Radioiodinated Somatostatin Analog Scintigraphy in Small-Cell Lung Cancer

Dirk J. Kwekkeboom, Eric P. Krenning, Willem H. Bakker, H. You Oei, Ted A. W. Splinter, G. Siang Kho, and Steven W. J. Lamberts

Departments of Nuclear Medicine, Medicine, Oncology, and Pulmonology, University Hospital Dijkzigt, Rotterdam, The Netherlands

Somatostatin receptors have been characterized on biopsy specimens from small-cell lung carcinoma (SCLC) and on cultured human SCLC cells. We recently described the in vivo visualization of various somatostatin receptor-positive tumors, such as carcinoids and endocrine pancreatic tumors, after injection of ^{123}I-Tyr-3-octreotide, a radiolabeled somatostatin analog. In the present study, this imaging procedure using ^{123}I-Tyr-3-octreotide is reported in 11 patients with lung tumors. In five of eight patients with SCLC (63%), we were able to demonstrate tumor deposits using ^{123}I-Tyr-3-octreotide scintigraphy. Unexpected metastases were found in two patients. In one of three patients with SCLC in whom tumor was not visualized, nonvisualization may have been caused by tumor necrosis and recent radiotherapy. In one of two patients with malignant small-cell tumors as described by Askin, the neoplasm was visualized. Like SCLC, these tumors are thought to derive from neuroendocrine cells. In one patient, a squamous-cell carcinoma and a bronchial adenoma were not visualized. We conclude that in the majority of patients with SCLC, the tumor and its metastases can be visualized using ^{123}I-Tyr-3-octreotide scintigraphy. However, the value of this new technique in terms of specificity and sensitivity requires further studies in a larger group of patients.

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Small-cell lung cancer (SCLC) accounts for about 25% of all lung cancers. The vast majority of these tumors have spread at the time of diagnosis, and despite chemotherapy and irradiation the 2-yr survival is poor, ranging from 5% to 15% (*1*).

Staging procedures to differentiate between limited and extensive disease include physical examination, chest x-ray, CT scan or ultrasound of the upper abdomen, isotope bone scanning and unilateral or bilateral bone marrow biopsy. A simpler and less burdensome procedure would be most welcome.

Somatostatin receptors have been characterized on biopsies from SCLC and on cultured human SCLC, both in vitro and on tumors grown in athymic nude mice (*2–4*). We recently described the in vivo visualization of various somatostatin receptor-positive tumors after injection of ^{123}I-Tyr-3-octreotide, a radiolabeled somatostatin analog (*5–7*). In the present study, we report on the in-vivo visualization of SCLC using ^{123}I-Tyr-3-octreotide scintigraphy.

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For reprints contact: D.J. Kwekkeboom, MD, PhD, University Hospital Dijkzigt, L 442, 40 Dr. Molewaterplein, 3015 GD Rotterdam, The Netherlands.

PATIENTS AND METHODS

Patients

Patients with lung cancer in whom ^{123}I-Tyr-3-octreotide scintigraphy was performed were studied. In every patient, histologic confirmation of the diagnosis was obtained. All patients gave informed consent to participate in the study, which was approved by the ethical committee of our hospital.

Methods

The somatostatin analog, Tyr-3-octreotide (204-090), was obtained from Sandoz, Basel, Switzerland. Tyr-3-octreotide was iodinated as described elsewhere (*7*).

Scintigraphy with ^{123}I-Tyr-3-octreotide was performed as previously described (*5–7*). Depending on the result of the labeling procedure and the interval between injection and scintigraphy, the dose of ^{123}I-Tyr-3-octreotide, injected as an intravenous bolus, was 40 MBq in one patient and ranged from 480 to 800 MBq in the others. The usual labeling yield was 70%–80%, and SEP-PAK C18 separations resulted in more than 99% peptide-bound radioiodine, which was injected (*7*). There were no side effects of administration of ^{123}I-Tyr-3-octreotide. Whole-body scintigraphy was done directly after injection, after 1 or 2 hr, and after 24 hr. In one patient, because of his worsening clinical condition, a 24-hr image was not made.

RESULTS

Patient features and results of ^{123}I-Tyr-3-octreotide scintigraphy are listed in Table 1. In five of eight patients with SCLC, abnormal sites of radioactive accumulation were found. In one of two patients with a malignant small-cell tumor of the thoracopulmonary region as described by Askin (*8*), the tumor was also visualized. In one patient, a squamous-cell carcinoma and a bronchial adenoma were not detected on the ^{123}I-Tyr-3-octreotide scintigrams.

In Patient 1, the tumor localizations in the right lung and hilum were visualized up to 1 hr after injection of ^{123}I-

TABLE 1
Patient Data and Results of ^{123}I-Tyr-3-octreotide Scintigraphy

Patient	Age	Sex	Tumor type	Previous/Current therapy	Tumor localizations on octreotide scintigrams
1	60	M	SCLC	None	Right middle lobe and hilum
2	66	F	SCLC	Chemo and RT	Right lower lobe and hilum
3	73	M	SCLC	None	Paramediastinal and right lower lobe
4	76	M	SCLC	None	None
5	67	M	SCLC	RT	None
6	71	F	SCLC	Chemo	Right lower lobe and skull
7	73	M	SCLC	None	Near right clavicle
8	58	M	SCLC	RT	None
9	15	F	Askin	Chemo, RT, and surgery	Right lung; near liver?
10	16	F	Askin	Chemo	None
11	68	M	Squamous-cell and adenoma	None	None

Chemo = chemotherapy and RT = radiotherapy.

Tyr-3-octreotide. However, at 24 hr the concentration of radioactivity at these sites had not increased.

Patient 2, with limited disease, had obtained remission after chemotherapy and radiotherapy, which was interpreted as complete, despite a remaining partial atelectasis of the right lower lobe. Repeated CT scanning, bronchoscopies and biopsies showed narrowing of a segmental bronchus with normal epithelium and absence of tumor cells at microscopy. One month after scintigraphy, which showed abnormal accumulation of radioactivity in the right lung and right hilar region, the patient had a proven relapse of SCLC, accompanied by the syndrome of inappropriate ADH section.

In Patient 3, a tumor in the right bronchus growing into the mediastinum and a smaller tumor extending into the pleura were visualized up to 2 hr after octreotide injection (Fig. 1). Enlarged lymph nodes around the ascending aorta that were detected during CT scanning were not seen at this time. However, at 24 hr postinjection, a region of increased accumulation of radioactivity was seen which included the two spots previously visualized and projected over the heart figure. Physical examination, ultrasound and electrocardiography did not indicate pericarditis.

In Patient 4, an intermediate-type SCLC with multiple bone metastases was not visualized. In Patient 5, the primary lung tumor and liver metastases were not visualized up to 1 hr after octreotide injection. No subsequent images were acquired from this patient.

In Patient 6, the primary tumor accumulated labeled octreotide. An unexpected metastasis in the skull was also found (Fig. 2). CT scanning and bone scintigraphy did not reveal any abnormalities on that or any other spot in the

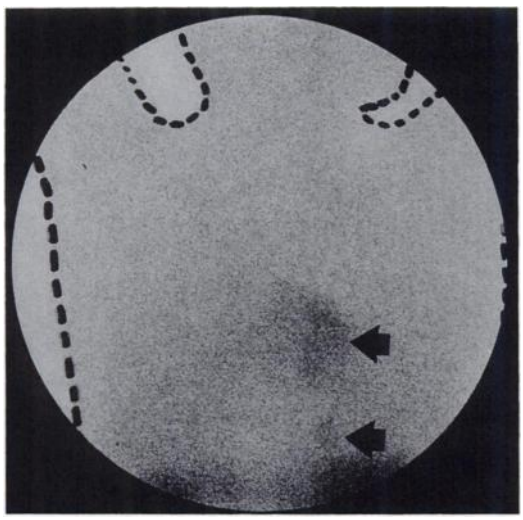

FIGURE 1. Posterior chest image of Patient 3 2 hr after injection of ^{123}I-Tyr^3-octreotide. Arrows indicate tumor sites.

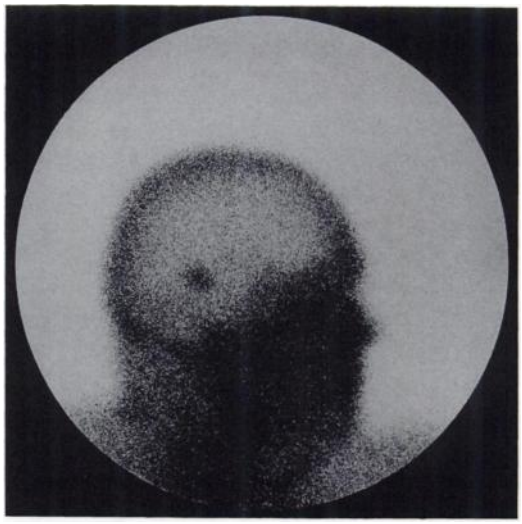

FIGURE 2. Right lateral image of the skull of Patient 6 2 hr after injection of ^{123}I-Tyr^3-octreotide.

skull. However, bone scintigraphy performed 1 yr later demonstrated the presence of skull metastases.

In Patient 7, the primary tumor in the right hilum was not detected using ^{123}I-Tyr-3-octreotide scintigraphy. On the spot near the right clavicle which accumulated radioactivity, ultrasound demonstrated a lymphoma. A fine-needle biopsy from this lymph node contained SCLC.

Patient 8 underwent a mediastinotomy 2 wk before octreotide scintigraphy. A necrotizing SCLC was found without evidence of spread. Up to one day before octreotide scintigraphy, which was negative, the patient was treated with radiotherapy. During this period, the superior vena caval syndrome of which the patient suffered, disappeared.

In Patient 9, a slight accumulation of radioactivity at the site of a thoracal Askin-tumor was found. Below the diaphragm, the liver appeared enlarged and an abnormal band of radioactivity connected the liver with the spleen. CT scanning demonstrated a tumor posterior of the liver, possibly connected with the thoracal tumor. Because SPECT imaging was not performed we could not differentiate liver activity from potential tumor activity below the diaphragm. Octreotide scintigraphy was performed 5 mo after radiotherapy and chemotherapy.

In Patient 10, a soft-tissue tumor, as described by Askin, was not visualized. In this patient, octreotide scintigraphy was performed 2 wk after the last chemotherapy. In Patient 11, a squamous-cell carcinoma and a bronchial adenoma did not accumulate ^{123}I-Tyr-3-octreotide.

DISCUSSION

SCLC is characterized by neuroendocrine properties. These tumors may synthesize and secrete various polypeptide hormones and are thought to arise from amine precursor uptake and decarboxylation (APUD) cells (*9–11*). Like other endocrine tumors that have APUD characteristics (e.g., carcinoids, gastrinomas, and insulinomas), SCLC possesses high affinity somatostatin receptors (*2–4, 12*). In this study we demonstrate that, like other somatostatin receptor-positive tumors, SCLC can be visualized in vivo after injection of ^{123}I-Tyr-3-octreotide.

In five of eight patients with SCLC (63%), we were able to demonstrate tumor deposits using ^{123}I-Tyr-3-octreotide scintigraphy. The period between injection and scintigraphy varied between patients. In our experience, somatostatin receptor-positive tumors in the chest can be visualized at any time from 30 min after the administration of the isotope because the background level of radioactivity is low by that time. Also, the optimal dose seems to be 500–600 MBq, although in one patient a lung tumor could be visualized after the injection of only 40 MBq ^{123}I-Tyr-3-octreotide.

In Patient 1, tumor localizations were visualized only up to 1 hr after injection of the isotope. This may indicate that the visualization of tumor spots in this case was not fully due to receptor binding of ^{123}I-Tyr-3-octreotide. Since the radioactivity in plasma after injection of ^{123}I-Tyr-3-octreotide decreases very rapidly, accumulation of radioactivity at the tumor sites during the first hour only might have been partly caused by abundant perfusion of hypervascularized tumor spots. However, at least some specific receptor binding at these sites must have been present during that period, since the heart and other blood-pooling structures cannot be visualized 1 hr after injection.

As carcinomatous pericarditis was not likely in Patient 3, the enlarged region of isotope concentration found after 24 hr, which projected over the heart, probably indicates lymphatic spread of the tumor in this region. This explanation is in accordance with the CT finding of enlarged lymph nodes around the ascending aorta in this patient.

In Patients 6 and 7, previously unexpected additional tumor sites were found, but in Patient 7 the primary tumor was not visualized. In an in vitro study of a cultured human SCLC cell line, Taylor et al. (*3*) found that after transplantation of tumor cells in nude mice, the number of somatostatin receptors was reduced by 90%, compared with the number during in vitro growth. This could mean that dedifferentiation of these tumors occurs during cell replication in vivo, causing a loss of somatostatin receptors.

In three patients with SCLC, we were not able to visualize the tumor. In one patient (Patient 8), this may have been due to tumor necrosis and recent radiotherapy. The influence of previous chemotherapy and/or radiotherapy on the somatostatin receptor number is unknown, but it might also have influenced the results of the scintigraphy in other patients.

In one of two patients with malignant small-cell tumors as described by Askin (*8*), the neoplasm was visualized. These tumors contain small granules on electron microscopy, and a neuroendocrine origin has been postulated (*8, 13*). To our knowledge, the somatostatin receptor status of biopsy specimens of these tumors has not yet been investigated. Our findings prompt such an investigation.

A squamous-cell carcinoma and a bronchial adenoma were not visualized using ^{123}I-Tyr-3-octreotide scintigraphy. This is in accordance with the fact that no somatostatin (analog) receptors have been found on these tumors (*2*).

Unfortunately, we did not obtain tumor specimens from our group of patients to study somatostatin receptors. However, others have demonstrated that somatostatin receptors are present on SCLC, but not on non-SCLC (*2, 14*).

Somatostatin receptors have been characterized on SCLC biopsies as well as on human SCLC cell lines. Treatment with somatostatin analogs results in a reduced growth of cultured SCLC cells (*4*), possibly as a consequence of reduced secretion from these cells of gastrin-releasing peptide (bombesin-like peptide) or insulin-like growth factor I, compounds shown to be autocrine growth factors in vitro (*15–17*). If treatment with somatostatin

analogs would be considered in patients with SCLC, ^{123}I-Tyr-3-octreotide scintigraphy could be used to select the patients with somatostatin receptor-positive tumors.

In conclusion, in the majority of patients with SCLC, the tumor as well as its metastases can be visualized using ^{123}I-Tyr-3-octreotide scintigraphy. However, the value of this technique in terms of specificity and sensitivity requires further studies in a larger patient group.

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