·Review·

# Research advancement in local ablation therapy for liver cancer

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**[Abstract]** After developing for more than 20 years, image-guided local ablation therapy has become one of the major treatments of hepatocellular carcinoma (HCC). In particular, percutaneous radio-frequency ablation has been widely accepted as the first-line treatment of early-stage HCC. A number of randomized controlled trials have shown some differences between these local ablation techniques. This article reviewed the development of local ablation therapy in the past few years.

**Key words:** liver neoplasm, treatment, radiofrequency ablation, microwave coagulation

Primary liver cancer is one of the five most common malignant tumors, with an incidence of 5.5–14.9 per 100 000 persons.[1] In China, the incidence of liver cancer accounts for 50% of the newly diagnosed cases all over the world. It is the second most common malignancy in men and the fourth in women, and mortality is second among all malignant tumors.[2]

The only potentially curative method is surgery, including partial hepatectomy and liver transplantation. Although liver transplantation may achieve good clinical outcomes, the organ resource is limited and few patients have the opportunity to receive liver transplants. Most patients undergo partial hepatectomy. With strict election of patients, the 5-year survival rate can reach as high as 60%–73%.[3] Nonetheless, due to the insidious onset of the disease, 70% of patients cannot be treated operatively on the initial evaluation. The common reasons are the large size of the tumor, multiple or extensive metastases, severe cirrhosis, and other coexisting complications that compromise the patient's ability to tolerate surgery. Even if the patient undergoes surgery, the 5-year recurrence rate is 50%–80%. Thus the development of other therapeutic modalities aside from surgery is of vital importance. Current alternative modalities include transcatheter arterial chemoembolization (TACE), local ablation therapy, radiation therapy, chemotherapy, and traditional Chinese medicine. Of them, the local ablation therapy, which is a novel way to treat liver cancer, has developed most rapidly.

Local ablation refers to the technique that uses chemical or physical means to damage the tumor tissue in situ with the assistance of imaging techniques [B-mode ultrasound, computed tomography (CT), magnetic resonance imaging (MRI), or laparoscopy]. The technique falls into two broad categories: one is chemical ablation, which inject substances (anhydrous alcohol, 50% acetic acid, hyperthermal distilled water, and hyperthermal carboplatin) that can kill tumor cells percutaneously; the other is physical ablation, which kills the tumor with energy output, such as percutaneous radiofrequency ablation (PRFA), percutaneous microwave coagulation therapy (PMCT), percutaneous laser ablation (PLA), cryotherapy, and radioactive seed implantation. Although exterior radiation treatment and high-intensity focused ultrasound also belong to the category of local treatment, they are quite different from invasive local ablation and are beyond the scope of this article. Currently, the commonly used local ablation techniques for treating liver cancer include percutaneous ethanol injection (PEI), PRFA, and PMCT.

## Percutaneous ethanol injection (PEI)

PEI is the oldest local ablation technique for treating liver cancer. Japanese investigators reported their experience in 1985.[4] With the injection into the tumor cells of ethanol at a concentration of 95% or above, the tumor tissue showed coagulation necrosis with protein degeneration and cell dehydration. The doses of ethanol are generally based on the maximum diameter of the tumor without a standard calculating method. Giorgio et al doubled the maximum tumor diameter (cm) to be the number of milliliters of ethanol. Chinese researchers used the formula $V = 4\pi \times (D/2 + 0.5)^3/3$. These two methods are quite different from each other. In clinical practice, the dose can be adjusted according to the acoustic changes detected using B-mode ultrasound. With ethanol injection, the echo in the center of the injection point is observed to expand until the whole lesion is covered. If the lesion is large, one point injection is

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likely to be insufficient and multiple injections at different sites may be necessary. Even multiple treatments may be required to reduce the risk of complications and to improve therapeutic effect.

A national multicenter investigation in Japan ($n$=4 037) showed that the 1-, 2- and 3-year survival rates were 89%, 63%, and 43%, respectively, which is similar to surgical data.[5] Taniguchi et al.[6] observed 31 patients that underwent PEI as first-line treatment. A total of 42 lesions had diameters less than 1.5 cm. A 15-year follow-up was performed. The results showed that the 3-, 5-, 7-, and 10-year survival rates were 74.1%, 49.9%, 27.2%, and 14.5%, respectively. The 5-, 7-, and 10-year survival rates of patients with Child-Pugh grade A were 76.0%, 42.2%, and 15.8%, respectively, which was better than those with Child-Pugh grade B ($P$ = .025). A prospective randomized clinical trial (RCT) from Taiwan enrolled 76 patients and compared the effects of PEI and surgery in treating small liver cancer (diameter ≤3 cm). The result shows no significant difference.[7]

PEI is limited by its liquid preparation, which diffuses unevenly and might result in incomplete ablation. When the tumor is larger than 3 cm, the local recurrence rate is high. The possible mechanisms include the following: 1) Large tumors might contain a fibrous septum and have an uneven consistency, which influences the distribution of ethanol; 2) After injection, the ethanol that exudates to the tumor margin might be diluted or mixed in with vessels, which significantly reduces its effects; 3) The tumor capsule makes it difficult to obtain a safety margin with PEI. In an attempt to solve these problems, some researchers developed a novel quadrafuse needle, which can extrude fine needles in various directions, and each of these fine needles has small injection pores. Theoretically, this technique can expand the scope of ethanol injection and make the distribution more even. However, the limitation of the liquid preparation cannot be completely conquered. Meanwhile, the small pores may be obstructed. Thus, the safety and effects of this technique require further investigation.[8]

Besides ethanol, agents used for intratumor injection include 50% acetic acid, hyperthermal distilled water, hyperthermal carboplatin, and so on, though these are less commonly used. A Japanese study included 125 patients receiving PEI or percutaneous acetic acid injection (PAAI), and the long-term follow-up results showed that the patients that underwent these procedures required fewer cycles of treatment times and had better survival rates.[9]

## Percutaneous radiofrequency ablation (PRFA)

Treating liver cancer with PRFA was first reported by Rossi in 1995,[10] and has become the most commonly used local ablation technique. In the process, the radiofrequency current (range, 200-1200 kHz) travels through tumor tissue and oscillates the surrounding negative and positive ions in rapid frequency. The device connects the patient to a circuit with two electrodes. The needle-shaped electrode penetrating the tumor tissue is small in area as compared with the negative pole plate, so the ions are concentrated around the needle electrode and the rapidly oscillating ions produce large amounts of heat to damage tumor tissues. The influence of tumor texture on RFA is relatively less than it on PEI. Nevertheless, the electrical resistance of the necrotic tissue increases remarkably, which inhibits further transmission of the energy. The tissue can be carbonized when the temperature rises above 100℃, which increases electrical resistance considerably, thereby limiting the scope of the ablation.

Retrospective study and a few RCTs demonstrate that PRFA has high success rates for small liver cancer. Although its local recurrence rate is higher than surgical outcomes, the residual or recurrent lesions can be treated complementarily after initial treatment, reaching a long-term survival rate similar to surgery.[11,12] The size and number of tumors, liver function, Child-Pugh scoring, and the coverage of the safety margin are independent factors predicting ablation effects, and rising levels of α-fetoproteins (AFP) is an independent risk factor of intrahepatic metastases.[13-16]

The radiofrequency electrode has experienced a variety of improvements in the hope of enlarging the scope of single-needle ablation, including a multiple warhead electrode, an internal cooling electrode, a perfusion electrode, and a bipolar electrode. Recently, the concept of multipolar RFA was proposed, which refers to the insertion of 2 or 3 bipolar electrodes (without grounding line) into the tumor and a circuit formed along 4 or 6 electrodes to focus the energy on the ablation target. Large tumors can be damaged with this technique. Theoretically, complications caused by monopolar RFA, such as skin burn, can be eradicated with this technique. However, the long-term outcome requires further investigation.[17]

**Table 1 Randomized control trials of RFA**

| Reference | Technique compared with RFA | Cases | Favorable technique |
|---|---|---|---|
| Shiina et al.,[18] 2005 | PEI | 232 | RFA |
| Lancioni et al.,[19] 2003 | PEI | 102 | RFA |
| Brunello et al.,[20] 2008 | PEI | 139 | NS |
| Cheng et al.,[21] 2008 | RFA combined TACE | 291 | Combination |
| Liao et al.,[22] 2008 | RFA combined TACE | 36 | Combination |
| Kobayashi et al.,[23] 2007 | Hepatic arterial occlusion during RFA | 20 | Occlusion |

RFA, radiofrequency ablation; PEI, percutaneous ethanol injection; TACE, transcatheter arterial chemoembolization; NS, no significance.

RCTs regarding PRFA are primarily focused on comparisons with other therapeutic modalities or combinations with other techniques (Table 1). An RCT from Japan enrolling 232 patients showed that the effects of RFA was superior to PEI with a 4-year survival rate of 74% vs 57% ($P$<0.05). The RFA was also superior in terms of treatment times, ablation scope, hospital stay, and recurrence rate.[18] There are similar studies in Europe. In an Italian study, Lancioni obtained the same result as the Japanese study.[19] However, a recent study by Brunello did not obtain such definite results. When evaluated with complete response, RFA was significantly better than PEI ($P$<0.01), indicating the complete ablation rate of RFA was higher than PEI. But there was no significant difference with respect to overall survival.[20] RCTs from Ji'nan and Taiwan compared the effects of RFA combined with TACE in treating liver cancer with diameters > 3 cm and found that the combination was better than RFA or TACE alone.[21,22] An RCT from Japan showed that RFA combined with a temporary obstruction of the hepatic artery can expand the scope of the ablation (25.3 $cm^3$ vs 16.1 $cm^3$, $P$= 0.005).[23]

# Percutaneous microwave coagulation therapy (PMCT)

Microwave coagulation therapy (MCT) was first reported by Tabuse` for patients with liver rupture.[24] In the past 20 years, treating liver cancer with MCT has developed rapidly, applied during both open abdominal surgery and laparoscopic hepatectomy. The percutaneous procedure was first reported in 1994.[25] A microwave needle is introduced into the lesion and heats the tumor tissue by microwave radiation, resulting in coagulation necrosis. MCT is less influenced by the capsule and fibrous septum, and has a complete necrosis rate of more than 95% for primary hepatocellular carcinoma (HCC) with diameters ≤ 5.0 cm.[26,27]

An RCT conducted by the First Affiliated Hospital of Sun Yat-sen University showed that the 3-year survival rates of PRFA and PMCT were 86.4% and 87.1%, respectively, and recurrence rates were 16.7% and 27.5% , respectively (neither were statistically significant). Nonetheless, hospital stay, duration of treatment, blood transfusion, and therapy-associated complications of the ablation group were significantly lower than the surgery group.[12,28] In a retrospectively study at the same institution, the 4-year survival rate of MCT was higher than RFA (again, with no statistical significance).[29,30]

Interestingly, it is found that MCT may enhance antitumor immunity. The necrotic tumor tissue is likely to act as an antigen to stimulate a specific antitumor antibody,[31] which is in contrast with compromised immunity after surgery. However, there is no clinical trial exploring whether patients benefit from this immune response.

# Percutaneous laser ablation (PLA)

A laser is introduced into the tumor mass with fine optical fiber (0.2–0.6 mm). Radiated and scattered energy is then absorbed by the tumor tissue. The scope of the damaged lesion is correlated with the wave length, power, and duration. The neodymium:yttrium-aluminum-garnet (Nd:YAG) laser is the most commonly used and has the widest ablation scope available (1.5 cm). In recent years, cooling systems have been introduced to the optical fiber in European countries, such as Britain, Germany, and Italy, which expands the scope of the ablation and can be used for metastatic tumors and HCC with diameters less than 4-5 cm. However, there are no randomized studies in this field. In 2006, Pacella retrospectively reported 148 patients with HCC [diameter= (2.6±0.8) cm] who underwent PLA and found that the 1-, 3-, and 5-year survival rates were 89%, 52%, and 27%, respectively.[32] In 2007, Ferriri et al.[33] compared PLA and RFA [N=81, diameter = (2.79±0.78) cm] and found that the 1-, 3-, and 5-year survival rates were 88.6%, 56.6%, 22.9%, and 92.2%, 61.3%, 40.9%, respectively. The PLA group results were inferior to the RFA group results, yet without statistical significance. Other indices such as complete ablation rate, treatment time, and tumor-free survival time were all worse than the RFA group. A multicenter study from Italy[34] [$n$=520, diameter = (3.2±1.7) cm] reported that severe complications were 1.5%, mortality was 0.8%, and the one-time ablation rate for tumors with diameters ≤ 3 cm was 81%, indicating that the scope of ablation was the critical factor influencing clinical outcome.

# Argon helium cryotherapy (AHC)

A needle that delivers argon and helium is introduced into the tumor lesion. With the passage of argon, the temperature at the tip of the needle drops to -185℃, which lowers the surrounding temperature rapidly (below -35℃) to form an "ice ball." Three minutes later, helium is introduced to restore the tissue temperature to normal. Then the needle is pulled out. The tumor cells are killed by the cold and hot alteration. There are two setbacks to this procedure: 1) The necrotic area is smaller than PRFA and PMCT; and 2) Residual tumor cells can survive in the therapeutic area, especially at the tumor margins where the temperature drop is slow and the inactivation of tumor cells is uncertain. Published reports on this technique are few, and most focus on metastatic liver cancer. For instance, Kerkar investigated the prognosis of 98 patients with liver malignancy who underwent cryotherapy and found that the 1-, 3-, and 5-year survival rates were 81%, 48%, and 28%, respectively, including 14 cases of HCC with 1-, 3-, and 5-year survival rates of 77%, 57%, and 40%.[35] As compared with RFA, the incidence of complications such as hemorrhage, pleural effusion, and thrombocytopenia are significantly higher in AHC,[36] as well as the intrahepatic recurrence rate.

# Several issues regarding local ablation techniques

## Complications

Pain and fever are common after local ablation. They are relatively mild and will disappear in a week. Pleural fluid and ascites are common in patients with severe hepatic cirrhosis. The incidence of severe complications is less than 10%, including bile duct injury, abdominal bleeding, hepatic abscess, decompensated liver function, and injury of neighboring organs (gallbladder, stomach, intestines, and diaphragm).[37] Several cases of acute respiratory distress syndrome (ARDS), hepatic infarction, and pseudoaneurysm were reported after thermal ablation. Cryotherapy may also cause hypothermia or cryoshock syndrome. The mortality rate within 3 months of treatment is 0.3%–1.4%, the direct causes include liver failure, tumor progression, vascular injury, and bowel perforation. A total of 179 papers in the past 20 years were reviewed in the UK and the results showed that the incidence of needle tract metastasis from PEI is higher than from thermal ablation. Pretreatment biopsy increases the risk of needle tract metastasis.[38] A multicenter study from Japan found that the incidence of severe complications and needle tract metastasis at centers with small sample sizes were higher than centers with larger cumulative sample sizes, indicating that sophistication and standardized work-ups can reduce such complications.[37] In conclusion, despite the safety of local ablation, attention should be paid to the potentially life-threatening complications. The superiority of local ablation can be realized only with strict selection of patients, thorough understanding of the devices, sophisticated performance, and the accuracy of the scope of ablation.

### Indications

Early on, local ablation was used for patients deemed inappropriate for surgery, including those with severe hepatic cirrhosis, deep tumor location, or those awaiting liver transplants. The diameters of the tumor should be ⩽ 3 cm,[10] liver function should have a Child-Pugh rating A–B, and there are no distant metastases with no bleeding tendency.

Research has shown that both PEI and thermal ablation can achieve similar 5-year survival rates compared to surgery for small liver cancer (diameter < 3 cm). RFA as the first-line therapy for small liver cancer has reached consensus.[11,12] Tumors with diameters between 3–5 cm, on the liver surface, or on the neighboring gallbladder, major vessels, diaphragm, or intestines are considered inappropriate to undergo thermal ablation. However, retrospective studies showed that the safety and complications were not significantly different from those in safe sites, except with increased postoperative pain.[39,40] Tumors located in the caudate lobe are no longer a contraindication of thermal ablation.[41] We are looking forward to prospective studies to provide more cogent evidence.

Many studies show that PMCT or PRFA are more effective than PEI. The latter is more economical and safer and can be a choice for tumors with diameters < 3 cm. PEI is now more commonly used for liver cancer that involves neighboring hollow organs or tracts, or when combined with thermal ablation to improve efficacy.[42] To date, the comparison between PRFA and PMCT has not showed a significant difference.[29,30,43] The simultaneous deployment of multiple radiofrequency electrodes or microwave antenna can undoubtedly expand the scope of the ablation, but this is more expensive and requires much more accurate localization. The single-point ablation scope is still an important parameter in evaluating the quality of ablation equipment.[44]

Comprehensively, thermal ablation (PMCT or PRFA) and surgical resection can be parallel first-line therapies for small liver cancer (single lesion ≤ 5 cm or at most three lesions ≤ 3 cm). If the tumor is located deep in the liver or severe cirrhosis exists, thermal ablation can be the first choice. For patients with contraindications for surgery, the limitations of tumor size and number can be lifted. In addition, PEI or TACE can be combined if appropriate (TACE is first, followed by local ablation). A single application of PEI is not recommended, except to provide treatment to a patient with limited finances or in tumors < 3 cm.

Local ablation and imaging

Local ablation is performed with the assistance of imaging equipment, and the imaging technique is crucial to therapeutic effects. Ultrasound is good at real-time localization, is easy to perform, and is cheap and timesaving, but it is demanding in imaging expertise and has a "blind area" because of the overlying pulmonary lobe, bowel, and ribs. The difficulty in visualizing the lesion will definitely influence the therapeutic effects. Sometimes, artificial pleural effusion or ascites can be created to assist visualization and protect neighboring organs.[45] With multiple-needle ablation, acoustic changes brought by the first needle therapy will influence the subsequent procedures. Some clinicians proposed deploying multiple needles under ultrasound to accurately cover the lesion. CT can locate the lesion accurately without a blind area, but, without real-time monitoring, the needle insertion is blind. CT has high risk and is time-consuming. Ablation with laparoscopic assistance can achieve similar results and even discover lesions that have been overlooked during preoperative CT or MRI examinations. Laparoscopy can only view the surface, under which endoscopic ultrasound is needed to locate the lesion. This complex procedure is mainly used for tumors on the surface of the liver, which can prevent injury to the abdominal wall.[43,46] The development of an imaging technique that is conducive to the process of local ablation-for instance, a three-dimensional ultrasound-would help in accurate lesion localization.[47] Contrast-enhanced ultrasound can identify more satellite foci and blood supply vessels preoperatively, which can evaluate the residual lesions promptly after treatment, whereby reducing recurrence rate and improving therapeutic effects.[48,49] More and more accurate imaging techniques are important for the early identification of liver cancer, thereby improving complete ablation rates.

## Shortcomings and prospects

PEI, radiofrequency, and microwave ablation techniques all have following advantages: 1) minimally invasive; 2) good repeatability; 3) less severe complications; and 4) lower costs. The disadvantages are remarkable. 1) The placement of ablation equipment is demanding. Sometimes, the mass site is inappropriate. In other circumstances, the intercostal space is narrow or there are important structures in the only puncture pathway, which make percutaneous ablation very difficult or even infeasible. 2) The scope of the ablation using the single-needle method is limited. When the tumor is large, the recurrence rate is high even with multiple-needle ablation. 3) Complications are unavoidable. These shortcomings can be overcome with the development of local ablation techniques and equipment. For instance, the radiofrequency electrode and microwave needle are expanding their treatment scope. The applications of 3-D ultrasound and contrast-enhanced ultrasound may make the ablation more accurate and complete. And these maturing techniques may reduce complications to the nadir level. As screening improves, the proportion of patients with early-stage liver cancer may increase. In the near future, local ablation techniques may play an increasingly important role in the management of liver cancer, and, in combination with other modalities, help us realize our goal of individualized treatment.

## References


[1] Mazzanti R, Gramantieri L, Bolondi L. Hepatocellular carcinoma: epidemi- ology and clinical aspects [J]. Mol Aspects Med, 2008,29(1-2):130-143.

[2] Yang L, Li LD, Chen YD, et al. Cancer incidence and mortality estimates and prediction for year 2000 and 2005 in China [J]. Zhongguo Weisheng Tongji, 2005,22(4):218-221. [in Chinese]

[3] Bruix J, Sherman M. Management of hepatocellular carcinoma [J]. Hepatology, 2005,42(5):1208-1236.

[4] Shinagawa T, Ukaji H, Iino Y, et al. Intratumor injection of absolute ethanol under ultrasound imaging for treatment of small hepatocellular carcinoma: attempts in three cases [J]. Acta Hepatol Jpn, 1985,26(5):99-105.

[5] Arii S, Yamaoka Y, Futagawa S, et al. Results of surgical and nonsurgical treatment for small-sized hepatocellular carcinomas: a retrospective and nationwide survey in Japan. The Liver Cancer Study Group of Japan [J]. Hepatology, 2000,32(6):1224-1229.

[6] Taniguchi M, Kim SR, Imoto S, et al. Long-term outcome of percutaneous ethanol injection therapy for minimum-sized hepatocellular carcinoma [J]. World J Gastroenterol, 2008,14(13):1997-2002.

[7] Huang GT, Lee PH, Tsang YM, et al. Percutaneous ethanol injection versus surgical resection for the treatment of small hepatocellular carcinoma: a prospective study [J]. Ann Surg, 2005,242(1):36-42.

[8] Ho CS, Kachura JR, Gallinger S, et al. Percutaneous ethanol injection of unresectable medium-tolarge-sized hepatomas using a multipronged needle: efficacy and safety [J]. Cardiovasc Intervent Radiol, 2007,30(2):241-247.

[9] Tsai WL, Cheng JS, Lai KH, et al. Review article: percutaneous acetic acid injection versus percutaneous ethanol injection for small hepatocellular carcinoma-a long-term follow-up study [J]. Aliment Pharmacol Ther, 2008,28(3):304-311.

[10] Rossi S, Di Stasi M, Buscarini E, et al. Percutaneous radiofrequency interstitial thermal ablation in the treatment of small hepatocellular carcinoma [J]. Cancer J Sci Am, 1995,1(1):73-81.

[11] Chen MS, Zhang YJ, Li MQ, et al. Randomized clinical trial of percutaneous radiofrequency ablation plus absolute ethanol injection compared with radiofrequency ablation alone for small hepatocellular carcinoma [J]. Zhonghua Yixue Zazhi, 2005,85(2): 80-83. [in Chinese]

[12] Lv MD, Huang M, Liang LJ, et al. Surgical resection versus percutaneous thermal ablation for early-stage hepatocellular carcinoma: a randomized clinical trial [J]. Zhonghua Yixue Zazhi, 2006,86(12):801-805. [in Chinese]

[13] Peng ZW, Zhang YJ, Chen MS, et al. Risk factors of survival after percutaneous radiofrequency ablation of hepatocellular carcinoma [J]. Surg Oncol, 2008,17(1):23-31.

[14] Lencioni R, Cioni D, Crocetti L, et al. Early-stage hepatocellular carcinoma in patients with cirrhosis: long-term results of percutaneous image-guided radiofrequency ablation [J]. Radiology, 2005,234(3):961-967.

[15] Kim YS, Rhim H, Cho OK, et al. Intrahepatic recurrence after percutane-ous radiofrequency ablation of hepatocellular carcinoma: analysis of the pattern and risk factors [J]. Eur J Radiol, 2006,59(3):432-441.

[16] Lam VW, Ng KK, Chok KS, et al. Incomplete ablation after radiofrequency ablation of hepatocellular carcinoma: analysis of risk factors and prognostic factors [J]. Ann Surg Oncol, 2008,15(3):782-790.

[17] Terraz S, Constantin C, Majno PE, et al. Image-guided multipolar radiofre- quency ablation of liver tumours: initial clinical results [J]. Eur Radiol, 2007,17(9):2253-2261.

[18] Shiina S, Teratani T, Obi S, et al. A randomized controlled trial of radiofrequency ablation with ethanol injection for small hepatocellular carcinoma [J]. Gastroenterology, 2005,129(1):122-130.

[19] Lencioni RA, Allgaier HP, Cioni D, et al. Small hepatocellular carcinoma in cirrhosis: randomized comparison of radio-frequency thermal ablation versus percutaneous ethanol injection [J]. Radiology, 2003,228(1):235-240.

[20] Brunello F, Veltri A, Carucci P, et al. Radiofrequency ablation versus ethanol injection for early hepatocellular carcinoma: a randomized controlled trial [J]. Scand J Gastroenterol, 2008,43(6):727-735.

[21] Cheng BQ, Jia CQ, Liu CT, et al. Chemoembolization combined with radiofrequency ablation for patients with hepatocellular carcinoma larger than 3 cm: a randomized controlled trial [J]. JAMA, 2008,299(14):1669-1677.

[22] Liao GS, Yu CY, Shih ML, et al. Radiofrequency ablation after transarte-rial embolization as therapy for patients with unresectable hepatocellular carcinoma [J]. Eur J Surg Oncol, 2008,34(1):61-66.

[23] Kobayashi M, Ikeda K, Kawamura Y, et al. Randomized controlled trial for the efficacy of hepatic arterial occlusion during radiofrequency ablation for small hepatocellular carcinoma——direct ablative effects and a long-term outcome [J]. Liver Int, 2007,27(3):353-359.

[24] Tabuse K. A new operative procedure of hepatic surgery using a microwave tissue coagulator [J]. Nippon Geka Hokan, 1979,48(2):160-172.

[25] Seki T, Wakabayashi M, Nakagawa T, et al. Ultrasonically guided percutaneous microwave coagulation therapy for small hepatocellular carcinoma [J]. Cancer, 1994,74(3):817-825.

[26] Dong BW, Liang P, Yu XL, et al. Long-term results of percutaneous sonographically-guided microwave ablation therapy of early-stage hepatocellular carcinoma [J]. Zhonghua Yixue Zazhi, 2008,86 (12):797-800. [in Chinese]

[27] Yamashiki N, Kato T, Bejarano PA, et al. Histopathological changes after microwave coagulation therapy for patients with hepatocellular carcinoma: review of 15 explanted livers [J]. Am J Gastroenterol, 2003,98(9):2052-2059.

[28] Angonese C, Baldan A, Cillo U, et al. Complications of radiofrequency thermal ablation in hepatocellular carcinoma: what about "explosive" spread? [J]. Gut, 2006,55(3):435-436.

[29] Xu HX, Xie XY, Lu MD, et al. Ultrasound-guided percutaneous thermal ablation of hepatocellular carcinoma using microwave and radiofrequency ablation [J]. Clin Radiol, 2004,59(1):53-61.

[30] Lu MD, Xu HX, Xie XY, et al. Percutaneous microwave and radiofre-quency ablation for hepatocellular carcinoma: a retrospective comparative study [J]. J Gastroenterol, 2005,40(11):1054-1060.

[31] Dong BW, Zhang J, Liang P, et al. Sequential pathological and immunolo-gic analysis of percutaneous microwave coagulation therapy of hepatocellular carcinoma [J]. Int J Hyperthermia, 2003,19(2):119-133.

[32] Pacella CM, Bizzarri G, Francica G, et al. Analysis of factors predicting survival in patients with hepatocellular carcinoma treated with percutaneous laser ablation [J]. J Hepatol, 2006,44(5):902-909.

[33] Ferrari FS, Megliola A, Scorzelli A, et al. Treatment of small HCC through radiofrequency ablation and laser ablation. Comparison of techniques and long-term results [J]. Radiol Med, 2007,112 (3):377-

393.
[34] Arienti V, Pretolani S, Pacella CM, et al. Complications of laser ablation for hepatocellular carcinoma: a multicenter study [J]. Radiology, 2008,246(3):947-955.
[35] Kerkar S, Carlin AM, Sohn RL, et al. Long-term follow up and prognostic factors for cryotherapy of malignant liver tumors [J]. Surgery, 2004,136(4):770-779.
[36] Tait IS, Yong SM, Cuschieri SA. Laparoscopic in situ ablation of liver cancer with cryotherapy and radiofrequency ablation [J]. Br J Surg, 2002,89(12):1613-1619.
[37] Kasugai H, Osaki Y, Oka H, et al. Severe complications of radiofrequency ablation therapy for hepatocellular carcinoma: an analysis of 3,891 ablations in 2,614 patients [J]. Oncology, 2007,72 Suppl 1: 72-75.
[38] Stigliano R, Marelli L, Yu D, et al. Seeding following percutaneous diagnostic and therapeutic approaches for hepatocellular carcinoma. What is the risk and the outcome? Seeding risk for percutaneous approach of HCC [J]. Cancer Treat Rev, 2007,33(5):437-447.
[39] Wong SN, Lin CJ, Lin CC, et al. Combined percutaneous radiofrequency ablation and ethanol injection for hepatocellular carcinoma in high-risk locations [J]. AJR Am J Roentgenol, 2008,190 (3):W187-195.
[40] Ohmoto K, Mimura N, Iguchi Y, et al. Percutaneous microwave coagulation therapy for superficial hepatocellular carcinoma on the surface of the liver [J]. Hepatogastroenterology, 2003,50 (53):1547-1551.
[41] Peng ZW, Liang HH, Chen MS, et al. Percutaneous radiofrequency ablation for the treatment of hepatocellular carcinoma in the caudate lobe [J]. Eur J Surg Oncol, 2008,34(2):166-172.
[42] Chen MS, Zheng Y, Zhang YQ, et al. Combining with radiofrequency ablation and ethanol injection for treatment of patients with liver cancer [J]. Aizheng, 2001,20(7):759-761. [in Chinese]
[43] Sakaguchi H, Seki S, Tsuji K, et al. Endoscopic thermal ablation therapies for hepatocellular carcinoma: a multi-center study [J]. Hepatol Res, 2008,39(1):47-52.
[44] Zheng Y, Li QJ. Sonographically guided percutaneous "air-cooled" microwave coagulation in live pig liver: an experimental study [J]. Aizheng, 2004,23(6):609-613. [in Chinese]
[45] Zheng Y, Zhang YQ, Zhou RH, et al. Artificial hydrothorax in aid of sonographically guided local therapy for liver tumors in the hepatic dome [J]. Zhongshan Daxue Xuebao, 2005, 26(6):696-699. [in Chinese]
[46] Casaccia M, Andorno E, Nardi I, et al. Laparoscopic US-guided radiofre-quency ablation of unresectable hepatocellular carcinoma in liver cirrhosis: feasibility and clinical outcome [J]. J Laparoendosc Adv Surg Tech A, 2008,18(6):797-801.
[47] Hotta N, Fukuzawa Y, Ayada M, et al. A case of hepatocellular carcinoma (HCC) treated with radiofrequency ablation (RFA) using 4D real-time ultrasound system [J]. Hepatogastroe- nterology, 2005,52(64): 1224-1227.
[48] Chen MH, Wu W, Yang W, et al. The use of contrast-enhanced ultrasonography in the selection of patients with hepatocellular carcinoma for radio frequency ablation therapy [J]. J Ultrasound Med, 2007,26 (8):1055-1063.
[49] Chen MH, Yang W, Yan K, et al. The role of contrast-enhanced ultrasound in planning treatment protocols for hepatocellular carcinoma before radiofrequency ablation [J]. Clin Radiol, 2007,62(8):752-760.