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Differences in other-cause mortality in metastatic renal cell carcinoma according to partial vs. radical nephrectomy and age: A propensity score matched study

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A R T I C L E I N F O

Keywords:
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RCC

A B S T R A C T

Introduction: It is unknown whether the benefit from partial nephrectomy regarding lower other-cause mortality is applicable to older patients with metastatic renal cell carcinoma.
Materials and methods: Using Surveillance Epidemiology and End Results database, patients with metastatic renal cell carcinoma, undergoing partial or radical nephrectomy, were stratified according to age (<60, 60–69, and ≥70 years). After propensity score matching, Kaplan-Meier survival analyses and multivariable Cox regression models were used.
Results: Of 2,390 patients with metastatic renal cell carcinoma, 885 (37%) were aged <60 years, and 90 (10%) underwent partial nephrectomy; 824 (34%) were aged 60–69 years, and 61 (7%) underwent partial nephrectomy; and 681 (29%) were aged ≥70 years, and 64 (9%) underwent partial nephrectomy. After propensity score matching, in patients aged <60 years, partial nephrectomy was associated with lower other-cause mortality (hazard ratio 0.22; $p = 0.02$); in patients aged 60–69 years, partial nephrectomy was associated with lower other-cause mortality (hazard ratio 0.38; $p = 0.03$); but not in patients aged ≥70 years.
Discussion: In metastatic renal cell carcinoma, partial nephrectomy is associated with lower other-cause mortality in patients aged <60 years and in patients aged 60–69 years, but not in patients aged ≥70 years. In consequence, consideration of partial nephrectomy might be of great value in younger metastatic renal cell carcinoma patients.

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1. Introduction

The oncological efficacy, as well as the safety of partial nephrectomy have been demonstrated in non-metastatic renal cell carcinoma (RCC) in historical [1–4] and contemporary studies [5,6]. Likewise, partial nephrectomy can be safely performed in patients with metastatic renal cell carcinoma (mRCC) [7–9]. Furthermore, patients treated with partial nephrectomy are less likely to die of non-cancer-related causes compared to patients treated with radical nephrectomy in the localized [10–12] and the metastatic RCC setting [9].

However, it is not known whether the other-cause mortality (OCM) benefit in mRCC is operational across all ages. Based on this knowledge gap, we hypothesized that the association between partial nephrectomy and lower OCM is operational across all age categories and tested this hypothesis relying on three specific age categories, namely <60, 60 to 69, and ≥70 years, in a contemporary population-based cohort of patients with mRCC and a primary tumor size of 7 cm or less, who underwent partial or radical nephrectomy in the United States.

2. Materials and Methods

2.1. Data source and study population

Using the Surveillance, Epidemiology, and End Results (SEER) database, we identified patients aged ≥18 years and diagnosed between 2004 and 2020 with histologically confirmed mRCC (International Classification of Disease for Oncology [ICD-10] site code C64). All autopsy- or death certificate- only cases as well as cases with missing follow-up or unknown cause of death were excluded. Only patients who underwent partial nephrectomy (Surgery site code 30) or radical nephrectomy (Surgery site codes 50, 70, and 80) were included in the study population. Patients included in the study harbored primary tumor size less or equal than 7 cm, as larger tumors seem to pose significant challenges for resection via partial nephrectomy from a clinical point of view. Additionally, partial nephrectomy also appears technically difficult for tumors invading beyond Gerota fascia. Thus, we also excluded these tumors from the study cohort.

2.2. Definition of variables for analyses

Patients included in the study population were stratified according to age at diagnosis into three age categories (<60, 60–69, and ≥70 years), according to tertials. OCM, the primary end point of the study, was defined as death due to any cause except for mortality from RCC (cancer-specific mortality) according to SEER mortality code. Covariates consisted of age at diagnosis (years, continuously coded), tumor size (cm, continuously coded), sex (male vs. female), systemic therapy (yes vs. no), perinephric fat invasion (yes vs. no), lymph node invasion (yes vs. no vs. unknown), grade (low-grade vs. high grade vs. unknown), and histology (clear cell vs. non-clear cell).

2.3. Statistical analyses

First, baseline characteristics of each age category were tabulated. Descriptive statistics included medians and interquartile ranges (IQR) for continuously coded variables and frequencies and proportions for categorical variables. Second, propensity score matching (ratio 1:2) according to the nearest neighbor between partial and radical nephrectomy was applied for tumor size, sex, perinephric fat invasion, and lymph node invasion separately within each age category (<60, 60–69, and ≥70 years) to maximally reduce the effect of bias and confounding [13]. Third, Kaplan-Meier survival analyses were separately performed within each age category after propensity score matching. Kaplan-Meier plots were used to display rates of OCM-free survival according to the type of surgery (partial vs. radical nephrectomy) for each age category according to previously used methodology [11,14–16]. Since all patients have metastatic stage and thus will experience cancer-specific mortality at a very high rate regardless of the surgical approach, we assumed that death due to cancer-specific mortality is equivalent to non-informative censoring and that all actual censored patients would have died of cancer-specific mortality. Subsequently, univariable, and multivariable Cox regression models were fitted for OCM prediction. Hazard ratios (HR) depicted the probability of OCM in partial vs. radical nephrectomy patients. Adjustment variables consisted of age at diagnosis, systemic therapy, grade, and histology.

All analyses and their reporting followed the SEER reporting

Table 1
Descriptive characteristics of metastatic renal cell carcinoma (mRCC) patients, according to the type of surgery (partial nephrectomy vs. radical nephrectomy) within the three age categories (<60, 60–69, and ≥70 years) prior to propensity score matching.

	<60 years			60–69 years			≥70 years		
Characteristic	Partial nephrectomy, n = 90 (10%)[a]	Radical nephrectomy, n = 795 (90%)[a]	p-value[b]	Partial nephrectomy, n = 61 (7%)[a]	Radical nephrectomy, n = 763 (93%)[a]	p-value[b]	Partial nephrectomy, n = 64 (9%)[a]	Radical nephrectomy, n = 617 (91%)[a]	p-value[b]
Age (in years)	51 (47, 56)	53 (48, 56)	0.3	65 (62, 67)	65 (62, 67)	1.0	75 (73, 78)	75 (72, 79)	0.9
Tumor size (in cm)	3.8 (2.6, 5.1)	5.5 (4.3, 6.5)	**<0.001**	4.3 (3.0, 5.0)	5.5 (4.2, 6.5)	**<0.001**	4.0 (3.0, 5.0)	5.6 (4.4, 6.5)	**<0.001**
Male sex	61 (68%)	582 (73%)	0.3	43 (70%)	538 (71%)	0.9	42 (66%)	397 (64%)	0.8
Systemic therapy	23 (26%)	353 (44%)	**<0.001**	12 (20%)	295 (39%)	**0.003**	14 (22%)	214 (35%)	**0.04**
Perinephric fat invasion	19 (21%)	444 (56%)	**<0.001**	13 (21%)	461 (60%)	**<0.001**	21 (33%)	378 (61%)	**<0.001**
Lymph node invasion			**<0.001**			**0.001**			**0.01**
Yes	10 (11%)	270 (34%)		7 (11%)	228 (30%)		6 (9%)	151 (24%)	
No	79 (88%)	498 (63%)		50 (82%)	516 (68%)		56 (88%)	443 (72%)	
Unknown	1 (1%)	27 (3%)		4 (7%)	19 (2%)		2 (3%)	23 (4%)	
Grade			**<0.001**			0.3			**0.03**
Low grade (G1-G2)	47 (52%)	207 (26%)		24 (39%)	227 (30%)		28 (44%)	191 (31%)	
High grade (G3-G4)	39 (43%)	507 (64%)		34 (56%)	474 (62%)		28 (44%)	374 (61%)	
Unknown	4 (5%)	81 (10%)		3 (5%)	62 (8%)		8 (12%)	52 (8%)	
Clear cell	56 (62%)	460 (58%)	0.4	41 (67%)	500 (66%)	0.8	33 (52%)	384 (62%)	0.1

[a] Median (Interquartile range [IQR]); n (%).
[b] Wilcoxon rank sum test; Fisher's exact test; Pearson's Chi-square test.

Table 2
Descriptive characteristics of metastatic renal cell carcinoma (mRCC) patients, according to the type of surgery (partial nephrectomy vs. radical nephrectomy) within the three age categories (<60, 60–69, and ≥70 years) after propensity score matching (ratio 1:2).

	<60 years			60–69 years			≥70 years		
Characteristic	Partial nephrectomy, n = 89 (33%)[a]	Radical nephrectomy, n = 178 (67%)[a]	Absolute standardized mean difference	Partial nephrectomy, n = 59 (33%)[a]	Radical nephrectomy, n = 118 (67%)[a]	Absolute standardized mean difference	Partial nephrectomy, n = 64 (33%)[a]	Radical nephrectomy, n = 128 (67%)[a]	Absolute standardized mean difference
Age (in years)	51 (47, 56)	53 (48, 55)	–[b]	65 (63, 67)	65 (62, 67)	–[b]	75 (73, 78)	75 (72, 80)	–[b]
Tumor size (in cm)	3.8 (2.6, 5.1)	4.3 (3.2, 5.1)	0.1	4.3 (3.0, 5.0)	4.0 (2.8, 5.0)	0.04	4.0 (3.0, 5.0)	4.0 (3.0, 5.0)	0.04
Male sex	61 (69%)	131 (74%)	0.1	42 (71%)	83 (70%)	0.02	42 (66%)	80 (63%)	0.07
Systemic therapy	23 (26%)	66 (37%)	–[b]	12 (20%)	38 (32%)	–[b]	14 (22%)	36 (28%)	–[b]
Perinephric fat invasion	19 (21%)	49 (28%)	0.1	12 (20%)	26 (22%)	0.04	21 (33%)	49 (38%)	0.1
Lymph node invasion									
Yes	10 (11%)	13 (7%)	0.1	6 (10%)	10 (9%)	0.06	6 (9%)	11 (9%)	0.03
No	78 (88%)	162 (91%)	0.1	49 (83%)	102 (86%)	0.09	56 (88%)	115 (90%)	0.07
Unknown	1 (1%)	3 (2%)	0.05	4 (7%)	6 (5%)	0.07	2 (3%)	2 (1%)	0.09
Grade									
Low grade (G1-G2)	46 (52%)	72 (40%)	–[b]	23 (39%)	55 (47%)	–[b]	28 (44%)	50 (39%)	–[b]
High grade (G3-G4)	39 (44%)	89 (50%)	–[b]	34 (58%)	53 (45%)	–[b]	28 (44%)	69 (54%)	–[b]
Unknown	4 (4%)	17 (10%)	–[b]	2 (3%)	10 (8%)	–[b]	8 (12%)	9 (7%)	–[b]
Clear cell	55 (62%)	107 (60%)	–[b]	41 (69%)	78 (66%)	–[b]	33 (52%)	78 (61%)	–[b]

[a] Median (Interquartile range [IQR]); n (%).
[b] Variable not included in propensity score matching.

guidelines. Due to the anonymously coded design of the SEER database, study-specific Institutional Review Board ethics approval was not required. R software environment was used for statistical computing and graphics (R version 4.2.2; R Foundation for Statistical Computing, Vienna, Austria). All tests were two sided, with a level of significance set at $p < 0.05$.

2.4. Availability of data and materials

The dataset supporting the conclusions of this article is available in the SEER Incidence Data, 1975–2020 repository, https://seer.cancer.gov/data/.

3. Results

3.1. Descriptive characteristics

Within the SEER database, we identified 2,390 mRCC patients with a primary tumor size of 7 cm or less who underwent partial or radical nephrectomy between 2004 and 2020 (Table 1). Of those, 885 (37%) were aged <60 years and 90 (10%) underwent partial nephrectomy; 824 (34%) were aged 60–69 years and 61 (7%) underwent partial nephrectomy; and 681 (29%) were aged ≥70 years and 64 (9%) underwent partial nephrectomy.

In general, partial nephrectomy patients harbored smaller tumors (tumor size median (IQR): 3.8 (2.6–5.1), 4.3 (3.0–5.0) and 4.0 (3.0–5.0) cm vs. 5.5 (4.3–6.5), 5.5 (4.2–6.5) and 5.6 (4.4–6.5) cm; each $p < 0.001$), lower rates of perinephric fat invasion (21, 21, and 33% vs. 56, 60 ,and 61%; each $p < 0.001$), lower rates of lymph node invasion (11, 11, and 9% vs. 34, 30, and 24%; $p < 0.001$, $p = 0.001$, and $p = 0.01$), and lower rates of high-grade tumor (43, 56, and 44 % vs. 64, 62, and 61%; $p < 0.001$, $p = 0.3$ and $p = 0.03$) compared to radical nephrectomy patients.

After propensity score matching (partial vs. radical nephrectomy), no statistically significant residual differences remained in age, tumor size, sex, systemic therapy rate, perinephric fat invasion rate, lymph node invasion rate, grade, and histology between the two respective groups within each age category (Table 2).

3.2. Other-cause mortality rates according to partial vs. radical nephrectomy

After propensity score matching, in patients aged <60 years, five-year OCM-free survival was 100 after partial nephrectomy vs. 87% after radical nephrectomy (Δ 13%; $p = 0.002$; Fig. 1A); in patients aged 60–69 years, five-year OCM-free survival was 94 after partial nephrectomy vs. 83% after radical nephrectomy (Δ 11%; $p = 0.04$; Fig. 1B); and in patients aged ≥70 years, five-year OCM-free survival was 75 after partial nephrectomy vs. 69% after radical nephrectomy ($p = 0.5$; Fig. 1C).

In multivariable Cox regression models, in patients aged <60 years, partial nephrectomy was associated with lower OCM (HR 0.22; 95% confidence interval [CI]: 0.07–0.75; $p = 0.02$; Table 3); in patients aged 60–69 years, partial nephrectomy was associated with lower OCM (HR 0.38; 95% CI: 0.16–0.89; $p = 0.03$); but not in patients aged ≥70 years (HR 0.92; 95% CI: 0.50–1.71; $p = 0.8$).

4. Discussion

Partial nephrectomy is associated with the same cancer outcomes as radical nephrectomy in both localized [1–5,17], as well as metastatic RCC [7,8,18]. The benefit of partial nephrectomy consists of lower OCM relative to radical nephrectomy. This observation was made in patients with localized [4,6,10–12], as well as metastatic RCC [9,18]. However, it has not been studied whether the benefit of partial nephrectomy regarding lower OCM is applicable in mRCC across all age categories. Based on this knowledge gab, we tested this hypothesis on the most contemporary population-based cohort of the SEER database and made several noteworthy observations.

First, the rate of partial nephrectomy in mRCC was 9% in the current study. This rate is higher than in previous historical series. In the most historical report, the rate of partial nephrectomy was only 2% [7] and in subsequent less historical reports, this rate went up to 4% [9,19]. Finally, in the previously reported series of partial nephrectomy-treated

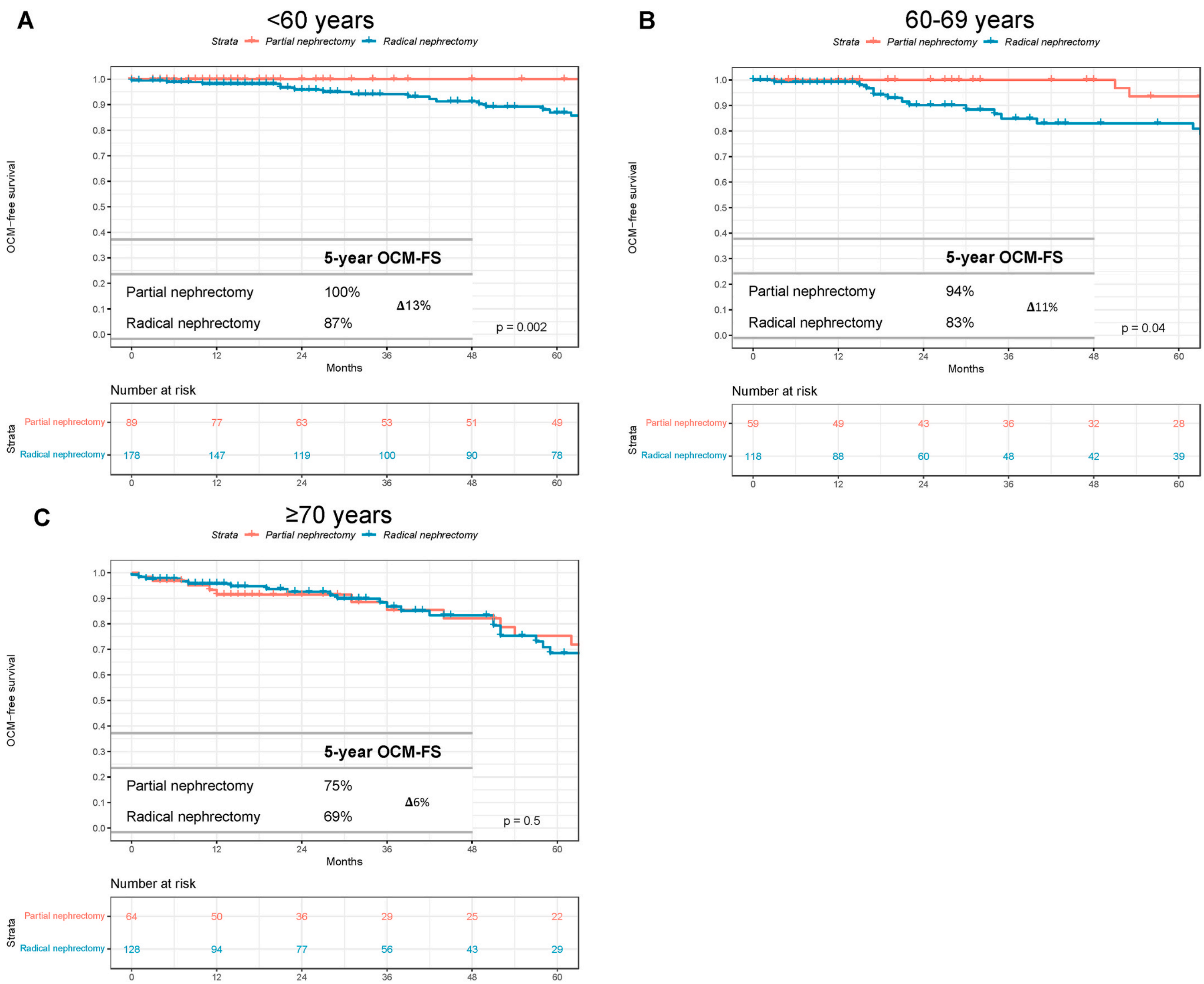

Fig. 1. Kaplan-Meier survival analyses for other-cause mortality (OCM)-free survival (FS) according to the type of surgery (partial nephrectomy vs. radical nephrectomy) after propensity score matching within the three age categories (A: <60 years; B: 60–69 years; and C ≥70 years).

Table 3
Separate multivariable Cox regression models testing for other-cause mortality (OCM) according to the type of surgery (partial nephrectomy vs. radical nephrectomy) adjusted for age, systemic therapy, grade, and histology within the three age categories (<60, 60–69, and ≥70 years).

	<60 years		60–69 years		≥70 years	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Partial nephrectomy vs. <!–Soft-enter replaced as Radical nephrectomy	**0.22** (0.07 0.75)	**0.02**	**0.38** (0.16, 0.89)	**0.03**	0.92 (0.50, 1.71)	0.8

Abbreviations: CI = confidence interval; HR = hazard ratio.

mRCC patients the rate increased to 8% [18]. These observations indicate that the use of partial nephrectomy is gradually increasing in the urologic community within the United States. This observation validates the increasing importance of partial nephrectomy in the surgical management of mRCC. It also validates the need for the current study to confirm or reject its benefit across all age categories.

Second, despite previous observations by Baillargeon-Gagné, identifying age as an independent predictor for receiving an partial nephrectomy [1], the rates of partial nephrectomy did not differ according to the age categories of our contemporary study population (<60 years: 10%, 60–69 years: 7%, ≥70 years: 9%; $p = 0.1$). This observation indicates that the use of partial nephrectomy is not age dependent. Unfortunately, no previous study tested for rates of partial nephrectomy in mRCC patients according to age. In consequence, these rates cannot be directly compared with any previous study.

Third, we identified important differences in baseline characteristics between partial vs. radical nephrectomy mRCC patients. In general, partial nephrectomy patients harbored smaller tumors (tumor size median: 3.8, 4.3, and 4.0 cm vs. 5.5, 5.5, and 5.6 cm; each $p < 0.001$), lower rates of perinephric fat invasion (21, 21, and 33% vs. 56, 60, and 61%; each $p < 0.001$), and lower rates of lymph node invasion (11, 11, and 9% vs. 34, 30, and 24%; $p < 0.001$, $p = 0.001$, and $p = 0.01$), compared to radical nephrectomy patients. Based on these differences, it is imperative to apply propensity score matching (partial vs. radical nephrectomy) to maximally reduce or ideally eliminate uncontrolled bias or confounding due to patient and tumor characteristics' differences, as was done in the current study. Indeed, after propensity score matching, no meaningful residual differences remained between partial and radical nephrectomy mRCC patients.

Fourth, we tested for OCM differences between partial and radical nephrectomy mRCC patients according to age categories as defined and made important observations. In patients aged <60 years and in patients aged 60–69 years, partial nephrectomy was associated with lower absolute OCM rates (<60 years: 100 vs. 87%; $p = 0.002$; 60–69 years: 94 vs. 83%; $p = 0.04$). Moreover, in these two age categories, partial nephrectomy was an independent predictor of lower OCM (<60 years: HR 0.22; $p = 0.02$; and 60–69 years: HR 0.38; $p = 0.03$). Conversely, in patients aged ≥70 years, partial nephrectomy was not associated with either a lower absolute or a lower relative OCM rate compared to radical nephrectomy. Taken together, these observations indicate that partial nephrectomy should be strongly considered in patients up to 69 years of age. Conversely, partial nephrectomy may not warrant consideration over and beyond radical nephrectomy than OCM is considered as an end point in older patients. To the best of our knowledge, we are the first to report on age stratified analyses of the association between partial nephrectomy and OCM in mRCC. In consequence, our findings cannot be directly compared with any previous studies.

Despite its novelty, the present study has limitations. First, due to its retrospective nature, a potential for residual selection biases, despite strict and systematic adjustment for biases and confounders, remained. This limitation is applicable to all retrospective studies [1–3,9–12,18–20]. It is unlikely, that a prospective trial testing partial nephrectomy relative to radical nephrectomy in mRCC will ever be designed and completed. Second, despite the large and exhaustive size of the SEER database, mRCC patient numbers treated with either partial or radical nephrectomy are relatively low. The numbers of partial nephrectomy patients are expectedly much lower than those of radical nephrectomy-treated individuals. Despite small sample size, the OCM rate associated with partial nephrectomy was highly statistically significant in patients aged less than 60 years, as well as in those aged 60–69 years. However, the benefit could not be identified in the older counterparts aged 70 years or higher. This observation may be interpreted as an internal validation for presence of a factorial association between partial nephrectomy and lower OCM in younger patients, but no such association in older patients. Third, the SEER database does not allow us to stratify between open versus minimally invasive partial nephrectomy, as well as radical nephrectomy. Moreover, the SEER database does not provide any information regarding perioperative complications that may have influenced OCM. Additional variables, such as Heng risk criteria, as well as the individual variables underlying the Heng classification are also unavailable in the SEER database and cannot be adjusted for in the analyses. This limitation is shared with all previous analyses examining nephrectomy in mRCC, except for the International Metastatic RCC Database Consortium (IMDC) analysis [21], where the Heng risk criteria were developed from and established.

5. Conclusions

In mRCC, partial nephrectomy is associated with lower OCM in patients aged <60 years and in patients aged 60–69 years, but not in patients aged ≥70 years. In consequence, consideration of partial nephrectomy might be of great value in younger mRCC patients.

Ethical Approval and Consent to participate

All analyses and their reporting followed the SEER reporting guidelines. Due to the anonymously coded design of the SEER database, study-specific Institutional Review Board ethics approval was not required.

Consent for publication

All authors gave their consent for publication.

Availability of data and materials

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

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CRediT authorship contribution statement

Carolin Siech: Writing – original draft, Methodology, Conceptualization. **Reha-Baris Incesu:** Methodology, Conceptualization. **Simone Morra:** Methodology, Conceptualization. **Lukas Scheipner:** Methodology, Conceptualization. **Andrea Baudo:** Writing – review & editing, Validation. **Letizia Maria Ippolita Jannello:** Writing – review & editing, Validation. **Mario de Angelis:** Writing – review & editing, Validation. **Jordan A. Goyal:** Writing – review & editing, Data curation. **Zhe Tian:** Writing – review & editing, Data curation. **Fred Saad:** Writing – review & editing. **Shahrokh F. Shariat:** Writing – review & editing. **Derya Tilki:** Writing – review & editing. **Nicola Longo:** Writing – review & editing. **Luca Carmignani:** Writing – review & editing. **Ottavio de Cobelli:** Writing – review & editing. **Sascha Ahyai:** Writing – review & editing. **Alberto Briganti:** Writing – review & editing. **Philipp Mandel:** Writing – review & editing. **Luis A. Kluth:** Writing – review & editing. **Felix K.H. Chun:** Supervision. **Pierre I. Karakiewicz:** Writing – review & editing, Supervision, Conceptualization.

Declaration of competing interest

The authors declare no conflicts of interest.

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