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REVIEW

Interventional therapies for hepatocellular carcinoma

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Abstract

Hepatocellular carcinoma is the third most common cause of cancer-related death. In the past few years, staging systems have been developed that enable patients to be stratified into treatment algorithms in a multidisciplinary setting. Several of these treatments involve minimally invasive image-guided therapy that can be performed by radiologists.

Keywords: *Hepatocellular carcinoma; radiofrequency ablation; embolization.*

Introduction

Hepatocellular carcinoma is the third most common cause of cancer-related deaths worldwide. Owing to changes in the prevalence of the hepatitis B and C viruses, its incidence and death rate continue to rise throughout the developed world[1−3]. Cirrhosis is the strongest predisposing factor for hepatocellular carcinoma (HCC)[4]. Approximately 80% of cases of HCC develop in a cirrhotic liver[5]. The most common etiologic agent for cirrhosis in Asia and Africa is the hepatitis B virus; in Japan, Europe and America, 80% is attributed to the hepatitis C virus, 20% to the hepatitis B virus, and the remainder to alcoholic liver disease, hepatic steatosis, hemochromatosis and primary biliary cirrhosis[6,7]. Concomitant factors such as hepatitis C infection together with alcoholism, tobacco use, diabetes or obesity increase the relative risk of HCC[8,9].

Staging

Treatment of HCC is determined by various staging systems. The Barcelona Cancer of the Liver Clinic (BCLC) staging system is increasingly endorsed and validated as an appropriate system with which to determine optimal treatment strategies[10−13]. The BCLC has been approved by the European Association for the Study of the liver (EASL) and the American Association for the Study of

Liver Diseases (AASLD). The system takes into account the degree of hepatic dysfunction related to cirrhosis as defined by the Child−Pugh score, serum bilirubin and albumin levels, portal hypertension, and the patient's performance status, as well as tumour burden, presence or absence of vascular invasion, and the presence or absence of extrahepatic spread. It is combined with a treatment algorithm (Fig. 1)[14,15].

Patients should be considered on an individual basis at a multidisciplinary team meeting and stratified according to staging and treatment options. There has been an increase in the use of non-invasive local and regional therapies for the treatment of HCC in recent years[16].

Patients exceeding the criteria for either transplantation or resection are characterized as having non-resectable or non-surgical HCC. Depending on the performance status, vascular invasion and extrahepatic spread, this non-resectable group is then divided into an intermediate stage or an advanced stage. It is this intermediate group that is considered suitable for hepatic artery chemoembolization.

Patients who are characterized as at an earlier stage (single nodule or 3 nodules <3 cm) than intermediate stage are also divided into 2 groups: very early stage and early stage (Fig. 1). Again depending on the performance status and constitutional symptoms, the patients are stratified into treatment pathways including resection,
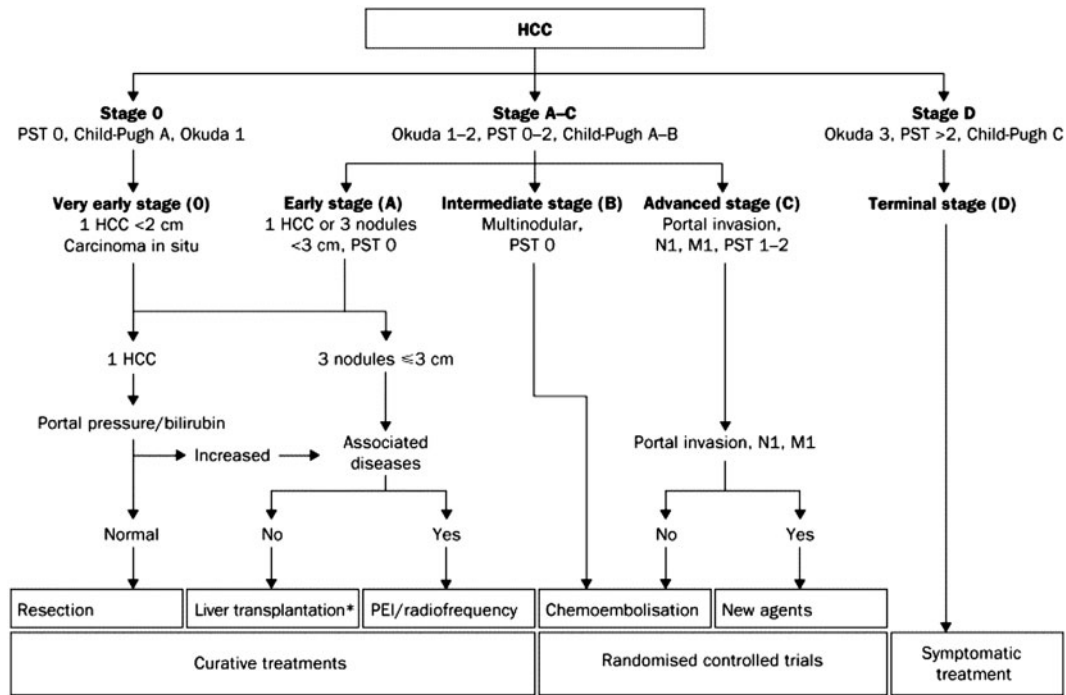
Figure 1   **The treatment algorithm.**

radiofrequency ablation (RFA) and percutaneous ethanol injection (PEI).

Local ablation: RFA

RFA uses an alternating electric current, which induces agitation of tissue ions causing hyperthermia-induced coagulation necrosis of the hepatic parenchyma[17]. A needle with an insulated shaft and an active non-insulated tip is placed within the tumour either percutaneously or in the operating room environment during a laparotomy procedure. Depending on the type of needle used, the temperature of the tissue surrounding the needle tip is raised to at least 50°C.

The advantages of RFA include lower complication rates in comparison with surgery, as well as lower cost. The procedure can be repeated if necessary. There is some consensus that lesions measuring greater than 5 cm in maximum dimension are too large for RFA. RFA should be limited to patients with 3 or fewer tumours[18]. Treatment success depends on the size of the tumours(s); treatment is more successful for smaller lesions (Fig. 2)[19,20]. Size greater than 2.5 or 3.0 cm is associated with a greater risk of local recurrence[21]. Survival ranges from 78–94% at 1 year and 58–96% at 3 years[19].

Immediate complications include pain and haemorrhage. Later complications include abscess formation, tumour seeding along the electrode track, burns from the grounding pads, bile duct injury and thermal injury to adjacent organs. However, the capsule of the liver is relatively robust and the risk of capsular rupture is low. Blood flow in nearby blood vessels can create a heat sink effect, caused by dissipation of heat from the ablation zone resulting in less effective cell necrosis.

The organ most vulnerable to accidental thermal ablation is the bowel. Techniques to prevent this from happening include placing the patient in an alternative position to allow the bowel to fall away with gravity, or instilling sterile water (hydrodistension) or gas to displace it.

Local ablation: PEI

PEI involves the repeated injection of alcohol into the tumours[22]. In the early 1990s it was considered the primary percutaneous treatment for HCC. Fine-needle injection with 95% ethyl alcohol is performed under ultrasound guidance. Its efficacy is predicated on the soft tissue of the tumour being surrounded by hard cirrhotic tissue, which restricts the alcohol from diffusing out into the liver. It is a low-cost procedure with a low rate of complications, but the need for repeat treatments and the inability to achieve complete necrosis in larger tumours has led to this technique being largely superseded by RFA[23,24]. PEI is still used in areas where RFA equipment is less readily available. It is also used for exophytic tumours where thermal damage to the capsule can cause intraperitoneal bleeding or a bile leak, and for tumours that lie adjacent to blood vessels to avoid the heat sink phenomenon.
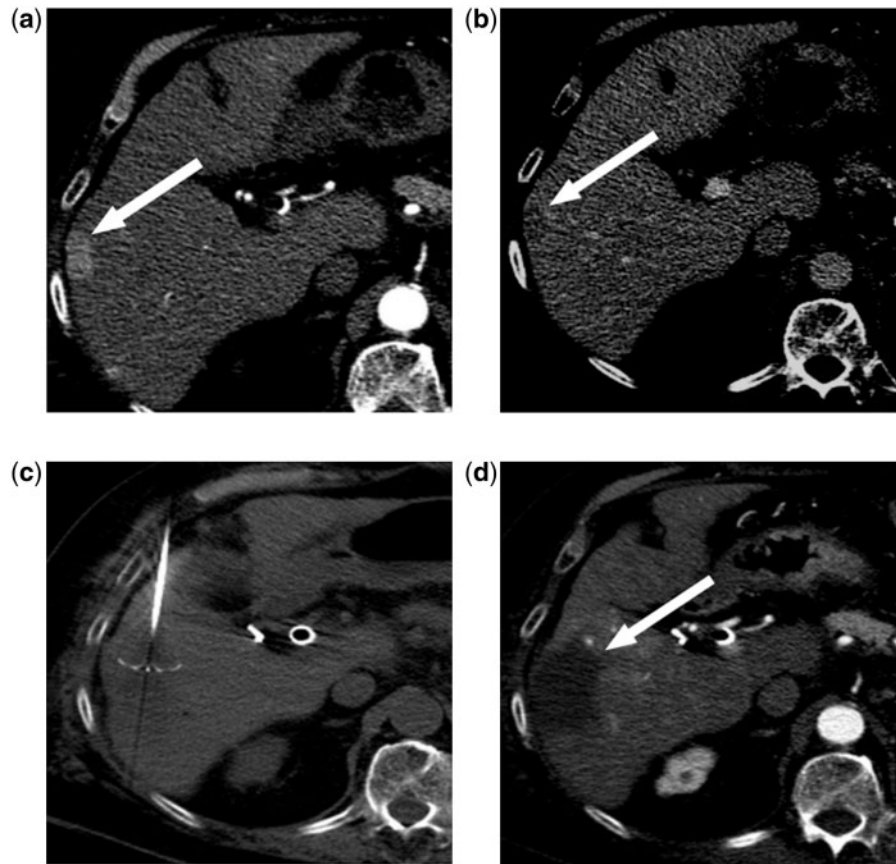
Figure 2   **Arterial phase computed tomography (CT) (a) shows a right subcapsular 2.4-cm arterial enhancing lesion (arrow), which washes out on the delayed phase (b). RFA was performed from an anterior subcostal approach (c). CT 6 weeks after the procedure shows an ablation cavity (arrow), no extracapsular rupture, and no residual arterial enhancement (d).**

Local ablation: comparative studies

Two randomized controlled trials have compared local resection with RFA. The first, although undermined by a short follow-up period of 4 years and some cross treatment between local ablative therapy and local resection, showed similar results in terms of survival and disease-free survival, although there was a higher complication rate with surgery[25]. The other trial demonstrated a superiority for local resection in both survival and disease-free survival, although in this study there was a high rate of loss to follow-up, cross treatment, and some selection bias with more multinodular HCC in the RFA group[26].

A single randomized controlled trial comparing PEI and local resection for lesions measuring up to 3 cm shows equal rates of effectiveness and safety[27]. However, 5 randomized controlled trials involving 701 patients have compared the efficacy of RFA vs PEI[28]. A meta-analysis of these studies shows an overall superiority of RFA in comparison with PEI in 3-year survival rates and cancer-free survival rates, tumour response and tumour recurrence[29]. It is suggested that the better results of RFA can be explained by the stronger and larger coagulation effect of thermal ablation on the

HCC nodules and on the tumour microsatellites compared with the chemical damage induced by ethanol[29].

A large retrospective Italian study of 478 cirrhotic patients comparing resection with ablative techniques including 214 treated with RFA and 83 with PEI showed that in patients with a single HCC measuring greater than 5 cm, and in patients with 2 or 3 HCCs larger than 3 cm, local resection is superior, but in patients with 1 HCC smaller than 5 cm and 2 or 3 HCCs smaller than 3 cm, the results were comparable[30].

Transarterial chemoembolization (TACE)

HCC is supplied mainly by the hepatic artery, in contrast with the normal liver parenchyma, which is largely supplied by the portal vein. Techniques have therefore developed that are based on the principles of embolization of the feeding arteries as well as on targeted infusion of cytotoxic chemotherapy to the tumour(s). Bland embolization with lipiodol, an iodinated ester derived from poppy-seed oil, has been used successfully for the treatment of unresectable or recurrent HCC[31,32]. Lipiodol is
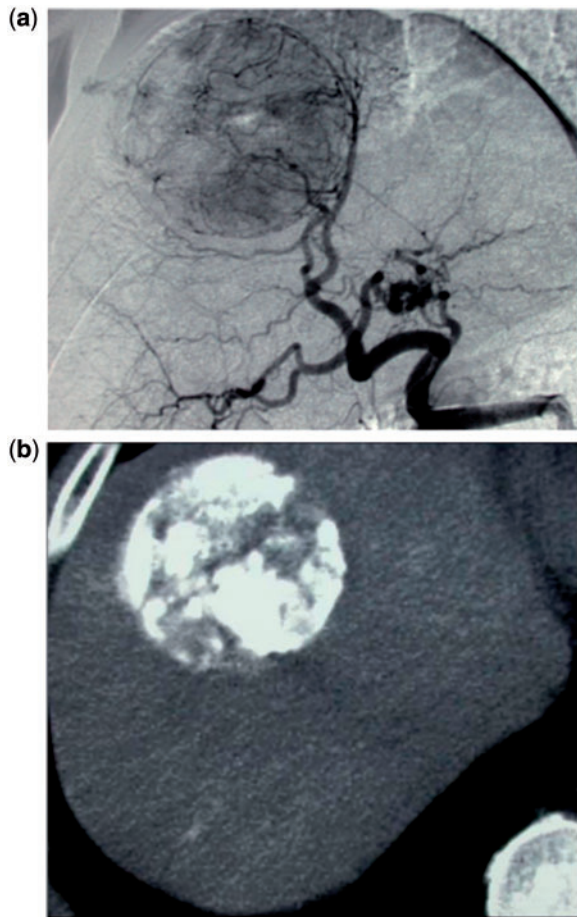
Figure 3 **A right hepatic arteriogram shows a hypervascular lesion (a). Following embolization, the mass shows filling with lipiodol on CT (b).**

selectively taken up and retained by HCCs (Fig. 3)[33,34]. However, increased survival rates, although not statistically significant, have been shown with a combination of embolization and chemoembolization[35,36]. The theory behind the combined technique is that embolization should enhance the effect of chemotherapy by causing metabolically active cell membrane pumps to fail, thereby overcoming drug resistance[37].

The TACE procedure involves catheterization of the hepatic artery and selection of either the right or left hepatic artery. Further super-selection can be performed if the tumour burden is limited to one or more segments and not the whole lobe. This normally requires the use of a microcatheter inserted coaxially through the main catheter. If there is bilateral disease, sequential treatment can be performed at least 1 month apart as concurrent bilobar treatment may provoke a serious liver injury.

There is some variation in the chemotherapy drugs used for HCC. Randomized controlled trials have failed to show an advantage of one agent over another[38]. The most common cocktail is a mixture of doxorubicin, cisplatin and mitomycin C. These can be mixed with either iodinated contrast or lipiodol, as suggested above, although there is a school of thought that the entire dose of chemotherapy should be administered before the embolization agent[39].

Selection is generally limited to patients with Child Pugh A or B cirrhosis and unresectable lesions without vascular invasion or extrahepatic spread. Portal vein and inferior vena cava tumour thrombus confer a high risk of low survival in comparison with patients without these complications, particularly if the portal invasion is in the main trunk or the first order branch[40]. TACE has generally not been used in patients with major portal vein (PV) invasion due to the possibility of liver failure following embolization due to hepatic infarction. However, recent studies have shown that TACE using less aggressive embolization can be performed safely in patients with major PV thrombosis with no increase in morbidity or mortality[41]. TACE is also used as an adjunct to liver resection or RFA to prevent recurrence, and as a bridge to orthotopic liver transplant[5,42,43].

Post-procedure care normally includes admission for observation and pain control, as well as antibiotics and anti-emetics. The combination of abdominal pain and nausea and vomiting, known as post-embolization syndrome, seems to be less severe with the use of drug-eluting beads than with the chemotherapy drug cocktail mixed with lipiodol[44].

Complete response to TACE is seen in only about 2% of patients (Fig. 4). Although impressive radiographic response is seen more frequently, tumour recurrence is often seen at subsequent examinations, resulting in a tendency for many centres to repeat the TACE procedure at regular intervals.

When used in the treatment of a large unresectable tumour, or for multifocal tumours, there can be a 35—40% reduction in tumour bulk[45—47]. Many tumours do not decrease in size and therefore other markers of response are used including lack of contrast enhancement, lipiodol deposition, and a decline in the serum alpha feta protein[48,49].

Evidence for the survival benefits of TACE for a period remained equivocal[46,47,50—53]. Two randomized controlled trials and 2 meta-analyses have, however, shown survival benefit for arterial embolization over best supportive care, with survival rates following TACE ranging from 57 to 82% at 1 year and 31—63% at 2 years in comparison with 32—63% at 1 year and 11—27% at 2 years for the control groups[36,47,49,51].

Absolute contraindications to TACE include hepatic encephalopathy, jaundice, biliary obstruction and biliary sepsis. The most common complication of TACE is that of post-embolization syndrome, which manifests as nausea, abdominal pain, ileus, pyrexia and elevated liver enzymes. This normally lasts for 3—5 days. Liver failure can occur, particularly in patients with higher pre-TACE bilirubin levels[54,55]. Other complications include hepatic abscess, gastroduodenal ulcer and
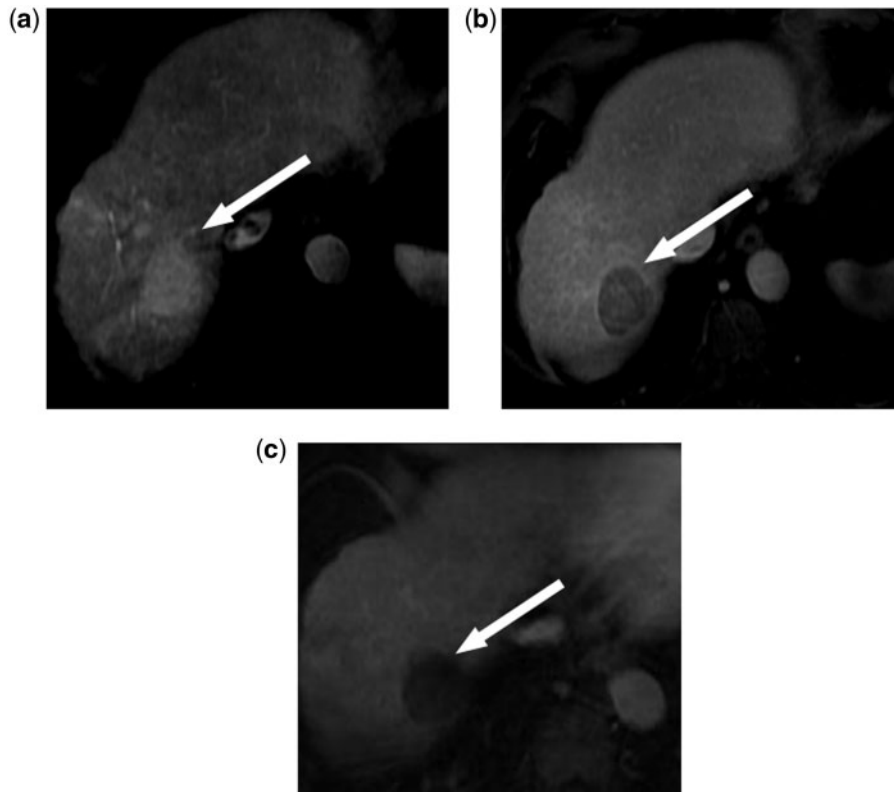
Figure 4 **MRI with gadolinium shows an aterial enhancing lesion (arrow) at the dome of the liver on the right (a) with washout (b). Follow-up MRI in the arterial phase 6 months after TACE (c) shows no residual enhancement at the site of the tumour (arrow).**

cholecystitis[36]. The latter two entities are related to non-target embolization.

## Drug-eluting beads (DEB-TACE)

The technique for DEB-TACE is almost the same as that for TACE, except that the former involves the injection of the beads into the tumour-feeding artery. The procedure is performed without lipiodol, and is therefore not as aesthetically pleasing to watch. The beads are mixed with iodinated contrast so the course of the injection can be monitored, but there is no residual contrast material left within the tumour to visualize on post-procedure imaging or on follow-up computed tomography (Fig. 5). There is, however, a combined embolization and chemotherapy effect. The chemotherapy is sustained by the controlled release of doxorubicin over time. Pre-prepared doxorubicin-eluting beads are approved in Europe and Canada (DC Bead, Biocompatibles International Inc. In the United States, LC beads (Angiodynamics, Inc) are used in 100–300 µm, 300–500 µm or 500–700 µm sizes. The smaller range of beads is normally used to optimize deep penetration into the tumour bed. There is some risk of non-target embolization with beads measuring less than 100 µm. The larger beads are used for larger tumours where there is an intent to achieve angio-embolization as well

as drug delivery. The larger beads, however, are associated with a higher complication rate attributed to hepatic ischemia[56]. Doxorubicin doses range from 75 to 150 mg.

The use of drug-eluting beads for chemoembolization has produced promising early results[44,57–61], and 2 prospective randomized controlled trials have shown favourable response rates, fewer recurrences and better tolerability in comparison with conventional TACE[62,63]. A review of the clinical outcomes demonstrating the benefits of drug-eluting beads over conventional TACE was published in 2011[64]. The rates of post-embolization syndrome and serious liver toxicity are reduced with DEB-TACE in comparison with conventional TACE[44].

Radioembolization

Radioembolization involves the delivery of radioactive isotopes (yttrium-90 or iodine-131) to the tumour via the hepatic artery in a similar fashion to TACE[65,66]. Yttrium-90 (^{90}Y) is delivered in glass (TheraSphere) or resin (SIR-spheres). There are no randomized controlled trials comparing ^{90}Y and TACE, but early results appear to be promising for disease response (Fig. 5)[67–69]. The procedure is complex to set up, expensive and, although
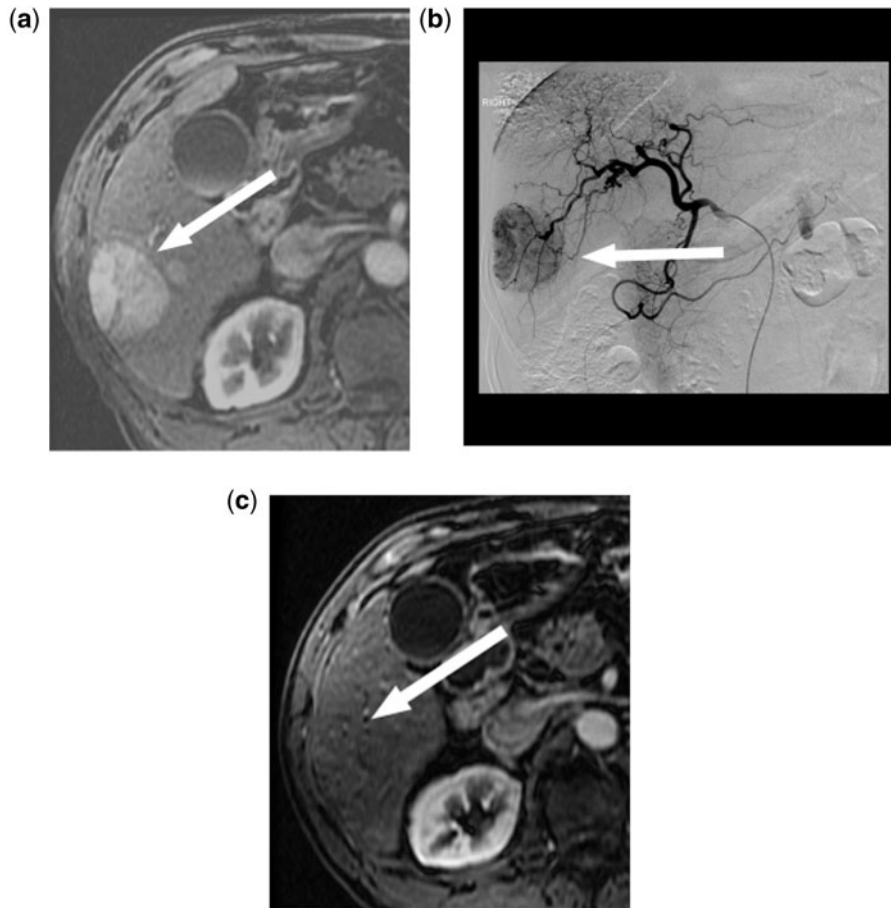
Figure 5 **MRI shows a 4-cm arterial enhancing mass (arrow) in the right lobe with a satellite nodule (a). A common hepatic arteriogram before DEB-TACE confirms the tumour (arrow) (b). MRI 6 months later in the arterial phase (c) shows no residual enhancement in the tumour (arrow).**

reimbursable in the United States, is not universally available.

Radioembolization has been shown to downstage disease so that patients fall within transplant criteria[70,71]. Radioembolization is also used for palliation in patients with multifocal disease. A radiologic–pathologic analysis has shown very high rates of complete tumour necrosis[72]. Because of the minimal embolic effect, ^{90}Y is safer than TACE in the treatment of patients with PV involvement[73–75]. Bilobar treatment can be performed at the same session, unlike with TACE, unless the hepatic reserve is low. Dosimetry is performed in conjunction with the radiation oncology team and depends on tumour burden, size of the liver, degree of shunting and hepatic function.

^{90}Y microspheres are contraindicated in patients who demonstrate the potential for lung or gastrointestinal tract exposure. Non-target embolization can result in serious radiation injury to either of these organs. Because of this, a week prior to treatment, a technetium-99 m macroaggregated albumin (MAA) scan is performed to map the area targeted for treatment. The hepatopulmonary shunt fraction is calculated as the ratio of uptake in the lung compared with that in the liver. A shunt fraction of greater than 20% is a contraindication to the procedure. Careful angiographic evaluation of the superior mesenteric, coeliac and hepatic arteries is carried out and coil embolization of the gastroduodenal, right gastric or other accessory artery is performed if required to prevent radiation injury to the gastrointestinal tract and gall bladder. The MAA is then injected into the target artery in the liver and the patient proceeds to the nuclear medicine department for gamma camera views of the liver, lungs and abdomen to evaluate for any extrahepatic distribution of the MAA.

Complications include gastritis, liver dysfunction, pneumonitis and pancreatitis, all radiation induced[68].

Combination treatments

The combined use of RFA and TACE is predicated on the increased sensitivity of tumour cells to heat following chemoembolization[76]. To date only a single small randomized controlled trial has compared the outcomes of combination therapy with RFA and TACE for tumours measuring 3.1–5.0 cm with RFA alone, showing a lower
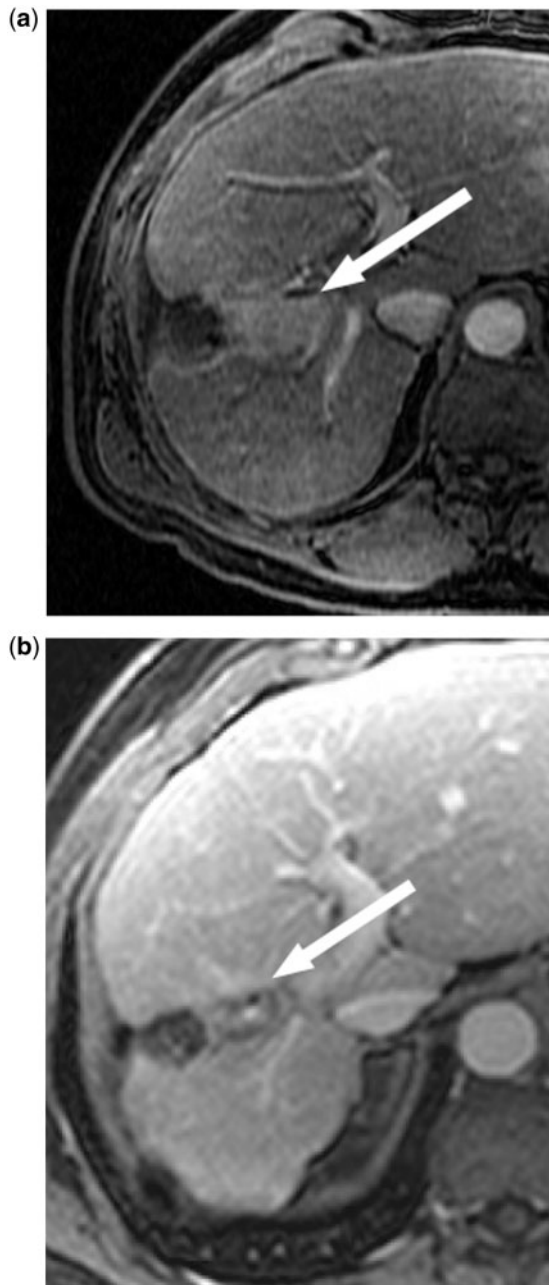
Figure 6 **MRI shows the liver of a patient who has undergone resection for HCC. There is tumour recurrence adjacent to the resection site (arrow) (a). 24 months after treatment with ^{90}Y there is no residual tumour (arrow) at the site of recurrence (b).**

tumour progression rate with the combined treatment, and no statistical difference in survival rates[77]. In several other studies, local control and long-term survival were increased with combination RFA and chemoembolization compared with either procedure alone.[78]

Future directions

The optimal strategy for the use of TACE has yet to be established and more evidence is required in the comparison of the efficacy of drug-eluting beads with conventional TACE. TACE can be repeated, but the optimal number of treatments before switching to sorafenib is not yet known. There is also a rationale for combined treatment with TACE and sorafenib, as TACE has been shown to produce a proangiogenic response that would encourage the growth of new tumours[79,80]. The anti-angiogenic properties of sorafenib would help to counteract this response. Clinical trials using this combination of therapies are ongoing. Drug-eluting beads combined with sorafenib would also be worthy of investigation as a combination therapy.

Conclusion

There are multiple treatment options for HCC based on knowledge of its molecular pathogenesis that are selected in a multidisciplinary environment based on staging and treatment stratification. Several of these treatments require image guidance and are performed by radiologists trained in the interpretation of pre- and post-treatment imaging and image-guided procedures.

PEI and RFA are used for early stage tumours as an alternative to surgical resection. TACE is the option for patients with unresectable HCC and preserved liver function in whom the tumour is too large or multifocal for RFA. Drug-eluting beads as an alternative to conventional TACE, and radioembolization, are more recently developed forms of targeted therapy that demonstrate very good early results and offer more options for more advanced disease including PV involvement.

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