

# Imaging and radiological intervention in hepatocellular carcinoma

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**Hepatocellular carcinoma is the second most common cause of death from malignancy in Hong Kong. The prognosis of patients with hepatocellular carcinoma depends on the hepatic function, tumour size, and tumour extent at diagnosis. Ultrasound, computed tomography, Lipiodol computed tomography, hepatic angiography, and magnetic resonance imaging are useful imaging modalities for the diagnosis of hepatocellular carcinomas and in assessing their operability. Transcatheter arterial chemoembolization, selective internal radiation therapy, and percutaneous transhepatic ethanol injection are promising interventional radiological techniques that have been introduced in the treatment of patients with inoperable disease. The indications for these treatment modalities and their efficacy are discussed.**

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## Introduction

Hepatocellular carcinoma (HCC) is extremely common in Southeast Asia, China, and Japan and is the second most common cause of death from malignancy in Hong Kong. Worldwide, HCC is the most common malignancy in man with an incidence estimated to be 1 million per year. Hepatitis B viral infection is the most common aetiological factor associated with HCC in Southeast Asia and China, while hepatitis C viral infection is the most common aetiological factor causing HCC in Japan. Infection with both hepatitis B and C viruses further potentiates the risk of developing HCC.

Unfortunately, HCCs are fast-growing tumours and remain asymptomatic until they are large. More than 80% of HCCs are inoperable when an individual presents with symptoms. If inoperable, and no other treatment is given, the prognosis is grave with the median survival time varying from 3.5 to 7.5 weeks in such patients in Hong Kong.<sup>1-3</sup> The outcome, however, is considerably more favourable if the tumours are

detected when they are small by regular screening with serum  $\alpha$ -fetoprotein estimation and ultrasound scan of the liver, although poor hepatic function and tumour multiplicity will adversely affect the prognosis even if the tumours are relatively small at the time of diagnosis. The 2-year survival rates for Chinese patients with HCC who present with symptoms and those with asymptomatic HCCs are 1% and 63%, respectively.<sup>2</sup> Efforts should therefore be made to detect HCCs while they are relatively small and hopefully still operable or at least amenable to other modes of therapy. Radiology plays an important role in the diagnosis, staging, and treatment of HCCs. This paper discusses the contributions that imaging and interventional radiology make in the management of patients with HCC.

## Imaging in the detection of hepatocellular carcinoma

### Ultrasound

Ultrasound (US) is non-invasive, relatively cheap, and widely available. An HCC smaller than 2 cm in size is usually hypoechoic on US. As the tumour grows, it becomes isoechoic with a peripheral hypoechoic rim. When larger than 3 cm, the tumour is usually hyperechoic.<sup>4</sup> The extent of the tumour is usually delineated adequately by US, which detects the presence of daughter nodules, and demonstrates the patency of

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the portal veins, the hepatic veins, and inferior vena cava. Ultrasound is therefore most useful as a screening tool in the detection of small HCCs in high risk patients: namely, known cirrhotics, hepatitis B and hepatitis C carriers, and relatives of patients with HCC. The optimal frequency of screening should be at an interval between eight to 10 months. After discovery of a suspected HCC, fine needle aspiration biopsy or Trucut biopsy of the lesion is often performed under US guidance. Unfortunately, it is occasionally difficult to detect small HCCs in the presence of cirrhosis, especially if they are smaller than 1 cm. Moreover, the appearance of HCCs on US is non-specific and cannot be differentiated from regenerative nodules, haemangiomas, adenoma, focal nodular hyperplasia, or hepatic metastases.

Since colour Doppler US displays the blood flow in and around a hepatic lesion, its application may increase the specificity of US in the characterisation of hepatic lesions. Tanaka et al<sup>5</sup> observed that peritumoural pulsatile flow (basket pattern) and intratumoural pulsatile flow were present in 75% and 65% of HCCs respectively, while a "detour" pattern with dilated portal veins meandering around the tumour was seen in hepatic metastases. In half of their cases of haemangiomas, a "spot pattern" with colour-stained dots in the central region of the tumour was demonstrated. They concluded, therefore, that colour Doppler US is helpful in differentiating HCCs from other tumours. Numata et al<sup>6</sup> found, on the other hand, that both peritumoural and intratumoural pulsatile flow were seen in most vascular tumours. They reported, however, that the mean peak systolic flow velocity seen in HCCs (0.52 m/sec) exceeded that seen in haemangiomas (0.16 m/sec) and this measurement was useful in differentiating between the two types of lesions. Moreover, they observed that vascular tumours with peak systolic flow velocities exceeding 0.80 m/sec were associated with either arteriovenous shunting or portal vein occlusion on the angiogram.

With the use of an intravenous galactose-based US contrast agent (SH U 508) at a concentration of 400 mg/mL, Fujimoto et al<sup>7</sup> reported that the detection rate of intra-tumoural pulsatile flow in HCCs was 83%. Tano et al<sup>8</sup> demonstrated that intra-tumoural colour signals in colour Doppler US appear in all HCCs and half of haemangiomas less than 2 cm in size after the intravenous administration of a galactose-based US contrast agent at a concentration of 400 mg/mL, although such signals were absent prior to the injection of the contrast agent. They also observe that the colour signals are stronger during cardiac systole in HCCs

but unrelated to cardiac contraction in haemangiomas. Contrast-enhanced colour Doppler US is therefore helpful in differentiating HCCs from haemangiomas and avascular tumours, especially when the tumours are smaller than 2 cm. Further larger clinical trials have to be done, however, to confirm the applicability of this technique.

### **Computed tomography**

Computed tomography (CT) is the most useful modality in the imaging of HCCs. With conventional CT, an HCC is usually hypodense on the pre-contrast scan. After intravenous contrast, there is heterogeneous enhancement in the tumour, which remains hypodense compared with the normal liver (Fig 1). Necrosis is frequently present within a large HCC. Computed tomography demonstrates accurately the extent of the tumour in relation to the segmental anatomy of the liver, the presence of daughter nodules, and extra-hepatic metastases within the abdomen. After intravenous contrast, the portal vein, hepatic vein, and inferior vena cava are visualized and invasion of these structures by tumour can be demonstrated (Fig 2). Computed tomography therefore plays an important role in determining whether an HCC is resectable or amenable to transcatheter arterial chemoembolization. In a ruptured HCC, blood may be seen around the liver or within the peritoneal cavity and active bleeding may occasionally be seen after intravenous contrast on a dynamic scan (Fig 3).

When an HCC is small, it may not be detected by conventional CT, especially in the presence of severe cirrhosis. To increase the detectability of small HCCs, two-phase dynamic incremental CT has recently been introduced.<sup>9-11</sup> In our institution, the two-phase dynamic incremental CT is done on a fast helical CT scanner and the entire liver is scanned with one breath-hold. The first and second phases are initiated 40 and 80 seconds, respectively, after the commencement of intravenous injection of 100 to 120 mL of non-ionic contrast by a pump at the rate of 2 to 2.5 mL/sec. During the first or arterial phase, a vascular HCC becomes hyperdense (Figs 4a and 4b). During the second or portal phase, the HCC becomes rapidly hypodense again. Unfortunately, most small well differentiated HCCs are hypovascular and will therefore be isodense during the first phase. However, a large proportion of these small HCCs are hypodense during the second phase and can thus be detected. Occasionally, vascular HCCs smaller than 1 cm may be missed by the two-phase dynamic CT. Lipiodol CT, on the other hand, might be able to detect such early tumours. With this technique, unenhanced CT is performed 7 to 14 days

after the injection of 2 to 5 mL of Lipiodol into the hepatic artery during hepatic angiography. Lipiodol accumulates within the HCC and enhances the differentiation between tumours and normal liver tissue (Fig 5).<sup>12,13</sup> The overall sensitivity of Lipiodol has been reported to be 97.1%.<sup>13</sup> In HCCs, there are two patterns of Lipiodol uptake—dense homogeneous or dense patchy uptake at the periphery or centre of the tumour. When the uptake is dense homogeneous, the post-test probability of the lesion being an HCC is 92.8%.<sup>13</sup> When the uptake is dense patchy, only 76% of the lesions are HCCs because haemangioma, metastasis, and focal nodular hyperplasia also have this pattern.<sup>13</sup> With the combination of both two-phase dynamic incremental CT and Lipiodol CT, most small HCCs, whether vascular or well differentiated, can be detected.

### ***Hepatic angiography and arterial porto-venography***

Most HCCs, with the exception of small well differentiated tumours, are very vascular. Pathological vessels, venous lakes, and tumour blush are frequently seen on the angiogram (Figs 6a and 6b).<sup>14</sup> In HCC of the diffuse type, the vascular abnormalities are less obvious. Arteriovenous shunting from the hepatic arteries into branches of the portal veins or hepatic veins can be seen on angiography in one third of patients with HCC (Figs 7a and 7b). Arteriovenous shunting, which cannot be demonstrated on CT, has grave clinical significance as its presence precludes transcatheter arterial chemoembolization. The portal venous system is visualized in the venous phase after injection of contrast into the superior mesenteric artery. Both hepatic resection and transcatheter arterial chemoembolization are contraindicated if the main portal vein is occluded by tumour thrombus. Lastly, a hepatic angiogram is normally required before surgery to provide a road map showing the topographical relationship of the hepatic arteries to the tumour.

### ***Magnetic resonance imaging***

Most HCCs are hypointense on T1-weighted images and hyperintense on T2-weighted images on magnetic resonance imaging (MRI). The imaging characteristics of early small HCCs, however, may be different. Muramatsu et al<sup>15</sup> report that such small tumours are mainly hyperintense or isointense on T1-weighted images and isointense on T2-weighted images. The status of the portal vein, hepatic veins, and inferior vena cava are also visualized on the T2-weighted sequence on MRI. Tumour thrombus within the lumen of such vascular structures are accurately demonstrated. After intravenous injection of contrast (Gadolinium DTPA), there is rapid enhancement of vascular

HCCs on T1-weighted images (Fig 8), but the intensity of the enhancement rapidly fades with time.

Winter III et al<sup>16</sup> compared the sensitivities of two phase dynamic incremental CT and T1- and T2-weighted MRI without contrast in the detection of early HCCs and found that the detectability rates were comparable at 81% and 83%, respectively. On the other hand, Larson et al<sup>17</sup> report that sinusoid-phase FLASH imaging after intravenous injection of contrast is marginally superior to two phase dynamic incremental CT in the detection of hypervascular malignant liver tumour. Although MRI may potentially be more sensitive than CT in detecting HCCs, the quality of the images in some patients may be affected to an unacceptable degree by respiratory movements because the scan time is much longer in MRI compared with fast helical CT. Because of the high cost and limited availability of MRI, two phase dynamic CT is still the imaging modality of choice in our institution in the diagnosis of HCC.

### **Interventional radiology in inoperable hepatocellular carcinoma**

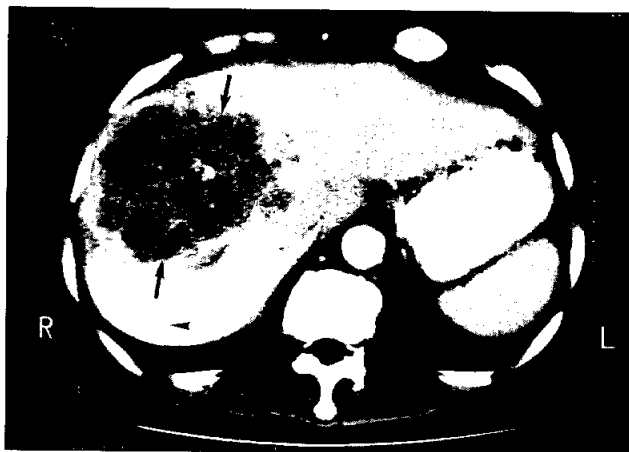
In recent years, a number of interventional radiological techniques have been introduced for the treatment of patients with inoperable HCC. Of these, transcatheter arterial chemoembolization, selective internal radiation therapy, embolization in ruptured HCC, and percutaneous transhepatic ethanol injection hold the most promise. The application of these techniques is described and their efficacy critically appraised.

#### ***Transcatheter arterial chemoembolization***

The liver has a dual blood supply—by the hepatic artery and the portal vein. An HCC is almost exclusively supplied by branches of the hepatic artery.<sup>18</sup> Occlusion of the hepatic artery either by surgical ligation or embolization will inevitably result in a varying degree of necrosis in the HCC. After such procedure, the normal parts of the liver will continue to be perfused by branches of the portal vein provided that the main portal vein is patent. Goldstein et al<sup>19</sup> embolized the hepatic artery of three patients with primary liver tumour using gelfoam pellets and observed that the tumours decreased in size in two patients.

When an emulsion of iodized oil (Lipiodol) and a cytotoxic drug is injected via a catheter into the hepatic artery during hepatic angiography, the Lipiodol is accumulated within an HCC, carrying with it the cytotoxic drug, which is slowly released and deliv-

ered to the tumour in a high concentration. The amount of cytotoxic drug reaching the rest of the body is small, thus sparing the patient the unwanted side effects of systemic chemotherapy. Applying this principle, Konno et al<sup>20</sup> treated 44 patients with HCCs with an emulsion of Lipiodol and neocarzinostatin and report a marked reduction in serum  $\alpha$ -fetoprotein level and decrease in tumour size in the treated patients.



**Fig 1.** A hypodense HCC with heterogeneous enhancement after intravenous contrast on CT (arrows). A small hypodense daughter nodule is also present (arrowhead).

Combining the above two techniques, Takayasu et al<sup>21</sup> used an emulsion of Lipiodol and Adriamycin followed by gelfoam embolization in treating patients with HCC and found more extensive necrosis of the HCCs in this group compared with those treated by a combination of Lipiodol and Adriamycin alone. Kasugai et al<sup>22</sup> observed that an emulsion of Lipiodol and cisplatin followed by gelfoam was superior to a Lipiodol and Adriamycin combination in the treatment of inoperable HCCs. Moreover, this combination resulted in necrosis not only in the main HCC, but also in daughter nodules and occasionally even in tumour thrombi within the portal veins.

In the past few years, transcatheter arterial chemoembolization using different combinations of Lipiodol, cytotoxic drug, and gelfoam, has been practised in many specialised centres in the management of patients with HCCs. The frequency and total number of chemoembolization sessions given vary from centre to centre. Indications for transcatheter arterial chemoembolization include inoperable HCC because of the extent of the tumour, the presence of daughter nodules in the opposite lobe, poor liver function in someone with otherwise resectable tumour, or recurrent tumour in a patient who has had previous hepatic

resection and in whom the liver remnant cannot withstand another resection. The technique is contraindicated when there is complete portal vein obstruction, arteriovenous shunting (except of a minor degree), serum bilirubin level above 60  $\mu$ mol/L, extrahepatic metastases, and probably HCCs of the diffuse type, which rarely respond to the procedure. Side effects are relatively mild; nausea and vomiting occur in two-thirds while abdominal pain and pyrexia occur in just over 50% of patients.<sup>23</sup> Serum bilirubin and transaminase levels are transiently elevated in all patients after the procedure. More severe complications such as gastric and duodenal bleeding, perforation of duodenal ulcers, pancreatitis, liver abscess, septicaemia, acute cholecystitis, and hepatic and renal failure have also been encountered.<sup>23-27</sup> In between chemoembolization sessions, most patients remain well and do not experience the side effects of systemic chemoembolization such as loss of hair, bone marrow suppression, and renal toxicity. Most patients whose tumour responds experience an improvement in appetite as well as a feeling of well-being, and many gain weight.<sup>23</sup>

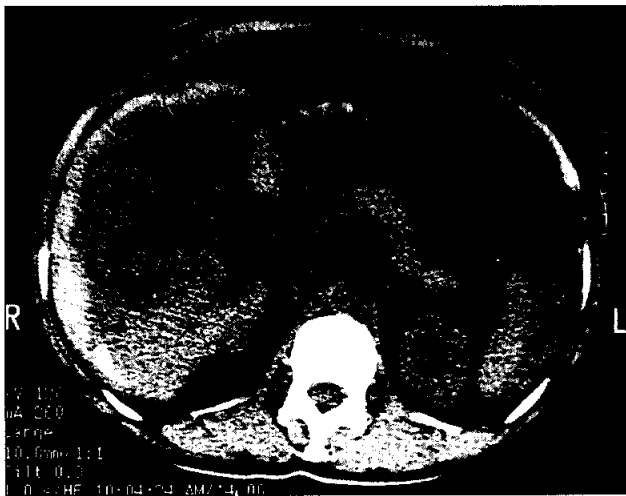


**Fig 2.** An HCC in the right lobe of the liver. Contrast CT shows that the right portal vein is occluded by a tumour thrombus (arrows), which enhances slightly.

Stuart et al<sup>24</sup> used a combination of doxorubicin and Lipiodol, followed by gelfoam powder or pledgets, in the treatment of 52 patients who had unresectable HCCs and report a partial response rate of 43% and a minor response rate of 26%. Their 1-year survival rate is 60% (median survival, 16 months).

Brownowicki et al<sup>26</sup> used an emulsion of Lipiodol and either doxorubicin, epirubicin or cisplatin, followed by gelfoam, to treat 127 patients with inoperable HCC. They report survival rates of 64%, 38%, 27%, and 27%, respectively at 1, 2, 3, and 4 years.

This compares favourably with the survival rates of 18%, 6%, and 5%, respectively at 1, 2, and 3 years in patients in the untreated group.



**Fig 3. Ruptured HCC.** Pre-contrast CT shows presence of sub-capsular blood (arrowheads), which is hyperdense relative to the HCC.

In Hong Kong, Ngan et al<sup>28</sup> treated 132 patients with inoperable HCCs between 0.3 and 33.0 cm in size (median, 8.0 cm) with repeated transcatheter arterial chemoembolization using Lipiodol and a low dose of cisplatin (2 mg to 20 mg per treatment session). This was followed by gelfoam pellets in 104 patients. The chemoembolization sessions were repeated every six to 12 weeks in most patients. The number of chemoembolization sessions each patient underwent varied from one to 18 (mean, 4.8 sessions). The HCCs decreased in size, or disappeared completely, in 56.1% of patients (Figs 9a and 9b). The initial tumour size influenced the response to chemoembolization—72% of tumours 9 cm or smaller, 40% of tumours between 9 cm and 18 cm, and 14% of tumours larger than 18 cm responded to treatment. The addition of gelfoam embolization also enhanced the response in tumours larger than 9 cm, but not in those smaller than this. After initial response, the presenting HCC increased in size again in only 9.5% of patients. However, new daughter nodules appeared in sites remote from the presenting tumour in 54.1% of patients, although 60% of these new daughter nodules responded again to further chemoembolization. Rapid emergence of new HCC nodules in apparently normal areas of the liver has also been observed after successful hepatic resection or percutaneous ethanol injection.<sup>14,29</sup> This phenomenon supports the concept that the cirrhotic liver is pre-malignant and that recurrence is due not so much to recrudescence of the originally resected or treated tumour as it is to the appearance of a new lesion in a HCC-prone liver.

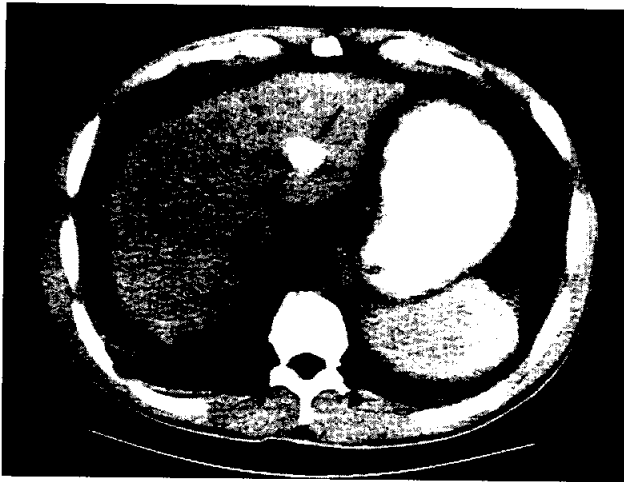
A recent study by Muto et al<sup>30</sup> demonstrates that oral polyphenolic acid, an acyclic retinoid, can prevent the appearance of a second primary HCC in patients who have had a surgical resection or percutaneous ethanol injection for HCC. This work is of immense interest and holds great promise in the control of the emergence of new daughter nodules in such patients. Ngan et al<sup>28</sup> report overall 1-, 2-, 3- and 4-year survival rates of 55%, 33%, 25%, and 21%, respectively (median survival, 14 months). The initial tumour size is an important prognostic factor regarding survival, as the median survival was 22 months in patients with tumours of 9 cm or smaller, 9 months with tumour sizes between 9 cm and 18 cm, and 2.5 months with tumours larger than 18 cm. The median survival time was 26 months in patients with responsive tumour and five months for those with non-responsive tumour.



**Fig 4a. Pre-contrast CT.** No lesion is visible in the liver.



**Fig 4b. First-phase dynamic incremental CT of the same patient.** Dense enhancement of a hypervascular HCC (arrows), 2.4 cm in size, in the posterior part of the right lobe.



**Fig 5. Lipiodol CT. An HCC, 1.5 cm in size, with dense homogeneous uptake of Lipiodol in the left lobe (arrows). A small amount of ascites is also present.**

In a randomized, multi-centre trial, Trinchet et al<sup>27</sup> compared the results of transcatheter arterial chemoembolization, using Lipiodol and a relatively high dose of cisplatin (70 mg) followed by gelfoam, in 50 patients with inoperable HCCs (without severe hepatic disease) with that of a control group; the difference between the survival rate of 62% in the treated group and that of 43.3% in the control group was not statistically significant but there was a trend favouring the treated group. As expected, tumour growth and the incidence of portal vein occlusion were reduced in the treated group. The rather disappointing survival rate in the chemoembolization group might be partly explained by the fact that as many as 24 centres participated in the chemoembolization of 50 patients and that treatment had to be stopped in 10% of patients before all four planned courses of chemoembolization could be given because of occlusion of the hepatic artery. Moreover, liver failure occurred in 61% of the treated patients, probably because of the relatively high dose of cisplatin given. As a result, the benefits obtained from tumour regression may have been offset by the deterioration in liver function. To settle the controversy that has arisen as a result of this study and to demonstrate that transcatheter arterial chemoembolization actually improves survival, a prospective, unicentre, randomized, controlled trial is urgently needed.

***New approaches in transcatheter arterial chemoembolization***

A relatively small HCC may not respond favourably to transcatheter arterial chemoembolization if the periphery of the tumour is partly supplied by branches of the portal vein. To prevent failure in eradicating the

tumour under such circumstances, two new techniques have recently been introduced: namely, superselection transarterial chemoembolization and subsegmental transcatheter arterial embolization with balloon occlusion of the hepatic vein.



**Fig 6a. Hepatic angiogram showing pathological arteries in an HCC in the right lobe.**



**Fig 6b. Dense tumour blush in the HCC in the capillary phase.**

In superselective transarterial chemoembolization, the branch of the hepatic artery supplying the tumour-bearing hepatic segment, subsegment, or even sub-subsegment is selectively catheterized.<sup>31</sup> A mixture of Lipiodol and an anticancer agent is then rapidly infused. With such a technique, the Lipiodol-cytotoxic drug mixture reaches branches of the portal vein around the tumour by opening up arteriovenous communications and thus enables the mixture to be deposited in the whole of the tumour. Nishimine et al<sup>31</sup> report cumulative survival

rates in patients with small HCCs using such a technique as 89.2%, 69.4%, 58.9%, 44.0%, and 30.2% at 1-, 2-, 3-, 4-, and 5 years, respectively. These results were higher than those achieved with conventional transcatheter arterial chemoembolization. However, only a relatively small tumour confined to a hepatic segment can be treated with such a technique. Moreover, microcatheters, which are very expensive, often have to be employed in such superselective catheterization.

With the technique of subsegmental transcatheter hepatic arterial chemoembolization with balloon occlusion of the corresponding hepatic vein, the subsegmental branch of the hepatic artery that supplies the HCC is superselectively catheterized with a microcatheter. Following this, an occlusion balloon catheter is introduced through the femoral vein into the hepatic vein draining the tumour-bearing subsegment and then inflated to occlude the hepatic blood flow. This results in an increase in trans-sinusoidal and trans-tumoural arteriovenous communications between the hepatic artery and branches of the portal vein around the tumour. A mixture of Lipiodol and cytotoxic drug followed by gelfoam is then infused into the branch of the hepatic artery that supplies the tumour-bearing subsegment. With occlusion of the corresponding hepatic vein, a relatively low dose of Lipiodol-cytotoxic drug mixture bathes the occluded tumour-bearing subsegment with flow of the mixture into arteries feeding the tumour and branches of the portal vein around the tumour, thus increasing the concentration of the anti-cancer agent within the tumour.<sup>32</sup> This technique, however, is more complicated and expensive to perform than conventional transcatheter arterial chemoembolization. Moreover, the technique cannot be undertaken if the tumour has more than one draining vein or if the corresponding hepatic vein cannot be determined with certainty. At our present level of knowledge, this technique should only be performed on a patient with good hepatic function and in whom the HCC is confined to a single subsegment.

### ***Selective internal radiation therapy***

A novel method of treating inoperable HCC is by the infusion of a radioactive isotope into the hepatic artery with the aim of delivering a tumourcidal radiation dose to the liver without damaging non-tumourous liver tissue. Both Iodine-131-Lipiodol and Yttrium-90 microspheres have been used in internal radiation therapy.

Leung et al<sup>33</sup> treated 26 patients with inoperable HCCs (median size, 4.5 cm) with intra-arterial Iodine-131-Lipiodol. Twenty-three patients received a single

dose of 1110-2220 MBq while three patients received 2220-4440 MBq in three fractions. The dose of Iodine-131-Lipiodol given varied according to tumour size and no less than 10 000 cGy of radiation were delivered to the tumour. They observed an overall response rate of 52% and a median survival time of six months; systemic toxicity was minimal. The limitation of this technique is that only relatively small HCCs (smaller than 6 cm) are suitable for treatment. Moreover, a patient has to stay in an isolation ward for two to three weeks after treatment to wait for the activity of the radioisotope to decrease to a safe level before discharge.

Since Yttrium-90 is a pure beta emitter with a half-life of 64 hours and a mean beta-particle energy of 0.93 MeV, it is an ideal radioisotope for internal radiation therapy. Shepherd et al<sup>34</sup> treated 10 patients who had inoperable HCCs with transcatheter arterial instillation of Yttrium-90 glass microspheres that delivered a dose varying from 5000 cGy to 10 000 cGy to the tumour. They report that none of the treated patients had complete or partial response and the median survival time was 18 weeks. Although significant bone marrow or hepatic toxicity was not observed, radiation-induced duodenal ulceration was seen in one patient. Yan et al<sup>35</sup> treated 18 patients with HCCs with transcatheter infusion of 2442-5550 MBq of Yttrium-90 glass microspheres into the hepatic artery aiming to deliver 5000 to 10 000 cGy to the tumour. They observed a reduction of more than 50% in tumour size (by CT or hepatic angiography) in 13 patients. The 1-year survival rate was 33%. Although there were few side effects (e.g. nausea, vomiting, fever), four patients died from massive upper gastrointestinal haemorrhage one to two months after treatment.

Lau et al<sup>36</sup> gave Yttrium-90 resin-based microspheres through an arterial port placed during laparotomy to 18 patients with inoperable HCCs. A partial tumour response occurred in seven of eight patients receiving a tumour dose greater than 12 000 cGy while partial response occurred in only one of eight patients receiving less than this. The overall median survival time was 30.6 weeks and the treatment was well tolerated without any evidence of bone marrow suppression.

Currently, Yttrium-90 microspheres appear to be more suitable than Iodine-131-Lipiodol in the treatment of large HCCs. However, patients with extrahepatic shunting to the lungs of more than 13%, as determined by technetium-99m macroaggregated albumin gamma scintigraphy, must be excluded because of the risk of radiation pneumonitis.<sup>37</sup> Shunting to the

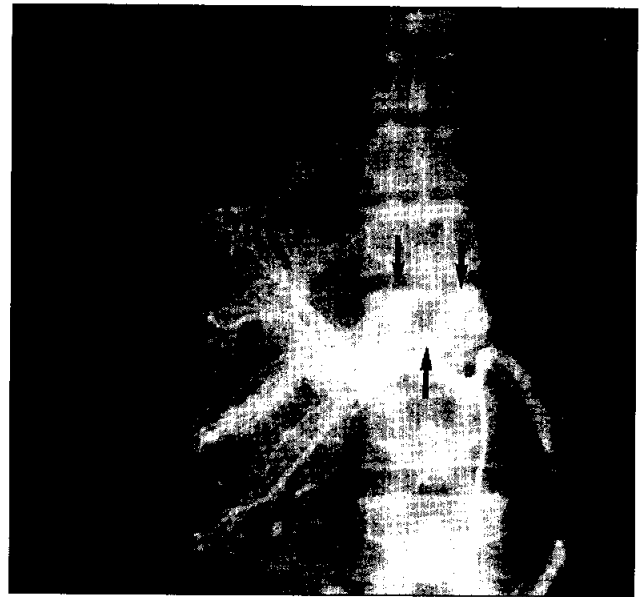
gastrointestinal tract may also result in gastric and intestinal ulceration. This can be avoided by a careful assessment of the hepatic and gastroduodenal vasculature prior to the procedure and by superselective catheterization of the branch of the hepatic artery supplying the tumour, whenever possible. Because of the higher cost of Yttrium-90 microspheres and the more complex nature of the technique, further study is needed to determine whether selective internal radiation using Yttrium-90 microspheres is superior to and can replace conventional chemoembolization.

### Ruptured hepatocellular carcinoma and transcatheter arterial embolization

The incidence of spontaneous rupture of HCC ranges from 2.9% to 14.5%.<sup>38,39</sup> Patients with spontaneous rupture present with shock, right upper abdominal pain, and abdominal distension. Abdominal paracentesis reveals haemoperitoneum and the diagnosis is usually confirmed by US or CT, which show the tumour and bleeding into the peritoneal cavity. In the presence of associated cirrhosis, massive tumour, and a large volume of blood loss, the prognosis is grave. Chearanai et al<sup>40</sup> report a mortality rate of 85% in patients managed conservatively, and a post-operative mortality rate of 64% after surgical procedures such as packing, suturing, and electric cauterisation of the bleeding site and ligation of the hepatic artery. Dewar et al<sup>41</sup> cite a post-operative mortality rate of 65% in patients with ruptured HCCs who had undergone surgery, including emergency liver resection, and that 80% of patients in the series died within four months of presentation.

Given the high operative mortality and the poor outcome of those who survive surgery, transcatheter arterial embolization has been advocated as a safer alternative in the management of patients with ruptured HCC. Before the procedure, both superior mesenteric and hepatic angiography are performed to assess the patency of the main portal vein and to show the arterial supply to the HCC. Complete occlusion of the main portal vein is an absolute contraindication to embolization because irreversible hepatic failure is inevitable under such circumstances. In the hepatic angiogram, extravasation of the contrast medium from the HCC can be seen in 13% to 24% of patients, while the balance demonstrate only hypervascular tumour stains as evidence of a ruptured HCC.<sup>42-44</sup> Gel foam pellets, Ivalon, or occasionally stainless-steel coils, are used to embolize the hepatic artery supplying the HCC until complete occlusion has been obtained. Hsieh et al<sup>44</sup> treated 17 patients with ruptured HCC with embolization and achieved haemostasis in all of them,

although three patients died immediately after the procedure.



**Fig 7a.** Hepatic angiogram at 1 sec. The right hepatic artery arises from the superior mesenteric artery. An HCC of the diffuse type is present in the right lobe. There is early filling of the left portal vein (arrows) inside which a tumour thrombus is present.



**Fig 7b.** Hepatic angiogram at 4 sec. More opacification of the left portal vein and branches (arrows).

Okazaki et al<sup>42</sup> undertook emergency embolization on 38 patients with ruptured HCC and report haemorrhage stopping in all patients after the procedure. How-



ever, 10 patients died within seven days as a result of liver failure and re-bleeding. Corr et al,<sup>43</sup> on the other hand, were only successful in occluding the artery feeding the tumour in eight of 15 patients who presented with ruptured HCC. The serum bilirubin level at the time of embolization is an important prognostic factor in predicting the outcome after the procedure. Okazaki et al<sup>42</sup> have shown that the mean survival time is 165 days in patients with serum bilirubin below 50  $\mu\text{mol/L}$ , while the mean survival time is only 13 days in those with serum bilirubin above this level. Presently, emergency embolization performed by a skilled interventional radiologist appears to be the treatment of choice in patients with ruptured HCCs, especially those with a reasonable hepatic reserve.



**Fig 8.** MRI fast gradient echo T1-weighted image. Enhancement of an HCC, 5 cm in size, in right lobe (arrow), 45 seconds after intravenous Gadolinium DTPA.

### Percutaneous transhepatic ethanol injection

In percutaneous transhepatic ethanol injection (PEI), 22-gauge Chiba needles are inserted percutaneously under US guidance into the centre of an HCC, followed by slow injection of absolute ethanol (99.5%). Ethanol causes cellular dehydration, coagulative necrosis, and vascular thrombosis in the HCC and the surrounding liver parenchyma. The amount of ethanol injected into each HCC depends on the tumour size and varies between 1 to 8 mL per session. The total number of sessions ranges between six and 12 with a treatment frequency of one to two sessions per week. An HCC becomes hyperechoic after ethanol injection on US. If necrosis has been induced, the tumour appears hypoechoic. Two phase dynamic incremental CT, however, is more accurate than US in assessing treatment response. Three months after PEI, a necrotic HCC

appears hypodense in both the first and second phases of the examination while residual or recurrent tumour appears hyperdense after contrast enhancement in the first phase of the examination.



**Fig 9a.** An HCC, 12 cm in size, opacified by Lipiodol after transcatheter arterial chemoembolization (arrows).



**Fig 9b.** Hepatic angiogram. The HCC has decreased to 7.5 cm in size after four sessions of chemoembolization (arrows).

Most patients experience pain during PEI. Pyrexia and elevation of serum transaminases occur in 48.4% and 13.7% of patients, respectively.<sup>29</sup> Complications, including portal vein thrombus,<sup>29</sup> severe hepatic vascular injury,<sup>45</sup> liver abscess,<sup>46</sup> fatal liver necrosis,<sup>47</sup> peritoneal bleeding,<sup>48</sup> and pleural effusion<sup>48</sup> have been encountered but are fortunately rare.

It is generally agreed that PEI is only suitable for patients whose HCCs are smaller than 3 cm and who have not more than three tumours in the liver. If the tumour is superficial, PEI should be avoided, because of the risk of tumour rupture and spillage of ethanol into the peritoneal cavity. As damage to the normal liver tissue surrounding the HCC is minimal, PEI is ideal for patients with poor liver function. Ebara et al<sup>29</sup> performed PEI on 95 patients with inoperable HCCs smaller than 3 cm and fewer than three in number and observed that all tumours injected either decreased in size or became undetectable. The 1-, 2-, 3-, 4-, and 5-year survival rates were 93%, 81%, 65%, 52%, and 28%, respectively. Shiina et al<sup>48</sup> treated 146 patients with PEI and report overall 1-, 2-, 3-, 4-, and 5-year survival rates of 79%, 64%, 46%, 38%, and 38 %, respectively.

Ebara et al found that although none of the HCCs injected regrew subsequently, new daughter nodules appeared in sites remote from the presenting HCCs in 66% of patients within three years, although PEI could be repeated in some of these patients.<sup>29</sup> Shiina et al<sup>48</sup> also report a recurrence rate at 1, 2, 3, 4, and 5 years of 26%, 38%, 51%, 60%, and 60%, respectively, and note that recurrence occurs in parts of the liver different from the original treated tumours in 84% of patients. Because of the low complication rate and good tumour response achieved in some institutions, PEI has been advocated as the treatment of choice in patients with small, deeply-situated HCCs in whom the liver function is so poor that neither surgery nor transcatheter arterial chemoembolization can be undertaken.

## Conclusion

Ultrasonography and CT are the mainstays in the diagnosis of HCCs and in the assessment of their resectability. Angiography is often required before surgery to show the topographical relationship of the hepatic vasculature to the tumour. It is usually unnecessary to use MRI in the diagnosis of HCCs; this should only be used to elucidate a particular problem. Since HCCs are usually large by the time an individual has symptoms, diagnosis at this stage is usually relatively easy. The detection of small asymptomatic HCCs, on the other hand, may occasionally pose a diagnostic challenge, especially if the tumours are well-differentiated. Since the prognosis of someone with HCC depends so much on the tumour size at diagnosis, concerted efforts should be made to detect small HCCs. Ultrasonography, two-phase dynamic incremental CT, and Lipiodol CT performed in this order are the preferred imaging modalities for this purpose.

With the availability of different modes of treatment for HCC, it may at times be difficult to select the appropriate one for a particular patient. Many factors, such as tumour size, tumour multiplicity, site of tumour, patency of the main portal vein and liver function have to be taken into account when deciding on the treatment. In our institution, hepatic resection remains the treatment of choice provided that the HCC is confined to one lobe and the liver function is satisfactory. Frequently, even if the disease is confined to one lobe, surgery is contraindicated because of poor liver function. Under such circumstances, transcatheter arterial chemoembolization is indicated, especially if the tumour is larger than 3 cm or more than three tumour nodules are present.

In bilobar disease, transcatheter arterial chemoembolization should be offered. On the other hand, in the presence of intrahepatic arteriovenous shunting, portal vein occlusion, or a serum bilirubin level above 60  $\mu\text{mol/L}$ , PEI is indicated provided that fewer than three tumour nodules smaller than 3 cm in size are present and that they are deeply situated. It cannot be over-stressed that co-operation between the physicians, surgeons, and radiologists working in a specialised centre is essential to ensure that the correct treatment modality is given. With judicious treatment choice, not only can the survival of patients with HCC be prolonged, but a relatively good quality of life can also be preserved.

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