The diagnostic role of ^{99m}Tc-dual receptor targeted probe and targeted peptide bombesin (RGD-BBN) SPET/CT in the detection of malignant and benign breast tumors and axillary lymph nodes compared to ultrasound

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Abstract

Objective: This study aimed to explore the diagnostic role of a new dual receptor-targeted probe, integrin $\alpha_v\beta_3$ and gastrin releasing peptide receptor (GRPR) targeted peptide Glu-c(RGDyK)-bombesin (RGD-BBN) labeled with technetium-99m (^{99m}Tc-RGD-BBN), using single photon emission tomography/computed tomography (SPET/CT) in the detection of breast tumor in comparison to ultrasound (US). **Subjects and Methods**: One hundred and twenty six female patients with suspicious breast lesions who had already been scheduled for biopsy or surgery were enrolled in this study. All patients had previously underwent breast US and ^{99m}Tc-RGD-BBN SPET/CT. The US findings were evaluated according to the breast imaging report and the data system (BI-RADS). Technetium-99m-RGD-BBN SPET/CT images were interpreted independently by two experienced nuclear medicine physicians. A final diagnosis was made by histopathology of the specimens. A total of 130 lesions, 77 malignant and 53 benign lesions were ascertained. One hundred and twelve breast lesions, 69 malignant and 43 benign lesions were above 10mm in diameter and 18 breast lesions (8 malignant lesions and 10 benign lesions) were below 10mm. **Results**:The overall sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy of ^{99m}Tc-RGD-BBN SPET/CT and US for breast lesions were 93.5% vs. 81.8% (P<0.05), 79.2% vs. 75.5% (P>0.05), 86.7% vs. 82.9% (P>0.05), 89.4% vs. 74.1% (P<0.05) and 87.7% vs. 79.2% (P>0.05). Technetium-99m-RGD-BBN SPET/CT detected all lesions ≥10mm and US only detected 57 (P<0.05). In malignant lesions <10mm, US was superior than ^{99m}Tc-RGD-BBN SPET/CT (75.0% vs. 37.5%, P<0.05). There swas no significant difference between the two methods no matter the size of the benign of the lesions. The overall sensitivity and specificity of ^{99m}Tc-RGD-BBN SPET/CT and US for axillae lymph nodes were 87.5% vs. 71.9% (P<0.05) and 77.6% vs. 68.9% (P>0.05), respectively. For the metastatic lymph nodes of ≥10mm, the sensitivity of ^{99m}Tc-RGD-BBN SPET/CT and of US was 88.5% and 72.1% respectively (P<0.05). Statistical analysis was not performed due to the small number of metastatic lesions of <10mm. The specificity of ^{99m}Tc-RGD-BBN SPET/CT and of US was not different, no matter the size of the axilla lymph nodes that had no metastases (P>0.05). Technetium-99m-RGD-BBN SPET/CT had higher sensitivity and NPV than US in detecting primary breast tumors and axilla lymph nodes and it also showed an advantage in distance metastatic lesions detection. On the contrary, specificity and PPV of the two methods were not different. **Conclusion**: Technetium-99m-RGD-BBN SPET/CT cannot totally replace US in the detection of primary breast cancer and axillary lymph nodes metastases. It can be used as an additional imaging tool of eliminating the necessity of surgical biopsy and histopathologic examination because of its high NPV.

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Introduction

Breast cancer is the most frequent cancer in women all over the world with a high mortality [1, 2]. In the United States, an estimated 232,670 new cases of invasive breast cancer and 62,570 new cases of in situ breast cancer were expected to be diagnosed in women during 2014 [3]. Also, the incidence rate is increasing year by year in China [4, 5]. Thus, early detection and thorough evaluation of primary breast cancer and its metastases may lead to a higher rate of successful treatment and extend patients' life.

At present, ultrasound (US) represents an imaging procedure of choice in breast cancer screening [6-8]. The US results largely rely on the clinician's opinion with a low negative pre-

dictive value (NPV). Many breast biopsies were often performed for lesions with no obvious malignant characteristics [9].

Recently, molecular imaging including receptor imaging have been introduced in the diagnosis and staging of the breast cancer [10-13]. For example, a dual receptor-targeted probe, integrin $\alpha_v\beta_3$ and gastrin releasing peptide receptor - GRPR targeted peptide, Glu-c(RGDyK)-bombesin (RGD-BBN) labeled with technetium-99m (^{99m}Tc-RGD-BBN) had been used tentatively for imaging in healthy volunteers and patients with breast cancer. It exhibited safe and excellent properies for detecting breast cancer [14]. Thus we were prompted to test the diagnostic performance of ^{99m}Tc-RGD-BBN using single photon emission tomography/computed tomography (SPET/CT) for more patients with suspicious breast lesions tentatively and verify its usefulness compared with US.

Materials and Methods

Subjects

One hundred and twenty six female consecutive patients with suspicious breast lesions who had already been scheduled for biopsy or surgery were enrolled in this study. Exclusion criteria included pregnancy or lactation. Written informed consent was obtained from all subjects. The study and application of the new radiotracer ^{99m}Tc-RGD-BBN were approved by the local independent Ethics Committees and the Institutional Review Boards of China-Japan Union Hospital, Changchun, China.

Ultrasound

All patients had previously undergone breast US and the US findings were evaluated according to the breast imaging report and data system (BI-RADS). The US reports of all patients were≥BI-RADS 4. Axillary lymph nodes were considered positive if they had more than 2 malignant signs.

Technetium-99m-RGD-BBN SPET/CT

Radiolabeling and quality control procedures for ^{99m}Tc-RGD-BBN were performed as described previously [14, 15]. Technetium-99m-RGD-BBN with a mean radioactivity of 649±145MBq (11.1MBq/kg) was administered via single intravenous bolus injection followed by a 10mL saline flush [14]. The Philips Healthcare Medical System was used. Images were acquired 4 hours after the administration of tracer with patients placed in supine positions with their arms elevated.

Single photon emission tomography (PET) images were acquired using a dual-head, large field-of-view scintillation camera equipped with a low-energy, parallel-hole collimator. The images were acquired every 20 seconds, at a 3°angle, in a circular orbit of 180° per detector array, using ^{99m}Tc with a 20% energy window centered on 140keV and 128×128 matrix.

Computed tomography images were acquired sequentially in a non-dedicated 3rd-generation scanner installed in the SPET camera gantry, with a 10mm slice thickness, a maximum current of 2.5mA and a 140kV potential.

The raw data from SPET and CT were transferred to workstation for the reconstruction and image fusion. After these steps, the images were reoriented to obtain transaxial, coronal, and sagittal views.

All images were independently interpreted by two experienced nuclear medicine physicians who were unaware of the clinical history and other test results of all patients. Single photon emission tomography was considered positive for breast, axillary lymph nodes or other organs involvement when one or more focal areas of increased uptake were identified as compared with the surrounding normal tissues. Disagreements in the analysis were resolved by consensus.

Evaluation standard and immunohistochemistry of $\alpha_v\beta_3$ and GRPR expression.

A final diagnosis was made by histopathology of the specimens including breast tissue and resected lymph nodes.

The immunohistochemistry of $\alpha_v\beta_3$ and GRPR expression was performed only in breast tissue sample as described previously with some modifications [16, 17]. The abnormal tissues were snap-frozen, sectioned (3μm) and fix with ice-cold acetone, rinsed with PBS and blocked with 10% goat serum for 30min at room temperature. The slices were incubated with goat anti-GRPR antibody (1:100; Santa Cruz Biotechnology, Santa Cruz, CA), humanized antihuman integrin $\alpha_v\beta_3$ antibody Abegrin (20μg/mL) (1:100; BD Biosciences, San Jose, CA) for 1h at room temperature. The intensity and amount of integrin $\alpha_v\beta_3$ or/and of GRPR positive tumor cells were performed independently by 3 senior pathologists who were unaware of the test results. Decision criteria are as follows: 1. no staining, 2. weak staining, 3. strong staining; 1. no cells stained, 2. less than 10% cells stained, 3. 10%-50% cells stained, 4. 50%-90% cells stained, 5. all cells stained. Tumors were considered positive if the sum score of intensity and amount was>6 that is, strong staining in at least 10% of cells or weak staining in over half of the tumor cell population [18].

Statistical analysis

Data were expressed as mean±SD. The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were determined by the standard methods. The $\chi 2$ test was employed to assess the statistical differences between US and ^{99m}Tc-RGD-BBN SPET/CT. A P value of <0.05 was considered statistically significant.

Results

Patient characteristics

Table 1 reports the clinicopathologic results of the patients. Seventy five patients underwent surgery and 46 patients underwent biopsy within 1 week. Five patients chose follow-up. Ultimately 76 cases were ascertained with 77 malignant lesions and 50 cases were diagnosed with 53 benign lesions. Among the 77 malignant lesions, 63 were invasive ductal carcinomas (IDC), 4 were invasive lobular carcinomas (ILC), 7 were ductal carcinomas in situ (DCIS), 1 was a cribriform carcinoma, 1 was papillary carcinoma and 1 was medullary carcinoma. Among 53 benign mammary lesions, all were confirmed by biopsy and were: 29 fibroadenomas, 19 adenosis, 2 cysts, and 3 lipomas.

One hundred and twelve breast lesions (69 malignant lesions and 43 benign lesions) were above 10mm and 18

***Table 1**. Characteristics of patients enrolled in the study*

Characteristics	Number
Mean age±SD (year)	49.6 ± 10.7
Weight in kg	63.2 ± 14.1
Malignant tumors	77
Invasive ductal carcinomas	63
Invasive lobular carcinoma	4
Ductal carcinoma in situ	7
Cribriform	1
Papillary carcinoma	1
Medullary carcinoma	1
Benign tumors	53
Fibroadenoma	29
Adenosis	19
Cyst	2
Lipoma	3

breast lesions (8 malignant lesions and 10 benign lesions) were below 10mm (Table 2, Table 3).

A total of 66 patients were submitted to axillary lymph node dissection (ALND): 122 axillary lymph nodes were examined histologically. Metastases were ascertained in 64 and non-metastases were ascertained in 58.

Diagnostic performance of ^{99m}Tc-RGD-BBN SPET/CT and US.

Table 2 demonstrated diagnostic performance of ^{99m}Tc-RGD-BBN SPET/CT and US on the evaluation of malignant breast lesions. Among 77 primary breast cancinomas, 72 showed intense ^{99m}Tc-RGD-BBN accumulation and 5 showed no ^{99m}Tc-RGD-BBN accumulation, with a sensitivity of 93.5%.

Figure 1 showned a true positive case with intense ^{99m}Tc-RGD-BBN uptake.

Ultrasound confirmed 63 malignant lesions with a sensitivity of 81.8% and there was a significant difference compared with

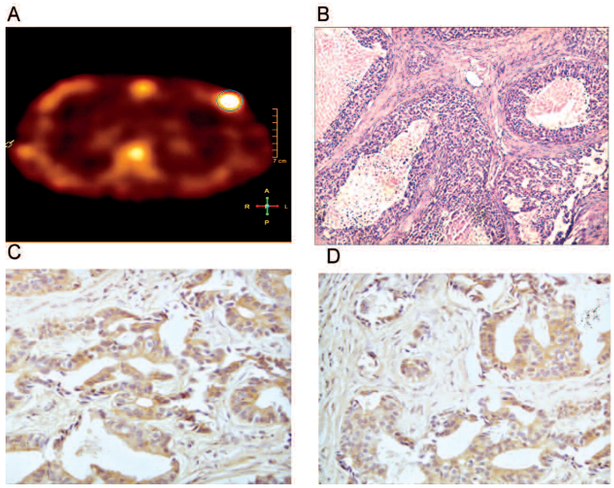

Figure 1. A 51 years old patient with a left breast carcinoma. A: High uptake of the radiotracer was observed in the lesion on ^{99m}Tc-RGD-BBN SPET (white arrow). B: Histopathology staining indicated a ductal carcinoma in situ. Scale bar: 100μm. C, D: Immunohistochemistry demonstrates intense $\alpha_v\beta_3$ and GRPR expression simultaneously in tumor vessels and tumor cells. Scale bar: 400μm.

^{99m}Tc-RGD-BBN SPET/CT (P<0.05). Technetium-99m- RGD-BBN SPET/CT detected all primary breast cancers with tumor size≥10mm and US only detected 57 (P<0.05). But for 8 malignant lesions<10mm, ^{99m}Tc-RGD-BBN SPET/CT only detected 3 and US detected 6. In this regard, US is superior than ^{99m}Tc-RGD-BBN SPET/CT for tiny lesions (75.0% vs. 37.5%, P<0.05).

Table 3 demonstrated diagnostic performance of ^{99m}Tc-RGD-BBN SPET/CT and US on the evaluation of breast benign lesions. Among 53 benign mammary lesions, 42 showed no ^{99m}Tc-RGD-BBN accumulation and 11 showed relatively high ^{99m}Tc-RGD-BBN accumulation. The overall specificity of ^{99m}Tc-RGD-BBN SPET/CT was 79.2%. Ultrasound showed a specificity of 75.5% for all benign lesions. There was no statistically

***Table 2**. Diagnostic performance of ^{99m}Tc-RGD-BBN SPET/CT and US on the evaluation of malignant breast lesions*

Findings	No. of lesions		Lesions size			
	(n=77)		≥10mm (n=69)	US	<10mm (n=8)	
	^{99m}Tc-RGD-BBN SPET/CT	US	^{99m}Tc-RGD-BBN SPET/CT		^{99m}Tc-RGD-BBN SPET/CT	US
True positive	72	63	69	57	3	6
Sensitivity	93.50%	81.80%	100%	82.60%	37.50%	75.00%
IDC	61	54	60	51	1	3
ILC	4	3	4	3	0	0
DCIS	4	4	2	1	2	3
Invasive cribriform carcinoma	1	1	1	1	0	0
Invasive papillary carcinoma	1	1	1	1	0	0
Medullary carcinoma	1	0	1	0	0	0
False negative	5	14	0	12	5	2
IDC	2	9	0	9	2	0
ILC	0	1	0	1	0	0
DCIS	3	3	0	1	3	2
Medullary carcinoma	0	1	0	1	0	0

significance between the two procedures (P>0.05).

Technetium-99m-RGD-BBN SPET/CT imaging of a patient with a fibroadenoma in the left breast is presented in Figure 2. If the benign lesions were subdivided according to size, 36 and 31 cases with the size≥10mm were confirmed by ^{99m}Tc-RGD-BBN SPET/CT and US, respectively 83.7% vs. 72.1%, (P>0.05). For lesions<10mm, 6 and 9 cases were found by ^{99m}Tc-RGD-BBN SPET/CT and US: 60.0% vs. 90.0%, (P>0.05-Table 3). There was a significant difference between the two methods which was unrelated to the size of the benign lesions.

The overall PPV and NPV of ^{99m}Tc-RGD-BBN SPET/CT and US were 86.7% vs. 82.9% (P>0.05) and 89.4% vs. 74.1% respectively (P<0.05). The overall accuracy of the two procedures was not significantly different (87.7% vs. 79.2%, P>0.05).

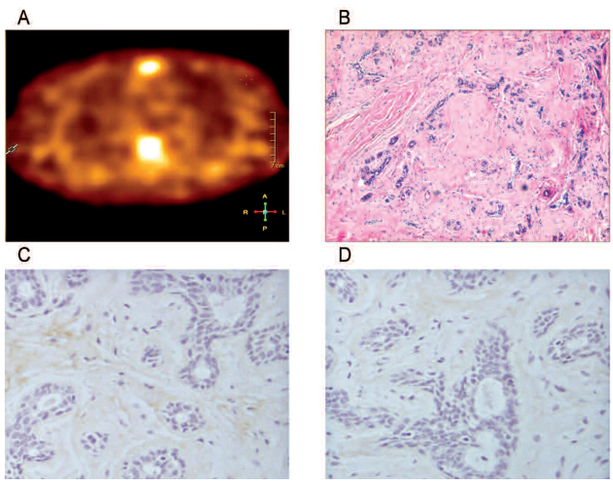

Figure 2. A 47 years old patient with fibroadenoma in left breast. A: No tracer uptake was observed in the lesion on ^{99m}Tc-RGD-BBN SPET (white arrow). B: Histopathology staining indicated fibroadenoma. Scale bar: 100μm. C, D: Immunohistochemistry demonstrates barely $\alpha_v\beta_3$ and GRPR expression in tumor vessels and tumor cells. Scale bar: 400μm.

The detection of axillary and distant metastases.

A total of 122 axillary lymph nodes in 66 patients were removed by surgery and the pathologic examination confirmed 64 metastatic lymph nodes. Table 4 reports the overall results of ^{99m}Tc-RGD-BBN SPET/CT and US in the detection of lymph nodes' metastases.

The overall sensitivity and NPV of ^{99m}Tc-RGD-BBN SPET/CT and US had significant difference (P<0.05), but the overall specificity and PPV of them had no difference (P>0.05). In the metastatic lymph nodes ≥10mm, the sensitivities of ^{99m}Tc-RGD-BBN SPET/CT and of US were 88.5% and 72.1%, respetively (P<0.05, Table 5 and Figure 3). Statistical analysis was not performed due to the small number of metastatic lesions of <10mm. The specificity of ^{99m}Tc-RGD-BBN SPET/CT and US were not different, no matter the size of the axillary nodes without metastases (P>0.05). One patient with multiple bone metastases was accidentally found with high ^{99m}Tc-RGD-BBN uptake and osteolytic bone changes which were missed by US Figure 4.

Immunohistochemistry of $\alpha_v\beta_3$ and GRPR expression.

For 77 malignant lesions, 35 cases were found with dual $\alpha_v\beta_3$ and GRPR expression (GRPR+/$\alpha_v\beta_3$+), 18 cases with only

***Table 4**. The results of ^{99m}Tc-RGD-BBN SPET/CT and US in 122 axillary lymph nodes 64 with metastases and 58 without metastases*

	^{99m}Tc-RGD-BBN SPET/CT	US
True positive	56	46
True negative	45	40
False positive	13	18
False negative	8	18
Sensitivity(%)	87.5	71.9
Specificity(%)	77.6	68.9
Positive predictive value(%)	81.1	71.8
Negative predictive value(%)	84.9	68.9
Accuracy(%)	82.8	70.5

***Table 3**. Diagnostic performance of ^{99m}Tc-RGD-BBN SPET/CT and US on the evaluation of benign breast lesions*

Findings	No. of lesions		Lesions size			
	(n=53)		≥10mm (n=43)	US	<10mm (n=10)	
	^{99m}Tc-RGD-BBN SPET/CT	US	^{99m}Tc-RGD-BBN SPET/CT		^{99m}Tc-RGD-BBN SPET/CT	US
True negative	42	40	36	31	6	9
Specificity (%)	79.2	75.5	83.7	72.1	60.0	90.0
Fibroadenoma	23	24	20	20	3	4
Adenosis	15	12	12	7	3	5
Cyst	2	2	2	2	0	0
Lipoma	2	2	2	2	0	0
False positive	11	13	7	12	4	1
Fibroadenoma	6	5	5	5	1	0
Adenosis	4	7	1	6	3	1
Lipoma	1	1	1	1	0	0

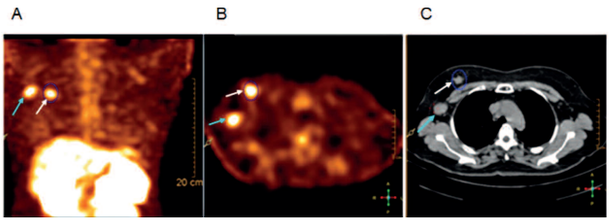

Figure 3. A case with invasive ductal carcinoma of the right breast (white arrow) and axillary lymph-node metastases on the right side (blue arrow) on planar imaging A, transverse imaging B and CT, C.

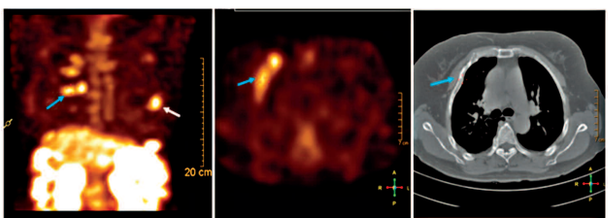

Figure 4. A case with invasive ductal carcinoma in the left breast (white arrow) and multiple bone metastases (blue arrow) on planar imaging A, transverse imaging B and CT, C.

GRPR positive expression (GRPR+/$\alpha_v\beta_3$-) and 24 cases with only integrin $\alpha_v\beta_3$ positive expression (GRPR-/$\alpha_v\beta_3$+). Seven benign lesions were found to only express GRPR (GRPR+/$\alpha_v\beta_3$-) and 4 benign lesions were found to only express $\alpha_v\beta_3$ (GRPR-/$\alpha_v\beta_3$+).

Discussion

It is necessary to select a proper imaging method for early diagnosing breast cancer with the purpose of successful treatment and management. When the traditional imaging method cannot differentiate benign from malignant breast lesions, the clinicians always turn to another noninvasive imaging modality or to surgical biopsy.

Previous studies confirmed receptor imaging methods with great diagnostic usefullness accuracy for breast tumors although not often used as the traditional methods [19, 20]. Breast cancer is a tumor with high expression of various receptors including integrin $\alpha_v\beta_3$ and GRPR. Many studies confirmed that receptor imaging was helpful for the detection, diagnosis and staging of breast cancer due to its high diagnostic performance and ability to detect tumor pathological conditions.

In this preliminary study, we investigated the efficacy of a new dual receptor-targeted probe, ^{99m}Tc-RGD-BBN, in patients with breast tumor and compared its diagnostic ability with US. If ^{99m}Tc-RGD-BBN SPET/CT can solve all diagnostic problems by one study, other unnecessary conventional imaging studies can be omitted.

The results showed that the ^{99m}Tc-RGD-BBN SPET/CT detected the primary breast lesions with an overall sensitivity of 93.5%, which was significantly higher than that of US (81.8%, P<0.05) and also higher than the integral sensitivity of SMM as reported by a meta-analysis of the Agency for Healthcare Research and Quality [21]. All primary lesions above 1cm were detected. The high prevalence of malignant patients with larger lesions in our studies may account for such a high sensitivity, most of whom were selected for biospy or surgery on the basis of suspicion of breast cancer. Meanwhile, this high sensitivity further verified the principle for rising ^{99m}Tc-RGD-BBN, as mentioned before, which can make a good image as long as integrin $\alpha_v\beta_3$ or GRPR has a positive expression.

The tumor size is a major factor for sensitivity and false negative cases of SPET/CT. In our study, ^{99m}Tc-RGD-BBN SPET/CT showed low sensitivity (37.5%) in the detection of lesions with sizes less than 10mm. Five false negative cases were found. All of them were smaller than 10mm. Such a size is generally difficult to investigate by SPET/CT.

There was no statistical difference between the overall specificity values of ^{99m}Tc-RGD-BBN and US (79.2% vs. 75.5%, P>0.05). We found 11 false positive cases in total using ^{99m}Tc-RGD-BBN SPET/CT. Histopathology identified 7 cases which only expressed GRPR (GRPR+/$\alpha_v\beta_3$-) and 4 cases which only expressed $\alpha_v\beta_3$ (GRPR-/$\alpha_v\beta_3$+). Tracer accumulation in these cases was due to nonspecificity of integrin $\alpha_v\beta_3$ receptor and GRPR receptor, both of which have been reported to cause high uptake in other studies performed with ^{99m}Tc-bombesin and ^{99m}Tc-3PRGD2 [19, 20, 22]. Previous reports confirmed high expression of integrin $\alpha_v\beta_3$ receptor not only in tumor angiogenesis and various tumor cells but also in inflammatory angiogenesis and other related procedures. Furthermore, is was reported that GRPR density on benign breast tissue and regional blood flow can also affect the imaging results [19, 23], while ^{99m}Tc-RGD-BBN not only can specifically bind to integrin $\alpha_v\beta_3$ but also to GRPR respectively. Therefore, a low specificity is inevitable. Beyond that, the low prevalence of benign patients in our studies may have affected this result. On the other hand ^{99m}Tc-RGD-BBN SPET/CT gained a high NPV which can affect patients' next decision. Patients with equivocal results in US can choose to be followed-up and not have biopsy or surgery.

For detecting metastatic axillary lymph nodes, ^{99m}Tc-RGD-BBN SPET/CT demonstrated the same characteristics as for the primary tumor. Technetium-99m-RGD-BBN SPET/CT hada higher sensitivity and NPV than US. Both methods had unsatisfactory results for smaller lesions because the size of the lesions was one of the important diagnostic factors.

One case of multiple bone metastases was found which was missed by US. This finding indicates that ^{99m}Tc-RGD-BBN SPET/CT may have an advantage in detecting metastatic lesions.

In our study, the T/N ratios of primary breast tumors and lymph nodes had not been measured, and even though immunohistochemistry of receptors was conducted, quantification and correlation with tracer uptake was also not performed. These remain to be determined by additional studies.

In conclusion, according to our findings, ^{99m}Tc-RGD-BBN SPET/CT had higher sensitivity and NPV than US in detecting primary breast tumors and axillary lymph nodes, and also showed an advantage in distant metastatic lesions de-

tection. The specificity and PPV of these methods were not different. So, ^{99m}Tc-RGD-BBN SPET/CT cannot solely replace US in primary breast cancer and axillary lymph nodes but it can be used as an additional imaging tool of eliminating the necessity for surgical biopsy and histopathologic examination because of its high NPV. The best approach may be to diagnostically combine different imaging modalities.

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The authors declare that they have no conflicts of interest.

Bibliography

1. DeSantis C, Siegel R, Bandi P et al. Breast cancer statistics, 2011. *CA Cancer J Clin* 2011; 61: 409-18.
2. R. Siegel, D. Naishadham, A. Jemal. Cancer statistics, 2012. *CA Cancer J Clin* 2012; 62: 10-29.
3. American Cancer Society. Cancer Facts & Figures 2014. *Atlanta: Am Cancer Soc*; 2014.
4. Song QK, Li J, Huang R et al. Age of diagnosis of breast cancer in China: almost 10 years earlier than in the United States and the Eu ropean union. *Asian Pac J Cancer Prev* 2014; 15(22): 10021-5.
5. Kim Y, Yoo KY, Goodman MT. Differences in incidence, mortality and survival of breast cancer by regions and countries in Asia and contributing factors. *Asian Pac J Cancer Prev* 2015; 16(7): 2857-70.
6. Alvarez S, Añorbe E, Alcorta P et al. Role of sonography in the diagnosis of axillary lymph node metastases in breast cancer: a systematic review. *Am J Roentgenol* 2006; 186: 1342-8.
7. Donnelly TT, Khater AH, Al-Bader SB et al. Arab women's breast cancer screening practices: a literature review. *Asian Pac J Cancer Prev* 2013; 14(8): 4519-28.
8. Ueda S, Tsuda H, Asakawa H et al. Utility of ^{18}F-fluoro-deoxyglucose emission tomography/computed tomography fusion imaging (^{18}F-FDG PET/CT) in combination with ultrasonography for axillary staging in primary breast cancer. *BMC Cancer* 2008; 8: 165.
9. Baruah BP, Goyal A, Young P et al. Axillary node staging by ultra sonography and fine-needle aspiration cytology in patients with breast cancer. *Br J Surg*, 2010.97: 680-3.
10. Wahl RL. Current status of PET in breast cancer imaging, staging, and therapy. *Semin Roentgenol* 2001; 36: 250-60.
11. Zangheri B, Messa C, Picchio M et al. PET/CT and breast cancer. *Eur J Nucl Med Mol Imaging* 2004; 31: 135-42.
12. Heusner TA, Kuemmel S, Umutlu L et al. Breast cancer staging in a single session: whole-body PET/CT mammography. *J Nucl Med* 2008; 49: 1215-22.
13. Almuhaideb A, Papathanasiou N, Bomanji J. ^{18}F-FDG PET/CT imaging in oncology. *Ann Saudi Med* 2001; 3: 3-13.
14. Chen Q, Ma Q, Chen M et al. An Exploratory Study on ^{99m}Tc-RGD-BBN Peptide Scintimammography in the Assessment of Breast Ma lignant Lesions Compared to ^{99m}Tc-3P4-RGD2. *PLoS One* 2015; 10(4): e0123401
15. Liu Z, Huang J, Dong C et al. ^{99m}Tc-labeled RGD-BBN peptide for small-animal SPET/CT of lung carcinoma. *Mol Pharm* 2012; 9: 1409-17.
16. Liu Z, Niu G, Wang F et al. ^{68}Ga-labeled NOTA-RGD-BBN peptide for dual integrin and GRPR-targeted tumor imaging. *Eur J Nucl Med Mol Imaging* 2009; 36: 1483-94.
17. Ma Q, Ji B, Jia B et al. Differential diagnosis of solitary pulmonary nodules using ^{99m}Tc-3P4-RGD2 scintigraphy. *Europ J of Nucl Med and Mol Imag*. 2011; 38: 2145-52.
18. Scott N, Millward E, Cartwright E et al. Gastrin releasing peptide and gastrin releasing peptide receptor expression in gastrointestinal car cinoid tumours. *J of Clin Pathol* 2004; 57: 189-92.
19. Spanu A, Schillaci O, Meloni GB et al. The usefulness of ^{99m}Tc-tetro fosmin SPET scintimammography in the detection of small size primary breast carcinomas. *Int J Oncol* 2002; 21: 831-40.
20. Liu L, Song Y, Gao S et al. ^{99m}Tc-3PRGD2 scintimammography in palpable and nonpalpable breast lesions. *Mol Imaging* 2014; 13: 1-7.
21. Bruening W, Uhl S, Fontanarosa J et al. *Noninvasive diagnostic tests for breast abnormalities: update of a 2006 Review*. Available at: http://effectivehealthcare.ahrq.gov/contact-the-effective-health-care-program/; USA. [Accessed 3 November 2013]. Centre for Reviews and Dissemination 2006; 62(10): 3491-2.
22. Ma Q, Chen B, Gao S et al. ^{99m}Tc-3P4-RGD2 scintimammography in the assessment of breast lesions: comparative study with ^{99m}Tc-MIBI. *PloS One* 2014; 9(9), e108349.
23. Scopinaro F, Di Santo GP, Tofani A et al. Fast cancer uptake of ^{99m}Tc-labelled bombesin (^{99m}Tc BN1). *In Vivo* 2005; 19: 1071-6.