Radiofrequency ablation of renal cell carcinoma: a follow up of outcomes

David Curry, MB,[1] Musaab Yassin, MBCHB,[1] Ali Thwaini, MBChB,[1]
Ajay Pahuja, MBChB,[1] Ammar H. Alanbuki, MBChB,[2]
Thiagarajan Nambi Rajan, MBChB,[1] Willie Loan, MB[3]

[1]Department of Urology, Belfast City Hospital, Belfast, Northern Ireland
[2]Department of Urology. Peterborough City Hospital, Peterborough, England
[3]Department of Radiology. Belfast City Hospital, Belfast, Northern Ireland

CURRY D, YASSIN M, THWAINI A, PAHUJA A, ALANBUKI AH, RAJAN TN, LOAN W. Radiofrequency ablation of renal cell carcinoma: a follow up of outcomes. *Can J Urol* 2014;21(1):7135-7140.

Introduction: *To present the oncological outcomes in a series of patients with cT1a renal cell carcinoma (RCC) treated with radiofrequency ablation (RFA) and its effect on the glomerular filtration rate (GFR).*

Materials and methods: *Forty-five patients (48 renal units) treated at the Belfast City Hospital, over 4 years. Average age is 61.5 years (range 41-80). Eighteen patients (22 renal units) were included with American Society of Anesthesiologists (ASA) II and III. The rest were ASA I. Average tumor size was 2.63 cm (range 1.2 cm-6 cm). Renal function before and after RFA was recorded by means of the estimated glomerular filtration rate (eGFR) and the changes are presented.*

Oncological outcomes were established from follow up imaging. A satisfactory response was defined by disappearance or a persistence of non-enhancing lesion of smaller size at follow up. A partial response was defined by a persistent but non-enhancing similar size lesion. A failed response was defined by enlarging or persistently enhancing lesions.

Results: *Mean follow up was 30.6 months (4-60 months). A good response was found in 33 (74%) patients. A partial response was found in 3 (8%) patients and failed response was identified in 8 (18%) patients. The average reduction in eGFR was 11 mL/min. Two patients had a 50% reduction in their eGFR. No patient required dialysis following treatment.*

Conclusion: *RFA presents safe treatment choice for patients with RCC, particularly those that are high risk surgical candidates and those who refuse surgery. Short term results suggest good oncological outcomes and preservation of renal function.*

Key Words: renal, tumor, radiofrequency, ablation, outcomes, complications, percutaneous

Introduction

Renal cell carcinoma (RCC) accounts for 3% of all adult malignancies in the United Kingdom (UK) (excluding non-melanoma skin cancer).[1] In the past two decades there has been an increase in the incidence of RCC in the UK, with an average of 6000 new cases per year, with an estimated 3000 annual deaths from the disease. In addition, the incidence of localized and small RCC has been increasing probably owing to the increase of non-invasive investigations. The majority of lesions are identified incidentally on scans organized for symptoms unrelated to the renal lesions.[2]

Historically radical nephrectomy (open and then laparoscopic) was the procedure of choice for the treatment of RCC, where oncological surgical principles can be achieved. However, due to the long term effect on the overall renal function following

Accepted for publication December 2013

Address correspondence to Dr. Ammar Hameed Alanbuki, Urology SPR, Ipswich Hospitals NHS Trust, Ipswich United Kingdom

radical nephrectomy, nephron sparing surgery (NSS) has now become the gold standard treatment of RCC gained increasing acceptance as they have the advantages of parenchymal preservation.3 The risk of complication with NSS is not insignificant, involving general anesthesia and inpatient hospital stay.

Management of smaller renal lesions particularly in elderly patients with uncertain life expectancy, or unfit for invasive procedures represents a dilemma for clinicians. Watchful waiting may be advocated in elderly patients with small renal lesions due to the tendency towards slow increase in size with minimal risk of progression or metastasis.[4]

Minimally invasive procedures, such as radiofrequency ablation (RFA) or cryoablation can be performed as out-patient procedures under local anesthesia (LA) providing a safe and cost effective alternative treatment option in the high risk surgical candidate.

We present our initial experience in radiofrequency ablation (RFA), with the complications encountered and outcomes over a 4 year period and a review of the relevant literature.

Materials and methods

Departmental and clinical audit division approvals were obtained for retrospective case-note study retrieval. Forty-five patients who underwent the RFA over 4 years were identified from the trust radiology database. Data concerning demographics, RCC characteristics, hospital stay and follow up were collected from the hospital databases and the relevant information was catalogued in a purposely designed questionnaire translated into excel sheet for analysis.

Procedure protocol and surgical technique

Patients were admitted on the day of the procedure. Routine blood tests were performed on the day of admission, including full blood picture (FBP), urea and electrolytes (U&Es) and clotting profile.

Our surgical technique is comparable to other centers.[5,6] RFA is delivered percutaneously under direct CT guidance. A single fine-needle biopsy is performed for histopathology.

A 25 cm 7.3Fr ablation electrode is placed in the renal mass its position is confirmed on imaging. Ablation is performed at a power setting of 200W generating a core temperature of 105^{0}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 cm to 1.0 cm beyond the CT measured maximum tumor diameter is obtained and CT is repeated to evaluate potential hematoma.

Although the procedure can be done in an outpatient setting, we admitted our patients for observations overnight as they were the first cohort in our department. FBP and U&Es were taken on the next day and when stable, patients were then discharged home provided there was no complication from the procedure.

Follow up

A follow up contrast enhanced CT scan was 1 month post RFA to assess response. In addition renal function was checked at this time. CT was then repeated every 3 months for the first 6 months and then six monthly for the first 2 years, and then annually for 5 years in keeping with the European guidelines on the follow up of RCC post treatment.[7]

Salvage RFA was offered to patients with persistently enhancing lesions.

Definition of outcomes

A satisfactory response was defined by either disappearance of the lesion treated or a persistent non-enhancing lesion of smaller size during follow up. A partial response was defined by a persistent but non-enhancing lesion of similar size. Non-responding lesions were defined as enlarging or those demonstrating persistent enhancement.

The study acknowledges the lack of well-proven radiographic parameters for treatment success post RFA.[8]

The effect of the RFA on the global renal function was measured by the difference in the preoperative and the postoperative estimated glomerular filtration rate (eGFR).

Results

The mean age of patients was 61.5 years (range 41-80). Patient demographics are illustrated in Table 1. Eighteen patients were included with American Society of Anesthesiologists (ASA) score of II and III. The remainder were ASA I. Five (15%) had a solitary kidney and three (7%) patients had bilateral RCCs.

All the tumors were diagnosed radiologically and discussed at a specialist uro-oncology multi-disciplinary team meeting. Subsequent biopsy was taken at the time of treatment. These showed RCC in 81.3% of the cases. Out of these, grade I and grade II were in 6.3% and 37.5% respectively while 37.5% could not be graded. Oncocytoma was found in 6.3% of the cases. The remaining biopsies contained insufficient tissue for diagnosis.

TABLE 1. **Demographics and treatment**

Variable	Mean/number (range/%)
Patients' demographics	
Age (years)	61.5 (41-80)
DM	11 (33%)
HTN	13 (39%)
IHD	9 (27%)
Genetic tumor predisposition	2 (6%)
Tumor characteristics	
Size (cm)	2.63 (1.2-4)
Right side	28 (62%)
Left side	17 (38%)
Multiple	5 (11%)
Bilateral	2 (4%)
No. of treatments	1.4 (1-3)
Embolization prior to RFA	3 (9%)
Hospital stay (days)	1.74 (1-10)
Follow up (months)	30.6 (4-60)

DM = diabetes mellitus; HTN = hypertension; IHD = ischemic heart disease; RFA = radiofrequency ablation

Mean tumor size was 2.63 cm (range 1.2 cm-6 cm), Figure 1, with an average procedure time of 35 minutes (range 20-45). Mean number of RFA treatments required was 1.4 (range 1-3). Three (9%) patients had embolization of their RCCs because their size exceeded 4 cm in diameter.

Mean hospital stay was 1.7 days (range1-10), Figure 2. One patient developed urinoma post RFA for a tumor close to the pelvi-calyceal system. This prolonged his stay to 10 days and this was resolved with percutaneous drainage.

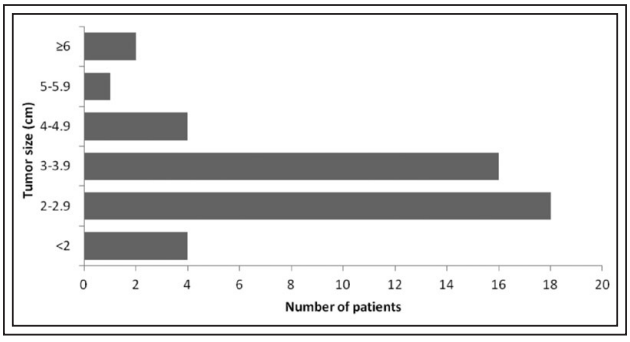

Figure 1. Tumor size.

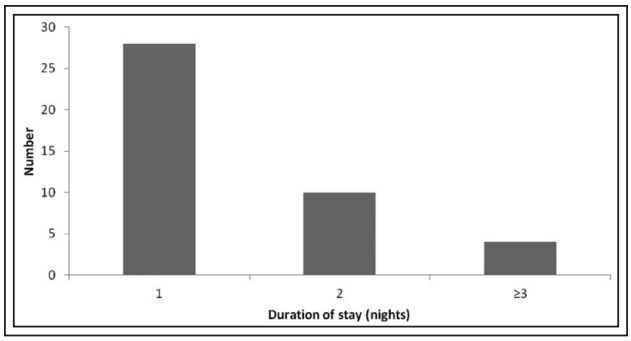

Figure 2. Duration of stay.

At mean follow up was 30.6 months (4-60 months) a good response was found in 34 (76%) patients. A partial response was found in 3 (6%) patients and failed response was identified in 8 (18%) patients, Table 2. Twelve (27%) patients required salvage RFA treatment due to persistent disease.

One patient subsequently underwent laparoscopic nephrectomy for failed treatment. This patient had multiple tumors in his kidney some of which were technically difficult to target with the RFA. Histology revealed viable cancer. Another patient underwent laparoscopic partial nephrectomy, due to an increase in tumor size, with the final histology revealing non-viable cancer.

The median decline in eGFR was 5.6 mL/min/1.73 m^2 (range 0-30). Two patients had a > 50% reduction in their eGFR. No patient required dialysis following treatment.

None of the patients developed metastasis and no disease related deaths were encountered during the follow up period.

TABLE 2. **Outcomes**

Outcome	Mean/number (range/%)
Good response	34 (76%)
Partial response	3 (6%)
Failed response	8 (18%)
Reasons	
Small lesion	1
Large lesion	1
Multiple lesions	2
Difficult access	4
eGFR decrease (mL/min/1.73 m^2)	5.6 (0-30) mL/min/1.73 m^2

EGFR = estimated glomerular filtration rate

Discussion

There has been a significant rise in incidental small renal masses (SRMs) on imaging performed for other reasons.[9] There is still a debate with regards to the natural history of these incidental masses, when surgically excised; 70%-80% are proven to be RCC and the rest benig n.[10] When possible, the standard of care for these SRMs has been partial nephrectomy with local and distant oncological outcomes well established.[11] In the last decade a minimally invasive approach with laparoscopy has largely replaced open surgery, at least in centers with all the facilities and expertise. More recently, ablative therapies such as RFA and cryoablation are taking a more prominent role as a practical approach for management of these SRMs. Both these modalities can be deployed in a minimally invasive fashion and appear to be safe methods of treating SRMs.

Whether these ablative technologies have the long term potential to replace excision has not yet been established. Certain reported advantages of ablative methods include reduced perioperative morbidity, shorter hospital stay and short recovery time. In older patients or those who are poor candidates for surgery these advantages are very appealing to the clinician.[12]

RFA of an exophytic renal mass prior to open radical nephrectomy was first described in 1997,[13] with the first report of RFA as a sole treatment option for a renal tumor published in 1999.[14]

RFA is delivered into the target lesion under CT or laparoscopy guidance, without jeopardizing the safety of injuring nearby structures. Current literature describes percutaneous access RFA in approximately 94% cases although it has been applied using open and laparoscopic approaches under various imaging modalities.[15,16] Radiofrequency waves are converted to heat within the probe (via a temperature or impedance based system). This results in generating 50W-120W with AC current of 500 kHz-1200 kHz causing frictional heating. When the temperature is > 50^{0}C but < 100^{0}C, optimal tissue ablation is achieved. If temperatures exceed 100^{0}C this results in tissue vaporization, leading to insufficient conductivity. In addition, excessive heating causes charring which limits further delivery of heat.

Oncological efficacy

In our series of 45 patients a good, complete response was found in 33 (74%) patients and partial or non-response in 11 (26%) patients. No metastatic spread or disease related deaths were recorded during our study.

Many papers describe short and intermediate term results demonstrating the safety and effectiveness of RFA in SRMs. Varkarakis et al described 94.6% successful local control at 2 years.[17] Stern et al published their results in 37 ASA 1-2 patients. Only one patient had a local recurrence in a period over 2 years and he was treated by radical nephrectomy without recurrence after 1 year follow up.[18] Stern also compared intermediate term results of partial nephrectomy and RFA and concluded that 3 year oncological outcomes were similar.[19]

Gervais and colleagues published a series of 85 patients with the treatment of 100 tumors percutaneously. One local recurrence was seen and there were 11 complications. Indeed, 100% of the tumors smaller than 3 cm achieved complete ablation while only 25% of tumors greater than 5 cm were treated completely.[20] In another paper of the same group, a cohort of 16 patients was reported with the longest term follow up available (4.6 years). Five patients died of unrelated causes and the 5 year cancer specific-survival was 100%.[21]

The natural history of small renal masses remains poorly defined, but Chawla et al demonstrated a growth rate of 0.28 cm/year with a metastatic rate of 1% after 34 months of follow up.[22] It is therefore difficult to draw any meaningful conclusions from most RFA series with short follow ups in terms of oncological efficacy.

In the most comprehensive study to date Psutka et al published long term oncological outcomes from 185 T1, biopsy proven, RCCs undergoing RFA with 6.4 year follow up. Their data showed 88% disease free survival, 2.2% metastatic spread and 1.6% disease specific mortality.[23] Unfortunately the study is still limited by retrospective nature and selection bias.

Follow up

With a mean follow up of 30.6 months (4-60 months) in our group it is essential to highlight that there are no agreed guidelines for follow up of RFA patients after ablation of renal tumors. Successful ablation post RFA is equated with radiological response. However, changes on imaging are not always predictable. There is no consistency in regression in size and in addition a peri-tumor halo may form due to fat infiltration. The standard to define necrosis and response has been the absence of contrast enhancement in the lesion on post-treatment CT and MRI and not by post-treatment serial biopsies. Tumors that are successfully treated do usually demonstrate a lack of enhancement on CT scans,[24] but it still remains unclear whether radiological response is an adequate marker for cancer control.

All the tumors in our group were diagnosed radiologically and discussed at a specialist uro-oncology multi-disciplinary team meeting and subsequent biopsy was taken at the time of treatment.

This was not uniform process and some groups have undertaken post-RFA biopsies to determine success of treatment. However, immediate post ablative biopsy and viability staining may not appropriately reflect pathophysiological cell death, and may erroneously guide to the conclusion that the treatment was unsuccessful.[25,26] A similar scenario may happen with delayed biopsies where the cell structure may be retained even at 6 months after ablation, mistakenly suggesting the presence of viable tissue. This can be looked at in the context of a known recurrence rate after ablation of 2%-13%.[27]

Residual tumors have been observed in nephrectomy specimens in one case in our group and this remains low compared to other studies. Two studies performed nephrectomy post RFA in order to accurately assess the histopathological outcome post RFA. Rendon et al found persistent cancer in 5%-10% of tumor volume and Matlaga et al found 2 out 10 to be incompletely ablated.[28,29]

Our series used a modification of European Association of Urology guidelines,[7] with the addition of a contrast CT 1 month post treatment. The importance of this is highlighted in the 27% salvage treatment rate. However the shortcomings of radiological follow up are highlighted by the case which proceeded to surgery, but was subsequently found to be non-viable tumor.

Complications

Although RFA is generally well tolerated procedure serious complications can occur. Johnson et al reported 11 complications in 133 cases (8.2%). The most commonly reported was pain and paresthesia at the site of electrode insertion for percutaneous RFA.[30] Studies have also reported perinephric hematoma, pelvi-ureteric junction obstruction, ureteric damage, ileus, urinary leak and nephrectomy.[31]

In our series one patient developed urinoma post RFA for a tumor close to the pelvi-calyceal system. This prolonged his stay to 10 days and this was resolved with percutaneous drainage. The patient suffered no long term sequelae from this complication.

Conclusion

Although RFA is a promising modality, the overall evidence still remains scant immature. There is a lack of prospective and randomized trials. Most studies report a follow up varying between 2-3 years; published long term outcomes are small in number. Insufficient evidence exists to allow RFA to be seen as a minimally invasive option for the treatment of all SRMs. Patient selection based on comorbid status, tumor characteristics and patient expectations is imperative.

Suitable follow up modality remains an area of debate, with no current technique offering the sensitivity required. Nephron-sparing surgery remains the gold standard of treatment in SRMs. □

References

1. Office for National Statistics, Cancer Statistics registrations: Registrations of cancer diagnosed in 2007, England. Series MB1 no.38. 2010, National Statistics: London.
2. Chow WH, Devesa SS, Warren JL, Fraumeni Jr JF. Rising incidence of renal cell cancer in the United States. *JAMA* 1999;281(17):1628-1631.
3. MacLennan S, Imamura M, Lapitan MC et al. UCAN Systematic Review Reference Group. EAU Renal Cancer Guideline panel. Systematic review of oncological outcomes following surgical management of localised renal cancer. *Eur Urol* 2012;61(5):972-993.
4. Bosniak MA, Birnbaum BA, Krinsky GA, Waisman J. Small renal parenchymal neoplasms: further observations on growth. *Radiology* 1995;197(3):589-597.
5. Johnson DB, Taylor GD, Lotan Y, Sagalowsky AI, Koenemann KS, Cadeddu JA. The effects of radio frequency ablation on renal function and blood pressure. *J Urol* 2003;170(6 Pt 1):2234-2236.
6. Altunrende F, Autorino R, Hillyer S et al. Image guided percutaneous probe ablation for renal tumors in 65 solitary kidneys: functional and oncological outcomes. *J Urol* 2011;186(1): 35-41.
7. Ljungberg B, Cowan NC, Hanbury DC et al. European Association of Urology Guideline Group. EAU guidelines on renal cell carcinoma: the 2010 update. *Eur Urol* 2010;58(3):398-406.
8. Weight CJ, Kaouk JH, Hegarty NJ et al. Correlation of radiographic imaging and histopathology following cryoablation and radio frequency ablation for renal tumors. *J Urol* 2008;179(4):1277-1281.
9. Pantuck AJ, Zisman A, Belldegrun AS. The changing natural history of renal cell carcinoma. *J Urol* 2001;166(5):1611-1623
10. Schlomer B, Figenshau RS, Yan Y, Venkatesh R, Bhayani SB. Pathological features of renal neoplasms classified by size and symptomatology. *J Urol* 2006;176(4 Pt 1):1317-1320.
11. Desai MM, Gill IS. Current status of cryoablation and radiofrequency ablation in the management of renal tumors. *Curr Opin Urol* 2002;12(5):387-393.
12. Raj GV, Reddan DJ, Hoey MF, Polascik TJ. Management of small renal tumours with radiofrequency ablation. *Urology* 2003; 61(1):23-29.
13. Zlotta AR, Wildschutz T, Raviv G et al. Radiofrequency interstitial tumor ablation (RITA) is a possible new modality for treatment of renal cancer: ex vivo and in vivo experience. *J Endourol* 1997; 11(4):251-258.
14. McGovern FJ, Wood BJ, Goldberg SN, Mueller PR. Radio frequency ablation of renal cell carcinoma via image guided needle electrodes. *J Urol* 1999;161(2):599-600.
15. Aron M, Gill IS. Minimally invasive nephron-sparing surgery (MINSS) for renal tumours. Part II: probe ablative therapy. *Eur Urol* 2007;51(2):348-357.
16. Mahnken AH, Penzkofer T, Bruners P, Günther RW, Brehmer B. Interventional management of a renal cell carcinoma by radiofrequency ablation with tagging and cooling. *Korean J Radiol* 2009;10(5):523-526.
17. Varkarakis IM, Allaf ME, Inagaki T et al. Percutaneous radio frequency ablation of renal masses: results at a 2-year mean follow up. *J Urol* 2005;174(2):456-460.
18. Stern JM, Gupta A, Raman JD et al. Radiofrequency ablation of small renal cortical tumours in healthy adults: renal function preservation and intermediate oncological outcome. *BJU Int* 2009;104(6):786-789.

19. Stern JM, Svatek R, Park S et al. Intermediate comparison of partial nephrectomy and radiofrequency ablation for clinical T1a renal tumours. *BJU Int* 2007;100(2):287-290.
20. Gervais DA, Arellano RS, McGovern FJ, McDougal WS, Mueller PR. Radiofrequency ablation of renal cell carcinoma: part 2, Lessons learned with ablation of 100 tumors. *AJR Am J Roentgenol* 2005;185(1):72-80.
21. McDougal WS, Gervais DA, McGovern FJ, Mueller PR. Long-term follow up of patients with renal cell carcinoma treated with radio frequency ablation with curative intent. *J Urol* 2005;174(1):61-63.
22. Chawla SN, Crispen PL, Hanlon AL, Greenberg RE, Chen DY, Uzzo RG. The natural history of observed enhancing renal masses: meta-analysis and review of the world literature. *J Urol* 2006;175(2):425-431.
23. Psutka SP, Feldman AS, McDougal WS, McGovern FJ, Mueller P, Gervais DA. Long-term oncologic outcomes after radiofrequency ablation for T1 renal cell carcinoma. *Eur Urol* 2013;63(3):486-492.
24. Matsumoto ED, Watumull L, Johnson DB et al. The radiographic evolution of radio frequency ablated renal tumors. *Urology* 2004;172(1):45-48.
25. Stern JM, Anderson JK, Lotan Y et al. Nicotinamide adenine dinucleotide staining immediately following radio frequency ablation of renal tumours—is a positive stain synonymous with ablative failure? *J Urol* 2006;176(5):1969-1972.
26. Anderson JK, Baker M, Jaffers Oet al. Time course of nicotinamide adenine dinucleotide diaphorase staining after renal radiofrequency ablation influences viability assessment. *J Endourol* 2007;21(2):223-227.
27. Matin SF, Ahrar K, Cadeddu JK et al. Residual and recurrent disease following renal energy ablative therapy: a multi-institutional study. *J Urol* 2006;176(5):1973-1977.
28. Rendon RA, Kachura JR, Sweet JM et al. The uncertainty of radio frequency treatment of renal cell carcinoma: findings at immediate and delayed nephrectomy. *J Urol* 2002;167(4):1587-1592.
29. Matlaga BR, Zagoria RJ, Woodruff RD, Torti FM, Hall MC. Phase II trial of radio frequency ablation of renal cancer: evaluation of the kill zone. *Urology* 2002;168(6):2401-2405.
30. Johnson DB, Solomon SB, Su LM et al. Defining the complications of cryoablation and radio frequency ablation of small renal tumors: a multiinstitutional review. *J Urol* 2004;172(3):874-877.
31. Weizer AZ, Raj GV, O'Connell M, Robertson CN, Nelson RC, Polascik TJ. Complications after percutaneous radiofrequency ablation of renal tumors. *Urology* 2005;66(6):1176-1180.