

## Somatostatin receptor imaging for neuroendocrine tumors

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**Abstract** Tumors and metastases that express the somatostatin receptor subtypes  $sst_2$ ,  $sst_3$  or  $sst_5$  can be visualized *in vivo* after injection of radiolabeled octapeptide somatostatin analogs, like  $^{111}\text{In}$ -pentetreotide.  $^{111}\text{In}$ -pentetreotide scintigraphy also allows for more accurate staging of the disease by demonstrating tumor sites, which were not shown by conventional imaging.  $^{111}\text{In}$ -pentetreotide scintigraphy may also detect resectable tumors that would have remained unrecognized using conventional radiological imaging techniques; it may prevent surgery with curative intent in those patients whose tumors have metastasized to a greater extent than could be detected with conventional radiological imaging and it may be used to select patients for treatment with the currently available octapeptide somatostatin analogs or with tumor targeted radioactive treatment with radiolabelled somatostatin analogs.

$^{111}\text{In}$ -pentetreotide scintigraphy has also been used to select patients with pituitary tumors for medical treatment with octapeptide analogs, but its clinical usefulness for this purpose seems to be limited. It further allows scar tissue to be differentiated from tumor recurrence after the pituitary surgery or radiotherapy. However, a large variety of lesions in and around the pituitary region also express somatostatin receptors and, therefore, can be visualized by  $^{111}\text{In}$ -pentetreotide scintigraphy.

**Keywords** Somatostatin · Receptor(s) ·  $^{111}\text{In}$ -Pentetreotide · Pituitary tumors · Neuroendocrine · Pheochromocytoma · Paraganglioma · Pancreas · Medullary thyroid carcinoma

### Introduction

Somatostatin-14 and somatostatin-28 act through high-affinity membrane receptors. Six somatostatin receptor subtypes have been cloned in human tissues and named  $sst_1$ ,  $sst_{2a}$ ,  $sst_{2b}$ ,  $sst_3$ ,  $sst_4$  and  $sst_5$ . They differ with regard to their binding of natural somatostatin-14, somatostatin-28 and somatostatin analogs, including the currently available octapeptide somatostatin analogs octreotide and lanreotide. Octreotide and Lanreotide bind with high affinity to  $sst_2$ , and with moderate affinity to  $sst_3$  and  $sst_5$ .  $Sst_{2,3}$  and 5-expressing (neuro-)endocrine tumors include pituitary adenomas, gastrointestinal and pancreatic neuroendocrine tumors and carcinoids, paragangliomas, pheochromocytomas, small cell lung cancers and medullar thyroid carcinomas (MTCs) [1–3]. The majority of somatostatin receptor-positive tumors simultaneously express multiple somatostatin receptor subtypes, although there is a considerable variation in somatostatin receptor subtype expression between the different tumor types and also heterogeneous expression in tumors of the same type [1–3]. The presence of octreotide-binding sites on tumors allows their *in vivo* visualization after the injection of a radionuclide-labeled octreotide analog [4–6].

Somatostatin receptor scintigraphy studies have started in 1988 and have initially used  $^{123}\text{I}$ - $^3\text{Tyr}$ -octreotide [7, 8]. Nowadays,  $^{123}\text{I}$ - $^3\text{Tyr}$ -octreotide has been abandoned both for practical and financial reasons.  $^{111}\text{In}$ -pentetreotide is currently used as radiopharmaceutical of first choice for the visualization of receptors for octapeptide somatostatin analogs. Alternatively,  $^{99\text{m}}\text{Tc}$ -EDDA-hydrazinonicotinyl(HYNIC)-

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Tyr<sup>3</sup>-octreotide (Tc-TOC), or <sup>99m</sup>Tc EDDA/HYNIC-octreotate can be used [9–11]. Imaging systems and protocols may vary; for more information see the “Procedure Guideline for Somatostatin Receptor Scintigraphy with <sup>111</sup>In-pentetreotide” [12]. Positron emission tomography (PET) is a noninvasive technique for characterization of tumor biochemistry. <sup>18</sup>F-fluorodeoxyglucose (<sup>18</sup>F-FDG) is widely used in clinical oncology for the study of increased glucose transport and metabolism in tumors. <sup>18</sup>F-FDG does not show sufficient uptake in well-differentiated neuroendocrine tumors, although it may be of limited value for the visualization of poorly differentiated, rapidly growing neuroendocrine tumors [13]. <sup>68</sup>Ga-DOTA-D-phe<sup>1</sup>tyr<sup>3</sup>-octreotide (<sup>68</sup>Ga-DOTATOC) and <sup>66</sup>Ga-DOTA-D-phe<sup>1</sup>tyr<sup>3</sup>-octreotide (<sup>66</sup>Ga-DOTATOC) are also used as tracers for (experimental) PET imaging of carcinoids and other neuroendocrine tumors [14–16].

#### Somatostatin receptor imaging of gastrointestinal neuroendocrine tumors (carcinoids) and pancreatic neuroendocrine tumors

Sst<sub>2</sub> and sst<sub>5</sub> are expressed in 70–90% of gastrointestinal neuroendocrine tumors and carcinoids. Therefore, radiolabelled somatostatin analogs, like <sup>111</sup>In-pentetreotide, can successfully visualize these tumors [17, 18]. The overall sensitivity of <sup>111</sup>In-pentetreotide scintigraphy for the detection of (metastatic) carcinoid tumors varies between 86% and 95% in different studies. The sensitivity of <sup>111</sup>In-pentetreotide scintigraphy for the detection of (metastatic) gastrinomas, vasoactive intestinal polypeptide-secreting tumors (VIPomas), and glucagonomas as well as clinically nonfunctioning pancreatic endocrine tumors varies between 75 and 100%. However, for benign insulinoma this is as low as 50–60%, because of absent sst<sub>2</sub> expression.

This scintigraphy also allows for more accurate staging of the disease by demonstrating tumor sites, which were not shown by conventional imaging. Somatostatin recep-

tor scintigraphy may detect resectable tumors that would have remained unrecognized using conventional radiological imaging techniques; it may prevent surgery with curative intent in those patients whose tumors have metastasized to a greater extent than could be detected with conventional radiological imaging and it may be used to select patients for treatment with the currently available octapeptide somatostatin analogs octreotide and lanreotide or with tumor targeted radioactive treatment with radiolabelled somatostatin analogs [4, 5, 19–23].

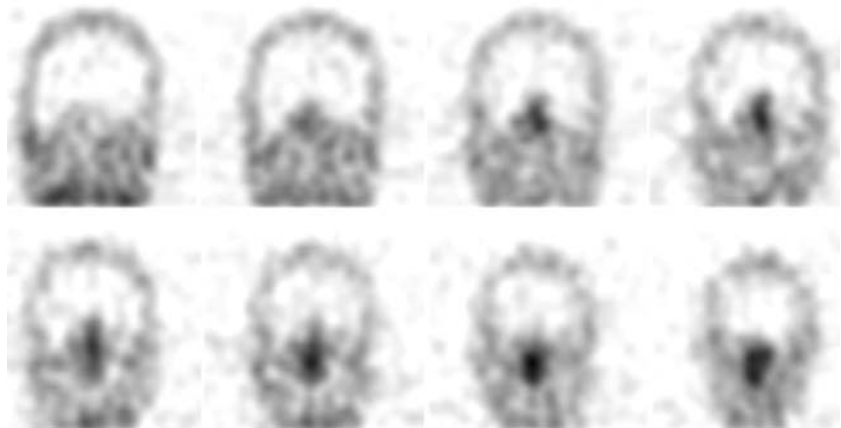
#### Somatostatin receptor imaging of pheochromocytomas and paragangliomas

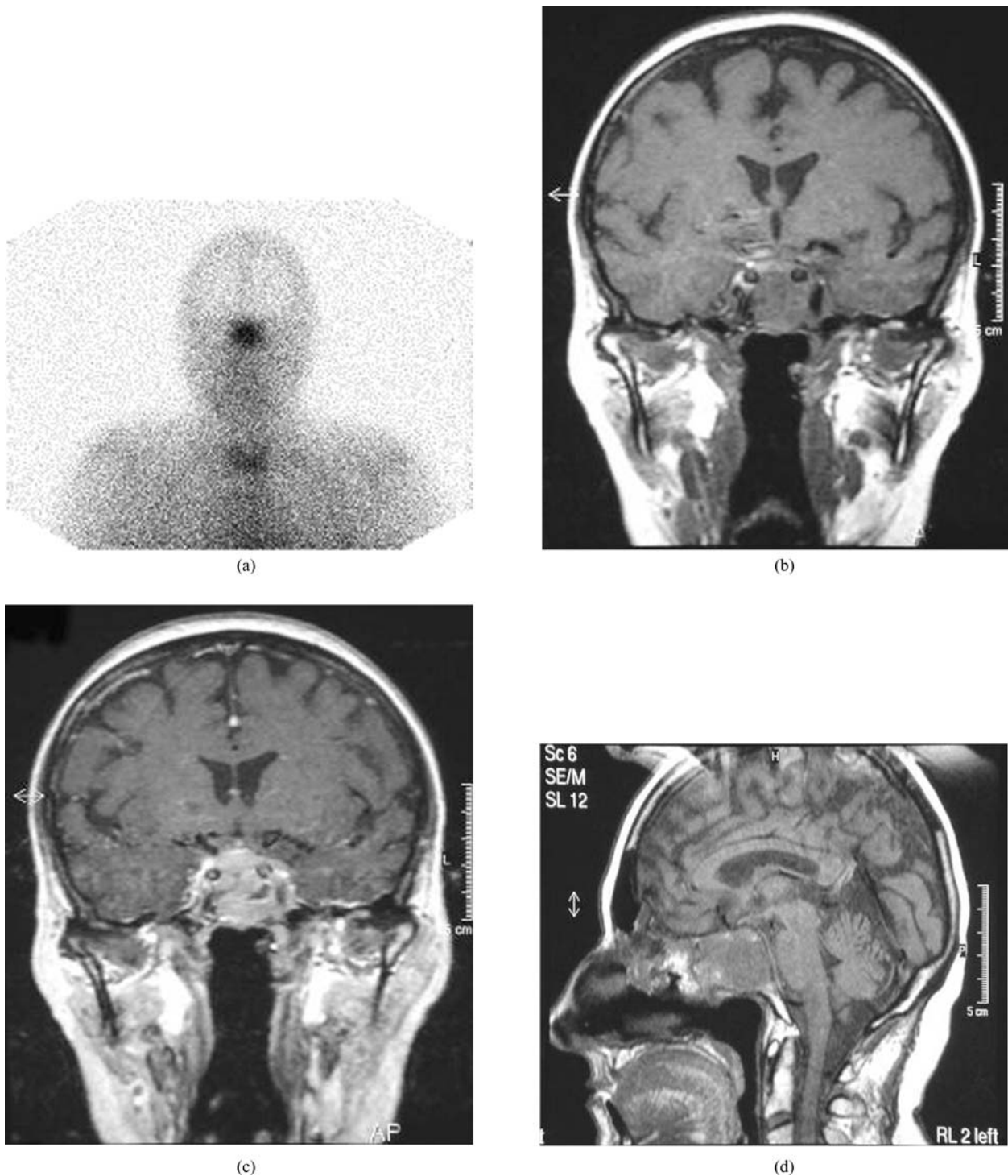
Somatostatin receptor imaging using <sup>111</sup>In-pentetreotide generally has a lower detection rate for benign pheochromocytomas than <sup>123</sup>I-MIBG scintigraphy, but it can have a complementary role for the staging of malignant pheochromocytomas. In these patients it can reveal <sup>123</sup>I-MIBG-negative lesions [24, 25]. It has also proven usefulness in the detection of extra-adrenal pheochromocytomas and (multicentric tumors or metastases of) paragangliomas [13, 26, 27].

#### Somatostatin receptor imaging of medullary thyroid carcinoma

The overall sensitivity of <sup>111</sup>In-pentetreotide scintigraphy for the detection of (metastases of) medullary thyroid carcinoma varies between 45 and 70% in different studies [28–30]. It has been used as a complementary imaging technique to CT or <sup>18</sup>F-FDG-PET. Somatostatin analogs have limited therapeutic value in some patients with metastatic medullary thyroid carcinoma [21]. Therefore, there is presently no role for this technique to select patients for treatment with the currently available octapeptide somatostatin analogs. Also tumor targeted radioactive treatment with radiolabelled somatostatin analogs in these patients is rather disappointing because of the limited tumor uptake of radioactivity.

**Fig. 1** Example of positive <sup>111</sup>In-pentetreotide scintigraphy in a patient with a GH-secreting pituitary macroadenoma





**Fig. 2** 70-years-old patient with a pituitary B-cell lymphoma. (a) Positive  $^{111}\text{In}$ -pentetreotide scintigraphy. (b) T1-weighted MRI in the coronal plane. (c) T1-weighted MRI in the coronal plane after the administration of Gadolinium-DTPA. (d) T1-weighted MRI in the sagittal plane

### Somatostatin receptor imaging of pituitary tumors

With regard to  $^{111}\text{In}$ -pentetreotide scintigraphy in patients with sellar and extrasellar tumors it is important to realize that the nonpathologic anterior pituitary gland also takes up  $^{111}\text{In}$ -pentetreotide [31]. Therefore, most studies have been

using either a visual scoring system, or cut-off values have been determined for an uptake index calculated from the uptake of radioactivity in the pituitary region of interest (ROI) divided by the uptake in a fixed background ROI. Conflicting results, especially in clinically nonfunctioning pituitary adenomas, may be caused by differences in subjective evaluation

of these images. A fixed ROI method without background correction might also be a reliable approach for measuring pituitary uptake of  $^{111}\text{In}$ -pentetreotide and may allow for separation of somatostatin receptor positive tumors from the normal pituitary [32].

The majority of GH-secreting adenomas express  $\text{sst}_2$  and  $\text{sst}_5$  (Fig. 1). Therefore, it can be expected that most GH-secreting tumors can be visualized using  $^{111}\text{In}$ -pentetreotide. In several studies an association between the increased  $^{111}\text{In}$ -pentetreotide uptake in the somatotroph pituitary tumor and the inhibition of the pathologic GH secretion by octapeptide somatostatin analogs could be found, whereas others were unable to demonstrate such a relationship [31, 33–37]. Similarly, a positive correlation between the increased  $^{111}\text{In}$ -pentetreotide uptake in TSH-secreting pituitary adenomas and the inhibition of excessive TSH secretion by octreotide has been shown [35, 38].  $^{111}\text{In}$ -pentetreotide scintigraphy was negative in patients with microprolactinomas and ACTH-secreting pituitary microadenomas [37, 39].  $^{111}\text{In}$ -pentetreotide scintigraphy was positive in patients with infiltrating macroprolactinomas and invasive ACTH-secreting macroadenomas [31, 37, 39].  $^{111}\text{In}$ -pentetreotide scintigraphy has been successful for the localization of extrapituitary ACTH- and CRH-secreting tumors and their metastases, especially in those difficult cases in which conventional radiological studies had initially failed to localize the tumors [40–51]. Similarly,  $^{111}\text{In}$ -pentetreotide scintigraphy has been shown to localize neuroendocrine tumors with ectopic GHRH secretion causing acromegaly [52].  $^{111}\text{In}$ -pentetreotide scintigraphy was also positive for a metastasis of a GH-secreting pituitary carcinoma [53].

Like in acromegaly, studies in clinically non-functioning pituitary adenomas have yielded conflicting results with regard to the presence or absence of a correlation between pituitary uptake of  $^{111}\text{In}$ -pentetreotide and the inhibition of tumor growth, or excessive hormonal secretion [35, 36].

Finally,  $^{111}\text{In}$ -pentetreotide scintigraphy allows post-surgical differentiation between scar tissue, radionecrosis and residual pituitary tumor or tumor recurrence [39, 54, 55].

A large variety of lesions in and around the pituitary region express  $\text{sst}_{2,3}$  and  $\text{sst}_5$  receptors and, therefore, can be visualized by  $^{111}\text{In}$ -pentetreotide scintigraphy. The majority of meningiomas and class III and IV gliomas, some metastases from breast carcinomas and other adenocarcinomas, osteosarcomas, Hodgkin and non-Hodgkin lymphomas (Fig. 2), abscesses and granulomatous lesions, angioleiomyomas, chordomas and hemangiopericytomas as well as fibrous dysplasia can be visualized by  $^{111}\text{In}$ -pentetreotide scintigraphy. Class I and II gliomas, neurinomas, neurofibromas epidermoids, ependymomas plasmacytomas, cranio-pharyngiomas and other cystic lesions are generally negative using  $^{111}\text{In}$ -pentetreotide scintigraphy [56–59].

## Conclusion

The role of somatostatin receptor scintigraphy in the diagnosis and differential diagnosis of pituitary tumors seems to be very limited. In registered indications for somatostatin analog therapy (acromegaly, TSH-secreting pituitary tumors), a trial of somatostatin analog therapy is more useful and provides direct information with regard to hormonal and tumor responses to these drugs. However, in gastro-enteropancreatic endocrine tumors except insulinoma, somatostatin receptor scintigraphy is considered a first-line imaging technique, generally providing whole-body information on tumor deposits and potentially predicting hormonal (and sometimes tumor) response to somatostatin analogs.

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