To determine serial changes in hepatocellular carcinomas (HCCs) treated with percutaneous radio-frequency ablation (PRFA) at long-term serial follow-up biphasic helical computed tomography (CT).

Thirty five HCCs (range, 2.1 – 7.0 cm in diameter; mean ± SD, 3.0 ± 1.5 cm) in 27 patients (mean age, 67.2 years) were enrolled in our study. Every patient will received biphasic spiral CT study before and immediately after PRFA, then follow up 3, 6 and 9 months after PRFA for determining the effectiveness of treatment. The serial changes in attenuation, enhancing pattern, shape, and diameter of the thermal lesions were analyzed.

Thirty-two (91%) of 35 thermal lesions were low attenuation, with absence of contrast enhancement at immediate and 3 month follow-up CT images, which is suggestive of successful treatment. Peripheral rim enhancement was identified in all of the lesions after treatment (100%). Intralesional air bubbles were seen within 10 thermal lesions (28%). The remaining three lesions (9%) showed peripheral nodular enhancement, suggesting residual viable tumor. Hemoperitoneum was demonstrated in one (4%) patient after PRFA. Eight (29%) of 27 patients had recurrent tumors elsewhere in the liver at follow-up CT study.

Biphasic helical CT can provide a diagnostic clue for determining the response of HCC treated with PRFA.

Key words: Computed tomography; Hepatocellular carcinoma; Liver neoplasms, therapy; Radiofrequency ablation

Approximately 80% of hepatocellular carcinomas (HCCs) develop in patients with liver cirrhosis, primarily as a consequence of hepatitis C or hepatitis B virus infection [1]. In Taiwan and other Asian countries, liver cirrhosis often accompanies HCC. Good results can be achieved for patients by surgical resection; however, only limited number of patients with HCCs can be treated by surgery because of their underlying liver dysfunction [2]. Most patients are now treated non-surgically with transcatheter arterial chemoembolization, local ablation techniques with a direct intratumoral injection of compounds such as absolute ethanol and hot saline, and thermal ablation techniques such as microwave ablation, interstitial laser photocoagulation, and radiofrequency (RF) ablation [2-7]. The potential benefits of these techniques include the ability to preserve more liver tissue than that surgical resection does and to reduce morbidity, as compared with that associated with surgery [8].

The recently developed RF thermal ablation works by converting RF waves into heat. A high-frequency alternating current (100 to 500kHz), mostly
460kHz, passes from an uninsulated electrode tip into the surrounding tissues and causes ionic agitation as the ions attempt to follow the change in the direction of the rapidly alternating current. The ionic agitation causes frictional heat of the tissue surrounding the electrode. Tissue heating also drives extracellular and intracellular water out of the tissue and results in further tissue destruction due to coagulative necrosis [7]. Recent results show that RF ablation is well tolerated and provides a high rate of local tumor control; however, longer follow-up is necessary to evaluate the benefit of treatment [8].

Imaging plays an important role in the follow-up of hepatic tumors treated with RF ablation, as it can evaluate local treatment efficacy, recurrent tumor, and some of therapy-induced complications. Although ultrasonography (US) is an efficient tool for monitoring RF treatment, the echogenicity of necrotic and viable tumor tissue may have similar sonographic features on posttreatment US images. Contrast-enhanced CT and MR images are at present considered the most useful modalities for assessment of treatment efficacy. However, MR imaging study for regular follow-up is not economical; it is selectively used as a problem-solving modality when an equivocal lesion is found at CT images. The purpose of this study is to evaluate the serial changes of HCCs on biphasic helical CT following PRFA.

MATERIAL AND METHODS

Patients

Between January 2002 and November 2004, 65 patients with hepatic tumors were referred for CT-guided PRFA. We excluded 38 patients with hepatic tumors which were metastasized from other origins or non-hepatocellular primary malignancy. Thirty five HCCs were found in the remaining 27 patients, including 17 men and 10 women, aged from 49 to 90 years (mean 67.2 years). Twenty patients were initially treated by PRFA, and the remaining 7 patients received PRFA after 1-5 times of TACE due to viable HCCs. Two patients had second PRFA due to recurrent HCC at the other site of liver parenchyma after initial treatment. The tumor size ranged from 2.1 to 7.0 cm in diameter (mean ± SD, 3.0 ± 1.5 cm). Biphasic helical CT was performed before and after intra-venous injection of 100ml contrast material at a rate of 3 mL/sec with an automatic power injector. The entire liver was scanned at 20 – 25 seconds (arterial phase) and at 120 seconds (hepatic venous phase) following the initiation of contrast material injection. In addition, α-fetoprotein titer and coagulation profile were measured before treatment. The diagnosis of HCC was established by either pervious surgical wedge resection biopsy or the combination of CT or angiography demonstrating typical imaging manifestations of HCC and an abnormal α-fetoprotein level (>200 ng/mL). In all patients, the following serum test results were checked before treatment and 24 hours after treatment: alkaline phosphate, bilirubin, electrolytes, creatinine, hemoglobin, fibrinogen, pro-thrombin activity, and blood cell counts.

Technique of RFA

We used two commercially available RF devices. During the early stage of the study, 8 patients underwent PRFA by using a 150 W RF generator (RITA, Radiofrequency Interstitial Thermal Ablation Medical Systems; California, USA), which was equipped with a 14-gauge and 15.0-cm-long electrode with a 1.0-cm-long exposed tip that was expandable by nine curved hooks, four of which contained a thermocouples in their tips that are used to measure the temperature of the adjacent tissue, to a maximum diameter of 5.0cm. A computer with dedicated software connected to the generator recorded the power delivered, impedance values, thermistor temperatures, and timing of each procedure. Two 13 × 21-cm grounding pads were fixed to the patient’s thighs and connected to the RF generator to close the electrical circuit. The RF generator power was generally maintained at 150 W to obtain a temperature of 100°C – 110°C. After the ablation cycle was completed, a temperature reading from the extended electrodes in excess of 50°C at 1 min was reported to indicate a satisfactory ablation. In the later period of study, 19 patients were treated with a cool-tip device equipped with a single or clustered probe and a 200 W generator (Radionics, Burlington, Massachusetts, USA). A single electrode with a 2- or 3-cm-exposed tip was used for tumors smaller than 3cm in diameter. Grounding was achieved by attaching two dispersive pads, each with a surface area greater than 400 cm², to the patient’s thighs. During the procedure, a thermocouple embedded within the electrode tip continuously measured local tissue temperature. Tissue impedance was monitored by using circuit incorporated within the generator. A peristaltic pump (Radionics, Burlington,
Massachusetts, USA) was used to infuse 0°C water into the lumen of the electrodes at a rate sufficient to maintain a tip temperature of 20 – 25°C. The ablation was performed in an automatic impedance control mode in which the radiofrequency current was automatically adjusted according to the impedance measured at the needle tip. Each ablation cycle lasted for 12 minutes. Multiple overlapping ablations were performed for tumors larger than 3 cm in diameter. After ablation of the tumor, the needle tract was thermocoagulated by continuing RF current in a manual mode when the needle was withdrawn slowly.

All RF ablation were performed percutaneously under CT guidance (percutaneous RF ablation, PRFA) by one experienced radiologist. The procedure was performed under intravenous conscious sedation and one-night hospital stay. The aim of the ablation was to ensure a thermal lesion to cover the entire tumor and a 0.5 – 1.0 cm safety margin of normal hepatic tissue surrounding the tumor. For tumors larger than 3 cm in diameter, multiple overlapping ablations were done. We observed the condition of the liver parenchyma during ablation by using US with a 3.5-MHz curved linear probe. As RF energy was applied to the probes, a hyperechoic focus developed around the uninsulated portion of the electrodes. This was attributed to tissue vaporization and cavitation. The area of increased echogenicity was round; most often progressively increased in size during the course of ablation, and generally enveloped the entire tumor with variable extension into the surrounding liver by the end of treatment. Hyperechoic microbubbles were often seen escaping into the hepatic vein during RF procedure.

CT Examinations

Every patient received biphasic helical CT (PQ6000, Picker Medical system, Ohio, USA) study immediately before and after RF ablation, then follow up in 3, 6 and 9 months after PRFA. A total of 100ml contrast material was administered intravenously at a rate of 3 mL/sec with an automatic power injector (OP 100, Medrad, Pennsylvania, USA). Scanning was performed before and at 20 – 25 seconds and 120 seconds after intravenous injection of contrast media, to obtain nonenhanced, hepatic arterial and hepatic venous phase images, respectively. The process of the CT scan was performed in craniocaudal direction during a single patient breath-hold, with collimation of 8 mm, table speed of 8 mm/sec and total scanning time of 15 – 20 seconds.

Image Analysis

Three experienced radiologists interpreted the CT images. The CT findings were recorded, including the size of the thermal lesion, the presence of peripheral nodular enhancement, peripheral rim enhancement, intrasional air, vascular changes, and complications. The tumors were considered successfully ablated when no enhancement was seen in the thermal lesion on images acquired during the hepatic arterial phase. If images of the ablation area showed peripheral nodular enhancement during the hepatic arterial phase, presence of viable tumor was considered. The viable part of the tumor or other intrahepatic recurrence was retreated with additional PRFA or transcatheter arterial chemoembolization. The presence of residual non-thermal tumor or local tumor progression at the margins of the thermal lesion on CT images represented unsuccessful RF ablation.

Statistical Analysis

All data were expressed as mean ± standard deviation. The statistical analyses were performed by using the t test. A p value < 0.05 was considered statistically significant.

RESULTS

Thirty-two (91%) of 35 thermal lesions were of low attenuation, with absence of contrast enhancement at immediate and 3 month follow-up CT images, which is suggestive of successful treatment. The diameter of these 32 thermal lesions before ablation was 2.1 – 7 cm (mean ± SD, 3.0 ± 1.5 cm). In all cases in our study, immediate and 3-month follow-up CT images showed the thermal lesion slight larger than the tumor before ablation (Fig. 1). The diameter of the thermal area at immediate follow-up CT image was 2.6 – 7.5 cm (mean ± SD, 3.9 ± 1.4 cm), which was statistically significant (p = 0.0161).

The other CT findings of HCCs after PRFA treatment are summarized in Table 1. On the immediate follow-up CT images, air bubbles are seen within ten (28%) of 35 thermal lesions (Fig. 2). They are usually small in size and number and have disappeared without exception (100%) on 3-month follow-up CT images. Peripheral rim enhancement was seen in all thermal lesions (100%) at CT performed immediately after ablation on hepatic arterial phase and isoattenuation on hepatic venous phase, and such condition was completely resolved in all lesions on 3-month follow-up images (Fig. 3). The peripheral rim enhancement is usually uniform in thickness and envelops the thermal lesion.

CT images acquired at 3-month follow-up after the first RF ablation in 3 HCCs (9%) of two patients
Table 1. Summary of CT findings of PRFA therapy in HCCs

<table>
<thead>
<tr>
<th>CT finding</th>
<th>Immediate</th>
<th>3 month</th>
<th>6 month</th>
<th>9 month</th>
<th>12 month</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral rim enhancement</td>
<td>27</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>27</td>
</tr>
<tr>
<td>Intralesional air</td>
<td>10</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td>Vascular change</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Peripheral nodular enhancement</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Recurrence (elsewhere in liver)</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>4</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>Retreated with PRFA</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Retreated with TACE</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>4</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>Complication</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

Figure 1. Successful PRFA in a 71-year-old woman with HCC. a. Axial contrast-enhanced hepatic arterial phase helical CT scan obtained immediately before RF ablation shows an enhancing 2.5-cm HCC in right lobe of the liver (arrow). b. Axial contrast-enhanced hepatic arterial phase helical CT scan obtained 3 months after RF ablation shows an unenhanced round thermal area with low attenuation (arrow).

Figure 2. Multiple small gas bubbles on hepatic arterial phase helical CT scan immediate after PRFA of HCC. a. Axial contrast-enhanced hepatic arterial phase helical CT scan obtained immediately after ablation shows small air bubbles (arrow) within the thermal lesion. b. Axial contrast-enhanced hepatic arterial phase helical CT scan obtained 3 months following the PRFA procedure shows that all of the air bubbles resolved (arrow).
showed residual non-thermal tumor tissue and local tumor progression at the thermal margin. Unfortunately, they expired 3 months later because of serious progression of the tumor. Eight (29%) of 27 patients after PRFA had recurrent tumors elsewhere in the liver at follow-up CT. One patient had recurrent tumor on 12 months follow-up study. The recurrent tumor located cephalic to the previous PRFA region. Then he was re-treated with PRFA (Fig. 4). Another patient with three recurrent tumors at 6-month follow-up was re-treated with PRFA. Unfortunately, the peripheral hepatic artery was injured during PRFA. Hemoperitoneum was evident on the immediate follow-up CT and immediate embolization of the branch of right hepatic artery was performed for bleeding control. Finally, the patient recovered and discharged without additional complication. The other six patients were treated with transcatheter arterial chemoembolization because of multiple intrahepatic recurrent tumors (Table 1).

The subsequent CT examinations showed gradual decrease in size of the thermal lesions (Fig. 5).

**DISCUSSION**

The development of imaging modalities such as ultrasound (US), CT, magnetic resonance imaging (MRI), and angiography has improved the detection rate of small to medium size HCC. The initial treatments of patients with HCC were surgical resection,
transcatheter arterial chemoembolization, and percutaneous local treatment, which have been performed alone or in combination [1-8]. Percutaneous ethanol injection (PEI) is performed widely as a percutaneous local treatment. However, this modality occasionally is ineffective because of inhomogeneous distribution of ethanol within the tumor [9].

Recently, PRFA has emerged as one of the most popular local ablative therapies for inoperable HCC because of its efficacy and safety demonstrated in early studies [9-12]. It also has several merits over other therapies for primary liver cancer. It can be performed as a percutaneous procedure, under the guidance of US or CT scan, with local anesthesia, and in out-patient department. The complications and morbidity are lower than hepatic resection and

**Figure 4.** Recurrent tumors after PRFA in a 68-year-old man with HCC in right lobe of liver. a. Axial contrast enhanced hepatic arterial phase CT scan obtained immediately before RF ablation shows an enhancing 4.7cm HCC in right lobe of liver (arrow). b. Axial contrast enhanced hepatic arterial phase CT scan obtained 3 months after RF ablation shows no marginal enhancement or viable tumor in the thermal region (arrow). c. Axial contrast enhanced hepatic arterial phase CT scan obtained 12 months after RF ablation, multiple enhancing nodules (arrow) demonstrated cephalad the thermal region. d. Axial contrast enhanced hepatic arterial phase CT scan obtained immediately after repeat RF ablation shows an unenhanced oval thermal area (arrow) with hyperemia (curved arrow) surrounding the tumor.

**Figure 5.** Successful RF ablation in a 73-year-old man with HCC. Axial contrast-enhanced hepatic arterial phase helical CT scan images obtained before and immediately after RF ablation and follow-up on 3, 6, 9 and 12 months show gradual decreasing in the diameter of the thermal lesion (arrows).
Percutaneous radiofrequency ablation

cryosurgery [13-14]. PRFA can be repeated for patients with recurrent tumors at the margin of treatment or new recurrences elsewhere in the liver. It has similar results as hepatic resection because it can destroy the tumors completely, just like liver surgery can do [15-16]. Thus, PRFA has desirable qualities over repeated partial hepatectomy. It is less invasive, with low morbidity and mortality rates.

PRFA treatment has been widely performed under US guidance. Preliminary results are encouraging and strongly support such minimally invasive image-guided regional therapy. However, the ultrasonographic appearance of the treated area changes rapidly after ablation, and the actual size of necrosis is difficult to be estimated by US [18]. In addition, three-dimensional tumor geometry is often asymmetric or irregular, and repositioning of the ablative device is frequently necessary for larger masses. Therefore, considering the development of an optimal minimally invasive alternative to surgery such as PRFA, the technique with CT-guidance was designed. By the aid of CT, that it is possible to replace the ablation device accurately into the tumor and detect the therapeutic effect immediately after PRFA.

Imaging plays an important role in the follow-up of hepatic tumors treated with RF ablation, as it is helpful to evaluate local treatment efficacy, recurrent lesion, and some of therapy-induced complications. Assessment of tumor regression with US study, however, is difficult because necrotic and viable tumor tissue may have similar echogenicity on posttreatment US images. Angiography is valuable for depiction of tumor degeneration, but it is invasive and therefore not suitable for routine follow-up. Contrast-enhanced CT and MR imaging are currently considered the most useful modalities for assessment of treatment efficacy [19]. MR imaging study for regular follow-up is relatively less economical; it is selectively used as a problem-solving modality when an equivocal lesion is found at CT. Therefore, our current imaging strategy after PRFA of HCC includes immediate biphasic helical CT study after treatment to evaluate early outcome and complications. If there is definite residual tumor, multiple overlapping ablations would be performed for residual areas. For the later follow-up, contrast-enhanced biphasic helical CT is then performed every 3 months thereafter.

The main goal of PRFA is complete eradication of tumor. On biphasic contrast enhanced CT immediately after PRFA, a hyperattenuating ring around the nonenhanced region was apparent in all patients. This ring was believed to be related to hyperemia and disappeared on follow-up CT images. On the CT scans obtained immediately after PRFA, the greatest dimension of the nonenhanced region was slightly larger than that the tumor before ablation. In other words, if the nonenhanced region on the biphasic contrast enhanced CT immediately after PRFA is slightly larger than of the enhanced tumor on the CT before ablation, then complete eradication of the tumor, including a safety margin, has been achieved [20]. The ideal goal is to ablate a 0.5 – 1.0 cm peripheral margin of normal hepatic tissue that surrounds the tumor, as well as the entire tumor itself [21]. In our study, all successfully thermal lesions appeared as areas of low attenuation without contrast enhancement at follow-up CT images. This nonenhancing low-attenuation area is believed to represent necrosis, as described by other investigators [22-23].

Minimal air bubbles are sometimes seen within the thermal lesion on the immediate follow-up CT images. These minimal amounts of air within the thermal area are aggregated microbubbles produced during the ablation and usually resolve within 1 month. They are thought to be generated as a result of tissue necrosis. Although minimal air bubbles within the thermal lesion can often be seen on CT performed immediately after ablation, new gas bubbles could signal an infection. Therefore, if a patient suffers from fever for over 1 week, the possibility of abscess formation should be considered. In our study, we found intralesional air bubbles in some patients, and the air bubbles were few and small only present on immediately follow-up CT after ablation, and they disappeared at 3-month follow-up images without abscess formation.

Bleeding is another important complication that occurs during and immediately after ablation. Several factors are related to bleeding after RF ablation. Coagulopathy in cirrhotic patients is the most commonly encountered problem. Screening for coagulopathy should be performed before the procedure because needle electrodes of large diameter (17 – 14 gauge) are used. The bleeding may develop due to direct mechanical injury to the vascular structure by the RF needle electrode rather than due to RF thermal injury to the vessel [24]. In our study, one patient developed hemoperitoneum after PRFA, and immediate embolization of the branch of rith hepatic artery was performed for bleeding control. Fortunately, he recovered well and discharged. Therefore, real-time monitoring of the whole procedure including positioning of the needle electrode is imperative. The risk of bleeding can be reduced if the operator is skillful in placing the RF needle safely without traversing major vessels and in
efficient and accurate needle repositioning. Furthermore, traversing sufficient normal hepatic parenchyma as well as cauteryization of the needle tract after ablation is useful to avoid bleeding.

If findings on short-term follow-up CT images are inconclusive and the suspicious viable or recurrent tumor is small, close follow-up is acceptable before an invasive diagnostic procedure or retreatment. Peripheral rim enhancement resulting from reactive hyperemia usually is uniform in thickness and envelops the thermal lesion, whereas residual tumor demonstrates focal and irregular peripheral enhancement [21]. The other useful point for differentiating the two conditions is that peripheral rim enhancement resulted from reactive hyperemia shows high- or iso-attenuation during portal venous or hepatic venous phases. Residual tumor usually becomes low attenuation during hepatic venous phase. In our study, peripheral rim enhancement appeared in every case on the immediately CT images and completely disappeared on later CT images. However, peripheral nodular enhancements were seen in two patients on 3-month follow-up CT images, indicating residual non-thermal tumor tissue or local tumor progression at the thermal margin. Unfortunately, they expired within 3 months because of serious tumor progression. Eight patients had recurrent tumors elsewhere in the liver on follow-up CT images. They were then treated with transcatheter arterial chemoembolization or PRFA.

Long-term follow-up CT shows gradual decrease in the size of the thermal lesion. This diameter change does not always indicate successful ablation, but is thought to represent only residual necrosis or fibrotic tissue during the absorption process [20]. When the PRFA achieve local temperatures and tissue destruction occurs, intracellular proteins denature, the lipid bilayer melts and cell death becomes inevitable. Thermal coagulation begins at 70°C and tissue desiccation at 100°C, resulting in coagulation necrosis of tumor tissue and surrounding hepatic parenchyma. Tissue heating also drives extracellular and intracellular water out of tissue and results in further destruction of tissue [25].

Our study has not yet counting on the result of long-term follow up because of limited case number and patient death. Further investigation is needed.

In conclusion, PRFA is an effective, safe, and relatively simple procedure for treatment of HCC. Successful treatment can be achieved in single-session procedure for patients with HCC by using PRFA under CT guidance. Our results also suggest that follow-up CT at regular intervals after PRFA can ensure early detection of viable or recurrent tumor.

REFERENCES

8. Liu LX, Jiang HC, Piao DX. Radiofrequency ablation of liver cancers. World J Gastroenterol 2002; 8: 393-399


利用雙相螺旋電腦斷層追蹤評估經皮射頻滅除術對肝細胞癌的治療效果

吳振豪1 黃振義1,4,5 熊小滿1 周宜宏2,4 李 章1,5 李三剛3,5

台中榮民總醫院 放射線部1
台北榮民總醫院 放射線部2
蘇澳榮民醫院 院本部3
國立陽明大學 醫學院4
私立中山醫學大學 醫學院5

長期追蹤經皮射頻滅除術治療後的肝細胞癌，並運用雙相螺旋電腦斷層影像上的一系列變化，來評估治療的效果。

有二十七個病人共35個肝細胞癌接受經皮射頻滅除術治療，每位病人都在術前及術後立刻做含動脈相及靜脈相的電腦斷層攝影，並且在3、6及9個月後進行追蹤影像檢查。獲得的影像也將判讀、描述出是否有殘餘或復發的顯影區及比對治療區域大小的改變。

35個肝細胞癌中有32個（91%）在術後的立即及三個月後追蹤的電腦斷層影像中呈現低密度及不顯影，代表腫瘤已成功治療。在立即追蹤的電腦斷層影像中，也發現治療後周圍組織的充血反應（100%）及一些微小氣泡在治療後的組織內（28%）。其餘的3個腫瘤（9%）呈現周圍的結節顯影，診斷為殘存的肝細胞癌。二十七個病人中有八個（29%）在治療完後，發現在肝臟其他位置有新的復發腫瘤。

用電腦斷層影像來評估，經皮射頻滅除術治療肝細胞癌的結果，確實可提供準確診斷殘餘或復發的腫瘤，並據此為病患做進一步的治療。

關鍵詞：電腦斷層：肝細胞癌：肝腫瘤，治療：射頻滅除術