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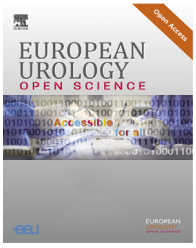

European Association of Urology

Kidney Cancer

Trends and Outcomes in Sarcomatoid Renal Cell Carcinoma: Analysis of the National Cancer Data Base

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Abstract

Background and objective: Our aim was to determine the clinical characteristics, temporal trends, and survival outcomes for sarcomatoid-dedifferentiated renal cell carcinoma (sRCC), as sRCC has historically had poor prognosis and a contemporary cohort has not been well characterized in a population-based study.
Methods: Data for 302 630 RCC cases from 2010 to 2019 were extracted from the National Cancer Data Base, of which 4.1% (12 329) were sRCC. Trend analyses were conducted using the Cochran-Armitage test. Multivariable analyses were used to assess factors associated with sRCC diagnosis and clinicopathologic characteristics associated with all-cause mortality (ACM). Overall survival (OS) was computed via Kaplan-Meier analysis.
Key findings and limitations: sRCC incidence increased from 3.9% in 2010 to 4.1% in 2019 (p = 0.020). The incidence of stage I sRCC increased from 14.5% in 2010 to 19.2% in 2019 (p < 0.001). sRCC diagnosis was associated with male sex, tumor size, cN1 status, and collecting duct histology. Worse ACM in localized sRCC was associated with age, tumor size, cN1 stage, collecting duct histology, and positive surgical margins; and was inversely associated with partial nephrectomy (hazard ratio [HR] 0.61, 95% confidence interval [CI] 0.49–0.76; p < 0.001). Worse ACM in metastatic sRCC was associated with age, tumor size, cN1, collecting duct histology, positive surgical margins, and no surgery at the primary site (HR 1.66, 95% CI 1.20–2.30; p = 0.006). The 5-yr OS rates for stage I, stage II, stage III, and stage IV sRCC were 74%, 63%, 42%, and 16%, respectively (p < 0.001).
Conclusions and clinical implications: The proportion of sRCC cases overall and of stage I sRCC cases increased from 2010 to 2019, supporting the hypothesis of stage

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migration and the potential for early sarcomatoid dedifferentiation. Further studies on the causal mechanisms underpinning better survival after partial nephrectomy in localized disease and after cytoreductive surgery in metastatic disease are warranted.

Patient summary: We analyzed trends and outcomes for a type of aggressive kidney cancer (sarcomatoid renal cell carcinoma, sRCC) using records from the National Cancer Data Base. We found that the percentage of sRCC cases among all kidney cancers increased from 2010 to 2019. Factors such as tumor size and patient age were linked to worse survival. Surgery to remove the cancer was linked to better survival.

1. Introduction

Renal cell carcinoma (RCC) with sarcomatoid dedifferentiation (sRCC) can manifest in any RCC histology [1]. In comparison to RCC without sarcomatoid dedifferentiation, sRCC is associated with worse cancer-specific mortality and all-cause mortality (ACM) across stages [2,3]. A significant proportion of sRCC cases present with synchronous metastases, while up to 20% of metastatic RCC cases have sarcomatoid dedifferentiation [2–5].

The past two decades have witnessed stage migration in RCC, driven by increasing use of abdominal imaging and subsequent incidental diagnosis of asymptomatic small masses [6]. However, the impact of stage migration on sRCC incidence and outcomes is unclear. We sought to analyze trends, management, and overall survival (OS) outcomes for sRCC using data from the National Cancer Data Base (NCDB). In particular, we assessed the effects of surgical intervention on the primary tumor with adjustment for patient-, demographic-, and disease-specific confounders.

2. Patients and methods

2.1. Study population and patient selection

We analyzed the NCDB, which contains data from >1500 hospitals and 70% of new cancer diagnoses [7]. All data are derived from chart review [8]. The patient selection process is presented in Figure 1. The study population consisted of adults aged ≥18 yr diagnosed with RCC from 2010 to 2019. Patients were classified as having RCC if they had International Classification of Diseases for Oncology-Third Edition (ICD-O-3) code C64.9. Patients with Histology ICD-0-3 code 8120, indicative of urothelial carcinoma, were excluded. Patients with Sequence Number 00, meaning they had only one primary malignancy in their lifetime, were included to ensure that analysis was not confounded by treatment for non-RCC malignancies. Cases diagnosed at the reporting facility but treated elsewhere (Class of Case 00) were excluded [9]. After applying these filters, 302 630 patients were eligible for inclusion.

We identified all patients with sRCC, specifically patients with: (1) sarcomatoid features on Site Specific Data Item 3925 (Site Specific Data Item Manual version 2.1), (2) Collaborative Stage (CS) Data Collection System, CS Site-Specific Factor 4 (Collaborative Staging Schema v02.05), or (3) Histology ICD-O-3 code 8318 or 8033 [10,11]. Given the high frequency of synchronous metastasis in sRCC, we excluded cases with missing data on whether the metastasis was synchronous (n = 4908). Application of these filters identified 12 329 patients with sRCC. We analyzed the following histologies: clear cell (ICD-O-3 codes 8005, 8310), papillary (code 8260), chromophobe (codes 8270, 8317), collecting duct (code 8319), medullary (code 8510), cyst-associated (code 8316), and RCC not otherwise specified (codes 8312, 8255), and classified the remaining cases as "other". NCDB classifies chemotherapy according to the Surveillance, Epidemiology and End Results (SEER) antineoplastic drugs database. Accordingly, tyrosine kinase inhibitors and mTOR inhibitors are classified as chemotherapy, while immune checkpoint inhibitors are classified as immunotherapy [11,12]. NCDB classifies follow-up as the time in months from the date of the initial diagnosis to the date of last contact or death.

2.2. Statistical analysis

Trend analyses were conducted using the Cochran-Armitage test; the annual average percentage change (AAPC) was computed by applying linear regression to computed percentages. We analyzed trends from 2010 to 2019 for the proportion of American Joint Committee on Cancer (AJCC) stage I–IV cases among all sRCC diagnoses.

Multivariable logistic regression was used to identify clinicopathological characteristics associated with sRCC diagnosis. Multivariable Cox proportional-hazards regression was conducted to analyze the impact of clinicopathological characteristics on ACM in locally resected and metastatic sRCC. 3173 cases with sarcomatoid dedifferentiation were coded under the Participant User File variable Histology rather than as a separate variable; these cases were excluded from the multivariable analyses to avoid multicollinearity. OS was estimated via the Kaplan-Meier method. All statistical analyses were performed on R Studio version 2022.12.0+353 (R Foundation for Statistical Analysis, Vienna, Austria). Holm's correction was applied in multivariable models to adjust for multiple comparisons when candidate variables had more than two categories [13]. All p values are two-tailed, with $p < 0.05$ considered statistically significant.

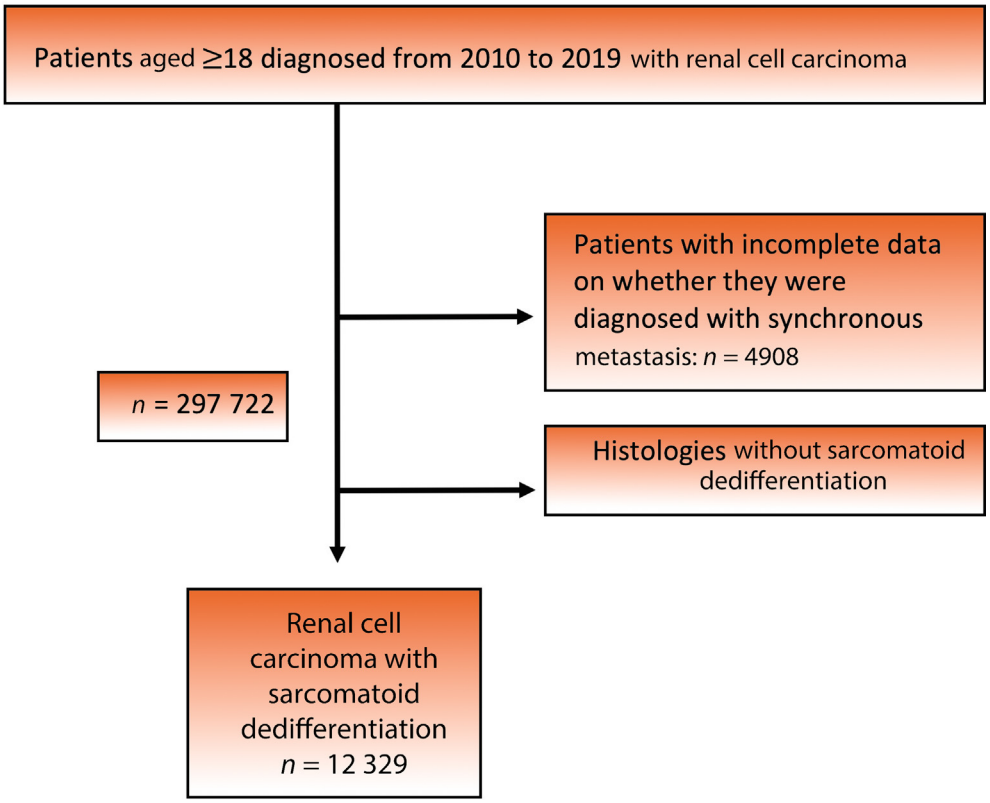

Fig. 1 – Selection criteria for the primary analytical cohort.

3. Results

3.1. Trend analysis

Table 1 lists the characteristics of RCC cases with and without sarcomatoid dedifferentiation from 2010–2019; 12 329 patients had sRCC (4.1%). The proportion of sRCC cases increased from 3.9% in 2010 to 4.1% in 2019 (Cochran-Armitage $p = 0.020$). In comparison to the non-sRCC group, the sRCC group had a larger primary tumor size (9 vs 5 cm; $p < 0.001$) and higher incidence of cN1 status (19% vs 4.4%; overall $p < 0.001$) and AJCC stage III (28% vs 13%; overall $p < 0.001$) and stage IV (46% vs 12%; overall $p < 0.001$). Supplementary Table lists sRCC management strategies by stage. Nephrectomy was performed in 54% of stage I, 92% of stage II, 94% of stage III, and 72% of stage IV sRCC cases. Partial nephrectomy (PN) was performed in 30% of stage I, 5.4% of stage II, 4.4% of stage III, and 1.9% of stage IV sRCC cases. Of the patients with stage IV sRCC, 18% received immunotherapy and 47% received chemotherapy.

Figure 2 shows the trend analysis from 2010 to 2019 for sRCC stratified by AJCC stage. Overall, 15% of sRCC cases presented as stage I, 8.2% as stage II, 30% as stage III, and 46% as stage IV. The proportion of stage I sRCC cases increased from 15% in 2010 to 19% in 2019, with AAPC = 0.4 (Cochran-Armitage $p < 0.001$). Changes in the proportions of stage II–IV sRCC cases were not significant. Specifically, the proportion of stage II sRCC cases increased from 7.7% in 2010 to 7.8% in 2019 (Cochran-Armitage $p = 0.19$). The proportion of stage III sRCC cases increased from 28% in 2010 to 29% in 2019 (Cochran-Armitage $p = 0.12$). The proportion of stage IV sRCC cases decreased from 49% in 2010 to 45% in 2019 (Cochran-Armitage $p = 0.6$).

3.2. Variables associated with sRCC diagnosis

Table 2 shows the multivariable logistic regression results for the association of variables with sRCC diagnosis in the entire RCC cohort. sRCC diagnosis was associated with year of diagnosis, male sex, diagnosis/treatment at an academic center, greater tumor size, cN1 status, higher AJCC stage, and collecting duct histology; and was inversely associated with older age in 10-yr increments, self-identification as black, and papillary and chromophobe histology.

3.3. Variables associated with ACM in locally resected sRCC

Table 3 lists multivariable Cox proportional-hazards regression results for the association of variables with ACM in locally resected and metastatic sRCC. Worse ACM in locally resected sRCC was associated with older age, Charlson score ≥2, greater tumor size (hazard ratio [HR] 1.03, 95% confidence interval [CI] 1.01–1.04; $p < 0.001$), cN1 status, stage III sRCC, collecting duct histology, and positive surgical margins; and was inversely associated with cryoablation or thermal ablation, and PN (HR 0.61, 95% CI 0.49–0.76; $p < 0.001$). Supplementary Table 2 lists the characteristics of patients with locally resected sRCC who underwent radical nephrectomy (RN) versus PN. Comparison of potential

Table 1 – Characteristics of patients with renal cell carcinoma with or without sarcomatoid dedifferentiation

Variable	RCC without SDD (*n* = 285 393)	RCC with SDD (*n* = 12 329)	*p* value
Median age, yr (interquartile range)	62 (53–70)	62 (54–70)	<0.001
Year of diagnosis 2016–2019, *n* (%)	187 206 (66)	8229 (67)	0.009
Male sex, *n* (%)	176 809 (62)	8400 (68)	<0.001
Race, *n* (%)			<0.001
White	235 956 (83)	10 511 (85)	
Black	34 077 (12)	1132 (9.2)	
Native American	1734 (0.61)	78 (0.63)	
Asian/Pacific Islander	6784 (2.4)	317 (2.6)	
Other/unknown	6842 (2.4)	291 (2.4)	
Hispanic, *n* (%)			0.2
Yes	23 635 (8.3)	1012 (8.2)	
Unclassified	7702 (2.7)	301 (2.4)	
Facility location, *n* (%)			<0.001
New England	13 004 (4.6)	591 (4.8)	
Middle Atlantic	39 490 (14)	1810 (15)	
South Atlantic	55 240 (19)	2339 (19)	
East North Central	47 090 (17)	2293 (19)	
East South Central	21 250 (7.4)	811 (6.6)	
West North Central	21 600 (7.6)	996 (8.1)	
West South Central	30 380 (11)	1332 (11)	
Mountain	11 572 (4.1)	469 (3.8)	
Pacific	29 954 (10)	1310 (11)	
Unclassified	15 813 (5.5)	378 (3.1)	
Facility type, *n* (%)			<0.001
Community	13 584 (4.8)	560 (4.5)	
Community comprehensive	93 299 (33)	3854 (31)	
Academic	111 360 (39)	5472 (44)	
Integrated cancer network	51 337 (18)	2065 (17)	
Unclassified	15 813 (5.5)	378 (3.1)	
Median income, *n* (%)			0.050
First quartile (lowest)	45 533 (16)	1900 (15)	
Second quartile	58 955 (21)	2558 (21)	
Third quartile	67 189 (24)	3028 (25)	
Fourth quartile	77 010 (27)	3315 (27)	
Unclassified	36 706 (13)	1528 (12)	
Charlson comorbidity score, *n* (%)			<0.001
0	193 869 (68)	8706 (71)	
1	57 107 (20)	2322 (19)	
2	19 738 (6.9)	759 (6.2)	
≥3	14 679 (5.1)	542 (4.4)	
Median tumor size, cm (interquartile range)	5.0 (3.0–7.0)	9.0 (6.0–12)	<0.001
Clinical T stage, *n* (%)			<0.001
cT1	170 670 (60)	2801 (23)	
cT2	36 576 (13)	3248 (26)	
cT3	22 211 (7.8)	2913 (24)	
cT4	3362 (1.2)	846 (6.9)	
Unclassifed	52 574 (18)	2521 (20)	
Clinical N stage, *n* (%)			<0.001
cN1	12 601 (4.4)	2398 (19)	
Unclassified	38 484 (13)	2136 (17)	
Clinical cM1 stage, *n* (%)	33 078 (12)	5280 (43)	<0.001
AJCC stage, *n* (%)			<0.001
Stage I	172 535 (60)	1786 (14)	
Stage II	23 210 (8.0)	972 (7.6)	
Stage III	37 219 (13)	3599 (28)	
Stage IV	35 899 (12)	5835 (46)	
Unclassified	21 022 (7.3)	553 (4.3)	
Histology, *n* (%)			<0.001
Clear cell	157 883 (55)	4890 (53)	
Papillary	33 969 (12)	499 (5.4)	
Chromophobe	15 525 (5.4)	289 (3.2)	
Collecting duct	342 (0.12)	70 (0.57)	
Medullary	190 (0.066)	19 (0.15)	
Cyst-associated	1054 (0.37)	8 (0.065)	
RCC not otherwise specified	68 638 (24)	3041 (33)	
Other	7792 (2.7)	340 (3.7)	
Tumor grade, *n* (%)			<0.001
Grade 1	26 952 (9.4)	110 (0.89)	
Grade 2	118 748 (42)	543 (4.4)	
Grade 3	66 469 (23)	1777 (14)	
Grade 4	13 342 (4.7)	7736 (63)	
Unclassified	59 882 (21)	2163 (18)	
Tumor necrosis, *n* (%)			<0.001
Yes	22 195 (7.8)	3744 (30)	

(*continued on next page*)

Table 1 (*continued*)

Variable	RCC without SDD (n = 285 393)	RCC with SDD (n = 12 329)	p value
Unclassified	129 472 (45)	5359 (43)	
Lymphovascular invasion, *n* (%)			<0.001
Yes	18 824 (6.6)	3363 (27)	
Unclassified	100 344 (35)	4329 (35)	
Surgery at the primary site, *n* (%)			<0.001
No surgery	36 706 (13)	1676 (14)	
Radical nephrectomy	130 014 (46)	9525 (77)	
Partial nephrectomy	99 451 (35)	898 (7.3)	
Cryoablation/thermal ablation	16 620 (5.8)	160 (1.3)	
Unclassified	2602 (0.91)	70 (0.57)	
Surgical margin status, *n* (%)			<0.001
Positive	13 475 (4.7)	1940 (16)	
Unclassified	55 954 (20)	2097 (17)	
Metastasectomy, *n* (%)			<0.001
Yes	8564 (3.0)	1320 (10.7)	
Unclassified	1512 (0.53)	46 (0.37)	
Chemotherapy receipt, *n* (%)			<0.001
Yes	18 203 (6.4)	3313 (27)	
Unclassified	2721 (1.0)	274 (2.2)	
Immunotherapy receipt, *n* (%)			<0.001
Yes	5950 (2.1)	1176 (9.5)	
Unclassified	699 (0.24)	41 (0.33)	
Median follow-up, mo (interquartile range)	48 (26–75)	21 (6.4–45)	<0.001
Unclassified (*n*)	32 765	1411	
Vital status at follow-up (*n*)			<0.001
Dead	63 373	6963	
Unclassified	32 886	1415	

RCC = renal cell carcinoma; SDD = sarcomatoid dedifferentiation; AJCC = American Joint Committee on Cancer.

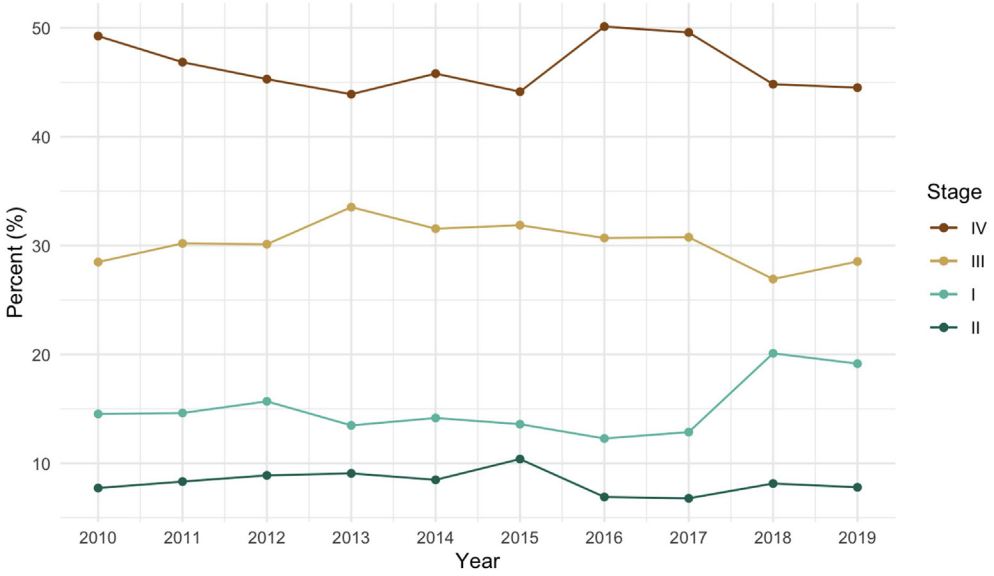

Fig. 2 – Proportion of renal cell carcinoma cases with sarcomatoid dedifferentiation stratified by American Joint Committee on Cancer stage.

confounders between these groups showed that the PN group had a smaller tumor size, lower prevalence of cN1 disease, and lower AJCC stage.

ACM in synchronous metastatic stage IV sRCC was positively associated with older age, greater tumor size (HR 1.02, 95% CI 1.01–1.03; $p < 0.001$), cN1 status, chromophobe histology, collecting duct histology, no surgery for the primary site (HR 1.66, 95% CI 1.20–2.30; $p = 0.006$), cryoablation or thermal ablation, and positive surgical margins; and was inversely associated with diagnosis/treatment at a community comprehensive center, academic center, or integrated cancer network, metastasectomy, chemotherapy, and immunotherapy. Supplementary Table 3 lists the characteristics of patients with metastatic sRCC who underwent cytoreductive RN versus no surgery. Comparison of potential confounders between the groups showed that metasta-

Table 2 – Multivariable logistic regression results for variables associated with a diagnosis of renal cell carcinoma with sarcomatoid dedifferentiation

	OR (95% CI)	*p* value
Age (per 10-yr increment)	0.93 (0.91–0.95)	<0.001
Year of diagnosis	1.06 (1.05–1.07)	<0.001
Male sex (vs female)	1.11 (1.06–1.17)	<0.001
Race		<0.001
White	Reference	
Black	0.81 (0.74–0.88)	
Native American	1.03 (0.77–1.34)	
Asian/Pacific Islander	1.01 (0.87–1.17)	
Other/unknown	1.04 (0.89–1.20)	
Hispanic ethnicity		0.001
No	Reference	
Yes	0.93 (0.86–1.02)	
Unclassified	0.92 (0.79–1.07)	
Facility location		<0.001
New England	Reference	
Middle Atlantic	1.10 (0.98–1.24)	
South Atlantic	1.00 (0.89–1.12)	
East North Central	1.16 (1.03–1.30)	
East South Central	0.91 (0.79–1.04)	
West North Central	0.99 (0.87–1.12)	
West South Central	0.95 (0.84–1.08)	
Mountain	0.87 (0.74–1.01)	
Pacific	0.89 (0.79–1.01)	
Unclassified	0.71 (0.58–0.87)	
Facility Type		<0.001
Community	Reference	
Community comprehensive	1.15 (1.03–1.29)	
Academic	1.24 (1.11–1.39)	
Integrated cancer network	1.09 (0.97–1.23)	
Median income		<0.001
First quartile (lowest)	Reference	
Second quartile	0.94 (0.87–1.02)	
Third quartile	1.03 (0.95–1.11)	
Fourth quartile	1.01 (0.94–1.09)	
Unclassified	1.07 (0.99–1.17)	
Charlson score ≥2 (vs 0–1)	0.95 (0.89–1.02)	0.005
Tumor size (per 1-cm increment)	1.08 (1.07–1.08)	<0.001
Clinical N stage		<0.001
cN0	Reference	
cN1	1.33 (1.25–1.42)	
Unclassified	1.04 (0.97–1.11)	
AJCC stage		<0.001
Stage I	Reference	
Stage II	2.66 (2.42–2.92)	
Stage III	6.03 (5.62–6.47)	
Stage IV	7.84 (7.27–8.46)	
Histology		<0.001
Clear cell	Reference	
Papillary	0.72 (0.65–0.80)	
Chromophobe	0.74 (0.65–0.84)	
Collecting duct	3.17 (2.39–4.13)	
Medullary	1.46 (0.84–2.39)	
Cyst-associated	0.51 (0.20–1.04)	
RCC not otherwise specified	1.24 (1.18–1.31)	
Other	0.57 (0.47–0.67)	

OR = odds ratio; CI = confidence interval; RCC = renal cell carcinoma; AJCC = American Joint Committee on Cancer.

sectomy was more frequent in the cytoreductive RN group, but tumor size, cN1 incidence, and rates of receipt of chemotherapy or immunotherapy were comparable.

3.4. OS in sRCC

Figure 3A shows Kaplan-Meier curves for OS in sRCC stratified by stage, while Figure 3B–F shows OS for each sRCC stage stratified by surgical treatment modality. The 5-yr OS rates were 74% (95% CI 71–76%) for stage I, 63% (95% CI 59–66%) for stage II, 42% (95% CI 40–44%) for stage III, and 16% (95% CI 15–17%) for stage IV sRCC (log-rank $p < 0.001$). For stage Ia sRCC tumors ≤4 cm, the 5-yr OS rates were 81% (95% CI 67–98%) after cryoablation or thermal ablation, 79% (95% CI 74–85%) after nephrectomy, and 91% (95% CI 87–95%) after PN (log-rank $p = 0.002$). For stage Ib sRCC tumors >4 cm, the 5-yr OS rates were 65% (95% CI 61–69%) after nephrectomy and 75% (95% CI 68–83%) after PN (log-rank $p = 0.012$). For stage II sRCC, the 5-yr OS rates were 65% (95% CI 61–69%) after nephrectomy and 62% (49–79%) after PN (log-rank $p = 0.6$). For stage III sRCC, the 5-yr OS rates were 43% (95% CI 41–46%) after nephrectomy and 62% (95% CI 54–72%) after PN (log-rank $p = 0.001$). For stage IV sRCC, the 5-yr OS rates were 19% (95% CI 17–21%) after nephrectomy and 19% (95% CI 11–30%) after PN (log-rank $p = 0.8$).

4. Discussion

We report findings from the largest contemporary analysis of trends, outcomes, and management for sRCC. We noted that the proportion of low-stage sRCC cases increased from 2010 to 2019 in conjunction with an increase in the overall proportion of sRCC cases, supporting the concept of stage migration in this aggressive histology and potential for early sarcomatoid dedifferentiation in the tumor life cycle. Furthermore, in locally resected sRCC, PN with negative surgical margins was not associated with worse ACM, while in synchronous metastatic stage IV sRCC, no cytoreductive surgery was associated with worse ACM in comparison to cytoreductive surgery. Further studies are warranted to investigate the causal mechanisms between PN and survival in localized disease, and between cytoreductive surgery and survival in metastatic disease.

In the past 30 years there has been an increase in the incidence of RCC. The increase in detection of asymptomatic early-stage RCC can be attributed to greater use of cross-sectional abdominal imaging, in addition to risk factors such as obesity, hypertension, and smoking [14,15]. While it has been suggested that this stage migration for RCC had stabilized by 2010 [16], our results suggest that stage migration is still observed for sRCC, with a significant increase in the proportion of stage I sRCC cases (from 15% to 19%; $p < 0.001$).

The molecular mechanisms driving sarcomatoid dedifferentiation in RCC have not been fully elucidated. Bi et al [17] showed that sarcomatoid components have a higher mutational burden than epithelial components. Furthermore, sRCC possibly develops from epithelial-derived RCC cells that undergo epithelial-to-mesenchymal transition [5,18]. These characteristics may increase metastatic potential in sRCC [19]. Our finding of a greater frequency of sarcomatoid dedifferentiation in small renal masses suggest that this process has potential to occur early in the tumor life cycle.

Our study represents the largest and most current analysis of PN versus RN in locally resected and metastatic sRCC. Given the predisposition to perform PN in younger, healthier patients with smaller tumors, we adjusted for these covariates in our logistic regression analyses. We found that in locally resected sRCC, with adjustment for patient and

Table 3 – Multivariable Cox proportional-hazards results for association of variables with all-cause mortality among patients with locally resected sRCC or synchronous metastatic stage IV sRCC

Variable	Locally resected sRCC		Synchronous metastatic sRCC	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Age (per 10-yr increment)	1.26 (1.20–1.33)	<0.001	1.11 (1.05–1.16)	<0.001
Male sex (vs female)	1.07 (0.96–1.19)	0.2	1.01 (0.91–1.12)	0.9
Race				
White	Reference		Reference	
Black	1.13 (0.95–1.36)	0.5	1.21 (1.02–1.44)	0.13
Native American	1.47 (0.78–2.77)	0.5	0.89 (0.55–1.46)	0.7
Asian/Pacific Islander	0.85 (0.60–1.21)	0.5	0.86 (0.62–1.18)	0.7
Other/unknown	0.69 (0.46–1.04)	0.3	0.79 (0.57–1.10)	0.5
Hispanic ethnicity				
No	Reference		Reference	
Yes	1.12 (0.91–1.37)	0.5	0.90 (0.75–1.09	0.6
Unclassified	1.08 (0.78–1.50)	0.6	0.90 (0.66–1.22	0.6
Facility location				
New England	Reference		Reference	
Middle Atlantic	0.92 (0.70–1.20)	1	1.01 (0.80–1.26)	1
South Atlantic	1.04 (0.80–1.35)	1	0.92 (0.74–1.15)	1
East North Central	1.00 (0.77–1.30)	1	0.96 (0.77–1.19)	1
East South Central	1.19 (0.88–1.62)	1	1.16 (0.90–1.50)	1
West North Central	1.09 (0.82–1.47)	1	0.87 (0.68–1.11)	1
West South Central	0.95 (0.72–1.27)	1	0.79 (0.62–1.02)	0.6
Mountain	1.11 (0.79–1.58)	1	0.89 (0.65–1.21)	1
Pacific	0.98 (0.73–1.31)	1	0.93 (0.73–1.17)	1
Unclassified	1.50 (0.89–2.52)	1	0.78 (0.52–1.18)	1
Facility type				
Community	Reference		Reference	
Community comprehensive	1.18 (0.91–1.52)	0.6	0.72 (0.58–0.89)	0.003
Academic	1.05 (0.81–1.34)	1	0.62 (0.50–0.77)	<0.001
Integrated cancer network	1.02 (0.78–1.34)	1	0.67 (0.53–0.84)	0.001
Median income				
First quartile (lowest)	Reference		Reference	
Second quartile	1.01 (0.85–1.18)	>0.9	0.96 (0.82–1.12)	0.9
Third quartile	0.91 (0.77–1.07)	0.5	0.94 (0.81–1.09)	0.9
Fourth quartile	0.85 (0.72–1.01)	0.2	0.87 (0.75–1.01)	0.2
Unclassified	0.73 (0.60–0.89)	0.006	0.72 (0.61–0.86)	0.001
Charlson score ≥2 (vs 0–1)r	1.61 (1.40–1.85)	<0.001	1.05 (0.89–1.23)	0.6
Tumor size	1.03 (1.01–1.04)	<0.001	1.02 (1.01–1.03)	<0.001
cN stage				
cN0	Reference		Reference	
cN1	1.59 (1.37–1.84)	<0.001	1.31 (1.18–1.45)	<0.001
Unclassified	0.96 (0.82–1.13)	0.7	1.13 (1.00–1.29	0.058
AJCC stage				
Stage I	Reference			
Stage II	1.17 (0.96–1.42)	0.13		
Stage III	1.92 (1.64–2.26)	<0.001		
Histology				
Clear cell	Reference		Reference	
Papillary	0.96 (0.78–1.18)	1	1.10 (0.84–1.44)	0.9
Chromophobe	1.11 (0.85–1.44)	1	1.56 (1.17–2.10)	0.009
Collecting duct	1.99 (1.25–3.16)	0.021	2.30 (1.51–3.51)	<0.001
Medullary	3.28 (1.03–10.4)	0.18	1.36 (0.59–3.14)	0.9
RCC not otherwise specified	1.17 (1.05–1.31)	0.024	1.22 (1.11–1.34)	<0.001
Other	1.15 (0.74–1.80)	1	2.26 (1.65–3.10)	<0.001
Margin status				
Negative	Reference		Reference	
Positive	1.60 (1.38–1.84)	<0.001	1.34 (1.21–1.50)	<0.001
Unclassified/not applicable	1.64 (1.12–2.40)	0.012	1.37 (1.02–1.85)	0.038
Surgery at the primary site				
Nephrectomy	–		Reference	
No surgery	Reference		1.66 (1.20–2.30)	0.006
Cryosurgery/thermal ablation	0.41 (0.19–0.88)	0.045	5.93 (2.13–16.5)	0.003
Partial nephrectomy	0.61 (0.49–0.76)	<0.001	1.07 (0.81–1.42)	0.6
Unclassified/other	0.72 (0.29–1.80)	0.5	1.96 (0.78–4.96)	0.3
Metastasectomy				
No			Reference	
Yes			0.85 (0.76–0.96)	0.013
Unclassified			1.78 (0.55–5.79)	0.3
Chemotherapy receipt				
No			Reference	
Yes			0.84 (0.76–0.93)	<0.001

Table 3 (*continued*)

Variable	Locally resected sRCC		Synchronous metastatic sRCC	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Unclassified			0.81 (0.59–1.09)	0.17
Immunotherapy receipt				
No			Reference	
Yes			0.49 (0.43–0.57)	<0.001
Unclassified			0.35 (0.13–0.95)	0.039

sRCC = renal cell carcinoma with sarcomatoid dedifferentiation; HR = hazard ratio; CI = confidence interval.

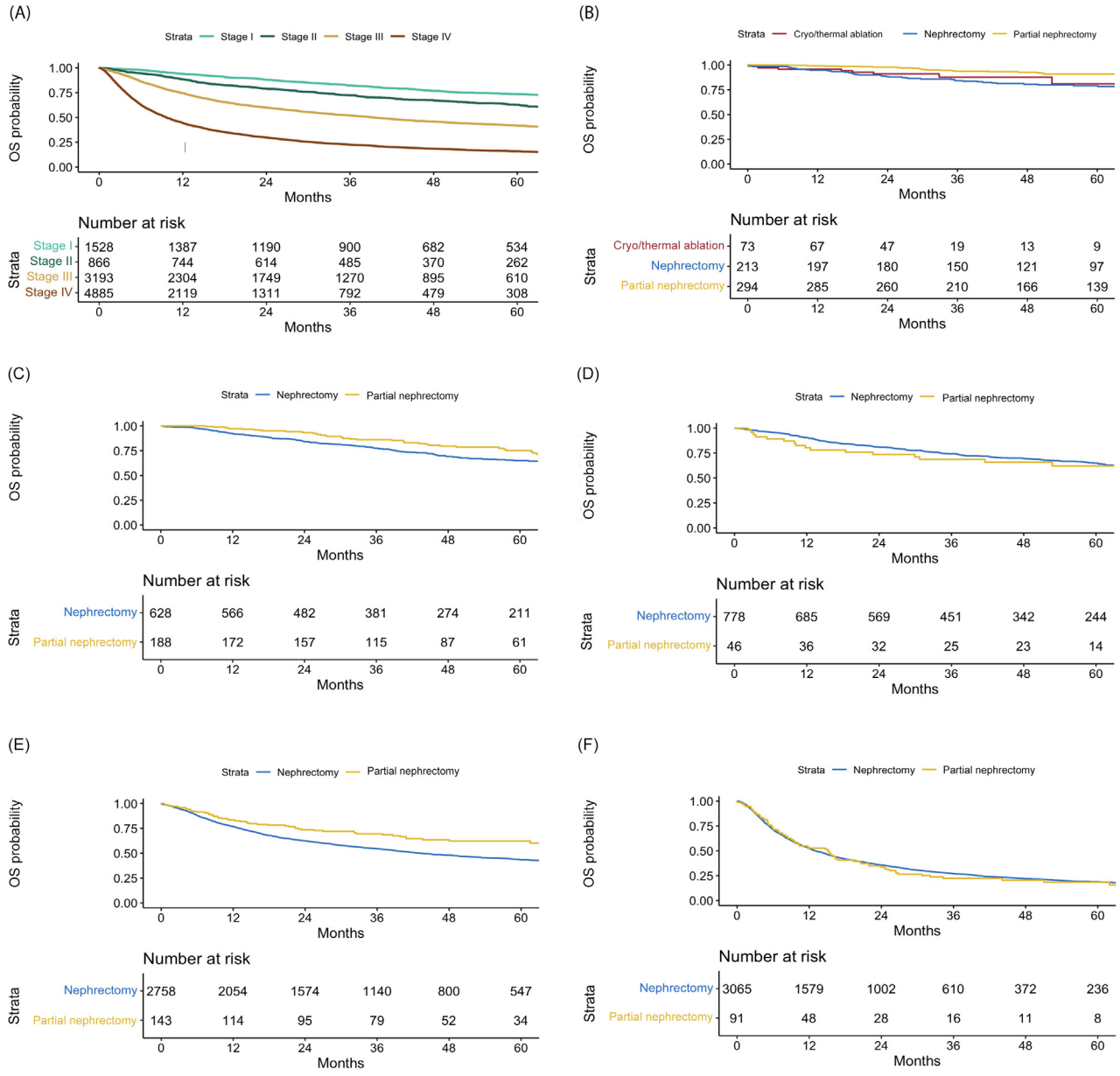

Fig. 3 – Kaplan-Meier analysis of OS in (A) stage I–IV sRCC (log-rank $p < 0.001$) and stratified by treatment received in (B) stage Ia sRCC (log-rank $p = 0.002$), (C) stage Ib sRCC (log-rank $p = 0.012$), (D) stage II sRCC (log-rank $p = 0.570$), (E) stage III sRCC (log-rank $p = 0.001$), and (F) stage IV sRCC (log-rank $p = 0.830$). OS = overall survival; sRCC = renal cell carcinoma with sarcomatoid dedifferentiation.

tumor characteristics and margin status, PN was associated with better ACM in comparison to RN ($p < 0.001$). While this finding suggests some evidence of a causal effect between PN and better ACM in selected patients with localized sRCC, the result should be interpreted with caution given the lack of more granular data on tumor complexity, tumor genetics,

and patient frailty and comorbidity, including the postoperative glomerular filtration rate, which are not reported in NCDB and could all influence survival. In addition, the PN group had smaller tumors, lower cN1 incidence, and lower AJCC stage (Supplementary Table 2). Thus, it is likely that inclusion of tumor size, cN1 status, and AJCC stage in the model does not completely control for associated unmeasured confounders such as tumor complexity, lymph node number and size, and sites of metastasis. These findings should ideally be confirmed in prospective studies that randomize patients with localized sRCC to PN or RN. However, the low incidence of sRCC and the fact that sarcomatoid dedifferentiation is typically identified on final pathology challenge the feasibility of such trials. Alternative observational studies with enhanced causal inference could include propensity score matching, larger samples, or an opportunistic study design, such as retrospective analysis of prospective studies of patients with RCC who underwent surgery (including sRCC cases) and were randomized to systemic therapy in the locally advanced or metastatic setting.

Our findings are increasingly relevant in view of KEYNOTE-564, which showed that adjuvant pembrolizumab after RN or PN for patients with high-risk clear cell RCC resulted better cancer-specific survival (77% vs 68%; HR 0.68; $p = 0.001$) [20]. Furthermore, a subanalysis of CheckMate-914, which tested adjuvant ipimulab and nivolumab in RCC, showed activity in 40 patients with sRCC (HR 0.29, 95% CI 0.09–0.91) [21]. While OS data are pending, these results suggest that patients with sRCC may benefit from adjuvant immunotherapy after definitive surgical resection.

In sRCC with synchronous metastasis, no surgery for the primary site was associated with worse ACM in comparison to RN on multivariable Cox regression. While this finding suggests some evidence of a causal effect of cytoreductive surgery in improving mortality, the result be interpreted with caution given that our analyses were not adjusted for the type of chemotherapy or immunotherapy or for the location of other organ(s) with metastasis. In addition, metastasectomy was more frequent in the cytoreductive RN group than in the no-surgery group; but tumor size, cN1 status, and chemotherapy/immunotherapy receipt were comparable between the groups (Supplementary Table 2). Thus, it is likely that inclusion of metastasectomy in the model does not completely control for unmeasured confounders, in particular the site(s) of metastasis resected. Our findings are similar to an exploratory analysis by Tully et al [22], who used 6 yr of NCDB data from 2010 to 2015 and found that cytoreductive surgery was associated with a lower risk of overall mortality (HR 0.51; $p < 0.001$) in stage IV sRCC.

A total of 148 patients underwent cryosurgery or thermal ablation, of whom 118 (80%) had T1a disease. To the best of our knowledge, this is the first analysis of ablation in sRCC. While it was noted that ablation was associated with a lower risk of ACM in localized disease overall (HR 0.41; $p = 0.045$), it is likely that this was driven by the preponderance of T1a tumors, and further evaluation of the T1a subgroup revealed a lower 5-yr OS rate for cryoablation or thermal ablation (81%) in comparison to PN (91%; $p < 0.001$). Given the lack of reports on the efficacy of ablation in sRCC, we hypothesize that diagnoses were made after analysis of periprocedural biopsy specimens. Our analysis suggests that detection of sRCC impacts survival in patients with T1a masses undergoing ablation, which has not been shown when comparing ablation to PN for non-sRCC patients [23]. Thus, caution is needed during postprocedure follow-up for patients with sRCC treated with ablation, and patients with T1a masses being considered for ablation but with imaging findings concerning for sRCC should undergo renal mass biopsy for risk stratification before ablation [24].

Our study has several limitations. Although the NCDB captures 70% of new cancer diagnoses in the USA, the data collected are hospital-based rather than population-based, and thus preclude estimation of cancer incidence rates. The NCDB reports OS data and does not collect cause-specific mortality data, which precludes assessment of cancer-specific outcomes. In addition, sites of metastasectomy and disease recurrence are not reported, which prevents comprehensive assessment of metachronous disease and recurrence-free survival. As with retrospective analyses of surgical outcomes, the retrospective data are limited in the ability to adjust for unmeasured confounders associated with surgeon bias, granular information on tumor complexity, lack of central pathology review, and the complexity of patient comorbidity, as only the Charlson score is used to estimate the comorbidity burden [25,26]. Despite these limitations, the NCDB has been cited as the largest clinical cancer registry in the world, which allows analysis of a rare entity such as sRCC that has sufficient power for obtaining meaningful results [25].

5. Conclusions

The proportion of stage I sRCC cases increased from 2010 to 2019 along with the overall proportion of sRCC cases among RCC diagnoses, which supports the concept of stage migration in this aggressive histology. Further studies are warranted to determine the casual mechanisms underpinning the associations between ACM and both cytoreductive surgery in metastatic sRCC, and PN with negative margins in locally resected sRCC. In particular, whether these associations are because of an effect of the respective interventions should be investigated. Further studies to investigate the underlying biology driving sarcomatoid dedifferentiation in RCC are also warranted.

Author contributions: Ithaar H. Derweesh had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Derweesh.
Acquisition of data: Wang.
Analysis and interpretation of data: Wang.
Drafting of the manuscript: Wang.
Critical revision of the manuscript for important intellectual content: Wang, Puri, Saitta, Liu, Afari, Meagher, Hakimi, Nguyen, Shah, Ghassemzadeh, Murphy, Javier-Desloges, McKay.
Statistical analysis: Wang.

Obtaining funding: Derweesh.
Administrative, technical, or material support: Derweesh, Puri.
Supervision: Derweesh.
Other: None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.euros.2024.10.002.

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