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SOMATOSTATIN RECEPTOR IMAGING IN THE DIAGNOSIS AND TREATMENT OF NEUROENDOCRINE TUMORS

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Summary—Somatostatin analogs are used in the control of hormonal hypersecretion and tumor growth of patients with acromegaly, islet cell carcinomas and carcinoids. Recently we showed that somatostatin receptor positive tumors can be visualized *in vivo* after the administration of radioactive isotope-labelled somatostatin analogs. Receptor imaging was positive in 18/21 islet cell tumors, 30/31 carcinoids, 26/28 paragangliomas, 9/14 medullary thyroid carcinomas, 5/7 small cell lung cancers, 6/7 neuroblastomas, 38/49 primary breast cancers, and 0/18 pancreatic adenocarcinomas. Also 11/11 meningiomas, 4/4 astrocytomas and 0/3 glioblastomas could be visualized. Somatostatin receptor imaging is an easy, harmless and painless diagnostic method. It is an *in vivo* method for the recognition of neuroendocrine cancers. It localizes multiple and/or metastatic tumors, predicts the successful control of hormonal hypersecretion by octreotide and seems of prognostic value in certain types of cancer. This scintigraphic method might help in patient selection for clinical trials with somatostatin analogs in the treatment of neuroendocrine cancers.

Somatostatin receptors have been shown to remain present on a variety of tumors which arise in tissues which also contain these receptors in the normal state. High numbers of high affinity somatostatin receptors have been found on most growth hormone secreting pituitary adenomas as well as on most metastatic endocrine pancreatic tumors and carcinoids [1–3]. In parallel chronic therapy with the somatostatin analog octreotide normalizes clinical symptomatology as well as the biochemical abnormalities in most acromegalic patients: both the hypersecretion of growth hormone, and the elevated circulating levels of insulin-like growth factor I (virtually) normalize in most instances [4]. Hormonal hypersecretion from (metastatic) endocrine pancreatic tumors and carcinoids is also well controlled during octreotide treatment of most patients, while in parallel the clinical symptomatology greatly improves. Interestingly evidence of control of tumor growth during somatostatin analog treatment has been observed in part of these patients [5]. These results led to an instant improvement in the quality of life of these patients, making the clinical introduction of octreotide a major breakthrough in the treatment of these endocrine cancers (see [6]).

We recently developed a technique, which allows the detection of somatostatin receptor positive tumors *in vivo* after the administration of a radioactive iodine-labeled analog [7]. In a way one might call this approach an "*in vivo* autoradiography" of somatostatin receptor positive tumors. Tyr^3-octreotide is a somatostatin analog with tyrosine in position 3, where phenylalanine is present at that place in octreotide. The biological activities of octreotide and Tyr^3-octreotide are similar. We initially coupled Tyr^3-octreotide to ^{123}I and injected about 10 mCi [^{123}I]-Tyr^3-octreotide i.v. in patients which were suspected to have somatostatin receptor positive tumors, while planar or ECT (emission computed tomographic) images were made with a gamma camera.

The [^{123}I]-Tyr^3-octreotide scanning procedure revealed the localization of the primary tumor and/or its previously unknown metastases in 18 or 21 patients with endocrine pancreatic tumors (86%). In a group of 5 of these positive tumors we could subsequently investigate the surgically removed tumor [8]. There was a close relationship between the *in vitro* detection of somatostatin receptors in these tumors using autoradiography and the gamma camera pictures obtained after injection of

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[^{123}I]-Tyr^3-octreotide. This indicates that the ligand binding to the tumor *in vivo* represents binding to specific somatostatin receptors. In addition we carried out preoperative *in vivo* and *in vitro* experiments with cultured tumor cells. Again there was a close parallel between the presence of somatostatin receptors on these tumors and the *in vivo* and *in vitro* effects of octreotide on hormonal secretion by these tumors. This means that a positive scan predicts a beneficial effect of therapy with octreotide on hormonal hypersecretion by these tumors.

In 30 of 31 patients with metastatic carcinoids we could visualize the primary and secondary tumors, while these "positive" patients were subsequently shown to respond beneficially to therapy with octreotide (see [9]).

[^{123}I]-Tyr^3-octreotide has two major drawbacks: it has a very short half-life and there is a high background of radioactivity in the abdomen. Therefore an alternative was developed by coupling DTPA (diethylenetriaminopentaacetic acid) to octreotide. [^{111}In-DTPA]-octreotide has a longer half-life, and is excreted via the kidneys. This new compound turned out to be able to visualize somatostatin receptor positive tumors at least as clearly as [^{123}I]-Tyr^3-octreotide.

Apart from endocrine pancreatic tumors and carcinoids we extended our studies to the use of the somatostatin-receptor imaging technique in other tumors with neuroendocrine characteristics. Also 26/28 paragangliomas, 5/7 small cell lung cancers, 3/5 pheochromocytomas and 9/14 medullary thyroid carcinomas could be visualized. In most instances multiple tumor localizations as well as metastatic disease could be demonstrated.

The *in vivo* receptor imaging technique can also be applied to patients with pituitary tumors. [^{123}I]-Tyr^3-octreotide administration does not result in the visualization of the normal pituitary gland, but [^{111}In]-octreotide does. In 4/4 acromegalic patients, in 2/2 patients with TSH-secreting pituitary tumors, as well as in 8/10 patients with so-called "non-functioning" pituitary tumors, the adenomas could be visualized after isotope-coupled somatostatin analog administration. In the patients with growth hormone- and TSH-secreting tumors hormone secretion was subsequently shown to be powerfully suppressed during octreotide therapy.

Most well-differentiated human brain tumors like meningiomas and low-grade astrocytomas contain somatostatin receptors, while undifferentiated brain tumors mainly contain EGF receptors [10–12]. All 11 meningiomas and 4 low-grade astrocytomas investigated so far could be clearly visualized with somatostatin receptor imaging techniques, while 3 glioblastomas were negative.

Other tumors which express enough somatostatin receptors to allow *in vivo* visualization include part of the neuroblastomas, Merkel cell tumors, Hodgkin and non-Hodgkin lymphomas, as well as $>50\%$ of primary breast cancers (see Fig. 1).

Somatostatin receptor imaging in patients with such a variety of cancers underline, but also broaden the *in vitro* observations done by pathologists over the last 25 years. The amine precursor uptake and decarboxylation (APUD) concept as introduced by Pearse [13] related to tumors which in virtually all instances express a high density of somatostatin receptors: the list of tumors with "classical" APUD characteristics includes pituitary adenomas, islet cell tumors, carcinoids, medullary thyroid carcinomas, pheochromocytomas, paragangliomas and small cell lung cancers. These tumors originate from endocrine cells, which can be recognized in normal conditions as endocrine organs or as groups or clusters of cells within organs. Over the years several observations have changed, but also expanded the APUD cell concept [14, 15]. Identical amines and peptides as found in the "classical" APUD cells are also present within the central nervous system, in peripheral nerves, as well as in more widely dispersed endocrine cells in organs like the gastrointestinal and respiratory tract. The term *neuroendocrine* has gradually replaced APUD. In parallel with these considerations the number of markers regarded to be "specific" for neuroendocrine cells also expanded considerably, and they include for example neuron-specific enolase, the chromogranins and synaptophysin. Apart from the "classical" Apudomas mentioned above, neuroendocrine tumors have been described in virtually every organ system of the body. While most of the Apudomas presented themselves clinically with syndromes related to hormonal ($-$metabolite) hypersecretion, many neuroendocrine tumors originating from dispersed neuroendocrine cells seem to represent subgroups of tumors arising in organs like the breast, brain, colon and lung.

In the present study we for the first time present a "neuroendocrine" marker, which can be demonstrated in *in vivo* studies, as well as

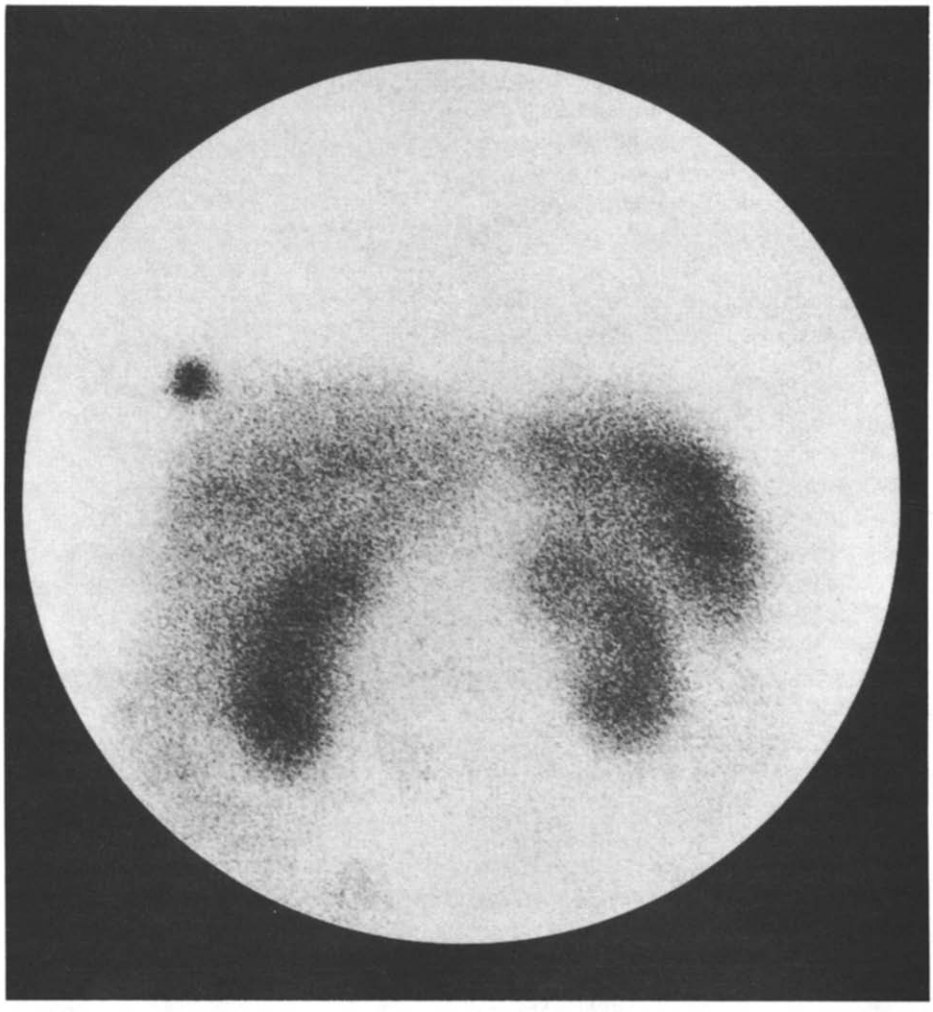

Fig. 1 Anterior view of the chest and upper part of the abdomen of a patient with primary breast cancer 24 h after the administration of [^{111}In-DTPA]-octreotide. The breast tumor in the right lower part of the right breast is clearly visualized (left on the photograph). Note also the "physiological" accumulation of radioactivity in the normal liver, spleen, and kidneys

in *in vitro* pathological studies. Somatostatin receptors have been recognized in a surprising variety of tumors, while in virtually all cases the number of binding sites found *in vitro* was enough to allow *in vivo* visualization of the tumors as well.

Somatostatin receptors are present at a high density in virtually all classical Apudomas. The primary as well as secondary deposits of most tumors can be visualized *in vivo*, and apart from distinct help in optimalizing therapeutic decisions with regard to primary treatment (surgery or not), a positive scan can predict a good response of chronic therapy with somatostatin analogs on clinical symptomatology related to hormonal hypersecretion (e.g. pituitary adenomas, islet cell tumors, carcinoids and to a lesser extent medullary thyroid carcinomas).

In parallel with the concept of "dispersed neuroendocrine cells", other human cancers also turned out to express so many somatostatin receptors that these tumors could be visualized with the scintigraphic technique. Examples are trabecular Merkel cell carcinomas of the skin, neuroblastomas, but also $>50\%$ of primary breast cancers. Preliminary evidence suggests that somatostatin receptor expression in breast cancer might be of predictive value with regard to the disease free interval and the absence of EGF receptors. Also a number of other adenocarcinomas presumably originating from the colon, rectum, ovary, kidney and/or other organs do not only show neuroendocrine characteristics, but also express somatostatin receptors in enough quantity to allow *in vivo* visualization. These observations might help in future studies to categorize and subdivide these types of tumor

with regard to their sensitivity to cytostatic drug therapy.

Somatostatin receptors have also been found on tumors arising from the brain and meninges and from leucocytes. With regard to glia-derived brain tumors somatostatin receptor expression is highest in the well-differentiated tumors, and here somatostatin receptor scintigraphy might be helpful as a prognostic factor. Virtually all lymphomas investigated so far were somatostatin receptor positive. The use of scintigraphy might not be diagnostic in these disease, but of importance as an easy, harmless procedure to stage non-Hodgkin lymphomas, especially in the lower abdomen and the chest.

Studies of surface antigen and oncogene expression, gene arrangements and neuroendocrine markers are currently used more and more in order to categorize and subdivide not only hematopoietic and lymphatic malignancies, but also breast, prostatic and ovarian cancers. Apart from classical histopathological examination of tumor specimens, these additional studies are included more and more in the routine investigations (e.g. estradiol and EGF receptors in breast cancer). Indeed this new approach has resulted in improving clinical decision making in certain cancer types. We now offer a new marker, which, for the first time can be used in *in vivo* studies of a variety of tumors mentioned above. The somatostatin receptor might just be one out of many peptide receptors, for which receptor visualization will be developed in the near future. However, as somatostatin seems in several organ systems to be an endogenous inhibitory growth factor, while exogenous somatostatin (analogs) are also inhibitory in their effects on the growth of a variety of tumors, it is tempting to speculate that the expression of somatostatin receptors in such a variety of cancers might represent a general inhibitory control mechanism, via which (well- differentiated) tumors are inhibited in their growth.

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