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The efficacy of treatment schedules according to Barcelona Clinic Liver Cancer staging for hepatocellular carcinoma – Survival analysis of 3892 patients

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ABSTRACT

The Barcelona Clinic Liver Cancer (BCLC) staging offers prognostic stratification and treatment allocation for hepatocellular carcinoma (HCC). We conducted this retrospective study to assess the efficacy of different treatment options for patients with initial HCC diagnosis. Survival rate and median survival times associated with different treatment options in each stage of BCLC classification were compared using the Kaplan–Meier method and log-rank test. A total of 3892 patients were enrolled. Overall survival rates were 46.2% at 1 year and 16.6% at 5 years. The median survival times decreased from 57.7 months in very early stage to 1.6 months in terminal stage. Surgical resection offered the best survival benefit for patients in very early, early and even intermediate stages. Transarterial embolisation and conformal radiotherapy offered survival benefits for selected patients in advanced and terminal stages. In conclusion, following the treatment schedules allocated by BCLC staging had survival benefits for HCC patients.

1. Introduction

Hepatocellular carcinoma (HCC) is one of the most common cancers in the world, and has been the leading cause of cancer death in Taiwan, claiming an estimated 7000 lives annually.[1,2] The prognoses of patients with HCC are determined by *tumour* status, liver function reserve, general health status and efficacy of treatment.[3] A staging system which takes into considerations all these factors is important in predicting prognosis and comparing outcomes for HCC patients from different geographical areas.

There are several prognostic staging systems used in predicting the survival of patients with HCC, but consensus as to which system is best has not been reached.[4] The Barcelona Clinic Liver Cancer (BCLC) staging system has recently been applied for stratification of patients with HCC in practice

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guidelines established by the American Association for the Study of Liver Disease.[5] The BCLC proposal includes variables related to *tumour* status, liver function status and physical status, and was developed through an evidence-based approach.[6] Its stratification capacity in predicting prognosis has been cross-validated in several cohorts of HCC patients.[7–10] In addition to estimating prognosis, the main advantage of the BCLC staging system is the establishment of links between staging and treatment indications. However, there has been no large cohort study of patients to validate the treatment indications proposed for each subgroup according to BCLC staging classification. This retrospective study, based on a large cohort of HCC patients, compared survival rates of HCC patients and sought to assess the recommended treatment options stratified according to the BCLC classification.

2. Patients and methods

We reviewed medical records of patients with an initial diagnosis of HCC admitted between 1986 and 2002 at our institute. The study protocol was approved by the Institutional Review Board and carried out in compliance with the Helsinki declaration.

2.1. Patients

Patients with sufficient information on tumour size, tumour number, liver function reserve, and either with or without minimal clinical symptoms, were enrolled in this study. Patients were classified according to the BCLC staging system as very early, early, intermediate, advanced and terminal stages, as suggested by the American Association for the Study of Liver Disease guideline for HCC management[5] (Table 1). Clinical characteristics, treatment options and survival rates of these patients were analysed by review of their clinical records.

2.2. Initial treatment options

Treatment options include surgical resection, percutaneous local ablation (PLA), transarterial embolisation (TAE), conformal radiation therapy (RT), systemic chemotherapy, and supportive care. Surgeons used indocyanine green retention rates at 15 min to identify the best candidates for HCC resection. Either hepatic lobectomy or segmentectomy were performed for HCC resection. Percutaneous local ablation included ethanol injection and microwave coagulation therapy. To ablate the tumour, percutaneous ethanol injection was performed with multiple sessions of 99.5% ethanol injection. Percutaneous microwave coagulation therapy (Microtaze; Azwell Inc., Osaka, Japan) was performed with electrodes 1.6 or 2 mm in diameter for one or two sessions. TAE was performed using digital subtraction angiography techniques via the femoral artery approach. After identifying the feeding artery, a mixture of 99.5% ethanol and Lipiodol was injected.[11] Then gelatin sponge was used to embolise the feeding artery. Three-dimensional conformal RT was performed by using computed tomography-simulation to acquire the images, and three-dimensional computerised treatment planning to design the treatment fields and dose calculation. A 10 MV linear accelerator was used to deliver a total dose of 55–64 Gy in 22–32 fractions. Systemic chemotherapy was performed using various combinations of Cisplatin, Doxorubicin, Fluorouracil, Etoposide and Tamoxifen. Radiofrequency ablation and liver transplantation were not regular treatments in this hospital until 2002. Thus, these two treatments were excluded from analysis in this study.

2.3. Survival analysis

Survival was the only measure used in assessing treatment options for each BCLC stage. Survival was defined as the interval between the diagnosis and either the death of the patient or the end of 2004. The identification of mortality was based on national mortality datasets up to the end of 2004, established by the Statistics Office, Department of Health, Taiwan. Cumulative survival rates were analysed by the Kaplan–Meier curves, and differences between survival curves and linear trends in groups and subgroups were statistically compared by log-rank test. Groups and subgroups with less than 20 patients were not analysed. Statistical analysis was performed using SPSS 10.0 for Windows (SPSS Inc., Chicago, IL, USA) and SigmaStat® 3.1. Survival curves were constructed using SigmaPlot® 9.0.

3. Results

3.1. Patient characteristics

A total of 3892 patients with an initial HCC diagnosis were enrolled. Table 2 showed the demographics, clinical information, BCLC stage and treatment modality. There were 134 (3.4%), 847 (21.8%), 1469 (37.8%), 878 (22.6%) and 564 patients (14.5%) classified as very early, early, intermediate, advanced and terminal stages, respectively. Surgical resection, PLA, TAE, conformal RT and systemic chemotherapy were the treatment options for 459 (11.8%), 172 (4.4%), 1555 (40%), 237 (6.1%) and 4 patients (0.1%), respectively.

Table 1 – The Barcelona Clinic Liver Cancer (BCLC) classification of hepatocellular carcinoma

BCLC stage	Tumour status	Liver function reserve (Child–Pugh)	Performance status
Very early	Single / ≤2cm	A	0
Early	Single / ≤5cm or ≤3 tumours / each≤3cm	A or B	0
Intermediate	Multiple / Large	A or B	0
Advanced	Vascular invasion or extrahepatic spread	A or B	1–2
Terminal	Any	C	3–4

Table 2 – Demographic, clinical information, BCLC stage and treatment modalities of 3892 patients with hepatocellular carcinoma (HCC)

Age (mean ± SE)	57.8 ± 12.5
Sex, *n* (%)	
Male	3000 (77.1)
Female	892 (22.9)
Etiology, *n* (%)	
Hepatitis B virus	1709 (43.9)
Hepatitis C virus	1021 (26.2)
Hepatitis B and C virus	325 (8.4)
Non hepatitis B or C virus	374 (9.6)
Not available	463 (11.9)
Child–Pugh classification, *n* (%)	
A	2059 (52.9)
B	1269 (32.6)
C	554 (14.5)
HCC diagnosis, *n* (%)	
Histology/Cytology	1921 (49.4)
Image[a] and alpha-fetoprotein (≧400ng/ml)	1217 (31.3)
Typical image findings[b]	754 (19.3)
BCLC stage, *n* (%)	
Very early	134 (3.4)
Early	847 (21.8)
Intermediate	1469 (37.8)
Advanced	878 (22.6)
Terminal	564 (14.5)
Treatment modality, *n* (%)	
Resection	459 (11.8)
Percutaneous local ablation	172 (4.4)
Transarterial embolisation	1555 (40)
Conformal radiation therapy	237 (6.1)
Systemic chemotherapy	4 (0.1)
Supportive care	465 (37.6)

a Dynamic computed tomography with/without contrast enhancement at arterial phase.
b Dynamic computed tomography showed contrast enhancement at arterial phase and washout at portal phase.

3.2. *Overall survival rate and survival time*

The overall survival rates were 46.2%, 24.8% and 16.6% at 1 year, 3 years and 5 years, respectively. The median survival time was 10 months. For very early, early, intermediate, advanced and terminal stages, the median survival time was 57.7 months, 36.9 months, 13.8 months, 2.9 months and 1.6 months, respectively (Table 3). Fig. 1 illustrates the Kaplan–Meier survival curve of HCC patients stratified according to the BCLC classification. There were statistically significant differences in survival rates among each group, and a decreasing linear trend ($p < 0.001$) from the very early stage to the terminal stage was noted.

3.3. *Very early and early stage HCC*

Fig. 2a and b illustrate the Kaplan–Meier survival curves of different treatment options for very early and early stages respectively. For very early stage HCC ($n = 127$), surgical resection ($n = 31$) yielded significantly better survival rates than TAE ($n = 65$) (p-value = 0.015). Although there was a better survival rate for surgical resection compared to PLA ($n = 31$), it did not reach a statistically significant level (p-value= 0.066). There was no significant difference in survival rate between PLA and TAE (p-value = 0.875). For early stage HCC ($n = 847$), surgical resection ($n = 171$) yielded the best survival results. PLA ($n = 99$) yielded better survival rates than TAE ($n = 453$), but TAE was better than no treatment (PLA versus TAE, p-value = 0.016; other pairs, p-value < 0.001). A decreasing linear trend from surgical resection to supportive care was noted (very early stage, $p = 0.048$; early stage, $p < 0.001$).

3.4. *Intermediate stage HCC*

Fig. 2c illustrates the Kaplan–Meier survival curve of different treatment options for intermediate stage HCC ($n = 1469$). Surgical resection ($n = 243$) yielded better survival rates than PLA ($n = 20$), but the differences were not statistically significant (p-value = 0.145). There were, however, significantly better survival rates for surgical resection and PLA than for TAE ($n = 741$), conformal RT ($n = 20$) and no treatment ($n = 445$), but TAE yielded significantly better survival rates than conformal RT and no treatment (p-value = 0.046 and <0.001). However, conformal RT yielded no survival benefit when compared with no treatment (p-value = 0.182). There was a decreasing linear trend from surgical resection to supportive care ($p < 0.001$).

3.5. *Advanced stage HCC*

Fig. 2d illustrates the Kaplan–Meier survival curves of different treatment options for advanced stage HCC. For advanced stages ($n = 852$), TAE ($n = 200$) yielded better survival rates than conformal RT ($n = 193$) and conservative treatment ($n = 459$) (p-value = 0.023 and <0.001), whereas conformal RT yielded better survival rates than no treatment (p-value < 0.001). A decreasing linear trend from TAE to supportive care was noted ($p < 0.001$).

3.6. *Terminal stage HCC*

Fig. 2e illustrates the Kaplan–Meier survival curves of different treatment options for terminal stage HCC. In the terminal stage ($n = 553$), TAE ($n = 96$) yielded better results than conformal RT ($n = 28$) and supportive treatment ($n = 429$) (p-value = 0.001 and <0.001). Conformal RT yielded better results than no treatment (p-value = 0.038). There was a decreasing linear trend from TAE to supportive care ($p < 0.001$).

4. Discussion

Many staging systems for HCC have been proposed in both Western and Asian countries, taking into account both liver function reserve and tumour progression. The choice of an appropriate staging system will differ according to particular purposes and situations. The Okuda staging system, Cancer of the Liver Italian Programme , Chinese University Prognostic Index and Groupe d'Etude de Traitement du Carcinoma Hepatocellulaire are favourable staging systems for advanced stages of the disease.[12–15] On the other hand, the Japan

Table 3 – The patient population, survival rates and median survival times of different treatment schedules stratified according to the BCLC classification

BCLC Stage Treatment Schedule	Total *n* (%)	Survival Rate (%)			Median Survival (month)	*p* value for linear trend
		1 Yr	3 Yr	5Yr		
Very early stage	134 (3.4)	93.3	60.6	47.9	57.7 ± 10.5	
1. Surgery	31 (23.1)	93.5	73.1	73.1	100.8 ± 11.7	0.048
2. Percutaneous ablation	31 (23.1)	93.5	59.5	34.3	43.1 ± 9.0	
3. TAE	65 (48.5)	93.8	57.9	47.0	45.4 ± 14.1	
4. No treatment[a]	7 (5.2)	85.7	38.1	–	27.9 ± 12.7	
Early stage	847 (21.8)	81.2	51.0	35.0	36.9 ± 1.7	
1. Surgery	171 (20.2)	91.8	75.0	68.6	98.6 ± –	<0.001
2. Percutaneous ablation	99 (11.7)	86.9	56.6	42.8	44.0 ± 6.3	
3. TAE	453 (53.5)	83.9	48.2	27.2	35.4 ± 1.9	
4. No treatment	124 (14.6)	52.4	23.4	10.9	13.7 ± 2.0	
Intermediate stage	1469 (37.7)	53.7	27.9	18.2	13.8 ± 0.8	
1. Surgery	243 (16.5)	81.5	64.4	50.5	60.4 ± 6.1	<0.001
2. Percutaneous ablation	20 (1.4)	85.0	47.9	27.4	35.1 ± 8.7	
3. TAE	741 (50.4)	61.9	29.1	16.4	18.2 ± 1.1	
4. RT	20 (1.4)	40.0	10.0	10.0	7.9 ± 1.1	
5. No treatment	445 (30.3)	23.8	5.8	2.9	4.5 ± 0.4	
Advanced stage	878 (22.6)	13.7	3.3	1.9	2.9 ± 0.2	
1. Surgery[a]	14 (1.6)	57.1	28.6	28.6	13.2 ± 2.2	<0.001
2. Percutaneous ablation[a]	12 (1.4)	25.0	16.7	–	3.8 ± 0.5	
3. TAE	200 (22.8)	29.5	6.0	4.4	6.8 ± 0.5	
4. RT	193 (22)	12.4	3.1	0.9	3.8 ± 0.3	
5. No treatment	459 (52.3)	5.7	1.1	0.7	1.9 ± 0.1	
Terminal stage	564 (14.5)	13.3	2.6	0.7	1.6 ± 0.1	
1. Percutaneous ablation[a]	11 (2)	18.2	9.1	–	3.9 ± 1.3	<0.001
2. TAE	96 (17)	39.6	6.3	1.6	7.8 ± 1.8	
3. RT	28 (5)	7.1	–	–	3.0 ± 0.5	
4. No treatment	429 (76)	7.7	1.8	0.4	1.2 ± 0.1	
Total	3892 (100)	46.2	24.8	16.6	10.0 ± 0.4	

TAE, Transarterial embolisation; RT, Conformal radiation therapy.
a Sample size <20, not included for analysis.

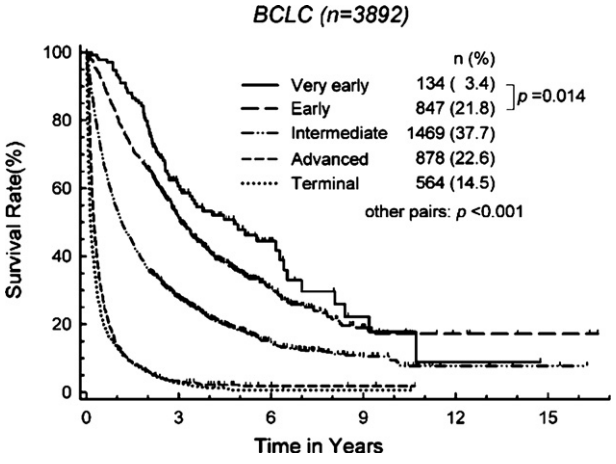

Fig. 1 – Kaplan–Meier survival curve of 3892 patients stratified according to the BCLC staging system. There are statistical differences in survival among different groups.

Integrated Staging score, the modified Japan Integrated Staging score and the Tokyo score are the favoured staging systems in Japan, where more patients undergo early stage HCC curative treatments.[16–20] The BCLC staging system was developed from several independent studies in both early and advanced patients, and might be an appropriate classification system for a patient population evenly distributed among early, intermediate and advanced stages of the disease. Our patient population was rather evenly distributed across the different disease stages. Consequently, BCLC staging might be more suitable for this patient population. Although we did not compare BCLC staging with other proposed systems, our results demonstrate that BCLC staging system is effective in estimating prognoses in our cohort of HCC patients. At the present time, BCLC staging provides good prognostic information and linkage to treatment options. However, there is debate that it is not appropriate to directly compare BCLC, solely as a treatment allocation system, with other staging proposals which are used to predict the prognosis of HCC patients.[21]

The benefits of HCC treatments should be assessed by means of randomised control trials and meta-analyses. However, a randomised control trial is not practical if cohort studies are better compared with the natural course of the disease. In our patient population, curative treatments, including surgical resection and PLA, provided better survival rates than among the untreated counterparts in the early and intermediate stages. Recent systemic reviews and cohort studies have shown the beneficial survival effect of TAE.[22,23] Our results also indicate that TAE provided survival rates better than the untreated counterparts in early, intermediate,

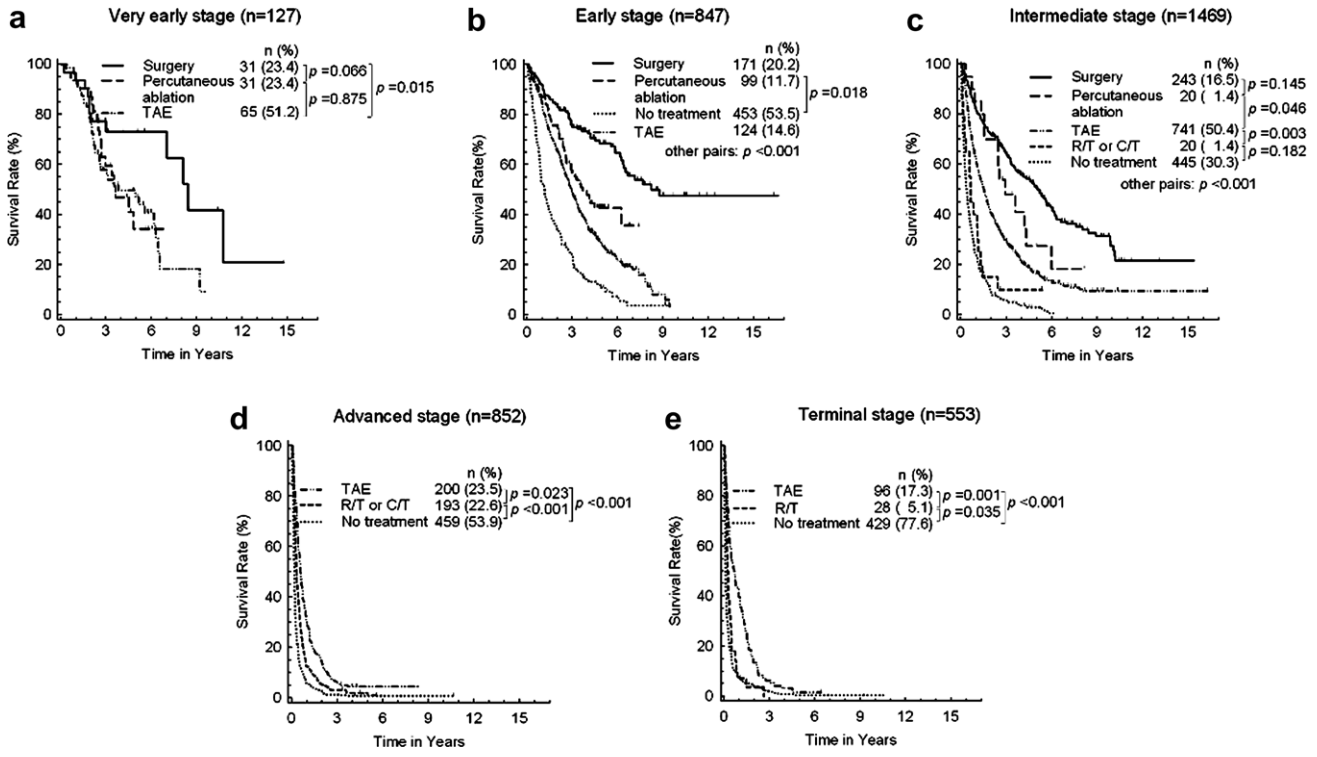

Fig. 2 – a. Kaplan–Meier survival curves of 127 patients in the BCLC very early stage, classified according to hepatic resection, percutaneous local ablation (PLA) and transarterial embolisation (TAE). Hepatic resection obtained the best rates of survival. b. Kaplan–Meier survival curves of 847 patients in the BCLC early stage, classified according to hepatic resection, PLA, TAE and no treatment. There were statistical differences in survival rates among the patients receiving different treatment options. c. Kaplan–Meier survival curves of 1469 patients in the BCLC intermediate stage, classified according to hepatic resection, PLA, TAE, conformal radiation therapy (RT) and no treatment. There were statistical differences in survival rates among patients undergoing hepatic resection, TAE, and no treatment. However, no significant differences existed between results for hepatic resection and PLA. There was also no significant difference between conformal RT and no treatment. d. Kaplan–Meier survival curves of 852 patients in the BCLC advanced stage, classified according to TAE, conformal RT and no treatment. There were significant differences in survival rates for the different treatment options. e. Kaplan–Meier survival curves of 553 patients in the BCLC terminal stage, classified according to TAE, conformal RT and no treatment. There were statistical differences in survival rates for the different treatment options.

advanced and terminal stages. Despite the fact that there are no proven advantages in terms of survival for radiation therapy or chemotherapy, some studies did demonstrate that a combination therapy of TAE and conformal RT was feasible and yielded overall survival benefits.[24] In our study, conformal RT also provided an overall survival benefit, but only for patients in the advanced stage. In general, our study with a large cohort of HCC patients demonstrated that treatment yields better survival rates than supportive care for properly selected patients.

For patients in the very early or early stages, surgical resection resulted in the best survival rates. In our study, patients in very early and early stages who underwent surgical resection had 5 year survival rates comparable with other reports from Japan and the West.[25] The BCLC treatment schedule recommends that resection be applied only for those very early stage patients without portal hypertension and normal bilirubin levels.[5] Portal hypertension is defined as the presence of either a hepatic venous pressure gradient >10 mmHg, oesophageal varices or splenomegaly with a platelet count <100000/mm^3.[25] However, measurement of hepatic venous pressure gradient is invasive and not routinely performed worldwide. It might be easier and simpler to use clinical portal hypertension, including oesophageal varices, splenomegaly with a platelet count <100,000/mm^3, and/or indocyanine green retention rate at 15 min, as the criteria in selection of the best candidates for resection.

In our study, most PLA were performed in very early and early stage patients not fit for resection. The 5 year survival rate is comparable to or lower than that of Japan and Europe.[26] Although one randomised control trial demonstrated no significant difference between resection and percutaneous ethanol injection for small HCC (<3 cm) in terms of 4 year survival rates, our data supports resection for carefully selected patients.[27] Recent randomised control trials comparing radiofrequency ablation with percutaneous ethanol injection supported radiofrequency ablation for early stage patients.[28–30] However, there was no trial in comparing the survival rate between surgical resection and RFA. In our very early and early stage populations, the majority of the patients received TAE treatment, which is not recommended by BCLC staging. One of the explanations is that,

while TAE has been performed for 20 years, percutaneous ethanol injection has been a regular and popular treatment option in this hospital for only the last 10 years. The other explanation is that TAE and computed tomography after TAE were performed to evaluate the patient's fitness for hepatic resection. If hepatic resection were not performed after evaluation, TAE would then be the ideal treatment option.

For patients in the BCLC intermediate stage, our results showed that curative treatment options, including resection and PLA, provide better survival rates than TAE which was the recommended treatment option. Patients who underwent hepatic resection had 5 year survival rates comparable with other reports.[25] Patients with a single large tumour, or multiple *tumours* restricted to a localised area, are usually the ideal candidates for hepatic resection. For those patients with multiple small tumours within both lobes, PLA might yield better survival benefits than TAE. Since the BCLC intermediate stage is a heterogenous patient population, we suggest that curative treatment might be another option for select patients.

While there have been no survival benefits of systemic treatment in patients with advanced HCC, long-term local control and survival have been reported in patients who underwent conformal RT.[24] In this study, TAE and conformal RT still showed survival benefits in terms of 5 year survival rates among patients classified as advanced stage. This is contrary to the recommendations of BCLC treatment schedules for the advanced stage, in which new drug trials are advised. We noticed that sequential conformal RT and TAE or vice versa is an effective approach for selected patients with portal vein thrombosis and well liver function reserve. For the BCLC terminal stage patients, symptomatic care is the only option. In this stage, however, patients who have received TAE or conformal RT obtain better survival benefits than patients who received only supportive care. Since discrepancies exist in terminal stage classification, it is too early to recommend TAE or conformal RT for all terminal stage patients. Selection of the patient population as to who will get the greatest benefit from conformal RT needs further study.

There were limitations to this study. Most of the enrolled patients were diagnosed as HCC a decade ago with performance status assessed retrospectively. This might lead to a large number of patients being assigned to an inaccurate stage. There might also be a large selection bias regarding the choice of treatment. The implementation of radiofrequency ablation and liver transplantation for early stage HCC patients might change the first-line treatment option proposed in our study. Instead of transarterial chemoembolisation, TAE has been the regular procedure for HCC patients.[11] Whether TAE with chemotherapeutic agents will affect survival rates in our patient population is unknown.

In conclusion, following the treatment schedules allocated by BCLC staging is beneficial in survival for patients with HCC. Hepatic resection should be the first treatment option for select patients in very early, early or intermediate stages, when liver transplantation is not a treatment option. TAE or conformal RT might have survival benefit for select patients in advanced stage.

Conflict of interest statement

None declared.

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