^{99m}Tc-MIBI scintimammography and digital mammography in the diagnosis of multicentric breast cancer

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Abstract

Objective: To compare diagnostic accuracy of scintimammography (SMG) and digital mammography (DS) in the diagnosis of multicentric breast cancer. **Subjects and Methods:** Three hundred and sixty seven women with histologically confirmed breast cancer were included in this analysis. All patients were candidates for conservative breast surgery and had cT1-3N0-1 stage of disease. Scintimammography was performed in prone position 5-10min after intravenous injection of 740MBq of technetium-99m-methoxy-isobtyl-isonitrile (^{99m}Tc-MIBI) with acquisition time of 10min for every lateral and anterior projection. Digital mammography was done in all women according to a standard clinical protocol. Final diagnosis was established by histopathology. Multicentric breast cancer was defined as 2 or more distinct invasive tumors located in more than one quadrant or additional lesions from the primary tumor of more than 4cm in size. **Results:** According to histopathological examinations multicentric breast cancer was diagnosed in 47 of 367 (12.8%) patients. Scintimammography was more effective than mammography in detecting multicentric breast cancer: sensitivity: 83.0% vs 40.4% (P<0.001), specificity: 97.8% vs 95.3% (P=0.4), accuracy: 95.9% vs 88.3% (P<0.001), positive and negative predictive values: 84.8% vs 55.9% (P=0.004) and 97.5% vs 91.6% (P<0.001), respectively. Combination of DM and SMG was characterized by increased sensitivity (93.6%), worse specificity (93.4%), accuracy (93.4%) and worse predictive value (67.7%) as compared to only SMG. **Conclusion:** Scintimammography was significantly much better by all statistical parameters than DM in the detection of multicentric breast cancer. High positive predictive value of scintimammography (84.8%) advocates it as a tool for surgery and radiotherapy planning.

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Introduction

An accurate diagnosis in order to differentiate between multifocal (MF) and multicentric (MC) breast cancer disease is important for prognosis and selection of treatment strategy. The prognostic value of MF and MC breast cancer was evaluated in several large retrospective series. Yerushalmi et al. (2012) [1], in 19,754 women with breast cancer, didn't find that MF or MC disease had a significant impact on the overall, disease specific or local relapse free survival. In another study of 6,134 patients Ataseven et al. (2015) [2] demonstrated that patients with MC disease had worse overall and disease free survival than the patients with unifocal (UF) or MF breast cancer. Other reports indicated that MF or MC breast cancer disease was associated with a substantial risk of local relapse after breast conservative surgery [3-5]. Others indicated that MF breast cancer can be effectively treated by conservative surgery and subsequent radiotherapy [1] while others reported that in MC breast cancer disease conservative treatment can be associated with significant increase of local recurrence rate [5]. At present, patients with MC breast cancer are not usually considered as candidates for breast conserving surgery. Therefore it is important to early diagnose MF and MC breast cancer disease.

The reported incidence of MF and MC disease varies from 9% to 40% [2, 6] with about 30%-45% of these cases being MC breast cancer. Mammography (MMG) is the standard imaging tests for the diagnosis of breast cancer and evaluation of its extent. At the same time numerous studies indicate that 19%-33% of MF and MC lesions are missed by this conventional imaging [7-9]. During the last decade it was shown that in comparison with MMG, breast imaging with technetium-99m-labeled methoxy-isobtyl-isonitrile (^{99m}Tc-MIBI) could significantly increase the detectability of early breast cancer lesions as in MF or MC breast cancer [10-12].

In this study, we studied the diagnostic accuracy of scintimammography (SMG) in detec-

ting MC breast cancer as compared with MMG. In addition, we tried to determine a possible diagnostic gain by combining both MMG and SMG in these patients.

Subjects and Methods

Patients

All 367 patients included in the study were candidates for breast conserving surgery and had clinical T1-3N0-1 stage of disease. The Institutional Ethical Committee approved this study in which we retrospectively compared the accuracy of digital MMG and SMG in detecting MC breast cancer. All examinations were performed between 09/01/2014 and 01/05/2016. Diagnostic images of 367 women (median age 53.2±12.7; range 24-82) with histologically confirmed breast cancer were independently reviewed by an experienced radiologist (C.A.V. and B.E.A.) and nuclear medicine specialists (N.S.N. and K.P.I.). Radiologists and nuclear medicine specialists were blinded to all other examinations.

Image acquisition

Mammographic digital images were obtained on Senographe DS «GE» unit with a flat panel detector (Se, 100μm) and image size-24x31cm^2=7.4 megapixels. Mammographic examination was performed with breast compression and included routine cranio-caudal and medio-lateral-oblique views of the breasts, additional projections and magnification views over the area of suspected lesions.

The obtained images were analyzed and described according to BI-RADS (Breast Imaging Reporting and Data System) lexicon [13]. Multicentric breast cancer was defined as 2 or more distinct invasive tumors occupying more than one quadrant or additional lesions noted more than 3cm from primary tumor. Detection of additional grouped calcifications of malignant type occupying a small portion of breast tissue (more than 15 pieces per sq.cm) was considered as another mammographic sign of MC breast cancer.

The mammographic density of the breasts was determined according to BI-RADS classification: A-entirely fatty, B-fatty with scattered areas of fibroglandular tissue, C-heterogeneously dense, and D-extremely dense. In our analysis cases with C and D patterns of the breast density were considered as "dense breast tissue". In evaluated 357 women with histologically confirmed breast cancer dense breasts were mentioned in 139 (39%) patients.

Breast imaging with ^{99m}Tc-MIBI was performed with a dual detector single photon emission tomography (SPET) unit «Forte» (Philips) with low energy, all purpose collimation. Images of both breasts were obtained 10-15min after injection of 740MBq of ^{99m}Tc-MIBI into a footstep vein. Planar scintigraphic images were acquired in anterior (supine) and lateral (prone) positions with a lead shield placed between two mammary glands. Ten minutes after the tracer injection images were acquired into 256x256 matrix with 600sec exposition of each projection and breast "in touch" with the detector. Special attention was paid to standardization of basic acquisition parameters: injected activity, time after injection, exposition time and distance between a breast and a detector. Multicentric breast cancer was defined as 2 or more distinct foci of increased ^{99m}Tc-MIBI uptake in the breast occupying more than one quadrant, or additional lesions noted more than 3cm away from the primary tumor.

Confirmation of multifocal or multicentric breast cancer

Finally, 224 of the 367 studied women underwent mastectomy and the remained 143 conserving breast surgery. Removed breast tissues were reviewed by experienced pathologists and tumors were categorized as unifocal, multifocal or multicentric breast cancer. The pathological report was used as the gold standard for final diagnosis. When diagnostic conclusion of breast imaging about MC breast cancer corresponded to pathology data, the result was considered as true positive, if pathology examination indicated a UF/MF breast cancer, diagnostic data were determined as false positive. The diagnostic test was classified as true negative when the UF/MF breast cancer on images corresponded to UF/MF breast cancer in the report of the pathologist. False negative results were noted in women with UF/MF breast cancer on images and MC breast cancer on pathology.

Statistics

Statistical analysis was performed using "Statistic" program. Chi-squared test was used to assess the statistical differences in the diagnostic performance of SMG, MMG and their combinations. Patient-based sensitivity, specificity, accuracy, negative and positive predictive values (PPV, NPV) were calculated.

Results

Breast cancer was diagnosed in all 367 cases by histological examination of the surgical samples, UF/MF involvement in 320 women (87.2%) and MC breast cancer in the remaining 47 (12.8%) cases. In patients with MC breast cancer invasive ductal carcinoma was diagnosed in 31 (65%), invasive ductal carcinoma with extensive intraductal component, in 4 (8,5%) and lobular carcinoma in 12 (25,5%) cases.

Diagnostic performance of MMG and SMG is presented in Table 1. The sensitivity of SMG with ^{99m}Tc-MIBI reached 83.0% and was significantly superior to MMG (P<0.001). In addition, SMG demonstrated a similar specificity 97.8%, (P=0.4) and higher overall accuracy 95.9% (P<0.001) in detecting MC breast cancer. Negative and positive predictive values of SMG were 97.5% (P<0.001) and 84.8% (P=0.004), respectively (Table 2).

The SMG and MMG correlation showed that false negative conclusions of SMG (5 observations) were mentioned more frequently in cases when MC disease manifested by MMG like an architectural distortion or small groups of microcalcifications with indistinct boundaries, of different density and shape, located along the convoluted ducts in several segments

of the breast.

In 2 women with false negative SMG results additional lesions were less than 10mm in diameter (Figure 1). In another case it was detected as microcalcifications (>15 per 1cm^2). On the contrary, false positive results of SMG usually were mentioned in women with proliferative fibroadenomas that manifested by large lesions of 30mm and more in diameter. Such changes were observed in 5 patients.

The main cause for the false negative results of MMG (20 cases) was high density of the breast tissues that prevents effective visualization of the anatomical changes caused by the tumour lesions (Figure 2). In another 8 cases the false negative results were found in women with fibrocystic lesions (Figure 3). The most frequent reasons for the false positive MMG results were the dishormonal hyperplastic mastopathy (10 cases) and fibrocystic breast condition (5 cases).

Table 1. *Patient-based analysis: diagnostic performance of mammography and scintimammography in the detection of multicentric breast cancer.*

Diagnostic performance	MMG	SMG	P
Sensitivity	40.4%	83.0%	<0.001
Specificity	95.3%	97.8%	=0.4
Accuracy	88.3%	95.9%	<0.001
PPV	55.9%	84.8%	=0.004
NPV	91.6%	97.5%	<0.001

SMG: scintimammography, MMG: mammography, PPV/NPV: positive/negative predictive value

Table 2. *Mammography and scintimammography diagnostic performance related to mammographic breast density.*

	Breast density	True positive	False positive	False negative	True negative	Sensitivity %	Specificity %	Accuracy %	Positive predictive value	Negative predictive value
MMG	Normal	18	10	23	204	43.9%	95.3%	87.1%	64.3%	89.9%
	Dense	1	5	5	101	16.7%	95.3%	91.1%	16.7%	95.3%
SMG	Normal	34	5	7	209	82.9%	97.7%	95.3%	87.2%	96.8%
	Dense	5	2	1	104	83.3%	98.1%	97.3%	71.4%	99%
MMG + SMG	Normal	38	18	3	196	92.7%	91.6%	91.8%	67.9%	98.5%
	Dense	6	3	0	103	100%	97.2%	97.3%	66.7%	100%

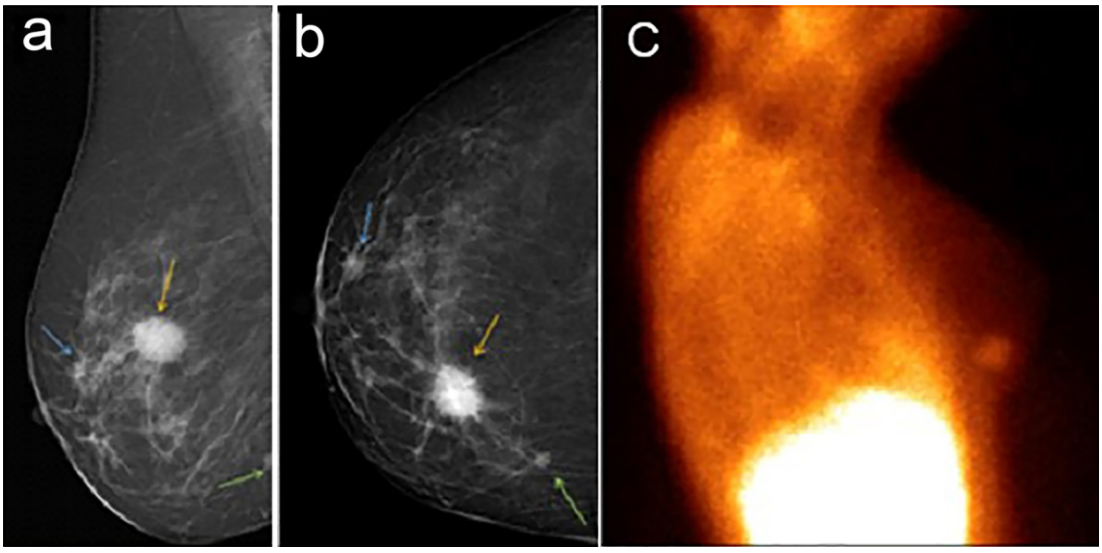

Figure 1. Medio-lateral-oblique (a) and cranio-caudal (b) mammograms of a 60 years old patient with non-palpable breast lesion. Mammography revealed 3 lesions (arrows) with spiculated irregular margins. Only one focus of ^{99m}Tc-MIBI uptake was identified on scintimammograms (c). Pathology diagnosis was, multicentic invasive ductal carcinoma.

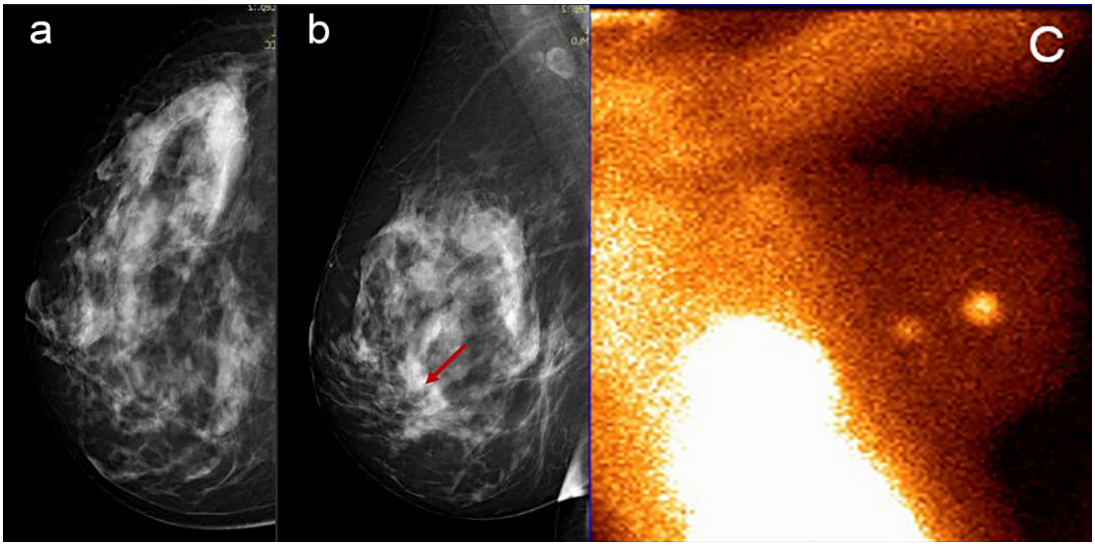

Figure 2. Cranio-caudal (a) and medio-lateral-oblique (b) mammograms of a 54 years old woman with non-palpable breast lesion. Unifocal solid mass with indistinct margins was shown clearly identified in the heterogeneously dense (type C) breast. Two foci of intensive ^{99m}Tc-MIBI uptake are clearly detected on the scintimammogram (c). Multicentic invasive non-specified breast cancer was confirmed by histological examination

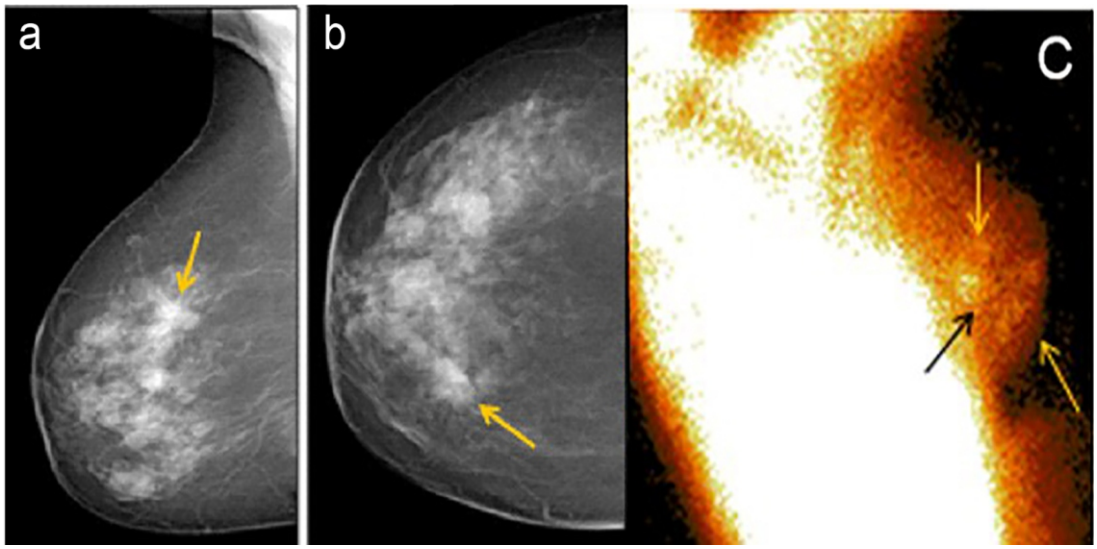

Figure 3. Medio-lateral-oblique (a) and cranio-caudal (b) mammograms of a 40 years old patient with non-palpable breast lesion. Multiple cysts are detected in the heterogeneously dense (type C) breast. Solid mass (20mm) with irregular speculated margins (arrows) was interpreted as unifocal breast cancer (Lesion BI-RADS 5). Scintimammography detected five foci of pathological ^{99m}Tc-MIBI uptake that were localized in different quadrants of the right breast. Multicentic invasive ductal carcinoma was diagnosed by histological examination.

Taking into account significant differences in the nature of false negative and false positive results on SMG and MMG, we assumed that the combination of these diagnostic methods would increase the accuracy of MC breast cancer detection or at least provide a significant increase of sensitivity. The obtained results showed that in cases when the MC disease was diagnosed in patients with SMG or MMG signs of MC breast cancer, the frequency of true positive results raised to 44 cases together with the increase of false positive conclusions (21 cases). This led to a significant growth of sensitivity and simultaneous specificity drop (Table 1). However, it has to be noted that the combination of SMG and MMG did not demonstrate significant increase in sensitivity compared to the SMG alone (P=0.11), rather it was associated with significantly loss specificity (P=0.007) and decrease of the positive predictive value (0.04).

Discussion

The obtained data demonstrated a sufficiently high frequency of MC breast cancer cases in the examined patients (13%). In the literature, the incidence of MC disease varies from 4.4% to 9.5% [2, 6, 14] and can even reach 21% [15]. According to the criteria used in our study, the multicentric character of breast cancer can be determined not only in

women with lesions localized in different breast quadrants but also in cases when the distance between the lesions is more than 3cm. This fact can prove a sufficiently high frequency of the identified multicentric changes.

Mammography still represents the methods of reference in both the diagnosis of breast cancer and its local staging. However, the accumulated clinical data indicated that in women with small lesions and/or dense breast tissues sensitivity of MMG can decrease to 61%-67% [16, 17]. The use of additional modalities (magnetic resonance imaging (MRI), positron emission tomography (PET), SMG) provides a significant additional value in diagnosis of early breast cancer and MF/MC disease [9, 18, 19].

A significant impact of scintigraphy is identifying MF/MC breast cancer was initially shown by Cwikle et al. (2001) [20]. The authors compared results of SMG, MMG and histopathologic assessments of breast tissue after mastectomy in 353 primary patients with breast cancer. They found that sensitivity of SMG in detection of MF/MC breast cancer was 52% in contrast with 22% sensitivity for combination of MMG and US. In our study SMG was able to visualize MC disease in 39/47 cases with 97.8% specificity. In the whole group sensitivity of SMG significantly outperformed mammography (83.0% vs 40.4%). The most promising results were obtained in women with dense breasts when sensitivity and specificity of SMG were 83.3% and 98.1%, respectively. This result is not surprising in the content of the reported high sensitivity of breast imaging with ^{99m}Tc-MIBI in the detection of early breast cancer in women with radiologically dense breasts [21-23].

High diagnostic performance of SMG in our study can be explained by several causes. First of all, we used SMG for detection of only MC breast cancer because of its obvious therapeutic and prognostic value [3-5]. Taking into account sufficient distance between lesions (at least 3cm) in women with MC breast cancer, it is possible to propose that the efficacy of MC breast cancer detection can be higher than in women with multifocal breast cancer. It is also possible to propose that the progress in technology of SPET cameras and rigorous standardization of the procedure can improve the accuracy of SMG. This is especially true for modern methods of SMG-breast-specific gamma imaging and molecular breast imaging [20, 21]. The main advantage of these techniques for breast cancer visualization with ^{99m}Tc-MIBI is a high spatial resolution, which gives opportunity to detect lesions as small as 4-6mm. Not surprisingly the sensitivity of molecular breast imaging for detection of breast cancer exceeded 90% [10, 11] and became comparable with MRI [23, 24]. At the same time, specificity of molecular breast imaging remained at the level of 80%-89% [21, 22, 25] significantly exceeding the MRI results, which vary around 60%-70% [22, 24]. Kim et al. (2012) [26] reported that in 66 women with suspicious lesions in dense breasts, specificity of molecular imaging with ^{99m}Tc-MIBI was more than 2 times higher than specificity of MRI: 92.3% versus 39.4%. Systematic review of the MRI data from 19 studies (2610 women with breast cancer) demonstrated that MRI detected additional lesions in 16% cases but with very high (33%) false positive rate since every third lesion was false positive [27]. On the contrary, Edwards et al. (2016) [28] reported that in 218 women with breast cancer, breast-specific gamma imaging with ^{99m}Tc-MIBI changed the treatment strategy from breast-conserving surgery to mastectomy in 11.9% of patients with no cases of overestimation of breast cancer extent. Other reports [29, 30] confirm that breast cancer visualization with ^{99m}Tc-MIBI can reveal lesions remote from primary tumour in 18%-22% patients with only 7%-10% false positive rate. Even-Sapir et al. (2016) [22] reported that in 61 patients with breast cancer which after local staging with mammography and US were scheduled for breast-conserving surgery, molecular breast imaging with ^{99m}Tc-MIBI revealed unexpected true positive lesions in 25% of the patients and so changed treatment planning. These findings changed initial choice of treatment approach in 15% of these cases.

Our data confirmed high specificity (97.8%) and overall accuracy (95.9%) of breast imaging with ^{99m}Tc-MIBI even when it was performed with conventional SPET cameras. In addition, we found incremental value of SMG and MMG combination in detecting MC breast cancer when sensitivity reached 93.6%. Low positive predictive value (67.7%) of this combination precludes its use as an instrument for surgical treatment planning but makes it a very promising tool for selection of patients for breast-conserving surgery with a subsequent partial breast irradiation. On the contrary, SMG can be successfully used for selecting women for breast conservation with subsequent whole breast irradiation that would probably be able to eradicate few MC lesions missed by SMG. Since 2017 in our practice we use the algorithm represented in Figure 4.

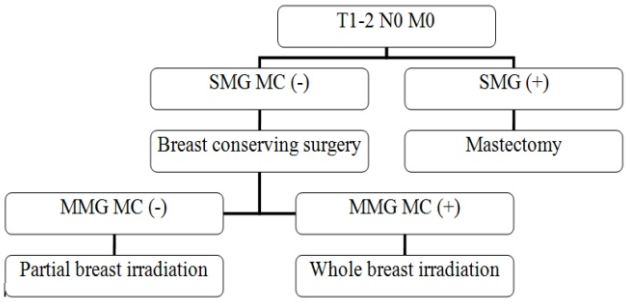

Figure 4. Flow-chart shows the role of using both scintimammography and mammography for therapy planning in patients with T1-2N0M0 breast cancer. Scintimmamography MC (-) means SMG without signs of multicentric breast cancer. Scintimmamography MC (-) means SMG demostrated signgs of multicentric breast cancer. Mammography MC (-) means MMG without signs of multicentric breast cancer. Mammography MC (+) means MMG demostrated signgs of multicentric breast cancer.

This study has several important limitations: Because of the retrospective nature of the study our data can be affected by selection bias. First of all, substantial number of the patients underwent breast-conserving surgery, and real frequency of MC disease in these women could be underestimated. In addition, decision-making on the surgical strategy was influenced by diagnostic imaging, mainly by SMG and MMG. This can influence the sensitivity values for both modalities. It must be considered that in retrospective studies the accuracy

of diagnostic conclusions can be affected by additional information from other available diagnostic modalities. We tried to overcome this limitation by blinded secondary reporting of SMG and MMG data.

For our knowledge this paper is the first report that proves significant advantage of SMG in diagnosis of MC breast cancer in women with radiologically dense breasts. In addition, we found that combination of MMG and SMG could deny MC character of breast cancer with a very high certainty.

In conclusion, our study has shown that SMG is significantly more sensitive (83.0%) than MMG (40.4%) in the detection of MC breast cancer, especially in women with dense breasts. Taking into account the very promising specificity (97.8%) of SMG, this procedure can be considered as a useful tool to guide surgeons to perform a more appropriate surgical treatment. The combination of SMG and MMG is characterized by exceptional sensitivity (93.6%) while all other statistical parameters are worse as compared to those when SMG was performed alone for detecting MC breast cancer. Thus SMG can be used among others and for selecting candidates for accelerated partial breast irradiation.

As it was mentioned above, MC breast cancer was most frequently missed by MMG in women with radiologically dense breasts. Therefore, we compared diagnostic performance of MMG and SMG in women with normal (A, B) and dense (C, D) breasts (Table 2). We found that accuracy of MMG and SMG was comparable in women with normal breast density but in women patients with dense breasts the SMG was significantly more sensitive in detecting MC breast cancer.

The authors declare that they have no conflicts of interest

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