8

Breast

Standard Imaging Methods for Breast

Introduction

In nearly all cases, the reason for diagnostic imaging of the breast region is breast cancer, and the purpose is to detect and diagnose it and evaluate its progression. Because the purpose varies according to the method used, the discussion is organized by method.

X-ray mammography (Fig. 1)

X-ray mammography ("mammography" below) is the most basic type of diagnostic imaging of the breast region and has long been used. It is currently used not only to diagnose breast disease, but also for breast cancer screening. Diagnostic mammography is the type discussed here. Mammography is indicated when breast disease is suspected. However, because its ability to detect masses is low in dense breasts, its use in young individuals and those in the lactation period requires consideration. Because imaging is performed with the breast compressed, another diagnostic method is considered if compression is not possible or advisable. Breast imaging systems that meet the specifications established by the Japan Radiological Society are used. They are used with detectors for breast imaging. The types of detectors used are: film-screen detectors, used in analog devices; imaging plate (IP) detectors, used in computed radiography (CR); and flat-panel detectors (FPDs), used for digital radiography (DR). Imaging is performed with a dose of ≤ 3 mGy per image. With digital mammography, imaging conditions that can be used to estimate the total radiation dose are specified (July 2005 Japan Radiological Society recommendation). The standard imaging views are the mediolateral oblique (MLO) and craniocaudal (CC) views.

1. Criteria for good images

① Mediolateral oblique (MLO) view (Fig. 1A)

(1) Left and right mammograms are symmetrical.

(2) The nipple is imaged in profile.

(3) The pectoralis major is shown up to the nipple level.

(4) The retromammary fat space is well visualized.

(5) The tissue of the thoracoabdominal wall of the inframammary area is included, and the inframammary fold is extended.

(6) There are no breast folds.

② Craniocaudal (CC) view (Fig. 1B)

(1) Left and right mammograms are symmetrical.

(2) The medial mammary tissue must always be visualized, and the lateral part included as much as possible.
(3) The chest wall is included to a deep level. (If possible, a part of the pectoralis major is displayed.)
(4) The nipple is imaged in profile.
(5) There are no breast folds.

2. Additional imaging

Additional imaging is performed as necessary. The main types of additional imaging are the following.

① Exaggerated craniocaudal (XCC) view

Performed when a lesion is in a lateral area and is not seen with the normal CC view.

② 90-degree lateral [mediolateral (ML) or lateromedial (LM)] view

Performed to accurately understand the vertical spatial relationship between a lesion and the nipple.

③ Magnified view (M)

Performed to evaluate calcification morphology in detail.

④ Spot compression imaging

Performed to eliminate local overlap.

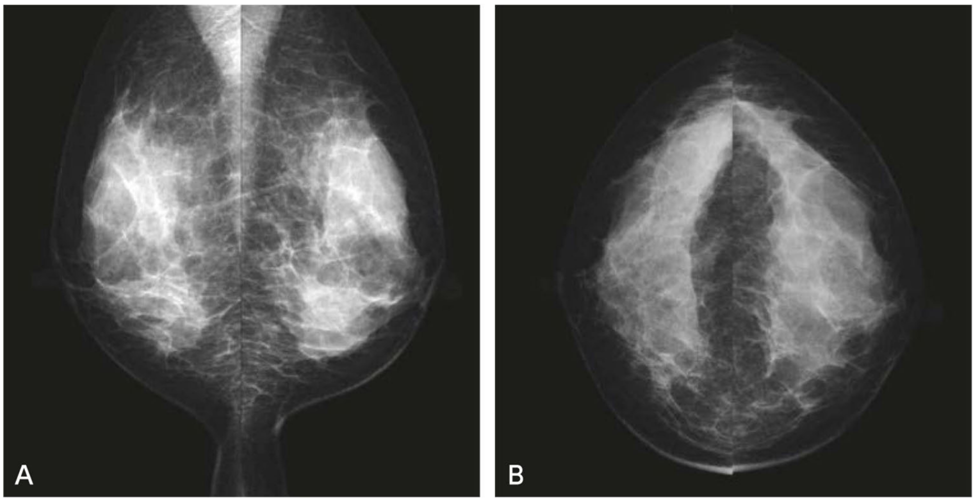

Figure 1. Normal breast (mammogram)
A: MLO view, B: CC view

Digital breast tomosynthesis (DBT, Fig. 2)

DBT is imaging technology that reconstructs cross-sections of arbitrary height from tomographic imaging performed once. With the breast compressed, the X-ray tube is moved to various limited angles (-theta to +theta) in relation to the detector, and tomograms are reconstructed from projection images obtained by multiple image acquisitions. In this way, images with little overlap are reconstructed.

Depending on the system, factors such as the angles to which the X-ray tube is moved, number of irradiations, imaging duration, and method of reconstruction vary greatly, as does the image quality obtained.

As with 2D mammography, the imaging views used are the MLO and CC views.

The method of breast compression is the same as for 2D imaging. However, the imaging method varies according to the system used. With some systems, 2D and DBT imaging can be performed simultaneously. With others, DBT imaging must be performed after 2D imaging.

Breast ultrasonography (Fig. 3)

Ultrasonography is widely used to diagnose breast disease. Because radiation is not used, it can be applied to any patient suspected of having a breast disease. However, it is inferior to mammography with respect to its ability to visualize calcification. In addition, it is often performed to detect and diagnose lesions simultaneously in real time. Consequently, the system settings and performance of the examiner affect diagnostic ability. The systems generally used are hand-held, real-time systems, and fully digital systems that can perform imaging processing by means such as tissue harmonics and spatial compounding are becoming widely used. The use of a high-frequency probe designed for the body surface is required. The gain, dynamic range, and focus are adjusted so that the characteristics of a lesion can be correctly determined. A basic test involves examination of the whole breast bilaterally. If malignancy is suspected, the lymph nodes are also examined. If a lesion is detected, the image is recorded. The basic approach is to record static images (Fig. 3). However, video can also be saved as necessary. For solid masses, imaging is performed in at least 2 views, and measurements are then performed. For lesions that do not form obvious masses, several typical cross-sections should be recorded, along with images of the same region of the contralateral breast. If breast cancer is suspected, the involvement of the surrounding tissue is evaluated, particularly the presence or absence of pectoralis major or skin invasion or intraductal foci.

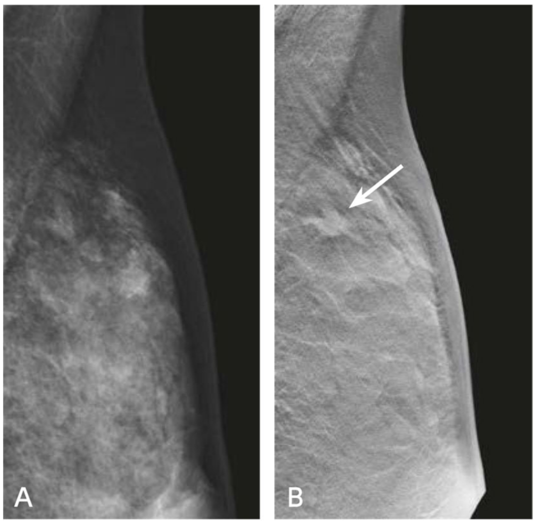

Figure 2. Invasive ductal carcinoma of the left breast

A: 2D mammogram, left MLO view: No obvious abnormality can be identified.
B: Tomosynthesis slice image: An irregularly shaped mass is clearly visualized in the left upper (U) region.

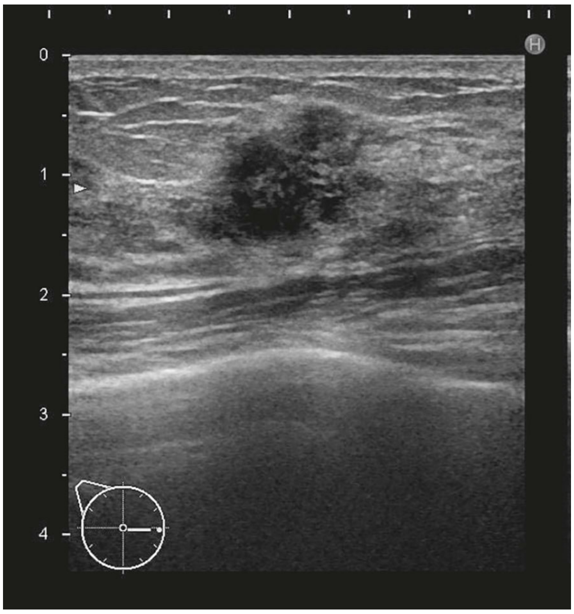

Figure 3. Invasive ductal carcinoma of the right breast

Ultrasonography shows an irregularly shaped hypoechoic mass with indistinct margin, posterior echo attenuation, and interruption of the anterior border.

MRI (Fig. 4)

Breast cancer is a tumor with relatively abundant blood flow that shows strong early enhancement and is distinctly visualized on contrast-enhanced MRI using gadolinium contrast media. Consequently, dynamic MRI is useful for diagnosing breast cancer.[1-4] With diffusion-weighted imaging, breast cancer can be visualized without the use of contrast media. However, the detectability of breast cancer does not surpass the detectability provided by dynamic MRI, and contrast studies are therefore essential for the careful investigation of breast cancer.[5]

It is recommended that imaging be performed 7 to 14 days after the start of menstruation.[3] Outside of this period, particularly during the latter half of the menstrual cycle, mammary fibroglandular tissue enhancement increases. This increases the risk of masking the enhancement of breast cancer and thereby obscuring it (false negative) or producing a finding that can be mistaken for breast cancer (false positive).[1, 3, 4] However, if necessary, imaging in the third week of the menstrual cycle may be considered, although it may not yield good results.[3] The treatment schedule should not be delayed in order to perform MRI at the optimal time.

Using a dedicated breast coil, imaging of both breasts simultaneously should be performed beginning from the early phase of contrast-enhanced imaging. This is so that latent minute breast cancer in the contralateral breast is not overlooked.[1, 2, 4] Moreover, left-right symmetry of mammary fibroglandular tissue enhancement is commonly seen. Consequently, comparing the left and right breasts aids in distinguishing between breast cancer and mammary fibroglandular tissue enhancement.[1)]

To obtain good image quality, a 1.5T or 3T MRI system should be used.[2-5)] The following types of imaging are recommended. A basic imaging plane at many facilities is the transverse plane.

① Fat-suppressed T2-weighted imaging
② T1-weighted imaging
③ Diffusion-weighted imaging
④ Dynamic MRI
⑤ Contrast-enhanced fat-suppressed T1-weighted imaging

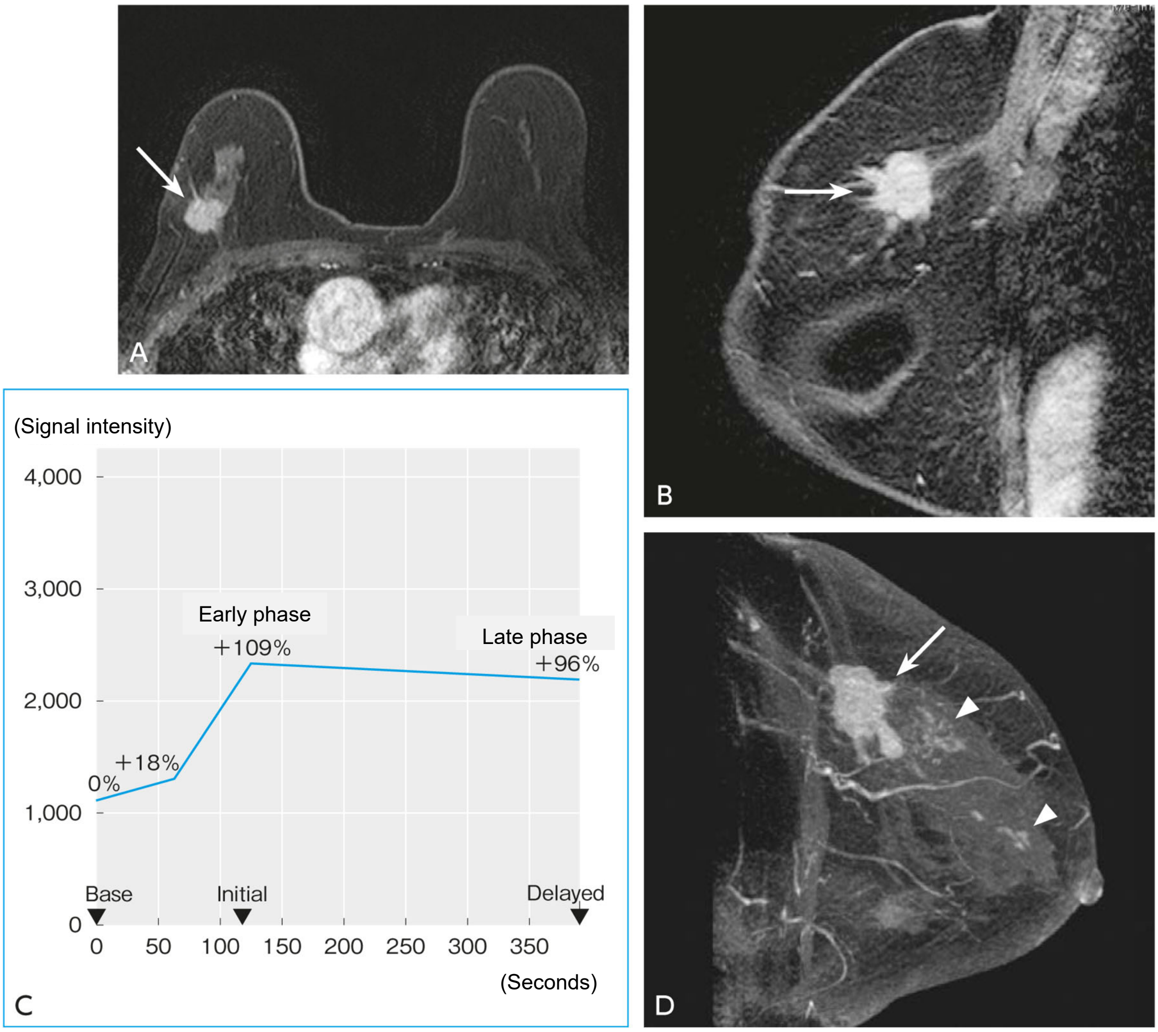

Figure 4. Breast cancer of the right breast (woman in her 70s)

A: Dynamic MRI, early-phase axial image
B: Contrast-enhanced MRI (fat-suppressed, T1-weighted, high-resolution sagittal image acquired between the early and late phases of dynamic MRI)
C: Time-intensity curve analysis
D: MIP image of B

A spiculated, irregularly shaped mass (→) is seen in the periphery of C area of the right breast on the early-phase image of dynamic MRI (A) and the contrast-enhanced fat-suppressed T1-weighted image (B). The time-intensity curve analysis (C) shows that the mass demonstrates a fast-washout kinetic pattern. Total mastectomy was performed (in accordance with the patient's wishes, preoperative chemotherapy was not performed), and invasive ductal carcinoma (scirrhous type, HER2-enriched) was proven pathologically. Non-mass enhancement (▷) extending towards the nipple seen on the MIP image (D) was proven to be extensive intraductal spread on pathological examination.

Breast cancer often shows isointensity to fibroglandular tissue and is indistinct on fat-suppressed T2-weighted images. Lesions such as cysts, fibroadenomas, and mucinous carcinomas are often clearly visualized as masses of high signal intensity due to the presence of abundant fluid.[1, 2, 6] Invasive ductal carcinoma is occasionally associated with edema in the surrounding area, which is visualized as a high signal intensity area.

On T1-weighted images, breast cancer often shows isointensity with fibroglandular tissue and is indistinct. Lipoma and hamartoma have fat tissue in the mass, which shows high signal intensity on T1-weighted images and low signal intensity on fat-suppressed T1-weighted images (precontrast images). Lesions such as complex cysts and duct ectasia, which have proteinaceous or hemorrhagic content, often show high signal intensity on T1-weighted and fat-suppressed T1-weighted images.[1)]

Table 1. Examples of breast MRI sequences (1.5T system, dedicated breast coil)

Imaging method	Sequence	TR/TE (ms)	Slice thickness (mm)	Notes
① T2-weighted / axial	FSE with fat suppression	3,000-5,000 / 80-100	4	
② T1-weighted / axial	Fast 3D-GRE	5-10 / minimum-in phase (flip angle, 10-20°)	1-2	
③ Diffusion-weighted / axial	Single-shot EPI with fat suppression	3,000-5,000 / minimum	4	b-value = 0, 800*-1,000 s/mm^2
④ Dynamic MRI / axial	Fast 3D-GRE with fat suppression	5-10 / minimum-in phase (flip angle, 10-20°)	1-2	Subtraction images are useful if fat suppression is not used
⑤ Contrast-enhanced T1-weighted / sagittal	Fast 3D-GRE with fat suppression	5-10 / minimum-in phase (flip angle, 10-20°)	1-2	Between early and late phase or after late phase Imaging at other cross-sectional planes High spatial resolution imaging

* b-value = 800 s/mm^2 is recommended by the working group of the European Society of Breast Imaging[5)]

On diffusion-weighted images, breast cancer, especially invasive ductal carcinoma, often shows high signal intensity and is clearly depicted. On the other hand, ductal carcinoma in situ, intraductal spread, and small or markedly fibrous invasive ductal carcinoma are often invisible or poorly depicted on diffusion-weighted images, and their detectability is limited. Benign lesions such as cysts and fibroadenomas that show marked high signal intensity on T2-weighted images often show high signal intensity and findings confused with breast cancer on diffusion-weighted images.[5)] Measuring ADC values makes it possible to quantitatively evaluate the diffusion of tumors. The ADC values decrease in breast cancer and increase in benign tumors, and they are therefore used to distinguish between benign and malignant tumors.[1, 5] For measurement of ADC values, it is recommended that a small ROI (≥ 3 pixels) be set in the area with the lowest value (black) in the lesion on the ADC map, while avoiding areas of necrosis and of poor enhancement indicated by dynamic MRI.[5]

On dynamic MRI, invasive ductal carcinoma is often visualized as a mass, and ductal carcinoma in situ and intraductal spread are visualized as non-mass enhancement. The diagnosis is made by analyzing their shapes, margins, internal enhancement characteristics, and distribution pattern. For this approach, it is desirable to image with fat suppression technique [4] and a spatial resolution with pixel size of 1 mm × 1 mm or less and slice thickness of 2.5-3 mm or less.[2, 4] Because peak enhancement of breast cancer occurs within 2 minutes after intravenous injection of contrast media, the early phase, the period from 1 to 2 minutes after injection, is best for tumor visualization. Although tumors can be depicted even in the late phase, 2 minutes or later after injection, tumor conspicuity is decreased because tumor enhancement weakens, and fibroglandular tissue enhancement strengthens.[2]

Breast cancer is strongly enhanced in the early phase and tends to show gradually decreasing enhancement in the late phase. In contrast, benign tumors and lesions often show weak enhancement in the early phase and gradually increasing enhancement in the late phase. Based on this idea of the contrast enhancement pattern, benign and malignant tumors are discriminated by time-intensity curve analysis.[1] Time-intensity curve analysis requires imaging at least 3 times: precontrast, early phase to evaluate peak tumor enhancement, and late phase to observe the changes of tumor enhancement over time after the peak. It is also considered important that imaging be performed with high temporal resolution by acquiring images for 1 to 2 minutes in each phase. An imaging time exceeding 2 minutes may risk missing the peak of tumor enhancement in the early phase, which leads to overlooking washout in the late phase.[2]

To obtain information to augment dynamic MRI, additional contrast-enhanced T1-weighted imaging at different cross-sections or higher spatial resolution is performed between early and late phase imaging or after late phase imaging in many institutions. The MIP image is highly useful post-processing for evaluating the extent of a tumor. It is also helpful for evaluating fibroglandular tissue enhancement and detecting unexpected lesions. Accurate evaluation of enhancement in lesions that shows high signal intensity originally before contrast media administration is difficult. For such lesions, generating and viewing subtraction images obtained by subtracting the precontrast image from the postcontrast image is recommended to confirm the presence or absence of enhancement.[1]

The Breast Imaging Reporting and Data System (BI-RADS) MRI of the American College of Radiology defines the lexicon to be used for findings when interpreting breast MRI, and this has now become the de facto global standard. It is recommended that interpretation reports are prepared in accordance with BI-RADS MRI.[1]

MDCT (Fig. 5)

MDCT is now mainly used for preoperatively staging of breast cancer and detection of postoperative recurrence and metastasis. MDCT was previously used in Japan to diagnose the extent of breast cancer in the breast. However, MRI is the best modality with respect to the problem of radiation exposure and the ability to diagnose breast cancer extent. It is therefore now recommended that the preferred method for diagnosing the spread of breast cancer in the breast is MRI. Consequently, MDCT is considered for patients who cannot undergo MRI, such as those with internal metal objects or claustrophobia and those for whom MRI contrast media are contraindicated.[7)] The usefulness of CT in distinguishing benign from malignant breast disease has not been established, and it is therefore not recommended for this purpose alone.[8)]

Nearly all of the reports indicating that MDCT is useful in breast disease have been reports of single-center studies, and the imaging methods used have varied between centers. An optimal MDCT imaging method has not yet been established.

1. Imaging methods

① Body position during imaging

The primary purpose of CT is to simultaneously evaluate lymph node metastasis and distant metastasis to areas such as the lungs. Consequently, the basic position for imaging is supine. However, to simulate surgery, CT imaging is also performed in a position that approximates the position during surgery.[9, 10)]

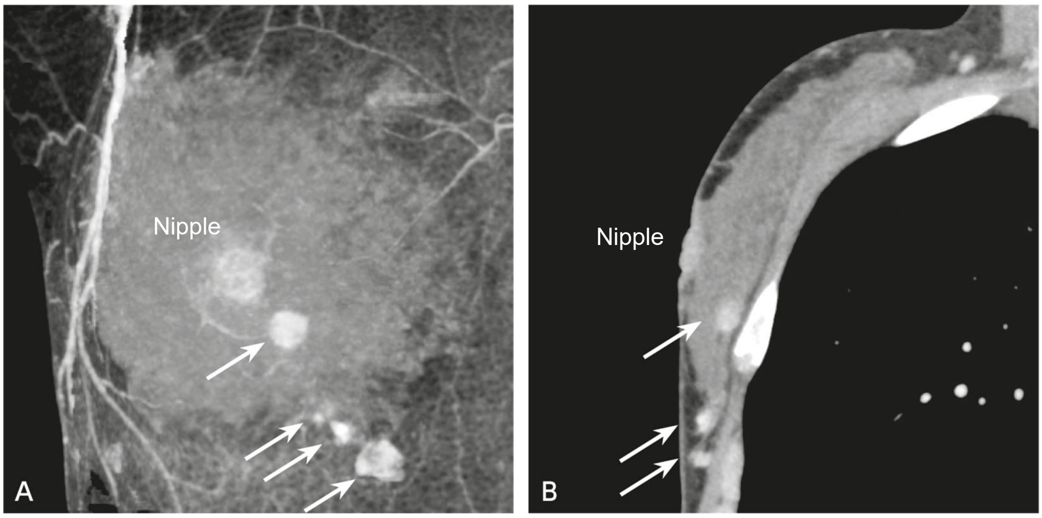

Figure 5. Invasive ductal carcinoma of the right breast

A: Contrast-enhanced CT, MIP image; B: Contrast-enhanced CT, oblique MPR image shows the relationship between the nipple and distal nodules. Numerous linearly distributed nodules are shown in the inner-lower part of the right breast. The relative locations of the nipple and lesions are clear.

② Imaging conditions

Imaging conditions that provide optimal images need to be specified based on a thorough understanding of the performance of the CT system being used at the facility. It is also important to select a protocol intended to reduce radiation exposure by means such as using CT automatic exposure control (CT-AEC) or iterative image reconstruction.

③ Contrast media

Because the ability to detect breast cancer on non-contrast CT is weak, use of a contrast medium is essential. Although intravenous injection of iodine contrast media at a concentration of 300 mg I/mL and injection rate of 2 to 3 mL/s is commonly reported, high concentrations (370 to 400 mg I/ml) of contrast media are also used.[11, 12] However, there have been almost no reports concerned with the optimal contrast medium injection dose and method of injection.

④ Timing of imaging

Many reports indicate that imaging for the early phase of contrast-enhanced imaging begins 60 to 90 seconds after the start of contrast medium injection, and that late-phase imaging is performed from 3 to 5 minutes after injection. As indicated in BI-RADS-MRI, it is recommended that early-phase imaging be performed within 2 minutes of injection, when breast cancer is most enhanced.[1] Delayed-phase imaging is also important to evaluate intraductal lesions, which have a delayed contrast peak. Delayed-phase imaging also enables the time-concentration curve to be evaluated. However, the usefulness of the time-concentration curve for distinguishing malignant from benign lesions with CT has not been established.

2. Interpretation method

MPR and MIP images should be prepared to diagnose the spread of breast cancer in the breast by multidirectional observation (Fig. 5). Although no diagnostic criteria have been established, it is recommended that the findings be evaluated and a final assessment (categorization) determined in conformance with BI-RADS-MRI.

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FQ 17 Is contrast-enhanced MRI recommended for the qualitative diagnosis of microcalcification without abnormal findings on ultrasonography?

Statement

Contrast-enhanced MRI can be considered to assist in selecting a diagnostic strategy.

Background

Microcalcification detected by mammography screening is an important sign that is suggestive of noninvasive carcinoma. The positive predictive value (PPV) of microcalcification of categories 3 and 4 of the BI-RADS system of the American College of Radiology (ACR) has ranged widely, from 0% to 19% and 20% to 65.8%, respectively. However, many reported PPVs of microcalcification on mammography have been ≤ 30%.[1-7] These results indicate that biopsy results for microcalcification are often benign. It has therefore been argued that stricter criteria for microcalcification biopsy ought to be established.

To avoid unnecessary biopsies, the usefulness of contrast-enhanced MRI to determine whether biopsy is indicated for microcalcification has been investigated in recent years. In Japan, stereotactic vacuum-assisted breast biopsy (SVAB) or tomosynthesis-guided vacuum-assisted breast biopsy (TVAB) is generally indicated for microcalcification without abnormal findings on ultrasonography. Although there have been several reports from Japan regarding the usefulness of contrast-enhanced MRI for qualitative diagnosis of microcalcifications without abnormal findings on ultrasonography, the evidence is still insufficient. Consequently, this was examined as an FQ.

Explanation

Reports regarding the usefulness of contrast-enhanced MRI in microcalcification have been published since 1996.[8, 9] After 2000, the diagnostic performance of contrast-enhanced MRI improved with technological developments, an example being simultaneous bilateral dynamic imaging, and the recognition of background parenchymal enhancement.[3, 4, 10-25] Moreover, due to the changes in the diagnostic strategy with the introduction of SVAB, reports recommending contrast-enhanced MRI for the qualitative diagnosis of microcalcification increased.

In a meta-analysis including 20 published studies, a finding of contrast enhancement of a microcalcification on contrast-enhanced MRI was found to be associated with the diagnosis of malignancy with high sensitivity (87%)[26] and specificity of 81%. The sensitivity and specificity of contrast-enhanced MRI in microcalcification based on BI-RADS category were as follows: 57% and 32%, respectively, for BI-RADS category 3 microcalcifications; 92% and 82%, respectively, for category 4; and 95% and 66%, respectively, for category 5. Thus, the improvement in diagnostic performance that resulted from the addition of contrast-enhanced MRI was particularly marked for BI-RADS category 4 microcalcifications, suggesting that, though it cannot be an alternative for biopsy, contrast-enhanced MRI is useful for excluding malignancy.

However, 6 of the studies examined in the above-mentioned meta-analysis included patients with other mammographic abnormalities in addition to microcalcifications.[11-13, 19, 21, 24] Moreover, the meta-analysis did not indicate whether there were abnormal findings on ultrasonography. The studies that clearly indicate "without abnormal findings on ultrasonography" were mainly from Japan. The sensitivity and specificity of contrast-enhanced MRI in these studies ranged from 79% to 100% and from 78% to 95%, respectively.[3, 10, 18, 20, 27] The studies varied regarding whether they included BI-RADS category 3 microcalcifications and whether the diagnostic criterion for malignancy on contrast-enhanced MRI was contrast enhancement or a BI-RADS-MRI category of ≥ 4. No consistent tendency can be identified with respect to the qualitative diagnostic performance of contrast-enhanced MRI in the condition of microcalcification without abnormal findings on ultrasonography.

In recent years, overdiagnosis has come to be considered problematic in breast cancer management. Overdiagnosis is the detection and diagnosis of cancer that does not affect the prognosis of the patient. Early-stage breast cancer that is low-grade and noninvasive carcinoma is highly likely to result in overdiagnosis.[28, 29] In the above-mentioned meta-analysis, the false-negative rate of contrast-enhanced MRI in the qualitative diagnosis of microcalcification was approximately 10%. However, in nearly all of these cases, the carcinoma was noninvasive. When invasive or microinvasive cancer was investigated, the negative predictive value of contrast-enhanced MRI was a very high 99%.[26] In noninvasive carcinoma, the detection rate with contrast-enhanced MRI has been reported to be high for high-grade noninvasive carcinoma, regardless of BI-RADS category of microcalcification, and many of the false-negatives have been found to be low-grade noninvasive carcinoma.[27] To avoid overdiagnosis and overtreatment of low-grade noninvasive carcinoma, the option of active surveillance by imaging is permitted for microcalcification without abnormal contrast-enhanced MRI findings.

As a prospect for the future, the different roles of contrast-enhanced MRI may be clarified to determine the indication for biopsy according to the subdivided categories based on the microcalcification characteristics or patient background characteristics, such as whether the patient is in a high-risk group. There is little evidence from Europe and the United States concerning the usefulness of contrast-enhanced MRI performed based on ultrasonography findings. Data should therefore be accumulated and analyzed in Japan. In addition, depending on the results of clinical trials of non-resection of low-grade noninvasive carcinoma,[30, 31] greater significance may be placed on the role of contrast-enhanced MRI. However, contrast-enhanced MRI is also associated with the problem of cost, and evidence needs to be accumulated to consider the balance between adverse effects and benefits.

In conclusion, contrast-enhanced MRI is not an alternative for SVAB or TVAB for diagnosing microcalcification without abnormal findings on ultrasonography. However, it may assist in selecting a diagnostic strategy, and its use can therefore be considered.

Search keywords and secondary sources used as references

PubMed was searched using the following keywords: breast neoplasm, breast, calcinosis, calcification, mammography, ultrasonography, magnetic resonance imaging, biopsy, needle, image-guided biopsy, diagnosis, diagnostic imaging, carcinoma, intraductal, and noninvasive.

In addition, the following was referenced as a secondary source.

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FQ 18 Is investigation recommended for incidental breast lesions detected by CT performed for non-breast disease?

Statement

Investigation of incidental breast lesions can be considered.

Background

Incidental breast lesions are occasionally discovered during CT for non-breast disease. These may include malignancies such as breast cancer. Consequently, watchful waiting is required at a minimum, and, depending on the case, investigation with another modality may also be necessary.

Explanation

The incidental discovery of a breast lesion by chest or cardiac CT is occasionally encountered. The reported detection rates of incidental findings range widely, from 0.63%[1] to 7.6%.[2] However, imaging conditions, such as whether a contrast medium was used and slice thickness, varied, as were the periods when the studies were conducted, indicating that differences in the systems used may have played a major role in the variability. Whereas observations were performed using a contrast medium and slice thickness of 1 mm in 1 study, the imaging conditions used in the other were not specified. With cardiac CT[3] and non-contrast-enhanced, low-dose CT for lung cancer screening, which has become common in recent years,[4] detection rates are fairly low.

The rate of malignancy of detected lesions also ranges widely, from 9% to 60%.[5] Round to oval shape, distinct borders, and weak enhancement are findings suggestive of a benign lesion. Large size, irregular or lobular shape, spiculation, strong enhancement, and the presence of enlarged axillary lymph nodes are considered suggestive of a malignant lesion.[5-15] Non-mass enhancement with contrast-enhanced CT has also been found to be suggestive of malignancy.[11]

The probability of a detected lesion being malignant has been found to be higher in older individuals than in younger individuals.[11, 14, 16] However, the absence of an age difference with respect to the distribution of malignant and benign lesions has also been reported.[5, 8] The distributions of the test subjects may have affected the results.

With regard to the management of incidental findings, if previously acquired images of the lesions are available for comparison, it is recommended that lesions that have enlarged and newly developed lesions be actively investigated.[4] If the above-described CT findings suggestive of a benign lesion are obtained, watchful waiting is an option. However, an article that evaluated the economic considerations concluded that investigating such incidental breast lesions detected by CT results in less of a financial burden than a screening program for detecting primary breast cancer.[17] Consequently, such lesions can be investigated.

As mentioned above, although studies have been conducted of incidental breast lesions found on CT, there has been large variability in the lesions examined and the imaging methods and types of imaging used. Further evidence is awaited.

Search keywords and secondary sources used as references

PubMed was searched for the period from 1992 through May 2020 using the following keywords: chest CT, cardiac CT, breast neoplasm, and incidental. Hits were obtained for 53 articles. Sixteen articles were extracted during screening. Of these, 17 were reviewed, including 1 article designated as a reference.

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CQ 18 Is contrast-enhanced breast MRI recommended to determine a treatment strategy before breast cancer surgery?

Recommendation

Contrast-enhanced breast MRI is weakly recommended to determine a treatment strategy before breast cancer surgery.

Recommendation strength: 2, strength of evidence: moderate (B), agreement rate: 100% (10/10)

Background

Contrast-enhanced breast MRI is highly sensitive for breast cancer and widely used clinically. In Japan, contrast-enhanced breast MRI is commonly performed to diagnose the extent of lesions preoperatively in patients definitively diagnosed with breast cancer. It often assists in determining the local surgical procedure. The Clinical Practice Guidelines for Breast Cancer 2018 of the Japanese Breast Cancer Society weakly recommend contrast-enhanced breast MRI to select a treatment strategy before breast cancer surgery.

However, it has been noted that the specificity of contrast-enhanced breast MRI for breast cancer is relatively low compared with its high sensitivity, and the false-positive rate for MRI-detected lesions is high. It has therefore been noted that performing contrast-enhanced breast MRI before breast cancer surgery may increase the likelihood of total mastectomy for early-stage breast cancer. Consequently, the uniform use of contrast-enhanced breast MRI before breast cancer surgery is a subject of debate in Europe and the United States.

Based on these considerations, the usefulness of contrast-enhanced breast MRI for selecting a treatment strategy before breast cancer surgery was evaluated for this CQ. The evaluation took into account, in addition to the accuracy of contrast-enhanced breast MRI in diagnosing breast cancer extent, factors such as the false-positive rate for MRI-detected lesions, the relationship between preoperative MRI and total mastectomy, and the reduction in the rate of postoperative local recurrence.

Explanation

As a newly considered beneficial outcome related to breast cancer surgery, the present qualitative systematic review examined the decrease in the rate of repeat breast cancer surgery, with the increase in total mastectomy examined as an adverse outcome. These outcomes were examined in addition to the outcomes used for this CQ in the Clinical Practice Guidelines for Breast Cancer 2018: the reduction in the local recurrence rate, improvement in the accuracy of diagnosis of breast cancer extent, increased sensitivity for breast cancer, and the reduction in the recurrence rate of the contralateral breast.

Beneficial outcomes related to the initial surgery for preoperative contrast-enhanced breast MRI that were examined in the qualitative systematic review were improvement in the accuracy of diagnosis of breast cancer extent, reduction in the rate of repeat surgery, and increased sensitivity for breast cancer. Adverse outcomes examined were increases in the false-positive rate and total mastectomy.

Ten articles on case-control studies were used to examine the improvement in the accuracy of diagnosis of breast cancer extent.[1-10] Although the studies that were compiled used different criteria, they generally showed contrast-enhanced MRI to be superior to mammography and ultrasonography for diagnosing breast cancer extent. Specifically, the concordance rates of contrast-enhanced MRI with postoperative pathology were higher than those of other modalities.[1, 2] Moreover, the diagnostic accuracy of MRI (66% to 98%) was higher than that of mammography and ultrasonography (52% to 56%).[3-5] On the other hand, the overall trend was for MRI to underestimate tumor extent less often than mammography, but to overestimate it more often.[2, 5, 6, 8, 10]

With regard to the rate of repeat surgery after initial breast cancer surgery, the articles referenced as a whole, particularly the report of a 2010 randomized, controlled study (COMICE study),[11] reported no significant differences between the groups that underwent MRI (1.6% to 29%) and those that did not (3.3% to 45%).[11-20] However, in 2 cohort studies reported in articles newly included in the present review in which propensity score matching was performed (patients with invasive lobular carcinoma were the subjects of 1 study), significantly lower repeat surgery rates were found in the groups that underwent preoperative MRI than in the groups that did not.[19, 20]

With regard to increased sensitivity for breast cancer, the current qualitative systematic review examined the increase in the ability to detect additional malignancies provided by preoperative MRI of the ipsilateral and contralateral breasts.[13, 16, 20-22] The reference standards were the true positive rate for MRI-detected lesions that underwent additional biopsy and the true positive rate including postoperative pathology results. Thus, variability was seen between the reports. However, additional malignancies were seen in the breast with known breast cancer detected by preoperative MRI in 7.3% to 22% of patients, and contralateral breast cancer was detected in 1.9% to 5.7% of patients.

However, in the articles included in the current review as a whole, MRI-detected lesions were seen in 15.2% to 40% of patients, with false-positive rates ranging from 34% to 66%.[13, 16, 17, 20-27] The addition of preoperative MRI detects a certain amount of additional breast cancer not identifiable by mammography or ultrasonography in the ipsilateral and contralateral breasts (increased breast cancer sensitivity: beneficial outcome). At the same time, however, it is certain to increase false positives (increased false positives: adverse outcome).

With regard to the increase in total mastectomy as initial surgery, the rates of total mastectomy in the articles examined in the present review as a whole were 7.1% to 42.9% in the groups that underwent preoperative MRI and 0% to 47.9% in the groups that did not.[11, 13, 16-21, 28] Specifically, in 2 relatively old cohort studies,[13, 21] in addition to the COMICE study,[11] the rate was significantly higher in the groups that underwent preoperative MRI than in the groups that did not. However, in the relatively new studies added to this review (1 randomized, controlled study,[17] 5 cohort studies,[18-21, 28]) no significant differences in the total mastectomy rate were seen between these groups.

Next, a qualitative, systematic review regarding decreases in the local recurrence rate and contralateral breast recurrence rate was conducted. These measures were considered beneficial outcomes of the addition of preoperative contrast-enhanced breast MRI that was related to prognosis following initial surgery. In the referenced articles as a whole,[11-15, 19, 21, 23, 28-32] the local recurrence rates after breast cancer surgery tended to be lower in the groups that underwent MRI before breast cancer surgery (0.3% to 6.1%) than in those that did not (1% to 9%). However, the differences were significant in 3 of 13 studies, indicating uncertainty that the local recurrence rate was reduced in the preoperative MRI groups.

Four cohort studies and four case-control studies were used to examine the decrease in the rate of contralateral breast cancer recurrence.[13, 14, 19, 20, 29-31, 33] Although these included studies with short follow-up periods, the contralateral breast recurrence rates in the studies used in this review as a whole were 1% to 3.2% in the group that underwent preoperative MRI and 1.3% to 21.7% in those that did not. Thus, some articles reported high rates of contralateral breast recurrence in the groups that did not undergo MRI. However, significant differences were seen in 3 of the 8 studies, indicating uncertainty that the contralateral breast cancer recurrence rate was reduced in the groups that underwent preoperative MRI.

Based on these findings, it is unclear whether preoperative breast MRI produces the beneficial outcomes considered the most important, i.e., reductions in the rates of local recurrence and repeat surgery. Moreover, the false-positive rate, considered the most important adverse outcome, was high, and the possibility that this was related to increased total mastectomy cannot be ruled out. Consequently, it cannot be said with certainty that the benefits of preoperative breast MRI outweigh the adverse effects.

However, the data from the 2010 COMICE study, which examined the relationship between breast MRI performed before breast cancer surgery and breast cancer surgery, are old. Moreover, subsequent to that study, MRI diagnostic criteria were standardized, and accuracy controls and methods of managing MRI-identified lesions, including MRI-guided biopsy, underwent refinement. As a result, the findings of that study are removed from current clinical practice. Consequently, points that should be considered are that the newer controlled studies that were included in the present review for the first time reported that the repeat-surgery rate was reduced in the groups that underwent preoperative MRI, and that the use of MRI was not associated with increased total mastectomy. In studies other than randomized, controlled studies, it has been noted that preoperative breast MRI tends to be performed in high-risk patients, such as those who are younger or have dense breasts or invasive lobular carcinoma. The most recent cohort studies, which performed propensity score matching, found that repeat-surgery rates were significantly lower in groups that underwent MRI. With regard to increased total mastectomy, the newer controlled studies that were included in the present review noted that the use of MRI may not lead to an increase because of the appropriate evaluation of MRI-detected lesions and determination of a treatment strategy to manage such lesions (through the use of MRI-guided biopsy or multidisciplinary team conferences for multidisciplinary decisions on procedures).

Based on the current review, no definitive associations were found between preoperative MRI and reductions in the rates of postoperative local and contralateral breast recurrence. Whether additional postoperative treatment (local radiation therapy or postoperative adjuvant therapy) was administered was a more significant factor than whether MRI was performed. Moreover, contrast-enhanced breast MRI showed high sensitivity for breast cancer, which was specified as another beneficial outcome for this CQ. It is clear that contrast-enhanced breast MRI was able to detect ipsilateral and contralateral breast cancer that could not be identified by mammography or ultrasonography. The accuracy of breast MRI in diagnosing breast cancer extent is higher than that of mammography or ultrasonography. Consequently, it may assist in determining whether a new breast cancer surgical procedure (e.g., nipple- or skin-sparing total mastectomy) is indicated. Such procedures are based on breast reconstruction, which is increasing in recent years and requires more accurate diagnosis of breast cancer extent. In determining the strength of the recommendation for Japan, the number of MRI units and the low cost of MRI in Japan (healthcare environment that facilitates MRI use) should be taken into account.

Based on the above considerations, contrast-enhanced breast MRI is weakly recommended to select a treatment strategy before breast cancer surgery. To detect contralateral breast cancer, bilateral imaging using a breast-specific coil is necessary. Moreover, consideration should be given to the adverse effects of MRI, and the appropriate evaluation and management of MRI-detected lesions are required. The treatment strategy, including aspects such as the surgical procedure to be used, should be determined in a multidisciplinary fashion by a multidisciplinary team conference.

Search keywords and secondary sources used as references

As in the case of CQ 6 of secondary source 2, the Clinical Practice Guidelines for Breast Cancer, PubMed was searched using the following keywords: breast neoplasms, magnetic resonance imaging, neoplasm recurrence, local, false positive reactions, neoplasm invasiveness, preoperative period, preoperative care, neoplasm staging, diagnosis, and diagnostic imaging. The period searched was from the date of the search performed for the above-mentioned guidelines (December 2016) to June 2019; hits were obtained for 184 articles. The Ichushi and Cochrane Library databases were also searched using the same keywords. In the secondary screening, 5 articles were extracted, and 5 articles were added with a hand search. A qualitative, systematic review was performed of these articles together with those used for the above-mentioned CQ 6.

In addition, the following were referenced as secondary sources.

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FQ 19 Which imaging examinations are recommended to evaluate the axillary lymph nodes before breast cancer surgery?

Statement

Ultrasonography is recommended for the preoperative evaluation of the axillary lymph nodes.

There is an insufficient scientific basis for using CT, MRI, or FDG-PET (PET/CT) for the sole purpose of preoperatively evaluating axillary lymph node metastasis.

Background

The presence or absence of axillary lymph node metastasis is important for staging and considering a treatment strategy. However, there are currently limitations to its evaluation by diagnostic imaging, and pathological evaluation is therefore considered necessary. Patients who undergo axillary lymph node dissection may experience impairment of the upper extremity and shoulder joint (restricted joint range of motion, upper extremity edema, sensory impairment, pain) of the operative side. Consequently, methods that are minimally invasive have come to be selected. Currently, standard treatment for breast cancer that is clinically negative for axillary lymph node metastasis is to omit axillary lymph node dissection if sentinel lymph node (SLN) biopsy is negative for metastasis. As of recently, axillary lymph node dissection may be omitted even in patients positive for SLN metastasis if the patients undergo radiation therapy. Under such circumstances, appropriate evaluation of the axillary lymph nodes is necessary to determine whether SLN biopsy is indicated.

Explanation

This question was examined by performing a literature search using the keywords indicated below, with survival rate improvement, false positives, sensitivity, overevaluation of microscopic metastasis, and cost-effectiveness as outcomes. There were no articles on survival rate improvement with diagnostic imaging or cost-effectiveness.

SLN biopsy is currently the standard treatment for primary breast cancer considered clinically negative for axillary lymph node metastasis (N0; secondary source 1). Generally, a blue dye or radioisotope is injected into the breast and enters a lymph duct. The first lymph node it reaches is identified as the SLN and resected. If the SLN is positive for metastasis based on an intraoperative rapid pathology examination, axillary lymph node dissection is performed to level II. However, since the results of the ACOSOG Z0011 study were reported, there has been debate regarding whether axillary lymph node dissection can be omitted even if metastasis to the SLN is seen.[1)] The NCCN guidelines (secondary source 2) indicate that SLN biopsy is indicated if metastasis is suspected in up to 2 lymph nodes based on imaging studies. If 1 or 2 SLNs are metastasis-positive, they recommend that axillary lymph node dissection be omitted and breast-conserving surgery and radiation therapy be performed. Consequently, under the current circumstances, the question of how to use diagnostic imaging can no longer be considered by simply comparing the diagnostic performance of each modality.

Ultrasonography is noninvasive, and its use is recommended to evaluate the axillary region, as well as for the widely performed preoperative breast evaluations. An examination of the diagnostic performance of ultrasonography reported sensitivity of 49% to 87% and specificity of 55% to 94%.[2)] Improvement in diagnostic performance has been reported by combining size (short-axis diameter > 5 mm considered positive) and morphological criteria (findings of round shape, hypoechoic pattern, cortical thickening, disappearance of the hilum, and lobularity) and blood flow information obtained by modalities such as color Doppler imaging.[3)] For lymph nodes suspected of involvement based on ultrasonography, confirmation by ultrasound-guided axillary lymph node biopsy (cytology and histology) is recommended.[4)] In a systematic review of 6 studies in 4,271 patients who underwent diagnosis by ultrasound-guided biopsy, axillary lymph node metastasis was seen is ≤ 2 nodes in 78.9% of patients who were negative for metastasis by ultrasound-guided biopsy and 43.2% of patients who were positive for metastasis. It was therefore concluded that, even in patients who are positive on ultrasound-guided biopsy, axillary lymph node dissection may be unnecessary in roughly half.[5)] Thus, it has recently become necessary to consider whether SLN biopsy is indicated based not only on an assessment of whether lymph node metastasis has occurred, but also on whether it has occurred in 2 or fewer nodes.

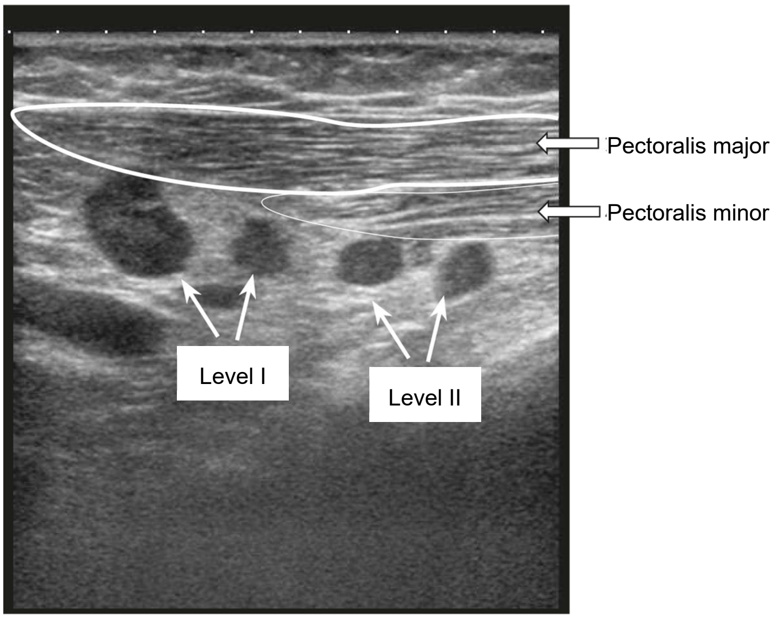

Figure. Ultrasonography performed for preoperative staging of breast cancer

Enlarged lymph nodes are seen in right axillary region levels I and II. Metastasis was suspected based on morphology, and malignancy was diagnosed by aspiration biopsy cytology. Axillary lymph node dissection was performed, and metastasis was confirmed histopathologically.

MRI is commonly performed to diagnose breast disease, with MRI of the axillary region performed as secondary imaging.[3] Examination of the diagnostic performance of MRI in the axillary lymph nodes in a recent meta-analysis showed sensitivity of 48% to 62% (pooled sensitivity, 55%) and specificity of 82% to 89% (pooled specificity, 86%).[6] Compared with ultrasonography, MRI is viewed as enabling more objective evaluation with little operator dependence.[3] However, it cannot be said that appropriate methods of imaging and diagnosis have been established at this point. Consequently, the imaging range does not always adequately include the axillary region.

FDG-PET/CT may be performed to evaluate the axillary lymph nodes together with whole-body metastasis screening. In a meta-analysis, its sensitivity and specificity were found to range from 47% to 63% (pooled sensitivity, 56%) and from 87% to 93% (pooled specificity, 91%), respectively.[6] Although technological innovations such as system improvements and the 3D time-of-flight (TOF) method are thought to have improved the ability to detect lesions, detecting small lymph node metastases (< 5 mm in diameter or patients with microscopic metastasis) is particularly difficult.[7]

With CT, the axillary region may be evaluated at the same time as screening for chest lesions or metastasis to areas including the abdomen. CT can provide more objective data than ultrasonography. However, an examination of diagnostic performance using previous reports showed sensitivity ranging from 60% to 78% and specificity ranging from 76% to 97%.[8-10] Thus, CT cannot be considered effective in its diagnostic performance.[3]

The above findings indicate that axillary lymph node diagnosis based on diagnostic imaging has limitations and cannot substitute for SLN biopsy. The use of ultrasonography to preoperatively evaluate the axillary lymph nodes is recommended in view of considerations such as exposure to radiation and contrast media and because it can be performed noninvasively and used in interventions.

Search keywords and secondary sources used as references

PubMed was searched using the following keywords: breast cancer, axillary lymph node, ultrasound, ultrasonography, MRI, CT, and PET/CT.

In addition, the following were referenced as secondary sources.

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FQ 20 Is whole-body screening by CT, PET, or PET/CT recommended before breast cancer surgery?

Statement

In primary breast cancer of stage I or II, which shows no signs of metastasis, whole-body screening by CT, PET, or PET/CT before breast cancer surgery is generally not recommended. However, in stage II disease, whole-body screening by PET or PET/CT is considered depending on the breast cancer subtype, tumor grade, and patient background. Whole-body screening by CT, PET, or PET/CT is essentially recommended in stage III disease.

Background

In the previous guidelines, whole-body screening before primary breast cancer surgery was recommended in disease of stage III or higher. However, it was not recommended in stage I or II disease, which has a low rate of distant metastasis (secondary sources 1 to 4).

In the General Rules for Clinical and Pathological Recording of Breast Cancer (18th edition, secondary source 5), the clinical staging classification used is the anatomic stage classification based on the TNM classification conforming to the TNM Classification of Malignant Tumours of the Union for International Cancer Control (eighth edition, UICC; secondary source 6). Recently, however, the treatment strategy for breast cancer has been determined using the breast cancer subtype based on biomarkers, as well as the clinical stage. In addition, the American Joint Committee on Cancer (AJCC) staging manual (8th edition, secondary source 7) incorporated the prognostic stage, which combines the tumor grade and subtype classification with the anatomic stage classification, and this has been used since January 2018 in the United States.

With regard to whole-body screening before primary breast cancer surgery, there is also a need in Japan to consider not only the clinical stage, which has conventionally been used, but also the breast cancer subtype, tumor grade, and patient background. Consequently, the usefulness of such screening by CT, PET, or PET/CT was examined based on the currently available evidence.

Explanation

Whole-body screening by diagnostic imaging before breast cancer surgery is often performed to screen for distant metastasis, which may result in a change in the treatment plan. In The Diagnostic Imaging Guidelines 2016 (secondary source 4), preoperative screening for distant metastasis by CT, PET, or PET/CT was not recommended in stage I or II breast cancer if there were no clinical findings strongly suggestive of metastasis. There was a lack of scientific evidence for such use. There was scientific evidence for its use in stage III breast cancer, and it was therefore recommended in that case. Moreover, the Japanese

Breast Cancer Society Clinical Practice Guidelines for Breast Cancer 2018 weakly recommend that preoperative whole-body screening by CT, PET, or PET/CT not be performed in stage I or II breast cancer.

A review of several studies showed that distant metastasis was found in 2.6% of the patients who underwent examinations in stage I or II.[1-8] The proportion with distant metastasis was 0.4% for stage I, 6.9% for stage II, 5.3% for stage IIA, and 10.9% for stage IIB. Thus, the frequency of distant metastasis was low in patients with stage I breast cancer, indicating that preoperative whole-body screening is not very useful in these patients.

An examination by modality found that CT (chest and abdomen) was more useful than chest radiography and liver ultrasonography for detecting pulmonary or liver metastasis, although CT false-positives were common in stages I and II.[9] False positives on chest CT have been reported to occur frequently in stage I and II breast cancer, resulting in additional imaging examinations and increased radiation exposure and cost.[10] Consequently, the usefulness of CT in stage I and II disease is considered low.

With PET and PET/CT, the ratio of false positives to true positives has been found to increase as the stage of disease decreases.[11] Consequently, whole-body screening with PET and PET/CT is not recommended for stage I disease.[12-15] For diagnosing axillary lymph node metastasis, sentinel node biopsy (SNB) is the gold standard, and PET and PET/CT cannot substitute for it.[14, 16] Previous guidelines from Japan, Europe, and the United States do not recommend whole-body screening by PET and PET/CT in stage II disease (secondary sources 1 to 4). However, a systematic review found that, with the addition of PET and PET/CT to conventional diagnostic imaging to classify patients with stage II breast cancer, the distant metastasis detection rate increased from 1.2% to between 3.3% and 34.3%.[1] The results of several other studies also suggested that PET and PET/CT are useful for detecting distant metastasis in stage II breast cancer.[3, 4, 14-18] Moreover, PET and PET/CT were reported to result in a change of treatment plan in 8% to 18% of stage II patients.[19] In stage II breast cancer, many studies have found PET and PET/CT to be useful in patients positive for axillary lymph node metastasis and in stage IIB disease.[3, 4, 14-16] However, evidence for this is lacking. Further evaluation in large, multicenter studies is considered necessary to evaluate the role of PET and PET/CT in patients with stage II disease and disease in the stage IIA and IIB subgroups to elucidate the clinical stages in which PET and PET/CT can be systematically performed in a cost-effective manner.[11, 13, 15, 19] In stage III or locally advanced breast cancer, numerous studies have reported that PET and PET/CT were useful, detecting distant metastasis and changing the treatment plan in 10% to 29% of patients.[1, 13-16, 20] The sensitivity of PET and PET/CT in detecting distant metastasis has ranged from 78% to 100%, which is higher than the 37% to 78.6% sensitivity of non-metabolic imaging examinations that reflect morphological and anatomical changes, such as conventional ultrasonography and CT.[1] The diagnostic accuracy of PET and PET/CT in bone metastasis may be higher than that of bone scintigraphy.[2, 16] Another advantage of PET and PET/CT is that it can be used to examine not only the chest, abdomen, and bones, but also the extra-axillary lymph nodes in a single examination.[11, 14, 15] However, evidence regarding its cost-effectiveness is lacking.[13]

Whether the clinical stage alone should be considered when examining whether preoperative whole-body screening is needed is also a subject of debate. In a study by Riedl et al. of 134 patients aged < 40 years with stage I to IIIC breast cancer, stage IV lesions were seen by PET or PET/CT in 10% of patients with asymptomatic stage I or II disease, with distant metastasis seen in 17% of patients with stage IIB disease.[4] Compared with elderly breast cancer patients, patients < 40 years old are more likely to have higher biological malignancy or metastasis.[14] Early detection of distant metastasis may be helpful in changing the survival rate or treatment of such patients. In breast cancer patients < 40 years old, whole-body screening by PET or PET/CT may be beneficial even in stage I or II breast cancer (particularly stage IIB). Studies have suggested that it may be particularly useful if high-risk disease is involved.[4, 13]

Studies of subtypes have found that, in patients with stage II breast cancer, those negative for hormone receptors, HER2-positive younger patients, and HER2-positive or triple-negative patients undergo diagnostic imaging more frequently for clinical staging.[21, 22] With regard to distant metastasis detection in patients with stage II breast cancer, bone and liver metastases are often detected with the luminal B (HER2-positive) and HER2-positive subtypes, and bone, liver, and pulmonary metastases are often detected with the basal-like subtype. Screening for metastasis in these subtypes has been found to be helpful.[12] However, the finding of no significant differences in the metastasis detection rate between the hormone-receptor positive, HER2-positive, and triple-negative subtypes has also been reported.[22, 23]

Whether whole-body screening is needed in stage II (particularly stage IIB) breast cancer and whether patient background such as subtype, patient age, and high-risk disease need to be taken into account remain subjects of considerable debate. Large, prospective, adequately planned, multicenter studies are therefore needed. Moreover, studies based on prognostic staging classification are likely to increase in number in the future.

Finding distant metastasis through preoperative whole-body screening with CT, PET, or PET/CT would result in a change of treatment plan that could avoid unnecessary surgery. If no metastasis is found, such screening could alleviate the patient’s anxiety. However, within the scope of the literature search, there were no reports relevant to improving overall survival time. Moreover, although radiation exposure increases with screening, within the scope of the literature search, there were no articles that presented evidence regarding the risk versus benefit of the increased exposure. With regard to increased cost, such screening is likely much less expensive in Japan than in Europe and the United States. However, there were no articles that presented evidence regarding its cost-effectiveness.

Based on the above considerations, whole-body screening is currently not recommended before breast cancer surgery in stage I or II primary breast cancer without signs of metastasis. However, depending on patient background such as the cancer subtype, tumor grade, the patient’s age, and breast cancer risk, whole-body screening may be considered.

Search keywords and secondary sources used as references

PubMed was searched using the following keywords: breast neoplasms, preoperative period, preoperative care, diagnosis, diagnostic imaging, neoplasm staging, metastasis, CT, and PET. The period searched was through June 2019; hits were obtained for 354 articles. Although a hand search was also performed, there were no articles that examined the usefulness of preoperative whole-body screening based on prognostic staging classification.

In addition, the following were referenced as secondary sources.

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FQ 21 Which breast imaging surveillance is recommended for the ipsilateral or contralateral breast of women treated with breast-conserving surgery?

Statement

For the early detection of ipsilateral local recurrence and contralateral breast cancer after breast-conserving surgery, periodic ultrasonography should be performed in addition to annual mammography. MRI is recommended only in patients with mammography-negative dense breasts at the initial examination and should be performed for patients who understand its disadvantages, such as adverse reactions to the contrast medium, high cost, and increased recall and biopsy rates.

Background

Routine mammography for ipsilateral local recurrence and contralateral breast cancer after breast-conserving surgery (BCS) has been reported to improve prognosis, and postoperative annual mammography is strongly recommended.[1)] However, other imaging examinations were performed experimentally as routine examination after BCS, but the scientific evidence was insufficient, and there is currently no standardization of the methods and interval.

For this FQ, we examined the usefulness of some imaging examinations (tomosynthesis, ultrasonography, MRI, CT) in periodic follow-up for ipsilateral local recurrence and contralateral breast cancer after BCS. Mammography was excluded from this study because mammography is recommended every 1 or 2 years after BCS (secondary source 1) according to other countries' guidelines, and it is performed at many facilities in Japan. Moreover, in patients with hereditary breast and ovarian cancer syndrome, a group at high risk of breast cancer, bilateral or contralateral risk-reduction mastectomy has been found not only to reduce the risk of breast cancer, but also to improve overall survival. However, surveillance by breast MRI is recommended for patients who have not undergone risk-reduction mastectomy, and it has been covered by national health insurance since April 2020 (secondary source 2). Because surveillance by annual mammography and contrast-enhanced MRI is recommended for high-risk groups, these modalities were excluded from the present study.

Explanation

A report from South Korea, an Asian country like Japan, showed that ipsilateral local recurrence detected on mammography often presented with calcification (21.2%), whereas contralateral breast cancer was often detected by masses (51.3%).[2)] There was no significant difference in the presence of no detectable lesions on mammography: 39% for ipsilateral local recurrences and 40% for contralateral breast cancers. The reasons for this, in the case of ipsilateral local recurrence, were related to dense breasts, changes in mammary tissue due to postoperative scarring and positioning due to breast deformity, and in the case of contralateral breast cancer, to poor delineation of the primary breast cancer[3]. Recently, tomosynthesis has been reported to be useful for mammography-negative dense breasts.[4] In a comparison of mammography alone and mammography plus tomosynthesis after surgery or radiation therapy, the addition of tomosynthesis to mammography reduced the false-positive rate from 6.9% to 4.9% and increased the cancer detection rate from 4.9% to 6.9%[5]. On the other hand, the false-positive rate of tomosynthesis vs ultrasonography for women with dense breasts on screening mammography, like that for lesions difficult to detect, was not significantly different, but the cancer detection rate was significantly higher with ultrasonography than with tomosynthesis, at 7.1/1,000 tests and 4.0/1,000 tests, respectively.[6] The combination of mammography and tomosynthesis is considered more useful than mammography alone for periodic follow-up of ipsilateral local recurrence and contralateral breast cancer after BCS. However, the screening data show that the combination of mammography and ultrasonography is better. Moreover, because radiation exposure increases with the combined use of tomosynthesis, the use of ultrasonography in combination with mammography is given priority. In addition, The Japanese Breast Cancer Society Clinical Practice Guidelines for Breast Cancer indicate that the use of ultrasonography is useful for the early diagnosis of local recurrence after BCS, especially for luminal type breast cancer, and they recommend the combined use of other modalities for other histological subtypes of breast cancer (secondary source 3).

In a study that compared the diagnostic performance of mammography and MRI for local recurrence after BCS, the sensitivity, specificity, recall rate, and PPV3* (mammography vs. MRI) were 70.3% vs. 61.4%, 88.5% vs. 88.2%, 12.2% vs. 12.6%, and 30.5% vs. 19.5%, respectively. The false-positive rate, the rate of biopsy within 1 year, and the cancer detection rate for mammography vs MRI were 3.5 vs. 6.8/1,000 tests, 4.0% vs. 10.1%, and 8.2 vs. 10.8/1,000 tests, respectively, all higher for MRI[7]. The differences in the cancer detection rate and the rate of biopsy within 1 year were significant, indicating that MRI is useful for recurrence detection. In a cohort study of women ≤ 50 years of age who had undergone BCS, the cancer detection rate of mammography, ultrasonography, and MRI alone was 4.4, 5.2, and 7.3/1,000 tests, respectively. Thus, diagnostic performances of ultrasonography and of MRI were higher than for mammography, but increases in the recall and biopsy rates were also seen. Moreover, when ultrasonography or MRI was combined with mammography, the cancer detection rate was 6.8 and 8.2/1,000 tests, respectively, both higher than that of mammography alone, and that of the combined MRI group was higher than that of the combined ultrasound group. Although the detection rate of early breast cancer improved by combined use of these modalities, the disadvantages of combined use of ultrasound and MRI were the recall rate of 13.0% vs. 13.8%, the biopsy rate of 1.4% vs 2.7%, and PPV3* of 37.9% vs 28.6%, respectively, with the disadvantages increasing in the MRI group[8].

With regard to contralateral breast cancer, an MRI surveillance study of 322 postoperative breast cancer patients showed a 20% reduction in the risk of contralateral invasive breast cancer (to detect noninvasive cancer). On multivariate analysis of the useful factors on MRI, it was significantly more useful in patients with breast cancer that was difficult to detect at initial diagnosis, such as patients with dense breasts (p <

0.0007) or those with mammography-negative breast cancer ($p < 0.0001$), regardless of the histological type of breast cancer at initial onset.[9)]

For the early detection of ipsilateral local recurrence and contralateral breast cancer after BCS, mammography combined with ultrasonography or MRI is more useful than mammography alone, and mammography combined with MRI is superior to mammography combined with ultrasonography. However, the combined use of MRI is accompanied by increased disadvantages, as indicated by increased recall and biopsy rates. Consequently, the use of MRI for surveillance is permitted if the patient first adequately understands its disadvantages, such as the side effects of contrast media, the high cost, and increases in the recall and biopsy rates. Ultrasonography, on the other hand, as compared with other modalities, results in little exposure to radiation and pharmaceutical preparations and is inexpensive even if used frequently. It permits frequent follow-up of suspicious lesions without necessarily performing biopsies, with little disadvantage for the patient. In conclusion, periodic follow-up should be performed by ultrasonography in addition to mammography for the early detection of ipsilateral local recurrence and contralateral breast cancer after BCS. The use of MRI is permitted if the patient understands the disadvantages associated with the examination.

Non-contrast CT has a low detection rate of ipsilateral local recurrence and contralateral breast cancer, and it is not recommended for postoperative surveillance of breast cancer. For contrast-enhanced CT, there are no new reports of detection of local recurrence alone, but rather of postoperative systemic surveillance. The use of contrast media is necessary to detect breast lesions on CT examination, but the side effects of contrast media and associated radiation exposure are considered disadvantageous for patients. Therefore, CT is not recommended for the early detection of ipsilateral local recurrence or contralateral breast cancer after BCS.

* PPV3: The value obtained by dividing the number of breast cancer findings by the number of patients with BI-RADS categories 4 and 5 final assessments (diagnostic category) who underwent tissue biopsy (cytology), (= the number of breast cancer/number of biopsies).

Search keywords and secondary sources used as references

PubMed was searched using the following keywords: breast-conserving therapy, ipsilateral breast recurrent cancer, contralateral recurrent breast cancer, mammography, ultrasound, ultrasonography, MRI, CT, local recurrence, recurrence, high-risk group, and BRCA1/2.

In addition, the following were referenced as secondary sources.

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FQ 22 Is whole-body imaging recommended for periodic surveillance after surgery for anatomic stage I and II breast cancer?

Statement

Essentially, it is recommended that periodic whole-body imaging not be performed after surgery for anatomic stage I and II breast cancer. However, the method of surveillance should be determined for each patient by taking into account the breast cancer subtype along with the anatomic stage.

Background

Multiple guidelines from Japan and other countries recommend not performing whole-body imaging for periodic surveillance after breast cancer surgery. However, in clinical practice, more than a few facilities do perform whole-body imaging after such surgery. The studies that provided the basis for the guidelines were designed and conducted in the 1980s.[1-3] Since then, the clinical environment in which breast cancer treatment, metastasis, and recurrence occur has changed greatly as a result of advances in drug therapy and diagnostic imaging. This FQ was examined based on the current evidence concerning whether whole-body imaging is recommended for the postoperative periodic surveillance of anatomic stage I and II breast cancer, which is considered unlikely to recur.

Explanation

Two prospective studies that compared surveillance consisting only of periodic examination and mammography after breast cancer surgery and surveillance that also involved various imaging and blood tests (intensive surveillance) showed no improvement in the survival rate with intensive surveillance.[1-3] Moreover, a meta-analysis of these studies found no difference in the survival rate or recurrence-free survival rate, and a subgroup analysis by age, tumor diameter, and lymph node metastasis status also showed no significant differences.[4]

Based on these results, the guidelines of the American Society of Clinical Oncology (ASCO), National Comprehensive Cancer Network (NCCN), European Society for Medical Oncology (ESMO), and European School of Oncology (ESO) recommend periodic patient interviews, clinical breast examinations, and mammography for the surveillance of asymptomatic patients after breast cancer surgery. They do not recommend periodic chest radiography, bone scintigraphy, ultrasonography, CT, or PET/CT to detect distant metastasis. The purpose of surveillance after breast cancer surgery is to detect local recurrence or contralateral breast cancer early, rather than to find asymptomatic distant metastasis.

However, the studies that provided the basis for this approach were designed and conducted in the 1980s. Since then, major advances have been achieved in drug therapy and diagnostic imaging, and the survival rates for metastatic and recurrent breast cancer have improved. Particularly in the case of oligometastasis, as compared with multiple metastases, localized treatment such as surgery has been found to be useful for improving prognosis.[5] Consequently, the significance of early detection of distant metastasis may change in the future.[6]

Moreover, it has recently been shown that the risk of recurrence varies according to the breast cancer subtype, which is classified based on biomarkers. The most recent edition of the American Joint Committee on Cancer (AJCC) staging manual, the 8th edition, incorporated a prognostic stage, which combines the tumor grade and subtype classification, into the anatomic stage based on the previous TMN classification for breast cancer staging. The prognostic stage has been reported to enable more accurate staging with respect to survival and prognosis than the anatomic stage.[7, 8] In breast cancer subtypes with a high risk of recurrence and breast cancer with an advanced prognostic stage, better treatment efficacy and quality of life (QOL) improvement are likely if metastasis is detected and treatment started at a stage when the tumor load is small, such as in oligometastasis, even in asymptomatic patients. Consequently, periodic whole-body imaging after breast cancer surgery is acceptable if it is in accordance with the patient's wishes.

However, there have been no reports of studies that have examined the effectiveness of intensive surveillance after breast cancer surgery according to subtype or based on prognostic stage. Its effectiveness with respect to the survival rate and QOL in breast cancer with a high risk of recurrence has also not been demonstrated. In Japan, a prospective, clinical study of the usefulness of intensive surveillance using imaging examinations for a group at high risk of recurrence based on the breast cancer subtype and lymph node metastasis has begun, and the results of the analysis are awaited.[9]

From the perspective of healthcare costs, the cost of testing increases with intensive surveillance. Periodic intensive testing is unlikely to be cost-effective for breast cancer with a low risk of metastasis or recurrence. Moreover, the increase in radiation exposure that results from CT, bone scintigraphy, and PET/CT is a type of risk. Adverse reactions such as allergic reactions to contrast media represent another type of risk. Furthermore, intensive testing increases the risk of false-positive lesions and may increase the psychological burden on the patient unnecessarily and increase unnecessary invasive testing.

The effectiveness of periodic whole-body imaging to detect distant metastasis after surgery for anatomic stage I and II breast cancer has not been demonstrated. Consequently, it is basically recommended that periodic whole-body imaging not be performed. However, the method of surveillance should be determined for each patient by taking into account the breast cancer subtype along with the anatomic stage.

Search keywords and secondary sources used as references

PubMed was searched using the following keywords: breast neoplasm, neoplasm staging, tomography, X-ray computed, postoperative period, postoperative care, mastectomy, follow-up studies, prognosis, neoplasm metastasis, diagnostic imaging, receptor, ErbB-2, receptor, and estrogen. The period searched was through June 2019; hits were obtained for 343 articles. Although a hand search was also performed, there were no articles that examined the effectiveness of intensive surveillance after breast cancer surgery based on cancer subtype or prognostic stage.

In addition, the following were referenced as secondary sources.

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