Somatostatin Receptor Scintigraphy in Small-Cell Lung Cancer: Results of a Multicenter Study

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The aims of this study were to determine the accuracy of somatostatin receptor scintigraphy in the detection of the primary tumor and its metastases in small-cell lung cancer (SCLC) in a large patient population, and to investigate the course of somatostatin uptake in primary tumors during therapy. **Methods:** In a total of 100 patients, 134 examinations were performed. Twenty-seven of the patients were examined before and after chemotherapy. Planar whole-body images were acquired 4 hr and 24 hr after injection of approximately 200 MBq ^{111}In-pentetreotide. SPECT of the thorax was performed after 24 hr. Tumor-to-background (T/B) ratios for the primary tumor were averaged from anterior and posterior projections. **Results:** Compared to conventional investigations, somatostatin receptor scintigraphy (SRS) visualized the primary tumor with varying degrees of uptake in 96% of the examinations. Regional metastases and distant metastases were detected in 60% and 45% of the examinations, respectively. The uptake of the somatostatin analog by the primary tumor was significantly lower in the patients examined during chemotherapy as compared to those examined before treatment (T/B ratio = 1.94 ± 0.79 versus 2.35 ± 0.9, $p < 0.005$). A decrease in T/B ratio was noted in patients with remission at the time of SRS (from 2.40 ± 1.56 to 1.63 ± 0.72, $p < 0.05$). No difference in the pretreatment uptake of octreotide by the primary tumor was identified between patients with tumor progression and those with partial or complete remission. **Conclusion:** Somatostatin receptor scintigraphy has a high sensitivity in the detection of the primary tumor in SCLC but fails in the detection of metastases. Thus, SRS does not provide useful information for staging of SCLC. Since somatostatin uptake by the primary tumor is affected by chemotherapy, it may be used to follow up on the course of SCLC.

Key Words: octreotide; small-cell lung cancer; sensitivity; uptake

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Small-cell lung cancer (SCLC) accounts for about 20% of all malignant lung tumors and for 3%–6% of all malignancies. Its present incidence is 25 cases per 100,000 inhabitants in Europe and 20,000–42,000 cases per year in the United States. The rate of SCLC appears to be increasing (*1–3*).

Due to the poor prognosis of this cancer, various attempts have been made to improve the early detection and the staging procedures.

SCLC originates in Kulchitsky's cells of the bronchial mucosa, which, in turn, derive from the amine precursor uptake and decarboxylation cell system. Somatostatin receptors have been identified in various tissues and tumors, as well as on cells of amine precursor uptake and decarboxylation-omas. On the cells of SCLC, they were demonstrated in 50%–75% of the cell cultures. In this tumor, of the five known subtypes, mainly SR 1 and SR 2 are found (*4,5*).

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On the basis of these findings, efforts have been made to detect these lung tumors and their metastases by scintigraphy using radiolabeled somatostatin analogs. Somatostatin receptor scintigraphy (SRS) was initially performed with [^{123}I-Tyr^3]-octreotide, followed by [^{111}In-DTPA-D-Phe^1]-octreotide (^{111}In-pentetreotide). So far, all SRS studies in SCLC have been performed in limited numbers of patients only (*6–19*).

This study was performed to investigate the role of SRS in the diagnosis of SCLC and its metastases in a larger patient population by compiling the results of four centers. Another question addressed in this study was whether the intensity of octreotide uptake by the primary tumor in the course of the disease might be of any prognostic significance or help to predict response to therapy.

MATERIALS AND METHODS

Patients

A total of 100 patients (25 women, 75 men; age range 41–78 yr; mean age = 59 yr) were included in this study. Thirty-four of these 100 patients underwent scintigraphy twice (Table 1). Among these 34 patients, 27 patients were examined before and after a cycle of chemotherapy. The final diagnosis was confirmed by histology in all patients.

Differentiation between limited and extensive disease was achieved by conventional imaging procedures (radiography, CT of the chest and neck, ultrasound of the abdomen and bone scintigraphy). The findings of these examinations served as a reference standard for SRS.

Methods

The SRS was performed by a standardized method. Whole-body images from anterior and posterior view with speeds of 10 and 7 cm/min, respectively, were acquired 4 and 24 hr after injection of 102–362 MBq (mean = 203 MBq) of ^{111}In-pentetreotide (OctreoScan; Mallinckrodt, Petten, The Netherlands). SPECT of the chest and, in patients with suspicious uptake, SPECT of the abdomen was performed at 24 hr. Optimal emptying of the bowel before the 24-hr examination was ensured. Tomographic data acquisition was performed in 64 projections with a 64 × 64 matrix. The imaging time was 40 sec per projection. We used a double-headed gamma camera (Multispect 2; Siemens, Erlangen, Germany) and large-field-of-view gamma cameras (Bodyscan, Diacam, Siemens, Erlangen, Germany), equipped with medium-energy collimators. The energy windows were set to 172 keV and 242 keV, with a 20% window.

The SPECT images were reconstructed by a filtered backprojection algorithm using a Butterworth filter of order 7 and a cutoff between 0.3 and 0.6 of the Nyquist frequency.

In addition, planar spot images (500 kilocounts per image) of the thorax and/or abdomen were performed in 14 patients. Whole-body, spot and SPECT images, respectively, were analyzed visually by two independent experienced observers.

TABLE 1
Patients with Small-Cell Lung Cancer Included in the Multicenter Trial

Center	No. of patients	No. of patients examined twice	No. of men	No. of women	LD	ED
Berlin	30	11	19	11	9	21
Homburg	19	0	14	5	12	7
Kiel	20	4	15	5	12	8
Magdeburg	31	19	27	4	6	25
Total	100	34	75	25	39	61

LD = limited disease; ED = extensive disease.

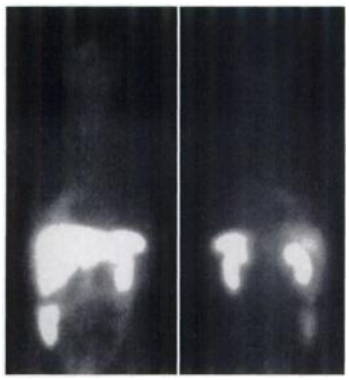

FIGURE 1. Anterior and posterior chest image of a patient with SCLC of the right lower bronchus and right basal retention pneumonia.

The region-of-interest technique was applied to determine the tumor-to-background (T/B) uptake ratio of the radiolabeled somatostatin analog in the primary tumor, whereby geometric means of the anterior and posterior whole-body images were calculated.

Statistical Analysis

Differences in somatostatin uptake between treated and untreated tumors were tested for significance using the Mann–Whitney-U test. Differences in octreotide uptake by the tumor in relation to the tumor stage were tested with Wilcoxon's test. A p value of <0.05 was considered statistically significant.

RESULTS

Detectability of Small-Cell Lung Cancer by Somatostatin Receptor Scintigraphy

Primary Tumor. The results of the 134 SRSs performed in the 100 study patients were compared with the findings of CT obtained shortly before or after scintigraphy. The CT detected the primary tumor in 125 locations. No CT correlate was found in nine patients who were in remission at the time of examination. In comparison, SRS yielded 120 true-positive findings, corresponding to a sensitivity of 96% (Table 2).

There was no significant difference in the detection of the primary tumor by SRS between the 77 untreated and the 57 treated patients.

Of the 120 primary tumors correctly identified by SRS, 117 were detected on planar spot and whole-body images (sensitivity = 94%), and three were by SPECT only. Thus, the sensitivity in the detection of the primary tumor was increased by only 2% using SPECT.

Five patients with an increased uptake of activity in the primary tumor additionally showed diffuse accumulation in adjacent lung regions, which corresponded to retention pneumonias on radiographs (Fig. 1).

Metastases. Metastases from SCLC were divided into regional and distant metastases, with tumor spread to hilar and to the ipsilateral lung, mediastinal or supraclavicular lymph nodes on the side of primary tumor counting as regional metastases.

SRS detected only 60% of the regional metastases and had an even lower sensitivity in the detection of distant metastases (45%), resulting in an overall sensitivity in the detection of metastases of SCLC of 54% (Table 3). There was no difference in detecting and localizing metastases comparing whole-body and planar scans (8 of 8).

The sensitivity of SRS in our study population was lowest for adrenal metastases and for metastases in hilar and extrathoracic lymph nodes. In the liver, both hot spots (n = 8) and cold spots (n = 3) were seen and read as metastases. In one patient with skeletal metastases detected by SRS, the bone scan was normal.

SPECT demonstrated more metastases than did planar scintigraphy especially in mediastinal lymph nodes, lung and liver. This resulted in an increase of sensitivity from 42% to 54% compared to CT (Table 3). Somatostatin receptor scintigraphy did not lead to an upgrading in our patients with limited disease.

Uptake of Indium-111-Pentetreotide in the Primary Tumor

Uptake of the radiolabeled somatostatin analog in the primary lesion varied widely between individual patients (Fig. 2). However, there was no correlation of T/B ratios and the tumor sizes determined by CT (r = 0.2683).

In contrast, a statistically significant difference of octreotide uptake by the primary tumor was seen between the patients who were examined before chemotherapy (77 of 134 investigations) and those who were examined after or during chemotherapy (54 of 134 investigations). The T/B ratios before therapy 2.35 ± 0.91 (range = 1.2–6.1; median = 2.19) were significantly ($p = 0.0016$) higher than those obtained after therapy 1.94 ± 0.79 (range = 1.0–4.6; median = 1.69).

Twenty-seven of the 100 patients included in this study were examined both before and after chemotherapy. Of these, 21 were in complete or partial remission at the time of the second examination. Table 4 shows the tracer uptake by the primary tumor, measured as T/B ratio in the different stages of the disease. The T/B ratio was significantly lower at the time of remission than it was before the start of therapy, whereas there was no change of T/B ratio in the six patients with tumor progression or standstill. No difference in octreotide uptake by the primary tumor in the initial examination was seen between the 21 patients with remission after chemotherapy and the five patients with progression after treatment.

TABLE 2
Sensitivity of Somatostatin Receptor Scintigraphy in the Detection of the Primary Tumor in 134 Examinations of 100 Patients*

Patients	SRS	Primary tumor in CT	True-positive	False-positive	True-negative	False-negative
Untreated	77	75	73	0	2	2
After treatment	57	50	47	1	6	3
Total	134	125	120	1	8	5

*Sensitivity = 96%.

TABLE 3
Sensitivity of Somatostatin Receptor Scintigraphy in the Detection of Regional (n = 149) and Distant (n = 94) Metastases

Localization	Planar/SPECT*	Sensitivity†
Hilar lymph nodes	4/6	30% (6/20)
Mediastinal lymph nodes	38/54	71% (54/76)
Supraclavicular lymph nodes	11/11	65% (11/17)
Pulmonary metastases	12/19	53% (19/36)
Regional metastases	65/90	60% (90/149)
Liver metastases	8/11	50% (11/22)
Bone metastases	9/11	55% (11/20)
Brain metastases	5/5	63% (5/8)
Adrenal metastases	4/4	25% (4/16)
Extrathoracic lymph nodes	6/7	39% (7/18)
Other extrathoracic metastases	4/4	40% (4/10)
Distant metastases	36/42	45% (42/94)
Total metastases	101/132	54% (132/243)
Sensitivity	42%/54%	

*No. of metastases detected by planar scintigraphy/SPECT.
†Parentheses = no. of metastases detected by SRS/other imaging modalities.

DISCUSSION

Because of the poor prognosis of SCLC, efforts are being made to improve staging procedures to improve therapeutic decision-making. However, a reliable staging of SCLC is very extensive and time-consuming because numerous noninvasive and invasive diagnostic procedures have to be applied. Receptor scintigraphy with the radiolabeled somatostatin analog ^{111}In-pentetreotide, therefore, appeared to be a suitable alternative to assess the extent of the disease, with little discomfort for the patient. However, our results do not suggest that this goal can be reached by SRS.

Detectability

In this study, the primary lesion in SCLC was detected with a high sensitivity, but SRS performed poorly in demonstrating metastases, particularly distant metastases.

Studies published so far on the role of SRS in the diagnostic assessment of SCLC (Table 5) are in agreement with our results for the detection of primary lesions. Compared to the conventional imaging modalities, however, SRS did not provide any additional information for detecting SCLC.

Published data on the sensitivity in demonstrating metastases vary from 45% to 80% (Table 5). This variation can probably be attributed to the small numbers of patients investigated in these studies. Even with a large number of patients, however, the sensitivity in detecting metastases found in our study is in the lower range of the results reported in the literature.

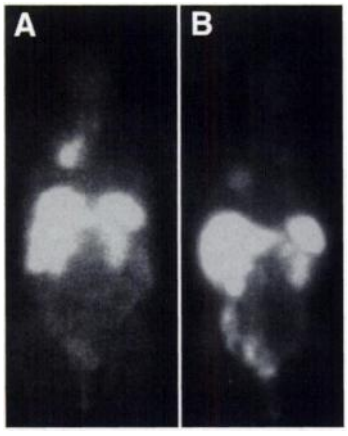

FIGURE 2. Anterior chest images of two patients with SCLC of the right bronchus, with high (A) and low (B) tracer accumulation in the primary tumor.

TABLE 4
Tumor-to-Background Ratio of the Primary Tumor During the Course of Small-Cell Lung Cancer

No. of patients (n = 27)	Phase	T/B ratio before therapy (mean ± s.d.)	T/B ratio after therapy (mean ± s.d.)
21	Remission	2.40 ± 1.56*	1.63 ± 0.72†
5	Progression	2.45 ± 1.10*	2.66 ± 1.13*
1	No change	1.97	2.10

*No significant difference.
†$p < 0.05$.

The too-high speed of whole-body scanning may be discussed as one reason of low sensitivity for metastases. However, we could not observe any difference in detecting single lesions, comparing planar spot images of the abdomen and thorax with whole-body scans. Kirsch et al. (*11*), who set the scan speed to 3 cm/min for the 24-hr images, found a lower sensitivity (45%) in the detection of metastases than we did in this study (54%).

Rather, the low sensitivity of SRS may be due to a low receptor density on metastases and/or their loss of somatostatin receptor expression (*11,20*). Another cause may be the presence of other subtypes (*18,21*) that are not detectable using octreotide. In the treated patients, an additional reduction of somatostatin receptor expression by chemotherapy has to be taken into consideration. Finally, detectability of distant metastases in the abdomen is impaired by overlaying effects resulting from the high physiological activity in the liver, kidneys and bowel. However, this fact is limited by our scanning protocol, which did not include SPECT images of the abdomen of every patient.

Liver metastases were visualized as cold spots in three patients. A possible explanation for this phenomenon is the blocking of tumor receptors by somatostatin produced endogenously (*20*). Necrotic areas may mostly result in a negative contrast lesion as well.

An improved sensitivity in the detection of metastases, in particular mediastinal ones, by SPECT compared to planar scintigraphy has also been observed by other investigators (*8,18*). This did not, however, improve staging.

In contrast to the results of Kwekkeboom et al. (*12,22*), our results of SRS did not lead to an up-staging in any patient. The main reason may be that only 39% of our patients were staged

TABLE 5
Somatostatin Receptor Scintigraphy in Small-Cell Lung Cancer: Published Results

Study	No. of examinations	Primary tumor	Metastases
Kwekkeboom et al.* (6)	8	63%	—
Leitha et al.* (8)	20	84%	65%
Krenning et al. (7)	34†	100%	—
Maini et al. (9)	15	87%	—
O'Byrne et al. (10)	13	100%	50%
Kirsch et al. (11)	25	96%	45%
Kwekkeboom et al. (12)	26†	100%	60%
Bombardieri et al. (18)	21	95%	80%
All literature	162	91%	59%
This study	134	96%	54%

*Iodine-123-Tyr^3-octreotide.
†Same study group.

in limited disease by conventional imaging modalities as compared to 54% of their patients.

Somatostatin receptor scintigraphy is not a specific procedure for diagnosing SCLC. Accumulation of somatostatin analogs was found in peritumoral areas (*23,24*) and in inflammatory (*12,25*) and granulomatous processes (*26*), as well as on the surface of activated lymphocytes and in other tumors of the lung (*11,12*). In some patients with SCLC, we also observed uptake in inflammatory areas, such as pneumonias, in addition to accumulation in the primary tumor.

Uptake

The observation made in our study that primary tumors of SCLC vary considerably in the degree of octreotide uptake and that there is no correlation with tumor size has also been reported by other authors (*11,12*). Thus, tumor size does not limit the detectability of SCLC by SRS; rather, the limiting factor is the degree of uptake, which, in turn, is determined by the receptor density on tumor cells.

The observed decrease in the accumulation of somatostatin analogs by the primary tumor during regression and the uptake differences in patients examined before, during and/or after chemotherapy suggest that, besides the reduction of tumor volume, the somatostatin receptors on the tumor surface may be reduced during therapy and/or that there is a decrease in the cells' capacity to express these receptors. Other possible mechanisms underlying this observation are a therapy-induced reduction of somatostatin receptor-carrying tumor cells or a reduction of peritumoral vessels capable of expressing somatostatin receptors.

In vitro studies have shown that somatostatin and its analogs exert growth-inhibiting activity by direct action on tumor cell growth (*25,27*). This antiproliferative action has also been demonstrated in experiments on the effects of somatostatin analogs in SCLC xenografts in nude mice (*4*). The clinical effectiveness of somatostatin analogs in patients with SCLC is being currently investigated (*28*). The observation made in our study that tumor uptake is only marginally influenced by progression of the disease or even shows a tendency to increase in progressive disease suggests that such patients might benefit from somatostatin therapy. However, this observation is limited by the fact that our study included only five patients with such a course and, therefore, requires confirmation in a larger number of patients.

Another question that remains to be investigated in larger studies is whether patients who have primary tumors with a high uptake but no metastases might also benefit from treatment with somatostatin or somatostatin analogs labeled with beta emitters.

Our initial hypothesis that the degree of octreotide uptake in the primary tumor might play a role as a prognostic indicator is refuted by our results. No difference in uptake before therapy was seen between patients who had a remission later on and those in whom there was a tumor progression.

CONCLUSION

Our results show that SRS is a suitable procedure for the assessment of the primary tumor in SCLC, for both establishing the initial diagnosis and follow-up. However, it is not suitable for staging because of its poor sensitivity in detecting metastases, which holds not only for distant but also for regional metastases. In individual cases, it may yield some additional information to conventional imaging modalities.

The degree of uptake in the primary tumor appears to be of no prognostic value.

Follow-up examinations may yield information on the response to chemotherapy. Further longitudinal studies are required to determine whether SRS is able to identify patients who might benefit from somatostatin therapy.

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