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Clinical Studies

A novel display of reconstruction computed tomography for the detection of small hepatocellular carcinoma

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Abstract: *Purpose:* To evaluate the usefulness of the alternate display of arterial and equilibrium phase images (ADAEI) of 2 mm-pitch reconstruction computed tomography (CT) in the detection of hepatocellular carcinoma (HCC). *Materials and methods:* One hundred and eleven nodules in 72 patients were confirmed as HCC by radiology, histology, or clinical course. Blinded to the outcome, we retrospectively reviewed the CT images obtained with dual-phase spiral CT (Radix Prima, Hitachi Medical, Tokyo, Japan) by ADAEI and by conventional display on cut films. Scanning for the arterial and equilibrium phases was initiated at 33 and 120 s, respectively, after starting the injection of contrast medium (iopamidol 3 ml/s) with a section thickness of 5 mm and a table feed speed of 5–7 mm/s. In ADAEI, all images were reconstructed with a 2-mm interval, and displayed on the monitor in an alternating fashion so that an image in the arterial phase was followed by the corresponding image in the equilibrium phase, and then by the next pair of images in the craniocaudal direction. *Results:* All 20 HCC nodules larger than 20 mm in diameter were detected by both ADAEI and the conventional display (NS). On the other hand, detectability of smaller HCC nodules was 91/91 (100%) and 72/91 (79%), respectively ($P<0.0001$ by McNemar' test). False-positively identified HCC nodules, including those diagnosed as possible HCC, were 11 by ADAEI and eight by conventional display. *Conclusion:* The novel, alternate display, ADAEI of 2 mm-pitch reconstruction CT images was useful in detecting small HCC nodules while not requiring additional equipment or expense.

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Key words: hepatocellular carcinoma – reconstruction CT – spiral CT

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Hepatocellular carcinoma (HCC) is one of the most common malignancies in the world and claims more than 30 000 deaths in Japan every year (1). Therefore, detecting HCC at an early stage without miss is all the more important (4–8).

HCC nodules usually show artery-dominant blood supply, and comparison between computed tomography (CT) images obtained during arterial and delayed (equilibrium) phases is essential in the diagnosis of HCC (9–10). Previous studies on CT-based HCC diagnosis have been primarily focused on specifications of hardware, modes of X-ray scanning, or characteristics of contrast materials (11–14). Although those studies have contributed greatly to the improvement of tumor visualization, the final diagnosis of HCC still depends primarily on the human eye's capability to detect differences in density.

Conventionally, CT images obtained in the arterial phase are sequentially examined on a cut film or a monitor, followed by those obtained in the portal phase, and finally the two series are compared with each other. However, viewing many images in such a way is rather inconvenient in clinical practice, especially when there are a great number of images to be examined because of thin-slice reconstruction. In this article, we introduced a new method of displaying reconstruction CT images, the alternate display technique of arterial and equilibrium phase images (ADAEI), which was developed to emphasize the contrast difference between corresponding

images in each phase. All CT images are reconstructed with an interval of 2 mm and displayed on a monitor in an alternating fashion so that the image in the arterial phase is directly followed by its counterpart in the equilibrium phase, which is then followed by all subsequent pairs of images in the craniocaudal direction. The reviewer pages these images on a monitor at adjustable speed.

To validate its usefulness in the screening for HCC, we conducted the current study to compare HCC detectability of ADAEI with that of conventional image viewing.

Materials and methods

Patients

We performed contrast-enhanced dual-phase spiral CT on 159 patients with chronic liver diseases at Kowa hospital, affiliated with our department, between February 1999 and March 1999. These patients had been suspected of liver tumor by ultrasound or clinically judged to be at high risk for HCC. We found at least one HCC nodule by ADAEI, as confirmed by subsequent examination and/or observation, in 72 of them (59 men, 13 women; age range, 48–84 years (mean, 65 years)). We compared the detectability for HCC between ADAEI and conventional display in a blinded fashion consecutively, involving a total of 159 patients.

CT conditions

Spiral CT was performed with Radix Prima (Hitachi Medical, Tokyo, Japan) using iopamidol (300 mg/ml, Iopamilon 300; Japan Shering, Osaka, Japan) as the contrast medium, injected into the antecubital vein through 20-gauge plastic intravenous catheter at a rate of 3 ml/s by automatic injector. CT scanning was initiated 33 s (arterial phase) and 120 s (equilibrium phase) after starting contrast medium injection. Each series of CT images was obtained with a section thickness of 5 mm and a table feed speed of 5–7 mm/s, using X-ray emission of 120 kVp, 200–225 mA s.

ADAEI

In ADAEI, the alternate display, all images were reconstructed at a 2 mm interval, which produced about 150–200 images for each patient. In preliminary studies, we compared ADAEI with 1–5-mm-pitch reconstruction and found that 2-mm-pitch reconstruction was most favorable in terms of resolution and signal/noise ratio. These reconstruction images were displayed on a monitor in an alternating manner meaning that the image in the arterial phase was followed by the image at the same level of the body in the equilibrium phase. This display pattern was repeated with the sequential pairs of images in the craniocaudal direction. The image display unit we used, as well as a few of other recent models, was able to order images alternatively from two series, the arterial and equilibrium phases in the current case. Sometimes, we had to adjust the level of the first images manually and it took a couple of minutes. The monitor was adjusted to maximally emphasize the contrast of lesions by using a window width of 120–140 HU for both arterial and equilibrium phases and a window level of 65–80 for the arterial, and 70–85 for the portal phase. Reviewers looked for differences in contrast while paging the images. A lesion of 10 mm in diameter will flicker at least four times on the monitor (Fig. 1). The speed of image paging was freely adjustable but was usually set at around 1 image/s. It took 5 min or less to review the whole set of images of one patient.

Conventional viewing

By the conventional display, CT images were viewed as follows: (1) Images in the arterial phase at a 5-mm interval were sequentially printed out on a cut film, followed by those in the equilibrium phase on a separate film. A window width of 150–250 HU was used for both phases; a window level of 70–100 was used for the arterial, and 90–120 for the portal phase. (2) A reviewer set the cut films on an X-ray viewer and checked for space-occupying lesions, focusing primarily on density differences from the surrounding liver tissue. (3) When a lesion was suspected, the reviewer looked for the corresponding image in

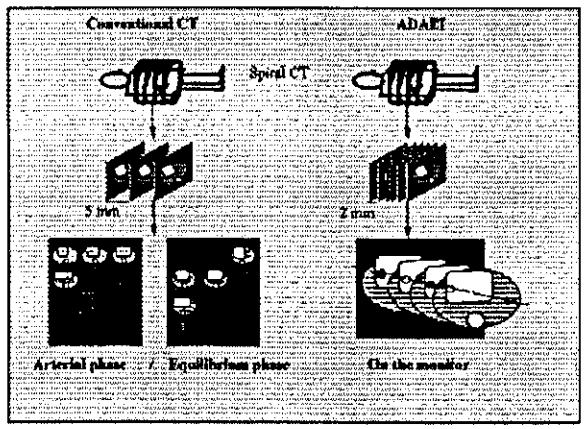

Fig. 1. Comparison of alternate display of arterial and equilibrium phase images (ADAEI) and conventional method. In ADAEI, a reconstructed computed tomography image in the hepatic arterial phase and the corresponding one in the equilibrium phase are alternately displayed.

the other phase and evaluated the form of nodule, enhancement pattern, etc.

All CT images were viewed with ADAEI by one of three investigators (T. T., S. S., S. O.) randomly, and with the conventional method by one of the remaining two. The reviewers were blinded to the identity of the patients.

Diagnosis of HCC

Radiological diagnosis of HCC was based on the same criteria in ADAEI and conventional viewing. The enhancement pattern of a hepatic nodule was classified into four categories: (1) hyperattenuation in the arterial phase and hypoattenuation in the equilibrium phase (H–L pattern, Fig. 2), (2) hyperattenuation in the arterial phase and isodensity (not discernible) in the equilibrium phase (H–I pattern), (3) isodensity in the arterial phase and hypoattenuation in the equilibrium phase (I–L pattern), and (4) hypoattenuation in both phases (L–L pattern, Fig. 3). We experienced no other combinations of enhancement pattern.

The H–L pattern indicates increased arterial blood flow with decreased portal flow, a combination strongly suggestive of HCC (12, 14). The H–I pattern indicates HCC, atypical dysplastic nodule, or arterio-portal shunting. Arterio-portal shunting usually assumes a wedge shape as it spreads toward the liver surface (15). Except when arterio-portal shunting was diagnosed, we performed ultrasound-guided tumor biopsy for a differential diagnosis. When the increase in arterial blood flow is less conspicuous, an HCC, especially at an early stage, may appear in the I–L pattern (16). In this case, differentiation between HCC and non-malignant lesion is difficult by CT images alone, and usually requires follow-up observation or histological examination. An HCC lesion may even show an L–L pattern. Cystic lesions can be easily ruled out by checking the CT value. However, differentiation from other non-malignant lesions is difficult and usually requires follow-up or histological examination.

During follow-up observation (1–13 months (mean, 4.9 months)), an increase in diameter by more than 50% from the previous determination was considered indicative of HCC (Fig. 4). On the other hand, HCC was ruled out if there was no increase in size for at least 2 years. Ultrasound-guided tumor biopsy was performed when there was an intermediate increase in size. When HCC was otherwise suspected, for example, on the basis of elevated serum biomarker for HCC, ultrasound-guided tumor biopsy was performed promptly even if CT images were not strongly suggestive of malignancy. Hepatic lesions were also diagnosed as HCC if they accumulated iodized oil after transcatheter arterial embolization intended for other HCC lesions. In this article, the diagnosis of HCC was based on the final diagnosis achieved in this manner.

Fig. 2. Case: 62-year-old male. A nodule 11 mm in diameter (arrows) in the lateral segment of the left hepatic lobe showed high attenuation in the hepatic arterial phase (a) and low attenuation in the equilibrium phase (b) of 2 mm-pitch reconstruction computed tomography images. These two images will be serialized in alternate display technique of arterial and equilibrium phase images. The tumor was subsequently proven to be moderately differentiated hepatocellular carcinoma by fine needle biopsy.

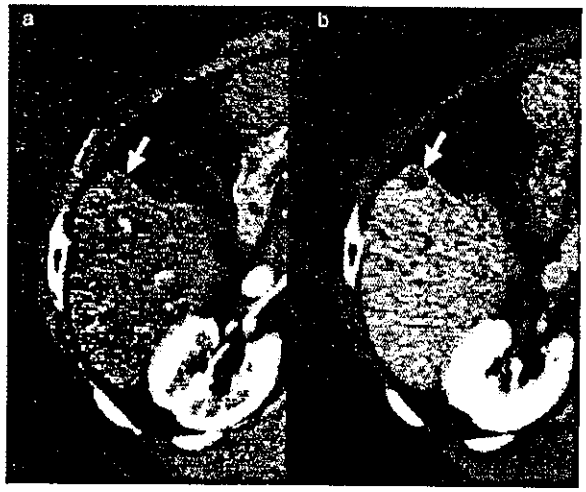

Fig. 3. Case: 84-year-old male. A 10-mm nodule in the anterior segment of the right lobe (arrows) showing hypoattenuation in both hepatic arterial (a) and equilibrium phases (b). Proven to be well differentiated hepatocellular carcinoma.

Statistics

The detectability of HCC was assessed by specificity and positive predictive value. Since we were not able to evaluate false negatives, sensitivity was not defined. Detectability was compared with McNemar's test, assuming one case at each blank discordant level.

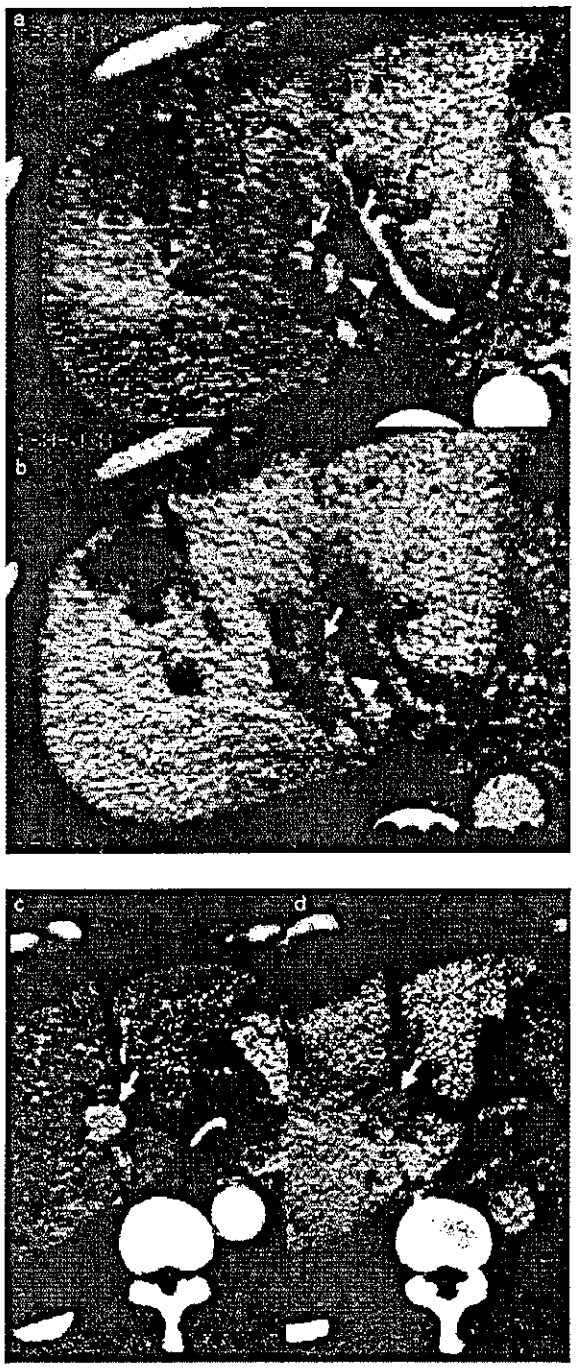

Fig. 4. Case: 63-year-old male. An 8-mm nodule adjacent to the umbilical portion of the portal vein (arrows) showing hyperattenuation in the hepatic arterial phase (a) and hypoattenuation in the equilibrium phase (b). This tumor was not detectable by ultrasound. One year later, the size increased to 20 mm (c, d), and the tumor was visualized with ultrasound and diagnosed as hepatocellular carcinoma by needle biopsy.

Results

Detectability of HCC nodules

In the 72 patients, a total of 111 nodules, which were confirmed to be HCC as the final diagnosis (85 nodules were diagnosed HCC by biopsy, 13 nodules by iodized oil accumulation, 13 nodules by natural growth), were detected by the new display method, ADAEI, while 92 (83%) of them were discerned by the conventional display method ($P<0.0001$ by McNemar's test, Table 1). All HCC nodules detected by the conventional method were also detected by ADAEI, and the latter found 19 additional HCC nodules. All HCC nodules larger than 20 mm in diameter were detected by ADAEI and by the conventional method. In contrast, the detectability differed for smaller HCC nodules, 91/91 (100%) and 72/91 (79%) by ADAEI and the conventional method, respectively ($P<0.0001$).

Table 1. Detectability of HCC by conventional method and ADAEI

HCC nodules	Conventional method	ADAEI	*P* value
>20 mm ($n=91$)	72 (79%)	91 (100%)	<0.0001
>20 mm ($n=20$)	20 (100%)	20 (100%)	

Data are presented as number of lesions. HCC, hepatocellular carcinoma; ADAEI, alternate display of arterial and equilibrium phase.

Eighty-seven nodules were diagnosed as HCC on the basis of hyperattenuation in the arterial phase and hypoattenuation in the equilibrium phase, typical of HCC (H–L pattern), and/or histologic examination of ultrasound-guided biopsies. The other 24 nodules, mostly small ones, showed an enhancement pattern not specific to HCC, and histologic examination was not conclusive either because biopsy did not hit the tumor tissue or ultrasound visualization was poor. These nodules were diagnosed as HCC during the follow-up observation.

False-positive HCC detection

In addition to the 111 nodules proven to be HCC, ADAEI detected 11 nodules that were diagnosed as possibly being HCC but afterwards proved otherwise by ultrasound-guided histologic examination or follow-up observation. Similarly, the conventional display method detected eight false-positive nodules. The positive predictive values did not differ between the two methods ($P=0.8150$ by Fisher's exact test, Table 2).

Enhancement patterns

Enhancement patterns of hepatic nodules as classified into the four patterns described above, plus no detection, were compared between ADAEI and the conventional display method and summarized in Table 3. As shown in the table, most of the 14 HCC nodules not detected by the conventional method were visualized as

Table 2. Positive predictive values of the two methods

	Conventional method	ADAEI	*P* value
Detected nodules	100	122	
HCC nodules	92	111	
False-positive nodules	8	11	
PPV (%)	92	91	0.8150

Data are presented as number of lesions and percentage. HCC, hepatocellular carcinoma; ADAEI, alternate display of arterial and equilibrium phase; PPV = positive predictive values.

Table 3. Enhancement pattern by conventional method and ADAEI

	ADAEI				
Conventional method	H–L	H–I	I–L	L–L	Total
H–L	66	2	0	0	68
H–I	4	5	0	0	9
I–L	3	0	9	2	14
L–L	0	0	0	1	1
Undetected	14	2	1	2	19
Total	87	9	10	5	111

Data are presented as number of lesions. ADAEI, alternate display of arterial and equilibrium phase; H–L, high attenuation at the arterial phase and low attenuation at the equilibrium phase on dynamic CT; H–I, high attenuation at the arterial phase and isodensity (undetectable) at the equilibrim phase; I–L, isodensity (undetectable) at the arterial phase and low attenuation at the equilibrium phase; L–L, low attenuation at the arterial phase and low attenuation at the equilibrium phase.

the H–L pattern by ADAEI. In addition, three nodules revealed with the I–L pattern by conventional method were detected as the H–L pattern by ADAEI. Thus, ADAEI was superior to the conventional method not only in the sensitivity of detecting nodules but also in the quality of the differential diagnosis of HCC.

Discussion

There have been a number of reports that discussed the sensitivity and specificity of spiral CT for HCC detection, chiefly based on the examination of specimens from subsequently performed hepatic resection (9–12). Murakami et al. (12) reported the sensitivity of spiral CT in case of hypervascular HCC as 86%. In addition, several studies examined the sensitivity of dynamic CT performed before transplantation by comparing it with explanted liver and reported a lesion-by-lesion sensitivity of 71–88% (13, 17–18). These values were compatible with the sensitivity observed in the current study of spiral dynamic CT as viewed by the conventional display (86%), validating our diagnostic criteria of HCC based on enhancement pattern, tumor biopsy, and subsequent observation for at least 2 years. Consequently, the even higher sensitivity of ADAEI was also strongly supported. Moreover, it was thought that tumor vascularity was evaluated more precisely by ADAEI than by conventional method, since the reviewers could adjust both the window width and the level on the CT monitor so as to emphasize the contrast of lesions to a maximum degree. Therefore, it could be determined whether a lesion had slight hyperattenuation or hypoattenuation at each phase. One report mentioned the routine interpretation of liver window scans for abdominal CT scans. Therein, it was suggested that routine interpretation of the liver window has limited added utility in detecting hepatic disease, but that the selective use of liver windows in the setting of known neoplasms has additional benefit (19).

Recently, CT hepatic arteriography (CTHA) and CT arterial portography (CTAP) were reported to have a combined detection sensitivity of 93% in detecting HCC lesions 2 cm or less in diameter (20). Comparison data between CTHA/CTAP and ADAEI are not available. However, the latter obviously has the merit of being less invasive and less expensive than CT angiographies. In addition, false-positive findings, often a problem with CTHA/CTAP (21–24), are not frequent with ADAEI, as explained above.

Ultrasound, a virtually non-invasive and less expensive modality, has been widely applied in the screening of hepatic tumors. However, the detectability of small HCC nodules by ultrasound is controversial (25–28). Among the 111 HCC nodules examined in the current study, 20/20 (100%) nodules larger than 20 mm in diameter were detected by ultrasound performed within 1 month after CT examination, while 22/91 (24%) nodules smaller than 20 mm were not been detected even after being identified by CT. Thus, contrast-enhanced dual-phase CT has a certain advantage over ultrasound in detecting small HCC lesions, and this advantage will be augmented by the use of the alternate display, ADAEI. In the clinical practice at the authors' institution, we perform CT routinely for the screening of HCC when ultrasound condition is poor because of advanced atrophy of the liver, coarse hepatic parenchymal images, or obesity. In addition, we use CT in combination with ultrasound for cirrhotic patients who are at a high risk of HCC development. While we have shown that ADAEI has better detectability for HCC than conventional CT viewing, its true sensitivity is not known. We have to analyze patients without detected HCC to evaluate sensitivity. In fact, we carefully followed these patients and HCC developed later in some of them. However, we cannot determine whether the lesion had existed at the

time of ADAEI. In addition, when three of the coauthors were randomly allotted to ADAEI reading, the study design did not permit intra- and interobserver validation and may contain bias.

In conclusion, the novel display method of 2-mm-pitch reconstruction dual-phase spiral CT, ADAEI, is superior to conventional display in detecting small HCC nodules in the liver. Sorting CT images in an alternating order between the arterial and equilibrium phases is the only requisite for ADAEI, which can be easily performed with most current CT apparatuses without additional cost or equipment. It is highly recommended for the screening of HCC in high-risk patients.

Summary

The novel display method, ADAEI of 2-mm-pitch reconstruction CT images is superior to conventional display in detecting small HCC nodules in the liver while not requiring additional equipment or expense.

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Clinical Studies

Evaluation of transcatheter arterial embolization prior to percutaneous tumor ablation in patients with hepatocellular carcinoma: a randomized controlled trial

Akamatsu M, Yoshida H, Obi S, Sato S, Koike Y, Fujishima T, Tateishi R, Imamura M, Hamamura K, Teratani T, Shiina S, Ishikawa T, Omata M. Evaluation of transcatheter arterial embolization prior to percutaneous tumor ablation in patients with hepatocellular carcinoma: a randomized controlled trial.
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Abstract: *Background:* Transcatheter arterial embolization (TAE) may reduce the risk of hepatocellular carcinoma (HCC) recurrence when performed before percutaneous tumor ablation (PTA), either percutaneous ethanol injection therapy (PEIT) or radiofrequency ablation (RFA). We conducted a randomized, controlled trial comparing the use of TAE combined with percutaneous ethanol injection therapy (TAE/PEIT) to the use of PEIT only to assess the effects on HCC recurrence and survival. We continued the study after the introduction of RFA and compared TAE combined with RFA (TAE/RFA) with RFA only. *Methods:* Between March 1997 and April 2001, 42 HCC patients were enrolled who satisfied the following inclusion criteria: (1) uninodular HCC as determined by angiography under computed tomography, (2) arterial hypervascularity, and (3) no prior history of HCC treatment. Twenty-two patients were treated with TAE/PTA (PEIT, 12; RFA, 10) and 20 patients with PTA only (PEIT, 14; RFA, 6). *Results:* There were four cases of local recurrence in the PTA-only group and none in the TAE/PTA group ($P = 0.043$). The four patients with local recurrence were treated with PEIT. None of the patients treated with RFA showed local recurrence. The effect of TAE on overall recurrence was not significant ($P = 0.4179$). In the multivariate analysis, prior TAE was not significant for survival ($P = 0.514$). *Conclusions:* TAE has a limited use in suppressing local recurrence when performed before PEIT but not before RFA.

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Key words: hepatocellular carcinoma (HCC) – percutaneous ethanol injection therapy (PEIT) – radiofrequency ablation (RFA) – transcatheter arterial embolization (TAE)

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The incidence of hepatocellular carcinoma (HCC) has been increasing worldwide (1–3). For the most part, hepatectomy has been performed as a potentially curative treatment when impaired liver function does not preclude surgery: however, percutaneous tumor ablation (PTA) with ethanol (percutaneous ethanol injection therapy (PEIT)), microwave (percutaneous microwave coagulation therapy (PMCT)), or radiofrequency (radiofrequency ablation (RFA)) has come to play an important role in HCC treatment (4–8). One of the advantages of PTA over surgery is its applicability to patients with poor liver function who cannot undergo surgery. This advantage becomes especially important because most patients with HCC have cirrhosis as the background liver disease. However, the drawback of PTA is that only those lesions that can be visualized by imaging can be treated, which means that possible microscopic lesions in the vicinity of the main lesion may be left untreated.

Transcatheter arterial embolization (TAE) is another treatment modality for HCC, the principle of which is based on the fact that HCC nodules are supplied predominantly by arterial blood flow while surrounding liver tissue receives both arterial and portal flow (9–11). When performed alone, TAE can rarely achieve complete

necrosis of macroscopic HCC nodules: however, it may attain complete necrosis of microscopic lesions and thus compensate for the above-mentioned demerit of PTA. In addition, if TAE is performed prior to PTA, the hydrostatic pressure inside the tumor tissue may be decreased by the elimination of arterial blood flow, reducing the risk of tumor-cell seeding that sometimes occurs subsequent to PTA. These effects taken together mean that TAE prior to PTA may work to decrease the incidence of HCC recurrence after PTA.

A previous report demonstrated that TAE prior to PEIT reduced the risk of local HCC recurrence. This study was limited, however, in that it included only cases with small HCC nodules less than 3 cm in diameter, which are less prone to local recurrence than larger nodules (12–16). Moreover, TAE prior to RFA, a recently developed modality of PTA, was not studied even though RFA is thought to be less likely to yield local recurrence than PEIT.

For more than a decade, we have been treating HCC patients with mainly PTA: however, to date, more than 700 patients have been treated with PEIT and as of December 2002, 697 patients with RFA (17, 18). Based on our own data on effectiveness and safety, we found it unnecessary to exclude large HCC nodules from the PTA indication solely because of size. However, since large HCC nodules tend to have microscopic satellite lesions and abundant arterial blood flow, TAE prior to PTA may be especially useful. In this randomized, controlled trial, we compared the combined use of TAE and PEIT with PEIT only, and assessed the effects on local HCC recurrence, and patient survival. After RFA was introduced as the primary modality of PTA, we extended the study to compare TAE plus RFA with RFA only.

Patients and methods

Study design

Between March 1997 and April 2001, 42 HCC patients who fulfilled all of the following criteria and provided informed consent were enrolled in this study. HCC diagnosis was based on typical findings from imaging studies such as arterial hyperattenuation and portal hypoattenuation on angiography under computed tomography (CT). Patients had to fulfill the following criteria: (1) a solitary HCC nodule detectable by angiography under CT, (2) the hypervascular nodule, i.e., positively enhanced on hepatic arteriography under CT, and (3) no prior history of HCC treatment.

A randomized sealed envelope method was used to determine patient assignment. PTA was originally performed as PEIT when we started this study, but after the introduction of RFA into our clinical practice in February 1999, the modality of PTA in this study also changed to RFA. As a result, 22 patients were treated by TAE/PTA (PEIT 12, RFA 10) and 20 patients received PTA only (PEIT, 14; RFA, 6).

TAE

A catheter was introduced through a puncture made in the femoral artery and guided into the trunk of the hepatic artery with the use of fluoroscopy. After identifying the HCC nodule through angiography, the catheter was further advanced to the most selective position located proximal to all arteries feeding into the nodule. After injecting lipiodol (average 8.0 ml), an ionized oil used as a radiographic marker of HCC lesions, gelatin sponges (Gelform; Upjohn, Kakamazoo, MI) were dispersed from the catheter tip until the obliteration of arterial flow to HCC was angiographically confirmed.

PTA

PEIT: A detailed description of the PEIT procedure can be found in previous papers (17, 19, 20). Briefly, the HCC lesion was carefully scanned using ultrasonography to select the optimum route for needle approach. After local anesthesia, the puncture needle, 21 gauge, 15 or 20 cm in length (Daimon, Koshigaya, Japan) was inserted into the HCC nodule under ultrasonographic monitoring. An average of 50.6 ml ethanol was injected each time. Repeated injections were performed if it was necessary to relocate the tip of the needle (21).

RFA: We performed RFA according to the procedure described in previous papers (7, 17). Briefly, the RFA electrode (Radionics, a division of the Tyco Healthcare Group LP, Burlington, MA) was inserted into the HCC nodule under ultrasonographic monitoring. Next, a radiofrequency electromagnetic wave was emitted from the electrode, which was converted into heat, in turn causing necrosis of the tumor. We used an emission power of 40–160 kW for 720 s for nodules 2 cm and 1440 s for those nodules 3 cm in diameter.

Evaluation of PTA

After PTA (PEIT or RFA), we assessed the necrotic area with contrast-enhanced CT. The area of necrosis was depicted as a low-density

area in both arterial and portal phases. PTA was considered complete when the necrotic area was larger than the area of HCC lesion before PTA, which was demarcated by lipiodol accumulation if angiography was performed, with a safety margin of at least 5 mm. If necrosis was incomplete, we repeated PTA until complete necrosis was confirmed as described above. We were able to achieve complete necrosis in all patients under the allotted PTA modality.

Follow-up of patients

All patients were checked for HCC recurrence every 3 months by abdominal ultrasound, and every 6 months by contrast-enhanced CT. A determination of serum HCC-specific tumor markers, α-fetoprotein (AFP), its lectin fraction 3, and des-γ-carboxy prothrombin was also made every 1–2 months (22, 23). The follow-up period was defined as the interval starting from the end of HCC treatment and lasting until the detection of recurrence. The final observation was made in March 2002, after a mean follow-up period of 3.16 ± 1.29 years (range, 1.03–5.01 years).

Statistical analysis

Values were shown as the mean and standard deviation unless otherwise specified. Differences of means were assessed with the unpaired Student's *t*-test or Mann–Whitney *U* test, and frequency distribution was assessed using the χ^2 test. Cumulative survival and recurrence-free survival curves were calculated by the Kaplan–Meier method, and the difference between the groups was assessed by the log-rank test. Predictors of survival were identified using the Cox proportional hazard regression. A *P* value less than 0.05 was considered statistically significant.

Results

Patients

The demographics of 42 patients enrolled in this study are summarized in Table 1. Except for the gender ratio, host and tumor characteristics did not differ between the TAE/PEIT group and the PEIT-only group or between the TAE/RFA group and the RFA-only group.

Complications

No major complications occurred after TAE or PTA. Minor complications included fever and controllable right upper-quadrant pain often observed after TAE and right upper-quadrant abdominal pain observed in about half of the patients treated with RFA.

Recurrence of HCC

The recurrence-free survival rates shown in Fig. 1 are 86.4%, 67.9%, and 33.8% at 1, 2, and 3 years in the TAE/PTA group and 70.0%, 41.1% and 34.3%, respectively, in the PTA-only group. Although the recurrence rate within 2 years appeared to be smaller in the TAE/PTA group, the difference was no longer significant at 3 years ($P = 0.4179$).

We defined local HCC recurrence as a nodule located adjacent to the original lesion. After defining recurrences as local or non-local, there were four cases of local recurrence in the PTA-only group and none in the TAE/PTA group ($P = 0.043$) (Fig. 2). By multivariate analysis, TAE prior to PTA reduced the risk of local recurrence. Tumor size was also significant in that larger tumors indicated higher risk. The four patients diagnosed with local recurrence were treated with PEIT. None of the patients treated with RFA showed local HCC recurrence.

Table 1. Profiles and laboratory tests of the patients

	PTA alone ($n = 20$)		TAE+PTA ($n = 22$)			
Characteristics	PEIT (A) ($n = 14$)	RFA (B) ($n = 6$)	TAE+PEIT (C) ($n = 12$)	TAE+RFA (D) ($n = 10$)	*P* (A vs C)	*P* (B vs D)
Age	64.5 ± 9.69	65.8 ± 9.48	63.3 ± 10.6	69.2 ± 11.1	0.772	0.546
Gender (M:F)	(13:1)	(5:1)	(6:6)	(3:7)	0.026	0.119
Positive HBs Ag	2 (14.3%)	1 (16.7%)	0 (0%)	1 (10%)	0.483	0.999
Positive HCV Ab	9 (64.3%)	5 (83.3%)	11 (91.7%)	7 (70%)	0.170	0.999
Fibrous staging (CH:LC)	(7:7)	(6:0)	(2:9)	(3:5)	0.208	0.999
Child-Pough (A:B/C)	(12:2)	(18:2)	(7:5)	(7:3)	0.190	0.250
Size of tumor	29.1 ± 11.2	27.2 ± 5.81	25.9 ± 7.31	27.5 ± 7.41	0.403	0.927
AFP positive (≥ 100 ng/ml)	1/14 (7.14%)	1/6 (16.7%)	4/12 (33.3%)	2/10 (20%)	0.148	0.999

TAE, transcatheter arterial embolization; PTA, percutaneous tumor ablation; PEIT, percutaneous ethanol injection therapy; RFA, radiofrequency ablation; HB, hepatitis B; HCV, hepatitis C virus; CH, chronic hepatitis; LC, liver cirrhosis; AFP, α-fetoprotein.

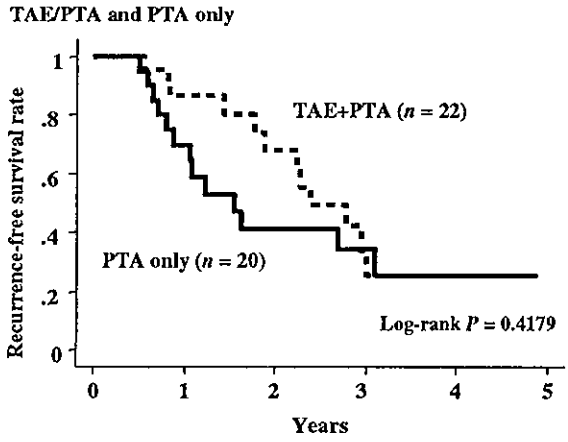

Fig. 1. Kaplan–Meier estimates of recurrence in 22 patients assigned to transcatheter arterial embolization (TAE) and subsequent percutaneous tumor ablation (PTA) and 20 patients assigned to PTA only ($P = 0.4179$ by the log-rank test).

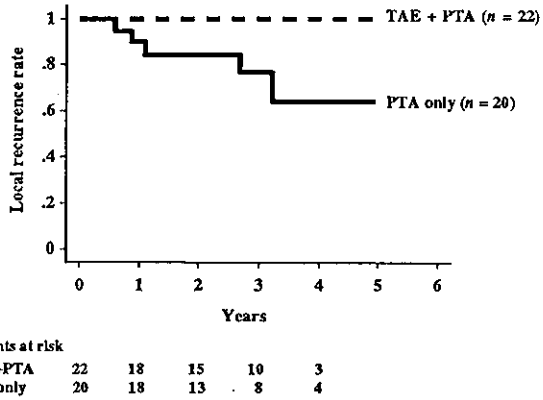

Fig. 2. Kaplan–Meier estimates of local recurrence in 22 patients assigned to transcatheter arterial embolization (TAE) and subsequent percutaneous tumor ablation (PTA) and 20 patients assigned to PTA only.

In contrast, there was no difference in non-local intrahepatic recurrence between the TAE/PTA group and the PTA-only group (60.5% vs. 48.3% at 3 years; $P = 0.5904$). Tumor-cell seeding did not occur in any patients.

Survival

By the end of the observation period, six patients from the TAE/PTA group and six patients from the PTA-only group had died. Cumulative survival rates did not differ between the two groups ($P = 06551$; Fig. 3). The 1-, 2-, and 3-year survival rates were 100%, 82.4%, and 82.4%, respectively, in the TAE/PTA group and 95.5%, 95.5%, and 82.2%, respectively, in the PTA-only group. The causes of death are shown in Table 2. For liver-unrelated deaths, the causes were subarachnoid hemorrhage in the TAE/PTA group, and brain contusion, ARDS, and a car accident in the PTA-only group.

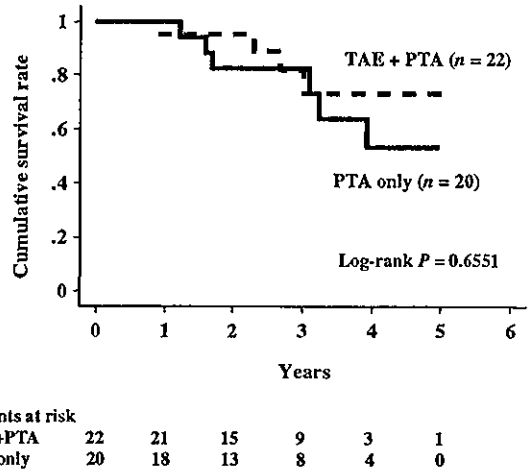

Fig. 3. Kaplan–Meier estimates of survival in 22 patients assigned to transcatheter arterial embolization (TAE) and subsequent percutaneous tumor ablation (PTA) and 20 patients assigned to PTA only ($P = 0.6551$ by the log-rank test).

Table 2. Cause of death

	TAE+PEIT (3/12)	PEIT only (6/14)	TAE+RFA (3/10)	RFA only (0/6)
Tumor progression	–	1 (16.7%)	1 (33.3%)	–
Hepatic failure	2 (66.6%)	1 (16.7%)	–	–
Esophageal varies rupture	1 (33.3%)	–	1 (33.3%)	–
Liver non-related death	–	3 (50.0%)	1 (33.3%)	–
Unknown	–	1 (16.7%)	–	–

TAE, transcatheter arterial embolization; PTA, percutaneous tumor ablation; PEIT, percutaneous ethanol injection therapy; RFA, radiofrequency ablation.

With multivariate analysis, the presence or absence of prior TAE was not significant to survival ($P = 0.942$) (Table 3). There was no significant difference in survival between the TAE/PEIT group and the PEIT-only group ($P = 0.518$) or between the TAE/RFA group and the RFA-only group ($P = 0.387$).

Discussion

One of the major concerns about PTA, as compared with subsegmental surgical resection, is that microscopic neighboring lesions may be left viable, resulting in local recurrence (24). We investigated whether TAE prior to PTA would suppress local recurrence, presumably by destroying these satellite lesions and found that local recurrence occurred solely in the PTA-only

Table 3. Predictive factors for survival

	Risk ratio (95% CI)	*P*-value
Combination TAE (vs. no TAE)	1.057 (0.239–4.673)	0.942
Child (A vs. B, C)	0.260 (0.056–1.204)	0.085
DCP (≥ 62.5 IU/l)	2.202 (0.583–8.322)	0.245
RFA (vs. PEIT)	0.444 (0.098–2.004)	0.291

TAE, transcatheter arterial embolization; RFA, radiofrequency ablation; DCP, des-r-carboxy prothrombin; PEIT, percutaneous ethanol injection therapy.

group. Patients with larger lesions had a higher risk of local recurrence, which was also compatible with our hypothesis.

There was no subsequent local recurrence when HCC was treated with RFA. Although we applied the same safety margin of 5 mm for both PEIT and RFA, RFA appeared to be more effective at eliminating neighboring lesions. This may be explained by the fact that the effect range of RFA could be precisely determined by adjusting the output, while the dispersion of ethanol in tissue was not entirely predictable. TAE prior to RFA was not as useful as TAE prior to PEIT.

TAE prior to PTA is theoretically effective not only against adjacent lesions but also against distant intrasubsegmental metastases. We categorized the distant metastases as non-local recurrences and found that non-local recurrence rates did not differ between TAE/PTA and PTA-only groups. Thus, either the non-adjacent, intrasubsegmental metastases are rare, or TAE is not effective against them. This idea needs to be further investigated by comparing PTA with surgery.

More importantly, intrahepatic recurrence was very common regardless of whether TAE had been used, and the hazard did not decrease, but rather increased with time after the original treatment. It seems that a substantial portion of the recurrent nodule was not because of residual metastases but because of *de novo* carcinogenesis. Even after curative treatment of the original HCC lesion, the background liver, often cirrhotic, remained at high risk for HCC. Indeed, the HCC recurrence rate after curative surgery is reportedly 15–20% (25), which is compatible with the recurrence rate after PTA-only found in this study. Thus, the effect of TAE or subsegmental resection on overall recurrence seems to be limited.

In conclusion, we prospectively compared HCC recurrence after TAE/PTA (PEIT or RFA) or PTA only. TAE prior to PEIT suppressed local recurrence, especially after the treatment of large HCC nodules. In contrast, local recurrence after RFA was uncommon even without prior TAE. The effect of TAE prior to PTA with regard to overall recurrence was not significant because of a high incidence of non-local recurrences, and there was no effect on survival. Thus, TAE has a limited use in suppressing local recurrence when performed prior to PEIT but not before RFA.

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Regression of Liver Fibrosis in Patients Treated By Interferon

Key words: Fibrosis, HCV, Interferon

In the past, histological classification of chronic hepatitis were, in a sense "philosophical"; terms like chronic "active" hepatitis, chronic "aggressive" hepatitis, or "persistent" hepatitis were among many of the examples. These terms seem to reflect the ideas of pathologists and clinicians who tried to include the notion of how the liver lesion progresses to the more serious condition in view of the microscope slide. Unfortunately, the natural course of chronic hepatitis was not clearly elucidated at that time, not even to mention the etiology. Thus, a lot of debate among pathologists on the classification of chronic hepatitis had existed. Since the discovery of two important hepatitis viruses (HBV and HCV), it became unnecessary to input speculated etiology and suspected prognosis into the histological classification of chronic hepatitis, and the terms like "aggressive", "active" or "persistent" were dropped from the classification, and the simple semiquantitative evaluation such as activity grade and fibrosis stage (F1 to F4) was introduced (1, 2). This modification of histological classification of liver biopsies made it possible to assess the changes of fibrosis state and inflammatory activity in a semiquantitated manner. And this coincided with the time when the eradication of HCV became possible by interferon treatment. Therefore, it was of great interest to elucidate fibrosis "progression" and "regression" rate, if it would ever occur, in hepatitis C virus infection which were speculated to have step-wise but very slow progression of fibrosis toward cirrhosis and hepatocellular carcinoma. These assessment could not be possible without the modification of previous histological classification.

A study by Poynard et al indicated that the fibrosis progression rate per year was approximately 0.13 indicating that it may take 8 years on average to move up one step, for example from F1 to F2, in the untreated patients (3). We also demonstrated that the fibrosis progression of 600 paired biopsied patients with an interval of approximately 4 years was 0.1/year (4). These data indicate that the natural course of chronic hepatitis C is fairly slow, and it may take 8 to 10 years to move up one step fibrosis stage. Fibrosis stage 4 (F4) has been set as cirrhosis and F1 to F3 are subclasses of chronic hepatitis. Therefore, it may take 30–40 years to reach the stage of cirrhosis (F4) following HCV infection. Sometimes, it may take much longer than that. This classification has a very practical usage for everyday medical care. For example, if the patient came with F1 at age 68, you may roughly calculate the age when the patient develops hepatocellular carcinoma as 108 years old. During these studies, more concern was paid on whether the "irreversible" fibrosis can be resolved after eradication of HCV, fibrosis of the liver is conceptionally regarded as "irreversible". Fibrosis improvement by interferon therapy was reported previously (5–9). Shiratori et al calculated the fibrosis regression rate as –0.28/year in paired biopsy taken from patients who has cleared the virus (4). Therefore, fibrosis of the liver could not be regarded as "irreversible" and down in one step fibrosis stage can be expected within 4 years on average if the virus is eradicated. In this issue of the Journal Arima et al (10) actually quantified the amount of fibrosis using computer software. If you take into consideration the measures such as histological assessment of the fibrosis by quantitative measure, almost all of the cases in which the virus was eradicated by interferon showed regression of fibrosis to a varying extent. In contrast, fibrosis progression was unvariably seen in those who did not respond to the treatment.

See also p 902.

There has always been a debate on the reliability of liver biopsies regarding the assessment of the structure and fibrosis staging because the sampled tissue is only a tiny piece of the liver. This study indicated that despite the sampling variation, the regression of fibrosis is obviously seen and it supports the previous studies done in semiquantitative manner.

The treatment of HCV infection has now improved drastically. Previously, the eradication rate of HCV in Genotype II which is the minority of our general population is relatively high and now is expected to be as high as 90%. However, the majority of HCV carriers, approximately 75%, have Genotype I which is difficult to treat. Single agent treatment by interferon yields only 7 to 8% eradication rate. But the most recent treatment protocol by PEG interferon and Rivabirin gives an eradication rate of approximately 50% or more of those treated. If the virus is eradicated, even irreversible fibrosis can be resolved. Therefore, our goal for the treatment is now set to reduce fibrosis and to reduce hepatocellular carcinoma by the treatment.

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Treatment of Hepatocellular Carcinoma by Percutaneous Tumor Ablation Methods: Ethanol Injection Therapy and Radiofrequency Ablation

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In Japan, ~30,000 patients died of hepatocellular carcinoma (HCC) in 2003. Ten percent had hepatitis B virus infection and 80% had hepatitis C virus (HCV) infection, indicating that viral hepatitis accounted for >90% of cases of HCC. In comparison, only 3% (1.5%, hepatitis B virus; 1.5%, HCV) of the general population is infected with these viruses. We treated 1238 patients between 1992 and the end of 2003 by means of percutaneous tumor ablation (PTA): 524 patients, by percutaneous ethanol injection therapy (PEIT); 85 patients, by percutaneous microwave coagulation therapy; and 629 patients, by radiofrequency ablation (RFA). Three-, 5-, 7-, and 10-year survival rates of the 1238 patients were 69%, 50%, 34%, and 19%, respectively. When limited to tumors ≤3 cm in diameter and ≤3 in number of cancer nodules (3-3 rule), 5-year survival rates reached 64.7% for PEIT. However, to achieve a 40% survival rate in year 5 after PEIT, the indication for treatment can be expanded to a 4 (size)-3 (number) rule or 5 (size)-1 (number) rule. The recent introduction of RFA may further change the rules. HCV-related HCC generally develops on the background of advanced fibrosis/cirrhosis. An issue of much concern is that it may subsequently recur in a location other than that of the primary lesion. We initiated a prospective controlled study to evaluate treatment with PTA and interferon. Results suggest that if the virus is eradicated, a 5-year survival rate as high as 80% can be expected.

The recent increase in incidence of hepatocellular carcinoma (HCC) in Japan has been remarkable, with 34,000 deaths occurring in 2003, almost 5 times as many as in 1970. There are several possible explanations for the increase. Our data, as well as those of others, indicate that the majority of the increment is caused by hepatitis C virus (HCV) infection. We have shown that seropositivity rates for HCV antibody and hepatitis B surface antigen in patients with HCC are 81% and 10%, respectively.[1,2] Although previously, ~30% of HCC cases were caused by hepatitis B virus, the contribution of this virus has declined, to be replaced by HCV, which continues to increase dramatically. Thus, it is crucial to understand the natural course of HCV infection to prevent the occurrence of HCC.[3] With better understanding of the natural course of HCV infection, the optimal way to treat HCC at tertiary-care centers like our hospital will be well elucidated. It appears that HCC develops with a stepwise progression of hepatic fibrosis.[1,3] Thus, even if we find HCC nodules while small and surgically resect them successfully, remote or de novo recurrence of HCC is inevitable.[4,5]

At the Gastroenterology Department of the University of Tokyo, Japan, we have used treatment modalities less invasive than surgical resection for the last 12 years.[6,7] The number of treated cases has now reached 2780 among 1238 patients. In this report, we present our experience and discuss future tactics against HCC.

Patients and Methods

Patients

This is a single-institute experience. We analyzed clinical features of consecutive patients treated by means of percutaneous tumor ablation (PTA) from 1992 to the end of 2003 at the Department of Gastroenterology, University of Tokyo. The diagnosis of HCC was made by means of imaging modalities, including ultrasound and computed tomography (CT), and confirmed by means of tumor-targeted biopsies. Patients were referred from all over the country, and some were from outside Japan (Figure 1). In this study, patients treated with transarterial embolization (TAE) alone or those sent to the Surgery Department for resection or transplantation without undergoing PTA at our department were not included. Those treated by means of surgical resection or TAE at other hospitals were included in the analysis if they subsequently were treated using PTA at our department.

Abbreviations used in this paper: CLIP, Cancer of the Liver Italian Program; CT, computed tomography; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; PEIT, percutaneous ethanol injection therapy; PMCT, percutaneous microwave coagulation therapy; PTA, percutaneous tumor ablation; RFA, radiofrequency ablation; TAE, transarterial embolization.

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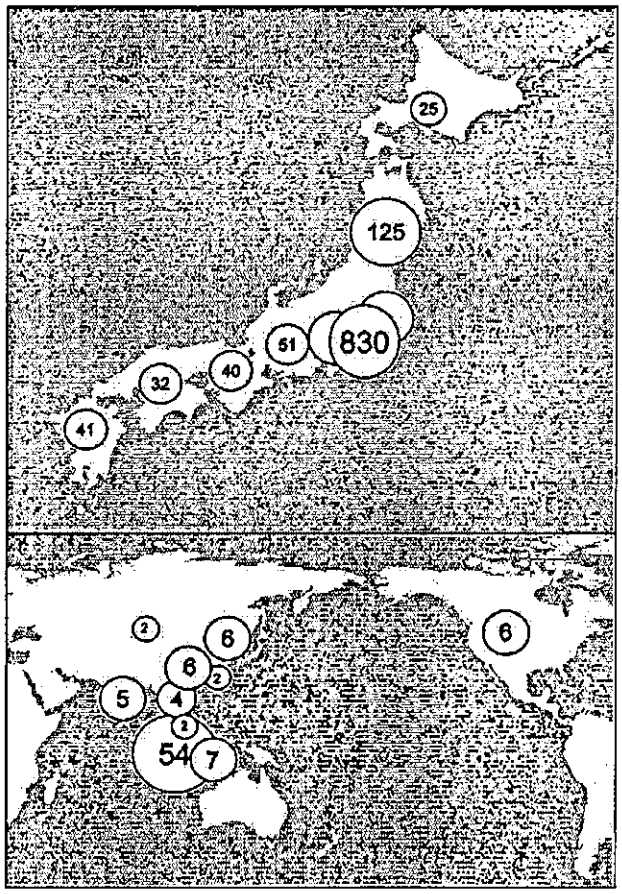

Figure 1. Source of referred patients who came from Japan and abroad. Circles show numbers of patients referred from different geographic regions for percutaneous tumor ablation.

Percutaneous Tumor Ablation

Several methods of PTA were used, including percutaneous ethanol injection therapy (PEIT), percutaneous microwave coagulation therapy (PMCT), and radiofrequency ablation (RFA). All treatments were performed on an in-patient basis.

Percutaneous ethanol injection therapy. Details of the procedure were described previously.[8] In short, after local anesthesia, a 21 G needle (PEIT needle; Silux, Saitama, Japan) is inserted into the distal edge of the lesion. Before injecting ethanol, additional needles are inserted to the proximal edge and midposition of the cancer nodule. Ethanol is injected through the first needle, which is withdrawn before the second injection of ethanol. The amount of ethanol injected by a single shot is 0.5–1.0 mL; a total of 2–8 mL is injected in this multiple-insertion technique.[8] However, it varies depending on the size of cancer nodules, distribution pattern of the liquid, and patient compliance.

Percutaneous microwave coagulation therapy. After local anesthesia, a microwave electrode, 1.6 mm in diameter and 25 cm in length, connected to the microwave generator (Microtaze; Azwell, Osaka, Japan) with a soft coaxial cable inserted under ultrasound guidance. The generator emits a 2450-MHz microwave, and radiation for dielectric heating is performed at 65–85 W for 60 seconds. Because the necrotized volume produced by 1 ablation of PMCT is 2.5 × 1.5 cm, we designed an introducing needle (Daimon, Saitama, Japan), a stopper for the electrode (Daimon), and guide needles with scales (Daimon) so the electrode can be inserted systematically into each portion of the lesion.

Radiofrequency ablation. After local anesthesia, an 17 G cooled-tip electrode with a 2- or 3-cm exposed tip (Radionics, Burlington, MA) is attached to a radiofrequency generator (CC-1 Cosman Coagulator; Radionics) and inserted under ultrasound guidance.[9] Temperature and tissue impedance are monitored during ablation. Cooled saline is infused to maintain the tip temperature at <20°C. Radiofrequency energy is delivered for 6–12 minutes for each application. For large lesions, the electrode is inserted into additional sites of the tumor nodule.

Completion of ablation procedure. Spiral CT is used to judge whether the tumor nodule has been completely ablated and necrotized after a few days of PTA. If ablation is suspected to be incomplete, treatment is repeated until sufficient areas surrounding the tumor nodule have been ablated. With the use of spiral CT after each ablation, complete necrosis of tumor nodules is achieved.

Follow-Up

After treatment, patients are followed up at the outpatient clinic of the University of Tokyo Hospital 3–4 times/y. At every visit, serum is obtained to test tumor markers (α-fetoprotein, des-carboxy abnormal prothrombin, and α-fetoprotein lectin-binding 3 fraction), and abdominal ultrasound is performed. If recurrence is suspected by the incremental increase in levels of tumor markers and/or abnormal ultrasound findings, the presence of recurrent tumor is confirmed immediately by means of spiral CT and CT-angiography.

Percutaneous Tumor Ablation for Recurrence

If the tumor recurs, PTA usually is repeated. However, if the tumor nodules exceed 5 in number or are diffuse, TAE is performed. In selected and advanced cases, an indwelling catheter is inserted, and continuous infusion of a chemotherapeutic agent is added.

Results

Percutaneous Tumor Ablation for Recurrence

From 1992 to the end of 2003, a total of 1238 patients were treated. Because many patients were treated more than twice, 2780 treatments were given to 1238 patients (Table 1). Thus, on average, 1238 patients underwent PTA on 2.2 occasions (treatments).

Changes in Percutaneous Tumor Ablation Procedure

The first percutaneous procedure introduced to treat HCC was the ethanol injection method (Figure 2).

Table 1. Percutaneous Tumor Ablation Performed at the Gastroenterology Department, University of Tokyo Hospital, on 1238 Patients from 1992 to 2003

Treatment modality	No. of patients	No. of treatments
Percutaneous ethanol injection therapy	524	1230
Percutaneous microwave coagulation therapy	85	176
Radiofrequency ablation	629	1374
Total	1238	2780

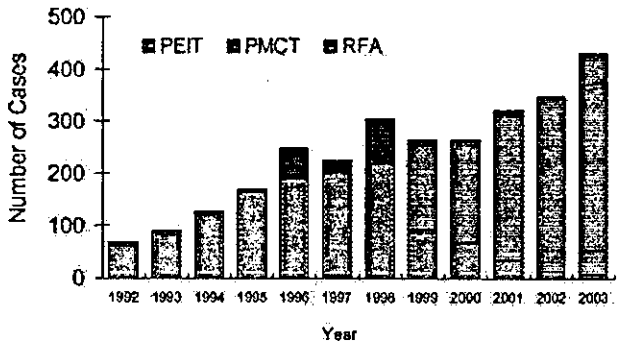

Figure 2. Percutaneous tumor ablation procedures by year used at the Department of Gastroenterology, University of Tokyo Hospital. PEIT, percutaneous ethanol injection therapy; PMCT, percutaneous microwave coagulation therapy; RFA, radiofrequency ablation.

After that, PMCT was used in Japan. This method used a large introducing needle (14 G). Then RFA became available as one of the percutaneous methods of treating HCC.[10] As shown in Figure 2, currently, the majority of our patients are treated by the RFA method.

Survival of All Patients Administered Percutaneous Ethanol Injection Therapy, Percutaneous Microwave Coagulation Therapy, and Radiofrequency Ablation

We analyzed survival rates of the 1238 patients treated by one of the PTA (PEIT, PMCT, and RFA) methods at our department. Patient demographic features are listed in Table 2. Overall survival of 1238 patients treated by means of PTA is shown in Figure 3*A*. Three-, 5-, 7-, and 10-year survival rates are 68.8%, 49.6%, 34.2%, and 18.7%, respectively.

Survival of Naive and Referral Patients

Many patients had been treated previously outside the University of Tokyo Hospital and were referred to us (referral patients; Figure 3), and their prognosis may differ from that of patients who underwent PTA at our department for the first time (naive patients; Figure 3*B*).

When survival time is defined as the interval between the first ablation at our department and either death or latest follow-up visit, 3-, 5-, 7-, and 10-year survival rates of the 902 naive patients are 73.3%, 55.7%, 38.2%, and 22.2%, respectively. Three-, 5-, 7-, and 10-year survival rates of the 336 referral patients are 56.2%, 30.7%, 21.8%, and 8.7%, respectively. The difference between the 2 groups is statistically significant ($P < .0001$; Figure 3*B*).

Survival by Percutaneous Ethanol Injection Therapy in Naive and Referral Patients

For the 3 techniques, we have sufficient long-term follow-up data for a large number of patients treated by means of PEIT (Figure 4*A*). Therefore, we performed a survival analysis on patients treated by PEIT in relation to the size and number of HCC nodules and background liver damage. Three-, 5-, 7-, and 10-year survival rates of all 524 patients treated by PEIT are 65.9%, 47.7%,

Table 2. Demographic Features of the 1226 Patients Treated by Percutaneous Transluminal Ablation at the Department of Gastroenterology, University of Tokyo

	Percutaneous ethanol injection therapy (N = 524)	Percutaneous microwave coagulation therapy (N = 85)	Radiofrequency ablation (N = 629)
Age	64.1 ± 8.7	63.6 ± 8.4	66.1 ± 8.2
Male (%)	373 (71.2)	56 (65.9)	424 (67.4)
Hepatitis B surface antigen positive (%)	56 (10.7)	10 (11.8)	73 (11.6)
Hepatitis C virus antigen positive (%)	443 (85)	70 (82)	494 (79)
Hepatitis B surface antigen negative/ Hepatitis C virus antibody negative (%)	32 (6.1)	7 (8.2)	69 (11.0)
Albumin (*g/dL*)	3.5 ± 0.5	3.5 ± 0.4	3.6 ± 0.5
Bilirubin (*mg/dL*)	1.0 ± 0.6	1.0 ± 0.5	0.9 ± 0.5
Child's class			
A (%)	299 (57.1)	51 (60.0)	440 (70.0)
B (%)	199 (38.0)	34 (40.0)	182 (28.9)
C (%)	26 (5.0)	0 (0.0)	7 (1.1)
Tumor			
Size (*mm*)	29.7 ± 15.8	28.8 ± 17.5	27.9 ± 12.3
No.	2.3 ± 2.2	2.0 ± 1.3	2.1 ± 1.8

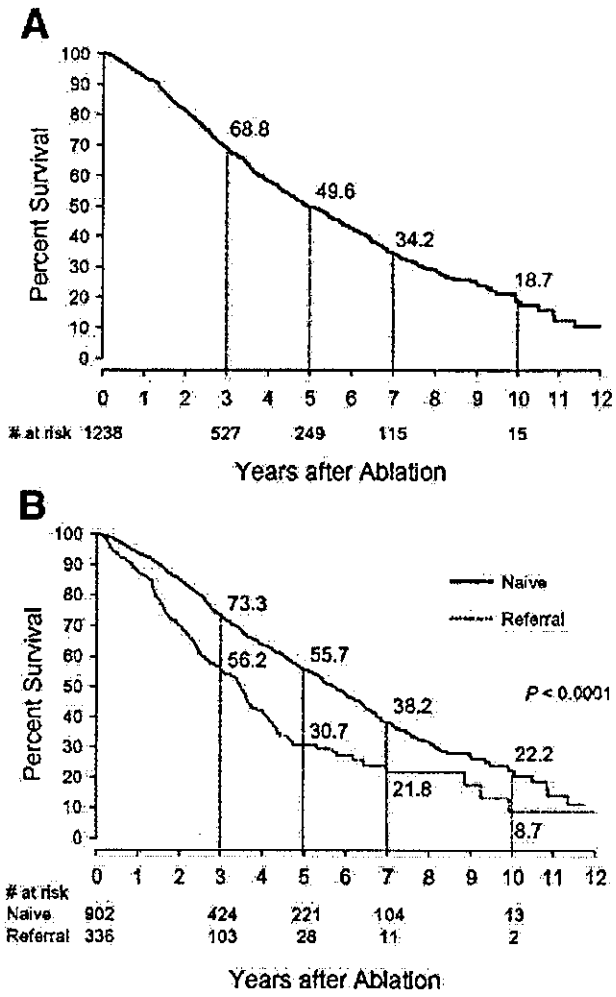

Figure 3. (*A*) Survival of 1238 patients treated by percutaneous tumor ablation (PTA) at the Department of Gastroenterology, University of Tokyo. (*B*) The 1238 patients were divided into 2 groups (naive and referral). The 902 naive patients did not have prior treatment of the HCC before receiving PTA. The 336 referral patients had received some form of therapy for HCC at other hospitals and subsequently were referred for ablation therapy. Survival was calculated based on the interval between the first ablation session and either death or the latest follow-up visit.

32.3%, and 17.3%, respectively. We also performed survival analyses on patients who underwent PEIT as treatment for HCC for the first time at our department (410 naive patients) and who were referred to us after treatment at other hospitals (114 referral cases; Figure 4*B*). Survival was substantially better in naive patients than referral patients (Figure 4*B*; $P < .0001$).

Survival According to Size and Number of Hepatocellular Carcinoma Nodules Using Percutaneous Ethanol Injection Therapy on Naive Patients

There may have been confounding factors involved in survival, especially when referral cases were included. Thus, the following analysis on the influence of tumor size and number on survival was conduct solely among naive patients treated by means of PEIT.

It was apparent that survival was better if the maximum size of the HCC nodules was smaller (Figure 5*A*). Of note, there was little difference in survival rates between the group with tumor size in the range of 2–3 cm and the group with a size of 3–4 cm (Figure 5*A*). Similarly, there was little difference in survival among patients who had <3 HCC nodules (Figure 5*B*).

Survival by Percutaneous Ethanol Injection Therapy Within the 3-3 Rule

Mazzaferro et al[11] reported that survival of patients with HCC treated by transplantation was excellent

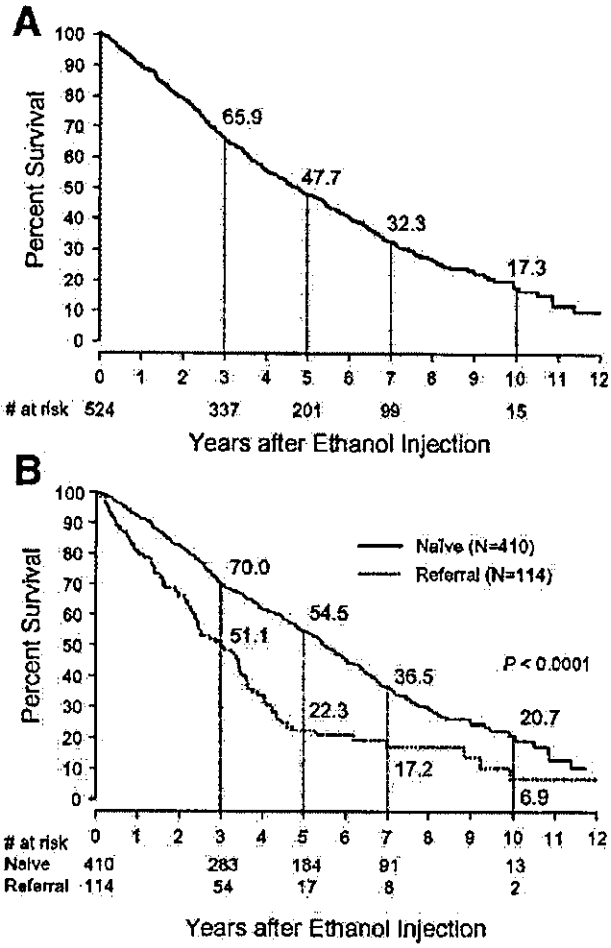

Figure 4. (*A*) Survival of 524 patients treated with percutaneous ethanol injection therapy (PEIT) of their tumors. (*B*) Survival of 524 patients treated with PEIT of their tumors separated into groups of 410 naive patients who had no previous therapy for HCC and 114 referral patients who had received previous treatment for HCC. Survival among naive subjects was significantly better than that for referral patients ($P < .0001$).

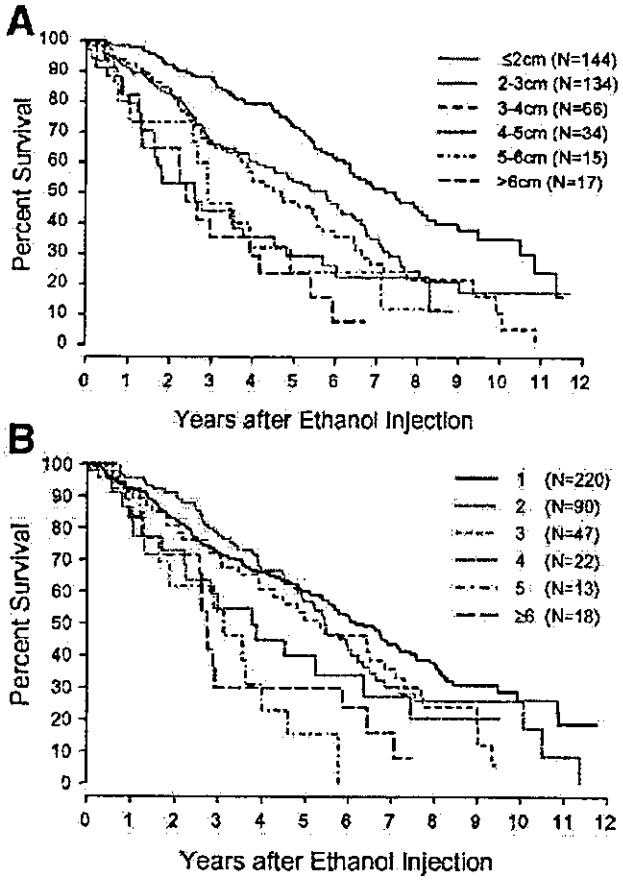

Figure 5. Survival of 410 naive patients treated by percutaneous ethanol injection therapy according (*A*) maximum size of tumor nodules and (*B*) number of tumor nodules.

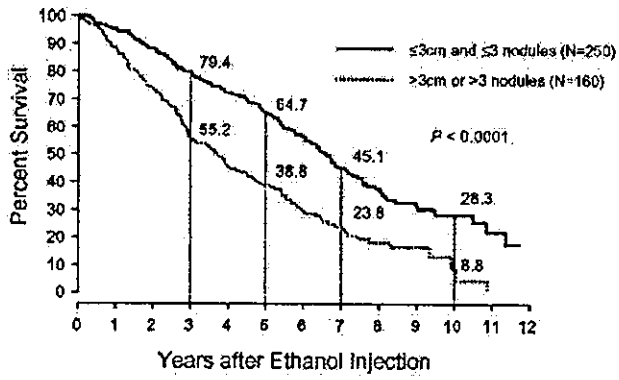

Figure 6. Survival of 410 naive patients treated by percutaneous ethanol injection therapy according the 3-3 rule, defined by size and number of hepatocellular carcinoma nodules; 250 patients had ≤3 tumors, none >3 cm; 160 patients did not fulfill these criteria, with tumors >3 cm or >3 tumors.

when tumor nodules were <3 cm in diameter and <3 in number (3-3 rule) or a single nodule was <5 cm in diameter (5-1 rule).

Also from our previous results, longer survival was expected in patients with HCC nodules <3.0 cm and <3 in number. Three-, 5-, and 7-year survival rates by PEIT were 79.4%, 64.7%, and 45.1% among the 250 patients who met criteria of the 3-3 rule, and 55.2%, 33.8%, and 23.8% among the 160 patients who were outside the 3-3 rule, respectively (Figure 6). The difference was statistically significant ($P < .0001$).

Survival of Patients Outside the 3-3 Rule

Because we treated patients who had HCC nodules >3.0 cm or >3 in number, we analyzed the survival of these patients according to 2 parameters (size and number) combined (Table 3). If we can expect a 5-year survival rate of ~40%, perhaps we can expand the criteria to a 4 (size)-3 (number) or 5 (size)-1 (number) rule (Table 3).

Survival by Percutaneous Ethanol Injection Therapy and Prognosis Discriminating Score From the Cancer of the Liver Italian Program

Because the prognosis of patients with HCC obviously is influenced by background liver damage, we analyzed the survival of our 410 naive patients treated by means of PEIT. Five-year survival rates were 72.4%, 57.4%, 29.6%, 31.2%, and 0% according to Cancer of the Liver Italian Program (CLIP) scores of 0, 1, 2, 3, and 4, respectively (Figure 7).

Comparison of Percutaneous Ethanol Injection Therapy and Radiofrequency Ablation

Recently, we have been treating the majority of patients with HCC by means of RFA. Therefore, a number of cases have accumulated for analysis for survival. This provided the opportunity to compare survival rates between PEIT- and RFA-treated naive patients. It ap-

Table 3. Five-Year Survival Rates of Naive Patients Treated by Percutaneous Ethanol Injection Therapy Based on Tumor Size and Number

No. of nodules	Size of maximum nodule (*cm*)					
	<2	2–3	3–4	4–5	5–6	>6
1	74 (92)	61 (73)	43 (30)	46 (13)	25 (4)	13 (8)
2	75 (32)	44 (27)	62 (14)	33 (9)	30 (5)	67 (3)
3	40 (9)	62 (17)	64 (11)	25 (4)	25 (4)	50 (2)
4	88 (8)	14 (7)	0 (3)	0 (3)	0 (0)	0 (1)
5	0 (2)	40 (5)	0 (2)	0 (3)	0 (0)	0 (1)
≥6	0 (1)	50 (5)	33 (6)	0 (2)	0 (2)	0 (2)

NOTE. Values expressed as percent (number of patients).

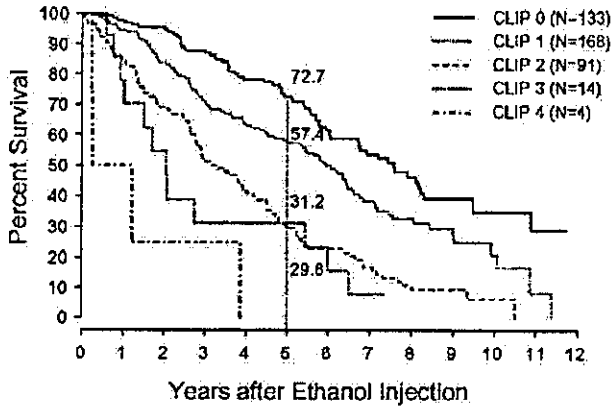

Figure 7. Survival of 410 naive patients treated by percutaneous ethanol injection therapy according Cancer of the Liver Italian Program staging scores.

pears that the 434 patients treated by RFA had the advantage of a 5%–8% better survival (Table 4).

Discussion

To our knowledge, this is the largest series describing medical treatment for HCC by PTA as a single-institution experience. It appears that both the increase in incidence of HCC in Japan and the attraction of patients to our department as a specialized tertiary care center have contributed to that large number (Figure 1). The PTA procedure was performed by 2–3 physicians at 1 time without other comedical staff attending, clearly showing how efficiently these treatments can be performed with enormous cost-effectiveness. However, this has not been accomplished with ease. The number of cases performed in 1992 was only 70, but reached 431 in 2003. In addition, during these 12 years, we shifted the method of PTA from PEIT to RFA (Figure 2).

In this study, we analyze the survival of all 1238 patients treated by 1 of the 3 methods. Three-, 5-, 7-, and 10-year survival rates are 68.8%, 49.6%, 34.2%, and 18.7%, respectively (Figure 3*A*). There are other data on the survival of patients with HCC treated by PEIT.[12–15] However, our patient characteristics are different from those of persons reported in the previous studies. PEIT was used on most occasions for HCCs <3.0 cm in size. This probably is because pure ethanol is a substance that induces necrosis to HCC, but the total amount of injected ethanol is limited to <10 mL, and sometimes it is difficult to penetrate through all parts of the tumor nodules when the size of the HCC is too large.

In this study, we were able to analyze survival according to the maximum size of tumors. It appears that survival worsens as tumor size increases, but there is no sudden decrease in survival between 3.0 and 4.0 cm (Figure 5*A*). Rather, the cutoff value may be between 4.0 and 5.0 cm (Figure 5*A*). This information might help define the indication for PTA because rules for size and number of tumor nodules have been decided empirically by several studies that included small numbers of patients. We may expand our eligibility criteria for PTA from 3.0 to 5.0 cm, especially when a method such as RFA allows extensive ablation of larger tumors with fewer sessions.

Regarding the indication for treatment on the background of liver damage, we empirically use the following eligibility criteria: total bilirubin level < 3 mg/dL, platelet count > 50,000/μL, and prothrombin time no less than 50%. These rules are not based on long-term survival data after treatment, but rather are intended to avoid posttreatment hepatic failure. Using these criteria, even medical therapy should be indicated and can be performed as safely as surgical resection. In this study, we analyzed the 5-year survival of patients with Child's classes A, B, and C cirrhosis. Survival was much better in persons with Child's classes A and B than those with Child's class C cirrhosis (data not shown). Thus, we should consider background liver damage, as well as size and number of HCC nodules, as the most important factors that influence the outcome of the treatments.

We gradually switched from PEIT to RFA in the last 12 years (Figure 2). The number of cases treated by RFA now exceeds 400 each year and is 6 times the number treated by PEIT in 1992. In this study, we analyze the survival of 434 consecutive patients treated by RFA (Table 4) and compared them with 322 patients treated by PEIT. One-, 3-, and 4-year survival rates were 92.4% vs 95.3%, 70.0% vs 77.8%, and 61.4% vs 68.0% for PEIT and RFA, respectively. These data suggest that the introduction of RFA may have further improved the prognosis of patients. However, these are nonrandomized study data, and we have to await results of well-controlled trials.

In this study, we were able to compare different treatment modalities of PTA, ie, PEIT, PMCT, and RFA. However, it also is necessary to compare PTA with other treatment modalities, eg, surgical resection, TAE, and transplantation. Of course, randomized controlled

Table 4. Comparison of Survival Rates of Naive Patients Treated With Percutaneous Ethanol Injection Therapy and Radiofrequency Ablation

	1 y	2 y	3 y	4 y
Percutaneous ethanol injection therapy (N = 410)	92.4	82.6	70.0	61.4
Radiofrequency ablation (N = 434)	95.3	87.5	77.8	68.0