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Staging classifications for hepatocellular carcinoma

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Evaluation and treatment of patients with hepatocellular carcinoma is dependent on accurate staging. Tumor-specific factors and the degree of underlying liver disease must be considered when evaluating patients with hepatocellular carcinoma. Clinical staging classification systems based on preinterventional data are predictive of survival and influence patient selection for various therapeutic modalities. Pathologic staging systems accurately assess prognosis and influence additional treatment post resection. The various staging systems for hepatocellular carcinoma are reviewed in detail. The benefits and limitations of these classification systems are discussed in this review. Considerable controversy remains over which classification system provides the optimum staging of hepatocellular carcinoma. The revised American Joint Committee on Cancer/International Union Against Cancer emphasizes the importance of major vascular and microvascular invasion as independent predictors of death and the negative impact of severe fibrosis/cirrhosis on survival following resection of hepatocellular carcinoma. As such, it is currently the most accurate staging system in this group of patients. Its applicability in those patients who are not candidates for resection is uncertain.

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Accurate staging is important in the evaluation and treatment of patients with cancer. Implementation of appropriate therapeutic strategies is dependent on accurate staging, as it allows the identification of patients who would benefit from aggressive treatment approaches and the recognition of patients who would be best served by supportive care. Additionally, improved accuracy in staging allows enhanced comparison and stratification among groups of patients in therapeutic trials. This results in the improved ability of clinical research to discriminate subtle differences in patient characteristics such as relevant risk factors and responses to treatment, as well as compare groups of patients from separate studies. Finally, improved accuracy in staging offers potentially improved ability to determine prognosis.

Hepatocellular carcinoma (HCC) is the most common form of primary hepatic carcinoma and the fifth most common cancer in the world [1]. While relatively infrequent in developed countries, its incidence has increased in Japan, the UK, France and the USA over the last 20–30 years [2–5]. HCC usually arises in the setting of chronic hepatitis or cirrhosis. Advances in both the evaluation and treatment of patients with chronic hepatitis and cirrhosis have resulted in earlier diagnosis of HCC, making accurate staging of paramount importance.

Staging of HCC is complex, as it depends not only on tumor-specific factors, including size, morphology and vascular involvement, but also on the degree of underlying liver disease. Accurate classification and staging systems must incorporate both types of variables to be effective. Staging systems based on preinterventional assessments (clinical staging) allow estimation of patient survival and influence patient selection for various therapeutic modalities. These classification systems are applicable to all patients with HCC, including those who are candidates for surgical resection and those who are most appropriate for nonsurgical interventions. Staging systems incorporating postresection evaluation (pathologic

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Table 1. Child–Pugh classification.

Points	Bilirubin	Albumin	Prothrombin time	Encephalopathy	Ascites	Child–Pugh classification	Total points
1	<2	>3.5	INR <1.7	Absent	Absent	A	5–6
2	2–3	3–3.5	INR 1.7–2.3	Moderate	Moderate	B	7–9
3	>3	<3	INR >2.3	Severe	Tense	C	10–15

staging) accurately assess prognosis, influence further treatment strategies, and offer improved discriminatory ability, but may not be readily applied to most patients with HCC or those who are not candidates for surgical intervention.

Basis for staging in hepatocellular carcinoma

Tumor characteristics

The traditional Tumor Node Metastasis (TNM) system is useful in the evaluation of many types of cancers. It relies on the classification of the tumor and its spread, by assessing the tumor, the presence or absence of nodal disease and the presence or absence of distant metastases. Alone, it is of limited utility in the evaluation of HCC, as it does not address liver function, nor is it predictive of recurrence or survival.

Assessment of liver function

The Child–Pugh classification accurately assesses the severity of liver dysfunction by evaluating the patient's serum albumin and bilirubin levels, degree of ascites and encephalopathy, and prothrombin time (TABLE 1) [6].

Clinical staging systems

Comprehensive classification schemes including clinical assessments of both tumor characteristics and liver function parameters were subsequently developed to guide initial therapy in those patients with HCC and liver dysfunction.

Okuda

In 1985, Okuda published a retrospective review of 850 patients with HCC using a staging scheme based on tumor size (<50% or >50% liver replacement), the presence or absence of ascites, serum bilirubin level and serum albumin level [7]. This was the first classification system to consider both tumor factors and an assessment of liver function in relation to survival (TABLES 2A & B). While it has been regarded as the most standardized staging system for patients with advanced cirrhosis, it has limited ability to discriminate among asymptomatic patients presenting in the earlier stages of disease. This finding has been confirmed in various studies comparing the prognostic ability of alternative staging systems with that of the Okuda staging system [8–12]. Furthermore, the Okuda staging system does not include any evaluation of important tumor factors, which have subsequently been found to have prognostic significance in patients with HCC.

Cancer of the Liver Italian Program

In 1998, the Cancer of the Liver Italian Program (CLIP) investigators published a retrospective review of 435 patients with HCC [8]. Their goal was to evaluate known prognostic factors and produce an index with increased sensitivity and discriminatory ability compared with TNM and Okuda staging. The CLIP score incorporates Child–Pugh staging, assessment of tumor morphology (single vs. multiple, <50% or >50% liver replacement), serum α-fetoprotein level and the presence or absence of portal vein thrombosis (TABLE 3A).

As expected, an increased CLIP score was associated with decreased median survival (TABLE 3B). While the ability of the CLIP score to provide an accurate prognostic forecast has been prospectively validated, it has limitations [9–12]. First, tumor morphology in the best prognostic group (uninodular and tumor extent < 50%) can include patients with significantly different degrees of tumor burden. This limits the ability of the CLIP score to accurately determine the prognosis among patients in this, the best prognostic group. Second, most patients are classified as CLIP 0–2, implying limited ability to stratify patients. Finally, it cannot discriminate survival differences in those patients with advanced disease (CLIP 4–6). However, this is of limited clinical significance as a result of the poor overall survival of these groups.

Table 2A. Okuda Staging System.

Variable	Score	
	0	1
Size of tumor	<50% of liver	>50% of liver
Ascites	No	Yes
Albumin (g/dl)	≥3.0	<3.0
Bilirubin (mg/dl)	<3.0	>3.0

Stage I, Score 0; Stage II, Score 1–2; Stage III, Score 3–4

Table 2B. Okuda Staging System results.

Stage/group	Number of patients	Median survival (months)
Entire group	850	4.1
Stage I	272	11.5
Stage II	466	3.0
Stage III	112	0.9

Table 3A. Cancer of the Liver Italian Program score.

Criteria	Score		
	0	*1*	*2*
Child–Pugh stage	A	B	C
Tumor morphology	Uninodular and extent ≤50% of liver	Multinodular and extent ≤50 % of liver	Massive or extent >50% of liver
α-fetoprotein (ng/ml)	<400	≥400	
Portal vein thrombosis	No	Yes	

Table 3B. Cancer of the Liver Italian Program results.

Cancer of the Liver Italian Program score	Median % of patients	Median survival (months)
0	13.7	42.5
1	29.4	32.0
2	29.8	16.5
3	13.5	4.5
4	8.2	2.5
5 and 6	8.0	1.0

Barcelona Clinic Liver Cancer

In 1999, the Barcelona Clinic Liver Cancer (BCLC) staging classification was published [13]. Initially developed for patients undergoing hepatic resection, the BCLC system provides a treatment algorithm based on anticipated survival rather than a prognostic index. The BCLC includes assessment of performance status, tumor status (tumor and Okuda stage) and liver function (presence or absence of portal hypertension, serum bilirubin and Child–Pugh classification) to classify patients into four stages (TABLE 4).

The recommendations proposed by the BCLC are as follows. Early HCC (stage A) includes asymptomatic patients who are appropriate for radical, potentially curative surgical therapies, including resection, orthotopic liver transplantation and percutaneous treatments (ethanol injection or radiofrequency ablation). Intermediate HCC (stage B) and advanced HCC (stage C) include patients who would benefit from palliative treatments or new agents in the setting of randomized controlled clinical trials. End-stage HCC (stage D) includes patients with extremely poor prognosis, who are appropriate for supportive therapies only. One major limitation of the BCLC is its reliance on the subjective evaluation of performance status. The BCLC has not been prospectively validated.

Pathologic staging systems

While clinical staging systems may be predictive of survival, pathologic TNM staging systems have traditionally been used to accurately assess prognosis and evaluate patients regarding additional therapies following resection. Modifications incorporating the detailed pathologic evaluation of vascular invasion, nodal status and degree of fibrosis/cirrhosis have subsequently been proposed.

Izumi

In 1994, Izumi and coworkers performed a retrospective analysis of 104 patients undergoing hepatic resection [14]. They found that the current pathologic TNM classification failed to discriminate between Stages I and II and between Stages III and IVA. Based on their findings, they proposed a modification of the TNM classification incorporating clinical and pathologic findings regarding vascular invasion (TABLE 5).

Table 4. Barcelona Clinic Liver Cancer staging.

Stage	Performance status	Tumor status		Liver functional status
		Tumor stage	*Okuda stage*	
A: early				
A1	0	Single	I	No portal hypertension, normal bilirubin
A2	0	Single	I	Portal hypertension, normal bilirubin
A3	0	Single	I	Portal hypertension, abnormal bilirubin
A4	0	Three tumors <3 cm	I–II	Child–Pugh A–B
B: intermediate	0	Large multinodular	I–II	Child–Pugh A–B
C: advanced	1–2	Vascular invasion or extrahepatic spread	I–II	Child–Pugh A–B
D: end stage	3–4	Any	III	Child–Pugh C

Table 5. Izumi Tumor Node Metastis modification.

Stage	Modification
I	Solitary tumor without vascular invasion
II	Solitary or multiple tumor(s) adjacent to vessel branch
III	Tumor(s) involving major vessel branch or with regional lymph node metastasis
IV	Tumors with distant metastasis

The modified Izumi classification was subsequently validated by Staudacher and coworkers, as it was able to demonstrate significant differences in survival and disease-free survival between Stages I and II and between Stages III and IVA in a retrospective review of 53 cirrhotic patients undergoing resection of HCC [15]. In a similar fashion, Marsh and coworkers demonstrated that depth of vascular invasion, lobar distribution of tumor, lymph node status and largest tumor size were independent predictors of tumor-free survival in a retrospective evaluation of 307 patients undergoing orthotopic liver transplant for HCC [16]. These results in this specific patient population may not be directly translated to the majority of patients with HCC. Nonetheless, this study supports the prognostic significance of pathologic evaluation.

Japan Integrated Staging score

Recently, Kudo and coworkers proposed the Japan Integrated Staging (JIS) score, based on a separate classification scheme, the TNM by the Liver Cancer Study Group of Japan (LCSGJ). In the TNM by LCSGJ, T stage is dependent on three criteria: single tumor morphology, tumor size less than 2 cm and the absence of macroscopically detectable vascular invasion (TABLE 6A). The discriminatory ability of the TNM by LCSGJ classification system has been validated outside of the Japanese population [17]. This classification system has the ability to provide prognostic information prior to intervention, as it is based on macroscopic findings. The JIS Score combines TNM by the LCSGJ and Child–Pugh classification (TABLE 6B) [18]. A total of 722 patients with HCC were analyzed and evaluated in regard to both CLIP staging and the proposed JIS. This classification scheme was applied to patients prior to intervention. Interventions included resection, percutaneous ablation therapies, transcatheter arterial embolization, intra-arterial infusion chemotherapy, or the best supportive therapy. They found that the JIS provided improved stratification of all patients compared with the CLIP scoring system, particularly in regard to discrimination of patients in the most favorable prognostic group.

Limitations of the JIS include its potential applicability in the Western world, as it has not been utilized or validated outside of the Japanese population, unlike the TNM by LCSGJ. More importantly, it assumes that the three major criteria of the TNM staging by LCSGJ, tumor morphology, tumor size and macroscopic vascular invasion are of equivalent prognostic significance. Finally, it does not include any evaluation of microscopic vascular invasion, recently identified as an equally important predictor of survival in those patients following resection.

AJCC/UICC

The American Joint Committee on Cancer/International Union Against Cancer (AJCC/UICC) staging system for HCC, proposed in 1988, uses a TNM classification system to predict patient survival following resection of HCC (TABLES 7A & B) [19].

The T classification, based on the number and location of tumor nodules, size of the largest nodule and the presence of vascular invasion or adjacent organ invasion, was considered to be unnecessarily complex. More importantly, the AJCC/UICC staging system was considered to be limited in its ability to adequately stratify patients with respect to prognosis. In 2002, Vauthey published a retrospective, multicenter review of 557 patients who underwent complete resection of HCC, evaluating the ability of the AJCC/UICC staging system to stratify patients with regard to survival [20]. The independent predictors of survival following resection were identified and subsequently integrated into a simplified T classification and revised staging system (TABLE 8).

The following factors were identified as independent predictors of death. The presence of major vascular invasion had the most significant impact on survival, followed by microvascular

Table 6A. Japan TNM staging system.

Factors	T stage	Stage
I. Single tumor	T1 – Fulfilling three factors	I – T1N0M0
II. Size <2 cm	T2 – Fulfilling two factors	II – T2N0M0
III. No vessel invasion	T3 – Fulfilling one factor	III – T3N0MO
	T4 – Fulfilling no factors	IVA – T4N0M0 or T1–4, N1M0
		IVB – T1–4, N0–1, M1

TNM: Tumor Node Metastasis.

Table 6B. Japan Integrated Staging Score.

Criteria	Scores			
	0	1	2	3
Child–Pugh	A	B	C	
TNM (Liver Cancer Study Group of Japan)	I	II	III	IV

Summation of the tumor staging score and the Child–Pugh score equals the Japan Integrated Staging score.
TNM: Tumor Node Metastasis.

Table 7A. American Joint Committee on Cancer/ International Union Against Cancer T classification (1997).

T stage	Description
T1	Solitary, ≤2 cm, without vascular invasion
T2	Solitary, ≤2 cm, with vascular invasion Multiple, one lobe, ≤2 cm, without vascular invasion Solitary, >2 cm, without vascular invasion
T3	Solitary, >2 cm, with vascular invasion Multiple, one lobe, ≤2 cm, with vascular invasion Multiple, one lobe, >2 cm, with or without vascular invasion
T4	Multiple, more than one lobe Invasion of major branch of portal or hepatic veins Invasion of adjacent organs other than gallbladder Perforation of visceral peritoneum

Table 7B. American Joint Committee on Cancer/ International Union Against Cancer TNM staging.

Stage	Description
I	T1N0M0
II	T2N0M0
IIIA	T3N0M0
IIIB	T1–3, N1M0
IVA	T4, any N, M0
IVB	Any T, any N, M1

TNM: Tumor Node Metastasis.

invasion and severe fibrosis/cirrhosis in the adjacent liver. Multiple tumors and tumor size greater than 5 cm were also associated with diminished survival.

Patients were subsequently stratified into three groups on the basis of vascular invasion. The 5-year survival was 48% ± 3% in patients with no vascular invasion, 33% ± 4% in patients with microvascular invasion and 14% ± 5% in patients with major vascular invasion. The impact of tumor number on survival was then evaluated. In patients with no evidence of vascular invasion and single tumors, survival was improved compared with patients with multiple tumors (55% ± 4% vs. 30% ± 6%). In patients with microvascular or major vascular invasion, no differences in survival were demonstrated between patients with single tumors versus multiple tumors. Tumor size was similarly evaluated. No effect of tumor size was identified in patients with single tumors. A significant effect of tumor size greater than 5 cm was seen only in patients with multiple tumors and no major vascular invasion (36% ± 6% vs. 15% ± 5%).

With these results, a simplified staging classification was proposed for patients following resection. Patients with single tumors with no vascular invasion are classified as sT1. Patients with single tumors with microvascular invasion or multiple tumors (none >5 cm) are classified as sT2, while patients with multiple tumors (any >5 cm) and patients with tumors with major vascular invasion are classified as sT3.

Additionally, the effect of fibrosis stage on survival was evaluated with detailed pathologic evaluation. The presence of severe fibrosis/cirrhosis had a negative impact on survival in these patients. Interestingly, most patients in this study were considered Child–Pugh A, but had moderate to severe fibrosis/cirrhosis on pathologic evaluation. Child classification was available for 443 patients and pathologic data regarding stage of fibrosis were available for 529 patients.

The major limitation of the revised AJCC/UICC relates to the prognostic significance of microvascular invasion, a post-resection pathologic evaluation. As such, this classification system can only be utilized in the evaluation of those patients who undergo resection.

In 2003, Poon compared the revised AJCC/UICC with the original AJCC/UICC and TNM by LCSGJ in regard to their ability to accurately provide prognostic information [17]. A total of 542 Chinese patients undergoing resection of HCC were evaluated in a prospective fashion.

When classified by the original AJCC/UICC, statistically significant survival differences between Stages II and IIIA and Stages IIIA and IVA were noted, but no statistical differences were seen between Stages I and II or Stages IVA and IVB. When classified by the revised AJCC/UICC, statistically significant survival differences between Stages I and II, Stages II and IIIA, and Stages II and IIIB were noted. No statistical differences

Table 8. Simplified American Joint Committee on Cancer/International Union Against Cancer TNM classification and staging.

Classification	sT1 – single tumor without vascular invasion
	sT2 – single tumor with vascular invasion or multiple tumors, none >5 cm
	sT3 – multiple tumors, any >5 cm or tumor(s) involving major branch of portal or hepatic vein(s)
Fibrosis	F0 – grade 0–4 fibrosis (none to moderate fibrosis)
	F1 – grade 5–6 fibrosis (severe fibrosis/cirrhosis)
Stage grouping	Stage I – sT1N0M0
	Stage II – sT2N0M0
	Stage IIIA – sT3N0M0
	Stage IIIB – any sT, N1M0
	Stage IV – any sT, any N, M1

TNM: Tumor Node Metastasis.

were seen between Stages IIIA and IIIB, IIIA and IV, or IIIB and IV. When classified by the TNM by LCSGJ, statistically significant survival differences between Stages I and II, Stages II and III, and Stages III and IVA were seen. No statistically significant differences were seen between Stages IVA and IVB.

The findings of this evaluation validate the prognostic ability of the simplified staging system provided by the revised AJCC/UICC. It confirms the importance of major vascular invasion (hazard ratio 3.112, $p < 0.001$) and pathologic microvascular invasion (hazard ratio 1.683, $p < 0.001$) as independent predictors of death. Additionally, the presence of cirrhosis was identified as an independent adverse prognostic factor for survival (hazard ratio 1.384, $p = 0.023$). This study supports separate reporting of fibrosis scoring in addition to the pathologic staging of the tumor, thereby enhancing the prognostic value of the revised AJCC/UICC.

Expert opinion

Accurate staging of HCC is complex, as it depends not only on tumor-specific factors, including size, morphology and vascular involvement, but also on the degree of underlying liver disease. Considerable controversy remains over which classification system provides the optimum staging of HCC. The revised AJCC/UICC classification scheme is now the most accurate and effective means of assessing the prognosis of patients following resection of HCC. It emphasizes the importance of major vascular and microvascular invasion as independent predictors of death, and the negative impact of severe fibrosis/cirrhosis on survival in these patients. Its applicability to the evaluation of patients who are not candidates for resection has not yet been demonstrated. Further studies evaluating the AJCC/UICC staging system in these patient populations are needed.

Five-year view

The revised AJCC/UICC classification scheme is currently the most accurate and effective means of assessing the prognosis of patients following resection of HCC.

Future improvements in the staging of HCC will require the inclusion of genetic determinants. A thorough understanding of the molecular mechanisms for the development and growth is mandatory. The addition of specific genetic markers into the new classification schemes will significantly improve the accuracy of staging.

Key issues

- Accurate staging is important in the evaluation and treatment of patients with cancer.
- Hepatocellular carcinoma (HCC) is the most common form of primary hepatic carcinoma and the fifth most common cancer in the world.
- Staging depends on tumor-specific factors and the degree of underlying liver disease.
- Classification schemes based on tumor-specific factors and an assessment of liver function were developed.
- Modifications incorporating pathologic evaluation of vascular invasion, nodal status and degree of fibrosis/cirrhosis have been proposed.
- Major vascular invasion and microvascular invasion were found to be independent predictors of death.
- The presence of severe fibrosis/cirrhosis had a negative impact on survival.
- The revised American Joint Committee on Cancer/International Union Against Cancer classification is currently the most accurate and effective means of assessing the prognosis of patients following resection of HCC.

References

Papers of special note have been highlighted as:
- • of interest
- •• of considerable interest

1 Bosch FX, Ribes J, Borras J. Epidemiology of primary liver cancer. *Semin. Liver Dis.* 19, 271–285 (1999).

2 Okuda K, Fujimoto I, Hanai A, Urano Y. Changing incidence of hepatocellular carcinoma in Japan. *Cancer Res.* 47, 4967–4972 (1987).

3 Taylor-Robinson SD, Foster GR, Arora S, Hargreaves S, Thomas HC. Increase in primary liver cancer in the UK, 1979–94. *Lancet* 350, 1142–1143 (1997).

4 Deuffic S, Poynard T, Buffat L, Valleron AJ. Trends in primary liver cancer. *Lancet* 351, 214–215 (1998).

5 El-Serag HB, Mason AC. Rising incidence of hepatocellular carcinoma in the United States. *N. Engl. J. Med.* 340(10), 745–750 (1999).

6 Pugh RNH, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. *Br. J. Surg.* 60, 646–649 (1973).

7 Okuda K, Ohtsuki T, Obata H *et al*. Natural history of hepatocellular carcinoma and prognosis in relation to treatment. *Cancer* 56, 918–928 (1985).
•• First system to include tumor-related factors and assessment of liver function.

8 The Cancer of the Liver Italian Program (CLIP) Investigators. A new prognostic system for hepatocellular carcinoma: a retrospective study of 435 patients. *Hepatology* 28, 751–755 (1998).
•• Increased discriminatory ability of Cancer of the Liver Italian Program compared with Tumor Node Metastasis (TNM) and Okuda staging.

9 The Cancer of the Liver Italian Program (CLIP) Investigators. Prospective validation of the CLIP score: a new prognostic system for patients with cirrhosis and hepatocellular carcinoma. *Hepatology* 31, 840–845 (2000).

10 Ueno S, Tanabe G, Sako K *et al*. Discrimination value of the new western prognostic system (CLIP Score) for hepatocellular carcinoma in 662 Japanese patients. *Hepatology* 34, 529–534 (2001).

11 Farinati F, Rinaldi M, Gianni S, Naccarato R. How should patients with hepatocellular carcinoma be staged? Validation of a new prognostic system. *Cancer* 89, 2266–2273 (2000).

12 Levy I, Sherman M. The Liver Cancer Study Group of the University of Toronto. Staging of hepatocellular carcinoma: assessment of the CLIP, Okuda, and Child–Pugh staging systems in a cohort of 257 patients in Toronto. *Gut* 50, 881–885 (2002).

13 Llovet JM, Bru C, Bruix J. Prognosis of hepatocellular carcinoma: the BCLC staging classification. *Semin. Liver Dis.* 19, 329–338 (1999).

• Barcelona Clinic Liver Cancer provides treatment algorithm based on anticipated survival.

14 Izumi R, Shimizu K, Ii T *et al*. Prognostic factors of hepatocellular carcinoma in patients undergoing hepatic resection. *Gastroenterology* 106, 720–727 (1994).

15 Chiappa A, Zbar AP, Podda M *et al*. Prognostic value of the modified TNM (Izumi) classification of hepatocellular carcinoma in 53 cirrhotic patients undergoing resection. *Hepatogastroenterology* 48, 229–234 (2001).

16 Marsh JW, Dvorchik I, Bonham CA, Iwatsuki S. Is the pathologic TNM staging system for patients with hepatoma predictive of outcome? *Cancer* 88, 538–543 (2000).

17 Poon RT, Fan S. Evaluation of the new AJCC/UICC staging system for hepatocellular carcinoma after hepatic resection in Chinese patients. *Surg. Oncol. Clin. N. Am.* 12, 35–50 (2003).

•• Validated the accuracy of the revised American Joint Committee on Cancer (AJCC)/International Union Against Cancer (UICC) in predicting survival differences in patients with early stages of disease (Stage I vs. II, Stage II vs. IIA).

18 Kudo M, Chung H, Osaki Y. Prognostic staging system for hepatocellular carcinoma (CLIP score): its value and limitations, and a proposal for a new staging system, the Japan Integrated Staging Score (JIS score). *J. Gastroenterol.* 38, 207–215 (2003).

•• Japan Integrated Staging score incorporates TNM stage by the Liver Cancer Study Group of Japan and Child–Pugh classification.

19 *Manual for Staging Cancer, fifth edition*. Beahrs OH, Hensen DE, Hutter RVP *et al.* (Eds), JB Lippincott, PA, USA (1997).

20 Vauthey JN, Lauwers GY, Esnaola NF *et al*. Simplified staging for hepatocellular carcinoma. *J. Clin. Oncol.* 20, 1527–1536 (2002).

•• Revised AJCC/UICC identifies major vascular invasion, microvascular invasion and the presence of severe fibrosis/cirrhosis as independent predictors of death.

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