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Papillary type 2 versus clear cell renal cell carcinoma: Survival outcomes

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Abstract

Aim: To compare the cancer specific survival (CSS) between p2-RCC and a Propensity Score Matched (PSM) cohort of cc-RCC patients.
Methods: Fifty-five (4.6%) patients with p2-RCC and 920 cc-RCC patients were identified within a prospectively maintained institutional dataset of 1205 histologically proved RCC patients treated with either RN or PN. Univariable and multivariable Cox regression analyses were used to identify predictors of CSS after surgical treatment.

A 1:2 PSM analysis based on independent predictors of oncologic outcomes was employed and CSS was compared between PSM selected cc-RCC patients using Kaplan–Meier and Cox regression analysis.
Results: Overall, 55 (4.6%) p2-RCC and 920 (76.3%) cc-RCC patients were selected from the database; p2-RCC were significantly larger ($p = 0.001$), more frequently locally advanced ($p < 0.001$) and node positive ($p < 0.001$) and had significantly higher Fuhrman grade ($p < 0.001$) than cc-RCC.

On multivariable Cox regression analysis age ($p = 0.025$), histologic subtype ($p = 0.029$), pN stage ($p = 0.006$), size, pT stage, cM stage, sarcomatoid features and Fuhrman grade (all $p < 0.001$) were independent predictors of CSS.

After applying the PSM, 82 cc-RCC selected cases were comparable to 41 p2-RCC for age ($p = 0.81$), tumor size ($p = 0.39$), pT ($p = 1.00$) and pN ($p = 0.62$) stages, cM stage ($p = 0.71$) and Fuhrman grade ($p = 1$).

In this PSM cohort, 5 yr CSS was significantly lower in the p2-RCC (63% vs 72.4%; $p = 0.047$). At multivariable Cox analysis p2 histology was an independent predictor of CSM (HR 2.46, 95% CI 1.04–5.83; $p = 0.041$).
Conclusions: We confirmed the tendency of p2-RCC to present as locally advanced and metastatic disease more frequently than cc-RCC and demonstrated p2-RCC histology as an independent predictor of worse oncologic outcomes.

Keywords: Histologic subtypes; Papillary; Prognosis; Renal cell carcinoma

Introduction

According to the Heidelberg classification system, histological subtypes of Renal Cell Carcinoma (RCC) include clear cell (cc)-RCC, with a frequency of 70–88% in most series, papillary (p)-RCC accounting for 10–15% and chromophobe, collecting duct and unclassified RCC accounting for less than 10%.[1,2]

p-RCC is an established entity with distinct morphological, immunohistochemical and cytogenetic features: papillary type 1 (p1)-RCC is characterized by small basophilic cells covering thin papillae with a single line of uniform nuclei and small nucleoli, while the papillae, in papillary type 2 (p2)-RCC, are covered by large eosinophilic cells, with pleomorphic nuclei and prominent nucleoli.[3,4]

Compared to p1-RCC, p2-RCC tend to present more frequently as locally advanced disease and is associated

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with more aggressive clinicopathologic features and significantly worse outcome.[5–8] However, the results of multivariable analyses assessing the prognostic significance of p2 histological subtype are inconsistent.[7,8]

Several studies have uniformly supported p-RCC as a favorable prognosis histology, compared with the more common cc-RCC[9–11]; nevertheless, whether p2-RCC histology might be considered a distinct entity independently associated with worse oncologic outcomes remains to be addressed.

The aim of this study was to assess differences in the clinic-pathologic features between p2-RCC and cc-RCC and to perform a Cancer Specific Survival (CSS) analysis between these two RCC histological subtypes.

Materials and methods

Between March 2001 and September 2013 data of 1205 patients, who underwent Radical Nephrectomy (RN) or Partial Nephrectomy (PN) with either curative or cytoreductive intent for renal tumors, were prospectively collected in a single-center Institutional Review Board (IRB) approved Institutional database. Within this cohort we retrieved data of 55 (4.6%) patients with p2-RCC and 920 (76.3%) cc-RCC patients.

Tumors were classified according to the 2002 Tumor Node Metastasis (TNM) staging system. Tumor size was defined as the greatest tumor diameter in centimeters on pathologic specimens. Histologic subtypes were stratified according to the 2002 American Joint Committee on Cancer/Union Internationale Contre le Cancer (AJCC/UICC) classifications.[12]

All patients underwent a standard preoperative staging including preoperative blood tests and Computed Tomography (CT) scan of the chest, abdomen and pelvis.

Lymph-node dissection (LND) was performed only in patients with clinical suspicion of retroperitoneal nodal metastases. PN or RN were performed based on tumor stage and on surgeon preference.

Patients with clinical evidence of metastases at presentation underwent cytoreductive treatment and were referred to oncologist for adjuvant therapies. Adjuvant treatment was only administered to patients who underwent cytoreductive treatment.

RCC follow-up schedule included physical examination and routine blood work up, at 3, 6, 12, 18 and 24 months postoperatively, alternatively abdominal ultrasonography and chest X-ray or CT scan at 6-month intervals for the first 2 years and CT scan yearly thereafter.

Survival data were obtained from medical records, by treating physicians or by death certificate.

Univariable Cox regression analysis and multivariable Cox regression analyses were employed on the whole cohort to identify the independent predictors of lower CSS probabilities. Independent predictors of CSS were entered into a subsequent 1:2 propensity-score matching (PSM) analysis to assess the prognostic role of p2-RCC vs cc-RCC histology while minimizing bias of retrospective analysis of data.

The analysis was performed with tumor histology as the dependent variable, demographic data and all significant predictors of oncologic outcomes as the independent variables. The analysis was performed to provide a standardized mean difference $<10\%$ between covariates.

Kaplan–Meier method was performed to compare the CSS probabilities of the PSM cohorts. Survival rates were computed at 2, 5, and 10 yr after surgery and the log rank test applied to assess statistical significance between the two groups. Parametric continuous variables were reported as mean ± SD; non-parametric continuous variables were reported as median and IQR. Student's t test and χ^2 tests were used to compare means and proportions, respectively. All tests were two sided, and statistical significance was set at $p < 0.05$. Statistical analysis was performed using the SPSS v.21 (IBM Corp., Armonk, NY, USA) and the R statistical package (v.2.14.2).

Results

Out of 1205 histologically confirmed RCC patients, 920 were cc-RCC (76.3%), 87 cases p1-RCC (7.2%), 55 cases p2-RCC (4.6%), 14 cases mixed p-RCC (1.2%), 88 cases chromophobe RCC (7.3%), 16 cases collecting duct RCC (1.3%) and 25 cases remained unclassified (2.1%).

Demographic, clinical and pathologic data of cc-RCC and p2-RCC patients were summarized in Table 1. The two groups were comparable for age, gender, distant metastases at presentation, surgical treatment, positive surgical margins rate and presence of sarcomatoid differentiation, whereas p2-RCC were significantly larger (mean tumor size 6.7 cm vs 5.2 cm, $p = 0.001$), more frequently locally advanced (pT stage >2: 30.9% vs 23.5%, $p < 0.001$) and node positive (23.6% vs 3.2%, $p < 0.001$), with a higher rate of Fuhrman grade (FG) 3–4 (56.3% vs 40.5%, $p \leq 0.001$). Results of univariable Cox regression analysis were summarized in Table 2. At multivariable Cox regression analysis of the whole cohort, p2 histology ($p = 0.029$), age ($p = 0.025$), nodal metastasis ($p = 0.006$), size, pT stage, cM stage, sarcomatoid features and higher FG (all $p < 0.001$) were independent predictors of lower CSS probabilities (Table 2).

For the purpose of this study, in a 1:2 PSM analysis, 41 p2-RCC patients were matched with 82 cc-RCC cases. In the PSM selected cohorts, covariates did not show any significant imbalance (all $p \geq 0.22$; Table 1).

At Kaplan–Meier analysis p2-RCC cohort demonstrated significantly lower CSS probability compared with selected cc-RCC cohort (2-yr CSS 72.8% vs 81.7%, 5-yr CSS 63% vs 72.4%, 10-yr CSS 31.5 vs 72.4%; log rank p 0.047. Fig. 1). At multivariable Cox regression analysis, higher FG ($p < 0.001$), nodal metastases ($p = 0.006$) and p2-

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