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A computer-based diagnostic and prognostic system for assessing urinary bladder tumour grade and predicting cancer recurrence

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Abstract. *Purpose*: A computer-based system was designed, incorporating subjective criteria employed by pathologists in their usual microscopic observation of tissue samples and measurements of nuclear characteristics, with the purpose of automatically assessing urinary bladder tumour grade and predicting cancer recurrence.
Material and Methods: Ninety-two cases with urine bladder carcinoma were diagnosed and followed-up. Forty-seven patients had cancer recurrence. Each case was represented by eight histological (subjective) features, evaluated by pathologists, and thirty-six automatically extracted nuclear features. Grading and prognosis were performed by neural-network based classifiers employing both histological and nuclear features.
Results: Employing a combination of histological and nuclear features, highest classification accuracy was 82%, 80.5%, and 93.1% for tumours of grade I, II and III respectively. The prognostic-system, gave a significant prognostic assessment of 72.8% with a confidence of 74.5% that cancer might recur and of 71.1% that might not, employing two histological features and two textural nuclear features.
Conclusions: The system for grading and predicting tumour recurrence may serve as a second opinion tool and features employed for designing the system may be of value to pathologists using descriptive grading systems.

Keywords: Computer-based diagnosis; Prognostic system; Classification; Tumour recurrence

1. Introduction

Malignant description of epithelial bladder tumours is highly dependent on various morphological characteristics of tissue, cell and nuclear appearance [1]. These features are used to evaluate the degree of tumour malignancy with several grading systems [2–6]. The grading system most commonly being used is that of the World Health Organization (WHO) classification system, which divides urothelial carcinoma into three categories or grades I, II, and III [7, 8].

Histological grade of bladder carcinoma is generally used to predict the biological behavior of a tumour and consequently may affect patient management [9, 10]. However, some researchers have revealed that although histological grading is a powerful prognostic indicator for patient survival, it is less significant for tumour progression and even unsatisfactory for predicting the recurrence of the tumour [11, 12]. Additionally, the low inter- and/or intra-

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observer grade reproducibility [13], due to the subjectivity coupled to visual observation of tissue sections from tumour biopsies, has further degraded the prognostic value of histological grading [14].

Digital image analysis of tissue and cell characteristics in microscopic images for the quantitative analysis of tumours started in the late sixties [15] and is now a continuing growing field. At the tissue level, various studies have described methods to measure differentiations between regular and irregular organization of cells [16, 17]. Furthermore H-K Choi *et al* [18] and T. Jarkrans *et al* [19], tried to design automatic grading systems based on tissue characteristics, structural or textural.

At the cellular level, research groups have documented the close statistical correlation between measurements of nuclear size, shape, and texture with histological grading [11, 12, 20–22]. Some studies have indicated that quantitative nuclear features not only carry useful diagnostic information for tumour grade differentiation but they are also reliable predictors of survival recurrence and progression of bladder cancer [12, 14, 23, 24]. In recent work published by our group [25], a pattern recognition system employing nuclear features was designed to grade tissue sections of urinary bladder tumours into low-risk and high-risk.

Although the diagnostic and prognostic value of nuclear features has been previously mentioned, no attempt has been made to investigate the potential of nuclear features in combination with subjective criteria employed by physicians in grading tissue sections of urine bladder carcinomas. Furthermore, to our knowledge, there is no previous work that employs subjective and objective nuclear features in a pattern recognition system to predict urine bladder cancer recurrence.

In the present study our aim was to design a computer-based system for estimating the grade of urine bladder cancer and for assessing the probability of cancer-recurrence. For this we quantified eight subjective features, used by pathologists in grading tissue sections of urine bladder cancer, and we evaluated in total 36 morphological and textural nuclear features. We developed a diagnostic-classification system, based on neural networks (NN) and a tree-structured scheme, which is much closer to the way subjective grading is performed by the pathologists, to investigate the discriminatory ability of the subjective and nuclear features in grading urinary bladder cancer. We also designed a prognostic-classification system, based on NN, for predicting urine bladder cancer recurrence.

2. Material 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 tumour in a time ranging between one month and five years. Histological material (92 tissue sections-slides) from the 92 patients (cases) stained with Haematoxylin-Eosin (HE) were reviewed retrospectively by two independent pathologists to safeguard against reproducibility in assigning histological grade.

The 92 tissue sections were visually characterized and classified according to the WHO grading system as follows: Eighteen cases as grade I, 45 as grade II and 29 as grade III.

2.2. *Image acquisition*

Images (fields) from tissue specimens were captured using a light microscopy imaging system consisting of a Zeiss KF2 microscope and an Ikegami color video camera. In each section a region of interest, the most representative for subjective grading, was chosen by a pathologist. From this region, up to three random fields were captured at a magnification of $\times 400$. Each digitized image ($768 \times 576 \times 24$-bit resolution) was converted into an 8-bit gray scale image for further processing and analysis (Figure 1).

2.3. *Design of the grading diagnostic-system*

For the automatic grading of urine bladder tissue sections, a two-level hierarchical decision tree classification system was built. The first level of the hierarchical tree was to classify all cases into two classes: the low-risk (C_L) class, consisting of grades I and II cases, and the high-risk class (C_H), consisting of grade III cases. The second level was to further separate grade I cases (C_I) from the intermediate group of grade II (C_{II}).

At each level of the hierarchical tree, a neural network classifier was implemented. The structure of the NN (number of layers and nodes per layer) at each level resulted after multiple experimentation for optimal classifier performance. A back propagation algorithm with a momentum term (a=0.8) was used for training the NN. The learning rate was μ=0.1 [26]. During training, the available training vectors were used iteratively for a thousand epochs. The back propagation algorithm was implemented in the batch mode [27], in which the weights of the NN were updated once all the training pairs had appeared in the network (epoch). The above classification scheme was chosen in preference

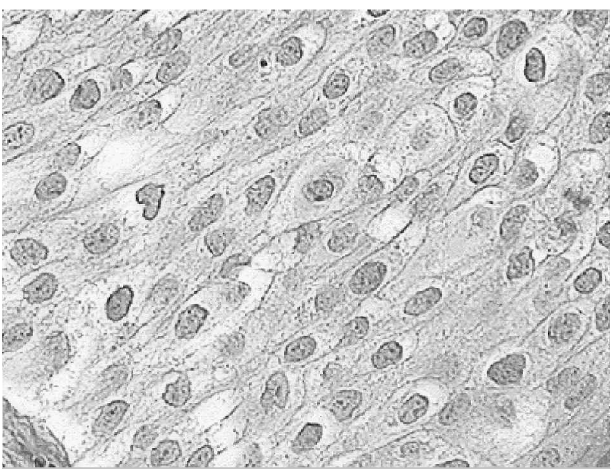

Figure 1. Tissue sample of bladder carcinoma.

to a single classifier – which assigns an unknown case directly to one of the three classes of grade – on the view that an hierarchical decision tree approach is much closer to the way subjective grading is performed by the pathologists [19].

The classification performed at the first level of the hierarchical tree is of special interest because it is equivalent to the first decision phase in the pathologist's subjective grading, where a case is characterized as a low or high-risk case [28]. From a clinical point of view, it is important to distinguish low-risk tumours, which can generally be treated conservatively in contrast to high-grade tumours. The latter often require a more aggressive therapy because of a high-risk cancer progression [29]. In this way, the performance of the classifier at the first level of the decision tree could also be interpreted in terms of sensitivity and specificity. That is sensitivity is the percentage of high-risk tumours correctly classified and specificity is the percentage of low-risk tumours correctly classified.

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

The prognosis of urine bladder cancer-recurrence was also seen as a two-class classification problem separating those patients who experienced recurrence from those who are known to have been recurrence-tumour free for at least 60 months. For this purpose a NN classifier was designed, following a similar procedure as previously described in the grade classification task.

2.5. *Feature generation*

For each case, 36 parameters were estimated automatically from morphological and textural nuclear features. Additionally, 8 parameters were resulted from the quantification of selected histological/cellular features subjectively evaluated by pathologists.

2.5.1. Extraction of nuclear features: From each slice, an adequate number of nuclei (about 70) were extracted, from one or more fields from a region of interest indicated by a pathologist. 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 in a two-step procedure [30]: Firstly, nuclei regions were automatically recognized employing a NN and textural features from nuclei and tissue background (Figure 2). Secondly a series of morphological operations were used to integrate the final shape of nuclei (Figure 3). Finally, the original image (Figure 1) was combined with the logical operation AND with the nuclei masks (Figure 3), to give the final result of nuclei segmentation (Figure 4).

For each nucleus two kind of quantitative parameters were estimated:

1. morphological features related to nuclear size and shape distribution
2. textural features related to nuclear chromatin organization

Regarding morphological features, they comprised measurements of nucleus area, roundness and concavity [25]. 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.

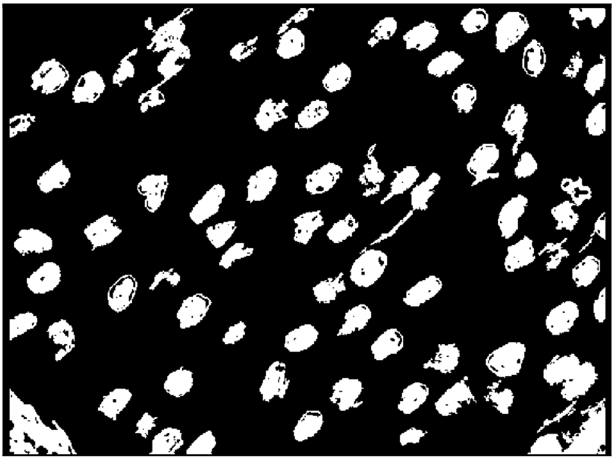

Figure 2. Nuclei regions were automatically recognized employing a NN and textural features from nuclei and tissue background.

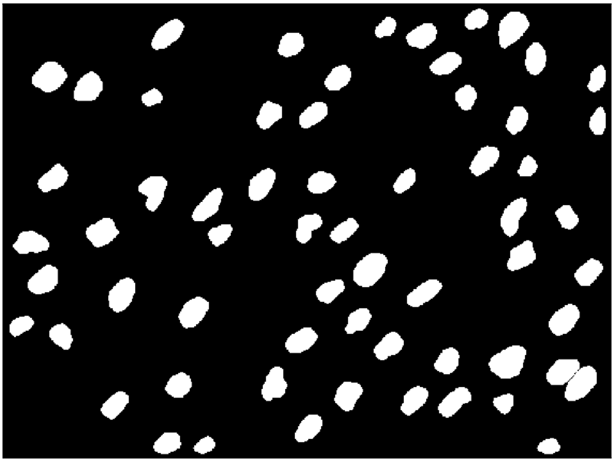

Figure 3. Nuclei regions were corrected by a series of morphological operations.

To quantify texture properties of nuclei, textural features were formed from first order statistics and from spatial gray tone co-occurrence probability matrices [31–33].

2.5.2. Histological features extracted from the visual inspection of the urinary bladder tissue sections: From each tissue section (case) eight selected histological features related to tissue architecture and cellular/nuclear appearances were evaluated (Table 1). These features were selected from bibliography and are routinely used by the pathologists in grading bladder tumours [6, 34–35].

The qualitative form used to describe the 8 characteristics was transformed to a numerical value using the following formula [36]:

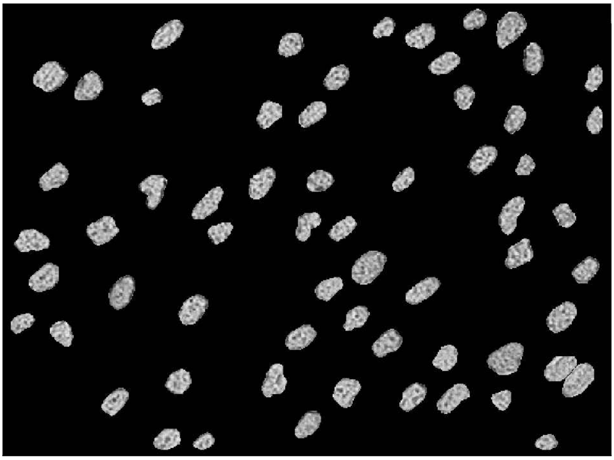

Figure 4. Original image (Figure1) was combined with the nuclei masks (Figure 3) to give the final result of nuclei segmentation.

Table 1. Histological features used for assessing tumours.

Histological feature	Assessment
Cell distribution	even, clustered
Cell size	uniform, pleomorphic
Cell number	numerous, variable
Cytoplasm	homogeneous, variable
Nuclei	uniform, irregular, very irregular, bizarre
Nucleoli	inconspicuous, evident, prominent
Necrosis	inconspicuous, frequent
Mitosis	absent-rate, occasional, numerous

$$submitted\ value = \frac{(option\ selected - 1)}{(total\ number\ of\ options - 1)} \quad (1)$$

In this way, the numerical values assigned to histological features were all in the range of [0, 1].

2.6. *Feature pre-processing*

Feature preprocessing was particular important before features were used as input to a NN. Feature normalization ensures that all the input and target variables are of order of unity, so that weights can be given random initialization prior network training [37]. In the present work, data pre-processing was performed using the whitening transform [38] as described in the Appendix I.

2.7. *Feature selection and system performance evaluation*

Feature selection procedure was carried out by using a class separability criterion J [39] (see Appendix II), where feature sets' effectiveness was tested according to the following two requirements [40]:

(i) Small intra-class variance
(ii) Large inter-class separation

For the optimal feature vector location an exhaustive search 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 in dimension feature-vector providing the highest NN-classification accuracy (employing the leave-k-out method [41]) was selected for optimum NN-classifier design.

3. Results

3.1. *Diagnostic-system classification*

The 44 subjective and nuclear features were taken in all possible combinations and were tested according to the class separability criterion J. For the first discrimination task between low-risk (C_L) and high- risk (C_H) cases, the criterion J indicated best feature combination the following vector: range of area, standard deviation of area, nuclei, and mitosis. This feature vector was used as an input to the NN classifier at the first level of the hierarchical tree. The system exhibited an overall classification performance of 96.7%. As shown in Table 2, 98.4% (62/63) of the total low-risk cases were correctly classified while only one low-risk case was misclassified as high risk tumour. In the high-risk group, the correct classification was 93.1% (27/29) that is 2 cases were misclassified as low-risk. The NN architecture used was 8 : 1. This configuration means that we used one hidden layer with eight nodes and one output unit.

For the second discrimination task, between cases of grade I (C_I) and grade II (C_{II}), the following feature vector was selected according to the criterion J: area, kurtosis of concavity, cell distribution, and nucleoli. The NN classification

Table 2. Truth table for the first stage of hierarchical classifier in discriminating low-risk from high-risk tumours.

Histological finding	System classification C_L	C_H	accuracy
C_L	62	1	98.4%
C_H	2	27	93.1%
Overall accuracy			96.7%

Table 3. Truth table for the second stage of hierarchical classifier in discriminating tumours of grade I from tumors of grade II.

	System classification		
Histological finding	C_I	C_{II}	accuracy
C_I	15	3	83.3%
C_{II}	8	36	81.8%
Overall accuracy			82.3%

performance, for the two groups of grades I and II, at the second level of the hierarchical tree was 82.3% (Table 3). The classification accuracy for grade I tumours was 83.3% (15/18). Two cases were misclassified as grade II. Tumours of grade II, were classified with an accuracy of 81.8 % (36/44). Eight cases of grade II were incorrectly classified as grade I. NN classifier configuration was 7 : 1, that is one hidden layer with seven nodes and one output unit.

To estimate the overall classification accuracy of the hierarchical tree-structure, scores at each level had to be multiplied (Table 4). Thus for grade I, overall accuracy resulted from multiplying the corresponding scores of the 1st (0.984) and 2nd (0.833) levels giving the probability of correct classification for grade I (0.82).

3.2. *Prognostic-system classification.*

Repeating the same feature selection procedure over the total 44 features, the most effective feature vector for separating patients into two prognostic groups, according to tumour recurrence was obtained. This feature vector consisted of four features; two objectively measurements of nuclear texture estimated from the co-occurrence matrices: energy and correlation, and two subjective features: cell distribution and mitosis. When these features were used as an input to a NN the classification system exhibited an overall accuracy of 72.8% (Table 5). The classification accuracy for the group of cases with recurrence (C_{REC}) was 74.5% (35/47). The correct classification for the second group who revealed a good prognosis ($C_{NON\text{-}REC}$) was 71.1% (32/45). NN topology used for the separation of patients into two prognostic groups was 9 : 3 : 1.

4. Discussion

The diagnostic assessment of histological grade by pathologists is based on the visual recognition of certain histological features [1]. Previous studies have investigated the extent to which these histological features – and subsequently tumour grade –, reflect real differences in biological behavior of tumours [10]. They found that histological grade is of prognostic value regarding patient survival and tumour progression but it is a poor prognostic indicator for tumour recurrence. Additionally, inter- and intra- observer inconsistency could

Table 4. Overall classification accuracy of the hierarchical tree.

Grade	I	II	III
Classification accuracy	82%	80.5%	93.1%

Table 5. Truth table for the tumours recurrence prediction.

	System classification		
Patient Outcome	C_{REC}	$C_{NON\text{-}REC}$	accuracy
C_{REC}	35	12	74.5%
$C_{NON\text{-}REC}$	13	32	71.1%
Overall accuracy			72.8%

invalidate the usefulness of grading in clinical decisions [14]. In the present study, we designed a computer-based system a) for estimating the grade of urine bladder cancer and b) for assessing the probability of cancer-recurrence.

Regarding tumour grading, a hierarchical tree structure was designed, employing NN-classifiers. The diagnostic-system gave high discrimination accuracy of 96.7% (Table 2) in discriminating between high and low-risk tumours. This high percentage of correct classification indicates that a certain combination of histopathological and nuclear features can segregate significantly high-risk from low-risk tumour types. This is an important outcome that can influence patient management and follow up [28]. As shown in table 3, separating low-risk tumours into tumours of grade I and II is performed with high accuracy of 82.3% by the diagnostic-system. This may be of value, since pathologists, using descriptive grading systems, grade urinary bladder cancers of grade I or II with lower [13] confidence levels. Table 4 shows the diagnostic-system's classification accuracy in characterizing a tumour as grade I, II, or III. This table provides the degree of confidence with which we can rely on the diagnostic-system's outcome. An other important outcome is that the intermediate-grade tumours are discriminated with a relative high confidence from grade I and III. This would be particular helpful for pathologist who find difficulty in assessing grade II tumours [42]. Considering overall diagnostic-system performance, 78 cases were correctly classified giving an overall accuracy of 84.8% (78/92). This accuracy is however subject to pathologist's reproducibility in evaluating cell distribution, mitosis, nucleoli, and nuclei, which were employed in the design of the diagnostic-system.

Assessing tumour recurrence may be of value in selecting appropriate therapy and planning the follow-up for patients with urinary bladder cancer. In a previous study on recurrent urinary bladder tumours, morphological features have been found that revealed statistically significant differences between recurrent and non-recurrent patients [12]. In the present work, a combination of histopathological and nuclear features employed by the prognostic-system, gave a significant (72.8%) prognostic assessment. Such a system may be suggestive of the level of confidence that a tumour might recur (74.5%) or might not (71.1%) and may thus influence patient treatment (table 5). Additionally, taking into consideration these histopathological features (cell distribution and mitosis) as well as the nuclear features (energy and correlation) by assessing chromatin structure, it could be of value to practicing pathologists who use tumour grade and tumour stage in assessing tumour prognosis in everyday practice, which is not a good recurrence indicator.

In summary, we designed a computer-based diagnostic and prognostic system for assessing urinary bladder tumour grade and predicting tumour recurrence. Some of the features employed for designing the system, may be of value to pathologists using descriptive grading systems.

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APPENDIX I

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

$$\overline{\mathrm{x}} = \frac{1}{N}\sum_{i=1}^{N} x_i \tag{1}$$

$$\sum = \frac{1}{N-1}\sum_{n=1}^{N}(x_i - \overline{\mathrm{x}})(x_i - \overline{\mathrm{x}})^T \tag{2}$$

If the eigenvalue equation for the covariance matrix is introduced:

$$\sum \mathrm{u_j} = \lambda_\mathrm{j}\mathrm{u_j} \tag{3}$$

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

$$\mathrm{x_i'} = \Lambda^{-1/2}\mathrm{U^T}(x_i - \overline{\mathrm{x}}) \tag{4}$$

where

$$U = (u_1, \ldots, u_d) \quad (5)$$

$$\Lambda = \mathrm{diag}(\lambda_1, \ldots, \lambda_d). \quad (6)$$

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

APPENDIX II

J was estimated as following:

$$J = \mathrm{trace}\{S_w^{-1} S_m\} \quad (7)$$

Where S_w is the within-class scatter matrix:

$$S_W = \sum_{i=1}^{2} P_i S_i \quad (8)$$

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

$$m_0 = \sum_{i=1}^{2} P_i m_i, \quad (9)$$

where m_i is the mean vector for class ω_i