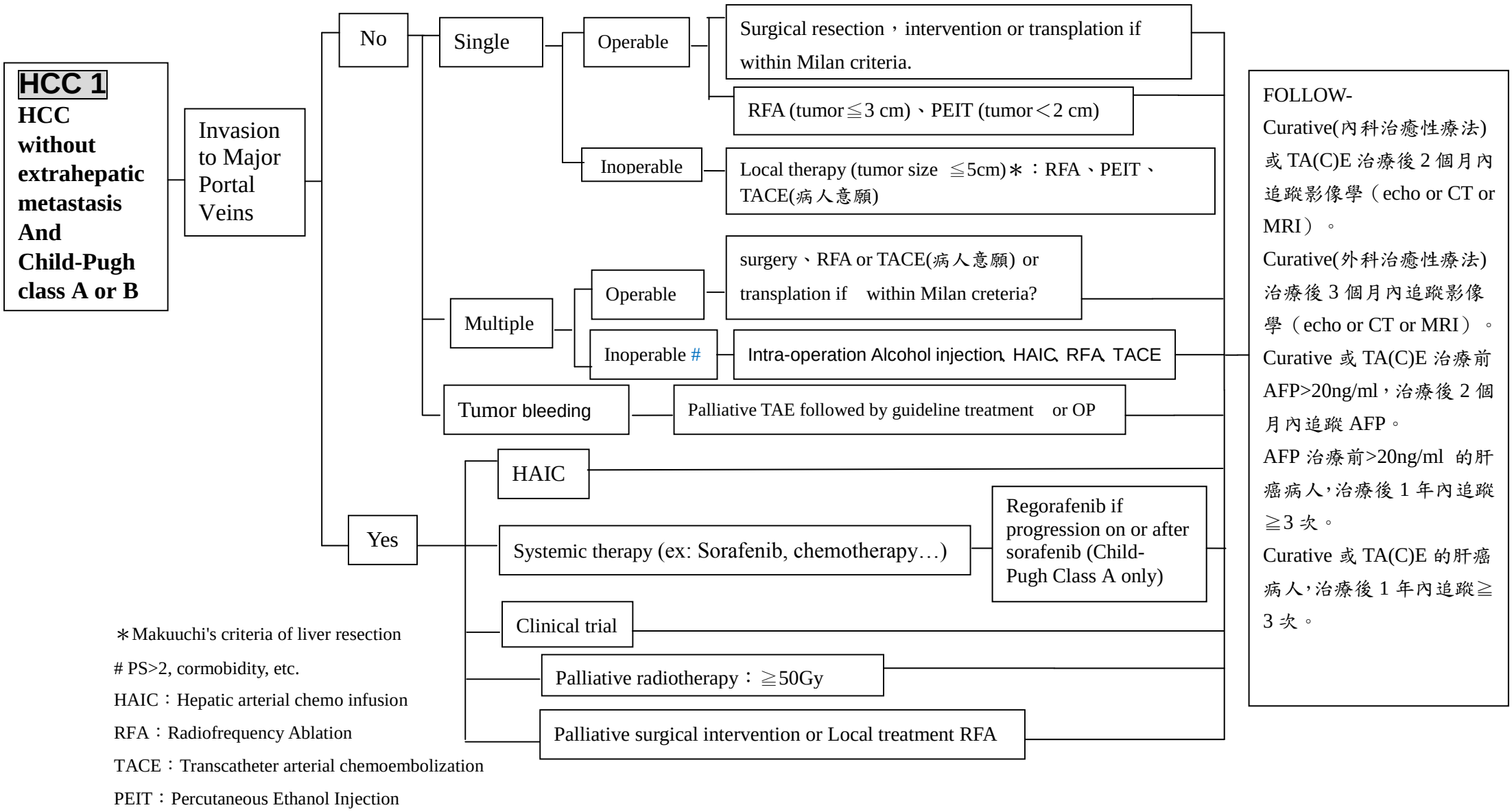
8.Makuuchi’s criteria

9. Y90-SIRT:不適合手術切除肝臟,體能狀態為 0 - 1，腫瘤主要位於單一器官，沒有明顯感染，肝臟功能正常，沒有腹水或肝臟衰竭的其它症狀。


Ascites
None or controlled
Not controlled
Total bilirubin
Normal
1.1-1.5mg/100ml
1.6-1.9mg/100ml
≧2.0mg/100ml
ICG 15%
Limited resection
Enucleation
Not indicated for hepatectomy
Normal
10-19%
20-29%
30-39%
≧40%
Trisectoriectomy
Bisectoriectomy
Left hepatectomy
Monosectoriectomy
Segmentectomy
Limited resection
Enucleation



¡Positive AFP >100 ng/mL: (Waidely E, Al-Yuobi AR, Bashammakh AS, et al. Serum protein biomarkers relevant to hepatocellular carcinoma and their detection Analyst 2016;141:36-44), or if AFP increases by ≥7 ng/mL/month on at least 3 determinations (Arrieta O, Cacho B, Morales-Espinosa D, et al. The progressive elevation of alpha fetoprotein for the diagnosis of hepatocellular carcinoma in patients with liver cirrhosis. BMC Cancer 2007;7:28). Positive AFP should prompt CT or MRI regardless of US results.



＊Makuuchi's criteria of liver resection

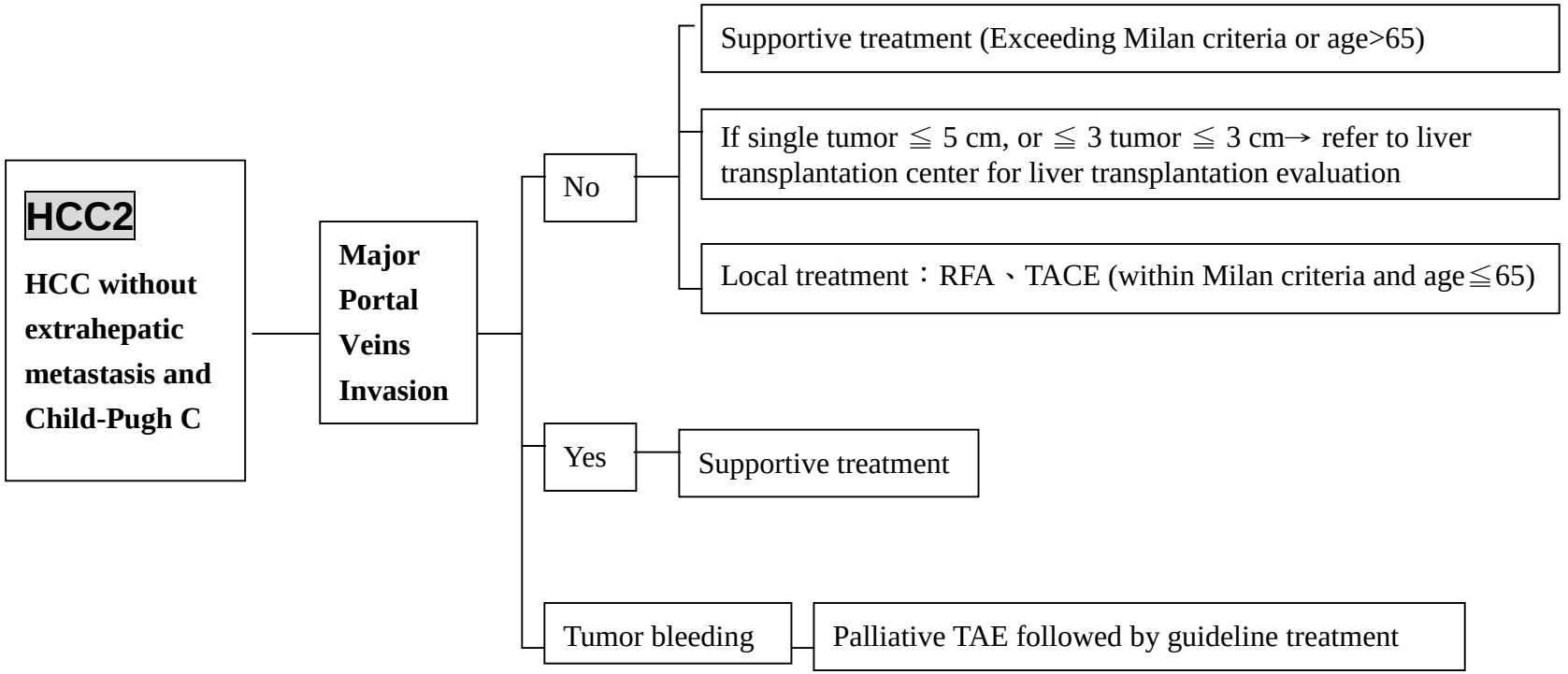
PS>2, cormobidity, etc.

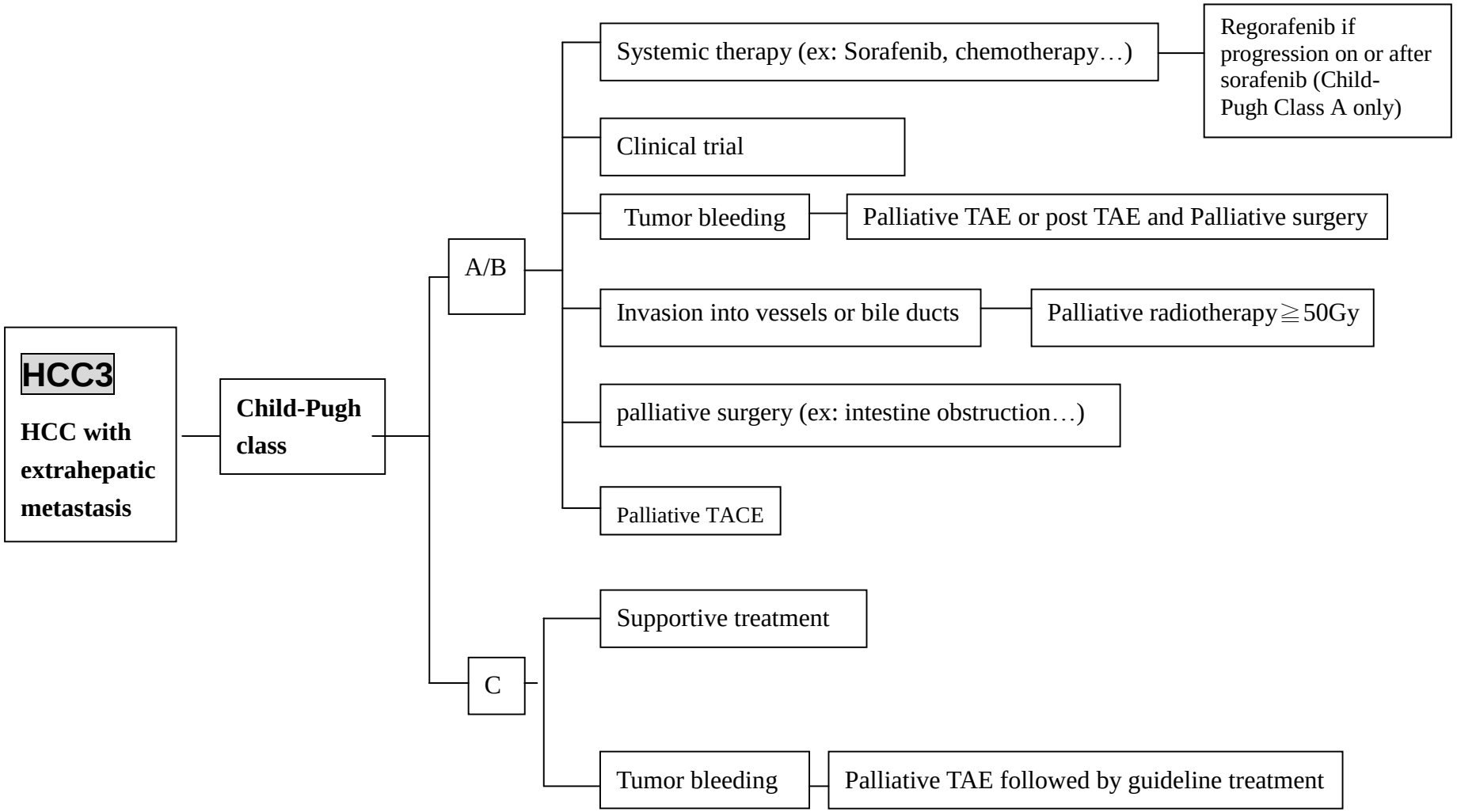
HAIC：Hepatic arterial chemo infusion

RFA：Radiofrequency Ablation

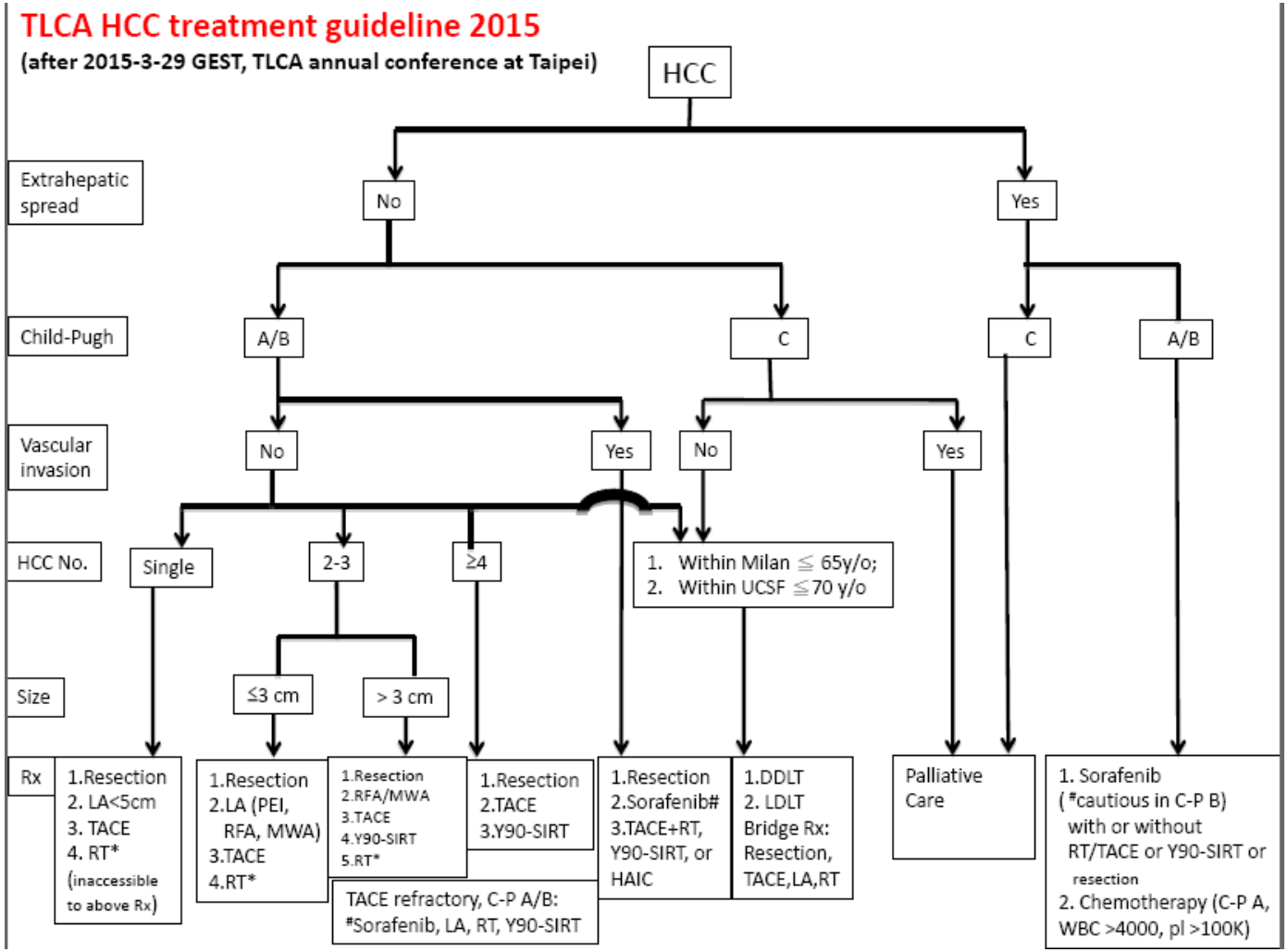
TACE：Transcatheter arterial chemoembolization

PEIT：Percutaneous Ethanol Injection


HCC2
HCC without extrahepatic metastasis and Child-Pugh C
Major Portal Veins Invasion
No
Supportive treatment (Exceeding Milan criteria or age>65)
If single tumor ≦ 5 cm, or ≦ 3 tumor ≦ 3 cm→ refer to liver transplantation center for liver transplantation evaluation
Local treatment：RFA、TACE (within Milan criteria and age≦65)
Yes
Supportive treatment
Tumor bleeding
Palliative TAE followed by guideline treatment


HCC3
HCC with extrahepatic metastasis
Child-Pugh class
A/B
Systemic therapy (ex: Sorafenib, chemotherapy…)
Regorafenib if progression on or after sorafenib (Child-Pugh Class A only)
Clinical trial
Tumor bleeding
Palliative TAE or post TAE and Palliative surgery
Invasion into vessels or bile ducts
Palliative radiotherapy≧50Gy
palliative surgery (ex: intestine obstruction…)
Palliative TACE
C
Supportive treatment
Tumor bleeding
Palliative TAE followed by guideline treatment

TLCA HCC treatment guideline 2015



標靶藥物治療

Sorafenib（如 Nexavar)：(98/10/1、100/6/1、101/8/1、104/6/1、105/11/1、106/1/1)

晚期肝細胞癌部分：(101/8/1、105/11/1)

(1)轉移性或無法手術切除且不適合局部治療或局部治療失敗之晚期肝細胞癌，並符合下列條件之一：

Ⅰ.肝外轉移（遠端轉移或肝外淋巴結侵犯）的 Child-Pugh A class 患者。

Ⅱ.大血管侵犯（腫瘤侵犯主門靜脈或侵犯左/右靜脈第一分支）的 Child-Pugh A class 患者。

III.經導管動脈化學藥物栓塞治療（Transcatheter arterial chemoembolization,T.A.C.E.）失敗之晚期肝細胞癌的 Child-Pugh A class 患者，需提供患者於六個月內 >=3 次局部治療之記錄。

(2)需經事前審查核准後使用，每次申請之療程以 2 個月為限，送審時需檢送影像資料，每 2 個月評估一次。

六、安寧緩和照護原則

若預期疾病難以治癒時，病人存活期小於 6 個月便適合安寧療護(Pomeranz & Brustman, 2005；Waldrop & Rinfrette, 2009) 。
若藉由症狀、檢驗數據、及確切的腫瘤診斷，證實臨床上該惡性腫瘤已經廣泛侵犯、或進展快速；功能分數（Palliative Performance Scale）低於 70%；拒絕進一步腫瘤治癒性治療，或者在治療之下仍持續惡化者，即可轉介緩和醫療團隊（彭等，2006）。

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