Comparing Outcomes for Patients with Clinical T1b Renal Cell Carcinoma Treated With Either Percutaneous Microwave Ablation or Surgery

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OBJECTIVE To compare perioperative and oncologic outcomes for patients with clinical T1b renal cell carcinoma following treatment with microwave ablation (MW), partial nephrectomy (PN), or radical nephrectomy (RN).

METHODS Comprehensive clinical and pathologic data were collected for nonmetastatic renal cell carcinoma patients with cT1b tumors following MW, PN, or RN from 2000 to 2018. Local recurrence-free, metastasis-free, cancer-specific and overall survival were estimated using Kaplan-Meier method. Prognostic factors for complications and survival were determined using logistic regression and Cox hazard models, respectively.

RESULTS A total of 325 patients (40 MW, 74 PN, and 211 RN) were identified. Patients treated with MW were older with higher Charlson comorbidity indices compared to surgical patients. Median length of hospitalization was shorter for MW compared to surgical patients (1 day vs 4 days, P <.0001). Post-treatment estimated glomerular filtration rate decreased by median 4.5% for MW compared to 3.2% for PN (P = .58) and 29% for RN (P <.001). Median follow-up was 34, 35, and 49 months following MW, PN, and RN, respectively. Estimated 5-year local recurrence-free survival was 94.5% for MW vs 97.9% for PN (P = .34) and 99.2% for RN (P = .02). Two patients recurred after MW and underwent repeat ablation without subsequent recurrence. No difference in 5-year metastasis-free survival or cancer-specific survival was found among MW, PN, or RN. Four (10%) MW patients had high-grade complication. Only prior abdominal surgery predicted high-grade complication (OR 6.29, P = .017).

CONCLUSION Microwave ablation is a feasible alternative to surgery in select comorbid patients with clinical T1b renal cell carcinoma. UROLOGY 135: 88−94, 2020. © 2019 Elsevier Inc.

For small (<4 cm) localized renal cell carcinoma (RCC), physicians counsel patients about treatment options including surgery, thermal ablation, and active surveillance. The choice of treatment is based upon the individual patient's health and tumor characteristics.[1,2]

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Especially in older, comorbid patients, thermal ablation of small renal tumors (<4 cm) provides an active treatment with minimal risk of procedural complications,[3-7] and discussion of ablation is endorsed in treatment guidelines for small renal masses.[8] For 4-7 cm localized RCCs, the recommended treatment options are less clear.

For healthy patients with clinical T1b (cT1b) tumors, partial nephrectomy (PN) or radical nephrectomy (RN) are standard therapies, but alternatives to surgical treatment are unclear for patients who are highly comorbid or refuse surgery. Prior ablation studies have generally focused on smaller tumors, with only small cohorts of cT1b tumors. These studies demonstrate mixed results following treatment with cryoablation or radiofrequency ablation (RFA).[4,6-8] Although cryoablation and RFA have demonstrated efficacy for treatment of small RCC,[9]

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these modalities may be technically limited in larger tumors.[10] The theoretical advantages of high-powered modern microwave ablation (MW) may enable treatment of larger tumors due to rapid tissue heating at higher temperatures, the ability to overcome tissue perfusion-related heat loss, and no reliance on tissue electrical conductivity.[11] The purpose of this study was to compare perioperative and oncologic outcomes for patients with cT1b RCC following treatment with percutaneous MW, RN, or PN.

MATERIALS AND METHODS

An institutional review board approved prospectively maintained RCC database was used to identify patients with RCC pathologic diagnosis and radiographic 4-7 cm tumor diameter who were treated with either percutaneous MW, PN, or RN between January 2000 and June 2018 at the University of Wisconsin. Exclusion criteria included: advanced RCC (presence of tumor thrombus or metastatic disease) and patients with hereditary RCC syndromes. All patients were evaluated in urology clinic to discuss treatment options. For any patient treated with thermal ablation, percutaneous renal mass biopsy was performed to obtain a pathologic diagnosis of RCC and discussed with patient prior to ablation.[12] Nonsurgical patients with cT1b RCC who refused active surveillance or patients with tumor diameter growth >5 mm/y on imaging surveillance were offered MW. The technique for percutaneous MW was performed according to previous descriptions.[13] All ablations were performed under general anesthesia and immediate postablation computed tomography (CT) was performed to ensure adequate tumor destruction. Ablations were performed with a 2.45 GHz, gas-cooled MW system using 17-gauge antennas (Certus 140, NeuWave Medical). Within this cohort of patients, 2/40 (5%) required 1 microwave antenna, 11/40 (27.5%) required 2 antennas, 26/40 (65%) required 3 antennas, and 1/40 (2.5%) required 4 antennas.

After MW treatment, surveillance imaging was obtained every 6 months for 2 years and annually thereafter consisting of contrast enhanced abdominal CT or magnetic resonance imaging and chest imaging. All studies were reviewed by fellowship trained abdominal radiologists. Local recurrence was defined as a contrast enhancing mass within the ablation site after initially negative imaging. Incomplete treatment was defined as an enhancing mass within the ablation zone on the first postoperative imaging. Following PN and RN, patients were followed with contrast-enhanced abdominal CT or magnetic resonance imaging at 6, 12, 24, and 36 months after surgery, and annually after. Local recurrence was defined as recurrent tumor within the ipsilateral kidney for PN and within nephrectomy bed for RN. Metastatic progression in all groups was defined as distant RCC recurrence outside the ipsilateral kidney or nephrectomy bed.

Baseline patient and tumor characteristics (including RENAL nephrometry score[14]) were compared between ablation and surgical patients. Complications were classified using the Clavien-Dindo grading system.[15] High-grade complications were considered ≥grade IIIa. Renal functional outcomes were measured at 3 months postoperatively based on the estimated glomerular filtration rate (eGFR). Wilcoxon rank-sum test was used to compare medians and Fisher's exact or chi-squared test used to compare proportions. Logistic regression was performed to determine predictors of complications. Survival analysis was performed between the MW, PN, and RN cohorts. Local recurrence-free survival (LRFS), metastasis-free survival (MFS), and cancer-specific survival (CSS) were determined using the Kaplan-Meier method. Univariable and multivariable Cox proportional hazard regression was performed to assess the relationships between variables and survival outcomes.

RESULTS

Patient and Tumor Characteristics

A total of 325 RCC patients with 4-7 cm RCC tumors were treated (40 MW, 74 PN, and 211 RN). Clinical and pathologic variables among groups are shown in Table 1. Rationale for choosing treatment with MW included: patient refusal of surgery and active surveillance (n = 30, 75%) or tumor growth (>5 mm/y) while on active surveillance (n = 10, 25%). Patients in MW cohort were older (P <.001) with higher Charlson comorbidity index (CCI) (P <.001) compared to the PN and RN groups. The median maximum radiographic tumor diameter for MW patients was similar to the PN group (4.4 cm vs 4.7 cm, P = .71), but was smaller when compared to patients treated with RN (5 cm, P = .002). An open surgical approach was used for 60 (81%) PN patients and 44 (21%) RN patients, with the remaining undergoing laparoscopic or robotic surgery (P <.001). Tumor grade was higher in the surgery group compared to the MW cohort (P <.001). No differences were found between histologic type and treatment modality, with the majority of patients having clear cell RCC. Median follow-up interval for MW, PN, RN was 33.9 months (IQR 21.7-61.2), 35.1 months (IQR 9.5-89), and 49.5 months (IQR 16.1-87.7), respectively.

Perioperative Outcomes

Following MW, 2 patients (5%) had residual tumor identified on initial postoperative imaging requiring a second ablation due to incomplete initial treatment. A total of 7 (17.5%) MW patients, 18 (24.3%) PN patients, and 28 (13.3%) RN patients had any complication identified within 90 days postoperatively (P = .006), including high-grade complications in 4 (10%) MW patients, 4 (5.4%) PN patients, and 7 (3.3%) RN patients. No significant difference was found in the rate of high-grade complications among treatment groups (P = .17). Complications are listed in supplementary Table 1. Following multivariable logistic regression, prior abdominal surgery was the only independent predictor of high-grade complication (odds ratio 6.29, 95% CI 1.39-28.6; P = .017). Type of treatment (PN vs RN vs MW) was not associated with overall or high-grade complications.

Median length of hospitalization was shorter for the MW group than PN or RN groups, 1 day (IQR 1-1) vs 4 days (IQR 3-6) or 4 days (IQR 3-4), respectively (P <.0001). Blood transfusion rate was not statistically different among the 3 treatment groups (2.5% MW, 8.1% PN, 4.9% RN; P = .38). The median percent-change in eGFR at 3 months postoperatively was: MW (−4.5%, IQR −19.6% to 7.6%), PN (−3.2%, IQR −20% to 10%) and RN (−29%, IQR −39% to −19%). There was no difference in the change in eGFR between MW and PN (P = .65); however, the reduction in eGFR was significantly greater for the RN group compared to the MW group (P <.001) and PN group (P <.001).

Local Recurrence

The overall local recurrence rate was 4/325 (1.2%) and more common in patients treated with MW 2/40 (5.0%) vs PN 1/74 (1.4%) or RN 1/211 (0.5%). Figure 1a demonstrates LRFS by treatment type. The estimated 5-year LRFS for MW, PN, and RN was 94.5% (95% CI 79.8%-98.6%), 97.9% (95% CI 85.8%-99.7%), and 99.2% (95%CI 94.5%-99.9%), respectively.

Table 1. Clinical and pathologic features of patients with clinical T1b renal cell carcinoma treated with microwave ablation, partial nephrectomy, or radical nephrectomy

Variable	Microwave Ablation (*n* = 40)	Partial Nephrectomy (*n* = 74)	Radical Nephrectomy (*n* = 211)	*P* value (MW vs PN)	*P* value (PN vs RN)	*P* value (MW vs PN + RN)
Age, y, median (IQR)	69 (65–77)	58 (51–65)	59 (51–71)	<.001	.14	<.001
Gender, no. (%)				.33	.79	.21
Male	30 (75)	49 (66)	136 (65)			
Female	10 (25)	25 (34)	75 (35)			
BMI, median (IQR)	33 (28.7–38.9)	31.1 (26.7–37.2)	30.4 (26.6–34.9)	.32	.44	.12
Prior abdominal surgery, no. (%)	25 (61)	32 (44)	105 (50)	.08	.38	.13
eGFR, median (IQR)						
Preoperatively	60.5 (54–78)	74.65 (58–83.6)	69.7 (55.7–86.1)	.07	.54	.09
3 mo post-op percent change	−4.5% (−19.6–7.6%)	−3.2% (−20–10%)	−29% (−39.1–19.4%)	.58	<.001	.0001
Radiographic tumor diameter, cm, median (IQR)	4.4 (4.1–5)	4.7 (4.1–5.3)	5 (4.5–6)	.71	.002	.01
Nephrometry score, median (IQR)	8 (6.5–9)	7 (7–9)	9 (7–9)	.30	<.001	.16
Charlson comorbidity index excluding age, median (IQR)	4 (4–4)	0.5 (0–2)	1 (0–2)	<.001	.27	<.001
Surgical approach, no. (%)				–	<.001	–
Open	–	60 (81)	44 (21)			
Laparoscopic/ robotic	–	14 (19)	167 (79)			
RCC pathologic subtype, no. (%)				.32	.11	.70
Clear cell	35 (87.5)	54 (73)	173 (82)			
Papillary	3 (7.5)	13 (18)	19 (9)			
Chromophobe	1 (2.5)	5 (7)	8 (4)			
Unclassified	1 (2.5)	2 (3)	11 (5)			
Tumor pathologic T stage, no. (%)				–	.19	–
pT1	–	63 (85.1)	179 (84.8)			
pT2	–	3 (4.1)	6 (2.8)			
pT3	–	7 (9.5)	25 (11.8)			
pT4	–	1 (1.4)	1 (0.5)			
Tumor pathologic grade, no. (%)						
1-2	39 (97.5)	55 (74)	150 (71)	.001	.59	<.001
3-4	1 (2.5)	19 (26)	61 (29)			
Sarcomatoid features, no. (%)	0 (0)	0 (0)	2 (1)	–	.4	.59

IQR, interquartile range; MW, microwave ablation; PN, partial nephrectomy; RCC, renal cell carcinoma; RN, radical nephrectomy.

Estimated 5-year LRFS rate was lower for MW vs RN ($P = .02$); however, no difference was identified between patients treated with MW vs PN ($P = .15$) or PN vs RN ($P = .37$). After univariable Cox regression, local recurrence was not associated with MW treatment ($P = .06$), age ($P = .29$), tumor diameter ($P = .17$), Nephrometry score ($P = .59$), CCI ($P = .34$), RCC subtype ($P = .67$), and tumor grade ($P = .87$).

Both MW patients with local recurrence underwent repeat ablation without subsequent recurrence on follow-up imaging. The duration of follow-up for the 2 patients with local recurrence after repeat MW was 38 and 44 months. One PN patient presented with both local and metastatic recurrence on follow-up and died 22 months after PN. One RN patient underwent local excision of isolated retroperitoneal recurrence and died of unrelated causes at 32 months without evidence of cancer.

Progression to Metastatic RCC

Progression to metastatic disease occurred in 23/325 (7.1%) of patients with clinically localized RCC. Zero patients treated with MW had metastatic progression identified. Four PN

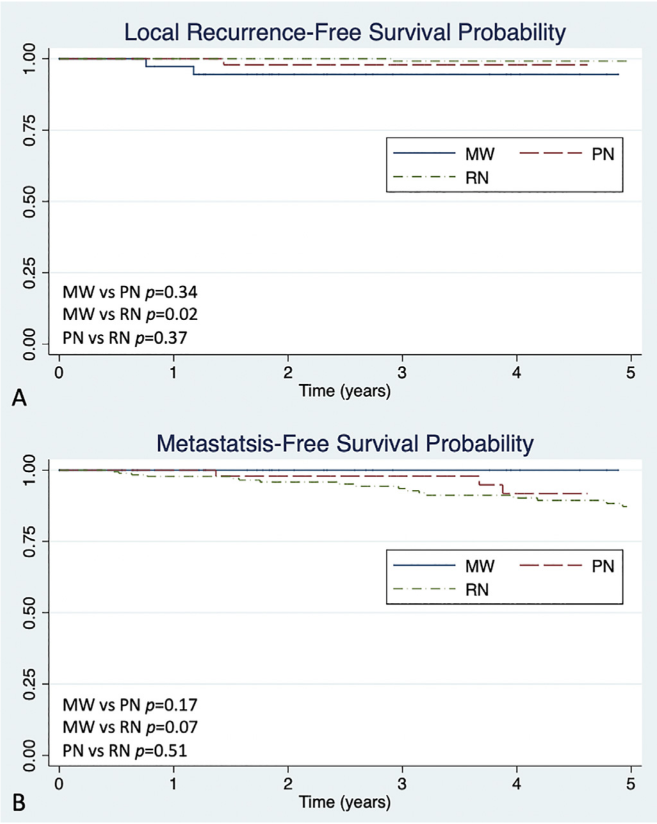

Figure 1. (**A**) Local recurrence-free survival and (**B**) Metastasis-free survival. MW, microwave ablation; PN, partial nephrectomy; RN, radical nephrectomy. (Color version available online.)

patients (5.4%) developed metastatic disease at median 45 months (IQR 37-67). Nineteen RN patients (9.0%) developed metastasis at median 35 months (IQR 18-48.5). The 5-year MFS rates for MW, PN, and RN were 100%, 91.8% (95%CI 76.2%97.3%), and 87.2% (95%CI 80.0%-92.0%) ($P = .19$). Figure 1b demonstrates estimated MFS by treatment type. On univariable Cox regression analysis, metastatic progression was associated with tumor grade 3-4 (hazard ratio [HR] 7.49 95% CI 3.13-17.9; $P < .001$) and sarcomatoid features (HR 12.36 95% CI 1.64-93.52; $P = .015$). After multivariable Cox regression, only high-tumor grade was associated with progression to metastatic disease (HR 7.08, 95% CI 2.92-17.19; $P < .001$).

Cancer Specific Mortality

CSS according to treatment is shown in Figure 2. No patient treated with MW died from cancer-specific causes. Three (4.1%) PN patients and 12 (5.7%) RN patients died from RCC at a median of 123.6 months (IQR 27.8-136.7) and 61.7 months (IQR 49.1-124.8), respectively. The 5-year CSS rates for MW, PN, and RN were 100%, 97.6% (95%CI 84.3%-99.7%) and 95.5% (95%CI 89.3%-98.1%). Figure 2 demonstrates estimated CSS by treatment type. No difference was noted in CSS among the treatment types ($P = .62$). Univariable Cox regression demonstrated that only high-tumor grade was associated with cancer-specific mortality (HR 11.5, 95% CI 3.78-34.77; $P < .001$).

DISCUSSION

MW is an alternative treatment for selected patients with 4-7 cm clinically localized RCC. Renal functional preservation is similar to PN and length of hospital stay is shorter for ablation vs surgical procedures. Similar to ablation studies for treatment of <4 cm RCC,[16] local recurrence is more common following ablation of larger RCC compared to surgery. However, all local recurrences after ablation were treated with a repeat ablation without subsequent recurrence. Importantly, progression to metastatic disease and cancer-specific mortality were similar between surgery and ablation procedures. Taken collectively, these data suggest that MW is a safe and feasible alternative treatment for select patients with clinical T1b RCC.

For renal mass patients with a limited life expectancy because of comorbidities or concurrent nonrenal malignancy, surveillance may be preferred over active treatments because of a smaller risk of RCC mortality relative to other causes of mortality.[17,18] Multiple studies have demonstrated the safety of surveillance for small renal masses but there are fewer data for active surveillance of larger tumors.[19,20] Metastatic progression and cancer mortality are more likely in larger renal cancers,[17] with 1 recent series showing a 10% metastasis rate for surveillance of masses more than 4 cm.[20] Given the higher risk of cancer progression for larger tumors on active surveillance, some comorbid patients may choose thermal ablation over surveillance. In addition, some patients who have accelerated tumor growth while on active surveillance may require delayed intervention.[21] In the current series, approximately 1 quarter of patients treated with

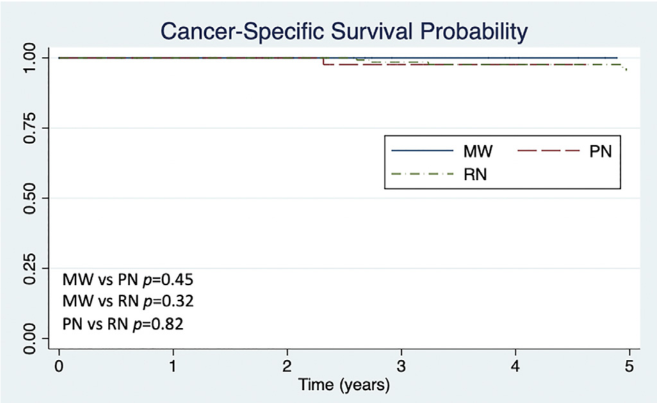

Figure 2. Cancer-specific survival. MW, microwave ablation; PN, partial nephrectomy; RN, radical nephrectomy. (Color version available online.)

MW were initially on surveillance but demonstrated growth >5 mm/y prompting treatment.

Perioperative outcomes for patients treated with MW compare favorably to PN or RN, especially when considering the highly comorbid patients in MW cohort. Multiple studies have demonstrated that perioperative complications are directly related to age, tumor diameter, and comorbidity status following surgery for localized RCC.[22,23] Previous observations have demonstrated that in patients undergoing kidney surgery, a CCI >2 resulted in a 6-fold higher rate of complications compared to CCI 0 patients.[24] In this study, the ablation cohort had a median CCI of 4 compared to 1 and 0.5 for RN and PN cohorts. Despite significantly older age and higher number of comorbidities, there was no significantly increased risk of high-grade complications for patients treated with MW. However, it should be noted that the rate of high-grade complications was higher for T1b tumors compared to other studies of small renal masses.[9] Importantly, renal preservation was similar for patients treated with MW compared to PN and significantly better than RN. The ability to preserve renal function with larger tumors may be especially significant for patients with multiple comorbidities, given that chronic kidney disease is associated with decreased survival from comorbid conditions.[25]

Similar to studies of smaller renal masses (<4 cm), rates of local recurrence were higher for T1b patients treated with thermal ablation compared to surgery.[16] Estimated 5-year LRFS was 94.5% for T1b RCC treated with MW, which is comparable to prior studies with RFA (91.9%)[4] or cryotherapy (92.7%).[26] Two patients in this study required a repeat MW procedure for local recurrence and have not subsequently recurred. Importantly, there were no differences identified in MFS or CSS for patients with cT1b tumors treated with MW or surgery in this study. These findings are similar to a meta-analysis that included ablation and surgical studies for small RCCs.[16] There are few studies of thermal ablation that have described treatment of cT1b tumors (Table 2) or compared treatments to partial or RN. When compared to other ablation modalities, modern MW has theoretical advantages, which may enable treatment of larger tumors. MW does not require an electrically conductive path so that microwaves can propagate at any temperature or water content to overcome heat sink effects due to its rapid tissue-heating.[10,13] In some cryoablation studies, a percentage of patients are pretreated with embolization to increase treatment efficacy and decrease the risk of postprocedural bleeding due to the lack of an intrinsic cautery effect with application of cold temperatures.[27] In this study, embolization was not required for either of these purposes. Although there are no randomized trials comparing outcomes among ablation modalities, this study describes clinical efficacy associated with the theoretical benefits of MW for cT1b RCC.

In this study, all patients had a pathologic RCC diagnosis prior to treatment and ablation outcomes were compared to outcomes following radical or PN. Limitations of this study include the retrospective analysis, which may increase the risk for selection bias. Multivariable analysis was used to evaluate the impact of different treatments on outcomes, but it is possible that unmeasured differences exist. Also, multivariable analysis modeling is limited by the low number of events among the treatment modalities. Longer follow-up is necessary to measure durable cancer outcomes in patients treated with ablation; however, most RCC recurrences are known to occur within the first 3 years following treatment.[28] Baseline differences in the cohorts of patients (eg, MW patients were older and had more comorbidities) may not allow generalization of these findings to all cT1b RCC patients. Higher grade tumors were more present in surgical patients, which may represent a selection bias, but tumor grade is often difficult to determine on biopsy given tumor heterogeneity.[29] Careful selection is typical for patients considering ablation, which is often utilized in older, comorbid populations. Additionally, outcomes in this study are described from an institution experienced with thermal ablation[30] and findings may not be applicable at all centers. Future multi-institutional studies should evaluate the utility of MW for treatment of selected cT1b RCC patients.

Table 2. Thermal ablation studies for tumors 4-7 cm

Author	Date	Ablation Modality	Surgery	Tumor Size	Number of Ablation Patients With RCC diagnosed		Median Follow-up (mo)		Ablation Outcomes	
					Ablation	Surgery	Ablation	Surgery	Local Recurrence-free Survival	Incomplete Treatment
Psutka et al[4]	2013	RFA	–	cT1b	42/42 (100%)	–	77	–	5 yr LRFS 91.9%	8 (19.1%)
Chang et al[*,8]	2015	RFA	PN	cT1b	27/27 (100%)	29/29 (100%)	65.9	70.2	5 yr LRFS 81.0%	2 (7.4%)
Caputo et al[†,7]	2017	CA	PN	cT1b	22/31 (71%)	28/31 (90%)	30.1	13.0	23% recurred	4 (13%)
Andrews et al[‡,26]	2019	CA	PN	cT1b	35/52 (67%)	272/324 (84%)	72	104.4	5 yr LRFS 92.7%	Not Reported
Present study		MW	PN and RN	cT1b	40/40 (100%)	PN: 74/74 (100%) RN: 211/211 (100%)	33.9	PN: 35.1 RN: 49.5	5 yr LRFS 94.5%	2 (5%)

CA, cryoablation; CSS, cancer-specific survival; LRFS, local-recurrence-free survival; MFS, metastasis-free survival; MW, microwave ablation; RFA, radiofrequency ablation.
* Chang et al reported as mean follow-up.
† Number of RCC patients reported after matching.
‡ Andrews et al reported based on clinical follow-up.

CONCLUSION

Percutaneous MW is a feasible alternative treatment for appropriately selected patients with cT1b RCC tumors.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.urology.2019.09.024.

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