

Prognostic Features, Treatment Outcomes and Survival of Hepatocellular Carcinoma Patients in National Kidney and Transplant Institute

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Abstract

Background: Hepatocellular carcinoma (HCC) is a primary tumor of the liver, which develops in the setting of chronic liver disease. In the Philippines, despite being the third leading site of cancer, there are limited studies on prognostic factors, treatment outcomes and survival.

Objectives: This study aims to investigate prognostic features, treatment outcomes and survival of HCC patients in our institution.

Methodology: Retrospective cohort study was employed. All consecutive patients diagnosed with HCC in our institution from January 2008 to December 2014 were included. Demographic data, tumor characteristics, risk factors and treatment outcomes were retrieved through review of medical records. Cox regression and Kaplan-Meier survival analyses were used to identify prognostic factors and estimate survival, respectively. Statistical analyses were performed with STATA v13.

Results: A total of 346 patients were included. Mean age

was 61.47±13.08 years. 55.78% had hepatitis B virus (HBV) infection, 65.15% had cirrhosis solitary nodule (55.08%) was the dominant tumor pattern, mostly involving the right lobe (51.85%) and >3cm (85.48%) in diameter. 43.5% were barcelona clinic liver cancer (BCLC) stage B and 43.81% had advanced stage on presentation (BCLC C/D). Majority did not have portal vein thrombosis (PVT) and distant metastasis. Overall median survival was 13.17 months (range, < one month - 92 months). Those who had locoregional therapy had the longest median survival (30.33 months), followed by systemic chemotherapy (26.67 months) then surgery (13.17 months).

Conclusion: Among HCC patients in our institution, chronic hepatitis B was found to be the primary risk factor for its development. Median survival was 13.17 months with longest median survival among those who received locoregional treatment. Child-Turcotte-Pugh C (CTP C), BCLC stages C and D were independent predictors of mortality.

Keywords: retrospective, hepatocellular carcinoma, survival

Introduction

Hepatocellular carcinoma (HCC) is a primary tumor of the liver, which usually develops in the setting of chronic liver disease, particularly viral hepatitis. HCC has unique geographic, sex, and age distributions that are likely determined by specific etiologic factors.

HCC is diagnosed in more than half a million people worldwide annually. Most of the burden of disease is borne in developing countries, with highest incidence rates reported in regions where Hepatitis B is endemic. It rarely occurs at before age 40, and peaks at approximately age 70. In the Philippines, HCC is the third leading site of cancer for both sexes. The Philippines is considered a hyperendemic region for Hepatitis B with a 55-68% exposure

rate based on serological detection of at least one HBV marker.²

In several studies conducted in Western Countries, 30% to 40% of patients with hepatocellular carcinoma did not have chronic HBV or HCV but had features of fatty liver disease and metabolic syndrome.

Major risk factors for hepatocellular carcinoma include infection with HBV or HCV, alcoholic liver disease, and most probably non alcoholic fatty liver disease. Adverse prognostic features include ascites, jaundice, vascular invasion and elevated alpha fetoprotein (AFP).¹

Multiple clinical staging for HCC have been described, but there is no consensus as to which staging system is best in predicting the survival of patients with HCC. A recent study showed that the Barcelona Clinic Liver Cancer (BCLC) staging system had the best independent predictive power for survival when compared with the other six prognostic systems.³ The choice of treatment is driven by cancer stage, the resources available and the level of practitioner expertise.

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HCC is an aggressive tumor that frequently occurs in the setting of chronic liver disease and cirrhosis. It is typically diagnosed late in the course of these diseases, and the median survival following diagnosis ranges from approximately six to 20 months.⁴

A population study by Davila et al. showed a variety of important risk factors for the development of HCC. These include the hepatitis B carrier state, chronic hepatitis C virus (HCV) infection, hereditary hemochromatosis, and cirrhosis of almost any cause.⁵ While a retrospective analysis of medical records was performed for 314 patients in Boston showed presence of cirrhosis, history of alcohol use, low albumin, high bilirubin, abnormal AFP and portal vein obstruction were associated with shorter survival as was advanced age.⁶

In terms of treatment outcomes and survival, a retrospective study among Medicare patients was done in the US on 2963 patients. Median overall survival was 104 days following HCC diagnosis with the longest survival in the transplant group (825 days) and shortest survival in the group without treatment (58 days). Neither ablation nor Transarterial Chemoembolization (TACE) yielded prolonged survival (three-year survival was less than 10%).⁷

Despite being one the leading sites of cancer in our country, there are limited studies on prognostic factors, treatment outcomes and survival of HCC in the Philippines. Investigating and determining prognostic factors and treatment outcomes would help us determine treatment strategies which are more applicable for our HCC patients in our country. This study could also be used to gauge if our treatment outcome for HCC patients is at par with other countries.

OBJECTIVES

General objective: To investigate prognostic features, treatment outcomes and survival of Hepatocellular Carcinoma patients at the National Kidney and Transplant Institute (NKTi).

Specific objectives:

1. To describe the demographic, clinical and laboratory characteristics of HCC patients at presentation.
2. To determine predictors of mortality of hepatocellular cancer patients at NKTi
3. To determine the survival of hepatocellular cancer patients at NKTi as to the different treatment modalities.

Methodology

Medical charts of all consecutive HCC patients in NKTi from January 2008 to December 2014 diagnosed either via imaging (ultrasound, Dynamic CT scan, MRI using liver specific contrast), elevated AFP, and through biopsy were retrieved. Diagnosis of HCC followed the algorithm as suggested by the American Association for the Study of Liver Diseases (AASLD) (Appendix).

Parameters were examined including age, sex, co morbid, risk factor, presence of cirrhosis, Child Pugh score, diagnostic test, tumor size (largest lesion), lobar involvement, number of tumors, presence of metastases, portal vein thrombosis, AFP level, BCLC stage, model for end-stage liver disease (MELD) score and initial treatment modality. Patient's charts were followed up at their most recent admission and/or the time of death.

Statistical Analysis

The cohort was described with estimates of central tendency (means and medians) and spread (standard deviation and range) for continuous variables and frequencies and percentages for categorical variables. Patient survival rates were determined with Kaplan-Meier analysis.

Univariate data comparison was performed by Kaplan-Meier estimation using the log-rank test to assess statistical significance. Variables with p values of <0.05 in the univariate analysis or those thought to be clinically relevant were included in the final multivariate model. Multivariate analysis was performed with the Cox proportional hazard regression model.

We analyzed the association between patient survival and prognostic factors. Patient-related factors included gender, age, etiology of liver disease, presence/absence of cirrhosis, Child Turcotte Pugh Classification. Tumor-related factors included AFP level, tumor size, presence/absence of portal vein thrombosis, BCLC stage and treatment modality received.

All valid data from evaluable subjects were included in the analysis. No estimation for missing values was done. Since data were retrospectively collected, we acknowledge the potential influence of missing data on our analysis. To address this problem, we used the complete case analysis or listwise deletion approach in which we simply omitted those cases with missing data. All statistical analyses were performed with STATA version 13. All reported p values were 2-tailed, and all confidence intervals were 95%.

Results

A total of 706 medical records with HCC were identified based on database search at NKTl. Three hundred forty-six (346) patients were confirmed cases of HCC. Three hundred sixty (360) medical records were excluded due to repeated admissions of some patients (291 charts), and some were diagnosed as either metastatic liver disease or cholangiocarcinoma (69 charts).

Baseline Clinical Profile of Patients with ACS

The mean age of the subjects was 61.47+13.08. There were 281 (81.79%) males and 65 (18.79%) females. On initial presentation, 174 (50.73%) patients had abdominal pain. Other signs on presentation included abdominal enlargement/ascites (11.08%), jaundice, GI bleeding, anorexia, weight loss, weakness, and palpable mass. Forty patients were asymptomatic and HCC was incidentally found on routine imaging (11.66%). Most of the patients have an underlying comorbidity. Majority had hypertensive cardiovascular disease 135 (39.02%), followed by diabetes mellitus 91 (26.30%). For the etiology of HCC, chronic hepatitis B alone was present in 193 (55.78%) patients, chronic hepatitis C alone in 9 (2.6%) patients while five (1.45%) patients had co-infection of hepatitis B and C. Other etiologies were alcohol (8.96%) and non-alcoholic steatohepatitis (7.8%). Eighty-one (23.41%) patients had no identifiable etiology. Two hundred fifteen (65.15%) patients had underlying cirrhosis while 115 (34.85%) patients were non cirrhotic. Among the cirrhotic patients, 51 (29.14%) had compensated liver disease (CTPA), 124 (70.86%) patients had decompensated liver disease, 68 (38.86%) and 56 (32%), CTP B and CTPC, respectively (Table I).

Tumor Characteristics and Treatment Modalities

In more than half of the patients (56.1%), the diagnosis of HCC was confirmed by triphasic CT scan. The dominant tumor pattern was a single nodule (55.08%). Most tumors involved the right liver lobe (51.85%). Tumor diameter was >3 cm in 85.48% of patients. More than half of tumors did not present with portal vein thrombosis on initial diagnosis (73.62%). Distant metastases (lung, bone, and adrenal) were seen in 73 (21.22%) patients. One hundred twenty-one (45.83%) patients had alpha-feto protein (AFP) levels of > 400 ng/ml. Based on the BCLC staging, 42 (12.69%) patients had a very early HCC (i.e. BCLC A). One hundred forty-four (43.50%) patients were BCLC B., while 145 (43.81%) patients had advanced HCC on presentation (BCLC C and D).

For the treatment modalities 44 patients (12.94%) underwent surgical treatment. 99 patients (29.12%) had TACE and/or RFA while 26 patients (7.65%) had systemic/oral chemotherapy. 171 (50.29%) patients had supportive care (Table II).

Table I. Baseline and clinical characteristics of patients with hepatocellular carcinoma.

Patient Characteristics	Mean $\pm$ SD or n (%)
Age (in years)	61.47+13.08
Sex Male Female	(N=346) 281(81.21%) 65(18.78%)
Symptoms/Signs on presentation	(N=343)
Abdominal pain	174 (50.73%)
Abdominal enlargement / ascites	38 (11.08%)
Incidental finding (asymptomatic)	40 (11.66%)
Jaundice	19 (5.54%)
GI bleeding	12 (3.50%)
Other symptoms (weakness, decreased sensorium, palpable mass)	60 (17.49%)
Comorbidities	
Cardiac disease	135 (39.02%)
Diabetes Mellitus	91 (26.30%)
Pulmonary Tuberculosis	12 (3.47%)
COPD	11 (3.18%)
Other malignancy	8 (2.31%)
Asthma	4 (1.16%)
Etiology	(N=346)
Chronic Hepatitis	193 (55.78%)
Undetermined etiology	81 (23.41%)
Alcohol	31 (8.96%)
NASH	27 (7.80%)
Chronic Hepatitis C	9 (2.60%)
Hepatitis B and C co-infection	5 (1.45%)
Liver Cirrhosis	(N=330)
with Cirrhosis	215 (65.15%)
without Cirrhosis	115 (34.85%)
A	51 (29.14%)
B	68 (38.86%)
C	56 (32.00%)

Table II. Tumor characteristics of patients with hepatocellular carcinoma

Parameters	N (%)
Diagnosis of HCC	(N=335)
CT scan	188 (56.12%)
Histologic diagnosis	98 (29.25%)
Ultrasound	45 (13.43%)
MRI	4 (1.19%)
Tumor size (cm)	(N=310)
≤ 3	45 (14.52%)
4 to 9	124 (40%)
> 9	141 (45.48%)
Number of tumors	(N=325)
Single	179 (55.08%)
Multiple	142 (43.69%)
Infiltrative	4 (1.23%)
Distant metastases	(N=344)
With distant metastases	73 (21.22%)
Without distant metastases	271 (78.78%)
Portal vein thrombosis	(N=326)
With portal vein thrombosis	86 (26.38%)
Without portal vein thrombosis	240 (73.62%)
AFP level (ng/ml)	(N=264)
≤ 200	127 (48.11%)
201 to 399	16 (6.06%)
≥ 400	121 (45.83%)
MELD score (mean ± SD)	12.27+ 8.49
BCLC Stage	(N=331)
A	42 (12.69%)
B	144 (43.50%)
C	102 (30.82%)
D	43 (12.99%)
Treatment	(N=340)
TACE/RFA	99 (29.12%)
Surgical treatment	44 (12.94%)
Oral/systemic chemotherapy	26 (7.65%)
Supportive care	171 (50.29%)

Patient Survival

The overall median survival of our cohort was 13.17 months, (range,< one month - 92 months, Figure 1), with total mortality of 112 out of 346 patients (from January 2008 to December 2014). Median survival time between those with and without liver cirrhosis was significantly different (9.43 months vs 38.47 months, $p < 0.001$, Figure 2). Similarly, median survival time across Child Pugh Classification for cirrhosis were significantly different (CTP A 35.33 months vs CTP B 15.5 months vs CTP C 1.7 months, respectively, $p < 0.0001$, Figure 3). Median survival time between those with and without PVT (5.57 months vs 17.77 months, $p < 0.002$, Figure 4) was also significantly different. Difference in median survival times across BCLC stages (BCLC A 68.23 months vs BCLC B 26.67 months vs BCLC C 9.9 months vs BCLC D 1 month, $p < 0.001$, Figure 5) and

treatment modalities (Surgery, 13.17 months vs TACE and/or RFA, 30.33 months vs Systemic chemotherapy, 26.67 months vs supportive care, 2.23 months, $p < 0.001$, Figure 6) were also significant.

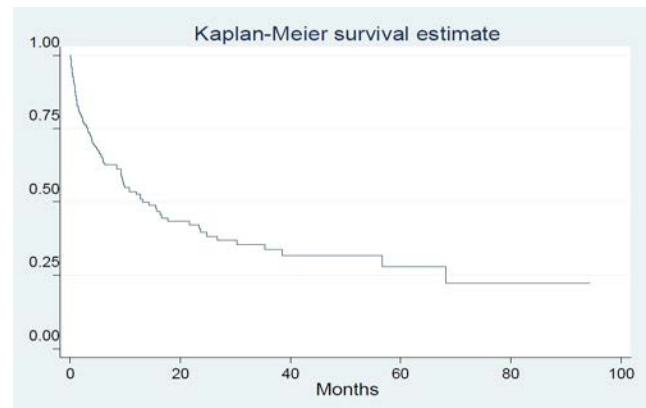


Figure 1. Overall Patient Survival estimates

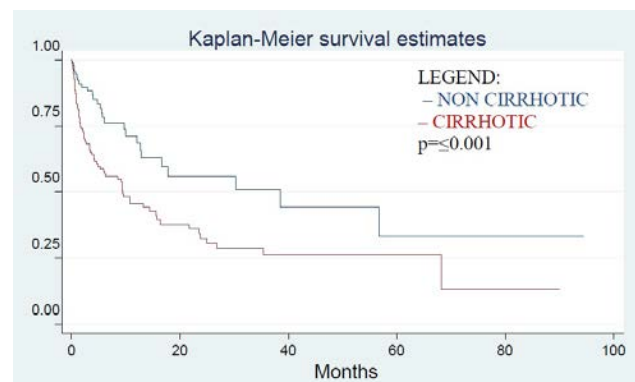


Figure 2. Survival estimates according to presence or absence of cirrhosis

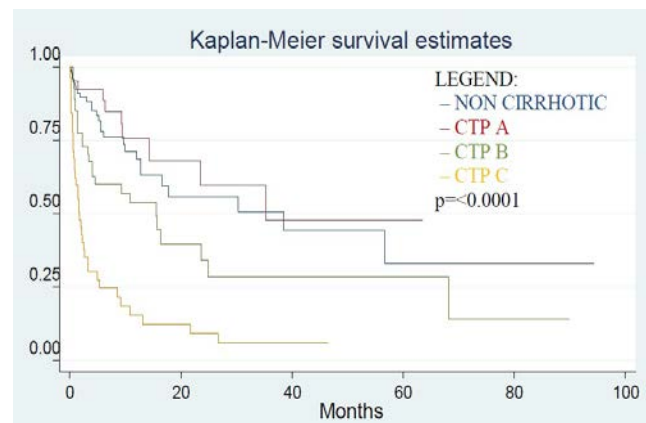


Figure 3. Survival estimates according to Child Turrcotte Pugh Classification

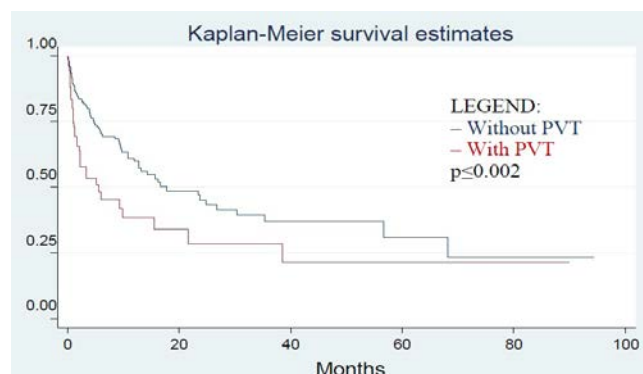


Figure 4. Survival estimates according to presence or absence of portal vein thrombosis (PVT)

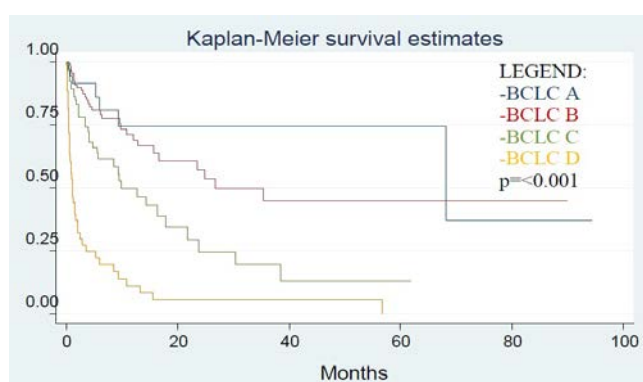


Figure 5. Survival estimates according to BCLC stage

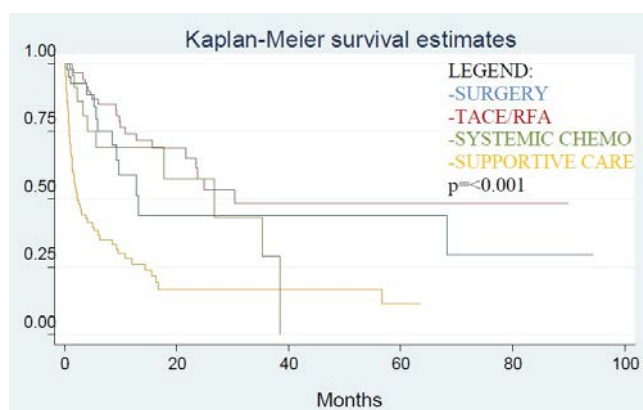


Figure 6. Survival estimates according to treatment modality

However, if we exclude those patients who received supportive care, the median survival among patients who underwent surgery, TACE/RFA and oral/systemic chemotherapy did not show significant difference.

Factors Associated With Mortality

In the univariate analysis, the following variables were significantly associated with increased risk of death among patients with HCC: presence of cirrhosis, CTP Class B and C, presence of PVT, AFP level of ≥ 400 ng/ml, tumor size

Table III. Univariate cox regression predicting mortality

Characteristic	Hazard Ratio	95% CI	p-value
Age (years)	1	0.97, 1.00	0.054
Gender (male)	1.19	0.75, 1.88	0.451
Etiology			
Chronic Hepatitis B	-	-	-
Chronic Hepatitis C	2.03	0.74, 5.61	0.171
Hepatitis B and C co-infection	1.77	0.55, 5.65	0.335
Alcohol	0.90	0.46, 1.75	0.752
Non-alcoholic steatohepatitis	0.47	0.21, 1.03	0.059
No identifiable etiology	1.05	0.68, 1.65	0.804
Presence of Cirrhosis	2.07	1.34, 3.20	0.001*
Child Turcotte Pugh Class			
A	0.78	0.38, 1.61	0.503
B	1.88	1.05, 3.08	0.030*
C	5.14	3.13, 8.45	<0.001*
AFP level (ng/ml)			
< 200	-	-	-
201 – 399	1.78	0.74, 4.29	0.198
≥ 400	2.59	1.57, 3.96	0.001*
Tumor Size (cm)			
≤ 3	-	-	-
4 – 9	1.85	0.95, 3.44	0.060
> 9	1.96	1.01, 3.62	0.038*
Presence of Portal vein thrombosis	1.87	1.25, 2.81	0.002*
MELD Score *	1.06	1.04, 1.08	<0.001*
BCLC Stage			
Stage A	-	-	-
Stage B	1.50	0.66, 3.42	0.335
Stage C	3.11	1.37, 7.07	0.006 *
Stage D	10.55	4.68, 23.76	<0.001*
Treatment			
Surgery	-	-	-
TACE/RFA	0.66	0.33, 1.31	0.232
Oral and systemic chemotherapy	1.24	0.54, 2.85	0.612
Supportive care	3.34	1.78, 5.97	0.001*

* Significant at 5% level

Table IV. Multivariate cox regression predicting mortality

Characteristic	Hazard Ratio	95% CI	p-value
BCLC Stage			
Stage B	1.67	0.72, 3.93	0.232
Stage C	3.70	1.59, 8.56	0.002*
Stage D	7.12	3.04, 16.67	<0.001*
Child Pugh Score for Cirrhosis (CTP)			
A	0.94	0.45, 1.97	0.877
B	1.65	0.96, 2.83	0.069
C	3.52	2.01, 6.14	<0.001*

* Significant at 5% level

of >9.0 cm, BCLC Stage C and D, patients receiving supportive care and MELD score (Table III).

Using Multivariate Cox regression, BCLC stage C (HR:3.70; $p=0.002$) and D (HR:7.12; $p<0.001$, and CTP class C (HR:3.52; $p<0.001$) were shown to be independent predictors of reduced survival or death (Table IV).

Discussion

We determined in this study that chronic hepatitis B (55.78%) is the primary risk factor for the development of HCC in our study cohort. This is similar to a study done by El Seraqi¹ and to two other local studies done at another tertiary hospital.^{8,9} The above finding did not come as a surprise since the Philippines is still hyperendemic for chronic hepatitis B. Moreover, 65.15% of our cohort had cirrhosis which is also an established risk factor for the development of HCC.

Our patients with HCC were predominantly male (81.79%) and above 50 years old. Abdominal pain (50.73%) was also the most common symptom on presentation, which are consistent with previous findings in other studies.^{8,9}

More than half of our patients were diagnosed with dynamic imaging (56.12%). Currently, the diagnosis of HCC can be increasingly made with the use of noninvasive tests in accordance with the latest consensus of the Asia Pacific Association for the Study of the Liver (APASL).¹⁰ Current recommendations stated that serum AFP is not a reliable diagnostic test for HCC, but AFP level of 400ng/ml or higher is still predictive of HCC.¹ In our study, 45.83% of the cohort have AFP level >400ng/ml, which is considered to be the diagnostic level for HCC in most consensus guidelines for HCC.

Furthermore, our study showed that the dominant tumor pattern was a solitary nodule (55.08%), mostly involving the right lobe (51.85%) and measuring more than 3.0 cm (85.48%) in diameter. 43.5% had BCLC B and another 43.81% had advanced stage on presentation (i.e. BCLC C and D). Most did not have distant metastasis and portal vein thrombosis.

Half (50.29%) of our patients received supportive care and did not receive any form of curative treatment since most of the patients had an advanced BCLC stage. However, 64/186 (34.4%) did not have advanced HCC but did not receive any form of treatment because of patient's preference, significant comorbid conditions precluding initiation of treatment and prohibitive cost of available treatment options. Of the 64 patients, 10 patients were BCLC stage A and 54 patients were BCLC stage B. The other half of patients received treatment modalities which

were mostly based on the BCLC staging system. Most of them received locoregional treatment in the form TACE and or RFA (29.12%), surgery (curative resection) (12.94%) and oral/systemic chemotherapy (7.65%). A study done by El Serag et al showed that majority of patients with HCC did not receive potentially curative therapy due to several factors such as severity of liver disease, comorbid illness and functional status.⁷

The median overall survival (OS) of HCC patients in this study was 1.18 years (14 months). This was similar to the studies done by Abdelaziz et al¹¹ and Alacacioglu, et al.¹² which showed a median OS of 13 months and 14 months, respectively. However, the OS of our cohort was slightly lower than the Italian cohort of Borzio et al¹³ which had a median OS of 19.7 months. Compared to our cohort in, which 71% (i.e. CTP B and C combined) have decompensated liver disease, majority (59%) of their patients had compensated liver disease (i.e. CTP A). Our cohort, therefore, have a much worse prognosis as to their hepatic function and therefore had a higher risk for worse outcomes and death.

Univariate analyses showed that presence of liver cirrhosis negatively impacts on patient survival. Patients with cirrhosis had a shorter median survival compared to those who are non cirrhotic (9.43 months versus 38.47 months, $p<0.001$). Likewise, the severity of liver cirrhosis by CTP Classification greatly impacted on patient survival. Patients with compensated liver disease (i.e. CTP A) have a longer median survival compared to patients with CTP B and C (CTP A 35.33 months vs CTP B 15.5 months vs CTP C 1.7 months, respectively, $p<0.0001$). Tumor size of more than 9.0 cm was also noted to be associated with mortality as it is associated with advanced stage of HCC.

Presence of portal vein thrombosis likewise carried a significant risk for mortality compared to those without portal vein thrombosis (5.57 months vs 17.77, $p\leq0.002$) as it is also associated with advanced stage of HCC. HCC patients with BCLC stage A survived longer than those with BCLC stages B, C, D ($p<0.001$). These results were consistent with the studies by Alacacioglu, et al in Turkey and Borzio et al in Italy. In our study, we also noted that higher MELD score has a significant risk for mortality. It is expected since MELD scoring is used to measure mortality risk in patients for patients with end stage liver disease.

Surprisingly, as to the treatment modality, our study showed that those who had TACE and/or RFA had the longest median survival (30.33 months). It was followed by systemic chemotherapy (26.67 months) then surgery (13.17 months). This may be due to any or a combination of the following reasons: 1.) Majority (29%) of our patients who were able to receive treatment underwent TACE and/or RFA and therefore may be a source of potential bias, 2.)

curative surgery but due to significant comorbidities were considered poor surgical risks, 3.) the treatment received by some of the patients may have been due to personal preference or their attending physicians' preference. However, excluding the patients who did not receive any form of treatment or those who had received supportive care only, the univariate cox analysis showed that the three modalities did not have any significant difference in terms of survival. Patients who did not receive any form of treatment had the shortest median survival (2.23 months). This was shorter than the one observed in the cohort of Giannini et al¹⁴ in which the overall median survival was nine months.

On multivariate analysis, we identified the following as independent predictors of mortality: CTP class (CTPC) and BCLC stage (C and D) among patients with HCC. These findings are similarly observed in other studies.^{11,12,13,14}

Due to the innate limitations of a retrospective study, our group recommends a multicenter prospective study to determine the association between severity of disease and treatment outcomes and survival.

Conclusion

The profile of HCC patients in our institution are similar to those reported in previous local studies and other countries. Chronic hepatitis B is still the primary risk factor for the development of HCC. CTPC, BCLC stages C and D are independent predictors of mortality in HCC patients in our institution. Median overall survival of our patients is 13.17 months.

Our study showed that those who had TACE and/or RFA had the longest median survival (30.33 months). It is followed by systemic chemotherapy (26.67 months) then surgery (13.17 months).

Acknowledgment

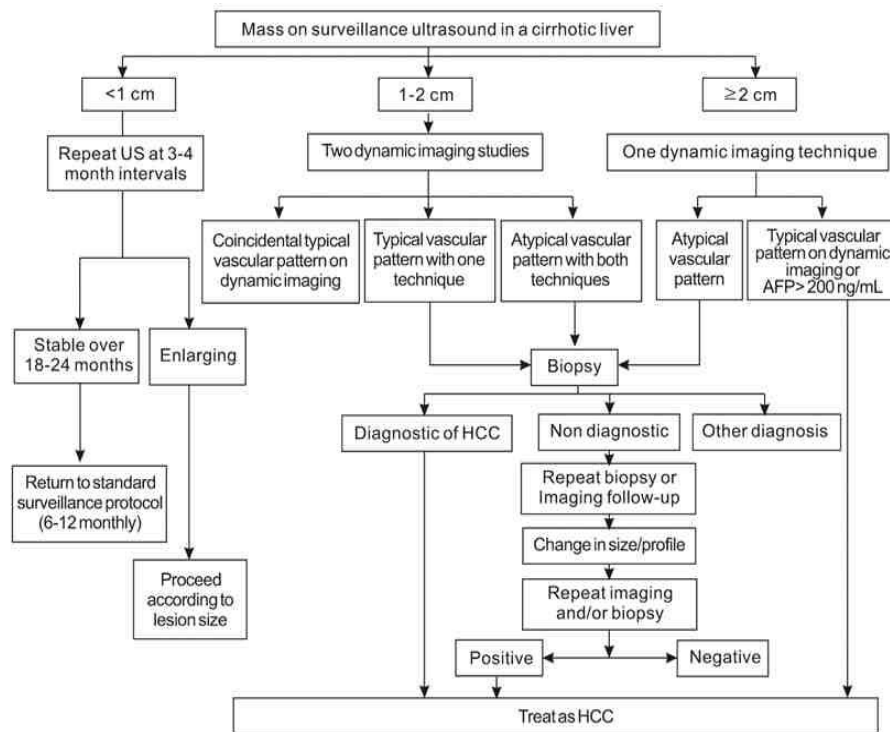
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Appendix

Appendix A: This algorithm is adapted from American Association for the Study of Liver Diseases Practice Guidelines for Hepatocellular Carcinoma¹⁵



Appendix B. Barcelona clinic liver cancer (BCLC) staging classification

