CORRELATION OF LUNG GALLIUM-67 SCINTIGRAPHY WITH LUNG X-RAY AND PULMONARY FUNCTION TESTS IN PATIENTS WITH SARCOIDOSIS

Antonija Ivičević [1], Tatjana Peroš-Golubičić [1], Dražen Huić [2], Stanko Težak [2], Marjan Gorečan [1], Jasna Tekavec-Trkanjec [1] and Marija Alilović [1]

[1]Jordanovac University Hospital for Lung Diseases; [2]University Department of Nuclear Medicine and Radiation Protection, Zagreb University Hospital Center, Zagreb, Croatia

SUMMARY – In order to assess the usefulness of Ga-67 scintigraphy in the evaluation of sarcoidosis activity, 44 patients including 14, 20 and 10 patients with radiologic stage I, II and III, respectively, were examined. Control group consisted of 22 subjects with healthy lungs who underwent Ga-67 scintigraphy for extrathoracic disease. An objective method of quantitative computer analysis was used on scintigram interpretation. Results were expressed as mean impulse count *per* pixel of the given area in the left and right hilar region, left and right lung, and in the area of focal accumulation if present. In sarcoidosis patients, the mean impulse count was statistically significantly higher in all regions than in the control group ($p<0.0001$ for left hilum, right hilum and right lung; and $p<0.001$ for left lung). The mean impulse count showed correlation with pathologic finding. Pathologic accumulation of Ga-67 in the hilar region was evident in 37 (84.1%) patients, and in the region of pulmonary parenchyma in 31 (70.5%) patients, and showed statistically significant correlation with radiologic staging of sarcoidosis ($p<0.01$). However, scintigraphy supplemented radiologic staging by providing additional information on the disease extent. In 35.7% of patients with x-ray stage I sarcoidosis, scintigraphy revealed pathologic accumulation of Ga-67 also in pulmonary parenchyma, whereas in as many as 70% of patients with x-ray stage III sarcoidosis the pathologic accumulation of Ga-67 pointed to the disease activity in the lymph nodes of the hilum. Only three (6.7%) patients were free from any form of pathologic Ga-67 accumulation. The patients with pathologic Ga-67 accumulation in the lung parenchyma ($n=31$) had a more severe form of the disease with lower values of pulmonary function tests, i.e. forced vital capacity (FVC), forced expiratory volume in first second (FEV_1), diffusion capacity for carbon monoxide (DLCO) and arterial blood partial oxygen pressure (pO_2). Forced vital capacity as an indicator of ventilation restrictive impairments was statistically significantly lower in the group of patients with pathologic accumulation of Ga-67 in pulmonary parenchyma as compared with the group of patients without it ($p<0.01$). The decrease in diffusion capacity correlated statistically significantly with the increase in the pathologic accumulation of Ga-67 in pulmonary parenchyma ($p<0.01$). Thus, lung Ga-67 scintigraphy was found to be a highly sensitive marker of the extent and activity of sarcoidosis, however, due to the low specificity of the method its use in good clinical practice should be reserved for diagnostically and therapeutically vague cases, with due consideration of the irradiation dose and cost.

Key words: *Lung diseases, radiography; Lung diseases, radionuclide imaging; Sarcoidosis, diagnosis; Sarcoidosis, radiography; Gallium radioisotopes, diagnostic use*

Correspondence to: *Antonija Ivičević, M.D.*, Jordanovac University Hospital for Lung Diseases, Jordanovac 104, HR-10000 Zagreb, Croatia

Received January 16, 2003, accepted in revised form May 28, 2003

Introduction

Sarcoidosis is a multisystemic granulomatosis of unknown etiology, characterized by CD4+ T-lymphocyte accumulation that results in Th-1 immune response in the organs and tissues involved. The disease mostly affects young adults and manifests with hilar lymphadenopathy, lung infiltration, and skin and ocular lesions[1]. Besides distinct clinical and radiologic picture, the diagnosis is confirmed by the histologic finding of noncaseous granulomata.

The disease generally shows a favorable course with complete resolution, however, in 8% - 15% of cases it may lead to irreparable structural and functional lung lesions of a variable grade (lung fibrosis), or even fatal outcome. The mortality from sarcoidosis is mostly caused by lesions of pulmonary parenchyma, whereas the morbidity and symptomatology are frequently consequential to extrapulmonary localization of the disease. As lung lesions are found in 90% - 100% of sarcoidosis cases, the known concepts on the disease have been mostly derived from pulmonary sarcoidosis.

Once the diagnosis of sarcoidosis has been made, the extent, activity and progression of the disease should be determined. The disease activity markers can be clinical, biochemical, immunologic or functional. The role of each of these markers of the disease activity is to point to the presence and extent of granulomatous inflammation, which they generally do, however, their value in predicting the course and outcome of the disease has proved inadequate and uncertain.

Many studies have been focused on the disease activity, i.e. the presence of granulomatous inflammation, in order to identify, with due respect to a series of parameters, those patients in whom sarcoidosis may have an unfavorable course, thus requiring corticosteroid therapy. On disease activity assessment, clinical picture, lung x-ray and pulmonary function studies as well as serum angiotensin converting enzyme (ACE) determination, bronchoalveolar lavage analysis and gallium 67 (Ga-67) scintigraphy, primarily lung scintigraphy, are used. Standard studies such as lung x-ray and pulmonary function tests provide summation data on overall events in the lungs without differentiating a potentially reversible stage of alveolitis and granuloma from the irreversible stage of pulmonary fibrosis. Ga-67 scintigraphy is a noninvasive method allowing selective visualization of the disease inflammatory component, which can be repeated during the disease follow-up.

The aim of the present study was to assess the extent and activity of the disease in patients with sarcoidosis by the method of Ga-67 scintigraphy, and to correlate the values obtained with traditional studies, i.e. lung x-ray and pulmonary function tests. The purpose of the study was to determine and present the method sensitivity and value in the given conditions.

Patients and Methods

Patients

Forty-four patients with sarcoidosis underwent Ga-67 scintigraphy to assess its value in this disease. In all patients, the diagnosis of sarcoidosis was made during their stay at the Jordanovac University Hospital for Lung Diseases in Zagreb, and was based on the clinical picture, lung x-ray, and pathohistologic (transbronchial lung biopsy) or cytologic (transtracheal tracheal carina biopsy) finding in the materials collected on bronchoscopy. Newly diagnosed sarcoidosis patients requiring complete examination were included in the study. Therefore, this patient series could not be considered to represent normal distribution of patients with sarcoidosis according to the disease x-ray stage. The principal interest was to include as many patients with pulmonary parenchyma involvement as possible. Patients with any other accompanying lung disease were excluded from the study. During the study, the patients did not receive corticosteroid therapy, and in only three patients this therapy had been initiated about a week before the Ga-67 scintigraphy was technically available. Control group included 22 patients with healthy lungs in whom Ga-67 scintigraphy was performed for extrathoracic diseases.

Methods

In patients with sarcoidosis, pulmonary function studies and Ga-67 scintigraphy were performed in addition to radiologic examination of the lungs.

Lung x-ray. According to radiologic findings (summation x-ray of the lung and tomography), the disease was traditionally classified into three x-ray stages: stage I denoting a disease radiologically limited to enlarged hilar and mediastinal lymph nodes; stage II denoting pulmonary parenchymal involvement in addition to lymph node enlargement; and stage III denoting exclusively pulmonary parenchymal involvement. Stage 0 denotes normal lung x-ray finding.

Pulmonary function tests. Functional breathing testing included measurement of forced vital capacity (FVC),

forced expiratory volume in first second (FEV_1), diffusion capacity for carbon monoxide using single inspiration method (DLCO), and arterial blood partial oxygen pressure (pO_2) measured on Body-Screen II, Transfer-Screen II (Jaeger) and IL System 1302 pH/Blood Gas analyzer (Instrumentation Laboratory) devices.

According to CECA standards[16], FVC values <80% of expected value and FEV_1/%FVC values <75% of expected value were considered decreased, whereas DLCO values <80% of expected value were considered pathologic. The borderline pO_2 value was set at 80 mm Hg, as all study subjects were below age 75.

Lung Ga-67 scintigraphy. Patients were intravenously administered 2 mCi Ga-67 citrate, and scintigraphy in anterior and posterior projection was performed 48 hours from application. Total impulse count *per* scintigram was 500,000. Scintigrams were computer stored and subsequently submitted to quantitative analysis and processing by use of respective software. Quantification was done by the method of region of interest, positioning it in the region of hilum, lung parenchyma and in the area of focal lesions if present. A special computer software was used to generate total impulse count and mean impulse count *per* pixel in a particular region. The mean impulse counts *per* pixel were taken as quantitative data.

Lung Ga-67 scintigraphy was performed in all sarcoidosis patients and control group subjects. Control group included 22 patients free from lung diseases, in whom Ga-67 scintigraphy was indicated for identification of other, extrapulmonary lesions. Thus, mean impulse values (arithmetic mean) were obtained for the regions of left hilum, right hilum, left lung and right lung in healthy lungs, and taken as reference values. An impulse count exceeding 2 standard deviations from the reference value for the respective region was considered pathologic Ga-67 accumulation in the hila and parenchyma of the lung. According to distribution, pathologic Ga-67 accumulation was classifed, by analogy with x-ray stages, as follows: 0 – no pathologic accumulation; 1 – pathologic accumulation only recorded in the hila; 2 – pathologic accumulation found in the hila and lung; and 3 – pathologic accumulation found exclusively in the lung. Focal intraregional accumulation was specifically recorded, if present.

Statistical analysis

Study results were expressed as arithmetic mean and standard deviation or in case of irregular distribution as median and range. Between-group arithmetic mean differences were statistically analyzed by t-test for independent samples, and median differences by Mann-Whitney test for independent samples. Frequency distribution of particular variables and correlation probability were assessed by χ^2-test, and degree of correlation by correlation tests r and ro.

Results

General patient data

Forty-four patients with sarcoidosis were included in the study group. There were 35 (79.5%) women and nine (20.5%) men, mean age 41.5 years. Control group had 22 subjects, 14 (63.6%) women and eight (36.4%) men, mean age 54.5 years (Table 1). According to x-ray findings, x-ray stage I, II and III sarcoidosis was present in 14 (31.8%), 20 (45.5%) and ten (22.7%) patients, respectively (Table 2). Ga-67 scintigraphy of the lung was performed in all sarcoidosis patients and control group subjects free from pulmonary disease.

Table 1. General patient data

Patient group	
Number of patients	44
Female	35 (79.5%)
Male	9 (20.5%)
Mean age (range), yrs	41.5 (25-65)
Control group	
Number of subjects	22
Female	14 (63.6%)
Male	8 (36.4%)
Mean age (range), yrs	54.5 (34-69)

Lung Ga-67 scintigraphy

Mean impulse counts recorded in the left and right hila, and left and right lungs in the sarcoidosis group and control group patients are shown in Table 3. The considerably

Table 2. Patient distribution according to sarcoidosis x-ray staging

Sarcoidosis x-ray stage	Number (%) of patients
Stage I	14 (31.8)
Stage II	20 (45.5)
Stage III	10 (27.7)

stronger Ga-67 accumulation in the lungs of sarcoidosis patients as compared with healthy lungs of control subjects was statistically significant at the probability level of 0.01% ($p<0.0001$) for the left and right hila and right lung, and 0.1% ($p<0.001$) for the left lung. In both sarcoidosis and control group, the values recorded in pulmonary parenchyma were regularly lower than those found in the corresponding hilum ($p<0.001$).

Lung Ga-67 scintigraphy and lung x-ray

The mean impulse counts in particular x-ray stages of sarcoidosis are presented in Table 4. In x-ray stage I sarcoidosis, the mean impulse counts in the left and right hila were statistically significantly increased in comparison with control group values ($p<0.0001$), whereas no such difference was recorded in the mean impulse counts in the left and right lung parenchyma. In patients with x-ray stage I sarcoidosis, hilar activity ranged widely with high standard deviation, whereas parenchymal activity showed great homogeneity.

In x-ray stage II sarcoidosis, the mean impulse counts in the hila and pulmonary parenchyma were significantly higher than those recorded in the control group. Both parenchymal and hilar activities showed great variation. In patients with x-ray stage III sarcoidosis in whom only pulmonary parenchymal involvement was observable, the mean impulse counts in the hila still exceeded the values recorded in the control group but were significantly lower than those in x-ray stages I and II sarcoidosis ($p<0.05$). Like stage II, in x-ray stage III sarcoidosis the mean impulse count in pulmonary parenchyma was significantly increased in comparison with control group ($p<0.001$).

The mean impulse counts in the left and right hilus showed statistically significant differences between the groups with visible lymph node enlargement (x-ray stages I and II) and the group without lymph node enlargement (x-ray stage III) ($p<0.05$). Also, the mean impulse count in the left and right lungs differed statistically significantly between the group without overt pulmonary parenchymal involvement (x-ray stage I) and groups with radiologically visible interstitial reaction (x-ray stages II and III) ($p<0.001$). There were wide within-group ranges.

The prevalence of pathologic findings of lung Ga-67 scintigraphy in particular x-ray stages of sarcoidosis is presented in Tables 5 and 6. The measured borderline values were 197 impulses in the left hilum, 195 impulses in the right hilum, 158 impulses in the left lung, and 153 impulses in the right lung. Table 5 shows frequencies of particular types of Ga-67 pathologic accumulation according to x-ray stages of sarcoidosis. In x-ray stage I, pathologic accumulation of Ga-67 in the hila and pulmonary parenchyma was detected in four patients, and in pulmonary parenchyma only in one patient, whereas no pathologic accumulation was observed in one patient. In x-ray stage II, pathologic accumulation of Ga-67 in the hila alone was found in two patients, and in pulmonary parenchyma alone in one patient. In x-ray stage III, pathologic accumulation of Ga-67 in both pulmonary parenchyma and hila was detected in as many as seven patients. Focal accumulation was observed in six of 44 (10.1%) patients. Considering all three x-ray stages of sarcoidosis, three of 44 (6.8%) patients were free from any pathologic accumulation of Ga-67 in either hila or pulmonary parenchyma.

The frequency of Ga-67 pathologic accumulation in the hila and pulmonary parenchyma according to x-ray stages is shown in Table 6. Both hilar and parenchymal pathologic accumulation of Ga-67 was evident in 35.7% of patients with x-ray stage I sarcoidosis, although the process is radiologically limited to hilar lymph nodes in this stage of the disease. In x-ray stage III sarcoidosis, where the disease is radiologically evident only in pulmonary parenchyma, pathologic Ga-67 accumulation was also detected in hilar lymph nodes in as many as 70% of patients with this stage of the disease. Overall, hilar pathologic Ga-67 accumulation was recorded in 37 of 44 (84.1%) patients, without statistically significant frequency difference among particular x-ray stages of sarcoidosis. Pathologic accumulation of Ga-67 in pulmonary parenchyma was found in 31 of 44 (70.5%) patients, with a statistically significant difference in the frequency of accumulation among particular x-ray stages of sarcoidosis ($p<0.01$).

Pulmonary function tests and x-ray stages of sarcoidosis

The frequencies of pathologic pulmonary function test findings in all sarcoidosis patients and according to particular x-ray stages of the disease are presented in Table 7. FVC was decreased in 20.5%, FEV_1/%FVC in 18.2%, DLCO in 36.4%, and pO_2 in 27.7% of sarcoidosis patients. Although the frequency of pathologic findings differed among particular x-ray stages, only the difference in the frequency of decreased DLCO among x-ray stages approached the level of statistical significance ($p=0.06$).

Lung Ga-67 scintigraphy and pulmonary function tests

Table 8 shows results of pulmonary function studies (FVC, FEV_1/%FVC, DLCO and pO_2) in the groups of pa-

Table 3. Mean impulse count on lung Ga-67 scintigraphy in sarcoidosis group and control group subjects ($\chi \pm SD$)

Localization	Sarcoidosis group	Control group	t-test
Left hilum	252 ± 69.5	167 ± 15.3	p<0.0001
Right hilum	265 ± 78.4	165 ± 15.2	p<0.0001
Left lung	168 ± 43.7	134 ± 12.4	p<0.001
Right lung	173 ± 50.0	129 ± 12.1	p<0.0001

tients with and without pathologic Ga-67 accumulation in pulmonary parenchyma. Testing for differences revealed all FVC, FEV_1, DLCO and pO_2 values to be lower in patients with pathologic Ga-67 accumulation, however, only the difference in FVC values between these two groups reached statistical significance ($p<0.01$).

Testing for correlation between Ga-67 impulse count in pulmonary parenchyma (arithmetic mean of impulse counts in the left and right lung) and pulmonary function tests in all patients yielded clear negative correlation between gallium and diffusion capacity ($r=-0.3862$, $p<0.01$), and mild negative correlation between gallium and FVC (Table 9, Figs. 1 and 2).

Discussion

The problem of quantification has been present since the introduction of lung Ga-67 scintigraphy as a method useful in the assessment of the disease extent and activity. The computed quantitative method of result expression used in this study enables objective differentiation between normal and pathologic findings, comparison of findings in serial studies, and correlation with other quantitatively expressed activity markers[3,19,20]. Therefore, the method is superior to subjective qualitative and semiquantitative methods of scintigram interpretation[10,12,18]. The only subjective issue is the sequence of the regions of interest chosen.

The significantly higher mean impulse counts recorded in sarcoidosis patients as compared with healthy lungs confirmed the value and justifiability of this examination in patients with sarcoidosis (Table 3). Considering the overall population of sarcoidosis patients, the variability in Ga-67 activity in the hila and pulmonary parenchyma most probably reflected differences in the disease activity.

The results of mean impulse count determination in the hila and pulmonary parenchyma in particular x-ray stages of the disease indicated high correlation between the radiologic and scintigraphic visualization of the lung involvement with sarcoidosis (Table 4). Other authors also report similar results, however, the difference in the mean impulse count between particular x-ray stages was less distinct[14,15]. The more so, the difference in pulmonary parenchyma Ga-67 activity among x-ray stages I, II and III reported by Alberts *et al.* was not statistically significant[17].

In our study, the frequency of pathologic Ga-67 accumulation in the hila and pulmonary parenchyma in particular x-ray stages of sarcoidosis (Table 6) pointed to the high sensitivity of lung Ga-67 scintigraphy as a method to assess the spread of the disease. Scintigraphy revealed the presence of granulomatous inflammation also in the lung regions that appeared to be unaffected on radiologic finding. So, pathologic Ga-67 accumulation in pulmonary parenchyma was detected in 35.7% of x-ray stage I sarcoidosis patients where pulmonary parenchyma appeared unaffected radiologically. Also, pathologic hilar Ga-67 accu-

Table 4. Mean impulse count according to sarcoidosis x-ray stages ($\chi \pm SD$)

X-ray stage	Left hilum	Right hilum	Left lung	Right lung
Stage I	260 ± 63.1	295 ± 87.9	139 ± 16.8	137 ± 17.3
			**p<0.001	**p<0.001
Stage II	271 ± 76.6	269 ± 74.2	176 ± 49.0	175 ± 43.4
Stage III	204 ± 38.4	215 ± 48.7	196 ± 36.7	219 ± 59.0
	*p<0.05	*p<0.05		

*p<0.05 (x-ray I+II/x-ray III); **p<001 (x-ray I/x-ray II+III)

Table 5. Frequency of Ga-67 pathologic accumulation according to sarcoidosis x-ray stages

Ga-67 accumulation	X-ray stage I	X-ray stage II	X-ray stage III	No. (%) of patients
Ga 0	1	1	1	3 (6.8)
Ga 1	8	2	0	10 (22.7)
Ga 2	4	16	7	27 (61.4)
Ga 3	1	1	2	4 (4.1)
Focal	1/14 (7%)	3/20 (15%)	2/10 (20%)	6/44 (10.1)
Total patient No. (%)	14 (31.8)	20 (45.5)	10 (22.7)	44 (100)

mulation was found in as many as 70% of x-ray stage III sarcoidosis patients without radiologically altered lymph nodes. The frequencies of pathologic Ga-67 accumulation obtained in the present study slightly exceeded those reported in a multicenter European study[9], which will have to remain without any relevant explanation except for the smaller number of patients. However, these reports appear to be void of precise data on the correlation between x-ray staging and pathologic Ga-67 accumulation in the hila and pulmonary parenchyma.

The high sensitivity of lung Ga-67 scintigraphy on assessing the extent of the disease was confirmed by the results listed in Table 6, showing that only three (6.8%) patients were free from pathologic Ga-67 accumulation in either the hila or pulmonary parenchyma.

Ga-67 scintigraphy of the lung is a good indicator of sarcoidosis activity, which was also confirmed by the statistically significant difference in the frequency distribution of Ga-67 accumulation in pulmonary parenchyma among particular x-ray stages of the disease ($p<0.01$) (Table 6). Lung Ga-67 scintigraphy depends on the macrophage activity of granulomatous inflammation. Comparing histologic findings in sarcoidosis with those obtained by lung Ga-67 scintigraphy, Abe *et al.* have demonstrated high correlation between the histology of pulmonary interstitial granuloma and positive lung scintigraphy[11].

Increased focal accumulation within particular regions of pulmonary parenchyma, also observed in 10.1% of patients in the present study, may serve as a useful indicator of the appropriate site for transbronchial biopsy.

Analysis of the pulmonary function studies (Table 7) revealed a decreased CO diffusion capacity to be most common (36.4%) which is, along with decreased vital capacity, consistent with the expected restrictive lung lesions in sarcoidosis. However, obstructive ventilation impairments are also found in sarcoidosis, mostly in advanced stages of the disease[7,23]. Our results are in agreement with this concept, showing highest prevalence of decreased FEV_1 in x-ray stage III sarcoidosis. Obstructive ventilation disturbances may occasionally occur in early stages of sarcoidosis, which appears to be associated with bronchial hyperreactivity[22].

Considering frequency distribution of pathologic pulmonary function test findings according to x-ray stages, a

Table 6. Prevalence of pathologic Ga-67 scintigraphy findings according to sarcoidosis x-ray stages

	All patients	X-ray stage I	X-ray stage II	X-ray stage III	Level of significance
GA-67	44	14	20	10	
Hilum positive	37/44 (84.1%)	12/14 (85.7%)	18/20 (90%)	7/10 (70%)	NS
Lung positive	31/44 (70.5%)	5/14 (35.7%)	17/20 (85%)	9/10 (90%)	$p<0.01$

NS=nonsignificant

Table 7. Frequency of pathologic FVC, FEV_1/%FVC, DLCO and pO_2 values according to sarcoidosis x-ray stages

	All patients	X-ray stage I	X-ray stage II	X-ray stage III	Level of significance
	44	14	20	10	
FVC <80%	9/44 (20.5%)	1/14 (7.1%)	5/20 (25%)	3/10 (30%)	NS
FEV_1 <75%	8/44 (18.2%)	0/14 (0%)	5/20 (25%)	3/10 (30%)	NS
DLCO <80%	16/44 (36.4%)	2/14 (14.3%)	8/20 (40%)	6/10 (60%)	p=0.06
pO_2 <80%	10/44 (27.7%)	4/14 (28.6%)	5/20 (25%)	1/10 (10%)	NS

NS=nonsignificant

higher rate of pathologic findings except for pO_2 were recorded in higher x-ray stages of the disease (Table 7). However, only the value of DLCO approached statistical significance (p=0.06) pointing to the interdependence of diffusion capacity values and x-ray stage of the disease as well as to the sensitivity of DLCO on disease staging. The results obtained in the study were consistent with the current concepts according to which diffusion capacity is reduced in 30% of x-ray stage I patients and 70% of x-ray stage II and III patients, which frequently precedes the respiratory volume reduction[21].

The patients with pathologic Ga-67 accumulation had lower mean values of all pulmonary functions than those without pathologic Ga-67 accumulation, however, a statistically significant difference was only recorded for FVC (Table 8). The findings suggested the patients with pathologic Ga-67 accumulation to suffer from a more severe form of the disease.

Comparison of Ga scan with pulmonary function studies (Table 9) yielded distinct negative correlation only between Ga-67 scintigraphy and diffusion capacity. As the measurements of pulmonary functions in sarcoidosis have frequently produced contradictory results, most authors agree that these studies cannot determine the type and grade of pulmonary parenchymal lesiosn, but are a useful parameter in the follow-up of the course of disease in individual patients[21].

Table 9. Correlation of lung Ga-67 scintigraphy with pulmonary function parameters

FVC	– 0.274	p=0.07
FEV_1	– 0.1426	NS
DLCO	– 0.3862	p<0.01
pO_2	0.0683	NS

NS=nonsignificant

Although the mechanism of Ga-67 accumulation in chronic inflammatory conditions has not yet been fully clarified, it has been postulated that gallium is being ac-

Table 8. Significance of functional parameter differences between patients with and without pathologic Ga-67 accumulation in pulmonary parenchyma

	All patients	Ga negative	Ga positive	Level of significance
FVC (%)	89.2 ± 14.5	98 ± 17.5	85.5 ± 11.4	p<0.01
FEV_1 (%)	83.5 ± 15.7	90.6 ± 17.8	80.5 ± 13.9	NS
DLCO (%)	82.6 ± 15.3	88.8 ± 13.2	80 ± 15.5	NS
pO_2 (mm Hg)	86.1 ± 9.2	87.2 ± 8.2	85 ± 9.7	NS

NS=nonsignificant

cumulated by activated macrophages, thus Ga-67 accumulation reflecting the macrophage activity of granulomatous inflammation[6]. Besides pulmonary sarcoidosis, Ga-67 scintigraphy is also a useful tool in the diagnosis of extrathoracic sarcoidosis. The morphological patterns of Ga-67 accumulation in lacrimal and parotid glands (so-called Panda form) along with its accumulation in the hilar lymph nodes (so-called lambda form) and/or radiologically evident bihilar lymph node enlargement are highly specific for sarcoidosis[2]. Some consider histologic verification of the disease unnecessary in these cases.

Gallium activity is believed to provide better insight into the overall inflammatory events in the lungs than other markers of the disease activity which, being obtained by bronchoalveolar lavage, reflect the events in a particular lung segment, whereas ACE reflects the inflammatory activity of extrathoracic sarcoidosis as well.

Based on the results obtained, Ga-67 scintigraphy of the lungs cannot be considered valuable in predicting the disease outcome, however, patients with chronic lung sarcoidosis showing a tendency to develop irreversible lung fibrosis are probably recruited from the group of patients with positive Ga-67 accumulation.

Conclusion

Ga-67 scintigraphy of the lungs is a highly sensitive test to assess the extent and activity of the disease in patients with sarcoidosis. However, specificity of the test is quite low, since pathologic Ga-67 accumulation in hilar lymph nodes and pulmonary parenchyma also occurs in other chronic diffuse inflammatory interstitial processes as well as in tumors, primarily lymphoma.

Objective quantitative computer analysis of the scintigram should be preferred to qualitative or semiquantitative methods.

In sarcoidosis patients, lung Ga-67 scintigraphy provides additional information on the disease extent and supplements radiologic staging by pointing to pulmonary parenchymal involvement in some x-ray stage I cases, or to the activity in hilar lymph nodes in x-ray stage III cases.

Pathologic accumulation of Ga-67 in sarcoidosis patients is accompanied by pulmonary function impairment. Based on the study results, Ga-67 scintigraphy of the lungs does not appear to be of a predictive value for the disease outcome, however, it seems likely that patients with chronic lung sarcoidosis showing a tendency to develop irreversible lung fibrosis are recruited from the group of patients with positive Ga-67 accumulation.

In good clinical practice, Ga-67 scintigraphy as a good marker of the sarcoidosis extent and activity is indicated in diagnostically and therapeutically vague cases, with due consideration of the radiation dose and cost.

References

1. HUNNINGHAKE GW, COSTABEL U, ANDO M, BAUGHMAN R, CORDIER JF, du BOIS R, EKLUND A, LYNCH J, RIZZATO G, ROSE C, SELROSE O, SHARMA OP. ATS/ERS/WASOG Statement on Sarcoidosis. Sarcoidosis Vasc Diff Lung Dis 1999;16:149-74.
2. SULAVIK SB, SPENCER RP *et al.* Recognition of distinctive patterns of gallium-67 distribution in sarcoidosis. J Nucl Med 1990;31:1909-14.
3. HUIĆ D, DODIG D, JURAŠINOVIĆ Ž, TEŽAK S, POROPAT M, IVIČEVIĆ A *et al.* Simple quantitative analysis of Ga-67 lung scintigraphy – normal values. Radiol Oncol 1995;29:12-4.
4. De REMEE RA. The roentgenographic staging of sarcoidosis: historic and contemporary perspectives. Chest 1983;83:128-32.
5. NEVILLE E, WALKER AM, JAMES DG. Prognostic factors predicting the outcome of sarcoidosis: an analysis of 818 patients. Q J Med 1983;208:525-33.
6. FLINT K, CHIRB, JOHNSON N. Intrathoracic sarcoidosis. Semin Respir Med 1986;8:41-51.
7. BROWN JK. Pulmonary sarcoidosis: clinical evaluation and management. Semin Respir Med 1991;12:215-28.
8. MISHKIN FS, NIDEN AH. Clinical application of gallium-67 citrate imaging in sarcoidosis. In: LIBERMAN J, ed. Sarcoidosis. Orlando: Grune & Stratton, 1985; pp. 161-78.
9. RIZZATO G, BLASI A. A European survey on the usefulness of 67 Ga lung scan in assessing sarcoidosis. Ann NY Acad Sci 1986;465:463-78.
10. BEAUMONT D, HERRY JY, SAPENE M *et al.* Gallium-67 in the evaluation of sarcoidosis: correlations with serum angiotensin converting enzyme and bronchoalveolar lavage. Thorax 1982;37:11-8.
11. ABE S, MUNAKATA M, NISHIMURA M *et al.* Gallium-67 scintigraphy, bronchoalveolar lavage, and pathologic changes in patients with pulmonary sarcoidosis. Chest 1984;85:650-5.
12. LINE BR, HUNNINGHAKE GW, KOEGH BA *et al.* Gallium 67 scanning to stage the alveolitis of sarcoidosis: correlation with clinical studies, pulmonary function studies and bronchoalveolar lavage. Am Rev Respir Dis 1981;123:440-6.
13. HUCHON GJ, BERRISSOUL F *et al.* Comparison of bronchoalveolar lavage and gallium-67 lung scanning to assess the activity of pulmonary sarcoidosis. In: CHRETIEN J, MARSAC J, SALTIEL JC, eds. Sarcoidosis and other granulomatous disorders. Paris: Pergamon Press, 1983.
14. Van UNNIK JG, van ROYEN EA, ALBERTS C *et al.* A method of quantitative 67 Ga scintigraphy in the evaluation of pulmonary sarcoidosis. Eur J Nucl Med 1983;8:351-3.
15. FAJMAN WA, GREENWALD LV, STATON G *et al.* Assessing the activity of sarcoidosis: quantitative 67 Ga-citrate imaging. AJR Am J Roentgenol 1984;142:683-8.

16. CECA – Commission des Communautes Europeennes, Collection d'Hygiene et de Medicine du T ravail, No. 11. Aide-memoire pour la pratique de l'e xamen de la function ventilatoire par la spirographie. 2e edition revue et completee. L uxembourg, 1971.
17. ALBERTS C, ven der SCHOOT JB. Standardised quantitative 67 Ga scintigraphy in pulmonary sarcoidosis. Sarcoidosis 1988;5:111-8.
18. ALBERTS C, van der SCHOOT JB, GREEN AS. 67- Ga scintigraphy as an inde x of disease activity in pulmonary sarcoidosis. Eur J Nucl Med 1981;6:205-12.
19. WESSELIUS LJ, WITZUTUM KF *et al.* Computer -assisted *versus* visual lung gallium-67 inde x in normal subjects and in patients with interstitial lung disorders. Am R ev Respir Dis 1983;128:1084-9.
20. BISSON G, DRAPEA U G, LAMOUREUX G *et al.* Computer -based quantitative analysis of gallium-67 uptak e in normal and diseased lung. Chest 1983;84:513-7.
21. WINTERBAUER RH, HUT CHINSON JF. Use of pulmonary function tests in management of sarcoidosis. Chest 1980;78:640-7.
22. PRESAS FM, COLOMER PR, SANCHON BR. Bronchial hyper - reactivity in fresh stage I sarcoidosis. Ann NY Acad Sci 1986;465:523-9.
23. SHARMA OP, IZUMI T. The importance of airway obstruction in sarcoidosis. Sarcoidosis 1988;5:119-20.

Sažetak

KORELACIJA SCINTIGRAFIJE PLUĆA GA-67 S RTG PLUĆA I TESTOVIMA PLUĆNE FUNKCIJE U OBOLJELIH OD SARKOIDOZE

A. Ivičević, T. Peroš-Golubičić, D. Huić, S. Težak, M. Gorečan, J. Tkavec-Trkanjec i M. Alilović

Radi procjene značenja scintigrafije pluća s Ga-67 u oboljelih od sarkoidoze ispitana su 44 bolesnika, i to 14 u I., 20 u II. i 10 u III. radiološkom stadiju bolesti. K ontrolnu sk upinu činile su 22 osobe sa zdravim plućima u kojih je scintigrafija s Ga-67 rađena zbog ekstratorakalne bolesti. P ri tumačenju scintigrama rabljena je objektivna metoda kvantitativne kompjutorsk e analize gdje se rezultat izražava kao prosječan broj impulsa po kvadrantu zadane regije u području lijevog i desnog hilusa, lijevog i desnog pluća, te u području žarišnog nak upljanja ako je ono izraženo. U oboljelih od sarkoidoze prosječan broj impulsa za svak u regiju bio je statistički značajno viši od onoga u kontrolnoj sk upini ($p<0,0001$ za lijevi hilus, desni hilus i desno pluće, te $p<0,001$ za lijevo pluće). P rosječan broj impulsa pratio je radiološki nalaz. P atološko nak upljanje Ga-67 u području hilusa bilo je očito u 37 (84,1%) bolesnika, a u području plućnog parenhima u 31 (70,5%) bolesnika, uza statistički značajnu korelaciju s radiološkim stadijem sarkoidoze ($p<0,01$). Međutim, scintigrafija je dopunila radiološko određivanje stadija bolesti pruživši dodatne informacije o proširenosti bolesti. T ako je kod 35,7% bolesnika u I. rtg stadiju bolesti patološko nak upljanje Ga-67 bilo očito i u plućnom parenhimu, dok je u čak 70% bolesnika s III. rtg stadijem patološko nak upljanje GA-67 upućivalo na aktivnost procesa i u limfnim čvorovima hilusa. Samo troje (6,7%) bolesnika nije imalo patološko nak upljanje Ga-67 u bilo kojem oblik u. Bolesnici s patološkim nak upljanjem Ga-67 u plućnom parenhimu ($n=31$) imali su teži oblik bolesti s nižim vrijednostima testova plućnih funkcija, tj. forsiranog vitalnog kapaciteta, forsiranog ekspiracijskog volumena u prvoj sek undi, difuzijskog kapaciteta za ugljični monoksid i parcijalnog tlaka kisika u arterijskoj krvi. F orsirani vitalni kapacitet kao pokazatelj restriktivnih smetnja ventilacije bio je statistički značajno niži u sk upini bolesnika s patološkim nak upljanjem Ga-67 u plućnom parenhimu u usporedbi sa sk upinom bez patološkog nak upljanja ($p<0,01$). P ad difuzijskog kapaciteta je statistički značajno korelirao s porastom patološkog nak upljanja Ga-67 u plućnom parenhimu ($p<0,01$). Dakle, scintigrafija pluća s Ga-67 vrlo je osjetljiv biljeg proširenosti i aktivnosti kod sarkoidoze, međutim, ima nisk u specifičnost, pa ovu metodu u dobroj kliničkoj praksi treba rabiti u dijagnostički i terapijski dvojbenim slučajevima, vodeći pritom računa o dozi ozračivanja i cijeni.

Ključne riječi: *Plućne bolesti, radiografija; Plućne bolesti, radionuklidni slikovni prikaz; Sarkoidoza, dijagnostika; Sarkoidoza, radiografija; Radioizotopi galija, dijagnostička primjena*