A new endoscopic ultrasonography image processing method to evaluate the prognosis for pancreatic cancer treated with interstitial brachytherapy

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Abstract

AIM: To develop a fuzzy classification method to score the texture features of pancreatic cancer in endoscopic ultrasonography (EUS) images and evaluate its utility in making prognosis judgments for patients with unresectable pancreatic cancer treated by EUS-guided interstitial brachytherapy.

METHODS: EUS images from our retrospective database were analyzed. The regions of interest were drawn, and texture features were extracted, selected, and scored with a fuzzy classification method using a C++ program. Then, patients with unresectable pancreatic cancer were enrolled to receive EUS-guided iodine 125 radioactive seed implantation. Their fuzzy classification scores, tumor volumes, and carbohydrate antigen 199 (CA199) levels before and after the brachytherapy were recorded. The association between the changes in these parameters and overall survival was analyzed statistically.

RESULTS: EUS images of 153 patients with pancreatic cancer and 63 non-cancer patients were analyzed. A total of 25 consecutive patients were enrolled, and they tolerated the brachytherapy well without any complications. There was a correlation between the change in the fuzzy classification score and overall survival (Spearman test, \( r = 0.616, P = 0.001 \)), whereas no correlation was found to be significant between the change in tumor volume (\( P = 0.663 \)), CA199 level (\( P = 0.659 \)), and overall survival. There were 15 patients with a decrease in their fuzzy classification score after brachytherapy, whereas the fuzzy classification score increased in another 10 patients. There was a significant difference in overall survival between the two groups (67 d vs 151 d, \( P = 0.001 \)), but not in the change of tumor volume and CA199 level.

CONCLUSION: Using the fuzzy classification method to analyze EUS images of pancreatic cancer is feasible, and the method can be used to make prognosis judgments for patients with unresectable pancreatic cancer treated by interstitial brachytherapy.

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Key words: Digital image processing; Fuzzy classification; Endoscopic ultrasonography; Pancreatic cancer; Interstitial brachytherapy; Prognosis

Core tip: Digital image processing (DIP) of endoscopic ultrasonography (EUS) images has been proven to be useful in diagnosis of malignant tumor. Currently commonly used method of DIP is only to concludes the dif-
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The application of digital image processing (DIP) in endoscopic ultrasonography (EUS) images and other imaging scenarios has been proven to be a useful adjunct to endoscopic diagnoses and often comparable with specialists’ interpretation in different pathologic settings. The texture parameters of EUS images are extracted and classified from the returned echoes to identify the tissue type present in the images. One effective approach is to use DIP based on a support vector machine (SVM), which is a computer algorithm that learns by example to assign labels to objects. The SVM technique, as a subclass of digital signal processing, has been applied to a series of pathologically proven diseases.

The typical method of SVM, which is only able to provide a differential diagnosis for solid tumors (“yes” or “no”), cannot provide numerical data describing the texture parameters in the EUS image. EUS-guided brachytherapy has been applied preliminarily in the study of advanced pancreatic cancer. However, prognosis judgment of these patients was still difficult. So we develop a fuzzy classification method to score texture features of pancreatic cancer in EUS images to supply more information and validated its utility in prognosis judgment of patients with unresectable pancreatic cancer treated by EUS-guided interstitial brachytherapy.

MATERIALS AND METHODS

The whole study protocol was approved by the Institutional Review Board and Ethics Committees of the Second Military Medical University. All patients had provided their written informed consent before the study. DIP of EUS images using the fuzzy classification method was retrospective, whereas its application in the prognosis evaluation was prospective.

Principle of fuzzy classification

Given that the unidentified object \( u \) had \( p \) classes, which meant there were \( p \) cases that such an object could be classified to, a number of features were extracted from the object \( u \), and the sum of these features had a membership degree \( A \) to every class. Therefore, the membership degree of the unidentified object \( u \) to each class was \( A_1(u), A_2(u), \ldots, A_s(u) \). It is generally assumed that the larger the membership degree’s value of a certain class is, the greater the feature value of the objects belonging to this class will be.

Given that the \( j \)th feature extracted from the unidentified object \( u \), its membership degree to the \( j \)th feature of class \( i \) is:

\[
A_i(u) = \left(1 + \frac{(u \cdot a_j)^2}{\sigma_i^2}\right)^{-1} \quad (1)
\]

where \( a_j \) is the \( j \)th feature’s mean value for the training data belonging to class \( i \), and \( \sigma_i^2 \) was the variance.

Thus, every feature of the unidentified object \( u \) could obtain a membership degree to class \( i \). In addition, a corresponding weight \( a_i \) was also assigned to it. Therefore, the membership degree of belonging to class \( i \) should be:

\[
A_i(u) = \sum_{j=1}^{n} (a_i \times A_j(u)) \quad (2)
\]

The weights could be optimized by taking advantage of the training data.

In terms of the application object in this study, there were two classes: pancreatic cancer and non-pancreatic cancer. For an unidentified case, its membership degree to the two categories \( A_1 \) and \( A_2 \) was computed, and then the feature value was obtained according to the following normalized evaluation function:

\[
Evalu = \frac{A_1}{(A_1 + A_2)} \times 100\%
\]

The object is more likely to be a cancer as the feature value gets closer to 100%, and vice versa. Thus, the fuzzy classification of pancreatic cancer was achieved.

Processing of the fuzzy classification method

The analysis database of EUS images was compiled from data collected between March 2005 and December 2007, which was described in a previous study of our group. All EUS procedures were performed with an Olympus GF-UM2000 at 7.5 MHz. Regions of interest (ROIs) of all EUS images were manually outlined by endoscopic specialists who were blind to the final diagnosis. Texture features were extracted from every ROI and analyzed using a C++ program. Texture features generally referred to the spatial arrangement and interconnection of the basic elements of images. The sequential forward search algorithm was applied to select the features after extracting the feature. Then, a few optimum feature combinations were obtained. Finally, real time was taken into account, and 22 features falling into three categories were selected. First, the mean feature value of the image was extracted. It was a first-order statistical feature. Second, the gray level co-occurrence matrix (GLCM) features were selected, which were based on the second-order joint feature distribution matrix of the images proposed by Haralick et al. GLCMs for four directions \((0^\circ, 45^\circ, 90^\circ, 135^\circ)\) were constructed. For each matrix, five features were extracted, which were energy, entropy, moment of inertia, correlation, and local stationary. Finally,
the fractal feature was obtained. Recently, the fractal dimension feature has been widely used in pattern recognition and texture analysis. In this study, the second-order multi-fractal dimension feature was used, and the differential box-counting approach was applied to calculate the fractal dimension[19,20]. The previously described fuzzy classification method assessed all the features contained in the ROI of the EUS image and estimated a score between 0 and 100. Given that two states existed - cancer and a normal pancreas - 0 represented all the features of a “normal pancreas” that were contained in the ROI with no “cancer” features, whereas 100 represented all the features of “cancer” with no “normal pancreas” features.

**Application of the fuzzy classification method**

Written informed consent for EUS-guided interstitial brachytherapy (EUS-guided iodine 125 radioactive seed implantation) was required from all included patients. Patient eligibility criteria included histologically confirmed unresectable pancreatic adenocarcinoma. To be included in the study, patients had to have a Karnofsky performance status score ≥ 60 and be expected to survive for more than 2 mo after diagnosis; in addition, they had to exhibit adequate bone-marrow function (absolute neutrophil count ≥ 1.5 × 109 cells/L, platelet count ≥ 100 × 109/L, and hemoglobin ≥ 100 g/L), kidney function (serum creatinine ≤ 132.6 μmol/L), and a prothrombin time within 3 s of the control. Exclusion criteria included the inability to give informed consent. Abdominal pain and other accompanying diseases had to be controlled in all patients before inclusion in the study. While receiving implantation treatment, the patients received other necessary treatments such as chemotherapy or biological therapy. The procedure used for radioactive seed implantation was the same one detailed in our previous description[21].

All patients received repeated EUS before and after brachytherapy. All images were reviewed by endoscopists who were blinded to the prognosis. A total of 10 EUS images, 5 images each before and after brachytherapy, were chosen for each patient. The boundary of the ROI was manually delineated, and all the feature values within the ROIs were averaged together. By setting the appropriate range for the estimated scores, the influences of necrotic tissue and radioactive seeds on the calculation results were avoided. The fuzzy classification method calculated two scores for every patient.

All patients were evaluated by weekly physical examinations, complete blood counts, and chemistry profiles. The serum level of carbohydrate antigen 199 (CA199) was measured every 3 wk after the therapy. Standard WHO response criteria were used to define the best anti-tumor effects, toxicities, complications, and adverse events[22]. Tumor assessment was conducted by a Mann-Whitney U test. The results were considered statistically significant at P < 0.05. Statistical analyses were performed using the Statistical Package for Social Sciences software (SPSS version 18.0).

**RESULTS**

**Database of EUS images**

Between March 2005 and December 2007, 153 patients with pancreatic cancer and 63 non-cancer patients with a normal pancreas (20 patients) or chronic pancreatitis (43 patients) were included in the analysis database. All EUS images of these patients were analyzed. The ROIs were drawn, and texture features were extracted and selected.

**Characteristics of the included patients**

From April 2007 to March 2009, a total of 25 consecutive patients were enrolled. There were fourteen men and eleven women, with a median age of 67 years (range 54-80 years) and a median KPS score of 80 (range 60-90). Five patients were in stage III, and twenty were in stage IV. The average number of seeds (0.5 mCi per seed) implanted was 14.6 per patient (range 5-30 per patient). All patients tolerated the brachytherapy well without any complications throughout the study.

**Change of the fuzzy classification score**

A total of 250 EUS images from the 25 patients were analyzed using the fuzzy classification method, and every patient was scored twice. There was a correlation between the change in the fuzzy classification score and overall survival (r = 0.616, P = 0.001), whereas no correlation was found to be significant between the change of tumor volume (r = 0.663), CA199 level (P = 0.659), and overall survival. There were 15 patients with a decrease in the fuzzy classification score after the brachytherapy, whereas the fuzzy classification score increased in other 10 patients (Table 1). There was a significant difference in the overall survival between the two groups (67 d vs 151 d, P = 0.001, Figure 1). There was no significant difference in the change of tumor volume (P = 0.345) and CA199 level (P = 0.371) between the two groups (Table 1).
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Table 1 The change in the fuzzy classification result and clinical parameters after brachytherapy in 25 unresectable pancreatic cancer patients

| No. | FCS before brachytherapy | FCS after brachytherapy | FCS | Tumor volume | CA199 | Survival time (d) |
|-----|--------------------------|-------------------------|-----|--------------|-------|-----------------|
| 1   | 22.30                    | 80.40                   | -260.50 | -93%         | -53%  | 58              |
| 2   | 16.30                    | 33.52                   | -105.60 | 14%          | 69%   | 69              |
| 3   | 70.60                    | 88.61                   | -25.50  | 42%          | 75%   | 50              |
| 4   | 50.30                    | 60.24                   | -19.80  | 53%          | 0%    | 80              |
| 5   | 52.60                    | 56.80                   | -8.60   | 2%           | 0%    | 68              |
| 6   | 60.30                    | 63.50                   | -5.30   | 0%           | 8%    | 67              |
| 7   | 87.52                    | 90.31                   | -3.20   | 0%           | 66%   | 198             |
| 8   | 88.50                    | 90.20                   | -1.90   | 320%         | 17%   | 54              |
| 9   | 83.10                    | 83.68                   | 0.70    | 0%           | NA    | 103             |
| 10  | 90.80                    | 91.20                   | 0.40    | 12%          | 0%    | 125             |
| 11  | 88.20                    | 87.20                   | 0.10    | -15%         | NA    | 20%             |
| 12  | 90.20                    | 88.93                   | 1.40    | -171%        | 0%    | 143             |
| 13  | 91.30                    | 88.70                   | 2.80    | 0%           | 0%    | 138             |
| 14  | 92.43                    | 89.20                   | 3.50    | 48%          | 0%    | 221             |
| 15  | 95.10                    | 88.20                   | 7.30    | -1%          | 6%    | 312             |
| 16  | 89.21                    | 80.12                   | 10.20   | -104%        | -30%  | 108             |
| 17  | 93.70                    | 81.10                   | 13.40   | 71%          | 85%   | 61              |
| 18  | 87.52                    | 75.21                   | 14.10   | 44%          | -265% | 182             |
| 19  | 92.20                    | 61.23                   | 33.60   | 96%          | 0%    | 122             |
| 20  | 82.30                    | 47.60                   | 42.20   | 78%          | -3%   | 200             |
| 21  | 78.56                    | 44.03                   | 44.00   | -66%         | -1%   | 156             |
| 22  | 75.90                    | 35.62                   | 53.10   | 42%          | 13%   | 104             |
| 23  | 51.20                    | 18.30                   | 64.30   | 40%          | -358% | 151             |
| 24  | 90.10                    | 22.70                   | 74.80   | 61%          | 96%   | 194             |
| 25  | 89.30                    | 18.64                   | 79.10   | 4%           | 95%   | 378             |

Groups
Increase (n = 10) (interquartile range) -6.7% (43.9%) 1% (44%) 8% (68%) 67 (49)
Decrease (n = 15) (interquartile range) 14.1% (49.6%) 40% (76%) 0% (41%) 151 (78)

*The parameter change was calculated by (pre-post)/pre; When the levels of carbohydrate antigen 199 (CA199) were larger than 100 μmol/L before and after treatment, 0% meant no improvement; P = 0.001. FCS: Fuzzy classification score; NA: Not available.

DISCUSSION

The analysis of texture features is the core of DIP of digital images. Texture features are helpful for classifying lesions on sonography, and the potential of sonographic texture analysis to improve tumor diagnosis has already been demonstrated[2,13]. However, only a few reports exist about the application of DIP techniques to EUS. For the diagnosis of pancreatic cancer, research using DIP and pattern recognition remains rare. Two recent studies successfully used neural network analysis of EUS images to differentiate pancreatic cancer from chronic pancreatitis[28]. Das et al[3] reported high sensitivity (93%) and specificity (92%), with excellent positive predictive values (87%) and negative predictive values (96%). An SVM model was evaluated as a potential method to differentiate between malignant and benign lesions with excellent accuracy rates[28]. Its performance characteristics in differentiating pancreatic cancer from benign lesions or normal tissue of the pancreas are closely rivaling those of EUS-FNA.

In our study, the feature extraction and selection based on fuzzy classification was applied to EUS images of pancreatic cancer patients. All the work was carried out by the developed C++ program. According to the fuzzy algorithm, the classification result was not just “yes” or “no”, but a score from 0 to 100[21,22]. Compared with the SVM method[13], the fuzzy classification method proposed in our study could additionally give the precise numerical difference between a cancer case and a non-cancer case.

EUS-guided brachytherapy has been applied preliminarily in the study of advanced pancreatic cancer[23]. Two clinical series showed that pancreatic cancer could be treated safely with EUS-guided brachytherapy with pain control[31,32]. The number of patients enrolled in these two series was 22 and 100, respectively, with stage III or IV pancreatic cancer in a majority of cases. The estimated median overall survival in the two studies was 9.0 and 7.0 mo. The brachytherapy's effect on overall survival was uncertain because of the lack of a control. Meanwhile, making prognosis judgments for these patients is still difficult. Given that brachytherapy aims to destroy the tumor locally, if it were effective, the EUS images of pancreatic cancer ought to change to be more similar to those from a normal pancreas, and the fuzzy classification score of EUS images after the brachytherapy ought to show a decrease. Thus, the change of the fuzzy classification score most likely reflected the treatment effect to some extent and the prognosis after brachytherapy. Our study results validated this hypothesis. First, the change of the fuzzy classification score was significantly correlated with overall survival, which meant the more the score decreased, the longer the patient survived. Second, 15 of 25 patients (60%) had a decreased fuzzy classification score after the
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brachytherapy. The median overall survival was nearly 5 mo. As a control, the fuzzy classification results increased in 10 patients after treatment, and the median overall survival was only approximately 2 mo. The log-rank test indicated a significant difference between these two groups.

The tumor volume is an important candidate for making prognosis evaluations for pancreatic cancer. In our study setting, the metal package of radioactive seeds made it difficult to measure the tumor volume by computed tomography. Thus, the EUS scan was a more suitable and convenient way to measure the volume. Meanwhile, as a diagnostic marker, CA199 is also another candidate for prognosis evaluation. However, our results found no association between the change of tumor or CA199 and the overall survival, which meant they were not a suitable prognosis marker in the patient population.

There were some limitations in our study. The new method can distinguish pancreatic cancer from chronic pancreatitis or a normal pancreas, but it cannot differentiate different cancer types. The probable approach to overcome this problem is to train multiple, 1-"all classifiers. Furthermore, enlarging the sample size and selecting new effective features are future possibilities for further study to improve the practicability of the technique.

In conclusion, the fuzzy classification method to score texture features of pancreatic cancer in EUS images is feasible and can be used as an effective tool to judge the prognosis of patients with unresectable pancreatic cancer treated by interstitial brachytherapy.

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