Original Article

Evaluation of a new ^{99m}Tc-Bombesin analog in differentiation of malignant from benign breast tumors

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ABSTRACT

Introduction: The gastrin releasing peptide (GRP) receptor is over expressed in a variety of common human tumors. Radiolabeled bombesin analogues have exhibited high binding affinity for these receptors. The aim of this study was to assess the value of a new ^{99m}Tc-bombesin analog in the differentiation of malignant from benign breast tumors.

Methods: ^{99m}Tc-bombesin scans were performed in 21 patients (45±21years) with breast tumor. Post-injection of 555-740 MBq ^{99m}Tc-bombesin, the dynamic imaging of the chest with 60 seconds for each frame up to 20 minutes was acquired. Subsequently, 360◦ image SPECTs of the chest was performed in 120 steps, 20 seconds per projection. In addition, whole-body anterior and posterior views were obtained 60 and 180 min after injection. Definite diagnosis was based on excisional biopsy and histopathological examination.

Results: Thirteen patients demonstrated breast carcinoma and 8 patients were diagnosed as benign lesions. 11 out of 13 patients with breast carcinoma showed radiotracer uptake in the breast lesion. Nine out of 13 patients with breast carcinoma showed axillary lymph node involvement from which only two revealed radiotracer accumulation in the axillary lesion. All patients with benign lesions revealed negative scan. Delayed planar whole body images showed no additional diagnostic information in comparison to one-hour images. The sensitivity, specificity, PPV and NPV of ^{99m}Tc-bombesin scan were 84.6%, 100%, 100% and 80%, respectively.

Conclusion: Our data suggest that this new ^{99m}Tc-bombesin analog could be useful in SPECT imaging of primary breast cancer.

Key words: ^{99m}Tc-bombesin; Breast cancer; Malignant; Imaging

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INTRODUCTION

Breast cancer is the most common cancer in females all over the world [1]. Early diagnosis of primary tumors and distant metastases is essential to improve odds of curing or controlling the disease [2]. Although Mammography is commonly beneficial to achieve this aim, its shortcomings in imaging of patients with breast implants, postsurgical recurrence, or dense breast tissue cannot be ignored [3]. Therefore, introducing effective modalities that can help in better imaging of primary breast carcinoma is one of major concerns for researchers and physicians working in this field [3-11]. Among available imaging techniques, nuclear imaging, which targets physiological differences of cancer cells in comparison to normals, such as level of receptor expression, rate of metabolism, angiogenesis and so on, are considered as excellent tools for research and development. Accordingly, there is particular interest in the development of novel radiotracers that can be helpful in imaging primary breast carcinoma [12]. For instance, the expression of GRP receptors has been reported in human cancers, such as prostate and breast carcinomas [13-16]. Bombesin (BN) is a tetradecapeptide, initially isolated from the skin of a tree frog, targets gastrin releasing peptide (GRP) receptors with high affinity and specificity [17]. The present study aimed to evaluate the uptake of a new ^{99m}Tc-BN analogue [18] by breast cancer to find out whether this radiotracer is useful for the diagnosis of breast cancer and its differentiation from benign lesions.

METHODS

Radiopharmaceutical

Tc-99m was obtained from a commercially available ^{99}Mo/^{99m}Tc generator (AEOI, Iran) and ^{99m}Tc-BN was prepared according to the previously published report [18].

Study population

The study was approved by the committee of ethics at Tehran University of Medical Sciences. Twenty-one patients (female, mean age 45.67±14 years with age range of 15 to 68 years) who based on physical exam and radiologic imaging were suspicious for breast malignancy, were studied with ^{99m}Tc-BN. All selected patients were inquired into having no pervious breast surgical resection or biopsy. A written consent was obtained, after giving a full explanation of the procedure to each patient.

Study measurements

Immediately after intravenous injection of 10 MBq/kg (range: 555-740 MBq) ^{99m}Tc-BN, imaging procedure was started with patients in supine position, using a SPECT/CT (Symbia T, Siemens Medical Solutions) equipped with low energy high resolution (LEHR) collimator. The dynamic imaging of the chest with 60 seconds for each frame up to 20 minutes post-injection was acquired with 128×128 matrix. Subsequently, 360◦ image SPECTs of the chest was performed in 120 steps, 20 seconds per projection, and reconstruction with iterative method (iteration 2, subset 8). In addition, whole-body anterior and posterior views were obtained 60 and 180 min after injection. A 10% window was centered at peak of 140 KeV.

When tumor showed increased uptake in the dynamic images, background-corrected region of interest (ROI) were manually drawn on summed tumor images of dynamic data sheets and the diagram of radiotracer uptake versus time was depicted in a time-activity curve. The Scan results were qualitatively interpreted by at least two nuclear physicians. Any uptake more than 1.5 times of background activity was considered as positive. From nineteen patients who underwent surgery, tissue samples were fixed and stained with haematoxylin/eosin for histopathologic investigations.

Statistical analysis

Sensitivity, specificity, positive predictive value and negative predictive value of ^{99m}Tc-BN scintigraphy were calculated. All data were analyzed with SPSS 16.

RESULTS

No adverse reaction was noticed during acquisition and afterwards. Nineteen of patients at least, four days after their scan, underwent surgery. Two patients who did not underwent surgery, were followed up closely with physical examination and radiologic evaluation for 6-12 months. In 13 patients, increased uptake was observed in the tumor; 11 in breast carcinoma and 2 in fibroadenoma. The plotted curve according to the ROI analysis of images indicated that in 11 patients, the uptake reached a plateau after an early rapid up-slope phase with no significant change for 20 minutes (Figure 1); whereas in two other patients, down-slope pattern of the curve, 12-15 minutes after radiotracer injection, was indicative of rapid washout of the radiotracer (Figure 2). Image findings of these cases along with the pathologic results are summarized in Table 1. No significant difference was found between 60 and 180min whole body imaging. Final diagnoses based on the pathologic reports were breast carcinoma for 13 patients and benign lesion in 6 patients.

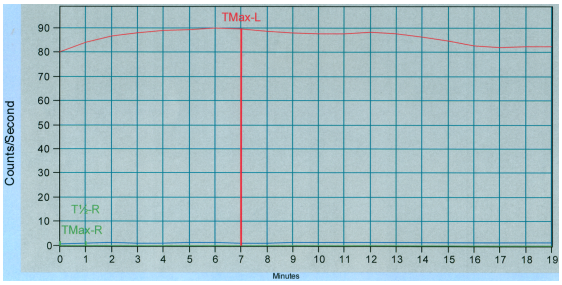

Fig 1. Time/activity curves on the regions of interest (ROIs) of patients with invasive lobular carcinoma in the right breast. The diagram shows rapid radiotracer uptake with no significant changes for 20 min.

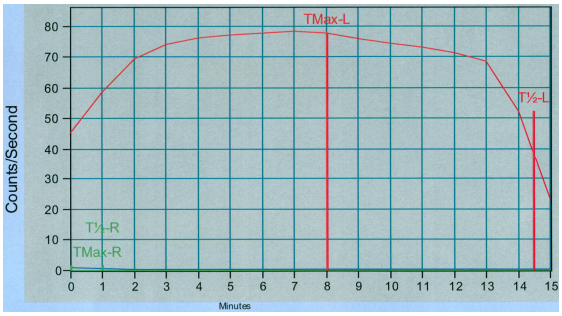

Fig 2. Time/activity curve of patents with fibroadenoma (benign lesion). The diagram reveals rapid radiotracer uptake in tumor and rapid washout after 13 min.

Two patients, who were followed for 6-12 months, showed no significant changes, so their final diagnoses were considered as benign.All lesions with persistent tracer uptake (plateau pattern) were confirmed to be malignant, while two patients with rapid washout (down-slope pattern) proved to be benign lesions. With respect to our findings, high probability of malignancy is assumed if ^{99m}Tc-BN is strongly accumulates in breast lesion and rapid washout of activity is not observed. In other words, the time in which radiotracer concentration reaches half ($T_{1/2}$) was more than 20 minutes for the malignant breast lesion. All patients with increased tumor uptake, radiotracer accumulation occurred within 1 min after injection. Mean time to peak radiotracer in lesions was 4 min. Sensitivity, specificity, PPV and NPV for detection of breast cancer were calculated as 84.6%, 100%, 100% and 80% respectively (P=0.001 according to Pearson Chi-Square test). Moreover, sensitivity and specificity for axillary lymph node involvement were calculated as 22.2% and 100%, respectively.

DISCUSSION

Our study was designed to describe a standard protocol for cancer imaging with ^{99m}Tc-BN and to determine sensitivity, specificity, NPV and PPV for detection of breast cancer. The present study showed that dynamic imaging and ROI analysis is the most important and indivisible part of the imaging which can differentiate benign from malignant lesions (Figures 3, 4 and 5).

Table 1: ^{99m}Tc-Bombesin imaging results with histopathologic correlation.

no	Age	Dynamic images	WBS in 60 min	WBS in 180 min	SPECT images	ROI analysis	Scan result	Pathologic result	Considerations
1	46	-	-	-	-	-	-	IDC	
2	35	+	+	+	+	-	-	Fibroadenoma	
3	44	+	+	+	+	+	+	ILC+LN involment	
4	41	+	+	+	+	+	+	IDC+LN involvement	LN involvement was seen in scan.
5	62	+	+	+	+	+	+	IDC+LN involvement	
6	66	+	+	+	+	+	+	ILC+LN involvement	
7	23	-	-	-	-	-	-	Fibroadenoma	
8	58	+	+	+	+	+	+	IDC+LN involvement	LN involvement was seen in scan.
9	68	+	+	+	+	+	+	IDC+LN involvement	
10	50	+	+	+	+	+	+	IDC+LN involvement	
11	15	+	+	+	+	-	-	Fibroadenoma	
12	41	-	-	-	-	-	-	IDC+LN involvement	
13	49	-	-	-	-	-	-	-	Patient under follow up for 1 year.
14	49	-	-	-	-	-	-	Fibro adenoma	
15	29	-	-	-	-	-	-	WBC, Lacteal collection	
16	42	-	-	-	-	-	-	-	Patient under follow up for 6 mounts.
17	38	-	-	-	-	-	-	Atypical ductal hyperplasia	
18	47	+	+	+	+	+	+	ILC	
19	55	+	+	+	+	+	+	ILC	
20	65	+	+	+	+	+	+	IDC+LN involvement	
21	39	+	+	+	+	+	+	IDC	

+: Positive for malignancy; -: Negative for malignancy; IDC: Invasive ductal carcinoma; ILC: Invasive lobular carcinoma; LN: Lymph node

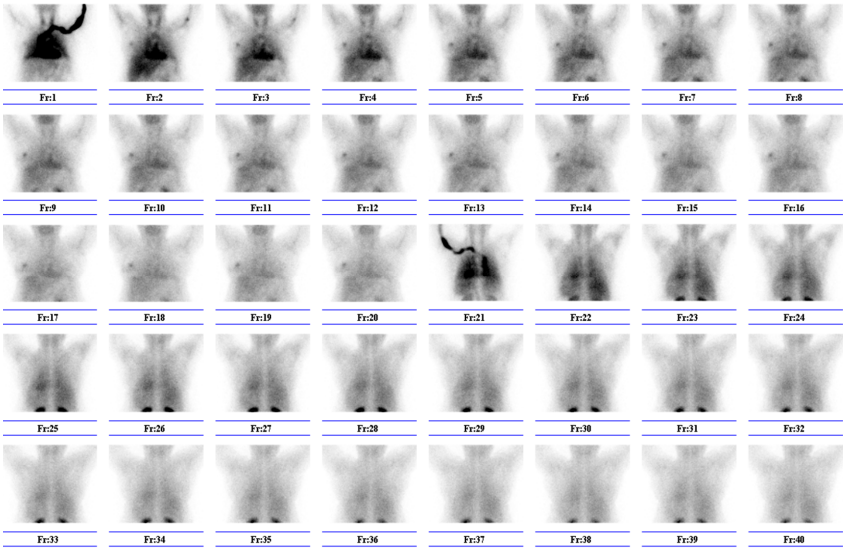

Fig 3. Anterior and posterior dynamic images of the chest wall shows increased radiotracer uptake corresponding to the palpable mass in the right breast.

Fast initial uptake in some benign lesions could be explained by hyperemia, but lack of enough target receptors with subsequent internalization of radiotracer which might lead to radiotracer degradation by serum enzymes over the first 10-15 min. Dynamic imaging as well as SPECT scintigraphy of the chest was essential to determine location of the tumor in the breast. Whole body scan after 1hour is recommended to detect possible distant metastases.

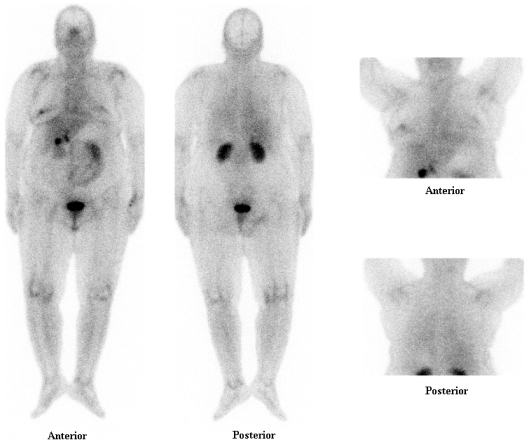

Fig 4. Whole body scan and spot views one hour after radiotracer injection showing asymmetrical uptake in breast areola. In radiologic imaging, tumor is located posterior to areola.

Further imaging seems to be unnecessary after 180 min. Our study showed that fast radiotracer uptake occurs in malignant lesions probably due to increased blood flow and receptor expression. Some previous studies reported similar early ^{99m}Tc-BN uptake [19-23]. Our data showed imaging with ^{99m}Tc-BN correctly helps in diagnosing of axillary lymph node metastases. In two of nine patients, involvement of axillary lymph nodes has been confirmed histologically. Sensitivity and specificity of detection were estimated about 22.2% and 100%, respectively.

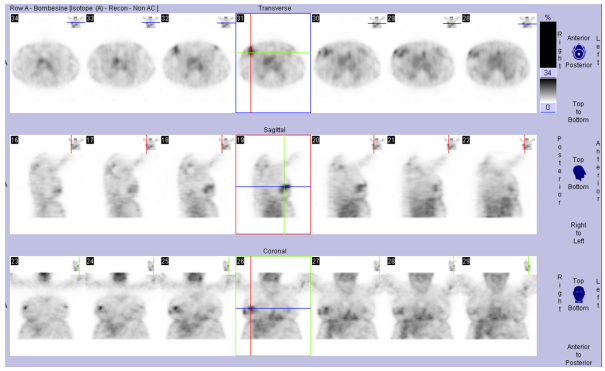

Fig 5. The chest SPECT images of the same patient (see Fig. 4) exhibit the tumor located in the same area.

These findings were not in accordance with results reported by Scopinaro et al. in prostate cancer or Van de Wiele et al. in the breast cancer [22, 24]. Finally, further studies with large patient population are necessary to assess the accuracy, reliability and effectiveness of breast cancer diagnosis with ^{99m}Tc-BN imaging.

CONCLUSION

Our data suggests that SPECT imaging by this new analog of ^{99m}Tc-BN could be useful in detection of primary breast cancer.

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