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Survival Outcome and Treatment Response of Patients with Late Relapse from Renal Cell Carcinoma in the Era of Targeted Therapy

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Abstract

Background: A subset of primarily localized renal cell carcinoma (RCC) patients will experience disease recurrence ≥5 yr after initial nephrectomy.
Objective: To characterize the clinical outcome of patients with late recurrence beyond 5 yr.
Design, setting, and participants: Patients with metastatic RCC (mRCC) treated with targeted therapy were retrospectively characterized according to time to relapse. Relapse was defined as the diagnosis of recurrent metastatic disease >3 mo after initial curative-intent nephrectomy. Patients with synchronous metastatic disease at presentation were excluded. Patients were classified as early relapsers (ERs) if they recurred within 5 yr; late relapsers (LRs) recurred after 5 yr.
Outcome measurements and statistical analysis: Demographics were compared with the Student *t* test, the chi-square test, or the Fisher exact test. The survival time was estimated with the Kaplan-Meier method, and associations with survival outcome were assessed with univariable and multivariable Cox regression analyses.
Results and limitations: Among 1210 mRCC patients treated with targeted therapy after surgery for localized disease, 897 (74%) relapsed within the first 5 yr and 313 (26%) (range: 5–35 yr) after 5 yr. LRs presented with younger age ($p < 0.0001$), fewer with sarcomatoid features ($p < 0.0001$), more clear cell histology ($p = 0.001$), and lower Fuhrman grade ($p < 0.0001$). Overall objective response rates to targeted therapy were better in LRs versus ERs (31.8% vs 26.5%; $p = 0.004$). LRs had significantly longer

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progression-free survival (10.7 mo vs 8.5 mo; $p = 0.005$) and overall survival (OS; 34.0 mo vs 27.4 mo; $p = 0.004$). The study is limited by its retrospective design, noncentralized imaging and pathology review, missing information on metastatectomy, and nonstandardized follow-up protocols.

Conclusions: A quarter of patients who eventually developed metastatic disease and were treated with targeted therapy relapsed over 5 yr from initial nephrectomy. LRs have more favorable prognostic features and consequently better treatment response and OS.

1. Introduction

More than two-thirds of renal cell carcinoma (RCC) patients are diagnosed with localized disease [1]. However, up to 30% of these patients will ultimately develop metastatic RCC (mRCC) [2,3]. Using the criteria of adjuvant clinical trials in RCC, a recent retrospective study of primary localized RCC patients who were at high risk for disease recurrence found the median time to disease recurrence between 1.0 and 1.3 yr [3]. Consequently, it is common clinical practice to stop follow-up visits for patients at low risk and extend the periods for follow-up visits for patients with intermediate and high risk after a disease-free interval of approximately 5 yr [2,4]. However, disease relapse can virtually take place at any time even after periods >5 yr.

Disease recurrence after a disease-free interval of numerous years is commonly characterized by uncertainty for both physicians and patients. Although risk features generally associated with the risk of disease recurrence and late recurrence in particular have been intensively studied [2,3,5], there is currently no robust characterization of treatment response and survival outcome after late recurrence. The International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) risk model provides information to stratify patients for clinical trials and for patient counseling to prognosticate overall survival (OS) [6,7]. Nonetheless, risk models like the IMDC are not sufficient to take every circumstance into consideration that may be of additional importance for patients' individual outcome.

The aim of the current study was to characterize the treatment response and survival of patients who were diagnosed with metastatic disease from RCC after a disease-free interval >5 yr. The current study did not aim to develop a new prognostication tool. It was the ultimate goal to provide clinical information on this unique subset of mRCC patients. The current study is a project of the IMDC, a collaboration of 20 academic centers.

2. Patients and methods

2.1. Study populations

The IMDC database includes centers from North America (Canada, United States), Europe (Denmark, Greece), and Asia (Singapore, Japan, South Korea). Data were collected from August 15, 2008, until February 1, 2013. At the time of analysis, the database contained data on 2754 patients who had received first-line targeted therapy between 2003 and 2013. Relapse from RCC was defined as a diagnosis of recurrent metastatic disease >3 mo after nephrectomy for localized disease based on criteria that were applied in recent adjuvant clinical trials. All patients finally included in the analyses were free of distant metastatic disease (M0) at diagnosis.

Patients with synchronous metastatic disease at presentation, uncertain nephrectomy status, or diagnosis of metastatic disease <3 mo after initial diagnosis ($n = 1544$) were excluded from analyses. Patients were classified as early relapsers (ERs) if they had disease recurrence >3mo and ≤5 yr, whereas late relapsers (LRs) were diagnosed with metastatic disease >5 yr according to previous large surgical reports [5].

All centers obtained local institutional review board approvals before submitting data into the IMDC database. Baseline patient characteristics included demographic, clinicopathologic, and laboratory data as described previously [7]. Survival data were retrospectively collected from medical chart reviews and electronic records. Uniform data templates were used to ensure consistent data collection at each institution. Most of the patients had been treated as standard of care, but a subset may have been part of clinical trials. All patients were collected in consecutive series to avoid selection bias.

2.2. Statistical analyses

The primary end point of this study was to evaluate the survival outcome by comparing progression-free survival (PFS) and OS. The secondary aim was to characterize treatment response to the current standard of care targeted therapy agents. OS was defined as the time period between targeted therapy initiation and the date of death, or censored on the day of the last follow-up visit. PFS was defined as the time period between treatment from targeted therapy initiation to progression, drug cessation, death, or censored at the last follow-up visit. Progression was determined when there was clinical progression, treatment discontinuation due to toxicity, or radiographic criteria using the Response Evaluation Criteria in Solid Tumors (RECIST v.1.0) [8].

Patient and tumor characteristics were compared using the Student *t* test for continuous variables or the chi-square test and Fisher exact test for categorical variables.

The Kaplan-Meier method was used to estimate the median OS and PFS. Differences in survival between ERs and LRs were compared with the log-rank test. The association (presence or absence) of LRs and predefined prognostic factors were assessed with univariable and multivariable Cox regression. The analyses were performed with a backward stepwise selection criteria, and the significance was tested with the Wald statistic [7]. In multivariable analyses, the IMDC (Heng) risk criteria were applied for adjustment. The IMDC risk criteria are the time from diagnosis to treatment <1 yr, Karnofsky performance score (KPS) <80, anemia, hypercalcemia, thrombophilia, and neutrophilia. Upper and lower limits of normal of the laboratory parameters were based on institutional limits [6,7]. The IMDC risk factors were compared by the separated risk factors and not within risk groups because many of the ERs have per se one more risk factor because they relapsed within 1 yr, whereas this risk factor is impossible in the group of LRs.