TEN YEARS REVIEW OF HEPATOCELLULAR CARCINOMA IN HOSPITAL UNIVERSITI SAINS MALAYSIA (1996-2005)

By

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II. ABSTRACT

Hepatocellular carcinoma (HCC) is the most common primary malignancy of the liver and one of the most common causes of death from cancer. Local literature on HCC are rather scare and hence the need for a study of this nature.

One hundred eight (108) patients were diagnosed of HCC in a period of ten years from 1996 to 2005 at Hospital Universiti Sains Malaysia were studied to determine the pattern of the disease and to highlight the clinical presentation, common risk factors, mode of investigation, stage at presentation, modalities offered for treatment and the survival rate.

The mean age of occurrence was 57.9 ± 11.5 years. Male to female ratio was 3:1 and predominantly affecting the Malays (83.3%). Hepatitis B was the main risk factor for HCC in 68(63%), where as Hepatitis C was positive in 9(8.3%). The clinical presentations included abdominal discomfort in 98(90.7%), abdominal pain in 55(50.9%), abdominal distension in 68(62.7%), loss of weight in 62(57.4%), stigmata of chronic liver disease in 51(47.2%) and jaundice in 52(48.1%) patients. Solitary type of lesion in 30(72.2%) and multiple type in 78(72.2%) patients. The largest diameter varied from <5cm in 33(30.5%), 5-10cm in 66(61.1%) to >10 cm in 9(8.3%) patients. Portal vein thrombosis presented in 59(54.6%) and 27(25%) already with distant metastases.

Severity of liver impairement as assesed by Child Pugh Classification, 39(36.1%) presented with Child's A, 40(37%) with Child's B and 29(26.9%) with Child's C. Tumor grading by TNM staging showed patients presented with unresectable tumor due to locally advanced stage were 66(61.1%) and advanced stage 32(29.6%). Where as 10(9.3%) of patients at resectable stage of tumor. Most patients 77(71.3%) given supportive treatment. Anti tumour agent only given to 4(3.7%) patients and 1(0.9%) patient underwent emergency surgical resection. Death mainly related to HCC, account for 82.4%(89). Overall mean survival was 5.2 months. Statistically showed that sex, location of tumour, Child Pugh Classification, Okuda staging and mode of treatment were related with the survival in this study.

In conclusion, most hepatocellular carcinoma cases admitted to HUSM presented in advanced stage put them unsuitable for surgical resection or anti tumour treatments modalities. More effort should be taken to detect early stage of HCC so that curative treatment can be aimed to prolong the survival rate.

III. ABSTRAK

Kanser sel hati adalah merupakan jenis kanser yang paling kerap berasal dari hati dan antara penyebab utama kematian yang berkaitan kanser . Pada masa kini, kajian tempatan masih terhadap kanser ini. Oleh itu, suatu kajian perihal kanser sel hati amatlah perlu.

Seratus lapan orang pesakit kanser sel hati yang dirawat sepanjang tempoh sepuluh tahun dari tahun 1996 hingga 2005 di Hospital Universiti Sains Malaysia telah dikaji selidik. Kajian ini melibatkan tanda-tanda klinikal/simptom pesakit, faktor-faktor penyebab barah, kaedah penyiasatan, tahap penyakit, kaedah rawatan dan kadar jangkahayat pesakit.

Hasil kajian mendapati umur purata pesakit adalah 57.9 $\pm$ 11.5 tahun. Nisbah pesakit lelaki kepada wanita adalah 3 : 1. Kaum Melayu meliputi 83.3 %. Hepatitis B dikesan pada 68(63%) pesakit manakala hepatitis C pada 9(8.3%) pesakit. Tanda-tanda klinikal meliputi ketidakselesaan perut 98(90.76%), kasakitan pada perut 55(50.95%), kehilangan berat badan 62(57.45%), tanda-tanda penyakit hati kronik 51(47.25%) dan kekuningan pada 52(48.1%) pesakit. Kanser jenis 'solitary' dikesan pada 30(72.2%) pesakit dan jenis 'multiple' pada 78(72.2%) pesakit. Kepelbagaian saiz kanser adalah dari < 5cm dalam 33(30.5%), 5-10cm 66(61.1%) dan >10cm dalam 9(8.3%) pesakit. Penyumbatan vena portal dikesan pada 59(54.6%) pesakit dan didapati 27(25%) pesakit, kanser telah merebak ke bahagian organ lain.

Klasifikasi 'Child Pugh' digunakan untuk menentukan tahap kerosakan hati, dimana 39(36.1%) pesakit pada peringkat 'Child A', 40(37%) peringkat 'Child B'dan 29(26.9%) peringkat 'Child C'. Tahap keterukan kanser melalui 'TNM staging' menunjukan peringkat kanser yang merebak di sekitar hati adalah seramai 66(61.1%) dan peringkat yang sudah merebak ke organ lain seramai 32(29.6%). Manakala 10(9.3%) pesakit adalah peringkat kanser yang belum merebak dan masih boleh dibedah. Kebanyakan pesakit 77(71.3%) hanya diberikan rawatan sokongan, 4(3.7%) menerima rawatan anti kanser dan 1(0.9%) pesakit menjalani pembedahan kecemasan untuk membuang kanser. Kematian kebanyakannya 89(82.4%) adalah berkaitan dengan kanser, dimana purata jangkahayat pesakit adalah 5.2 bulan. Secara statistiknya menunjukkan jantina, lokasi kanser, klasifikasi 'Child Pugh', 'OKUDA staging' dan jenis rawatan yang diberikan mempunyai kaitan dengan jangkahayat pesakit.

Kesimpulanya, kebanyakan kes-kes kanser sel hati yang dirawat di HUSM adalah pada peringkat yang teruk, dimana tiada rawatan pembedahan ataupun ubat rawatan barah yang dapat diberikan. Usaha patut dilakukan untuk mengesan barah sel hati pada peringkat awal supaya rawatan yang berkesan dapat diberikan untuk meningkatkan jangka hayat pesakit.

IV. TABLE OF CONTENT

V. LIST OF TABLES.

VI. LIST OF FIGURES.

VII. ABBREVIATIONS.

AFP	Alpha Fetoprotein
Cm	Centimeter
CT	Computed Tomography
FNAC	Fine Needle Aspiration Cytology
GIT	Gastrointestinal tract
HCC	Hepatocellular Carcinoma
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HUSM	Hospital Universiti Sains Malaysia
IGC	Indocyanine Green
USA	United State of America
US	Ultrasound

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1 INTRODUCTION

Hepatocellular carcinoma (HCC) comprises more than 90% of all primary liver cancers. It ranks 5th in frequency among all malignancies worldwide, causing nearly a million annual deaths.[1] HCC has a heterogeneous geographic distribution with greatest incidence in Asia and Sub-Saharan Africa, where hepatitis B is endemic [2]. Cirrhosis whatever the cause is a dominant risk factor for HCC [3]. However, HCC often develops in patients with chronic hepatitis B infection in the absence of cirrhosis in Asian countries where infection most commonly occurs during early life [4].

According to the Malaysian Cancer Registry 2002, HCC ranked 12th in men and 18th in women. The rate for liver cancer in that registry was 4.2 per 100,000 population. It was emphasized that there was definite under reporting of this cancer for all age groups. Lack of histological confirmation was believed to contribute to the under reporting. It cautioned the reader that the registration figures for HCC is incomplete and the statistics are lower than the true incidence in the population [5].

According to the Wikipedia Free Encyclopedia web site of "List of Countries by Population- 2005"; the population of Kelantan State was given as 1.4×10^6 people [6].

In the Malaysian Cancer Registry 2002 report, the incidence of liver cancer were 4.2 in males, 1.5 in females and 2.9 in both per 100,000 population. Taking 2.9 per 100,000 incidence of HCC, the expected HCC in Kelantan state would be approximately 41 per year. That would come to an expected 410 patients with HCC in a 10-year period. The records of HUSM yielded 131 cases with diagnosis of HCC during 1995 – 2005. This averages to 13 cases a year which is only (1/3 of expected).

It is known that 80% of HCCs at presentation have advanced disease and based on the number, size and location of lesions and severity of underlying cirrhosis, are not candidates for transplantation, surgical resection or liver directed therapies [7].

In the decade under consideration little is known about the HCC cases that were managed in HUSM regarding the following:

1. Age, sex and ethnic distribution
2. Associated risk factors
3. Clinical presentation
4. Investigations done for diagnosis
5. Clinical staging of the cases at presentation, was it applied at all?
6. The treatments offered; curative, palliative, symptomatic?
7. Was treatment in accordance to the clinical staging of the cancer?
8. The outcome of treatment and the survival rate

It is hoped that by shedding light on such basic raw clinical data of the disease, it may become possible to optimize the management of HCC from clinical, diagnostic laboratory, imaging investigations and treatment aspects in the future. When the National resolve towards Transplantation including the liver, is at it's height, future management of HCC might contribute to the success of the liver transplant program also. Should some important risk factor e.g. hepatitis B or C be shown to be important the study might point out the need for a screening program and other preventive measures to alleviate the incidence and suffering from this dreaded cancer.

2 LITERATURE REVIEW

2.1 INTRODUCTION

Liver cancer is the sixth most common cancer worldwide in terms of numbers of cases (626,000 or 5.7% of new cancer cases) but because of the very poor prognosis, the number of deaths is almost the same (598,000). It is therefore the third most common cause of death from cancer. Survival rates are 3% to 5% in cancer registries from the United States and developing countries. 82% of cases (and deaths) are in developing countries, (55% in China alone).

2.2 INCIDENCES

The areas of high incidence are sub-Saharan Africa, eastern and Southeastern Asia. The incidence is low in developed areas, Latin America, and South-Central Asia (only in southern Europe is there any substantial risk). The overall sex ratio (male: female) is around 2.4, much greater in the high-risk areas and less in low-risk areas. The burden of HCC is irregularly distributed in the world, for the most part following the prevalence of the hepatitis B virus. Of the estimated 350 000 new cases per year, one-third occurred in China and another third elsewhere in Asia. There are about 30 000 cases per year in Europe and 23 000 in Japan. The USA has about 7000 cases per year and there are at least six times that number in Africa. Men are afflicted at least twice as often as women are. Although HCC ranks eighth in frequency among cancers worldwide, it is sixth among men and eleventh among women. Crude incidence rates do not tell the whole story, and a case can be made that HCC in different places is a different disease, primarily depending upon poorly defined host factors and the age when hepatitis virus

was acquired. In Chinese men, age-specific rates show a peak in the 50's in Qoidong Province and in the late 70's in Shanghai. Africans get HCC earlier than Japanese do. The highest recorded rate of HCC in the USA occurs among ethnic Chinese in Los Angeles, a rate lower than that of indigenous Chinese. Studies of emigrants from areas of high incidence of HCC to areas of low incidence have shown that it may take generations for cancer rates to fall.

2.3 RISK FACTORS

Worldwide, the major risk factors for liver cancer are infection with the hepatitis B and C viruses, both of which increase the risk of liver cancer some 20-fold. Because hepatitis B virus (HBV) is more prevalent, the distribution of infection worldwide largely explains the patterns of liver cancer. The exception is Japan, where chronic infection with HBV is low, but where the generations most at risk of liver cancer have a relatively high rate of infection with hepatitis C virus (HCV). More than 75% of cases worldwide, and 85% of cases in developing countries, are caused by these two viruses. Exposure to aflatoxins is probably also an important contributor to the high incidence of liver cancer in those tropical areas of the world where contamination of food grains with the fungus Aspergillus fumigatus is common. There is a multiplicative interaction between aflatoxin exposure and chronic HBV infection, suggesting different carcinogenic mechanisms [8].

More than 80% of patients with HCC have cirrhosis. HCC is unusual in patients with primary biliary cirrhosis but common when the cirrhosis is secondary to chronic viral hepatitis. Untreated genetic haemochromatosis is an especially severe premalignant state. The risk of death from HCC in patients with haemochromatosis has been as high

as 45% in some series. Iron depletion, if done before the onset of cirrhosis, reduces the incidence of HCC, but if cirrhosis has already developed, the risk of HCC persists despite iron depletion.

Chronic infection with HBV is a strong risk factor for HCC. The epidemiological evidence for this is very convincing. In a prospective study of over 20 000 men in Taiwan, the risk ratio for HCC was greater than 100 for those who were HBsAg positive at the start of the study. The age of acquisition of HBV plays an important part in the eventual development of cancer. Infants and young children exposed to HBV have a much greater chance of becoming chronic carriers than newly infected adults do; and adults who experience acute HBV infection and recovery have little if any increased risk of HCC. The relation between HCC and chronic infection by HBV is reinforced by animal models. Peking ducks, ground squirrels, and woodchucks are infected with species-specific HEPADNA viruses. This virus family demonstrates homology not only in genomic structures and tissue tropism but also in the ability to cause chronic infection and liver cancer, albeit at rates (for cancer) that are much lower than those seen in men. This homology does not extend to the HEPADNA virus X gene. HBV possesses this gene, as do the woodchuck and ground squirrel viruses. The Peking duck virus does not, and, unlike the other two animal models and man, these ducks do not develop HCC.

Not long after the discovery of HBV and its epidemiological association with HCC, unsettling reports appeared from Japan. While the rate of HCC in Japanese males was increasing, the proportion of cases related to HBV was falling. The discovery of hepatitis C virus and its associated antibodies provided the tools to demonstrate that while deaths from HBV-related HCC were constant in Japan from 1975 to 1992, death rates from HCV related HCC more than tripled. Studies with newer and more sensitive tests are still in progress but up to half of all cases of HCC in the USA may be due to

HCV. However, HCV, unlike HBV, does not integrate into host DNA so the mechanism of hepatic carcinogenesis is likely to be different for the two viruses. The transforming potential of the NS3 region of HCV (helicase and protease proteins) and the HCV core protein may have a role here. Chronic infection with hepatitis C appears to increase the risk of HCC at about the same rate as chronic HBV infection does. The cancers almost always occur in cirrhotic livers. No one genotype of HCV is more oncogenic than any other but significant geographical variability in the risk of HCC from HCV makes continued research into host factors a priority. Treating chronic type C hepatitis with interferon decreases the risk of HCC, if the patient responds to this therapy. Alcohol-related cirrhosis constitutes a major risk factor for HCC in the USA and in other places where the incidence of chronic viral hepatitis is low. About 15% of American cases are in patients presumed to have alcohol related cirrhosis. A high percentage of individuals with cirrhosis and a history of alcohol abuse are also positive for HCV. The combination of heavy alcohol use and chronic infection with HCV increases the risk of HCC beyond that due to either risk factor alone. Aflatoxins have long been suspected as an environmental contaminant important in the oncogenesis of HCC [9].

2.4 CLINICAL PRESENTATION

HCC presents in three principal ways; a right-upper quadrant mass , a worsening of the general health of a patient with cirrhosis, or asymptomatically as a result of a radiological examination. When HCC presents as a mass (as it commonly does in sub-Saharan Africa), abdominal pain, malaise, and inanition are frequent accompanying signs and symptoms. Because the tumour is not constrained by a deeply fibrotic liver it commonly grows very large. HCCs which infiltrate a cirrhotic liver often severely compromise already impaired hepatic function. They may do this by replacing

functioning hepatic mass, by causing portal or hepatic vein thrombosis, or by compression of intrahepatic vasculature. HCCs in densely cirrhotic livers (as in most Japanese and American cases) thus cause death before the tumour becomes very large. Liver weights at necropsy of African patients average twice those of Japanese patients who die from HCC [10].

2.5 DIAGNOSIS

2.5.1 Tumour Markers

Although a number of tumour markers have been used to aid the management of patients with HCC, α-fetoprotein (AFP) is the only established marker for clinical application. Using the radioimmunoassay technique, an elevated AFP level is usually found in tumours of 5 cm or more in diameter. A level of 400 ng/dl is considered diagnostic, and a level between 20 and 400 ng/dl can be found in various forms of liver disease and other malignancies. Among patients with small HCCs of less than 5 cm, serial change of the AFP level is more informative than the absolute titer itself. Indeed, any continuous elevation of the AFP titer even if below the diagnostic range in patients with chronic liver disease might indicate an occult HCC, and this can be excluded by appropriate investigations. The use of AFP assay is also useful in monitoring the progress of patients after complete macroscopic extirpation of the tumour. As normal liver regeneration does not induce AFP synthesis, a persistent elevated titer above the normal range in the postoperative period suggests residual disease. Furthermore, a steady rise of the AFP titer after initial normalization should raise the possibility of recurrent disease. Besides diagnosis, the serum AFP level may also have a prognostic significance. A correlation between the serum AFP titer at presentation and the duration of survival had been demonstrated in patients who have had various modes of treatment,

including surgery. A similar correlation exists between serum AFP, survival and tumour size. The general consensus is that patients with a markedly elevated preoperative titer have a worse survival after surgery irrespective of the different cut-off levels chosen for analysis [11].

2.5.2 Ultrasonography

Real-time ultrasound examination of the liver is noninvasive and, in experienced hands, highly accurate in the detection of HCC. The echogenic pattern of the lesion varies with the size of the tumour. While all large tumours are usually hyperechoic, the echogenic pattern of early HCCs up to 1–2 cm in diameter is hypoechoic with weak internal echoes, these become isoechoic and finally hyperechoic as they grow to 3 cm or more. ***As a single test for screening, percutaneous ultrasound is perhaps a more sensitive means for early cancer detection than serum AFP assay.*** On the other hand, as false-positive results are frequently found by ultrasound examination alone, the addition of AFP measurement is recommended to enhance the diagnostic accuracy. Based on the doubling time of the tumour, repeated examination using a combination of percutaneous ultrasonography and serum AFP assay at 4–5 months intervals is adequate for early cancer diagnosis. A reasonable assessment of the resectability of the lesion can be made by percutaneous ultrasonography. After localization and measurement of the size of the lesion, patency of the portal and, the hepatic venous system is determined. The extent of liver resection required for macroscopic tumour clearance is judged by the distance between the edge of the lesion and the closest hepatic vein. The size of the proposed hepatic remnant, evidence of concomitant cirrhosis such as the presence of ascites, and splenomegaly can also be determined with fair accuracy [12-15].

2.5.3 Computed Tomography

CT is useful in the localization of HCC. Conventional examination should be performed with intravenous contrast medium as tumours might only be visualized on the pre- or post-contrast radiographs. False-negative results are possible, especially with isodense lesions or very small tumours. When Lipiodol is injected into the hepatic artery, the lipid lymphographic agent is selectively retained in HCC and some secondary liver cancers, which probably relates to the architectural structure of the tumour together with the enhanced permeability and sluggish flow inside its well-developed neovasculature. The timing of CT examination should be scheduled at about 2 weeks after Lipiodol injection. The majority of HCCs have a homogeneous or dense, patchy uptake of Lipiodol. In a series of 34 patients in Hong Kong, the overall sensitivity, specificity and accuracy of Lipiodol CT examination for HCC were 97, 77 and 88%, respectively. The combination of hepatic arteriography and Lipiodol CT is perhaps the most sensitive diagnostic test for HCC [16-18].

2.5.4 Arteriography

Hepatic arteriography is an important modality in the management of patients with HCC. Knowledge of the hepatic vascular anatomy is helpful when a major liver resection is planned. The characteristic features of large HCCs (> 5 cm) include increased neoplastic arterial blood supply, vascular lakes and channels, and arterioportal shunts. During the venous phase of superior mesenteric arteriography, the patency of

the portal venous system can also be determined. Although a combination of imaging studies will lead to the diagnosis, arteriography seems to be most specific and sensitive. However, when small HCC are considered, localized stains in the capillary phase might be the only angiographic feature present. Even using special techniques such as infusion hepatic angiography, the diagnosis can still be difficult as some large regenerative nodules have similar radiological characteristics. About 18% of small HCC are angiographically undetectable. These small HCC are usually well-differentiated tumors without tumor capsules [19-21].

2.5.5 Liver Function Tests

The high incidence of concomitant cirrhosis among Asian patients suffering from HCC has made a thorough evaluation of liver function essential in the assessment of resectability. Cirrhotic patients exhibit impaired liver regeneration and are at increased risk for posthepatectomy liver failure. Despite efforts to evaluate hepatic reserve, the results serve only as a guide for patient selection. As the liver has many and varied functions, no single test provides a complete reflection of its functional reserve. ***The risk of posthepatectomy liver failure is still unpredictable even when the results of preoperative evaluation of liver function are satisfactory.*** Routine laboratory tests which include serum total bilirubin, serum albumin and prothrombin time allow the identification of advanced cirrhotic patients. The bromsulphthalein retention test has been used in the past and patients with a retention of over 30% at 45 minutes excluded from major liver resection. This test has been replaced by indocyanine green (ICG) clearance measurements in many parts of Japan and in Hong Kong. The significance of the maximal clearance rate of ICG (ICG-R_{max}) was introduced in the 1970s. A suitable

surgical candidate should have a maximal rate of more than 0.4 mg/(kg min). In addition to ICG-Rmax, the retention rate of ICG has also been used. A normal value at 15 minutes after an intravenous bolus injection of 0.5 mg/kg of ICG should be less than 15%. The predictive value of both parameters has been substantiated by multivariate analysis. Information on the volume of the hepatic remnant measured by CT may enhance the accuracy of assessment. When a combination of the ICG retention rate at 15 minutes and the 'parenchymal hepatic resection rate' (which represent the proportion of non-tumorous functional liver tissue resected together with the tumour) are used, a reasonably satisfactory prediction of the outcome after liver resection has been claimed. Refinement of the concept includes the use of scintigraphy to document the 'effective liver volume' state [22-25].

2.5.6 Other Investigations

Information gathered at splenic venoportography has been replaced by the venous phase of the superior mesenteric arteriogram or by a contrast enhanced CT scan. An inferior vena cavogram is rarely indicated. Even when the vessel is distorted by the lesion, the inferior vena cava is usually compressed without any direct infiltration. At the Queen Mary Hospital, Hong Kong, laparoscopy has in the past been a routine examination for all patients before an exploratory laparotomy. Detection of small tumour nodules in the contralateral lobe, visual assessment of the type and severity of the concomitant cirrhosis and the volume of the hepatic remnant and, occasionally, guidance of percutaneous biopsy could be accomplished with a low procedure-related morbidity and mortality. In contrast to exploratory laparotomy, which carries a mortality rate of up to 42%, the corresponding figure for laparoscopy is only between