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Development of models of „virtual patients“ for simulation tests of the SPECT/CT method

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Received July 10, 2024
Revised October 14, 2024
Accepted October 21, 2024.

A relevant task of the single-photon emission computer tomography (SPECT) combined with computer tomography (CT) is development of quantitative assessment of generated images of pathological regions and optimization of a protocol of the procedure for patient examination using this method. Solution of these tasks requires a great number of the studies. Development of the mathematical modeling method is a relevant task in the field of nuclear medicine concerning ethical limitations due to a radiation load. In order to solve this task, it is necessary to create the models of the „virtual patients“, which describe distribution of a delivered radiopharmaceutical in the organs and the tissues and its accumulation in pathological foci. The present paper proposes approaches for creating the mathematical models of the patients (phantoms) to study diagnostics accuracy of the SPECT method combined with computer tomography (SPECT/CT). Two approaches for creating the models of the„virtual patients“ have been developed. The first approach Constructive Solid Geometry (CSG) based on the equations of analytical geometry constructs models of an average patient. The second approach creates the so-called „digital twins“ based on segmentation of clinical SPECT/CT images of real patients. The CSG phantoms were successfully applied in the simulation modelling directed at the studies of and solving the general problems of SPECT/CT visualization. These problems include the studies of optimum parameters of the data collection protocol and a problem of a false apical defect in the nuclear cardiology.The „digital twins“ can the most accurately model clinical cases and evaluate errors on reconstructed images. Both the approaches to creation of the models of the „virtual patients“ have their own niche of research. The problems to be solved by a large number of tests with varying several anatomical parameters (for example, a patient habitus, angular orientation, the thickness of the walls of and the size of myocardium of left ventricle) are the most suitably studied using the geometrical CSG models.The „digital twins“ shall be used when studying real clinical cases as well as for verification of solutions and conclusions obtained in the studies using the CSG models.

Keywords: phantom, single-photon emission computer tomography, computer tomography, modeling.

DOI: 10.61011/TP.2025.04.61219.225-24

Introduction

The mathematical modeling becomes an important field of modern medical science. The models and the methods developed in mathematical physics and computational mathematics are successfully applied for describing phenomena and processes in a human body which obey laws of physics. A large variety and complexity of these processes still make it difficult to create the integrated human model. The modeling of the human usually include distinguishing and studying a specific phenomenon and, depending on a posed problem, using the models with different level of description (molecular, cellular and organic). The literature provides the mathematical models which describe an anatomical human structure with various morphological characteristics of biological tissues [1–3] as well as the models which describe mechanics of heart motion and respiratory excursion [4–6], blood dynamics [7,8], kinetics of substance distribution (including drugs) in the body [9], dynamics of pathological processes [10], etc.

Many tasks of medicine modeling require mathematical representation of anatomy of the human body or its specific parts. The digital models of anatomy of the human body (computational phantoms) are used when modeling physiological processes in the human body and diagnostic studies of patients, when preparing for surgical operations as well as in radiation therapy and radionuclide therapy [1–3]. The computational phantoms are created using various mathematical approaches and methods of computer engineering. The earlier works created anthropomorphic phantoms based on combinations of geometrical figures described by equations of solid geometry. The English publications refer to this method as Constructive Solid Geometry (CSG). In the 1960s, in the USA the first phantom was created under the name MIRD (Medical Internal Radiation Dose) including 22 organs [11]. Later, in the 80s, using the CSG technology, the FRG had created the gender-distinguished phantoms ADAM and EVA close in their structure to the MIRD phantom [12]. The models of this type describe the anatomical organs just very schematically and therefore are called stylized phantoms. The 1990s saw active development of nuclear medicine visualization methods - the single-photon emission computer tomography (SPECT) and the positron emission tomography (PET). It required the phantoms created for medical research with internal radiation sources. Based on the MIRD model, in these years in the USA's Northern Caroline University has developed the first phantom specifically designed for nuclear cardiology studies MCAT (Mathematical Cardiac-Torso) [13,14]. In Russia, the MSU's Skobeltsyn Institute of Nuclear Physics (Moscow) developed the phantom including the skeleton models and 19 internal organs [15]. Externally, this phantom was very close to the MIRD phantom. The Institute of Theoretical and Applied Mechanics (Novosibirsk) developed the mathematical phantoms for computer modeling in the field of nuclear medicine [16,17]. These phantoms were characterized by a higher level of anatomical realism as compared to the MIRD-model-based phantoms.

With developing of technologies of computer tomography (CT) and magnetic resonance imaging (MRI), for phantom creation a new method started to be applied by being based on clinical CT and MRI digital images. In order to create the 3*D*-phantoms, the CT and MRI data of population of patients selected by gender, age and weight are segmented, and statistically weighed sizes and organ contours are determined and then the tissue properties required for research are assigned to these objects. These anatomical models are named „voxel phantoms". One of the first developers of the voxel phantoms in the world was the group led by the professor Maria Zankl in the Helmholtz Munich — German Research Center for Environmental Health [18,19]. It included the name voxel phantoms DONNA, FRANK, HELGA, IRENE, GOLEM, LAURA. In Russia, in the years 2010–2012 the Nuclear Power Engineering Institute (Obninsk) has created the voxel phantoms of specific parts of the human body: a head, a spinal column, human legs [20].

The similar approach to phantom creation was developed in the USA under support of National Health Institute based on photographs of slices of the frozen human body using the high-resolution optics (Visible Human Project — VHP) [21,22]. This project had resulted in generally available three-dimensional images of the male and the female human body. In Russia, the VHP phantoms were used in the studies in the group led by Yu. V. Vasilevskyi [23].

Another method of constructing the computational phantoms started in the beginning of the 2000's in the USA using the computer graphics technology Boundary REPresentation (BREP). These phantoms are created based on the method of non-uniform rational B-splines (NURBS). In the English publications, the human models created by this method are named BREPphantoms or NURBS-based phantoms [24]. The phantoms were built based on the CT data segmentation. Then the organ boundaries were determined by a set of control points, on which a smooth surface was stretched using the splines. One of the most demanded phantom of this class is the XCAT phantom (eXtended CArdiac-Torso) [25] for virtual computer experiments in various medical fields. In Russia, the phantoms of this type have not been developed.

Until recently, all the above-mentioned methods of phantom construction (except for VHP) were aimed at creating population-averaged computational phantoms. Usually, the created phantoms were those of healthy patients. However, the studies in the field of tumor visualization, preparing for surgical operations as well as tasks of the radionuclide therapy require personalized phantoms, which realistically represent specific patients with pathologies in order to reflect anatomical variations of real clinical cases and scenarios. Recently, more and more works appear to create personalized phantoms — „digital twins", which describe anatomical structures based on the CT and MRI data of real patients. However, in the field of nuclear medicine the phantom shall describe distribution of the delivered radiopharmaceutical which usually do not coincide with the anatomical structures. Virtually, no such work exists.

These phantoms are necessitated by development of the SPECT/CT method. Since appearing in clinics in the middle of 90's to about the year 2010 this diagnostical method had been used for determining presence or absence of pathological foci without their quantitative assessment. The quantitative assessment is very important in oncology since it makes it possible to differentiate malignant and benign formations and to dynamically assess efficiency of delivered therapy. Development of mathematical processing software and measurement technologies in the SPECT method resulted in possibility of the quantitative assessment. Another important task is optimization of the examination protocol in order to reduce a procedure time of patient immobilization. However, solution of these tasks requires a great number of the studies. The clinical methods are limited in such studies due to radiation load and no reference for evaluating accuracy of the obtained images. The ideal method for the studies of accuracy of the quantitative assessment and protocol optimization is the mathematical simulation modeling using the digital models of patients. In recent years, the Institute of Theoretical and Applied Mechanics named after S.A Khristianovich and Laboratory of modeling in nuclear medicine of Novosibirsk State University have been developing the software package (SP) „Virtual platform for simulation tests of the SPECT/CT method". This SP include the module „Virtual Patient", which is based on creation of mathematical digital models of patients. Ten years have been spent on the way from creation of the CSG phantoms based on analytical geometry equations to the personalized „digital twins" of real patients. The present paper proposes approaches for creating the mathematical models of the patients (phantoms) to study diagnostics accuracy of the single-photon emission computer tomography method combined with the computer tomography (SPECT/CT). The present work is aimed at presenting various approaches to creation of the mathematical models of patients (phantoms) and demonstrating

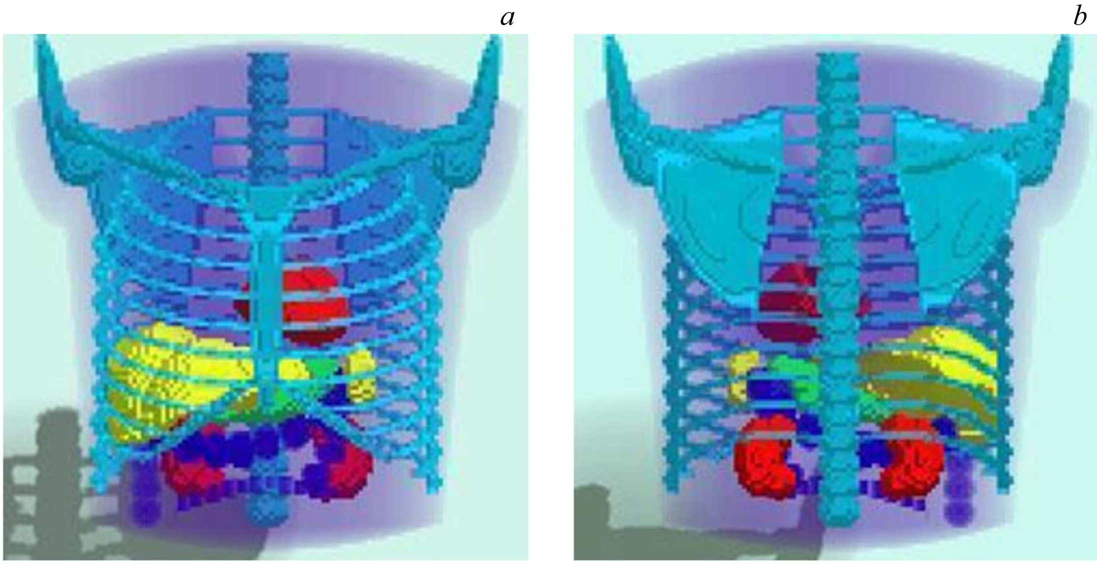

Figure 1. Three-dimensional MMT phantom simulating the anatomical structure of the average male patient in the position with hands up. Anterior (*a*), posterior (*b*).

their successful application in the simulation tests of the SPECT/CT method, that are carried out with the clinical studies of the real patients.

1. Methods

1.1. Specifics of model construction of the „virtual patients" (phantoms) in nuclear medicine

During the diagnostics studies by the SPECT method, the dedicated radiopharmaceutical (RP) is delivered to the patient, which is selectively accumulated (or, vice versa, is not selectively accumulated) in the pathological foci. In connection with development of the radionuclide therapy, the relevant task is accurate quantitative assessment of accumulated activity in the pathological foci. The studies aimed at solving this task are carried out mainly using standardized real NEMA phantoms including 6 spheres of a different diameter which simulate tumor lesions [26]. However, performance of such clinical studies with real phantoms is limited due to the radiation exposure of the researchers and the high cost of such experiments. Moreover, the NEMA phantom foci are represented by uniform RP distribution, whereas the majority of real injuries is heterogeneous. That is why the nuclear medicine has a relevant task of developing the method of simulation mathematical modeling.

In our studies, we have developed the following general diagram of constructing the phantom for modeling the SPECT/CT method. First of all, it includes creation of a basic anatomical phantom, which describes the anatomical structure of the patient. RP accumulation in the injury foci usually does not coincides with the anatomical structures. This is why in includes additional construction of the model distribution of the delivered RP in the organs and tissues which is called an „activity map". Besides, for calculation of transfer of gamma radiation in the biological tissue of a different density, a3*D*-„attenuation map" is created to describe attenuation coefficients for gamma quanta with different energy values. The construction of the „activity map" and the „attenuation map" based on the basic anatomical phantom is specifics of construction of the computational phantoms for studies in the field of diagnostics nuclear medicine unlike CT and MRI. When developing the software package (SP) „Virtual platform for simulation tests of the SPECT/CT method" it has used two approaches to creation of the models of the „virtual patients". The first approach is based on the CSG technology, while the second one is based on segmentation of the clinical SPECT/CT images using the software package 3*D*-Slicer [27]. Actually, both the cases had the digital voxel phantoms created. The difference is that in the first approach surfaces (boundaries) separating the anatomical structures with different characteristics have been constructed based on the analytical geometry equations. In the second approach, the boundaries between the organs have been defined using methods of segmentation of the clinical SPECT/CT images.

1.2. Development of the models of the „virtual patients" based on the CGS technology and their application in the studies

Two basic mathematical CSG models of the „virtual patients" are created using the analytical geometry equations. The first model, which is the mathematical model of torso (MMT) of Fig. 1, describes the organs of the rib cage

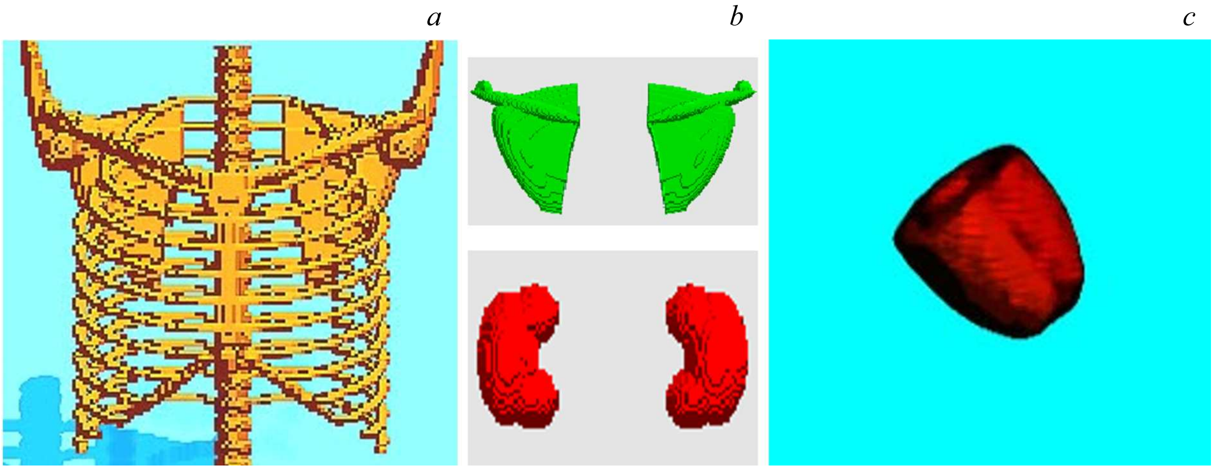

Figure 2. View of specific anatomical structures of the MMT phantom which are constructed based on the analytical geometry equations (the CSG method). *a* — the bone system of the rib cage, *b* — the scapulas (above), the kidneys (below), *c* — the myocardium of the left and right ventricles of the heart

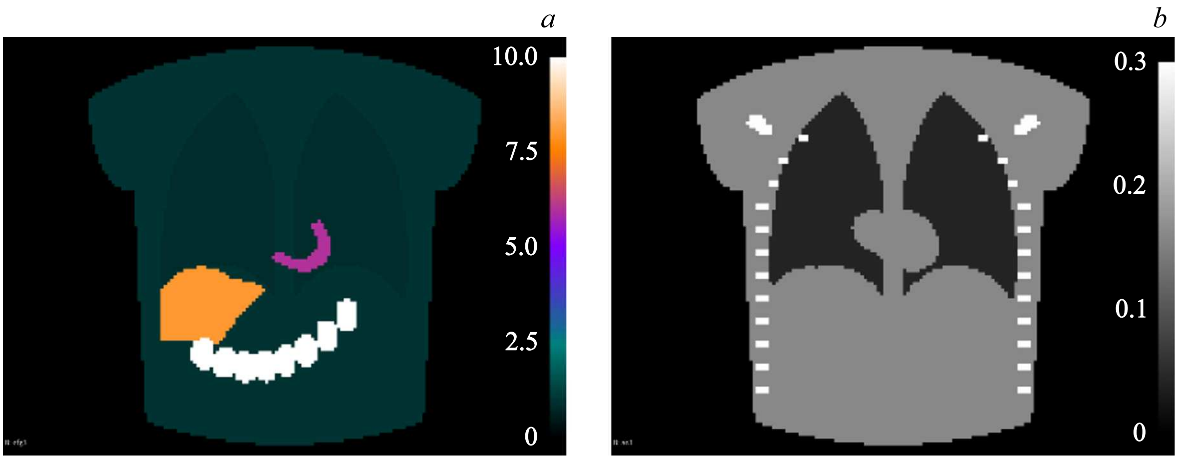

Figure 3. coronary slice of the „activity map“, which describes 3*D*-distribution of RP 99mTc-MIBI in the MMT phantom (*a*), the coronary slice of the „attenuation map“ of the MMT phantom (*b*).

of the average male patient in a position with hands up. The anatomical structures of this phantom were constructed using the Constructive Solid Geometry (CSG) method, which is based on using the algebraic equation of the first and second orders in discrete representation on the grid $128 \times 128 \times 128$ in the Cartesian coordinate system. The MMT model has been created for the studies in the field nuclear cardiology, so it was important to provide correct spatial position of and angular orientation of a long axis of the heart left ventricle (LV). The anatomical parameters, such as the organ sizes, their position and orientation were determined by means of the data from Anatomy Atlas [28]. Fig. 2 shows some segment of the MMT phantom: a part of the bone system, the scapulas, the heart and the kidneys.

An important feature of modeling in nuclear medicine is that it is necessary to create the „activity map“ and the „attenuation map“ of the basic phantom. At the same time, it is necessary to take into account characteristics and properties of a specific RP. Fig. 3 shows the slices of three-dimensional maps: the „activity map“, which describes distribution of RP 99mTc-MIBI and the „attenuation map“, as generated based on the MMT model. The „activity map“ has been created using the clinical SPECT data from patient examination. Figure 4 exemplifies some of clinical images used when constructing the MMT phantom, which are presented by by National Medical Research Center (NMRC) for Cardiology named after Chazov. The arrows show average values of the activity in the units pulse/voxel in the LV myocardium (*a*), the liver (*b*) and in the adipose tissue (*c*). These values depend on the delivered RP dose, the time of data collection at each rotational angle of the gamma camera. So, when creating the „activity map“ relative dimensionless values of activity were given. For the MMT phantom, these data are given in the work [29]. For the obtained „activity map“ the projection data are calculated so as the total number of gamma quanta recorded

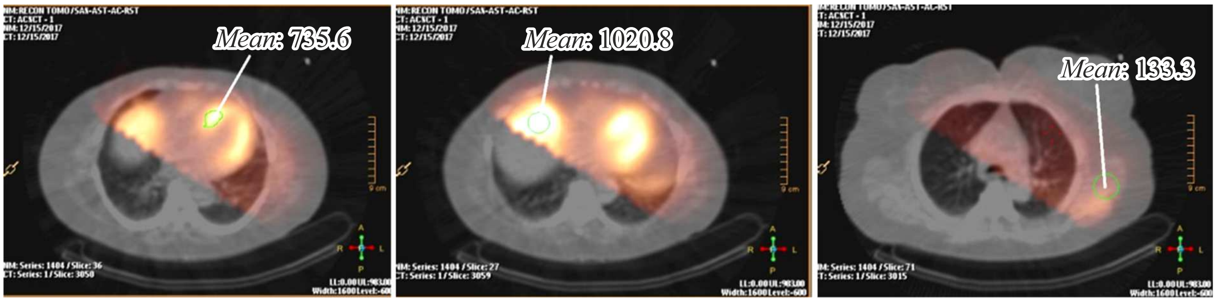

Figure 4. Clinical SPECT/CT images They include axial slices with the specified values of accumulated activity in units pulse/voxel in the LV myocardium (*a*), the liver (*b*) and in the adipose tissue (*c*). The clinical images are provided by Chazov Cardiology Center (Moscow). The images are obtained on Philips BrightView XCT SPECT/CT hybrid system.

during modeling is approximately equal to the total number of gamma quanta recorded in the clinical examination. Thus, the modeling process gets a value of Poisson noise equal to the clinical case.

Creation of the „attenuation map“ in the MMT phantom has distinguished four media: air, bones, soft tissue and adipose tissues. The values of the attenuation coefficients in these media for gamma quanta with the energy of 140 keV, emitted by the radionuclide 99mTc, were calculated based on the composition of materials taken from the report ICRU-44 [30]. The attenuation coefficients for these materials were calculated by interpolation of tables based on NIST XCOM [31]. The bone structures attenuation coefficient was calculated using the data for the material B 100 Bone Equivalent Plastic, since its attenuation coefficient is selected so as to match the average attenuation coefficient of the main bone components - a cortical and a cancellous part The lungs were modeled as Lung Tissue with the density equal to the air density. It is the „activity map“ and the „attenuation map“ that represent the „virtual patient“ in simulation modeling of the examination procedure of the SPECT/CT method. All the studies in the field of nuclear cardiology were performed together with radiologist doctors from NMRS named after the academician E.I. Chazov [32,33].

The second mode, the Mathematical Model of the whole Body (MMB) of the „virtual patient “ in full height with hands down on the discrete grid $128 \times 128 \times 384$. This model is shown in Fig. 5, *a*. Fig. 5, *b* shows the model of the skeleton part of the MMB phantom. It should be noted that the CSG method can modify the created phantoms for modeling the patients with another anatomical structure. Fig. 6, *a* exemplifies the clinical plane image of the adolescent bone system, as obtained by the scintigraphic method. This clinical case was modeled by reconstructing the skeleton of the „adult phantom“ of Fig. 5, *b* and shown in Fig. 6, *b*. It is clear that there is substantial difference in the form of the rib chest between Fig. 5, *b* and Fig. 6, *b*, which correspond to the adult and the adolescent. It is quite easy to make such anatomical variations in the phantoms that are built based on the CSG method. It

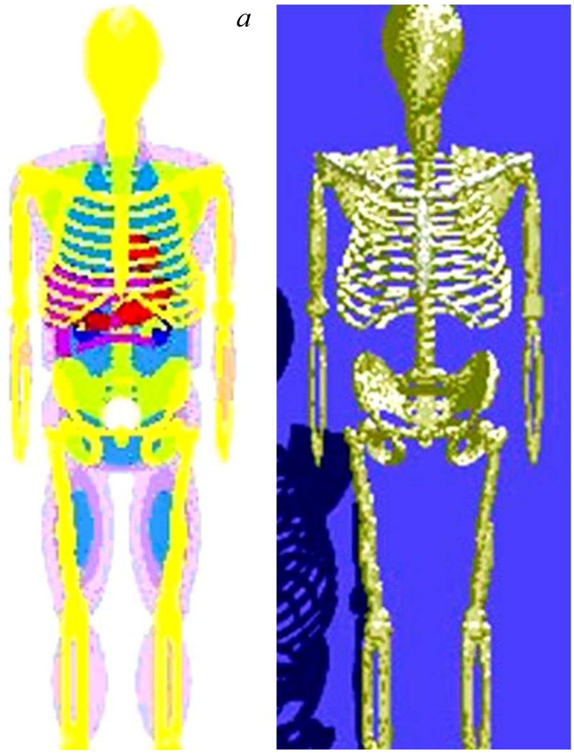

Figure 5. Three-dimensional MMB phantom constructed based on the analytical geometry equations — front view (*a*), the bone system of the MMB phantom (*b*).

is necessary to change the coefficients in the analytical geometry equations that describe the organs and the bones of such phantoms. In the work [32], when studying the cause of occurrence of the false apical defect on the clinical SPECT/CT images in the MMT phantom, the position, the size and the thickness of the walls of the LV myocardium were varied. The results of these studies are presented in the work [32]. The MMT and MMB phantoms were verified by comparing with the clinical data from Chazov Cardiology Center and National Medical Research Center (NMRC) named after the academician E.N. Meshalkin.

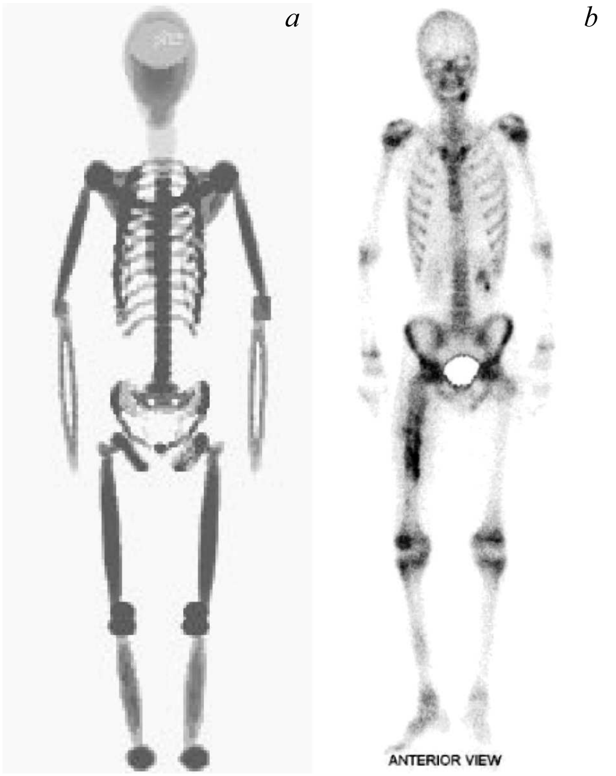

Figure 6. Clinical plane image of the adolescent bone system as obtained in NMRC named after the academician E.N. Meshalkin via the scintigraphic method (*b*); for modeling of this clinical case the skeleton of the „adult phantom" of Fig. 5, *a* was transformed into the „adolescent skeleton" (*a*).

These phantoms were successfully used for studying general medical problems. However, the tasks of the quantitative SPECT and radionuclide therapy require the personalized phantoms, which realistically represent specific patients in order to reflect the anatomical variations of the real clinical cases and scenarios.

1.3. Development of personalized models of the „virtual patients" based on segmentation of the clinical images and their application in the studies

The realistic simulation studies in the diagnostics nuclear medicine require representative models of the patients with pathologies. Section 1.3 contains the method of creation of personalized computational phantoms — the „digital twins" of the real patients. The method is based on using the software package 3*D* Slicer, which is publicly available and widely used by researcher in the field of medicine [27]. 3*D* Slicer makes it possible to operate directly the clinical data in the DICOM format. In our studies we manually segment the SPECT/CT images by means of the Segment Editor module. The image segmentation is a method of dividing the digital image into separate subgroups which are called image segments. Then, the same value (label) is assigned to all the voxels belonging to the same segment. The most useful tools of this stage are usual means of contouring (paint, erase), interlayer filling (fill between slices) and of evening (smoothing). After that, the highlighted segments can be used by the mask volume tool for filling the images with the given values, for example, for creating the 3*D* „attenuation map" or the 3*D* „RP activity map".

The basic anatomical model was created using the CT data. The CT images are a three-dimensional matrix of Hounsfield units (HU) which denote the coefficient of attenuation of X-ray radiation in a substance. For air $HUP = -1000$, for water $HU = 0$. The soft tissues and the bones have HU above 0, while the adipose tissues can have the HU of-150 and higher. The Threshold tool is designed to specify the lower and upper threshold values of HU, so, various structures can be distinguished by means of it. In our studies, using the Threshold tool, we usually distinguished the lungs, the bones, the adipose and soft tissues. Based on this model, using the mask volume module, we have generated the „attenuation map". The „activity map " was created by means of the SPECT images. The main problem was determination of boundaries of the injury foci and specification of their nonuniformity. Section 1.3 contains the „digital twins" of the patients as developed for the studies within the software package „Virtual platform for simulation tests of the SPECT/CT method".

The „digital twin" of the organs of the rib cage of the patient with peripherical squamous-cell cancer of the upper portion of the right lung was created based on the clinical data provided by NMRS named after the academician E.N. Meshalkin (Novosibirsk). In a department of NMRC named after the academician E.N. Meshalkin, the patient diagnosed with „Peripherical cancer of the upper portion of the right lung T3N1Mo IIIAst. DN 2" was treated by SPECT/CT at 600 MBq with 99mTc-MIBI. The study has been performed on the GE Discovery NM/CT 670 appliance with the matrix parameters 128×128 pixels, 30 seconds per frame, revolution of each detector by 180°. Fig. 7, *a* shows the basic voxel phantom of this patient generated based on the CT images. In the upper portion of the right lungs, there is a tumor lesion in blue color. The phantom is specified on the grid $128 \times 128 \times 128$ in the Cartesian coordinate system. The size of the voxel side in the transverse section plane was 4.4 mm. The digital „activity map" of this patient was created by means of the clinical SPECT images. The values of accumulated activity in the units pulse/voxel were determined from the clinical reconstructed images of the real patient in the planes (axial, coronal, sagittal) as average values across the highlighted area (organ). However, the values of activity and the ratios between the accumulation values in the various organs (in particular, the ratio „tumor/background") in the clinical SPECT images can mismatch the true ratios of accumulation. This is due to reconstruction errors, especially, of small foci with RP accumulation surges. The errors result from limitation

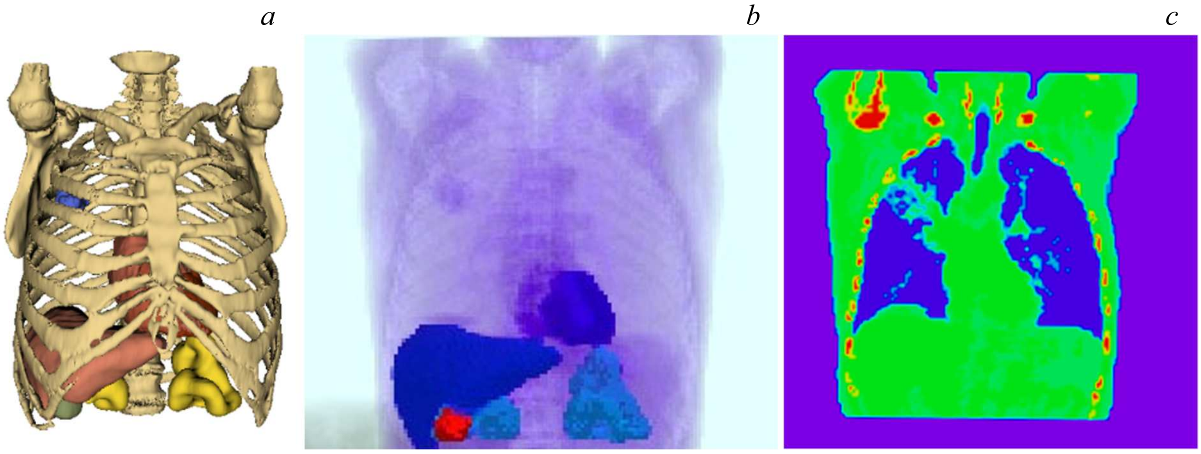

Figure 7. The personalized basic phantom means the „virtual patient“ that is created based on the SPECT/CT clinical data from scanning the real patient with tumor injury in an upper portion of the right lung. For clarity, the soft tissues and the lungs are deleted on this image (*a*). The „activity map“ which describes distribution of the pharmaceutical 99mTc-MIBI in the basic phantom (*b*). The coronary slice of the three-dimensional „attenuation map“ (*c*). The clinical SPECT/CT images are provided by NMRC named after the academician E.N. Meshalkin (Novosibirsk).

of modern algorithms of image reconstruction as well as absence of corrections for RP gamma radiation scattering in the body tissues and for effects of a partial volume and dead time of pulse recording. In this respect, it is more correct to focus on the clinical measured „raw“ data. That is why from the „activity map“ of the phantom the „raw“ data were calculated by the Monte Carlo method, and they were compared to the clinical „raw“ data obtained from the real patient.

The Monte Carlo method implies physically correct modeling of a projection data collection procedure since it generates a history of gamma quanta based on the random number generator. The modeling by the Monte Carlo method takes into account all main probabalistic processes that occur with the gamma quantum, starting from the time and the direction of its emittance and ending with processes of scattering, absorption and recording by the detector. From the generated history of the set of gamma quanta, the projection data are formed by statistical processing, which are now considered to be the most approximate to the clinical tests. More details about the application of the Monte Carlo method are given in the work [29].

Based on the results of comparison of the clinical and modeled projection data, the „activity map“ was correspondingly corrected. The „raw“ were mainly used for such estimates, since they have not reconstruction errors. The value of such corrections was evaluated by the average value of activity in the interest regions and heavily depended on the size of these regions. Thus, for the tumor formation in the upper portion of the right lung, on the phantom presented in the work [34] and in Fig. 7, *a*, we had to increase the activity in ~ 5 times. But in large regions, like the liver, usually no correction is needed.

Fig. 7, *b* shows the „activity map“ with the tumor lesion in the upper portion of the right lung. In order to create the „attenuation map“ 5 types of the structures were selected in the basic digital phantom: air, lungs, bones, soft and adipose tissues. Fig. 7, *c* shows the coronary slice of the three-dimensional „attenuation map“. The studies with application of this phantom and the obtained results are described in the work [34].

The next „digital twin“ was developed for the case of the patient with injury of the bone system. Fig. 8 shows the basic anatomical phantom, its three-dimensional „activity map“ and one of the coronary slices of the „attenuation map“. This phantom was created based on the clinical data provided by NMRC named after the academician E.N. Meshalkin. The patient was treated with SPECT/CT with RP pyrfotech — 99mTc. After intravascular injection, this pharmaceutical is actively absorbed in the bones with accumulation in foci of pathological changes of the skeleton, so almost no soft tissue is visible on the image of the three-dimensional „activity map“ (Fig. 8, *b*). The first preliminary results of modeling showed good compliance between the clinically-reconstructed SPECT images of the real patient and the images obtained in the imitation modeling using the developed phantom. Fig. 9 provides comparison of two coronary sections of the reconstructed images obtained in the clinical SPECT/CT studies and the virtual tests.

Creation of the models of the „virtual patients“ in pediatrics is of great importance for studying problems related to quantitative estimates of accumulated activity in the foci during SPECT examination with 123I-MIBG as well as for calculation of absorbed doses. Using the above-described technology, based on the software package 3*D* Slicer the „digital twin“ of the 4 years old patient was created. The clinical data are provided by Dmitry Rogachev National Medical Research Center of Pediatric Hematology, Oncology and

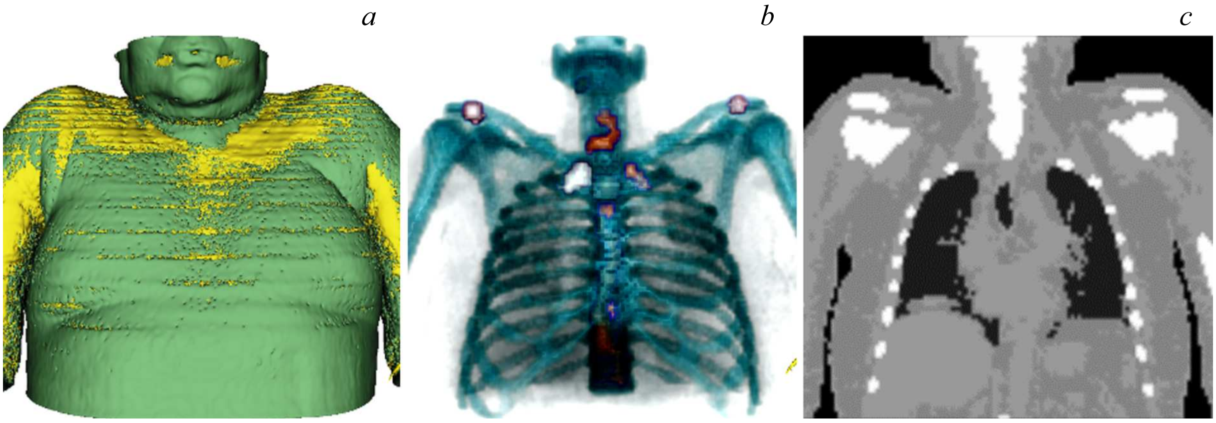

Figure 8. „Digital twin“ of the patient with metastatic injury of the bone system. Appearance of the basic anatomical phantom is shown (*a*), so is its three-dimensional „activity map“, describing distribution of the pyrfotech pharmaceutical 99mTc (*b*), so is one of the coronary slices of the „attenuation map“ (*c*). The clinical SPECT/CT images are provided by NMRC named after the academician E.N. Meshalkin (Novosibirsk).

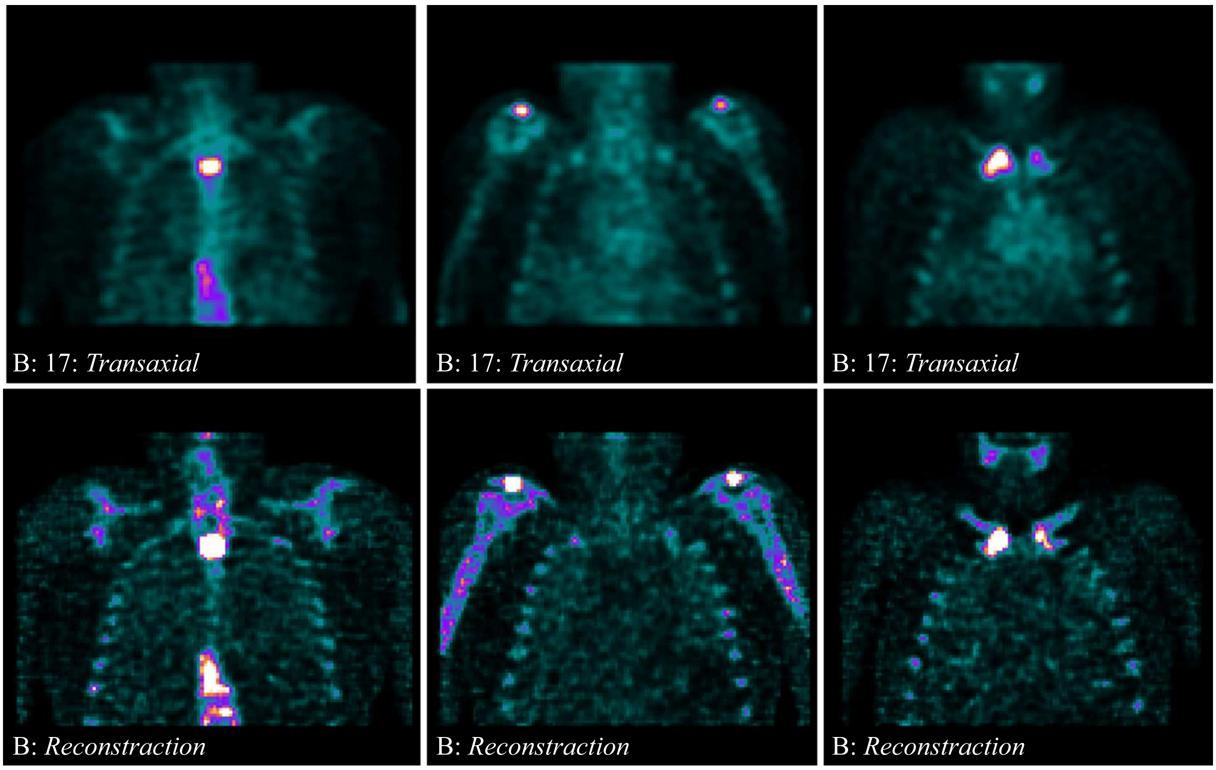

Figure 9. Comparison of the reconstructed images obtained in the clinical SPECT/CT studies and the virtual tests. The clinical images in three highlighted coronary sections are shown in the upper row, while the results of modeling in the same sections are shown in the lower row.

Immunology; Fig. 10 shows the „activity map“ describes distribution of the pharmaceutical 123I-MIBG in the organs of the „virtual patient“ and its „attenuation map“. Fig. 11 shows comparison of the images in the same coronary section that are obtained during clinical examination of the real patient and when reconstructing the raw data calculated for the „virtual patient“.

2. Results and discussion

The modern trend in development of the SPECT/CT methods consists of transition from qualitative to quantitative assessments of accumulated activities in injury foci. The quantitative approach becomes a powerful tool in assessment of a disease stage and patient management. However, for transition to the quantitative SPECT the

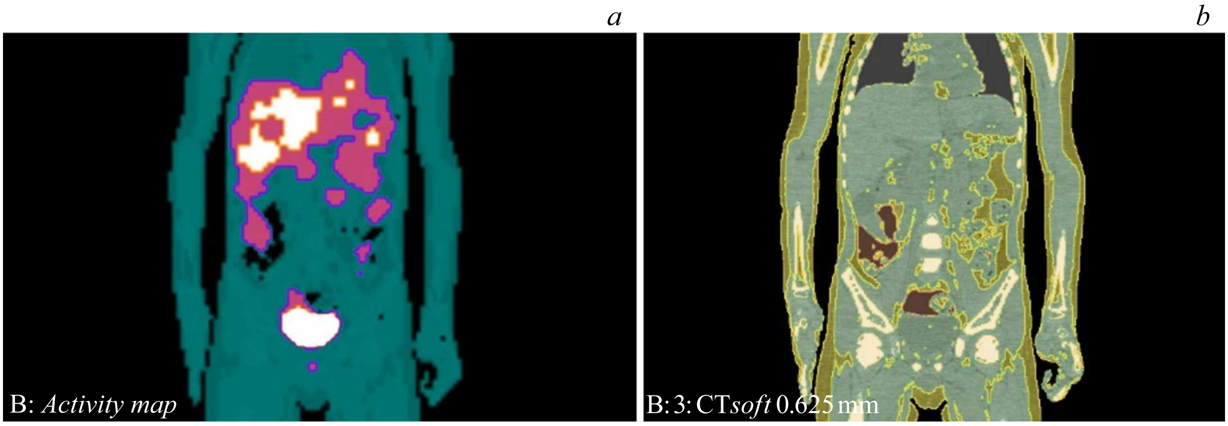

Figure 10. „Digital twin“ of the patient in nuclear pediatrics. It shows the coronary slice of the three-dimensional „activity map“, which describes distribution of the pharmaceutical 123I-MIBG (*a*) and the coronary slice of the „attenuation map“ (*b*). The clinical SPECT/CT images are provided by Dmitry Rogachev National Medical Research Center of Pediatric Hematology, Oncology and Immunology (Moscow).

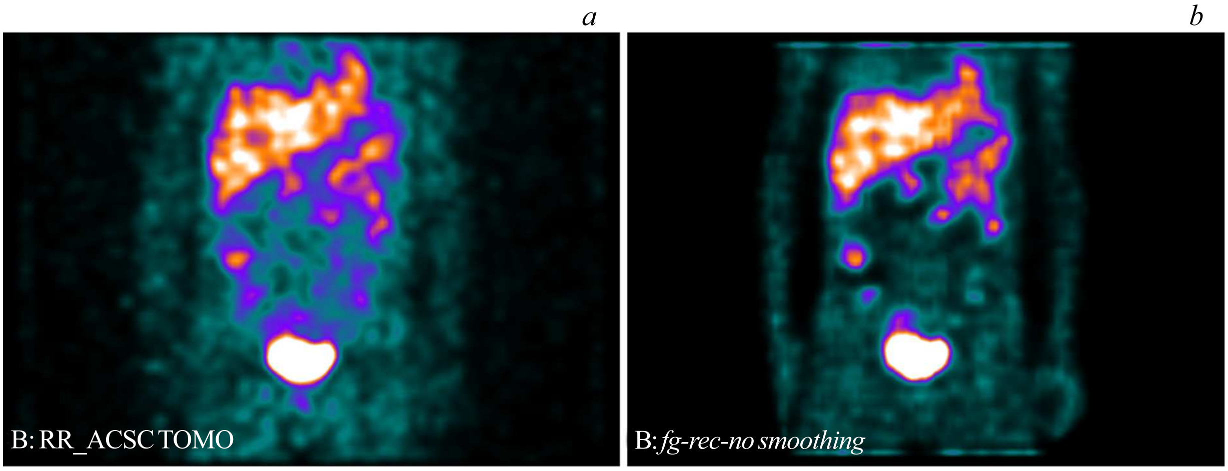

Figure 11. Comparison of the reconstructed images obtained in the clinical SPECT/CT studies and the virtual tests. The clinical image in the highlighted coronary section (*a*), the results of modeling in the same section (*b*).

standard calibration of the SPECT system is insufficient for a specific radionuclide. There are mathematical problems of reconstruction algorithms, which are slightly discussed in the literature, but without their solution it is impossible to speak of the diagnostics accuracy of the SPECT quantitative method. One of the unsolved problems is edge artefacts on the images of pathological foci. The literature analysis shows that nowadays the studies of these problems are primarily performed using real, standardized NEMA phantoms [35]. The phantom includes 6 spheres of a various diameter simulating tumor lesions. However, this phantom does not reflect the variety of different clinical cases and heterogeneity of the foci, whereas performance of the measurements is limited due to radiation load on researchers and high cost. The mathematical modeling method is a promising alternative to such experiments. In virtual tests, the real patient is replaced by its mathematical model. The advantage of the simulation studies as compared to the clinical tests is that there is a phantom with the known „activity map“, which is a reference for quantitative assessment of the reconstructed images.

The present work presents two approaches to creation of the patient model:

1) development of programs for constructing the population phantoms using the analytical geometry equations (CSG technologies);

2) development of the personalized models — „digital twins“ — based on segmentation of the clinical data of the real patients using the software package 3*D* Slicer.

Both types of the phantoms have been successfully tested in the simulation modeling close to the clinical practice. It should be noted that the results of the computational „virtual tests“ under the clinical protocol have demonstrated the same artefacts (errors) that were observed on the clinical images. The work [32] has studied the false apical defect using the MMT phantom shown in Fig. 1–3. The false apical defect on the LV myocardium images is observed in about 60% of the patients. Then there is a question: on what its origin depends? There were about a thousand (!) numerical experiments which simulated a procedure of myocardium perfusion examination by the SPECT/CT method. In doing so, the sizes and angular orientation of LV, the thickness of its wall and the patient habit were varied. These studies are predominated by the CGS phantoms, which can easily vary the anatomical parameter by changing coefficients in the respective equations. The work [33] has used the MMT phantom to evaluate the diagnostics accuracy of various approaches of the „polar map" methodology to evaluation of the LV myocardium state in the nuclear cardiology. The results and the estimates obtained in the simulation modeling corresponded to conclusions of leading clinicians in this field of the studies. The CSG-based mathematical phantom was used in the work [36] for simulation modeling of the diagnostics studies by the SPECT/CT method for single tumor lesions in the nuclear oncology. The modeling results have revealed occurrence of the edge artefacts similar to those which were observed on the clinical SPECT images of the tumor lesions.

The „digital twins" such as those of Fig. 7 allow most accurately model the clinical cases and evaluate errors on the reconstructed images, but it is almost impossible to vary the sizes and the position of the organs in them. Further methodology for phantom operation can be built up as follows: the general problems are studied using the averaged CGS phantoms, while the results and conclusions obtained in these studies must be verified on the clinical cases using the „digital twins".

Conclusion

Due to development of the image texture analysis methods and engineering of software packages of segmentation of medical images, in recent year the medicine field has seen a trend of creation of the personalized phantoms — the „digital twins" — based on the CT and MRI data of the real patients. These phantoms describe the anatomical structures with various morphological properties. The model of the „virtual patients" in the nuclear medicine significantly differ from the anatomical models of CT and MRI. The specific of these phantoms is that it is necessary to create the „activity map", which does not coincide with the anatomical structure, as well as the „attenuation map". The present work has developed two approaches to creation of the models of the „virtual patients" for performing virtual computer tests of visualization by the SPECT/CT method. The first approach represents improved CSG phantoms, which demonstrated good results in the simulation tests, in which it is necessary to vary the anatomical parameters. The framework of the second approach includes proposed methods of constructing the „digital twins" based on the clinical data of the real patients. In the further studies, the general problems of the SPECT/CT method (edge artefacts, quantitative assessments of accumulation of activity in the pathological foci, etc.) can be studied using the averaged CSG phantoms, and the results and conclusions obtained in these studies must be verified on the real clinical cases using the „digital twins".

Acknowledgments

The authors are grateful for cooperation and provided clinical data to S.M. Minin, cand. of med. science, a research fellow of Science & Research Oncology and Radiation Therapy Department of Oncology and Neural Surgery of FSBE „NMRS named after the academician of E.N. Meshalkin " (Novosibirsk); Zh.Zh. Anashbaev, radiologist doctor of Radiation Therapy Department of „NMRS named after the academician E.N. Meshalkin" (Novosibirsk); Yu.N. Likar', a head of PET and Radionuclide Diagnostics Department of FSBE of „NMRS of Child Hematology, Oncology and Immunology" belonging to Russian Ministry of Healthcare (Moscow); A.A. Ansheles, doctor of medical science, a leading researcher of Department of Radionuclide Diagnostics and Positron-Emission Tomography of „Cardiology NMRS named after the academician E.I. Chazov" (Moscow); V.B. Sergienko, doctor of medical science, the head of Department of Radionuclide Diagnostics and Positron-Emission Tomography of „Cardiology NMRS named after the academician of E.I. Chazov " (Moscow).

Funding

The study was carried out under the state assignment by RAS SB ITAM (state registration number: 124021400036-7).

Conflict of interest

The authors declare that they have no conflict of interest.

References

[1] W. Kainz, E. Neufeld, W.E. Bolch, C.G. Graff, C.H. Kim, N. Kuster, B. Lloyd, T. Morrison, P. Segars, Y.S. Yeom, M. Zankl, X.G. Xu, B.M.W. Tsui. IEEE Trans. Radiat. Plasma Med. Sci., **3** (1), 1 (2019). DOI: 10.1109/TRPMS.2018.2883437

[2] N.V. Denisova. Meditsinskaya radiologiya i meditsinskaya bezopasnost', **67** (6), 51 (2022). (in Russian)

[3] E. Abadi, W.P. Segars, B.M.W. Tsui, P.E. Kinahan, N. Bottenus, A.F. Frangi, A. Maidment, J. Lo, E. Samei. J. Med. Imag., **7** (04), 1 (2020). DOI: 10.1117/1.JMI.7.4.042805

[4] P.S. Golysheva, A.E. Medvedev. J. Appl. Mech. Tech. Phys., **64** (6), 1041–5 (2023). DOI: 10.1134/S0021894423060147

[5] P. Morais, J.M.R.S. Tavares, S. Queirós, F. Veloso, J. D'hooge, J.L. Vilaça. Med. Phys., **44** (11), 5638–49 (2017). DOI: 10.1002/mp.12559

[6] J. Yao, S. Chen, J.M. Guccione. Bioengineering, **9** (8), 334 (2022). DOI: 10.3390/bioengineering9080334

[7] A. Chupakhin, A. Cherevko, A. Khe, N. Telegina, A. Krivoshapkin, K. Orlov, V. Panarin, V. Baranov. Patalogiya krovoobrashcheniya i kardiokhirurgiya, (in Russian) **16** (4), (2012). DOI: 10.21688/1681-3472-2012-4-27-31
[8] Yu.V. Vasilevskii, S.S. Simakov, T.M. Gamilov, V.Yu. Salamatova, T.K. Dobroserdova, G.V. Kopytov, O.N. Bogdanov, A.A. Danilov, M.A. Dergachev, D.D. Dobrovol'skii, O.N. Kosukhin, E.V. Larina, E.Yu. Mychka, V.Yu. Kharin, K.V. Chesnokova, A.A. Shipilov. Komp'yuternye issledovaniya i modelirovaniye, **14** (4), 2022. (in Russian) DOI: 10.20537/2076-7633-2022-14-4-911-930
[9] R.M. Reilly. *The Fundamental Principles of Compartmental Pharmacokinetics Illustrated by Radiopharmaceuticals Commonly Used in Nuclear Medicine Continuing Education for Nuclear Pharmacists And Nuclear Medicine Professionals* (University of New Mexico Health Sciences Center, Albuquerque, 2013)
[10] A.V. Kolobo, M.B. Kuznetsov. Komp'yuternye issledovaniya i modelirovaniye, **7** (2), (2015). (in Russian) DOI: 10.20537/2076-7633-2015-7-2-361-374
[11] H.L.J. Fisher, W.S. Snyder (Oak Ridge, TN: Oak Ridge National Laboratory, 1966), p. 221–28.
[12] G. Williams, M. Zankl, W. Abmayr, R. Veit, G. Drexler. Phys. Med. Biol., **31** (4), 449–52 (1986). DOI: 10.1088/0031-9155/31/4/010
[13] B.M.W. Tsui, J.A. Terry, G.T. Gullberg. INVESTIGATIVE RADIOLOGY, **28** (12), 1101–12 (1993). DOI: 10.1097/00004424-199312000-00004
[14] P.H. Pretorius, W. Xia, M.A. King, B.M. Tsui, T.S. Pan, B.J. Villegas. J. Nucl. Med., **38** (10), 1528–35 (1997).
[15] L.V. Evseenko, A.A. Kurakhin, A.V. Tultaev, A.P. Chernyaev. *Matematicheskaya model' fantoma cheloveka v radionuklidnoi diagnostike i terapii* (NIIYaF MGU, M., 2002) (in Russian)
[16] N.V. Denisova, V.P. Kurbatov, I.N. Terekhov. Meditsinskaya fizika, (2), 55 (2014). (in Russian)
[17] N. Denisova, M. Ondar, H. Kertesz, T. Beyer. Computer Methods in Biomechanics and Biomedical Engineering: Imaging & Visualization, **11** (3), 433–41 (2023). DOI: 10.1080/21681163.2022.2074308
[18] M. Zankl, R. Veit, G. Williams, et al., Radiat. Environ. Biophys., **27**, 153 (1988). DOI: 10.1007/BF01214605
[19] M. Zankl, A. Wittmann. Radiat. Environ. Biophys., **40** (2), 153–62 (2001). DOI: 10.1007/s004110100094
[20] D.N. Moiseenko, Yu.A. Kurachenko. Meditsinskaya fizika, (3), 27, (in Russian) (2012).
[21] X.G. Xu, T.C. Chao, A. Bozkurt. Health Phys., **78** (5), 476–86 (2000). DOI: 10.1097/00004032-200005000-00003
[22] Electronic source. Available at: https://visiblehumanproject.com/
[23] A.S. Yurova. *Metody avtomatizirovannoi segmentatsii KT-izobrazhenii bryushnoi polosti* (Kand. diss., MGU, M., 2018), 159 s. (in Russian)
[24] W. Segars. *Development and application of the new dynamic NURBS-based cardiac-torso (NCAT) phantom* (Ph.D, The University of North Carolina at Chapel Hill, North Carolina, 2001)
[25] W.P. Segars, G. Sturgeon, S. Mendonca, J. Grimes, B.M.W. Tsui. Med. Phys., **37** (9), 4902–15 (2010). DOI: 10.1118/1.3480985
[26] S. Gnesin, P. Leite Ferreira, J. Malterre, P. Laub, J.O. Prior, F.R. Verdun. Computational and Mathematical Methods in Medicine, **2016**, 1 (2016). DOI: 10.1155/2016/4360371
[27] Electronic source. Available at: https://www.slicer.org/
[28] R.D. Sinel'nikov, Ya.R. Sinel'nikov. *Atlas anatomii cheloveka* (Novaya volna, 2022), v 4-kh t. (in Russian)
[29] M.A. Gurko, N.V. Denisova. ZhTF, **92** (5), 747 (2022). (in Russian) DOI: 10.21883/JTF.2022.05.52381.264-21
[30] *Tissue Substitutes in Radiation Dosimetry and Measurement* (International Commission on Radiation Units and Measurements, 1989)
[31] M.J. Berger, J.H. Hubbell, S.M. Seltzer, J. Chang, J.S. Coursey, R. Sukumar, D.S. Zucker, K. Olsen. NIST, PML, Radiation Physics Division, (2010). https://dx.doi.org/10.18434/T48G6X
[32] N.V. Denisova, A.A. Ansheles. Biomed. Phys. Eng. Express, **4** (6), 065018 (2018). DOI: 10.1088/2057-1976/aae414
[33] N.V. Denisova, M.A. Gurko, I.P. Kolinko, A.A. Ansheles, V.B. Sergienko. Digital Diagnostics, **4** (4), 492 (2023). DOI: 10.17816/DD595696
[34] N.V. Denisova, M.A. Gurko, S.M. Minin, Zh.Zh. Anashbaev, A.A. Zheravin, E.A. Samoilova, S.E. Krasil'nikov. Sibirskii onkologicheskii zhurnal, **22** (2), (2023). (in Russian) DOI: 10.21294/1814-4861-2023-22-2-14-25
[35] S.M.B. Peters, N.R. Van Der Werf, M. Segbers, F.H.P. Van Velden, R. Wierts, K.A.K. Blokland, M.W. Konijnenberg, S.V. Lazarenko, E.P. Visser, M. Gotthardt. EJNMMI Phys., **6** (1), 29 (2019). DOI: 10.1186/s40658-019-0268-5
[36] A.V. Nesterova, N.V. Denisova. ZhTF, **92** (7), 1018 (in Russian) (2022). DOI: 10.21883/JTF.2022.07.52659.331-21

Translated by M.Shevelev

Used terminology

SPECT — single-photon emission computer tomography — is a diagnostics method of nuclear medicine based on visualization of distribution of the delivered radiopharmaceutical (RP) in the patient body by its gamma radiation. The RP is specially selected so as it is substantially accumulated (or, vice versa, not accumulated) in the regions of pathological changes as compare to the healthy tissues. The different pathologies are diagnosed by different RPs.

The SPECT images describe pathological foci rather than the patient anatomy.

CT — X-ray computer tomography — is a diagnostics method based on visualization of biological tissues with a various density, so the CN images are detailed anatomical description of the patient.

SPECT/CT — is a hybrid method combining the SPECT and the CT. The CT is used for taking into account the attenuation effect when gamma radiation passes through biological tissues of the various density as well as for determining anatomical localization of the pathological foci recorded by the SPECT method.

The radiopharmaceutical — is a drug compound, which usually consists of a target molecule and a radioactive „label“ linked thereto. The specific target molecule can be aimed at interaction (accumulation) with specific types of pathologies.

The „virtual patient", the anthropomorphic computational phantom — this term comes out to denote the mathematical model approximate to certain characteristics of the real patient. In different fields of medicine, the „virtual patient" (phantom) can be represented in a different way. For example, during the CT studies the biggest interest is paid to the patient anatomy, which is expressed in Hounsfield units (the substance density) for calculating transmission of X-ray radiation through various biological tissues. In the SPECT method, the „virtual patient" describes distribution of internal sources of gamma radiation by the delivered RP and by the density of various biological tissues for describing the effects of transmission of gamma radiation.

The simulation tests of the SPECT/CT — are computational computer experiments approximate to clinical practice of examination of the patient by the SPECT/CT method.

The pathological focus — is a region of increased of decreased RP accumulation as compared to normal healthy tissues.

The accumulated activity — the quantity which characterizes a degree of RP accumulation in the interest region. It is defined as a number of emitted gamma quanta per unit time from unit volume.

The „raw" or projection data — are two-dimensional data obtained usually by means of two gamma cameras which rotate around the patient body. At certain angles of rotation each camera stops for a certain time (15–30 s) and registers gamma radiation from the patient. It is measured in a number of pulses per pixel.

The image reconstruction algorithms — are means of mathematical processing of „raw" measured data for obtaining the images which describe RP distribution in the patient organs.

The scintigraphic method — is a method of obtaining a two-dimensional image by means of gamma radiation emitted by the RP delivered into the patient body.