Original Article

Adherence to AASLD Recommendation Guideline for Treatment Hepatocellular Carcinoma: Single Center Analysis of the Regional Hospital of Thailand

Arunchai Chang MD[1], Ritt Utarabhand MD[2], Araya Khaimook MD[3], Apiradee Songjamrat MD[4],
Songklod Pakdeejit MD[4], Attapon Rattanasupa MD[1]

[1] Division of Gastroenterology, Hatyai Hospital, Songkhla, Thailand
[2] Department of Internal Medicine, Hatyai Hospital, Songkhla, Thailand
[3] Division of Minimal Invasive Surgery, Hatyai Hospital, Songkhla, Thailand
[4] Division of Intervention Radiology, Hatyai Hospital, Songkhla, Thailand

Background: The American Association for Study of Liver Disease (AASLD) Guideline for treatment hepatocellular carcinoma (HCC) might not be adopted in the real-life practice because of differences in populations characteristics and medical resources among countries.

Objective: To assess the rate of adherence to AASLD guideline for treatment HCC and the reasons of non-adherence.

Materials and Methods: The 198 cirrhotic patients first diagnosed HCC in Hatyai Hospital (enrolled between January 2014 and December 2016) were retrospectively evaluated. Patients were classified according to the Barcelona Clinic Liver Cancer (BCLC) staging system into five stages, very early stage (BCLC 0), early stage (BCLC A), intermediate stage (BCLC B), advanced stage (BCLC C), and terminal stage (BCLC D). The rate of adherence to the AASLD guideline for treatment of HCC was evaluated and the reasons of non-adherence were explored.

Results: Patients were stratified by the BCLC stages, 10 (5.1%) for BCLC 0, 44 (22.2%) for BCLC A, 61 (30.8%) for BCLC B, 50 (25.3%) for BCLC C, and 33 (16.7%) for BCLC D. Only 123 (62%) patients were found to be adherent to the AASLD guideline. The rates of adherence to guideline according to BCLC stage 0, A, B, C, and D were 90.0%, 59.1%, 72.1%, 26.0%, and 93.9%, respectively. Reasons for non-adherence were cost (45.3%), patient opting for best supportive care (29.3%), technical limitation in primary choice of treatment (12.0%), limited number of liver donors (8.0%), and aggressive treatment recommended by experts (5.3%).

Conclusion: Mainly 62% of the patients diagnosed with HCC for the first time were treated according to AASLD guideline. Treatment non-adherence was due to cost, technical limitation, and regional culture background.

Keywords: Hepatocellular carcinoma (HCC), Treatment, Adherence, AASLD, BCLC Thailand

Hepatocellular carcinoma (HCC) is the fifth most common solid organ tumor in the world and the third leading cause of malignancy-related death worldwide[1]. There is a high prevalence of HCC among populations in Southeast Asia and Africa[2,3], the endemic area of chronic viral hepatitis infection, which is the most important risk factor of global HCC[4,5].

Unlike other solid organ tumors, there are many unique characteristics of HCC, including multifocal tumorigenesis, frequent vascular invasion, high rate of recurrence, and background of baseline cirrhosis. All of these manifestations make the HCC difficulty to cure. Care of HCC patients require multidisciplinary teams including hepatologists, surgeons, liver transplantation teams, oncologists, and intervention radiologists[6,7]. Recommended treatment strategies for HCC consists of liver resection (LR), liver transplantation (LT), local ablative therapy (LAT) including percutaneous ethanol injection (PEI) and radiofrequency ablation (RFA), transcatheter arterial chemoembolization (TACE), molecular targeted therapy (Sorafenib), and best supportive care (BSC)[5,6].

The offered therapy for the HCC patients is based on tumor staging and the underlying liver dysfunction[4]. In the last decade, many staging and prognostic systems for HCC patients were developed to overcome the

Correspondence to:

Chang A. Division of Gastroenterology, Department of Internal Medicine, Hatyai hospital, Songkhla 90110, Thailand.
Phone: +66-74-273261, **Fax**: +66-74-273264
Email: busmdcu58@gmail.com

inefficiency of the classical Child-Turcotte-Pugh (CTP)[8], Okuda[9], and Tumor-Node-Metastasis (TMN)[10] staging systems. The most reliable and widely used staging systems for classifying HCC are the Cancer of the Liver Italian Program (CLIP)[11], Barcelona Clinic Liver Cancer (BCLC) staging system[12], and the Japan Integrated Staging score (JIS)[13]. Among these, BCLC staging system was proposed to be validated by several groups in the United States and Europe to offer the best staging classification of HCC.

The guidelines on the management of HCC proposed by the American Association for the Study of Liver Disease (AASLD) and the European Association for the Study of the Liver, European Organization for Research and Treatment of Cancer (EASL-EORTC) rely on BCLC staging system[5-7] because it provides not only reliable prognosis prediction but also outlines choice of treatments for each stage. This innovative approach evaluates the tumor status, performance status (PS), and liver function[14]. However, although this staging system is developed from large trials conducted in referral centers, it is hardly applied in real-life practices because of peculiar differences in population characteristics and medical resources among countries.

Within Hatyai Hospital, the regional referral center in southern Thailand, the AASLD guideline is used as a reference for therapeutic decisions. Each HCC patient's treatment modality is a result of careful multidisciplinary analysis of the risks and benefits of the limited available treatment.

The aim of the present study was to assess the rate of adherence to the AASLD guideline for treatment of HCC, and to identify the reasons for non-adherence in a regional hospital in Thailand, a developing country in Southeast Asia.

Materials and Methods
Study population

The present report was a retrospective observational study, conducted in a single center, Hatyai Hospital, using data collected between January 2014 and December 2016. All patients diagnosed as HCC were enrolled in Hatyai Hospital in the 3-year period. Exclusion criteria were patients that received previous treatment of HCC and HCC in non-cirrhotic liver (AASLD guideline are specially for patients with baseline cirrhotic liver). The diagnosis of cirrhosis was made using histological examination or a combination of physical examination, laboratory tests and imaging data. HCC was diagnosed using non-invasive diagnosis criteria in the AASLD update proposed in 2010[6] or histological examination. Patient's baseline characteristics recorded during diagnosis include age, sex, body mass index (BMI), the Eastern Cooperative Oncology Group (ECOG) performance status, medical history, alcohol intake, etiologies of underlying liver disease, comorbidities, presenting symptom at diagnosis of HCC, complete blood count, liver function and other routine biochemistry, alpha-fetoprotein (AFP), marker of viral hepatitis and autoimmune hepatitis, CTP score, model for end stage liver disease (MELD) score, surveillance of HCC and regularity, and time of treatment start. Data on HCC surveillance included either with or without ultrasound (US) surveillance. Regular surveillance was defined as US performed at least 6 to 12 months before the first detection of HCC. Details of HCC were also recorded at baseline, including modalities of diagnosis and tumor characteristics (number, site, location, portal invasion, and extrahepatic spread). Evidence of portal hypertension was defined by indirect criteria: the presence of esophagogastric varices detected by esophagogastroduodenal endoscopy, ascites, or splenomegaly and a platelet count of less than 100,000/mm³.

Determination of staging and treatment options according to BCLC system

Initial tumor staging of HCC patient was classified into five stages base on BCLC staging system (0, A, B, C, D), as shown in Table 1. After determining the tumor stage, patients were recommended the corresponding treatment in AASLD guideline by a multidisciplinary team[6,7]. Patients whom the recommended treatment could not be applied were offered details of the advantages and disadvantages of both the standard option recommended by the guideline and alternative

Table 1. Barcelona Clinic Liver Cancer (BCLC) staging system

Stage	Tumor status	Child-Turcotte-Pugh	Performance status
Very early stage (BCLC 0)	Single nodule <2 cm	A	0
Early stage (BCLC A)	Single nodule <5 cm or ≤3 nodules with each nodule <3 cm	A-B	0-2
Intermediate stage (BCLC B)	Multinodular	A-B	0-2
Advanced stage (BCLC C)	Portal invasion or extrahepatic spread (N1, M1)	A-B	0-2

options.

Using the BCLC staging and the AASLD 2010 guideline, stage 0 patients were recommended LR and LAT including PEI and RFA, stage A patients were recommended LR, LT, and LAT, stage B patients were recommended TACE, stage C patients were recommended Sorafenib, and stage D patients were recommended BSC. Patients with a single HCC in BCLC 0 or single tumor in BCLC A, who did not meet Milan criteria[15], and did not have portal hypertension were recommended LR. Patients with a single HCC or up to three nodules lesser than 3 cm in diameter who had portal hypertension or increased bilirubin were recommended LT (if they met the Milan criteria and were under 70 years of age, abstained from alcohol, and absent of severe associated diseases) or LAT. Because LT is not available in the study center, patients compatible with Milan criteria were advised to refer to other referral centers for treatment. Finally, the decision of treatment was made by the patient and whose formal document was certified before starting of the treatment.

All the patients' medical records were retrospectively evaluated to analyze the rate of adherence to AASLD guideline for treatment of HCC in clinical practice and identify the reasons for non-adherence. The present study was approved by the Ethic Committee on Human Rights for Researches Involving Human Subjects of Hatyai Hospital (Protocal number 26/2560).

Statistical analysis

Descriptive statistics (e.g., mean, standard deviation and range) were used for continuous variables. Categorical variables were summarized using frequency statistics (e.g., frequencies, percentage). All analyses were performed using SPSS package version 22.0 (IBM Crop., Armonk, NY, USA).

Results
Patient characteristics

Two hundred twenty-two patients were approached and included 198 that patients were included in the present study (24 patients were excluded as 22 patients received previous treatment for HCC, and two were non-cirrhotic patients). Baseline characteristics of the patients according to the BCLC staging system are summarized in Table 2. The mean age of all patients was 59.18 years old. Male made up 70.7% of the patients. The etiologies of cirrhosis were viral hepatitis B (HBV) infection (39.4%), alcoholism (38.9%), viral hepatitis C (HCV) infection

(21.2%), and HBV/HCV co-infection (1.5%). Most comorbidities were diabetes mellitus and hypertension accounting for 24.7% and 17.7%, respectively. Forty-eight patients (24.2%) were diagnosed HCC using US surveillance, 75% of these patients adhering to regular surveillance. Approximately 50% of patients were asymptomatic at the time of HCC diagnosis. Abdominal distension and abdominal pain were the most common presenting symptoms accounting for 16.3% and 14.4%, respectively. The numbers of patients in CTP score A, B, and C were 99 (50.3%), 71 (35.9%), and 28 (14.1%), respectively.

Number of patients classified according to each BCLC stage were 10 (5.1%) for very early stage (BCLC 0), 44 (22.2%) for early stage (BCLC A), 61 (30.8%) for intermediate stage (BCLC B), 50 (25.3%) for advanced stage (BCLC C), and 33 (16.7%) for end stage (BCLC D). Baseline characteristics of patients in each group are also shown in Table 2.

Real-life treatment of HCC compared to guideline recommendations and reasons for nonadherence

Stage 0: Out of 10 patients classified as very early stage (BCLC 0), two patients had a single nodule less than 2 cm without portal hypertension. Both patients were eligible for resection and finally treated with LR. For the other eight patients who had portal hypertension or elevated bilirubin, four were treated with PEI, three were treated with RFA, and one with portal hypertension was treated with LR as an "aggressive treatment" recommended by a multidisciplinary team, including surgeons.

Stage A: Forty-four patients were classified as early stage. The treatment recommended by the AASLD guideline for this stage is LT (for patients meeting the Milan criteria) or PEI/RFA. Six patients whom LT was recommended (as criteria described earlier) refused to undergo LT due to the limitation of liver donors. As a result, alternative treatments were performed and three patients were treated with LR, one patient was treated with PEI, and two patients were treated with RFA. For the other 38 patients who did not meet the Milan criteria, 26 patients were treated with LR and LAT according to the recommendations. The remaining 12 patients (31.5%) were "under treatment" where nine patients underwent TACE due to the technical limitation of intervention and three patients were treated with BSC (two patients opted for best supportive treatment while the other chose it due to cost).

Stage B: Sixty-one patients classified in this stage

Table 2. Baseline characteristics of studied patients categorized by BCLC staging system

	All (n = 198)	Stage 0 (n = 10)	Stage A (n = 44)	Stage B (n = 61)	Stage C (n = 50)	Stage D (n = 33)
Age (years), mean ± SD	59.18±11.88	57.20±5.03	60.36±11.03	60.21±11.57	60.60±12.29	54.12±13.48
Male gender, n (%)	140 (70.7)	8 (80.0)	27 (61.4)	40 (65.6)	39 (78.0)	26 (78.8)
BMI (kg/m^2): mean ± SD	23.53±4.48	26.33±4.07	25.47±4.30	23.21±4.32	21.46±3.91	23.64±4.56
Underlying diseases, n (%)						
Autoimmune hepatitis	3 (1.5)	-	2 (4.5)	1 (1.6)	-	-
Alcoholism	77 (38.9)	7 (70.0)	14 (31.8)	20 (32.8)	24 (48.0)	12 (36.4)
Asthma and/or COPD	5 (2.5)	1 (10.0)	1 (2.3)	2 (3.3)	1 (2.0)	-
Chronic kidney disease	1 (0.5)	-	1 (2.3)	-	-	-
Diabetes mellitus	49 (24.7)	1 (10.0)	15 (34.1)	17 (27.9)	9 (18.0)	7 (21.2)
Dyslipidemia	6 (3.0)	-	3 (6.8)	2 (3.3)	1 (2.0)	-
Hepatitis B virus infection	78 (39.4)	2 (20.0)	15 (34.1)	24 (39.3)	21 (42.0)	16 (48.5)
Hepatitis C virus infection	42 (21.2)	3 (30.0)	14 (31.8)	13 (21.3)	6 (12.0)	6 (18.2)
HBV/HCV co-infection	3 (1.5)	1 (10.0)	-	-	-	2 (6.1)
Hypertension	35 (17.7)	2 (20.0)	9 (20.5)	11 (18.0)	9 (18.0)	4 (12.1)
Laboratory investigations						
Hemoglobin (g/dL), mean ± SD	11.45±2.39	13.13±1.38	12.09±1.88	11.56±2.19	11.36±2.64	10.00±2.56
Hematocrit (%), mean ± SD	34.32±6.99	39.38±3.81	35.88±5.01	35.34±7.16	33.85±7.33	29.39±6.86
Platelet count (×10^3/μL), median (IQR)	146 (91 to 244)	123 (40 to 184)	98 (74 to 140)	132 (97 to 250)	233 (172 to 413)	165 (89 to 225)
Creatinine (mg/dL), median (IQR)	0.81 (0.7 to 1)	0.85 (0.75 to 1.08)	0.82 (0.73 to 1.02)	0.8 (0.67 to 1.02)	0.76 (0.69 to 0.95)	0.92 (0.68 to 1.05)
eGFR (CKD-EPI) (mL/minute/1.73 m^2), median (IQR)	93 (73 to 111)	81 (75 to 106)	87 (75 to 102)	90 (73 to 111)	98 (83 to 115)	91 (65 to 117)
Total bilirubin (mg/dL), median (IQR)	1.4 (0.8 to 2.4)	1.6 (0.8 to 2.5)	1.3 (0.8 to 1.9)	1.2 (0.6 to 2.0)	1.2 (0.8 to 2.1)	3.2 (2.1 to 5.3)
AST (U/L), median (IQR)	84 (52 to 137)	54 (35 to 93)	62 (41 to 84)	67 (44 to 112)	124 (86 to 180)	123 (78 to 219)
ALT (U/L), median (IQR)	46 (28 to 72)	27 (23 to 76)	42 (26 to 66)	40 (24 to 63)	56 (32 to 83)	53 (36 to 77)
ALP (U/L), median (IQR)	149 (104 to 229)	122 (87 to 160)	107 (84 to 157)	136 (100 to 184)	240 (149 to 387)	178 (117 to 348)
Albumin (g/dL), mean ± SD	3.26±0.68	3.73±0.44	3.41±0.66	3.39±0.69	3.34±0.47	2.53±0.51
Glbulin (g/dL), median (IQR)	4.2 (3.7 to 4.8)	4.3 (4.2 to 4.7)	4.0 (3.4 to 4.8)	4.1 (3.7 to 4.7)	4.3 (3.8 to 4.7)	4.5 (3.9 to 5.4)
Alpha-fetoprotein (ng/mL), median (IQR)	48.30 (7.78 to 1,886.32)	7.82 (3.74 to 20.51)	11.41 (4.79 to 66.14)	42.92 (10.04 to 4,146.07)	601.14 (54.36 to 53,948)	136.81 (9.05 to 6,637.54)
PT (seconds), median (IQR)	13.7 (12.5 to 15.0)	13.4 (12.5 to 14.3)	13.2 (12.2 to 14.8)	13.7 (12.6 to 14.8)	13.2 (12.2 to 14.6)	16.7 (14.5 to 19)
INR, median (IQR)	1.21 (1.10 to 1.35)	1.22 (1.10 to 1.25)	1.20 (1.07 to 1.33)	1.17 (1.06 to 1.32)	1.16 (1.09 to 1.32)	1.46 (1.28 to 1.65)
Surveillance of HCC, n (%)	48 (24.2)	6 (60.0)	22 (50.0)	9 (14.8)	3 (6.0)	8 (24.2)
Regularity	36/48 (75.00)	5/6 (83.33)	18/22 (81.82)	7/9 (77.78)	2/3 (66.67)	4/8 (50)
Clinical presentation at diagnosis of HCC, n (%)						
Asymptomatic	96 (49.5)	8 (80.0)	36 (81.8)	34 (55.7)	15 (31.3)	3 (9.1)
Abdominal distension	32 (16.3)	-	2 (4.5)	6 (9.8)	12 (25.0)	12 (36.4)
Abdominal pain	28 (14.4)	-	1 (2.3)	7 (11.5)	14 (29.2)	6 (18.2)
Jaundice	4 (2.0)	-	1 (2.3)	-	-	-
Fatigue	1 (0.5)	-	-	1 (1.6)	-	-
Liver abscess	1 (0.5)	-	-	1 (1.6)	-	-
Metastatic presentation	1 (0.5)	-	-	0 (0.0)	1 (2.1)	-
Ruptured HCC	2 (1.0)	-	-	1 (1.6)	-	1 (3.0)
Thrombocytopenia	2 (1.0)	1 (10.0)	1 (2.3)	-	-	-
Upper gastrointestinal bleeding	23 (11.7)	1 (10.0)	3 (6.8)	9 (14.8)	4 (8.3)	6 (18.2)
Weight loss	4 (2.0)	-	-	2 (3.3)	1 (2.1)	1 (3.0)
Child-Turcotte-Pugh classification, n (%)						
A	99 (50.0)	10 (100)	29 (65.9)	35 (57.4)	23 (46.0)	2 (6.1)
B	71 (35.9)	-	15 (34.1)	26 (42.6)	27 (54.0)	3 (9.1)
C	28 (14.1)	-	-	-	-	28 (84.8)
HCC nodules, n (%)						
1	68 (34.3)	10 (100)	33 (75.0)	10 (16.4)	10 (20.0)	5 (15.2)
2 to 3	44 (22.2)	-	11 (25.0)	21 (34.4)	8 (16.0)	4 (12.1)
>3	86 (43.4)	-	-	30 (49.2)	32 (64.0)	24 (72.7)
Size (cm), median (IQR)	4.10 (2.40 to 9.13)	1.45 (1.28 to 1.65)	2.30 (1.93 to 2.70)	5.00 (3.40 to 7.50)	11.10 (5.40 to 13.70)	6.05 (2.90 to 10.38)
MELD score, n (%)						
≤9	110 (61.8)	6 (60.0)	28 (63.6)	39 (69.6)	29 (74.4)	8 (27.6)
10 to 19	62 (34.8)	4 (40.0)	15 (34.1)	17 (30.4)	10 (25.6)	16 (55.2)
20 to 29	6 (3.4)	-	1 (2.3)	-	-	5 (17.2)
≥30	-	-	-	-	-	-
Timing for starting treatment (day), median (IQR)	22 (6 to 41)	42 (21 to 76)	39 (26 to 70)	27 (10 to 45)	7 (1 to 19)	7 (1 to 18)

SD = standard deviation; IQR = interquatile range; BMI = body mass index; COPD = chronic obstructive pulmonary disease; HBV = hepatitis B virus; HCV = hepatitis C virus; eGFR = estimated glomerular filtration rate; CKD-EPI = Chronic Kidney Disease Epidemiology; ALT = alanine aminotransferase; AST = aspartate aminotransferase; ALP = alkaline phosphatase; PT = prothrombin time; INR = international normalized ratio; HCC = hepatocellular carcinoma; MELD = Model for End-Stage Liver Disease

of HCC were recommended TACE. Forty-four patients were treated with TACE, which adhered to AASLD guideline. For the remaining 17 patients, 16 patients received BSC on their own decision (12 patients) and due to cost for four patients, while one was treated with PEI as an "aggressive treatment" recommended by experts. This last patient had a complete response without a recurrence at the end of the study (nine months after treatment).
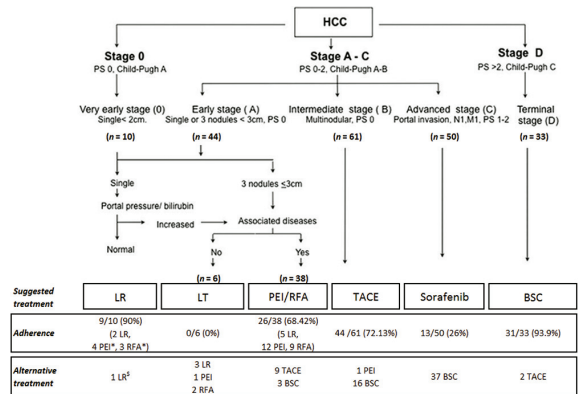
Stage C: Fifty patients were classified as BCLC stage C. According to the updated AASLD guideline 2010, Sorafenib, a new molecularly targeted agent, was proposed as the treatment of choice. Thirteen patients (26%) were treated with Sorafenib. The remaining 37 patients chose BSC (29 patients) due to cost and willing to BSC (eight patients).

Stage D: Thirty-three patients were classified as terminal stage. More than 90% (31 patients) were managed with best supportive care, which adhered to the AASLD recommendation. The remaining two cirrhotic CTP C patients were aggressively treated with TACE within the agreement of the multidisciplinary team to relieve pain symptom of the tumor.

The rates of adherence to the AASLD guideline recommendation, actual treatment deviation from to guideline and reasons for non-adherence are reported in Figure 1, Table 3 and 4.

Discussion

The AASLD guideline for treatment of HCC, produced in 2005 and updated in 2010, is considered

Suggested treatment	LR	LT	PEI/RFA	TACE	Sorafenib	BSC
Adherence	9/10 (90%) (2 LR, 4 PEI*, 3 RFA*)	0/6 (0%)	26/38 (68.42%) (5 LR, 12 PEI, 9 RFA)	44 /61 (72.13%)	13/50 (26%)	31/33 (93.9%)
Alternative treatment	1 LR‡	3 LR 1 PEI 2 RFA	9 TACE 3 BSC	1 PEI 16 BSC	37 BSC	2 TACE

* Due to portal hypertension or elevated bilirubin, $‡$ Aggressive treatment by expert opinions

Figure 1. Distribution of patients and treatment carried out relying on the therapeutic algorithm from AASLD recommendation. LR = liver resection; LT = liver transplantation; PEI = percutaneous ethanol injection; RFA = radiofrequency ablation; TACE = transcatheter arterial chemoembolization; BSC = best supportive care.

as the standard reference for therapeutic decisions for HCC treatment worldwide[16]. However, it cannot be completely applied in real-life practices for various reasons, including patient's characteristics, availability of medical resources, or regional culture. Supporting evidence by previous studies demonstrated that the non-adherence rate ranged from 10% to 90% depending on types of recommendations and population of the study[14,16,17]. The present study showed real-life practices in a regional referral center

Table 3. Mode of the first specific treatment and reason for nonadherence

	All (n = 198) n (%)	Stage 0 (n = 10) n (%)	Stage A (n = 44) n (%)	Stage B (n = 61) n (%)	Stage C (n = 50) n (%)	Stage D (n = 33) n (%)
First specific treatment						
Liver resection	11 (5.6)	3 (30.0)	8 (18.2)	-	-	-
Liver transplantation	-	-	-	-	-	-
Percutaneous ethanol injection	18 (9.1)	4 (40.1)	13 (29.5)	1 (1.6)	-	-
Radiofrequency ablation	13 (6.6)	3 (30.0)	11 (25.0)	-	-	-
Transcatheter arterial chemoembolization	57 (28.8)	-	10 (22.7)	44 (72.1)	-	2 (6.1)
Sorafenib	13 (6.6)	-	-	-	13 (26.0)	-
Systemic chemotherapy	-	-	-	-	-	-
Best supportive care	86 (43.4)	-	2 (4.5)	16 (26.2)	37 (74.0)	31 (93.9)
Adherence to guideline						
Adherence to treatment	123 (62.1)	9 (90.0)	26 (59.1)	44 (72.1)	13 (26.0)	31 (93.9)
"Under-treated" management	71 (35.9)	-	18 (40.9)	16 (26.2)	37 (74.0)	-
"More aggressive" management	4 (2.0)	1 (10.0)	-	1 (1.6)	-	2 (6.1)
Reasons of discrepancy						
Aggressive treatment by expert opinions	4 (5.3)	1 (100)	-	1 (5.9)	-	2 (100)
Cost	34 (45.3)	-	1 (5.6)	4 (23.5)	29 (78.4)	-
Willing to best supportive care	22 (29.3)	-	2 (11.1)	12 (70.6)	8 (21.6)	-
Limitation of liver donors	6 (8.0)	-	6 (33.3)	-	-	-
Technical limitation for primary choice of treatment	9 (12.0)	-	9 (50.0)	-	-	-

Table 4. Actual treatment compares with AASLD recommendation and reasons for nonadherence to guideline

BCLC stage	AASLD treatment recommendation	Eligible for recommendation (patients)	Adhered treatment n (%)	Reasons for nonadherence n (%)	Actual treatment n (%)
0	Liver resection or PEI/RFA if presence of portal hypertion/elevated bilirubin	10	9 (90.0)	• Presence of portal hypertension but aggressive treatment with resection by experienced surgeon (n = 1)	• Resection (n = 1)
A	Liver transplantation (compatable with Milan criteria)	6	0 (0.0)	• The limitation of liver donors (n = 6)	• Resection (n = 3) • PEI (n = 1) • RFA (n = 2)
	PEI/RFA (incompatible with Milan criteria)	38	26 (68.4)	• Technical limitation in primary choice of treatment (n = 9) • Cost (n = 1) • Willing to best supportive care (n = 2)	• TACE (n = 9) • Best supportive care (n = 3)
B	TACE	61	44 (72.1)	• Aggressive treatment by expert opinion (n = 1) • Cost (n = 4) • Willing to best supportive care (n = 12)	• PEI (n = 1) • Best supportive care (n = 16)
C	Sorafenib	50	13 (26.0)	• Cost (n = 29) • Willing to best supportive care (n = 8)	• Best supportive care (n = 37)
D	Best supportive care	33	31 (93.9)	• Aggressive treatment by expert opinions (n = 2)	• TACE (n = 2)

PEI = percutaneous ethanol injection; RFA = radiofrequency ablation; TACE = transcatheter arterial chemoembolization

in southern Thailand, a developing country in Southeast Asia. In Hatyai Hospital, medical resources are limited, and most patients are of low-socioeconomic status, low levels of education, and of a unique cultural background.

During the 3-year observation period of the present study, 5.1%, 22.2%, 30.8%, 25.3%, and 16.7% of the patients were classified according to BCLC stage 0, A, B, C, and D, respectively. Compared to previous studies[14,16,17], the majority of the patients in the present study were diagnosed at more advance stages (BCLC B, C, and D). This finding could be explained by a low rate of surveillance for HCC. Patients had unrecognized cirrhosis before diagnosis of HCC or did not follow up with physicians. The rate of adherence to the AASLD guideline for treatment of HCC in the present study was 62.12% in cirrhotic patient newly diagnosed with HCC. Of the recommended treatments, BSC and TACE were adhered most, whereas LR, LAT, and Sorafenib had higher rate of non-adherence.

Potential factors that affected the final treatment decision were explored. Firstly, the BCLC staging system used to classify patients is based on only tumor size and number, not location. In the present study, BCLC A patients with HCC located near vascular/biliary structure, in sub-capsular area, or areas that are hardly approached with ultrasonography had their treatment changed to TACE[7,18,19]. Secondly, LT is not

available as a treatment option in real-life practice. In Thailand, only few referral centers are able to perform the liver transplant and organ donation rate is very low. The number of cadaveric donors per million population in Asia is less than five compared to 10 to 35 in western countries[17]. Data from a single experienced center in Thailand showed that the number of liver transplants was 6 to 20 cases per year, and LT of HCC accounted for less than 50%[20]. In the authors' study, all six BCLC A patients who met the Milan criteria refused to undergo LT despite intensive discussions advantages and disadvantages. The main reasons were limitation in number of LT centers and liver donors and high cost associated with LT minimized the accessibility of patients to LT centers.

Moreover, most of the population in rural areas of Thailand is of low socio-economic status and the regional cultural background is unique. More than 70% of BCLC C patients did not agree to get Sorafenib, mainly because of the cost and unviable cost-benefit of the treatment. Despite many studies proving the efficacy of Sorafinib in prolonging life[21,22], many did not opt for it due to costs being relatively high in Thailand. Furthermore, because of cultural background, non-curative malignant patients preferred BSC. As a result of these factors, most non-curative HCC patients especially BCLC C decided to get BSC as an alternative treatment.

The limitations of the present study included reported data being collected from a single center, small number of patients in the study, and the LT was not available in the present center. All of these may result in the present study not representing the real-life practices.

In conclusion, the authors' study demonstrated the rate of adherence to the AASLD guideline for treatment of HCC to be at nearly 62%. The main reasons for non-adherence to guideline recommended treatments were the cost, technical limitation, and regional cultural background.

What is already known on this topic?

The guidelines on the treatment of HCC proposed by the AASLD and the EASL-EORTC rely on the BCLC staging system. Although this staging system is developed from large clinical trials conducted in the referral centers, its application is not adopted to real-life practices because of peculiar differences in populations and medical resources among countries.

What this study adds?

Although, the AASLD guideline for management of HCC is used as the reference for therapeutic decision in Hatyai Hospital in southern Thailand, the rate of adherence to guideline in new diagnosed of HCC on cirrhotic patient is only 62%. The main reasons for non-adherence were cost, technical limitation, and regional culture background.

Acknowledgement

Potential conflicts of interest

The authors declare no conflict of interest.

References

1. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. CA Cancer J Clin 2005;55:74-108.
2. Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. CA Cancer J Clin 2014;64:9-29.
3. El-Serag HB. Hepatocellular carcinoma. N Engl J Med 2011;365:1118-27.
4. Cunningham SC, Tsai S, Marques HP, Mira P, Cameron A, Barroso E, et al. Management of early hepatocellular carcinoma in patients with well-compensated cirrhosis. Ann Surg Oncol 2009;16:1820-31.
5. European Association for the Study of the Liver; European Organisation for Research and Treatment of Cancer. EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. J Hepatol 2012;56:908-43.
6. Bruix J, Sherman M. Management of hepatocellular carcinoma: an update. Hepatology 2011; 53:1020-2.
7. Bruix J, Sherman M. Management of hepatocellular carcinoma. Hepatology 2005;42:1208-36.
8. Pugh RN, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. Br J Surg 1973; 60:646-9.
9. Okuda K, Ohtsuki T, Obata H, Tomimatsu M, Okazaki N, Hasegawa H, et al. Natural history of hepatocellular carcinoma and prognosis in relation to treatment. Study of 850 patients. Cancer 1985; 56:918-28.
10. Vauthey JN, Lauwers GY, Esnaola NF, Do KA, Belghiti J, Mirza N, et al. Simplified staging for hepatocellular carcinoma. J Clin Oncol 2002;20: 1527-36.
11. A new prognostic system for hepatocellular carcinoma: a retrospective study of 435 patients: the Cancer of the Liver Italian Program (CLIP) investigators. Hepatology 1998;28:751-5.
12. Llovet JM, Brú C, Bruix J. Prognosis of hepatocellular carcinoma: the BCLC staging classification. Semin Liver Dis 1999;19:329-38.
13. 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 2003;38:207-15.
14. Leoni S, Piscaglia F, Serio I, Terzi E, Pettinari I, Croci L, et al. Adherence to AASLD guidelines for the treatment of hepatocellular carcinoma in clinical practice: experience of the Bologna Liver Oncology Group. Dig Liver Dis 2014;46:549-55.
15. Mazzaferro V, Regalia E, Doci R, Andreola S, Pulvirenti A, Bozzetti F, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med 1996;334:693-9.
16. Borzio M, Fornari F, De S, I, Andriulli A, Terracciano F, Parisi G, et al. Adherence to American Association for the Study of Liver Diseases guidelines for the management of hepatocellular carcinoma: results of an Italian

field practice multicenter study. Future Oncol 2013;9:283-94.

17. Kim SE, Lee HC, Kim KM, Lim YS, Chung YH, Lee YS, et al. Applicability of the BCLC staging system to patients with hepatocellular carcinoma in Korea: analysis at a single center with a liver transplant center. Korean J Hepatol 2011;17:113-9.

18. Llovet JM, Vilana R, Brú C, Bianchi L, Salmeron JM, Boix L, et al. Increased risk of tumor seeding after percutaneous radiofrequency ablation for single hepatocellular carcinoma. Hepatology 2001;33:1124-9.

19. McGhana JP, Dodd GD 3rd. Radiofrequency ablation of the liver: current status. AJR Am J Roentgenol 2001;176:3-16.

20. Nonthasoot B, Sirichindakul B, Suphapol J, Taesombat W, Sutherasan M, Nivatvongs S. Orthotopic liver transplantation at King Chulalongkorn Memorial Hospital: a report. J Med Assoc Thai 2015;98 (Suppl 1):S127-30.

21. Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, et al. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 2008; 359:378-90.

22. Cheng AL, Kang YK, Chen Z, Tsao CJ, Qin S, Kim JS, et al. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. Lancet Oncol 2009;10:25-34.