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
2016 年 12 月修訂
2017 年 12 月修訂
2018 年 5 月修訂

## Reference:


1. **AASLD management guideline**

   **AASLD GUIDELINES FOR THE TREATMENT OF HEPATOCELLULAR CARCINOMA 2017 ;**

   This practice guideline was approved by AASLD on December 8, 2016.

2. **APASL management guideline**

   Asia–Pacific clinical practice guidelines on the management of hepatocellular carcinoma: a 2017 update

3. **Taiwan Liver Cancer Association -TLCA**

   Management consensus guideline for hepatocellular carcinoma: 2016 updated by the Taiwan Liver Cancer Association and the Gastroenterological Society of Taiwan ; Journal of the Formosan Medical Association (2017)

4. **Hepatobiliary Cancer NCCN Guidelines**

   Hepatobiliary Cancers, Version 1.2017 ; Featured Updates to the NCCN Guidelines

5. **全民健康保險藥品給付規定一百零六年版.**

# 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. **a 6 month interval with a range of 3-12 months** ( 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)

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

・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)

**＊Primovist MRI might be considered before liver biopsy. ( E: 3, R: C- TLCA 2016)**

***Gadoxetic acid-enhanced magnetic resonance imaging (EOB-MRI) diagnostic accuracy and sensitivity for HCC were significantly higher (accuracy: 0.88, 95% CI: 0.80, 0.97; sensitivity: 0.85, 95% CI: 0.74, 0.96) than with MDCT (accuracy: 0.74, 95% CI: 0.65, 0.82; sensitivity: 0.69, 95% CI: 0.59, 0.79) ($P < 0.001$). (TLCA 2016)

・**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)

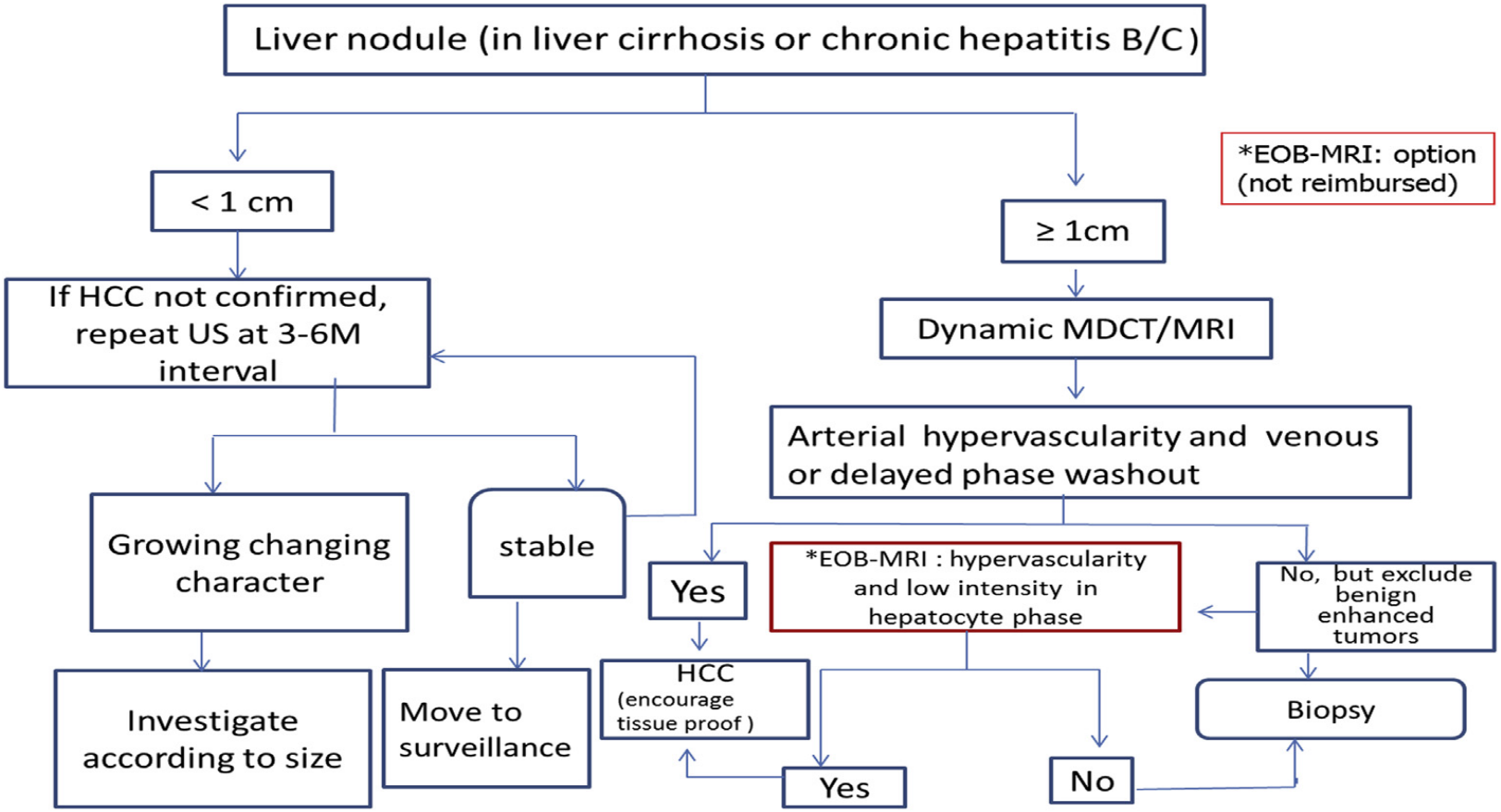
・However , if vascular pattern on imaging are not characteristic , or if nodules are detected in a non-cirrhotic liver , biopsy should be performed.(E-2)

・**For nodule < 1 cm** : 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)

**Diagnostic algorithms of liver tumor.**



## Therapy：

### 1. Resection

- For single HCC and good liver function , regardless of cirrhosis , resection is recommended .(E-2)
- 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 recommended.(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(本院未有此治療，若有需要轉院治療)

- 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)

### 3.1.Local Ablation

- RFA and PEI are both effective for HCC ＜2cm.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(RFA：tumor size up to 4cm ).(E-1)

## 3.2. TACE

• TACE is recommended as the 1st line non-curative therapy for patients with unresectable large/multi-focal HCC who do not have vascular invasion or extrahepatic spread (BCLC-B).(E-1)

• TACE discouraged in decompensated liver disease, advanced liver dysfunction, macroscopic invasion or extra-hepatic spread (E-1A,R-1B)

• Drug-eluting beads-TACE (DEB-TACE) :similar therapeutic efficacy with less systemic adverse events compared with cTACE (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)

## 4. Systemic Therapy

### 4.1 Target Therapy

˙VEGFR and multi-kinase inhibitors have shown survival benefits in advanced HCC ( EASL 2017)

- Fisrt line : sorafenib and lenvatinib (本院未有此藥)
- Second line : regorafenib (and cabozantinib and ramucirumab - 本院未有此藥)

˙**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：

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。

**Regorafenib**- is recommended as second-line treatment for patients :
(EASL 2018; high level evidence, strong recommendation)
I. Tolerating and progressing on sorafenib
II. With well-preerved liver function (Child-Pugh class A)
III. With good performance status

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

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

## 5. 放射線治療

• 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。

• 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。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 IV 期病患之轉移部位(腦或是骨)時施行緩解性放射治療之選擇(證據強度等級三)

• The efficacy,side effects and long-term prognosis of radiotherapy and HAIC(本院無此治療，若有需要轉院治療) still need more evidences.(E-2)

(1) 劑量處方(dose prescription)：

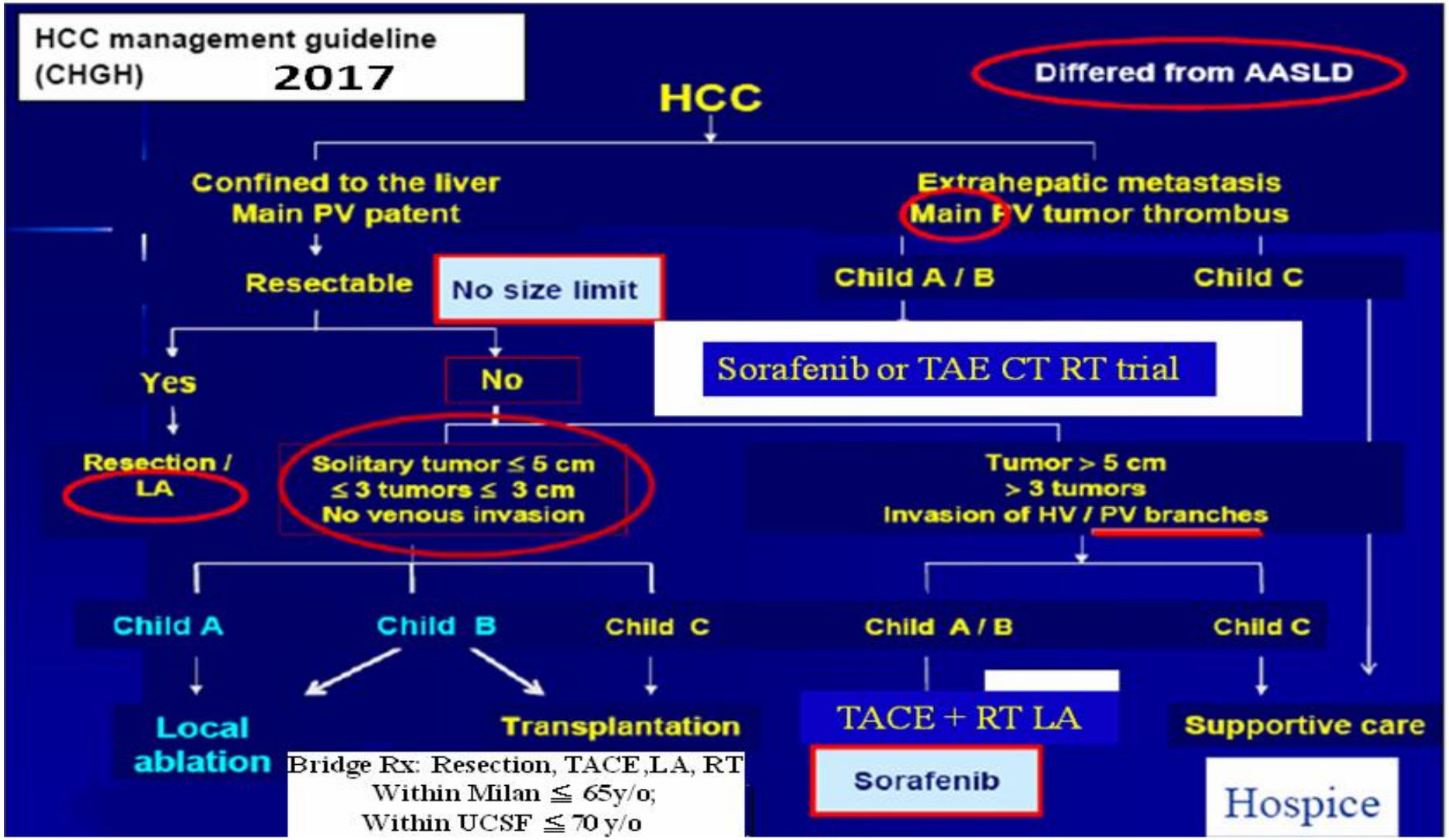
每分次 1.8-2.0Gy，每週五分次，劑量為 CTV_L: 30 Gy / 15 fractions (for microscopy disease); CTV_H: 40-54 Gy / 20-27 fractions (for macroscopic disease); GTV: 60Gy/30fx

(2) 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.2.2017)**
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**


HCC management guideline
(CHGH) 2017
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 reduce HCC.(E-1)

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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)

**Staging:**

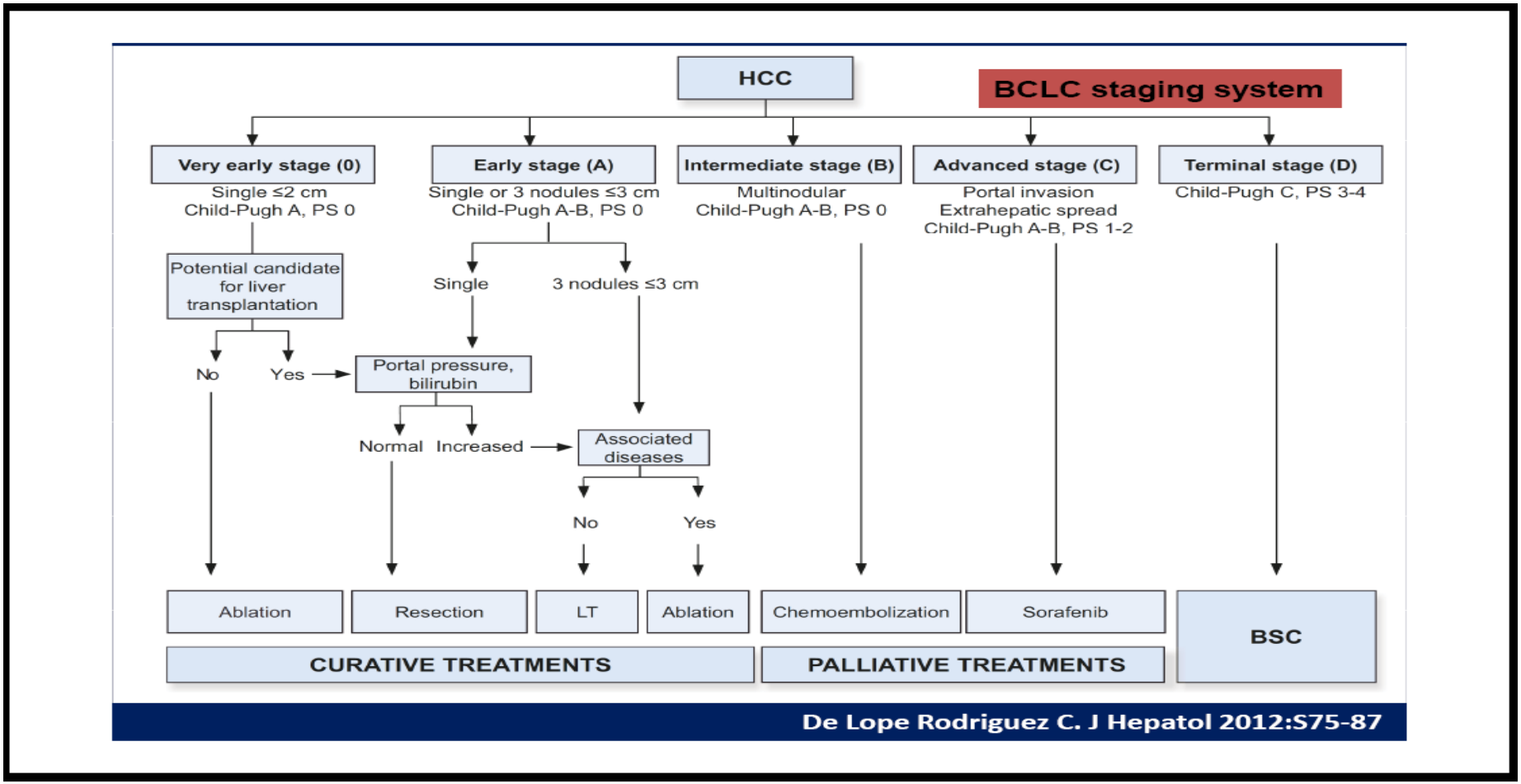
˙For assessing the prognosis , the staging system should consider tumor stage , liver reserve , and treatment.

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

| . | |
|---|---|
| **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** |

| 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 |

TNM: tumor, node, Mmtastasis; AJCC: American Joint Committee on Cancer; UICC: Union for International Cancer Control.


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
Single
3 nodules ≤3 cm
No
Yes
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.*