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ORIGINAL ARTICLE

Comparison of survival outcomes in patients with metastatic papillary vs. clear-cell renal cell carcinoma: a propensity-score analysis

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Abstract

Background To compare survival outcomes of metastatic patients harbouring either papillary (pRCC) or clear-cell (ccRCC) renal cell carcinoma in overall population and according to treatment modality.

Methods Within the Surveillance, Epidemiology and End Results database (2006–2015), we identified 6800 patients (585 papillary and 6215 clear-cell) with metastatic RCC. Propensity-score (PS) matching, Kaplan–Meier plots and multivariable Cox-regression models (CRMs) were used.

Results Overall, 585 (8.6%) patients harboured pRCC. Rates of nodal metastases were higher in patients with pRCC (49.7 vs. 23.3%; $p < 0.001$). Median overall survival (OS) was 13 vs. 18 months for pRCC vs. ccRCC patients. After multivariable adjustments, no difference in OS was recorded. Furthermore, after propensity-score matching, virtually the same results were recorded. Median OS of pRCC vs. ccRCC was 8 vs. 4 months for no treatment (NT), 11 vs. 12 months for targeted therapy alone (TT), 17 vs. 35 months for cytoreductive nephrectomy alone (CN) and 18 vs. 25 months for combination of CN with TT.

Conclusions Metastatic pRCC patients exhibit poor survival, regardless of treatment received. Moreover, pRCC patients are more likely to present nodal metastases, compared to ccRCC patients, as demonstrated by twofold higher rates of lymph node invasion at diagnosis. These observations indicate that papillary variant represents more prognostically unfavorable tumor histology, in the context of metastatic RCC.

Keywords Combination therapy · Cytoreductive nephrectomy · Histology · Kidney cancer · SEER database · Targeted therapy

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Introduction

Renal cell carcinoma (RCC) histological subtypes consist of clear-cell, papillary, chromophobe, collecting duct and unclassified RCC subtypes, according to the International Union Against Cancer (UICC) and the American Joint Committee on Cancer (AJCC) recommendations [1]. Despite abundant literature on non-clear cell histology in non-metastatic RCC, the natural history of non-clear cell metastatic RCC is less well documented. Recently, Patel et al. [2] demonstrated stable rate of metastatic disease at diagnosis in RCC patients over time, but improved overall survival. To the best of our knowledge, only few small retrospective studies showing conflicting results [3–8] tested for survival differences between ccRCC and the most prevalent non clear cell variant, namely papillary, both in localized than in metastatic RCC patients [9]. Based on this unmet need, we analyzed the differences on overall survival (OS) in patients with metastatic renal cell carcinoma, harboring either the papillary or the clear-cell variant. Moreover, we also hypothesized that survival differences may also exist between papillary RCC and clear-cell RCC patients, regardless of treatment received [10, 11].

Materials and methods

Study population

Within the Surveillance, Epidemiology and End Results (SEER) database, we focused on patients older than 18 years with metastatic either clear-cell or papillary renal cell carcinoma (International Classification of Disease for Oncology C64.9), between 2006 and 2015. Death certificate only, autopsy cases and patients with missing surgery information, who underwent partial nephrectomy or focal ablation were excluded (Fig. 1).

Variables definition

Histological subtypes were coded as either clear-cell or papillary renal cell carcinoma, according to SEER histological categories. Covariates included continuously coded age, year of diagnosis, ethnicity (Caucasian, Afro-American, other), socio-economic status (1st quartile, 2nd,3rd,4th quartile), Fuhrman grade [12] (G1/G2, G3/G4, GX), T-stage (T1,T2, T3,T4, Tx–T0), N-stage (N0, N1), type of treatment (no treatment, targeted therapy, cytoreductive nephrectomy, combination of cytoreductive nephrectomy with targeted therapy). Overall survival (OS) and cancer-specific survival (CSS) were our end-points of interest.

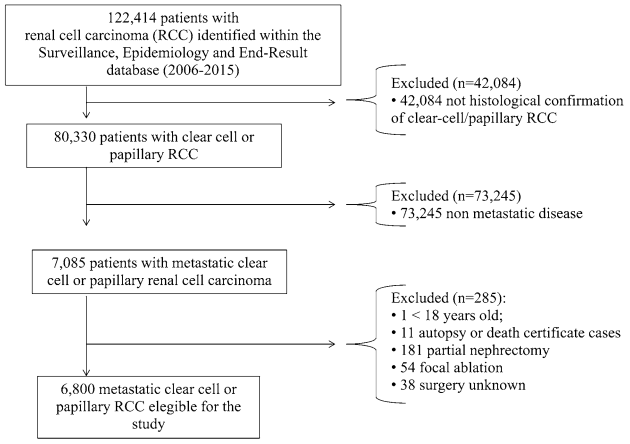


Fig. 1 CONSORT diagram of 6800 patients with metastatic clear-cell ($n=6215$) or papillary ($n=585$) renal cell carcinoma within the surveillance, epidemiology and end-result database (2006–2015) eligible for the study

Statistical analysis

Descriptive statistics included frequencies and proportions for categorical variables. Means, medians, and ranges were reported for continuously coded variables. The Chi-square tested the statistical significance in proportions' differences. The *t* test and Kruskal–Wallis test examined the statistical significance of means' and medians' differences. Three sets of analyses were performed. First, within each cohort, we relied on propensity score matching according to the nearest neighbor between patients who harbored clear-cell variant vs. papillary variant, to reduce the effect of selection bias. The propensity score matching was calculated based on logistic regression and the matched cohorts of papillary and clear-cell were balanced according to all the following covariates: (a) gender; (b) age at diagnosis; (c) ethnicity; (d) tumor grade; (e) T-stage; (f) N-stage; (g) treatment modality. Second, we tested the effect of histological subtype on OS and CSS using Kaplan–Meier plots and multivariable Cox-regression models (CRMs) before and after propensity-score matching. Finally, we tested the effect of treatment modalities according to histological subtype on OS and CSS using Kaplan–Meier plots. Covariates in multivariable CRMs consisted of histology, age at diagnosis, gender, year at diagnosis, ethnicity, socio-economic status (SES), Fuhrman grade, T-stage, N-stage and treatment modalities. For all statistical analyses R software environment for statistical computing and graphics (version 3.4.3) was used. All tests were two sided with a level of significance set at $p<0.05$.

Results

Descriptive analyses before propensity score matching

Overall, 66,602 (81.9%) patients harbored ccRCC vs. 14,658 (18.1%) pRCC. Of these, 6215 (10.1%) ccRCC exhibited metastatic disease vs. 585 (4.6%) pRCC patients. Compared to ccRCC patients, most pRCC patients were male (77.9 vs. 69.4; $p < 0.001$), African-American (27.0 vs. 6.6%; $p < 0.001$), with lower Fuhrman grade ($G_{3–4}$ 34.5 vs.45.8%; $p < 0.001$), lower T-stage ($T_{1–2}$ 37.2 vs. 32.1%; $p < 0.001$)

Table 1 Clinical and pathological characteristics of patients with metastatic renal cell carcinoma stratified according to histological subtype (clear-cell vs. papillary) before and after 4:1 propensity score matching

Overall cohort			Clear-cell ($n = 66,602$)			Papillary ($n = 14,658$)
M-stage, *n* (%)	Metastatic		6215 (10.1)			585 (4.6)
	Unmatched			Matched		
	Clear cell ($n = 6,215$; 91.4%)	Papillary ($n = 585$; 8.6%)	*p* value	Clear cell ($n = 1,959$; 77.5%)	Papillary ($n = 570$; 22.5%)	*p* value
Age at diagnosis, years						
Mean (STE)	63.2 (0.141)	62.7 (0.572)	0.4	63 (0.255)	62.7 (0.583)	0.6
Median	63	64	0.6	63	64	0.5
Range	55–71	54–72		55–71	54–72	
Sex, *n* (%)						
Female	1904 (30.6)	129 (22.1)	**< 0.001**	462 (23.6)	127 (22.3)	0.5
Male	4311 (69.4)	456 (77.9)		1497 (76.4)	443 (77.7)	
Ethnicity, *n* (%)			**< 0.001**	1486 (75.9)	389 (68.2)	**< 0.001**
Caucasian	5,336 (85.9)	389 (66.5)				
African–American	411 (6.6)	158 (27.0)		335 (17.1)	143 (25.1)	
Other	468 (7.5)	38 (6.5)		138 (7.0)	38 (6.7)	
Tumor grade, *n* (%)						
G1/G2	1179 (19.0)	99 (16.9)	**< 0.001**	363 (18.5)	96 (16.8)	0.2
G3/G4	2845 (45.8)	202 (34.5)		724 (37.0)	198 (34.7)	
Unknown	2191 (35.3)	284 (48.5)		872 (44.5)	276 (48.4)	
Tumor stage, *n* (%)						
T1	974 (15.7)	119 (20.3)	**< 0.001**	393 (20.1)	112 (19.6)	0.9
T2	1018 (16.4)	98 (16.8)		311 (15.9)	95 (16.7)	
T3	2732 (44.0)	194 (33.2)		689 (35.2)	193 (33.9)	
T4	657 (10.6)	65 (11.1)		218 (11.1)	63 (11.1)	
Tx–T0	834 (13.4)	109 (18.6)		348 (17.8)	107 (18.8)	
Nodal stage, *n* (%)						
N1	1450 (23.3)	291 (49.7)	**< 0.001**	852 (43.5)	276 (48.4)	0.1
Treatment, *n* (%)						
No treatment	1224 (19.7)	123 (21.0)	**0.04**	413 (21.1)	120 (21.1)	0.7
Targeted therapy	1464 (23.6)	162 (27.7)		512 (26.1)	159 (27.9)	
Cytoreductive nephrectomy	1726 (27.8)	156 (26.7)		512 (26.1)	151 (26.5)	
C. nephrectomy + T. therapy	1801 (29.0)	144 (24.6)		522 (26.6)	140 (24.6)	
Socio-economic status (SES), *n* (%)						
1 Quartile	1693 (27.2)	138 (23.6)	0.06	502 (25.6)	136 (23.9)	0.4
2–3–4 Quartile	4522 (72.8)	447 (76.4)		1,457 (74.4)	434 (76.1)	
Year of diagnosis, *n* (%)						
2006–2010	2,723 (43.8)	242 (41.4)	0.3	869 (44.4)	231 (40.5)	0.1
2011–2015	3,492 (56.2)	343 (58.6)		1,090 (55.6)	339 (59.5)	

Bold values indicate statistical significance

and higher rates of regional lymph node invasion [13] (49.7 vs. 23.3%; $p < 0.001$) (Table 1).

Descriptive analyses after propensity score matching

Of 585 patients with metastatic pRCC, 97.4% could be matched with metastatic ccRCC patients ($n = 1959$, 31.5% of original cohort before matching) in a 1:4 ratio. After propensity score matching, no significant differences existed in covariate distribution between metastatic pRCC vs. ccRCC patients, except for residual differences in ethnicity that resulted from an important predilection for pRCC in African-American patients, prior to any data manipulation (Table 1).

The effect of histological subtype on OS and CSS

Between 2006 and 2015, 4190 deaths occurred. Of these, 93.3% were related to RCC. In the unmatched cohort, median OS (13 vs. 18 months) and median CSS (12 vs. 18 months) were lower in pRCC than in ccRCC patients. Similarly, 2-year OS (33.1 vs. 41.8%; $p < 0.001$) and 2-year CSS (35.1 vs. 44.2%; $p < 0.001$) were also lower in pRCC than ccRCC patients (Fig. 2a, c). In multivariable Cox-regression models, after adjusting for all covariates, neither difference on OS (HR 1.01, CI 0.90–1.13; $p = 0.8$) nor on CSS (HR: 1.02, CI 0.90–1.14; $p = 0.8$) was recorded between pRCC and ccRCC. (data not shown).

In the matched cohort, median OS (11 vs. 14 months) and median CSS (12 vs. 15 months) were lower in pRCC than ccRCC patients. 2-year OS was 32.9 vs. 38.7% and 2-year CSS was 34.9 vs. 41.3% for pRCC vs. ccRCC, respectively. However, no statistically significant difference neither on OS nor on CSS was recorded between pRCC and ccRCC (all $p > 0.05$) (Fig. 2b, d). In multivariable Cox-regression models, after adjustment for all covariates, neither difference on OS (HR 1.01, CI 0.9–1.14; $p = 0.7$) nor on CSS (HR 1.02, CI 0.90–1.15; $p = 0.7$) was recorded between pRCC and ccRCC patients (Tables 2, 3).

The effect of treatment modality on OS and CSS according to histological subtype

In pRCC patients, between 2006 and 2015, 370 deaths were recorded. Of these, 345 (93.2%) were related to RCC. In Kaplan–Meier analyses, median OS was 8, 11, 17 and 18 months and 2-year OS was 26.0, 20.6, 44.7 and 37.4% for no treatment, targeted therapy, cytoreductive nephrectomy and combination of cytoreductive nephrectomy with targeted therapy, respectively (Fig. 3a). Similarly, median CSS was 9, 11, 19, 18 months and 2-year CSS was 28.4, 22.5, 48.6 and 37.7% for no treatment, targeted therapy, cytoreductive nephrectomy and combination of cytoreductive nephrectomy with targeted therapy, respectively (Fig. 3c).

In ccRCC patients, between 2006 and 2015, 3,820 deaths were recorded. Of these, 3566 (93.3%) were related to RCC. In Kaplan–Meier analyses, median OS was 4, 12, 35 and 25 months and 2-year OS was 17.7, 27.0, 58.7 and 50.4% for no treatment, targeted therapy, cytoreductive nephrectomy and combination of cytoreductive nephrectomy with targeted therapy, respectively (Fig. 3b). Similarly, median CSS was 5, 12, 40, 27 months and 2-year CSS was 20.8, 28.9, 60.8 and 52.7% for no treatment, targeted therapy, cytoreductive nephrectomy and combination of cytoreductive nephrectomy with targeted therapy, respectively (Fig. 3d).

Discussion

Few studies analyzed the prognostic value of histological subtype in metastatic kidney cancer and survival outcomes of patients with pRCC are not well established. Based on this unmet need, we hypothesized that survival in metastatic RCC patients with papillary histological variant is worse than that of metastatic clear-cell patients. Moreover, we postulated that the effect of available treatment modalities for metastatic RCC is less beneficial in pRCC than in ccRCC patients. Our study showed several important observations.

First, we observed a small proportion of metastatic RCC patients with metastatic papillary histology (8.6%). Among metastatic RCC population, clear-cell variant is the most common metastatic histotype (88.7%), followed by papillary (8.3%), chromophobe (1.5%) and collecting duct (1.5%). In consequence, metastatic pRCC accounts for the majority of non-clear cell RCC patients. However, this proportion is substantially lower than in non-metastatic RCC, where papillary accounts for approximately 15% [9]. Moreover, in our report, 4.6% of pRCC vs. 10.1% of ccRCC patients have metastatic disease at diagnosis. This implies that a smaller fraction of papillary tumors progress to metastatic disease, compared to clear-cell variant. A previous report from a single institution [9] also demonstrated a lower rate of metastatic progression within pRCC (5.7% vs. 11.9%) than within ccRCC patients.

Second, we identified important differences in patient distribution between pRCC and ccRCC. First, the rate of African-American patients was four-fold higher in metastatic pRCC than in metastatic ccRCC. This observation indicate a predilection for metastatic progression in African-Americans within pRCC (fertile soil phenomenon in African-American ethnicity) [14]. This finding is consistent with Lipworth et al. [15] who showed that African-American patients more frequently harbor papillary variant compared to Caucasians (35.7 vs. 13.8%). Second, the rate of lymph node invasion was more than two-fold higher in pRCC patients than ccRCC

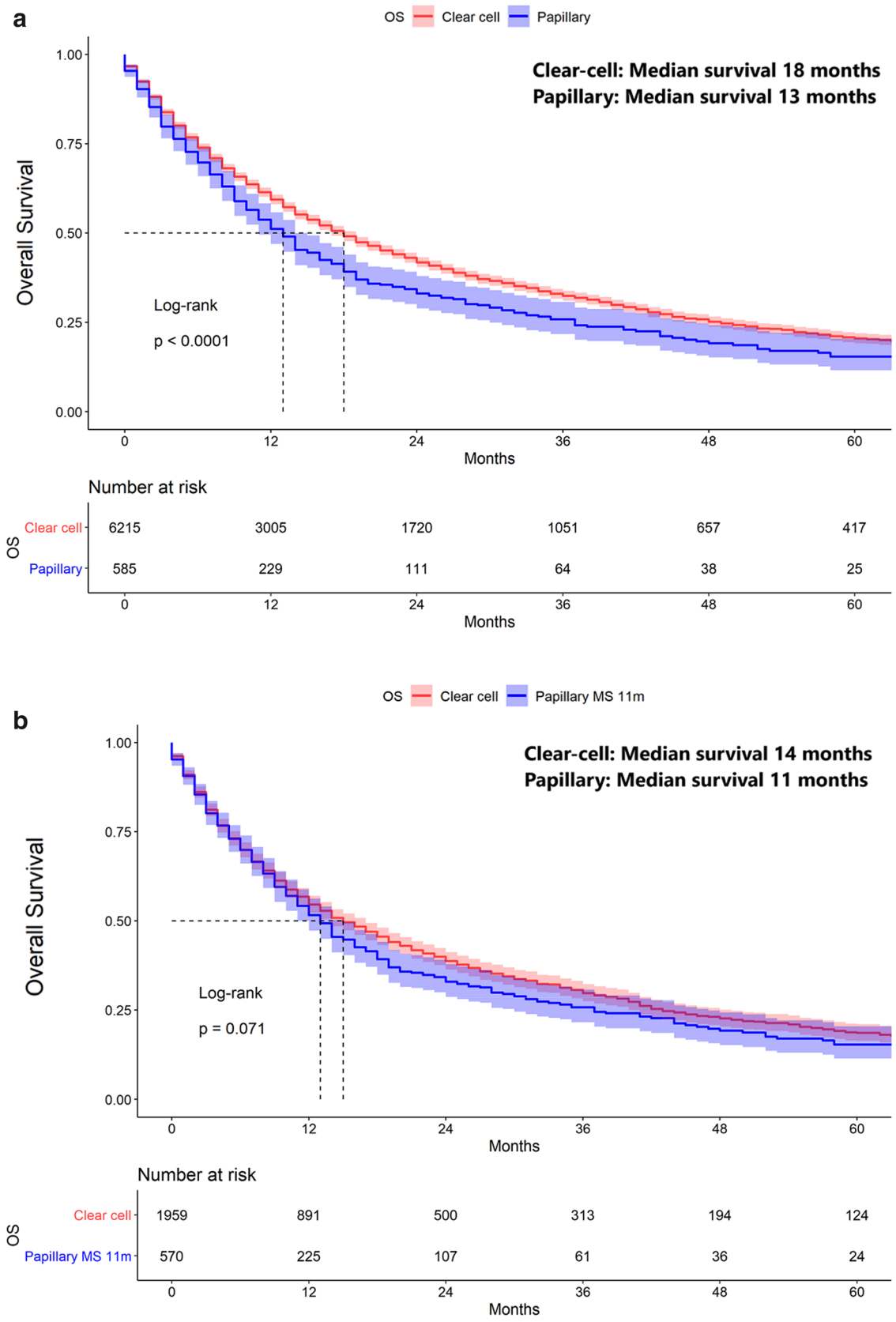


Fig. 2 Kaplan–Meier curves depicting overall survival (OS; **a**, **b**) and cancer-specific survival (CSS: **c**, **d**) before (**a**, **c** and after (**b**, **d**) 4:1 propensity score matching in patients with metastatic clear cell vs. papillary renal cell carcinoma

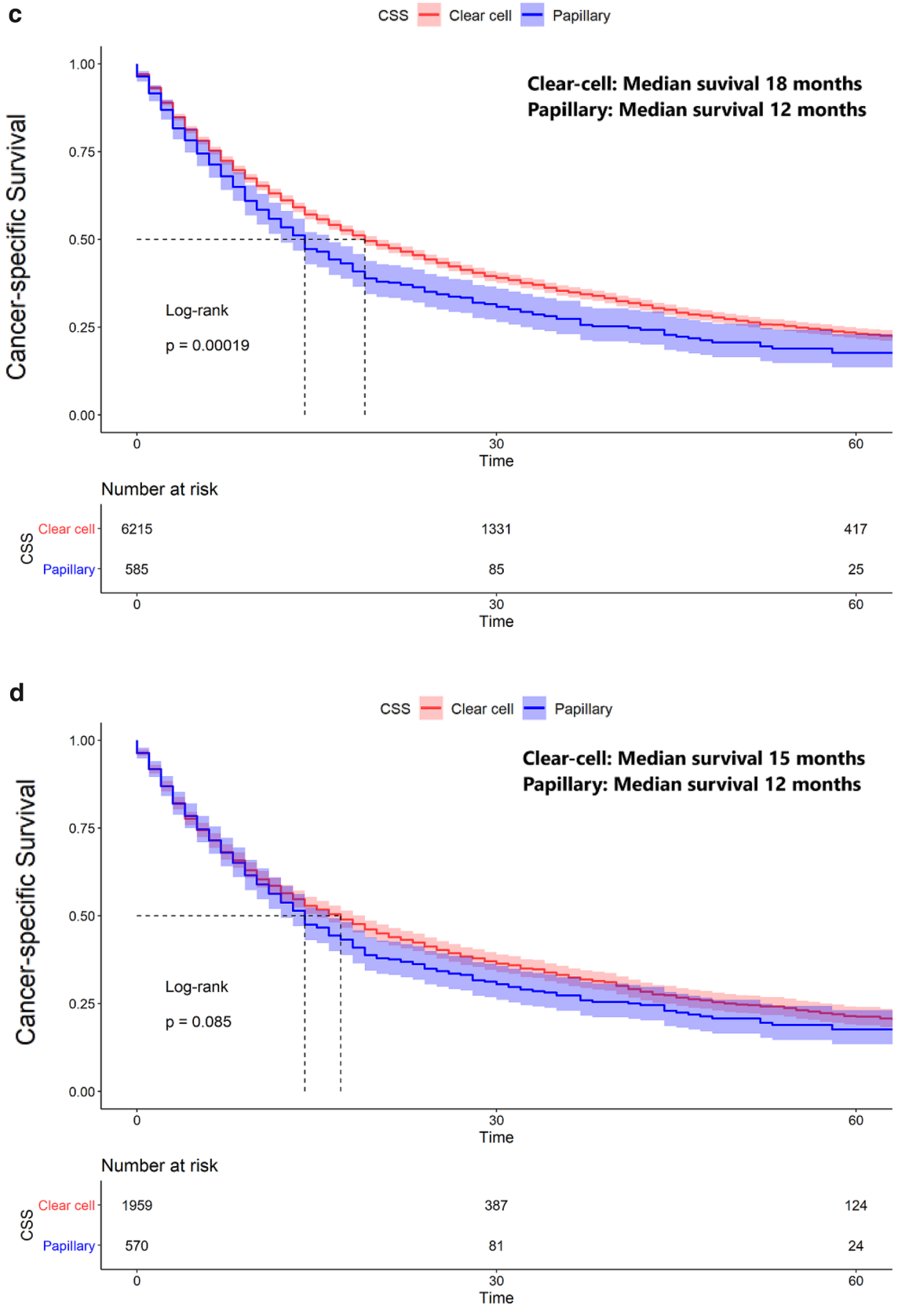


Fig. 2 (continued)

Table 2 Cox-regression models predicting overall mortality (OM) after 4:1 propensity score matching in patients with metastatic clear cell or papillary renal cell carcinoma

	Univariable matched OM			Multivariable matched OM		
	HR	CI	*p* value	HR	CI	*p* value
Clear-cell	Ref.			Ref.		
Papillary	1.11	(0.99–1.25)	0.07	1.01	(0.90–1.14)	0.7
Age	1.00	(0.99–1.00)	0.09	0.99	(0.99–1.00)	0.9
Female	Ref.			Ref.		
Male	0.96	(0.86–1.08)	0.5	0.98	(0.87–1.10)	0.7
Caucasian	Ref.			Ref.		
African–American	1.05	(0.92–1.19)	0.4	1.03	(0.90–1.17)	0.6
Other	1.09	(0.90–1.32)	0.3	1.18	(0.97–1.43)	0.08
G1/G2	Ref.			Ref.		
G3/G4	1.30	(1.12–1.51)	**< 0.001**	1.38	(1.18–1.61)	**< 0.001**
Unknown	1.91	(1.65–2.20)	**< 0.001**	1.22	(1.05–1.43)	**< 0.01**
T1–T2	Ref.			Ref.		
T3–T4	1.03	(0.93–1.13)	0.5	1.27	(1.14–1.42)	**< 0.001**
N0	Ref.			Ref.		
N1	1.70	(1.54–1.87)	**< 0.001**	1.61	(1.45–1.79)	**< 0.001**
No treatment	Ref.			Ref.		
Targeted therapy	0.68	(0.60–0.79)	**< 0.001**	0.63	(0.55–0.72)	**< 0.001**
Cytoreductive nephrectomy	0.32	(0.28–0.37)	**< 0.001**	0.29	(0.24–0.34)	**< 0.001**
C. nephrectomy + T. therapy	0.36	(0.32–0.42)	**< 0.001**	0.27	(0.23–0.33)	**< 0.001**
1 Quartile	Ref.			Ref.		
2–3–4 Quartile	1.11	(0.99–1.25)	0.05	1.07	(0.95–1.20)	0.2
2004–2010	Ref			Ref.		
2011–2015	1.04	(0.94–1.15)	0.4	0.93	(0.84–1.04)	0.2

Bold values indicate statistical significance

HR hazard ratio, *CI* confidence interval

patients (49.7 vs. 23.3%; $p < 0.001$). This observation is also consistent with previous findings of more historical studies (SEER 2000–2005; SEER 1988–2004) [16, 17].

Third, overall mortality was higher in metastatic pRCC than in ccRCC prior to matching. Specifically, median OS was 13 vs. 18 months and 2-year OS was 33.1 vs. 41.6% in, respectively, pRCC vs. ccRCC patients. However, OS differences disappeared after matching for demographics and clinical characteristics, despite incomplete matching for race. It is of note that due to heavy predilection for African-American race in pRCC, perfectly balanced matching for race cannot be accomplished. These findings are consistent with Connor Wells et al. [6] who relied on IMDC database (2005–2016) and showed that metastatic pRCC patients has worse survival than ccRCC (median OS 13.8 vs. 21.3 months). As previously discussed, pRCC patients presented substantially higher rates of lymph node invasion at diagnosis (49.7 vs. 23.3%; $p < 0.001$), compared to ccRCC patients. Moreover, African–Americans were more likely to harbour pRCC than ccRCC histological subtype. It is of note that lymph node invasion is one of the most important predictor of survival, in patients with RCC [18–20]. For instance, 5-year mortality in RCC patients with lymph node metastases is > 50%, significantly higher relative to pN0 counterparts [18]. It is also noteworthy that Rose et al. [21] observed a survival disadvantage in African–American patients with advanced RCC, compared to Caucasians, regardless of treatment received. In consequence, it can be postulated that higher rates of well established risk factors for poor oncologic outcomes in pRCC histological subtype, namely lymph node invasion and African-American ethnicity, led to worse survival in pRCC patients but, after accounting for these demographics and tumor discrepancies, no survival differences remained.

Fourth, analyses of the effect of treatment modalities available for metastatic RCC on OS revealed lower median survival in pRCC patients, compared to ccRCC, regardless of treatment received. These observations indicate that, regardless of treatment, papillary variant is a prognostically unfavorable histology, in the context of metastatic RCC. However, the overall pattern of treatment efficacies, was virtually the same between the two histological subtypes, namely it was highest for cytoreductive nephrectomy alone, second highest for combination of cytoreductive nephrectomy with targeted therapy and lowest for targeted therapy alone. Historically, cytoreductive nephrectomy was

Table 3 Cox-regression predicting cancer-specific mortality (CSM) after 4:1 propensity score matching in patients with metastatic clear cell or papillary renal cell carcinoma

	Univariable matched CSM			Multivariable matched CSM		
	HR	CI	*p* value	HR	CI	*p* value
Clear-cell	Ref.			Ref.		
Papillary	1.11	(0.98–1.25)	0.08	1.02	(0.90–1.15)	0.7
Age	1.00	(0.99–1.00)	0.4	0.99	(0.99–1.00)	0.3
Female	Ref.			Ref.		
Male	0.97	(0.86–1.09)	0.6	0.97	(0.86–1.10)	0.7
Caucasian	Ref.			Ref.		
African–American	1.01	(0.89–1.16)	0.8	0.99	(0.86–1.14)	0.9
Other	1.06	(0.87–1.30)	0.5	1.15	(0.94–1.40)	0.1
G1/G2	Ref.			Ref.		
G3/G4	1.39	(1.19–1.62)	**< 0.001**	1.46	(1.23–1.72)	**< 0.001**
Unknown	2.01	(1.73–2.34)	**< 0.001**	1.27	(1.08–1.49)	**< 0.01**
T1–T2	Ref.			Ref.		
T3–T4	1.06	(0.95–1.17)	0.2	1.31	(1.17–1.48)	**< 0.001**
N0	Ref.			Ref.		
N1	1.73	(1.57–1.92)	**< 0.001**	1.60	(1.44–1.79)	**< 0.001**
No treatment	Ref.			Ref.		
Targeted therapy	0.70	(0.60–0.80)	**< 0.001**	0.63	(0.55–0.73)	**< 0.001**
Cytoreductive nephrectomy	0.31	(0.27–0.36)	**< 0.001**	0.27	(0.22–0.32)	**< 0.001**
C. nephrectomy + T. therapy	0.37	(0.32–0.43)	**< 0.001**	0.26	(0.22–0.32)	**< 0.001**
1 Quartile	Ref.			Ref.		
2–3–4 Quartile	1.09	(0.97–1.23)	0.1	1.06	(0.94–1.19)	0.3
2004–2010	Ref.			Ref.		
2011–2015	1.03	(0.93–1.14)	0.5	0.92	(0.83–1.02)	0.1

Bold values indicate statistical significance

HR hazard ratio, *CI* confidence interval

a common clinical practice in metastatic RCC for patients with good performance status, based on the benefit shown by prospective trials in the interferon era and retrospective trials in the targeted therapies era.[22]. Despite the CARMENA trial [23] showed non-inferiority of targeted therapy alone vs. after cytoreductive nephrectomy on survival outcomes, cytoreductive nephrectomy is still highly performed. However, European guidelines [24] recommend immediate cytoreductive nephrectomy in patients who do not require systemic therapy, in presence of good performance status. Conversely, this treatment is strongly discouraged in poor risk patients, classified according to the Heng criteria. In consequence, better performance status of patients treated with cytoreductive nephrectomy alone, may have resulted in better overall survival in this patient population, compared to patients treated with combination of cytoreductive nephrectomy and targeted therapy. Unfortunately, the SEER database does not allow us to account for some clinical-pathological variables, such as performance status or serum levels of calcium, which are used for the stratification according to the Heng criteria. In consequence, we could not evaluate these differences, between patients who underwent treatment rather than other.

Our findings regarding the different OS according to treatment in patients with metastatic pRCC vs. ccRCC are in agreement with other more historical studies. Specifically, Aizer et al. [25] relied on the SEER database (2000–2009) and showed worse survival in pRCC patients treated with cytoreductive nephrectomy, compared to ccRCC patients. Similarly, Ravaud et al. [26] also showed worse survival in metastatic pRCC patients treated with targeted therapy, compared to ccRCC patients. However, none of these studies considered all four treatment options within the same analyses (no treatment, cytoreductive nephrectomy, targeted therapy, combination of cytoreductive nephrectomy with targeted therapy). In consequence, we are the first to compare single treatment modality to no treatment, as well as combination of cytoreductive nephrectomy with targeted therapy vs. other treatments alone.

Taken together, these observations validate our hypothesis that differences in survival outcomes exist between metastatic pRCC and ccRCC patients, even after more detailed analyses according to different treatment received.

Our study represents the largest retrospective population-based analysis. Nonetheless it has limitations. First, we cannot distinguish between type 1 and type 2 pRCC.

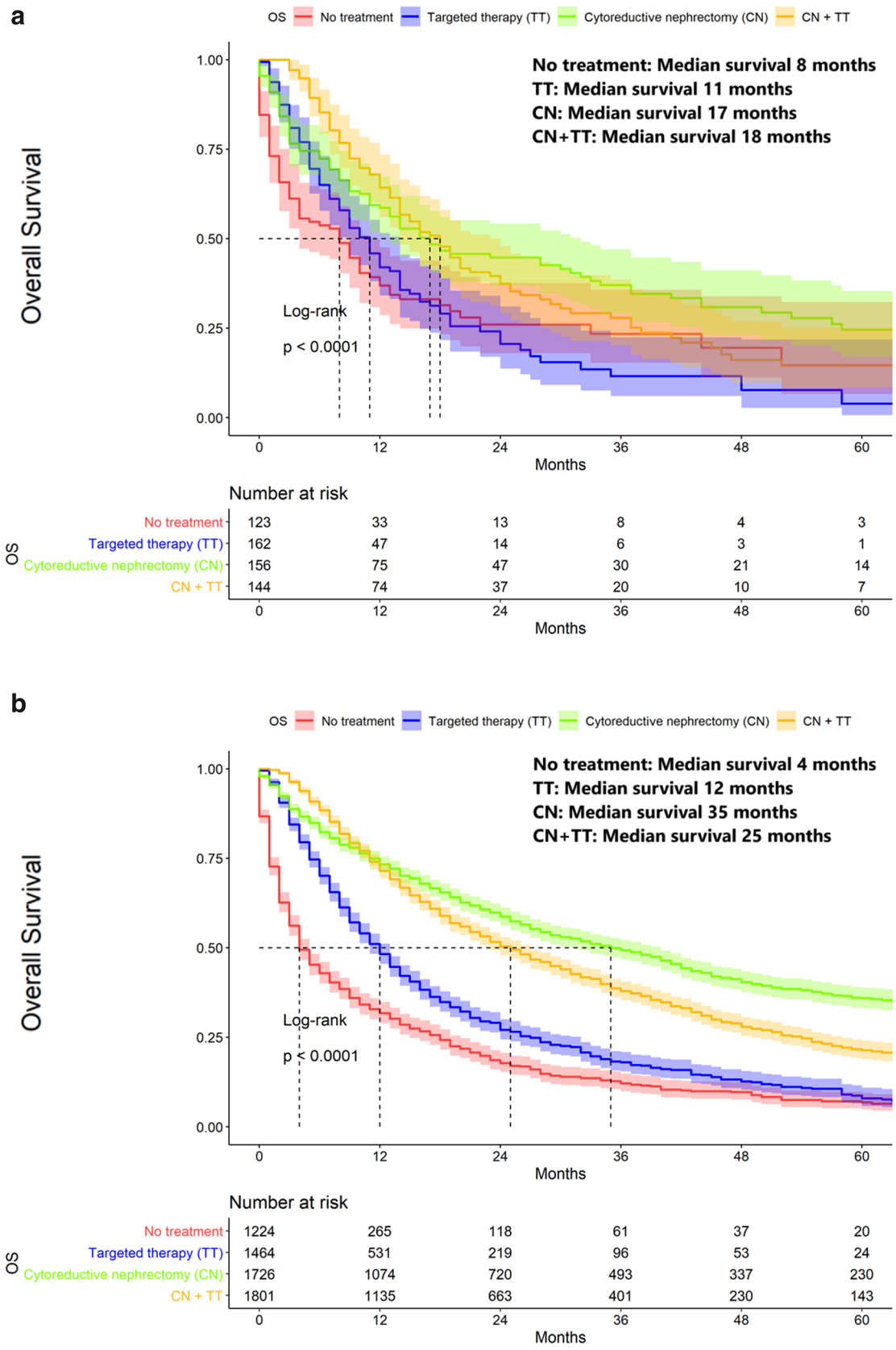
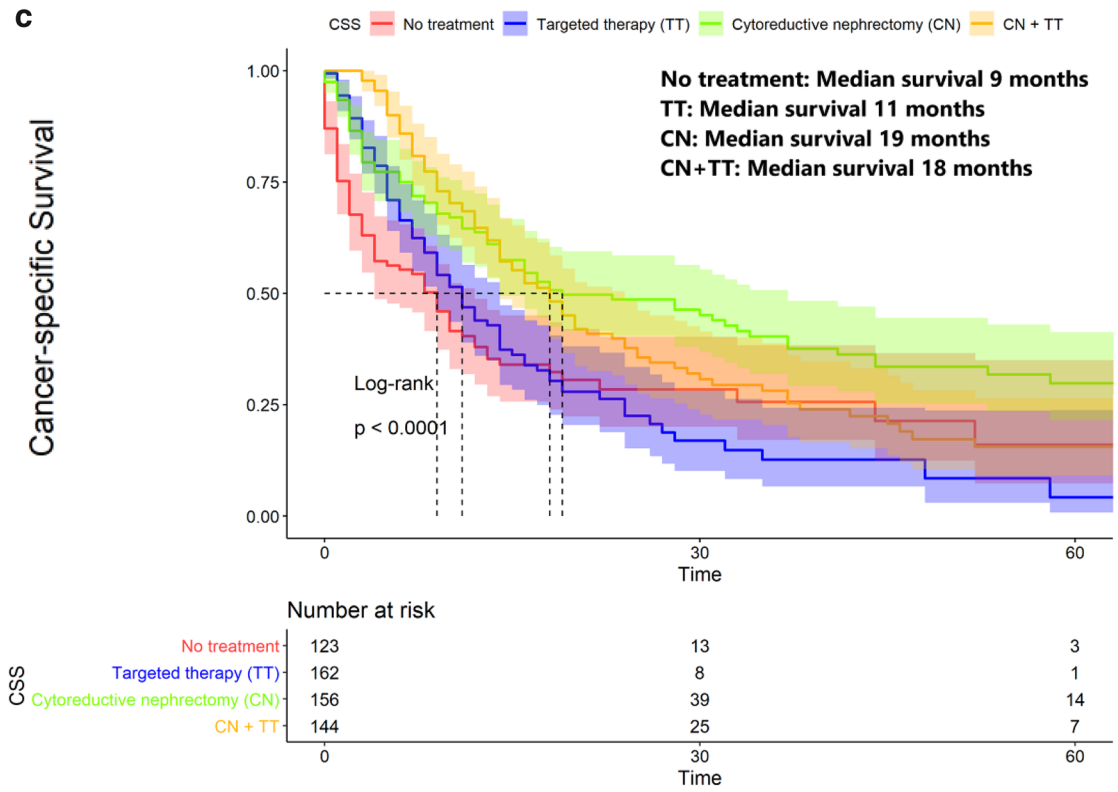


Fig. 3 Kaplan–Meier curves depicting overall survival (OS; **a**, **b**) and cancer-specific survival (CSS: 3c-d) according to treatment in patients with metastatic papillary (**a**, **c**) and clear-cell (**b**, **d**) renal cell carcinoma



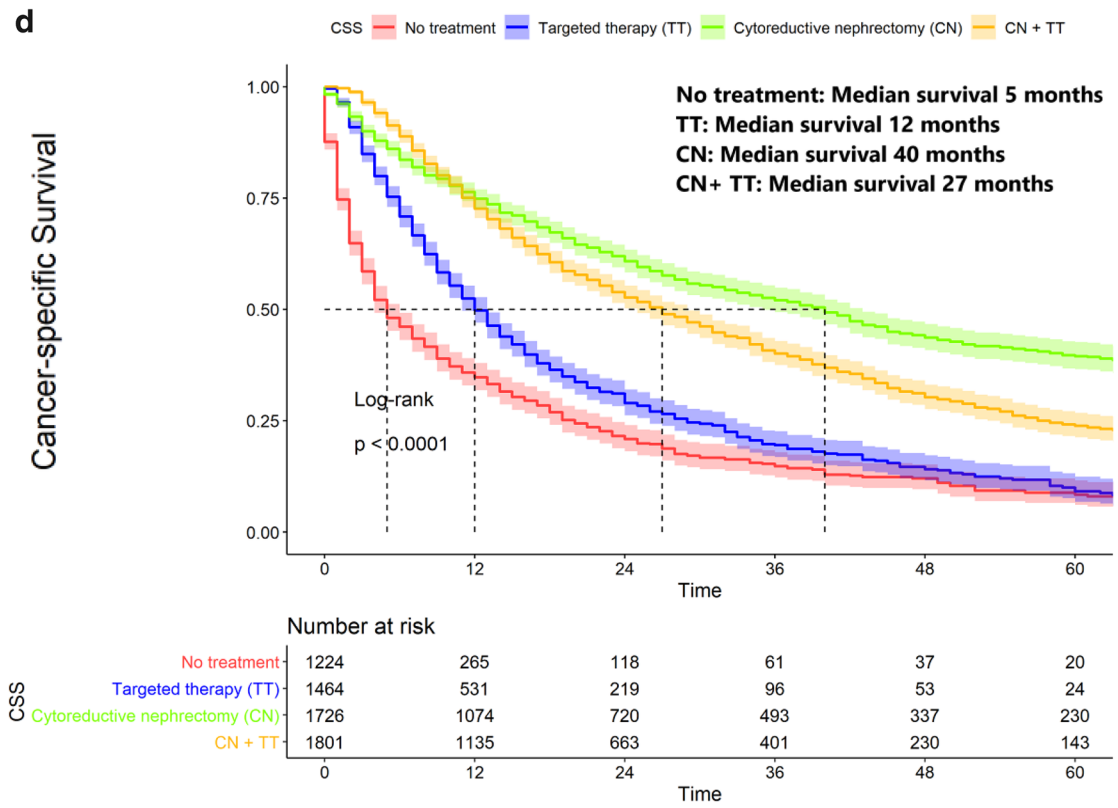


Fig. 3 (continued)

Nonetheless, it is of note that the proportion of metastatic pRCC type 1 is considerably lower than type 2 (5–7% for pRCC type 1 and vs. 35–69% for pRCC type II) [6, 27] and that type 1 pRCC has better prognosis, such as better pathological features than type 2 pRCC variant [28]. Second, within the SEER database information on specific systemic therapy type administrated (such as tyrosine-kinase inhibitor vs. immunotherapy) and its dose and duration are not available. Third, information regarding Heng criteria, such as performance status, time to metastasis, serum levels of hemoglobin, neutrophils, platelets and calcium, are unavailable in the SEER database. Availability of variables allowing to account for Heng criteria would have allowed us to compare the characteristics of our population to those of Connor Welles. It is of note that the population of clear-cell patients analyzed by Connor Wells exhibited substantially better survival than our ccRCC patients, as evidenced by, respectively, median OS of 21 vs. 12 months. Similarly, we could not apply the Heng criteria to pRCC patients. However, our population of metastatic pRCC patients exhibited similar survival characteristics within the current analyses to those described in IMCD analyses (median OS 11 vs. 13 months, respectively). Fourth, we relied on the SEER database, which includes North American patients. For this reason, our findings can only be applied to the population of United States but may be not generalizable to other parts of the world, such as Europe or even Canada. However, these limitations as well as all other limitations related to the retrospective nature of the SEER database apply to all other population-based analyses that were derived from the SEER, National Cancer DataBase (NCDB) or other similar large-scale data repositories.

Conclusion

Metastatic pRCC patients exhibit poor survival, regardless of treatment received. Moreover, pRCC patients are more likely to present nodal metastases, compared to ccRCC patients, as demonstrated by twofold higher rates of lymph node invasion at diagnosis. These observations indicate that papillary variant represents more prognostically unfavorable tumor histology, in the context of metastatic RCC.

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Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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