LAPAROSCOPIC PARTIAL KIDNEY ABLATION WITH HIGH INTENSITY FOCUSED ULTRASOUND


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ABSTRACT

Purpose: High intensity focused ultrasound has been performed for transrectal and extracorporeal thermal ablation of tissues. We developed and tested a laparoscopic probe that allows real-time ultrasound imaging during partial renal ablation using high intensity focused ultrasound.

Methods: A Sonablate 200 (Focus Surgery, Indianapolis, Indiana) high intensity focused ultrasound system with a modified 18 mm laparoscopic probe was used in all experiments. In 13 Yucatan mini-pigs a 5Fr ureteral catheter was inserted into the renal pelvis and 10 cc air were instilled into the collecting system. The kidney was laparoscopically dissected, the high intensity focused ultrasound probe was inserted through a 33 mm laparoscopic port and the targeted renal pole was treated.

Results: Renal lesions were created in 12 of 13 treated kidneys under real-time ultrasound visualization. Median operative time was 180 minutes, average high intensity focused ultrasound activation time was 18.3 minutes and lesion size was 23 × 17 × 11 mm. At 4 and 14 days 4 (acute group) and 6 (subacute group) animals were available for renal functional and anatomical evaluation, respectively. No difference in renal function was seen in treated and untreated kidneys. Pathological examination at 14 days revealed homogenous and complete tissue necrosis throughout the whole volume of the lesion with sharp demarcation from adjacent normal tissue.

Conclusions: We were able to refine a probe for laparoscopic high intensity focused ultrasound delivery capable of simultaneous ultrasound imaging. Partial renal ablation using this probe is feasible and safe, and resulted in homogenous, complete and reproducible lesions.

KEY WORDS: kidney; laparoscopy; ultrasonic therapy; equipment and supplies; swine, miniature

Laparoscopic partial nephrectomy for treating small renal tumors is increasingly recognized as an acceptable alternative to open partial nephrectomy with similar short-term results.1–3 However, technical difficulties resulting in renal ischemic injury, inadequate hemostasis and postoperative urine leakage have fueled research into minimally invasive technologies to assist or even replace partial nephrectomy. Renal cryoablation and radio frequency ablation,4–7 which have been successfully used, involve inserting probes percutaneously or under laparoscopic guidance into the tumor. However, tumor cell spillage during this puncture remains a theoretical concern.8

In this report we present an alternative laparoscopic tissue ablation approach using a modified Sonablate 200 high intensity focused ultrasound system. The potential advantages of laparoscopically delivered high intensity focused ultrasound over other ablative technologies include the use of the same probe for imaging and tissue ablation, and the delivery of tissue ablation energy by direct contact on the exterior of the kidney rather than after tumor puncture.

MATERIALS AND METHODS

High intensity focused ultrasound delivery system. The Sonablate 200 system was equipped with an especially designed laparoscopic probe that transmits the side firing high intensity focused ultrasound energy through a water filled latex sheath (figs. 1 and 2). The probe is a modification of a standard Sonablate transrectal probe used for benign and malignant prostate ablation.9 To meet the requirements of laparoscopic surgery the probe tip was made narrower and longer (18 × 30 mm.). In this design a new piezoelectric transducer (4 MHz. center frequency, 30 mm. focal length and 12 × 30 mm. aperture) was mounted in the tip of the probe to act as a source of high intensity focused ultrasound energy during tissue ablation and pulsed ultrasound during imaging. A 17 mm. at 4 and 14 days

Accepted for publication July 19, 2002.

Supported by grants from Focus Surgery, New Energy Development Organization, Japan and Methodist Research Institute.

* Financial interest and/or other relationship with Focus Surgery.
acoustic power (26 W.), high intensity focused ultrasound exposure on/off time (5/6 seconds), planned lesion size (21 × 17 × 10 mm.) and planned average treatment time (20 minutes). After treatment was completed the peritoneum overlying the kidney was closed to reduce inflammatory adhesions of bowel to the kidney, followed by closure of all port sites.

Harvest and pathological analysis. At 4 or 14 days the animals were administered a general anesthesia. Abdominal exploration documented any complications of the initial surgery. Each distal ureter was dissected and cannulated with a 5Fr ureteral catheter. Venipuncture (serum creatinine) was done and 30-minute urine samples were then obtained. Split creatinine clearance in the treated and nontreated kidney was calculated. The kidneys and proximal ureters were excised and placed in 10% formalin. The animal was sacrificed. The kidney was serially sectioned and the length, width and height of the gross high intensity focused ultrasound lesion was recorded. The lesion and surrounding tissue were then embedded in paraffin and stained with hematoxylin and eosin for histological analysis.

RESULTS

Median operative time was 180 minutes (range 65 to 230) with an average high intensity focused ultrasound activation time plus or minus SD of 18.3 ± 1.7 minutes. Seven right and 6 left kidneys were treated with lesions in the upper pole in 7 animals and in the lower pole in 6. High intensity focused ultrasound lesions were visualized sonographically during treatment (hyperechoic lesion) in 12 of the 13 animals. Notably the single animal that did not have ultrasound evidence of a high intensity focused ultrasound lesion at surgery failed to have pathological evidence of a lesion at harvest. Treatment failure in this animal was due to improper coupling of the high intensity focused ultrasound probe to the kidney surface caused by a latex sheath that was later found not to be acoustically transparent. Split creatinine clearance in the treated kidney and the nontreated contralateral kidney was similar in the acute and subacute groups (see table).

Due to complications only 4 animals in the acute and 6 in the subacute group were available for analysis. The 3 animals excluded from study included 2 in the acute group that underwent early sacrifice due to intra-abdominal abscess formation and sepsis, and 1 in the subacute group with pneumonia. In the 2 acute group animals with intra-abdominal sepsis the latex sheath on the high intensity focused ultrasound probe ruptured during treatment and in 1 of them the Veress needle also punctured the bowel during laparoscopic access. This animal required mini-laparotomy to repair the bowel and it was treated later with high intensity focused ultrasound. In addition, 3 cases of right proximal hydrouretrionephrosis, including 2 of an upper pole lesion in the acute group and of 1 a lower pole lesion in the subacute group, were noted at scheduled harvest and in 1 in the subacute group a ureteral stricture had developed. In 1 animal a skin abscess developed and another had dehiscence at the 33 mm. flank port, while 1 sustained an upper pole.

Split creatinine clearance in the treated and nontreated contralateral kidney in 4 pigs each in the acute and subacute high intensity focused ultrasound treatment groups

<table>
<thead>
<tr>
<th></th>
<th>Mean Ml./Min. Creatinine Clearance ± SD</th>
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<tr>
<td>Kidney</td>
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<tr>
<td>Contralat. Kidney</td>
<td></td>
</tr>
<tr>
<td>Treated</td>
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</tr>
<tr>
<td>Acute</td>
<td>23.7 ± 11.5</td>
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<tr>
<td>Subacute</td>
<td>32.6 ± 10.1</td>
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<tr>
<td>Contralat.</td>
<td>29.8 ± 10.1</td>
</tr>
<tr>
<td>Kidney</td>
<td>20.8 ± 9.4</td>
</tr>
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Split creatinine clearance in 2 subacute animals could not be calculated due to incomplete laboratory data, and no statistical analysis was performed due to small sample size groups.
hematoma due to ureteral catheter perforation. All 3 animals were sacrificed as planned.

Pathological findings varied with the duration of followup. Immediately after the procedure the gross appearance of the high intensity focused ultrasound lesion showed a whitish area on the kidney surface. However, by 4 days a red rim had developed around the well delineated pale lesion (fig. 3, a). Average lesion size was $23 \pm 3 \times 17 \pm 3 \times 11 \pm 1 \text{ mm}$, remarkably similar to our intended lesion size of $21 \times 17 \times 10 \text{ mm}$. No alteration in the surrounding renal parenchyma or the collecting system wall was found and histological findings were remarkably consistent. A well defined border between the high intensity focused ultrasound lesion and surrounding parenchyma was present and at the edge of the lesion there were pronounced vascular congestion and minimal inflammatory cell infiltration. Within the high intensity focused ultrasound lesion coagulative necrosis was the predominant finding (fig. 4). The lumina of the tubules were obliterated, cell borders were indistinct and the nuclei were pyknotic and hyperchromatic. In the acute survival group we found scattered areas within the lesion where cellular viability was difficult to discern. However, by 14 days no viable cells were noted within the lesion.

**DISCUSSION**

High intensity focused ultrasound is a type of thermotherapy that destroys tissue by coagulative necrosis. Lesion evolution can be followed on ultrasound as a hyperechoic region that starts at the focus of the probe and then builds toward the transducer as the treated tissue reflects the high intensity focused ultrasound waves. This change in acoustical impedance of treated tissue to reflect high intensity focused ultrasound energy back towards the transducer results in the characteristic wedge-shaped high intensity focused ultrasound lesion (fig. 3, b). The presence of air along the energy path can also reflect the ultrasound waves. In our study air in the renal collecting system was used to shield potentially the wall of the collecting system to prevent tissue necrosis. However, we did not assess the direct effect of air versus no air in the collecting system on the safety and efficacy of high intensity focused ultrasound as part of our experiment.

An advantage of this therapy is the ability to plan preoperatively a lesion of defined size, as in our experiment, in which the intended lesion size of $21 \times 17 \times 10 \text{ mm}$ was similar to the actual average lesion size of $23 \times 17 \times 11 \text{ mm}$. Another advantage is the short duration of treatment (average 18.3 minutes), making this thermal modality competitive with renal cryoablation and radiofrequency ablation. Importantly the surface application required to deliver energy avoids the theoretical concern of tumor spillage associated with other tissue ablative methods using probes to pierce the tumor. In addition, our short-term study of high intensity focused ultrasound for partial renal ablation did not lead to any impairment in the remaining renal parenchyma anatomically or functionally (see table). Although incomplete tissue destruction by this therapy remains a concern, by 14 days after treatment no viable cells were observed within high intensity focused ultrasound lesions. Furthermore, the combination of imaging and energy delivery through the same probe was of great benefit. Hyperechogenicity at the site of high intensity focused ultrasound lesion formation has been well described. In the single animal with no lesion on ultrasound we found no discernible lesion on pathological evaluation. Given the deep penetration of energy into the renal parenchyma, simple observation alone would have missed this failed treatment.

Although high intensity focused ultrasound has many advantages over other ablative technologies, a number of shortcomings were noted. Total operative time in our study was long due to the time requirements of preparing and testing the prototype ultrasound probe and performing the initial imaging evaluation. In addition, a number of technical difficulties and complications occurred. Air blebs on the kidney
surface developed during therapy in a few cases that needed to be removed before continuing treatment. Also, great rotation of the probe, especially after the latex sheath was inflated, led to rupture of the latex sheath. In addition, the 3 cases of right proximal hydroureteronephrosis are cause for concern with no clear etiology. However, they may have been due to injury during ureteral catheter passage, during initial renal dissection using electrocautery or as an inflammatory reaction to the lesion.

High intensity focused ultrasound has been extensively studied for the ablation of normal and malignant renal tissue.\textsuperscript{16–20} Watkin et al studied the tissue effects of extracorporeal high intensity focused ultrasound in a porcine model and reported the successful creation of lesions in 13 of 18 treated kidneys.\textsuperscript{16} However, the extracorporeal delivery of this energy source resulted in skin changes in 10 cases (skin burn in 1 and skin induration in 9). In addition, wide variation in the extent of renal damage was believed to have resulted from the narrow acoustical window in the flank, respiratory movement of the nonparalyzed animal and energy attenuation during transmission through the skin and abdominal wall. Although air at the skin surface could have resulted in decreased energy penetration and skin injury, this group reported no clear correlation of the presence of a skin burn or skin induration with damage within the kidney.

Along the same lines, Chapelon et al studied the effect of extracorporeal high intensity focused ultrasound (1 MHz. transducer) on canine kidneys and reported renal lesions in 10 of 16 treated animals (63%).\textsuperscript{17} However, in 13 of 16 dogs (81%) collateral damage occurred (injury to the spleen in 8, left colon in 3, lung in 1 and pancreas in 1). In addition, in all 6 high acoustical intensity and 6 of 10 moderate acoustical intensity treated dogs skin burns developed. A study of 29 rabbit VX-2 kidney tumors with high intensity focused ultrasound with open surgical exposure of the kidneys and direct contact in 9 and transcutaneously in 9 using a 4 MHz. transducer.\textsuperscript{18} The animals were sacrificed 4 hours (direct contact group) or 1 week (transcutaneous group) after treatment. Although renal damage was reported in all 9 direct contact and 7 of 9 transcutaneous treated rabbits, tumor ablation was seen in only 7 and 2, respectively. In addition, 4 of 9 transcutaneous treated rabbits showed 1 cm. circular skin burns at the site of probe contact with the abdominal wall. This group reported that the imaging capability of the probe inadequately depicted the renal tumor, resulting in incomplete destruction. Again, respiratory movement of the kidneys during therapy was believed to have affected the results and the group recommending future coupling of the extracorporeal high intensity focused ultrasound treatment unit to imaging modalities, such as 3-dimensional ultrasound, computerized tomography or magnetic resonance imaging, to improve lesion tracking during energy activation. Briefly, these studies show the potential for noninvasive transcutaneous delivery of high intensity focused ultrasound energy. However, the limitations of incomplete or absent tissue treatment and skin burns argue for pursuing more controlled direct coupling of the probe to the tissue of interest.

Clinical application of extracorporeal high intensity focused ultrasound for treating renal cell carcinomas has been reported.\textsuperscript{19,20} Vallancien et al treated 4 patients with stages T2 to T3 renal adenocarcinoma with extracorporeal high intensity focused ultrasound 2, 6, 8 and 15 days before nephrectomy, respectively.\textsuperscript{19} Histological examination of the treated kidneys revealed coagulative necrosis in the targeted tumor area with a skin burn in 1 patient. Similarly Körhmann et al performed extracorporeal high intensity focused ultrasound to treat 3 renal tumors in a patient with a solitary kidney.\textsuperscript{20} Multiple sessions (3) with the patient under general anesthesia or sedation analgesia were required to treat the tumors with 2 lesions effectively treated at the 6-month radiological followup. Unfortunately 1 lesion (upper pole) was inadequately treated due to ultrasound energy absorption by the interposed ribs. Again these studies highlight the great potential of extracorporeal high intensity focused ultrasound for renal malignancies. However, until the problems of skin burns and incomplete tissue destruction are overcome, minimally invasive laparoscopic direct coupling of high intensity focused ultrasound energy to tumor may be a more effective cancer treatment.

CONCLUSIONS

Our study shows the feasibility of the direct application of high intensity focused ultrasound energy via a probe specifically designed for laparoscopic use. A uniform lesion within the kidney was created with no viable cells within the lesion at 2 weeks after treatment. This study represents another step in the quest to develop a noninvasive high intensity focused ultrasound delivery system for treating small renal tumors.

Tracy Robinson, Stephanie Derdak and Ed Brizendine provided assistance.

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