RESEARCH ARTICLE

Clinical Factors Predictive of Metastases from Renal Cell Carcinomas

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Abstract

Background: Lymph node and distant metastases are known as the prognostic factor in renal cell carcinoma (RCC). Clinical parameters are needed to predict metastases preoperatively. The aim of this study was to assess clinical predictive factors for lymph node and distant metastases. Materials and Methods: We collected RCC data from January 1995 until December 2015 at Cipto Mangunkusumo hospital in Jakarta. We only reviewed data that had renal cell carcinoma histopathology by operation or biopsy. Clinical information such as patient age, gender, hemoglobin (Hb), erythrocyte sedimentation rate (ESR), and tumor size (clinical T stage) were reviewed and analyzed by Chi-squre and logistic regression to establish clinical predictive value. Results: A total of 102 patients were reviewed. There were 32 (31.4%) with lymph node metastases and 27 (26.5%) with distant metastases. Age, Hb and clinical T staging were associated with nodal metastases. However, only Hb and clinical T staging were found to be associated with distant metastases. By logistic regression, we found T3-4 in clinical T-stage to be the only predictor of nodal metastases (OR 5.14; 1.87 - 14.09) and distant metastases (OR 3.42; 1.27 - .9.23). Conclusions: Clinical T-stages of T3 and T4 according to The AJCC TNM classification could be used as independent clinical predictive factors for lymph node or distant metastases in patients with RCC.

Keywords: Renal cell carcinoma - metastases - factors - age/gender - hemoglobin - erythrocyte sedimentation - stage

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Introduction

Renal cell carcinoma (RCC) accounts for about 3% of cancers in adults as well as 85% of all primary malignancies arising from the kidney (Cohen and McGovern, 2005). It is a devastating disease, with an estimated 116,368 deaths in 2008, worldwide (Naito et al., 2013). Increasing incidence trends have been reported worldwide, including most Asian countries. In China, RCC incidence has been increasing among men (average annual percentage change (AAPC) 7.6%), while increasing incidence in women have been observed in India (AAPC 2.4%) (Znaor et al., 2015). In Indonesia, the overall incidence of kidney cancer is estimated to be 2.4-3 cases/100 000 population, which is increased from earlier estimation 1.4-1.8 cases/100 000 population (Umbas et al., 2015).

RCC is commonly large at presentation and symptoms may not occur until relatively late in the disease (Furniss et al., 2008). Nearly 25% of the patients presents with advanced disease, which includes either nodal or distant metastases (Hutterer et al., 2007; Karakiewicz et al., 2007). Moreover, half of the organ-confined patients who underwent nephrectomy will develop metastases (Belldegrun, 2007). In general, RCC with nodal or distant metastases are associated with a poor prognosis and shorter survival periods (Furniss et al., 2008). Recently, efforts at identifying markers of disease progression in RCC have focused on readily available and cost-effective clinical indices or preoperative laboratory values (Cross et al., 2012). Better ability to identify patients with metastases can be useful in pre-operative counseling, targeting patients for the potential involvement in adjuvant therapy trials, and assist in surgical planning if more extensive or complete nodal dissections are contemplated (Hutterer et al., 2007).

Cipto Mangunkusumo hospital as tertiary and national refferal hospital in Indonesia has many cases of RCC that underwent radical nephrectomy. Due to poorer prognosis in metastatic RCC, we would like to evaluate clinical predictive factors for metastatic incidence. In this study, we analyzed several clinical data such as age, gender, hemoglobin (Hb), erythrocyte sedimentation rate (ESR), and tumor size (T-staging) in relation with nodal and distant metastases.

Materials and Methods

Patient population

Patient records were retrieved from Urologic Department of Cipto Mangunkusumo hospital database which were collected prospectively. This study included 102 patients that were diagnosed histopathologically

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with RCC between January 1995 and December 2015 and treated either by biopsy or nephrectomy. We exclude any RCC patients with missing data such as age, gender, hemoglobin, erythrocyte sedimentation rate, and tumor size (clinical T staging).

Clinical evaluation

All patients were examined clinically and staged pre-operatively according to the findings on peripheral blood examination, CT-scan of the abdomen, chest CT or chest X-ray. CT of the brain, bone scan and angiography were undertaken when necessary. The AJCC TNM classification was used to stage all the patients. Clinical information such as patient's age, gender, hemoglobin (Hb), erythrocyte sedimentation rate (ESR), and tumor size (clinical T staging) were documented prior to surgery. For statistical evaluation, preoperative Hb level and ESR was divided into two groups. The preoperative Hb was categorized as normal and anemia. The normal Hb was defined by Hb more than 13.5 g/dL for male or 12.0 g/dL for female. The ESR was categorized as normal and elevated. The ESR was considered elevated when ESR was more than 22 mm/h for male or 29 mm/h for female. The presence of nodal metastases was defined by CT-scan abdomen pre-operatively, intra-operative findings, and histopathological findings. The lymph node metastases (N) classification was divided into two, N-negative (no metastases in lymph node) and N-positive (N1 according to AJCC TNM 2010 classification). The presence of distant metastases was confirmed based on radiographic findings. It was classified into no metastases and any metastases founded on lung, liver, bone or brain (M1 according to AJCC TNM 2010 classification).

Statistical analyses

The clinical predictive value for lymph node and distant metastases was analyzed by logistic regression. Age, gender, Hb, ESR, and clinical T-staging were used as covariates addressing the presence of nodal and distant metastases. Variables that achieved statistical significance by univariate analysis were subsequently entered into multivariate analysis. The criterion for statistical significance was established at P<0,05. All analysis were performed using statistical package SPSS v21.0.0 from IBM.

Results

This study consisted of 102 patients who underwent either nephrectomy or biopsy of the kidney due to RCC. The characteristics of the patients in this study are shown in table 1. At the time we diagnosed the majority of patients (49.0%) were classified as T2 according to AJCC TNM classification. Nodal metastases were detected in 32 (31.4%) cases, while 27 (26.5%) cases were diagnosed with distant metastases.

Bivariate analysis

We performed bivariate analysis and found that gender, Hb, and T-staging were significantly associated with nodal metastases. However only Hb and T-staging were significantly associated with distant metastases (table 2). Then we continued by performing multivariate analysis and found T3 and T4 on T-staging were statistically significant to predict nodal and distant metastases.

Table 1. Characteristics of the RCC Patients

Variables	n (%)
Gender	
- Male	68 (67%)
- Female	34 (33%)
Age (years)	
- Mean (SD)/(Range)	51.4 (13.33)/(14-79)
Hemoglobin (g/dl)	
- Mean (SD)/(Range)	11.6 (2.15)/(6.3-17.0)
ESR (mm)	
- Median (Range)	55.0 (2.0-145.0)
Clinical T stage	
- T1	10 (9.8%)
- T2	50 (49.0%)
- T3	29 (28.4%)
- T4	13 (12.7%)
Metastases	
- Nodal metastases	32 (31.4%)
- Distant Metastases	27 (26.5%)

Table 2. Bivariate Analysis for Predicting the Probability of Nodal and Distant Metastases

Predictors	Nodal metastasis		Distant metastasis	
	n (%)	p value	n (%)	p value
Age		0.96		0.623
- < 51.0	18 (31.6%)		14 (24.6%)	
- > 51.0	14 (31.1%)		13 (28.9%)	
Gender		0.035		0.634
- Male	26 (38.2%)		19 (27.9%)	
- Female	6 (17.6%)		8 (23.5%)	
Hb		0.025		0.013
- Normal Hb	6 (17.1%)		4 (11.4%)	
- Anemia	26 (38.8%)		23 (34.3%)	
ESR		0.813		0.474
- Normal	8 (33.3%)		5 (20.8%)	
- Elevated	24 (30.8%)		22 (28.2%)	
T staging		<0.001		0.001
- T1-2	10 (16.7%)		9 (14.8%)	
- T3-4	22 (53.7%)		18 (43.9%)	

Table 3. Multivariate Logistic Regression Model Predicting the Probability of Nodal and Distant Metastases

Predictors	OR (95% CI)	p value
Nodal metastasis		
Gender (Male)	2.88 (0.97 – 8.51)	0.056
Anemia	1.54 (0.49 - 4.83)	0.457
T3-4	5.14 (1.87 - 14.09)	0.001
Distant metastasis		
Anemia	2.54 (0.74 – 8.73)	0.14
T3-4	3.42 (1.27 - 9.23)	0.015

Multivariate analysis

Logistic regression was performed for all variables that had p value <0.25 in bivariate analysis to predict the probability of nodal and distant metastases. In nodal

metastases, we include gender (0.035), Hb (p 0.025), and T staging ($p < 0.001$) for multivariate analysis. We found T3-4 in clinical T-staging could be used as independent predictor for nodal metastases (p=0.001, OR 5.14, 95% CI 1.87-14.09). We found similar results in distant metastases that T3-4 in clinical T-staging could be used as predictor ($p = 0.015$, OR 3.42, 95% CI 1.27-9.23) (table 3).

Discussion

Renal cell carcinoma is the most common solid lesion within the kidney and considered as the most lethal urological cancers. It is predominant in men with peak incidence in sixth and seventh decades (Lam et al., 2005; Ljungberg et al., 2011; Rampersaud et al., 2014; Ljungberg et al., 2015). In our study, the mean age at diagnosis was 51 years which is nearly similar to the finding of Sidharth et al (Sidharth et al., 2011). Despite more RCC are detected incidentally by imaging tools, 25–30% of patients still present with metastatic disease because the majority of renal tumors are largely asymptomatic (Toyoda et al., 2007; Adibi et al., 2015). In the current study of 102 patients with RCC, nodal metastases was found in 32 cases (31.4%) and distant metastases was found in 27 cases (26.5%) at the time we diagnosed the patient, which is similar with previous studies (Lam et al., 2005; Belldegrun, 2007; Hutterer et al., 2007; Karakiewicz et al., 2007; Furniss et al., 2008; Umbas et al., 2015).

The presence of lymph node and distant metastases have always been considered as the most important prognostic factors in renal cell carcinoma besides primary tumor local extension (Ficarra et al., 2007). The outcome for patients with metastatic RCC is remained poor, with 5-years survival rate less than 10% (Motzer et al., 2004; Choueiri et al., 2007). Unfortunately there were no specific tumor markers have been identified for RCC. However, efforts have been done to find any clinical feature of preoperative laboratory values that can be used to predict the course of disease. A study by Motzer et al in 670 patients with advanced RCC at the Memorial Sloan-Kettering Cancer Center (MSKCC) showed the relationship between pretreatment clinical features and survival. Pretreatment features associated with a shorter survival were low Karnofsky performance status (<80), low Hb levels (less than the lower limit of normal), high lactate dehydrogenase (>1.5 times the upper limit of normal), high-corrected serum calcium (>10 mg/dL), and absence of nephrectomy (Motzer et al., 1999; Motzer et al., 2004; Procopio et al., 2012). A study in 1075 RCC patients by Sengupta et al. demonstrated that an elevation in ESR is associated with every adverse pathologic feature of RCC including lymph node and distant metastases (Sengupta et al., 2006). Elevation of ESR were observed in 47% of patients which was consistent with previously reported rates (Sengupta et al., 2006). A retrospective study of 101 RCC patients by Miyata et al. showed that a high serum ferritin levels may indicate any lymph node and distant metastases (Miyata et al., 2001). Masuda et al. concluded that immunosuppressive acidic protein (IAP) appears to be a valuable predictor for lymph node and distant metastases in patients with RCC (Masuda et al., 1997).

A study by Yap et al suggested that the TNM staging and palpable abdominal mass were independent predictors for survival in RCC patients. The strong prognostic indication of palpable mass could be associated with the size of the tumor (Yap et al., 2013). Tumor size was considered as independent predictors for nodal and distant metastases (Guethmundsson et al., 2011). It was similar with our study that gender, Hb, and T-staging were associated with nodal metastases and except gender for distant metastases. But only, T-staging could be independent predictor of the probability of nodal and distant metastases. Similar results were shown by prior study that tumor stage and size were an independent predictors for lymph node metastases (Lam et al., 2005; Hutterer et al., 2007). In addition, Leibovich et al. found that tumor stage had significant association with progression to metastatic in patients underwent radical nephrectomy for clinically localized RCC (Leibovich et al., 2003).

Although a lymph node dissection in RCC is controversial and only recommended in the presence of clinically positive lymph nodes (Ljungberg et al., 2015). The results of our study suggested that a lymph node dissection should be considered in clinically T3-T4 RCC.

Several limitations apply to our study. First, this study included small number of patients as it was a single center database. Second, we did not analyze other factors such as Calcium and Lactate Dehydrogenase (LDH) that were known as survival prognostic factor in RCC due data limitation. And third, majority of our diagnosed of lymph node metastases was based on radiological findings since lymph node dissection was not routine performed.

In conclusions, Clinical T-staging of T3 and T4 according to The AJCC TNM classification were the valuable clinical predictive factors for lymph node or distant metastases in patients with RCC. Thus, a lymph node dissection and closed follow up is considered in T3-T4 RCC.

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