COMPUTER-AIDED DIAGNOSIS OF THYROID NODULES MALIGNANCY

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Abstract: *Purpose*: To design a computer-based method for the automated discrimination of thyroid nodules into two degrees of clinical significance (benign and malignant). *Materials and Methods*: Ninety-two Fine Needle Aspiration biopsies of thyroid nodules were characterized as benign (56/92) or malignant (36/92) by a histopathologist (P.R.). Images were segmented using a pixel-based classification technique. This technique relies on the principle of classifying each image pixel as belonging to nuclei or surrounding background based on the textural properties of a small neighborhood region around each pixel. After segmentation of all images, automatic characterization of thyroid nodules was performed, based on morphological and textural features extracted from segmented nuclei. These features were fed to a three-classifier ensemble classification scheme, which was designed to identify benign from malignant nodules. *Results*: The three-classifier scheme gave the maximum accuracy (95.8%) for both discriminating benign (92.8%) and malignant nodules (100%) compared to single classifiers. *Conclusions*: The proposed system could be used as a second opinion tool for avoiding the risk of excessive invasive re-examinations.

Introduction

Nodular thyroid disease is a common clinical problem that often leads to cancer-related deaths [1]. It occurs mostly after the age of 30, and its aggressiveness increases significantly with age. The annual incidence rate shows that one in 12 to 15 women and one in 40 to 50 men have a thyroid nodule [2].

The clinical routine technique, which is used to investigate the malignancy of thyroid diseases, is a microscopy examination of cytological material, obtained by Fine Needle Aspiration (FNA) [3]. Still, the complex nature of nuclei has been proven to frequently complicate the physicians' decisions forcing them to repeat biopsies [4]. Computer-aided diagnosis systems [5-8], have been shown to assist experts towards more accurate decisions. To support this conclusion, a comparative study was performed for investigating the diagnostic value of computer-based image analysis in assessing benign from malignant thyroid follicular neoplasms [6]. Results have indicated that positive and negative predictive values of image analysis versus clinical evaluation were 46.6% versus 30.4% for positives and 92.8% versus 74.3% for negatives, respectively.

The automatic characterization of thyroid diseases by means of computer-aided diagnosis systems has been mostly seen as a pattern classification problem using various methods such as statistical analysis [8] and Neural Networks [7]. In this study, a novel classification methodology is introduced, which is based on the principle of combining different classifiers in order to improve classification accuracy, in the task of discriminating benign from malignant thyroid nodules. The goal is to minimize false positives cases, which are benign nodules erroneously diagnosed as malignant, while optimizing the success in detecting true negatives for assisting experts to reduce unnecessary invasive re-examinations.

Materials and Methods

Clinical material comprised 92 FNA biopsies of thyroid nodules, collected from the Department of Pathology of the University Hospital of Patras, Greece. Biopsies were stained with Hematoxylin and Eosin (H&E) and were characterized as benign (56/92) or malignant (36/92) by an experienced histopathologist (P.R.). From each biopsy, the histopathologist specified the most representative region and marked it on the microscopy slide. According to this region, images (1300x1030x24bit) were acquired using a light Zeiss Axiostar-Plus microscope (ZEISS; Germany) connected to a Leica DC 300 F color video camera (LEICA; Germany). Each digitized image was converted to 8-bit gray scale for further processing and analysis.

Images were segmented using a pixel-based classification technique. This technique relies on the principle of classifying each image pixel as belonging to nuclei or surrounding background based on the textural properties of a small neighborhood region around each pixel. In detail, three textural features (the spread, the cross relation and the sum of the autocorrelation

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function) [9] were extracted from 100 randomly sampled 5x5 pixel regions of nuclei and background respectively. Based on these features a majority vote ensemble classification scheme was designed, consisting of three classifiers (Least square Minimum Distance: LSMD, Quadratic-LSMD: QLSMD, Cubic-LSMD: CLSMD) [10] to identify nuclei regions. A more detailed description of this method can be found elsewhere [5].

After segmentation of all 92 images, 40 morphological and textural nuclear features were quantified from each image to encode thyroid nodules malignancy. Morphological features describe the size and shape of nuclei and comprised measures of area, roundness and concavity [11]. For each one of these features the mean value, standard deviation, range, skewness, kurtosis, and maximum value was calculated. Textural features encode the variations in chromatin distribution within nuclei. As texture descriptors were selected features calculated from first order statistics and the co-occurrence matrices [12].

After feature generation, each image was represented by a 40-dimensional feature vector, where each vector element was the mean feature value of all examined nuclei. The same classifiers that were used for image segmentation (i.e. the LSMD, QLSMD, and CLSMD) were designed to discriminate benign from malignant cases. An exhaustive search in the feature space was utilized to extract the best feature vector combination [13]. Each combination was evaluated using the leave-one-out method [13]. The best combination selected, was the one that gave the smallest classification error.

In addition, a majority vote (MV) scheme for combining the three classifiers was designed, to investigate whether combining of classifiers may improve classification results, compared to the use of single classifiers. Classification outputs, from each classifier separately, were combined and the final classification decision was based on the decision of the majority of the classifiers [13].

Results

The results of the segmentation process for benign (see figure 1.1) and malignant (see figure 2.1) H&E-FNA cytological thyroid images are demonstrated in figures 1.2 and 2.2 respectively.

The LSMD classifier optimized its performance (86.9%) employing as best feature vector combination the *concavity*, *range of roundness* and *angular second moment* (co-occurrence matrix-based feature). The QLSMD classifier succeeded higher accuracy (91.7%) using 3 features, namely *maximum of roundness*, *mean value* and *correlation* (co-occurrence matrix-based feature). The same accuracy (91.7%) was achieved by the QLSMD classifier using 4 features (*area*, *range of roundness*, *maximum of roundness* and *correlation)* (see table 1).

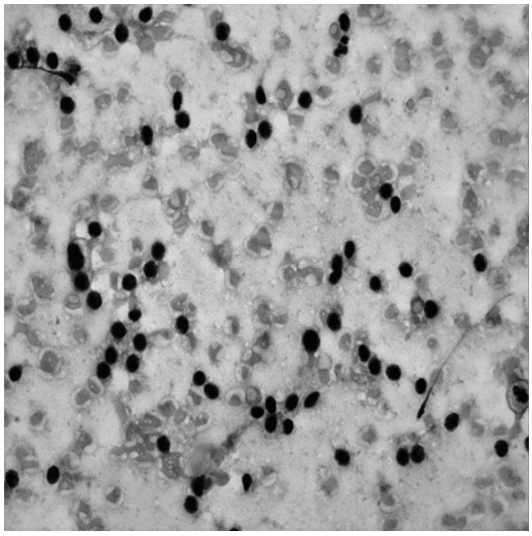

Figure 1.1: H&E-FNA stained benign thyroid image

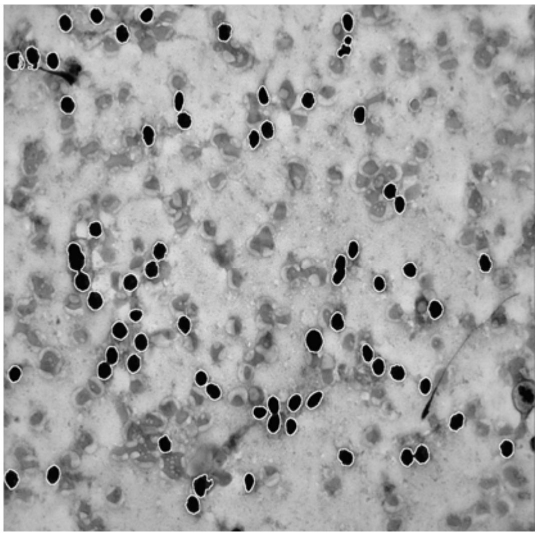

Figure 1.2: Segmented image using the pixel-based classification algorithm.

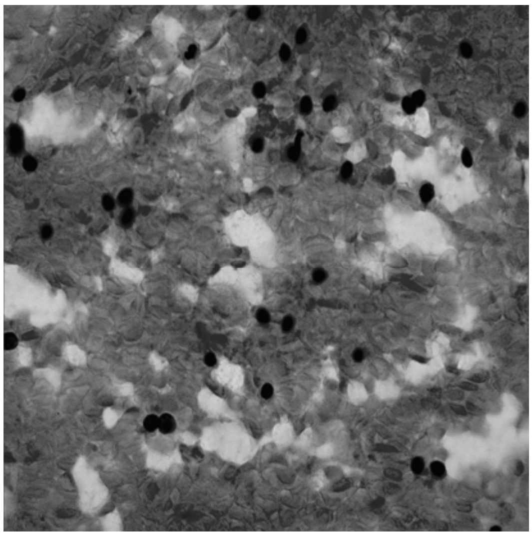

Figure 2.1: H&E stained malignant thyroid image

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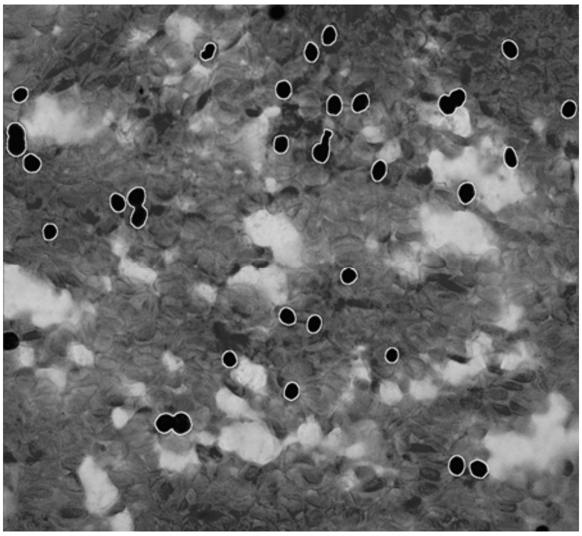

Figure 2.2: Segmented image using the pixel-based classification algorithm.

The majority vote scheme significantly improved the detection of benign (92.8%) and malignant nodules (100%), in comparison with the respective results achieved by using single classifiers (see table 1 and figure 3).

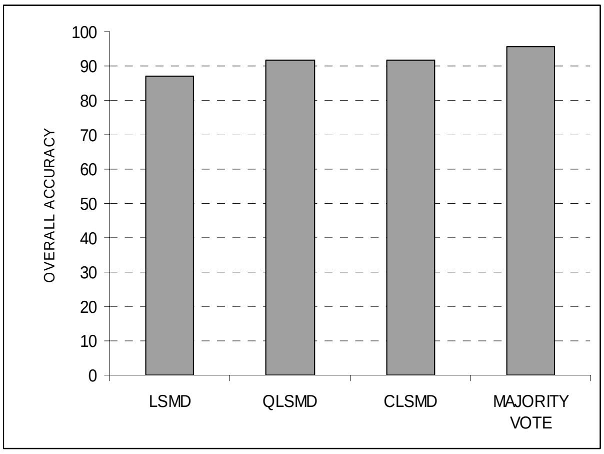

Figure 3: Classification performance of all the classifiers and the Majority Vote scheme in the task of discriminating benign from malignant thyroid nodules.

Table 1: Classification results of all classifiers and of the Majority Vote scheme

	Classification task (%)		
Classifiers	Benign	Malignant	Overall accuracy
LSMD	85.7	88.9	86.9
QLSMD	92.8	88.9	91.7
CLSMD	92.8	88.9	91.7
Majority Vote	92.8	100	95.8

Discussion

Automated detection of thyroid diseases is an active research field until today, due to the need to improve the accuracy of diagnosis and reduce patients that are subjected to timely and costly invasive re-examination. Among the most recent studies towards this direction, two important studies are the automated characterization of non-Hodgkin's thyroid lymphomas, by means of statistical analysis [8], and the determination of malignancy of suspected thyroid lesions, using back propagation Neural Networks and morphometry [7].

In this study, we have investigated whether classifier combination may improve the important discrimination of benign from malignant thyroid nodules. Results have indicated that the classifier combination scheme significantly outperformed single classifiers' accuracies (95.8% against 86.9% and 91.7%). Although ensemble classification methods are being extensively studied currently, to the best of our knowledge, these methods have not been used for classification of microscopy images of thyroid nodules.

Regarding the feature selection process, results indicate important conclusions. Morphological differences in nuclei characteristics of thyroid nodules (concavity, roundness and the kurtosis of area) proved significant for the separation of benign from malignant nodules. Bigger and irregular shaped nuclei appeared more frequently into the malignant nodules, whereas in the benign cases, nuclei were mostly circular with almost constant size. Additionally, textural differences have also highlighted differences in smoothness and coarseness between benign and malignant nuclei. Malignant nuclei showed a significantly coarser nature than benign nuclei.

Conclusions

The proposed system could be used as a second opinion tool to the pathologists for avoiding the risk of excessive invasive thyroid re-examinations, thus decreasing the time/cost of diagnosis.

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