OPTIMIZATION OF QUANTITATIVE PROCESSING DATA OF POSITRON EMISSION TOMOGRAPHY WITH 18F-FDG IN PATIENTS WITH LUNG CANCER

UDC 616.24–006–073.756.8
Received 18.10.2011

© **A.M. Granov,** D.Med.Sc., Professor, academician of the RAMS, Director[1];
L.A. Tyutin, D.Med.Sc., Professor, Deputy Director on Scientific Work[1];
M.S. Tlostanova, PhD, Radiologist, Senior Research Worker of the Department of Positron Emission Tomography[1];
A.O. Avetisyan, PhD, Head of the Department of Differential Diagnostics and Thoracic Surgery[2];
D.V. Ryzhkova, D.Med.Sc., Deputy Director of Educational Activities[1]

[1]Russian Scientific Centre of Radiology and Surgical Technologies, Ministry of Health and Social Development, Saint Petersburg;
[2]Scientific Research Institute of Phthisiopulmonology, Ministry of Health and Social Development, Saint Petersburg

The aim of the investigation is to increase efficiency of positron emission tomography (PET) with ^{18}F-FDG in differential diagnostics of lung cancer and non-neoplastic diseases by means of quantitative processing data optimization.

Materials and Methods. PET findings of 347 patients with focal or infiltrative changes in the lungs were studied. Quantitative processing of the findings included the measurement of scintigraphic size of the focus, SUV index calculations and SUV size. Diagnostic value of the indicated criteria was assesses with and without regard to the size of the revealed foci.

Results. PET examination revealed the foci of abnormal accumulation of radiopharmaceuticals in 273 of 347 patients with various bronchopulmonary diseases. Quantitative criteria (SUV and SUV/size) characterizing the metabolic activity rate were determined in all patients with focal glucose hypermetabolism. The comparative analysis of PET sensitivity and specificity in differential diagnostics of lung cancer and nonneoplastic conditions with or without regard to the size of the revealed foci was carried out.

Conclusion. Threshold points of SUV and SUV/size assessed with regard to pathologic focus size significantly increase PET possibilities in differentiating malignant and nonneoplastic process in the lung.

Key words: positron emission tomography, ^{18}F-FDG, lung cancer, SUV, SUV/size.

The widespread use of modern imaging techniques in clinical practice has increased the detection of pulmonary mass lesions including lung cancer (LC) in the early stages of the disease [1–5]. However, the use of X-ray examination does not always solve the problem of identifying the nature of the pathological process. Many problems of differential diagnosis are successfully handled by using different types of biopsies. In those cases when it is difficult to obtain histological material, a case follow-up and/or ex juvantibus therapy is used to make a differential diagnosis [2, 6]. But it should be noted that at present time this method of differential diagnosis is increasingly recognized as ineffective due to the fact that the loss of time, the implementation of radical treatment is not possible because of the disease progression [7, 8]. Positron emission tomography (PET) with 18F-fluorodeoxyglucose (FDG) along with other imaging techniques is successfully used to diagnose lung cancer. FDG PET allows determining accurately the malignant tumors and the majority of benign pulmonary tumors, thereby limiting the use of invasive diagnostic techniques, and in some cases avoiding unnecessary surgical intervention [9–11]. However, the difficulties of differential diagnosis due to the local increase of glycolysis in lung cancer and some non-neoplastic diseases (NND) cause the search of new ways of PET data postprocessing. In recent years researchers are studying the various methodological aspects of PET examination and data processing to find new simple quantitative criteria for alternative to standardized uptake value (SUV) for 18F-FDG [11–14].

The prerequisites for our research were our own PET studies for differential diagnosis of lung cancer and NND, as well as data of the authors from the US, who found SUV increase in patients with lung cancer and NND in proportion to the increase of the focus size of glucose hypermetabolism [15]. The observed relationship was fundamental in introducing a new criterion for the quantitative analysis of PET — SUV/size.

The aim of the investigation is to improve the efficiency of positron emission therapy with 18F-FDG in the differential diagnosis of lung cancer and non-neoplastic diseases by optimizing the quantitative data postprocessing.

Materials and Methods. The data of PET in 347 patients with focal and/or infiltrative lesions of the lungs were analyzed. The distribution of patients according to the morphological diagnosis was as follows.

Malignant tumors — 189, including squamous cell carcinoma — 99, adenocarcinoma — 49, bronhioloalveolar cancer (BAR) — 15, small cell carcinoma of lungs — 19, large cell carcinoma — 2, mucoepidermoid cancer — one case, carcinoid — 4.

For contacts: Tlostanova Marina Sergeevna , tel.: 8(812)596-66-49, +7 911-970-49-22; e-mail: lipex69@yandex.ru

Benign tumors — 65, including chondrogamartoma — 60, hemangiopericytoma — 3, angioleiomyoma — 1, neuroma — 1.

Non-tumoral diseases — 93, including sarcoidosis — 7, tuberculosis — 46, acute pneumonia — 4, chronic (carnification) pneumonia — 2, Wegener's granulomatosis — 2.

The main group consisted of patients with pulmonary adenocarcinoma, squamous cell carcinoma, tuberculosis, and hondrogamartoma.

All the patients underwent comprehensive clinicoradiological examination, which included laboratory diagnosis, bronchoscopy, fluorography or chest X-ray, CT scans of the chest and abdomen that preceded FDG PET. These data were confirmed by the results of morphological analysis or follow-up and revive CT and PET studies.

FDG PET in all patients was performed according to standard protocol including a sequential scanning of neck, chest, abdomen, pelvis in 112.69±1.96 min after FDG injection.

PET data processing was performed by calculating the maximum focus size of FDG uptake and the maximal SUV (SUVmax). SUVmax was calculated automatically as the ratio of tissue radioactivity concentration (MBq/g) at time T, CPET(T) and injected dose (MBq) at the time of injection divided by body weight (kg).

SUVbw=CPET(T) /(Injected dose/Patient's weight)

SUV/size criterion was calculated as the ratio between the SUVmax in the lesion focus and its scintigraphic size.

Statistical processing was performed using MedCalc 11.0.1 for Windows by the methods of parametric and nonparametric statistics. The methods of descriptive statistics included the evaluation of arithmetic mean (M), an average error of mean value (m) — for signs having a continuous distribution; as well as the frequency of occurrence for attributes with discrete values. The critical level of reliability of the statistical null hypothesis (no significant differences or factor effects) assumed to be equal 0.05. To identify the threshold criterion for SUV and SUV/size, as well as calculation of sensitivity and specificity of PET with FDG statistical processing included ROC-analysis (Receiver Operating Characteristic) consisting of characteristic curve tracing, the curve reflecting the results of binary classification.

Results and Discussion. FDG hypermetabolism was revealed in 274 of 347 examined patients by visual analysis of PET data. In 188 out of 189 cases of increased FDG uptake was due to the presence of malignant tumor. FDG PET imaging was false negative in one patient with low-grade carcinoid and false positive in one case with benign tumor (probably because of a high proliferative index of tumor cells). In 85 out of 93 patients with NND increase uptake of FDG was due to inflammation. There were mostly the patients suffering from tuberculosis. In other cases of NND the FDG uptake in the mass lesion was the same as in the intact lung parenchyma.

Revealed FDG uptake foci were different in shape, structure and size. Their maximum size ranged from 1.0 to 6.0 cm (average 3.89±0.14 cm). The mean values of SUVmax, and SUV/size in patients with lung cancer, and NC were originally analyzed regardless the size of the FDG uptake focus: SUV in LC — 8.82±0.44, NND — 308 ±0.24; SUV/size in LC — 2.67±0.12, NND — 0.93±0.07 ($p<0.0001$).

The calculated values in patients with lung cancer were significantly higher than those in patients with NND.

According to the ROC-analysis carried out regardless the size of the FDG uptake focus (threshold SUV>4.3), the sensitivity of PET in the diagnosis of lung cancer was 75.5%, specificity — 80.4%. In the SUV/size ratio threshold >1.28, the sensitivity increased to 83.3% and the specificity of PET slightly decreased up to 76.7% (Fig. 1).

Further processing of PET in patients with lung cancer and NND was performed taking into account the identified relationship between SUVmax, SUV/size ratio and the scintigraphic size of lesion (Fig. 2). Mean values of SUVmax and the SUV/size ratio calculated in the conditions of ranking data due to the size of the FDG uptake focus in patients with lung cancer with any size of tumor were significantly higher than those in patients with NND (Table 1). In-depth analysis of the data showed SUV increase from group to group to be statistically significant ($p<0.05$) in patients with lung cancer. However, in patients with NNDa such significant dependence was not found ($p>0.05$).

The results of ROC-analysis of patients with lung cancer and patients with NND carried out taking into account the size of the FDG uptake focus (Table 2) indicate that when using them with the correction of the focus size, FDG PET sensitivity does not change and varies in the range of 71.4–82.8% . The specificity of FDG PET has also no significant difference and is defined within the range of 83.3–100.0%. But in the second group, when calculating the criterion SUV/size, the specificity of PET was still higher than that of in SUVmax calculation.

Our results mostly agree with those of M. Khalaf et al. [15] but only in the detection of the statistical relationship between the size of the FDG uptake focus and SUVmax.

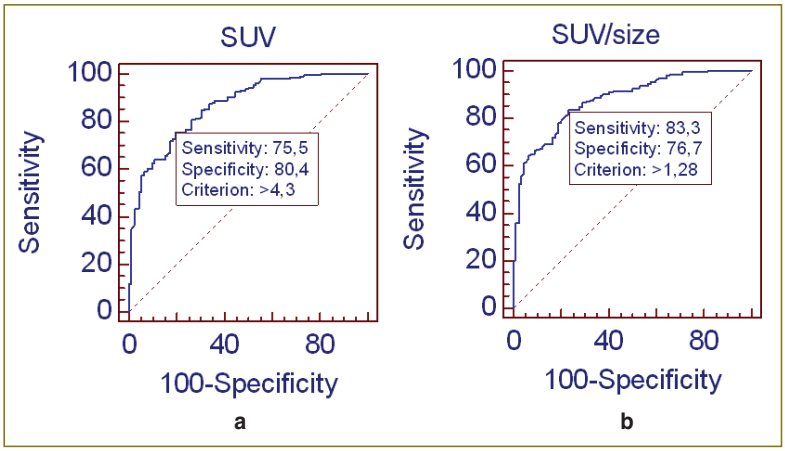

Fig. 1. Sensitivity and specificity of PET with 18F-FDG in the differential diagnosis of lung cancer using SUVmax regardless to the size of the FDG uptake focus (*a*) and SUV/size ratio (*b*) ($p<0.0001$)

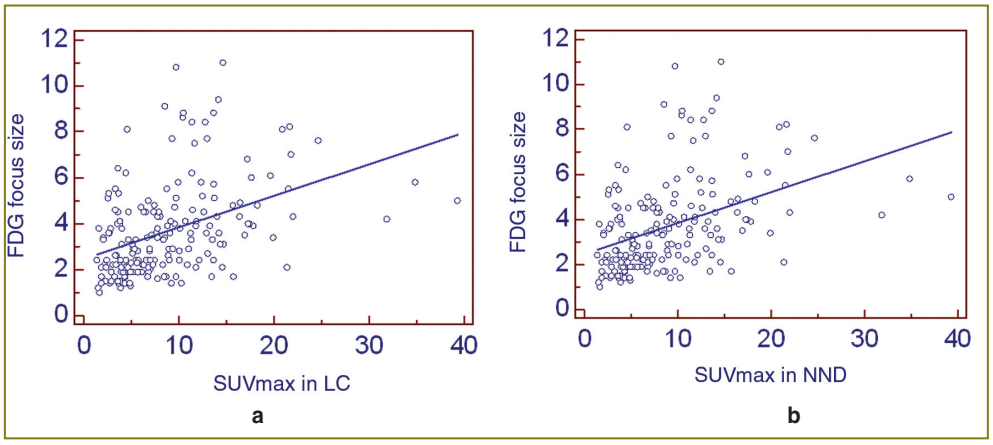

Fig. 2. Regression curve between the size of FDG uptake focus and SUVmax: *a* — in patients with lung cancer (r=0.42; p<0.0001) and *b* — in patients with NND (r=0.43; p<0.0001)

Table 1

Mean values of SUVmax and the SUV/size ratio in patients with LC and NND calculated with due account of the size of the FDG uptake focus (M ± m)

The group number	The lesion size, cm	LC SUV	NND SUV	p	LC SUV/size ratio	NND SUV/size ratio	p
1	1.0–2.0	5.54±0.53	2.20±0.25	<0.0001	3.40±0.32	1.36±0.14	<0.0001
2	2.1–3.0	6.93±0.55	2.68±0.34	<0.0001	2.89±0.25	1.0±0.12	<0.0001
3	3.1–4.0	8.80±0.82	2.50±0.48	<0.0001	2.51±0.22	0.75±0.15	<0.0001
4	4.1–5.0	11.46±1.53	2.72±0.51	0.0001	2.54±0.53	0.61±0.11	0.0002
5	5.1–6.0	11.92±2.33	5.15±0.93	0.0440	2.14±0.40	0.93±0.15	0.0422

Table 2

SUV and SUV/size ratiothresholds, sensitivity and specificity of PET in the diagnosis of lung cancer, calculated with due account of the size of the FDG uptake focus

The group number	Criterion type	Threshold criterion	Sensitivity, %	Specificity, %	p
1	SUV	>3.3	75.7	85.2	<0.0001
	SUV/size ratio	>1.91	81.1	85.2	<0.0001
2	SUV	>4.3	75.5	94.4	<0.0001
	SUV/size ratio	>1.85	73.5	100.0	<0.0001
3	SUV	>4.8	82.5	83.3	<0.0001
	SUV/size ratio	>1.0	82.5	83.3	<0.0001
4	SUV	>5.16	82.8	100.0	<0.0001
	SUV/size ratio	>1.1	82.8	100.0	<0.0001
5	SUV	>8.5	71.4	100.0	0.0106
	SUV/size ratio	>1.42	71.4	100.0	0.0264

Thus, using this SUVmax threshold of 2.5 and three groups with the range of lesion size from 1.1 to 2.0 cm, 2.1–3.0 cm and more than 3.0 cm the authors reported the sensitivity and specificity of PET to be 91 and 47%, 94% and 23%, 100 and 17% respectively. Our results show higher specificity of the method when threshold SUV is rising with the increase of FDG uptake focus size. So, the specificity of PET is 83.3–100.0% when the mass size ranges from 1.0 to 6.0 cm and SUVmax thresholds — from 3.3 to 8.5. Besides, to our opinion, the decrease in SUV threshold from 2.5 to 1.8 for small (6–10 mm) size of lesions seems unreasonable. In this case, according to M. Khalaf et al., the specificity of PET decreases from 36 to 0%. To our opinion, the use of SUV threshold 2.5 as a universal criterion for the differential diagnosis of pulmonary lesions should be recognized as erroneous way leading to a marked decrease in diagnostic accuracy of positron emission tomography.

Conclusion. To improve the efficiency of PET in the differential diagnosis of lung cancer the evaluation of FDG uptake using SUVmax should be made with due account of the size of the lung lesion. At the same time the increase in the lesion size is associated with an increased FDG uptake threshold. According to our results, SUV/size ratio can be an alternative to conventional calculation of the SUVmax.

References

1. Kaneko M. *Vestn Ross Onkol Naucn Centra Im N.N. Blohina RAMN* 2004; 4: 61–62.
2. Rostovtsev M.V., Vazhenin A.V., Lukin A.A. et al. *Vestn Rentgenol Radiol* 2003; 1: 32–35.
3. Gamova E.V., Nudnov N.V. *Vestn Rentgenol Radiol* 2005; 4: 24–28.
4. Gamova E.V., Nudnov N.V. *Vestin Rentgenol Radiol* 2006; 4: 19–23.
5. Khoruzhik S.A., Bogushevich E.V., Sprindzhuk M.V. et al. *Vopr Onkol* 2011; 57(1): 25–35.
6. Naruke Ts. *Vestn Ross Onkol Naucn Centra Im N.N. Blohina RAMN* 2004; 4: 69–73.
7. Kharchenko V.P., Chernichenko N.V., Gvarishvili A.A. et al. *Vopr Onkol* 2009; 55(4): 459–462.

8. Barchuk A.A., Arsen'ev A.I., Levchenko E.V. *Vopr Onkol* 2009; 55(1): 7–14.
9. Nomori Kh., Vatanabe K., Otsuka T. et al. *Vestn Ross Onkol Naucn Centra Im N.N. Blohina RAMN* 2004; 4: 74–81.
10. Mavi A., Lakhani P., Hongming Z. Fluorodeoxyglucose-PET in characterizing solitary pulmonary nodules, assessing pleural diseases, and the initial staging, restaging, therapy planning, and monitoring response of lung cancer. *Radiol Clin N Am* 2005; 43: 1–21.
11. Cloran F.G., Banks K.P., Song W.S. et al. *Lung Cancer* 2009 Jun 24; 24(1): 65–68.
12. Chen C., Lee B., Yao W. Dual-Phase ^{18}F-FDG PET in the diagnosis of pulmonary nodules with an initial standard uptake value less than 2.5. *AJR* 2008; 191: 475–479.
13. Hashimoto Y., Tsujikawa T., Kondo C. Accuracy of PET for diagnosis of solid pulmonary lesions with 18F-FDG uptake below the standardized uptake value of 2.5. *J Nucl Med* 2006 Mar; 47(3): 426–431.
14. Aslanidi I.P., Mukhortova O.V., Shurupova I.V. et al. *Med Radiol Radiac Bezop* 2010; 55: 46–57.
15. Khalaf M., Abdel-Nabi H., Baker J., Shao Y., Lamonica D., Gona J. Relation between nodule size and 18F-FDG-PET SUV for malignant and benign pulmonary nodules. *J Hematol Oncol* 2008 Sep; 1: 13.