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Prognostic factors in renal cell carcinoma

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Summary. We studied 569 cases of renal cell carcinoma in the files of the Department of Pathology of the Norwegian Radium Hospital from 1964 to 1974. A nephrectomy had been perfornied in all cases. Clinical information on sex, age, survival time and metastases was traced. The histological slides were examined and tumour growth pattern, cell type, cell shape, nuclear atypia, abnormal nucleoli, nuclear grade, vascular invasion and tumour demarcation mere all evaluated.

Besides well-known prognostic factors such as tuniour stage, presence or absence of metastases and vascular invasion, nuclear grade was found to be a useful prognostic factor. Younger patients were found to do better than older, and women better than men. Smaller tumours carried a better prognosis than larger and clear cell tumours had a better prognosis than those composed of eosinophilic or basophilic cells. The presence of spindle cells was a bad prognostic omen.

Key words: Prognostic factors-Renal carcinoma

Introduction

Renal cell carcinoma usually strikes between the fourth and eighth decades of life and, in all age groups, is twice as frequent among men than women (Dayal and Kinman, 1983).

There is considerable international variation in the incidence and mortality of these tumours. The incidence ranges from 8.5% to 1.1% for males, and from 5.4% to 0.9% for females, in Sweden and Japan respectively (Dayal and Kinman, 1983). The incidence is higher in Northern Europe and North America than in the rest of the world. In addition to tobacco and phenacetin, many different carcinogens, of which nitrosamines have been the most thoroughly studied, can induce renal carcinomas. The preponderance of males might be explained by the more efficient metabolic activation of carcinogens by renal enzyme that are induced by male hormones (Outzen and Maguire, 1983).

A small minority of human renal carcinomas are familial. In a strain of rats investigated by Eker and co-workers (1981) renal adenomas and adenocarcinomas developed spontaneously, and this disposition was transferred as an autosomal dominant gene.

Renal cell carcinomas usually make themselves known because of symptoms related to the primary tumour, and about 25-30% of patients will have metastatic disease at the time of diagnosis (Skinner et al., 1971; Middleton, 1973; Tolia et al., 1975). Surgery is the treatment of choice for patients with early disease (Harris and Maguire, 1983). The size of the primary tumour, its macroscopic and microscopic relationship to surrounding tissues, vascular invasion and tumour stage are all important prognostic factors. Cell type, cell grade and the various histochemical properties of the tumour cells are considered to be of minor importance. However, the studies carried out so far are not in complete agreement with regard to the importance of the various prognostic factors. This might reflect the heterogeneity in cell types and grades seen in renal cell tumours (Droller, 1980).

In this study we have examined 569 cases of renal cell carcinoma and correlated clinical and morphological features to prognosis.

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Materials and methods

The diagnosis of renal cell carcinoma was made in 607 cases in the Department of Pathology in The Norwegian Radium Hospital, from 1964 to 1974. Of these cases, 38 were excluded from the present study because nephrectomy had not been performed. Clinical information about sex, age, date of diagnosis, survival time and metastases was traced in the remaining 569 cases with the cooperation of The Cancer Registry of Norway. The actuarial method was used to evaluate the survival rate. Observed survival, relative survival and standard deviation of the relative survival rate were estimated using the methods described by the Cancer Registry of Norway (1980). The surgical pathology reports were reviewed to determine size and extent of the primary tumour.

An average of 7.7 histological slides per tumour were examined for morphological evaluation of the tumours, tumour growth pattern, cell type, cell shape, nuclear atypia, nucleolar appearance, vascular invasion and tumour demarcation.

Size was on record in 488 cases and the tumours were divided into the following 5 groups: less than 3 cm, 3-6 cm, 6-10 cm, 10-15 cm and more than 15 cm in diameter.

The border with surrounding tissue was described as sharp (pseudocapsule), unsharp but with the tumour surrounded by renal parenchyma, and unsharp with the tumour infiltrating extrarenal tissue.

Tumour growth pattern was split into 4 basic patterns or combinations of these patterns. Solid tumours composed of uniform sheets of cells; glandular (adenomatous) tumours containing cells forming lumina or alveolar spaces; papillary tumours composed of cells lining fibrovascular stalks, and alveolar tumours containing cells forming solid alveolar structures.

The following cell types were evaluated: clear cells, eosinophilic cells, poorly differentiated eosinophilic granular cells, well differentiated eosinophilic granular cells (oncocytes) and basophilic cells. The tumours were classified according to the cell type or types present.

The shape of the tumour cells was described as polygonal, cubic, cylindric, polymorphic and spindle-shaped.

Nuclear atypia was the basis for the nuclear grading system, and grade was determined by using the following criteria: Tumours composed of cells with small nuclei resembling the normal cell nuclei were designated grade 1. Grade 2 tumours had bigger and moderately irregular nuclei and a moderate grade of hyperchromasia. Grades 3 and 4 had irregular and hyperchromatic nuclei and grade 4 tumours exhibited monstrous nuclei as well. Nucleolar evaluation was not used as a grading factor but the presence or lack of abnormal nucleoli was evaluated separately as a prognostic factor. By this system, the tumours were divided into those with abnormal nucleoli in the majority of the tumour cells and those in which they were only rarely encountered.

Results

The patients were 301 men and 268 women, all of whom had been treated by nephrectomy. The relative survival for the whole material after 1, 3, 5 and 10 years is shown in Table 1. A better overall prognosis is seen for women. Relative survival after 10 years was 36.6% for men and 46.4% for women. Fig. 1 shows the observed survival compared with expected survival.

Age

The patients' age distribution is shown in Table 2. 57.8% of the men and 65.7% of the women were between 55 and 74 years old.

The relative survival in the age group 15-54 was correlated to the age group 55-74 (Table 3). For both sexes, a slightly better outcome for the younger group was observed.

Metastases or vascular invasion or both (Table 4)

At the time of surgery, 259 men and 247 women were without observed metastases. The presence of vascular invasion meant a more severe prognosis; 27.1% of men and 24.0% of women with vascular invasion survived 10 years compared with 40.4% of men and 49.8% of women without.

The group with metastases at the time of diagnosis included 42 men (14%) and 17 women (6.3%) with a mean age for both sexes of 62.3. Because of the small number of patients, this group was not split up further. Metastases were observed in skeleton in 25%, lung in 27%, lymph nodes in 22% and other organs in 31%. The prognosis for such patients is severe: 50% die within 2 years. However, 2 patients with metastases treated by surgery, irradiation and chemotherapy were still alive after 5 years.

Size

The number of cases in each size group is shown in Fig. 2. The largest diameter of most of the tumours was between 6 and 10 cm.

Only 13 cases had a primary tumour with a diameter of 3 cm or less. Further statistical analysis of this group was not performed. Only one patient in this group died within the period, and this tumour was described as walnut-sized. The patient died 3 months later with widespread disease.

Relative survival for the other groups is plotted in Table 5. Women always had a higher relative survival than men and this was particularly noticeable when the tumours were less than 6 cm in diameter.

Tumour border

In 214 tumours, the surrounding border was sharp, and unsharp in 210 cases. In 66 cases the tumours infiltrated extrarenal tissues. Both observed and relative survival in relation to tumour border are shown in Table 6. The

Fig. 1. Survival for the whole material (301 men and 268 women).

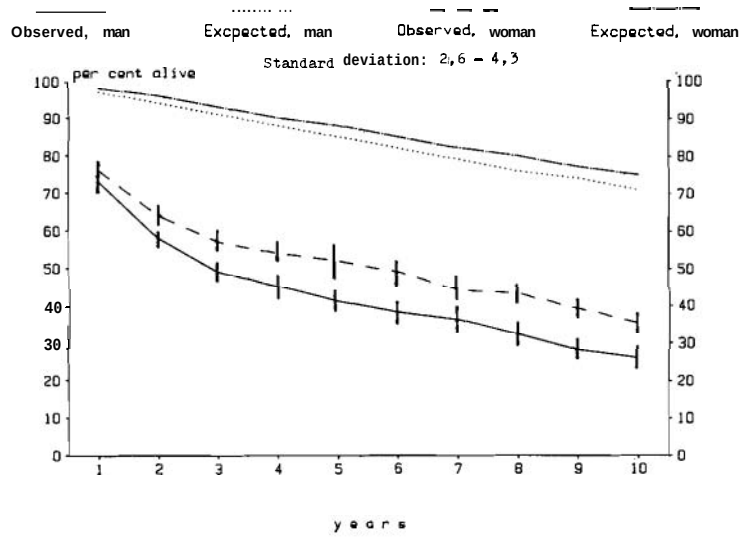

Fig. 2. Distribution of tumours in relation to size

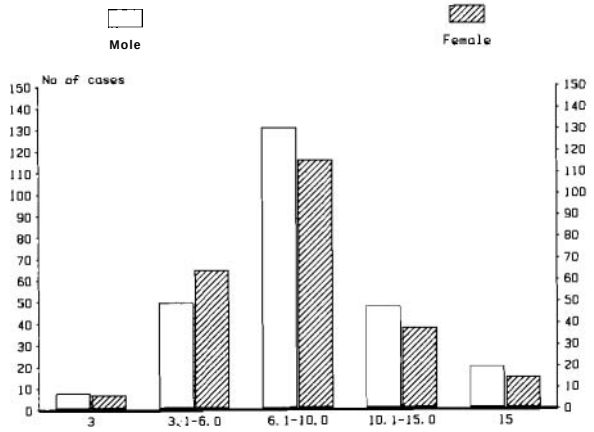

Fig. 3. Renal cell carcinoma, clear cell type. Nuclear grade 1. Haematoxylin/eosin (HE) x *350*

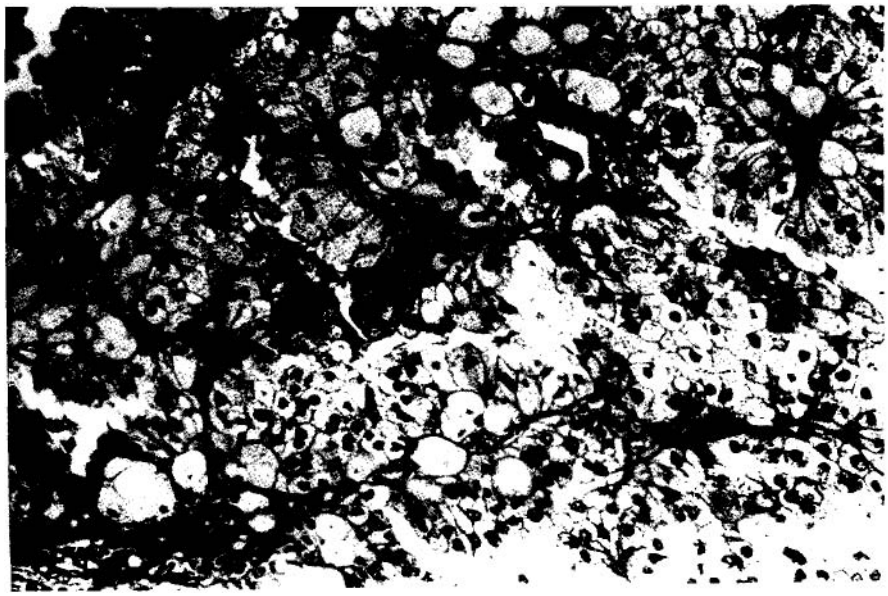

Fig. 4. Poorly differentiated eosinophilic granular cell carcinoma. Nuclear grade 3. HE x *350*

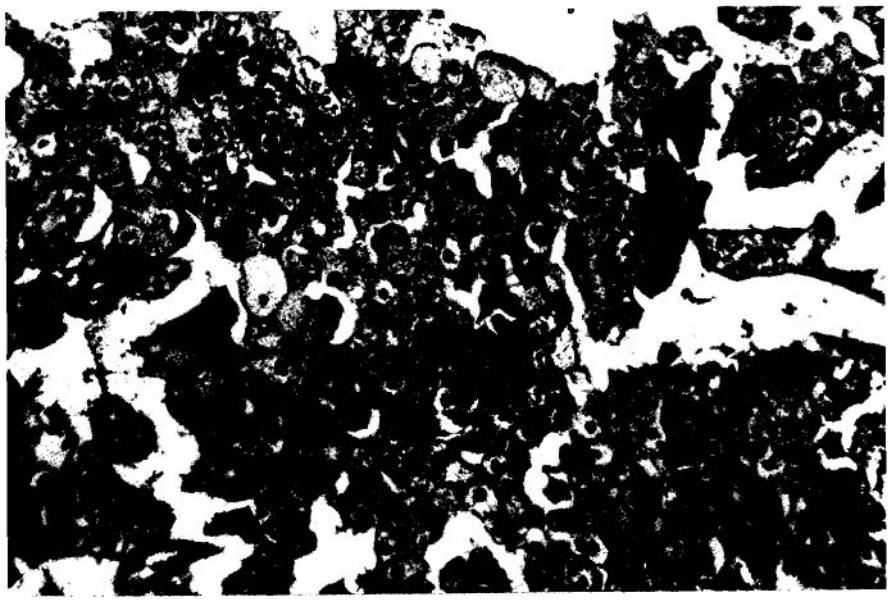

Fig. 5. Renal cell carcinoma growing in solid sheets. Nuclear grade 4. HE x *350*

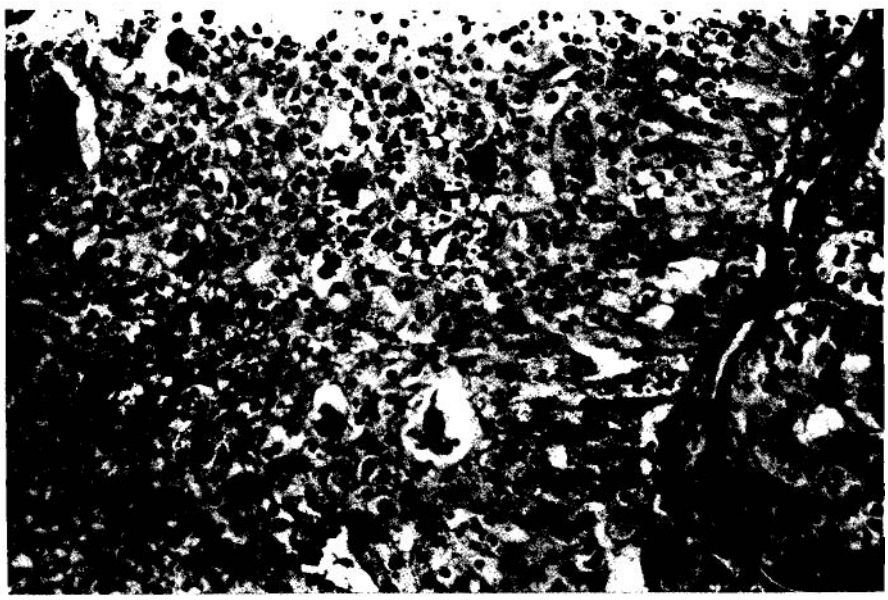

Fig. 6. Adenomatous renal cell carcinoma. Nuclear grade 2. HE x 350

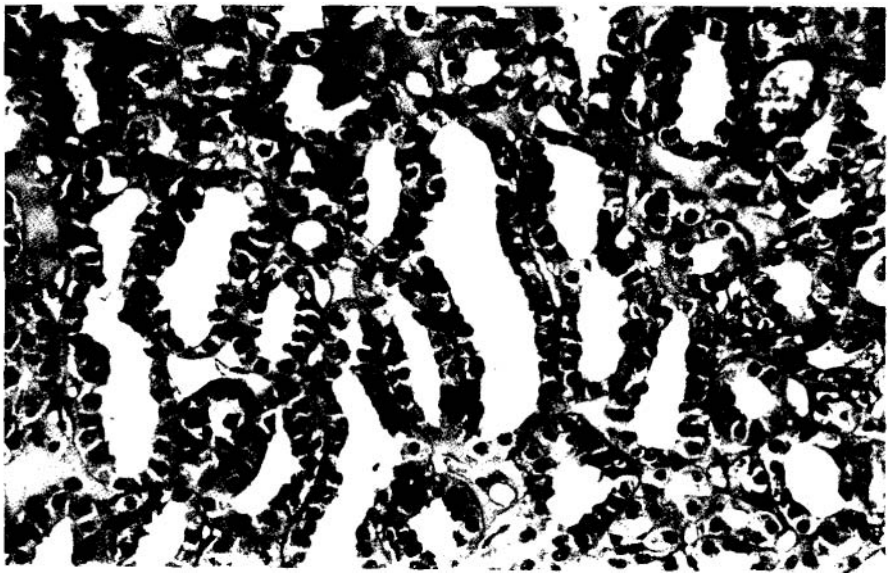

Fig. 7. Renal cell carcinoma with a solid alveolar growth pattern. Nuclear grade 1. HE x 350

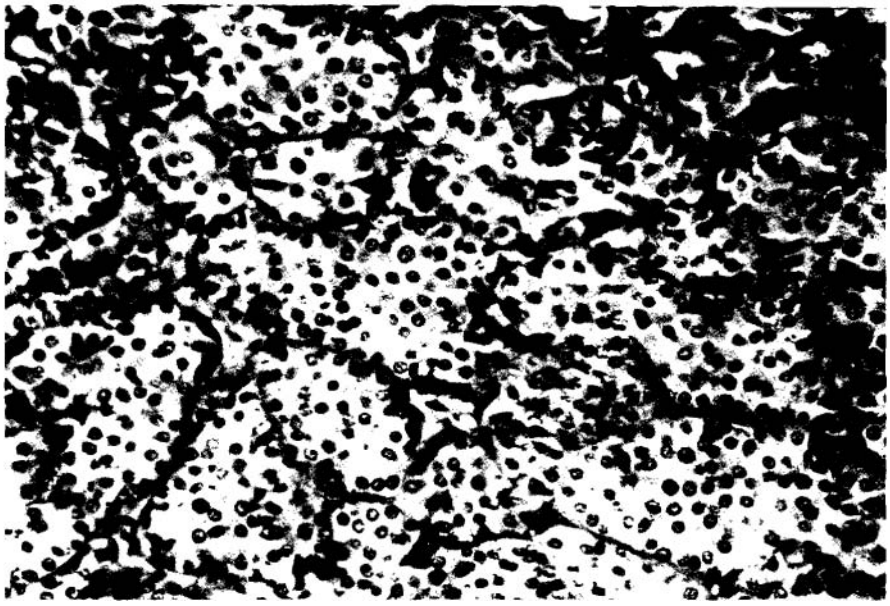

Fig. 8. Spindle-shaped renal cell carcinoma. HE x 140

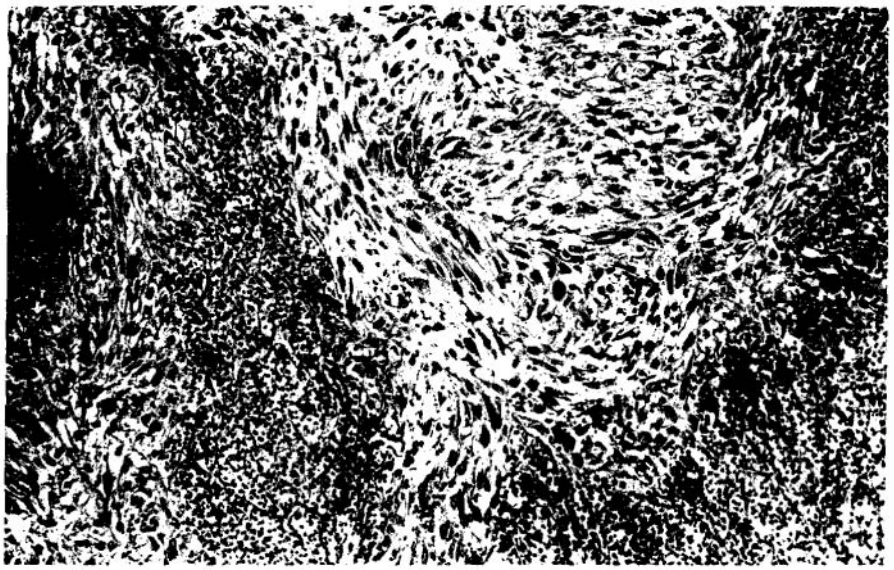

Table 1. Relative survival (Total material).

	1	3	5	10 years
Men (301 cases)	75.2	54.1	47.7	36.6
	SR 2.6	3.2	3.3	4.0
Women (268 cases)	75.6	61.4	59.7	46.4
	SR 2.7	3.3	3.5	4.5

Table 2. Age distribution

Age	Males	% of males	Females	% of females
15-54	96	31.9	53	19.8
55-74	174	57.8	176	65.7
> 75	31	10.3	39	14.5
Total	301	100%	268	100%

Table 3. Relation between age and relative survival.

Age	No.	Males 5 y.	Males 10 y	Females 5 y.	Females 10 y
15-54	96	48.2	38.8	65.2	46.7
55-74	174	46.4	31.4	57.3	46.9

Table 4. Relation between vascular invasion/metastases and survival.

	1 y. (SR)	3 y. (SR)	5 y. (SR)	10 y. (SR)
No metastases				
Men (259 cases)	78.7 (2.7)	59.1 (3.4)	52.9 (3.6)	40.9 (4.2)
Women (247 cases)	79.2 (2.7)	64.6 (3.3)	62.3 (3.6)	49.8 (4.4)
No vascular invasion				
Men (207 cases)	79.2 (3.0)	57.4 (3.7)	51.7 (3.9)	40.9 (4.5)
Women (181 cases)	84.7 (2.9)	71.5 (3.7)	69.4 (4.1)	57.5 (5.2)
Vascular invasion				
Men (93 cases)	65.7 (5.2)	45.5 (5.7)	37.4 (5.8)	27.1 (6.8)
Women (84 cases)	57.4 (5.6)	39.7 (5.7)	36.1 (5.7)	24.7 (6.4)

Table 5. Relation between tumour size and relative survival

	Males					Females				
	No (%)	1 y	3 y	5 y	10 y	No (%)	1 y	3 y	5 y	10 y
< 3 cm	7 (3.1)	Too few cases				6 (2.5%)	Too few cases			
	SR									
3.1-6 cm	49 (19.4)	84.3	58.8	48.5	25.9	64 (27.1)	80.2	71.1	70.1	59.4
		5.7	7.9	8.4	9.6		5.3	6.4	7.0	9.9
6.1-10 cm.	130 (57.4)	75.1	52.8	48.7	38.4	115 (49.7)	76.2	59.3	57.4	39.1
	SR	4.0	4.8	5.1	6.3		4.1	4.9	5.2	6.6
10.1-15 cm	47 (18.5)	74.2	53.1	38.8	32.6	37 (15.7)	71.8	54.9	51.5	41.1
	SR	6.7	7.9	8.0	8.9		7.7	8.8	9.3	10.6
> 15 cm.	19 (7.5%)	Too few cases				14 (5.9%)	Too few cases			

Table **6.** Relation between tumour border and survival

	Males						Females				
	No.		Survival 1	2	5	10 y.	No.	Survival 3	5	10 y.	
Sharp	106	Obs	87.7	69.8	65.9	41.7	108	90.7	77.8	73.0	50.1
		Rel.	90.2	76.7	74.5	58.4		92.7	83.6	82.8	65.8
Unsharp	110	Obs.	71.8	40.9	31.2	18.2	100	69.0	47.0	39.6	28.5
		Rel.	73.8	44.5	36.2	24.8		70.5	50.4	44.9	37.5
Infiltrating extrarenal tissue	39	Obs.	48.7	30.8	23.1	12.8	27	29.6	18.5	14.8	10.6
		Rel.	50.2	33.9	27.5	19.2		30.5	20.3	17.4	15.8
Total	255						235				

Table **7.** Cell type.

Cell type	No. of men	No. of women
Purely clear cells	70	82
Purely eosinophilic cells	73	62
Purely basophilic cells	7	6
Purely oncocytes	1	3
Clear/eosinophilic cells	119	97
Poorly differentiated granular eosinophilic cells	36	30
Basophilic/eosinophilic cells	34	26

Table 8. Relative survival in relation to cell type

Cell type		1 y (SR)	3 y (SR)	5 y (SR)	10 y (SR)
Clearleosinophilic	Men	80.3 (3.9)	58.7 (5.0)	49.7 (5.3)	39.1 (6.1)
	Women	71.7 (4.8)	59.9 (5.4)	61.0 (5.8)	38.2 (7.7)
Basophilic/ eosinophilic	Men	57.5 (8.8)	35.6 (8.8)	30.8 (9.0)	29.7 (11.2)
	Women	66.7 (9.5)	53.2 (10.4)	46.9 (10.8)	44.4 (13.1)
Clear	Men	82.0 (4.9)	66.6 (6.3)	58.5 (6.9)	47.5 (8.9)
	Women	84.6 (4.2)	69.0 (5.6)	67.0 (6.1)	62.9 (7.7)
Eosinophilic	Men	66.2 (5.2)	47.8 (6.3)	42.6 (6.6)	27.9 (8.4)
	Women	78.0 (5.6)	65.2 (6.8)	59.8 (7.4)	36.9 (10.5)
Poorly differentiated granular eosinophilic cells	Men	65.8 (8.2)	51.9 (9.1)	39.4 (9.3)	26.9 (10.0)
	Women	71.1 (8.5)	56.0 (9.6)	51.1 (10.0)	26.0 (10.4)
Oncocytes		Too few cases			

Table **9.** Tumour growth pattern.

	No. of men	%	No. of women	%	Total	%
Adenomatous	174	57.8	123	45.9	297	52.3
Solid alveolar	164	54.5	163	60.8	327	57.5
Solid sheets	239	79.4	215	80.2	454	79.8
Solid alveolarlsheets	133	44.2	128	47.8	261	45.9
Adenomatouslsolid alveolar	93	30.9	73	27.2	166	29.2
Adenomatouslsolid alveolarlsheets	72	23.9	50	18.7	92	16.2
Adenomatous/papillomatous	49	16.3	29	10.8	78	13.7
Purely adenomatous	43	14.3	29	10.8	72	12.7
Purely adenomatous/papillomatous	38	12.6	21	7.8	59	10.4
Purely solid sheets	55	18.5	54	20.1	109	19.2
Purely solid alveolar	10	3.3	12	4.5	22	3.9

Table **10.** Relative survival in relation to tumour growth pattern

	Males						Females					
	No.	%	1 y.	3 y.	5 y.	10 y.	No.	%	1 y.	3 y.	5 y.	10 y.
Solid sheets	239	79.4	73.2	50.0	42.3	29.6	215	80.2	72.7	59.3	56.2	41.2
		SR	3	3.5	3.7	4.2			3.2	3.6	3.9	4.8
Solid alveolar	164	54.5	83.5	64.3	55.5	40.6	163	60.8	78.5	62.9	60.8	49.1
		SR	3.1	4.3	4.6	5.8			3.4	4.2	4.5	5.9
Adenomatous	174	57.8	76.8	55.2	48.7	39.5	123	45.9	78.8	64.9	61.6	48.2
		SR	3.4	4.0	4.4	5.2			3.9	4.7	5	6.7
Solid alveolar/sheets	133	44.2	84.6	63.1	53.2	36	128	47.8	76	62.4	58.9	46.1
		SR	3.4	4.7	5.2	6.2			4	4.7	5.1	6.5
Adenomatous/solid alveolar	93	30.9	81.8	61	52.3	40.6	73	27.2	79.5	64	62.3	48.7
		SR	4.3	5.6	6	7.4			4.9	6.1	6.5	8.4
Adenomatous/solid alveolar/sheets	72	23.9	82.9	59.4	49	36.1	50	18.7	75.5	64	60.4	42.8
		SR	4.8	6.4	6.8	8.2			6.3	7.4	7.9	9.9
Adenomatous/solid papillomatous	49	16.3	65.3	45.1	38.5	34.2	29	10.8	70.8	63.8	55.8	38.5
		SR	7.1	7.8	8	9.2			8.8	9.9	10.8	16.6
Purely solid sheets	55	18.5	55.9	31.4	28.7	23.1	54	20.1	64.2	51.3	51.8	36
		SR	6.9	6.6	6.8	7.6			6.7	7.2	7.6	8.6

Table **11.** Relation between growth pattern and cell type.

Cell type	Number	Adenomatous	Solid alveolar	Solid sheets	Papillomatous
Eosinophilic	387"	228	195	318	74
		% 58.9	50.4	82.2	19.1
Clear	392"	197	280	327	25
		% 50.3	71.4	83.4	6.4
Basophilic	91"	55	38	75	20
		% 60.4	41 6	82.4	21.8
Oncocytic× •	70*	33	25	68	11
		% 47.1	35.7	97.1	15.7
Pure eosinophilic	137	75	40	98	39
		% 54.7	29.2	71.5	28.5
Pure clear	155	58	120	115	3
		% 37.4	77.4	74.2	1.9
Pure basophilic	13	9	4	8	4

* Total number of tumours with the cell type in question as the only cell type or as a component of a mixed tumour
** Solely oncocytic cells and poorly differentiated granular eosinophilic cell tumours.

Table 12. Relation between cell shape and relative survival

Cell shape	Males No.	%	1	3	5	10 y.	Females No.	%	1	3	5	10 y.
Polygonal	272*	90.4	75.3	54.4	48.4	36.8	260	97.0	75.2	60.9	58.9	46.1
	SR		2.8	3.3	3.5	4.2			2.8	3.3	3.5	4.5
Cuboidal	154*	51.2	80.1	59.5	53.5	29.1	108	40.5	79.6	62.7	60.6	44.9
	SR		3.4	4.4	4.7	5.7			4.1	5.1	5.5	7.7
Cylindric	69*	22.9	80.5	64.2	62.4	40.5	45	16.8	75.4	62.8	61.1	40.4
	SR		5.1	6.6	7.2	8.9			6.8	8.0	8.6	12.2
Polymorphic	35*	11.6	55.9	43.8	33.1	28.9	47	17.5	56.7	46.1	48.1	33.4
	SR		8.7	9.1	8.9	9.8			7.4	7.8	8.3	11.5
Spindle	36*	12.0	54.4	33.9	33.2	0	31	11.6	49.6	28.1	30.0	36.0
	SR		8.6	8.5	8.9	0			9.2	8.5	9.1	11.0
Purely polygonal	**85**	**28.2**	**76.4**	**54.4**	**49.1**	**44.5**	102	38.0	79.1	67.3	63.2	50.7
	SR		**4.9**	**6.0**	**6.4**	**8.0**			4.2	5.1	5.6	7.0

• Tumours with only the cell type in question and mixed tumours with that cell type as a component.

Table 13. Relation between cell shape and cell type.

	Number	% Polymorphic	% Poligonal	% Cuboidal	% Cylindric	% Spindle
Basophilic						
Males	51	13.7	88.2	47.0	19.6	29.4
Females	40	25.0	95.0	52.5	25.0	32.5
Clear						
Males	200	6.0	96.5	53.0	22.0	9.0
Females	189	1.1	98.9	37.0	14.8	10.0
Eosinophilic						
Males	213	14.1	94.5	54.9	24.9	13.0
Females	172	23.3	95.3	47.1	20.3	14.5
Purely clear						
Males and females	**155**	**3.2**	**96.8**	**32.9**	**12.3**	**1.9**
Purely eosinophilic						
Males and females	137	25.5	83.9	47.4	25.5	10.9

Table 14. Relation between abnormal nucleolus and relative survival.

	Males No.	1	3	5	10 y	Females No	1	3	5	10 y
Abnormal nucleolus	**122**	**65.9**	**42.3**	**37.3**	32.6	**98**	**69.9**	**50.5**	**46.3**	40.4
SR		**4.5**	**4.8**	**5.0**	5.9		**4.8**	**5.4**	**5.7**	**6.7**
No abnormal nucleolus	**176**	**82.3**	**62.6**	**55.1**	**39.7**	169	78.7	67.4	66.3	51.2
SR		**3.1**	**4.1**	**4.4**	**5.4**		3.3	4.0	4.3	5.7
Total	**298**					267				

Table 15. Relation between abnormal nucleolus, cell type and cell shape.

	Males No.	Males Abnormal Nucleolus +	Males Abnormal Nucleolus %	Females No.	Females Abnormal Nucleolus +	Females Abnormal Nucleolus %
Basophilic	51	20	39.2	40	17	43.5
Clear	200	69	34.5	189	64	33.8
Eosinophilic	213	112	52.6	172	84	48.8
Oncocytic**	37	29	78.4	33	21	63.6
Polymorphic	35	25	71.4	47	29	61.7
Poligonal	273	106	38.8	262	98	37.4
Cuboidal	185	65	41.9	108	46	42.6
Cylindric	70	32	45.7	45	22	48.9
Spindle	36	20	55.5	31	10	32.3

** Purely oncocytic and poorly differentiated granular eosinophilic cell tumours

Table **16.** Relation between nuclear grade and relative survival.

Grade	Males No.	Males 5	Males 10 y.	Females No.	Females 5	Females 10 y
1	9	All alive		8	1 dead	
2	109	62.5	49.1	102	81.5	67.7
3	100	34.5	26.7	74	40.3	30.2
4	83	35.5	22.9	84	46.1	28.8

Table **17.** Relation between tumour border and relative survival in nuclear grade 2 turnours.

	Males No	Males 5 year	Females No.	Females 5 year
Sharp	49	86.5	57	85.4
Unsharp	35	43.1	24	71.1

Table **18.** Relation between cell type and nuclear grade.

	No.	1 (%)	2 (%)	3 (%)	4 (%)
Eosinophilic	387	17 (4.4)	96 (24.8)	126 (32.6)	148 (38.7)
Clear	392	2 (0.5)	169 (43.1)	139 (35.5)	82 (20.9)
Basophilic	92	3 (3.2)	17 (18.5)	26 (28.3)	45 (50.0)
Oncocytic**	70	1 (1.4)	8 (11.4)	12 (17.2)	49 (70.0)

** Purely oncocytic and poorly differentiated granular eosinophilic cell tumours

Table **19.** Relation between cell type, nuclear grade and relative survival

A) Clear cell tumours

NO. of cases	Males 1	Males 3	Males 5	Males 10 years	No. of cases	Females 1	Females 3	Females 5	Females 10 years
II 82	90.2	74.2	66.0	53.2	84	92.3	83.8	82.5	67.2
SR	3.7	5.6	6.3	7.5	SR	3.3	4.8	5.4	7.6
III 77	76.0	45.1	38.7	33.0	57	66.0	42.6	42.4	30.8
SR	5.1	6.1	6.2	6.8	SR	6.4	6.9	7.1	7.5
IV 39	71.8	60.0	48.9	32.6	42	61.2	44.0	41.1	40.2

B) *Eosinophilic cell tumours*

II 57	85.1	65.7	58.0	43.4	37	92.3	83.3	85.3	56.4
SR	5.2	7.7	7.8	9.0	SR	5.3	7.8	8.5	13.7
III 72	71.2	37.7	33.6	28.6	51	68.0	52.1	48.0	34.9
SR	5.6	6.1	6.2	6.7	SR	6.7	7.4	7.7	8.5
IV 74	61.1	47.1	37.3	25.7	73	64.5	50.0	48.0	78.9
SR	5.9	6.3	6.3	7.3	SR	5.8	6.3	6.5	8.4

Table 20. Relation between cell shape and nuclear grade.

	No	1	(%)	2	(%)	3	(%)	4	(%)	3 + 4
Cylindric	117	3	(2.6)	55	(47.0)	40	(34.2)	19	(50.4)	50.4%
Cuboidal	265	14	(5.3)	106	(40.0)	92	(34.7)	53	(20.0)	54.7%
Polygonal	537	10	(1.9)	192	(35.7)	175	(32.6)	160	(29.8)	629%
Spindle	67	0	(0)	4	(6.0)	14	(20.0)	49	(94.0)	94.0%
Polymorphic	84	0	(0)	2	(2.4)	8	(9.5)	74	(88.1)	97.6%

Table 21. Relation between growth pattern and nuclear grade.

	NO1		(%)	2	(%)	3	(%)	4	(%)	3 + 4
Adenomatous	301	13	(4.3)	119	(39.57	101	(33.6)	68	(22.6)	56.2%
Solid alveolar	330	5	(1.5)	153	(46.4)	108	(32.7)	64	(19.4)	52.1%
Solid sheets	460	4	(0.9)	139	(23.1)	154	(33.5)	163	(35.5)	69.0%
Papillary	81	10	(17.3)	28	(34.6)	22	(27.2)	21	(25.9)	53.1%

unfavourable prognosis for tumours infiltrating extrarenal tissue is particularly obvious. The relative 10-year survival for this group was 19.2% for men and 15.8% for women, compared to 58.4% and 65.8% for men and women with sharply limited tumours. The apparently slightly better prognosis for men in this group is not statistically significant, but the prognosis for women in the other groups with sharp and unsharp borders is remarkably better.

Cell type

Tumours containing only one cell type were rare. Tumours dominated by clear cells (Fig.3) or eosinophilic cells were most frequent (Table 7). Clear cell tumours were slightly more frequent in women whereas eosinophilic tumours were slightly more frequent in men.

There were 13 tumours consisting of only basophilic cells and 4 tumours composed of well differentiated eosinophilic and granular cells (oncocytes). Poorly differentiated eosinophilic granular cells were, however, present in a considerable number of cases (Fig. 4). Relative survival is shown in Table 8. Clear cell tumours had a better outcome than eosinophilic tumours. Men had a 10 year relatice survival of 47.5% and 36.9% respectively and women 62.9% and 36.9% in our study. The figures for basophilic tumours (7 men and 6 women) were too small to allow any evaluation of survival rate, but of the 7 men, 6 died within 3 years and of the 6 women, 5 died within 4 years, which may indicate a poor prognosis for this type of tumour.

Tumour growth pattern

Tumours with only one growth pattern were uncommon (Table 9). Areas with solid sheets were present in about 80% of the tumours in both sexes (Fig. 5). Adenomatous structures were more frequently seen in men than in women (57.8% and 45%) (Fig. 6). The combination of solid alveolar structures (Fig. 7) and solid sheets wac frequently seen. in 44.2% and 47.8% of the tumourc in rnen and women, respectively.

Table 10 shows the relative survival. Since about 80% of the tumours contained areas with cells growing in solid sheets, the 5 and 10-year survivals are almost identical to that for the whole material. However, tumours growing only in sheets, a5 well as papillomatous structures, had a bad prognosis compared with tumours with solid alveolar structures.

The relationship between growth pattern and cell type is shown in Table 11. Tumours with only clear cells, or cell mixtures including clear cells, had a tendency towards solid alveolar growth pattern compared with eosinophilic and basophilic cell tumours that preferred an adenomatous or papillomatous pattern.

Cell shape (Table 12)

In men, 90.4% of tumours and, in women, 97% of tumours had areas with polygonal tumour cells but only 28.2% and 38% respectively had polygonal neoplastic cells only. In both sexes, spindle-shaped cells were present in about 12% of the cases (Fig. 8) and these cases had a remarkably bad prognosis with a 5 and 10-year survival of 33.2% and 0% in men and 30% and 3.6% in women. Purely polygonal cell tumours carried the best prognosis, 44.5% and 50.7% relative survival after 10 years for men and women, respectively.

Table 13 shows that polymorphic cells were present in only 3.2% of the purely clear cell tumours, whereas the frequency in purely eosinophilic tumours was 25.5%.

Spindle-shaped cells were present in 1.9% and 10.9% of the same cell types. Tumours containing basophilic cells had a high percentage of spindle-shaped cells (about 30% in both sexes) and polymorphic cells (13.7% in men and 25% in women). Clear cell tumours had 96.5% and 98.9% polygonal cells (men and women, respectively), as expected for the better prognosis of clear cell tumours. Eosinophilic tumours had a high percentage of cubic (≈ 50%) and cylindric (≈ 22%) cells.

Nucleolar appearance (Table 14)

Abnormal nucleoli were a frequent feature in about half of the cases and were associated with an unfavourable outcome. 10-year survival in men was 32.6% compared with 39.7% in cases without abnormal nucleoli. 10-year survival in women, was 40.4% in the group with abnormal nucleoli and 51.2% in the group without abnormal nucleoli. Again, women had a better outcome than men.

The relationship between cell type and shape and presence of abnormal nucleoli is shown in Table 15. Abnormal nucleoli were most frequently encountered in tumours composed of oncocyte-like cells, followed by eosinophilic, basophilic and clear cell tumours.

Abnormal nucleoli were present in 71.4% (men) and 61.7% (women) of polymorphic cell tumours, and in 55.5% (men) and 32.3% (women) of spindle cell tumours. No sex difference was observed in relation to the other cell shapes.

Nuclear grading

The results are shown in Table 16. The number of patients in Group 1 was small, but indicate a good prognosis (Figs. 1 and 5). One single patient with Grade I tumour died 3 years after the diagnosis was determined, obviously due to inadequate resectioning of the primary tumour. Grade 2 tumours (Fig. 6) were associated with a better prognosis than Grade 3 (Fig. 4) and 4 (Fig. 5) tumours. Between the latter two grades it was not possible to establish any separation in survival rate.

The possible relationship between the nuclear grade and the border of the tumour was studied. A sharp limitation of grade 2 tumours indicated a favourable prognosis (85-86% relative 5-year survival in both sexes) compared with grade 2 tumours with an unsharp border (43.1% relative 5-year survival in men and 71.1% in women) (Table 17).

The association between clear cell tumours and nuclear grade 2 (43.1%) was more frequent than that between eosinophilic tumours and grade 2 (74.8%) (Table 18). The percentage of clear cell tumours associated with nuclear grades 3 and 4 was lower (35.5% and 20.9%) and without any distinct difference from the frequency of eosinophilic tumours in the same nuclear grade groups. 50% of basophilic and 70% of oncoytoma-like tumours (purely oncocytic tumours and poorly differentiated eosinophilic granular cell tumours) were associated with nuclear grade 4 tumours.

The relationship between cell type (clear cells and eosinophilic cells), nuclear grade and relative survival is shown in Table 19. Nuclear grade 1 tumours were not included because there were too few cases. The prognosis for women with nuclear grade 2 tumours was significantly better than for men, independent of cell type.

A higher frequency of spindle-shaped and polymorphic cells was observed in nuclear grade 3 and 4 tumours (Table 20). In nuclear grade 2 tumours, cylindric cells were found in 47%, cubic cells in 40% and polygonal cells in 35.7%.

Table 21 shows the association between tumour growth pattern and nuclear grade. There were 153 (50%) tumours with a solid alveolar pattern belonging to nuclear grade 2, consistent with the observation that clear cell tumours showed about the same percentage of nuclear grade 2 tumours. Tumours growing in solid sheets comprised about 70% of nuclear grade 3 and 4 turnours.

A study of the relationship between nuclear grade and presence of metastases at the time of surgery revealed that 0% of grade 1 tumours had metastasized, 3% of grade 2, 10% of grade 3, and 20% of grade 4 tumours.

Discussion

Mostofi and coworkers (1981) defined renal cell carcinoma as a malignant epithelial tutnour of the renal parenchyma (1981). In addition, the authors state that the distinction between adenomas and small Grade I carcinomas may not be possible on a histological basis, but single layer of cells with little cytoplasm and small regular nuclei and the presence of prominent fibrovascular stalks in papillary tumours favour a benign diagnosis.

Renal cell carcinomas and adenomas are considered to arise in proximal alveolar cells (Eker et al., 1981). Hellsten and coworkers (1981) defined renal cell carcinomas as all tumours of 2 cm or more in diameter and included smaller tumours if metastases, vascular invasion or local invasion were present. However, to distinguish between benign and malignant tumours by size alone is less than satisfactory. Bennington (1973) claimed that renal adenomas do not exist and that even the small tumours are carcinomas. We are not sure whether he is correct, but obviously even the large malignant tumours must have been smaller than 2 cm in diameter when they became cancerous. Warter (1983) considered renal adenoma and carcinoma related lesions, but with different potential.

The natural history of renal cell carcinomas is varied. Occasional patients live many years with metastasis, others die within a few months. The present study shows that, by using a combination of clinical and morphological factors, it is possible to predict the outcome to a certain extent, not only for patients with advanced disease, but also for patients in early stages.

Prognostic factors in renal cell carcinomas have been thoroughly studied (Hand and Broders, 1932; Fryfogle et al., 1948; Foot et al., 1949; Foot el al., 1951; Murphy and Fishbein, 1961; Arner et al., 1964; Mathisen et al., 1965; Murphy and Mostofi, 1965; Mostofi, 1967; Robson et al., 1969; Bottinger, 1970; Skinner et al., 1971; Holland, 1973; Mathisen, 1973; Varkarakis et al., 1974; Amtrup et al., 1974; Petkovic. 1975a and b; Petkovic, 1976; Mancilla-

Jimenez et al., 1976; Hermanek et al., 1976a and b; Syrjänen and Hjält, 1978; von Lieven et al., 1978; Petkovic, 1978; Droller, 1980; Fuhrrnan et al., 1982; Merino and Livolsi, 1982; Tannenbaum, 1984; Ritchie and Chisholm, 1984).

The importance of staging is generally accepted, although Fuhrrnan and colleagues (1982) cast doubts on the predictive value for patients with limited disease.

In our study, a sharp tumour border against the surrounding tissue was associated with a better prognosis with a 5-year relative survival of 65.9% for men and 73% for women compared to 31.7% and 39.6% respectively, in tumours with unsharp borders. lnfiltration of perirenal fat is also a bad prognostic omen with a 5-year relative survival of 23.1% for men and 14.8% for women. It is also associated with a higher (27%) occurrence of metastases compared with 7-8% when the tumour is confined to the renal tissue (Arner et al., 1964; Mostofi, 1967; Robson et al., 1969; Bottinger, 1970; Skinner et al., 1971; Mathisen, 1973; Holland, 1973; Amtrup et al., 1974; Varkarakis et al., 1974; Mancilla-Jimenez et al., 1976; Hermanek et al., 1976; Syrjänen and Hjält, 1978; Fuhrman et al., 1982; Tannenbaum, 1984).

The prognostic importance of renal vein involvement is not a subject of general agreement. Skinner and coworkers (1971) observed that renal vein involvement did not alter the prognosis for patients in stage 1 and 2. This view is shared by Petkovic (1975a and b) and Fuhrman et al. (1982), whereas most other authors (Hand and Broders, 1932, McDonald and Priestly, 1973; Bell, 1950; Robson et al., 1969; Arner et al., 1964; Mostofi, 1967; Meyers et al., 1968; Robson et al., 1969; Bottinger, 1970; Skinner et al., 1971; Holland, 1973; Mathisen, 1973; Amtrup et al., 1974; Varkarakis et al., 1974; Hermanek et al., 1976; Mancilla-Jimenez et al., 1976; Syrjänen and Hjalt, 1978; Patel et al., 1978; Tannenbaum, 1983; Tannenbaum, 1984), consider renal vein involvement to worsen the diagnosis. This was also confirmed in the present study.

Bottinger (1970) observed that the vast majority of patients with metastases died within 2 years. Only 18% lived into their third postoperative year. This gloomy outlook is confirmed in our material. Most metastases go to the lungs, lymph nodes, liver and bones, but almost no organ or tissue is safe from involvement in renal cell carcinoma (Mostofi, 1967).

Fetter and Snyder (1963) and Mostofi (1967) claim that younger patients with renal cell carcinomas do better than older patients and we share this view, especially with regard to men. The relative survival in the age group from 15 to 54 was 48.7% after 5 years and 38.8% after 10 years. Between 55 and 74 the relative survival rates after 5 and 10 years were 46.2% and 31.4%.

The prognosis for patients with renal cell carcinoma is better in women than in men within each cell type, growth pattern, cell shape and size, at least when tumours with vascular invasion and tumours with infiltrating borders are excluded.

Tumours smaller than 3 cm in diameter rarely metastasize (Bell, 1950) and usually have an excellent prognosis (Fuhrman et al., 1982), and the larger the tumour, the worse the prognosis (Bell, 1950; Kay, 1968; Arner et al., 1975; Fuhrman et al., 1982; Tannenbaum, 1984). For the majority of patients, however, tumour size is not of prognostic value because most tumours fall into the intermediate category (Fuhrman et al., 1982). We found a markedly better outcome for women in the group with tumour size between 3 and 6 cm (Table 9).

Pure clear cell tumours are generally considered to have a better outcome than eosinophilic cell tumours (Murphy and Fishbein, 1961; Murphy and Mostofi, 1965: Mostofi, 1967; Skinner et al., 1971; Holland, 1973; Amtrup et al., 1974; Varkarakis et al., 1974; Fuhrman et al., 1982). However, most tumours consist of a mixture of clear and eosinophilic cells. Skinner and coworkers (1971) found the survival rate for patients with renal cell carcinomas of mixed cellular type similar to the rate in patients with tumours of purely granular or eosinophilic cell type. We found a relative survival for patients with tumours of mixed eosinophilic and clear cell type between the rate for cases with purely clear, and the rate for cases with purely eosinophilic cell tumours (Table 8).

Of the 768 renal cell carcinomas examined by Fryfogle and coworkers (1948), 29 had small basophilic cells. The 5-year survival rate in these cases was 25% for men and 67% for women. The 13 cases of pure basophilic cell tumours in our series had a bad prognosis, as only 2 patients were still alive after 4 years.

Renal oncocytoma is a rare tumour with an excellent prognosis (Hamperl, 1962; Hamperl, 1964; Klein and Valensi, 1976; Johnson et al., 1979; Ejeckam et al., 1979; Landier et al., 1979; Pearse and Houghton, 1979; Yu et al., 1980; Bokinsky, 1981; Lieber et al., 1981; Choi et al., 1983; Barnes and Beckman 1983; Alanen et al., 1983; Eble and Hull, 1984). The neoplastic cells are large and the cytoplasm eosinophilic, due to abundant mitochondria. The morphologic criteria for separating renal oncocytomas from renal carcinomas are somewhat vague. Poorly differentiated eosinophilic granular cell tumours have an oncocytoma-like appearance and can be very difficult to separate from "true" oncocytomas (Lieber et al., 1981; Barnes and Beckman, 1983). In our series, we found only four "true", but not less than 66 tumours with poorly differentiated granular eosinophilic cells. Poorly differentiated granular eosinophilic cell tumours had a similar outcome to that of eosinophilic cell tumours and it is therefore important to separate them from the "true" and rather innocuous oncocytomas.

Spindle cell tumours are known to be associated with a severe prognosis (Skinner et al., 1971; Waters-Richie, 1979 and Fuhrrnan et al., 1982). This was also observed in our material. We found that basophilic cell tumours had a higher occurrence of spindle cells (30%) than clear and eosinophilic cell tumours, (less than 14%). We also recorded an unfavourable outcome for patients with polymorphic cell tumours.

Skinner and coworkers (1971) made a distinction between alveolar, papillomatous tumours and tumours growing in cords and sheets. No significant influence on

prognosis was observed and this was later confirmed by Amtrup and colleagues (1974) and Syrjänen and Hjalt (1978).

Certain patterns of tumour cell arrangement have been associated with a favourable prognosis; the groups of Boczko (19747 and Mancilla-Jimenez (1976) reported a better outcome for patients with papillary tumours, whereas Fuhrman and coworkers (1982) found that papillary tumours were more aggressive than nonpapillary tumours. In our material, tumours with a solid alveolar growth pattern were the only tumours having a better prognosis than the other groups. This may be due to the fact that 3 out of 4 clear cell tumours showed a tendency to grow in a solid alveolar pattern, whereas adenomatous and papillomatous growth patterns were more frequent in eosinophilic cell tumours.

The presence of abnormal nucleoli is an unfavourable prognostic sign and is relied upon in various grading systems (Skinner et al., 1971; Syrjänen and Hjalt, 1978; Fuhrman et al., 1982). Skinner and coworkers (1971) introduced a nuclear grading system applicable to all tumour types and found it superior to all other histological classification systems with regard to predicting the outcome. While Skinner and coworkers (1971) did not accept abnormalities of the nucleoli in grade 2 tumours, Fuhrman and coworkers (1982) allowed the presence of nucleoli in grade 2 tumours when studied under high (400X) power.

Our results confirm that the presence of abnormal nucleoli represents an unfavourable prognostic sign. In our grading system, 14% of grade 2 tumours had abnormal nucleoli. The prognostic value of nuclear grading was good in both sexes, but the outcome was generally better in women.

There is a relationship between tumour grade and tumour border (Syrjänen and Hjält, 1978) and, in the present study, grade II tumours with sharp borders had a better prognosis than tumours with diffuse borders.

Final **Remarks**

The prognosis in patients with renal cell carcinomas depends on well-known factors, such as tumour stage, sex, age, and presence or absence of metastases. The present study indicates that the following morphological factors must also be taken into consideration:

1. Relation to surrounding tissue. Infiltration in extrarenal tissue indicates a severe prognosis.
2. Vascular invasion means a severe prognosis.
3. Tumour size: small tumours do better than large. Tumours smaller than 3 cm in diameter have an excellent prognosis but even small tumours can metastasize. Women with tumours between 3 and 6 cm in diameter have a very good prognosis.
4. Cell shape is of less importance, except for the presence of polymorphic and spindle-shaped cells which means an unfavourable prognosis.
5. Clear cell tumours have a better prognosis than eosinnphilic cell tumours. Basophilic cell tumours indicate a poor prognosis.
6. Growth pattern is of minor importance, but presence of only solid sheets is more often found in tumours with an unfavourable prognosis.
7. Nuclear grade is the most important prognostic factor. Patients with Grade 1 tumours have an excellent prognosis. Men with Grade 2 tumours with a sharp border and women with Grade 2 tumours with both sharp and unsharp borders have a very good prognosis.
8. Abnormal nucleoli are more commonly found in tumours with an unfavourable prognosis.

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