Original Article

Renal Cell Carcinoma in Young Patients is Associated with Poorer Prognosis

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Abstract

Introduction: Renal cell carcinoma (RCC) in young patients is uncommon but thought to represent a distinctive clinical entity from older patients with different clinico-pathologic features and outcomes. We evaluated the association of age at the time of diagnosis with pathological staging, histological parameters, disease recurrence and overall survival (OS) following radical or partial nephrectomy for non-metastatic RCC in native kidneys. Materials and Methods: A retrospective review of 316 patients with RCC after nephrectomy at a single institution between January 2001 and June 2008 was performed. Eligible patients included all histologically proven primary non-metastatic RCC treated by radical or partial nephrectomy. They were categorised into group A (≤40 years at diagnosis) and B (>40 years). Differences in clinical parameters were analysed using the Mann Whitney U test. The prognostic potential of age at diagnosis was evaluated using Cox proportional hazards regression. Survival was estimated using the Kaplan Meier method. Results: There were 33 patients in group A and 283 patients in group B. There were more non-clear cell tumours in the younger group (30% vs 14%, *P* <0.05). No statistical differences were found in the stage and grade of both groups. At a median follow-up time of 41 months, the younger group had a higher metastatic rate (18% vs 10.5%, *P* <0.05), lower 5-year cancer-specific survival (82% vs 98%, *P* <0.05) and lower 5-year OS (82 % vs 95%, *P* <0.05). Conclusion: Younger patients were more likely to have non-clear cell RCC with higher disease recurrence and lower OS. They should not be assumed to have similar features and outcomes as screen-detected early RCC in older patients.

Ann Acad Med Singapore 2011;40:401-6

Key words: Age, Cancer recurrence, Overall survival, Renal cell carcinoma, Nephrectomy

Introduction

Recent studies show a steady rise in the incidence of renal cell carcinoma (RCC).[1] The increase had been attributed to screen-detected renal tumours in asymptomatic patients, leading to a corresponding stage migration to smaller localised renal tumours and better disease specific survival.[2] Interestingly, the incidence of malignant renal neoplasms in young individuals remains uncommon.[3-5] The existing literature suggests that these tumours behave in a distinct clinical behaviour, instead of representing a stage migration with earlier diagnosis. However, some of these studies are not comparative,[5,6] or include only patients in restricted age groups,[3,7] or have short follow-up periods.[4] Therefore, the role of patient age at the time of diagnosis as a prognostic factor for RCC is not clear.

The aim of our study is to evaluate the association of age at diagnosis with clinical features, pathological staging, and histological parameters, and to elucidate its impact on disease recurrence and overall survival (OS) following radical or partial nephrectomy for clinically non-metastatic RCC.

Materials and Methods

Data from 316 consecutive patients with RCC after nephrectomy at a single institution between January 2001 and June 2008 were reviewed retrospectively from our genito-urinary cancer database. Eligible patients included all histologically proven Stage I to III RCC in native kidneys treated by radical or partial nephrectomy. All patients with known familial RCC syndromes were included. The exclusion criteria included patients with Stage IV disease at

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presentation or those with postoperative follow-up periods of less than 6 months. The data was correlated with patient charts, and approval from the Institutional Research Board Consent (CIRB # 2009/950/D) was obtained.

All cases were staged using the 2006 AJCC TNM staging and graded according to the Fuhrman grading system.[8] Radiological staging was done using contrast-enhanced computed tomography of the thorax, abdomen and pelvis (CTAP), and magnetic resonance imaging (MRI) where CTAP was contraindicated. All patients had preoperative full blood count, serum electrolytes, liver function test and a bone panel (serum calcium, phosphate and alkaline phosphatase levels).

After surgery, patients were reviewed at 6 monthly intervals with serum creatinine measurement and CTAP according to the UISS protocol.[9] Disease recurrence was defined as development of a metachronous lesion in the ipsilateral renal fossa following radical nephrectomy, or in the parenchymal resection bed following partial nephrectomy. Distant metastasis was said to be present when there was radiological or histological evidence of interval development of distant malignant para-aortic lymphadenopathy or visceral metastasis.

For analysis, the patients were categorised into group A (≤40 years at diagnosis) and B (>40 years at diagnosis). Differences in clinical parameters were analysed using the Mann Whitney U test for ordinal variables and chi-square test for categorical variables. The prognostic potential of age at diagnosis was evaluated using Cox proportional hazards regression, correcting for pathological stage, Fuhrman grade and histological subtype. Survival was estimated using the Kaplan Meier method. Statistical significance was established at P <0.05.

Results

A total of 316 patients were analysed, with 33 patients in group A and 283 patients in group B. There were 7 patients excluded due to inadequate follow-up. Another 41 patients who presented with upfront metastatic disease in the study period were also excluded (N = 1 from group A, N = 40 from group B).

There was no significant difference in the gender or racial distribution. The majority of patients were symptomatic at presentation (58% in both groups), with macroscopic hematuria being the commonest symptom. The mean tumour size was 5.6 cm in both groups (median 5.0 cm, group A ranging from 1.6 cm to17 cm, group B ranging from 0.8 cm to 17 cm). Most patients in this series were treated by radical nephrectomy, while partial nephrectomy was performed in 22% and 16% of patients in group A and group B respectively. In cases where lymphadenectomy was performed, the hilar lymph nodes were dissected. The detailed demographic profile, clinical features and pathological parameters for each group are shown in Table 1.

Table 1. Patient, Clinical and Pathological Characteristics

	Group A	Group B	*P* value
Total Number, N (%)	33	283	
Male (%)	21 (64%)	184 (65%)	0.95
Female (%)	12 (36%)	99 (35%)	
Mean Age at Dx, years (median) (range)	35 (37) (26-40)	59 (58) (42-91)	<0.05 *
Race			
Chinese	26 (79%)	233 (82%)	
Malay	3 (9%)	21 (8%)	0.26
Indian	1 (3%)	15 (5%)	
Others	3 (9%)	14 (5%)	
Follow-up time (months)			
Mean (median, range)	43 (38, 6-94)	41 (36, 6-134)	0.09
Symptoms at presentation, N (%)			
Asymptomatic	14 (42%)	120 (42%)	0.70
Symptomatic	19 (58%)	163 (58%)	
Size of tumour, cm			
Mean (median, range)	5.6 (5.0, 1.6-17)	5.6 (5.0, 0.8-17)	0.59
T stage at diagnosis, N (%)			
T1	23 (70%)	155 (55%)	
T2	3 (10%)	39 (13.5%)	0.20
T3	7 (20%)	89 (31%)	
Nodal staging, N(%) **Clinical nodal staging**			
Positive	1 (3%)	2 (1%)	0.47
Negative	32 (97%)	281 (99%)	
Pathological nodal staging			
Positive	2 (6%)	4 (1%)	
Negative	14 (42%)	111 (40%)	0.16
Unknown	17 (52%)	168 (59%)	
Histological subtype , N (%)			
Clear	23 (70%)	245 (86%)	
Papillary	5 (15%)	28 (10%)	
Chromophobe	1 (3%)	6 (2%)	<0.05*
Sarcoma	1 (3%)	1 (0.5%)	
Clear with papillary	3 (9%)	3 (1%)	
Fuhrman Grade, N (%)			
1	8 (24%)	43 (15%)	
2	19 (58%)	156 (55%)	
3	4 (12%)	70 (25%)	0.11
4	2 (6%)	12 (4.5%)	
Not known	-	2 (0.5%)	

Table 1 (Con't)

	Group A	Group B	*P* value
Mode of Treatment, N (%)			
Radical nephrectomy	27 (82%)	244 (86%)	0.35
Partial nephrectomy	6 (18%)	39 (14%)	
Oncological Outcome			
Local recurrence, N (%)	3 (3%)	4 (1.5%)	<0.05*
Systemic recurrence, N (%)	6 (18%) (3 with local recurrence)	29 (10.5%)	<0.05*
Overall mortality, N (%)	6 (18%)	15 (5.5%)	<0.05*
Cancer specific mortality, N (%)	6 (18%)	6 (2.5%)	<0.05*

*indicates significant *P* value

Most patients were diagnosed with pathological stage T1 RCC. No statistical differences were found in the stage and grade of both groups. There were more young patients with positive lymph nodes, but the difference was not statistically different (3% in group A vs 1% in group B)

There were more non-clear cell tumours in the younger group (30% vs 14%, *P* <0.05). Most of these cases were of the papillary subtype (group A-N = 5, group B-N = 28) (Table 1). The subtypes of papillary carcinoma were reported in 17 patients. In group A, there was 1 case of type II. In group B, there were 6 cases of Type I and 10 cases of type II. In the other cases, the subtypes of papillary carcinoma were not reported.

At a mean follow-up time of 43 months (median 38, range 6 to 94) (group A) and 41 months (median 36, range 6 to 134) (group B) respectively, younger patients were found to have a higher local disease recurrence (3% vs 1.5%, *P* <0.05), higher rate of distant failure (18% vs 10.5%, *P* <0.05), lower 5-year cancer-specific survival (82% vs 98%, *P* <0.05) and lower 5-year OS (82% vs 95%, *P* <0.05). The Kaplan-Meier curves for overall and cancer survival outcomes are shown in Figures 1a and 1b respectively. There were 9 patients (3%) in group B with non-RCC related mortalities.

In each group, there was 1 patient with von Hippel Lindau disease. The patient from group A was treated by partial nephrectomy for a pathological stage T1 Fuhrman grade 1 clear cell RCC. He did not develop disease recurrence at a follow-up of 75 months. The patient in Group B had bilateral partial nephrectomies for clear cell RCC and developed a local recurrence on the left side. The other patients in this study were not known to have familial syndromes for renal tumours.

There was a lack of complete data on the status of surgical margins, especially from patients operated earlier in the series. Of the 7 patients with local recurrence, one patient had a pT1 tumour with clear surgical margins. The other 6 patients had pathological stage T3 tumours, which were

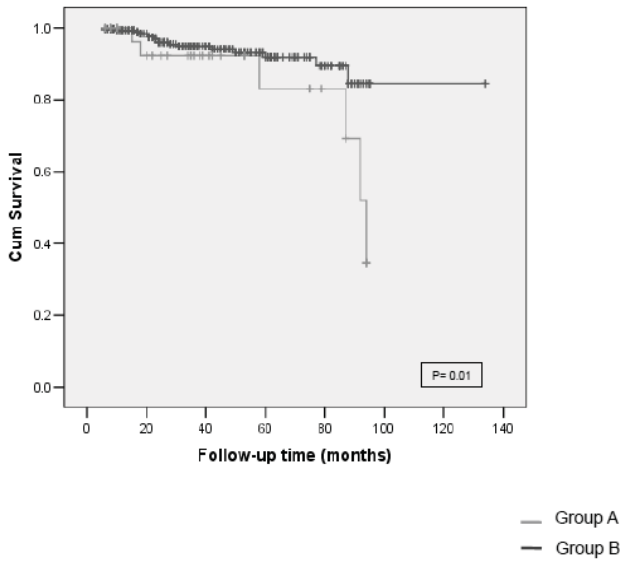

Fig. 1a. Kaplan Meier curve of overall survival.

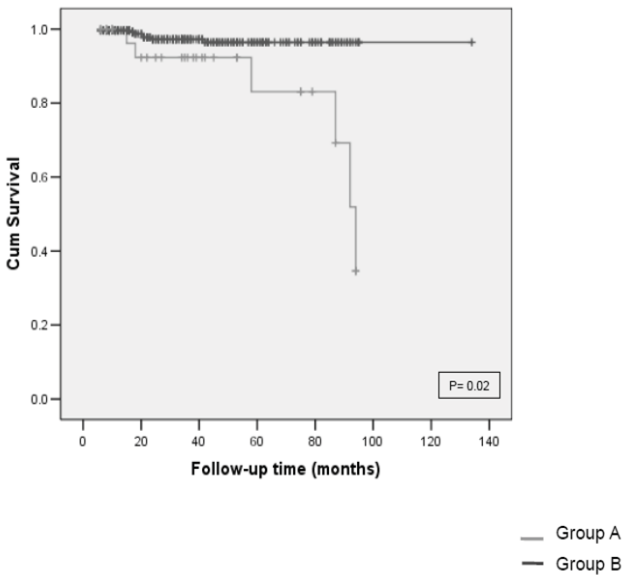

Fig. 1b. Kaplan Meier curve of cancer specific survival.

Table 2. Comparative Studies of Young Vs Older Patients with RCC (Published in English Language)

S/N	Author	Period of study	Young patients, N	Older patients, N	Mean follow-up period (months)	Oncological outcome in young patients	Remarks
1	Rainwater et al[12]	1970-1986	41	34	57 (young), 30 (old)	5 year survival similar	
2	Gillett et al[7]	1970-2000	107	958	118 (young), 88 (old)	5 and 10 year survival similar	Older patients : 60 to 70 years only
3	Schiff et al[11]	1948-1980	37	486	120 months (in 356 patients)	5 year survival better	
4	Taccoen et al[10]	1988-2000	93	1140	60 (young), 50 (old)	5 year cancer specific survival better	
5	Goetzl et al[4]	1989-2000	34	99	15 (young), 26 (old)	5 year survival similar	
6	Sanchez-Ortis et al[3]	1992-2002	106	145	37 (median follow up)	5 year recurrence free and disease specific survival better	Older patients : 58 to 61 years only
7	Siemer at al[14]	1975-2004	87	2164	80	10 year cancer specific survival better	
8	Present study	2001-2008	33	285	43 (young), 41 (old)	5 year cancer specific and overall survival poorer	

inherently associated with locally advanced disease and higher local recurrence rates.

Subgroup analysis was performed after separating the study population into different histological subtypes (clear cell versus non-clear cell), Fuhrman grade categories (grades 1 to 2 vs 3 to 4) and pathological T stages (pT1 vs pT2-4). Poorer survival outcomes were seen in younger patients with advanced pathological T stage (T2 and above), and those with higher Fuhrman grades (3 to 4) (P <0.05). We performed multivariate analysis with Cox regression, and analysed patient age as a continuous variable, with correction for histological subtypes, Fuhrman grades and pathological stage. This showed a statistically lower hazard ratio for mortality in the older patients. A high Fuhrman grade was also statistically significant in predicting poorer survival, while histological subtype and pathological stage was marginally short of statistical significance (P = 0.07 and 0.08 respectively).

Discussion

Our study suggests that sporadic localised malignant renal tumours of native kidneys in younger patients have distinct clinical, pathological and oncological features compared to their older counterparts. Kidney cancers in young patients do not necessarily represent a stage migration of incidental renal masses detected on axial imaging.

The findings that are similar in this study and the others include a higher proportion of non-clear cell histological subtypes in younger patients,[3,9,10] whereas in the older patient cohort, there was a tendency for more advanced pathological stage at presentation[3,10] and higher non-cancer specific mortality rates.[11] The tumour pathological Fuhrman grade was also found to be prognostic for disease specific survival.[10]

Of younger patients with non-clear cell histology, the most common subtype in this study was of the papillary variant, which was also described by Rainwater et al.[12] In another study, chromophobe RCC was the most common non-clear cell variant.[7] In addition, this study did not demonstrate a significant difference in nodal metastasis between both groups at presentation, although Sanchez-Ortiz et al[3] showed a higher incidence of nodal disease in young patients. Admittedly, the lack of complete pathological node staging in this study precludes a reasonable comparison.

The disease recurrence and survival outcomes were poorer for the younger patients in our series. Our data are supported by the study from Boykin et al,[13] which suggested that renal tumours in young patients had a more aggressive behaviour. They showed that poorer outcomes in patients with advanced pathological stage at presentation had an overall survival of 50%. Our results, however, run counter to data from several other (more recent) comparative studies in literature,[3,7,10,14] where young patients with RCC have been found to have better or comparable disease specific survival compared to their older counterparts. Sanchez-Ortis et al[3] showed that although there was a greater proportion of non-clear cell histological subtypes and lymph node metastasis in younger patients, they had better 5-year disease specific survival. In another study, Gillett et al[7] showed comparable 5 and 10 year survival rates. Although these 2 studies had larger patient cohorts, the cohort of older patients were limited to ages between 60 and 71 years. According to the authors, the rationale behind this specific age band include selection of patients belonging to the mean age of RCC

diagnosis based on historical data,[7] minimising the effect of competing comorbidities in older patients and avoiding masking potential biological differences in tumours of patients between 41 and 57 years old.[3] In our opinion, the clinical evidence behind this selection is not robust, but it is likely to contribute towards a selection bias (Table 2).

There may be several reasons behind the distinct oncological outcome observed in this study. To our knowledge, this is the first comparative study (published in the English language) in a predominantly Asian population. We postulate that the distinct Asian ethnic make-up of this study population may explain the difference in oncological outcome. Although a previous study did not show specific cytogenetic alterations in RCC cases in Southeast Asian patients, it was a small study and would probably require validation with larger populations.[15] The (slightly) higher proportion of sarcoma in group A may also explain the poorer outcome observed in this group. The observation of a significantly greater proportion of hybrid clear and papillary tumours in group A is an interesting one, in view of preliminary evidence suggesting that these cases have a higher risk of lymph node and distant metastasis.[16] Although histological subtype was not found be a statistically significant prognostic factor in multivariate analysis, this may have been limited by small case numbers of hybrid pathology cases. The higher incidence of non-RCC related mortalities in the group B may have also exerted some influence on the overall survival assessment in this study. This aspect is predictable as there was intentional inclusion of all surgically fit patients regardless of age, so as to allow a more realistic study that was reflective of real life clinical practice. Sanchez-Ortiz et al[3] postulated that better oncological outcomes were seen in younger patients with stage I-III RCC due to more vigorous immunological responses. The patients in group A in this study were not known to be immunocompromised, and therefore, it is unlikely that the inferior oncological outcomes seen were the sequelae of inadequate immunological response.

Our study population is also unique in its heterogeneity of more than 4 different race groups. There were no significant differences between the pathological T stage and the patients' racial group. There were also no significant differences in the pathological T stage or the presence of clinical symptoms between patients in group A and B. Therefore, there is no evidence to suggest that adverse oncological outcomes were related to cultural or social factors affecting the access to medical care.

The role of adjuvant systemic therapy was not analysed, as most of our patients did not have routine administration of immunotherapy or tyrosine kinase inhibitors. However, it may be worthwhile to consider inclusion of age as a prognostic parameter in normograms or in risk stratification criteria in clinical trials, especially with the increasing availability of targeted therapy for renal cell carcinoma. This would require verification in future trials.

Our study was limited by a lack of central pathological review to minimise inter-observer variation in pathological stage and Fuhrman grade reporting. As this is a single institutional study at a tertiary referral centre, there may be inherent biases in referral patterns and patient selection that may not allow our findings to be extrapolated to other centres. The shortcomings of this study include the lack of generalised genetic testing and the possibility of missing other hereditary cancers such as familial papillary renal carcinoma, which may explain a higher preponderance of papillary histological subtypes in the younger patient group. However, the low numbers of local recurrence in both groups of patients are suggestive that these familial syndromes are not prevalent.

This study excluded patients who were metastatic at presentation and those with no histopathological evaluation. It would be interesting to evaluate if oncological outcomes were different between the 2 groups in those presenting with upfront systemic disease. In addition, patients with localised disease but not physically fit for surgery were not studied. However, we expect these to be confined to the older cohort and to be few in number, with their survival outcomes strongly influenced by competing comorbidities.

An extension from this study would be the elucidation of the cytogenetic aberrations in group A patients, followed by correlation with oncological outcomes, and also as a comparison with group B patients. If these tumours show a distinct genetic background, this would lend weight into classifying RCC in younger patients as a clinical entity and give insight towards their pathogenesis.

Conclusion

Our study suggests that younger patients were more likely to have a non-clear cell RCC with higher disease recurrence and lower OS. Younger patients with RCC should not be assumed to have similar features and outcomes as screen-detected early RCC in the older age group.

Acknowledgements

The authors would like to thank Huang Hong Hong for assistance with data retrieval and Stephanie Fok for assistance in statistical analysis.

REFERENCES

1. Altekruse SF, Kosary CL, Krapcho M, Neyman N, Aminou R, Waldron W, et al. SEER Cancer Statistics Review, 1975-2007, National Cancer Institute.
2. Patard JJ, Rodriguez A, Rioux-Leclercq N, Guillé F, Lobel B. Prognostic significance of the mode of detection in renal tumours. BJU Int 2002;90:358-363.
3. Sanchez-Ortiz RF, Rosse CJ, Madsen LT, Swanson DA, Wood CG. Young age is an independent prognostic factor for survival of sporadic renal cell carcinoma. J Urol 2004;171:2160-5.
4. Goetzl MA, Desai M, Mansukhani M, Goluboff ET, Katz AE, Sawczuk IS, et al. Natural history and clinical outcome of sporadic renal cortical tumors diagnosed in the young adult. Urology 2004;63:41-5.
5. Abou El Fettouh HI , Cherullo EE, El-Jack M, AI Maslamani Y, Novick AC. Sporadic renal cell carcinoma in young adults: presentation, treatment and outcome. Urology 2002;60:806-10.
6. Eggener SE, Rubenstein JN, Smith ND, Nadler RB, Kontak J, Flanigan RC, et al. Renal tumors in young adults. J Urol 2004;171:106-10.
7. Gillett MD, Cheville JC, Karnes RJ, Lohse CM, Kwon ED, Leibovich BC, et al. Comparison of presentation and outcome for patients 18 to 40 and 60 to 70 years old with solid renal masses. J Urol 2005;173:1893-6.
8. Fuhrman S, Lasky LC, Limas C. Prognostic significance of morphologic parameters in renal cell carcinoma. Am J Surg Pathol 1982;6:655-63.
9. Lam JS, Shvarts O, Leppert JT, Pantuck AJ, Figlin RA, Belldegrun AS. Postoperative surveillance protocol for patients with localized and locally advanced renal cell carcinoma based on a validated prognostic nomogram and risk group stratification system. J Urol 2005;174:466-72
10. Taccoen X, Valeri A, Descotes JL, Morin V, Stindel E, Doucet L, et al. Renal cell carcinoma in adults 40 years old or less: young age is an independent prognostic factor for cancer-specific survival. Eur Urol 2007;51:980-7.
11. Schiff M Jr, Herter G, Lytton B. Renal adenocarcinoma in young adults. Urology 1985;25:357-9.
12. Rainwater LM, Zincke H, Farrow GM, Gonchoroff NJ. Renal cell carcinoma in young and old patients. Comparison of prognostic pathologic variables (cell type, tumor grade and stage, and DNA ploidy pattern) and their impact on disease outcome. Urology 1991;38:1-5.
13. Boykin WH, Bright KE, Zeidman EJ, Thompson IM. Renal tumours in young adults. Urology 1992;40:503-5.
14. Siemer S, Hack M, Lehmann J, Becker F, Stockle M. Outcome of renal tumors in young adults. J Urol 2006:1240-4.
15. Lau LC, Tan PH, Chong TW, Foo KT, Yip S. Cytogenetic alterations in renal tumors: a study of 38 Southeast Asian patients. Cancer Genet and Cytogenet 2007;175:1-7.
16. Mai KT, Kohler DM, Roustan Delatour NL, Veinot JP. Cytohistopathologic hybrid renal cell carcinoma with papillary and clear cell features. Pathol Res Pract 2006;202:863-8.