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Time to recurrence is a significant predictor of cancer-specific survival after recurrence in patients with recurrent renal cell carcinoma – results from a comprehensive multi-centre database (CORONA/SATURN-Project)

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Objectives

- To assess the prognostic impact of time to recurrence (TTR) on cancer-specific survival (CSS) after recurrence in patients with renal cell carcinoma (RCC) undergoing radical nephrectomy or nephron-sparing surgery.
- To analyse differences in clinical and histopathological criteria between patients with early and late recurrence.

Patients and Methods

- Of 13 107 patients with RCC from an international multicentre database, 1712 patients developed recurrence in the follow-up (FU), at a median (interquartile range) of 50.1 (25–106) months.
- In all, 1402 patients had recurrence at ≤5 years (Group A) and 310 patients beyond this time (Group B).
- Differences in clinical and histopathological variables between patients with early and late recurrence were analysed.
- The influence of TTR and further variables on CSS after recurrence was assessed by Cox regression analysis.

Results

- Male gender, advanced age, tumour diameter and stage, Fuhrman grade 3–4, lymphovascular invasion (LVI), and pN + stage were significantly more frequent in patients with early recurrence, who had a significantly reduced 3-year CSS of 30% compared with patients in Group B (41%; $P = 0.001$).
- Age, gender, tumour histology, pT stage, and continuous TTR (hazard ratio 0.99, $P = 0.006$; monthly interval) independently predicted CSS.
- By inclusion of dichotomised TTR in the multivariable model, a significant influence of this variable on CSS was present until 48 months after surgery, but not beyond this time.

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Conclusions

- Advanced age, male gender, larger tumour diameters, LVI, Fuhrman grade 3–4, pN + stage, and advanced tumour stages are associated with early recurrence.
- Up to 4 years from surgery, a shorter TTR independently predicts a reduced CSS after recurrence.

Keywords

renal cell carcinoma (RCC), time to recurrence, early recurrence, late recurrence, prognostic parameters, cancer-specific survival, nephrectomy

Introduction

Surgical therapy is the only curative treatment option with a grade-A recommendation based on current guidelines for patients with localised RCC [1–3]. However, 20–40% of patients will develop recurrence after surgery with curative intent, which is associated with poor prognosis. In most cases recurrence will develop within the first 5 years after primary surgery; however, in 6–10% of patients recurrence develops later (up to 45 years) in the follow-up (FU) [4–9]. Time and pattern of metastasis show strong individual variations, and knowledge about those patients who are at risk for recurrence at different time-points would allow for an individualised aftercare in these patients and potentially also for initiation of early salvage treatment after detection of disease recurrence.

The prognostic influence of time to recurrence (TTR) on cancer-specific survival (CSS) after disease recurrence is controversial [10–13]. The consideration that TTR is of prognostic relevance is provided by the Memorial Sloan-Kettering Cancer Center (MSKCC) score for patients with metastatic RCC, which integrates time from surgery to metastasis with a 12-month threshold as a prognostic parameter [12,13]. Further studies are mainly based on small patient groups and partially suffer from inappropriate endpoints and selection criteria or lack multivariable analysis [10,11]. Although few prognostic models have been developed to predict recurrence risk, significant knowledge about differences in clinical and histopathological criteria of patients with early and late relapse and about prognostic parameters for CSS after recurrence is lacking [10,14–17]. As the vast majority of publications on this topic use a 5-year threshold for distinction of early and late recurrences, we also used this value for analysis of differences in clinical and histopathological criteria between patients with early and late recurrence. Patient information was retrieved from a large comprehensive database comprising of the multi-institutional CORONA (Collaborative Research on Renal Neoplasms Association) and SATURN (Surveillance and Treatment Update Renal Neoplasms) projects including European and American patients with RCC. Furthermore, we analysed the prognostic impact of TTR and further variables on CSS after recurrence.

Patients and Methods

After local Ethics Committee approval, clinical and pathological data of 13 107 consecutive patients with localised RCC who underwent nephron-sparing surgery or radical nephrectomy at 23 urological departments from Europe and the USA (period, 1992–2010) were summarised in one database (all centres are members of the CORONA/SATURN projects). Preoperatively, all patients were staged M0 as described before [9]. None of the patients received adjuvant or neoadjuvant perioperative treatment.

The median (interquartile range, IQR) postoperative FU of all patients was 49.5 (24–92) months. The study group comprised 1712 patients (13.1%) who developed recurrence within this period at a median (IQR) FU of 50.1 (25–106) months. In all, 1402 patients (81.9%) experienced recurrence at ≤5 years after surgery (Group A), 310 patients (18.1%, Group B) beyond this period. Patients were followed according to protocols according to current guideline recommendations as described previously [9]. Recurrence was defined as tumour relapse in the operative field, regional lymph nodes, and/or distant metastasis. Isolated occurrence in the contralateral kidney or in the ipsilateral kidney after nephron-sparing surgery was not considered recurrence. Whereas information on localisation of metastasis was available in all patients with late recurrence, in 24.2% of patients with early recurrence no specification of distant metastasis was available. Duration of FU was assessed from surgery until last FU. Death was designated as cancer-related or not. The CSS analysed from time of recurrence to cancer-related death was the primary endpoint of this study; furthermore overall survival (OS) was analysed. Cause of death was determined by treating physicians, chart review corroborated by death certificates or death certificates alone. To reduce bias in attribution to cause of death and to clearly distinguish between disease-specific death and death from other causes, only patients who had RCC listed on the death certificate with previous disease progression were considered to have died from cancer. Perioperative mortality at ≤30 days of surgery was censored at the time of death for CSS analyses. The database was frozen in November 2011.

Pathological assessment was performed by experienced genitourinary pathologists at each institution. Pathological stage was reassigned according to the 2009 American Joint Committee on Cancer (AJCC) TNM staging system [18]. Tumour histology was assessed according to the Heidelberg classification of renal tumours [19]. For assessment of cell differentiation Fuhrman grade was applied [20]. Lymphovascular invasion (LVI) was defined as the presence of tumour cells within endothelium-lined spaces without underlying muscular walls.

The Shapiro–Wilk normality test was used to investigate normal distribution of continuous variables. Continuous variables are presented as median with IQRs. Pertinent characteristics of both study groups were compared. The Wilcoxon rank-sum (Mann–Whitney *U*) test was used for variables lacking normal distribution. Comparison between categorical variables was performed using Fisher's exact and chi-squares tests.

CSS and OS were estimated using the Kaplan–Meier method as period between recurrence and cancer-related death, as well as death from any cause, respectively; the log-rank test was used to compare survival curves. Univariable and multivariable Cox proportional hazards regression models were used to assess the influence of clinical and pathological parameters (TTR, age, gender, pathological T stage, N stage, histological subtype, LVI, Fuhrman grade) on cancer-specific mortality (CSM) after recurrence. Due to only incomplete information on metastasis localisation in patients with early recurrence, this variable was not included in multivariable models. In all models, proportional hazards assumptions were verified using the Grambsch-Therneau residual-based test [21]. To account for non-linearity of TTR, Martingale residual processes and natural log (ln) transformed hazard ratios (HRs) were plotted and aggregated over the study group vs time as an omnibus procedure to check the goodness-of-fit of the multivariable model [22].

The internal model validity was evaluated by bootstrapping based on 1000 bootstrap samples. Differences between coefficients in the original and the bootstrap samples are reflected by the slope (or shrinkage) index as a measure for optimism. Normally, slope values lie between 0 and 1 with a value of 1 indicating no optimism.

The clinical impact of dichotomised TTR on CSM in multivariable models was assessed using the Omnibus test for the model quality with analysis of the changing deviance (–2 multiplied log-likelihood) by means of the development of chi-squared (percentage change of quality of a model integrating TTR as categorical instead of continuous variable) [23]. Furthermore, the predictive accuracy (PA) of the models was evaluated by measures of the area-under-the-curve (AUC) value (c-index) according to Harrell, to quantify increments of PA associated with the addition of continuous TTR to a base set of predictor variables, with a c-index of 1.0 indicating perfect discrimination of patients with different outcomes and a value of 0.5 indicating no predictive information [24]. Comparison of the PAs was performed using the Mantel–Haenszel test [25]. To prove adequate power of statistical analysis, *post hoc* power analysis was used.

Data were analysed using R statistical package (v.2.12.2) and SPSS 19.0 (SPSS Inc. Chicago, IL, USA). Reported *P* values are two-sided with a statistical significance level of ≤0.05.

Results

Patient characteristics are shown in Table 1. The median (IQR) FU after recurrence of patients alive at the study end was 14 (3–37) months. Patients developing recurrence at ≤5 years from surgery (Group A) were significantly older than patients in group B (64.1 vs 61.8 years, $P = 0.002$), more often men (64.6% vs 58.4%, $P = 0.043$), and had larger tumours at primary diagnosis (7 vs 6 cm, $P < 0.001$). Significantly more frequent LVI (41.5% vs 29%, $P < 0.001$), Fuhrman grade 3–4 (52% vs 27.4%, $P < 0.001$), pN + stage (7.1% vs 1%, $P < 0.001$), and advanced tumour stages (≥pT3: 56.2 vs 43.5%, $P < 0.001$) were found in patients with early recurrence, whereas distribution of histological subtypes did not significantly differ between both groups. Patients with early and late recurrence, respectively, mainly developed simultaneous recurrence at multiple localisations (37.1% vs 54.1%, respectively). In those patients with recurrence at single organ sites, localisations varied widely in all patients (Table 2).

CSS rates for the entire study group calculated from time of recurrence at 6, 12, 24, 36, and 60 months were 74%, 59%, 43%, 32%, and 23%, respectively. Kaplan–Meier analysis showed significantly different 3-year CSS rates for Group A and B patients with 30% and 41% ($P < 0.001$), respectively. By further distinguishing patients with early recurrence based on a TTR of ≤12 months and >12–60 months, CSS rates after 3 years were 24% and 35%, respectively ($P < 0.001$, Fig. 1).

In univariable analyses, age, gender, tumour histology and size, pT stage, LVI, Fuhrman grade and continuous TTR, as well as TTR up to an interval of 108 months influenced CSS (Table 3). Based on multivariable analysis of the complete study group, age, gender, tumour histology, pT stage, and continuous TTR (HR 0.99, $P = 0.006$; monthly interval) were independently associated with CSM, whereas LVI, Fuhrman grade, and pN status had no significant influence (Table 4). Our study confirmed TTR as an independent prognostic parameter until 48 months after primary surgery based on evaluation of several categorical thresholds (from 12 to 120 months), which were applied in separate multivariable models (Table 4). The relative risk of dying from cancer in patients who had recurrence beyond these thresholds was 0.79–0.84 ($P \leq 0.012$) compared with patients with recurrence before each of these thresholds; the best model quality was provided

Table 1 Characteristics of 1712 patients with RCC (all of them M0 at time of surgery) with recurrence after surgery by time of recurrence.

Characteristic	Overall	Group A Recurrence ≤5 years	Group B Recurrence >5 years	*P*
Number of patients	1712	1402	310	
Median (IQR):				
Age at surgery, years	63.9 (55.9–70.0)	64.1 (56.0–70.8)	61.8 (55.3–68.1)	0.002
Tumour size, cm	7.0 (5.0–9.5)	7.0 (5.0–10.0)	6.0 (4.5–8.0)	<0.001
N (%):				
Female gender	625 (36.5)	496 (35.4)	129 (41.6)	0.043
Partial nephrectomy	280 (16.4)	228 (16.3)	52 (16.8)	0.800
ccRCC	1437 (83.9)	1178 (84.0)	259 (83.5)	0.864
LVI*	521 (38.6)	431 (41.5)	90 (29.0)	<0.001
Fuhrman grade 3–4	814 (47.5)	729 (52.0)	85 (27.4)	<0.001
pT stage (2009)				<0.001
pT1a	236 (13.8)	183 (13.1)	53 (17.1)	
pT1b	308 (18.0)	234 (16.7)	74 (23.9)	
pT2a	167 (9.8)	132 (9.4)	35 (11.3)	
pT2b	77 (4.5)	64 (4.6)	13 (4.2)	
pT3a	536 (31.3)	450 (32.1)	86 (27.7)	
pT3b	289 (16.9)	240 (17.1)	49 (15.8)	
pT3c	27 (1.6)	27 (1.9)	0	
pT4	72 (4.2)	72 (5.1)	0	
pN stage (2009)				<0.001
pN0/pNx	1610 (94.0)	1303 (92.9)	307 (99.0)	
pN+	102 (6.0)	99 (7.1)	3 (1.0)	
Median (IQR):				
FU after surgery, months	50.1 (25–106)	36.6 (21–61)	130.6 (104–155)	<0.001
FU after recurrence, months	14.0 (3–37)	13 (4–35)	19.8 (3–41)	0.105

*ccRCC, clear cell RCC; *Information on LVI was only available in 1348 patients.*

Table 2 Localisations of recurrence in patients with early and late recurrence.

Site of recurrence	Group A Early recurrence	Group B Late recurrence
Number of patients	1402	310
N (%):		
Local recurrence only	21 (1.5)	16 (5.2)
Multiple localisations	759 (54.1)	115 (37.1)
Solitary metastasis	283 (20.2)	179 (57.7)
Lung/thorax	122 (8.7)	84 (27.1)
Bone	52 (3.7)	28 (9.0)
Brain	32 (2.3)	17 (5.5)
Lymph nodes	34 (2.4)	15 (4.8)
Abdomen	17 (1.2)	12 (3.9)
Pancreas	0	6 (1.9)
Liver	12 (0.9)	6 (1.9)
Thyroid gland	2 (0.1)	5 (1.6)
Adrenal gland	10 (0.7)	3 (1.0)
Dermis	3 (0.2)	3 (1.0)
Distant metastasis with not specified localisation	339 (24.2)	0

by the 12-month threshold (Table 4). If recurrence occurred >4 years after surgery, it was no longer associated with significantly reduced CSS (Table 4). Stratification of patients according to a TTR of <12 months, 12–48 months, and >48 months provided significantly different CSS rates and is shown in Fig. 2. Accordant Kaplan–Meier curves for OS related to both stratifications are displayed in Figs S3 and S4, respectively, each showing significantly different survival rates as well.

Table 3 Results of univariable analyses of several clinical and histopathological parameters for CSM after recurrence.

Factors	HR (95% CI)	*P*
Age at surgery, continuous	1.02 (1.01–1.03)	<0.001
Female gender (reference: male)	0.78 (0.69–0.89)	<0.001
Partial nephrectomy (reference: radical nephrectomy)	0.66 (0.55–0.79)	<0.001
Clear cell RCC (reference: non-clear cell RCC)	0.83 (0.70–0.98)	0.027
Tumour size, continuous	1.04 (1.02–1.05)	<0.001
LVI present (reference: LVI absent)*	1.34 (1.19–1.52)	<0.001
Fuhrman grade 3–4 (reference: Fuhrman grade 1–2)	1.23 (1.09–1.38)	0.001
pT stage (8 stages)	1.12 (1.08–1.15)	<0.001
Positive nodes (reference: pN0/pNx)	1.38 (1.09–1.74)	0.007
TTR, continuous (in months)	0.99 (0.99–0.99)	<0.001
TTR ≤12 months	1	Reference
TTR >12 – ≤60 months	0.73 (0.64–0.83)	<0.001
TTR >60 months	0.80 (0.73–0.87)	<0.001
TTR >12 months (reference: ≤12 months)	0.71 (0.62–0.80)	<0.001
TTR >24 months (reference: ≤24 months)	0.75 (0.66–0.84)	<0.001
TTR >36 months (reference: ≤36 months)	0.74 (0.65–0.84)	<0.001
TTR >48 months (reference: ≤48 months)	0.73 (0.63–0.84)	<0.001
TTR >60 months (reference: ≤60 months)	0.75 (0.64–0.89)	0.001
TTR >72 months (reference: ≤72 months)	0.73 (0.61–0.88)	0.001
TTR >84 months (reference: ≤84 months)	0.72 (0.58–0.89)	0.003
TTR >96 months (reference: ≤96 months)	0.73 (0.58–0.93)	0.010
TTR >108 months (reference: ≤108 months)	0.75 (0.57–0.98)	0.038
TTR >120 months (reference: ≤120 months)	0.73 (0.53–1.01)	0.060

**Information on LVI was only available in 1348 patients.*

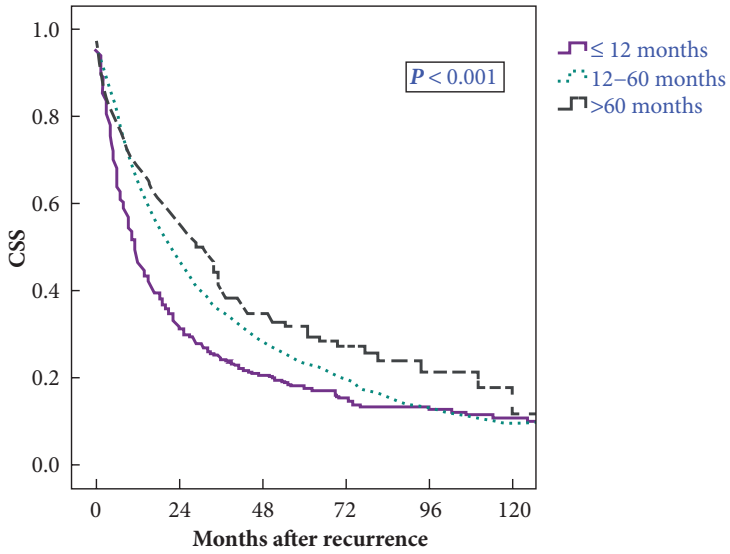

Fig. 1 CSS after disease recurrence by risk stratification related to TTR (≤12, >12–60, >60 months).

Number of patients at risk / Number of cumulative events	0 months	24 months	48 months	72 months	96 months	120 months
Recurrence within 12 months	596/0	126/350	59/387	33/401	21 /406	15/409
Recurrence after 12 to 60 months	806/0	254/355	111/444	64/475	34/494	13 /501
Recurrence after 60 months	310/0	108/117	46/150	20/159	8/162	2/164

Table 4 Results of separate multivariable Cox regression analyses with inclusion of clinical and histopathological parameters for CSM after recurrence.

Factor	HR (95% CI)	P	Improvement of model quality†, % (reference 100%)
Age at surgery, continuous	1.02 (1.01–1.03)	<0.001	
Female gender (reference: male)	0.78 (0.68–0.89)	<0.001	
Clear cell RCC (reference: non-clear cell)	0.82 (0.70–0.98)	0.026	
LVI present (reference: LVI absent)[#]	1.01 (0.86–1.19)	0.866	
Fuhrman grade 3–4 (reference: Fuhrman grade 1–2)	1.10 (0.97–1.25)	0.125	
pT stage (8 stages)	1.10 (1.06–1.15)	<0.001	
Positive nodes (reference: pN0/pNx)	1.08 (0.85–1.38)	0.541	
TTR, continuous (in months)	0.99 (0.99–0.99)	0.006	
Results of separate multivariable models each with inclusion of one threshold value for TTR instead of continuous TTR together with all other parameters according to the original model			
TTR (≤12, >12–60, >60 months)*	0.85 (0.78–0.93)	<0.001	+3.74
TTR >12 months (referent: ≤12 months) *	0.79 (0.69–0.89)	<0.001	+5.52
TTR >24 months (referent: ≤24 months)*	0.84 (0.74–0.95)	0.006	+1.06
TTR >36 months (referent: ≤36 months)*	0.84 (0.73–0.96)	0.009	−0.01
TTR >48 months (referent: ≤48 months)*	0.83 (0.71–0.96)	0.012	−0.72
TTR >60 months (referent: ≤60 months)*	0.87 (0.73–1.02)	0.094	−3.39
TTR >72 months (referent: ≤72 months)*	0.85 (0.70–1.03)	0.094	−3.54
TTR >84 months (referent: ≤84 months)*	0.82 (0.66–1.02)	0.076	−3.29
TTR >96 months (referent: ≤96 months)*	0.85 (0.67–1.08)	0.192	−4.37
TTR >108 months (referent: ≤108 months)*	0.90 (0.68–1.18)	0.437	−5.15
TTR >120 months (referent: ≤120 months)*	0.90(0.64–1.25)	0.528	−5.25

*[#]Information on LVI was only available in 1348 patients; *P values, HRs, and 95% CI refer to separate multivariable models in which either continuous TTR or one different threshold value for TTR was analysed together with all other parameters; [†]improvement of the model quality refers to the multivariable model with inclusion of continuous TTR as reference (100%).*

The regression coefficients of these models were corrected for optimism by multiplying the original coefficients by the shrinkage factor (slope indices: 0.96–0.98). The PA of the multivariable model including information on continuous TTR in comparison with a model without integration of this variable were 62.2% (95%CI 59.5–65) and 61.7% (95%CI 59–64.5), respectively, which was not significantly different (PA gain 0.5%, $P = 0.112$). However, based on the Omnibus

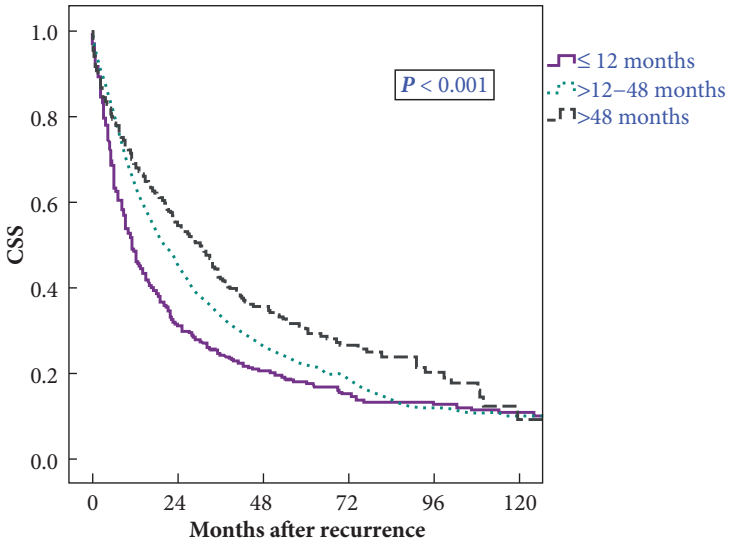

Fig. 2 CSS after disease recurrence by risk stratification related to TTR (≤12, >12–48, >48 months).

Number of patients at risk / Number of cumulative events	0 months	24 months	48 months	72 months	96 months	120 months
Recurrence within 12 months	596/0	126/350	59/387	33/401	21/406	15/409
Recurrence after 12 to 48 months	694/0	203/311	86/385	51/409	26/425	12/428
Recurrence after 48 months	422/0	159/161	71/209	33/225	16/231	3/237

test, integration of TTR as a three-categorical (≤12, >12–60, >60 months) and dichotomized variable (≤12, >12 months), respectively, resulted in a robust improvement of the model quality by 3.7% and 5.5%, respectively (each $P < 0.001$), compared with a model with continuous inclusion (Table 4).

Based on statistical power analysis, differences within the significance level (α err probability <0.05) could be determined for a small effect size (0.2) with a power of 96.2%.

Discussion

Based on previous reports, about one-third of patients with localised RCC will develop disease recurrence after primary surgery with curative intent [1–9,15]. Effective surveillance protocols should allow individually tailored aftercare based on parameters predicting recurrence and possibly also time of recurrence. Few protocols have been developed to stratify patients according to their individual risk of recurrence in general and at different time-points mainly based on the TNM system, grading, and tumour necrosis [15–17]. Furthermore, TTR was also assessed as prognostic parameter hinting at early recurrence ≤12 months as a predictor of reduced survival [10–13]. However, information was received from study cohorts of primary M1 patients only or small patient cohorts undergoing surgery, sometimes lacking multivariable analysis or using inappropriate endpoints, so that reliable information about the exact influence of TTR on CSS after recurrence is still lacking.

The present study provides enhanced information on this topic based on the most comprehensive multicentre database published to date including >13 000 patients with initially localised RCC. Furthermore, it represents the first analysis of the predictive value of several threshold values of TTR for CSS after recurrence.

The results of the present study prove several statements. First, we could define tumour stage and histological subtype as criteria assessed at primary surgery as well as gender and age as independent prognostic parameters for CSS after detection of recurrence. Interestingly, neither Fuhrman grade nor LVI and pN stage significantly influenced CSS in this context.

Secondly, the results prove a short period between primary surgery and recurrence as an indicator for reduced CSS after recurrence, which supports previously published data. Rodriguez-Covarrubias et al. [10] found that TTR had an independent influence on CSS; however, based on only 66 patients with recurrence and related to overall CSS but not on CSS after recurrence. Eggener et al. [11] also reported TTR to be predictive for OS in 118 patients with recurrent disease, multivariable analysis, however, was lacking. Also Leibovich et al. [26] reported that recurrence ≤2 years after primary surgery was associated with reduced CSS based on a study cohort of patients with metastatic RCC. Based on the present data, the usually applied threshold of 5 years could be challenged in favour of 48 months for distinction of early and late recurrences, as up to this time prognosis of patients was

reduced with every day that recurrence occurred earlier, but not beyond a threshold of 48 months. When looking at the baseline parameters with significant differences in prevalence between patients with early and late recurrences based on the 5-year threshold, these parameters still showed significantly different frequencies in the two resulting patient groups when the 48-month threshold was applied (data not shown). Stratification of patients according to a TTR of <12 months, 12–48 months, and >48 months provided significantly different CSS, as well as OS rates. Yet, beside a significant improvement of the model quality, an integration of continuous TTR in the multivariable model only resulted in a marginal improvement of the PA of this stable multivariable model.

As mentioned above, we detected significantly different distributions of some criteria in patients with early and late tumour recurrence regardless of using the 60-month or the 48-month threshold for definition of late recurrence. Beside tumour size, LVI, Fuhrman Grade, pT and pN stage, also older and male patients were significantly more prevalent in cases of early recurrence. These results are concordant with the results published by Adamy et al. [17], who found that late recurrence in 44 patients was associated with smaller tumour size and less aggressive disease at first presentation.

The robustness of the present data is furthermore corroborated by considering lead-time bias occurring in recurrence diagnosis. While early recurrence regularly will be detected earlier in asymptomatic patients, as aftercare is provided at shorter intervals, late recurrence will be detected later, as regular aftercare is normally not provided anymore after >5 years. In the present study, patients with late recurrence survived longer despite this lead-time bias, which confirms the significance and reliability of the present data.

A further interesting point is that, despite an adequately long FU, only 12% of patients in the present study group developed recurrence in contrast to previous published data with recurrence rates of 20–40%, which might indicate a generally improved prognosis for patients with RCC today. This might be based on improvements in surgical treatment or on increasing detection of tumours at earlier stages with less risk of recurrence after surgery.

Despite being based on the largest database reported to date on this topic, with inclusion of a many patients with recurrent disease than reported before, the present study has all the limitations inherent in retrospective and multicentre evaluations, e.g. missing standardisation of diagnosis, therapy, and aftercare, as well as possible limitations in quality of data assessment and the risk of unmeasured confounding. Information on symptoms and treatment in cases of recurrence, concomitant comorbidities, and further laboratory parameters, which are for example included in the MSKCC score (such as haemoglobin or calcium), were not available for all patients and, hence, not analysed. Information on LVI was also not available for all patients included. Furthermore, central pathological review was not performed, as this would have gone beyond the scope of a study group comprised of >13 000 patients. For a fraction of patients with early recurrence, localisation of distant metastasis was not available and thus not analysed. In addition, beside standard clinical and histopathological parameters, molecular markers should also ideally be incorporated into multivariable models in future studies, which was not performed in the present as well as in all other studies regarding this issue. Besides, with a median FU of 50.1 month a potential era effect resulting in marginally altered patient group composition and slight disparities between patients with early and late recurrences has to be considered as a potential confounder, which might also lead to subtly nuanced HRs. However, based on the distribution of recurrences in the database and anticipated recurrences in the course of disease, during this median FU nearly 77% of recurrences have already occurred, which limits the potential risk of bias.

In conclusion, besides age, gender, tumour histology, and pT stage, TTR is a significant predictor of CSS after recurrence in patients with RCC who undergo primary surgery with curative intent. The earlier after surgery recurrence occurs, the more reduced is survival after recurrence. Vice versa, the prognosis of patients with recurrent disease is improved with every day a patient stays disease-free after surgery up to 4 years from surgery, but not beyond this time. Advanced age, male gender, advanced tumour diameter and stage, LVI, Fuhrman grade 3–4, and pN + stage were more frequent in patients with early recurrence, which might provide the possibility of risk adapted aftercare. Furthermore, these data may also be useful for implementation as an important stratification tool in clinical trials to avoid bias, e.g. to allow for equal representation of early and late recurrence patients in treatment arms.

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Conflict of Interest

None declared.

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Abbreviations: AJCC, American Joint Committee on Cancer; AUC, area under the curve; CORONA, Collaborative Research on Renal Neoplasms Association; CSM, cancer-specific mortality; CSS, cancer-specific survival; FU, follow-up; IQR, interquartile range; HR, hazard ratio; LVI, Lymphovascular invasion; MSKCC, Memorial Sloan-Kettering Cancer Center; OS, overall survival; PA, predictive accuracy; SATURN, Surveillance and Treatment Update Renal Neoplasms; TTR, time to recurrence.

Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Fig. S1 OS after disease recurrence by risk stratification related to TTR (≤12, >12–60, >60 months).
Fig. S2 OS after disease recurrence by risk stratification related to TTR (≤12, >12–48, >48 months).