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INTRACAPSULAR CLEAR CELL RENAL CARCINOMA: PLOIDY STATUS IMPROVES THE PROGNOSTIC VALUE OF THE 2002 TNM CLASSIFICATION

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ABSTRACT

Purposes: The TNM classification has been revised for the 2002 edition of the UICC publication to better stratify patients with intracapsular renal cell carcinoma (RCC) but few studies have been published to date to validate this new classification. Moreover, additional prognostic factors seem to be necessary to improve the prediction of intracapsular tumor aggressiveness and the definition of patient subgroups at high risk for metastases. We report the long-term results of the new TNM scheme. We evaluated the impact of DNA content, S-phase and MIB-1 (Dako, Glostrup, Denmark) score.

Materials and Methods: A total of 136 patients with intracapsular clear cell RCC and a mean followup of 74 months were reclassified. Tumor specific survival (TSS) was compared with nuclear grade (NG), DNA content and proliferative status (S-phase fraction and MIB-1 score).

Results: TSS was 92%, 81.1% and 40.1% for pT1a, pT1b and pT2, respectively ($p < 0.05$). TSS according to DNA ploidy status (diploid vs aneuploid) was pT1a—95.2% vs 68.6% ($p < 0.05$), pT1b—90% vs 46.7% ($p < 0.05$) and pT2—49.2% vs 25% (p not significant). DNA ploidy was also significantly associated with survival when adjusted for NG. There was no significant association between TSS and MIB-1 score or tumor S-phase fraction.

Conclusions: The 2002 TNM classification is a useful prognostic factor for evaluating organ confined RCC of the clear cell subtype. Evaluation of the DNA content in clear cell RCC appears to significantly improve the predictive value of the TNM staging system, especially in the pT1a and pT1b categories. Fuhrman NG alone or combined should be routinely used in such patients.

KEY WORDS: kidney; carcinoma, renal cell; adenocarcinoma, clear cell; ploidies; cell proliferation

Renal cell carcinoma (RCC) has an unpredictable natural history, including several distinct entities with a range of biological and clinical behaviors from relatively favorable to extremely aggressive. There is a consensus regarding the ominous prognosis in lymph nodal and distant metastases, while it remains difficult to evaluate patient prognosis in organ confined disease. The available published evidence indicates that tumor stage and nuclear grade (NG) are significant independent predictors of cancer specific survival for intracapsular RCC.[1–4] In an effort to better stratify patients with tumors limited to the kidney the TNM classification system was changed in 1997 and 2002.[5,6] The most significant change from the 1987 to the 1997 edition was an increase in the size threshold between pT1 and pT2 tumors from 2.5 to 7.0 cm.[5] We and others[3,7,8] reported that, although pT1 tumors behave more indolently than pT2 or more advanced lesions, this category is nevertheless highly heterogeneous and the 7 cm threshold is too imprecise to clearly define prognosis in these patients. Ideal thresholds of 4.0 to 5.5 cm[9,10] have been proposed by different groups. The 2002 TNM classification introduced a size threshold of 4.0 cm for pT1 tumors, that is tumors confined to the kidney that are 4 cm or less in greatest dimension correspond to T1a and tumors greater than 4 but 7 cm or less are now classified as pT1b.[6]

However, the TNM classification, which considers tumor greatest dimension as the only prognostic indicator for intracapsular RCC, will never succeed in obtaining prognostically homogeneous groups of patients regardless to the size threshold chosen. Indeed, additional prognostic factors seem to be necessary to improve the prognostic prediction of intracapsular tumor aggressiveness and the definition of patients subgroups at high risk for metastases.

Studies of DNA content, the S-phase cell fraction (SPF) and the Ki-67 proliferative fraction provide conflicting results for detecting patients with organ confined RCC who are at greater risk for tumor progression.[2,7,11–13] We report our findings in a series of 136 intracapsular clear cell RCCs restaged according to TNM 2002 and followed a mean of 74 months. The impact of other prognostic variables, such as the DNA index (DI), SPF and the proliferative index (MIB-1 score), was analyzed.

MATERIALS AND METHODS

This study comprised 136 patients with a mean age of 62 years (range 28 to 85) with intracapsular clear cell RCC (pT1a, pT1b and pT2) who underwent radical nephrectomy at our institution from 1991 to 2001 and for whom paraffin tissue blocks were available. Preoperative evaluation included ultrasonography of the kidney, ureter and bladder, computerized tomography (CT) of the abdomen and chest

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TABLE 1. *DNA ploidy, SPF and MIB-1 score by TNM 2002 tumor stage and nuclear grade in intracapsular clear cell RCC*

	No. Pts (%)	No. pT1a (%)	No. pT1b (%)	No. pT2 (%)	No. G 1–2 (%)	No. G 3–4 (%)
TNM 2002 NG	136 (100)	57 (42)	61 (45)	18 (13)	80 (59)	56 (41)
pT1a	57 (42)	—	—	—	43 (75)	14 (25)
pT1b	61 (45)	—	—	—	33 (54)	28 (46)
pT2	18 (13)	—	—	—	4 (22)	14 (78)
NG:						
1–2	80 (59)	43 (54)	33 (41)	4 (5)	—	—
3–4	56 (41)	14 (25)	28 (50)	14 (25)	—	—
Diploid	105 (81)	44 (84.6)	48 (80)	13 (76.5)	66 (86.8)	39 (73.6)
Nondiploid	24 (19)	8 (15.4)	12 (20)	4 (23.5)	10 (13.2)	14 (26.4)
SPF:						
2.45 or Less	32 (46)	14 (56)	15 (44.1)	3 (30)	24 (63)	8 (26)
Greater than 2.45	37 (54)	11 (44)	19 (55.9)	7 (70)	14 (37)	23 (74)
MIB-1:						
0.001 or Less	45 (51)	19 (44.2)	23 (67.6)	3 (27)	27 (54)	18 (47)
Greater than 0.001	43 (49)	24 (55.8)	11 (32.4)	8 (73)	23 (46)	20 (53)

T stage vs DNA ploidy chi-square: p = 0.7028, grade vs DNA ploidy chi-square: p = 0.0570, t stage vs SPF chi-square: p = 0.3536, grade vs SPF chi-square: p = 0.002, t stage vs MIB-1 score chi-square: p = 0.0295 and grade vs MIB-1 score chi-square: p = 0.5376.

x-ray in all patients. Bone scintigraphy was performed in a small subset of patients in the presence of high serum alkaline phosphatase and/or bone pain.

The tumor was on the right side in 70 patients (51.5%) and on the left in 66 (48.5%). Overall 65 patients underwent regional lymph node dissection and none was found to have lymph node metastases (pN0). None of the remaining 71 patients had preoperative or intraoperative results suspicious for positive nodes. All patients were free of distant metastases at surgery (M0).

Patient status was last evaluated in November 2003. The followup schedule included blood chemistries, chest x-ray, CT of the abdomen and bone scintigraphy 6 months after surgery. Blood chemistries, chest x-ray and abdominal ultrasonography were then repeated every 6 months for the first 2 years and yearly thereafter. CT of the abdomen was done yearly for the following 2 years. Bone scintigraphy was performed only in clinically suspicious cases. Mean followup was 74 months (range 5 to 154). During the study period 32 patients died, including 24 of RCC and 8 of causes independent of RCC. Mean followup in the remaining 104 patients who remained tumor-free during the study period was 85 months (range 30 to 154).

All patients were re-staged according to 2002 TNM criteria.[6] NG was assigned according to the criteria proposed by Fuhrman et al.[1] Nuclear and whole cell dimensions were also determined using a computerized image analysis system. Histopathology was reviewed according to the new classification (1997 UICC and American Joint Committee on Cancer).[14]

All available hematoxylin and eosin stained slides in each case were reviewed independently by 2 pathologists (AC and CDC). Sections containing at least 75% viable tumor cells were selected for each patient. Sections (4 μm) were cut from select blocks for immunohistochemical analysis. A 50 μm section from the same paraffin block was used for DNA content and S-phase evaluation.

Flow cytometry. The DI of each RCC was measured by flow cytometry. Tissue samples were chosen according to the highest NG present. Samples of normal renal parenchyma served as controls for DI. Cases showing a distinct abnormal peak different from that of the normal diploid control peak were referred to as aneuploid. The tumor proliferative fraction was calculated by adding the S-phase to the G2/M-phase (FP = S + G2/M), when feasible.

Immunohistochemistry. Tumor sections were deparaffinized and endogenous peroxidase was blocked with 0.6% hydrogen peroxide in methanol. Antigens were retrieved by microwaving the slide at 360 W for 5 minutes (3 cycles) in 1 mmol/l citrate buffer, pH 7. Commercially available monoclonal Ki-67 antibody (clone MIB-l), 1:10 dilution, was used in

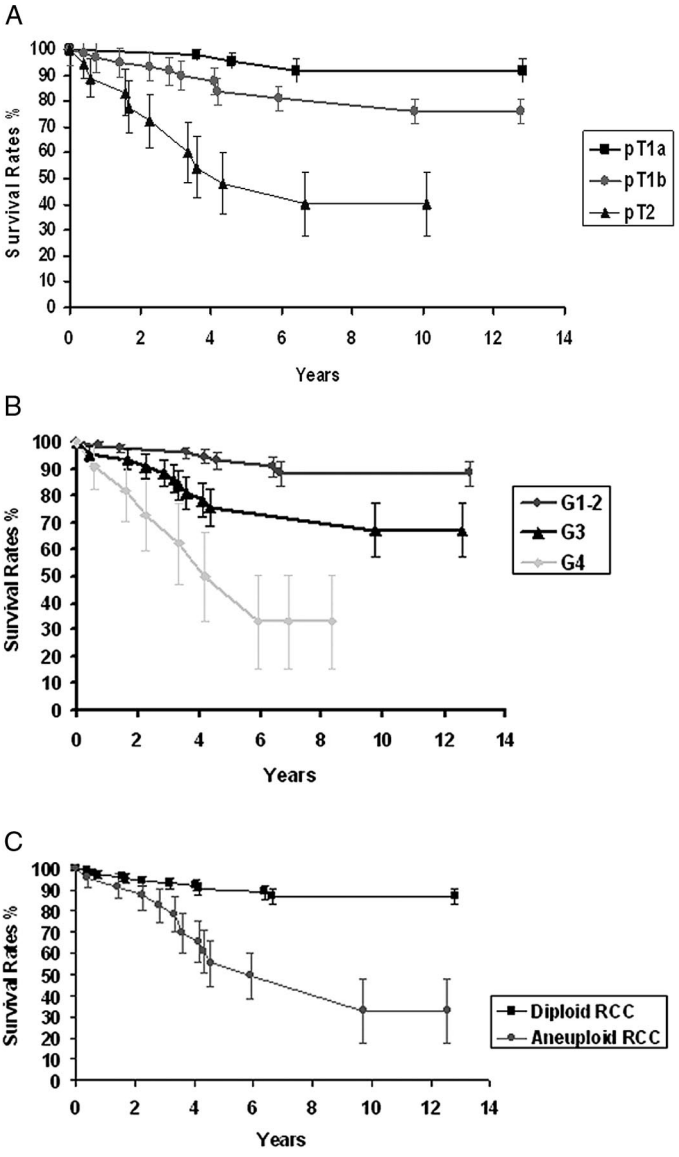

FIG. 1. Kaplan-Meier cancer specific survival rates. *A*, pT1a, pT1b and pT2 clear cell RCC according to 2002 TNM classification system (pT1a vs pT1b p = 0.0439, pT1a vs pT2 p = 0.0001 and pT1b vs pT2 p = 0.0008). *B*, Fuhrman nuclear grading system (G1 and 2 vs 3 p = 0.0124, G1 and 2 vs 4 p = 0.0001 and G3 vs 4 p = 0.0257). *C*, DNA content (p = 0.0001).

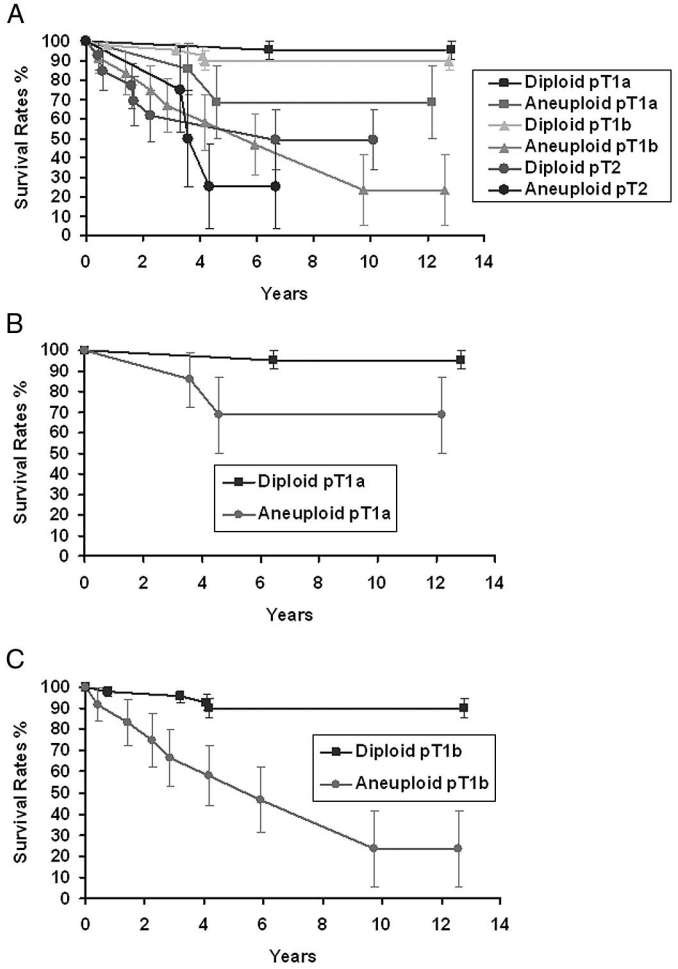

FIG. 2. Kaplan-Meier cancer specific survival rates. *A*, DNA content in all patients with intracapsular tumor stratified by 2002 TNM classification. *B*, DNA content in patients with pT1a clear cell RCC (p = 0.0088). *C*, DNA content in patients with pT1b clear cell RCC (p = 0.0001).

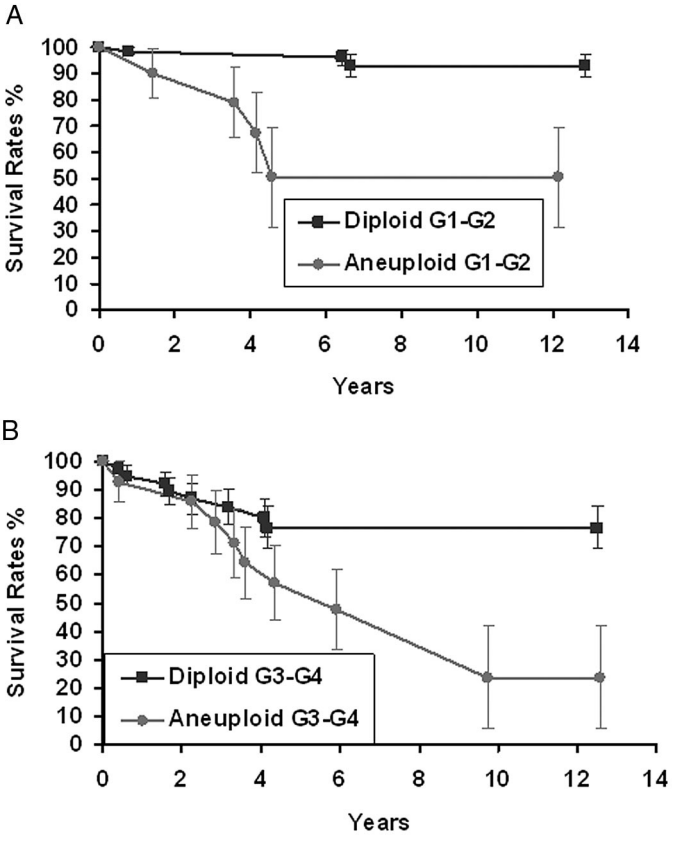

FIG. 3. Kaplan-Meier TSS. *A*, DNA content in patients with G1 and 2 intracapsular clear cell RCC (p = 0.0001). *B*, DNA content in patients with G3 and 4 intracapsular clear cell RCC (p = 0.0422).

an automated system. The avidin-biotin-peroxidase system was used to visualize the reaction.

Immunohistochemical expression of Ki-67 was estimated with a quantitative method using an automated system by counting the number of positive cells in 2,000 neoplastic cells. MIB-1 score was arbitrarily assigned as positive or negative when the total number of positive cells was greater or less than the median value of cases.

Statistical analysis. The probability of survival was estimated by the Kaplan-Meier method with the log rank test used to estimate differences among levels of analyzed variables. The median Ki-67 labeling index and SPF were used to define groups with low and high proliferative activity values, and survival curves were plotted accordingly. A multivariate Cox proportional hazard model was used to estimate the relative importance of variables for predicting survival. The variables analyzed were tumor stage (pT), NG and DI, adjusted by patient age and sex.

RESULTS

Table 1 lists patient distribution by stage and grade. Tumor specific survival (TSS) in all patients was 83.8% and 79.9% at 5 and 8 years, respectively. Eight-year TSS for pT1a, pT1b and pT2 cases was 92%, 81.1% and 40.1%, respectively (pT1a vs pT1b p = 0.0439, pT1a vs pT2 p = 0.0001 and pT1b vs pT2 p = 0.0008, fig. 1, *A*). Eight-year TSS for NG 1 and 2, 3 and 4 was 88.3%, 75.6% and 33.2%, respectively (NG 1 and 2 vs 3 p = 0.0124, NG 1 and 2 vs 4 p = 0.0001 and NG 3 vs 4 p = 0.0257, fig. 1, *B*).

Ploidy status was determined in 129 cases (table 1). SPF determined in 69 patients was 0% to 30% (mean 3%, median 2.45%) (table 1). Table 1 shows the distribution of DNA ploidy and SPF fraction by tumor stage and NG. There was no correlation between ploidy, and tumor stage and NG, whereas SPF significantly correlated with NG only (p = 0.002, table 1).

The distribution of DNA ploidy was also evaluated in relation to tumor size according to different size thresholds (greater than vs less than or equal to). None and 6.2% of aneuploid tumors were found in patients in whom the primary tumor was 1 to 2 and 2 to 3 cm in greatest diameter, respectively. In patients in whom tumor size was 3 to 4 cm (36), 4 to 5 (27), 5 to 6 (17), 6 to 7 (16) and greater than 7 (17) aneuploid status was 19.4%, 22.2%, 17.6%, 18.7% and 23.5%, respectively.

Eight-year TSS for diploid and nondiploid tumors was 87% and 49.1%, respectively (p = 0.0001, fig. 1, *C*). Eight-year survival for SPF 2.45% or less and 2.46% or greater was 80% and 71%, respectively (p not significant).

Tumor stage survival rates were then adjusted for DNA ploidy (fig. 2, *A*). For pT1a tumors the 8-year TSS rate was 95.2% for diploid and 68.6% for aneuploid lesions (p = 0.0088, fig. 2, *B*). For pT1b tumors the 8-year TSS rate was 90% for diploid and 46.7% for nondiploid lesions (p = 0.0001, fig. 2, *C*). In pT2 cases ploidy status did not correlate with TSS (diploid and aneuploid 49.2% and 25%, respectively, p = 0.6474). DNA ploidy was also significantly associated with survival when adjusted with NG. Patients with NG 1 and 2 diploid lesions had 8-year TSS of 92.9%, whereas patients with NG 1 and 2 aneuploid lesions had 50.6% TSS (p = 0.0001, fig. 3, *A*). In patients with NG 3 and

TABLE 2. *Multivariate Cox proportional hazard model for different variables for predicting tumor specific death risk*

	dF	Coefficient	p Value	RR	95% CI
T1a vs T1b	1	1.375	0.0468	3.956	1.019–15.352
T1a vs T2	1	2.425	0.0012	11.308	2.601–49.165
G1–2 vs G3	1	0.011	Not significant	0.989	0.324–3.022
G1–2 vs G4	1	2.388	0.0003	10.890	3.003–39.485
Diploid vs nondiploid	1	1.111	0.0208	3.037	1.184–7.793

4 tumors 8-year TSS was 76.7% and 47.6% for diploid and nondiploid tumor cell content, respectively ($p = 0.0422$, fig. 3, *B*).

MIB-1 score determined in 88 patients was 0% to 30% (mean 2.3%, median 0.001%). Table 1 shows the distribution of MIB-1 score according to pT status and NG. MIB-1 score correlated statistically only with tumor stage ($p = 0.0295$). Eight-year TSS for tumor MIB-1 negative cases (Ki-67 expression 0.001 or less) was 83%, while it was 79.1% in MIB-1 positive cases (Ki-67 expression greater than 0.001) (p not significant).

The multivariate Cox model showed that DNA ploidy, TNM 2002 tumor stage and Fuhrman grade were significant independent predictors of tumor specific survival (table 2).

DISCUSSION

Recent studies suggest that the clinical behavior of different histological RCC subtypes (chromophobe cell, papillary cell and conventional clear cell) could differ significantly.[15] Therefore, although there is no conclusive evidence,[3,16] a pure population of intracapsular clear cell carcinomas was selected to avoid the possible bias of histological subtype.

In the current series there was a statistically significant difference in TSS among pT1a, pT1b and pT2 tumors. This finding appears to support the validity of 4 cm as a threshold for subdividing pT1a and pT1b tumors, at least for the most common histological subtype, that is clear cell carcinoma. A statistically significant difference in TSS between pT1a and pT1b was also recently reported by Ficarra et al.[16] In addition to tumor size, other variables such as NG, tumor DNA content and proliferative indexes, are commonly listed as predictive factors for defining the final prognosis in patients with RCC.

Fuhrman NG can add important information about patient prognosis. Published evidence suggests that NG is a significant independent prognostic factor for TSS in intracapsular RCC.[2–4] The current results confirm this evidence.

Studies of DNA content provide conflicting results. Some studies show that DNA content has prognostic significance in RCC,[7,11,13,17] whereas others contradict its usefulness.[18,19] For intracapsular RCC the data are even less defined[7,11] and to our knowledge no data have been published to date on the significance of DNA ploidy as a prognostic factor in pT1a and pT1b RCC. Di Silverio et al found that the relative risk of disease progression in patients with intracapsular nondiploid tumors was almost 22 times higher than in patients with intracapsular diploid tumors,[7] while in their study of 52 intracapsular clear cell RCCs Gelb et al did not find that DNA content contributed additional prognostic information to NG and tumor size.[2]

In some of these studies 3 to 8 samples were taken because of clonal heterogeneity.[7,11,18,20] Multiple sampling of the tumor increases the number of nondiploid findings but the presence of a single nondiploid cell population is sufficient to compromise patient survival.[17,20] Moreover, in locally confined clear cell RCC intratumor heterogeneity is less frequent. Indeed, Di Silverio et al found only a 10% heterogeneous DNA pattern in intracapsular tumors and they explained this low incidence by the progressive genomic instability related to tumor growth.[7]

In the current series DI appeared to be an independent risk factor for intracapsular clear cell renal cell tumors with a calculated risk ratio of 3.0 for diploid vs aneuploid lesions. DI improved the prognostic stratification of patients with intracapsular clear cell RCC, as defined by the 2002 TNM system. To our knowledge no studies published to date have evaluated the usefulness of DNA ploidy as a prognostic factor in pT1a and pT1b clear cell RCC. In fact, diploid tumors had a significantly better prognosis than aneuploid tumors in the pT1a and pT1b subgroups (fig. 2, *B* and *C*). On the other hand, stratifying pT2 cases by DNA content did not give a statistically significant result. This may be attributable to a lack of power since there were few pT2 tumors in the study (fig. 2, *A*). By adding aneuploid status to tumor stage it was possible to identify patients with intracapsular clear cell RCC who had a worse prognosis but were not recognizable using the 2002 TNM system and NG separately or combined. This was true especially for tumors 7 cm or less in greatest dimension. Indeed, 8-year TSS for pT1a, pT1a NG 3 and 4, and pT1a aneuploid RCC was 92%, 88.9% and 68.6%, respectively. Eight-year TSS for of pT1b, pT1b NG 3 and 4, and pT1b aneuploid RCC was 81.1%, 70.2% and 46.7%, respectively.

When DNA ploidy was evaluated in relation to different size thresholds (greater than vs less than or equal to), 0% and 6.2% of aneuploid tumors were found in patients in whom the primary tumor was 1 to 2 and 2 to 3 cm in greatest diameter, respectively. For a tumor greatest dimension of greater than 3 cm the nondiploid status rate was almost constant at around 20% of patients. Whether aneuploidy is a cause or a consequence of cancer has long been debated. Our data show that aneuploid status does not represent an early event in the carcinogenesis of clear cell RCC but, when it is present, because of incompletely reported genomic alterations, it tends to worsen the prognosis.

As far as the proliferative activity of RCC is concerned, published data concerning Ki-67 expression and SPF are inconclusive. In their study of 52 intracapsular clear cell RCCs Gelb et al observed that MIB-1 score and SPF did not contribute additional prognostic information to NG and tumor size.[2] Similarly in a large, retrospective, recent series of T1 clear cell RCC MIB-1 was not a significant and independent prognostic factor on multivariate analysis after adjusting for tumor size, NG and tumor necrosis.[12] There was also no significant association in the current series of intracapsular clear cell RCCs between tumor proliferative activity (MIB-1 score and SPF) and TSS or tumor size.

CONCLUSIONS

The current data support the validity of 4 cm as a threshold for subdividing pT1a and pT1b tumors, at least for the most common histological subtype, that is clear cell carcinoma. By adding DNA content when estimating the prognosis of clear cell RCC, the predictive value of the TNM staging system and NG alone or combined can be improved considerably as far as TSS is concerned. This is particularly true for tumors 7 cm or less in greatest dimension. It may serve as a useful adjunct to the 2002 TNM system to better evaluate the prognosis and guide any available further treatment. Therefore, the routine evaluation of tumor DNA content is strongly recommended to

further stratify pT1a, pT1b and pT2 clear cell RCC according to the 2002 TNM system.

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EDITORIAL COMMENT

The literature contains an extensive array of ways to assess the prognosis of localized RCC. Heading the list are stage and NG, which have long been known as good independent predictors of prognosis. However, the system is not perfect for several reasons, among which is tumor heterogeneity as measured by grade. Therefore, other parameters are needed. To this end these authors looked at the impact of ploidy (DNA content) and 2 measures of proliferative status (S-phase or SPF and MIB-1 score) on the new 2002 TNM staging system with respect to TSS. Multivariate analysis demonstrated that, in addition to stage and grade, ploidy independently correlated with TSS, while proliferative status indexes, including SPF and MIB-1, did not. Furthermore, the data support the stratification parameters, as defined by the 2002 TNM system.

The importance of this study is 2-fold. 1) It reaffirms the value of ploidy as an independent predictor of TSS, in addition to tumor stage (TNM 2002) and Fuhrman grade. This vote of confidence is needed because numerous ploidy studies in the last 30 years have yielded inconsistent results. 2) This information adds fuel to the new wave of enthusiasm for the occasional delayed treatment/watchful waiting approach to small renal masses. Nuclear sampling of such masses may give the clinician insight as to which tumor can be followed safely. In this particular study it is interesting that none of the tumors 2.0 cm or less were aneuploid, which correlates perfectly with a 0% incidence of metastasis in a recent study of watchful waiting in 108 patients with tumors 3.0 cm or less followed a mean of 5 years.[1]

Hopefully this information provided by the authors can be extended to provide correlation with other histological subtypes of RCC and provide correlation to tumor progression as well as TSS.

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