WJN World Journal of Nephrology

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DOI: 10.5527/wjn.v5.i3.283

World J Nephrol 2016 May 6; 5(3): 283-287
ISSN 2220-6124 (online)
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MINIREVIEWS

Kidney function outcomes following thermal ablation of small renal masses

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Author contributions: Raman JD, Jafri SM and Qi D wrote the manuscript; Jafri SM and Qi D performed the literature review.

Conflict-of-interest statement: No conflicts of interest associated with this article.

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Received: December 27, 2015
Peer-review started: December 28, 2015
First decision: January 15, 2016
Revised: February 13, 2016
Accepted: March 22, 2016
Article in press: March 23, 2016
Published online: May 6, 2016

Abstract

The diagnosis of small renal masses (SRMs) continues to increase likely attributable to widespread use of axial cross-sectional imaging. Many of these SRMs present in elderly patients with abnormal baseline renal function. Such patients are at risk for further decline following therapeutic intervention. Renal thermal ablation presents one approach for management of SRMs whereby tumors are treated *in situ* without need for global renal ischemia. These treatment characteristics contribute to favorable renal function outcomes following kidney tumor ablation particularly in patients with an anatomic or functional solitary renal unit.

Key words: Radiofrequency ablation; Cryoablation; Modification of diet in renal disease equation; Kidney function; Dialysis

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Core tip: Because of increased abdominal imaging, an increasing number of incidental small kidney masses are being detected. Renal thermal ablation is one treatment strategy used for the management of these tumors. Oncologic outcomes in published series appear favorable. Thermal ablation allows treatment of kidney masses *in situ* without the need for complete ipsilateral renal ischemia. As a consequence, ablation may be an attractive alternative for patients with baseline kidney dysfunction owing to medical comorbidities who would be at risk for declining kidney function following surgery.

Raman JD, Jafri SM, Qi D. Kidney function outcomes following thermal ablation of small renal masses. *World J Nephrol* 2016; 5(3): 283-287 Available from: URL: http://www.wjgnet.com/2220-6124/full/v5/i3/283.htm DOI: http://dx.doi.org/10.5527/wjn.v5.i3.283

INTRODUCTION

The incidence of small renal masses (SRMs) has continued to increase over the past twenty years[1]. While several factors may contribute to this observation, the most significant has been the increasing use of abdominal cross-sectional imaging[2]. Specifically, routine and widespread use of imaging modalities including (but not limited to) ultrasound, computerized tomography, and magnetic resonance imaging has led to a 2.3% to 4.3% annual increase in renal cell carcinoma with incidental detection of small renal tumors increasing by 60%[3].

Surgical extirpation in the form of radical (RN) or partial (PN) nephrectomy has served as the mainstay for management of enhancing renal masses[4]. Over time, however, the utilization of RN to manage SRMs has waned. The loss of normal renal parenchyma with RN for clinical T1 disease is substantial, and RN has been implicated as an independent risk factor for chronic kidney disease (CKD)[5]. Furthermore, recent data underscores an association between CKD and cardiovascular morbidity and all-cause mortality[6,7]. Therefore, PN is now more broadly accepted as a treatment alternative with equivalent oncologic results and superior renal function outcomes compared to RN for appropriately selected patients[8-10].

The majority of incidentally detected renal tumors are relatively small (defined as < 4 cm, clinically stage T1a), low Fuhrman grade, with slow growth kinetics (< 0.35 cm/year), and low potential for metastasis[11-13]. Furthermore, many of these tumors are detected in older individuals with pre-existing comorbidities. In these individuals, surgical complications may pose a higher risk than the small renal tumor itself. Concerns regarding over diagnosis and overtreatment of patients with relatively low-risk, indolent small renal tumors have led to an increased interest in minimally invasive, ablative therapies as an alternative to extirpative surgical intervention for select patients[14,15].

THERMAL ABLATION

Thermal ablative techniques include radiofrequency ablation (RFA) and cryoablation (CA) which can be accomplished by open, percutaneous, or laparoscopic approaches[3]. The underlying concept of RFA involves transfer of electrical current from a generator through needle probes (electrodes) into target tissue. The generator produces high-frequency, alternating electrical current which promotes ionic agitation of cells and subsequent molecular friction. Collectively, these effects contribute to intense heat production and thermal damage. In contrast, CA involves freezing and thawing target tissues through use of a cryoprobe. The freezing action mediates cellular death by creating a direct cytotoxic effect through intracellular ice crystallization. The thaw cycle promotes delayed microcirculatory failure and resultant ischemia. The thermal effect of CA is based on both of these cellular processes.

The American Urological Association SRM guidelines indicate that thermal ablation is an accepted alternative to extirpative techniques in patients with kidney tumors who are poor surgical candidates[12]. Long-term oncological outcomes appear to be durable for both RFA and CA in appropriately selected clinical T1a lesions[3,16-19].

RENAL FUNCTION FOLLOWING SURGICAL EXTIRPATION

Despite its many benefits when compared to RN, deterioration of renal function does occur in a significant percentage of patients following PN. In 2015, Mir *et al*[20] published a comprehensive literature review with the PRISMA criteria and highlighted that decline in renal function in the operated kidney averaged approximately 20%. This occurrence is attributable to a host of different factors, including baseline kidney function, volume of preserved renal parenchyma, and duration of ischemia time[21,22]. Specifically, lower baseline eGFR has widely been reported as a significant risk factor for both short-term and long-term decline in renal function[23]. Recent data from Mukkamala *et al*[24] of a cohort of 358 patients undergoing minimally invasive partial nephrectomy (PN) revealed that lower pre-operative eGFR, longer ischemia time, and larger tumor size were all significantly associated with progression to lower CKD classes.

RENAL FUNCTION CHANGES FOLLOWING THERMAL ABLATION

Kidney ablation has been described as a treatment alternative in comorbid patients who are poor candidates for major surgery. This cohort of patients includes those with baseline renal insufficiency suffering from CKD. An advantage of ablation is that it does not require clamping of the renal hilar vessels and therefore avoids the need for total ipsilateral kidney ischemia. Thus, it is quite attractive in patients with baseline kidney function disease. At present, several different groups have attempted to better define quantify the magnitude of impact of ablation on global renal function. It is important to note that at present there are no randomized control trials investigating kidney function comparing ablative strategies *vs* extirpative modalities. Therefore, the subsequent data are all based on single or multicenter observational experiences.

Initially, in 2006, Hegarty *et al*[25] published a study comparing oncologic and perioperative outcomes of RFA *vs* CA. While not a primary endpoint of this study, the authors noted no significant difference in serum creatinine for either approach when comparing baseline to post-treatment (RFA: 1.35 mg/dL *vs* 1.70 mg/dL; CA: 1.35 mg/dL *vs* 1.3 mg/dL; P for both > 0.05).

Subsequently, in 2008, Lucas *et al*[26] reported on kidney function outcomes for patients with SRMs (< 4 cm) who underwent RFA, PN, or radical nephrectomy (RN). In all cases included in this study, the index patient had a normal appearing contralateral kidney on preoperative imaging and the Modification of Diet in Renal Disease (MDRD) equation was to estimate glomerular filtration rate (GFR). At a baseline, approximately 25% of each cohort had stage 3 CKD (GFR < 60 mL/min per 1.73 m^2) with the mean pretreatment GFR being 73.4, 70.9, and 74.8 mL/min per 1.73 m^2 for the RFA, PN, and RN groups, respectively. Following the index intervention, the authors specifically reported on stage 3 CKD. In particular, they noted that the 3-year freedom from stage 3 CKD was 95.2% for RFA, 70.7% for PN, and 39.9% for RN. Additionally, patients undergoing RN were 34-times more likely and those undergoing PN were 11-fold more likely to develop stage 3 CKD compared to their RFA counterparts. This study highlighted that even in patients with an anatomically appearing normal contralateral kidney, thermal ablation may be more "renoprotective" compared to surgical extirpation.

Stern *et al*[27] similarly presented GFR and cancer outcomes in a series of patients with clinical T1a renal tumors managed by RFA. In this study of 63 patients who were ASA Ⅰ or Ⅱ, the average tumor size was 2.1 cm (range, 1.0-4.0). At the time of initial diagnosis, 20% of the cohort had evidence of baseline CKD. The median eGFR is before (76.3 mL/min per 1.73 m^2) and after (74.3 mL/min per 1.73 m^2) thermal ablation remained stable. The authors suggested that RFA might be a reasonable alternative for the healthy renal tumor patient with intermediate outcomes suggesting preservation of renal function.

More recently, in 2012, Wehrenberg-Klee *et al*[28] examined the impact of percutaneous renal thermal ablation on kidney function amongst patients with baseline CKD. In this study of 48 patients with a baseline eGFR of less than 60 mL/min per 1.73 m^2, 22 underwent CA and 26 were managed by RFA. The mean tumor diameter was 3.4 cm. Overall, in the entire cohort, the mean overall eGFRs did not change significantly between baseline (39.8 mL/min per 1.73 m^2) and at 1 mo post-ablation (39.7 mL/min per 1.73 m^2) ($P = 0.85$). Thirty-eight patients had eGFR measurements available 1-year following ablation with the mean eGFR being 40.9 mL/min per 1.73 m^2 compared with a pre-ablation eGFR of 41.2 mL/min per 1.73 m^2 ($P = 0.79$). The authors further provided data on the subgroup of patients undergoing CA and RFA. For CA, the mean eGFRs at 1 mo and 1 year following treatment were 41.4 mL/min per 1.73 m^2 and 44.4 mL/min per 1.73 m^2 compared with respective baseline GFRs of 41.1 mL/min per 1.73 m^2 and 42.1 mL/min per 1.73 m^2 ($P = 0.75$ and $P = 0.19$, respectively). Similarly, in the RFA cohort, mean eGFRs at 1 mo and 1 year post-treatment were 38.2 mL/min per 1.73 m^2 and 37.8 mL/min per 1.73 m^2, compared with respective baseline GFRs of 38.7 mL/min per 1.73 m^2 and 40.4 mL/min per 1.73 m^2 ($P = 0.58$ and $P = 0.09$, respectively). Based on these data, the authors concluded that percutaneous renal ablation (either RFA or CA) did not appear to significantly negatively impact renal function among patients with significant baseline kidney dysfunction.

In 2014, Ma *et al*[29] reported long-term oncologic and renal function outcomes in healthy patients managed by RFA for SRMs. In this series, the Cockgroft-Gault formula was used to the estimated GFRs before and after RFA. Within the cohort of 52 patients (58 renal tumors), paired analysis at a median follow-up of 40 mo demonstrated no significant difference in eGFR before and after RFA (106.3 mL/min *vs* 99.2 mL/min, $P = 0.06$). Also, in 2014, Wah *et al*[30] reviewed outcomes of 200 renal tumors ablated in 165 patients with a focus on oncologic and kidney function outcomes (measured by the MDRD equation). Estimated GFR before and after renal RFA was 54.7 mL/min per 1.73 m^2 *vs* 52.7 mL/min per 1.73 m^2 with a mean percentage change from baseline of 3.1 mL/min per 1.73 m^2. Within this cohort of patients, only four patients developed significant renal function deterioration (> 25% decrease in eGFR). In all, 161 (98%) of the 165 patients had preservation of renal function. Finally, in a multivariate model querying potential risks for declining kidney function, the authors no association between the percentage of eGFR change with tumor size, polar position, tumor location, and size of tumor.

Collectively, studies described above noted that in general there were no significant changes from baseline renal function following probe ablative therapy.

KIDNEY FUNCTION CHANGES IN A SOLITARY KIDNEY MODEL

Perhaps the most interesting population to examine when considering renal function outcomes following therapy is patients with kidney tumors in a solitary kidney. This has long been a treatment challenge for urologists, as this population not only exhibits a baseline deficiency in renal function but also susceptibility to further decrement in function following interventional therapy. In this regard, in 2008 Raman *et al*[31] reported on a small series of 16 patients with 21 renal masses (cT1a, ≤ 4 cm) in solitary kidneys managed by RFA. The mean pre-treatment GFR using the modified MDRD equation was 54.2 mL/min per 1.73 m^2 consistent with stage 3 CKD. Mean follow-up was just over 30 mo. At last follow-up, the mean eGFR declined by 11.8% to 47.5 mL/min per 1.73 m^2. Additionally, for those patients with multiple early serum Cr values, it was apparent that following an initial 7.5% decline 6 wk following RFA, eGFR remained relatively stable up to 18 mo and later. These authors concluded that RFA adequately preserves renal function in patients with small renal tumors in a solitary kidney.

To further this analysis, several groups have specifically compared kidney function outcomes of renal ablation *vs* PN in a solitary kidney model. In 2010, in a multi-institutional study, Raman *et al*[32] reported on 89 patients with 98 renal tumors in a solitary kidney managed by RFA or open PN (OPN) with cold ischemia.

Renal function was calculated using the modified MDRD equation. When comparing the two groups, the median tumor size was greater for those managed by OPN (3.9 cm *vs* 2.8 cm, $P = 0.001$), while the median preoperative eGFR was lower in the RFA group (46.5 mL/min per 1.73 m^2 *vs* 55.9 mL/min per 1.73 m^2, $P = 0.04$). Compared to RFA, patients treated with OPN had a greater decline in eGFR at all times evaluated, including early after the procedure (15.8% *vs* 7.1%), 12 mo after surgery (24.5% *vs* 10.4%) and at the last follow-up (28.6% *vs* 11.4%, P for all < 0.001). Additionally, for patients with a pretreatment eGFR of > 60, there was a new onset decline < 60 in 7% of RFA patients *vs* 35% of OPN patients. Similarly, for patients with pre-ablation eGFR of > 30 mL/min per 1.73 m^2, there was a new onset of decline in < 30 7% of patients after RFA and 17% after OPN. Based on these findings, the authors suggested that further emphasized the potential benefit of ablative techniques for managing tumors in solitary renal units.

Similar observations were noted by Krambeck *et al*[33] who reported a single institution series of percutaneous or open RFA in 30 patients with 55 total tumors in a solitary kidney system. In contrast to the above mentioned studies, the Cockroft-Gault formula was used for calculation of renal function changes. No difference in preoperative and postoperative calculated creatinine clearance was noted (61.5 mL/min *vs* 58.4 mL/min, $P = 0.072$). Additionally, there was no difference in systolic ($P = 0.102$) and diastolic ($P = 0.790$) blood pressure before and after ablation. This group summarized that RFA of renal masses in the solitary kidney appears to be relatively safe with no adverse effects on renal function and blood pressure.

Finally, in 2009, Turna *et al*[34] reviewed their experience with laparoscopic PN, CA, and RFA for tumors in solitary renal units focusing on oncologic and kidney function outcomes. This study patients who underwent laparoscopic PN ($n = 36$), CA ($n = 36$) and RFA ($n = 29$), respectively. These investigators observed a mean decrease in eGFR calculated one month post-treatment by 18% (PN), 3% (CA), and 7% (RFA). Furthermore, 5 of 36 patients undergoing laparoscopic PN required some form of hemodialysis, in contrast to 0 patients in the CA and RFA arms. The authors concluded that although oncological outcomes are superior for laparoscopic PN, there appears to be somewhat poorer renal function outcomes than those patients managed by CA and RFA.

Collectively, these data comparing experience in solitary kidney systems underscore a renal function benefit when considering thermal ablation *vs* PN.

CONCLUSION

Thermal ablation is an increasingly utilized treatment option for comorbid patients presenting with SRMs. Studies to date highlight that renal preservation is superior when compared to partial or RN. Such considerations may be more significant when evaluating anatomic or functional solitary renal units at particular risk for post-treatment kidney injury. Prospective studies are requisite to better define the role of probe ablative therapy in managing small kidney tumors.

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