Abstract. Aim: We investigated the clinicopathological features in patients with recurrent RCC within 5 years or more than 5 years after nephrectomy and determined predictors of survival and response treatment after recurrence. Materials and Methods: We retrospectively evaluated 144 patients with disease recurrence; 73 had recurrence more than 5 years after radical nephrectomy. We compared clinicopathological characteristics in patients with disease recurrence before vs. after 5 years. In addition, we investigated predictors of survival and response to treatment after recurrence. Results: Seventy-one patients (49%) were diagnosed with recurrence within 5 years after radical nephrectomy (early recurrence) and 73 patients (51%) were diagnosed with recurrence more than 5 years after radical nephrectomy (late recurrence). Fuhrman grade, tumor necrosis and lymphovascular invasion were statistically significantly different between the two groups (p<0.001, p=0.013, p=0.026, respectively). The late recurrence patients were significantly associated with the Memorial Sloan Kettering Cancer Center (MSKCC) favorable risk group compared to patients with early recurrence (p=0.001). From the time of disease recurrence, median Overall Survival (OS) was 36.0 (95% Confidence Interval (CI) 30.7-41.2) months in the late recurrence group, and 19 (95% CI 15.4-22.5) months in the early recurrence group (p=0.01). The median Progression Free Survival (PFS) was 6 (95% CI 3.87-8.12) months in the early recurrence group, and 18 (95% CI 15.4-20.5) months for the late recurrence group (p<0.001). Conclusion: Early recurrence was significantly associated with Fuhrman grade 3-4, tumor necrosis, lymphovascular invasion, MSKCC poor-risk group compared to patients with late recurrence. The study also demonstrated a potential prognostic value of late recurrence in terms of PFS and OS.

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Kidney cancer is the third most common genitourinary tumor and accounts for 3% of all adult malignancies. Renal cell carcinomas (RCC) make up 85% of renal malignancies in adults (1). The worldwide incidence of kidney cancer is approximately 209,000 new cases per year with a mortality of 102,000 deaths per year (2). Most patients presenting with organ-confined disease can be cured with surgery. The highest risk of recurrence is in the first 3 to 5 years after surgery, but, only 10% of patients with disease recurrence develop late recurrence more than 5 years post-nephrectomy (3, 4). Several clinical, histological, anatomical and molecular variables can be employed to predict the cancer-related survival probability of patients with RCC (5).

Although the Fuhrman’s grade, performance status and the TNM Classification of Malignant Tumours (TNM) stage, are the most widely recognized prognostic factors in RCC, the prognosis for patients with RCC is dependent primarily on disease stage. Patients with histopathological stage pT1 or pT2 (organ confined) disease have the best prognosis, with 5-year cancer-specific survival rates after nephrectomy ranging from 74% to 100%. However, once RCC has metastasized, the 5-year survival rate is less than 10% (3, 6, 7). In patients with recurrent RCC, the clinical course can vary, and survival can be stratified by an objective parameter called the Memorial Sloan-Kettering Cancer Center (MSKCC) system which identifies five prognostic factors. The five most prominent negative prognostic factors that were identified by multivariate analysis included a time from diagnosis to start of systemic therapy of less than 1 year, elevated serum lactate dehydrogenase (greater than 1.5 times the upper limit of normal), high corrected serum calcium (greater than 10 mg/dl), anemia (below the lower limit of normal), and low performance status (less than 80%). Patients with zero risk factors were assigned a favorable-risk status; those with one or two risk factors, an intermediate-risk status; and those with three or more risk factors, a poor-risk status (8-10). On the other hand, there is limited information on the clinical characteristics, prognostic factors, and outcomes in patients with late-recurring RCC (11, 12). Research continues to identify easy and strong available prognostic parameters that may help to classify patients in groups with different risks for death from kidney cancer. We evaluated patients with disease recurrence within 5 years or more after nephrectomy, describing the clinical characteristics and response to treatment and analyzing survival predictors in this patient group.

Materials and Methods

Patients. Data were obtained from chart reviews of RCC patients in twelve oncology Departments in Turkey. We retrospectively evaluated 144 patients who were diagnosed with recurrence within 5 years and more than 5 years after radical nephrectomy due to localized RCC from January 1991 to January 2014. Preoperatively all cases were staged properly with abdominal computerized tomography (CT), chest imaging, a serum exhaustive metabolic panel and bone or brain imaging, as indicated by laboratory values or symptoms. The pathologic stage was determined by the American Joint Committee on Cancer TNM staging system. Tumor cell differentiation was determined according to the Fuhrman’s grading system. Follow-up evaluation consisted of history and physical examination, routine blood tests with serum metabolic panels and imaging every 3 to 6 months during the first 2 years, every 6 months from the 3rd to the 5th year, and annually thereafter. Additional imaging examinations were conducted when the patient presented with symptoms related to cancer recurrence. The sites and number of recurrence were determined according to radiological findings of disease on ultrasound, CT, PET/CT or bone scan. Disease recurrence was described as radiographic evidence; suspect imaging findings were followed by biopsy of the doubted lesion and classified as disease recurrence after pathological confirmation. We used the validation prognostic scoring system of Motzer et al. to categorize patients with recurrence. This model includes five adverse predictive variables, including corrected serum calcium of more than 10 mg/dl, hemoglobin less than the gender specific lower limit of normal, serum lactate dehydrogenase more than 1.5 times the normal level, Karnofsky performance status less than 80% and time from initial diagnosis to systemic treatment of less than 12 months. All five parameters were collected and recorded at the time of disease recurrence. Each patient was then categorized into the favorable (0 points), intermediate (1 or 2 points) or poor (3 or 4 points) risk group. After recurrence, treatment was determined at the physician’s and patient’s discretion.

Statistical analysis. For statistical analyses of the study data the SPSS 18.0 software was used (IBM company). Associations between time to recurrence (five years or more than vs. less than five years), and categorical and continuous variables were evaluated using the Fisher’s exact tests and Student’s t, respectively. Survival analysis was performed using the Kaplan–Meier method, and the differences among the groups were determined using the log-rank test. Survival was defined as time from disease recurrence to death or last follow-up. Each variable was investigated using a univariate analysis for overall survival predictors. Multivariate analysis was not performed because of the limited sample size and the low number of outcome events. All p-values represent 2-sided tests of statistical significance, with p<0.05 being considered statistically significant.

Results

A total of 144 patients who underwent radical nephrectomy for localized RCC were evaluated; out of these, 71 patients (49%) were diagnosed with recurrence within 5 years after radical nephrectomy (early recurrence) and 73 patients (51%) were diagnosed with recurrence more than 5 years after radical nephrectomy (late recurrence). Tables I and II show the demographic and histopathological characteristics of the two patient groups. Fuhrman grade, tumor necrosis and lymphovascular invasion were statistically significantly different between the two groups (respectively, p<0.001,
However, there was no statistically significant difference in the other clinicopathological variables such as age, gender, tumor size, histological subtypes between the early- and late-recurrence groups. According to the MSKCC risk scoring system, 49% of patients were classed as favourable-risk (n=70), 39%, as intermediate-risk (n=57), and 12% as poor-risk (n=17). Late recurrence was significantly associated with the MSKCC favorable-risk group compared to patients with early recurrence (p<0.001).

One hundred and five patients received tyrosine kinase inhibitors, sunitinib (Sutent, Pfizer) and sorafenib (Nexavar, Bayer) or interferon alfa-2b (Intron-A, Merck) as first-line systemic treatment from the time of recurrence. The treatment data of the remaining thirty-nine patients were not available (this is because twenty-three patients had a comorbid disease and none of these patients received treatment while sixteen patients were lost to follow-up). Fifty two (49.5%), 26 (24.7%) and 27 (25.7%) patients received sunitinib, sorafenib and interferon alfa-2b as first-line systemic treatment respectively. Twenty seven (52%), 12 (22%) and 16 (22%) patients received sunitinib, sorafenib and interferon alfa-2b in the early-recurrence group. Twenty four (52%), 12 (26%) and 16 (22%) patients received sunitinib, sorafenib and interferon alfa-2b in the late-recurrence group. There was no significant difference according to treatment groups between the late disease recurrence and the early recurrence group (p=0.52).

Overall, the median follow-up from time of disease recurrence was 14 months (range=1-58 months). The end of the study, scored 82 alive patients (57%). Median PFS was 15 (95% CI=11.6-18.3), 16 (95% CI=11.1-20.8), and 3 (95% CI=1.74-4.25) months for the sunitinib-, sorafenib-, and interferon-treatment groups respectively (p<0.001). From the
time of disease recurrence, the median OS was 35 (95% CI=11.1-58.8), 20 (95% CI=13.5-26.4), and 12 (95% CI=3.75-20.2) months for the sunitinib-, sorafenib-, and interferon-treatment groups, respectively (p<0.001). Median PFS stratified by MSKCC risk status was 15 (95% CI=11.0-19.0), 10 (95% CI=5.52-14.4), and 3 (95% CI=0.06-5.93) months for favorable-, intermediate-, and poor-risk patients respectively (p=0.008) (Figure 1). Median OS was 35 (95% CI=23.3-46.6), 19 (95% CI=14.9-23.0), 16 (95% CI=2.41-29.5) months for favorable-, intermediate-, and poor-risk patients respectively (p=0.011) (Figure 2). Median PFS was 6 (95% CI=3.87-8.12) months in the early-recurrence group, and 18 (95% CI=15.4-20.5) months for the late recurrence group (p<0.001) (Figure 3). From the time of disease recurrence, the median OS was 36.0 (95% CI=30.7-41.2) months in the late recurrence group, and 19 (95% CI=15.4-22.5) months in the early recurrence group (p=0.01) (Figure 4).

Discussion

Disease recurrence in patients with localized kidney cancer after curatively-designed radical nephrectomy can appear at any time. However, late recurrence after radical nephrectomy is not prevalent. The clinicopathological features are not clearly defined for patients with late recurrence RCC after a nephrectomy for localized disease. Ten percent of patients with disease recurrence develop late recurrence more than 5 years post-nephrectomy (3, 4). We evaluated patients with disease recurrence 5 years or more after nephrectomy, describing the clinical characteristics, response treatment and analyzing survival predictors in this patient group. In our study, at a median postoperative follow-up of 49 months, disease recurred in 144 patients, including 73 with recurrence after 5 years and 71 with recurrence before 5 years from nephrectomy. Several studies have been performed to determine the clinicopathological characteristics of late recurrence of localized RCC after radical nephrectomy (11-25). However, no consensus has been reached regarding the parameters predicting late recurrence of localized RCC because of the limited number of participating patients. Brookman-May et al. (11) conducted a study including a total of 310 patients with cancer recurrence more than 5 years after nephrectomy and compared the characteristics of these patients with recurrence-free patients. They showed that Fuhrman grade 3-4, lymphovascular invasion and pT stage pT1 were significantly associated with late recurrence. Adamy et al. evaluated 44 patients with late recurrence (more than 5 years after nephrectomy); patients with late recurrence were found have fewer initial symptoms, smaller tumor size, and less aggressive disease compared with patients with early recurrence. Adamy et al. also found that patients with late recurrence were associated with the MSKCC favorable-risk group compared with patients with early recurrence (12).

Son et al. showed that tumor necrosis was associated with late recurrence disease (26). Minervini et al. also proved that histological tumor necrosis is a statistically significant prognostic factor in patients with non-metastatic clear cell RCC (27). In our study, we showed that patients with late recurrence tend to be in the MSKCC favorable-risk group compared to patients with early recurrence (p<0.001). Also, we detected that Fuhrman grade 3-4, tumor necrosis, and lymphovascular invasion exhibited a significant statistical difference in the late-recurrence and early-recurrence groups. These data were similar with some other studies (11, 12, 16, 26, 27). No statistically significant difference between late disease recurrence and other clinicopathological parameters such as age, sex, initial clinical symptoms, and tumor size was observed. These results were contrary to some studies (12, 14, 15) showing differences possibly due to the retrospective nature of the analysis performed, different number of patients and differential characteristics of patients between studies.

The MSKCC risk stratification has been improved to predict outcomes in patients with metastatic RCC, and has been modified for trials of targeted therapy (28). In addition to its use for estimating survival, it provides relevant clinical information to patients receiving therapy. For example, multi-targeted tyrosine kinase inhibitors such as sunitinib or bevacizumab-plus-interferon alfa have been cited as the preferred treatment options for metastatic RCC patients with favorable- or intermediate-risk features (29). On the other hand, mammalian Target of Rapamycine-mTOR inhibitors, such as temsirolimus, are recommended as a preferential treatment selection for RCC patients with poor-risk features (30). To identify patients who would benefit from targeted treatment, more predictive and prognostic markers are needed. In a retrospective study by Heng et al. on the prognostic factors for OS in patients receiving Vascular Endothelial Growth Factor (VEGF)-targeted agents, the authors planned and inwardly validated a model that boosts the Motzer system and employs 4 of the 5 Motzer criteria (corrected calcium, Karnofsky PS, hemoglobin and time from diagnosis to treatment) in addition to neutrophil and platelet counts (31). Patil et al. prospectively studied patients treated with first-line sunitinib or interferon alfa in a phase III clinical trial. For sunitinib, a multivariate analysis of PFS determined five independent predictors: serum Lactate Dehydrogenase (LDH), presence of 2 or more metastatic sites, no prior nephrectomy, Eastern Cooperative Oncology Group (ECOG) PS, and baseline platelet count. Moreover, a multivariate analysis of OS determined corrected serum calcium, serum LDH, time from diagnosis to treatment, ECOG PS, hemoglobin and presence of bone metastasis as predictors (32). In our study, laboratory parameters (anemia, hypercalcemia, and high LDH) and histopathologic data were not associated with adverse outcomes.
Motzer et al. (number of reference) assessed 463 patients with advanced RCC who were administered interferon-α as first-line systemic therapy. In their study, according to the MSKCC risk scoring system, 18% of the patients were classed as favorable-risk, 62% as intermediate-risk, and 20% as poor-risk. This work also shows, median survival times of 29.6, 13.8, and 4.9 months for the favorable-, intermediate-, and poor-risk groups, respectively. Mekhail et al. reported that according to the MSKCC risk scoring system, 19% of patients were favorable-risk, 70% were intermediate-risk,
and 11% were poor-risk in 353 previously-untreated metastatic RCC patients and the median survival times were 28.6, 14.6, and 4.5 months for the favorable-, intermediate-, and poor-risk groups, respectively (34). These results were obtained from patients who received a variety of single-agents and combination therapies; however, the majority of patients (77%) were treated with immunotherapy-alone, primarily with IL-2– or IFN-α–based regimens (56%). In the current study, 49% of the patients were classified as favorable-risk, 39%, as intermediate-risk, and 12% as poor-risk; median PFS stratified by MSKCC risk status was 15, 10 and 3 months for favorable-, intermediate- and poor-risk patients respectively ($p=0.008$). Median OS was 35, 19 and 16 months for favorable-, intermediate-, and poor-risk patients respectively ($p=0.011$). These results differ from those of other studies (34, 35) possibly due to the different number of participating patients in the MSKCC-risk groups and the variety of treatment agents employed.

The median PFS was 15, 16, and 3 months for the sunitinib, sorafenib, and IFN treatment groups respectively ($p<0.001$). From the time of disease recurrence, the median OS was 36.0 months in the late-recurrence groups, and 19 months for the early-recurrence group ($p=0.01$). Median PFS was 6 months in the early recurrence group, and 18 months for the late recurrence groups ($p<0.001$). This is the first study to compare late with early recurrence of disease in terms of response to treatment. Late recurrence of disease may be associated with less than aggressive tumour biology, tumor burden and indolent tumor biology similar to the MSKCC risk score and may account for the better response to treatment exhibited by patients with late recurrence.

As a result, early recurrence was significantly associated with Fuhrman grade 3-4, tumor necrosis, lymphovascular invasion and MSKCC poor-risk group compared to patients with late recurrence. In addition, the study demonstrated a potential prognostic value of late recurrence in terms of PFS and OS.

References


