Title

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SKIN-TO-TUMOR DISTANCE PREDICTS TREATMENT FAILURE OF T1A RENAL CELL CARCINOMA FOLLOWING PERCUTANEOUS CRYOABLATION

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Abbreviations: Percutaneous cryoablation (PCA), Renal cell carcinoma (RCC) Small renal mass (SRM), skin-to-tumor distance (STT), computed tomography (CT), magnetic resonance imaging (MRI), renal cell carcinoma (RCC)

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ABSTRACT

Objective: To determine the impact of skin-to-tumor (STT) distance on the risk for treatment failure following PCA.

Methods: We retrospectively reviewed patients who underwent PCA with documented T1a recurrent renal cell carcinoma (RCC) at two academic centers between 2005 and 2015. Patient demographics, tumor characteristics, perioperative and post-operative course variables were collected. Additionally, we measured the STT by averaging the distance from the skin to the center of the tumor at 0, 45 and 90 degrees on preoperative computed tomography imaging.

Results: We identified 86 patients with documented T1a RCC. The mean age at the time of surgery was 69 years (range 37 – 91 years), and the mean tumor size was 2.7 cm (range 1.0 - 4.0 cm). With a mean follow up of 24 months (range 3 – 63 months), 11 (12.8%) treatment failures occurred. Patients with treatment failure had significantly higher mean STT than those without: 11.0 cm (range 6.3 – 20.1 cm) compared to 8.4 cm (range 4.4 - 15.2 cm), respectively (p=0.002). STT was an independent predictor of treatment failure (OR 1.32 CI 1.04-1.69, p= 0.029). STT greater than 10 cm had a 4-fold increased risk of tumor treatment failure (OR 4.43, CI 1.19-16.39, p= 0.018). Tumor size, R.E.N.A.L. Nephrometry score, and number of cryoprobes placed were not associated with treatment failure.

Conclusions: STT, an easily measured preoperative variable, may inform the risk of RCC treatment failure following PCA.

INTRODUCTION:

Renal cell carcinoma (RCC) is the 14th most common cancer in the world, with an estimated 61,000 people diagnosed in the United States in 2015[1]. The widespread use of diagnostic imaging has increased the detection of T1a renal cell carcinoma variants, allowing for more timely intervention and thereby better cancer-specific survival[1,2]. While extirpation remains the gold standard for treatment of small renal masses (SRM), percutaneous cryoablation (PCA) is an alternative, minimally invasive approach that is effective in select patients[3-5]. The American Urological Association and European Association of Urology

guidelines support the use of ablation modalities in patients with T1a (<4cm) disease, those at increased risk of multiple tumors (i.e. Von Hippel-Lindau syndrome), solitary kidney, or in patients with significant comorbidities who are poor surgical candidates[6,7]. However, while durable disease response is favorable in patients who have undergone PCA, reported local treatment failure rates remain relatively high, from 5- 30% in comparison to less than 2% following partial nephrectomy[8,9,10].

Tumor and patient characteristics such as tumor size, location, depth, and patient body mass index (BMI) account for the complexity of a procedure and potentially lead to higher treatment failure and complication rates[11-13]. Current reports support the assertion that PCA should only be applied to T1a (<4cm) renal cell carcinoma variants, with early evidence corroborating that tumor size directly affects oncologic outcomes[14]. Further, the location of the tumor such as anterior or upper pole lesions, may have significant impact on the difficulty of needle deployment and proper lesion targeting[12,15]. In addition, proximity of the tumor to hilar vessels, has also been hypothesized to contribute to treatment failure due to the possibility of "heat sink", or the inability for the juxtavascular probe to reach temperatures low enough to induce complete tumor necrosis[11,12,14]. Treatment algorithms that take into account the size, location, and proximity to surrounding retroperitoneal and abdominal structures have been developed that are predictive of treatment difficulty and complications, however, few studies combining patient and tumor specific variables to predict long-term procedural outcomes have been conducted[16]. Pareek and colleagues first introduced the concept of skin-to-target (stone) distance as a predictor of outcomes for stone disease in the setting of shockwave lithotripsy[17]. Subsequently, Blute and colleagues described skin-to-tumor (STT) distance for renal cortical neoplasms in a heterogeneous population of patients with benign, malignant, and indeterminant tumors of all sizes[13]. Herein we evaluated skin-to-tumor distance as a predictor of treatment failure following percutaneous cryoablation in

patients with biopsy proven T1a RCC. It is our hypothesis that tumors deeper in the body may be harder to eradicate with contemporary cryoablation.

METHODS:

Study Design

After Institutional Review Board approval, we conducted a retrospective chart review of all patients with biopsy proven T1a RCC who underwent primary treatment with PCA at two academic institutions between December 2005 and June 2015. Only patients with available preoperative imaging were included in this analysis. We collected and analyzed patient demographics, peri- and post-operative characteristics to determine preoperative factors predictive of treatment failure following primary PCA.

Measurements

Preoperative computed tomography (CT) and magnetic resonance imaging (MRI) scans were used to determine STT distances for all patients according to the methods of Pareek and colleagues (2005). The average of the three measurements at 0 degrees posteriorly, 45, and 90 degrees laterally from the skin to the center of the tumor were recorded as the STT[17] (Figure 1). Probe distance was taken as the average distance from surface of the skin to tip of the probe for each probe based on inter-procedural CT images.

Tumor size (i.e. largest axial diameter), tumor polarity, and tumor depth were recorded. With regard to polarity, tumors that crossed the midline between the upper and lower poles were classified as interpolar. Tumors protruding more than 50% from the renal parenchyma were categorized as exophytic, while those that were protruding less than or equal to 50% were deemed mesophytic. Tumors entirely confined within the renal parenchyma were categorized as endophytic. A R.E.N.A.L. Nephrometry score was determined for each tumor based on the method of Kutikov and colleagues[18].

Surgical Technique

At both institutions, all PCA were performed in a hospital-based interventional radiology suite as a combined effort between interventional radiologist and urologist. The PCA technique used at both institutions involved a double freeze thaw cycle as previously described[17,21]. The total number of probes placed was based on the tumor size. Probe placement was confirmed prior to each procedure with CT imaging. Treatment success was determined by an inter-procedural CT scan documenting extension of the ice ball at least 1

cm beyond the tumor in every dimension. A diagnostic CT with intravenous contrast was performed immediately following the procedure.

Imaging Follow-up

Following the procedure, CT or MRI was obtained at 3 to 6 months, 1 year, and then annually. Treatment failure was defined as enhancement in the region of the ablated tumor or tumor growth on follow-up imaging. Patients with persisting tumors were offered a variety of options: surveillance, repeat cryoablation, partial nephrectomy or radical nephrectomy. All patients with persistent tumors elected to undergo either repeat PCA or laparoscopic partial nephrectomy.

Statistical analysis

The primary outcome measure was absence of enhancement or tumor growth on follow up imaging. Chi- square analysis was used to compare frequency and distribution of treatment failure and R.E.N.A.L. Nephrometry scores. Pearson correlations and Fisher exact tests were used to assess correlation between STT, probe distance, and BMI. Finally, predictive preoperative, patient and disease specific variables were used to determine treatment failure using logistic regression analysis. Statistical significance was defined as a p value of ≤ 0.05.

RESULTS:

A total of 169 patients underwent PCA for a small renal mass. Of these, we identified 86 patients with biopsy proven T1a RCC. The mean age at the time of surgery was 69 years (range 37-91 years) and the mean tumor size was 2.7 cm (range 1.0 - 4.0 cm). Patient demographics and clinical characteristics are presented in Table 1.

With a mean follow-up of 24 months (range 3 – 64 months), there were 11 (12.8%) treatment failures. Mean time identification of treatment failure was 15 months (range 6- 24 months). Patients with treatment failure had a mean age of 62 years (range 47-79 years) while patients without treatment failure were older (i.e. 71 years (range 37-91 years), (p=0.014)). A greater proportion of patients with treatment failure were ASA III, 60% vs. 49%, ($p < 0.001$). A greater proportion of patients with treatment failure had a solitary kidney (3 of 11 or 27%) versus those who underwent successful treatment (4 of 75 or 5%), (p=0.042). Lesion size and R.E.N.A.L. Nephrometry score did not correlate with treatment failure (p=0.600 and p=0.536, respectively). Similarly, tumor depth (endophytic, mesophytic, or exophytic character), polarity (upper verses lower) and nearness to the renal hilum was not significant (p=0.191, p=0.805, p= 0.518, respectively). The number of probes used was not significantly different between patients with and without treatment failure (p=0.864) nor was the number of probes per centimeter of tumor (p=0.885)(Supplementary Table 1). There was no significant difference in probe per centimeter of tumor in patients with paired and solitary kidney (p=0.331) and, similarly, probe per centimeter of tumor in patients with solitary kidney was not different between those with treatment failure and those without (p=0.102). The mean STT in patients with treatment failure was significantly greater than in patients whose disease was successfully eradicated (11.0 and 8.4 cm, respectively, p=0.002). Patients with solitary kidney had a significantly longer STT compared to patients with a paired kidney (10.8 cm vs. 8.6 cm, p=0.037). However, there was no significant difference in STT in patients with a solitary kidney who failed compared to those whose treatment was successful (11.6 and 10.1 cm respectively, p=0.561). In all patients, probe distance was highly correlated with STT (Pearson correlation coefficient 0.746, $p<0.001$). Similar to STT, probe distance was also greater in patients with treatment failure (11.3 cm (8.2 -18.9 cm) vs. 9.7 cm (5.2- 14.2 cm), p= 0.040). Finally, patients with treatment failure trended toward a higher BMI (mean 31.3 (24.7-40.6) vs. 27.9 (18.0-42.4), p=0.131). Pearson correlation revealed that STT was highly correlated with BMI (Pearson correlation coefficient 0.55, $p<0.001$) (Table 1).

When treated as a continuous variable, STT was significantly associated with treatment failure on univariate logistic regression analysis (OR 1.37 CI 1.08-1.72, p= 0.008) and multivariate analysis (OR 1.32 CI 1.03- 1.69 p= 0.029) indicating a 32% increased risk of treatment failure for every increased centimeter of STT. Overall, a total of 6 treatment failures occurred in 21 patients (28.6%) with a STT greater than 10 cm. Treatment failure rate among patients with an STT less than or equal to 10 cm was 7.7% (5 of 65). **Supplementary table 1** indicates the distribution of STT among patients with and without treatment failure and Supplementary Table 2 indicates the percentage of treatment failures corresponding to every centimeter of STT. When treated as a dichotomous variable, STT greater than 10 cm was associated with a 4- fold increased risk of treatment failure (OR 4.43, CI 1.20- 16.39, p= 0.018). BMI was not significantly associated with tumor treatment failure on univariate analysis (OR 1.11 CI 0.97-1.22 p=0.126). While a tumor in a solitary kidney was associated with higher treatment failures on univariate analysis (OR 6.656 CI 1.26- 35.20 p= 0.026), it was not significant on multivariate analysis (p=0.173). Finally, on multivariate analysis, younger age at the time of surgery was associated with an increased risk of treatment failure (OR 0.94 CI 0.88-0.999, p= 0.047) (Table 2 and Supplementary Table 2).

Ten complications (12%) were noted (Supplementary table 3). Neither R.E.N.A.L. score nor STT was associated with complication rate (p=0.099 and p=0.85, respectively).

Two of the 11 patients who experienced treatment failure underwent subsequent partial nephrectomy successfully. One elected active surveillance and ultimately underwent radical nephrectomy due to tumor progression. The remainder underwent successful repeat cryoablation with no patient progressing to metastasis or tumor related death (mean follow up 21 months, range 3-36 months).

DISCUSSION:

Current guidelines recommend surgical extirpation for all renal cortical masses despite the finding that upwards of 30% of these lesions are benign or of low malignant potential[19]. Over the past decade, PCA has emerged as an effective, less morbid, alternative treatment modality. PCA preserves renal parenchyma and minimizes morbidity, convalescence time, and costs versus surgical excision[20,21]. Moreover, PCA offers similar cancer specific and metastasis free survival to the gold standard, partial nephrectomy[9]. Still, reported local treatment failure after PCA is higher than with surgical extirpation indicating that better patient selection or improved ablation techniques are needed. To this end, we compared patient and tumor characteristics relevant to PCA procedural planning and complexity in patients with documented T1a disease.

Previous PN studies have demonstrated that tumor specific variables such as size, depth within the kidney, and tumor polarity and location relative to the renal hilum significantly impact outcomes including perioperative complications and oncological outcomes[11,12,22]. However, this does not seem to be the case for PCA. Indeed, in our study of pathological T1a renal cancers treatment failure rates following PCA were not dependent on the aforedescribed tumor specific variables. This is consistent with previous findings that PCA, may be used to successfully treat even anteriorly located tumors independent of tumor size and proximity to the renal hilum[11,23-25]. It is important to note that the selection criteria of the current manuscript include only T1a RCC variants, which are, by definition, all ≤4cm. As such, we continue to prefer to limit cryoablation to tumors that are 3 cm or smaller. While the relevance of tumor size and location for SRM remains concerning, the use of multiple probes, facile use of intra-operative monitoring of ablative margins, and surgeon's experience appear to contribute to successful ablation.

The R.E.N.A.L. Nephrometry score is a proven metric of complexity that has utility for surgical planning and has been demonstrated to be predictive of outcomes following either PN or PCA[26,27]. In a study of 751 mixed renal tumors, Schmit and colleagues found that a R.E.N.A.L. Nephrometry score greater than 8 correlated with risk of early and overall treatment failure following both PCA and radiofrequency ablation (RFA)[24]. Camacho and colleagues similarly found that the R.E.N.A.L. Nephrometry score was significantly associated with treatment failure following PCA and RFA[22]. In contrast, in the present study,

tumor complexity, as indicated by the R.E.N.A.L. Nephrometry score, was not a significant predictor of treatment failure after PCA. One reason for this discrepancy could be that in both studies evaluated PCA and RFA together; as such, the Nephrometry score may indeed be less predictive for PCA when considered alone. Also it is also possible that our negative Nephrometery results are secondary to a pretreatment selection bias. In general, tumors chosen for PCA in the current series were small (i.e. all T1a) and of low to moderate complexity, hence we may have had too few patients with a higher Nephrometry score to allow for a more balanced analysis.

It is clear that an important variable that contributes to complexity of the PCA procedure is intracorporeal distance. In 2005, Pareek and colleagues introduced the concept of skin-to-stone distance, changing the management of renal stones by demonstrating that skin-to-stone distance greater than 10 cm predicts extracorporeal shock-wave lithotripsy failure[17]. In 2012, Blute and colleagues found STT, similarly measured by taking the average of the distances from the center of the tumor to the surface of the skin at 0, 45, and 90 degrees on axial imaging, predicted treatment failure after PCA in a heterogeneous patient population with malignant, benign, and indeterminate tumors of all sizes[13]. The present study is the first to test the impact of STT specifically on the treatment of pathological T1a renal cancer with PCA.

In agreement with the earlier study by Blute and colleagues, we noted that increased skin-to-tumor distance predicts subsequent treatment failure. Indeed, with every centimeter of increased STT, the risk of treatment failure rose by 32%. Moreover, in patients with STT greater than 10 cm, risk of treatment failure was increased four fold versus those with a STT less than 10 cm. These findings are consistent with recent observations by Prince and colleagues, which demonstrate that greater STT is associated with higher failure rates of percutaneous renal biopsy[28]. Taken together, it is likely that greater STT complicates effective targeting of renal lesions be it for biopsy or for PCA.

It is also possible that increased tumor depth within the body may result in a heat sink phenomenon along the cryoablation probe itself. Previous observations have revealed that the use of multi-point temperature sensing needles allows for precise measurement of the lethal freeze temperature within the target lesion. With the insurance that lethal temperatures have been reached, treatment failure rates may be all but eliminated[29]. Unfortunately, it is not standard of practice to employ multi-point temperature sensing needles, and relative freeze temperatures cannot be confirmed within the current cohort.

Notably, increased BMI was not significantly associated with treatment failure. This finding is consistent with previous findings by Vricella and colleagues[30]. Prince and colleagues also failed to find an association between BMI and success of renal biopsy[28]. An explanation is that BMI fails to represent the distribution of adipose tissue and, thus, does not reliably reflect the distance over which a biopsy or cryoablation needle must travel. Further exploration of the relationship between the amount of perirenal fat, flank adipose tissue, and BMI is needed to more completely explain this discordance.

Based on our results, we believe that STT may be used as a measure of technical difficulty that can inform treatment choice and procedural planning, counseling and follow-up. In patients with STT greater than 10 cm, physicians may consider partial nephrectomy or, if PCA is to be done, alterations in ablation technique. These alterations could include use of additional cryoablation needles, placement of multi-point temperature sensing needles, or altering patient positioning in order to minimize STT.

Another variable that may have significant impact on treatment outcomes is presence of a solitary kidney. We observed a disproportionate number of failures among patients with a solitary kidney. Previously, our team showed that solitary kidney patients who underwent cryoablation had higher tumor recurrence rates compared to those who underwent PN[31]. It is possible that the presence of a solitary kidney impacts how aggressively the tumor is treated with PCA. In the current study, there was no difference in the number of probes per centimeter of tumor used in patients with a solitary kidney compared to those with a paired kidney. Importantly, patients with a solitary kidney had a greater STT than patients with a paired kidney, therefore the above finding may reflect the impact of STT rather than the presence of a solitary kidney.

Finally, in the current study, younger age at the time of surgery was a predictor of treatment failure. Older age has previously been implicated as a worse prognostic indicator in patients with T1a disease[32]. Paradoxically, consistent with our findings, a recent epidemiological study showed a survival benefit in patients between the ages of 50-59 undergoing partial nephrectomy compared to tumor ablation[33]. Further exploration of the relationships between age, tumor type, and ablative outcomes is very much needed.

Limitations of our study are most certainly related to its retrospective design. Also, the relatively small number of treatment failures limits the statistical power of the analysis and may introduce bias into our findings. Certainly the creation of a national tumor registry that would separate percutaneous ablation between cryoablation and radiofrequency ablation is

needed as, currently, in SEER data bases as well as other data bases, the two are lumped together. Finally, a larger, prospective analysis is recommended to further test the findings in the present study.

CONCLUSIONS:

STT is an easily measured preoperative variable that is linearly associated with increased risk of RCC treatment failure following PCA of T1a tumors. An STT of > 10 cm is predictive of a 4 fold higher rate of treatment failure.

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Figure 1: Axial imaging demonstrating presence of renal tumor and method of measuring skin-to-tumor at 0°, 45°, 90°

Supplementary Figure 1: Point plot displaying STT distribution of patients with treatment failure and patients who underwent successful PCA

Table 1: Demographics and disease characteristics

	Overall		Treatment Failure		Successful Treatment		*p*
No. of patients	86		11		75		
Mean age (range), years	69	(37-91)	62	(47-79)	71	(37-91)	**0.014**
Gender, m(f)	64(22)		10(1)		54(21)		*0.173
ASA score							
I, II	40	51%	4	40%	36	53%	**<0.001
III	38	49%	6	60%	32	47%	
Solitary Kidney	7	8%	3	27%	4	5%	**0.042
Mean (range) BMI, kg/m2	28.4	(18.0-42.4)	31.3	(24.7-40.6)	27.9	(18.0-42.4)	0.131
Mean (range) tumor size, cm	2.70	(1.0 - 4.0)	2.80	(1.0-4.0)	2.70	(1.0-4.0)	0.600
Polarity							**0.805
Upper	20	24%	3	27%	17	23%	
Interpolar	33	40%	5	46%	28	39%	
Lower	30	36%	3	27%	27	38%	
Tumor Depth							**0.191
Exophytic	44	51%	3	27%	42	56%	
Mesophytic	28	33%	6	55%	21	28%	
Endophytic	14	16%	2	18%	12	16%	
Mean (range) RENAL Nephrometry score	6.69	(4- 11)	7	(4- 10)	6.64	(4- 11)	**0.536
Low (4-6)	40	47%	5	46%	35	45%	
Moderate (7-9)	38	44%	4	36%	36	47%	
High (10-12)	8	9%	2	18%	6	8%	
RCC subtype							
Clear cell	57	66%	**7**	**64%**	**50**	**67%**	
Papillary	15	17%	**2**	**18%**	**13**	**17%**	
Chromophobe	5	6%	**0**	**0**	**5**	**7%**	
Not specified	9	11%	**2**	**18%**	**7**	**9%**	
Grade							
1	16	19%	3	27%	13	17 %	
2	33	38%	3	27%	30	40%	
3	19	22%	2	18%	17	23%	
4	1	1%	0	0	1	1%	
Not specified	17	20%	3	27%	14	19%	
Mean (range) skin-to-tumor, cm	**8.7**	**(4.4**	**11.**	**(6.3-**	**8.4**	**(4.4- 15.2)**	**0.002**

		- 20.1)	**0**	**20.1)**			
Mean probe distance (range), cm	**9.9**	**(5.2 - 18.9)**	**11. 3**	**(8.2- 18.9)**	**9.7**	**(5.2- 14.2)**	**0.040**
Mean no. probes	2.47	(1- 8)	2.4 6	(1-4)	2.47	(1- 7)	0.864
Mean (range) no. probes/ cm tumor	1.3	(0.5 - 3.7)	1.3	(0.7-2.2)	1.3	(0.5- 3.7)	0.885

* Fisher exact test

** Pearson Chi- square

Table 2: Univariate Logistic Regression

Patient characteristics			
Variable	**OR**	**CI 95%**	***p***
Skin-to-tumor (continuous)	**1.37**	**(1.08-1.72)**	**0.008**
Skin-to-tumor (dichotomous variable, >10cm)	**4.43**	**(1.20-16.39)**	**0.018**
BMI	1.11	(0.97-1.22)	0.126
Age at surgery	**0.95**	**(0.88-0.99)**	**0.019**
Solitary kidney	6.66	(1.26- 35.20)	0.026

Figure 1.