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ANATOMICAL PATHOLOGY

Percentage grade 4 tumour predicts outcome for clear cell renal cell carcinoma

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Summary

Heterogeneity of tumour grading is common in clear cell renal cell carcinoma (ccRCC). WHO/ISUP grading specifies that RCC should be graded based on the highest grade present in at least one high power field. This does not take into account the proportion of high grade tumour present in a cancer, which may itself influence outcome. Cases of ccRCC accessioned by Aquesta Uropathology, Brisbane, Australia, between 2008 and 2015, were reviewed and grading assigned according to WHO/ISUP criteria. For tumours classified as grade 3 (G3) and 4 (G4), the percentage of tumour showing G3 and G4 morphology was assessed for each case. Survival analysis, with time to the development of metastases as the clinical outcome, was performed for six grading subclasses (G3 <10%, G3 10–50%, G3 >50%, G4 <10%, G4 10–50%, G4 >50%). Of the 681 cases of ccRCC in the series, there were 153 cases classified as G3 (91 cases) and G4 (62 cases) for which follow-up was available. During the follow-up period of <1–89 months, 19 (20.9%) patients with G3 and 30 (48.3%) patients with G4 cancers developed metastatic disease. The three subgroups of <10%, 10–50% and >50% G3 tumour were not significant in predicting outcome (p=0.47). Separating G3 into two groups of $\leq$50% vs >50% was also not significantly associated with outcome (p=0.22). For the three subgroups of G4 ccRCC (<10%, 10–50% and >50% G4) a higher percentage of G4 correlated with time to the development of metastases (p=0.01). Even though G4 tumours as a whole had a significantly worse outcome than G3 tumours (p=0.0004), the difference between G4 <10% and G3 tumours was not significant (p=0.27). On multivariate analysis, that included pT staging category and tumour size, there was a significant difference in survival between G4<10% and G4>50% tumours (p=0.018). The results of the study suggest that for ccRCC, WHO/ISUP G4 category should incorporate the percentage of G4 tumour present.

Key words: Renal cell carcinoma; grade; World Health Organization; International Society of Urological Pathology; prognosis.

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INTRODUCTION

The grading of renal cell carcinoma (RCC) has undergone considerable evolution since the first classification of grading of renal malignancies proposed by Hand and Broders in 1932.[1] More recent classifications have focused on nuclear features, with the recently adopted World Health Organization (WHO)/International Society of Urological Pathology (ISUP) classification being based upon nucleolar size for the first 3 grades, while grade 4 tumours require the identification of extreme nuclear pleomorphism, including atypical tumour giant cells, and/or sarcomatoid/rhabdoid differentiation.[2–4] Validation studies have shown this grading system to correlate with outcome for clear cell and papillary RCC.[5–8] Clear cell RCC usually does not show uniform grade throughout the whole tumour if sampled widely and currently WHO/ISUP grading is based upon the single high power field having the highest grade within the sampled component of the tumour. This implies that the tumour clone exhibiting the highest grade has the greatest influence on outcome. This recommendation is not unusual in pathology practice, although for some malignancies the volume of the specific components of a tumour are taken into account when assigning a final grade. The most obvious example of this is Gleason scoring of prostate adenocarcinoma. In the 2005 modification of Gleason score, as well as the recently developed ISUP grading system, grading of a needle biopsy is based upon both the highest-volume and highest-grade tumour pattern.[9]

The WHO/ISUP grading system for RCC does not take into account the extent of assigned grade and the assumption is that a small focus of high grade tumour has a similar outcome to a tumour that is predominantly high grade. In an earlier study the prognostic significance of percentage of high grade carcinoma in RCC was assessed,[10] with cases divided into 0% grade 3 + grade 4 (i.e., grade 1 and 2 tumours), 1–50% grade 3 + grade 4 and 51–100% grade 3 + grade 4 tumours. A significant difference in outcome, determined as time to metastases, time to cancer specific death or last follow-up, and overall survival of time to last follow-up, was demonstrated. The authors suggested that the incorporation of percentage of high grade tumour into the reporting of RCC may lead to the stratification of patients into prognostic

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groups and promote the development of individualised follow-up schedules. This study was based upon Fuhrman grading and consisted of a variety of RCC morphotypes. Further, this study failed to take into account the behaviour of tumours according to each of the constituent grades. This would mean that a tumour with 60% high grade cancer, consisting of 90% grade 3 and 10% grade 4 would be treated as being the same as a tumour with 60% high grade cancer consisting of 10% grade 3 and 90% grade 4. While both tumours would be classified as WHO/ISUP grade 4, it is uncertain if the higher proportion of grade 4 cancer in a tumour would influence the outcome.

This present study was undertaken to determine if the quantitation of WHO/ISUP grade 3 and/or grade 4 is of prognostic significance, utilising an extensively sampled and well-characterised series of clear cell RCC.

MATERIALS AND METHODS

Cases of clear cell RCC accessioned by Aquesta Specialised Uropathology between the inclusive years 2008 and 2015 were retrieved from file. Tumours from those patients who had been treated surgically with curative intent, by partial or radical nephrectomy, were identified and sections from these cases were independently reviewed by two urological pathologists (HS and JD) in order to confirm the diagnosis and assure adequacy of tumour sampling. All tumours had been liberally sampled, with small tumours being sampled in entirety or a minimum of 15 sections taken, whatever was the greater. For larger tumours the number of sections of tumour taken ranged from 15 to 28 per case.

Specimen handling and reporting, as a minimum, satisfied the published guidelines of the Royal College of Pathologists of Australasia (RCPA),[11] the ISUP Vancouver Consensus Conference on Renal Neoplasia[12] and the International Collaboration on Cancer Reporting (ICCR),[13] with respect to sampling of the renal sinus, renal vasculature and perinephric fat. Tumours were graded according to the criteria of the WHO/ISUP grading system[4] and those tumours containing components of grade 3 or grade 4 carcinomas were selected for further study. The proportion of the highest grade component (grade 3 or 4) present was assessed subjectively, with cases divided into three groups representing the percentage of either grade 3 or grade 4 in all sections, i.e., <10%, 10–50% and >50% of total tumour. pT staging category was assigned according to the recommendations of the American Joint Committee on Cancer TNM Staging (8th edition).[14] Clinical findings and follow-up data were provided by the attending clinician, with follow-up ranging from <1 to 89 months (mean 34 months) and the development of metastatic disease being taken as the clinical endpoint.

Survival curves were estimated by the Kaplan–Meier product limit method and where appropriate, subgroup differences in survivor functions were assessed using the log rank test. Multivariate analyses were undertaken utilising multivariate Cox proportional hazards models.

Approval for this study was obtained from the Aquesta Pathology Ethics Committee (Ethics approval number 2016/06).

RESULTS

During the study period 681 cases of clear cell RCC were accessioned by Aquesta Specialised Uropathology. Of these, follow-up was available for 376 cases with 153 cancers containing foci of tumour that satisfied grade 3 or grade 4 criteria of the WHO/ISUP grading system for RCC. The patient population was predominantly male (73%) with a mean age at diagnosis of 63 years. The mean tumour diameter of all cases was 6.3 cm (range 1.2–16.0 cm). Tumours were localised to the kidney in 57 cases (pT1 56 cases, pT2 1 case), 92 cases showed regional spread (pT3) while four cases were pT4. On formal grading of tumours, 91 were WHO/ISUP grade 3 and 62 were WHO/ISUP grade 4. Follow-up data were available for all 153 patients and the clinical and pathological characteristics of the cases, divided according to the percentage of grade 3 or grade 4 tumour present, are shown in Table 1.

During the follow-up period 19 of 91 (20.9%) patients with grade 3 cancers developed metastatic disease, while 30 of 62 (48.3%) patients with grade 4 cancers had metastases at the time of diagnosis or at follow-up. For patients with grade 3 tumours, metastases were seen in two cases with <10%, seven with 10–50% and 10 with >50% grade 3 tumour. On univariate analysis the division of cases according to percentage of grade 3 tumour showed no significant association with outcome (p=0.47). Similarly, division of cases according to ≤50% and >50% grade 3 components showed no significant association with outcome (p=0.22).

For patients having a WHO/ISUP grade 4 component to their tumour, with division of cases according to percentage of grade 4, metastases were seen in eight cases with <10%, 11 cases with 10–50% and 11 cases with >50% grade 4 component. The time to the development of metastases differed significantly between these groups (p=0.01) (Fig. 1). Simple Cox regression of tumours with a grade 4 component showed pT staging category and tumour size to also be statistically significant predictors of outcome in this series (p=0.0001 and p=0.003, respectively).

While tumours with a grade 4 component had a worse outcome than grade 3 tumours (p=0.0004) (Fig. 2), the gap between the Kaplan–Meier curves of patients with tumours having >50% grade 3 component and <10% grade 4 component was not significantly different (p=0.75). Although patients with <10% grade 4 component appeared to have a slightly worse outcome than those with grade 3 tumours as a whole, the difference did not reach statistical significance (p=0.27).

On multivariate analysis the outcome between <10% grade 4 tumours, when compared to tumours with 10–50% grade 4 was not significant (p=0.636), and tumours with 10–50% grade 4 just failed to achieve a significant difference in outcome when compared to tumours with a >50% grade 4 component (p=0.051). Conversely, the difference in outcome between tumours with <10% and >50% grade 4 component, along with tumour size, were significantly associated with time to the development of metastases (p=0.018 and p=0.006, respectively).

Table 1 Clinical and pathological parameters for clear cell renal cell carcinomas in the study

	WHO/ISUP Grade	
	Grade 3 (n=91)	Grade 4 (n=62)
Mean age, years	63.8	61.8
Tumour size, cm	5.5	7.6
Gender		
Male	68	43
Female	23	19
pT category		
pT1	42	14
pT2	1	0
pT3	48	44
pT4	0	4
% grade		
<10%	13	25
10–50%	42	22
>50%	36	15