Diagnosis of Hepatic Tumors With Texture Analysis in Nonenhanced Computed Tomography Images

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Rationale and Objectives. Computed tomography (CT) after iodinated contrast agent injection is highly accurate for diagnosis of hepatic tumors. However, iodinating may have problems of renal toxicity and allergic reaction. We aimed to evaluate the potential role of the computer-aided diagnosis (CAD) with texture analysis in the differential of hepatic tumors on nonenhanced CT.

Materials and Methods. This study evaluated 164 liver lesions (80 malignant tumors and 84 hemangiomas). The suspicious tumor region in the digitized CT image was manually selected and extracted as a circular subimage. Proposed preprocessing adjustments for subimages were used to equalize the information needed for a differential diagnosis. The autocovariance texture features of subimage were extracted and a support vector machine classifier identified the tumor as benign or malignant.

Results. The accuracy of the proposed diagnosis system for classifying malignancies is 81.7%, the sensitivity is 75.0%, the specificity is 88.1%, the positive predictive value is 85.7%, and the negative predictive value is 78.7%.

Conclusions. This system differentiates benign from malignant hepatic tumors with relative high accuracy and is therefore clinically useful to reduce patients needed for iodinated contrast agent injection in CT examination. Because the support vector machine is trainable, it could be further optimized if a larger set of tumor images is to be supplied.

Keywords. Hepatic tumor; liver lesion; computed tomography; computer-aided diagnosis; support vector machine; texture analysis

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The best way to reduce deaths due to liver cancer is to treat the disease at an earlier stage. Earlier treatment requires early diagnosis. Early diagnosis requires an accurate and reliable diagnostic procedure that allows physicians to differentiate benign hepatic tumors from malignant ones. The most frequently adopted medical imaging studies for early detection and diagnosis of liver carcinomas include ultrasonography (US), magnetic resonance imaging (MRI), angiography, and computed tomography (CT). Ultrasonography, although noninvasive and of nonradiation, is very operator dependent. There is a considerable overlap of benignancy and malignancy in US images and interpretation is subjective. MRI, with its endogenous high tissue contrast and multiplanar capability, affords superior diagnostic ability for detection and differentiation of hepatic tumors. However, the cost of examination is very expensive and therefore it is not as popular as CT. Angiography is an invasive procedure with potential complications. Routinely, nonenhanced CT is included as a part of CT examination. This set of images alone cannot afford conclusive diagnostic information (1). A computer-aided diagnosis (CAD) system would therefore be ex-
pected to be helpful in diagnosing liver cancer because of the difficulty of such diagnoses. CT scan after bolus injection of iodinated contrast agent and by acquisition of arterial phase and portovenous phase images is highly accurate for diagnosis of hepatic tumors but may have problems of renal toxicity and allergic reaction.

An artificial neural network classifier was designed to diagnose hepatic masses in the abdominal US images (2); that study found that the overall accuracy of abdominal ultrasound is 75%. Moreover, Yoshida et al. (3) purposed a method of wavelet-based texture analysis for distinguishing benign from malignant focal liver lesions in B-mode US images. A neural network was performed to classify focal liver lesions using selected multiscaled wavelet texture features. Neural networks have proved to be an interesting and useful alternate processing strategy (4). With good understanding of their capabilities and limitations, neural networks may be applied productively to problems in early detection and diagnosis of cancer (5). Specific applications of neural networks for cancer detection and diagnosis (6–10) include breast cancer, liver cancer, and lung cancer. However, the learning procedures of neural networks are very time consuming and initial parameter dependent; that is, the number of neurons, learning rate, and moment value are hard to decide. Unfortunately, the selections of initial parameters will affect the results drastically, whereas the support vector machine (SVM) has feasibility and superiority to extract higher-order statistics. The SVM has become extremely popular in terms of classification and prediction. This study uses the SVM as a classifier to determine whether a hepatic tumor is benign or malignant in CT images without iodinated contrast agent injection. The diagnosis system proposed herein is able to more accurately and efficiently classify the nonenhanced CT images of hepatic tumor. The SVM classifier is a reliable choice for the proposed CAD system because it trains well and computes efficiently. If this proposed system is useful for differential diagnosis of hepatic tumors in nonenhanced CT images, the necessity of iodinated contrast agent administration can be reduced remarkably; medical cost, radiation dose, and potential allergic reaction will also be reduced.

**MATERIALS AND METHODS**

Many general-purpose image-processing techniques have been used to assist physician to locate the focus in CT images, such as contrast adjustment transformation, sharpening filtering, and noise reduction filtering. In this study, we supposed that physician has already identified the hepatic tumor in nonenhanced CT images. The proposed CAD system used the intensity variation and inter-pixel texture information from the nonenhanced CT images to diagnose hepatic tumors. The circular subimages from the suspicious tumor regions are first drawn on liver CT images by an experienced radiologist, and then the computer analyzed the subimage to make a differential diagnosis.

**Images Acquisition**

The CT image database contained 164 hepatic tumors before iodinated contrast agent injection. These images were collected in a period of 1 year from September 2001 to August 2002. All CT examinations were performed in a Picker PQ 5000 CT scanner (Picker International, Highland Heights, OH). The criteria for enrollment of CT images included that the lesion size be smaller than 5 cm, that the lesion can be visualized in preenhanced CT images set, and that the lesion was a tumor in nature according to postenhanced CT images and clinical data. The database was divided into two groups including 80 images of malignant tumors and 84 images of benign tumors. The malignant group included primary hepatocellular carcinoma (n = 68) and metastatic tumors (n = 12). The benign group included hemangioma only. Hepatocellular carcinoma was diagnosed by significantly elevated alpha-fetoprotein (n = 68) and pathological proof (n = 32). Postenhanced CT images in these 68 tumors also showed typical features of hepatocellular carcinoma, namely, well-enhanced hyperdense lesions in arterial phase images and washout hypodense lesions in portovenous images. All metastatic tumors had history of primary malignancy in colon and showed typical imaging features of poorly enhanced lesions in CT.

All the CT images were supplied by authors (J.-H. Chen and W.-C. Shen). The suspicious tumor regions were delineated in CT images by one of the authors, J.-H. Chen, an experienced radiologist. Furthermore, circular region of interest (ROI) was taken in order to include the largest possible area of the suspicious tumor region, while avoiding the margins of the tumor. The ROI subimage was then saved as a file for later analysis. Figure 1a illustrates a digitized monochrome CT image. Figure 1b presents an ROI for the hepatic tumor.
Different tissues in a CT image always have significantly different textures. The textural variation between benign and malignant in the CT image is an efficient feature to classify hepatic tumors. The CT scan without iodinated contrast agent injection, however, is the cause of the unapparent textural information. In this study, a preprocessing adjustment is carried out before the extraction of textural features. The principal purpose of adjustment is to preprocess the ROI subimage so that the result is more suitable than the original for textural analysis. In image processing techniques, histogram manipulation can be used effectively for image contrast adjustment (11). The histogram equalization is a good approach because the method automatically enhances digital image and the results from this technique are predictable. Thus histogram equalization was adopted to preprocess the CT images. Figures 2b and 2d show the preprocessed images of performing histogram equalization on Figures 2a and 2c, respectively. The result shows significant improvement in image contrast. Although histogram equalization is known to enhance noise in the image, we have found the differential effect of the autocovariance coefficients is indeed improved. The increase in contrast resulting from it was enough to render the more conspicuous textural features.

**Textural Features**

This study used the correlation between neighboring pixels within the images as features to identify hepatic tumors. The two-dimensional normalized autocovariance coefficients (12) used to reflect the interpixel correlation within an image. The autocovariance coefficients between pixel \((i, j)\) and pixel \((i + \Delta m, j + \Delta n)\) in an image with size \(M \times N\) is defined as

\[
\gamma(\Delta m, \Delta n) = 1 - \frac{A(\Delta m, \Delta n)}{A(0, 0)}, \tag{1}
\]
A(Δm, Δn) = \frac{1}{(M - Δm)(N - Δn)} \sum_{x=0}^{M-1-Δm} \sum_{y=0}^{N-1-Δn} \left| (f(x,y) - \bar{f})(f(x + Δm, y + Δn) - \bar{f}) \right|, \quad (2)

where \( \bar{f} \) is the mean value of \( f(x, y) \). The autocovariance coefficients were performed as the textural feature vector for representing each ROI subimage, and then the feature vectors were used to distinguish the differences between benign and malignant tumors. Table 1 lists the mean and standard deviation of the equalization preprocessed feature vector (autocovariance coefficients with Δm and Δn are 5) for malignant cases and benign cases, and the mean difference between the two groups. The significant mean differences of the two groups can prove whether autocovariance coefficients are good features for distinguishing malignant and benign cases. With larger value of Δm + Δn, the mean difference is larger. Moreover, the preprocessing adjusted image feature coefficients are quite conspicuous in comparison with the aboriginal image feature coefficients, as illustrated in Figure 3.

**Support Vector Classification**

The aim of support vector machine (SVM) is to devise a computationally efficient way of learning separating hyperplanes in a high dimensional feature space (13,14). The SVMs have been shown to be an efficient method for many real-world problems because of its high generalization performance without the need to add a priori knowledge. Recently, SVMs have attention much as a useful tool for image recognition, hand-written digit recognition, and bioinformatics (15–18). The SVM can map the input vectors into a high dimensional feature space through some nonlinear mapping, chosen a priori. In this space, an optimal separating hyperplane is constructed. Generally, the SVM is an implementation of the structural risk minimization principle whose object is to minimize the upper bound on the generalization error. Given a set of training vectors (1 in total) belonging to separate classes,
\[(x_1, y_1), (x_2, y_2), (x_3, y_3), \ldots, (x_i, y_i)\], where \(x_i \in \mathbb{R}^n\) denotes the \(i\)th input vector and \(y_i \in \{+1, -1\}\) is the corresponding desired output. The maximal margin classifier aims to find a hyperplane \(w^T x + b = 0\) to separate the training data. In the possible hyperplanes, only one maximizes the margin (distance between the hyperplane) and the nearest data point of each class. Figure 4 shows the optimal separating hyperplane with the largest margin. The support vectors denote the points lying on the margin border. The solution to the classification is given by the decision function

\[f(x) = \text{sign}\left(\sum_{i=1}^{N_{SV}} \alpha_i y_i k(s_i, x) + b\right)\]

where \(\alpha_i\) is the positive Lagrange multiplier, \(s_i\) are the support vectors (\(N_{SV}\) in total), and \(k(s_i, x)\) is the function for convolution of the kernel of the decision function.

The radial kernels performs best in our experimental comparison, hence is chosen in the proposed diagnosis system. The radial kernels is defined as

\[k(x, y) = \exp(-\eta ||x - y||^2),\]

where \(\eta \in \mathbb{R}\) is a nonzero parameter.

This study utilized the two-dimensional normalized autocovariance matrix for the input of the SVM. The dimension of the matrix can be fixed for any size of image. In this study, both \(\Delta m\) and \(\Delta n\) are 5, so an equalization of adjusted CT image produces a \(5 \times 5\) autocovariance matrix, i.e., 25 autocovariance coefficients. The value of \(\gamma\) (0, 0) is always 1 for a normalized autocovariance matrix.

Excluding the element \(\gamma\) (0, 0), other autocovariance coefficients are formed as a 24-D textural feature vector. The vector is used as the input of the SVM. Moreover, the value produced by the output node is used to decide whether a tumor image is benign or malignant. Notice that the output value of the SVM is either \(-1\) or \(1\). When the output value of a subimage of suspicious tumor region is \(1\), the system will classify the tumor in the CT image as malignant. Conversely, when the output value is \(-1\), the hepatic tumor will be diagnosed as benign.

**RESULTS**

The \(k\)-fold cross-validation method (19) is used to estimate the performance of the proposed CAD system. The CT images in the database are randomly divided into \(k\) groups. The first group is set aside and the remaining \((k - 1)\) groups are used to train the SVM. Because the radial kernels perform best in the experimental results, the kernels are chosen in the proposed SVM diagnosis system. Figure 5 shows the diagnosis performance for the SVM system with different \(\eta\) values. With the \(\eta\) ranged from 0.02 to 0.03, the CAD obtained a stable and the highest accuracy. Once trained, the SVM is then tested on the group that was set aside. The second group is then removed, and the remaining \((k - 1)\) groups are trained and the network is tested on the excluded group. This process is repeated until all \(k\) groups have been used in turn as the group that is set aside and used for testing. In the simulations, the value of \(k\) was 10.
The system correctly identifies 60 of 80 the malignant tumors and 74 of 84 hemangiomas. Table 2 lists the number of misdiagnosed cases of the CAD for each test set in the image database.

<table>
<thead>
<tr>
<th>Test set</th>
<th>Proposed system</th>
<th>Malignant cases</th>
<th>Benign cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2/8</td>
<td>0/9</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>5/8</td>
<td>0/9</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>1/8</td>
<td>2/9</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>2/8</td>
<td>1/9</td>
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</tr>
<tr>
<td>5</td>
<td>4/8</td>
<td>0/8</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>2/8</td>
<td>2/8</td>
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<td>7</td>
<td>2/8</td>
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<td>8</td>
<td>1/8</td>
<td>3/8</td>
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<tr>
<td>9</td>
<td>1/8</td>
<td>0/8</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>0/8</td>
<td>1/8</td>
<td></td>
</tr>
</tbody>
</table>

The improvements with the preprocessing adjustment were statistically significant.

Table 2
The number of misdiagnosed cases of the proposed CAD for each test set in the image database

DISCUSSION

In diagnosing liver lesions, CT has become one of the major imaging modalities. The full expression of its diagnostic role for this category of disease depends on multiple sets of images including nonenhanced and enhanced arterial and enhanced venous phase images. Nonenhanced CT is frequently performed for diagnosis of parenchymal diseases such as fatty liver, calcification, and location of focal liver lesions that can be taken as a reference compared with those of enhanced CT images. Highly accurate diagnosis of different kind of liver lesions requires dynamic information of contrast enhancement afforded in different phase of CT images. Benign and malignant hepatic tumors need different therapeutic rationale. Malignant hepatic tumors including primary and metastatic ones require aggressive treatments such as operative resection, minimally invasive tumor ablation, transarterial chemoembolization, or systemic chemo/ or radiotherapy. Benign liver lesion such as hemangioma, requiring no further management, is very usually seen in the daily practice and has a typical imaging feature in postenhanced CT images. Exclusion of this category of benign lesions is therefore important. The idea of this study comes from the assumption that since hemangioma is a blood-pooling lesion, the texture characteristics, namely, the correlations between the CT numbers of neighboring pixels, might be different from those of malignant hepatic tumors that are usually solid ones. Nonenhanced CT images alone can therefore be used for analysis of lesion texture. The potential diagnostic role of this technique might omit multiple acquisitions of CT images within single CT examination and therefore reduce irradiation dose to the patient and omit administration of an iodinated contrast agent if possible. The potential renal toxicity and allergic reaction caused by injected contrast agent can be avoided.

This report proposes an efficient diagnosis system using SVM to differentiate between benign and malignant hepatic tumors. The ability of SVM to extract higher-order statistics is particularly valuable when the dimension of the input vector is large. Moreover, the SVM can “learn” from experience to solve some difficult problems. Conventional discrimination algorithms, such as discriminate analysis and tree-based classifiers, always fail to achieve prospective objective. SVM generalized from the training samples performs well on independent test data. Besides, the main advantage in the proposed system is that the training procedure of SVM was very fast and
stable. The training and diagnosis procedure of the proposed system is almost 700 times faster than that of multilayer perception neural networks (MLPs). With the growth of the database, supplementary CT images can be collected and used as reference cases while performing diagnoses. This study reduces the training and diagnosis time dramatically.

CAD systems have been developed for diagnosis of many human diseases on medical imaging (20–28). An ingenious CAD system is able to assist radiologists and physicians in differentiating benign from malignant lesions on medical images. The results produced by CAD can be used as a “second opinion” to assist radiologists in their interpretations and improve diagnostic accuracy (29–31). Obviously, CAD has practical value in radiological diagnosis. Radiological physicists and technologists who have a strong interest in CAD research will be good partners for radiologists in developing CAD systems. The proposed system diagnoses hepatic tumors using interpixel textural features within nonenhanced CT. From the highly satisfactory specificity and sensitivity of our results, the proposed system is expected to be a helpful tool for classifying benign and malignant tumors in nonenhanced CT images and can provide a second reading to reduce misdiagnosis. However, several limitations exist in this study. First, the liver lesion to be analyzed must be identified in nonenhanced CT, or contrast enhanced CT is still needed for further diagnosis. Further, benign hepatic tumors such as adenoma and focal nodular hyperplasia, although not commonly encountered in our daily practice, were not included in this study. This might bear the potential of false-positive diagnosis of malignant tumors. The malignant group consisted of both primary and secondary tumors in this study. However, the interpixel texture analysis cannot further differentiate these two categories of liver lesions due to their similar solid nature. Further studies are under way using other representative classifiers, such as the unsupervised learning models on a larger test set of tumor images.

Table 3

<table>
<thead>
<tr>
<th>CT image classification</th>
<th>Proposed system</th>
<th>Without preprocessing adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Benign*</td>
<td>Malignant*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benign</td>
<td>TN 74</td>
<td>FN 20</td>
</tr>
<tr>
<td>Malignant</td>
<td>FP 10</td>
<td>TP 60</td>
</tr>
<tr>
<td>Total</td>
<td>84</td>
<td>80</td>
</tr>
</tbody>
</table>

TN = true-negative; FN = false-negative; FP = false-positive; TP = true-positive.

*Histological finding.

Table 4

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Proposed system</th>
<th>Without preprocessing adjustment</th>
<th>$P^*$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Accuracy (%)</td>
<td>81.7</td>
<td>66.5</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Sensitivity (%)</td>
<td>75.0</td>
<td>63.8</td>
<td>NS</td>
</tr>
<tr>
<td>Specificity (%)</td>
<td>88.1</td>
<td>69.0</td>
<td>&lt;.025</td>
</tr>
<tr>
<td>PPV (%)</td>
<td>85.7</td>
<td>66.2</td>
<td>&lt;.025</td>
</tr>
<tr>
<td>NPV (%)</td>
<td>78.7</td>
<td>66.7</td>
<td>&lt;.01</td>
</tr>
</tbody>
</table>

Accuracy = (TP + TN)/(TP + TN + FP + FN); sensitivity = TP/(TP + FN); specificity = TN/(TN + FP); PPV = TP/(TP + FP); NPV = TN/(TN + FN).

*P value was obtained with the $\chi^2$ test. NS = not significant.

REFERENCES