RESEARCH ARTICLE

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Comparison of Overall Survival between Transarterial Chemoembolization and Best Supportive Care in Intermediate-Stage Hepatocellular Carcinoma

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Abstract

Objective: The Thailand management guideline allows the use of transarterial chemoembolization (TACE) for the treatment of intermediate-stage hepatocellular carcinoma (HCC) in patients with decompensated cirrhosis, whereas other guidelines do not. The aim of this study was to compare the overall survival between TACE and the best supportive care (BSC) in HCC patients with Child–Pugh score 5–8 cirrhosis and in subgroups with compensated cirrhosis (Child–Pugh score 5–6) and early decompensated cirrhosis (Child–Pugh score 7–8). **Methods:** This retrospective study comprised 118 patients with intermediate-stage HCC. The overall survival was compared between TACE and BSC using the Kaplan–Meier method. **Results:** The median overall survival time for all patients was 21.4 months in the TACE group and 8.2 months in the BSC group (P <0.001). In the subgroup analyses, the overall survival times for TACE and BSC were 26 months and 9 months, respectively, for compensated cirrhosis (P <0.001), and 14.5 months and 6.9 months, respectively, for early decompensated cirrhosis (P <0.001). In the Cox proportional-hazards model, TACE was an independent prognostic factor for prolonged overall survival in all patients [hazard ratio (HR) 0.29; 95% confidence interval (CI), 0.17–0.49; P <0.001], patients with compensated cirrhosis (HR, 0.31; 95% CI, 0.16–0.62; P <0.001), and patients with early decompensated cirrhosis (HR, 0.16; 95% CI, 0.061–0.44; P <0.001). **Conclusion:** TACE improves the overall survival in patients with intermediate-stage HCC and compensated or early decompensated cirrhosis.

Keywords: Hepatocellular carcinoma- chemoembolization- cirrhosis

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Introduction

The European Association for the Study of the Liver (EASL) recommends the Barcelona clinic liver cancer (BCLC) staging system for prognostic prediction and treatment of hepatocellular carcinoma (HCC) (European Association for the Study of the Liver, 2018). According to the newest EASL clinical practice guideline, transarterial chemoembolization (TACE) is an acceptable treatment for intermediate-stage HCC in patients with compensated cirrhosis (Child–Pugh score 5–6). However, the Thailand Guideline for Management of Hepatocellular Carcinoma allows the use of TACE in patients with early decompensated cirrhosis (Child–Pugh score 7–8). Therefore, there was a gap that many Thai HCC patients with early decompensated cirrhosis underwent TACE, which is beyond the EASL guideline. For this reason, we initiated the idea to explore the overall survival in this group.

The primary aim of this study was to compare the overall survival between TACE and the best supportive care (BSC) in HCC patients with Child–Pugh score 5–8 cirrhosis. As a secondary aim, a subgroup analysis compared treatment-related overall survival in HCC patients with compensated or decompensated cirrhosis.

Materials and Methods

Study population

This retrospective study was approved by the ethics committee of Hatyai Hospital Institutional Review Board and carried out in accordance with the Declaration of Helsinki (Study code: HYH EC 108-64-01). The need for informed consent was waived, and identifying patient information was anonymized before the analysis. Patients with intermediate-stage HCC who underwent TACE and

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BSC as the primary therapy between 2014 and 2018 at the HCC clinic in Hatyai Hospital were screened for eligibility. The exclusion criteria were as follows: 1) curative treatment for HCC before TACE; 2) cirrhosis classified as Child–Pugh >8; 3) renal, cerebral, or cardiopulmonary dysfunction; and 4) concurrent malignancies. Clinical information at the time of diagnosis, including baseline demographic data, serum laboratory data, liver function, and tumor etiology, characteristics, and stage, was collected from the medical records. The Thailand civil registration database was reviewed for death declarations. Overall survival was defined as the time from the date of diagnosis to either the last follow-up or death. The censored date is January 1, 2021.

Definitions

Child–Pugh score

The Child–Pugh scoring system was developed approximately 50 years ago to predict the prognosis of patients with cirrhosis after surgery for portal hypertension (Child and Turcotte, 1964). The Child–Pugh score is determined by assigning point values to five liver disease-related parameters, namely, albumin level, bilirubin level, prothrombin time, extent of ascites, and encephalopathy grade. Based on the total number of points, cirrhosis is classified as least severe (Child–Pugh A: 5–6 points), moderately severe (Child–Pugh B: 7–9 points), or most severe (Child–Pugh C: 10–15 points).

Compensated and decompensated cirrhosis

The natural course of fibrosis consists of two phases: the compensated phase, which is long-lasting and mostly asymptomatic, and the subsequent decompensated phase, which progresses rapidly and is characterized by clinical signs of portal hypertension-associated complications and/or liver function impairment (e.g., ascites, variceal bleeding, encephalopathy, and jaundice) (Ginés et al., 1987; de Franchis, 2000; D'Amico et al., 2006) In this study, we defined compensated cirrhosis as Child–Pugh score 5–6 and early decompensated cirrhosis as Child–Pugh score 7–8.

3. Intermediate-stage HCC (BCLC stage B) is defined as multinodular, unresectable HCC without portal vein thrombosis.

TACE procedure and evaluation of response

TACE treatment was based on the consensus among the gastroenterologists, interventional radiologists, and patients. All TACE procedures were performed by two experienced interventional radiologists. The patients were admitted 1 day before each TACE session to evaluate clinical status and blood tests.

In an aseptic procedural room, the patients received antiemetics, sedatives, and fluids intravenously and TACE was then performed. A femoral artery was catheterized. Angiography of the superior mesenteric and hepatic artery was performed to assess portal vein patency, vascular anatomy, and tumor vascularity. After the assessment of the hepatic arterial branch afferent to the segment where the tumor was located, a mixture of a cytotoxic drug (such as doxorubicin or mitomycin C) and iodized oil (Lipiodol; Guerbet, Milan, Italy) was injected, followed by embolization using gelatin sponge particles under fluoroscopic monitoring.

The treatment responses were scheduled in 4–6 weeks post-procedure using multiphasic hepatic computed tomography (CT) or magnetic resonance imaging (MRI). The complete response (CR) was defined as the disappearance of any intra-tumor enhancement in all target lesions, following the modified Response Evaluation Criteria In Solid Tumors (Lencioni and Llovet, 2010). Patients who achieved CR were regularly followed up with multiphasic CT of the abdomen and serum alpha-fetoprotein (AFP) every 3 months for the first year and then every 6 months in cases without evidence of recurrent HCC.

Statistical analysis

Continuous data were presented as mean and standard deviation or median and interquartile range. Differences between the two groups (TACE and BSC) were assessed using Student's t-test or the Wilcoxon rank-sum test. Categorical data were presented as number and percentage and analyzed using the Pearson chi-square test or Fisher's exact test. The Kaplan–Meier method and log-rank test were used for the survival analysis. We identified survival-influencing variables using the Cox proportional hazards model. $P < 0.05$ was considered significant. Statistical analyses were performed using STATA software (version 15.1; StrataCorp LLC, College Station, TX).

Results

The HCC clinic had received 405 patients from 2014 to 2018. In accordance with the inclusion and exclusion criteria, a total of 118 patients were finally included in this study. Thirty-two patients (27.1%) were women, and the mean age was 59.0 ± 11.4 years. Seventy-nine patients (66.9%) had compensated cirrhosis, and 39 (33.1%) had early decompensated cirrhosis. The Eastern Cooperative Oncology Group score was 0 in 83 patients (70.3%) and 1 in 35 patients (29.6%). The median number of TACE sessions (IQR) was 2 (1–3) sessions and 2 (1–3) sessions for compensated cirrhosis and early decompensated cirrhosis, respectively.

The baseline characteristics of the patients who received TACE or BSC are presented in Table 1 (all patients), Table 2 (patients with compensated cirrhosis), and Table 3 (patients with early decompensated cirrhosis). The median overall survival time for all patients was 21.4 months in the TACE group and 8.2 months in the BSC group ($P < 0.001$) (Figure 1). In the subgroup analyses, the survival times for TACE and BSC were 26 months and 9 months, respectively, for compensated cirrhosis ($P < 0.001$) (Figure 2A), and 14.5 months and 6.9 months, respectively, for early decompensated cirrhosis ($P < 0.001$) (Figure 2B).

In the Cox proportional hazard analysis, TACE independently predicted prolonged overall survival in all patients [hazard ratio (HR), 0.29; 95% confidence interval (CI), 0.17–0.49; $P < 0.001$], patients with compensated cirrhosis (HR, 0.31; 95% CI, 0.16–0.62; $P < 0.001$), and

Table 1. Comparison of the Baseline Characteristics of All Patients who Received Transarterial Chemoembolization (TACE) versus Best Supportive Care (BSC)

Characteristics	BSC (n=26)	TACE (n=92)	P value
Male sex	18 (69.2%)	68 (73.9%)	0.626
Age (years): mean ± SD	60.5 ± 11.5	58.6 ± 11.5	0.454
BMI (kg/m^2): mean ± SD	21.68 ± 4.2	23.6 ± 4.5	0.053
Etiology of chronic liver disease			
Hepatitis B infection	13 (50.0%)	37 (40.2%)	0.38
Hepatitis C infection	1 (3.8%)	27 (29.2%)	0.007
Alcohol-related liver disease	5 (19.2%)	28 (30.4%)	0.261
Portal hypertension	9 (34.6%)	63 (68.5%)	<0.001
Laboratory data			
Hemoglobin (g/dL): mean ± SD	10.5 ± 3.8	12.1 ±1.9	0.006
Platelet median (x103/mL): median (IQR)	216 (138 to 311)	125 (80 to 218)	0.143
Serum creatinine (mg/dL): median (IQR)	0.91 ± 0.29	0.88 ± 0.26	0.606
Serum Albumin (g/dL): mean ± SD	3.4 ± 0.6	3.5 ± 0.6	0.55
Total bilirubin (mg/dL): median (IQR)	1.2 (0.8 to 1.5)	1.1 (0.7 to 1.9)	0.765
INR: mean ± SD	1.0 ± 0.5	1.2 ± 0.2	0.001
Alpha-fetoprotein (IU/mL): median (IQR)	187.2 (2.0 to 3134.0)	27.1 (7.9 to 832.7)	0.548
Alpha-fetoprotein > 200 (IU/mL)	13 (50.0%)	35 (38.0%)	0.273
ECOG score			0.005
0	12 (46.2%)	71 (77.2%)	
1	14 (53.8%)	21 (22.8%)	
Multinodular	16 (61.5%)	43 (46.7%)	0.183
Tumor > 5 cm	23 (88.5%)	64 (69.6%)	0.053
Median longest tumor size (cm): median (IQR)	6.5 (4.0 to 12.8)	4.8 (3.4 to 8.1)	0.06

Data are expressed as number (%) unless otherwise specified; BMI, body mass index; SD, standard deviation; INR, international normalized ratio; IQR, interquartile range; ECOG, Eastern Cooperative Oncology Group

patients with early decompensated cirrhosis (HR, 0.16; 95% CI, 0.061–0.44; P <0.001) (Table 4).

Discussion

Liver cirrhosis affects the management and prognosis of patients with primary liver cancer or non-hepatic malignancies. The prognosis of such patients is not only determined by the cancer itself but also by the degree of underlying liver cirrhosis (Pinter et al., 2016). Child–Pugh A (compensated cirrhosis) is a strong prognostic variable in patients with HCC after treatment (Lencioni et al., 2005; Choi et al., 2007; Hasegawa et al., 2013; Akarapatima et al., 2021), as are tumor size and response to treatment

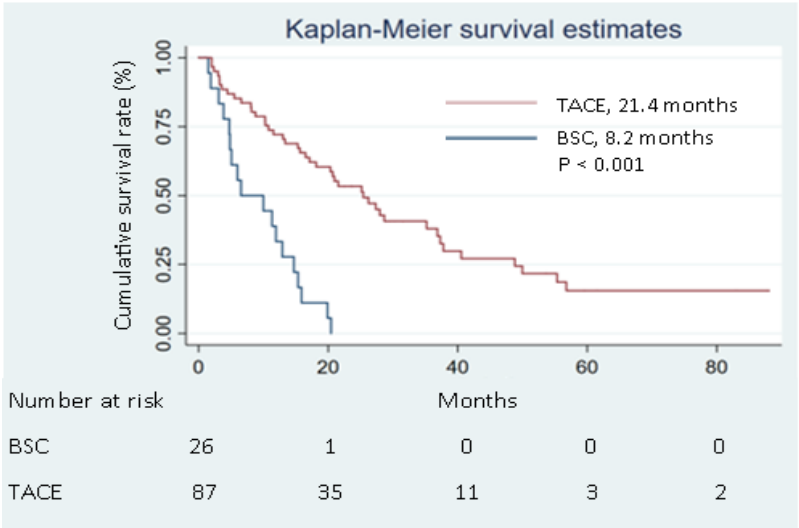

Figure 1. Overall Survival for Compensated and Early Decompensated Cirrhosis. TACE, transarterial chemoembolization; BSC, best supportive care

Table 2. Comparison of the Baseline Characteristics of Patients with Compensated Cirrhosis who Received Transarterial Chemoembolization (TACE) versus Best Supportive Care (BSC)

Characteristics	BSC (n=18)	TACE (n=61)	P value
Male sex	13 (72.2%)	45 (73.8%)	1
Age (years): mean ± SD	61.3 ± 10.9	59.0 ± 11.9	0.472
BMI (kg/m^2): mean ± SD	21.2 ± 4.1	23.3 ± 4.5	0.081
Etiology of chronic liver disease			
Hepatitis B infection	9 (50.0%)	28 (45.9%)	0.759
Hepatitis C infection	1 (5.6%)	15 (24.6%)	0.101
Alcohol-related liver disease	4 (22.2%)	17 (27.9%)	0.767
Portal hypertension	5 (27.8%)	39 (63.9%)	0.001
Laboratory data			
Hemoglobin (g/dL): mean ± SD	10.7 ± 4.4	12.2 ±1.9	0.165
Platelet median (x10^3/mL): median (IQR)	216 (138 to 311)	129 (96 to 254)	0.143
Serum creatinine (mg/dL): median (IQR)	0.93 ± 0.31	0.89 ± 0.24	0.547
Serum Albumin (g/dL): mean ± SD	3.5 ± 0.5	3.8 ± 0.5	0.049
Total bilirubin (mg/dL): median (IQR)	0.9 (0.7 to 1.3)	1.0 (0.6 to 1.4)	0.856
INR: mean ± SD	1.0 ± 0.5	1.1 ± 0.1	0.136
Alpha-fetoprotein (IU/mL): median (IQR)	1,610.3 (6.7 to 18,099.4)	29.6 (7.8 to 1,258)	0.254
Alpha-fetoprotein > 200 (IU/mL)	11 (61.1%)	23 (37.7%)	0.078
ECOG score			0.03
0	10 (55.6%)	50 (82.0%)	
>0	8 (44.4%)	11 (18.0%)	
Multinodular	15 (83.3%)	41 (67.2%)	0.186
Tumor > 5 cm	11 (61.1%)	28 (45.9%)	0.257
Median longest tumor size (cm): median (IQR)	7.0 (4.0 to 12.8)	4.9 (3.5 to 9.5)	0.179

Data are expressed as number (%) unless otherwise specified. BMI, body mass index; SD, standard deviation; INR, international normalized ratio; IQR, interquartile range; ECOG, Eastern Cooperative Oncology Group

(Sala et al., 2004).

In our study, the median overall survival was significantly longer in the TACE group than in the BSC group when all patients (21.4 versus 8.2 months) and only patients with compensated cirrhosis (26 versus 9 months) were examined. The reported median overall survival time for untreated patients with intermediate-stage HCC (BCLC stage B) was 16 months (Llovet and Bruix, 2003). In cohort studies, the median overall survival time for well-selected TACE-treated patients was approximately 40 months (Burrel et al., 2012; Takayasu et al., 2012); similar to our results, the overall survival was longer in patients who received TACE than in those who received BSC. Longer collection periods and greater number of participants may account for the longer TACE-associated survival times in the previous studies than in the present study.

The median overall survival was also significantly

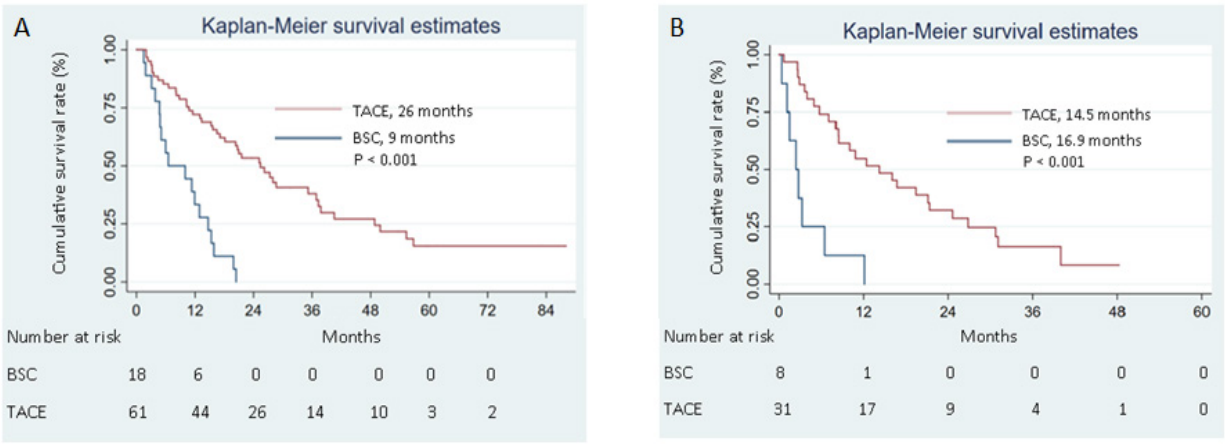

Figure 2. Overall Survival for Compensated Cirrhosis (A) and early compensated (B). TACE, transarterial chemoembolization; BSC, best supportive care

Table 3. Comparison of the Baseline Characteristics of Patients with Early Compensated Cirrhosis who Received Transarterial Chemoembolization (TACE) versus Best Supportive Care (BSC)

Characteristics	BSC (n=8)	TACE (n=31)	P value
Male sex	5 (62.5%)	23 (74.2%)	0.663
Age (years): mean ± SD	58.8 ± 13.5	57.7 ± 10.7	0.812
BMI (kg/m^2): mean ± SD	22.8 ± 4.6	24.2 ± 4.7	0.453
Etiology of chronic liver disease			
Hepatitis B infection	4 (50.0%)	9 (29.0%)	0.402
Hepatitis C infection	0 (0%)	12 (38.7%)	0.042
Alcohol-related liver disease	1 (12.5%)	11 (35.5%)	0.394
Portal hypertension	4 (50%)	24 (77.4%)	0.012
Laboratory data			
Hemoglobin (g/dL): mean ± SD	10.2 ± 1.7	11.7 ± 1.9	0.051
Platelet median (x10^3/mL): median (IQR)	198 (137.5 to 378.5)	98 (69 to 178)	0.022
Serum creatinine (mg/dL): median (IQR)	0.9 ± 0.2	0.9 ± 0.3	0.937
Serum Albumin (g/dL): mean ± SD	3.2 ± 0.8	3.0 ± 0.4	0.432
Total bilirubin (mg/dL): median (IQR)	1.8 (1.5 to 2.1)	1.9 (1.1 to 2.7)	0.626
INR: mean ± SD	1.1 ± 0.5	1.3 ± 0.2	0.275
Alpha-fetoprotein (IU/mL): median (IQR)	40.7 (2.0 to 187.2)	20 (9.7 to 726.4)	0.321
Alpha-fetoprotein > 200 (IU/mL)	2 (25.0%)	12 (30.8%)	0.686
ECOG score			0.049
0	2 (25.0%)	21 (67.7%)	
1	6 (75.0%)	10 (25.7%)	
Multinodular	8 (100%)	23 (74.2%)	0.168
Tumor > 5 cm	5 (62.5%)	15 (48.4%)	0.695
Median longest tumor size (cm): median (IQR)	7.0 (4.0 to 12.8)	4.9 (3.5 to 9.5)	0.186

Data are expressed as number (%) unless otherwise specified. BMI, body mass index; SD, standard deviation; INR, international normalized ratio; IQR, interquartile range; ECOG, Eastern Cooperative Oncology Group

Table 4. Association between Transarterial Chemoembolization and Overall Survival in Patients with Hepatocellular Carcinoma According to the Child-Pugh Score

Patient population	Multivariate analysis†		
	Hazard ratio	(95% CI)	P value
All patients (n=118)	0.292	0.173-0.493	<0.001
Child-Pugh A (n=79)	0.314	0.160-0.615	0.001
Child-Pugh B (n=39)	0.164	0.061-0.439	<0.001

CI, confidence interval; †Adjusted for sex, age, alpha-fetoprotein, and Eastern Cooperative Oncology Group performance status

better in the TACE (14.5 months) group than in the BSC (6.9 months) group when patients with early decompensated cirrhosis were considered. Because the EASL guideline limits the use of TACE to patients with compensated cirrhosis, the effect of TACE on patients with decompensated cirrhosis has not been investigated previously. Our study indicates that TACE is a more effective treatment for patients with intermediate-stage HCC and early decompensated cirrhosis than is BSC. This finding is clinically relevant, and prospective studies are warranted.

As limitations, this study was retrospective and performed at a single tertiary care hospital. Most of the participants were Thai nationals who lived in southern Thailand. Owing to their culture and religion, many natives in this region tend to treat themselves (Chang et al., 2018). This tendency might have affected our results, and it limits the application of our results to patients with HCC worldwide. Other limitations include missing data and unclear causes of death in some instances.

In conclusion, although not recommended by the EASL guideline, TACE significantly improved the overall survival in patients with intermediate-stage HCC and decompensated cirrhosis.

Author Contribution Statement

Conceptualization: KA, AC; Methodology: KA, AC, TP, NP; Formal analysis and investigation AC, KA; Writing - original draft preparation: KA, AC; Resources: AR, KA, TP, AS, SP; critical revisions to the article and Supervision: KA, AC; All authors read and approved the final manuscript.

Acknowledgements

Ethical Declaration and Approval

The study protocol was approved by the Ethics Committee of Hatyai Hospital Institutional Review Board and was carried out in accordance with the Declaration of Helsinki (Study code: HYH EC 108-64-01). This study is

not part of an approved student thesis.

Data Availability

If apply to your research.

Conflict of Interest

Keerati Akarapatima, Arunchai Chang, Tanaporn Prateepchaiboon, Nuttanit Pungpipattrakul, Apiradee Songjamrat, Songklod Pakdeejit and Attapon Rattanasupar declare that they have no conflicts of interest or financial ties to disclose.

References

Akarapatima K, Chang A, Prateepchaiboon T, et al (2021). Comparison between Child-Turcotte–Pugh classification and albumin-bilirubin grade predict survival for hepatocellular carcinoma patients undergoing transarterial chemoembolization. *J Gastrointest Cancer*, **2021**.

Burrel M, Reig M, Forner A, et al (2012). Survival of patients with hepatocellular carcinoma treated by transarterial chemoembolisation (TACE) using Drug Eluting Beads. Implications for clinical practice and trial design. *J Hepatol*, **56**, 1330-5.

Chang A, Utarabhand R, Khaimook A, et al (2018). Adherence to AASLD recommendation guideline for treatment hepatocellular carcinoma: Single Center Analysis of the Regional Hospital of Thailand. *J Med Assoc Thai*, **101**, 1708-15.

Child CG, Turcotte JG (1964). Surgery and portal hypertension. *Major Probl Clin Surg*, **1**, 1-85.

Choi D, Lim HK, Rhim H, et al (2007). Percutaneous radiofrequency ablation for early-stage hepatocellular carcinoma as a first-line treatment: Long-term results and prognostic factors in a large single-institution series. *Eur Radiol*, **17**, 684-92.

D'Amico G, Garcia-Tsao G, Pagliaro L (2006). Natural history and prognostic indicators of survival in cirrhosis: A systematic review of 118 studies. *J Hepatol*, **44**, 217-31.

de Franchis R (2000). Updating consensus in portal hypertension: Report of the Baveno III Consensus Workshop on definitions, methodology and therapeutic strategies in portal hypertension. *J Hepatol*, **33**, 846-52.

European Association for the Study of the Liver (EASL) (2018). EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. *J Hepatol*, **69**, 182-236.

Ginés P, Quintero E, Arroyo V, et al (1987). Compensated cirrhosis: Natural history and prognostic factors. *Hepatology*, **7**, 122-8.

Hasegawa K, Kokudo N, Makuuchi M, et al (2013). Comparison of resection and ablation for hepatocellular carcinoma: A cohort study based on a Japanese nationwide survey. *J Hepatol*, **58**, 724-9.

Lencioni R, Cioni D, Crocetti L, et al (2005). Early-stage hepatocellular carcinoma in patients with cirrhosis: Long-term results of percutaneous image-guided radiofrequency ablation. *Radiology*, **234**, 961-7.

Lencioni R, Llovet JM (2010). Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. *Semin Liver Dis*, **30**, 52-60.

Llovet JM, Bruix J (2003). Systematic review of randomized trials for unresectable hepatocellular carcinoma: Chemoembolization improves survival. *Hepatology*, **37**, 429-42

Pinter M, Trauner M, Peck-Radosavljevic M, Sieghart W (2016). Cancer and liver cirrhosis: Implications on prognosis and management. *ESMO Open*, **1**, e000042-e.

Sala M, Llovet JM, Vilana R, et al (2004). Initial response to percutaneous ablation predicts survival in patients with hepatocellular carcinoma. *Hepatology*, **40**, 1352-60.

Takayasu K, Arii S, Kudo M, et al (2012). Superselective transarterial chemoembolization for hepatocellular carcinoma. Validation of treatment algorithm proposed by Japanese guidelines. *J Hepatol*, **56**, 886-92.