REVIEW ARTICLE

Percutaneous Ablation Therapy for Hepatocellular Carcinoma: Current Practice and Future Perspectives

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Worldwide, hepatocellular carcinoma (HCC) is a common, refractory, malignant tumor. Surgical resection is feasible in only a few patients, because of limited hepatic reserve and multifocality of tumors at diagnosis. Percutaneous ablation therapies, including injection of ethanol (PEI) or acetic acid (PAI), radiofrequency ablation (RFA), and microwave coagulation therapy (MCT), have been the major treatments for unresectable HCC in the past decade. PEI is well established for small (< 3 cm) HCC, and PAI is equally as effective as PEI, but with fewer treatment sessions. RFA has recently been suggested to have excellent tumor-ablating ability because it produces a fixed and predictable tumor necrosis zone. Although RFA is also effective for medium-sized HCC, the overall complication rate may be higher than previously assumed. MCT is similar to RFA in its clinical application and potential adverse effects. A combination approach using percutaneous ablation therapy and transcatheter arterial embolization was shown to be effective for large HCC. Other approaches, such as injection of hot saline or yttrium-90 microspheres, cryoablation, or interstitial laser photocoagulation, are less often used nowadays. Multimodal, image-guided, tailored therapy, rather than a fixed treatment algorithm, might be more practical for unresectable HCC. In conclusion, although long-term survival is possible in selected patients with HCC, the overall prognosis remains suboptimal, especially in patients with unfavorable tumor characteristics. While newer anti-tumor therapies with improved efficacy are needed, information about a more rational approach to the use of existing therapeutic options may help to enhance treatment strategies for HCC. [*J Chin Med Assoc* 2005;68(4):155–159]

Key Words: hepatocellular carcinoma, microwave coagulation therapy, percutaneous acetic acid injection, percutaneous ethanol injection, radiofrequency ablation

Introduction

Hepatocellular carcinoma (HCC) is a common malignant neoplasm that principally affects individuals from Asia and Africa.[1] However, recent epidemiologic surveys suggest that prevalence and mortality rates for HCC are increasing in North America and Europe.[2,3] Several treatments for HCC have been developed during the past 2 decades. Surgical resection is generally believed to be the standard form of curative therapy; however, it is possible only in a small subgroup of patients because of the presence of multifocal tumors or compromised hepatic reserve at diagnosis.[4] Liver transplantation is another treatment option, especially for patients with advanced cirrhosis, but patients on the waiting list for transplantation far outnumber potential cadaveric or living hepatic donors. Among the various non-surgical interventions, percutaneous ultrasound-guided therapy, including injection of ethanol or acetic acid, and thermal ablation using radiofrequency or microwave energy, are the mainstays of current clinical practice.[5] These therapies

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have the advantages of preserving unaffected liver parenchyma, and avoiding potential complications from major liver surgery. Numerous studies have shown that these methods may prolong survival in patients with unresectable HCC, and combination therapy with these various approaches may also enhance treatment responses.

Percutaneous Ethanol Injection (PEI)

The PEI technique was first initiated by Japanese researchers in the 1980s, when real-time ultrasound guidance became possible. Injected pure ethanol induces local tumor necrosis by protein denaturation, cell dehydration, and thrombosis of tumor vessels. HCC is often a hypervascular structure, but is well encapsulated by a tumor capsule that can limit the spread of ethanol within the tumor nodule, which is usually soft in consistency. These features make PEI one of the most commonly used methods of percutaneous ablation therapy.

PEI has the advantages of being safe, relatively inexpensive, and easy to perform. In addition, PEI allows the selective treatment of HCC without damaging adjacent, unaffected liver parenchyma. Adverse effects are minimal, and include abdominal pain, fever, and transient elevation of liver enzymes. Although treatment criteria for PEI may vary from center to center, most investigators agree that tumor nodules < 3 cm in size, and no more than 3 nodules, are the most suitable for PEI.[6] Indeed, tumor size is an important indicator of HCC prognosis in patients undergoing surgical resection and/or percutaneous injection therapy.[6–8] Small HCC nodules (< 3 cm) treated with PEI may have a complete response rate of ≥ 80%, although the response rate may decrease significantly with increasing size of the nodules.[9]

Previous, non-randomized studies showed that patients undergoing PEI had a 3-year survival rate of 47–77%,[10–13] although the 2-year tumor recurrence rate often exceeded 50%.[11,12] Such a high recurrence rate should not be considered a specific defect of percutaneous injection therapy. Patients who undergo curative hepatectomy are also at risk of tumor recurrence after resection. This is possibly related to unnoticed synchronous tumors, undetected even by highly-sensitive imaging techniques, at diagnosis.[14,15] Retrospective studies of patients with small HCC indicate that PEI therapy may be as effective as surgical resection,[16,17] but prospective, randomized trials are required before a firm conclusion can be made. A recent study also suggested that PEI may have a role as salvage therapy in HCC patients who are unlikely to receive arterial embolization or other non-surgical treatments.[18]

Percutaneous Acetic Acid Injection (PAI)

Acetic acid 15–50% induces profound tumor necrosis through a similar mechanism to ethanol.[19] It has a strong ability to penetrate and dissolve lipids and collagen in tumor septa and capsules, and is theoretically superior to ethanol in treating HCC because it frequently induces a persistent state of complete tumor necrosis.[20] Further, a randomized trial comparing PAI with PEI was conducted in 60 patients with small HCC, and the local 2-year recurrence rate was considerably less for PAI than PEI (10% vs 44%).[21] However, the efficacy of PEI in the latter study was much poorer than that reported by other investigators.[9–13] Our recent study of PAI versus PEI efficacy in HCC showed that recurrence rates and long-term survival rates were similar between the 2 groups, and that patients given PAI had fewer treatment sessions and a shorter hospital stay.[22]

The efficacy of PAI was compared with that of transcatheter arterial chemoembolization (TACE) in HCC patients with tumors of up to 6 cm:[23] no significant difference in progression-free or overall survival was noted between the 2 treatment groups; this also applied in a subgroup analysis of patients with small HCC (< 3 cm). However, in patients with tumors > 3 cm, TACE tended to produce a better long-term outcome than PAI, suggesting a less satisfactory effect for PAI in large HCC.[23]

Radiofrequency Ablation (RFA)

RFA has recently become a widely used treatment for HCC.[5] In this procedure, the puncture probe has an insulated shaft and a non-insulated tip, which is inserted into the lesion under ultrasound guidance. The patient forms part of the electric circuit, with grounding pads on the thighs or back. The radiofrequency energy emitted from the needle tip induces ionic agitation and frictional heat. Thus, it is the surrounding tissue, rather than the electrode itself, that produces heat energy to destroy tumor cells. Because of its excellent necrotizing effect, RFA has become a highly effective, local ablative therapy for HCC.

A study comparing the efficacy of RFA with that of PEI in small HCC showed no significant difference between rates of complete tumor necrosis (90% vs 80%).[24] In a recent, randomized trial, 2-year survival

rates were also not significantly different between patients undergoing RFA versus PEI (98% vs 88%); however, patients in the RFA group had a much lower 2-year local recurrence rate than those in the PEI group (4% vs 38%).[25] Another study showed, from explanted livers, that viable tumor was still present in 7 of 12 patients who underwent RFA before liver transplantation.[26] The reason for the therapeutic advantage of RFA over PEI is that the zone of tumor necrosis in RFA is generally fixed and predictable, whereas the effect of PEI is highly dependent on the diffusion pattern of ethanol in the tumor nodule. A major advantage of RFA over PAI or PEI is that RFA can be used to treat medium- or large-sized HCC (≤ 8 cm in diameter).[27,28] For small HCC, RFA was reported to have efficacy comparable to that of surgical resection.[29] Moreover, RFA is an effective treatment for post-resection tumor recurrence,[30] and can be used to "bridge" patients to liver transplantation.[31]

While RFA is generally considered a safe procedure, a recent study found, from a systematic survey, that the complication rate for RFA was higher than previously assumed.[32] In addition, different treatment protocols and electrode types may affect treatment responses and tumor recurrence rates, and besides its potentially high complication rate, RFA has other limitations. For example, when the tumor nodule is close to major blood vessels, the radiofrequency energy will be carried away by the blood flow (the "heat-sink" effect), resulting in a suboptimal treatment response. Another drawback is that if the electrode tip becomes too hot during ablation, tissue charring may lead to increased tissue impedance and a smaller thermal-ablated area. Post-treatment tumor seeding is also a serious concern. From a Spanish study group, 4 of 32 patients (12.5%) developed needle-track seeding up to 1.5 years after RFA.[33] Tumors located in subcapsular regions, or with aggressive behavior, often had neoplastic seeding after treatment. Although there is increasing evidence to show that RFA is highly effective, and although some investigators have suggested that RFA may become the treatment of choice for patients with unresectable HCC,[34] more studies are required to confirm the overall efficacy of RFA relative to other treatments.

Microwave Coagulation Therapy (MCT)

With a similar thermal-ablation mechanism to RFA, MCT uses a microwave coagulator that generates and transmits microwave energy to a needle electrode inserted in the tumor nodule. MCT has been studied in patients with HCC, and in those with hepatic metastasis.[35–37] It can be used with percutaneous or laparoscopic methods to destroy tumor nodules, and can also be used to control tumor bleeding from ruptured HCC, or to prevent massive blood loss in liver surgery.[38]

The therapeutic efficacy of MCT was 70% for small HCC (< 3 cm) and 55% for large HCC (> 3 cm).[35] Another report showed that the 9-month, local recurrence rate was 2% in patients with small HCC, compared with 8% in large HCC;[39] the reported 3-year survival rate ranged from 73–86%.[39–41] Compared with PEI in patients with moderately or poorly differentiated HCC, MCT produced better local control and longer survival.[42] MCT is generally safe and well tolerated. Its limitations and complications are similar to those of RFA, including abscess or biloma formation, bleeding, liver failure, and cancer dissemination.[35–42]

Combination Therapy and Treatment Algorithm

By using different anti-tumor mechanisms in combination therapy, treatment responses may be enhanced and treatment targets might be extended to include medium (3–5 cm) or large (> 5 cm) HCC. Examples of combination therapy include TACE + PEI,[43,44] TACE + MCT,[45] TACE + PAI,[46] and RFA after arterial occlusion.[47] Combination therapy frequently induces a higher rate of complete tumor necrosis than single interventions. This may have important prognostic significance because an initial complete response could reduce the risk of tumor dissemination and recurrence,[48] and indeed, there is evidence that tumor recurrence may induce hepatic decompensation.[49] However, it should be noted that the overall complication rate may also increase in patients undergoing combination therapy, as the risk of adverse events is likely to be additive from constituent treatments.

A recent study proposed that multimodal, image-guided, tailored therapy, rather than a "fixed" treatment algorithm, may be more practical for unresectable HCC.[50] Nevertheless, although it has not been completely agreed, RFA may be considered the first-choice intervention; PEI or PAI is preferred for nodules at risk from RFA complications; and selective TACE is preferred for nodules not recognizable at ultrasound examination, for nodules not re-treatable after an unsuccessful ablation technique, and for multiple satellite nodules. Other percutaneous ablation therapies that have been reported in the literature include the injection of hot saline or yttrium-90 microspheres,[51,52] interstitial laser photocoagulation,[53] and cryoablation.[54] Although these methods were potentially effective

in HCC, they are not frequently used nowadays. Aggressive tumor-ablation therapy for HCC patients with decompensated cirrhosis is not recommended, because the expected survival in such patients is usually very limited; moreover, the risk of treatment-induced liver failure is substantially high, and there appears to be no solid survival benefit for these patients.

Future Perspectives

The clinical scenarios of HCC at presentation may vary widely.[55] The severity of co-existing cirrhosis is the key non-tumoral factor limiting survival. The choice of ablation therapy depends on experience and facilities at the referral center. Although long-term survival is possible in selected patients with unresectable HCC, overall outcomes remain unsatisfactory, especially in patients with unfavorable prognostic indicators. While awaiting newer anti-tumor therapies with improved efficacy, it is clear that the design of a more rational approach to use of existing treatments may help to overcome some of the limitations of existing treatments and improve therapeutic outcomes. Further well-designed studies are required to resolve the remaining controversial issues regarding the treatment of patients with unresectable HCC.

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