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# Extracorporeal high intensity focused ultrasound for renal tumours: a 3-year follow-up

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## OBJECTIVE

To determine whether primary extracorporeal high-intensity focused ultrasound (HIFU) is safe, feasible and effective for managing small renal tumours.

## PATIENTS AND METHODS

Although surgery currently remains the standard treatment for localized renal cell carcinoma (RCC), the increasing incidence of small renal cancers has led to a shift towards nephron-sparing surgery, with associated morbidity in 20–25% of cases, and minimally invasive ablative therapies present an alternative management. HIFU results in 'trackless' homogenous tissue ablation and when administered via an extracorporeal device, is entirely noninvasive. The study comprised 17 patients (mean tumour size 2.5 cm) with radiologically suspicious renal tumours who underwent extracorporeal HIFU using the Model-JC System (Chongqing HAIFU™, China), under general anaesthesia with one overnight hospital stay. Real-time diagnostic ultrasonography was used for targeting and monitoring. Patients were followed with a clinical review and gadolinium-enhanced magnetic resonance imaging at 12 days and every 6 months for a mean of 36 months. The outcomes measures were patient morbidity and oncological efficacy of HIFU treatment.

## RESULTS

Of the 17 patients, 15 were treated according to protocol; two procedures were abandoned due to intervening bowel. There were no major complications related to HIFU. Radiological evidence of ablation was apparent at 12 days in seven of the 15 patients. Before the 6-month follow-up one patient had surgery due to persisting central enhancement. Fourteen patients were evaluated at the 6-month follow-up; eight tumours had involuted (mean 12% decrease in tumour area). Four patients had irregular enhancement on imaging and had alternative therapies. Ten patients remain on follow-up at a mean (range) of 36 (14–55) months after HIFU (mean 30% decrease in tumour area). There was central loss of enhancement in all.

## CONCLUSIONS

Renal HIFU achieves stable lesions in two-thirds of patients, with minimal morbidity, and might be appropriate in selected cases. Further trials with accurate histological follow-up are essential to fully evaluate this novel technique.

## KEYWORDS

high-intensity focused ultrasound, renal cell carcinoma, minimally invasive surgery, therapeutic hyperthermia

## INTRODUCTION

The last 30 years have seen a dramatic shift in the epidemiology and clinical presentation of renal cancer. Improved abdominal imaging and a genuine increase in the occurrence of renal tumours has led to a significant overall increase in incidence and early detection [1–3]. Notably, the greatest increase in incidence has occurred in the older population, with the percentage of patients aged >65 years nearly doubling [3].

This change has led urologists to question how best to manage renal tumours, particularly incidental small renal masses (SRMs). Observations of renal cancer show that low-grade, low-stage masses grow slowly and are not an immediate threat to a patient's life [4,5]. Further studies also showed that synchronous metastatic disease was detected in just 5% of tumours of <3 cm and does not occur with tumours of <2.0 cm [6].

Active surveillance of the SRM is a reasonable strategy. However, the odds of synchronous metastatic disease increase by 22% with every 1 cm tumour growth and double with 3.5 cm of growth [6]. Radiographic imaging alone is unable to determine high-risk tumours and consequently current opinion is that active surveillance should be considered for selected groups only, when surgery is not an option [7].

Surgery remains the default position for renal tumours. It is accepted that partial nephrectomy should be undertaken for T1a tumours, given its favourable effect on renal function compared with radical surgery [8,9]. However, complications occur in 21% of laparoscopic and open partial nephrectomies, and half of these are medical [10]. Surgery in the elderly population is particularly risky, with a 15% perioperative mortality rate in octogenarians undergoing nephrectomy in two European institutions [11].

| Variable | Mean, mean (range) or n |
|---|---|
| Age, years | 67 |
| Kidney | |
| Right | 12 |
| Left | 5 |
| Tumour size, cm | 2.5 |
| Tumour position | |
| Upper pole | 6 |
| Interpolar | 2 |
| Lower pole | 9 |
| Tumour location | |
| Entirely endophytic | 4 |
| <50% exophytic | 7 |
| >50% exophytic | 6 |
| Mean BMI, kg/m$^2$ | 25.8 |
| **Intra-operative data** | |
| Insonication time, min | 21 (3–26) |
| Total treatment time, min | 218 (165–300) |
| Tissue thickness, cm | |
| Skin | 0.5 (0.3–1.0) |
| Subcutaneous | 2.6 (1.4–4.3) |
| Skin to superficial tumour | 4.1 (3.6–6.5) |
| Skin to deep tumour | 6.4 (4.3–9.0) |
| Complete tumour treatment | 15 |
| Length of stay, days | 1 |

*TABLE 1*
*Baseline demographics and intraoperative data of the 17 patients (17 tumours)*

Is there a role for minimally invasive low-morbidity ablative techniques in the management of SRMs? Both cryotherapy and radiofrequency ablation (RFA) have become established techniques, and medium-term data show reasonable rates of tumour control. A meta-analysis of >1300 treatments found rates of local tumour progression of 5.2% for cryotherapy and 12.9% for RFA. Distant metastases subsequently occurred in 1% of those lesions treated with cryotherapy and 2.5% of those treated with RFA [12].

High-intensity focused ultrasound (HIFU) has been proposed as a technique for extracorporeal ablation [13]. HIFU can be used to create homogenous coagulative necrosis in an accurately targeted area, without surgical incision and with minimal damage to surrounding tissue. Serious complications occur rarely and discharge is invariably possible within 24 h.

The preliminary results from the present study showed radiological evidence of ablation in two-thirds of treated kidneys [13]; here we report outcome data and the oncological follow-up of 17 patients managed with primary extracorporeal HIFU.

## PATIENTS AND METHODS

We conducted a phase I study of patients presenting with nonmetastatic renal tumours. The primary endpoints were adverse effects and changes in blood indices, and were completed at 30 days after treatment. Continued routine radiological follow-up provided oncological outcome data. The trial was approved by the Oxfordshire Regional Ethics Committee and conducted in accordance with Good Clinical Practice guidelines.

In all, 17 patients were recruited during 2004–6; all had renal lesions suspicious for cancer on cross-sectional imaging, and who declined or were considered a high risk for surgical intervention. Lack of suitability for surgery was determined by a consultant urologist; patients declining surgery did so after careful counselling on all treatment options and outcomes. All patients provided informed consent.

The technique of extracorporeal HIFU was described previously [13,14]. Briefly, all treatments were conducted under general anaesthesia using the Model-JC HIFU System (Chongqing HAIFU Company, China), using a HIFU transducer driven at 0.83 MHz. Dual-lumen endotracheal intubation facilitated single-lung ventilation to minimize target movement during treatment. The tumour was targeted with diagnostic ultrasonography, which allowed treatment planning and real-time imaging. Treatment parameters were calculated intraoperatively using grey-scale change as a surrogate marker for coagulative necrosis [15,16].

Treatment side-effects were recorded according to the Common Toxicity Criteria (Version 2, final 30/1/98) and there was regular symptom review after treatment.

The follow-up was standardized according to the International Working Group on Image-Guided Tumor Ablation, which categorizes study goals into: (a) technical success, (b) technique effectiveness, (c) patient morbidity, and (d) oncological outcomes [17]. Technical success was judged at the time of the procedure and technique effectiveness was determined by cross-sectional imaging at 12 days afterward. Oncological outcome was determined by serial imaging follow-up which comprised contrast-enhanced MRI, at baseline and repeated at 12 days and at 3, 6 and 12 months, and annually thereafter. Imaging was assessed by digital subtraction of the pre-contrast fast-acquisition, multiple-excitation series subtracted from the 1-min postcontrast series. MRI was reviewed by the same radiologist in all cases.

## RESULTS

The baseline patient demographics are outlined in Table 1, and Fig. 1 is a flowchart of the trial conduct. The treatment duration, categorized by anaesthetic, positioning, treatment and insonication time, are also shown in Table 1.

Treatment according to protocol was possible in 15 of the 17 patients. Two treatments were abandoned due to intervening bowel in the treatment field. The first treatment was stopped before starting HIFU and the second was curtailed after a short period of insonication; neither patient had complications. After appropriate counselling on the risks of surgery, both patients underwent resection and subsequent histology showed RCC.

Sixteen patients had HIFU treatment and were evaluated for adverse effects; complications due to HIFU treatment are outlined in Table 2. There was mild to moderate discomfort in most patients, and this was managed with oral analgesia. All skin-related complications resolved completely without specific treatment. There was one serious complication (unrelated to HIFU exposure), pulmonary oedema after reversal of anaesthesia; this was managed conservatively and fully resolved within hours. All patients were discharged within 24 h of treatment.

There was a transient decrease in haemoglobin level immediately after HIFU (mean 1.0 g/dL), which relates to a dilutional effect of i.v. fluids. There was a mild increases in both serum white cell count (mean increase $1.71 \times 10^{-9}$/L) and C-reactive protein (mean increase 9.8 mg/L) after HIFU. There were no changes in biochemical markers of renal or liver function.

Fifteen patients completed their HIFU treatment and were therefore evaluated for treatment accuracy and effectiveness (Table 3). There was no radiological evidence of ablation in eight patients evaluated at 12 days. Four of these patients ultimately proceeded to alternative treatments; three had a partial nephrectomy and one RFA. Of those undergoing surgery, histology showed RCC in all three, with no histological evidence of ablation within the examined specimen.

There was radiological evidence of ablation in seven patients at 12 days. In the five patients in whom the zone of ablation was smaller than the tumour area, ablation lay entirely within the targeted tumour. In two patients the zone of ablation was larger than the tumour area and as such, there was an ablation margin containing some surrounding normal renal parenchyma.

There was ablation in one of the four patients completing treatment with an entirely endophytic tumour, compared to six of 10 completing treatment with exophytic lesions. There was no ablation in either clinically obese patients (body mass index, BMI, >30 kg/m$^2$). Otherwise, there was no positive or negative correlation between BMI and evidence of ablation in this small series ($P$ = 0.61, two-tailed Fisher's exact test).

There was ablation in one of five patients with left-sided tumours and in six of 10 with right-sided tumours ($P$ = 0.15). Upper-pole tumours showed radiological ablation in three of five after HIFU, compared with four of 10 inter- and lower-pole tumours ($P$ = 0.61).

Fourteen patients completed 6 months of radiological assessment without undergoing other interventions, and were thus evaluable for oncological outcome. One patient (no. 10, Table 3) had surgery before the 6-month follow-up due to an area of persisting central enhancement on follow-up imaging; the surgical resection specimen showed RCC with no evidence of tumour ablation.

There was involution of the zone of ablation in eight patients of this group. Overall, there was a mean 12% decrease in the dimensions of the ablation zone in the 6 months after treatment. The imaging in four of 14 patients showed evidence of irregular enhancement suggestive of recurrent tumour, and these patients therefore had alternative therapies, as outlined above. Of the remaining 10 patients, involution occurred in eight; the zone of ablation decreased by a mean of 18% at 6 months. Further follow-up shows continuing involution of the ablation zone, with a mean decrease of 30% from the original pretreatment tumour dimensions at a mean of 36 months of follow-up. Imaging in all patients showed a thin crescent-like rim of enhancement at the lesion periphery, but there was central loss of enhancement in all 10 patients.

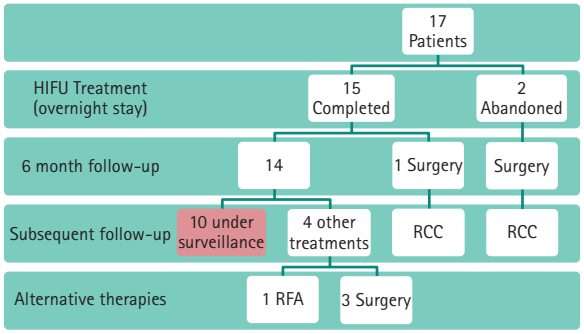


*FIG. 1.*
*A flow chart of the trial conduct.*

| Variable | Common Toxicity Criteria grade, n | | |
|---|---|---|---|
| | I, mild | II, moderate | III, severe |
| Discomfort | 10 | 3 | 0 |
| Skin toxicity | 5 | 0 | 0 |
| Oedema (treatment site) | 5 | 1 | 0 |
| Others | 4 | | |
| Lethargy | 2 | | |
| Skin pigmentation | 1 | | |
| Skin thickening | 1 | | |
| Gout | | 1 | |
| Pulmonary oedema | | | 1 |

*TABLE 2*
*Complications of HIFU treatment*

## DISCUSSION

Cellular damage in response to hyperthermia is well-documented and is temperature-dependent. At *in-vivo* temperatures up to 43°C there is no clear histological damage even if exposure times reach 30 min [18]. However, as temperatures increase to >45°C, histological cell damage becomes evident; an exposure of just 1 s is required to produce cell death at 60°C [18]. When an ultrasound beam of sufficiently high energy is brought to a focus, local temperatures can increase by >20°C [19].

Early clinical studies of HIFU show that it was feasible to create precise, defined and accurate areas of coagulative necrosis in the human kidney [20]. Later, Wu *et al.* [21] reported the resolution of haematuria and flank pain in nine of 10 patients with advanced RCC. A further clinical study showed only limited evidence of tissue ablation in 19 patients undergoing

*TABLE 3 Radiological follow-up data*

| Patient no. | BMI kg/m$^2$ | Tumour size, max, cm | Tumour size, max area, cm$^2$ | Tumour position: Side | Tumour position: Pole | Tumour position: Exo or endo | 12-day scan: Area of ablation | 12-day scan: Ablation/tumour area | 6-month scan: Lesion size, cm | 6-month scan: Change in size, % | Latest scan: Follow-up months | Latest scan: Lesion size, cm | Latest scan: Change, % |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 23.0 | 1.9 | 3.2 | R | U | Endo | HIFU abandoned | | | | | | |
| 2 | 23.4 | 2.8 | 7 | R | I | Endo | Nil seen | 0 | 4.8 | –31 | Surgery | | |
| 3 | 28.2 | 3.0 | 5.9 | R | Lo | Exo | 9.6 | 1.63 | 5.5 | –7 | 55 | 1.8 | –69 |
| 4 | 29.4 | 3.6 | 10.8 | L | Lo | Exo | Nil seen | 0 | 12.6 | +17 | Surgery | | |
| 5 | 21.4 | 1.8 | 2.7 | R | I | Exo | 2.3 | 0.85 | 1.8 | –33 | 51 | 1.2 | –56 |
| 6 | 25.3 | 2.6 | 6.5 | R | U | Endo | 2.4 | 0.35 | 7.8 | +20 | 47 | 3.0 | –54 |
| 7 | 22.8 | 1.5 | 2.3 | L | U | Exo | Nil seen | 0 | 2.3 | – | Surgery | | |
| 8 | 21.9 | 3.3 | 5.9 | R | U | Exo | 5.9 | 1.00 | 4.2 | –29 | 42 | 2.9 | –51 |
| 9 | 31.1 | 1.3 | 1.3 | L | Lo | Endo | Nil seen | 0 | 0.4 | –91 | 37 | 0 | –100 |
| 10 | 26.5 | 3.6 | 10.8 | R | U | Exo | 0.3 | 0.03 | | | Surgery | | |
| 11 | 23.6 | 3.0 | 6.4 | R | I | Exo | Nil seen | 0 | 5.7 | –11 | 35 | 5.7 | –11 |
| 12 | 26.9 | 2.1 | 4.2 | R | I | Exo | Nil seen | 0 | 5.0 | +19 | 14 | 5.0 | +19 |
| 13 | 31.5 | 1.6 | 2.6 | L | I | Endo | Nil seen | 0 | 2.6 | – | 33 | 5.4 | +108 |
| 14 | 22.7 | 1.1 | 1.1 | L | I | Exo | HIFU abandoned | | | | | | |
| 15 | 26.1 | 3.5 | 10.9 | L | I | Exo | 0.5 | 0.05 | 7.3 | –33 | 20 | 7.3 | –33 |
| 16 | 28.4 | 2.6 | 5.1 | R | I | Exo | 1.3 | 0.25 | 4.4 | –14 | 29 | 2.4 | –53 |
| 17 | 23.2 | 1.9 | 3.4 | R | U | Exo | Nil seen | 0 | 4.4 | +29 | RFA | | |
| Mean (for n) | | | | | | | | | | | | | |
| All patients (17)* | | 2.5 | 5.3 | 6 L, R 11, U 6, I 8, Lo 3 | | Exo 12 Endo 5 | 1.5 (15) | 0.28 (15) | 4.9 (14) | –12 (14) | | | |
| Other treatments (5)† | | 2.7 | 6.9 | L 2, R 3 U 6, I 8, Lo 3 | | Endo 1 Exo 4 | 0.1 | 0.01 | 6.7 (4) | +10 (4) | | | |
| No other treatments (10)‡ | | 2.5 | 5.2 | L 3, R 7 U 2, I 6, Lo 2 | | Endo 7 Exo 3 | 2.2 | 0.41 | 4.5 | –18 | 36 | 3.5 | –30 |

**Of the 17 patients, 15 completed treatment and day-12 imaging, 13 completed the 6-month follow-up with no other treatment; †5 patients completed treatment and day-12 imaging and subsequently required alternative treatment after HIFU; ‡10 patients completed treatment, day-12 imaging and 6 months follow-up and did not undergo alternative treatment. R, right; L, left; U, upper; I, inter; Lo, lower; Exo, exophytic; Endo, endophytic.*

extracorporeal renal HIFU followed by immediate radical nephrectomy [22].

Our feasibility study showed that extracorporeal renal HIFU is safe. Despite the long treatment duration, there was no evidence of significant morbidity associated with prolonged anaesthesia. Extracorporeal HIFU is not associated with the risks of urinary leakage and haemorrhage.

The present study showed that HIFU can achieve tumour ablation in two-thirds of patients. Central loss of enhancement in all 10 lesions during the follow-up implies tumour destruction and is the hallmark of successful HIFU ablation [23]. The presence of a thin, symmetrical, smooth peripheral rim of enhancement on follow-up imaging is an accepted finding after ablation, and is known as benign peri-ablational enhancement [23]. It represents a fibrotic response to thermal injury and should not be considered to represent residual tumour.

It is clear that persisting central enhancement is a sign of viable tumour and should be managed actively. However, the role of early cross-sectional imaging in establishing treatment success remains uncertain. Half of the patients with no evidence of ablation on imaging at 12 days required alternative treatment, suggesting persistent viable tumour. Indeed, evidence of viable tumour cells was found in those undergoing surgery. However, despite the lack of evidence of ablation at 12 days in the remaining four patients, subsequent imaging follow-up showed no central enhancement, with subsequent involution in two patients. Hyperthermic injury can occur in the absence of a sufficient temperature increase to cause coagulative necrosis, and therefore consideration should be given to further imaging after 12 days before the treatment is defined as a failure.

Overall two-thirds of patients who completed the treatment protocol were managed by HIFU alone. A mean tumour shrinkage of 30% provides reassuring evidence of successful ablation; the natural history of renal cancer would suggest a dimensional growth of

0.6 cm or volume growth of 8 mL in the mean 3-year follow-up period [24].

We accept that there remain concerns with renal HIFU, given the rates of treatment failure. The key difficulty with the extracorporeal route is ensuring that the acoustic energy reaches its intended target unhindered. Attenuation of ultrasound occurs predominantly at interfaces between tissues with significantly differing acoustic transmission speeds. Notably, the path of the beam from the transducer to the kidney encounters several of these interfaces, i.e. the skin surface, the rib cage, the abdominal musculature and the peri-nephric fat.

Reducing the effect of the abdominal wall and rib cage remains a major challenge. A laparoscopic approach is feasible and allows direct delivery of energy, but detracts significantly from the non-invasiveness of the extracorporeal approach [25]. Techniques that switch off the elements that lie in the beam pathway of the ribs show promise and allow additional power to be diverted to those elements with a good acoustic view of the target [26]. Respiratory motion tracking and correction will also allow tissue temperatures to increase more rapidly, thus reducing insonication times and reducing the heating of the prefocal tissues [27,28].

Finally, there is evidence to suggest that HIFU treatment might up-regulate antitumour immunity [29–32]. Cryptic antigens contained within tumours might be released after mechanical cell damage, thus stimulating an immunogenic response with the formation of tumour-specific T-cells which might prevent both local and systemic relapse. Indeed, animal studies suggest that HIFU can protect against tumour re-challenge after initial treatment [33]. Whether antitumour immune up-regulation plays a role in lesion stability and involution cannot be determined from this study, but should be investigated in future clinical trials.

This study suggests that renal HIFU might be effective in appropriately selected cases. Lesion stability is achievable in two-thirds of patients, with minimal treatment side-effects. The most appropriate cases for HIFU are yet to be defined and cannot be determined from this study; however, future advances in ablation speed, respiratory motion sensors and treatment monitoring will improve outcomes for all treatments. Further studies with accurate histological analysis after treatment are an essential next step in determining oncological efficacy.

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## CONFLICT OF INTEREST

None declared.

## 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 **Jayson M, Sanders H.** Increased incidence of serendipitously discovered renal cell carcinoma. *Urology* 1998; **51**: 203–5

3 **Luciani LG, Cestari R, Tallarigo C.** Incidental renal cell carcinoma-age and stage characterization and clinical implications: study of 1092 patients (1982–97). *Urology* 2000; **56**: 58–62

4 **Birnbaum BA, Bosniak MA, Megibow AJ, Lubat E, Gordon RB.** Observations on the growth of renal neoplasms. *Radiology* 1990; **176**: 695–701

5 **Bosniak MA.** Observation of small incidentally detected renal masses. *Semin Urol Oncol* 1995; **13**: 267–72

6 **Kunkle DA, Crispen PL, Li T, Uzzo RG.** Tumor size predicts synchronous metastatic renal cell carcinoma: mplications for surveillance of small renal masses. *J Urol* 2007; **177**: 1692–6

7 **Van Poppel H, Joniau S.** Is surveillance an option for the treatment of small renal masses? *Eur Urol* 2007; **52**: 1323–30

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 **McKiernan J, Simmons R, Katz J, Russo P.** Natural history of chronic renal insufficiency after partial and radical nephrectomy. *Urology* 2002; **59**: 816–20

10 **Porpiglia F, Volpe A, Billia M, Scarpa R.** Laparoscopic versus open partial nephrectomy: analysis of the current literature. *Eur Urol* 2008; **53**: 732–42

11 **Liguori G, Trombetta C, Pomara G *et al.*** Major invasive surgery for urologic cancer in octogenarians with comorbid medical conditions. *Eur Urol* 2007; **51**: 1600–4

12 **Kunkle DA, Uzzo RG.** Cryoablation or radiofrequency ablation of the small renal mass: a meta-analysis. *Cancer* 2008; **113**: 2671–80

13 **Illing RO, Kennedy JE, 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

14 **Kennedy JE, Wu F, ter Haar GR *et al.*** High-intensity focused ultrasound for the treatment of liver tumours. *Ultrasonics* 2004; **42**: 931–5

15 **ter Haar G, Sinnett D, Rivens I.** High intensity focused ultrasound – a surgical technique for the treatment of discrete liver tumours. *Phys Med Biol* 1989; **34**: 1743–50

16 **Vaezy S, Shi X, Martin R *et al.*** Real-time visualization of high-intensity focused ultrasound treatment using ultrasound imaging. *Ultrasound Med Biol* 2001; **27**: 33–42

17 **Goldberg SN, Charboneau JW, Dodd GD *et al.*** Image-guided tumor ablation: proposal for standardization of terms and reporting criteria. *Radiology* 2003; **228**: 335–45

18 **Miller MW, Ziskin MC.** Biological consequences of hyperthermia. *Ultrasound Med Biol* 1989; **15**: 707–22

19 **ter Haar G.** Intervention and therapy. *Ultrasound Med Biol* 2000; **26** (Suppl. 1): S51–4

20 **Susani M, Madersbacher S, Kratzik C, Vingers L, Marberger M.** Morphology of tissue destruction induced by focused ultrasound. *Eur Urol* 1993; **23** (Suppl. 1): 34–8

21 **Wu F, Wang Z, Chen W, Bai J, Zhu H, Qiao T.** Preliminary experience using high intensity focused ultrasound for the treatment of patients with advanced stage renal malignancy. *J Urol* 2003; **170**: 2237–40

22 **Hacker A, Michel MS, Marlinghaus E, Kohrmann KU, Alken P.** Extracorporeally induced ablation of renal tissue by high-intensity focused ultrasound. *BJU Int* 2006; **97**: 779–85

23 **Goldberg SN, Grassi CJ, Cardella JF *et al.*** Image-guided tumor ablation: standardization of terminology and reporting criteria. *Radiology* 2005; **235**: 728–39
24 **Abou Youssif T, Kassouf W, Steinberg J, Aprikian AG, Laplante MP, Tanguay S.** Active surveillance for selected patients with renal masses: updated results with long-term follow-up. *Cancer* 2007; **110**: 1010–4
25 **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
26 **Bobkova S, Shaw A, Gavrilov L, Khokhlova V, Hand J.** Feasibility of HIFU tissue ablation in the presence of ribs using a 2D random phased arrange array. ISTU, 9th International Symposium on Therapeutic Ultrasound, Vol. 'HIFU tissue erosion'. Aix-en-Provence, France. International Society of Therapeutic Ultrasound, 2009: Presentation S2B-1
27 **Marquet F, Pernot M, Aubry JF, Tanter M, Montaldo G, Fink M.** In-vivo non-invasive motion tracking and correction in high intensity focused ultrasound therapy. *Conf Proc IEEE Eng Med Biol Soc* 2006; **1**: 688–91
28 **Marquet F, Aubry J, Pernot M, Tanter M, Fink M.** Real time motion correction for transcostal liver therapy experiments. ISTU; 9th International Symposium of Therapeutic Ultrasound, Volume 'Ultrasound Guided HIFU'. Aix-En-Provence, France. International Society of Therapeutic Ultrasound, 2009. Presentation S3A-8
29 **den Brok M, Sutmuller R, van der Voort R *et al.*** In situ tumor ablation creates an antigen source for the generation of antitumor immunity. *Cancer Res* 2004; **64**: 4024–9
30 **Hu Z, Yang X, Liu Y *et al.*** Release of endogenous danger signals from HIFU-treated tumor cells and their stimulatory effects on APCs. *Biochem Biophys Res Commun* 2005; **335**: 124–31
31 **Wu F, Wang Z, Lu P *et al.*** Activated anti-tumor immunity in cancer patients after high intensity focused ultrasound ablation. *Ultrasound Med Biol* 2004; **30**: 1217–22
32 **Xu Z, Zhu X, Lu P, Zhou Q, Zhang J, Wu F.** Activation of tumor-infiltrating antigen presenting cells by high intensity focused ultrasound ablation of human breast cancer. *Ultrasound Med Biol* 2009; **35**: 50–7
33 **Hu Z, Yang X, Liu Y *et al.*** Investigation of HIFU-induced anti-tumor immunity in a murine tumor model. *J Transl Med* 2007; **5**: 34

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Abbreviations: **HIFU**, high-intensity focused ultrasound; **RFA**, radiofrequency ablation; **SRM**, small renal mass; **BMI**, body mass index.