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Clinicopathological and survival analysis of clinically advanced papillary and chromophobe renal cell carcinoma

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Abstract

Introduction: Clinically, the papillary (pRCC) and chromophobe (chRCC) histologic subtypes of renal cell carcinoma (RCC) are viewed as more indolent compared to the more-common clear cell histology (ccRCC). However, there remain advanced cases of these purportedly less-aggressive histologies that lead to significant mortality. We therefore sought to evaluate outcomes of advanced pRCC and chRCC compared to ccRCC utilizing the National Cancer Database's registry of RCC patients.

Materials and methods: A total of 115,365 ccRCC patients, 28,344 pRCC patients, and 11,942 chRCC patients met eligibility criteria. Overall survival (OS) was estimated using the Kaplan-Meier method (median follow-up 3.6 years). OS was compared between stage III and IV ccRCC, pRCC, and chRCC using multivariable Cox proportional hazards model adjusted for clinical and treatment characteristics.

Results: A total of 25.7% of ccRCC patients, 14.1% of pRCC patients, and 14.8% of chRCC patients had stage III to IV disease. The 5-year OS for stage III ccRCC, pRCC, and chRCC was 66.9%, 63.6%, and 80.5%, respectively. The 5-year OS for stage IV ccRCC, pRCC and chRCC was 19.7%, 13.3%, and 22.0%, respectively. The hazard of death was significantly higher for stage IV pRCC vs. ccRCC (hazard ratio = 1.29; 95% confidence interval = 1.19, 1.39; $P < 0.01$) and similar for stage IV chRCC vs. ccRCC (hazard ratio = 1.01; 95% confidence interval = 0.85, 1.21; $P = 0.885$).

Conclusions: pRCC and chRCC are rare but similarly fatal compared to ccRCC when advanced or metastatic. With most clinical trials devoted toward ccRCC, greater efforts to identify aggressive variants and treatment strategies for metastatic pRCC and chRCC are necessary.

Keywords: Renal cell carcinoma; Chromophobe; Papillary; Survival; Stage

1. Introduction

Renal cell carcinoma (RCC) represents 2% to 3% of adult cancers, and is expected to result in more than 65,000 new cases and 14,970 deaths in the United States in 2018 [1,2]. RCC is commonly classified into several histologic subtypes based on morphological characteristics, the most common of which is clear cell (ccRCC) at 75-90%, followed by papillary (pRCC) at 10% to 18% and chromophobe (chRCC) at 4% to 10% [3–5]. In addition to pathological variation, these subtypes have distinct genetic differences and therapeutic responses [6,7].

Clinically, pRCC and chRCC are viewed as less aggressive compared to ccRCC. Several studies suggest that patients with pRCC and chRCC present with lower stage and grade and ultimately have prolonged survival compared to patients with ccRCC [8,9]. The papillary and chromophobe subtypes are still; however, malignant forms of RCC that recur, metastasize, develop resistance to targeted therapies, and cause mortality. In a clinical trial of first line everolimus monotherapy for metastatic pRCC, 50% of patients progressed at 4 months [10]. Similarly, a retrospective

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study of 109 patients with metastatic chRCC treated with one or more vascular endothelial growth factor (VEGF) or mammalian target of rapamycin tyrosine kinase inhibitors showed that treatment failed in 50% of patients at 6.9 months [11]. Identification of optimal treatment in clinical trials, as well as characterization of outcome and pathologic attributes have been limited by the small number of patients that present with metastatic chRCC or pRCC. Indeed, a recent systematic review conducted by the European Association of Urology RCC Guidelines Panel found no statistically reliable evidence for a recommended treatment for advanced non-ccRCC [12].

Considering the scarcity of non-ccRCC and relative lack of targeted clinical trials, we utilized a national database to analyze the clinicopathological and survival analysis of 28,344 patients pathologically diagnosed with pRCC and 11,942 patients pathologically diagnosed with chRCC, in order to garner a better understanding of their aggressive potential.

2. Materials and methods

2.1. Patient population

The American College of Surgeons' National Cancer Database (NCDB) was utilized to identify 197,659 patients with diagnosed clear cell, papillary, or chromophobe RCC from 2004 to 2013. The NCDB is a collaborative project of the American College of Surgeons and the American Cancer Society and contains patient-level and hospital-level data from 1,500 commission on cancer hospitals, including an estimated 70% of all new cancer diagnoses in the United States. Patients with incomplete data on pathologic staging ($n = 33,555$) were excluded. Patients were also excluded if they did not receive appropriate stage-based treatment ($n = 8,553$). Specifically, for stages I and II RCC we included only those patients who received nephrectomy (partial or radical) alone. For stage III RCC we included patients who received nephrectomy ± systemic therapy, and for stage IV RCC we included patients who received nephrectomy alone, systemic therapy alone, or a combination of 2. Overall, there were 155,551 patients that met eligibility criteria including 115,365 patients with ccRCC, 28,244 patients with pRCC, and 11,942 patients with chRCC.

2.2. Pathologic variables

Pathologic variables available in the NCDB that were analyzed included American Joint Committee on Cancer (AJCC) pathologic stage, pT stage, pN stage, presence of clinical or pathologic distant metastases, sites of distant metastases, and grade and surgical margin status. Frequencies and percentages were calculated for each variable for each histologic subtype.

2.3. Survival outcome

The Kaplan-Meier method was used to evaluate overall survival (OS) for each subtype at 1, 5, and 10 years. The Kaplan-Meier method was also used to evaluate OS for ccRCC, pRCC, and chRCC for each pathologic AJCC stage. Kaplan-Meier analyses included 87,268 ccRCC cases, 21,575 pRCC cases, and 8,738 chRCC cases. A total of 37,970 cases were excluded from Kaplan-Meier analysis that lacked survival data, including 28,097 ccRCC cases, 6,669 pRCC cases, and 3,204 chRCC cases. Time from diagnosis to the event (death or right censorship) was used as the time scale at median follow-up 3.6 years (interquartile range: 1.9–5.7 years; range: 0.003–10.9 years). Using a multivariable Cox proportional hazards regression model, OS between ccRCC, pRCC, and chRCC, was compared. This was done adjusting for age, sex, race, Charlson-Deyo score, primary insurer, income, and education based on zip code, region, facility type and location, distance in miles to the treatment center, year of diagnosis, Fuhrman grade, and treatment type. Statistical significance was considered at the $P < 0.05$ level, and this analysis was conducted using R version 3.1.3.

3. Results

3.1. Clinical characteristics

Demographic, socioeconomic, and treatment characteristics are presented in Table 1. Among RCC patients reported to the NCDB, ccRCC, pRCC, and chRCC accounted for 74.2%, 18.2% and 7.7% of cases, respectively. Patients with ccRCC, pRCC, and chRCC had a mean age of 60.8, 61.9, and 59.5 years, respectively. Male patients made up 60.7% of ccRCC cases, 74.9% of pRCC cases, and 56.0% of chRCC cases. The majority of all 3 groups were white, and black patients made up 7.1% of ccRCC, 26.2% of pRCC cases, and 12.7% of chRCC cases. Among patients with stage IV ccRCC, 34.3% of cases were treated with nephrectomy alone, 36.1% received both nephrectomy and systemic therapy, and 29.6% received systemic therapy alone. For patients with stage IV pRCC, 35.6% of cases were treated with nephrectomy alone, 30.4% received both nephrectomy and systemic therapy, and 34.1% received systemic therapy alone. Among stage IV chRCC cases, 48.9% were treated with nephrectomy alone, 27.5% received combined nephrectomy and systemic therapy, and 23.5% received only systemic therapy.

3.2. Pathologic outcome

Pathologic characteristics of RCC subtypes are presented in Table 2. For patients with ccRCC, the rate of high-grade (3–4) disease was 32.6%, the rate of pT stage 3–4 was 20.8%, the rate of pathologic nodal metastases was 4.1%, and the rate of distant metastases was 9.5%.

Table 1
Demographic and socioeconomic data of patients with clear cell, papillary, and chromophobe renal cell carcinoma

	Clear Cell	Papillary	Chromophobe	*P* (ccRCC vs. pRCC)	*P* (ccRCC vs. chRCC)
N	115,365 (74.2%)	28,344 (18.2%)	11,942 (7.7%)		
Age (mean, SD)	60.8 (12.3)	61.9 (11.9)	59.5 (13.8)	**<0.01**	**<0.01**
Sex				**<0.01**	**<0.01**
Male	69,988 (60.7%)	21,161 (74.9%)	6,691 (56.0%)		
Female	45,377 (39.3%)	7,083 (25.1%)	5,251 (43.9%)		
Race				**<0.01**	**<0.01**
White	102,051 (89.5%)	20,077 (71.9%)	9,876 (84.0%)		
Black	8,066 (7.1%)	7,307 (26.2%)	1,493 (12.7%)		
Other	3,881 (3.4%)	516 (1.9%)	387 (3.3%)		
Charlson Deyo score				**<0.01**	**<0.01**
0	79,648 (69.0%)	19,821 (70.2%)	9,146 (76.6%)		
1	26,914 (23.3%)	6,062 (21.5%)	2,209 (18.5%)		
2+	8,803 (7.6%)	2,361 (8.4%)	587 (4.9%)		
Insurance				**<0.01**	**<0.01**
None	3,739 (3.3%)	675 (2.4%)	312 (2.7%)		
Government	52,730 (46.5%)	14,476 (52.3%)	5,026 (42.9%)		
Private	56,940 (50.2%)	12,542 (45.3%)	6,384 (54.5%)		
Income				**<0.01**	**<0.01**
<$38,000	18,714 (16.4%)	5,580 (19.9%)	1,803 (15.3%)		
$38–$47,999	27,740 (24.3%)	6,316 (22.6%)	2,455 (20.8%)		
$48–$62,999	31,825 (27.9%)	7,085 (25.4%)	3,102 (26.2%)		
≥$63,000	35,768 (31.4%)	8,931 (32.0%)	4,464 (37.8%)		
Education				**<0.01**	**<0.01**
Q1	18,979 (16.6%)	5,064 (18.1%)	2,842 (15.6%)		
Q2	29,644 (25.9%)	7,440 (26.6%)	2,762 (23.4%)		
Q3	38,541 (33.8%)	8,876 (31.8%)	3,856 (32.6%)		
Q4	26,939 (23.6%)	6,544 (23.4%)	3,368 (28.5%)		
Treatment facility				**<0.01**	**<0.01**
Comprehensive community	46,788 (42.7%)	10,207 (37.5%)	4,192 (38.4%)		
Community	7,506 (6.8%)	1,692 (6.2%)	575 (5.3%)		
Academic	47,584 (43.4%)	13,189 (48.5%)	5,230 (47.9%)		
Other	7,828 (7.1%)	2,099 (7.7%)	908 (8.3%)		
Region				**<0.01**	**<0.01**
New England	5,533 (5.0%)	1,462 (5.4%)	649 (5.9%)		
Mid Atlantic	17,524 (15.9%)	5,045 (18.6%)	2,238 (20.5%)		
South Atlantic	19,412 (17.7%)	6,337 (23.3%)	2,221 (20.4%)		
East North Central	19,414 (17.7%)	4,811 (17.7%)	1,767 (16.2%)		
East South Central	7,575 (6.9%)	2,148 (7.9%)	708 (6.5%)		
West North Central	11,679 (10.7%)	2,155 (7.9%)	864 (7.9%)		
West South Central	10,271 (9.4%)	2,243 (8.2%)	843 (7.7%)		
Mountain	5,057 (4.6%)	860 (3.2%)	460 (4.2%)		
Pacific	13,241 (12.1%)	2,135 (7.9%)	1,155 (10.6%)		
Hospital location				**<0.01**	**<0.01**
Metropolitan	91,568 (81.8%)	23,454 (85.5%)	9,972 (85.8%)		
Urban	17,952 (16.0%)	3,511 (12.8%)	1,480 (12.7%)		
Rural	2447 (2.2%)	459 (1.7%)	171 (1.5%)		
Distance to Tx center (mean, SD)	38.4 (115.3)	35.1 (110.3)	38.6 (139.2)	**<0.01**	0.903
Year of diagnosis (median, range)	2009 (2004–2013)	2009 (2004–2013	2009 (2004–2013)		
Stage I treatment				**<0.01**	**<0.01**
Partial Nx	34,423 (46.3%)	11,202 (54.4%)	3,918 (49.9%)		
Radical Nx	39,863 (53.7%)	9,406 (45.6%)	3,920 (50.0%)		
Stage II treatment				**<0.01**	**0.01**
Partial Nx	585 (5.9%)	474 (15.5%)	164 (7.7%)		
Radical Nx	9,412 (94.2%)	2,580 (84.5%)	1,954 (92.3%)		
Stage III treatment				**<0.01**	**<0.01**
Partial Nx	1,622 (9.1%)	655 (25.3%)	281 (19.1%)		
Radical Nx	15,330 (86.2%)	1,808 (69.9%)	1,141 (77.6%)		
Nx + Systemic	841 (4.7%)	124 (4.8%)	48 (3.3%)		
Stage IV treatment				**<0.01**	**<0.01**
Nx alone	3,920 (34.3%)	459 (35.6%)	121 (48.9%)		
Nx + systemic	4,128 (36.1%)	392 (30.4%)	68 (27.5%)		
Systemic alone	3,376 (29.6%)	440 (34.1%)	58 (23.5%)		

Bold font indicates statistical significance.

Table 2
Pathologic data of patients with clear cell, papillary, and chromophobe renal cell carcinoma

	Clear cell	Papillary	Chromophobe	*P* (pRCC vs. ccRCC)	*P* (chRCC vs. ccRCC)
AJCC pathologic stage				**<0.01**	**<0.01**
1	75,473 (65.4%)	21,131 (74.8%)	8,003 (67.0%)		
2	10,223 (8.9%)	3,146 (11.1%)	2,176 (18.2%)		
3	18,245 (15.8%)	2,676 (9.5%)	1,516 (12.7%)		
4	11,424 (9.9%)	1,291 (4.6%)	247 (2.1%)		
Pathologic T Stage				**<0.01**	**<0.01**
pT1	76,580 (68.8%)	21,348 (76.9%)	8,038 (67.7%)		
pT2	11,522 (10.4%)	3,347 (12.1%)	2,217 (18.7%)		
pT3	22,177 (19.9%)	2,879 (10.4%)	1,568 (13.2%)		
pT4	1,072 (0.9%)	158 (0.6%)	47 (0.4%)		
Pathologic N stage				**<0.01**	**<0.01**
pN0	50,775 (95.9%)	12,865 (94.6%)	5,774 (97.9%)		
pN1	2,141 (4.1%)	734 (5.4%)	126 (2.1%)		
Clinical or pathologic distant mets				**<0.01**	**<0.01**
M0	104,387 (90.5%)	27,043 (95.6%)	11,726 (98.2%)		
M1	10,956 (9.5%)	1,200 (4.3%)	214 (1.8%)		
Sites of distant metastases					
Bone	1,736 (36.3%)	149 (30.4%)	30 (35.7%)	**0.09**	0.916
Brain	461 (9.6%)	26 (5.3%)	3 (3.6%)	**0.02**	0.64
Liver	618 (12.9%)	94 (19.1%)	19 (22.4%)	**<0.01**	**0.11**
Lung	2,621 (54.9%)	196 (40.2%)	28 (33.3%)	**<0.01**	**<0.01**
Fuhrman grade				**<0.01**	**<0.01**
1	12,955 (13.0%)	2,849 (12.6%)	634 (7.8%)		
2	54,099 (54.3%)	12,179 (53.7%)	4,394 (54.0%)		
3	26,918 (27.0%)	6,939 (30.6%)	2,657 (32.7%)		
4	5,603 (5.6%)	694 (3.1%)	449 (5.5%)		
Surgical margin status				0.622	**0.06**
Negative	104,371 (94.7%)	25,751 (94.8%)	11,093 (95.3%)		
Positive	5781 (5.3%)	1,405 (5.2%)	542 (4.7%)		

Bold font indicates statistical significance.

For patients with pRCC, the rate of high-grade (3–4) disease was 33.7%, the rate of pT stage 3–4 was 11.0%, the rate of pathologic nodal metastases was 5.4%, and the rate of distant metastases was 4.3%.

For patients with chRCC, the rate of high-grade (3–4) pathology was 38.2%, the rate of pT stage 3–4 was 13.6%, the rate of pathologic nodal metastases was 2.1%, and the rate of distant metastases was 1.8%.

3.3. Survival outcome

The OS for ccRCC at 1, 5, and 10 years was 93.4%, 75.5%, and 54.2%. For pRCC, OS at 1, 5, and 10 years was 94.3%, 78.4%, and 57.3%, while 1-, 5-, and 10-year OS for chRCC was 97.1%, 86.3%, and 67.0% (Fig. 1).

Kaplan-Meier curves for OS by stage are presented in Fig. 1. Number at risk at each time interval for Kaplan-Meier analyses are presented in Table 3.

The 5-year OS for stage I ccRCC, pRCC, and chRCC was 86.1%, 84.5%, and 88.6%, respectively. Multivariable analysis showed no significant difference in hazard of death for stage I pRCC vs. ccRCC (hazard ratio [HR] = 1.03; 95% confidence interval [CI] = 0.98, 1.09; $P = 0.221$) and prolonged OS for stage I chRCC vs. ccRCC (HR = 0.78; 95% CI = 0.72, 0.86; $P < 0.01$).

The 5-year OS for stage II ccRCC, pRCC, and chRCC was 78.8%, 76.9%, and 89.1%, respectively. Multivariable analysis showed no significant difference in hazard of death for stage II pRCC vs. ccRCC (HR = 1.02; 95% CI = 0.92, 1.14; $P = .709$) and prolonged OS for stage II chRCC vs. ccRCC (HR = 0.62; 95% CI = 0.52, 0.74; $P < 0.01$).

The 5-year OS for stage III ccRCC, pRCC, and chRCC was 66.9%, 63.6%, and 80.5%, respectively. Multivariable analysis showed that the hazard of death was significantly higher for stage III pRCC vs. ccRCC (HR = 1.26; 95% CI = 1.15, 1.37; $P < 0.01$) and prolonged OS for stage III chRCC vs. ccRCC (HR = 0.59; 95% CI = 0.51, 0.69; $P < 0.01$).

The 5-year OS for stage IV ccRCC, pRCC, and chRCC was 19.7%, 13.3%, and 22.0%, respectively. Multivariable analysis showed that the hazard of death was significantly higher for stage IV pRCC vs. ccRCC (HR = 1.29; 95% CI = 1.19, 1.39; $P < 0.01$) and similar OS for stage IV chRCC vs. ccRCC (HR = 1.01; 95% CI = 0.85, 1.21; $P = 0.885$; Fig. 2).

4. Discussion

Since the initial classification of histologic subtypes of RCC in 1997, much of the literature examining prognostic

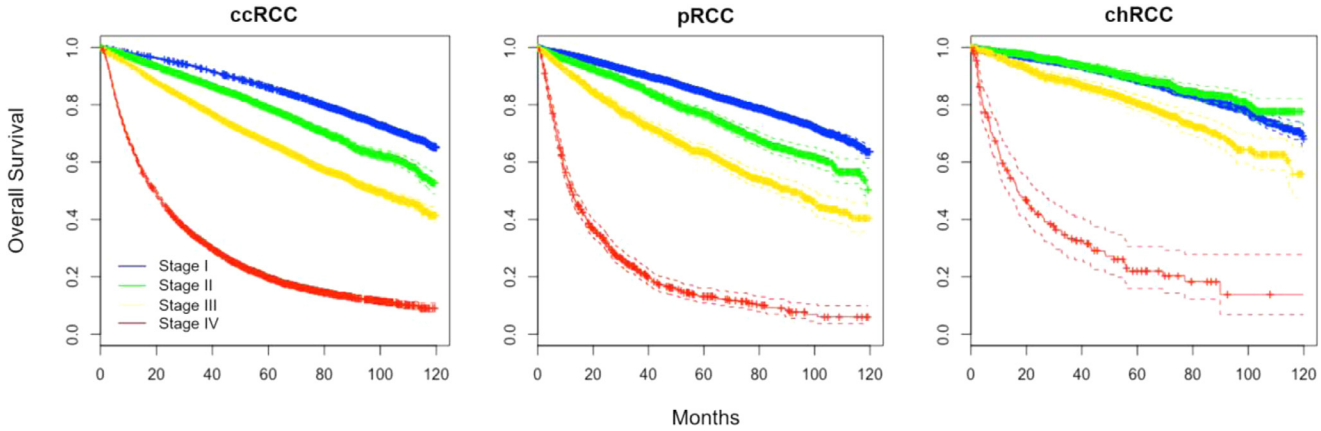

Fig. 1. Overall survival for clear cell, papillary, and chromophobe RCC by stage.

Table 3
Number at risk for Kaplan-Meier analyses

Time (mo)	0	24	48	72	96	120
ccRCC (N)						
Stage I	56,482	44,797	27,557	13,446	4,465	480
Stage II	7,911	6,167	3,762	1,894	620	64
Stage III	14,078	10,025	5,544	2,471	777	74
Stage IV	8,797	3,277	1,236	440	135	17
pRCC (N)						
Stage I	16,128	12,772	7,869	4,174	1,540	172
Stage II	2,445	1,886	1,207	601	219	27
Stage III	2,053	1,434	789	402	151	11
Stage IV	949	270	93	42	12	0
chRCC (N)						
Stage I	5,984	4,813	3,167	1,711	651	63
Stage II	1,467	1,210	785	435	168	15
Stage III	1,111	845	526	265	94	16
Stage IV	176	63	31	11	2	1

differences among them has indicated a better prognosis for pRCC and chRCC compared to ccRCC, particularly in lower-stage disease [5,9,13]. Still, there are cases of both non–clear cell histologies with poor prognosis, and the precise prognostic value of histology among more advanced cases remains uncertain. In our cohort, 25.9% of patients presented with pRCC or chRCC, which is in accordance with reported rates in the literature of 14% to 28% [3–5]. Despite the reputation of papillary and chromophobe histologies having a more favorable prognosis, our analysis shows that these histologic subtypes indeed have metastatic potential and are as lethal as ccRCC when reaching this stage. Accordingly, our analysis of stage IV RCC showed worse OS for pRCC compared to ccRCC, and similar OS between stage IV chRCC and ccRCC.

One possible explanation for this increased hazard of death in late-stage pRCC is limited histology-specific drug development. Metastatic RCC do not respond well to chemotherapy, and alternative systemic therapies are limited [3]. Furthermore, studies of targeted therapies for RCC are generally focused on ccRCC, as it is the most common histologic subtype. It is estimated that histologies other than ccRCC make up less than 10% of patient populations in RCC clinical trials [14], whereas the incidence of these histologies in our cohort was roughly 25%. It follows that efficacy of treatments for RCC is primarily determined by how effective these modalities are in treating ccRCC, and not other histologies. Though differences in surgical outcomes based on histologic subtype have not been seen [15], the potential for differences in response to adjuvant or neoadjuvant therapies remains.

Our study shows that a large proportion of advanced non-ccRCC cases are treated with adjuvant or neoadjuvant systemic therapy. Specifically, 64.5% of pRCC patients and 51% of chRCC patients within our cohort were treated systemically to some degree. However, results from randomized control trials in recent years show that non-ccRCC patients have worse outcomes in terms of resposnse rates, progression-free survival (PFS), and OS compared to ccRCC [7]. In a phase II trial on everolimus, a selective inhibitor of mammalian target of rapamycin kinase, results showed a median PFS and OS of 5.2 and 14.0 months, respectively, in patients with non-ccRCC histologies, including papillary, chromophobe, collecting duct, sarcomatoid, and unclassifiable tumors [16]. In contrast, a phase II trial studying the efficacy of everolimus only on patients with predominantly ccRCC histology found median PFS and OS of 11.2 and 22.1 months, respectively [17]. In an efficacy assessment study of sunitinib, a tyrosine kinase receptor inhibitor that targets the VEGF receptor, among other tyrosine kinase receptor inhibitors, the non-ccRCC subgroup showed a median PFS and OS of 7.8 and 13.4 months, respectively, compared to 10.9 and 18.4 months in the overall study population [18]. These results were echoed in a recent phase II trial comparing everolimus to sunitinib in both clear cell and non-clear cell patients (RECORD-3). The authors reported a median PFS of 5.1 and 8.1 months for everolimus in patients with non-ccRCC and ccRCC, respectively, and a median PFS of 7.2 and 10.8

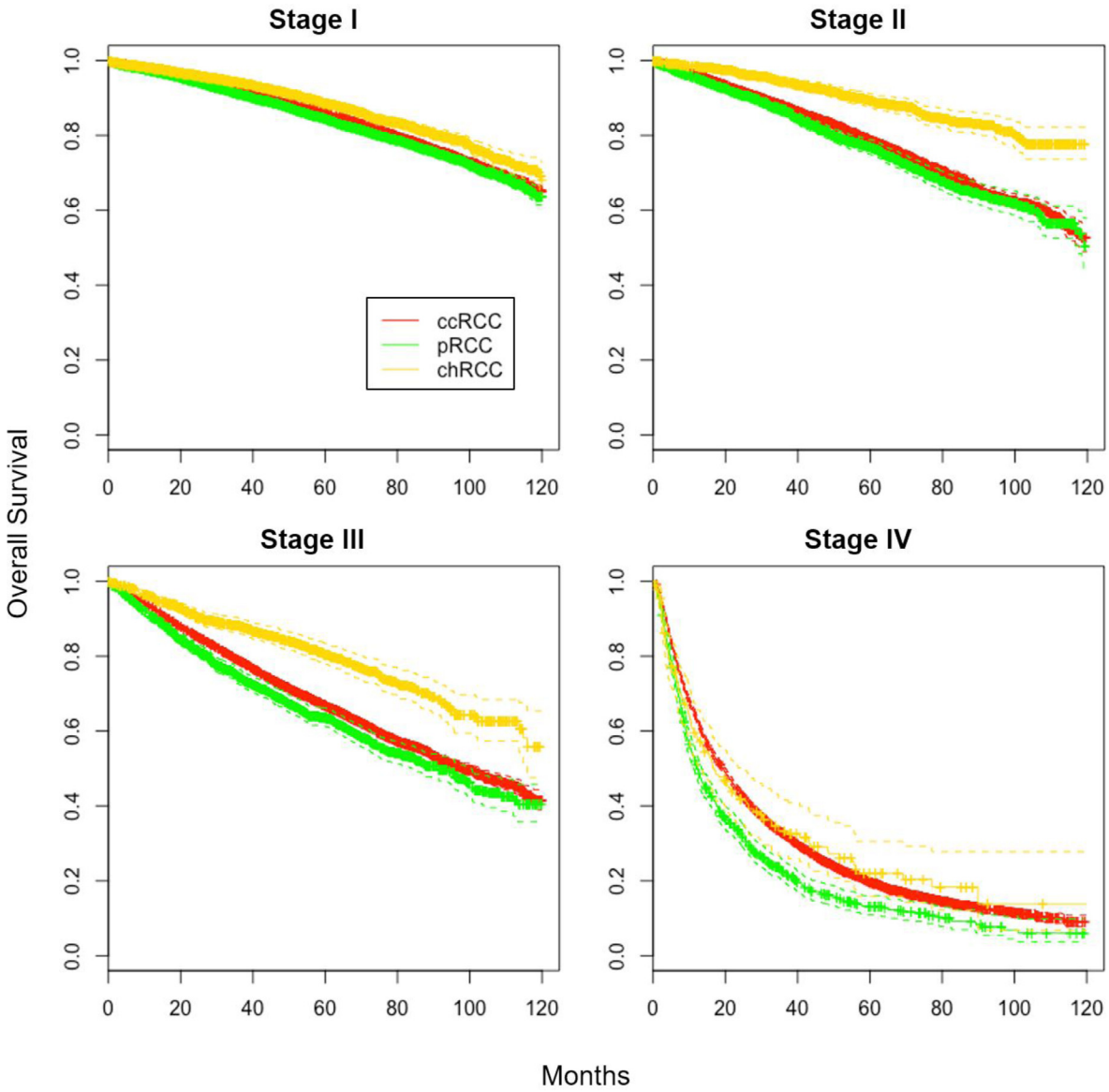

Fig. 2. Overall survival for stage I, II, III, and IV RCC by histology.

months for sunitinib in patients with non-ccRCC and ccRCC, respectively [19]. These poorer outcomes for non-ccRCC in clinical trials support our findings with regards to OS for stage IV chRCC and pRCC compared to ccRCC.

It should be noted that there have been increasing efforts in recent years to evaluate targeted therapy specifically toward non-ccRCC patients. Most notably, the ESPN and ASPEN trials, which each compared the efficacy of everolimus and sunitinib exclusively in non-ccRCC patients, reported median PFS of 4.1 vs. 6.1 months (ESPN, everolimus vs. sunitinib) and 5.6 vs. 8.3 months (ASPEN, everolimus vs. sunitinib) [20,21]. Still, median PFS results from these trials remain lower than those for ccRCC in the aforementioned trials, as well as the overall median PFS of ccRCC patients (10.5 months) based on the meta-analysis conducted by Vera-Badillo et al [7]. Furthermore, these trials continue to be outnumbered by those that are not histology specific, further compounding the issue of diminished outcomes among non-ccRCC cases.

Another possible explanation for the decreased survival seen in late-stage pRCC is the lack of discrimination between Type 1 pRCC (pRCC1) and Type 2 pRCC (pRCC2) in our analysis, as the NCDB does not contain data on pRCC1 vs. pRCC2. pRCC1 and pRCC2 are known to have different histologies, genotypes, and clinical features [22]. Of note, pRCC2 has been found to be associated with higher stage and grade, as well as worse survival compared to pRCC1 [23]. Furthermore, pRCC1 is more common than pRCC2, making up 60% to 70% of papillary tumors [3]. Thus, it may be that Type 2 pRCC comprises a higher proportion of the metastatic cases in our papillary cohort compared to Type 1 pRCC, which may explain both the similar OS observed for stages I/II and the worse OS observed for stages III/IV pRCC vs. ccRCC.

Most of our demographic results reflected what has already been established in the literature. Patients are known to present with RCC around the sixth decade of life, which coincides with our mean age of presentation in both histologic subtypes. There is also a known predominance of RCC in men over women, however this predominance has been shown to be less pronounced among chRCC, which has a similar incidence in both sexes [3,24]. Lastly, papillary RCC has been shown to have a higher occurrence among black patients compared to other histologic subtypes, which was also seen in our cohort, where black patients made up 26.2% of pRCC cases but only 12.7% of chRCC cases [25].

Our results also showed that 66.0% of stage IV pRCC and 76.4% of stage IV chRCC patients were treated with nephrectomy, either alone or in combination with systemic therapy, showing a larger proportion of stage IV chRCC cases who received nephrectomy compared to pRCC cases. In a study using the Surveillance, Epidemiology, and End Results database, Aizer et al found that patients with metastatic non-ccRCC who received cytoreductive nephrectomy showed improved survival compared those who did not, but that the survival benefit was greatest among chRCC and least among pRCC [26]. In our cohort, more patients with stage IV chRCC received treatment with nephrectomy compared to stage IV pRCC patients. If these chRCC patients also had a higher likelihood of actually benefitting from nephrectomy, this could partly account for the OS of stage IV chRCC being as good as that of stage IV ccRCC. Likewise, the lower survival benefit of nephrectomy in stage IV papillary patients could have contributed to the decreased OS in stage IV pRCC vs. ccRCC. Still, recent studies of metastatic RCC, including the CARMENA trial, have shown that outcomes following nephrectomy depend greatly on clinical characteristics such as extent of disease and performance status, which are difficult to account for in large retrospective analyses such as the study presented here, and it is important to consider such limitations when interpreting results [27].

Another point noted in our analysis was that chromophobe RCC had significantly better survival compared to clear cell and papillary for stages I, II, and III. This could mean that localized chRCC has a better prognosis than localized pRCC or ccRCC, a finding that has been shown in prior peer-reviewed studies as well [28].

Ultimately the differences between histologic subtypes of RCC stem from genomic differences. ccRCC, for instance, has been shown to be associated with loss of the von Hippel-Lindau tumor suppressor gene, leading to stabilization of hypoxia-inducible factor, which induces several targets downstream, including VEGF [6]. Type 1 pRCC, on the other hand, has been associated with the proto-oncogene *MET*, and Type 2 pRCC with *CDKN2A*, while chRCC is known to be associated with variations in the *TERT* promoter region leading to *TERT* upregulation [29,30]. Such characterization studies are imperative in identifying potentially druggable pathways, and continued efforts must be made toward improving our understanding of the genomic differences separated histologic subtypes of RCC.

One of the greatest strengths of this study is the vast number of patients, which is to our knowledge the largest cohort studied to date comparing survival among RCC histologies. Furthermore, the NCDB represents about 70% of newly diagnosed cancers throughout the United States, providing multi-institutional data that is representative of a majority of the US population. This study is inherently limited by the use of NCDB data, which is retrospective and susceptible to unobserved confounders and missing data. Furthermore, due to its multicenter nature, there was no central histopathologic review, a limitation further compounded by the lack of differentiation between pRCC1 and pRCC2 within the NCDB. Another key limitation is that the NCDB provides data on OS as opposed to cancer-specific survival data. Further research and more clinical trials are necessary to identify optimal treatment strategies for these select patients diagnosed with non–clear cell RCC.

5. Conclusions

In our cohort 25.9% of patients presented with either pRCC or chRCC. The rates of advanced ccRCC, pRCC, and chRCC were found to be 25.7%, 14.1%, and 14.8%, respectively. Although pRCC and chRCC are less likely to be advanced than ccRCC, aggressive cases of these non–clear cell histologies do exist with similar survival to ccRCC when advanced. Further genomic efforts to characterize advanced non-ccRCC are imperative to allow for more improved design of clinical trials, greater precision in risk stratification of patients, better patient counseling, and, ultimately, improved outcomes for advanced pRCC and chRCC.

Authors' contributions

Alain Kaldany: Writing manuscript, data gathering, and conceptualization. David Paulucci: Formal analysis and writing manuscript. Muthumeena Kannappan: Formal analysis. Alp Tuna Beksac: Writing, review, and editing. Harry Anastos: Writing, review, and editing. Kennedy Okhawere: Formal analysis. John P. Sfakianos: Conceptualization, review, and editing. Ketan K. Badani: Conceptualization, review, and editing.

Conflicts of interest

None.

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