A prognostic-classification system based on a probabilistic NN for predicting urine bladder cancer recurrence

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Abstract: In this paper our purpose was to design a prognostic-classification system, based on a probabilistic neural network (PNN), for predicting urine bladder cancer recurrence. Ninety-two patients with bladder cancer were diagnosed and followed up. Images from each patient tissue sample were digitized and an adequate number of nuclei per case were segmented for the generation of morphological and textural nuclear features. Automatic urine bladder tumor characterization as potential to recur or not was performed utilizing a PNN. An exhaustive search based on classifier performance indicated the best feature combination that produced the minimum classification error. The classification performance of the PNN was optimized employing a 4-dimensional feature vector that comprised one texture feature and three descriptors of nucleus size distribution. The classification accuracy for the group of cases with recurrence was 72.3% (35/47) and 71.1% (32/45) accuracy for the group of cases with no recurrence. The proposed prognostic-system could prove of value in rendering the diagnostic nuclear information a marker of disease recurrence.

1. INTRODUCTION

Urine bladder cancer is now the 5^{th} most common type of cancer and the 12^{th} leading cause to cancer death. Even if the initial tumor is effectively removed by surgical or other conventional techniques, approximately 30% of treated subjects suffer from cancer recurrence that eventually leads to patient death [1]. Therefore, the major problems in treating patients with urothelial bladder carcinomas are cancer recurrence and progression. Histological grade of bladder carcinoma is generally used to predict the biological behavior of a tumor and consequently may affect patient management [2]. The grade is defined by the pathologists from the bladder biopsy and gives an idea of how fast the cancer might be growing or how aggressive it might be. Thus the prognosis is best for patients, whose initial tumor is of low-grade, whereas it is worse when it is of high-grade. However, some researchers have revealed that although histological grading is a powerful prognostic indicator for patient survival it is less significant for tumor progression and even unsatisfactory for predicting the recurrence of the tumor [3]. Additionally, the low inter- and/or intra-observer grade reproducibility, due to the subjectivity coupled to visual observation of tissue sections from tumor biopsies, has further degraded the prognostic value of histological grading [4].

Digital image analysis of tissue and cell characteristics in microscopic images for the quantitative analysis of tumors provide their share of information to the characterization of tumor aggressiveness in more objective and reproducible way. Recent studies have indicated that nuclear attributes carry useful diagnostic and prognostic information for various types of cancer [5]. The extraction of cell nuclei 'hidden' biological information in the form of quantitative nuclei attributes could provide an objective index for assessing tumor malignancy characteristics. Although the diagnostic and prognostic value of these features has already been mentioned, no attempt has been made to investigate the potential of such features to address the problem of predicting urine bladder cancer recurrence.

In the present study our aim was to design a prognostic-classification system, incorporating the useful information of nuclear characteristics, and the efficient processing of the probabilistic neural networks in handling the problem of predicting urine bladder cancer recurrence. For this we evaluated in total 36 morphological and textural nuclear features

2. MATERIALS AND METHODS

2.1 Material

Ninety-two patients with bladder cancer were diagnosed and followed up during the period 1991-1998 at University Hospital of Patras in Greece. The followed up period was at least 60 months. Of the 92 patients, 45 had no recurrence during the observation time. The rest 47 patients experienced recurrence of the tumor in a time ranging between one month and five years.

Images (fields) from tissue specimens were captured at a magnification of x400 using a light microscopy imaging system consisting of a Zeiss KF2 microscope and an Ikegami color video camera. Each digitized image (768x576x24-bit resolution) was converted into an 8-bit gray scale image for further processing and analysis.

2.2 Design of the prognostic-system to predict urine bladder cancer-recurrence.

The prognosis of urine bladder cancer-recurrence was seen as a two-class classification problem separating those patients who experienced tumour recurrence from those who are known to have been tumour free for at least 60 months.

For this purpose a PNN was designed. This type of neural network is based on concepts used in classical pattern recognition problems. In particular, the PNN models the Bayesian classifier, which minimizes the expected risk of classifying patterns in the wrong category [6]. The PNN used in the present study consisted of an input layer followed by two computational layers and one output unit. The first computation layer also called pattern-layer has k units, one for each training pattern and computes distances from the input vector to the training input vectors. A vector whose elements indicate how close the input is to a training input thus is produced. This vector is exponentiated by a radial basis activation function (1) and is passed as an input to the next computation layer.

$$f(n)=\exp(-(\frac{n*0.8326}{spread})^2) \qquad (1)$$

Equation (1) indicates that if a unit's vector is at a distance of "spread" from the input vector, the output of the activated unit will be 0.5 (figure1). The value of spread determines the width of an area in the input space to which each unit responds. The choice of spread will affect the estimation error of the PNN and is determined experimentally by comparing the accuracies obtained for different values of the parameter.

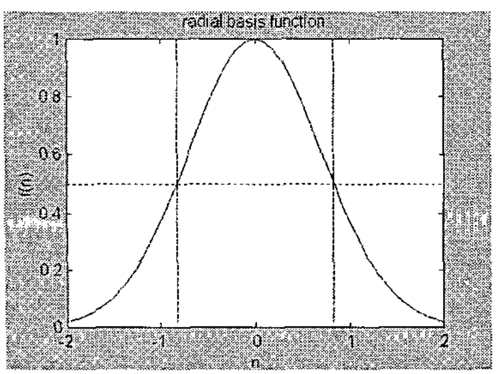


Figure1. Plot of the radial basis function

In the second computation layer, the pattern-layer outputs are selectively connected to two summation units depending on the class of patterns they represent. Since each summation unit integrates inputs from pattern units of the same class, their output is an estimate of the class probability density function. Finally the output unit produces a binary output signal indicating the most probable class membership for a particular input vector.

2.3Feature generation

Each one of the 92 cases was represented by 36 features automatically estimated from a representative sample of nuclei.

From each slice, an adequate number of nuclei (about 70) were extracted, from one or more fields. Since nuclei appearance was not altered significantly from field to field, this sample of nuclei was assumed to be representative. The method of nuclei segmentation was performed employing a NN and textural features from the nucleus and tissue background [7].

For each nucleus two kind of quantitative parameters were estimated:

- morphological features related to nuclear size and shape distribution
- textural features related to nuclear chromatin organization

Regarding morphological features, they comprised measurements of nucleus area, roundness and concavity [7]. For each case, the mean value, standard deviation, range, skewness, and kurtosis, of each morphological feature were computed. Additionally the maximum value for each morphological feature was estimated, by averaging the three largest values.

To quantify texture properties of nuclei, textural features were formed from first order statistics and from spatial gray tone co-occurrence probability matrices [8].

2.4Feature pre-processing

Feature preprocessing was particular important before features were used as input to a PNN. This is a consequence of the fact that pattern-layer units compute the Euclidean distances from the input vector to the training input vectors. In the present work, instead of transforming features independently, another more efficient method of data pre-processing was used, where transformation took place on feature vectors. The transformation is known as *whitening* [9].

Assuming that x_i input variables are grouped into a feature vector $\mathbf{x}=(x_1,...,x_d)^T$, which has sample mean vector and covariance matrix with respect to the N data points of training set given by:

$$\bar{\mathbf{x}}=\frac{1}{N}\sum_{i=1}^{N}x_i \qquad (2)$$

$$\mathbf{\Sigma}=\frac{1}{N-1}\sum_{n=1}^{N}(x_i-\bar{\mathbf{x}})(x_i-\bar{\mathbf{x}})^T \qquad (3)$$

If the eigenvalue equation for the covariance matrix is introduced:

$$\mathbf{\Sigma u}_j=\lambda_j\mathbf{u}_j \qquad (4)$$

then a vector of linearly transformed input variables can be defined which is given by:

$$\mathbf{x}_i'=\mathbf{\Lambda}^{-1/2}\mathbf{U}^T(x_i-\bar{\mathbf{x}}) \qquad (5)$$

where

$$\mathbf{U}=(\mathbf{u}_1,\ldots,\mathbf{u}_d) \qquad (6)$$

$$\Lambda=\text{diag}(\lambda_1,\ldots,\lambda_d). \qquad (7)$$

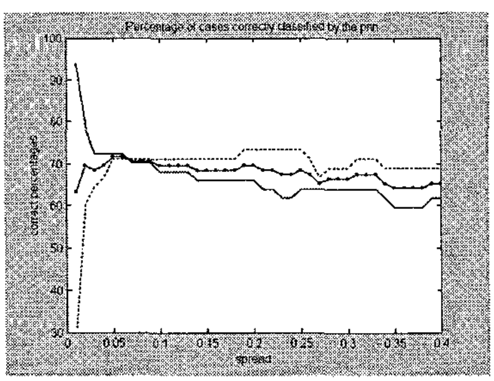
In the transformed coordinates, the data set has zero mean and a covariance matrix given by the unit matrix.

2.5Feature selection and system performance evaluation

The very fast and direct training of the PNN enabled us to perform an exhaustive search on feature space and select the best feature combination that produced the minimum classification error. For each feature combination the classifier performance was tested by means of the leave-one-out method [10]. The parameter of spread (1) found experimentally from a few test on classification accuracy.

3. RESULTS

The most effective feature vector for separating patients into two prognostic groups, according to tumor recurrence was consisted of four features: one measurement of nuclear texture estimated from the co-occurrence matrices -the feature of correlation-, and three morphological measurements of nuclear size distribution, namely the range of area, maximum area and skewness of area. Testing the classifier performance for a range of values for the spread parameter, we obtained that the performance of the classifier was optimised for spread=0.06 (figure3). The PNN classifier exhibited an overall accuracy of 71.7% (Table I). The classification accuracy for the group of cases with recurrence (C_{REC}) was 72.3% (34/47). The correct classification for the second group who revealed a good prognosis ($C_{NON\text{-}REC}$) was 71.1% (32/45).



--------- *% Correct non recurrent cases*

———— *% Correct recurrent cases*

•-•-•-•-• *% Overall correct classification*

Figure3. Comparing accuracies obtained for different values of spread

Table I: Truth table for the tumour recurrence prediction

	System classification		
Patient Outcome	C_{REC}	$C_{NON\text{-}REC}$	accuracy
C_{REC}	34	12	72.3%
$C_{NON\text{-}REC}$	13	32	71.1%
Overall accuracy			71.7%

4. DISCUSSION

Assessing tumor recurrence may be of value in selecting appropriate therapy and planning the follow-up for patients with urinary bladder cancer. Previous studies have investigated the extent to which various histological features - and subsequently tumor grade-, reflect real differences in biological behavior of tumors [2]. They found that histological grade is of prognostic value regarding patient survival and tumor progression but it is a poor prognostic indicator for tumor recurrence [3]. Additionally, inter- and intra- observer inconsistency could invalidate the usefulness of grading in clinical decisions. In a previous work on recurrent urinary bladder tumors, the authors have found morphological nuclear features such as nuclear size and its standard deviation that revealed statistically significant differences between recurrent and non-recurrent patients [3]. In the present study, we designed a computer-based system for quantifying textural and morphological nuclear characteristics and assessing the probability of cancer recurrence by the use of a probabilistic neural network. Since the output of a PNN is an estimate of probability it may be of value in presenting likelihood of tumor potentiality to recur or not to pathologists.

Employing a combination of nuclear features the prognostic-system, gave a significant (71.7%) prognostic assessment. Such a system may be suggestive of the level of confidence that a tumor might recur (72.3%) or might not (71.1%) and may thus influence patient treatment. Additionally, taking into consideration nuclear features, such as nuclei size distribution and textural appearance by assessing chromatin structure, it could be of value to practicing pathologists who use tumor grade and tumor stage in assessing tumor prognosis in everyday practice, which is not a good recurrence indicator.

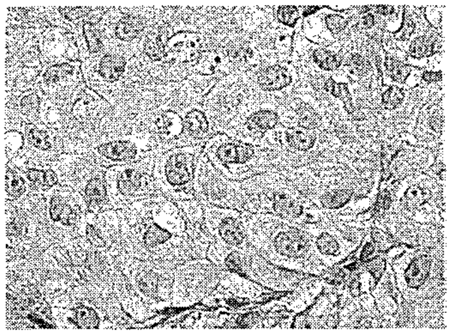


Figure1: Tissue sample from non-recurrent high-grade tumor

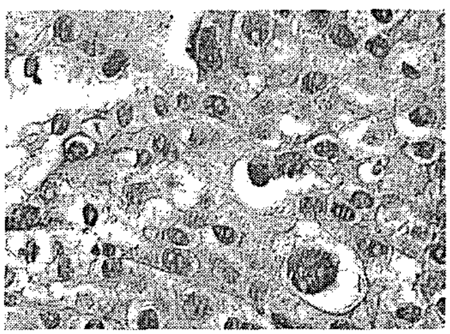


Figure 2: Tissue sample from recurrent high-grade tumor

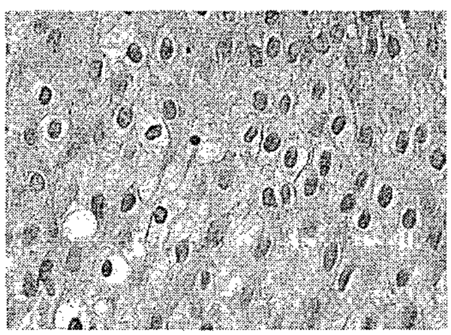


Figure3: Tissue sample from non-recurrent low-grade tumor

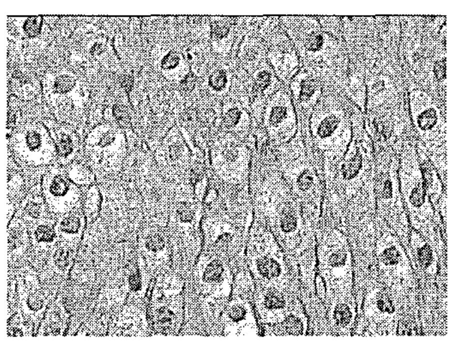


Figure 4: Tissue sample from recurrent low-grade tumor

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