Esophageal Scintigraphy of Systemic Sclerosis

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Esophageal involvement is common in systemic sclerosis, and esophageal scintigraphy can be used to detect and follow esophageal dysfunction. This study assesses the value of visual and quantitative analysis of esophageal scintigraphy performed as a multiple swallow test in normals and patients with systemic sclerosis. **Methods:** Forty patients with systemic sclerosis and 40 sex- and age-matched healthy subjects (controls) were studied. A multiple swallow technique was used and both quantitative and qualitative analyses were performed. Visual analysis of condensed images was performed independently by two physicians. Each swallow was assigned a score on a scale from 1 to 4. In the quantitative analysis, time-activity curves based on the mean condensed images were used to calculate the following 3 parameters: residual activity 12 or 25 sec after the beginning of the swallow, measured with or without baseline correction, respectively, and time from onset of swallow to 50% of peak activity. **Results:** Both visual and quantitative analysis showed a highly significant (p < 0.001) difference between the patient group and the control group. Visual analysis was best reflected by the residual activity 25 sec after the beginning of the swallow without correction for background. Receiver operating characteristic curves were used to study the ability to separate the two groups using visual or quantitative analysis. A high rate of positive tests in the patient group was achieved only at the cost of a relatively high rate of positive tests in the control group. **Conclusion:** Our results indicate high variability in esophageal motility in controls. This variability impairs the possibilities of developing a screening test to identify asymptomatic patients early in the disease course.

Key Words: esophageal transit scintigraphy; systemic sclerosis; technetium-99m-sulfur colloid

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Esophageal transit scintigraphy offers the most accurate assessment of the actual progression of a bolus of food through the esophagus. The method is noninvasive, entails a low radiation dose and can be evaluated both qualitatively and quantitatively. A high correlation has been shown between esophageal scintigraphy and manometry, which is generally considered the gold standard for diagnosing esophageal motor dysfunction (*1*). Several studies

describing scintigraphic techniques to monitor swallowing have been presented since the first report by Kazem in 1972 (*2*). The test, however, has been performed in many different ways and a well-evaluated standard technique is lacking. The patient, for example, could be examined in a sitting, supine or prone position and single or multiple swallows of liquid, semi-solid or solid boluses could be used. Different methods of quantitative analysis have also been presented.

Several scintigraphic studies (*3–6*) have shown substantial intrasubject variation between repetitive swallows, both for patients and normal subjects. Richter et al. (*7*) studied esophageal manometry in healthy volunteers and found that "abnormal" patterns were common in normal subjects. The analysis of multiple swallows is routine in manometry. Tatsch et al. (*5*) developed a scintigraphic multiple swallow test to accurately assess a subject's swallowing ability. Recently, the same group presented a study in which their scintigraphic method was performed simultaneously with esophageal manometry (*8*). Their analysis of the relations between the methods showed that normal and various abnormal swallows presented analogous findings in both modalities.

According to Tatsch et al. (*5*), the multiple swallow test was adopted with a few minor alterations at the Department of Clinical Physiology in Lund in late 1991. Our experience with quantitative analysis of the scintigram, the esophageal emptying rate, revealed some problems. High emptying rates (considered as normal) were calculated from swallows which were clearly abnormal based on visual analysis of the condensed images. The reason for this could be a problem of background correction. An exploration of alternative treatments of this problem was proposed in an editorial in *JNM* (*9*), since residual activity represents not just simple background but a residual intraesophageal volume to which the new bolus is added. Furthermore, the normal limit of 80% for the esophageal emptying rate established by Tatsch et al. was based on the results of 15 patients without esophageal abnormalities. The size and composition of this control group and the method of baseline correction inspired further exploration of ways to improve an otherwise excellent method.

Esophageal dysfunction is common in systemic sclerosis (*10*). Diagnostic methods that can identify asymptomatic patients early in the disease course and monitor disease progression would be clinically useful. Such methods must

be sensitive and quantitative. Esophageal scintigraphy has been proposed as the method of choice. This study assesses the value of visual and quantitative analysis of esophageal scintigraphy performed as a multiple swallow test in healthy subjects and patients with systemic sclerosis.

MATERIALS AND METHODS

Study Population

Esophageal function was studied in 40 consecutive patients who were referred for diagnostic investigation because of suspected systemic sclerosis (n = 25) and patients with previously diagnosed systemic sclerosis (n = 15). All patients had esophageal scintigraphy at this institution. A total of 32 patients fulfilled the criteria of the American College of Rheumatology (ACR, formerly the American Rheumatism Association) for systemic sclerosis (11). Twenty-five of the patients had skin thickening restricted to the extremities and face (limited cutaneous systemic sclerosis) and seven had skin sclerosis also on the trunk (diffuse cutaneous systemic sclerosis). Four patients had sclerodactyly or puffy fingers and Raynaud's phenomenon but did not fulfill the ACR criteria for systemic sclerosis, two had overlap syndromes, one had mixed connective tissue disease and one had sclerodermatomyositis. The median disease duration was 5 yr (range 0.5–20 yr) for the 25 patients with limited cutaneous systemic sclerosis and 5 yr (range 0.5–18 yr) for the 7 patients with diffuse cutaneous systemic sclerosis.

A group of 40 healthy subjects without any history of esophageal disease or gastroesophageal reflux served as the control group, which was matched for sex and age to the patient group. Each group contained 29 women and 11 men, aged 31–82 yr, median age 49 yr for the patient and 48.5 yr (range 35–76 yr) for the control group. The study was approved by the local ethical committee.

Esophageal Scintigraphy

The subjects were examined in the prone position after an overnight fast. All subjects had a triangular pillow under the abdomen to facilitate the gamma camera position posterior and slightly left of center position. We used a gamma camera connected to a computer. The field of view covered an area including the throat and upper abdomen. For the esophageal transit studies, the subjects ingested a semi-solid infant food purée. The purée (90 g) was mixed with 40 MBq ^{99m}Tc-sulfur colloid and administrated in portions of 10 ml per swallow, i.e. approximately 4 MBq ^{99m}Tc-sulfur colloid for each bolus. An inactive test bolus (10 ml purée) was given to the subjects immediately prior to the examination, as a practice session. During dynamic data acquisition (400 frames; 0.5 sec/frame; 64 × 64 matrix), six radiolabeled boluses were offered to the subjects. The subjects were asked to ingest the bolus by a single deglutition and to avoid swallowing for the next 30 sec until the next bolus was offered.

Study Design

Data from the 80 subjects were evaluated both qualitatively and quantitatively. The original dynamic swallow sequences were first compressed by the condensed image technique, as described by Tatsch et al. (5). This technique can be thought of as a way of eliminating one spatial dimension, which does not carry any information (the transesophageal direction), from each frame of a dynamic sequence. The esophagus is delineated by an ROI, from which data are projected by summation in the transesophageal

direction in each frame. The projected data of the whole sequence display the swallowing event in an image having one spatial (mouth-stomach) and one temporal dimension. Minor differences from the implementation by Tatsch et al. (5) were: 0.5 sec frames instead of 0.8 sec, a 64- rather than 32-column matrix for each condensed image; standardization was made of each swallow to start in the seventh column rather than the sixth; a 3 × 3 smoothing filter was applied to the condensed images before calculating the time-activity curves rather than smoothing the curves themselves. A typical study overview is shown in Figure 1. The condensed images of the six swallows were used to calculate a mean condensed image for each subject.

Each of the six swallows from the 80 subjects were scored based on visual analysis of the condensed images. The images were scored independently by two physicians, who were quite familiar with the method and had no knowledge of which subjects were controls and which were patients. Each swallow was assigned a single digit on a scale from 1 to 4: 1 = normal swallow characterized by rapid transfer of the bolus through the esophagus without any significant fragmentation; 2 = diffuse fragmentation of a minor part of the bolus or a small but distinct part of the bolus with slower transfer through the esophagus; 3 = similar to 2 but the abnormal portion of the bolus is greater; and 4 = the main part of the bolus has slow transfer through the esophagus (Fig. 2).

The time-activity curves of condensed images were used to calculate the following three parameters (Fig. 3):

I. Residual activity 12 sec after the beginning of the swallow with the baseline correction of Tatsch et al. (5).
II. Residual activity 25 sec after the beginning of the swallow without baseline correction.
III. Time from onset of swallow until esophageal activity fell to 50% of the peak activity.

The third parameter is closely analogous to the t_3 parameter used by Åkesson et al. (10).

The parameters were calculated using mean condensed images rather than taking the mean or median of the parameters obtained from the six swallows for each individual. This choice was based on the observation that some features, seen to produce outlier values for individual swallows, would, by the suppression in the mean image, only marginally affect this parameter value. Visual interpretation was based on the mean of twelve scores of six swallows for each individual, allowing the two observers to make a subjective evaluation of the overall status of six swallows. As alternatives, parameters based on both the mean and the median of six swallows and the visual index based on the median score, rather than the mean, were investigated. None of these approaches, however, resulted in better delineation between controls and patients than the use of mean condensed images for the parameters and the mean score for the visual index.

Manometry, often considered the gold standard for esophageal dysfunction, was not performed in this study. Consequently, true estimates of sensitivity and specificity for esophageal dysfunction could not be presented. The ability to differentiate the control group from the patient group was studied. The performance of both visual and the parametric analyses was presented in receiver operating characteristic (ROC) curves. For each of the four curves, the area under that part of the curve corresponding to false-positive rates between 0 and 20% was computed. To test whether the four methods differed in that respect, an ANOVA-like test was performed in which the variances of the areas were estimated by the bootstrap technique (12).
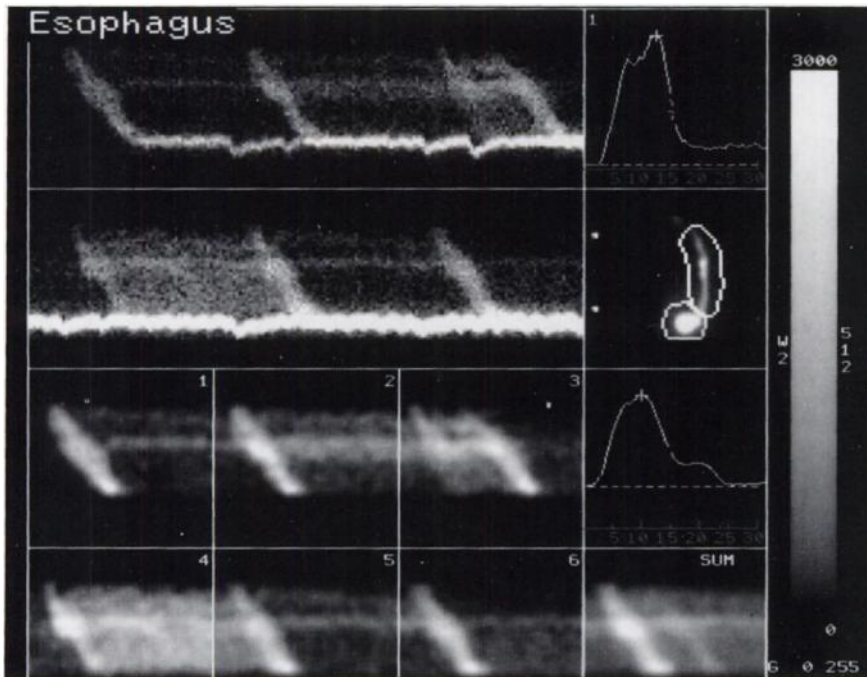
FIGURE 1. Condensed image shows a swallow sequence of 200 sec (upper left-most panel continues in panel below); a summed planar image with ROIs delineating the esophagus and the stomach; six condensed images standardized to the starting point and normalized with stomach data removed (six lower left panels); a summed and normalized condensed image (lower right); and two time-activity curves, one for the first swallow (upper right) and one for the summed condensed image (lower right).

RESULTS

Each observer independently and blindly scored 480 (6 × 80) swallows, and in 77.9% of these, an identical score on the 1–4 scale was given. In 21.7% of the swallows, the score differed by 1 unit and in 0.4% by 2 units. There was a minute bias between the two observers: one observer scoring on average 0.08 and 0.12 units higher than the other for controls and patients, respectively. In view of this concordance, the twelve scores for each subject were pooled, resulting in a single value denoted visual index.

Both the visual index and the quantitative parameters I–III showed a highly significant difference between the patient and control groups (p < 0.001). The relation between the visual index and the parameters I–III are shown in Figure 4. The visual index, although not a priori superior to the quantitative parameters, does stem from more information than the parameters, which are based on time-activity curves only. Parameter II, the residual activity after 25 sec without baseline correction, reflects the visual index best. The overlap between controls and patients was considerable for the visual index as well as the parameters I, II and III.

ROC curves for the entire study population and for the subgroup of patients with disease duration greater than 3 yr are shown in Figure 5. The curves demonstrate the relation between true-positive and false-positive rates. For the 0%–20% false-positive rate, which often is the most clinically interesting interval, parameters II or III performed best. Although not statistically significant, this ranking persisted irrespective of whether the evaluation was performed using mean condensed images and the mean visual index or if other approaches (e.g., median values) were used. A high
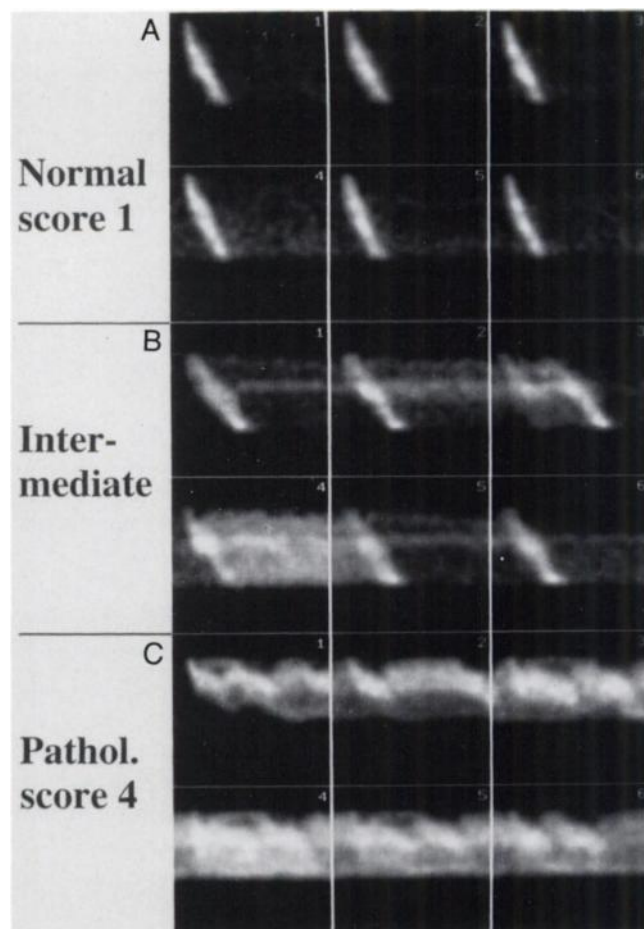

FIGURE 2. Condensed images scored by the two observers. (A) Six swallows to which both observers assigned a score of 1 (normal), (B) six intermediate swallows and (C) six swallows to which both observers scored as 4 (pathological).
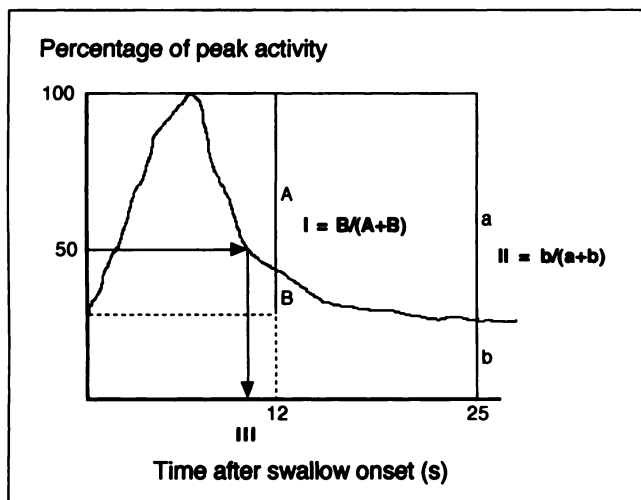
FIGURE 3. Schematic diagram illustrating the definitions of parameters I, II and III. The parameters were calculated from the mean condensed image.

true-positive rate can be achieved only at the cost of a high false-positive rate. A clinically acceptable false-positive rate would at most probably be 20%, for which the true-positive rate is merely 50%–60% for the entire study population and 70%–80% in the subgroup of patients with disease of more than 3 yr duration.

DISCUSSION

Detection of esophageal involvement in patients with systemic sclerosis is of great clinical interest. Esophageal scintigraphy is easy to perform and demonstrates the progression of a bolus of food through the esophagus. The performance of the method that can delineate controls from patients with systemic sclerosis has been evaluated in several studies. Davidsson et al. (13) performed esophageal scintigraphy in a group of patients with diffuse systemic sclerosis and a control group. Abnormalities were present in 87% of the patients and in none of the controls. Carette et al. (14) found abnormal esophageal scintigrams in 91% of patients with systemic sclerosis, but in our present study, 21% of the controls were classified as abnormal. The frequency of abnormal findings in the patient groups is similar in these studies, but the results in the control groups indicate a great difference in diagnostic performance of esophageal scintigraphy. The ROC curves in Figures 4 and 5 illustrate the dramatic change in the true-positive rate in the 0%–25% interval for false-positive rates, a common finding for diagnostic methods. Consequently, it is important to consider both false-positive and true-positive rates when evaluating a diagnostic test. In this study, there was a great overlap between the control and patient groups, both in the qualitative and quantitative analyses. The results are similar to those of Carette et al. (i.e., a high true-positive rate is combined with a relatively high false-positive rate).

Differences in the materials studied partly explain the

variances in the results. Patients without esophageal involvement or patients at the mild end of a spectrum of severity are likely to have a negative test. The distribution between mild cases and patients with severe dysfunction will have great influence on the results. In this study, the results for the total patient group compared to the results for the subgroup of patients with disease duration greater than 3 yr illustrates the importance of the composition of the study group.

If the esophageal dysfunction occurs intermittently, it will be difficult to detect. Another result of intermittent dysfunction could be a false indication of differences in diagnostic performance between varying scintigraphic techniques or between scintigraphy and other diagnostic methods. An elegant way to circumvent this problem was presented by Tatsch et al. (8). They performed esophageal scintigraphy and manometry simultaneously. This approach, however, is not applicable in a study such as this, in which controls and patients were studied using the same method. A standard approach for situations with great variation in the signal, such as intermittent esophageal dysfunction, is to examine a number of events. Therefore, the multiple swallow test presented by Tatsch et al. (5) is a theoretically sound method.

A visual index score of 3 or greater was found in 4 of the 40 normal subjects. Emptying rates less than 80% (corresponding to residual activity greater than 20%), which should be considered pathological, according to Tatsch (5,8), was found in 20 of the controls. Abnormal swallows, however, in normal subjects have been reported. In a study by Sand et al. (15), a good bolus without fragmentation was found in less than half the group of control subjects (24/49). Bolus fragmentation resulted in residual esophageal activity. Jörgensen et al. (6) also found high variation in residual activity in healthy subjects. In a group of 49 controls, they found a mean residual activity of 10.8% and a wide 95% range of 2%–45%.

Condensed images facilitate qualitative assessment of intraesophageal events. Tatsch et al. demonstrated that a pattern in condensed images specifically reflects the events in the simultaneous manometric recordings. They concluded that major findings in manometry are detectable with condensed images. Analysis of the condensed images, however, i.e., the visual index, was not superior to quantitative parameters for delineating patients and controls. Visual analysis could give other information, i.e. reflux, which is not considered in this study. This is a good example of how the combination of qualitative and quantitative analyses of scintigraphic data improves the quality of the examination.

CONCLUSION

Our results indicate high variability in esophageal motility in control subjects. This variability impairs the possibility of developing a screening test to identify asymptomatic patients early in the disease course. Quantitative
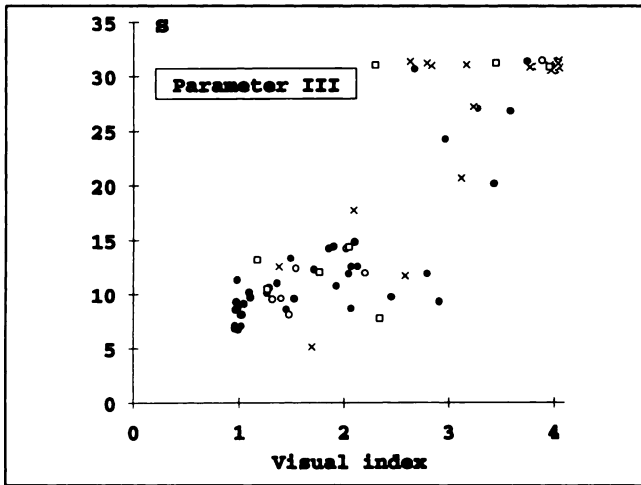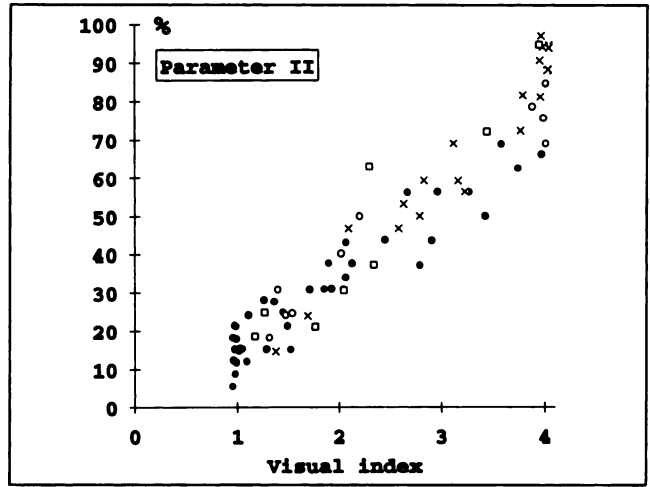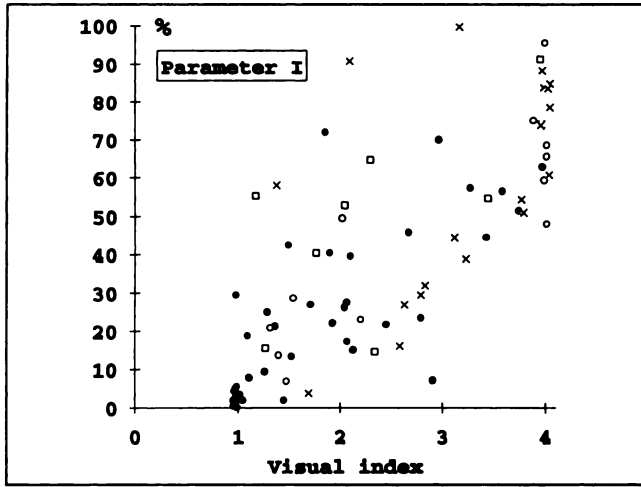
FIGURE 4. Relation between the visual index and quantitative parameters I, II and III. (●) Normal subjects; patients with a disease duration >3 yr (X); (O) patients with disease duration ≤3 yr; (–) patients not fulfilling AHA criteria for systemic sclerosis.
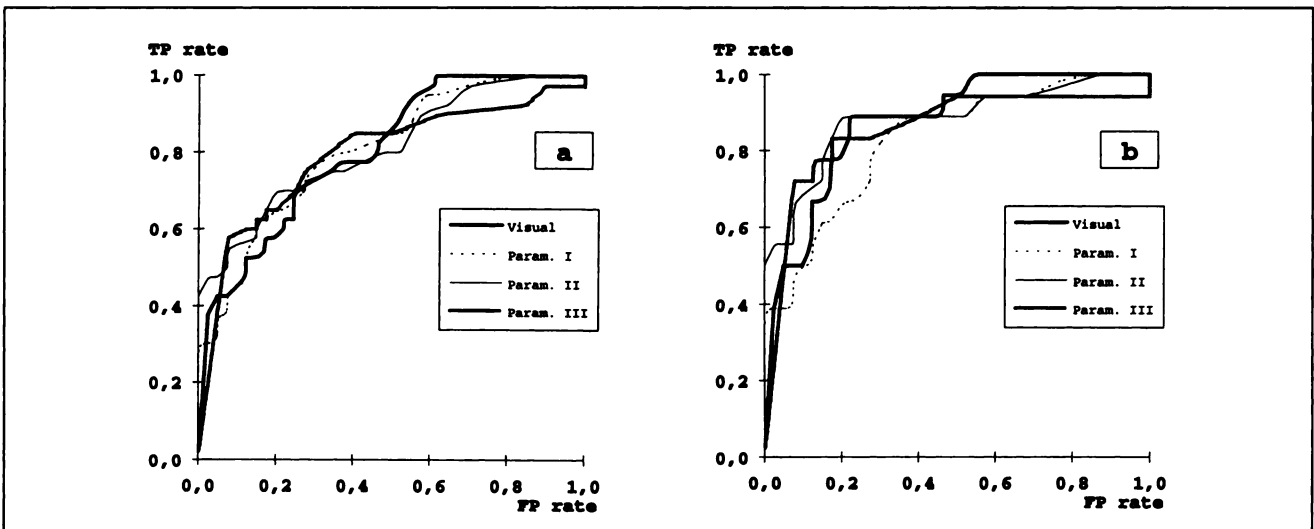

FIGURE 5. ROC curves for the visual index and parameters I, II and III based on (A) the entire study population and (B) the controls and subgroup of patients with disease duration greater than 3 yr.

analysis of mean condensed images reflects the visual impression of a multiple swallow test. A parameter describing the progression of a bolus through the esophagus would be clinically useful to monitor the development of esophageal disease.

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FIRST IMPRESSIONS

A ^{99m}Tc-pyrophosphate study was ordered to evaluate a recently transplanted kidney for acute tubular nephrocalcinosis. What was confirmed?
For acquisition information, turn to page 1653.