Original Article

Theranostics potential of somatostatin receptor scintigraphy in both small and non-small cell lung cancers: a preliminary study

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Background: The expression of somatostatin receptors (SSTRs) has been shown on the surface of some lung cancer cells according to the previous studies. The purpose of this study was to evaluate the effectiveness of somatostatin receptor scintigraphy (SRS) with ^{99m}Tc-octreotide as an SSTR analogue for staging primary lung cancer (LC) patients with positive contrast-enhanced computed tomography (CECT) and histologically proven LC.

Methods: In this study, primary LC patients with positive CECT and histologically confirmed LC underwent SRS. The patients were classified into small-cell LC (SCLC) and non-SCLC (NSCLC) based on histopathology. NSCLC patients were further categorized into squamous cell carcinoma (SCC), adenocarcinoma, and large cell carcinoma (LCC). For comparison of CECT and SRS images, the lung was divided into five anatomical lobes: right upper lobe (RUL), right middle lobe (RML), right lower lobe (RLL), left upper lobe (LUL), and left lower lobe (LLL). Each lung portion was considered positive if a non-physiological mass in computed tomography (CT) or radiotracer uptake in scintigraphy was observed.

Results: A total of 28 patients with a median age of 74.5 (range, 48–90) years, including 17 males (60.7%) and 11 females (39.3%), underwent SRS. Of the 28 patients, 3 cases were SCLC and 25 cases were NSCLC, with 19 cases of SCC and 6 cases of adenocarcinomas. Of the 28 cases, 26 patients (93%) showed positive SRS. The median Krenning score (KS) was 1, with a range of 1–2. The ranges of accuracy, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of scintigraphy in each lobe were obtained at 88–100%, 80–100%, 89–100%, 57–100%, and 95–100%, respectively.

Conclusions: Based on these results, it can be concluded that SRS can be considered as an effective non-invasive imaging modality for staging primary LC with high accuracy, sensitivity, and specificity since radiotracer uptake was observed in all types of primary LC. Due to the high SSTR expression according to SRS with ^{99m}Tc-octreotide, peptide receptor radionuclide therapy (PRRT) might be considered as an alternative therapeutic option for LC patients. However, further studies with a large sample size are needed to confirm these findings.

Keywords: Somatostatin receptor scintigraphy (SRS); theranostics; ^{99m}Tc-octreotide; lung cancer (LC); contrast-enhanced computed tomography (CECT)

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Introduction

Primary lung cancer (LC), also known as lung carcinoma, is a malignancy of the lung that is classified into two main types: small-cell LC (SCLC) and non-SCLC (NSCLC). SCLC is the most aggressive and accounts for about 10–15% of all cases of LC. NSCLC, which is the most common type of LC, accounts for about 85% of all cases and is further classified into adenocarcinomas, squamous cell carcinomas (SCCs), and large cell carcinomas (LCCs). The most common available treatment procedures for managing LC are surgery, radiotherapy, and chemotherapy (1). The overall 5-year relative survival rate for LC is 15.9%. However, this rate increases to about 50% for patients in the early stages of primary LC without lymph node involvement and metastasis. Therefore, early diagnosis is crucial in the management of patients (2).

Anatomical imaging modalities, such as chest X-ray, magnetic resonance imaging (MRI), and computed tomography (CT), are usually used for the evaluation of LC. While these modalities are considered the first choice in suspected LC, they only provide morphological features of lung lesions and show slight biological features. Therefore, they have a high percentage of equivocal diagnosis. As a result, researchers are focusing on molecular imaging methods, such as radiopharmaceuticals, which can target malignant lung lesions (3,4).

^{18}F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET) has widely been used for the diagnosis and follow-up of patients with LC. However, due to its high cost and unavailability, inflammatory and infectious pulmonary diseases can show ^{18}F-FDG uptake, leading to false positive results. Another radiopharmaceutical used for the diagnosis of LC is ^{99m}Tc-labeled hexakis-2-methoxyisobutylisonitrile (^{99m}Tc-MIBI). This radiopharmaceutical has shown a high detection rate (about 90%) and sensitivity (85–90%) as well as a specificity of 75–100% (5,6).

According to the previous studies, expression of somatostatin receptors (SSTRs) has been shown on the surface of some LC cells (3,7-9). Naturally, SSTRs are expressed in neuroendocrine tumors (NETs) (7,10). Due to expression of SSTRs on some LC cells, the use of radiolabeled SSTR analogues as a diagnostic and therapeutic option has been evaluated in the previous studies. Although the use of radiolabeled SSTR analogues, clinically, may have no significant difference in detection of lung malignancy in comparison with other radiopharmaceuticals and even other imaging modalities, they have an advantage, which is their theranostics features i.e., both therapeutic and diagnostic radiotracers can be radiolabeled to SSTR analogues and targeted radionuclide therapy can be performed for the previously imaged disease simultaneously (11). Several radiolabeled SSTR analogues have been assessed including ^{99m}Tc-depreotide (12), ^{111}In-pentetreotide (3), ^{99m}Tc-octreotide (13), and newly, ^{68}Ga-DOTATATE (14) as diagnostic agents, and ^{188}Re-depreotide, ^{177}Lu-DOTATATE (15) as therapeutic agents.

The aim of this study is to evaluate the effectiveness of SSTR scintigraphy (SRS) with ^{99m}Tc-octreotide as a diagnostic SSTR analogue for staging primary LC patients with positive contrast-enhanced CT (CECT) and histologically proven LC. We present this article in accordance with the STARD reporting checklist (available at https://tro.amegroups.com/article/view/10.21037/tro-23-22/rc).

Highlight box

Key findings

- In this study, somatostatin receptor (SSTR) expression was observed in all types of lung cancer (LC), including small-cell LC (SCLC) and non-SCLC (NSCLC), using SSTR scintigraphy (SRS) with ^{99m}Tc-octreotide. Therefore, SRS can be considered an effective and non-invasive imaging method for accurately staging primary LC, with high accuracy, sensitivity, and specificity. Additionally, peptide receptor radionuclide therapy (PRRT) could be an alternative treatment option for LC patients. However, further studies with a larger sample size are necessary to validate these findings.

What is known and what is new?

- According to previous studies, SSTR expression has been confirmed in SCLC, but there is limited research on NSCLC.
- SSTR expression was observed in both SCLC and NSCLC. Therefore, SRS and PRRT can be considered non-invasive options for managing LC.

What are the implications, and what should change now?

- Due to the high SSTR expression observed with SRS using ^{99m}Tc-octreotide, PRRT could be considered as an alternative therapeutic option for LC patients. However, further studies with a larger sample size are needed to confirm these findings.

Methods

Between June 2018 and December 2020, 28 primary LC patients who tested positive for CECT and were histologically diagnosed with LC underwent SRS. The patients were classified into SCLC and NSCLC based

on histopathologic results. NSCLC patients were further classified into SCC, adenocarcinoma, and LCC. All patients were in the staging step and did not undergo any conventional therapy. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013), and approved by the Ethics Committee of Bushehr University of Medical Sciences (IR.BPUMS.REC.1398.083). Informed consent was obtained from patients.

Chest CT

All patients underwent CECT (Lightspeed 16, GE Medical Systems, GE Healthcare, Anaheim, CA, USA) with the usual protocol [collimation 16 mm × 1.5 mm, reconstruction interval (RI) =1 mm, reconstruction width (RW) =2 mm, 120 kV, 150 mAs, rotation time 0.75 seconds, pitch 1.5] within 2 weeks before ^{99m}Tc-octreotide scintigraphy. Contrast agent was injected at 2 mL/kg body weight at a rate of 4 mL/s. The chest scan was started 35 seconds after the contrast injection. The images were reviewed by two expert radiologists.

99mTc-octreotide scintigraphy

For SRS, ^{99m}Tc-octreotide (Pars Isotope Co., Tehran, Iran) was prepared according to the manufacturer's instructions. Scintigraphy was acquired within 2 to 4 hours after intravenous injection of 740 MBq (20 mCi) ^{99m}Tc-octreotide with a dual-head gamma camera [Philips (ADAC) Vertex Plus, Milpitas, CA, USA] equipped with a low-energy high-resolution collimator, and the energy window was set at 140 keV ±20%. All patients underwent examination with a whole-body scan (WBS) and chest SPECT. WBS was acquired in anterior and posterior views with a matrix size of 256×1,024 and a speed of 15 cm/min. The single-photon emission CT (SPECT) was acquired with a matrix size of 128×128 in 360-degree rotation and 64 projections (20 seconds/projection). Image reconstruction was performed using an iterative algorithm without attenuation correction.

All images were reviewed by two nuclear medicine specialists. Any non-physiological and focal radiotracer accumulation higher than the background was considered a suspicious LC lesion. For semi-quantitative analysis of SRS images, the Krenning score (KS) was used, which is ranged from 0–4 (0, none; 1, much lower than the liver; 2, slightly less than or equal to the liver; 3, greater than the liver; 4, greater than the spleen) according to the radiotracer uptake in the lesion.

Image interpretation

To compare CECT and SRS images, the lung was divided into five portions, including the right upper lobe (RUL), right middle lobe (RML), right lower lobe (RLL), left upper lobe (LUL), and left lower lobe (LLL). Each lung portion was considered positive if a non-physiological mass in CT or radiotracer uptake in scintigraphy was observed.

Statistical analysis

All data were presented as median with a range. The chi-square test was used to evaluate categorical variables, and a P value <0.05 was considered statistically significant. The Wilcoxon test was used to assess statistical significance between groups. The values of accuracy, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) in different lobes of the lung were calculated for ^{99m}TC-octreotide scintigraphy (the result of CECT was considered as the gold standard). Data analysis was performed using SPSS (Windows software version 20, SPSS, IBM Corp., Armonk, NY, USA).

Results

In this study, 28 histopathologically proven primary LC patients with positive CECT and a median age of 74.5 (range, 48–90) years, including 17 males (60.7%) and 11 females (39.3%), underwent SRS with ^{99m}Tc-octreotide. According to the histopathology results, out of 28 patients, 3 cases were SCLC and 25 cases were NSCLC, of which 19 cases were SCC, and 6 cases were adenocarcinomas. According to CT results, the median diameter of tumors was 5 cm with a range of 2–9 cm. Out of 28 cases, 26 patients (93%) showed positive SRS. One case with adenocarcinoma and one with SCC showed normal SRS. The median KS was 1 with a range of 1–2. Baseline characteristics of the patients are presented in *Table 1*.

Table 2 shows the detailed comparison of CECT and SRS in different lobes of the lung, which showed no significant difference (P>0.05). In RUL, out of 28 cases, 27 cases showed the same results in both modalities, but one case showed positive CECT and negative SRS. In LUL, both modalities showed the same results in all cases. In RML, three cases showed negative CECT and positive scintigraphy, and one case showed positive CT and negative SRS. In RLL, one case showed negative CECT and positive scintigraphy, and one case showed positive CECT and

negative scintigraphy. Finally, in LLL, one case showed negative CECT and positive scintigraphy. Additionally, *Table 3* showed the values of accuracy, sensitivity, specificity, PPV, and NPV in different lobes of the lung for ^{99m}TC-octreotide scintigraphy.

Furthermore, no significant difference was obtained in evaluating the effect of several factors, including age, sex, tumor size, and type of tumor on scintigraphy results and KS (P>0.05). *Figure 1* presents the images of a patient with SCC.

Table 1 Baseline characteristics of the patients

Characteristics	Value (n=28)
Sex, n (%)	
Male	17 (60.7)
Female	11 (39.3)
Age (years)	
Median	74.5
Range	48–90
Type of cancer, n (%)	
SCLC	3 (10.7)
NSCLC	25 (89.3)
SCC	19 (67.9)
Adenocarcinoma	6 (21.4)
KS	
Median	1
Range	1–2
Tumor size (cm)	
Median	5
Range	2–9

SCLC, small-cell lung cancer; NSCLC, non-small-cell lung cancer; SCC, squamous cell carcinoma; KS, Krenning score.

Discussion

In recent years, the development and use of theranostic agents in oncology has increased for the management of several cancer types. Numerous theranostic agents have been studied in the last few decades. Radiolabeled SSTR analogues, such as ^{68}Ga/^{177}Lu-DOTATATE, are one of the most common theranostic agents for the management of NETs. This approach has become a promising method with high detection rates and therapy efficacy in recent years (16-19). In addition to NETs, various studies have been performed on the use of SSTR analogues in the management of non-NET tumors such as medullary thyroid cancer, neuroblastoma, and glioblastoma, with low toxicity (10,20-27).

Various studies have suggested that LC cell might generate and secrete somatostatin (3,12,28-30), therefore, we performed a study on the expression of SSTR for staging various types of LC, including SCLC and NSCLC with positive CECT and proven histopathology. For the evaluation of SSTR expression, all patients underwent ^{99m}Tc-octreotide scintigraphy. The lung was classified into five main lobes: RUL, RML, RLL, LUL, and LLL. Then, the results of the scintigraphy were compared with CECT for each lobe. In our experience, all ^{99m}Tc-octreotide scans were positive irrespective of the histological type of the tumor and whether or not they were NET. The ranges of accuracy, sensitivity, specificity, PPV, and NPV of scintigraphy in each lobe were obtained and were 88–100%, 80–100%, 89–100%, 57–100%, and 95–100%, respectively. According to the previous studies, the accuracy and sensitivity of SRS compared to CT were about 65% (3) and 90–100% (4,31) for primary lung tumors, respectively. Wang *et al.* evaluated the clinical efficacy of a combination of CT and SRS with ^{99m}Tc-octreotide in differentiating cancer from benign pulmonary nodules (9). They showed that ^{99m}Tc-octreotide uptake was significantly higher in LC compared to benign

Table 2 The comparison of both CECT scan and ^{99m}Tc-octreotide scintigraphy in different lobes of lung

Scintigraphy	CECT									
	RUL		RML		RLL		LUL		LLL	
	Positive	Negative	Positive	Negative	Positive	Negative	Positive	Negative	Positive	Negative
Positive	6	0	3	3	7	1	9	0	2	1
Negative	1	21	1	21	1	19	0	19	0	25

CECT, contrast-enhanced computed tomography; RUL, right upper lobe; RML, right middle lobe; RLL, right lower lobe; LUL, left upper lobe; LLL, left lower lobe.

Table 3 The values of accuracy, sensitivity, specificity, PPV, and NPV in different lobes of lung for ^{99m}TC-octreotide scintigraphy

Value	RUL	LUL	RML	RLL	LLL
Accuracy (%)	96	100	88	93	96
Sensitivity (%)	88	100	80	89	100
Specificity (%)	100	100	89	95	96
PPV (%)	100	100	57	88	66
NPV (%)	95	100	96	95	100

PPV, positive predictive value; NPV, negative predictive value; RUL, right upper lobe; LUL, left upper lobe; RML, right middle lobe; RLL, right lower lobe; LLL, left lower lobe.

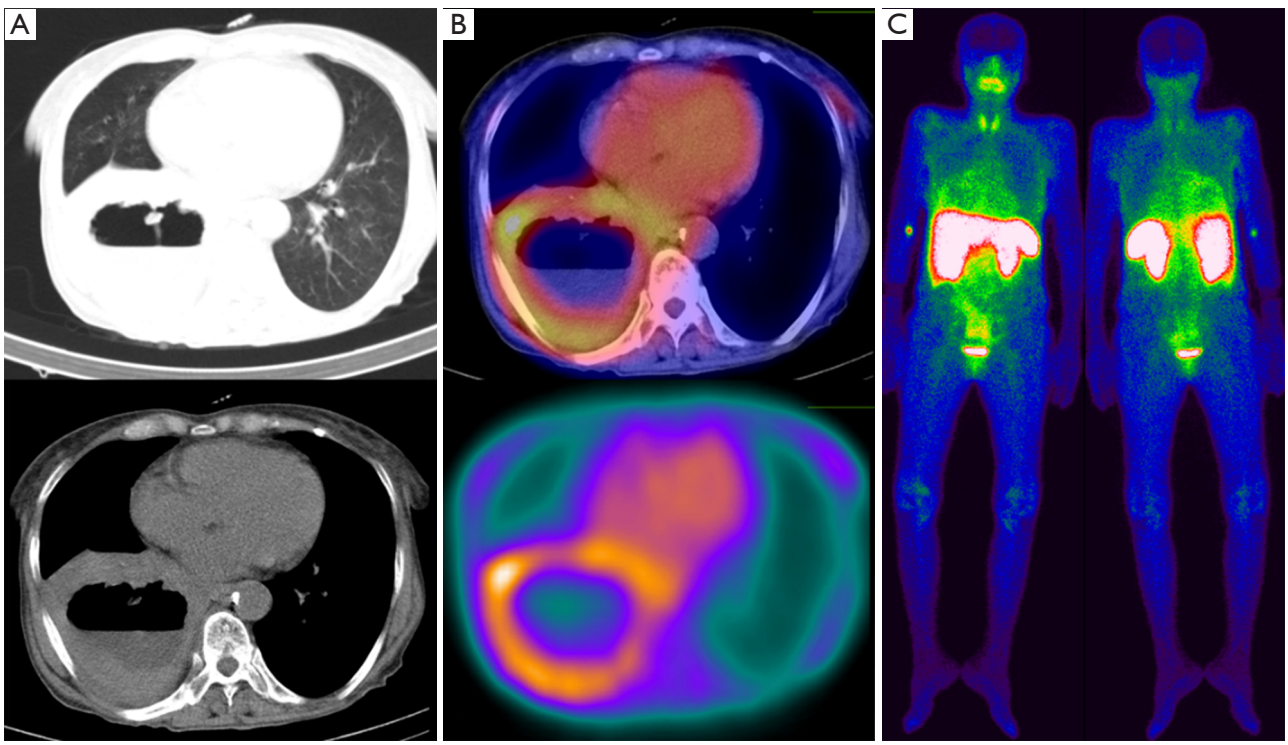

Figure 1 A 73-year-old female with a lesion in the RLL measuring 75 mm × 65 mm according to lung CT (A) and histologically proven SCC underwent ^{99m}Tc-octreotide scintigraphy. The scintigraphy revealed radiotracer uptake in the lesion with a KS of 1 and central photopenia (B,C). RLL, right lower lobe; CT, computed tomography; SCC, squamous cell carcinoma; KS, Krenning score.

lesions. The specificity of SRS was 72.7% compared to 63.6% for CT for the diagnosis of pulmonary malignant tumors. When both modalities were used in combination, the specificity was 81.8% (9). Axelsson *et al.* evaluated the diagnostic value of SRS with ^{99m}Tc-depreotide in suspected LC patients (28). Of the 99 evaluated patients, SRS was positive in 62 out of 66 malignancies but was false positive in 16 out of 33 patients with benign lesions. The sensitivity and specificity of ^{99m}Tc-depreotide were 98% and 52%, respectively, for LC (28).

Nowadays, ^{18}F-FDG PET is widely utilized for the diagnosis of LC. In a study, the clinical efficacy of SRS with ^{99m}Tc-octreotide was compared to ^{18}F-FDG PET in the detection of patients with suspected LC. It was indicated that the sensitivity of both ^{99m}Tc-octreotide and ^{18}F-FDG was 100%. However, the specificity, PPV, and NPV of ^{99m}Tc-octreotide were 75.7%, 90.1%, and 100%, respectively, while those of ^{18}F-FDG were 46.1%, 83.8%,

and 100%, respectively (13). The uptake of ^{18}F-FDG in inflammatory and infectious lung diseases in an important disadvantage. According to the mentioned study, SRS showed higher uptake in malignancy compared to benign lesions (13), which could be the advantage of SRS over ^{18}F-FDG for diagnosis of LC.

There are several studies in use of various theranostic agents including chemokine receptor CXCR4 (32), fibroblast activation protein inhibitor (FAPI) (33,34) and SSTR analogues (14,35,36) for management of patients with LC. In a study, the feasibility of CXCR4 in SCLC patients was evaluated by using ^{68}Ga-pentaxifor PET/CT in comparison with ^{18}F-FDG PET/CT and ^{68}Ga-DOTATATE PET/CT. ^{68}Ga-pentaxifor was positive in 80% of patients and showed more lesions with significantly higher tumor-to-background ratios in comparison with ^{68}Ga-DOTATATE PET/CT. Of six patients had both ^{68}Ga-pentaxifor PET/CT and ^{18}F-FDG PET/CT, two patients who were positive on ^{18}F-FDG PET were missed by ^{68}Ga-pentaxifor PET/CT and in the remainder ^{68}Ga-pentixafor detected an equal (n=2) or higher (n=2) number of lesions (32).

In the view of theranostics with SSTR analogues, there are several studies on the use of these as theranostics agents for diagnosis and therapy of several non-gastroenteropancreatic NETs (non-GEP-NETs) with high SSTR expression. We previously reported acceptable efficacy of ^{68}Ga/^{177}Lu-DOTATATE for management of patients with Non-GEP-NETs including neuroblastoma (22), prostate cancer (10), high-grade glioma (25,26), meningioma (21), and pituitary adenoma (20) with low toxicity (23,24). Therefore, one of most important advantages of SSTR analogues compared to other diagnostic modalities is their theranostics feature. According to the results of our study indicating uptake of ^{99m}Tc-octreotide and expression of SSTR in all types of primary LCs, therapeutic SSTR analogues such as ^{177}Lu-DOTATATE can be considered as an alternative option in these patients specially in the cases who are refractory to conventional treatments. In a study, Lapa *et al.* evaluated SSTR expression in SCLC with ^{68}Ga-DOTATATE PET/CT revealed that PET/CT was positive in 47% of patients (36). In addition, peptide receptor radionuclide therapy (PRRT) with ^{177}Lu-DOTATATE was performed for four patients with intensive SSTR expression resulted in one partial response and one stable disease (36). Mirvis *et al.* evaluated efficacy of PRRT with ^{90}Y-DOTATATE and/or ^{177}Lu-DOTATATE in advanced metastatic bronchial NETs demonstrating partial response in 10 patients (40%), stable disease in 12 patients (48%) and progressive disease in 2 patients (8%) (37). A further patient (5%) died after two cycles without any follow-up scan and is also classified as having progressed (37).

Our study has several limitations. First, the patients should be classified into different groups according to their cancer types for evaluation of SSTR expression but it was impossible due to low sample size. Second, lack of SPECT/CT for better anatomical assessment. Third, unavailability of PET is another limitation of our study because in the view of theranostics, for more accurate evaluation of SSTR expression in primary LC, it is better to use ^{68}Ga-DOTATATE instead of SRS since the low spatial resolution of gamma camera may cause lesions less than 2 cm in diameter not detected in planar imaging, specially.

Conclusions

As radiotracer uptake was observed in all types of primary LC, it can be concluded that SRS with ^{99m}Tc-octreotide is an effective non-invasive imaging modality for diagnosing primary LC with high accuracy, sensitivity, and specificity. Due to the high SSTR expression in LC according to SRS with ^{99m}Tc-octreotide, PRRT could be an alternative therapeutic option for LC patients. However, further studies with a larger sample size are needed.

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Footnote

Reporting Checklist: The authors have completed the STARD reporting checklist. Available at https://tro.amegroups.com/article/view/10.21037/tro-23-22/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tro.amegroups.com/article/view/10.21037/tro-23-22/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013), and approved by the Ethics Committee of Bushehr University of Medical Sciences (IR.BPUMS.

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