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Classic diseases revisited

Hepatocellular carcinoma

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Summary

Primary hepatocellular carcinoma is one of the 10 most common tumours, and the most common primary liver malignancy, in the world. In the majority of cases, it occurs against a background of hepatitis B or C viral infection and/or liver cirrhosis, and is associated with a dismal prognosis of a few months. Current treatments in routine clinical practice are surgical resection and liver transplantation, but these therapies are applicable to only a small proportion of patients and prolongation of survival is restricted. Other treatment options include intra-arterial chemotherapy, transcatheter arterial chemoembolisation, percutaneous ethanol injection, cryotherapy, thermotherapy, proton therapy, or a wide range of their possible combinations. The current lack of definitive data, however, limits the use of these therapies. Another option is gene therapy, which although in its infancy at the present time, may have a significant role to play in the future management of hepatocellular carcinoma.

Keywords: hepatocellular carcinoma; hepatic resection; liver transplantation; transcatheter arterial chemoembolisation

Hepatocellular carcinoma
• the most common primary liver malignancy • chronic hepatitis B/C infection and cirrhosis are important predisposing factors

Box 1

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Primary hepatocellular carcinoma (HCC), sometimes called hepatoma, is the most common form of primary liver malignancy[1] and is among the 10 most common tumours[2] in the world. There is, however, significant geographical variation in distribution; in some parts of Asia and Africa the prevalence is more than 100/100 000 population, whereas in Europe and North America it is estimated as 2–4/100 000 population.[3 4] Within each region, Afro-Caribbeans have approximately a four-fold higher risk than Caucasians, and worldwide there is a clear predominance in males, ranging from 8:1 in countries with a high frequency of HCC, to approximately 2:1 in populations with a low frequency.[5]

Pathogenic factors

Chronic hepatitis B or C viral infection appears to be the most important risk factor for HCC.[6] In addition, over 70% of HCC patients in Western countries have underlying liver cirrhosis (box 1).[3] The risk of developing HCC varies according to the cause of the cirrhosis itself, with viral hepatitis and alcoholic cirrhosis carrying the greatest risks at 40% and 25%, respectively. Other causes of cirrhosis, such as primary or secondary haemachromatosis, α1-antitrypsin deficiency, Wilson's disease and primary biliary cirrhosis, are less frequently complicated by HCC.[2 3]

Cirrhosis is not, however, a prerequisite for HCC. For example, hereditary tyrosinaemia has a 40% risk of developing HCC despite adequate dietary control; porphyria cutanea tarda and acute intermittent porphyria are complicated by HCC[7]; Thorotrast (now an obsolete contrast agent) and anabolic steroids are also thought to have HCC-inducing properties.[3] In all cases, the pathogenesis remains unclear. Contributing factors may include aflatoxin B1 in food, p53 gene mutations, repeated cycles of necrosis and regeneration, and chronic inflammation.[2 5]

Morphology

Hepatocellular carcinoma may appear macroscopically as nodular, massive or diffuse types (figure 1). All three forms may cause hepatomegaly. Areas of necrosis, haemorrhage and fatty infiltration are often present, giving rise to a polychromic appearance (yellow, red and green), and HCCs may take on a green hue when composed of well-differentiated hepatocytes capable of secreting bile. Microscopically, HCCs range from well-differentiated to highly anaplastic undifferentiated lesions. They may be trabecular, sinusoidal, pseudoglandular or solid; a single tumour may exhibit elements of all types. A single large hard 'scirrhous' tumour with fibrous bands represents the fibrolamellar carcinoma, a variant of HCC which tends to occur in young women. This tumour has no association with hepatitis B or C virus or cirrhosis, and carries a significantly better prognosis.[3 5]

Clinical features

The presentation of HCC varies according to the size of the lesion(s). With greater use of imaging techniques such as ultrasound, small lesions are increasingly discovered incidentally.[3] In many cases, the clinical manifestations are masked by features of underlying cirrhosis or chronic hepatitis.[5] Large tumours may cause pressure effects and presentation may be with ill-defined upper abdominal pain, malaise, weight loss, fatigue and sometimes an awareness of an abdominal mass or fullness. Jaundice, a result of compression of the common bile duct, or occasionally tumour embolisation, and ascites may occur and suggest advanced disease or co-existing cirrhosis (box 2). Other presentations include the paraneoplastic syndrome, hypercalcaemia, hormonal imbalance, gastrointestinal or oesophageal variceal bleeding and tumour-necrosis induced fever.[3 5]

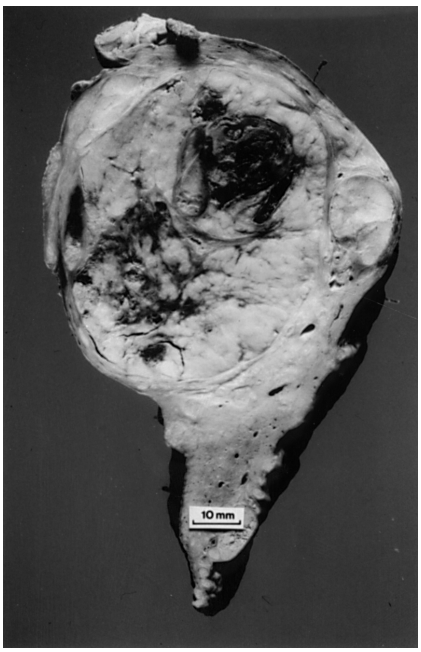

Figure 1 Hepatocellular carcinoma in left liver lobe specimen cut vertically. Reproduced with kind permission of the Gordon Museum, Guy's Hospital, London

Presentation

- varies according to the size of the lesion
- small tumours often detected on ultrasound performed for other reasons
- large tumours may present with ill-defined upper abdominal pain, weight loss and non-specific malaise
- jaundice and ascites suggest advanced disease or co-existing cirrhosis

Box 2

Diagnosis

A focal liver lesion is usually first identified by ultrasound and further evaluation is required in order to differentiate between benign and malignant tumours. Clinical examination and liver function tests are simple first-line bases. Alkaline phosphatase in particular may be raised, but this offers little diagnostic significance alone. Alpha-fetoprotein is produced by over 80% of HCCs and may be of value if markedly elevated and combined with a low β-human chorionic gonadotropin (α-fetoprotein levels may also be raised in testicular teratoma, benign liver disease, normal pregnancy and obstetric abnormalities). Carcinoembryonic antigen levels are less often elevated and less specific; they are usually raised with colorectal liver metastases. Des-γ-carboxyprothrombin, a prothrombin precursor resulting from failure to carboxylate glutamic acid residues, may be detected in the serum of 75–90% of HCC patients.[8] Tumour markers such as α-fetoprotein are, however, particularly helpful in monitoring HCC activity after treatment and in screening cirrhotic patients at risk of developing HCC.

Further investigations employed vary worldwide, but imaging the lesion usually begins with ultrasound (if not already performed), which provides information on the shape, echogenicity, growth pattern and vascular involvement of the tumour.[9] Computed tomography (CT) or magnetic resonance imaging (MRI) is then used to evaluate the extent of HCC.[10] The value of these modalities may be increased by the use of contrast agents.[11] Many combinations of precise technique and agent have been proposed; examples include CT following intra-arterial injection of Lipiodol (a lipid derived from poppyseed oil containing iodine), which was shown in one study to detect a greater proportion of small HCCs in 22 patients who were subsequently surgically treated (86% *vs* 70% ultrasound, 65% CT, 62% MRI, 73% digital subtraction angiography; $p<0.05$).[12] Helical CT hepatic arteriography combined with CT performed during arterial portography is another example and has been suggested to be diagnostically more accurate than several forms of MRI (spin-echo, phase-shift gradient-recalled echo and triple-phasic dynamic GRE) in the pre-operative detection of HCC in 37 patients with cirrhosis.[13]

MRI techniques have, however, produced favourable results in other studies. Arterial-phase dynamic MRI has been reported to allow greater detection of HCC than arterial-phase CT (but not for the delayed phase),[14] and MRI during arterial portography has been suggested in another study to have greater benefit than CT during arterial portography, in terms of the ability to identify benign lesions and pseudolesions.[15] Despite numerous approaches which have been proposed, no single investigation has been shown to be clearly superior and it may be that MRI and CT scanning simply yield similar detection rates for HCC.[16]

When aggressive treatment of HCC is considered and the diagnosis remains uncertain, a percutaneous liver biopsy or fine needle aspirate under ultrasound or CT guidance may aid diagnosis.[4] In a study of 121 patients with suspected HCC of 3 cm or less on ultrasound, 118 were finally diagnosed as HCC by percutaneous biopsy, CT and angiography.[17] Retrospective analysis of results produced a correct diagnosis of HCC in 87.3% by histology, 55.1% by CT and 52.5% by angiography. When tumours of 1.5 cm or less were studied in these patients, the correct diagnosis was obtained in 88.5%, 34.6% and 23.1%, respectively. Based on these findings, it has been suggested that percutaneous biopsy and histological examination may be the most reliable method of making a definitive diagnosis of small HCC.

Histological confirmation of all primary liver tumours, however, is controversial; risks of haemorrhage, inadequate sampling and needle track metastases *versus* false positive results of imaging alone make this a debatable issue. Jourdan and Stubbs[18] reported two patients with resectable liver tumours in whom percutaneous biopsy resulted in needle track seeding. Subsequent hepatic resection was not curative due to biopsy track tumour recurrence, and the authors suggest that such percutaneous biopsy of potentially resectable tumours may not be beneficial. The safety of the biopsy procedure may, however, be improved if the length of interposing liver parenchymal track is not less than 1 cm, as shown in a study of 139 liver biopsies in which two cases of bleeding after the procedure occurred, both having interposing tracks of less than 1 cm.[19]

Finally, tumours are staged by CT or MRI to determine the extent of disease, with the aid of laparoscopy if required.[3] The severity of chronic liver disease where appropriate is estimated using the Child-Pugh classification of groups A, B or C, based on bilirubin and albumin levels, the presence of ascites and encephalopathy and the state of nutrition.[20]

Morphological indicators of HCC[24]

- nuclear shape factor of less than 0.93
- coefficient of variance of nuclei of more than 5%
- average width of trabecular cords greater than three cells
- nucleocytoplasmic ratio increased to more than 0.3
- cellular density of more than 40 liver cells
- individual nuclear dimension larger than 50 μm

Box 3

DIFFERENTIAL DIAGNOSIS

Radiological imaging of hepatic lesions has improved dramatically over the last two decades, but the differential diagnosis of a liver nodule may still be difficult.[21] In particular, liver cell adenoma and focal nodular hyperplasia are benign lesions which, although themselves rarely producing serious clinical consequences, may do so when radiologically or histologically mistaken for HCC.[22] Adenomatous hyperplasia (AH) and atypical AH should be distinguished from well-differentiated HCC,[23] and poorly differentiated HCC from metastatic poorly differentiated adenocarcinoma.[21] Hepatic haemangioma, abscess, regenerative nodular hyperplasia, focal fatty change, carcinoid tumour and metastases may also resemble HCC.[21 23–26]

In order to address the difficulties encountered in differentiating between HCC and other liver lesions, Motohashi *et al* performed histopathological and morphometrical analyses on 208 cases of various hepatic diseases with the aid of an image analyser.[24] Six features suggestive of HCC were identified and are presented in box 3.

Natural course

The natural course of HCC is progressive tumour growth until it encroaches on hepatic function, and spreads usually first to the lungs and then to other sites.[5] All patterns of HCC have a tendency to invade blood vessels, producing extensive intrahepatic metastases, and occasionally extension into the portal vein or inferior vena cava may occur, spreading in extreme cases into the right atrium.

The prognosis has traditionally depended upon tumour stage and residual hepatic function. Zhou *et al*[27] analysed 1248 cases of HCC and reported that discovery approach, stage, original γ-glutamyl transpeptidase, resection, radical resection, tumour size, number and capsule all had highly significant effects on prognosis (all $p<0.001$); cirrhosis, HBsAg, local resection and tumour embolus in the portal vein had a lower but still significant effect (all $p<0.05$). This study demonstrated, however, that age, sex, hepatitis and, surprisingly, differentiation of primary HCC cells, had no significant effect on prognosis (all $p>0.05$).

Median survival lengths have been reported as under 13 months, eg, 0.9–12.8 months for patients receiving no specific treatment[6] and 3–6 months after the onset of symptoms.[7] In a retrospective study of 157 untreated patients, 18% of whom had extrahepatic metastases at the time of diagnosis, the median survival was 8.7 weeks.[28] Common causes of death in these patients were upper gastrointestinal haemorrhage 34.1%, cancer-related causes (cachexia, HCC rupture, metastatic disease) 31.8%, and hepatic failure 25.0%.

Amongst the dismal figures in survival rates, Kaczynski *et al*[29] reported a case of spontaneous regression of HCC. This tumour was found incidentally in a 73-year-old man during a laparotomy for evaluation of gastric retention, and subsequent histological and immunohistological features were found to be compatible with a diagnosis of well-differentiated HCC. Despite no treatment being given, he improved with no evidence of tumour on coeliac angiography at 15 months and by exploratory laparotomy at 3 years. The patient died 15 years after the diagnosis of HCC with no evidence of tumour recurrence. It is not known how this phenomenon occurred, but the authors suggest that, as the case was found incidentally, spontaneous regression of HCC may not be as rare as expected.

Treatment options

SURGICAL RESECTION

The aim of surgical resection is to remove the entire portal territory of the neoplastic segment(s) with a 1 cm clear margin, while preserving maximum liver parenchyma to avoid hepatic failure. In non-cirrhotic HCC patients, greater resection is tolerated as the capacity for liver regeneration is not compromised.[3]

Surgical resection appears to be the only potential curative treatment for primary HCC, associated with a significant prolongation of survival.[3 30 31] Less than 20% of HCC patients are suitable for surgical resection, however, due to the presence of cirrhosis, anatomically unresectable disease or extrahepatic and vascular spread. Cirrhosis affects postoperative survival in several debilitating ways and remains the major determinant in postoperative survival[32]:

- liver regeneration cannot occur in the cirrhotic remnant
- recurrent HCC develops in the remnant
- pre-operative clotting is abnormal in cirrhosis
- the hepatic reserve is poor.[3]

The pre-operative Child-Pugh classification, hepatic reserve,[33] and indocyanine green 15-minute retention rate[34] may also correlate with postoperative

prognosis. In non-cirrhotic HCC patients, partial hepatectomy is associated with a 5-year survival of over 30%[35 36] and as high as 68% in one study.[37] In cirrhotic HCC patients, operative mortality is higher and of those who survive the surgery, a 5-year survival of 25–30% has been recorded.[35]

Wu *et al*[38] suggested that the size of the tumour is also a significant determining factor in survival. In their study of 2051 cases, 'small' tumours of ⩽ 5 cm in diameter had a post-resection 5-year survival of 79.8% and within this group, those with 'very small' tumours of ⩽ 3 cm had 5-year survival rates of 85.3%.

HCC recurrence, however, has been reported as varying between 20% and 70%, with almost all relapses occurring within 2 years of surgery.[37] Documented complications associated with surgical resection include haemorrhage, bile leakage, stress ulceration complicated with bleeding, transient haemobilia, atelectasis, and inflammatory changes in the right lung.[39] Hospital mortality rates for resection alone vary from 5 to 24%[3]; mortality is mainly due to hepatorenal or cardiorespiratory failure, and also occasionally to myocardial infarction or disseminated intravascular coagulation.[39]

LIVER TRANSPLANTATION

Management of HCC by transplantation remains a debatable issue due to restricted availability of organ donors and a high rate of recurrence after liver transplantation,[30] thought to be due to circulating HCC cells implanting in donor hepatic tissue.[3] In addition to the standard investigations used in diagnosing HCC, patients should undergo chest and abdominal CT scans to exclude metastases or nodal disease.

Two subgroups of patients have been enrolled into liver transplant trials. In one group are large and unresectable HCCs, in the other are small incidentally discovered HCCs with concomitant cirrhosis. The variable expected prognoses of these two groups even before transplantation have led to 3-year survival rates ranging between 16% and 82%[40 41] and 5-year survival figures between 19.6% and 36%.[42 43] Survival does not appear to be influenced by patient age or gender, extent of HLA matching, rejection, immunosuppressive regimen or surgical technique used.[41] Recurrent HCC in the grafted liver, or lung/bone, may occur in over 80% of the large and unresectable tumour group at 2 years but less so in the small tumour group, where a less than 5% recurrence rate has been reported.[41 43] In addition, cytomegalovirus infection, acute rejection, atelectasis, pleural effusion, pneumonia, hepatic encephalopathy, invasive fungal infection and neurological disease have all been observed after liver transplantation.[30] Chronic liver rejection is also a major problem,[22] as are intra- and post-operative mortality rates which approach 10 to 20%.[31 42]

SURGICAL RESECTION *VERSUS* LIVER TRANSPLANTATION

Five-year survival rates for resection or transplantation alone have been reported as being in the region of 30%, depending upon the presence of cirrhosis and/or the tumour size. Although both resection and transplantation yield approximately the same results in terms of 5-year survival, it appears that transplantation achieves a better recurrence-free survival during the same time interval. In a study by Gugenheim *et al*,[44] 34 patients underwent liver resection and 30 patients with cirrhosis had liver transplantation for HCC. The results showed a 5-year survival of 13% and 5-year recurrence of 92.6% after resection, with the diameter of nodules a significant predictive factor in outcome. In the transplanted group, 5-year survival was 32.6%, 5-year recurrence 40.9% and the predictive factor for outcome this time was the number of nodules. From this, two groups of patients were identified: those with large HCC (> 5 cm and/or >three nodules) and those with small HCC (⩽ 5 cm and ⩽ three nodules), and the data were re-analysed. The study concluded that liver transplantation seems to be the best treatment for small HCCs, mainly because of a lower recurrence rate (11.1% *vs* 82.6%), but that both treatments had a high recurrence rate in large HCCs (72.3% resection, 100% transplantation).

SYSTEMIC CHEMOTHERAPY

There have been few randomised controlled trials of systemic chemotherapy, and as such, its use is limited to study groups. Many of these studies have enrolled patients with poor prognostic factors (impaired liver function, ascites, jaundice) and it is not altogether surprising that reported response rates are less than 20%, with a median survival of 2–6 months.[45–47]

The first chemotherapeutic agent used was fluorouracil,[45 48] which produced response rates of 0–10% and a median survival of 3–5 months. Combination with high-dose folinic acid did not show any improvement in outcome.[49] Variations of regimen have been more promising, such as continuous infusion fluorouracil with epirubicin and cisplatin.[50] Doxorubicin has also been considered in

the management of HCC, and response rates of 3–32% have been reported.[51] A randomised controlled trial comparing doxorubicin with no treatment, however, failed to observe a statistical difference in survival.[52] Other agents employed include epirubicin, mitoxantrone, mitomycin, platinum compounds, amsacrine, vinblastine, fludarabine, zidovudine and doxifluridine. None of these agents, either alone or in combination, have produced a significant improvement in survival. In addition, toxicity and multi-drug resistance have proven to be major complications.

INTRA-ARTERIAL CHEMOTHERAPY

This technique delivers a chemotherapeutic agent through the hepatic artery through a catheter inserted by laparotomy or angiography. The drug can be given as a 'one-shot treatment',[53] pump-driven continuous drip, or using a Port-a-catheter for repeated long-term injection.[54] Intra-arterial chemotherapy is based on the principles that:

- normal hepatic tissue is supplied by both the hepatic artery and portal vein, whereas HCC tumours derive most of their blood supply from the hepatic artery
- a lower drug dose is required, lower toxicity produced and a higher concentration of drug in tumour tissues achieved, compared with systemic chemotherapy.[55]

Fluorouracil and anthracyclines have been used intra-arterially, the latter producing response rates of up to 42%.[56] When used in combination with floxuridine, leucovorin and cisplatin, Patt *et al*[57] reported a 64% response rate to the anthracycline doxorubicin, but with significant toxicity (three related deaths). Other drugs used include mitomycin, cisplatin and mitoxantrone which have yielded 50%, 55% and 25% response rates, respectively.[58–60] These studies may not, however, reflect the potential role of intra-arterial chemotherapy in the management of HCC, as two problems have been demonstrated:

- patients selected for these studies are characterised by good performance status, good liver function and the absence of metastases[30]
- inadequate drug dosages, statistically inadequate patient numbers, and differences in regimen have been employed.

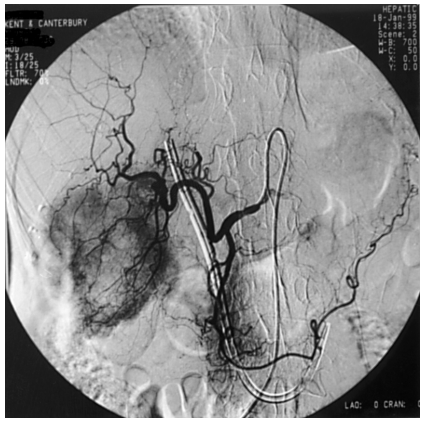

Figure 2 Chemoembolisation of a highly vascular hepatocellular carcinoma supplied by the right hepatic artery (note Carey-Coon shunt in place). Courtesy of Dr M O Downes, Kent & Canterbury Hospital

TRANSCATHETER ARTERIAL CHEMOEMBOLISATION (TACE)

This technique combines intra-arterial chemotherapy with intermittent occlusion of the hepatic artery by embolic material, in order to prolong the contact time between drug and tumour, and to induce massive tumour necrosis by ischaemia (figure 2). Normal liver tissue is permitted a degree of 'ischaemic escape' *via* portal vein blood flow, thus main portal vein thrombosis is a contraindication to TACE therapy, along with insufficient liver reserve, severe clotting abnormalities and significant arteriovenous shunting to the portal/hepatic vein.[30] The use of CO_2 microbubble-enhanced sonographic angiography may help reveal tumour vascularity before embarking upon treatment.[61]

The embolic material used is often gelatin foam powder or particles. Lipiodol is now less commonly used. These compounds have been used alone in transcatheter arterial embolisation, but the results are limited by tumour type, size and extension. Most trials documented have combined these embolic materials with chemotherapeutic agents, but as there is no standard protocol, a large number of combinations have been used. For example, Ryder *et al*[62] studied the effect of doxorubicin and Lipiodol on 67 unresectable HCC patients, and reported a $\geqslant$50% reduction in tumour size in 10 of 18 patients with small tumours (< 4 cm); five of 49 patients with large or multifocal tumours also showed a response to treatment. Survival ranged between 3 days and 4 years, with a median survival of 36 weeks. This study concluded that TACE has promising effects on small tumours but that large tumours show a poor response and indeed a higher rate of complications.[62]

Despite encouraging figures for small tumours, several randomised trials have shown no significant improvement in survival with TACE treatment; 1-year survival 24% TACE *vs* 31% no treatment,[63] 1-year survival 62% TACE *vs* 43.5%.[64] In addition, the use of TACE is associated with fever, pain and vomiting in over 60% of patients.[65 66] These complications are thought to be secondary to stretching of the liver capsule, pancreatitis, gallbladder infarction, peptic ulceration and necrosis, and are known as the 'post-embolisation syndrome'. Fortunately this is a transient side-effect and in most cases can be controlled by dipyrone or hydrocortisone.[30] Less common complications include hepatic failure, liver abscess, arteritis[67] and ruptured HCC[68] (box 4).

Treatment options

- surgical resection and liver transplantation have both produced 5-year survival rates in the region of 30%
- liver transplantation may be more effective for small tumours
- TACE combines intra-arterial chemotherapy with intermittent occlusion of the hepatic artery by embolic material and is increasingly used in clinical practice

Box 4

Selection criteria for PEI[30]

- tumour size less than 3 cm
- no severe hepatic dysfunction
- no more than three lesions
- Child A or B disease

Box 5

PERCUTANEOUS ETHANOL INJECTION (PEI)

The mechanism of action of PEI is thought to be a protein degenerative effect and a thrombotic effect,[45 69] which may induce between 70% and 100% coagulation necrosis of tumour.[70] Using local anaesthetic at the skin site, abdominal wall and liver capsule, a 22-gauge Chiba needle is introduced percutaneously into the liver tumour under ultrasound or other guidance system. Absolute alcohol (99.5%) is slowly injected, with frequent adjustment of the needle tip to achieve distribution within the whole tumour. PEI can be repeated several times a week according to tumour size and patient compliance. Contraindications to its use are gross ascites, severe clotting abnormalities and obstructive jaundice.

Good survival rates following PEI have been achieved, such as 5-year figures of 44% in Child A patients (good liver function, no ascites/encephalopathy), 34% in Child B patients (adequate liver function, mild ascites/encephalopathy),[71] and 3-year figures of 63% in patients with single lesions and 31% in those with multiple lesions.[69] Box 5 contains suggested selection criteria for PEI derived from this and similar studies.

The encouraging survival figures, however, have been derived from uncontrolled studies. In a cohort of PEI (n=30) compared with surgical resection (n=33), there was no difference in 1 to 4-year survival between the two treatments and recurrence at 2 years was higher in the PEI group (66% *vs* 45%).[72] Combination treatment with TACE and PEI may be of value[73] but a controlled trial is unlikely to be approved on ethical grounds of withholding surgical treatment from those patients with tumours thought to be resectable.[30]

Complications associated with PEI include pain, fever and transient drunkenness. Haemorrhage, needle track seeding[74] and hepatic failure are more serious adverse effects.[75] Other agents used in local injection therapy include acetic acid, demonstrated in one randomised controlled trial of 60 patients with tumours smaller than 3 cm to have a higher survival rate when compared with PEI (92% *vs* 63% at 2 years) and a lower recurrence rate (8% *vs* 37% at 2 years).[76]

CRYOTHERAPY

This form of HCC treatment involves freezing the tumour and a 1-cm margin of healthy tissue[77] using liquid nitrogen delivered by a vacuum-insulated cryoprobe, inserted under ultrasound guidance or during a laparoscopy or laparotomy. There are limited data available on the efficacy of this therapy; Zhou and Tang[78] reported a 37.9% 5-year survival in 191 treated patients and a 53.1% rate in 56 patients with tumours smaller than 5 cm in diameter. Follow-up treatment with alcohol ablation after cryotherapy may be a useful adjunct in treating residual tumour and controlling recurrences.[79]

The major complication associated with cryotherapy is damage to adjacent structures, particularly to the portal and hepatic veins. Other reported adverse effects are temperature rise, liver failure, pleural effusion and basal atelectasis.[80]

IMMUNOTHERAPY

Immunologically active agents are theoretically of use in HCC treatment, as interferons are known to play a role in viral reproduction, ie, hepatitis B/C, and as the activity of lymphokine-activated killer (LAK) cells is often reduced in HCC patients.[81] Immunotherapy has not, however, been demonstrated to achieve any significant impact on patient survival and high incidences of intolerable complications have been reported. Agents studied include interferon-α (IFN-α) alone[82] and in combination with doxorubicin[83] or fluorouracil.[84] Other studies have used IFN-γ, IFN-β, OK-432, LAK, interleukins, antibodies against α-fetoprotein, ferritin or HCC-specific antigen and bifunctional antibodies, all with no significant improvement in survival.

HORMONAL THERAPY

The use of hormonal agents, in particular tamoxifen, for the treatment of HCC has been suggested. This is based on the observations that:

- HCC tissues contain oestrogen and androgen receptors (although perhaps not in a significantly greater proportion of HCC patients when compared with normal or cirrhotic liver)[30]
- there is a clear predominance of HCC in men
- success with hormonal therapy has been achieved in other cancers.[77]

Reports on the effectiveness of tamoxifen for HCC have, however, been conflicting; some studies demonstrate an increased survival[85] in women in particular,[86] whereas others have shown no impact on survival[87] and no enhanced effect in women.[88] Other agents employed include flutamide,[89] ketoconazole[90] and buserelin,[91] all with no significant impact on survival.

Questions

1 What are the most important risk factors for hepatocellular carcinoma?
2 What are the common presenting complaints?
3 Which investigations should be performed?
4 What are the current treatment options and are these of recognised value in the majority of patients?
5 What other treatments may be available?

The answers can be found on p 64 of this issue.

Box 6

OTHER SUGGESTED THERAPIES

Treatment of HCC with external radiotherapy,[45] intra-arterial radiotherapy[92] and yttrium-90[93] has been attempted with questionable effectiveness. Proton therapy, although costly, may be of use; Matsuzaki *et al*[94] reported tumour reductions of over 50% in the majority of their 35 patients, with minimal side-effects. Retinoic acid,[95] flavinoid quercitin, octreotide[96] and the herbal medicine Inchin-ko-to[97] have been reported to have some activity in HCC. Thermotherapy, in which an echo guide is used to insert a probe which destroys the tumour by microwave-generated heat, has shown promising results in advanced cirrhosis and tumours of up to 9 cm, with an overall survival of 60% at 5 years.[98] Thermotherapy has also been performed using laser-induced heat[99] and radio-frequency electrocautery[100] but more studies are required to assess the benefit of these treatment modalities. Finally, gene therapy is an alternative approach to HCC treatment and although currently at the preclinical and experimental stage, it may play a significant role in HCC treatment in the future.[101 102]

TREATMENT COMBINATIONS

A wide range of combinations of the treatment discussed have been considered. In particular, adjuvant medical treatment pre- or post-surgical resection may be of use but few studies have shown any real benefit. Pre-operative TACE remains controversial; reportedly advantageous[103] but only in patients with good hepatic function.[104] Postoperative TACE has been shown to produce a worse outcome[105]; postoperative systemic or regional chemotherapy may be a more benenficial option,[35 45] producing a greater relapse-free survival.[106]

Prevention of HCC

Perhaps the most useful mechanisms to prevent HCC are prevention of hepatitis viral infections in the first place and limitation of known risk factors for cirrhosis, both strongly linked to the development of HCC. Universal immunisation programmes against hepatitis B have proven to be effective in reducing hepatitis B carrier rates by more than 10-fold.[107] Education regarding hepatitis B/C infection amongst intravenous drug users should be promoted,[108] as should safer sex globally.

It has been recommended that cirrhotic patients be regularly screened for liver tumours.[30] Such screening, usually using α-fetoprotein levels and ultrasound imaging, is widely practised, although Sherman[2] suggested that survival may not be improved as the presence of cirrhosis may limit the number of patients who can undergo resections, recurrences or second primary tumours are common, and the presence of chronic liver disease means that survival is in any case restricted.

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1 Johnson RC. Hepatocellular carcinoma. *Hepatogastroenterology* 1997;**44**:307–12.
2 Sherman M. Hepatocellular carcinoma. *Gastroenterologist* 1995:**3**:55–66.
3 Bain I, McMaster P. Benign and malignant liver tumours. *Surgery* 1997;**15**:169–74.
4 Duvoux C. Epidemiology and diagnosis of HCC in cirrhosis. *Ann Chir* 1998;**52**:511–7.
5 Cotran RS, Kumar V, Robbins SL. *Robbins Pathologic basis of disease*, 5th edn. Saunders Publ, pp 879–82.
6 Wallner I, Hartmann H, Ramdori G. Current therapeutic strategies in HCC, Part 1. *Leber Magen Darm* 1994;:**24**:150–4.
7 Paraskevopoulos JA. Management options for primary HCC. An overview. *Acta Oncol* 1994;:**33**:895–900.
8 Soulier JP. A new method to assay des-gamma-carboxyprothrombin. Results obtained in 75 cases of HCC. *Gastroenterology* 1986;**91**:1258.
9 Bolondi L, Gaiani S, Benzi G, *et al.* Ultrasonography and guided biopsy in the diagnosis of HCC. *Ital J Gastroenterol* 1992;**24**:46–9.
10 Dalla Palma L, Pozzi-Mucelli RS. Computed tomography and magnetic resonance imaging in diagnosing HCC. *Ital J Gastroenterol* 1992;**24**: 87–91.
11 Rummeny EJ, Marchal G. Liver imaging. Clinical applications and future perspectives. *Acta Radiol* 1997;**38**:626–30.
12 Bartolazzi C, Lencioni R, Caramella D, *et al.* Small HCC. Detection with US, CT MRI, DSA and Lipiodol-CT. *Acta Radiol* 1996;**37**:69–74.
13 Kanematsu M, Hoshi H, Murakami T, *et al.* Detection of HCC in patients with cirrhosis: MRI *versus* angiographically assisted helical CT. *AJR* 1997;**169**:1507–15.
14 Yamashita Y, Mitsuzaki K, Yi T, *et al.* Small HCC in patients with chronic liver damage: prospective comparison of detection with dynamic MRI and helical CT of the whole liver. *Radiology* 1996;**200**:79–84.
15 Yu JS, Kim KW, Lee JT, Yoo HS. MRI during arterial portography for assessment of HCC: comparison with CT during arterial portography. *AJR* 1998;**170**:1501–6.
16 Born M, Layer G, Kreft B, Schwarz N, Schild H. MRI, CT and CT arterial portography in the diagnosis of malignant liver tumours in liver cirrhosis. *Rofo Fortschr Geb Rontgenstr Neuen Bildgeb Verfahr* 1998;**168**:567–72.
17 Matsushiro Y, Ebara M, Ohto M, Kondo F. Usefulness of percutaneous biopsy under sonographic control and histological examination in the early diagnosis of HCC. *Nippon Shokakibyo Gakkai Zasshi* 1993;**90**:655–64.
18 Jourdan JL, Stubbs RS. Percutaneous biopsy of operable liver lesions: is it necessary or advisable? *NZ Med J* 1996;**109**:469–70.
19 Chu Yu S, Metreweli C, Lau WY, *et al.* Safety of percutaneous biopsy of HCC with an 18 gauge automated needle. *Clin Radiol* 1997;**52**:907–11.
20 Rambo WM. *Surgery*. Blackwell Science Publishing, 1996; p10.
21 Hytiroglou P, Theise ND. Differential diagnosis of hepatocellular nodular lesions. *Sem Diag Radiol* 1998;**15**:285–99.
22 Underwood JCE. *General and systemic pathology*, 2nd edn. Churchill Livingstone, 1996; pp 472–6.
23 Nakashima O, Kojiro M. Pathomorphologic characteristics and differential diagnosis of small HCC. *Gan To Kagaku Ryoho* 1996;**23**: 827–34.
24 Motohashi I, Okudaira M, Takai T, Kaneko S, Ikeda N. Morphological differences between HCC and hepatocellular carcinomalike lesions. *Hepatology* 1992;**16**:118–26.
25 Ito K, Honjo K, Fujita T, *et al.* Liver neoplasms: diagnostic pitfalls in cross-sectional imaging. *Radiographics* 1996;**16**:273–93.
26 Shimizu S, Takayama T, Kosuge T, *et al.* Benign tumours of the liver resected because of a diagnosis of malignancy. *Surg Gynaecol Obstet* 1992; **174**:403–7.
27 Zhou X, Tang Z, Yu Y. Prognostic factors of primary liver cancer. *Chung Hua Nei Ko Tsa Chih* 1996;**35**:527–9.
28 Pawarode A, Voravud N, Sriuranpong V, Kullavanijaya P, Patt YZ. Natural history of untreated primary HCC: a retrospective study of 157 patients. *Am J Clin Oncol* 1998;**21**:386–91.
29 Kaczynski J, Hansson G, Remotti H, Wallerstedt S. Spontaneous regression of HCC. *Histopathology* 1998;**32**:147–50.

30 Colleoni M, Audisio RA, De Braud F, *et al.* Practical considerations in the treatment of HCC. *Drugs* 1998;**55**:367–82.
31 Dalgic A, Mirza DF, Gunson BA, *et al.* Role of total hepatectomy and transplantation in HCC. *Transpl Proc* 1994;**26**:3564–5.
32 Kawadarada Y, Ito F, Sakurai H, *et al.* Surgical treatment of HCC. *Cancer Chemother Pharmacol* 1994;**33**:12–7.
33 Funivies JM, Fritsch A, Herbst F, *et al.* Primary hepatic cancer - the role of limited resection and total hepatectomy with orthotopic liver replacement. *Hepatogastroenterology* 1988;**35**:316–20.
34 Bismuth H, Chiche L, Adam R, *et al.* Liver resection versus transplantation for HCC in cirrhotic patients. *Ann Surg* 1993;**218**:145–51.
35 Farmer DG, Rosove MH, Shaked A, *et al.* Current treatment modalities for HCC. *Ann Surg* 1994;**219**:236–47.
36 Zibari GB, Riche A, Zizzi HC, *et al.* Surgical and non-surgical management of primary and metastatic liver tumors. *Am Surg* 1998;**64**:211–20.
37 Nagasue N, Yukay H, Ogawa Y, *et al.* Clinical experience with 118 hepatic resections for HCC. *Surgery* 1986;**99**:694–701.
38 Wu M, Chen H, Yao X. Surgical treatment of primary liver cancer. *Chung Hua Wai Ko Tsa Chih* 1996;**34**:707–10.
39 Snarska J, Puchalski Z, Sokolowski Z, Pruszynski K. Complications after surgical resection of liver parenchyma. *Wiad Lek* 1997;**50** Su1 Pt2:284–8.
40 Moreno-Gonzalez EM, Gomez R, Garcia I, *et al*. Liver transplantation in malignant hepatic neoplasms. *Am J Surg* 1992;**163**:395–400.
41 Mazzoferro V, Regalia E, Doci R, *et al.* Liver transplantation for the treatment of small HCC in patients with cirrhosis. *N Engl J Med* 1996;**334**:693–9.
42 Pichlmayr R, Weimann A, Oldhafer KJ, *et al.* Role of liver transplantation in the treatment of unresectable liver cancer. *World J Surg* 1995;**19**: 807–13.
43 Selby R, Kadry Z, Carr B, *et al.* Liver transplantation for HCC. *World J Surg* 1995;**19**:53–8.
44 Gugengeim J, Baldini E, Casaccia M, *et al*. Hepatic resection and transplantation for HCC in patients with cirrhosis. *Gastroenterol Clin Biol* 1997;**21**:590–5.
45 Nerenstrone SR, Ihde DC, Friedman MA. Clinical trials in primary HCC: current status and future directions. *Cancer Treat Rev* 1988:**15**: 1–31.
46 Colleoni M, Gaion F, Liessi G, *et al*. Medical treatment of HCC: any progress? *Tumori* 1994;**80**:315–26.
47 Falkson G, Moertel C, Lavin P, *et al.* Chemotherapy studies in primary liver cancer - a prospective randomised clinical trial. *Cancer* 1978;**42**:2149–56.
48 Brennan M, Taley R, San Diego E, *et al.* Critical analysis of 594 cancer patients treated with 5-FU. In: Platner A, ed. *Proceedings of the International Symposium on Chemotherapy of Cancer*. New York: Elsevier, 1964; pp118–9.
49 Zaniboni A, Simoncini E, Marpicati P, Marini G. Phase II study of 5-FU and high dose folinic acid in HCC. *Br J Cancer* 1988;**57**:319.
50 Ellis PA, Norman A, Hill A, *et al*. Epirubicin, cisplatin and infusion of fluorouracil in hepatobiliary tumors. *Eur J Cancer* 1995;**31**:1594–8.
51 Chlebowski R, Brzechwa-Adjukiewicz A, Cowden A, *et al.* Doxorubicin for HCC: clinical and pharmacokinetic results. *Cancer Treat Rep* 1984; **68**:487–91.
52 Lai CL, Wu PC, Chan GCB, *et al.* Doxorubicin versus no anti-tumor therapy in inoperable HCC: a prospective randomised trial. *Cancer* 1988;**62**:479–83.
53 Soga K, Nomoto M, Ichida T, *et al*. Clinical evaluation of TAE and one-shot chemotherapy in HCC. *Hepatogastroenterology* 1988;**35**:116–20.
54 Toyoda H, Nakano S, Kumada T, *et al*. The efficacy of continuous local arterial infusion of 5-FU and cisplatin through an implanted reservoir for severe advanced HCC. *Oncology* 1995; **52**:295–9.
55 Chen H, Gross J. Intra-arterial infusion of anticancer drugs: theroretical aspects of drug delivery and review responses. *Cancer Treat Rep* 1980;**64**:31–40.
56 Doci R, Bignami P, Bozzetti F, *et al*. Intrahepatic chemotherapy for unresectable HCC. *Cancer* 1988;**61**:1983–7.
57 Patt YZ, Charnsangavej C, Yoffe B, *et al.* Hepatic arterial infusion of floxuridine, leucovorin, doxorubicin and cisplatin for HCC: effects of hepatitis B and C viral infection on drug toxicity and patient survival. *J Clin Oncol* 1994;**12**: 1204–11.
58 Kinami Y, Takashima S, Tanaka T, *et al* .Intra-arterial continuous infusion in patients with advanced and recurrent cancer of the digestive system. *Gan To Kagaku Tyoho* 1985;**12**: 1990–8.
59 Onohara S, Kobayashi H, Itoh Y, *et al.* Intra-arterial cisplatinum infusion with sodium thiosulphate protection and angiotensin II induced hypertension for treatment of HCC. *Acta Radiol* 1988;**29**:197–202.
60 Shepherd FA, Evans WK, Blackstein ME, *et al*. Hepatic arterial infusion of mitoxantrone in the treatment of primary HCC. *J Clin Oncol* 1987;**5**:635–40.
61 Hashimoto M, Watanabe O, Hirano Y, Kato K, Watarai J. Use of carbon dioxide microbubble-enhanced sonographic angiography for transcatheter arterial chemoembolization of HCC. *Am J Roentgenol* 1997;**169**:1307–10.
62 Ryder SD, Rizzi PM, Metivier E, Karani J, Williams R. Chemoembolisation with lipiodol and doxorubicin: applicability in British patients with HCC. *Gut* 1996;**38**:125–8.
63 Pelletier G, Roche A, Ink O, *et al.* A randomised trial of hepatic arterial chemoembolisation in patients with unresectable HCC. *Hepatology* 1990;77:181–4.
64 Groupe d'etude et de traitement du carcinome hepatocellulaire. Comparison of lipiodol chemoembolisation and conservative treatment for unresectable HCC. *N Engl J Med* 1995;**332**: 1256–61.
65 Kanematsu T, Furuta T, Takenata K, *et al.* A 5-year experience of lipiodolisation: selective regional chemotherapy for 200 patients with HCC. *Hepatology* 1989;**10**:89–102.
66 Carr BI, Zaiko A, Bron K, *et al.* Phase II study of spherex (degradable starch microspheres) injected into the hepatic artery in conjunction with doxorubicin and cisplatin in the treatment of advanced stage HCC. *Semin Oncol* 1997;**24**: 97–9.
67 Belli L, MagistrettiG, Puricelli GP *et al*. Arteritis following intra-arterial chemotherapy for liver tumors. *Eur Radiol* 1997;7:323–6.
68 Liu CL, Ngan H, Lo CM, Fan ST. Ruptured HCC as a complication of trans-arterial oily chemoembolisation. *Br J Surg* 1998;**85**:512–4.
69 Livraghi T, Bolondi L, Lazzaroni S, *et al.* PEI in the treatment of HCC in cirrhosis. *Cancer* 1992; **6**:925–9.
70 Shiina S, Tagawa K, Unuma T, *et al*. PEI therapy for HCC: a histopathological study. *Cancer* 1991;**68**:1524–30.
71 Okuda K, Okuda H. Primary liver carcinoma. In: McIntyre N, Benhamou J P, Bircher J *et al.*, eds. *Oxford textbook of clinical hepatology*, Vol 2, Oxford University Press 1991; pp 1019–52.
72 Castells A, Bruix B, Bru C, *et al*. Treatment of small HCC in cirrhotic patients: a cohort comparing surgical resection and PEI. *Hepatology* 1993;**18**:1121–6.
73 Bartolozzi C, Lencioni R, Armillotta N. Combined treatment of HCC with chemoembolisation and alcohol administration. Long-term results. *Radiol Med* 1997;**94**:19–23.
74 Shimada M, Maeda T, Saitoh A, Morotomi I, Kano T. Needle track seeding after percutaneous ethanol injection therapy for small HCC. *J Surg Oncol* 1995;**58**:278–81.
75 Di Stasi M, Buscarini L, Livraghi T, *et al.* PEI in the treatment of HCC. A multicentre survey of evaluation practices and complication rates. *Scand J Gastroenterol* 1997;**32**:1168–73.
76 Ohnishi K, Yoshioka H, Ito S, Fujiwara K. Prospective randomised controlled trial comparing percutaneous acetic acid injection and percutaneous ethanol injection for small HCC. *Hepatology* 1998;**27**:67–72.
77 Lin DY, Lin SM, Liaw YF. Non-surgical treatment of HCC. *J Gastroenterol Hepatol* 1997; **12**(suppl):S319-S328.
78 Zhou XD, Tang ZY. Management of HCC: long term outcome in 2639 cases. *Gan To Kagaku Ryoho* 1997;**24**(suppl 1):9–16.
79 Wong WS, Patel SC, Cruz FS, Gala KV, Turner AF. Cryosurgery as a treatment for advanced stage HCC: results, complications and alcohol ablation. *Cancer* 1998;**82**:1268–78.
80 Kane RA. Ultrasound guided hepatic cryosurgery for tumor ablation. *Semin Intervent Radiol* 1993;**10**:132–42.
81 Son K, Kew M, Rabson AR. Depressed natural killer cell activity in patients with HCC: *in vitro* effects of interferon and levamisole. *Cancer* 1982:**50**:2880–3.
82 Sachs E, Dibiscerglie AM, Dusheiko GM, *et al*. Treatment of HCC with recombinant leukocyte interferon: a pilot study. *Br J Cancer* 1985;**52**: 105–9.
83 Lai CL, Wu PC, Lok ASF, *et al.* Recombinant alpha 2 interferon is superior to doxorubicin in inoperable HCC: a prospective randomised trial. *Br J Cancer* 1987;**60**:928–33.
84 Patt Y, Yoffe B, Charnsangavef C, *et al.* Low serum alpha-fetoprotein levels in patients with HCC as a predictor of response to 5-FU and interferon-alpha-2b. *Cancer* 1993;**72**:2574–82.
85 Cerezo FJ, Tomas A, Donoso L, *et al.* Controlled trial of tamoxifen in patients with advanced HCC. *J Hepatol* 1994;**20**:702–6.
86 Manesis E, Giannoulis G, Zoumboulis P, Vatiadou I, Hadziyannis SJ. Treatment of HCC with combined suppression and inhibition of sex hormones: a randomised controlled trial. *Hepatology* 1995;**21**:1535–42.
87 Castells A, Bruix J, Bru C, *et al.* Treatment of HCC with tamoxifen: a double-blind placebo-controlled trial in 120 patients. *Gastroenterology* 1995;**109**:917–22.
88 Cheng AL, Chen YC, Yeh KH, *et al.* Chronic oral etoposide and tamoxifen in the treatment of far-advanced HCC. *Cancer* 1996;**77**:872–7.
89 Chao Y, Chan WK, Huang YS, *et al.* Phase II study of flutamide in the treatment of HCC. *Cancer* 1996;**7**:635–9.
90 Yamashita T, Takhashi M, Koga Y, *et al.* Prognostic factors in the treatment of HCC with TAC and arterial infusion. *Cancer* 1991;**67**: 385–91.
91 Falkson G, Ansell S. Phase II trial of buserelin in HCC. *Eur J Cancer* 1989;**25**:1339–40.
92 Leung WT, Lau WY, Ho S, *et al.* Selective internal radiation therapy with intra-arterial iodine-131-Lipiodol in inoperable HCC. *J Nucl Med* 1994;**35**:1313–8.
93 Lau WY, Leung WT, Ho S, *et al*. Treatment of inoperable HCC with intra-hepatic arterial yttrium-90 microspheres: a phase I and II study. *Br J Cancer* 1994;**70**:994–9.
94 Matsuzaki Y, Osuga T, Chiba T, *et al*. New, effective treatment using proton irradiation for unresectable HCC. *Intern Med* 1995;**34**:302–4.
95 Hsu SL, Lin HM, Chou CK. Suppression of tumorigenicity of human hepatoma hep3B cells by long term retinoic acid treatment. *Cancer Lett* 1996;**99**:79–85.
96 Kouroumalis E, Skordilis P, Thermos K, *et al*. Treatment of HCC with octreotide: a randomised controlled study. *Gut* 1998;**42**:442–7.
97 Yamamota M, Ogawa K, Morita M, Fukuda K, Komatsu Y. The herbal medicine Inchin-ko-to inhibits liver cell apoptosis induced by transforming growth factor β1. *Hepatol* 1996;**23**: 552–9.
98 Sato M, Watanabe Y, Ueda S, *et al.* Microwave coagulation therapy for HCC. *Gastroenterology* 1996;**110**:1507–14.
99 Vogl T, Muller PK, Hammerstingl R, *et al.* Malignant liver tumours treated with MR imaging-guided laser-induced thermotherapy: technique and prospective results. *Radiology* 1995;**196**:257–65.
100 Rossi S, Fornari F, Buscarini L. Percutaneous ultrasound-guided radiofrequency electrocautery for the treatment of small HCC. *J Intervent Radiol* 1993;**8**:97–103.
101 Ferry N. Gene therapy of primary cancers of the liver: hopes and realities. *Bull Cancer* 1997;**84**:431–4.
102 Huang H, Chen SH, Kosai K, Finegold MJ, Woo SL. Gene therapy for HCC: long-term remission of primary and etastatic tumors in mice by interleukin-2 gene therapy *in vivo*. *Gene Ther* 1996;**3**:980–7.
103 Bismuth H, Morino M, Sherlock D, *et al*. Primary treatment of HCC by arterial chemoembolisation. *Am J Surg* 1992;**63**:387–94.
104 Nagasue N, Kohno H, Uchida M. Evaluation of preoperative TAE in the treatment of resectable primary liver cancer. S*emin Surg Oncol* 1993;**9**:327–31.
105 Izumi R, Shimuzu K, Iyobe T, *et al*. Postoperative adjuvant arterial infusion of lipiodol containing anti-cancer drugs in patients with HCC. *Hepatology* 1994;**20**:295–301.
106 Lygidakis NJ, Potolakis J, Konstantinou AE, *et al.* HCC: surgical resection versus surgical resection combined with pre and postoperative locoregional chemoimmunotherapy. A prospective randomised study. *Anticancer Res* 1995;**5**: 543–50.
107 Chang MH. Hepatitis B: long-term outcome and benefits from mass vaccination in children. *Acta Gastroenterol Belg* 1998;**61**:210–3.
108 Alter MJ, Moyer LA. The importance of preventing hepatitis C virus infection among injection drug users in the United States. *J Acquir Immune Defic Syndr Hum Retrovirol* 1998: **18**(suppl 1):S6–10.