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Laparoscopic high-intensity focused ultrasound for renal tumours: a proof of concept study

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Study Type – Therapy (case series)
Level of Evidence

What's known on the subject? and What does the study add?
Renal cancer is increasingly diagnosed when tumours are small and asymptomatic, during routine abdominal imaging. Whilst surgery is an effective and potentially curative option, it carries a significant risk of complications. Recent work suggests that thermally ablative therapies (RFA, cryotherapy, HIFU) may be suitable minimally invasive treatment options in selected patients.

The success of extracorporeal HIFU has been limited by the abdominal wall and rib-cage limiting energy delivery. For this study, a purpose-built laparoscopic HIFU probe was designed to allow direct application of the transducer to the tumour surface, thus facilitating tumour destruction. Successful and accurate tumour destruction was demonstrated, paving the way for further clinical trials, subject to device modifications.

OBJECTIVE

- To test and establish clinical proof of concept for a laparoscopic high-intensity focused ultrasound (HIFU) device that facilitates delivery of ultrasound by direct application of a probe to the tumour surface.

PATIENTS AND METHODS

- Twelve patients with renal tumours were treated with laparoscopic HIFU using a newly designed probe inserted via an 18-mm laparoscopic port.
- HIFU treatment was targeted at a pre-defined proportion of the tumour and immediate laparoscopic partial or radical nephrectomy was then performed.

RESULTS

- No tumour ablation was seen in the first five patients which made modifications in the treatment protocol necessary. After this, definite histological evidence of ablation was seen in the remaining seven patients.
- The ablated zones were within the targeted area in all patients and no intra-lesional skipping was seen.
- Subcapsular skipping was seen at the probe–tumour interface in two patients with viable tumour cells seen at microscopy.
- One patient did not undergo surgical extirpation; subsequent biopsy revealed no viable tumour cells.
- There were no intraoperative or postoperative complications directly related to HIFU therapy and patients have reached a mean (range) follow-up of 15 (8–24) months with no evidence of metastatic disease or late complications.

CONCLUSIONS

- Tumour ablation with laparoscopic HIFU is feasible.
- Homogenous ablation can be achieved with no vital tissue within the targeted zone.
- The technique is associated with low morbidity and may have a role in the definitive management of small tumours.

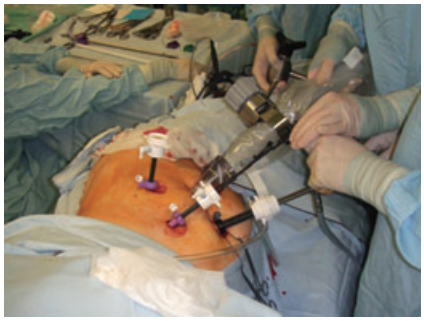
KEYWORDS

kidney neoplasms, high-intensity focused ultrasound, HIFU, nephrectomy, renal cancer, minimally invasive therapy

INTRODUCTION

The incidence of renal cancer is increasing; recent USA and UK statistics suggest an annual increase of 2–4% depending on sex and ethnic origin [1,2]. This increase is partly, but not entirely, attributable to the increased use of abdominal imaging [1,3]. There is evidence that both the stage and tumour dimensions at the time of diagnosis are decreasing [4,5] and more than 60% of these are discovered in the absence of symptoms attributable to the pathology [6]. These changes have resulted in a new entity – the small renal mass (SRM). The best management of these SRMs is uncertain and is made more challenging by the marked increase in incidence of SRMs in the elderly and co-morbid. Conventionally, the SRM has been considered to be slow growing. Indeed, a study of 287 tumour-bearing (up to 4 cm) kidneys found nearly 20% were benign and more than 85% of the malignant lesions were Fuhrman grade I or II [7]. In contrast, the same

FIG. 1. Patient positioning and the laparoscopic HIFU system.



study also demonstrated that of the 3–4 cm tumours, 25% were of Fuhrman grade III or IV and more than 35% were stage 3a or greater; 8% of these tumours had metastasized at the time of diagnosis.

Currently the 'gold standard' management for radiologically suspicious SRMs (clinical stage T1a) is partial nephrectomy. Studies have shown similar oncological outcomes with less impact on renal function in comparison with radical nephrectomy [8–10]. However, complication rates associated with partial nephrectomy may approach 20%, whether performed openly or laparoscopically [11]. Of these complications, nearly half are medical (renal failure, myocardial infarction, pulmonary embolism), reflecting the co-morbidity within the population group.

As a result of high rates of benignity and high surgical complication rates, minimally invasive ablative technologies have developed over the last 20 years. Thermal damage can result in tumour destruction without the need for surgical incision into the highly vascular renal parenchyma [12]. This can be done using radiofrequency ablation (RFA), cryoablation (CA) or high-intensity focused ultrasound ablation (HIFU) [13–15]. Of these methods, RFA and CA are the most developed and seem to give acceptable medium term oncological outcomes with low complication rates [16]. Extracorporeal HIFU for kidney tumours has been assessed in phase I/II trials with some success. However, early promise with extracorporeal devices was dampened by sub-optimal dose delivery because of attenuation of the abdominal wall and rib cage, coupled with the inherent difficulties of patient movement during tumour targeting [17].

To overcome the problems associated with the abdominal wall, a HIFU transducer attached to a laparoscopic probe has been designed to apply directly to the renal tumour surface. *In vivo* large animal studies using this device (Sonoblate® 500; Misonix Inc., Farmingdale, NY, USA) have demonstrated that repeatable, well delineated necrotic lesions could be created in a highly vascular organ such as the kidney [18]. The present clinical trial, using the same device, was designed to establish whether similarly accurate ablative lesions could be created in the fully vascularized human kidney without significant HIFU-related adverse events.

PATIENTS AND METHODS

Ethical approval for this trial was obtained from local committees (Oxford, UK; Turin, Italy). In total, 12 patients were recruited (Oxford – Ox 1–7; Turin – Tu 1–5) into this feasibility trial. All patients had a recent diagnosis of a radiologically suspicious renal lesion(s) on contrast-enhanced CT. All were deemed suitable for surgical resection, with no evidence of locally advanced or metastatic disease. Informed consent was obtained to undertake laparoscopic HIFU treatment of a pre-defined proportion of renal tumour before immediate laparoscopic partial nephrectomy (LPN) or laparoscopic radical nephrectomy (LRN) during the same procedure. Selection criteria for oncological treatment were based on standard surgical principles: tumours >4 cm were managed with LRN; tumours <4 cm were managed with LPN where surgically feasible. The decision to undertake LPN was made by the operating surgeon based on preoperative cross-sectional imaging. In two of five patients with <4 cm tumours, LPN was not possible because of the presence of more than one tumour, therefore LRN was performed.

One patient (Tu 5), had significant co-morbidity and thus laparoscopic HIFU was undertaken without subsequent surgical excision. Biopsy of the tumour was performed post-HIFU to assess for residual viable tumour cells.

LAPAROSCOPIC HIFU TECHNIQUE

The laparoscopic HIFU technique has been described previously [19]. All procedures were performed transperitoneally under general anaesthesia (Fig. 1). Laparoscopic access was obtained using 4-port access; the laparoscopic probe was placed through an 18-mm port inserted via a previous 12-mm port site with no increase in incision length. After treatment of patient Ox1, peri-nephric fat overlying the tumour was removed before positioning the probe adjacent to the tumour using real-time diagnostic ultrasound. The HIFU system used (Misonix Inc.) comprises a 4-MHz therapeutic transducer with 35-mm focal length identical to that described previously [19].

A volume of tumour was visualized using bi-planar diagnostic ultrasound and a treatment volume mapped using the HIFU system with power levels of 8–35W. HIFU was conducted in continuous mode with the tumour furthest from the transducer treated first to avoid attenuation of the beam by (more proximal) ablated tissue with its differing acoustic properties.

High-intensity focused ultrasound treatment was performed with a fully vascularized kidney; after treatment a routine LPN or LRN was performed with intact specimen removal.

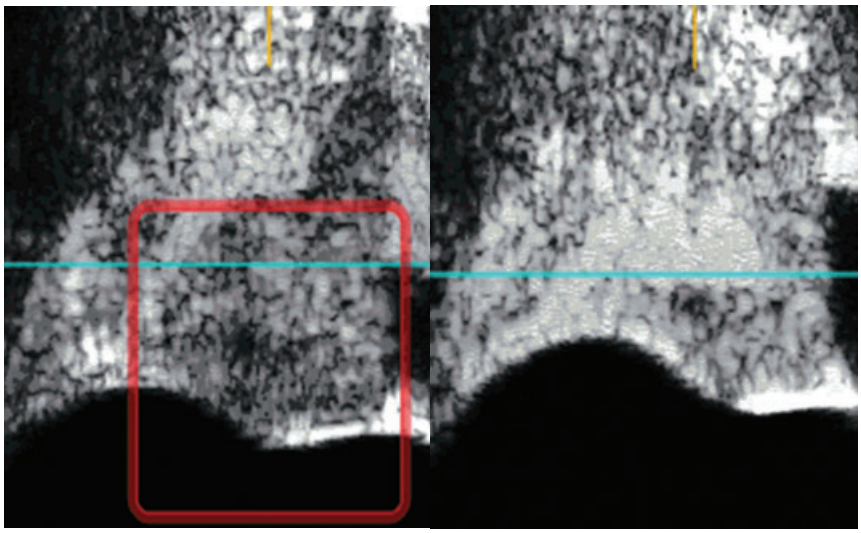
TREATMENT MONITORING

The HIFU treatment was monitored using B-mode ultrasound images taken during HIFU-off time every 30 s. Greyscale has been shown to be a useful marker for cellular necrosis (Fig. 2) [20]. Pre- and post-ablation B-mode images are automatically displayed on screen during off time, allowing both a qualitative and quantitative comparison – hyperechoic regions imply successful ablation. As such, the power level was increased in a stepwise fashion until hyperecho was visualized in the target zone, using the minimum power necessary. Careful monitoring is essential as excessive heating of pre-focal tissues causes significant image degradation requiring temporary cessation of the treatment to allow cooling.

SPECIMEN ANALYSIS

Specimens were sent unfixed on ice for immediate cut-up and macroscopic assessment by an expert urological pathologist. The tumour was sectioned parallel to the axis of the probe to enable accurate correlation between targeted and actual ablation. Macroscopic images were obtained (Fig. 3) and whole-mount or standard-size sections were made using routine formalin fixed and paraffin embedded material, with haematoxylin and eosin (H&E)

FIG. 2. Real-time greyscale ultrasound changes.



Pre-treatment B-mode ultrasound image of tumour

Post-treatment image demonstrating greyscale change

FIG. 3. Macroscopic appearance of zone of ablation (A) in resected specimen.

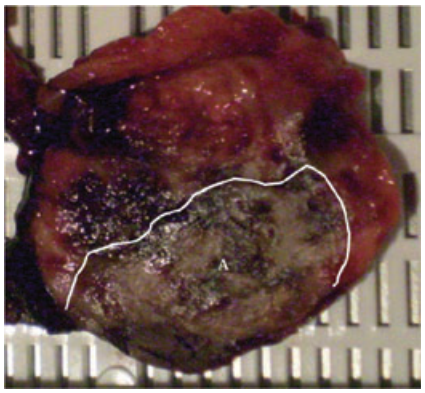
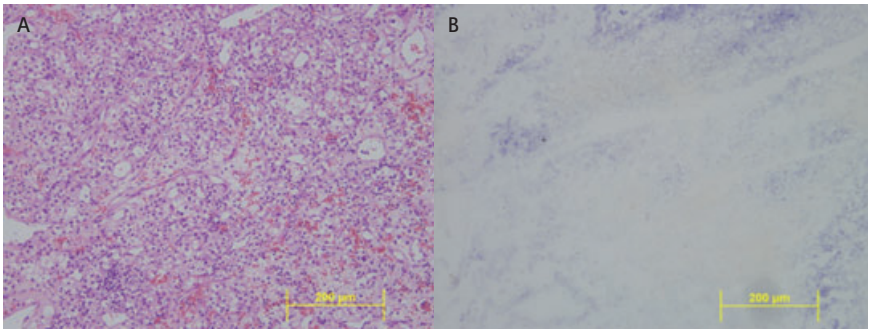


TABLE 1 Patient demographics

Variable	Mean (range) or n
Age, years	72 (49–85)
Tumour size, cm	3.8 (2.0–4.7)
Kidney	
Right	5
Left	7
Tumour position	
Upper pole	2
Interpolar	5
Lower pole	5
Tumour location	
Entirely endophytic	2
<50% exophytic	6
>50% exophytic	4
HIFU treatment	
HIFU insonication time, min	29 (13–40)
Volume targeted, cm^3	14 (4–24)

FIG. 4. Histological evidence of ablation. ***A****, H&E of ablated tumour in patient Ox 5 showing signs of ablation including: erythrocyte homogenization; variation of shape, size and lysis of red cells within blood vessels; endothelial damage and granular protein deposits on vessel walls; homogenization of vascular smooth muscle; shrinkage and loss of cell membrane detail of tumour cells; and pyknosis of nuclei.* ***B****, NADH stain of tissue in Fig. 5A. The lack of uptake of the vitality stain indicates that the histological signs shown in Fig. 5A represent thermal ablation and not morphological features of the tumour itself.*



staining to assess for evidence of thermal ablation and coagulative necrosis (Fig. 4A). In addition, matching sections of fresh tissue were taken from ablated areas of tissue and snap frozen in liquid nitrogen. Frozen sections were subsequently stained using nicotinamide adenine dinucleotide (NADH) as a marker for cell death to establish feasibility for its use in future HIFU studies (Figs 4B, 5).

Postoperatively, patients were managed routinely for a LRN or LPN. Patients were assessed regularly for evidence of any complications and serum creatinine levels were monitored daily for at least 3 days. Patients were followed for a mean (range) of 15 (8–24) months. Routine postoperative cross-sectional imaging was undertaken at 3 months to assess for evidence of disease recurrence or metastasis and then 6-monthly or annually thereafter.

RESULTS

Table 1 outlines the patient demographics and Table 2 describes the HIFU treatment variables, outcomes and final histology.

INITIAL EXPERIENCE (OX 1–4; TU 1–2)

Notably, no definitive histological evidence of ablation was seen in the first five patients treated (Ox 1–3; Tu 1–2). In the first patient (Ox 1), significant peri-nephric fat necrosis was seen on histological sectioning because of pre-focal ablation. After this case, all peri-nephric fat overlying the tumour was removed before probe positioning.

In patients Ox 2, Ox 4 and Tu 1, a cystic tumour was treated. Significant greyscale changes were seen on the post-ablation ultrasound images and were interpreted as successful

TABLE 2 HIFU treatment variables and outcomes

Patient no.	Max. tumour dimension (cm)	Tumour location	Surgery	Treatment details	Volume targeted (cm^3)	Histology	HIFU damage in target zone (%)	Comment
Ox 1	4.5	Left interpolar <50% exophytic	LRN	TT 29 min, dense peri-nephric fat	14	RCC	0	No evidence of ablation
Ox 2	4.4	Left interpolar >50% Exophytic	LRN	TT 16 min, cystic tumour	6	RCC	<10	Partial ablation in solid tumour
Ox 3	4.7	Left interpolar >50% Exophytic	LRN	TT 40 min	14	Oncocytoma	0	No evidence of ablation
Ox 4	3.5	Right upper pole Endophytic	LRN	TT 36 min, multiple tumours, ablation of normal kidney	4	RCC	0 (tumour) 100 (normal)	No evidence of ablation in tumour; clear ablation in normal kidney
Ox 5	4.5	Left lower pole <50% exophytic	LRN	TT 21 min	6	RCC	100	Evidence of ablation in target zone; no skipping
Ox 6	4.5	Right lower pole >50% exophytic	LRN	TT 30 min	14	RCC	100	Evidence of ablation in target zone; no skipping
Ox 7	4.1	Left lower pole <50% exophytic	LRN	TT 25 min	14	RCC	100	Evidence of ablation in target zone; no skipping
Tu 1	4.0	Left lower pole Endophytic	LRN	TT 15 min, part cystic tumour	18	RCC	0	No evidence of ablation
Tu 2	3.2	Right interpolar <50% exophytic	LPN	TT 45 Mins	24	RCC	0	No evidence of ablation
Tu 3	2.0	Left lower pole >50% exophytic	LPN	TT 37 mins	4	Oncocytoma	95	Evidence of ablation in target zone; 5% subcapsular skipping
Tu 4	3.0	Right upper pole <50% exophytic	LRN	TT 45 mins, multiple tumours	23	Oncocytoma	90	Evidence of ablation in target zone; 10% subcapsular skipping
Tu 4	3.0	Right upper pole <50% exophytic	LRN	TT 45 min, multiple tumours	23	Oncocytoma	90	Evidence of ablation in target zone; 10% subcapsular skipping
Tu 5	2.8	Right interpolar <50% Exophytic	Lap B	TT 13 min	22	RCC	100 (biopsy)	Evidence of ablation in target zone; no skipping

Lap B, laparoscopic biopsy; TT, treatment time.

ablation. Despite this, clear histological thermal damage was not seen except in a small area in the solid component of the tumour in patient Ox 2. It became clear that greyscale feedback from lesions with fluid components may be misleading as the creation of boiling bubbles within the cyst fluid may incorrectly signify successful ablation of the malignant cyst walls. Subsequently, only patients with predominately solid tumours were recruited into the trial.

After treatment of patients Ox 3 and Tu 2, histological evidence of ablation was not achieved using the power levels determined from animal studies. This was despite evidence of greyscale change on intraoperative ultrasound imaging. As a result, the device and its software were altered to increase energy delivery by both increasing the power output and slowing the movement of the transducer during treatment.

During treatment of the fourth patient in Oxford (Ox 4), both renal tumour and normal surrounding renal parenchyma were targeted to confirm ablation was possible in renal parenchyma and to test the effectiveness of the NADH vitality stain (Fig. 5). This stain confirmed clear evidence of cell death within the targeted area and sharp demarcation between ablated and unablated tissue.

FURTHER EXPERIENCE (OX 5–7; TU 3–5)

Definite histological evidence of ablation was seen in all specimens from the remaining patients (Ox 5–7; Tu 3–5). Histological criteria used to diagnose ablation included: coagulative necrosis of tumour and stromal cells with cytoplasmic eosinophilia and

nuclear pyknosis; disruption of cellular membranes; homogenization of intravascular erythrocytes; and smooth muscle within the walls of small vessels around the rim of the ablated area (Figs 4A, 6). All ablation occurred within the targeted area and no intra-lesional skipping was seen within any of the ablated areas. However, small areas of subcapsular skipping at the tumour surface were seen in two patients (Tu 3 and 4) with viable tumour cells seen at microscopy. The area of ablation was always accurate and within the targeted area on preoperative diagnostic ultrasound.

One patient (Tu 5) was treated with primary HIFU (entire tumour targeted) and did not undergo surgical extirpation of the lesion. Subsequent biopsy of the lesion revealed no evidence of viable tumour cells and follow-up imaging indicates complete tumour ablation.

ADVERSE EVENTS

High-intensity ultrasound treatment was universally safe in both centres with no complications directly attributable to the HIFU process. Mild to moderate discomfort was common and consistent with that expected after LRN or LPN. This was managed with appropriate analgaesia. No blood transfusions were required and there no were converted procedures.

In the postoperative period, one patient developed haematological indices consistent with disseminated intravascular coagulation (DIC). The complication presented with prolonged bleeding from a cannulation site; subsequent blood analysis revealed an elevated International Normalised Ratio (INR). This was managed conservatively and the patient made a full recovery.

FOLLOW-UP

After treatment, patients have been followed with regular cross-sectional imaging for a mean (range) of 15 (8–24) months. No local or distant tumour recurrence has been noted and no delayed complications have developed.

DISCUSSION

The purpose of this study was to establish clinical proof of concept. Our experience from this clinical trial has demonstrated that many of the problems encountered related to both the technology and tumour selection. Many of these issues were successfully addressed during the trial and the later results of the trial demonstrate proof of successful ablation using this device.

The impact of peri-nephric fat on delivery of ultrasound energy has not previously been considered in porcine animal trials [18]. Indeed, the absence of peri-nephric fat around the porcine kidney meant this was not considered before human trials. The attenuation of peri-nephric fat has not previously been investigated but the extensive pre-focal ablation evident in our patients suggests it is clinically significant. It is clear that removal of peri-tumour fat is essential to allow direct application of the laparoscopic probe to the kidney surface and allow optimal delivery of ultrasound energy. Removal of this fat is considered routine during LPN as it is during laparoscopic CA and should not affect oncological efficacy.

At the inception of the trial, ideal clinical treatment parameters had not been established and this is demonstrated in the failure to achieve clear histological evidence of ablation early in the trial. Animals study parameters were used to guide clinical treatments and led to under-treatment. This is most likely due to the high vascularity of the human kidney and the inherent morphological heterogeneity of renal tumours causing variable attenuation of ultrasound energy. This is emphasized in the case of patient Ox 4 where ablation was detected in normal kidney parenchyma but not in the tumour, despite using the same treatment parameters.

It is reassuring that after optimization of treatment parameters definite ablation was seen in all specimens thereafter. Treatment targeting was accurate and the ablated tissue was always within the targeted area. However, concerns have been raised about skipping lesions within treated areas [21]. In our series, there was evidence of subcapsular skipping in two patients. Subcapsular skipping occurs as a result of excessive cooling at the probe–tumour interface and this can be modified through changes in coolant volume and temperature. It is clear that careful probe design with this technique is paramount – an effective coupling medium is essential to ensure effective delivery of acoustic energy.

FIG. 5. NADH stain demonstrating lack of uptake of vitality stain (A) in zone of ablation with sharp demarcation from unablated area (B).

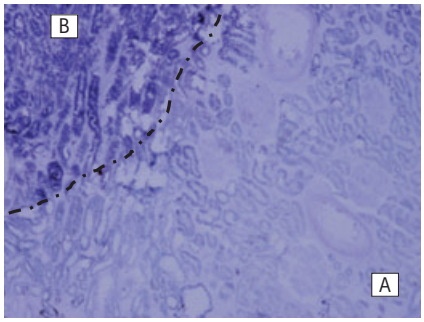
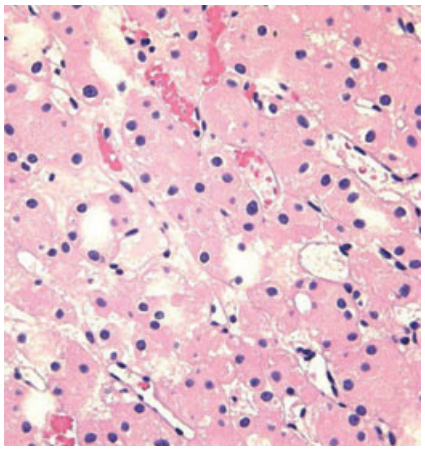


FIG. 6. High power microscopy of ablated tissue demonstrating erythrocyte homogenization, variation in red cell size and shape and nuclear pyknosis.



This medium must be appropriately cooled; excessive cooling will prevent ablation at the tumour surface whilst inadequate cooling results in over-treatment of the proximal tumour and prevents both treatment and imaging of distal targets.

Whilst we accept that evidence of viable tumour raises significant concerns, we are confident that probe modification can eliminate the lack of ablation in tissue immediately adjacent to the probe. Intra-lesional skipping is much more concerning and suggests that sufficient energy cannot be delivered to the depth required. In contrast to other series, no intra-lesional skipping was seen in our series [21].

Given the study design, it is not possible to devise detailed patient selection criteria for

laparoscopic HIFU from this trial. However, with the current transducer focal length of 35 mm, tumours whose deep margin lies greater than this distance from the probe cannot be successfully ablated. Additionally, tumours with predominately cystic components should not be selected as treatment feedback is misleading and cyst wall ablation is challenging.

Successful ablation was achieved in both right- and left-sided tumours as well as upper, inter and lower pole tumours. Provided an adequate kidney dissection can be undertaken with complete removal of peri-nephric fat, tumour location should not significantly impact on treatment outcomes.

The laparoscopic approach effectively eliminates the risk of bowel injury during HIFU treatment itself. Establishment of pneumoperitoneum and the dissection of the kidney clearly carry risks of visceral injury similar to that found with laparoscopic CA.

Insertion of the probe and its placement did not cause any complications in our study. HIFU treatment was conducted without complication in all patients; specifically there was no evidence of haemorrhage or collecting system injury as a result of insonication. The laparoscopic approach avoids any skin burns, the commonest complication of extracorporeal HIFU.

The development of DIC postoperatively warrants further discussion. It occurs as a result of tissue factor-mediated thrombin generation, coupled with dysfunctional anticoagulant systems. Tissue destruction is produced with a fully vascularized kidney during HIFU treatment and it is possible that this could result in cytokine release and subsequent coagulation abnormalities. DIC as a result of HIFU treatment has not previously been reported, but is well documented in major surgery, polytrauma and sepsis. It is not possible to conclude with absolute certainty that HIFU was not a causative factor in the development of this condition, however, the short period of time in which the damaged tissue remains *in vivo*, in our opinion, makes this scenario unlikely.

In the later patients in the trial, clear histological changes were seen using standard H&E stains. However, formal histological criteria for HIFU ablation have yet to be established. The ablative process occurs over time and is not simply limited to the immediate delivery of thermal energy [22]. Interpreting HIFU-induced changes within clear RCCs using this staining technique can be challenging; these tumours commonly display morphology such as cyst formation, variegated areas of hyaline fibrosis, haemorrhage and necrosis which may be difficult to distinguish from thermal damage. It has previously been shown that negative NADH staining is consistent with non-viability of renal tumours following ablative therapy [23]. In our series, we correlated abnormalities on H&E staining with negative NADH staining, confirming HIFU-induced ablation. The use of the NADH vitality stain may therefore play a key role in establishing HIFU changes, particularly in recently treated tissue when features of ablation may not be present.

The role of laparoscopic renal HIFU is yet to be determined. It appears no more invasive than laparoscopic renal CA but more invasive than both percutaneous RFA and extracorporeal HIFU. Currently evidence suggests that CA is the most effective ablative therapy for renal tumours [24]. The vast majority of renal CA is performed laparoscopically and its safety profile compares similarly with our study technique except that tumour puncture is not required with HIFU. As such, should laparoscopic HIFU achieve acceptable oncological control in curative studies, it will compete directly with CA and its use will be determined by local availability.

CONCLUSIONS

Laparoscopic ablation of renal tumours with HIFU is safe and feasible. Homogenous intra-lesional coagulative necrosis is seen but there remain concerns about subcapsular skipping at the tumour surface. Further studies following refinement of the treatment probe and treatment protocol are required before phase II follow-up studies can safely be carried out. In the context of minimally invasive renal therapies, laparoscopic HIFU can be justified provided oncological efficacy is comparable with currently available options.

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CONFLICT OF INTEREST

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REFERENCES

1 **Chow W, Devesa S, Warren J, Fraumeni JJ.** Rising incidence of renal cell cancer in the United States. *JAMA* 1999; **281**: 1628–31
2 **UK Kidney Cancer Statistics, Cancer Research UK.** Available at: http://info.cancerresearchuk.org/cancerstats/types/kidney/index.htm. Accessed November 2009
3 **Collins S, McKiernan J, Landman J.** Update on the epidemiology and biology of renal cortical neoplasms. *J Endourol* 2006; **20**: 975–85
4 **Kane C, Mallin K, Ritchey J, Cooperberg M, Carroll P.** Renal cell cancer stage migration: analysis of the National Cancer Data Base. *Cancer* 2008; **113**: 78–83
5 **Cooperberg M, Mallin K, Ritchey J, Villalta J, Carroll P, Kane C.** Decreasing size at diagnosis of stage 1 renal cell carcinoma: analysis from the National Cancer Data Base, 1993 to 2004. *J Urol* 2008; **179**: 2131–5
6 **Jayson M, Sanders H.** Increased incidence of serendipitously discovered renal cell carcinoma. *Urology* 1998; **51**: 203–5
7 **Remzi M, Ozsoy M, Klingler H *et al.*** Are small renal tumors harmless? Analysis of histopathological features according to tumors 4 cm or less in diameter. *J Urol* 2006; **176**: 896–9
8 **Clark A, Breau R, Morash C, Fergusson D, Doucette S, Cagiannos I.** Preservation of renal function following partial or radical nephrectomy using 24-hour creatinine clearance. *Eur Urol* 2008; **54**: 143–52
9 **Crispen P, Boorjian S, Lohse C *et al.*** Outcomes following partial nephrectomy by tumor size. *J Urol* 2008; **180**: 1912–7
10 **Patard J, Shvarts O, Lam J *et al.*** Safety and efficacy of partial nephrectomy for all T1 tumors based on an international

multicenter experience. *J Urol* 2004; **171**: 2181–5, quiz 435
11 **Porpiglia F, Volpe A, Billia M, Scarpa R.** Laparoscopic versus open partial nephrectomy: analysis of the current literature. *Eur Urol* 2008; **53**: 732–42; discussion 42–3
12 **Rehman J, Landman J, Lee D *et al.*** Needle-based ablation of renal parenchyma using microwave, cryoablation, impedance- and temperature-based monopolar and bipolar radiofrequency, and liquid and gel chemoablation: laboratory studies and review of the literature. *J Endourol* 2004; **18**: 83–104
13 **Yohannes P, Pinto P, Rotariu P, Smith A, Lee B.** Retroperitoneoscopic radiofrequency ablation of a solid renal mass. *J Endourol* 2001; **15**: 845–9
14 **Uchida M, Imaide Y, Sugimoto K, Uehara H, Watanabe H.** Percutaneous cryosurgery for renal tumours. *Br J Urol* 1995; **75**: 132–6
15 **Köhrmann K, Michel M, Gaa J, Marlinghaus E, Alken P.** High intensity focused ultrasound as noninvasive therapy for multilocal renal cell carcinoma: case study and review of the literature. *J Urol* 2002; **167**: 2397–403
16 **Mouraviev V, Joniau S, Van Poppel H, Polascik T.** Current status of minimally invasive ablative techniques in the treatment of small renal tumours. *Eur Urol* 2007; **51**: 328–36
17 **Illing R, Kennedy J, Wu F *et al.*** The safety and feasibility of extracorporeal high-intensity focused ultrasound (HIFU) for the treatment of liver and kidney tumours in a Western population. *Br J Cancer* 2005; **93**: 890–5
18 **Tavakkoli J, Mehta A, Miller C *et al.*** Laparoscopic high intensity focused ultrasound: application to kidney ablation. *Proc International Symposium Therapeutic Ultrasound* 2002; 202–10
19 **Marberger M.** Ablation of renal tumours with extracorporeal high-intensity focused ultrasound. *BJU Int* 2007; **99**: 1273–6
20 **Orvieto M, Zorn K, Lyon M *et al.*** High intensity focused ultrasound renal tissue ablation: a laparoscopic porcine model. *J Urol* 2009; **181**: 861–6
21 **Klingler H, Susani M, Seip R, Mauermann J, Sanghvi N, Marberger M.** A novel approach to energy ablative therapy of small renal tumours: laparoscopic high-intensity focused ultrasound. *Eur Urol* 2008; **53**: 810–6; discussion 7–8
22 **Nikfarjam M, Malcontenti-Wilson C, Christophi C.** Focal hyperthermia produces progressive tumor necrosis independent of the initial thermal effects. *J Gastrointest Surg* 2005; **9**: 410–7
23 **Stern JM, Anderson JK, Lotan Y, Park S, Cadeddu JA.** Nicotinamide adenine dinucleotide staining immediately following radio frequency ablation of renal tumors-is a positive stain synonymous with ablative failure? *J Urol* 2006; **176**: 1969–72; discussion 72
24 **Kunkle DA, Uzzo RG.** Cryoablation or radiofrequency ablation of the small renal mass: a meta-analysis. *Cancer* 2008; **113**: 2671–80

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Abbreviations: **HIFU**, high-intensity focused ultrasound; **SRM**, small renal mass; **RFA**, radiofrequency ablation; **CA**, cryoablation; **LPN**, laparoscopic partial nephrectomy; **LRN**, laparoscopic radical nephrectomy; **H&E**, haematoxylin and eosin; **NADH**, nicotinamide adenine dinucleotide; **DIC**, disseminated intravascular coagulation.