Radiofrequency Ablation of Small Renal Masses: Outcomes, Complications and Effects on Renal Function

David Curry\textsuperscript{a}  Ajay Pahuja\textsuperscript{a}  Willie Loan\textsuperscript{b}  Ali Thwaini\textsuperscript{a}

Department of \textsuperscript{a}Urology and \textsuperscript{b}Radiology, Belfast City Hospital, Belfast, UK

Key Words
Radiofrequency • Renal cancer • Minimally invasive

Abstract

\textbf{Introduction:} To describe oncological outcomes, effects on renal function and complications with radiofrequency ablation (RFA) of T1 renal tumors in an 8-year experience. \textbf{Materials and Methods:} A retrospective study of RFA in 89 consecutive patients between 2005 and 2013 was undertaken. Those with metastatic disease, incomplete follow-up, genetic pre-disposition to renal tumors and biopsy proven benign pathology were excluded, with 79 patients meeting inclusion criteria. Data was collected on demographics, oncological outcomes, complications and effects on renal function. \textbf{Results:} We demonstrate 94\% disease-free survival at median follow-up of 29 months in a population consisting of 42 T1a and 37 T1b tumors. No disease related deaths were recorded in the follow-up period. Post-RFA decline in renal function was shown to correlate with tumor size and increased age (p = 0.0009/0.0021). Pre-existing renal impairment was a risk for post-RFA function decline (p < 0.005). Two complications were encountered in the series. \textbf{Conclusion:} RFA produces durable oncological outcomes in T1 tumors with a minimal effect on renal function and low risk of complications. Patients at risk of developing renal impairment can be identified from described risk factors.

Introduction

Renal cell carcinoma (RCC) accounts for 3\% of all adult malignancies in the UK (excluding non-melanoma skin cancer). Over the last decade the incidence of RCC has increased by 22\%, reflecting both an increasing prevalence and increasing detection rates [1]. With this, the incidence of small renal masses has risen, with up to 66\% being detected incidentally [2]. Despite this increase in early detection, mortality rates continue to rise with nearly 4,000 annual deaths in the UK [1].

Historically, radical nephrectomy (open then laparoscopic) was the gold standard treatment for RCC, in which oncological surgical principles can be satisfied. However due to the long-term effect on renal function of this surgery, nephron sparing surgery has gained increasing acceptance and is now considered the optimal treatment of localized tumors [3].

Management of small renal masses, particularly in an ageing population with uncertain life expectancy and significant co-morbidities may represent a challenge for clinicians. Watchful waiting is advocated in small lesions in the elderly, due to a natural history of slow growth and low metastatic risk [4].

Minimally invasive procedures such as radiofrequency ablation (RFA) carry the dual advantages of being an outpatient procedure and completed under local anesthetic. Given this they represent an alternative treatment option for the high risk surgical candidate.
The objective of this study was to assess oncological outcomes of RFA treatment. Secondary outcomes recorded include salvage treatment rates, effect on renal function and complication rates.

Materials and Methods

Cohort Selection

Departmental approval was obtained for retrospective case-note analysis conducted in accordance with Declaration of Helsinki and Good Clinical Practice principles. Electronic and paper records of 89 consecutive patients who underwent RFA in our institution between April 2005 and January 2013 were reviewed and data collected regarding demographics, pathology, treatment and outcomes. The data was recorded in a purpose designed database for analysis. Charlson co-morbidity index was used to classify co-morbid status and specific status was recorded with regard to diabetes, hypertension and vascular disease (ischemic heart disease, stroke, and peripheral vascular disease).

Indications for RFA consideration were cT1 tumor with solitary functioning kidney, high risk surgical candidate, or informed patient preference. Patients were excluded if they had known metastatic disease at the time of treatment (n = 3), failed to attend follow-up (n = 2), were followed-up in the independent medical sector (n = 2), had genetic condition predisposing to renal tumors (n = 1), or subsequent benign pathology on biopsy (n = 2). This resulted in cohort of 79 eligible patients.

Procedure Protocol

Following diagnosis and discussion of available treatment options, with a consultant uro-oncologist, images were reviewed in the local uro-radiology X-ray conference to assess suitability. Patients were admitted on the day of the procedure. Routine blood tests were performed, including renal function.

Technique used throughout the series is comparable to other centres [5, 6], with RFA delivered percutaneously under CT guidance in all cases with intravenous analgesia and sedation. A fine needle biopsy was performed and sent for histological examination where equipment allowed.

A 25 cm 7.3 Fr ablation electrode is placed in the renal mass; its position is confirmed on imaging. Ablation is performed at a power setting of 200 W generating a core temperature of 105°C. Target temperature is maintained for 10 minutes. The number of cycles used is determined by tumor size with tumors greater than 3.5 cm in diameter treated with probe repositioning to create overlapping ablation sites. A target ablation margin 0.5 to 1.0 cm beyond the CT measured maximum tumor diameter is obtained and CT is repeated to evaluate potential hematomas.

Observations were taken post-procedure and patients transferred to acute urology ward. Although outpatient procedures are possible, patients were offered admission the night following procedure.

Follow-Up

Patients were followed radiologically with a locally agreed imaging protocol. Initial contrast enhanced CT was performed at 1 month, 6 months, then 6 monthly for 2 years and yearly for 5 years (unless precluded by suboptimal renal function). This represents a modification on the European Association of Urology guidelines [7], with the addition of a CT at 1 month to assess for residual disease.

Renal function monitoring was carried out at the time follow-up imaging and at incidental medical encounters.

Definition of Outcomes

The authors acknowledge the lack of well-defined outcome criteria following RFA. Definitions were adapted from the International Working Group on Image-Guided Tumor Ablation [8].

Residual tumor was defined as persistent enhancement of 10 Hounsfield Units within the tumor site, on initial imaging. These patients were offered salvage RFA, to a maximum of 3 treatments, or alternative intervention dependent on co-morbid status.

Recurrent tumor was defined as new enhancement within the ablation site, with previously documented non-enhancement, or an increase in tumor size. These patients were reassessed at uro-oncology multi-disciplinary team (MDT) and treatment offered dependent on clinical condition.

Successful treatment was defined as exclusion from the above categories during the follow-up period.

Renal impairment was defined as a modification of diet in renal disease estimated glomerular filtration rate (eGFR) < 60. All values are quoted in ml/min/1.73m². Effect of RFA was established by decline from pre-procedure to best subsequent eGFR.

| Variable | Median (range)/n (%) |
|----------|---------------------|
| Age, year | 66 (40–84)         |
| Gender   |                     |
| Male     | 48 (61%)           |
| Female   | 31 (39%)           |
| Co-morbidities |             |
| Charlson co-morbidity index | 4 (2–9) |
| Diabetes | 20 (25%)          |
| Hypertension | 34 (43%)     |
| Vascular disease | 26 (33%)   |
| Pre-existing eGFR < 60 | 29 (36.7%) |
| Solitary kidney | 7 (8.95)   |
| Staging  |                     |
| Tumor size, cm | 3 (1–6)   |
| T1a      | 42 (53.2%)        |
| T1b      | 37 (46.8%)        |
| No Biopsy | 31 (39.2%)       |
| Biopsy   |                     |
| RCC (unspecified) | 16 (20.3%)   |
| RCC G1   | 11 (13.9%)        |
| RCC G2   | 11 (13.9%)        |
| RCC G3   | 2 (2.5%)          |
| Oncocytoma | 2 (2.5%)        |
| No diagnosis | 6 (7.6%)    |

Table 1. Demographics, co-morbidities and pathology

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Statistical Analysis

Statistical analysis was performed using Prism® software (GraphPad Software Inc). Statistical significance was set at p < 0.05. Categorical variables were compared using Fisher’s exact test, medians using Mann-Whitney U and correlation assessed using Spearman’s rank.

Results

Cohort demographics and co-morbidities are shown in table 1. Seventy-nine patients were treated with median tumor size of 3 cm [interquartile range (IQR) 2.2–3.5 cm] and 42 classified as T1a and 37 T1b.

Oncological Outcomes

Residual tumor was present in 14 (18%) patients on initial imaging with 10 of these proceeding to successful salvage RFA. Tumor size was not a predictor of residual disease (p = 0.49). Two patients were considered too unwell for further intervention and 2 elected to proceed to nephrectomy, with viable tumor confirmed in both cases.

Tumor recurrence was seen in 4 (5%) patients with a median time to recurrence of 15 months (IQR 6.25–33.75 months). Criteria defining recurrence was new enhancement in 3 patients and tumor enlargement in 1. The patient with tumor enlargement underwent nephrectomy; this showed no viable tumor present. Two of the remaining patients were considered unfit for further intervention, whilst the third underwent repeat RFA.

Two patients developed tumors on the contralateral kidney during the follow-up period, neither had evidence of recurrence of treated tumors. A further patient was found to have a lung lesion on follow-up imaging. Biopsy of this revealed tumor cells of uncertain origin. After regional MDT discussion this was felt not be metastatic as original pathology had shown a 2.6 cm T1aG2 RCC, with no radiographic evidence of post-RFA recurrence or residual disease.

Ninety-four percent of patients were disease free at median follow-up of 29 months (IQR 18–46 months) with all cause mortality of 11% (9 patients). No disease related deaths were recorded.

Functional Outcomes

In total 29 (37%) patients had baseline renal impairment with a median eGFR of 45 (IQR 35–55).
Nineteen (24%) patients had a subsequent deterioration in eGFR with a median change of 7 (IQR 5–11). Renal function deterioration was seen significantly more frequently and at a significantly greater level (fig. 1) in the cohort of patients with pre-existing renal impairment (p < 0.005/p = 0.001). No significant difference in number affected or level of deterioration was seen for gender (p = 0.1/p = 0.069), diabetes (p = 1.0/p > 0.99), hypertension (p = 0.296/p = 0.213) or vascular disease (p = 1.0/p = 0.14) (fig. 1).

In those patients with a solitary kidney an impression of greater impairment is seen, however the small number of patients in this category meant this did not reach statistical significance (n = 7).

Additionally tumor size (p = 0.0009) and increased age (p = 0.0021) were identified as having positive correlation with subsequent renal function deterioration (fig. 2, 3).

Complications

In this series of 89 RFA treatments (10 salvages) only 2 complications were encountered. The most serious of these was formation of an urinoma due to compromise of the collecting system at the ureteropelvic junction during treatment of a central lower pole tumor. This was treated conservatively and spontaneously resolved, a subsequent intravenous urogram and MAG-3 renogram showed normal drainage (Clavien grade II). Another patient developed hematuria day 4 post-RFA. CT imaging was unremarkable and this settled without intervention (Clavien grade I). No long-term sequelae were encountered from either complication [9].

Discussion

The challenge of an increasing burden of small renal masses, with unpredictable progression, in a population with uncertain life expectancy proves a difficult scenario for clinicians; this has led to the emergence of ablative techniques. Gold standard treatment of partial nephrectomy may not be suitable in those with significant co-morbidities and high anesthetic risk. Ablative techniques offer the advantages being performed in an outpatient setting without general anesthetic, reducing potential complications.

Our study shows that RFA can achieve satisfactory durable oncological outcomes, with 94% disease-free survival at median follow-up of 28 months. An overall survival rate of 88% reflects the significant co-morbidities present within the cohort, but no disease related deaths were recorded in the follow-up period. Additionally this highlights the imperative of careful patient selection and counselling in a population with uncertain life expectancy. The longest follow-up of RFA in published series reports an 87.6% disease-free survival at median of 6.43 years [10]. An increasing evidence base for active surveillance of T1 tumors, in selected populations, is seen in recent literature [11]; however no studies to date have directly compared outcomes to RFA.

Of interest in our study 1 patient with a 2.6 cm T1aG2 RCC was found to have a malignant lung lesion on subsequent imaging. Formal imaging of the chest had not been carried out pre-RFA. Fine needle aspirate revealed malignant non-small cell carcinoma. Post-treatment appearances of the RCC were satisfactory. Following MDT discussion this was felt to represent a co-incident lung primary and radiotherapy was offered. Whilst the exact pathology in this case was unclear it highlights the unpredictable nature of small renal masses. This was demonstrated in a 2005 paper by Minardi et al. [12] showing distal metastases at 2 years in 2.4% of patients with RCC < 3 cm.

Of further interest in this series is the patient with 2.6 cm G1 RCC deemed to have a recurrence based on tumor enlargement, without enhancement, at 1 month imaging. Nephrectomy was performed but showed no viable malignancy. Davenport et al. [13] showed in a 2009 series of RFA follow-up that the post-ablation beds of tumors < 3 cm could show enlargement up to 2 months. The role of biopsy has conflicting evidence, limited by high false positive rates due to heat fixing effects on tissue [14] but demonstrated to identify malignant disease in the absence of radiological signs [15]. The post-RFA optimal follow-up and recurrence criteria remain poorly defined.

One of the major advantages of RFA is the nephron-sparing nature. From meta-analysis of healthy donor studies we see approximately 10 ml/min/1.73m² decreases in GFR after the loss of a kidney [16]. Combined with the demonstration of > 90% 5-year survival of patients with T1 tumors [17] we begin to see the importance of renal preservation. This is demonstrated further in a paper by Thompson et al. [18], which showed decrease in overall survival of patients under 65 with tumors < 4 cm treated by radical nephrectomy when compared to nephron-sparing surgery. In an important 2008 paper by Lucas et al. [19] the benefits of nephron-sparing approach and indeed ablative techniques were demonstrated by a 95% 3-year freedom from chronic kidney disease, compared to 70 and 40% for partial and radical nephrectomy.
respectively. In this study we have demonstrated 24% of RFA patients to be affected by decline in renal function post treatment, with pre-existing renal impairment and increased tumor size and age significant risk factors for this. Twelve percent of patients with normal renal function developed subsequent impairment (eGFR < 60), higher than demonstrated in previous studies. With the increasing evidence for active surveillance in certain populations [11], potential effect on renal function must be considered in clinical decision making.

Our study is limited by a number of factors. As this cohort includes the initial cases performed in our unit operator learning curve and equipment evolution may have adversely influenced early results. Using eGFR as an indicator of loss of renal function may not provide a sensitive measure as significant loss of renal units is needed before an effect on eGFR is seen.

RFA is an appropriate treatment option in T1 RCC with durable oncological outcomes and low complication rates. However certain patient populations are at significant risk of deterioration of renal function. Further study is required to clarify this effect and potential risks.

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