Somatostatin receptor imaging with ^{111}In-pentetreotide in gastro-intestinal tract and lung neuroendocrine tumors-Impact on targeted treatment

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Abstract

Somatostatin is a neuropeptide that confers a wide range of pharmacological properties. Indium-111-tagged pentetreotide (^{111}In-P) is a radiolabeled analogue of somatostatin indicated for the in vivo scintigraphic localization of neuroendocrine tumors (NET). In cases of NET of the gastro-intestinal tract we describe the sensitivity compared to conventional anatomical imaging modalities and especially the possibility that ^{111}In-P may change therapeutic management into up one fourth of the patients. In cases of small cell lung carcinoma it has been used for the evaluation of somatostatin receptor status and a substantial tool for differentiation between limited and extensive disease, especially when combined with anatomical imaging methods. We also describe the radiolabeled with yttrium-90 or lutetium-177 somatostatin analogue peptides in the treatment of NET and also the use of ^{111}In-P for the selection of patients for targeted treatment.

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Introduction

Somatostatin (SS) is a naturally occurring neuropeptide that encompasses a wide range of pharmacological properties, main as inhibiting growth hormone release and suppressing insulin and glucagon secretion [1]. The presence of SS receptors (SSR) has been documented in neuroendocrine cells and hence in a large number of neuroendocrine tumors (NET) [2]. Somatostatin is inhibiting excessive production of hormones released by NET, including carcinoids, gastrinomas, insulinomas, small cell lung carcinomas and pituitary tumors [3-6]. Radiolabelled forms of SS analogues bind to SSR on tumors, allowing visualization of primary NET and their metastases [7].

Indium-111 tagged pentetreotide (^{111}In-P) is a radiolabeled analogue of SS indicated for the in vivo scintigraphic localization of NET. Pentetreotide is an octapeptide analogue of SS coupled with a diethyleno triamino penta acetic acid (DTPA) moiety. The octapeptide portion of pentetreotide confers the receptor properties of the radiopharmaceutical, whilst the DTPA portion enables stable labeling with ^{111}In [8].

In this review we summarize the main applications and clinical impact of SS receptors scintigraphy (SSRS) in NET cases of gastro-entero-pancreatic (GEP) tumors and small cell lung NET.

Gastro-entero-pancreatic tumors

Neuroendocrine tumors of the gastro-intestinal tract (GIT) is not a common clinical entity. It has been assumed that these tumors derive from the endocrinal cells of the GIT. Visualization of the primary focus is of special clinical interest, since in some cases this procedure is time consuming and unsuccessful [10]. Computerized tomography (CT) and magnetic resonance imaging (MRI) are widely used procedures, but their usefulness (especially that of CT) seems to be limited, since these methods are not functional and GEP tumors express SSR in a high density [11]. However, some authors consider limits in SSRS, because not all GEP tumors are enriched with SSR and in some cases secondary lesions to the liver cannot be visualized due to normal accumulation [12].

Klöppel et al (2004) classified GEP-NET on basis of the World Health Organization (WHO) plus morphological and biological criteria and distinguished between benign NET, tumors with malignant potential, and tumors showing low grade and high grade malignancy [13].

In a study comprising 134 patients with GEP-NET carcinomas (WHO groups 2-4), Scintigraphy with ^{111}In-P showed superior specificity than CT (85% versus 75%) in WHO-group 2, whilst sensitivity was the same (97 versus 96% respectively). In WHO-groups 3 and 4, sensitivity of SSRS was less than 50% whilst in CT this value was as high as 100%. In WHO-group 3 patients SSRS revealed a better specificity compared to CT (100 versus 67%) [14].

The aggressive behaviour of this type of tumors was detected by means of ^{18}F-FDG-PET, with a sensitivity in groups WHO 3 and 4 of 100%. The authors conclude that diagnostic imaging of GEP-NET, consider anatomical and functional techniques, which should be read together. The ^{18}F-FDG-PET seems to be a very attractive imaging functional modality in case of patients with WHO 3 and 4 [14]. In another study with 36 patients referred for GEP tumors, no clinical, radiological or endoscopic diagnostic modalities had been able to identify the primary tumor. Functional radionuclide SSRS prompted surgery in 17% of cases and was suggestive of possible site of the primary lesion in 39% of patients [15]. Other authors comparing CT and SSRS results observed that the former detected three more lesions than anatomical imaging, whilst the latter revealed one liver lesion with no ^{111}In-P findings [16]. According to histo-pathological findings the sensitivity of SSRS was 93.8% and the specificity 86.9% [16]. In another study, with 81 GEP tumor patients, SSRS in metastatic liver disease proved to have a sensitivity of 89%, versus 81% and 88% for CT and ultrasound, respectively [17]. In nineteen (23%) of those patients, lesions were found with SSRS which had been missed using the other diagnostic modalities (Fig. 1). Finally, in 26% of the abovementioned 81 patients the therapeutic approach was modified after SSRS [17]. In a different study of 131 patients the sensitivity of SSRS in GEP tumors was 62% in the detection of the primary focus, 90% in hepatic involvement and 66% for lesions in other tissues, whilst the respective CT results were 43%, 78% and 66% respectively [18]. The specificity of radionuclide imaging with SSRS, can be improved using semi-quantitative methods, compared to qualitative criteria (88 versus 76%) [19]. The sensitivity of SSRS was higher in a series of 52 patients when single photon emission tomography (SPET) is used (89.6%), compared to 72.6% of conventional anatomical imaging modalities [20]. In this study it is reported that SSRS changed therapeutic management in 18.7% of cases. Identical were the results in a different study comprising a large number of patients (253) from three Italian hospitals [21].

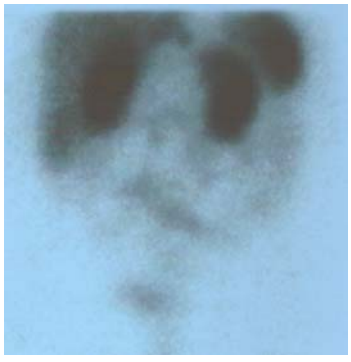

Figure 1. Insulinoma at the body of the pancreas-insulin examinations and glucose tests were positive.

In cases of pancreatic NET, SSRS results were true positive in 18/19 patients and false negative in one patient with insulinoma. Moreover, 52% of patients had management plans modified after SSRS study [22]. Other authors having studied 23 patients with GEP tumors support that in cases of pancreatic NET, SSRS contributes to the management of patients with GEP tumours in the following ways: a) localization of a primary occult tumor, allowing surgical removal, b) staging of the disease for optimal therapy-surgical excision or systemic treatment and c) identification of receptor status of the metastases for octreotide treatment or chemotherapy [23].

Although ^{18}F-FDG has been successfully and widely employed in oncology, its uptake is not high in well differentiated neuroendocrine lesions. The majority of NET is expressing SSR, they are well differentiated and therefore the role of ^{18}F-FDG-PET in these cases is limited [14]. On the contrary, other positron emitter tracers seem to be more promising. A serotonin precursor 5-hydroxytryptophan (5-HTP) labelled with ^{11}C has shown an increased uptake in carcinoids. This uptake seems to be selective and some data showed that it allows the detection of more lesions with PET than with CT or octreotide scintigraphy. Another PET radiopharmaceutical under development is carbon-11-L-desoxyphenylanine (^{11}CL-DOPA), which seems to be useful in visualizing endocrine pancreatic tumors [24]. In another study ^{18}F-FDG-PET sensitivity was at the level of 78% in cases of malignant NET of the GIT. According to authors' opinion, ^{18}F-FDG-PET proved to be a second line technique in neuroendocrine digestive tumors [25]. In this study, PET results improved clinical staging of disease and are related to survival in malignant cases of NET of the GIT [25].

Small cell lung carcinoma

Small cell lung cancer (SCLC) is a common and aggressive disease. Combined multi-agent chemotherapy and radiotherapy can improve short-term prognosis, but long-term prognosis remains dim. Somatostatin receptors have been identified on the cellular surface of subsets of this cancer and may be associated with less aggressive evolution [26]. Moreover, medical therapy with somatostatin analogues holds promise for neoplastic growth control. Thus, ^{111}In-P is a suitable radiopharmaceutical for in vivo evaluation of somatostatin receptor status of SCLC [27]. It has been postulated that ^{111}In-P scintigraphy is a suitable method for the detection of SCLC primary tumors, combined with anatomical imaging modalities, and a substantial tool for differentiation between limited and extensive disease, if combined with ultrasonography of the upper abdomen [28].

In a multicenter study concerning the diagnosis and follow-up of patients with SCLC, SSRS visualized the primary tumor with varying degrees of uptake in 96% of the examinations. Regional metastases and distant metastases were detected in 60% and 45% of the examinations, respectively (Fig. 2a and 2b). The uptake of the somatostatin analogue by the primary tumor was significantly lower in the patients examined during chemotherapy as compared to those examined before treatment. A decrease in tumor to background ratio was noted in patients with remission at the time of SSRS. Thus, this functional imaging modality may be used to follow up the course of SCLC [29]. Other authors observed that SSRS showed more extensive disease than expected by CT and no significant modification in tumor uptake of ^{111}In-P was observed in 3 out of 19

patients studied before and after chemotherapy [30]. In another study concerning evaluation of patients with SCLC it has been found that staging with ^{111}In-P successfully located the primary tumour site with a sensitivity of 92%. Although detection of mediastinal lymph node dissemination by SSRS was also relatively high (83%), this method failed to detect most of the metastatic lesions outside the thorax (9 of 36, 25%) [30].

The sensitivity of SSRS for the detection of malignant secondary of SCLC lesions in the liver, adrenals, and bones, was 56%, 33% and 17%, respectively [31]. The authors conclude that ^{111}In-P may be used in addition to

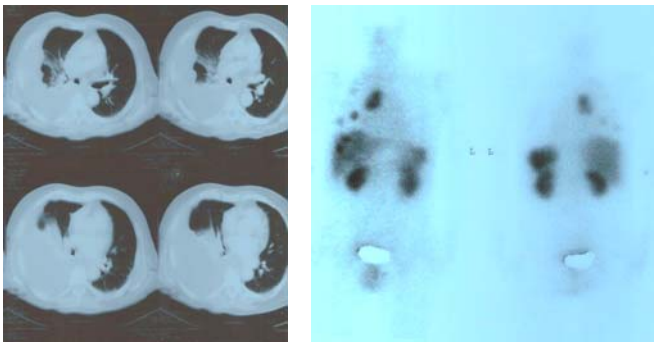

Figure 2a. Chest CT of a patient with small cell lung carcinoma showing infiltration of the hilum of the right lung plus parenchymal involvement. **2b.** The same patient's SSRS showing matching results with CT, with accumulation of the radiopharmaceutical at the hilum and lower field of the right lung, plus foci at the liver (secondary involvement)-compatible with tumor of neuroendocrine origin.

current SCLC staging methods [31].

Somatostatin receptor scintigraphy with ^{111}In-P has high sensitivity for detecting the primary tumor in SCLC, but low sensitivity for the detection of distant bone metastases. That is presumably due to the absence of SSR with high affinity for SS or to the presence of SSR subtypes with low affinity for SS. Bone scintigraphy is a more sensitive modality to detect bone abnormalities in patients with SCLC compared to SSRS, possibly due to low expression of SSR [32]. Other authors compared the value of CT and conventional bone scan with that of novel SS analog ^{68}Ga-1,4,7,10-tetraazacyclododecane-N,N',N'',N'''-tetraacetic-acid-d phe(1)-tyr(3)-octreotide (^{68}Ga-DOTATOC) in the detection of such metastases. Molecular (PET) imaging with ^{68}Ga-DOTATOC detected bone metastases at a significantly higher rate than did CT. Furthermore, conventional bone scans confirmed the results of SSR PET but did not reveal additional tumours sites [33]. The authors conclude that ^{68}Ga-DOTATOC PET is a reliable, novel method for the early detection of bone metastases in patients with NET. Conventional bone scintigraphy and CT scans are less accurate than ^{68}Ga-DOTATOC PET in the primary staging or restaging of NET.

In another study concerning non-small cell lung carcinoma (NSCLC) imaging with SSRS, the method correctly identified sites of tumour involvement as detected by chest CT and surgery in all 10 patients with NSCLC [34]. Functional imaging with SSRS in cases of NSCLC may serve as a potentially useful adjunct to CT for identifying obscured or equivocal lesions and as an aid in localizing tissue for biopsy [34].

Role of somatostatin analogues in the treatment of neuroendocrine tumors

Neuroendocrine tumors that contain SSR may be susceptible to supplementary treatment with SS analogues. Several groups started treatment of patients suffering from NET SSR-positive tumours with multiple doses of ^{111}In-P with promising results; a remission rate of up to 8% was achieved and stabilization of previously progressive tumours was seen in a high percentage of patients, with the best efficacy obtained in cases with high uptake of radioactivity in the tumour [35-37]. At present the therapeutic use of SS analogues can be schematised as a) pharmacological treatment (with cold octreotide); b) surgical treatment (radioguided surgery); c) radiometabolic treatment with tagged octreotide [37]. Ytrium-90-labelled octreotide achieved better therapeutic results than those with ^{111}In-octreotide [38].

Treatment with radiolabeled SS analogues is a promising new tool in the management of patients with inoperable or metastasized, well-differentiated NET. Symptomatic improvement may occur with all ^{111}In, ^{90}Y, or ^{177}Lu-labeled SS analogues that have been used for peptide receptor radionuclide therapy. The results that were obtained with [^{90}Y-DOTA(0), tyr(3)]octreotide and [^{177}Lu-DOTA(0), tyr(3)]octreotate are very encouraging in terms of tumor regression [39]. The median duration of the treatment response for these radiopharmaceuticals is 30 and 40 months, respectively [39]. Such therapy may well become the treatment of first choice in patients with metastasized or inoperable NET [40].

The first SS analogue labelled with ^{90}Y and applied for radionuclide treatment of NET was ^{90}Y-DOTA(0), tyr(3)]octreotide (^{90}Y-DOTATOC), in which in comparison with ^{111}In-DTPA-octreotide, presents a higher affinity to subtype 2 of SS (sst2) receptors, due to replacement of phenylalanine in position 3 with tyrosine. This is leading to higher uptake in sst2 positive tumors [41]. In addition, another radiopharmaceutical used for treatment of NET, [tyr(3)]octreotate DOTA, has higher affinity for sst2 compared to ^{90}Y-DOTA(0), tyr(3)]octreotide (DOTATOC) [41]. High-administered activity ^{111}In-octreotide (HA-Oc) therapy has been used for patients with disseminated NET with high SSR expression. Combining HA-octreotide with radiosensitizing 5-fluorouracil (5FU) chemotherapy could enhance efficacy. In 15 consecutive patients with NET who received 3 cycles of combined treatment with HA-octreotide and 5-FU, disease stabilization was achieved in the majority of patients with previously progressive disease. Accordingly to ^{111}In-P imaging, stabilization was mentioned in 95% and accordingly to CT imaging in 80% of patients [42].

Radionuclide treatment with ^{90}Y-DOTA(0), tyr(3)]octreotide (DOTATOC) is an experimental treatment used in patients with tumors which show an enhanced sst2 receptors expression [43]. Prerequisite for a ^{90}Y-DOTATOC treatment is an enhanced ^{68}Ga-DOTATOC PET study in the tumors prior to therapeutic approach [44]. Therapeutic effect is expected mainly in the sst2 receptors positive lesion, which was the primary tumor. However, there are cases of pancreatic NET with advanced liver metastases, in which no recurrence of the tumor or other metastases were found at the one year follow-up after treatment with ^{90}Y-DOTATOC [45]. In addition, in a case report concerning a patient with medullary thyroid carcinoma with right ventricular secondary involvement, treatment with ^{90}Y-DOTATOC

had a good therapeutic result, with stabilization of the disease [46].

In cases of targeted treatment with SS analogues and because of the excretion of the radiopharmaceutical through the kidneys, nephrotoxicity can be produced due to reabsorption of the radiopharmaceutical from the renal tubules [47]. This side effect can be avoided through the intravenous infusion of amino-acids, before, during and 4h after the radiopharmaceutical administration. Thus, radiation burden to the kidneys and bone marrow is reduced below safety limits for the patients [48]. Also, in cases of treatment with ^{90}Y-DOTATOC, reversible grade 2 and grade 3 haematological toxicity was found in patients injected with 5.18GBq, which was defined as the maximum tolerated dose per cycle [49, 50].

In conclusion, functional radionuclide imaging with ^{111}In-P is a well established method for the diagnosis of various tumors expressing SSR. In cases of GEP NET its high sensitivity has established it as method of choice compared to US and CT and in SCLC, if combined with anatomical imaging modalities is a suitable radiopharmaceutical for evaluation of SSR status and a substantial tool for differentiation between limited and extensive disease. In addition, it can be used for the selection of patients for targeted treatment with radiolabeled SS analogues. Side effects of targeted treatment on the kidneys can be avoided through infusion of aminoacids.

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Sunrise at Chalkidiki. The sun rises behind the top of the Holy Mountain Athos (3rd peninsula) and shines the sea between the 2nd and 1st peninsulas of Chalkidiki. Photographed by Professor I. Dokmetzioglou.