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Needle biopsy DNA ploidy status predicts grade shifting in prostate cancer.

Ross JS, Sheehan CE, Ambros RA, Nazeer T, Jennings TA, Kaufman RP Jr, Fisher HA, Rifkin MD, Kallakury BV.

Department of Pathology and Laboratory Medicine, Albany Medical College, New York 12208, USA.

DNA ploidy analysis of prostate needle biopsy specimens was performed to determine whether ploidy status could predict tumor grade shifting at radical prostatectomy. The paired needle biopsy and radical prostatectomy specimens from 111 randomly selected men with prostate cancer were obtained from the surgical pathology files of the Albany Medical Center Hospital. The original tumor grades were assigned by a staff of 12 surgical pathologists according to the Gleason system. Tumors with original Gleason scores < or = 6 were classified as low grade, and tumors with scores of > or = 7 were considered high grade. DNA ploidy analysis was performed on the needle biopsy specimens using the CAS 200 image analyzer (Becton Dickinson Immunocytometry Systems, Mountain View, CA, USA) on Feulgen stained 5-microm tissue sections. There were 88 diploid and 23 nondiploid cases. Thirty-eight of 111 (34%) of cases had grade shifting from needle biopsy to radical prostatectomy specimens. Of 89 low-grade needle biopsy cases, 28 (31%) were upgraded at radical prostatectomy. Of 22 high-grade needle biopsy cases, 10 (45%) were downgraded to low grade at radical prostatectomy. Of the 28 low-grade needle biopsy specimens that were upgraded at radical prostatectomy, 19 (68%) featured an aneuploid histogram and 9 (32%) were diploid. Nineteen of 28 (68%) of aneuploid low-grade tumors on needle biopsy became high-grade at radical prostatectomy. Nine of 10 (90%) diploid high-grade tumors at needle biopsy became low-grade at radical prostatectomy. Of the 38 cases in which ploidy and grade were incongruous, 28 (74%) had grade shifting. In a multivariate regression analysis, a high-grade Gleason score on radical prostatectomy specimens correlated significantly with needle biopsy ploidy ($p = 0.0001$) but not with needle biopsy grade ($p = 0.15$). The sensitivity of the needle biopsy grade in the detection of high-grade tumors on radical prostatectomy was 30%, and the specificity was 86%. The sensitivity of ploidy status in the prediction of high grade at radical prostatectomy was 78%, and the specificity was 96%. With a prostate-specific antigen (PSA) level of >0.4 ng/ml as the indicator of post-radical prostatectomy disease recurrence on a subset of 106 patients, on univariate analysis, disease recurrence was predicted by needle biopsy ploidy ($p = 0.001$) and radical prostatectomy grade ($p = 0.04$) but not by needle biopsy grade ($p = 0.39$). On multivariate analysis, needle biopsy DNA ploidy status independently predicted disease recurrence ($p = 0.002$), whereas needle biopsy and prostatectomy grade did not. These results indicate that DNA ploidy analysis of needle biopsy specimens of prostate cancer predicts grade shifting, that it is a more sensitive and specific indicator of final tumor grade at radical prostatectomy than is the original needle biopsy grade, and that ploidy status independently predicts postoperative disease recurrence.

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Needle Biopsy DNA Ploidy Status Predicts Grade Shifting in Prostate Cancer

Ross, Jeffrey S. M.D.; Sheehan, Christine E. B.S.; Ambros, Robert A. M.D.; Nazeer, Tipu M.D.; Jennings, Timothy A. M.D.; Kaufman, Ronald P. Jr. M.D.; Fisher, Hugh A.G. M.D; Rifkin, Matthew D. M.D.; Kallakury, Bhaskar V.S. M.D.

Author Information
From the Departments of Pathology and Laboratory Medicine (J.S.R., C.E.S. R.A.A., T.N., T.A.J., B.V.S.K.), Surgery (Urology) (R.P.K.), and Radiology (M.D.R.), Albany Medical College, Albany, New York.
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Address correspondence and reprint requests to Dr. Jeffrey S. Ross, Department of Pathology and Laboratory Medicine (A-81), Albany Medical College, 47 New Scotland Avenue, Albany, NY 12208, USA.

Abstract

DNA ploidy analysis of prostate needle biopsy specimens was performed to determine whether ploidy status could predict tumor grade shifting at radical prostatectomy. The paired needle biopsy and radical prostatectomy specimens from 111 randomly selected men with prostate cancer were obtained from the surgical pathology files of the Albany Medical Center Hospital. The original tumor grades were assigned by a staff of 12 surgical pathologists according to the Gleason system. Tumors with original Gleason scores <=6 were classified as low grade, and tumors with scores of >=7 were considered high grade. DNA ploidy analysis was performed on the needle biopsy specimens using the CAS 200 image analyzer (Becton Dickinson Immunocytometry Systems, Mountain View, CA, USA) on Feulgen stained 5-μm tissue sections. There were 88 diploid and 23 nondiploid cases. Thirty-eight of 111 (34%) of cases had grade shifting from needle biopsy to radical prostatectomy specimens. Of 89 low-grade needle biopsy cases, 28 (31%) were upgraded at radical prostatectomy. Of 22 high-grade needle biopsy cases, 10 (45%) were downgraded to low grade at radical prostatectomy. Of the 28 low-grade needle biopsy specimens that were upgraded at radical prostatectomy, 19 (68%) featured an aneuploid histogram and 9 (32%) were diploid. Nineteen of 28 (68%) of aneuploid low-grade tumors on needle biopsy became high-grade at radical prostatectomy. Nine of 10 (90%) diploid high-grade tumors at needle biopsy became low-grade at radical prostatectomy. Of the 38 cases in which ploidy and grade were incongruous, 28 (74%) had grade shifting. In a multivariate regression analysis, a high-grade Gleason score on radical prostatectomy specimens correlated significantly with needle biopsy ploidy ($p = 0.0001$) but not with needle biopsy grade ($p = 0.15$). The sensitivity of the needle biopsy grade in the detection of high-grade tumors on radical prostatectomy was 30%, and the specificity was 86%. The sensitivity of ploidy status in the prediction of high grade at radical prostatectomy was 78%, and the specificity was 96%. With a prostate-specific antigen (PSA) level of >0.4 ng/ml as the indicator of post-radical prostatectomy disease recurrence on a subset of 106

patients, on univariate analysis, disease recurrence was predicted by needle biopsy ploidy ($p = 0.001$) and radical prostatectomy grade ($p = 0.04$) but not by needle biopsy grade ($p = 0.39$). On multivariate analysis, needle biopsy DNA ploidy status independently predicted disease recurrence ($p = 0.002$), whereas needle biopsy and prostatectomy grade did not. These results indicate that DNA ploidy analysis of needle biopsy specimens of prostate cancer predicts grade shifting, that it is a more sensitive and specific indicator of final tumor grade at radical prostatectomy than is the original needle biopsy grade, and that ploidy status independently predicts postoperative disease recurrence.

Among the various traditional and newly developed markers designed to determine prognosis in prostate cancer, tumor grading remains a cornerstone. There is general consensus that men with higher-grade tumors experience a progressively decreasing life expectancy.[2] Serum prostate-specific antigen (PSA) screening with transrectal ultrasound guided automatic needle biopsy has become the standard of primary diagnosis of prostate cancer in the United States. Thus, in order for tumor grading to play a pivotal role in the prospective selection of therapy for men with the disease, it must be determined on the original needle biopsy specimen. However, considerable controversy exists as to the accuracy of tumor grading of needle biopsy specimens.[6,7,10,15,18,20-22,27,31,36-38] Although some investigators have found predictive value in the needle biopsy tumor grade,[30] others have emphasized the variability in the grading of biopsy specimens.[23] In the United States, the Gleason system is the most widely accepted method of tumor grading.[16,17] However, a wide range in the correlation rates between needle biopsy and radical prostatectomy tumor grades has been reported,[12] and the problem of the undergrading of needle core biopsy specimens has received particular emphasis.[12]

The presence of nondiploid total DNA content patterns in prostatic adenocarcinoma has generally been associated with early disease relapse and shortened patient survival.[1,8,11,13,14,19,25,26,28,29,32-36,39,41-43] However, most of these studies have been performed on disaggregated prostatectomy tissues, and prospective studies designed to test the prediction of disease outcome by measuring DNA content in prostate cancer needle biopsy specimens are limited.[1,14,24,27] Moreover, the specific utility of total DNA content measurements for prediction of the accuracy of tumor grading on prostate cancer needle core biopsy specimens has not been considered. In the following study, DNA ploidy analysis was performed by image cytometry on prostate needle biopsy specimens to determine whether ploidy status could predict tumor grade shifting at radical prostatectomy.

MATERIALS AND METHODS

Patients

One hundred eleven men with a diagnosis of prostate cancer by needle biopsy and treated by radical prostatectomy at the Albany Medical Center Hospital during the years 1989-1996 were included in this study. The original study group consisted of 124 patients, but 13 (10%)

cases were eliminated from the study because the coefficients of variation of the G_0/G_1 peaks in the DNA ploidy histograms were too large (>15%), or the biopsy specimens contained insufficient tumor cell nuclei (<100 nuclei) to enable the DNA ploidy analysis to be performed. The medical records of all patients were reviewed, and the needle biopsy and corresponding radical prostatectomy tumor grades were obtained from the surgical pathology reports. The preoperative and postoperative serum PSA levels (Hybritech method; Hybritech, San Diego, CA) were also recorded. After surgery, the patients were evaluated quarterly, and a postprostatectomy serum PSA level > 0.4 ng/ml was considered positive for biochemical disease recurrence. Clinical follow-up was available in a subset of 106 patients and ranged from 2 to 71 months, with a mean of 27 months.

Tumor Grading

The original tumor grades assigned to the needle biopsy and radical prostatectomy specimens were derived by use of the Gleason system.[16,17] In all cases, the original grades supplied by the reporting pathologists (members of a 12-person surgical pathology university faculty practice) were used. In all cases, tumor grading was performed on 5-μm, hematoxylin and eosin stained, formalin-fixed, paraffin-embedded tissues. Tumors with Gleason scores of <=6 were recorded as low grade, and tumors with Gleason scores of >=7 were recorded as high grade.

DNA Content Analysis

Total DNA content (ploidy) was determined as previously described, with certain modifications.[8] After calibration of the CAS 200 image analyzer (Becton Dickinson Immunocytometry Systems, Mountain View, CA, USA), total DNA content was measured on Feulgen-stained 5-μm-thick prostate needle biopsy specimens. To account for nuclear fragmentation on the histologic sections, the mathematical algorithm to correct for variation in section thickness published by Bacus and Bacus was used.[3] A histogram including a minimum of 100 cells was developed for each specimen. In all cases, the histograms were obtained from the tumor areas that appeared to have the highest tumor grades. The coefficients of variation for the G_0G_1 peaks of nontumoral prostate acinar cells analyzed by this method varied from 9% to 23%. To accommodate this relatively wide coefficient of variation for normal prostatic acinar cells, a DNA index of 0.77-1.23 was considered to be in the diploid range. Cases featuring G_0G_1 peaks in the diploid range with G_2M components in the tetraploid range of <5% of the total tumor cell population were considered diploid. All tumors with a DNA index >1.23 and tumors with tetraploid peaks >5% of the total cell population were considered nondiploid (aneuploid).

Statistical Calculations

Analysis of the correlation between needle biopsy DNA ploidy status and needle biopsy tumor grade with radical prostatectomy tumor grade was performed by univariate and multivariate regression analysis. Univariate and multivariate analysis of the association of needle biopsy DNA ploidy status and needle biopsy and radical prostatectomy tumor grades with disease recurrence was performed with the Cox regression method. A p value <0.05 was

considered to be significant.

RESULTS

The 111 men ranged in age from 44 to 74 years (mean 63.5 years). The preoperative serum PSAs ranged from 1.2 ng/ml to 87.8 ng/ml (mean 12.6 ng/ml). There were 67 (60%) pathologic Stage 2 cases, 37 (33%) Stage 3 cases, and 7 (6%) Stage 4 cases in the study.

Incidence of Grade Shifting

The frequency of grade shifting from the original needle biopsy grade to the final prostatectomy grade is summarized in Table 1. Of 89 tumors reported as low-grade on needle biopsy, 61 (69%) remained low-grade on the prostatectomy specimen, and 28 (31%) were upgraded. Of 22 tumors reported as high-grade on needle biopsy, 12 (55%) remained high-grade in the radical prostatectomy specimen and 10 (45%) were downgraded. Of the total 111 cases, 38 (34%) of the tumors featured grade shifting from the biopsy specimens to the resection specimens.

	Radical prostatectomy low grade (cases)	Radical prostatectomy high grade (cases)	Grade shifting (%)
Needle biopsy low grade (89 cases)	61	28	31
Needle biopsy high grade (22 cases)	10	12	45

Low grade, Gleason ≤ 6; high grade, Gleason ≥ 7.

TABLE 1. Tumor grade shifting from needle biopsy to radical prostatectomy

Correlation with DNA Ploidy Status

The association of ploidy status with the incidence of grade shifting is summarized in Table 2. Of the 38 cases in which DNA ploidy status and tumor grade were incongruous on the needle biopsy specimen (i.e., diploid and high grade, and nondiploid and low grade), 28 (74%) had grade shifting at prostatectomy (Figs. 1 and 2).

	Diploid cases (n)	Nondiploid cases (n)	Prediction of grade shift (%)
Upgraded (28 cases)	9	19	68
Downgraded (10 cases)	9	1	90

TABLE 2. DNA ploidy status and the prediction of grade shifting

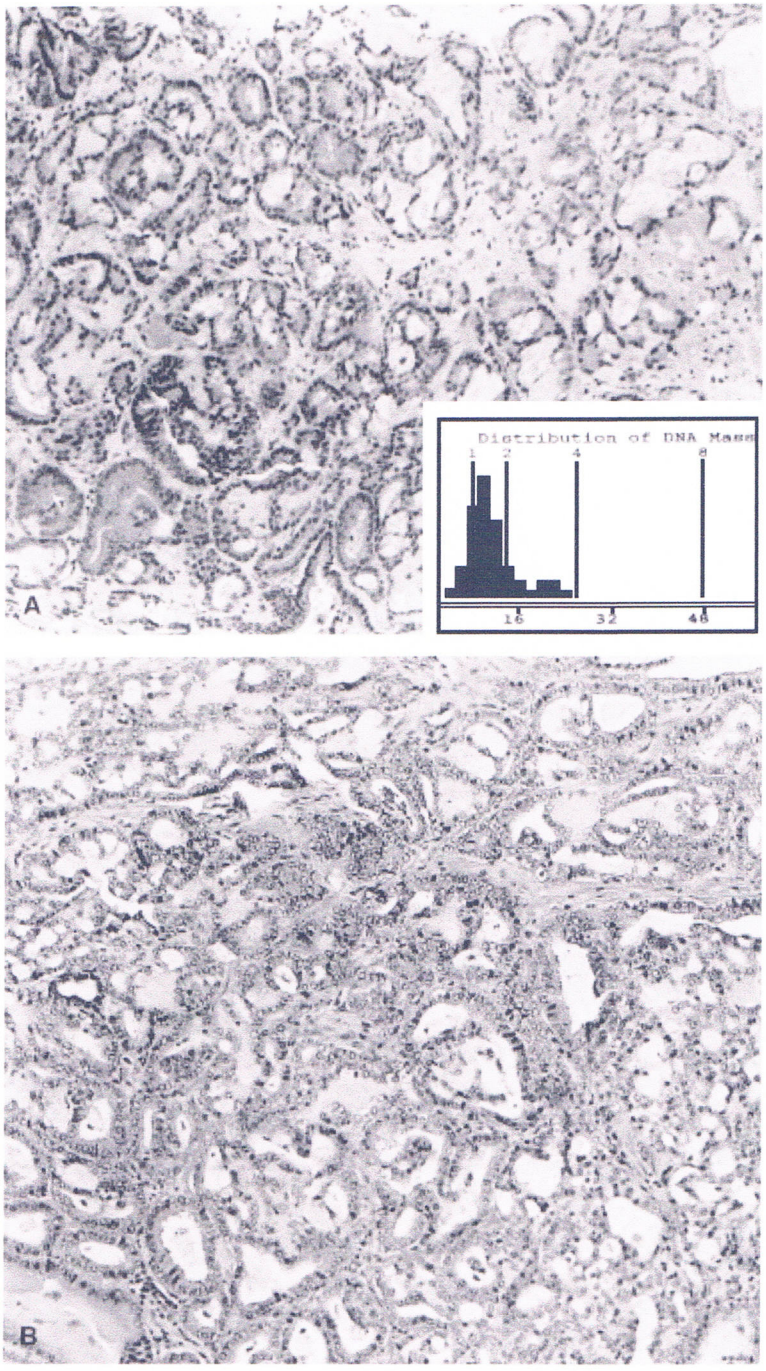

FIG. 1. DNA ploidy and upgrading. (A) Low-magnification view of an 18 gauge needle biopsy specimen of prostatic adenocarcinoma originally graded as Gleason score 3 plus 6 = 6/10 (low grade) from a 58-year-old Caucasian man with a preoperative serum prostate-specific antigen level of 4.6 ng/ml. The DNA ploidy histogram obtained from image analysis of the Feulgen stained 5-μm tissue section of the needle biopsy specimen (inset) reveals a hyperdiploid-aneuploid (nondiploid) pattern with a DNA index of 1.28. In this case, the DNA ploidy pattern predicted the upgrading of the specimen at radical prostatectomy. (B) Low-magnification view of the radical prostatectomy specimen that was graded as Gleason pattern 3 plus 4 = 7/10 (high grade).

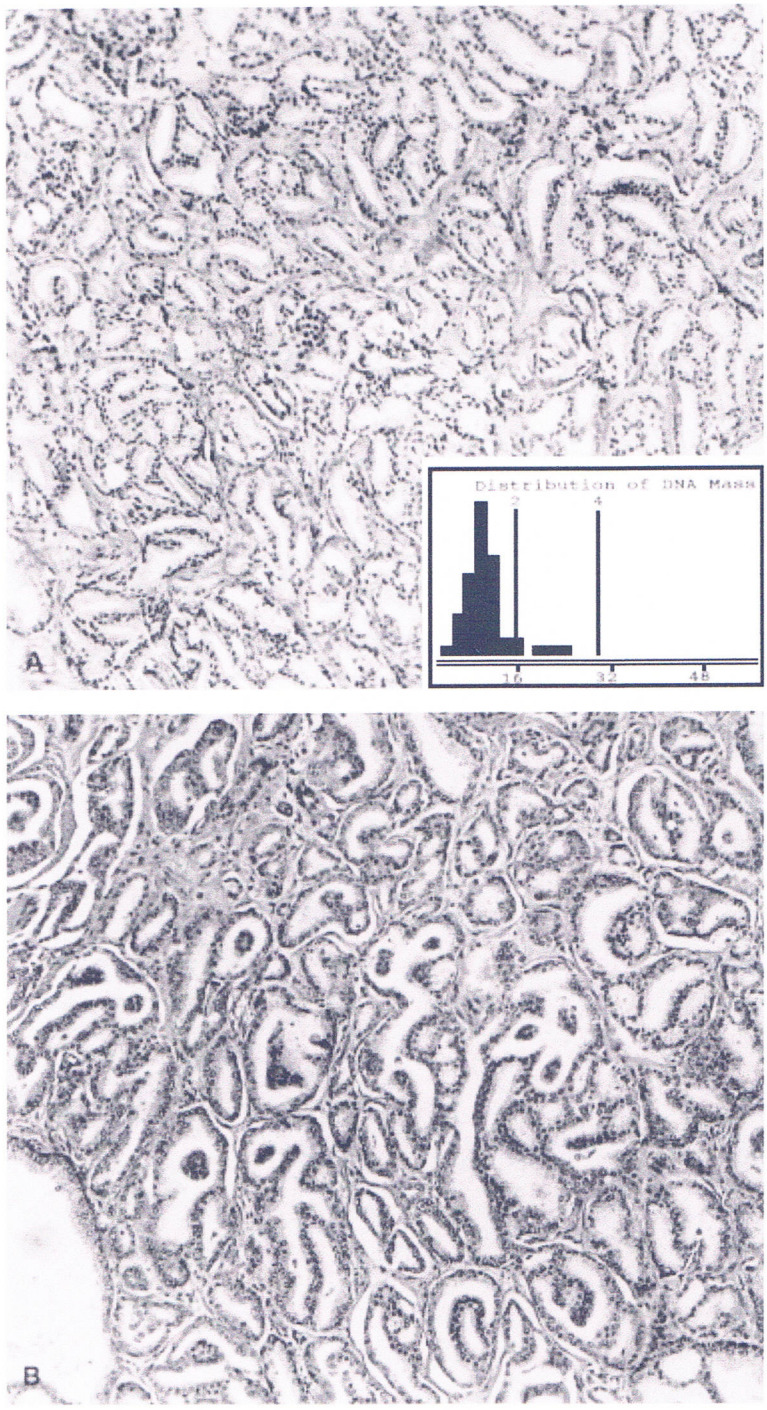

FIG. 2. DNA ploidy and downgrading. (A) Low-magnification view of a hematoxylin and eosin stained 18 gauge needle biopsy specimen of the prostate from a 65-year-old Caucasian man with a preoperative serum prostate-specific antigen level of 51 ng/ml featuring an adenocarcinoma originally graded as Gleason score 3 plus 4 = 7/10 (high grade). The Feulgen stained image analysis-derived DNA ploidy histogram from the needle biopsy specimen (inset) shows a diploid pattern with DNA index of 1.02 predicting the downgrading from biopsy to resection specimens. (B) Low-magnification view of the corresponding radical prostatectomy specimen, which received a final grade of 3 plus 3 = 6/10 (low grade).

On multivariate regression analysis, only biopsy DNA ploidy status correlated with prostatectomy tumor grade ($p = 0.0001$). On multivariate analysis, tumor grade on the needle biopsy did not independently predict tumor grade on the prostatectomy specimen ($p = 0.15$).

If biopsy grade and biopsy ploidy status were considered as "tests," the sensitivity of the biopsy grade for the prediction of final grade at prostatectomy was 30%, and the specificity was 86%. The sensitivity of DNA ploidy status for the prediction of tumor grade at prostatectomy was 78%, and the specificity was 96%.

Disease Outcome/Biochemical Recurrence

On univariate analysis, when a serum PSA level > 0.4 ng/ml was used as the indicator of post-radical prostatectomy biochemical recurrence, both needle biopsy DNA ploidy status ($p = 0.001$) and radical prostatectomy grade ($p = 0.04$) predicted disease relapse. Needle biopsy grade did not predict postprostatectomy biochemical disease recurrence ($p = 0.39$). On multivariate analysis comparing biopsy and prostatectomy grade and biopsy ploidy status, only needle biopsy ploidy status independently predicted biochemical disease recurrence ($p = 0.002$) (beta coefficient 0.34).

DISCUSSION

The value of tumor grading for the prediction of outcome and planning of therapy for prostate cancer is generally well accepted by urologists and pathologists.[2] Given the controversies concerning the accuracy of needle biopsy grading,[6,7,10,12,15-18,20-23,27,30,31,36-38] a readily available marker that could determine the accuracy of the needle biopsy grade and predict the likelihood of grade shifting should a prostatectomy be performed would be of significant interest to physicians caring for patients with prostatic adenocarcinoma. Although not universally confirmed, DNA ploidy status has frequently been found to be an independent predictor of prostate cancer outcome.[1,8,11,13,14,19,25,26,28,29,32-36,39,41-43] The ability of ploidy status to predict grade shifting could provide an added benefit for DNA content analysis of needle biopsy specimens. Several studies have considered discrepancies between needle biopsy and radical prostatectomy tumor grades in prostate cancer.[6,7,10,15,18,20-22,27,31,36-38] Possible factors that may contribute to biopsy/prostatectomy grade discrepancies as summarized by Epstein include the following: pathologist error in grading, tumor patterns that straddle two grades, sampling error (major pattern not present in needle biopsy specimen), and reverse sampling error (needle biopsy detects minor pattern not included in final grade).[12] Whereas some investigators have found a substantial correlation between needle biopsy and radical prostatectomy grades,[6,7,38] others have reported high frequencies of grade shifting.[7,15,20-22,27,36] In general, grade shifting from needle biopsy to prostatectomy specimens has been more often encountered in low-grade tumors [6,15,22,27] and has not been associated with clinical understaging.[6,7,27,37] The caliber of the needle biopsy specimen does not appear to be a significant factor, as similar grade shifting rates have been reported with 14 gauge [7,15,20,22,27] and 18 gauge [6,36,37] needle biopsy specimens. Recently, the correlation of prostate needle biopsy and radical prostatectomy Gleason grades was compared between expert (academic subspecialists) and community hospital settings.[38] The correlation rate (identical Gleason scores on both specimens) at the academic setting (the Johns Hopkins Hospital) was 58%, compared with 34% for the referring community hospital-based pathologists. When limited to a one Gleason digit change, these results improved to 93% and 67%, respectively.[38] From this study, it appears that although there are inherent problems with the application of an architecture-based grading system to a small tissue sample, nonexpert pathologists can be educated in their application of the Gleason system to needle biopsies and significantly improve their results. In the present study, the tumor grades

used for both the needle biopsy and radical prostatectomy specimens were obtained from the original pathology reports provided by a group of surgical pathologists practicing in a university setting rather than from "expert" regraded cases. The rationale for this approach was to test the ability of DNA content analysis to predict grade shifting in a group practice setting, where the majority of prostate cancer needle biopsy specimens are regularly graded in the United States.

It should be noted that although the frequency of undergrading of the needle biopsy specimens in the present study was similar to that previously reported,[38] the incidence of overgrading was significantly higher in than the published experience.[38] From the data analysis, it appears that the Gleason pattern 4 was overrecognized by the group of general surgical pathologists who performed the original needle biopsy grading. The finding of a diploid DNA content in the majority of these cases further supports the ability of the ploidy status to predict the likelihood of grade shifting at prostatectomy for these cases. Given the significantly different number of cells available for analysis, the shifting of the DNA ploidy pattern from the needle biopsy to the prostatectomy specimen has also been a concern to investigators. Interestingly, sampling issues do not appear to cause significant ploidy shifting, and a substantial correlation between biopsy and prostatectomy ploidy status has been reported.[36]

Various new algorithms and computer-generated mathematical models have recently been developed in an attempt to improve the accuracy of prostate cancer tumor grading.[3-5,9,14,24,25,40] Using a variety of measurements, including architectural, morphometric, and photometric features as well as neural networks and statistical classifier systems, these studies show promise in resolving such issues as interobserver and intraobserver variability. However, the value of computerized prostate cancer grading will similarly be lessened if the methods require prostatectomy specimens and are not successful when needle biopsy specimens are used. The accuracy and predictive value of conventional tumor grading of radical prostatectomy specimens is generally well accepted. However, in daily clinical practice, if tumor grading requires a prostatectomy specimen to achieve accuracy and reproducibility, its value for patient counseling and therapy selection is markedly diminished. The results of the present study are also consistent with our previous report of a different set of 89 patients in which needle biopsy DNA ploidy status and radical prostatectomy grading significantly correlated with other disease outcome predictors.[36] In this earlier study, prostatectomy grade independently predicted extracapsular spread and lymph node metastasis, but, as seen in the present patient group, only DNA ploidy status independently predicted biochemical disease recurrence.[36]

In summary, these findings indicate that DNA content measurement by image analysis of prostate cancer needle biopsy specimens can confirm grading accuracy, indicate the likelihood of grade shifting, and add prognostic information independently of tumor grade. This approach shows significant potential for the stratification of newly diagnosed cases of the disease and a more precise selection of therapy.

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Key Words: Gleason grade; Prostate cancer; Radical prostatectomy; Gleason score; DNA ploidy

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	Radical prostatectomy (low grade cases)	Radical prostatectomy (high grade cases)	Grade shifting
Needle biopsy (low grade) (81 cases)	61	20	31
Needle biopsy (high grade) (22 cases)	10	12	45

Low grade: Gleason ≤ 6; high grade: Gleason ≥ 7.

Table 1

	Diploid cases (n)	Nondiploid cases (n)	Prediction of grade shift (%
Upgraded (28 cases)	9	19	68
Downgraded (10 cases)	9	1	90

Table 2

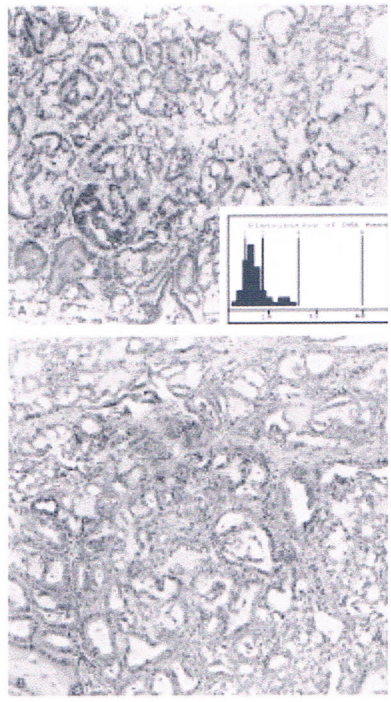

Fig. 1

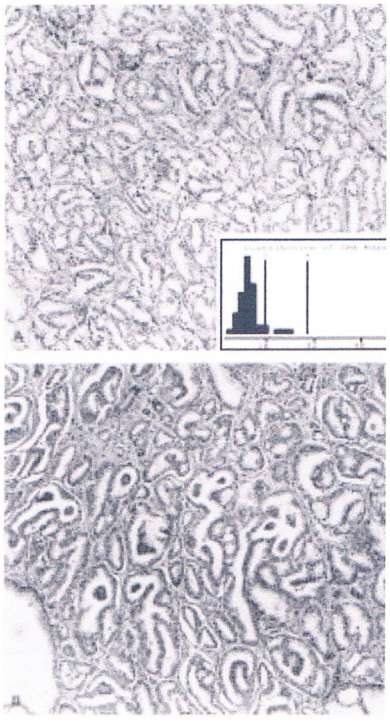

Fig. 2