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Prognostic significance of morphologic parameters in renal cell carcinoma*

ABSTRACT The prognostic significance of morphologic parameters was evaluated in 103 patients with renal cell carcinoma diagnosed during 1961–1974. Pathologic material was classified as to pathologic stage, tumor size, cell arrangement, cell type and nuclear grade. Four nuclear grades (1–4) were defined in order of increasing nuclear size, irregularity and nucleolar prominence. Nuclear grade was more effective than each of the other parameters in predicting development of distant metastasis following nephrectomy. Among 45 patients who presented in Stage I, tumors classified as nuclear grade 1 did not metastasize for at least 5 years, whereas 50% of the higher grade tumors did so. Moreover, among Stage I tumors there was a significant difference in subsequent metastatic rate between nuclear grades 1 and 2. There was an apparent positive relationship between cell type and metastatic rate; clear cell tumors were less aggressive than predominantly granular cell tumors (metastatic rate 38% versus 71%). This relationship is in part a function of the nuclear grade: only 5% of grade 3 and 4 tumors consisted of clear cells, whereas such high grades were seen in 57% of granular cell tumors. The size of the primary correlated well with the stage at the time of surgery. However, with the exception of extremely large and small tumors, the size was not useful in predicting the subsequent course of patients treated for Stage I tumors. Nuclear grade was the most significant prognostic criterion for the outcome of Stage I renal cell carcinoma.

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Renal cell carcinoma (RCC) is a tumor of varying histologic appearance and clinical behavior. Previous studies have attempted to identify morphologic parameters which correlate with biologic behavior of these neoplasms and therefore have predictive value.[1,2,11,14,17,19,20] The results have often been contradictory, and only a few concepts have achieved clinical importance and are widely used by practicing pathologists. Presently, the prognosis of patients with renal cell carcinoma is determined by the pathologic stage of the disease at the time of presentation, and little significance, if any, is attached to cytologic characteristics. However, there is significant variation in the outcome among patients presenting in the same stage, particularly when the long-term course is considered.

Cytologic grading of RCC has been attempted,[1,2,6,20] but the proposed grading systems have found very limited application to routine diagnostic pathology. In reviewing a large number of these tumors, we were impressed by the fact that certain cytologic characteristics consistently correlated with low or high metastatic potential and could be used as predictors of long-term outcome. We thus devised and tested a simple grading system for RCC which has discriminative power and can be applied to everyday practice. The proposed grading system is based exclusively on nuclear features and is prognostically more effective than other morphologic parameters which have previously been used for the same purpose. In this study, we present data that cytologic grading reflects the biologic potential of the tumor prior to its clinical expression and there-

fore discriminates among patients presenting in early stages but having quite different chances of metastases.

MATERIALS AND METHODS

The diagnosis of renal cell carcinoma was made on 157 patients at the Minneapolis Veterans Administration Hospital from 1961 to 1974. Excluded from the study were 54 cases, either because tissue from the primary tumor was not available or, as was the case in seven tumors, the original diagnosis of renal cell carcinoma could not be confirmed. The final study group consisted of 103 patients. Material from 85 patients who had either completed a minimum 5-year period of follow-up or died with well-documented evidence of their disease status through biopsy or autopsy was used in analyses involving metastatic potential. Material from an additional 18 patients who had inadequate documentation for presence or absence of metastatic disease was used only for correlations unrelated to metastatic potential. Clinical information utilized included date of initial diagnosis, mode of therapy, date of diagnosis and treatment of subsequent metastases, and date of death. The surgical pathology reports were reviewed to determine size and local extent of primary tumor, and the autopsy protocols and death certificates were the source of information about the terminal state of the patient.

Histologic sections were reviewed by two of us (SAF and CL) independently and then together. Morphologic parameters were examined as follows: renal vein involvement, stage, size, tumor pattern, nuclear grade, and cell type.

Pathologic staging utilized the system of Robson et al.[19] with the exception that renal vein involvement was evaluated as a separate parameter because of the controversy regarding its significance in prognosis. Stage I was defined as a tumor confined to the kidney, with no involvement of perinephric fat; Stage II as a tumor extending into the perinephric fat but confined to Gerota's fascia. The regional lymph nodes in these patients were negative. Stage III tumors involved regional lymph nodes and a Stage IV tumor infiltrated contiguous visceral structures or had distant metastases.

Size was documented in 73 tumors. For statistical analysis, five groups of tumors were defined as follows: ≤ 3 cm, 3.1–5, 5.1–8, 8.1–12, and >12 cm.

The tumors were categorized into four basic patterns of tumor cell arrangement or combinations of these patterns. Solid tumors were composed of monotonous sheets of cells, tubular or glandular tumors contained cells forming lumina or alveolar spaces, papillary tumors were composed of cells lining fibrovascular stalks, and spindled tumors exhibited at least some areas of sarcomatoid or spindle cell pattern.

The tumors were divided into three cell types: tumors composed entirely or over 75% of clear cells, those composed entirely or over 75% of dark (granular) cells, and those composed of a mixture of both types; in the last, the minority populations were over 25%.

Nuclear grade was determined utilizing the following criteria: Grade 1 tumors were composed of cells with small (approximately 10 μ) round uniform nuclei with inconspicuous or absent nucleoli (Fig. 1*A*). Grade 2 tumors had larger (approximately 15 μ) nuclei which exhibited irregularities in outline and nucleoli when examined under high (400×) power (Fig. 1*B*). Grade 3 tumors had even larger nuclei (approximately 20 μ) with an obviously irregular outline and prominent large nucleoli even at low (100×) power (Fig. 1*C*). Grade 4 tumors exhibit features similar to the grade 3 tumors with the addition of bizarre, often multilobed nuclei and heavy chromatin clumps (Fig. 1*D*). These tumors often had areas of spindled-shaped cells resembling sarcomas. Each tumor was graded by the most malignant or highest grade exhibited even if only focal. Multiple grades coexisted in 15% of tumors.

Data were analyzed using the University of Minnesota Computing Center's Control Data Corporation Cyber computers. The calculations and data storage were accomplished using the Statistical Package for the Social Sciences (SPSS Inc., Evanston, Ill.). Analytic techniques included the use of χ^2 and survival analyses. The statistical difference between survival in various groups was calculated using the nonparametric technique of Desu.[9]

RESULTS

Medical record evaluation revealed little variation in treatment methods between patients. The majority of patients (82%) were treated by nephrectomy. In some cases, adjuvant chemotherapy or radiation therapy was administered. Of the 18% of patients who did not undergo nephrectomy, 66% had advanced metastatic tumor. These patients were treated with radiation, chemotherapy, or supportive measures.

The patients ranged in age from 37 to 84 years with a mean age of 62.5 years. There were only four

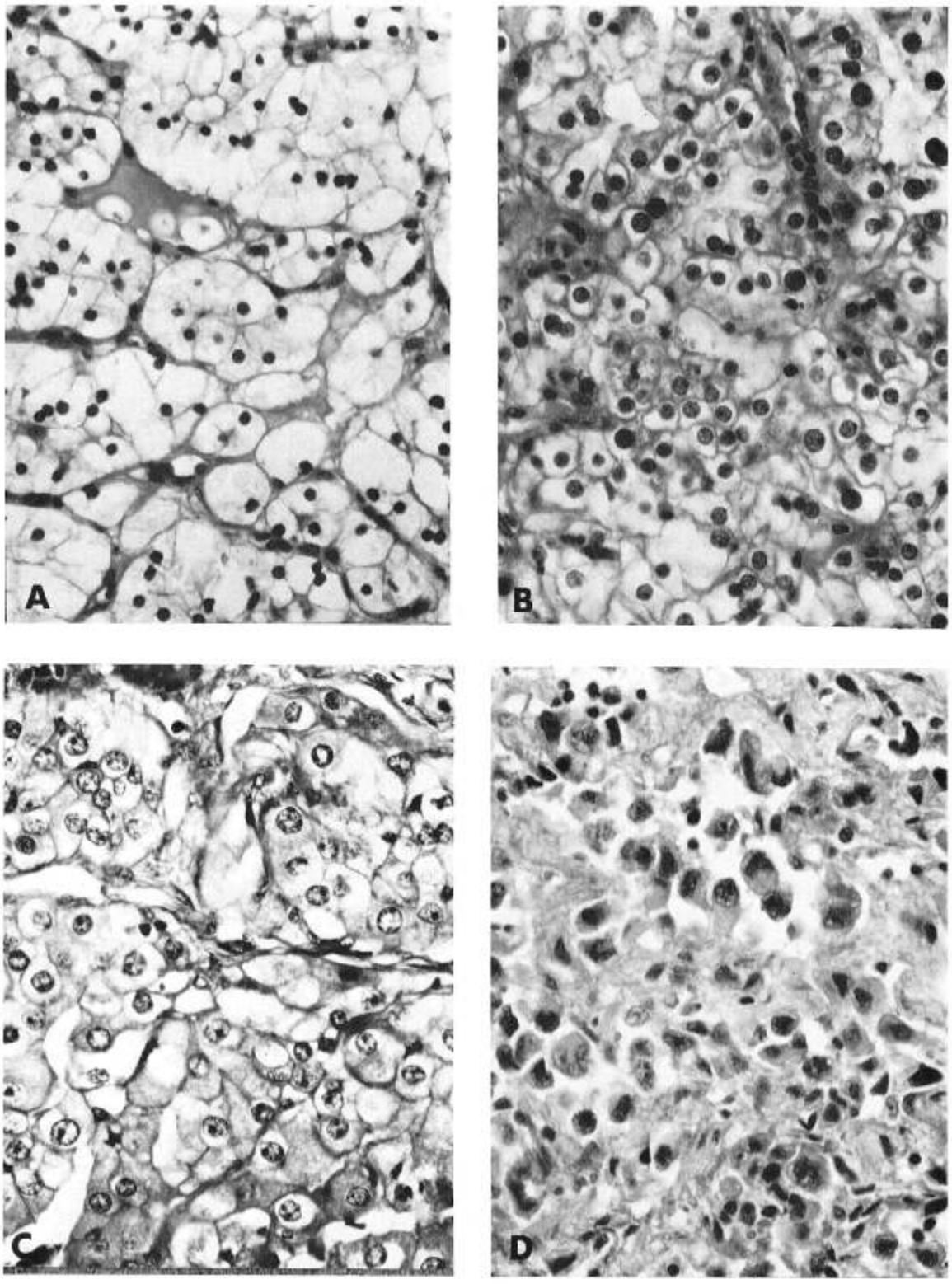

FIGURE 1
(*A*) Grade 1 renal cell carcinoma. There is a solid arrangement of clear cells which exhibit regular, uniform round nuclei comparable in size to the red blood cells seen in the field. Nucleoli are absent. (*B*) Grade 2 renal cell carcinoma. Solid sheet of cells with nuclei varying in size, generally larger than in the grade 1 tumors. The nuclear outlines are slightly irregular and nucleoli are frequently visible at high power. (*C*) Grade 3 renal cell carcinoma. Cells exhibit large nuclei with hyperchromasia along with marked variability in size and shape. Nucleoli are large and conspicuous. (*D*) Grade 4 renal cell carcinoma. Solid clusters of cells which have large pleomorphic nuclei, with extremely irregular outlines, often multilobed and with chromatin clumping and conspicuous nucleoli.

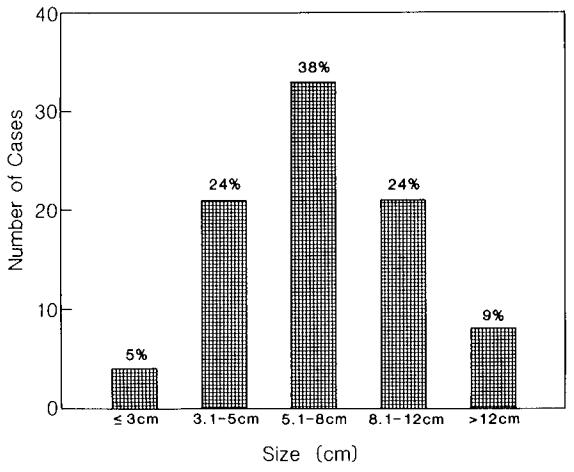

FIGURE 2
Distribution of tumors by size.

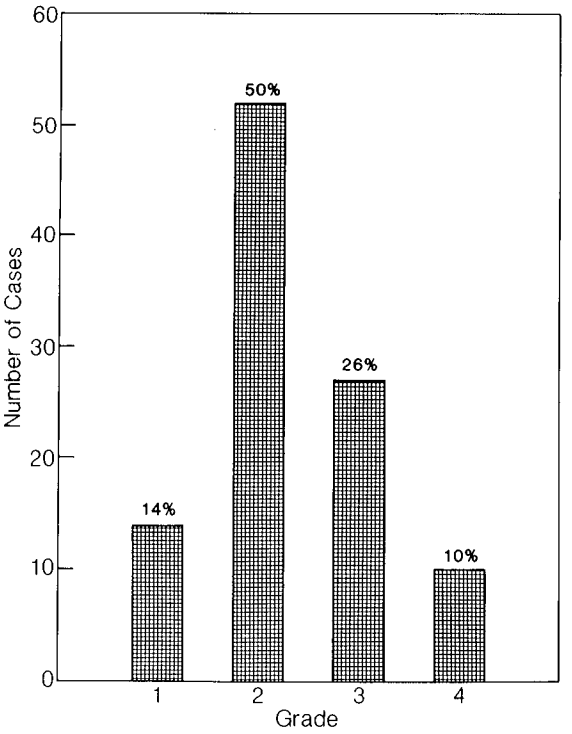

FIGURE 3
Distribution of tumors by grade.

female patients in the study because of the predominant male population at the Veterans Administration Hospital.

The distribution of patients according to tumor size and nuclear grade (Figs. 2 and 3) is approximately Gaussian; most patients had tumors of intermediate size and grade. Over 80% of the patients either had Stage I (58%) or Stage IV (22%) tumors (Fig. 4). Slightly more than half the cases (52%) were classified as solid, 16% tubular, and 4% papillary. Combinations of these patterns were seen in 18% of tumors (Fig. 5). Tumors with a spindled cell component comprised 10% of the series. The three categories of tumors according to cell type were equally represented with clear, granular, and mixed each comprising a little over 30% of this population.

Renal vein involvement and stage

Ten of the 45 patients with tumors otherwise classified as Stage I had renal vein involvement and four (40%) of these developed distant metastases. The same metastatic rate (40%) was observed among patients of the same stage but without renal vein involvement (14 of 35 cases). This would suggest that for Stage I patients renal vein involvement does not affect prognosis. Stage II and III patients exhibited higher metastatic rates than Stage I patients (Table 1). Furthermore, the results demonstrate that there is excellent correlation between stage and short-term (3-year) survival (Fig. 6).

TABLE 1.

Relationship between Stage and Subsequent Development of Metastasis

Stage	No. of Patients	No. of Patients with Subsequent Metastasis
I	45	18 (40%)
II	14	7 (50%)
III	5	5 (100%)
Total	64	30 (47%)

Size

A marked difference in metastatic potential was observed between the two extremes of tumor size (Table 2). None of the patients with a tumor mea-

TABLE 2.

Relationship between Primary Tumor Size and Metastatic Potential

Size (cm)	No. of Patients	No. of Patients with Distant Metastasis
≤3	3	0
3.1–5	16	9 (56%)
5.1–8	30	13 (43%)
8.1–12	17	13 (76%)
>12	7	6 (86%)
Total	73	41 (56%)

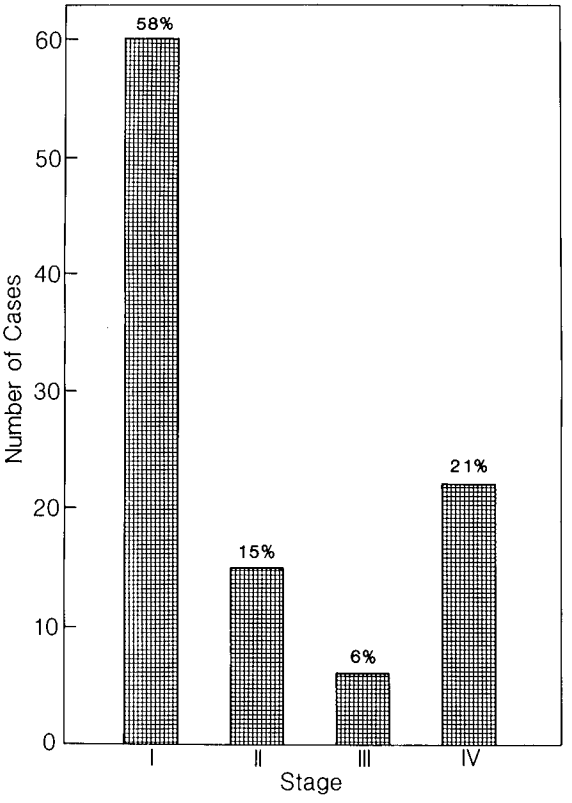

FIGURE 4
Distribution of tumors by stage.

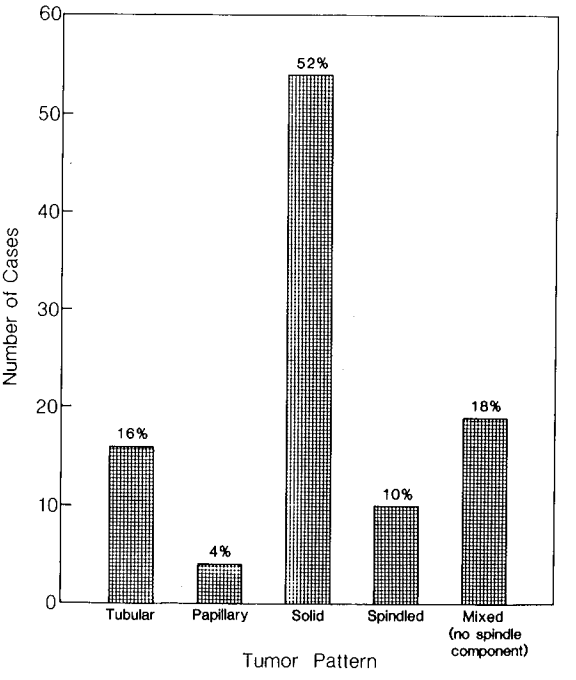

FIGURE 5
Distribution of tumors by tumor pattern.

suring 3 cm or less developed metastasis as contrasted to 86% of the tumors in excess of 12 cm in diameter. The majority of tumors (62%) measured 3.1–8 cm. Within this size range, no statistically significant relationship between metastatic rate and size could be discerned. There also appeared to be no correlation between 5-year survival and tumor size. However, tumor size did predict stage at a level of borderline significance ($p = 0.06$).

Tumor pattern

Tumor pattern was a poor prognosticator of outcome with the exceptions of tumors with a spindle cell component and, possibly papillary tumors.

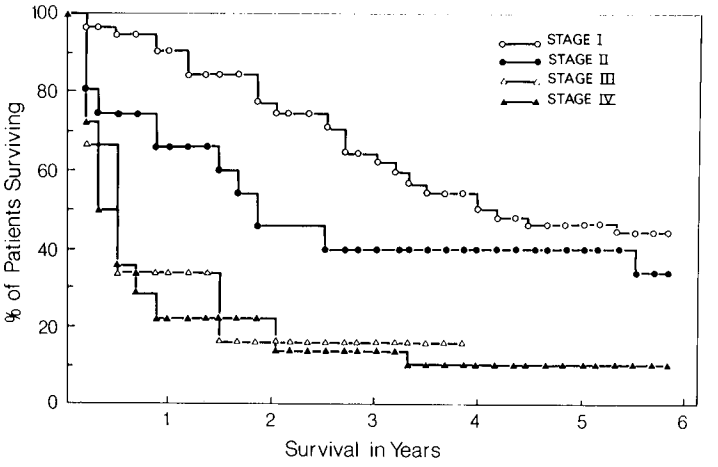

FIGURE 6
Life table survival curves by stage. Differences between these curves are statistically significant ($p = 0.001$).

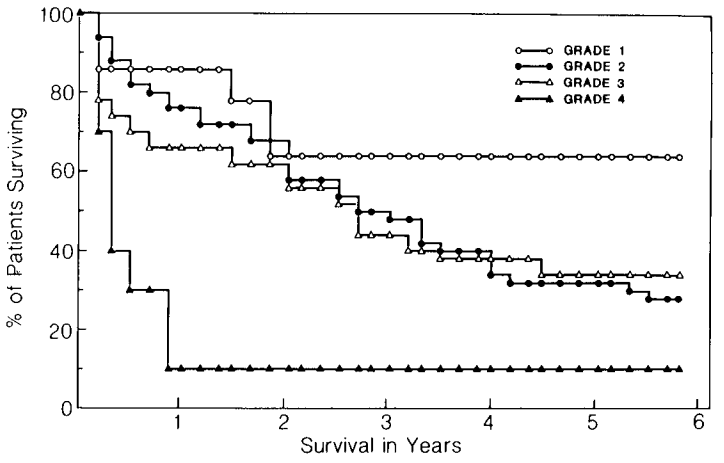

FIGURE 7
Life table survival curves by grade. Differences between these curves are statistically significant when grade 2 and grade 3 are analyzed as one group (p = 0.004).

Spindle cell tumors showed a high metastatic rate; seven of nine patients developed distant metastases. Four patients had purely papillary tumors and their prognosis was poor; all four patients developed metastases. In addition, six patients had a papillary component in conjunction with other patterns and they also had a relatively high metastatic rate (50%).

Nuclear grade

There was a significant difference ($p < 0.001$) in metastatic rate between grade 1 (9%) and the combined grade 2–4 tumors (68%) (Table 3). Moreover, the metastatic rate in grade 1 tumors was significantly lower ($p < 0.01$) than in grade 2 tumors (9% vs. 61%). Similar differences between grades were seen when only Stage I patients were evaluated for metastatic rate (Table 4). There was an inverse relationship between grade and 5-year survival (Fig. 7) which was statistically significant ($p < 0.005$) when the data were analyzed with grade 2 and grade 3 patients as one group. Nuclear grading predicted prognosis in terms of both survival and metastatic potential.

Cell type

Clear cell tumors had a lower rate of metastases (38%) compared to granular and mixed cell type tumors (81%, 62%) (Table 5). However, clear cell tumors were lower grade (Table 6); 37% were grade 1, whereas granular and mixed tumors were almost exclusively higher grade. More than half (57%) of granular and mixed tumors were grade 3 or 4. Conversely, only 5% of grade 3 and 4 tumors were composed entirely of clear cells. Thus, the relationship of cell type to prognosis is largely determined by grade, and is not an independent variable.

TABLE 3.
Relationship between Primary Tumor Grade and Metastatic Potential

Grade	No. of Patients	No. of Patients with Distant Metastasis
1	11	1 (9%)[a]
2	41	25 (61%)
3	24	19 (79%)
4	9	6 (67%)
Total	85	51 (60%)

[a] Grade 1 tumors have a statistically significant lower metastatic rate when compared to grade 2–4 tumors ($p < 0.001$).

TABLE 4.
Relationship between Grade and Subsequent Development of Metastasis in Stage I Tumors

Grade	No. of Patients Presenting in Stage I	No. of Patients with Subsequent Metastasis
1	9	0 (0%)[a]
2	25	11 (44%)
3	9	6 (67%)
4	2	1 (50%)
Total	45	18 (40%)

[a] Grade 1 tumors have a statistically significant lower metastatic rate when compared to grade 2–4 tumors ($p < .05$).

TABLE 5.
Relationship between Cell Type and Metastatic Potential

Cell Type	No. of Patients	No. of Patients with Distant Metastasis
Clear	29	11 (38%)
Granular	27	22 (81%)
Mixed (clear & granular)	29	18 (62%)
Total	85	51 (60%)

TABLE 6.
Relationship between Primary Tumor Cell Type and Grade

Grade	No. of Patients	
	Clear	Granular or Mixed
1	13 (93%)	1 (7%)
2	20 (38%)	32 (62%)
3	2 (7%)	25 (93%)
4	0	10 (100%)
Total	35	68

DISCUSSION

Pathologic staging is of indisputable value in determining the short-term prognosis in RCC,[1,2,6,19,20] but the long-term outcome for any given patient with a low stage tumor (I or II) is largely unpredictable. In other words, staging is important in identifying patients with a dismal prognosis, e.g., for those who die of the disease within 2 years, but has little predictive value for patients who present with limited disease. This limitation of the staging system will become more apparent as more patients are diagnosed earlier (Stage I).

Previous reports[3,7,13,15,18,19] which maintained that renal vein involvement is associated with significantly worse prognosis have been challenged.[20,22] Our findings also support the notion that renal vein involvement in the absence of lymph node metastases or perinephric fat involvement does not adversely affect prognosis. Renal vein involvement does not influence the future development of metastases in patients who are otherwise classified in Stage I.

Because of the disagreements in classifying patients with renal vein involvement, the distribution of the population by stage varies considerably from study to study.[20,22] In the present series, the high proportion of patients in Stage I (Fig. 1) reflects the fact that renal vein involvement was not considered in staging. As expected, the percentage in Stage IV was constant in this and in other studies.[20,22]

Bell[3] showed that small renal tumors (less than 3 cm) rarely metastasize and arbitrarily classified them as "adenomas," although even such small tumors have metastatic potential.[21] The entity of renal cell adenoma was challenged by Bennington,[4] who maintained that, except for size, small renal tumors are identical to tumors that are known to metastasize and should be designated as carcinomas. Nevertheless, small tumors have an excellent prognosis because the chance for metastases relates in part to absolute tumor mass. This phenomenon is also reflected in our results: very large tumors tended to present in higher stages and were associated with an increased rate of metastases. It is important to note, however, that for the majority of our patients, tumor size was not of prognostic value because most (62%) tumors were in the intermediate categories. With the exception of patients with tumors at the extremes of size, knowledge of size offered no clue for the outcome.

Certain patterns of tumor cell arrangement have been associated with a favorable prognosis. For example, Mancilla-Jimenez et al.[12] reported a series of 34 patients with papillary tumors, 85.2% of which presented in Stage I and had an 84% 5-year survival. This was significantly better than in other patterns. Tumors classified as papillary by these authors exhibited greater than 50% papillary pattern. Boczko et al.[5] corroborated these findings in a series of six cases. In the present series, four tumors were purely papillary and another six had a papillary component. These patients did not fare any better; in fact, they did worse than those with nonpapillary tumors. However, with so few papillary tumors in this series, conclusions about this pattern are tenuous. The greater malignant potential of sarcomatoid tumors was recognized previously[20,22] and confirmed by this study.

Attempts to grade renal cell tumors have been made in the past. Most of these grading systems utilized a combination of morphologic characteristics including cell type,[17] necrosis,[1] and tumor delineation from normal kidney.[2] Grading on the basis of nuclear morphology was introduced by Skinner et al., who found an excellent correlation between grade and survival.[20] The grading system we devised is also based on nuclear characteristics and classifies renal cell tumors into four grades: 1-4. The survival data (Fig. 7) suggest that the patients fall into three distinct groups: those with favorable prognosis (grade 1), those with a dismal prognosis (grade 4), and a large group of patients who fall in between (grades 2 and 3). Although survival was similar for grade 2 and 3 tumors, these two grades were morphologically quite distinct. Consequently,

we chose to separate them, keeping in mind that analysis of larger series or longer follow-up may uncover differences in metastatic rate, survival, or treatment response.

It is especially interesting to note the dramatic difference in metastatic rate between grade 1 (0%) and grade 2–4 tumors (50%) which are diagnosed and similarly treated in Stage I (Table 4). The grade 1 tumors were clearly less malignant. However, when they attain a large size, they may penetrate the capsule and eventually metastasize.

The greatest difference in survival and metastatic rate for patients presenting in Stage I was observed between grade 1 and grade 2 tumors, suggesting that even modest deviation from normal nuclear morphology reflected a profound change in biological behavior. Skinner et al.,[20] using their nuclear grading system, found the greatest contrast between grades 2 and 3, apparently due to different grading criteria.

Taking into account the low metastatic potential in grade 1 tumors, more conservative surgery (e.g., partial nephrectomy) may be considered under certain circumstances for such tumors. The major drawback in determining the grade by biopsy stems from the fact that more than one grade was found within the same tumor in approximately 15% of our patients. Since the highest grade present in a tumor determines the prognosis, and because sampling by biopsy may yield an erroneously lower grade, preoperative grading should be interpreted with caution.

Considerable controversy exists in the literature regarding the prognostic significance of cell type. Murphy and Mostofi[17] noted that patients with granular (dark) cell tumors fare worse in both survival and chance of metastasis, compared to patients with clear cell tumors. Similar findings were reported by Skinner et al.[20] and Amtrup et al.,[1] but others[6,11] could not corroborate these observations. McNichols et al.[14] found the majority of pure granular tumors to be of low grade and low stage with a prognosis similar to clear cell tumors of same grade and stage.

Our data showed the highest (81%) metastatic rate for tumors of granular cell type, the lowest (38%) for clear cell type, and an intermediate value (62%) for mixed cell type. We noted a relationship between nuclear grade and cytoplasmic texture; 95% of the higher grade tumors (grades 3 and 4) were granular or mixed. Further evaluation of this relationship revealed that the majority (93%) of grade 1 tumors were composed entirely of clear cells and, more importantly, only 5% of grade 3 and 4 tumors were composed entirely of clear cell. Thus, the relationship of cell type to prognosis, which had been noted for quite some time, may in fact be a function of nuclear grade. Granular cell tumors with low-grade nuclear characteristics are indeed rare and they correspond morphologically to the so-called "renal oncocytomas."[8,10,16] In the present study, there was only one patient with a grade 1 granular tumor. He survived 13 years and had no evidence of tumor at autopsy.

In conclusion, compared to other morphologic parameters, nuclear characteristics are more valuable in predicting the long-term course of renal tumors. Nuclear grading is applicable to all tumors of any size, pattern, or cell type and is therefore a unifying concept that can be easily understood and reproduced. This method may prove superior to staging because it reflects the biological potential of the neoplasm even before its clinical expression. In this context, grading may become indispensable as more and more tumors are discovered early and the metastatic potential rather than the presence of clinical metastases must be evaluated so that appropriate systemic therapy can be instituted in a timely manner. Any grading system accepted so far in the practice of pathology suffers to some degree from subjectivity, but this should not necessarily detract from its use. For certain tumors, e.g., transitional cell carcinoma of the bladder, grading has become common practice and has proven valuable both in guiding therapy and improving our understanding of tumor pathobiology. □

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