Laparoscopy

A Novel Approach to Energy Ablative Therapy of Small Renal Tumours: Laparoscopic High-Intensity Focused Ultrasound

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Abstract

Objective: High-intensity focused ultrasound (HIFU) permits targeted homogeneous ablation of tissue. The objective of this phase 1 study was to evaluate the feasibility of HIFU ablation of small renal tumours under laparoscopic control.

Patients and methods: Ten kidneys with solitary renal tumours were treated with a newly developed 4.0 MHz laparoscopic HIFU probe. In the first two patients with 9-cm tumours, a defined marker lesion was placed prior to laparoscopic radical nephrectomy. In eight patients with a mean tumour size of 22 mm (range, 11–40), the tumour was completely ablated as in curative intent, followed by laparoscopic partial nephrectomy in seven tumours. One patient had post-HIFU biopsies and was followed radiologically. Specimens were studied by detailed and whole-mount histology, including NADH stains.

Results: Mean HIFU insonication time was 19 min (range, 8–42), with a mean targeted volume of 10.2 cm³ (range, 9–23). At histological evaluation both marker lesions showed irreversible and homogeneous thermal damage within the targeted site. Of the seven tumours treated and removed after HIFU, four showed complete ablation of the entire tumour. Two had a 1- to 3-mm rim of viable tissue immediately adjacent to where the HIFU probe was approximated, and one tumour showed a central area with about 20% vital tissue. There were no intra- or postoperative complications related to HIFU.

Conclusion: The morbidity of laparoscopic partial nephrectomy mainly comes from the need to incise highly vascularized parenchyma. Targeted laparoscopic HIFU ablation may render this unnecessary, but further studies to refine the technique are needed.

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1. Introduction

Renal tumours with a diameter < 4 cm are reliably cured by partial nephrectomy [1,2], but there is an associated complication rate of up to ~15%, which mainly comes from the need to incise the highly perfused renal parenchyma [3]. Less invasive energy ablative techniques avoiding this therefore appear attractive, especially when performed through a percutaneous route. Percutaneous needle ablation using radiofrequency has been utilized extensively for this purpose, but recent meta-analyses reflect residual tumour/early recurrences in up to 14–18% of patients [4,5]. Reports on needle cryoablation give similar failure rates [6,7]. The obvious problem comes from the need for precise percutaneous needle placement in a mobile organ and a fairly small target. Energy ablative techniques administered under laparoscopic control are more reliable because the needles can be placed under visual and laparoscopic ultrasonography control. Radiofrequency ablation has an inherent problem of skipping even in this situation [8], but cryoablation achieves reliable tumor ablation, with residual/recurrent tumour rates of 1.6% with follow-up over 3 yr [9]. Nevertheless, the tumour still has to be punctured, which may result in bleeding [10] and carries an inherent risk of tumour cell spillage [11]. A technique ablating the tumour clearly appears more attractive.

High-intensity focused ultrasound (HIFU) avoids the need to puncture because ultrasound waves are focused to achieve high temperatures sufficient for immediate thermal destruction of all tissues within the target zone. Ideally this procedure is done by an extracorporeal approach; however, because of the acoustic complexity of intervening structures and the mobility of the kidney, attempts at this approach were unsatisfactory [12]. Such problems are avoided if the HIFU transducer is brought directly to the target (ie, with laparoscopic HIFU). This study examines the histological effects of laparoscopic HIFU ablation of small renal tumours to determine the viability of the approach from the standpoint of complete tumour ablation and potential technical limitations.

2. Materials and methods

After being approved by the Institutional Ethics Review Board (EK 536/2005), we conducted this clinical phase 1 study between November 2006 and March 2007. The selection for oncological treatment was based on standard surgical principles (laparoscopic radical nephrectomy for large tumours, laparoscopic partial nephrectomy in tumours < 4 cm, and palliative renal tumour treatment in metastasized renal cell carcinoma [RCC]). Ten patients with a solitary renal mass suspicious for RCC on the basis of helical computed tomography (CT) or magnetic resonance imaging (MRI) scans were treated with laparoscopic HIFU. In two patients with 9-cm tumours, a defined marker lesion was generated with HIFU at the external side of the tumour followed immediately by laparoscopic radical nephrectomy to prove feasibility of the technique. HIFU ablation of the entire tumour with a margin of 2–3 mm of surrounding parenchyma (“curative intent”) was performed in the remaining eight patients with small tumors.

In seven patients, laparoscopic partial nephrectomy with temporary clamping of the renal artery was conducted post-HIFU as described elsewhere [8]. The plane of resection was well outside of the treatment zone to be able to evaluate the extent of ablation and to prove efficacy of HIFU ablation. In patient 10 who had high comorbidity and proven lung metastases, the tumour was not excised after HIFU, but the same target zone was treated twice. Biopsies were performed before and after HIFU. The patient was subsequently followed with helical CT scans.

Laparoscopic surgical access, with the use of four 12-mm access ports, was performed under general anesthesia as a standard transperitoneal procedure with the patient in a 45° lateral decubitus position. In all patients, the diseased kidney was completely mobilized and cleared of fat. The hilar structures were dissected, but the artery was not primarily occluded. Intraoperative renal power Doppler ultrasonography was performed with a 10-Hz laparoscopic ultrasound probe (BK Medical, Denmark) to precisely locate the renal lesion to be treated. Prior to HIFU treatment, two core tumour biopsies were obtained from the tumour with an 18-G biopsy needle (Boston Scientific, USA). One port was then changed to an 18-mm port (Ethicon, USA) to allow access for the HIFU probe.

The laparoscopic HIFU system (Sonatherm®, Misonix Inc, Farmingdale, NY, USA) used consisted of the treatment console, an articulated probe arm, a pump unit, and the laparoscopic probe (Fig. 1). The latter is gas-sterilisable and covered with a flexible bolus through which gas-free cold
Fig. 2 – Intraoperative view of laparoscopic high-intensity focused ultrasound of lower pole renal cell cancer; the kidney is held in place with an endoretractor.

Fig. 3 – Marker lesion in large renal cell cancer (patient no. 2). (a) Overview: The area within the dotted line shows "homogeneous severe thermal damage" (a), viable tissue (v). (Hematoxylin-eosin stain; original magnification: ×40.) (b) Detail of 3a, showing "severe thermal damage" defined as diffuse pycnosis of nuclei, rupture of cell membranes, erythrocytes with disrupted cell membranes. (Hematoxylin-eosin stain; original magnification: ×200.)

Table 1 summarises patient characteristics prior to treatment, the treatment protocol used in individual patients, and the final histological results.
Respiratory movement and/or kidney morbidity did not impact delivery of HIFU energy. Comparison of images taken at treatment planning with those during insonication showed that target motion was always <5 mm.

The two marker lesions in patients 1 and 2 with extensive RCC showed homogenous severe thermal damage that matched the site and volume targeted almost precisely (Fig. 3a and b).

The mean diameter of the tumours treated in “curative intent” in patients 3–10 was 22 mm (range, 11–48). Mean HIFU exposure time was 19 min (range, 8–42), whereas the time needed for the entire HIFU procedure (including port placement, probe insertion and positioning, treatment planning, and probe removal) was 39 min (range, 27–59). Patients 3 and 4 showed a subcapsular rim of 1–3 mm of vital tissue immediately adjacent to where the HIFU probe was approximated to the kidney, with otherwise homogenous severe thermal damage of the entire tumour (Fig. 4). Assuming that this outcome was caused by too aggressive cooling of the probe, we subsequently increased the temperature of the coolant to 18 °C, and this observation was not experienced again. The tumour treated in patient 7 showed vital tissue in about 20% of the tumour, located centrally, with homogenous severe thermal damage of the rest (Fig. 5). The other four tumours removed by partial nephrectomy after HIFU were all found to have homogenous severe thermal damage ablation within target.

Table 1 – Pertinent patient characteristics and treatment details

<table>
<thead>
<tr>
<th>Pat no.</th>
<th>Age (yr)</th>
<th>Tumour size (mm)</th>
<th>Intention to treat</th>
<th>Treatment details</th>
<th>Targeted volume</th>
<th>Final histology of tumour</th>
<th>Severe thermal damage ablation wtin target</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 54</td>
<td>90</td>
<td>Marker Lap N</td>
<td>2 treatment zones</td>
<td>2.4 cm × 32²: 13:58 min 2.0 cm × 42²: 15:09 min</td>
<td>11 cm³ (33 W) 9 cm³ (34 W)</td>
<td>Clear-cell RCC pT3a, G2</td>
<td>100%</td>
</tr>
<tr>
<td>2 65</td>
<td>90</td>
<td>Marker Lap N</td>
<td>2 treatment zones</td>
<td>2.0 cm × 32²: 17:09 min and 1.4 cm × 24²: 8:45 min</td>
<td>9 cm³ (35 W) 5 cm³ (35 W)</td>
<td>Clear-cell RCC pT3b, G4</td>
<td>100%</td>
</tr>
<tr>
<td>3 42</td>
<td>28</td>
<td>Curative Lap NSS</td>
<td>1 treatment zone</td>
<td>2.8 cm × 46²: 31:39 min</td>
<td>15 cm³ (30–32 W)</td>
<td>Clear-cell RCC pT1a, G2</td>
<td>95%</td>
</tr>
<tr>
<td>4 77</td>
<td>25</td>
<td>Curative Lap NSS</td>
<td>1 treatment zone</td>
<td>2.3 cm × 26²: 9:50 min</td>
<td>7 cm³ (34–38 W)</td>
<td>Clear-cell RCC pT1a, G2</td>
<td>96%</td>
</tr>
<tr>
<td>5 50</td>
<td>15</td>
<td>Curative Lap NSS</td>
<td>1 treatment zone</td>
<td>2.6 cm × 50²: 24:35 min</td>
<td>15 cm³ (32–33 W)</td>
<td>Angiomyolipoma</td>
<td>100%</td>
</tr>
<tr>
<td>6 75</td>
<td>20</td>
<td>Curative Lap NSS</td>
<td>1 treatment zone</td>
<td>3.6 cm × 52²: 30:16 min</td>
<td>21 cm³ (33–36 W)</td>
<td>Chronic inflammatory cyst</td>
<td>100%</td>
</tr>
<tr>
<td>7 79</td>
<td>10</td>
<td>Curative Lap NSS</td>
<td>1 treatment zone</td>
<td>1.6 cm × 26²: 10:06 min</td>
<td>5 cm³ (30 W)</td>
<td>Clear-cell RCC pT1a, G2</td>
<td>80% skipping</td>
</tr>
<tr>
<td>8 33</td>
<td>48</td>
<td>Curative Lap NSS</td>
<td>1 treatment zone</td>
<td>3.4 cm × 58²: 41:50 min</td>
<td>23 cm³ (30–34 W)</td>
<td>Angiomyolipoma</td>
<td>100%</td>
</tr>
<tr>
<td>9 75</td>
<td>12</td>
<td>Curative Lap NSS</td>
<td>1 treatment zones</td>
<td>2.4 cm × 32²: 13:58 min</td>
<td>8 cm³ (35–37 W)</td>
<td>Clear-cell RCC pT1a, G2</td>
<td>100%</td>
</tr>
<tr>
<td>10 55</td>
<td>23</td>
<td>Ablative Lap Bx</td>
<td>1 treatment zone treated twice</td>
<td>1.8 cm × 26²: 7:46 min</td>
<td>5 cm³ (35–37 W)</td>
<td>Clear-cell RCC pT1a, G2</td>
<td>100%</td>
</tr>
</tbody>
</table>

Pat, patient; Lap N, laparoscopic nephrectomy; Lap NSS, laparoscopic nephron-sparing surgery; Lap Bx, laparoscopic biopsy; RCC, renal cell carcinoma.

Fig. 4 – Renal cell cancer treated with curative intent showing a subcapsular rim of viable tissue adjacent to entry of high-intensity focused ultrasound energy (v) with otherwise homogenous severe thermal damage of entire tumor (a) (patient no. 3). (Hematoxylin–eosin stain; original magnification: ×40.)
thermal damage of the entire tumour without
evidence of skip lesions (Fig. 6).

In patient 10 intraoperative power Doppler ultra-
sonography showed no sign of residual perfusion
after HIFU ablation, and core biopsies taken imme-
diately thereafter likewise demonstrated homoge-
neous severe thermal damage. Follow-up helical CT
scans after 3 and 6 mo showed no contrast
enhancement and shrinking of the lesion.

Patient 1 had a tumour 9 cm in diameter in the
upper half of the left kidney. At radical nephrectomy
the tail of the pancreas was lacerated when the left
adrenal gland was removed. This complication
resulted in prolonged wound drainage, but required
no further treatment. Otherwise no complications
were observed in the entire group. Follow-up for all
patients now is a mean 7.2 mo (range, 6–11). Follow-
up CT scans showed no evidence of hematoma,
residual/recurrent tumour, or any other abnorm-
ality.

4. Discussion

As an ultrasound wave propagates through biolo-
gical tissues, it is progressively absorbed and its
mechanical energy converted to heat. If brought to
a tight focus at a selected depth within tissues
(HIFU), the high energy density produced in this
region rapidly results in temperatures exceeding
the threshold of irreversible protein degradation
and subsequently coagulative necrosis [19]. The
energy decreases sharply outside the focal zone, so
that surrounding tissues remain unharmed. This
permits targeted ablation within organs without
the need of directly accessing the target site. As
heat generation is extremely rapid, potential heat
sinks such as large blood vessels impact lesioning
to a lesser degree than with other, slower
techniques of thermal ablation [19]. Obviously
for the same reason, HIFU of malignant tumours
has not been shown to cause tumour cell dis-
semination or an increased rate of metastases
[20,21].

Unfortunately these principles of HIFU ablation
also require fairly homogeneous tissue structures
without significant acoustic interphases along the
path of ultrasound delivery and a stationary target.

Fig. 5 – Renal cell cancer treated with curative intent with
homogeneous severe thermal damage within dotted line,
but viable tissue shown centrally (patient no. 7).

Fig. 6 – Renal cell cancer treated with curative intent
(patient no. 9). (a) Overview: The entire tumor shows
homogeneous severe thermal damage including margins
of normal parenchyma; viable tissue is only outside
treatment zone (v). (Hematoxylin-eosin stain; original
magnification: ×40.) (b) Histochemical nicotinamide
adenine dinucleotide (NADH) stain from same patient.
Black arrows: positive NADH staining in a rim of normal
renal parenchyma (v); red arrows: homogeneous severe
thermal damage (a) with complete depletion of NADH.
achieved trans-scrotally to the testis [22], transrectally to the prostate [19,23], and even to the kidney when the organ is surgically exposed [16]. HIFU of renal tumors by an extracorporeal approach has proven unreliable both in animal experiments and clinical pilot studies [24–26]. The acoustical complexity of the abdominal wall and perirenal structures, and the mobility of the kidney are eliminated if the transducer is brought directly to the kidney. With the laparoscopic HIFU transducer with an overall diameter of 18 mm used in this study, this approach becomes feasible with standard laparoscopic techniques and equipment. Albeit more invasive than an extracorporeal HIFU approach, the time needed compares well with laparoscopic cryoablation. The morbidity of nephron-sparing excision of renal tumours mainly arises from the need to incise the renal parenchyma, with or without clamping the renal artery [3]. This complication is avoided by laparoscopic HIFU ablation. No HIFU-specific complications were observed in the study.

Homogeneous and severe thermal damage of the entire targeted zone was documented histologically in six of nine masses. Not all lesions treated were confirmed to be RCC. In a similar study of radiofrequency ablation, angiomyolipomas and septated, cystic tumours showed most pronounced skipping [8]. In contrast all nonmalignant tumours treated herein, including the vascularised angiomyolipoma and the complex cyst, showed homogeneous severe thermal damage of the entire lesion and 2–3 mm of surrounding parenchyma. The superficial zone of vital tissue observed in two of the first patients with renal cancer treated with curative intent was assumed to result from overzealous cooling of the HIFU probe. It was not observed again when the cooling was limited to 18 °C. It may also have resulted from insufficient energy coupling from the probe to the kidney at HIFU insonication, which was routinely performed by securing the kidney in place with a fan retractor and by generous application of sterile ultrasonography gel. The gel tends to dissipate rapidly during insonication, and only with growing experience was the problem mastered satisfactory. The one tumour documented to have a central area of vital tissue remains a reason for concern. It had a homogeneous structure and was correctly insonicated according to the intraoperative ultrasonography documentation. Unnoticed problems at energy coupling are also the most likely explanation because we found small air bubbles at the HIFU probe at the end of the procedure. The air bubbles may have interfered with energy deposition, even if the amount of air was small.

The objective of this phase 1 study was to establish clinical proof of principle and to document safety. These goals were achieved and underline the results in porcine kidneys [15]. Laparoscopic HIFU of small peripheral renal tumours is clinically feasible and resulted in no HIFU-specific complications. Nevertheless, it is important to note the limitations of the study and the technique applied. Because of the probe’s focal distance, only tumours (or target lesions) less than 3.5 cm diameter and in a peripheral exophytic position were treated. With larger or more centrally located tumours, the entire lesion cannot be insonicated and incomplete ablation has to be assumed. It appears fair to point out that central and very large tumours are poorly suited for energy ablative therapy in general and have a high failure rate regardless of the technique used [8,26,27]. Although all lesions were assumed to be solid tumours at preoperative imaging, one was actually a complicated cyst and three were benign tumours. This reflects the clinical experience when treating these tumours [28]. The ablation technique, especially concerning energy coupling and defining target volume, was modified during the study in incremental steps with growing experience, but the optimum technique may still not have been reached. Finally the completeness of ablation was concluded from homogeneity of histological signs of severe acute thermal damage. Although the criteria defined have been shown to correlate with irreversible cell damage and, with more time between thermal insult and histological evaluation, the extent of coagulative necrosis [16,19,22], they cannot automatically be equated. Repair processes, but also additional posttraumatic malperfusion injury also impact the extent of ablation ultimately achieved. Defining the clinical efficacy of laparoscopic HIFU ablation of renal tumours requires long-term follow-up studies [29], with serial cross-sectional imaging and percutaneous biopsy of any residual contrast-enhancing lesion, and ultimately long-term data on recurrence-free survival.

5. Conclusion

The morbidity of laparoscopic partial nephrectomy mainly comes from the need to incise highly vascularized parenchyma. Targeted laparoscopic HIFU ablation may render this unnecessary, but further studies to refine the technique are needed.
Conflicts of interest

The HIFU equipment and the 18-mm disposable ports were provided free of charge for this study by Focus Surgery Inc (Indianapolis, IN, USA) and Misonix Inc (Farmingham, NY, USA).

R. Seip and N. Sanghvi are employees of Focus Surgery Inc. The other authors have no financial connection with Focus Surgery Inc or other conflicts of interest.

References


Editorial Comment on: A Novel Approach to Energy Ablative Therapy of Small Renal Tumours: Laparoscopic High-Intensity Focused Ultrasound

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Technological advances as well as cultural and economic vectors have caused a dramatic shift from traditional “Robsonian” open, radical nephrectomy to nephron-sparing surgery (NSS) using laparoscopy and minimally invasive techniques. Three locomotives are driving the process: (1) NSS provides lifelong advantage (ie, freedom from dialysis) [1]. (2) NSS for T1 masses provides a curative outcome that is as good as nephrectomy [2]. (3) Laparoscopy is less morbid than the supracostal open approach. For a long period, high-intensity focused ultrasound (HIFU) has promised to deliver the ultimate non-invasive extracorporeal tumor ablation. Only recently has HIFU, in conjunction with improved imaging capabilities, materialized into a clinical option additional to laparoscopic partial nephrectomy, radiofrequency ablation, and cryoablation. Within this framework, the authors report on a phase 1 study in a small group of patients with limited follow-up using laparoscopic-guided extracorporeal HIFU ablation of small renal tumors [3]. Turning to laparoscopic guidance as opposed to an extracorporeal approach suggests that for the time being, extracorporeal HIFU ablation is facing great technical difficulties. This is intensified by the disturbing rate of residual viable tumor reported by the authors. Two patients had a 1–3-mm rim of viable tissue immediately adjacent to where the HIFU probe was approximated to the tumor. One patient had a central area of vital tissue of about 20% of its volume. Having that said, this is the newest ablative technique introduced and still in the process of development. By no means will HIFU be judged in the future by its ability to turn into an effective extracorporeal procedure in a competitive environment. On one hand the indication for NSS is already being extended but, on the other hand, elderly patients or those with poor surgical risk are being followed expectantly within the frame of few experimental studies. Although controversial, ablative measures may perhaps have a role in the cytoreduction of primary tumors in patients with metastatic disease in the present era of more effective targeted therapies.

References


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Editorial Comment on: A Novel Approach to Energy Ablative Therapy of Small Renal Tumours: Laparoscopic High-Intensity Focused Ultrasound

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The widespread use of abdominal computed tomography and ultrasonography complicates the management of small incidentally detected renal masses. Their slow growth and the difficulty in differentiating benign from malignant lesions preoperatively make the clinical significance of such lesions unclear. Although partial nephrectomy is currently considered the standard of care for these lesions, minimally invasive probe ablation techniques are now emerging as potential alternative approaches [1,2]. Although laparoscopic cryoablation represents the most widely used of these novel techniques, high-intensity
focused ultrasound (HIFU) ablation has shown promise in the treatment of solid tumors [3,4]. In this original study [5], Klingler et al report on their initial phase 1 experience with laparoscopic intracorporeal HIFU ablation of small renal tumors. Ten patients with radiographic suspicion of renal cell carcinoma (RCC) underwent laparoscopic HIFU ablation, followed by, in nine of these patients, laparoscopic nephrectomy to pathologically validate the HIFU ablation.

The objective of this phase 1 study was to demonstrate proof of principle and to document safety and should only be considered as such. As far as a new ablative measure, it has to be further refined because the rate of residual viable tumor is worrisome. Their experience is limited due to the small number of patients (n = 10) and the quite short reported median follow-up of 7.2 mo.

In conclusion, these results show that laparoscopic HIFU ablation is not a suitable option for the treatment of RCC, but further studies might ultimately demonstrate otherwise. Moreover, one has to wonder if this study signals that the attempts for extracorporeal HIFU ablation of renal masses are concluded, for the time being, due to technical limitations.

References


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