RESEARCH ARTICLE

Clinical Prognostic Factors and Survival Outcome in Renal Cell Carcinoma Patients - A Malaysian Single Centre Perspective

Ning Yi Yap[1], Keng Lim Ng[1,2], Teng Aik Ong[1], Jayalakshmi Pailoor[3], Glenda Carolyn Gobe[2], Chong Chien Ooi[1], Azad Hassan Razack[1], Norman Dublin[1], Christudas Morais[2], Retnagowri Rajandram[1,2,4]*

Abstract

Background: This study concerns clinical characteristics and survival of renal cell carcinoma (RCC) patients in University Malaya Medical Centre (UMMC), as well as the prognostic significance of presenting symptoms. Materials and Methods: The clinical characteristics, presenting symptoms and survival of RCC patients (n=151) treated at UMMC from 2003-2012 were analysed. Symptoms evaluated were macrohaematuria, flank pain, palpable abdominal mass, fever, lethargy, loss of weight, anaemia, elevated ALP, hypoalbuminemia and thrombocytosis. Univariate and multivariate Cox regression analyses were performed to determine the prognostic significance of these presenting symptoms. Kaplan Meier and log rank tests were employed for survival analysis. Results: The 2002 TNM staging was a prognostic factor (p<0.001) but Fuhrman grading was not significantly correlated with survival (p=0.088). At presentation, 76.8% of the patients were symptomatic. Generally, symptomatic tumours had a worse survival prognosis compared to asymptomatic cases (p=0.009; HR 4.74). All symptoms significantly affect disease specific survival except frank haematuria and loin pain on univariate Cox regression analysis. On multivariate analysis adjusted for stage, only clinically palpable abdominal mass remained statistically significant (p=0.027). The mean tumour size of palpable abdominal masses, 9.5±4.3cm, was larger than non palpable masses, 5.3±2.7cm (p<0.001). Conclusions: This is the first report which includes survival information of RCC patients from Malaysia. Here the TNM stage and a palpable abdominal mass were independent predictors for survival. Further investigations using a multicentre cohort to analyse mortality and survival rates may aid in improving management of these patients.

Keywords: Prognostic factor - renal cell carcinoma - survival - symptoms - Malaysia

Asian Pac J Cancer Prev, **14 (12)**, 7497-7500

Introduction

Prevalence of renal cancer varies across continents with higher rates recorded in Europe, North America, and Australia while lower in India, Japan, Africa, and China (Ferlay et al., 2010). The age standardised incidence in Malaysia was 2.3 per 100,000 in 2005 and remained stable at 2.4 per 100,000 in the year 2006 (NCR, 2005; 2006). However, in Singapore, kidney cancer is currently the 9th most common cancer among males, with an age standardised incidence of 7.7 per 100,000 in 2011 (SCR, 2011). Globally, there are approximately 271000 new cases of renal cancers and 116000 deaths in 2008 (Ferlay et al., 2010). Renal cell carcinoma forms the majority of kidney cancers, accounting for 90% of renal malignancies.

The improvement and availability of medical imaging technologies have increased incidental findings of asymptomatic localised renal tumours. Incidentally discovered tumours are likely to be of lower stage and grade. Conventionally, the classic triad of haematuria, flank pain and palpable abdominal mass are indicative of renal tumours. Paraneoplastic signs and symptoms, often associated with more advanced disease may also be present in localised tumours. Studies have shown that symptomatic tumours, especially paraneoplastic related ones, have poor survival prognosis (Patard et al., 2003). However, most studies have analysed symptomatic tumours as a group compared to asymptomatic tumours (Lee et al., 2002; Schips et al., 2003). The prognostic influence of individual signs and symptoms was often not evaluated. To our knowledge, only Kim et al. has evaluated the presenting signs and symptoms separately and cachexia was the strongest prognostic factor for survival (Kim et al., 2003; 2004).

As mortality and prognostic data on renal tumours are lacking in Malaysia, we present the first report of

*[2]Centre for Kidney Disease Research, University of Queensland, Brisbane, Australia, [1]Department of Surgery, [3]Department of Pathology, [4]University of Malaya Cancer Research Institute, University of Malaya, Kuala Lumpur, Malaysia *For correspondence: rretnagowri@gmail.com*

survival data and detailed clinical characteristics of RCC patients. Additionally, we examined the prognostic value of presenting clinical signs and symptoms individually. Symptoms at presentation may offer an early prognostic insight before any treatment including surgery.

Materials and Methods

Patients and data source

Patients diagnosed and treated for RCC from 2003 to 2012 were identified retrospectively through the University Malaya Medical Centre (UMMC) database and urology surgical operation list. All patients' information was collected from UMMC online database or patients' medical record folders and recorded on a standardised RCC pro forma. Ethical approval was obtained from UMMC Ethical Committee (Ref no: 848.17). Symptoms at presentation were determined by the attending physicians during pre-treatment history and physical assessment. Frank haematuria, flank pain, fever, lethargy and loss of weight and appetite were reported by the patients. The presence of palpable abdominal mass was reported during physical examination by the attending physician. Blood test results were taken from pre-treatment assessments.

Elevated alkaline phosphatase (ALP) was defined as ALP higher than 136 IU/L and hypoalbuminemia was defined as serum albumin lower than 35 g/L. A patient with corrected calcium higher than 2.60 mmol/L was grouped as hypercalcaemic. Thrombocytosis was defined as a platelet count higher than 400×10^9 /L. Women and men with haemoglobin less than 120 g/L and 130 g/L respectively were grouped as anaemic. Detection was considered incidental when patients were asymptomatic at presentation, diagnosed during investigation into an unrelated symptom or during routine health screening. Histological type was determined from the pathologist's report. The histological type was unspecified for any metastatic RCC patient who did not undergo surgery or biopsy. The 2002 TNM system proposed by the American Joint Committee on Cancer was used for pathological tumour staging (Greene, 2002). Tumour grading was assigned according to the Fuhrman's classification. Survival status of patients was attained from the UMMC patients' records and Malaysian National Registration Department.

Statistical analysis

Statistical analyses were carried out using IBM SPSS Statistics version 20 (IBM, USA). The Cox proportional hazards regression method was performed to determine prognostic factors for disease specific survival based on the symptoms at presentation. Factors that were statistically significant in the univariate analysis were subjected to multivariate analysis, which was adjusted for stage. Survival curves and survival rates were obtained from the Kaplan-Meier and life table analyses. Survival differences between stages or groups with and without symptoms were evaluated using the log rank test. A p value of less than 0.05 was considered statistically significant.

Results

A total of 151 RCC patients treated at UMMC were analysed. Patients who were operated or initially received treatment in other centres were excluded as there was insufficient information on presenting symptoms. Patients' demographics and clinical characteristics are listed in Table 1. Out of this cohort, 76.8% were symptomatic at presentation. The most common signs and symptoms reported were anaemia, hypoalbuminemia, loin pain and loss of weight (Table 1). However, incidental detection

Table 1. Patient Characteristics and Clinical Presentations

Characteristics		Sample size
Number of patients		151
Mean age (range) years		60.7 (34-83)
Men/women (%)		66.9/33.1
Ethnicity (%)	Malay	39 (25.8)
	Chinese	81 (53.6)
	Indian	29 (19.2)
	Others	2 (1.3)
Tumour side (%)	Left	77 (50)
	Right	73 (48.3)
	Bilateral	1 (0.7)
Mean tumour size (range) cm		6.5 (1.5-17.3)
Histological type (%)	Clear cell	120 (87.6)
	Papillary	13 (9.5)
	Chromophobe	3 (2.2)
	Multilobular cystic	1 (0.7)
Pathological stage (TNM, 2002) (%)		
	Stage I	66 (43.7)
	Stage II	25 (16.6)
	Stage III	10 (6.6)
	Stage IV	50 (33.1)
Metastases (%)	No metastasis	88 (58.3)
	Metastasis at presentation	50 (33.1)
	Metastasis post operation	13 (8.6)
Fuhrman's grade (%)	G1	11 (11.6)
	G2	50 (52.6)
	G3	24 (25.3)
	G4	10 (10.5)
Presentation (%)	Incidental	35 (23.2)
	Symptomatic	116 (76.8)
Signs and Symptoms (%)	Frank haematuria	54/151 (35.8)
	Loin pain	60/151 (39.7)
	Palpable abdominal mass	48/151 (31.8)
	Loss of weight	60/151 (39.7)
	Fever	20/151 (13.2)
	Lethargy	20/151 (13.2)
	Anaemia	63/148 (42.6)
	Hypoalbuminemia	58/144 (40.3)
	Hypercalcaemia	11/100 (11)
	Elevated ALP	27/143 (18.9)
Treatment (%)	Radical nephrectomy	104 (68.9)
	Partial nephrectomy	17 (11.3)
	Radiofrequency Ablation (RFA)	2 (1.3)
	Cryosurgery	1 (0.7)
	No surgery	27 (17.9)

Table 2. Disease Specific Survival of UMMC RCC Patients

	Survival rate (%)	
	1 Year	5 Years
Stage I	98	98
II	96	90
III	79	67
IV	49	13
Overall	80	69

Table 3. Univariate and Multivariate Analysis of Prognostic Factors for Disease Specific Survival

	Univariate analysis			Multivariate analysis adjusted for stage		
	Hazard ratio	95% CI	p value	Hazard ratio	95% CI	p value
Frank hematuria	1.03	0.55-1.90	0.937	-	-	-
Loin pain	1.23	0.67-2.25	0.501	-	-	-
Abdominal mass	4.34	2.35-8.02	<0.001	2.77	1.12-6.74	0.027
LOW	2.42	1.32-4.43	0.004	1.82	0.76-4.63	0.169
Fever	3.69	1.84-7.39	<0.001	2.38	0.50-4.20	0.493
Lethargy	2.76	1.35-5.60	0.005	0.99	0.44-3.39	0.711
Anaemia	5.00	2.50-10.02	<0.001	2.95	0.62-5.30	0.282
Hypercalcaemia	7.08	3.26-15.34	<0.001	4.45	0.91-6.61	0.075
Hypoalbuminemia	7.74	3.69-16.28	<0.001	3.00	0.99-8.87	0.051
Thrombocytosis	3.33	1.71-6.49	<0.001	1.48	0.52-4.64	0.428
Elevated ALP	4.65	2.52-8.60	<0.001	1.13	0.30-2.28	0.298

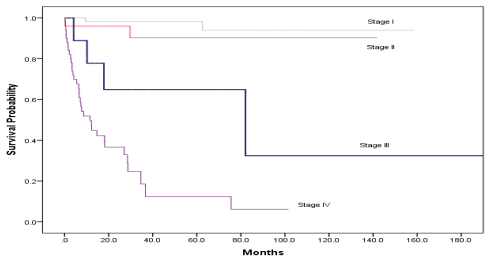

Figure 1. Pathological Staging of the Tumour (TNM, 2002) Significantly Affects the Disease Specific Survival Probability. Log rank p<0.001

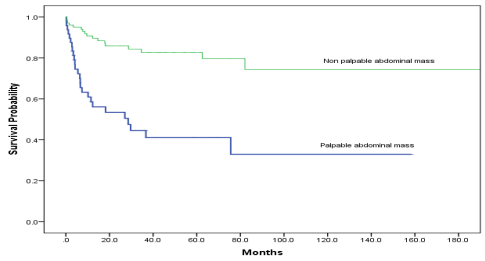

Figure 2. Disease Specific Survival Probability of Patients with Palpable Abdominal Mass is Lower Than Patients with Non-palpable Abdominal Mass. Log Rank p<0.001

had increased from 19.6% to 25.3% between 2003-2007 and 2008-2012 respectively.

Median follow up of the RCC patients was 26 months with a range from 0.2-193.6 months. The survival rates are shown in Table 2. The TNM staging significantly affects survival (p<0.001), with stage 4 patients having the worst prognosis (Figure 1) but Fuhrman grading was not significantly correlated with survival in our case series (p=0.088). Symptomatic tumours have worse survival prognosis compared to asymptomatic or incidentally detected tumours (p=0.009; HR 4.74, 95% CI 1.47-15.36). Symptomatic tumours are also significantly larger (p<0.001), with a mean size of 7.2±3.8 cm compared to incidentally detected tumours, at 4.3±2.1cm.

In a univariate Cox regression analysis to determine prognostic indicators, all factors significantly affect disease specific survival except frank haematuria and loin pain (Table 3). However, when adjusted for stage in a multivariate analysis, only abdominal mass remained statistically significant (p=0.027) while hypoalbuminemia had a near significant value (p=0.051). The mean tumour size of palpable abdominal mass, 9.5±4.3cm, was significantly larger than non palpable mass, 5.3±2.7cm (p<0.001). Figure 2 shows poor survival prognosis for patients with palpable abdominal mass (p<0.001).

Discussion

The incidence of reported kidney cancer in Malaysia is lower than Singapore, a country with geographical proximity and similar ethnicity. The rapid rise in kidney cancer incidence in Singapore from 2002 to 2011 could be due to increased public health awareness as well as the widespread availability and access to medical imaging modalities. This trend is similarly seen around the world where incidence is higher in developed compared to developing nations (Ljungberg et al., 2011; Jemal et al., 2011). In Malaysia, there is a lack of data on the survival rates of RCC patients as National Cancer Registries have only reported the incidence of kidney cancer in general. Likewise, other neighbouring South East Asian countries such as Thailand, Indonesia and Philippines do not have sufficient information on RCC mortality. This has encouraged the establishment of a more comprehensive RCC database in UMMC. In this report, we focused on the clinical characteristics of RCC, survival rates as well as signs and symptoms affecting survival.

The 5 year survival rates of RCC patients in UMMC is lower than that reported in Singapore General Hospital (SGH) with 69% compared to 86% (Kanesvaran, 2009). The lower incidental detection of RCC in UMMC might have affected the survival rate, as a report of RCC cases in SGH (2001-2008) noted that 42% of tumours were detected incidentally, compared to 23.2% in UMMC (Lee et al., 2011). Based on personal opinions of medical personnel, it was estimated that approximately 80-90% of tumours are symptomatic in Malaysia (Naito et al., 2010). The reason for the high incidence of symptomatic RCC at presentation could be multifactorial and dependent on access to health care facilities, disease awareness or health seeking behaviour. A study exploring issues influencing health seeking behaviour in Malaysian cancer patients cited lack of belief in personal susceptibility and financial constraints among obstacles in health screening for cancers (Farooqui et al., 2013). Furthermore, RCC symptoms such as loin pain, fever or loss of weight can mimic other diseases, hence patients may not suspect it as renal cancer.

Asymptomatic renal tumours were reported to have a favourable independent effect on prognosis in two large case series from Italy and Iceland (Ficarra et al., 2003; Palsdottir et al., 2012). This trend is similarly found in our RCC patients where symptomatic tumours predict shorter survival. Strong evidences on the prognostic value of clinical symptoms has prompted Lee et al. and Patard et al. to propose a classification system based on symptoms at presentation (Lee et al., 2002; Patard et al., 2003). Symptoms were grouped as incidental, localised or paraneoplastic. Paraneoplastic symptoms were associated with the most unfavourable prognosis followed by localised and incidental detections (Patard et al., 2003;

Lee et al., 2002).

Kim et al. (2003) was the first group to analyse all clinical signs and symptoms separately. Similarly, to determine the prognostic effect of each symptom, we analysed the presenting signs and symptoms individually. Not surprisingly, all paraneoplastic related signs and symptoms like fever, lethargy, LOW, anaemia, hypercalcaemia, thrombocytosis and elevated ALP were significantly associated with survival in the univariate analysis. Palpable abdominal mass was the sole classic triad symptom significantly associated with survival, and the only symptom which was consistently significant even after stage adjustment. This was different from the findings of Kim et al. (2003) as cachexia related symptoms were the independent factors in their case series. Differences in the proportions of presenting symptoms could possibly account for the different outcomes. Only 4.4% of their patients presented with palpable mass compared to 31.8% in our case series. The strong prognostic indication of palpable abdominal mass could be associated with the size of the tumour. Palpable abdominal mass tumours are significantly larger compared to non palpable tumours. Other studies have demonstrated that a larger tumour size confers a disadvantage to survival (Kinouchi et al., 1999; Frank et al., 2002). Symptomatic tumours were also associated with a larger mean tumour size in this analysis.

The relevance of classic triad of presenting symptoms, which usually accounts for less than a third of patients, has often been considered increasingly obsolete in detecting RCC with the improvement of imaging technologies. However, this might not be entirely true in situations where incidental detection is still low as in this study. Besides palpable abdominal mass, staging by the TNM classification remains a strong predictor for survival. Interestingly, Fuhrman grading did not reach statistical significance. Intraobserver variability might have affected the results as grading was done by different pathologists (Bektas et al. 2009; Delahunt, 2009). Furthermore, tumours were not routinely graded in pathology reports before 2004 and this has reduced the number of cases analysed for Fuhrman grading. Patients with metastatic disease who did not undergo surgical removal also had no consistent definitive pathological tumour grading.

Sample size was a limitation in our case series as it was a single centre database. Nonetheless, this is the first report which includes survival information of RCC patients and it can be taken as a reference for future databases. Here, the TNM staging and palpable abdominal mass were independent predictors for survival. An establishment of a multicentre database of Malaysian RCC patients would give a more accurate projection of mortality and survival. Database collection with mortality data provides valuable information on patient outcome and this may hopefully improve on patient management.

Acknowledgements

This study was completed with the aid of University of Malaya Research Grant RG524/13HTM. We would also like to thank the Urology Team at UMMC for their help in compiling the RCC database.

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