Risk Based Surveillance after Surgical Treatment of Renal Cell Carcinoma

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Purpose: We assessed the accuracy of the UISS (UCLA Integrated Staging System) to predict the postoperative recurrence of renal cell carcinoma. We also evaluated whether including patient age and tumor histology would improve clinical decision making.

Materials and Methods: We analyzed the records of 1,630 patients treated with nephrectomy at a single academic center. The accuracy of the UISS model to predict early (12 months or less) and late (more than 60 months) recurrence after surgery was compared with a new model including patient age and disease histology.

Results: The new model and the UISS model showed high accuracy to predict early recurrence after surgery (AUC 0.84, 95% CI 0.81–0.88 and 0.83, 95% CI 0.80–0.87, respectively). In patients diagnosed with low risk tumor types (eg papillary type 1 and chromophobe lesions) the average risk of early recurrence significantly decreased in each UISS risk category when tumor histology was added to the predictive model (low risk 1.6% vs 0.6%, intermediate risk 5.5% vs 1.9% and high risk 45% vs 22%). Kaplan-Meier analysis showed no difference in the risk of late recurrence among the UISS risk categories.

Conclusions: The UISS model should be applied to tailor the early followup protocol after nephrectomy. Patients with low risk histology deserve less stringent followup regardless of the UISS risk category. Our results do not support a risk stratification model to design a surveillance protocol after 5 years postoperatively.

Key Words: kidney neoplasms, nephrectomy, risk factors, watchful waiting, patient care planning

Abbreviations and Acronyms

AUA = American Urological Association

EAU = European Association of Urology

ECOG PS = Eastern Cooperative Oncology Group Performance Status

NCCN® = National Comprehensive Cancer Network®

RCC = renal cell carcinoma

UISS = UCLA Integrated Staging System

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DESPITE the efficacy of current treatments 20% to 30% of patients with localized RCC experience disease recurrence during followup.[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 postoperative setting remains controversial,[8,9] the timely detection of metastases could affect survival.[10]

There is as yet no consensus regarding the optimal followup protocol after surgery for RCC.[11] The design of an effective surveillance protocol requires accurate stratification of the risk of postoperative recurrence. The

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AUA guidelines[12] and the NCCN Guidelines®[13] recommend a postoperative surveillance protocol based on TNM staging to stratify patient risk. However, it was demonstrated that this strategy does not accurately predict RCC recurrence after surgery.[14] The EAU guidelines rely on a prognostic model for a more accurate estimate of the risk of relapse after surgery and recommend the UISS as one of the more accurate RCC prognostic models, allowing for the identification of low, intermediate and high risk categories to customize the followup protocol.[15,16]

Commonly available prognostic factors such as patient age and tumor histology are not considered by the UISS risk model. Kidney cancer histology subtypes have been associated with the risk of recurrence[17–19] and previous studies showed better oncologic outcomes in young patients.[20] The 2 factors can be easily assessed by the physician when counseling the patient for postoperative followup.

For these reasons we were interested in testing the accuracy of the UISS risk stratification system to predict RCC recurrence after treatment and assess the clinical benefit of adding patient age and tumor histology to the UISS model. We evaluated 2 clinical scenarios, including 1) early recurrence—within 1 year after surgery and 2) late recurrence—5 years postoperatively and beyond.

Accurate prediction of early recurrence can help determine the need for and the frequency of imaging studies in postoperative year 1. If a patient is at low risk for recurrence by 12 months, imaging before 12 months could be avoided. Predicting late recurrence is helpful to plan the discontinuation of imaging. The EAU Guidelines suggest stopping surveillance in men at low risk when they remain recurrence-free for 5 years postoperatively.[16] The AUA guidelines[12] and the NCCN Guidelines[13] leave the decision up to the judgment of the physician after 5 years or before for patients at low risk.

PATIENTS AND METHODS

Data were collected on a cohort of 2,359 patients with RCC treated with radical or partial nephrectomy 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 pathological data, including the ECOG PS score, pathological stage (TNM classification), Fuhrman grade and histology were collected for each patient. No patient received neoadjuvant or adjuvant therapy.

The followup protocol was based on clinical evaluation and chest-abdomen computerized tomography performed 3 to 6 and 12 months after surgery in year 1 and annually thereafter. Bone scan and brain imaging were done only when clinically indicated. Additional interim evaluations were performed throughout followup if patient symptoms raised clinical suspicion of relapse.

Relapse after treatment was defined as local recurrence or distant metastases demonstrable on imaging at least 1 month after treatment. Patients who did not experience relapse were censored at the date of the last followup. The 128 patients (6%) missing clinical or pathological data were excluded from analysis. Moreover, 601 patients (25%) were lost to followup since a relevant proportion residing in regions far from our center were frequently followed elsewhere after surgery regardless of disease characteristics.

The aim of the study was to compare the UISS model, which includes TNM pathological staging, ECOG PS score and Fuhrman grade, and further stratifies patients into low, intermediate and high risk categories,[15] to a new model that includes age and tumor histology to follow patients after surgery for RCC. The 2 models were compared based on accuracy for predicting early postoperative recurrence (within posttreatment year 1).

According to our protocol patients scheduled for a 12-month posttreatment scan could have been assessed as much as 3 months later. Therefore, all patients in whom recurrence was detected 15 months or less after surgery were considered for study inclusion. A complete longitudinal followup assessment was not available in all patients. Thus, to properly assess the risk of early relapse we considered for outcome assessment only patients with at least 1 negative followup assessment within 10 to 15 months after surgery or those with subsequent negative followup evaluations. We excluded from study the 81 patients (4.9%) with a last negative evaluation before 10 months postoperatively and the 120 (7.3%) with relapse after 15 months postoperatively but without a previous negative evaluation within 10 to 15 months. The early recurrence subcohort comprised 1,429 patients (88%).

Logistic regression analysis was done with early recurrence considered a binary outcome. Using the AUC we evaluated the accuracy of the UISS model, considering the model with separate variables and the simplified risk group categorization, and the new model. The estimated probability of early recurrence according to the 2 models was stratified by disease histology and displayed graphically.

We performed decision curve analysis to evaluate the clinical consequences of model predictions by comparing the net benefit, based on positive and false-positive findings, at various threshold probabilities of recurrence.[21] Because it is unlikely that a physician would order imaging if the probability of relapse was less than 5%, or would avoid imaging if the probability of relapse was greater than 20%, we examined the range of probabilities at a threshold between 5% and 20%. The accuracy of the models and the decision curves was corrected for overfitting using tenfold cross validation.

As a second study aim we tested whether the risk stratification system was accurate for predicting late RCC recurrence. We performed a landmark time analysis in the subset of patients who were recurrence-free 5 years after surgery. Only those with a followup evaluation after 60 months postoperatively were considered to assess this outcome. The late recurrence subcohort comprised 669