Neural network analysis of dynamic sequences of EUS elastography used for the differential diagnosis of chronic pancreatitis and pancreatic cancer

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Background: EUS elastography is a newly developed imaging procedure that characterizes the differences of hardness and strain between diseased and normal tissue.

Objective: To assess the accuracy of real-time EUS elastography in pancreatic lesions.

Design: Cross-sectional feasibility study.

Patients: The study group included, in total, 68 patients with normal pancreas (N = 22), chronic pancreatitis (N = 11), pancreatic adenocarcinoma (N = 32), and pancreatic neuroendocrine tumors (N = 3). A subgroup analysis of 43 cases with focal pancreatic masses was also performed.

Interventions: A postprocessing software analysis was used to examine the EUS elastography movies by calculating hue histograms of each individual image, data that were further subjected to an extended neural network analysis to differentiate benign from malignant patterns.

Main Outcome Measurements: To differentiate normal pancreas, chronic pancreatitis, pancreatic cancer, and neuroendocrine tumors.

Results: Based on a cutoff of 175 for the mean hue histogram values recorded on the region of interest, the sensitivity, specificity, and accuracy of differentiation of benign and malignant masses were 91.4%, 87.9%, and 89.7%, respectively. The positive and negative predictive values were 88.9% and 90.6%, respectively. Multilayer perceptron neural networks with both one and two hidden layers of neurons (3-layer perceptron and 4-layer perceptron) were trained to learn how to classify cases as benign or malignant, and yielded an excellent testing performance of 95% on average, together with a high training performance that equaled 97% on average.

Limitation: A lack of the surgical standard in all cases.

Conclusions: EUS elastography is a promising method that allows characterization and differentiation of normal pancreas, chronic pancreatitis, and pancreatic cancer. The currently developed methodology, based on artificial neural network processing of EUS elastography digitalized movies, enabled an optimal prediction of the types of pancreatic lesions. Future multicentric, randomized studies with adequate power will have to establish the clinical impact of this procedure for the differential diagnosis of focal pancreatic masses. (Gastrointest Endosc 2008;68:1086-94.)

Abbreviations: EUS-FNA, EUS-guided FNA; MLP, multilayer perceptron; NN, neural network; NPV, negative predictive value; PPV, positive predictive value; ROC, receiver operating characteristic; SD, standard deviation.

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EUS elastography is a newly developed imaging procedure that characterizes the differences of hardness and strain between diseased tissue and normal tissue. The elastography information is displayed in real time as a transparent color overlay in a defined region of interest, similar to color Doppler examinations.[1-3] EUS elastography was already used in several studies for the characterization and

differentiation of benign and malignant lymph nodes, with variable sensitivity, specificity, and accuracy, better than results obtained by conventional EUS criteria.[2,3] A certain number of pitfalls, however, were reported in these initial investigations, including possible perception errors and motion artifacts, as well as the impossibility of controlling tissue compression.[4] Because of the inherent bias induced by selection of images from a dynamic sequence of EUS elastography, we previously reported on the utility of using computer-aided diagnosis by averaging images from a dynamic sequence and calculating hue histograms, as a better way to describe, semiquantitatively, EUS elastography movies.[5]

EUS-guided tissue sampling methods (EUS-guided FNA [EUS-FNA] and EUS-guided trucut biopsy) have slowly become the procedures of choice used to obtain tissue diagnosis and confirmation of malignancy in focal pancreatic masses.[6-10] However, several recent imaging procedures, including power Doppler EUS, contrast-enhanced EUS, and EUS elastography might challenge conventional EUS as imaging methods that attempt to better describe tissue characteristics, including tissue vascularization and hardness.[11-16] The feasibility of EUS elastography was previously tested in pancreatic diseases, with fair and plausible results.[16,17] The aim of our study was to prospectively assess the accuracy of EUS elastography to differentiate between normal pancreas, chronic pancreatitis, and pancreatic cancer. A postprocessing analysis based on specially designed software was used to analyze the EUS elastography movies by calculating hue histograms of each individual image. Furthermore, an extended neural network (NN) analysis based on mean hue histograms of the EUS elastography movies was tested to differentiate benign versus malignant EUS elastography patterns.

Capsule Summary

What is already known on this topic

- EUS elastography reveals the differences of hardness and strain between diseased and normal tissue, displaying information in real time as a transparent color overlay in a defined region of interest, similar to color Doppler examinations.

What this study adds to our knowledge

- In a study group that included patients with a normal pancreas, chronic pancreatitis, and pancreatic cancer, the sensitivity, specificity, and accuracy of differentiation of benign and malignant masses by using EUS elastography were 91.4%, 87.9%, and 89.7%, respectively; positive and negative predictive values were 88.9% and 90.6%, respectively.

PATIENTS AND METHODS

Patients

The study design was prospective and included a total of 68 patients. The patients were divided in 2 groups consecutively included at the Department of Gastrointestinal Surgery, Gentofte University Hospital, Copenhagen, Denmark (between August 2005 and November 2006), and subsequently at the Department of Gastroenterology, University of Medicine and Pharmacy Craiova, Craiova, Romania (between December 2006 and September 2007). The study prospectively included patients with normal pancreas (N = 22), chronic pancreatitis (N = 11), pancreatic adenocarcinoma (N = 32), and pancreatic neuroendocrine tumors (N = 3) (Table 1). A subgroup analysis was also performed for the patients with focal pancreatic masses, including the patients with pancreatic cancer and the patients with chronic pseudotumoral pancreatitis.

Methods

Two types of analyses were performed by assuming a classification of the results as either ''positive'' (malignant pancreatic focal mass) or ''negative'' (pseudotumoral chronic pancreatitis or normal pancreatic tissue). Initially, a conventional receiver operating characteristic (ROC) analysis was done to compute a cutoff for the differential diagnosis, based on the mean hue histogram values of the EUS elastography individual frames (images), which were averaged for each individual patient movie. Analysis of the EUS elastography movies was based on specially dedicated software developed during a previous study.[5] Furthermore, an extended NN analysis was subsequently performed to improve the accuracy of diagnostic testing. This analysis was again based on the hue histogram values averaged during a 10-second EUS elastography movie. All this information was condensed into an input vector with 256 components for each individual patient and was fed into specific NN software.

Because the concrete database size was not very large (68 cases), the 10-fold cross-validation was used. Accordingly, the classification performance was computed 10 times, each time leaving out one of the subsamples from the computation and using that subsample as a test sample for cross-validation, so that each subsample was used 9 times in the learning stage and just once as the test sample, a complete cycle. To assess the robustness of this method, a complete cycle (ie, 10-fold cross-validation computer run) was run 30 times and provided the average performance values, together with the corresponding standard deviations (SDs).

Protocol of examination

The following data were prospectively collected for all the patients: personal data (name, surname, sex, age, examination date, personal numeric code, diagnosis at admission, and clinical history), conventional EUS

TABLE 1. Patient characteristics

	Age (mean [SD])	Sex (male/female)	Diagnosis
Normal pancreas (N = 22)	49.4 ± 15.4	14/8	US, CT, EUS, follow-up
Chronic "pseudotumoral" pancreatitis (N = 11)	55.1 ± 17.0	9/2	US, CT, EUS, follow-up
Pancreatic cancer (N = 35)	62.3 ± 12.9	24/11	US, CT, EUS-FNA, surgery, follow-up

examination with EUS-FNA if needed, EUS elastography results, and the final diagnosis obtained by EUS-FNA cytology and/or surgical pathology. Written informed consent was obtained for all the patients before EUS-FNA and EUS elastography. All the patients received sedoanalgesia with midazolam and/or propofol.

EUS, EUS-FNA, and EUS elastography of the pancreas were performed during the same EUS examination by using a US system with an embedded Sonoelastography module (Hitachi 8500; Hitachi Medical Systems Europe Holding AG, Zug, Switzerland), used in conjunction with a Pentax linear endoscope (EG 3830UT or EG 3870 UTK; Pentax, Hamburg, Germany). All EUS examinations with EUS-FNA were performed by 3 endoscopists (A.S., P.V., H.H.) according to a common protocol. EUS-FNA procedures were performed with a 22-gauge Sonotip 2 (MediGlobe GmbH, Achenmühle, Germany) or a 22-gauge single-use biopsy needles (Olympus Optical Co [Europe], Hamburg, Germany). EUS-FNA was performed with at least 3 passes for each pancreatic mass, with continuous suction, according to a technique described in detail elsewhere.[18,19]

EUS elastography was performed during the EUS examinations, with 2 movies of at least 10 seconds recorded onto the hard disk drive, embedded in the US system, to minimize variability and to increase repeatability of acquisition. A 2-panel image with the usual conventional gray-scale B-mode EUS image on the right side and with the elastography image on the left side was used (Figs. 1 to 3). The examination frequency during EUS elastography was usually set at 7.5 MHz (between 5.0 and 10.0 MHz).

Computer-enhanced dynamic analysis

Each acquired movie was subjected to a computer-enhanced dynamic analysis by using a public domain Java-based image processing tool (ImageJ) developed at the National Institutes of Health, Bethesda, Maryland.[20] To minimize the human bias, all the postprocessing and computer analysis of digital movies was performed within the Information Technology Center, University of Medicine and Pharmacy of Craiova, with all programmers and statisticians were blinded to the clinical and pathologic information. Each EUS elastography movie, of approximately 10 seconds (125 frames), was transformed into numerical form, characterized by a single average hue histogram vector. Each individual value of the vector corresponded to the number of pixels of each color, in other words, to the number of pixels that correspond to each elasticity level, from 1 to 256. The same methodology was previously described in detail.[5]

NN analysis

The NN represents an information processing paradigm that is inspired by the way the human brain processes information.[21-23] The key of this paradigm is the novel architecture of the information processing system, which consists of a large number of highly organized processing elements (artificial neurons), interconnected in a layered parallel structure (the network), and working together to solve specific problems. The procedure used to perform the learning process is typically achieved through progressive adjustments of the weighted interconnections (synaptic weights) to attain a desired design objective.

During the classification process concerning the pancreatic lesion types, we only used the multilayer perceptron (MLP) model with both one hidden layer and two hidden layers with a different number of neurons in each layer and the back-propagation procedure as a training algorithm. To evaluate the classification efficiency, both the training and the testing performance of the network were computed. Before using NN to discriminate between pancreatic lesions we converted the EUS elastography sample movies into a numerical matrix form (aij) and summarized the information into a vector form, by using the formula $a_j = 1/125 \sum_{i-1}^{n} a_{ij}$. Thus, the NN is fed with a vector that represents an average hue histogram, which summarizes the information provided by EUS elastography sample movies. Let us mention that, by taking into account that NN represents a high adaptive machine learning,[23] this particular artificial intelligence technique was generalizable to all pancreatic diseases. The NN calculations were performed by using Statistica Neural Networks v. 4.0 E (Statsoft Inc, Tulsa, Okla).

Final diagnosis

The patients were considered as having a normal pancreas in the absence of any presumable pancreatic pathology or history of acute pancreatitis, as well as normal imaging tests during the initial clinical evaluation (by US, CT, EUS, and clinical follow-up). Based on these imaging

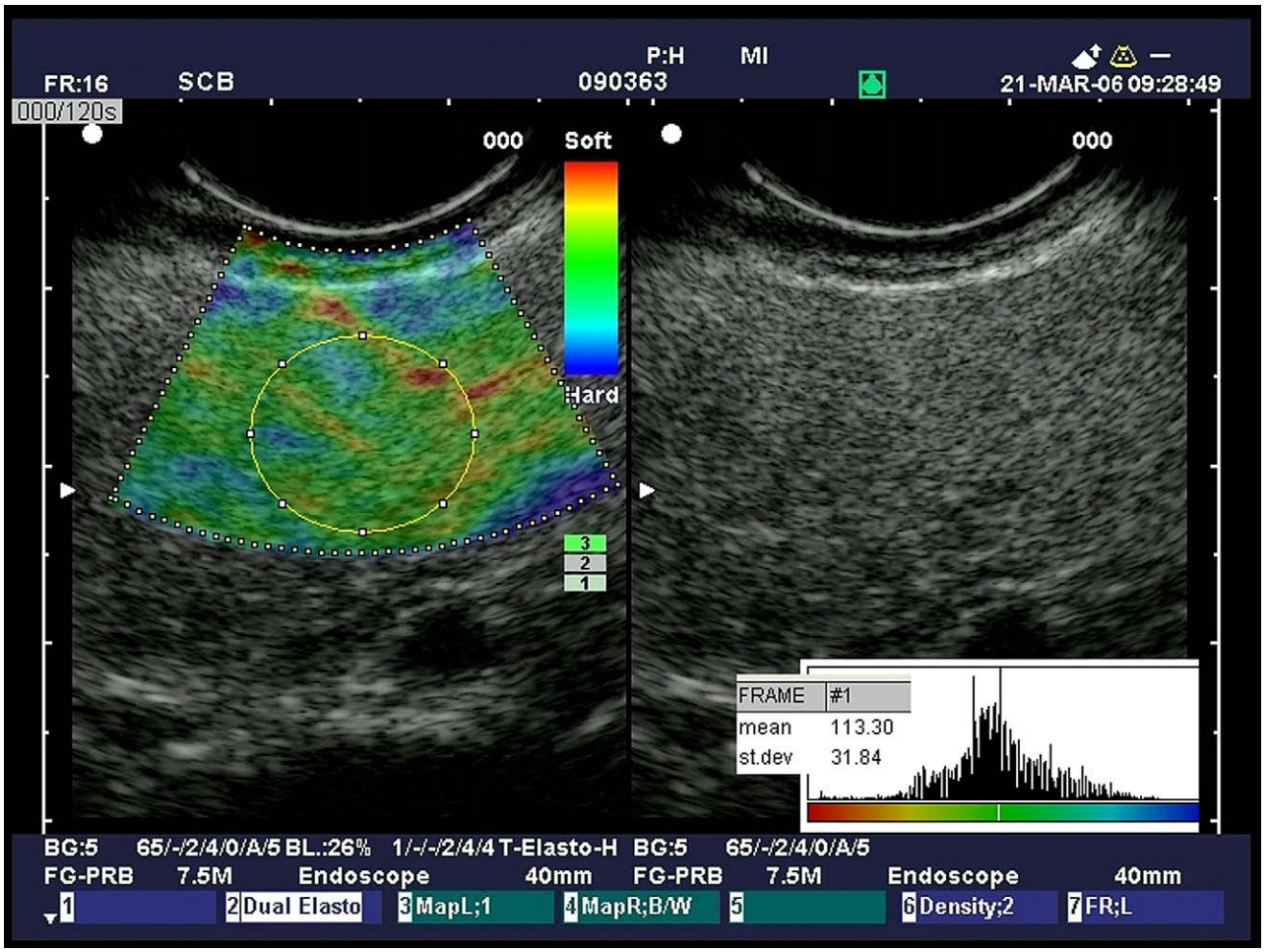

Figure 1. EUS elastography of the normal pancreas, with low mean (SD) values of the hue histogram analysis (113.3 ± 31.8).

methods, the presence of chronic pancreatitis or focal pancreatic masses was excluded in the subgroup of patients with a normal pancreas.

The diagnosis of chronic ''pseudotumoral'' pancreatitis was based on the clinical information (history of alcohol abuse, previous diagnosis of chronic pancreatitis or diabetes mellitus), a combination of imaging methods that showed a mass-like lesion (transabdominal US and CT), as well as clinical follow-up. At least 4 criteria of chronic pancreatitis during conventional US or CT were considered for the positive diagnosis, including the presence of hyperechoic strands and foci, a ''honeycomb'' pattern of the parenchyma, a dilated pancreatic duct, hyperechoic and irregular margins of the pancreatic duct, calcifications, and pseudocysts.[24] The diagnosis of chronic ''pseudotumoral'' pancreatitis was always confirmed by surgery or by a follow-up of at least 6 months to exclude malignancy in the patients who did not have surgery.

A positive cytologic diagnosis was taken as final proof of malignancy of the pancreas mass. The diagnoses obtained by EUS-FNA were further verified either by surgery or during a clinical follow-up of at least 6 months.

Statistical analysis

The comparison of patient subgroups was performed by the 2-sample *t* test (2 independent samples), whereas the corresponding assumptions concerning normality and equality of variances have been previously checked (Kolmogorov-Smirnov and Shapiro-Wilk W normality tests, as well as the Levene's test with F-Fisher statistics). Moreover, the Mann-Whitney *U* test was also used, because, in some instances, it may offer greater power than the *t* test. The one-way analysis of variance method was used to look at all the data simultaneously. All statistical calculations were performed with Statistica for Windows v. 6.0 (Statsoft).

ROC analysis was done to display the range of trade-offs between true-positive and false-positive rates possible with EUS elastography, but also to summarize the performance of each NN model. The sensitivity, specificity, positive predictive values (PPV), negative predictive value (NPV), and accuracy for the differential diagnosis between benign and malignant pancreatic masses were thus calculated for EUS elastography by comparing the results of dynamic analysis (mean hue histogram values of the region

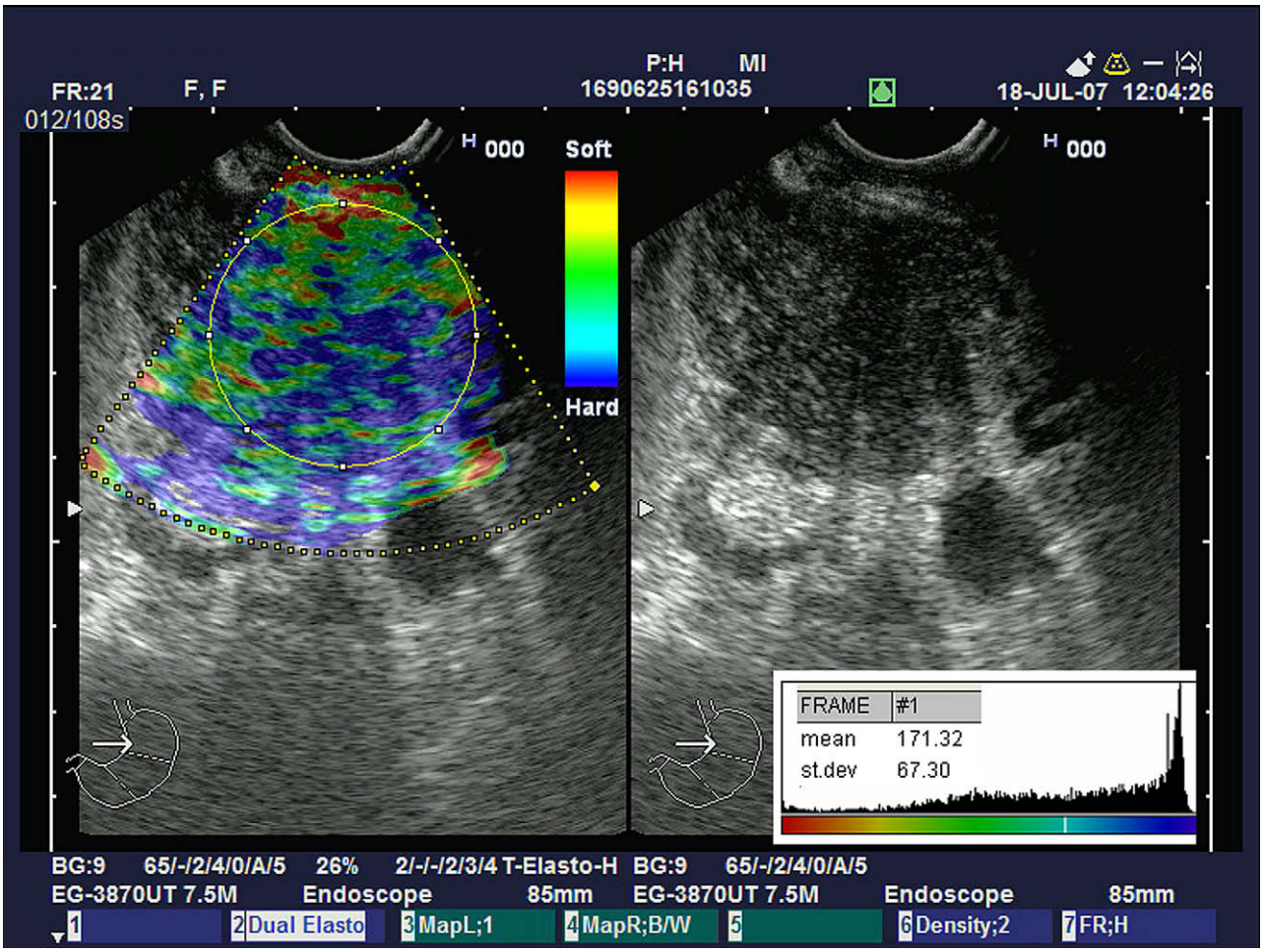

Figure 2. EUS elastography in pseudotumoral chronic pancreatitis, with intermediate mean (SD) values of the hue histogram analysis (171.3 ± 67.3).

of interest averaged during a movie) with the final diagnosis, as a function of the initial ROC analysis cutoff values.

RESULTS

A total of 68 patients (Table 1) were examined by linear EUS with real-time elastography. The EUS elastography movies obtained for each individual patient were averaged, and the distribution of mean hue histogram values is depicted in Figure 4. ROC analysis yielded an area under the curve of 0.932 [95% CI, 0.875-0.988] ($P < .0001$). The results of ROC analysis with a cutoff value of 175 were thus used to differentiate between benign (normal pancreas and chronic pseudotumoral pancreatitis) and malignant (pancreatic cancer and neuroendocrine tumors) cases based on the EUS elastography movies. Quantification of the hues inside the region of interest through histogram analysis of EUS elastography movies helped to obtain a better classification of ''benign'' and ''malignant'' pancreatic lesions, as opposed to a simple ''blue'' versus ''green'' visual categorization used in some of the previous studies. Consequently, the sensitivity, specificity, and accuracy of the hue histogram classification for the differential diagnosis of benign and malignant pancreatic lesions were 91.4%, 87.9%, and 89.7%, respectively. The PPV and NPV were 88.9% and 90.6%, respectively.

A subgroup analysis was further performed by excluding the patients with neuroendocrine tumors and the patients with normal pancreas. These cases are usually excluded during conventional EUS or EUS-FNA cytology diagnosis. Consequently, the main diagnostic problem is represented by the differential diagnosis between pancreatic cancer and chronic pancreatitis. The distribution of mean hue histogram values for these patient subgroups is shown in Figure 5. ROC analysis yielded an area under the curve of 0.847 [95% CI, 0.721-0.972] ($P < .0001$). Consequently, the sensitivity, specificity, and overall accuracy of the hue histogram classification for the differential diagnosis of focal pancreatic masses were 93.8%, 63.6%, and 86.1%, respectively. The PPV and NPV were 88.2% and 77.8%, respectively. If the cutoff were raised to 190, then the corresponding values of the sensitivity and specificity would be 56.3% and 90.9%, respectively, and the PPV and NPV would be 94.7% and 41.7%, respectively.

To increase the accuracy of diagnosis testing, we further applied both a 3-layer MLP NN and a fourth-layer MLP NN

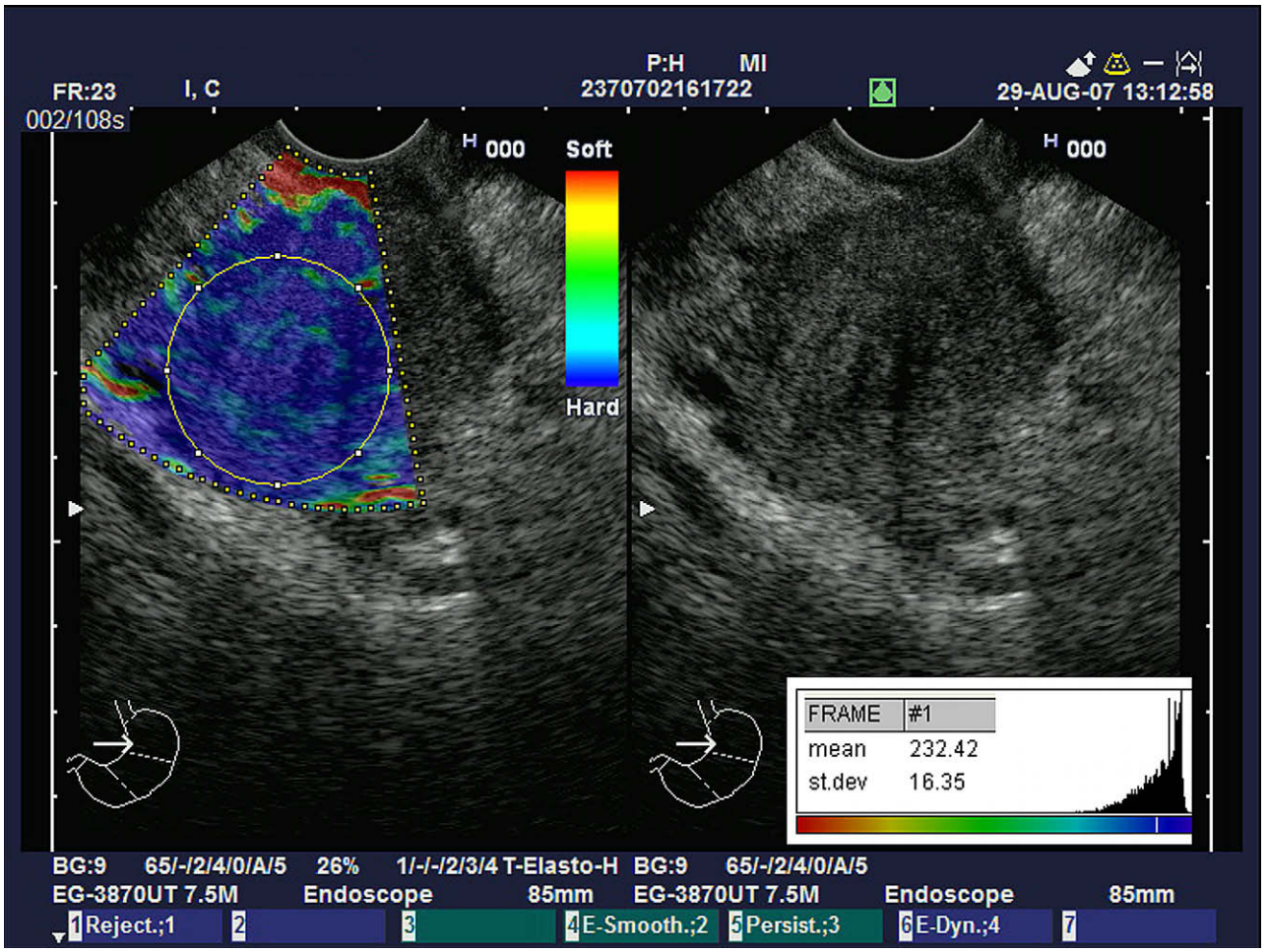

Figure 3. EUS elastography in pancreatic adenocarcinoma, with high mean (SD) values of the hue histogram analysis (232.4 ± 16.4).

with different numbers of computation units. The main results obtained by running a complete performance testing cycle 30 times are presented in Table 2, which depicts the average MLP performance. This illustrates the way NNs learn to discriminate between benign and malignant lesions by using digitalized EUS elastography sample movies. A very good testing performance of 95% on average was obtained, together with a high training performance that equaled 97% on average. Because the 2 measures are close enough (approximately 2%), this indicates a low over-learning level, which is a balanced training and/or testing process. Moreover, the corresponding SDs, which equaled 3.6% (for testing performance) and 6.3% (for training performance), indicate a high stability of the model. The optimum number of hidden units (neurons) in the network equals 17, with a relative high SD of 14. Thus, it is possible to have a relatively simple network structure, nevertheless, a very fast NN, with a very good performance. The area under the ROC curve (0.957) confirmed the high classification performance.

Both NNs models were also used for subgroup analysis, including only the patients with focal pancreatic lesions (pancreatic cancer and chronic pseudotumoral pancreatitis). The main results are presented in Table 2, and show a good testing performance of 90% on average, together with a high training performance of 97% on average; the corresponding SDs were 3.2% and 12.3%, respectively, and indicate a high stability of the model, whereas the area under the ROC curve (0.965) indicates a very good classification performance.

DISCUSSION

EUS elastography represents a recently added tool used to obtain information about the relative hardness or softness of the examined lesions compared with the surrounding tissues.[25,26] Because of the inherent problems related to the qualitative assessment of EUS elastography movies and images, we developed special software that allows the quantification of the color information in a defined region of interest. Previous studies already emphasized that it is difficult to assume that a specific level of hardness would be equivalent with the diagnosis of

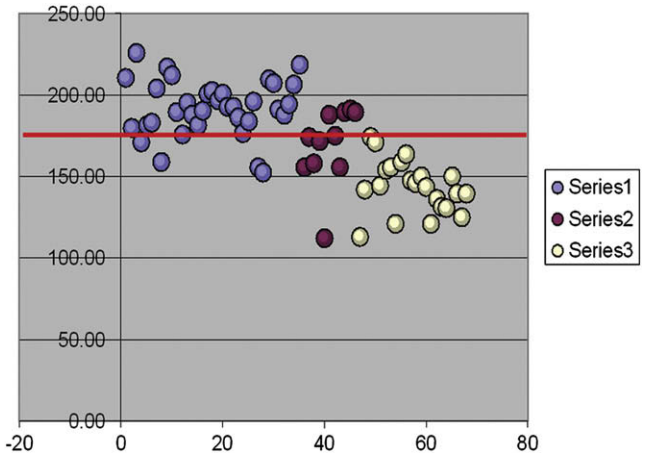

Figure 4. Distribution of the mean hue histogram values of the averaged EUS elastography movies for the patients with pancreatic cancer and neuroendocrine tumors (*series 1*), chronic pancreatitis (*series 2*), and normal pancreas (*series 3*), in relation with the computed cutoff of 175.

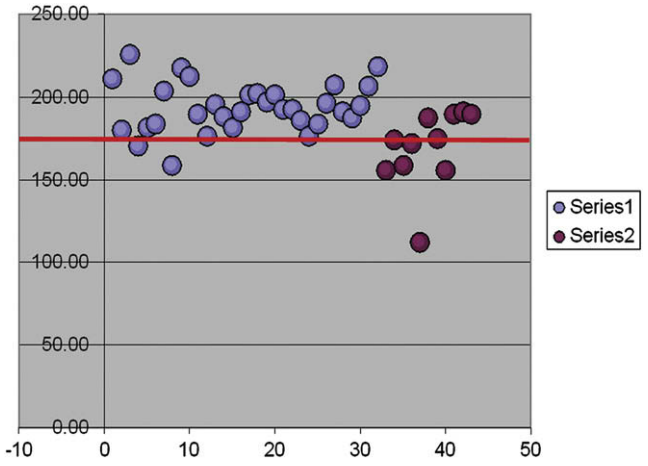

Figure 5. Distribution of the mean hue histogram values of the averaged EUS elastography movies for the patients with pancreatic cancer (*series 1*) and chronic pseudotumoral pancreatitis (*series 2*), in relation with the computed cutoff of 175.

TABLE 2. NN performance for differentiating benign and malignant pancreatic lesions, and chronic "pseudotumoral" pancreatitis and pancreatic cancer

	Average ± SD hidden units	Average ± SD training performance (%)	Average ± SD testing performance (%)	ROC curve
Benign vs malignant pancreatic lesions (N = 68 cases)	17 ± 14	97.29 ± 3.64	95.31 ± 6.25	0.957
Chronic "pseudotumoral" pancreatitis vs pancreatic cancer (N = 43 cases)	24 ± 11	97.39 ± 3.20	90.01 ± 12.31	0.965

malignancy, because some of the benign lesions are very hard (focal chronic pancreatitis), whereas some of the malignant tumors are very soft (eg, mucinous or cystic adenocarcinomas, tumors with extensive necrosis).[25] A recent study also concluded that it is not possible to differentiate pseudotumoral chronic pancreatitis from malignant tumors, especially because of similarities in the mechanical structure of the examined lesions.[16] However, the investigators used a qualitative analysis of the EUS images, which included the elastographic patterns: predominant color, distribution of colors, and constancy of pattern. We previously stated that this kind of analysis is accompanied by a strong bias, as well as possible perception errors, because of the incomplete characterization of all color hues.[5] Moreover, a correlation between the EUS elastography results and histology is still highly desirable, either to complement the information provided by conventional EUS imaging or for the real-time guidance of biopsies in stiffer areas of the lesions, with a possible increase in accuracy for EUS-FNA in the setting of chronic pancreatitis.[2,3]

EUS has a high sensitivity for the detection of pancreatic masses, but it has a limited ability to differentiate between inflammatory masses and malignant masses.[27] The addition of EUS-FNA is useful, but the accuracy for the detection of malignancy is variable, between 80% and 95%.[28,29] This is especially evident in the context of previous chronic pancreatitis, in which the sensitivity of EUS-FNA usually drops to less than 75%, and as low as 54% in some studies.[30,31] The present study proved that analysis of the EUS elastography movies allows the differentiation between benign and malignant pancreatic lesions with a good sensitivity, specificity. and accuracy. One limitation of the study was the inclusion of normal pancreas cases to describe normal EUS elastography aspects. Indeed, EUS has a high NPV, up to 100%, so the absence of a focal mass reliably excludes pancreatic carcinoma.[32] It is therefore not necessary to enhance conventional EUS examinations by EUS elastography to exclude pancreatic carcinoma. However, we have used normal pancreas cases to test the feasibility and reproducibility of EUS elastography in normal patients, and the computer analysis was performed blinded by the information technology specialists, independent of the gray-scale information and medical expertise. All the normal pancreas cases yielded average values of the mean hue histogram analysis less than the computed cutoff of 175, which indicated that higher values are always pathologic.

To completely exclude any bias induced, for example, by a subjective choice of the cutoff, we further used a neural computing approach. Consequently, the diagnostic process can be fully automated and devoid of any observer bias, through the use of raw data only, without a previous data preprocessing that implied both image filtration and exploratory data analysis techniques. The results were good enough, proving the robustness and reliability of this machine learning approach. We only used the MLP, but other intelligent systems might be used in future studies, with possible better results: evolutionary algorithms, support vector machines, classification and decision trees, etc.

We performed a subgroup analysis of the patients with focal pancreatic masses, after exclusion of normal cases, as well as exclusion of cases with neuroendocrine tumors that are usually diagnosed by EUS-FNA. As expected from the physical characteristics of pancreatic adenocarcinoma and pseudotumoral chronic pancreatitis, the results were not so impressive, in agreement with a previous study.[16] By using a dynamic hue histogram analysis, it was possible to differentiate benign from malignant focal pancreatic masses with a fair sensitivity (93.8%) but very low specificity (63.6%), and with an overall accuracy of only 86.1%. However, we do consider that this information would have a high clinical impact, especially in the cases in which EUS-FNA is negative. Because of the low NPV of EUS-FNA, a negative biopsy cannot reliably exclude pancreatic cancer. The high PPV (88.2% for a cutoff of 175, 94.7% for a cutoff of 190, and 100% for a cutoff of 191) of the mean hue histogram values averaged through EUS-elastography movies would certainly imply a high risk of malignancy and influence the clinical decision making accordingly, even if EUS-FNA were negative.

By using the MLP model, we obtained a good testing performance (90%), used for the differential diagnosis of focal pancreatic masses. Moreover, the area under the ROC curve was 0.965 ($P < .0001$), which indicated excellent values of sensitivity, specificity, and accuracy of this imaging approach for the differential diagnosis of pancreatic cancer and pseudotumoral chronic pancreatitis. This is essential in borderline cases, in which the value of EUS-FNA is limited by the low sensitivity.[28-30] Because EUS-FNA in patients with focal pancreatic lesions has a low NPV, the utility of a neural computing approach of EUS elastography recordings cannot be underestimated.

When working with medical imaging data, one of the major problems is caused by the high dimension of the data samples (an issue known as the ''curse of dimensionality''). The solution to this problem is represented by data preprocessing with techniques of dimensionality reduction, such as principal components analysis, singular value decomposition,[33] and dynamic nonlinear wrapping.[34,35] In this study, the MLP input consisted only of raw data. Because NNs are noise, redundancy, and error tolerant, the results, obtained without any preprocessing analysis, confirmed this particular ability. However, future studies will certainly need a previous analysis to reduce dimensionality by selecting the most relevant features and thus to increase the computation speed.

As previously stated, we strongly suggest that EUS elastography imaging offers complementary information added to conventional EUS imaging with minimal prolongation of the examination time, minimum costs, and no added morbidity or mortality. The currently developed methodology, based on artificial NN processing of the EUS elastography digitalized movies, enables exploration and analysis by automatic means of large quantities of data to obtain an optimal prediction of the type of pancreatic lesion. The essential finding of our study was the improved testing performance of the NN approach compared with a simple ROC analysis when using mean hue histogram values. Future multicentric, randomized studies with adequate power will have to establish the clinical impact of machine-learning approaches for the differential diagnosis of focal pancreatic masses. Improvements of the software used and quantification of the EUS elastography information might also add to the quality of the results.

DISCLOSURES

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