Therapeutic effect of high-intensity focused ultrasound combined with transarterial chemoembolisation for hepatocellular carcinoma <5 cm: comparison with transarterial chemoembolisation monotherapy—preliminary observations

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Objective: To retrospectively compare the therapeutic effects of combined high-intensity focused ultrasound (HIFU) and transarterial chemoembolisation (TACE) with TACE alone for the treatment of non-advanced hepatocellular carcinomas (HCCs) <5 cm.

Methods: We retrospectively reviewed the tumour responses of 32 HCCs of 25 patients who underwent combined HIFU and TACE, and 46 HCCs of 32 patients who underwent TACE only. The mean follow-up observation of the TACE+HIFU group was on average 31 months and that of the TACE group was 33 months. Those patients who had undergone any other treatment modality (including systemic chemotherapy) during the follow-up observation period were excluded. The therapeutic effects were classified according to the modified Response Evaluation Criteria In Solid Tumors (mRECIST): complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD). Additionally, we defined CR', PR', SD' and PD' as the therapeutic effects ''per tumour''.

Results: The disease control rate calculated using the RECIST criteria (CR+PR+SD/All) was 48% in the HIFU+TACE group and 47% in the TACE group ($p=0.78$, Fisher's exact test). The disease control rate ''per tumour'' (CR'+PR'+SD'/All) was 78% in the HIFU+TACE group and 54% in the TACE group ($p=0.035$, Fisher's exact test). In the HIFU+TACE group, no HIFU-related complications requiring treatment were observed. The median survival time was 57 months in TACE+HIFU group and 36 months in the TACE group ($p=0.048$).

Conclusion: This preliminary study shows that the combination therapy of HIFU and TACE is more effective than TACE monotherapy for treating HCCs <5 cm.

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Primary liver cancer is the fourth leading cause of the cancer death worldwide. According to the statistics published by the National Statistical Office of Korea, 22.7 in 100 000 persons die of liver cancer per year, and this is the second highest cancer death rate after lung cancer [1]. Hepatocellular carcinoma (HCC) is the most frequent cancer among the primary liver cancers, accounting for approximately 75% of all the cases of liver cancer in the Republic of Korea. The prognosis of HCC is poor with a 5 year survival rate of approximately 23.9% [1–3]. The best treatment method for HCC is liver transplantation, but it is difficult to obtain a donor. The treatment modalities other than transplantation include resection, transarterial chemoembolisation (TACE) and direct cauterisations such as radiofrequency ablation (RFA), laser ablation, cryotherapy, microwave therapy, high-intensity focused ultrasound (HIFU), and others [4–10].

Among the non-surgical treatments, TACE has been performed most widely, and combined therapies of TACE with other local treatment methods have been attempted to increase the treatment effect. Studies on the combination of TACE with percutaneous alcohol injection or combination therapy with TACE and RFA have shown better treatment outcomes than those of TACE monotherapy [7, 8]. Some studies have reported that TACE and HIFU combination therapies for advanced liver cancers have shown good outcomes [9, 10].

HIFU is a non-invasive treatment method that induces coagulation necrosis of the target tissues *in vivo* by ultrasound waves without injuring the adjacent normal tissues [11]. The ultrasound waves treat the target solid tumours by (1) the heating effects of the high (>80°C) temperature that induce coagulation necrosis and (2) ''acoustic cavitation'', which is the formation and

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collapse of bubbles in liquid that is irradiated by intense ultrasound, and this induces necrosis of the tissues [12].

Despite the fact that the TACE and HIFU combination therapy for advanced HCCs has already shown good outcomes, there have been no studies that have compared TACE monotherapy with TACE and HIFU combination therapy for medium-sized HCCs. In this current study, we assessed the treatment outcomes of TACE monotherapy and TACE + HIFU combination therapy for non-advanced HCCs <5 cm diameter.

Methods and materials

Patients

This study was a retrospective analysis of all patients who underwent HIFU treatment for HCC. Our institutional ethics committee did not require its approval or informed consent for the retrospective component of our study. However, an informed consent form was obtained from all patients. Among the HCC patients treated with TACE and HIFU combination therapy at our hospital from January 2006 to February 2009, 25 patients (32 HCC tumours) who met the following inclusion criteria were selected as the TACE and HIFU combination therapy group (the TACE + HIFU group). The criteria were: (1) total number of tumours ≤3; (2) tumour size <5 cm; (3) no portal vein thrombosis; and (4) available imaging follow-up studies for at least 1 year after the first treatment with TACE. Those patients who had undergone other treatments such as surgery during the follow-up observation period were excluded from the study. Three patients who had undergone hepatic lobectomy prior to the HIFU procedure were excluded.

Among the HCC patients treated with TACE for the first time at our hospital from January 2006 to December 2007, 32 patients (46 HCC tumours) who met the following inclusion criteria were selected as the TACE monotherapy group (TACE group). The criteria were: (1) total number of tumours ≤3; (2) tumour size <5 cm; (3) no portal vein thrombosis; and (4) available imaging follow-up studies for at least 1 year after the first treatment with TACE. Those patients who had undergone any other treatment modality including systemic chemotherapy during the follow-up observation period were excluded. All the study data were retrospectively collected and assessed.

Transarterial chemoembolisation procedures

TACE was performed in all patients by one interventional radiologist who had more than 10 years of clinical experience. After puncture of the right femoral artery, 5-F angiographic catheters were introduced to perform coeliac or common hepatic arteriography. Arteries feeding the HCC were selected with a microcatheter. An emulsion of iodised oil (Lipiodol®; Andre Guerbet, Aulnay-sous-Bois, France) and doxorubicin hydrochloride (Adriamycin RDF®; Ildong Pharmaceutical, Seoul, Republic of Korea) was administered in the feeding vessels. An emulsion of 1–10 ml of iodised oil and 10–40 mg of doxorubicin hydrochloride was used according to the tumour size. Thereafter, absorbable gelatin sponge particles (Gelfoam®; Upjohn, Kalamazoo, MI), which were 1 mm in diameter and which had been soaked in a mixture of mitomycin C (Kyowa Hakko Kogyo, Tokyo, Japan) and 10 ml of non-ionic contrast material, were administered into the feeding vessels until stasis of arterial flow was achieved. Post-embolic coeliac or common hepatic arteriography was performed to confirm no viable tumour or additional feeding artery existed.

High-intensity focused ultrasound procedure

HIFU ablation was always performed after TACE treatment. For all the patients, colonic irrigation was performed for 3 days prior to the procedure, and this was done to protect the intestine located in front of the treatment area. General anaesthesia was necessary during HIFU treatment to prevent the patient from experiencing intolerable pain and to ensure immobilisation. A HIFU system (Chongqing Haifu, Chongqing, China) was used for all treatments, and the treatments were done under real-time ultrasound guidance. Probes with a 150 mm diameter, a 135 mm focal distance and a 0.8 MHz output were used. The ultrasound intensity was adjusted to between 100 and 400 W cm^2 according to the echogenic change of the tumour. The abdominal wall of the patient was completely immersed in cold water and the temperature of the water was controlled automatically by setting the temperature of the water influxed from the outside at <10 °C. During the surgery, a water ball was made from surgical gloves and it was placed in between the probe and the abdominal wall in order to completely compress the abdomen of the patient. This was done to reduce the risk of perforation of the intestines by moving the intestine located in front of the pancreas to other areas. During surgery, the probe was placed away from the abdominal wall and the skin condition was examined to prevent burns. To prevent injury to the stomach located around the treatment area, 300–500 ml cold saline was injected through a nasogastric tube, and any potential haemorrhage due to mucosal injury was monitored by frequently checking the colour of the gastric juice.

The average period of the HIFU procedure, which was the duration that the ultrasound waves were emitted for actual treatment, was 61 min (range 23–272 min). In 10 patients, the procedure was performed without artificial pleural effusion. In 15 patients, the procedure was performed after injecting artificial pleural effusion fluid with normal saline, and the volume was on average 787 cm^3 (range 500–1000 cm^3).

Analysis of the results and follow-up observation

Follow-up imaging examinations, including CT and MRI, were performed to detect evidence of residual or local recurrent tumour in the treated lesions, to assess the changes in tumour size with time and to monitor the development of new hepatic lesions. CT imaging was performed before TACE or the HIFU treatment, and at 2 weeks and 3, 6, 9, 12, 18 and 24 months after the HIFU or

the TACE treatment. CT scans were obtained with a 16-slice multidetector CT imager (LightSpeed®; GE Healthcare, Milwaukee, WI). For the contrast-enhanced images, patients were administered 150 ml of iopamidol solution (Ultravist® 370; Schering, Berlin, Germany) by means of a power injector at a rate of 2–3 ml s^{-1}. All the patients in the TACE + HIFU group and 6 of the 32 patients in the TACE group underwent contrast-enhanced MRI examinations with a 1.5 T imager (Signa®; GE Healthcare) before and after treatment.

In the two groups, the tumour size changes were assessed by comparing the earliest imaging tests (CT or MRI) obtained just before the first TACE with the most recent imaging tests. All the images were analysed by two experienced radiologists (STH and SEJ, with 20 and 15 years of experience in clinical CT, respectively) who were blinded to the treatment methods, and a consensus was reached for each patient. The treatment outcomes were assessed in two ways: per patient and per individual tumour. For assessment of the treatment outcomes per patient, the modified Response Evaluation Criteria In Solid Tumors (mRECIST) were used [13]. These criteria assess the treatment response through the summation of the longest diameters of all the arterial enhancing lesions. A HCC showing no arterial phase enhancement was defined as a complete response (CR), those with the viable portion reduced by >30% were a partial response (PR), those with the viable portion increased by >20% or where there newly developed lesions were progressive disease (PD) and the rest were assigned as stable disease (SD). In addition, the disease control rate was defined as (CR+PR+SD)/(CR+PR+SD+PD). For the assessment of the treatment outcomes per tumour, we also used the mRECIST criteria, but the diameter of each treated tumour was assessed, and not the ''summation''. For those patients with newly detected lesions, if the lesions were >1 cm away from the old lesions, then they were considered as new masses, while new lesions that developed within 1 cm were considered as local tumour progression or local recurrence.

Safety assessment

After HIFU treatment, hepatic function tests were checked daily for 1 week. Side effects that related to HIFU, including skin burn, abdominal pain, rib fracture, jaundice, bleeding and gastrointestinal perforation, were monitored in each patient by one observer (SHC).

Statistical analysis

Statistical analysis was performed using SPSS® software (SPSS Inc., Chicago, IL). The treatment outcomes and the disease control rates between the two groups were compared by using Fisher's exact test in a 2×2 table. The survival was estimated from the date of initial treatment. No patients were lost to follow-up. A cumulative survival rate was evaluated by using the Kaplan–Meier method, in which the difference between the treatment groups was calculated by using a log-rank test. A p-value <0.05 was regarded as statistically significant.

Results

Comparison of the patient groups

The TACE + HIFU group included 25 patients (18 males and 7 females) and the TACE group included 32 patients (23 males and 9 females). The age of the TACE + HIFU group was on average 57 years (range 44–67 years) and that of the TACE group was on average 65 years (range 43–89 years). In the TACE + HIFU group, the numbers of patients corresponding to the Child–Pugh classifications A and B were 21 patients and 4 patients, respectively, and those for the TACE group were 27 patients and 5 patients, respectively. None of the patients in either group were Class C. The size of the HCCs in the TACE + HIFU group was on average 3.2 cm (range 0.6–5.0 cm), and that of the TACE group was 2.7 cm (range 0.5–5 .0 cm). The mean follow-up period of the TACE + HIFU group was 31 months (range 12–54 months) and that for the TACE group was also 31 months (range 13–48 months). The average frequency of the HIFU procedure of the TACE + HIFU group was 1.3 times (range 1–3 times). The average frequency of the TACE procedure of the TACE + HIFU group was 9.7 times (range 2–20 times) and that of the TACE group was 7.5 times (range 3–14 times). There were statistically significant differences in the patients' ages, tumour sizes and the number of TACE sessions between the two groups (Table 1).

Tumour response

Per patient

In the TACE + HIFU group, the distribution of 25 patients' treatment responses was as follows: 5 patients (20%) had a CR, 2 patients (8%) had a PR, 5 patients (20%) had SD and 13 patients (52%) had PD. The disease control rate was 48% (Figure 1). For the distribution of the treatment responses of the 32 patients in the TACE group, 9 patients (28%) had a CR, 2 patients (6%) had a PR, 4 patients (13%) had SD and 17 patients (53%) had PD. The disease control rate was 47%. There was no statistically significant difference in the treatment response between the two groups (Table 2).

Per tumour

The distribution of the 32 tumours in the TACE + HIFU group was as follows: 16 tumours (50%) showed a CR, 3 tumours (9%) showed a PR, 6 tumours (19%) showed SD and 7 tumours (22%) showed PD. The disease control rate was 78% (Figure 2). The distribution of the 46 tumours in the TACE group was as follows: 19 tumours (41%) showed a CR, 2 tumours (4%) showed a PR, 4 tumours (9%) showed SD and 21 tumours (46%) showed PD. The disease control rate was 54%. The disease control rate of the TACE + HIFU group was significantly higher ($p=0.035$; Table 3).

Table 1. Characteristics

Characteristics	TACE + HIFU group (n=25)	TACE group (n=32)
Age (years; mean ± standard deviation)[a]	56±7.2	65±10
Sex (male/female)	18/7	23/9
Child–Pugh Class (A/B/C)	21/4/0	27/5/0
Number of lesions (mean ± standard deviation)	1.4±0.65	1.5±0.67
Maximal diameter of lesion (cm; mean ± standard deviation)[a]	3.2±1.3	2.7±1.2
TACE session number (mean ± standard deviation)[a]	9.7±4.7	7.5±3.2
Follow-up period (months; mean ± standard deviation)	31±13	31±9.3

HIFU, high-intensity focused ultrasound; TACE, transarterial chemoembolisation.
[a]p<0.05.

Survival

Survival rates were better in thte TACE + HIFU group than in the TACE group (Figure 3). Cumulative survival rates were better in the TACE + HIFU group than in the TACE only group (p=0.047). The median survival time was 57 months for patients treated in the TACE + HIFU group and 36 months for patients treated in the TACE group. The difference in mean survival time between the two groups was statistically significant (p=0.048).

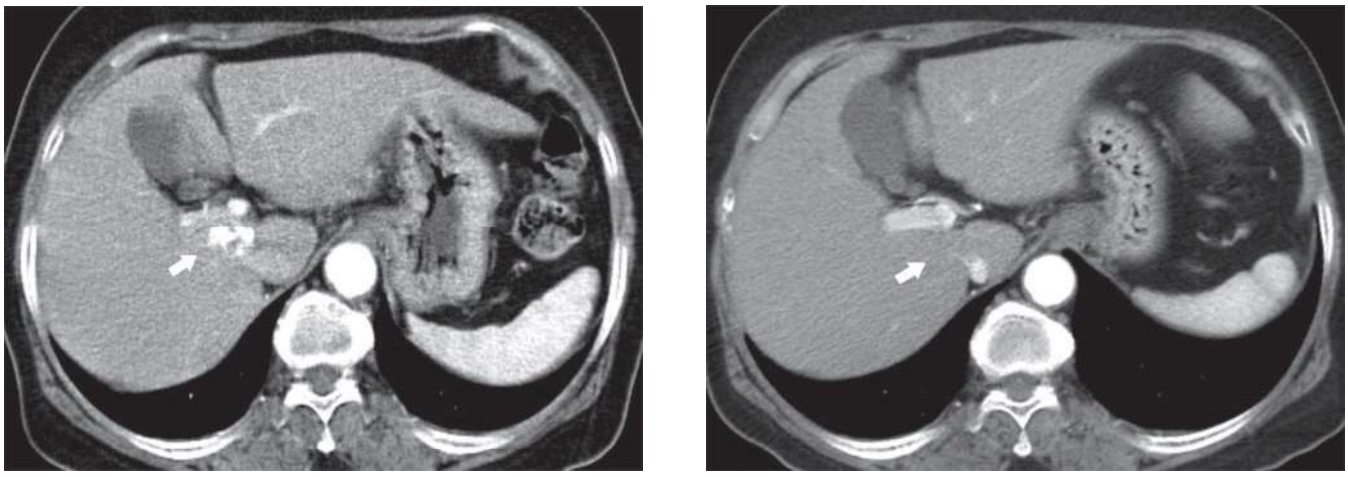
Complications

After the HIFU procedure, one patient developed right pleural effusion. However, it resolved with only conservative treatment. Two patients had skin burn caused directly by HIFU, although these were not severe. One patient had a low-grade fever that persisted for approximately 4 days after HIFU. Four patients presented with pain after treatment, which was resolved by analgesics. There were no major complications associated with the HIFU procedure that required treatment. No dilatation of the common bile duct and portal vein thrombosis was visible at follow-up imaging. After TACE, all patients had transient impairment of hepatic function. No patients had hepatic failure, abscess or renal failure caused by TACE.

Discussion

Several studies showing the good outcomes of HIFU for HCC have already been reported [9, 10, 14, 15]. Wu et al [9] and Li et al [10] compared TACE monotherapy and TACE + HIFU combination therapy in a prospective randomised study, and they reported a reduction in tumour size and a better 5 year survival rate with the TACE + HIFU combination therapy. However, the patients in the two studies were in an advanced stage (>Stage IV A) and were inoperable because of multicentricity, tumour adjacency to major vessels and severe liver cirrhosis [9] or because their tumours were >5 cm [10]. Since the effectiveness of TACE monotherapy for advanced stage disease has been proven, it is not difficult to predict that combination therapy would also be more effective than TACE monotherapy for non-advanced medium-sized tumours. However, no direct comparison studies have been reported.

Li et al [10] compared TACE + HIFU combination therapy with TACE monotherapy for HCCs >5 cm. The total effective rate (CR+PR/All) of the TACE + HIFU



(a) (b)

Figure 1. Example of a complete response: a 60-year-old female with hepatocellular carcinoma (HCC) who underwent seven sessions of transarterial chemoembolisation (TACE) and one session of high-intensity focused ultrasound (HIFU). (a) Between the initial TACE and the first HIFU, contrast-enhanced CT of the arterial phase shows HCC with Lipiodol uptake in the caudate lobe of the liver (arrow). (b) After 52 months from the initial HIFU (after seven sessions of TACE and one session of HIFU ablation), the tumour disappeared completely (arrow).

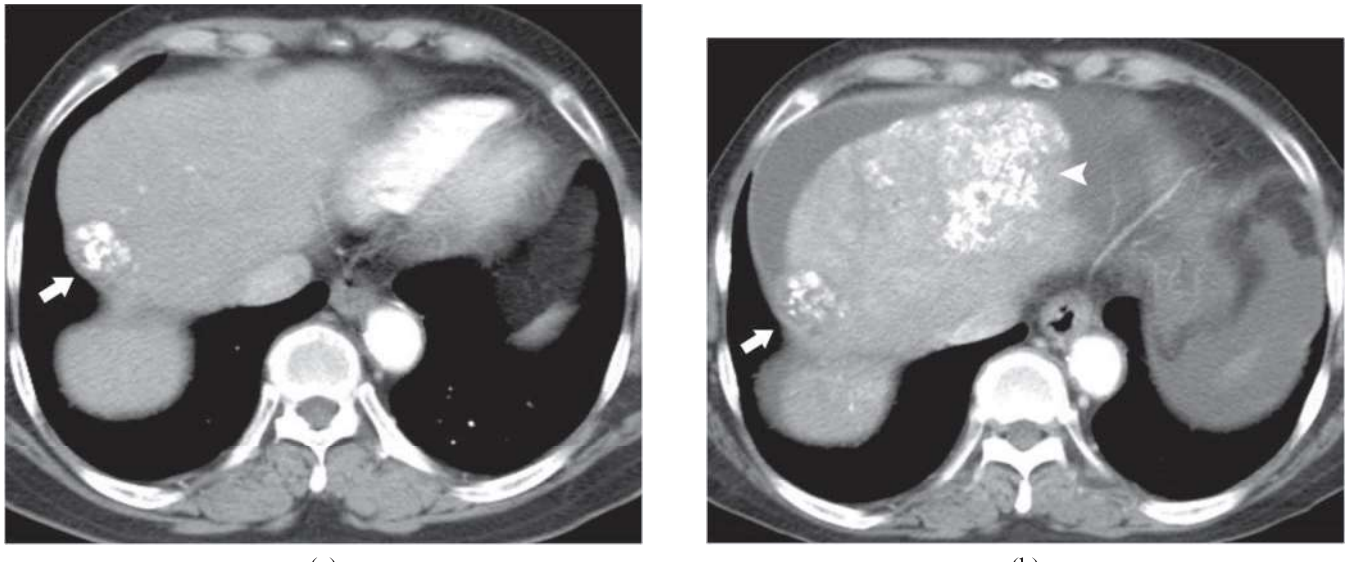
Table 2. Tumour responses (individual)

Responses	TACE + HIFU group (n=25)	TACE group (n=32)
CR	5 (20%)	9 (28%)
PR	2 (8%)	2 (6%)
SD	5 (20%)	4 (13%)
PD	13 (52%)	17 (53%)
Disease control rate (CR+PR+SD/All)[a]	12/25 (48%)	15/32 (47%)

CR, complete response; HIFU, high-intensity focused ultrasound; PD, progressive disease; PR, partial response; SD, stable disease; TACE, transarterial chemoembolisation.
[a]p=1.

group was 72.8%, while that of the TACE group was 44.5%: the total effective rate was significantly higher in the TACE + HIFU group [10]. However, in our study, the disease control rate of the two groups was shown to be 48% and 47%, respectively. Although not presented in the results, when the total effective rate was calculated, it was found to be 28% and 34% for the two groups, respectively; disappointingly, the TACE + HIFU group showed a worse outcome, even though this was not statistically significant (p=0.78). Li et al [10] calculated the total effective rate by using imaging tests performed 4–6 weeks after the beginning of treatment. On the other hand, our imaging tests were done with at least 1 year of follow-up (average 31 months), so we can speculate that the different follow-up periods affected the results of the studies. For our cases, the average frequency of performing a HIFU procedure was 1.3 times, which was less than the 1.66 times of Li et al, and this also might have affected the results. In addition, it should be considered that the data from our study were collected during the early stage of the introduction of HIFU treatment equipment.

In an attempt to properly compare the treatment efficacies, we followed up the individual tumours treated with HIFU, and not per patient. It was found that the disease control rate ''per tumour'' was 78% (the combination group) and 54% (the TACE monotherapy group); the disease control rate per tumour was significantly higher in the TACE + HIFU group than in the TACE group. The combination therapy was not more effective than the TACE monotherapy on the per patient analysis, but it was more effective on the per tumour analysis; this discrepancy can be explained by the following reasons. For a patient treated for HCC who achieved a CR state and in whom no new lesions developed, that patient was designated as a CR either per patient or per tumour. However, if the treated tumour itself achieved a CR state but new lesions developed, then this was classified as a CR per tumour but as PD per patient. The chance of new tumour formation was relatively high in the TACE + HIFU group because of the previously mentioned longer disease duration.



(a) (b)

Figure 2. Example of a complete response ''per tumour'', but a progressive disease ''per patient'': a 64-year-old female with hepatocellular carcinoma (HCC) who underwent seven sessions of transarterial chemoembolisation (TACE) and one session of high-intensity focused ultrasound (HIFU). (a) After four sessions of TACE and before the first session of HIFU, contrast-enhanced CT of the arterial phase shows a HCC with Lipiodol uptake with a viable portion in S8 of the liver (arrow). (b) After 24 months from the initial HIFU (after seven sessions of TACE and one session of HIFU ablation), the tumour itself shows no arterial enhancement, yet a new infiltrative HCC (arrowhead) developed in the left lobe.

Table 3. Tumour responses (tumour)

Responses	TACE + HIFU group (n=32)	TACE group (n=46)
CR′	16 (50%)	19 (41%)
PR′	3 (9%)	2 (4%)
SD′	6 (19%)	4 (9%)
PD′	7 (22%)	21 (46%)
Disease control rate (CR′+PR′+SD′/All)[a]	19/32 (78%)	21/46 (54%)

CR′, complete response per tumour; HIFU, high-intensity focused ultrasound; PD′, progressive disease per tumour; PR′, partial response per tumour; SD′, stable disease per tumour; TACE, transarterial chemoembolisation.
[a]p=0.035.

Our study had a limitation mainly related to the study design. Our study was a retrospective study, so the frequency of TACE and the characteristics such as the age distribution or tumour size of the two subject groups were different; that is to say, this is not a true two-arm study. The two groups statistically differ from each other significantly in age, in the number of TACE sessions and also in tumour size. Despite this limitation of an unplanned retrospective analysis, this study has significance because it suggested that the TACE + HIFU combination therapy is more effective than TACE monotherapy not only for advanced HCCs, but also for relatively small HCCs. The results of our study show evidence to support the hypothesis that TACE followed by HIFU ablation would be better than TACE alone in patients with non-advanced HCC. First, the median survival time and cumulative survival rate for the TACE + HIFU group were much greater than for the TACE group. Although the 5 year clinical benefits of HIFU treatment are still unproven, the results suggest that HIFU treatment may play an important role in the treatment of HCC. Second, the treatment response in the TACE + HIFU group was better than that in the TACE group. These results could be attributed to a greater tumour necrosis. TACE has been widely used to treat HCC, and TACE can be considered as the first choice of treatment for patients refusing surgery or for those who are unsuitable for an operation. When treating with TACE, other local treatments (such as RFA) are often combined with it to maximise the treatment effect. Our study proved that HIFU can be another option for combined treatment with TACE.

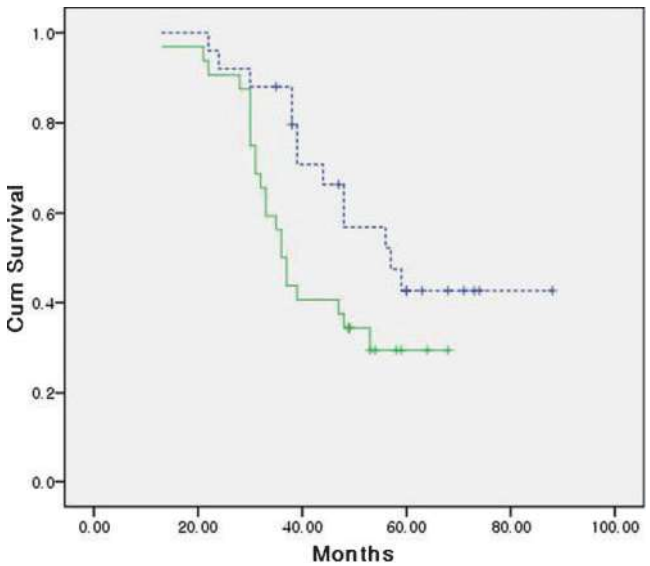


Figure 3. Cumulative survival curves, calculated with the Kaplan–Meier method, for patients treated with either transarterial chemoembolisation (TACE) and high-intensity focused ultrasound (HIFU; dashed line, n=25) or TACE alone (solid line, n=32). Patients treated with TACE and HIFU had higher survival rates (p=0.047, log-rank test) than those treated with TACE alone. The median survival time was 57 months in the TACE + HIFU group and 36 months in the TACE group (p=0.048).

In summary, our preliminary results suggest that the TACE + HIFU combination therapy showed a better outcome for treating non-advanced HCCs <5 cm than did TACE monotherapy. To confirm this, randomised controlled studies are required to compare TACE + HIFU combination therapy with other conventional treatment methods.

References

1. Ministry for Health, Welfare and Family Affairs. Annual report of cancer incidence (2005) and survival (1993–2005) in Korea. Seoul, Republic of Korea: Ministry for Health, Welfare and Family Affairs; 2008.
2. Korean National Statistical Office. Annual report on the cause of death statistics. Seoul, Republic of Korea: Korean National Statistical Office; 2009.
3. Park KW, Park JW, Kim TH, Choi JI, Kim SH, Park HS, et al. Five-year survival analysis of a cohort of hepatocellular carcinoma patients who were treated at the National Cancer Center, Korea. Korean J Hepatol 2007;13:530–42.
4. Mazzaferro V, Regalia E, Doci R, Andreola S, Pulvirenti A, Bozzetti F, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med 1996;334:693–9.
5. Poon RT, Fan ST, Lo CM, Liu CL, Wong J. Long-term survival and pattern of recurrence after resection of small hepatocellular carcinoma in patients with preserved liver function: implications for a strategy of salvage transplantation. Ann Surg 2002;235:373–82.
6. Llovet JM, Bruix J. Systematic review of randomized trials for unresectable hepatocellular carcinoma: chemoembolization improves survival. Hepatology 2003;37:429–42.
7. Becker G, Soezgen T, Olschewski M, Laubenberger J, Blum HE, Allgaier HP. Combined TACE and PEI for palliative treatment of unresectable hepatocellular carcinoma. World J Gastroenterol 2005;11:6104–9.
8. Yamakado K, Nakatsuka A, Takaki H, Yokoi H, Usui M, Sakurai H, et al. Early-stage hepatocellular carcinoma: radiofrequency ablation combined with chemoembolization versus hepatectomy. Radiology 2008;247:260–6.
9. Wu F, Wang ZB, Chen WZ, Zou JZ, Bai J, Zhu H, et al. Advanced hepatocellular carcinoma: treatment with high-intensity focused ultrasound ablation combined with transcatheter arterial embolization. Radiology 2005;235:659–67.

10. Li C, Zhang W, Zhang R, Zhang L, Wu P, Zhang F. Therapeutic effects and prognostic factors in high-intensity focused ultrasound combined with chemoembolisation for larger hepatocellular carcinoma. Eur J Cancer 2010;46: 2513–21.
11. Kennedy JE. High-intensity focused ultrasound in the treatment of solid tumours. Nat Rev Cancer 2005;5:321–7.
12. Dubinsky TJ, Cuevas C, Dighe MK, Kolokythas O, Hwang JH. High-intensity focused ultrasound: current potential and oncologic applications. AJR Am J Roentgenol 2008;190: 191–9.
13. Lencioni R, Llovet JM. Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. Semin Liver Dis 2010;30:52–60.
14. Li YY, Sha WH, Zhou YJ, Nie YQ. Short and long term efficacy of high intensity focused ultrasound therapy for advanced hepatocellular carcinoma. J Gastroenterol Hepatol 2007;22:2148–54.
15. Zhang L, Zhu H, Jin C, Zhou K, Li K, Su H, et al. High-intensity focused ultrasound (HIFU): effective and safe therapy for hepatocellular carcinoma adjacent to major hepatic veins. Eur Radiol 2009;19:437–45.