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ORIGINAL ARTICLE

Oncologic surveillance after surgical treatment for clinically localized kidney cancer: UroCCR study n. 129

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ABSTRACT

BACKGROUND: In 2021, the EAU Guidelines implemented a novel, expert opinion-based follow-up scheme, with a three-risk-category system for clear cell (cc) and non-cc renal cell carcinoma (non-ccRCC) after surgery with curative

intent. We aimed to validate the novel follow-up scheme and provide data-driven recurrence estimates according to risk groups, to confirm or implement the oncologic surveillance strategy.
METHODS: We identified 5,320 patients from a prospectively maintained database involving 28 French referral centers. The risk of recurrence, as either loco-regional or distant, was evaluated with the Kaplan-Meier method for each group (low- intermediate- or high-risk) according to ccRCC or non-ccRCC histology. The noncumulative distribution of recurrences was graphically investigated through the LOWESS smoother.
RESULTS: Two thousand two hundred ninety-three (58%), 926 (23%), and 738 (19%) had low-, intermediate, and high-risk ccRCC, and 683 (50%), 297 (22%), and 383 (28%) had low-, intermediate, and high-risk non-ccRCC, respectively. Median follow-up for survivors was 46 months. Overall, 661 patients experienced recurrence. Over time, the noncumulative risk of recurrence was approximately 10% for low-risk cc-RCC, non-ccRCC, and intermediate-risk non-ccRCC, with non-significant difference among the three recurrence functions (P=0.9). At 5-year, time point after which imaging should be de-intensified to biennial, the noncumulative risks of recurrence were: for intermediate risk ccRCC and non-ccRCC: 15% and 11%, respectively; for high-risk ccRCC and non-ccRCC: 24% and 8%, respectively. Among high-risk non-ccRCC patients there were 9 recurrences at 3-month. There was no significant difference between the recurrence function of high-risk non-ccRCC patients with negative imaging at 3-month and the one of intermediate-risk ccRCC (P=0.3).
CONCLUSIONS: Given the relatively low recurrence risk of patients with intermediate-risk non-ccRCC, those individuals could be followed up with a similar strategy to the low-risk category. Similarly, patients with high-risk non-ccRCC with negative imaging at 3-month, could be followed up similarly to intermediate-risk ccRCC after the 3-month time point.

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KEY WORDS: Carcinoma, renal cell; Follow-up studies; Recurrence; Guidelines as topic.

Renal cell carcinoma (RCC) is the most common kidney malignancy and accounts for most of all kidney neoplasms.[1] RCC consists of different subtypes with specific histopathological and genomic characteristics, with clear cell (ccRCC), papillary (pRCC) and chromophobe (chRCC) being the most common ones.[2] Irrespective of the histological subtype, the gold standard treatment for clinically localized kidney cancer is surgical extirpation, in the forms of either partial or radical nephrectomy, which lead to 5-year cancer-specific survival rates of approximately 81%, 82% and 91% for ccRCC, pRCC and chRCC respectively.[3]

In addition to the RCC subtype, other prognostic factors include tumor grade and stage, lymphovascular invasion, tumor necrosis, and invasion of the collecting system.[4, 5] These factors, in different combinations, have been included in several prognostic models aimed at estimating the risk of recurrence or the eventual need for adjuvant treatments.[5-8]

Indeed, after surgery with curative intent, a proper surveillance scheme is needed to monitor kidney function and to timely detect local and/or distant relapse(s).[9, 10] Based on the available evidence, the Guideline Panel of the European Association of Urology (EAU) for RCC has recently proposed a novel structured follow-up scheme for oncologic surveillance following surgery with curative intent.[11]

Given the lack of randomized controlled trials in this domain and the complexity of implementing such trials, current recommendations are mostly based on expert opinion or multi-institutional registries that have been built *ad hoc* to evaluate the optimal oncologic surveillance strategy.[12, 13]

The most recent modification to the EAU guidelines for oncologic surveillance following surgery — implemented in 2021 — stratifies individuals into low-, intermediate- and high-risk groups.[11] The ultimate goal of such a subdivision is to provide a risk-based approach to reduce unnecessary imaging in patients at lower risk of recurrence while still allowing a timely relapse detection for individuals with worse disease features. In each risk group, different time points, at which a CT scan of both abdomen and thorax should be obtained, are proposed. Specifically, for patients falling in the low-risk category, imaging should be obtained at 6 months after surgery, yearly thereafter, for up to three years, and then biennially. In the Intermediate-risk group, imaging should be obtained at 6 and 12 months after surgery, yearly thereafter for up to five years, and then biennially. Finally, for high-risk individuals, imaging should be obtained at 3

months after surgery, semiannually for the first two years, yearly thereafter for up to five years, and then biennially.

As the follow-up recommendations are based on expert opinion, we aimed to validate and potentially improve the follow-up imaging strategy for patients who undergo surgery with curative intent for clinically localized RCC.

Materials and methods

Patient population and variables of interest

We relied on a prospectively maintained multi-institutional databased endorsed by the French Network for Research on Kidney Cancer—UroCCR (NCT03293563). We selected patients who underwent surgical treatment, as either partial or radical nephrectomy, for clinically localized kidney cancer and did not receive any form of neo-adjuvant or adjuvant treatment. For the purpose of the study we extrapolated, from the UroCCR database, clinical data from patients at surgery (age, sex, Body Mass Index [BMI], American Society of Anesthesiologists [ASA] Score, type of surgery [PN or RN] and presence of multiple tumors) pathology data (pTN stages, histology, tumor grade, tumor's diameter, necrosis, surgical margins status) and follow-up data. Patients were staged according to the 2017 TNM version. Tumor grade was based on the Fuhrman's system.[14] Data on recurrence was stratified as either loco-regional (resection bed, in case of PN or renal fossa in case of RN or regional lymph nodes) or distant metastatic disease.

Given the nature of the study which was aimed at evaluating the updated EAU oncologic surveillance scheme following surgical treatment of kidney cancer, we classified patients as either harboring ccRCC or non-ccRCC. Patients falling in the former category were further sub-stratified based on the Leibovich score, while individuals in the latter category were stratified as suggested by the EAU guidelines as follows: low risk: pT1a-T1b pNx-0 and histological grade 1 or 2, intermediate risk: pT1b pNx-0 and/or histological grade 3 or 4; high risk: pT2-4 or pN1.

Only individuals with complete data for the aforementioned variables and without a known genetic syndrome were considered; from an initial patient population of 5849 patients who underwent a total of 28,784 follow-up visits, we excluded 529 patients due to incomplete or missing data for the variables of interest. Reasons for patient's exclusion are provided in Supplementary Digital Material 1, Supplementary Figure 1. Patients were treated between 2011 and 2022.

In general, follow-up was performed in accordance to the EAU guidelines. While this changed over time, generally patients were followed up for oncologic surveillance biannually for the first three years and annually thereafter. At physician's discretion, visits were anticipated in case of symptoms attributable to disease recurrence; vice-versa, visits could have been postponed in case of low recurrence risk, based on a shared decision with patients.

Recurrence was defined as a radiological evidence of disease relapse. In case of multiple recurrences, only time to first recurrence was considered. At each center, imaging was reviewed by dedicated radiologists.

Ethical approval

This study was conducted in line with the principles of the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. In accordance with French laws, the use of personal data was approved by the French data protection agency for the UroCCR project (NCT03293563), which is approved by the institutional review boards of the participating sites under the authorization number (CNIL) DR-2013-206 (Comité de Protection des Personnes Sud-Ouest et Outremer III: DC 2012/108 (CCTIRS)).

All patients provided written consent before being included in the UroCCR database. All patients received oral and written information about the objectives and methodology of the UroCCR project. The database was updated *ad hoc* for the project in November 2022.

Statistical analysis

Descriptive characteristics of the two groups of patients, *i.e.* harboring ccRCC or non-ccRCC disease, were obtained. Medians (interquartile ranges [IQR]) or frequencies (proportions) were reported for continuous or categorical variables, respectively.

Median follow-up for survivors was evaluated according to the reverse Kaplan-Meier method. The risk of recurrence for each risk group, as low- intermediate- or high-risk was evaluated with the Kaplan-Meier estimator, classified according to ccRCC or non-ccRCC disease. The log-rank test was employed to test the equality of the survivor functions.

The noncumulative distribution of recurrence against time from surgery was evaluated through the locally weighted scatterplot smoothing (LOWESS) to evaluate the recurrence risk over time.[15]

Time to the event of interest was computed from the time of surgery. For the purpose of study, we evaluated time to either loco-regional or distant relapse, whichever occurred first. In fact, the EAU guidelines recommend performing cross-sectional imaging of both abdomen and thorax at the given follow-up time points and for this reason, the two events were not investigated as distinct events.

Statistical analyses were performed with Stata 14 (Stata Corp., College Station, TX, USA).

Results

Patient population

We relied on 5320 patients with complete data. Detailed information on the patient population is reported in Table I. A total of 1788 (34%) individuals underwent RN; on final pathology, 1363 (26%) individuals harbored non-clear cell disease.

Among patients with ccRCC, 2293 (58%), 926 (23%), and 738 (19%) fell in the low-, intermediate, and high-risk group, respectively, whereas for patients with non-cc histology, 683 (50%), 297 (22%), and 383 (28%) fell in the low-, intermediate, and high-risk group, respectively. non-ccRCC histology encompassed: 470 (9%) chromophobe, 810 (15%) papillary (523 had type papillary I), 30 (0.6%) collecting duct, and 53 (1%) other variants. Median follow-up for survivors was 46 months and 42 for the whole cohort. A total of 661 patients experienced recurrence during follow-up, of them, 226 were loco-regional.

TABLE I.—*Descriptive characteristics of the patient population.*

	Clear cell, N.=3957 (74%)	Non-clear cell, N.=1363 (26%)
Age, yr	64 (54, 71)	63 (54, 70)
Sex, N. (%)		
Male	2770 (70.0%)	949 (69.6%)
Female	1187 (30.0%)	414 (30.4%)
Body Mass Index, kg/m^2	27.1 (24.2, 30.7)	26.2 (23.4, 29.4)
ASA score, N. (%)		
1	1128 (28.5%)	413 (30.3%)
2	1983 (50.1%)	675 (49.5%)
3	806 (20.4%)	265 (19.4%)
4	40 (1.0%)	10 (0.7%)
Type of surgery		
Partial nephrectomy	2506 (63%)	1026 (75%)
Radical nephrectomy	1451 (37%)	337 (25%)
Multiple tumors		
No	3900 (99%)	1321 (97%)
Yes	57 (1%)	42 (3%)
Pathological T stage		
1a	1787 (45%)	703 (52%)
1b	713 (18%)	281 (21%)
2a	173 (4%)	110 (8%)
2b	51 (1%)	41 (3%)
3a	1087 (27%)	210 (15%)
3b	106 (3%)	9 (1%)
3c	19 (0%)	2 (0%)
4	21 (1%)	7 (1%)
Pathological N stage		
Nx	2591 (65%)	945 (69%)
N0	1293 (33%)	371 (27%)
N1-2	73 (2%)	47 (3%)
Tumor grade		
1	198 (5%)	51 (4%)
2	1862 (47%)	497 (36%)
3	1338 (34%)	318 (23%)
4	559 (14%)	60 (4%)
Not assigned°	0 (0%)	437 (32%)
Sarcomatoid features		
Absent	3650 (92%)	1323 (97%)
Present	307 (8%)	40 (3%)
Max diameter§	4.0 (3.0, 6.0)	3.6 (2.5, 6.0)
Necrosis		
Absent	2957 (75%)	925 (68%)
Present	1000 (25%)	438 (32%)
Surgical margins status		
Negative	3778 (95%)	1292 (95%)
Positive	179 (5%)	71 (5%)

°Grade not assigned to certain non-clear cell subtypes as per WHO recommendations; §computed considering the largest tumor, in case of multiple tumors.

The Kaplan-Meier functions for recurrence are displayed in Figure 1A-C, for the various risk groups and are each stratified by histological subtype. There was a significant difference between the recurrence-free survival functions

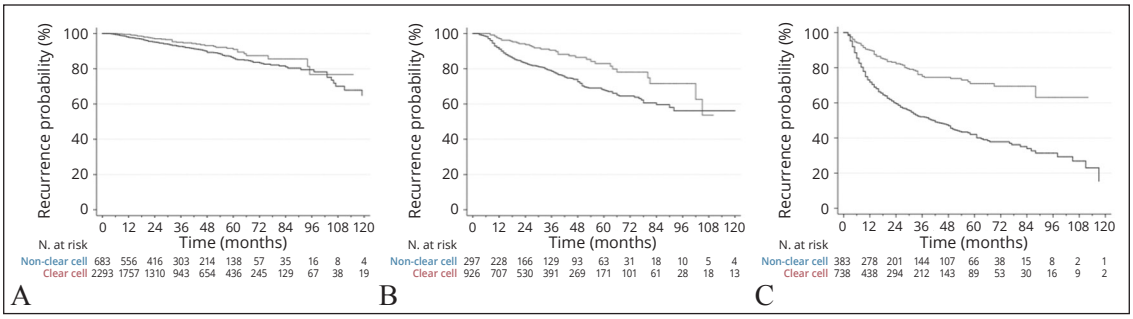

Figure 1.—Kaplan-Meier recurrence function for patients falling in the low- (A), intermediate- (B) or high-risk (C) categories by clear cell or non-clear cell histology. Risk categories are based on the Leibovich score for clear cell renal cell carcinoma (ccRCC), while individuals with non-ccRCC are stratified as suggested by the EAU guidelines as follows: low risk: pT1a-T1b pNx-0 and histological grade 1 or 2, intermediate risk: pT1b pNx-0 and/or histological grade 3 or 4; high risk: pT2-4 or pN1.

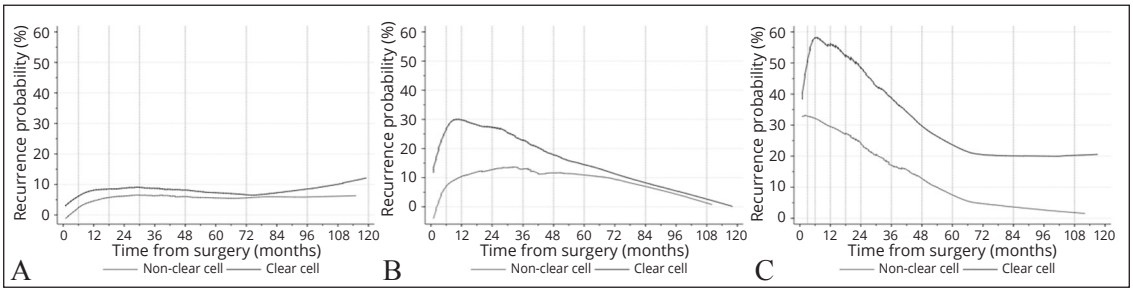

Figure 2.—Non-cumulative risk of recurrence for patients falling in the low- (A), intermediate- (B) or high-risk (C) categories by clear cell or non-clear cell histology. The time points at which cross sectional imaging of thorax and abdomen should be obtained, according to the EAU Guidelines recommendations, are represented by vertical lines.

of patients with cc and non-cc disease across the various risk groups, with non-cc patients having prolonged recurrence-free survival (all P≤0.01).

Recurrence according to risk groups

The non-cumulative risk of recurrence for each risk group is displayed in Figure 2A-C for the low- intermediate-, and high-risk groups, respectively. Each figure is stratified according to histological subtype. The time points at which cross sectional imaging of thorax and abdomen should be obtained, according to the EAU Guidelines recommendations, are represented by vertical lines.

In the low-risk group, the risk of recurrence was lower than 10% during the analyzed time period for both cc and non-cc subgroups. In the intermediate risk group, the recurrence risk was less than 30% for cc patients and less than 14% in the non-cc group within the first three years from surgery. At 5-year, time point after which imaging frequency should be de-intensified to biennially, the risk of recurrence was 15% and 11% for cc and non-cc subgroups, respectively.

In the high-risk group the recurrence risk exceeded 50% for patients with cc disease, while it was less than 34% in the non-cc group within the first two years from surgery. At 5-year, time point after which imaging frequency should be de-intensified to biennially, the risk of recurrence was 24% and 8% for cc and non-cc subgroups, respectively.

Proposed modifications to the EAU follow-up scheme

For patients with non-cc histology in the intermediate group (N.=297) there were 7 recurrences within 12 months from surgery, for a recurrence-free rate of 97% (95% CI: 94%, 99%). When the recurrence function of patients with intermediate risk non-cc histology with negative CT scan at 12-month from surgery was evaluated against

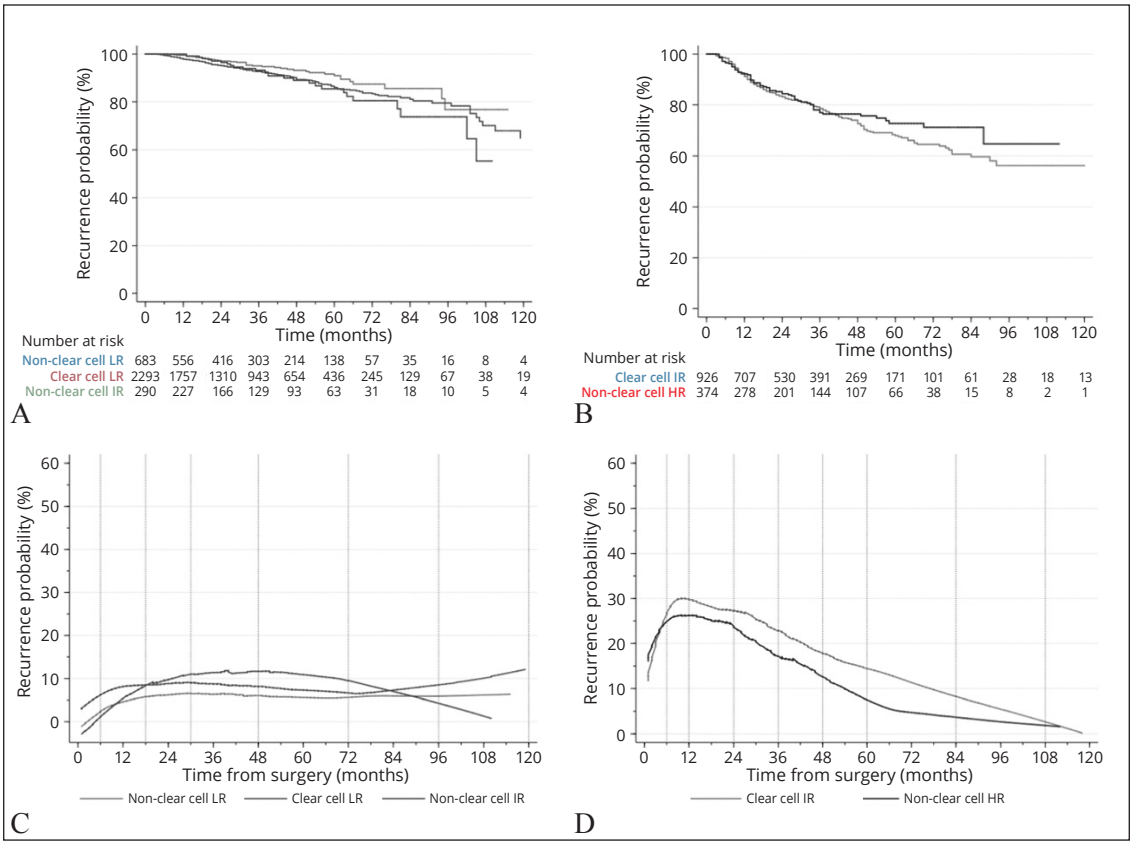

Figure 3.—Kaplan-Meier recurrence function for patients falling in the low-risk clear cell renal cell carcinoma (ccRCC), low-risk non-ccRCC and intermediate-risk non-ccRCC (A) and non-cumulative risk of recurrence for patients falling in the low-risk clear cell renal cell carcinoma (ccRCC), low-risk non-ccRCC, and intermediate-risk non-ccRCC (B). Kaplan-Meier recurrence function for patients falling in the intermediate-risk clear cell renal cell carcinoma and high-risk non-ccRCC (C) and non-cumulative risk of recurrence for patients falling in the intermediate-risk clear cell renal cell carcinoma and high-risk non-ccRCC (D).

the one of cc low-risk patients (Figure 3A), the log-rank test did not demonstrate significant difference (P=0.9). The non-cumulative incidence of recurrence for the three categories, namely low-risk cc and low- and intermediate-risk non-cc, against the time points when imaging should be obtained for current low risk patients is displayed in Figure 3B.

Among patients with non-cc histology falling in the high-risk group there were 9 recurrences within 3 months from surgery. When the recurrence function of patients with high-risk non-cc histology with negative imaging at 3-month was evaluated against the one of intermediate risk clear-cell patients (Figure 3C), the log-rank test did not demonstrate any significant difference (P=0.3). The non-cumulative incidence of recurrence for the two categories, namely intermediate risk cc and high-risk non-cc, against the time points when imaging should be obtained for current intermediate risk patients is displayed in Figure 3D.

Discussion

Evaluating the optimal follow-up strategy following surgery for any cancer is a matter of debate,[15, 16] as high imaging frequency exposes patients to the risk of second primary cancers, when ionizing radiations are employed, and might result in unnecessary expenditures.[17] Specifically, the risk of second malignancy after a single chest, abdominal and pelvic CT scan is approximately one in 2,000[18] and this rises to ap-

proximately one in 300 in case of seven CT scans received in a 5-year period.[19]

To the best of our knowledge, this is the first study that evaluated the proposed oncologic surveillance scheme that was introduced with the 2021 EAU Guidelines.[11] This novel surveillance scheme classified patients into three groups, whereas the scheme prior to 2021 classified patients in two main risk categories.[20]

Our study provides valuable information for patient counseling on the risk of recurrence after surgery. Also, we demonstrated that the recurrence risk of patients with intermediate risk non-cc carcinoma was similar to the one of the patients who currently fall in the low-risk category for both clear cell and non-clear cell disease. For this reason, we would propose to include patients with non-clear cell histology with pT1b pNx-0 and/or histological grade 3 or 4 (currently included in the intermediate risk group for follow-up) in the low-risk group. The result of this theoretical approach is presented in Figure 3B.

Also, we showed that the recurrence risk of patients with non-cc histology falling in the current high-risk group, who had negative cross-sectional imaging at 3-month from surgery was similar to patients with clear-cell histology who currently fall in the intermediate risk category. For this reason, for patients with non-cc disease with pT2-pT4 with any histological grade or pT any, pN1 with any histological grade who had negative imaging at 3-month, we would propose a similar follow-up strategy to patients with clear-cell histology falling in the intermediate risk disease (Figure 3D). In other words, patients with high-risk non-cc disease could be followed up with a scheme similar to patients with intermediate risk cc disease if the first CT scan at 3-month is negative. The revised follow-up scheme is presented in Table II; patients with non-ccRCC with pT1b pNx-0 and/or histological grade 3 or 4 (non-ccRCC intermediate-risk as per EAU 2021 Guidelines) would be followed up similar to patients with ccRCC and Leibovich Score 0–2 and non-ccRCC pT1a-T1b pNx–0 M0 and histological grade 1 or 2. Patients with non-ccRCC pT2-pT4 with any histological grade or pT any, pN1 cM0 with any histological grade (non-ccRCC high-risk as per EAU 2021 Guidelines) could be followed up similarly to patients

TABLE II.—*Proposed revision of the EAU scheme for oncologic surveillance following surgery with curative intent for clinically localized renal cell carcinoma (RCC).*

	Risk profile	Oncological follow-up after date of surgery							
		3 mo	6 mo	12 mo	18 mo	24 mo	30 mo	36 mo	> 3 yrs
1	ccRCC: Leibovich Score 0–2 non-ccRCC: pT1a-T1b pNx-0 M0 and histological grade 1 or 2, and pT1b pNx-0 and/or histological grade 3 or 4.	-	CT	-	CT	-	CT	-	CT once every two yrs
2	ccRCC: Leibovich Score 3-5	-	CT	CT	-	CT	-	CT	CT once yr
3	non-ccRCC: pT2-pT4 with any histological grade or pT any, pN1 cM0 with any histological grade	CT	CT	CT	-	CT	-	CT	CT once yr
4	ccRCC: Leibovich Score>6	CT	CT	CT	CT	CT	-	CT	CT once yr

Lines 1, 2, 3, 4, correspond to low-, intermediate, intermediate/high, and high-risk groups for follow-up. Based on the study findings, patients with non-ccRCC with pT1b pNx-0 and/or histological grade 3 or 4 (non-ccRCC intermediate-risk as per EAU 2021 Guidelines) could be followed up similar to patients with ccRCC and Leibovich Score 0-2 and non-ccRCC pT1a–T1b pNx-0 M0 and histological grade 1 or 2. Patients with non-ccRCC pT2-pT4 with any histological grade or pT any, pN1 cM0 with any histological grade (non-ccRCC high-risk as per EAU 2021 Guidelines) could be followed up similarly to patients with ccRCC intermediate risk given negative imaging at 3-month.In bold: suggested changes to the 2021 EAU guidelines follow-up scheme.
The EAU guidelines suggest for low-risk profiles at >3 years and intermediate-risk at >5 years of follow-up respectively, to consider counselling patients about terminating oncological follow-up imaging based on assessment of comorbidities, age, life expectancy and/or patient wishes. Recommendations at and beyond the 5-year time point are not shown.

with ccRCC intermediate risk given negative imaging at 3-month. This would result in the introduction of a new risk category for non-ccRCC pT2–pT4 with any histological grade or pT any, pN1 cM0 with any histological grade, which has a surveillance scheme that is hybrid between intermediate and high-risk. We named the new category intermediate/high risk. We acknowledge that the intermediate risk non-cc group had a slightly higher risk of recurrence at 5-year (11% *vs.* 8%) relative to the high-risk group. This is likely attributable to the fact that, overall, the majority of individuals in the high-risk group tend to present with recurrence within the first few years after surgery. Our proposed modification of the follow-up scheme is similar to the one of the American Urological association whose surveillance scheme is divided into four groups.[21]

Defining the optimal follow-up scheme following surgery is not an easy task. Most of the times, the follow-up regimens are based on historical schemes that have been defined "a priori" by expert recommendations. Prospective evidence regarding the intensification of follow-up examinations is, to date, available for breast and colon cancer, where no benefit has been found in case of a more intense follow-up regimen.[22-25] Over the past decade, we have observed a shift in the opposite direction in terms of follow-up intensity, *i.e.* toward follow-up de-intensification. This is the case, for example, of imaging frequency following orchiectomy, where Joffe *et al.* proved that a less intense scheme with three instead of seven cross sectional imaging scans over 5 years was non-inferior to detect relapse.[19] It is important to note that non-inferiority in relapse detection might not translate into non-inferiority in terms of subsequent recurrence(s) or survival. On this matter, Dabestani *et al.* introduced the definition of probably curable and probably incurable disease at the time of recurrence, finding that high risk recurrences, *e.g.* probably incurable, were associated with poorer outcomes. Future efforts should be focused on how to detect and optimize outcomes of patients with probably incurable recurrences.

In the context of kidney cancer, the RECUR group has led the efforts in modifying the follow-up scheme following nephrectomy, as either partial or radical.[12, 13, 26] In our study, we evaluated the appropriateness of the updated recurrence scheme and suggested that imaging could be further de-intensified for certain patients. Additionally, we provide recurrence rates from a contemporary database across the present EAU follow-up risk groups that can be used to counsel patients on how to best shape their follow-up. The identification of a potential time point when to interrupt oncologic surveillance, based on comorbidities, age, life expectancy and/or patient wishes is still a matter of controversy.[11, 27] In this context, the EAU guidelines recommend counselling patients about terminating oncological follow-up after 3- and 5-years from surgery for individuals with a low- and intermediate- risk profile, respectively, based on the aforementioned factors.[11] Indeed, this is still an area that should be the focus of future research, together with potentially factoring in patient's quality of life during follow-up, increasing age and new comorbidities.

In KEYNOTE-564,[28] the administration of adjuvant pembrolizumab was associated with a lower recurrence rate, relative to placebo for patients with pT2N0M0 Fuhrman 4 or sarcomatoid differentiation, or pT3/4N+M0, or M1 with no evidence of disease within one year from nephrectomy and oligo-metastasectomy. Presently, the EAU guidelines do not provide recommendations on whether follow-up should be de-intensified for patients who receive adjuvant pembrolizumab. Notably, the frequency of imaging in the trial is more intense than the one proposed by the EAU guidelines, making it difficult to extrapolate recommendations on follow-up. In fact, while on trial, imaging was obtained every 12 weeks in the first 2 years, every 16 weeks in the third to fifth years, and every 24 weeks thereafter.[28]

Limitations of the study

Our study is not devoid of limitations. First of all, our findings are based on data from patients treated at different centers over a relatively long period of time. Indeed, our approach leaves room to a certain degree of unaccounted variability and bias, and prospective validation of our findings is warranted. While overall, patients were generally followed up according to the EAU

guidelines, physicians might have not been fully compliant with the guidelines on a case-to-case basis. Again, while this might introduce some degree of unaccounted variability, it is also representative of day-to-day practice. Finally, the EAU guidelines have changed over time and this might have altered the follow-up strategy for individuals treated more recently. However, this limitation would apply to any study from centers, within Europe or not, whose follow-up strategy is based on the EAU recommendations. Another limitation is the fact that all non-cc subtypes were analyzed together. While this is in compliance with the EAU guidelines, it is an inherent limitation to our study. Further research on different histological subtypes is warranted as they comprise heterogeneous diseases.

Conclusions

In this study we evaluated the surveillance scheme that was introduced with the 2021 EAU Guidelines. Based on the low recurrence risk of patients with intermediate risk non-cc histology, patients falling in this category could be followed up with a similar strategy to those falling in the low-risk category. Similarly, patients with high-risk non-cc histology with negative imaging at 3 months, could be followed up similarly to individuals with cc disease falling in the intermediate risk group after the 3-month time point. Our proposed revision of the follow-up strategy could potentially result in lower imaging per patient, hence reducing follow-up related costs and radiation exposure.

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Conflicts of interest

The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Authors' contributions

Conception and design: Alberto Martini, Jean B. Beauval; acquisition of data: all authors; analysis and interpretation of data: Alberto Martini, Jean B. Beauval, Ugo G. Falagario, Jean-Christophe Bernhard; drafting of the manuscript: Alberto Martini, Ugo G. Falagario, Jean B. Beauval; critical revision: all authors; statistical analysis: Alberto Martini, Ugo G. Falagario, Arna Geshkovska; supervision: Jean B. Beauval, Jean-Christophe Bernhard. All authors read and approved the final version of the manuscript.

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Supplementary data

For supplementary materials, please see the HTML version of this article at www.minervamedica.it