Human Pathology (2015) **46**, 1411–1417

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Human PATHOLOGY

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Original contribution

Papillary renal cell carcinoma: correlation of tumor grade and histologic characteristics with clinical outcome☆

Kristine M. Cornejo MD[a,b,*,1], Fei Dong MD[a,b], Amy G. Zhou MD[c], Chin-Lee Wu MD, PhD[a,b], Robert H. Young MD[a,b], Kristina Braaten MD[a,b], Peter M. Sadow MD, PhD[a,b], G.P. Nielsen MD[a,b], Esther Oliva MD[a,b]

[a]*James Homer Wright Pathology Laboratories, Massachusetts General Hospital, Boston, MA 02114*
[b]*Department of Pathology, Harvard Medical School, Boston, MA 02114*
[c]*Department of Pathology, University of Massachusetts Medical School, Worcester, MA 01605*

Received 14 March 2015; revised 22 June 2015; accepted 1 July 2015

Keywords:
Papillary renal cell carcinoma;
Fuhrman grade;
International Society of Urological Pathology nucleolar grade;
Prognosis;
PRCC;
ISUP

Summary Histologic prognostic parameters in papillary renal cell carcinoma (PRCC) are unclear. The aims were to review the clinicopathological features of PRCC, including Fuhrman grade and International Society of Urological Pathology (ISUP) nucleolar grade, and to identify parameters that may be independent prognostic indicators. PRCCs in patients treated by nephrectomy were retrieved from the pathology files from 1984 to 2010. Parameters studied included tumor multifocality, size, PRCC type (1 or 2), Fuhrman grade, ISUP nucleolar grade, presence of necrosis, lymphovascular invasion, and stage at presentation. Cancer-specific survival (CSS) and overall survival (OS) were used as prognostic measures. Of 154 PRCCs, 112 (73%) were type 1, and 42 (27%), type 2. A total of 125 patients were male, and 29, female, with ages from 26 to 86 (mean, 62.7) years. Fuhrman grade was 1 in 8 (5%), 2 in 95 (62%), 3 in 49 (32%), and 4 in 2 (1%) tumors, respectively. ISUP nucleolar grade was 1 in 47 (31%), 2 in 56 (36%), 3 in 49 (32%), and 4 in 2 (1%) tumors, respectively. Mean follow-up interval was 73.9 months (0.13-222 months). ISUP nucleolar grade was a significant predictor of both CSS and OS in univariate (CSS, $P = .001$; OS, $P = .004$) and multivariate (CSS, $P = .04$; OS, $P = .008$) analyses, whereas Fuhrman grade was only predictive of CSS in univariate ($P = .001$) and multivariate ($P = .04$) analyses. Only ISUP nucleolar grade and lymphovascular invasion were independently prognostic for CSS and OS in univariate and multivariate analyses. Therefore, the ISUP nucleolar grade appears to be superior in predicting survival in patients with PRCC.

1. Introduction

Many prognostic factors have been identified for renal cell carcinoma (RCC), but few histologic features have consistently shown a significant association with outcome. In 1997, the Rochester Renal Cell Carcinoma Consensus Conference

☆ Disclosures: None to declare.

* Corresponding author at: Department of Pathology, UMass Memorial Healthcare, One Innovation Drive, Biotech 3, Worcester, MA 01605.
E-mail address: Kristine.Cornejo@umassmemorial.org (K. M. Cornejo).
[1] Present affiliation: Department of Pathology, University of Massachusetts Medical School, Worcester, MA 01605.

http://dx.doi.org/10.1016/j.humpath.2015.07.001
0046-8177/

evaluated a wide variety of parameters and found histologic grade, along with histologic type, sarcomatoid differentiation, TNM classification, gross margin involvement, and metastases to have prognostic significance [1-3]. Among various proposed grading systems for RCC, nuclear grading schemes appear to be better prognostic indicators than other grading systems that lack nuclear information [4]. In the United States, the Fuhrman system is the most widely used and accepted nuclear grading system [4,5]. It has been shown to correlate with outcome in clear cell RCC [6-8]. However, the data is limited regarding the prognostic significance of Fuhrman grading in papillary RCC (PRCC) [6,9,10]. Recently, the 3 components of the Fuhrman system were assessed independently for prognostic significance, and only nucleolar prominence was retained on multivariate analysis in PRCCs, proposing the use of nucleolar grading instead of Fuhrman grading for PRCC [11]. However, an additional study revealed the Fuhrman grade to be statistically superior to nucleolar grade [12].

Because the validity of both Fuhrman and nucleolar grading systems in PRCC has been questioned, the aim of our study was to review the clinicopathological features of PRCC, including Fuhrman and the International Society of Urological Pathology (ISUP) nucleolar grades, to determine which parameters are independent prognostic indicators in this subgroup of renal tumors.

2. Materials and methods

PRCCs from patients treated by radical or partial nephrectomy were retrieved from the surgical pathology files of the Massachusetts General Hospital from 1984 to 2010. Only tumors for which hematoxylin and eosin–stained slides were available for review were included. If concurrent types of RCC such as clear cell or chromophobe carcinoma, sarcomatoid, or rhabdoid differentiation were found, the case was excluded from the study. In addition, other types of RCC with papillary morphology such as clear cell papillary and Transcription Factor E (TFE)-related RCC were also excluded. The medical records were reviewed if available, with the approval of the institutional review board.

Pathologic parameters studied included tumor multifocality, size, PRCC type (1 or 2), Fuhrman grade, ISUP nucleolar grade, presence of necrosis, lymphovascular invasion (LVI), and pTNM stage at presentation. Cancer-specific survival (CSS) and overall survival (OS) were used to measure prognosis.

2.1. Grading methods

The Fuhrman and ISUP nucleolar grades were evaluated in the area containing the greatest degree of cytological atypia. Fuhrman grade was determined by nuclear size and shape and nucleolar prominence [5]. Grade 1 tumors had round and small nuclei (<10 μm), with smooth nuclear contours and absent or inconspicuous nucleoli. Grade 2 tumors had slightly enlarged and irregular nuclei (15 μm), with small nucleoli not easily visible at original magnification ×100, but at ×400. Grade 3 tumors showed large irregular nuclei (20 μm), with prominent nucleoli easily seen at ×100. Grade 4 tumors contained even larger nuclei (>20 μm), displaying pleomorphism, multilobation, and macronucleoli.

ISUP nucleolar grade was determined based on nucleolar prominence [10,13]. Grade 1 tumors contained absent or inconspicuous nucleoli at ×400. Grade 2 tumors displayed nucleoli easily visible at ×400. Grade 3 tumors showed nucleoli easily visible at ×100, and grade 4 tumors contained giant tumor cells with nuclear pleomorphism.

Table 1 Patient demographics and tumor characteristics

Characteristic	Cases
Patients (n)	154
Mean age (y)	62.7
Male (%)	125 (81%)
Female (%)	29 (19%)
Treatment (%)	
Radical nephrectomy	86 (56%)
Partial nephrectomy	68 (44%)
Tumor size (cm)	
Mean	5.1
Range	0.4-17.0
Fuhrman grade (%)	
Grade 1	8 (5%)
Grade 2	95 (62%)
Grade 3	49 (32%)
Grade 4	2 (1%)
ISUP nucleolar grade (%)	
Grade 1	47 (31%)
Grade 2	56 (36%)
Grade 3	49 (32%)
Grade 4	2 (1%)
pTNM classification (%)	
T1	107 (70%)
T2	14 (9%)
T3	33 (21%)
T4	0 (0%)
Nx/N0	149 (97%)
N1	5 (3%)
Mx/M0	153 (99%)
M1	1 (1%)
TNM stage (%)	
Stage I	107 (69%)
Stage II	14 (9%)
Stage III	32 (21%)
Stage IV	1 (1%)
Histologic features (%)	
Multifocality	12 (8%)
Necrosis	40 (26%)
LVI	4 (3%)

Abbreviation: LVI, lymphovascular invasion.