Development of a Risk-stratified Approach for Follow-up Imaging After Percutaneous Thermal Ablation of Sporadic Stage One Renal Cell Carcinoma

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OBJECTIVE To analyze risk factors and patterns of RCC recurrence following percutaneous ablation for stage 1 tumors and develop risk-stratified follow-up imaging protocols.

METHOD Biopsy-proven sporadic stage 1 RCC patients treated with percutaneous microwave ablation (MWA) or cryoablation (CA) from 2002 to 2017 were included. Kaplan-Meier analysis was used to estimate local and distant recurrence-free survival, cancer-specific survival and metastatic-free survival. Multivariable models were used to identify risk factors associated with recurrence.

RESULTS A total of 256 patients with stage 1 RCC (215 T1a, 41 T1b) were treated with percutaneous MWA (178 subjects) or CA (78 subjects). Recurrence was identified in 23 patients (16 local, 7 distant). Clinical T stage (HR 2.46, 95% CI 1.06-5.72, $P = .04$) and tumor grade (HR 4.17, 95% CI 1.17-14.76, $P = .03$) were independent predictors of recurrence. Recurrence was not associated with Nephrometry score, cystic tumors, ablation modality (CA vs MWA) or gender. Five-year cancer-specific survival, and metastatic-free survival were 98.6% and 97.4%, respectively. Patients were stratified into 2 groups: reduced risk stage 1 (no risk factors) or elevated risk stage 1 (≥1 risk factor). Recurrence risk was higher in the elevated-risk group (HR = 3.19, 95% CI 1.35-7.53, $P = .008$). Five-year overall recurrence-free survival (local + distant) was higher in reduced-risk vs elevated-risk cohorts, 88% vs 69%, $P = .005$.

CONCLUSION High nuclear grade or T1b tumors have increased recurrence risk following percutaneous thermal ablation for stage 1 RCC. Current postablation follow-up protocols may be modified for individual recurrence risk to allow more frequent imaging for elevated-risk patients, while enabling less frequent imaging for reduced-risk patients. UROLOGY 134: 148–153, 2019.

Thermal ablation (TA) is increasingly being utilized for treatment of small localized renal cell carcinoma (RCC). A recent study from the National Cancer Database showed that 14% of small renal mass patients from 2010 to 2014 were treated with ablative therapy,[1] which had increased from 4% from 2004 to 2007 in a similar study using the Surveillance, Epidemiology and End Results database.[2] Recent guidelines from American Urological Association[3] and the American Society of Clinical Oncology[4] recommend considering TA as a treatment option for selected patients with small RCC. However, there are no standardized recommendations for imaging surveillance following RCC ablation and institutional protocols vary widely in regards to timing and frequency of imaging follow-up.

Serial abdominal imaging is necessary to identify local recurrences which are more common following ablation vs surgery for RCC but can often be salvaged with a second ablation procedure to achieve long-term recurrence-free survival rates similar to extirpative surgery.[5] Current surveillance protocols obtain between 7 and 8 abdominal computed tomography (CT) or magnetic resonance imaging (MRI) scans during the first 5 years following ablation (Supplemental Fig. 1).[6-9] However, given the indolent

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growth patterns for many small RCC and the low risk of cancer mortality following ablation,[10] it is unclear whether aggressive surveillance is beneficial for all patients. In addition, none of the current surveillance protocols are adjusted for the individual patient's recurrence risk, although prior studies have suggested recurrence is less common in smaller tumors.[11] Therefore, the purpose of this study is to analyze risk factors and patterns of RCC recurrence following percutaneous ablation for stage 1 tumors to develop risk-stratified imaging surveillance protocols.

METHODS

After IRB approval, consecutive nonmetastatic stage 1 RCC patients treated with percutaneous cryoablation (CA) or microwave ablation (MWA) from October 2002 to December 2017 were identified. Patients with prior RCC history, hereditary RCC syndromes, or multiple tumors at presentation were excluded. Comprehensive clinical, pathologic, and radiological data were collected and RENAL Nephrometry scores were calculated for each patient.[13] Images from the ablation procedures and follow-up were independently reviewed by a fellowship trained abdominal radiologist experienced in tumor ablation for this study.

Patients with renal masses are initially evaluated in Urology clinic and biopsy is obtained in patients considering ablation. Following diagnosis of RCC, selected patients are offered TA after multidisciplinary discussion with urologists and radiologists experienced in tumor ablation. Cryoablation (Endocare, Inc., Irvine, CA) has been used since 2002, while MWA (NeuWave Medical, Madison WI) became available March 2011. The choice of ablation modality is made by the treatment team on a patient-by-patient basis. Institutional techniques for percutaneous CA and MWA ablation have been described previously.[12,14] Procedures were performed in a procedural CT suite utilizing either ultrasound or CT fluoroscopy for guidance of probe placement. Contrast-enhanced CT was performed immediately following the ablation procedure to confirm treatment success and evaluate for complications.

Postablation surveillance imaging with contrast-enhanced CT abdomen/pelvis or MRI abdomen without and with contrast, chest X-ray, and laboratories (complete blood count, comprehensive metabolic panel) were obtained at routine target intervals of 3, 6, 12, 18, and 24 months and annually thereafter (supplemental Fig. 1). Residual disease was defined by radiographic evidence of tumor enhancement within or adjacent to the ablation bed at first postablation follow-up scan performed at 3-6 months following ablation.[15] Recurrence included both local and distant recurrences. Local recurrence (LR) was defined radiographically as new enhancing tumor within the ablation zone after prior complete ablation. Distant kidney recurrence is defined radiographically as tumor in the contralateral kidney or at a site remote from ablation bed within the ipsilateral kidney.[15] Metastatic recurrences were identified as tumors outside of either kidney and pathologically confirmed as RCC.

Univariate and multivariable Cox proportional hazards analysis were used to identify associations between recurrence and common patient or tumor characteristics. The Kaplan-Meier method was used for survival analyses, which included recurrence-free survival (local + distant), local recurrence-free survival, metastatic-free survival, and cancer-specific survival. Survival functions were compared using a log-rank test. Stata version 15.0 (College Station, TX) was used for all analyses.

RESULTS

A total of 256 patients were treated with percutaneous TA for cT1 RCC from October 2002 to December 2017. Patient and tumor characteristics are shown in Supplemental Table 1. Clinical T stage was T1a in 215/256 (84.0%) or T1b for 41/256 (16.0%) patients, and 8/256 (3.1%) patients had nuclear grade 3 or 4 tumors. After treatment with ablation, residual tumor was present in 7/256 (2.7%) patients including 2 cT1a tumors (2 CA, 0 MWA) and 5 cT1b tumors (2 CA, 3 MWA). Six of 7 patients with residual tumor were successfully retreated with ablation (4 CA, 2 MWA) without subsequent recurrence. One patient with residual disease is being followed with active surveillance. Fifteen patients were lost to follow-up following ablation. The median overall imaging follow-up interval was 31.6 months (IQR 17.4-52.0) for all patients who received imaging surveillance.

During the follow-up period, recurrence was identified in 23 patients (Table 1). Initial presentation was isolated local recurrence (16) isolated contralateral kidney (3) and metastatic (4). No patients presented with synchronous local or distant recurrences. Estimated 5-year recurrence-free survival (any site) was 85.1%. For 16 patients with isolated local recurrences, 11 patients were retreated with ablation, 3 with nephrectomy, 1 with active surveillance, and 1 was lost to follow-up. Estimated 5-year local recurrence-free survival was 89.0% overall. Five-year local recurrence-free survival increased to 95.3% when including 11 patients who required repeat ablation (secondary efficacy). Distant kidney recurrences (contralateral kidney) were identified in 3 patients. All distant kidney recurrences were treated with ablation without recurrence. Five patients developed metastatic disease. All metastatic recurrences were biopsy confirmed and demonstrated concordance with initial pathology. Four patients presented with metastatic disease (lung, liver, femur, and bladder) without local recurrence. One patient developed lung metastases 15 months after initial local recurrence. Two patients died from RCC (both T1a, 1 treated with MW, and 1 treated with CA) following recurrence in the bladder neck and femur at 14 and 16 months, respectively. Three patients are alive with metastatic disease. Kaplan-Meier estimated 5-year cancer-specific survival was 98.6% and metastasis-free survival was 97.4%.

Univariate and multivariable Cox proportional hazards analysis identified factors associated with RCC recurrence (Table 2). Independent predictors included clinical stage T1b (HR 2.46, 95% CI 1.06-5.72, $P = .04$) and high grade (HR 4.17, 95% CI 1.17-14.76, $P = .03$). Association with recurrence was not identified for Nephrometry score, cystic tumors, ablation modality (CA vs MWA), or gender. Patients were stratified into 2 groups: reduced risk stage 1 (both low grade and cT1a) and elevated risk stage 1 (either high grade or cT1b). Kaplan-Meier estimated 5-year recurrence-free survival at any location was 87.9% for reduced risk stage 1 cohort vs 68.9% for the elevated risk stage 1 cohort, $P = .005$ (HR = 3.19, 95% CI 1.34-7.53, $P = .008$) (Fig. 1).

For the 211/256 (82.4%) patients in the reduced risk stage 1 cohort (cT1a, low grade), recurrence was identified in 15 patients (11 LR, 2 contralateral kidney, and 2 metastatic) at a median of 16.5 months (IQR 10.3-29.1) following ablation. Of the 45/256

Table 1. Recurrence patterns for reduced risk stage 1 vs. elevated risk stage 1

	Tumor Diameter (cm)	Grade	RCC Subtype	Time to Recurrence (mo)	Total follow-up (mo)	Site of Initial Recurrence
Reduced risk stage 1	2.3	2	CC	29.1	47.7	Local
	3	2	CC	17.4	67	Local
	2.8	2	CC	12.2	17	Local
	3	2	CC	14.4	33.6	Local
	2.2	1	CC	17.8	137.4	Local
	2.8	2	CC	9.6	81	Local
	2.8	1	CC	14.7	24.4	Metastatic bladder
	2.3	2	Pap	29.1	81.9	Contralateral kidney
	2.3	2	Pap	7.8	40.6	Contralateral kidney
	2.4	None	CC	35.6	38	Local
	2.6	None	CC	33.4	131.9	Local
	2.1	2	CC	16.5	21.5	Metastatic femur
	3.5	Low	CC	9.8	17.4	Local
	2.7	2	CC	32.2	32.2	Local
	3.6	2	CC	24.2	81.3	Local
Elevated risk stage 1	5	None	CC	6.1	48.1	Contralateral kidney
	2.3	4	CC	20.5	22.4	Metastatic liver
	4.3	None	Pap	17.2	31.6	Metastatic lungs
	6.7	2	CC	14.1	59.17	Local
	4.1	3	CC	12.2	12.7	Local
	4.4	2	CC	21.1	38.6	Local
	7	1	CC	20.7	109.1	Local
	2.8	4	CC	14.2	25	Local

Table 2. Clinical and pathologic factors associated with RCC recurrence following percutaneous thermal ablation

	Univariate		Multivariable	
Variable	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
High grade (3 or 4) vs low grade (1 or 2)	4.93 (1.46-16.59)	.010	4.17 (1.17-14.76)	.027
Clinical stage T1b vs T1a	3.71 (1.77-7.81)	.0010	2.46 (1.06-5.72)	.037
Clear cell vs non-clear RCC	3.59 (1.09-11.83)	.040	2.21 (0.51-9.63)	.29
*Tumor diameter per cm	1.80 (1.39-2.33)	<.001		
Cryoablation vs microwave	1.47 (0.71-3.03)	.30		
Nephrometry score	1.16 (0.95-1.410	.14		
Cystic disease	0.69 (0.21-2.26)	.54		
Female gender	0.68 (0.30-1.53)	.36		

* Not included in MV analysis given collinearity with clinical T stage.

(17.6%) patients in the elevated risk stage 1 cohort, recurrence was identified in 8 (5 LR, 1 contralateral kidney, and 2 metastatic) patients at a median 15.7 months (IQR 13.2-20.6) following ablation. Compared to patients with 0 risk factors, patients with 1 risk factor were 4 times more likely (HR = 4.26, P <.001) and patients with 2 risk factors were 7 times more likely (HR = 7.47, P = .055) to experience recurrence at any location. Both local (within ablation bed) and distant recurrences (new renal tumor and metastasis) were more common in the elevated risk stage 1 cohort vs the reduced risk stage 1 cohort (Supplemental Figs 2 and 3). Five-year overall recurrence-free survival rates (local + distant) were lower in the elevated risk stage 1 group vs the reduced risk stage 1 group, 87.8% vs 68.9%, as were local recurrence-free survival rates, 78.9% vs 90.7%, P = 0.05. Five-year distant recurrence-free survival (distant kidney recurrences or metastases) was 96.9% for the reduced risk stage 1 cohort and 87.4% for the elevated risk stage 1 cohorts, P = .03.

COMMENT

Percutaneous TA is used for treatment of approximately 1 in 7 patients with small RCC.[1] Despite higher rates of local recurrence compared to surgery, the rates of metastatic progression and cancer mortality following ablation are low and comparable to surgery for small RCC.[5] Serial postablation imaging is necessary to identify patients who recur and may be treated with salvage ablation or surgery. In this study of 256 patients with biopsy-proven cT1 RCC, 6.6% were treated with a second ablation procedure for residual or recurrent tumor, and the 5-year cancer-specific survival rate was 99%. Tumor size and tumor grade were identified as risk factors for recurrence and patients were stratified into reduced risk stage 1 (both low grade and cT1a) or elevated risk stage 1 (either high grade or cT1b). The risk of local and distant recurrences were significantly different between the 2 cohorts and therefore 2 separate protocols are proposed (Fig. 2) to enable a risk-stratified approach for postablation imaging surveillance.

Clinical stage and tumor grade were identified as prognostic risk factors for recurrence in our study. Multiple studies investigating the effect of tumor size on recurrence following therapy for localized RCC have demonstrated that larger diameter tumors have higher recurrence risks

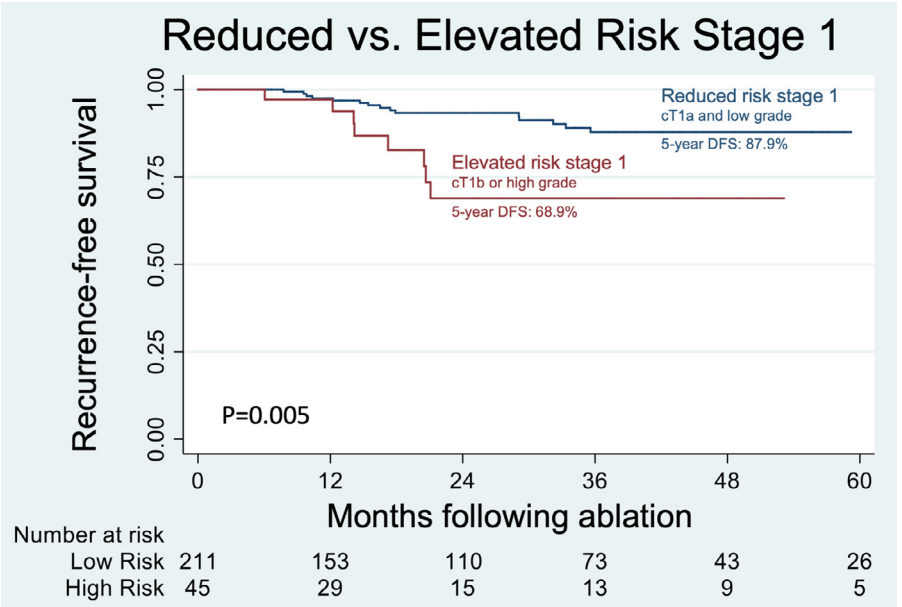

Figure 1. Recurrence-free survival for patients with reduced risk stage 1 RCC vs elevated risk stage 1 RCC after percutaneous thermal ablation. (Color version available online.)

following either surgery[16] or TA[6,11]. In addition, high tumor grade is a well-known prognostic factor for postsurgical RCC recurrence,[17-19] but few data have been evaluated for high-grade RCC treated with TA. It is also important to acknowledge that biopsy diagnosis may underestimate grade[20] although aggressive RCC histology is less common in small tumors.[16] In addition, there may be a selection bias for surgical treatment of higher grade tumors since most ablation series contain only a small minority of patients with high-grade RCC. In this study, patients assigned to the elevated risk stage 1 cohort based on clinical T stage and tumor grade had significantly greater recurrence risk. This simple system for patients treated with ablation is similar to multiple systems that estimate recurrence risk following surgery[17-19] and allow post-treatment imaging to be adjusted to patient's individual risk.

Urologists participate actively in more than half of renal tumor ablations,[21] but there is minimal guidance from the American Urological Association regarding the optimal schedule for postablation imaging follow-up.[22] Surveillance protocols vary significantly between providers and across institutions[5,18,21,23] but frequent imaging is commonly recommended after ablation to identify potential recurrences. However, it is important to consider the increased economic costs[24] and exposure to radiation[25] with more aggressive imaging follow-up. Data from prospective active surveillance studies demonstrate slow growth patterns for most small, untreated renal tumors,[26] with similar imaging surveillance recommended for untreated tumors. For example, patients in the Delayed Intervention and Surveillance for Small Renal Masses active surveillance clinical trial receive 7 imaging studies during the first 5 years for untreated renal tumors[27] compared to 7-8 imaging studies during the first 5 years postablation.[6-9] In the current study, 4 of 5 patients are classified as reduced risk stage 1, for whom less aggressive imaging follow-up is proposed. Conversely, more frequent imaging surveillance is recommended for 1 in 5 patients who are classified as elevated risk stage 1. When compared to the conventional follow-up protocol at our institution, the proposed risk-stratified protocols (Fig. 2) will theoretically reduce the total number of postablation abdominal CT and MRI scans by approximately half.

Limitations of the current study include the retrospective approach, which may be associated with selection bias. At our institution, RCC patients are seen in Urology clinic and receive extensive counseling prior to making a decision for treatment. Given that surgery (partial nephrectomy when feasible) is considered the gold standard treatment for T1 RCC,[28] there is a known selection bias for surgery in healthier younger patients with more aggressive tumors. Patients with larger tumors or high-grade tumors are counseled about higher risk of recurrence following ablation. Multivariable analysis has been used to analyze prognostic factors for recurrence, but it is possible that unmeasured factors could impact the analysis. The published postablation follow-up recommendations[22] and institutional protocols[6-9] were developed using expert opinion and retrospective data. The rationale for the proposed follow-up protocols in this study are supported by data from previous studies but validation using independent cohorts in a prospective study is necessary. Although there is a risk of progression with any protocol for cancer surveillance, it is unlikely that the risk following ablation is significantly greater than the risk for untreated RCC. Furthermore, the slow growth rate for most small RCC likely creates a large therapeutic window for patients to be treated with salvage procedures similar to untreated small RCC.

Standard oncologic end points are difficult to evaluate in many ablation studies because RCC pathologic

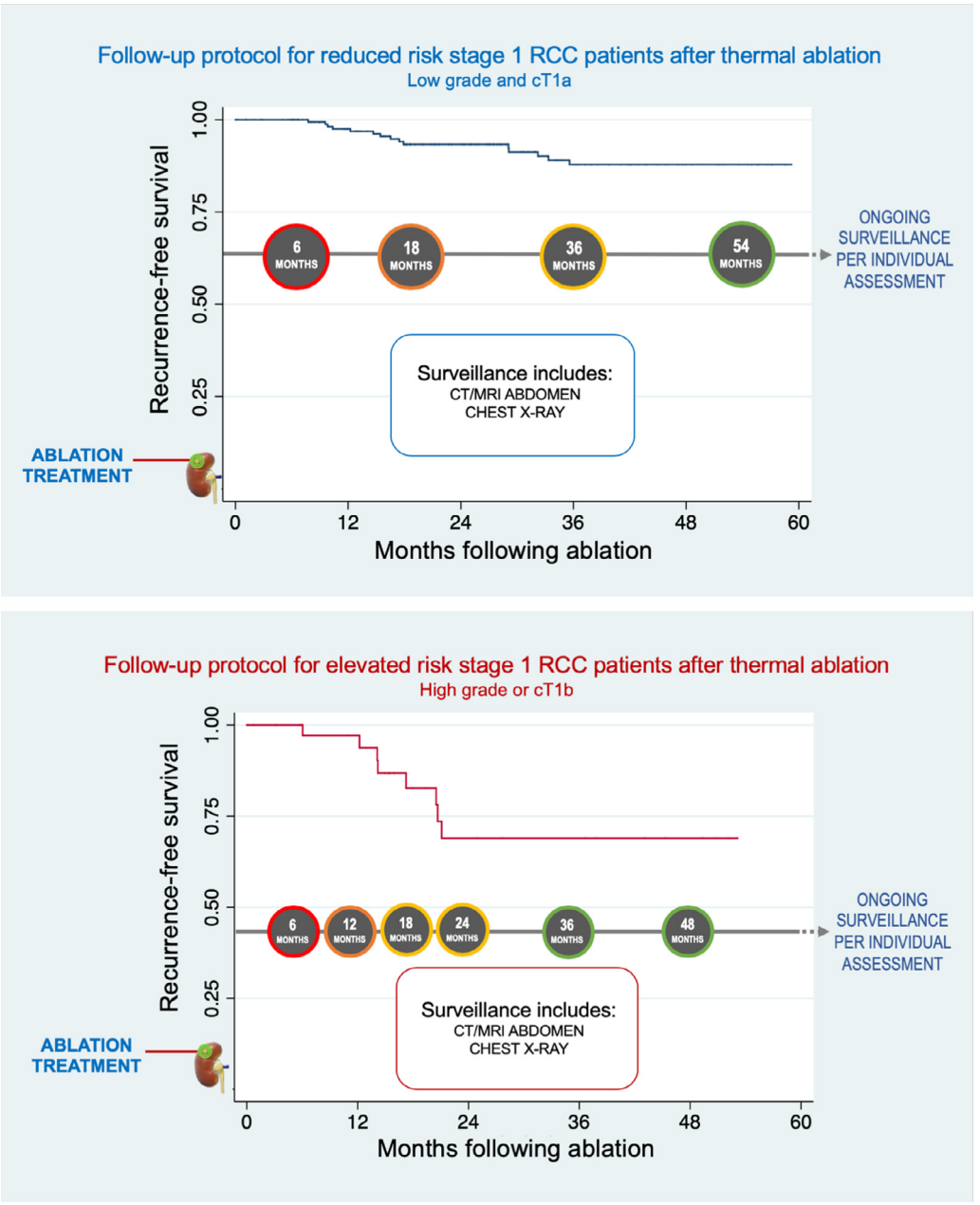

Figure 2. Proposed surveillance protocol for reduced risk stage 1 RCC patients (top, cT1a, and nuclear grade 1 or 2) and elevated risk stage 1 RCC patients (bottom, cT1b, or nuclear grade 3 or 4). (Color version available online.)

diagnosis is not always obtained prior to treatment.[23] All patients in the current study had a pathologic RCC diagnosis prior to ablation and the 5-year recurrence-free and cancer-specific survival rates of 85% and 99% are similar to other reported series.[5,10,29] Finally, it is important to acknowledge that recurrence patterns may vary with institutional experience or technique and some findings may not be applicable to other centers.

CONCLUSION

Stage 1 RCC patients who are treated with percutaneous TA can be stratified by recurrence risk based on clinical tumor stage and tumor grade. Patients with high nuclear grade tumors and/or clinical T1b stage (4-7 cm diameter) have approximately 3-fold risk of recurrence and should receive frequent surveillance based on proposed follow-up protocols. Less frequent imaging follow-up is appropriate for patients with clinical T1a stage and low tumor grade.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.urology.2019.08.022.

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