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ORIGINAL ARTICLE

Assessment of local tumor ablation and non-interventional management *versus* partial nephrectomy in T1a renal cell carcinoma

Carlotta PALUMBO [1, 2] *, Francesco A. MISTRETTA [1, 3], Sophie KNIPPER [1, 4], Elio MAZZONE [1, 5], Angela PECORARO [1, 6], Zhe TIAN [1], Paul PERROTTE [7], Alessandro ANTONELLI [2], Francesco MONTORSI [5], Shahrokh F. SHARIAT [8, 9, 10, 11, 12], Fred SAAD [1, 6], Claudio SIMEONE [2], Alberto BRIGANTI [5], Luke T. LAVALLEE [13], Pierre I. KARAKIEWICZ [1, 6]

[1]Unit of Cancer Prognostics and Health Outcomes, University of Montreal Health Center, Montreal, QB, Canada; [2]Unit of Urology, Department of Medical and Surgical Specialties, Radiological Science and Public Health, ASST Spedali Civili of Brescia, University of Brescia, Brescia, Italy; [3]Department of Urology, European Institute of Oncology, Milan, Italy; [4]Martini Klinik, University Medical Center Hamburg-Eppendorf, Hamburg, Germany; [5]Unit of Urology, Division of Experimental Oncology, Urological Research Institute (URI), IRCCS San Raffaele Hospital, Vita-Salute San Raffaele University, Milan, Italy; [6]Department of Urology, San Luigi Gonzaga Hospital, University of Turin, Orbassano, Turin, Italy; [7]Division of Urology, University of Montreal Hospital Center (CHUM), Montreal, QB, Canada; [8] Department of Urology, Comprehensive Cancer Center, Medical University of Vienna, Vienna, Austria; [9]Departments of Urology, Weill Cornell Medical College, New York, NY, USA; [10]Department of Urology, University of Texas Southwestern, Dallas, TX, USA; [11]Department of Urology, Second Faculty of Medicine, Charles University, Prague, Czech Republic; [12]Institute for Urology and Reproductive Health, I.M. Sechenov First Moscow State Medical University, Moscow, Russia; [13]Division of Urology, The Ottawa Hospital, University of Ottawa and the Ottawa Hospital Research Institute, Ottawa, ON, Canada

*Corresponding author: Carlotta Palumbo, Unit of Urology, Department of Medical and Surgical Specialties, Radiological Science and Public Health, ASST Spedali Civili of Brescia, University of Brescia, Piazzale Spedali Civili 1, 25123 Brescia, Italy.
E-mail: palumbo.carlotta@gmail.com

ABSTRACT

BACKGROUND: Local tumor ablation (LTA) and non-interventional management (NIM) emerged as alternative management options for T1a renal cell carcinoma (RCC). We investigated trends and cancer-specific mortality (CSM) after LTA and NIM, compared to partial nephrectomy (PN).

METHODS: Within the Surveillance, Epidemiology, and End Results database (2004-2015), T1a RCC patients treated with PN, LTA or NIM were identified. Estimated annual proportion change methodology (EAPC), 1:1 ratio propensity score (PS) matching, cumulative incidence plots and multivariable competing risks regression models (CRR) were used to compare LTA *vs.* PN and NIM *vs.* PN. Subgroup analyses focused on patients <65 and ≥65 years.

RESULTS: Overall 4524 patients underwent LTA *vs.* 1654 NIM *vs.* 25,435 PN. Annuals rates increased for NIM (EAPC: +3.3%, P<0.001), but not for either LTA or PN. After PS-matching in multivariable CCR, LTA (HR 1.9, P<0.001) and NIM (HR 3.0, P<0.001) showed worse 5-year CSM, relative to PN. In subgroup analyses, LTA showed no CSM disadvantage relative to PN in younger patients (HR 2.0, P=0.07). In older patients 1.64-fold CSM increase was recorded. Conversely, NIM younger (HR 3.1, P=0.001) and older (HR 3.1, P<0.001) patients exhibited higher CSM relative to PN.

CONCLUSIONS: In T1a RCC patients, NIM rates showed a modest but significant increase, while LTA and PN rates remained stable. In survival analyses, LTA exhibited higher CSM rates only for elderly patients. Conversely, NIM exhibited higher CSM rates in both younger and older patients.

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KEY WORDS: Carcinoma, Renal Cell; Nephrectomy; Ablation techniques; Observation.

Both European and North American guidelines[1, 2] recommend partial nephrectomy (PN) as standard treatment for clinical stage T1a renal cell carcinoma (RCC), when technically feasible. In the last decade, both observation (non-interventional management, NIM) and ablative techniques (local tumor ablation, LTA) emerged as alternative approaches for either elderly patients or poor surgical candidates.[3-6]

Data regarding LTA *versus* nephrectomy originating from 7 institutional studies (from 1998 to 2012) formed the basis of a recent meta-analysis,[7] which showed a 3.4-fold increase of cancer specific mortality (CSM) when LTA was performed instead of partial (PN) or radical nephrectomy (RN). Conversely, of five population based studies,[8-12] only one[9] showed worse CSM for LTA relative to PN. However, their historic nature represents a limitation; the most recent included patients diagnosed from 2004 to 2013.[12] Moreover, with the exception of SEER-Medicare studies[10, 11] that exclusively focused on patients older than 65 years, no stratification was performed according to age. Finally, only two studies relied on competing risks regression.[9, 11]

Very similar limitations apply to NIM. Only two institutional studies compared NIM to either RN or PN.[13, 14] Both found no differences in 5-year CSM. Conversely, data from four population based studies that relied on patients treated from 1988 to 2011 with either NIM or surgery[15-19] reported significantly worse 5-year CSM for NIM. However, the disadvantage of NIM disappeared, when only patients older than 75 years[16] or those at higher cardiovascular risk[18] were compared. Only one[11] of the four population based studies specifically compared NIM to PN. Finally, only two[17, 19] of four relied on competing risks regression models that account for other-cause mortality (OCM) and for elderly patients.

Taken together, no contemporary data allows to ascertain whether LTA or NIM might predispose T1a patients to higher CSM relative to PN. This lack of comparative data is particularly important for elderly individuals who are at high risk of OCM. To address this unmet need, we hypothesized that no CSM disadvantage exists when contemporary LTA or NIM are used in elderly individuals, especially when OCM is accounted for. We tested our hypothesis in the 2004-2015 version of the SEER database and relied on multivariable competing risks models adjusted for OCM in addition to detailed propensity-score adjustment.

Materials and methods

Data source and patient selection

Within the SEER databases (2004 to 2015),[20] we focused on patients aged 18 years or older with non-metastatic T1a histologically confirmed RCC (International Classification of Disease for Oncology [ICD-O] site codes C64.9). We only included patients submitted to NLM, LTA or partial nephrectomy, as primary treatment.

Death was defined according to the SEER mortality code, as either CSM (death from RCC) or other cause mortality (OCM, death from any other causes). All autopsy or death certificate cases and those with missing follow-up data were excluded.

Statistical analysis

Statistical analyses consisted of four analytical steps. First, we evaluated overall rates of NIM, LTA and PN. Second, we examined the estimated annual percentage changes (EAPCs) for NIM, LTA and PN in the overall population and according to age groups (<65 and ≥65 years). Third, we relied on 1:1 propensity score (PS) matching according to the nearest neighbor to minimize differences that may distinguish LTA or NIM patients from their PN counterparts. The PS-matched cohorts (LTA *vs.* PN and NIM *vs.* PN) were balanced according to age at diagnosis, gender, race, year of diagnosis, population density, marital status, socioeconomic status, tumor grade, histology and tumor size. In the fourth step, we relied on PS-matched comparisons between LTA *vs.* PN and NIM *vs.* PN. Specifically, cumulative incidence plots depicted CSM and OCM rates. The statistical significance of CSM and OCM difference was tested with the Gray test. Finally, we relied on PS-matched data for purpose of multivariable comparisons between LTA *vs.* PN and NIM *vs.* PN. Specifically, multivariable competing risks regression models

(CRR) predicted CSM and OCM according to treatment type. Adjustment variables consisted of age at diagnosis, gender, race, year of diagnosis, population density, marital status, socioeconomic status, tumor grade, histology and tumor size. Subgroups analyses according to age (<65 and ≥65 years) were performed for the comparison between LTA *vs.* PN and NIM *vs.* PN.

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/).

Results

Patient and tumor characteristics

The comparison between LTA and PN prior to any matching relied on 4,524 (15.1%) LTA and 25,435 (84.9%) PN patients (Table I). Relative to PN patients, LTA patients were older (median age 68 *vs.* 59 years, P<0.001), and less frequently treated in more contemporary years (for period 2010-2015, 63.2 *vs.* 64.9%, P<0.001).

The comparison NIM *vs.* PN prior to any matching relied on 1,654 (6.2%) NIM patients and 25,435 (93.8%) PN patients (Table II). Relative to PN patients, NIM patients were older (median age 70 *vs.* 59 years, P<0.001) and more frequently treated in the more contemporary years (for period 2010-2015, 68.8 *vs.* 64.9%, P<0.001).

Analyses based on annual rates of treatment types

In the overall population, the absolute rates of LTA changed from 11.2% to 15.6% (EAPC: +0.4%, P=0.71), those of NIM changed from 4.1

TABLE I.—*Descriptive characteristics of 29,959 patients treated with either local tumor ablation (N.=4524) or partial nephrectomy (N.=25,435) for non-metastatic T1a renal cell carcinoma identified within the surveillance, epidemiology, and end results database from 2004 to 2015.*

Variables		A. Overall (N.=29,959)		
		Local tumor ablation (N.=4524; 15.1%)	Partial nephrectomy (N.=25,435; 84.9%)	P value
Age, years	Median (IQR)	68 (60-76)	59 (50-67)	<0.001
Size, N. (%)	≤20	1429 (31.6)	9116 (35.8)	<0.001
	>20	3095 (68.4)	16319 (64.2)	
Histological subtype, N. (%)	ccRCC	2457 (54.3)	15899 (62.5)	<0.001
	pRCC	812 (17.9)	4401 (17.3)	
	chRCC	194 (4.3)	1601 (6.3)	
	RCC NOS	1061 (23.5)	3534 (13.9)	
Tumor grade, N. (%)	G1/G2	2501 (55.3)	17647 (69.4)	
	G3/G4	249 (5.5)	4532 (17.8)	
	Unknown	1774 (39.2)	3256 (12.8)	
Race, N. (%)	White	3785 (83.7)	20861 (82)	<0.001
	Black	511 (11.3)	2777 (10.9)	
	Other	228 (5.0)	1797 (7.1)	
Gender, N. (%)	Male	2882 (63.7)	15687 (61.7)	0.01
	Female	1642 (36.3)	9748 (38.3)	
Marital Status, N. (%)	Married	2780 (61.5)	16334 (64.2)	<0.001
	Never Married	554 (12.2)	3784 (14.9)	
	Previously Married	982 (21.7)	3943 (15.5)	
	Unknown	208 (4.6)	1374 (5.4)	
Population density, N. (%)	Rural	1583 (35.0)	8164 (32.1)	0.001
	Urban	2941 (65.0)	17271 (67.9)	
Socioeconomic status, N. (%)	1 quartile	1218 (26.9)	6223 (24.5)	<0.001
	2-3-4 quartile	3306 (73.1)	19212 (75.5)	
Year of diagnosis, N. (%)	2004-2009	1665 (36.8)	8930 (35.1)	0.03
	2010-2015	2859 (63.2)	16505 (64.9)	

IQR: interquartile range; ccRCC: clear-cell renal cell carcinoma; pRCC: papillary renal cell carcinoma; cRCC: chromophobe renal cell carcinoma; RCC NOS: renal cell carcinoma not otherwise specified.

to 6.4% (EAPC: +3.3%, P<0.001) and those for PN from 84.7 to 78% (EAPC: -0.3%, P=0.18). Virtually the same treatment rates were recorded, when data were stratified according to age <65 and ≥65 years.

Matched cumulative incidence plots and multivariable competing risks regression models: comparison between LTA *vs.* PN

After 1:1 PS-matching, no statistically significant differences remained between LTA and PN patients (N.=4307 LTA *vs.* N.=4307 PN patients in the overall cohort; N.=1,693 LTA *vs.* N.=1,693 PN in patients aged <65 years; N.=2584 LTA *vs.* N.=2584 PN in patients aged ≥65 years).

In the overall matched cohort, five-year CSM rates were 2.6% *vs.* 1.1% (P=0.004) and five-year OCM rates were 8.4 *vs.* 5.8% (P<0.001), for respectively LTA and PN patients (Figure 1A). In the subgroup aged <65 years, five-year CSM rates were 1.0% *vs.* 0.8% (P=0.4) and five-year OCM rates of 5.7% *vs.* 3.1% (P<0.001), for respectively LTA and PN patients (Figure 1B). In the subgroup aged ≥65 years, five-year CSM rates were 3.4% *vs.* 1.4% (P=0.001) and five-year OCM rates were 9.9% *vs.* 7.4% (P=0.001), for respectively LTA and PN patients (Figure 1C).

In PS-adjusted multivariable competing risks regression models (Table III), in the overall cohort LTA independently predicted higher CSM in the overall cohort (HR: 1.6, P=0.003) and higher OCM (HR: 1.5, P<0.001), relative to PN. In the subgroup aged <65 years, LTA independently predicted higher OCM (HR: 1.7, P<0.001), but not CSM (HR: 1.3, P=0.5). Finally, in the subgroup aged ≥65 years, LTA independently predicted higher CSM (HR: 1.8, P=0.002) and OCM (HR: 1.3, P=0.003).

B. Younger than 65 years (N.=18,528)			C. 65 years or older (11,431)		
Local tumor ablation (N.=1695; 9.1%)	Partial nephrectomy (N.=16,833; 90.9%)	P value	Local tumor ablation (N.=2829; 27.4%)	Partial nephrectomy (N.=8602; 73.6%)	P value
57 (51-61)	54 (46-59)	<0.001	74 (69-79)	70 (67-75)	<0.001
637 (37.6)	6352 (37.7)	0.92	792 (28.0)	2764 (32.1)	<0.001
1058 (62.4)	10481 (62.3)		2037 (72.0)	5838 (67.9)	
948 (55.9)	10848 (64.4)	<0.001	1509 (53.3)	5051 (58.7)	<0.001
311 (18.3)	2662 (15.8)		501 (17.7)	1739 (20.2)	
59 (3.5)	986 (5.9)		135 (4.8)	615 (7.1)	
377 (22.2)	2337 (13.9)		684 (24.2)	1197 (13.9)	
988 (58.3)	11946 (71)	<0.001	1513 (53.5)	5701 (66.3)	<0.001
94 (5.5)	2796 (16.6)		155 (5.5)	1736 (20.2)	
613 (36.2)	2091 (12.4)		1161 (41.0)	1165 (13.5)	
1367 (80.6)	13712 (81.5)	<0.001	2418 (85.5)	7149 (83.1)	0.001
235 (13.9)	1891 (11.2)		276 (9.8)	886 (10.3)	
93 (5.5)	1230 (7.3)		135 (4.8)	567 (6.6)	
1071 (63.2)	10359 (61.5)	0.19	1811 (64.0)	5328 (61.9)	0.05
624 (36.8)	6474 (38.5)		1018 (36.0)	3274 (38.1)	
1017 (60)	10705 (63.6)	<0.001	1763 (62.3)	5629 (65.4)	<0.001
342 (20.2)	3095 (18.4)		212 (7.5)	689 (8)	
260 (15.3)	2119 (12.6)		722 (25.5)	1824 (21.2)	
76 (4.5)	914 (5.4)		132 (4.7)	460 (5.3)	
618 (36.5)	5469 (32.5)	0.001	965 (34.1)	2695 (31.3)	0.006
1077 (63.5)	11364 (67.5)		1864 (65.9)	5907 (68.7)	
459 (27.1)	4177 (24.8)	0.04	759 (26.8)	2046 (23.8)	0.001
1236 (72.9)	12656 (75.2)		2070 (73.2)	6556 (76.2)	
628 (37.1)	5962 (35.4)	0.19	1037 (36.7)	2968 (34.5)	0.04
1067 (62.9)	10871 (64.6)		1792 (63.3)	5634 (65.5)	

TABLE II.—*Descriptive characteristics of 27,089 patients treated with either non-interventional management (N.=1654) or partial nephrectomy (N.=25,435) for non-metastatic T1a renal cell carcinoma identified within the surveillance, epidemiology, and end results database from 2004 to 2015.*

Variables		A. Overall (N.=27,089)		
		Non-interventional management (N.=1654; 6.2%)	Partial nephrectomy (N.=25,435; 93.8%)	P value
Age, years	Median (IQR)	70 (61-78)	59 (50-67)	<0.001
Size, N. (%)	≤20	471 (28.5)	9116 (35.8)	<0.001
	>20	1183 (71.5)	16319 (64.2)	
Histological subtype, N. (%)	ccRCC	794 (48.0)	15899 (62.5)	<0.001
	pRCC	261 (15.8)	4401 (17.3)	
	chRCC	62 (3.7)	1583 (6.2)	
	RCC NOS	537 (32.5)	3435 (14.0)	
Tumor grade, N. (%)	G1/G2	689 (41.7)	17647 (69.4)	<0.001
	G3/G4	92 (5.6)	4532 (17.8)	
	Unknown	873 (52.8)	3256 (12.8)	
Race, N. (%)	White	1306 (79.0)	20861 (82.0)	<0.001
	Black	245 (14.8)	2777 (10.9)	
	Other	103 (6.2)	1797 (7.1)	
Gender, N. (%)	Male	1047 (63.3)	15687 (61.7)	0.02
	Female	607 (36.7)	9748 (38.3)	
Marital Status, N. (%)	Married	815 (49.3)	16334 (64.2)	<0.001
	Never Married	272 (16.4)	3784 (14.9)	
	Previously Married	478 (28.9)	3943 (15.5)	
	Unknown	89 (5.4)	1374 (5.4)	
Population density, N. (%)	Rural	553 (33.4)	8164 (32.1)	0.27
	Urban	1101 (66.6)	17271 (67.9)	
Socioeconomic status, N. (%)	1 quartile	388 (23.5)	6223 (24.5)	0.37
	2-3-4 quartile	1266 (76.5)	19212 (75.5)	
Year of diagnosis, N. (%)	2004-2009	516 (31.2)	8930 (35.1)	0.001
	2010-2015	1138 (68.8)	16505 (64.9)	

IQR: interquartile range; ccRCC: clear-cell renal cell carcinoma; pRCC: papillary renal cell carcinoma; cRCC: chromophobe renal cell carcinoma; RCC NOS: renal cell carcinoma not otherwise specified.

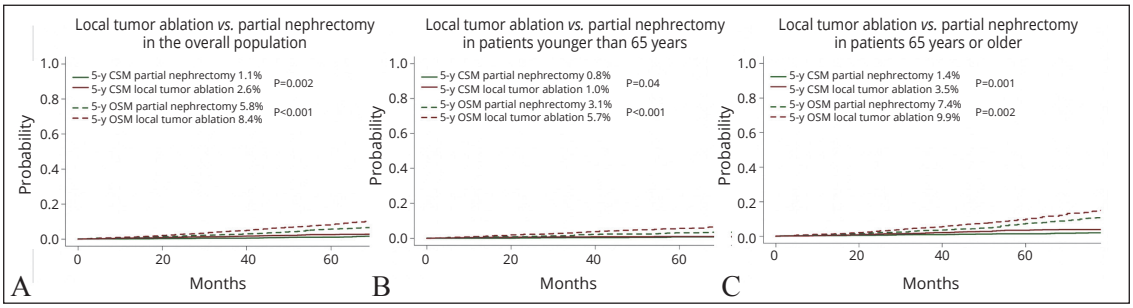

Figure 1.—Cumulative incidence plots depicting cancer-specific mortality (CSM) and other-cause mortality (OCM) rates in T1a renal cell carcinoma patients treated with either local tumor ablation or partial nephrectomy, in the overall cohort (A), subgroup of patients younger than 65 years (B) and subgroup of patients aged 65 years or older (C).

Matched cumulative incidence plots and multivariable competing risks regression models: comparison between non-invasive management and PN

After 1:1 PS-matching, no statistically significant differences remained between NIM and PN patients (N.=1556 NIM *vs.* N.=1556 PN patients in the overall cohort; N.=541 NIM *vs.* N.=541 PN patients in the subgroup aged <65 years; N.=998 NIM *vs.* N.=998 PN patients in the subgroup aged ≥65 years).

In the overall matched cohort, five-year CSM

B. Younger than 65 years (N.=18,528)			C. 65 years or older (11,431)		
Non interventional management (N.=552; 3.0%)	Partial nephrectomy (N.=16,833; 97.0%)	P value	Non interventional management (N.=1102; 9.6%)	Partial nephrectomy (N.=8602; 91.4%)	P value
57 (50-61)	54 (46-59)	<0.001	75 (70-81)	70 (67-75)	<0.001
187 (33.9)	6352 (37.7)	0.07	284 (25.8)	2764 (32.1)	<0.001
365 (66.1)	10481 (62.3)		818 (74.2)	5838 (67.9)	
256 (46.4)	10848 (64.4)	<0.001	538 (48.8)	5051 (58.7)	<0.001
112 (20.3)	2662 (15.8)		149 (13.5)	1739 (20.2)	
20 (3.6)	986 (5.9)		42 (3.8)	615 (7.1)	
164 (29.7)	2337 (13.9)		373 (33.8)	1197 (13.9)	
239 (43.3)	11946 (71)	<0.001	450 (40.8)	5701 (66.3)	<0.001
30 (5.4)	2796 (16.6)		62 (5.6)	1736 (20.2)	
283 (51.3)	2091 (12.4)		590 (53.5)	1165 (13.5)	
401 (72.6)	13712 (81.5)	<0.001	905 (82.1)	7149 (83.1)	0.22
114 (20.7)	1891 (11.2)		131 (11.9)	886 (10.3)	
37 (6.7)	1230 (7.3)		66 (6.0)	567 (6.6)	
388 (70.3)	10359 (61.5)	<0.001	659 (59.8)	5328 (61.9)	0.18
164 (29.7)	6474 (38.5)		443 (40.2)	3274 (38.1)	
255 (46.2)	10705 (63.6)	<0.001	560 (50.8)	5629 (65.4)	<0.001
156 (28.3)	3095 (18.4)		116 (10.5)	689 (8.0)	
114 (20.7)	2119 (12.6)		364 (33.0)	1824 (21.2)	
27 (4.9)	914 (5.4)		62 (5.6)	460 (5.3)	
188 (34.1)	5469 (32.5)	0.47	365 (33.1)	2695 (31.3)	0.25
364 (65.9)	11364 (67.5)		737 (66.9)	5907 (68.7)	
133 (24.1)	4177 (24.8)	0.73	255 (23.1)	2046 (23.8)	0.66
419 (75.9)	12656 (75.2)		847 (76.9)	6556 (76.2)	
164 (29.7)	5962 (35.4)	0.006	352 (31.9)	2968 (34.5)	0.09
388 (70.3)	10871 (64.6)		750 (68.1)	5634 (65.5)	

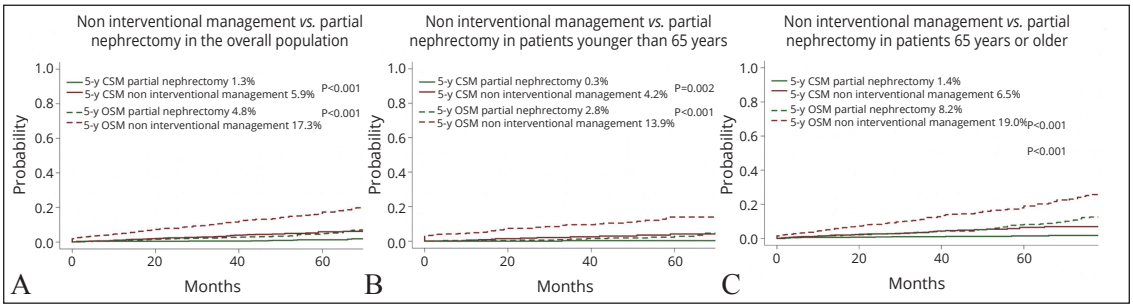

Figure 2.—Cumulative incidence plots depicting cancer-specific mortality (CSM) and other-cause mortality (OCM) rates in T1a renal cell carcinoma patients treated with either non-interventional management or partial nephrectomy, in the overall cohort (A), subgroup of patients younger than 65 years (B) and subgroup of patients aged 65 years or older (C).

rates were 5.9% *vs.* 1.3% (P<0.001) and five-year OCM rates of 17.3% *vs.* 4.8% (P<0.001), for respectively NIM *vs.* PN (Figure 2A). In the subgroup aged <65 years, five-year CSM rates were 4.2% *vs.* 0.3% (P<0.001) and five-year OCM rates were 13.9% *vs.* 2.8% (P<0.001), for respectively NIM *vs.* PN (Figure 2B). In subgroup aged ≥65 years, five-year CSM rates were 6.5% *vs.* 1.4% (P<0.001) and five-year OCM rates were 19.0% *vs.* 8.2% (P<0.001), for respectively NIM *vs.* PN (Figure 2C). In PS-adjusted multivariable competing risks regression models (Table IV), in

TABLE III.—*Propensity score adjusted multivariable competing risk regression models predicting cancer-specific mortality (CSM) and other-cause mortality (OCM) in T1a renal cell carcinoma treated with either local tumor ablation or partial nephrectomy.*

	Overall				Younger than 65 years				65 years and older			
	CSM		OCM		CSM		OCM		CSM		OCM	
	HR (CI)	P	HR (CI)	P	HR (CI)	P	HR (CI)	P	HR (CI)	P	HR (CI)	P
PN	1.0 (Ref.)	---	1.0 (Ref.)	---	1.0 (Ref.)	---	1.0 (Ref.)	---	1.0 (Ref.)	---	1.0 (Ref.)	---
LTA	1.6 (1.2-2.2)	0.003	1.5 (1.3-1.7)	<0.001	1.3 (0.6-2.6)	0.5	1.7 (1.3-2.4)	<0.001	1.8 (1.2-2.7)	0.002	1.3 (1.1-1.6)	0.003

All analyses were adjusted for age at diagnosis, gender, race, year of diagnosis, population density, marital status, socioeconomic status, tumor grade, histology and tumor size. Bold indicates P<0.05.
CSM: cancer specific mortality; OCM: other-cause mortality; HR: hazard ratio; CI: 95% confidence interval; PN: partial nephrectomy; LTA: local tumor ablation.

TABLE IV.—*Propensity score adjusted multivariable competing risks regression models predicting cancer-specific mortality (CSM) and other-cause mortality (OCM) in T1a renal cell carcinoma treated with either non-interventional management or partial nephrectomy.*

	Overall				Younger than 65 years				65 years and older			
	CSM		OCM		CSM		OCM		CSM		OCM	
	HR (CI)	P	HR (CI)	P	HR (CI)	P	HR (CI)	P	HR (CI)	P	HR (CI)	P
PN	1.00 (Ref.)	---	1.0 (Ref.)	---	1.00 (Ref.)	---	1.0 (Ref.)	---	1.0 (Ref.)	---	1.0 (Ref.)	---
NIM	3.3 (1.9-5.6)	<0.001	2.7 (2.1-3.4)	<0.001	5.1 (1.9-13.6)	0.001	4.5 (2.6-7.8)	<0.001	2.9 (1.6-5.1)	<0.001	2.1 (1.6-2.7)	<0.001

All analyses were adjusted for age at diagnosis, gender, race, year of diagnosis, population density, marital status, socioeconomic status, tumor grade, histology and tumor size. Bold indicates P<0.05.
CSM: cancer specific mortality; OCM: other-cause mortality; HR: hazard ratio; CI: 95% confidence interval; PN: partial nephrectomy; NIM: non-interventional management.

the overall cohort, NIM independently predicted higher CSM (HR: 3.0, P<0.001) and OCM (HR: 2.7, P<0.001) relative to PN. Similarly, NIM independently predicted higher CSM and OCM in the subgroup aged <65 years (HR: 3.1, P<0.001 and HR: 3.8, P<0.001, respectively) and in the subgroup aged ≥65 years (HR: 3.1, P<0.001 and HR: 2.0, P<0.001, respectively).

Discussion

We hypothesized that contemporary patient selection for LTA or NIM does not result in higher CSM than after PN, in younger and especially in elderly individuals at an elevated risk of OCM. Our population-based analysis represents the most contemporary comparison between LTA or NIM and PN, with specific subgroup analyses focusing on younger *vs.* older patients and with specific adjustment for OCM within CRR models. Our study resulted in several noteworthy findings.

First, the rates of NIM and LTA in subgroups aged <65 years and ≥65 years were significantly different. Specifically, the proportions of NIM and LTA patients was 3-fold higher in elderly patients than in younger patients. This indicates that age has an important effect on treatment type assignment. The rates recorded in the current study were similar to those reported previously. In previous reports, LTA rates ranged from 8.8% and 18%.[9-11, 16, 17, 19] However, in none of those previous reports, treatment assignment was analyzed according to age cut-off. In consequence, age-specific comparisons were not possible.

Second, regarding sociodemographic characteristics, both LTA and NIM patients were significantly older compared to PN patients, as in all previous population-based studies. Moreover, both LTA and NIM patients were more likely to be African-American. A SEER database study[21] on individuals diagnosed from 1988 to 2008 showed that African-American patients were 23% more likely to undergo LTA or NLT instead of nephrectomy.

Third regarding tumor characteristics, individuals treated with either LTA or NIM exhibited a significantly higher proportion of unspecified histology and of unknown tumor grade. These observations are expected and consistent with needle-biopsy derived histological subtype and tumor grade assignment.[22] However, rather unexpectedly a larger proportion (68.4% *vs.* 64.2%) of LTA patients than PN patients harbored tumors greater than 2 cm. Indeed, according to the National Comprehensive Cancer Network guidelines, LTA is not recommended for lesions than 3 cm^2, because of increasing risk of both recurrence and cancer-specific mortality.[23] However, this finding is consistent with other reports. This finding is also consistent with other reports form SEER[12] (mean size of 24.6 mm for LTA) and SEER-Medicare[10] (36% of NIM measured 3 cm or more).

Fourth, regarding annual rates, LTA use increased from 11.2% to 15.6%, but not in a statistically significant fashion. Conversely, NIM rates increased marginally from 4.6% to 6.2%. This increase achieved statistical significance, but its clinical importance is limited. Previous studies on more historical SEER database[24, 25] have shown a significant increase in trends of both NIM and LTA starting from 2004. To the best of our knowledge, no other more contemporary studies reported on annual rates of LTA and NIM use.

Fifth, in the final part of the analysis we focused on potential CSM disadvantages that might be associated with the use of LTA or NIM, relative to PN. Since LTA and NIM patients are in general different with respect to sociodemographics and tumor characteristics from PN patients, we relied on PS-matching to maximally decrease such differences and associated selection biases. Moreover, we relied on CRR models which allow to control for OCM. This step might be particularly important in elderly patients, where an important probability of death may be attributable to non-cancer causes.[26]

In PS-adjusted comparisons between LTA and PN, the multivariable CRR models showed a 2-fold increase in CSM rate, when LTA was used. After stratification according to age, the CSM disadvantage disappeared in individuals <65 years, but persisted in those ≥65 years, however at a lower rate (HR 1.8). It is of note that the corresponding five-year OCM rates were respectively 8.4%, 5.7% and 9.9% for the entire cohort, the subgroup aged <65 and the subgroup aged ≥65 years. Our findings are in agreement with Whitson *et al.*,[9] who reported a 2-fold increase in CSM after LTA *vs.* nephrectomy (HR 1.9, P=0.02) within a more historical SEER cohort (1998-2007). Conversely, Xing *et al.*[11] found no CSM disadvantage for LTA *vs.* PN in a more recent SEER cohort (2002-2011). Their study relied on CRR analyses and exclusively focused on patients aged ≥75 years. A recent meta-analysis[7] of institutional studies reported a 3.8-fold increase in CSM when LTA was used instead of PN. However, all the above studies allowed the inclusion of both T1a and T1b patients. In our analyses only elderly patients exhibited higher CSM after LTA. The PS-matching, as well as the CRR models, accounted for possible differences in tumor biology and OCM that may exist between younger and older patients. Therefore, the residual difference in CSM may originate from differences in treatment efficacy between LTA and PN. However, we were unable to adjust for subsequent therapies that may have been delivered to patients with disease recurrence and/or progression, such as surgery, radiation and/or medical therapies. It is possible that elderly patients benefitted of fewer opportunities for treatment of recurrence and/or progression, relative to younger patients. In consequence, the differences in LTA and PN in young patients may have been obliterated by the differential use of these subsequent therapies that favored younger patients.

In PS-adjusted comparisons between NIM *vs.* PN, the CRR models showed a 3-fold higher CSM for NIM, which was equally operational in younger and older patients, when subgroup analyses were performed. Our results are in agreement with previous studies,[18, 19] which showed a lower rates of death due to RCC for surgery compared to NIM (HR 0.4, P<0.001 and HR 0.6, P<0.01, respectively). However, both studies relied on historical SEER-Medicare database, including patients from 1991 to 2007.

Our study resulted in several important take home messages. First, the rates of NIM are the

lowest and increased marginally. This observation indicates that a marginal proportion of patients are selected for NIM, in agreement with guidelines. The rates of LTA are intermediate and have not increased over time. This observation is in disagreement with guidelines, especially in younger patients, where LTA is not recommended. Moreover, an unexpectedly elevated proportion of patients with tumor size greater than 3 cm are selected for NIM. Second, regarding CSM, no disadvantage was recorded for younger patients and a modest CSM disadvantage was recorded for elderly patients selected for LTA, relative to PN, suggesting an adequate LTA selection process. Conversely, a different scenario applied to NIM. Here, a CSM disadvantage applied to younger and to older patients that were selected for NIM instead of PN. However, OCM rates that were substantially higher in NIM patients emphasized the important difference that exists between NIM and PN patients. From a clinical perspective, LTA may be considered as an alternative to surgery in T1a RCC patients, due to a modest CSM disadvantage. Conversely, NIM is associated with an increased risk of CSM. Therefore, NIM may be reserved for patients at elevated risk for OCM, for whom the morbidity associated with surgery may be higher.

Limitations of this study

Despite its strengths, significant limitations of this study need to be acknowledged, as the retrospective nature, absence of comorbidities information, inability to assess whether NIM patients were observed with an active surveillance protocol *vs.* watchful waiting without intent for cure, the lack of standardized specimen handling, as well as of central review regarding histological subtype, and the 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.

Conclusions

In T1a RCC patients, NIM rates showed a modest but significant increase, while LTA and PN rates remained stable. In survival analyses, LTA exhibited higher CSM rates only for elderly patients. Conversely, NIM exhibited higher CSM rates in both younger and older patients.

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