Predictors of mortality in patients submitted to nephrectomy for non-metastatic renal cell carcinoma at a referral center in Northeastern Brazil

Preditores de mortalidade em pacientes submetidos à nefrectomia por carcinoma de células renais não metastático em um centro de referência no Nordeste Brasileiro

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A B S T R A C T

Objective: to identify predictors of mortality in patients submitted to nephrectomy for non-metastatic renal cancer. **Methods:** we conducted a retrospective cohort study based on the records of patients with renal cancer submitted to radical or partial nephrectomy at the Ceará Cancer Institute. **Results:** we studied 117 patients, with mean and median age of 59.14 and 59 years, respectively. The male gender was slightly predominant. The right kidney was most frequently affected (64%). The most common histopathological diagnosis was clear-cell carcinoma (77%). Stage pT1 and Fuhrman grade II were predominant. The only predictive variables of overall survival were pathological stage (pT) and lymph node involvement. **Conclusion:** pathological stage (pT) and lymph node involvement are important prognostic factors in patients undergoing nephrectomy for non-metastatic renal cancer.

Keywords: Kidney Neoplasms. Nephrectomy. Carcinoma, Renal Cell. Survival. Prognosis.

INTRODUCTION

Kidney cancer accounts for approximately 3.8% of all neoplasms reported annually in the United States, where in 2014 the estimated figures were 63,920 new cases and 13,860 deaths. It is the seventh most common malignant neoplasm in men, with an incidence of 4%, and the eighth most common in women, with an incidence of 3%[1,2]. In both genders, it is the eighth most diagnosed annually malignant neoplasm and the thirteenth in causes of cancer death, also being the second most common type of cancer of the urinary tract[1,2]. Renal carcinoma is considered the most lethal of urological neoplasms[3].

Its incidence is continually increasing worldwide. In the United States, for example, the incidence of new cases rose from ten to 15 cases per 100,000 inhabitants per year in the last 20 years[4]. In Brazil, the described incidence – considering the high rates of national underreporting – varies from seven to ten cases per 100,000 inhabitants per year in more developed areas, with lower rates in less developed regions[5]. According to the first National Study on Kidney Cancer in Brazil, the disease is more common in men (59%) and Caucasians (79%), with a mean age of 59 years[6].

The clear cell variant is the most common subtype, accounting for 75% of renal cell carcinomas (RCC). Based on morphological, histochemical and cytogenetic aspects, renal carcinoma does not constitute a single neoplasm, but a group comprising four main tumor subtypes: clear cells, papillary type I, papillary type II and chromophobe, with incidence of 75%, 5%, 10% and 5%, respectively. Among these, clear-cell RCC is the one that displays the most aggressive behavior[7].

There is great heterogeneity in renal cancer regarding both age, histological subtype, degree of differentiation or staging. This fact justifies the great clinical importance of this disease and the search for knowledge for a better clinical and surgical approach. About 75% of renal cancer cases occur in individuals

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over 60 years of age[2,8]. The disease is more common in men at a 3:2 ratio[2,8].

Several clinical and pathological variables have been studied for the prediction of overall survival, including the presence of symptoms at diagnosis, hematuria, flank pain, palpable abdominal mass, anemia, hypercalcemia, hypoalbuminemia, thrombocytosis, as well as gender, age, tumor laterality, size (pT), histological type, grade, angiolymphatic invasion, presence of tumor necrosis, sarcomatoid differentiation and lymph node involvement[9,10]. This study aims to identify prognostic factors for patients with non-metastatic RCC undergoing nephrectomy, so that they serve as predictive variables of mortality.

METHODS

This is a retrospective cohort study, which used data obtained from review of medical records of patients with RCC who underwent radical or partial nephrectomy at the Ceará Cancer Institute from January 1999 to December 2010. As exclusion criteria, we adopted the identification of metastasis at the time of diagnosis or within six months thereafter, as well as the presence of a second primary tumor.

The independent variables analyzed were gender, age, tumor laterality, histological subtype, degree of differentiation (Fuhrman), tumor size, presence of tumor necrosis, lymph node involvement, and angiolymphatic invasion. Lymphadenectomy was performed only in patients who had lymph nodes suspected of metastatic involvement in the preoperative period (through imaging tests) or during the intraoperative period (if there were changes in the abdominal cavity inventory). Surgeons followed the National Comprehensive Cancer Network (NCCN) recommendations for primary lymphadenectomy. Patients who did not undergo lymphadenectomy were considered pNx, that is, no lymph node histology was available. We used the TNM 7th Edition (2009) as reference. After surgery, all patients were followed regularly according to their staging. The majority were submitted to a semiannual consultation with serum creatinine dosage, in addition to chest X-rays and computed tomography of the abdomen. Recurrence was defined as the appearance of suspicious and growing lesions at typical sites of disease progression (retroperitoneal or mediastinal lymph nodes, liver, lungs, bones, brain, adrenals and contralateral kidney) or atypical sites with diagnostic biopsy. We calculated the survival time as the time interval between the surgery and the last known follow-up. We used overall survival as the dependent variable.

We tabulated, stored and processed data with the statistical program Statistical Package for Social Science (SPSS) Version 18.0 for Windows. We assessed survival using the Kaplan-Meier method and carried out comparisons with the Log-Rank test. We adopted a significance level of 5%.

This work was submitted and approved by the Ethics in Research Committee of the Cancer Institute of Ceará, under the number 026/2011.

RESULTS

From an initial sample of 160 patients with RCC, we excluded 23 patients with metastatic tumor at the time of diagnosis or within six months after diagnosis, and 20 patients who had another primary cancer before or after RCC diagnosis. We selected 117 patients for analysis. Follow-up averaged 47.9 months, ranging from one to 158. The overall survival rate in this period was 41.1%. There were 26 deaths at the end of follow-up.

Regarding the clinical condition, macroscopic hematuria was present in 42.7% of the patients (50), followed by abdominal pain in 32.4% (38), palpable abdominal mass in 31.6% (37), low back pain in 24.7% (29), cachexia or weight loss in 20.5% (24), anorexia or hyporexia in 4.2% (5), fever in 3.4% (4) and increase in abdominal volume in 2.5 % (3). Only 8.5% (10) of the patients were asymptomatic at the time of diagnosis. The classic clinical triad represented by macroscopic hematuria, palpable abdominal mass and abdominal pain occurred in only 14.53% (17) of the patients.

The patients' age at diagnosis ranged from 19 to 85 years, with a median of 59. The majority received the diagnosis after 45 years of age. This group

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Table 1. *Outcome versus surgical technique.*

Final status	Conventional						Laparoscopic					
	Partial nephrectomy		Radical nephrectomy		Total		Partial nephrectomy		Radical nephrectomy		Total	
	N	N%	N	N%	N	N%	N	N%	N	N%	N	N%
Alive	7	8.6%	74	91.4%	81	100%	1	10.0%	9	90.0%	10	100%
Dead	0	0.0%	25	100.0%	25	100%	0	0.0%	1	100.0%	1	100%
Total	7	6.6%	99	93.4%	106	100%	1	9.1%	10	90.9%	11	100%

of patients did not display a greater overall mortality (Figure 1). The male gender represented 53.8% (63) and the female, 46.1% (54). The right kidney was the most affected, with 63.2% (74) of the cases. A bilateral tumor was present in 1.7% (2) of patients.

For unilateral tumors, radical nephrectomy was performed in 93% (107) of the cases, and partial nephrectomy, in 6.9% (8). The bilateral tumors were treated with radical left nephrectomy and right partial nephrectomy (2). The laparoscopic route was used in 9.4% (11) of the cases, represented by five pT1A stage tumors and six pT1B lesions (Table 1).

Unilateral tumors (115) had the following characteristics: clear cell carcinoma (89 – 77.3%), chromophilic carcinoma (16 – 13.9%), chromophobic carcinoma (8 – 6.9%) and mixed carcinoma (2 – 1.7%). Stages: pT1A in 16.5% (19), pT1B in 25.2% (29), pT2 in 33.0% (38), pT3A in 20.0% (23) and pT3B in 5,2% – we did not observepT3C or pT4 stages. Grade was GI in 21 patients (21.6%), GII in 59 (60.8%) and GIII

and GIV in 17 (17.5%) – we highlight the absence of this data (Gx) in 18 patients (15, 6%); Angiolymphatic invasion was present in 12.1% (14); Tumor mass necrosis occurred in 55.6% (64); 3.4% (4) of the cases had sarcomatoid differentiation.

As for the bilateral tumors (2), all showed clear cell histology, both in the right and left kidney. One of the patients presented with stages pT2 and pT1A, and the other, pT4 and pT1A. One displayed GIV grade and contralateral GI grade, and the other, GII and contralateral GI. There wereno angiolymphatic invasion or sarcomatoid differentiation. Tumor mass necrosis was present in only one lesion on the left with pT4/GII stage.

Lymph node involvement in patients with unilateral tumors (115) was present (pN1) in 8.7% (10) of the cases; it was absent (pN0 – 32) or could not be assessed (pNx – 73) in 91.30% (105). In patients with bilateral tumors (2), no lymphadenectomy was initially performed, since they were clinically negative.

p = 0.152
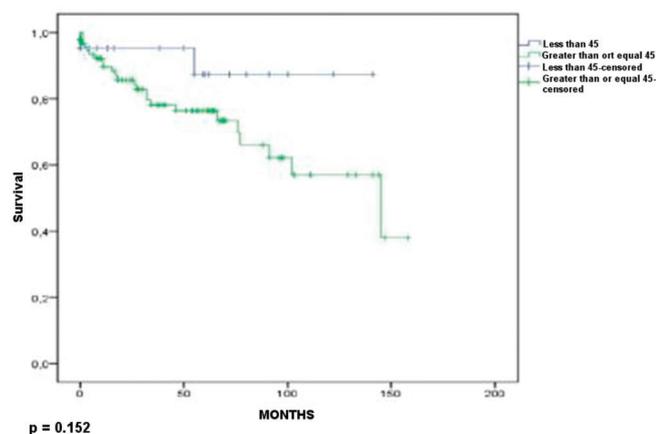
Figure 1. *Probability of survival in patients with non-metastatic renal cell carcinoma, according to age.*

p = 0.013
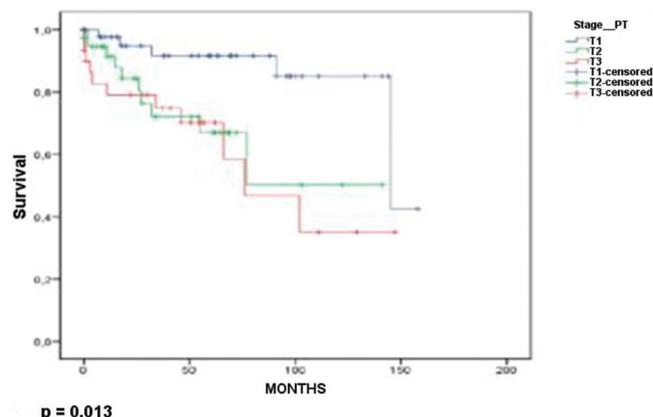
Figure 2. *Probability of survival in patients with non-metastatic renal cell carcinoma, according to the pathological stage (T).*

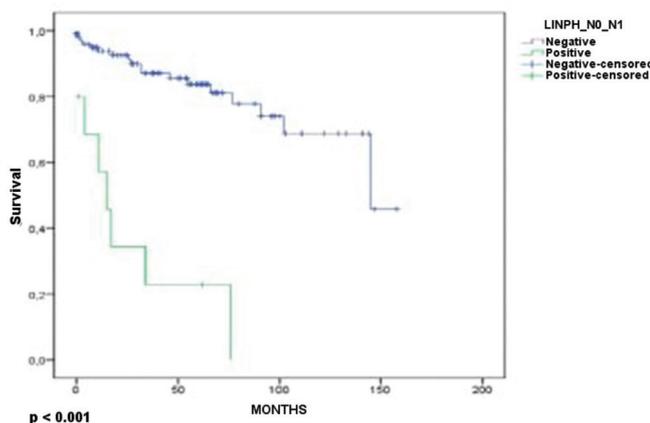260   *Predictors of mortality in patients submitted to nephrectomy for non-metastatic renal cell carcinoma at a referral center in Northeastern Brazil*

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Figure 3. *Probability of survival in patients with non-metastatic renal cell carcinoma, according to lymph node involvement.*

Figure 4. *Overall survival of patients with non-metastatic renal cell carcinomain months.*

Pathological staging (pT) and lymph node involvement (N+) were variables that presented significant statistical significance when related to overall survival in univariate analyzes. The histological grade, angiolymphatic invasion, presence of tumor necrosis and tumor laterality were also studied variables related to overall survival in univariate analyzes, but without statistical significance. (Figures 2, 3, 4 and 5).

DISCUSSION

The incidence of renal cancer, unlike other genitourinary tumors, is increasing[11]. This may be partly explained by the greater use of imaging methods such as magnetic resonance, computed tomography and ultrasound[11]. In our sample, only 8.55 % (10) of the patients were asymptomatic at the time of diagnosis. However, not only localized disease but also advanced disease is increasingly prevalent. The mortality rate continues to increase, suggesting that the elevation of incidence is not merely driven by better detection of early tumors[12]. Although international studies indicate that up to 60% of renal carcinomas are coincidentally diagnosed by imaging tests still in the asymptomatic phase[13,14], our sample of patients from a Brazilian Northeastern state showed that 91.5% (107/117) of the patients had symptoms at the time of diagnosis. This is a very relevant data and reflects the reality of the population studied, typical of a referral hospital in the public health care through the Unified Health System
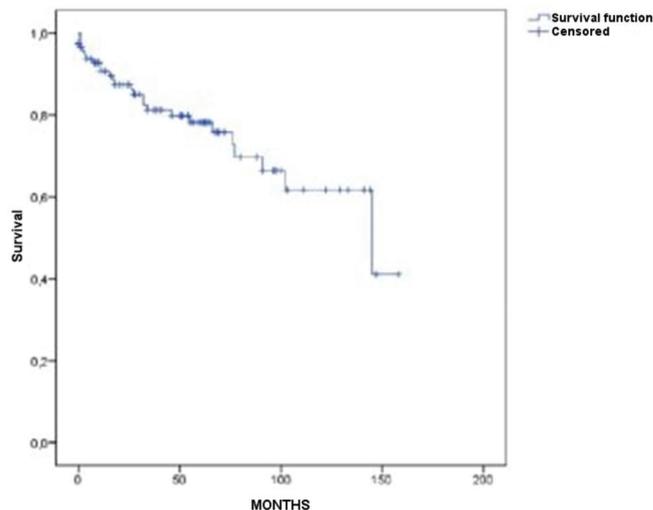
(SUS), characterized by attending patients from regions with scarce access to medical care, notably in the case of neoplastic disease. Possibly, therefore, about 58.2% of patients had tumor size greater than 7 cm (pT2) or invasion of renal vein/inferior vena cava or adrenal gland, limited to the Gerota (pT3). This fact may justify the large number of symptomatic patients at diagnosis and the high rate of radical nephrectomies, certainly influencing mortality on this sample.

There is no consensus regarding age being associated with an increased risk of mortality in RCC patients. According to Lee *et al.*[15], young patients are more likely to have non-clear cell tumors, with the greater possibility of recurrence and lower overall survival. On the other hand, Cai *et al.*[16], in a study that included 1,147 patients undergoing unilateral RCC nephrectomies (T1 to T2 N0 and M0), concluded that age above 45 years is associated with a higher incidence of cancer-specific mortality in localized RCC. In our study, the majority of patients received diagnosis after 45 years of age and this group did display a greater overall mortality (Figure 1).

Grivas *et al.*[17], in a study of clinical and pathological prognostic factors of renal cell carcinoma, concluded that the pathological stage and Fuhrman grade are strongly associated with survival. Besides that, in localized disease, such factors can be used in the follow-up to identify high-risk patients who could be the target of adjuvant therapy studies. In that study, as
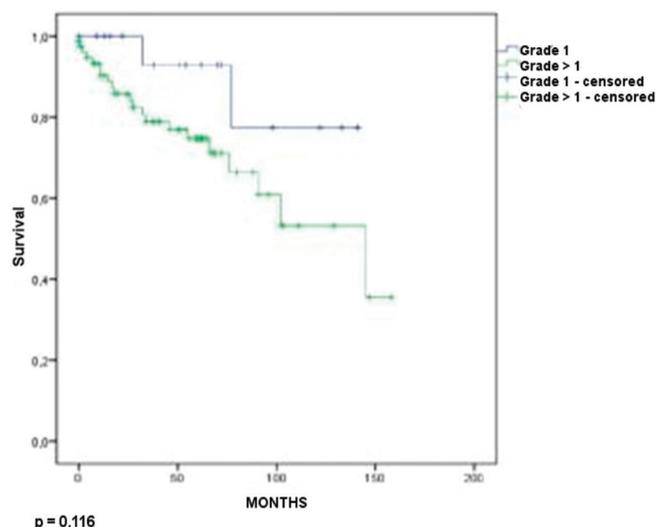
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Figure 5. *Probability of survival versus histological grade.*

in ours, gender was not a predictor of survival. Ornellas *et al.*[18] studied prognostic factors in renal cell carcinoma in 227 patients and found that the histological subtype, tumor necrosis, Fuhrman's grade and angiolymphatic

invasion were predictive factors of survival, a fact that was not reproducible in our sample.

In the evaluation of lymph node involvement as an independent survival predictor, Zhuang-fei *et al.*[10] stated that T1-3M0 patients with N (+) have a worse prognosis, being an independent predictor of cancer-specific and disease-free survival. They also showed that Fuhrman's grade and T stage are also predictors of cancer-specific survival. It is noteworthy that they considered Nx the cases in which no initial lymphadenectomy was performed, since they did not present lymph node enlargement at imaging or perioperative examination.

Our study demonstrated that staging (pT – p=0.013) and lymph node involvement (N+ – p<0.001) were significantly associated with a higher overall mortality rate in univariate analysis in patients with non-metastatic RCC who underwent radical or partial nephrectomy. We also verified that 91.5% (107/117) of patients had symptoms at the time of diagnosis.

R E S U M O

Objetivo: identificar fatores prognósticos envolvidos no carcinoma de células renais não metastático. **Métodos**: estudo tipo coorte retrospectivo, utilizando dados obtidos em revisão de prontuários de pacientes portadores de carcinoma de células renais, submetidos à nefrectomia radical ou parcial, no Instituto do Câncer do Ceará. **Resultados**: foram estudados 117 pacientes com média de idade de 59,14 anos e mediana de 59 anos. Não houve predominância de sexo, o rim direito foi o mais acometido (64%) e o tipo histopatológico mais comum foi o carcinoma de células claras (77%). Predominou o estádio pT1 e o grau GII. Das variáveis analisadas, apenas o estadiamento patológico (pT) e o acometimento linfonodal revelaram-se preditoras de sobrevida global. **Conclusão**: o estadiamento patológico (pT) e o acometimento de linfonodos regionais são fatores prognósticos importantes em pacientes portadores de carcinoma de células renais não metastáticos submetidos a nefrectomia.

Descritores: Neoplasias Renais. Nefrectomia. Carcinoma de Células Renais. Sobrevida. Prognóstico.

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