RESEARCH ARTICLE

Epidemiology and Survival of Hepatocellular Carcinoma in North-east Peninsular Malaysia

Bachok Norsa'adah*, Che Ghazali Che Nurhazalini-Zayani

Abstract

The incidence of hepatocellular carcinoma (HCC) is relatively high in Southeast Asia. Globally, HCC has a high fatality rate and short survival. The objectives of this retrospective cohort study were to review the epidemiology and survival of HCC patients at a tertiary centre in north-east of Peninsular Malaysia. Subjects were adult HCC patients diagnosed by histopathology or radio-imaging. Secondary liver carcinoma was excluded. Kaplan Meier and multiple Cox proportional hazard survival analyses were used. Only 210 HCC cases from years 1987-2008, were included in the final analysis. The number of cases was increasing annually. The mean age was 55.0 (SD 13.9) years with male:female ratio of 3.7:1. Approximately 57.6% had positive hepatitis B virus, 2.4% hepatitis C virus, 20% liver cirrhosis and 8.1% chronic liver disease. Only 2.9% had family history and 9.0% had frequently consumed alcohol. Most patients presented with abdominal pain or discomfort and had hepatomegaly, 47.9% had an elevated α-fetoprotein level of 800 IU/ml or more, 51.9% had multiple tumors and 44.8% involved multiple liver lobes. Approximately 63.3% were in stage 3 and 23.4% in stage 4, and 82.9% did not receive any treatment. The overall median survival time was 1.9 months (95% confidence interval (CI): 1.5, 2.3). The 1-month, 6-month, 1-year and 2-year survival rates were 71.8%, 23.3%, 13.0% and 7.3% respectively. Significant prognostic factors were Malay ethnicity [Adjusted hazard ratio (AHR) 1.6; 95%CI: 1.0, 2.5; p=0.030], no chemotherapy [AHR 1.7; 95%CI: 1.1, 2.5; p=0.017] and Child-Pugh class C [AHR 2.6; 95%CI: 1.4, 4.9; p=0.002]. HCC in our study affected a wide age range, mostly male, in advanced stage of disease, with no treatment and very low survival rates. Primary prevention should be advocated in view of late presentation and difficulty of treatment. Vaccination of hepatitis virus and avoidance of liver toxins are to be encouraged.

Keywords: Hepatocellular carcinoma - hepatoma - primary liver cancer - Malaysia

Asian Pac J Cancer Prev, **14 (11)**, 6955-6959

Introduction

Hepatocellular carcinoma (HCC) incidence is reported to be highest in sub-Saharan Africa and Eastern Asia, with China contributing half of the cases (El-Serag and Rudolf, 2007). These areas had the highest incidence rates that were related to the endemicity of hepatitis B virus (HBV) infection in the region. It was reported that several part of Thailand had the highest incidence of HCC (Kamsa-ard et al., 2011). Countries in Southern Europe had medium-high incidence rates, while low-incidence areas included South and Central America, and the rest of Europe (Nordenstedt et al., 2010). The incidence of HCC in many parts of countries had declined due to the effect of hepatits B vaccination and change of staple food form corn to rice (El-Serag and Rudolf, 2007).

However, the Surveillance, Epidemiology and End Results program of the United States reported an increase incidence of HCC between 1975 and 1998 (El-Serag et al., 2003). The highest increment was observed among white middle age men. Another study also reported that liver and intrahepatic bile duct cancer had the highest increment of mortality in male and female from the year 1990-2007 (Siegel et al., 2011). On the other hand, the population-based Netherlands Cancer Registry reported a stable incidence of HCC during years 1989-2000 (Verhoef et al., 2004).

In Malaysia, the age-standardised rate of HCC in 2007 among men and women was 4.7 and 1.6 per 100,000, respectively (Zainal and Nor Saleha, 2011). The National Cancer Registry reported that liver cancer was the tenth most common cancer and the sixth cancer in men in year 2007 with 605 new cases (Zainal and Nor Saleha, 2011). The incidence was the highest in 70's age group and the majority of cases (62%) were presented in stage 4 of disease (Zainal and Nor Saleha, 2011). Many cases may not be diagnosed because lacking of ultrasound, CT scan or liver biopsy facilities. Ultrasound and CT scan of liver are available in only general hospitals in Malaysia while biopsy is an invasive test that many patients may refuse.

The variation of HCC incidence by geography, age, sex and ethnicity is related to its' association as a complication

*Unit of Biostatistics and Research Methodology, School of Medical Sciences, Universiti Sains Malaysia, Kelantan, Malaysia *For correspondence: norsaadah@kb.usm.my*

of viral infection or excessive alcohol intake. The main risk factors for HCC are chronic infection of HBV and hepatitis C virus (HCV) (Chen et al., 1997, Gao et al., 2012). Together HBV and HCV accounted for 80-90% of all HCC worldwide (Nordenstedt et al., 2010). More than 50% of HCC cases worldwide and 70-80% of HCC cases in highly HBV endemic regions were attributable to HBV (Nguyen et al., 2009). HBV is one of the major HCC risk factor worldwide, including Malaysia although its importance will most likely decrease in the future due to the widespread use of the HBV vaccine in the newborns. HCV has been the dominant viral cause in HCC in North America, some Western countries and Japan (Nordenstedt et al., 2010). Liver cirrhosis is another most important risk factor that presented in about 80-90% of HCC patients (Nordenstedt et al., 2010, Gao et al., 2012).

Other factors associated with the increased risk of HCC include male sex, older age, smoking (Nguyen et al., 2009), genetic, chemicals and environmental factors (Wong and Corley, 2008). Diabetes and obesity may be also associated with the occurrence of HCC (Gao et al., 2012). There will be more cases of HCC in the future as the prevalence of obesity and diabetes are increasing throughout the world, if they were proven as HCC risk factors.

HCC is a cancer that has high mortality rate, that the annual mortality rate is almost the same as the annual incidence rate. The 5-year relative survival rate in the United States in year 1999-2006 was 14% (Siegel et al., 2011). There are no reliable and universally acceptable prognostic factors for HCC. However, the most important prognostic factors are; *i*) the stage, aggressiveness and growth rate of the tumour; *ii*) the general health of the patients; *iii*) the liver function of the patients; and *iv*) specific intervention (Bruix et al., 2001).

This study was conducted to identify the epidemiology and survival of HCC patients admitted at Universiti Sains Malaysia (USM) Hospital, which is the only centre in the north-east area of Peninsular Malaysia that serves oncology and radiotherapy services. USM hospital is a teaching hospital located in north-eastern peninsular Malaysia. It is a tertiary referral center for the area and serves rural population that has a low socio-economic status.

Materials and Methods

This was a retrospective cohort study. Medical records of adults with HCC diagnosed by histopathology or radio-imaging registered in USM hospital were reviewed. We included radio-imaging diagnosis as well because not many patients had agreed for liver biopsy. We excluded secondary liver carcinoma and those records that had more than 30% missing data from final analysis. A list of HCC patients from year 1987-2008 was obtained from the Record Department. Each of the listed patients' record was traced and reviewed. Information from the record was retrieved and entered into information performa. The staging of HCC was using the pathologic tumor-node-metastasis (pTNM) and Cancer of the Liver Italian Program (CLIP) staging systems (Befeler and Bisceglie, 2002). Only patients who had tests for hepatitis B or C and positive result were reported as positive.

Statistical analyses

PASW SPSS version 18 software was used for data analysis. Numerical data was summarised as mean, standard deviation (SD) or median, inter quartile range (IQR), 95% confidence interval (CI) depending on the normality of distribution. While categorical data were presented asfrequency and percentage. Kaplan Meier survival analysis was used to determine the median and percentage rate of survival. The differences of median survival time between subgroups were compared using log-rank test. Cox proportional hazard regression was used to determine the prognostic factors of HCC. The time event was measured from date of diagnosis to the date the patients died due to HCC. The event was the death status and censors were cases who were alive at the end of study or lost to follow up. The date of death was provided by the Department of National Registration. Results were presented as adjusted hazard ratio (AHR), 95%CI and p value. The p value less than 0.05 was considered statistically significant.

Results

Out of 259 HCC cases from year 1987 to 2008 in the list from the Medical Record Department, 12 records were not traceable and 37 records were destroyed. Only 210 (81%) HCC cases were reviewed. Figure 1 shows the number of HCC cases in USM hospital increasing annually.

The age ranged from 16 to 82.7 years with mean 55.0

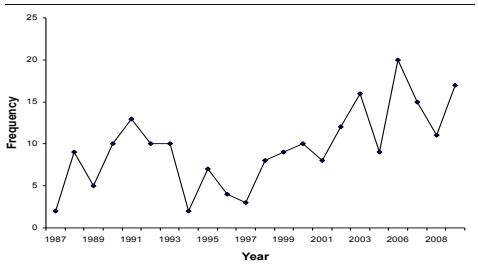

Figure 1. Annual Number of HCC Cases in North-east of Peninsular Malaysia in Year 1987-2008

Table 1. Socio-demographic Factors of HCC Patients in North-east of Peninsular Malaysia

Socio-demographic		Frequency (%) N=210
Age (year)	<40	30 (14.3)
	40-49	39 (18.6)
	50-59	61 (29.0)
	≥60	80 (38.1)
Gender	Male	165 (78.6)
	Female	45 (21.4)
Ethnicity	Malay	181 (86.2)
	Others	29 (13.8)
Occupation	Unemployed	108 (51.4)
	Employed	102 (48.6)
Marital Status	Married	188 (89.5)
	Not married	22 (10.5)

(SD 13.9) years (Table 1). The male:female ratio was 3.7:1, 57.6% had HBV, 2.4% HCV, 20% liver cirrhosis and 8.1% chronic liver disease. Only 2.9% had family history and 9.0% had taken frequent alcohol (Table 2). The range of symptom duration was 0-24 months, with the median of one month. Most patients presented with abdominal pain or discomfort and had hepatomegaly, 51.9% had multiple tumours and 44.8% involved both sites of liver lobes (Table 3). Table 4 shows that 47.9% had AFP ≥800 IU/ml. Figure 2 shows the staging distribution of HCC. Approximately 63.3% were in stage 3 and 23.4% in stage 4. Table 5 shows the treatment and survival status of HCC cases. There were 82.9% who did not have any treatment, 19 (9.0%) had embolization and only 3 (1.4%) had radiofrequency ablation.

At the end of our study, only 12 (5.7%) subjects were censored, 6 (2.9%) died due to other causes and 192 (91.4%) died due to HCC. The overall median survival time was 1.9 months (95% confidence interval (CI): 1.5, 2.3). The 1-month, 6-month, 1-year and 2-year survival rates were 71.8%, 23.3%, 13.0% and 7.3% respectively. The significant prognostic factors were Malay ethnic (AHR 1.6; 95%CI: 1.0, 2.5; p value=0.030), no chemotherapy (AHR 1.7; 95%CI: 1.1, 2.5; p value=0.017) and Child-Pugh class C (AHR 2.6; 95%CI: 1.4, 4.9; p value=0.002).

Figure 3 shows the survival curves for ethnicity. Malay ethnicity had significantly lower median survival time [3.8 months (95%CI: 3.1, 4.4)] compared to the non-Malay [5.6 months (95%CI: 1.8, 9.4), p value=0.024]. Figure 4 shows the survival curves for chemotherapy. Patients who did not received chemotherapy had significantly lower median survival time [3.7 months (95%CI: 3.2, 4.1)] compared to those who received chemotherapy [8.9 months (95%CI: 6.8, 11.1), p value=0.024]. Figure 5 shows the survival curves for Child-Pugh class. Child-Pugh class C had significantly lower median survival time [2.4 months (95%CI: 1.7, 3.2)] compared to class A [4.6 months (95%CI: 3.5, 5.6), p value=0.003]. There was no significant difference in the median survival between class A and class B [3.4 months (95%CI: 2.8, 4.1), p value=0.138] and between class B and C (p value=0.165).

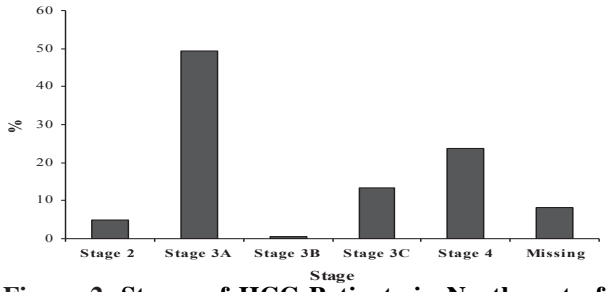

Figure 2. Stages of HCC Patients in North-east of Peninsular Malaysia According to TNM System

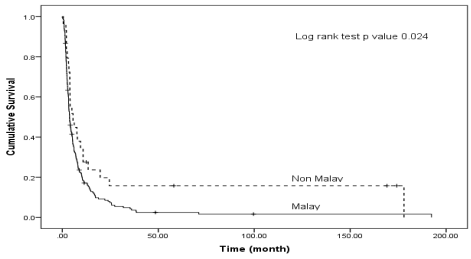

Figure 3. Comparison of Survival Curves for HCC Patients of Malay and Non Malay Ethnicity

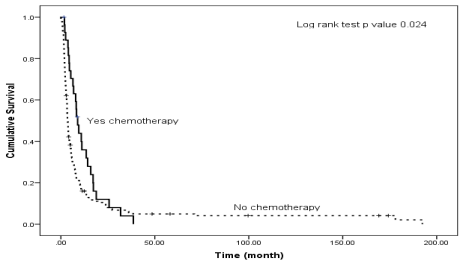

Figure 4. Comparison of Survival Curves for HCC Patients Who Received and Did Not Received Chemotherapy

Table 2. Medical History of HCC Patients in North-east of Peninsular Malaysia

Medical history		Frequency (%) N=210
Family history of liver cancer		6 (2.9)
Smoking status	Non-smoker	92 (43.8)
	Current smoker	85 (40.5)
	Previous smoker	33 (15.7)
Taken alcohol regularly		19 (9.0)
Hepatitis B positive		121 (57.6)
Hepatitis C positive		5 (2.4)
Had liver cirrhosis		42 (20.0)
Had chronic liver disease		17 (8.1)
Liver abscess history		8 (3.8)

Table 3. Clinical Presentation of HCC Patients in North-east of Peninsular Malaysia

Clinical Presentation	Frequency (%) N=210
Abdominal pain	121 (57.6)
Abdominal discomfort	58 (27.6)
Abdominal mass	50 (23.8)
Abdominal distension	43 (20.5)
Loss of appetite	114 (54.3)
Loss of weight	104 (49.5)
Hepatomegaly	106 (50.5)
Jaundice	69 (32.9)
Splenomegaly	27 (12.9)

Table 4. Blood Test Results on First Presentation of HCC Patients in North-east of Peninsular Malaysia

Blood test	N	Frequency (%)	Median (IQR)
α-fetoprotein ≥800 IU/ml	194	93 (47.9)	300 (50, 9869)
Aspartate Transferase >100 IU/L	206	124 (60.2)	127 (69, 213)
Alkaline Phosphatase >200 IU/L	205	117 (56.8)	218 (146, 374)
Alanine Transferase >100	206	59 (28.1)	63 (41, 112)
Bilirubin >40mmol/L	201	58 (27.6)	21 (11, 48)
Index Normal Ratio >1	192	166 (86.5)	1.2 (1.0, 1.5)
Activate Partial Thromboplastin Time >45.8 seconds	194	30 (15.5)	35.7 (31.6, 42.1)

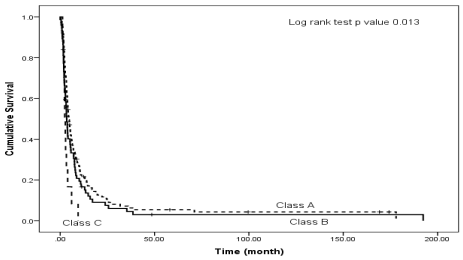

Figure 5. Comparison of Survival Curves for HCC Patients with Child-Pugh Class A, B and C

Table 5. Treatment and Status of HCC Patients in North-east of Peninsular Malaysia

		Frequency (%) N=210
Treatment	No treatment	174 (82.9)
	Chemotherapy alone	24 (11.4)
	Surgery alone	5 (2.4)
	Radiotherapy alone	3 (1.4)
	Surgery & chemotherapy	3 (1.4)
	Chemotherapy & radiotherapy	1 (0.5)
Status	Died from HCC	192 (91.4)
	Died from other causes	6 (2.9)
	Alive/status unknown	12 (5.7)

Discussion

This was one of the biggest review of HCC in Malaysia that contributed to the gap of knowledge about the trend and distribution of HCC in Asian countries. The trend of HCC in USM hospital from 1987-2008 was increasing annually which might reflect the increasing incidence of HBV. Nearly 70% of our cases were in age group of 50 years and above. The incidence of HCC was higher in men than women, which was similar as in other study (Bosch et al., 2004). The male:female ratio in our study was 3.7:1 compared to those reported in Europe (Deuffic et al., 1998) and China (Zhou et al., 2000); with higher ratio 7-8.8:1 and in Pakistan 3.2:1 (Yusof et al., 2007). This was partly explained by the sex-specific prevalence of the risk factors.

Our study demonstrated that among HCC, 57.6% had HBV, 2.4% HCV, 20% liver cirrhosis and 8.1% chronic liver disease. A large study in China reported that 54.8% had a history of hepatitis and 78.2% liver cirrhosis (Zhou et al., 2000), and while in Pakistan the percentage with HCV and HBV were 43.5% and 19.5%, respectively (Yusof et al., 2007). The majority of HCC cases in Spain had an underlying liver disease consisted of liver cirrhosis in 88.2% and chronic active hepatitis in 3.9% (Sangro et al., 1998). The attributable risk for HCC in Asia was 60% for hepatitis B and 20% for hepatitis C (Bosch et al., 2004). Alcohol as a risk factor for HCC was not prominent in our study because most of the subjects' were Muslim, which alcohol was forbidden.

The clinical presentation of HCC in our study had a similar pattern as elsewhere. In the most cases, this cancer was diagnosed in the late stage because of non-specific common symptoms such as abdominal pain, unexplained fever, unexplained weight loss, nausea and lethargy. The percentage of common symptoms were high in our study (57.6% had abdominal pain, 32.9% jaundice, 54.3% anorexia, 49.5% weight loss) reflecting of advance disease. These was compared to a study in Italy with 32% of HCC had abdominal pain, 8% jaundice, 6% anorexia, 4% weight loss (Trevisani et al., 1996). The early symptoms of HCC are usually vague and not specific to liver disease and there is a long lag time between the beginning of tumour growth and signs of disease (Groen, 1999). Furthermore, there was no screening program to detect HCC early in Malaysian population. In China, there was 6 monthly AFP and ultrasound screening for high risk population, which include history of hepatitis, liver cirrhosis and hepatitis B positive (Zhou et al., 2000). Only 47.9% of our cases had AFP above 800 IU/ml, compared to a study in China where 72.1% of cases had AFP above 20ng/ml (Zhou et al., 2000). The majority of our HCC cases were diagnosed in stage 3A, compared to the Malaysia Cancer Registry which 62% of HCC presented in stage 4 of disease (Zainal and Nor Saleha, 2011). While, the majority of HCC diagnosed in stage II in China (Zhou et al., 2000).

The main treatments for HCC were hepatic resection, transcatheter arterial embolization, percutaneous ethanol injection therapy and regional chemotherapy (Takano et al 2000). There are many optional treatments available if HCC was diagnosed early. Unfortunately, many of our patients presented late, with some up to 2 years and had taken traditional medication prior coming to hospital. Most of HCC patients in our institution did not receive any treatment. Studies reported that no treatment was 84.5% in Pakistan (Yusof et al., 2007), 73% in Netherland (Verhoey et al., 2004) and 30.5% in China (Zhou et al., 2000).

Liver transplant is the best treatment for the liver cancer with the 5-year survival rate was 70-75% (Hasegawa et al., 2009). There were 66.6% of HCC in China had liver resection (Zhou et al., 2000). In our study, there were only eight patients who had liver resection and chemo- or radio-embolism was not practiced in our hospital due to lacking facilities and expertise. A randomised controlled trial of unresectable hepatocellular carcinoma showed chemoembolisation had significant survival benefits compared with conservative treatment (Llovet et al., 2002).

The overall median survival time of HCC in our study was 1.9 months, which was similar with a study in Japan in 1985 (Okuda et al., 1985), which reported 1.6 months survival among those who received no specific treatment. However, studiesin Pakistan and Spain reported median survival of HCC were about 10 months (Sangroet al., 1998, Yusof et al., 2007). The survival of HCC has been improving since then with the latest technology of treatment.

The 1-year survival rate of our study was lower compared to other studies (Sangro et al., 1998; Bruix and Llovet, 2002) which might be due to 83% of our patients received no treatment at all. The survival rates at 1- and 3-year of HCC in Spain were 38% and 23%, respectively (Sangro et al., 1998). The 1-year survival rate was 70% China (Zhou et al., 2000) and 45% in Pakistan (Yusof et al., 2007). A study in Taiwan discovered that the overall 3-, 5- and 10-year survival rates for HCC were decreasing from 59.0%, 46.4%, and 27.7%, respectively (Soong et

al., 2011).

The survival rate of HCC patients was affected by the treatment modalities. In East Asian region, the 5-year survival was 35% in surgically treated patients and 10% for non resectable tumor (Teoand Fock, 2001). A study reported the 1-year survival for those who received chemotherapy or no specific therapy was 13% (Sangro et al., 1998) which was similar with our study. The highest survival was among those with liver transplant with 81%, followed by hepatectomy 72%. HBV-related HCC has poor median survival less than 16 months. Survival rates of HBV-related HCC ranged from 36% to 67% after 1 year and from 15% to 26% after 5 year of diagnosis (Nguyen et al., 2009).

Our study showed that the significant prognostic factors for HCC in our institution were ethnicity, treatment and tumour classification. The population-based Netherlands Cancer Registry reported that the 5-year survival rate was higher among HCC cases with stage I/II/III compared to stage IV and surgically treated compared to not treated (Verhoeferet al., 2004). Child-Pugh classification system was a significant prognostic factor in our study but TNM system was not, as supported by Yusof et al. (2007).

There many limitations of our study. Many known risk factors were not recorded, some investigative tests were not done and there was no uniformity of reporting data. A prospective study is not possible in this disease due to the low risk of disease. Risk factors such as hemochromatosis, Wilson's disease, alpha-1 antitrypsin deficiency and autoimmune liver disease were not investigated. Not many patients had surgery or biopsy thus the histo-pathological examination was not possible.

In conclusion, HCC in our study affected a wide age range, mostly male, in advanced stage of disease, had no treatment and very low survival rates. HCC is preventable by modifying its risk factors. Primary prevention should be advocated in view of late presentation and difficulty of treatment. Vaccination of hepatitis virus and avoidance of liver toxin from food and drugs are encouraged. A screening process may help in identify HCC in early stage and better survival through the treatment.

References

Befeler AS, Di Bisceglie AM (2002). Hepatoellular carcinoma: diagnosis and treatment. *Gastroenterol*, **122**, 1609-19.

Bosch FX, Ribes J, Diaz M, Cleries R (2004). Primary liver cancer: worldwide incidence and trends. *Gatroenterol*, **127**, 5-16.

Bruix J, Llovet JM (2002). Prognostic prediction and treatment strategy in hepatocellular carcinoma. *Hepatol*, **35**, 519-24.

Bruix J, Sherman M, Llovet JM, et al (2001). Clinical management of hepatocellular carcinoma.Conclusions of the Barcelona-2000 EASL Conference. *J Hepatol*, **35**, 421-30.

Chen CJ, Yu MW, Liaw YF (1997). Epidemiological characteristics and risk factors of hepatocellular carcinoma. *J Gastroenterol Hepatol*, **12**, 294-308.

Deuffic S, Poynard T, Buffat L, Valleron AJ (1998). Trends in primary liver cancer. *Lancet*, **351**, 214-5.

El-Serag H, Rudolf L (2007). Reviews in basic and clinical gastroenterology. *Gastroenterol*, **132**, 2557-76.

El-Serag HB, Davila JA, Petersen NJ, McGlynn KA (2003). The continuing increase in the incidence of hepatocellular carcinoma in the United States: an update. *Ann Intern Med*, **139**, 817-23.

Gao J, Xie L, Yang WS, et al (2012). Risk factors of hepatocellular carcinoma - current status and perspectives. *Asian Pac J Cancer Prev*, **13**, 743-52.

Groen KA (1999). Primary and metastatic liver cancer. *Sem Oncol Nurs*, **15**, 48-57.

Hasegawa K, Kokudo N (2009). Surgical treatment of hepatocellular carcinoma. *Surg Today*, **39**, 833-43.

Kansa-ard S, Wiangnon S, Suwanrungruang K, et al (2011). Trends in liver cancer incidence between 1985 and 2009, Khon Kaen, Thailand: cholagiocarcinoma. *Asian Pac J Cancer Prev*, **12**, 2209-13.

Llovet JM, Real MI, Montaña X, et al (2002). Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. *Lancet*, **359**, 1734-9.

Nguyen VTT, Law MG, Dore GJ (2009). Hepatitis B-related hepatocellular carcinoma: epidemiological characteristics and disease burden. *J Virus Hepatitis*, **16**, 453-63.

Nordenstedt H, White DL, El-Serag HB (2010).The changing pattern of epidemiology in hepatocellular carcinoma. *Dig Liver Dis*, **42**, 206-14.

Okuda K, Ohtsuki T, Obata H, et al (1985). Natural history of hepatocellular carcinoma and prognosis in relation to treatment study of 850 patients. *Cancer*, **56**, 918-28.

Sangro B, Herráiz M, Martínez-González MA, et al (1998). Prognosis of hepatocellular carcinoma in relation to treatment: a multivariate analysis of 178 patients from a single European institution. *Surg*, **124**, 575-83.

Siegel R, Ward E, Brawley O, Jemal A (2011). Cancer statistics, 2011. The impact of eliminating socioeconomic and racial disparities on premature cancer deaths. *CA Cancer J Clin*, **61**, 212-36.

Soong RS, Yu MC, Chan KM, et al (2011). Analysis of the recurrence risk factors for the patients with hepatocellular carcinoma meeting University of California San Francisco criteria after curative hepatectomy. *World J Surg Oncol*, **9**, 9.

Srivatanakul P, Sriplung H, Deerasamee S (2004). Epidemiology of liver cancer: an overview. *Asian Pac J Cancer Prev*, **5**, 118-25.

Takano S, Watanabe Y, Ohishi H, et al (2000). Multinodality treatment for patients with hepatocellular carcinoma: a single institution retrospective series. *Eur J Surg Oncol*, **26**, 67-72.

Teo EK, Fock KM (2001). Hepatocellular carcinoma: an Asian perspective. *Dig Dis*, **19**, 263-8.

Trevisani F, D'Intino PE, Grazi GL, et al (1996). Clinical and pathologic features of hepatocellular carcinoma in young and olderItalian patients. *Cancer*, **77**, 2223-32.

Verhoef V, Visser O, de Man RA, et al (2004). Hepatocellular carcinoma in the Netherlands incidence, treatment and survival patterns. *Eur J Cancer*, **40**, 1530-8.

Wong R, Corley DA (2008). Racial and ethnic variations in hepatocellular carcinoma incidence within the United States. *Am J Med*, **121**, 525-31.

Yusuf MA, Badar F, Meerza F, et al (2007). Survival from hepatocellular carcinoma at a cancer hospital in Pakistan. *Asian Pac J Cancer Prev*, **8**, 272-4.

Zainal AO, Nor Saleha IT (2011). National Cancer Registry Report. Malaysia Cancer Statistics- Data and Figure 2007. National Cancer Registry, Ministry of Health Malaysia: Kuala Lumpur.

Zhou XD, Tang ZY, Yang BH, Zhang BH (2000). Hepatocellular carcinoma: the role of screening. *Asian Pac J Cancer Prev*, **1**, 121-6.