

Utility of ^{99m}Tc -PEG₄-E[PEG₄-c(RGDfK)]₂ in Posttherapy Surveillance of Patients with Reelevated Carcinoembryonic Antigen Levels

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Key Words

^{99m}Tc -PEG₄-E[PEG₄-c(RGDfK)]₂ · Integrin $\alpha_v\beta_3$ · Carcinoembryonic antigen · Recurrence · Single photon emission computed tomography

Abstract

Objectives: To evaluate the efficacy of ^{99m}Tc -PEG₄-E[PEG₄-c(RGDfK)]₂ (^{99m}Tc -3PRGD2) single photon emission computed tomography (SPECT) in monitoring the recurrence of malignancies. **Materials and Methods:** ^{99m}Tc -3PRGD2 SPECT was performed on 28 patients (10 females and 18 males; median age 49.2 years) suspected of recurrent malignancies due to an asymptotically reelevated carcinoembryonic antigen level. The SPECT was performed 0.5 h after an intravenous injection of 11.1 MBq/kg (0.3 mCi/kg) of ^{99m}Tc -3PRGD2. The SPECT and concurrent contrast-enhanced computed tomography (ceCT) findings were analyzed with reference to the histopathological findings and/or clinical follow-up data. **Results:** Recurrences were identified in 20 out of the 28 patients (prevalence 71.4%) with altogether 26 lesions. Fifteen lesions were confirmed by histopathological findings, and the other 11 lesions were confirmed by serial radiological or clinical follow-up. Of the 20 patients with recurrent malignancies, 12 (60%) were correctly identified by

^{99m}Tc -3PRGD2 SPECT. In the patient-based analysis, the sensitivity and specificity of ^{99m}Tc -3PRGD2 SPECT were 60 and 100%, respectively, and the positive and negative predictive values were 100 and 50%, respectively. In the lesion-based evaluation, the sensitivity and specificity were 62 and 100%, respectively. The sensitivity and specificity of the ceCT in the patient-based evaluation were 60 and 75%, respectively, and the positive and negative predictive values were 86 and 40%, respectively. In the lesion-based evaluation, the sensitivity and specificity of the ceCT were 70 and 84%, respectively. **Conclusions:** ^{99m}Tc -3PRGD2, as a new SPECT tracer targeting the integrin $\alpha_v\beta_3$ receptor, was more useful in distinguishing recurrences as compared to ceCT.

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Introduction

Carcinoembryonic antigen (CEA), present in carcinomas originating from many organs, is the most widely used indicator in determining recurrent malignancies [1]. An elevation of CEA raises the suspicion of cancer recurrence, requiring the performance of imaging tests such as ultrasonography, computed tomography and magnetic resonance imaging for confirmation. Recently, positron emission to-

mography (PET) with ^{18}F -labeled fluorodeoxyglucose (^{18}F -FDG) has been used for this purpose, and it is reported to be superior over conventional diagnostic imaging in sensitivity [2–6]. However, with the progress of targeted therapies, there is a growing demand for imaging modalities that allow for response assessment and pretherapeutic stratification of patients receiving such therapies [7].

$^{99\text{m}}\text{Tc}$ -PEG₄-E[PEG₄-c(RGDfK)]₂ ($^{99\text{m}}\text{Tc}$ -3PRGD2), a new single photon emission computed tomography (SPECT) tracer targeting the integrin $\alpha_v\beta_3$ receptor, has been used preclinically in tumor imaging, evaluating angiogenesis and monitoring antiangiogenic drug efficacy [8–10]. It has been demonstrated that a significant correlation of angiogenic activity and ^{18}F -FDG uptake exists in tumor xenografts as well as in tumor lesions [11]. ^{18}F -FDG has been widely adopted in tumor recurrence surveillance [4, 5], but few studies had focused on how 3PRGD2 behaves in detecting malignant recurrences in patients with reelevated CEA levels.

Materials and Methods

Synthesis of the labeling precursor, kit preparation and subsequent $^{99\text{m}}\text{Tc}$ -labeling were performed as previously described [12].

A total number of 28 patients (10 women and 18 men; median age 49.2 years, range 25.4–72.0) who received treatment for malignancies between March 2011 and June 2013 were enrolled in this study. Six of them had been diagnosed as having gastric adenocarcinoma, 3 ovarian cancer, 4 lung adenocarcinoma, 3 breast cancer and the remaining 12 as having colorectal cancer. The patients were suspected of having tumor recurrence due to their asymptotically elevated CEA levels. The median interval between primary diagnosis and suspected recurrence was 16.3 months (range 4.8–44.5), and the median CEA level at $^{99\text{m}}\text{Tc}$ -3PRGD2 SPECT was 11.2 ng/ml (range 4.4–36.1). The study was approved by the Ethics Committee of the First Affiliated Hospital of Xi'an Jiaotong University, and informed written consent was obtained from all the patients.

$^{99\text{m}}\text{Tc}$ -3PRGD2 SPECT and coregistered CT were performed 0.5 h after the intravenous injection of 11.1 MBq/kg (0.3 mCi/kg) of $^{99\text{m}}\text{Tc}$ -3PRGD2. All SPECT scans were performed from the thorax to the pelvis. The scanners were dual-head gamma cameras, using low-energy high-resolution collimators and a 20% energy window centered on 140 keV. The Dicom image files of each patient were saved on optic discs and transferred to a Xeleris 2.0 workstation (GE Healthcare) for centralized reconstruction, reading and analysis.

Contrast-enhanced computed tomography (ceCT) was performed concurrently also with $^{99\text{m}}\text{Tc}$ -3PRGD2 SPECT using a 64-channel CT scanner [Philips (China) Investment Co., Ltd.]. All scans were performed from the thorax to the pelvis, including the head if brain metastases were clinically suspected. Scans were performed in deep inspiration in the portal venous phase 70 s after the injection of 150 ml of iodine contrast agent by a power injector (Imeron 300, Altana) at a flow of 3 ml/s followed by a saline bolus (40 ml, 3 ml/s).

Table 1. Characteristics of the patients with recurrences (n = 20)

Age, years	46.5 (25.4–64.2)
Gender, male/female	15/5
Origin of the tumor	
Gastric adenocarcinoma	4
Ovarian cancer	2
Lung adenocarcinoma	3
Breast cancer	3
Colorectal cancer	8
Differentiation, poor/moderate/good	6/8/6
Treatments; CT/non-CT	14/6
Patients received targeted therapies	0
CEA at $^{99\text{m}}\text{Tc}$ -3PRGD2 SPECT, ng/ml	14.1 (5.2–36.1)
Period between diagnosis and SPECT, months	11.3 (4.8–30.9)

Values represent numbers or medians with ranges given in parentheses. CT = Chemotherapeutical regimens; non-CT = nonchemotherapeutical protocols.

Image Analysis

$^{99\text{m}}\text{Tc}$ -3PRGD2 SPECT images were visually interpreted by the consensus of three experienced nuclear medicine physicians Yang Aimin, Zhang Fenru, Gao Rui with reference to SPECT/CT fusion and CT images. A positive result was defined as the focal accumulation of $^{99\text{m}}\text{Tc}$ -3PRGD2 above its normal level in the surrounding tissue, excluding physiologically increased uptake. For semiquantitative analysis, tumor-to-background ratios of SPECT images were measured and calculated by the same person using a consistent standard.

Statistical Analysis

The SPECT and concurrent ceCT findings were compared with the gold standard (histopathological findings, serial radiological or clinical follow-up). True-positive, false-positive, true-negative and false-negative cases were defined as previously reported [5]. According to these results, the sensitivity, specificity and positive and negative predictive values of $^{99\text{m}}\text{Tc}$ -3PRGD2 were calculated. Both lesion-based and patient-based analyses were performed. Spearman's rank correlation (r_s) was carried out to evaluate the relationship between the tumor-to-background ratios of the lesions in the positive 3PRGD2 cases and their serum CEA levels. SPSS version 13.0 (SPSS Inc., Chicago, Ill., USA) was used for statistical analysis.

Results

Of the 28 patients, recurrences were identified in 20 (71.4%), with a total of 26 lesions. Of the 26 lesions, 15 (57.7%) were confirmed by histopathological findings and the remaining 11 (42.3%) by serial radiological or clinical follow-up as given in table 1. All of the patients with recurrences were asymptomatic, and the presence of the lesions was not detected by taking the patient's history or through physical examination before $^{99\text{m}}\text{Tc}$ -3PRGD2 SPECT.

Table 2. ^{99m}Tc-3PRGD2 SPECT true-positive findings (n = 12 cases with 16 lesions)

No.	Origin of tumor	CEA at SPECT, ng/ml	Recurrent site	Follow-up, months	Type of evidence
1	Stomach	5.8	Lymph node	11.6	Biopsy
2	Stomach	11.5	In situ recurrence	8.7	Postoperative pathology
3	Lung	36.1	Lung	15.4	Biopsy
4	Lung	9.4	Pleura	9.1	Biopsy
5	Lung	16.2	Lung	7.4	Biopsy
6	Breast	8.2	Lung	12.3	Biopsy
7	Breast	17.9	Bone	10.0	ceCT
8	Breast	33.5	Bone	16.8	ceCT
9	Colon	13.6	Lymph node	18.2	Biopsy
10	Colon	14.8	Lymph node	13.7	Biopsy
11	Colon	10.2	Lymph node, lung and vertebra	11.5	Postoperative pathology and ceCT
12	Colon	12.2	Lung	10.9	Postoperative pathology

Of the 20 patients with recurrences, 12 (60%) were correctly identified by ^{99m}Tc-3PRGD2 SPECT, with a total of 16 lesions detected (table 2). Of the 16 lesions, all 4 (25%) lymph node recurrences, 1 in the cervical region and 3 in the mediastinal region, were successfully distinguished. Seven (43.75%) thoracic lesions, including 6 lung lesions and 1 pleura lesion, were detected and confirmed by biopsy or postoperative pathology. The 4 (25%) osteoblastic lesions were identified and confirmed by subsequent radiological examinations. The remaining 1 (6.25%) in situ recurrence was proved by postoperative pathology (fig. 1). The median diameter of the lesions was 3.3 cm (range 0.9–12.6). The serum CEA levels of these 12 patients are given in table 2. There was no correlation between the CEA levels and the tumor-to-background ratios of the 16 lesions ($r_s = 0.53$, $p > 0.05$).

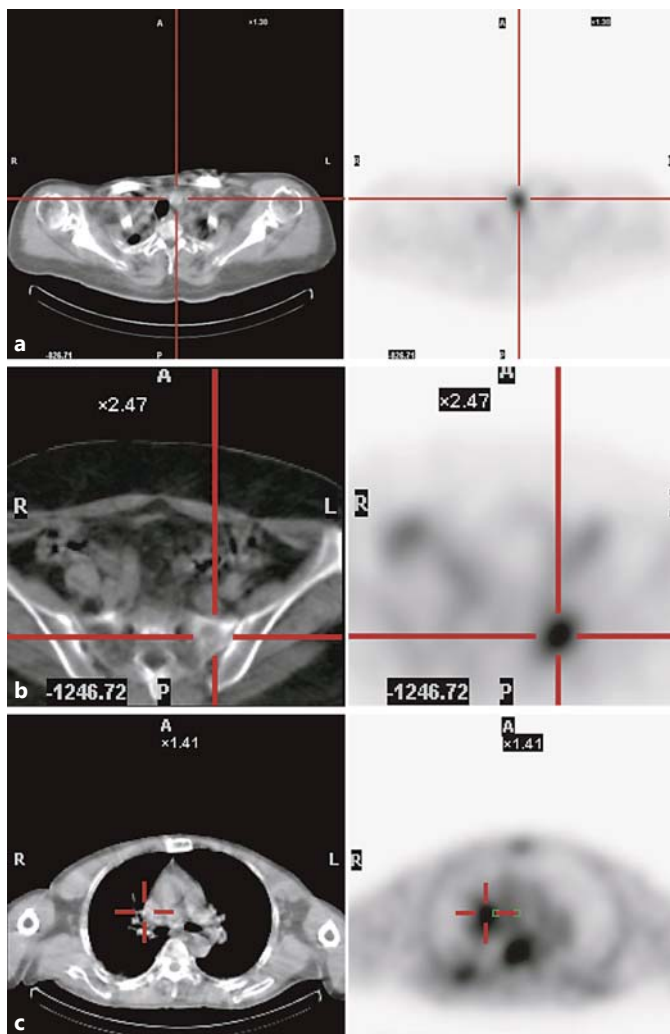
^{99m}Tc-3PRGD2 SPECT had 8 true-negative and 8 false-negative results. No false-positive case was observed. The 8 true-negative cases, 2 gastric cancer, 1 ovarian cancer, 1 lung adenocarcinoma and 4 colon cancer, were followed up for at least 15.3 months, and no detectable recurrence was seen on serial radiological examinations or during clinical follow-up. The median CEA level of these patients decreased spontaneously from 6.5 to 3.2 ng/ml during the follow-up period. Altogether, 10 lesions were detected in the 8 false-negative cases, and the median diameter of the lesions was 2.2 cm (range 1.3–7.6). Two of the false-negative cases had in situ recurrences, 2 were with metastases in the abdominal cavity, and the other 4 were with liver metastasis (fig. 2). The details of these 8 patients are shown in table 3. All 4 metastatic liver cases were not discovered with ^{99m}Tc-

3PRGD2 SPECT, indicating that it was difficult to detect lesions in the liver.

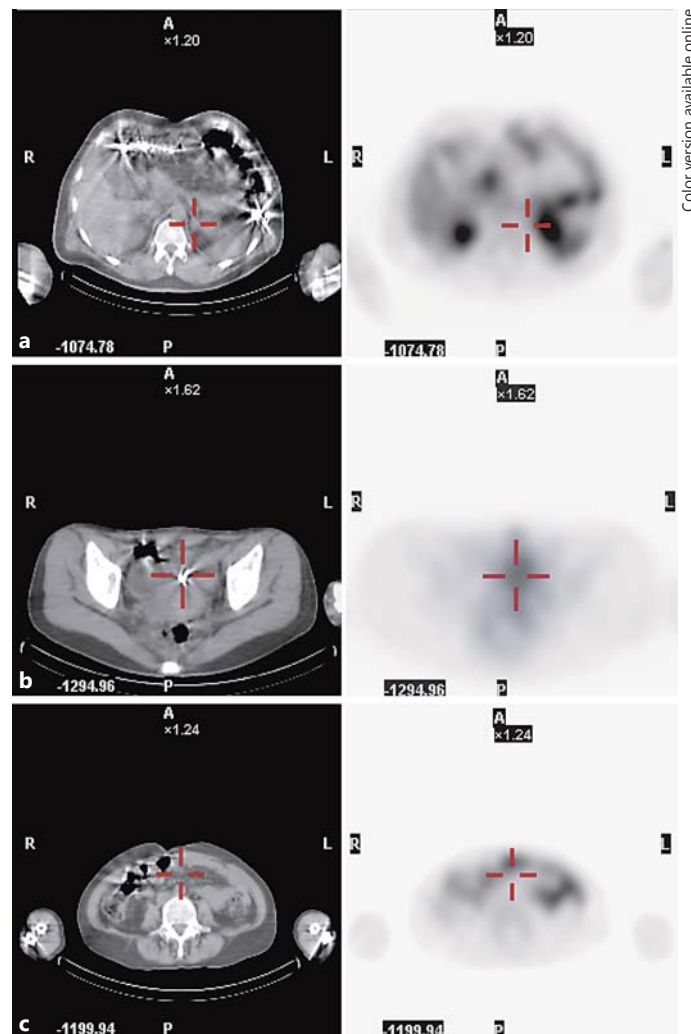
In the patient-based analysis, the sensitivity and specificity of ^{99m}Tc-3PRGD2 SPECT in the detection of cancer recurrence were calculated as 60 and 100%, respectively. The positive and negative predictive values were 100 and 50%, respectively. In the lesion-based analysis, 3PRGD2 values were 100% out of 26 recurrent foci in the whole patient group (table 2). The respective sensitivity and specificity of ^{99m}Tc-3PRGD2 SPECT were 62 and 100% in the lesion-based evaluation. The median CEA level in the true-positive patients at the time of SPECT was 12.9 ng/ml (range 5.8–36.1). The ceCT did not detect the recurrences in 8 patients. The sensitivity and specificity of the ceCT were 60 and 75%, respectively, and the positive and negative predictive values were 86 and 40%, respectively. In the lesion-based evaluation, the sensitivity and specificity of the ceCT were 70 and 84%.

Discussion

In this study, all the lesions in the lungs were successfully distinguished by ^{99m}Tc-3PRGD2 SPECT. This high sensitivity for the detection of thoracic metastasis might be due to the low normal uptake of ^{99m}Tc-3PRGD2 in the thoracic region [12], as the biodistribution of ^{99m}Tc-3PRGD2 in different regions is the most important factor influencing the detection efficiency of SPECT [8]. Though the sensitivity in detecting lung lesions observed in this group of patients is similar to that of our previous report [12], the specificity is obviously better. This difference



Color version available online



Color version available online

Fig. 1. True-positive images of ^{99m}Tc -3PRGD2 SPECT. **a** A colon cancer case with lymph node recurrence in the mediastinal region. **b** A breast cancer case with bone recurrence. **c** A colon cancer case with recurrence in the hilar, lung and vertebral regions.

Fig. 2. False-negative images of ^{99m}Tc -3PRGD2 SPECT. **a** An adrenal metastasis in the lymph node confirmed by postoperative pathology. **b** An in situ recurrence of colon cancer confirmed by endoscopy biopsy. **c** Abdominal cavity metastases confirmed by cytological examination.

Table 3. ^{99m}Tc -3PRGD SPECT false-negative findings (n = 8 cases with 10 lesions)

No.	Origin of tumor	CEA at SPECT, ng/ml	Recurrent site	Follow-up, months	Type of evidence	CEA at final diagnosis
1	Stomach	5.2	Adrenal metastasis	12.6	Postoperative pathology	11.8
2	Stomach	16.4	Liver metastasis	9.5	ceCT	19.2
3	Ovarian	17.7	Abdominal cavity metastases	11.6	Cytological examination	45.9
4	Ovarian	35.9	Abdominal cavity metastases	7.7	Clinical evolution	-
5	Colon	11.4	In situ recurrence	16.3	Endoscopy biopsy	25.6
6	Colon	18.6	Liver metastasis	6.2	Clinical evolution	-
7	Colon	14.5	Liver metastasis	7.9	ceCT	29.4
8	Colon	8.8	Liver metastasis	8.1	ceCT	37.0

might be due to the difference in the origin of the 2 groups of patients. While lung lesions were suspicious in the former group, the existence of malignancies was confirmed in this group, which definitely raised the odds of malignant lesions.

The diagnosis of malignant recurrence in normalized or moderately enlarged lymph nodes remains a problem for all structural or anatomic imaging modalities [13]. FDG PET is reported to be useful in detecting metabolic alterations in tumor-infiltrated lymph nodes [14, 15]. However, the cost and radiation risk are greater disadvantages of ^{18}F -FDG imaging when compared with SPECT imaging. $^{99\text{m}}\text{Tc}$ -3PRGD2 SPECT successfully identified all 4 cases of lymph node metastases, including 1 gastric cancer and 3 colon cancers, with a total of 4 lesions in the cervical and mediastinal regions. This indicates that $^{99\text{m}}\text{Tc}$ -3PRGD2 SPECT can effectively differentiate between benign and malignant lymph nodes. Although most of the organs located in the cervical and mediastinal regions have a moderate-to-intense accumulation of $^{99\text{m}}\text{Tc}$ -3PRGD2 making the assessment of metastases in these regions relatively challenging, the recurrent lesions in the cohort of patients included in this study were successfully recognized with the assistance of the coregistered CT.

All of the 3 bone recurrences with 4 lesions were successfully identified by $^{99\text{m}}\text{Tc}$ -3PRGD2 SPECT, which were subsequently confirmed by the coregistered CT images. This suggests that the imaging agent $^{99\text{m}}\text{Tc}$ -3PRGD2 might be sensitive to (mainly osteogenic) bone metastasis. The ability of $\alpha_v\beta_3$ imaging in recognizing tumors with low glycolytic activity was previously reported in the study of Aide et al. [16], in which $\alpha_v\beta_3$ imaging discovered mature teratoma in patients with negative FDG PET scans. Moreover, in Zhao et al. [17], all the differentiated metastatic thyroid cancer lesions were found to be positive on the $^{99\text{m}}\text{Tc}$ -3PRGD2 SPECT images. These metastatic lesions were traced by $^{99\text{m}}\text{Tc}$ -3PRGD2 because of their highly neovascularized tissues owing to the comparatively differentiated tumor cells [18]. Thus, we speculate that imaging of $\alpha_v\beta_3$ expression might produce a better result for lesion identification and tumor staging in malignancies with low FDG uptake. Moreover, unlike the studies with FDG, our study showed that there was no correlation between the 3PRGD2 uptakes of the recurrent lesions with the elevated CEA levels. As the tracer 3PRGD2 is a potential parameter of angiogenesis in tumors with $\alpha_v\beta_3$ expression, our results suggest that the $\alpha_v\beta_3$ expression and CEA secretion are not closely correlated in tumor lesions [2].

Two of the 6 false-negative cases were ovarian cancer patients with metastases in the abdominal cavity. This suggests that 3PRGD2 imaging, similarly to FDG, also has difficulty in identifying the disseminating lesions secreting mucus [19]. In addition to that, none of the 4 liver lesions in this cohort of patients was detected, indicating that lesions in the liver are difficult to be identified by 3PRGD2 SPECT. This result is similar to that in the study by Beer et al. [20] on the biodistribution and dosimetry of ^{18}F galacto-RGD in cancer patients. The unsatisfactory detection performance might be caused by the relatively high background activity in the liver, as these authors suggest.

As reported, ^{18}F -FDG PET can identify substantially more lesions than 3PRGD2 SPECT does [21, 22]. This is verified by the results of the present study. In our patient group, only 12 out of 20 patients with recurrences, with 16 out of 26 lesions being metachronous malignancies, were detected by the 3PRGD2 scan. The sensitivity of $^{99\text{m}}\text{Tc}$ -3PRGD2 SPECT was obviously lower than that of FDG PET in either patient-based or lesion-based evaluation. Compared with FDG PET, which remains superior for the primary staging of cancer patients, $^{99\text{m}}\text{Tc}$ -3PRGD2 SPECT holds the advantage of being broadly available and may provide additional information for the planning and response evaluation of antiangiogenic therapies [17]. Moreover, the primary intention for the development of the RGD tracer was not to replace ^{18}F -FDG or to improve tumor staging but, rather, to create a tool for the molecular imaging of processes related to $\alpha_v\beta_3$ expression.

One limitation of this study was the small number of patients enrolled. The results obtained here should be confirmed by follow-up studies with more patients. Besides, the results would be more convincing if FDG PET and 3PRGD2 SPECT were performed simultaneously for comparison. In this study, ceCT, the conventional imaging technique in clinics, was used for contrast. Further studies are needed to compare the uptake of $^{99\text{m}}\text{Tc}$ -3PRGD2 and ^{18}F -FDG in the lesions.

Conclusion

In the posttherapy surveillance of malignant recurrences in the studied patients with unexplained increased CEA levels, $^{99\text{m}}\text{Tc}$ -3PRGD2 SPECT provided positive findings in 12 of the 20 patients with documentable disease on biopsy and/or intermediate-term clinical follow-up. Although the detection rate was not satisfactorily high, the specificity of 3PRGD2 imaging was

100%. The high positive predictive value for a positive SPECT result supports the clinical utility of ^{99m}Tc -3PRGD2 in confirming recurrences. Further studies are necessary to assess the impact of the technique on patient survival.

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