Neural Network–Based Segmentation and Classification System for Automated Grading of Histologic Sections of Bladder Carcinoma

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OBJECTIVE: To develop an image analysis system for automated nuclear segmentation and classification of histologic bladder sections employing quantitative nuclear features.
STUDY DESIGN: Ninety-two cases were classified into three classes by experienced pathologists according to the WHO grading system: 18 cases as grade 1, 45 as grade 2, and 29 as grade 3. Nuclear segmentation was performed by means of an artificial neural network (ANN)–based pixel classification algorithm, and each case was represented by 36 nuclei features. Automated grading of bladder tumor histologic sections was performed by an ANN classifier implemented in a two-stage hierarchic tree.
RESULTS: On average, 95% of the nuclei were correctly detected. At the first stage of the hierarchic tree, classifier performance in discriminating between cases of grade 1 and 2 and cases of grade 3 was 89%. At the second stage, 79% of grade 1 cases were correctly distinguished from grade 2 cases.
CONCLUSION: The proposed image analysis system provides the means to reduce subjectivity in grading bladder tumors and may contribute to more accurate diagnosis and prognosis since it relies on nuclear features, the value of which has been confirmed. (Analyt Quant Cytol Histol 2002;24:317–324)

Keywords: neural networks (computer), computer-assisted diagnosis, histological techniques, bladder cancer.

Histologic grading of bladder tumors is important for predicting their biologic function and for planning therapy.[1] In tumor pathology, grading is used to describe how closely a tumor resembles normal tissue and to suggest how fast the tumor is likely to grow.[2] According to the World Health Organization (WHO) classification system,[3] bladder tumors are divided into three categories: grade 1, 2 and 3. Grade 1 covers low grade tumors, whereas grades 2 and 3 denote intermediate and high grades, respectively. Most grade 1 tumors are considered to have a good prognosis, while grade 3 is associated with

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more aggressive tumors.[4] Tumors of grade 2 have more heterogeneous clinical behavior. The classification of tumor malignancy is based on a range of structural changes, such as tissue architecture; various cytoplasmic features; and nuclear appearance.[5] However, grading systems that are based on subjective evaluation of various histologic features have a high rate of interobserver and intraobserver variability and poor reproducibility.[6-8]

Recent developments in digital image analysis techniques and classification systems offer potential solutions to the objective grading of tumors. Several studies have attempted to quantify the degree of bladder malignancy by analyzing structural or textural tissue characteristics.[9,10] Although recent studies have indicated that nuclear features are reliable predictors of survival, recurrence and progression of various types of cancer,[11-14] no attempt has been made to investigate the potential of such features in designing automated classification systems. The reason behind this is that this nucleus-oriented approach for assessing bladder tumors is highly dependent on the method of image segmentation into nuclei and background; that is a difficult task to achieve in a stable and reliable way.[10]

In this study, a computer-based image analysis system was developed to automatically grade bladder carcinomas. An artificial neural network (ANN)–based segmentation algorithm was designed for the automated detection of nuclei in digitized microscopic images of hematoxylin-eosin (H-E)–stained histologic tissue sections. Morphologic and textural features from segmented nuclei were employed to train an ANN classifier to assess tumor malignancy.

Materials and Methods

In the present study we used 92 conventionally H-E–stained tissue sections from 92 patients (cases) with bladder carcinoma. All cases were provided by the Department of Pathology, University of Patras, Greece, and had been characterized by four pathologists using the WHO grading system. Eighteen cases had been classified as grade 1, 45 as grade 2, and 29 as grade 3. Images from tissue specimens were captured using a light microscopy imaging system consisting of a Zeiss KF2 microscope (Göttingen, Germany) and Ikegami video camera (Ikegami Tsushinki Co., Tokyo, Japan). The objective used was a Zeiss Plan with the following characteristics: magnification 40×, numerical aperture 0.65, tube length 160 mm and coverslip thickness 0.17 mm. The sampling rate in the object plane was about 0.3 μm per pixel. From each case, up to three randomly selected fields were captured from regions predefined by pathologists. Each image was digitized at 768×576×8-bit resolution.

Design of Image Segmentation Algorithm

From each bladder image, about 30 small 5×5-pixel image samples from the nucleus and surrounding tissue were extracted to be used in the design of the segmentation algorithm. Segmentation was seen as an ANN-based pixel classification procedure.

Textural Features. From each image sample the following textural features were evaluated: the sum of autocorrelation function for all possible displacements m, n inside the 5×5-pixel window and two autocorrelation-spread measures: cross-relation S (1,1) and second-degree spread S (2,2)[15]:

$$S(u,v) = \sum_{m=0}^{5} \sum_{n=-5}^{5} (m-n_m)^u (n-n_n)^v A_F(m,n), \qquad (1)$$

where,

$$n_m = \sum_{m=0}^{5} \sum_{n=-5}^{5} m A_F(m,n), \qquad (2)$$

$$n_n = \sum_{m=0}^{5} \sum_{n=-5}^{5} n A_F(m,n), \qquad (3)$$

and

$$A_F(m,n) = \sum_j \sum_k F(j,k) F(j-m, k-n) \qquad (4)$$

is the autocorrelation function for displacements m, n.

ANN Algorithm for Nuclear Segmentation. These textural features were used as input to train a two-hidden-layer ANN classifier with three nodes in one and six in the other. The ANN structure resulted after extensive experimentation for optimal classifier performance. The back-propagation learning algorithm was used for training the ANN. Weights and bias values were updated according to the Levenberg-Marquardt numerical optimization technique.[16,17] This algorithm appeared to be the fastest method of training the ANN and subsequently the best for practical use in image segmentation. The network was constructed using the Matlab programming language (The MathWorks, Natick, Massachusetts, U.S.A.).

Segmentation was performed by scanning each bladder image with a 5×5-pixel mask, computing the set of textural features at each mask position and classifying each image pixel as nucleus or background on the basis of local texture estimations.

The result of classification was a binary image in which each pixel was labeled as either belonging or not belonging to the nucleus. Image segmentation was finally accomplished by eliminating small, noisy regions, performing a fill hole operation and smoothing nuclear boundaries by the use of the opening and closing morphologic operations[18]:

$$\mathbf{O}(I_o, SE1) = \mathbf{D}(\mathbf{E}(I_o, SE1), SE1), \text{ and} \quad (5)$$

$$\mathbf{C}(I_o, SE2) = \mathbf{E}(\mathbf{D}(I_o, SE2), SE2), \quad (6)$$

where, **D** denotes the dilation operation, **O** the opening operation, **E** the erosion operation and **C** the closing operation. SE_1 is an octagonal structuring element, 11×11, and SE2 an octagonal structuring element, 7×7.

Design of the Grading Classifier

Feature Generation. From each one of the 92 cases, a nuclear population (consisting of 30–70 nuclei) was extracted. From each nuclear population 36 morphologic and textural features were estimated. Textural features were formed from first-order statistics and from spatial gray tone co-occurrence probability matrices.[19-22] Regarding morphologic features, they consisted of measurements of nuclear area, roundness and concavity.[23,24] For each case, a feature vector was formed by computing the mean value of each textural feature and the mean value, standard deviation, range, skewness, kurtosis and maximum value of each morphologic feature. All features were normalized to have zero mean and unit variance before input into the ANN,[25] according to:

$$f_i' = \frac{f_i - \mu}{\sigma} \quad i = 1, 2 \ldots \quad 92, \quad (7)$$

$$\text{where, } \mu = \frac{1}{N} \sum_{i=1}^{N} f_i, \quad (8)$$

and

$$\sigma = \sqrt{\frac{1}{N} \sum_{i=1}^{N} (f_i - \mu)^2}. \quad (9)$$

ANN Algorithm for Grade Classification. The automated classification algorithm for grading tissue sections of bladder tumors was designed as a two-stage hierarchic decision tree. The first stage was to classify all cases into two classes: $C_{I,II}$ (cases of grade 1 and 2) and C_{III} (cases of grade 3). In the second phase the first class was discriminated into grade 1 (class C_I) and 2 (class C_{II}). At each level of the hierarchic tree, a two-hidden-layer ANN was implemented with nine nodes in one and three in the other hidden layer, and one node in the output layer. All nodes were weighted with sigmoid functions. The ANN structure resulted after extensive experimentation with optimal classifier performance.

For training the ANN, a back-propagation algorithm was used, based on an iterative gradient descent procedure that adjusted weights to reduce the error between the desired and actual outputs of all nodes in the system.[26] To prevent the ANN from getting stuck in a shallow local minimum, the network was provided with a momentum term.[27] To ensure better-behaved convergence, the back-propagation algorithm was implemented in the batch mode, in which the weights of the ANN were updated once all the training pairs had appeared in the network (epoch).[27] The learning rate was $\mu = .1$, whereas the momentum term was adjusted to $\alpha = .8$. During training, the available training vectors were used iteratively for a 1,000 epochs.

Feature Selection and System Performance Evaluation. Ideally, the selection criterion would be obtained by training the ANN on the given subset of features and then evaluating its performance on an independent set of test data. Such an approach is likely to be impractical since the training and testing process would have to be repeated for each new choice of feature subset, and the computation requirements would become too great. Consequently, it is more common to use a simplified criterion in order to select the features and then use those features with the more sophisticated nonparametric model of ANN.[28] Generally it is expected that a set of features in which the classes are best separated will be a good one for input to an ANN. In the present study, in order to find a set of well-discriminating features, a class separability criterion, J, was adopted, according to which good feature sets are those which satisfy two requirements[29]: (1) small intraclass variance, and (2) large interclass separation.

J was estimated as follows[30]:

$$J = \mathrm{trace}\,[S_w^{-1} S_m], \qquad (14)$$

where S_w is the within-class scatter matrix:

$$S_W = \sum_{i=1}^{2} P_i S_i \qquad (15)$$

S_i is the covariance matrix for class ω_i, and P_i is the a priori probability of class ω_i.
S_m is the covariance matrix of the feature vector with respect to the global mean, m_0,

$$m_0 = \sum_{i=1}^{2} P_i m_i, \qquad (16)$$

where m_i is the mean vector for class ω_i.

An exhaustive search for the smallest-dimension feature vector was performed according to the following procedure. Features were combined in all possible ways (i.e., 2, 3, 4, 5, etc., feature combinations), each time choosing as optimum the feature vector with the highest J value. The smallest-dimension feature vector providing the highest ANN classification accuracy (employing the leave-k-out method[31]) was selected for optimum ANN classifier design.

Results

Segmentation

The segmentation algorithm applied on the digitized images of 92 patients demonstrated an accuracy of about 95% in efficiently detecting nuclei of urinary bladder carcinoma. About 5% of the nuclei were not recognized successfully, due to their poor discrimination from the background since they were located in a different focal plane. Of the detected nuclei, even after application of morphological filtering, about 5% were rejected as erroneous due mainly to nuclear overlapping. Finally about 90% of the detected nuclei were accepted as correctly delineated.

Figure 1 depicts a typical histological image of urinary bladder cancer. Pixel classification performed by the ANN resulted in the binary image of Figure 2, where most nuclei were detected successfully. In Figure 3 small erroneous regions were removed by size filtering (pixel-clusters less than 350 were removed) and correcting nuclear shape by morphological operations. Finally, Figure 4, displays the final result of nuclear segmentation.

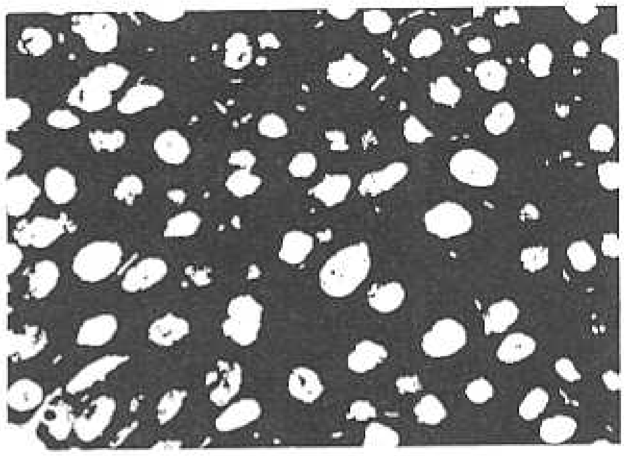

Figure 2 ANN performance in automatically delineating nuclei.

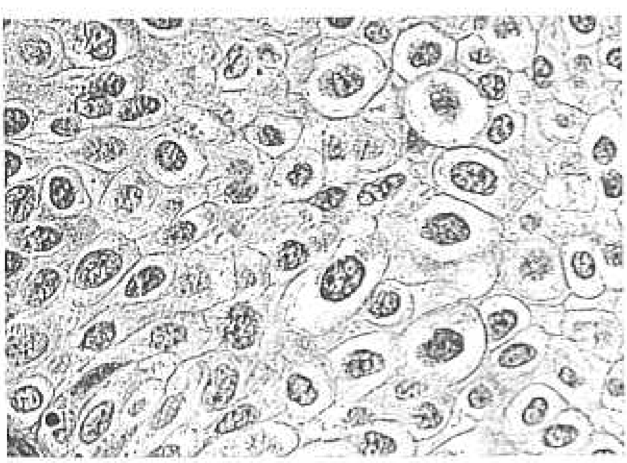

Figure 1 Typical histologic image of bladder carcinoma.

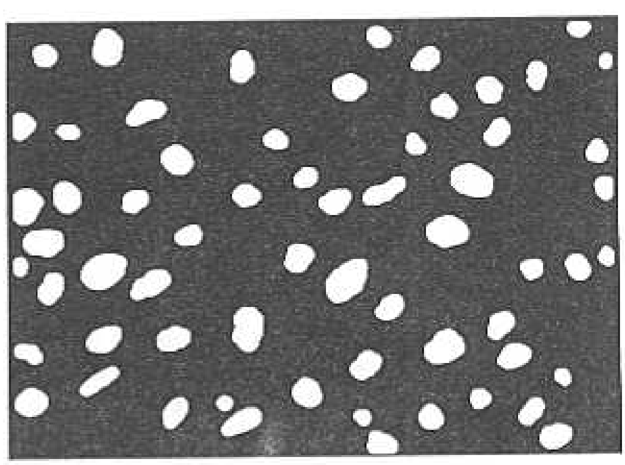

Figure 3 Enhancement of nuclear shape by the use of morphologic operations.

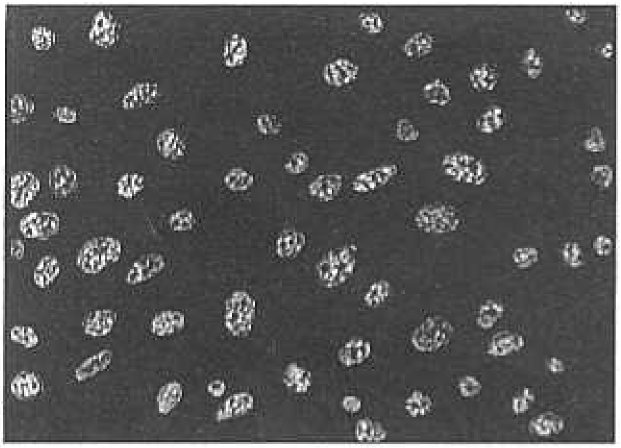

Figure 4 Segmented nuclei resulting from the combination of images from Figures 1 and 3.

Grade Classification

ANN classification performance in discriminating between $C_{I\text{-}II}$ and C_{III} at the first level of the hierarchic tree was 89% (Table I), employing five features: three textural features from the co-occurrence matrices estimated for intersample spacing, d = 3, and two morphologic features. The best feature vector thus contained the following features: energy, local homogeneity, correlation (Appendix A, equations A2–A8), standard deviation of area and standard deviation of concavity.[24] As shown in Table I, 92% (58/63) of the total cases of grades 1 and grade 2 were correctly classified, while five cases (one of grade 1, and four of grade 2) were misclassified as tumors of grade 3. In the high grade group, the correct classification was 83% (24/29), and five cases were misclassified as grade 1 or 2.

At the second stage of the ANN classifier the discrimination accuracy for the two groups, grades 1 and 2, was 79% (Table II). The best feature vector employed the following features: the textural feature estimated from the co-occurrence matrices for d = 3 (namely, the cluster shade [Appendix A, equation A9]) and the morphologic features of area, maximum roundness (Appendix A), standard deviation of roundness and standard deviation of area. The classification accuracy for grade 1 tumors was 82% (14/17). Three cases were misclassified as grade 2. Tumors of grade 2, were classified with an accuracy of 78% (32/41). Finally, nine cases of grade 2 were incorrectly classified as grade 1.

Table I *Truth Table for the First Stage of the Hierarchic Classifier*

	System classification		
Histologic finding	$C_{I\text{-}II}$	C_{III}	Accuracy (%)
$C_{I\text{-}II}$	58	5	92
C_{III}	5	24	83
Overall accuracy			89

Table II *Truth Table for the Second Stage of the Hierarchic Classifier*

	System classification		
Histologic finding	C_I	C_{II}	Accuracy (%)
C_I	14	3	82
C_{II}	9	32	78
Overall accuracy			79

Discussion

Assessment of tumor grade is a highly subjective process and may be influenced by various factors such as the psychophysiologic performance of the diagnostician and the quality of the definition of each category of histologic type.[32] Hence, the usefulness of tumor grading has been limited by poor interobserver reproducibility.[6-8]

To resolve this problem, several studies have attempted to assist the pathologic diagnosis by introducing semiautomated and automated computerized image analysis techniques for morphometric evaluation of various histopathologic features over the past 30 years.[32-35] The aim of the present study was to examine the potential role of nuclear features the prognostic and diagnostic value of which had been confirmed by many researchers for various types of cancer[14,22,23] combined with ANNs in the discrimination of bladder tumor malignancy. In contrast to previous studies,[9,10] it was our objective from the beginning to rely on the WHO[3] histologic typing and grading system, which is widely adopted by pathologists,[36] and to employ morphologic and textural features of nuclear interpretation, including such features as bizarre nuclear shape and chromatin patterns used in visual grading.[37] In this way our method was closely associated with the work performed by pathologists.

In order to segment the histologic image into meaningful regions of nuclei, we applied ANN-based pattern recognition techniques. Segmentation results on all images revealed a high percentage (about 95) of accuracy in automatically locating nuclei. ANN performance in detecting nuclear regions was fast and stable for all cases tested. About 5% of the nuclei were rejected as erroneous, due mainly to nuclear overlapping or touching. In comparison to previous studies,[11] ours provided better results in segmenting nuclei, probably due to the employment of ANN to discriminate between nuclear and background pixels.

Previous studies[9,10] on computer-aided classification of bladder carcinoma have relied on different features, with no particular focus on the nucleus, have employed a different subjective tumor grading system and have used a different tissue-staining procedure. In addition, they have relied on linear discriminant classification techniques. However, medical data are inherently noisy and often exhibit significant nonlinear intervariable relationships.[38]

In this study a two-stage ANN hierarchic tree was trained to classify a set of 92 cases into three classes according to the degree of malignancy. At the first level of the hierarchic tree the ANN classification performance was 89% in discriminating between C_{I-II} and C_{III} employing three textural features from the co-occurrence matrices and two morphologic features. It was interesting that only one case of grade 1 was misdiagnosed as grade 3. The results appear satisfactory considering that only nuclear features were used for training ANN, which may contain important information on the nature and progression or recurrence of disease. This concept highlights our conviction that nuclear features can be used to achieve more objective grading of low- and high-risk bladder tumors[24]; that is important for managing the patient.

At the second level the discrimination between tumors of grades 1 and 2 was 79%, employing one texture feature and four morphologic ones. The relative accuracy of ANN in discriminating grade 2 bladder tumors from tumors of grades 1 and 3 (nine cases of grade 2 misclassified as grade 1 and 4 as grade 3) was not surprising given the heterogeneity of the intermediate grade 2 tumors. However, our result is in accordance with that referred to in the literature, assessing grade 2 tumors as a confusing category; that underlines the continuum between grades 1 and 3.[32]

In conclusion, an automated image analysis method was developed providing objective quantitative and reproducible nuclear features, and an ANN classifier was designed for automated classification of histologic sections of bladder cancer according to the WHO grading system. The method was efficient in delineating nuclei from background tissue and provided diagnostic information with high accuracy.

Appendix A

The highest ANN classification performance in discriminating between C_{I-II} and C_{III} at the first level of the hierarchic tree was obtained by the following feature vector: $\text{energy}_{(d=3)}$, local $\text{homogeneity}_{(d=3)}$, $\text{correlation}_{(d=3)}$, standard deviation of area and standard deviation of concavity.

At the second stage of the hierarchic tree the highest classification accuracy in discriminating between C_I and C_{II} was obtained by employing the following feature combination: cluster $\text{shade}_{(d=3)}$, area, standard deviation of area, maximum roundness and standard deviation of roundness.

Energy, local homogeneity correlation and cluster shade are texture features estimated from the co-occurrence matrix:

$$P(i,j|d) = \frac{1}{4} \cdot \sum_{\Phi=0,45,90,135} P(i,j|d,\Phi) \qquad \text{(A1)}$$

Each P (i,j|d,Φ) is the probability of going from gray level i to gray level j, given that the intersample spacing is d and that the direction is given by angle Φ.

$$\text{Energy} = \sum_i \sum_j [P(i,j|d)]^2. \qquad \text{(A2)}$$

$$\text{Local homogeneity} = \sum_i \sum_j \frac{1}{1=(i-j)^2} P(i,j|d). \qquad \text{(A3)}$$

$$\text{Correlation} = \frac{\sum_i \sum_j (i-\mu_x)(j-\mu_y)P(i,j|d)}{\sigma_x \sigma_y}, \qquad \text{(A4)}$$

where

$$\mu_x = \sum_i i \sum_j P(i,j|d), \qquad \text{(A5)}$$

$$\mu_y = \sum_j j \sum_i P(i,j|d), \qquad \text{(A6)}$$

$$\sigma_x^2 = \sum_i (i-\mu_x)^2 \sum_j P(i,j|d), \text{ and} \qquad \text{(A7)}$$

$$\sigma_y^2 = \sum_j (j-\mu_y)^2 \sum_i P(i,j|d). \qquad \text{(A8)}$$

$$\text{Cluster shade} = \sum_i \sum_j ((i-\mu_x)+(j-\mu_y))^3 P(i,j \mid d).$$ [22] (A9)

Roundness is determined by the formula:

$$roundness = \frac{perimeter^2}{4 * pi * area} \quad \text{(A10)}$$

This number is minimized by a circular disk and increases with the irregularity of the boundary. The maximum value of roundness for each case is computed by averaging the three largest values derived from the nuclear sample.

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