Using Percentage of Sarcomatoid Differentiation as a Prognostic Factor in Renal Cell Carcinoma

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Abstract

Sarcomatoid histology in renal cell carcinoma (sRCC) is an indicator of poor prognosis. We conducted a single-institution retrospective review of sRCC cases and identified that the presence of 25% sarcomatoid change or more in the primary tumor of patients with nonmetastatic renal cell carcinoma is an independent predictor of poor overall survival. Patients with these features require vigilant follow-up.

Background: The objective of this study was to determine if the percentage of sarcomatoid differentiation (%Sarc) in renal cell carcinoma (RCC) can be used for prognostic risk stratification, because sarcomatoid RCC (sRCC) is an aggressive variant of kidney cancer. **Patients and Methods:** We performed a retrospective analysis of patients who underwent surgery for RCC at our institution between 1999 and 2012. Pathology slides for all sRCC cases were reexamined by a single pathologist and %Sarc was calculated. %Sarc was analyzed as a continuous variable and as a categorical variable at cut points of 5%, 10%, and 25%. Potential prognostic factors associated with overall survival (OS) were determined using the Cox regression model. OS curves were generated using Kaplan–Meier methods and survival differences compared using the log-rank test. **Results:** One thousand three hundred seven consecutive cases of RCC were identified, of which 59 patients had sRCC (4.5%). As a continuous variable %Sarc was inversely associated with OS ($P = .023$). Predictors of survival on multivariable analysis included pathologic (p) T status, tumor size, clinical (c) M status and %Sarc at the 25% level. OS was most dependent on the presence of metastatic disease (4 months vs. 21.2 months; $P = .001$). In cM0 patients with locally advanced ($\geq$ pT3) tumors, OS was significantly diminished in patients with $>$ 25 %Sarc ($P = .045$). However, %Sarc did not influence OS in patients with cM1 disease. **Conclusion:** Patients with sRCC have a poor overall outcome as evidenced by high rates of recurrence and death, indicating the need for more effective systemic therapies. In nonmetastatic patients, the incorporation of %Sarc in predictive nomograms might further improve risk stratification.

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Introduction

The presence of sarcomatoid differentiation in renal cell carcinoma (RCC) is associated with more aggressive tumor biology, higher rates of tumor recurrence, and poor survival.[1-5] Furthermore, sarcomatoid RCC (sRCC) demonstrates diminished efficacy to targeted therapy regimens or more traditional immunomodulators.[6-8] Several groups have attempted to clarify the specific effect of sRCC with regard to prognosis and to determine if patients with sRCC require different management strategies.[5,6,9] Although it is possible that a greater percentage of sarcomatoid differentiation (%Sarc) within the primary tumor could be associated with worse outcomes, specific risk categories have not been described, and no clinical algorithm, nomogram or published risk criteria incorporates a sarcomatoid element.[10-14] We report our single-institution experience with sRCC with the primary aim to determine whether quantifying the %Sarc affects clinical outcomes in patients with metastatic and nonmetastatic sRCC.

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Patients and Methods

With institutional review board approval, we retrospectively identified all patients who had undergone surgical excision of a renal mass from January 1999 to July 2012. Patients with a diagnosis of sRCC, spindled RCC, or RCC with spindle cells were further selected for analysis and pathologic review. Available slides from these cases were reexamined by a single expert genitourinary pathologist to confirm the presence of sarcomatoid elements, provide the %Sarc, estimate the percentage of tumor necrosis, determine the presence of lymphovascular invasion (LVI) and to identify the RCC subtype. All RCCs were classified according to the 2004 World Health Organization system.[15] Tumors with the following pathologic characteristics were considered unclassified RCC with sarcomatoid change after immunohistochemical confirmation: the epithelial component did not fit into a specific histologic category, there were apparent composites of recognized histologic subtypes present, or most if not the entire tumor was composed of sarcomatoid histology with no morphologically recognizable epithelial component. Additional pathologic data included pathologic T status (pT), tumor grade, surgical margin status, the presence of perineural invasion, tumor size, and pathologic lymph node status (pN; when a lymph node dissection was performed). Tumor staging was reported according to the seventh edition American Joint Committee on Cancer Staging Manual.[16] %Sarc was estimated by reviewing all of the tumor sections microscopically, then giving an approximate percentage of area of the sarcomatoid change present within the entire tumor. Patients with clinical or pathologic regional lymph node-positive disease were not considered to have distant metastases.

Overall survival (OS) was calculated from the date of surgery to date of last contact or date of death. OS was our primary end point as opposed to cancer-specific survival because most patients died of RCC, and we were unable to verify the cause of death in few cases. Follow-up data were available through our institution's tumor registry, which tracks patients' death certificates and follow-up at other medical facilities. Because our institution is a tertiary referral center, it is common for patients to continue surveillance or treatment locally after having surgery at our center.

Statistical Analysis

For evaluating the association between %Sarc and OS, %Sarc was analyzed as a continuous variable and then as a binary variable using cut points of 5%, 10%, and 25% based on the distribution of our cohort, which was approximately symmetrically distributed around the 25% point. Moreover, previous studies have demonstrated potential prognostic utility for sarcomatous differentiation in the 20% to 30% range.[6,17] We additionally selected 5% and 10% values for comparison and to ensure that we identified the lowest % Sarc cutoff value that might influence survival. Patient demographic and clinical characteristics were summarized using descriptive statistics stratifying patients into 2 subgroups based on the %Sarc in the specimen. Differences between subgroups were compared using the t test for continuous variables and Fisher exact test for categorical variables. Potential prognostic factors associated with OS were evaluated using the Cox regression model. Univariate and multivariate models were conducted. Potential prognostic factors with a P value of $< .1$ in the univariate model were included in the multivariate model. In addition, we evaluated the effect of %Sarc on OS in the subgroups of interest. Survival curves were generated using the Kaplan–Meier method, and survival differences were compared using the log-rank test.

Results

From January 1999 to July 2012, a total of 1608 patients underwent partial or radical nephrectomy for a renal mass. Of those, 1307 patients were diagnosed with RCC, of whom 66 were initially reported to have tumors with some sarcomatous or spindle cell histology. After pathologic review, 7 cases were reclassified as having no sarcomatous change (4 initially diagnosed with spindle-cell histology and 3 with sRCC) leaving 59 (4.5%) patients confirmed with sRCC. Four patients were excluded from statistical analysis because of absent clinical data.

Fifty-five patients were included in our final study cohort (Table 1). There were 42 men and 13 women with a mean age of 61 years. Surgical procedures consisted of open (n = 35) or laparoscopic (n = 18) radical nephrectomy and open partial nephrectomy (n = 2). Median tumor diameter was 9.3 cm and 47 patients had an element of tumor necrosis (85.5%). Histologic subtypes included clear cell, papillary, chromophobe, and unclassified. Clear-cell histology was the most predominant (41 patients [74.5%]). LVI was present in 13 (24%) tumors, but could not be determined in 2 patients. In one of these patients, tumor size was also unknown. We elected to maintain these patients in our cohort because of the isolated nature of the missing data. Thirty-six (66%) tumors were locally advanced, $\geq$ pT3. Fifty-three percent of patients presented with clinical metastatic disease (cM1). %Sarc ranged from $<$ 5% to 75%. There were 35 patients (64%) with a %Sarc of $\leq$ 25%, 9 patients (16%) with %Sarc in the range of 26% to 50%, and 11 patients (20%) with a %Sarc of 51% to 75%.

The mean length of follow-up was 21.5 months (range, 0.4-101 months). Two patients were excluded from survival analyses, 1 because of a perioperative death from a pulmonary embolus secondary to an inferior vena cava tumor thrombus and in the second patient clinical status was unknown. A total of 31 (58%) patients died, 25 confirmed because of disease. The median OS for all patients was 8.67 months from the date of surgery. In cM1 patients, median OS was only 4 months compared with 21.2 months for cM0 (P = .001). Nine of 26 cM0 patients (34.6%) experienced disease recurrence at a median of 6.0 months (range, 2.1-23.5 months). The sites of recurrence in the cM0 patients included lung (n = 4), retroperitoneal lymph nodes (n = 2), bone (n = 1), liver (n = 1), and ipsilateral adrenal gland (n = 1). Overall, 22 patients were alive at last follow-up (median 49.5 months), including 5 patients with disease (median, 17.6 months), and 17 patients without evidence of disease (median, 54.2 months). Only 3 cM0 patients received adjuvant therapy (sorafenib or sunitinib) as part of a clinical trial. We were unable to accurately verify the extent and the types of postoperative systemic therapy administration because most patients who experienced disease progression or tumor recurrence were managed by their local medical oncologists.

In univariate analysis, predictors of OS included pT and pN stage, cM status, tumor size, and %Sarc. Tumor necrosis and LVI were not predictors of survival in this analysis. The variables found to be significant were further analyzed in a multivariable model. Although pathologic nodal stage was significant in univariate