

CORRELATION OF MSCT AND SCINTIGRAPHICALLY DETECTED BONE METASTASES AND SERUM LEVELS OF CA 15-3 AND ALKALINE PHOSPHATASE IN BREAST CARCINOMA PATIENTS

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Breast cancer (BC) is the most common cancer type among women and the second most common cancer type overall, and has a high affinity for metastasis to the bone system. The aim of our work was to determine the predictive value of CA 15-3 and alkaline phosphatase (ALP) in predicting the presence of scintigraphically detectable BC metastases. The study included 453 patients who had surgery performed recently, with pathohistologically proven BC who were referred for MSCT and scintigraphy because of elevated CA 15-3 and ALP values, or because of clinical signs that could indicate the existence of bone metastases of BC. MSCT was performed according to the protocol for the examined region, and skeletal scintigraphy (BS) was performed according to the standard protocol of the European Association of Nuclear Medicine (EANM). Statistical data processing included the assessment of specificity, sensitivity, positive and negative predictive value and overall accuracy of elevated CA 15-3 as a standalone predictor and combination of elevated CA 15-3 and ALP in predicting the presence of MSCT and scintigraphically detectable bone metastases of BC. In prediction of the bone metastases on MSCT and BS, combination of elevated CA 15-3 and ALP showed better sensitivity, specificity, positive predictive value, negative predictive value and overall accuracy than elevated Ca

15-3 as a standalone predictor. MSCT and BS should be considered in BC patients with elevated Ca 15-3 and ALP values, to early detection of bone metastases.

Key words: Breast cancer, CA 15-3, Alkaline phosphatase, MSCT, Skeletal scintigraphy, Bone metastases.

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KORELACIJA MSCT I SKINTIGRAFSKI OTKRIVENIH KOŠTANIH METASTAZA I SERUMSKIH NIVOVA CA 15-3 I ALKALNE FOSFATAZE KOD PACIJENTKINJA SA KARCINOMOM DOJKE

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Karcinom dojke (KD) je najčešći tip raka kod žena i drugi najčešći tip raka uopšte, i ima visok afinitet za metastaziranje u koštani sistem. Cilj našeg rada bio je da se utvrdi prediktivna vrednost CA 15-3 i alkalne fosfataze (ALP) u predviđanju prisustva scintigrafski detektabilnih metastaza KD. Studija je obuhvatila 453 pacijentkinja koje su nedavno operisane, sa patohistološki dokazanim rakom dojke, koje su upućene na MSCT i scintigrafiju zbog povišenih vrednosti CA 15-3 i ALP, ili zbog kliničkih znakova koji bi mogli ukazivati na postojanje koštanih metastaza raka dojke. MSCT je urađen prema protokolu za ispitivanu regiju, a skeletna scintigrafija (BS) je urađena prema standardnom protokolu Evropskog udruženja za nuklearnu medicinu (EANM). Statistička obrada podataka obuhvatila je procenu specifičnosti, osetljivosti, pozitivne i negativne prediktivne vrednosti i ukupne tačnosti povišenog CA 15-3 kao samostalnog prediktora i kombinacije povišenog Ca 15-3 i ALP u predviđanju prisustva MSCT i scintigrafski detektabilnih koštanih metastaza KD. U predviđanju koštanih metastaza na MSCT i BS, kombinacija povišenog CA 15-3 i ALP pokazala je bolju osetljivost, specifičnost, pozitivnu prediktivnu vrednost, negativnu prediktivnu vrednost i ukupnu tačnost nego povišen Ca 15-3 kao samostalni prediktor. MSCT i BS treba uzeti u obzir kod pacijenata sa rakom dojke sa povišenim vrednostima Ca 15-3 i ALP, radi ranog otkrivanja koštanih metastaza.

Ključne reči: Karcinom dojke, CA 15-3, Alkalna fosfataza, MSCT, Scintigrafija skeleta, Metastaze u kostima

Introduction

Breast cancer (BC) is the most common cancer in the female population with over 2 million newly diagnosed cases annually and over 600,000 deaths directly related to breast cancer as the underlying disease (1).

Among the risk factors for the occurrence of BC, we most often find the age of the patient, the use of contraceptives, early menarche, as well as numerous genetic factors such as the presence of the BRCA 1 and BRCA 2 genes, which increase the risk of breast cancer by 5% to 10% in the general population (2). After the initial diagnosis and therapy, which includes surgical intervention and/or radiation and chemotherapy after tumor removal, patient monitoring continues with regular controls in the sense of monitoring radiological, scintigraphic and laboratory analyzes in terms of early detection of the appearance of distant secondary deposits that have the greatest impact on the survival rate of female patients from the population with BC.

In order to monitor the described group of patients, laboratory analyzes of CA 15-3 levels are used; and alkaline phosphatase (ALP), elevated levels of which may indicate the presence of distant secondary deposits. Evidence of the existence of bone secondary deposits is carried out by radiological methods, the most common of which is the MSCT methodology and nuclear medicine scintigraphy of the skeleton (BS) with ^{99m}Tc labeled diphosphonates.

The goal

In our work, we processed the correlation of MSCT and BS proven skeletal metastases of BC

with suspicious findings of biochemical indicators Ca 15-3 and ALP in order to recognize the predictive value of biochemical parameters for the existence of bone metastases of BC.

Patients and methods

In our study, a total of 453 women were examined in whom surgical intervention was performed in the previous period, the presence of BC was proven histopathologically, and initial radio and chemotherapy were carried out. The inclusion factor for inclusion in the study was the existence of a tumor without clinical and histopathological signs of the existence of distant metastases. The average age of our patients was 58 ± 17 years old. The period after the initial therapy until the radiological and scintigraphic diagnosis was an average of 3.7 ± 1.6 years. During the follow-up period, the patients underwent laboratory analysis of Ca 15-3, CEA and ALP as part of the regular protocol. Values of Ca 15-3 up to 30 U/mL, CEA up to 3.0 ng/mL and ALP up to 147 IU/L were considered normal and were therefore an exclusion factor for the inclusion of female patients in the study. Elevated values of the mentioned biochemical parameters, together with clinical signs in terms of the appearance of unexplained painful sensations in the skeletal system were an indication for conducting MSCT and later BS in order to detect the existence of distant bone metastases of BC.

Ca 15-3 levels; CEA and ALP were performed on a UniCel Dxl 600 (Beckman Coulter) with Hybritec Chemiluminescent Immunoassay with previously mentioned values considered normal and prescribed by the manufacturer.

Skeletal scintigraphy was performed on a SIEMENS E-Cam double-headed SPECT gamma camera according to the protocol of the European Association of Nuclear Medicine (EANM) in "Whole Body" (WBS) modalities, targeted static scintigrams and single photon tomography (SPECT) in regions that were suspicious for the existence of secondary deposits and had inconclusive findings on WBS and targeted skeletal scintigrams (3).

According to the protocol for BS, WBS was performed in AP and PA projections three hours after the intravenous application of the radiopharmaceutical (99mTc - DPD) which was marked according to the manufacturer's specification (Institute for Nuclear Sciences Vinca - Belgrade) with fresh eluate of Technetium (99mTc) in a dose of 740 MBq, with a speed of movement of the patient's body of 12 cm/min, with the use of acquisition parameters with tracking of the patient's body line, so that the total duration WBS scintigraphy was approximately 17 minutes. Targeted static scintigrams were performed in the time-lapse modality with an acquisition duration of 10 minutes per region of interest. SPECT was performed in 32 projections per region of interest with rotational movement of the SPECT System detector according to the acquisition parameters of 32 projections lasting 30 seconds per projection, at 5.6 degrees of rotation between projections in a total arc of 180 degrees. The reconstruction of the obtained tomograms was done in the sagittal, coronal and transverse axes with an extrinsic resolution of 3 to 6 mm per tomogram. The scintigram interpretation was done by two nuclear medicine specialists, without mutual consultation. A positive scintigraphic finding

was considered increased focal activity of 99mTc DPD in the regions of interest, with characteristic osteoblastic features of focal changes. Focal regions with significantly reduced radiopharmaceutical fixation but with the existence of a hyperfixation rim due to increased osteoblastic activity were considered osteolytic lesions.

MSCT of the abdomen and pelvis was performed in the supine position with both hands of the patient placed above the head at a voltage of 120 kVp. The initial scout is performed from the level above the diaphragm to the level below the lesser trochanter. The scanning direction is craniocaudal. The field of view (FOV) is adjusted according to the patient's dimensions. Contrast phases are arterial and venous phase. The scan was performed in the "single breath-hold" phase of respiration, i.e. in inspiration. Multiplanar reconstructions are: axial sections, coronal sections, sagittal sections, with a slice thickness of 1.25 mm.

A positive radiological finding meant:

- lytic metastases: bone lesions of soft tissue density - higher density than fatty tissue starting from -30 HU and upwards. Also, characteristics of lytic metastases are cortical destruction and/or periosteal reaction (6,7).
- sclerotic bone metastases: on MSCT, sclerotic bone metastases appear as hyperdense lesions with an approximate attenuation of 885-1060 HU (8,9).
- mixed osteolytic/osteosclerotic metastases: they present with a combination of signs of lytic and sclerotic bone metastases (10). A positive scintigraphic finding was considered the existence of one or more foci with significantly

increased fixation of radiopharmaceuticals, which corresponded to the existence of an osteoblastic response of the skeleton to the presence of a secondary deposit of prostate carcinoma in the skeleton. The existence of focal changes with significantly reduced fixation and the existence of a hyperfixation rim was considered the presence of osteolytic metastatic changes or the existence of a mixed osteoblastic-osteoclastic response to the presence of hematogenously spread metastatic prostate carcinoma disease in the skeleton.

Statistical processing was done with spss software, using descriptive testing, i.e. cross-tabulation of the obtained results. Normal and pathological Ca 15-3 and ALP values were correlated with the presence or absence of secondary deposits on the skeleton. Pathological Ca 15-3 values with the presence of secondary deposits on MSCT and skeletal scintigraphy were considered truly positive, normal Ca 15-3 values with normal MSCT and scintigraphic findings were considered truly negative. A false positive finding was a pathological Ca 15-3 value without MSCT and scintigraphically proven metastases in the skeleton, while a normal Ca 15-3 value with the presence of metastases on MSCT and scintigraphy was considered a false negative.

Correlation of MSCT and scintigraphic findings with combined values of Ca 15-3 and ALP was used, where detected secondary deposits in patients with elevated values of Ca 15-3 and elevated values of ALP were considered as a really positive finding. False positive findings were considered negative MSCT and BS findings with elevated Ca 15-3 and ALP values. The detection of metastatic changes on MSCT and

BS with normal values of Ca 15-3 and ALP were considered false negative values, while MSCT and BS without signs of secondary deposits with normal values of Ca 15-3 and ALP were observed as truly negative findings.

Results

Out of the total number of patients, the existence of secondary BC deposits was detected in 67% (Figures 1 and 2).

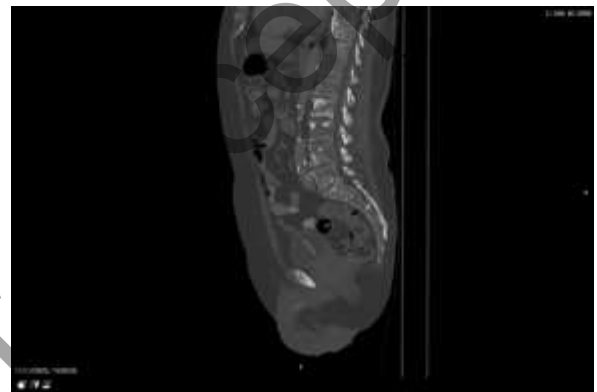


Figure 1. A 63-year-old patient with signs of multiple secondary deposits on MSCT

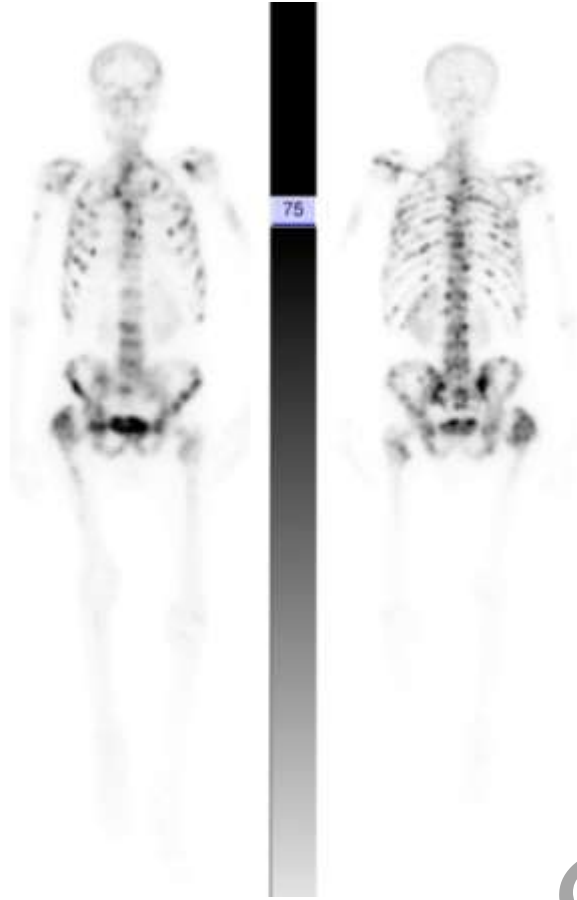


Figure 2. 99mTc-DPD bone scintigraphy in whole body modality, anterior and posterior projections. Multiple metastases in the skeletal system.

Apart from the existence of multiple metastatic changes, MSCT and BS showed a very high accuracy in the detection of individual metastatic changes in the skeletal system in patients with BC (Figures 3 and 4).

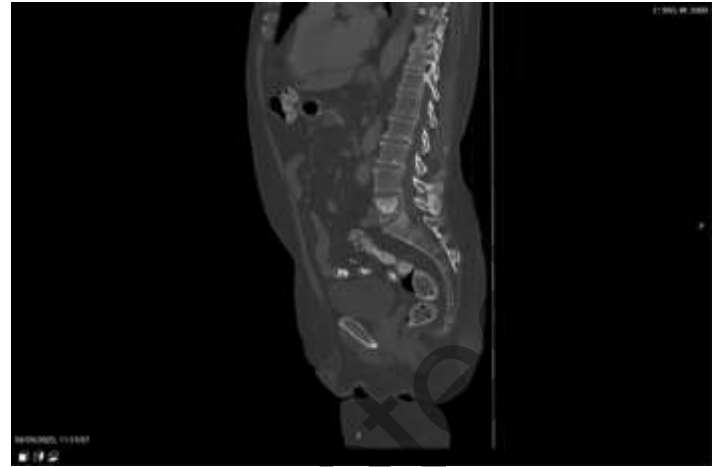


Figure 3. Suspected metastasis in L5 spinal vertebra confirmed by MSCT.

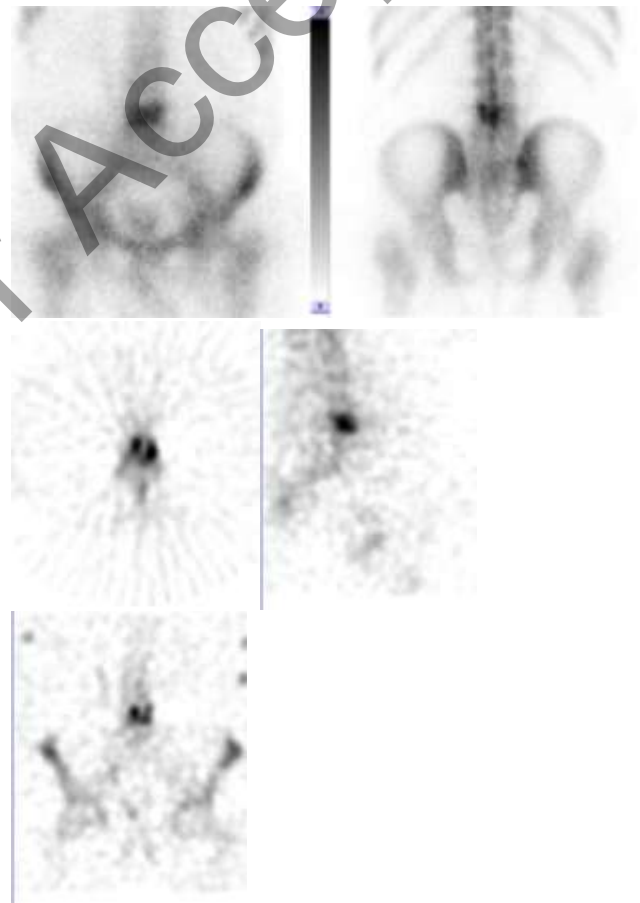


Figure 4. Suspected metastasis in L5 spinal vertebra confirmed by SPECT modality.

In 33% of patients, MSCT and BS findings were negative, i.e. without radiological or

scintigraphic signs of metastatic changes in the skeletal system (Figures 5 and 6).



Figure 5. A 65-year-old patient with no signs of secondary deposits on MSCT



Figure 6. ^{99m}Tc-DPD bone scintigraphy in anterior and posterior projections. Normal

scintigraphic finding without signs of metastases.

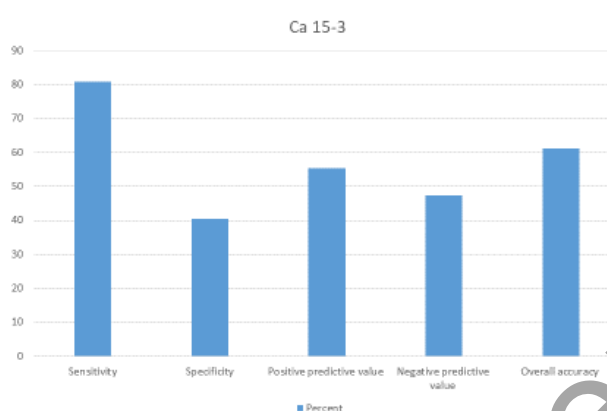
In patients with a positive result on MSCT and BS in terms of the existence of secondary deposits, Ca 15-3 showed pathological values in 53% of cases, while normal values of the same marker were found in 47% of patients with metastatic changes proven on MSCT. This result indicates a significant number of false-negative predictive values of Ca 15-3 as an independent marker for the existence of bone secondary BC deposits.

Comparing the positive findings of MSCT and BS with the combination of Ca 15-3 and ALP values showed that 87% of patients with metastatic changes on the skeleton have elevated Ca 15-3 and ALP values.

On the other hand, patients with negative MSCT and BS findings in terms of the presence of secondary deposits showed a positive Ca 15-3 finding in 36% of cases. By comparing the negative findings of metastatic changes on MSCT and the combination of Ca 15-3 and ALP, it was shown that only 5% of patients without metastatic changes on MSCT and BS have elevated values of the combination of Ca 15-3 and ALP.

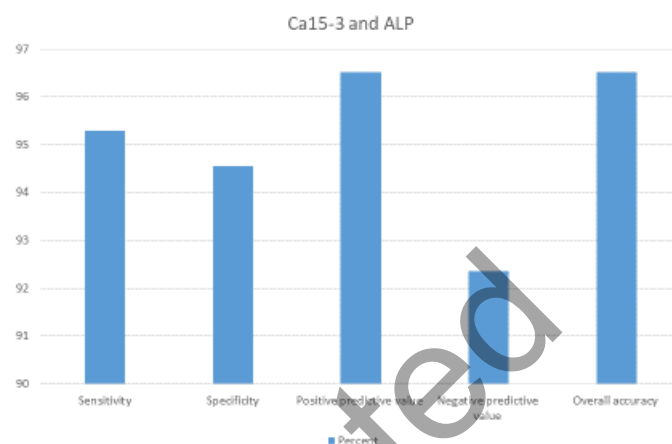
The cross-tabulation of the obtained results, in terms of comparing the level of Ca 15-3 values, the combination of Ca 15-3 values and ALP and MSCT and scintigraphic findings, yielded the following results:

Statistical processing of the obtained data yielded results that showed that serum Ca 15-3 values had a sensitivity of 80.88%; specificity of 40.5%; a positive predictive value of 55.40%; a negative predictive value of 47.33% and an overall accuracy of 61.22% (95% CI), for correlation with the existence of BC metastases on MSCT and BS. (Graph 1.)



Graph 1. Sensitivity, specificity, positive predictive value, negative predictive value, and overall accuracy of Ca 15-3 as a standalone predictor of bone metastases in patients with BC.

Statistical analysis showed that the combination of Ca15-3 and ALP in correlation to the existence of BC metastases in the skeleton on MSCT and BS had a sensitivity of 95.3%, specificity of 94.55%, positive predictive value of 96.51%, and negative predictive value of 92.36% and overall accuracy of 96.51% (95% CI) (Graph 2.)



Graph 2. Sensitivity, specificity, positive predictive value, negative predictive value, and overall accuracy of combination of elevated values of Ca 15-3 and ALP as a predictor of bone metastases in patients with BC.

Discussion

Breast cancer ranks infamously second in terms of incidence in the world. It is believed that every year a large number of female patients (about 600,000) have a fatal outcome of the disease as a direct consequence of the underlying disease of BC. (4).

Despite global efforts in the prevention of BC and increasing efforts in terms of the use of screening tests for the detection of BC, the number of female patients seems to be increasing year by year worldwide. Breast self-examinations, control mammography, the use of biochemical parameters in screening and possible early detection show certain results in terms of slowing down the incidence trend, but

the total number of BC in all countries of the world is still increasing (5).

Therapy of diagnosed BC in most cases involves surgical intervention, which can be mild or radical depending on the case. Sparing operations are of course preferable because, on the one hand, they indicate a timely diagnosis of BC, while on the other hand, they greatly contribute to an overall better quality of life after the surgical intervention. Planning of procedures and detection of sentinel lymph nodes preoperatively and intraoperatively play a major role in sparing operations (6).

After surgery, the usual therapeutic approach involves local radiation therapy and/or chemotherapy, which now represents a practically unavoidable path in the therapeutic treatment of BC.

After the initial therapies, in the protocol for the treatment and follow-up of BC, we come across the use of various diagnostic procedures, of which the detection of the possible existence of remote secondary deposits, which are expected in BC, even if they were not present during the initial diagnosis, plays a major role.

Breast cancer has a great tendency to form skeletal metastases, the detection of which is performed by radiological methods, including MSCT, but nuclear medicine methods, which include the use of skeletal scintigraphy with ^{99m}Tc -DPD (7).

Even if indisputable in the diagnosis of bone metastases, radiological and scintigraphic methods by the nature of their methodology imply the use of ionizing radiation, and the question of the necessity of their use is always raised, and even if we decide to use such a

diagnostic approach, we should always adhere to the as low as reasonably achievable (ALARA) principle, which boils down to the smallest possible use of ionizing radiation while achieving an adequate diagnostic response (8).

In order to have the most adequate approach in the use of radiological and scintigraphic methods in the detection of possible distant bone metastases of BC, the question of proper referral of patients to these diagnostic modalities arises.

To this end, non-invasive tests are found, if possible, that would indicate possible disorders of the bone system in the sense of the existence of metastases, which are mainly reduced to biochemical analyzes of tumor markers and other biologically active compounds whose elevated levels would indicate the possibility of the existence of secondary deposits of BC in the skeleton.

One of the tumor markers is Ca 15-3, which proved to be a relatively reliable marker in monitoring the existence of a possible relapse of the disease, or as a marker of the formation of remote secondary deposits in the skeleton of patients with BC after initial therapeutic treatments. Several studies have shown the positive nature of Ca 15-3 in the detection of both relapse and suspicion of metastatic skeletal changes in BC (9).

On the other hand, alkaline phosphatase is a very reliable marker for suspecting the development of skeletal secondary deposits in all cancers, including breast cancer. High ALP values can also be false positives in the case of metabolic disorders of the skeletal system, so it

is partially reliable as a specific marker in an independent sense.

In our study, we tried to correlate the values of Ca 15-3 as an independent marker in relation to the combination of Ca 15-3 and ALP in terms of predicting the existence of skeletal secondary deposits. Female patients were referred for radiological and nuclear medical diagnostics after obtaining elevated values of Ca 15-3 alone or a combination of elevated Ca 15-3 and ALP values.

In the study we performed on 453 women who underwent surgery for BC, we compared skeletal metastases detected radiologically and scintigraphically with initially elevated Ca 15-3 or with a combination of pathological findings of Ca 15-3 and ALI.

Our study showed significantly higher specificity, sensitivity and overall accuracy of the combination of pathological values of Ca 15-3 and ALP in terms of predicting the presence of skeletal metastases than pathological values of Ca 15-3 as an independent marker for secondary deposits of BC in the skeleton.

Conclusion

Ca 15-3 is a relatively reliable marker for establishing suspicion of relapse or formation of secondary BC deposits. The combination of pathological values of Ca 15-3 and ALP proved to be a much more reliable predictor for the existence of secondary deposits of the skeletal system originating from BC. The use of a combination of Ca 15 - 3 and ALP enables the timely use of radiological and nuclear medicine methods for diagnosing the existence of secondary BC deposits with the possible possibility of avoiding unnecessary referral of

patients to diagnostics that involve the use of ionizing radiation.

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