UK Guidelines for the management of suspected hepatocellular carcinoma (HCC) in adults

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1.0 Foreword

This document, on the management of patients with suspected hepatocellular carcinoma, was originally commissioned by the British Society of Gastroenterology (BSG) as part of a wider initiative to develop guidelines for clinicians in several areas of clinical practice. Initial guidelines were published in 2003 (1) and this document represents a revision in the light of new data and has been produced with input from a number of UK professional bodies involved in HCC patient management.

Cancer care has been the subject of increased scrutiny with the development of care guidelines forming a major part of the strategy to reduce cancer related mortality in the UK. There is a strong suggestion that HCC is a disease which will be seen more frequently over the next few years, given the increase in prevalence of chronic liver disease in the UK population

Previously, HCC has been a relatively rare tumour in the UK and much of the data pertaining to its diagnosis and therapy are derived from studies outside the UK. Because of the lack of screening programmes and the fact that a significant

proportion of HCC presents with symptomatic disease in individuals not known to have liver disease most patients have been treated with non-surgical therapies. Both the Department of Health and the Health Development Agency are keen to encourage better detection of rare cancers. There are a significant number of variables known to influence HCC prognosis, stage of underlying liver disease and tumour size at presentation being the most important. Controlling for these variables is difficult and these factors have contributed to a dearth of randomised controlled trials of treatment for this tumour. There is however a substantial amount of evidence available which can form the basis of a framework for diagnosis and management.

Guidelines are not rigid protocols and they should not be construed as interfering with local clinical judgement. Hence, they do not represent a directive of proscribed routes but a basis on which clinicians can consider the options available more clearly.

2.0 Introduction and objectives

These guidelines cover two areas of clinical practice relating to HCC, the first is its diagnosis including the surveillance of high-risk individuals, and the second is treatment of the patient where the diagnosis has been made. HCC remains one of the commonest malignant diseases in the world but it has not previously been a leading cause of death in the Western world. There is now conclusive evidence from the USA and a strong suggestion from the UK that HCC is becoming a more common cancer, primarily due to the hepatitis C (HCV) epidemic. These guidelines relate to adult medical practice; high-risk paediatric conditions predisposing to HCC and the management of paediatric patients with HCC will not be considered.

Guidelines are proposed on a number of issues; (a) which patients are at high risk of the development of HCC and should be offered surveillance, (b) what investigations are required to make a definite diagnosis and, (c) which treatment modality is most appropriate in a given clinical context.

3.0 Formulation of guidelines

A systematic review of the relevant literature and synthesis of available evidence with later phases of peer group appraisal and then expert review was performed. Draft proposals were amended at this stage. The strength and evidence used in these guidelines was that recommended by the north of England evidence-based guidelines development project.

CATEGORIES OF EVIDENCE

Ia Evidence from meta-analysis of randomised controlled trials

Ib Evidence from at least one randomised trial

IIa Evidence obtained from at least one well designed controlled study without randomisation.

IIb Evidence obtained from at least one other type of well-designed quasi-experimental study.

III Evidence obtained from well designed non-experimental descriptive studies such as comparative studies, correlation studies and case studies.

IV Evidence obtained from expert committee reports or opinions or clinical experiences of respected authorities.

GRADING OF RECOMMENDATIONS

Recommendations are based upon the level of evidence presented in support and are graded accordingly.

A Requires at least one randomised, controlled trial of good quality addressing the topic of recommendation

B Requires the availability of clinical studies without randomisation on the topic.

C Requires evidence from category IV in the absence of directly applicable clinical studies.

4.0 Summary of recommendations

Surveillance for HCC

- Surveillance using abdominal ultrasound and alpha-fetoprotein estimation can detect HCC of a smaller size than those presenting without screening (evidence grade IIa).
- The only potentially curative therapies depend on detection of small HCC (evidence grade IIa).
- Despite the above, there is no data confirming that these advantages in detection of earlier lesions produces an improvement in long-term survival or cost saving (evidence grade IIa).
- Surveillance for hepatocellular carcinoma should be considered in all male and females with cirrhosis who might be suitable candidates for treatment (evidence grade III, recommendation grade B). The risk seems highest in cirrhosis due to hepatitis B, hepatitis C and genetic haemochromatosis (evidence grade III, recommendation grade B)

- If surveillance is offered, it should be using six monthly abdominal ultrasound assessments in combination with serum alpha-fetoprotein estimation (evidence grade III, recommendation grade B). Abdominal ultrasonography should be undertaken with appropriate dedicated equipment and by an operator skilled in the assessment of patients with cirrhosis (evidence grade IIb, recommendation grade B).
- If surveillance is offered, patients should be aware of the implications of early diagnosis and the lack of proven survival benefit
- Screening and surveillance should be performed where possible at dedicated centres experienced in ultrasound imaging in cirrhosis (evidence grade IV)

Diagnosis of HCC

- Any patient with suspected HCC should be discussed at the regional multidisciplinary team (MDT) for hepatobiliary cancer as outlined in the National Cancer Plan. Formal links should exist from the MDT to a transplant unit.
- Patients with suspicious lesions should be referred within 7-14 days for immediate assessment and diagnostic tests (computerized tomography (CT) scan and alpha-fetoprotein (AFP)) at specialist liver centres, with diagnostic tests completed within 32 days in order to meet the 62 day target for cancer diagnosis and initiation of treatment
- A focal lesion in the liver of a patient with cirrhosis is highly likely to be HCC (evidence grade IIa).
- Initial assessment should be by CT of liver (local spread) and thorax (metastases) such CT scans should be performed to agreed cancer network protocols (evidence grade IIa, recommendation grade B).
- Magnetic resonance imaging (MRI) with contrast enhancement may increase accuracy of detection of other liver lesions (evidence grade III, recommendation grade C). Such scans should again be to a formal agreed protocol across the cancer network.
- CT evidence of nodules plus AFP > 400ng/ml is diagnostic of HCC

- Biopsy is rarely required for diagnosis as this can usually be established radiologically, and seeding of tumour in the needle tract occurs in 1-3%. Biopsy of potentially operable lesions should be avoided where possible although when biopsy is required in areas of significant doubt, this should only be performed after specialist review at a hepato-biliary MDT (evidence grade IIa, recommendation grade B).

Treatment of HCC

The only proven potentially curative therapy for HCC remains surgical, either hepatic resection or liver transplantation and patients should always have these modalities of treatment considered.

- Patients with suspected HCC should be diagnosed and assessed for treatment within the 62-day target
- Liver transplantation should be considered in any patient with cirrhosis and a small lesion (5cm or less single nodule, or up to five lesions of 3cm or less) or in patients with a single lesion greater than 5cm and less than or equal to 7cm diameter where there has been no evidence of tumour progression (volume increase by <20%; no extrahepatic spread; no new nodule formation) over a 6 month period. Locoregional therapy +/- chemotherapy may be given during that time. Locoregional therapy should be considered for all transplant list cases (evidence grade IIa, recommendation grade B).
- Hepatic resection should be considered as primary therapy in any patient with HCC and a non-cirrhotic liver (including fibrolamellar variant) (evidence grade IIa, recommendation grade B)
- Resection can be carried out in highly selected patients with hepatic cirrhosis and well preserved hepatic function (Child-Pugh A). Such surgery carries a high risk of post-operative decompensation and should be undertaken in units with expertise in hepatic resection and management of liver failure and in consultation with a liver transplant unit (evidence grade IIa, recommendation grade B).

Non-surgical management

Non-surgical therapy should only be used where surgical therapy is not possible. The techniques used are highly operator-dependant and should only be undertaken in accredited HPB units with sufficient expertise.

- Radiofrequency ablation (RFA) has been shown to be effective therapy in HCC less than 3cm in diameter (evidence grade IIb). Percutaneous ethanol injection (PEI) has been shown to produce necrosis of small HCC. It is best suited to peripheral lesions, less than 3cm in diameter (evidence grade IIb, recommendation grade B) and has been shown to be inferior to RFA in local tumour control. It may still have a role in specialist centres for small lesions difficult to treat with RFA.
- Chemoembolisation can produce tumour necrosis and has been shown to improve survival in selected patients with good liver reserve. Chemoembolisation using lipiodol is effective therapy for pain or bleeding from HCC (evidence grade IIa, recommendation grade B).
- Combined chemoembolisation with RFA has been shown to improve local tumour control and survival in tumours between 3 and 5cm in diameter (evidence grade 1b, recommendation grade A).

Systemic therapy for HCC

- Sorafenib has been shown to prolong survival in patients with advanced HCC and is the standard of care for patients with advanced HCC for whom no potential curative option is available (evidence grade Ib, recommendation grade A).
- Systemic chemotherapy with standard agents has a poor response rate (evidence grade I, recommendation grade A) but can be offered where no alternative therapy is available.

5.0 Background

5.1 Epidemiology of hepatocellular carcinoma

HCC causes approximately 1500 deaths per year in the United Kingdom. There is strong evidence from the USA that the incidence of HCC is rising (2): nine cancer registries reporting via the National Cancer Institute showed a 41% rise in mortality from primary liver cell cancer between 1980 and 1995 with a 70% rise in overall incidence. Similar although less robust evidence is emerging in the UK (3). HCC is unusual among human cancers in that the aetiological agent responsible is usually readily identifiable. The prevalence of HCC worldwide parallels that of viral hepatitis and the majority of cases are associated with hepatitis B and C. The increase in HCC incidence in the developed world is likely to be a direct result of the hepatitis C epidemic occurring some 20-30 years after the rise in this infection in target populations (4). Alcohol, genetic haemochromatosis and rarely primary biliary cirrhosis (PBC) are associated. The high rates of migration to the UK from areas with high levels of hepatitis B and C are likely to lead to an increase in incidence of HCC. In the UK, up to 40% of cases present with HCC as the first indication of underlying liver disease, in distinction to countries such as Japan where 80% of HCC are detected at an asymptomatic stage by screening of patients with known cirrhosis (5).

5.1.1 Factors influencing risk of hepatocellular carcinoma development.

(i) Gender

The risk of HCC development is much greater in men for the majority of aetiologies (6). This is independent of the fact that males are more likely to develop chronic HBV carriage than women. Hepatitis C may be a relative exception to this with a male to female ratio of 1.2:1 as compared to 1.9:1 for hepatitis B. The reasons for this are unclear (7).

(ii) Age

The average age of HCC development in the UK is 66 years which probably reflects the long-term nature of most underlying liver diseases producing tumour development. This tumour is rare below the age of 45 in areas with low levels of

hepatitis B virus infection. In high HBV prevalence areas, HCC has a bimodal age distribution with peaks at ages 45 and 65 (8)

(iii) The presence of hepatic cirrhosis

Chronic liver disease at the stage of cirrhosis is present in the vast majority of patients with HCC in the UK and Europe (9, 10). It is unclear if cirrhosis *per se* is biologically important in the tumourigenic pathway, or if tumour development and fibrogenesis take place concurrently but with fibrosis taking a shorter time period. Non-cirrhotic HCC occur in young patients (fibrolamellar variant) or patients without underlying disease predominantly in the elderly (apparent *de novo* HCC). Fibrolamellar HCC has an equal sex incidence and an average age at diagnosis of 30 years (11). Non cirrhotic HCC does occur in patients with viral liver disease, particularly hepatitis B (12) where direct viral integration into host DNA may play a role (13). Non-cirrhotic HCC is described in hepatitis C (14) and haemochromatosis (15) but is rare.

(iv) Aetiology of liver disease

There is a considerable variation in the risk of HCC development in follow-up studies of patients with cirrhosis of different aetiologies. Viral infection, either hepatitis B or C, carries a high risk, cirrhotic patients with either infection having approximately a 3-5% per year risk of HCC development (16, 17). In some studies the risk is even higher, up to 12% per year in HBV infected patients (18), but this may represent patient selection, those with more severe liver disease may be at greater risk. In hepatitis C infection there is compelling evidence that HCC development occurs with higher frequency at a very advanced stage of underlying liver disease (19), up to 30% of patients undergoing liver transplantation for end-stage HCV cirrhosis have undetected HCC found in the explanted liver (20).

In non-viral cirrhosis, again a great divergence of risk of HCC is seen with aetiology. Patients with cirrhosis due to genetic haemochromatosis who were iron loaded at presentation had a very high risk of HCC development, 7-9% per year (21), the risk falls with venesection but not to baseline levels (1-3% per

year)(22). In contrast, patients with the cirrhosis of autoimmune hepatitis have a very low risk of HCC development. Descriptions of HCC in this group in the literature are rare, despite a substantial number of cirrhotic individuals under long term follow-up. Those which do exist suggest hepatitis C co-infection may be an important factor (23). Alcoholic cirrhosis carries an increased risk of HCC development, this risk is difficult to quantify as mortality from continued alcohol consumption and cardiovascular disease is very high in this group. The available data suggest that abstinence from alcohol does not protect against HCC development, and that tumour development is seen in between 1 and 4% of male cirrhotics per year, a similar level to that produced by hepatitis B or C infection (24,25). The rate of HCC development in women with alcohol related cirrhosis is more difficult to establish but seems significantly lower with few reports in the literature (25). Primary biliary cirrhosis does carry a risk of HCC development, , and the available data suggests that women, even with established cirrhosis, have a relatively low risk but males have a similar risk to patients with alcohol related cirrhosis (26, 27). Overall risk of HCC in PBC is probably over three times that in the general population even if treated with ursodeoxycholic acid and may be higher in untreated patients (28).

Wilson's disease is rare, but an increasing number of patients are surviving into adulthood with pre-existing hepatic cirrhosis. HCC is well described despite adequate copper chelating therapy, although the true incidence is difficult to establish (29).

(v) Evolution from liver cell adenoma

The extent to which liver cell adenoma (LCA) predisposes to HCC is controversial. The reported prevalence of malignant transformation in LCA ranges from 5-18% (30, 31). However, histological distinction between LCA and well-differentiated HCC can be very difficult, particularly in needle biopsy specimens, and some cases where HCC appears to have developed from LCA may have been malignant from the outset. There are also potential problems with selection bias. Recent studies have developed a new molecular classification of

LCA (30, 32, 33). Beta-catenin mutated adenomas, which account for approximately 20% of cases, are more frequently seen in males and have a risk of malignant transformation of up to 40%. By contrast the risk of malignant transformation in other types of LCA is much lower (approximately 6%). It is likely that molecular categorisation of adenomas will become part of their routine histopathological assessment during the next 5 years.

5.2 Natural history of hepatocellular carcinoma

HCCs develop as small nodules. The majority of their growth takes place in an asymptomatic phase which may be years in length. Estimated doubling times of HCC vary between 1 and 19 months (34, 35), with a median of 6 months. There has been a suggestion that tumours with certain defined aetiologies may have more aggressive behaviour but there is no conclusive data to support this. There is data as to survival in untreated patients with HCC, showing that the major factors influencing overall survival are the severity of underlying liver dysfunction and the tumour size at initial detection. Between 50 and 90% of patients with Child-Pugh A cirrhosis will survive a year untreated compared to only 20% with Child-Pugh C (35, 36, 37). Small HCC at presentation have relatively long tumour doubling times and overall survival with tumours of less than 5cm was 81%-100% at a year and 21%-17% at 3 years with no therapy (35, 38).

5.3 Pathology of HCC

5.3.1 Evolution of HCC in cirrhosis

It is generally accepted that the evolution of HCC in the cirrhotic liver is a multi-step process, in which successive stages are associated with an increase in size of nodules, increasing molecular abnormalities and an increased risk of progression to invasive HCC. Histologically pre-neoplastic lesions progress from large regenerative nodules to dysplastic nodules (DNs), which may be low or high grade, before undergoing transformation to HCC (39, 40). Dysplastic nodules (DNs) and well-differentiated HCC have overlapping morphological features, making histological diagnosis difficult, particularly in needle biopsy

specimens. An important stage in the evolution of HCC is clonal expansion, producing the so-called “nodule-in-nodule” growth pattern – this lesion is seen in high grade DNs and early well-differentiated HCC, but because it occurs focally may not be detected when liver biopsy specimens are obtained from small hepatic nodules (< 20mm diameter) (41). The most reliable histological criterion for diagnosing malignancy is local invasion (capsular, vascular or stromal), but this is rarely seen in needle biopsy specimens. Other features that aid in the differential diagnosis between high grade dysplastic nodule (HGDN) and HCC are loss of reticulin (usually seen at least focally in HCC) and diffuse CD34 immunoreactivity of sinusoidal endothelium in HCC, although this can also be seen in some dysplastic nodules. Recent studies have used molecular approaches to distinguish DNs and well-differentiated HCCs (42, 43). Amongst the genes upregulated in HCC, glypican-3 expression can be demonstrated immunohistochemically in the majority of HCCs, whereas staining is usually negative in dysplastic nodules (42, 44).

5.3.2 Pathological assessment of liver resection specimens containing HCC

Pathological assessment of specimens obtained from patients undergoing liver resection or transplantation for HCC allows histological confirmation of the diagnosis, recording of prognostic features and correlation with pre-operative radiological findings (45). A disparity between pre- and post-operative diagnosis can be seen in up to 30% of cases. Important pathological prognostic features for liver resection and hepatectomy specimens are tumour size and number, histological grade, mitotic activity, vascular invasion and satellite nodules. It is recommended that the relevant pathological features are reported according to recent guidelines provided by the Royal College of Pathologists (46).

For patients undergoing liver resection for HCC, assessment of background liver disease severity (inflammatory grade and fibrosis stage) in the uninvolved liver is also prognostically important (47). Molecular approaches are also being used to identify prognostic markers in HCC (48, 49). There is emerging evidence to

suggest that HCCs with a biliary or progenitor cell phenotype have a worse prognosis (50, 51). This can be demonstrated by immunostaining for cytokeratin (CK) 19, with expression in more than 5% of tumour cells conferring a bad prognosis compared with CK19 negative tumours.

5.4 Potential screening tests for HCC

There is a need to screen at-risk patients, those with cirrhosis primarily. The aim is the detection of tumour nodules at a stage were curative therapy is possible.

Alpha-fetoprotein (AFP), a normal serum protein synthesised by foetal liver cells and yolk sac cells, is the most widely studied screening test used as a tumour marker for HCC. The normal range for AFP is 10-20 ng/mL and a level of >400ng/mL usually regarded as diagnostic. Two-thirds of HCC less than 4cm however have AFP levels less than 200ng/mL and up to 20% of HCC do not produce AFP even when very large (52). Modifications of AFP with differing carbohydrate structures may occur in HCC and can be detected by altered patterns of lectin binding. These altered profiles have led to the development of alternative diagnostic tests (53) but none are widely available or have been shown to markedly enhance diagnostic ability over AFP. Desgamma-carboxy prothrombin has been used as an alternative tumour marker for HCC, 67% of HCC have elevated levels but only 8% of small (<2cm) HCC have abnormal levels (54) and it has not gained wide acceptance. Using AFP testing also produces false positives, levels in the range 20-250 ng/mL are frequently seen in regenerating nodules in viral cirrhosis (55). A rising AFP over time, even if the level does not reach 400ng/mL is virtually diagnostic of HCC.

Ultrasound can detect large HCC with high sensitivity and specificity. It is less able to reliably identify smaller lesions, which are required if better therapy is to be offered. Expertise of the operator and dedicated equipment seem important in enhancing results, where this is available ultrasound detects 85-95% of lesions 3 to 5 cm in diameter and can achieve 60-80% sensitivity in the detection of

lesions of 1cm (56, 57). In the UK at present detection of lesions below 2cm by ultrasound is uncommon.

Combining AFP and ultrasound improves detection rates. Ultrasound screening was initially suggested at six monthly intervals on the basis of tumour doubling times. There is some evidence that more frequent examinations may enhance sensitivity but at the expense of more false positive tests (58, 59). Patients with a negative ultrasound and an elevated but not diagnostic level of AFP appear to be at high risk and more frequent ultrasound examination in this group, probably 3 monthly, may have a higher yield (57).

5.4.1 Screening studies in HCC

There are no randomised, controlled studies of screening for HCC development in cirrhosis of any aetiology. It is highly unlikely that any such randomised study could be undertaken now as surveillance of patients with cirrhosis is widely accepted and it would be almost impossible to recruit patients to a no screening arm of such a study. In the absence of such data, practice has been based on non-randomised studies either screening at risk populations or from clinic based series.

There are a number of series demonstrating the ability of either alpha-fetoprotein alone as a screening investigation or, more commonly, the combination of AFP and ultrasound. The largest study of screening is in the Alaskan population with a high HBV carriage rate (60). Screening was undertaken in the total population with HBsAg positivity, irrespective of viral replication. The results of this study show that from 1982 to 1998, 18 299 AFP estimations were undertaken in 2230 HBsAg positive individuals. Twenty patients developed HCC, 5 were inoperable at presentation, 14 had resections, but 6 recurred. A similar study of patients with hepatitis B, only 4% of whom had proven cirrhosis, detected 14 cancers in 1069 patients screened, with six curative surgical procedures undertaken (61). Prospective studies of patients with viral cirrhosis have been carried out using

ultrasound and AFP measurements and showed that 64-87% of detected tumours were single and 43-75% were 3cm or less in diameter (62, 63, 64, 65). In these studies, between 29 and 66% of the detected cancers were treated surgically with an attempt at cure. These studies are not directly comparable to the situation in the UK as few centres had liver transplantation available as a therapeutic option.

A systematic review and economic analysis of surveillance of cirrhosis for HCC (66) found that in a mixed-aetiology cohort, the most effective surveillance strategy is to screen with AFP assay and ultrasound imaging on a 6-monthly basis. The cost-effectiveness of such surveillance varied according to aetiology, appearing most cost-effective in those with hepatitis B-related cirrhosis and less likely to be effective in those with ALD-related cirrhosis. A French study has compared screening intervals of 3 versus 6 months with ultrasound alone and shown that 3 monthly interval detected more non-cancer nodules but did not significantly improve detection rates of small HCC (67).

5.5 diagnostic tests for HCC

Current targets require that all patients with suspected HCC should be managed within a target time of 62 days, such that within 31 days of presentation the diagnostic process, involving AFP and CT and ultrasound assessment should be completed.

5.5.1 AFP

When a patient presents with a liver mass, irrespective of screening, there is a requirement to make a diagnosis and to stage the disease. The commonest clinical scenario is a patient with a mass discovered on ultrasound, where the AFP may or may not be raised. If the patient is known to have pre-existing cirrhosis and the mass is greater than 2cm in diameter, there is a greater than 95% chance that the lesion is a HCC (68, 69). If the AFP is raised, this confirms the diagnosis and further investigation is only required to establish the most

appropriate therapy). If the AFP is normal, further radiological imaging is required. Research is on-going to identify better serological and tumour markers for early HCC detection.

5.5.2 Radiology in HCC

A diagnosis of HCC can usually be established, without the need for biopsy (70,71), using computed tomography, magnetic resonance imaging or contrast enhanced ultrasound, (CT, MRI, CEUS) whether cirrhosis is present or not. Once a putative diagnosis is made the secondary radiological objectives are to identify features that have a major role in determining the management strategy. The key additional findings to be documented include the full burden and distribution of malignant disease within the liver, the presence of major vascular invasion, to identify parenchymal liver disease in patients not known to be cirrhotic and features of portal hypertension. The presence or absence of metastatic disease also needs to be established.

The diagnosis of larger HCCs is usually more straightforward than lesions 2 cm or less in diameter as they tend to show more of the characteristic features helpful for diagnosis. Smaller lesions tend to be more uniform with greater overlap with benign nodules. Characteristics of HCC include a mosaic or “lesion within a lesion” morphology, where components separated by fibrous septae may demonstrate varying degrees of fatty metamorphosis, necrosis or haemorrhage (72). A capsule demarking the HCC is frequently visible on later post contrast images. Whilst contributing to the heterogeneity of such tumours seen on CT, fat is rarely identifiable as such on CT, whereas fat and the products of haemorrhage are easier to identify on MRI. In the absence of tissue characteristics of fat and haemorrhage, HCC on unenhanced MR tends to be of high signal on T2 and low signal on T1. All unenhanced imaging techniques are relatively insensitive for HCC detection and determining extent of disease. HCC

more commonly extends into the lumen of portal or hepatic veins than any other liver tumour.

The combination of the high temporal resolution of current imaging equipment and the use of conventional contrast agents for CT, MRI and the second generation US contrast agents enables changes in vascularity within nodules to be exploited. The liver can be repeatedly examined as contrast passes through vascular and interstitial spaces. HCCs and to a lesser extent high grade dysplastic nodules tend to be hypervascular compared to background liver and visualised during arterial dominant contrast enhanced phases. This hypervascularity is at least in part a consequence of neo-angiogenesis and the development of unpaired arterioles. Demonstrating this phenomenon with more than one imaging technique is the basis of the EASL and AASLD recommendations for the diagnosis of HCC in the absence of other diagnostic features and when the AFP is not diagnostic (73,74). It is important to optimise the imaging technique to maximise detection and characterisation. The delivery, volume of contrast and the relative timing of acquisitions are critical for both CT and MR with bolus tracking or the use of a test bolus desirable to compensate for physiological differences between patients (75,76). In order to optimise hypervascular lesion lesion conspicuity with CT 100-150mls of contrast, depending on the iodine concentration, needs to be administered at 4-5mls per second. Although more lesions are detected with an increase in number of passes through the liver, the late arterial and portal venous phase are the most important post contrast acquisitions with additional post-contrast acquisitions offering diminishing returns in detection and with CT an increased radiation dose. An unenhanced CT acquisition does not increase the diagnostic performance. There is a slight incremental value in performing a delayed acquisition at 3 minutes (77). CEUS enables real time passage of contrast through a lesion to be observed to enable characterisation but the whole of liver cannot be assessed in this way and therefore CT or MR is required (78).

The importance of small hypervascular nodules should not be over-emphasised, as not all HCC are hypervascular and not all hypervascular lesions are HCC. Using EASL non-invasive definitions of HCC (73) by demonstrating hypervascularity using 2 imaging techniques (CT and CEUS) 38% of HCC 1-2 cm in diameter and 16% of HCCs 2.1-3 cm were misclassified (79). Serial CT including invasive techniques (CT hepatic angiography and CT arterioportography) have also demonstrating early HCC to be predominantly hypovascular or iso-attenuationg to the background liver during the arterial phase but a tendency for HCC to become hypervascular as they become more advanced, with only 6% of advanced HCC hypovascular (80). The converse problem is the hypervascular nodule less than 2cm in diameter, on CT or MR, that cannot be identified on any acquisition other than the arterial dominant phase. These have to be regarded with caution and cannot be regarded as HCC and are the commonest source of false positive identification of HCC in transplant series (81). The proportion of lesions only demonstrated on the arterial phase shown to be HCC on follow up studies range from 5-28% (82,83,84,85). These lesions have different significance to those that demonstrate washout of contrast, ie a nodule which is of higher attenuation than the background liver on the arterial phase that becomes of lower attenuation than the background liver on subsequent vascular phases, as this is a feature of HCC (86).

Conventional Gadolinium chelates function as extra-cellular contrast agents in MR comparable to iodinated contrast agents used for CT as described above, but additional compounds are available for MR which exploit differences in cellular function within populations of liver cells. The 2 main classes of these liver specific agents are colloidal superparamagnetic iron oxide (SPIO), taken up by Kupffer cells, and specific gadolinium and manganese chelates which are taken up by hepatocytes. Combining extra-cellular and intracellular contrast agents allows assessment of both nodule vascularity and cellular function. The combination of increased arterialisation with diminished cellular function is highly specific for HCC (87, 88), whilst regenerative nodules show both normal

vascularity and normal cellular function. Hypervascular nodules with normal cellular function, and those with abnormal cellular function which are not hypervascular, should both be regarded as borderline and followed.

The relative performance of diagnostic tests in the literature is often difficult to assess, in general, the more rigorous the gold standard the worse the performance. The explanted liver with specified pathological evaluation is the ideal reference of truth but less robust gold standards are often used out of necessity and include liver resection specimens, lesion biopsy and other reference imaging or any combination. There has been a rapid pace of development of radiological technology and imaging protocols particular with MR vary widely and potentially yielding differing results limits the value of composite retrospective analyses. The population under test and prevalence of small HCCs will have a profound impact on the performance of any imaging test under evaluation. Systematic reviews have produced limited conclusion with US and CT found to be relatively specific but MR more sensitive (89). Detection rates for HCC greater than 2 cm are high (> 95%) (81) with sensitivity and specificity decreasing with lesion size. The highest detection rates for lesions 1-2cm in diameter in explant series have been obtained using MR and a combination of cellular and an extracellular contrast agents (88) but detection rates for lesions below 1cm are uniformly poor. The prognosis, however, is usually determined by larger lesions which tend to have the more adverse histological features. Published series are understandably from units with a large experience of cirrhotic patients, and whilst all radiology is dependent on the operator MR is technically more demanding than CT making it is less likely that the best MR results will be reproduced in centres with a low volume of such patients.

Once a diagnosis of HCC has been made metastases should be sought. The commonest sites for metastases are local lymph nodes, lungs, and bones with adrenal glands and peritoneum less common (90)). Peri-portal lymph nodes are often enlarged with cirrhosis and should not generally be used as a contra-

indication to treatment with curative intent (91) CT of the chest should be performed to look for lung metastases. 18F-flurodeoxyglucose positron emission tomography CT (FDG-PET CT) is generally regarded as having limited value in the primary diagnosis of HCC (92) and whilst staging HCC is not accepted as an indication for FDG-PET CT there is a growing body of evidence to suggest that it may have value in the detection of metastatic disease so there may be a future role (93, 94)

5.5.3 Role of biopsy in diagnosis of HCC

In cases where real diagnostic doubt persists, biopsy may be indicated. This is most common with lesions on imaging <2cm diameter where the level of diagnostic certainty over a diagnosis of HCC is low, probably 75% of such nodules turn out to be HCC (95). Again, other radiological techniques or a raised alpha fetoprotein may establish a definitive diagnosis. If not either a repeat examination to show enlargement of the lesion or percutaneous fine needle aspiration or biopsy may be indicated (96). The risk of seeding of HCC does not appear related to tumour size (97) and if surgical therapy is possible biopsy should be avoided . Seeding risk is probably higher in peripheral HCC and histopathogical diagnosis in fine needle aspirates and formal biopsy of small liver lesions can be difficult..The need for biopsy should always be established at a recognised hepatobiliary MDT.

In a patient not known to be cirrhotic, usually where the first presentation is with a liver mass, the initial investigation should be AFP. If raised in the absence of a testicular primary, this confirms the diagnosis. If the lesion is potentially operable, then biopsy of the non-tumour liver may be required to determine the best treatment option. If the AFP is normal, a search for other causes (non-liver primary), and further radiological assessment of the mass are required. If investigations suggest HCC, then again biopsy of non-tumour liver will determine the surgical approach.

5.6 HCC assessment

The prognosis of an individual with HCC depends not just on their tumour stage, but also on their underlying liver function and performance status (PST). For this reason, the classical TNM staging system is often unhelpful. A number of combination staging systems have been proposed. The Barcelona Clinic for Liver Cancer (BCLC) system predicts survival in untreated patients and can also be employed as a guide for treatment stratification in individuals with HCC arising on a background of chronic liver disease (98) Other combination systems include the OKUDA stage and the French, CLIP, CUPI and JIS scores. The advantages and disadvantages of these systems have been recently reviewed (99). Although none has been independently validated in the UK, the key role of staging in the management of HCC is well recognised (73, 47), and should be adopted in our own practice. Furthermore, as the benefit of emerging medical therapies is likely to be restricted to carefully staged patient groups, it is strongly recommended that a minimum staging dataset be prospectively collected to facilitate their most appropriate and cost effective application. This minimum dataset should include a record of whether or not the patient has underlying liver disease and the grade of fibrosis if known, patient symptoms (constitutional symptoms such as fatigue, weight loss, anorexia) and performance status (100), as well as clinical (ascites, encephalopathy, weight, BMI), laboratory (albumin, bilirubin, prothombin time, alpha-fetoprotein) and radiological (number of lesions, size of lesions, portal vein invasion, extrahepatic disease) parameters. Relevant information to aid patient prognostication is provided in Tables 1-5.

5.7 Treatment modalities

5.7.1 Surgery – Hepatic resection and liver transplantation

The only treatments that are capable of providing cure for HCC are hepatic resection and liver transplantation. Despite the lack of high grade evidence from randomised trials for either resection or transplantation, the results of these

treatments provide 5-year survival rates of up to 70% in selected patients (101). Advances in diagnostic, anaesthetic, and surgical techniques have led to significant reductions in perioperative morbidity and mortality such that resection is now an important arm in the multidisciplinary approach to HCC.

(i) Selecting patients for resection

Resection is the only curative treatment option for patients with HCC developing in a liver without background liver disease and for patients with fibrolamellar variant of HCC. In patients with fibrosis or cirrhosis, resection should be considered for patients with good synthetic liver function. Irrespective of the presence or absence of cirrhosis, the median perioperative mortality rate for papers quoting either 30-day or in-hospital mortality was a median of 4.7% with a range from 0 to 21.1%, with lower rates seen in series with larger volumes irrespective of underlying liver disease (102). Hepatic resection is indicated when all the tumour nodules can be resected with negative margins leaving behind a functioning liver parenchyma of at least 25-50% depending on the quality of remnant parenchyma (103). Absolute contraindications for resection include extra hepatic disease, tumour thrombus extending into inferior vena cava or main portal vein, poor functional status of remnant liver parenchyma (104).

Preoperative assessment

Preoperative assessment includes assessment of the extent of tumour , functional status of the liver, volumetry of the remnant liver, degree of portal hypertension and architecture of the remnant liver parenchyma.

Tumour Assessment:

This has been discussed in detail in the radiology section. There are no contraindications for resection based on size (105), multicentricity, presence of satellite nodules, local vascular invasion (104), history of previous rupture and bleeding and the levels of alpha-fetoprotein.

Functional Status of the liver:

Evaluation of the liver function is more important in patients with underlying chronic liver disease. In patients with fibrosis and/or cirrhosis, the Child-Pugh score is a reliable semi-quantitative means of classifying patients into risk based on presence or absence of ascites and encephalopathy, and measurement of albumin, bilirubin and prothrombin time. Resection of any extent is contraindicated in patients with Child-Pugh C score and selected patients with Child-Pugh B score are suitable candidates for minor segmental or non-segmental resections. Patients with Child-Pugh A score can undergo liver resection with acceptable morbidity and mortality. Further stratification of Child-Pugh A score patients based on degree of portal hypertension will enable selection for major resections in this group (103). The Model for End stage Liver Disease (MELD) score has recently been shown to predict the development of postoperative liver failure after hepatectomy for patients with cirrhosis undergoing resection of HCC, with a preoperative score of ≥ 11 being associated with a poor outcome (106). This needs further validation and comparisons with Child-Pugh score in prospective studies.

Various quantitative tests based on hepatic clearance of a substrate injected have been used for a more accurate functional assessment of the liver. Indocyanine Green (ICG) is the most popular and is a standard test in the algorithm for functional assessment in majority of far eastern centres. ICG retention at 15 minutes (ICG R) is the most widely used parameter and the normal value is <10%. Major resection is contraindicated even in patients with Childs Pugh A status if ICG R is >20% (107).

Volumetry of the remnant liver:

Patients with normal underlying parenchyma will tolerate liver resections with remnant volumes of about 25% with acceptable morbidity and mortality rates. However patients with abnormal liver parenchyma in form of fibrosis or cirrhosis would tolerate only limited resections. It has been proposed by several groups

that the safe limit for future liver remnant in this group of patients with Childs-Pugh A score would be about 40% (108). This limit has been extended to 50% if the ICG R is abnormal (10-20%) or in presence of portal hypertension (109). Patients needing major resections in form of right hepatectomy or more would benefit from preoperative portal vein embolisation (PVE) to increase the remnant liver parenchyma. Absence of liver regeneration after PVE would be a relative contraindication to proceed to liver resection. Combining transcatheter arterial chemoembolisation (TACE) with PVE has shown to be advantageous in form more complete tumour necrosis, more regeneration and higher 5 year survival by some groups (110). The future liver remnant (FLR) may be measured by three-dimensional computed tomography volumetry or using a mathematical formula relating liver volume to body surface area.

Degree of portal hypertension:

Assessment of the degree of portal hypertension has acquired significance since Bruix and colleagues demonstrated the importance of hepatic venous pressure gradient (HVPG) in predicting post hepatectomy decompensation (111). HVPG of >10 mm Hg has also been shown to be an adverse prognostic factor for long-term survival (9). Non-invasive assessment of portal hypertension is more commonly used. Various parameters assessed include splenomegaly, hypersplenism especially thrombocytopenia, presence of varices on endoscopy or cross sectional imaging. In general platelet counts of less than 100 x 109 /L should be considered a contraindication for major hepatectomy.

Architecture of remnant liver parenchyma:

Preoperative biopsy of remnant liver parenchyma has been advocated by some groups in the preoperative assessment. However there was no correlation demonstrated between the degree of architecture disruption and the rate of liver regeneration, postoperative complications. In addition the invasive nature of this investigation makes it difficult to justify its routine usage in patients know to have cirrhosis or fibrosis. Presence of inflammatory infiltrates has been shown to

predict poor outcome following liver resection (108). However marked serum transaminitis is a reliable predictor of hepatitis on histology and by itself can be used as a predictor for post hepatectomy complications.

(ii) Selecting patients for liver transplantation

Early results for liver transplantation for HCC were poor (112, 113) with 5 year survival figures well below 50% mainly due to tumour recurrence. It is now clear that this was the result of poor selection of patients for transplantation. It is well established that patients with single lesions of 5cm diameter or up to five lesions of less than 3cm in the absence of vascular invasion as defined by imaging, have an almost zero recurrence rate for the HCC and the prognosis after transplantation is the same as for a similar underlying liver disease without HCC (115, 116, 117).

The criteria for selection to the transplant list for cases with HCC has recently been revised and current UK guidelines from May 2008 (118) advise the following:

1. Radiological assessment should include both multidetecor (MD) CT and MRI with size being assessed by the widest dimensions on either scan.
2. A lesion (for the purposes of counting numbers) will require to be identified as an arterialised focal abnormality with portal phase washout on MDCT or Gd enhanced MR. Other lesions are considered indeterminate.
3. Tumour rupture and an ãFP > 10,000 iu/l are absolute contraindications to transplantation, as are extrahepatic spread and macroscopic vascular invasion.
4. The following are criteria for listing for transplantation;
    - a single lesion < 5 cms diameter or
    - up to 5 lesions all < 3 cms
    - single lesion > 5 cms < 7 cms diameter where there has been no evidence of tumour progression (volume increase

by <20%; no extrahepatic spread; no new nodule formation) over a 6 month period. Locoregional +/- chemotherapy may be given during that time. Their waiting list place may be considered from the time of their first staging scan.

5. Locoregional therapy should be considered for all transplant list cases.
6. Cases outwith current proposed selection criteria will not be selectable on to the transplant list after their tumour has been downsized by surgical or loco-regional treatments.

5.7.2 Ablative therapy

A number of non-surgical therapies are in clinical use for HCC, percutaneous ablative therapies are well described initially using ethanol injection. Radiofrequency ablation (RFA) is a newer technique, where high frequency ultrasound probes are placed into a liver mass, usually under ultrasound control. Series show that tumour necrosis can be produced and that morbidity and mortality are low for both techniques.

(i) Percutaneous ethanol injection (PEI)

Although percutaneous ethanol injection has not been subjected to randomised controlled trials there is a considerable literature on its use in HCC. In large series, complete response rates of 75% in tumours less than 3cm in diameter have been reported, with 5 year survival rates of between 35% and 75% (119, 120,121,122). Treatment of larger and multiple lesions is possible, often requiring repeated sessions and a general anaesthetic, but recurrence occurs in more than 50% at one year and only 10% of 3 to 4cm lesions were completely ablated (123). Treatment is technically very difficult in lesions affecting the posterior segments of the liver (124). Complications are uncommon, but seeding in the needle tract occurs in 3% (125) and serious bile duct injury in 1% (126, 120).

(ii) Radiofrequency ablation (RFA)

Radiofrequency ablation of HCC uses a high frequency ultrasound probe placed into the tumour mass, usually percutaneously (127, 128, 129, 130). High frequency ultrasound generates heat at the probe tip which can destroy tissue. A single probe can destroy lesions of up to 3cm and a multiple tipped probe has been used to target lesions up to 6cm in diameter. In a single series of 149 tumour nodules treated either percutaneously or at open operation, with an average tumour diameter of 3.5 cm, the local recurrence rate at 19 months was 3.6% with all nodules showing initial complete ablation (131). Distant metastases or a second tumour developed in 46%. Larger tumours can be treated by radiofrequency ablation, the largest series is 126 HCC greater than 3cm in diameter. Complete necrosis was produced in 47% (132) but there is a significantly higher local recurrence or incomplete ablation rate in lesions larger than 3cm treated by RFA.

A comparison of 112 patients treated by PEI or RFA showed that 47 out of 52 treated by RFA had complete tumour necrosis with a median of 1.2 treatment sessions versus 48 out of 60 having complete ablation by alcohol injection with 4.8 sessions required (133). The authors suggested that radiofrequency ablation was more effective but also had a higher complication rate.

Three small-scale randomised clinical studies comparing RFA with PEI in patients with early stage HCC each suggest that radiofrequency ablation yields better clinical outcomes and it is now widely accepted as primary ablative therapy (134, 135, 136). RFA can probably be regarded as curative therapy for small (<3cm) lesions but lesions above 3cm have a significant local recurrence rate.

5.7.3 Embolisation/chemoembolisation

Chemoembolisation has been widely used as primary therapy for inoperable HCC. The literature is difficult to interpret and to compare as the techniques used differ substantially and the patient groups treated are frequently those with

very advanced disease where the risk of therapy as well as potential benefits may be greatest.

Initial interest in radiological techniques producing tumour devascularisation developed in the 1970s (137). There is good evidence that it is effective at reducing tumour size (138, 139) and treating pain or bleeding from HCC (140, 141). In all of the six initial randomised controlled trials of chemoembolisation as primary treatment for HCC (142, 143, 144, 145, 146, 147) none show any increase in survival, although tumour shrinkage was seen. These trials all included patients with predominantly large tumours and severe underlying liver disease, which may have masked any beneficial effect. There is evidence from non-controlled series that small HCC are more likely to respond to chemoembolisation (139). This has been confirmed in a trial of repeated chemoembolisation using lipiodol and doxorubicin versus arterial embolisation without chemotherapy in patients with small tumours and good liver function (148). In the 38 patients treated with chemoembolisation survival was 63% at 2 years versus 50% (n=34) in the embolisation group and 27% (n=35) in the untreated arm. This study establishes the role of chemoembolisation in the treatment of HCC but it will only be applicable to a relatively small group of patients, 903 patients were screened for the trial to enrol 112. This has been confirmed in a further randomised trial which included patients with more advanced HCC (149).

Side effects of chemoembolisation are those of the chemotherapeutic agent used (usually Doxorubicin) in addition to the complications of the arterial embolisation, pain, fever, hepatic decompensation and rarely infarction of organs other than the liver (150, 151). Serious complications occur in 3-5% of treated patients. A small number of studies have combined ethanol injection with chemoembolisation (152, 153) and a single large randomised trial has now confirmed that tumours of 3-5cm have better survival given combined chemoembolisation and RFA than either therapy alone. This combination

therapy for this selected group of patients should be the standard of care (154). Chemoemobilsation should always be performed at specialist centres performing sufficient numbers of these procedures to demonstrate competence. Chemoembolisation should be performed with antibiotic prophylaxis and under conditions of adequate hydration. The efficacy of drug-eluting beads is still under investigation and until further data are available, these agents should only be used at specialist research centres.

5.7.4 Systemic therapy for HCC

Based on two prospective randomised trials, one undertaken in Europe (155) and one in Asia (156) , sorafenib, an oral multikinase inhibitor has now become the standard of care for patients with advanced HCC for whom no potential curative option is available. To date, benefit has only been convincingly shown in patients with good liver function (Child's grade A) and good performance status, where the improvement in median survival is between two and three months, representing a hazard ratio of between 0.6 and 0.7. Treatment with sorafenib is usually continued until there is radiological or symptomatic evidence of disease progression. Treatment is usually well-tolerated, the most common side-effects being the hand foot skin reaction and diarrhoea which occur in about 10% of cases.

Cytotoxic chemotherapy has response rates of around 10-15% (157, 158) {for example, doxorubicin or the combination of doxorubicin and cisplatin} and these agents can be used in HCC in situations where tumour progression has been seen with sorafenib, recognising that treatment should not be pursued unless there is clear evidence of response in terms of serological changes (AFP falls), tumour size reduction (on radiological grounds) or symptomatic improvement. There is a need for trials of combinations of sorafenib and conventional chemotherapy.

5.7.5 Prevention of second tumour development after successful initial tumour therapy:

Interferon therapy may have a role in the prevention of hepatocellular carcinoma in hepatitis C cirrhosis. There is a scientific rationale for this therapy as interferon alpha has a broad range of anti-tumour activity and is known to be effective therapy for some haematological malignancies. Initial data from both Japan and Europe show a lower risk of HCC in cohorts of patients with hepatitis c cirrhosis who were given interferon therapy compared to those who were not treated (159, 160, 161, 162). This effect was irrespective of the anti-viral effects of interferon alpha, and was seen with treatment duration of only three months. These studies were not randomised controlled trials and have inherent selection bias. There is other evidence showing no effect of interferon on tumour development rates (163, 164) and such tumour preventative therapy in patients with cirrhosis can only be currently recommended as a part of clinical trials. There is compelling evidence that treatment of hepatitis B reduces the risk of cancer development (165). There is no data on suppression of hepatitis B and tumour recurrence after resection or ablation but given the agents are safe and effective in suppressing HBV replication most centres would now give anti viral therapy post resection or ablation. Two other approaches to prevent tumour development have been used, retinoids and adaptive immunotherapy. Both of these approached have been used in the context of prevention of second tumour development after initial tumour resection or ablation. Adaptive immunotherapy, using primed peripheral lymphocytes showed a significant increase in tumour free survival (166). Retinoids and compounds involved in the vitamin A metabolic pathway and are known to be differentiation inducing agents with hypoproliferative effects. A single study using retinol showed a 20% reduction in second tumour development in patients who had been treated with percutaneous alcohol injection (167). Further studies are required in these areas.

5.8 Palliative Care in advanced HCC

In advanced stages of HCC efforts are directed at symptom control. Information about disease progression needs to be given honestly, but always with the assurance that symptoms can be palliated – “there is nothing more that can be done to help you” is both cruel and untrue and should never be said. The NICE Supportive and Palliative Care guidance (168) suggests that all cancer patients should receive regular reassessment of their cancer care support needs and have access to the SPCT, through The NHS End of Life Care Programme (169, 170, 171). The implementation of this programme appears to be making a difference (172), though measures of Health Related Quality of Life in HCC are still in their infancy (173), but will have an important role to play in studies of HCC patients receiving both oncological treatments, and palliative care.

Some patients with extensive HCC are remarkably symptom free. In some cases, there are no symptoms, but where diagnosis has been confirmed there are a number of symptoms which should be anticipated as the disease progresses. These include pain, jaundice, nausea, ascites and confusion.
Most patients with HCC become comatose and die very peacefully. In advanced HCC time may be limited, and the palliative care needs of carers should be included in any assessment of quality of life (174).

Recommendation for UK HCC data collection

The HUG writing committee support a UK-wide goal to collect HCC patient data for entry into a national registry/database. Using a simple data collection form, the aim of the registry would be to gather data based on Barcelona criteria and to collect mortality data. Such as registry-based dataset could help verify prognosis in HCC and would form the basis for providing contemporary HCC patient data to the NHS and for potential publication and review by the broader, international HCC community.

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Tables 1-5 defining staging systems and highlighting relevant information for patient prognostication.

Performance Status Test (PST) in cancer patients	
0	Normal activity
1	Some symptoms, near full ambulatory
2	Some symptoms, < 50% time in bed
3	Some symptoms, > 50% time in bed
4	Bedridden

Child-Pugh (CP) Score	**1**	**2**	**3**
Encephalopathy	None	Grade 1-2	Grade 3-4
Ascites	Absent	Mild	Moderate
Bilirubin (µmol/l)	17-34	35-49	>50
Albumin (g/l)	>35	28-35	<28
PT (seconds ↑)	1-4	5-10	>10
Grade A = 5-6; Grade B = 7-9; Grade C>9			

OKUDA Staging system			
Score	0	1	Median Survival (months)
Tumour size	<50% of liver	>50%	Score 0=stage 1 = 28; Score 1/2 = stage 2 = 8 Score 3/4 = stage 3 = 1
Ascites	No	Yes	
Albumin (g/dl)	>30	<30	
Bilirubin (mg/dl)	<50	>50	

BCLC Staging System				
Stage	PST	Tumour	Median Survival (%)	
0	0	Single < 2cm	50-70% at 5 yrs	with treatment
A	0	Single <5cm, or 3<3cm		
B	0	Larger, multi-focal	80,65,50 at 1,2,3yrs	with no treatment
C	1-2	PVT or extra hepatic disease	29,16,8 at 1,2,3 yrs	
D	3-4	Any	5% at 6 months	

CLIP Score	0	1	2	Median survival (months)
CP Stage	A	B	C	

Tumour Morphology	Uninodular < 50%	Multinodular < 50%	Massive >50%	= 32 Score 2 = 16.5; Score 3 = 4.5 Score 4 = 2.5; Score 5+6=1
AFP (ng/ml)	<400	>400		
PVT	no	yes		