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Comparing Oncologic Outcomes of Heat-Based Thermal Ablation and Cryoablation in Patients With T1a Renal Cell Carcinoma: A Population-Based Cohort Study From the SEER Database

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Objective: There is controversy among different guidelines regarding the use of thermal ablation to treat clinical T1a renal cell carcinomas with tumor sizes ranging from 3.1–4 cm. Therefore, we compared oncological outcomes between heat-based thermal ablation (hTA) and cryoablation (CA) in patients with solid T1a renal cell carcinomas, including those with a tumor size ≤3 cm and a tumor size of 3.1–4 cm.

Materials and Methods: Within the Surveillance, Epidemiology, and End Results database (2000–2019), we identified patients with clinical T1a renal cell carcinomas that were histologically confirmed and treated with hTA or CA. After propensity score matching using a 1:1 ratio, the overall survival (OS) and cancer-specific survival (CSS) were estimated and compared between the two methods. Cancer-specific mortality (CSM) was also analyzed, considering other-cause mortality as a competing risk.

Results: Of the 3513 assessable patients, 1426 (40.6%) and 2087 (59.4%) were treated with hTA and CA, respectively. After propensity score matching, the hTA and CA groups included 1393 and 1393 patients, respectively. hTA was associated with shorter OS than CA with a hazard ratio of 1.17 (95% confidence interval, 1.04–1.32; $P = 0.010$). The hTA and CA groups did not reveal statistically significant differences in CSS with a hazard ratio of 1.07 (95% confidence interval, 0.76–1.50; $P = 0.706$). The hTA and CA groups did not show statistically significant differences in CSM ($P = 0.849$). However, the hTA group showed a significantly higher other-cause mortality ($P = 0.011$).

Conclusion: In patients with clinical stage T1a renal cell carcinomas, hTA was comparable to CA in terms of CSS and CSM. However, hTA resulted in a slightly shorter OS than CA. Large-scale randomized clinical trials are required to obtain more robust evidence.

Keywords: Ablation techniques; Cryoablation; Thermal ablation; Small renal mass

INTRODUCTION

According to the most recent guidelines [1-3], partial nephrectomy is the gold standard for treating patients with clinical T1a solid renal masses, with oncological results comparable to those of radical nephrectomy and better renal function preservation. However, owing to comorbidities, renal insufficiency, and advanced age, some patients require minimally invasive procedures. Thermal ablation (TA), in the form of heat-based TA (hTA) and cryoablation (CA), is an alternative strategy for older individuals and those with competing health risks. The American Urological Association

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recommends TA only for tumors no more than 3 cm in length [1]. The European Association of Urology guidelines state that, while TA is an option for all clinical T1a tumors, CA is preferred over hTA in patients with a tumor size of 3.1–4 cm [2]. The most general guidelines come from the National Comprehensive Cancer Network, which recommends all TA modalities as viable options for clinical T1a tumors of all sizes [3].

A recent study using the Surveillance, Epidemiology, and End Results (SEER) database explored an important dilemma regarding small renal mass management by investigating cancer outcomes following hTA or CA in patients with a tumor size of 3.1–4 cm [4]; however, certain limitations should still be considered. Local tumor excision is not only less traumatic but also not inferior to partial nephrectomy in terms of relapse or mortality [5]; thus, it may not be appropriate to merge CA and any type of local tumor excision for analysis [6]. Additionally, a meta-analysis comparing radiofrequency ablation (RFA, a type of hTA) with CA for T1 (T1a and T1b included) renal tumors demonstrated no differences in terms of the primary technique efficacy rate or 5-year survival rate [7]. Nevertheless, most of the included studies reported shorter follow-up periods. Moreover, in a retrospective study with 12 years of experience, high technical success and local disease control were achieved for microwave ablation (MWA, another kind of hTA) and CA, and the cancer-specific survival (CSS) was equivalent for clinical T1a (≤4 cm) renal masses [8]. However, the overall power of this study may be limited by the sample size. Therefore, to address the limitations of the current studies and provide a better clinical reference, we relied on the SEER database (2000–2019) to compare the efficacy of hTA and CA in treating patients with clinical T1a renal cell carcinoma.

MATERIALS AND METHODS

Study Population

This study was conducted according to the Strengthening the Reporting of Cohort Studies in Surgery criteria [9]. Using SEER*Stat software version 8.4.0 (https://seer.cancer.gov/seerstat), we obtained patient data from the SEER Research Plus Data, 17 registries, Nov 2021 Sub (2000–2019). We recruited patients older than 18 years with clinical T1a renal cell carcinoma that was histologically confirmed and treated with hTA or CA between 2000 and 2019. The inclusion criteria were as follows: 1) patients who had a first diagnosis between 2000 and 2019, 2) patients who had a clinical T1a renal mass with no more than 4 cm in size, 3) patients with kidney cancer confirmed by site recoding ICD-O-3/WHO 2008 (kidney and renal pelvis), 4) patients who had confirmed positive histology, and the histological subtypes included clear cell (codes 8310 and 8313), papillary (codes 8050, 8260, and 8342), chromophobe (codes 8270 and 8317), and not otherwise specified renal cell carcinoma (codes 8010, 8140, and 8312), and 5) patients who had TA options, including CA (code 13) or hTA (code 15). The exclusion criteria were as follows: 1) patients with unknown tumor size, unknown or other treatment, or unknown vital status information, 2) patients with a survival time of less than one month, and 3) patients with incomplete follow-up data. According to the SEER mortality codes, death was classified as either cancer-specific mortality (CSM, death attributable to kidney cancer) or other-cause mortality (OCM, death attributable to any other cause). Ultimately, 3513 assessable patients were identified in the community based on the selection criteria.

All analyses and their reporting followed the SEER reporting guidelines. Owing to the anonymously coded design of the SEER database, study-specific Institutional Review Board ethics approval was not required. The need for informed consent was waived due to the retrospective nature of the study and anonymization.

Propensity Score Matching

The variables included demographic information (age, sex, race, and year of diagnosis) and clinicopathological characteristics (tumor grade, pathology, and tumor size). Race and pathology had *P*-values <0.05. To reduce residual and selection bias in the study cohort, we used propensity score matching (PSM) with the nearest neighborhood for every two groups in a 1:1 match (caliper: 0.02). A logistic regression model was used to generate the propensity score, and the variables considered in the PSM analysis included age, sex, race, tumor grade, pathology, and tumor size. The standardized mean difference (SMD) of patients' baseline variables between the two groups before and after matching was calculated, and a threshold of <0.1 in the SMD was employed.

Statistical Analysis

The statistical software package R (http://www.R-project.org), Empower-Stats (https://www.empowerstats.net, X&Y Solutions, Inc., Boston, MA, USA), and SPSS version 29.0 (IBM Corp., Armonk, NY, USA) were used for all analyses.

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A *P*-value of 0.05 or less was considered indicative of statistical significance. To reduce the possibility of randomization, a 1:1 PSM analysis was used. The baseline characteristics of the patients in the matched and unmatched cohorts were compared using the X^2 test for categorical data or Student's *t*-test for continuous data. Kaplan–Meier analysis was used to estimate the overall survival (OS) and CSS in the matched population. The Fine-Gray model was used for data analysis, accounting for OCM as a competing risk, and the cumulative incidence of CSM and OCM was calculated. Univariable Cox regression with hazard ratio (HR) and log-rank tests were used to compare survival statistics. According to the guidelines, ablation should be considered as an alternative approach for patients with tumors no larger than 3 cm; thus, to better compare hTA with CA, we repeated the survival analysis in two distinct subgroups: 1) patients with a tumor size ≤3 cm and 2) patients with a tumor size of 3.1–4 cm.

Protocol Registration

This study was registered in the Research Registry (http://www.researchregistry.com), and the unique identification number was researchregistry10166.

RESULTS

Patient Characteristics

Of the 3513 assessable patients, 1426 (40.6%) and 2087 (59.4%) were treated with hTA and CA, respectively. Patient characteristics before and after PSM are summarized in Table 1. Before PSM, race, year of diagnosis, and pathology differed significantly between the hTA and CA groups ($P < 0.05$). After PSM, the hTA and CA groups included 1393 and 1393 patients, respectively, with SMD values <0.1. Further details of the PSM results are provided in Supplementary Figure 1.

Comparison of hTA vs. CA in the cT1a Renal Mass

In the univariable Cox analysis after PSM (Table 2), hTA was associated with shorter OS with an HR of 1.17 (95% confidence interval, 1.04–1.32; $P = 0.010$), but there was no statistically significant difference in CSS with an HR of 1.07 (95% confidence interval, 0.76–1.50; $P = 0.706$).

In patients who underwent hTA or CA, the 5- and 10-year OS rates were 0.758 vs. 0.783 and 0.523 vs. 0.581 ($P = 0.009$; Fig. 1A), respectively, and the 5- and 10-year CSS rates were 0.957 vs. 0.965 and 0.940 vs. 0.9390 ($P = 0.706$; Fig. 2A), respectively. According to the competing risk analysis, the cumulative incidences of the 5- and 10-year CSM rates were 0.038 vs. 0.032 and 0.050 vs. 0.051 ($P = 0.849$; Fig. 3A), respectively, and the cumulative incidences of the 5- and 10-year OCM were 0.204 vs. 0.185 and 0.427 vs. 0.369 ($P = 0.011$; Fig. 4A), respectively.

Comparison of hTA vs. CA in cT1a Renal Mass With a Tumor Size ≤3 cm

In the subgroup analysis, among patients with a tumor size ≤3 cm, the 5- and 10-year OS rates for hTA vs. CA were 0.787 vs. 0.824 and 0.575 vs. 0.628 ($P = 0.054$), respectively (Fig. 1B); the 5- and 10-year CSS rates were 0.965 vs. 0.969 and 0.955 vs. 0.946 ($P = 0.614$), respectively (Fig. 2B); cumulative 5- and 10-year CSM were 0.032 vs. 0.029 and 0.039 vs. 0.047 ($P = 0.515$), respectively (Fig. 3B); and cumulative 5- and 10-year OCM were 0.181 vs. 0.147 and 0.386 vs. 0.326 ($P = 0.025$), respectively (Fig. 4B).

Comparison of hTA vs. CA in cT1a Renal Mass With a Tumor Size 3.1–4 cm

Among patients with a tumor size of 3.1–4 cm, the 5- and 10-year OS rates for hTA vs. CA were 0.666 vs. 0.867 and 0.365 vs. 0.445 ($P = 0.038$), respectively (Fig. 1C); the 5- and 10-year CSS rates were 0.932 vs. 0.955 and 0.885 vs. 0.917 ($P = 0.139$), respectively (Fig. 2C); cumulative 5- and 10-year CSM were 0.059 vs. 0.040 and 0.085 vs. 0.063 ($P = 0.198$), respectively (Fig. 3C); and cumulative 5- and 10-year OCM were 0.275 vs. 0.293 and 0.550 vs. 0.492 ($P = 0.171$), respectively (Fig. 4C).

DISCUSSION

TA is an important treatment option for patients with clinically diagnosed T1a renal masses. CA is one of the most studied ablation modalities for renal masses, and MWA, a newer option for hTA, has demonstrated high technical and clinical efficacies [10,11]. Compared with RFA, MWA is considered to achieve more homogenous heating, higher tissue temperatures, and larger ablation volumes and is less affected by the heat sink effect [12]; thus, MWA is associated with a relatively lower local recurrence rate [13]. However, current guidelines concerning hTA are mostly based on studies on RFA [14,15]. Although Sorce et al. [4] were the first to compare CA and hTA (including MWA) in patients with clinical T1a renal RCC with a tumor size of 3.1–4 cm [4,16], they did not distinguish CA from CA

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Table 1. Patient characteristics before and after 1:1 PSM

Characteristics	Before PSM					After PSM				
	Overall (n = 3513)	CA (n = 2087; 59.4%)	hTA (n = 1426; 40.6%)	*P*	SMD	Overall (n = 2786)	CA (n = 1393; 50%)	hTA (n = 1393; 50%)	*P*	SMD
Age group, yrs				0.549	0.045				0.616	0.045
18–39	70 (2.0)	42 (2.0)	28 (2.0)			58 (2.1)	31 (2.2)	27 (1.9)		
40–59	735 (20.9)	442 (21.2)	293 (20.5)			590 (21.2)	302 (21.7)	288 (20.7)		
60–79	2133 (60.7)	1277 (61.2)	856 (60.0)			1687 (60.6)	846 (60.7)	841 (60.4)		
≥80	575 (16.4)	326 (15.6)	249 (17.5)			451 (16.2)	214 (15.4)	237 (17.0)		
Sex				0.987	0				0.694	0.021
Male	2224 (63.3)	1321 (63.3)	903 (63.3)			1776 (63.7)	893 (64.1)	883 (63.4)		
Female	1289 (36.7)	766 (36.7)	523 (36.7)			1010 (36.3)	500 (35.9)	510 (36.6)		
Race				<0.001	0.084				0.997	0
White	2949 (83.9)	1793 (85.9)	1156 (81.1)			2310 (82.9)	1157 (83.1)	1153 (82.8)		
Black	356 (10.1)	181 (8.7)	175 (12.3)			321 (11.5)	158 (11.3)	163 (11.7)		
Asian or Pacific Islander	167 (4.8)	83 (4.0)	84 (5.9)			136 (4.9)	68 (4.9)	68 (4.9)		
American Indian/Alaska Native	34 (0.9)	25 (1.2)	7 (0.5)			15 (0.5)	8 (0.6)	7 (0.5)		
Unknown	9 (0.3)	5 (0.2)	4 (0.3)			4 (0.1)	2 (0.1)	2 (0.1)		
Year of diagnosis				0.016	-0.084				0.937	0
<2010	1175 (33.4)	665 (31.9)	510 (35.8)			986 (35.4)	494 (35.5)	492 (35.3)		
≥2010	2338 (66.6)	1422 (68.1)	916 (64.2)			1800 (64.6)	899 (64.5)	901 (64.7)		
Grade				0.423	-0.031				0.996	-0.003
G1	442 (12.6)	267 (12.8)	175 (12.3)			310 (11.1)	155 (11.1)	155 (11.1)		
G2	824 (23.5)	478 (22.9)	346 (24.3)			688 (24.7)	344 (22.1)	344 (24.7)		
G3	108 (3.1)	56 (2.7)	52 (3.6)			92 (3.3)	45 (3.2)	47 (3.4)		
G4	8 (0.2)	5 (0.2)	3 (0.2)			7 (0.3)	4 (0.3)	3 (0.2)		
Unknown	2131 (60.7)	1281 (61.4)	850 (59.6)			1689 (60.6)	845 (60.7)	844 (60.6)		
Pathology				0.041	-0.046				0.114	-0.050
ccRCC	1383 (39.4)	809 (38.8)	574 (40.3)			1076 (38.6)	525 (37.7)	551 (39.6)		
pRCC	433 (12.3)	238 (11.4)	195 (13.7)			351 (12.6)	162 (11.6)	189 (13.6)		
chRCC	124 (3.5)	83 (4.0)	41 (2.9)			96 (3.4)	55 (3.9)	41 (2.9)		
nosRCC	1573 (44.8)	957 (45.9)	616 (43.2)			1263 (45.3)	651 (46.7)	612 (43.9)		
Tumor size, mm	25.19 ± 7.625	25.39 ± 7.601	24.88 ± 7.652	0.050	-0.067	25.21 ± 7.720	25.50 ± 7.753	24.91 ± 7.678	0.051	-0.077

Data are presented as number (%) or mean ± standard deviation.

PSM = propensity score matching, CA = cryoablation, hTA = heat-based thermal ablation, SMD = standardized mean difference, ccRCC = clear cell renal cell carcinoma, pRCC = papillary renal cell carcinoma, chRCC = chromophobe renal cell carcinoma, nosRCC = not otherwise specified renal cell carcinoma

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Table 2. Univariable Cox regression analysis for overall survival and cancer-specific survival after 1:1 propensity score matching

Characteristics	Overall survival		Cancer-specific survival	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Type of ablation				
CA	Ref		Ref	
hTA	1.17 (1.04–1.32)	0.010	1.07 (0.76–1.50)	0.706
Age group, yrs				
18–39	Ref		Ref	
40–59	3.68 (1.17–11.56)	0.026	1706.16	0.829
60–79	7.76 (2.50–24.12)	<0.001	3509.46	0.813
≥80	16.66 (5.66–55.07)	<0.001	7699.60	0.795
Sex				
Male	Ref		Ref	
Female	0.90 (0.80–1.03)	0.114	0.83 (0.58–1.19)	0.309
Race				
White	Ref		Ref	
Black	0.93 (0.76–1.14)	0.474	0.60 (0.30–1.17)	0.134
Asian or Pacific Islander	0.91 (0.68–1.22)	0.526	1.16 (0.57–2.38)	0.684
American Indian/Alaska Native	1.36 (0.61–3.04)	0.453	1.61 (0.22–11.51)	0.638
Unknown	0	0.872	0	0.954
Year of diagnosis				
<2010	Ref		Ref	
≥2010	1.00 (0.87–1.14)	0.963	1.00 (0.69–1.44)	0.999
Grade				
G1	Ref		Ref	
G2	1.38 (1.09–1.73)	0.006	1.68 (0.83–3.40)	0.150
G3	1.32 (0.89–1.96)	0.165	2.71 (1.03–7.13)	0.043
G4	0.47 (0.07–3.38)	0.455	0	0.956
Unknown	1.29 (1.04–1.59)	0.018	1.49 (0.83–3.08)	0.164
Pathology				
ccRCC	Ref		Ref	
pRCC	0.80 (0.66–1.37)	0.051	0.53 (0.27–1.03)	0.060
chRCC	0.95 (0.66–1.37)	0.784	0.21 (0.03–1.50)	0.119
nosRCC	1.07 (0.95–1.21)	0.240	0.93 (0.65–1.33)	0.705
Tumor size, mm	1.05 (1.04–1.06)	<0.001	1.06 (1.04–1.09)	<0.001

HR = hazard ratio, CI = confidence interval, CA = cryoablation, Ref = reference, hTA = heat-based thermal ablation, ccRCC = clear cell renal cell carcinoma, pRCC = papillary renal cell carcinoma, chRCC = chromophobe renal cell carcinoma, nosRCC = not otherwise specified renal cell carcinoma

combined with local tumor excision, which demonstrated superior oncologic outcomes to those of TA [6].

In our study, patient demographics and tumor characteristics were similar to those reported previously [4,17]. There was no statistically significant difference between hTA and CA in cancer-specific outcomes not only in the entirety of the PSM cohort but also in the subgroups of patients with a tumor size ≤3 cm and those with a tumor size of 3.1–4 cm. As for OS, there was no significant difference between the two groups, only for patients with a tumor size ≤3 cm. A meta-analysis of single-arm studies conducted by Martin & Athreya [18] to compare MWA (7 studies) and CA (44 studies) in patients with small renal masses demonstrated a significantly larger tumor size in the MWA group and similar local tumor recurrence and CSS rates between treatments. According to Wu et al. [11], MWA demonstrated favorable short- to intermediate-term oncological outcomes (pooled 1-, 3-, and 5-year CSSs of 100%, 100%, and 97.7%, respectively; pooled 1-, 3-, and 5-year OS rates of 99.0%, 96.0%, and 88.1%, respectively), including the T1b subset (pooled 1-, 3-, and 5-year CSS rates of 98.2%, 97.2%, and 98.1%, respectively; pooled 1- and 3-year OS rates of 94.3% and

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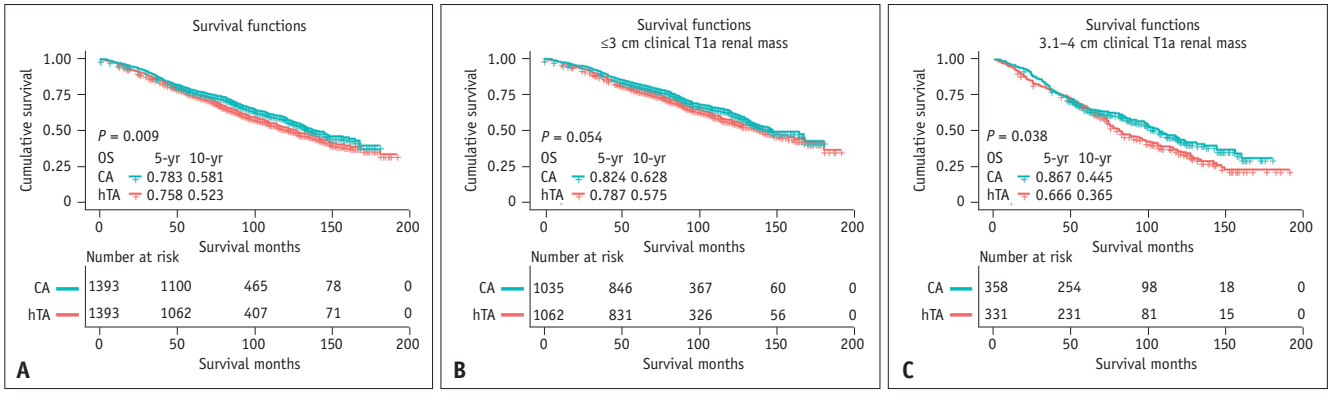

Fig. 1. OS of the hTA group versus the CA group after 1:1 propensity score matching in patients with clinical T1a solid renal masses. **A:** OS in the overall cohort. **B:** OS of patients with a tumor size ≤3 cm. **C:** OS of patients with a tumor size of 3.1–4 cm. OS = overall survival, hTA = heat-based thermal ablation, CA = cryoablation

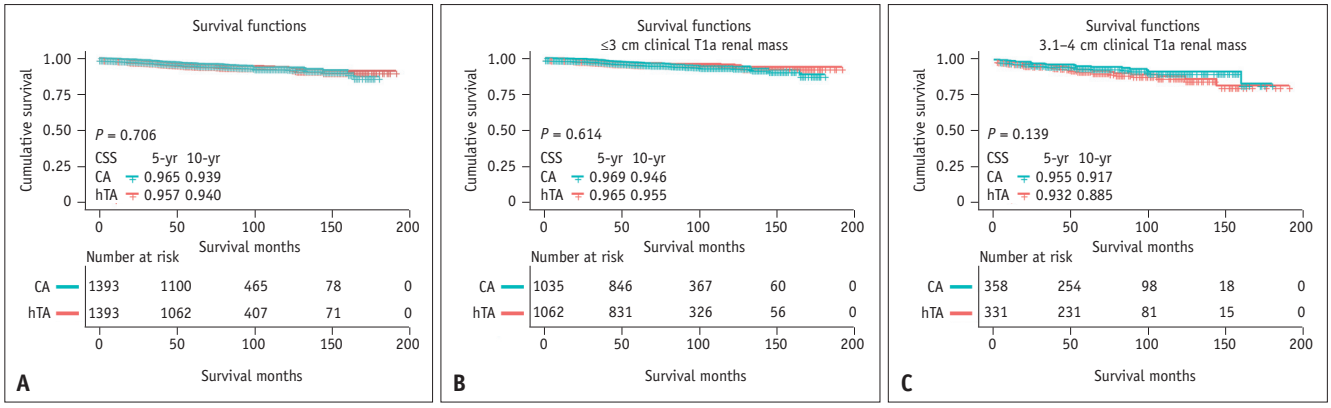

Fig. 2. CSS of the hTA group versus the CA group after 1:1 propensity score matching in patients with clinical T1a solid renal masses. **A:** CSS in the overall cohort. **B:** CSS of patients with a tumor size ≤3 cm. **C:** CSS of patients with a tumor size of 3.1–4 cm. CSS = cancer-specific survival, hTA = heat-based thermal ablation, CA = cryoablation

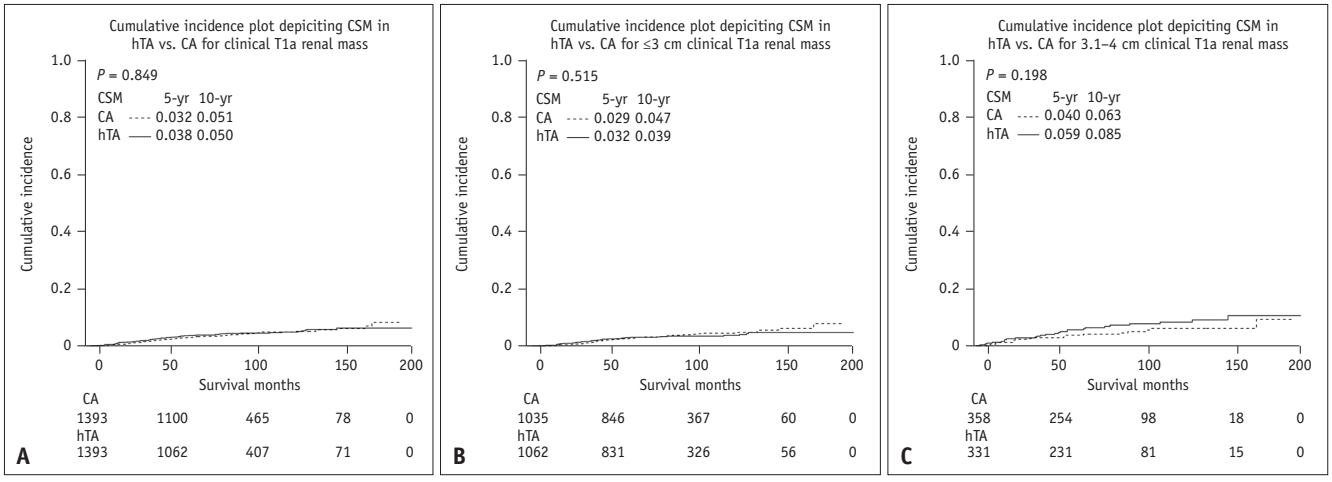

Fig. 3. CSM of the hTA group versus the CA group after 1:1 propensity score matching in patients with clinical T1a solid renal masses. **A:** CSM in the overall cohort. **B:** CSM of patients with a tumor size ≤3 cm. **C:** CSM of patients with a tumor size of 3.1–4 cm. CSM = cancer-specific mortality, hTA = heat-based thermal ablation, CA = cryoablation

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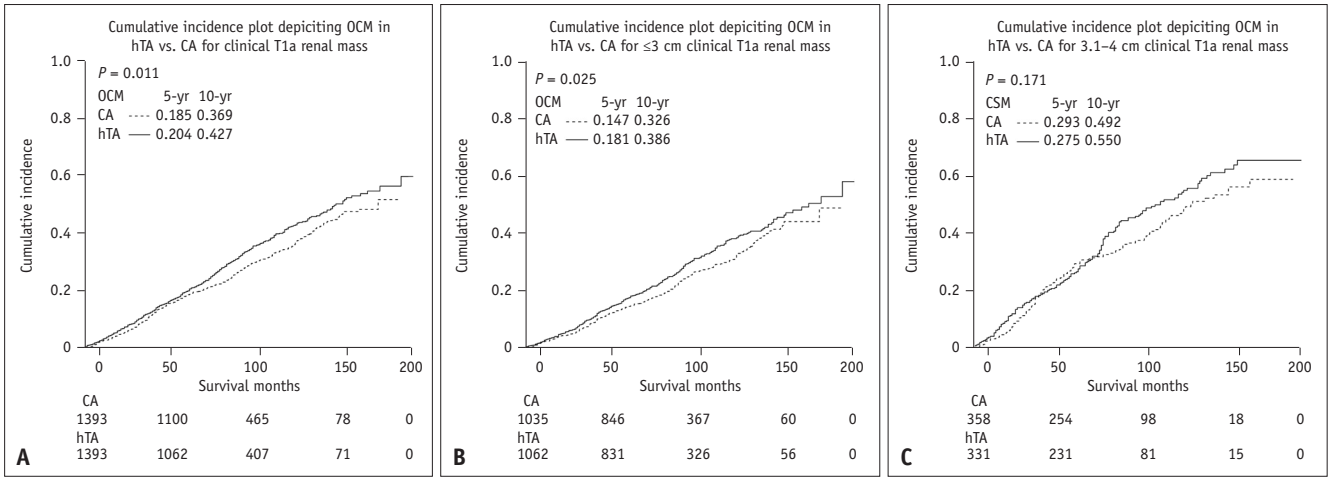

Fig. 4. OCM of the hTA group versus the CA group after 1:1 propensity score matching in patients with clinical T1a solid renal masses. **A:** OCM in the overall cohort. **B:** OCM of patients with a tumor size ≤3 cm. **C:** OCM of patients with a tumor size of 3.1–4 cm. OCM = other-cause mortality, hTA = heat-based thermal ablation, CA = cryoablation

89.3%, respectively). A single-arm pooled meta-analysis suggested that compared with CA, MWA significantly improved the 1-year local tumor recurrence rate, and the 1- and 5-year OS estimates were 98% and 87%, respectively, for both modalities [19].

A meta-analysis by Choi et al. [20] revealed a local recurrence rate of 2.1% for MWA, which is slightly better than that reported in other studies for RFA (3.2%–13.0%) or CA (2.7%–8.7%) [21-25]. Thus, in the present study, the cancer-specific outcomes of hTA were comparable to those of CA. A possible explanation for the lower incidence of MWA recurrence can be found in the study by Bhardwaj et al. [26], who investigated the histological findings of ablations produced by MWA, RFA, and CA in rat livers. Although all procedures induced macroscopically distinct ablated lesions, microscopic analysis revealed significant differences. MWA showed the clearest zone of coagulative necrosis and a microscopically sharp demarcation zone between the ablated and unablated tissues, whereas with CA, hepatocyte survival toward the edge of the ablation was observed, especially when the vessels were close to the ablation margin. Furthermore, RFA sections showed the most irregular burn edges of the three ablative techniques, and, as with CA, islands of viable hepatocytes were found within the ablated tissue.

Contrary to previous studies [4,27], our investigation revealed no statistically significant difference between hTA and CA in cancer-specific outcomes in patients with renal masses measuring 3.1–4 cm in size. Similarly, in a network meta-analysis of local recurrence and other oncologic outcomes after TA in T1b RCC, no differences were found between TA techniques [28]; however, the limited and variable follow-up between studies made it more difficult to pool the results. Thus, a larger cohort of patients with a tumor size of 3.1–4 cm and longer systematic imaging follow-up is necessary.

The novelty of our study is that hTA is comparable to CA in the treatment of clinical T1a renal masses, even those with a tumor size of 3.1–4 cm. However, several limitations should be considered when drawing these conclusions. First, this study was retrospective. Moreover, standardized specimen management, central pathology evaluation, data on complications, and early cancer control endpoints such as local recurrence or disease-free survival are lacking. Second, the only available information concerns the initial treatment. Subsequent treatments may have been used; however, they were not directly addressed in the current study. Third, the SEER database does not include data on tumor complexity (RENAL or PADUA score) or the number of kidney tumors. These factors are associated with varying degrees of morbidity and, as a result, may affect patient survival. Finally, the longtime span may have influenced ablation techniques, with a shift toward more minimally invasive and personalized patient approaches. Furthermore, better-quality prospective studies with protocol-driven inclusion and exclusion criteria, appropriate controls, standardized outcome measures, and adequate follow-up are needed to confirm our findings.

In conclusion, in patients with clinical T1a RCC, hTA was comparable to CA in terms of CSS and CSM, regardless of

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the tumor size. However, hTA resulted in a slightly shorter OS than did CA. Future large-scale and cross-regional randomized clinical trials are needed to validate our findings and the impact of different TA modalities on patient outcomes more precisely.

Supplement

The Supplement is available with this article at https://doi.org/10.3348/kjr.2024.0462.

Availability of Data and Material

All data generated for this analysis were from the SEER database. The code for the analyses will be made available upon request.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

Author Contributions

Conceptualization: Run-Qi Guo, Yuan-Ming Li. Data curation: Run-Qi Guo, Jin-Zhao Peng. Formal analysis: Run-Qi Guo, Jin-Zhao Peng, Jie Sun. Funding acquisition: Run-Qi Guo, Yuan-Ming Li. Supervision: Yuan-Ming Li. Writing—original draft: all authors. Writing—review & editing: all authors.

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