Comparative Analysis of Surgery, Thermal Ablation, and Active Surveillance for Renal Oncocytic Neoplasms

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OBJECTIVE To compare oncological and procedural outcomes for renal oncocytic tumors treated with surgery, thermal ablation, or active surveillance.

METHODS Clinical and pathologic data were collected for consecutive patients with a histologic diagnosis of oncocytoma, oncocytic neoplasm, or chromophobe renal cell cancer (chRCC) from 2003 to 2016. Independent pathology and radiology reviews were performed for this study.

RESULTS Of 171 patients, tumor histology included oncocytoma (n = 122), chRCC (n = 47), and oncocytic neoplasm not otherwise specified (n = 2). At the initial diagnosis, 67, 14, and 90 patients were treated with surgery, thermal ablation, and active surveillance. In 3 of 19 patients (16%) who had biopsy and subsequent surgery, diagnosis changed from oncocytoma to chRCC. The median follow-up was 39.9 months with no difference among choices of treatment modalities (P = .33). Of 90 patients who began active surveillance, 32 (36%) switched to active treatments (19 underwent thermal ablation and 13 underwent surgery). The median linear growth rate for patients on active surveillance was 1.2 mm/y. No patients who were managed with active surveillance developed metastatic renal cell cancer (mRCC). mRCC was identified in 3 patients and was the cause of death in 2 patients. Patients who developed metastatic disease presented with symptomatic tumors of >4 cm and were treated with immediate surgery. For oncocytic masses of ≤4 cm (n = 126), the 5-year cancer-specific survival was 100%.

CONCLUSION Renal oncocytic neoplasms have favorable oncological outcomes. Active surveillance is safe and is the preferred management for small (≤4 cm) oncocytic renal tumors in selected patients. UROLOGY 112: 92–97, 2018. © 2017 Elsevier Inc.

The increasing use of renal mass biopsy[1] may enable diagnosis of oncocytic renal neoplasms before treatment. Although renal oncocytomas are generally accepted to be benign, they may be difficult to distinguish pathologically from chromophobe renal cell carcinoma (chRCC)[2] or hybrid tumors that contain both oncocytoma and chRCC. The inability to reliably distinguish between oncocytoma and chRCC appears to be especially significant when using percutaneous biopsy because only limited amounts of tissue are available for analysis.[3] As a result, even when biopsy identifies oncocytoma, physicians may question the accuracy of biopsy pathology and may recommend a more aggressive treatment based on a potential risk of chRCC.

Renal oncocytomas represent approximately 15%-20% of small renal masses (≤4 cm) and 75% of all benign renal tumors.[4] chRCC tumors are slightly more rare, representing approximately 5% of renal tumors.[5] Although chRCC has a more favorable prognosis than clear cell RCC following surgery,[5,6] there are limited data for thermal ablation or active surveillance for renal tumors with oncocytic features.[7,8] The purpose of the present study was to compare outcomes for patients with either oncocytoma or chRCC treated with surgery, thermal ablation, or observation.

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METHODS

After institutional review board approval, clinical and pathologic data were collected for consecutive patients with a histologic diagnosis of oncocytoma or chRCC from 2003 to 2016. Two patients had a biopsy diagnosis of oncocytic neoplasm and were not able to be further classified. An expert genitourinary pathologist (W.H.) reviewed pathologic specimens for this project using colloidal iron staining, immunohistochemistry, and electron microscopy as indicated to differentiate between oncocytoma and chRCC. One fellowship-trained abdominal radiologist (L.M.G.) reviewed computed tomography (CT), ultrasound (US), and magnetic resonance imaging results and measured tumor diameters for all patients with oncocytic tumors. Complications were recorded for 90 days following surgery or ablation and were stratified according to the Clavien-Dindo system.[9]

All percutaneous renal tumor biopsies were performed with US or CT guidance and utilized an 18-gauge biopsy core technique. Fine needle aspiration was not utilized for biopsy. Thermal ablation was performed using microwave or cryoablation techniques percutaneously (n = 29) with CT or US imaging guidance or laparoscopically (n = 3). Collectively, partial and radical nephrectomies were performed by 9 surgeons using a combination of open, laparoscopic-robotic, hand-assisted approaches based on the patient characteristics and tumor features.

Primary end points of the present study included recurrence, cancer-specific mortality, and all-cause mortality. Other outcomes, including complications within 90 days, glomerular filtration rate (GFR) using modification of diet in renal disease formula at 1 and 3 years following interventions, and length of hospitalization, are also described. SAS version 9.3 (SAS Institute, Cary, NC) was used for all statistical analyses. Categorical variables were assessed using chi-square test, and continuous variables were assessed with a *t* test with assumption of equal variance, both at a significance level of $\alpha = 0.05$ (2-tailed *P*).

RESULTS

A total of 171 patients were identified with a histologic diagnosis of oncocytoma, chRCC, or oncocytic neoplasm not otherwise specified (NOS). At the initial diagnosis, 67 patients were treated with surgery, 14 were treated with thermal ablation, and 90 chose active surveillance (Supplemental Fig. S1). All patients treated with active surveillance or ablation had a biopsy diagnosis. Of 19 patients who had preoperative biopsy and subsequent surgery, 16 of 19 patients (84.2%) had concordant histopathologic diagnoses. For 3 patients diagnosed with oncocytoma from biopsy, surgical pathology demonstrated chRCC or hybrid tumor (Supplemental Table S1).

Patient and disease characteristics are shown in Table 1. A total of 122 and 47 patients had a histologic diagnosis of oncocytoma and chRCC, respectively. Patients diagnosed with oncocytoma were older vs chRCC (69.5 years vs 57.0, $P < .01$) and tended to present with smaller masses (81.8% ≤ 4 cm vs 54.1%, $P = .003$). Patients with oncocytoma diagnosis were more likely to initially undergo active surveillance vs chRCC (64.8% vs 19.2%, $P < .001$). There was no difference in the median follow-up time between oncocytoma (39.8 months), chRCC (40.0 months), or oncocytic neoplasm NOS (79.5 months) groups ($P = .78$). The median growth rate (mm/y) was similar for patients with chRCC vs those with oncocytoma and oncocytic neoplasm NOS (5.3 vs 1.1 and 1.4, $P = .64$).

For 122 patients who had a histologic diagnosis of oncocytoma, no patients subsequently developed metastatic chRCC or died from RCC. Of 47 patients with a pathologic diagnosis of chRCC, 3 patients (6.5%) developed metastatic renal cell cancer (mRCC) and 2 patients (4.3%) died from mRCC. Of those patients who developed metastatic chRCC (Supplemental Table S2), the size at presentation ranged from 5.0 to 12.6. All 3 patients were symptomatic at presentation. Two of three demonstrated sarcomatoid features on final histopathologic diagnosis.

Table 1. Patients with renal oncocytic neoplasms according to tumor histology, 2003-2016

	Oncocytoma (N = 122), n (%)	chRCC (N = 47), n (%)	*P* Value
Age, median (IQR)	69.5 (62.7-74.5)	57.0 (43.5-67.5)	<.001
Sex			
M	80 (64.5)	25 (53.2)	.17
F	44 (35.5)	22 (46.8)	
Size at presentation (cm)			
<2	35 (28.2)	7 (14.9)	.008
2.0-4.0	66 (53.3)	18 (38.3)	
4.1-6.9	15 (12.1)	10 (21.2)	
>7	8 (6.6)	12 (25.5)	
Initial management			
Radical nephrectomy	14 (11.3)	22 (46.8)	<.001
Partial nephrectomy	19 (15.3)	12 (25.5)	
Ablation	10 (8.0)	4 (8.5)	
Surveillance	81 (65.3)	9 (19.2)	
Median follow-up (mo) (IQR)	39.8 (14.3-71.2)	40.0 (14.3-91.9)	.78
Median increase in tumor diameter (mm/y), IQR	1.1 (–0.3 to 2.9)	5.3 (–3.9 to 15.9)	.64

chRCC, chromophobe renal cell cancer; IQR, interquartile range; NOS, not otherwise specified.

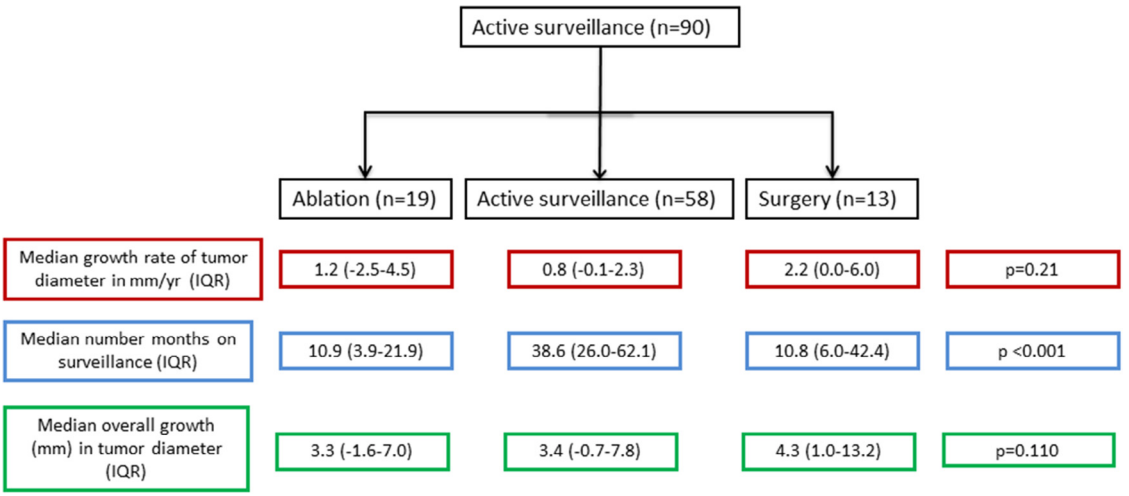

Figure 1. Growth rate of patients treated with active surveillance for renal oncocytic neoplasms. (Color version available online.)

Two patients were identified with oncocytic tumors that were unable to be classified as either oncocytoma or oncocytic neoplasm. Patient 1 presented with a 3.3-cm renal mass, was treated with thermal ablation, and had no evidence of disease at 62 months following treatment. Patient 2 presented with a 3.6-cm renal mass and has been followed up with active surveillance for 33 months without change in tumor diameter or progression of disease. There were 5 patients with hybrid tumors composed of both oncocytoma and chRCC. The median size at presentation was 3.0 cm (IQR 3.0-5.6 cm). Two patients were treated with thermal ablation, 2 patients were treated with partial nephrectomy, and 1 patient was treated with radical nephrectomy. At a follow-up median of 26.1 months (IQR 22.8-34.7 months), no patient with a hybrid tumor had evidence of recurrence or metastasis.

Active surveillance was the initial management for 90 patients (78 with oncocytoma, 10 with chRCC, and 2 with oncocytic neoplasm NOS), of which 19 and 13 patients were eventually treated with thermal ablation or surgery, respectively. The rationale for switching to active treatment from surveillance was tumor growth (21, 66.7%), patient preference or concern (6, 7.8%), provider opinion (4, 12.9%), and bleeding (1, 2.9%). The median time from surveillance to intervention was 14.9 months (IQR 7.5-58.1 months). The median growth rate trended toward a more rapid rate for patients who switched to surgery (2.2 mm/y) vs patients who remained on active surveillance (0.8 mm/y) or ablation (1.2 mm/y), although this was not significantly different (Fig. 1).

Of 33 patients treated with thermal ablation (20 cryoablation, 13 microwave ablation), 3 recurred locally within the ablation bed at a median of 18 months (range 16-43 months) after the initial ablation. Two patients were treated with salvage microwave ablation and are currently no evidence of disease at 21 and 17 months following the procedure. One patient had a stable lesion size 17 months after beginning active surveillance.

Patients who were treated with surgery were more likely to have larger tumors (P <.001) and were more likely to have a diagnosis of chRCC (P <.001). Given that the vast majority of patients with larger tumors were treated surgically (Table 2), comparative analysis among treatments was confined to tumors of ≤4 cm. For 126 oncocytic masses of ≤4 cm, the 5-year cancer-specific survival was 100%, and the 5-year overall survival was 88.1%. Cancer-specific and overall survival did not significantly differ based on the initial management choice (surgery, ablation, and active surveillance) or tumor histology (oncocytoma vs chRCC), as shown in Figure 2A-D.

Overall procedure complications within 90 days were more common in patients following radical nephrectomy (29.3%) and partial nephrectomy (38.9%) compared with ablation (9.1%) or active surveillance (0%) (P <.001). Most common complications included wound infection (n = 4), postoperative ileus (n = 3), deep vein thrombosis (n = 2), and atrial fibrillation (n = 2). Major complications (≥Clavien 3) (n = 4) included an incisional hernia requiring repair, the need for dialysis, pleural effusion requiring thoracentesis (all radical nephrectomy), and a colonic fistula or abscess requiring percutaneous drainage (ablation).

Renal function following treatment was lower for patients following radical nephrectomy at 1 (78.5% GFR) and 3 (77.4% GFR) years vs partial nephrectomy (94.2% and 96.6%), ablation (90.0% and 94.2%), and surveillance (99.6% and 95.9%) (P <.01). The length of hospitalization after intervention was also higher for radical nephrectomy (median 4.0 days) and partial nephrectomy (3.0 days) vs ablation (1.0 day) (P <.001).

DISCUSSION

Renal mass biopsy has enabled the pretreatment diagnosis of renal oncocytic tumors, but the difficulty of pathologically distinguishing between benign oncocytoma and

Table 2. Perioperative and cancer-specific outcomes by final treatment, 2003-2016

	Nephrectomy n, (%)		Ablation	Active Surveillance	
	Partial (n = 36)	Radical (n = 44)	(n = 33)	(n = 58)	*P* Value
Size at presentation (cm)					
<2	6 (16.7)	3 (6.8)	15 (45.8)	17 (27.8)	<.001
2.0-4.0	24 (66.7)	13 (29.5)	16 (47.8)	32 (55.2)	
4.1-7.0	5 (13.9)	11 (25.0)	2 (6.3)	7 (12.1)	
>7	1 (2.8)	17 (38.6)	0 (0)	2 (3.5)	
Percentage eGFR following intervention					
1 y	94.2	78.5	90.0	99.6	.003
3 y	96.6	77.4	94.2	95.9	<.001
Pathology					
Oncocytoma	23 (63.9)	19 (43.1)	24 (72.7)	58 (100)	<.001
chRCC	13 (36.1)	25 (56.8)	9 (27.2)	0 (0)	
Cancer outcomes					
Local recurrence	0	0	3 (9.4)	0	.04
Metastatic progression	0	3 (7.3)	0	0	.03
Died from mRCC	0	2 (4.7)	0	0	.12
Died of another disease	1 (2.8)	2 (4.7)	4 (12.1)	8 (13.8)	.34
90-d Complication					
Clavien grades 1 and 2	14 (38.9)	9 (22.0)	2 (6.1)	0	<.001
Clavien grade 3+	0 (0)	3 (7.3)	1 (3.1)	0	.11
Median hospital length of stay (d) (IQR)	3.0 (2.0-4.0)	4.0 (2.5-5.0)	1.0 (1.0-1.0)	n/a	<.001

eGFR, estimated glomerular filtration rate; mRCC, metastatic renal cell cancer.

malignant chRCC may limit the clinical utility of this information for many patients. The present study has demonstrated the favorable oncological outcomes for most patients treated with either surgery, ablation, or active surveillance. Progression to mRCC occurred in only 3 patients, all of whom presented with symptomatic larger tumors and who were treated surgically. None of the 126 patients with small (≤4 cm) oncocytic renal tumors developed metastatic cancer, and none of the 90 patients followed up with active surveillance developed cancer progression. Given the risks of procedural morbidity and the lack of improved oncological outcomes following surgery or thermal ablation, active surveillance should be considered as the preferred management for most patients with small (≤4 cm) renal oncocytic tumors.

Active surveillance was developed as a treatment strategy for small renal masses and is designed to limit the morbidity of treatment by restricting treatment to patients with the highest risk of RCC-related death.[10,11] Using an observation strategy is well suited for many patients with RCC because of the low risk of RCC-specific mortality in small tumors[12] and the competing causes of mortality that are present in patients with a median age of 64 years at diagnosis.[13] Using this rationale, active surveillance in small (≤4 cm) oncocytic renal tumors appears to be an ideal approach given the minimal risk of cancer progression in this population.[7] In patients with RCC being followed with active surveillance, the risk of developing metastasis is estimated from serial measurements of tumor growth, which allows for the identification and subsequent treatment of high-risk patients who are most likely to benefit from surgery or thermal ablation. Similar to prior studies, we have demonstrated that tumor growth is variable in oncocytic tumors and that growth occurs in benign tumors.[14] Interestingly, about one-third of patients in the present study chose treatment with surgery or ablation after an initial period of active surveillance. However, this decision was independent of tumor growth and was based primarily on patient and physician preference, highlighting the individual nature of each treatment decision. Accordingly, surgeons should carefully counsel patients individually about treatment options considering the patient's age, comorbidities, quality of life, risk of cancer, and the availability of future imaging. In patients not willing or unable to follow small tumors with active surveillance, partial nephrectomy and thermal ablation are options that preserve kidney function with excellent cancer outcomes.

For oncocytic renal tumors of >4 cm and younger patients, the preferred treatment is less straightforward. The risk of being diagnosed with chromophobe renal cell carcinoma increases from 19.8% to 46.7% in oncocytic tumors of ≤4 cm vs >4 cm, and increases to 60% for oncocytic tumors of >7 cm. In addition, the median age at diagnosis for chRCC was more than 12 years younger than oncocytoma, as observed in other series.[5] Therefore, surgery should remain as the standard treatment for larger tumors and for younger, healthier patients because of the increased cancer risk and the decreased utility of prolonged surveillance in patients with many decades of life expectancy. Thermal ablation and active surveillance are less commonly utilized treatments for larger tumors, but remain alternatives for some older and comorbid patients, given the small (6.6%) risk of cancer progression even in oncocytic tumors of >4 cm.

Improving the ability to distinguish benign renal oncocytoma from other oncocytic tumors is the first step to improving management in these patients. However, there are multiple challenges to improving the current approach for

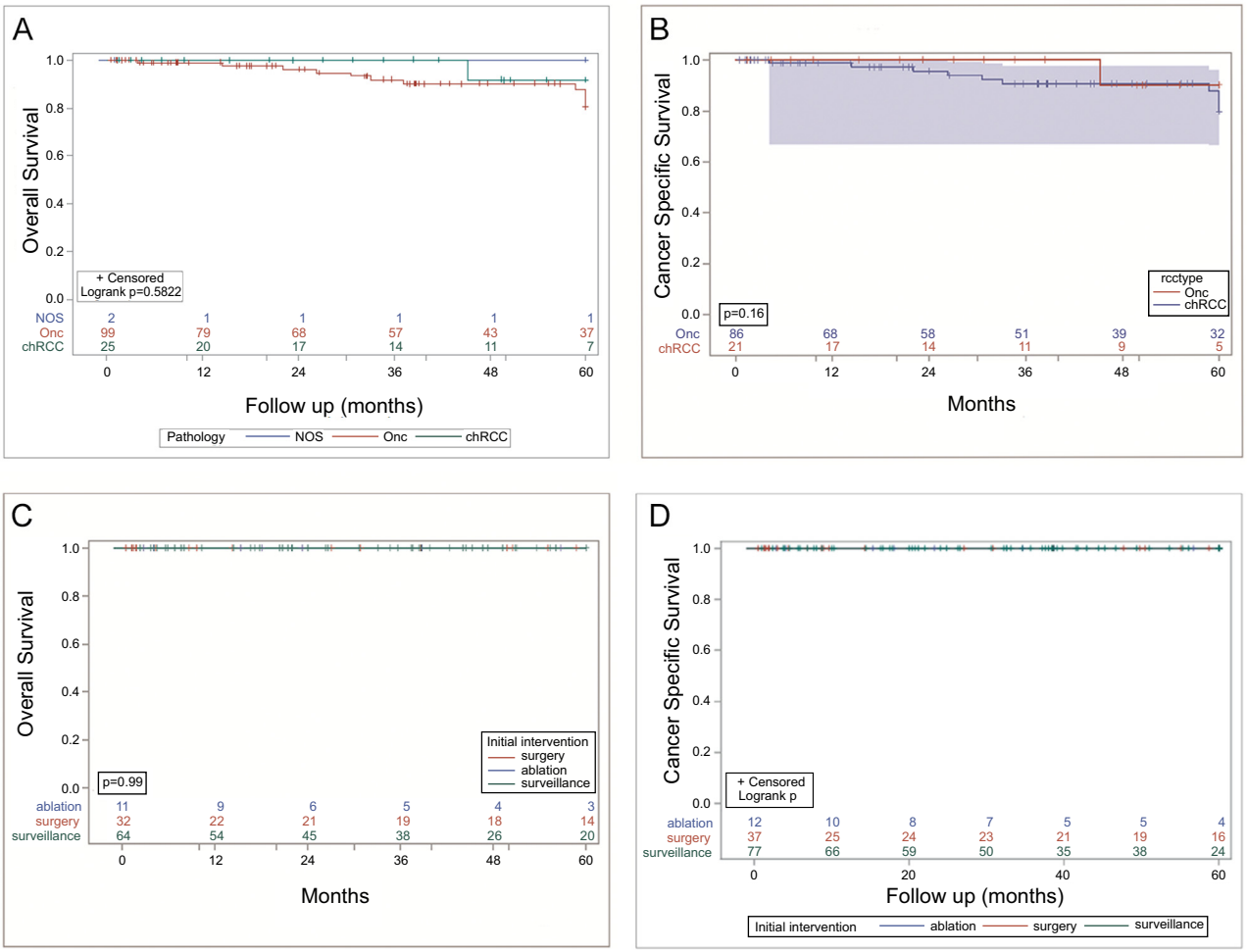

Figure 2. **(A)** Overall survival according to tumor histology for renal oncocytic tumors of ≤4 cm. **(B)** Cancer-specific survival according to tumor histology for renal oncocytic tumors of ≤4 cm. **(C)** Overall survival according to treatment modality for renal oncocytic tumors of ≤4 cm. **(D)** Cancer-specific survival according to treatment modality for renal oncocytic tumors of ≤4 cm. chRCC, chromophobe renal cell cancer; IQR, interquartile range; NOS, not otherwise specified; Onc, oncocytoma. (Color version available online.)

identifying benign oncocytic neoplasms. First, there is a considerable variation in what features are definitively diagnostic of oncocytoma, even among expert genitourinary pathologists.[15] Second, renal mass biopsy obtains only a small amount of tissue, which increases the difficultly of making a definitive diagnosis. Although few data are available, the reported concordance between biopsy and surgical pathology for oncocytic tumors is clearly not optimal. A recent meta-analysis identified only 48 oncocytic tumors of 1677 biopsies reviewed that had both biopsy and surgical pathology. The authors calculated a positive predictive value of 67%,[3] lower than the 84% value observed in this series. The evaluation of accuracy for identifying oncocytoma from biopsy may be affected by sampling error, difference in techniques, variation in pathologic interpretation, low numbers of patients, and the bias for treating more aggressive-appearing tumors surgically. Because of the known limitations of biopsy, radiological techniques using technetium-99m-sestamibi single-photon emission CT have created optimism for distinguishing renal oncocytoma with imaging alone.[16] However, in a recent series, 2 of 9 tumors (22%) identified as benign from radiological techniques were actually chRCCs, which is a similar rate to biopsy and highlights the need for improved techniques to distinguish renal oncocytoma from malignant tumors.

The present study compares outcomes for contemporary patients with oncocytic renal tumors treated with surgery, active surveillance, and thermal ablation in a contemporary cohort. Increased utilization of percutaneous biopsy enables diagnosis of renal oncocytic tumors,[17] and the present study confirms the low metastatic potential whether tumors are followed with active surveillance[7,18] or treated with thermal ablation[19] or surgery.[5,6,20] Despite the known limitations of biopsy[21] to distinguish between oncocytoma and chRCC,[3] oncocytic tumors have favorable outcomes, suggesting that these tumors should be managed with surveillance, especially in smaller tumors and in older patients. If fewer patients are actively treated, treatment-related morbidity is lowered in this population. Given that 15%-20% of small renal tumors are

oncocytic neoplasms,[4] the resulting decrease in morbidity and cost of treatment is substantial, providing a rationale for the increased use of pretreatment biopsy.

Limitations of the current study include the retrospective approach and inherent bias with this approach. Independent expert pathology and radiology reviews were obtained for the present study. As mentioned previously, there may be a disagreement about diagnostic criteria among expert genitourinary pathologists,[15] and it is possible that another pathologist would diagnose tumors differently. Given the potential for different diagnoses especially in biopsy specimens, all oncocytic neoplasms were included in the analysis. In addition, multiple surgeons counseled patients during the study period and utilization of pretreatment biopsy increased over the study period, which may have biased treatment recommendations. Although the comparative survival analysis for cT1a tumors did not differ by histology or management, the sample size and the limited number of events make confirmation by other studies important. Finally, all patients underwent treatment at a single tertiary referral center with expertise in percutaneous biopsy and thermal ablation, which may not be available in all settings.

CONCLUSION

Despite the limits of percutaneous biopsy to distinguish oncocytoma from chRCC, oncocytic renal neoplasms have minimal malignant potential. Active surveillance is safe in oncocytic renal tumors and should be the preferred approach for patients with tumors of ≤4 cm.

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APPENDIX

Supplementary Data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.urology.2017.09.016.