RESEARCH ARTICLE

Epidemiology and Survival of Hepatocellular Carcinoma in the Central Region of Thailand

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Abstract

Background: Hepatocellular carcinoma (HCC) is one of the most common cancers in men and the third most common cancer in woman in Thailand. This retrospective study was designed to assess the prevalence, clinical manifestations, treatment outcomes and prognosis of HCC in the central region of Thailand. Materials and Methods: The authors retrospectively reviewed all HCC patients aged more than 15 years old in Thammasat university hospital (TUH) during the period from January 2007 to December 2012. Clinical information, biochemical tests and radiologic findings were collected from review of medical records. Results: There were 308 patients with HCC, which accounted for the prevalence of 5.19% of all cancers diagnosed in TUH during the study period. Of these, 125 (40.5%) had complete information retrievable from their medical records and met the inclusion criteria, 99 (79.2%) were males. The mean age was 57.4 years. A quarter of HCC patients in this study presented without any symptom before diagnosis. The common clinical presentations in the remaining patients were hepatomegaly 64/125 (51.2%), abdominal pain 56/125 (44.8%) and ascites 16/125 (20.8%). Cirrhosis was seen in almost all patients (92.8%). The most common causes of HCC in this study were chronic hepatitis B (49.6%) and C (19.2%). Based on Barcelona Clinic Liver Cancer staging, 75.4% presented at intermediate or late stage. Patients receiving curative therapy with either surgical treatment or radiofrequency ablation had significantly longer survival time after the HCC diagnosis than the palliative therapy group (11.0 months *vs* 4.0 months, p value= 0.004). The mean survival time after the HCC diagnosis was 10.5 months. Conclusions: The common causes of HCC in central region of Thailand were chronic hepatitis B and C. Surgical therapy or RFA seemed to provide better outcomes than other treatments but only in patients with early stage lesions. Most of the patients in this study presented with advanced diseases and had grave prognosis. Appropriate screening patients at risk for HCC might be an appropriate way to achieve early diagnosis and improve the treatment outcome.

Keywords: Hepatocellular carcinoma - cirrhosis - chronic hepatitis B - Central Thailand

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Introduction

Hepatocellular carcinoma (HCC) is the sixth most common cancer and the third cancer related death worldwide (El-Serag 2011, de Lope et al., 2012). HCC accounts more than 90% of primary liver cancers and is one of the major global health problems (El-Serag, 2011). Most cases of HCC arise in Asia and sub-Saharan Africa, where the prevalence of chronic hepatitis B virus (HBV) infection is substantially high. Chronic hepatitis C virus (HCV) infection, which is another important cause of HCC is also a growing disease in this region (Bruix, Sherman et al., 2011; Forner et al., 2012). In addition, the majority of HCC patients occur in established background of chronic liver diseases especially from HBV and HCV infection (de Lope et al., 2012; Forner et al., 2012).

Several lines of evidence suggest that the incidence of HCC in Asia is decreasing as a result of nationwide HBV vaccination across many Asian countries (Yeo et al., 2013). Indeed, the result from a recent population-based study in Thailand was in agreement with this finding (Wiangnon et al., 2012). However, HCC is still considered as a fatal disorder, which carries a grave prognosis (Bruix et al., 2011, Singal et al., 2013). A significant number of HCC patients in Thailand presented in advanced stage, thus precluding them from curative therapy. Recent study from Southern region of Thailand demonstrated that patients with HCC there also presented in late stage and had a grave prognosis with an overall median survival only 2.1 months (Sithinamsuwan et al., 2000). To date, study on natural history, clinical manifestations and treatment outcomes of patients with HCC applying current standard staging system (Barcelona Clinic Liver Cancer: BCLC) especially in Central region in Thailand are limited. The aim of this study was to depict the natural history, clinical manifestations, radiologic finding, staging and treatment

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outcomes of patients with HCC in Thammasat University Hospital (TUH), which is a referral university hospital in Central region of Thailand.

Materials and Methods

A retrospective study was conducted in TUH, Pathumthani, Thailand. All patients with a diagnosis of solid organ or hematologic malignancy in population-based registry between January 2007 and December 2012 and were aged 15 or more were selected and reviewed. Those who were diagnosed with hepatocellular carcinoma (code of C22.0 according to International Classification of Disease for Oncology) were eligibly considered enrolled in this study. The diagnosis of HCC was based on the diagnostic criteria used by the American association study of liver disease (AASLD) which established in the following situations: (1) histological proof of HCC; (2) when a focal lesion >2 cm in diameter, assessed by arterial hypervascularization using two-contrast-enhanced methods (CT-scan and MRI), or when there was an association between serum AFP>200 ng/ml plus early arterial hypervascularization, assessed by one contrast-enhanced method (Bruix et al., 2005; 2011). All the clinical information of eligible patients was reviewed and relevant data were entered into a clinical collecting form. Recorded information included clinical manifestations, method of diagnosis, staging, radiologic findings, complications and treatment outcome of all HCC patients. The study was conducted according to the good clinical practice guideline as well as the Declaration of Helsinki and was approved by our local ethics committee.

Statistical analysis

Statistical analyses were performed using SPSS Statistics version 19.0 (IBM Corp., Armonk, NY). All results are expressed as frequency, median and range or mean±standard deviation (SD) as appropriate. Categorical variables were compared using chi-square or Fisher's exact test. Continuous variables were compared using the two tailed Student's t-test. The cumulative probability of mortality was computed using the Kaplan-Meier method and compared by the log-rank test. The p-values <0.05were considered to be statistically significant.

Results

A total of 5,929 patients were diagnosed with solid organ or hematologic malignancy in TUH during the study period. Of which, 308 (5.19%) had a final diagnosis of HCC. HCC is the third most common type of cancer in men and ninth most common cancer in women in our hospital. The medical charts of 183 patients were permanently damaged due to the National historical flooding crisis in 2011 in our country. Finally, total of 125 patients with HCC were included in this study. Demographic characteristics and initial manifestations leading to the diagnosis of HCC are demonstrated in Table 1.

Ninety-nine out of 125 patients (79.2%) were men. The mean age at diagnosis was 57.4±12.7 years. Thirty-one patients (24.8%) were asymptomatic at the time of diagnosis. Those who were symptomatic, hepatomegaly (51.2%), abdominal discomfort (44.8%) and ascites (20.8%) were common presenting symptoms. The mean duration to the diagnosis was 24 days. Nearly all patients (92.6%) had biochemical, radiologic or histological features of cirrhosis when HCC was documented.

Specific serological and biochemical tests were performed in all patients in order to identify etiology

Table 1. Baseline Characteristics of 125 HCC Patients

Characteristics	N (%)
Men	99 (79.2%)
Age at diagnosis (yr, mean±SD)	57.4±12.7
Associated disorders	
Diabetes mellitus	30 (24%)
Hypertension	29 (23.2%)
Dyslipidemia	21 (16.8%)
Chronic renal failure	4 (3.2%)
Cerebral infarction	4 (3.2%)
Coronary artery disease	3 (2.4%)
Chronic obstructive pulmonary disease	2 (1.6%)
HIV infection	2 (1.6%)
Symptoms and signs at diagnosis	
Asymptomatic	31 (24.8%)
Hepatomegaly	64 (51.2%)
Abdominal discomfort	56 (44.8%)
Ascites	26 (20.8%)
Weight loss	19 (15.3%)
Jaundice	17 (13.6%)
Fever	13 (10.4%)
Edema	10 (8%)
Anemia	8 (6.4%)
Palpable abdominal mass	7 (5.6%)
Splenomegaly	7 (5.6%)
Gastrointestinal bleeding	3 (2.4%)
Cause of chronic liver disease	
Chronic HBV infection	50 (40%)
Chronic HCV infection	20 (16%)
Alcohol	18 (14.4%)
NASH	2 (1.6%)
Chronic HBV infection and alcohol	10 (8%)
Chronic HCV infection and alcohol	3 (2.4%)
Chronic HBV/HCV infection and alcohol	1 (0.8%)
Chronic HBV infection and NASH	1 (0.8%)
Cryptogenic	20 (16%)

Table 2. Staging and Complications of HCC Patients

		N (%)
BCLC staging	Stage 0 (very early)	12 (9.6%)
	Stage A (early)	20 (16%)
	Stage B (intermediate)	47 (37.6%)
	Stage C (advance)	14 (11.2%)
	Stage D (terminal)	32 (25.6%)
Initial treatment	Hepatic resection	18 (14.4%)
	RFA	27 (21.6%)
	TACE	52 (41.6%)
	Palliative	28 (22.4%)
Complication	Ruptured HCC	20 (16%)
	Recurrence of HCC	6 (4.8%)
	Spontaneous bacterial peritonitis	6 (4.8%)
	Septicemia	4 (3.2%)
	Variceal bleeding	2 (1.6%)

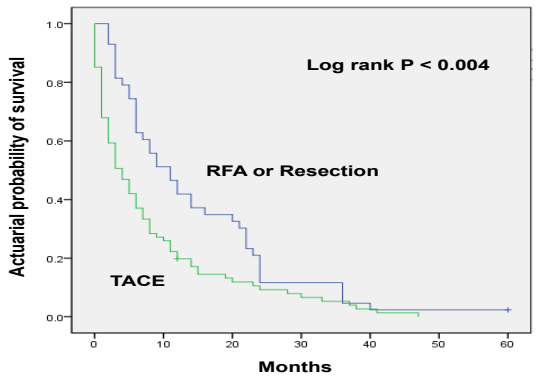

Figure 1. Actuarial Probability of Survival Rate of Patients who Received RFA or Hepatic Section Compared to those Received TACE as Initial Therapy

of chronic liver disease. The most common cause was chronic hepatitis B infection (49.6%) follow by alcohol consumption (26%), chronic HCV infection (19%), cryptogenic cirrhosis (16%) and non-alcoholic steatohepatitis (2.4%). In non-cirrhotic patients (9 cases), chronic HBV infection was found to be the causative factor of HCC.

Majority of patients (80%) were diagnosed based on a typical tumor vascular pattern in contrast-enhanced CT or MRI. The rest of the HCC patients were diagnosed by histological study plus typical imaging studies. Tumor staging was based on the Barcelona Clinic Liver Cancer (BCLC) staging system (Bruix et al., 2005; 2011). As shown in Table 2, most patients were at intermediate or late stage at diagnosis (37.6% with stage B, 11.2% with stage C and 25.6% with stage D). Hepatic resection, percutaneous radiofrequency ablation (RFA) and trans-arterial chemoembolization (TACE) were assigned as an initial treatment in 18 (14.4%), 27 (21.6%) and 52 (41.6%) patients, respectively. The remaining patients were assigned to palliative therapy. However, during follow-up six patients with hepatic resection were subsequently documented with recurrent diseases and treated with TACE as recue therapy. Median survival of all HCC patients in this study was 10.5 months. Regarding median survival, the asymptomatic patients had longer life expectancy compared to symptomatic group (11 *vs* 5 months; p value=0.004).

One third of HCC patients developed at least 1 complication during the course of disease. Spontaneous rupture of HCC (16%) was the most common complication followed by spontaneous bacterial peritonitis (4.8%), septicemia (3.2%) and variceal bleeding (1.6%). Interestingly, as shown in figure 1, the median survival of patients received curative therapy with resection or RFA was significantly longer than palliative therapy with TACE patients (11 *vs* 4 months, p value= 0.004). However both groups had a poor long-term outcome (5-year survival less than 5%).

Discussion

Hepatocellular carcinoma (HCC) is the leading cause of death among patients with cirrhosis (Alazawi et al., 2010). It is estimated that there are 500,000-1,000,000 new HCC cases and approximately 600,000 patients die globally from the disease each year (Belghiti and Fuks 2012). In Thailand, previous study reported the overall age standardized rates (ASR) of HCC were 30.3 and 13.1 per 100,000 in males and females (Wiangnon et al., 2012). Our study also indicated that HCC was more prevalence in male during the age between 50-60 years. This study demonstrated that almost quarter of patients was asymptomatic at diagnosis and this group of patient had better survival compared to symptomatic patients. This information emphazied the screening program for patients at high risk of developing HCC such as chronic HBV or cirrhotic patients in order to promptly start the definite treatment and obtain the better outcome.

Cirrhosis is a well-known major risk factor of HCC. In our study, we found that most of HCC patients (90%) had cirrhotic liver compatible with the literature findings (Pourhoseingholi et al., 2010, El-Serag, 2011, Forner et al., 2012). Chronic HBV infection was the common cause of HCC in Asian countries and also demonstrated as a leading cause of HCC in this study (Yang et al., 2002, Parkin et al., 2005). Several host and viral factors, including HBV mutation, have been proposed as a risk factor of HBV-induced carcinogenesis (Liang et al., 2013). Our findings support the role of current recommendations suggesting an interval HCC screening program in chronic HBV infection in both patients with or without cirrhosis(Bruix et al., 2011, El-Serag 2011). Interestingly, Chronic HCV infection accounts for nearly one-fifth of HCC in the present study. This finding remarks the importance of HCV screening in high-risk populations. In addition, several efforts is now focusing on the development of vaccine against HCV infection (Keyvani et al., 2012).

In recent years, Barcelona Clinic Liver Cancer (BCLC) staging system has gained more acceptances and being an international criterion for HCC diagnosis (Llovet et al., 1999, Bruix et al., 2005, Marrero et al., 2005). The main advantage of this system is that it includes prognostic variables related to tumor status, liver function and health performance status and links staging with treatment modalities. To date, there is no prior study evaluating treatment outcome of HCC patients in Thailand by using BCLC staging system. Our study demonstrated that most patients in BCLC stage B-D, which classified as incurable stage, had less likely chance to receive curative treatment: such as hepatic resection or radiofrequency ablation, whereas our HCC patients with BCLC stage A, classified as curable stage, had better chance to receive the curative therapy and finally had a better survival. Thus, applying the BCLC staging system should be encouraged as a valuable guideline for HCC management in Thailand. Previous HCC studies in Thailand and Malaysia demonstrated HCC patients in this region had a poor outcome with an overall median survival only for 2 months (Sithinamsuwan et al., 2000, Norsa, 2013). However, our study indicated much longer median survival of 10.5 months. The explanation is possibly due to the difference in number of patients subjected to treatment as well as an improvement in efficacy of HCC treatment modality in recent years. The limitation of this study might be from some permanent loss data during national flood in 2011, resulting in the

smaller number of HCC patients than our expectation. Large multicenter and prospective studies are required to clarify other aspects of HCC in Thailand in order to improve screening program, early detection and enhance treatment outcome of this important cancer in our country.

In conclusion, HCC is a fatal complication in patients with chronic liver disease. Chronic HBV infection is a major risk factor of HCC among Thai patients. Most of HCC patients are diagnosed at late stage, which results in a very poor long-term outcome. Thus, strictly following screening policy in patients who are at high risk of developing HCC should be highly encouraged.

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