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Risk-based surveillance after surgical treatment of renal cell carcinoma

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Abstract

Background—Risk stratification for recurrence of renal cell carcinoma (RCC) after surgery is the cornerstone of planning post-treatment surveillance.

Objective—To assess the accuracy of the European Association of Urology (EAU) Guidelines risk-stratification model in predicting postoperative recurrence of RCC, and to evaluate whether including patient age and tumor histology may improve clinical decision-making.

Design, Setting and Participants—We identified 1,630 patients treated with nephrectomy at a single academic center.

Intervention—All patients were followed up after surgery with a standard surveillance protocol, regardless of their individual risk.

Outcome Measurements—The accuracy of the University of California Los Angeles Integrated Staging System (UISS) adopted by the EAU Guidelines to predict early (< 15 months) and late (>60 months) recurrence after surgery was compared with a new model that includes patient age and disease histology.

Results and Limitations—Both models showed high accuracy in predicting early recurrence after surgery, with an AUC of 0.84 (95% CI: 0.81, 0.88) for the new model and 0.83 (95% CI: 0.80, 0.87) for the UISS model. Both models showed a good net benefit in predicting early recurrence at decision curve analysis. For patients diagnosed with low-risk tumor types (e.g., papillary type 1 and chromophobe), the average risk of early recurrence significantly dropped within each UISS risk category when tumor histology was added to the predictive model (1.6% vs. 0.6% in the low-risk category; 5.5% vs. 1.9% for intermediate-risk; 45% vs. 22% for high-risk).

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Kaplan-Meier analysis showed no difference in the risk of late recurrence among UISS risk categories. The retrospective study design is the major limitation of this study.

Conclusions—The UISS model should be applied, as recommended by the EAU Guidelines, to tailor the follow-up protocol in the early period after surgical treatment of RCC. Patients with low-risk histology deserve a less stringent follow-up, regardless of their UISS risk category. Our results do not support the use of a risk-stratification model to design a surveillance protocol after five years post-surgery.

Patient summary

Follow-up after surgery for RCC should be based on stratification of the risk of relapse according to guidelines. Future research is needed to define when patients should be discharged from surveillance.

Keywords

Nephrectomy; Renal cancer; Surveillance

Introduction

Despite the efficacy of current treatments, from 20 to 30% of patients with localized renal cell carcinoma (RCC) experience recurrence of the disease during the postoperative follow-up period [1–3]. Previous reports support the benefit of early treatment of metastases and local recurrences after surgery [4–7]. Similarly, although the advantage of systemic therapy in the post-surgical setting remains controversial [8, 9], the timely detection of metastases could affect survival [10].

There is as yet no consensus regarding the optimal follow-up protocol after surgical treatment of RCC [11]. The design of an effective post-treatment surveillance protocol requires accurate stratification of the risk of recurrence after surgery. Both the American Urological Association (AUA) [12] and the National Comprehensive Cancer Network (NCCN) [13] Guidelines recommend a post-surgical surveillance protocol based on TNM staging to stratify patients' risk [12, 13]; however, it has been demonstrated that this strategy does not accurately predict recurrence of RCC after surgery [14]. The European Association of Urology (EAU) Guidelines rely on the use of a prognostic model for a more accurate estimate of the risk of relapse after surgery, and recommend the University of California, Los Angeles Integrated Staging System (UISS) as one of the more accurate RCC prognostic models [15]. The UISS model allows the identification of low-, intermediate-, and high-risk categories to customize the follow-up protocol [15, 16].

Commonly available prognostic factors such as patient age and tumor histology are not taken into account by the UISS risk model. Kidney cancer histology subtypes have been associated with risk of postoperative recurrence [17–19], and previous studies showed better oncologic outcomes for young patients [20], along with a lower risk of early recurrence after surgery in this group [21].

For these reasons, we were interested in testing the accuracy of the UISS risk stratification system adopted by the EAU Guidelines for predicting recurrence of RCC after treatment, and to assess the clinical benefit of adding patient age and tumor histology to the UISS model. We evaluated two different clinical scenarios: early recurrence (less than 12 months after surgery) and late recurrence (five years post-surgery and beyond). Accurate prediction of early recurrence can help to determine the need for and frequency of imaging studies in the first postoperative year. If a patient has a low risk of recurrence by 12 months, then imaging before 12 months could be avoided. Predicting late recurrence is helpful in planning the discontinuation of imaging; for instance the EAU Guidelines suggest stopping surveillance for low-risk men when they remain recurrence-free for five years after surgery.

Methods

Patients

Data were collected from a cohort of 2,359 patients with RCC who were treated with either radical or partial nephrectomy (RN or PN) from January 1995 to June 2016 at a single academic center. All patients had histology-proven malignant disease and were free of metastases at preoperative staging. Clinical and pathologic data, including the Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) score, pathologic stage (TNM classification), Fuhrman grade, and histology were collected for each patient. The follow-up protocol was based on clinical evaluation and total-body CT scans performed at three to six months and at 12 months after surgery over the first year, and annually thereafter. Additional interim evaluations were performed throughout the follow-up period if the patient's symptoms raised clinical suspicion of relapse.

Relapse after treatment was defined as either local recurrence or distant metastases demonstrable on imaging at least one month after treatment; patients who did not experience relapse were censored at the date at the last follow-up. Patients missing clinical or pathologic data [128 (6%)] were excluded. Moreover, 601 (25%) were lost to follow-up due to a relevant proportion of them coming from regions far from our center and frequently being followed-up after surgery in other institutes for personal reasons, regardless of their disease characteristics.

Statistical analysis

The aim of the study was to compare the accuracy of the risk-stratification model recommended by the EAU Guidelines (based on the UISS system, which includes TNM pathologic staging, ECOG-PS score, and Fuhrman grade, and further stratifies patients into low-, intermediate-, and high-risk categories [15]) and a new model that includes patient age and tumor histology to follow up patients after surgery for RCC. The two models were compared on the basis of their accuracy in predicting early (within the first year post-treatment) recurrence after surgery. According to our protocol, patients scheduled for a 12-month post-treatment scan could have been assessed as much as three months later, so all patients with a detected recurrence 15 months after surgery were considered. Due to the retrospective study design, a complete longitudinal follow-up assessment was not available for all patients; to assess the risk of early relapse, only patients with at least one negative

follow-up assessment within 10 to 15 months after surgery or those with subsequent negative follow-up evaluations were considered for the outcome assessment; thereof, 81 patients (4.9%) with a last negative evaluation before 10 months post-surgery and 120 patients (7.3%) with a relapse after 15 months post-surgery but without a previous negative evaluation within 10 to 15 months, were excluded [early recurrence sub-cohort: 1,429(88%)].

Logistic regression analysis was used considering early recurrence as a binary outcome. The accuracy of the UISS model (considering both the model with separate variables and the simplified risk-group categorization) and of the new model were evaluated by area under the curve (AUC). The estimated probability of early recurrence according to the two models was stratified for disease histology and displayed graphically.

We used decision curve analysis to evaluate the clinical consequences of model predictions by comparing net benefit, based on true positives and false positives, at various threshold probabilities of recurrence [22]. Because it is unlikely that a physician would scan a patient if the probability of relapse was <5% or would avoid an imaging assessment if the probability of relapse was >20%, we examined the range of probabilities threshold between 5% and 20%. The accuracy of the models and decision curves was corrected for overfitting using 10-fold cross-validation.

As a second aim of the study, we tested whether the risk stratification system was accurate in predicting late recurrence of RCC. We performed a landmark time analysis in the subset of patients who were recurrence-free five years after surgery; only the patients with a follow-up evaluation after 60 months post-surgery were considered for assessment of this outcome [late recurrence sub-cohort; 669 (41%)]. A Cox regression analysis tested the accuracy of the two models in this subset of patients. Finally, the cumulative incidence of recurrence after five years according to the UISS risk categories was calculated and graphically displayed with Kaplan-Meier analysis. Statistical analyses were conducted using Stata 13.0 (StataCorp, College Station, TX, USA).

Results

Clinical and pathologic characteristics of the entire cohort are reported in Table 1. Overall, 854 patients (52%) were treated with RN and 776 (48%) were treated with PN. The most frequent histology at postoperative pathologic evaluation was clear cell [1273(78%)]; papillary type 2, papillary type 1, and chromophobe tumors were found in 113 (6.9%), 137 (8.4%), and 107 (6.6%) patients, respectively.

Early recurrence

Table 2 illustrates multivariable logistic regression analysis testing the UISS model and the new model for the prediction of early recurrence after surgery. Both models were highly predictive, with an AUC of 0.84 (95% CI: 0.81, 0.88) for the new model and 0.83 (95% CI: 0.80, 0.87) for the UISS model after cross-validation. A significantly lower AUC of 0.74 (95% CI: 0.70, 0.78) was estimated when variables were grouped in a risk-categorization system ($p<0.0001$). Tumor histology was associated with early recurrence after surgery, showing a significantly lower risk for patients with papillary type 1 and chromophobe

disease compared with clear cell and papillary type 2 (OR: 0.31; 95% CI: 0.14 – 0.69). Age was not found to be an independent predictor of disease recurrence (OR: 1.00; 95% CI: 0.98 – 1.01).

Decision curve analysis (Figure 1) demonstrates that both the UISS model and the new model that includes patient age and histology are associated with a net benefit for discriminating patients at higher risk of recurrence that needs to be followed up within the first year after treatment rather than waiting to assess at 12 months. Both models perform better compared with protocols in which all patients or no patients are scanned within the first year post-treatment, when examined within the threshold recurrence probability of 5% to 20%. The net benefit is lower when patients are grouped in a risk categorization system.

Figure 2 shows the adjusted estimated probability of early recurrence according to the two models, stratified for histologic subtypes; the average probability of recurrence for patients with low-risk histology (e.g., papillary type 1 and chromophobe) differs significantly according to the two models, being 1.6% vs. 0.6% in the low-risk category, 5.5% vs. 1.9% in the intermediate-risk category, and 45% vs. 22% in the high-risk category according to the UISS model vs. the model that includes histology, respectively.

Late recurrence

In the Cox regression analysis predicting late recurrence in patients free of disease 60 months post-surgery (Table 3), no variables were statistically significant. The Kaplan-Meier analysis (Figure 3) predicted a probability (95% CI) of relapse at 96 months of 5% (2 – 10), 6% (4 – 9), and 13% (6 – 10) for patients in the low-, intermediate- and high-risk categories, respectively, with no significant difference among groups ($p=0.2$).

Discussion

We assessed the accuracy of the UISS model recommended by the EAU Guidelines, in predicting the risk of early recurrence after surgical treatment of RCC, compared with a new model that includes two additional and easily available variables: patient age and tumor histology. Our results showed a lower risk of early recurrence post-surgery for patients with chromophobe and papillary type 1 disease compared with clear cell and papillary type 2 disease; patient age did not affect the risk of recurrence. The accuracy of the UISS model to predict early recurrence was not significantly improved by the inclusion of the patient's age and disease histology. Moreover, we found no difference in terms of clinical benefit when either the UISS model or the model that includes disease histology was used to select patients to receive scans to detect early postoperative recurrence within the first year post-treatment, although a lower net benefit was associated with a model that groups patients into a simplified risk-categorization system.

Tumor histology may be of particular value for patients in the intermediate-risk category, who could be spared additional radiologic examinations. Patients in the UISS intermediate-risk category showed a 1.9% probability of early recurrence in the presence of chromophobe or papillary type 1 disease, which is comparable to the 1.6% probability of recurrence estimated for patients in the low-risk category, regardless of pathologic findings. When

patients with low-risk features are diagnosed with low-risk histology, the probability of recurrence drops to an average of 0.6%, eventually questioning the need to follow-up these patients at least within the first year after surgery. The UISS model has been shown to accurately predict recurrence-free survival, outperforming other RCC prognostic models. [15, 23] Lam et al. reported 90.4%, 61.8%, and 41.9% five-year recurrence-free survival rates for patients in the low-, intermediate-, and high-risk UISS-categories [24]. Median time to recurrence was 9.5 months for high-risk patients, a finding that supports the need for a stringent follow-up within the first year after surgery.

The effect of including patient age and disease histology in prognostic models for patients with RCC has been previously investigated. In a large multicenter dataset of 13,107 patients, advanced age was found to be independently associated with a higher risk of early recurrence [21]; however, the authors defined early recurrence as occurring within five years post-surgery, rather than one year, as in our study [21]. Other series showed better disease-specific survival for young men with RCC [20, 25, 26], although younger patients may have received more aggressive treatments when recurrence developed. In line with our findings, other authors reported no significant effect of patient age on the risk of recurrence after surgery for RCC when this data was included in multivariable models [26–28].

Histologic subtypes have been shown to independently affect the outcome of RCC patients [17–19, 29], with better prognosis demonstrated for chromophobe and papillary type 1 tumors compared with clear cell and papillary type 2 subtypes [16, 18, 19]. Leibovich et al. reported a higher risk of metastases for patients with clear cell disease compared with papillary and chromophobe subtypes in a series of 3,062 patients surgically treated for RCC, after accounting for other predictive factors [29]. In line with our results, the inclusion of disease histology in prognostic models did not have a large impact on the predictive accuracy of oncologic outcomes after treatment for RCC [18, 19]. However, we have provided evidence to show that including histologic subtypes when assessing risk of recurrence could lead to a significant re-estimation of patient risk according to a strong predictive model such as the UISS system.

As a second study aim, we tested the accuracy of the UISS model for predicting recurrence after 60 months post-surgery. The EAU Guidelines recommend discontinuing surveillance after five years for patients in the low-risk UISS-category, while a biannual assessment is suggested for patients in the intermediate- or high-risk category. In our series, patients at low risk of recurrence according to the UISS model showed a 5% probability of relapse eight years after surgery, with no significant difference compared with intermediate- and high-risk groups. These findings suggest that stopping the surveillance protocol on the basis of a risk-stratification system, as indicated by the EAU Guidelines, could be ineffective. It has been previously reported that discharging patients from surveillance after five years or even earlier, according to their risk profiles, could result in a 31 to 33% rate of non-detected recurrences [14]. These results support previous findings suggesting that an individualized approach to follow-up based on the interplay of competing factors such as the patient's comorbidities, should be adopted for counseling patients about the duration of follow-up, rather than relying on disease characteristics alone [30].

Our study is not devoid of limitations. Given its retrospective design, bias in patient selection could not be completely ruled out. Although our follow-up protocol is standardized for all patients, some patients with higher-risk features may have received more stringent follow-up than others, at least in the early post-treatment period. For this reason, rather than performing a time-to-event analysis assessing the impact of investigated factors throughout the entire follow-up period, we assessed the probability of early and late recurrence as the most clinically relevant outcomes with direct impact on the design of the follow-up protocol itself. A relatively small number of patients were at risk of recurrence at 60 months post-treatment in our cohort, which could explain the non-significant difference in the probability of late recurrence among the risk-group categories. Clearly, there is a need for larger prospective trials to investigate the predictors of late recurrence of RCC post-surgery.

Conclusions

Our results support the use of the UISS model to stratify the risk of early recurrence of RCC after surgery to tailor the follow-up protocol in the early period, as recommended by EAU Guidelines. However, less stringent follow-up could be recommended for patients with low-risk histology, regardless of their risk category. We did not find evidence for stopping the surveillance protocol according to UISS risk categories, although larger prospective studies should be conducted to clarify the appropriate duration of postoperative surveillance.

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Figure 1.

Decision curve analysis assessing net benefit for prediction of early recurrence after surgery. The thin black line represents the net benefit of using the University of California, Los Angeles Integrated Staging System (UISS) model. The grey line represents the benefit of using the UISS model augmented with age and histology. The dotted line represents the benefit of using the UISS risk categorization system adopted by the European Association of Urology (EAU) Guidelines. The thick solid line represents the “scan-none” strategy. The dashed line represents the “scan-all” strategy.

Figure 2.

Estimated probability of early recurrence according to the two models. The circle plot represents patients with high-risk histology (clear cell/papillary type 2). The plus plot represents patients with low-risk histology (chromophobe/papillary type 1). (EAU, European Association of Urology; UISS, University of California, Los Angeles Integrated Staging System)

Figure 3.

Kaplan-Meier curves showing the probability of late recurrence stratified according to the UISS-risk categories; the solid black line represents high-risk patients; the solid grey line represents intermediate-risk patients; the dashed line represents low-risk patients. The log-rank test showed no significant difference between groups ($p=0.2$). (UISS, University of California, Los Angeles Integrated Staging System)

Table 1.

Clinical and pathologic characteristics of the study cohort (N=1,630)

Age [yrs] Median (IQR)	62 (52, 70)
EGOG-PS	
0	510 (31%)
1	879 (54%)
2	228 (14%)
3	13 (0.8%)
Fuhrman grade	
G1	154 (9.4%)
G2	1028 (63%)
G3	386 (24%)
G4	62 (3.8%)
Histology	
Clear cell	1273 (78%)
Papillary type 1	137 (8.4%)
Papillary type 2	113 (6.9%)
Chromophobe	107 (6.6%)
Type of treatment	
RN	854 (52%)
PN	776 (48%)
pN stage	
N0/Nx	1,571 (96.3%)
N1	59 (3.6%)
pT stage	
T1	1107 (68%)
T2	163 (10%)
T3	342 (21%)
T4	18 (1.1%)
EAU/UISS risk categories	
low	320 (20%)
intermediate	1018 (64%)
high	265 (17%)

IQR, interquartile range; ECOG-PS, Eastern Cooperative Oncology Group Performance Status; RN, radical nephrectomy; PN, partial nephrectomy; EAU/UISS, European Association of Urology/University of California, Los Angeles Integrated Staging System

Table 2.

Logistic regression analysis predicting early recurrence (N=1429)

	EAU/UISS risk categories OR; (95% CI) <i>p</i> value	UISS model OR; (95% CI) <i>p</i> value	Augmented model OR; (95% CI) <i>p</i> value
Risk category			
Low	ref		
Intermediate	4.04; (1.74, 9.39) 0.001	-	-
High	41.61; (17.79, 97.32) <0.0001		
Stage 1			
Stage 2		ref	ref
Stage 3	-	3.43; (1.85, 6.36) <0.0001	3.65; (1.95, 6.83) <0.0001
Stage 4		9.77; (6.31, 15.11) <0.0001	9.80; (6.32, 15.18) <0.0001
		56.17; (11.24, 280.85) <0.0001	58.19; (11.64, 290.92) <0.0001
Grade 1–2			
Grade 3–4	-	ref	ref
		4.37; (2.95, 6.48) <0.0001	4.09; (2.75, 6.07) <0.0001
ECOG-PS 0			
ECOG-PS ≥1	-	ref	ref
		1.77; (1.14, 2.72) 0.01	1.81; (1.13, 2.90) 0.014
Histology			
Clear cell – Papillary type 2	-	-	ref
Papillary type 1- Chromophobe			0.31; (0.14, 0.69) 0.004
Age	-	-	1.00; (0.98, 1.01) 0.7

EAU/UISS, European Association of Urology/University of California, Los Angeles Integrated Staging System; OR, overall risk; CI, confidence interval; ECOG-PS, Eastern Cooperative Oncology Group Performance Status

Table 3.

Cox regression analysis predicting late recurrence (N=669)

	EAU/UISS risk categories HR; (95% CI) <i>p</i> value	UISS model HR; (95% CI) <i>p</i> value	Augmented model HR; (95% CI) <i>p</i> value
Risk category			
Low	ref		
Intermediate	1.65; (0.79, 3.44) 0.1	-	-
High	2.27; (0.76, 6.81) 0.1		
Stage 1–2			
Stage 3–4	-	ref	ref
		1.11; (0.49, 2.49) 0.7	1.11; (0.49, 2.47) 0.7
Grade 1–2			
Grade 3–4	-	ref	ref
		1.90; (0.97, 3.72) 0.05	1.82; (0.93, 3.56) 0.07
ECOG-PS 0			
ECOG-PS ≥1	-	ref	ref
		1.10; (0.62, 1.96) 0.7	0.91; (0.49 – 1.71) 0.7
Histology			
Clear cell – Papillary type 2	-		ref
Papillary type 1 - Chromophobe			0.55; (0.23, 1.30) 0.1
Age	-	-	1.01; (0.99, 1.04) 0.2

EAU/UISS, European Association of Urology/University of California, Los Angeles Integrated Staging System; HR, hazard ratio; CI, confidence interval; ECOG-PS, Eastern Cooperative Oncology Group Performance Status