

# Tumor laterality in renal cancer as a predictor of survival in large patient cohorts

## A STROBE compliant study

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### Abstract

To assess whether left and right-sided renal cell carcinoma (RCC) carry side-specific outcomes.

Surgically treated RCC patients were included from the United States Surveillance, Epidemiology and End Results database (Surveillance, Epidemiology and End Results database [SEER]; 2013 version) and the German Centre for Cancer Registry Data (ZfKD; 2000–2014). Bilateral RCC, those with missing RCC staging, follow-up time, and survival status were excluded. Cancer-specific survival (CSS) according to RCC side was compared using multivariable Cox regression.

Seventeen thousand seven hundred nine SEER patients and 41,967 ZfKD patients were included. In both datasets, patients with left-sided RCC had higher T status and more often presented with nodal positive or metastatic disease. In the SEER dataset 1258 (14.33%) patients with left-sided RCC underwent lymphadenectomy (LAD), compared to 908 (10.17%) LADs in right-sided RCC ( $P < .001$ ). CSS was inferior for left-sided in both datasets after multivariable adjustment (SEER HR = 1.187, 95% CI 1.048–1.345,  $P = .007$ ,  $P = .008$ ; ZfKD HR = 1.155, 95% CI 1.046–1.275,  $P = .004$ ).

In the SEER population, site-specific CSS differences were driven by whether or not a LAD was performed. Among SEER patients with LAD no statistically significant differences in laterality were observed (HR 1.096, 95% CI 0.8977–1.337,  $P = .396$ ) whereas, in absence of LAD, CSS was shorter for individuals with left-sided tumor (HR = 1.176, 95% CI 1.002–1.38,  $P = .0468$ ).

Although the overall survival difference was only marginal, left-sided RCC in surgically treated patients tends to present at more advanced stage and has in general worse CSS, especially in patients without LAD. Site-specific lymphogenic spread patterns might contribute to these findings. Further prospective studies should evaluate, whether side-adapted LAD protocols influence outcomes in RCC patients.

**Abbreviations:** CSS = cancer-specific survival, LAD = lymphadenectomy, RCC = renal cell carcinoma, SEER = Surveillance, Epidemiology and End Results database, ZfKD = German Centre for Cancer Registry Data.

**Keywords:** anatomy, nephrectomy, renal cell carcinoma, risk factors, survival analysis

### 1. Introduction

Worldwide, renal cell cancer (RCC) is responsible for 2% to 3% of malignancies with an incidence of approximately 338,000 cases in 2012, of which 64,000 were diagnosed in the US and

84,400 in Europe.<sup>[1–3]</sup> RCC mortality is estimated at 143,600 annual deaths worldwide.<sup>[3]</sup>

The kidneys are paired organs but slightly differ in size and their anatomical position with the right kidney being situated

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All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

As only anonymized cancer registry data were analyzed, no formal approval by the local ethics committee was necessary.

Informed consent was obtained from all individual participants included in the study by the responsible authorities of the cancer registries.

The authors declare that they have no conflict of interest.

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around 1 cm more caudal than its counterpart.<sup>[4–6]</sup> Therefore, the time to detection of RCC might vary because visibility of the left kidney during ultrasound examination can be reduced by the more cranial position. Further variations are evident in arterial supply, and venous as well as lymphatic drainage between left and right organ.<sup>[4]</sup> Both kidneys have in common a lymphatic drainage to their respective hilar region but the left kidney drains into the pre-, retro-, and paraaortic lymph nodes whilst the right kidney drains into the pre-, para-, retro-, and interaortocaval lymph nodes followed by a drainage into the paracaval lymph nodes.<sup>[7]</sup> Therefore, time to lymphatic spread and distant metastases might vary between both sites. In addition, outcomes of surgical treatment could differ by laterality as accessibility of the organ itself as well as its lymph nodes are influenced by site.

These variations may contribute to site specific differences not only in tumor stage upon diagnosis but also in treatment outcomes. Dedicated assessments on site-specific differences in RCC outcomes are rare, and the scarce literature is contradictory: While some authors reported site-specific differences in RCC incidence, stage, and outcomes,<sup>[8,9]</sup> others did not find statistically significant discrepancies.<sup>[10,11]</sup> Some of these studies are limited by small sample sizes and lack generalizability.

To date, it remains unclear whether tumor laterality has an influence on clinical outcomes in surgically treated RCC patients.

The purpose of this study was to evaluate the impact of tumor laterality on survival among RCC patients who underwent surgical treatment using representative national databases from 2 distinct countries to ensure well-powered analyses and generalizability of the results.

## 2. Methods

We evaluated the most recent kidney cancer data file for patients diagnosed between 2000 and 2014 from the German Centre for Cancer Registry Data (ZfKD) provided by the Robert Koch-Institute. As transatlantic counterpart, we used the 2013 urinary tumor dataset from the United States Surveillance, Epidemiology and End Results (SEER) program run by the National Cancer Institute (NCI) as part of the National Institutes of Health (NIH). No ethics committee approval was necessary because all data was received and analyzed anonymously.

We included adult patients with pathologic diagnosis of RCC coded by the ICD-10 code C64. All included patients had documented follow up for survival after unilateral RCC diagnosis and surgical treatment including partial, radical or extended nephrectomy. The latter is a variable level in the SEER data indicating a nephrectomy together with resection of (parts of) other organ (s) for example, colon or bladder. Furthermore, T, N, M stage, and grading had to be documented. We excluded patients with unknown laterality or bilateral kidney cancer.

To bypass potential bias by comorbidities which are not specified in any of the datasets, cancer-specific survival (CSS) was selected as primary outcome.

Descriptive analyses were performed comparing tumor characteristics such as TNM-status and grading as well as epidemiologic parameters including gender, age at diagnosis, race, and marital status between left and right sided RCC. For comparison of discrete variables  $\chi^2$ -tests were used whereas continuous data were compared using *t* tests or Wilcoxon rank-sum tests. Comparisons of CSS and OS depending on tumor laterality were performed with univariate and multivariable Cox proportional hazards models. Variable selection in multivariable

models was based on thoughtful inclusion process not only accounting for significances but also for clinically important variables.

For the analyses of CSS in the ZfKD dataset, N status was dichotomized in order to ensure validity of the Cox proportional hazards assumption into N0 versus N1 or higher.

Kaplan Meier estimators were utilized to plot survival curves for tumor laterality. Furthermore, multiplicative effect measure modification with tumor laterality in the Cox proportional hazards models was evaluated via interaction terms. Model diagnostics for violation of the Cox proportional hazards assumption were performed via scaled Schoenfeld residuals.

All statistical analyses were performed with R version 3.4.2 and R studio version 1.1.383. All statistical tests are 2-sided and considered statistically significant at an alpha-level of 0.05. The study was conducted in accordance with the STROBE guidelines.<sup>[12]</sup>

## 3. Results

### 3.1. SEER data

A total of 17,709 SEER patients fulfilled the inclusion criteria with characteristics detailed in Table 1. In general, SEER patients with left-sided RCC were older, had larger tumor diameter, more advanced TNM status and stage compared to right-sided RCC ( $P < .05$ , respectively). Radical and extended nephrectomy were more often applied to left-sided versus right-sided RCC and so was lymphadenectomy (LAD) ( $P < .05$ , respectively).

At a median follow-up time of 21.00 months, cancer-specific survival (CSS) was inferior for left-sided versus right-sided RCC with a hazard ratio (HR) of HR = 1.27, 95% CI 1.122–1.438,  $P < .001$ , as depicted in Figure 1. Two-year survival was 94.1% (95% CI 93.5%–94.7%) for patients with right-sided tumor and 92.6% (95% CI 92.0%–93.3%) for patients with left-sided RCC. Survival differences between both sides increased from 1.5% after 1 year to 1.9% after 3 years.

As shown in Table 2, the CSS disadvantage for left-sided RCC was confirmed even after adjustment for confounding variables, including histology, T, N, and M status, cancer grade, type of surgery, LAD and age at diagnosis with HR = 1.187 (95% CI 1.048–1.345,  $P = .007$ ) comparing left to right side.

A statistically significant interaction between laterality and LAD was detected wherefore we performed subgroup analyses depending on LAD status.

No side-specific CSS differences were found in patients who underwent LAD ( $n = 2166$ , 12.23%) comparing left-sided RCC with right-sided RCC (HR = 1.096, 95% CI 0.8977–1.337,  $P = .369$ ). However, individuals who did not receive any LAD ( $n = 15,543$ , 87.77%) had statistically significant worse outcome for left-sided RCC compared to right-sided RCC (HR = 1.176, 95% CI 1.002–1.38,  $P = .0468$ ). Corresponding survival curves are depicted in Figure 1.

Model diagnostics did not reveal any violation of the Cox proportional Hazards assumption. Sensitivity analyses including only patients with clear cell RCC for yielded similar results.

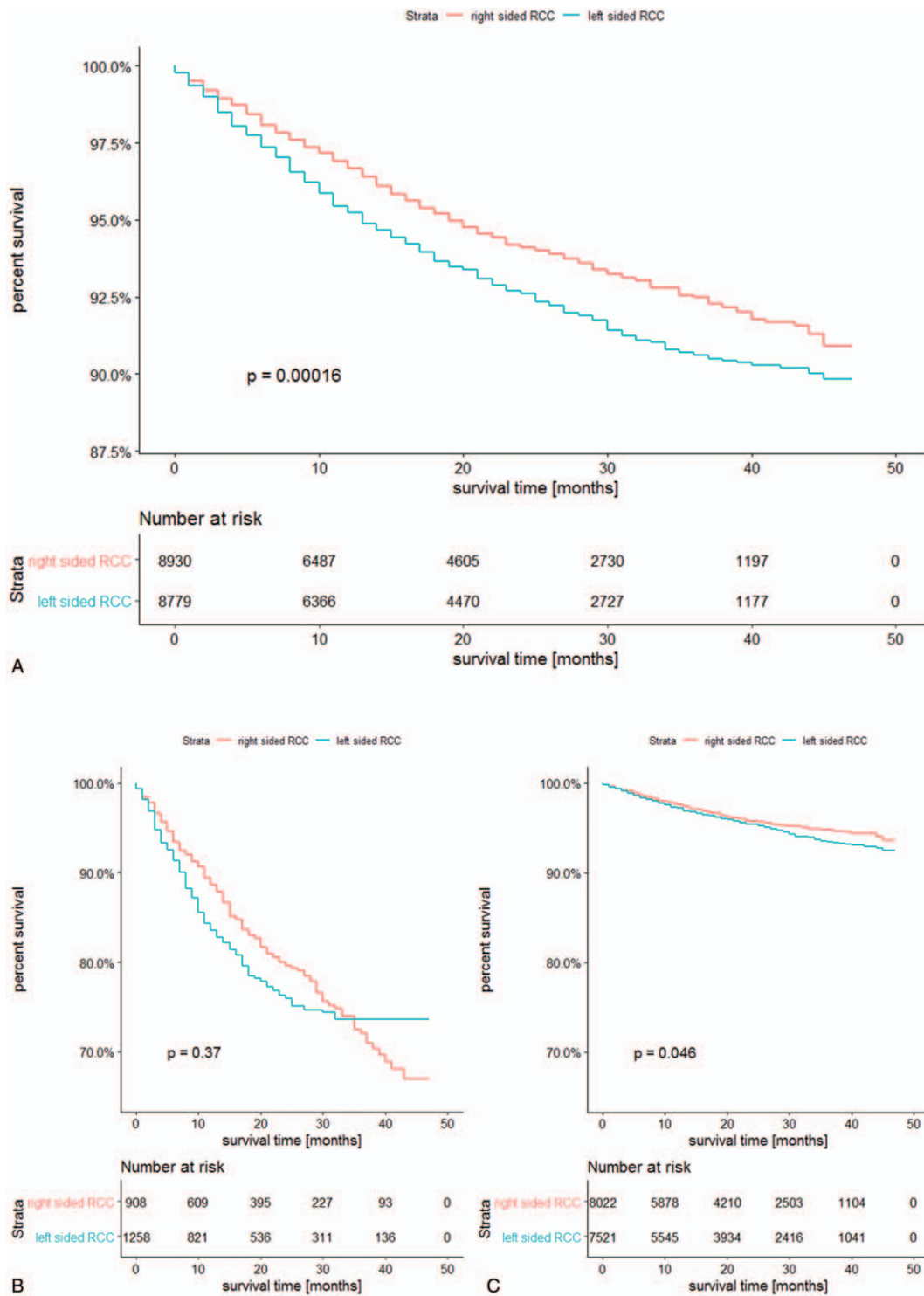
### 3.2. ZfKD data

The patient characteristics of the 41,967 RCC patients who fulfilled the inclusion criteria are detailed in Table 3. Patients from the ZfKD data with left-sided RCC had more advanced TNM status, compared to patients with right-sided RCC ( $P < .05$ , respectively).

**Table 1**  
**Baseline characteristics of included patients, SEER data.**

	<b>Total No. 17,709</b>	<b>Right No. 8930</b>	<b>Left No. 8,779</b>	<b>P value</b>
Gender				.19
Male	11,127 (62.83%)	5653 (63.30%)	5474 (62.35%)	
Female	6582 (37.17%)	3277 (36.70%)	3305 (37.65%)	
Age at diagnosis [yr]	60.85 (±12.35)	60.67 (±12.35)	61.03 (±12.34)	.019
Race				.30
White	14,869 (83.96%)	7511 (84.11%)	7358 (83.81%)	
Others	690 (3.90%)	328 (3.67%)	362 (4.12%)	
African-american	2150 (12.14%)	1091 (12.22%)	1059 (12.06%)	
Marital status				.74
Single	2435 (13.75%)	1214 (13.59%)	1221 (13.91%)	
Married	10,958 (61.88%)	5549 (62.14%)	5409 (61.61%)	
Others	4316 (24.37%)	2167 (24.27%)	2149 (24.48%)	
histology				.57
Clear cell	11,005 (62.14%)	5519 (61.80%)	5486 (62.49%)	
Papillary	2256 (12.74%)	1119 (12.53%)	1137 (12.95%)	
Chromophobe	781 (4.41%)	408 (4.57%)	373 (4.25%)	
Adenocarcinoma with mixed subtypes	448 (2.53%)	226 (2.53%)	222 (2.53%)	
Sarcomatoid	150 (0.85%)	81 (0.91%)	69 (0.79%)	
Others	3069 (17.33%)	1577 (17.66%)	1492 (17.00%)	
Tumor size	54.67 (±63.47)	54.21 (±65.75)	55.14 (±61.07)	.0009
T				.001
T1	12,060 (68.10%)	6162 (69.00%)	5898 (67.18%)	
T2	1872 (10.57%)	925 (10.36%)	947 (10.79%)	
T3	3507 (19.80%)	1735 (19.43%)	1772 (20.18%)	
T4	270 (1.52%)	108 (1.21%)	162 (1.85%)	
N				.0003
Nodal negative	17,160 (96.90%)	8695 (97.37%)	8465 (96.42%)	
Nodal positive	549 (3.10%)	235 (2.63%)	314 (3.58%)	
M				.005
M0	16,643 (93.98%)	8437 (94.48%)	8206 (93.47%)	
M1	1066 (6.02%)	493 (5.52%)	573 (6.53%)	
Grade				.058
Grade I	2061 (11.64%)	1024 (11.47%)	1037 (11.81%)	
Grade II	9269 (52.34%)	4743 (53.11%)	4526 (51.55%)	
Grade III	5077 (28.67%)	2546 (28.51%)	2531 (28.83%)	
Grade IV	1302 (7.35%)	617 (6.91%)	685 (7.80%)	
Stage				.006
Stage I	11,885 (67.11%)	6070 (67.97%)	5815 (66.24%)	
Stage II	1686 (9.52%)	847 (9.48%)	839 (9.56%)	
Stage III	2,941 (16.61%)	1464 (16.39%)	1477 (16.82%)	
Stage IV	1197 (6.76%)	549 (6.15%)	648 (7.38%)	
Year of diagnosis				.66
2010	4324 (24.42%)	2163 (24.22%)	2161 (24.62%)	
2011	4382 (24.74%)	2191 (24.54%)	2191 (24.96%)	
2012	4498 (25.40%)	2271 (25.43%)	2227 (25.37%)	
2013	4505 (25.44%)	2305 (25.81%)	2200 (25.06%)	
Type of surgery				.023
Partial nephrectomy	6854 (38.70%)	3524 (39.46%)	3330 (37.93%)	
Radical nephrectomy	10,683 (60.33%)	5332 (59.71%)	5351 (60.95%)	
Extended nephrectomy	172 (0.97%)	74 (0.83%)	98 (1.12%)	
Lymphadenectomy				<.0001
No LAD	15,543 (87.77%)	8022 (89.83%)	7521 (85.67%)	
LAD	2166 (12.23%)	908 (10.17%)	1258 (14.33%)	
Survival status				.002
Living	15,908 (89.83%)	8085 (90.54%)	7823 (89.11%)	
Kidney cancer related death	1007 (5.69%)	449 (5.03%)	558 (6.36%)	
Other cancer related death	251 (1.42%)	123 (1.38%)	128 (1.46%)	
Non-cancer related death	543 (3.07%)	273 (3.06%)	270 (3.08%)	

LAD=lymphadenectomy, RCC=renal cell carcinoma, SEER=Surveillance, Epidemiology and End Results database.



**Figure 1.** Kaplan–Meier plots for CSS for all included patients (A) as well as for patients who did not receive LAD (B) and patients with LAD (C), SEER data. CSS = cancer-specific survival, LAD = lymphadenectomy, RCC = renal cell carcinoma, SEER = Surveillance, Epidemiology and End Results database.

At a median follow-up time of 56.54 months, CSS was inferior for left-sided versus right-sided RCC (HR = 1.198, 95% CI 1.085–1.322,  $P < .001$ ), as depicted in Figure 2. Two-year survival was 98.1% (95% CI 97.9%–98.3%) for patients with right-sided tumor and 97.7% (95% CI 97.5%–97.9%) for patients with left-sided RCC. Five-year survival was 96.4% (95%

CI 96.1%–96.7%) for patients with right-sided tumor and 95.9% (95% CI 95.5%–96.2%) for patients with left-sided RCC. Survival differences between both sides increased from 0.3% after 1 year to 0.4% after 3 years and 1% after 8 years.

Again, multivariable survival analyses yielded an HR = 1.155 (95% CI 1.046–1.275,  $P = .004$ ) comparing left to right side after

**Table 2**  
**Multivariable model for CSS, SEER data.**

term	HR	Lower 95% CI	Upper 95% CI	P value
Left sided tumor vs right sided tumor	1.187	1.048	1.345	.007
Papillary vs clear cell histology	1.228	0.971	1.553	.087
Chromophobe vs clear cell histology	0.548	0.332	0.902	.018
Sarcomatoid vs clear cell histology	1.581	1.218	2.053	<.001
Mixed histology vs clear cell histology	2.481	1.919	3.207	<.001
Other histology vs clear cell histology	1.318	1.128	1.54	<.001
T2 vs T1	2.702	2.123	3.439	<.001
T3 vs T1	3.639	2.964	4.468	<.001
T4 vs T1	6.804	5.142	9.003	<.001
N1 vs N0	1.944	1.632	2.315	<.001
M1 vs M0	5.009	4.318	5.812	<.001
Tumor grade II vs grade I	1.22	0.788	1.888	.373
Tumor grade III vs grade I	2.698	1.756	4.144	<.001
Tumor grade IV vs grade I	4.75	3.06	7.375	<.001
Radical vs partial nephrectomy	2.227	1.688	2.937	<.001
Extended vs partial nephrectomy	1.484	0.941	2.34	.089
Lymphadenectomy (LAD) vs no LAD	1.261	1.084	1.466	.003
Age at diagnosis [yr]	1.026	1.021	1.032	<.001

CSS=cancer-specific survival, SEER=Surveillance, Epidemiology and End Results database.

adjustment for histology, T, N, and M status, grade, gender, and age at diagnosis. Table 4 details the multivariable model.

Among subgroup analyses for nodal positive patients (n=2484, 5.9%), statistically significant differences for patients with left-sided tumor compared to right-sided RCC were found (HR=1.237, 95% CI 1.043–1.467,  $P=.0147$ ) while no significant difference was observed among nodal negative patients (n=39,483, 94.1%) comparing left-sided tumor to right-sided RCC (HR=1.111, 95% CI 0.9841–1.225,  $P=.0889$ ). The corresponding survival curves are depicted in Figure 2.

Model diagnostics did not reveal any violation of the Cox proportional Hazards assumption. Sensitivity analyses including only patients with clear cell RCC for yielded similar results.

The following differences between both datasets were evident:

The ZfKD dataset was 6-fold larger than the SEER dataset with longer follow-up. Both patient cohorts differed with respect to the age at diagnosis (ZfKD patients were older), histology (62% of the SEER patients had clear cell RCC compared to 35% in the ZfKD data) N, M status, and grading: In the ZfKD data 6% of the patients were nodal positive whereas only 3% of the SEER-patients were labeled as N+. Nevertheless, more SEER-patients had metastatic disease and worse grading. In addition, differences in the composition of the German population and the SEER-cohort are well known as the US-American population is much more diverse with respect to race and ethnicities. Lastly, more patient information was available for the SEER datasets including race, marital status, type of surgery, and LAD.

Summarizing the results of both datasets, the observed disadvantages of left-sided RCC were marginal but evident in the SEER and in the ZfKD data with similar effect sizes and statistical significance.

#### 4. Discussion

As paired organs, the kidneys differ with regard to anatomic constitution, vascular supply as well as lymphatic drainage. So far, there is no comprehensive literature evaluating whether these

differences translate into site-specific outcomes discrepancies in renal cell carcinoma (RCC).

Using 2 distinct databases representative for the United States and Germany, we showed that left-sided RCC carries an inferior CSS compared to right-sided RCC. These findings were independent from potential confounders, including histology, T, N, and M status, cancer grade, and age at diagnosis. Effect sizes ranged from a 16% to 18%, which is a meaningful impact and should not be disregarded in RCC outcomes research. Using the SEER data, we found site-specific differences to be persistent among patients treated with LAD, whereas among individuals receiving no LAD no statistically significant effect of laterality was observed.

Scientific literature concerning tumor laterality of RCC is sparse and contradictory. Hollingsworth et al reported a higher proportion of small renal masses at the right side, supporting our findings.<sup>[8]</sup> Alane et al used SEER data to investigate surgical outcomes in a subset of patients with T2 renal masses.<sup>[9]</sup> The authors reported that patients with left-sided tumors were less likely to undergo partial nephrectomy, which is in line with our larger SEER analysis.

Conflicting findings were presented by Roychoudhuri et al investigating site-specific differences in incidence rate ratios and patient survival for different malignancies of paired organs.<sup>[10]</sup> The authors found no statistically significant differences for renal malignancies with respect to incidence rates and survival. Similarly, Russo et al did not find any statistically significant difference for postoperative 5-year PFS and OS comparing left-sided to right-sided RCC.<sup>[11]</sup>

One explanation for our results is the site-specific lymphogenic spread and current recommendations for surgery in RCC patients. Both datasets showed a higher proportion of left-sided nodal positive RCC patients. In addition, in the SEER dataset, the effect of RCC laterality disappeared when LAD was performed. This indicates that there are not only site-specific patterns in RCC lymphogenic spread, but that their clinical relevance differs depending on the primary RCC side. A recent study by Nini and colleagues confirms side-specific lymphogenic spread: the authors reported that left-sided RCC is

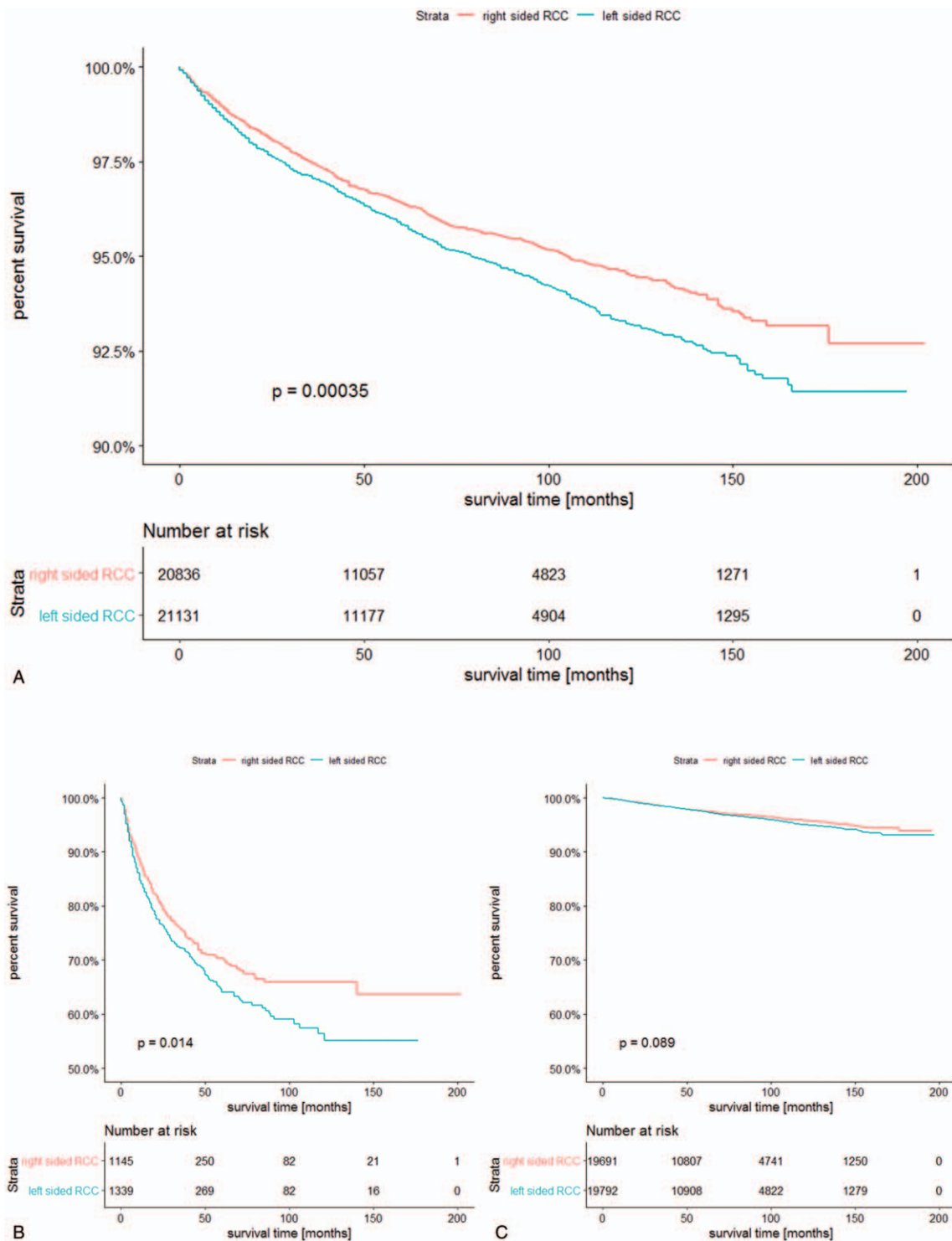
**Table 3**  
**Baseline characteristics of included patients, ZfKD data.**

	Total No. 41,967	Right No. 20,836	Left No. 21,131	P value
Gender				.75
Male	26,274 (63%)	13,061 (63%)	13,213 (63%)	
Female	15,693 (37%)	7775 (37%)	7918 (37%)	
Age at diagnosis [yr]	66 ( $\pm$ 11)	66 ( $\pm$ 11)	66 ( $\pm$ 11)	.60
Histology				.12
Clear cell	14,574 (35%)	7189 (35%)	7385 (35%)	
Chromophobe	1777 (4%)	868 (4%)	909 (4%)	
Papillary	2814 (7%)	1353 (6%)	1461 (7%)	
Granular cell	251 (1%)	125 (1%)	126 (1%)	
Sarcomatoid	178 (0%)	78 (0%)	100 (0%)	
Bellini duct	111 (0%)	49 (0%)	62 (0%)	
Others	22,262 (53%)	11,174 (54%)	11,088 (52%)	
T				<.0001
T1	28,271 (67%)	14,260 (68%)	14,011 (66%)	
T2	4244 (10%)	2103 (10%)	2141 (10%)	
T3	9092 (22%)	4296 (21%)	4796 (23%)	
T4	360 (1%)	177 (1%)	183 (1%)	
N				.001
N0	39,483 (94%)	19,691 (95%)	19,792 (94%)	
N1	2045 (5%)	945 (5%)	1100 (5%)	
N2	438 (1%)	199 (1%)	239 (1%)	
N3	1 (0%)	1 (0%)	0 (0%)	
M				.003
M0	40,713 (97%)	20,266 (97%)	20,447 (97%)	
M1	1254 (3%)	570 (3%)	684 (3%)	
Grade				.20
Grade I	8467 (20%)	4282 (21%)	4185 (20%)	
Grade II	27,265 (65%)	13,508 (65%)	13,757 (65%)	
Grade III	5906 (14%)	2885 (14%)	3021 (14%)	
Grade IV	329 (1%)	161 (1%)	168 (1%)	
Radiationtherapy				.11
Yes	356 (1%)	163 (1%)	193 (1%)	
No	33,423 (80%)	16,764 (80%)	16,659 (79%)	
Missing	8188 (20%)	3909 (19%)	4279 (20%)	
Chemotherapy				.35
Yes	614 (1%)	296 (1%)	318 (2%)	
No	33,182 (79%)	16,635 (80%)	16,547 (78%)	
Missing	8171 (19%)	3905 (19%)	4266 (20%)	
Immunotherapy				.63
Yes	207 (0%)	108 (1%)	99 (0%)	
No	25,957 (62%)	13,058 (63%)	12,899 (61%)	
Missing	15,803 (38%)	7670 (37%)	8133 (38%)	
Other therapies				.29
Yes	2337 (6%)	1190 (6%)	1147 (5%)	
No	5258 (13%)	2606 (13%)	2652 (13%)	
Missing	34,372 (82%)	17,040 (82%)	17,332 (82%)	
Survival status				.002
Kidney cancer related death	1583 (4%)	717 (3%)	866 (4%)	
Living	28,734 (68%)	14,295 (69%)	14,439 (68%)	
Non-kidney cancer related death	11,650 (28%)	5824 (28%)	5826 (28%)	
Autopsy				.27
Yes	216 (1%)	99 (0%)	117 (1%)	
No	8799 (21%)	4385 (21%)	4414 (21%)	
Missing	32,952 (79%)	16,352 (78%)	16,600 (79%)	

ZfKD = German Centre for Cancer Registry Data.

associated with a higher proportion of side-specific and hilar metastatic lymph nodes when compared to right-sided RCC.<sup>[13]</sup> In patients with 1 positive nodal area, they reported side-specific and hilar metastatic lymph nodes in 67% of left-sided RCC versus 44% in right-sided RCC, and in those with 2 positive nodal areas 91% versus 7%.

In this context, it has to be highlighted that current evidence does not advocate LAD in RCC.<sup>[14]</sup> From our local experience as well, LAD in RCC patients is not adapted based on the primary RCC side. Nevertheless, few studies have so far evaluated LAD outcomes depending on the primary RCC side. Taking the results by Nini et al and



**Figure 2.** Kaplan–Meier plots for CSS for all included patients (A) as well as for nodal positive (B) and nodal negative (C) patients, ZfKD data. CSS = cancer-specific survival, ZfKD = German Centre for Cancer Registry Data.

those of our study into consideration, it might well be that patients with left-sided RCC will profit from a LAD. On the other hand, LAD might be not useful in right-sided RCC patients.

Further building on our results and those of Nini et al, side-specific lymphogenic RCC spread might well manifest as

metastatic distant lymph node sites over time or could manifest as distant organ metastases. Future studies must focus on longitudinal data of RCC patients to ultimately guide individualized follow-up regimes.

Our study is not devoid of limitations, which are mainly inherent to its data sources.

**Table 4**  
**Multivariable model for CSS, ZfKD data.**

Term	HR	lower 95% CI	upper 95% CI	P value
Left sided tumor vs right sided tumor	1.155	1.046	1.275	.004
Papillary vs clear cell histology	0.839	0.671	1.049	.123
Chromophobe vs clear cell histology	0.575	0.419	0.791	<.001
Sarcomatoid vs clear cell histology	1.638	1.181	2.272	.003
Other histology vs clear cell histology	0.744	0.667	0.829	<.001
T2 vs T1	2.107	1.772	2.506	<.001
T3 vs T1	3.526	3.099	4.011	<.001
T4 vs T1	5.544	4.216	7.292	<.001
N1 or greater vs NO	4.884	4.186	5.699	<.001
M1 vs M0	1.587	1.337	1.884	<.001
Tumor grade II vs grade I	1.557	1.27	1.91	<.001
Tumor grade III vs grade I	3.359	2.696	4.186	<.001
Tumor grade IV vs grade I	4.492	3.171	6.364	<.001
Female gender vs male gender	0.879	0.792	0.976	.016
Age at diagnosis [yr]	1.026	1.021	1.031	<.001

CSS = cancer-specific survival, ZfKD = German Centre for Cancer Registry Data.

The greatest concerns might be raised for detection bias. Time to diagnosis for patients with left-sided RCC might be longer, for example, because of the more cranial position of the left kidney and therefore sometimes difficult ultrasound visualization compared to the right organ. Subsequently, patients with left-sided RCC present with more advanced disease upon diagnosis, as confirmed by both datasets. To minimize detection bias we used multivariable statistical models adjusting for T, N, M status, and tumor grade at diagnosis. Both datasets do not provide information on comorbidities and surgical complications that also might bias survival outcomes. We sought to eliminate most of this confounding by choosing CSS as the primary outcome. Concerns have been raised that the coding for reason of death might be imperfect in the SEER data, which probably applies to the ZfKD data as well.<sup>[15]</sup> Nevertheless, this miscoding would only bias our results if miscoding was unequally distributed for right and left-sided RCC, thereby making it less relevant for our key findings. Although almost 18,000 and 42,000 patients were included in our study, subgroup analyses might have been underpowered. Still, the subgroup of patients without LAD in the SEER dataset included 15,543 patients and the subgroup of nodal negative patients in the ZfKD dataset included 39,483 individuals which should have made it possible to detect any relevant difference. Not only potentially underpowered subgroup analyses for interaction between tumor site and nodal status in the SEER data, but also differences between both datasets might contribute to differential outcome results. However, these differences reflect the heterogeneity of US-American and German populations as well as the diversity of cancer registers which emphasizes that the evidence from cohort studies must be understood as a range of estimates encircling the true value. Moreover, some of the German states started patient inclusion into the ZfKD register in the 1990ies. These patients have had no option to undergo modern laparoscopic or robotic surgery and have not benefited from novel RCC pharmacotherapy. This might translate into generally lower survival rates for the early registry years when compared to SEER data. Another limitation is that the follow-up for RCC patients in the SEER dataset is only 21 months: thus, site-specific differences could change with a longer follow-up period. Still, the results from the SEER dataset

are supported by similar findings in the ZfKD data with longer follow-up. The larger sample size and a follow up of 63.54 months let the ZfKD data seem more trustworthy, even though less patient information was available for this cohort. Nevertheless, there is need for further research: If possible, long-term observation data and information about site-specific patterns of lymph node metastasis development and recurrence should be integrated.

The narrow effect sizes of tumor laterality raise questions about the clinical relevance of our findings. Other outcome predictors such as tumor stage or grade have a higher impact than laterality. Nevertheless, we believe that our findings should be communicated to the scientific world as they might raise the interest in RCC tumor side as outcome predictor. Clinical trialists could specifically plan analyses for this variable which might influence the development of new risk scores. Side-specific histopathologic evaluations of resected lymph nodes or follow-up imaging could further support our findings and might guide individualized patient care.

Our study is the first comparing influences of RCC laterality in 2 large population-based datasets representative for the US and Germany as member of the EU.

## 5. Conclusions

Using 2 distinct, representative national databases, our study shows that patients with left-sided RCC present more often with higher tumor status, nodal positivity and distant metastases than right-sided disease, which translates into inferior CSS. Those survival differences are predominantly observed among patients undergoing LAD with left-sided disease having worse CSS compared to patients with right-sided tumor. Side specific lymphogenic spread patterns might contribute to these findings. Although the differences were marginal, future prospective trials should assess whether side-adapted LAD protocols influence outcomes in RCC patients. In general, healthcare providers should be aware of differences in tumor laterality, not only for cancer diagnostics but also providing individualized follow-up schemes for patients based on their RCC characteristics.



## Author contributions

**Conceptualization:** Arne Strauss, Johannes Uhlig, Joachim Lotz, Lutz Trojan, Annemarie Uhlig.

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