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TRANSITIONAL CELL CARCINOMA OF THE RENAL PELVIS AND URETER: PROGNOSTIC RELEVANCE OF NUCLEAR DEOXYRIBONUCLEIC ACID PLOIDY STUDIED BY SLIDE CYTOMETRY: AN 8-YEAR SURVIVAL TIME STUDY

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ABSTRACT

In 72 patients with urothelial carcinoma of the renal pelvis or ureter the ploidy, deoxyribonucleic acid (DNA) heterogeneity and counts of cell cycle phases in the tumor were analyzed by means of single cell DNA cytophotometry with the intention of finding new prognostic factors in addition to those already known (stage and grade). Followup ranged from 1 to 8 years. The results of the DNA analyses were related to the tumor categories, histopathological grading of the tumors and clinical course. Malignancy grade 1 tumors showed DNA frequency peaks in the diploid range, while tumors assessed as malignancy grade 2 showed heterogeneous DNA distribution patterns. Malignancy grade 3 tumors exhibited 71% aneuploid and 29% tetraploid DNA values. The proliferation rate of the tumor cells was statistically significantly higher in malignancy grades 2 and 3 than in malignancy grade 1.

The prognosis for grade 1 tumors is good, whereas it is unfavorable in the case of grade 3 tumors. For these 2 groups (patients with grades 1 and 3 tumors) DNA ploidy affords no additional prognostic information. Grade 2 tumors, on the other hand, are heterogeneous in respect to DNA ploidy although they exhibit the same histomorphological degree of differentiation. These tumors can be subclassified as aneuploid (biologically aggressive) and diploid or tetraploid (biologically less aggressive) tumors.

There was also a positive correlation between T category and DNA ploidy. The cell lines were aneuploid in 38% of the patients with stage T1 tumors, 56% with stage T2 tumors and almost 85% with stage T3, N+ tumors. A significant correlation was found between the results of DNA cytophotometry and the clinical course of the disease. Patients with diploid tumor cell nuclei had no metastases and no local tumor progression for up to 8 years, whereas patients with aneuploid tumor cell nuclei suffered metastasis and local tumor progression within 24 to 36 months. The patients died of the tumor 36 months after primary diagnosis on the average. The determination of DNA ploidy, tumor heterogeneity and tumor cell proliferation by means of DNA cytophotometry affords valuable clues as to prognosis.

KEY WORDS: carcinoma, transitional cell; ureteral neoplasms; kidney pelvis; kidney neoplasms; DNA, neoplasm

The histomorphological classification of tumors of the urothelium is a difficult task even today, mainly because there is no grading system that affords reliably reproducible results.[1–3] Urothelial tumors that are not highly differentiated constitute a heterogeneous group with overlapping histological characteristics, clinical courses and biological behaviors.[1,2] Far more accurately than is possible with visual morphology, the different malignancy potentials of the tumor cell nuclei can be evaluated with the aid of deoxyribonucleic acid (DNA) cytophotometry of the actual tumor cell,[4–8] and the progression of these tumors can, thus, be predicted more exactly. The combined information obtained by the 2 methods, morphology and DNA cytophotometry, provides valuable prognostic indicators that have an influence on treatment and followup.[4–9]

According to Bennington and Beckwith,[10] and Mostofi et al,[11] the decisive pathomorphological criterion for tumor prognosis is loss of differentiation. For Sandritter[12] and Leuchtenberger et al[13] a deviation of the DNA content of tumor cells from the normal (2c) DNA content as established by DNA cytophotometry is indicative of an aneuploid tumor cell population. The heterogeneity of tumor cells has recently received great interest by clinicians because of its significant interrelationship with the course of the tumor before and during treatment, and because of its value as a prognostic indicator. This fact has also been noted by several studies on malignant tumors in a wide variety of organs.[4–8,14–19] In our prospective study the ploidy, DNA heterogeneity and counts of cell cycle phases in the individual malignancy grades were investigated by single cell DNA absorption cytophotometry with the aim of finding new cell-related prognostic factors to complement those conventionally used (stage and grade).

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PATIENTS AND METHODS

Between February 1982 and December 1990, 72 patients underwent radical nephroureterectomy with a bladder cuff and lymphadenectomy for carcinoma of the renal pelvis and ureter. The average age of these patients (38 women and 34 men) was 67 years, with a range of 43 to 85 years. Patients with some other malignant tumor were excluded from the study. Of the patients 52 (72%) were diagnosed as having a tumor of the renal pelvis and 20 (28%) as having a tumor of the ureter (table 1). Abuse of analgesics was reported by 15% of the patients during a 10 to 25-year period and 97% reported recurrent macroscopic hematuria (for an average of 5 to 34 months) before hospitalization. Followup examinations included exfoliative urine cytology every 6 weeks; sonography, cystoscopy

TABLE 1. *Clinical, pathological and DNA cytophotometric parameters in 72 patients with transitional cell carcinoma of the renal pelvis and ureter*

	No. Pts. (%)
Renal pelvis	52 (72)
Ureter	20 (28)
Multiplicity:	
Single	54 (75)
Multiple	18 (25)
Grade:	
1	17 (24)
2	36 (50)
3	19 (26)
Stage:	
1	32 (45)
2	19 (26)
3	21 (29)
DNA ploidy:	
Diploid	23 (32)
Tetraploid	23 (32)
Aneuploid	26 (36)
Analgesics abuse (phenacetin)	10 (15)
Status:	
Alive	41 (57)
Dead	31 (43)
Cause of death:	
Transitional cell Ca	26 (36)
Other	5 (7)

and lavage cytology, and, if necessary, also DNA cytophotometry every 3 months; chest radiography; excretory urogram and, if necessary, also computerized tomography every 6 months.

A total of 72 patients with radiological filling defects indicative of tumors in the renal pelvis or ureter underwent lavage cytology and brush biopsy preoperatively. The technical procedures used have been described previously.[20] After the diagnosis had been confirmed by cytomorphological results, radical nephroureterectomy with removal of a bladder cuff and lymphadenectomy were performed.

Immediately after removal of the tumor-bearing kidney the renal pelvis was dissected and 1 or several wedge-shaped segments were excised from the tumor, the number depending on the size of the tumor. Several cytological scrape preparations were made of the sagittal cut surface of these sections and of several macroscopically normal areas of the renal pelvis or ureter, and they were fixed with a spray fixative. Some of the preparations were stained with Papanicolaou's stain for cytomorphological evaluation. These specimens were later compared with the final histological results. For the determination of DNA the preparations were stained by Feulgen's reaction (30-minute hydrolysis in 5 N. hydrochloric acid at room temperature), which is specific for DNA (fig. 1). Leukocytes from peripheral blood from healthy donors treated in the same manner as the test material were used as reference preparations for the determination of DNA diploidy. As a rule, approximately 100 tumor cell nuclei were measured, occasionally more. The DNA content of these nuclei was determined by means of single cell absorption photometry.

The fine scanning procedure with a Leitz MPV-2 cytophotometer was used to measure the cell nuclei. The scanning stage, measuring procedure and recording of the absorption were controlled by a Digital pdp 8a process computer. The respective total extinction values measured were printed together with the mean value, standard deviation, variance and coefficient of variation. The results are printed in the form of a histogram in which the number of tumor cell nuclei measured is marked as n on the ordinate, and the relative DNA content of the individual cell populations, given in relative c and expressed in arbitrary units, is plotted against the abscissa. Figure 2 shows typical DNA histograms. The tumors exhibit either a diploid or several aneuploid or tetraploid DNA cell lines.

Data analysis. The computer of the University Institute for Medical Statistics and BMDP Software were used for documentation and data analysis. The statistical analysis of survival curves was made according to the Kaplan-Meier model for censored data.[21] The individual survival curves were compared by means of the multivariate analysis according to the methods of Breslow,[22] Mantel[23] and Cox.[24]

RESULTS

Tumor stage—histological and cytomorphological classification. The dissemination of the tumor was determined according to the tumor, nodes and metastasis classification recommended by the International Union Against Cancer.[25] Of the patients 32 (45%) had stage pT1 pNO, 19 (26%) stage pT2 pNO, 14 (19%) stage pT3 pNO and 7 (10%) stage pT3 pN+ disease (table 1). The tumors were classified histologically according to the guidelines issued by the World Health Organization,[11] whereas the evaluation of cellular anaplasia in the cytological preparations was assessed according to the classification suggested by Mostofi et al,[11] and Bennington and Beckwith (fig. 3).[10] The histological malignancy grade 2 was found to prevail, at 50%, in the entire case material, followed by malignancy grades 3 (26%) and 2 (24%, table 1).

DNA ploidy and grade of malignancy. A positive correlation was found between the cellular anaplasia of the tumor cells and their DNA content. A total of 117 DNA histograms, 11 of which were histograms of lymph node metastases, was analyzed. In the 17 patients (24%) with grade 1 tumors 88% of the tumor cell nuclei measured exhibited diploid (2c), 5% tetraploid (4c) and 7% aneuploid DNA distribution patterns (fig. 2, *A*). The 2c deviation index established for the DNA histograms of grade 1 tumors was 1.9 and the 4.5c exceeding rate was 8.2% (table 2). The 36 patients with grade 2 tumors showed heterogeneous DNA distribution patterns, with DNA frequency peaks in the diploid, tetraploid and aneuploid ranges, although the carcinomas exhibited the same morphological degree of differentiation.

The DNA content measured in the tumor cell nuclei was in the diploid range in 23%, in the tetraploid range in 35% and in the aneuploid range in 42% of the specimens (fig. 4). Patients with aneuploid DNA distribution patterns showed DNA frequency peaks in the diploid (2c) and tetraploid (4c) ranges as well as scattered values from 1c to 13c (fig. 2, *B*). The 2c deviation index was 28.3 and the 4.5c exceeding rate was 40.2%. The DNA content measured in the tumor cell nuclei of the 19 patients with grade 3 tumors was tetraploid in 29% and aneuploid in 71% as demonstrated by the ploidy distribution (figs. 2, *C* and 4). The 4.5c exceeding rate was 71%.

DNA ploidy and pathological tumor stage. There was also a positive correlation between DNA ploidy and tumor stage. The DNA cell lines were aneuploid in 38% of the patients with stage T1 tumors, 56% with stage T2 tumors and almost 85% with stage T3 tumors, with or without lymph node infiltration (fig. 5).

Grade of malignancy and 4.5c exceeding rate. A reliable diagnosis of the malignancy of a tumor can be made by using the 4.5c exceeding rate, a statistical parameter that indicates the percentage of clearly aneuploid tumor cell nuclei. The DNA distribution patterns established for the 72 patients in this study are shown in table 2. The rate of aneuploid cells found in grade 1 tumors was only 8.2%, while it was 40.2% for grade 2 tumors and 71% for grade 3 tumors.

DNA ploidy and abuse of analgesics. It is noteworthy that the nuclear DNA distribution measured in the 11 patients with carcinoma of the renal pelvis or ureter who had reported phenacetin abuse was aneuploid. In addition to multifocal tumor dissemination, these patients exhibited severe cellular anaplasia even at 6 cm. from the tumor. These findings were established by scrape cytology and confirmed by the broad DNA distributions demonstrated by DNA cytophotometry (fig. 2, *C* and *D*). Of the 11 patients 8 had DNA distribution patterns with several cell lines, a 2c deviation index of 58 and a 4.5c exceeding rate of 85%.

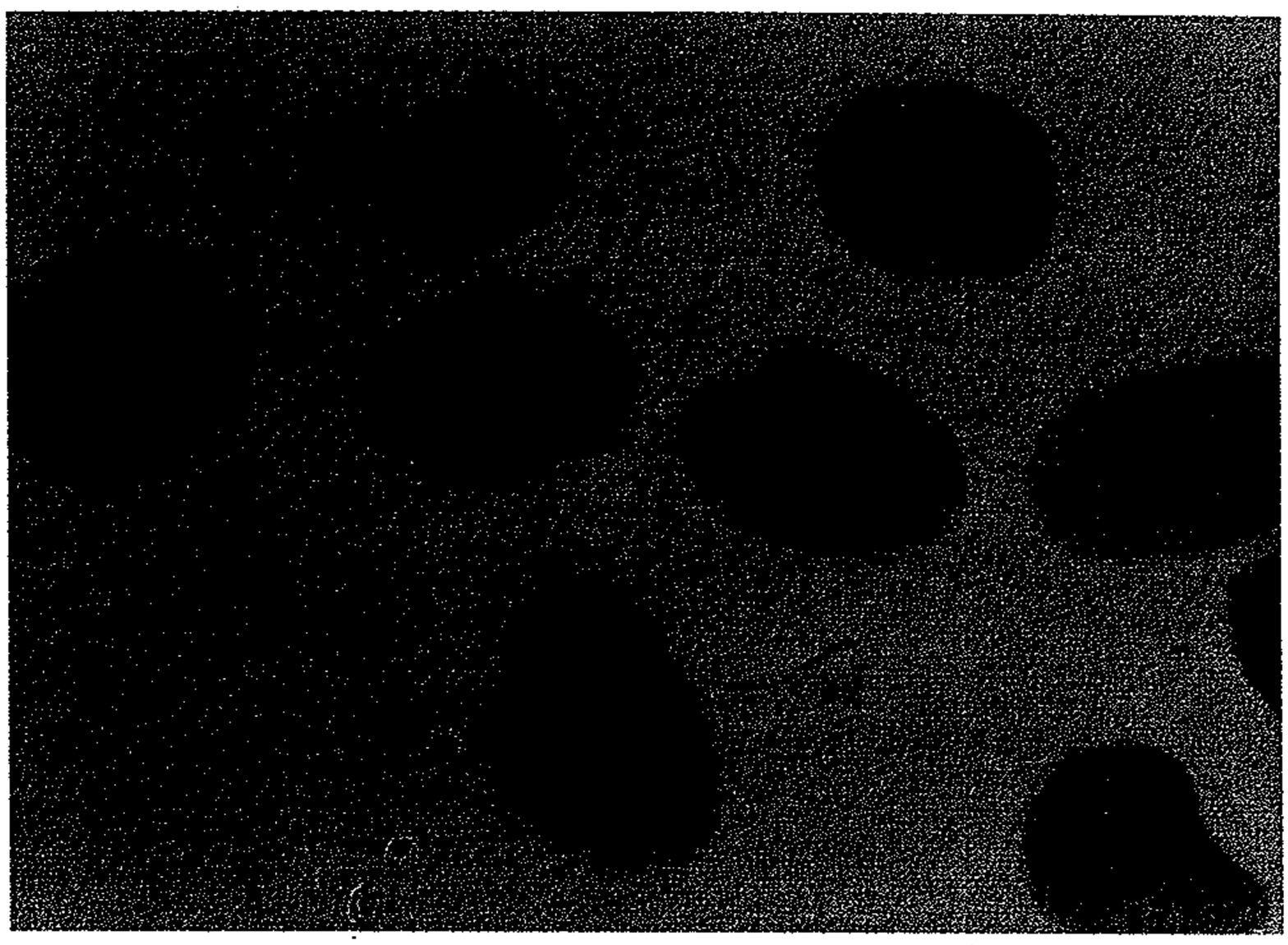

FIG. 1. Feulgen's reaction shows isolated, clearly distinguishable cell nuclei without overlapping or artifacts. Reduced from ×1,000

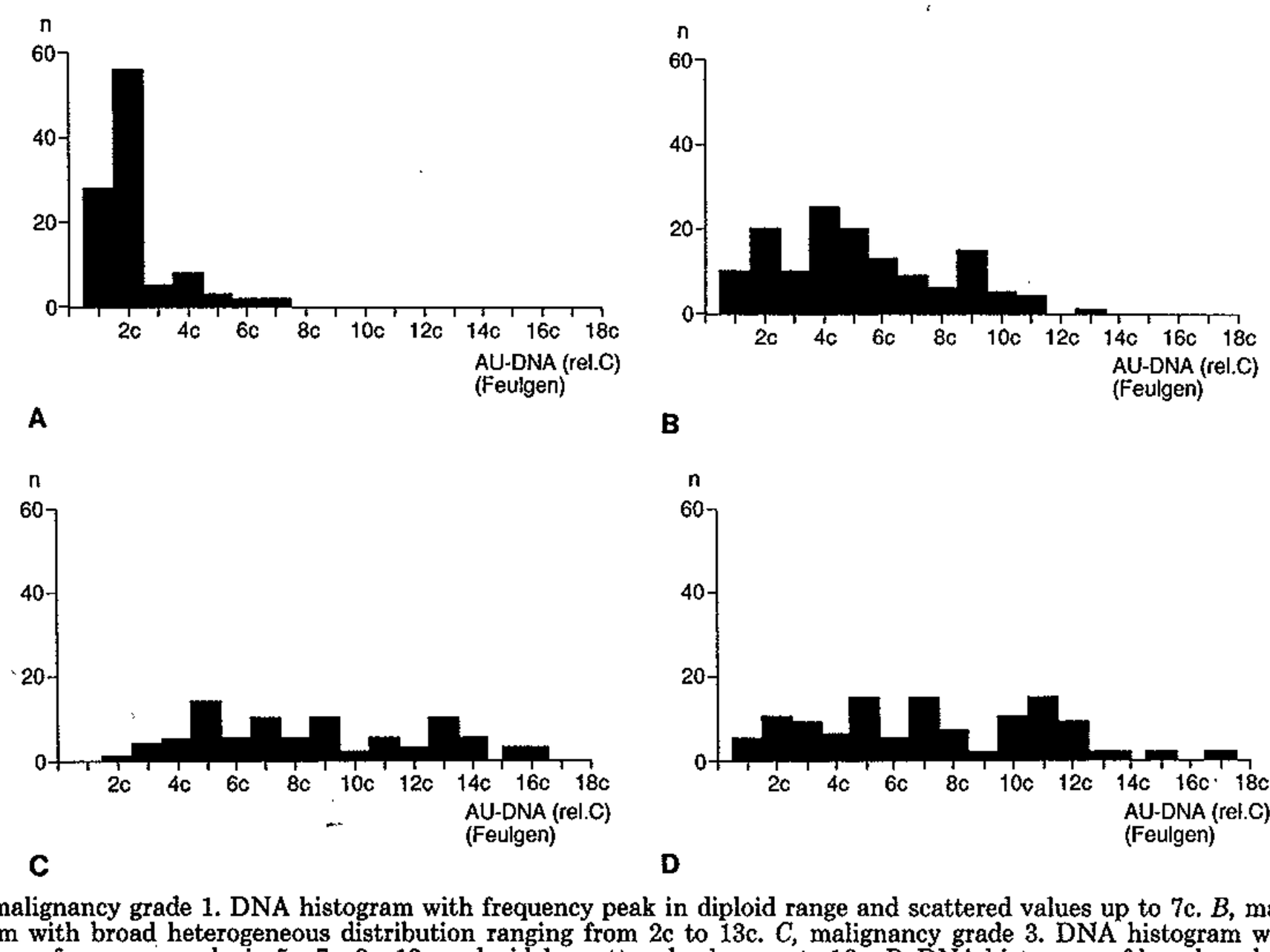

FIG. 2. *A*, malignancy grade 1. DNA histogram with frequency peak in diploid range and scattered values up to 7c. *B*, malignancy grade 2. DNA histogram with broad heterogeneous distribution ranging from 2c to 13c. *C*, malignancy grade 3. DNA histogram with heterogeneous distribution shows frequency peaks in 5c, 7c, 9c, 13c and widely scattered values up to 16c. *D*, DNA histogram of lymph node metastasis shows aneuploid DNA distribution. *AU-DNA (rel. C)*, arbitrary units.

DNA ploidy and relapse in ureteral stumps. In 3 patients nephrectomy alone was performed because it would have been too dangerous to have prolonged the operation time. Tumor occurred in the ureteral stumps of 2 of these 3 patients within 5 and 11 months, respectively. Nuclear DNA histograms for these 2 patients showed aneuploid and tetraploid DNA distributions.

DNA ploidy and multiplicity of the tumor. Of the 26 patients whose tumors showed DNA aneuploidy 18 (69%) exhibited multifocal spreading (table 3). In these patients scrape cytology even showed microscopic changes indicative of carcinoma in situ in the urothelium in the immediate vicinity of the tumor.

DNA ploidy and lymph node status. DNA analyses of the cell nuclei in the lymph node metastases of carcinomas of the renal pelvis and ureter of 7 patients showed the same percentage of aneuploidy as the primary tumors (DNA histogram, fig. 2, *D*).

FIG. 3. *A*, cytological smear of grade 1 carcinoma shows slight nuclear polymorphism and prominent nucleoli. *B*, cytological smear of grade 2 carcinoma reveals moderate nuclear polymorphism and hyperchromatism. Prominent nucleoli have lost circular shape. Locally, nuclei have more than 1 nucleolus. There is disturbance of nuclear arrangement. *C*, cytological smear of grade 3 carcinoma shows distinct nuclear polymorphism and hyperchromatism with polymorphic nucleoli. Papanicolaou stain, reduced from ×1,000.

TABLE 2. *Distribution of 4.5c exceeding rate according to grade of malignancy*

Grade	4.5 Exceeding Rate
1	8.2
2	40.2
3	71

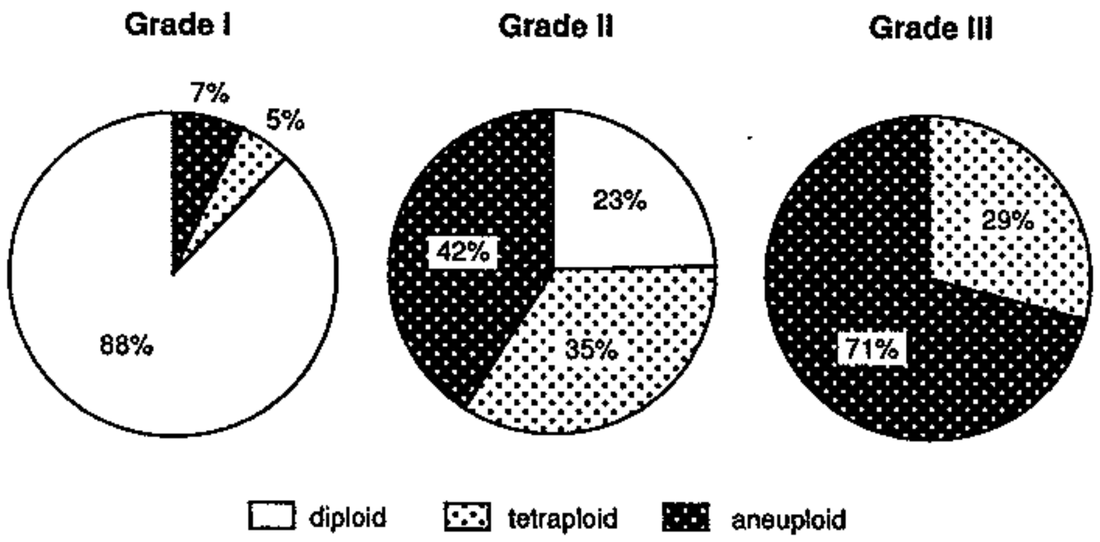

FIG. 4. Correlation of DNA ploidy and grades of malignancy in 72 patients with carcinoma of renal pelvis and ureter.

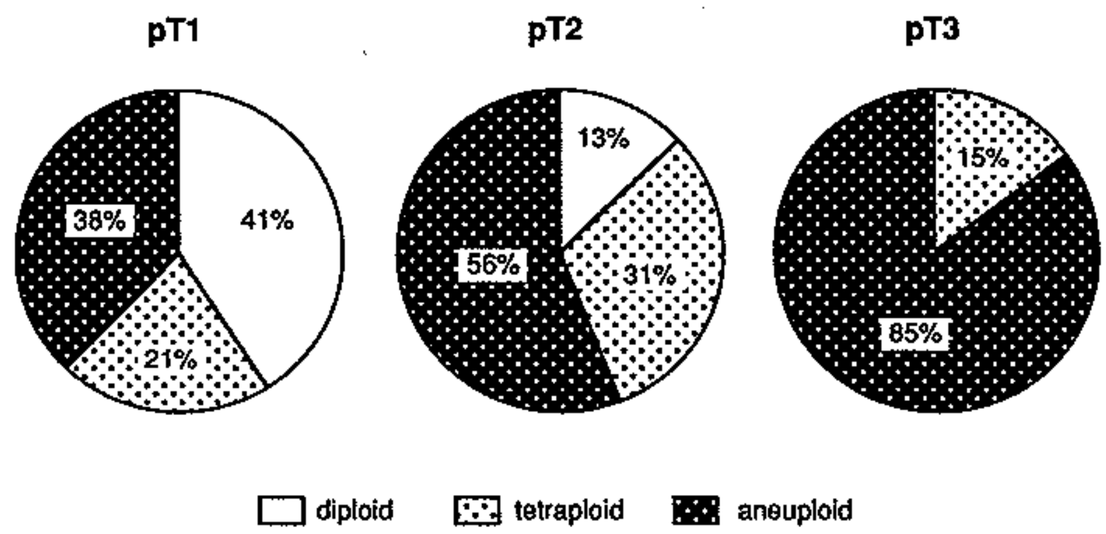

FIG. 5. Correlation of DNA ploidy and histological staging of urothelial carcinoma of renal pelvis and ureter in 72 patients.

TABLE 3. *Multiplicity distribution of transitional cell carcinoma of the renal pelvis and ureter in 18 patients*

Multiplicity	No. Pts. (%)
Renal pelvis	5 (28)
Ureter	3 (17)
Renal pelvis and bladder	4 (22)
Bilat. renal pelvis	4 (22)
Bilat. renal pelvis, ureter and bladder	2 (11)

Significant differences in DNA distribution as compared with the primary tumor were not seen in our patients.

DNA ploidy and metastatic dissemination. A total of 23 patients with diploid DNA distribution patterns (DNA frequency peak in the 2c range) had no metastases during the 8-year observation period and none died of carcinoma. Of the patients with aneuploid tumors, however, and especially patients with reported phenacetin abuse, 84% suffered tumor progression with metastases to other organs (that is retroperitoneal lymph nodes in 43%, lungs in 32% and bones in 26%) within 28 to 36 months and they died of the tumors.

Prognostic significance of DNA ploidy. The DNA ploidy and cell line heterogeneity were significant for the prognosis. Patients with aneuploid DNA distribution patterns died sooner than patients with diploid cell lines. Of the patients with diploid or tetraploid DNA distribution patterns 5 (7%) died of cardiopulmonary disease: 3 had diploid and 2 had tetraploid DNA distribution patterns. Of the 26 patients with aneuploid DNA distribution patterns 22 (84%) died of metastasis of the primary disease. Two patients had metastases in the lymph nodes, bones and lungs within 16 and 21 months after tumor nephrectomy but they have been clinically stable with methotrexate, vinblastine, doxorubicin and cisplatin chemotherapy.[26] Two patients were clinically stable while exhibiting neither metastases nor tumor progression at 11 and 17 months postoperatively. The remaining 41 patients (57%) have shown no signs of progression of the primary disease (table 4 and fig. 6, *C*).

Multivariate analysis. To confirm DNA ploidy and histological grade as significant and independent factors in the prognosis of urothelial carcinoma, regression analysis as described by Breslow,[22] Mantel[23] and Cox[24] was used to compare 5 variables in relation with the corrected survival time: 1) patient age at primary diagnosis, 2) sex, 3) histological grade, 4) stage of the tumor and 5) grade of DNA ploidy. There were no significant differences in survival times between stages 1 versus 2 and between diploid versus tetraploid DNA patterns, nor were there such differences with respect to patient sex and biological age (less than or greater than 60 years old, table 5). The other parameters, that is malignancy grades 1 versus 2 ($p < 0.01$) versus 3 ($p < 0.001$), stages 1 versus 3 ($p < 0.001$) and diploid versus aneuploid ($p < 0.001$) versus tetraploid ($p < 0.05$) DNA distribution patterns, show statistically significant differences. In the multivariate analysis, all of these parameters, that is histological grade, extent of tumor infiltration (stage) and DNA ploidy, must be taken as significant and noninterdependent prognostic variables, which strongly correlate with survival time. If the histological malignancy grading was excluded because of its insufficient interindividual reproducibility, DNA ploidy and tumor stages would be regarded as reliable, objective

TABLE 4. *Correlation of nuclear DNA patterns and clinical course in 72 patients with transitional cell carcinoma of the renal pelvis and ureter*

DNA Histogram Pattern	No. Pts.	Died of Metastatic Transitional Cell Ca No. (%)
Diploid	23	—
Tetraploid	23	4 (17)
Aneuploid	26	22 (84)

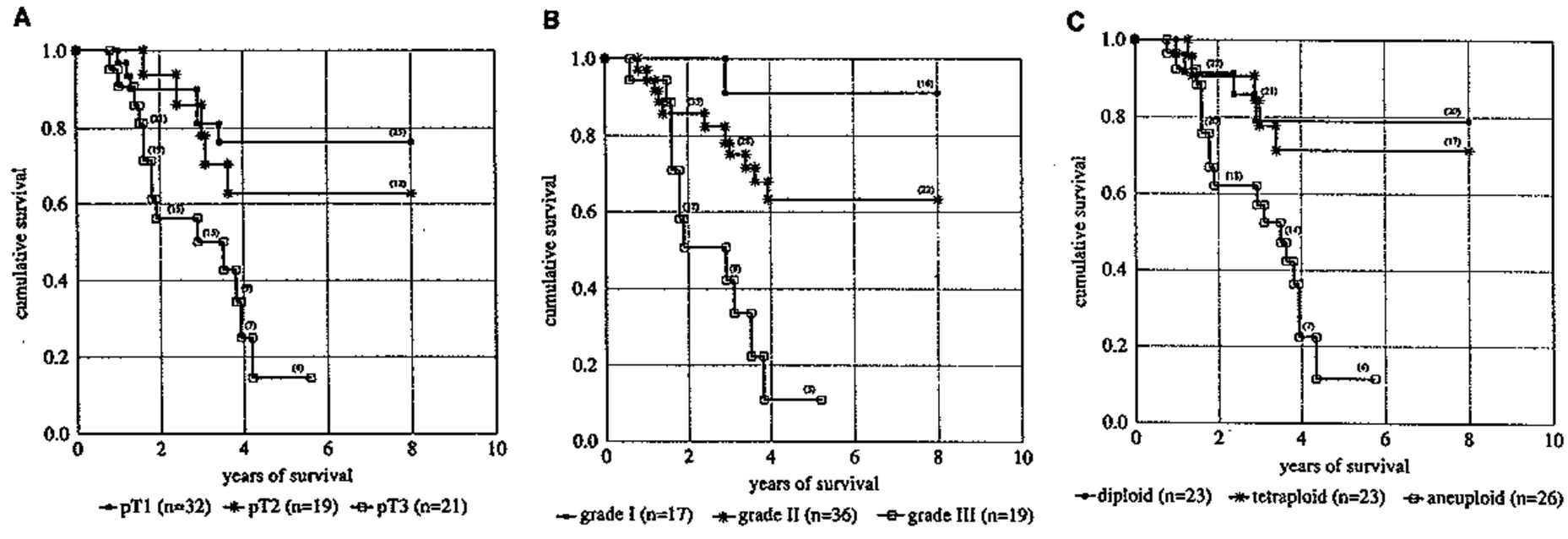

FIG. 6. Survival times of 72 patients with transitional cell carcinoma. *A*, grouped according to stages 1 versus 2 ($p > 0.5$) versus 3 ($p < 0.001$). *B*, grouped according to tumor grades 1 versus 2 ($p < 0.01$) versus 3 ($p < 0.001$). *C*, grouped according to DNA ploidy: diploid versus tetraploid ($p > 0.5$) versus aneuploid ($p < 0.001$).

TABLE 5. *Multivariate analysis: correlation of survival rates with clinical, pathomorphological (stage and grade) and DNA cytometric parameters in 72 patients with transitional cell carcinoma of the renal pelvis and ureter*

	No.	P Value Breslow (Wilcoxon)/ Savage (Mantel-Cox)	P Value
Pt. age (yrs.):			
Less than 60	11	0.338	Not significant
Greater than 60	61	0.417	
Men	37	0.983	Not significant
Women	35	0.818	
Stage:			
pT1 versus pT2		0.933/0.697	>0.50
pT1 versus pT3		0.0008/0.0008	<0.001
pT2 versus pT3		0.0161/0.0197	<0.05
Ploidy:			
Diploid versus tetraploid		0.713/0.507	>0.50
Diploid versus aneuploid		0.0006/0.0005	<0.001
Tetraploid versus aneuploid		0.0539/0.0377	<0.05
Grade:			
1 versus 2		0.045/0.045	<0.01
1 versus 3		0.0004/0.0001	<0.001
2 versus 3		0.0015/0.0017	<0.01

and independent parameters in respect to tumor progression and prognosis for the patient.

Our results show that the prognosis for grade 1 tumors is good, whereas it is unfavorable in the case of grade 2 tumors. For these 2 groups (patients with grades 1 and 3 tumors) DNA ploidy affords no additional prognostic information. Grade 2 tumors, on the other hand, are heterogeneous in respect to DNA ploidy although they exhibit the same histomorphological degree of differentiation. These tumors can be subclassified as aneuploid (biologically aggressive) and diploid or tetraploid (biologically less aggressive) tumors with the aid of DNA cytometry.

DISCUSSION

According to Bergkvist et al the stage and pathohistological grading of a tumor do not suffice to judge its biological aggressiveness in respect to recidivation, invasion and metastatic growth.[1] Since histological grading is subjective and not uniform,[2,3] it is necessary to assess the grade of malignancy and tumor stage objectively by means of prognostic methods of investigation.[4-6,14,16] Presently, there are 2 different methods of measuring the nuclear DNA content of malignant and benign tumors: 1) flow through cytophotometry, which is the most common method, and 2) single cell cytophotometry, which is used less often.

Comparative studies of the 2 methods have shown that single cell cytophotometry yields exact information on the DNA content because it permits measurement of cells that have already been diagnosed visually as tumor cells. Single cell cytophotometry is time-consuming, however, since it involves placing each individual cell on the scanning stage of the photometer. The time disadvantage (2 to 4 minutes per cell nucleus) is outweighed by the advantage afforded by the fact that it is possible to perform qualitative cell morphology and quantitative measurement of nuclear DNA in the same material, and to match the results. The position of a cell on a slide can be recorded for subsequent analyses. Another crucial advantage of single cell cytophotometry is the possibility of performing cytochemical analyses in cytomorphologically identified cells. However, it is an absolute prerequisite for a morphologist who wants to use single cell cytophotometry to have profound cytomorphological knowledge.

The introduction of flow through cytophotometry made it possible to analyze up to 1,000 cells within 1 second due to the high measuring speed of the apparatus. This advantage is exploited by researchers in various areas of cytobiological tumor research. A disadvantage of the method, however, is that it is impossible to assign the DNA contents measured to the morphology of the respective cells. Another disadvantage lies in the fact that it often is not possible to analyze the cell cycle in specimens with various cell populations.[5,6,27-31]

Researchers often use autoradiographic examinations to assess the proliferative activity of a tumor. However, this method is not suitable for clinical application because of the procedures it involves. The results of our DNA analyses indicate that urothelial carcinomas exhibit different biological growth patterns and, thus, are presumably a heterogeneous class. The few studies on urothelial tumors published to date, most of which are based on flow through cytophotometry, report diverse results and high DNA values for poorly differentiated urothelial carcinomas of the bladder.[4,7,8,16,17] To our knowledge this is the first prospective study on urothelial carcinoma of the renal pelvis and ureter in which DNA analyses have been conducted by single cell cytophotometry for a followup of 8 years. Our results show that the DNA ploidy, tumor heterogeneity and distribution of the individual cell cycle phases of the tumors are independent factors that are of considerable value for predicting patient survival.

Detailed investigations have shown that nuclear DNA analysis can contribute to the existing clinical and morphological parameters by the prognostically supplementary information it affords. In this context we would like to mention our previous studies on 329 patients with prostatic carcinoma, 112 with renal cell carcinoma and 127 with urothelial carcinoma of the bladder conducted during a followup of 9 years.[6,29-31] The results of the study on 409 patients with mammary carcinoma conducted by Fallenius underline the prognostic significance of DNA ploidy.[32] Other investigations based on flow through

cytophotometry indicate a correlation between the histological grade of malignancy of a tumor and the DNA content of the tumor cell nuclei.[4,7,8]

During the last few years various working groups have reported that it is possible to measure DNA by flow through cytophotometry in cell material embedded in paraffin. In 1988 a research team at the Mayo Clinic used this method in 119 cases of urothelial carcinoma of the renal pelvis and confirmed the prognostic relevance of DNA ploidy that we had shown using single cell cytophotometry.[17] In our study we found an aneuploidy rate of 7% in highly differentiated urothelial tumors and a 71% rate in poorly differentiated tumors. Others who used flow through cytophotometry to investigate tumors of the lungs found aneuploidy rates of up to 85%.[33]

A negative turn of prognosis in the individual case can be deduced from a broad scattering of DNA values as manifest in the histogram. A similar conclusion can be drawn from the ratio of diploid cells to aneuploid cells. This ratio is particularly important for carcinomas with grade 2 malignancy, which are uniform with regard to morphology but heterogeneous with respect to malignancy potentials.

DNA histograms show the distribution of the cell cycle phases in a cell population measured. The individual tumor cell nuclei are assigned to the different phases of the cell cycle (G0/G1, S phase and G2/M phases) according to the DNA content. Changes in cellular genetics result in corresponding changes in the DNA histograms.[12,13] The prognosis for patients with more than 88% diploid cells (G0/G1 phase) is better than for those with a lower percentage of diploid cells. As a rule, a high percentage of G0/G1 cells is a sign of a slow growth rate of the tumor. The differences in survival times associated with the rates of diploid cells and proliferating aneuploid cells are not only evident in the patients with malignancy grade 1 but also in those with malignancy grades 2 and 3 (fig. 6).

The patients with nephropathy caused by analgesic abuse who also showed multifocal tumor dissemination exhibited high DNA values with predominantly aneuploid DNA distribution and several DNA cell lines in DNA cytophotometry. Prolonged phenacetin abuse presumably provokes aggressive cytochemical and morphological changes in the epithelial cells, which lead to the development of a biologically highly aggressive tumor.

CONCLUSIONS

DNA histograms define the biological characteristics of a tumor more precisely than the criteria by which the clinical status of the disease is judged. Only in the case of grades 1 and 3 tumors does the histological grading correlate with the nuclear DNA content. Our study has shown that the prognosis for grade 1 tumors is good, whereas it is unfavorable for grade 3 tumors. For both of these groups DNA ploidy affords no additional prognostic information. Grade 2 tumors, on the other hand, are heterogeneous in respect to DNA ploidy, although they exhibit the same histomorphological degree of differentiation. These tumors can be subclassified as aneuploid (biologically aggressive) and diploid or tetraploid (biologically less aggressive) with the aid of DNA cytometry. Analyses of DNA ploidy and tumor cell heterogeneity by means of DNA cytophotometry afford additional valuable information. Our results of DNA cytophotometry in tumors of the renal pelvis and ureter, as well as the retrospective studies conducted by Zincke and Neves in 1984[34] and by Nagel et al in 1989[9] indicate that nephroureterectomy with lymphadenectomy and removal of a bladder cuff is the treatment of choice in most cases, particularly for nephropathy caused by phenacetin abuse. Segmental resection of tumors of the renal pelvis and ureter, and also endoscopic resection or laser therapy appear to be applicable to special cases, such as patients with a solitary kidney, decreased function of the contralateral kidney or highly differentiated carcinoma.

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