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Primary tumor ablation in metastatic renal cell carcinoma

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Abstract

Background: The role of primary tumor ablation (pTA) in metastatic renal cell carcinoma (mRCC) is unknown. We compared pTA-treated mRCC patients to patients who underwent no local treatment (NLT), as well as patients who underwent cytoreductive nephrectomy (CN).

Methods: Within the Surveillance, Epidemiology, and End Results database (SEER, 2004−2020), we identified mRCC patients who underwent either pTA, NLT or CN. Endpoints consisted of overall survival (OM) and other-cause mortality (OCM). Propensity score 1:1 matching (PSM), multivariable cox regression models (OM), as well as, multivariable competing risk regressions (CRR) models (OCM) were used.

Results: We identified 27,087 mRCC patients, of whom 82 (0.3%) underwent pTA, 17,266 (64%) NLT and 9,739 (36%) CN. In comparisons of pTA vs. NLT mRCC patients addressing OM, after 1:1 PSM, median survival was 19 months for pTA vs. 4 months for NLT patients (multivariable HR 0.3, 95% CI 0.22−0.47, $P < 0.001$). No statistically significant OCM differences were recorded in multivariable CRR (HR 1.13 95%, CI 0.52−2.44, $P = 0.8$). In comparisons of pTA vs. CN, after 1:1 PSM, no statistically significant differences in OM (HR 1.22, 95% CI 0.81−1.83, $P = 0.32$), as well as OCM (HR 1.4, 95% CI 0.56−3.48, $P = 0.5$) were recorded.

Conclusion: In mRCC patients, pTA is associated with significantly lower mortality compared to NLT. Interestingly, OM rates between pTA and CN mRCC patients do not exhibit statistically significant differences. This preliminary report may suggest that pTA may provide a comparable survival benefit to CN in highly selected mRCC patients.

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Abbreviations: CN, cytoreductive nephrectomy; CRR, competing risk regression; HR, hazard ratio; IQR, interquartile range; mRCC, metastatic renal cell carcinoma; NCDB, national cancer database; NLT, no local treatment; OCM, other-cause mortality; OM, overall mortality; PSM, propensity-score matching; pTA, primary tumor ablation; RCC, renal cell carcinoma; SEER, surveillance, epidemiology, and end results; SMD, standardized mean difference

1. Introduction

In the context of localized renal cell carcinoma, primary tumor ablation (pTA) has demonstrated comparable outcomes to surgical resection [1−3]. As a result, pTA is currently recommended as an alternative treatment approach in patients with small renal masses [4,5]. In the metastatic setting, cytoreductive nephrectomy (CN) represents the gold standard in patients with favorable prognosis [4]. However, there is a lack of viable alternatives for patients who are deemed unfit for surgery. The use of minimally invasive techniques in the treatment of metastatic cancer is gaining attention, offering potential alternatives where traditional surgical options may not be feasible [6]. To date, primary tumor ablation (pTA) has only received limited attention as an alternative treatment modality in metastatic renal cell carcinoma (mRCC). To the best of our knowledge, only *3* studies have addressed pTA in the context of mRCC so far [7−9]. The complexity of treating metastatic disease, where systemic therapy is often prioritized, as well as the lack of robust clinical data supporting its efficacy in this setting, have likely contributed to the limited exploration of pTA as a viable option in mRCC treatment. In consequence, the effect of primary tumor ablation (pTA) on overall survival (OS) in metastatic renal cell carcinoma (mRCC) is unknown. We postulated, that pTA may be associated with a benefit in overall survival compared to no local treatment (NLT). Moreover, we also hypothesized, that pTA may exhibit a comparable association with mortality relative to cytoreductive nephrectomy (CN). We tested both hypotheses within the Surveillance, Epidemiology, and End Results (SEER) database (2004−2020).

2. Methods

2.1. Study population

Within the SEER database (2004−2020), we identified patients ≥ 18 years old, with histologically confirmed metastatic RCC (International Classification of Disease for Oncology site code C64.9) [10]. Autopsy or death certificate only cases were excluded, in order to avoid underestimation of survival [11]. Primary tumor ablation was defined as either cryoablation (codes 13 and 23) or heat-based thermal ablation (code 15), in accordance with established methodology [12,13]. Death was defined according to the SEER mortality code as overall mortality (OM) [14]. Additionally, other-cause mortality status (OCM; death unrelated to mRCC) was also recorded for each patient [14]. Owing to the anonymously coded design of the SEER database, study-specific ethics approval was waived by the institutional review board [15].

2.2. Variables of interest

Demographic covariates consisted of age at diagnosis (years, continuously coded) and sex. Tumor characteristics consisted of primary tumor size (<3.0 cm vs. ≥3.0 cm & <6.0 cm vs. ≥6.0cm vs. unknown), primary tumor extent (organ-confined vs. non-organ-confined vs. unknown), N-stage (N0 vs. N1 vs. NX), histological subtype (clear-cell vs. others) and systemic therapy (received vs. not received) [16].

2.3. Statistical analyses

First, baseline characteristics of the cohort were analyzed. Descriptive statistics included frequencies and proportions for categorical variables. Medians and interquartile ranges (IQR) were reported for continuously coded variables. Second, to optimize the comparisons between pTA vs. NLT patients, as well as pTA vs. CN patients, we relied on 1:1 propensity-score matching (PSM), according to the nearest neighbor. Specifically, in comparisons between pTA vs. NLT, PSM was applied for age, sex, primary tumor size, primary tumor extent, histological subtype and systemic therapy exposure. In comparisons between pTA vs. CN, PSM was applied for age, sex, primary tumor size, N-stage, histological subtype and systemic therapy exposure. For all propensity-score matched variables, a threshold of <0.1 in standardized mean difference (SMD) was used. The latter is indicative of clinically insignificant differences [17]. Third, Kaplan-Meier curves were used to depict OM between pTA and NLT patients, as well as pTA and CN patients. Additionally, multivariable Cox-regression models, adjusting for age, sex, primary tumor size, primary tumor extent, N-stage, histological subtype, systemic therapy exposure and year of diagnosis, were fitted to test for differences between pTA and NLT, as well as for differences in pTA and CN mRCC patients. Furthermore, we relied on cumulative incidence plots, as well as multivariable competing risks regression (CRR) models to test for differences in OCM between the groups [18]. All tests were *2* sided, with a level of significance set at $P < 0.05$. R software environment for statistical computing and graphics (version 4.1.1; R Foundation for Statistical Computing, Vienna, Austria) was used for all analyses [19].

3. Results

3.1. Overall population

The overall population consisted of 27,097 mRCC patients. Of those, 82 (0.3%) underwent pTA, 17,266 (64%) underwent no local treatment (NLT) and 9,739 (36%) underwent CN. Compared to the NLT and CN patients, pTA-treated patients were older (70 vs. 66 vs. 61 years), more often female (45 vs. 32 vs. 29%) and were less likely to undergo systemic therapy (21 vs. 39 vs. 44%). Differences in tumor characteristics existed for primary tumor size (≥ 6.0 cm: pTA 16% vs. NLT 56% vs. CN 79%), primary tumor extent (non-organ-confined: pTA 21% vs. NLT 34% vs. CN 75%), N-stage (N1: pTA 20% vs. NLT 32% vs. CN 40%) and histological subtype (clear-cell: pTA 44% vs. NLT 29% vs. CN 62%; Table 1).

3.2. Primary tumor ablation vs. no local treatment

After 1:1 PSM, 82 pTA vs. 82 NLT mRCC patients remained. Based on SMD criteria of <0.1, no clinically meaningful differences remained between pTA and NLT patients after PSM.

3.2.1. Overall mortality

In Kaplan-Meier analyses, median survival in pTA patients was 19 months vs. 4 months in NLT patients (hazard ratio [HR] 0.39, $P < 0.0001$; Fig. 1). In multivariable Cox regression analyses, pTA independently predicted lower OM (HR 0.32, $P < 0.001$; Table 3).

3.2.2. Other-cause mortality

In cumulative incidence plots, OCM in pTA patients was 15% vs.11% for NLT patients ($P = 0.8$). In multivariable CRR models, no statistically significant differences in OCM between pTA and NLT patients were recorded ($P = 0.8$; Table 4).

3.3. Primary tumor ablation vs. cytoreductive nephrectomy

After 1:1 PSM, 82 pTA vs. 82 CN mRCC patients remained. Based on SMD criteria of <0.1, no clinically meaningful differences remained between pTA and CN patients after PSM Table 2.

3.3.1. Overall survival

In Kaplan-Meier analyses, median survival in pTA patients was 19 months vs. 27 months for CN mRCC patients ($P = 0.4$; Table 3, Fig. 2). In multivariable cox regression analyses, no statistically significant differences in OM were recorded between pTA and CN patients ($P = 0.3$; Table 3).

3.3.2. Other-cause mortality

In cumulative incidence plots, OCM in pTA patients was 11% vs.7% for CN patients ($P = 0.3$; Table 4). In

Table 1
Descriptive characteristics of 27,087 metastatic renal cell carcinoma patients, according to treatment (primary tumor ablation [pTA] vs. non local treatment [NLT] vs. cytoreductive nephrectomy [CN]), identified within the Surveillance, Epidemiology and End Results (SEER) database (2004–2020)

Characteristic	N	Overall, N = 27,087[a]	pTA, N = 82 (0.3%)[a]	NLT, N = 17266 (64%)[a]	CN, N = 9739 (36%)[a]	p-value[b]
Age	27,087	64 (57, 73)	70 (60, 78)	66 (58, 75)	61 (54, 69)	<0.001
Sex	27,087					<0.001
Female		8,398 (31%)	37 (45%)	5,518 (32%)	2,843 (29%)	
Primary tumor size	27,087					
<3		1,144 (4.2%)	26 (32%)	827 (4.8%)	291 (3.0%)	
≥3 & <6		4,461 (16%)	35 (43%)	3,025 (18%)	1,401 (14%)	
≥6		17,317 (64%)	13 (16%)	9,633 (56%)	7,671 (79%)	
Unknown		4,165 (15%)	8 (9.8%)	3,781 (22%)	376 (3.9%)	
Primary tumor extent	27,087					<0.001
T1-T2		8,303 (31%)	53 (65%)	6,221 (36%)	2,029 (21%)	
T3-T4		13,159 (49%)	17 (21%)	5,873 (34%)	7,269 (75%)	
TX		5,625 (21%)	12 (15%)	5,172 (30%)	441 (4.5%)	
Histological subtype	27,087					<0.001
clear-cell		11,043 (41%)	36 (44%)	4,929 (29%)	6,078 (62%)	
other		16,044 (59%)	46 (56%)	12,337 (71%)	3,661 (38%)	
N- stage	27,087					<0.001
N0		15,114 (56%)	57 (70%)	9,585 (56%)	5,472 (56%)	
N1		9,349 (35%)	16 (20%)	5,439 (32%)	3,894 (40%)	
NX		2,624 (9.7%)	9 (11%)	2,242 (13%)	373 (3.8%)	
Systemic therapy	27,087					<0.001
received		11,120 (41%)	17 (21%)	6,772 (39%)	4,331 (44%)	

[a] Median (IQR); n (%).
[b] Kruskal-Wallis rank sum test; Pearson's Chi-square test.

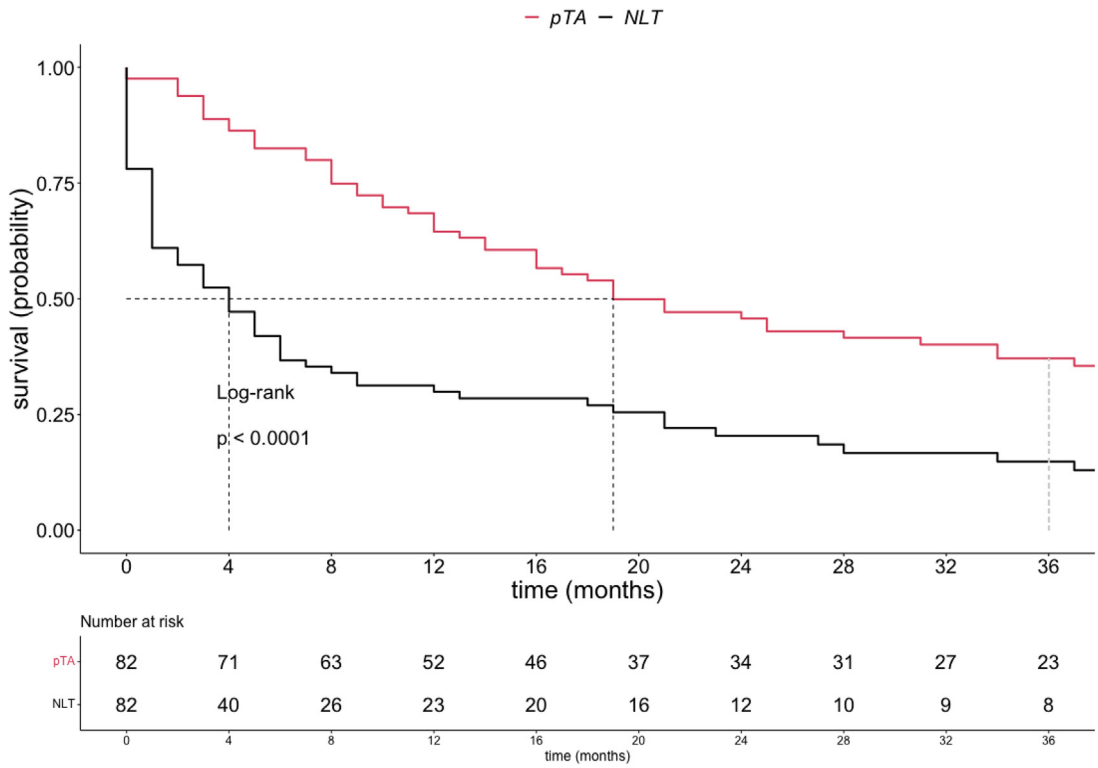

Fig. 1. Kaplan-Meier curve depicting overall survival (OS) for metastatic renal cell carcinoma (mRCC) patients who received either primary tumor ablation (pTA) or no local treatment (NLT), after 1:1 propensity score matching (PSM).

Table 2
Descriptive characteristics of 1) primary tumor ablation (pTA) vs. non-local treatment (NLT) metastatic renal cell carcinoma patients (mRCC), as well as 2) pTA vs. cytoreductive nephrectomy (CN) mRCC patients, after 1:1 propensity score matching

		1) pTA vs. NLT			2) pTA vs. CN		
Characteristic	N	pTA, N = 82 (50%)[a]	NLT, N = 82 (50%)[a]	p-value[b]	pTA, N = 82 (50%)[a]	CN, N = 82 (50%)[a]	p-value[b]
age	164	70 (60, 78)	70 (60, 77)	0.9	70 (60, 78)	71 (60, 77)	0.9
Sex	164			0.8			0.8
Female		37 (45%)	39 (48%)		37 (45%)	39 (48%)	
Primary tumor size	164			>0.9			<0.001
< 3cm		26 (32%)	28 (34%)		26 (32%)	5 (6.1%)	
≥ 3cm & < 6cm		35 (43%)	32 (39%)		35 (43%)	19 (23%)	
≥ 6cm		13 (16%)	13 (16%)		13 (16%)	50 (61%)	
Unknown		8 (9.8%)	9 (11%)		8 (9.8%)	8 (9.8%)	
Primary tumor extent	164			>0.9			>0.9
Organ-confined		53 (65%)	52 (63%)		53 (65%)	54 (66%)	
Non-organ-confined		17 (21%)	18 (22%)		17 (21%)	17 (21%)	
Unknown		12 (15%)	12 (15%)		12 (15%)	11 (13%)	
N-stage	164			0.6			>0.9
N0		57 (70%)	60 (73%)		57 (70%)	58 (71%)	
N1		16 (20%)	18 (22%)		16 (20%)	15 (18%)	
NX		9 (11%)	4 (4.9%)		9 (11%)	9 (11%)	
Histological subtype	164			0.3			0.9
clear-cell		36 (44%)	33 (40%)		36 (44%)	37 (45%)	
other		46 (56%)	49 (60%)		46 (56%)	45 (55%)	
Systemic therapy	164			0.8			0.8
received		17 (21%)	16 (20%)		17 (21%)	18 (22%)	

[a] Median (IQR); n (%).
[b] Standardized Means difference.

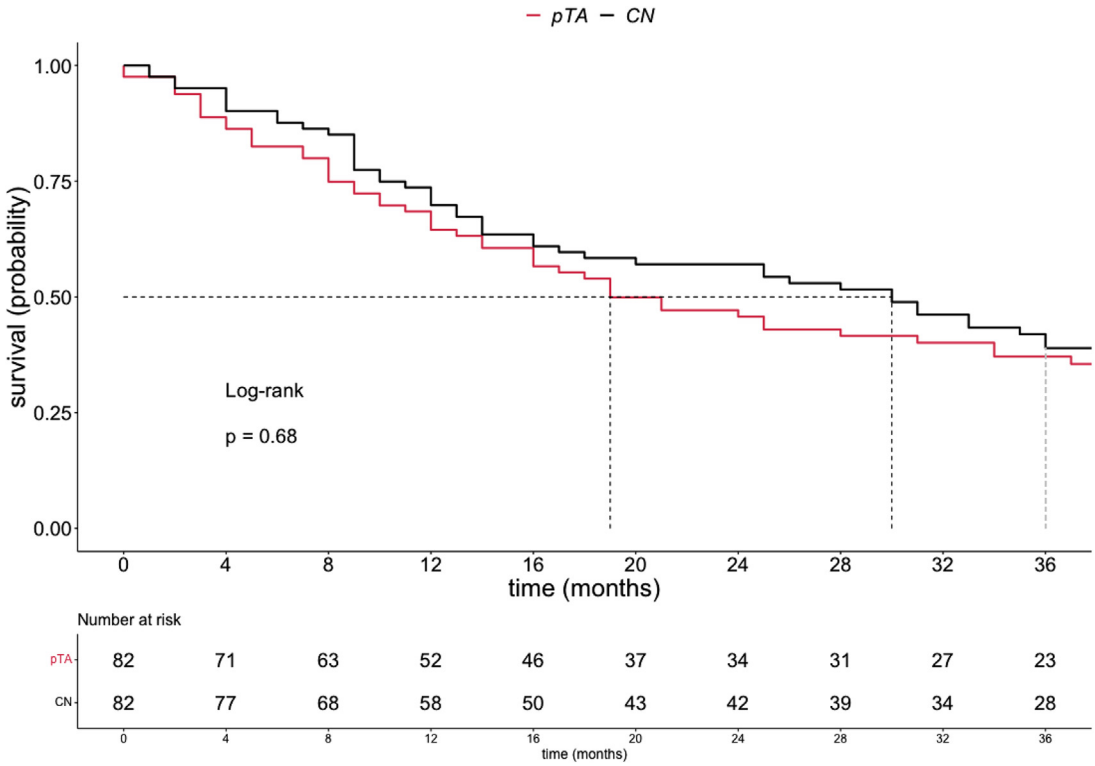

Fig. 2. Kaplan-Meier curve depicting overall survival (OS) for metastatic renal cell carcinoma (mRCC) patients who received either primary tumor ablation (pTA) or cytoreductive nephrectomy (CN), after 1:1 propensity score matching (PSM).

multivariable CRR models, no statistically significant differences in OCM were recorded between pTA and CN patients (P = 0.5; Table 4).

4. Discussion

It is unknown, whether in mRCC, primary tumor ablation (pTA) is associated with a survival benefit compared to patients who underwent no local treatment (NLT). To address this knowledge gap, we compared OM rates of pTA-treated mRCC patients to those who underwent NLT. Additionally, we compared OM rates of pTA patients to those of CN-treated mRCC patients. We hypothesised that OM is lower in pTA-treated patients relative to their counterparts, who underwent NLT. We also hypothesized that OM is not different in pTA patients relative to their CN-

Table 3
Cox regression analyses predicting overall mortality (OM) in metastatic renal cell carcinoma after 1:1 propensity score matching, comparing primary tumor ablation (pTA) vs. non local treatment (NLT); as well as comparing primary tumor ablation vs. cytoreductive nephrectomy (CN)

	Primary tumor ablation vs. non local treatment		Primary tumor ablation vs. cytoreductive nephrectomy	
	univariable	multivariable[a]	univariable	multivariable[a]
OM	**HR 0.39 (0.27−0.56); $P < 0.001$**	**HR 0.32 (0.22−0.47); $P < 0.001$**	HR 1.17(0.82−1.69); P = 0.4	HR 1.22 (0.81−1.83) P = 0.3

[a] Covariates in multivariable model: age, sex, primary tumor size, primary tumor extent, N-stage, histological subtype, systemic therapy, year of diagnosis.

Table 4
Competing risks regression analyses predicting other-cause mortality (OCM), adjusting for cancer-specific mortality (CSM), after 1:1 propensity score matching, comparing primary tumor ablation (pTA) vs. non local treatment (NLT); as well as comparing pTA vs. cytoreductive nephrectomy (CN)

	Primary tumor ablation vs. non local treatment		Primary tumor ablation vs. cytoreductive nephrectomy	
	univariable	multivariable[a]	univariable	multivariable[a]
OCM	HR 1.11 (0.54−2.27); P = 0.8	HR 1.13 (0.52−2.44); P = 0.8	HR 1.43(0.69−2.96); P = 0.3	HR 1.40 (0.56−3.48) P = 0.5

[a] Covariates in multivariable model: age, sex, primary tumor size, primary tumor extent, N-stage, histological subtype, systemic therapy, year of diagnosis.

treated counterparts. To address potential bias that may originate from differences in OCM rates, additional comparisons addressed that endpoint (OCM). We relied on the Surveillance, Epidemiology, and End Results (SEER) database (2004−2020) to test these hypotheses. Our analyses resulted in several noteworthy observations.

First, of 27,097 mRCC patients identified within SEER between 2004−2020, only 82 patients underwent pTA. This observation indicates the extreme rarity of pTA in the setting of mRCC. Indeed, available evidence supporting the use of pTA in mRCC is scarce. To the best of our knowledge, only *3* studies addressed pTA in the context of mRCC [7−9]. Moreover, all of these studies were based on even smaller cohorts of pTA patients compared to the number of patients included in the current study. For example, Liu et al. compared 67 pTA-treated mRCC patients who also received sorafenib to patients who exclusively received sorafenib [8]. Similarly, Gu et al. [9] compared 65 pTA-treated mRCC patients who also received sunitinib to patients who exclusively received sunitinib. The extremely low numbers of pTA-treated patients in the context of mRCC recorded in the current study, as well as in all previous studies, strongly suggests the need for multi-institutional studies or population-based data repositories such as SEER or National Cancer Database (NCDB), in future analyses.

Second, we recorded important differences in baseline characteristics between pTA-, NLT- and CN-treated mRCC patients (Table 1). Specifically, pTA-treated patients were oldest (median age 70) followed by NLT- (66 years) and CN-(61 years) treated patients. In addition, they harbored significantly smaller primary tumors (<3.0 cm: pTA 32% vs. NLT 5% vs. CN 3%). Furthermore, pTA patients were least likely to undergo systemic therapy (pTA: 21% vs. NLT: 39% vs. CN 44%). Based on the presence of these important differences, we relied on multivariable adjustment to maximally reduce, or ideally eliminate, bias that may originate from these patient characteristics. Multivariable adjustment for potential patient and tumor related biases has not been applied in previous studies that addressed the association between pTA and various cancer-control outcomes in mRCC [7−9]. Additionally, we also addressed potential differences in OCM that may distinguish pTA patients from their NLT counterparts, as well as pTA patients from their CN counterparts. Here we relied on multivariable CRR modeling to maximally reduce potential bias. Previous reports have also not addressed this potentially important source of bias [7−9].

Third, in addition to multivariable adjustment, we also relied on PSM to simulate methodology used in prospective, randomized trials [20]. PSM relied on age, sex, primary tumor size, primary tumor extent, histological subtype and systemic therapy exposure in comparisons of pTA to NLT mRCC patients. Conversely, in comparisons of pTA to CN mRCC patients, PSM was applied to age, sex, primary tumor size, N-stage, histological subtype and systemic therapy exposure. Slight modifications in PSM criteria were necessary due to the limited sample size of the groups. In consequence, the current study provides the most structed, formal and complete adjustment for potential differences between pTA and other patients.

Fourth, in comparisons between pTA vs. NLT mRCC patients, after PSM, using OM as the endpoint, we recorded a median survival of 19 months in pTA patients vs. 4 months in NLT patients (HR 0.39, $P < 0.001$). After extensive multivariable adjustment, pTA independently predicted lower OM (HR 0.32, $P < 0.001$). These observations suggest a survival advantage in pTA patients relative to their NLT counterparts. Since we are the first to report population-based results of pTA use in mRCC patients, our findings cannot be directly compared to other studies. However, our findings may be interpreted in the light of existing studies that compared pTA to NLT in smaller patient subsets [7−9]. Of those, only *1* study addressed North-American patients treated with pTA (n=15) vs. no pTA (n=14) in tremelimumab-treated patients [7]. Unfortunately, the primary endpoint of the study was safety of the treatment combination, and therefore this study cannot be compared with the current study. Conversely, the *2* remaining studies relied on Chinese patient-populations [8,9]. Specifically, Liu et al. compared pTA vs. NLT in sorafenib-treated mRCC patients unsuitable for surgical treatment [8]. In their analyses, the median survival was 36 vs. 29 months for pTA vs. NLT patients, which resulted in a univariable HR of 0.58 ($P < 0.05$). Similar to this study, Gu et al. compared pTA vs. NLT in sunitinib-treated mRCC patients [9]. Here, the median survival was 20 vs. 14 months for pTA vs. NLT patients ($P < 0.001$), respectively. Unfortunately, the absolute median survival values in these *2* Chinese cohorts are very different from the ones recorded in the current North-American study. Similarly, the relative rates expressed as hazard ratios are also of different magnitude. Taken together, the current study validates the benefit of pTA on the survival of mRCC patients in a north-American population. However, the previous reports originating from populations other than North-Americans, cannot be truly compared regarding absolute or relative survival benefits since these metrics drastically differ from metrics recorded in North-American cohorts.

Fifth, we also compared OM between pTA- vs. CN-treated mRCC patients, based on the hypothesis that pTA may be associated with similar OM as CN. After PSM, the median survival of pTA-treated mRCC patients was 19 months vs. 27 months for CN-treated mRCC patients ($P = 0.4$). However, after additional multivariable adjustment, no statistically significant differences in OM between pTA- and CN-treated mRCC patients ($P = 0.3$) were recorded. Taken together, this observation suggests, that in highly selected mRCC patients treated with pTA, survival may be comparable to that of mRCC patients treated with CN. However, such a comparison is fraught with limitations due to the scarcity and highly selective nature of mRCC patients who underwent pTA. Future studies, relying on similar

large-scale databases (e.g., NCDB) should ideally validate or refute the current study's findings.

In addition to direct comparisons of OM between pTA vs. NLT, as well as pTA vs. CN, we also addressed OCM differences in both comparisons. In pTA vs. NLT patients, no differences in OCM were recorded ($P = 0.8$). Similarly, in pTA vs. CN comparisons, also no differences in OCM were recorded ($P = 0.5$). Lack of statistically significant differences in OCM in pTA vs. NLT comparison indicates that the recorded survival benefit in pTA patients is neither driven by OCM, nor is it confounded by significant OCM differences. Similarly, lack of statistically significant OM differences in pTA vs. CN mRCC patients also did not result from confounding due to the effect of OCM. This additional adjustment adds to the robustness of the observations in favor of the OM advantage between pTA and NLT as well as, in the comparison between pTA vs. CN where no statistically significant OM difference was recorded. Unfortunately, these results cannot be compared to any previous study, since no such study exists.

Taken together, the current study represents the largest and most comprehensive study examining OM according to pTA vs. NLT in mRCC patients. Similarly, our study also shows no significant OM differences when pTA is compared to CN. This observation suggests a potential survival benefit of comparable magnitude to CN in highly selected mRCC patients who underwent pTA. Both observations warrant validation in future large-scale population based such as the National Cancer Database (NCDB) or other multi-institutional studies.

Despite the interesting findings of this study, several limitations need to be addressed. First and foremost, the retrospective nature of these analyses inevitably leads to a selection bias. This limitation is shared with all other non-prospective, nonrandomized studies. In order to minimize selection bias and account for potential confounding factors, we employed several statistical tools, including PSM and multivariable CRR models. Nonetheless, despite this statistical effort, we cannot exclude residual bias from confounders that were not recorded in the SEER database. Second, this study is limited by its relatively small sample-size of pTA patients. Despite being the largest study to date to address this topic, this limitation needs to be taken into consideration in the interpretation of our results. Third, given the relatively long time span of the study, pTA techniques may have changed or evolved towards more minimally invasive approaches. Moreover, the landscape of systemic treatment for mRCC has changed significantly during the time span covered by this study, most notably with the introduction of immunotherapy. These changes in treatment may have contributed to outcome variations in mRCC patients. To address this, all our multivariable models were adjusted for year of diagnosis. However, future prospective studies incorporating more contemporary systemic treatments will be crucial to assess their interaction with pTA and better understand the evolving treatment landscape for mRCC.

5. Conclusion

In mRCC patients, pTA is associated with significantly lower mortality compared to NLT. Interestingly, OM rates between pTA and CN mRCC patients do not exhibit statistically significant differences. This preliminary report may suggest that pTA may provide a comparable survival benefit to CN in highly selected mRCC patients. However, further studies are needed to validate these findings and better understand the potential role of pTA in the treatment of mRCC.

Availability of data and materials

All data generated for this analysis were from the Surveillance, Epidemiology, and End Results Research Plus (SEER) database. The code for the analyses will be made available upon request.

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Declaration of competing interest

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CRediT authorship contribution statement

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