Extracorporeal high intensity focused ultrasound ablation in the treatment of 1038 patients with solid carcinomas in China: an overview

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Abstract

The ideal treatment of localized cancer should directly cause an irreversible and complete death of tumor cells without damage to surrounding normal tissue. High intensity focused ultrasound (HIFU) is such a potential treatment, which induces a complete coagulative necrosis of a tumor at depth through the intact skin. The idea that using an extracorporeal source of therapeutic ultrasound was introduced more than 50 years ago [J. Gen. Physiol. 26 (1942) 179]. However, up to now, most of the studies on HIFU have been dealing with animal experiments because this extracorporeal technique is very complicated in clinical applications. The purpose of this study is to introduce Chinese clinical experience of using extracorporeal HIFU for the treatment of patients with various kinds of solid tumor. From December 1997 to October 2001, a total of 1038 patients with solid tumors underwent HIFU ablation in China. Among them, 313 patients were treated at the Chongqing University of Medical Sciences, China. Pathological examination showed that the target region presented clear evidence of cellular destruction. Small blood vessels less than 2 mm in diameter were severely damaged. Follow-up diagnostic imaging revealed that there was no, or reduced, blood supply, and no uptake of radioisotope in the treated tumor after HIFU, both indicating a positive therapeutic response and an absence of viable tumor. Imaging at 6–12 months showed obvious regression of the lesion. Four-year follow-up data were significantly observed in patients with hepatocellular carcinoma, osteosarcoma, and breast cancer. An extremely low major complication rate was noted. It is concluded that HIFU ablation is a safe, effective, and feasible modality for the ablation of carcinomas.

Keywords: High intensity focused ultrasound; Focused ultrasound surgery; Neoplasm; Ablation; Therapeutic ultrasound

1. Introduction

As a non-invasive modality, high intensity focused ultrasound (HIFU) therapy is receiving increasing interest for the treatment of localized solid malignancies. This idea that using an extracorporeal source of focused
ultrasound energy was introduced by Dr. Lynn in 1942 [1], and it could provide a potential possibility of inducing coagulative necrosis in targeted tissue without damaging overlying and surrounding vital structures.

In the past few decades, several clinical HIFU projects have been conducted by various research groups, and significant results indicate that HIFU treatment would be safe, effective, and feasible in clinical application [2–7]. In China the first HIFU treatment performed was on a male patient with tibia osteosarcoma on December 10, 1997. Up until October 2001, a total of 1038 patients with solid tumors, have undergone extracorporeal HIFU ablation. The categories of solid malignant tumors treated by HIFU ablation include primary and metastatic liver cancer, malignant bone tumor, breast cancer, soft tissue sarcoma, kidney cancer, pancreatic cancer, and advanced local tumors. Solid benign tumors such as uterine myoma, benign breast tumor, and hepatic hemangioma have also been treated with HIFU thermal ablation. Herein, we will introduce our experience of using extracorporeal HIFU for the treatment of patients with various kinds of solid tumor, describe follow-up imaging for assessing efficacy of HIFU, and report 4-year follow-up data observed in patients with hepatocellular carcinoma, osteosarcoma, and breast cancer.

2. Materials and methods

The same HIFU therapeutic system [Chongqing Haifu (HIFU) Tech Co., Ltd, Chongqing, China] was used in all hospitals. As described in detail previously [7,8], the therapeutic US energy is produced by a 12-cm diameter piezoelectric ceramic PZT-4 transducer. A diagnostic US device is used for the guidance of HIFU thermal ablation. The US imaging probe situated in the center of therapeutic transducer can provide real-time sonography to target the lesions to be treated, to guide US energy deposition, and to assess acute coagulation necrosis in the targeted tissue during the therapeutic procedure. The focal lengths used in clinical applications are 90, 130, or 160 cm. The US frequencies used for treatment are 0.8 and 1.6 MHz. So there are 4–6 therapeutic transducers in each HIFU device, and one is selected from them for the individual treatment of cancer patient. The integrated transducer is mounted in a water reservoir, and can be moved by electric motors in the six directions with millimetric precision. The water bag is filled with degassed, distilled water. The co-axial US imaging device was used to establish the 3D image of the whole tumor. For therapeutic purposes, the whole tumor was divided into slices with 5–10 mm separation using US images. By scanning the HIFU beam in successive sweeps from the deep to the shallow regions of the tumor, the targeted regions on each slice were completely ablated. This process was repeated slice by slice to achieve complete tumor ablation.

<p>| Table 1 | Categories of patients with solid tumors treated by HIFU ablation |</p>
<table>
<thead>
<tr>
<th>No. of patients</th>
<th>No. of patients in Chongqing</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Solid malignancies</strong></td>
<td></td>
</tr>
<tr>
<td>Primary and metastatic liver cancer</td>
<td>474</td>
</tr>
<tr>
<td>Malignant bone tumor</td>
<td>153</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>106</td>
</tr>
<tr>
<td>Soft tissue sarcoma</td>
<td>77</td>
</tr>
<tr>
<td>Kidney cancer</td>
<td>27</td>
</tr>
<tr>
<td>Pancreatic cancer</td>
<td>10</td>
</tr>
<tr>
<td>Abdominal metastatic cancer</td>
<td>20</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>4</td>
</tr>
<tr>
<td>Others</td>
<td>31</td>
</tr>
<tr>
<td><strong>Benign tumors</strong></td>
<td></td>
</tr>
<tr>
<td>Uterine myoma</td>
<td>85</td>
</tr>
<tr>
<td>Benign breast tumor</td>
<td>28</td>
</tr>
<tr>
<td>Benign soft tissue tumor</td>
<td>13</td>
</tr>
<tr>
<td>Benign liver tumor</td>
<td>4</td>
</tr>
<tr>
<td>Others</td>
<td>6</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>1038</strong></td>
</tr>
</tbody>
</table>
tion, in a manner resembling that of cutting away slices of bread. In this study the extent of HIFU treatment was larger than the tumor extent in order to obtain a sufficient tumor-free margin. It included the breast lesion and its marginal breast tissue about 1.5–2.0 cm around the visible tumor. In this study, the target tissue was exposed at acoustic focal peak intensities from 5000 to 20,000 W cm\(^{-2}\). The scanning speed ranged 1–3 mm s\(^{-1}\), and the track length was 20 mm.

Thirty patients, including 23 patients with breast cancer, six patients with HCC, and one patient with osteosarcoma, received conventional surgery to remove the treated tumors no later than 2 weeks after HIFU treatment in Chongqing. The specimens were fixed in 10% phosphate-buffered formalin (pH = 7), embedded in paraffin, and stained with hematoxylin and eosin (H & E) for assessment of standard histology.

Prior to each treatment episode, and as follow-up, color and power Doppler US, computerized tomography (CT) and magnetic resonance imaging (MRI), digital subtraction angiography (DSA), and single photon emission computed tomography (SPECT) were performed to evaluate local therapeutic response of targeted tumors. SPECT is a radionuclide scanning technique that uses a radioisotope as a tracer to assess abnormal tumor function rather than to provide simple anatomy in the patient with solid malignancies. The patients who underwent HIFU ablation received one or several ones among the listed examinations for the assessment of HIFU effects on tumor vascularity, tumor cellular survival, and the change in tumor size. The patients were followed after treatment to observe complications related to HIFU and long-term therapeutic efficacy. Survival was estimated from the date of initial treatment. A cumulative survival rate was calculated by using the Kaplan-Meier method.

3. Results

3.1. Histological changes

Macroscopic examination showed that the treated region presented clear evidence of coagulative necrosis 1–2 weeks after HIFU treatment. There was a sharp boundary between the cellular destruction and viable tissue. The HIFU-induced lesion extent included the tumor mass plus a margin of treated normal tissue about 1.5–2.2 cm around the cancer. Outside the boundary the tissue was normal. In the boundary, the treated tissue appeared complete coagulative necrosis. It was felt firmer on palpation than normal tissue. On the marginal area of the ablation was a ring of congestion. Microscopic examination showed homogeneous coagulative necrosis in the treated region with distorted tumor cells, pyknotic nuclei, and shrinkage of nuclei, cell debris. A clear border between the treated and untreated areas was extremely sharp and comprised only several cell layers. Small amount of granulation tissue was formed with the presence of immature fibroblasts, many inflammatory cells, and new capillaries in the boundary region.

Small tumor vascular vessels, including branches of arteries and veins, were heavily damaged. In the center of treated tumor tissue, severely damaged tumor vessels showed that endothelial cells nuclei disappeared, cellular margins were not distinct, and junctions between individual cells were disrupted, which indicated the endothelial cell death. Vascular structure displayed cellular discohension, disruption of the smooth muscle and tunica media. Scattered intravascular thrombi were frequently observed in the destructive vessels.

3.2. Follow-up imaging changes

Based on histologic findings of tumor treated with HIFU, two kinds of diagnostic modality were used to evaluate the therapeutic effects of HIFU on tumor cells and tumor vascular vessels. Follow-up contrast-enhanced CT, contrast-enhanced MRI, DSA, and color Doppler US imaging were used to assess tumor vascularity because tumor blood vessels were severely destroyed. These anatomical imaging methods revealed that there was no, or reduced, blood supply in the treated-tumor, indicating a positive therapeutic response. SPECT, a functional imaging that demonstrates the active metabolism of viable cancer cells, showed that no uptake of radioisotope was observed after HIFU, indicating an absence of viable tumor. The most striking changes were seen in post-HIFU enhanced MR images, where it was common to observe the absence of contrast enhancement in the treated region and a thin peripheral rim of enhancement surrounding the coagulative necrosis. Imaging at 6–12 months showed obvious regression of the lesion and the region of induced coagulative necrosis. Most frequently, the nonenhancing treated volume shrunked by less than 20–50% in volume.

3.3. Follow-up results

It should be appreciated that the clinical data below is not intended to be exhaustive, but should serve as an overview of our clinical experience to date. As much of the HIFU clinical application is very recent in China, long-term follow-up results from the various teams will follow in subsequent publications. Any available survival data in this paper are from the Clinical Center for Tumor Therapy, 2nd Affiliated Hospital of Chongqing University of Medical Sciences, and they will be included in the relevant sections of following paragraphs.
3.3.1. HIFU treatment for liver cancer
A total of 474 patients with liver cancer (including HCC and metastatic liver cancer) received HIFU treatment. In Chongqing Center 55 unresectable HCC patients (43 men, 12 women; mean age, 51.6 ± 13.05; age range, 24–73 years) with cirrhosis were treated with HIFU. Two tumors were less than 5 cm in diameter, 32 tumors were 5.1–10 cm in diameter, and 21 tumors were more than 10 cm in diameter. The mean diameter for all tumors was 8.18 ± 3.37 cm (range from 4 to 14 cm in diameter). The follow-up time in these 55 patients ranged from 6 to 34 months (mean time, 13 months). The median survival time, survival rates of 6 months and 1 year were 13.4 months, 82.6% and 53.4%, respectively.

3.3.2. HIFU treatment for breast cancer
A total of 106 patients with biopsy-proven breast cancer underwent extracorporeal HIFU ablation. Of 22 patients received breast conservation treatment with HIFU in Chongqing center, in combination with adjuvant chemotherapy, postoperative axillary node dissection or/and postoperative radiation therapy. The mean follow-up time for patients with breast conservation treatment in our center was 22 months (range 10–36 months). Total resorption of ablated tumor was found half of them within 1–2 years after HIFU treatment, which mainly correlated with the increase of follow-up time and tumor size. All patients are still alive in the follow-up time and all but one is disease-free. One case presented with local recurrence after 18 months in the targeted region and this patient was subsequently treated by the modified radical mastectomy.

3.3.3. HIFU treatment for osteosarcoma
HIFU treatment was performed in 153 patients with primary and metastatic malignant neoplasms. In Chongqing Center the efficacy of HIFU ablation were assessed in 44 patients with primary malignant bone tumor for the purpose of conserving the diseased-limb. Thirty-four patients who had in stage IIb disease (Enneking classification) underwent HIFU ablation as a noninvasive limb-salvage treatment, in combination with new adjuvant chemotherapy. Ten patients with stage IIIb disease (nine patients with lung metastasis) were treated with HIFU as a palliative modality. The largest extent of tumor ranged from 5 to 46 cm. Mean follow-up time was 23 months (range 10–39 months). Total survival rate was 85% (38/44). One stage IIb case died of brain metastasis, and 5 stage IIIb patients with lung metastasis died of their metastases after HIFU treatment. Five patients underwent amputation because of local recurrence after HIFU treatment.

3.3.4. HIFU treatment for soft tissue sarcoma
A total of 77 patients with soft tissue sarcoma underwent HIFU treatment. All almost of them were local recurrent patients following surgery, and of 18 patients were treated in Chongqing Center. Follow-up time varied from 11 to 39 months (mean 21 months). Sixteen patients with STS are still alive (survival rate, 90%), and two cases died of metastasis after HIFU treatment. Three patients had local recurrence, and then underwent second HIFU treatment again for the purpose of control.

3.3.5. HIFU treatment for other solid malignancies
A total of 27 patients with advanced renal cell cancer (RCC) had undergone HIFU ablation, and among them, nine patients with advanced RCC were successfully treated in Chongqing Center. Mean follow-up time was 9 months (range 1–22 months). After HIFU treatment, two patients with extensive lung metastasis died of cachexia and dyspnea caused by severe lung infection at 1 and 3 months, respectively. The remaining seven patients were still alive, and more significantly, chest X-ray revealed that the lung metastases seen in the patients preoperatively, were stable postoperatively.

Extracorporeal HIFU ablation was successfully performed in 10 patients with unresectable pancreatic cancer. One of the most remarkable clinical features was that chronic pain was immediately relieved following HIFU treatment. Although the anatomy surrounding the pancreas was very complicated, no local complication was found during or after HIFU treatment.

For the purpose of analgesia, HIFU treatment alone was performed in advanced cancer patients who had severe pain related to their cancer. Most of the patients had been provided with appropriate pain medications, including antineoplastic therapy, and pharmacological approaches preoperatively, but the cancer pain was still not well controlled. The results indicated that HIFU was able to control the pain successfully, without any local complication. After HIFU treatment, severe cancer pain was significantly relieved, and patients’ daily activities, quality of life, and psychological status were markedly improved.

3.4. Complications of HIFU treatment
Among 1038 patients treated with HIFU, an extremely low major complication rate has been observed. 5–10% patients had low-grade fever up to 38.5 °C that persisted for approximately 5–7 days after HIFU ablation. The severity and time of fever seems to be directly related to the amount of destroyed tissue. With large-volume tissue ablations the fever is often observed. Several patients with huge HCC are reported to have severe fever as high as 39.5 °C which last for as long as 2–3 weeks.

At the beginning of the HIFU clinical trial, 10–20% patients had HIFU-induced skin burns though these were not severe. The reason for this is mostly lack of
experience in performing HIFU ablation and in evaluating damaged-skin changes on real-time US imaging. However, at the present time the rate of skin burn has significantly decreased (less than 5%). Some treated-patients (20–30%) experience slight and mild local pain within 1 week after HIFU ablation. But only 5–10% patients were given 3–5 days prescription for oral analgesics. Six of 474 patients with liver cancer had hepatic abscesses within 2–3 weeks of HIFU treatment. Four of 153 patients with malignant bone tumors had local infection within 1–3 months of HIFU treatment. Tumor bleeding or large blood vessel rupture have never been detected following HIFU ablation. Four patients with malignant tumors had bowel perforation because of severe abdominal cohesion induced by previous operation. It caused HIFU mis-targeting, such that the treated-region included the tumor and cohesive bowel. Four patients with primary malignant tumor had complete bone fracture in the treated region. Fortunately, two of them recovered and new normal bone has grown, and 3 months after damage it was united with new normal bone tissue. Nerve fiber damage has been caused by HIFU in four patients with malignant bone tumor. However nerve functions including sensation and motion recovered completely in two patients, and partially the other two patients partially recovered within 1 year after HIFU.

4. Discussion

The energy deposition of HIFU on target tissue causes coagulative necrosis of tumors. In this study, pathological examination revealed that both tumor cells and tumor vessels presented a typical appearance of coagulative necrosis with severe nuclear damage, resulting in the absence of viable cancer cells and significant tumor vascular disruption, as well as vessel occlusion. As postoperative biopsy does not provide histological results for the whole treated tumor, follow-up imaging is essential in order to evaluate the early efficacy of HIFU ablation. Thus, diagnostic imaging methods are used to determine the therapeutic effects of HIFU on both tumor vascularity, and on tumor cellular activity. In our clinical applications it is found that follow-up color and power Doppler US imaging, CT, MRI, and DSA reveal that there is no, or reduced, blood supply in the treated tumor. Compared to other imaging methods, contrast-enhanced MRI is much better in the rapid assessment of therapeutic response of target tumor treated by HIFU ablation. It is common to observe the absence of contrast enhancement in the treated region and a thin peripheral rim of enhancement surrounding the coagulative necrosis in postoperative enhanced MR images. After HIFU treatment SPECT showed no uptake of radioisotope in the treated tumor, indicating an absence of viable tumor cells.

The goal of tumor treatment is the complete destruction of all cancer cells within the patient’s body. For patients with early-stage cancer, the therapeutic plan for his disease must be a multiple therapeutic plan, which includes local and systemic modalities. Combination therapy used for some patients who underwent HIFU ablation is curative. A similar multi-disciplinary approach including other modalities such as chemotherapy is useful in the treatment of solid malignancies. But, for patients with advanced-stage cancer, or for whom conventional tumor therapies, including surgery, chemotherapy and radiotherapy, have failed to control tumor, HIFU treatment still can be used as a palliative modality to impede tumor growth and to improve the quality of life. Our clinical results indicate that HIFU is able to relieve the tumor-origin pain successfully in patients whose pain was not well controlled by antineoplastic therapy, and pharmacological approaches.

Long-term results of HIFU ablation for solid malignancies are scant because this is a fairly new technique. However, our early work demonstrates that HIFU complete ablation of tumor is feasible, and cures may be possible. Although more than 1000 patients have undergone HIFU treatment in China since 1997, HIFU technology is still in development. Our own 4-year preliminary clinical study indicates that HIFU treatment is a safe, effective, and feasible modality for the destruction of malignant solid tumors. These results are exciting and encouraging, but longer follow-up is necessary to fully determine the true efficacy of this non-invasive therapeutic modality.

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