

Complement of ^{99m}Tc -octreotide scintimammography to mammography in evaluating breast cancers

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Abstract In this paper, the ^{99m}Tc -octreotide scintimammography as a useful complementary technique of mammography was evaluated in diagnosing breast cancers. The 45 breast lesions were consecutively detected by mammography, and ^{99m}Tc -octreotide scintimammography, and both combination technique on the basis of self-examination, physical examination. Clinical diagnosis was confirmed by histopathologic analysis. Radioactivity uptake ratios for tumor vs normal breast tissues (T/NT) were calculated using regions of interest. In the breast cancer groups and the benign lesion groups, the average uptake ratios of the ^{99m}Tc -octreotide were 1.63 ± 0.19 and 1.09 ± 0.13 , respectively, and t was 9.638 ($P < 0.001$). Based on sensitivity, specificity, accuracy, positive predicting value, and negative predicting value, ^{99m}Tc -octreotide scintimammography was 87%, 79%, 84%, 90%, and 73%, the mammography was 65%, 64%, 64%, 80%, and 45%, and both combination was 95%, 100%, 97%, 100% and 92%, respectively. This showed that the ^{99m}Tc -octreotide scintimammography was more useful than mammography in the evaluating suspected breast cancers, and the combination technique can accurately discriminate lesions.

Key words Breast cancer diagnosis, ^{99m}Tc -octreotide scintimammography, Mammography

1 Introduction

Breast cancer, as second cause of death in women, is of rapid increase in China^[1]. Mammography, being used as a useful diagnostic method, has difficulties in identifying dense breasts cancer, and heterogeneously dense breasts cancer, especially after radiotherapy, surgery, and biopsy^[2-4]. Exploring complementary diagnostic procedure is therefore of importance to its accuracy improvement.

In 1973, Brazeau found that somatostatin (SST) was a tetradecapeptide in the hypothalamus. It inhibites the release of growth hormone as one of hypothalamic regulatory hormones^[5,6], and distributes throughout the central nervous system and major peripheral organs^[7-9]. Somatostatin receptors (SSTR) expressing with various densities have been identified in human tissues, such as brain, gut, pancreas, adrenals,

thyroid, and lymphoid organs etc.^[10-12]. Up to now, five subtypes of SSTR have been cloned in human tissues, including SSTR1, SSTR2, SSTR3, SSTR4, and SSTR5^[10,11], and have been found in many tumours^[13,14]. In primary breast carcinoma, the SSTR expression varied from 46% to 98% depending on its status^[14-16]. In diagnosing and treating various kinds of neuroendocrine tumors and gastrointestinal disorders^[13], SST is not used directly as an imaging agent because of its short half-life (< 2 min.)^[10], but long life agents of octreotide or lanreotide are used instead. Among the five subtypes to octreotide, the affinity of SSTR2 and SSTR5 are the highest, while SSTR3 has moderate affinity, and SSTR1 and SSTR4 do not bind at all^[16,17]. Although *in vivo* imaging of SSTR positive tumors with (^{111}In -DTPA)-octreotide has been documented^[10,16,18], ^{99m}Tc labeling could offer such clinical advantage as optimal energy, good availability

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and fast tumor visualization in one day protocol. And ^{99m}Tc -labeled octreotide can be used for detecting tumors^[19,20]. In this study, we evaluated whether the ^{99m}Tc -octreotide scintimammography can improve the efficacy in breast cancer diagnosis as a complementary technique of mammography.

2 Material and methods

2.1 Patients

From July 2005 to December 2008, 45 breast nodular lesions (age range of 26–75, averaged at 47) were consecutively detected by mammography, the ^{99m}Tc -octreotide scintimammography and combination of the two techniques on the basis of self-examination and physical examination. Surgery of the patients was scheduled at Department of Surgical Oncology, No. 1 Hospital of Xiamen Affiliated to Fujian Medical University (FMU). The protocol was approved by the ethical committee of FMU. An informed consent was received by all patients before participation. The final diagnosis was confirmed by surgical resection and histopathologic findings.

2.2 Preparation of ^{99m}Tc -octreotide

A ^{99m}Tc -octreotide kit (Syncor Star Medicinal Technology Co. Ltd., Beijing, China) was dissolved in 2 mL saline containing 740 MBq pertechnetate (^{99m}Tc) for 5 min. Radiochemical purity of ^{99m}Tc -octreotide, determined according to the instructions, was over 98% at room temperature.

2.3 Imaging studies

2.3.1 Scintimammography

The ^{99m}Tc -octreotide scintimammography for patients was obtained by a dual-headed gamma camera (FORTE, Philips) in two weeks. Parallel-hole, low-energy, and high-resolution collimators were used. Relative to the affected breast, the ^{99m}Tc -octreotide was intravenously injected into the contralateral ulnar vein using a dose of 740 MBq. The planar imaging was performed using 256×256 matrix as an acquisition in 15 min. The anterior and lateral views were obtained 1 h after injection.

2.3.2 Mammography

Mammography for patients was performed by

craniocaudal and mediolateral oblique views using a full-field digital mammography (Senographe 2000D, GE). In addition, projections or coned compressions were obtained by magnification. The mammography images were independently interpreted by at least two experienced radiologists.

2.4 Image analysis

The scintigraphic images of the ^{99m}Tc -octreotide were independently evaluated by two experienced nuclear medical physicians. The ^{99m}Tc -octreotide scintimammography images were classified by visual interpretation. The radiopharmaceutical accumulation of breast cancers higher than that of contralateral normal breast tissue was considered as a positive, and otherwise as a negative. For quantification of radioactivity uptake, regions of interest (ROIs) were drawn over primary lesions (T) and contralateral normal breast tissues (NT). The pixels of ROIs were kept constant, and the T/NT was calculated.

2.5 Statistical analysis

Data were analyzed by SPSS 13.0 software as mean $\pm$ S.D. Statistical differences for T/NT ratios was assessed using *t* test, and significance was set at $P < 0.05$.

3 Results and discussion

In histopathologic findings, the 31 cases were breast cancers, and 14 patients were benign tumors. The final diagnoses followed as, the infiltrating ductal carcinoma, the infiltrating lobular carcinoma, the mixed infiltrating ductal and lobular carcinoma, the mucinous carcinoma, the medullary carcinoma, the ductal hyperplasia, the hyperplasia and cystic changes, and the fibroadenoma were 17, 6, 4, 3, 1, 7, 4, and 3 patients, respectively.

Of the mammography results, 20 cases were true-positive (TP) (Fig. 1A), and 11 cases were false-negative (FN) (Fig. 2A) in 31 cases of breast cancers. Similarly, 5 cases were false-positive (FP) (Fig. 3A), and 9 cases were true-negative (TN) (Fig. 4A) in the benign lesions. The FN was attributed to dense breasts (5 patients), heterogeneously dense breasts (3 patients), previous breast biopsy (2 patients) and young patient

(one patient was younger than 30). The mammography showed 65% sensitivity, 64% specificity, and 64% accuracy, positive predictive value (PPV) of 80% and negative predictive value (NPV) of 45% (Table 1).

The results suggested that mammography is of limited value in detecting breast cancer. Therefore, an alternative noninvasive imaging approach is urgently needed for early detection of breast cancer.

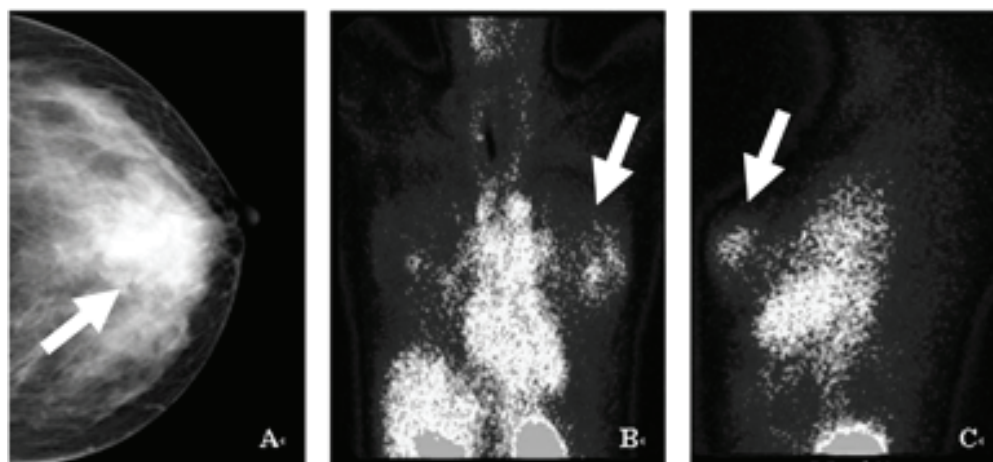


Fig. 1 A 45-years-old female with infiltrating ductal carcinoma. Mammography showed neoplasm in the left breast (A, arrow), and scintimammography showed intense ^{99m}Tc uptake in the anterior (B, arrow) and left lateral (C, arrow).

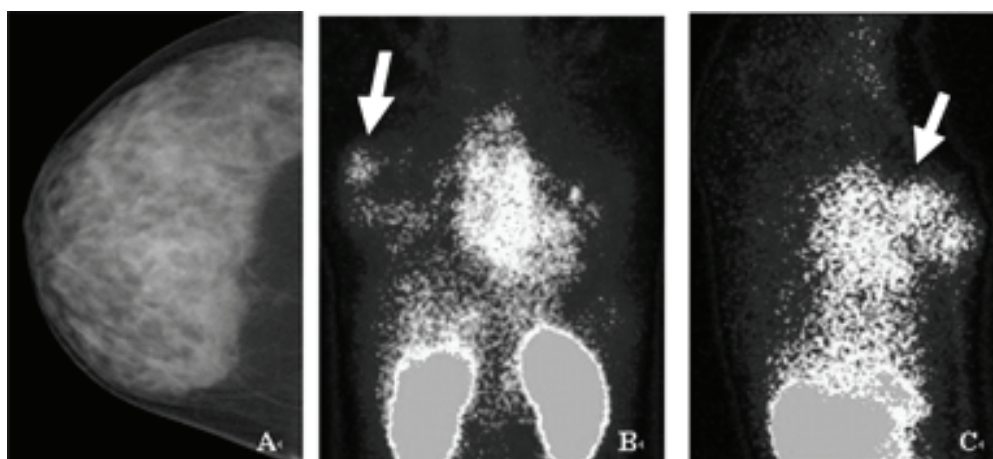


Fig. 2 A 59-year-old female with infiltrating lobular carcinoma. Mammography showed dense parenchyma with focal asymmetry in right breast (A), and scintimammography showed intense ^{99m}Tc uptake in anterior (B, arrow) and right lateral (C, arrow).

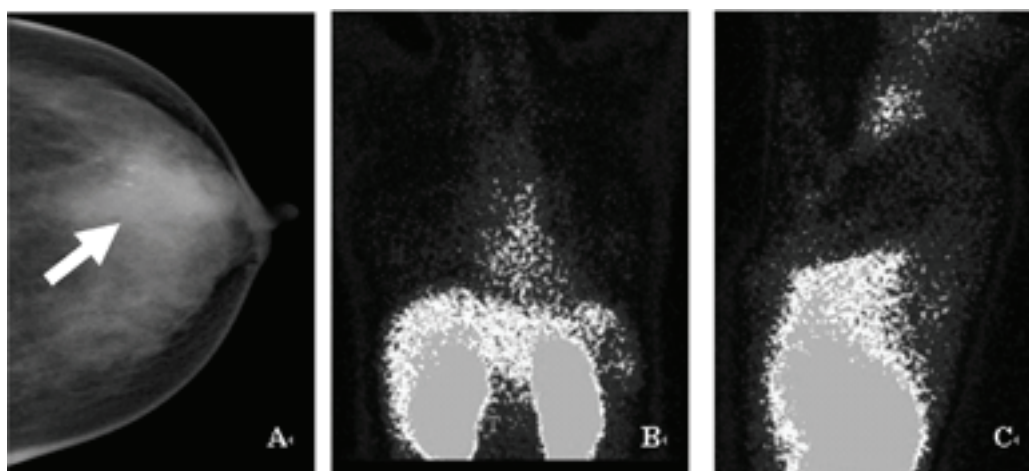


Fig.3 A 36-year-old female with hyperplasia and cystic changes. Mammography showed irregular mass with multiple annular calcifications in the left breast (A, arrow), but anterior (B) and left lateral (C) ^{99m}Tc -octreotide scintimammography were negative.

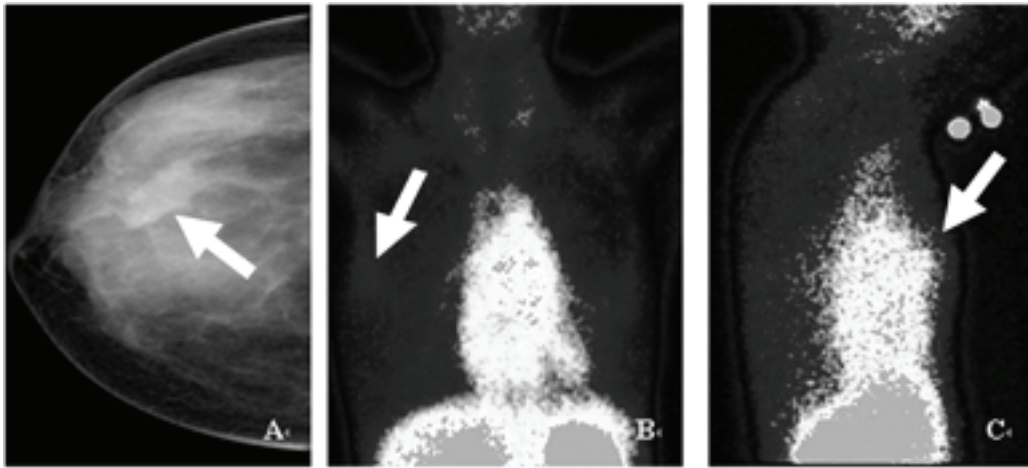


Fig. 4 A 41-year-old female with fibroadenoma. Mammography showed a high-density nodule in the right breast (A, arrow), and scintimammography showed intense ^{99m}Tc uptake in the anterior (B, arrow) and right lateral (C, arrow).

Table 1 Efficacy of ^{99m}Tc -octreotide scintimammography for detecting breast cancer compared with mammography.

Imaging	Cases	Sensitivity/%	Specificity/%	Accuracy/%	PPV/%	NPV/%
OCT	45	87 (27/31)	79 (11/14)	84 (38/45)	90 (27/30)	73 (11/15)
MG	45	65 (20/31)	64 (9/14)	64 (29/45)	80 (20/25)	45 (9/20)
OCT+MG	33	95 (21/22)	100 (11/11)	97 (32/33)	100 (21/21)	92 (11/12)

In the breast cancer groups, the tumor could be significantly identified within 1 h after injection of the ^{99m}Tc -octreotide due to a higher radioactivity accumulation than that of the contralateral normal breast tissue (Figs.1B, and 1C, Fig. 2B, and 2C). The average uptake ratio of the ^{99m}Tc -octreotide was 1.63 ± 0.19 (Table 2). In the benign lesion groups, because the T/ NT ratio was 1.09 ± 0.13 , the radioactivity of primary lesion was less than or similar to contralateral normal breast tissue (Table 2, Fig.3B, and 3C). The results showed that there was a significant difference for T/NT ratios between the two groups ($t = 9.638$, $P < 0.001$). Our results implicated that the ^{99m}Tc -octreotide scintimammography was a positive tumor imaging approach for breast cancer detection using one-step labeling reaction, without any complications or side effects, and the labeling method is very effective.

Of the ^{99m}Tc -octreotide scintimammography, 27 cases were true-positive (TP) (Fig 1B, and 1C, Fig 2B, and 2C), and 4 cases had no ^{99m}Tc -octreotide uptake, that is, false-negative (FN) in 31 cases of breast cancers. Similarly, 11 cases were true-negative (TN) (Fig.3B, and 3C), and 3 cases with fibroadenomas were false-positive (FP) (Fig. 4B, and 4C) in the benign lesions. These also indicated higher SSTR2 and/or SSTR5 expression of breast malignant

tissue.

However, some overlaps may exist between breast carcinomas and fibroadenoma due to tumor heterogeneity. The FN may be due to the small diameter (<1.0 cm) lesions (compared to resolution of the camera) and partial volume effects or absent expression of SSTR2 and/or SSTR5. The sensitivity, specificity and accuracy of the ^{99m}Tc -octreotide scintimammography were 87%, 79%, and 84% with a PPV of 90% and NPV of 73%, respectively (Table 1). Therefore, the ^{99m}Tc -octreotide scintimammography was advantageous over mammography in detecting breast carcinoma. In addition, the mammography has major limitations in some cases, such as dense breasts, heterogeneously dense breasts, young females or breasts with scarring after surgery, biopsy or radiation therapy, the ^{99m}Tc -octreotide scintimammography was a useful technique as a complement to mammography.

Table 2 T/NT of ^{99m}Tc -octreotide scintimammography vs histopathologic findings ($\pm$ S.D.)

Histopathologic findings	Cases	T/NT
Breast cancer	31	1.63 ± 0.19
Benign tumor	14	1.09 ± 0.13
t	–	9.638
p	–	<0.001

For reducing the number of biopsies for benign lesions, Prats *et al.*^[4] proposed a joint mammography/^{99m}Tc-MIBI scintimammography evaluation protocol in analyzing 90 breast cancers with mammographic suspicion of breast cancer. They concluded that the jointed protocol would have reduced the total number of biopsies performances to 34%, importantly to 65% in the low and indeterminate mammographic suspicion groups. In our study with the combined techniques, 21 cases were true-positive, and 11 cases were true-negative, and 1 case was false-negative in 33 patients, with congruent results of the ^{99m}Tc-octreotide scintimammography and mammography. Combining mammography with scintimammography of ^{99m}Tc-octreotide, 96% sensitivity, 100% specificity, 97% accuracy, 100 % PPV, and 92% NPV could be achieved (Table 1). The results showed that above adoption provided an excellent diagnosis for detecting breast cancer.

4 Conclusion

In detecting and diagnosing breast cancer, the ^{99m}Tc-octreotide scintimammography showed a higher sensitivity, specificity, positive predictive value, and negative predictive value than that of mammography. The mammography had the limitations of dense breasts, heterogeneously dense breasts, young patients, following radiation, surgery and biopsy, and that the ^{99m}Tc-octreotide scintimammography was a valuable complementary to mammography. The two combinations were very effective in breast carcinoma.

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