Hepatocellular carcinoma treated with interventional procedures: CT and MRI follow-up

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Abstract

In the past decade, a variety of interventional procedures have been employed for local control of hepatocellular carcinoma (HCC). These include transcatheter arterial chemoembolization (TACE) and several tumour ablation techniques, such as percutaneous ethanol injection (PEI), radio-frequency ablation (RFA), or percutaneous microwave coagulation therapy (PMCTC), laser-induced interstitial thermotherapy (LITT), etc. For a definite assessment of the therapeutic efficacy of interventional procedures, histological examination using percutaneous needle biopsy may be the most definite assessment of the therapeutic efficacy of interventional therapy, however, it is invasive and the specimen retrieved does not always represent the entire lesion owing to sampling errors. Therefore, computed tomography (CT) and magnetic resonance imaging (MRI) play a crucial role in follow-up of HCC treated by interventional procedures, by which the local treatment efficacy, recurrent disease and some of therapy-induced complications are evaluated. Contrast enhanced axial imaging (CT or MR imaging) may be the most sensitive test for assessing the therapeutic efficacy. The goal of the review was to describe the value of CT and MRI in the evaluation of interventional treatments.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the most common cancers in the world[1]. Its mortality is secondary to lung cancer in urban and gastric carcinoma in countryside in China[2]. So far, surgical treatments including hepatic resection and liver transplantation are considered as the most effective treatment of HCC. However, less than 20% of HCC patients have been treated surgically, mainly because of multi-focal diseases, proximity of tumour to key vascular or biliary structures that precluded a margin-negative resection, potentially unfavorable biology with the presence of multiple liver metastases, or inadequate functional hepatic reserve related coexistent cirrhosis[3]. Palliative treatment of patients with inoperable HCC, including transcatheter arterial chemoembolization (TACE)[4], percutaneous ethanol injection (PEI)[5], laser-induced interstitial thermotherapy (LITT)[6], and local thermal ablation techniques (such as percutaneous microwave coagulation therapy (PMCTC)[8] and radio-frequency ablation (RFA)[10]) have been tried. Despite initial remission of HCC, results of various therapeutic modalities in the treatment of HCC and the survival benefits of patients treated with them were not satisfactory because of frequent recurrences following the treatment. Therefore, to prevent recurrences following the initial excellent response may be crucial to improve the long-term outcomes of patients with HCC treated by these modalities[11]. Early detection of a residual or locally recurrent tumour after interventional treatments is critical and can facilitate successful retreatment at early stage. Late diagnosis is associated with peripheral regrowth and makes retreatment difficult owing to unfavorable geometry[12]. Histological examination using percutaneous needle biopsy may be the most definite assessment of the therapeutic efficacy of interventional therapy, however, it is invasive and the specimen retrieved does not always represent the entire lesion owing to sampling errors. Therefore, computed tomography (CT) and magnetic resonance imaging (MRI) play a crucial role in follow-up of HCC treated by interventional procedures.

MATERIALS AND METHODS

Resection or transplantation provides the potentially curative or survival-enhancing treatment. The aims of palliative treatment are to slow down tumour progression and provide palliation, and to improve survival. Which includes the use of TACE alone or in combination with other local treatments. Each treatment plan is tailored to the individual patients according to their tumour stage, symptomatology, age and overall health, needs and wishes[13]. Most combined multimodal interventional therapies have enormous advantages as compared with any single therapeutic regimen alone, and play more important roles in treating unresectable HCC[14]. Non-surgical palliative techniques include the following.

Radio-frequency ablation

Similar to other ablation techniques, RFA depends on several factors, such as clinical status, stage of liver cirrhosis and HCC of patients. RFA can be performed percutaneously, laparoscopically or after laparotomy[15]. In comparison with PEI, RFA could achieve tumour necrosis in fewer sessions, and create large volumes of tumour necrosis in a shorter period of time than either laser or microwave therapy. RFA showed good control of tumors with necrosis in more than 90% of HCCs smaller than 5 cm in diameter[16-19]. In HCCs larger than 5 cm in diameter, results were unsatisfactory with complete necrosis in less than 30%[20].

The mechanism of RF is that a high-frequency alternating current (100 to 500 kHz), mostly 460 kHz, passes from an uninsulated electrode tip into the surrounding tissues and causes ionic vibrations as the ions attempt to follow the change in the direction of the rapidly alternating current. Such ionic vibrations cause frictional heating of the tissues surrounding the electrode, rather than the heat generated from the probe itself. The goal of RFA is to achieve local temperatures so that tissue destruction occurs. At the temperature above 60 °C, intracellular protein changes including collagen denaturation,
lipid bilayer melt and cell death are inevitable. Thermal coagulation begins at 70°C and tissues desiccate at 100°C, producing coagulation necrosis of tumor tissue and surrounding hepatic parenchyma. Tissue heating also drives extracellular and intracellular water out of the tissue and results in further destruction of the tissues due to coagulative necrosis[31,32].

Andrea et al. reported that most frequent complications reported in literature were capsular necrosis, intraportal hemorrhage (usually self-limiting), subcapsular hematoma, cholecystitis, hepatic abscesses. Needle track seeding after RFA was reported with a low incidence of complications (0.6-2.8%). Frequency of major complications related to the procedure was low, ranging from 5% to 15%[23,24]. Self-limiting intraportal bleeding, liver abscess and right pleural effusions were the most frequently reported complications[25]. Tumor seeding along the needle tract was also described, but its incidence from 0.6% to 12%, has been a matter of debate[26-29]. Curley and Izzo[30] suggested that RFA could be performed for unresectable hepatic malignancies less than 6.0 cm in diameter. In addition, equipments used for RFA were less expensive than either laser or microwave equipments. RFA could provide local control of advanced liver tumours with a low recurrence and an acceptable morbidity[31].

**Percutaneous ethanol injection**

Livraghi et al. reported that in 746 HCCs with cirrhosis treated by PEI, the 5-year survival rate for a single HCC <5 cm was 47% for Child A, 29% for Child B and 0% for Child C, respectively[32]. PEI was contraindicated in the presence of gross ascites, bleeding, or obstructive jaundice. PEI has been widely used with excellent results in patients with less than three HCCs[33,34]. Ethanol in PEI acts by diffusing within the cells, which causes immediate dehydration of cytoplasmic proteins with consequent coagulation necrosis followed by fibrosis, and by entering the circulation, which induces necrosis of endothelial cells and platelet aggregation with consequent thrombosis of small vessels followed by ischemia of the neoplastic tissues. Advantages for using PEI include[35,36]: no remarkable damage to the remaining parenchyma, relative safety, easy repetition when new lesions appear as in the majority of patients followed up for 5 years, application anywhere due to its low cost and easy operation, and fairly good long-term results.

**Percutaneous microwave coagulation**

It is well known that percutaneous microwave coagulation therapy (PMC) under local anesthesia is a palliative and effective therapy when carried out on a single occasion to treat HCC located near the liver surface, and it could be safely performed under direct visual guidance[37]. MCT might be superior to PEI for the local control of moderately or poorly differentiated small HCC[38], and for treating patients with HCC greater than or equal to 15 cm in diameter. In such patients with well-differentiated HCC, PEI was as effective as PMC[39].

**Laser-induced interstitial thermoablation**

Laser-induced interstitial thermoablation (LITT) is another minimally invasive and attractive method for destroying relatively larger tumours within solid organs by causing carbonization and vaporization in tissues[40]. MR-guided LITT is a local effective therapy with a low morbidity for malignant liver tumours with a maximum quantity of 5 and a size less than or equal to 5 cm in diameter[41]. LITT may be also equivalent to limited hepatic resection and may influence the long-term survival comparable to that of segmentectomy, but local recurrence could occur even in small HCC, but infrequent[42,43].

**Transcatheter arterial chemomembolization**

TACE uses combined agents to compromise the flow of hepatic artery. The agents include gelatin (gelfoam), iodized oil (lipiodol), and a cytotoxic agent. Retreatment can be performed in 6-12 wk. The 5-year survival rate was reported to be 6-22%. TACE has been shown to reduce systemic toxicity and increase local effects thus improving the therapeutic results. However, its perceived benefit for survival has not been substantiated in randomized trials, presumably because its anticancer effect is offset by its adverse effects on liver functions. Its therapeutic effect is also limited due to lack of appropriate and reliable embolic agents and when the tumour is infiltrative in nature or is too large or too small.

**LOCAL ABLATION THERAPY**

Local ablation therapies fall into one or two categories: direct intratumoural injection of compounds such as absolute ethanol (PEI) or hot saline, and thermal ablation techniques such as laser-induced interstitial thermoablation (LITT), percutaneous microwave coagulation therapy (PMC) and radiofrequency thermal ablation (RFA). These techniques produce coagulation necrosis of tumours with use of cytotoxic compounds or thermal energy. So the lesion should be avascular, if it has been treated successfully. For example, a typical RFA treatment producing a local tissue temperature over 100°C could result in coagulative necrosis of the tumor tissue and surrounding hepatic parenchyma.

The tissue microvasculature was completely destroyed, and thrombosis of hepatic arterial, portal venous or hepatic venous branches less than 3 mm in diameter occurred. For the assessment of therapeutic responses to these techniques, the same diagnostic criteria previously reported for lesions treated with TACE and PEI could be applied[43-45]. The imaging appearances of the lesions after these treatments were very similar, regardless of which local ablation technique was used[46].

**IMAGING FOLLOW UP OF RADIO FREQUENCY ABLATION CT**

Contrast-enhanced helical CT has been widely used in the evaluation of residual or recurrent tumours or of complications such as abscess, infarction, or hemorrhage in patients who have undergone percutaneous ablation therapy for a hepatic tumour[47]. All successfully ablated lesions appeared as areas of low attenuation without contrast enhancements at follow up CT. This unenhanced low-attenuation area is believed to represent necrosis[48,49]. Any focal enhancement in the treated region should be considered as an indicative of residual or recurrent lesions[50]. All of the peripheral enhanced lesions at a short-term follow-up CT performed within 1 mo after treatment should not to be regarded as a residual viable tumour[51]. Reactive hyperemia surrounds the ablation lesions in tissue. It represents inflammatory reactions in the thermal injury frequently occurred during this period. Similar findings at CT have been reported in patients who underwent percutaneous ethanol injection therapy and microwave coagulation therapy[52]. Peripheral rim enhancement resulting from reactive hyperemia was usually uniform in thickness and enveloped the ablated lesion, whereas a residual tumour showed focal and irregular peripheral enhancements. The other useful differentiating point between the two conditions was the peripheral rim enhancement, indicating that the reactive hyperemia had a high or isoattenuation during portal venous and equilibrium phases[53]. The residual tumour usually became low in attenuation during the equilibrium phase. In addition to reactive hyperemia, nontumorous wedge like enhancement could occur at the periphery of the ablated lesion owing to iatrogenic arteriovenous shunt[54,55].

It is well known that percutaneous needle biopsy and ethanol injection therapy could produce arteriovenous shunt along the needle tract[56,57]. It was usually easy to differentiate residual...
tumours from arteriovenous shunt at multiphase helical CT, because a residual tumour usually showed a high attenuation during the hepatic arterial phase and a low attenuation during the portal and equilibrium phases\(^6\). If the finding of short-term follow-up CT was inconclusive, follow-up CT at 1-3 mo intervals could be helpful before invasive diagnostic procedures, such as percutaneous biopsy or retreatment were performed if the suspected lesion was small. Nontumourously enhanced lesions produced by reactive hyperemia and arteriovenous shunt were usually resolved by this time. During this period, even if one failed in detecting small residual tumours, they have seldom grown to a size for which successful retreatment was not feasible.

The absence of contrast enhancement in the ablated lesion at short-term follow-up CT within 3 mo after treatment could not always indicate successful treatment, as later follow up studies would demonstrate tumour regrowth at the periphery of the ablated lesion\(^6\). Mitsuzaki \textit{et al.}\(^6\) reported that 8 of 38 ablated lesions with the absence of contrast enhancement at 1-mo follow-up CT showed tumour recurrence at the margin of the treated lesions at subsequent follow-up CT performed 4-13 mo after treatment.

**MRI**

MR imaging may have an edge over CT in the early detection of local regrowth due to the high sensitivity of T2-weighted images. Two months after RF therapy, a uniform hypointensity on T2-weighed images, associated with lake of enhancement of RF-treated areas on contrast-enhanced T1-weighed images, always corresponded to complete efficient treatment\(^6\). Most of the RF-treated areas were hyperintense on unenhanced T1-weighed images, which was probably due to hemorrhage or a proteinaceous material within the RF-treated area\(^6\). Most of the RF-treated areas were hypointense on T2-weighed images, and this hypointensity could be explained by the dehydrating effect of RF-induced thermal damage resulting in coagulative necrosis. However, a marked hyperintensity on T2-weighed images, found in 14% of the successful treated areas, could signify bilomas or liquefactive necrosis, as an active tumour always displayed a less T2 signal intensity\(^6\).

The higher sensitivity of MR imaging over CT was mostly due to the T2 weighted images, which were the only imaging study capable of depicting tumours in two cases at two months\(^6\). The superior sensitivity of T2-weighed images could be explained by an increase in contrast between the coagulated area, which had a low signal intensity and the viable residual tumour, which had high signal intensity. Moderately hypointense areas on T2-weighed images corresponded to the presence of residual viable tumour in all cases. Therefore, T2-weighed imaging was demonstrated to be highly specific. Moreover, the moderately hypointense areas on T2-weighed imaging associated with corresponding enhancement on contrast-enhanced T1-weighed imaging could offer an optimal specificity (100%) for residual viable tumours in all cases\(^6\).

Local regrowths were always depicted at the peripheral of the treated area either as irregular thickening of one margin of the treated area or a new tumour nodule. These peripheral locations of treatment failures could be explained by lower energy deposition and reduced heating that was remote from the needle electrode\(^6\). Furthermore, tissue perfusion could lower heat accumulation to cooling, and this phenomenon was even more marked in tissues in contact with large vessels. Indeed, regrowth close to large vessels arose in two of nine cases in their study and was described by others\(^6\).

Peripheral regrowth should not be diagnosed when a thin and regular (<1 mm) rim of progressive contrast enhancement was present at 2 mo in 32% of the entire RF-treated area and better seen at the later phase after contrast material administration.

It has been shown by comparison with histological findings that the thin ring is vascularized inflammatory reaction with granulation tissues surrounding the zone of coagulation necrosis\(^6\). Similar findings were less frequently described in hepatocellular carcinoma treated with alcohol injection\(^7\) and in hepatic metastases treated with laser-induced thermotherapy\(^7\). The peripheral rim disappeared with time and was present in only 8% of RF-treated areas at 4 mo\(^7\). It could easily be differentiated from an active tumour whose area of contrast enhancement was thicker and irregular. Another RF-induced modification was the presence of wedge-shaped enhancement on arterial phase images in the liver parenchyma adjacent to the RF-treated area. This enhancement probably corresponded to peripheral arterioportal shunts caused by either needle punctures and/or thermal damage. These wedge-shaped areas should not be misinterpreted as tumour contrast material uptake\(^7\).

Although there are many similarities between the radiological aspect of RF-induced destruction and the necrosis induced by ethanol\(^7\), some differences need to be pointed out. First, T2-weighted MR imaging was demonstrated to be the best indicator of the efficacy of RF-treatment\(^7\). In contrast, Sironi \textit{et al.}\(^7\) and Fujita \textit{et al.}\(^7\) described a limited value of T2-weighted signal intensity pattern of tumours injected with alcohol in ascertaining the viability of the tumour. This might be due either to differences in technical parameters (fast spin echo with respiratory monitoring versus standard spin echo with a higher rate of motion artifacts in their studies), or to histopathologic nature of the initial tumours, which was very different in their study from that of previous reports. Second, the area of RF-induced coagulation necrosis shrank more slowly than that of ethanol-induced necrosis. Indeed, in their study, 66% of the treated areas shrank, achieving a mean reduction of 15% at 6 mo, and 35% at 12 mo.

**IMAGING FOLLOW UP OF TACE**

Iodized oil is widely used with TACE. Because iodized oil shows a prolonged uptake in tumours and is readily identified by CT. The degree of uptake and the distribution within the tumour and the surrounding hepatic parenchyma could provide useful information on the degree of tumour necrosis and strategy for the subsequent TACE\(^7\). Since it is difficult to completely kill the tumor cells once by TACE, the treatment efficacy of TACE is influenced by many factors, such as the size of tumours, blood supply and the ultra- selectivity of the catheter, etc. TACE is a liver-directed therapy that takes advantages of the relatively selective vascularization of hepatic arterial tumours. HCC could derive approximately 80% to 85% of their blood supply from the hepatic artery, whereas the portal vein as well as the hepatic artery supplied the normal hepatic parenchyma\(^8\). Chemotherapeutic agents could thus be delivered angiographically with concomitant embolization to increase the local chemotherapeutic dwelling time and induce tumor ischemia. It is very important to objectively assess the viability and necrosis of the tumors after TACE in HCC, and to give further treatment to improve the general therapeutic effects and the survival rate.

After ablation therapy, contrast-enhanced CT is a reliable method for the assessment of therapeutic efficacy. On contrast-enhanced CT, necrotic tissues were unenhanced and viable tumours were enhanced. After TACE with iodized oil, however, retained iodized oil of high attenuation made it difficult to determine the presence of contrast enhanced within the tumour. It is generally agreed that the areas with retained iodized oil after a certain period (e.g. >4 wk) could be considered indicative of necrosis.

The complete disappearance of tumour was designated as complete remission, a 50% or more decrease in tumour as partial response, a less than 50% decrease or 25% increase in tumour as no response, and a 25% or more increase as progressive
disease. The focal defect in the mass with iodized oil or focal washout of iodized oil during follow-up suggested the presence of a viable tumour in the corresponding area, and further TACE was recommended. Sometimes, branches of hepatic arteries were totally obliterated and collateral vessels could feed the part of the tumour. Each collateral vessel supplies a specific area. The inferior phrenic artery supplies the right subphrenic area. The inferior phrenic artery supplies the right subphrenic area, the internal mammary artery supplies the area in the midline, and the ovarian branches supply the anterolateral subcapsular location. Focal washout of iodized oil from those areas suggests the presence of collateral vessels. Therefore, a careful search for the appropriate collateral vessel should be made during subsequent TACE.

Generally, the CT follow-up of patients treated with oily chemoembolization could be affected by artefacts produced by high concentrations of lipiodol, making it difficult to evaluate the characteristics of the lesion. On the other hand, the homogeneous and complete deposition of lipiodol within the lesions would indicate the high degree necrosis of the tumors, but it was difficult to judge the viability and necrosis of the tumors correctly due to the inhomogeneous deposition, because lipiodol negative areas could not actually represent the viability of the tumor. The necrosis within the lesions before TACE was also a lipiodol negative area.

Several authors considered that MR imaging was valuable in the evaluation of therapeutic efficacy of TACE, especially on spin echo (SE) T2WI, most of viable tumors were hyperintense and the coagulative necrosis within the tumors considered as a positive response to TACE was hypointense. But a signal intensity of the tumors after TACE was variable on SE T1WI and T2WI, but all of viable tumors, hemorrhage, liquefied necrosis and inflammatory infiltration could also result in hypointensity on the T2WI. Therefore, it was difficult to assess the viable tumors of HCC after TACE by conventional SE imaging. However, it was reliable to judge coagulative necrosis on T1WI, especially the changes during the process of intratumor hemorrhage after TACE presenting as a hyperintensity and then turned into coagulative necrosis presenting a hypointensity. It was significant to compare the signal intensity of HCC on T1WI before and after TACE to evaluate the degree of coagulative necrosis. The original hyperintensity of HCC turned to hypointensity indicated the presence of coagulative necrosis after TACE.

Fast multiplanar spoiled gradient-recalled (FMPSPGR) dynamic contrast scanning plays a very important role in the detection and characterization of HCC. It is possible to obtain high quality images of the whole liver during a single breathhold with rapid acquisition. It could demonstrate accurately the blood supply of tumors and reveal the contrast enhancement patterns of HCC. HCC is hypervascular and enhanced rapidly and obviously at the dynamic early phase scanning and declined at the late phase. FMPSPGR dynamic contrast scanning also has a great value in the evaluation of therapeutic efficacy of TACE. The residual viable tumors were shown as rapidly enhanced portions within the lesions, homogeneous or inhomogeneous, when necrotic portions had no enhancement at the contrast early phase scanning. At the late phase scanning, the enhancement of the most lesions became hypointense, and just a few lesions showed a persistent enhancement. Pathologically, both viable tumors and inflammatory infiltration could present such changes, so the contrast early phase scanning was more reliable in the evaluation of viable tumors combined with conventional SE sequence, and more accurate to assess the viability and necrosis of tumors and useful in the follow-up of HCC patients after TACE.

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