Chapter 4   Percutaneous Ablation Therapy

- **Introduction**

Over the past quarter of a century, various methods have been developed as local therapies for HCC. In 1979, Yamada et al. developed transcatheter arterial embolization (TAE), the first treatment method to clearly demonstrate the efficacy of local therapy for HCC.

Later, with the widespread and technological advancement of diagnostic abdominal ultrasound devices, Sugiura et al. developed percutaneous ethanol injection (PEI) in 1983. PEI can be considered as the grass root for a variety of local therapies performed under the guidance of ultrasonography. Because the technique is simple and both local injection needles and ethanol are inexpensive, this method has quickly spread not only throughout Japan but globally, and it has come to be highly valued as a primary treatment for HCC. However, because liquid ethanol is injected during PEI therapy, problems of residual tumor and local recurrence may occur if the ethanol does not uniformly diffuse throughout the tumor or cannot pass through the septum or capsule.

In order to overcome the abovementioned drawback of PEI, a method that involves the transmission of microwaves or radiofrequency ablation (RFA) through an inserted needle to achieve thermal coagulation of the tumor was developed. In 1994, Seki et al. introduced percutaneous microwave coagulation therapy (PMCT), which involves the percutaneous application of microwaves and is conventionally used surgical technology.

Furthermore, in 1993, Rossi et al. reported that percutaneous RFA was effective against small HCC, and since then, RFA for HCC readily began to draw much attention. Since 1999, this therapy has been used in many institutions, even in Japan. The range of necrosis achieved with one session of RFA exceeds that achieved with one session of PMCT; therefore, PMCT has been largely replaced since the clinical introduction of RFA. RFA was finally approved in Japan by the National Health Insurance in April 2004. A randomized controlled trials (RCTs) that compared

PEI and RFA were published domestically and internationally around the time of publication of the 2005 edition of these guidelines. All results showed that RFA extends the vital prognosis compared with PEI. On the basis of this evidence, RFA is now considered the standard therapy among percutaneous ablation therapies.

Evidence related to PEI, PMCT, and RFA that was published as of the end of December 2011 has been consolidated in this chapter.

- **Document Selection**

Local therapies have been categorized by treatment method.

1) PEI 2) PMCT 3) RFA

The MEDLINE and Igaku Chuo Zasshi (in Japanese) databases were searched from 1983 through late December 2011 for information regarding each therapy. A list of literature references was created, and documents that appeared useful for guideline development were selected. The abstracts were read, and a second list of original articles was created that required further reading, from which we selected those with the highest level of evidence. Articles were evaluated on the basis of the purpose or type, number of included patients, and study design.

CQ32　Who are eligible candidates for percutaneous ablation therapy?

Recommendation

Percutaneous ablation is indicated for patients with Child–Pugh class A or B liver function, 3 or fewer tumors, and tumor diameters of 3 cm or less **(Grade B)**.

- **Scientific Statement**

Twenty-five documents were selected from studies that compared the treatment outcomes of liver resection and those of RFA in patients who met the Milan criteria or had 3 or fewer tumors with

diameters of 3 cm or less. The upper row in Table 2 lists two studies that provided level I evidence, and the lower row lists six studies that provided level II evidence with a study population exceeding 400 patients. In terms of survival, liver resection was significantly better in one of the two level I studies, and no significant difference was observed in the other study (L3F04414[1] Level 1b, L3F05846[2] Level 1b). Liver resection appeared to be superior in three of the six level II studies, while no significant difference was observed in the remaining three (L3F05892[3] Level 2a, L3F05890[4] Level 2b, L3F03325[5] Level 2b, L3F05856[6] Level 2a, L3F01797[7] Level 2b, L3F05876[8] Level 2b).

Murakami et al. examined the local recurrence rate in 258 consecutive HCC patients with 2–3 tumors measuring 3 cm or smaller or solitary tumors measuring 5 cm or smaller after treatment with RFA or transcatheter arterial embolization (TACE), and RFA was found to be significantly superior to TACE (p = 0.013; LF11840[9] Level 2b). In addition, the local recurrence rate of PEI increased when the tumor diameter was greater than 3 cm (LF01555[10] Level 2a).

- **Explanation**

According to the treatment algorithm, in principle, patients who can undergo liver resection, percutaneous ablation therapy, and TACE are recommended to undergo treatment in that order. Percutaneous ablation therapy has been set as the second-line treatment on the basis of the estimated difference in prognoses between first-line hepatectomy and third-line TACE therapy. However, the difference in prognoses is presumed to change according to liver function and tumor characteristics.

The outcomes of percutaneous ablation therapy are particularly favorable for Child–Pugh class A patients with solitary tumors measuring 2 cm or smaller (5-year survival rate: 60%–74%; LF10949[11] Level 2b, LF10449[12] Level 2b). Nevertheless, there is no conclusive evidence supporting the fact that percutaneous ablation therapy can replace liver resection as a first-choice treatment, even for patients with good hepatic function and early-stage HCC. First-time treatment options for initial HCC must be supported by solid evidence, which will be provided by the SURF

study*, a multicenter, cooperative study in progress since April 2009. The SURF study is an RCT verifying the efficacy of surgery and RFA in patients with initial HCC who have a Child–Pugh score of 7 or lower and fulfill the tumor criteria of 3 or fewer tumors with diameters of 3 cm or lesser. We are awaiting the results of this study, which will provide evidence in a Japanese population.

The objectives of liver resection and percutaneous ablation therapy are the same in that both aim to achieve local control. Nevertheless, during percutaneous ablation therapy, it can be difficult to secure the ablation margin if the tumor diameter is large; therefore, the individual performing the procedure should consider the tumor requirements, their own skill level, and the patient's background in order to determine the indication for therapy in each case. If the treatment is limited to patients with unresectable disease, the applicability of percutaneous ablation therapy is determined on the basis of comparisons with the third-line therapy, i.e., TACE. Murakami et al. treated 258 consecutive HCC patients with 2–3 tumors measuring 3 cm or smaller or solitary tumors measuring 5 cm or smaller using RFA or TACE. The local recurrence rates were analyzed, and RFA was found to be significantly superior to TACE (p = 0.013; LF11840[9] Level 2b). No RCT has compared the survival rates of patients treated with TACE and those of patients treated with percutaneous ablation therapy for tumors fulfilling these criteria; however, this evidence can be used to recommend percutaneous ablation therapies for patients with unresectable HCCs that are 3 or fewer in number and measure 3 cm or smaller.

Many PEI studies have concluded that patients with 3 or fewer tumors measuring 3 cm or smaller are indicated for percutaneous ablation therapy; however, when the tumor diameter exceeds 3 cm, the local recurrence rate increases after PEI. It is possible, in principle, to extend the ablation areas with RFA by increasing the number of punctures. However, extending the ablation areas and increasing the number of punctures will likely lead to an increase in complication risks. Because most RFA electrodes have an ablation range of 3 cm, RFA is indicated for patients with 3 or fewer tumors measuring 3 cm or smaller.

- **References**

1) L3F04414   Chen MS, Li JQ, Zheng Y, Guo RP, Liang HH, Zhang YQ, et al. A prospective randomized trial comparing percutaneous local ablative therapy and partial hepatectomy for small hepatocellular carcinoma. Ann Surg 2006;243(3):321-8.

2) L3F05846   Huang J, Yan L, Cheng Z, Wu H, Du L, Wang J, et al. A randomized trial comparing radiofrequency ablation and surgical resection for HCC conforming to the Milan criteria. Ann Surg 2010;252(6):903-12.

3) L3F05892   Hasegawa K, Makuuchi M, Takayama T, Kokudo N, Arii S, Okazaki M, et al. Surgical resection vs. percutaneous ablation for hepatocellular carcinoma: a preliminary report of the Japanese nationwide survey. J Hepatol 2008;49(4):589-94.

4) L3F05890   Takayama T, Makuuchi M, Hasegawa K. Single HCC smaller than 2 cm: surgery or ablation?: surgeon's perspective. J Hepatobiliary Pancreat Sci 2010;17(4):422-4.

5) L3F03325   Liu JG, Wang YJ, Du Z. Radiofrequency ablation in the treatment of small hepatocellular carcinoma: a meta analysis. World J Gastroenterol 2010;16(27):3450-6.

6) L3F05856   Hung HH, Chiou YY, Hsia CY, Su CW, Chou YH, Chiang JH, et al. Survival rates are comparable after radiofrequency ablation or surgery in patients with small hepatocellular carcinomas. Clin Gastroenterol Hepatol 2011;9(1):79-86.

7) L3F01797   Huang J, Hernandez-Alejandro R, Croome KP, Yan L, Wu H, Chen Z, et al. Radiofrequency ablation versus surgical resection for hepatocellular carcinoma in Childs A cirrhotics: a retrospective study of 1,061 cases. J Gastrointest Surg 2011;15(2):311-20.

8) L3F05876   Yun WK, Choi MS, Choi D, Rhim HC, Joh JW, Kim KH, et al. Superior long-term outcomes after surgery in Child-Pugh class a patients with single small hepatocellular carcinoma compared to radiofrequency ablation. Hepatology International 2011;5(2):722-9.

9) LF11840   Murakami T, Ishimaru H, Sakamoto I, Uetani M, Matsuoka Y, Daikoku M, et al. Percutaneous radiofrequency ablation and transcatheter arterial chemoembolization for

hypervascular hepatocellular carcinoma: rate and risk factors for local recurrence. Cardiovasc Intervent Radiol 2007;30(4):696–704.

10) LF01555   Ishii H, Okada S, Nose H, Okusaka T, Yoshimori M, Takayama T, et al. Local recurrence of hepatocellular carcinoma after percutaneous ethanol injection. Cancer 1996;77 (9):1792–6.

11) LF10949   Lencioni R, Cioni D, Crocetti L, Franchini C, Pina CD, Lera J, et al. Early-stage hepatocellular carcinoma in patients with cirrhosis: long-term results of percutaneous image-guided radiofrequency ablation. Radiology 2005;234(3): 961-7.

12) LF10449   Omata M, Tateishi R, Yoshida H, Shiina S. Treatment of hepatocellular carcinoma by percutaneous tumor ablation methods: Ethanol injection therapy and radiofrequency ablation. Gastroenterology 2004;127(5 Suppl 1):S159-66.

Table 2   Comparison of survival rates between RFA and liver resection for hepatocellular carcinoma

Author	Year of publica-tion	Study design	Number of patients (RFA/ liver resection)	Tumor character-istics	Survival rate (%) (RFA vs. liver resection)	p value
Chen[1]	2006	RCT	90/90	≤5 cm, single	67.9 vs. 64.0 (4 years)	NS
Huang[2]	2010	RCT	115/115	Milan criteria	54.78 vs. 75.65 (5 years)	0.001
Hasegawa[3]	2008	Prospective cohort	3,022/2,857	≤3 cm, ≤3 tumors	93.0 vs. 94.5 (2 years)	NS
Takayama[4]	2010	Retrospective cohort	1,315/1,235	≤3 cm, ≤3 tumors	95 vs. 94 (2 years)	0.28
Liu[5]	2010	Meta-analysis	787/735	Milan criteria	62.5 vs. 63.6 (3 years)	NS
Hung[6]	2011	Retrospective cohort	190/229	≤5 cm	67.4 vs. 79.3 (5 years)	0.009
Huang[7]	2011	Retrospective cohort	413/648	≤5 cm, ≤3 tumors	53.34 vs. 76.47 (5 years)	<0.001

Author	Year of publication	Study design	Number of patients (RFA/ liver resection)	Tumor character-istics	Survival rate (%) (RFA vs. liver resection)	p value
Yun[8]	2011	Retrospective cohort	255/215	≤3 cm	87 vs. 94 (5 years)	0.002

NS: not significant

(Footnote)

*SURF Study: Efficacy of surgery vs. radiofrequency ablation for primary HCC

CO33　　How should a type of percutaneous ablation therapy be selected?

Recommendation

RFA is recommended for percutaneous ablation therapy **(Grade A)**.

If gastrointestinal perforation is suspected, other methods (e.g., RFA with artificial ascites and PEI) are effective **(Grade B)**.

- **Background**

Percutaneous ablation therapy was first introduced with the development of PEI in the 1980s, followed by percutaneous acetic acid injection (PAI) and PMCT, leading to the current preferred therapy, RFA. In addition to these four treatment methods, we searched the literature for information regarding percutaneous ablation therapies such as cryoablation.

- **Scientific Statement**
- Local recurrence and survival

A total of five RCTs that compared RFA and PEI were identified from a search conducted up to December 31, 2011 (LF10941[1] Level 1b, LF10457[2] Level 1b, LF11869[3] Level 1b, LF10468[4] Level 1b, LF12126[5] Level 1b), four of which were meta-analyses (L3F05851[6] Level 1a, L3F05867[7] Level 1a, L3F05916[8] Level 1a, L3F00400[9] Level 1a). Because the results of these meta-analyses were nearly identical, five RCTs and the results of Germani et al. that represent the

five RCTs are listed in Table 3. The report by Brunello et al. was excluded because local recurrence data were missing, although RFA was superior to PEI according to the other four articles. Survival was significantly better with RFA than with PEI according to three reports, and no difference was observed in two reports. A meta-analysis comparing RFA and PEI showed that the hazard ratio (95% confidence interval) was 0.27 (0.16–0.45) for local recurrence and 0.52 (0.35–0.78) for survival; therefore, RFA was superior to PEI in terms of both parameters.

- Complications

Bertot et al. performed a meta-analysis of 34 reports on RFA, PMCT, and PEI (L3F06565[10] Level 1a). The overall mortality rate associated with percutaneous ablation therapy was 0.16% (95% confidence interval: 0.10–0.24). In addition, when categorized by therapy, the rates for RFA, PMCT, and PEI were 0.16% (0.10–0.24%), 0.15% (0.08–0.23%), and 0.23% (0.0–0.58%), respectively. The overall risk of developing serious complications was 3.29% (2.43–4.28%), with a 0.5% risk of dissemination, 0.37% risk of intra-abdominal hemorrhage, 0.32% risk of liver abscess, 0.27% risk of ascites, 0.14% risk of pleural effusion requiring treatment, 0.13% risk of hepatic infarction, 0.11% risk of liver failure, 0.11% risk of gastrointestinal perforation, and 0.09% risk of hemothorax. Furthermore, the frequencies of serious complications resulting from therapy are 4.1% (3.3%–5.1%) for RFA, 4.6% (0.7–11.8%) for PMCT, and 2.7% (0.28–7.4%) for PEI. In contrast, a meta-analysis conducted by Germani et al. showed that there was no significant difference in the frequency of complications between RFA and PEI (odds ratio: 1.21, 95% confidence interval: 0.89–1.63, p = 0.22; L3F00400[9] Level 1a).

- **Explanation**

PEI is a technically established treatment method with 3-year survival rates ranging from 48% to 67% (L3F05867[7] Level 1a). However, septal fibrosis and capsule formation in the tumor can interfere with ethanol diffusion; therefore, curability with PEI tends to decrease with increasing tumor diameter. Alternatively, RFA has the potential to induce necrosis in areas surrounding the tumor, including satellite nodules, and the 3-year survival rate is reportedly 63%–74%

(L3F05867[7]) Level 1a). A meta-analyses have strongly suggested that RFA is superior in terms of local recurrence and survival rates (L3F05867[7] Level 1a, L3F05851[6] Level 1a, L3F00400[9] Level 1a). Furthermore, subgroup analysis has revealed a large difference in treatment outcome for tumors measuring 2 cm or larger (L3F00400[9] Level 1a).

Bertot et al. reported significant differences in the complication rate depending on the treatment method (L3F06565[10] Level 1a), although no differences were reported in Asian countries, including Japan. Meta-analyses by Bouza et al. and Germani et al. also showed no differences in the frequency of complications between RFA and PEI (L3F05851[6] Level 1a, L3F00400[9] Level 1a). Although the nature and frequency of complications vary from report to report, the majority of the latest search reported no significant difference between RFA and PEI. However, complications tend to occur at sites that are in contact with the hepatic portal area or extrahepatic organs (L3H00048[11] Level 2b); therefore, caution must be exercised when using needle puncture and electrode output. Complications of gastrointestinal perforation, in particular, have often been reported with RFA, and the risk of perforation is high among patients with postoperative adhesions (L3F06565[9] Level 1a). In such situations, RFA with artificial ascites (L3H00056[12] Level 4) and PEI are effective treatment options.

- ■ **References**

1) LF10941   Lencioni RA, Allgaier HP, Cioni D, Olschewski M, Deibert P, Crocetti L, et al. Small hepatocellular carcinoma in cirrhosis: randomized comparison of radio-frequency thermal ablation versus percutaneous ethanol injection. Radiology 2003;228 (1):235–40.

2) LF10457   Lin SM, Lin CJ, Lin CC, Hsu CW, Chen YC. Radiofrequency ablation improves prognosis compared with ethanol injection for hepatocellular carcinoma < or = 4 cm. Gastroenterology 2004;127(6):1714–23.

3) LF11869   Shiina S, Teratani T, Obi S, Sato S, Tateishi R, Fujishima T, et al. A randomized controlled trial of radiofrequency ablation with ethanol injection for small hepatocellular carcinoma. Gastroenterology 2005;129 (1):122–30.

4) LF10468   Lin SM, Lin CJ, Lin CC, Hsu CW, Chen YC. Randomised controlled trial comparing percutaneous radiofrequency thermal ablation, percutaneous ethanol injection, and percutaneous acetic acid injection to treat hepatocellular carcinoma of 3 cm or less. Gut 2005;54 (8):1151–6.

5) LF12126   Brunello F, Veltri A, Carucci P, Pagano E, Ciccone G, Moretto P, et al. Radiofrequency ablation versus ethanol injection for early hepatocellular carcinoma: A randomized controlled trial. Scand J Gastroenterol 2008;43(6):727-35.

6) L3F05851   Bouza C, López-Cuadrado T, Alcázar R, Saz-Parkinson Z, Amate JM. Meta-analysis of percutaneous radiofrequency ablation versus ethanol injection in hepatocellular carcinoma. BMC Gastroenterol 2009;9:31.

7) L3F05867   Cho YK, Kim JK, Kim MY, Rhim H, Han JK. Systematic review of randomized trials for hepatocellular carcinoma treated with percutaneous ablation therapies. Hepatology 2009;49(2):453-9.

8) L3F05916   Orlando A, Leandro G, Olivo M, Andriulli A, Cottone M. Radiofrequency thermal ablation vs. percutaneous ethanol injection for small hepatocellular carcinoma in cirrhosis: meta-analysis of randomized controlled trials. Am J Gastroenterol 2009;104 (2):514–24.

9) L3F00400   Germani G, Pleguezuelo M, Gurusamy K, Meyer T, Isgrò G, Burroughs AK. Clinical outcomes of radiofrequency ablation, percutaneous alcohol and acetic acid injection for hepatocellular carcinoma:a meta-analysis. J Hepatol 2010;52(3):380-8.

10) L3F06565   Bertot LC, Sato M, Tateishi R, Yoshida H, Koike K. Mortality and complication rates of percutaneous ablative techniques for the treatment of liver tumors: a systematic review. Eur Radiol 2011;21(12):2584-96.

11) L3H00048   Teratani T, Yoshida H, Shiina S, Obi S, Sato S, Tateishi R, et al. Radiofrequency ablation for hepatocellular carcinoma in so-called high-risk locations. Hepatology 2006;43(5):1101-8.

12) L3H00056 Kondo Y, Yoshida H, Shiina S, Tateishi R, Teratani T, Omata M. Artificial ascites technique for percutaneous radiofrequency ablation of liver cancer adjacent to the gastrointestinal tract. Br J Surg 2006;93(10):1277-82.

Table 3   Comparison of RFA and PEI for HCC

Author	Year of publica-tion	Study design	Treatment method (number of patients)	Local recurrence		Overall survival ratio	
				Hazard ratio*	p value	Hazard ratio*	p value
Lencioni[1]	2003	RCT	RFA(52), PEI(50)	0.17	0.02	0.20	0.138
Lin[2]	2004	RCT	RFA(52), PEI(52), High dose PEI(53)	0.37† 0.49‡	0.012† 0.037‡	0.34† 0.39‡	0.014† 0.023‡
Shiina[3]	2005	RCT	RFA(118), PEI(114)	0.12	0.006	0.54	0.02
Lin[4]	2005	RCT	RFA(62), PEI(62), PAI(63)	0.35† 0.41§	0.012† 0.017§	0.42† 0.45§	0.031† 0.038§
Brunello[5]	2008	RCT	RFA(70), PEI(69)	ND	—	0.88	0.476
Germani[9]	2010	Meta-analysis	RFA(356), PEI(347)	0.27¶	<0.00001	0.52	0.001

*hazard ratio for RFA vs. PEI (lower the hazard ratio, greater the benefits)

† Comparison of RFA and PEI

‡ Comparison of RFA and high-dose PEI

§ Comparison of RFA and PAI

¶ Report by Burunello et al. is excluded

ND: not described

CQ34   Does a combination of TACE and percutaneous ablation therapy improve prognosis?

Recommendation

TACE before RFA extends the range of necrosis **(Grade A).**

A favorable prognosis can be expected if local control is achieved. However, there is inadequate evidence demonstrating that pretreatment with TACE will improve RFA outcomes **(Grade C1)**.

- **Scientific Statement**

- Ablation area

Kitamoto et al. reported that necrosis was significantly more widespread in the hepatic TACE + RFA group than in the RFA alone group (mean long- and short-axes dimensions of ablation areas for the TACE + RFA group and RFA only group: 39.9 mm and 32.3 mm vs. 34.6 mm and 26.0 mm, respectively; $p < 0.05$; LF10032[1] Level 2b).

According to Morimoto et al, the mean long- and short-axes dimensions for the ablated areas in the TACE + RFA group were 50 mm and 41 mm, respectively, whereas those in the RFA group were 58 mm and 50 mm, respectively ($p = 0.012$; L3F04325[2] Level 1b).

- Survival

Studies comparing TACE + RFA therapy and RFA only therapy are listed in Table 4 (L3F04325[2] Level 1b, L3F04331[3] Level 2a, L3F00229[4] Level 2b). Although conditions differed, the survival rate with TACE + RFA therapy was better than that with RFA monotherapy in one report, whereas no differences were observed in two other reports.

- **Explanation**

We examined studies in which RFA was performed as percutaneous ablation therapy. There were no comparative studies that examined survival after RFA with balloon occlusion of the hepatic artery; therefore, this treatment has not been included in this edition.

All reports found that the application of TACE before RFA extends the ablation area, which helps in decreasing the number of ablation sessions and local recurrence rates. In particular, Morimoto et al. reported significantly fewer treatment sessions (TACE + RFA vs. RFA: 1.1 vs. 1.4, $p < 0.01$) and local recurrence (TACE + RFA vs. RFA: 6% vs. 39%, $p = 0.012$) (L3F04325[2] Level 1b). The majority of studies have also reported no differences in complication rates. In addition, the timing of pretreatment with TACE varies greatly from same-day treatment to treatment administered within 2 months; however, the timing is usually within 1 month of RFA according to Japanese reports.

A meta-analysis showed that the prognosis tends to improve even with percutaneous ablation therapy, particularly if TACE is performed before PEI (L3F00310[5] Level 1a). However, whether or not TACE before RFA improves prognosis remains to be determined. A subgroup analysis by Peng et al. has shown that prognosis is significantly improved in patients with a solitary tumor measuring 5 cm or larger (p = 0.031) and multiple tumors (p = 0.032; L3F00229[4] Level 2b); this will continue to be a topic of discussion.

- **References**

1) LF10032　Kitamoto M, Imagawa M, Yamada H, Watanabe C, Sumioka M, Satoh O, et al. Radiofrequency ablation in the treatment of small hepatocellular carcinomas: comparison of the radiofrequency effect with and without chemoembolization. AJR Am J Roentgenol 2003;181(4):997-1003.

2) L3F04325　Morimoto M, Numata K, Kondou M, Nozaki A, Morita S, Tanaka K. Midterm outcomes in patients with intermediate-sized hepatocellular carcinoma: a randomized controlled trial for determining the efficacy of radiofrequency ablation combined with transcatheter arterial chemoembolization. Cancer 2010;116(23):5452-60.

3) L3F04331　Shibata T, Isoda H, Hirokawa Y, Arizono S, Shimada K, Togashi K. Small hepatocellular carcinoma: is radiofrequency ablation combined with transcatheter arterial chemoembolization more effective than radiofrequency ablation alone for treatment? Radiology 2009;252(3):905-13.

4) L3F00229　Peng ZW, Chen MS, Liang HH, Gao HJ, Zhang YJ, Li JQ, et al. A case-control study comparing percutaneous radiofrequency ablation alone or combined with transcatheter arterial chemoembolization for hepatocellular carcinoma. Eur J Surg Oncol 2010;36(3):257-63.

5) L3F00310　Wang W, Shi J, Xie WF. Transarterial chemoembolization in combination with percutaneous ablation therapy in unresectable hepatocellular carcinoma: a meta-analysis. Liver Int 2010;30(5):741-9.

Table 4 Comparison of TACE + RFA therapy and RFA monotherapy (2009 and thereafter)

Author /Year of publication	Study design	Number of patients (TACE + RFA /RFA)	Requirements	Survival rate (%) (TACE+RFA vs. RFA)			p value
				1-year	3-year	5-year	
Morimoto[2] /2010	RCT	19/18	Single, 3.1–5 cm	100 vs. 89	93 vs. 80	— —	0.369
Shibata[3] /2009	NRCT	46/43	1–2 tumors, ≤3 cm	100 vs. 100	84.5 vs. 84.5	74.0 vs. 72.7 (4-years)	0.515
Peng[4] /2010	NRCT	120/120	Single tumors, ≤7 cm 2–3 tumors, ≤3 cm	93 vs. 89	75 vs. 64	50 vs. 42	0.045

CQ35 Are contrast-enhanced ultrasound and fusion imaging useful guides for percutaneous ablation therapy?

Recommendation

Contrast-enhanced ultrasound (US) and fusion imaging are useful guides for treating HCC lesions that are difficult to visualize on B-mode US **(Grade B)**.

- **Background**

Successful treatment with ultrasound-guided percutaneous ablation therapy depends on whether an HCC lesion can be clearly visualized on B-mode ultrasound (US). However, visualization can be difficult on B-mode US if the tumor borders are indistinct because of incomplete capsule formation or other reasons, if multiple, large, recurrent nodules are being confused with small lesions, or if locally recurrent lesions appear the same as the necrotic areas from the previous therapy on ultrasound. According to Minami et al., 5.2% of 485 HCC nodules treated with RFA were not clearly depicted in B-mode ultrasound (L3H00049[1] Level 2b).

- **Scientific Statement**

- Ultrasonography:

Maruyama et al. reported that out of 55 hypervascular liver tumors that were difficult to visualize on B-mode US (mean tumor diameter: 1.3 ± 0.5 cm), 53 (96%) were detectable by Sonazoid®-enhanced US, and of these, 42 were successfully treated with percutaneous ablation therapy guided by contrast-enhanced ultrasound (L3F03905[2] Level 4).

Minami et al. treated 108 HCC nodules that were poorly depicted on B-mode US with RFA guided by Sonazoid®-enhanced US and reported that the mean number of treatment sessions was 1.1 ± 0.3 (L3F03910[3] Level 4).

Masuzaki et al. (L3F01387[4] Level 2b) reported that the number of treatment session s was significantly lower in 291 patients treated with RFA guided by Sonazoid®-enhanced US than in 2,261 patients in a similar control group (1.33 vs. 1.49, p = 0.0019).

- Fusion imags

Fusion imaging uses previously acquired volume data from CT or MRI scans and synchronizes positional information from an US probe equipped with a magnetic sensor. This system displays B-mode US images in real time with approximate multiplanar reconstruction (MPR) images. The combination of ultrasound and other imaging modalities is reportedly useful for providing supportive imaging findings for therapy (L3F03517[5] Level 2b, L3F05905[6] Level 4, LF11791[7] Level 4). In one study, HCC lesions that were poorly depicted on B-mode US were effectively treated using Real-time Virtual Sonography (RVS)®-guided RFA compared with B-mode US guided RFA (mean number of treatment sessions: 1.1 vs. 1.3, p = 0.021, L3F03517[5] Level 2b).

- **Explanation**

As US contrast agents have evolved from Levovist® to Sonazoid®, stable visualization of lesions has become possible because continuous monitoring is possible at any phase, targeting of defect images in the postvascular phase has improved visual confirmation of lesions, and defect reperfusion imaging has facilitated local and qualitative diagnoses of HCC lesions that are poorly

visualized on B-mode ultrasound. Therefore, although ultrasound-guided RFA became complicated with Levovist®, the procedure is now simplified. Caution must be exercised, however, when treating patients with deep lesions or advanced cirrhosis because it is occasionally difficult to visualize lesions. Fusion imaging can also be effective for percutaneous ablation therapy, particularly in the aforementioned situation. One of the merits of fusion imaging is its ability to provide reference images when imaging is difficult with contrast-enhanced US. Nonetheless, fusion imaging do not always completely match up with B-mode US images, particularly for tumors located in the right lobe of the liver, where the degree of image misalignment tends to be greater. Because therapy using both procedures is possible, contrast-enhanced US and fusion imaging are not competing methods; the treatment objective must essentially be localized control with one or both methods, as best fits the situation.

- **References**

1) L3H00049　Minami Y, Kudo M, Kawasaki T, Chung H, Ogawa C, Shiozaki H. Treatment of hepatocellular carcinoma with percutaneous radiofrequency ablation: usefulness of contrast harmonic sonography for lesions poorly defined with B-mode sonography. AJR Am J Roentgenol 2004;183(1):153-6.

2) L3F03905　Maruyama H, Takahashi M, Ishibashi H, Okugawa H, Okabe S, Yoshikawa M, et al. Ultrasound-guided treatments under low acoustic power contrast harmonic imaging for hepatocellular carcinomas undetected by B-mode ultrasonography. Liver Int 2009;29(5):708-14.

3) L3F03910　Minami Y, Kudo M, Hatanaka K, Kitai S, Inoue T, Hagiwara S, et al. Radiofrequency ablation guided by contrast harmonic sonography using perfluorocarbon microbubbles (Sonazoid)for hepatic malignancies: an initial experience. Liver Int 2010;30(5):759-64.

4) L3F01387　Masuzaki R, Shiina S, Tateishi R, Yoshida H, Goto E, Sugioka Y, et al. Utility of contrast-enhanced ultrasonography with Sonazoid in radiofrequency ablation for

hepatocellular carcinoma. J Gastroenterol Hepatol 2011;26(4):759-64.

5) L3F03517   Minami Y, Chung H, Kudo M, Kitai S, Takahashi S, Inoue T, et al. Radiofrequency ablation of hepatocellular carcinoma: value of virtual CT sonography with magnetic navigation. AJR Am J Roentgenol 2008;190(6):W335-41.

6) L3F05905   Minami Y, Kudo M, Chung H, Inoue T, Takahashi S, Hatanaka K, et al. Percutaneous radiofrequency ablation of sonographically unidentifiable liver tumors. Feasibility and usefulness of a novel guiding technique with an integrated system of computed tomography and sonographic images. Oncology 2007;72(Suppl 1):111-6.

7) LF11791   Hirooka M, Iuchi H, Kumagi T, Shigematsu S, Hiraoka A, Uehara T, et al. Virtual sonographic radiofrequency ablation of hepatocellular carcinoma visualized on CT but not on conventional sonography. Am J Roentgenol 2006;186(5 Suppl):S255-60.

CQ36   What type of diagnostic imaging is useful for assessing treatment response of percutaneous ablation therapy?

Recommendation

Dynamic CT/MRI is the fundamental method for determining the outcomes of percutaneous ablation therapy. Contrast-enhanced ultrasound may be substituted in patients with allergies to contrast media or renal impairment **(Grade A).**

- **Background**

Unlike liver resection, with percutaneous ablation therapy it is difficult to pathologically determine whether the therapeutic target, that is the entire tumor, has been covered. Thus, since treatment outcome is determined by comparing pre- and post-treatment images, we have examined which imaging tests are appropriate to be used.

- **Scientific Statement**

Because the diagnosis of HCC requires dynamic CT/MRI, these imaging tests are inevitably used to determine treatment outcomes as well. Of the two, dynamic CT is used more frequently because of its high capability and is the most realistic standard test method. In addition, Gd-EOB-DTPA-enhanced MRI may have superior accuracy (sensitivity/specificity) in evaluating tumor margins compared with CT (L3F01963[1] Level 1, L3F03285[2] Level 1). Furthermore, contrast-enhanced ultrasound using Sonazoid® is less sensitive than dynamic CT, although it is superior in terms of specificity (L3F01725[3] Level 1).

- **Explanation**

When selecting imaging tests to determine the outcome of percutaneous ablation therapy, although pathological evaluation by liver resection is the gold standard, this approach poses ethical difficulties. The second-best gold standard is follow-up monitoring for local recurrence. In many cases, however, lesions suspected of apparent residual tumors require further treatment, and the ease of evaluating the presence or absence of a margin tends to become the end point. Dynamic CT was used as the gold standard in the majority of studies we examined, and from the perspective of its availability, dynamic CT was determined to be the recommended standard test method. Gd-EOB-DTPA-enhanced MRI may surpass CT in terms of margin assessment, and as additional evidence is collected, it may become the most frequently recommended imaging test. Many of the studies examining contrast-enhanced ultrasound used first-generation Levovist®, and several reports claimed that it was equivalent to CT. However, it was not selected because of several drawbacks and because it cannot be used in Japan at this time. Long-term monitoring can be performed with the second-generation ultrasound contrast agent Sonazoid®, which is better suited for determining treatment outcomes.

- **References**

1) L3F01963　Yoon JH, Lee EJ, Cha SS, Han SS, Choi SJ, Juhn JR, et al. Comparison of gadoxetic acid-enhanced MR imaging versus four-phase multi-detector row computed

tomography in assessing tumor regression after radiofrequency ablation in subjects with

hepatocellular carcinomas. J Vasc Interv Radiol 2010;21(3):348-56.

2) L3F03285　Hwang J, Kim SH, Kim YS, Lee MW, Woo JY, Lee WJ, et al. Gadoxetic

acid-enhanced MRI versus multiphase multidetector row computed tomography for

evaluating the viable tumor of hepatocellular carcinomas treated with image-guided tumor

therapy. J Magn Reson Imaging 2010;32(3):629-38.

3) L3F01725　Shiozawa K, Watanabe M, Takayama R, Takahashi M, Wakui N, Iida K, et al.

Evaluation of local recurrence after treatment for hepatocellular carcinoma by

contrast-enhanced ultrasonography using Sonazoid: comparison with dynamic computed

tomography. J Clin Ultrasound 2010;38(4):182-9.