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ORIGINAL ARTICLE

Visual and semi-quantitative analyses of dual-phase breast-specific gamma imaging with Tc-99m-sestamibi in detecting primary breast cancer

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Abstract

Objectives Breast cancer is the most common malignancy for females worldwide. This study was to evaluate the application of dual-phase breast-specific gamma imaging (BSGI) in detecting primary breast cancer.

Methods Seventy-six patients with indeterminate breast lesions that underwent dual-phase BSGI enrolled in this study. All included lesions were confirmed by pathology. BSGI was evaluated based on the visual interpretation and dual-phase semi-quantitative indices of lesion to non-lesion ratio (L/N), which were compared with pathological results. The optimal visual analysis and L/N for double-phase were calculated through receiver operating characteristic curve analysis.

Results Among 76 patients, 92 lesions were finally confirmed by the surgery and pathology, with 54 malignant and 38 benign lesions. Both early and delayed L/N of malignant breast diseases were significantly higher than those of benign (3.18 ± 1.57 vs 1.53 ± 0.59, and 2.91 ± 1.91 vs 1.46 ± 0.54, $P < 0.05$). The optimal visual interpretation is over grade 3, and cut-off L/N was 2.06 and 1.77 for early and delayed imaging, respectively. Compared with visual analysis over grade 3 (77.8 and 81.6 %), optimal early L/N (81.5 and 92.1 %) or delayed L/N (79.5 and 89.5 %) alone, the sensitivity and specificity of visual combined with early-phase L/N in diagnosing primary breast cancer are higher, which were 85.2 and 92.2 %, respectively.

Conclusions The combination of visual and semi-quantitative analysis could improve the sensitivity and specificity of BSGI in detecting primary breast cancer. In addition, the potential value of delayed BSGI in diagnosing primary breast cancer should be further investigated in large samples.

Keywords Dual-phase · Breast-specific gamma imaging (BSGI) · Primary · Breast cancer

Introduction

Breast cancer is the most frequent female malignancy in the western world [1]. Over the decades, the incidence of female breast cancer was markedly increasing both in urban and rural areas of China [2]. In early 2010, "breast disease survey in China" reported by Chinese Population Association, showed that the mortality of breast cancer increased by 38.91 %, and the incidence became the first malignancy for female in urban. Therefore, it is essential to make the early diagnosis, to guide the therapy protocols, and to improve breast cancer patients' survival rates.

H. Tan and L. Jiang equally contributed to this work.

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In the current days, imaging modalities, including mammography (MMG), ultrasound (US), and magnetic resonance imaging (MRI), are frequently used to screen and diagnose breast cancer. MMG is the standard screening modality for breast cancer with the sensitivity from 78 to 85 %, but it has decreased to 30–48 % in dense breast tissues [3, 4]. US have sufficiently high sensitivity to detect breast cancer regardless of breast density [5]. However, the false positive of US is high and the specificity was low [5, 6]. Breast MRI is more accurate in morphological appearance of tumor with limitation in specificity [7].

Tc-99m-Sestamibi (Tc-99m-MIBI) scintimammography (SMM) has been known to be a useful tool in the diagnosis of primary breast cancer. Tc-99m-MIBI SMM has been proven to have the potential to reduce the number of false-negative MMG findings and also has a comparable diagnostic accuracy. However, due to its intrinsic resolution, it is limited to detect $\leq$1 cm lesions [8, 9]. Compared with SMM, breast-specific gamma imaging (BSGI) is with a smaller field of view and higher resolution. At present, most studies mainly focus on single-phase BSGI or only visual analysis in the diagnosis of primary breast cancer. Therefore, in this study, we assess the value of dual-phase BSGI in diagnosing primary breast cancer based on the combination of visual analysis and semi-quantitative indices lesion to non-lesion ratio (L/N).

Materials and methods

Patients

From Mar 2012 to Oct 2012, 119 women with suspected breast mass underwent BSGI examinations in our institution. The patients who had carried out the biopsy of breast tissue and axillary lymph nodes were excluded. Finally, a total of 76 female patients with pathological results were enrolled in this study. The patient's mean age was 51.0 $\pm$ 11.8 years, with the range from 28 to 80 years. This study was approved by the Institutional Review Board of our institution, and the informed consents were signed by all included patients.

Dual-phase BSGI

Dual-phase BSGI examinations were performed in early phase (10–15 min) and delayed phase (90–120 min) after the patients were administrated 740–925 MBq (15–20 mCi) Tc-99m-MIBI (Shanghai GMS Pharmaceutical Co., Ltd) through an antecubital vein. Vein injection was taken in the contralateral arm of suspicious breast lesions to avoid false-positive uptake in the axillary lymph nodes. The patients were seated for the procedure, and craniocaudal and mediolateral oblique images were obtained of the bilateral breasts using a high-resolution breast-specific gamma camera (Dilon 6800; Dilon Technologies, USA). The collimator is low energy general purpose, and the energy window is $\pm$10 % centered on 140 keV. The acquisition time for each image was $\sim$6 min, and 100,000 counts per image were defined as the minimal range.

Visual analysis of dual-phase BSGI

Breast-specific gamma imaging images were analyzed and interpreted by two experienced Nuclear Medicine physicians who were blind to the patients' clinical information and pathology results. According to the 2010 American Society of Nuclear Medicine (SNM) guideline [10], the visual analysis grades of BSGI were as follows: Grade 1: no abnormal increased uptake in either early or delayed images, Grade 2: mildly increased uptake in the early image without retention in the delayed image, Grade 3: mildly increased uptake in the early image with retention in the delayed image, Grade 4: definite focal increased uptake in the early image without retention in the delayed image, and Grade 5: definite focal increased uptake in the early image with retention in the delayed image. In cases of discrepancy regarding BSGI findings, a consensus was reached after mutual discussion between two experienced Nuclear Medicine physicians.

Semi-quantitative analysis of dual-phase BSGI

Lesion to non-lesion ratio (L/N) was considered as the semi-quantitative indices of dual-phase BSGI. The maximum region of interest (ROI) in 9 pixels was analyzed on different craniocaudal and mediolateral oblique images (RCC: right craniocaudal, RMLO: right mediolateral oblique, LCC: left craniocaudal, and LMLO: left mediolateral oblique), and drawn around L/N in the same breast. Then, the early L/N and delayed L/N of craniocaudal and mediolateral oblique images were separately calculated, and the maximum L/N of each phase was selected as the quantitative index of this phase.

Statistical analysis

The optimal visual grade and cut-off value of early and delayed phase were obtained through the receiver operating characteristic analysis (ROC) by SPSS 19.0. The standard errors, 95 % confidence intervals, areas under the curve (AUC), and the sensitivity and specificity of BSGI were calculated. Student's *t* test was used for statistical comparison of semi-quantitative indices between the malignant and benign breast disease groups.

Results

Clinical and histological results

On the basis of pathological results, 49 of all 76 patients (49/76, 64.5 %) were finally diagnosed malignant breast diseases, and the rest 27 cases (27/76, 35.5 %) were detected benign.

Among the malignant group, 49 patients (mean age: 60.5 ± 10.6 years, range 32–80 years) were detected with 54 malignant lesions, including 45 patients with a single mass, 3 patients with 2 lesions, and 1 patient with 3 lesions. As shown in Table 1, the pathological types of 54 malignant breast lesions covered infiltrating ductal carcinoma (45 lesions), ductal carcinomas-in situ (5), infiltrating lobular carcinoma (2), malignant phyllodes tumor (1), and Pagets' disease(1) (Table 1).

For the benign group, the mean age of 27 female patients was 50.3 ± 12.6 years (range 28–72 years). The histology confirmed that these 27 cases were with 38 benign lesions, which contained 18 patients with a single mass, 9 patients with 2 lesions, and 2 breast cancer patients with a benign lesion in contralateral breast. The histological types of benign breast lesions were fibrocystic change (12), fibroadenoma (11), intraductal papilloma (8), chronic inflammation (4), benign phyllodes tumor (2), and lipoma (1) (Table 1).

Comparison of dual-phase BSGI L/N between malignant and benign lesions

Early L/N of malignant breast disease was significantly higher than that of benign breast disease (3.18 ± 1.57 vs 1.53 ± 0.59, $P < 0.05$). Similarly, delayed L/N of malignant lesions was significantly higher than that in benign group (2.91 ± 1.91 vs 1.46 ± 0.54, $P < 0.05$).

Table 1 Pathological types of breast lesions

Lesions	Pathology	No. of lesions
Benign lesions	Fibrocystic change	12
	Fibroadenoma	11
	Intraductal papilloma	8
	Chronic inflammation	4
	Benign phyllodes	2
	Lipoma	1
Total		38
Malignant lesions	Infiltrating ductal carcinoma	45
	Ductal carcinomas-in situ	5
	Infiltrating lobular carcinoma	2
	Malignant phyllodes	1
	Pagets' disease	1
Total		54

Visual and semi-quantitative analysis of dual-phase BSGI

Receiver operating characteristic analyses were performed to determine the optimal visual grade and cut-off values of early and delayed L/N in detecting primary breast cancer. The optimal visual grades were more than grade 3 (Fig. 1). When grade 3 was used as the cut-off value, BSGI correctly diagnosed 42 of 54 malignant lesions and 31 of 38 benign. The sensitivity and specificity of BSGI in the detection of primary breast cancer were 77.8 and 81.6 %, respectively (Table 2). The AUC was 0.843 (standard error 0.043; 95 % CI 0.759–0.928).

As shown in Fig. 1, the cut-off values of early L/N and delayed L/N by ROC analyses were 2.06 and 1.77, respectively. The corresponding AUC values were 0.870 (standard error 0.041; 95 % CI 0.790–0.949) and 0.863 (standard error 0.042; 95 % CI 0.781–0.946), respectively. The sensitivity of the early and delayed semi-quantitative analysis in diagnosing of primary breast cancer was 81.5

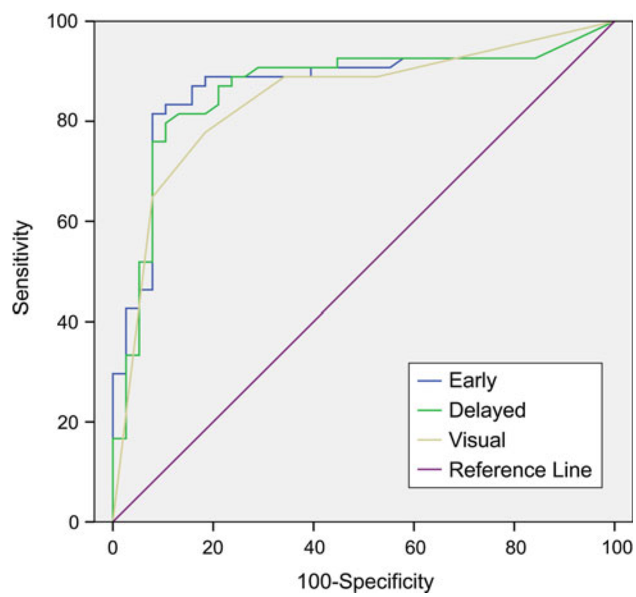

Fig. 1 ROC analysis for determining cut-off value of visual interpretation grade, optimal early, and delayed L/N in the detection of primary breast cancer. When over grade 3 of visual grade was used as cut-off value in the defection of primary breast cancer, the sensitivity and specificity of BSGI in detecting primary breast cancer was 77.8 and 81.6 %, respectively. The area under the curve was 0.843 (standard error 0.043; 95 % CI 0.759–0.928). When 2.06 in early phase was used as cut-off value, the sensitivity and specificity were 81.5 and 91.2 %, respectively. The AUC was 0.870 (standard error 0.041; 95 % CI 0.790–0.949). When 1.77 in delayed phase was applied, the sensitivity and specificity were 79.6 and 89.5 %, respectively. The AUC was 0.863 (standard error 0.042; 95 % CI 0.781–0.946)

Table 2 Sensitivity and specificity of visual analysis and/or semi-quantitative indices in diagnosing primary breast cancer

	Visual analysis alone (%)	Early L/N only (%)	Delayed L/N only (%)	Visual analysis + early L/N (%)	Visual analysis + delayed L/N (%)
Sensitivity	77.8	81.5	79.5	85.2	83.3
Specificity	81.6	92.1	89.5	92.2	89.5

Table 3 Lesions misdiagnosed by visual analysis and (or) semi-quantitative indices in the benign group

	Visual analysis	Early L/N	Delayed L/N	Pathology
Lesion 1	Grade 4	1.57	1.71	Chronic inflammation
Lesion 2	Grade 4	2.05	1.68	Chronic inflammation
Lesion 3	Grade 4	1.91	1.90	Chronic inflammation
Lesion 4	Grade 4	1.87	1.54	Intraductal papilloma
Lesion 5	Grade 5	3.66	2.83	Intraductal papilloma
Lesion 6	Grade 5	3.12	2.47	Benign phyllodes tumor
Lesion 7	Grade 5	3.01	3.70	Benign phyllodes tumor

and 79.5 %, respectively. And the specificity was 92.1 and 89.5 %, respectively (Table 2).

Combined visual analysis with early semi-quantitative index, BSGI revealed that 46 of 54 in the malignant group as malignancy and 35 of 38 in the benign group as benign diseases. Therefore, the sensitivity and specificity of early-phase BSGI in detecting primary breast cancer were 85.2 and 92.2 %, respectively (Table 2). On the basis of combination of visual analysis and delayed semi-quantitative index, BSGI correctly diagnosed 45 of 54 in the malignant group and 34 of 38 in the benign group. And the sensitivity and specificity were 83.3 and 89.5 %, respectively (Table 2).

False-negative and false-positive lesions

As shown in Table 3, there were 7 lesions in the benign group misdiagnosed as malignant by the visual analysis with grade over 3, including 3 lesions with chronic inflammation, 2 with benign phyllodes tumor (Fig. 2), and 2 with intraductal papilloma. Among these lesions, Nos. 1, 2, and 4 (Fig. 3) were with early L/N lower than 2.06 and delayed L/N lower than 1.77. In addition, the early L/N of No. 3 was 1.91, but its delayed L/N was 1.90. Therefore, combined visual analysis with semi-quantitative indices, 4 lesions was correctly diagnosed and 3 lesions were still wrongly judged.

For the malignant breast diseases, 12 lesions were misjudged as benign based on visual analysis alone, which were with grade $\leq$3 (Table 4). It consisted of 3 lesions with ductal carcinomas-in situ, 3 infiltrating ductal carcinoma, 4 multifocal malignancy (3 infiltrating ductal carcinoma and 1 infiltrating lobular carcinoma), 1 infiltrating lobular carcinoma (Fig. 4), and 1 Pagets' disease. Both early L/N and delayed L/N of No. 1, 11, and 12 lesions were higher than 2.06 and 1.77, but No. 2–10 were lower than semi-quantitative indices. Finally, only 3 lesions were correctly diagnosed as malignant. In the contrast, No. 13–14 lesions in the Table 4 were analyzed as grade 4 by visual analysis and correctly diagnosed as malignant. However, their early L/N and delayed L/N were lower than the cut-off value, and misjudged as benign.

Discussion

Owing to limitations of traditional imaging modalities, such as MMG and US, in detecting the primary breast cancer, nuclear medicine techniques as functional imaging are increasingly applied in clinic. Compared with widely accepted Tc-99m-MIBI SMM, BSGI is with a smaller field of view and higher resolution. Some studies [11, 12] demonstrated that with the help of visual analysis, BSGI was accurate in detecting breast cancer, of which sensitivity and specificity were 83–100 % and 70–87.9 %, respectively. Our study showed that the sensitivity and specificity of BSGI in diagnosing primary breast cancer by visual analysis alone were 77.8 and 81.6 %, respectively. Compared with other studies, the sensitivity in this study was slightly lower. The reason may be that the research objects were different, that is lesions in this study but cases in others.

In previous studies [13–17], double-phase Tc-99m-MIBI SMM has been reported to be used in the detection of primary breast cancer, which revealed the beneficial value of the delayed imaging. However, Kim et al. [7] and Lu et al. [18] reported that delayed L/N of SMM revealed no incremental value in the detection of primary breast cancer, and the delayed SMM should not be routinely performed for the purpose of primary breast cancer diagnosis. In our study, the sensitivity and specificity of delayed L/N of BSGI were lower than those of early L/N, which was consistent with the previous studies. However, the patients enrolled in our study were relatively small, and the value of the delayed image of BSGI in more patients should be further investigated.

This study displayed 7 false-positive lesions judged by visual diagnosis, including benign phyllodes tumors, intraductal papilloma (ductal epithelial hyperplasia

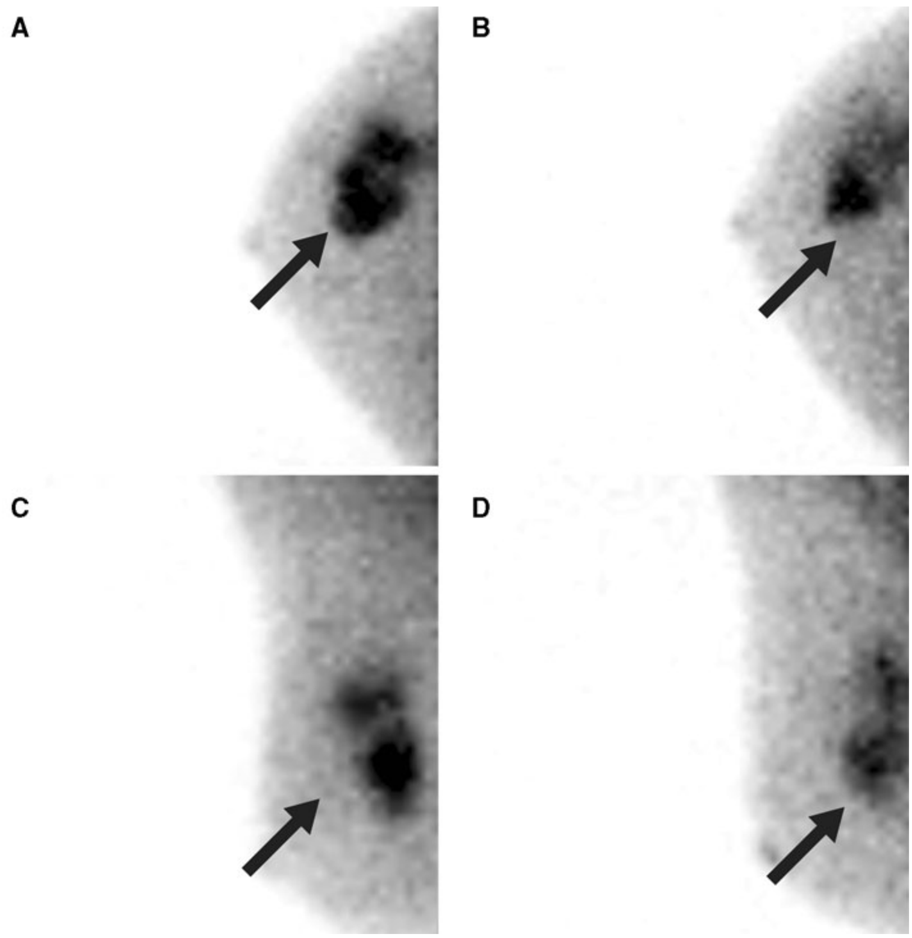

Fig. 2 A 71-year-old woman consciously found right breast mass for half 1 month. The early-phase BSGI (**a** RCC, **c** RMLO) demonstrated that one lobular lesion with intense focal uptake was in the upper outer quadrant area (↑). The visual analysis of lesion was grade 5, and the early L/N of RCC and RMLO was 3.01 and 3.12, respectively. Compared with early-phase BSGI, the delayed-phase BSGI (**b** RCC, **d** RMLO) displayed that the radioactivity uptake of lesion became weaker, and the delayed L/N of RCC and RMLO was 2.47 and 2.38, respectively. Finally, the mass was detected in the right breast mastectomy, and pathology confirmed that it was benign phyllodes tumor with the size of 5.5 × 2.5 cm

significantly), and chronic inflammation. It may be local perfusion increased for inflammatory lesions, the areas with increased mitochondrial activity or hyperproliferative disease [19]. But 3 chronic inflammation lesions and 1 intraductal papilloma lesion of those were accurately diagnosed by the early-phase L/N. Moreover, there were 12 false-negative lesions by visual diagnosis. The reasons for non-visualization are probably as follows: (1) BSGI, as a planar imaging, does not accurately reflect the numbers of the lesions. (2) The multidrug resistance and over-expressed Bcl-2 gene [19]. (3) Tumor size, tumor location within breast, the degree of tumor differentiation, distance of the tumor from the camera, and soft tissue attenuation. Finally, the cut-off value semi-quantitative analysis made 3 cases correctly diagnosed. Compared with the visual, the early-phase L/N or delayed-phase L/N alone, the combination of the visual with semi-quantitative L/N analysis, especially visual analysis and the early-phase L/N could improve the sensitivity and specificity of BSGI in diagnosing primary breast cancer, which were 85.2 and 92.2 %, respectively. Thus, the visual and semi-quantitative analysis of BSGI should be combined to make the diagnosis of breast diseases in clinic.

Moreover, Kim et al. [16] reported that L/N of malignant breast diseases revealed by Tc-99m-MIBI SMM was 2.00 ± 1.88, while L/N of benign breast diseases was 0.60 ± 0.70. Taillefer et al. [17] reported L/N of breast malignancy detected by Tc-99m-MIBI SMM was 2.2 ± 0.7. Our study demonstrated that both early and delayed L/N of BSGI in detecting malignant breast disease were 3.18 ± 1.57 and 2.91 ± 1.91, respectively, and those of benign breast disease were 1.53 ± 0.59 and 1.46 ± 0.54, respectively. These different results could be influenced by many factors, such as different imaging modality (SMM and BSGI), the cases enrolled in the study, the imaging time after injection of radiotracer, and so on [16].

In addition, there were some potential limitations in this study. First, it is a small population. To obtain objective cut-off values of early and delayed L/N ratios, larger cases should be further performed. Second, BSGI was mainly performed in patients with highly suspected breast cancer, which lead to relatively high proportion of breast cancer cases (49/76, 64.5 %) in our study. Finally, due to the limited field of view, axillary LN metastases evaluated by BSGI are not included in this study.

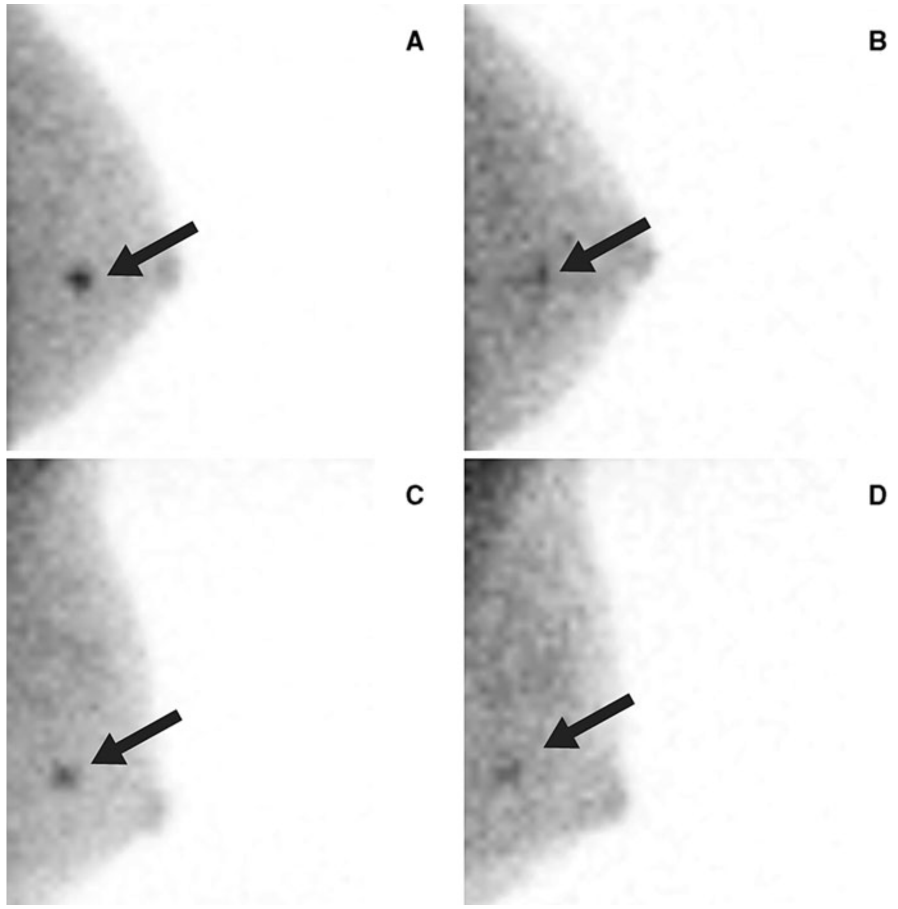

Fig. 3 A 36-year-old woman was detected breast bump by US 1 year ago, and it was gradually increasing during the follow-up. The early-phase BSGI (**a** LCC, **c** LMLO) displayed that one round lesion with focal radioactivity uptake was in the upper within quadrant area (↑). The visual analysis of lesion was grade 4, and the early L/N of LCC and LMLO was 1.87 and 1.77, respectively. Compared with early-phase BSGI, the delayed-phase BSGI (**b** LCC, **d** LMLO) showed that the radioactivity accumulation of lesion was lighter, and the delayed L/N of LCC and LMLO was 1.54 and 1.43, respectively. The patient was carried out the left breast surgery, and the nature of lesion was intraductal papilloma with atypical hyperplasia with the size of 1.8 × 0.7 cm

Table 4 Lesions misdiagnosed by visual analysis and (or) semi-quantitative indices in the malignant group

	Visual analysis	Early L/N	Delayed L/N	Pathology
Lesion 1	Grade 3	2.14	2.14	Ductal carcinomas
Lesion 2	Grade 3	2.06	1.72	Ductal carcinomas
Lesion 3	Grade 3	1.81	1.54	Ductal carcinomas
Lesion 4	Grade 1	1.32	1.33	Infiltrating ductal carcinoma
Lesion 5	Grade 3	1.94	1.69	Infiltrating ductal carcinoma
Lesion 6	Grade 1	1.21	1.17	Infiltrating ductal carcinoma
Lesion 7	Grade 3	1.51	1.65	Multifocal infiltrating ductal carcinoma
Lesion 8	Grade 1	1.31	1.22	Multifocal infiltrating ductal carcinoma
Lesion 9	Grade 1	1.43	1.18	Multifocal infiltrating ductal carcinoma
Lesion 10	Grade 1	1.26	1.37	Multifocal infiltrating lobular carcinoma
Lesion 11	Grade 3	2.27	2.06	Infiltrating lobular carcinoma
Lesion 12	Grade 3	3.38	2.52	Pagets' disease
Lesion 13	Grade 4	1.70	1.65	Infiltrating ductal carcinoma
Lesion 14	Grade 4	1.77	1.69	Infiltrating ductal carcinoma

In conclusion, the optimal visual grade for BSGI in the diagnosis of primary breast cancer were over grade 3, and the cut-off values of L/N were 2.06 and 1.77 for early and delayed imaging, respectively. Compared with visual analysis or semi-quantitative indices alone, visual and semi-quantitative analysis should be combined to make the diagnosis of breast lesions in clinic. Moreover, although the delayed L/N ratio of BSGI did not show incremental value for diagnosing primary breast cancer, the large sample should be further taken.

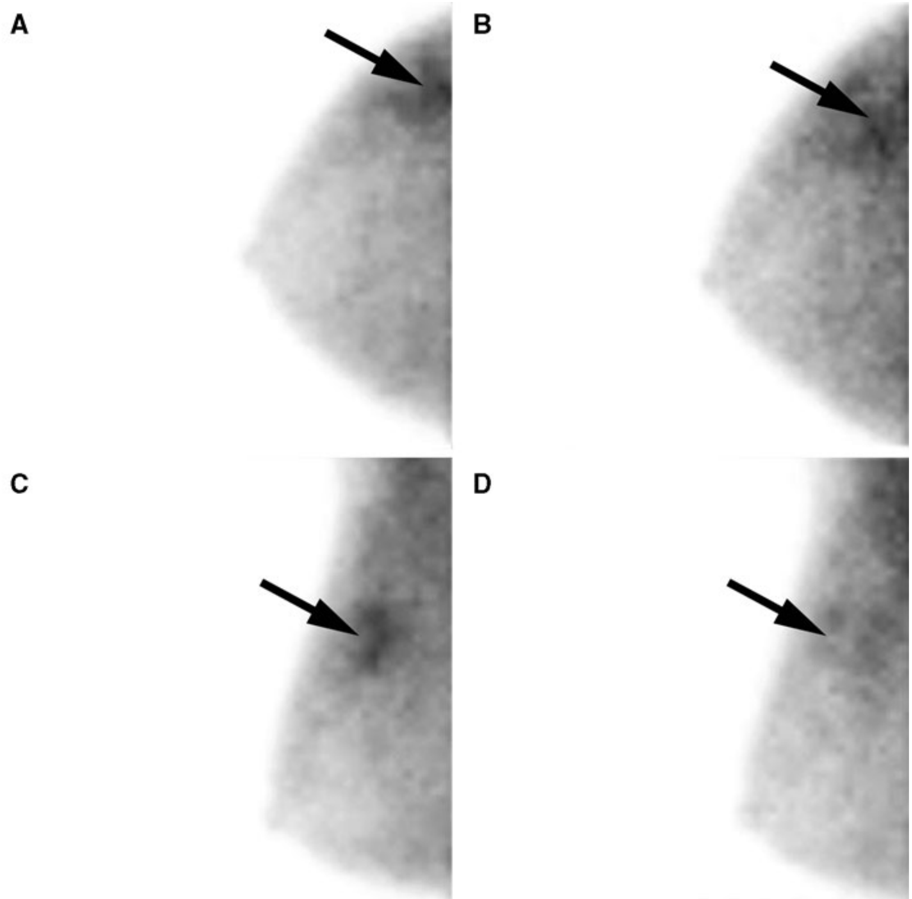

Fig. 4 A 45-year-old woman consciously found right breast mass for 3 months. The early-phase BSGI (**a** RCC, **c** RMLO) demonstrated that one irregular lesion with mildly patchy uptake was in the upper outer quadrant area (↑). The visual analysis of lesion was only grade 3, but the early L/N of RCC and RMLO was 2.27 and 2.25, respectively. Compared with early-phase BSGI, the delayed-phase BSGI (**b** RCC, **d** RMLO) displayed that the radioactivity uptake of lesion was lighter, and the delayed L/N of RCC and RMLO was 2.06 and 1.54, respectively. Finally, the mass was detected in the right breast mastectomy, and pathology confirmed that it was infiltrating lobular carcinoma with the size of 1.5 × 0.7 cm

Conflict of interest There is no conflict of interest existed.

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