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Time to Recurrence after Nephrectomy as a Predictor of Cancer-Specific Survival in Localized Clear-Cell Renal Cell Carcinoma

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Key Words
Renal cell carcinoma · Recurrence · Prognosis · Nephrectomy

Abstract
Objective: To evaluate the prognostic impact of early recurrence (within 12 months) after surgery on cancer-specific survival (CSS) of patients with localized clear-cell renal cell carcinoma (ccRCC). ***Methods:*** Patients with surgically treated localized ccRCC were studied. Using the Kaplan-Meier method, we calculated CSS; by univariate and multivariate models we analyzed the association of early recurrence with cancer-related mortality. ***Results:*** We identified 259 patients with pT1–4/NX/0M0 ccRCC treated between February 1981 and September 2009; of 66 (25.5%) with disease recurrence, 29 (43.9%) had early relapse. Overall, 43 patients (16.6%) died from ccRCC. The 5- and 10-year CSS for those without, late and early recurrence was 98.5 and 96.5%, 53 and 39.8%, and 23 and 23%, respectively ($p < 0.0001$). In the multivariate Cox model, pT stage ($p = 0.01$) and early recurrence ($p < 0.0001$) independently predicted CSS. ***Conclusions:*** Recurrent disease after localized ccRCC confers a poor prognosis, especially if detected within 12 months after surgery. Thus, this criterion should be included as an independent risk factor for cancer-related mortality.

Introduction

Renal cell carcinoma (RCC) comprises up to 85% of renal malignancies in adults and about 70% of these are of the clear-cell subtype (ccRCC) [1–3]. Despite the established role of radical nephrectomy as the standard of care in past decades, at present nephron-sparing techniques including partial nephrectomy are established options with the advantage of conferring excellent oncological outcome while preserving renal function [4].

Long-term survival may vary among different stages of RCC, ranging from 90% in organ-confined tumors to less than 5% in metastatic disease [5]. Regardless of surgical excision, an important proportion of patients with clinically localized tumors, ranging from 20 to 40%, will experience disease relapse [6]. Furthermore, while 91–100% of those with pT1–2 tumors will be free of recurrence at 5 years, up to 40% of pT3 tumors will relapse within 3 years after surgery [7, 8]. At the same time, nuclear grade is an important predictor of failure [9]. Although the prognostic role of histologic subtype is con-

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troversial, some studies have demonstrated differences in the outcome of different morphologic variants of RCC [10].

RCC has a highly variable natural history and several factors may influence prognosis, including patient and tumor features. Clinical and laboratory findings have been evaluated and, along with pathological characteristics, are used to improve the prognostic accuracy of current diagnostic tools [10, 11].

Time to recurrence is a well-indentified prognostic factor in other malignancies. In such a case, patients with earlier recurrence are at higher risk of cancer-related mortality [12]. In RCC, time to recurrence has been included as a component in risk group classifications of patients with recurrent disease in order to predict survival from the time of relapse [13]. However, to our knowledge it has not been assessed in a multivariate fashion. We hypothesized that early recurrence of RCC is an independent prognostic factor associated with cancer-related mortality. Thus, we evaluated the prognostic impact of metachronous early recurrence (within 12 months) on the cancer-specific survival (CSS) of patients with surgically treated localized ccRCC.

Methods

We analyzed our prospectively maintained renal tumor database of 395 consecutive patients treated with radical or partial nephrectomy. Preoperatively, all patients were evaluated by abdominal imaging; although abdominal ultrasound and intravenous pyelography were the standard at the beginning of our series, this approach has been progressively replaced by computed tomography (CT) scanning since the late 1980s. In addition, chest imaging (X-ray or CT), a comprehensive serum metabolic panel and, when indicated, brain imaging or bone scintigraphy were performed to complete the initial evaluation.

The patients were followed postoperatively according to the discretion of the treating urologist. Most patients had annual follow-ups with evaluation of medical history, physical examination, serum chemistries and chest X-ray. Although many patients underwent regular abdominal CT scans or ultrasound, there was not a standardized patient selection criterion or imaging interval. Adjuvant therapy was offered at the discretion of the treating oncologist rather than in a routine fashion.

We retrospectively assessed the role of pT stage (TNM 2002 system), nuclear grade, lymphovascular invasion, sarcomatoid differentiation and time to recurrence (early vs. late) as predictors of CSS. Patients with benign tumors and hereditary conditions (i.e. von Hippel-Lindau disease) were excluded. Moreover, since survival differences may be found among different histologic subtypes, we evaluated only ccRCC variety. In addition, to minimize bias we only included patients with no evidence of lymph node invasion (clinically or histologically) or distant metastases (NX/0M0) at diagnosis.

We also performed a subset analysis of patients with recurrent disease to assess the role of pT stage, nuclear grade, sarcomatoid differentiation, location of recurrence (local vs. distant) and time to recurrence as predictors of CSS in this group of patients. We also assessed possible risk factors for early recurrence in these patients.

Statistical Methods

Recurrence was rated at the time of clinical, radiological or histologic confirmation and was defined as early if demonstrated within 12 months postoperatively. The endpoint was CSS defined as the time in months from nephrectomy to death from cancer. Survival was calculated using the Kaplan-Meier method and the results compared by the log rank test. Univariate and multivariate Cox proportional hazards models were used to assess the predictive value of pathological variables and early recurrence. The relationship between survival and each variable was summarized using hazard ratios (HR) and 95% CI. $p < 0.05$ was considered statistically significant.

Results

Of the 395 patients, 259 were treated surgically for pT1–4/NX/0M0 ccRCC between February 1981 and September 2009. Of these, 241 underwent radical nephrectomy (93%). The median follow-up was 36 months (range: 1–271 months). The demographic and pathological characteristics are summarized in table 1.

Pathological Characteristics

The tumor diameter was >7 cm in 51.7%, nuclear grade 1–2 was demonstrated in 68.9% and organ-confined tumors (stages pT1–2) were seen in 64.4% of the patients.

Adjuvant Therapy

Thirty-four patients (13.2%) received additional therapy consisting of chemotherapy (initial years of this series) in 15 (5.8%), immunotherapy in 3 (1.2%), thalidomide in 5 (1.9%), thalidomide plus immunotherapy in 6 (2.3%), immunotherapy plus chemotherapy in 4 (1.6%) of the cases, and chemotherapy plus a tyrosine kinase inhibitor in 1 case (0.4%).

Recurrence

A total of 66 patients (25.5%) experienced disease recurrence, with a median time to recurrence of 17 months (range: 1–129 months). Of these, 29 (43.9%) presented relapse within the first year after surgery, and 49 (74.2%) had a single-site recurrence. The most frequent locations were lung (24%) and bone (22%).

Cancer-Specific Survival

Overall, 43 patients (16.6%) died from ccRCC, with a median time to death of 33 months (range: 4–129 months). When compared to survivors, patients dying from the disease had larger tumors (mean tumor diameter: 11.2 ± 7.3 cm vs. 7.1 ± 3.5 cm; $p \leq 0.0001$), a higher frequency of nuclear grade 3–4 tumors (58 vs. 26%; $p = 0.0001$) and lymphovascular invasion (41 vs. 16%; $p = 0.0002$), and experienced early recurrence more frequently (44 vs. 4%; $p < 0.0001$).

The 5- and 10-year CSS in the whole cohort was 78.2 and 72.8%, respectively. When stratified according to disease recurrence, patients without and late relapse (included in a single group) had 5- and 10-year CSS of 86 and 80% in comparison with those with early recurrence, who had 5- and 10-year CSS of 23 and 23%, respectively ($p < 0.0001$). Furthermore, when analyzed in separate groups, the difference remained statistically significant since the 5- and 10-year CSS for those without, late and early recurrence was 98.5 and 96.5%, 53 and 39.8%, and 23 and 23%, respectively ($p < 0.0001$) (fig. 1). Univariate analysis showed that pT stage ($p < 0.0001$), nuclear grade ($p < 0.0001$), lymphovascular invasion ($p = 0.0002$), sarcomatoid differentiation ($p < 0.0001$) and early recurrence ($p < 0.0001$) were predictors of CSS. In the multivariate Cox proportional hazards regression model, pT stage ($p = 0.01$) and early recurrence ($p < 0.0001$) remained as independent predictors of CSS (table 2).

CSS in Patients with Disease Recurrence

We performed a subset analysis including only 66 patients with recurrent disease. When stratified according to management of recurrent disease, those with metastasectomy had 5- and 10-year CSS of 76.9 and 52.7% vs. 28 and 18.7% in those with nonresected metastases ($p = 0.0005$). Univariate analysis showed that pT stage ($p = 0.003$), nuclear grade ($p = 0.007$), sarcomatoid differentiation ($p = 0.0002$), distant recurrence (in comparison to local relapse; $p = 0.04$) and early recurrence ($p = 0.0003$) were predictors of CSS. In the multivariate Cox proportional hazards regression model, pT stage ($p = 0.005$), nuclear grade ($p = 0.01$) and early recurrence ($p = 0.0008$) remained independently associated with CSS in patients with recurrent disease (table 3).

Risk Factors for Early Recurrence

In univariate analysis we found that pT stage, nuclear grade, tumor diameter of >7 cm and sarcomatoid differentiation were associated with early recurrence. In multivariate assessment, nuclear grade, pT stage and tumor

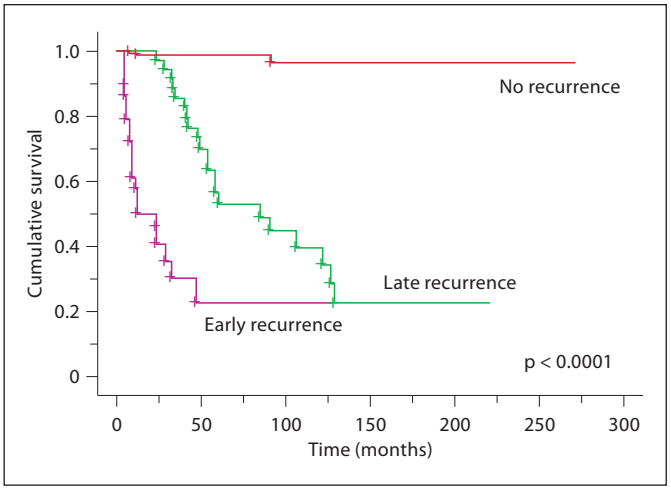

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Fig. 1. CSS of 259 patients with pT1–4/NX/0M0 ccRCC according to pattern of disease recurrence.

Table 1. Demographic and pathological characteristic of 259 patients with pT1–4/NX/0M0 ccRCC treated by nephrectomy

Age at diagnosis, years	64.4 ± 6.7
Gender	
Female	107 (41)
Male	152 (59)
Surgery	
Radical	241 (93)
Partial	18 (7)
Tumor diameter, cm	7.8 ± 4.6
Pathological tumor stage	
pT1a	39 (15.1)
pT1b	51 (19.7)
pT2	77 (29.7)
pT3a	48 (18.5)
pT3b	39 (15.1)
pT3c	2 (0.8)
pT4	3 (1.1)
Nuclear grade, %	
1–2	68.9
3–4	31.1
Lymphovascular invasion	
Yes	54 (20.8)
No	205 (79.2)
Sarcomatoid differentiation	
Yes	9 (3.5)
No	250 (96.5)

Values denote numbers with percentages in parentheses or means ± SD unless stated otherwise.

Table 2. Cox proportional hazards model for CSS of 259 patients with pT1–4/NX/0M0 ccRCC treated by nephrectomy

	Univariate			Multivariate		
	HR	95% CI	p	HR	95% CI	p
pT stage	1.96	1.5–2.5	<0.0001	1.66	1.1–2.5	0.01
Nuclear grade	2.20	1.5–3.1	<0.0001	1.39	0.9–2.0	0.1
Lymphovascular invasion	3.22	1.7–5.9	0.0002	1.64	0.6–4.2	0.2
Sarcomatoid differentiation	13.10	4.6–36.5	<0.0001	0.85	0.2–2.7	0.7
Recurrence ≤12 months	13.62	7.2–25.5	<0.0001	19.12	8.2–44.4	<0.0001

Table 3. Cox proportional hazards model for CSS of 66 patients with recurrent ccRCC after nephrectomy

	Univariate			Multivariate		
	HR	95% CI	p	HR	95% CI	p
pT stage	1.54	1.1–2.0	0.003	1.73	1.1–2.5	0.005
Nuclear grade	1.96	1.3–2.9	0.007	1.69	1.0–2.5	0.01
Sarcomatoid differentiation	7.50	2.5–22.0	0.0002	0.80	0.2–3.1	0.7
Local vs. distant recurrence	4.91	1.0–22.5	0.04	0.96	0.1–6.5	0.9
Recurrence ≤12 months	3.33	1.7–6.3	0.0003	4.60	1.8–11.2	0.0008

Table 4. Cox proportional hazards model for predicting early recurrence (≤12 months) in patients with pT1–4/NX/0M0 ccRCC treated by nephrectomy

	Univariate			Multivariate		
	HR	95% CI	p	HR	95% CI	p
Nuclear grade	2.33	1.5–3.4	<0.0001	1.64	1.0–2.5	0.02
pT stage (pT1–2 vs. pT3–4)	2.89	1.3–6.0	0.004	2.22	1.0–4.7	0.03
Sarcomatoid differentiation	9.75	3.9–24.1	<0.0001	2.50	0.9–6.9	0.07
Tumor diameter >7cm	4.72	1.8–12.3	0.001	3.02	1.1–8.3	0.03

diameter remained as independent predictors of early relapse in NX/0M0 ccRCC. Sarcomatoid differentiation showed a trend toward association to CSS without reaching significance (table 4).

Discussion

Controversy remains about outcome predictors in RCC. Although many parameters have been evaluated, only a few are currently used in clinical practice. TNM stage, tumor size and Fuhrman nuclear grade are among the most commonly accepted prognostic factors in localized disease [14]. Regarding metastatic disease, poor performance status, elevated lactate dehydrogenase, low serum hemoglobin and high corrected serum calcium can be used as well [15]. Although current prognostic models have largely been based on these variables, the long-term outcome after nephrectomy remains unpredictable. One of the most important factors influencing outcome in RCC is pT stage [7]. While patients with organ-confined disease have an estimated 5-year recurrence-free survival of 90%, up to 38% of those with pT3a–b RCC experience relapse within 3 years postoperatively [7]. In ad-

dition, tumor size and nuclear grade have been demonstrated to be significantly associated with survival after surgical resection of RCC. Early recurrence has been analyzed as an adverse predictive variable in tumors such as prostate cancer, placing patients with biochemical recurrence before 36 months at higher risk of cancer-related mortality [12]. In RCC, early relapse has been included in prognostic instruments to predict survival from time to recurrence to death from cancer [13]. Nevertheless, to our knowledge, early recurrence has not been tested multivariately as an independent prognostic factor to predict cancer-related mortality. We selected 12 months as the cutoff point to define early recurrence since 83% of high-risk patients (i.e. stage pT3a–b) have a relapse within the first 24 months after nephrectomy, and 49% experience recurrence within 12 months [7].

In this study we included only NX/0M0 tumors because they have clinical and pathological characteristics different from those initially diagnosed with nodal involvement or distant metastases; moreover, in such cases the probability of disease recurrence could be higher. In addition, we evaluated only ccRCC to minimize the potential bias secondary to outcome differences among histologic subtypes. The frequency of disease recurrence in our series is consistent with that reported in previous reports.

Early recurrence conferred worse prognosis, a finding confirmed by multivariate analysis. Our findings suggest that in the absence of lymph node or metastatic involvement, the strongest predictors of cancer-related mortality in ccRCC are pathological stage and early recurrence, with a 1.66- and 19.12-fold increase in the risk of mortality, respectively. According to our results, patients with high-grade lesions, in stages pT3–4 and with diameters of >7 cm are at a higher risk of early recurrence. In addition, sarcomatoid differentiation, currently recognized as an adverse prognostic factor [16–18], showed a trend toward association with the likelihood of early relapse. Based on our findings and those by other investigators [7], we propose a risk-adapted surveillance protocol for these patients after surgery. They should be evaluated every 6 months during the first 2 years by clinical assessment, serum tests and chest imaging. Abdominal CT scanning at 6, 12, 24 and 36 months postoperatively is also recommended.

Although several outcome prediction models have recently emerged [19–21], their ability to accurately predict the outcome of RCC can be improved by the incorporation of readily available variables significantly associated with survival. Therefore, we suggest the integration of time to recurrence into clinical algorithms to stratify patients into risk groups. Since each of the therapies currently available for recurrent and metastatic disease is associated with a significant risk of toxicity, the identification of patients at higher risk of cancer-related mortality is crucial for counseling and clinical decision making [10]. Patients with the highest likelihood of a short time to recurrence (i.e. high nuclear grade and tumor diameter >7 cm) may benefit from early detection of recurrent disease and aggressive additional therapy.

Our study has some limitations, particularly its retrospective design. As a consequence, the surveillance protocol after surgery could vary among patients, leading to a relative underestimation of disease recurrence rates. The strength of our investigation lies in the inclusion of a homogeneous cohort of patients, all with localized tumors and the same histologic variety, resulting in more accurate prognostic estimations. Although the prognostic impact of early recurrence appears obvious, we believe that the stratification of patients according to time to recurrence would potentially justify the design of adjuvant clinical trials of a targeted therapy for those with risk factors for early recurrence and cancer-related mortality.

In conclusion, postoperative cancer surveillance is a critical aspect of oncological care. The pattern of recurrence reflects the potential biological behavior of the disease. Our results demonstrate that recurrent disease after localized ccRCC confers a poor prognosis, especially when recurrence occurs before 12 months. This criterion should be considered an independent risk factor for death associated with cancer. The identification of patients at high risk of short time to recurrence and death from cancer will allow better clinical decision making.

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