7 Intra-arterial Radiopeptide Infusions with High Activity of ^{111}In-Octreotide: From "Aretaieion Protocol" to the Temporal Intra-arterial Port Installation

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7.1 Introduction

Contemporary aspects of neuroendocrine tumors (NETs) emerge on tissues containing cells derived from the neural crest, the neuroectoderm, and the embryonic endoderm [1]. Although these tumors can occur everywhere in the human body, the majority of them appear along the axis of the gastrointestinal tract, particularly lungs, mediastinum, stomach, intestine, pancreas (Fig. 7.1), including gastrinomas, insulinomas, VIPomas, glucagonomas, PPomas, somatostatinomas, and carcinoids [1]. Catecholamine-secreting neoplasms such as pheochromocytomas, paragangliomas, the myeloid carcinoma of the thyroid gland, the primary neuroendocrine carcinoma of the skin [also known as Merkel-cell carcinoma (Fig. 7.2)], tumors of the pituitary and parathyroid gland and broncho-pulmonary neoplasms belong to the family of non-gastroenteropancreatic neuroendocrine tumors (non-GEP-NETs). Non-GEP-NETs can occur in the frame of hereditary neoplastic syndromes. These include multiple endocrine neoplasms type 1 and 2 (MEN1 and MEN2), von Hippel Lindau disease (VHL), type 1 neuro-fibrosis (NF1), and Carney syndrome [1–5]. However, the majority, of non-GEP-NETs appear as nonhereditary (sporadic) single tumors.

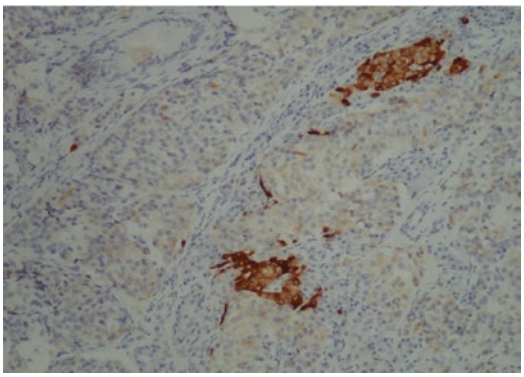

Fig. 7.1 Histological section of a well-differentiated pancreatic NET; positive immunore-action to somatostatin (Immunostain ×10)

Neuroendocrine tumors are rather rare neoplasms with an incidence today of about 6/100,000 [6]. They are categorized in functional and nonfunctional, the latter often presenting as a large solid bleeding mass. The functional NETs take up precursors of biologically active amines to produce active ones after subsequent intracellular decarboxylation and to store them in secretory vesicles. As a result, these **A**mine **P**recursor **U**ptake and **D**ecarboxylation cells, enabled to develop distinct clinical syndromes, i.e. flushing, skin rush, diarrhea, and hypoglycemia (the so-called carcinoid syndrome), are named APUD according to AGE Pearse, in 1969 [7], (Fig. 7.3) [8]. About one-half

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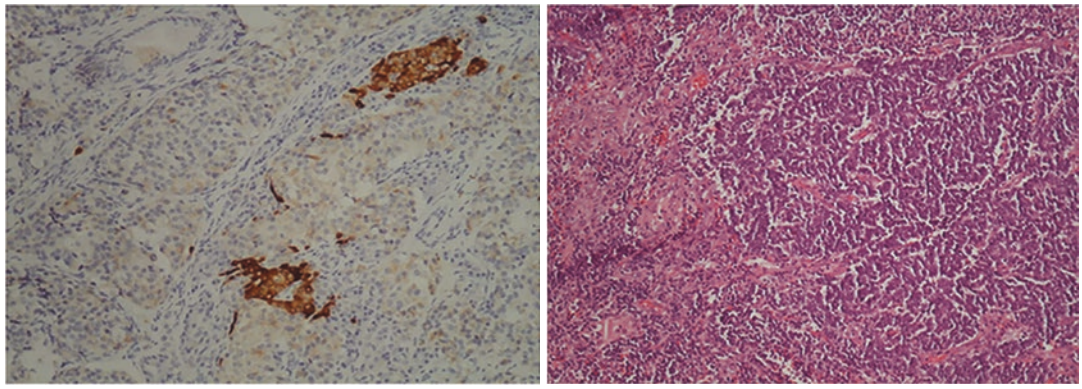

Fig. 7.2 Histological section of a Merkel cell carcinoma of the skin, metastatic to lymph node (Hematoxylin + Eosin ×10)

Fig. 7.3 Anthony Guy Everson Pearse 1906–2003 [8, 7]

of all NETs are described as nonfunctional, meaning that the patients do not have hormone-related symptoms. Both functional and nonfunctional have the unique feature of several somatostatin peptide receptor over-expressions.

7.2 The Therapeutic Approach of NENs

7.2.1 NETs' Treatment Background

Albeit the worldwide research, it is worth to note that over the last 30 years, no significant improvement in the survival of patients with NETs in the general population could be observed. For this reason, to promote the optimum care provided to these neoplasms, a better understanding of their biology might be needed, with emphasis on molecular genetics and the improvement of experimental models. Furthermore, at clinical practice level, it is important to develop more reliable serological markers as well as methods to allow for accurate tumor detection for even smaller lesions.

Treatment for neuroendocrine tumors depends upon the location of the tumor, whether the cancer has given metastases, spread to other areas of the body i.e. liver, bone, lymph nodes, and if the tumor is secreting hormones, responsible for symptoms. Treatment modalities against primary or metastatic neuroendocrine tumors can be categorized as: (a) invasive, i.e. *surgical resection*, (b) minimally invasive or ablative or locoregional, i.e. selective trans-

arterial (chemo) *embolization* [TA (C) E], radiofrequency *ablation* [RFA], laser-induced thermotherapy [LITT], selective internal radiotherapy [SIRT], and (c) systemic standard therapy.

7.2.2 NETs and Curative Surgery (In This Volume, Chaps. 18 and 19)

Curative surgery should be considered whenever possible even in the presence of metastatic disease, including localized metastatic disease to the liver, if considered potentially resectable and the patient can tolerate the surgery. Surgical resection is the treatment of choice for NETs. Specifically, GEP-NET patients should be considered potential candidates for curative surgery. Curative resection of the primary tumor and locoregional lymph node metastases improves outcomes in these patients, resulting in excellent 5- and 10-year survivals of 100% in stage 1 and stage 2 patients, and still favorable outcomes in stage 3 disease with 5- and 10-year survivals of more than 95% and 80%, respectively [9–14].

7.2.3 NETs and Minimally Invasive Modalities

The choice of the ablative or loco-regional procedures or minimally invasive modalities [15], i.e. radiofrequency ablation (RFA) [16–18] laser-induced thermotherapy (LITT) [19, 20] selective hepatic trans-arterial embolization (TAE) [21–24], trans-arterial chemoembolization (TACE) [25, 26] and selective internal radiotherapy (SIRT) [27–31], depends on the local expertise, number and size of lesions, and location of liver involvement (in this volume, Chaps. 20 and 21).

7.2.4 NETs and Systemic Standard Treatment [32–35]

The use of *somatostatin analogs*, i.e. octreotide [36] pasireotide [37, 38] and lanreotide [39], is a standard therapy in functioning NETs of any size to confrontate flushing and diarrhea, being the cornerstone treatment for patients with advanced NETs. *Interferon alpha* [40] may also be considered for symptom control in some patients and is usually used as second-line therapy due to its less-favorable toxic profile. *Everolimus* [34, 35], registered for treatment of pancreatic NETs worldwide, inhibits *mammalian target of rapamycin* (mTOR), a serine–threonine kinase that stimulates cell growth, proliferation, and angiogenesis. *Sunitinib* [33] *and Pazopanib* [41, 42] are potent and selective multitargeted receptor tyrosine kinase inhibitors that block tumor growth and inhibit angiogenesis. They have been approved for renal cell carcinoma and soft tissue sarcoma by numerous regulatory administrations worldwide. Chemotherapy [32], on the other hand, with doxorubicin, streptozocin, fluorouracil, chlorozotocin [43, 44], or in combination shows equivocal and mediocre results.

Though surgery consists the only curative option for NETs, there is a lack of precision-consensus between their management and guidelines regarding optimal treatment approaches in the unresectable and/or metastatic setting. Consequently, on account of the limited availability of high-level clinical evidence, a multidisciplinary approach [15] for the management of NETs is a first-class strategy to ensure a consistent and optimal level of care (Table 7.1).

Table 7.1 Multidisciplinary team approach for neuroendocrine neoplasms

Nuclear medicine physician	Tumor surgeon
Interventional radiologist	Radiation physicist
Medical oncologist	Pathologist
Gastroenterologist	Dedicated nursing staff

Table 7.2 Classification of neuroendocrine neoplasms of the gastroenteropancreatic system (WHO 2017)

Grade	Differentiation	Ki-67%	Mitotic index (hpf)
G1	Well-differentiated NET	<3	**<2/10**
G2	Well-differentiated NET	3–20	2–20/10
G3	Well-differentiated NET or Poorly differentiated NET or NEC small and large cell type	>20	>20/10
≠	MiNEN*	≠	≠

NEN Neuroendocrine neoplasm (also called NET = neuroendocrine tumor), *NEC* neuroendo-crine carcinoma, *HPF* high power field, ≠ A mixed neoplasm with components of a nonendocrine carcinoma (mostly ductal adenocarcinoma or acinar cell carcinoma) combined with a neuroendocrine neoplasm. Usually both components are high-grade malignant carcinomas (G3), but occasionally one of the two or both components may belong to the G1/G2 category. Therefore, the components should be individually graded, using the respective grading systems for each
*Mixed neuroendocrine/non-neuroendocrine neoplasm

Recently, the new classification guidelines [45] for GEP-NETs (4th edition) and the World Health Organization (WHO) from 2017 [46] are enriched adding the proliferation Ki-67 and Mitotic Indexes[1] to the differentiation criteria (Table 7.2). Accordingly, well-differentiated tumors are grade 1 (Ki-67 <3% and MI <2/10 high power field (HPF)), grade 2 (Ki-67 3–20% and MI 2–20/10 HPF), and grade 3 (Ki-67 >20% and MI >20/10 HPF). There is a subdivision of tumors with a Ki-67 >20% and an MI >20/10 HPF into well-differentiated grade 3 NET and poorly differentiated neuroendocrine carcinoma (NEC), the latter being categorized into small cell and large cell carcinomas.

[1]**Ki-67** is a *nuclear antigen* expressed in proliferating cells and is expressed during the GI, S, G2, and M phases of the cell cycle. Cells are then stained with a Ki-67 *antibody*, and the number of stained nuclei is then expressed as a percentage of total tumor cells. The name is derived from the city of origin (Kiel, Germany) and the "67" number of the original clone in the 96-well plate.

The **Mitotic Index**, expressed *as the number of cells per microscopic field* is determined by counting the number of cells undergoing mitosis through a light microscope on hematoxylin and eosin (H and E) stained sections. Usually the number of mitotic figures is expressed as the total number in a defined number of high-power fields, i.e., 10 mitoses in 10 high power fields. Since the field of vision area can considerably vary between different microscopes, the exact area of the high-power fields should be defined in order to compare results from different studies.

7.2.5 NETs and the Intra-arterial Peptide Receptor Radionuclide Therapy (PRRT) Concept; A Brief Introduction

In our Institution, PRRT was performed from 1997 up to 2012 using n.c.a. ^{111}In-Octreotide, routinely in high activities (12 cycles of 4070–5920 MBq (110–160 mCi) per session, per patient, intra-arterially) and thenceforth replaced by non-carrier added (n.c.a.) ^{177}Lu-DOTA-TATE (6 cycles of 7000 MBq (189 mCi) per session, per patient, intra-arterially, too), rather exclusively focused in cases with hepatic secondaries. A PRRT dosimetry-guided protocol was followed of a more personalized character for each case, based on patients' hematotoxicity, tumor behavior (RECIST 1.1.criteria), chromogranin-A serum levels and clinical (symptoms') profile, not exceeding the 2 Gy absorbed dose to bone marrow or the 23 Gy to the kidneys [47–52]. The PRRT therapeutic scheme was implemented in combination with octreotide-Long-Acting-Repeatable (30 mg per 20 days) or lanreotide (60 mg up to 120 mg per 20 days), as first-line therapy. As a final result, objective tumor response (CR + PR) was achieved in 47/86 (54.65%) patients, disease control (CR, PR or SD) in 70/86 (81.39%) with a 32 and 46.5 months median progression-free survival and overall survival, respectively. We describe the outcome of the n.c.a. ^{111}In-Octreotide treatment in 86 patients of various NET histotypes, where approximately more than 800 infusions were intra-arterially implemented after catheterization of the hepatic artery, a novelty unique worldwide in humans.

7.3 Patients and Methods

A total of 86 patients were treated with n.c.a. ^{111}In-Octreotide from April 1997 to February 2012 in our Institution. Patients were Greek citizens with NETs treated according to a standard

protocol called "Aretaieion Protocol" [15, 53], devoted to the name of the University Hospital of the Nuclear Section in which it was developed.

Selective hepatic angiography was conducted with a digital angiographic unit (Optimus, Phillips, the Netherlands). A 5.0-F valved sheath (Introducer II-long sheath; Terumo; Tokyo, Japan) was inserted into the femoral artery with the patient under local anesthesia, which was induced by injecting 10 mL of 2% lidocaine subcutaneously (Xylocaine; Astra, Sweden). After obtaining arterial access, a diagnostic visceral arteriogram was performed to delineate the arterial supply to the tumor, determine the presence of variant arterial anatomy, and confirm portal vein patency, even though portal vein thrombosis does not necessarily constitute a contraindication to perform trans-catheter arterial radionuclide infusion. Celiac and superior mesenteric arteriography was performed with a Cobra II 5.0-F catheter (Glidecath; Terumo, Japan), which was advanced into the proper hepatic artery by using a 0.035-inch gliding guide wire (Guide Wire M; Terumo, Japan). The catheter was then selectively inserted into the right or left hepatic or proper hepatic artery, dependent on the tumor intra-hepatic location. In seldom cases, when a very super-selective catheterization was necessary, a 2.8-F micro-catheter (Terumo, Japan) was coaxially used. The size and location of the neuroendocrine nodules was assessed using the Couinaud nomenclature [55] according to which the liver is divided into eight independent segments; each of which has its own vascular inflow, outflow, and biliary drainage (Fig. 7.4). Tumor size and location was evaluated

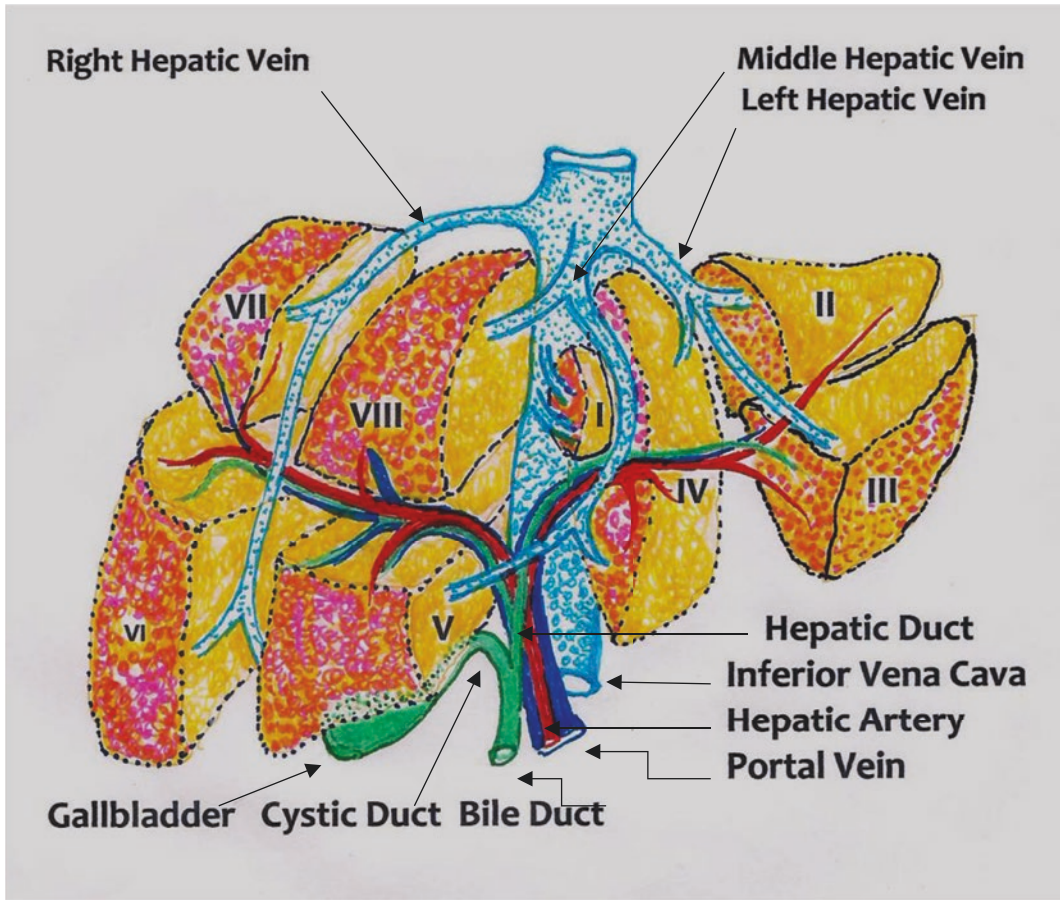

Fig. 7.4 Segmental anatomy of the liver, according to Couinaud nomenclature [54] nomenclature

by means of a consensus between two observers who compared the images obtained. Having safely positioned the catheter within the nearest artery to the tumor, intra-hepatic radionuclide infusion followed.

Angiogenesis is a key event in neoplasm progression and therefore a promising target in cancer treatment. SST-2 receptors, over-expressed in the endothelium of neuroendocrine character neo-plasmatic disease and used as the target of radiolabeled somatostatin analogues, are proved to serve as powerful anti-angiogenic targets with consequently potent anti-tumor activity (Fig. 7.5).

For evaluation, only patients who received at least in total 330 mCi (12.210 GBq) ^{111}In-Octreotide were included. The analysis of treatment efficacy comprises NET types, categorized into (Figs. 7.6 and 7.7), foregut, other foregut, midgut, hindgut, and NETs of unknown origin. Other foregut NETs comprised two NETs of the brain (one meningioma and one oligodendroglioma), one of the stomach, one of the mesothorax, and three hepatocellular carcinomas with neuroendocrine characteristics. Assumption for PRRT with ^{111}In-Octreotide was a visual score 3–4 on OctreoScan scintigraphy prior to PRRT[2].

[2]Uptake on the OctreoScan was scored on planar images using a four-point scale; [grade 1: activity (uptake) equal to that in the normal liver, grade 2: activity (uptake) greater than that in the normal liver but less than that in the left kidney and spleen, grade 3: activity (uptake) equal to that in the left kidney, grade 4: activity (uptake) at least equal to the half of the sum of the activities in spleen and left kidney]. Purpose of this four-point scale is to assess candidacy for peptide receptor radionuclide therapy (PRRT), with a score mandatorily greater than 2, i.e., 3 and 4.

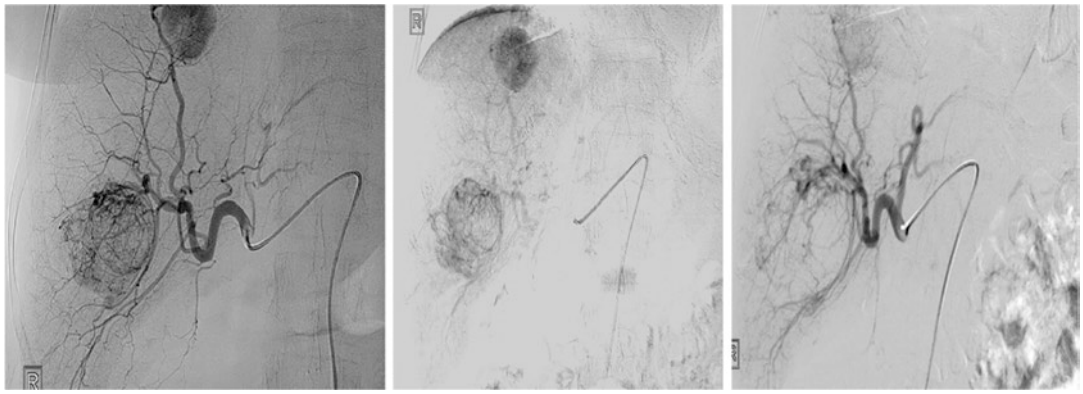

Fig. 7.5 Serial angiography of a patient with multiple hepatic metastases due to neuroendocrine tumor obviously shows the neo-vessel being destroyed after combined ^{111}In/^{177}Lu-radiopeptide treatment

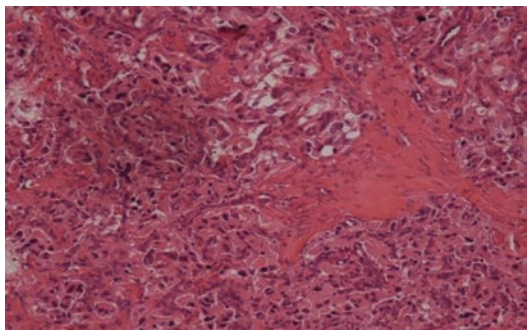

Fig. 7.6 Histological section of a well differentiated mammary NET (Hematoxylin + Eosin ×10)

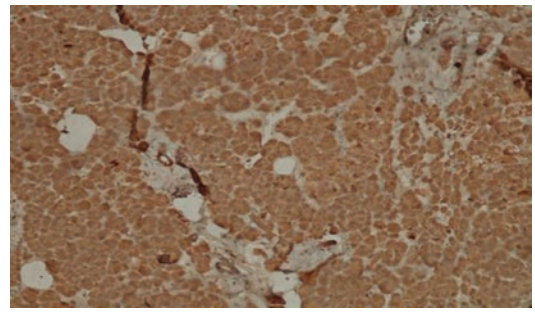

Fig. 7.7 Histological section of a well-differentiated pancreatic NET, showing extensive immunoreactions to Chromogranin (Immunostain ×10)

Other inclusion criteria were serum hemoglobin ≥9.7 g/dL, total white blood cell (WBC) count ≥2 × 10^9/L, platelet count ≥75 × 10^9/L, serum creatinine concentration ≤1.7 mg/dL), and Karnofsky Index (KI) ≥40. Preliminary results in a subgroup of these patients with GEP-NETs were reported previously [15]. All patients gave written informed consent, which was approved by the medical ethical committee of our hospital. ^{111}In-Octreotide was obtained from Mallinckrodt (Petten, Holland) and prepared "in house" as already described [15]. Before the infusion of the radiopharmaceutical, Ondansetron 8 mg was injected intravenously. To reduce the radiation dose to the kidneys, intravenous infusion of amino acids (2.5% arginine and 2.5% lysine in 1 L 0.9% NaCl) was started 30 min before the administration of the radiopharmaceutical and lasted for 4 h. The radiopharmaceutical was co-administered intravenously over 30 min. In cases of longer subacute hematologic toxicity, the intended continuing interval between treatments was 9 and 10 weeks. Patients were treated up to a cumulative intended activity from 330 mCi (12.210 GBq) to 2560 mCi (94.720 GBq) ^{111}In-Octreotide except in one case with excised bronchopulmonary primary, infused once, who received a cumulative activity of only 185 mCi (5 GBq).

7.3.1 Follow-Up and In Vivo Measurements

Routine hematology, liver, and kidney function tests were performed per three therapy cycles. Tumor response was assessed trimonthly on U/S and as far on CT or MRI before and at least 6 months after the initialization of the treatment or at the end of the entire therapeutic scheme, according to the Response Evaluation Criteria in Solid Tumors 1.1 (RECIST 1.1) criteria [51]. Thereafter every case was seen as an outpatient for follow-up.

7.3.1.1 Posttreatment and Follow-Up Studies

The aforementioned radionuclide infusion procedure was repeated 4–6 weeks apart. Initially, before the commencement of the treatment CT and/or MRI scans and U/S imaging was performed, being considered as the baseline of the pre-therapy lesion status. U/S was repeated monthly, just before the beginning of each session and being the main tool of the follow-up estimation. A second CT or MRI scan was requested at the end of the entire therapy scheme. Routine measurement of complete blood count, liver and kidney function tests, Chromogranin-A (Cr-A), and hormone levels as previously described will be measured before each session and at follow-up visits.

CT images Non-enhanced as well as contrast-enhanced CT images (5 mm slice thickness, 7-mm collimation, 1.50 pitch, 120 kVp, 220–250 mAs) was performed with model PQ 6000 (PICKER International, Highland Heights, Ohio) and Hi-Speed Advantage (GE Medical Systems, Milwauckee Wis) Spiral scanners (Fig. 7.8).

MR tomoscans Magnetic resonance (MR) images were obtained by using a 1.5-T Magnetom Vision Unit (Siemens) and two pulse sequences: T2-weighted turbo spin echo (4200/83 or 165 [repetition time ms/echo time ms], 7-mm slice thickness, 128 × 256 matrix, 3-min imaging time) and T1-weighted gradient echo with a fast low-angle shot technique (174.9/4.1, 80° flip angle, 7-mm section thickness, 128 × 256 matrix, 22-s imaging time) (Fig. 7.9).

U/S tomoscans The U/S scan images were acquired in the sagittal, transverse, and intercostal planes by using ATL 3000-HDI (Advanced Technology Laboratories, Bothell, Wash) and AU 590 (Esaote Biomedica, Genoa, Italy) units and a convex 4–2 MHz probe (Fig. 7.10).

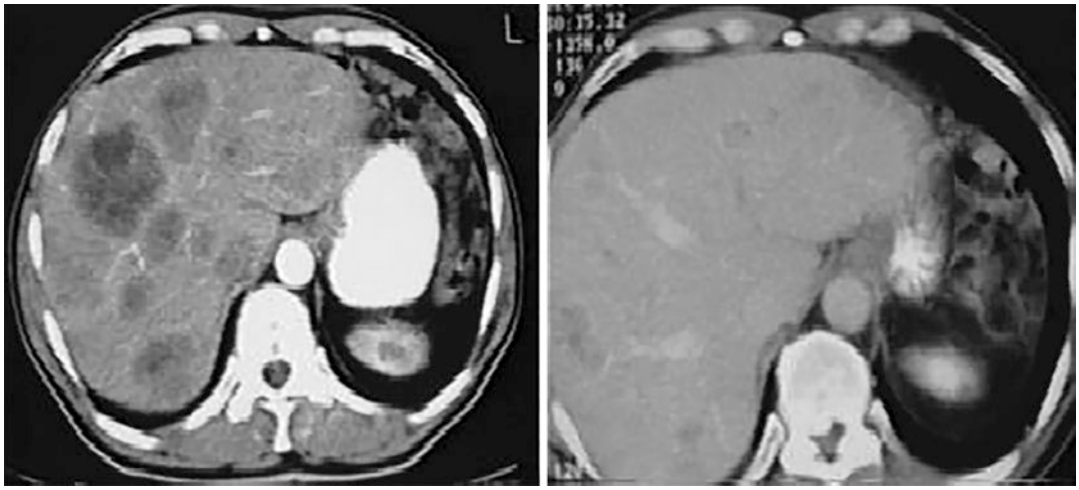

Fig. 7.8 Liver CT before [left] and after [right] the radiopeptide treatment completion

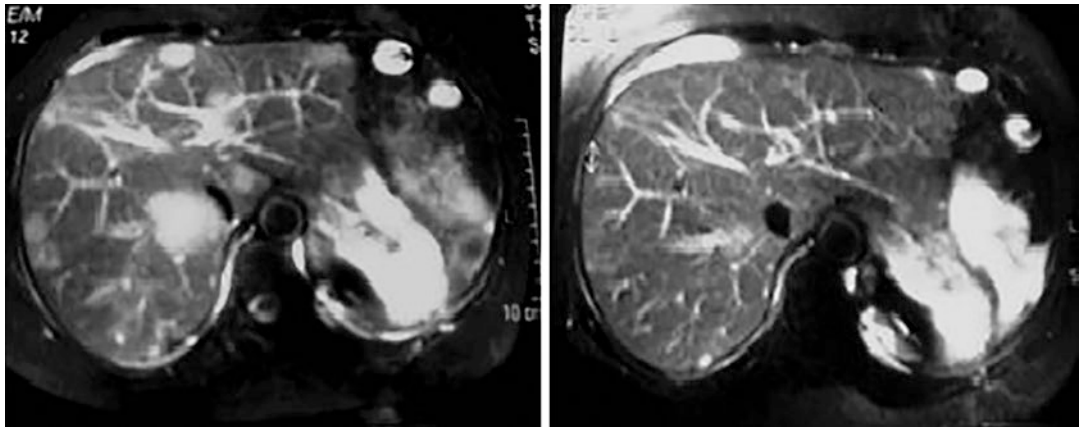

Fig. 7.9 Liver MRI before [left] and after [right] the radiopeptide treatment completion

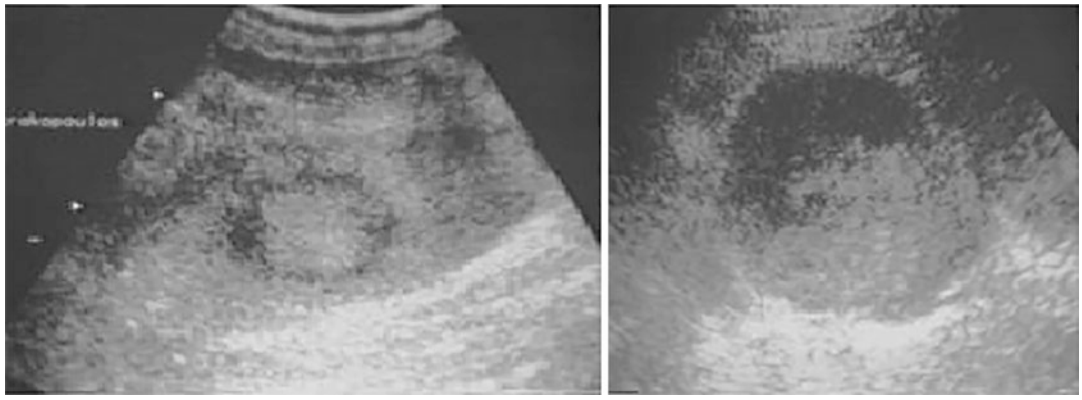

Fig. 7.10 Liver U/S [left] after the fourth and [right] the ninth session with ^{111}In-Octreotide completion

7.4 ^{111}In-Octreotide Treatment Evaluation

Baseline patient characteristics and response rates are presented in Table 7.3. All patients were under somatostatin analogues treatment. Best objective response rate (ORR) was defined as the proportion of patients achieving complete response (CR) and partial response (PR) at follow-up according to the RECIST 1.1 criteria. The ORR in the entire 86 patients was (47/86) 54.65%. SD was found in 23/86 (26.74%) of patients. PD as treatment outcome was observed in 16/86 (18.6%) of patients. For the entire group of 86 NET patients, the median OS was 46.5 months (95% CI, 11–120 months), whereas the median PFS was 32 months (95% CI, 0–110 months). The median OS ranged from 44 to 54 months with the longest OS in favor of the midgut cases. Exceptionally, the three cases of unknown origin reached a much longer OS of 61 months. Risk factors that might shorten/cut down/burden OS are bone morrow secondaries, nonmeasurable disease, and high Ki-67 index at baseline.

7.5 Discussion

According to Ertl et al. [56], Hofer and Hughes [57], Bradley et al. [58] and Feinendegen et al. [59] Auger electron emitters can be highly radiotoxic when they decay in the vicinity of DNA of the cell nucleus. After Howell et al. [60] and Rao et al. [61]some of them can be as radiotoxic as polonium-210 (^{210}Po) which emits 5.3 MeV alpha particles. Furthermore, reviews on the biological effects of Auger electron emitters published by Sastry and Rao in 1984 [62], Kassis in 2004 [63], Buchegger et al. in 2004 [64] and 2006 [65], and Nikjoo et al. in 2006 [66] consist of an excellent resource for a first-class detailed background and analysis on the field. The extreme radiotoxicity of Auger electron emitters prompted the aforementioned scientists to extensively investigate the radiobiological effects of Auger electrons and some others, among them our group (Figs. 7.11 and 7.12), to implement them routinely for therapeutic reasons in humans after the consent of the Ethical and Scientific Committee of our institution ("Aretaieion" University Hospital). Furthermore, we intended to prove their therapeutic efficacy to successfully confront mainly small (less than 20 mm) and micro-metastatic lesions, positive in somatostatin 2 (sst2) receptors. Worth mentioning is the support by the colleagues and leading scientists from the Interventional Radiology Clinic (Profs Vlahos Lambros and Chatzioannou Achilles), from the Oncology Unit (Prof Gennatas Konstantinos) from the II Surgery Clinic (Profs Voros Dionysios and Fragulidis Georgios), the Director of the Gastroenterological Clinic of National Health System Dr. Nikou Georgios of the "Laikon"

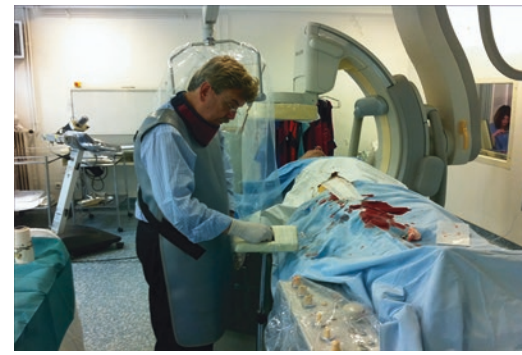

Fig. 7.11 National and Kapodistrian University of Athens-"Aretaieieon" Hospital Hemodynamic Theatre-I Department of Radiology: On the course of the intra-arterial procedure (GS Limouris)

Fig. 7.12 National and Kapodistrian University of Athens—"Aretaieion" Hospital Hemodynamic Theatre-I Department of Radiology: On the course of the intra-arterial procedure (from left to right: V Skiadas, O Doryforou, A Chatziioannou, GS Limouris)

Table 7.3 Characteristics and response rates in patients treated with ^{111}In-Octreotide

Primary NET localization	No. of patients	Tumor histotype	CR (%)	PR (%)	SD (%)	PD (%)	Median PFS (months)	Median OS (months)
Foregut	39	smi, pancr, brpln	**2**	**16**	**12**	**9**	31	44
Non-PD	30	pancr, brlpn, hcc + neur, gastr, brain, hep hilus	2 (6.7)	16 (53.3)	12 (40.0)	0 (0.0)	42.5	50.6
PD	9	pancr, brlpn, mediast	0	0	0	9 (100)	3	17
Other foregut	7	hcc + neur, ming,dndrglio, gastr, mesent	**1** (14.3)	**2** (28.6)	**3** (42.8)	**1** (14.3)	31	38
Non-PD	6	Brain, gastr, hcc + neur	1	2	3	0	31	38
PD	1	hcc + neur, mediast	1 (16.7)	2 **(33.3)**	3 (50.0)	0 (0.0)	5	19
Midgut	27	mesent	**0**	**18**	**5**	**4**	36	54
Non-PD	23	smi, asc col, cecum, mesent	0 (0.0)	18 (72.3)	5 (21.7)	0 (0.0)	39	56
PD	4	smi	0	0	0	4 (100)	9	26.5
Hindgut	10	rect, colorect, prg	**0**	**5**	**3**	**2**	32.5	45
Non-PD	8	desc col, colorect, rect prg	0	5 (62.5)	3 **(37.5)**	0 (0.0)	37.5	51.0
PD	2	rect, desc col	0	0	0	2 (100)	6	***22***
Unknown	3	–	**0**	**3**	**0**	**0**	60	61
Functional	16	brlpn(2), gastr(1), jej(4), nisid(1), MEN I(1), desc col(2), uo(1), pancr(4),	0 (0.0)	7 (43.7)	5 (31.25)	4 (25.0)	23	34.5
Nonfunctional	70	pancr(22), brlpn(9), smi(11), jej(1), rect(1), hcc + neur(2), uo(2), desc col(3), gastr(1), rect prg(1), asc col(2), colorect(1), mesent (3), mening(1), dndrglio(1), liver hil(1), ile(5), sigm(2), cecum(1)	3	38	16	11	33.5	51
Total	86		**3**	**44**	**23**	**16**	32	46.5

General Hospital and the MD PhD radiologist Dr. Dimitropoulos Nikolaos who encouraged us (the specialized physicians, physicists, PhD candidates and me) at the Nuclear Medicine Section to infuse ^{111}In-Octreotide as first-line therapy since 1997 up to 2012, performing exclusively intra-arterially, more than 800 infusions; additionally, to continue thereafter with non-carrier added ^{177}Lutetium DOTA TATE (around 50 infusions).

This scientific effort has led to the establishment of the "Aretaieion Protocol" [15, 53], where appart from the intra-arterially radionuclide infusion technique, nephroprotection with amino-acids and bone-marrow prophylaxis with 75 mg DTPA were taken as *"sine qua non"*. Furthermore, the temporary implementation of a port-system for those patients who wanted to avoid the discomfort of the intra-arterial procedure (Chap. 8, in this volume), was a special achievement, during this period; it has to be taken into account that PRRT with ^{111}In-Octreotide necessitated 12 sessions for an expected successful therapeutic result as well as the introduction of the "sonoporation concept" (Chap. 9, in this volume).

The results of this study demonstrate that PRRT with ^{111}In-Octreotide is a potent therapeutic option for liver metastasized patients with advanced grade 1 to 2 and even grade 3 NENs, which are of less than 20 mm in size or of micrometastases. This treatment has limited side effects and is undisputably safe.

Preliminary results in initial ^{111}In clinical studies and efficacy: Analyzing the results of the first and initially (with ^{111}In-Octreotide) treated cohort 1 of 17 (6%) in 2008 [15] (Table 7.1) patients achieved a complete response (CR), 8 of 17 (47%) showed partial response (PR) and 3 (18%) stable disease (SD), whereas in the remaining 5 (29%) patients the disease progressed, the therapy was discontinued and the patients died shortly thereafter. Consequently, 71% of the patients showed some radiological benefit (CR or PR or SD) from the treatment. Worldwide, only a limited number of authors reported until today on the efficacy of treatments in GEP-NET-patients using high doses of ^{111}In-Octreotide (Table 7.1). Our results in the CR/PR group (53%, 9/17) substantially differ compared to those of Valkema et al. (8%, 2/16 patients [67], of Buscombe et al. (17%, 2/12 patients) [68] of Anthony et al. (8%, 2/6 patients) [69] and of Delpassand et al. (7%, 2/29 patients) [70]. A similar diverge is obvious in the SD group 18% (3/17 pts) compared to the 58% (15/26 pts) of Valkema et al. [67], 58% (7/12 pts) of Buscombe et al. [68], 81% (21/26 pts) of Anthony et al. [69], and 55% (16/29 pts) of Delpassand et al. [70]. The superiority of our results compared to the aforementioned authors might be explained by the intra-arterial route of infusions, where the tumor mean absorbed dose per session was estimated to be markedly higher compared to i.v. application (Table 7.3); a finding also reported by other authors [71, 72]. Summarizing the results of previous studies, it might/can be concluded that the application of ^{111}In-Octreotide leads indisputably to disease stabilization (SD) in previously progressive tumors, clinical symptomatic improvement, and biochemical (Cr-A) decline. The

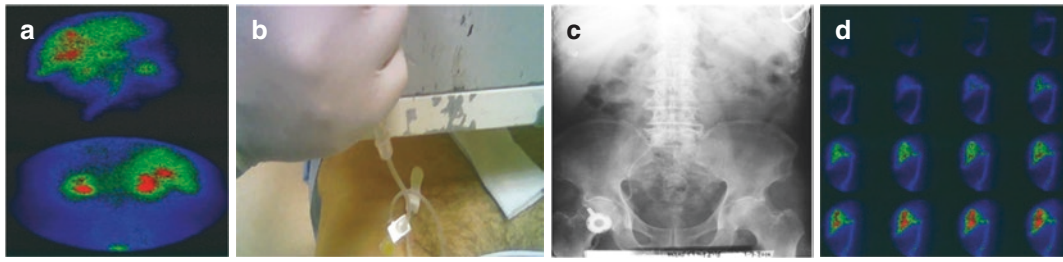

Fig. 7.13 (**a**) Radionuclide infusion through the drum-port system, temporarily implanted subcutaneously in the right iliac fossa area, (**b**) X-ray image (anterior view) of the patient's abdomen, (**c**) Dynamic (60 s, anterior view) scintimages obtained on the course of the infusion initialization and (**d**) static ones (anterior/posterior view) just after the end of the infusion (treatment) procedure

Table 7.4 Experts working with ^{111}In-Octreotide

Author	No of pts	cumul. activ. (GBq)	CR	PR	SD	PD
Krenning et al. (1994) [99]	1	20.3	–	1 (100%)	–	–
Caplin et al. (2000) [100]	8	3.10–15.200	–	–	7 (87.5%)	1 (12.5%)[a]
Tiensuu Janson et al. (1999) [101]	5	18.00	–	2 (40%)	3 (60%)	–
Nguyen et al. (2004) [102]	15	21.00	–	–	13 (87%)	2 (13%)
Valkema et al. (2002) [67]	26	4.7–160.0	–	2 (8%)	15 (58%)	9 (35%)
Anthony et al. (2002) [69]	26	6.7–46.6	–	2 (8%)	21 (81%)	3 (11%)
Buscombe et al. (2003) [68]	12	3.1–36.6	–	2 (17%)	7 (58%)	3 (25%)
Delpassand et al. (2008) [70]	29	35.3–37.3	–	2 (7%)	16 (55%)	11 (38%)[b]
Limouris et al. (2008) [15][c]	17	13.0–77.0	1 (6%)	8 (47%)	3 (18%)	5 (29%)

[a]Unrelated to the tumor cause
[b]Not clearly reported
[c]Exclusively intra-arterially

results of the clinical evaluation of the Auger electron emitter indium-111 conjugated to somatostatin analogues that target and exploit its receptor over-expression on neuroendocrine cells are encouraging, particularly as it was thereafter proven successful, for the eradication of small volume tumors [15] (Tables 7.4, 7.5 and 7.6).

7.5.1 The "Gnosti-Thera" Principle ["Gnosti-Thera" vs. "Thera-Nostics"]

In their Letter to the Editor [73] entitled: Why should we be concerned about a "g"? Frangos S and Buscombe JR aptly reported on the etymology of the term "Theranostics" (the concept from "diagnosis to therapy") which is uttered linguistically erroneously worldwide by the entire medical community.

The term "Theranostics," in addition to being an awkward title for a reputable international scientific journal, is repeated not only by colleagues noneducated in ancient Greek and Latin language but also strangely enough by native Greek- or Latin-originated scientists.

Additionally, the term "Theranostics" is also by definition wrong because therapy logically follows diagnosis and linguistically the appropriate approach is the synergy of these two words, where "diagnosis" precedes "therapy."

Table 7.5 Tumor-absorbed dose comparison between i.v. and i.a. administration of ^{111}In-Octreotide

Organ	Intra-arterial infusion	Intravenous infusion
Liver dose	0.14 (mGy/MBq)	0.40 (mGy/MBq)
Kidney dose	0.41 (mGy/MBq)	0.51 (mGy/MBq)
Tumor dose	15.20 (mGy/MBq)	11.20 (mGy/MBq)
Spleen dose	1.40 (mGy/MBq)	1.56 (mGy/MBq)
Bone marrow dose	0.0035 (mGy/MBq)	0.022 (mGy/MBq)
Tumor/liver dose ratio	108.57[a]	28.00
Tumor/kidney dose ratio	37.07	21.96

[a]The average absorbed dose per session to a tumor for a spherical mass of 10 g was estimated to be 10.8 mGy/MBq, depending on the histotype of the tumor

Furthermore, the second moiety (suffix) of the term "nostics" is leading inevitably towards the Greek word "νόστος" (nóstos) originated from the word "νέομαι" (néomai) meaning "repatriation" and furthermore nostalgy for return home (Sehnsucht nach etwas! in German); a linguistically erroneous word which alone does not express the precise meaning "from diagnosis to therapy".

Thus, the indisputable addition of "g" on the head of nostics, i.e., "gnostics" as it was aptly pointed out by the two colleagues, is a sine qua non, etymologically originated from the Greek

word "know," "diagnosis" or the Latin word "cognosco," "diagnosis," and furthermore to reorder these two words (moieties) in their appropriate sequence.

According to the above exlanation, the proposed term "Gnosti-Thera," although not euphonic but etymologically correct, could be suggested for use in the place of "Thera-Nostics" or "Thera-Gnostics."

7.5.2 The Intra-arterial Infusion Concept

Intrahepatic radionuclide infusion after selective hepatic artery catheterization has proved to be simple to perform safe and effective therapeutic management of small (≤20 mm) neuroendocrine hepatic secondaries, which are considered as inoperable. Compared to the other interventional techniques [74, 75] the methodology is almost invasive and short time lasting with negligible side effects. A relative drawback of the method is the slow tumor necrosis rate, requiring multiple treating sessions. Tumor melting areas shown on U/S scans are slowly growing, binding to each other and finally forming a large cavity, indicating necrosis. These tissue consistency changes can be easily followed up and evaluated by ultrasonography [76] (Fig. 7.13). The melting areas observed concern the neuroendocrine nodules, sparing the surrounding non-neuroendocrine healthy hepatic tissue. This is achieved due to the very short range of the Auger and Conversion electrons, the killing capability of which is limited up to 2–3 cells per decay [28]. Unfortunately, this very short range of the Auger and Conversion electrons consists a disadvantage of the procedure since multiple sessions are required for a potent tumor-cell destruction.

The radiopharmaceutical starts diffusing from the endpoint of the catheter into the branches of the hepatic artery towards the sinusoids of the neuroendocrine metastatic nodules following a pressure gradient that drains through rich vascular communications into the portal and/or hepatic veins [77, 78]. The radioactive distribution within and around the neuroendocrine nodules is related to the somatostatin receptor density of the cells as well as to the difference in vascularization between the neuroendocrine nodules and the surrounding normal hepatic parenchyma. The latter having a dual blood supply is mainly nourished by the hepatic artery [79], which provides about two-thirds of the blood flow, whereas the remaining one-third is provided by the portal vein [80, 81]. On the other hand, the increased somatostatin receptor-density acts like a magnet; the higher the receptor density of the tumor, the stronger the tracer gradient towards the receptors and hence the accumulation of the radiopharmaceutical.

Another parameter that gravely anticipates the large melting of the tumor and consequently the efficacy of the technique is the tumor shape and size. Neuroendocrine nodules of large volume of infiltrations spread into the hepatic parenchyma (Fig. 7.14) have shown poor response from the

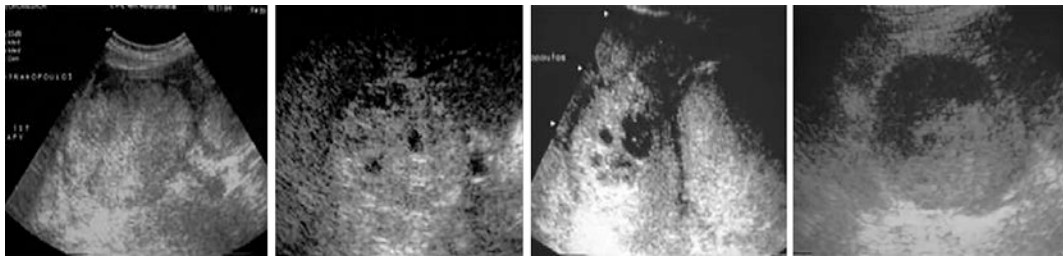

Fig. 7.14 Ultrasonographic evaluation of liver nodule before (5) and after (6) 5 sessions of octreotide treatment. Cystic degeneration of the nodule center and peripheral rim edema, as response to the therapeutic scheme. Cavity-type cystic degeneration of liver nodule in ultrasonographic examination. Swiss-cheese microcystic degeneration of liver nodule in ultrasonographic examination. Peripheral rim edema of liver nodule as first sign of tumor regression in U/S examination (Limouris et al. [76])

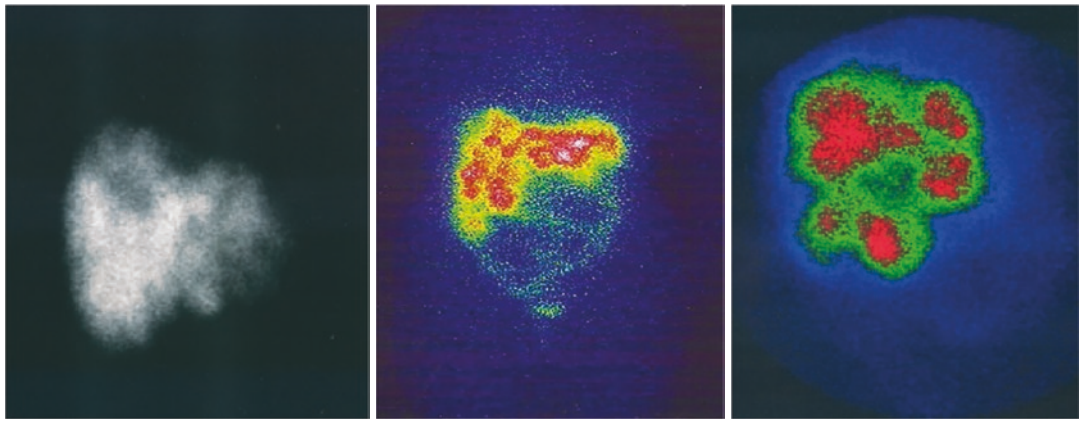

Fig. 7.15 Neuroendocrine secondaries of excised pancreatic NETs of large volume of infiltrations spread into the hepatic parenchyma (anterior view)

beginning of the treatment, because the indium-111 Auger and Conversion Electron ranges are insufficient to kill large tumor cell populations and essentially inhibit the progressive tumor growth (Fig. 7.15) [82].

The proliferation marker Ki-67 (this volume, Chap. 24) was almost routinely used for the grading of NETs [45, 83, 84]. A sample of 14 NEN patients out of the 86 treated with ^{111}In-Octreotide is tabulated in Table 7.6, related to their diameter.

7.5.3 Co-infusion of DTPA During Peptide Receptor Radionuclide Therapy with ^{111}In-Octreotide Reduces the Ionic Indium Contaminants

The Concept: In Peptide Receptor Radionuclide Therapy (PRRT) ^{111}In-Octreotide according to the manufacturer contains ~0.1% trivalent free ions of ^{111}In ($T_{ph1/2}$ = 2.83 days) and ^{114}In ($T_{p1/2}$ = 49.5 days). However since the mean patient activity per session usually ranges from 4070 MBq (110 mCi) to 7030 MBq (190 mCi) the amount of free $^{111}In^{3+}$ and $^{114}In^{+3}$ might provoke undesirable radiological burden to the patient, i.e., the often observed post-infusion myelotoxicity. According to pharmacokinetics, Indium trivalent (+3) ions accumulate in bone, liver, and spleen [85], bound to transferrin, a 80 kDa iron binding protein [86], inducing unwanted irradiation, particularly in bone marrow. Furthermore the trivalent indium anions mimic calcium bivalent ones accumulated in bone tissue where they participate in the hydroxyl-apatite formation. The tandem i.v. co-infusion of 75 mg of DTPA, diluted in 200–250 mL normal saline, 30 min before the commencement of the PRRT session in trip-trop infusion, continuing on the course of the procedure and lasting 4 h thereafter, competes with transferrin, forms trivalent DTPA complexes, by rerouting the ionic (free) indium fraction to renal clearance, and thus, effectively reducing blood pool activity and particularly bone marrow burden (Fig. 7.16).

Materials and Methods: Eighteen patients with neuroendocrine disease, age range 26–72 years, were treated with ^{111}In-Octreotide after selective hepatic artery catheterization. Nine out of them received a DTPA (Bristol-Myers Squibb) co-infusion in a dosage of 75 mg in 200 mL NaCl solution, in drip drop infusion, 30 min before the initialization of the session, lasting for about 4 h. Quantification of whole body scintigrams (30 min, 24 and 4 h p.i.) was performed [*MIRD Pamphlet No. 16 (J Nucl Med 1999, 40: 37S–61S)*]. Urinary and blood samples were collected during the patients' hospitalization and measured in a well-type scintilla-

Table 7.6 Ki-67 index vs tumor diameter in post-treated patients with ^{111}In-Octreotide

Patient's name	No. of foci	ø ≤ 2 cm	ø > 2 cm up to 4 cm	ø > 4 cm	Posttreatment foci/ response	Ki-67
1. GAG.KON	5	–	–	4.8, 4.2, 6.8, 4.1	5/PD	>20%
2. XAT. VAS	2	–	–	4.1, 7.2	2/PD	>20%
3. SIM. PAN	3	–	–	4.6, 5.0, 5.2	3/PD	>20%
4. MPO.NAN	2	–	–	5.4, 6.3	2/PD	>20%
5. DRO.IOA	3	–	–	4.2, 5.0, 5.2	3/SD	>2–<20%
6. POL.IOA	3	–	2.8, 3.4, 3.2	–	3/SD	>2–<20%
7. TSO.GRI	5	0.8, 1.2, 1.1, 1.6, 1.9	–	–	1/PR	<2%
8. THER/ KYR	4	0.8, 1.6, 1.9, 1.0	–	–	4/SD	>20%
9. BISTH. THEO	6	1.8, 1.1, 1.4, 0.8, 1.0, 1.6	–	–	6/SD	>20%
10. SOTH. STAV	5	1.4, 1.8, 1.6, 08, 1.2	–	–	5/SD	>20%
11. XRI.PAN	5	0.9, 1.2, 1.4, 1.8, 1.0	–	–	3/PR	<2%
12. BAT.ALE	5	–	2.0, 2.1, 3.1, 2.8, 3.5	–	2/PR	<2%
13. KAL. ANN	5	1.2, 0.8, 1.5, 1.8, 1.0	–	–	1/PR	<2%
14. POUT. AR	6	–	2.4, 2.0, 2.8, 3.0, 3.4, 3.8	–	3/PR	<2%

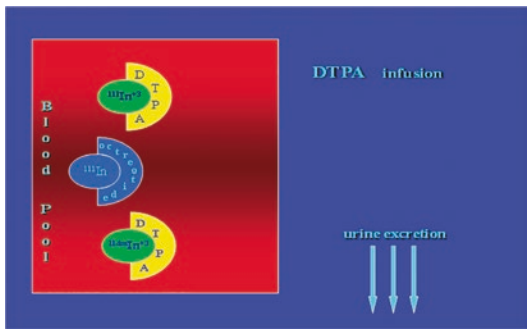

Fig. 7.16 Co-infusion of DTPA during peptide receptor radionuclide therapy with ^{111}In-Octreotide

tion counter. Exposure rate at 1 m patient's distance was recorded by means of an ionization chamber (Fig. 7.17).

Exposure rate measurements at 1 m distance from the patient were accomplished by means of an ionization chamber. The dose was estimated according to the MIRD schema [*MIRD Pamphlet No. 5 (revised J Nucl Med 1978)*].

Results: The activity and exposure rate half lives (h) in blood were 2.2 ± 0.4 and 1.2 ± 0.5 (rapid phase) without and with DTPA, respectively ($p < 0.05$) and for the slow phase 14 ± 8 and 12 ± 5 ($p > 0.05$). For the whole body the rapid phase for ^{111}In was 11 ± 3 and 8.1 ± 2 ($p < 0.001$) without DTPA and with DTPA respectively. For the whole body slow phase was 33 ± 12 and 33 ± 11 ($p > 0.05$) (Table 7.7).

Conclusion: DTPA co-infusions in PRRTs accelerate ^{111}In clearance, leading to the optimization of radiation protection of the clinical staff, the members of the family, and the public (97/43 EURATOM Directive); also, they significantly reduce the patients' radiobiological burden, contributing to the optimization of the treatment. Consequently it is strongly recommended in every PRRT [87].

Side effects of PRRT originated in general from bone marrow and kidneys. Co-infusion of lysine and arginine starting just before therapy

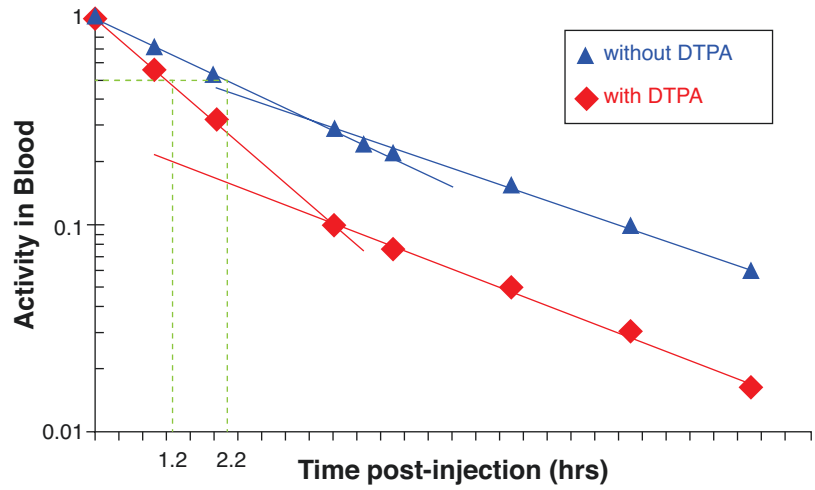

Fig. 7.17 Blood pool activity with and without DTPA co-infusion

Table 7.7 Activity and expose rate half life (h)

	Without DTPA	With DTPA	Difference
Blood (rapid)	2.2 ± 0.4	1.2 ± 0.5	$p < 0.05$
Blood (slow)	14 ± 8.0	12 ± 5.0	$p > 0.05$
Whole body	11 ± 3.0	7.8 ± 1.1	$p < 0.001$

lowers the radiation dose to the kidneys in patients treated with ^{90}Y or ^{177}Lu peptides, whereas for PRRT using ^{111}In-peptide intra-arterially it is practically not the case based on investigations performed by Kwekkeboom et al. (2001) and de Jong et al. (2004). Both authors proved that the pathlength of ^{111}In particularly can reach and affects the inner cortical zone of them and accordingly the kidney cannot by virtue be considered as a dose-limiting organ [88]. In his study, De Jong et al. [89] reported that ^{111}In-Octreotide distribution in the human kidney was investigated using SPECT scanning before and ex vivo kidney-autoradiography after surgery and indium's-111 radioactivity was localized predominantly in the inner zone of the renal cortex. Furthermore in the cortex, radioactivity is not distributed homogeneously, forming a striped pattern. These findings show that the average dose calculations using the MIRD scheme, assuming homogeneous renal radioactivity distribution, are virtually inadequate to accurately and precisely estimate the radiation dose to various parts of the kidney after PRRT.

On the course of the infusion, no pain was noticed, except for some abdominal discomfort in almost all patients, fatigue, headache, a temporary chest and head rush in 15 and blood pressure drop (from 140 to 9 mmHg)) in 21, as well as nausea, vomit, and diarrhoea on the first day p.i. All side effects disappeared shortly thereafter without any specific medical intervention. WHO toxicity grade I anemia occurred in 5 and grade I leuko-cytopenia and thrombocytopenia in 3. Severe (grade III and IV), mostly reversible, acute bone marrow toxicity was observed in 8/86 (10.5%) patients as a persistent hematological dysfunction. In 2/88 hairy cell leukemia was diagnosed and died shortly. Serum creatinine, transaminases, and alkaline phosphatase did not change in the entire group. Regarding the hormone levels, there were no abnormal values throughout the study for the whole group of patients. In contrast, a clear decrease in serum Cr-A was observed in SD and more obvious in partial and complete responders (Fig. 7.18), whereas in patients with progressive disease, a marked increase could be noticed.

Renal impairment and myelodysplasia (MDS) We have observed renal impairment in six patients during follow-up after this therapy, not related to PRRT, as according to their medical history, all six candidates for therapy presented with impaired serum creatinine ranging from >1.2 mg% up to 2.0 mg% [90–94]. Acute leukemia and MDS are severe complications related to PRRT and occurred

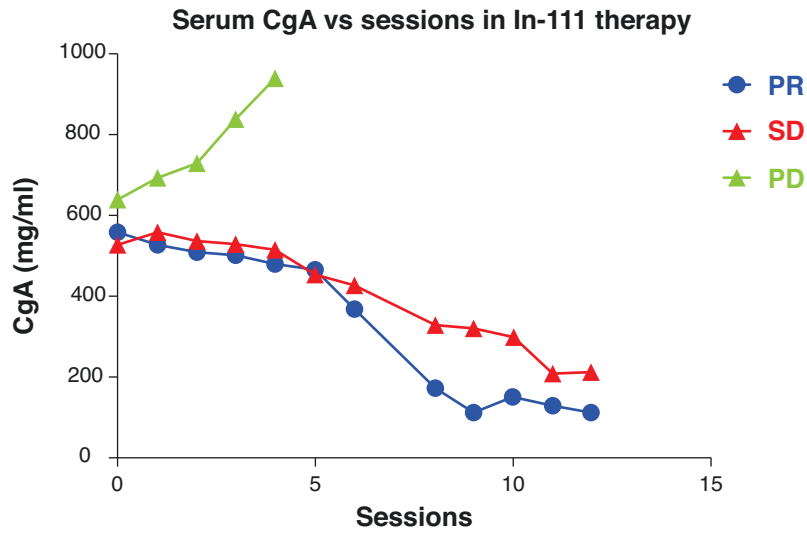

Fig. 7.18 Serum chromogranin-A levels during ^{111}In-Octreotide therapy in patients with PR, SD, and PD [1]

on average at 28 months after the first cycle with ^{177}Lu-DOTATATE for MDS, and after a median of 55 months for acute leukemia. Although none of our patients treated with ^{111}In-Octreotide were diagnosed with acute leukemia or MDS prior chemotherapy, recent reports suggest that there might be a higher risk of MDS or acute leukemia after alkylating chemotherapy [90–94].

Hormone-related side-effects or hormonal crises after PRRT with ^{111}In-Octreotide were not observed. However, when treating patients with functional neuroendocrine tumors, these hormone-related side effects should be taken into serious concern.

In the last two decades, many european authors have extensively reported on PRRT using [^{90}Y-DOTA^{0},Tyr^{3}]-Octreotide [90, 95–98]. Because of its higher energy, as compared with Indium-111, serious side effects have been noticed, e.g., transient grade 3 to 4 hematologic toxicity in 12.8% of patients and permanent grade 4 to 5 renal toxicity in 9.2% [90].

In 2008, we reported on 17 GEP-NET patients who were treated with n.c.a. ^{111}In-Octreotide [15]. In contrast to the former report, in this 86-patient cohort, the follow-up was much longer and the results are more representative in regard to the Auger electron efficacy in a multivariability of GEP-NET subtypes.

In this randomized study, the patients were all treated strictly according to the inclusion criteria, whereas an insistent active follow-up for many years makes the results by virtue noteworthy. Large tumor load or functional disease was dramatically slowed down, because PRRT was the best available treatment option at that time point. However, analysis of the patients with PD at baseline demonstrated only small differences in PFS and OS compared with all other NEN patients.

7.6 Conclusion

Considering the favorable high linear energy transfer of indium-111 Auger electron emission, it can be anticipated that the majority of diagnostically positive OctreoScans in small (less than 20 mm) neuroendocrine liver nodules, seems to be a first class candidates for this kind of treatment. The results so far are promising for the local control of such a histotype of malignancies. On the other hand, the relatively satisfactory long (>7 years) follow-up period of these patients encourages for a reliable estimation of the successful responders. The intra-arterial catheterization technique highly optimizes the received dose to the tumor, reducing consequently the burden of the critical organs. The tumoricidal effectiveness of PRRT with indium-111 Auger electron emission is judged by the overall survival and survival rate of these patients.

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