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3 1 **Increased use of cross-sectional imaging for follow-up does not improve post-**
4 **recurrence survival of surgically treated initially localized RCC: results from a**
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7 **European multicenter database (RECUR).**

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3 50 **Abstract**
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5 51 **Objective:** Modality and frequency of image-based renal cell carcinoma (RCC) follow-up (FU) strategies are
6 52 based on risk of recurrence. Using the RECUR-database; we studied frequency of imaging in regard to
7 53 prognostic risk groups. Furthermore, whether imaging modality utilised in contemporary FU were
8 54 associated with outcome after detection of recurrence. Moreover, we compared outcome based on
9 55 whether the assessment of potential curability was a predefined set of criteria's (per-protocol) or stated by
10 56 the investigator.
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14 57 **Materials and Methods:** Consecutive non-metastatic RCC patients (n=1,612) treated with curative intent at
15 58 12 institutes across 8 European countries between 2006 and 2011 were included. Leibovich or UISS risk
16 59 group, recurrence characteristics, imaging modality, frequency and survival were recorded. Primary
17 60 endpoints were overall survival (OS) after detection of recurrence and frequency of features associated
18 61 with favourable outcome (non-symptomatic recurrences and detection within the FU-program).
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22 63 **Results:** Recurrence occurred in 336 patients. Within low, intermediate and high risk for recurrence groups,
23 64 the frequency of FU imaging was highest in the early phase of FU, and decreased significantly over time
24 65 ($p < 0.001$). However, neither the image modality for detection nor $\geq 50\%$ cross-sectional imaging during FU,
25 66 were associated with improved OS after recurrence. Differences between per protocol and investigator
26 67 based assessment of curability, did not translate into differences in OS.
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29 68 **Conclusions:** As expected, the frequency of imaging was highest during early follow-up. Cross-sectional
30 69 imaging use for detection of recurrences following surgery for localised RCC did not improve OS post-
31 70 recurrence. Prospective studies are needed to determine the value of imaging in follow-up.
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34 71 **N=249 (max. 250)**
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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 ($\geq 50\%$ 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.

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3 154 **2.3. Statistical analysis**

4 155 Descriptive statistics were presented as categorical variables with percentages and continuous
5 156 variables as median and interquartile range (IQR). For categorical and non-parametric data, exact Chi-
6 157 square test and Mann-Whitney U-test or Kruskal-Wallis test, respectively, were used. Correlation for
7 158 group allocation for PC/PI was evaluated with Kappa statistics. Kaplan-Meier method with Log-Rank
8 159 test was performed for overall survival. For all statistical comparisons, a two-tailed p-value of <0.05 was
9 160 considered significant. SPSS-version 23 (IBM corporation, Armonk, New York, USA) and R version 3.3.2
10 161 (R Foundation for Statistical Computing, Vienna, Austria) were used.
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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 ($\geq 50\%$) 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

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

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3 252 a retrospective setting, the need for limitation of potential confounders are important and might be
4 253 better solved by a per protocol approach. However, for a study to be considered valid and useful, the
5 254 results need to be recognized by clinicians. Therefore, to reconcile a per protocol assessment to an
6 255 investigator based assessment is important. In this study, we found differences in the assessment, but
7 256 these did not translate into significant differences in overall survival post recurrence for the PC and PI
8 257 groups. In our opinion, these results reinforce the decision to use a per protocol assessment of
9 258 curability within RECUR.

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13 259 As our study is retrospective, and thus has obvious limitations, interpretations must be made with
14 260 caution. All RECUR institutes used their own follow-up protocols with varying intervals between each
15 261 imaging performed. Therefore, it was not possible to demonstrate to what extent each patient
16 262 underwent imaging at the recommended time point. We acknowledge that CT detects lesions with
17 263 higher resolution than ultrasound/CXR [27]. However, there is little evidence that CT have impacted
18 264 the results significantly. The fact that all histological RCC subtypes were included in the current
19 265 analysis may be a further limitation. Indeed there are published histological subtype-specific follow-up
20 266 strategies but nevertheless, the major guidelines (EAU, AUA and NCCN) currently continue to provide
21 267 FU strategies indiscriminately of RCC subtype [2-4].

25 268 The present study did not evaluate quality of life aspects. Follow-up definitely serves a psychosocial
26 269 need which may be as important as the aspect of oncological control. Anxiety after surgery for cancer
27 270 leaves patients with a timely reassurance that they remain free of disease. Therefore some kind of
28 271 routine follow-up is probably indicated. However, the present study questions the need to increase
29 272 the use of static and regular follow-up imaging.

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33 273 It is likely that improved risk stratification tools will become available. Several molecular panels have
34 274 shown prognostic utility [28-30]. Competing risk analyses have been introduced for tailoring follow-up
35 275 programs to the individual patient factoring in age and comorbidities [19, 31], suggesting that routine
36 276 follow-up be reduced in patients where the risk of death of other causes supersedes the risk of dying
37 277 from RCC. The future of RCC follow-up is most likely to be much more personalized and routine follow-
38 278 up will be replaced by tailored imaging during periods when recurrences are most likely to occur.
39 279 Moreover, in the future, new follow-up programmes will have to be cost-effective [32].
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3 281 **5. Conclusion**
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5 282 The present study suggests that the mode of imaging for follow-up, detection of recurrences and the
6 283 frequency at which imaging is applied do not affect subsequent overall survival. Prospective studies
7 284 are needed to confirm these findings and help design optimal follow-up strategies which may be less
8 285 intense but more personalised than those currently used.
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3 287 **6. Figure legends**
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5 288 Figure 1. Flowchart demonstrating inclusion and exclusion criteria for the present study.
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10 290 Figure 2.
11 291 a) Kaplan-Meier plots for overall survival after recurrences for patients stratified on curability and
12 292 their recurrence detected by conventional (Conv-continuous lines) methods or cross sectional
13 293 imaging (CSI-dotted lines). There was no significant difference within the potential curable (PC-
14 294 red) or the probably incurable (PI-black) group.
15 295 b) Kaplan-Meier plots for overall survival after recurrences for patients stratified on curability and
16 296 if the majority of follow-up imaging was by conventional (<50% CSI-dotted) methods or cross
17 297 sectional imaging (≥50% CSI-continuous lines). There was no significant difference within the
18 298 potential curable (PC-red) or the probably incurable (PI-black) group
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21 301 Figure 3.
22 302 a) Kaplan-Meier plots for overall survival after recurrences for patients stratified on curability and
23 303 their recurrence classified by global per protocol (GPP-continuous lines) assessment or by
24 304 investigator based assessment (IBA-dotted lines). There was no significant difference within the
25 305 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].

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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.**

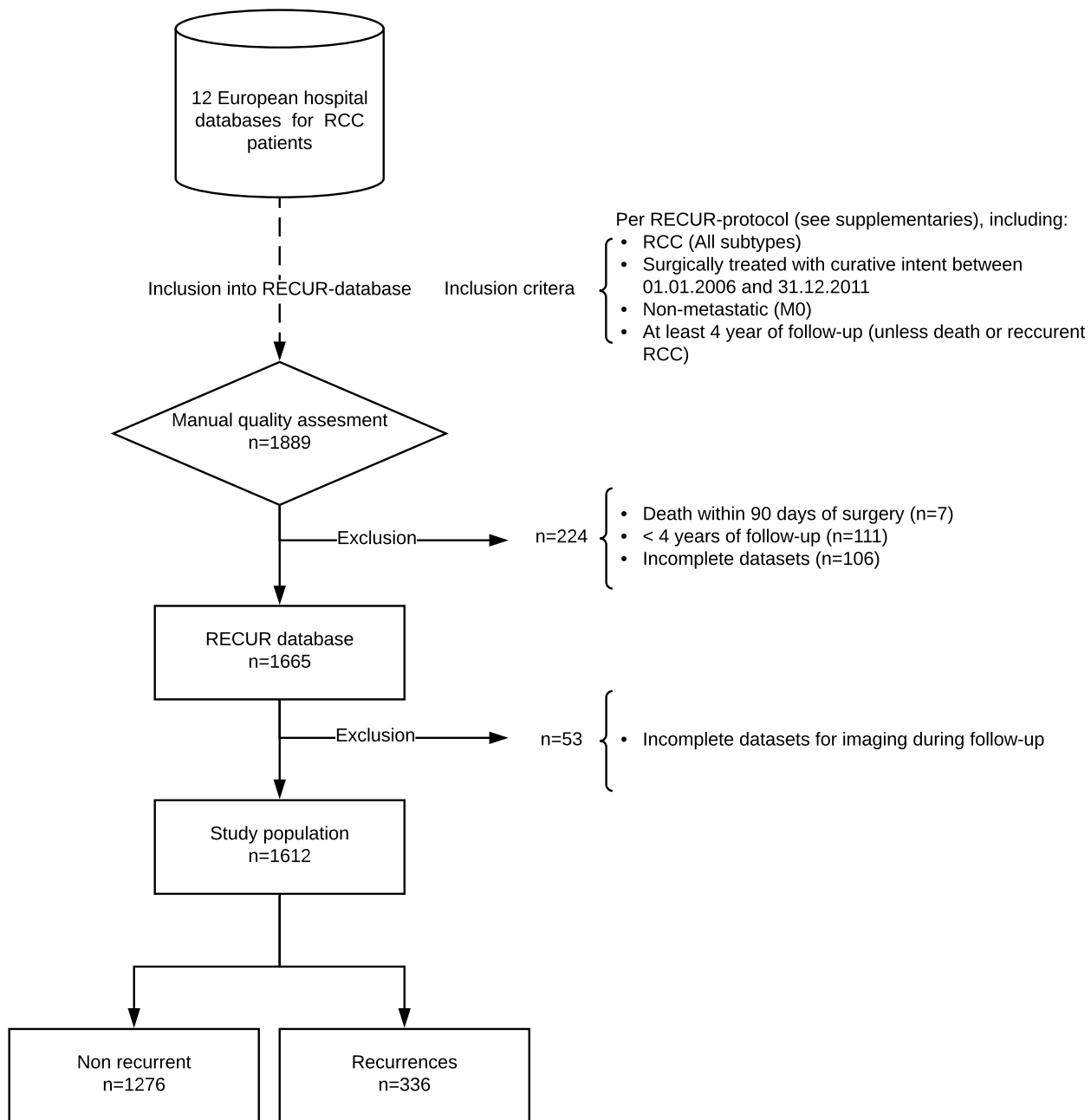
Table 4. Patient features divided by high CSI ($\geq 50\%$ CSI) and low CSI ($< 50\%$ CSI) during FU.

| Risk group | n | Feature | <50% CSI | $\geq 50\%$ 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



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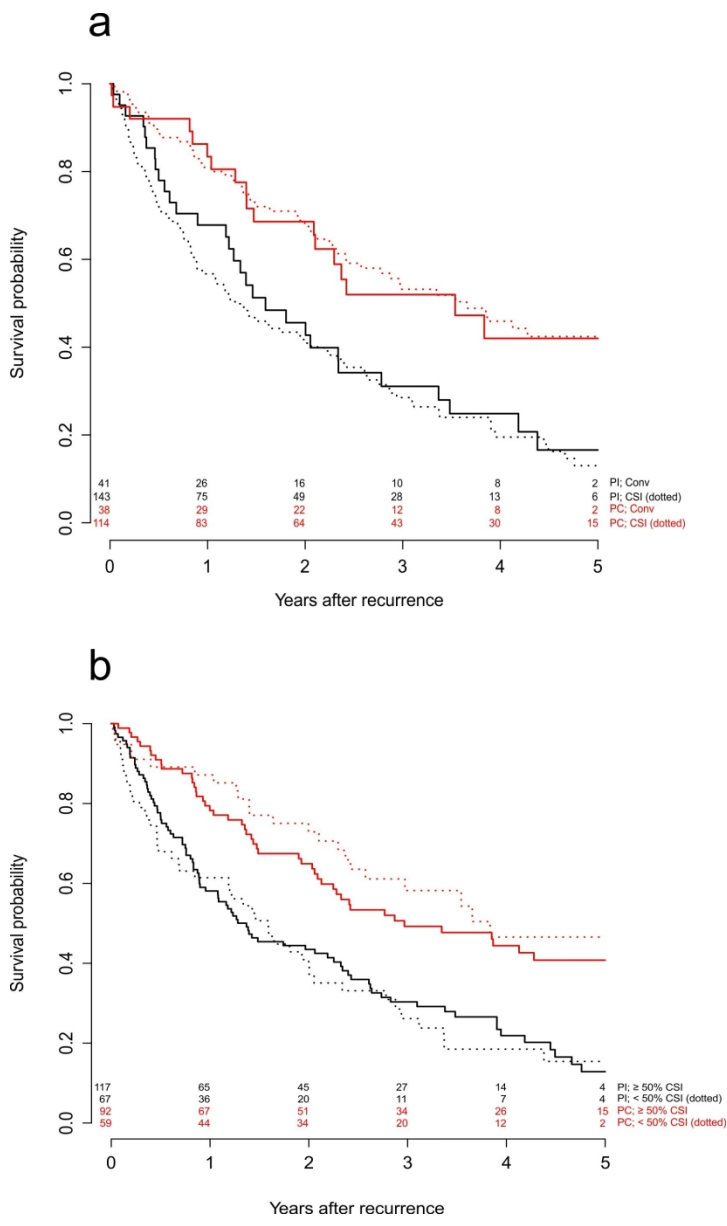
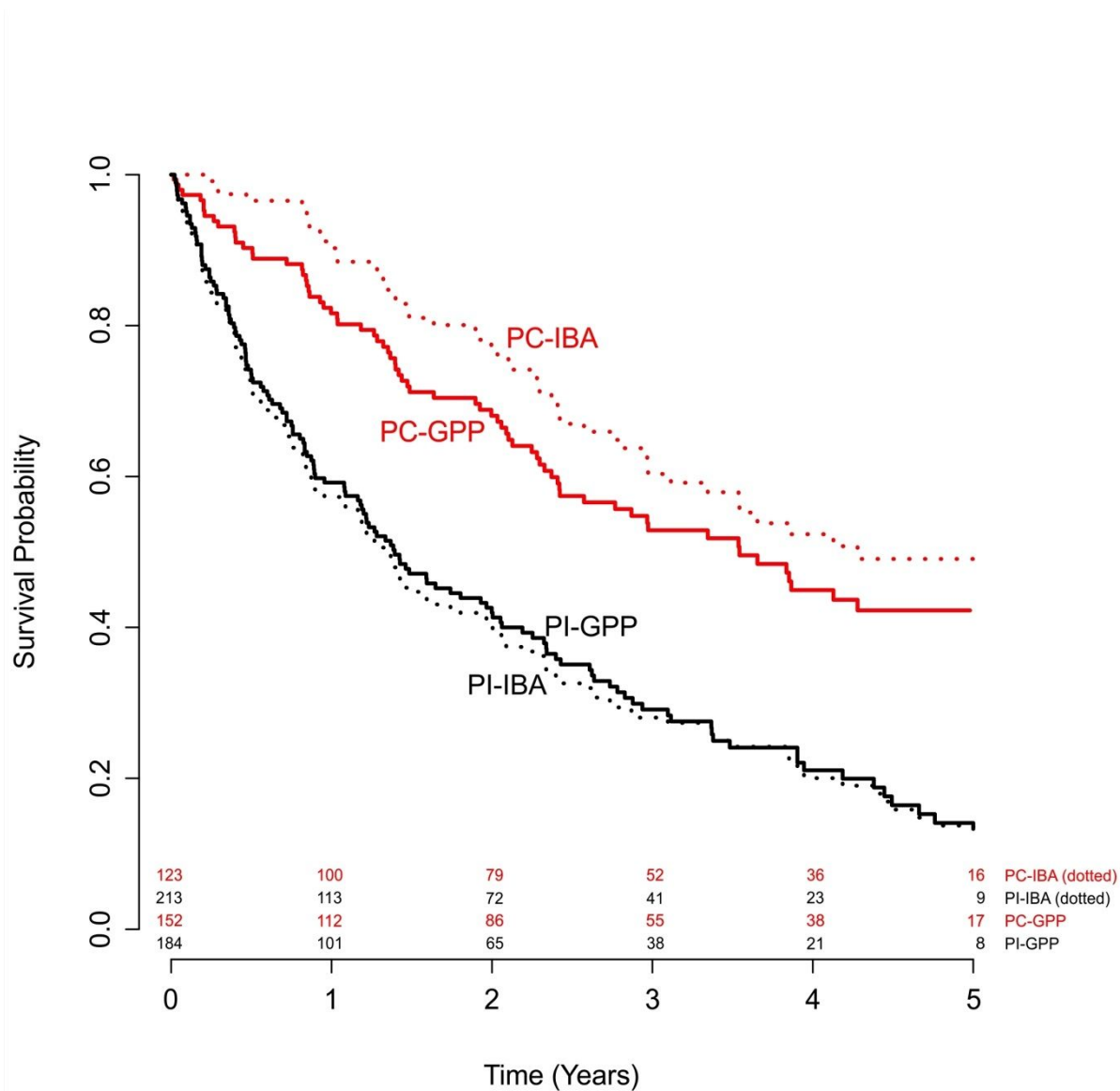


Figure 3

143x239mm (300 x 300 DPI)



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

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).

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.

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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 |
| Landspítali 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 |
| Cabueñas 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