Percutaneous Local Ablation Therapy in Small Hepatocellular Carcinoma

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Periodic screening programs conducted in various countries, applying sonography and serum alfa-fetoprotein to patients with chronic liver disease, have identified numerous small hepatocellular carcinoma (HCC). Although surgical resection is generally preferred for curative ablation, the long-term survival rates following resection are no better than those following local ablation. Current local ablation modalities are typically easily performed, safe and repeatable procedures, and include percutaneous ethanol injection (PEI), percutaneous acetic acid injection (PAI), radiofrequency ablation (RFA) and microwave coagulation therapy (MCT). The mechanisms of PEI or PAI are based on the dehydration, intracellular protein damage, and thrombo-ischemic effects of absolute ethanol or acetic acid on the tumor cells. Meanwhile, the mechanisms of RFA or MCT are based on the generation of friction heat between the tissue and electric current or microwave emitted by an RF or microwave electrode into the tumor. The heat causes coagulation, followed by cellular death as soon as the temperature in the target area exceeds 60°C. From previous comparative studies of these procedures, RFA may be superior to PEI, PAI or MCT owing to its larger ablation volume, fewer treatment sessions and more predictable ablation size. The rate of complete necrosis of the target tumors was approximately 90-98% by RFA, 80-95% by PEI, 90-95% by PAI and 94% by MCT. Moreover, the survival rates of these four modalities were approximately 90% at 1 year, 70% at 3 years, and 40-50% at 5 years. In tentative conclusion, RFA is the preferred local ablation therapy for most small HCC. However, PEI is a useful alternative where RFA is unavailable. *(Chang Gung Med J 2003;26:308-14)*

Key words: small hepatocellular carcinoma, percutaneous ethanol injection, percutaneous acetic acid injection, radiofrequency ablation, microwave coagulation therapy.

Hepatocellular carcinoma (HCC) is one of the most prevalent malignant diseases in Asia.[1,2] Notably, the incidence of this condition is strongly correlated with hepatitis B virus (HBV) and hepatitis C virus (HCV) infection.[3] Over 80% of HCC develops in patients with cirrhosis.[4] The prognosis of patients with HCC depends mainly on tumor size, tumor number and hepatic function.[5]

Because most patients with HCC present too late for effective treatment, early detection of small HCC is crucial for improving survival. Small HCC is generally defined as three or fewer tumors, where the longest dimension of individual tumor is less than 3 cm. Periodic screening using combined alfa-fetoprotein (AFP) and sonography examinations can detect HCCs of 1cm and above. Various treatment options are available. Surgical resection may be effective in selected patients with single small tumor, but fewer than 20% of patients are candidates for surgery.[6] Additionally, surgical resection leaves the

patient with a diseased liver and the associated risk of tumor recurrence or death from underlying hepatic failure. In contrast, orthotopic liver transplantation is a rational treatment for patients with decompensated cirrhosis and a small HCC, but is expensive, necessitates immunosuppression, reactivates the virus and many countries lack sufficient donors. Consequently, various targeted or local therapies, both individually or in combination, have been proposed and accepted as possible modalities for treating HCC. These therapies are easily performed, safe, economic and repeatable procedures, and include percutaneous ethanol injection (PEI), percutaneous acetic injection (PAI), radiofrequency ablation (RFA), and microwave coagulation therapy (MCT).

Percutaneous ethanol injection (PEI)

PEI is considered the most practical and effective modality of direct ablation therapy for HCC. PEI was first proposed by Sugiura et al in 1983.[7] Nowadays, small HCC are generally agreed to be suitable for PEI,[8,9] and indeed PEI is preferred for HCC that are 2 cm or less in size. However, PEI is contraindicated in patients with gross ascites, bleeding tendency, and obstructive jaundice, owing to the risk of postprocedural bleeding, bile peritonitis, bile duct injury or abscess formation. If the HCC tumor is situated at or protruding from the liver surface, the increased risk of bleeding and tumor seeding should be considered, although these risks have been reported to be minimal.[9] Under local anesthesia, a 22 or 21 gauge PTC or Chiba needle was introduced into the tumor under sonographic or computed tomography (CT) scan guidance. Absolute (99.5%) ethanol was slowly injected into the tumor, and the needle position was shifted slowly to achieve uniform and adequate instillation and ensure tissue necrosis within and around the tumor. Ethanol injection quantity was adjusted according to tumor size. Total volume can be approximated by the equation $V \text{ (ml)} = 4/3 \times 3.14 \pi (\gamma + 0.5)^3$, where γ represents tumor radius in centimeters. From 2-10 ml absolute ethanol was injected during each session. Absolute ethanol induces cellular dehydration, coagulative necrosis, and vascular thrombosis, and thus causes tumor cells destruction. Following ethanol injection, 1 to 2 ml 2% lidocaine was injected before needle removal. Alternatively, the needle was left in position for 3 to 5 minutes after the injection to minimize local pain

elicited by ethanol leaking through the needle tract into the peritoneal cavities. The procedure was repeated twice weekly until hyperechoic change of the tumor was complete or nearly complete, or for up to 4-6 sessions for each tumor measuring 3 cm or less.

As a general standard, the effect of PEI is assessed using dynamic CT scan 2-4 weeks after the last injection session. Hypoattenuation of the target tumor is assumed to represent complete necrosis of the tumor following PEI. A further PEI booster is administered if CT scan demonstrates nodular or patch enhancement. Complete ablation is generally defined as persistent hypoattenuation on CT at least 4 to 6 months following the final session of PEI. Following complete ablation, abdominal sonography, serum AFP and CT scan are used to detect local or new HCC recurrence at 2-6 monthly intervals.

Various studies have reported satisfactory results of PEI for small HCC.[5,9-11] Specifically, the survival rates were 93% at 1year, 47% at 7 years and 26% at 10 years.[12] According to the 14th report of the Liver Cancer Study Group of Japan, which included a significant survey of 8840 patients with HCCs below 5 cm in 829 Japanese hospitals, the survival rates were 91.1% at 1 year, 36.7% at 5 years, and 11.9% at 9 years. During the cohort period, the survival rate of 16887 patients with surgically treated HCC below 5 cm was 86.8% at 1 year, 50.8% at 5 years, and 28.1% at 9 years.[5] An Italian group gathered data of 746 patients with HCC treated with PEI and reported that in patients with single HCC measuring 5 cm or smaller, the 1, 3, 5-year survival rates were 98%, 79%, 47% for Child A (N=293); 93% 63% 29% for Child B (N=149); and 64%, 12%, 0% for Child C (N=20), respectively.[13]

Our unit has performed PEI since 1989. The results to date, including 47 cirrhosis patients with 61 HCC ≤ 5 cm, reveal 1-, 3-, and 4-year survival rates of 85%, 61% and 31%, respectively. Furthermore, the 1-, 3-, and 4-year recurrence rates were 24%, 69% and 79%, respectively. HCC recurred more frequently in patients with two or three tumors ($p < 0.02$).[14]

The reported survival and recurrence rates achieved by treating HCC patients with PEI and surgical resection were comparable.[5,11,13,15] Moreover, serious complication rates were low for PEI, ranging from 1.3% to 2.4%.[13,15,16] An Italian multicenter sur-

vey of evaluation practices revealed a death rate of 0.09% (1/1066 patients), while the rate of major complications (defined as those requiring attention) was 1.4%, with the specific complications being hemorrhage (8 cases) and tumor cell seeding (7 cases).[16] From the numerous literature results, because of the risk of new lesion recurrence in the remnant of the liver, coexisting liver cirrhosis and operative damage associated with surgery, PEI may be considered as an alternative to surgery for most patients with small HCC.

Percutaneous acetic acid injection (PAI)

Acetic acid is an alternative to ethanol for local ablation therapies, and its effect was reported to be stronger than that of ethanol owing to lipid dissolution and the extraction of collagen fiber in the tumor.[17] In one randomized comparative study, PAI was reported to be superior to PEI because of its higher survival rate and lower recurrence rate.[18] The 1-, 2-, 3-, 4- and 5-year survival rates in HCC below 3cm were 95%, 87%, 80%, 63%, and 49%, respectively.[19]

Our unit also began to perform PAI since 1996 because of its better 2-year survival rate and lower 2-year recurrence rate compared to PEI in small HCC, as reported by Ohnishi et al.[18] From our own experience, PAI achieves a similar effect to PEI, but requires fewer treatment sessions. However, consistent with the literature, the experience at our unit revealed a slightly higher rate of major complications such as liver abscess, cholangitis and mild renal dysfunction with PAI compared to PEI, as reported elsewhere.[20] Consequently, large dose (>4 ml) injections of 50% acetic acid should not be administered in a single session for patients below 50 kg (Tamai T, International Hepatology Communications, 1997). Additionally, necrotic change or amorphous debris of HCC following PAI and good correlation with dynamic CT findings were also reported in our series.[21] However, owing to sampling limitations, cytologic or pathologic examination was only indicated where uncertainty existed between complete and partial necrosis displayed on sonography or CT scan.

Radiofrequency ablation (RFA)

The mechanism of RFA is based on high frequency alternating current flows from a noninsulated electrode tip into the tumor or surrounding tissue, with heat then being produced by friction between these current flows and the tissue. The heat thus generated causes cellular injury and death. As the tissue temperature rises to 60-100 ℃, irreversible cellular damage is immediately induced.[22] Lower temperatures (50-60 ℃) may induce coagulation in minutes. However, temperatures below 50-60 ℃ generally are insufficient for ablation, and over 30-40 minutes of heating is required in these cases.[22] During the months following RFA, fibrosis and scar tissue gradually replace the necrotic area.

Recently, RFA has been employed as an effective treatment for HCC and hepatic metastasis.[23] The preliminary results are encouraging and promising.[22-27] Furthermore, comparing RFA with PEI, the former achieves a higher rate of complete necrosis (90% vs. 80%) and requires fewer treatment sessions (1.2 vs. 4.8) in treating small HCC.[24] Although the rate of major complications is slightly higher in RFA than PEI (2% vs. 0%),[24] the literature reported no RFA-related mortality. Furthermore, the expandable or cluster electrode can achieve a larger volume of target tumor necrosis, meaning that HCC smaller than 5 cm can be successfully treated in a single session. Three RFA systems were approved by the Federal Drug Administration for soft tissue tumor ablation, namely: LeVeen needle (RadioTherapeutice Corp., Mountain View, CA) with power roll-off after achieving maximal impedance; RITA expandable electrode (RITA Medical Systems, Mountain View, CA) with multiple point temperature measurement, and cool-tip single or cluster electrode (Radionics Inc., Burlington, MA) with internal water circulation to cool the tissue adjacent to the electrode.

A typical treatment session comprises 10-30 minutes of active ablation and typically produces a 3.0 to 5.5-cm spherical coagulative necrosis. The treatment area is monitored ultrasonographically to detect increased echogenicity during the procedure. The increases in echogenicity correspond to the formation of water vapor microbubbles from the heated tissue, and are used to estimate the boundaries of the treatment sphere. Multiple overlapping ablations are generally required for larger tumors to ensure complete tumor desiccation along with a circumferential rim of normal hepatic tissue.

The effect of RFA is generally assessed using the postprocedural CT scan conducted 2-4 weeks

after RFA. If CT scan displays a nonenhancing region enveloping the target tumor, complete ablation is achieved. A further RFA booster can be performed if the enhancement persists. Complete ablation is defined as persistent hypoattenuation over the target tumor as revealed by CT scan 4-6 months following final RFA.

A four-series review of RFA for small HCC (< 3 cm in diameter) displayed a near-complete necrosis rate of 90% at 6 months; however, approximately 67% of the patients remained tumor free during the 12-23-month mean follow-up.[25] The long-term results remain unknown. Rossi et al. reported a sample involving a longer time span and containing 39 patients with hepatic tumors sized 3 cm or smaller, and obtained estimated survival rates of 94% at one year, 86% at 2 years, 68% at 3 years and 40% at 5 years, respectively.[26] Our unit began to perform RFA from March 1999.[27,28] A retrospective analysis of 112 HCC (1-6.7 cm) in 97 patients treated with either standard or power-enhanced interactive RFA using a LeVeen needle revealed complete necrosis in 98% of 89 small HCC (< 3 cm) and 87% of 23 HCC measuring 3.1 and 6.7 cm. Following a median of 352 days (range, 78-458 days) after RFA, the rate of local recurrence at the site of the initial ablation was 12%. New HCCs were present in 22 (23%) of 97 patients within 90-421 days following ablation. Meanwhile, the rate of local recurrence ranged from 0% to 30-50% in other reports.[26,29] Finally, the rate of complete necrosis was 96% in our series, comparable to the rate of 98% in a surgical series of comparable size.[29]

The complication rate associated with RFA in treating liver tumors has been estimated as below 3%.[26,29,30] Complications may be specific to thermal damage (grounding pad burns, damage to adjacent bowel or bile duct), or related to other risks of needle manipulation (seeding, bleeding, infection). However, the predictable thermal area by RFA frequently assigns a relatively low risk of collateral damage to nearby structures, and may be superior to that with PEI or PAI, meaning that the diffusion of ethanol or acetic acid in the tumor may be inhomogenous.

Consequently, RFA may be employed as the first choice of non-surgical treatment for most small HCC. If RFA is not available or is contraindicated, PEI or PAI thus can be alternatives to RFA.

Microwave coagulation therapy (MCT)

MCT works through the heating effect of microwaves emitted from a needle electrode inserted directly into the tumor. In a retrospective, nonrandomized comparative study, overall 5-year survival rates were 70% for patients with well-differentiated HCC treated with MCT, compared to 78% for those treated with PEI; moreover, the rates were 78% for patients with moderately or poorly differentiated HCC treated with MCT, compared to 35% for those treated with PEI ($p = 0.03$).[31] Because of the smaller volume of thermal ablation caused by the 2 cm diameter electrode, MCT is optimally applied to HCC below 2 cm in diameter. Multiple overlapping electrode insertion should be performed for tumors exceeding 2 cm, but this manipulation generally can not accurately encompass the entire target tumor. Nowadays RFA is gradually replacing MCT for HCC treatment owing to a wider range of target thermal sizes.

Conclusion

Regular periodic screening programs using sonography and AFP examination have created numerous small HCC in many countries.[32] Therefore, effective, safe, repeatable and inexpensive treatment modalities are required in many centers. In the absence of randomized trials comparing resection, PEI, PAI, RFA or MCT, it is very difficult to reach a consensus on the therapeutic options (Table 1). From retrospective comparative studies, surgical resection assures the highest possibility of completely ablating the tumor, but post-surgery survival rates are roughly comparable to those obtained with PEI. These comparable survival rates probably indicate that the two therapies offer similar benefits and risks. In fact, PEI survival rates are always better than the rates for resected patients with adverse prognostic factors. Consequently, HCC patients with good survival rates after resection should display all the following factors: age less than 65 years, Child's A with a single HCC smaller than 3 cm, with capsule intact, and at an easily accessible site to resection.[33]

Local ablation therapy should be considered if the above favorable factors for resection are lacking. RFA is superior to PEI in predictable size of ablation and fewer therapeutic sessions, but is significantly more costly on average than PEI. PAI is reported to be superior to PEI in terms of higher acetic acid pen-

Table 1. Results of Resection and Percutaneous Local Ablation Therapy for Heaptocelular Carcinoma

Author	Date	Treatment method	Patients No.	Tumor size (cm)	Survival rates (%)							
					1-yr	2-yrs	3-yrs	4-yrs	5-yrs	7-yrs	9-yrs	10-yrs
Chen[6]	1989	Resection	25	≤5	85	58	58	58	58			
Ebara[9]	1992	PEI	112	≤3	94	84	63	49	39	-		
Livraghi[13]	1995	PEI	169	≤3	99	96	86	69	48			
Ohnishi[19]	1996	PAI	91	≤3	95	87	80	63	49	-		
Rossi[27]	1996	RFA	39	≤3	94	86	68	-	40			
Seki[32]	1998	MCT	23*	<2	-	-	-	-	70			
		MCT	25#	<2	-	-	-	-	78			
Lin[14]	1999	PEI	47	≤5	85	78	61	31	-			
Arii[5]	2000	PEI	8840	≤5	91.1	76.3	61.8	47.8	36.7	20.9	11.9	
	2000	Resection	16887	≤5	86.8	77.2	68.3	59.0	50.8	36.6	28.1	
Shiina[12]	2001	PEI	349	≤3	93	-	74	-	47	38	-	26

*Well-differentiated HCC, #: moderately and poorly differentiated HCC
Abbreviations: PEI: percutaneous ethanol injection; PAI: percutaneous acetic acid injection; RFA: radiofrequency ablation; MCT: microwave coagulation therapy.

etration of the tumor and the need for fewer treatment sessions. However, these comparative conclusions are not truly valid because of the lack of further larger comparative trials and the likely technical bias of PEI in a single reported study. RFA is gradually replacing MCT because of the smaller thermal region when using MCT. In conclusion, RFA should be the first treatment option in patients with small HCC who refuse resection or present with adverse prognostic factors, but RFA can still be considered for resectable HCC, especially for tumors smaller than 3 cm and without peripheral satellites. PEI remains a valid tool where RFA is unavailable or cost is a consideration.

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小型肝細胞癌的經皮局部消除療法

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　　以超音波及血清甲型胎兒蛋白檢查，定期篩檢慢性肝炎或肝硬化患者，已能大規模的早期發現小型肝癌 (指數目≤3個、每個最大直徑≤3公分)。雖然手術切除仍爲完全根治性療法的最優先選擇，但是術後五年的存活率仍只能與局部消除療法相當。時下的數種局部消除療法經常具有簡易、安全、可重覆操作的特性，它們包括經皮酒精注射(PEI)，經皮醋酸注射(PAI)，無線高頻消除 (RFA)、以及微波電凝治療 (MCT)。PEI及PAI的機轉是藉由酒精 (99.5%) 或醋酸 (25%-50%) 在腫瘤内造成脫水、蛋白質變性、細血管栓塞造成腫瘤缺血壞死的效果，RFA及MCT則藉由導電探針放射出的高頻及微波產生熱量造成凝結性壞死。依照過去比較性的研究結果顯示，RFA具有可以造成較大範圍的壞死、治療次數最少而且灼燒範圍最能臆測等優點，因此在四種方法中爲最優先選擇。PAI在僅有的一篇仍具爭議性的文獻報告中指出，因爲治療次數較少且有較高的腫瘤壞死率，因此優於PEI。然而因爲PEI較無嚴重的副作用如膽管炎、腎衰竭或肝膿瘍，因此在沒有RFA的裝備下，PEI仍被絕大多數的醫學中心視爲最佳的治療。這四種治療的腫瘤完全壞死率在RFA約爲90-98%，PEI爲80-95%，PAI爲90-95%，MCT則爲94%。整體四種經皮局部消除療法的第一年存活率約爲90%，第三年爲70%，第五年爲40-50%。結論：對大多數小型肝癌的經皮局部消除療法，RFA爲最優先的選擇治療方法，若無RFA，則PEI爲最佳選擇。(長庚醫誌 2003;26:308-14)

關鍵字：小型肝細胞癌，經皮酒精注射，經皮醋酸注射，無線高頻消除治療，微波電凝治療。