PRELIMINARY EXPERIENCE USING HIGH INTENSITY FOCUSED ULTRASOUND FOR THE TREATMENT OF PATIENTS WITH ADVANCED STAGE RENAL MALIGNANCY

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ABSTRACT

Purpose: We present the preliminary results of patients with advanced stage renal malignancy treated with high intensity focused ultrasound (HIFU), and investigate the safety and feasibility of using HIFU in the treatment of selected patients with renal tumors.

Materials and Methods: HIFU treatment was performed in 12 patients with advanced stage renal cell carcinoma and 1 patient with colon cancer metastasized to kidney. Patients were followed after treatment to observe complications and long-term therapeutic efficacy. Complications and changes in symptoms seen at presentation were recorded. Midstream urine specimens were sent for microscopy and serum creatinine was measured postoperatively. Follow-up radiological examinations were performed to detect tumor response to the ablation.

Results: A total of 13 patients received HIFU treatment safely, including 10 who had partial ablation and 3 who had complete tumor ablation. After HIFU hematuria disappeared in 7 of 8 patients and flank pain of presumed malignant origin disappeared in 9 of 10 patients. Postoperative images showed decrease in or absence of tumor blood supply in the treated region and significant shrinkage of the ablated tumor. Of the 13 patients 7 died (median survival 14.1 months, range 2 to 27) and 6 were still alive with median followup of 18.5 months (range 10 to 27).

Conclusions: This preliminary experience suggests that HIFU could be safe and feasible in the treatment of patients with advanced renal malignancy.

KEY WORDS: ultrasound, high-intensity focused, transrectal; kidney, neoplasms, neoplasm metastasis, carcinoma

Renal cell carcinoma (RCC) is one of the most common urological malignancies. Surgery is the only curative modality in the treatment of RCC. In recent decades nephron sparing surgery has been performed with increasing frequency as the preferred surgical treatment for early stage renal carcinoma with outcome comparable to total nephrectomy. As a result, minimally invasive techniques such as radio frequency, cryoablation, microwave and laser therapies have also had an increasing role in the management of small renal tumors. Such techniques may eventually replace conventional open surgery, but to date they have principally been performed in patients with small RCC no greater than 3 to 4 cm in diameter, and they all require at least percutaneous or laparoscopic access for tumor ablation.

As an extracorporeal technique, high intensity focused ultrasound (HIFU) could ablate large tumors noninvasively. In animal experiments it has been demonstrated that HIFU can selectively induce coagulative necrosis of target region in normal renal parenchyma and destroy implanted renal tumors. Most recently the efficacy of HIFU has been demonstrated in the treatment of prostatic disease. In this study we report our preliminary experience of using HIFU for the treatment of advanced and metastatic renal malignancy, investigating its safety and feasibility.

MATERIALS AND METHODS

HIFU therapeutic system. All patients were treated using the same HIFU therapy system as described previously.

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Study received local ethics committee approval.

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HIFU treatment. The first 6 patients received epidural anesthesia and the remaining 7 patients received general. Vital signs were monitored during the procedure. Real-time ultrasound (US) imaging was used to target the tumor, to guide US energy deposition and to assess the extent of coagulation necrosis during the procedure. Of the patients 10 had locally advanced or metastatic disease. Therefore, they received partial HIFU ablation of the renal tumor as a palliative treatment to impede tumor growth and improve quality of life by relieving pain of malignancy. The remaining 3 patients had organ confined disease and underwent complete HIFU treatment with a 1 cm margin of tissue with curative intent.

Followup. Any changes from the presenting symptoms were recorded. Midstream urine specimens were sent for microscopy at 1, 3, 7 and 14 days postoperatively, and serum
creatinine was measured 3, 7 and 14 days after HIFU ablation. Physical examination, complete blood counts, electrolytes and liver function tests were monitored weekly. Potential complications caused by HIFU including skin burns, hemorrhage, urinary extravasation and urinary obstruction were sought in all patients during followup. A cumulative survival rate was calculated with the Kaplan-Meier method.

Color and power Doppler sonography, and chest radiography were performed in all patients within 1 week after HIFU treatment, and then at least once at 2- to 3-month intervals. Followup computerized tomography was performed on 3 patients and 7 received at least 1 postprocedural magnetic resonance imaging (MRI). Only 1 patient consented to a biopsy evaluation at 18 months after HIFU treatment.

**RESULTS**

*Treatment data.* HIFU treatment was successfully performed in all patients. In 3 of the 13 the target tumor was completely ablated and the remaining 10 patients underwent partial HIFU ablation. The ablative extent ranged from 40% to 90% of target tumor volume. The number of HIFU sessions ranged from 1 to 2 (median 1.3). Acoustic focal peak intensities ranged from 5,000 to 20,000 W cm⁻². Scanning speed ranged from 2 to 5 mm s⁻¹, and the track length from 20 to 40 mm. HIFU treatment time ranged from 1.5 to 9 hours (median 5.4). Treatment data are summarized in table 2.

*Laboratory evaluation.* A slight increase in mean serum creatinine was observed on postoperative days 3 and 7. No statistically significant differences were observed in these data between preoperative and postoperative values, even in the 2 patients with a solitary kidney. The most striking changes were seen in the microscopy of mid stream urine specimens. In 7 patients gross or microscopic hematuria disappeared immediately after HIFU. During followup microscopic examination showed these changes to be sustained.

*Postoperative images.* Color Doppler ultrasound imaging was performed at 1 week, 1, 3, 6, 12, 18 and 24 months postoperatively. The percentage of change in tumor size was assessed according to the formula: (a × b) – (a’ × b’)/(a × b) × 100%, where a and a’ are the largest diameters and b and b’ are the perpendicular diameters of the tumor measured on sonography before and after HIFU ablation. Results are shown in table 2. Compared with US images before HIFU color Doppler sonography showed a partial increase in tissue grey scale and a reduction or absence of tumor blood supply in 10 of 13 treated patients 1 to 4 weeks after HIFU.

At least 1 MRI examination was performed on each of 7 patients after HIFU treatment. Compared with preprocedural images unenhanced MRI revealed increased or decreased signal changes on T1 and T2 weighted sequences after HIFU ablation. The most striking changes were seen in postprocedural enhanced MRI, where it was common to observe the absence of contrast enhancement in the treated region (see figure) indicative of coagulative necrosis.

*Followup.* Presenting symptoms were obvious in 11 patients before HIFU. These included hematuria in 8 cases, flank pain sufficient to merit oral analgesia (either oral opiates or ibuprofen) in 10 and fever in 1 case. After HIFU either gross or microscopic hematuria ceased to develop in 7 of 8 patients, and pain resolved in 9 of 10 patients immediately after HIFU (table 2). Lung metastases were stable after treatment and no new lung metastasis was seen.

After a median followup of 14.1 months (range 2 to 27) 6 of the 13 patients had died and 6 patients were still alive at the time of writing. One patient was lost to followup 6 months after HIFU. Survival times were less than 6 months in 2 cases, 6 to 12 months in 1, 12 to 18 months in 2, and more than 18 months in 1, respectively. At this writing 6 patients are still alive. Median followup for them is 18.5 months (range 10 to 27). The tumors of 2 patients which had previously been considered unresectable because of proximity to the abdominal aorta, sufficiently decreased in size after HIFU to allow radical nephrectomy after 8 and 11 months, respectively. One patient with bilateral RCC had local recurrence proven by needle biopsy on left diseased kidney 18 months after HIFU, and partial nephrectomy was immediately performed. Partial coagulation necrosis in the treated region was observed in these surgical specimens.

*Complications.* A minor skin burn was observed in the first patient, which had healed 2 weeks after HIFU. The patient who had fever before treatment had a persistent fever of 38.0 to 39.0°C lasting 2 months after HIFU. To our knowledge tumor hemorrhage or large blood vessel rupture has never been detected after HIFU. There was no evidence of postoperative urine extravasation or urinary obstruction in any patients during followup. Renal dysfunction or renal abscess caused directly by HIFU treatment did not develop in any patient.

**DISCUSSION**

The absorption of high intensity focused ultrasound energy results in targeted tissue coagulative necrosis. We presented a preliminary analysis of the safety and feasibility of extracorporeal HIFU ablation for human renal malignancies. A
total of 13 patients with renal malignancy were treated with HIFU and a low major complication rate was noted. These results indicate that HIFU is safe in the treatment of patients with renal malignancies.

A group of 10 patients with RCC underwent partial HIFU ablation for local palliation in the setting of metastatic RCC. After HIFU treatment the most striking change in patients was that the preoperative presenting symptoms disappeared immediately. Severe renal pain was relieved in 9 of 10 patients and hematuria disappeared in 7 of 8. However, after HIFU treatment of the 12 patients with RCC 4 died of cachexia directly caused by RCC, 1 of severe pneumonia possibly related to lung metastasis and 1 of coronary heart disease. Although the patients had advanced stage disease with distant metastases median survival time was 11 months and 2 patients survived for more than 18 months.

In this study 6 of 13 patients were still alive at the time of writing. Median followup for them was 18.5 months (range 10 to 27). Postoperative images showed that there was significant shrinkage of the treated tumors. The 2 patients who had previously been considered to have unresectable RCC were able to undergo radical nephrectomy after HIFU. This result implies that HIFU could be used as a therapy for the cytoreduction of unresectable renal tumors, and then radical nephrectomy could be performed after the decrease in tumor size. In the patients with lung metastases, the metastases were neither seen to reduce in size nor disappear after thermal ablation of primary RCC. However, most significantly, chest radiographs showed that metastatic lung nodules, when presented preoperatively were stable postoperatively. In addition, no new lung metastases were seen after HIFU treatment during followup. Although the mechanism remains unclear an immunological effect from the thermal ablation could be responsible for the temporary stability.11–13

There are disadvantages to the HIFU technique in its current form and anesthesia might be considered one. It can raise potential risks particularly to patients in a weakened state. Another problem is treatment time. In this series median treatment time was 5.4 hours (range 1.5 to 9). This long treatment time could be explained by the fact that most tumors treated in this study were large RCC. Also, in the early development of a new technique, long procedure times are often needed. With technical development therapy time could be significantly decreased in the future.

CONCLUSIONS

To our knowledge these clinical data demonstrate for the first time that patients with renal malignancy can be treated noninvasively with extracorporeal HIFU. This preliminary experience suggests that HIFU is a safe and feasible modality in the treatment of patients with renal malignancy. However, a randomized clinical trial with longer followup is necessary to determine the future role of this novel treatment of renal cell carcinoma.

REFERENCES

