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Histologic diversity in chromophobe renal cell carcinoma does not impact survival outcome: A comparative international multi-institutional study

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Highlights

- *Grading of chromophobe RCC is difficult.*
- *Adverse prognostic features were recently established.*
- *No prognostic data were available for rare subtypes.*
- *A multiinstitutional study showed no difference between classic and variant morphology.*

Abstract

Predicting the clinical behavior and trajectory of [chromophobe renal cell carcinoma](#) (ChRCC) by histologic features has so far proven to be challenging. It is known that ChRCC represents a heterogeneous group of neoplasms demonstrating variable, yet distinctive morphologic and genetic profiles. In this international multi-institutional study, we aimed to assess the impact of histologic diversity in ChRCC (classic/eosinophilic versus rare subtypes) on survival outcome.

This is an international multi-institutional matched case-control study including 14 institutions, examining the impact of histologic subtypes of ChRCC on survival outcome. The study group (cases) included 89 rare subtypes of ChRCC. The control group consisted of 70 cases of ChRCC including classic and [eosinophilic](#) features, age- and tumor size-matched.

Most of the rare subtypes were adenomatoid cystic/pigmented ChRCC (66/89, 74.2%), followed by multicystic ChRCC (10/89, 11.2%), and papillary ChRCC (9/89, 10.1%). In the control group, there were 62 (88.6%) classic and 8 (11.4%) [eosinophilic](#) ChRCC. There were no statistically significant differences between the study and control groups for age at diagnosis, gender distribution, tumor size, presence of [tumor necrosis](#), presence of [sarcomatoid](#) differentiation, and [adverse outcomes](#). No statistically significant differences were found in clinical outcome between the rare subtypes and classic/eosinophilic groups by tumor size, necrosis, and [sarcomatoid](#) differentiation. Further, no statistically significant differences were found in clinical outcome between the two groups, stratified by tumor size, necrosis, and sarcomatoid differentiation.

Our findings corroborated previous studies that both sarcomatoid differentiation and [tumor necrosis](#) were significantly associated with poor clinical outcome in classic/eosinophilic ChRCC, and this was proven to be true for ChRCC with rare histologic subtypes as well. This study suggests that rare morphologic patterns in ChRCC without other aggressive features play no role in determining the clinical behavior of the tumor.

Introduction

Chromophobe renal cell carcinoma (ChRCC) is the third most common renal epithelial malignancy. Predicting the clinical behavior and trajectory of ChRCC by histologic features has so far proven to be challenging. It is known that the clinical significance of conventional grading systems, such as Fuhrman nuclear grade (historical system) and the World Health Organization (WHO)/International Society of Urological Pathology (ISUP) nucleolar system, could not be demonstrated for ChRCC [1]. In contrast to clear cell RCC (CCRCC) and papillary RCC (PRCC), the WHO/ISUP grading system is not applicable to ChRCC [1], [2].

Historically, evaluating risk assessment by histological grading of ChRCC has not proven successful [3], [4], [5], [6], [7]. One of the earlier studies conducted by Paner et al. [8] proposed a grading scheme, which ultimately did not meet clinical practice application. Subsequently, there was number of studies attempting to develop a grading system in which the clinical and prognostic behavior of ChRCC can accurately and reliably be predicted. For instance, a three-tiered grading system [8] was proposed, correlating geographic nuclear crowding and anaplasia with clinical outcome for patients with ChRCC. A subsequent study, however, found that this grading system did not provide additional prognostic information once tumor stage and sarcomatoid features were included [7]. Similarly, Ohashi et al. [3] were not able to validate the proposed three-tiered grading system or the four-tiered WHO/ISUP grading system for outcome determination in ChRCC. Instead, they proposed a two-tiered grading system, based on sarcomatoid features and necrosis, which was successful at the multivariate level. In another large study, a modified tumor grading scheme using mitotic index, cytologic eosinophilia, and architecture was not significantly associated with outcome [9]. Summarizing the current knowledge, it seems that histology alone is insufficient in predicting the behavior of ChRCC and that rather tumor size, small vessel invasion, sarcomatoid features, and microscopic necrosis affect clinical outcome in ChRCC [3], [4], [5], [6], [7], [9], [10]. It is important to note that the above proposed grading schemes/criteria are

not exactly grading *sensu stricto*, but rather well defined adverse morphologic parameters in predicting the behavior of ChRCC.

It is known that ChRCC represents a heterogeneous group of neoplasms demonstrating variable, yet distinctive morphologic and genetic profiles. In fact, multiple studies in the last few decades have expanded our knowledge of the wide histologic spectrum of ChRCC, including adenomatoid cystic/pigmented, multicystic, neuroendocrine, small cell-like, and papillary patterns [11], [12], [13], [14], [15], [16], [17], [18], [19], [20]. Nevertheless, the predictive value of ChRCC histological subtype on prognosis remains an open question.

In this international multi-institutional study, we aimed to assess the impact of histologic subtypes of ChRCC (classic/eosinophilic versus rare subtypes) on survival outcome. To the best of our knowledge, this is the first study to examine predictive value of histologic subtypes of ChRCC on prognosis.

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