振興醫療財團法人振興醫院

肝癌診療指引

肝癌多專科團隊

2008 年 10 月制訂
2009 年 05 月修訂
2010 年 10 月修訂
2011 年 12 月修訂
2012 年 05 月修訂
2012 年 09 月修訂
2012 年 12 月修訂
2013 年 09 月修訂
2014 年 12 月修訂
2015 年 12 月修訂

Reference:

1. **AASLD management guideline**
   2010 by the American Association for the study of liver disease and published online at www.aasld.org.This version was updated July 2011.
2. **APASLA management guideline**
   Asian Pacific Association for the Study of the Liver consensus recommendations on hepatocellular carcinoma.Received:11 February 2009/ Accepted:9 December 2009/Published online:18 March 2010 Asian Asian Pacific Association for the Study of the Liver 2010.
3. **HCC management consensus guideline 2015 (Taiwan Liver Cancer Association -TLCA)**
4. **Hepatobiliary Cancer NCCN Guidelines V1.2015.**
5. **全民健康保險藥品給付規定一百零二年版.**

Table of Content

Levels of Evidence

Level 1:At least one well-designed RCT

1a:meta-analysis of RCTs

1b:at least one RCT

Level 2:Comparative studies:non-RCT,well-designed cohort or case-control studies(Prospective or retrospective),and outcomes research.

Level 3:Non-comparative studies:case series,case report or not well-designed clinical studies.

Level 4:Opinion of respected authorities,descriptive epidemiology or report committee.

levels of Recommendation

A. Strongly recommended
B. Recommended
C. Considerable but insufficient evidence
D. Not recommended

If the evidence is controversial or marginal beneficial,we do not provide recommendation though high grade of evidence(1 or 2)

Surveillance:

● **Recommendation** 1

Patients at high-risk for developing HCC should enter Surveillance programs.(E-1b)

High-risk defined as follows:(E-1, R-A)

－Chronic hepatitis B

－Chronic hepatitis C

－Primary biliary cirrhosis

－Autoimmune hepatitis

－Cirrhosis from various etiologies: alcoholic cirrhosis,non-alcoholic steatohepatitis,hemochromatosis,alpha1-antitrypsin deficiency

● **Recommendation** 2

Surveillance for HCC should use ultrasonography(E-1, R-A) and AFP.(E-2,R-B)

● **Recommendation** 3

Patients at high-risk for HCC should be screened at 6-12 months intervals. (E-1, R-A)

Cirrhotic patients could be screened at 3-6 months intervals.(E-4)

Patients with HCC after curative treatment could be screened minimal every 3-6 months within first 2 years and every 3-6 months after 2 years.(E-3)

Pre-Treatment Workup:

- **Complete medical history and physical exam**
- **Blood test**

  -CBC、Albumin,bilirubin、BUN/Creatinine、PT/APTT、ALT/AST、Alkaline phosphatase/r-GT、Indocyanine green(ICG)test
- **Tumor marker**

  -Alpha feto-protein(AFP)
- **Virological profiles**

  -HBsAg , Anti-HBc

  -Anti-HCV , Anti-HBs
- **Radiological imaging**

  -Abdominal sono

  -Contrast-enhanced CT

  -Abdominal MRI

  -Celiac angiography
- **Liver biopsy**

Diagnosis:

・For nodules >1 cm in cirrhosis , ＊ characteristic vascular patterns on a 4-phase MDCT or MRI, HCC could be diagnosed without biopsy.(E-2,R-B)(AASLD 2010)

・However ,if the vascular pattern on imaging are not characteristic ,or if nodules in non-cirrhotic liver ,histology or liver biopsy should be performed.(E-2,R-B)

＊ characteristic vascular pattenrns：arterial hypervascularity AND venous or delayed phase washout

・For 1-2cm nodule in cirrhosis they should be investigated with the dynamic imagings.(CEUS,CT,or MRI)(E-2)

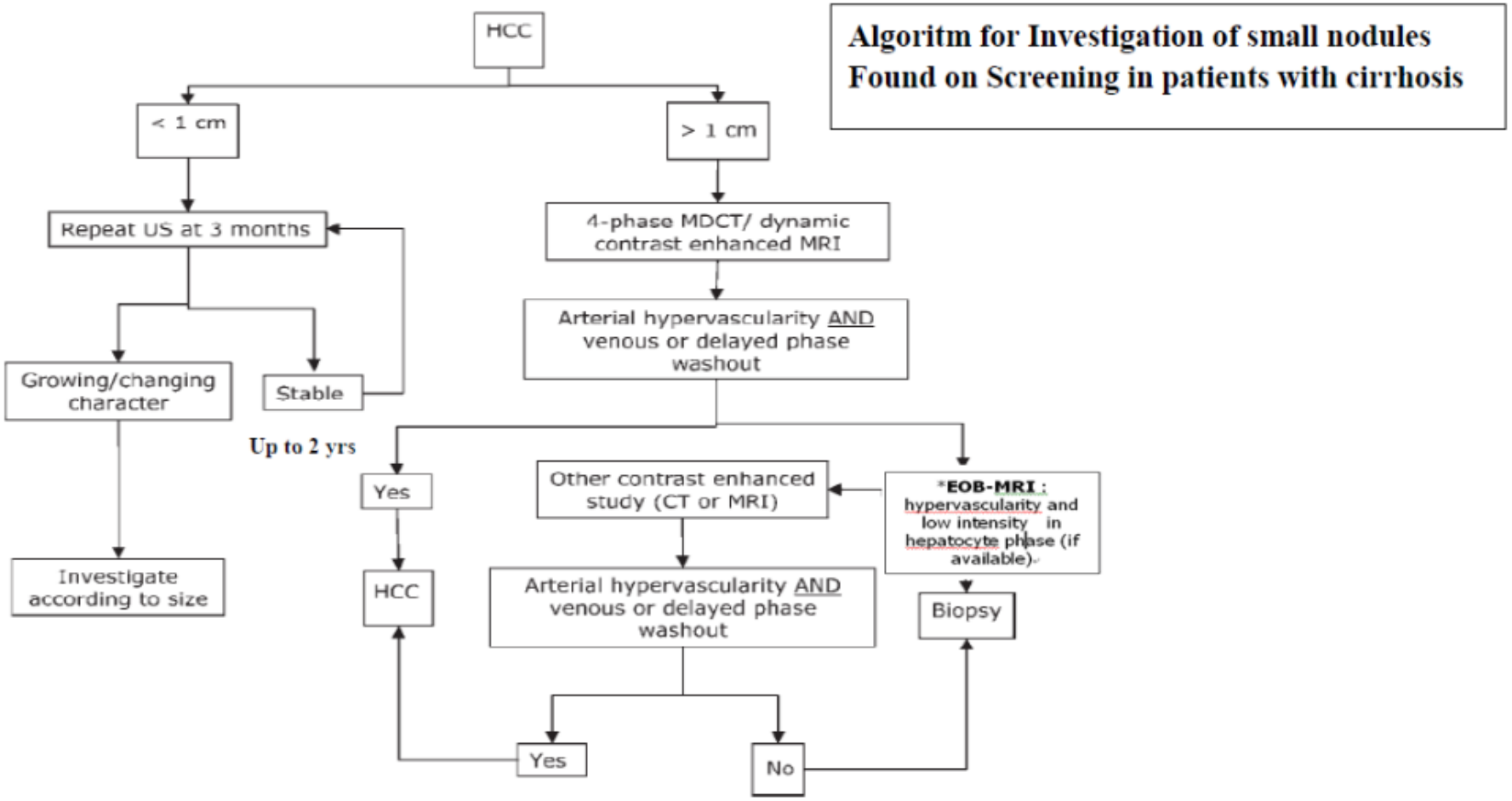
・IF the lesions have characteristic vascular pattern in one dynamic study plus serum AFP>200ng/ml (E-2) or plus typical arterial angiographic findings , they could be treated as HCC.(AASLA 2010)

・However , if vascular pattern on imaging are not characteristic , or if nodules are detected in a non-cirrhotic liver , biopsy should be performed.(E-2)

・For nodule < 1 cm that malignancy cannot be confirmed should be followed with US at 3-6 months interval.(E-3)

・If the size an US character of the nodules are not changed for two years, they could revert to routine surveillance.(E -4)

・If biopsy is negative for HCC , patients should be followed by US or CT/MR every 3-6 months until nodule either disappears , enlarges, or displays diagnostic characteristics of HCC for 2 years.(E-4)


Algoritm for Investigation of small nodules Found on Screening in patients with cirrhosis
HCC
< 1 cm
> 1 cm
Repeat US at 3 months
4-phase MDCT/ dynamic contrast enhanced MRI
Arterial hypervascularity AND venous or delayed phase washout
Growing/changing character
Stable
Up to 2 yrs
Yes
Other contrast enhanced study (CT or MRI)
*EOB-MRI : hypervascularity and low intensity in hepatocyte phase (if available)
Investigate according to size
HCC
Arterial hypervascularity AND venous or delayed phase washout
Biopsy
Yes
No

Therapy：

1. Resection

- For single HCC and good liver function , regardless of cirrhosis , resection is recommended .(E-2)
- Besides, multiple resectable tumors are also suitable for resection.(E-2)
- However , for those with solitary tumor ≦ 5 cm or up to three nodules ≦ 3 cm, local ablations can be performed(E-2) ;beyond this criteria controversial.
- Preoperative chemoembolization is not recomemded.(E-2)
- Post-resection adjuvant therapy is controversial.(E-3)
- Preoperative Liver Function Assessment(ICG test):

Serum Total bilirubin level		ICG test (%)	Operative
Normal	<1.0 mg/dl	10%	Rt lobectomy resection、Trisegmentectomy
Limited resection	1.1-1.5 mg/dl	10%-19%	Segmentectomy
Enucleation	1.6-1.9 mg/dl	20-29%	Subsegmentectomy
Hepatectomy not	>2.0 mg/dl	30-39%	Limited

2. Liver Transplantation

- OLT is effective and suitable for patients with poor liver reserve and HCC within Milan criteria：single ＜ 5 cm or up to 3 nodules ＜ 3cm.(E-2)
- In Taiwan , surgeons could consider OLT if the tumors beyond Milan criteria, but within UCSF criteria ：single tumor ≦ 6.5 cm or up to 3 modules ≦ 4.5 cm and the total diameter ≦ 8 cm.(E-3)
  UCSF：University of California in San Francisco.

- Preoperative bridge therapy can be considered if the waiting list of liver transplantation exceed 6 months .
  Local ablation or TACE are recommended.(E-2,R-B)
  TACE ：transarterial chemoembolization.

3. Loco-regional therapy

- Local ablation and TACE are safe and effective for patients who cannot undergo resection , or as a bridge to OLT.(E-2,R-B)

4.Local Ablation

- RFA and PEI are both effective for HCC ＜ 2 cm.Nevertheless. The necrotic effect of RFA is more predictable in all tumor sizes.(E-1,R-A)

- In addition, treatment sessions, hospital stay,complete necrosis rate,local tumor progression, and overall survival are also superior than PEI in larger tumors.(E-1)

5. TACE

- TACE is recommended as the 1st line non-curative therapy for patients with large/multi-focal HCC which are not suitable for resection.(E-1)
- BCLC B, no vasc invas or extra-hepatic spread (E1iiA, R1A). TACE discouraged in decompen. liver disease, advanced liver dysfunction, macroscopic invasion or extra-hepatic spread (E-1A,R-1B)
- similar response but less systemic adverse events (E1D,R2b)
- super-selective (sub-seg) TACE can be performed in early HCC where RFA is not feasible due to location or medical co-morbidities (E3,R-C)

6. Systemic Therapy

6.1 Target Therapy

- Sorafenib could be recommended for patients at advanced stages of HCC with preserved liver function.(E-1)
- It should be used with caution for patients with Child-Pugh B.(E-2)
- Sorafenib健保給付條件:

(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：

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

(3)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。

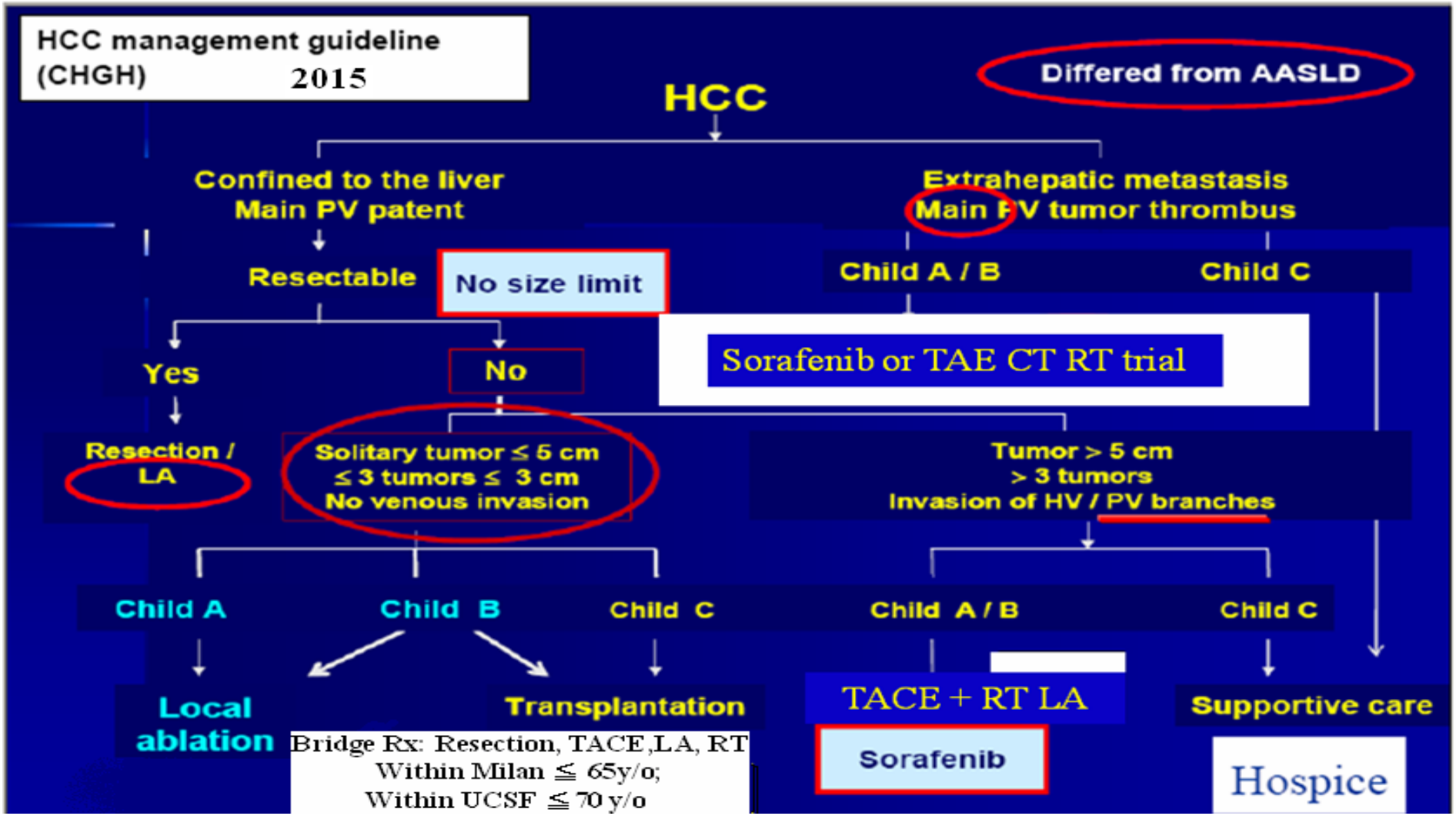
(4)需經事前審查核准後使用，每次申請之療程以 2 個月為限，送審時需檢送影像資料，每 2 個月評估一次。

6.2. Tamoxifen,anti-androgen,octreotide,hepatic artery ligation,are not recommended as 1st line therapy.(E-1)

6.3. Immunotherapy,radio-labeled lipiodol(E-4),radio-labeled Y ttrium glass beads (E-3)are not recommended as standard therapy for advanced HCC.

7. 放射線治療

- 可作為肝癌患者發生主要血管侵犯(肝門靜脈或下腔靜脈)或是轉移(腦或是骨)時之選擇(證據強度等級三)
- The efficacy,side effects and long-term prognosis of radiotherapy and HAIC still need more evidences.(E-2)


HCC management guideline
(CHGH) 2015
HCC
Differed from AASLD
Confined to the liver
Main PV patent
Extrahepatic metastasis
Main PV tumor thrombus
Resectable
No size limit
Child A / B
Child C
Yes
No
Sorafenib or TAE CT RT trial
Resection / LA
Solitary tumor ≤ 5 cm
≤ 3 tumors ≤ 3 cm
No venous invasion
Tumor > 5 cm
> 3 tumors
Invasion of HV / PV branches
Child A
Child B
Child C
Child A / B
Child C
Local ablation
Transplantation
Bridge Rx: Resection, TACE,LA, RT
Within Milan ≦ 65y/o;
Within UCSF ≦ 70 y/o
TACE + RT LA
Sorafenib
Supportive care
Hospice

Prevention:

1. Vaccination for hepatitis B virus (HBV) has been reportedly associated with reduced occurrence of hepatocellular carcinoma (HCC). (E-IB, R-A)
2. Prevention of viral transmission through blood contamination, iatrogenic medical setting and illicit drug use is effective in reducing viral hepatitis and HCC. (E-II, R-A)
3. For patients with CH-B or CH-C,anti viral therapy could prevent HCC.(E-1)
4. Anti-viral therapy after curative therapies for HCC could reduce HCC recurrence.(E-1)
5. The effect of interferon-based therapies in tertiary prevention of HBV induced HCC is still controversial by the current data. (E-IA, R-C)
6. Interferon-based therapies might reduce the incidence of recurrence for HCV induced HCC after curative therapies. (E-IA, R-B)

放射線治療準則

肝癌的治療指引以肝癌多專科團隊訂定的治療準則為依據。以下僅就放射治療的適應症、治療技術、治療劑量、以及正常組織的劑量限制來說明肝癌放射治療政策及執行程序。

一、放射治療政策

(一) 單純治癒性放射治療(definitive curative radiotherapy alone)：目前並沒有明確的證據認為放射治療對存活率有幫助，但對於不適合其他局部治療(手術、局部消除治療、或動脈栓塞化學療法)之患者，放射治療可作為替代選擇。

(二) 針對第 IV 期病患之轉移部位(如骨骼、腦等部位)施行緩解性放射治療。

二、放射治療執行程序(procedures)：

(一)電腦斷層模擬攝影(CT-based simulation)

1. 仰臥、双手置於頭頂，並以真空氣墊(vaccum pillow) or alpha cradle 固定姿勢

2. 以雷射光於病人腹部、身體兩側劃上等中心(isocenter)記號

3. 每 3-5 毫米擷取一張電腦斷層影像

4. 將影像傳送至電腦治療計劃系統(radiation treatment plan, RTP system)

(二)體外放射治療技術 (external radiotherapy technique)：

1. 三維順形放射治療(3-Dimension Conformal Radiation Therapy, 3D-CRT)

2. 強度調控放射治療(Intensity Modulation Radiation Therapy, IMRT)

3. 影像導引放射治療(Image-guided Radiation Therapy, IGRT)

(三)描繪標靶體積 (contouring target volume)

勾劃出腫瘤體積 (gross tumor volume, GTV)、臨床腫瘤體積(clinical tumor volume, CTV)和計劃靶區體積(planning target volume, PTV)的位置，定義如下:

Target volumes	Definition and description
GTV (gross tumor volume)	Liver tumor: intrahepatic-enhancing tumor on arterial-phase contrast CT with washout on venous or delayed phase CT Lipiodol retaining tumor: lipiodol (white) contiguous to the enhancing tumor Vascular tumor thrombus: arterial enhancing thrombus with washout on venous phase CT

Target volumes	Definition and description
CTV_H	Liver tumor: the intrahepatic-enhancing tumor on arterial-phase contrast CT Lipiodol retaining tumor: TACE zone contiguous to the enhancing tumor included in GTV enhancing tumor vascular thrombus
CTV_L	4-5 mm margin around intrahepatic GTV 2-3 mm margin around the tumor thrombus GTV Bland thrombus adjacent to tumor thrombus GTV Radiofrequency ablation zone adjacent to GTV TACE zone not directly adjacent to GTV
PTV	CTV or GTV + 5-20 mm (may be asymmetric).

（四）劑量處方(dose prescription)：

每分次 1.8-2.0Gy，每週五分次，劑量為 CTV_L: 30 Gy / 15 fractions (for microscopy disease); CTV_H: 40-54 Gy / 20-27 fractions (for macroscopic disease); GTV: 60Gy/30fx

(五) Organs At Risk (OAR) and dose constrain :

1. Whole liver:

(1) Whole liver < 21Gy
(2) 2/3 liver <50.4Gy
(3) 1/3 liver <68.4Gy

2. 小腸：45-50.4Gy/25-28fx
3. 腎: 1/3 < 20Gy
4. 脊髓: 45 Gy/25fx

參考資料:

1. **NCCN clinical practice guideline in oncology-Hepatobilliary cancer (V.2.2012)**

2. **Principles and practice of radiation oncology, 5th ed.**

3. **Target Volume Delineation and Field Setup: A Practical Guide for Conformal and Intensity-Modulated Radiation Therapy, Nancy Y. Lee & Jiade J. Lu, 2013**

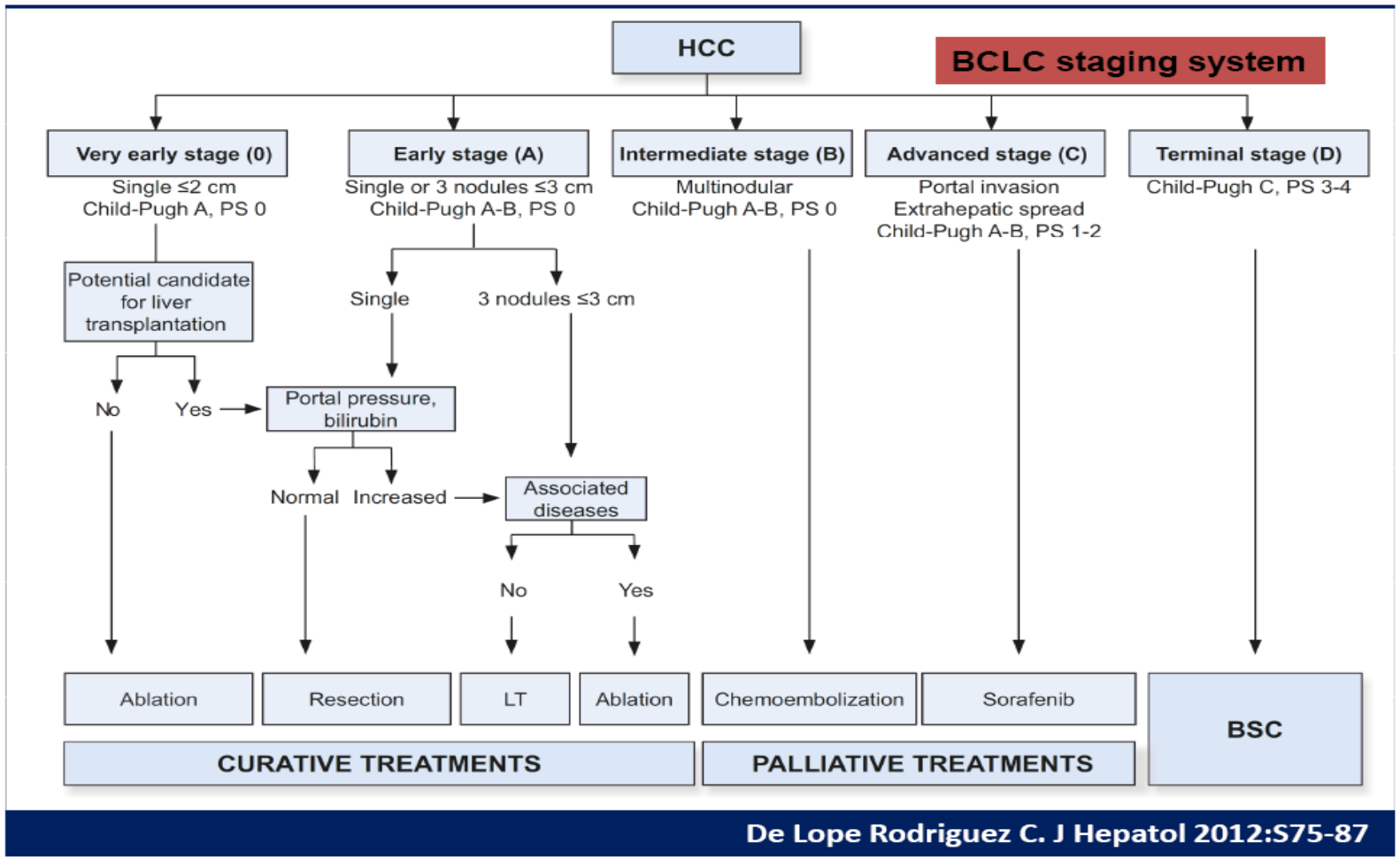
Staging:

˙For assessing the prognosis , the staging system should consider tumor stage , liver reserve , and treatment.

Okuda , BCLC , CLIP ,JIS and TNM system are all validated and applied in Taiwan.

LIVER STAGING FORM	
STAGE CATEGORY DEFINITIONS	
PRIMARY TUMOR (T)	
TX	**Primary tumor cannot be assessed**
T0	**No evidence of primary tumor**
T1	**Solitary tumor without vascular invasion**
T2	**Solitary tumor with vascular invasion or multiple tumors none more than 5 cm**
T3a	**Multiple tumors more than 5 cm**
T3b	**Single tumor or multiple tumors of any size involving a major branch of the portal vein or hepatic vein**
T4	**Tumor(s) with direct invasion of adjacent organs other than the gallbladder or with perforation of visceral peritoneum.**
REGIONAL LYMPH NODES (N)	
NX	**Regional lymph nodes cannot be assessed**
N0	**No regional lymph node metastasis**
N1	**Regional lymph node metastasis**
DISTANT METASTASIS (M)	
M0	**No distant metastasis (no pathologic M0; use clinical M to complete stage group)**
M1	**Distant metastasis**

ANATOMIC STAGE • P ROGNOSTIC GROUPS			
CLINCAL			
GROUP	T	N	M
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	AnyN	M1
Stage unknown			


HCC
BCLC staging system
Very early stage (0)
Single ≤2 cm
Child-Pugh A, PS 0
Early stage (A)
Single or 3 nodules ≤3 cm
Child-Pugh A-B, PS 0
Intermediate stage (B)
Multinodular
Child-Pugh A-B, PS 0
Advanced stage (C)
Portal invasion
Extrahepatic spread
Child-Pugh A-B, PS 1-2
Terminal stage (D)
Child-Pugh C, PS 3-4
Potential candidate for liver transplantation
No
Yes
Single
3 nodules ≤3 cm
Portal pressure, bilirubin
Normal
Increased
Associated diseases
No
Yes
Ablation
Resection
LT
Ablation
Chemoembolization
Sorafenib
BSC
CURATIVE TREATMENTS
PALLIATIVE TREATMENTS
De Lope Rodriguez C. J Hepatol 2012:S75-87

Child - Pugh Classification

Parameter	Points assigned		
	1	2	3
Ascites	Absent	Slight	Moderate
Bilirubin	<2 mg/dL (<34.2 micromol/liter)	2-3 mg/dL (34.2 to 51.3 micromol/liter)	>3 mg/dL (>51.3 micromol/liter)
Albumin	>3.5 g/dL (35 g/liter)	2.8-3.5 g/dL (28 to 35 g/liter)	<2.8 g/dL (<28 g/liter)
Prothrombin time			
Seconds over control	<4	4-6	>6
INR	<1.7	1.7-2.3	>2.3
Encephalopathy	None	Grade 1-2	Grade 3-4

Modified Child-Pugh classification of the severity of liver disease according to the degree of ascites, the plasma concentrations of bilirubin and albumin, the prothrombin time, and the degree of encephalopathy. A total score of 5-6 is considered grade A (well-compensated disease); 7-9 is grade B (significant functional compromise); and 10-15 is grade C (decompensated disease). These grades correlate with one- and two-year patient survival: grade A - 100 and 85 percent; grade B - 80 and 60 percent; and grade C - 45 and 35 percent.

Okuda		
	Parameter	Score
1.Tumor size	＜50％ of liver	0
	＞＝50％ of liver	1
2.Ascites	No	0
	Yes	1
3.Albumin	＞3g/dl	0
	＜＝3g/dl	1
4.Bilirubin	＜3mg/dl	0
	＞＝3mg/dl	1

ECOG PERFORMANCE STATUS*

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

* As published in Am. J. Clin. Oncol.:

Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.