Analysis of Diffuse Parenchymal Liver Disease by Liver Scintigrams: Differential Diagnosis Using Neuro and Fuzzy

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Key Words: colloid liver scintigram, diffuse parenchymal liver disease, chronic hepatitis, fibrosis, cirrhosis, fuzzy inference, neural network

Summary

In colloid liver scintigraphy, diagnosis of diffuse parenchymal liver disease such as chronic hepatitis or cirrhosis is evaluated by size and distortion of the liver, distribution of tracer in the liver, size and activities of tracer in the spleen, visualization of the bone marrow and so on. It is not difficult to read a scintigram which shows a typical pattern of normal, chronic hepatitis and cirrhosis; however in some cases it is difficult to distinguish normal or chronic hepatitis and chronic hepatitis or cirrhosis visually. Therefore, we tried to use fuzzy inferences to perform differential diagnosis in chronic hepatitis (CH), severe fibrosis (SF) and liver cirrhosis (LC). First, five features in colloid liver scintigrams were measured or evaluated visually. These features were liver size index (left lobe/right lobe), splenomegaly, the degree of visualization of the bone marrow, liver deformity, and distribution of tracer in the liver. Having fuzziness in these data, certain characteristics of these features were considered to be fuzzy sets and thus could be expressed in membership functions. Fuzzy inference was carried out using these data and fuzzy rules. Using fuzzy inference, differential diagnosis in LC could be performed up to 100%, but those of CH and SF could not be performed sufficiently. Using neural network CH, SF and LC could be diagnosed up to 63%, 80%, and 88%, respectively. But fuzzy inference had the merit to evaluate the degree of disturbance by the center of gravity of the resulting membership function. There-
fore by combining neural network and fuzzy inference, CH, SF, and LC could be
differentiated to the degree 77%, 80%, and 100%, respectively.

Introduction

Colloid liver scintigraphy (1, 2) is extensively used for the diagnosis of various
liver diseases. In one diagnostic study of small hepatocellular carcinoma, the
sensitivity of scintigraphy was 39%, ultrasonography was 50% and CT was 56%
(3). Colloid liver scintigraphy is based on phagocytosis of foreign matter by
reticuloendothelial cells in the liver and provides information about liver mor-
phology, splenomegaly, changes in bone marrow and intrahepatic radionuclide
distribution. This method is still useful in the diagnosis of diffuse parenchymal
liver diseases. Accuracy was given in one comparison of three methods as 64% by
CT, 51% by ultrasonography and 70% by scintigraphy (4). Scintigraphic diagnosis
is performed usually by reading images visually. Since we can read the morpho-
logical change and function of the liver with scintigrams for the diagnosis of
diffuse parenchymal liver disease, such as chronic hepatitis or cirrhosis, it is useful
in diagnosing the degree of the disturbance of liver function. The differential
diagnosis between normal and chronic hepatitis or chronic hepatitis and cirrhosis
is difficult in some cases by conventional methods. Therefore several features of
liver scintigrams were examined and fuzzy inference (5, 6) was performed to im-
prove the true positive ratio. The true positive ratio (7) was as follows; normal:
92% (23/25), chronic hepatitis: 79% (30/38) and cirrhosis: 90% (36/40). In this
study the analyzed results were compared with histopathological findings. Recently
histopathological findings of chronic liver disease for diagnosis are based on the
following two categories; the grade of inflammatory activity and the stage of
fibrosis (8, 9). Thus, based on the new criterion for histopathological findings,
the diagnosis was analyzed. A study using neural network (NN) (10, 11) was also
attempted. The NN is an artificial neural network simulating functional models of
nervous system, which is an information processing of parallel dispersing type of
high level. The reason for the use of NN is as follows: By training input and
output data on NN, the relationship between input and output data improves
automatically. Also, by analyzing the inner structure of NN, the relationship
between synaptic weights (connection weights) and hidden layer and output layer
could also be analyzed. The possibility of combination of NN and fuzzy inference
(Neuro and Fuzzy) (12) was examined.
Materials and methods

1. Criterion of histopathological diagnosis. Diagnosis of the parenchymal liver disease is usually considered to be based on histopathological findings. The grade of inflammation can also be evaluated by hematologic findings to some degree. Thus according to the histopathological criterion, we tried to evaluate the stage of fibrosis using liver scintigrams. In this study, the disease which was equivalent to the stage of fibrosis 1-2 (1: mild, 2: moderate) was considered to be chronic hepatitis (CH), stage 3 for severe was considered to be severe fibrosis (SF), and stage 4 for cirrhotic was considered to be liver cirrhosis (LC). There were a total of 36 patients in this study: 13 CH, 10 SF, and 13 LC. They were all confirmed by liver biopsy. Referring to Table 1, No. 1-No. 13 were CH patients, No. 14-No. 23 were SF patients and No. 24-No. 36 were LC patients.

2. Features of liver scintigrams. Liver scintigrams were taken 20-30 minutes after injection of $^{99m}$Tc-phytate (111MBq) using the scinticamera (Siemens corporation ZLC DIGITALC 7500) with high resolution collimator. The anterior and posterior view images were used for the reading. As liver scintigrams show distinctive pattern of the degree of liver disfunction, features of liver scintigrams were measured or evaluated visually and quantified. The features of liver scintigrams were as follows; Liver size index: left lobe/right lobe, spleen size index: splenomegaly, the degree of visualization of bone marrow, liver deformity and distribution of tracer in the liver. Liver size index (left lobe/right lobe) and splenomegaly were estimated by measuring the rates b/a and c/d as shown in Fig. 1. The degree of visualization of bone marrow was estimated in the degree [0, 2], liver deformity [0, 2] and distribution of tracer in the liver [0, 1], respectively at 0.5 intervals. For example, when no visualization of bone marrow was observed on the scinti-

![Figure 1. Features of a colloid liver scintigram.](image)

Left lobe/right lobe = b/a  Splenomegaly = c/d  (size of spleen)
gram, it was considered to be in the degree 0. No liver deformity and the uniform distribution of tracer in the liver were also considered to be in the degree 0. If

Table 1 Features of various kinds in liver scintigrams

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<tr>
<th>Subject</th>
<th>Histopathological findings *</th>
<th>Liver size index **</th>
<th>Splenomegaly</th>
<th>Visualization of bone marrow</th>
<th>Liver deformity</th>
<th>Distribution of tracer in the liver ***</th>
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* CH, Chronic hepatitis; SF, Severe fibrosis; LC, Liver cirrhosis.

** Liver size index: Left lobe/ right lobe, b/a in Fig. 1.

*** Uniform distribution, " 0 "; non-uniform distribution, " 1 "; intermediate, " 0.5 ".
the degree of visualization of bone marrow and the liver deformity are high, and the distribution of tracer in the liver is non-uniform, then the larger values are assigned i.e. the degree of abnormality is expressed in proportion to the evaluated values. Table 1 shows features of each liver disease corresponding to histopathological findings. As the values were estimated visually, they have fuzziness. Therefore the features indicated in Table 1 are considered to be fuzzy sets (13) and the fuzzy inference was performed based on these data.

3. Fuzzy inference. In this analysis, fuzzy singleton-type inference (14) was used. First, adaptable degree $h_i$ between antecedent and consequent part for each if-then rule was obtained. The results of the inference for each fuzzy rule were calculated as the resulting consequent part (the variable is a real number: $Z_i$). The final result ($Z_0$) of the inference was obtained using the following formula.

$$Z_0 = \frac{h_1 w_1 z_1 + h_2 w_2 z_2 + \ldots + h_i w_i z_i}{h_1 w_1 + h_2 w_2 + \ldots + h_i w_i} \quad \text{Eq. 1}$$

where $w_i$ is the coefficient of “degree of emphasis” in the results of each inference. The antecedent variables were liver size index (left lobe/right lobe), splenomegaly, the degree of visualization of bone marrow, liver deformity and distribution of tracer in the liver. The consequent part variables were regarded as reflecting the degree of diffuse parenchymal liver disease.

4. Determination of membership function. As stated above, features of liver scintigrams were considered to be able to show liver size index (left lobe/right lobe), splenomegaly, the degree of visualization of bone marrow, liver deformity and distribution of tracer in the liver. Features of liver size index (left lobe/right

![Membership functions](image-url)
lobe) and splenomegaly were divided into 3 kinds: small, medium and large. The membership functions of the antecedent are shown in the upper part (a) and (b) of Fig. 2. The degree of visualization of bone marrow, liver deformity and the distribution of tracer in the liver were evaluated in the degree [0, 2], [0, 2], [0, 1], respectively as mentioned before. The degree of visualization of bone marrow and liver deformity were determined as none, slight and marked. Distribution of tracer in the liver was determined as uniform and non-uniform. These membership functions of the antecedent were expressed to show the lower part (c), (d), (e) of Fig. 2. The membership functions of the consequent part were each real number and represented a singleton-type. The order for the staging progress of the liver disease is normal (N), CH, SF and LC. Therefore if the center or gravity in fuzzy inference is around 10, 20, 30 and 40, the disease is evaluated as N, CH, SF and LC, respectively.

5. Fuzzy rules. Analyzing liver scintigrams, the following fuzzy rules were considered to be standard. 1) If the liver size index (left lobe/right lobe) is small, splenomegaly is small, the degree of visualization of bone marrow is none, the liver deformity is none and the distribution of tracer in the liver is uniform, then the result is N. 2) If the liver size index (left lobe/right lobe) is medium, splenomegaly is medium, the degree of visualization of bone marrow is none, the liver deformity is slight and the distribution of tracer in the liver is uniform, then the result is CH. 3) If the liver size index (left lobe/right lobe) is large, splenomegaly is large, the degree of visualization of bone marrow is slight and the liver deformity is slight, then the result is SF. 4) If the liver size index (left lobe/right lobe) is large, splenomegaly is large, the degree of visualization of bone marrow is marked and the liver deformity is marked, then the result is LC. Based on these rules, fuzzy inference was performed.

6. Neural Network. Analysis of diffuse parenchymal liver disease by NN was performed using the features of the above data. For the input signal of NN, the scale in the features was changed to the range 0-1.0 according to the following formula.

\[ X_{\text{new}} = aX_{\text{old}} + b \]  
Eq. 2

where Xold is the value before the scale change and Xnew is the value after the scale change. The values a and b were calculated to be maximum at 1.0 and minimum at 0 for the feature after the change.

7. Structure of NN and learning method. As shown in Fig. 3, the structure of NN consists of three layer structures. The input layer corresponds to 5 units (X₁, X₂, X₃, X₄, X₅) and the hidden and output layers correspond to 2 units (Y₁, Y₂ and Z₁, Z₂) each. In general the output values of the hidden layer (Yj) and
output layer (Zk) were calculated using the following formulae, respectively.

\[ Y_j = f(\Sigma W_{ij} \cdot X_i) \quad \text{Eq. 3} \]
\[ Z_k = f(\Sigma V_{jk} \cdot Y_j) \quad \text{Eq. 4} \]

where \( W_{ij} \) is the connection weight (coefficient of weight) from input layer to intermediate layer (hidden layer) and \( V_{jk} \) is the connection weight from hidden layer to output layer. Threshold values are expressed as \( W_{0j} \) and \( V_{0k} \). In Fig. 3 \( W_{11} \) is the connection weight from \( X_1 \) to \( Y_1 \), \( W_{12} \) from \( X_1 \) to \( Y_2 \) etc. "\( V_{11} \)" is the connection weight from \( Y_1 \) to \( Z_1 \), \( V_{12} \) from \( Y_1 \) to \( Z_2 \) etc. "\( f \)" is a sigmoid function of the following formula.

\[ f(u) = \frac{1}{1+\exp(-u/T)} \quad \text{Eq. 5} \]

where \( T \) of Eq. 5 is a coefficient determining the slant of the sigmoid curve. "\( T \)" is assumed to be 0.2. The teaching signals to train the connection weight were "0, 0" for CH, "1, 0" for SF and "1, 1" for LC. Five cases of CH, SF and LC, respectively were used as training data for the connection weight. The training data were selected for CH, SF and LC as characteristic values for the category. The features in Table 2 are the values after the scale change for normalization. Training of NN was completed when the output values corresponded to the teaching signals. The back propagation algorithm (10) was used to train the connection weight of NN.

8. Neuro and Fuzzy. Combination of fuzzy inference and neural network was examined in this study. As shown in Fig. 4, the values of fuzzy inference were corrected by the outputs of NN.
Table 2  Teacher data (Input data) and output data of hidden layer, and output layer (2nd and 3rd layer) in neural network

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<th>Input signal</th>
<th>Output</th>
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Figure 4. The structure of Neuro and Fuzzy
X₁ X₂ X₃ X₄ X₅, Input data; Zo, Center of gravity of output by Neuro and Fuzzy
Results

1. Fuzzy inference. The results of fuzzy inference for liver scintigrams are shown in Fig. 5 as the position of center of gravity based on Eq. 1. From this figure, the position of the center of gravity can be evaluated for CH to be from 16 to 23,
for SF from 24 to 35 and for LC from 36 to 40. These results are compared with histopathological diagnosis shown in Table 3. In 13 cases diagnosed as CH by biopsy, 1 N case, 7 CH cases and 5 SF cases. In 10 cases of SF, 4 cases appeared as CH, 3 SF cases and 3 LC cases by fuzzy inference. Using fuzzy inference, it was difficult to find rules to distinguish CH and SF, and the difference between CH and SF could not be evaluated sufficiently. However, all 13 cases of LC were evaluated correctly in this study in compliance with the histopathological diagnosis.

Table 3 Results of fuzzy inference with reference to the histopathological diagnosis in diffuse parenchymal liver disease

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N, Normal; CH, Chronic hepatitis; SF, Severe fibrosis; LC, Liver cirrhosis

* Note: In a total of 13 cases diagnosed as CH by biopsy, one case “Normal” and five cases “Severe fibrosis” were included according to the fuzzy inference.

2. Neural network. First, the relationship between error of learning process by NN (sum of squares of difference between teaching signals and output values) and correct rate was examined. When 1500 learnings were performed, the error was 0.0026 and the correct rate was 100%. Even if the number of learnings was increased further, rate of the error did not decrease very much. On the right column of Table 2 the output values of hidden layer (2nd layer Y₁, Y₂) and output layer (3rd layer Z₁, Z₂) of each liver disease for 1500 learnings are shown. As can be seen in the table, the output values of hidden layer (Y₁) was about zero in the range of 0-0.2 for CH. The output values of SF and LC were almost unity in the range of 0.7-1; therefore the values of Y₁ indicate either CH about zero or not CH about unity. On the other hand, from the values of Y₂, CH and SF were about unity in the range of 0.9-1 and LC was about zero in the range of 0-0.12. This means that the values of Y₂ distinguish LC or not LC. As shown on the last column of Table 2, the values of output layer (Z₁, Z₂) for CH, SF and LC
corresponded approximately to the teaching signals "0, 0", "1, 0", "1, 1" respectively. The value of the connection weight $W_{ij}$ is shown in Table 4. $W_{i1}$ is the connection weight influencing the value of $Y_1$. The factor primarily affecting the difference between CH and not CH corresponded to the degree of visualization of bone marrow which has the maximum value of $W_{i1}$ in Table 4; splenomegaly and the distribution of tracer in the liver proved to a lesser degree the factor to distinguish CH and not CH. On the contrary, $W_{i2}$ is the connection weight influencing the value of $Y_2$. In this case the factors affecting the difference between LC and not LC corresponded to the degree of visualization of bone marrow and the liver deformity which has the negative value but a large absolute value of $W_{i2}$ in Table 4. The percentage of coincidence of the results analyzed by NN excluding the training data with histopathological diagnosis was in the study as follows; CH, 63% (5/8); SF, 80% (4/5); LC, 88% (7/8) and overall rate, 76% (16/21).

3. Neuro and Fuzzy. As shown in Table 5, by combining fuzzy inference and neural network, CH, SF, and LC could be differentiated 77%, 80%, and 100% respectively. The true positive ratio of fuzzy inference was improved by correction with analyzed results of NN.

4. Examples of scintigrams. The example in Fig. 6 was a case diagnosed as CH (CPH: chronic persistent hepatitis) by liver biopsy. The left image is the anterior view, and the right one is the posterior view of the colloid liver scintigram. The features were evaluated as follows. Liver size index (Left lobe/right lobe) = 0.52, splenomegaly = 0.33, the degree of visualization of bone marrow = 0, liver deformity = 0.50, the distribution of tracer in the liver = 0. Based on the findings from the reading of the scintigrams it was diagnosed CH by expert. Position of the center of gravity by fuzzy inference and Neuro and Fuzzy were 17, 19, respectively. The

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Table 4 Connection weight in neural network

<table>
<thead>
<tr>
<th>Items</th>
<th>$W_{i1}$</th>
<th>$W_{i2}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$X_1$: Left lobe/Right lobe</td>
<td>1.62</td>
<td>0.73</td>
</tr>
<tr>
<td>$X_2$: Splenomegaly</td>
<td>3.14</td>
<td>0.11</td>
</tr>
<tr>
<td>$X_3$: Visualization of bone marrow</td>
<td>3.49</td>
<td>-2.42</td>
</tr>
<tr>
<td>$X_4$: Liver deformity</td>
<td>-1.62</td>
<td>-1.65</td>
</tr>
<tr>
<td>$X_5$: Distribution of tracer in the liver</td>
<td>2.60</td>
<td>0.38</td>
</tr>
</tbody>
</table>

Threshold value: $W_{i1} = -1.09$, $W_{i2} = 1.29$
Table 5 Results analysed by neuro and fuzzy for histopathological diagnosis in diffuse parenchymal liver diseases

<table>
<thead>
<tr>
<th>Liver biopsy</th>
<th>Neuro and Fuzzy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CH</td>
</tr>
<tr>
<td>CH</td>
<td>10</td>
</tr>
<tr>
<td>SF</td>
<td>0</td>
</tr>
<tr>
<td>LC</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>10</td>
</tr>
</tbody>
</table>

CH, Chronic hepatitis; SF, Severe fibrosis; LC, Liver cirrhosis

values of output by NN were 0.01, 0.00; therefore it was evaluated as CH. This was found to be a correct evaluation in comparison with the histopathological diagnosis.

On the other hand, the case in Fig. 7 was diagnosed as CH (CAH2A: chronic active hepatitis, moderate activity) by liver biopsy. In the same method, the values were evaluated as follows; Liver size index (Left lobe/right lobe) = 0.69, splenomegaly = 0.37, the degree of visualization of bone marrow = 0, liver deformity = 1.0, the distribution of tracer in the liver = 0.5. The findings from the reading of the scintigrams were CH~LC. Position of the center of gravity by fuzzy inference and Neuro and Fuzzy were 29, 30, respectively, and the values of output by NN were 1.00, 0.03. These values indicate SF, which was different from histopathological
Analysis of Diffuse Parenchymal Liver Disease by Liver Scintigrams

Figure 7. Example of a colloid liver scintigram in chronic active hepatitis.

diagnosis. This was a difficult case to differentiate.

Discussion

In diagnosis of liver disease, histopathological diagnosis has a special characteristic in which the liver tissue could be used directly, and it is considered to be the final correct diagnosis. But the grade of inflammation and the stage of fibrosis may differ from site to site and it is considered to be the grade of inflammation and stage of fibrosis at the biopsied site of tissue. Clinically, it is important to differentiate between normal, chronic inactive hepatitis, chronic active hepatitis and cirrhosis. This study was carried out based on the new criterion for histopathological diagnosis i.e. CH, SF and LC. Using fuzzy inference, LC could be differentiated in all cases, but accuracy of differentiation of CH was 54% (7/13), and that of SF was 30% (3/10). It was difficult to establish fuzzy rules that were characteristic to CH and SF; thus the differentiation was difficult. But, the relationship between CH, SF and LC which is the stage of fibrosis in pathological tissue that has not been studied from features of liver scintigrams could be evaluated to some extent with this method. Liver scintigraphy is a non-invasive method and shows the shape and function of the liver. It was useful to differentiate between LC and not LC. Fuzzy inference has the ability to evaluate the degree of liver disturbance by the center of gravity of the resulting membership function. Medical information is often not clear-cut and the use of fuzzy theory in the diagnostic process has been tried before (15-19). It is necessary to determine fuzzy rules for fuzzy inference. Until now fuzzy rules have been determined by trial and error and according to clinical experience. To determine fuzzy rules objectively and quickly, use of genetic algorithm (20) is considered to be an optimizing
technique based on mechanisms of natural selection.

NN is the method used to simulate the function of nervous system and can determine the relationship between input and output. The model has since been applied to various fields including medicine (21-25). Therefore we studied the adaptation of NN in this study and obtained a good result for the difference between normal, chronic hepatitis and cirrhosis (22). We adapted this method for the data which distinguish CH, SF and LC and obtained a good result. The results of NN excluding the training data were as follows: of 8 cases diagnosed as CH, 5 cases were CH (63%) and 3 cases were SF; of 5 cases diagnosed as SF, 4 cases were SF (80%) and 1 case was LC; of 8 cases diagnosed as LC, 7 cases were LC (88%) and 1 case was SF. However using fuzzy inference alone, LC was correctly diagnosed in all cases, but the difference between CH and SF was difficult to evaluate. On the other hand, using NN, the difference between CH and SF could be evaluated reasonably well. Therefore, by combining NN and fuzzy inference, the results were greatly improved in distinguishing CH, SF and LC. The difference of true positive ratio between ‘fuzzy inference’ and ‘Neuro and Fuzzy’ was recognized in P=0.0274<0.05 by Fisher’s test. The use of NN does not require any rules of differentiation as in the case of fuzzy inference, and when analyzing the inner structure, it is advantageous to analyze the relationship between the connection weights and the hidden layer and the output layer.

Features of liver scintigrams were estimated visually and analysis of fuzzy inference was performed. Differentiation by fuzzy inference was especially good for distinguishing LC or not LC and useful differential data was obtained. Using NN, differential diagnosis of CH, SF and LC could be performed reasonably well. Therefore, by combining fuzzy inference and NN, improved differential diagnosis could be expected.

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References


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