• REVIEW •

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 transcather arterial chemoembolization (TACE) and several tumour ablation techniques, such as percutaneous ethanol injection (PEI), radio-frequency ablation (RFA), or percutaneous microwave coagulation therapy (PMC), 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.

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 transcather arterial chemoembolization (TACE)[4], percutaneous ethanol injection (PEI)[5], laser-induced interstitial thermotherapy (LITT)[6,7], and local thermal ablation techniques

(such as percutaneous microwave coagulation therapy (PMC)[8,9] 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 ℃, intracellular protein changes including collagen denaturation,

lipid bilayer melt and cell death are inevitable. Thermal coagulation begins at 70 ℃ and tissues desiccate at 100 ℃, 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[21,22].

Andrea *et al.* reported that most frequent complications reported in literature were capsular necrosis, intraperitoneal 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 intraperitoneal 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 mm in diameter. In such patients with well-differentiated HCC, PEI was as effective as PMC[39].

Laser-induced interstitial thermotherapy

Laser-induced interstitial thermotherapy (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[42,45].

Transcather arterial chemoembolization

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 thermotherapy (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 ℃ 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, nontumourous 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[58]. 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[44,59]. Mitsuzaki *et al*.[60] 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 sensity 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[61]. 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[62]. 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[63].

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[64]. 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 hyperintense 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 hyperintense 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[65].

Local regrowths were always depicted at the periphery 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[66]. 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[67].

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[68,69].

Similar findings were less frequently described in hepatocellular carcinoma treated with alcohol injection[70] and in hepatic metastases treated with laser-induced thermotherapy[71,72]. The peripheral rim disappeared with time and was present in only 8% of RF-treated areas at 4 mo[73]. 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[74].

Although there are many similarities between the radiological aspect of RF-induced destruction and the necrosis induced by ethanol[75], 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[76]. In contrast, Sironi *et al*. and Fujita *et al*.[75] 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 with 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[77]. 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 tumors, 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 tumors. 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[78]. 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 location near the bare area, the internal mammary artery supplies the near falciform ligament, and the omental branches supply the anterolateral subcapsular location, *etc*[74]. 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 tumors[79,80]. 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 efficiency of TACE, especially on spin echo (SE) T_2WI, most of viable tumors were hyperintense and the coagulative necrosis within the tumors considered as a positive response to TACE was hypointense[81,82]. But a signal intensity of the tumors after TACE was variable on SE T_1WI and T_2WI, but all of viable tumors, hemorrhage, liquefied necrosis and inflammatory infiltration could also result in hyperintensity on the T_2WI. 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 T_2WI, 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 T_2WI 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 breath-hold with rapid aquisition. 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[83,84] 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.

SUMMARY

In summary, CT and MRI have advantages and disadvantages for evaluating the local treatment efficacy, recurrent disease and some of the therapy-induced complications. Surgeons and interventional radiologists have to choose the most suitable imaging means for patients who are treated by interventional procedures. Contrast enhanced CT or MR imaging may be the most sensitive test for assessing the therapeutic efficacy. For the later follow up, contrast-enhanced CT or MRI is then performed at 1 mo and every 3-mo thereafter. A short-term follow-up CT or MRI within 1 mo after treatment is not a reliable method for assessing the precise therapeutic effectiveness, because reactive hyperemia and/or arteriovenous shunt often make an accurate evaluation difficult. Knowledge of the serial changes at long-term follow-up CT and MRI is helpful in assessing the therapeutic response to HCC after interventional treatments.

REFERENCES

1   **Schafer DF**, Sorrell MF. Hepatocellular carcinoma. *Lancet* 1999; **353**: 1253-1257

2   **Tang ZY**. Hepatocellular carcinoma- cause, treatment and metastasis. *World J Gastroenterol* 2001; **7**: 445-454

3   **Alsowmely AM**, Hodgson HJ. Non-surgical treatment of hepatocellular carcinoma. *Aliment Pharmacol Ther* 2002; **16**: 1-15

4   **Llovet JM**, Real MI, Montana X, Planas R, Coll S, Aponte J, Ayuso C, Sala M, Muchart J, Sola R, Rodes J, Bruix J. Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. *Lancet* 2002; **359**: 1734-1739

5   **Livraghi T**. Radiofrequency ablation, PEIT, and TACE for hepatocellular carcinoma. *J Hepatobiliary Pancreat Surg* 2003; **10**: 67-76

6   **Vogl TJ**, Straub R, Eichler K, Woitaschek D, Mack MG. Malignant liver tumors treated with MR imaging-guided laser-induced thermotherapy: experience with complications in 899 patients (2,520 lesions). *Radiology* 2002; **225**: 367-377

7   **Pacella CM**, Bizzarri G, Magnolfi F, Cecconi P, Caspani B, Anelli V, Bianchini A, Valle D, Pacella S, Manenti G, Rossi Z. Laser thermal ablation in the treatment of small hepatocellular carcinoma: results in 74 patients. *Radiology* 2001; **221**: 712-720

8   **Seki T**, Wakabayashi M, Nakagawa T, Imamura M, Tamai T, Nishimura A, Yamashiki N, Okamura A, Inoue K. Percutaneous microwave coagulation therapy for patients with small hepatocellular carcinoma: comparison with percutaneous ethanol injection therapy. *Cancer* 1999; **85**: 1694-1702

9   **Itamoto T**, Katayama K, Fukuda S, Fukuda T, Yano M, Nakahara H, Okamoto Y, Sugino K, Marubayashi S, Asahara T. Percutaneous microwave coagulation therapy for primary or recurrent hepatocellular carcinoma: long-term results. *Hepatogastroenterology* 2001; **48**: 1401-1405

10 **Livraghi T**, Goldberg SN, Lazzaroni S, Meloni F, Solbiati L, Gazelle GS. Small hepatocellular carcinoma: treatment with radio-frequency ablation versus ethanol injection. *Radiology* 1999; **210**: 655-661

11 **Lee JK**, Chung YH, Song BC, Shin JW, Choi WB, Yang SH, Yoon HK, Sung KB, Lee YS, Suh DJ. Recurrences of hepatocellular carcinoma following initial remission by transcatheter arterial chemoembolization. *J Gastroenterol Hepatol* 2002; **17**: 52-58

12 **Vogl TJ**, Eichler K, Zangos S, Mack M, Hammerstingl R. Hepatocellular carcinoma: Role of imaging diagnostics in detection, intervention and follow-up. *Rofo Fortschr Geb Rontgenstr Neuen Bildgeb Verfahr* 2002; **174**: 1358-1368

13 **Cao X**, He N, Sun J, Wang S, Ji X, Fan H, Wang J, Zhang C, Yang J, Lu T, Li J, Zhang G. Interventional and synthetic therapy of advanced hepatocellular carcinoma. C*hin Med J* 2002; **115**: 1883-1885

14 **Qian J**, Feng GS, Vogl T. Combined interventional therapies of hepatocellular carcinoma. *World J Gastroenterol* 2003; **9**: 1885-1891

15 **Allgaier HP**, Galandi D, Zuber I, Blum HE. Radiofrequency thermal ablation of hepatocellular carcinoma. *Dig Dis* 2001; **19**: 301-310

16 **Curley SA**, Marra P, Beaty K, Ellis LM, Vauthey JN, Abdalla EK, Scaife C, Raut C, Wolff R, Choi H, Loyer E, Vallone P, Fiore F, Scordino F, De Rosa V, Orlando R, Pignata S, Daniele B, Izzo

F. Early and late complications after radiofrequency ablation of malignant liver tumors in 608 patients. *Ann Surg* 2004; **239**: 450-458

17 Horkan C, Ahmed M, Liu Z, Gazelle GS, Solazzo SA, Kruskal JB, Goldberg SN. Radiofrequency ablation: Effect of pharmacologic modulation of hepatic and renal blood flow on coagulation diameter in a VX2 tumor model. *J Vasc Interv Radiol* 2004; **15**: 269-274

18 Giovannini M, Moutardier V, Danisi C, Bories E, Pesenti C, Delpero JR. Treatment of hepatocellular carcinoma using percutaneous radiofrequency thermoablation: results and outcomes in 56 patients. *J Gastrointest Surg* 2003; **7**: 791-796

19 Shibata T, Iimuro Y, Yamamoto Y, Maetani Y, Ametani F, Itoh K, Konishi J. Small hepatocellular carcinoma: comparison of radio-frequency ablation and percutaneous microwave coagulation therapy. *Radiology* 2002; **223**: 331-337

20 Livraghi T, Goldberg SN, Lazzaroni S. Hepatocellular carcinoma: radio-frequency ablation of medium and large lesions. *Radiology* 2000; **214**: 761-768

21 Buscarini L, Buscarini E, Di Stasi M, Vallisa D, Quaretti P, Rocca A. Percutaneous radiofrequency ablation of small hepatocellular carcinoma: long-term results. *Eur Radiol* 2001; **11**: 914-921

22 Livraghi T, Solbiati L, Meloni F, Ierace T, Goldberg SN, Gazelle GS. Percutaneous radiofrequency ablation of liver metastases in potential candidates for resection: the "test-of-time approach". *Cancer* 2003; **97**: 3027-3035

23 Mulier S, Mulier P, Ni Y, Miao Y, Dupas B, Marchal G, De Wever I, Michel L. Complications of radiofrequency coagulation of liver tumours. *Br J Surg* 2002; **89**: 1206-1222

24 de Baere T, Risse O, Kuoch V, Dromain C, Sengel C, Smayra T, Gamal El Din M, Letoublon C, Elias D. Adverse events during radiofrequency treatment of 582 hepatic tumors. *Am J Roentgenol* 2003; **181**: 695-700

25 Galandi D, Antes G. Radiofrequency thermal ablation versus other interventions for hepatocellular carcinoma. *Cochrane Database Syst Rev* 2004; **2**: CD003046

26 Llovet JM, Vilana R, Bru C, Bianchi L, Salmeron JM, Boix L, Ganau S, Sala M, Pages M, Ayuso C, Sole M, Rodes J, Bruix J. Increased risk of tumor seeding after percutaneous radiofrequency ablation for single hepatocellular carcinoma. *Hepatology* 2001; **33**: 1124-1129

27 Bolondi L, Gaiani S, Celli N, Piscaglia F. Tumor dissemination after radiofrequency ablation of hepatocellular carcinoma. *Hepatology* 2001; **34**: 608

28 de Sio I, Castellano L, De Girolamo V, di Santolo SS, Marone A, Del Vecchio Blanco C, Marone G. Tumor dissemination after radiofrequency ablation of hepatocellular carcinoma. *Hepatology* 2001; **34**: 609-610

29 Goldberg SN, Solbiati L. Tumor dissemination after radiofrequency ablation of hepatocellular carcinoma. *Hepatology* 2001; **34**: 609

30 Curley SA, Izzo F. Radiofrequency ablation of hepatocellular carcinoma. *Minerva Chir* 2002; **57**: 165-176

31 Yamasaki T, Kurokawa F, Shirahashi H, Kusano N, Hironaka K, Okita K. Percutaneous radiofrequency ablation therapy with combined angiography and computed tomography assistance for patients with hepatocellular carcinoma. *Cancer* 2001; **91**: 1342-1348

32 Livraghi T, Giorgio A, Marin G, Salmi A, de Sio I, Bolondi L, Pompili M, Brunello F, Lazzaroni S, Torzilli G. Hepatocellular carcinoma and cirrhosis in 746 patients: long-term results of percutaneous ethanol injection. *Radiology* 1995; **197**: 101-108

33 Huo TI, Huang YH, Wu JC, Lee PC, Chang FY, Lee SD. Survival benefit of cirrhotic patients with hepatocellular carcinoma treated by percutaneous ethanol injection as a salvage therapy. *Scand J Gastroenterol* 2002; **37**: 350-355

34 Koda M, Murawaki Y, Mitsuda A, Ohyama K, Horie Y, Suou T, Kawasaki H, Ikawa S. Predictive factors for intrahepatic recurrence after percutaneous ethanol injection therapy for small hepatocellular carcinoma. *Cancer* 2000; **88**: 529-537

35 Livraghi T. Role of percutaneous ethanol injection in the treatment of hepatocellular carcinoma. *Dig Dis* 2001; **19**: 292-300

36 Livraghi T. Percutaneous ethanol injection in the treatment of hepatocellular carcinoma in cirrhosis. *Hepatogastroenterology* 2001; **48**: 20-24

37 Seki S, Sakaguchi H, Kadoya H, Morikawa H, Habu D,

Nishiguchi S, Shiomi S, Kitada T, Kuroki T. Laparoscopic microwave coagulation therapy for hepatocellular carcinoma. *Endoscopy* 2000; **32**: 591-597

38 Seki T, Wakabayashi M, Nakagawa T, Imamura M, Tamai T, Nishimura A, Yamashiki N, Okamura A, Inoue K. Percutaneous microwave coagulation therapy for patients with small hepatocellular carcinoma: comparison with percutaneous ethanol injection therapy. *Cancer* 1999; **85**: 1694-1702

39 Horigome H, Nomura T, Saso K, Itoh M. Standards for selecting percutaneous ethanol injection therapy or percutaneous microwave coagulation therapy for solitary small hepatocellular carcinoma: consideration of local recurrence. *Am J Gastroenterol* 1999; **94**: 1914-1917

40 Pacella CM, Bizzarri G, Cecconi P, Caspani B, Magnolfi F, Bianchini A, Anelli V, Pacella S, Rossi Z. Hepatocellular carcinoma: long-term results of combined treatment with laser thermal ablation and transcatheter arterial chemoembolization. *Radiology* 2001; **219**: 669-678

41 Vogl TJ, Straub R, Eichler K, Woitaschek D, Mack MG. Malignant liver tumors treated with MR imaging-guided laser-induced thermotherapy: experience with complications in 899 patients (2,520 lesions). *Radiology* 2002; **225**: 367-377

42 Pacella CM, Bizzarri G, Magnolfi F, Cecconi P, Caspani B, Anelli V, Bianchini A, Valle D, Pacella S, Manenti G, Rossi Z. Laser thermal ablation in the treatment of small hepatocellular carcinoma: results in 74 patients. *Radiology* 2001; **221**: 712-720

43 Livraghi T, Goldberg SN, Lazzaroni S, Meloni F, Ierace T, Solbiati L, Gazelle GS. Hepatocellular carcinoma: radio-frequency ablation of medium and large lesions. *Radiology* 2000; **214**: 716-718

44 Li YH, Wang CS, Liao LY, Wang CK, Shih LS, Chen RC, Chen PH. Long-term survival of Taiwanese patients with hepatocellular carcinoma after combination therapy with transcatheter arterial chemoembolization and percutaneous ethanol injection. *J Formos Med Assoc* 2003; **102**: 141-146

45 Koda M, Murawaki Y, Mitsuda A, Oyama K, Okamoto K, Idobe Y, Suou T, Kawasaki H. Combination therapy with transcatheter arterial chemoembolization and percutaneous ethanol injection compared with percutaneous ethanol injection alone for patients with small hepatocellular carcinoma: a randomized control study. *Cancer* 2001; **92**: 1516-1524

46 Catalano O, Esposito M, Nunziata A, Siani A. Multiphase helical CT findings after percutaneous ablation procedures for hepatocellular carcinoma. *Abodom Imaging* 2000; **25**: 607-614

47 Solbiati L, Goldberg SN, Ierace T, Dellanoce M, Livraghi T, Gazelle GS. Radio-frequency ablation of hepatic metastes: postprocedural assessment with a US microbubble contrast agent-early experience. *Radiology* 2000; **211**: 643-649

48 Chen Y, Chen H, Wu M, Zhou W, Wei G, Wang P, Li X. Curative effect of percutaneous microwave coagulation therapy for hepatocellular carcinoma. *Zhonghua Zhongliu Zazhi* 2002; **24**: 65-67

49 Ohmoto K, Tsuduki M, Kunieda T, Mitsui Y, Yamamoto S. CT appearance of hepatic parenchymal changes after percutaneous microwave coagulation therapy for hepatocellular carcinoma. *J Comput Assist Tomogr* 2000; **24**: 866-871

50 Witczak-Malinowska K, Zadrozny D, Studniarek M, Szurowska E, Michalska Z, Stalke P, Sikorska K, Lakomy EA. Preliminary assessment of utility of radiofrequency ablation technique in treatment of primary hepatocellular carcinoma (HCC) in patients with hepatic cirrhosis. *Med Sci Monit* 2003; **93**: 68-72

51 Yamasaki T, Kurokawa F, Shirahashi H, Kusano N, Hironaka K, Okita K. Percutaneous radiofrequency ablation therapy with combined angiography and computed tomography assistance for patients with hepatocellular carcinoma. *Cancer* 2001; **91**: 1342-1348

52 Catalano O, Esposito M, Lobianco R, Cusati B, Altei F, Siani A. Multiphasic spiral computed tomography in hepatocarcinoma. An evaluation following different percutaneous ablative procedures. *Radiol Med* 1999; **98**: 500-508

53 Ohmoto K, Tsuduki M, Kunieda T, Mitsui Y, Yamamoto S. CT appearance of hepatic parenchymal changes after percutaneous microwave coagulation therapy for hepatocellular carcinoma. *J Comput Assist Tomogr* 2000; **24**: 866-871

54 Lim HK, Choi D, Lee WJ, Kim SH, Lee SJ, Jang HJ, Lee JH, Lim JH, Choo IW. Hepatocellular carcinoma treated with percutaneous evaluation with follow-up multiphase helical CT. *Radi-*

ology 2001; **221**: 447-454

55   **Choi D**, Lim HK, Kim SH, Lee WJ, Jang HJ, Kim H, Lee SJ, Lim JH. Assessment of therapeutic response in hepatocellular carcinoma treated with percutaneous radio frequency ablation: comparison of multiphase helical computed tomography and power Doppler ultrasonography with a microbubble contrast agent. *J Ultrasound Med* 2002; **21**: 391-401

56   **Lee SJ,** Lim JH, Lee WJ, Lim HK, Choo SW, Choo IW. Transient subsegmental hepatic parechymal enhanced on dynamic CT: a sign of postbiopsy arterioportal shunt. *J Comput Assist Tomgr* 1997; **21**: 355-360

57   **Lim JH**, Lee SJ, Lee WJ, Lim HK, Choo SW, Choo IW. Iodized oil retention due to postbiopsy arterioportal shunt: a false positive lesion in the investigation of hepatocellular carcinoma. *Abdom Imaging* 1999; **24**: 165-170

58   **Kim SK,** Lim HK, Kim YH, Lee WJ, Lee SJ, Kim SH, Lim JH, Kim SA. Hepatocellular carcinoma treated with radio-frequency ablation: spectrum of imaging findings. *Radiographics* 2003; **23**: 107-121

59   **Meloni MF**, Goldberg SN, Livraghi T, Calliada F, Ricci P, Rossi M, Pallavicini D, Campani R. Hepatocellular carcinoma treated with radiofrequency ablation: comparison of pulse inversion contrast-enhanced harmonic sonography, contrast-enhanced power Doppler sonography, and helical CT. *Am J Roentgenol* 2001; **177**: 375-380

60   **Mitsuzaki K**, Yamashita Y, Nishiharu T, Sumi S, Matsukawa T, Takahashi M, Beppu T, Ogawa M. CT appearance of hepatic tumors after microwave coagulation therapy. *Am J Roentgenol* 1998; **171**: 1397-1403

61   **Kettenbach J**, Blum M, Kilanowicz E, Schwaighofer SM, Lammer J. Percutaneous radiofrequence-ablation of liver cell carcinoma: a current overview. *Radiologe* 2004; **44**: 330-338

62   **Shibata T,** Iimuro Y, Yamamoto Y, Maetani Y, Ametani F, Itoh K, Konishi J. Small hepatocellular carcinoma: comparison of radio-frequency ablation and percutaneous microwave coagulation therapy. *Radiology* 2002; **223**: 331-337

63   **Dromain C**, de Baere T, Elias D, Kuoch V, Ducreux M, Boige V, Petrow P, Roche A, Sigal R. Hepatic tumors treated with percutaneous radio-frequency ablation: CT and MR imaging follow-up. *Radiology* 2002; **223**: 255-262

64   **Kang BK**, Lim JH, Kim SH, Choi D, Lim HK, Lee WJ, Lee SJ. Preoperative depiction of hepatocellular carcinoma: ferumoxides-enhanced MR imaging versus triple-phase helical CT. *Radiology* 2003; **226**: 79-85

65   **Sironi S**, Livraghi T, Meloni F, De Cobelli F, Ferrero C, Del Maschio A. Small hepatocellular carcinoma treated with percutaneous RF ablation: MR imaging follow-up. *Am J Roentgenol* 1999; **173**: 1225-1229

66   **Curley SA**, Izzo F, Delrio P, Ellis LM, Granchi J, Vallone P, Fiore F, Pignata S, Daniele B, Cremona F. Radiofrequency ablation of unresectable primary and metastatic hepatic malignancies: results in 123 patients. *Ann Surg* 1999; **230**: 1-8

67   **Solbiati L**, Ierace T, Goldberg SN, Sironi S, Livraghi T, Fiocca R, Servadio G, Rizzatto G, Mueller PR, Del Maschio A, Gazelle GS. Percutaneous US-guided radio-frequency tissue ablation of liver metastases: treatment and follow-up in 16 patients. *Radiology* 1997; **202**: 195-203

68   **Rossi S**, Buscarini E, Garbagnati F, Stasi MD, Quaretti P, Rago M, Zangrandi A, Andreola S, Silverman D, Buscarini L. Percutaneous treatment of small hepatic tumors by an expandable RF needle electrode. *Am J Roentgenol* 1998; **170:** 1015-1022

69   **Bartolozzi C**, Crocetti L, Cioni D, Donati FM, Lencioni R. Assessment of therapeutic effect of liver tumor ablation procedures. *Hepatogastroenterology* 2001; **48**: 352-358

70   **Cioni D**, Lencioni R, Bartolozzi C. Percutaneous ablation of liver malignancies: imaging evaluation of treatment response. *Eur J Ultrasound* 2001; **13**: 73-93

71   **Vogl TJ**, Straub R, Eichler K, Sollner O, Mack MG. Colorectal carcinoma metastases in liver: laser-induced interstitial thermotherapy-local tumor control rate and survival data. *Radiology* 2004; **230**: 450-458

72   **Isbert C**, Ritz JP, Schilling A, Roggan A, Heiniche A, Wolf KJ, Muller G, Buhr HJ, Germer CT. Laser induced thermotherapy (LITT) of experimental liver metastasis-detection of residual tumors using Gd-DTPA enhanced MRI. *Lasers Surg Med* 2002; **30**: 280-289

73   **Arch-Ferrer JE**, Smith JK, Bynon S, Eckhoff DE, Sellers MT, Bland KI, Heslin MJ. Radio-frequency ablation in cirrhotic patients with hepatocellular carcinoma. *Am Surg* 2003; **69**: 1067-1071

74   **Dromain C**, de Baere T, Elias D, Kuoch V, Ducreux M, Boige V, Petrow P, Roche A, Sigal R. Hepatic tumors treated with percutaneous radio-frequency ablation: CT and MR imaging follow-up. *Radiology* 2002; **223**: 255-262

75   **Fujita T**, Honjo K, Ito K, Arita T, Koike S, Takano K, Tamura S, Matsumoto T, Matsunaga N. Fan-shaped hepatic parenchymal damage after ethanol injection therapy for hepatocellular carcinoma: MRI appearances. *Abdom Imaging* 1999; **24**: 56-60

76   **Kurokohchi K**, Masaki T, Miyauchi Y, Funaki T, Yoneyama H, Miyoshi H, Yoshida S, Himoto T, Morishita A, Uchida N, Watanabe S, Kuriyama S. Percutaneous ethanol and lipiodol injection therapy for hepatocellular carcinoma. *Int J Oncol* 2004; **24**: 381-387

77   **Takayasu K**, Arii S, Matsuo N, Yoshikawa M, Ryu M, Takassaki K, Sato M, Yamanka N, Shimamura Y, Ohto M. Comparison of CT findings with resected specimens after chemoembolization with iodized oil for hepatocellular carcinoma. *Am J Roentgenol* 2000; **175**: 699-704

78   **Uraki J**, Yamakado K, Nakatsuka A, Takeda K. Transcatheter hepatic arterial chemoembolization for hepatocellular carcinoma invading the portal veins: therapeutic effects and prognostic factors. *Eur J Radiol* 2004; **51**: 12-18

79   **Enomoto Y**, Itsubo M, Kawabe T, Koike K, Onoda H, Komuro O, Tsuno S, Toda G. Two cases of transcatheter therapy to hepatocellular carcinoma supplied by the right internal mammary artery. *Nippon Shokakibyo Gakkai Zasshi* 2000; **97**: 585-589

80   **Saccheri S**, Lovaria A, Sangiovanni A, Nicolini A, De Fazio C, Ronchi G, Fasani P, Del Ninno E, Colombo M. Segmental transcatheter arterial chemoembolization treatment in patients with cirrhosis and inoperable hepatocellular carcinomas. *J Vasc Interv Radiol* 2002; **13**: 995-999

81   **Kubota K**, Hisa N, Nishikawa T, Fujiwara Y, Murata Y, Itol S, Yoshida D, Yishida S. Evaluation of hepatocellular carcinoma after treatment with transcatheter arterial chemoembolization: comparison of Lipiodol-CT, power Doppler sonography, and dynamic MRI. *Abdom Imaging* 2001; **26**: 184-190

82   **Chan JH**, Tsui EY, Luk SH, Yuen MK, Cheung YK, Wong KP. Detection of hepatic tumor perfusion following transcatheter arterial chemoembolization with dynamic susceptibility contrast-enhanced echoplannar imaging. *Clin Imaging* 1999; **23**: 190-194

83   **Tsui EY**, Chan JH, Cheung YK, Cheung CC, Tsui WC, Szeto ML, Lau KW, Yuen MK, Luk SH. Evaluation of therapeutic effectiveness of transarterial chemoembolization for hepatocellular carcinoma: correlation of dynamic susceptibility contrast-enhanced echoplanar imaging and hepatic angiography. *Clin Imaging* 2000; **24**: 210-216

84   **Onaya H**, Itai Y. MR imaging of hepatocellular carcinoma. *Magn Reson Imaging Clin N Am* 2000; **8**: 757-768

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