DIAGNOSTIC NUCLEAR MEDICINE

Critical Evaluation of Lung Scintigraphy in Cystic Fibrosis: Study of 113 Patients

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A long-term study has been performed on 285 lung perfusion scintigrams obtained from 113 patients with cystic fibrosis. Tranverse and longitudinal comparisons with clinical and radiological scores, as well as retrospective analysis of the deceased patients, were the methods used in order to evaluate the importance of the scintigraphic images. It appears that lung scintigraphy is the best index of the regional lung impairment, and contributes, as does a chest radiograph, to the early detection of lung lesions, the two methods being complementary. The survival rate of CF patients reached 0.80 at 9 yr when initial scintigraphy was normal or only moderately impaired, but fell to 0.18 when severe lesions were seen on the first scintigrams.

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In 1973 we presented a preliminary report on lung perfusion scintigraphy in 73 patients suffering from cystic fibrosis (*1*). A significant correlation existed between the severity of the scintigraphic lesions and the Kulczycki–Shwachman score, as long as comparisons were made during a remission phase of the disease. It was emphasized by repeating the studies in the same patients, that the lesions were permanent, with remarkable reproducibility in their topography. In contrast, acute phase images showed considerable fluctuations within short time intervals.

Several long-term studies of cystic fibrosis have shown that the survival rate of the patients has improved dramatically during the past decades. This increased survival has been ascribed mainly to early and reliable diagnosis and treatment of the progressive lung disease (*2–5*). The present study consists of a long-term follow-up with scintigraphic images in order to evaluate more accurately the contribution of the technique to the precise description of lung changes, to the early detection of pulmonary involvement, and to the estimation of the prognosis in patients suffering from cystic fibrosis.

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MATERIAL AND METHODS

From 1969 to 1977, 285 lung perfusion scintigrams were performed on 111 patients (61 boys and 50 girls) ages from 2 mo to 20 yr. The diagnosis of their disease was established on the basis of the sweat test with the iontophoresis pilocarpine method. All the patients regularly attend the specialized clinic for cystic fibrosis and are on treatment, including pancreatic enzymes, inhalation therapy, postural drainage, mist-tent therapy, and antibiotics.

Scintigrams. For each patient, one to six perfusion scintigrams were available during a follow-up period of 1–9 yr. The scintigrams were performed after i.v. injection of 50 μCi/kg body weight of Tc-99m macroaggregated albumin or Tc-99m-labeled microspheres.

A scintillation camera was used, equipped with a parallel-hole or diverging collimator according to the size of the chest. Since 1976, a larger camera with a parallel-hole, high-sensitivity collimator has been used. Anterior, posterior, and, for the older children, lateral views were available for each test. Posterior oblique views have been systematically added since 1977.

The estimated absorbed radiation dose was less than 1 rad to the lung and less than 30 mrads to the gonads (*6*). For the purpose of comparison with other clinical

parameters, a scintigraphic score was established. Each lung was divided into three parts, and for each part a score from 0–2 was attributed, depending on the severity of the regional impairment (0 = no lesion, 1 = moderate lesion, 2 = severe lesion). Thus, a normal perfusion pattern was associated with a zero score (100% of normal) whereas the maximum score of 12 represented the highest grade of disease (0% of normal). All the scintigrams were independently scored by two examiners.

Clinical score. The clinical score was expressed as a percentage of normal, taking into account the general activity, the physical examination, and the nutrition, using the criteria established by Kulczycki and Shwachman (*2*).

Radiological score. In order to clarify the comparisons, chest radiographs have been separately scored, either by Schwachman criteria (*2*) or, since 1976, on the classification of Chrispin and Norman (*7*). Here again the results were expressed as a percentage of normal.

Types of comparisons. Two types of comparison were made between lung perfusion scintigraphy on the one hand and clinical or radiological score on the other.

1. Transverse comparisons between the two types of examination were made at the same stages of the evolution. For each patient one to several transverse comparisons were available. The clinical, radiological, and scintigraphic data were interpreted as follows: normal pattern: >80%; moderate impairment: 60–80%; severe impairment: <60%.

2. Longitudinal comparisons took into account the entire profile of evolution of each considered parameter (no change or less than 15% change on one hand, 15% change or more on the other). Thus, for each patient, only one comparison between two parameters was available during the same time interval.

Survival curves. These were calculated using the Kaplan-Meier product limit estimate (*8*). Comparisons of the survival curves among three groups of patients, classified according to the intensity of the lesions on the initial scintigrams, were made using the log-rank test as described by Peto et al. (*9*).

TABLE 1. TRANSVERSE COMPARISON BETWEEN CLINICAL AND SCINTIGRAPHIC SCORES

Scintigraphic evaluation	Clinical evaluation			
	Normal	Moderate lesions	Severe lesions	Total
Normal	85	22	5	112
Moderate lesions	45	15	5	65
Severe lesions	19	38	26	83
Total	149	75	36	260

RESULTS

Scintigraphic scoring method. A difference of more than one unit in the score established by the two examiners was found in less than 5% of the cases.

Comparison between clinical and scintigraphic scores. *Transverse comparisons (260 pairs of data).* Analysis of the results (Table 1) showed agreement in 126 out of 260 comparisons (49%). In 64 cases (25%) significant lung defects were observed by scintigraphy whereas the clinical score remained normal. In 27 cases, a normal scan was associated with an impaired clinical score. A more detailed review of these cases revealed obvious clinical lung alterations in only 14 cases (5%).

Longitudinal comparisons. The following data could be established comparing the profiles of clinical and scintigraphic evolution in 93 patients. In 49 patients (52%) the evolution of the two parameters was similar, the situation remaining unchanged or showing progressive impairment; in 43 patients (46%) scintigraphic deterioration was observed whereas the clinical score remained unchanged (Fig. 1); in 26 out of these 43, clinical deterioration occurred 6 mo to 2 yr after the scan became obviously abnormal; and in the 17 remaining cases, clinical aggravation could not be demonstrated. In only one patient was clinical progression of the lung disease observed in the absence of scintigraphic indication.

Comparison between scintigraphic and radiologic data.

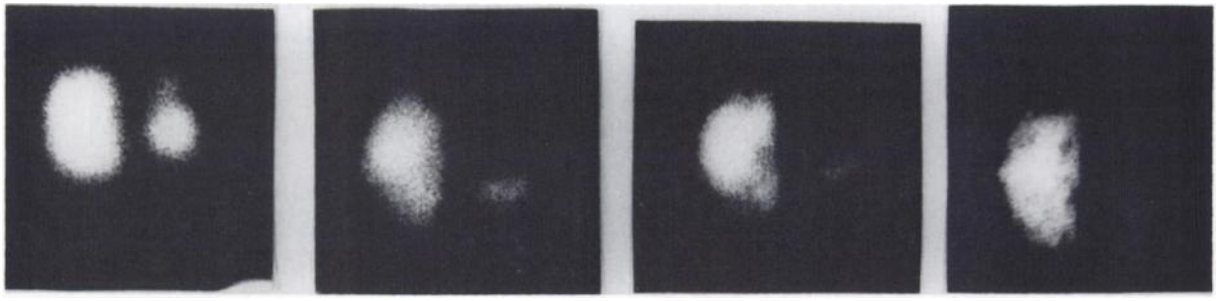

FIG. 1. Example of striking scintigraphic deterioration, while clinical score remained unchanged.

TABLE 2. TRANSVERSAL COMPARISON BETWEEN RADIOGRAPHIC AND SCINTIGRAPHIC SCORES

Scintigraphic score	Chest radiographic score			
	Normal	Moderate lesions	Severe lesions	Total
Normal	29	9	5	43
Moderate lesions	7	1	14	22
Severe lesions	2	2	32	36
Total	38	12	51	101

Transverse comparisons (101 pairs of data). Concordance was noted in 62 out of 101 comparisons and discordance in 39 (Table 2). In 11 cases, scintigraphic lesions were predominant and in 28 the radiologic findings were more pronounced. An abnormal scan was associated with a normal chest radiograph in nine cases; the contrary occurred in nine cases (Fig. 2).

Longitudinal comparisons. For 40 patients Table 3 shows the evolution of scintigraphy, clinical score, and chest radiograph during the same periods. Scintigraphic deterioration occurred in two thirds of the cases, clinical degradation in half, and radiographic degradation in one third of the cases, either because the radiogram was initially normal and remained normal during further evolution or, more frequently, because radiographic score was markedly altered from the start and did not show any further changes.

Retrospective study of the deceased patients. Complete data were available from 28 patients who died during the period of the present study. For these we have tried to determine to what extent the different clinical parameters, assessed during the years preceding death, were representative of the lung impairment.

In Fig. 3 the clinical, radiologic, and scintigraphic scores are represented as a function of the time interval between the test and the death of the patient. The correlation coefficient is highest for the scintigraphic findings, being significantly greater than for either radiographic or clinical score. On combining radiographic and clinical score—thus using a real Kulczycki-Shwachman score—the correlation coefficient appears slightly lower than for scintigraphy alone, the differences not being statistically significant (Fig. 3).

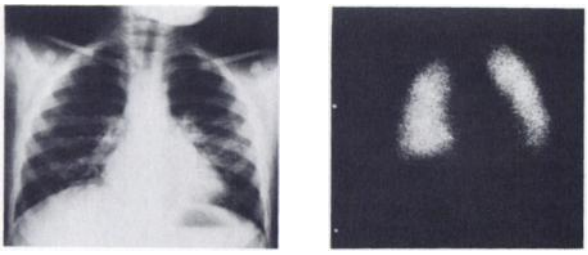

FIG. 2. Marked bilateral lesions by radiograph with normal scintigraphy.

TABLE 3. LONGITUDINAL COMPARISON BETWEEN SCINTIGRAPHY, CLINICAL SCORE AND CHEST RADIOGRAPHY (40 PATIENTS)

Evolution	Scan	Clinical score	Radiograph
Aggravation	26 patients	19 patients	10 patients
No change	14 patients	21 patients	30 patients

Prediction of the survival rate from the initial scintigraphy. Figure 4 indicates the predictability of survival by means of the initial scintigraphic score. When the scintigraphic pattern was normal (Score $\neq 2$), the survival rate at 9 yr reached 0.80; with moderate impairment (Scores 3–4) the survival rate was 0.83 but did not differ significantly from the normal group. However, when striking lesions were observed on the initial scintigrams (Scores >4), the survival rate fell to 0.18 at 9 yr and was significantly different from the combination of the two other groups ($p < 0.0005$).

DISCUSSION

Before using lung scintigraphy as a criterion of re-

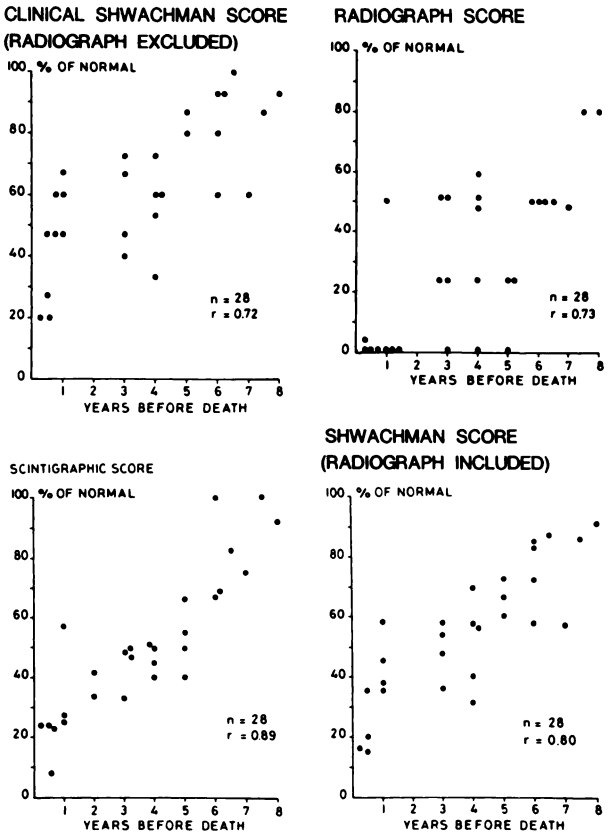

FIG. 3. Clinical, radiological, and scintigraphic scores, and the combination of the first two, as related to the time interval between the evaluation and the death of the patient.

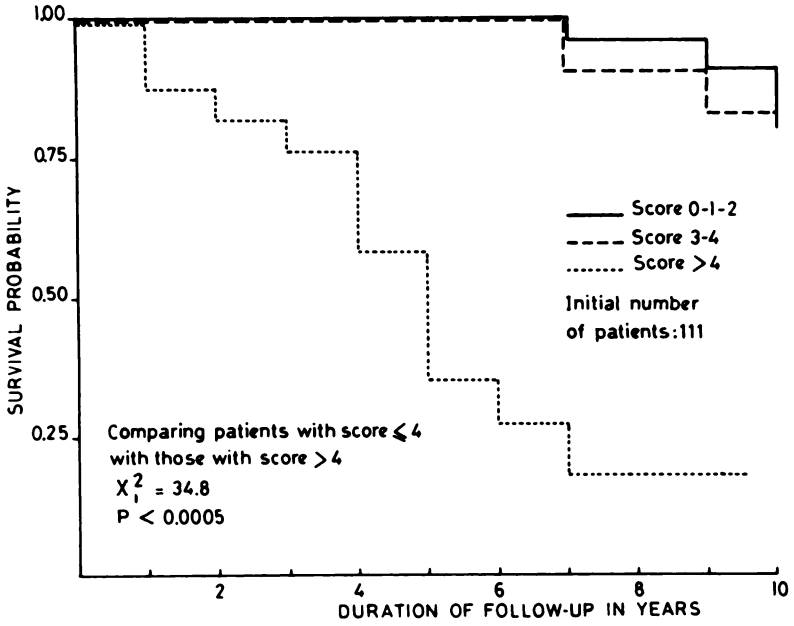

FIG. 4. Survival as related to score at initial scintigraphy.

gional lung impairment, it was necessary to show that scintigraphic lesions were reproducible as far as their size and topography were concerned. This held true in our previous study (*1*) as long as the tests were performed during a remission phase of the disease.

The correlation with the age of the patient and the Kulczycki-Shwachman score seemed encouraging in providing useful information on the progress of lung changes without recourse to subjective assessment of the patients. It was obvious, however, that the real advantage of scintigraphy, compared with other classical methods, could be established only on the basis of a longitudinal study. For the purpose of comparing with radiographic and clinical status, the scintigraphic classification in four categories used in the previous work has now been replaced by a more detailed scoring system that has been found reproducible when independently applied by two examiners. The use of a technique describing the perfusion impairment in an obstructive disease like cystic firbrosis seemed justified on the basis of previous studies, since chronic ventilation impairment is closely associated with a corresponding perfusion disturbance (*10–18*).

The comparison of perfusion scintigraphy and clinical index provides good evidence that scintigraphy constitutes a better method for detecting early pulmonary changes; the longitudinal comparison indicates that the clinical score, in some cases showing an aggravation only 2 yr after the scan, probably underestimates the degree of lung damage.

The 17 cases where scintigraphic deterioration was obvious without at any time a comparable clinical degradation, could be explained by a shorter follow-up period.

When comparing the contribution of radiography and scintigraphy to the early detection of lung impairment, we find that each technique detected a certain number of lesions that were completely missed by the other. The two techniques seem to be complementary from this particular point of view. It must be emphasized that only a relatively small number of cases showed progression of the lesions by chest radiography (one third of the cases) whereas progressive deterioration could be demonstrated in two thirds by scintigraphic follow-up.

One possible explanation could be that scintigraphy has proved to represent mainly a functional index as opposed to the more structural changes seen by radiograph.

The better description of the regional functional damage by scintigraphy is also illustrated by the retrospective analysis of the deceased patients; the scintigraphic score is directly related to the survival. Such a relation is much less obvious for the clinical and the radiological scores, the first underestimating, and the latter probably overestimating, the progress of the disease, with the combination of both giving a more or less exact idea of the actual state of lung impairment. Note that the relation between scintigraphy and survival interval cannot be generalized to include the patients still alive, since for this particular study, only the deceased patients have been selected. A very low scintigraphic score does not necessarily signify a very early fatal outcome.

Alderson (*16*) has shown that the fractional exchange of air measured by computer-assisted radionuclide studies correlates well with standard pulmonary function tests. Such correlations are not included in this paper because of the lack of pulmonary function data before the age of six. Other papers are concerned with the prediction of the survival of cystic fibrosis patients, taking into account the clinical status or the chest radiograms during the first year of treatment (*2–5*). The

present study shows the contribution of the initial scintigraphy to this prediction, the survival rate being much lower when severe lesions are observed on the initial scan. It should be mentioned that the prognosis is the same when scintigraphic images are either normal or moderately impaired.

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