Increased use of cross-sectional imaging for follow-up does not improve post-recurrence survival of surgically treated initially localized RCC: results from a European multicenter database (RECUR).

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Abstract

Objective: Modality and frequency of image-based renal cell carcinoma (RCC) follow-up (FU) strategies are based on risk of recurrence. Using the RECUR-database; we studied frequency of imaging in regard to prognostic risk groups. Furthermore, whether imaging modality utilised in contemporary FU were associated with outcome after detection of recurrence. Moreover, we compared outcome based on whether the assessment of potential curability was a predefined set of criteria's (per-protocol`) or stated by the investigator.

Materials and Methods: Consecutive non-metastatic RCC patients (n=1,612) treated with curative intent at 12 institutes across 8 European countries between 2006 and 2011 were included. Leibovich or UISS risk group, recurrence characteristics, imaging modality, frequency and survival were recorded. Primary endpoints were overall survival (OS) after detection of recurrence and frequency of features associated with favourable outcome (non-symptomatic recurrences and detection within the FU-program).

Results: Recurrence occurred in 336 patients. Within low, intermediate and high risk for recurrence groups, the frequency of FU imaging was highest in the early phase of FU, and decreased significantly over time ($p<0.001$). However, neither the image modality for detection nor ≥50% cross-sectional imaging during FU, were associated with improved OS after recurrence. Differences between per protocol and investigator based assessment of curability, did not translate into differences in OS.

Conclusions: As expected, the frequency of imaging was highest during early follow-up. Cross-sectional imaging use for detection of recurrences following surgery for localised RCC did not improve OS post-recurrence. Prospective studies are needed to determine the value of imaging in follow-up.

N=249 (max. 250)

1. Introduction

Among the purposes for follow-up after radical treatment of RCC are observation of renal function, recovery from surgery, oncological control to detect recurrence of disease manifestations and finally, a psychosocial need for both patient and physician following cancer treatment [1].

It seems deeply rooted that early detection of cancer recurrences results in more effective treatment which improves survival. Based on this assumption, most of the readily used RCC follow-up strategies adapt their imaging modality and frequency to the risk and potential site of recurrence [2-4]. During the last decades, this risk-based approach to follow-up has resulted in increased recommendations for follow-up imaging and subsequently an increased use of cross-sectional imaging in RCC follow-up [2, 5-12]. The literature investigating the impact of follow-up imaging after RCC treatment is limited [13-15], but a recent study failed to show superiority in regard to post-recurrence survival for more intensive use of follow-up imaging [12]. However, to our knowledge, there are no comparative studies exploring if a specific imaging modality actually translates into improved overall survival after RCC recurrence.

The European Association of Urology (EAU) RCC Guidelines Panel has established a collaborative multicentre consortium (RECUR) to investigate comparators for evidence-based follow-up recommendation for localized RCC. In contrast to previously published follow-up studies, the focus of RECUR is on further management and outcome once a recurrence is detected. To achieve uniform definitions for comparisons between groups, the RECUR database utilizes per protocol-based data collection. However, arbitrary global per protocol assessments of potential curability of RCC recurrence may be disputed, and as such an investigator based assessment of curability is also registered in the RECUR database.

The aim of the present study was primarily to describe contemporary frequencies of follow-up imaging stratified by risk of recurrence groups. Secondly, to look for potential differences in outcome after recurrence, based on the imaging modalities used for follow-up and recurrence detection. Finally, to explore if there were significant differences in the outcome results dependent on use of global per protocol or investigator based assessments of curability of the recurrences.

2. Materials and Methods

2.1. The RECUR-database, quality assurance, exclusions and ethical considerations

RECUR collected data from 1889 patients with localised RCC from 12 centres (all with appropriate institutional approval) in 8 European countries (see supplementary text) in this current study. Eligible patients underwent surgery with curative intent from January 2006 (the start of the Tyrosine kinase inhibitor era) to December 2011, allowing for a minimum of 4 years of follow-up for patients still alive and without recurrence at inclusion in the study. All data were audited for quality and completeness by a urological surgeon (SD). After exclusions (figure 1), the final study population consisted of 1612 patients for the current analysis. The median follow-up for patients who did not experience recurrence or died was 63 months (IQR 58–76). Patient characteristics are shown in table 1.

2.2. Definitions used for analyses

The validated risk grouping system described by Leibovich [16, 17] was used for clear cell RCC while the University of California Los Angeles Integrated Staging System (UISS) system [18] was used for non-clear cell RCC. Overall survival after recurrence was defined as the time from recurrence until death of any cause or, for patients still alive, to the date of last FU.

Imaging frequency was defined as the total number of imaging studies during follow-up until recurrence or last follow-up, divided by years of follow-up. As most of the institutional FU imaging strategies utilized were both risk-and time-dependent, with more imaging in the early years after treatment, we devised three follow-up groups (follow-up until recurrence or last follow-up or death of other causes): short-term follow-up (0-2.49 years), mid-term follow-up (2.5-5.49 years) and long-term follow-up (>5.5 years)) after treatment of primary tumor for all three risk groups, resulting in nine patient groups.

Methods of imaging were cross-sectional imaging (CSI; computerized tomography (CT) or magnetic resonance imaging (MRI)) or conventional (chest x-ray (CXR) or ultrasound (US)). Ratio`s for abdominal and thoracic imaging were calculated by dividing cross-sectional by conventional imaging.
All patients were further divided into two groups depending on their CSI percentage of the total number of imaging tests (≥50% vs. <50%). The cut point for dichotomisation was chosen for simplicity as it was close to the median.

The primary endpoints were detection of recurrence either as non-symptomatic or detection within institutional follow-up, as this may serve as surrogate indicators of improved outcome after recurrence [19]. Secondary analyses were: (i) the relationship between the primary endpoints and methods of imaging during FU; and (ii) the correlation between methods of imaging and overall survival after recurrence.

The global per protocol definition of a potentially curable (PC) RCC recurrence was, as previously published [12, 19], taken to be local recurrence, single metastasis or oligometastasis (≤3 lesions at a single site). All other recurrences were considered probably incurable (PI). Additionally, the investigator based assessment of each patient with recurrence (investigator based assessment based PC or PI) were also established by an investigator from each contributing RECUR institute.

2.3. *Statistical analysis*

Descriptive statistics were presented as categorical variables with percentages and continuous variables as median and interquartile range (IQR). For categorical and non-parametric data, exact Chi-square test and Mann-Whitney U-test or Kruskal-Wallis test, respectively, were used. Correlation for group allocation for PC/PI was evaluated with Kappa statistics. Kaplan-Meier method with Log-Rank test was performed for overall survival. For all statistical comparisons, a two-tailed p-value of <0.05 was considered significant. SPSS-version 23 (IBM corporation, Armonk, New York, USA) and R version 3.3.2 (R Foundation for Statistical Computing, Vienna, Austria) were used.

3. Results

3.1. *Imaging modalities and frequencies*

Of 17,333 follow-up imaging procedures performed, 4,929 (28%) were CT Abdomen (CTA), 3024 (17%) CT Thorax (CTT), 6,540 (38%) CXR, 2,651 (15%) US and 189 (1.1%) abdominal MRIs. The CTT:CXR-ratio decreased significantly across the risk groups, and was 1.0, 0.46 and 0.35 in the high, intermediate and low risk group, respectively ($p<0.001$). Moreover, the overall CTA:US-ratio also decreased from the high to the low RG (3.2, 1.7 and 1.7, respectively; $p<0.001$)(table 2).

Irrespective of risk group, the highest frequency of imaging was during early follow-up, and decreased significantly with longer follow-up (overall $p<0.001$). The median frequency of imaging increased with increasing risk group allocation in all follow-up groups. The frequency of imaging was not significantly different between patients who developed recurrences and those who did not, except for the mid-term follow-up group of high risk group patients, where those with recurrences underwent more imaging ($p=0.002$; table 3).

3.2. *Recurrences and outcome*

Recurrences were detected by CSI in 257 of 336 patients (76%), and 210 patients (63%) had >50% of their follow-up imaging performed by CSI. In the low and intermediate risk groups, more recurrences were detected as part of regular follow-up when >50% CSI was performed during follow-up. The difference, however, was only statistically significant for the intermediate risk group (table 4). For detection of non-symptomatic recurrences, no significant difference was seen between the high and low CSI group (table 4).

There was a non-significant tendency towards more recurrences being detected via routine follow-up and being non-symptomatic at detection if the frequency of imaging was above median rather than below the median (see supplementary table 1).

There was no significant difference in overall survival between PC and PI patients stratified for the type of imaging resulting in detection of their recurrence (figure 2a). Similarly, neither was there any significant difference in overall survival after recurrence based on high (≥50%) or low (<50%) CSI percentage during follow-up (figure 2b). Moreover, exploratory analyses with quartiles for CSI frequencies gave in similar results.

3.3. *Global per protocol assessment vs. Investigator based assessment of curability*

Of 336 recurrences, by the global per protocol definition of recurrence curability, 152 (45%) were classified as PC, while the remaining 184 (55%), with multiple metastases, were considered PI. When applying the investigator based assessment of recurrence curability, the numbers were 123 (37%) and 213 (63%) for PC and PI, respectively. Investigator based assessment classified 40 PC patients as PI and 11 PI patients as PC. The kappa value for the scoring was 0.69.

In 20 of 70 solitary, 16 of 38 oligometastatic and 4 of 25 local recurrences, investigator based assessment classified them as PI rather than PC. These patients were older (68 years vs. 65 years, $p=0.102$), and in approximately 50% of cases there was an investigator's note in the RECUR database stating comorbidity and/or patient's wishes prohibiting curative intended procedures (surgery/ablation/radiation (i.e. stereotactic radiotherapy)). Kaplan-Meier estimates showed that the median overall survival for PC patients was 50 months vs. 43 months for the investigator based assessment and global per protocol groups, respectively ($p=0.2$) (figure 3). For PI patients the median

overall survival was 16 months for both the investigator based assessment and global per protocol assessment.

4. Discussion

It is generally believed that regular imaging has the potential to reveal recurrences early while small and asymptomatic. However, for such imaging strategies to be useful the disease has to behave in a predictable pattern in the majority of patients, with recurrences growing linearly, disseminating to predetermined sites and in a predictable fashion. We have previously shown that only 2% of patients with initially localised RCC in the high RG will, after recurrence detection, remain disease free after resection of recurrence [19]. In this study we showed that the frequency of cross-sectional imaging and mode of imaging at detection for patients with recurrent disease had no bearing on the oncological outcome.

Imaging in most cancer follow-up protocols follows defined intervals and with the highest frequency in periods for which historic data have shown that recurrences are most likely to be diagnosed. Our results demonstrate that the participating institutions, during the study period, used follow-up imaging relatively similar to the present recommendations from EAU [3],both in regard to use of imaging based on risk stratification and the duration of follow-up. As the frequency of imaging for RCC patients developing recurrence and those remaining disease free is relatively similar, our figures most likely represent the daily practice at the institutions.

In the 2017 edition, the EAU RCC guidelines removed CXR from the follow-up recommendation. The present study in patients treated between 2006 to 2011, shows that CXR was the most used modality for investigation of the thorax. Similarly, the use of ultrasound was more frequent than recommended by the EAU guidelines. With the updated recommendations in mind, it is intriguing that imaging modality utilised does not seem to translate into a survival benefit. If no gain can be identified by the use of CTT instead of CXR, questions about cost-effectiveness and increased radiation exposure may be justified.

It is well documented that micrometastatic RCC cells may remain dormant for a long time before they develop into macroscopic, detectable disease. The reasons for dormancy may be multiple [20]; including genomic classification [21], inability to recruit blood vessels, immune surveillance, cell cycle arrest or tumor microenvironment interactions. There may be several causes for these disease foci to start growing at some time point. Some of these are tumor regulated such as the onset of chromosomal instability [22], but they may also be triggered by external factors such as other diseases and surgical [23] or other traumas (e.g. fractures or other traumatic injuries). It is hypothesized that increased levels of growth factors may stimulate several dormant tumors at the same time, resulting in disseminated visible metastatic disease in a short period of time [23, 24]. Moreover, unlike some other cancers with predicable patterns of recurrence, e.g. prostate cancer, RCC has the potential to metastasize to most organs. The sites of RCC recurrences not covered by CT of the thorax and abdomen are not negligible and up to 16% is reported [25]. Hence, such an image based FU program has an *a priori* inherent failure rate. Furthermore, these recurrences will in most cases be detected as symptomatic, with known poorer prognosis [25, 26].

Within the RECUR collaboration, a global per protocol assessment of potential curability has been established [12, 19]. The definite advantage of this methodology is that it only accounts for disease related factors such as type and number of metastatic sites, and is thus uniform and reproducible. In contrast, an investigator based assessment is subjective and appears to be affected by both disease and patient related factors like age, comorbidity and patients choices. In our opinion, and especially in

a retrospective setting, the need for limitation of potential confounders are important and might be better solved by a per protocol approach. However, for a study to be considered valid and useful, the results need to be recognized by clinicians. Therefore, to reconcile a per protocol assessment to an investigator based assessment is important. In this study, we found differences in the assessment, but these did not translate into significant differences in overall survival post recurrence for the PC and PI groups. In our opinion, these results reinforce the decision to use a per protocol assessment of curability within RECUR.

As our study is retrospective, and thus has obvious limitations, interpretations must be made with caution. All RECUR institutes used their own follow-up protocols with varying intervals between each imaging performed. Therefore, it was not possible to demonstrate to what extent each patient underwent imaging at the recommended time point. We acknowledge that CT detects lesions with higher resolution than ultrasound/CXR [27]. However, there is little evidence that CT have impacted the results significantly. The fact that all histological RCC subtypes were included in the current analysis may be a further limitation. Indeed there are published histological subtype-specific follow-up strategies but nevertheless, the major guidelines (EAU, AUA and NCCN) currently continue to provide FU strategies indiscriminately of RCC subtype [2-4].

The present study did not evaluate quality of life aspects. Follow-up definitely serves a psychosocial need which may be as important as the aspect of oncological control. Anxiety after surgery for cancer leaves patients with a timely reassurance that they remain free of disease. Therefore some kind of routine follow-up is probably indicated. However, the present study questions the need to increase the use of static and regular follow-up imaging.

It is likely that improved risk stratification tools will become available. Several molecular panels have shown prognostic utility [28-30]. Competing risk analyses have been introduced for tailoring follow-up programs to the individual patient factoring in age and comorbidities [19, 31], suggesting that routine follow-up be reduced in patients were the risk of death of other causes supersedes the risk of dying from RCC. The future of RCC follow-up is most likely to be much more personalized and routine follow-up will be replaced by tailored imaging during periods when recurrences are most likely to occur. Moreover, in the future, new follow-up programmes will have to be cost-effective [32].

5. Conclusion

The present study suggests that the mode of imaging for follow-up, detection of recurrences and the frequency at which imaging is applied do not affect subsequent overall survival. Prospective studies are needed to confirm these findings and help design optimal follow-up strategies which may be less intense but more personalised than those currently used.

6. Figure legends

Figure 1. Flowchart demonstrating inclusion and exclusion criteria for the present study.

Figure 2.

a) Kaplan-Meier plots for overall survival after recurrences for patients stratified on curability and their recurrence detected by conventional (Conv-continuous lines) methods or cross sectional imaging (CSI-dotted lines). There was no significant difference within the potential curable (PC-red) or the probably incurable (PI-black) group.
b) Kaplan-Meier plots for overall survival after recurrences for patients stratified on curability and if the majority of follow-op imaging was by conventional (<50% CSI-dotted) methods or cross sectional imaging (≥50% CSI-continuous lines). There was no significant difference within the potential curable (PC-red) or the probably incurable (PI-black) group

Figure 3.

a) Kaplan-Meier plots for overall survival after recurrences for patients stratified on curability and their recurrence classified by global per protocol (GPP-continuous lines) assessment or by investigator based assessment (IBA-dotted lines). There was no significant difference within the potential curable (PC-red) or the probably incurable (PI-black) group.

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Table 1. Patient characteristics (n=1,612)

		n	%
Age (yrs) - Mean (median, IQR)		62.9 (64.0, 55-72)	
Gender	Male	1036	64.3
	Female	576	35.7
Tumour size (cm) - Mean (median, IQR)		5.9 (5.0, 3-8)	
RCC Subtype	Clear Cell RCC	1227	76.1
	Papillary RCC	233	14.5
	Chromophobe RCC	113	7.0
	Other RCC	39	2.4
Primary pT-stage	pT1a	590	36.6
	pT1b	395	24.5
	pT2a	161	10.0
	pT2b	101	6,3
	pT3a	276	17.1
	pT3b	70	4,3
	pT3c	6	0.4
	pT4	13	0.8
Primary pN-stage	pNx-0	1579	98.0
	pN1-2	33	2.0
Risk group*	High	309	19.2
	Intermediate	497	30.8
	Low	806	50.0
Surgical procedure	Radical nephrectomy	1141	70.8
	Partial nephrectomy	471	29.2
Recurrences by presentation (n=336)	Symptomatic	125	37.2
	Asymptomatic	211	62.8
Recurrences detected by regular follow-up (n=336)	Yes	238	70.8
	No	98	29.2

n-number of patients, yrs-years, SEM-standard error of the mean, IQR-Inter Quartile Range, cm-centimeter, RCC-Renal cell carcinoma, pT-pathological tumor stage, pN-pathological lymph node stage, *- for clear cell RCC the risk group allocation is based on the system by Leibovich [16] and for non-clear cell RCC by the UISS system [18].

Table 2. The table demonstrates the use of follow-up imaging for the three risk groups of RCC in the RECUR-cohort.

Risk Groups		Imaging							
		Total	Thoracal imaging			Abdominal imaging			MRI
			CT	CXR	CT/ CXR	CT	US	CT/US	
		n	n	n	Ratio	n	n	Ratio	n
Low	**(n=806)**	8986	1300	3694	0.35	2445	1439	1.70	108
Intermediate	**(n=497)**	5560	951	2071	0.46	1554	921	1.69	63
High	**(n=309)**	2787	773	775	1.00	930	291	3.20	18
Total	**(n=1612)**	17333	3024	6540	0.46	4929	2651	1.86	189

CT – Computer tomography, CXR – Chest X-ray, US – Ultrasound, MRI – Magnetic Resonance Imaging, n- Number, Exact Chi-square test demonstrates that the distribution of CT and conventional imaging is statistically significant different ($p<0.001$) between the different risk groups for both thoracal and abdominal imaging. The only exception is between the low risk and intermediate risk group for abdominal imaging

Table 3. Frequency of imaging (images per year) by Risk groups and groups of follow-up

Risk Group (RG)	Groups of Follow-Up (FU)									p-value[a]
	Short-term FU (0 – 2.49 yrs, n=292)			**Mid-term FU** (2.5 – 5.49 yrs, n=846)			**Long-term FU** (> 5.5 yrs, n=482)			
	n	IF Median (IQR)	p-value[c]	n	IF Median (IQR)	p-value[c]	n	IF Median (IQR)	p-value[c]	
LOW RG (n=806)	60	3.3 (1.6-6.3)		490	2.2 (1.8-2.6)		256	1.7 (1.2-2.4)		<0.001
Recurrences	20	4.6 (2.6-6.7)	0.064	35	2.0 (1.5-2.8)	0.458	10	1.7 (1.3-2.4)	0.754	
Non-recurrences	40	2.4 (1.3-5.4)		455	2.2 (1.8-2.6)		246	1.7 (1.2-2.4)		
INTERM. RG (n=497)	92	3.9 (2.7-4.7)		242	2.3 (1.9-2.9)		163	2.0 (1.3-2.6)		<0.001
Recurrences	63	3.8 (3.0-4.5)	0.930	37	2.5 (1.8-3.4)	0.355	8	1.6 (0.6-2.2)	0.211	
Non-recurrences	29	4.0 (2.0-6.1)		205	2.3 (1.9-2-8)		155	2.1 (1.3-2.6)		
HIGH RG (n=309)	132	4.4 (3.0-6.1)		114	2.6 (2.1-3.3)		63	2.0 (1.3-2.6)		<0.001
Recurrences	123	4.4 (3.0-6.0)	0.524	36	3.2 (2.3-4.2)	0.002	4	2.3 (0.8-3.8)	0.796	
Non-recurrences	9	3.2 (1.8-6.3)		78	2.5 (1.8-3.1)		59	2.0 (1.3-2.4)		
p-value[b]	0.084[d]			<0.001			0.057[e]			

IF – Imaging Frequency, IQR – interquartile range, n-numbers of patients, [a] – Non-parametric Kruskal-Wallis test for equal distribution of imaging frequency within each risk group across all periods of follow-up, [b] - Non-parametric Kruskal-Wallis test for equal distribution of imaging frequency within each period of follow-up across all risk groups, c – Mann-Whitney U-test for equal distribution of imaging frequency between patients with and without recurrences grouped by risk group and group of follow-up, [d] – testing two and two categories by MWU-test demonstrated that none of the three groups had a significant different IF distribution, [e] - testing two and two categories by MWU-test demonstrated that IF in the late FU-group of the LRG was significantly lower than for the IRG (p=0.029), none of the other comparisons demonstrated significant differences. Non-recurrences in the Short-term FU group are patients dead of other causes.

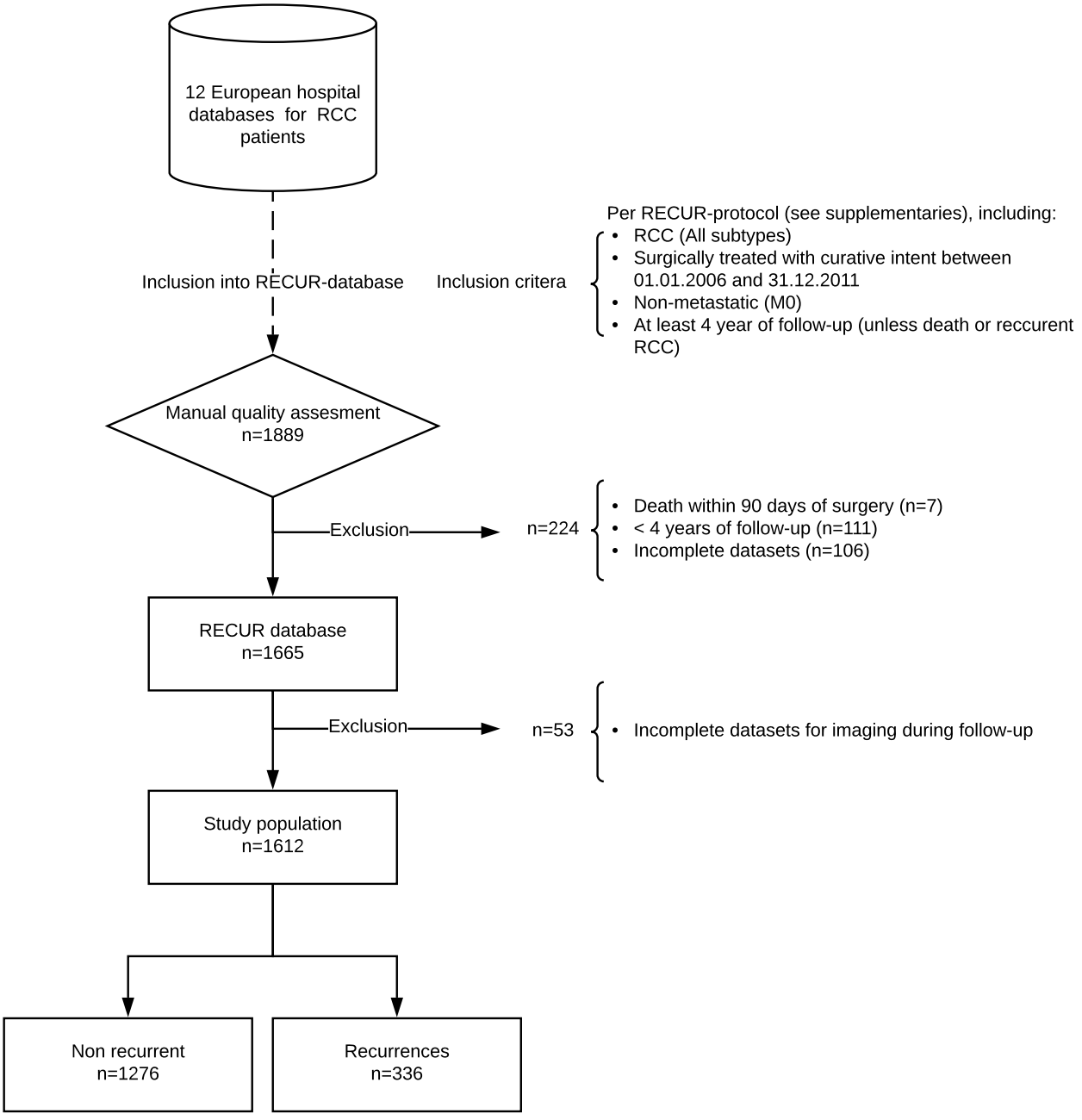
Table 4. Patient features divided by high CSI (≥50% CSI) and low CSI (<50% CSI) during FU.

Risk group	n	Feature	<50% CSI	≥50% CSI	p-value[a]
Low Risk	65	Detected in reg. FU	15 (50%)	24 (69%)	0.204
		Non-Symptomatic recurr.	15 (50%)	25 (71%)	0.124
Intermediate Risk	108	Detected in reg. FU	30 (58%)	48 (86%)	0.001
		Non-Symptomatic recurr.	32 (62%)	40 (71%)	0.311
High Risk	163	Detected in reg. FU	31 (70%)	90 (76%)	0.547
		Non-Symptomatic recurr.	30 (68%)	69 (58%)	0.280

CSI – Cross sectional Imaging, n – number of patients, [a] – exact Chi-square test, Detected in reg. FU – detected in regular follow-up program. Recurr. – recurrence.

The figures for patients not detected in regular FU and with symptomatic recurrences are not shown, but can be calculated from the presented data.

Figure 1


12 European hospital databases for RCC patients
Inclusion into RECUR-database
Inclusion critera
Per RECUR-protocol (see supplementaries), including:
RCC (All subtypes)
Surgically treated with curative intent between 01.01.2006 and 31.12.2011
Non-metastatic (M0)
At least 4 year of follow-up (unless death or reccurent RCC)
Manual quality assesment n=1889
Exclusion
n=224
Death within 90 days of surgery (n=7)
< 4 years of follow-up (n=111)
Incomplete datasets (n=106)
RECUR database n=1665
Exclusion
n=53
Incomplete datasets for imaging during follow-up
Study population n=1612
Non recurrent n=1276
Recurrences n=336

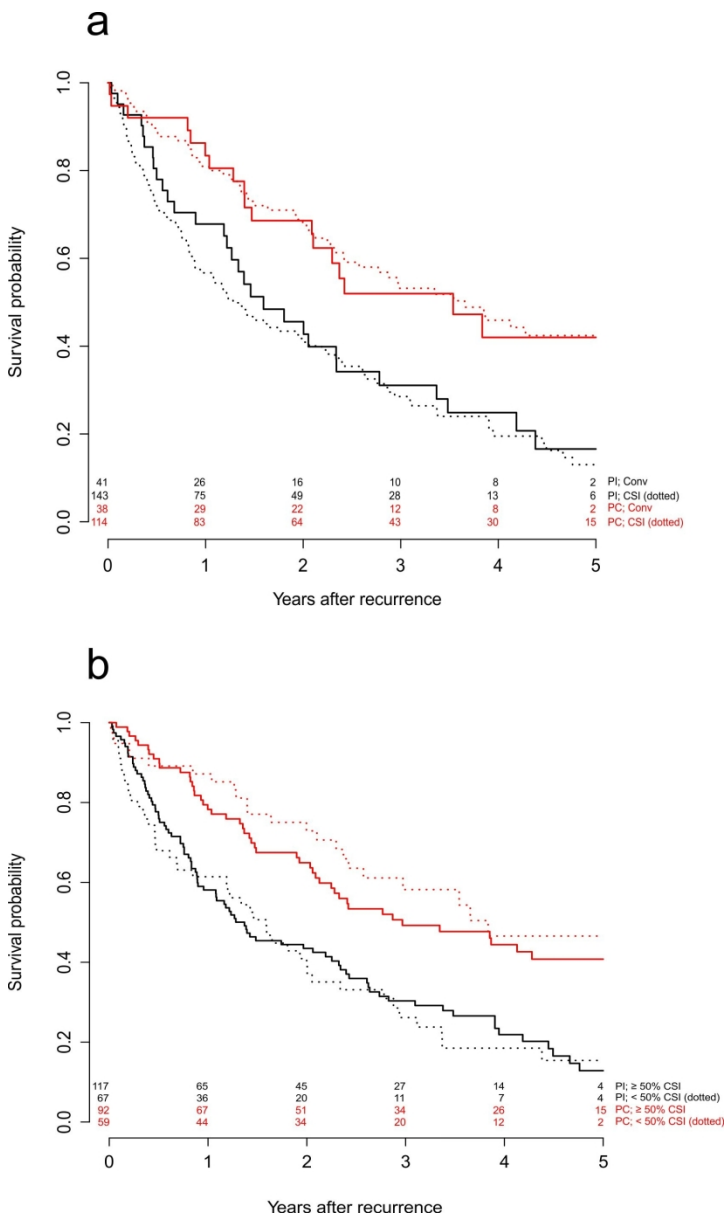
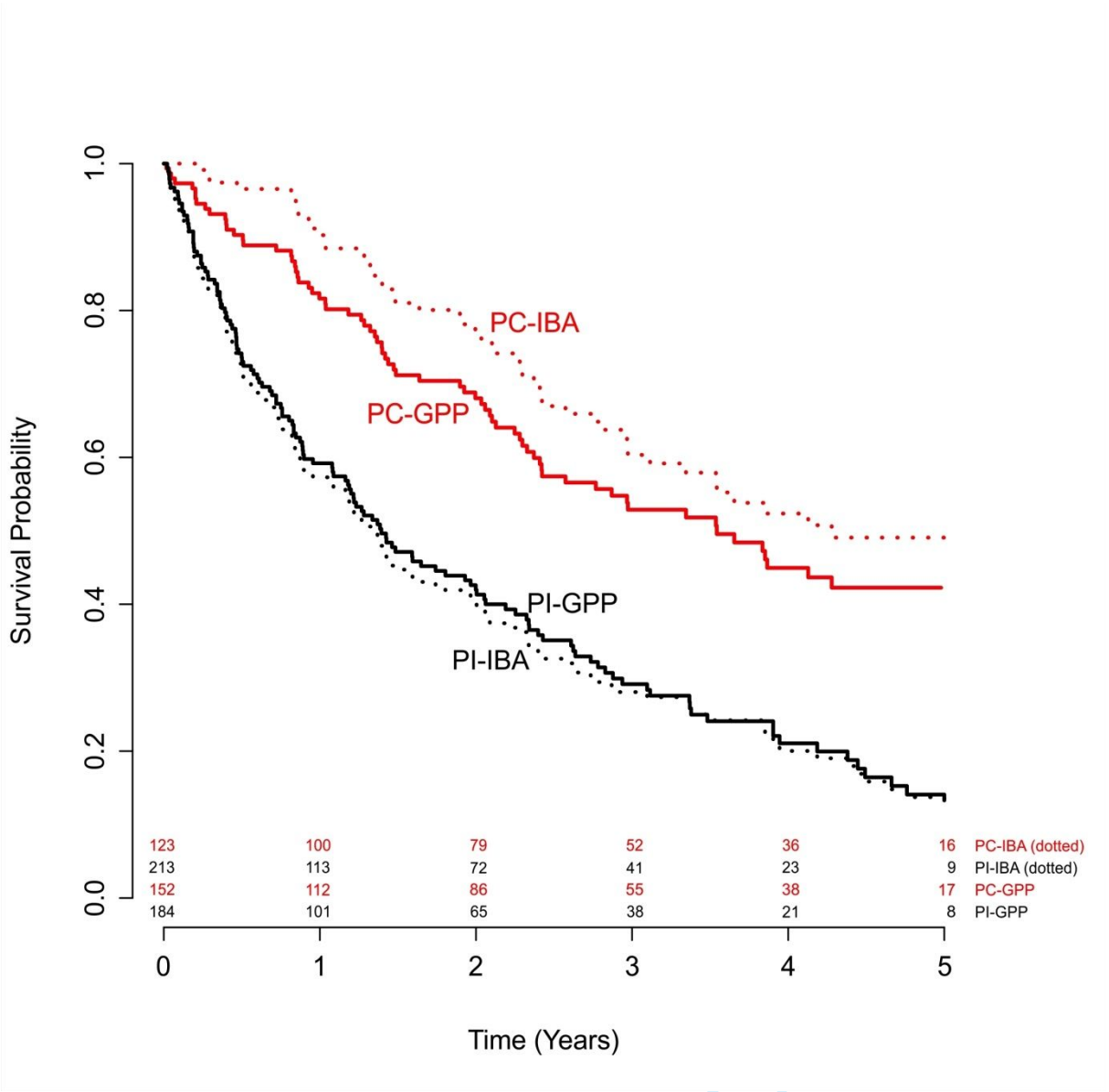


Figure 3

143x239mm (300 x 300 DPI)


Survival Probability
0.0
0.2
0.4
0.6
0.8
1.0
PC-IBA
PC-GPP
PI-GPP
PI-IBA
123 100 79 52 36 16 PC-IBA (dotted)
213 113 72 41 23 9 PI-IBA (dotted)
152 112 86 55 38 17 PC-GPP
184 101 65 38 21 8 PI-GPP
0
1
2
3
4
5
Time (Years)

Supplementary table 1. Patient features divided by high IF (above median) and low IF (below median) at the time of recurrence.

Risk Group	GoFU	n	Feature	Low IF	High IF	p-value[a]
Low Risk	Short-term FU	20	Detected in reg. FU	4 (57%)	9 (69%)	0.651
			Non-Symptomatic recurr.	5 (71%)	10 (77%)	1.000
	Mid-term FU	35	Detected in reg. FU	10 (53%)	12 (75%)	0.293
			Non-Symptomatic recurr.	10 (53%)	12 (75%)	0.293
	Long-term FU	10	Detected in reg. FU	3 (50%)	1 (25%)	0.571
			Non-Symptomatic recurr.	2 (33%)	1 (25%)	1.000
Intermed. Risk	Short-term FU	63	Detected in reg. FU	21 (66%)	29 (94%)	0.011
			Non-Symptomatic recurr.	20 (63%)	26 (84%)	0.088
	Mid-term FU	37	Detected in reg. FU	12 (75%)	9 (67%)	0.723
			Non-Symptomatic recurr.	11 (69%)	3 (62%)	1.000
	Long-term FU	8	Detected in reg. FU	1 (20%)	1 (33%)	1.000
			Non-Symptomatic recurr.	1 (20%)	1 (33%)	1.000
High Risk	Short-term FU	123	Detected in reg. FU	40 (61%)	9 (81%)	0.069
			Non-Symptomatic recurr.	31 (51%)	37 (62%)	0.367
	Mid-term FU	36	Detected in reg. FU	13 (93%)	17 (77%)	0.370
			Non-Symptomatic recurr.	14 (100%)	16 (73%)	0.062
	Long-term FU	4	Detected in reg. FU	0 (0%)	1 (50%)	1.000
			Non-Symptomatic recurr.	0 (0%)	1 (50%)	1.000

IF – imaging Frequency, Gofu – Group of follow-up, n – number of patients, [a] – exact Chi-square test, Detected in reg. FU – detected in regular follow-up program. Recurr. – recurrence.

The figures for patients not detected in regular FU and with symptomatic recurrences are not shown, but can be calculated from the presented data.

Dabestani, Beisland et al. (2019); Increased use of cross-sectional imaging for follow-up does not improve post-recurrence survival of surgically treated initially localized RCC: results from a European multicenter database (RECUR).

SUPPLEMENTARY TEXT (Materials and Methods – Expanded chapters)

The RECUR – Database (description of Ethics, Inclusion, Exclusion, Coding of data – this chapter is mostly similar to the supplementary text of the earlier RECUR-papers [1, 2]

The current study is the second study performed under the auspices of the euRopEan association of urology renal cell carcinoma guidelines panel Collaborative multicenter consortium for the studies of follow-Up and recurrence patterns in Radically treated renal cell carcinoma patients (RECUR). The full RECUR protocol is available as an online appendix to the first paper [1]. After appropriate institutional review board ethical approval, consecutive non-metastatic (M0) RCC patients treated surgically with curative intent between 1st January 2006 and 31st Dec 2011 were included by retrospective patient encrypted data collection in an Excel file according to our RECUR protocol. This time frame was chosen for 2 reasons: (1) Targeted therapy was only introduced from 2006 onwards, i.e. limiting the study period to after 2006 excluded patients not considered for targeted therapeutic options, which may have influenced RCC recurrence outcomes. (2) Limiting the study to the end of 2011 enabled a minimum of 4 years of follow-up data to be accrued considering that first set of data collection started in beginning of 2016. Patients that died or recurred within 4 years of FU were included for the analyses. Patients that did not die or recur were excluded if their FU was less than 4 years. Data lock for the current analysis was on May 1st 2017.

Overall, 1,889 patients were included in RECUR. 164 were excluded from the analysis due to lack of baseline data or death <90 days after primary surgery. Furthermore, 111 patients were excluded due to follow-up <4 years and finally, 53 were excluded due to lack of follow-up imaging data.

Table A (below) shows the centers with patients included in the study.

All subtypes of RCC were recorded according to the RECUR protocol and for the current study.

M0 was defined as preoperative imaging not revealing any signs of metastatic disease in the chest or abdomen. Baseline characteristics (gender, age and type of surgery), tumor (side, size and histology), Type of surgery (radical nephrectomy (RN), partial nephrectomy (PN), either open, laparoscopic or robot assisted), number and type of imaging to recurrence or last FU (Computed Tomography (CT) abdomen, CT chest, plain chest X-ray (CXR), Ultrasound (US) and magnetic resonance imaging (MRI)), recurrence characteristics (time to recurrence, site, symptoms, exact dates of all FU imaging leading detection of recurrence and detection modality) and their intent (curative, palliative or observation only) and subsequent management (focal: none, metastasectomy, radiotherapy or ablative, systemic; none, anti-vascular endothelial growth factor (anti-VEGF)/tyrosine kinase inhibitors (TKI), Mammalian Target of Rapamycin inhibitor (mTOR), monoclonal antibody (mAB), Immunotherapy (interferon) or best supportive care) together with survival outcomes (alive, free of RCC, alive with RCC, death due to RCC, death by other cause) were recorded from medical records.

Patients who died within 90 days after primary surgery were excluded as their deaths were considered as most likely postoperative complications and/or risk of introducing a staging bias on mortality rates. The 7th edition of the American Joint Committee on Cancer (AJCC) tumor node metastasis (TNM) classification from 2010 was used [3]. It has to be acknowledged that the staging of lymph nodes has changed since the introduction of the Leibovich score. However, as both pN1 and

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pN2 receive an equal amount of points in the score a reclassification with an older TNM was not necessary. In patients with two ipsilateral or contralateral tumors undergoing surgery, the clinical and histological features of the largest and/or most aggressive tumor were used for the analysis. Patients with hereditary disease (e.g. Von Hippel-Lindau, Birt-Hogg-Dubé syndrome and Hereditary Papillary Renal Cell Carcinoma) were excluded as were benign tumors (e.g. angiomyolipoma and oncocytoma).

Patients were stratified into low, intermediate and high risk groups by Leibovich score in cases of predominantly clear cell RCC (ccRCC) and Union Internationale Contre le Cancer(UICC)/AJCC score if a non-clear cell RCC (non-ccRCC) subtype, i.e. papillary RCC (pRCC), chromophobe RCC (chRCC), or other types of RCC (oRCC) were present [3, 4]. Presence of sarcomatoid RCC (sRCC) was additionally registered. Isolated local, solitary and oligometastatic (≤3 lesions at a single site) recurrences were considered potentially curable (PC) by local therapeutic strategies while all others were regarded as probably incurable (PI), i.e. >3 lesions at a single site or dissemination to ≥2 distant sites. Definition of local recurrence was for PN, a local recurrence in the kidney parenchyma while local recurrence in patients with RN was any recurrence in the renal bed not including peritoneal recurrence (which indicated disseminated disease) nor hilar lymph node metastases (which were defined as retroperitoneal recurrences) in our database. For detection of recurrences, CT and MRI were considered cross-sectional imaging modalities while CXR, US and clinical examination were considered conventional. Whether patients were symptomatic at time point of recurrence detection and whether recurrences were detected within or outside the respective institutions FU protocols were also recorded. Time points of FU imaging collected were based on FU protocols of respective treating centers and their local standards.

References

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4. Leibovich BC, Blute ML, Cheville JC, Lohse CM, Frank I, Kwon ED, Weaver AL, Parker AS, Zincke H: **Prediction of progression after radical nephrectomy for patients with clear cell renal cell carcinoma: a stratification tool for prospective clinical trials**. *Cancer* 2003, **97**(7):1663-1671.

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Table A – Number of RCC cases per center in RECUR database

Institute/center	Country	N total	N excluded	N recurrence
Skane University Hospital	Sweden	308	15	52
Umea University Hospital	Sweden	151	6	32
Landspitali University Hospital	Iceland	161	30	29
Edinburgh University	United Kingdom	277	131	35
University of Aberdeen	United Kingdom	150	31	34
Haukeland University Hospital	Norway	249	2	25
UMCU/NCI	The Netherlands	186	11	44
Coimbra University Hospital	Portugal	150	4	29
Cabueñes University Hospital	Spain	131	1	35
San Agustin University Hospital	Spain	73	1	13
UEP	Italy	53	45	8
Total	**NA**	**1889**	**277**	**336**

NA = Not Applicable. NCI = National Cancer Institute, Amsterdam. UEP = University of Eastern Piedmont, Novara. UMCU = University Medical Center Utrecht