Changing role of somatostatin receptor targeted drugs in NET: Nuclear Medicine's view

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This publication is dedicated to the late Antoine A. Noujaim. Tony was a great researcher with a never resting mind who triggered a number of important ideas and developments. Above all, he was a true friend for over 20 years (R.P.B.).

INTRODUCTION

The present era of oncology is characterized by manifold and rapid advances in the management of solid tumors. New treatment modalities and new agents such as neo-adjuvant chemoradiation in rectal cancer or targeted therapies in non-small cell lung cancer have not only remarkably prolonged the survival, but also improved the quality of life of an ever increasing number of patients with solid neoplasms.

At the same time, and without receiving comparable attention, similar advances have been made in the treatment of neuroendocrine tumors (NET). NET are a heterogeneous group of neoplasm originating from endocrine cells (pluripotent stem cells) (1) and characterized by the ability to synthesize and store various biogenic amines and peptides (2). Several metabolic pathways of neuroendocrine cells for diagnosis as well as therapy have been recently identified. While most of the symptoms associated with functionally active NET are due to a variety of biogenic amines, the polypeptide serotonin is indeed responsible for the majority of clinical manifestations in NET disease. The discovery in 1980s that NET express peptide receptors had a major impact on the management of NET first due to the development of pharmacological agents acting as antagonists of the peptide disease mediators, and later due to the design of peptide-specific radio-receptor therapies.

The natural history of NET usually parallels the slow progression of other indolent solid neoplasms. Most NET are slow growing (well differentiated), however, aggressive (poorly differentiated) variants can be observed at initial diagnosis or, more frequently, during the final stage of the disease. During the course of disease progression, patients are increasingly encumbered by symptoms such as diarrhea, flush, pain and weight-loss caused by amines secreted in ever increasing concentration by an increasingly bulky disease (2). Blocking the release of such amines by specific antagonists can cause significant relief to patients with NET in the terminal symptomatic phase of their malignancy. Traditionally, the most well known and active agent in this class of drugs has been Somatostatin (SST).

SOMATOSTATIN AND SOMATOSTATIN RECEPTORS

Somatostatin (SST) is a naturally occurring peptide with diverse functions. It was first isolated in 1973 (3) based upon the observations of Krulich et al. (4) during the search for a growth hormone-releasing factor. Since its discovery, various subtypes of SST have been isolated: SST-14 with 14 amino acids, prosomatostatin (SST-28) with 28 amino acids and preprosomatostatins with 120 amino acids (5-7).

Native SST is an inhibitory peptide displaying exocrine, endocrine, paracrine and autocrine functions (7). It primarily inhibits the release of growth hormone and gastrointestinal hormones. In contrast to these hormones, the inhibitory function of SST also modulates gastric acid secretion, gastric motility, intestinal absorption, as well as pancreatic enzyme and bicarbonate secretion. Because of the wide number of organs on which SST imposes its inhibitory activity, it is often characterized as the "universal endocrine off-switch".

The action of somatostatin is mediated through several membrane bound receptors (SSTR). At present, five different subtypes of SSTR have been recognized (SSTR1-5), with SSTR2 having been further classified into subtypes SSTR2A and SSTR2B (2,8).

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The most commonly used technique for studying the expression of various subtypes of SSTRs is based upon detection of corresponding mRNA using Northern blots, in situ hybridization, RNase protection assays and RT-PCR (Reverse Transcription-Polymerase Chain Reaction); RT-PCR is the most sensitive method, however, lack of specificity and insufficient reliability and reproducibility of quantitative measurements due to over-sensitive assays remain a problem (9,10).

The distribution of various SSTR subtypes in the normal physiologic tissues and tumors have been extensively studied. Many of these studies have been conducted by Reubi and his co-workers using autoradiographic techniques. Their work has shown that most of the NET overexpress the SSTR2 subtype. A list of tumors and their preferential

SSTR expression based upon the studies of Reubi et al. (11) is shown in Table 1.

In discussing the biology of this peptide, it should be kept in mind that many normal tissues also express SSTR such as the pituitary gland, cerebellum, salivary glands, thyroid, parathyroid, vessels, lymphocytes, monocytes, macrophages, spleen, activated lymph nodes (germinal center), gastric mucosa, duodenum, ileum, colon, pancreas, bronchial gland, testes, ovary, and myocardium (8,11,12). Currently, it is assumed that SSTRs, irrespective of subtype, decrease intracellular cAMP concentration after activation by a specific ligand (13). Ongoing research is dedicated to delineate the intracellular mechanisms effected by different SSTRs with regards to their effect on cellular proliferation and possibly also the induction of apoptosis.

Table 1. Tumors having documented somatostatin receptor expression

Tumor types	Receptor subtypes
Gastroenteropancreatic NET	sstr1, **sstr2**, sstr5
Neuroblastoma	**sstr2**
Meningioma	**sstr2**
Breast cancer	**sstr2**
Medulloblastoma	**sstr2**
Lymphoma	**sstr2**,sstr5
Renal cell carcinoma	**sstr2**
Paraganglioma	sstr1, **sstr2**, sstr3
Small cell lung cancer	**sstr2**
Hepatoma	**sstr2**
Prostate cancer	**sstr1**
Sarcoma	**sstr1**, sstr2, sstr4
Inactive pituitary adenoma	sstr,1, sstr2, **sstr3**, sstr5
Growth hormone producing pituitary adenoma	**sstr2**, sstr3, **sstr5**
Gastric carcinoma	**sstr1**, **sstr2**, sstr5
Ependydomas	sstr1
Pheochromocytoma	**sstr1**, **sstr2**, sstr5
Non-small cell lung cancer	-
Pituitary adenoma	-
Medullary thyroid carcinoma	-
Merkel cell skin carcinoma	-
Ganglioma	-
Ganglioneuroblastoma	-

Diagnosis of NET

Once clinical suspicion has been raised, the secretion of various, well characterized biogenic amines and peptides make the diagnosis of NET

relatively easy. However, not all NET secrete hormones or amines high enough above the physiological level to produce the typical clinical symptoms. Therefore, NET can be grossly

categorized into a functional and a nonfunctional group, the latter being relatively difficult to diagnose at an early stage. In such tumors (approximately 30-50% of NET) the clinical symptoms are mainly due to the effect of large tumor burden.

Confirmation of the clinical diagnosis of a functional NET requires the measurement of biochemical tumor markers such as serotonin (SST), chromogranin A (CGA) and neuron specific enolase (NSE). Amongst these, CGA is most commonly measured, however, it is also frequently elevated in non-functioning NET. CGA levels are significantly elevated in the majority of NET, specifically in classical mid-gut NET where levels may rise as high as 100- to 1000-fold. Since CGA is a very stable molecule, no special preparation is needed to store the serum or plasma. Several radioimmunoassays and ELISA tests are commercially available for the detection and quantification of CGA in serum.

Once the diagnosis of suspected NET has been ascertained by the identification of typical biochemical markers, various imaging techniques have to be employed to determine location, size and extent of primary tumors and of metastatic disease. Computed tomography (CT), ultrasound (USG), and magnetic resonance imaging (MRI) are most frequently employed, however, neither of these technologies is capable of providing information about the functional status of NET. Moreover, CT, USG and MRI are much less precise and much slower in detecting response to therapy of NET when compared with functional imaging.

For these reasons, diagnosis, staging and assessment of treatment response in NET are the domain of an increasingly sophisticated and reliably array of nuclear medicine imaging techniques. Utilizing the over-expression of SSTR on NET, several somatostatin analogues have been radiolabeled to assist in the diagnosis of SSTR positive NET using a gamma camera (preferentially single photon emission computed tomography, SPECT, Figures 1a and 1b) or Positron Emission Tomography (PET).

Somatostatin receptor scintigraphy (SRS) using ^{111}In-DTPA-OC (^{111}In-DTPA- D-Phe1-octreotide, Octreoscan) is considered as the 'gold standard' in
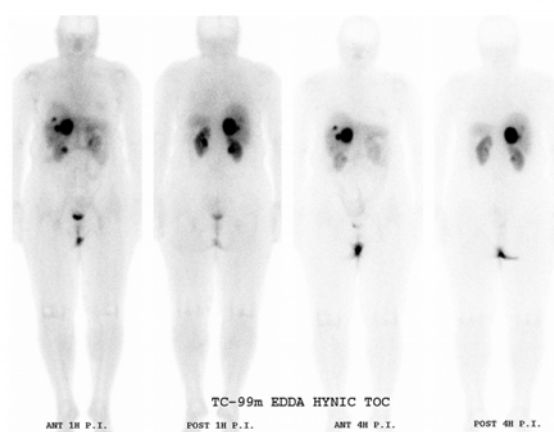

Figure 1a. Whole-body scintigraphy (anterior and posterior views, 1 hr and 4 hrs p.i. of a Tc-99m labeled somatostatin anlogue (99mTc EDDA Hynic TOC): intense somatostatin receptor expression in multiple liver metastases of a neuroendocrine carcinoma.
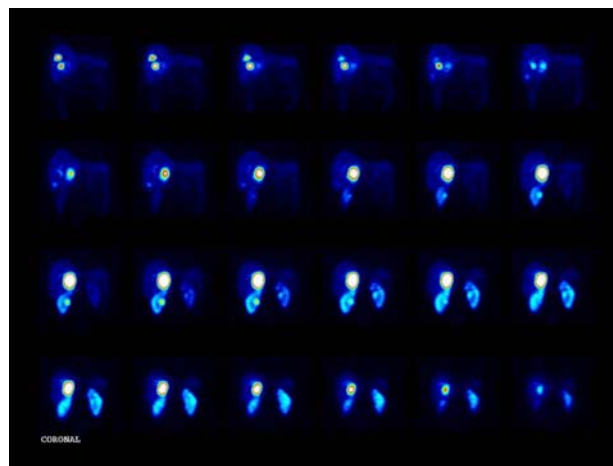

Figure 1b. Coronal SPECT slices enable detection of relatively small liver metastasis (about 10 to 15 mm in diameter).

the diagnosis, staging and follow-up of patients with NET. However, the use of more suitable somatostatin analogues {DOTA-TOC (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid), DOTA-NOC (DOTA-1-Nal[3]-octreotide), DOTA-TATE (DOTA-D-Phe[1]-Tyr[3]-Thr[8]-octreotide) DOTA-NOC-ATE((DOTA-1Nal[3],Thr[8])-octreotide), DOTA-BOC-ATE ((DOTA, BzThi[3], Thr[8])-octreotide)}(2,14) tagged with positron emitting radionuclides (^{68}Ga, ^{64}Cu) in PET-CT has lead to

levels of sensitivity and specificity even highs than those achieved by ^{111}In-DTPA-Octreotide SPECT.

Our group has introduced ^{68}Ga-DOTA-NOC (Figure 2) and ^{68}Ga-DOTA–TATE for routine receptor PET/CT (over 1,500 studies as of March 2007) and ^{90}Y-DOTA-TATE / ^{177}Lu-DOTA-TATE for peptide receptor radionuclide therapy of neuroendocrine tumors (utilized in more than 350 patients as of December 2006). In an intra-individual study comparing the diagnostic efficacy of ^{68}Ga-DOTA-NOC and ^{68}Ga-DOTA–TATE, we have demonstrated for the first time that ^{68}Ga-DOTA-NOC is superior to ^{68}Ga-DOTA–TATE (15).

Several other radiopharmaceuticals have also been successfully employed (Table 2). SSTR antagonists, (NH(2)-CO-c(DCys-Phe-Tyr-DAgl(8)(Me,2-naphthoyl)-Lys-Thr-Phe-Cys)-OH (sst(3)-ODN-8) and (sst(2)-ANT) have also been labeled with ^{111}In, and their superiority over SSTR agonists in mice models for in-vivo targeting of SSTR2 and SSTR3 rich tumors, as shown by the group of Reubi (16,17), has led to them being now considered as additional tools for tumor diagnosis.

NET offers the unique possibility for disease-specific functional imaging and peptide-specific serological monitoring during the treatment of a human solid tumor. However, competent and complete histopathological confirmation remains highly important in these rare tumors to allow for an exact classification and treatment stratification of NET. One key feature is the ascertainment that sufficient tumor material is collected for grading the tumor into differentiated and undifferentiated tumors.
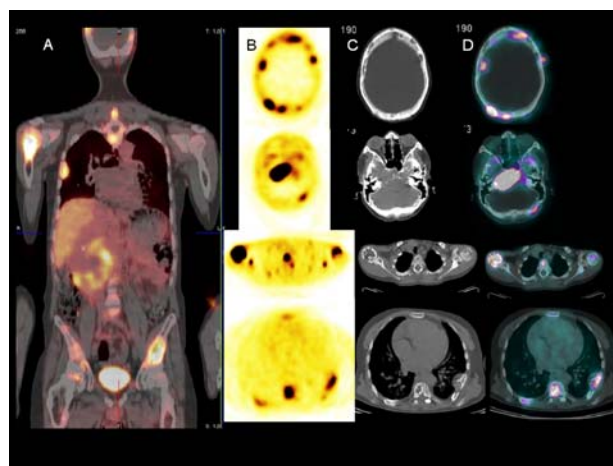

Figure 2. *[68]Ga DOTA-NOC receptor PET/CT (A: maximum intensity projection images (MIP) image) in a 24-year old paraganglioma patient 7 years after the first PRRT with ^{90}Y DOTA-TOC (1.85 GBq). Transversal PET slices (B), CT scans (C), and fused images (D) show multiple osteolytic lesions in the skull, the humeri, the ribs and the vertebra with intense SMS-receptor expression.*

Table 2. Various radiopharmaceuticals currently in use for imaging of NET

Imaging	Radiopharmaceuticals
PET and PET/CT	^{18}F-FDG
	^{68}Ga-DOTA-NOC, ^{68}Ga-DOTA-TOC, ^{68}Ga-DOTA-TATE,
	^{68}Ga-AMBA (bombesin anologue), ^{68}Ga-minigastrin (gastrin analogues)
	^{11}C-5-HTP
	^{11}C-DOPA
	^{18}F-DOPA
	^{18}F-FDA
	^{64}Cu-TETA-octretoide
	^{18}F-FP-Gluc-TOCA
	^{11}C-Ephidrine
	^{11}C-Hydroxyephidrine
Gamma camera (SPECT)	^{111}In-somatostatin analogues, e.g. ^{111}In-DTPA-octreotide
	^{99m}Tc-HYNIC-TOC and –TATE
	^{131}I-MIBG
	^{123}I-MIBG
	[99m]Tc DMSA(V)

Parameters relevant for this crucial classification are tumor size, invasion of nearby tissue or wall, invasion beyond the submucosa, angioinvasion, perineural space invasion, presence of necrosis, solid, organoid structure, Ki-67 index >2%, more than two mitoses per high power field, loss of chromogranin A (CgA) immunoreactivity and argyrophilia or hormone expression.

The current classification of NET as provided by WHO (World Health Organisation) is based upon histopathology (Table 3).

Table 3. WHO classification of endocrine tumors

Category
• Well differentiated endocrine tumor
• Well differentiated endocrine carcinoma
• Poorly differentiated endocrine carcinoma
• Mixed exocrine-endocrine tumor
• Tumor like lesion

THERAPY

Curative treatment of NET usually requires the possibility of complete surgical resection of the primary tumor and perhaps regional lymph node metastases. However, effective palliative therapies are also available at all stages of the disease and can be applied even to advanced conditions with a crippling symptomacy. As opposed to most other solid tumors - with the exception of differentiated thyroid cancer - the advent of more effective and specific palliative treatment strategies in NET has largely depended on newly developed nuclear medicine therapies such as peptide receptor radionuclide therapy (PRRT)

Depending upon tumor stage, size, localization and degree of differentiation, treatment protocols for NET are currently based upon the following therapeutic modalities:
1. Surgery
2. Intra-arterial chemoembolisation
3. Immunological therapy (Interferon)
4. Chemotherapy
5. Therapy with somatostatin analogues
6. Peptide receptor radionuclide therapy (PRRT)
7. Intra-arterial PRRT

This article will focus primarily on the role of therapy with somatostatin analogues and PRRT. Other therapeutic options will be briefly discussed.

Surgery

As with most other solid tumors, surgery remains the mainstay for curative treatment of NET. Apart from removing primary tumors and resectable metastases with curative intent, cytoreduction by tumor-debulking and palliation of symptoms by targeted resection of symptomatic tumor sites are important forms of operative approaches in NET. Technically, the term cytoreductive surgery may include surgical resection of tumor, cryotherapy, radiofrequency ablation or other forms of localized tumor destruction.

The primary goal of cytoreductive surgery is to lessen tumor burden. In suitable cases, this maneuver can lead to a pronounced and prolonged improvement quality of life by alleviating symptoms due to excessive hormone production. Resecting of a significant majority of malignant tissue in patients with NET can moreover lead to improved survival in selected individuals. A meta-analysis of the results of cytoreductive surgery in NET showed that the mean 5-year survival rate in mid-gut NET patients undergoing cytoreduction, and in patients with metastatic islet cell tumors following partial hepatectomy, is more than 50%.

When inoperable or intractable hepatic metastases are documented in the absence of extrahepatic disease, orthotopic liver transplantation by specialized centers is another surgical treatment option. Five-year survival rates of patients following orthotopic liver transplantation for metastatic NET is ~50% with a median survival of 5.1 years (18).

Intra-arterial chemoembolisation
Liver is the most common site of metastases in NET. Hepatic intra-arterial chemoembolisation (using cytotoxic chemotherapy combined with local ischemia) has achieved significant success in controlling locoregional disease (tumor shrinkage) and its associated symptoms.

Interferon
Interferon has been used in mid-gut NET for more than two decades in spite of a plethora of side-effects (flu-like syndrome, autoimmune reactions, etc) because of its documented ability to induce tumor reduction in up to 15% of patients, and symptomatic and/or biochemical improvement in more than 50% of patients. However, when the

choice exists between somatostatin and interferon, the former is the preferred drug (1-19).

Chemotherapy
Another peculiarity that separates NET from most other solid tumors (except thyroid cancer, GIST tumors, and carcinosarcomas) is the deplorable fact that chemotherapy is largely ineffective regardless of the choice of drugs, regimens or dose intensity. The only, yet notable, exception are pancreatic tumors, some of which can be effectively palliated by cytotoxic agents. For all other NET, the anti-tumor activity of streptozocin (STZ), doxorubicin, fluorouracil (FU), dimethyltriazenoimidazole (DTIC), mitoxantrone and paclitaxel has been investigated as single drugs, or in combination with very little success. Unlike other endodermal tumors, NET are as a rule relatively chemoinsensitive. In pancreatic NET, STZ alone or in combination with FU/doxorubicin is commonly utilized in advanced stage (20-23). A major concern with the use of these drugs in this setting is the prohibitive toxicity (diarrhea, renal toxicity, liver failure, cardiac toxicity).

Therapy with somatostatin analogues
The use of somatostatin analogues in NET is perhaps the most important, and certainly one of the most interesting areas of research. Currently, somatostatin analogues are primarily used for controlling the symptoms associated with NET. Some reports have also suggested a moderate antiproliferative effects associated with the use of this agent.

For a number of reasons, native Somatostatin is unsuitable for the therapy of patients with NET.

The most important problems are:
- short duration of action (half life < 3 minutes)
- need for parenteral (i.v.) administration
- rebound hypertension post infusion (4,24).

These features (that mirror the biochemical activities of Somatostatin in the healthy human organism) necessitated the development of synthetic somatostatin analogues more suitable for the treatment of human malignancies derived from neuroendocrine tissues. The most commonly utilized synthetic somatostatin analogues are octreotide, lanreotide, and vapreotide, all of which differ in their affinity to different SSTR subtypes

(2,25-28). Table 4 shows comparative affinity profile of these analogues.

Octreotide was the first synthetic analogue with a significantly prolonged half-life to be developed. It can be administered both subcutaneously (s.c.) or intramuscularly (i.m.) and does not cause rebound hypersecretion. The long-acting reagent (LAR) formulation (Sandostatin LAR) is injected intramuscularly every 4 weeks whereas the s.c. administration is given several times per day. The inhibitory function of somatostatin analogues is responsible for counterbalancing the hypersecretion of biogenic amines/hormones and in the control the symptoms. These effects are most pronounced in patients having SSTR2/SSTR5 positive tumors (Table 1). Some antiproliferative activity is also observed (29). Since most (>80%) of the NET express SSTR2, the clinical effects of these analogues are often impressive.

Before the initiation of treatment with SST analogues, it is imperative to document the presence of SSTR expression, either by use of an *S*RS/somatostatin-receptor (SR) scintigraphy (OctreoScan) or by SR-PET/CT. Where SR imaging is not available, demonstration of a decrease of 50 % of the secreted peptide/amine after s.c. administration of 100 μg Octreotide can be an option. The role of somatostatin analogues in the treatment of non-functioning NET is questionable and is generally not recommended.

Both lanreotide and octreotide are very effective in controlling diarrhea and flushing (with octreotide being more effective than lanreotide, Table 5). Octreotide is available in both, short and long acting forms, while lanreotide is only available as long acting release formulation. The side effects (nausea, abdominal cramps, loose stool, mild steatorrhea) commonly observed with the use of these agents are probably related to a suppression of exocrine pancreatic functions. The side effects are dose dependent, begin within hours of the first injection and subside spontaneously within the first few weeks of treatment.
Other significant side effects are glucose intolerance, overt diabetes mellitus and (rarely) gastric atony (30,31).

Table 4. Affinity profile (IC_{50} expressed in nanomoles) of various somatostatin analogues

Compound	SSTR	SSTR2	SSTR3	SSTR4	SSTR5
Native somatostatin (14)	0.93 ± 0.12	0.15 ± 0.02	0.56 ± 0.17	1.5 ± 0.4	0.29 ± 0.04
Native somatostatin (28)	5.2	2.7	7.7	5.6	4.0
Octreotide	180 ± 20	0.54 ± 08	14 ± 9	230 ± 40	17 ± 5
Lanreotide	280 ± 80	0.38 ± 0.08	7.1 ± 1.4	>1000	6.3 ± 1.0
SOM230	9.3 ± 0.1	1.0 ± 0.1	1.5 ± 0.3	>100	0.16 ± 0.01
In-DTPA-octreotide	>10,000	22	182	>1000	237
In-DOTA-[Tyr3]octreotide (DOTA-TOC)	>10,000	4.6	120	230	130
Y-DOTA-TOC	>10,000	11	389	>10,000	114
Ga-DOTA-TOC	>10,000	2.5	613	>1000	73
DOTA-lanreotide (DOTA-LAN)	>10,000	26	771	>10,000	73
DOTA-[Tyr3]octreotate (DOTA-TATE)	>10,000	1.5	>1000	453	547
In-DOTA-[1-Nal3]octreotide (DOTA-NOC)	>10,000	2.9	8	227	11.2
Y-DOTA-[1-Nal3]octreotide (DOTA-NOC)	>1000	3.3	26	>1000	10.4
In-DOTA-NOC-ATE	>10,000	2	13	160	4.3
In-DOTA-BOC-ATE	>1000	1.4	5.5	135	3.9

Table 5. Comparison of octreotide and lanreotide (modified from Oberg et al.[32])

Symptom	Octreotide	Lanreotide
Diarrhea	50 % ↓	45 % ↓
Flushing	68 % ↓	54 % ↓
Gastrointestinal disorders, biliary disorders, pain at the injection site	+	+
Short acting formulation	Available	Not available
Administration interval	Daily (s.c.) / every 4 weeks (LAR)	2-4 weeks

Table 6. Radionuclides commonly used for PRRT of NET. The pathlength equivalent in cells is calculated assuming the average cell diameter to be 20 µm, based upon the study of O'Donoghue et al.[38].

Radionuclide	Radiation emitted	Half life	Pathlength in tissue
[111]In*	Auger electrons and γ radiation	2.8 days	10 µm (< 1 cells)
[90]Y	Beta particles	2.7 days	12 mm (~600 cells)
[177]Lu	Beta particles and γ radiation	6.7 days	2 mm (~100 cells)

*Efficacy has not been demonstrated in a controlled clinical trial

Because of these potential adverse effects, it is advisable to use s.c. somatostatin analogue first, and the subsequently switch to the LAR formulation once drug tolerance with the shorter acting drug has been documented.

Somatostatin-induced inhibition of the gall bladder motility, cholecystokinin secretion and increased production of deoxycholic acid is responsible for the gall stone formation in roughly 50% of patients with metastatic gastrointestinal NET or islet cell tumors. Despite the high incidence of gall stone formation in patients treated with somatostatin analogues, only ~1% of patients require cholecystectomy for symptomatic disease. Nonetheless, given the high incidence of gall stone

formations in these patients, it is often recommended to perform an add-on cholecystectomy in NET patients undergoing bowel surgery/cytoreductive surgery (debulking).

Patients are first tested for tolerability for 3-7 days giving s.c. injection (100-500 µg, 2-4 times/day), and, if tolerant, receive the LAR intramuscular injection (10-30 mg/28 days) under a protective cover of further s.c. injections for another 14 days. The rationale for this approach is based on the observation that additional s.c. dosing for breakthrough symptoms is frequently required when LAR drugs are utilized alone during this phase of therapy.

The dose of the LAR formula is then further increased under cover of s.c. injections until a satisfactory symptom control can be achieved by LAR treatment alone. Therapy with octreotide in patients with NET often has to be continued for the duration of the disease, i.e. lifelong. Follow-up of treatment efficacy depends upon a critical assessment of symptoms and biochemical markers (CgA, 5-HIAA) using SRS, SR-PET/CT or CT/MRI/USG (32), and should be performed at least every 3 to 6 months. Response criteria used for monitoring octreotide therapy are reduction of >50 % tumor markers in serum/urine, and RECIST criteria/WHO criteria. We wish to emphasize that in our experience the application of RECIST criteria alone using CT, USG, or MR is often misleading or insufficient in NET; here, information provided by more sophisticated and specific techniques such as SR-PET/CT using ^{68}Ga-DOTA-NOC PET/CT usually is of largely superior clinical utility.

The role of somatostatin analogue therapy in NET as antineoplastic drug has always been, and remains highly controversial, mainly because the intrinsic antiproliferative action of somatostatin is quite weak. A meta-analysis of 22 case reports, 5 phase I, 47 phase II trials, and 8 randomized clinical trials showed that synthetic somatostatin analogues (octreotide, lanreotide, vapreotide) have a high therapeutic index and good efficacy in controlling symptoms; however, their use as an antineoplastic drug outside clinical trials could not be recommended (33), despite the fact that conversion of progressive disease to stable disease upon the

institution of octreotide therapy was observed in up to one third of the patients in some studies (34).

In an open Phase III trial, conducted by Erikson et al. (35) in 35 patients, stabilization of disease was achieved in 68 % of patients receiving s.c. somatostatin, whereas progressive disease was seen in 24 % of patients at 6 months. In another study by the same group, using lanreotide, partial remission (PR) was achieved in 5 % of patient while 70 % of patients showed stable disease (SD) (36). In another study by Wymenga et al. in patients with gastroenteropancreatic tumors tumor regression was seen in only 6 % (2/31) of patients receiving long acting lanreotide (37).

So far, the efficacy of somatostatin analogue therapy for control of symptoms has not been compared to the effects of peptide receptor radionuclide therapy (PRRT), another treatment concept, based upon the over-expression of SSTR on NET.

PRRT

Based on the success achieved by SRS, somatostatin analogues were labeled with particle emitters such as ^{90}Y, ^{177}Lu, ^{111}In and used for therapy. These three radionuclides differ significantly in their physical properties. ^{111}In emits auger electron and conversion electrons which have a path length in tissue of only 0.02-10 and 200-500 µm, respectively. Studies demonstrating the internalization of ^{111}In DTPA-octreotide in tumor cells have clearly shown that the therapeutic effect of this radionuclide is due to the auger electrons and not to the conversion electrons. The low tissue penetration path-length of auger electrons results in reduced tissue toxicity, however, in our mind it is not sufficient for achieving a satisfactory therapeutic effect due to lack of a 'cross fire' effect whereby non SSTR positive cells could also receive lethal radiation damage.

The limitation in the therapeutic utility of ^{111}In DTPA-octreotide led to tagging of SSTR analogues with beta particle emitting radionuclides such as ^{90}Y and ^{177}Lu. Numerous studies have documented that the tumor shrinking capacity of ^{90}Y and ^{177}Lu labeled SSTR analogues is much higher than that achieved with ^{111}In labeled SSTR agents. The most

important physical properties of these three radionuclides are presented in Table 6 (38).

Based upon a mathematical model for determining tumor curability in relation to tumor size (38), de Jong et al. (39,40) have demonstrated in a rat model that ^{90}Y is more effective in killing bulky tumors, whereas ^{177}Lu is more effective in small tumors; a combination of both radionuclides resulted in better control of both, small and large tumors.

The clinical efficacy of different radiolabeled somatostatin analogues varies from tumor to tumor because of their affinity to different SSTR subtypes. As can be seen from Table 4, unlabeled octreotide ('cold') has highest affinity for sstr2, binds with somewhat lower affinity to sstr3 and 5 and does not bind to sstr1 and sstr4. In contrast, ^{111}In-Octreotide binds with lower affinity to sstr2, sstr3 and sstr5. Since most of the metastatic tumors express sstr2, the decreased binding affinity of ^{111}In-octreotide to all SSTR subtypes does not affect the scintigraphic results (41,42).

Several other studies have also documented that for PRRT it is primarily more important to have the somatostatin analogue with the highest affinity for sstr2. In fact we found that ^{90}Y-DOTA-NOC, which has higher affinity for sstr3 and sstr5, is more toxic than ^{90}Y-DOTA-TATE (DOTA-Octreotate), probably because of the higher uptake in normal tissues. Therefore DOTA-NOC is no longer used for PRRT at our centre.

Selection criteria for PRRT

Because of the potential for renal and hematologic toxicity associated with PRRT, it is important to define patient subgroups that will most likely benefit from this specialized therapy. A recent article, based upon the survey of phase I and phase II clinical trials conducted so far, provided the following selection criteria for gastroentero-pancreatic neuroendocrine tumors:

Inclusion criteria
1. Intense SSTR expression of the tumor/metastases (as demonstrated by SRS or SR-PET/CT, Figure 3)
2. Hemoglobin, WBC and platelet count should be ≥ 6 mmol/L, 4×10^9/L and 100×10^9/L, respectively.
3. Serum creatinine should ≤ 110 μmol/L or creatinine clearance ≥ 50 mL/min. In view of the authors, wherever there is a possibility to determine the glomerular filtration rate (GFR) by using [99m]Tc-

DTPA (or using plasma clearance methods), it is advisable to do so. In addition, the tubular extraction rate (TER) should be determined by dynamic renal scintigraphy using ^{99m}Tc-MAG3 before and serially after PRRT.
4. Karnofsky Index ≥ 50
5. Average life expectancy should be > 6 months

Exclusion criteria
1. Pregnancy/lactation
2. Chemotherapy within 6 weeks prior to the PRRT
3. Second malignancies with short term survival (e.g. metastatic melanoma).

Apart from this, patients should not be on cold octreotide therapy at least 6 weeks prior to therapy as it has been shown that there is a competitive inhibition of radiolabeled somatostatin analogues with cold octreotide for SSTR and PRRT. The authors have also shown that there is a significant reduction of ^{68}Ga-DOTA-NOC uptake in SSTR rich normal organs/tumors in patients treated with somatostatin analogues (43).

Indications for PRRT

Based upon the clinical results gathered over the last decade, it is suggested that PRRT should be reserved for patients with metastasized NET with documented evidence of disease progression after surgery or in some patients with inoperable tumors (e.g., inoperable primary tumors of the pancreas, Figure 4).
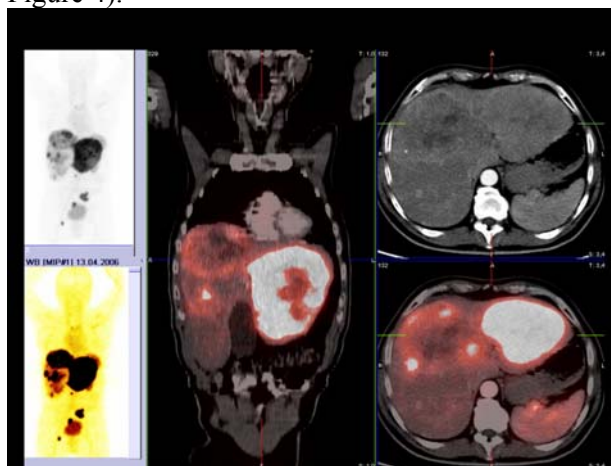

Figure 3a. [68]Ga DOTA-NOC PET/CT : maximum intensity projection image (MIP) on the left (PET), coronal (middle, PET/CT fusion image) and transversal slices (right, PET/CT fusion image) in a patient with extensive, bilobular liver metastases (unknown primary tumor, CUP).
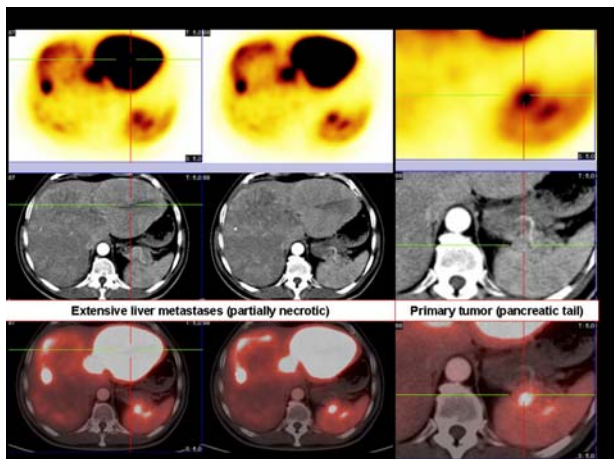
Figure 3b. Transversal slices through the liver and the pancreatic region: Detection of the primary tumor in the pancreatic tail by ^{68}Ga DOTA-NOC receptor PET/CT. Mind the different intensity of somatostatin receptor expression in various liver metastases in the right and left lobe.

Figure 3c. Detection of a previously unknown bone metastasis (not seen on CT scan) by ^{68}Ga DOTA-NOC receptor PET/CT (transversal slices).

The definitive role of PRRT as first-line treatment modality has not yet been defined by centres specialized in NET patient care. However, most patients who have been referred to our nuclear medicine centre for PRRT were already in an advanced stage of disease. In view of the authors, it would very likely be promising to apply PRRT to high risk patients immediately after surgery, rather than waiting for the tumor to metastasize on therapy with cold octreotide, chemotherapy, or interferon therapy.

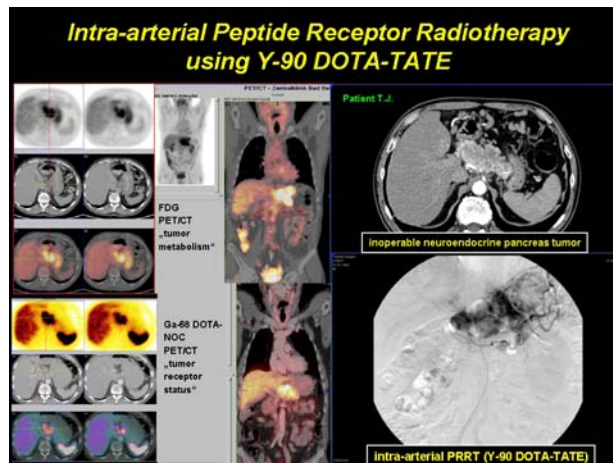Prior to PRRT, all lab values, morphologic and functional imaging results must be available.

Figure 4. Large, inoperable neuroendocrine carcinoma of the pancreas. Comparison between tumor glucose metabolism (upper left, ^{18}FDG PET) and ^{68}Ga DOTA-NOC receptor PET/CT (lower left). The MIP images in the middle demonstrate a match between metabolism and receptor expression. On the upper right, the transversal CT scan shows infiltration of nearby structures and abdominal vessels by the tumor. Intra-arterial treatment was performed by injection of ^{90}Y DOTA-TATE in the tumor feeding artery (lower right). The patient showed a very good response to PRRT.

Again, since functional changes precede morphologic changes, it is advisable to use SR-PET/CT for monitoring therapy response post PRRT, and for the detection of relapse or progression during follow-up of patients after completion of therapy.

A newly emerging, and highly interesting indication for PRRT is the intracavitary treatment of inoperable, progressive brain tumors (Figure 5), and of other SMS-receptor positive, irresectable tumors (e.g., glomus tumors, meningeomas).

Dosing schedule and quantity of radioactivity administered

After more than a decade of practicing PRRT, the issue of optimal dosing schedules still remains highly controversial. The most important criteria to decide upon when and how frequently PRRT can be and should be administered, are clinical stage of the disease, response to first PRRT, hematologic toxicity and renal function parameters. As mentioned earlier, currently PRRT is indicated only after documented evidence of disease progression in patients with metastasized NET.
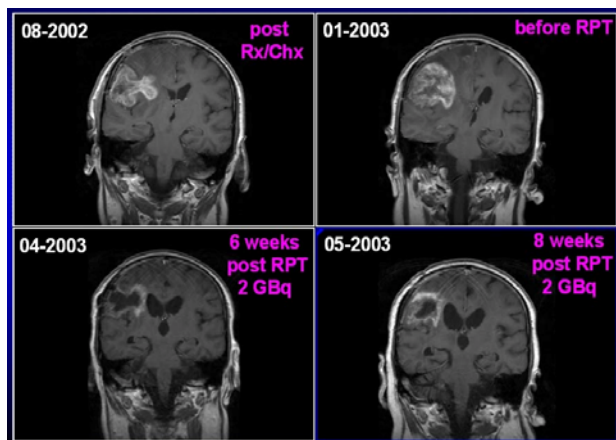
Figure 5. Intracavitary radiopeptide therapy using ^{90}Y DOTA-TATE of a progressive astrocytoma (WHO grade III) after surgery chemotherapy and external beam radiation therapy. Serial follow-up coronal MR images are shown. The patient died in a car accident (but was tumor-free as proven by autopsy).

The amount of radioactivity chosen to be administered is primarily dependent upon renal function parameters, SSTR expression (quantitative and visual) on SR-PET/CT (if SR-PET/CT not available then SRS) and the extent of the disease (single vs. multiple metastases, tumor burden). Many centres apply repeat PRRT (^{90}Y-DOTA-TOC, ^{90}Y-DOTA-TATE, ^{177}Lu-DOTA-TATE) at various and alternating time intervals. Our experience in more than 1,000 PRRT cycles, administered in over 350 patients (with a maximum of 8 PRRT cycles in some patients) suggests that it is advisable to administer lower amounts of radioactivity at more frequent and prolonged intervals (3-6 months in between therapies), rather than giving high activities at short intervals. We dubbed this strategy the **"Bad Berka PRRT concept"** based on the rationale that slowly growing tumors are probably more susceptible to frequent low dose hits rather than to 2 or 3 "big bangs".

Clinical results
The results of PRRT have varied widely depending upon which kind of radionuclide and somatostatin analogue was utilized. At first, the emission of auger electrons from ^{111}In was utilized to treat somatostatin receptor positive tumor with up to 160 GBq of ^{111}In-DTPA-octreotide. Partial remissions have been described in 8 % of patients as well as stabilization of disease in a higher proportion of

patients (44-46) by some authors, whereas others did not see any objective response. Auger electron emission is a major drawback for the treatment of larger tumor. In contrast, using ^{90}Y-DOTA-TOC in phase I and II clinical trials, complete or partial remissions were observed in nearly 27 % of patients (47,48). In these studies patients received 3 or more equal amounts of radioactivity.

Waldherr et al. (49,50), using a different treatment regime (patients received 4 or more single injections of ^{90}Y-DOTA-TOC with increasing amounts of radioactivity administered at 4-week-intervals), showed a partial response in 24 % of the patients.
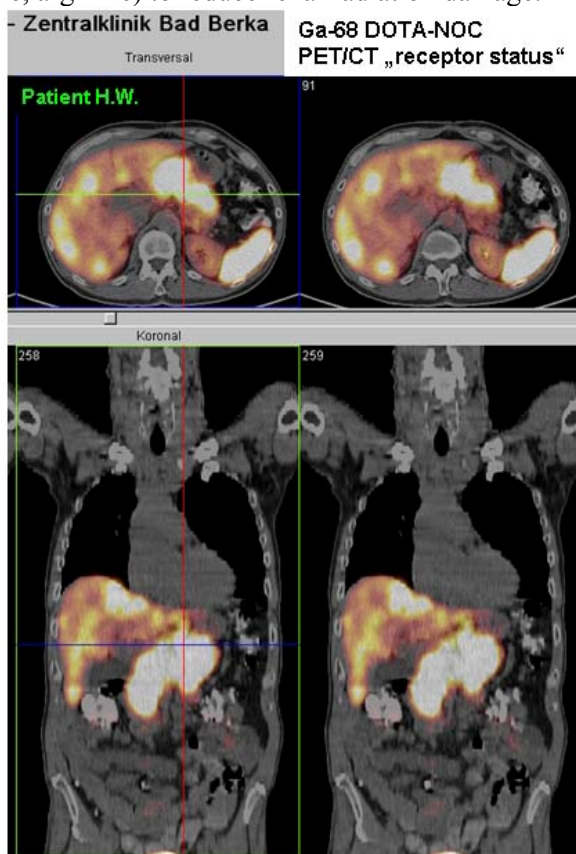
A comparison of two different treatment protocols used in 400 patients at the University Hospital Basel (one group of patients received 4 equal injections of 1,850 MBq/m^2 at 6 weeks intervals, whereas the other group received two equal injections of 3,700 MBq/m^2 at an interval of 8 weeks) has demonstrated that patients receiving higher doses at an 8 week-interval had a slightly better response rate (34% vs. 24% PR).

Kwekkeboom et al. (51) reported complete remissions in 2 %, and PR in 26 % of 139 patients with GEP NET treated with ^{177}Lu-DOTA-TATE with a very low toxicity profile. In our center, using ^{90}Y-DOTA-TATE and ^{177}Lu-DOTA-TATE either alone or in combination (mostly sequentially), partial remissions were achieved in 39 % of the patients and in 9/302 patients a complete remission was observed (unpublished data). A measurable clinical benefit (improvement of symptoms) was seen in over 90 % of the patients (Figure 6). A study conducted by Kwekkeboom et al. to assess the quality of life (QoL) in patients with GEP treated with ^{177}Lu-DOTA-TATE demonstrated that global health/QoL improved significantly in patients post treatment.

Toxicity profile: PRRT vs. other treatment options
The primary concern of many non-nuclear medicine physicians prior to referring a patient for PRRT is radiation-induced toxicity. In fact, radiolabeled somatostatin analogues are primarily excreted through the kidneys and, with regards to toxicity, the kidney is the primary organ of interest. Therefore, PRRT is administered under

nephroprotective agents such as amino acids (lysine, arginine) to reduce renal radiation damage.
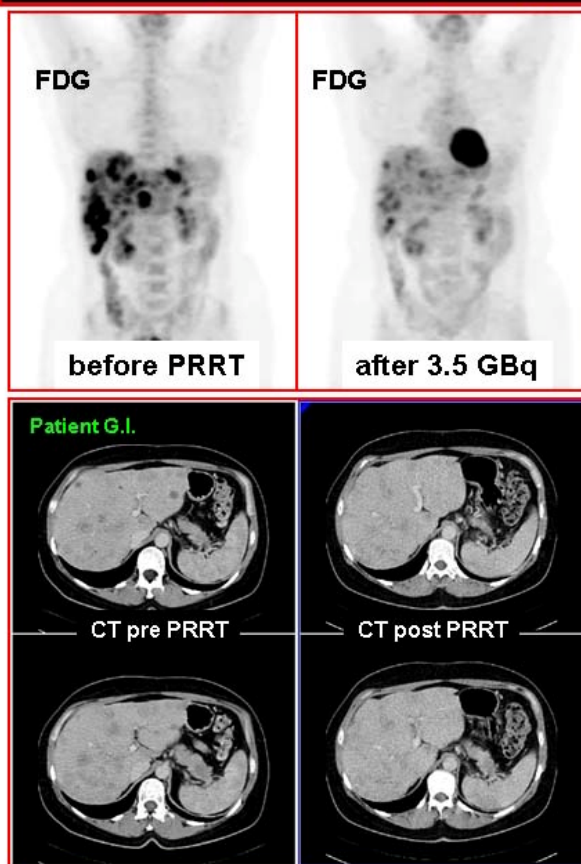

Figure 6. Large neuroendocrine pancreatic carcinoma with extensive liver metastases (left, Ga-68 DOTA-NOC receptor PET/CT). In this case, systemic PRRT was performed. Right: [18]FDG PET MIP images before and after PRRT of diffuse liver metastases of a neuroendocrine GEP tumor are shown: dramatic response with drop in SUV of over 50% after one single treatment course using ^{90}Y DOTA-TATE (4 GBq), whereas CT scans (lower right) show only minor changes ("metabolism precedes morphology"). Clinically, the patient experienced a dramatic improvement of symptoms (e.g. frequency of diarrhea reduced from more than 12-15 bowel movements per day to fewer than 3 b.m./day).

A novel approach is the use of gelatine (gelofusine) prior to PRRT for reducing renal toxicity; initial results are promising (52-54). With ^{111}In-DTPA-octreotide, high cumulative radioactivity doses can be administered without any significant deterioration in renal function (45). Few studies have reported significant renal toxicity after ^{90}Y-DOTA-TOC therapy, for the most part even in the absence of renal protection (55-60).

With the advent of improved protective agents renal toxicity can be reduced even further. In our centre, in patients with normal kidney function before PRRT, no terminal kidney insufficiency has been observed so far at a mean follow up time of several years (Figure 7). Other adverse effects which are experienced, like hematological and liver toxicity, are usually mild and mostly reversible.

In a phase I study conducted in 47 patients in Rotterdam, Brussels and Tampa with ^{90}Y-DOTA-TOC, one patient with secondary myelodysplastic syndrome was observed, one showed liver toxicity, and three patients developed grade 4 thrombocytopenia (39,61). Studies using ^{177}Lu-DOTA-TATE have documented less and mostly transient toxicity with only minimal bone marrow suppression (51,62,63).

In comparison to chemotherapy, PRRT using ^{177}Lu DOTA-TATE have been shown to be less toxic (62,63): Kwekkeboom et al. (51) observed hematological toxicity in less than 2 % of the patients as compared to 5-61 % toxicity observed in

patients treated with chemotherapy (20-22,64-67). Similarly, renal toxicity was found to be much less as compared to that with chemotherapy (51).
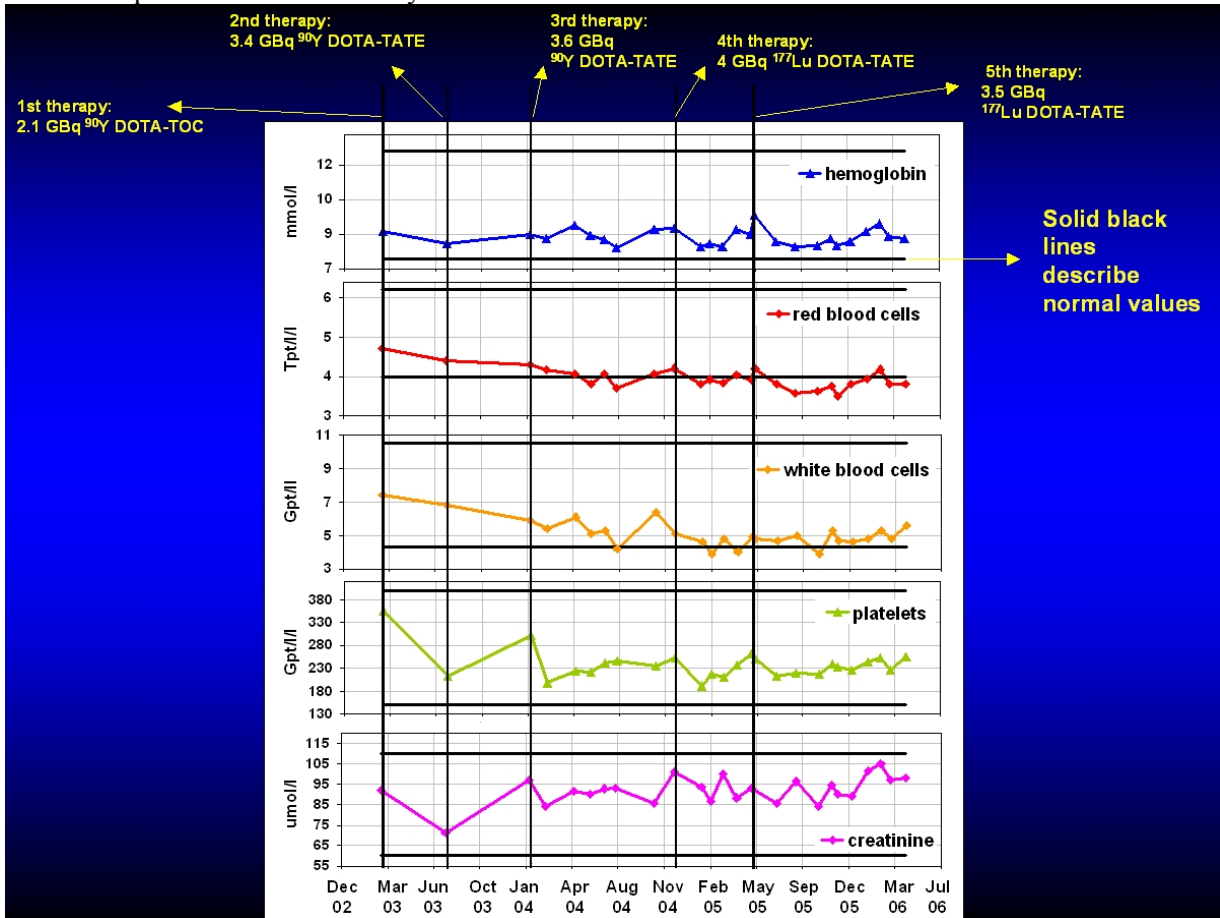

Figure 7. Serial follow-up of hematological data by measuring hemoglobin, red blood cells (RBC), white blood cells (WBC) and platelets (PLT) as well as serum creatinine. There is no significant hematological toxicity after 3 cycles of [90]Y- and 2 additional cycles of ^{177}Lu DOTA-TATE therapy.

Multimodality Approach
In recent years, the value of combining different treatment modalities in order to achieve better disease control in metastatic or inoperable NET has been increasingly investigated. Randomized clinical trials are underway to compare the efficacy of PRRT alone, and in combination with chemotherapy. The concept of **COMBIERT** (**C**ombined **I**nternal **E**xternal **R**adiotherapy), developed by R.P. Baum, aims at combining internal and external radiation therapy for better efficacy. Initial results in patients with neuroendocrine tumors (e.g. inoperable primary pancreatic NET as well as in recurrent glomus tumors (Figure 8) and paragangliomas) are

promising. Similarly, the use of PRRT for tumor debulking prior to surgery (neoadjuvant therapy) should also be considered.

CONCLUSION

The significant and undeniable effects exerted by PRRT, even to the extent of being curative in individual cases (Figure 9), has had a major impact on how patients with NET are treated in some European countries. However, in spite of being an effective treatment option, PRRT is practiced in Europe only at a few specialized centers (and even less in the U.S. and Canada), mainly due to the lack of commercially available [90]Y- and [177]Lu- labeled

somatostatin-derived peptides (radiopharma-ceuticals). Studies that directly compare the clinical results of standard octreotide therapy with PRRT are unfortunately missing. These and other yet unresolved questions regarding the optimal

therapy of patients with localized and metastatic NET should be addressed by newly designed, cooperative multicentre trials.
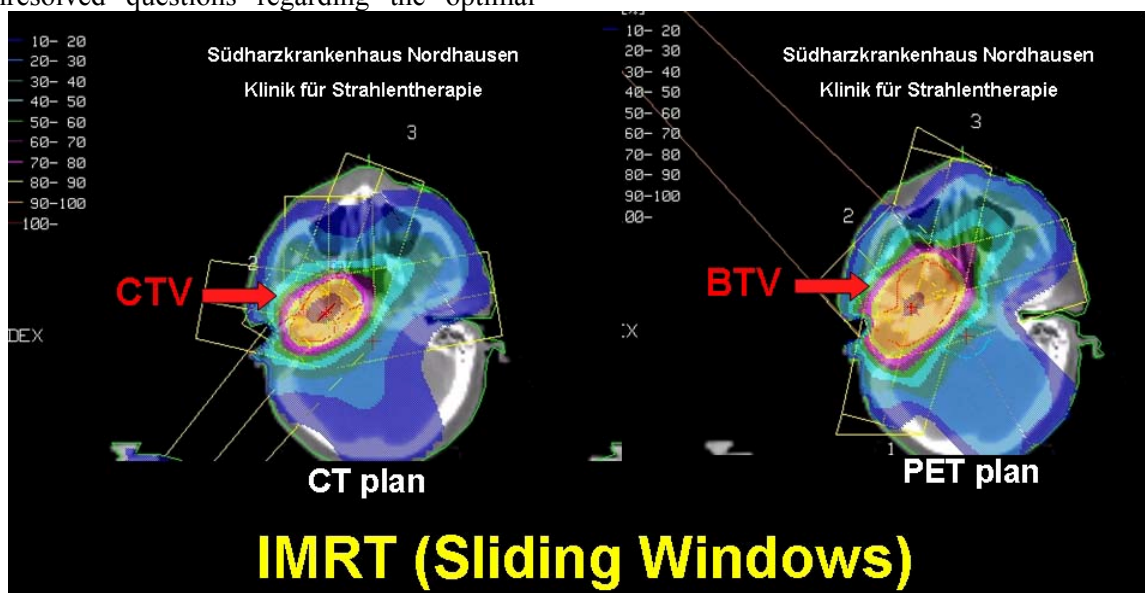

Figure 8. MRTP (molecular radiation treatment planning) in a patient with recurrent, inoperable glomus tumor (over the last 25 years, a total of 13 operations had been performed). Comparison of IMRT plan using morphological data (CT scan) and molecular data (PET scan).

Figure 9. Same patient as described in Fig. 8 with tumor-induced paralysis of the facial nerve (hanging mouth and open eye). After combined external and internal radiation therapy (COMBIERT), all clinical symptoms disappeared. On the left lower row, a fusion of SMS-receptor imaging slices (SPECT) and MRI is shown (software image fusion).

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