Editorial

High-intensity focused ultrasound (HIFU) for the treatment of hepatocellular carcinoma: is it time to abandon standard ablative percutaneous treatments?

Claudio Zavaglia[1], Andrea Mancuso[1], Antonella Foschi[1], Antonio Rampoldi[2]

[1]Gastroenterology and Hepatology Department, and [2]Interventional Radiology Department, Ospedale Niguarda, Milano, Italy

Corresponding to: Dr. Claudio Zavaglia, M.D. Ospedale Niguarda Ca' Granda, Struttura Complessa di Gastroenterologia ed Epatologia "Crespi", P.zza Ospedale Maggiore 3, Milano 20162, Italy. Email: claudio.zavaglia@ospedaleniguarda.it.

Submitted Apr 15, 2013. Accepted for publication May 13, 2013.
doi: 10.3978/j.issn.2304-3881.2013.05.02
Scan to your mobile device or view this article at: http://www.thehbsn.org/article/view/2603/3486

Hepatocellular Carcinoma (HCC) is the leading cause of death in patients with cirrhosis (1). Despite recent advances in early detection programs and the diffusion of surveillance protocols in patients with cirrhosis, only 30% to 40% of patients are diagnosed at an early stage and can benefit from radical therapies (1). Surgical resection, liver transplantation or local ablation, either with radiofrequency (RFA) or percutaneous ethanol injection (PEI) are generally considered curative first-line therapeutic options for early-stage HCC. In this setting, in well selected patients, these treatments are associated with 5-year survival rates of 50-70% (1). Among percutaneous ablative treatments, radiofrequency or percutaneous ethanol injection are considered the standard of care for patients with early stage tumors not suitable for surgery (1,2). Although both techniques achieve complete responses in more than 90% of cases with good long-term outcome in tumors <2 cm (1,3), in most instances RFA has replaced multisession PEI due to a significantly better control of the neoplastic disease. The main advantages of image-guided tumour ablation techniques are the widespread availability, the low peri-procedural morbidity and mortality and the short hospital stays (4). However, recurrences occur in the majority of the treated patients (5). Recurrent tumors are frequently treated with a multimodality therapeutical approach and locoregional percutaneous procedures are commonly used in this setting. Data concerning the outcome of patients with recurrences are scanty and difficult to analyze. In a recent retrospective study Kim Y-s *et al.* assessed 10-year outcome of 1,305 CHILD A or B patients, treated with percutaneous RFA as first-line therapy for solitary HCC ≤5 cm or plurifocal HCC (≤3 nodules ≤3 cm) (5). Most of the patients (62%) experienced recurrences that were treated mainly with RFA or TACE with no mortality and major complications in only 2%. The median survival was 75 months and overall actuarial 3-, 5- and 10-yr survival were 77.9%, 59.7% and 32.3%, respectively.

High-intensity focused ultrasound (HIFU) is a relatively novel technique which ensures non-invasive ablation of tumors. Under magnetic resonance imaging (MRI) or diagnostic ultrasound (US) guidance, the ultrasound beam, generated by a high-power transducer, can be directed to the targeted tissue at a selected depth, resulting in a rapid local temperature increase, that, above the threshold of protein denaturation (65-85 °C), induces coagulative necrosis without damaging the surrounding tissue. Over the last decade, several studies have tested the feasibility and safety of HIFU for the treatment of benign and malignant tumors of the prostate, pancreas, liver, breast, kidney, uterus, bone and brain (6,7).

Concerning liver tumours, the main clinical application of HIFU is currently the ablation of hepatocellular carcinoma and liver metastasis from colon and stomach cancers (7,8). The main advantage of HIFU over other conventional thermal ablation techniques such as RFA is that it does not require puncturing the tumor, thereby avoiding the risk of bleeding or seeding of tumor cells along the needle tract. However, several factors limit the clinical applicability of this procedure. First, HIFU equipment is available in only a few centers; Second, the cost is high especially when MRI is used as guidance; Third, HIFU is a time-consuming procedure; Fourth, it requires either

general or epidural anaesthesia.

Chan and his co-workers explored the feasibility of HIFU and survival in patients with intrahepatic recurrences after a first-line therapy with either hepatectomy or RFA (9). In a non-randomized study, they treated 27 patients with HIFU while 76 patients underwent RFA, either percutaneously (n=46) or open (n=30). Inclusion criteria were: patients with CHILD A cirrhosis with monofocal tumor less than 5 cm or plurifocal with less than 3 nodules ≤3 cm. However, selected CHILD B patients were also enrolled and were overrepresented in patients treated with RFA as compared with those who underwent HIFU (32.9% *vs.* 11.1%, P=0.03). Ninety-three % and 72% of patients were males, respectively in the HIFU group or in patients treated with RFA. There was no difference in tumor characteristics between the two groups. In the majority (81%), the recurrence was solitary, with extrahepatic diffusion in 8 (7.7%). Median tumor size was 1.7 cm in the HIFU group and 1.8 cm in the RFA group. HIFU ablation was performed under general anesthesia. Artificial pleural effusion or ascites were created if deemed necessary for improvement in the efficiency of ultrasound transmission. All the patients underwent MRI 1 month after the treatment to assess the efficacy of the therapy. Complete tumor ablation was obtained in more than 80% of both treatment groups (85.2% in the HIFU group and 87.8% in the RFA group). The 3-year survival rates were similar (69.8% in the HIFU group and 64.2% in the RFA group). No difference in survival was observed even after adjustment for the CHILD stage (3-year survival was 70.2% in the HIFU group compared to 64.6% in the RFA group). The morbidity rates were comparable. Skin burns and pleural effusion were the only complications associated with HIFU treatment. No mortality was reported after HIFU but 2 cases of death were related to RFA procedure.

Although the application of HIFU technology in the management of patients with hepatocellular carcinoma is still in its early stages, several studies concerning HIFU treatment of liver tumors have been already reported. In all clinical trials, treated lesions were located in the right hepatic lobe, left lobe, or in both left and right lobes of the liver, and were not candidates for surgical resection, nor suitable for other treatments such as radiofrequency ablation, or percutaneous ethanol injection, because of the size and location of the tumour. As reported for ablative percutaneous treatments, complete ablation of the target region at MRI can be taken to infer histological success (10). The initial experience of HIFU treatment of hepatocellular carcinoma was obtained from researchers in China, using the JC HIFU system, which was also used in the majority of the trials reported. In a study by Wu F *et al.* (11), 55 patients with large HCC (mean tumour diameter of 8.14 cm) and liver cirrhosis received HIFU treatment. No major complications were observed. Despite the size of the tumours, complete ablation rate was high (69.2%). The overall survival rates were 61.5% at 12 months and 35.3% at 18 months. In another study by the same group (12), the efficacy of HIFU combined with chemoembolization was compared with that of chemoembolization alone in 50 patients with advanced HCC. Survival rate was significantly better in patients who underwent combined treatment than in those who received chemoembolization alone. No severe complication was associated with HIFU treatment. In a trial by Li YY *et al.*, 249 patients with surgically unresectable advanced HCC and liver cirrhosis Child A or B were divided into two groups: 151 received HIFU plus supportive treatment, while 30 patients, who decided to try traditional Chinese medicine or did not want any therapeutic modalities were enrolled in the control arm. No major complications were recorded. In the HIFU group, complete and partial response were achieved in 28.5% and 60.3% of cases, respectively. The overall response rate was significantly greater in the HIFU group than in the control group (88.8% *vs.* 16.7%). Moreover, in the HIFU arm, the 1- and 2-year survival rate were 50% and 30.9% respectively, which was significantly higher than in controls (13). In recent years, other studies about the use of HIFU for the treatment of HCC in particular settings were performed by Chinese researchers. Zhang L *et al.* treated with HIFU 39 patients with cirrhosis Child A or B and unresectable HCC adjacent to major hepatic veins and therefore ineligible for RFA or PEI due to the location. The results were encouraging as the complete necrosis rate after a single HIFU was more than 50%, indicating that HIFU can achieve complete tumor necrosis even when the lesion is located adjacent to the major hepatic blood vessels. No major complications were observed and the overall survival rates at 1, 3, and 5 years were 75.8%, 49.8% and 31.8 %, respectively (14). Similar findings were reported by Orsi *et al.* who after HIFU achieved complete response in 100% of 6 patients with HCC nodules situated in difficult locations (that is, tumors adjacent to a main hepatic blood vessel, the heart, the bowel, the stomach, the gall bladder and bile ducts), without any complication (15).

When considering the validity of any therapeutic option, the crucial issue is careful evaluation of the procedure-related complications. In this respect, the high mortality

rate reported by Chan after RFA (2.6%) is unexpected. In a systematic review including 9531 patients treated with RFA, Bertot LC *et al.* reported pool mortality and major complications rates of 0.16% and 4.1%, respectively (4). An Italian multicenter study, focused on assessing the safety of RFA, reported 6 deaths (0.3%) with additional 2.3% major complications after treatment of 3,554 focal liver lesions (16). Concerning safety, in the largest series published so far, HIFU was used in the treatment of 1038 patients with solid carcinoma (17). Fever (severe and long lasting in some cases), skin burns and mild local pain were the most common complications. However, six of 474 patients with primary or metastatic liver cancer developed hepatic abscesses within 2-3 weeks of HIFU treatment. Hospital mortality rate can reach 2% with an 8.1% complication rate after HIFU for ablation of hepatocellular carcinoma tumors (median size 2.2 cm, range 0.9-8 cm) (18). Following a median number of HIFU sessions of 1.3 per patient, Li JJ *et al.* observed both systemic and local complications (fever, supraventricular tachycardia, acute cholecystitits, hematuria, cholangiectasis, pleural and pericardial effusions, impairment of peripheral nerves and of vertebral column) (19). However, HIFU has generally proven to induce short to medium-term cancer control, with a low rate of complications comparable to those of established therapies. Chan *et al.* performed HIFU in 103 patients without significant complications. HIFU safely achieved tumor ablation even in patients with HCC nodules positioned in difficult location (14,15).

Although the treatment efficacy and survival benefit of HIFU for patients with liver cancer were well documented in previous studies, clinico-pathological factors that could influence the complete ablation rate and patient survival rates were not studied in details. Further studies are therefore needed. Although HIFU is not widely available, it has proven to be an effective and safe treatment procedure for unresectable HCC, with a favourable survival outcome, though at present very few studies have compared this technique to other tumor ablation techniques. Cheung *et al.* performed a comparative study also in patients with early hepatic cancer (20). They retrospectively assessed the outcome of patients with HCCs smaller than 3 cm after treatment either with HIFU or with RFA. Although Child-Pugh B patients were more frequent in the HIFU group than in the RFA group (34% *vs.* 8.5%) there was no difference in the 3-year survival rate (81.2% *vs.* 79.8%, respectively). No death occurred and only minor complications were associated with HIFU treatment (20).

The main limits of the study of Chan and his co-workers (9) are its retrospective nature and the small study population. Patients were not allocated to each treatment arm on the basis of a randomization, but the choice of treatment for recurrent HCC was related to the sonographic feature of the tumor, its location in relation to adjacent organs and to patient consent. HIFU was offered especially in patients with periductal tumor, who can develop bile duct injury with RFA. However, at the moment, there are no other comparative studies and a randomized trial comparing HIFU and RFA would be difficult to organise. Due to the high costs and the limited availability of HIFU equipment, HIFU should be reserved for the treatment of patients with unresectable tumours, especially when localized in sites difficult to treat with standard ablative percutaneous techniques. Further studies to compare its effectiveness with other ablation modalities are warranted.

Acknowledgements

Disclosure: The authors declare no conflict of interest.

References

1. European Association For The Study Of The Liver; European Organisation For Research And Treatment Of Cancer. EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. J Hepatol 2012;56:908-43.
2. Kudo M, Izumi N, Kokudo N, et al. Management of hepatocellular carcinoma in Japan: Consensus-Based Clinical Practice Guidelines proposed by the Japan Society of Hepatology (JSH) 2010 updated version. Dig Dis 2011;29:339-64.
3. Ebara M, Okabe S, Kita K, et al. Percutaneous ethanol injection for small hepatocellular carcinoma: therapeutic efficacy based on 20-year observation. J Hepatol 2005;43:458-64.
4. Bertot LC, Sato M, Tateishi R, et al. Mortality and complication rates of percutaneous ablative techniques for the treatment of liver tumors; a systematic review. Eur Radiol 2011;21:2584-96.
5. Kim YS, Lim HK, Rhim H, et al. Ten-year outcomes of percutaneous radiofrequency ablation as first-line therapy of early hepatocellular carcinoma: analysis of prognostic factors. J Hepatol 2013;58:89-97.
6. Ward JF. High-intensity focused ultrasound for therapeutic tissue ablation in surgical oncology. Surg Oncol Clin N

Am 2011;20:389-407, ix.
7. Al-Bataineh O, Jenne J, Huber P. Clinical and future applications of high intensity focused ultrasound in cancer. Cancer Treat Rev 2012;38:346-53.
8. Wijlemans JW, Bartels LW, Deckers R, et al. Magnetic resonance-guided high-intensity focused ultrasound (MR-HIFU) ablation of liver tumours. Cancer Imaging 2012;12:387-94.
9. Chan AC, Cheung TT, Fan ST, et al. Survival analysis of high-intensity focused ultrasound therapy versus radiofrequency ablation in the treatment of recurrent hepatocellular carcinoma. Ann Surg 2013;257:686-92.
10. Leslie TA, Kennedy JE, Illing RO, et al. High-intensity focused ultrasound ablation of liver tumours: can radiological assessment predict the histological response? Br J Radiol 2008;81:564-71.
11. Wu F, Wang ZB, Chen WZ, et al. Extracorporeal high intensity focused ultrasound ablation in the treatment of patients with large hepatocellular carcinoma. Ann Surg Oncol 2004;11:1061-9.
12. Wu F, Wang ZB, Chen WZ, et al. Advanced hepatocellular carcinoma: treatment with high-intensity focused ultrasound ablation combined with transcatheter arterial embolization. Radiology 2005;235:659-67.
13. Li YY, Sha WH, Zhou YJ, et al. Short and long term efficacy of high intensity focused ultrasound therapy for advanced hepatocellular carcinoma. J Gastroenterol Hepatol 2007;22:2148-54.
14. Zhang L, Zhu YJ, Jin C, 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.
15. Orsi F, Zhang L, Arnone P, et al. High-intensity focused ultrasound ablation: effective and safe therapy for solid tumors in difficult locations. AJR Am J Roentgenol 2010;195:W245-52.
16. Livraghi T, Solbiati L, Meloni MF, et al. Treatment of focal liver tumors with percutaneous radio-frequency ablation: complications encountered in a multicenter study. Radiology 2003;226:441-51.
17. Wu F, Wang ZB, Chen WZ, et al. Extracorporeal high intensity focused ultrasound ablation in the treatment of 1038 patients with solid carcinomas in China: an overview. Ultrason Sonochem 2004;11:149-54.
18. Ng KK, Poon RT, Chan SC, et al. High-intensity focused ultrasound for hepatocellular carcinoma: a single-center experience. Ann Surg 2011;253:981-7.
19. Li JJ, Gu MF, Luo GY, et al. Complications of high intensity focused ultrasound for patients with hepatocellular carcinoma. Technol Cancer Res Treat 2009;8:217-24.
20. Cheung TT, Fan ST, Chu FS, et al. Survival analysis of high-intensity focused ultrasound ablation in patients with small hepatocellular carcinoma. HPB (Oxford) 2013;15:567-73.

Cite this article as: Zavaglia C, Mancuso A, Foschi A, Rampoldi A. High-intensity focused ultrasound (HIFU) for the treatment of hepatocellular carcinoma: is it time to abandon standard ablative percutaneous treatments? Hepatobiliary Surg Nutr 2013;2(4):184-187. doi: 10.3978/j.issn.2304-3881.2013.05.02

