

Guidelines for the diagnosis, assessment and treatment of hepatocellular cancer (HCC).

Summary

Hepatocellular cancer (HCC) is a common malignancy with a particularly poor prognosis. It is associated with chronic liver diseases, particularly those secondary to viral infection or toxic agents such as alcohol. Over the last 10-20 years significant advances have been made in both the ways we detect these tumours as well as in the ways in which we treat them. Unfortunately, although tumours diagnosed early may be cured by resection, liver transplantation or ablation, the majority of patients with this disease are still diagnosed at an intermediate or advanced stage. Advances in care for later stage individuals have not been as successful, hence early detection and established recall procedures, as well as accurate staging can each have a major influence on the success of treatment. In order to deliver appropriate and safe care in accordance with NHS policy on the management of patients with cancer, the guidelines outlined below are largely evidence based and practiced within a multidisciplinary team environment. All patients with a suspected HCC should be referred to the HPB team. This can be done directly, to either **Caroline Baker or Sister Alison McDonald, who co-ordinate the HPB MDM**, or to Mrs Helen Dobson (Tel: 0191 2137210 Fax: 0191 2231249), secretary to Dr Helen Reeves, or to any of the liver unit surgeons or hepatologists. The HPB MDM is the ideal environment for optimal patient investigation and management, but also for recruiting patients to trials of novel therapies, either in isolation in Newcastle, or in collaboration with other liver units across the UK and further afield. This document provides the background and rationale for the Newcastle Hospitals MDT management of HCC introduced in July 2004, revised in July 2007, and February 2010.

Background

Hepatocellular carcinoma (HCC) is the commonest primary liver tumour, the incidence of which is rising worldwide [1]. The major risk factors for HCC vary to some extent with its geographical distribution, but include cirrhosis of the liver regardless of its aetiology, viral infection and chemicals or toxins. Chronic hepatitis B (HBV) and hepatitis C (HCV) contribute to HCC development in as many as 80% of cases. Chemicals include Aflatoxin B1 (AFB1) uptake, cigarette smoking and heavy alcohol consumption. Each is an independent risk factor, but they do have synergistic effects [2]. The prevalence of hepatitis C has major clinical implications as it is the major contributor in Western developed countries where HCC is increasing [3]. The rising incidences of non-alcoholic fatty liver disease (NAFLD) [4] associated with diabetes or obesity are also a major cause for concern, as not only do these conditions predispose to the development of HCC [4-6], but emerging data supports accelerated HCV disease in fat diabetics [7]. The synergistic effect of alcohol and increased risk of HCC development in the presence of hepatitis B and C or diabetes is well recognised [5]. The reality is that these diseases are all increasing and whatever the aetiology or synergistic mechanisms leading to chronic liver disease, it has been shown that HCC is currently the leading cause of death in cirrhotic patients [8-11]. Thus, both prevention and treatment of this neoplasm are major health concerns.

Risk Factors and Prevention on Disease

- *Immunise at risk individuals against Hepatitis B**
- *Educate HCV patients about risks of transmission**
- *Educate all patients about controlling synergistic risk factors, i.e. alcohol intake, obesity, diabetic control.**

Effective prevention of HCC should wherever possible prevent the occurrence of the causative liver disease i.e. 'primary prevention'. Often this is not possible and 'secondary preventive' measures, preventing the progression of active inflammatory disease to cirrhosis, are the focus of health care workers. In HBV infection the virus itself may have direct genetic or epigenetic effects as it gets integrated into host genome and this is accompanied by rearrangement and increased mutagenesis. This explains why tumours often arise in pre-cirrhotic HBV-related disease. HBV is the main cause of HCC in the world and it could be prevented by vaccination. [12] **In the UK, individuals with an increased risk of contracting HBV, including health care workers or family members of infected individuals, receive immunisation.**

As there is no effective vaccine against HCV, primary preventive measures are limited to health education highlighting the methods of viral transmission. Secondary prevention, namely preventing the progression of inflammatory disease to cirrhosis, is of critical importance for those infected with the virus. This includes anti-viral therapy in pre-cirrhotic disease and advice about limitation of other factors, such as alcohol, which adversely affect disease progression. Chemoprevention of HCC by treating individuals with established cirrhosis with interferon has also been proposed, but current data regarding this strategy are conflicting in nature [13-15].

Most of the non-viral causes of HCC including chronic alcohol intake, obesity related liver diseases, metal storage diseases and aflatoxin exposure are characterised by the generation of reactive oxygen species (ROS) leading to oxidative stress. Either the ROS themselves or the products of lipid peroxidation may be involved in hepatocarcinogenesis by reacting directly with DNA and causing mutations in cancer-related genes. Primary prevention in these diseases is currently limited to health education, which may well be stepped up in coming years given the increasing health burden attributable to alcohol and obesity in Western countries. Whether or not increased oral intake of antioxidants reduces the risk of cancer development is unknown.

Surveillance in cirrhotic patient and Diagnosis of HCC

- *Six monthly OP review, LFT, α FP**
- *Annual abdominal USS**
- *Assess possible disease using a contrast investigation e.g. contrast enhanced USS, CT scan, or MRI pre and post Gadolinium.**
- *Either CT or MRI is required for assessing the extent of disease, including presence of extra-hepatic disease and vessel involvement**
- *Biopsy of a liver lesion is considered if the lesion is atypical on imaging, especially if the AFP is normal. All lesions arising in the absence of chronic liver disease require biopsy to confirm the diagnosis and assess the underlying liver if the patient is fit enough for therapeutic intervention.**

***Biopsy of liver lesions is avoided where possible in patients being assessed for possible liver transplantation.**

The mean annual incidence of HCC in cirrhotic patients in the West is 3-4%. The risk increases in parallel to liver function deterioration. Additional risk predictors include irregular regeneration, high proliferative stage, the presence of dysplastic foci, the most powerful being male sex and increased alpha-feta protein (α FP) concentration [8]. Surveillance for HCC in at risk patients has been advocated for years, even though data indicating a benefit in survival is limited [11, 16, 17]. The purpose of surveillance is to recognise HCC at an early stage, where the tumour could be cured. The failure of previous studies to show a survival benefit is likely a result of a number of factors, including poor US performance, the absence of clear-cut diagnostic criteria and the absence of early curative treatments. It is now generally believed that, even accounting for the contribution of lead-time bias (i.e. patients apparently surviving longer, simply because their tumours were diagnosed earlier) and length-time bias (the interval between screening misses the more aggressive tumours that will be detected upon symptoms appearance), improved methods of surveillance, diagnosis and treatment will lead to improved cost effectiveness of surveillance programs [18]. Consequently, both the European Association for the Study of the Liver (EASL) panel of experts and the American Association for Study of Liver Disease (AASLD) recommends six monthly abdominal ultrasound scanning (USS) and α -fetoprotein (α FP) measurements for high risk individuals [8, 19]. Nevertheless, α FP is known to have poor sensitivity and while it identifies some patients at higher risk, even its repeated measurement has not been shown to be cost-effective [20]. Nodules less than 1cm that are detected in a cirrhotic liver are malignant in approximately 50% of cases and therefore close follow-up every 3 months to detect any increase in size is recommended. Fine needle biopsy is generally recommended for nodules 1-2cm in diameter, but even in these larger lesions does not necessarily rule out malignancy if negative, as cyto-histology is falsely negative in 30-40% these cases. For nodules greater than 2cm within a cirrhotic liver, the diagnosis of HCC can usually be made on the basis of a single imaging technique (CT or MRI scan, contrast-enhanced US) confirming characteristic arterial hypervascularisation. If there is doubt, imaging indicating arterial hypervascularisation in association with an α FP greater than 200ng/ml may be helpful [19]. US, spiral computed tomography and MRI are the imaging modalities conventionally used to assess disease extension prior to consideration of therapy. With the improvements in these techniques, angiography for diagnostic and staging purposes is rarely necessary. For lesions which remain indeterminate, biopsy should be considered.

To biopsy or not to biopsy

The prognosis of cancers typically depends on the histologically determined tumour grade in association with its radiological and clinical staging. This is clouded somewhat in liver cancer assessment as the degree to which the underlying liver function itself is impaired is an additional important determinant of outcome. An additional limitation is the general reluctance of carers to biopsy liver lesions. The reasons for this are two-fold. First, malignant seeding during percutaneous biopsy is a rare but recognised complication.[21] Second, the significant advances in radiological imaging have lead clinicians to question the additional benefit of liver biopsy in HCC diagnosis. The advantages of biopsy, however, are not simply to confirm the diagnosis, but to stage and characterise the disease in a way that can

have dramatic consequences on patient treatment – hence it is not surprising that avoiding liver biopsy remains a highly contentious issue.

Some units insist on positive histological proof of HCC before liver transplantation in all cases. The value here is clear-cut. Histological assessment can A) confirm the diagnosis and avoid radical intervention inappropriately for benign or non-HCC disease, B) indicate the likelihood of 5 year survival post transplant relative to other treatment modalities, based on histological features, avoiding inappropriate transplant for individuals with histologically advanced disease. This is an important issue not just for the welfare of the individual concerned, but also for those patients dying on liver transplant waiting lists – appropriate use of precious donor organs is a critical issue. This practice is supported by data from the BCLC, indicating that on their unit the risk attached to fine needle aspiration is below 0.01%. In addition, recent evidence from Fan and colleagues at a tertiary referral centre in Hong Kong have shown, after studying 828 patients with suspected HCC in whom 91 underwent fine needle aspiration and cytology (FNAC) and 737 did not, that preoperative FNAC had no adverse effect on the operability or long term survival of the patients [22].

Newcastle Hospitals NHS Trust policy: While it is preferable to establish the diagnosis and histological grade in all possible tumours before considering the most appropriate treatment, we do not feel it appropriate to biopsy lesions in which there is very little doubt about the underlying diagnosis. Even if biopsy of suspected lesions is only be performed under expert guidance, the risks of tumour seeding or life threatening haemorrhage is not zero. Furthermore, waiting for biopsies to be done laparoscopically by experienced surgeons can introduce significant delay to the commencement of appropriate therapy. As a compromise, our current practice is to biopsy indeterminate lesions only. These include lesions arising in the absence of established chronic liver disease, any atypical lesion arising in a cirrhotic liver, particularly if the AFP is not elevated. If a lesion is biopsied, it is usual to biopsy the non-tumour liver also, as this can provide useful information about the status of the underlying liver that may aid management decisions. It is not currently our practice to biopsy likely HCC lesions in cirrhotic individuals being assessed for transplant unless there is significant doubt about the underlying diagnosis. Presently, no transplant for HCC has been ‘inappropriate’ with this practice on our unit.

For those undergoing biopsy, there are two routes: 1) **the percutaneous route.** Accuracy is aided by the use of USS performed by a senior radiologist. This practice is limited to lesions which do not abut the capsule and to individuals with normal clotting. If the radiologist is uncomfortable about the location, or degree of vascularity, the approach is deferred to the laparoscopic route. Occasionally, an alternative is to biopsy a lesion at the same sitting as treatment angiography or radiofrequency ablation, as experts are on hand with equipment available to detect early bleeding and deal with it (embolisation via the hepatic artery; ablation of the bleeding point/tract); 2) **the laparoscopic route.** Laparoscopic assessment in association with doppler USS is very useful, particularly in the case of multiple lesions. In addition, lesions abutting the liver capsule can be biopsied ‘through’ non-malignant liver in order to reduce the risk of seeding. The laparoscopic assessment is performed by only experienced surgeons. A recent series of laparoscopic assessment and biopsy of primary and secondary hepatic tumours in 310 patients confirmed no complications and no incidences of malignant seeding.[23]

To reduce the incidence of negative biopsy findings, an additional biopsy 5-10 cm from the lesion is performed. Comparative histological analysis reduces negative reporting [24]. The total number of passes on one occasion does not exceed 3, particularly in the case of percutaneous biopsies. The incidence of complication for percutaneous biopsy, while small, has been shown to increase above this number [25, 26]. USS guided biopsies are performed with either a 16G or 18G tru-cut needle. While there is no definitive human data indicating that increased size of biopsy needle increases the complication rate [27], biopsy studies in anaesthetised pigs do indicate, as one might suspect, that there is statistically more bleeding when comparing 14G (2.1mm) with 16G (1.6mm) or 18G (1.2mm)[28].

Staging systems in HCC

***All patients should be staged according to BCLC, Okuda & CLIP (see Appendix A) prior to consideration of treatment options**

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.[29] 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.[30] Although none has been independently validated in the UK, the key role of staging in the management of HCC is well recognised [8, 19] 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 an assessment and 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 [31], 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. Their Child-Pugh score, reflecting their functional liver reserve, should be calculated, and their stage according to OKUDA and CLIP scores determined. These can provide a helpful prognostic guide for frank discussions with the patient when considering treatment options.

Child-Pugh (CP) Score	1	2	3
Encephalopathy	None	Grade 1-2	Grade 3-4
Ascites	Absent	Mild	Moderate
Bilirubin ($\mu\text{mol/l}$)	17-34	35-49	>50
Albumin (g/l)	>35	28-35	<28
PT (seconds \uparrow)	1-4	5-10	>10
Grade A = 5-6; Grade B = 7-9; Grade C>9			

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

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	

CLIP Score	0	1	2	Median survival (months)
CP Stage	A	B	C	Score 0 = 42.5; Score 1 = 32 Score 2 = 16.5; Score 3 = 4.5 Score 4 = 2.5; Score 5+6=1
Tumour Morphology	Uninodular ≤ 50%	Multinodular ≤ 50%	Massive >50%	
AFP (ng/ml)	<400	>400		
PVT	no	yes		

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	

The Barcelona-Clínic- Liver-Cancer (BCLC) staging system [29, 32] was constructed based on the results obtained in the setting of several cohort studies and randomised clinical trials (RCTs) by the Barcelona group. The proposal, shown in Figure 1 and discussed in some depth below, is not a scoring system, but rather a regularly updated staging classification resulting from the combination of the data of several independent prognostic studies in different disease stages and treatments. As a whole, it has become a widely used clinical tool to guide treatment decision making. It includes variables related to tumour stage, liver functional status, physical status and cancer related symptoms. It identifies those with early disease who may benefit from curative therapies, those who may benefit from palliative treatments, as well as those with a particularly poor outlook who should receive symptomatic care only. Patients diagnosed at an early stage may achieve a 5-year survival between 50% and 70%. Those that are diagnosed at an intermediate or advanced stage belong to the so-called non-surgical HCC category and their survival depends on the existence of cancer related symptoms and the presence of vascular invasion or extrahepatic spread - those asymptomatic without invasion or dissemination may achieve a 50% survival at 3 years, while the median survival those with an adverse profile is less than one year.

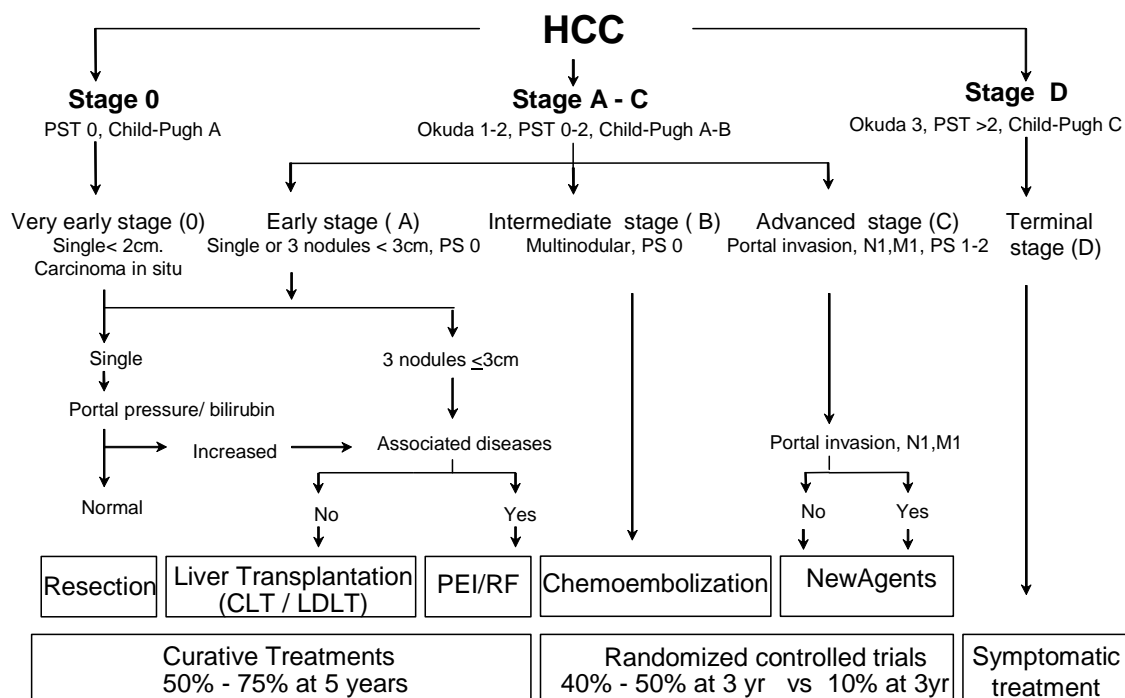


Figure 1. Staging system and treatment strategy according to the BCLC criteria, modified for Newcastle NHS Combined Trust. Patients are stratified according to their clinical, tumour and biochemical characteristics into four major strata: early, intermediate, advanced and terminal. Treatment selection is decided according to stage allocation. Any patient undergoing resection or transplant that develops recurrent disease will be eligible for local ablative, chemoembolic, or New Agent therapy. Any patient receiving ablative therapy or chemoembolisation deemed to be a treatment failure at three months (as determined by clinical assessment, α FP, and follow up CT-scan) will become eligible for New Agent therapy. 'New Agent Therapy' presently describes consideration for entry into a medical trial in the NCCC.

Treatments

Treatment options for HCC patients include curative interventions, such as resection, liver transplantation and percutaneous ablation, as well as palliative chemoembolisation. Before any decision regarding treatment is made, however, the initial patient assessment should address and answer a number of key issues. These are discussed below, but are also **summarised in the treatment algorithm shown in Figure 1.**

The status of the non-tumorous liver

Knowledge of the status of the non-tumour liver is essential. Patients with non-cirrhotic disease are good candidates for liver resection or other potentially liver damaging therapies such as chemoembolisation. The vast majority of HCC patients, however, have either established cirrhosis (85-90%) or non-cirrhotic chronic liver disease. The management of these patients presents a challenge. Clearly, individuals with decompensated cirrhosis cannot undergo any invasive therapy that

may precipitate or accelerate liver failure. These include both surgical and some targeted approaches such as chemoembolization. The first line option for these decompensated individuals, if they meet additional criteria, is liver transplantation [32]. In fact, only individuals with Child-Pugh A chronic liver disease should ever be considered for resection and only after a more sophisticated assessment to identify the subgroup that will perform well after surgery. This includes individuals with a normal serum bilirubin and/or those without even mild portal hypertension. (portal venous pressure gradient less than 10mmHg)[33, 34].

The size and extension of the tumour

Evaluation of tumour extension, with a search for the presence of daughter nodules, extra hepatic disease and/or portal vein thrombosis is necessary in all cases. This can be performed using a combination of US and CT-scan or MRI. Angiography has largely been superseded by these less invasive techniques. It still occasionally has a place, for example in individuals unable to undergo MRI scan in whom CT scan information is insufficient. The search for extra-hepatic disease may include chest CT-scan or a bone scan. The presence of tumoral portal invasion or metastatic disease leads to a bleak prognosis and precludes curative intervention.

The general condition of the patient

The general condition of the patient should be assessed before taking any therapeutic decision. This includes consideration of co-morbid conditions that may increase peri-operative or intervention related morbidity and mortality, but also by the assessment of cancer-related symptoms as reflected by their performance status (PS) score. This is used to quantify functional status in cancer patients [31] and if heavily affected (PS=3-4) serves to identify patients with advanced or terminal disease that will not benefit from any form of active intervention[35].

Resection

This is the treatment of choice for HCC in non-cirrhotic patients i.e. 5% of cases in western countries and up to 40% of cases in Asia owing to the increased frequency of HBV-related disease. In cirrhotic patients, however, the 3 year survival post resection 20 years ago was less than 50% [36, 37]. Several major advances have steadily improved these figures in recent years, including earlier diagnosis in asymptomatic phases of disease, accurate staging of the disease identifying favourable tumour characteristics, and refined functional evaluation of the underlying liver function enabling the prediction of outcome post surgical intervention.

Most groups restrict the indication for resection to patients with a single tumour as shown by state of the art imaging techniques. The size of the tumour is not a clear cut limiting factor – the risks of vascular invasion and dissemination increase with size, but occasionally tumours may grow slowly to a huge size, without evidence of invasion or satellite disease. In these cases the risk of recurrence post resection is not significantly increased compared to smaller tumours. Some groups perform chemoembolisation of larger tumours, hoping to convert larger non-surgical lesions into resectable ones [38]. Others use portal vein embolisation of the hepatic lobe hosting the tumour in order to induce compensatory liver growth in the non-affected lobe in order to increase its functional capacity if a major resection is planned [39]. The benefits of these interventions in large series are not well established. Large RCTs defining the risks and benefits of these practices are required.

For many years the selection of candidates with potentially resectable tumours has been based upon the Child-Pugh score. However, even Child-Pugh A patients may perform poorly. The Japanese groups rely on the Indocyanine retention test of hepatic function, using the rate of hepatic clearance of the dye, to guide their decisions regarding the appropriateness and extent of liver resection [40]. Portal pressure and bilirubin have been established as the best parameters to select optimal surgical candidates in Europe [34]. Clinically relevant portal hypertension (PHT) can be defined as the presence of either a hepatic vein pressure gradient of >10mmHg, oesophageal varices, or splenomegaly with a platelet count of <100,000/mm³. Subjects without relevant PHT and normal bilirubin achieve 5 year survival rates of 70%, whereas this decreases to 50% in patients with PHT, and to 25% in those with PHT and a raised bilirubin. **In Newcastle, if it is unclear whether or not a patient has PHT, hepatic vein pressure gradient is estimated using radiologically placed a venous catheter.** Occasionally, selective portal vein embolisation may be performed, aiming to encourage proliferation and hypertrophy of the non-tumour liver, if this is regarded as small pre-operatively. This is at the discretion of the surgical team responsible for the patient.

Even restricting resection to the best candidates, tumour recurrence rates exceed 50% at 3 years. When present, it influences long-term survival. The most powerful predictors of post-operative recurrence are the presence of microvascular invasion, poor differentiation and satellite lesions [34, 41-43]. This reflects the fact that the majority of recurrences result from dissemination from the primary tumour, rather than being *de novo* HCC [44]. Currently there is no effective method proven to diminish recurrence. Pre-operative chemoembolisation or adjuvant chemotherapy have no efficacy and may complicate the intervention [45]. Preliminary studies indicating benefit from internal radiation [46] and adoptive immunotherapy [47] (using activated lymphocytes) require validation, as do the apparent successes of retinoids [48] and interferon in preventing *de novo* tumours [49] or recurrence after percutaneous ablation [50].

Liver Transplantation

Individuals with HCC played a major role in the pioneering days of liver transplantation. At a time when the success of this radical intervention was unknown, the risks were considered acceptable for HCC patients, owing to the lack of alternative treatments and a dismal life expectancy. Although recurrence was high in the early years (32-54%) and survival poor (<40% 5 years), this practice changed the treatment strategy for HCC and was instrumental in defining the criteria we now use for selection of favourable candidates [51]. By selecting the 'optimal patients' i.e. those with a single HCC \leq 5cm or up to three nodules \leq 3cm, the 5 year survival is 70% with a recurrence rate below 15% [34, 52, 53].

Although many believe that transplantation should be the first line option for treatment of early HCC, as it cures both the tumour and the underlying disease, the shortage of donors and long waiting list times impose a grim reality even for those eligible at the time of first assessment. The United Network of Organ Sharing (UNOS) data indicate that almost as many patients are excluded while waiting, as a result of progressive disease, as are effectively transplanted [54]. In the United States, UNOS adopted the model for End-Stage Liver Disease (MELD) system to rank or prioritise patients awaiting orthotopic liver transplantation. A composite score based on the

bilirubin, prothrombin time, creatinine and aetiology is used for non-cancer patients and a variable score was initially granted to HCC patients [55]. Patients in stage I (single < 2cm) received 24 points and patients in stage II (single 2-5cm or 3≤3cm) 29 points. However, this resulted in an unfair priority for HCC patients as compared to non-cancer patients [56]. Although the MELD scoring system is widely used in the UK, patients with an HCC are noted and prioritised locally, rather than being given an automatic points advantage.

According to estimates from available data, a waiting time of 6 months would reduce the drop-out of HCC patients from transplant waiting lists to less than 10%. For waiting times above this, several strategies to impede tumour progression while waiting for a donor have been proposed. Systemic chemotherapy has no efficacy despite encouraging preliminary data [57]. Robust RCTs comparing active intervention versus no therapy for these individuals are lacking. Most groups perform transarterial chemoembolisation upon listing because it reduces tumour burden and delays tumour progression [38, 58]. As this treatment may induce liver failure and death in patients with decompensated disease it cannot be applied to all candidates. Patients with small tumours can be ablated by percutaneous ethanol injection or radiofrequency ablation [59]. One potential draw back of this practice is seeding due to tumour puncture. The risk is mostly restricted to peripheral tumours that cannot be accessed through a rim of non-tumoral liver [60], and is more likely using larger needles. As ethanol injection uses thinner needles, this may be the most appropriate course of action, but direct puncture of nodules without a rim of non-tumour liver should always be avoided. A laparoscopic approach and radiofrequency ablation for peripheral tumours may circumvent this issue.

An alternative solution to the long waiting list times is to expand the numbers of available livers. While strategies here include the use of marginal livers as well as domino or split liver transplantation, it is the introduction of living donor liver transplantation (LDLT) [61] that possibly has the greatest potential. Over 2000 adult LDLTs using the right hepatic lobe have been performed throughout the world. The drawbacks are the 0.5% donor mortality and 20% recipient morbidity. At present, recipient survival post LDLT appears similar to cadaveric transplantation, but the long term outcome is unknown [62]. There is a suggestion, for example, that re-infection of the graft in HCV patients is more severe in live recipients than cadaveric [63]. While accepting that long term data are still awaited and live donation programs are likely to face the problems of patient and/or donor refusal, blood group incompatibility, medical contraindications and funding restrictions, there may be potential within LDLT practice to extend the limits currently applied to HCC transplantation. Since the transplant can be done without delay, with highly accurate staging, a set of expanded criteria have been proposed by several groups [64, 65]. The Barcelona Liver Unit proposes the following limits for live donation: single tumour ≤ 7cm, 3 nodules ≤ 5cm, 5 nodules ≤ 3 cm, or a down-staging to conventional criteria after local or regional therapy lasting more than 6 months [35]. It is expected that survival will still exceed 50% at 5 years, but the applicability of this program is clearly reduced. In general, live donation may not only benefit some individuals with more extensive disease, but also reduce waiting list times for cadaveric recipients. LDLT is being actively explored in the UK and it is likely that this alternative may well be available within Newcastle shortly.

Initial concerns that immunosuppression post transplant may accelerate the growth of recurrent or metastatic HCC [66] are now thought unfounded [67], adherence to selection criteria being the single key factor predicting post-operative recurrence. There is currently no data indicating that systemic chemotherapy pre or post transplant for these individuals has any impact on disease recurrence. Some centres administer systemic chemotherapy to all individuals with satellites or vascular invasion at pathological examination post transplant, but there is no data to support this policy.

Percutaneous Treatments

Destruction or ablation of tumour cells can be achieved percutaneously by the injection of chemical substances (ethanol, acetic acid, and boiling saline) or by inserting a probe that modifies local tumour temperature (radiofrequency, microwave, laser, and cryotherapy). These are the best options for patients with early HCC who are ineligible for resection or transplantation [68-73]. Whether or not they may be the best option for all patients is unknown due to the lack of RCTs comparing them with resection. Some Japanese centres, however, do offer ablation as first line therapy [74] and the debate surrounding this continues.[75]

Percutaneous ethanol injection (PEI), usually performed under US guidance, is the best known and studied of the percutaneous therapies. It is highly effective for small HCCs and has a low rate of adverse effects. It achieves complete tumour necrosis in 90-100% of HCCs smaller than 2cm in diameter. This is reduced to 70% in 2-3 cm tumours and 50% in 3-5 cm tumours [69, 76]. The injection is repeated on successive days and the efficacy of ablation assessed at 1 month by dynamic CT [8]. The absence of contrast uptake in the tumour reflects tumour necrosis, while the recognition of contrast uptake constitutes treatment failure. The 5 year survival of Child-Pugh A candidates with a complete response is 50% [70]. Complete necrosis in tumours larger than 3cm, however, is rarely achieved, possibly because of the presence of septae preventing the ethanol accessing the whole tumour volume. Overall, the rate of recurrence is similar to that seen for surgical resection and occurs within the vicinity of the treated nodule.

Radiofrequency ablation (RFA) is the most extensively used alternative to PEI. It can be applied through single or multiple cooled-tip electrodes, either percutaneously, laparoscopically, or intra-operatively. It is claimed to achieve the same objective response as PEI in significantly fewer sessions(87;88). Theoretically it may be superior in tumours greater than 3 cm by disrupting intra-tumoral septae. Presently, RFA can be considered as the treatment of choice for lesions less than 2cm, [77] but close follow-up is advised. For larger lesions, RFA should not be regarded as a curative therapy and liver transplantation should be offered if appropriate. Up to 70% of lesions treated with RFA show evidence of recurrence at 18 months. A size greater than 3cm predicts both a high likelihood of recurrence and the development of additional tumours. [78] The main drawbacks of RFA are its higher cost and associated mortality of 0.5% and morbidity of 10%. Superficial tumours should not be treated percutaneously by direct puncture because of the risk of tumour seeding [60]. In addition, tumours in close proximity to the hilum or gall bladder should not be treated by RFA as there is a high risk of damaging the biliary tree. Treatment of tumours in close proximity to the heart or major vessels should also be avoided.

Palliative therapy

As the majority of HCC patients over the last 25 years have been diagnosed at advanced stages of disease, where no standard therapy has been universally established, a whole host of alternative therapies have been advocated. In the main, relatively small studies have analysed the effectiveness of treatments such as embolisation, chemoembolisation, arterial or systemic chemotherapy, internal radiation with I¹³¹, proton beam radiation, hormonal compounds, and immunotherapy [79]. Systematic review and meta-analyses of all available studies indicated, until very recently, that only chemoembolisation has a beneficial impact in survival [79]. Estrogen blockade with tamoxifen unequivocally lacks anti-tumoral effect and has no impact in survival. Other treatment approaches, including internal irradiation with I¹³¹ [80, 81], octreotide [82, 83] and IFN [84, 85], have been assessed in the setting of too few small studies that do not have the statistical power as yet to provide solid conclusions. Similarly, systemic chemotherapy (most often doxorubicin) has marginal activity (<10% response rate) with no proven impact on survival [86, 87].

Sorafenib is a multikinase inhibitor which has recently been shown, in two independent international randomised controlled trials, [88, 89] to delay progression and to improve median survival by a few weeks in a very select group of patients. Patients were those with very advanced tumours, but with an otherwise excellent performance status and normal liver function, which in reality describes a small minority of our patients. Neither of these studies demonstrated an improvement in patient quality of life. Sorafenib has become the standard medical therapy for patients with advanced HCC in the USA and in some European countries. Based on the cost of this drug, in particular its cost per QALY, this drug has not been approved by the National Institute for Clinical Excellence (NICE), and is not available as an NHS treatment in the UK. While this is disappointing, as this is the only medical therapy shown to have any benefit at all in patients with HCC, it should be remembered that it is only proven to be effective in a very small number of patients. For this particular group, we encourage active participation in medical trials, through collaboration with Dr Kate Sumpter in the NCCC (Northern Centre for Cancer Care) in the Sir Bobby Robson Cancer Trials Research Centre. Here patients have the opportunity to receive novel agents which may have anti-tumour effects. Sorafenib is now the accepted 'control' arm for some of these studies, funded by the pharmaceutical industry, rather than the NHS at the present time.

Arterial Embolisation

The majority of hepatic blood flow in a normal liver arises from the portal vein (70%) while the remainder arises from the hepatic artery. In contrast, HCC are predominantly supplied by the hepatic artery. Arterial neo-angiogenic activity in malignant tumours typically results in lesions that are hypervascular. This characteristic forms the pathologic basis of both the typical diagnostic radiological features of HCC and the therapeutic rationale supporting arterial obstruction. Embolisation of the arterial blood supply to the tumour is a practice typically considered for individuals with non-surgical HCC that are also excluded from percutaneous ablation (often because of multifocal disease or tumour size), but in whom there is no extra hepatic disease. The main contra-indication is the lack of portal blood flow (secondary to portal vein obstruction with thrombosis or tumour, porto-systemic anastomosis or hepatofugal flow) as in these individuals the arterial supply may be the predominant liver blood supply and any intervention obstructing

this may precipitate liver failure. Patients with advanced disease (Child-Pugh C) should also be excluded from this treatment.

Obstruction of the hepatic artery induces extensive tumour necrosis. Gelfoam prepared as 1mm cubes is the most commonly used agent, but polyvinyl alcohol, alcohol, starch microspheres, blood clots and metallic coils have all been used. Hepatic artery obstruction is performed during an angiographic procedure and is known as transarterial, or transcatheter arterial, embolisation (TAE). The procedure requires the advancement of the catheter into the hepatic artery and then lobar and segmental branches. The aim is to interrupt blood flow to the tumour in as selective a way as possible, avoiding injury to the surrounding non-tumour liver as much as possible. This may not be possible if treating multifocal HCC involving both right and left hepatic lobes. The injection is done slowly to avoid the backward flow of embolic particles that could embolise arterial vessels outside the liver. Care to avoid obstruction of the cystic artery and ensuing necrosis of the gall bladder is standard practice.

When TAE is combined with injection into the hepatic artery of a chemotherapeutic agent, most commonly doxorubicin, the procedure is known as transarterial chemoembolisation (TACE). Prior to January 2009, it was usual to suspend the chemotherapeutic agent in lipiodol, an oily contrast agent that is selectively retained within the tumour. With this method, however, the chemotherapeutic agent is not retained in the tumour and the side effects of intra- are the same as for systemic administration, namely nausea, vomiting, bone marrow suppression, alopecia and renal impairment. As of January 2009, the TACE procedure has been performed with drug eluting beads (DEB-TACE), the obvious advantage being that both bead and chemotherapy agent are retained in the tumour, with fewer chemotherapy related side effects[90, 91] . Audit of this change in practice is ongoing. Whichever form of TACE is employed, hepatic artery obstruction with induced necrosis of the tumour may be associated with what is known as 'post-embolisation syndrome'. This is seen in more than 50% of individuals and consists of fever, abdominal pain and a moderate degree of ileus. It is usually self limiting and most patients can be discharged within 48 hours. Fasting is required for 24 hours prior to the procedure and intravenous hydration is mandatory. Prophylactic antibiotics are used, but this policy is regularly reviewed with microbiology staff. Post-procedure fever is usually a reflection of tumour necrosis, but if it persists severe infectious complications such as a hepatic abscess or cholecystitis should be considered.

A partial response, accompanied by delayed tumour progression and vascular invasion, is induced by both TAE and TACE in 15-55% of patients [58, 79] and can be assessed by the decrease in concentration of tumoral markers and/or the identification of intra-tumoral necrosis and reduced tumour burden on dynamic CT scan or MRI. However, the residual tumour typically recovers its blood supply and repeated treatment is necessary. In the cumulative meta-analysis of all RCTs [58, 92-97], a significant survival benefit (41% at 2 years versus 27% in the control group) has been shown for chemoembolisation, but never confirmed for embolisation alone [79].

Summary page

Patients with established cirrhosis should be followed up by a hepatologist and undergo HCC surveillance

Patients with a suspected HCC should be referred to the HPB MDM. Contact Caroline Baker; Sister Alison MacDonald; or Helen Dobson (secretary to Dr Helen Reeves. Tel: 0191 2137210 Fax: 0191 2231249)

Diagnosis is dependent on whether or not the patient has evidence of underlying liver disease, and will include imaging, AFP and possibly biopsy.

Staging for HCC is necessarily combined with parameters reflecting liver function and performance status, as these are key to prognosis.

Treatment options are dependent on the stage, and include surgical resection, liver transplantation, local ablation, chemoembolisation, or possibly a medical therapy within the setting of a medical trial.

Good communication with G.P. and local hospital, as well as local/regional palliative care teams is essential.

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