REVIEW ARTICLE

Screening for Hepatocellular Carcinoma

I Merican, FRCP, Department of Medicine, Hospital Kuala Lumpur, 50586 Kuala Lumpur

Summary

Hepatocellular carcinoma (HCC) is one of the commonest cancers in Asian males. In Malaysia, it is one of the ten most common cancers amongst the male population[2]. Most of our patients with HCC present to us rather late and almost all die within 4 months of diagnosis. HCC occurs more commonly in patients with cirrhosis associated with hepatitis B and C infections. Screening for HCC can lead to early detection of small tumours (< 5 cm) that are more amenable to surgical resection, resulting in improved survival rates. The average 5-year survival rate for those who have undergone surgical resection is 68% (range, 22-73%). Better results are obtained with the smaller tumours (< 2 cm in diameter). Patients with chronic hepatitis B and C infection especially those who are > 45 years of age, who have concomitant cirrhosis or have a family history of HCC should be examined every 3-6 months with periodic serum alpha-fetoprotein (AFP) measurements and abdominal ultrasound examinations. Abdominal ultrasound is useful in the detection of small tumours. While mass screening for HCC is not cost-effective in countries of low incidence of HCC, screening of high risk groups may be justified in countries with a high endemicity of HBV infection. Screening for HCC in Japan, Taiwan and China appears to yield better results than those in the West. Nonetheless, primary prevention with mass hepatitis B vaccination and blood donor screening for anti-HCV is expected to make a much greater impact in the control of HCC in the years to come.

Key Words: Hepatocellular carcinoma, Hepatoma, Screening, Early detection

Introduction

Hepatocellular carcinoma (HCC), a highly malignant tumour with a very poor prognosis, is one of the most common cancers in Asian males. About one million cases are estimated to occur worldwide every year[1]. Based on available data (unpublished) from the Institute of Radiotherapy and Oncology in Hospital Kuala Lumpur, HCC ranks 9th amongst the ten most common cancers in Malaysia. Data obtained from a study conducted in the West Coast States of Peninsular Malaysia between the years 1988 and 1990[2] indicated that HCC was the eighth most common cause of cancer amongst the males with a recorded ASR (Age-standardized rate per 100,000 population per year) of 2.2. This figure may however be a gross underestimate of the true incidence in this country. In Singapore HCC was the fourth commonest cause of cancer amongst Singapore men with an ASR of 23.4 between the years 1983 and 1987. The majority of cases of HCC in this region occur amongst chronic HBV carriers. The prevalence rate of HBV carriers in both countries may therefore indicate the actual number of people at risk of getting HCC. The HBV carrier rate in Singapore is 5-6% and that in Malaysia is probably higher[3].

The actual incidence of HCC in this country is not known because we do not have at present, a National Cancer Registry. We do know, however, that by the time patients with HCC present to us, they are already symptomatic or have HCC that is already too far advanced for any meaningful treatment to be instituted. Patients with symptomatic HCC have a mean survival time of less than 4 months and have tumours which are unresectable mainly because of extensive involvement of the liver, invasion of the hepatic or portal veins, metastases or advanced hepatocellular disease. There have been encouraging

reports in the literature of improved survival in patients who had undergone resection for small tumours detected at an early asymptomatic stage[4]. Several countries especially those in the Far East have embarked on screening for HCC over the last 10 years to detect small (< 2-3 cm in size), asymptomatic tumours for surgical resection and have reported improved survival rates. Malaysia should seriously consider embarking on a nationwide screening programme in patients who at risk in order to detect small HCC early.

Criteria for screening

Certain criteria need to be fulfilled before one embarks on screening. Firstly, one has to ascertain whether there is a recognisable early stage for the disease and if so, whether treatment at this stage would be more beneficial than that given at a later stage. Secondly, there must be a suitable and acceptable test that can be done to detect such early cases. Thirdly, adequate facilities for diagnosis and treatment must be made available. Selection of target groups to be screened and the frequency of screening must be made clear. Finally, the cost-benefit ratio of such an exercise must be given serious consideration. Using this criteria, screening for HCC appears worthwhile because persons at high risk can already be identified and tests to detect early tumours are now available. However there are still questions regarding the cost-effectiveness and the value of screening as not all studies have produced consistent results regarding its effectiveness in improving survival.

Natural history of HCC

The natural history of HCC appears to vary in different parts of the world. It tends to run a more aggressive course in Subsaharan African Blacks compared to the Orientals[5,6]. An asymptomatic stage lasting 2 years or more has also been reported and early detection of such cases for surgical resection may lead to prolonged survival[7,8]. The disease has several characteristics that allow for early diagnosis. It has for instance a fairly predictable doubling time of 1-14 months (mean, 4 months)[9]. However it is also known that the growth rates of HCC may vary even within the same patient. Periodic measurement for AFP and Ultrasound examination are currently the recommended screening methods for the detection of HCC at the early asymptomatic stage in high-risk individuals[10-12].

The mean survival time of patients with untreated HCC is two years[13]. More patients are surviving longer in recent times because of the aggressive screening of high-risk patients. Small tumours which are detected at an early stage doing such screening can be offered limited surgical resection. The average 5-year rate for such patients is 68% (range, 22-73%)[14]. Table I shows the results of resection from various studies. It is worthwhile noting that all these reports were confined to Asian patients. The Shanghai group had 100% 5-year survival rate for patients with tumours < 2 cm in diameter and a 10-year survival rate of almost 50%. These impressive results unfortunately have not been repeated by other workers. Patients found to have unresectable tumours via screening can still benefit from other therapeutic options which have been shown to decrease early morbidity although not mortality. Such options include intratumour injection of ethanol, lipoidal targetted chemotherapy and transcatheter arterial embolisation (TAE).

Table I
Survival after resection of small hepatocellular carcinoma

Authors	Survival (%)					
	n	1 year	2 year	4 year	5 year	10 year
Tang *et al*[15]	66	79.1	67.8	55.5		
Kanematsu *et al*[16]	32	85.0	70.0		22.0	
Yu Y-Q *et al*[17]	250				66.3*	48.9

**100% for tumours < 2 cm in diameter*

Which patients should we screen?

Several prospective studies have shown a high incidence of HCC in chronic HBV carriers. Those at especially high risk of developing HCC include male carriers who are >45 years of age, those with concomitant cirrhosis and those with a family history of HCC[18]. There is now evidence of a strong association of Hepatitis C and HCC. 60-70% of Japanese patients with HBsAg-negative HCC were found to have antibodies to the hepatitis C virus (HCV). In Europe, 65-75% of a similar group of patients were anti-HCV positive[19]. A synergistic association between HBV and HCV has also been suggested because patients with both viral markers (anti-HCV and anti-HBc) are more likely to have HCC than those with either one[20].

HBV infection is associated with more than 70% of cases of HCC in most of Asia and all of Africa. HCV however appears to be the more important virus associated with HCC in the Western population. The majority of patients with HCC worldwide have underlying liver cirrhosis. The cause of cirrhosis also varies. In the Far East, it is secondary to chronic hepatitis B and C infection whereas in the West, chronic ethanol consumption is the main aetiological factor. Patients with cirrhosis due to other causes like haemochromatosis are also at risk. However HBsAg-positive cirrhotics have been found to more likely to develop HCC compared to those who are HBsAg-negative[21].

Screening methods for HCC

Current methods used for the screening of HCC in high-risk populations are periodic measurements of serum alpha-fetoprotein (AFP) and abdominal ultrasound examination (US) to detect small liver nodules. Periodic combined AFP measurements and US examinations may detect HCCs of 1 cm in diameter. The use of lipoidol angiography can detect even smaller tumours[22].

Serum alpha-fetoprotein (AFP)

Earlier attempts to detect early asymptomatic tumours make use of AFP measurements only. Over the years, the sensitivity of the test has improved largely because of improved techniques. There is sufficient evidence from prospective studies to indicate that AFP is elevated in most HBsAg positive carriers with resectable HCC. A study of HBsAg positive carriers in Taiwan found AFP levels of > 20 ng/ml in 81% of asymptomatic persons with HCC[23]. The value of AFP depends to a large extent on the cutoff levels. Using a high cutoff level increases its specificity but decreases its sensitivity. In patients with confirmed HCC, the sensitivity of AFP measurement is 65-70% using a cutoff level of 20 ng/ml[24]. In one study[25], 65% of HCCs 2 cm or less would have been missed if only AFP levels of 100 ng/ml had been used. It is true however that the higher the levels the greater the specificity but levels of more than 400 ng/ml only occur in one third of cases. More than 50% of small tumours < 3 cm in diameter will be missed if the cutoff is > 500 ng/ml[26]. It is also worth noting that serum AFP may be less frequently elevated in HBsAg-negative patients with HCC compared to those who are HBsAg positive. In addition, false positives can occur in pregnancy, active hepatitis and testicular tumours.

Despite the above limitations, AFP has a definite place in HCC screening. There is sufficient evidence from prospective studies to indicate that it is elevated in the majority of HBsAg carriers with resectable HCC.

Abdominal Ultrasound (US) and other imaging modalities

Serial measurements of AFPs with US are currently recommended in the screening for HCC in the hospital-based population. A study[10] comparing the various imaging techniques reported the superiority of US (92% sensitivity) over computed tomography (73%) and radionuclide imaging (50%). Two studies[25,27] showed that US is superior to CT scan and angiography in the detection of tumours which are < 3 cm. No difference was however observed for the bigger tumours (> 5 cm). See Table II. Unfortunately there are also false positives with US examination. In a cirrhotic patient, a suspicious nodule may turn out to be a regenerative nodule or a haemangioma. This may sometimes be resolved by CT scanning with IV contrast, hepatic angiography or magnetic resonance imaging (MRI) which is particularly useful for the diagnosis of haemangiomas. Lipiodol angiography followed by CT liver scan can also help in the diagnosis. Lipiodol, a contrast medium containing iodine, is selectively retained in tumours as small as 2

mm and can be visualised by CT scan of the liver performed 10-14 days after intrahepatic injection of lipiodol[28]. Another factor to be considered when using US for screening is the fact that it is operator-dependent with the possibility of two different radiologists arriving at different diagnoses from similar observations on the US.

Other tumour markers

Des-gamma-carboxy-prothrombin (DCP) or PIVKA-II (Prothrombin induced by Vitamin K absence or antagonist-II) measurements may be useful. Studies have shown that it can be found in patients with small tumours but without raised ALP levels[29]. It is however not as sensitive or as specific as AFP. Other tumour markers like Gamma glutamyl transferase (GGT), Carcinoembryonic antigen (CEA) and Alpha-1-fucosidase have not been found to be very useful.

Frequency of follow-up

As noted earlier, the mean doubling time for HCC is 4 months[9]. It follows therefore that patients with a high risk of developing HCC i.e. those with evidence of cirrhosis on US or with unexplained elevation in AFP levels should be followed up every 3-6 months. Those with chronic viral hepatitis without evidence of underlying cirrhosis and those with normal AFP levels are at lower risk and may require only yearly follow-up. The National University Hospital in Singapore performs US and AFP measurements every 3 months over the last four years. 40% of their patients with HCC had resectable tumours[30].

What about the situation in Malaysia?

Most hepatologists or gastroenterologists in this country follow up asymptomatic HBV carriers every 6 months with US examinations and AFP measurements. Patients with concomitant cirrhosis will be followed up more frequently. Although the pick up rate of small HCC is small, tumours of < 2 cm have been detected via US. The outcome of on-going screening programmes in HBV-associated cirrhotics in Malaysia is still uncertain. What is certain is the fact that most of our patients with HCC present to us rather late. Public awareness campaigns and patient education should therefore be amplified.

Is screening for HCC cost-effective?

The usefulness of screening for HCC appears to vary in different parts of the world. Screening appears to be beneficial in Asian patients (most of whom have

Table II
Detection of hepatocellular carcinoma
(Comparison of ultrasound with other imaging modalities)

Diagnostic modalities	Ultrasound (n=27)	CT Scan (n=20)	Amgiography (n=20)	Liver scan (n=22)
Tumour size (cm)				
< 3	100%	61.5%	55.5%	7.6%
3-5	100%	100%	100%	40.0%
Subtotal	100%	72.2%	76.6%	16.6%
> 5	100%	100%	100%	100%
Total	100%	75%	80.0%	31.8%

(Sheu J-C et al, 1985)

underlying HBV-related cirrhosis) as it has helped to identify an increasing number of patients with small tumours that are suitable for hepatic resection. The experience in the West is however different. Studies in Italy and France[21,33] have failed to increase the detection rate of potentially resectable tumours in patients with cirrhosis. One possible reason for this is the different behaviour of HCC in the different geographical areas. For instance it is known that 80-92% of Oriental patients had solitary nodules when first detected by US[24,26]. Only half this number was observed amongst Italian patients[33].

Significant costs will be incurred with population or clinic-based screening as periodic US examinations and AFP measurements are expensive. The calculated cost for detecting one HCC patient with US and AFP measurements done 4X per year and CT scan done every 8 months is about RM11,000 (for a 10% detection rate/year) to RM23,000 (for a 5% detection rate/year). Using this strategy, Okuda *et al.* analysed 300 consecutive cases of HCC detected during a 5-year period and found tumours smaller than 5 cm and 2 cm at the time of diagnosis in 57.3% and 14.6% of cases respectively[31]. In Singapore, the estimated cost per early HCC detected is S$ 15,000 if AFP level is measured every 4 months, US, examination every 6 months or both every 18 months[29]. A recent report[32] from Japan on mass screening for HCC obtained a detection rate of 1.12% after screening 8090 individuals using both AFP and US. The authors felt that the detection rate was high and that mass screening should be encouraged. Mass screening of the general population, however, is not cost-effective in countries with low incidence of HCC. Screening carried out in countries with a high HBV carrier rate have been shown a better pick up rate amongst HBV cirrhotics[33]. Studies in Japan[31] showed an annual detection rate of between 4-13% in patients with cirrhosis who made regular outpatient visits. Our current practice is to follow-up patients with cirrhosis and chronic active hepatitis at intervals of 3-4 months and every 6 months respectively.

Conclusion

There is at present enough evidence to recommend screening for HCC in patients with Chronic HBV infection. HBsAg-positive carriers should be screened with periodic determinations of AFP levels, preferably twice a year but at least once a year with more frequent determinations in specific cases. Those with additional risk factors such as cirrhosis or a family history of HCC should be considered for periodic US examinations in addition to AFP determinations. For HBsAg-negative patients with cirrhosis or other chronic liver diseases, more data is required before specific recommendations can be made for screening them. Large prospective studies of patients with chronic liver disease at risk for HCC need to be conducted to determine the true incidence in the various groups and the usefulness of screening with serum AFP and/or US examinations.

While screening may help detect potentially resectable tumours, the better strategy for controlling HCC would be primary prevention. Since both HBV and HCV infections are the major causes of HCC in this part of the world and since both of these infections can be controlled, strategies aimed at controlling these infections would be expected to decrease the incidence of HCC in future. Mass hepatitis B vaccination and blood donor screening for anti-HCV are expected to control HCC in 20-40 years. We have started HBV vaccination for all newborns since 1989 and anti-HCV screening for all blood donors in 1994. We may therefore expect a decline in the incidence of HCC in the future.

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