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ABSTRACT

of the dissertation for the degree of Doctor of Philosophy

THE ROLE OF IMAGING METHODS IN THE DIAGNOSIS OF BONE METASTASES AND IN THE EVALUATION OF TREATMENT OUTCOMES

Speciality: 3225.01 – "Radiation diagnostics and therapy"

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GENERAL CHARACTERISTICS OF THE RESEARCH

Relevance of the topic. Bone metastases in oncological patients constitute a clinical condition of particular importance from both a diagnostic and a treatment standpoint. The probability of metastasis to bone tissue is especially high in malignant tumours of breast, prostate, lung, and renal origin, and these metastases can cause severe complications in patients, such as intense pain, pathological fractures, spinal cord compression, and others. The timely detection of these conditions is of important significance in terms of improving the patient's quality of life and prolonging survival.[1]

Studies in the United States show that, on average, some 280,000 bone metastases (BM) are registered as new cases each year[2]. ccording to data from the SEER (Surveillance, Epidemiology, and End Results) database, the annual incidence rate was 18.8 cases per 100,000 population during 2010–2015.[3] In general, the skeletal system is considered the site where metastases are most densely localized after the lungs and liver.

BM are considered one of the leading causes of cancer-related mortality. The skeletal system is one of the major sites of metastasis from malignant tumors of various primary locations. Skeletal metastases are particularly common in breast cancer (BC) and prostate cancer (PC). In addition, bone metastases are also observed in lung, kidney, and other solid tumors. The incidence of BM varies depending on the location of the primary tumor and the stage of the disease. The patterns of skeletal metastatic involvement also differ among various primary malignancies.[4,5]

BM may be detected in clinical practice in various ways. In the first scenario, metastatic lesions are incidentally identified during

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[1] Macedo F. Bone metastases: an overview/ Macedo F., Ladeira K., Pinho F. [et al.] // Oncol Rev. 2017;11(1):321. -p.43-49

[2] Garbar, V. Palliative Radiation Therapy For Bone Metastases / V.Garbar, S.Richter // StatPearls [Internet]. – Treasure Island (FL): StatPearls Publishing. – 2024. – p.4–12.

[3] Ryan, C. Epidemiology of bone metastases / C. Ryan, K.C. Stoltzfus, S. Horn [et al.] // Bone. -2022. v.158. -Art. 115783. -p.569-577

[4] Dillekås, H. Are 90% of deaths from cancer caused by metastases? / H.Dillekås, M.S.Rogers, O.Straume // Cancer Med. – 2019. v.8(12), – p.5574–5576.

[5] Huang, J.F. Incidence of patients with bone metastases at diagnosis of solid tumors in adults: a large population-based study / J.F.Huang, J.Shen, X.Li [et al.] // Annals of Translational Medicine. – 2020. v.8(7), – p.1–17.

routine follow-up examinations (e.g., bone scintigraphy or other imaging modalities) in patients with an established diagnosis of a malignant tumor. In the second scenario, BM are detected during the investigation of symptoms such as bone pain, functional impairment, or pathological fractures in patients with a known malignancy. In the third scenario, examinations performed in individuals with no previously known history of cancer, prompted by the sudden onset of bone pain, functional impairment, or a pathological fracture, reveal that the bone lesion is metastatic in nature and associated with an occult primary malignant tumor present in the body [6].

Various imaging methods are used in the detection of BM. Although radiography (RG) is used for the initial assessment, its sensitivity is limited. At present, in this respect, magnetic resonance imaging (MRI), computed tomography (CT), osteoscintigraphy (OSG), and computed tomography combined with positron emission tomography (PET-CT) are more widely used. Each method has its specific advantages and limitations.

In "cryptogenic bone metastases", the primary focus of the neoplasm is unknown. Such cases occur in 30% of all BM. In these cases, the primary focus cannot be determined by clinical-anamnestic data, physical examinations, laboratory tests, or diagnostic methods.[7]

Today, the application of modern diagnostic technologies, the identification of new tumour markers, and the development of immunohistochemical and chromosomal analyses have made important contributions to the early-stage detection of the primary focus.[8, 9,10]

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[6] Çelik, Z.E. Metastatik Kemik Tümörlü 129 Olgunun Retrospektif Olarak İncelenmesi / Z.E.Çelik, İ.Harmankaya, B.K.Aydın, [ve b.] // Genel Tıp Dergisi. – 2021. – C.31. – №1. – s. 59–64.

[7] Piccioli, A. Bone metastases of unknown origin: epidemiology and principles of management / A.Piccioli, G.Maccauro, M.S.Spinelli [et al.] // J Orthop Traumatol. – 2015. v.16(2), – p.81–86.

[8] Suva, L.J. Bone metastasis: mechanisms and therapeutic opportunities / L.J.Suva, C.Washam, R.W.Nicholas, R.J.Griffin // Nature Reviews Endocrinology. – 2011. v.7(4), – p.208–218

[9] Hao, Y. Potential biomarkers for the early detection of bone metastases / Y.Hao, F.Zhang, Y.Ma [et al.] // Front Oncol. -2023. v.13. -p.1-16.

[10] Suster, D., Suster, S. Genetic characteristics and molecular diagnostics of bone tumors // J Cancer Metastasis Treat. -2021. v.7. -Art. 8.-p.1-22

The particular relevance of our study is also connected with the analysis of diagnostic approaches in BM with an unknown primary focus. In these patients, the detection of metastatic neoplasms occurs, but the localization of the primary tumour remains unknown. In such cases, the correct choice of imaging methods and probabilistic diagnostic approaches based on the type of neoplasm (osteoblastic, osteolytic, mixed) and the region of its location come to the fore. In particular, at this stage the application of diagnostic algorithms helps to determine the probable source of the primary focus and to direct targeted examinations.

In addition, the post-treatment radiological assessment of patients with BM is also one of the relevant aspects of the study. For this purpose, although international criteria such as RECIST (Response Evaluation Criteria in Solid Tumors) – a system of criteria based on anatomical dimensions used to assess the response to treatment in solid neoplasms – and PERCIST (PET Response Criteria in Solid Tumors) – a set of criteria assessing the response to treatment on the basis of metabolic activity in FDG PET-CT imaging – are applied in ocological practice , in BM these criteria are sometimes not suitable, because metastatic changes encompass not only size but also structural and functional changes of the bones.[11]

Object and subject of the research. The research included the analysis of the retrospective and prospective results of 170 patients treated and examined at the Oncological Clinic of Azerbaijan Medical University of the Ministry of Health of the Republic of Azerbaijan and at the National Centre of Oncology during the years 2013–2023. 138 patients were included in the main group; BM were detected in these patients. 32 patients without BM were included in the control group. In the patients in the main group, the primary tumour was breast cancer (BC), prostate cancer (PC), lung cancer (LC), renal cancer (RC), naso-pharyngeal cancer, or bladder cancer. In the control group, patients with multiple myeloma and patients with traumatic, dysplastic, and degenerative bone lesions were studied.

[11] Fournier, L. Twenty Years On: RECIST as a Biomarker of Response in Solid Tumours – an EORTC Imaging Group–ESOI Joint Paper / L.Fournier, L.-F.de Geus-Oei, D.Regge [et al.] // Front Oncol. – 2022. v.11, – p.1–17.

Aim of the study: The aim of the research is to investigate the possibilities of radiological examination methods in the differential diagnosis of the radiological image of bone metastases, in the determination of the primary tumour focus in cryptogenic bone metastases, and in the evaluation of treatment outcomes.

Objectives of the study: To achieve the stated aim, the following objectives were defined:

1. Assessment of the diagnostic possibilities and informativeness of the radiological examination methods (radiography, computed tomography, magnetic resonance imaging, and osteoscintigraphy) used in the diagnosis of bone metastases
2. Analysis of the radiological and morphological characteristics of bone metastases depending on the primary tumour focus, as well as their interrelation with clinical and laboratory indices
3. Determination of the radiological criteria for carrying out the differential diagnosis between bone metastases and bone lesions characterized by similar radiological images
4. Study of the role of radiological criteria in determining the primary tumour focus on the basis of the radiological characteristics of bone metastases with an unknown primary focus, and the development of a diagnostic algorithm based on those criteria
5. Study of the place and role of radiological examination methods in the evaluation of the outcomes of the treatment applied in patients with metastatic bone lesions

Research methods: In the research work, the results of Radiography, Computed Tomography, Magnetic Resonance Imaging, Osteoscintigraphy and clinical-laboratory examinations were analysed; the choice of examination method was determined on the basis of the anatomical localization, type, and degree of spread of the metastasis. In the radiological assessment, the type, number, size, and character of the metastases were evaluated, and the data obtained were processed by statistical methods.

Main provisions submitted for defence:

1. The radiological appearance of bone metastatic lesions depends on the primary tumor and is directly associated with the number, localization, characteristics and imaging features of the lesions

2. In cryptogenic bone metastases, the primary tumor can be predicted with high accuracy based on the radiological appearance of the metastatic lesions

3. The results of the relationship between the morphological type of bone metastases and the response to the treatment administered showed that, based on CT findings, in radiological imaging, regression is observed more often in osteolytic metastases, whereas in mixed and osteoblastic types of metastases the course of the process differs, being more often stable and in some cases of a regressive and progressive character

Scientific novelty of the study:

The study comprehensively analysed the capabilities of various imaging methods in the diagnosis of bone metastases, an area that has not been studied sufficiently systematically in the existing literature and some aspects of which are the subject of scientific debate and differences of opinion; in particular, the radiological and morphological characteristics of bone metastases were investigated depending on the primary tumour focus. In addition, the relationship between the morphological type of bone metastases and the response to the treatment administered was studied, and an algorithm was developed that makes it possible to predict the location of the probable primary tumour focus on the basis of the radiological characteristics of cryptogenic bone metastases

Practical significance of the study:

The radiodiagnostic characteristics of bone metastases are of great importance in the early diagnosis of the process and in the differential diagnosis from diseases that produce a similar radiological appearance. On the basis of the proposed diagnostic algorithm, when cryptogenic bone metastases are detected, the location of the primary tumour focus can be predicted with high probability from the radiological appearance. On the basis of dynamic radiological images, the relationship between the morphological type of bone metastases and the response to the treatment administered is assessed, and, where necessary, indications for further examinations are determined.

Approbation of the dissertation

The results of the dissertation work were discussed at the scientific-practical conference dedicated to the 90th anniversary of the

birth of professor Z.A.Zeynalova (Baku, 2022), at the scientific-practical conference dedicated to the 100th anniversary of National Leader H.A. Aliyev (Baku, 2023), at the First Congress of Oncologists of Turkic States (Baku, 2025) at the scientific-practical conference "Mustafa Topchubashov: Academic Heritage – 130" (Baku, 2025) and at the Congress of the Russian Society of Radiology (Moscow, 2026).

The results of the dissertation work were reported and discussed at the interdepartmental meeting of the AMU of the MoH of the RA on 26 December 2025, and at the Scientific seminar of the FD 1.02 Dissertation council operating at the National Centre of Oncology of the MoH of the RA on 19 June 2026 (Protocol No. 3).

The most important theoretical and practical theses of the dissertation are reflected in 19 scientific works. In total, 7 articles and 12 abstracts have been published. Scientific works on the topic of the study have been published both abroad (4 articles, 4 abstracts) and in Azerbaijan (3 articles, 8 abstracts).

Implementation of the Results:

The results of the research have been implemented into the clinical and diagnostic practice of the Polyclinic-Diagnostic Department at the Oncology Clinic of Azerbaijan Medical University, as well as into the teaching curriculum of the Department of Radiology at Azerbaijan Medical University

Name of the organization where the dissertation work was carried out:

The dissertation was performed at the Oncology Clinic of Azerbaijan Medical University of the Ministry of Health of the Republic of Azerbaijan.

Volume and structure of the dissertation:

The dissertation work is printed on 156 pages (210,951 characters) and consists of an introduction, a review of the literature, materials and methods, the exposition of the results of the personal research (3 chapters), a summary, conclusions, practical recommendations, and the statistics of the literature sources. The introduction consists of 10,552 characters, the review of the literature of 58,183 characters, the materials and methods of 23,986 characters, the three chapters of the personal research of 65,546 characters, the summary of 49,703

characters, and the conclusions and practical recommendations of 2,981 characters. The dissertation work comprises 10 tables, 25 figures, and 14 graphs. The list of references encompasses 141 sources, comprising the works of 7 Azerbaijani and 134 foreign scholars**.**

MATERIALS AND METHODS

The research included the retrospective and prospective analyses of 170 patients examined and treated at the Oncological Clinic of Azerbaijan Medical University and at the National Centre of Oncology during the years 2013–2023. The results of observations were studied in 170 patients, comprising 57 (33.5%) men and 113 (66.5%) women. Of these patients, 80 (47%) were retrospective and 90 (53%) prospective. The age range of the examined patients was 19–87 years, with a mean age of 59.9 ± 0.9 years.

The patients were divided into the following groups:

– Main group – patients with bone metastasis: 138 (81.17%) persons.

– Control group – patients with a non-metastatic focus in the bone: 32 persons (18.82%).

Among the 170 patients included in the study, 100 (58.8%) had BC (18 control group), 22 (12.9%) PC) 28 (16.5%) lung cancer (LC), 14 (8.2%) multiple myeloma (control group), 3 (1.8%) RC, 2 (1.2%) bladder cancer, and 1 (0.6%) nasopharyngeal cancer (carcinoma of the nasopharynx). As regards the number of metastases, 1 metastatic site was detected in 23 (16.7%) patients, 2–5 in 50 (36.2%) patients, and more than 5 in 65 (47.1%) patients.

RG was performed in 92 (54.1%) patients, OSG in 85 (50%), computed tomography in 157 (92.4%), and MRI in 59 (34.7%).

In the 100 (59%) BC patients in the study group, additional examinations for immunohistochemical and laboratory markers were also carried out.

The X-ray examinations used in the research were obtained on Shimadzu Flexavision and Shenzhen Lanmage Medical Technology Co. Digital Fluoroscopic Radiography X-Ray system devices; the CT examinations were obtained on Toshiba Asteion single slice, Fujifilm 32 slice, and Siemens Definition Flash Dual energy 2×128 slice devices, with the corresponding reconstructions carried out and the

examination results studied. CT examinations were performed without contrast enhancement.The OSG examinations were carried out on a 670 GE SPECT/CT device.

MRI examinations were performed using a 1.5-Tesla Siemens MAGNETOM Avanto and a 3-Tesla Siemens MAGNETOM Skyra scanner. The examinations were conducted in accordance with standard clinical MRI protocols, taking into account the patients' clinical indications and the suspected localization of the lesions. Depending on the anatomical region examined, images were acquired in the axial, sagittal, and coronal planes.

The imaging protocols mainly included T1-weighted spin-echo (SE), T2-weighted fast spin-echo (FSE), and fat-suppressed STIR (Short Tau Inversion Recovery) sequences. In selected cases, diffusion-weighted imaging was performed when clinically indicated. T1-weighted images were used to assess the normal fatty architecture of the bone marrow and cortical bone anatomy, whereas T2-weighted and STIR sequences were used to detect bone marrow infiltration, edema, and pathological lesions.

Invasive biopsy procedures were not carried out on the metastatic bone neoplasms. Histological confirmation of bone origin was available only in patients with a diagnosis of multiple myeloma. In other cases, the diagnosis was determined on the basis of the clinical course and the results of radiological follow-up carried out over a period of 6–12 months.

The immunohistochemical analyses were carried out on Dako Autostainer and Ventana Benchmark automated systems.

The research work was defined as follows: by design – analytical; by type – scientific; by method – clinical; by volume – selective; by material – retrospective and prospective; by place – clinical.

The sensitivity of a test is taken as a positive result of the study in a patient; if a positive result is determined in all examined persons who definitely have the disease and a negative result in healthy persons, the sensitivity of the test amounts to 100%. The specificity of a test is the probability of obtaining a negative result in an examined healthy person. If the test result is negative in all examined persons who do not suffer from the given disease, then the specificity is taken as 100%.

The quantitative and qualitative indices obtained in the course of the study were processed in the IBM SPSS Statistics-26 program with the application of variation, discriminant, dispersion, correlation, and ROC-analysis methods. In all analysis methods, a threshold of $p < 0.050$ was established for testing the "null" hypothesis.

The quantitative (numerical) indices were expressed by mean (M, ±m) and mean structural (Me, Q1, Q3) indices; expressed by mean structural indices, non-parametric criteria were used for the comparison of the series (the U-Mann-Whitney test for the comparison of the indices of 2 groups, and the H-Kruskal-Wallis test for the comparison of the indices of more than 2 groups).

The qualitative (categorical) indices were expressed by relative indices (%), the share value was calculated, and Pearson's χ^2 criterion was used for comparison. The comparative analysis of the individual examinations in diagnosis was assessed by the k-test (Kappa test).

RESULTS OF THE RESEARCH AND THEIR DISCUSSION

Results of Radiological Imaging of Metastatic Bone Lesions. Within the framework of the research, RG examination was carried out in 92 patients (54.1%).

In the thoracic bones, the sensitivity of RG was low (Sn = 24.5%, Sp = 100%); false-negative results predominated (FN−) = 40 (51.9%)). For the spine, RG shows a sensitivity of 41.7% and a specificity of 100% (FN(−) = 7); the agreement was $k = 0.299 \pm 0.137$, $p = 0.024$. In the pelvic region, RG was performed in 6 (6.5%) patients. It was determined as $k = 0$, which indicated the absence of any agreement between the evaluators. In this region FN(−) = 5. Sn = 16.7%. In the limb bones, only 1 (1%) patient was examined by X-ray, and metastasis was detected.

CT examination was applied in 157 (92.4%) patients. CT examination of the skull bones was carried out in only 2 (1.3%) patients. Metastatic foci were registered on the images (100%). However, owing to the very small number of patients (n = 2) for assessment, the kappa statistic could not be calculated, and the results were considered statistically unreliable. For the thorax, FN(−) = 3

(2.7%), k = 0.816 ± 0.060, and statistical reliability was obtained ($p < 0.001$). It showed Sn =96.5% and Sp 92.3%. CT examination of the spine was carried out in 90 (57.3%) patients, and it was determined as FN(−) = 4 (4.4%), k = 0.729 ± 0.070, $p < 0.001$. This is considered statistically reliable. In our study, CT in this region had Sn = 93.8%, Sp = 92%.

CT of the pelvic bones was carried out in 70 (44.5%) patients, and with true positive TP(+) = 52, FN(−) = 5, true negative TN(−) = 10 (7 + 3), FP(+) = 3, k = 0.664 ± 0.110; $p < 0.001$. The sensitivity of CT was 91.2% and the specificity 76.9%. In the limb bones, complete agreement was registered, with p = 0.001. The sensitivity and specificity were 100%. The sensitivity of CT was 86% in osteoblastic metastasis, 92.5% in osteolytic, and 75.6% in mixed metastasis.

Osteoscintigraphy was carried out in 85 (50%). For the skull bones, OSG had TP(+) = 5, FN(−) = 1, TN(−) = 31, false positive FP(+) = 3, k= 0.713 ± 0.127 ($p < 0.001$). This is considered statistically reliable. In the skull bones, OSG had Sn = 83.3%, Sp = 91.2%. In the thoracic bones, FN(−) = 4 (5.2%). For this region k = 0.789 ± 0.069 ($p < 0.001$), which indicates a high degree of reliability. Sn = 91.1%, Sp = 92.3%. In the pelvis, FN(−) = 6. The result of this assessment was k = 0.769 ± 0.082, $p < 0.001$, and it is considered reliable. The sensitivity for the pelvic bones is 83.3%, the specificity 95%. For the spine, OSG false-negative cases were 4 (6.1%). It was assessed as k = 0.774 ± 0.074, $p < 0.001$, and this index was considered statistically significant. OSG for the spine had Sn = 90.5%, Sp = 91.7%. In the OSG imaging results for the limb bones, FN(−) = 1. Among the results, the evaluator was k = 0.708 ± 0.118, $p < 0.001$; Sn = 90.9%, Sp = 88.9%.

The sensitivity of OSG was calculated as 95.5% in the osteoblastic type, 52.6% in the osteolytic, and 12.5% in the mixed.

For the skull bones, 2 (1.2%) patients were assessed by MRI (Sn = 100%). For the thoracic bones, 19 patients were analysed. TP(+) = 6, FN(−) = 2, TN(−) = 10, FP(+) = 1. The sensitivity of the MRI examination was 75.0% and the specificity 90.9%. For this region, agreement was determined between the MRI results and the final diagnosis (k = 0.719 ± 0.129; $p < 0.001$). MRI of the pelvic bones was carried out in 34 (20%) patients, and a high level of agreement was

observed ($p < 0.001$). FN(−) = 2 (5.8%) was registered in the patients; Sn = 91.3% and Sp = 81.8%.

MRI of the spine was carried out in 42 patients. On the MRI examination, metastasis was detected in 22 of the 24 patients with metastasis (91.7%); Sn = 91.7%, Sp = 83.3%, $p < 0.001$. MRI of the limb bones was carried out in 7 (4.1%) patients. For this region, complete agreement was observed between MRI and the final diagnosis ($k = 1.000$; $p < 0.001$).

The assessment of the morphological type of the bone foci by MRI was carried out in 54 patients.

For osteoblastic metastases, the sensitivity of MRI amounted to 100%. For the osteolytic type, the sensitivity amounted to 95%. Mixed-type metastases, on the other hand, were detected by MRI with a lower sensitivity (Sn = 40%).

As a result of the analysis, a statistically significant difference was observed between the main and control groups with respect to the MRI results ($p = 0.015$). No statistically significant dependence between the groups was determined for the other imaging methods (on the RG $p=0.291$, on the OSG $p=0.433$ and on the CT $p=0.252$).

Comparative Analysis of the Radiological and Morphological Characteristics of Bone Metastases and Clinical and Laboratory Parameters According to the Primary Tumor Site

In the patients participating in the study, the relationship between the primary neoplasms and the morphological type of BM was statistically significant ($p < 0.001$). According to the results obtained, of the 100 patients with BC, a non-metastatic focus was observed in 18 (18%), osteoblastic metastases in 29 (29%), osteolytic in 17 (17%), and mixed-type in 36 (36%). In the 22 patients with PC, osteoblastic metastasis was registered most frequently – 11 (50%) – followed by osteolytic – 7 (31.8%) – and mixed-type – 4 (18.2%). In LC (n=28), osteolytic-type metastases predominated – 18 (64.3%) – with osteoblastic – 3 (10.7%) – and mixed-type – 7 (25%). In RC (n=3), only osteolytic metastasis was determined, in 3 (100%) patients. In bladder cancer (n=2), 1 osteoblastic and 1 mixed type, and in nasopharyngeal cancer (n=1), 1 mixed-type metastasis were determined.

In the main group, the statistical association between the morphological types of BM and histological subtypes was investigated in patients with lung cancer

Analysis of the overall structure of the molecular subtypes showed that Luminal A was identified in 40 (40.0%) patients, Luminal B/HER2+ in 9 (9.0%), Luminal B/HER2− in 35 (35.0%), HR−/HER2+ in 12 (12.0%), and triple-negative breast cancer (TNBC) in 4 (4.0%). Overall, a non-metastatic focus was identified in 18 (18.0%) of the 100 BC patients, and BM were detected in 82 (82.0%). Across the entire BC group, osteoblastic bone lesions were recorded in 29 (29.0%) patients, osteolytic in 17 (17.0%) and mixed-type in 36 (36.0%).

Analysis of the structure of bone lesions in the 40 patients with the Luminal A subtype identified a non-metastatic focus in 13 (32.5%) patients, osteoblastic lesions in 11 (27.5%), osteolytic lesions in 6 (15.0%) and mixed-type lesions in 10 (25.0%).

Of the 9 patients with the Luminal B/HER2+ subtype, a non-metastatic focus was identified in 1 (11.1%). Of the remaining cases, osteoblastic bone lesions were recorded in 4 (44.4%) and mixed-type lesions in 4 (44.4%). No osteolytic lesions were detected in this molecular subtype.

A different distribution of bone lesions was observed in the Luminal B/HER2− subtype. Of the 35 patients in this group, a non-metastatic focus was recorded in only 1 (2.9%), while osteoblastic bone lesions were identified in 9 (25.7%), osteolytic in 7 (20.0%) and mixed-type in 18 (51.4%).

A more even distribution of bone lesions was found in the 12 patients with the HR−/HER2+ subtype. Namely, a non-metastatic focus was recorded in 3 (25.0%) patients, osteoblastic lesions in 3 (25.0%), osteolytic lesions in 3 (25.0%) and mixed-type lesions in 3 (25.0%).

The triple-negative BC (TNBC) subtype comprised 4 patients. No non-metastatic focus was recorded in this group. Osteoblastic bone lesions were identified in 2 (50.0%) of the patients, osteolytic in 1 (25.0%) and mixed-type in 1 (25.0%).

However, as a result of the statistical analysis carried out, no statistically significant relationship was detected ($p = 0.094$).

The patients were divided into the subgroups of infiltrative

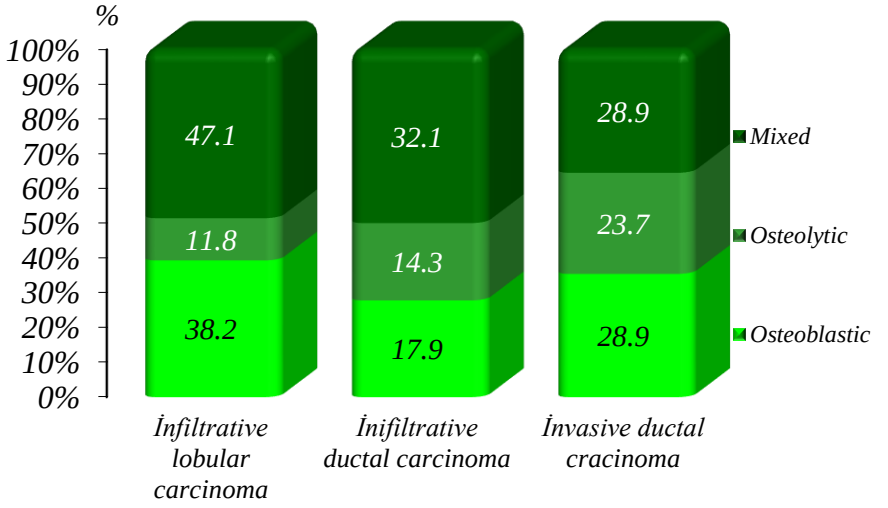
lobular carcinoma, infiltrative ductal carcinoma, and invasive ductal carcinoma, and the type of BM was analysed for each.

In cases of invasive ductal carcinoma, osteoblastic and mixed-type metastases were each detected in 11 patients (28.9%), whereas osteolytic metastases were identified in 9 patients (23.7%).

In cases of infiltrating ductal carcinoma, mixed-type metastases were identified in 9 patients (32.1%), osteoblastic metastases in 5 patients (17.9%), and osteolytic metastases in 4 patients (14.3%).

Among patients with infiltrating lobular carcinoma, mixed-type metastases were found to predominate. Specifically, mixed-type metastatic lesions were recorded in 16 patients (47.1%), osteolytic lesions in 4 patients (11.8%), and osteoblastic lesions in 13 patients (38.2%).

The results obtained showed that a statistically significant relationship was detected between the histological subtypes and the metastasis morphology, with p = 0.022 (Graph).



Graph. Distribution of the type of bone metastases according to the histological subtypes of breast cancer

The morphological characteristics of BM according to the histological types of LC were analysed. A total of 28 patients were analysed. In the 11 (39.3%) patients with adenocarcinoma of the lung, it was determined that the BM were predominantly of the osteolytic type (in 5 patients,45.4%). In this group, osteoblastic and mixed-type metastases were registered with equal frequency (in 3 patients, 27,3%). In the 10 (35.7%) patients with peripheral alveolar carcinoma of the lung, the predominant form of BM was the osteolytic type (8, 80%). In this histological type, mixed metastases were observed in 2 (20%) patients, and no osteoblastic metastasis was registered. In the 7 (25%) patients with clear-cell carcinoma of the lung, osteolytic metastases also predominated (in 5 patients,71.4%). Mixed-type metastases were detected in 2 (28.6%) patients, and no osteoblastic-type metastasis was observed.

No statistically significant association was found between the morphological type of BM and the histological type of lung cancer ($p=0.211$).

In order to assess the relationship of BM with molecular indices, a control group of 18 persons consisting only of patients with BC was compared with the main group. Initially, the relationship between the Ki-67 proliferation index and the presence of BM in patients with BC was investigated. According to the results of the statistical analysis, a statistically significant difference in the Ki-67 indices was determined between the main and control groups ($p = 0.029$). The results obtained show that proliferative activity is higher in patients with BM and underscore the prognostic significance of the Ki-67 index. In this respect, the Ki-67 index can be assessed as a potential predictor of the risk of BM.

According to the comparative analysis carried out for various anatomical regions in the main and control groups, the Ki-67 proliferation index was higher in the metastatic cases compared with the non-metastatic and focus-free groups. The Ki-67 indices were higher in patients with metastasis. The most notable differences were observed in the limb bones ($p =0.018$). In the groups with a non-metastatic focus, the Ki-67 index was in most cases registered at a lower level.

In the analyses carried out, it was observed that the risk of BM

in BC patients varied according to the molecular subtype.

Of the 40 patients with Luminal A-type breast cancer included in the study, BM were detected in 27 (67.5%). In the remaining 13 patients (32.5%), no BM were detected. Of the 9 patients in the Luminal B/HER2+ group, BM were detected in 8 (88.9%), while no BM were detected in 1 patient (11.1%).

Of the 35 patients with Luminal B/HER2− BC, BM were detected in 34 (97.1%), while no BM were detected in 1 patient (2.9%). Of the 12 patients in the HR−/HER2+ group, BM were detected in 9 (75.0%), while no BM were detected in 3 patients (25.0%). BM were detected in all 4 patients (100.0%) in the TNBC group.

Thus, the highest frequency of BM was observed in the TNBC group (100.0%), followed by the Luminal B/HER2− (97.1%), Luminal B/HER2+ (88.9%), HR−/HER2+ (75.0%), and Luminal A (67.5%) groups.

In order to assess the classification ability of the laboratory indices used in the patients observed with BM , a ROC analysis was carried out. For this purpose, ROC curves were constructed on the basis of the Ki-67 proliferation index and the CEA (carcinoembryonic antigen) and CA 15-3 (cancer antygen 15-3) levels, and the AUC (Area Under the Curve) values were calculated.

The area of the ROC curve (AUC) of the Ki-67 proliferation index amounted to 0.665 ± 0.072. The 95% confidence interval for the AUC was 0.525–0.806. The fact that the AUC index is higher than 0.5 indicates that the Ki-67 marker has a non-random discriminatory ability in the prediction of metastasis. The index obtained as a result of the ROC analysis was statistically significant ($p = 0.029$).

The AUC of the CEA index was found to be 0.723. The standard error for the AUC was 0.065. The 95% CI was determined as 0.595–0.851. The p for the AUC was 0.021, and this result is considered statistically significant ($p=0.021$).

CA 15-3 had AUC = 0.806, standard error 0.044. The 95% CI of the AUC index was calculated as 0.719–0.893. The value obtained for the ROC was ($p < 0.001$), and this result has very high statistical reliability. Consequently, CA 15-3 is assessed as a strong and statistically reliable predictor marker for the assessment of the risk of

BM. Overall, the ROC analyses showed that all three markers give statistically significant results in the differentiation of metastatic and non-metastatic cases.

Radiological Differentiation of Bone Metastases from Non-Metastatic Bone Lesions

As a control group, 32 patients without BM were included in the study. Of these, 14 persons (43.75%) had a diagnosis of multiple myeloma, and 18 persons (56.25%) were patients under observation with a diagnosis of BC but in whom post-traumatic changes, dysplastic bone islands, and cystic degenerative changes were encountered on the bone images. Comparative analysis of the clinical and radiological characteristics of metastatic and non-metastatic bone lesions revealed significant differences between the groups. Unclear borders margins were observed in 100 % of the metastatic group compared with 31.3% of the control group, and the difference was statistically significant ($p<0.001$). Cortical destruction was detected in 94.2% of the BM group and 18.8% of the control group ($p<0.001$), while a soft-tissue component was identified in 66.7% and 21.9% of cases, respectively ($p<0.001$). During follow-up, dynamic changes were observed in 26.8% of the BM group and 9.4% of the control group, with a statistically significant difference between the groups ($p=0.036$). Although pain was more frequently reported in the BM group than in the control group (69.6% vs. 56.3%), the difference was not statistically significant ($p=0.149$).

In 14 (43.75%) of the 32 patients included in the control group, a diagnosis of multiple myeloma was confirmed. The examinations carried out in the patients: RG was performed in 7 (50%) patients, OSG in 7 (50%) patients, CT in 7 (50.1%) patients, and MRI in 10 (71.4%) patients.

On the RG examinations, osteolytic changes in the bone were observed in the patients – in particular, destructive areas in the ribs, the pelvic bone, and the vertebral bodies. Osteoscintigraphy rarely gives a specific change in myeloma, because the disease is characterized not by osteoblastic but by increased osteoclastic activity.

CT examination was effective in particular in the assessment of destructive changes in the bone structure. In these patients: the

observation of multiple “punched-out” type osteolytic defects – lytic foci within the bone with sharp contours, round or oval in shape, showing no sclerotic marginal reaction; the absence of sclerosis (the non-observation of a reactive sclerotic zone at the periphery of the lesions helps in the differentiation of myeloma from metastatic lytic neoplasms); and cortical destruction (the selective thinning or destruction of the cortical layer by the neoplasms) indicates the aggressive intraosseous spread of myeloma.

On MRI, signal changes were observed in the patients in the bone marrow – hypointense on the T1 sequence and hyperintense on the T2 and STIR sequences.

In all cases the diagnosis was confirmed by the results of a bone marrow biopsy.

Creation and substantiation of a diagnostic algorithm based on the radiodiagnostic criteria of bone metastases with an unknown primary focu.

In 50 patients with an unknown primary focus, several examinations were applied together in order to clarify the diagnosis. The number, type, and region of location of the metastatic focus were investigated in the patients.

It was shown that there is a statistically significant relationship between the type of metastatic neoplasms and the primary diagnosis ($p=0.048$) and there is no statistically reliable relationship between the number of metastatic neoplasms and the primary diagnosis ($p=0.236$).

The diagnostic results in these patients were as follows: lung cancer in 17 (34%), BC in 16 (32%), PC in 15 (30%), and RC in 2 (4%) patients. On the basis of the results of the comparative analyses carried out, 3 general diagnostic algorithms corresponding to each of the three metastasis types were developed. The algorithm constructed for osteolytic metastases shows that, when a single osteolytic metastasis is detected, the lesion is most often in the pelvic or limb bones, and this pattern is associated more often with BC. A single osteolytic focus can also be observed in renal and lung tumours, but in the observed patient group the best fit for this combination was with BC (Figure 1).

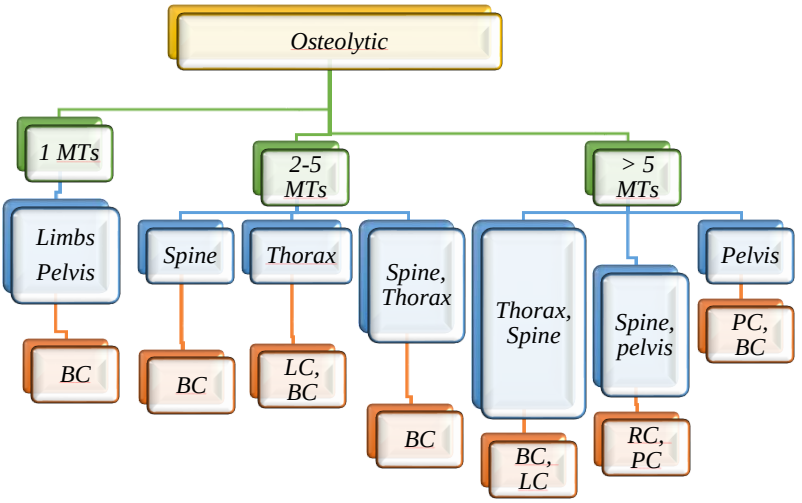


Figure 1. Diagnostic algorithm in osteolytic-type metastases

When the number of metastatic foci is between 2 and 5 and the localization is concentrated, if the predominance is in the thorax, LC and BC are more strongly probable. Combined involvement of the spine and the thorax corresponds to BC, and in this case the probability of BC increases. In cases where > 5 metastatic foci are detected, since simultaneous metastatic involvement of the thorax and the spine is characteristic of both BC and LC, both probabilities are taken into account. Combined osteolytic lesion of the spine and pelvis, on the other hand, is associated with RC and PC. Although PC usually produces osteoblastic metastasis, since a mixed and osteolytic form may be observed in the late stages, the probability of PC is not excluded. Multiple osteolytic metastases in which the pelvis is dominant are, again, most often associated with PC and BC.

The algorithm constructed for osteoblastic metastases: when there is one metastatic focus, if the lesion is most often in the thorax or the thorax–spine, it is associated more often with BC. Combined lesion of the skull and thorax may also be observed, and this too corresponds to the osteoblastic metastatic pattern characteristic of BC (Figure 2).

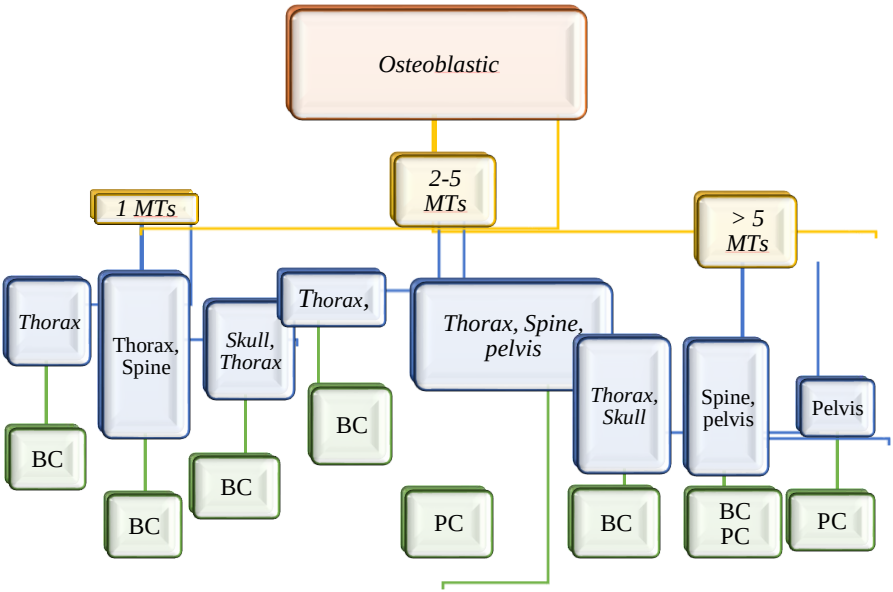


Figure 2. Diagnostic algorithm in osteoblastic-type metastases

When the number of metastases is between 2 and 5, if the metastases are predominantly in the thorax, the probability of BC and LC remains high. However, combined involvement of the spine and pelvic bones in addition to the thorax is encountered more often in cases of PC. If the number of metastases is > 5 and osteoblastic, then the most frequently affected areas – the combination of the spine and pelvic bones – are considered a typical osteoblastic spread pattern for both BC and PC, but widely disseminated vertebro-pelvic lesion appears with a higher frequency particularly in PC patients. Single and extensive involvement of the pelvis, on the other hand, is a pattern that further strengthens the probability of PC.

In mixed-type metastases, when one metastatic focus is observed, the lesion is often located in the limb bones or in a single vertebra of the spine, and these cases are associated more often with BC.

When the number of metastases is between 2 and 5, they involve mainly the spine and thoracic bones. This localization was encountered more often in BC patients. However, in cases where the metastases

involve the spine and pelvis simultaneously, the probability of PC and RC increases (Figure 3).

When the number of metastatic foci is > 5 in mixed-type foci, if extensive involvement is observed particularly along the thorax–pelvis, in our results this is characteristic of BC. Dominant involvement of the pelvis, on the other hand, is characteristic of PC and BC (Figure 3). Thus, a small number of metastases is associated mainly with BC; in the case of a moderate number of involvements, both BC and PC/RC probabilities are taken into account; and in disseminated mixed metastases, spine and pelvsi involvement increases the probability of BC.

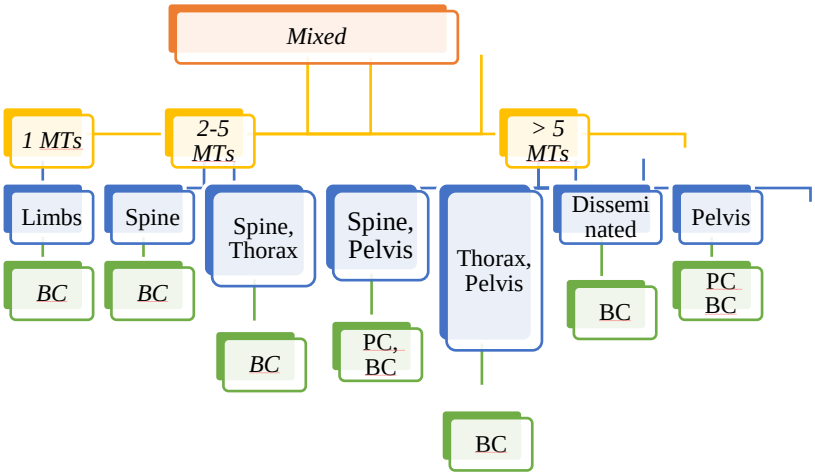


Figure 3. Diagnostic algorithm in mixed-type metastases

Evaluation of radiological imaging (CT) in the assessment of treatment outcomes in bone metastases.

The post-treatment results of 59 patients were evaluated.

The analysis of the primary oncological diagnoses showed that BC was registered in 52 of the patients (66.6%), PC in 20 (25.6%), LC in 3 (3.8%), renal-cell carcinoma in 2 (2.6%), and bladder cancer in 1 (1.3%).

Among the 59 patients who underwent CT examination after treatment, stable disease was observed in 46 (78.0%), progression in 7

(11.9%), and regression in 6 (10.2%).

The statistical association between the type of BM and the radiological response to treatment was investigated. Among 20 patients with osteolytic metastases, regression was observed in 6 (30%), while stable disease was recorded in 14 (70%). Of the 23 patients with sclerotic (osteoblastic) metastases, 19 (82.6%) demonstrated stable disease, whereas progression was observed in 4 (17.4%). No regression was detected on CT imaging in this group. Among 16 patients with mixed-type metastases, progression was observed in 3 (18.8%), while stable disease was recorded in 13 (81.2%). Regression was observed exclusively in patients with osteolytic metastases. Thus, the potential association between metastatic lesion type and treatment response was analyzed in a total of 59 patients. The analysis revealed a statistically significant association between the type of BM and CT-based treatment response ($p = 0.004$).

CONCLUSIONS

1. In the diagnosis of bone metastases, the sensitivity indices (Sn) were observed in CT (91.2–100%) and in MRI (75–100%). In OSG, Sn varied between 83.3–90.9%, and in RG between 16.7–41.7%. The specificity indices (Sp) amounted to 81.8–100% in MRI, 76.9–100% in CT, 88.9–95% in OSG, and 66.7–100% in RG. [4, 6, 15, 17].
2. A statistically significant association was found between the localization of the primary tumor and the morphological type of bone metastases. ($p<0.001$). In breast cancer, no statistically significant relationship was detected between the type of metastasis and the molecular subtypes ($p=0.094$); a statistically significant relationship was determined between the histological subtypes of BC and the type of metastasis ($p=0.022$). In lung cancer, no statistically significant relationship was detected between the histological type and the morphological type of the metastasis ($p=0.211$). In the ROC analysis, CA 15-3 showed the highest discrimination (AUC = 0.806; 95% CI: 0.719–0.893; $p < 0.001$). For CEA the AUC was 0.723 95% CI: 0.595–0.851; $p = 0.021$) and for Ki-67 the AUC was 0.665 95% CI: 0.525–0.806 $p=0.029$ [13,16,19].

3. In the comparative analysis of the clinical and radiological characteristics of metastatic and non-metastatic bone lesions, an irregular margin was identified in 10 (31.3%) and 138 (100.0%) patients in the control and main groups, respectively ($p < 0.001$); cortical destruction in 6 (18.8%) and 130 (94.2%) ($p < 0.001$); and a soft-tissue component in 7 (21.9%) and 92 (66.7%) ($p < 0.001$). Pain was observed in 96 (69.6%) patients in the main group and in 18 (56.3%) in the control group, and the difference was not statistically significant ($p = 0.149$). Dynamic change was recorded in 37 (26.8%) patients in the main group and in 3 (9.4%) in the control group ($p = 0.036$) [11].
4. According to the results of the examinations performed in 50 patients with an unknown primary focus, the predominant metastases were as follows: in prostate cancer, osteoblastic (7; 46.7%), more than 5 in number (10; 66.7%) and located mainly in the pelvic bones (10; 66.7%); in lung cancer, osteolytic (11; 64.7%), 1–5 in number (10; 58.8%) and located mainly in the thoracic bones (13; 76.5%); and in breast cancer, mixed-type (7; 43.8%), more than 5 in number (11; 68.7%) and located mainly in the thoracic bones (13; 81.3%) [10].
5. In the evaluation of treatment outcomes, regression was identified in 6 (30.0%) and a stable response in 14 (70.0%) of the 20 patients with osteolytic bone metastases; a stable response in 19 (82.6%) and progression in 4 (17.4%) of the 23 patients with osteoblastic metastases; and a stable response in 13 (81.2%) and progression in 3 (18.8%) of the 16 patients with mixed-type metastases. On CT examination, regression was recorded only in the lytic metastasis type ($p = 0.004$) [9].

PRACTICAL RECOMMENDATIONS

1. The proposed diagnostic algorithm can be used in clinical practice to determine the primary focus in cryptogenic metastases.
2. When bone foci resembling BM are observed, it is advisable to take the history of trauma into account in the differential diagnosis. Oval sclerotic foci that do not disrupt the cortical margins may be more suggestive of non-metastatic changes. The presence of a soft-tissue

component, on the other hand, can be regarded as a sign that increases the probability of myeloma or a metastatic process.

3. In the radiological reports (protocols) of bone metastases, the main diagnostic criteria – the structural type of the metastasis (lytic, blastic, mixed), its location, the condition of the cortical layer and the presence of a soft-tissue component – should be stated.

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LIST OF ABBREVIATIONS

AUC – Area Under the Curve
BC – breast cancer
BM - bone metastases
CT – Computed Tomography
CEA – Carcinoembryonic antigen
FN (−) – false negative
FP (+) – false positive
LC – lung cancer
MRI – Magnetic Resonance Imaging
OSG – Osteoscintigraphy
PET-CT – Positron Emission Tomography
PC – prostate cancer
RC – renal cancer
RG – Radiography
ROC – Receiver Operating Characteristic
Sn – sensitivity
Sp – specificity
TN(−) – true negative
TP(+) – true positive

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