peer reviewed **ARTICLE OF INTEREST**

Breast cancer: update on imaging modalities

Johannes Peters[1] *MBBS* | **Gudrun Peters**[2] *MD, FRANZCR* | **Anne Margaret Lynch**[3] *MBChB, FRANZCR*

[1]*Royal Perth Hospital, Australia*
[2]*I-Med Radiology Network, Regional Imaging- Southern Tasmania, Australia*
[3]*Breast Screen Monash, Victoria, Australia*

ABSTRACT

Breast cancer is the most commonly diagnosed cancer in women worldwide. Conventional mammography and ultrasound no longer present the only options for imaging, in the detection of breast cancer. The imaging modalities currently available are described in the paper. Breast MRI is compared with contrast enhanced mammography, which is an emerging modality in breast cancer detection. These two modalities use intravenous contrast (i.v.) to provide functional information. They are compared in terms of sensitivity, specificity, radiation dose, rates of contrast reactions, as well as availability.

Keywords review, breast magnetic resonance imaging (MRI), contrast enhanced mammography (CEM), breast tomosynthesis, mammography

LAY ABSTRACT

The different types of imaging methods for cancer of the breast are discussed. The focus is on comparing magnetic resonance imaging with a fairly recent advance of using contrast for visualising breasts.

INTRODUCTION

Breast cancer is the most commonly diagnosed cancer and leading cause of cancer-related death in women worldwide, including in South Africa.[1,2] In 2013, breast cancer was responsible for 20.8% of female cancers and 10% of the entire cancer disease burden in South Africa.[2] A summary of current imaging modalities, namely, conventional mammography, ultrasound, digital breast tomosynthesis, breast magnetic resonance imaging (MRI), and contrast enhanced mammography (CEM), is presented. The focus is however on breast MRI and CEM.

CONVENTIONAL MAMMOGRAPHY

Mammography is the only breast imaging modality proven to reduce breast cancer mortality through screening.[3,4] South Africa does not have a publicly funded national breast screening programme for the population wide detection of breast cancer.[2,3]

In mammography the breast is physically compressed and x-ray images captured. X-ray attenuation of the breast tissue enables radiologists to identify morphological abnormalities that may be suspicious for malignancy.[5] Sensitivity for mammography ranges between 30-80% in the screening population. The sensitivity is dependent on breast tissue density as normal dense tissue can mask signs of breast cancer.[2,4,6,7]

Radiation doses for conventional mammography are dependent on equipment and settings used, and range from 1.2mGy to 1.7mGy.[8] The safe upper limit for average glandular dose exposure in breast imaging is 3mGy.[9]

ULTRASOUND

Breast ultrasound (US) can be used as an adjunct to conventional mammography that increases the overall sensitivity for breast cancer detection to 97%, in the diagnostic setting,[10] when the two modalities are combined. The addition of breast US to mammography can be especially valuable in women with dense breasts,[2] where increases of sensitivity from 47.6 to 76.1% have been reported.[11]

Breast US as an adjunct to mammography increases diagnostic yield by 3-4 additional cancers per 1000 in above average risk women.[12] However, it is labour-intensive, dependent on operator skill and has higher recall rates and false positive biopsy rates than conventional mammography.[11] Breast US has a clear role in diagnostic imaging; currently its role in screening remains unclear.[2]

DIGITAL BREAST TOMOSYNTHESIS

Digital breast tomosynthesis (DBT) is a recent development in mammography-based imaging. Around the world it is being utilised as a diagnostic modality.[13] Some prospective and retrospective studies have investigated the use of DBT as a primary screening modality.[14]

Conventional mammography is often limited by superimposition of normal tissue mimicking pathology, or by normal tissue overlying and obscuring a mass. This leads to decreased sensitivity and increased false positives. In DBT an x-ray tube and digital detector scan the breast in an arc acquiring a series of low dose cross sectional images. These are digitally reconstructed into 1mm thick slices. The 3D volume which is acquired may then be viewed in these thin slices, reducing the effect of superimposed tissue.[7] The individual slices can also be digitally reconstructed into a 2D mammographic view, or 'synthesised mammogram', of similar quality to a conventional mammogram.[7,15,16] By digitally reconstructing the 2D mammographic view, a conventional mammogram may no longer be required (Figure 1). Acquisition of this 3D dataset, in addition to a synthesised 2D mammogram, has been shown to improve cancer detection rates, and reduce false positives in international prospective screening trials.[17,18,19,20] The radiation dose of a 3D tomosynthesis scan with a 'synthesised mammogram' is similar to conventional mammography alone.[20]

A meta-analysis pooling data from 38 studies with 488099 patients, found breast tomosynthesis to have a sensitivity of 88% and specificity of 84%. These results suggest breast tomosynthesis is superior in the diagnostic setting, but more studies are required to confirm its accuracy in screening.[21]

MRI

Breast MRI was first reported in the literature by Heywang et al. in 1986.[22] It is a contrast-enhanced imaging technique using a gadolinium-based agent, allowing contrast uptake and washout to be observed. Due to tumour associated neoangiogenesis, contrast may extravasate into the surrounding tissues resulting in an area of increased enhancement.[23,24,25] This provides both morphological and functional information for the area(s) of interest.[25,26]

MRI has been implemented as both a supplemental screening modality and diagnostic modality. It has been used in national screening programmes for asymptomatic women at a high risk of developing breast cancer.[2,25] Some of these groups include women with BRCA (BReast CAncer gene) mutations, mantle field radiation of the chest, > 20% lifetime risk.[25] In addition to high risk screening, breast MRI can be used for preoperative staging, evaluating neoadjuvant chemotherapy response, unknown primary identification in women with metastatic axillary lymph nodes and troubleshooting where equivocal findings are present in mammography and ultrasound (Figure 2).[27]

MRI, including breast MRI, may not be appropriate for some patients which include those with claustrophobia,[28] those who cannot complete the study due to body habitus, table weight limits, or other well-known MRI contraindications such as pacemakers or aneurysm clips.[28]

MRI has a high sensitivity for breast cancer detection of 90-96%. It has been utilised as a supplemental screening modality and diagnostic modality as an adjunct to conventional mammography and ultrasound.[8,24,29] Current evidence for MRI indicates specificity to be 88% in detection of breast cancer.[29]

CONTRAST ENHANCED MAMMOGRAPHY

One of the newest developments in breast imaging is contrast enhanced mammography (CEM).[2] It utilises a dual-energy x-ray technique in addition to an intravenous iodinated contrast agent during image acquisition.[4,5,10,30,31] Contrast is injected 2 minutes prior to low energy and high energy image acquisition in the standard mammographic imaging views.[5,10] Similar to MRI, contrast agent is taken up by cancerous cells, due

Figure 1. A patient at 12 month follow-up for breast imaging surveillance with a previous history of left breast Paget's disease. Tomosynthesis with 2D reconstructed mammographic views were obtained. Figure 1a shows no suspicious lesion on the 2D reconstructed mammographic views. There is a small spiculated lesion in the left central breast seen on review of the tomosynthesis images (Figure 1b). No suspicious lesion was seen on ultrasound. A mammographic biopsy under tomosynthesis guidance was performed and a small titanium clip placed (Figure 1c). An invasive cancer was proven. Final pathology revealed a 10mm grade 3 invasive ductal cancer NOS, ER/PR-, HER+, 2/2 sentinel lymph nodes negative.

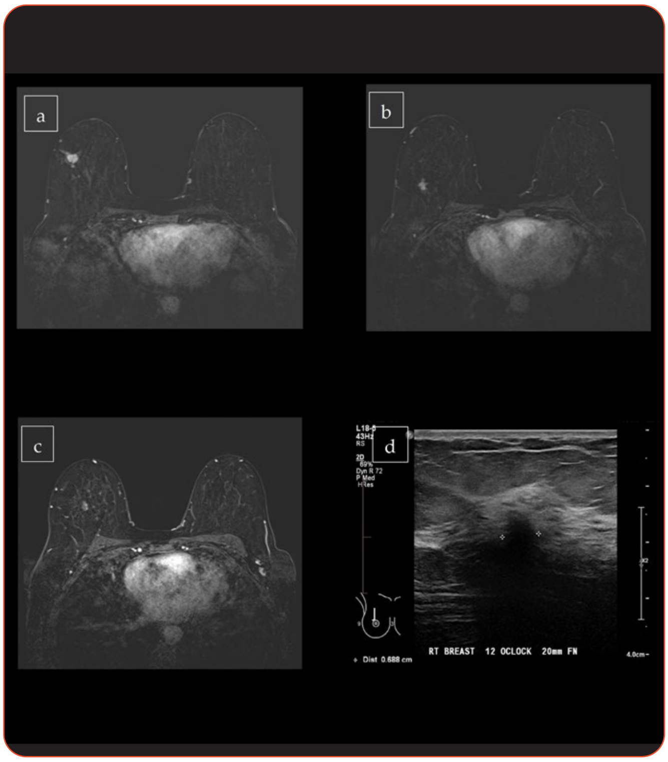

Figure 2. The patient had two biopsy proven cancers in the right breast when she presented to the department for preoperative assessment with breast MRI. MRI identified the two known breast cancers at the 10 o'clock position, 60mm from the nipple (Figure 2a) and 10 o'clock position 80mm from the nipple. A third mass lesion with irregular margins and plateau enhancement on kinetic assessment was seen at 12 o'clock, 20mm from the nipple (Figure 2c). Targeted ultrasound after the MRI study showed very subtle hypoechoic change in the area of lesion 3 at the 12 o'clock, 20mm from the nipple (Figure 2d). Final histopathology revealed for lesion 1: a 14mm grade 2 invasive ductal cancer NOS, lesion 2: 12mm grade 2 invasive ductal cancer NOS and for lesion 3: a 6mm grade 1 invasive ductal cancer NOS. Sentinel lymph node 1/1 negative.

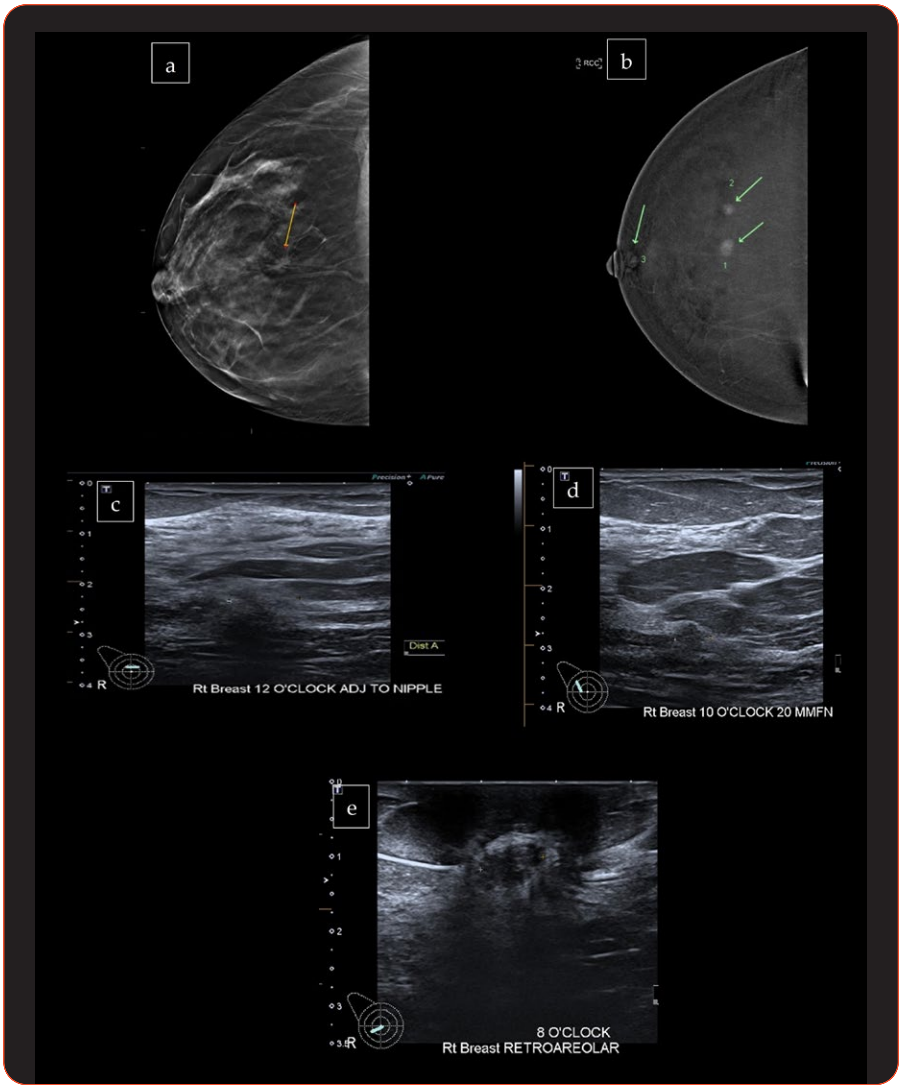

Figure 3. The patient presented with reddening of her right nipple. Initially tomosynthesis with 2D reconstructed mammographic views was performed. A small area of architectural distortion was identified in the right upper central breast, only seen on the tomosynthesis images (Figure 3a). The initial ultrasound did not show a suspicious lesion in the right breast. Contrast enhanced mammography was performed for preoperative assessment. Three mass lesions with suspicious contrast uptake were identified on the contrast mammography study. Lesion 1 corresponds to the lesion seen in the tomosynthesis study, lesion 2 is localised at the 10 'clock position, 20mm from the nipple, lesion 3 is localised in the right retro-areolar region adjacent to the nipple at the 8 o'clock position (Figure 3b). Targeted ultrasound after the contrast mammography study revealed very subtle hypoechoic change in those areas (Figure 3c, d, e). Ultrasound guided core biopsies confirmed invasive cancers for all three lesions and hookwire guided lumpectomy was consequently performed. The final histopathology showed multifocal invasive cancers, Not Otherwise Specified (NOS), all tumours grade 1, ER/PR-, HER+, 21, 9 and 7mm in maximum diameter, 3/3 sentinel lymph nodes negative.

Table 1. Comparison of MRI and CEM in breast imaging

	MRI	CEM
Radiation	None	1.06-1.86x conventional mammography [8,33,34]
Sensitivity	90-96% [8,24,29]	93-98% [6,8,29]
Contrast	Gadolinium	Iodine
Contrast reaction	0.17%, very uncommon severe [35,36]	0.47%, more likely to be severe [37]
Severe reaction	0.0003-0.0007% [35,36]	0.006% [36]
Cost	Expensive and time consuming [23,30]	Less expensive and more readily available than MRI [23,30]

to tumour driven neo-angiogenesis and extravasates into the surrounding tissue. Post-processing creates a digitally subtracted image that reduces fibroglandular tissue attenuation and increases areas of contrast uptake.[10,30]

CEM has sensitivity of 93-98% [6,8,29] and specificity of greater than 90% in the detection of breast cancers.[29] These values, in the detection of breast cancer, are greater than conventional mammography. They are also greater than US alone or US combined with conventional mammography.[30] CEM sensitivity is comparable to that of breast MRI and specificity may exceed that of breast MRI.[6,10,29,32]

CEM has similar indications and uses to breast MRI: inconclusive finding at mammography, preoperative planning and neoadjuvant response monitoring (Figure 3).[10,28]

The key differences between these two modalities are discussed below.

COMPARISON OF BREAST MRI vs CEM

Table 1 shows comparison as well as cited references.

- ***Sensitivity and specificity***

MRI sensitivity has been reported at 90-96%.[8,24,29] For CEM the literature reports comparable sensitivity to breast MRI.[6,10,29,32] Current evidence for MRI indicates MRI specificity to be 88% in detection of breast cancer. CEM specificity has been reported as high as 94%.[29]

- ***Radiation***

MRI does not utilise any ionising radiation.[25] CEM uses ionising radiation; the dose increase of a dual energy CEM in comparison to a conventional mammogram is only 1.06-1.8x greater than standard mammography.[6,8,33,34] These values still fall below the guidelines recommended 3mGy average glandular dose exposure for breast imaging.[9]

- ***Contrast reaction***

MRI utilises gadolinium based contrast agents, which have been shown to produce fewer contrast reactions than iodinated contrast agents. Only 0.17% of patients experience a contrast reaction, most of which are very mild. Severe anaphylactic reactions have been reported in the literature at rates of 0.0003-

0.0007%.[35,36] CEM utilises iodinated contrast agents which have been associated with a higher rate of contrast reactions. The chance of any type of contrast reaction with iodine contrast media has been reported at 0.48%. This would largely represent very mild reactions. However, severe reactions are more common with iodinated contrast than gadolinium.[6,37] Severe anaphylactic reactions to iodine contrast agents have been reported at rates of 0.006%.[36]

• *Availability*

Currently breast MRI is more accessible than CEM. It has well established capabilities for lesion biopsy which are not yet available with CEM.[38] In the future CEM may become the modality of choice due to breast MRI's longer acquisition and reporting times which lead to increased cost. CEM image acquisition is quicker for the patient, faster to evaluate and less expensive than MRI.[28] CEM has the potential to be more readily available as it may only require upgrade of existing equipment rather than purchase of new machines.[23,30]

CONCLUSION

Breast cancer is common, and a variety of imaging modalities may be used for its detection. Conventional mammography is the only imaging tool utilised, almost universally, for diagnostic and screening purposes. Sensitivity is impacted by breast density. Ultrasound improves the sensitivity if used as an adjunct to mammography, especially in dense breasts. DBT, with 'synthesised mammogram', improves cancer detection rates and reduces false positives with similar radiation doses to convention mammography. It is currently limited to diagnostic use. Prospective and retrospective international trials are investigating its use for screening. MRI is highly sensitive for detection of breast malignancy. It does not use ionising radiation; gadolinium contrast is better tolerated than iodine contrast. However, it has increased cost and reduced availability compared to CEM. CEM is a useful adjunct to conventional mammography with high sensitivity and specificity. It uses iodinated contrast agents which have higher rates of contrast reaction than gadolinium contrast agents. It is cheaper and potentially more readily available than MRI.

CONTRIBUTIONS OF AUTHORS

J.P., A.L. and G.P. contributed to the formulation, analysis of the literature, writing and editing of the manuscript.

COMPETING INTERESTS

None. The authors received no financial support for the research, authorship, and/or publication of this article.

REFERENCES

1. DeSantis CE, Bray F, Ferlay J, Lortet-Tieulent J, Anderson BO, Jemal A. International variation in female breast cancer incidence and mortality rates. Cancer Epidemiol Biomarkers Prev 2015;24, [10]: 1495-506.
2. Smilg JS. Are you dense? The implications and imaging of the dense breast. SA J Radiol 2018; 22, [2]: 1356.
3. Lipschitz S. Screening mammography with special reference to guidelines in South Africa. SA J Radiol 2018; 22, [2]: 1370.
4. Luczynska E, Heinze-Paluchowska S, Dyczek S, Blecharz P, Rys J, Reinfuss M. Contrast-enhanced spectral mammography: comparison with conventional mammography and histopathology in 152 women. Korean J Radiol 2014; 15, [6]: 689-96.
5. Perry H, Phillips J, Dialani V, Slanetz PJ, Fein-Zachary VJ, Karimova EJ, et al. Contrast-enhanced mammography: a systematic guide to interpretation and reporting. AJR Am J Roentgenol 2019; 212, [1]: 222-31.
6. Patel BK, Naylor ME, Kosiorek HE, Lopez-Alvarez YM, Miller AM, Pizzitola VJ, et al. Clinical utility of contrast-enhanced spectral mammography as an adjunct for tomosynthesis-detected architectural distortion. Clinical Imaging 2017; 46: 44-52.
7. Peters J, Peters G, Meerkotter DA, Daniels D, Shulman J. Comparison of imaging quality between 2D synthesised mammograms reconstructed from digital breast tomosynthesis and 2D full-field digital mammograms. British Journal of Medicine and Medical Research 2016; 18, [10]: 1-9.
8. Dromain C, Vietti-Violi N, Meuwly JY. Angiomammography: a review of current evidences. Diagn Interv Imaging 2019; 100 (10): 593-605.
9. Dance DR, Sechopoulos I. Dosimetry in x-ray-based breast imaging. Phys Med Biol 2016; 61, [19]: R271-R304.
10. Patel BK, Garza SA, Eversman S, Lopez-Alvarez Y, Kosiorek H, Pockaj BA. Assessing tumor extent on contrast-enhanced spectral mammography versus full-field digital mammography and ultrasound. Clinical Imaging 2017; 46: 78-84.
11. Brem RF, Lenihan MJ, Lieberman J, Torrente J. Screening breast ultrasound: past, present, and future. AJR Am J Roentgenol 2015; 204, [2]: 234-40.
12. Berg WA, Zhang Z, Lehrer D, Jong RA, Pisano ED, Barr RG, et al. Detection of breast cancer with addition of annual screening ultrasound or a single screening MRI to mammography in women with elevated breast cancer risk. Jama 2012; 307, [13]: 1394-404.
13. Gribble A, James S. Digital breast tomosynthesis: a literature review to inform BreastScreen Australia's position statement on the use of tomosynthesis in screening; 2018 [cited 2019 December 26]; Available from: http://www.cancerscreening.gov.au/internet/screening/publishing.nsf/Content/80DD22C5B2C00AA9CA257D85001A04A4/$File/Digital%20breast%20tomosynthesis%20A%20literatur%20-tScreen%20Australia%E2%80%99s%20position%20st.pdf?fbclid=IwAR20EokXQa8pzDPR2LiGEomRlOzOf6lPZEiUWxjRq1zZoCFGO3QkmgYBgos.
14. Marinovich ML, Hunter KE, Macaskill P, Houssami N. Breast cancer screening using tomosynthesis or mammography: a meta-analysis of cancer detection and recall. J Natl Cancer Inst 2018; 110, [9]: 942-9.
15. Bernardi D, Macaskill P, Pellegrini M, Valentini M, Fantò C, Ostillio L, et al. Breast cancer screening with tomosynthesis (3D mammography) with acquired or synthetic 2D mammography compared with 2D mammography alone (STORM-2): a population-based prospective study. Lancet Oncol 2016; 17, [8]: 1105-13.
16. Skaane P. Breast cancer screening with digital breast tomosynthesis. Breast Cancer 2017; 24, [1]: 32-41.
17. Caumo F, Zorzi M, Brunelli S, Romanucci G, Rella R, Cugola L, et al. Digital breast tomosynthesis with synthesised two-dimensional images versus full-field digital mammography for population screening: outcomes from the Verona screening program. Radiology 2018; 287, [1]: 37-46.
18. Ciatto S, Houssami N, Bernardi D, Caumo F, Pellegrini M, Brunelli S, et al. Articles: integration of 3D digital mammography with tomosynthesis for population breast-cancer screening (STORM): a prospective comparison study. Lancet Oncology 2013; 14: 583-9.
19. Skaane P, Bandos AI, Gullien R, Eben EB, Ekseth U, Haakenaasen U, et al. Comparison of digital mammography alone and digital mammography plus tomosynthesis

in a population-based screening program. Radiology 2013; 267, [1]: p47-p56.

20. Svahn TM, Chakraborty DP, Ikeda D, Zackrisson S, Do Y, Mattsson S, et al. Breast tomosynthesis and digital mammography: a comparison of diagnostic accuracy. Br J Radiol 2012; 85, [1019]: e1074-82.
21. Alabousi M, Zha N, Salameh JP, Samoilov L, Sharifabadi AD, Pozdnyakov A, et al. Digital breast tomosynthesis for breast cancer detection: a diagnostic test accuracy systematic review and meta-analysis. Eur Radiol 2020; 30, [4]: 2058-71.
22. Heywang SH, Hahn D, Schmidt H, Krischke I, Eiermann W, Bassermann R, et al. MR imaging of the breast using gadolinium-DTPA. J Comput Assist Tomogr 1986; 10, [2]: 199-204.
23. Kim EY, Youn I, Lee KH, Yun JS, Park YL, Park CH, et al. Diagnostic value of contrast-enhanced digital mammography versus contrast-enhanced magnetic resonance imaging for the preoperative evaluation of breast cancer. J Breast Cancer 2018; 21, [4]: 453-62.
24. Peters J, Tsai WC, Peters G. Large non-enhancing breast cancer on breast magnetic resonance imaging: a case report. Cureus 2018; 10, [3]: e2332.
25. Schoub PK. Understanding indications and defining guidelines for breast magnetic resonance imaging. SA J Radiol 2018; 22, [2]: 1353.
26. Lee-Felker SA, Tekchandani L, Thomas M, Gupta E, Andrews-Tang D, Roth A, et al. Newly diagnosed breast cancer: comparison of contrast-enhanced spectral mammography and breast mr imaging in the evaluation of extent of disease. Radiology 2017; 285, [2]: 389-400.
27. Mann RM, Balleyguier C, Baltzer PA, Bick U, Colin C, Cornford E, et al. Breast MRI: EUSOBI recommendations for women's information. Eur Radiol 2015; 25, [12]: 3669-78.
28. Covington MF, Pizzitola VJ, Lorans R, Pockaj BA, Northfelt DW, Appleton CM, et al. The future of contrast-enhanced mammography. AJR Am J Roentgenol 2018; 210, [2]: 292-300.
29. Fallenberg EM, Schmitzberger FF, Amer H, Ingold-Heppner B, Balleyguier C, Diekmann F, et al. Contrast-enhanced spectral mammography vs. mammography and MRI - clinical performance in a multireader evaluation. Eur Radiol 2017; 27, [7]: 2752-64.
30. Dromain C, Thibault F, Diekmann F, Fallenberg EM, Jong RA, Koomen M, et al. Dual-energy contrast-enhanced digital mammography: initial clinical results of a multireader, multicase study. Breast Cancer Res 2012; 14, [3]: R94.
31. Ong E. Preoperative imaging for breast conservation surgery-do we need more than conventional imaging for local disease assessment? Gland Surg 2018; 7, [6]: 554-9.
32. Luczynska E, Heinze-Paluchowska S, Hendrick E, Dyczek S, Rys J, Herman K, et al. Comparison between breast MRI and contrast-enhanced spectral mammography. Med Sci Monit 2015; 21: 1358-67.
33. James JR, Pavlicek W, Hanson JA, Boltz TF, Patel BK. Breast radiation dose with CESM compared with 2D FFDM and 3D tomosynthesis mammography. AJR Am J Roentgenol 2017; 208, [2]: 362-72.
34. Phillips J, Mihai G, Hassonjee SE, Raj SD, Palmer MR, Brook A, et al. Comparative dose of contrast-enhanced spectral mammography (CESM), digital mammography, and digital breast tomosynthesis. AJR Am J Roentgenol 2018; 211, [4]: 839-46.
35. Murphy KJ, Brunberg JA, Cohan RH. Adverse reactions to gadolinium contrast media: a review of 36 cases. AJR Am J Roentgenol 1996; 167, [4]: 847-9.
36. Sodagari F, Mozaffary A, Wood CG, 3rd, Schmitz B, Miller FH, Yaghmai V. Reactions to both nonionic iodinated and gadolinium-based contrast media: incidence and clinical characteristics. AJR Am J Roentgenol 2018; 210, [4]: 715-9.
37. Rosado Ingelmo A, Dona Diaz I, Cabanas Moreno R, Moya Quesada MC, Garcia-Aviles C, Garcia Nunez I, et al. Clinical practice guidelines for diagnosis and management of hypersensitivity reactions to contrast Media. J Investig Allergol Clin Immunol 2016; 26, [3]: 144-55; quiz 2 p following 55.
38. Papalouka V, Kilburn-Toppin F, Gaskarth M, Gilbert F. MRI-guided breast biopsy: a review of technique, indications, and radiological-pathological correlations. Clin Radiol 2018; 73, [10]: 908; e17-.e25.