Mammary carcinoma – current diagnostic methods and symptomatology in imaging studies

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Summary

Breast cancer is the most common neoplasm of the female population and its incidence is constantly rising. Social campaigns educating the public about the importance of the problem have been conducted for the past several years. Women are encouraged to self-examine on a monthly basis. Women aged 50–69 years can have an x-ray mammography performed once every 2 years as part of a prophylactic screening program. Ultrasound studies or MR mammography are adjuvant or, in some cases, alternative to x-ray mammography. Nuclear medicine techniques with application of oncophilic markers and receptor studies (this publication will not cover nuclear medicine methods) are not routinely used. Other techniques, such as computed tomography and conventional radiography are of no significance in the diagnostics of mammary cancer. However, together with isotopic methods, they are helpful in staging of the disease.

X-ray mammography is, up to date, the only method with proven value in decreasing mortality. It is also the best available method for visualization of microcalcifications. Ultrasound examination is complementary to x-ray mammography as it is a cheap, easily available method of imaging mammary glands with higher glandular tissue content. It is also the most commonly used modality aiding in targeted biopsy of mammary gland. To date, MR mammography, characterized by the highest sensitivity in cancer diagnostics, remained a method reserved for “special tasks”. MR is used for prophylaxis mainly in a population of women with particularly high risk of the disease and in cases where x-ray and ultrasound examinations are insufficient.

Picture of mammary carcinoma in imaging studies is heterogeneous. However, it most often presents as an irregularly demarcated mass. Moreover, each modality can aid in visualization of additional features of a lesion such as typical shape of microcalcifications in x-ray mammography, characteristic pattern of contrast enhancement in MR examination or less strain in elastography.

Key words: mammary carcinoma • magnetic resonance of mammary gland • breast ultrasound • x-ray mammography • elastography • breast cancer • BI-RADS • ACR scale • Tsukuba scale

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Background

The most common cause of mortality in a female population in Poland is cardiovascular disease – about 52% in 2010. Neoplasms place second, right after cardiovascular diseases, with 23%. Breast cancer is the most common of all cancers in a population of Polish women. This problem also affects men, although marginally. In 2009 there were almost 16 thousand new cases, which constituted about 22% of all cancer diagnoses. In 2009 breast cancer mortality was somewhat exceeded only by mortality from lung and bronchial cancer (5424 deaths due to breast cancer, 5947 due to lung and bronchial cancer). Incidence of breast cancer rapidly increases in women over 30 years old and affects mainly females in perimenopausal age. In 2009 it...
was the highest in a population women aged 50–65 years. Unfortunately, incidence of neoplastic diseases, including breast cancer, shows a rising trend [1,2]. Certainly, increase in the number of cancer diagnoses is related to greater disease awareness among women and, as a result, improved prophylaxis.

One of the most important issues for treatment of cancer is the earliest possible diagnosis of the disease. Cancer prophylaxis includes monthly self-palpation and self-observation. Such examination should be performed in the first phase of the menstrual cycle, preferably either 2–3 days after menstruation, when breasts are not swollen, or on a selected day of the month in case of non-menstruating women. Breasts should be examined by a doctor at least once a year. In Poland, women aged 50–69 years with standard disease risk, without previous diagnosis of breast cancer may participate once every 2 years in a screening program, which involves x-ray mammography examination. Ultrasound also plays an important role in diagnostics of breast diseases. This study is of particular significance in young patients with dense glandular tissue and is one of the most common adjunctive methods aiding in targeted biopsy. Magnetic resonance is the most sensitive method of mammary gland imaging to date. Unfortunately, its application is limited to patients with particularly high risk of cancer (e.g. BRCA1 and 2 mutation carriers) and cases where x-ray mammography and ultrasound may be ineffective (e.g. women with breast endoprosthesis) due to poor availability of the test related to, among other things, its cost.

Nuclear medicine techniques with oncophilic tracers (e.g. 99mTc MIBI, 99mTc tetrofosmin in planar or SPECT scintimammography) and receptor studies (PET examination for estrogen, progesterone, HER-2neu receptors) are not routinely used. However, scintigraphy is useful in identification of a sentinel node, which is important in light of current medical tendency for possibly least mutilating surgical treatment. One of the examples of indications for application of nuclear medicine techniques in search of the primary mammary tumor focus is so-called „occult” cancer (invisible on x-ray mammography and ultrasound) in patients with contraindications for magnetic resonance imaging.

Other imaging studies such as computed tomography or conventional radiography are or no significance in breast cancer diagnostics, but combined with isotopic methods are helpful in assessing the degree of advancement of the disease.

Following the diagnostic imaging of a mammary gland patient is classified according to the BI-RADS scale, which assesses the likelihood of malignancy. BI-RADS score is given on the basis of the most suspicious lesion present in either breast (Table 1).

**Review of the Most Important Methods Used in Mammary Gland Imaging**

**X-ray mammography**

This modality utilizes conventional and digital mammography. In the conventional technique an x-ray plate is the detector and carrier of the image. In indirect digital technique the image is saved immediately in an electronic form.

Data digitalization offers various possibilities such as image maneuvering and easy copying. It was also possible to create programs aiding the radiologists – so-called CAD system [4]. Current CAD system is good at recognizing spiculated nodules and microcalcifications, but does not do so well with abnormal tissue architecture. While considering the advantages and disadvantages of image digitalization one should note that conventional mammography is characterized by higher spacial resolution, while digital mammography has higher contrast resolution, which seems to balance out the losses resulting from worse spacial resolution [5].

To date, x-ray mammography is the only method, which has been proven to reduce mortality among women aged 40–70 years. Mortality reduction ranges between 20% and 45% and the greatest benefit is seen in a population of females aged 50–70 years [6].

Advantages of mammography include visualization of the entire mammary gland and relatively easy comparison with previous studies. It is also the best method for visualization and assessment of microcalcifications.

Use of ionizing radiation, although in small doses, is one of disadvantages of this method. However, it may result in
slight increase in the number of neoplasms. Severe breast compression causes patient discomfort. A group of women with breast endoprostheses is also problematic. Special methods of mammary gland imaging are used in this group, as there is a risk of damage to endoprosthesis. Gland assessment is also more difficult. Due to its technique (it is a summation study) sensitivity of this diagnostic method in detecting cancer worsens with increasing mammary gland density.

Two standard projections are used for mammary gland imaging using x-ray mammography:

1. **Oblique (MLO):** When performed correctly, it encompasses the entire mammary gland together with Spence’s tail; pectoral muscle is visible as a triangle to the level of mammary papilla. Inframammary skin fold should be also seen on the picture.

2. **Craniocaudal (CC):** It is complementary to the oblique projection. The entire mammary gland together with adipose tissue located posteriorly to the gland conus should be visible on a properly taken picture. Mammary papilla is projected and located centrally. According to some authors, a small fragment of pectoral muscle as well as medial and lateral skin folds should be visible. In order to ascertain that the entire mammary gland is included on the radiological picture, one may measure the distance from the edge of the film to mammary papilla and compare it to the length of the posterior retropapillary line in MLO projection – the difference should not exceed 1 cm [5,7].

Moreover, the edge of the skin should be visible on a properly exposed picture.

Whenever standard projections raise concerns with regard to the presence or absence of the disease, additional projections may be performed including:

1. **Targeted or scaled-up pictures** – most commonly used for better, focused imaging of the lesion/area in question and eliminate tissue superimposition.

2. **Lateral projection** – complements MLO and CC projections in case of ambiguous opacities, is helpful in localizing a lesion and assessment of microcalcifications. Only this projection will show the levels of white lime (calcium hydroxide) in microcysts (‘tea cup’), indicating their benign nature. A properly made lateral projection should visualize the entire breast with projected mammary papilla, a small fragment of pectoral muscle and inframammary fold.

3. **Craniocaudal projection** extended laterally or medially serves better visualization of lesions in external parts of breasts and in Spence’s tail.

4. **Static projection** (to the lesion) serves better assessment of a lesion localized in the skin and subcutaneous tissue.

5. **Valley view projection** – for better assessment of lesions in the medial part of the breast.

6. **„Cleopatra“ projection** – for visualization of the inferior part of axilla.

7. **Caudocranial projection** – used when the lesion is localized in the upper quadrants, patient suffers from postural abnormalities and in males.

Women with breast implants constitute a special group of patients, in which standard oblique and craniocaudal projections should be supplemented by craniocaudal and lateral views modified with Eklund technique (i.e. prosthesis is shifted to visualize only the mammary gland). Application of this technique may be difficult if the implant is surrounded by dense, fibrous capsule. [7].

According to the American College of Radiology a four-point confidence scale should be used with regard to the results of mammography (so-called report on breast density):

ACR 1 – fatty breast,

ACR 2 – fatty-glandular breast composition,

ACR 3 – glandular-fatty breast composition,

ACR 4 – glandular breast.

However, in its last report released in April 2012 ACR posed various objections to this scale, including the risk of false sense of security in women with predominantly fatty breasts (ACR 1). Women from high-risk groups, despite the fatty weaving of the breasts, have too high probability of malignancy to waive additional examinations such as ultrasound or MR.

The following mammographic signs suggest cancer:

1. focal lesion,

2. focal asymmetry,

3. microcalcifications (especially clustered ones),

4. disrupted architecture,

5. skin thickening.

Malignant neoplasm of a breast appears as a mass in mammography. A spiculated nodule is the most common lesion, but every new opacity requires additional diagnostics – usually assessment in ultrasound.

| Type 2 | Round, regular, without radiolucency in the middle | Usually benign, but may be present in intraductal cribriform carcinoma, BI-RADS-3 |
| Type 3 | Focal, barely visible, making their shapes difficult to determine | Lesion malignant in 36% of cases, BI-RADS-3 |
| Type 4 | Irregular, granular | Lesion malignant in 56% of cases, BI-RADS-4 |
| Type 5 | Vermicular, branching | Lesion malignant in 90% of cases, BI-RADS-5 |

Table 2. Types of microcalcifications according to Le Gala [7].
In case of microcalcifications, we determine their shapes, number and distribution. Disseminated microcalcifications do not raise suspicions to the same degree as clustered ones. On the other hand, even a single microcalcification of a suspicious shape should raise alert.

Le Gal divided microcalcifications into 5 types depending on shape (Table 2).

According to the classification mentioned above, all microcalcifications other than type 1 are associated with some risk of cancer and deserve careful attention or, at the least, observation. Classification of type 3 microcalcifications to BI-RADS 3 raises doubts, as according to the BI-RADS 3 definition, risk of malignancy should be below 2%.

Other than advancements in digital mammography methods, including programs aiding in cancer detection, most recent technical developments include tomosynthesis. This technology is currently under investigation and allows for acquisition of 3D mammograms. It is a breakthrough in mammography, which was a summation study until now [4] (Figure 1).

Ultrasonography

This method is very useful in diagnostics of breast cancer. It is relatively inexpensive, easily accessible and, in principle, inert to patient’s health, since standard breast ultrasound does not utilize ionizing radiation (as opposed to mammography) or contrast agents (as in MRI). It is also a good method of assessment of dense, glandular mammary glands, where the sensitivity of mammography is reduced.

To date, there is no evidence on the influence of ultrasound on mortality of women due to breast cancer, although increasing resolution of devices with broadband ultrasound transducers and advancements in computer software significantly improved the quality of examination. At the moment, even medium-standard devices are often equipped with 12–13 MHz probes.

There were multicenter studies conducted between 2004 and 2006 [8,9], which included almost 3 thousand women. The participants included in the studies had areas of heterogeneous breast density identified in at least one breast quadrant. During the screening they underwent mammography and ultrasound examinations. Some women included in the second study [9] were also examined by MR. All women were subjected to a year long follow-up. Adding ultrasound study to screening mammography resulted in detection of additional 29–30% of cancers. However, the added predictive value with regard to indications for biopsy established on a basis of ultrasound examination was significantly lower in comparison to mammography [8]. As a result, ultrasound technique was considered economically ineffective as a screening method due to an increased number of false positive results. On the other hand, this study showed an increase in frequency of detection of small cancers without lymph node involvement (such lesions were mostly invisible in mammography) due to ultrasound examination. However, small lesions are not only more difficult to detect, but their assessment is also more troublesome, hence the greater risk of a diagnostic error in ultrasound scan. Treatment of less advanced cancers is cheaper and less burdensome for the patient. Therefore, when we consider the general costs not only of disease diagnostics but also its treatment, then ultrasound screening will surely prove more cost-effective.

Other than its disputable specificity, disadvantages of this modality include difficulties in comparing to previous studies. However, there is ongoing work on improvement of this method. Elastography gains increasing significance with regard to improvement of specificity. On the other hand, there are technique-automatizing devices designed to facilitate comparison and repeatability – the first ultrasound transmission tomography (UTT) machine was constructed several years ago. While elastography is being introduced into the spectrum of available diagnostic methods, UTT remains in a testing phase.
In a „conventional” ultrasound imaging (B-mode, Doppler studies) breast cancer usually presents as a focal lesion with malignant features such as:

- acoustic shadow,
- hyperechogenicity,
- spicules,
- irregular margins,
- thick, hyperechogenic halo with desmoplasia around the lesion,
- blurriness,
- minute protuberances of the outline,
- height exceeding the width,
- calcifications,
- spreading along the ducts,
- presence of vessels; however, vascular supply of mammary carcinomas is very heterogeneous – vessels are better visible in well demarcated, hypercellular lesions than in spiculated nodules with high fiber content. Therefore, failure to visualize the vessels does not indicate the benign nature of the lesion [10].

Cancer can also present with non-specific features such as:
- disrupted architecture,
- only gland edema and skin thickening may be visible in case of inflammatory breast cancer.

Elastography is a new ultrasound technique aiming to improve the specificity of selecting malignant lesions in breast cancer diagnostics and reduce the number of unnecessary biopsies. It is mainly directed at uncertain lesions classified as BI-RADS 3 and 4, but does not change medical protocol in cases of BI-RADS 1, 2 and 5 lesions [11,12].

This modality allows for imaging of elastic properties of tissues. Until now, depending on the type of device, strain measurements in breast imaging were acquired by slight compression with the ultrasound probe or using chest movements. Therefore, strain was acquired longitudinally, in the direction of ultrasound wave propagation and elastograms were prepared on the basis of relative comparison of tissue elasticity. Shear-Wave Elastography (SWE) was developed in the course of further development of this technique. This method involved production of a mechanical wave in tissues. Subsequently, the device made point velocity readings of transversely spreading waves. SWE method allows for measuring the absolute values of Young (E) modulus, i.e. elastic deformation of a lesion. The advantages of this technique include independence from the operator and improved resolution.

Differentiation between focal lesions using elastography involves assessment of susceptibility to elastic deformation, based on the assumption that increased stiffness is associated with higher risk of malignancy.

In elastography performed with compression technique or using thoracic movements movement stiffness is assessed based on colors that were previously agreed upon. Soft lesions are red, intermediate are green and hard masses are blue (so-called elastogram). Subsequently, the lesion is classified according to Tsukuba scale and its stiffness relative to surrounding fat tissue is expressed in figures (Fat-Lesion Ratio, FLR). In cases of malignant lesions FLR is high and amounts to 4.10–4.18 depending on the author. For benign lesions FLR ranges between 1.54–1.69 [11,13].

Usually, the cut-off line between benign and malignant lesions is set between Tsukuba 3 and 4. However, literature recommends cytological and histopathological verification of Tsukuba 3 lesions [12,14].

Shear-wave elastography currently uses a reversed color scale. Soft lesions are blue, while hard lesions are red. A multicenter study was recently published [15] showing that in SWE the greatest specificity for benign lesions, not influencing sensitivity, is associated with Young modulus value E_{max} ≤ 80 kPa with homogeneously blue color of the lesion. On the other hand, E_{max} ≥ 160 kPa with heterogeneous appearance of a lesion in the color scale was most typical for malignant lesions.

Elastography exhibits high effectiveness in differentiating small cancers from benign lesions. However, just like any other method, it may give false negative and false positive results. For example, large cancers with areas of necrosis may present as soft lesions. Also, preinvasive cancers are often „softer” than infiltrating cancers [11]. On the other hand, hard lesions may turn out to be e.g. a fibroadenomas with areas of sclerosis (Table 3, Figures 2, 3).

### Magnetic resonance mammography

Magnetic resonance with contrast is currently the most sensitive method of diagnosing breast cancer even though, similar to ultrasound studies, there is no evidence that it decreases mortality. This method is reserved for special situations due to its cost among other things. However, the number of indications for magnetic resonance examination of breasts will certainly increase with improvement in availability.

According to EUSOMA guidelines [17] screening with magnetic resonance is indicated in the following populations:

1. Carriers of genetic mutations over 30 years old (i.e. BRCA1, BRCA2, TP53); with some mutations (TP53) screening is considered earlier (25-29 y.o. or even at 20 y.o.).
2. Patients who underwent wide-field radiotherapy before the age of 30 – screening should be commenced 8 years after the end of treatment.

Screening examinations should be performed once a year.

On the other hand, in a recently published study [9] addition of MR examination in women from high-risk populations as an adjuvant to screening with ultrasound and conventional mammography increased the number of detected cancers by only 8% at a cost of numerous false negative results.

Moreover, MR examination may be helpful under the following circumstances [17]:

1. Women with breast endoprosthesis when x-ray mammography and ultrasound are insufficient.
2. Search for a primary neoplastic focus in patients with negative x-ray mammography and ultrasound examinations, breast cancer metastases (usually to axillary lymph nodes) in women with high likelihood of response to treatment – so-called occult primary breast cancer.

3. Preoperative breast assessment in women:
   - with newly diagnosed lobular carcinoma (due to higher risk of multifocality),
   - from high-risk group or below 60 years old with significant differences in tumor size assessed in conventional studies,
   - preliminarily qualified for sparing surgery (however, after MR imaging the risk of unnecessary mastectomy increases).

Like in any other study, proper equipment is incredibly important. EUSOMA recommends use of devices with field induction of at least 1T, minimal gradients of 20 mT/m and coils dedicated to breasts. Application of contrast is a standard procedure (the only exception to the rule is examination of implant integrity).

The recommended minimum for study protocol [17]:
1. Bilateral examination with at least one sequence acquired without contrast; e.g. T2+/-FATSAT(SPIR) or STIR.
2. Bilateral examination in a dynamic T1-weighted dynamic sequence with simultaneous use of rapid 2D or 3D gradient-echo sequences with or without fat saturation sequences (slice thickness ≤3 mm, spacial resolution ≤1.5 mm², temporal resolution ≤120 s); contrast should be applied via an automatic syringe.
3. Analysis should also include:
   - subtraction images (obtained by subtracting the images acquired before giving contrast from images acquired after application of contrast),
   - time-signal intensity curve for each enhanced focal lesion ≥5 mm.

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**Table 3. Tsukuba scale and characteristics of cysts - BGR [16].**

| Tsukuba 1 | Pattern typical for benign lesions |
|-----------|-----------------------------------|
| ![Tsukuba 1](image) |

| Tsukuba 2 | Pattern typical also for benign lesions |
|-----------|----------------------------------------|
| ![Tsukuba 2](image) |

| Tsukuba 3 | Usually benign lesions, there is a risk of malignancy |
|-----------|------------------------------------------------------|
| ![Tsukuba 3](image) |

| Tsukuba 4 | Picture indicating malignancy |
|-----------|-------------------------------|
| ![Tsukuba 4](image) |

| Tsukuba 5 | Picture indicating a malignant lesion infiltrating surrounding tissues (blue color goes beyond the lesion) |
|-----------|------------------------------------------------------------------------------------------------|
| ![Tsukuba 5](image) |

| BGR | Pattern characteristic for a cystic lesion |
|-----|-------------------------------------------|
| ![BGR](image) |
4. Planes of examination before and after application of contrast are arbitrarily chosen by the radiologist.

5. Contrast dose [18]: 0.1-0.2 mmol Gd-DTPA/kg of body mass.

6. During analysis of dynamic enhancement [18] acquisition time should not exceed 90s, so that dynamic sequences would encompass the first 5 minutes from contrast application.

Disadvantages of magnetic resonance, other than the previously mentioned high costs, include lack of differentiation of calcifications, difficulty excluding cancer in women with inflammatory conditions of the breasts, necessity of contrast application, numerous false positive results, large number of general contraindications to MR compared to ultrasound or x-ray mammography such as cardiac pacemakers and other implantable medical devices, ferromagnetic foreign bodies in vital organs, claustrophobia, necessity of rigorous patient preparation:

– it is very important to coordinate the study with phases of menstrual cycle – patient should be between the 6th and the 13th day of the cycle (including women using hormonal contraception). In the first phase of the cycle normal glandular tissue undergoes weak enhancement, while in the second phase of the cycle intense enhancement of normal gland can obscure the enhancement of neoplastic lesion. Similarly, ultrasound examination should preferably be performed in the first phase of the cycle due to lesser breast swelling, which may cause ambiguity in assessment. However, the requirement for the first cycle phase is not as absolutely necessary as it is in MR,
– necessity of stopping HRT (examination may be performed 4 weeks after stopping treatment),
– preservation of a minimal time period of 3–6 months from surgery [4].

In MR imaging breast cancer may present as [7,18,19]:

1. Contrast-enhancing mass with features of malignancy:
   – a malignant mass (as in previous studies) is often irregular; however, identification of a well-demarcated tumor does not necessarily determine its benign nature,
   – the following patterns of contrast enhancement are considered features of malignancy.
- types of „malignant” intensity curves: so-called plateau of signal intensity or washout of signal intensity; i.e. in a 5-minute observation period we note a rapid enhancement phase (up to 2-3 minutes after commencing examination) followed by enhancement remaining at the same level (plateau curve) or gradual attenuation of enhancement (washout curve),
- lesion enhancement progresses from its periphery towards the center; contrast washout occurs in a similar manner;
- „blooming sign” – tissue surrounding the lesion enhances within the 1st minute, appearing as a blurry halo (visible in 63% of malignant lesions and 15% of benign ones),
- „hook sign” – a vessel connecting the lesion with the underlying pectoral muscle (noted in 33% of malignant lesions and 5% of benign ones).

2. Asymmetrical enhancement of mammary papilla without a tangible mass, especially exhibiting a „malignant” enhancement pattern, may correspond to Paget’s disease.
3. Diffuse contrast enhancement without a notable mass – may appear in lobular carcinoma (Figures 4, 5).
Breast carcinoma may also manifest in a less typical manner such as:

1. Focal lesion with atypical, delayed contrast enhancement (5% of lesions).
2. Inflammatory carcinoma with a presentation similar to acute mastitis: diffusely increased signal intensity in T2-weighted images with distinct contrast enhancement and thickening of the skin; in MR imaging mastitis is most often impossible to distinguish from inflammatory carcinoma.
3. LCIS is currently considered more of a breast cancer risk factor than a premalignant lesion. It may exhibit diffuse or focal enhancement and is often indistinguishable from fibrocystic dysplasia.
4. DCIS may present as linear or focal enhancement along the ducts but, beside an enhancement pattern typical for malignant lesions, atypical enhancement may be present or lack thereof.

We may also assess the degree of diffusion reduction (DWI) in MR imaging. In malignant lesions we observe a reduction of diffusion, giving a high-intensity signal in DWI images, while the apparent diffusion coefficient (ADC) remains low (cut-off values for malignancy are within 1.19–1.6×10^3 mm^2/s) [4,19]. This modality seems very promising in terms of assessment of early response to chemotherapy. Disadvantages of DWI imaging include lower resolution associated with difficulty in assessment of foci less than 1 cm in diameter and lesions that do not show as a mass, such as an invasive lobular carcinoma. On the other hand, intraductal papillomas and fibrocystic dysplasia are responsible for false positive results, while mucinous carcinoma exhibiting lower ADC values in comparison with other cancers may be the cause of a false negative result [19].

MR spectroscopy is another method involving the use of magnetic resonance. This modality uses choline as a marker of cellular membranes [19]. Increased proportion of choline is seen in breast cancer, some fibroadenomas and normal breasts during lactation. The limitation of this method is related to the size of the lesion, which should be at least 1 cm in diameter for precise assessment in spectroscopy. Long duration of this examination is also a disadvantage.

Elastography [19] is also one of the new trends in MR imaging. Similar to ultrasound examination, it assesses tissue...
strain basing on an assumption that the harder the lesion the higher the probability of malignancy (Figure 6).

**Breast cancer in other imaging modalities (Figures 7, 8)**

**Conclusions**

Every one of the currently used modalities for breast cancer diagnosis has its advantages, but is also associated with limitations. There is no single, ideal method for detection of breast neoplasms, particularly in light of the fact that beside a typical mass, this disease may take on various other forms. However, technological progress leads to improvement of available modalities and new technologies are subjected to clinical assessment. All of this makes diagnosis of breast cancer and differentiation from benign lesions increasingly effective.

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