Likelihood of Incomplete Kidney Tumor Ablation with Radio Frequency Energy: Degree of Enhancement Matters

Aaron H. Lay, Jeremy Stewart, Noah E. Canvasser, Jeffrey A. Cadeddu* and Jeffrey C. Gahan

From the Department of Urology, University of Texas Southwestern Medical Center, Dallas, Texas

Purpose: Larger size and clear cell histopathology are associated with worse outcomes for malignant renal tumors treated with radio frequency ablation. We hypothesize that greater tumor enhancement may be a risk factor for radio frequency ablation failure due to increased vascularity.

Materials and Methods: A retrospective review of patients who underwent radio frequency ablation for renal tumors with contrast enhanced imaging available was performed. The change in Hounsfield units (HU) of the tumor from the noncontrast phase to the contrast enhanced arterial phase was calculated. Radio frequency ablation failure rates for biopsy confirmed malignant tumors were compared using the chi-squared test. Multivariate logistic analysis was performed to assess predictive variables for radio frequency ablation failure. Disease-free survival was calculated using Kaplan-Meier analysis.

Results: A total of 99 patients with biopsy confirmed malignant renal tumors and contrast enhanced imaging were identified. The incomplete ablation rate was significantly lower for tumors with enhancement less than 60 vs 60 HU or greater (0.0% vs 14.6%, p=0.005). On multivariate logistic regression analysis tumor enhancement 60 HU or greater (OR 1.14, p=0.008) remained a significant predictor of incomplete initial ablation. The 5-year disease-free survival for size less than 3 cm was 100% vs 69.2% for size 3 cm or greater ($p < 0.01$), while 5-year disease-free survival for HU change less than 60 was 100% vs 92.4% for HU change 60 or greater (p=0.24).

Conclusions: Biopsy confirmed malignant renal tumors, which exhibit a change in enhancement of 60 HU or greater, experience a higher rate of incomplete initial tumor ablation than tumors with enhancement less than 60 HU. Size 3 cm or greater portends worse 5-year disease-free survival after radio frequency ablation. The degree of enhancement should be considered when counseling patients before radio frequency ablation.

Key Words: ablation techniques; image enhancement; radiation; carcinoma, renal cell

Abbreviations and Acronyms

CT = computerized tomography
DFS = disease-free survival
NS = nephrometry score
RCC = renal cell carcinoma
RFA = radio frequency ablation
SRM = small renal mass

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* Correspondence: Department of Urology, University of Texas Southwestern Medical Center, 5323 Harry Hines Blvd. J8, 106C, Dallas, Texas 75390.

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THE incidence of small renal masses is increasing, largely due to the increased detection of incidentally discovered tumors.[1,2] As such, the surgical treatment of SRMs has shifted toward minimally invasive approaches and nephron sparing surgery.[3] Focal ablative techniques such as radio frequency ablation and cryoablation have now matured with satisfactory long-term oncologic outcomes and are accepted treatment options for patients with SRMs.[4–7]

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RFA relies on the transfer of thermal energy to destroy targeted tissue.[8,9] Uniform temperatures greater than 60C are required to cause cell death and ensure optimal ablation success.[10,11] However, all thermal ablation technologies are sensitive to a heat sink effect as areas with high blood flow may shunt heat energy away from the target tissue.[12,13] As such, the tumor being treated may not entirely reach the necessary temperature for cell death.

Previous work has demonstrated that RFA outcomes are associated with tumor diameter and tumor histology, with larger size and clear cell histopathology associated with higher rates of recurrence.[14,15] The degree of tumor enhancement has not been evaluated as a factor. Clear cell carcinomas are typically more vascular and are distinguished from other tumor types by greater enhancement on contrast imaging.[16] However, the enhancement of clear cell and other types of SRMs can vary significantly. We hypothesized that the degree of kidney tumor enhancement, as a surrogate for tumor vascularity, may be an independent risk factor for incomplete radio frequency ablation and lower 5-year disease-free survival.

METHODS

After obtaining institutional review board approval a retrospective review of patients who underwent RFA for kidney tumors at our institution from 2005 to 2014 was performed. CT with and without contrast before RFA must have been available for inclusion in the analysis. Patient demographic data and tumor characteristics were recorded. The degree of tumor enhancement (change in HU) from the noncontrast phase to the contrast enhanced arterial phase was calculated. This was performed by identifying a region of interest within the tumor at its largest dimension on the axial images and obtaining the average HU (fig. 1).

Our RFA technique has been described previously.[15] Only patients who had biopsy confirmed RCC were included in the ablation failure and DFS analysis. Incomplete ablation was defined as persistent enhancement of greater than 15 HU in the targeted area at the first 6-week followup CT. Those who underwent repeat ablation after initial ablation failure had the entire volume of the tumor ablated. DFS was defined as freedom from local recurrence. Local recurrence was considered if there was enhancement on followup imaging within the site of ablation after successful initial ablation. Patients with an initial incomplete ablation were excluded from DFS analysis. This was done to maintain a homogeneous study population as not all who had initial ablation failure underwent repeat ablation.

For statistical analysis tumor size was categorized as less than 3 cm and 3 cm or greater, tumor NS was categorized by less than 6 and 6 or greater, and degree of enhancement was categorized as less than 60 and 60 HU or greater. This stratification was selected based on mean HU change in the cohort, which was 63.8. Incomplete ablation rates between the groups were compared using the chi-squared test. Multivariate logistic analysis was performed to assess predictive variables for incomplete ablation. DFS was calculated using Kaplan-Meier analysis and compared using the log rank test. Statistical analysis was performed using STATA® v14.

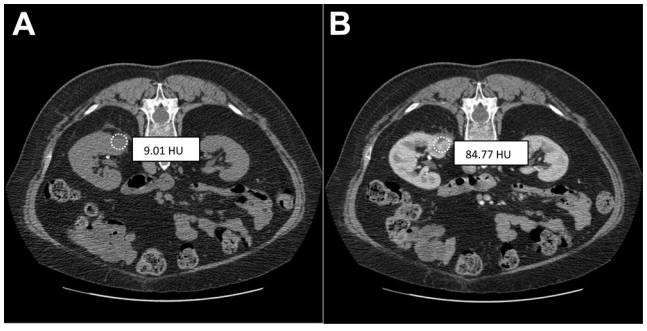

Figure 1. Measuring kidney tumor enhancement using region of interest to determine HU in noncontrast phase CT (*A*) and arterial contrast phase CT (*B*).

RESULTS

A total of 158 patients with preoperative contrast enhanced CT were available for review. Tissue diagnosis was achieved in 81% of patients based on biopsy before ablation. Mean change in tumor enhancement of each cell type is listed in table 1. Overall 99 patients were diagnosed with RCC and were included in the ablation success and DFS analysis. Patient demographics and tumor characteristics are shown in tables 2 and 3. Overall there were 7 (7.1%) patients who had initial incomplete ablation detected on the 6-week post-ablation CT. Six of the patients underwent repeat ablation while 1 patient was observed. That patient has followup to 6 years with evidence of tumor growth to 3.7 cm but has not experienced any signs of systemic disease.

Malignant tumors with a 60 HU or greater change had a 14.6% rate of incomplete ablation compared to 0% for malignant tumors with enhancement less than 60 HU (p=0.005). Tumor size, tumor histology and NS were not predictive of incomplete ablation (table 4). On multivariate logistic regression analysis change in enhancement

Table 1. *HU change by cell type*

	Mean (SD) HU Change
Clear cell (64)	70.6 (36.3)
Papillary (20)	33.4 (21.1)
Chromophobe (2)	70.5 (0.71)
RCC not specified (13)	75.9 (30.4)
Oncocytoma (15)	75.6 (45.8)
Nondiagnostic (3)	79.7 (11.7)
Benign not specified (10)	50.6 (41.1)
No biopsy (31)	58.1 (31.7)

Table 2. *Patient demographics and tumor characteristics of biopsy confirmed RCC*

Mean (SE) age	64.4 (12.8)
Mean (SE) cm tumor size	2.5 (0.73)
No. cm tumor size (%):	
Less than 3	74 (75.8)
3 or Greater	25 (25.3)
Mean (SE) NS	5.6 (0.13)
No. NS (%):	
Less than 6	56 (56.6)
6 or Greater	43 (43.4)
Mean (SE) HU change in enhancement	63.8 (3.61)
No. HU change in enhancement (%):	
Less than 60	51 (51.5)
60 or Greater	48 (48.5)
No. cell type (%):	
Clear cell	64 (64.6)
Nonclear cell	35 (35.4)

of 60 HU or greater remained a significant predictor of incomplete ablation (table 5).

Overall there were 5 (5.4%) patients who had disease recurrence during the followup period. Median followup was 30 months (range 3 to 108). The 5-year DFS was significantly different when stratified by size (69.2% for 3 cm or greater vs 100% for less than 3 cm, p <0.01). The 5-year DFS was not statistically significant based on tumor cell type (100% for nonclear cell vs 92.5% for clear cell, p=0.27) or degree of tumor enhancement (100% for less than 60 HU vs 92.4% for 60 HU or greater, p=0.24). Kaplan-Meier analyses stratified by tumor size, degree of enhancement and histological cell type are presented in figure 2.

DISCUSSION

RFA uses high frequency alternating current to generate heat and cause cell death in the form of coagulative necrosis.[10] Consequently RFA is sensitive to heat sinks such as large vessels that run in close proximity to the targeted tumor. This occurs because blood can shunt heat energy away, thereby preventing the desired temperature from being reached.[13] Gervais et al showed that ablation was more likely to fail in central tumors, which are closer to the hilum.[17] Atwell et al similarly showed that tumors near the hilum had higher rates of failure.[18] Recently we published our results demonstrating that tumor histology also influences RFA efficacy with clear cell carcinomas having lower DFS than papillary tumors.[15] One reason performance may be poor in clear cell tumors compared to papillary tumors is the degree of tumor vascularity.[16,19–21] Therefore, we hypothesized that tumors with significant contrast enhancement (a surrogate for increased vascularity) would likely have poorer RFA outcomes.

Tumors with enhancement 60 HU or greater had a 14.6% risk of initial incomplete ablation compared to 0% for tumors with enhancement less than 60 HU (p=0.005). This would be consistent with our hypothesis that the degree of enhancement can stratify RFA outcomes. While it may appear intuitive that the degree of preoperative enhancement will predict RFA failure because of the way in which failure is defined (residual enhancement on CT), this study still holds merit and clinical significance as repeat ablation is frequently performed in patients with residual enhancement. Thus, these data are useful when counseling patients before RFA and may help in patient selection for the procedure. In addition, to our knowledge this is the first report that correlates degree of enhancement to outcomes of RFA in malignant renal tumors. Interestingly we did not find tumor size to be a significant predictor of incomplete ablation. However, the rate of

Table 3. *Tumor characteristics stratified by degree of enhancement*

	HU less than 60	HU 60 or Greater	p Value
Mean cm tumor size	2.40	2.52	0.42*
No. cm tumor size (%):			
Less than 3	40 (78.4)	34 (70.8)	0.38†
3 or Greater	11 (21.6)	14 (29.2)	
Mean NS	5.61	5.50	0.69*
No. NS (%):			
Less than 6	27 (52.9)	29 (60.4)	0.453†
6 or Greater	24 (47.1)	19 (39.6)	
No. cell type (%):			
Clear cell	22 (43.1)	13 (27.1)	0.09†
Nonclear cell	29 (56.9)	35 (72.9)	

* Two-sample t-test.
† Pearson's chi-squared test.

Table 4. *Incomplete ablation rates*

	Incomplete Ablation Rate (%)	p Value
Size (cm):		
Less than 3	5.4	0.266
3 or Greater	12.0	
NS:		
Less than 6	8.9	0.411
6 or Greater	4.7	
HU change:		
Less than 60	0	0.005
60 or Greater	14.6	
Cell type:		
Clear cell	5.7	0.697
Nonclear cell	7.8	

Table 5. *Multivariate logistic regression analysis of tumor factors predicting incomplete ablation*

Tumor Variable	OR for Incomplete Ablation (95% CI)	p Value
Size	1.06 (0.94–1.17)	
Reference: less than 3 cm		0.341
Enhancement change	1.14 (1.04–1.24)	
Reference: less than 60 HU		0.008
NS	0.96 (0.86–1.06)	
Reference: less than 6		0.470
Cell type	0.99 (0.89–1.10)	
Reference: nonclear cell		0.972

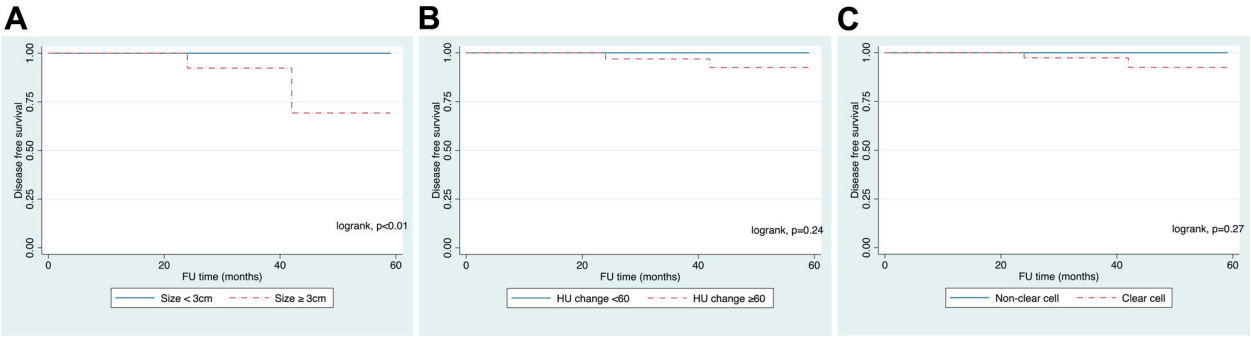

Figure 2. Kaplan-Meier survival curve for DFS stratified by size (*A*), HU change (*B*) and cell type (*C*). *FU*, followup.

incomplete ablation in tumors 3 cm or greater was more than double that in tumors less than 3 cm (12.0% vs 5.4%) and likely a larger sample size would have allowed the detection of a statistically significant difference.

In contrast to its influence on the rate of incomplete ablation, we did not find degree of enhancement on CT to be predictive of local recurrence (DFS). This finding suggests that while the degree of enhancement may predict initial ablation success, the longer term oncologic outcomes of RFA may be dependent on tumor burden (diameter). Best et al found that for tumors less than 3 cm the 5-year DFS was 95% vs 79% for tumors 3 cm or greater.[14] Psutka et al similarly found that for cT1a tumors the 5-year DFS was 91.5% vs 74.5% for cT1b tumors.[4] We corroborated these results as we found that 5-year DFS for tumors less than 3 cm was 100% vs 69.2% for size 3 cm or greater ($p < 0.01$). Of note, this difference in outcomes (size stratification) is not seen in partial nephrectomy series as the 5-year DFS for T1b tumors ranges from 90% to 93%.[22,23]

The 5-year DFS for nonclear cell tumors was 100% compared to 92.5% for clear cell tumors, although the difference was not significant in this small cohort of patients. These results confirm that small nonclear cell tumors are particularly suitable for RFA. We previously published a multi-institutional experience of RFA for papillary tumors compared to clear cell tumors and also found no recurrences with papillary tumors.[15] These findings suggest the value of a pre-ablation biopsy as patients with highly enhancing clear cell tumors could be counseled on the potentially increased recurrence rate.

There are limitations to this study. It is a retrospective review of our case series and included only patients who had a noncontrast and contrast enhanced CT, limiting the number that could be included. In addition, only those who had biopsy confirmed malignant renal tumors were included when calculating the rate of incomplete ablation and DFS. While performing the study in this manner does not allow an intent to treat analysis, it does provide a more homogeneous population from which to draw conclusions. Furthermore, the degree of enhancement within the tumor depends on the timing and amount of contrast agent used.[24] While standard protocols for the administration of contrast were implemented with each CT, there is likely some variation. In addition, most kidney tumors are heterogeneous[25] and the degree of enhancement can vary somewhat depending on which part of the tumor was measured. In this study the region of interest was taken at the largest cross-sectional diameter and every effort was made to include as much tumor area as possible (fig. 1). The results presented here validate our methods to some degree as the enhancement patterns calculated are consistent with the reported literature (70.6 and 33.4 HU for clear cell and papillary tumors, respectively).[16]

CONCLUSIONS

The degree of malignant renal tumor enhancement of 60 HU or greater is an independent predictor of initial RFA failure but not of long-term disease recurrence. Tumor size 3 cm or greater remains a significant risk factor for disease recurrence after RFA. These tumor characteristics should be considered when counseling patients before RFA.

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