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Impact of tumor size on cancer specific mortality after local tumor ablation in T1a renal cell carcinoma

Running title: Impact of tumor size after ablation in T1a RCC

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Abstract

Introduction

Institutional studies suggested that tumor size (TS) might be an independent predictor of recurrence after local tumor ablation (LTA). However, limited data exist to ascertain whether larger TS may also predispose to worse cancer-specific mortality (CSM).

Materials and methods

Patients treated with LTA for T1a non-metastatic RCC were identified within the SEER database (2004-2015). Estimated annual proportion change methodology (EAPC), cumulative incidence plots and multivariable competing risks (CCR) regression models before and after 1:1 ratio propensity score (PS) adjustment were used to compare LTA for TS≤30mm vs TS>30 mm. A comparison of cryosurgery vs thermal ablation according to TS was also performed.

Results

Of 3,946 LTA patients, 2,974 (75.3%) patients harbored TS≤30mm vs 972 (24.7%) harbored TS>30mm. The latter were significantly older (median age 67 vs 71 years, p<0.001), compared to TS≤30 mm. No differences were recorded in annual rates over time. In unmatched CRR models, after adjustment for other-cause mortality (OCM), LTA for TS>30mm showed worse 5-year CSM (HR 2.3, p<0.001), relative to TS≤30 mm. In PS and OCM-adjusted CRR models, LTA for TS>30mm still showed worse 5-year CSM (HR 2.86, p<0.001), relative to TS≤30 mm. Thermal ablation was associated with higher 5-year CSM, compared to cryosurgery (7.6 vs 3.9%, p=0.02), but only when TS was >30 mm.

Conclusions

TS>30 mm is an independent predictor of higher 5-years CSM rates in patients treated with LTA, even after adjustment for OCM. In consequence, when LTA is considered it ideally should be performed for TS≤30 mm.

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1. Introduction

In the last two decades, ablative techniques (local tumor ablation [LTA]) emerged as treatment option for management of renal masses, especially in the elderly and/or patients with comorbidities[1,2]. Existing reports do suggest that tumor size (TS) is a significant predictor of oncological outcomes after LTA, with good results for masses up to 30 mm[1,3].

However, these data originate from institutional retrospective series[4–9] with small sample sizes (range from 62[7] to 168 patients[8]), where oncological outcomes were mostly evaluated as recurrence free survival (RFS). Moreover, some of these studies[5,6] also included T1b renal cell carcinoma (RCC). Only one population based study[10] relying on Surveillance, Epidemiology, and End Results database (2004-2013) assessed 5-year cancer specific survival (CSS) rates according to TS in a cohort of 3,052 LTA patients. However, the prognostic role of TS on survival outcomes was not assessed.

Based on this evidence, European guidelines[11] suggest that definitive conclusions regarding oncological outcomes of LTA according to TS cannot be drawn. Conversely, the 2019th North American guidelines[12] recommend LTA for lesion less than 3 cm, based on potential for higher recurrence above this threshold.

Despite this recommendation, existing data regarding LTA are of limited robustness, especially for renal masses in excess of 3 cm. In consequence, we tested for differences in CSM rates after LTA according to tumor size (TS) ≤30 mm vs >30 mm. We hypothesize that LTA for TS>30 mm may results in higher CSM rates in T1a renal cell carcinoma (RCC), even when other-cause mortality (OCM) is accounted for. To test this hypothesis, we relied on propensity score matching and competing risks regression models within the SEER database (2004-2015).

2. Materials and Methods

2.1 Data source and patient selection

Within the SEER database (2004 to 2015), we focused on patients aged 18 years or older treated with LTA, as primary treatment, with histologically confirmed T1a RCC

(International Classification of Disease for Oncology [ICD-O] site codes C64.9). LTA was coded according to SEER coding manual[13] and only cryosurgery (surgery code 13 and 23) and thermal ablation (surgery code 15) were included. Death was defined according to the SEER mortality code, as either cancer specific mortality (CSM, death from RCC) or OCM (death from any other causes). All autopsy and death certificate, as well as missing follow-up data, were excluded.

Patients were stratified according to TS≤30 mm and TS>30 mm. These selection criteria yielded 3,946 assessable patients.

2.2 Statistical analyses

Statistical analyses consisted of six analytical steps. First, we evaluated overall rates of LTA for TS≤30 mm and TS>30 mm and we tested for statistically significance differences in means and proportions. Second, we examined the estimated annual percentage changes (EAPCs)[14] for TS≤30 mm and TS>30 mm, as well as according to LTA type in each TS group. Third, cumulative incidence plots depicted CSM and OCM rates according to both TS and LTA type; the statistical significance of differences was tested with the Gray test[15]. Fourth, multivariable competing risks regression models (CRR)[16] predicted CSM and OCM according to TS (≤30 mm versus >30 mm). Adjustment variables consisted of age at diagnosis, histology, Fuhrman grade, gender, marital status and ethnicity. Fifth, survival analyses were repeated after 1:1 propensity score (PS) matching according to the nearest neighbor[17]. The PS-matched cohorts (LTA for TS≤30 mm versus TS>30 mm) were balanced according to age at diagnosis, gender, ethnicity, socioeconomic status, population density, period of treatment, histology and Fuhrman grade. Lastly, we generated a graphical depiction of HRs reported within previous institutional retrospective studies[4–6,8,9], focused on recurrence-free survival (RFS) in LTA treated patients for TS≤30mm vs TS>30mm[4,5,8] and TS<30mm vs TS≥30mm[6,9].

All statistical tests were two-sided with a level of significance set at $p < 0.05$. Analyses were performed using the R software environment for statistical computing and graphics (version 3.4.1; http://www.r-project. org/).

3. Results

3.1 Sociodemographic and tumor characteristics of the overall population

Of 52,001 patients with T1a non-metastatic RCC, 4,578 patients (8.8%) were treated with LTA. Of these, 3,946 patients treated with either cryosurgery (3,028, 76.7%) or thermal ablation (918, 23.3%) were included in this study.

Table 1 summarizes baseline characteristics of the study population. Overall, 972 (24.7%) patients were treated with LTA for TS>30 mm. Compared to those with TS≤30 mm, patients treated with LTA for TS>30 mm were significantly older (median age at diagnosis 67 vs 71 years, p<0.001), more frequently male (62.0 vs 68.8%, p<0.001) and more frequently in the highest socioeconomic quartiles (71.6 vs 75.2%, p=0.03). No other sociodemographic characteristics differences were recorded. LTA type (cryosurgery vs thermal ablation) was evenly distributed in patients with TS ≤30 mm (76.4% vs 23.3%, respectively) and TS>30 mm (77.7% vs 22.3%, respectively). Patients treated for TS>30 mm more frequently harbored clear cell histology (53.7 vs 57.9%, p<0.001), compared to those treated for TS≤30 mm. No significant differences were recorded in Fuhrman grade distribution.

3.2 Temporal trend analyses

In the overall population, no statistically significant differences over time were recorded for both LTA for TS≤30 mm (from 71.7 to 74.9%; EAPC +0.6%, p=0.08) vs LTA for TS>30 mm (from 28.3 to 25.1%; EAPC -1.9%, p=0.06) (Figure 1A).

In LTA for TS≤30 mm cohort, both cryosurgery (EAPC +0.4%, p=0.47) and thermal ablation (EAPC +1.3%, p=0.26) remained stable over time (Figure 1B). In LTA for TS>30 mm cohort, cryosurgery remained stable over time (EAPC -0.6%, p=0.46). Conversely, thermal ablation rates decreased over time (from 9.1 to 6.2%, EAPC -6.9%, p=0.02) (Figure 1C).

3.3 Survival analyses of unmatched cohort

In the overall unmatched cohort, cumulative incidence plots showed 5-year CSM rates of 2.0 vs 4.7% (p<0.001) and 5-year OCM rates of 7.0 vs 13.7% (p<0.001), for respectively LTA for TS≤30 mm and TS>30 mm (Figure 2A). In unadjusted multivariable competing risks regression models (Table 2A), TS>30 mm independently predicted higher CSM (HR: 2.3, p<0.001) and higher OCM (HR: 1.81, p<0.001), relative to TS≤30 mm. Additionally, older age (HR: 1.07, p<0.001), never married status (HR: 1.98, p=0.04) and Fuhrman grade G3/G4 (HR 2.21, p=0.04) independently predicted higher 5-year CSM rates.

In LTA for TS≤30 mm cohort, cumulative incidence plots showed 5-year CSM rates of 1.9 vs 2.6% (p=0.96) and 5-year OCM rates of 6.6 vs 8.5% (p=0.07), for respectively cryosurgery and thermal ablation (Figure 2B). Conversely, in LTA for TS>30 mm cohort, cumulative incidence plots showed 5-year CSM rates of 3.9 vs 7.6% (p=0.02) and 5-year OCM rates of 13.9 vs 13.2% (p=0.27), for respectively cryosurgery and thermal ablation (Figure 2C).

3.4 Survival analyses of propensity score matched cohort

After 1:1 ratio PS-matching, 972 LTA for TS≤30 mm and 972 LTA for TS>30 mm remained for the purpose of subsequent analyses. No baseline differences were recorded between both cohorts after PS-matching.

Cumulative incidence plots showed 1.3 vs 4.7% 5-year CSM rates (p<0.001) and 7.9 vs 13.7% OCM rates (p<0.001), for respectively LTA for TS≤30 mm and LTA for TS>30 mm (Figure 2D).

In PS-adjusted multivariable competing risks regression models (Table 2B), TS>30 mm independently predicted higher CSM (HR: 2.86, p<0.001) and higher OCM (HR: 1.86, p<0.001), relative to TS≤30 mm. Moreover, older age (HR: 1.05, p<0.001) and Fuhrman grade G3/G4 (HR 3.8, p=0.02) were independent predictors of higher 5-year CSM rates.

3.5 Graphical depiction of hazard ratios of previous studies

Graphical depiction of hazard ratios for cancer recurrence after LTA in previous institutional studies (Figure 3) showed an almost 5-fold increase in recurrence rates after LTA for either TS>30[4,5,8] or TS≥30mm[6,9].

4. Discussion

We relied on the SEER database (2004-2015) to test the hypothesis that LTA for TS>30mm may results in higher CSM rates in T1a RCC, even when OCM is accounted for. Our analyses represent the first population-based study which investigated this topic. As opposed to previous institutional series, our study relied on a substantially larger sample size and more contemporary patients. Moreover, it relied on PS-matching and competing risks regression models and resulted in several noteworthy findings.

First, less that 10% (4,578 out of 52,001) patients with non-metastatic T1a RCC were treated with LTA within the SEER database. In our cohort of 3,946 LTA patients, the majority of these individuals (75.3%) harbored TS≤30 mm, while one quarter (24.7%) harbored tumors >30 mm. The latter were significantly older (median age at diagnosis 67 vs 71 years, $p<0.001$). These findings are in agreement with guidelines that recommend LTA as a treatment option for small renal masses and/or in elderly patients[11,12].

Second, survival analyses showed significantly higher CSM in patients with TS>30mm (4.7% vs 2.0 and 4.7% vs 1.3, in respectively unmatched and matched population), which was validated in CCR models (2.86-fold increase). Additionally, patients with TS>30 mm also experienced significantly higher OCM rates compared to those with TS≤30mm (13.7% vs 7.0% and 13.7% vs 7.9, in respectively unmatched and matched population), which was validated in CRR models (1.86-fold increase). Higher OCM rates, as well as older age of LTA patients with TS>30 mm, indicate that clinicians give higher priority for LTA with TS>30 mm to patients at higher risk of OCM. To the best of our knowledge, no other studies examined the concept of OCM after LTA. Moreover, all other institutional studies[4–8] relied on recurrence-free survival (RFS) and/or disease-free survival (DFS) as endpoints also without adjustment for OCM. In all five institutional studies[4–8] RFS and DFS are higher for TS greater or equal 30 mm. Our graphical depiction of HR of these studies showed an almost 5-fold increase of recurrence, while our analyses showed a 2.86-fold increase in CSM for TS>30mm. Even though different endpoints were used, our findings are highly consistent with the analyses on earlier endpoint (recurrence).

Third, CSM rates after thermal ablation were higher for TS>30 mm, compared to cryosurgery (7.6 vs 3.9%, p=0.02). Conversely, no CSM difference were identified according to LTA type for TS≤30mm. In consequence, cryosurgery should represent the preferred option for LTA in patients with TS>30 mm. Our findings are in agreement with a historical meta-analysis[18], where higher local progression rates were reported for thermal ablation compared to cryosurgery. Conversely, a more recent pooled analysis[19] reported similar proportions of clinical efficacy (described as no evidence of recurrence on imaging) for thermal ablation vs cryosurgery. However, the heterogeneity of the studies imposes to interpreter these results with caution.

Taken together, our findings validate the NCCN recommendation regarding use of LTA in patients with TS<30 mm. Second, a minority of patients are treated with LTA for TS>30mm. In general, these individuals are older and at substantially higher risk of OCM. These characteristics may justify LTA use above the recommended TS threshold. Nonetheless, CSM in LTA treated patients for TS>30 mm was 2.8-fold higher than in their counterparts treated for TS≤30mm. This observation should be considered in clinical decision making and at informed consent prior to LTA for TS>30mm.

Despite its strengths, limitations of this study include retrospective nature, absence of comorbidities information, lack of standardized specimen handling, as well as of central review regarding histological subtype, and lack of data regarding earlier cancer control endpoints, such as local recurrence and disease free survival. Nonetheless, our analyses relied on PS matching to maximally reduce biases and on competing risks regression models adjusted for OCM.

5. Conclusions

TS>30 mm is an independent predictor of higher 5-years CSM rates in patients treated with LTA, even after adjustment for OCM. In consequence, when LTA is considered it ideally should be performed for TS≤30 mm.

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Disclosure

No competing financial interests exist

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List of abbreviations

LTA local tumor ablation

TS tumor size

RFS recurrence free survival

RCC renal cell carcinoma

SEER Surveillance, Epidemiology, and End Results

CSM cancer-specific mortality

OCM other-cause mortality

EAPC estimated annual percentage changes

CRR competing risks regression

PS propensity score

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Table 1. Baseline characteristics of 3,946 patients with T1a renal cell carcinoma treated with local tumor ablation for tumor size≤30 mm (2,974) or tumor size>30 mm (972), identified within the Surveillance, Epidemiology, and End Results database from 2004 to 2015.

Variables		**Overall (n=3,946; 100%)**	**Tumor size ≤30 mm (n=2,974; 75.3%)**	**Tumor size >30 mm (n=972; 24.7%)**	**p value**
Age at diagnosis, years	Median (IQR)	68 (60-76)	67 (59-75)	71 (63-78)	<0.001
Gender, n (%)	Male	2514 (63.7)	1845 (62.0)	669 (68.8)	<0.001
	Female	1432 (36.3)	1129 (38.0)	303 (31.2)	
Ethnicity, n (%)	Caucasian	3305 (83.8)	2490 (83.7)	815 (83.8)	0.31
	African American	442 (11.2)	326 (11)	116 (11.9)	-
	Others	199 (5)	158 (5.3)	41 (4.2)	-
Marital status, n (%)	Married	2418 (61.3)	1831 (61.6)	587 (60.4)	0.38
	Never Married	483 (12.2)	374 (12.6)	109 (11.2)	-
	Previously Married	856 (21.7)	629 (21.1)	227 (23.4)	-
	Unknown	189 (4.8)	140 (4.7)	49 (5)	-
Population density, n (%)	Urban	3557 (90.1)	2683 (90.2)	874 (89.9)	0.68
	Rural	387 (9.8)	289 (9.7)	98 (10.1)	-
	Unknown	2 (0.1)	2 (0.1)	0 (0)	-

Socioeconomic status, n (%)	1 quartile	1086 (27.5)	845 (28.4)	241 (24.8)	0.03
	2-3-4 quartile	2860 (72.5)	2129 (71.6)	731 (75.2)	-
Period of treatment, n (%)	2004-2009	1392 (35.3)	1031 (34.7)	361 (37.1)	0.17
	2010-2015	2554 (64.7)	1943 (65.3)	611 (62.9)	-
Size, mm	Median (IQR)	25 (20-30)	22 (18-27)	35 (33-38)	<0.001
Histology, n (%)	Clear cell	2159 (54.7)	1596 (53.7)	563 (57.9)	0.002
	Papillary	694 (17.6)	560 (18.8)	134 (13.8)	-
	Chromophobe	172 (4.4)	135 (4.5)	37 (3.8)	-
	Others	7 (0.2)	7 (0.2)	0 (0)	-
	Unspecified	914 (23.2)	676 (22.7)	238 (24.5)	-
Fuhrman grade, n (%)	G1/G2	2169 (55)	1637 (55.0)	532 (54.7)	0.88
	G3/G4	207 (5.2)	153 (5.1)	54 (5.6)	-
	Unknown	1570 (39.8)	1184 (39.8)	386 (39.7)	-
Ablation technique, n (%)	Cryosurgery	3028 (76.7)	2273 (76.4)	755 (77.7)	0.45
	Thermal ablation	918 (23.3)	701 (23.6)	217 (22.3)	-

Table 2. Multivariable competing risks regression models before (a) and after (b) 1:1 propensity score match predicting cancer-specific mortality (CSM) and other-cause mortality (OCM) in T1a renal cell carcinoma treated with local tumor ablation (LTA) for either tumor size≤30 mm or tumor size>30 mm.

a. Before 1:1 propensity score match					
		Cancer-specific mortality		**Other-cause mortality**	
		HR	**p**	**HR other m**	**p**
Age		1.07 (1.05-1.09)	**<0.001**	1.03 (1.02-1.04)	**<0.001**
Size	**≤30 mm**	1.00 (Ref.)	---	1.00 (Ref.)	---
	>30 mm	2.3 (1.48-3.57)	**<0.001**	1.8 (1.43-2.27)	**<0.001**
Gender	**Male**	1.00 (Ref.)	---	1.00 (Ref.)	---
	Female	0.96 (0.61-1.5)	0.85	0.83 (0.65-1.07)	0.15
Marital status	**Married**	1.00 (Ref.)	---	1.00 (Ref.)	---
	Never Married	1.98 (1.02-3.85)	**0.04**	1.49 (1.03-2.16)	**0.04**
	Previously Married	1.03 (0.6-1.76)	0.91	1.52 (1.15-2.02)	**0.003**
	Unknown	2.01 (0.94-4.26)	0.07	1 (0.57-1.74)	1
Ethnicity	**Caucasian**	1.00 (Ref.)	---	1.00 (Ref.)	---
	African American	1.15 (0.57-2.33)	0.69	0.59 (0.37-0.93)	**0.02**
	Others	1.96 (0.92-4.16)	0.08	0.68 (0.4-1.16)	0.16
Fuhrman grade	**G1/G2**	1.00 (Ref.)	---	1.00 (Ref.)	---
	G3/G4	2.21 (1.03-4.77)	**0.04**	1.14 (0.7-1.87)	0.6
	Unknown	1.41 (0.88-	0.15	1.1 (0.86-1.4)	0.44

		2.26)			
Histology	**Clear cell**	1.00 (Ref.)	---	1.00 (Ref.)	---
	Papillary	1.25 (0.72-2.19)	0.43	0.75 (0.54-1.05)	0.09
	Chromophobe	0.51 (0.12-2.16)	0.36	0.63 (0.32-1.26)	0.19
	Unspecified	0.91 (0.53-1.55)	0.72	0.7 (0.53-0.92)	**0.01**
LTA technique	**Cryosurgery**	1.00 (Ref.)	---	1.00 (Ref.)	---
	Thermal ablation	1.33 (0.84-2.11)	0.23	1.26 (0.99-1.61)	0.06
b. After 1:1 propensity score match					
		Cancer-specific mortality		**Other-cause mortality**	
		HR	**p**	**HR other m**	**p**
Age		1.05 (1.02-1.08)	**<0.001**	1.03 (1.01-1.04)	**<0.001**
Size	**≤30 mm**	1.00 (Ref.)	---	1.00 (Ref.)	---
	>30 mm	2.86 (1.53-5.34)	**<0.001**	1.86 (1.37-2.53)	**<0.001**
Gender	**Male**	1.00 (Ref.)	---	1.00 (Ref.)	---
	Female	0.89 (0.51-1.58)	0.7	0.81 (0.58-1.14)	0.23
Marital status	**Married**	1.00 (Ref.)	---	1.00 (Ref.)	---
	Never Married	1.83 (0.75-4.45)	0.18	1.85 (1.15-2.98)	**0.01**
	Previously Married	1.31 (0.7-2.45)	0.4	1.32 (0.9-1.93)	0.16
	Unknown	1.9 (0.72-5.04)	0.2	0.95 (0.47-1.94)	0.89

Ethnicity	**Caucasian**	1.00 (Ref.)	---	1.00 (Ref.)	---
	African American	1.26 (0.54-2.94)	0.6	0.52 (0.29-0.95)	**0.04**
	Others	2.49 (0.92-6.77)	0.07	0.65 (0.33-1.3)	0.22
Fuhrman grade	**G1/G2**	1.00 (Ref.)	---	1.00 (Ref.)	---
	G3/G4	3.8 (1.54-9.37)	**0.004**	0.84 (0.4-1.77)	0.65
	Unknown	1.47 (0.78-2.75)	0.23	0.89 (0.65-1.22)	0.48
Histology	**Clear cell**	1.00 (Ref.)	---	1.00 (Ref.)	---
	Papillary	1.67 (0.8-3.48)	0.17	0.64 (0.39-1.05)	0.08
	Chromophobe	0 (0-0)	0	0.53 (0.19-1.53)	0.24
	Unspecified	0.98 (0.49-1.94)	0.95	0.74 (0.52-1.05)	0.09
LTA technique	**Cryosurgery**	1.00 (Ref.)	---	1.00 (Ref.)	---
	Thermal ablation	1.46 (0.82-2.6)	0.2	1.33 (0.96-1.83)	0.08

Figure Legends

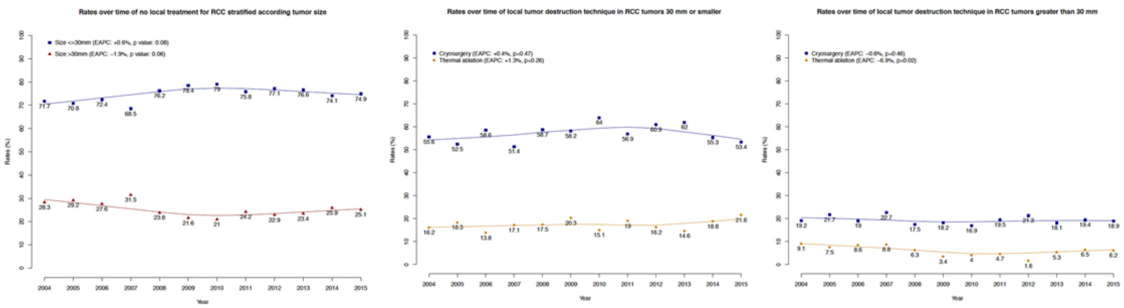

Fig. 1 Annual rates over time of patients with T1a non-metastatic renal cell carcinoma treated with local tumor ablation (LTA) for either tumor size≤30 mm and tumor size>30mm (a), identified within the Surveillance, Epidemiology and End Results database from 2004 to 2015. Subgroup analyses were performed according to LTA technique (cryosurgery vs thermal ablation) in tumor size≤30 mm (b) and tumor size>30 mm cohorts (c)

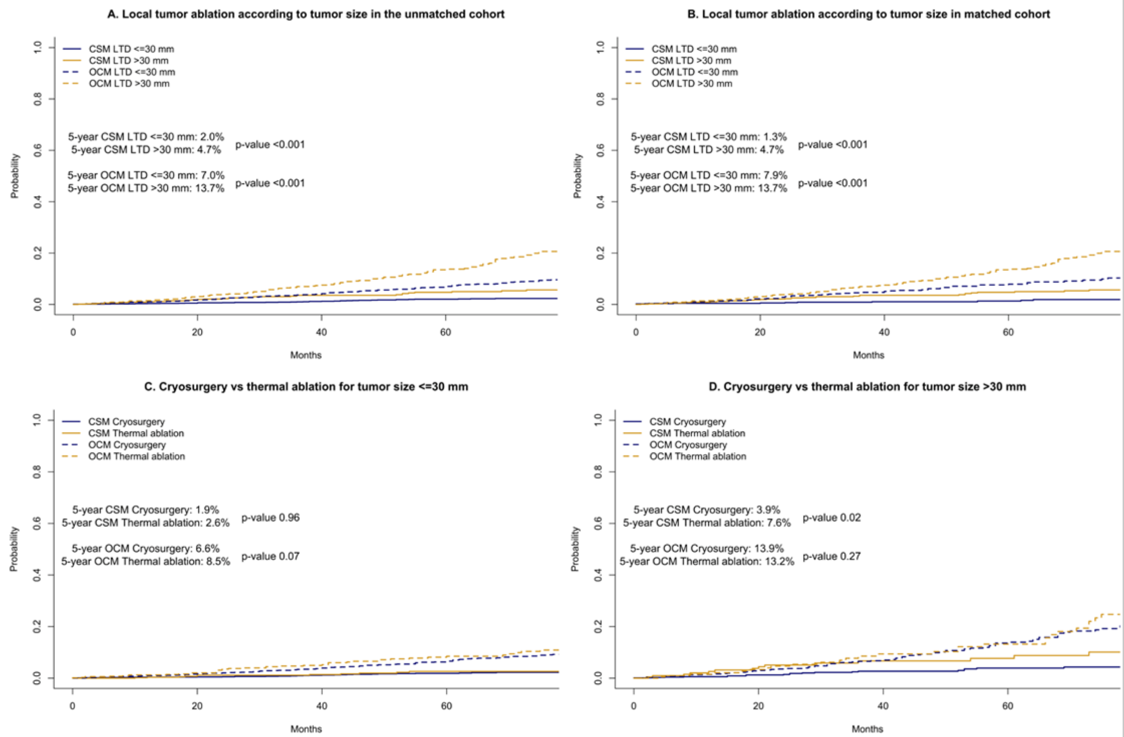

Fig. 2 Cumulative incidence plots depicting cancer-specific mortality (CSM) and other-cause mortality (OCM) rates in T1a non metastatic renal cell carcinoma patients treated with local tumor ablation (LTA) for either tumor size≤30 mm and tumor size>30mm, in the unmatched (a) and matched (b) cohorts. Subgroup analyses were performed according to LTA technique (cryosurgery vs thermal ablation) in tumor size≤30 mm (c) and tumor size>30 mm cohorts (d)

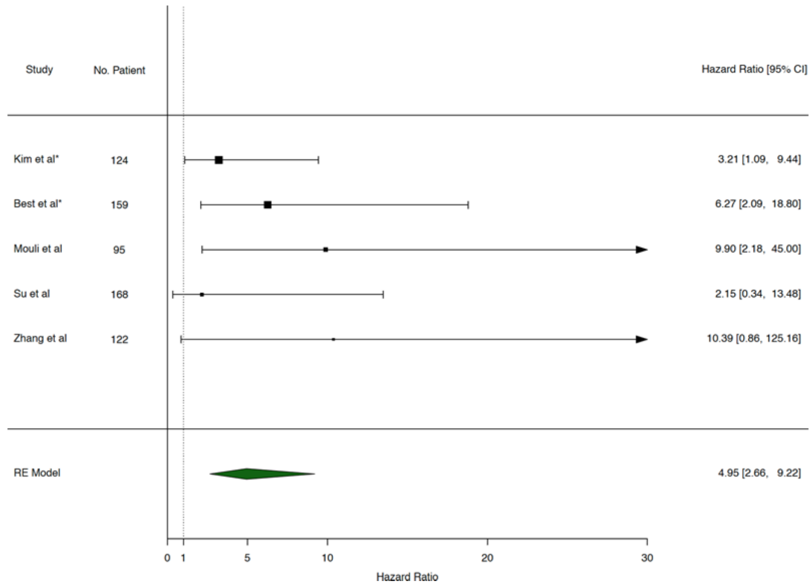

Fig. 3 Graphical depiction of the current HRs relative to those reported within the previous Institutional retrospective studies, focused on recurrence-free survival (RFS) in patients treated with local tumor ablation for tumor size≤30mm vs >30mm and tumor size<30mm vs ≥30mm

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