Abilities of the different methods of radiodiagnostic for detection bone metastases in patients with oncological diseases (review of the literature).

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Summary: Bone metastases are frequent and danger complications on patients with many oncological diseases. Early its diagnostic has crucial role for the correct treatment and prognosis of disease. Today there is no common approach for diagnostic of bone metastases. The abilities of the different radio diagnostic methods are considered and analyzed; their efficacy is compared for diagnostic bone lesions on patients with breast cancer, prostate cancer, lung cancer in this review. The conclusions about optimization of evaluation locomotors apparatus on oncological diseases are made.

Key words: bone metastases, radiodiagnostic, breast cancer, prostate cancer, lung cancer.

In case of multiple malignant diseases the osseous tissue is the most common location of metastasis. According to the autopsy results, patients suffering form breast cancer showed bone affection in 50 to 85% of cases, those with prostate cancer – in 50 to 70% of cases, those with lung cancer – in 30 to 50% of cases [2; 15; 27; 52]. Bone metastasis is rather proliferated and it may cause such grave complications as intensive pain syndrome, pathological fractures, hypercalcemia, compression of spinal marrow and nerve terminals, therefore it should be perceived as a rather complicated and dangerous process, requiring careful attention, correct and timely approach to treatment [15; 20; 23; 49; 52].

The resorption and formation processes in the normal osseous tissue are controlled through complex interactions of hormones generated by thyroid and parathyroid glands, corticosteroids, cytokines and the other biologically active substances. These substances affect synthesis, proliferation and apoptosis of osteoclasts, while the inverse relationship secures equilibrium of these processes [15; 20; 45; 52]. The mechanism of the metastases formation is based on the metabolism disorder in osseous tissue as a result of tumoral elements impact, which elements are hematogeneously brought into the red bone marrow due to high level of blood supply to the latter. Upon penetration into the bone matrix, malignant cells fuse adhesive molecules which fix such cells to stromal elements, as well as angiogenesis factors and factors of the bones' mineral components resorption [45]. Furthermore, the osseous tissue contains a great number of the immobilized growth factors, which are released and activated under influence of the resorption processes, creating fertile environment for growth of the malignant cells [15; 45; 52].

Subject to the type of the remodualtion disorder there are two major types of bone metastatic affection – osteolytic and osteoblastic metastasis, as well as then mixed forms, including both types of disregulatory changes [2; 15; 45]. In case of osteolytic metastases the bone elements destruction is caused by direct and indirect osteoclasts stimulation by tumors' metabolites.

Malignant cells secrete parathormone related peptide (primary stimulator of osteoclastgenesis), B-cell stimulatory factor 2, tumor necrosis factor, macrophage colony-stimulating factor etc., which intensify expression of receptor activator for nuclear factor kappa B (RANK) and its ligand (RANKL), induce formation of stromal elements and osteoclasts' predecessors, which causes destruction of trabecules and beams, resorption of osseous tissues [2; 45]. Under the dominance of osteoblast processes due to reactive osteosclerosis there is oversupply of trabecular elements, breaching the normal ratios inside the bone matrix [2, 45, 52]. The frequency of osteolytic metastases is 88% osteosclerotic metastases - 5.5%,

mixed metastases - 6.5% [2]. Thus, a minor number of tumor substrate causes significant metabolic changes due to the complex mechanism of biologically active substances' interaction, as histological verification of local bone metastases is uninformative as a rule. In addition, a rather great number of small size foci may significantly complicate the technical process of obtaining a biopsy [15, 20, 45]. Biochemical indicators of osteoblast activity is increasing in the serum levels of alkaline phosphatase, osteocalcin, procollagen-C propeptide of type I. Markers osteoclastic process include increasing the levels of C-terminal of type I collagen telopeptide, tartrate-resistant acid phosphatase in serum and collagen linked N-telopeptide urine.

However, the significance of the most of bone metabolism' biochemical markers is studied insufficiently and may not be used to monitor patients with bone metastases [15, 45, 52]. Under instructions of NCCN (National Comprehensive Cancer Network) only the level of alkaline phosphatase is taken into account [37]. Further, some authors define a statistically significant correlation of planar bone scintigraphy data with the level of CEA and Ca 15.3 tumor markers in patients with breast cancer [42, 43], but these may be treated as auxiliary parameters only, and do not provide a complete picture of the process progress.

Therefore, the main means for the bone metastases are those allowing visualizing the areas of structural and metabolic changes in the tissue, namely the methods of radiodiagnostics. These include the X-ray method (conventional radiography and X-ray computerized tomography (CT)), magnetic resonance imaging (MRI), planar bone scintigraphy and single-photon emission computed tomography (SPECT), positron emission tomography (PET), as well as combined technologies (SPECT / CT and PET / CT) [15, 30, 48, 52]. At present there is no consensus regarding optimal methods for detection of bone metastases and evaluating their treatment efficiency. The problem of detecting bone damages lies in the differences between the lytic and blastic affections, and various visualization methods based on the

direct receiving of anatomical images or indirect measurement of tumor metabolism. Each of these methods has its own well-defined opportunities, advantages and limitations [15, 20, 45].

Thus, conventional radiography can detect changes of bone structure both of lytic, sclerotic and mixed nature due to the ability to visualize well the cortical and trabecular bone elements. But this study found virtually no marrowy disorders, and metastatic affections may be determined in case of the bone density reduction by 30-75% [15, 45, 52]. CT has a much greater anatomical resolution and the ability to contrast bone and soft tissue structure. Its sensitivity for detection of bone metastases reaches 71-100%. It is lower in case of lytic affections and rather high in the presence of severe cortical destruction [2, 3]. CT is not used as a routine study in cancer patients for the purpose of finding metastases, but its value is in assessment of ambiguous foci identified through planar bone scintigraphy, and in identifying complications that accompany malignant bone affections, and if necessary biopsy. MRI has high spatial and contrast resolution, making it an optimal method for assessing bone marrow. It enables detection of intramedullary disorder before cortical destruction takes place, and visualization of more affected areas compared with planar bone scintigraphy. The MRI's disadvantage is relatively low specificity in determining the nature and metabolic activity of the process [16, 25, 26, 49]. Planar bone scintigraphy is most commonly used for diagnostics of bone metastases due to high sensitivity at the early stages of metabolic changes, ability to visualize the entire skeleton in one study and its relatively low cost. The method's levels of sensitivity and specificity range from 62 to 100% and from 78 to 100%, respectively [20, 44].PET is currently the most informative method of quantifying the accumulation and distribution of radiopharmaceutical, obtaining tomographic images of the whole body with highly contrasting resolution. It allows differentiating functional changes in the bone marrow and the mineral part of bone. Nowadays 2 main radiopharmaceuticals

earmarked for evaluation of bone tissue has been well studied and are widely used, namely: - 18F-fluorides, which fixing mechanism is similar to accumulation of phosphates, labeled with technetium (99mTc-MDP and others.). But it has a better capillary permeability and tissue clearance, which improves image contrast and increases the number of detected affections' foci. This preparation is not a routine one and it is used under negative results of planar bone scintigraphy if a high probability of metastatic affection exists. - 18F-FDG is a glucose metabolite. It enters the tumor cells by expressing membrane proteins glucose transport. The advantage of this radiopharmaceutical is the ability to detect both soft tissue and bone foci. The study sensitivity with this preparation is higher in relation to lytic affections (they have higher levels of glycolysis and relative hypoxia), but in case sclerotic bone metastases its sensitivity is lower compared with planar bone scintigraphy (fixation of 18F-FDG in them is lower). [4, 15, 16, 28, 36].

Recently the dominant position has been gained by combined research methods, combining obtaining of metabolic and structural information, such as SPECT / CT and PET / CT [15, 16, 17, 22, 33].Thus, despite the large number of the proposed diagnostic methods, nevertheless is no single generally accepted examination allowing to clearly diagnose presence of the bone metastases. Moreover, there are no clear criteria for prescribing certain examination method, but each of the diseases has certain features requiring justifying the optimal sequence of examination stages with minimal financial and time expenditures.

As it was said above, most of the bone metastases occur in patients with breast cancer, prostate cancer and lung cancer, therefore we propose to review the literature data regarding the use of radiodiagnostics and capabilities of each such method in case of these diseases.

Breast cancer

Quite often in the case of progressing breast cancer the osseous tissue is the first place which becomes affected with remote metastases, and this influence prescription of the local and systemic therapy, disease forecast and quality of the patient's life. Much of attention has been always paid to bone metastases detection at the early stages, as evidenced by the large number of studies devoted to this subject over many years [4, 8, 11, 13, 17, 23, 24, 33-36, 42, 43, 50, 51].In case of the breast cancer the metastases in the bones are the most inhomogeneous: most often it is an affection of lytic nature, but often with intense osteoblast component, less defined osteoblast and mixed foci. The review by Hamaoka T., defined modalities that allow to estimate various layers of bone (cortical and medullary) depending on the density, water content, vascularization or metabolic state [20]. The author reported that the appearance of osteolytic, or mixed osteoblast bone metastases may differ depending on the used visualization method, due to the different capabilities of these techniques. As you know, planar bone scintigraphy finds blastic, mixed-sclerotic changes and reparative bone formation in case of lytic affections, it is recommended to use it as a first-line study due to the high sensitivity at the early stages, including the asymptomatic course of disease [11]. CT is prescribed to evaluate ambiguous areas identified through planar bone scintigraphy, or in case of a risk of complications. In order to expand the capabilities of planar bone scintigraphy the tomographic and combined methods has be widely used over the recent decade. Thus, additional obtaining of SPECT may increase the number of detected affected areas by 20-50% [3, 15, 52].

The relatively low specificity of the planar bone scintigraphy is, inter alia, explained by the fact that traumatic and degenerative processes in osteoarticular structures lead to increased fixation of the radiopharmaceutical, which is difficult to differentiate from metastatic affections.

Thus, poor anatomic resolution complicates the differential diagnosis and may lead to false-positive conclusions. The combined method of SPECT / CT allows

classifying 90% of SPECT undefined areas as benign or malignant ones [44]. The accuracy of the method applying is enhanced due to improved visualization of anatomical areas of pathological fixation when reconciling with the CT [39, 46]. Subject to high probability of the bone metastases presence, as not detected by these methods, it is recommended to prescribe PET or PET / CT with 18F-FDG, since this radiopharmaceutical is accumulated predominantly in lytic areas with high glycolytic activity and relative hypoxia [15]. Given the high cost of this method, its implementation is recommended only subject to ambiguous results of the research. [11]. It is believed that PET and PET / CT with 18F-FDG could potentially improve diagnostics of bone metastases [51], however, one should keep in mind that the probability of false-positive results in case of benign affections is not excluded [20]. The review by Puglisi P. analyzed the literature data for the 30 year period to determine the diagnostic value of planar bone scintigraphy in case of the first discovered invasive breast cancer [42]. Most authors agree that at the early stages of the disease full routine staging involving planar bone scintigraphy is not economically reasonable due to the low probability of bone metastases in these patients. The review contains recommendations of the NCCN (National Comprehensive Cancer Network) [37] regarding fulfilling of the planar bone scintigraphy only in the presence of local symptoms or increase in alkaline phosphatase, as well at stage IIIA of breast cancer. The author took into account the results of the research carried out by a group of Canadian experts in breast cancer treatment (Breast Cancer Disease Site Group of the Cancer Ontario Practice Guidelines Initiative) to determine the recommended examinations for primary staging of breast cancer [42]. After detailed analysis of the literature (1966-2000 years) it was recommended to prescribe no planar bone scintigraphy for women with intraductal form and Stage I of breast cancer and in the clinical situations where the results of the planar bone scintigraphy do not significantly affect the treatment assignment (for women whose treatment is limited to tamoxifen or hormone therapy, or even is not planned for various reasons). Postoperative planar

bone scintigraphy is recommended for all women with stage III subject to invasive breast cancer and with high probability of bone metastases (pN2 and T4/pT4, or presence of suspicious symptoms or laboratory tests) [42, 43]. Given the great number of existing technologies to detect bone metastases, in 2011 the group of Australian and US researchers acting under STEP (Screening & Test Evaluation Program) program completed a systematic comparative review of different image modalities used for diagnosis of bone metastases in women with breast cancer [23]. It included analysis of 16 sources, describing various methods for diagnosis of bone metastasis. The following data was obtained: when comparing PET (18F-FDG) planar bone scintigraphy (7 sources) the most of the features proved sensitivity of these modalities: the average sensitivity for PET was 84% for planar bone scintigraphy - 80%. When assessing specificity according to four sources, it was the same, according to the results of the remaining 3 it was higher for PET [4, 28, 36].

When comparing PET / CT with planar bone scintigraphy according to some authors, the sensitivity and specificity of PET / CT was 100%, which was significantly higher than the specificity (88.3%) and sensitivity (33.3%) of planar bone scintigraphy [17, 33]. It should be noted that in all quoted studies the planar bone scintigraphy was carried in a standard planar mode "whole body." There was a generalization made saying that the results need further investigation and clarification due to heterogeneity of the completed studies, and since some PET studies were used as an additional test [6] after planar bone scintigraphy in selected subjects for further evaluation of the planar bone scintigraphy findings.

When comparing the X-ray CT with planar bone scintigraphy, it was found out that the sensitivity of these methods is virtually the same (97.7% and 100%, respectively), but the specificity of CT is significantly higher (100% and 68%, respectively) [8].

From 2000 to 2011 only one paper was published. It compared the data of scintigraphic tomographic study (SPECT) with PET (18F-FDG) [50]. According to this study, the sensitivity of SPECT is significantly higher than PET (18F-FDG) (85% and 17%, respectively), the accuracy of SPECT is also higher, as compared with PET (96% and 85%, respectively). Thus, there is no statistically significant difference between the specificity of these studies (99% and 100%, respectively). Under a separate consideration of various types of metastatic affections the osteoblast and mixed metastases in 90% of cases were classified using SPECT and 6% using PET, and osteolytic - 35% using SPECT and 90% using PET.

Two sources when comparing planar bone scintigraphy, conventional MRI and MRI of the entire body determined that the sensitivity of MRI is 10% higher [13]. The value of MRI is the ability to identify additional non-osseous affections (lungs, liver) that can cause changes in treatment. This technique can be used to evaluate individual areas of radiopharmaceuticals increased fixation on planar bone scintigraphy with ambiguous interpretation thereof [11, 44]. MRI may also detect more bone metastases than conventional radiography, CT or planar bone scintigraphy [13, 29]. However, it is relatively more expensive and has more technical restrictions (metal dentures, implants, stents, etc.). [11, 20].

According to the review the conclusions were that none of these methods can replace planar bone scintigraphy as a first-line study in visualization bone metastases strategy in case of breast cancer.

Thus, the planar bone scintigraphy remains a major study to identify bone metastases in case of breast cancer, while the use of SPECT and SPECT / CT provides improvement of the method informativity.

Prostate cancer

Bone metastases detected in about 10% of patients with newly diagnosed prostate cancer, the vast majority of whom are patients of the high risk group (the PSA level is over 100 ng / ml, Gleason stage is over 7, T3-4) [7, 49]. For these patients, early detection of bone metastases is crucial because the lack of bone affection allows a radical treatment. In case of the prostate tumors the osteoblast processes prevail, forming a lot of trabecular bone elements that make up the so-called "mineralization front", which leads to of phosphate compounds on them. The autoradiographic analysis showed that 99mTc-phosphates are visualized mainly in this area [15, 45, 49, 52]. Therefore planar bone scintigraphy for many years has been a first-line modality for screening for bone metastases in the case of prostate cancer. The sensitivity and specificity of planar bone scintigraphy represent 70% and 57% respectively. However, during SPECT of uncertain areas they increase to 92 and 82%, respectively. [16]. Advantages of SPECT in case of the lumbar spine study, as described in the Nozaki T., - sensitivity and specificity of SPECT constitute 95.9% and 73.1%, respectively [38]. The Helyar V. presented a retrospective analysis of 40 patients with prostate cancer, in which 50 areas of radiopharmaceuticals pathological fixation were discovered. 61% of these areas were not determined, but after the SPECT / CT the undetermined areas number reduced to 8%. [21].

Thus, it should be noted that the use of tomography and combined techniques for emanation of patients with prostate cancer significantly reduces the number of areas undetermined through planar bone scintigraphy.

CT in the case bone and muscular affections in patients with prostate cancer is used as a second-line method to clarify ambiguous areas hyperfixation when carrying out planar bone scintigraphy, which areas remains suspicious after conventional radiography and under suspicious neurological disorders [16, 19]. In this paper, Groves A.M. compared results of planar bone scintigraphy and CT in 43 patients with malignant diseases. Significant differences in sensitivity to

detection of bone metastases were observed, but X-ray examination of many sections significantly increased the patient's exposure to radiation. The findings indicate that the replacement of planar bone scintigraphy by CT is not feasible fore screening purposes [19]. High efficiency of MRI, which surpasses the capabilities of planar bone scintigraphy in identifying of bone metastases, quantitative evaluation thereof and sensitivity to theraphy has been well investigated by many authors [2, 18, 25, 26, 29, 49]. The advantage of MRI is its ability to detect the location of tumor cells in the hematopoietic compartment, at the relevant stage preceding the osteoblast reaction. However, the use of MRI in the first line of diagnostics is limited by its cost, relatively limited availability and technical features of the procedure [18].

When studying the use of PET and PET / CT (18F-FDG) in patients with prostate cancer it was concluded that these methods represent a little interest compared to other radiation research methods for these patients [18]. Application of PET and PET / CT with 18F-fluorides is on contrary more effective in detecting the bone metastases, the sensitivity and specificity of their reach 81-100% and 93 -100%, respectively [5, 16]. Application of new radiopharmaceutical for PET (18F-fluorocholine, 11C-choline) is widely studied, but the data showed no advantages over existing methods, limited availability and high cost of such studies reduces their implementation [5, 14, 41].

Lung cancer

In case of lung diseases the diagnostic methods include first-line X-ray examinations (radiography, CT with intravenous contrast) to assess the proliferation of the chest soft tissues affection and mediastinum, as well determining the prospects for further surgical treatment [1, 10, 15, 52].

In patients with small cell lung cancer the remote metastases are usually found in the course of primary diagnosis, so the results of planar bone scintigraphy do not affect the treatment and the disease forecast [52].

Meaning of the planar bone scintigraphy in case of non-small cell lung cancer is to clarify the stage of the first found disease, and to determine proliferation of the process and evaluation of the pain syndrome and possible complications before chemotherapy start [15]. Planar bone scintigraphy is separately assigned for patients with pain syndrome retained during or after the treatment course. However, one should keep in mind that about 40% of patients with non-small cell lung cancer have asymptomatic bone metastases [9, 15].

Regardless of the disease form, planar bone scintigraphy allows to diagnose patients with hypercalcemia and bone marrow suppression, which may affect the treatment prescription. Planar bone scintigraphy also provides an opportunity to identify heterotopic pulmonary osteoarthropathy as a cause of pain in the lower limbs, showing increased cortical fixation of the preparation in the diaphysis of bones. Moreover, it allows us to differentiate them from benign processes that can cause pain in the structures of the musculoskeletal system [27, 48, 52].

Many researchers suggest reinforce planar bone scintigraphy by holding tomographic studies (SPECT), an additional determination of alkaline phosphatase (ALP) serum for detection of bone metastases in patients with newly diagnosed lung cancer, which generally significantly increases the informativity of this method [32, 47]. Informativity of PET and PET / CT (18F-FDG) has been widely studied in patients with lung cancer [12, 31, 40], but the possibility of detecting bone metastases using this method does not always satisfy oncologists and requires further research. Therefore, many of the problems related to diagnosing metastatic bone affections have remained unresolved so far, namely: there is no single approach to the prescription a radiodiagnostic method for detection of bone

metastases. In the most fields of nuclear medicine the planar bone scintigraphy is carried out not in full (using dynamic and tomographic studies), but only in the front and rear planar projections. The importance of these problems and the need to clearly resolve them is evidenced by a large number of scientific papers.

Analyzing data from the literature, we would make some conclusions:

- under various cancer diseases there are specific features of forming metastatic bone affections, which must be taken into account when applying various methods of roentgen diagnostics;
- planar bone scintigraphy is the most informative and economical method for initial evaluation of all musculoskeletal system affections with minimal the exposure of the patient to radiation;
- the use of SPECT and SPECT / CT allows objectifying diagnosis of skeletal bones' metastatic affections and preventing the use of some more complex,
- invasive and expensive diagnostic methods.

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