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Original Article

Safety and Efficacy of Radiofrequency Ablation with Artificial Ascites for Hepatocellular Carcinoma

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The artificial ascites technique is often used during radiofrequency ablation (RFA) for hepatocellular carcinoma (HCC) treatment because it prevents visceral damage and improves visualization by minimizing interference of the lungs and mesentery. This study determined the efficacy and safety of RFA using the artificial ascites technique in HCC patients. We examined 188 HCC patients who were treated by RFA and fulfilled the Milan criteria. Treatment outcomes (complete ablation rate, local recurrence rate, complication rate, liver function including total bilirubin level, alanine aminotransferase level, albumin level, and prothrombin time) were compared among patients divided into 3 groups based on the volume of artificial ascites injected: Group Ⅰ (n = 86), no artificial ascites injected; Group Ⅱ (n = 35), < 1,000 ml artificial ascites injected; and Group Ⅲ (n = 67), > 1,000 ml artificial ascites injected. No significant difference was observed in complete ablation or local recurrence rates among the 3 groups, or in the extent of liver function damage after RFA. Artificial ascites disappeared within 7 days; additional diuretics were needed only in 5 (all from Group Ⅲ) of 102 patients. No serious complications such as intestinal perforation or intraperitoneal bleeding were observed. Thus, we found that artificial ascites injection during RFA is effective and safe, and can be used to prevent major procedural complications.

Key words: radiofrequency ablation, hepatocellular carcinoma, artificial ascites

Radiofrequency ablation (RFA) is widely used as the main line of treatment for hepatocellular carcinoma (HCC) [1–3]. Numerous reports have been published on the efficacy and complications of RFA [4–10]. Conventional RFA cannot be performed for certain conditions such as subdiaphragmatic tumors because the nodules are difficult to visualize by ultrasonography. In these cases, the treatment of choice would be artificial pleural effusion or the artificial ascites technique [11–15]. In addition, conventional RFA is not feasible in cases where the tumor is adjacent to other vital organs because of the risk of causing burns to these organs; the artificial ascites technique is also useful in such cases [11–15]. The artificial ascites technique has advantages over the artificial pleural effusion technique because it also avoids interference of the lungs and digestive tract at the same time. Several reports exist on the artificial ascites technique as well as its safety and usefulness; however, no report has described the influence of the technique on liver function parameters and diuretic use for post-operative control of induced artificial ascites

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or pleural effusion [14–16]. In this study, we evaluated changes in liver function parameters and the volume of residual ascites or pleural effusion following artificial induction in HCC patients who were undergoing RFA. Furthermore, we determined the efficacy, utility, and safety of this technique.

Patients and Methods

Patients. A total of 257 patients underwent RFA in our institution between January 2006 and March 2009. Among these, 188 HCC patients who fulfilled the Milan criteria and were classified as Child-Pugh A or B were analyzed retrospectively. Patients who received diuretics before RFA or who were classified as Child-Pugh C were excluded (Table 1), but were analyzed retrospectively. The mean tumor size was 20 ± 6 mm (range, 10–30 mm), the mean tumor number per liver was 2.2 ± 1.6 (range, 1–3), and mean number of treatment sessions was 1.4 ± 0.5. Patients were classified into 3 groups according to the volume of artificial ascites injected: Group Ⅰ, no artificial ascites injected; Group Ⅱ, $<1{,}000$ ml artificial ascites injected; and Group Ⅲ, $>1{,}000$ ml artificial ascites injected. We set the cut-off value at 1,000 ml because that volume was close to the median.

Indications for the artificial ascites technique. We used the artificial ascites technique in the following cases: (1) failure to detect a nodule by usual ultrasonography because of tumor location (*e.g.*, below the diaphragm or left edge of the left lobe); (2) inability to perform RFA by the usual method because of proximity of the tumor to other vital organs (*e.g.*, digestive tract or heart); and (3) lack of clarity in the ultrasonographic image because of mesenteric interference. In Group Ⅱ, 22 patients (62.9%) received artificial ascites based on reason (1), 7 patients (20.0%) received artificial ascites based on reasons (2) or (3), and 6 patients (17.1%) received artificial ascites based on reasons (1) (2), and (3). In Group Ⅲ, 34 patients (50.8%) received artificial ascites based on reason (1), 20 patients (29.9%) received artificial ascites based on reason (2) or (3), and 13 patients (19.4%) received artificial ascites based on reasons (1), (2) and (3).

Method of inducing artificial ascites. The breath-tuning method was used to induce artificial ascites. Following administration of local anesthesia to the skin and liver surface, the liver surface was penetrated (2 mm deep) using a venula needle (TOP, Japan) at the point of maximum inspiration. The needle's outer sheath was introduced immediately after the beginning of expiration. The needle tip was withdrawn from the liver at expiration, and the sheath was inserted between the liver and parietal peritoneum. Once the sheath was in place, 500–3,000 ml of 5% glucose was injected into the peritoneal space to induce ascites (Fig. 1).

Volume of injected ascites. We injected artificial ascites until ultrasonographic visualization was sufficient or until a clear separation between target nodules and vital organs was obtained, based on the reason for using artificial ascites. The minimum injected volume was 500 ml, and the maximum injected

Table 1 Characteristics of HCC patients treated by RFA. Complete ablation and local recurrence rates among the 3 groups

Group	Ⅰ	Ⅱ	Ⅲ	*p* value
Artificial ascites	0	$<1{,}000$ ml	$>1{,}000$ ml	
Case (male/female)	86 (71/15)	35 (29/6)	67 (57/10)	$p = 0.91$
Age (years)	64 (37–87)	64 (47–78)	68 (47–73)	$p = 0.83$
Tumor size (mm)	20 (10–30)	20 (10–30)	20 (10–30)	$p = 0.60$
Number of treatment sessions	1 (1–3)	1 (1–2)	1 (1–3)	$p = 0.09$
Virus HBV/HCV/NBNC	19/62/5	5/28/2	16/46/5	$p = 0.80$
Prothrombin time (%)	69 (48–102)	85 (37–98)	76 (50–91)	$p = 0.88$
Albumin (g/dl)	3.3 (1.9–4.6)	3.5 (2.6–4.1)	3.3 (2.2–4.7)	$p = 0.50$
Total bilirubin (mg/dl)	0.9 (0.3–3.2)	1.2 (0.4–2.3)	0.9 (0.3–2.5)	$p = 0.36$
Complete ablation rate (%)	86/86 (100)	35/35 (100)	67/67 (100)	–
Local recurrence rate (%)	4/86 (4.7)	2/35 (5.7)	3/67 (4.5)	$p = 0.96$

Values indicate the median (range) unless otherwise noted.

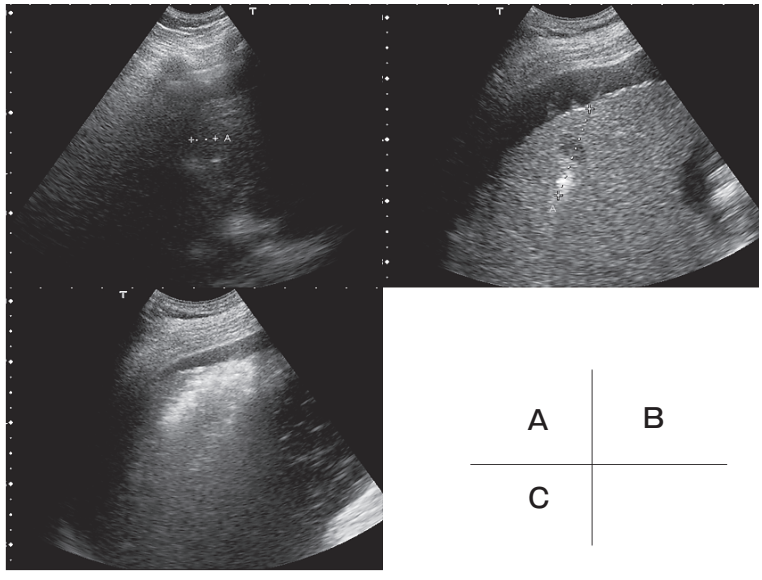

Fig. 1 Artificial ascites and RFA. **A**, Intercostal oblique ultrasonogram in the planning stage shows a subtle hypoechoic nodule only on deep inhalation; **B**, Ultrasonogram in the RFA targeting stage following artificial ascites induction shows the index tumor more clearly, even on shallow breathing. Note the radiofrequency electrode in the index tumor; **C**, Ultrasonogram taken at the RFA monitoring stage. Note that a hyperechoic RFA zone can be observed.

volume for optimal visualization was 2,000 ml.

RFA procedure and post-procedural follow-up. Percutaneous RFA was performed under ultrasonographic guidance using an internally cooled single electrode with a 200-W generator (Cool-tip, Valleylab, CO, USA). All patients were treated under conscious sedation with an intravenous injection of 15 mg pentazocine hydrochloride (Astellas Pharma, USA). The area from the skin to the liver capsule was anesthetized with 5–10 ml 1% lidocaine along the insertion route. If patients complained of intolerable pain during ablation, an additional 15 mg of pentazocine hydrochloride was administered intravenously.

We used 1- and 2-cm-long exposed metallic tip needles for tumors up to 1 cm and from 1 to 2 cm in diameter, respectively. A 3-cm-long exposed needle was used for tumors larger than 2 cm.

Following tumor ablation, we performed tract ablation during needle withdrawal to avoid peritoneal bleeding, which was evaluated after the procedure by Doppler ultrasonography. In case of persistent bleeding, the bleeding point at the surface of the liver was ablated using a 1-cm-long exposed needle. Contrast-enhanced computed tomography (CT) to evaluate the ablated area was performed 1–2 days after RFA. We completed the treatment series when HCC was ablated with a radial margin of 5 mm for curative purpose and without a margin for palliative purpose, and we defined both of them as complete ablation. We did not drain the injected artificial ascites. The injected artificial ascites generally moved from the abdominal cavity to the thoracic cavity because of negative pressure in the latter. In case of persistent ascites or pleural effusion on follow-up CT, we re-evaluated each patient 2 days after the procedure. Additional diuretics were administered if residual ascites or pleural effusion was confirmed, because such patients would have suffered too long with abdominal distension and chest dullness. Ultrasonography was performed 3 days after diuretic administration, and the volume of residual ascites was again evaluated. Diuretics were administered until complete elimination of residual ascites or pleural effusion.

Laboratory tests were performed on the day before and 1 day after RFA [total bilirubin (TB) level; alanine aminotransferase (ALT) level; albumin (Alb) level; and prothrombin time (PT)]. Follow-up CT or ultrasonography and tests for tumor markers were performed at maximum intervals of 3 months. Local recurrence was defined as a recurrent tumor that touched the ablated area, as identified by contrast-enhanced CT. Recurrence was evaluated 1 year after

RFA. Treatment was promptly repeated in patients with confirmed recurrence.

Statistical analysis. Differences in patient parameters were analyzed by ANOVA or Fisher's exact test. Local recurrence at 1 year after RFA was evaluated by chi-square test. Changes in laboratory parameters (TB, ALT, and Alb levels and PT) were analyzed by paired Student's *t*-test. The ratio of diuretics to artificial ascites volume was evaluated by the chi-square test. A value of $p < 0.05$ was considered significant. StatView version 5.0 software (Hulinks, Tokyo, Japan) was used for statistical analysis.

Results

Difference in patient parameters. The artificial ascites technique was attempted in 102 patients. We were unable to perform the technique in 3 patients because of mesenteric adhesions; these patients were treated by induction of artificial pleural effusion and excluded from further analyses. Consequently, Group Ⅰ had 86 patients (45.7%), Group Ⅱ had 35 patients (18.6%), and Group Ⅲ had 67 patients (35.6%). The success rate for artificial ascites induction was 97.1%. No significant differences were observed in this rate with respect to age, tumor size, or number of treatment sessions. Furthermore, no significant difference was observed in the complete ablation rate among the 3 groups (Table 1).

Complications. No severe complications such as peritoneal bleeding, intestinal perforation, liver abscess, liver infarction, pneumothorax, biliary tract injury, skin burns, lung burns, uncontrolled ascites, or uncontrolled pleural effusion were observed. However, a few mild complications were observed. We observed 1 patient with transient hypotension, 1 with hemothorax, 1 with hemobilia, and 1 with ruptured esophageal varices; all these patients belonged to Group Ⅰ.

The ALT level increased and PT decreased after RFA in all groups, and no significant difference was observed among the 3 groups. TB increased slightly only in Group Ⅱ patients (0.96–1.06 mg/dl) (Fig. 2). No significant differences were observed in Alb levels before and after RFA among the 3 groups.

Only 5 Group Ⅲ patients (7.5%) needed additional diuretics; Group Ⅰ and Ⅱ patients did not require diuretics (Table 2). In addition, no relationship was observed between Child-Pugh classification and diuretic use in Group Ⅲ patients; diuretics were used in 5.5% of Child-Pugh A patients and 16.7% of Child-Pugh B patients (Table 3). Regardless, in all cases, ascites were eliminated 1 week after RFA.

Local recurrence. Complete ablation was confirmed by contrast-enhanced CT in all patients. No significant difference was observed in local recurrence rates at 1 year ($p = 0.96$). The rates were as follows: 4.7% in Group Ⅰ, 5.7% in Group Ⅱ, and 4.5% in Group Ⅲ. Patients in these groups were all retreated by RFA at the time of recurrence.

Discussion

RFA has widespread use in HCC treatment because of its effectiveness and safety. However, complications (burns) can occur if vital organs such as the digestive tract, gallbladder, or bile duct are adjacent to ablation sites [6–9]. Subdiaphragmatic HCCs are difficult to detect, and the RFA needle may puncture the lungs during inspiration, causing pneumothorax. In our earlier experiences with liver RFA without using the artificial ascites technique, severe complications occurred in 7 patients (0.7%), including hemothorax (n = 3), pneumothorax (n = 1), lung burn (n = 1), gastric penetration (n = 1), and subphrenic abscess (n = 1).

The artificial pleural effusion technique, which is easier than the artificial ascites technique, is used in many institutions to prevent lung obstruction and avoid complications [11–13]. However, the results of our study indicated that the artificial ascites technique might be superior for the following reasons: (1) RFA for subdiaphragmatic HCCs and tumors adjacent to other vital organs can be performed, (2) diaphragmatic injury can be prevented by pooling ascites between the liver and diaphragm, (3) a clearer image can be obtained by ultrasonography because artificial ascites fill the gaps between organs (*e.g.*, between the mesentery and liver or between the intestine and liver), and (4) RFA can be performed with patients in a supine position so that virtual ultrasonography can be used, which synchronizes ultrasonography images with those of CT [17, 18].

We achieved a high complete ablation rate because artificial ascites eliminated the difficulties of ablation,

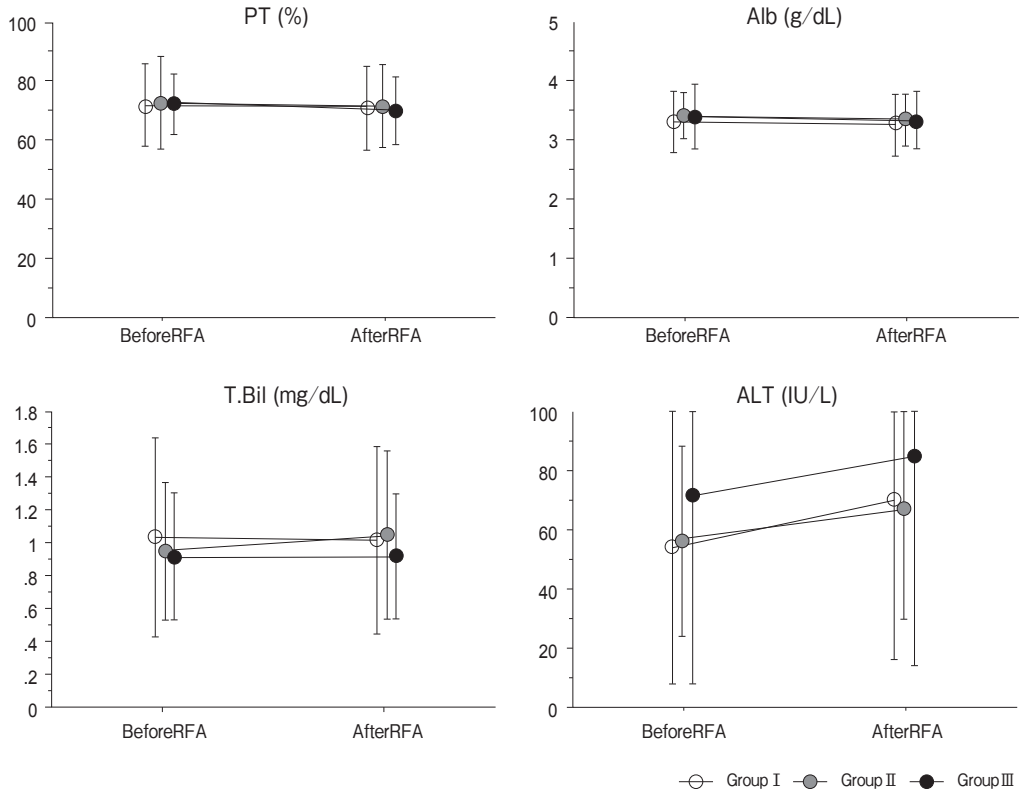

Fig. 2 Change in liver function parameters before and after RFA in each group. Comparison of laboratory parameters before and after RFA. The ALT level increased and prothrombin time (PT) decreased after RFA in all groups, and no significant difference was observed among the 3 groups. The TB level increased slightly only in Group Ⅱ patients (0.96–1.06 mg/dl). No significant difference in Alb levels before and after RFA was observed in any of the 3 groups.

Table 2 Additional diuretics after RFA among the 3 groups

Group	Ⅰ	Ⅱ	Ⅲ	
Additional diuretics	0/86 (0)	0/35 (0)	5/67 (7.5)	$p = 0.0097$

( ): %

Table 3 Additional diuretics after RFA according to the Child-Pugh classification in Group Ⅲ patients

Child-Pugh classification	A	B	
Additional diuretics	3/55 (5.5)	2/12 (16.7)	$p = 0.32$

( ): %

as reported by Song *et al.* [14]. As a result, the local recurrence rate was low (4.9%) in our study patients; this rate was not significantly different from that in patients who underwent RFA without artificial ascites (4.7%).

It is possible that artificial ascites could deteriorate liver function because of impaired portal blood flow from the excessive water load in the abdominal cavity, particularly in Child-Pugh B cirrhosis patients. Alb, TB, and ALT levels and PT were slightly altered the day after RFA, but not in a manner that would compromise the safety of the procedure. Furthermore, residual ascites usually disappeared spontaneously without diuretics; cases requiring post-procedural diuretics were few (6.6%). These findings indicated that performing RFA is safe even with a large volume of artificial ascites and that injecting artificial ascites is safe until tumors are clearly visualized or until the distance between the lesion and neighboring internal organs is sufficiently less so as to perform ablation, although we limited the volume to 2,000 ml.

A problem unique to the artificial ascites technique is the possibility of bleeding from the puncture site on

the liver surface; however, this bleeding is controllable. When bleeding was suspected by Doppler ultrasonography, it was easily controlled by an additional brief ablation of the site.

We performed RFA using the artificial ascites technique in 50% of our patients to avoid any concerns of complications that could occur otherwise. Furthermore, artificial ascites induction was easily performed by the breath-tuning method. The success rate of induction (97.1%) reported here is equal to or much higher than that reported in other studies (88–100%) [14–16]. Although experience to master this artificial ascites technique must be gained under the guidance of a skilled mentor, the technique is worth employing.

Failure to induce artificial ascites because of adhesions was an important issue, although this condition is infrequent. The pleural effusion technique was used in some patients with a history of abdominal surgery because of severe mesenteric adhesions. The benefits of the artificial ascites technique were not attainable for these patients, and laparoscopic or surgical treatments are occasionally necessary in such patients [16].

Although further research is required to resolve a few of the aforementioned issues, and a prospective study is needed to confirm our data, we conclude that artificial ascites induction is a safe and useful technique to prevent RFA-associated complications and improve ultrasonographic visualization.

References

1. Rossi S, Di Stasi M, Buscarini E, Quaretti P, Garbagnati F, Squassante L, Paties CT, Silverman DE and Buscarini L: Percutaneous RF interstitial thermal ablation in the treatment of hepatic cancer. Am J Roentgenol (1996) 167: 759–768.
2. Rossi S, Garbagnati F, Rosa L, Azzaretti A, Belloni G and Quaretti P: Radiofrequency thermal ablation for treatment of hepatocellular carcinoma. Int J Clin Oncol (2002) 7: 225–235.
3. Shiina S, Teratani T, Obi S, Hamamura K, Koike Y and Omata M: Nonsurgical treatment of hepatocellular carcinoma: from percutaneous ethanol injection therapy and percutaneous microwave coagulation therapy to radiofrequency ablation. Oncology (2002) 62 Suppl 1: 64–68.
4. Livraghi T, Goldberg SN, Lazzaroni S, Meloni F, Solbiati L and Gazelle GS: Small hepatocellular carcinoma: treatment with radiofrequency ablation versus ethanol injection. Radiology (1999) 210: 655–661.
5. Shibata T, Iimuro Y, Yamamoto Y, Maetani Y, Ametani F, Itoh K and Konishi J: Small hepatocellular carcinoma: comparison of radiofrequency ablation and percutaneous microwave coagulation therapy. Radiology (2002) 223: 331–337.
6. Mulier S, Mulier P, Ni Y, Miao Y, Dupas B, Marchal G, De Wever I and Michel L: Complications of radiofrequency coagulation of liver tumors. Br J Surg (2002) 89: 1206–1222.
7. Livraghi T, Solbiati L, Meloni MF, Gazelle GS, Halpern EF and Goldberg SN: Treatment of focal liver tumors with percutaneous radio-frequency ablation: Complications encountered in a multicenter study. Radiology (2003) 226: 441–451.
8. Yamamoto T, Kubo S, Hirohashi K, Tanaka S, Uenishi T, Ogawa M, Sakabe K, Hai S, Yamamoto S, Shuto T, Tanaka H and Kinoshita H: Secondary hemocholecyst after radiofrequency ablation therapy for hepatocellular carcinoma. J Gastroenterol (2003) 38: 399–403.
9. Scaife CL and Curley SA: Complication, local recurrence, and survival rates after radiofrequency ablation for hepatic malignancies. Surg Oncol Clin N Am (2003) 12: 243–255.
10. Ogawa T, Kawamoto H, Kobayashi Y, Nakamura S, Miyatake H, Harada R, Tsutsumi K, Fujii M, Kurihara N, Kato H, Hirao K, Mizuno O, Ishida E, Okada H and Yamamoto K: Prevention of biliary complication in radiofrequency ablation for hepatocellular carcinoma—Cooling effect by endoscopic nasobiliary drainage tube. Eur J Radiol. (2010) 73: 385–390.
11. Minami Y, Kudo M, Kawasaki T, Chung H, Ogawa C, Inoue T, Sakaguchi Y, Sakamoto H and Shiozaki H: Percutaneous ultrasound-guided radiofrequency ablation with artificial pleural effusion for hepatocellular carcinoma in the hepatic dome. J Gastroenterol (2003) 38: 1066–1070.
12. Koda M, Ueki M, Maeda Y, Mimura K, Okamoto K, Matsunaga Y, Kawakami M, Hosho K and Murawaki Y: Percutaneous sonographically guided radiofrequency ablation with artificial pleural effusion for hepatocellular carcinoma located under the diaphragm. AJR Am J Roentgenol (2004) 183: 583–588.
13. Fukuno H, Tamaki K, Urata M, Kohno N, Shimizu I, Nomura M, Ito S and Saito K: Influence of an artificial pleural effusion technique on cardio-pulmonary function and autonomic activity. J Med Invest (2007) 54: 48–53.
14. Song I, Rhim H, Lim HK, Kim YS and Choi D: Percutaneous radiofrequency ablation of hepatocellular carcinoma abutting the diaphragm and gastrointestinal tracts with the use of artificial ascites: safety and technical efficacy in 143 patients. Eur Radiol (2009) 19: 2630–2640.
15. Rhim H, Lim HK, Kim YS and Choi D: Percutaneous radiofrequency ablation with artificial ascites for hepatocellular carcinoma in the hepatic dome: Initial Experience. Am J Roentgenol (2008) 190: 91–98.
16. Hirooka M, Kisaka Y, Uehara T, Ishida K, Kumagi T, Watanabe Y, Abe M, Matsuura B, Hiasa Y and Onji M: Efficacy of laparoscopic radiofrequency ablation for hepatocellular carcinoma compared to percutaneous radiofrequency ablation with artificial ascites. Dig Endosc (2009) 21: 82–86.
17. Toyoda M, Kakizaki S, Horiuchi K, Katakai K, Sohara N, Sato K, Takagi H, Mori M and Nakajima T: Computed tomography-guided transpulmonary radiofrequency ablation for hepatocellular carcinoma located in hepatic dome. World J Gastroenterol (2006) 12: 608–611.
18. Kitada T, Murakami T, Kuzushita N, Minamitani K, Nakajo K, Osuga K, Miyoshi E, Nakamura H, Kishino B, Tamura S and Hayashi N: Effectiveness of real-time virtual sonography-guided radiofrequency ablation treatment for patients with hepatocellular carcinomas. Hepatol Res (2008) 38: 565–571.