

Comparison of high-intensity focused ultrasound therapy and radiofrequency ablation for recurrent hepatocellular carcinoma

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Hepatocellular carcinoma (HCC), which accounts for more than 90% of primary liver cancer, is a major health problem worldwide, and is the third most common cause of cancer-related death. It is the fifth most prevalent cancer in men and the seventh in women (1-3). The prognosis for untreated HCC is generally poor, and curative treatments consist of surgical resection, radiofrequency ablation (RFA), and liver transplantation (1-3).

Technical advances in surgery for HCC have improved the survival of HCC patients considerably during recent years. However, only 20% of HCC patients are amenable to surgical resection on presentation (4-6). Locoregional ablative therapies, such as RFA, percutaneous microwave ablation, cryoablation, transcatheter arterial chemoembolization (TACE), and percutaneous ethanol injection offer good alternatives to resection for HCC patients (7).

RFA therapy, an alternative modality to percutaneous ethanol injection, has been widely used as a curative treatment for HCC. Currently, RFA is considered the most promising locoregional treatment for HCC. This modality induces coagulative necrosis and tissue desiccation by delivering high-frequency alternating current via electrodes placed within tissues (7-9). RFA therapy for HCC is primarily accomplished by a percutaneous approach, although open laparoscopic or thoracoscopic approaches can also be used (7-9). RFA provides a valuable treatment option for unresectable HCC. As advances in RFA therapy for HCC continue to be made, it is gradually being performed in patients with resectable HCC, as well as in our country (Japan) (8,9). In addition, RFA is a repeatable procedure because it is less invasive than surgical resection, and it can be safely performed in elderly patients with

potentially comorbid diseases (7,9,10). However, there are several limitations associated with RFA for HCC despite its many potential favorable effects. These limitations include a limited ablation volume, technical limitations, expected complications dependent on tumor location, the heat sink effect, and tumor seeding (11,12).

High-intensity focused ultrasound (HIFU) ablation is an extracorporeal noninvasive ablation mode using focused ultrasound energy, which is capable of causing coagulative necrosis of the targeted HCC via intact skin without the need for surgical incision or insertion of instruments (13,14). This ablation uses a unique frequency of ultrasound waves of 0.8-3.5 MHz, which can be focused at a distance from the therapeutic transducer (13,14). HIFU can provide a potential therapeutic method for the precise ablation of entire liver tumors without damaging vital structure. HIFU also offers the first completely non-invasive approach for HCC and is therefore a promising locoregional treatment modality. Recently, HIFU has been receiving increasing interest for the management of liver tumors (13-15). However, at present, data on the long-term outcome of this treatment are limited. There have been several reports regarding the comparison between TACE plus HIFU and TACE (*Table 1*) (13,16,17), and whether HIFU obtains a survival benefit similar to that of RFA for patients with HCC remains unclear.

In this issue of *Annals of Surgery*, Chan *et al.* demonstrated in their retrospective comparative study, including patients with recurrent HCC, that with a median follow-up period of 27.9 months, the 1-, 2-, and 3-year disease-free survival rates were 37.0%, 25.9%, and 18.5%, respectively, for the HIFU group, and 48.6%, 32.1%, and 26.5%, respectively, for the RFA group (P=0.61).

Table 1 Reports of clinical studies of comparison between TACE plus HIFU and TACE alone (reported in English)

Author/ Country	Year	Treatment	No. of patients	Tumor size	PVTT (yes)	ORR	OS rate (%)	
							1 year	3 years
Feng <i>et al.</i> (13)/China	2005	TACE plus HIFU	24	10.0 cm (mean)	33%	21 (87.5%) [#]	42.9 [#]	NA
		TACE	26	11.3 cm (mean)	50%	11 (42.3%)	0	NA
Li <i>et al.</i> (16)/China	2010	TACE plus HIFU	44	NA	NA	72.8% [#]	72.7 [#]	50.0 [#]
		TACE	45	NA	NA	44.5%	47.2	2.8
Lin <i>et al.</i> (17)/China	2012	TACE plus PVE plus HIFU	32	5.1-12.3 cm (range)	40.6%	25.0%	56.3 [#]	9.3 [#]
		TACE plus PVE	36	4.0-15.3 cm (range)	38.9%	8.3%	30.6	0

TACE, transcatheter arterial chemoembolization; HIFU, high-intensity focused ultrasound ablation; PVTT, portal vein tumor thrombus; ORR, objective response rate; PVE, portal vein embolization; OS, overall survival; #, statistically significant; NA, not available

Additionally, the 1-, 2-, and 3-year overall survival rates were 96.3%, 81.5%, and 69.8%, respectively, for the HIFU group, and 92.1%, 76.1%, and 64.2%, respectively, for the RFA group (P=0.19). There was no hospital mortality in the HIFU group, whereas two deaths occurred in the RFA group. They concluded that using HIFU for recurrent HCC is safe and promising. Although their study was retrospective in nature and had a small sample size, it appears to be a novel and well-characterized study. In their article, they also described the following three advantages of HIFU therapy compared with RFA: (I) extracorporeal conformal therapy of HIFU, indicating no surgical exposure of this therapy; (II) tumor seeding along the needle tract, which often occurs in RFA therapy for HCC, is unlikely to occur and (III) avoidance of targeted tumor puncturing.

In terms of treatment efficacy of HIFU, Chan *et al.* reported that the complete ablation rate was greater than 80% in the HIFU group, which is slightly lower than that of RFA in previous reports (8,9,18). This may be due to the small number of patients in whom they performed HIFU therapy. With sufficient experience in clinical practice for HIFU therapy, the results of treatment efficacy of HIFU for HCC will improve. Notably, the rate of procedure-related morbidity in the HIFU group tended to be lower than that in the RFA group in their study [2 (7.4%) out of 27 patients in the HIFU group *vs.* 25 (22.4%) out of 76 patients in the RFA group, P=0.06] and the hospital mortality rate was 0% in the HIFU group. Their results indicated that HIFU therapy for recurrent HCC was a safe procedure. In Japan, the proportion of elderly patients with HCC and their average age is increasing. In general, elderly patients have a high incidence of comorbid diseases and are considered high-risk patients for treatment-related complications (10). Safety in HCC therapy is an essential issue, as well as

treatment efficacy.

In view of previous studies regarding HIFU for HCC, there are some difficulties that need to be overcome before HIFU can be used in everyday clinical practice (19). The main limitation to clinical application of HIFU is the fact that ablation of large tumors is still time consuming [median total operating time: 151 min (range, 24-360 min)], as reported by Chan *et al.* in this issue of *Annals of Surgery* (15,19,20). In contrast, the duration of a single ablation of RFA is approximately 12 min for the 3-cm electrode of the cool-tip needle (Radionics, Burlington, MA, USA) (8). This may be problematic, especially in patients with a poor physical condition. With technical improvement, the treatment time of HIFU could be gradually reduced in the future. Another challenge in HIFU for HCC therapy is the difficulty in targeting and monitoring because the liver is subject to respiratory movements. The motion of the liver can cause misdirected ultrasound energy, which could potentially result in damage of normal tissue and incomplete tumor ablation. In addition, in cases of HCCs located just behind the ribs, ultrasound energy cannot be easily transmitted through the overlying bone structures (20). Reflection of ultrasound beams by the ribs may cause damage to the bone and adjacent liver tissue (14,20). Therefore, novel technologies in HIFU therapy for HCC should be investigated to overcome these problems.

In conclusion, although there are several difficulties in HIFU therapy for HCC in clinical practice, Chan *et al.* showed in their comparative study of HIFU and RFA that HIFU therapy for recurrent HCC is a safe and promising procedure. With further technical advances, this treatment can be a first line non-invasive ablative therapy for unresectable HCC. Further clinical evidence of this therapy is expected.

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