METHOD, EFFECTIVENESS, AND COMPLICATIONS OF HIGH INTENSITY FOCUSED ULTRASOUND (HIFU) ABLATION ON HEPATOCELLULAR CARCINOMA (HCC) TREATMENT

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Abstract: Hepatocellular carcinoma (HCC) is one of the most common cancers in the world. High intensity focused ultrasound (HIFU) plays an important role in treatment of HCC. HIFU has two methods in tumor treatment, which have thermal and mechanical effects. The absorption of ultrasound energy causes a rise in temperature at the target point of the tumor. Although necrosis occurs, tissue located near the target tumor is not destroyed. Mechanical effects produce acoustic cavitations, causing tumors to be destroyed by microbubble formation. Many clinical trials have revealed that HIFU is an effective and safe procedure for HCC ablation, both in short-term and long-term follow-up. HIFU showed a good response rate in patients suffering from HCC damage, and improved several parameters in HCC treatment. The common complications of HIFU found in many clinical trials were slight fever, localized pain, and skin burns. However, patients recovered within a few weeks after treatment as severe or major complications were minimally observed. Nevertheless, further study to support the efficacy and safety of HIFU in a larger number of cancer patients will be necessary before it can be used in treatment for other cancers. This review will investigate the use of HIFU for treatment of HCC, and will describe the method, effectiveness, and complications of HIFU.

Keywords: high intensity focused ultrasound, HIFU, hepatocellular carcinoma, cancer

บทคัดย่อ: มะเร็งตับโดยเฉพาะอย่างยิ่ง hepatocellular carcinoma (HCC) เป็นหนึ่งในโรคมะเร็งที่พบได้บ่อย High intensity focused ultrasound (HIFU) จึงเข้ามามีบทบาทส าคัญในการรักษา HCC ซึ่ง HIFU มีกลไกในการทำลายเนื้องอกหรือมะเร็ง 2 ประการ ได้แก่ การใช้ความร้อน (thermal) และกระบวนการเชิงกล (mechanical). การดูดซึมพลังงานอัลตราซาวด์ทำให้เกิดการเดินทางของสุญญีที่เกิดขึ้นของสุญญีที่เกิดขึ้นทำให้เกิดการลดของเนื้องอก บาร์มขึ้น ในขณะที่เนื้องอกโดยไม่ได้รับความร้อนดังกล่าว กลไกของเนื้องอกเกิดการกัดและบางครั้งที่โครงการทดสอบของผู้ป่วยบางราย (cavitation) ทำให้เนื้องอกหรือมะเร็งถูกทำลายจากฟองอากาศในเนื้องอก ผลการทดลองของกลไกเหล่านี้แสดงให้เห็นว่า HIFU เป็นวิธีการรักษา HCC ที่มีประสิทธิภาพและความปลอดภัยสูงที่จะช่วยซับและระบาย ผู้ป่วยที่ได้รับการรักษาด้วย HIFU มีการระยะตอบสนองที่ดีและมีการเปลี่ยนแปลงต่าง ๆ (parameters) ดีขึ้น อาการแทรกซ้อนที่เกิดขึ้นได้เบาลง ได้แก่ ปวด local, ปวดผิวหนัง และผิวหนังไหม้ แต่ในผู้ป่วยบางรายที่ได้รับการรักษาด้วย HIFU นั้นมีเกิดขึ้นในกลไกไม่ได้ ส่งผล ไม่ได้พบการขึ้นของน้ำมันที่เกิดขึ้นจากการสิ่งที่เกิดขึ้นใน HIFU ในประชากรต่างๆ ที่มีความต่างกันที่จะพบอยู่ในการรักษาและพยากรณ์ ตามความนี้ได้สรุปว่าการใช้ HIFU ในการรักษามะเร็งตับ ลดอาการของอาการ ประสิทธิผล และผลข้างเคียงของ HIFU ด้วย

ค ำส ำคัญ: ไฮอินเท็นซิตี้โฟกัสอัลตราซาวด์ ไฮฟู มะเร็งตับ มะเร็ง
INTRODUCTION

Liver cancer is the fifth and the seventh most common malignant disease in men and women, respectively. Records state that 7.9% of all cancers in men, and 6.5% in women are liver related (American Cancer Society, 2011). Hepatocellular carcinoma (HCC) is the most common form of liver cancer, and more than 600,000 patients die from HCC each year (El-Serag, 2012). Treatment depends on the stage of the disease and on access to intricate regimens. Nevertheless, advanced stage liver cancer is not curable, and management of the disease is expensive and only marginally effective in increasing quality-adjusted life-years.

Most cases of HCC (approximately 80%) are associated with cirrhosis related to chronic hepatitis B and hepatitis C. Effective approaches include primary prevention of viral hepatitis, and hepatitis B vaccination in neonates. Avoiding alcohol abuse, as well as preventing the spread of hepatitis C virus and metabolic syndrome, is also pertinent. Another important undertaking is to inhibit aflatoxin formation in nuts, grains or legumes through proper care of agricultural products. A third approach is to increase awareness among the health-care community in order to encourage surveillance of patients who are at risk, so as to achieve earlier diagnosis and resection or ablation of small tumors (Ferenci et al., 2009). Alpha-fetoprotein (AFP) is used as a tumor marker for HCC. However, some research has showed that serum soluble interleukin-2 receptor (sIL-2R) levels are more sensitive tumor markers than serum AFP levels (Izzo et al., 1999). Nevertheless, ultrasound imaging is a highly important method on screening, surveillance, and clinical management of HCC patients (Maruyama et al., 2008).

There are many procedures for treatment of HCC, including curative treatment, palliative treatment, and symptomatic treatment. Resection, liver transplantation, and radiofrequency ablation (RFA) are curative treatments. Transcatheter arterial chemoembolization (TACE), Sorafenib is a multi-kinase inhibitor currently used in the palliative treatment of advanced HCC (Bruix and Sherman, 2011).

Local cancer ablation is mostly considered as a non-invasive or minimally invasive procedure, without insertion of any instruments into human body. High intensity focused ultrasound (HIFU) is a technique using thermal ablation with no skin incision and well-defined the target location of tumor. The applications of HIFU are growing rapidly, especially in solid tumor treatment (Padma et al., 2009). HIFU was first approved for the treatment of HCC in China in 1999. More than 80% of clinical trials on treatment of HCC use HIFU machines from China (Al-Bataineh et al., 2012). This review will investigate the use of HIFU for treatment of HCC, and will describe the method, effectiveness, and complications of HIFU.

METHOD OF HIFU

HIFU can produce both thermal and mechanical effects in the target tissue (Zhou, 2011). Thermal effects result from the tissue absorbing acoustic energy and transforming it to heat, however, different tissues absorb different amounts of acoustic energy (Foley et al., 2007). The absorption of ultrasound (US) energy into the tissues generates a rapid increase in temperature of 65-100 °C within seconds, causing irreversible cell death (Halpern, 2005). If the temperature surpasses 100 °C then boiling occurs at the target tissue and coagulation necrosis (accidental cell death) occurs instantly. Conversely, if the temperature not increased to 100 °C, thermal fixation will occur; although no autolysis takes place, the cells are no longer viable (Jang et al., 2010). Because there are lower intensities outside the focal region, this results in protection of tissue from thermal damage if it is placed between the transducer and the focal point (Padma et al., 2009). Acoustic cavitation is the most common mechanical
effect of HIFU. The microbubbles forming and interacting within the US field cause tissue damage due to the collapse of the microbubbles (Jenne et al., 2012; Shehata, 2012; Yao et al., 2008). The method of HIFU ablation is shown in Figure 1.

**Figure 1.** Method of HIFU ablation (Jenne et al., 2012)

The two devices used to monitor HIFU treatment are US imaging and magnetic resonance imaging (MRI). MRI showed more precise anatomic resolution than US. However, US provide clear real-time anatomic imaging, and produced real-time temperature mapping even when the movement occurred during HIFU (Orsi et al. 2010a).

**EFFECTIVENESS OF HIFU ON HCC ABLATION**

Many clinical trials were studied to evaluate the effectiveness of HIFU on HCC ablation. In 2007, a clinical trial investigated short term and long term efficacy of HIFU ablation for advanced HCC. The test group received both HIFU and supportive therapy (n=151), and the control group received supportive treatment only (n=30). Improvement in tumor imaging parameters, decrease in serum AFP levels, symptom relief (i.e. Karnofsky Performance Status and numerical rating scales), and response rates were monitored as short term efficacy. An increase in survival rate, and improvement of quality of life (QOL), were both monitored and reported as long term efficacy. Results revealed that tumor imaging parameters, serum AFP levels, and symptom scores improved significantly in the test group compared with the control group (P < 0.01). The total response rate was significantly better in the test group (88.8%) than in the control group (16.7%). The 1- and 2-year survival rates in the test group were 50.0% and 30.9%, respectively, which were significantly greater than those in the control group (3.4% and 0%, respectively). The QOL score was 83.1±8.0 at 3 months after HIFU, which was significantly greater than the pre-HIFU score (67.7±5.9) and the score at 3 months after treatment (69.0 ± 8.5) in the control group. The results from this trial showed that HIFU ablation improved symptoms in 84.8% of the group; serum AFP levels decreased in 71.7% of the 145 patients, and tumor size also reduced (Li et al., 2007). The 2-year survival rate of patient with stage Ib, Ila, and IIIa HCC were 80%, 51.4%, and 46.5%, respectively.
respectively. The data showed survival rate decreased with severity and stage of HCC (Xu et al., 2011).

In 2004, HIFU treatment was performed in 100 patients with liver cancer. Clinical symptoms, liver function tests, AFP, MRI or computed tomography (CT) before and after the treatment were used as monitoring parameters. After HIFU ablation, clinical symptoms were relieved in 86.6% of patients. ALT and AST liver function tests were reduced to normal levels in 83.3% and 72.9% of patients, respectively. Serum AFP level was decreased in 65% of patients. Data from MRI or CT showed that coagulation necrosis of tumor and blood supply was reduced or disappeared (Li et al., 2004).

When HCC lesions were located close to major hepatic veins, HIFU showed good efficacy and safety both at short-term and long-term follow-up. Thirty nine patients with 42 lesions were included in this study. Tumor necrosis in 21 of 42 lesions was completed, and the remaining had more than 50% of their tumor size ablated. The overall survival rates at 1, 2, 3, 4, and 5 years were 75.8%, 63.6%, 49.8%, 31.8%, and 31.8%, respectively. However, about 44% of patients died during a median of 16.5 months of follow-up. The cause of death included variceal bleeding, encephalopathy, liver function failure, and untreated progression of HCC. A recurrence of HCC was found in 10.3% of patients (Zhang et al., 2009). During the follow-up period of 7-15 months, the recurrence free survival rate was 88.9% in patients treated with HIFU was not found. Conversely, 1 out of 9 patients with HCC developed a recurrent lesion, but this was successfully ablated after a repeat HIFU treatment (Wang et al., 2010).

In a series of clinical trials in Japan in 2007 to 2008, 21 HCC patients were treated by HIFU ablation. Immediately and one month after HIFU, approximately 80% and 86% patients were adequately ablated (Numata et al., 2010). These results were similar to that of clinical trials conducted from 2006 to 2008, where data showed that 79% patients had been successfully treated by HIFU (Fuduka et al., 2012). In China, 27 HCC patients with 39 lesions were included in a trial. 72% of lesions were completely ablated by HIFU, 18% lesions recurred, and 10% lesions accumulated (Zhang et al., 2011).

Liver transplantation is a definitive treatment for patient with HCC or cirrhosis. During uncertain waiting times for liver grafts, HIFU has been used as a bridging therapy for HCC patients. In 2012, Cheung and colleagues published a case report that evaluated the efficacy of HIFU as a bridging therapy in stage 2 HCC patients with extremely low platelet counts. Results showed that the ablation was successful and liver function blood tests before and after HIFU were not different. In addition, no adhesion was found in the liver graft performed six months later (Cheung et al., 2012a). Another study used HIFU as a bridging therapy during a 9.5 month waiting time for transplantation in patients with cirrhosis. The data revealed that HIFU ablation is safe and effective as a bridging therapy of HCC for patients with advanced cirrhosis (Cheung et al., 2013).

Although TACE is effective in HCC treatment, it is not considered as a curative procedure (Sergio et al., 2008). Liang and colleagues evaluated sequential treatment of HIFU after TACE. Results showed TACE can enhance the therapeutic effects of HIFU, as the embolism effect of TACE can reduce blood flow in the tumor. No heat is lost during HIFU treatment and the agent used for TACE embolism, iodinated oil, offers a strong thermogenic action (Liang et al., 2009). The 6-month and 1-year survival rate of HIFU treatment after TACE were 80.4-85.4% and 42.9%, respectively. These results prove that TACE combined with HIFU is more effective than TACE alone in treating advanced HCC (Wu et al., 2005; Liao et al., 2013). The effective rate of TACE plus HIFU was 72.8%, compared with 44.5% in the TACE group alone (Li et al., 2010). A successful rate of 73 patients with HIFU after TACE was reported: 45.2% patients were successfully ablated, and 1-, 2-, 3-year survival rates were 49.1%, 18.8%, and 8.4%, respectively. At the end of follow-up 69.9% died from
progression of the disease, liver function failure, bleeding of upper digestive tract, and infection (Jin et al., 2011).

COMPLICATIONS OF HIFU ON HCC TREATMENT

Non-severe complications after treatment with HIFU have been reported, such as slight fever (<38.5 °C) and transient local pain for 2-5 days. Minor skin burns at operation spots occurred and pleural effusion was observed in 0.5% patients, but all of the above patients recovered within 2 weeks (Li et al., 2007). However, local edema and skin burns were not found in all patients in other trials.

The severity of hepatic function impairment was related to the size of the targeted area and the dosage of HIFU. No severe complications, such as liver failure or bleeding, were observed. Portal vein thrombosis was reported as a major complication, but was found in only 1 of 31 patients (Orsi et al., 2010b). Liver enzyme levels increase after HIFU ablation, but return to normal a few weeks later, but incident of these complications have not been reported (Li et al., 2007, Zu et al., 2009). The complications from a selection of studies are shown in Table 1.

Patients usually tolerate HIFU well. Age of the patient is the only factor that was reported to be significant in HIFU intolerance ($P = 0.022$). Complications were found in patients with an average age of 72 (51-75 years) compared with the no complications group (average age of 63 (34-85 years)) (Cheung et al., 2012b)

However, severe complications were observed in some studies. Liver abscesses, serious skin burns, and rib fractures were found in 1.4%, 4.1%, and 5.6% patients, respectively (Jin et al., 2011). Furthermore, 5% patients had biliary obstruction, symptomatic pleural effusion, pneumothorax, fistula formation between abdominal wall, abscesses and ablated tumors. Two out of 79 patients had delayed diaphragmatic rupture and rib fracture complications (Jung et al., 2011).
| Complications                  | Percentage          | Percentage | Percentage | Percentage | Percentage | Percentage | Percentage | Percentage | Percentage | Percentage | Percentage | Percentage | Percentage | Percentage | Percentage | Percentage | Percentage | Percentage | Percentage | Percentage |
|-------------------------------|---------------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|
| Slight fever                  |         | 13         | 4.2        | 100        |            |            |            |            |            |            |            |            |            |            |            |            |            |            |            |            |            |
| Local pain                    |         | 16.7       | 100        | 75         | 23.1       | 31.2       | 66         |            |            |            |            |            |            |            |            |            |            |            |            |            |
| Skin burn                     |         | 27         | 8.3        | 2.5        | 37.5       | 12.8       | 6.3        | 0          | 100        | 71         |            |            |            |            |            |            |            |            |            |            |
| Subcutaneous edema            |         |            |            |            |            |            |            |            |            |            |            |            |            |            |            |            |            |            |            |            |
| Skin sensitivity              |         |            |            |            |            |            |            |            |            |            |            |            |            |            |            |            |            |            |            |            |
| Rib necrosis                  |         |            |            |            |            |            |            |            |            |            |            |            |            |            |            |            |            |            |            |            |
| Pleural effusion              |         |            |            |            |            |            |            |            |            |            |            |            |            |            |            |            |            |            |            |            |
| Chest infection               |         |            |            |            |            |            |            |            |            |            |            |            |            |            |            |            |            |            |            |            |
| Renal impairment              |         |            |            |            |            |            |            |            |            |            |            |            |            |            |            |            |            |            |            |            |
| Variceal bleeding             |         |            |            |            |            |            |            |            |            |            |            |            |            |            |            |            |            |            |            |            |
| Right chest wall bruising     |         |            |            |            |            |            |            |            |            |            |            |            |            |            |            |            |            |            |            |            |
| Hyperbilirubinemia            |         |            |            |            |            |            |            |            |            |            |            |            |            |            |            |            |            |            |            |            |
| Liver abscess                 |         |            |            |            |            |            |            |            |            |            |            |            |            |            |            |            |            |            |            |            |
| Pneumothorax                  |         |            |            |            |            |            |            |            |            |            |            |            |            |            |            |            |            |            |            |            |
| Pancreatitis                  |         |            |            |            |            |            |            |            |            |            |            |            |            |            |            |            |            |            |            |            |
| Serum transaminase increase   |         |            |            |            |            |            |            |            |            |            |            |            |            |            |            |            |            |            |            |            |
| Acute cholecystitis           |         |            |            |            |            |            |            |            |            |            |            |            |            |            |            |            |            |            |            |            |
| Portal vein thrombosis        |         |            |            |            |            |            |            |            |            |            |            |            |            |            |            |            |            |            |            |            |

* HIFU for liver and kidney tumor
** HIFU after TACE
CONCLUSION

HIFU is a new non-invasive technique for treatment of HCC which has become popular in the last 10 years. HIFU destroys tumors by producing both thermal and mechanical effects. It is focused at specific target location without damaging surrounding tissues. Many clinical trials have revealed that HIFU is an effective and safe procedure for HCC ablation, both in the short-term and after long-term follow-up. The most common complications were slight fever, localized pain, and skin burns. There were few severe complications reported. In conclusion, HIFU is a highly potential technique for treatment of HCC with minimal complications. Nevertheless, further study to support the efficacy and safety of HIFU in a larger number of patients will be necessary before it can be used in treatment for other cancers.

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