Hepatocellular carcinoma (HCC) ranks third in frequency among cancers in Japan and its rising incidence is a serious problem in more developed countries. Although there is no doubt that early diagnosis and treatment improve survival (1), the criteria by which a specific treatment is selected as the first-line option remain to be established. Surgery offers the chance of potential cure, either by curative hepatic resection or transplantation. However, resection is applied only to patients with good hepatic reserve and localized tumors: the resectability rate in Japan is around 30%. Alternatively, local ablation therapy has gained a clinical position in treating small HCC (2).

Ablation therapy, most of which can be performed percutaneously under imaging guidance, was developed as a minimally invasive treatment for patients with small HCC. Percutaneous ethanol injection (PEI) is the prototype of ablation and modified methods include acetic acid injection, microwave coagulation and radiofrequency ablation (RFA). Both PEI and RFA are the most commonly used methods worldwide. PEI, first done at Chiba University in 1983, is aimed at producing tumor necrosis as a result of protein denaturation, cellular dehydration and occlusion of small vessels (2). Absolute ethanol is injected into the tumor through a thin needle and the procedure is repeated once or twice per week for up to four to six sessions, depending on the tumor size. Based on animal and clinical studies, HCCs smaller than 3 cm and with fewer than three nodules are considered to be suitable candidates for PEI. The therapeutic effect is usually evaluated by contrast-enhanced computed tomography; necrotic tumors are not enhanced and present a uniform low density, which is the most reliable finding of tumor necrosis. RFA, introduced by an Italian team in 1993, is a newcomer to ablation options (3). The method involves thermal ablation to produce rapid coagulation necrosis of HCC with r.f. energy delivered directly through a non-insulated electrode tip. Thermal lesions are created in a core of tissue that adheres to the tip owing to the heat generated by molecular friction. In early series, repeated insertions were required to destroy even small tumors because of the limited effective area. Recently, the use of expandable or cooled electrodes has made it possible to increase the volume of thermal lesions, thereby possibly reducing the number of sessions.

In clinical practice, PEI has been rapidly replaced by RFA, based on the assumption that RFA has a greater antitumor effect than PEI. In this issue, Ikeda et al. present data showing that RFA may be superior to PEI with respect to short-term outcome (4). Compared with PEI, RFA achieved a similar antitumor effect but with significant reductions in the number of sessions (on average from 4.0 to 1.5) and in-hospital stay (from 17 to 10 days). The damage to surrounding normal liver may be different between the methods, but in RFA-treated patients no clinically remarkable adverse events were documented. Their findings are consistent with those from other investigators (3,5). Reported benefits, however, were based on comparison with historical controls and conclusive findings supporting either method remain lacking.

The recent trend of switching from PEI towards RFA seems to depend on expectation rather than evidence. Therefore, as Ikeda et al. mentioned, randomized comparisons need to be conducted in order to be able to draw conclusions. Up to now, two randomized controlled trials comparing the therapeutic effectiveness of the two methods have preliminarily demonstrated that RFA is better than PEI in several respects. In Lencioni et al.’s series (n = 80) (6), the results between RFA and PEI with a median follow-up of 15 months were as follows: session number, 1.3 vs 3.3; complete necrosis, 91 vs 85%; and local recurrence, 4 vs 17%. The reason why the local recurrence rate in the PEI group was high is unknown, because the previously reported rate with this follow-up was less than 10% (2). In Shinya et al.’s series (n = 60) (7), there was a larger difference in session number (2.1 vs 7.3) to achieve a comparable antitumor effect. The hospital stay was significantly shorter with RFA than PEI (13 vs 30 days), which may be irrelevant in other countries where both ablations are usually performed on an outpatient basis. The outcomes derived from randomized trials provide evidence to confirm the findings of many ablation specialists and can therefore influence clinical practice in HCC ablation.

If the authors’ comments – ‘the prognosis of ablation-treated patients with small HCC is equivalent to that of surgical patients’ – are true, then surgeons should cease performing hepatectomy because morbidity and the cost of ablation are lower than for resection. Nevertheless, the conclusion was drawn from small, single-institution retrospective studies with limited follow-ups. The first step to settle the matter is therefore to review the standard results from each treatment based on an extensive survey. It is conceivable that The Liver Cancer Study Group of Japan could provide the most reliable information because it has accumulated data from more than 30,000 patients over three decades (8). After classifying the patients
according to tumor status and hepatic reserve, a total of 12 047 patients (8010 underwent surgery and 4037 underwent PEI) with HCCs smaller than 5 cm were analyzed with a median follow-up of about 8 years. In two-thirds of the patients, surgery achieved a significantly higher overall survival than did PEI; the 5-year survival rates following surgery were higher, by from 19 to 34% among various subgroups, than those following PEI. In the other third, the survival rates after surgery were non-significantly higher than or comparable to those after PEI. It therefore appears to be highly questionable whether the impact on survival is comparable between PEI and surgery, based on the results from such a nationwide case-control study with a sufficient follow-up. A previous attempt at a randomized comparison, involving more than 10 leading hospitals in Japan, failed to reach the predefined sample size owing to unexpectedly poor entry of patients, which had seemed to be influenced by doctors’ intentions. Hence at present this issue cannot be resolved.

Both case-control and randomized studies have clarified the superiority of RFA over PEI in technical and short-term respects. However, whether patients with small HCC are more likely to benefit from RFA than PEI is unknown. Because the most important endpoint is a patient’s survival, evidence of better long-term tumor control and prognosis is needed to justify the routine clinical use of RFA. Primary prevention and recurrence control of HCC is the clinical priority (9) and we are approaching this goal.

References