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Original article

Histological subtype of renal cell carcinoma significantly affects survival in the era of partial nephrectomy

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Abstract

Objectives: To analyze whether the histological subtype of renal cell carcinoma (RCC) affects survival after surgical resection in contemporary patients, and if so, whether prognostic significance differs according to the type of surgical resection or tumor stage.

Materials and methods: From 2006 to 2014, 2,237 patients underwent surgical resection (25% radical nephrectomy and 75% partial nephrectomy [PN]) for nonmetastatic RCC at a tertiary referral center. Estimated survival function curves and Cox regression models evaluated the effect of histological subtype on recurrence-free survival (RFS) and overall survival (OS). Interaction analyses tested whether the effect of histological subtype depends on the type of surgical resection or tumor stage.

Results: Patients with RCC stage T2 or lower and those with low-grade conventional clear cell, papillary or chromophobe RCC of any stage had 5-year RFS probabilities >90%. Patients with clear cell papillary RCC stage T3 or greater had predicted 5-year RFS of 81%. However, 5-year OS probabilities were >94% for clear cell papillary RCC of any stage. High-grade conventional clear cell and papillary RCC stage T2 or lower, low-grade conventional clear cell and chromophobe RCC of any stage conferred 5-year OS probabilities of >93%. Unclassified RCC demonstrated the lowest OS probabilities at any stage.

In multivariable analyses, histological subtype affected RFS ($P < 0.0001$) and OS ($P = 0.026$) following surgical resection, with no differences in this association for radical nephrectomy vs. PN (RFS, $P = 0.2$; OS, $P = 0.4$), and across pathologic stages (RFS, $P = 0.1$; OS, $P = 0.3$). Compared with low-grade conventional clear cell RCC, chromophobe (hazard ratio [HR] = 0.72, 95% CI: 0.30–1.75) and papillary RCC (HR = 0.30, 95% CI: 0.09–0.97) conferred lower risk of recurrence. Chromophobe (HR = 0.67, 95% CI: 0.30–1.52) and clear cell papillary RCC (HR = 0.91, 95% CI: 0.12–6.78) conferred the lowest risk of all-cause mortality.

Conclusions: In the era of PN for RCC, histological subtype remained a significant predictor of survival, regardless of type of surgical resection or tumor stage.

Keywords: Renal cell carcinoma; Histological subtype; Recurrence; Survival

1. Introduction

Pathologic stage, tumor grade, and performance status are the most established prognostic factors in renal cell carcinoma (RCC) [1]. The question remains whether histological subtype influences risk of recurrence or death in cases of RCC treated with surgical resection. Although early studies evaluating the effect of histological subtype yielded conflicting results [2–6], it is usually accepted that conventional clear cell histology portends a worse prognosis [7].

In 2012, the International Society of Urological Pathology (ISUP) consensus conference proposed 5 new epithelial neoplasias: tubulocystic RCC, acquired cystic disease–associated

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RCC, clear cell papillary RCC, microphthalmia family translocation RCC, and hereditary leiomyomatosis RCC syndrome–associated tumors [8]. Furthermore, most of the previous studies addressing the effect of the histological subtype of RCC on survival outcomes included patients who underwent radical nephrectomy (RN). However, the role of kidney-sparing surgery has seen great expansion in recent years [9].

In light of these recent developments, it is not well known whether survival outcomes vary according to histological subtype in contemporary patients. A population-based study reported that histological subtype does not confer prognostic value in patients undergoing partial nephrectomy (PN) [10]. Conflicting results have suggested that histological assignment allows better prognostic stratification for advanced and high-grade tumors only [3] or, conversely, for low-stage tumors only [5]. Here, we evaluate the effect of histological subtype on survival following surgical resection of clinically localized RCC in the era of elective PN.

2. Materials and methods

2.1. Patients

After obtaining institutional review board approval, we identified 2,518 patients who underwent surgical resection of renal cortical tumors at Memorial Sloan Kettering Cancer Center (MSKCC) from 2006 to 2014. Exclusion criteria were age <18 years ($n = 1$), T0 or Tx tumors ($n = 2$), metastatic disease at diagnosis ($n = 182$), and, to reduce heterogeneity, bilateral tumors or hereditary RCC ($n = 96$), leaving 2,237 patients for final analysis. Baseline patient characteristics were abstracted from a prospectively maintained database and included age, sex, body mass index, and American Society of Anesthesiologists (ASA) score.

2.2. Pathology

Pathologic data included tumor and nodal stage according to the 2009 American Joint Committee on Cancer TNM classification, tumor size, and histological subtype. Histological subtypes according to the Heidelberg classification included conventional clear cell carcinoma, chromophobe carcinoma, papillary carcinoma, and unclassified RCC [11]. Conventional clear cell carcinoma was stratified into low-grade (grades: 1–2) conventional clear cell carcinoma and high-grade (grades: 3–4) conventional clear cell carcinoma to take into account the prognostic value of tumor grade. Tumor grade was not incorporated into analyses of non–conventional clear cell RCC because it is not routinely assigned for these tumors at our institution [4]. In addition, clear cell papillary carcinoma, the most common of the newly recognized histological subtype [8], was added as a prognostic category. The rarer RCC variants had too few cases to be analyzed separately and were therefore reported together as "other histology"; these included collecting duct, medullary, mucinous tubular and spindle cell, tubulocystic, acquired cystic disease-associated, and microphthalmia family translocation. We chose not to differentiate between papillary RCC type 1 and type 2 in the analyses because the distinction was not available for all patients. Furthermore, the clinical significance of subtyping papillary RCC has been questioned recently [12].

2.3. Outcome measures

Patients were typically followed every 6 months for 3 years and annually thereafter. Surveillance included patient history, physical examination, comprehensive metabolic panel, abdominal computed tomography or ultrasound, and chest radiography. Recurrence information was based on clinical and radiologic findings and categorized as the first evidence of local recurrence or distant relapse. New tumors on the contralateral side were not considered recurrences. Death was documented according to medical records or death certificates. For patients who were followed up outside our institution, there was regular correspondence with their physician to ensure that recurrences and deaths were recorded. In cases where 14 months passed without a report from the physician, we wrote to the patient to request information (reply rate approximately 40%).

2.4. Statistical analyses

The Chi-square test and Mann-Whitney U test were used to compare baseline variables between RN and PN patients. Estimated survival function curves were created, stratified by histological subtype and adjusted for age, sex, type of surgical resection, pathologic stage, nodal stage, tumor size, and, for the outcome of overall survival (OS), ASA score. We then aimed to determine whether histological subtype was predictive of recurrence-free survival (RFS) or OS after surgical resection, and whether its predictive value differed between patients who had undergone RN vs. PN, or based on pathologic stage. To this end, we used Cox regression models adjusting for age, sex, type of surgical resection, pathologic stage (T1/T2 or T3/T4), nodal stage (N0/Nx or N+), tumor size (cm), and histological subtype (low-grade conventional clear cell, high-grade conventional clear cell, chromophobe, papillary, clear cell papillary, or unclassified). Of the 2,237 patients, 39 (1.7%) with rare variants that were classified as "other histology" were excluded from these models. As mentioned earlier, it was unclear before beginning this analysis whether histological subtype affected survival differently according to the type of surgical resection (RN vs. PN) [10] or tumor stage [3,5]. Therefore, interaction terms between either type of surgical resection and histological subtype or between pathologic stage and histological subtype were included in the Cox regression models. For OS, models were generated with the