Somatostatin Receptor Scintigraphy in Patients with Carcinoid Tumors: Comparison between Radioligand Uptake and Tumor Markers

Karl-Mikael Kälkner, Eva Tiensuu Janson, Sten Nilsson, Sten Carlsson, Kjell Öberg, and Jan-Erik Westlin

Department of Oncology, Section of Nuclear Medicine [K-M. K., S. N., J-E. W.], and Department of Internal Medicine, Endocrine Oncology [E. T. J., K. Ö.], Akademiska Sjukhuset, University of Uppsala, Uppsala, S-751 85, and Department of Medical Physics, Uddevalla Sjukhus, S-451 80 [S. C.], Sweden

Abstract

We have performed 100 scintigraphic investigations using $^{111}$In-diethylentriaminepentaaetic acid-o-Phe$^1$octreotide ($^{111}$In-octreotide) single photon emission tomography (SPECT) in patients with carcinoid tumors. One or several lesions could be detected in 77 cases, and true negative results were obtained in 11 cases. There were false-negative results in 12 cases compared with results from conventional radiological methods. The ratio between the SPECT signals from the area with the highest uptake and normal lung was used as a tumor:background ratio. An attenuation correction was made in all investigations. We found that lesions in untreated patients had lower tumor:background ratios compared with those in patients treated with somatostatin analogues (medians, 10 and 40, respectively; $P < 0.001$) or IFN (median, 23; $P = 0.03$). In untreated patients, there was a correlation between the tumor:background ratio and the levels of urinary 5-hydroxyindoleacetic acid (U-5HIAA) and p-chromogranin A. The data obtained in the present investigation indicate that somatostatin receptor expression might be influenced by the treatment; i.e., a higher tumor:background ratio is found in patients treated with either somatostatin analogues or IFN. Furthermore, it was found that somatostatin receptor expression correlates with the levels of U-5HIAA and p-chromogranin A in untreated patients, and that $^{111}$In-octreotide SPECT scintigraphy is more likely positive in patients with elevated U-5HIAA values. This indicates that somatostatin receptor expression and elevated U-5HIAA are more likely present in patients with highly differentiated tumors and, thus, could be of prognostic value.

Introduction

Somatostatin receptors are usually expressed in carcinoid tumors. This has been shown by autoradiography on tumor specimens obtained both from primary tumors and metastases (1, 2). In these studies, close to 90% of all carcinoid tumors express somatostatin receptors.

A new technique for the in vivo detection of tumors expressing somatostatin receptors has been developed using scintigraphy with $^{111}$In-octreotide (3, 4). During the last few years, somatostatin receptor scintigraphy has been used frequently in the detection of malignant carcinoid tumors (5, 6). The scintigraphic investigation has proven to be of value for the therapeutic considerations, because the presence of somatostatin receptors in carcinoid tumors, as detected by somatostatin receptor scintigraphy, can be used to predict whether the patient will respond to treatment with somatostatin analogues (7). This has been shown by autoradiography on tumor specimens obtained both from primary tumors and metastases (1, 2). In these studies, close to 90% of all carcinoid tumors express somatostatin receptors.

The aim of the present study was to investigate whether $^{111}$In-octreotide SPECT scintigraphy can provide information about the biological characteristics of the tumors and not only information about the distribution of the metastatic lesions. For this purpose, the tumor:background ratio has been calculated and compared with tumor markers. The possible impact of octreotide and IFN treatment has been considered also.

Materials and Methods

Patients. One hundred $^{111}$In-octreotide SPECT scintographies were performed in 80 patients with histopathologically verified carcinoid tumors. The patients' characteristics are shown in Table 1. The carcinoid tumors were divided into foregut, midgut, and hindgut. The patients were divided into three groups according to treatment: untreated patients ($n = 42$), patients who received treatment with a somatostatin analogue alone or in combination with IFN ($n = 35$), and patients treated with IFN or chemotherapy alone ($n = 23$).

Somatostatin analogue treatment was interrupted 3 days before the $^{111}$In-octreotide scintigraphy. Eleven patients were investigated after surgery. All of these patients had normal tumor markers and were considered free of disease. These 11 patients had negative investigations and were excluded when comparing the tumor:background ratios. Bone metastases were confirmed with $^{99m}$Tc scintigraphy.

$^{111}$In-octreotide Scintigraphy. The $^{111}$In-octreotide was delivered by Mallinckrodt Medical (Petten, The Netherlands). The labeling procedure and control process of the labeling yield have been described previously (3). The patients routinely received laxatives before the administration of the $^{111}$In-octreotide to avoid colonic accumulation of excreted radioactivity. The $^{111}$In-octreotide was administered as an i.v. bolus injection. The administered doses ranged from 73 to 289 megabecquerels (median, 122 megabecquerels).

A gamma scintillation single-headed SPECT camera, delivered by Nuclear Diagnostics (Högersten, Sweden) and equipped with a medium-energy general-purpose collimator, was used. The collection of data for SPECT analyses was performed as a 64-step rotation of 360° in a 64 X 64-word matrix. Energy windows of 173 and 247 keV ($\pm 10\%$) were used. The collection time for each angle was 40 s, amounting to approximately 20,000–35,000 counts/angle; the pixel size was 3 X 3 mm.

Planar images comprising the whole body were collected 19–24 h after injection. These images were evaluated, and an additional SPECT study was performed over the selected area of interest. In 8 cases, the thorax was investigated with SPECT, and in 92 cases the upper abdomen was investigated.

Image Analysis. Reconstruction was performed using the SPECT algorithm included in the Hermes software package working under X-Windows on a Sun Sparc station (Nuclear Diagnostics). Prefiltering was applied using the same Metz filter for all patients studies. The Sorenson algorithm for attenuation correction was applied using an attenuation coefficient of 0.12/cm (8). This value is a useful approximation for the true attenuation coefficient for $^{111}$In, which varies between 0.14 and 0.09/cm depending on the size and depth of the activity (8).

The ROI in a metastatic lesion was chosen as the highest value of 4 pixels. A background area located in the left lung was also used (Fig. 1). The tumor:background ratio was calculated finally after correction for differences in ROI sizes. In a case in which no tumor was detectable, the tumor:background ratio was defined as 1.0.

The number of lesions analyzed in each investigation was limited to eight, which is the upper limit of detectable lesions in the liver.

Tumor Markers. Urinary U-5HIAA was determined according to the method of Wahlund and Edlén (9) and was calculated as the mean of two 24-h collections (reference range, <80 μmol/24 h).

1 Presented at the "Fifth Conference on Radioimmunodetection and Radioimmunotherapy of Cancer," October 6–8, 1994, Princeton, N.J. This research was in part supported by Stiftelsen Onkologiska Klinikens i Uppsala Forskningsfond.

2 To whom requests for reprints should be addressed.

3 The abbreviations used are: $^{111}$In-octreotide, $^{111}$In-diethylentriaminepentaaetic acid-o-Phe$^1$octreotide; SPECT, single photon emission computed tomography; U-5HIAA, urinary 5-hydroxyindoleacetic acid; ROI, region of interest.

4 S. Ä. Starck and S. Carlsson, personal communication.
Plasma levels of chromogranin A were analyzed using the RIA method described by Eriksson et al. (10; p-chromogranin A reference range, <350 ng/ml).

Statistics. The tumor:background ratio is given with the median value and the range. The Mann-Whitney U Test was used when comparing differences in tumors with background ratios between two groups. The coefficient of correlation is calculated to describe the degree of relationship.

Results

Of 100 SPECT scintigraphies with 111In-octreotide, 77 revealed one or several pathological foci. Twelve 111In-octreotide investigations were negative, whereas computed tomographic and/or ultrasonic investigations had disclosed metastatic disease. No tumors were detected either by 111In-octreotide SPECT scintigraphy or by conventional radiology in 11 cases. The results in the three subgroups are demonstrated in Table 2. A total of 385 lesions were detected with 111In-octreotide scintigraphy, of which 333 were located in the liver, and 23 were located outside the liver in the abdomen. Twenty bone lesions and 9 lesions located in the thorax were detected.

Comparison between Tumor:Background Ratio and Localization. The tumor:background ratio in patients with at least one detected lesion ranged from 3 to 185, with a median of 33. Bone lesions (n = 10) were found to have significantly lower tumor:background ratios (median, 7; range, 2–33) compared with the 66 liver lesions (median, 33; range, 4–185; P < 0.001). The abdominal lesions (n = 23) had tumor:background ratios with a median of 23 (range, 7–63), which did not differ significantly from the median of the liver lesions (P = 0.1).

Comparison between Tumor:Background Ratios and Tumor Markers. The U-5HIAA was measured in 93 cases, with a median of 185 μmol/24 h (range, 4–2,220 μmol/24 h). p-chromogranin A was measured in 95 cases, with a median of 1,900 ng/ml (range, 150–100,000 ng/ml). The tumor:background ratios were significantly higher (P < 0.001) in patients with pathological levels of U-5HIAA and p-chromogranin A (Table 3). The medians of U-5HIAA and p-chromogranin A in patients with positive 111In-octreotide scinti-
The corresponding correlation coefficient between tumor:background can provide information concerning the prognosis of the disease.

Discussion

We have performed 100 investigations with 111In-octreotide SPECT scintigraphy in patients with carcinoid tumors. One or several lesions were detected in 77 cases, whereas 12 investigations were false negative compared with conventional radiological methods. We have reported similar results concerning the number of false negative lesions previously (5). Some of the false-negative patients have large, biopsy-verified, liver metastases. These false-negative results are, in some of the cases, most likely due to a lack of or a very low level of expression of the octreotide-binding somatostatin receptor subtypes (11). The reason for negative investigations in other patients, however, might be the result of the small sizes of the metastases, which makes them difficult to detect.

Octreotide is used in the treatment of patients with malignant carcinoid tumors, because many patients benefit from such treatment. Biochemical responses with a reduction of tumor markers have been noticed in about 72% of treated patients (12). We have shown previously that positive 111In-octreotide scintigraphy has the potential of predicting the response to somatostatin analogue treatment (7). In the present report, we have demonstrated further that positive 111In-octreotide scintigraphy also corresponds to elevated levels of both U-5HIAA and p-chromogranin A. This is in agreement with previous indications (7) suggesting that tumors with higher degrees of differentiation express somatostatin receptors and also produce different hormones to a higher extent. This might be of importance, because it can provide information concerning the prognosis of the disease. However, future studies will have to address this question in more detail.

The lung was selected as the background, because it was easily recognized and available in every investigation, and it has the smallest variability in radioligand uptake. The lesion ROI with the highest uptake was chosen, and this provides only information for one lesion per investigation. This procedure disregards the volume of the tumor, but the aim of the study was to evaluate whether 111In-octreotide scintigraphy can provide information about the biology of the tumor investigated and not about the distribution or sizes of metastases.

It was found that tumor:background ratios were significantly lower in untreated patients compared with patients treated with somatostatin analogues. It has been suggested that, during somatostatin analogue therapy, there is an up-regulation of somatostatin receptors. Indirect evidence of an up-regulation has been reported by Dörr et al. (13), who described higher-contrast images during octreotide treatment of neuroendocrine tumors compared with those without treatment. In patients with negative 111In-octreotide scintigraphy, a pretreatment with octreotide might enhance the possibility of detecting somatostatin receptor-expressing lesions. Patients treated with IFN also showed higher tumor:background ratios compared with untreated patients, and this may indicate that IFN can affect the somatostatin receptor content in carcinoid tumors.

There was a significant difference in the tumor:background ratio between lesions in the liver and bone. This can be due to the morphology of osseous metastases, in which the malignant cells are more scattered compared with those in the soft-tissue lesions.

We have found that positive 111In-octreotide SPECT scintigraphy correlates with elevated levels of U-5HIAA and p-chromogranin A in patients with carcinoid tumors, and that a high tumor:background ratio correlates with high hormone production in untreated patients. This might be used to determine the degree of differentiation of the tumors and may be of prognostic value. Treatment with a somatostatin analogue or IFN increases the tumor:background ratio, indicating that an up-regulation of somatostatin receptors takes place during treatment. This knowledge might be used to enhance the diagnostic potential of 111In-octreotide SPECT scintigraphy by pretreating patients with small lesions with a somatostatin analogue. 111In-octreotide SPECT scintigraphy provides information on tumor biology in carcinoid tumors, not only on the size and location of the malignancy.

References

Somatostatin Receptor Scintigraphy in Patients with Carcinoid Tumors: Comparison between Radioligand Uptake and Tumor Markers

Karl-Mikael Kälkner, Eva Tiensuu Janson, Sten Nilsson, et al.


Updated version
Access the most recent version of this article at:
http://cancerres.aacrjournals.org/content/55/23_Supplement/5801s

E-mail alerts
Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions
To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions
To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.