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SOMATOSTATIN RECEPTOR IMAGING. *IN VIVO* LOCALIZATION OF TUMORS WITH A RADIOLABELED SOMATOSTATIN ANALOG

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Summary—This paper presents the results of the visualization of somatostatin (SS) receptor positive tumors in man after the i.v. administration of the SS analog Tyr^3-octreotide coupled to ^{123}I. It is an easy, quick and harmless procedure which allows imaging of primary and (often unexpected) secondary deposits and/or multiple localizations of the majority of endocrine pancreatic tumors, metastatic carcinoids and pituitary tumors, as well as of a multitude of tumors with neuroendocrine characteristics and well-differentiated brain tumors and meningiomas. In the case of hormone-secreting tumors a positive scan in most instances also predicts the subsequent successful therapy with octreotide.

Somatostatin (SS) is a regulatory peptide which plays an inhibitory role in the normal regulation of several organ systems: (1) the central nervous system, the hypothalamus and the pituitary gland; (2) the gastrointestinal tract; and (3) the exocrine and endocrine pancreas [1–3]. SS receptors (SS-R) have been shown to be present at all main sites of action of SS in these tissues [4, 5]. These receptors are specific binding sites on the cell surface and their presence has been shown using both biochemical techniques (i.e. binding studies in tissue homogenates *in vitro* allowing the determination of the affinities and the number of SS-R), as well as with autoradiography, allowing visualization of the distribution of SS-R [4]. Various iodinated radioligands specific for SS-R, analogs of both natural SS-14, its precursor SS-28 or of octreotide (SMS 201-995, Sandostatin®) have been used in these studies [4].

Recently, octreotide became available for routine clinical use: it is an SS analog which has several advantages over native SS: (1) it inhibits growth hormone (GH) secretion preferentially over insulin; (2) it has a longer half-life in the circulation, causing a prolonged inhibitory effect in target organs of SS; (3) it is active after S.C. administration; and (4) administration of octreotide is not followed by rebound hypersecretion of hormones [5].

SS-R have been shown to be present on a variety of tumors which arise in tissues which also contain these receptors in the normal state. High numbers of high affinity SS-R have been found on most GH-secreting pituitary adenomas as well as on most metastatic endocrine pancreatic tumors and carcinoids [6–8]. In parallel, chronic therapy with octreotide normalizes clinical symptomatology as well as the biochemical abnormalities in most acromegalic patients: both the hypersecretion of GH, and the elevated circulating levels of insulin-like growth factor I (virtually) normalize in most instances [9]. 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 SS analog treatment has been observed in some of these patients [10]. 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 [5].

We found it remarkable that in the *in vitro* autoradiographic studies of most of these endocrine tumors (pancreatic and carcinoids) there was virtually always a very high density of SS-R present within these tumors which contrasted sharply with the virtual absence of visible binding sites in the surrounding "normal" tissue which was known to also contain these receptors [4, 6]. The presence of higher numbers

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and/or a higher affinity of the SS-R on many of these tumors seemed also to be reflected in the clinical observation that tumorous hormone secretion (i.e. in acromegalic and/or gastrinoma patients) was suppressed much longer after a single s.c. administration of octreotide than normal GH and/or gastrin secretion in healthy individuals [5].

These considerations led us to explore whether it might be possible to detect SS-R+ tumors *in vivo* after the administration of a radioactive iodine-labeled analog [11]. In a way one might call this approach an "*in vivo* autoradiography" of SS-R+ tumors. Tyr^3-octreotide is an SS 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 coupled Tyr^3-octreotide to ^{123}I and i.v. injected 37–555 MBq ^{123}I-labeled Tyr^3-octreotide

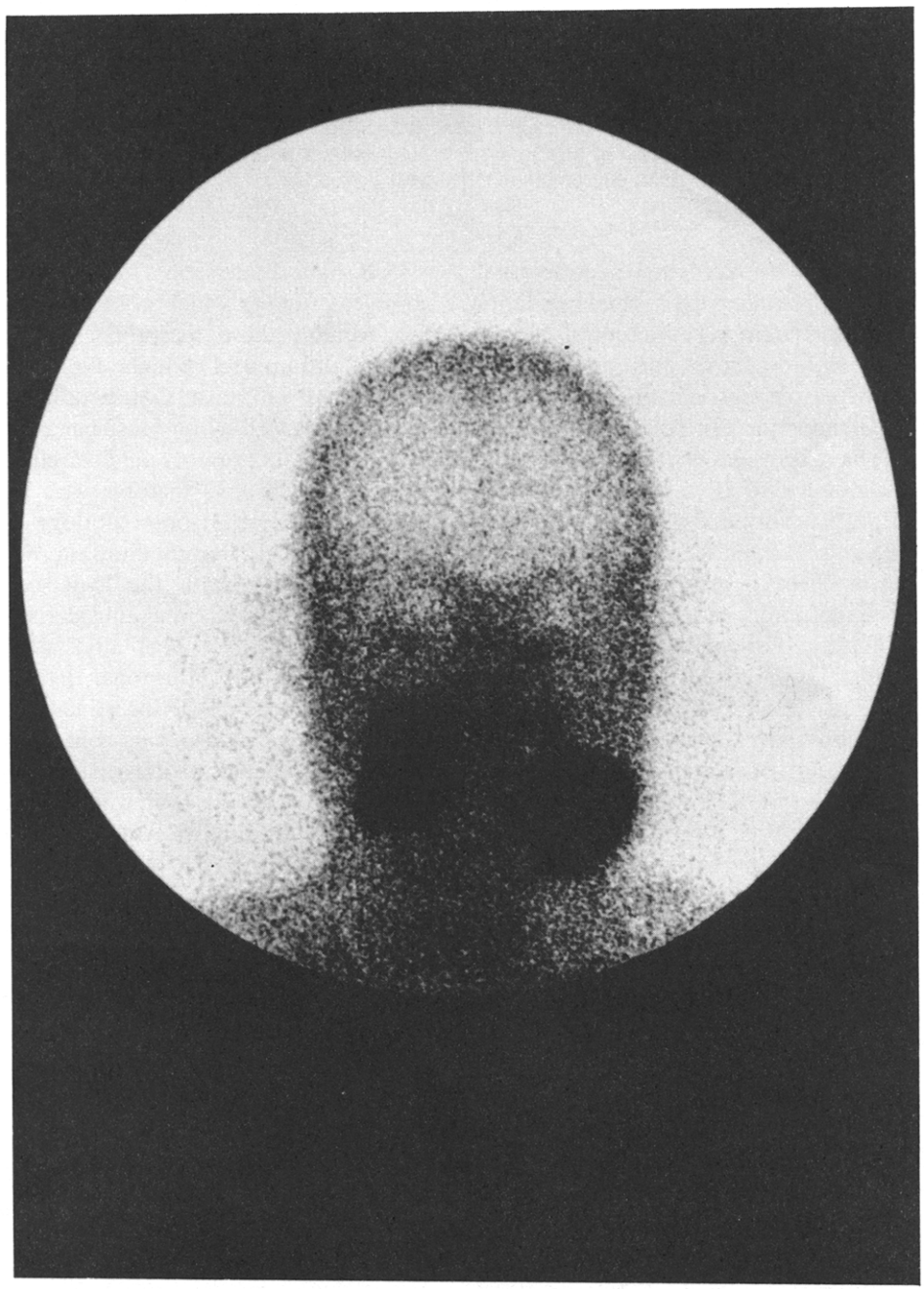

Fig. 1. The visualization of bilateral paraganglioma of the carotic sinus in a male patient. γ-Camera pictures were taken 3 h after ^{123}I-labeled Tyr^3-octreotide administration.

in patients which were suspected to have SS-R+ tumors, while planar or ECT (emission computed tomographic) images were made with a γ-camera.

After the bolus injection of radioiodinated Tyr^3-octreotide, rapid accumulation of radioactivity was seen in the liver. About 50% of the activity was cleared from the blood pool within 2 min after injection and the localization of a variety of tumors and their metastases was possible.

The ^{123}I-labeled Tyr^3-octreotide scanning procedure revealed the localization of the primary tumor and/or its previously unknown metastases in 7 of 9 patients with endocrine pancreatic tumors. In 5 of the 7 positive tumors we could subsequently investigate the surgically removed tumor [12]. There was a close relationship between the *in vitro* detection of SS-R in these tumors using autoradiography and the γ-camera pictures obtained after injection of ^{123}I-labeled Tyr^3-octreotide. This indicates that the ligand binding to the tumor *in vivo* represents binding to specific SS-R. 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 SS-R on these tumors and the *in vivo* and *in vitro* effects of SMS 201–995 on hormonal secretion by these tumors. This means that a positive scan predicts a beneficial effect of therapy with SMS 201–995 on hormonal hypersecretion by these tumors. In the 2 patients in whom an insulinoma could not be visualized after administration of ^{123}I-labeled Tyr^3-octreotide, the *in vitro* autoradiography of the subsequently removed tumor tissue showed an absence of octreotide binding sites, while SS-14 and SS-28 binding sites were present.

In 12 of 13 patients with metastatic carcinoids we could visualize the primary and secondary tumors, while only these 12 patients were subsequently shown to respond beneficially to therapy with SMS 201–995 [12].

Apart from endocrine pancreatic tumors and carcinoids we extended our studies on the use of the SS-R imaging technique to other tumors with neuroendocrine characteristics. Also, most paragangliomas (Fig. 1), part of the small cell lung cancers and a minority of pheochromocytomas and medullary thyroid carcinomas could be visualized. In most instances, multiple tumor localizations as well as metastatic disease could be shown clearly. It is at present unclear why amongst the latter two groups of tumors only a minority of tumors could be visualized.

The *in vivo* receptor imaging technique can also be applied to patients with pituitary tumors. ^{123}I-labeled Tyr^3-octreotide administration does not result in the visualization of the normal pituitary gland. However, in 3 acromegalic patients, in 2 patients with TSH-secreting pituitary tumors, as well as in 3 of 6 patients with so-called "non-functioning" pituitary tumors, the adenomas could be clearly visualized after isotope-coupled SS analog administration. In these patients with GH- 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 SS-R, while undifferentiated brain tumors mainly contain EGF receptors [13–15]. All 11 meningiomas and 3 low-grade astrocytomas investigated so far could be clearly visualized with the ^{123}I-labeled Tyr^3-octreotide imaging technique.

In conclusion, we have developed an easy, quick and harmless procedure in which the administration of an analog prepared from the endogenous peptide SS coupled to radioactive iodine readily visualized SS-R+ tumors. This technique seems to be a powerful alternative to monoclonal antibody technology, which, to date, seldom provides imaging of tumors with such a high success rate.

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