

First clinical implementation of histotripsy for liver tumors in Japan

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Abstract: Histotripsy is a nonthermal therapy that mechanically disrupts and liquefies tumor tissue by generating focused microbubbles using extracorporeal ultrasound. Following U.S. Food and Drug Administration approval for the treatment of liver tumors in 2023, its clinical use has rapidly expanded. Here, we report the first clinical implementation of histotripsy in Japan, focusing on its safety and feasibility. The first treatment was performed for a 1.8-cm postoperative recurrent hepatocellular carcinoma in segment 8, followed by a second treatment for a 2.5-cm recurrent colorectal liver metastasis in segment 2 after multiple resections of intra- and extra-hepatic metastases. Histotripsy treatment times were 22 and 40 min, respectively. Target tumor coverage was confirmed by intraoperative ultrasonography, and reduced tumor enhancement was confirmed by contrast-enhanced computed tomography performed the day after treatment. The patients were discharged on postoperative days 1 and 2, respectively. No major complications occurred during follow-up to postoperative days 14 and 19, respectively, although both patients experienced mild treatment-related pain and one developed fever. These initial experiences suggest feasibility of implementing histotripsy for liver tumors in Japan.

Keywords: histotripsy, hepatocellular carcinoma, liver metastasis

1. Introduction

Histotripsy is a nonthermal therapy that mechanically disrupts and liquefies tumor tissue by generating focused microbubbles using extracorporeal ultrasound (1). Because it does not require a surgical incision or needle puncture associated with conventional local ablative therapies, histotripsy has been described as an "incisionless" or "non-invasive" local treatment (2). It is expected to provide a new treatment option, particularly for patients with limited tolerance for conventional surgery. In the United States, histotripsy was approved by the Food and Drug Administration for treatment of liver tumors in 2023. It has also recently received the European CE mark, and its clinical application is expanding, although clinical experience remains limited in many countries. In Japan, regulatory approval of the treatment system has not yet been obtained, and no clinical use of histotripsy has been reported to date.

In July 2026, we performed the first histotripsy treatments for hepatocellular carcinoma (HCC) and colorectal liver metastasis (CRLM) in Japan under a specified clinical research protocol. Herein, we report treatment procedures and short-term outcomes through the first outpatient follow-up according to the study protocol.

2. Study protocol

The protocol for this first-in-Japan study (jRCTs052250263) was developed based on the #HOPE4LIVER multicenter study (3), which supported FDA approval of the technology, and previous reviews of histotripsy (4). Major inclusion criteria were as follows: *i*) typical HCC on contrast-enhanced CT or magnetic resonance imaging (MRI) or metastatic liver cancer, with a maximum tumor diameter of ≤ 3 cm; *ii*) no macroscopic vascular invasion or tumor thrombus; *iii*) entire target lesion

clearly visualized by abdominal ultrasonography without obscuration; and *iv*) a Child–Pugh score of ≤ 7 . Patients with significant portal hypertension, active concomitant malignancies, or severe cardiopulmonary disease were excluded.

Patients were admitted on morning of treatment and underwent histotripsy in the operating room in the afternoon. After treatment, they returned to a general ward. Blood tests and contrast-enhanced computed tomography (CT) were performed the following day, and patients were discharged on the same day if no clinically significant abnormalities were identified. Study follow-up was completed at an outpatient visit within 3 weeks after treatment if blood tests and abdominal ultrasonography showed no abnormalities. Adverse events were defined and graded according to Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

Histotripsy procedures were planned according to previously reported protocols (3,4). The operator (T.I.) observed histotripsy procedures at an overseas institution, completed manufacturer-provided training, and obtained certification. Before the first treatment, a simulation was also performed with operating-room nurses, clinical engineers, and anesthesiologists to familiarize the team with patient positioning, device setup, and preparation of degassed water.

The study protocol was approved by the Certified Review Board of Osaka Metropolitan University Hospital (CRB5200004/jRCTs052250263). Written informed consent was obtained from both patients for participation in this clinical trial and for publication of study findings.

3. Case presentation

3.1. Case 1

The first histotripsy treatment was performed for a 1.8-cm recurrent HCC in the dorsal region of segment 8 following robot-assisted posterior sectionectomy. Patient was offered repeat hepatectomy and ablation as conventional curative treatment options and chose histotripsy as a treatment that might impose less physical burden. On day of admission, the patient underwent histotripsy in the operating room under general anesthesia with one-lung ventilation and was placed in the left semidecubitus position. A membrane-covered frame was placed over the treatment area and filled with degassed water. Treatment head of the Histotripsy System (HistoSonics, Plymouth, MN, USA) was immersed in the water, and target lesion was identified. A spherical treatment volume with a 5-mm margin was planned while maintaining adequate clearance from the treatment head. Acoustic voltage was adjusted at the center and vertices of the treatment volume along the X-, Y-, and Z-axes based on visualization of the bubble

cloud and the audible cavitation sound. Treatment was then initiated with a single press of the start button. After dorsal-to-ventral histotripsy, conventional ultrasonography confirmed that the target tumor was encompassed by the treatment area, with increased echogenicity, and showed no immediate complications. General anesthesia was subsequently discontinued (Figure 1, A–F). Total anesthesia time was 250 min, and the histotripsy treatment time was 22 min.

3.2. Case 2

The second histotripsy treatment was performed for a 2.5-cm recurrent CRLM in segment 2 in a patient who had previously undergone multiple surgical treatments for the primary tumor and metastatic lesions, including laparoscopic sigmoidectomy, three open hepatectomies culminating in a right hepatectomy, lymphadenectomy of the hepatoduodenal ligament, right adrenalectomy, and resection of local peritoneal dissemination. No recurrent colorectal cancer other than the liver metastasis was identified by imaging. However, having undergone repeated treatments, the patient felt unable to undergo another surgery or chemotherapy and therefore chose histotripsy. Treatment protocol was similar to that used in the first case, except that the patient was placed in the supine/reverse Trendelenburg position and bilateral high-frequency jet ventilation was used (Figure 1, G–L). Total anesthesia time was 181 min, and the histotripsy treatment time was 40 min.

After treatment, both patients experienced mild pain at the treatment site, which gradually resolved. Blood tests and contrast-enhanced CT performed on the following day showed no evidence of bleeding, bile leakage, or abscess formation. The first patient was discharged on postoperative day 1. The second patient developed fever and was discharged on postoperative day 2.

At follow-up visits on postoperative days 14 and 19, respectively, inflammatory markers and transaminase levels had returned toward baseline, whereas biliary enzyme levels remained elevated in Case 2 (Table 1). No complications, including ascites, portal or hepatic vein thrombosis, bile leakage, or biliary dilatation or stenosis, were detected by abdominal ultrasonography.

4. Discussion

In this initial clinical study, both patients underwent histotripsy with only mild abdominal pain and transient fever, and were discharged after one or two nights of hospitalization. No severe complications were identified at the first outpatient follow-up. These findings suggest that histotripsy can be implemented in Japanese clinical practice according to a protocol based on previous clinical studies.

Regarding safety of histotripsy, a multicenter analysis of 230 patients reported only three Clavien–Dindo grade

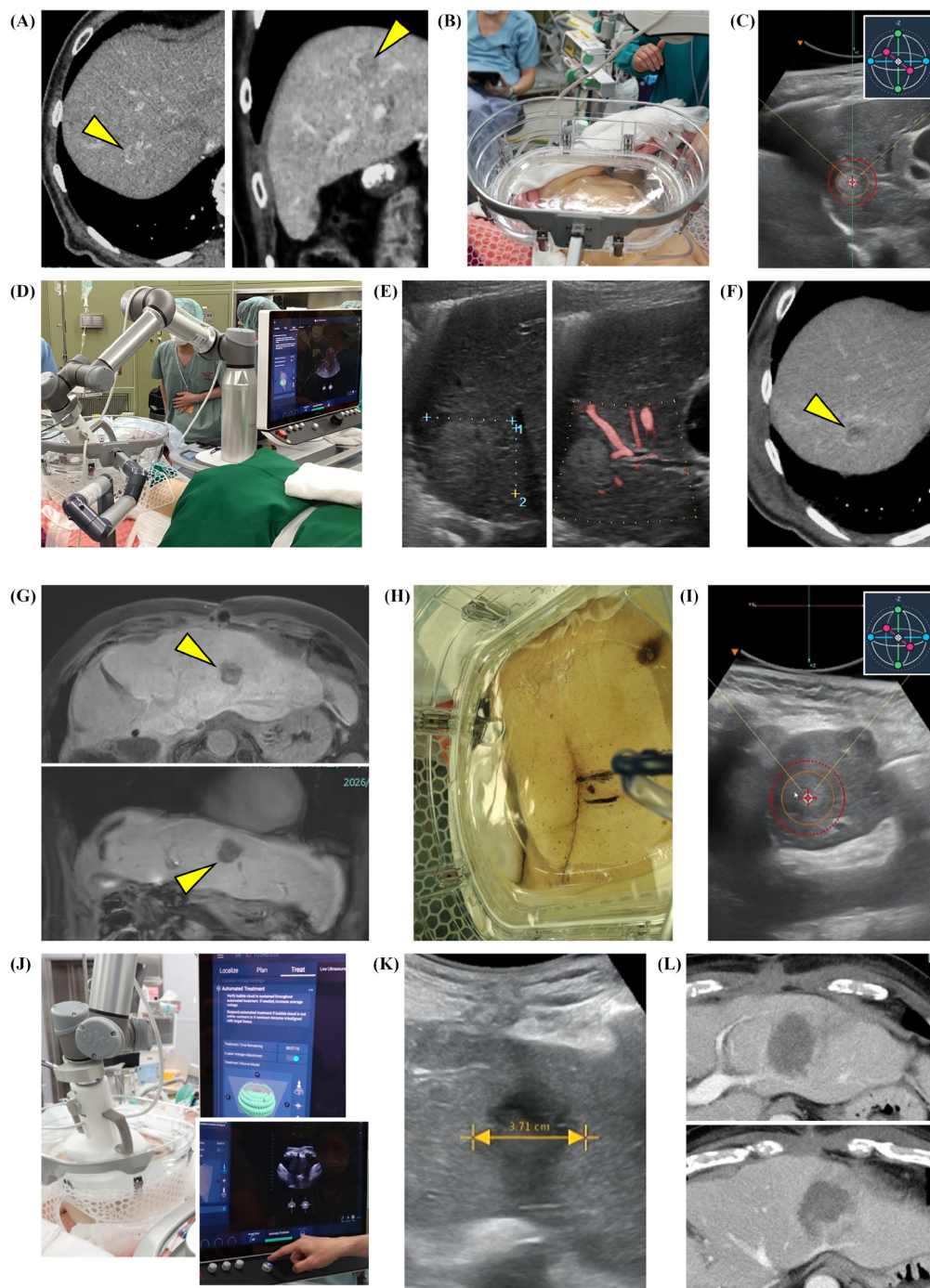


Figure 1. Histotripsy for hepatocellular carcinoma (Patient 1) and colorectal liver metastasis (Patient 2). **Patient 1:** Preoperative contrast-enhanced CT demonstrated a hyperenhancing tumor (arrowhead) in the dorsal region of segment 8 on the arterial-phase axial image (left) and a hypoenhancing lesion on the portal venous-phase coronal image (right) (A). Patient was positioned in the left semidecubitus position, and a membrane-covered frame was filled with degassed water (B). Intercostal ultrasonography using the Histotripsy System was performed to encompass the entire tumor within treatment volume (orange circle) while avoiding the lung, with a planned 5-mm treatment margin (red circle) (C). Histotripsy treatment was then initiated. Treatment volume was 15.3 cm³ and the mean acoustic voltage was 95% (D). Posttreatment ultrasonography demonstrated conversion of planned treatment area into a hyperechoic region (left) while preserving blood flow in the adjacent Glissonean pedicle (right) (E). Arterial-phase contrast-enhanced CT obtained the following day showed reduced tumor perfusion and hypoenhancement of the treated lesion (F). See Supplementary Video 1 (<https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=128>). **Patient 2:** Preoperative gadoxetic acid-enhanced MRI in the hepatobiliary phase demonstrated a hypointense tumor (arrowhead) in segment 2 of the hypertrophied left liver (G). Patient was positioned supine, and the membrane-covered frame was filled with degassed water; the previous hepatectomy scar was visible (H). Treatment volume was planned to avoid the heart (I). After adjustment of the acoustic voltage, histotripsy was initiated by pressing the start button. Treatment volume was 28.6 cm³ and the mean acoustic voltage was 60% (J). Posttreatment ultrasonography demonstrated a 3.7-cm hypoechoic area (K). Contrast-enhanced CT obtained the following day demonstrated a spherical hypoenhancing treatment zone encompassing the tumor. Except for a peripheral wedge-shaped area, arterial inflow to segment 2 (upper) and venous drainage from the segment 2 region into the left hepatic vein (lower) were preserved (L). See Supplementary Video 2 (<https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=129>).

Table 1. Patient demographics and perioperative blood test results

No.	Age (years) /sex	Diagnosis (maximum diameter) and previous surgical treatments	Blood tests	Before histotripsy	POD1	Outpatient Clinic*
1	78/M	HCC (1.8 cm) 1. Robot-assisted right posterior sectionectomy	WBC ($\times 10^3/\mu\text{L}$)	52	108	60
			CRP (mg/dL)	0.03	1.95	0.09
			Alb (g/dL)	4.3	3.5	4.2
			Cre (mg/dL)	1.09	0.85	1.07
			K (mmol/L)	4.1	4.2	4.4
			T-Bil (mg/dL)	0.8	1.1	0.8
			AST (U/L)	25	74	23
			ALT (U/L)	24	32	21
			ALP (U/L)	70	59	88
			γGTP (U/L)	107	81	131
			PT (INR)	1.02	1.09	1.05
2	76/M	CRLM (2.5 cm) 1. Sigmoidectomy 2. Open hepatectomies 3. Open hepatectomy with lymphadenectomy 4. Rt. adrenalectomy for peritoneal dissemination and lymphadenectomy 5. Open hepatectomy and resection of disseminated nodule	WBC ($\times 10^3/\mu\text{L}$)	52	72	57
			CRP (mg/dL)	0.49	3.04	1.19
			Alb (g/dL)	3.8	3.1	3.7
			Cre (mg/dL)	1.35	1.26	1.45
			K (mmol/L)	5.4	4.5	5.1
			T-Bil (mg/dL)	0.5	0.8	0.8
			AST (U/L)	31	568	57
			ALT (U/L)	12	275	45
			ALP (U/L)	156	166	416
			γGTP (U/L)	81	80	655
			PT (INR)	1.04	1.15	1.20

*At follow-up visits on postoperative days 14 for Case 1. and 19 for Case 2. *Abbreviations:* HCC, hepatocellular carcinoma; CRLM, colorectal liver metastasis; POD, postoperative day.

$\geq$ III complications (5). In the #HOPE4LIVER study, which included 47 patients (19 with HCC and 28 with metastatic tumors), pain ($> 22\%$) and pyrexia (12%) were the most common adverse device-related effects (ADEs), indicating that histotripsy is not completely symptom-free (3).

In the second case, the tumor was no longer separately identifiable within the treatment zone on contrast-enhanced CT performed the day after treatment, while marked elevation of transaminases was observed. A recent study by Chan *et al.* (6) similarly reported a median ALT level of approximately 130 U/L on postoperative day 1, with some patients showing levels exceeding 2,000 U/L. The authors suggested that increase in inflammatory cytokines accompanying transaminase elevation may be associated with tumor control; however, whether histotripsy induces an antitumor immune response remains unclear and requires further investigation. Conversely, portal vein thrombosis has been reported as a severe ADE in the #HOPE4LIVER study (3). Therefore, marked postoperative elevation of transaminases and biliary enzymes should be carefully evaluated for possible impaired blood flow or biliary congestion in the remnant liver parenchyma.

In the #HOPE4LIVER study, the 1-year local tumor control rate was 90% in the post-hoc analysis, whereas efficacy rate in the primary assessment was 63.4% (3). This discrepancy suggests that immediate post-treatment imaging may not reliably indicate local tumor control, as the treated area can show variable morphology and enhancement patterns after histotripsy.

Therefore, long-term clinical surveillance with imaging and tumor marker assessments is required to evaluate local tumor control in these two cases. Further randomized controlled studies with longer follow-up are required to determine role of histotripsy in relation to established curative-intent treatments, including surgical resection and thermal ablation, particularly for small HCCs. For liver metastases, it has been hypothesized that histotripsy may induce systemic antitumor immune responses through release of tumor antigens without thermal damage (7). Although reductions in non-targeted tumors have been reported (8,9), whether this potential "abscopal-like effect" can be reproduced remains to be demonstrated.

In conclusion, our first two clinical experiences suggest feasibility of implementing histotripsy for liver tumors in Japan. Further accumulation of cases and long-term follow-up are warranted to clarify its safety, local tumor control, and potential systemic antitumor effects.

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