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Original article

The key role of time in predicting progression-free survival in patients with renal cell carcinoma treated with partial or radical nephrectomy: Conditional survival analysis

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Abstract

Introduction: In surgically treated patients with renal cell carcinoma (RCC), the progression-free survival (PFS) rate may significantly change according to the progression-free postoperative period. To test this hypothesis, we set to evaluate the conditional PFS rate in surgically treated patients with RCC.

Methods: We evaluated 1,454 patients with RCC, surgically treated between 1987 and 2010, at a single institution. Cumulative survival estimates were used to generate conditional PFS rates. Separate Cox regression models were fitted to predict clinical-progression risk in patients who were progression free from 1 to 10 years after surgery.

Results: During the immediate postoperative period, the 5-year PFS rate was 88%, and it increased to 92%, 94%, and 97% in patients who remained progression free at, respectively, 1, 5, and 10 years after surgery. At multivariable analyses, where patients with stage I disease were considered as a reference, the highest clinical-progression risk was observed at the eighth postoperative year in patients with stage II disease (hazard ratio [HR]: 2.9) and during the immediate postoperative period in patients with stage III to IV disease (HR: 5.5). In comparison with patients with grade I disease, the highest clinical-progression risk was observed at the fourth (as well as eighth) postoperative year in patients with grade II disease (HR: 5.7), sixth postoperative year in patients with grade III disease (HR: 7.2), and during the immediate postoperative period in patients with grade IV disease (HR: 8.5).

Conclusions: The postoperative progression-free period has an important effect on the subsequent clinical-progression risk. This aspect should be considered along with tumor characteristics to plan the most cost-effective follow-up scheme for surgically treated patients with RCC.

Keywords: Renal cell carcinoma/surgery; Disease-free survival; Postoperative period; Survival analysis; Treatment outcome

1. Introduction

The incidence of renal cell carcinoma (RCC) continues to increase [1]. In Europe, every year about 88,400 new cases of RCC are reported, and it is responsible for approximately 39,300 deaths per year [2]. Surgical treatment (partial or radical nephrectomy) represents the most effective therapy for patients with clinically localized disease and may be curative in most cases [3–5]. Nevertheless, the postoperative risk of disease progression is still significant in contemporary patients [5–9]. In consequence, an accurate prediction of progression-free survival (PFS) might be of great importance for correct patient counseling, scheduling follow-up, and early detection of recurrent disease.

Virtually all previous reports that focused on RCC progression rate after surgery suggested stratifying patients' follow-up according to the disease characteristics [6–11]. In consequence, current guidelines recommend a 5-year follow-up of all patients, with a subsequent annual follow-up visit of patients with intermediate- and high-risk disease [3,4]. However, none of the previous studies accounted for

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the effect of time of progression-free survivorship on the subsequent risk of disease recurrence. This effect, otherwise known as conditional survival, has been previously examined and reported for several other tumors [12–15]. Conditional survival rates provide an accurate evaluation of the patient's changing risk over time and might be helpful for clinicians in planning appropriate follow-up and treatment.

To address this void, we set to evaluate the conditional PFS rates of surgically treated patients with RCC. We stratified our analyses according to anatomic stage and Fuhrman grade as these 2 characteristics represent the foremost predictors of PFS in patients with RCC [16–24].

2. Materials and methods

2.1. Patient population

Between 1987 and 2010, we identified 1,521 consecutive individuals, who were diagnosed with nonmetastatic, unilateral RCC (clear cell, papillary I, papillary II, or chromophobe) and were treated with nephrectomy (partial or total) at our institution. Patients with missing pathologic stage ($n = 3$), Fuhrman grade ($n = 7$), follow-up information ($n = 44$), and progression site data ($n = 13$) were excluded. These selection criteria yielded 1,454 assessable individuals. Our institutional review board approved this study.

2.2. Preoperative staging

The presence/absence of synchronous metastases at the time of referral for surgery was evaluated by abdominal computerized tomography (CT), magnetic resonance imaging, chest radiographs, chest CT scans, bone scans, and brain CT scans, as indicated. When present, the level of tumor thrombus was classified as limited to the renal vein, extending into the inferior vena cava below the diaphragm, or extending above the diaphragm. The cranial extent of the tumor thrombus was assessed by venocavography before 1995 and by magnetic resonance angiography or CT angiography from 1995 to 2010. In cases of intrahepatic-suprahepatic inferior vena cava invasion or atrial invasion or both, transoesophageal echocardiography was used to assess cardiac tumor involvement, as well as cardiac function. The nature of imaging studies performed in each patient was based on surgeon discretion. However, each patient had at least 1 abdominal and chest imaging preoperatively.

2.3. Surgical technique

Surgical procedure consisted of laparotomy with partial or radical nephrectomy as indicated. In case of radical nephrectomy, ipsilateral adrenalectomy and retroperitoneal lymphadenectomy were frequently performed. The lymphadenectomy was performed according to the surgeon's preference and on the basis of clinical and intraoperative findings. The lymphadenectomy template consisted of hilar, precaval, retrocaval, and interaortocaval nodes for the right kidney and interaortocaval and para-aortic nodes for the left kidney.

2.4. Surgical specimen pathologic examination

All surgical specimens were examined according to a standardized protocol [25]. Briefly, description of tumor extension beyond the kidney into perinephric fat, renal sinus fat, and renal vein was always addressed. Perinephric fat invasion was defined as the extension of the tumor into the fat surrounding the renal capsule; renal sinus fat invasion was characterized by the spread of the tumor into the fat of the renal sinus. Tumor stage was assigned according to the 2010 TNM classification of the American Joint Committee on Cancer [26].

2.5. Postoperative follow-up

After surgery, blood tests and chest and abdominal imaging studies (abdominal ultrasound and chest radiographs or thoracoabdominal CT) were performed every 4 months for the first year, then every 6 months up to the fifth year, and annually thereafter. In addition, a bone scan was performed every year, especially in patients with intermediate- to high-risk disease. PFS rates were calculated from the date of surgery to the last available follow-up (date of clinical progression in censored cases).

2.6. Variable definitions

Patient information included age at surgery (years), Charlson comorbidity index, gender, tumor laterality, symptoms at presentation (asymptomatic vs. local symptoms vs. systemic symptoms), pathologic tumor stage, pathologic nodal stage, Fuhrman grade, histologic cell type, and type of nephrectomy (partial vs. radical). Anatomic stage was defined according to American Joint Committee on Cancer staging (stage I: T1N0M0, stage II: T2N0M0, stage III: T1-2N1M0 or T3N0-1M0, and stage IV: T4N0-1M0).

2.7. Statistical analyses

Descriptive statistics of categorical variables focused on frequencies and proportions. Means, medians, and ranges were reported for continuously coded variables. Chi-square test and *t*-test were used to compare, respectively, proportions and means.

Our statistical analyses consisted of several steps. First, we estimated survival probabilities using the Kaplan-Meier method. Second, we calculated the conditional survival estimates using the multiplicative law of probability stratified, as previously described [15,27]. All survival analyses were stratified according to anatomic stage (I vs. II vs. III–IV) and Fuhrman grade (I vs. II vs. III vs. IV).