Workshop on Bio-Medical Instrumentation and related Engineering And Physical Sciences
Technological Educational Institute of Athens
Athens 6 July 2012

A PATTERN RECOGNITION SYSTEM FOR BRAIN TUMOUR GRADE PREDICTION BASED ON HISTOPATHOLOGICAL MATERIAL AND FEATURES EXTRACTED AT DIFFERENT OPTICAL MAGNIFICATIONS

Christos Konstandinou[1], Efthymios Maneas[1], Glotsos Dimitris[2], Kostopoulos Spiros[2], Ravazoula Panagiota[3], Dionisis Cavouras*[2]

[1]Department of Informatics and Telecommunications, National and Kapodistrian University of Athens, Greece
[2]Medical Image and Signal Processing Laboratory, Department of Medical Instruments Technology,
Technological Educational Institute of Athens, 12210, Egaleo, Athens, Greece
[3]Department of Pathology, University Hospital of Patras, 26504, Rio, Patras, Greece

* e-mail: cavouras@teiath.gr , web page: http://www.teiath.gr/stef/tio/medisp/index.htm

Keywords: Astrocytomas, brain cancer, biopsy, grade, diagnosis, pattern recognition

Abstract. *The purpose of this study is to develop a computer-assisted diagnosis system for improving diagnostic accuracy in brain cancer classification into grades of malignancy. The clinical material comprised biopsies of patients with confirmed brain cancer. Images were digitized from the original material using a digital light microscopy imaging system (LEICA Axiostar plus coupled with a LEICA DFC 420C camera, Leica Microsystems GmbH). The digitized images were processed for the separation of nuclei from the surrounding tissue using edge detection techniques. Then, features were extracted from segmented nuclei at different optical magnifications to describe each sample-patient malignancy status. Moreover, samples were examined by an expert pathologist (P.R.), who assessed qualitative a number of crucial histological characteristics that are used by the World Health Organization as criteria for tumours' grading. These features comprised the input to a pattern recognition system, which was designed in order to predict the risks of malignancy of each tumor. The system was structured using the Probabilistic Neural Network (PNN) and Support Vector Machine (SVM) classifier alternatively. Using the leave-one-out method, the PNN resulted in 94.4% accuracy, while the SVM showed 96.3%. To assess the generalization of the system to unknown data, the external cross validation was used and gave 77.8% prediction for both classifiers. Results show that computer-assisted diagnosis offers a valuable tool providing second opinion consultancy to expert physicians, which contributes towards a better and more accurate diagnostic conclusion.*

1 INTRODUCTION

Astrocytomas are among the most common primary tumors of the central nervous system[1]. Accurate diagnosis in astrocytomas is a significant issue due to intra and inter-observer reliability issues[2]. Research has proven that intra and inter-observer reliability provokes wrong diagnostic decisions[3]. Reliable prediction of the diseases' diagnostic assessment (basically the grade of tumours) is crucial for patient management and treatment planning. In most cases, the distinction of low from high grade astrocytomas, as well as the location of the lesion, specifies the type and the mode of radiotherapy and/or chemotherapy to be followed[4].

There are four gradings of malignancy according to the WHO (World Health Organization) system: grades 1, 2 are the less aggressive tumours, whereas grades 3, 4 comprise the most aggressive tumours.There are, also, more than one tumour malignancy grading systems, including the WHO system, such as the Kernohan and the Mayo system, which are used for tumour prognosis.Complication in classification of brain tumours relates with: a) the existence of so multiple grading systems, which provokes classification difficulties (scientists use different grading systems and consequently decide different diagnosis), b) the subjectivity (refers to the diagnosis variability among different histopathologists who assess the samples) and c) the wrong assessments that, as a consequence, lead to wrong classifications.

Many studies have proposed Computer-Aided Diagnosis (CAD) as a reliable solution for provision of second opinion for avoiding problems of erroneous diagnostic assessments[5-9]. These studies have been based on pattern recognition, artificial intelligence and morphology/texture extracted tumoral quantitative descriptors. This study's purpose was to develop a computer-assisted diagnosis system for improving diagnostic accuracy in brain astrocytomas classification into grades of malignancy. Textural and morphological features (quantitative features), extracted from digitized images, as well as eight crucial histological parameters (qualitative variables), according to the WHO guidelines [10], assessed by two expert histopathologists, comprised the input of the proposed CAD.

2 MATERIALS AND METHODS

Archive material from formalin-fixed paraffin-embedded tissue samples of astrocytomas were obtained from 96 patients who had undergone surgery at the University Hospital of Patras between 1993 and 2002. Hematoxylin-Eosin (H&E) stained sections were generated from the same block for each case (patient). Tumour grade was defined as low or high according the WHO grading system. Based on the archives, of the 96 biopsies, 21 were classified as low grade (grade II), 53 as high grade, whereas the remaining 22 cases were rejected from further analysis due to inter-observer variation between the archive diagnosis and a new diagnostic assessment that was asked from the participated histopathologist (P.R.) for each case.

The visual inspection of tissue slides was performed on a light microscopy imaging system consisted of a Zeiss Axiostar-Plus microscope (ZEISS; Germany). The objective was used at magnifications of 20x and 40x. Histological characteristics evaluated are presented at table 1. Table 2 shows the grading classifications according to the WHO system. Table 3 illustrates the different grading systems.

Histological Feature	Assessment	Score
Cellularity	Light, mild, marked	-1,0,1
Mitoses	Absent, present	-1,1
Apoptosis	Absent, present, marked	-1,0,1
Multinucleated cells	Absent, present, numerous	-1,0,1
Giant cells	Absent, present, numerous	-1,0,1
Vascular proliferation	Absent, present, marked	-1,0,1
Necrosis	Absent, present, marked	-1,0,1
Nuclear pleomorphism	Mild, moderate, marked	-1,0,1

Table 1. Evaluation and score assignment of 8 histological (qualitative) parameters under conventional glass slide microscopy

Malignancy Grading	Classification
Grade I	Low Grade
Grade II	
Grade III	High Grade
Grade IV	

Table 2. Grading of Astrocytomas according to the WHO

Name WHO	WHO Grade	Kernohan grade	St Anne/Mayo grade	St Anne/Mayo criteria
Pilocytic astrocytor	I	-	1	0 criterion
Diffuse astrocytom	II	1	2	1 criterion (usually Atypia)
Anaplastic astrocytoma	III	2	3	2 criteria (usually Atypia + Mitos
Glioblastoma	IV	3/4	4	3-4 Criteria

Table 3. Tumour Malignancy Grading Systems

At first, the histological features' assessment was transformed in a range of -1, 0 and 1 corresponding to different assessments of each one of them (table 1). The new index was converted to rank (1, 2 and 3) and then the rank was normalized as:

$$x = \frac{r-1}{R-1} \quad (1)$$

where **r** is the corresponding rank and **R** is the max(**r**) [11].

Four methods (Euclidean distance, Footrule distance, Spearman distance, Hamming distance [15]) for Ordinal Rating Scales (ORS) for the eight histological features mentioned above were used.

Following, images were digitized from the original material using a digital light microscopy imaging system (LEICA Axiostar plus coupled with a LEICA DFC 420C camera, Leica Microsystems GmbH). The digitized images were processed for the separation of nuclei from the surrounding tissue using edge detection techniques (Figure 1).

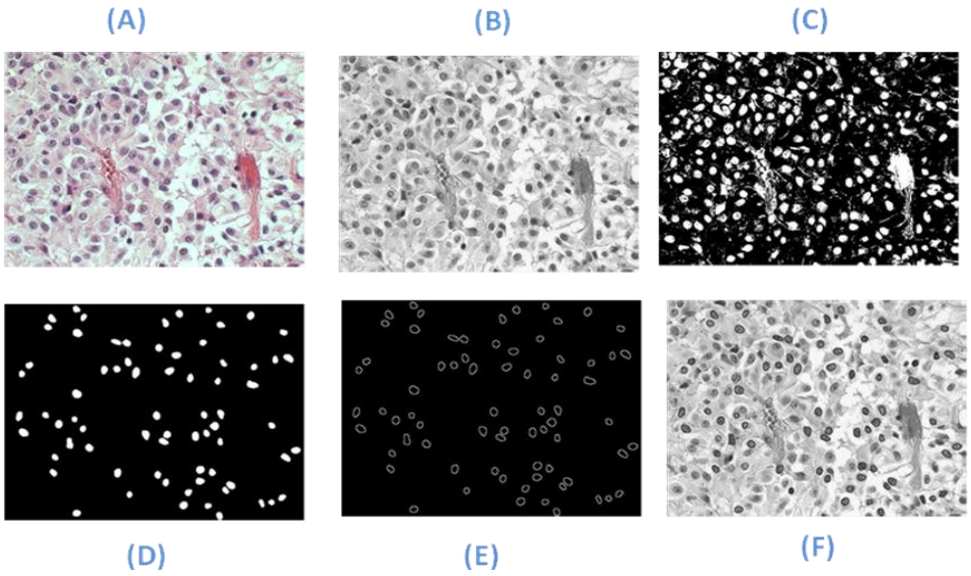

Figure 1 Image Processing Steps for quantitative feature extraction: (A) The Original Image (B) Gray scaling the original image (C) Thresholded Image (D) Image Segmentation to separate the nuclei from the surrounding tissue (E) The outline of the separating nuclei (Laplacian filter implementation) and (F) The last step derives from the combination of (B) and (E)

Then, features were extracted from segmented nuclei to describe each sample-patient malignancy status. Subsequently, the ORS for the evaluated histological parameters derived from Euclidean distance (Euclidean distance was the optimum method among the four ORS methods[19]) as well as the features extracted from the processed image comprised the input to a pattern recognition system, which was designed in order to predict the risks of malignancy of each tumor.

The pattern recognition scheme was designed to discriminate between low and high grade tumors using the exhaustive search[12] and the Leave One Out (LOO) [12] method for determining the best set up regarding features and classifiers. As classifiers the Probabilistic Neural Network (PNN) [13], and the Support Vector Machine (SVM) [14] were tested. Variations of these classifiers included PNN with Gaussian, Exponential and Reciprocal kernels and the SVM with polynomial and rbf kernels.

3 RESULTS AND DISCUSSION

Table 4 demonstrates the success rates for all classifiers and the corresponding kernels for every possible combination among 34 features (8 qualitative and 26 quantitative features) utilized. The SVM classifier with rbf kernel and four features (Cellularity, Multinucleated, Kurtosis, meanSRE) gave the best performance rate with 96.3% accuracy. Other classifiers' structures gave inferior results. Figure 2 displays the performance for PNN and SVM classifiers for the features in total by using all possible combinations between 2, 3 and 4 features. The SVM classifier with rbf kernel, which gave the highest classification accuracy (96.3 % overall accuracy), was optimized using the combination of two qualitative (Cellularity, Multinucleated cells) features and two quantitative (Kurtosis, meanSRE) features as well.

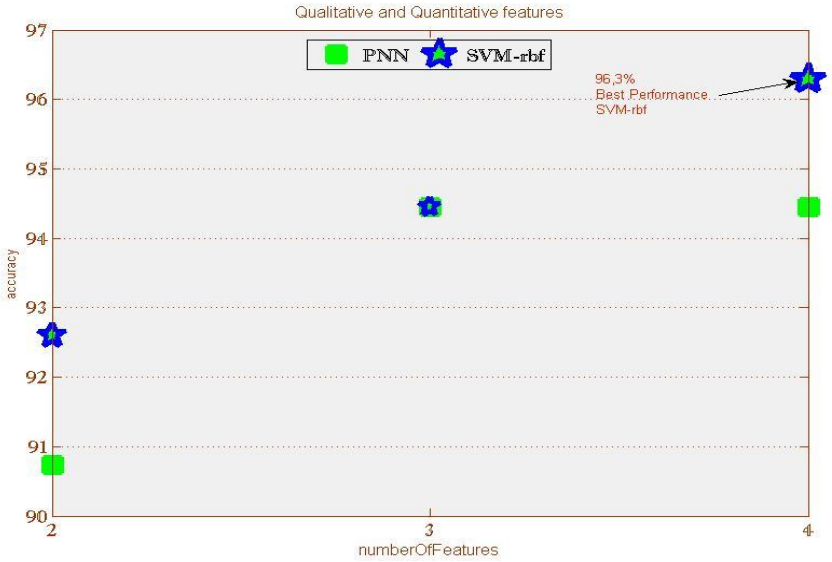

Figure 2. The best performance of each one of the classifiers for any combination between 2, 3 and 4 features. In the picture above, the best performance, which has been achieved by SVM with rbf kernel, can be noticed.

classifiers	kernels	Prediction	Features

PNN	Gaussian	S=0.05	77,8%	Cellularity, Apoptosis, diffSRE
		S=0.1	77,8%	Cellularity, Apoptosis, diffSRE
	Exponential	S=0.05	94,4%	Mitoses, apoptosis, meanRP, Eccentricity
		S=0.1	94,4%	Mitoses, apoptosis, meanRP, Eccentricity
	Reciprocal	S=0.05	88,9%	Cellularity, Apoptosis, Eccentricity
		S=0.1	88,9%	Cellularity, Apoptosis, Eccentricity
SVM	Rbf		**96,3%**	**Cellularity, Multinucleated Kurtosis, meanSRE**
	Polynomial (d=3)		85,2%	Mean, ASM, diffRP Eccentricity

Table 4. The best performance for each classifier and each one of its kernels when 8 qualitative and 26 quantitative features were combined into all possible combinations between 2, 3 and 4 features using the LOO method. The marked result with red lines is the classifier which has achieved the best performance. The features that optimize classifier's performance are discerned as well.

The External Cross Validation (ECV) method has been applied in order to determine the generalization ability of the proposed CAD system. The two classifiers achieved the same results 77,8 % accuracy. A comparison between the results of LOO method and ECV method is appeared in table 5.

Classifiers	**External cross validation applied to the total amount of the 34 features**	
	External Cross Validation Predictic	LOO's Best Prediction
PNN (Reciprocal, s=0.1)	**77,8%**	**88,9%**
SVM-rbf	**77,8%**	**96,3%**

Table 5. The best performance of each one of the classifiers applying the External Cross Validation method in order to assess the generalization ability of the proposed CAD.

Previous studies have examined a number of promising automatic grading approaches by utilizing quantitative nuclear features and descriptors of tissue morphology. Schad et al. [8] have established a system able to classify tumours according to kernohan grades with 94% accuracy. Decaestecker et al. [16] have proposed a nearest neighbor classification technique with 55% success rate. Belacel et al. [17] have presented a fuzzy-logic system analyzing nuclear features extracted from H&E stained images with 66% discrimination accuracy concerning the WHO grades. Nafe et al. [18] have used cross-validated discriminant analysis, ki-67 and the WHO system for of low (grade II) from high-grade (grade III) tumours with 88% accuracy. Glotsos et al. [9] have indicated that low from high grade tumours can be correctly separated with a certainty as high as 97.3%.

This study has investigated the effect of the combination between qualitative and quantitative features in brain tumours grading for the discrimination low (grade II) from high-grade (grade III) tumours. No previous study has been presented for evaluating the accuracy of these characteristics by means of computer aided diagnosis. The proposed CAD system resulted optimum performance as high as 96.3% using an *SVM classifier with rbf kernel* and the features *Cellularity, Multinucleated, Kurtosis, meanSRE*.

A potential future perspective of this study would involve the combination of more than four features; in this way, it would be feasible to investigate whether the combination of more than four features may result into CAD system of improved accuracy.

Concluding, it can be claimed that the combination between qualitative and quantitative features encapsulates predictive information which might be crucial for malignancy grade detection of astrocytomas, hence, specifying appropriately the patient's treatment.

REFERENCES

[1] Daumas-Duport, C., Scheitauer, B., O'fallon, J. and Kelly, P. , (1988), "Grading of astrocytomas. A simple and reproducible method" , Cancer, 62, 2152-2165.

[2] Coons, W., Jhonson, P., Sceithauer, B., Yates, A. and Pearl, D., (1997), "Improving diagnostic accuracy and interobserver concordance in the classification and grading of Primary Gliomas", Cancer, 79, 1381-93.

[3] Prayson, Ra, Agamanolis, Dp, Cohen, Ml et al., (2000), "Interobserver reproducibility among neuropathologists and surgical pathologists in fibrillary astrocytoma grading", J NEUROL SCI, 175, 33-39.

[4] Newton, H. B., Turowski, R. C., Stroup, T. J. and Mccoy, L. K., (1999), "Clinical presentation, diagnosis, and pharmacotherapy of patients with primary brain tumors", Annals of Pharmacotherapy, 33, 816-32.

[5] Decaestecker, C., Camby, I., Nagy, N. et al., (1998), "Improving morphology-based malignancy grading schemes in astrocytic tumors by means of computer-assisted techniques", Brain Pathology, 8, 29-38.

[6] Salmon, I., Rorive, S., Camby, I. et al., (1995), "Stereotactic biopsies from astrocytic tumors. Diagnostic information contributed by the quantitative chromatin pattern description", Analytical Quantitative Cytology and Histology, 17, 332-43.

[7] Mckeown, Martin J. and D., Ramsay, (1996), "Classification of Astrocytomas and Malignant Astrocytomas by Principal Component analysis and a Neural Net", J NEUROPATH EXP NEUR, 55, 1238-1245.

[8] Schad, L. R., Schmitt, H. P., Oberwittler, C. and Lorenz, W. J., (1987), "Numerical grading of astrocytomas", Medical Informatics, 12, 11-22.

[9] Glotsos, D., Kalatzis, I., Spyridonos, P. et al., (2008), "Improving accuracy in astrocytomas grading by integrating a robust least squares mapping driven support vector machine classifier into a two level grade classification scheme", Comput Methods Programs Biomed,

[10] Tumors, World Health Organization International Histological Classification Of, (1993), Histological typing of tumors of the central nervous system, Springer-Verlag, Berlin.

[11] A., Agresti, (2010), Analysis of Ordinal Categorical Data, 2nd Edition,

[12] Theodoridis, S. and Koutroubas, K., (1999), Pattern Recognition, Academic Press,

[13] Specht, D.F., (1990), "Probabilistic Neural Networks", Neural Networks, 3, 109-118.

[14] Burges, C., (1998), "A tutorial on support vector machines for pattern recognition", Data Mining and Knowledge Discovery, 2, 121-167.

[15] Teknomo, Kardi. Similarity Measurement.
Http:\\People.Revoledu.Com\Kardi\Tutorial\Similarity\.

[16] Decaestecker, C., Camby, I., Remmelink, M. et al., (1997), "Decision tree induction: a useful tool for assisted diagnosis and prognosis in tumor pathology", Laboratory Investigation, 76, 799-808.

[17] Belacel, N. and Boulassel, M., (2001), "Multicriteria fuzzy assignment method: a useful tool to assist medical diagnosis", Artificial intelligence in medicine, 21, 201-207.

[18] Nafe, R and Schlote, W, (2003), "Topometric analysis of diffuse astrocytomas", Analytical and Quantitative Cytology and Histology, 25, 12-18.

[19] Christos Konstantinou, S. Kostopoulos, D. Glotsos, P. Ravazoula, D. Cavouras, (July 2010) "Decision Support System based on Ordinal Scales for Grading of Brain Tumors" , «4th International Conference from Scientific Computing to Computational Engineering», Athens.