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Comparison of Grading Systems for Estimating the Prognosis of Renal Cell Carcinoma

A. USUBÜTÜN,* M. C. UYGUR,** A. AYHAN,* C. TOKLU,** A. ŞAHIN,** H. ÖZEN,** S. RUACAN*

Departments of *Pathology and **Urology, Hacettepe University, School of Medicine, Ankara, Turkey

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In this study histologic slides of 165 patients who were diagnosed as RCC between 1983 and 1993 were re-evaluated and each tumour was graded according to Thoenes, Fuhrman, Arner and Skinner's grading systems. According to Thoenes' system, patients with grade (G) 2 and 3 tumours had significantly shorter survival compared to patients with G 1 tumours. The survival difference between the subgroups of Fuhrman and Skinner's grading systems did not reach statistical significance. When the histologic differentiation was grouped as low grade (G 1&2) and high grade (G 3&4) tumours in Fuhrman and Skinner's systems, a statistically significant difference was noted between the groups in terms of survival.

Introduction

Renal cell carcinoma is a highly unpredictable neoplasm with a tendency to recur or progress and cause death many years after initial treatment. The best available predictor of outcome is stage at presentation. However, despite careful clinical staging, approximately 30% of patients with RCC confined to the surgical specimen have disease progression following surgery. Furthermore, within the same stage there exists a significant difference in outcome. Therefore, other prognostic parameters such as grade, and the cell type of the neoplasm attracted attention to supply additional information to predict the outcome in these patients [1–5]. There are several systems of grading available for RCC such as Thoenes, Arner, Fuhrman and Skinner [3, 6–8]. Since the superiority of one to another has not been confirmed universally, these systems were used in different institutions according to the accumulated experience. In this study we compared the various grading systems and tried to clarify the prognostic significance of the tumour grade in patients with RCC.

Materials and methods

Clinical, macroscopic features and follow-ups. A total of 165 patients who underwent radical nephrectomy between 1983 and 1993 were included in this study. Formal lymphadenectomy was not performed routinely in this group. Of

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the 165 patients included in this study 113 were males and 52 were females. The age of the patients varied between 27 and 78 years (mean 55 years). Tumour diameters varied from 2 cm to 21 cm (mean 8.5 cm). The average follow-up for 165 patients was 26 months (range 1 to 156 months) and 21 patients died due to their illnesses.

Tissue specimens. We re-evaluated haematoxylin-eosin stained slides prepared from nephrectomy materials of patients who were diagnosed as RCC between 1983 and 1993 at the Departments of Pathology and Urology of Hacettepe University, Medical School. All of the tissues were fixed in 10% formalin, embedded in paraffin and stained with haematoxylin-eosin. Pathology reports and clinical files were re-evaluated for macroscopic features of the tumours and follow-ups.

Grading of the tumour. All the tumours were graded by using the Thoenes et al. [3], Arner [6], Skinner et al. [7] and Fuhrman et al. [8] grading systems. With a hope of gaining additional information about the effect of these grading systems on survival, we combined the subgroups of Fuhrman and Skinner's grading systems to create two and three subgroups as follows: patients with grade 1 and 2 tumours were grouped together as "low-grade tumours" and grade 3 and 4 as "high-grade tumours", and grade 1 as "low-grade", grade 2 and 3 as "moderate grade", and grade 4 as "high-grade" into 3 groups. Cell types of the neoplasms were classified according to the Thoenes et al. classification for RCC and Robson's system was used for staging [3, 9].

Statistical analysis. Survival curves were plotted by the Kaplan–Meier method and were compared for significance of differences among subgroups by log rank test. Relations between grade and stage of the tumours were examined by using the chi-square test.

Results

Grading. Grades of 165 RCC according to different grading systems and its relation to survival of patients are presented in Table 1. Thoenes' grading system revealed a statistically significant prognostic value for RCC ($p=0.0146$). In Thoenes' grading system patients with grade 1 tumours had survival curves significantly different from those of patients with grade 2 and 3 tumours ($p=0.0276$ and $p=0.0040$, respectively), but the difference between the patients with grade 2 and 3 was not statistically significant ($p=0.1724$) (Fig. 1). The survival of the patients was not found to be statistically different in patients with various subgroups of Fuhrman and Skinner's grading systems ($p=0.0599$ and $p=0.0635$, respectively). However, when patients were combined into two groups as "low-grade" and "high-grade" tumours, the survival curves were significantly different (Fuhrman $p=0.0147$, Skinner $p=0.0193$) (Figs 2 and 3). Only the patients with "high-grade" and "low-grade" tumours revealed different survival curves, when the patients were divided into 3 groups as "low-grade", "moderate grade" and "high-grade" tumours by both Fuhrman and Skinner grading systems.

Table 1
Survival rates of patients graded according to the Fuhrman, Skinner and Thoenes grading systems

Grade	No. of cases	No. of deaths	2-year survival (%)	p value
(Thoenes)				
Grade 1	33	0	100	0.0146
Grade 2	82	11	80	
Grade 3	50	10	66	
(Skinner)				
Grade 1	23	0	100	
Grade 2	54	6	84	>0.05
Grade 3	38	5	80	
Grade 4	50	10	66	
(Skinner)				
Grade 1 (well-differentiated)	23	0	100	
Grade 2+3 (moderately-differentiated)	92	11	83	0.0286
Grade 4 (poorly-differentiated)	50	10	66	
(Skinner)				
Grade 1+2 (well-differentiated)	77	6	89	0.0193
Grade 3+4 (poorly-differentiated)	88	15	72	
(Fuhrman)				
Grade 1	32	1	97	
Grade 2	51	5	83	>0.05
Grade 3	32	5	78	
Grade 4	50	10	66	
(Fuhrman)				
Grade 1 (well-differentiated)	32	1	97	
Grade 2+3 (moderately-differentiated)	83	10	82	0.0354
Grade 4 (poorly-differentiated)	50	10	66	
(Fuhrman)				
Grade 1+2 (well-differentiated)	83	6	89	0.0147
Grade 3+4 (poorly-differentiated)	82	15	71	

Comparison of stage, cell type and grade. It was observed that whichever grading system was used the differentiation of the cells correlated with the stage as seen in Table 2; the higher the stage, the more the undifferentiated cells ($p<0.001$). In a given stage the grade of the neoplasm did not supply any additional prognostic information, whichever system and whichever categorization was used ($p>0.05$).

Cells of sarcomatoid and mixed carcinomas were usually high grade, cells of oncocytoma were generally well or moderately differentiated and cells of chromophobe cell carcinoma were usually moderately differentiated (Table 3).

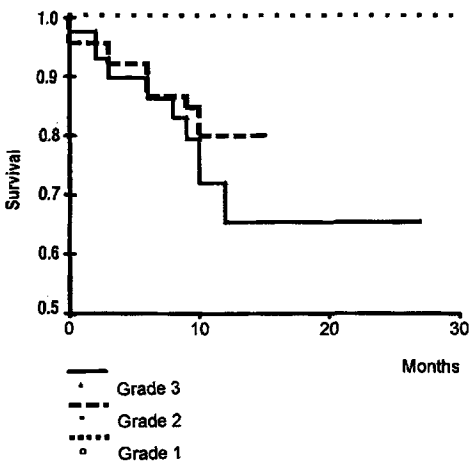

Fig. 1. Survival curves of patients graded by the Thoenes grading system (p=0.0146)

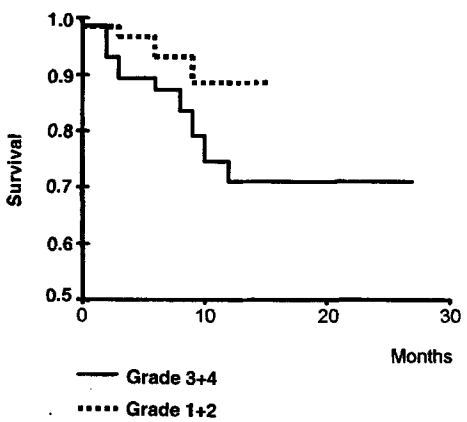

Fig. 2. Survival curves of patients graded by the Fuhrman grading system (p=0.0147)

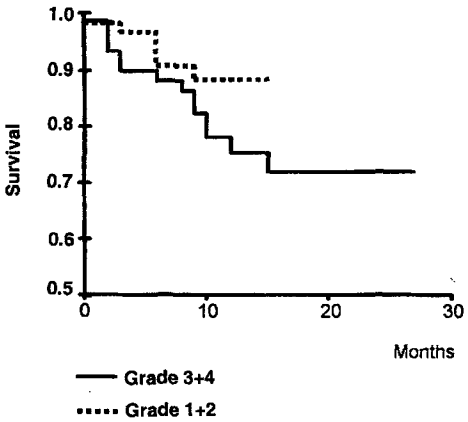

Fig. 3. Survival curves of patients graded by the Skinner grading system (p=0.0193)

Table 2
Relation of stage (Robson) and grade (Thoenes) of all RCC patients

	Grade 1	Grade 2	Grade 3	Total
Stage 1	26	49	12	87
Stage 2	3	11	6	20
Stage 3	2	8	13	23
Stage 4	2	14	19	35
Total	33	82	50	165

Table 3
Relation of cell type and grade (Thoenes) of all renal cell carcinomas

	Grade 1	Grade 2	Grade 3	Total
Clear cell	16	47	23	86
Chromophilic	12	26	12	50
Oncocytoma	3	3	–	6
Sarcomatoid	–	1	8	9
Mixed cell	1	1	6	8
Chromophobe	1	4	1	6
Total	33	82	50	165

Discussion

Studies have shown that the stage of the tumour, especially the presence of metastases, is the most important determinant of prognosis in RCC. The grade and the cell type of the tumour are other parameters that help further to predict the prognosis in RCC [5, 7, 10–14].

The grade of the neoplasm is usually higher in patients with advanced stages and lower in patients with early stages [11, 12]. Although some studies emphasized that the grade of the neoplasm may also give additional prognostic information for patients in a given stage [2, 14, 15–17], according to our results the grade of the neoplasm provides no extra prognostic value in a given stage. However, this study confirms that the grade of the neoplasm had an overall prognostic value. Although the prognostic value of the grade for RCC is widely accepted, there is no consensus for the grading system for RCC.

Arner et al. presented another grading system for RCC which contains parameters such as the extension of the tumour along with the differentiation of neoplastic tissue [6]. When grading RCC according to Arner's grading system, it is impossible to categorize some tumours because patients having high stage diseases may have well-differentiated tumours or vice versa. Accordingly, Arner's grading system was excluded from our study because it is not practical on individual patients.

In our study, all the grading systems that we compared had prognostic significance in renal cell carcinoma, although Thoenes' grading system was slightly more informative than Skinner's and Fuhrman's grading systems for predicting the prognosis. In Skinner and Fuhrman's grading systems only patients with well-differentiated tumours showed different survival curves compared to patients with poorly differentiated tumours; but patients with moderately differentiated tumours showed no statistically significant prognostic difference from others. In other words, whichever grading system was used the survival of patients was statistically different only between the highest and the lowest grades.

On the basis of our findings it is useful to group the patients in three distinct groups according to their survival as in the Thoenes study: patients with favourable prognosis, with intermediate survival, and with dismal prognosis [2, 3]. However, if the patients were to be grouped in two main categories the difference became more pronounced. In our study the Thoenes and with a modified grouping the Skinner and Fuhrman grading systems had approximately similar prognostic values for RCC. So it may be practical for the observers to use the grading system they are most familiar with, because the problem with grading of neoplasms is the difficulties of understanding and performing the strict criteria of the categories.

In conclusion, the Skinner, Fuhrman and Thoenes grading systems were found to be useful in predicting prognosis only between the lowest and the highest grades. Since all of these systems have similar pitfalls and advantages, pathologists should use the one they are familiar with, except Arner's system, until an easily applied, prognostically valuable new grading system is introduced for common use.

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