Korean J Urol Oncol 2016;14(3):138-143

Original Article

Risk Determination for Localised Renal Cell Carcinomas under 4 cm or Less: A Multi-institutional Analysis

Kwangmo Kim[1], Sangchul Lee[1], Sung Kyu Hong[1], Cheol Kwak[2], Yong-June Kim[3], Jinsoo Chung[4], Seok Ho Kang[5], Eu Chang Hwang[6], Sung Hoo Hong[7], Seok-Soo Byun[1]

[1]Department of Urology, Seoul National University Bundang Hospital, Seongnam, [2]Department of Urology, Seoul National University Hospital, Seoul, [3]Department of Urology, Chungbuk National University Hospital, Cheongju, [4]Department of Urologic Oncology Clinicic, National Cancer Center, Goyang, [5]Department of Urology, Korea University Hospital, Seoul, [6]Department of Urology, Chonnam National University Hospital, Gwangju, [7]Department of Urology, The Catholic University of Korea, Seoul St. Mary's Hospital, Seoul, Korea

Purpose: To determine the malignant potential in clinically localised small renal cell carcinoma (RCC) (≤4 cm) in patients using postoperative pathologic outcomes.

Materials and Methods: We performed a retrospective analysis of 2,085 patients in 7 urology centres with clinical T1a RCC who underwent nephrectomy. The pathologic upstaging group (PUG) was defined by pathologic T3a after the operation. Multivariate analyses were used to examine predicting factors for the risk of PUG. Next, Kaplan-Meier analysis was used to examine the PUG for worse recurrence-free survival during the follow-up period.

Results: The PUG had 73 patients (3.5%); they were older and had a larger tumour size than the other patients (all $p<0.001$). After adjusting for clinical characteristics, age (odds ratio [OR], 1.04; 95% confidence interval [CI], 1.02–1.06) and tumour size greater than 3 cm (OR, 1.94; 95% CI, 1.21–3.11) were found to be independent predictors for the PUG after nephrectomy. Furthermore, the PUG had worse recurrence-free survival during the follow-up period.

Conclusions: In this multi-institution analysis, RCC 3 cm or greater in older patients had a high malignant potential compared to relatively small tumours in younger patients. These results may be helpful for stratifying patients to manage small renal masses. **(Korean J Urol Oncol 2016;14:138-143)**

Key Words: Nephrectomy · Renal cell carcinoma · Stratification

INTRODUCTION

For decades, small renal cell carcinomas (RCCs) have been incidentally detected more frequently by abdominal imaging.[1] Radical nephrectomy is a standard treatment option with no size criteria; recently, partial nephrectomy has been recommended for treating clinically localised small RCC if technically feasible.[2] Recently, RCC surveillance might be an alternative to surgery if there is no progression or metastasis.[3] Active surveillance of small renal masses has been reported to be acceptable for short-term oncological outcomes.[3,4]

Although most small renal masses are known to have low malignant potential, certain patients under surveillance have developed progression or metastasis.[5,6] Furthermore, most studies

Received September 13, 2016, Revised October 6, 2016, Accepted October 20, 2016

Corresponding Author: Seok-Soo Byun
Department of Urology, Seoul National University Bundang Hospital, 82 Gumi-ro 173beon-gil, Bundang-gu, Seongnam 13620, Korea
E-mail: ssbyun@snubh.org
Tel: +82-31-787-7342, Fax: +82-31-787-4057

of small renal mass did not use a total cancer cohort, meaning the cohort consisted of malignant and benign masses, and the ratio of benign masses was approximately 20%–30%.[5,6] This finding is due to a low accuracy rate of the imaging, but a recent study noted that preoperative multiphasic computed tomography (CT) imaging has an accuracy for identifying malignancy of approximately 90%,[7] Another researcher also reported that perfusion CT significantly increased the accuracy of predicting RCC to 95%.[8] The more radiologic imaging has evolved, the more small RCCs have been detected accurately.

Therefore, if the surveillance of small RCC increases and is validated in selected patients,[9] determining the risk of small renal masses will be more important to enable physicians to decrease overtreatment and avoid missing aggressive tumours. Looking at the literature, few data exist for risk stratification for small RCCs. Factors that affect RCC prognosis can be summarised in various ways; the TNM staging classification system is known to be the most reliable prognostic factor based on a systematic review.[5] Above the TNM staging, advanced age is supposed to be one of considering factors to decide early treatment or delayed intervention.[10]

However, some of the small masses may have adverse final pathology like T3a. Thus, we investigated the prognostic significance of clinical features in patients with a small RCC by analysing postoperative pathologic outcomes.

MATERIALS AND METHODS

1. Study Patients

The current study included 2,085 patients with RCC who underwent partial or radical nephrectomy at 7 academic institutions between January 1990 and April 2014 and met the following criteria: (1) clinically localised tumour, (2) available pre- and postoperative medical records, (3) preoperative tumour size 4 cm or less on radiologic evaluation, and (4) age 20 years or older. We reviewed retrospectively a database consisting of age, sex, body mass index (BMI), past medical history, CT or magnetic resonance imaging (MRI), and pathologic data after approval from the Institutional Review Board at each institution. In classifying BMI, the subjects were defined as having a high BMI if $\geq$27.5 kg/m^2 according to the BMI criteria for Asians.[11] All patients provided medical history before surgery, stating whether he or she had ever been diagnosed with diabetes mellitus or hypertension. The estimated glomerular filtration rate was calculated using the Modification of Diet in Renal Disease study group equation.[12] The maximal tumour size was defined as the greatest dimension calculated in axial or coronal images on CT or MRI scan by radiologists. Pathologic data were based on the 7th TNM classification of the American Joint Committee on Cancer guideline by pathologists.[13] We categorised all patients into 2 groups: pathologic upstaging group (PUG) and nonupstaging group (NUG). The PUG was defined as at a pathologic stage of T3 after nephrectomy. The NUG was determined to be at a pathologic stage of T1–T2. All patients were evaluated postoperatively every 3 or 6 months for the first 2 years and yearly thereafter with radiologic investigations. Recurrence was defined as radiological local disease or metastasis during the follow-up periods.

2. Statistical Analyses

The 2 groups were compared with the chi-square test for categorical variables and for Student t-test for continuous variables. Univariate and multivariate analyses using logistic regression were performed to identify risk factors for the PUG after nephrectomy. An odds ratio (OR) and 95% confidence intervals (CIs) were computed. We used the Kaplan-Meier method to compare recurrence-free survival after nephrectomy between the PUG and the NUG. And, univariate and multivariate Cox regression analysis was used to found predictors for recurrence-free survival after surgical treatment. IBM SPSS Statistics ver. 21.0 (IBM Co., Armonk, NY, USA) was used for all statistical analyses. A $p<0.05$ was considered to indicate a statistically significant difference.

RESULTS

Table 1 shows the demographics for all of the patients in this study. On final pathology, 3.5% of all patients were categorised into the PUG. All the PUG patients had pathologic T3a (unpublished data). The PUG consisted of older patients with larger tumour sizes than the NUG patients (all $p<0.05$). There was no difference in histology between the groups (p=0.538).

Table 2 presents the results of the logistic regression analysis. In the univariate logistic regression analysis, age was found to be an independent predictor for the PUG (OR, 1.04; 95% CI, 1.02–1.06; $p<0.001$). Hypertension (OR, 1.55; 95% CI, 1.04–2.65; p=0.035) and larger tumour size ($\geq$30 mm)

Table 1. Demographics of all study patients

Demographic	Upstaging* (+)	Upstaging (-)	p-value
No. of patients (%)	73 (3.5)	2,012 (96.5)	
Age (y)	60.7±11.1	54.7±12.6	<0.001
Male sex	64 (74.0)	1,436 (71.4)	0.629
Body mass index (kg/m^2)			0.429
<27.5	58 (79.5)	1,670 (83.0)	
≥27.5	15 (20.5)	342 (17.0)	
Diabetes mellitus	15 (20.5)	266 (13.2)	0.072
Hypertension	35 (47.9)	719 (35.7)	0.033
eGFR (mL/min/1.72^2)	72.2±46.7	76.8±30.7	0.216
Tumor size (mm)	27.8±10.2	24.5±9.2	0.001
Histology, clear cell type	62 (84.9)	1,751 (87.4)	0.538
Follow-up (mo)	45.4±32.9	40.6±33.5	0.148

Values are presented as number (%) or mean±standard deviation.
GFR: glomerular filtration rate.
*Pathologic T3 or more after nephrectomy in clinical T1a renal cell carcinoma.

Table 2. Univariate and multivariate logistic regression analysis for predicting pathologic upstaging* after nephrectomy in small renal cell carcinoma

Variable	Univariate		Multivariate	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Age	1.04 (1.02-1.06)	<0.001	1.04 (1.02-1.06)	0.001
Male sex	0.88 (0.52-1.49)	0.629	0.84 (0.49-1.43)	0.512
Body mass index ≥27.5 kg/m^2	1.26 (0.71-2.25)	0.430	1.16 (0.64-2.09)	0.627
Diabetes mellitus	1.70 (0.95-3.31)	0.075	1.17 (0.63-2.15)	0.620
Hypertension	1.66 (1.04-2.65)	0.035	1.20 (0.72-2.00)	0.480
Tumor size ≥30 mm	1.96 (1.23-3.13)	0.005	1.94 (1.21-3.11)	0.001

OR: odds ratio, CI: confidence interval.
*Pathologic T3 or more after nephrectomy in clinical T1a renal cell carcinoma.

Table 3. Pathologic upstaging after nephrectomy according to the number of risk factors

	No. of risk factors*			p-value
	0	1	2	
Upstaging† (%)	15/838 (1.8)	34/961 (3.5)	24/286 (8.4)	<0.001

*Age ≥60 years or tumor size ≥30 mm. †Pathologic T3 or more after nephrectomy in clinical T1a renal cell carcinoma.

(OR, 1.96; 95% CI, 1.23-3.13; p=0.005) were also statistically significant predictors for the PUG. In the multivariate logistic regression analysis encompassing all variables, age (OR, 1.04; 95% CI, 1.02-1.06; p=0.001) and larger tumour size (≥30 mm) (OR, 1.94; 95% CI, 1.21-3.11; p=0.001) were observed to be significantly correlated with the PUG.

We stratified the study patients by the number of risk factors, consisting of old age (≥60 years) and larger tumour size (≥30 mm). We analysed the clinical importance of the risk factors using the PUG criteria; 8.4% (24 of 286) of the patients with 2 risk factors were in the PUG, compared to 1.8% (15 of 838) of the patients with no risk factor (Table 3).

The mean and median (interquartile range) follow-up duration after surgery for the 2,085 patients included in the present study were 40.9±33.5 months and 34.0 months (13.0-62.0 months), respectively. During follow-up, recurrence occurred in

2.9% of all subjects, with 11% (8 of 73) in the PUG and 2.6% (53 of 2,012) in the NUG. The Kaplan-Meier analysis demonstrated that patients in the PUG had a worse recurrence-free survival than the other group ($p<0.001$) (Fig. 1). In multivariate Cox regression analysis encompassing clincopathological variables, upstaging was observed to be an independent predictor for worse recurrence-free survival (hazard ratio [HR], 3.40; 95% confidence interval [CI], 1.57–7.34; p=0.002) along with tumour size≥30 mm (HR, 1.86; 95% CI, 1.11–3.12; p=0.018) (Table 4).

DISCUSSION

Delayed intervention for RCC is especially suited for the patients with a low malignant potential tumour. Currently, many studies for renal mass surveillance have been based of the patient's preference, age, comorbidities, and imaging study.[4-6] However, they did not focus on how to distinguish patients based on malignant potential. The growth rate on imaging studies is the most common way to assess malignant potential.[14] Deferred treatments made obtaining sequential images possible. Stratification in patients with RCC still remains a challenge. Although CT imaging showed no differences in size estimation compared to surgical specimens with small RCC, CT could not precisely estimate the actual malignant potential.[15] Percutaneous renal biopsy also could not outperform a multiparametric imaging study.[16] Therefore, the recent American Urological Association guidelines state that RCC surveillance should be accepted as an option after giving information for tumour progression to patients.[17]

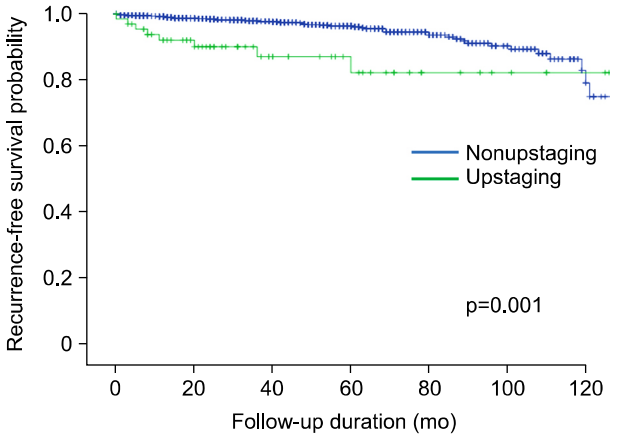

Fig. 1. Kaplan-Meier estimates of recurrence-free survival after nephrectomy according to pathologic upstaging.

To successfully selection for early intervention or delayed intervention, risk stratification for small RCCs must be essential. In this multicener-based study on the relationship between clinical features and postoperative pathologic outcomes for RCC, we investigated the prognostic importance of age and tumour size for pathologic T3a upstaging following nephrectomy. There was no difference in cell histology between the PUG and the NUG. Furthermore, we found that postoperative pathological upstaging may be a potential surrogate for recurrence-free survival after nephrectomy. Our findings were also observed in previously published data by other researchers. Smaldone et al.[5] have reported that increased age and initial greatest tumour dimension were associated with progression after metastasis in their systematic review (all $p<0.001$). Komai et al.[18] observed that young patients with RCC had a better cancer-specific survival, implying low malignant potential. The authors explained that non-clear cell type RCC is more prominent

Table 4. Univariate and multivariate Cox regression analysis for recurrence-free survival after nephrectomy in small renal cell carcinoma

Variable	Univariate		Multivariate	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Age	1.06 (0.99–1.03)	0.588	1.00 (0.98–1.02)	0.970
Male sex	1.28 (0.70–2.32)	0.426	1.21 (0.66–2.21)	0.531
Body mass index ≥27.5 kg/m^2	1.12 (0.82–1.54)	0.478	1.08 (0.57–2.06)	0.812
Diabetes mellitus	1.45 (0.71–2.95)	0.312	1.32 (0.62–2.81)	0.458
Hypertension	0.91 (0.51–1.62)	0.740	0.79 (0.42–1.49)	0.465
Tumor size ≥30 mm	1.96 (1.23–3.13)	0.005	1.86 (1.11–3.12)	0.018
Nonclear cell type	0.50 (0.18–1.37)	0.174	0.46 (0.16–1.28)	0.137
Upstaging*	3.36 (1.60–7.01)	0.001	3.40 (1.57–7.34)	0.002

HR: hazard ratio, CI: confidence interval.
*Pathologic T3 or more after nephrectomy in clinical T1a renal cell carcinoma.

in younger patients. Our results also corroborated the theory that the mean age of the clear cell group was significantly higher than that of the non-clear cell group (55.1 vs. 53.3, p=0.028). However, cell histology did not show additional impacts on the recurrence-free survival in present analysis. Oh et al.[19] have shown that recurrence-free survival after nephrectomy significantly correlates with tumour size. Nguyen and Gill[20] reported that the risk of metastasis depends on tumour size and that a 3-cm threshold was a useful cutoff value for their epidemiologic study. A larger tumour size (≥3 cm) was also a significant predictor for the PUG in our study. A threshold of 3 cm could be an acceptable cutoff to distinguish which tumours have a more aggressive potential.

In the present study, the primary end point was to define which clinical features correlate with pathological upstaging after nephrectomy. We had supposed that a pT3 tumour had more malignant potential than a pathologic T1 tumour. The TNM stage classification system is widely recommended for clinical use. Many clinical nomograms for RCC have introduced the pT stage as the most powerful prognostic factor.[21,22] We also found that the PUG had worse progression-free survival according to Kaplan-Meier and multivariate analyses. There have been many clinical trials for adjuvant therapy after nephrectomy. Those trials used the pT stage for eligibility for study inclusion.[23]

Our study has some limitations. First, a potential limitation is the relative retrospective design from several centers and it is possible influence of selection bias on the results. Moreover, we focused on RCC only, which is also a prone to selection bias. Second, only subjects of the same race were included in the present study; racial differences in tumour biology were overlooked. Third, central radiologic and pathology review probably enhances the quality of data, thus lack of central review dose appear to be a limitation. We believe that our results should be validated with further investigation. However, there was no consistent protocol for small RCCs. This study suggests that patient age and tumour size must be considered for evaluating indolent aggressiveness before treatment. Patients with 2 risk factors had a high risk of having pT3a ranging from 1.8% to 8.4% compared to patients with no risk factor.

In conclusion, age and tumour size could be useful in determining the malignant potential in patients with clinically localised small RCC and appropriate candidates for early or delayed treatment. For older patients with a relatively large RCC tumour, early treatment should be considered to be the first option.

CONFLICT OF INTEREST

The authors claim no conflicts of interest.

REFERENCES

1. Hollingsworth JM, Miller DC, Daignault S, Hollenbeck BK. Rising incidence of small renal masses: a need to reassess treatment effect. J Natl Cancer Inst 2006;98:1331-4
2. Ljungberg B, Cowan NC, Hanbury DC, Hora M, Kuczyk MA, Merseburger AS, et al. EAU guidelines on renal cell carcinoma: the 2010 update. Eur Urol 2010;58:398-406
3. Rais-Bahrami S, Guzzo TJ, Jarrett TW, Kavoussi LR, Allaf ME. Incidentally discovered renal masses: oncological and perioperative outcomes in patients with delayed surgical intervention. BJU Int 2009;103:1355-8
4. Jewett MA, Mattar K, Basiuk J, Morash CG, Pautler SE, Siemens DR, et al. Active surveillance of small renal masses: progression patterns of early stage kidney cancer. Eur Urol 2011;60:39-44
5. Smaldone MC, Kutikov A, Egleston BL, Canter DJ, Viterbo R, Chen DY, et al. Small renal masses progressing to metastases under active surveillance: a systematic review and pooled analysis. Cancer 2012;118:997-1006
6. Brunocilla E, Borghesi M, Schiavina R, Della Mora L, Dababneh H, La Manna G, et al. Small renal masses initially managed using active surveillance: results from a retrospective study with long-term follow-up. Clin Genitourin Cancer 2014;12:178-81
7. Monn MF, Gellhaus PT, Patel AA, Masterson TA, Tann M, Boris RS. Can radiologists and urologists reliably determine renal mass histology using standard preoperative computed tomography imaging? J Endourol 2015;29:391-6
8. Mazzei FG, Mazzei MA, Cioffi Squitieri N, Pozzessere C, Righi L, Cirigliano A, et al. CT perfusion in the characterisation of renal lesions: an added value to multiphasic CT. Biomed Res Int 2014;2014:135013
9. Thomas AA, Campbell SC. Small renal masses: toward more rational treatment. Cleve Clin J Med 2011;78:539-47
10. Kouba E, Smith A, McRackan D, Wallen EM, Pruthi RS. Watchful waiting for solid renal masses: insight into the natural history and results of delayed intervention. J Urol 2007;177:466-70
11. WHO Expert Consultation. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. Lancet 2004;363:157-63
12. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth

D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. Ann Intern Med 1999;130:461-70
13. Novara G, Ficarra V, Antonelli A, Artibani W, Bertini R, Carini M, et al. Validation of the 2009 TNM version in a large multi-institutional cohort of patients treated for renal cell carcinoma: are further improvements needed? Eur Urol 2010;58:588-95
14. Friberg S, Mattson S. On the growth rates of human malignant tumors: implications for medical decision making. J Surg Oncol 1997;65:284-97
15. Wagstaff PG, Zondervan PJ, de la Rosette JJ, Laguna MP. The role of imaging in the active surveillance of small renal masses. Curr Urol Rep 2014;15:386
16. Leveridge MJ, Finelli A, Kachura JR, Evans A, Chung H, Shiff DA, et al. Outcomes of small renal mass needle core biopsy, nondiagnostic percutaneous biopsy, and the role of repeat biopsy. Eur Urol 2011;60:578-84
17. Donat SM, Diaz M, Bishoff JT, Coleman JA, Dahm P, Derweesh IH, et al. Follow-up for Clinically Localized Renal Neoplasms: AUA Guideline. J Urol 2013;190:407-16
18. Komai Y, Fujii Y, Iimura Y, Tatokoro M, Saito K, Otsuka Y, et al. Young age as favorable prognostic factor for cancer-specific survival in localized renal cell carcinoma. Urology 2011;77:842-7
19. Oh JJ, Byun SS, Lee SE, Hong SK, Lee ES, Kim HH, et al. Partial nephrectomy versus radical nephrectomy for non-metastatic pathological T3a renal cell carcinoma: a multi-institutional comparative analysis. Int J Urol 2014;21:352-7
20. Nguyen MM, Gill IS. Effect of renal cancer size on the prevalence of metastasis at diagnosis and mortality. J Urol 2009; 181:1020-7
21. Karakiewicz PI, Briganti A, Chun FK, Trinh QD, Perrotte P, Ficarra V, et al. Multi-institutional validation of a new renal cancer-specific survival nomogram. J Clin Oncol 2007;25: 1316-22
22. Kanao K, Mizuno R, Kikuchi E, Miyajima A, Nakagawa K, Ohigashi T, et al. Preoperative prognostic nomogram (probability table) for renal cell carcinoma based on TNM classification. J Urol 2009;181:480-5
23. Pal SK, Haas NB. Adjuvant therapy for renal cell carcinoma: past, present, and future. Oncologist 2014;19:851-9