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Short Communication

Somatostatin Receptor Imaging in Small Cell Lung Cancer

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To determine its usefulness, we evaluated ^{111}In-DTPA-Octreotide (octreotide scintigraphy) in the initial staging of 19 patients with histologically proven small cell lung cancer (SCLC) and compared the results to those of conventional imaging. Images performed during initial staging demonstrated 21 known pulmonary lesions and two known supraclavicular nodes. We detected a previously unknown mediastinal lesion. The number of metastases was underestimated, with no liver (5), brain (1) or skin metastases detected. Bone lesions were identified in 4 out of 5 patients. There were fewer lesions detected with octreotide scintigraphy than with bone scintigraphy (except for one case). We therefore conclude that octreotide scintigraphy is a highly effective method for detecting SCLC primary tumour and supraclavicular nodes; the procedure is of limited value for distant metastasis. Further studies are needed to establish its ability for detecting residual intrathoracic disease, and confirm the value of octreotide scintigraphy in differentiating residual disease from other benign lesions.

Key words: somatostatin receptor, octreotide, small cell lung carcinoma, scintigraphy, indium 111
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INTRODUCTION

SMALL CELL lung cancer (SCLC) accounts for about 15 to 25 per cent of all lung cancers. Despite significant progress in chemotherapy and radiotherapy, the 2-year survival rate remains low (5–25%).

As the major prognostic factor is the extent of tumour dissemination, patients generally require a thorough and time-consuming staging examination (physical examination, chest X-ray, bronchoscopy, CT scan) to differentiate between limited and extensive disease. This is made according to a two-stage system proposed by the Veterans Administration Lung Cancer Study Group which seems to have a higher prognostic value than the commonly used TNM staging system [1].

SCLC belongs to the group of neuroendocrine tumours which are supposed to stem from amine precursor uptake and decarboxylation (APUD) cells and express somatostatin receptors [2, 3]. Scintigraphic imaging of these tumours with a radiolabelled somatostatin analogue ^{111}In-DTPA-Octreotide (octreotide scintigraphy), has been previously reported in various tumours [4, 5].

The aim of this study was to evaluate the usefulness of octreotide scintigraphy in SCLC staging.

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PATIENTS AND METHODS

Patients

19 consecutive patients (15 males, 4 females), with histologically confirmed SCLC were investigated from November 1992 to October 1994 (Table 1). Patients' age ranged from 36 to 72 years (mean 58 years).

They were examined at the time of disease diagnosis. In all cases, octreotide scintigraphy was carried out before or within the first 2 days of the first course of chemotherapy.

All patients gave their informed consent to participate in this study, which was approved by the Ethical Committee of our hospital. This study was a European trial on various applications sponsored by Mallinkrodt (Petten, The Netherlands).

Methods

SCLC staging. Conventional staging methods included: physical examination, chest X-ray, bronchoscopy with biopsies, thoracic and abdominal CT scans (including liver and adrenal glands imaging), abdominal ultrasonography, brain CT, bone scintigraphy.

Somatostatin receptor imaging. Radiopharmaceutical reconstitution (Octreoscan® 111) was performed by mixing ^{111}In as $InCl_3$ and 10 μg of [D-Phe1]octreotide as [DTPA-D-

Table 1. Presentation of patients with SCLC

Cases	Age	Sex	Tumor	Sub-clavicular nodes	Metastasis
Limited disease					
1	59	m	RH		–
2	55	m	LH		–
3	50	m	RSL		–
4	62	m	LH		–
5	63	m	LSL		–
6	68	m	RH/RIL		–
7	36	f	RH		–
8	64	f	RIL		–
9	44	m	RSL		–
10	47	m	RSL	+	–
11	72	m	RIL		–
Extensive disease					
12	56	m	LIL		bone
13	67	m	LH		liver, bone
14	45	m	LSL		bone, skin
15	60	f	LH/RSL		controlateral lung
16	70	m	RSL		bone, liver
17	60	f	RIL		liver
18	61	m	RSL	+	liver, bone, brain
19	69	m	RSL		liver

m = male; f = female; RSL = right superior lobe; RIL = right inferior lobe; LIL = left inferior lobe; LSL= left superior lobe; LH = left hilum; RH = right hilum; C = chemotherapy; RT = radiotherapy.

Phe1]octreotide. Labeling efficiency assessed by column chromatography was never less than 99%. Scintigraphy was performed after intravenous injection of 120 to 160 MBq of ^{111}In-(DTPA-D-Phe1)octreotide (SDZ 215-811, Mallinkrodt, Petten, The Netherlands). There was no preloading with unlabeled octreotide.

Static images (128 × 128, 300 s/frame) of the thorax (anterior, posterior, lateral view), abdomen (anterior, posterior view), head (lateral view) were obtained at 4 and 24 h after injection in all patients. Images were obtained at 48 h in only 16 patients because 3 were too sick to be examined. Of these 3 patients, 1 was imaged at 72 h. Scintigraphic imaging was performed with a General Electric 400AC gamma-camera using a medium energy parallel-hole collimator. The spectrometer selected two windows (20% width) centred over 173 keV and 245 keV.

Data analysis

The intensity of tumour uptake was scored visually on a five-point scale (0: no uptake, 1: very low, 2: faint, 3: moderate, 4: intense uptake). Images of the thorax were scaled with the maximum on liver activity, and each of the images were scored twice, one week apart, retrospectively, by two investigators, without knowledge of conventional staging results. In case of disagreement, the final interpretation was obtained by consensus reading.

RESULTS

No side-effects were observed after injection. Twenty-one pulmonary tumoral sites were detected in 19 patients by conventional methods. 2 patients (cases 6, 15) had two pulmonary lesions. All 21 tumours were detected by octreotide scintigraphy. The visual analysis of scintigraphic images showed variations in tumour uptake (Table 2). Tumour uptake was low in many cases (score <3 in 14/21). A consensus reading was performed in 2 cases.

Table 2. Visual analysis of scintigraphic images performed on initial staging

Score	0	1	2	3	4	Total
Number of lesions	0	5 23.8%	9 42.8%	3 14.3%	4 19%	21

Two sites were identified as known supraclavicular nodes. One additional site was detected which had not been previously detected by conventional imaging. It was categorised as a mediastinal node. No biopsy was performed.

According to conventional staging, 10 of the 19 patients had limited disease. The 9 other patients had extensive disease. During staging, 5 patients presented with liver and bone metastasis (multiple lesions). 1 patient had two skin lesions and 1 had brain metastasis (Table 1).

None of the hepatic, brain or skin metastasis were detected by octreotide scintigraphy. Bone lesions were identified in 4 of 5 patients. All patients presented multiple lesions in bone scintigraphy. In 3 of these patients, only one site was identified by octreotide scintigraphy. In the last patient (number 12), octreotide scintigraphy detected medullar involvement and multiple bone lesions in the hips, pelvis and spine agreeing with those detected by conventional imaging. Additional sites were detected by octreotide scintigraphy (Figure 1).

DISCUSSION

The efficacy of octreotide scintigraphy for staging SCLC was compared with radiological staging. This scintigraphic method seems to be very sensitive (100%) for the detection of thoracic lesions. Various authors have reported very similar results in SCLC with a sensitivity ranging from 94 to 100% [5–13]. Octreotide scintigraphy was also sensitive for the

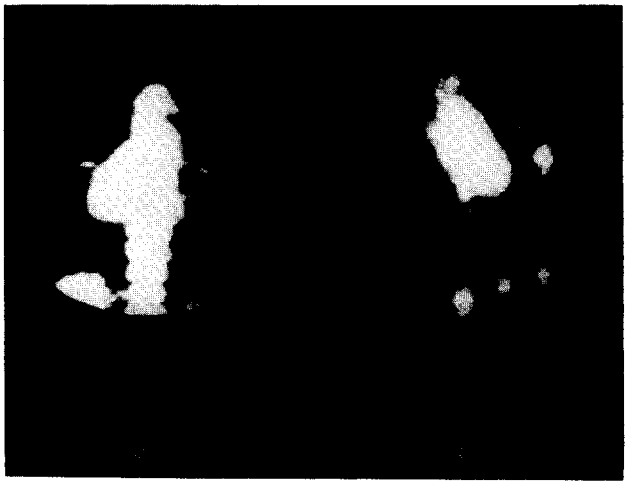

Figure 1. Octreotide scintigraphy in a patient with disseminated SCLC (case 12), 24 h after injection of ^{111}In-(DTPA-D-Phe1)octreotide. Scintigraphy demonstrates primary tumour (arrow), multiple bone lesions and medullar involvement. (a) Posterior view of thorax; (b) anterior view of thorax, arrow: primary tumour.

detection of supraclavicular nodes. As in this study, Kwekkeboom and colleagues [10], Bohuslavisky and coworkers [13], Mora and coworkers [14] detected all known supraclavicular nodes in their series.

In our study, we did not analyse separately mediastinal and hilar nodes contiguous to the primary tumour. In fact, such lesions are often analysed as metastasis. In addition, the presence of mediastinal nodes does not change staging [15].

Octreotide scintigraphy resulted in correct staging, separating limited from extensive disease in 5 patients, except in one case where the total number of metastasis was underestimated. Thus, the sensitivity is low in SCLC and completely different from the sensitivity achieved in imaging gastroenteropancreatic metastasis [5, 16]. It can be assumed that the subtype and/or density of somatostatin receptors are much lower in SCLC.

Like previous reports [6–10, 14], we found that octreotide scintigraphy failed to identify liver metastasis correctly. This was probably due to the physiological uptake of the tracer associated with a low level of metastasis uptake. This low uptake could be related to the presence of somatostatin receptors synthesised by the tumour itself and competing with the binding of radiolabelled somatostatin analogues to its receptors, as demonstrated in pheochromocytoma and medullary thyroid carcinoma [17], but not yet studied in SCLC. The low sensitivity of metastasis visualisation could also be attributed to an absence of somatostatin receptor expression. Sagman and coworkers found no receptors in SCLC bone metastasis of 1 patient [2]. Another hypothesis is that the type and density of somatostatin receptors could be different on primary tumour and metastasis. Bogden and colleagues [18] found, when comparing the density of somatostatin receptors in culture cell lines with the density after transplant of tumour cells in nude mice, that the number of receptors was reduced by a factor of 10. The surrounding extra-tumoral tissue might influence the expression of somatostatin receptors.

The precise effect of previous therapy on receptor expression is unknown. It might have influenced the results in our study, especially in the search for metastasis. However, it is unlikely that 1 or 2 days of chemotherapy, administered before octreotide scintigraphy, can fully explain the low sensitivity for metastasis detection. Despite absence of prior treatment, previous studies have not reported a high sensitivity in the detection of metastasis [6, 10, 12–14]. Moreover, we considered that it was not ethical to delay the treatment.

Therefore, assessment of residual intrathoracic disease and the ability of octreotide scintigraphy to differentiate residual disease from other benign entities remains to be investigated.

Our study confirms the results of other studies that the contribution of octreotide scintigraphy is quite small in SCLC staging. Further studies are necessary to assess the role of octreotide scintigraphy in the follow-up of SCLC. It might help in the detection of recurrence or guide the physician's decision to intensify treatment.

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