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Contrast-enhanced spectral mammography in the radiological assessment of response to neoadjuvant chemotherapy in breast cancer

Anna Grażyńska
Students' Scientific Society, Department of Radiology and Nuclear Medicine, Medical University of Silesia in Katowice, Poland
https://orcid.org/0000-0003-4786-6533
Corresponding author: grazynska.anna@gmail.com

Sofija Antoniuk
Students' Scientific Association, Department of Neurology, Faculty of Medical Sciences in Katowice, Medical University of Silesia, Katowice, Poland
https://orcid.org/0000-0003-3093-1108

Katarzyna Steinhof-Radwańska
Department of Radiology and Nuclear Medicine, Prof. Kornel Gibiński Independent Public Central Clinical Hospital, Medical University of Silesia in Katowice, Katowice, Poland
https://orcid.org/0000-0001-8127-8829

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ABSTRACT

Accurate morphological assessment and measurement of the residual disease following neoadjuvant chemotherapy are vital for the effective surgical treatment in patients with breast cancer. Neoadjuvant chemotherapy response is measured by RECIST 1.1 criteria (Response Evaluation Criteria in Solid Tumors), and the classification of the specific therapeutic responses is based on the difference in the tumour size prior to and after chemotherapy. There are currently a few methods of imaging used in the assessment of the neoadjuvant chemotherapy response. Conventional mammography remains the most popular method, whereas magnetic resonance imaging is considered the most effective ones. Nonetheless, the available methods tend to be imperfect and limited, and therefore, new methods are constantly investigated. Contrast-enhanced spectral mammography is a relatively new method used in breast cancer diagnosis, which involves the phenomenon of neoangiogenesis of cancerous tumours, allowing contrast enhancement in the areas of vessel proliferation in the background of the surrounding breast tissue. Contrast-enhanced spectral mammography presents sensitivity similar to magnetic resonance imaging in breast cancer detection, and can be an efficient method used in monitoring neoadjuvant chemotherapy response.

Introduction

Breast cancer is the most commonly found cancer in women. It affects almost 1.7M patients each year and constitutes one of the most frequent causes of death in this patient group. In Poland alone, breast cancer accounts for 22.5% of all cancers diagnosed in women, as well as for 15% of deaths [1,2]. Multidisciplinary treatment of patients with operable breast cancer combines

surgical therapy, radiotherapy, and systemic treatment which includes a wide range of medications. Drugs administered as systemic therapies comprise hormone therapy, chemotherapy, as well as targeted molecular therapy, which can be administered alone or used in multi-drug regimens. Depending on the timing of the therapy, it is possible to distinguish adjuvant therapy following the surgery, and neoadjuvant therapy preceding a surgical procedure. In terms of adjuvant therapy, it aims to remove latent micrometastases, whereas hormone therapy, chemotherapy, and anti-HER2 therapy based on different anti-cancer mechanisms can improve both disease-free and overall survival rates [3,4].

Neoadjuvant chemotherapy (NAC) is intended to cases where the aim is to decrease the tumour and to remove the micrometastases prior to the radical breast surgery. An accurate morphological assessment and measurement of the residual disease following NAC are crucial for the effective surgical treatment [5,6]. In addition to reducing a tumor and, thus offering better conditions for breast-conserving therapy, NAC provides professionals with unique opportunities to assess the sensitivity of tumour cells to chemotherapy in vivo, as well as to search for new biomarkers of therapeutic response. Furthermore, in the event of poor response and progression of the disease – it offers a chance to alter the treatment plan, or refer a patient for surgical treatment [7,8]. In fact, achieving full response following neoadjuvant therapy and surgical resection is associated with a better prognosis and an increase in the 5-year survival rate. NAC response assessment is based on RECIST 1.1 criteria (Response Evaluation Criteria in Solid Tumors), which are effective in the assessment of the therapeutic response based on a radiological examination. The classification of the individual therapeutic responses is based on the difference between tumour size before and after NAC. The abovementioned criteria include: complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD) [9,10].

RECIST methods in breast cancer

Currently, a few imaging techniques are available for the prediction of NAC response in breast cancer patients. Nevertheless, the most commonly used diagnostic modalities involve physical examination, ultrasonography (US), full-field digital mammography (FFDM), and magnetic resonance imaging (MRI). According to RECIST 1.1 guidelines, the US should not be used to measure tumour regression or progression of lesions due to its subjectivity, dependence on the operator, and no means of standardization [11,12]. Similarly, physical examination which is not only subjective, but it is also characterized by a significant inadequacy compared to other methods. In fact, it only has a 57% effective rate in comparison with FFDM (74%) and US (79%). Moreover, the limited effectiveness of physical examination stems from the lack of differentiation between irregularly-shaped tumours, poorly separated lesions, lesions with fibrous components, or ones with central necrosis [13].

Conversely, according to RECIST, FFDM remains an incomplete method, in spite of its frequent use. In fact, accuracy evaluation of FFDM depends on breast structure and infiltration morphology (tumour or architectural distortion). Furthermore, similarly to physical examination, the effectiveness of FFDM is reduced in cases where the tumour possesses spiculated or blurred margins, with dense breast tissue, and residual infiltration masked by glandular tissue. Additionally, fibrous lesions which are complications of previous diagnostic biopsies, as well as the presence of microcalcifications also constitute a challenge. Interestingly, studies show that up to 44% of microcalcifications following the treatment do not correlate with the presence of malignant processes [13–16].

MRI is the method considered to be the most effective according to the RECIST evaluation. Its main advantage is the ability to form high-quality images and assessing additional functional parameters, such as vascularization and permeability of tumour vessels. Breast MRI has evolved from a primarily contrast-enhanced technique to a multiparametric method in which T2-weighted, and diffusion-weighted imaging (DWI) are routinely performed. This, in turn, allows for obtaining information regarding the tumour diffusion restriction and its biochemical status. [17]. Moreover, MRI is also particularly useful in the high-quality assessment of multifocal and multicentric lesions, with specificity amount-

ing to 90%. However, some studies suggest that MRI may underestimate or overestimate the size of residual lesions in as much as 18% of cases [18]. It is worth bearing in mind that an individual response to NAC can vary significantly with the molecular subtype of breast cancer. Previous studies have shown that regression occurs significantly more often as concentric shrinkage (as opposed to tumour fragmentation, or 'crumbling' into scattered foci) in the case of triple-negative breast cancer (TNBC) than in the case of HER2-positive tumours and ER-positive/HER2 negative. This fact affects the assessment of the response to NAC using imaging examinations. Nevertheless, MRI accuracy remains highest in TNBC and HER2-positive breast cancer and lowest in hormone receptor-positive cancer [16,19].

Taking into account the disadvantages of the currently used diagnostic methods, new, effective modalities are constantly explored.

Contrast-enhanced spectral mammography

Contrast-enhanced spectral mammography (CESM) is a relatively new tool in the field of breast cancer imaging. CESM is a mammography technique involving double exposure of energy during a single compression of a single breast, following the administration of an iodinated contrast agent. Two minutes after injecting 1.5 mL/kg of contrast, classic mammography images are taken in the mediolateral oblique (MLO) and craniocaudal (CC) projections. Low-energy exposure uses the same X-ray energy spectrum as standard mammography, and the images obtained correspond to those of mammography. On the other hand, high-energy exposure is not suitable for diagnostic purposes, although it is used in post-processing in order to generate a recombined or iodine image showing areas of contrast enhancement. The images are created using the dual-energy weighted log subtraction technique, producing two sets of images. The combination of low-energy and high-energy images allows for the creation of a single image showing the impression of the contrast agent distribution within the breast, emphasizing the vascularity of the lesion [20,21].

CESM is a useful tool in the examination of high-risk patients, which is also employed in the assessment of a very dense glandular tissue, in the diagnostic assessment of suspicious lesions, as well as in determining the pathological stage of breast cancer and in designing the treatment [22]. In a study comprising 547 patients with 593 breast cancer lesions, Steinhof-Radwańska [23] has shown that the sensitivity of CESM in malignant tumour detection amounts to 97.86%. This result is similar to that obtained for MRI, which indicates that these are the most sensitive methods used in breast cancer. However, as pointed out by Łuczyńska [24], the specificity of CESM is significantly reduced, with 59.4% and 60%. Despite its low specificity, CESM presents a high negative predictive value (NPV, 95.76%) which, possibly, allows to exclude cancer in the absence of pathological contrast enhancement [23].

Contrast-enhanced spectral mammography in RECIST

In recent years, only a few authors have engaged in investigating the effectiveness of CESM in RECIST criteria. Two authors compared the

Table 1. A comparison of sensitivity, specificity, PPV and NPV of individual diagnostic methods in the detection of Complete Response (CR).

Author	Diagnostic method	Sensitivity [%]	Specificity [%]	PPV [%]	NPV [%]
Patel [18]	CESM	95	66.7%	55.8	96.7
	MRI	95	68.9	57.6	96.9
Iotti [19]	CESM	100	84	57	100
	MRI	100	60	32	92
Barra [20]	CESM	76	62.5	86.	45.4
	MRI	92	87.5	95	53.8
	FFDM	76	75	92	75

Abbreviations: PPV – positive predictive value, NPV – negative predictive value, CESM – contrast-enhanced spectral mammography, MRI – magnetic resonance, FFDM – mammography

potential of CESM and MRI in detecting the residual disease and CR with regard to the golden standard, i.e. a histopathological evaluation [25,26,27]. In the study of 65 patients, Patel [25] has shown that CESM is as effective as MRI in the assessment of residual tumour following NAC. Individual data concerning sensitivity, specificity, positive and negative predictive values are presented in **Table 1.**

However, as studies have shown, when correlating the sizes following NAC with the histopathological evaluation, MRI showed a higher compatibility with histopathology than CESM (Lin's concordance coefficient 0.75 (95% CI 0.62–0.83) for CESM, and 0.76 (95% CI 0.65–0.84) for MRI; Pearson correlation was 0.77 for CESM and 0.80 for MRI). Moreover, compared with the results of the histopathological examination, CESM decreased tumour size by 5 mm, whereas MRI reduced it by 5.4 mm. In the study by Iotti et al. [26] involving 46 patients, in the comparison of the tumour size following NAC with the histopathological examination, CESM showed greater consistency with histopathology than MRI (Lin's coefficient 0.81 and 0.59, respectively; CESM-MRI concordance difference 0.22, CI 0.07–0.58; PCC 0.85 and 0.67, respectively). Similarly, according to Patel et al. [26], both methods tend to underestimate the actual extent of a residual tumour (mean underestimation of 4.1 mm in CESM and 7.5 mm in MRI). The study of Barra et al. [27], comprising 33 patients, evaluated the CESM accuracy in the assessment of the residual disease following NAC as compared to MRI and FFDM. The concordance coefficient between the measurements of all the imaging methods and the size of the tumour was the highest for CESM (0.7 for CESM, 0.3 do FFDM, 0.4 for MRI). Furthermore, the Pearson correlation coefficient was also the lowest for CESM (0.8 for CESM, 0.3 for FFDM, and 0.5 for MRI). In comparison with the measurements performed using MRI, CESM, in 31.8% of the cases overstated the results by more than 1 cm with respect to the histopathological assessment.

Additionally, Tang et al. [28] in their meta-analysis demonstrated that the total sensitivity, specificity, positive likelihood ratio (PLR), negative odds ratio (NLR) and diagnostic odds ratio (DOR) of the pathological breast cancer response to NAC assessed by CESM were: 0.83 (95% CI, 0.66–0.93, 0.82 (95% CI, 0.68–0.91), 4.66 (95% CI, 2.59–8.41), 0.20 (95% CI, 0.10–0.43), 22.91 (95% CI, 8.66–60.62), respectively.

Underestimation of a residual lesion may result in an incomplete removal of the tumour and, thus, in the risk of re-operation. In contrast, overestimation may lead to an overly extensive surgery, and may result in poorer cosmetic results of a surgical procedure, as well as in the surrounding tissue damage. Therefore, in order to address this issue in the evaluation of NAC response, Xing et al. [29] suggested not to rely only on RECIST 1.1 criteria, but to create a mathematical model. This method is based on the combination of the largest tumour diameter measurements in the region of interest (ROI) and the subjective identification of the difference in the intensity of contrast uptake before and after neoadjuvant chemotherapy. Subsequently, a combination of the total number of pixels and their intensity within the area of interest before and after NAC is included. It should be noted that the implementation of this approach increases the sensitivity and specificity of CESM in the prediction and assessment of response to NAC, and reduces the frequency of inaccurate measurement of residual lesions.

Discussion

The aforementioned studies have demonstrated that CESM is equally effective as MRI in the assessment of residual lesions following NAC, which is currently considered the most effective examination method. CESM has been suggested as a primary tool for potential use instead of MRI, as it is less expensive, more accessible, and better tolerated by patients than breast MRI [30,31,32]. In fact, MRI lasts about 20–30 minutes in the prone position, and it is generally regarded as an unpleasant examination related to a forced body position, which additionally excludes patients suffering from such disorders as claustrophobia, or possessing older types of pacemakers. On the other hand, CESM lasts only about 7–10 minutes and the abovementioned inconveniences do not occur [33]. Moreover, CESM seems to be a better alternative for patients who are psychologically distressed by chemotherapy and face several repeated MRI examinations over the period of several months. Additionally, the possibility

of significant cost reductions compared to MRI renders CESM an appealing option in the economy of the health system [31]. Furthermore, CESM allows for the assessment of microcalcifications which is not possible with MRI [34,35]. Nevertheless, CESM has certain limitations, such as exposure to iodine contrast media which limits its use in patients allergic to iodine contrast media and with severe renal failure. Additionally, CESM exposes patients to a higher dose of radiation which is not desirable in patients receiving radiotherapy. It is also essential to take into consideration that both MRI and CESM tend to underestimate [25,26] or overestimate [27] the size of a residual tumour.

At present, apart from the previously mentioned methods (US, FFDM, CESM, MRI), nuclear imaging techniques are more frequently used, such as 2-deoxy-2[F-18]fluoro-D-glucose positron emission tomography (FDG-PET, assessment of glucose metabolism), fluorine 18 fluorothymidine positron emission tomography (FLT-PET, assessment of tumour proliferation), anti-1-amino-3–18F-fluorocyclobutane-1-carboxcylic acid positron emission tomography (FACBC-PET, assessment of amino acid metabolism) and C-choline positron emission tomography (assessment of choline metabolism). Although each of the available modalities has its limitations with regard to sensitivity and specificity, multiparameter (e.g. FTV / BPE / ADC) and multimodal (e.g. MRI / PET) methods should be implemented in order to improve the characteristics of the residual disease and to predict responses to NAC [16]. In addition, recent studies on radiomics-based analysis in predicting responses to NAC have produced very promising results. In terms of CESM, radiomics model achieved a significantly better discriminative ability compared to the standard clinical model (AUC, 0.81 vs. 0.55, p <0.01) [36,37]. Moreover, the development of deep-learning and machine-learning methods is also vital. The above-mentioned new techniques are expected to be employed in other breast imaging modalities and may play a crucial role in the detection, diagnosis and prediction of breast cancer outcomes. Therefore, additional studies are necessary, as well as exploring new methods for the most accurate assessment and a potential increase in the survival rate of patients.

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Conflict of interest statement
The authors declare no conflict of interest.

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References

1. Wojciechowska U, Didkowska J, Michałek I, Olasek P, Ciuba A. Nowotwory złośliwe w Polsce w 2018 roku. Warszawa: Ministerstwo Zdrowia; 2020.
2. Fahad Ullah M. Breast Cancer: Current Perspectives on the Disease Status. Adv Exp Med Biol. 2019;1152:51-64. doi: 10.1007/978-3-030-20301-6_4. PMID: 31456179.
3. Moo TA, Sanford R, Dang C, Morrow M. Overview of Breast Cancer Therapy. PET Clin. 2018 Jul;13(3):339-354. doi: 10.1016/j.cpet.2018.02.006. PMID: 30100074; PMCID: PMC6092031.
4. Merino Bonilla JA, Torres Tabanera M, Ros Mendoza LH. Breast cancer in the 21st century: from early detection to new therapies. Radiologia. 2017 Sep-Oct;59(5):368-379. English, Spanish. doi: 10.1016/j.rx.2017.06.003. Epub 2017 Jul 14. PMID: 28712528.
5. King TA, Morrow M. Surgical issues in patients with breast cancer receiving neoadjuvant chemotherapy. Nat Rev Clin Oncol. 2015 Jun;12(6):335-43. doi: 10.1038/nrclinonc.2015.63. Epub 2015 Apr 7. PMID: 25850554.
6. Esposito A, Criscitiello C, Curigliano G. Neoadjuvant Model for Testing Emerging Targeted Therapies in Breast Cancer. J Natl Cancer Inst Monogr. 2015 May;2015(51):51-5. doi: 10.1093/jncimonographs/lgv012. PMID: 26063887.
7. Hamdy O. Neoadjuvant Therapy Should Be the Standard of Care for Every Node Positive Breast Cancer Patient. J Breast Cancer. 2018 Dec 31;22(1):149-152. doi: 10.4048/jbc.2019.22.e3. PMID: 30941242; PMCID: PMC6438838.
8. Montemurro F, Nuzzolese I, Ponzone R. Neoadjuvant or adjuvant chemotherapy in early breast cancer? Expert Opin Pharmacother. 2020 Jun;21(9):1071-1082. doi: 10.1080/14656566.2020.1746273. Epub 2020 Apr 1. PMID: 32237920.
9. von Minckwitz G, Untch M, Blohmer JU, Costa SD, Eidtmann H, Fasching PA, Gerber B, Eiermann W, Hilfrich J, Huober J, Jackisch C, Kaufmann M, Konecny GE, Denkert C, Nekljudova V, Mehta K, Loibl S. Definition and impact of pathologic complete response on prognosis after neoadjuvant chemotherapy in various intrinsic breast cancer subtypes. J Clin Oncol. 2012 May 20;30(15):1796-804. doi: 10.1200/JCO.2011.38.8595. Epub 2012 Apr 16. PMID: 22508812.
10. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D, Verweij J. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009 Jan;45(2):228-47. doi: 10.1016/j.ejca.2008.10.026. PMID: 19097774.

11. Bogaerts J, Ford R, Sargent D, Schwartz LH, Rubinstein L, Lacombe D, Eisenhauer E, Verweij J, Therasse P; RECIST Working Party. Individual patient data analysis to assess modifications to the RECIST criteria. Eur J Cancer. 2009 Jan;45(2):248-60. doi: 10.1016/j.ejca.2008.10.027. Epub 2008 Dec 16. PMID: 19095437.
12. Croshaw R, Shapiro-Wright H, Svensson E, Erb K, Julian T. Accuracy of clinical examination, digital mammogram, ultrasound, and MRI in determining postneoadjuvant pathologic tumor response in operable breast cancer patients. Ann Surg Oncol. 2011 Oct;18(11):3160-3. doi: 10.1245/s10434-011-1919-5. Epub 2011 Sep 27. PMID: 21947594.
13. Weiss A, Lee KC, Romero Y, Ward E, Kim Y, Ojeda-Fournier H, Einck J, Blair SL. Calcifications on mammogram do not correlate with tumor size after neoadjuvant chemotherapy. Ann Surg Oncol. 2014 Oct;21(10):3310-6. doi: 10.1245/s10434-014-3914-0. Epub 2014 Jul 24. PMID: 25056851.
14. An YY, Kim SH, Kang BJ. Residual microcalcifications after neoadjuvant chemotherapy for locally advanced breast cancer: comparison of the accuracies of mammography and MRI in predicting pathological residual tumor. World J Surg Oncol. 2017 Nov 6;15(1):198. doi: 10.1186/s12957-017-1263-8. PMID: 29110671; PMCID: PMC5674773.
15. Wright FC, Zubovits J, Gardner S, et al. Optimal assessment of residual disease after neo-adjuvant therapy for locally advanced and inflammatory breast cancer--clinical examination, mammography, or magnetic resonance imaging?. J Surg Oncol. 2010;101(7):604-610. doi:10.1002/jso.21559
16. Fowler AM, Mankoff DA, Joe BN. Imaging Neoadjuvant Therapy Response in Breast Cancer. Radiology. 2017 Nov;285(2):358-375. doi: 10.1148/radiol.2017170180. PMID: 29045232.
17. Mann RM, Cho N, Moy L. Breast MRI: State of the Art. Radiology. 2019 Sep;292(3):520-536. doi: 10.1148/radiol.2019182947. Epub 2019 Jul 30. PMID: 31361209.
18. Expert Panel on Breast Imaging:, Slanetz PJ, Moy L, Baron P, diFlorio RM, Green ED, Heller SL, Holbrook AI, Lee SJ, Lewin AA, Lourenco AP, Niell B, Stuckey AR, Trikha S, Vincoff NS, Weinstein SP, Yepes MM, Newell MS. ACR Appropriateness Criteria® Monitoring Response to Neoadjuvant Systemic Therapy for Breast Cancer. J Am Coll Radiol. 2017 Nov;14(11S):S462-S475. doi: 10.1016/j.jacr.2017.08.037. PMID: 29101985.
19. Goorts B, Dreuning KMA, Houwers JB, Kooreman LFS, Boerma EG, Mann RM, Lobbes MBI, Smidt ML. MRI-based response patterns during neoadjuvant chemotherapy can predict pathological (complete) response in patients with breast cancer. Breast Cancer Res. 2018 Apr 18;20(1):34. doi: 10.1186/s13058-018-0950-x. PMID: 29669584; PMCID: PMC5907188.
20. Jochelson MS, Lobbes MBI. Contrast-enhanced Mammography: State of the Art. Radiology. 2021 Apr;299(1):36-48. doi: 10.1148/radiol.2021201948. Epub 2021 Mar 2. PMID: 33650905; PMCID: PMC7997616.
21. James JJ, Tennant SL. Contrast-enhanced spectral mammography (CESM). Clin Radiol. 2018 Aug;73(8):715-723. doi: 10.1016/j.crad.2018.05.005. Epub 2018 Jun 21. PMID: 29937340.
22. Lobbes MB, Lalji U, Houwers J, Nijssen EC, Nelemans PJ, van Roozendaal L, Smidt ML, Heuts E, Wildberger JE. Contrast-enhanced spectral mammography in patients referred from the breast cancer screening programme. Eur Radiol. 2014 Jul;24(7):1668-76. doi: 10.1007/s00330-014-3154-5. Epub 2014 Apr 3. PMID: 24696228.
23. Steinhof-Radwańska K, Grażyńska A, Barczyk-Gutkowska A, Kajor M, Powązka P, Lorek A, Szlachta-Świątkowska E, Morawska I, Okas K, Lelek Z, Bielińska M, Gisterek I, Casańas B, Pilch-Kowalczyk J. The new method, the old problem - role of contrast-enhanced spectral mammography in the diagnosis of breast cancer among Polish women. Pol J Radiol. 2020 Jul 27;85:e381-e386. doi: 10.5114/pjr.2020.97941. PMID: 32817772; PMCID: PMC7425219.
24. Łuczyńska E, Niemiec J, Hendrick E, Heinze S, Jaszczyński J, Jakubowicz J, Sas-Korczyńska B, Rys J. Degree of Enhancement on Contrast Enhanced Spectral Mammography (CESM) and Lesion Type on Mammography (MG): Comparison Based on Histological Results. Med Sci Monit. 2016 Oct 21;22:3886-3893. doi: 10.12659/msm.900371. PMID: 27768681; PMCID: PMC5077289.
25. Patel BK, Hilal T, Covington M, Zhang N, Kosiorek HE, Lobbes M, Northfelt DW, Pockaj BA. Contrast-Enhanced Spectral Mammography is Comparable to MRI in the Assessment of Residual Breast Cancer Following Neoadjuvant Systemic Therapy. Ann Surg Oncol. 2018 May;25(5):1350-1356. doi: 10.1245/s10434-018-6413-x. Epub 2018 Mar 7. PMID: 29516362.
26. Iotti V, Ravaioli S, Vacondio R, Coriani C, Caffarri S, Sghedoni R, Nitrosi A, Ragazzi M, Gasparini E, Masini C, Bisagni G, Falco G, Ferrari G, Braglia L, Del Prato A, Malavolti I, Ginocchi V, Pattacini P. Contrast-enhanced spectral mammography in neoadjuvant chemotherapy monitoring: a comparison with breast magnetic resonance imaging. Breast Cancer Res. 2017 Sep 11;19(1):106. doi: 10.1186/s13058-017-0899-1. PMID: 28893303; PMCID: PMC5594558.
27. Barra FR, Sobrinho AB, Barra RR, Magalhães MT, Aguiar LR, de Albuquerque GFL, Costa RP, Farage L, Pratesi R. Contrast-Enhanced Mammography (CEM) for Detecting Residual Disease after Neoadjuvant Chemotherapy: A Comparison with Breast Magnetic Resonance Imaging (MRI). Biomed Res Int. 2018 Nov 8;2018:8531916. doi: 10.1155/2018/8531916. PMID: 30533440; PMCID: PMC6250019.
28. Tang S, Xiang C, Yang Q. The diagnostic performance of CESM and CE-MRI in evaluating the pathological response to neoadjuvant therapy in breast cancer: a systematic review and meta-analysis. Br J Radiol. 2020 Aug;93(1112):20200301. doi: 10.1259/bjr.20200301. Epub 2020 Jul 2. PMID: 32574075; PMCID: PMC7446000.
29. Xing D, Mao N, Dong J, Ma H, Chen Q, Lv Y. Quantitative analysis of contrast enhanced spectral mam-

mography grey value for early prediction of pathological response of breast cancer to neoadjuvant chemotherapy. Sci Rep. 2021 Mar 15;11(1):5892. doi: 10.1038/s41598-021-85353-9. PMID: 33723322; PMCID: PMC7960703.
30. Zanardo M, Cozzi A, Trimboli RM, Labaj O, Monti CB, Schiaffino S, Carbonaro LA, Sardanelli F. Technique, protocols and adverse reactions for contrast-enhanced spectral mammography (CESM): a systematic review. Insights Imaging. 2019 Aug 2;10(1):76. doi: 10.1186/s13244-019-0756-0. PMID: 31376021; PMCID: PMC6677840.
31. Patel BK, Gray RJ, Pockaj BA. Potential Cost Savings of Contrast-Enhanced Digital Mammography. AJR Am J Roentgenol. 2017 Jun;208(6):W231-W237. doi: 10.2214/AJR.16.17239. Epub 2017 Apr 5. PMID: 28379734.
32. Lobbes MB, Lalji UC, Nelemans PJ, Houben I, Smidt ML, Heuts E, de Vries B, Wildberger JE, Beets-Tan RG. The quality of tumor size assessment by contrast-enhanced spectral mammography and the benefit of additional breast MRI. J Cancer. 2015 Jan 5;6(2):144-50. doi: 10.7150/jca.10705. PMID: 25561979; PMCID: PMC4280397.
33. Carpenter AP, Leemis LM, Papir AS, Phillips DJ, Phillips GS. Managing magnetic resonance imaging machines: support tools for scheduling and planning. Health Care Manag Sci. 2011 Jun;14(2):158-73. doi: 10.1007/s10729-011-9153-z. Epub 2011 Mar 29. PMID: 21533751.
34. Łuczyńska E, Heinze-Paluchowska S, Hendrick E, Dyczek S, Ryś J, Herman K, Blecharz P, Jakubowicz J. Comparison between breast MRI and contrast-enhanced spectral mammography. Med Sci Monit. 2015 May 12;21:1358-67. doi: 10.12659/MSM.893018. PMID: 25963880; PMCID: PMC4441288.
35. Kim YS, Chang JM, Moon HG, Lee J, Shin SU, Moon WK. Residual Mammographic Microcalcifications and Enhancing Lesions on MRI After Neoadjuvant Systemic Chemotherapy for Locally Advanced Breast Cancer: Correlation with Histopathologic Residual Tumor Size. Ann Surg Oncol. 2016 Apr;23(4):1135-42. doi: 10.1245/s10434-015-4993-2. Epub 2015 Dec 1. PMID: 26628432.
36. Massafra R, Bove S, Lorusso V, Biafora A, Comes MC, Didonna V, Diotaiuti S, Fanizzi A, Nardone A, Nolasco A, Ressa CM, Tamborra P, Terenzio A, La Forgia D. Radiomic Feature Reduction Approach to Predict Breast Cancer by Contrast-Enhanced Spectral Mammography Images. Diagnostics (Basel). 2021 Apr 10;11(4):684. doi: 10.3390/diagnostics11040684. PMID: 33920221; PMCID: PMC8070152.
37. Wang Z, Lin F, Ma H, Shi Y, Dong J, Yang P, Zhang K, Guo N, Zhang R, Cui J, Duan S, Mao N, Xie H. Contrast-Enhanced Spectral Mammography-Based Radiomics Nomogram for the Prediction of Neoadjuvant Chemotherapy-Insensitive Breast Cancers. Front Oncol. 2021 Feb 22;11:605230. doi: 10.3389/fonc.2021.605230. PMID: 33692950; PMCID: PMC7937952.