6 Intravenous Radiopeptide Infusions with High Activity of ^{111}In-Octreotide

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6.1 Introduction

The treatment of liver neuroendocrine metastases continues to be a major doctor's dilemma because a majority of the patients suffer from extensive unresectable disease. Apart from surgical resection which is the treatment of choice, *systemic therapy*, *hepatic artery (chemo) embolisation and radiofrequency ablation* have been claimed to have proven clinically beneficial. Patients with the objective of *surgery* with a curative intention are few because of the wide incidence of the disease [1, 2] and because this procedure is not allowed in many cases. In fact, in a majority of them, only an excision procedure is carried out, while complete resection is opted for less than 10% of the patients [3]. In *systemic therapy,* the use of intravenous chemotherapy does not lead to the best expected results. This is due to diverse variables that include type of chemotherapy, stage of disease, progression and toxicity [4, 5]. From the panel of local ablation techniques *(chemo) embolisation* [6, 7] and *percutaneous radiofrequency ablation* [8], two minimally invasive procedures are usually done in an interventional radiology department. For both these procedures, it is necessary that the number of liver lesions are limited, no more than 3, a criterion that should not be ignored as in a majority of the neuroendocrine liver metastases cases, these are more.

In 1993, Eric Krenning employed ^{111}In-Octreotide (Octreoscan, Mallinckrodt, Petten, the Netherlands) for therapeutic purposes in the treatment of NETs [9, 10] via intravenous infusions, exploiting the Auger and Internal Conversion Electron emission of Indium-111 [10, 11]. This treatment modality is aimed at destroying the tumor tissue with the help of the high linear energy transfer delivered from these electrons [12]. However, a disadvantage of this procedure was the increased retention of the radiolabel in the kidneys and spleen, considered as the critical organs [13, 14]. That study aimed to assess and evaluate the usefulness of the procedure in long term in non-resectable liver metastases caused by NETs.

To maximise the linear energy transfer onto the tumor, achieve a larger lesion, destroy and, in parallel, reducing the delivered dose to the critical organs (kidneys and spleen), we decided to modify, in our institution, the way of ^{111}In-Octreotide administration by applying radioactivity as close as possible to the malignancy after selective catheterisation of the hepatic artery [15, 16]. To the best of our knowledge, this is the first time that this approach has been adopted on a routine basis. However, while some cases could not be treated intra-arterially either because the patient refused to be catheterised or

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G. S. Limouris (ed.), *Liver Intra-arterial PRRT with ^{111}In-Octreotide*,
https://doi.org/10.1007/978-3-030-70773-6_6

the anatomic variants of the arterial net inhibited the intra-arterial approach. PRRT was performed intravenously in only 10 cases, while 86 treated intra-arterially.

According to Hirmas et al. [17], in the gastrointestinal system, particularly, the most common, malignant NETs arise from the midgut. For such patients presenting with metastatic disease, Yao et al. and Modlin et al. have reported a 5-year survival rate of less than 50% [18, 19]. NET classification was introduced by the European Neuroendocrine Tumor Society (ENETS) in 2006 and 2007 [20, 21], without taking into account the Ki-67 index. However, the ENETS, the American Joint Committee on Cancer (AJCC) and the WHO classification (2010) included the Ki-67 labelling cutoff of <3% to define low-grade (G1), 3–20% for intermediate-grade (G2) and >20% for high-grade (G3) NETs (Table 6.1) [20, 21].

To stratify the best possible NET treatment strategy, a multidisciplinary approach for their management is required that can ensure a consistent and optimal level of care (Table 6.2). If NETs are resectable, the surgery consists of the treatment of choice.

In the case of unresectable disease, in tandem treatments, including obligatory somatostatin analogue therapy with Octreotide or Lanreotide, PRRT, Everolimus (mTOR inhibitor) or Sunitinib (tyrosine kinase inhibitor) [22].

The purpose of this study was to study, evaluate and report on PRRT carried out by using ^{111}In-Octreotide, intravenously implemented, high dose treatment as a treatment option for unresectable, multiple and small-in-size (up to 20 mm in their major diameter) liver metastases.

Table 6.1 NETs 2010-WHO classification for digestive system NETs

Differentiation	Grade	Mitoses per 10 HPFs	Ki-67 index
Well-differentiated	Low-Grade (G1)	<2	<3%
Well-differentiated	Intermediate-Grade (G2)	2–20	3–20%
Poorly differentiated	High-Grade (G3)	>20	>20%

HPFs high power fields

Table 6.2 Multidisciplinary team's approach to review NET patients

Nuclear medicine physician	Hepatic surgeon
Interventional radiologist	Medical oncologist
Radiation physicist	Pathologist
Colorectal surgeon	Anesthesiologist
Gastroenterologist	Dedicated nursing staff

6.1.1 Patients

Ten patients (4 women, 6 men; age range: 49–76 years, median age 64, 5 years) with unresectable neuroendocrine liver metastases, confirmed by biopsy, were administered 4070–5920 MBq (110–160 mCi) per session intravenously (Table 6.3) after centesis of the dorsal vein hand system or the antecubital vein. Repetitions did not exceed the nine sessions, and the treatment intervals were of 5–8 weeks. The study was approved by the Institutional Committee on Human Investigation and Ethics of the "Aretaieion" University Hospital. Informed consent was signed by each of the patients participating in this study.

Liver metastases originating from mediastinum (n = 1) lungs (n = 4), head of pancreas (n = 2), sigmoid (n = 1) and small intestine (n = 2).

According to the RECIST criteria [23, 24], the disease was not measurable in two of the patients because the lesions were diffused within the liver parenchyma. The eligibility criterion for PRRT was the unresectable nature of the liver metastases that had shown resistance to systemic chemotherapy as could be seen in contrast with the help of a material-enhanced computed tomography (CT) scan and/or a magnetic resonance imaging (MRI) image. Besides the confirmed biopsy (Fig. 6.1) from the primaries, no additional histologic proof was obtained in the treated liver lesion because of the risk of possible biopsy complications (i.e. haemorrhage, metastatic spread). Contra-indications of PRRNT were a Karnofsky index of <40, pleural or abdominal effusions, renal impairment (serum creatinine

Table 6.3 Patients' characteristics and PRRT results using ^{111}In-Octreotide intravenously

Patient/gender	Age (in years)	No. of sessions/cumul. activ. (GBq)	CR	PR	SD	PD	PFS	OS
1. ANT.ANS./M	57	1/5.92	–	–	–	+	7	11
2. KAT.ALH./F[a]	70	5/29.60	–	–	–	+	3	6
3. MAN.NIK./M	53	4/23.32	–	–	–	+	10	19
4. SOT.STA./F	76	9/53.28	–	–	+	–	26	32
5. ROU.KON./M	68	4/23.68	–	–	–	+	9	19
6. MPO.NIK./M	60	3/17.20	–	–	+	–	12	17
7. THE.KYR./F	49	2/10.92	–	–	+	–	17	35
8. MPA.XRI./M	65	3/17.40	–	–	–	+	5	11
9. MAL.VAS./F	64	2/11.84	–	–	–	+	4	11
10. GAZ.NIK./M[a]	70	6/35.52	–	–	–	+	8	18

[a]Non-measurable disease; *CR* complete response; *PR* partial response; *SD* stable disease; *PD* progressive disease; *PFS* progression-free survival; *OS* overall survival

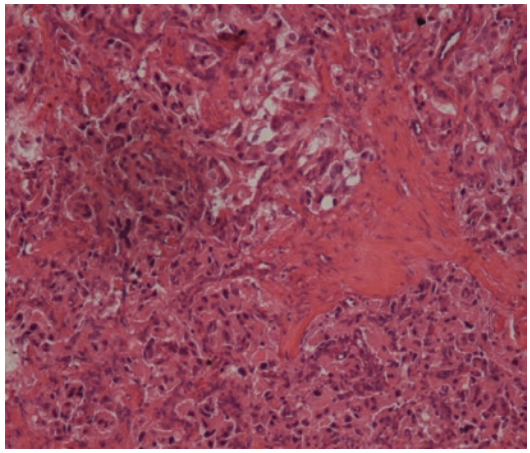

Fig. 6.1 Histological section of a well-differentiated mammary NET (Haematoxylin-Eosin ×10)

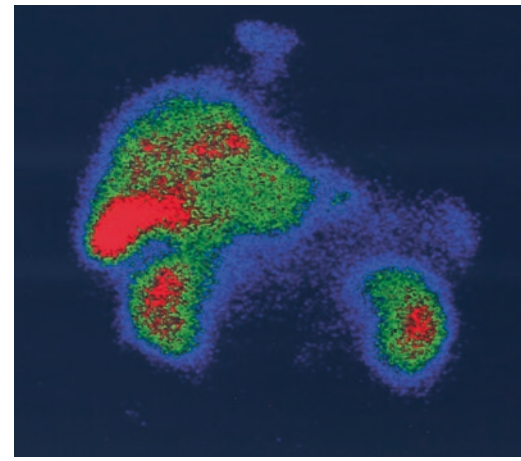

Fig. 6.2 A 'grade IV' OctreoScan visual score

>1, 7 mg/dL), serum haemoglobin ≤9.0 g/dL, total white blood cell (WBC) count ≤2×10^9/L, platelet count ≤75×10^9/L and serum creatinine concentration ≤1.7 mg/dL. All ten patients had undergone complete surgical resection of primary cancer.

The assumption for the patients to be treated with ^{111}In-Octreotide was that the intense degree of the radionuclide tumor uptake on the diagnostic OctreoScan scintigraphy to be as high as the half uptake in the normal parenchyma of the spleen and left kidney (visual score 4) before the therapy (Fig. 6.2).

6.1.2 Preliminary Results

In the sub-group of 17 GEP–NET-patients that were intra-arterially infused [25], CR was seen in 1 (6%), PR in 8 (47%), SD in 3 (18%) and PD in 5 (29%). ^{111}In-Octreotide was obtained from Mallinckrodt (Petten, Holland) and prepared 'in-house' as described previously [25]. Before the infusion of the radiopharmaceutical, Ondansetron (8 mg) was administered 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. Additionally, to reduce myelotoxicity, 75 mg of DTPA in trip-trop diluted in about 200 mL normal saline water was also infused 30 min before the initialisation of the radiopeptide therapy, also lasting for about 4 h. Patients were treated up to a cumulative intended dose from 160 mCi (5.92 GBq) to 1440 mCi (53.28 GBq) ^{111}In-Octreotide. Routine haematology, liver and kidney function tests were performed after three therapy cycles during follow-up. A CT or MRI scan was performed before and at the end of the entire therapeutic scheme. Thereafter, every case was seen as an outpatient.

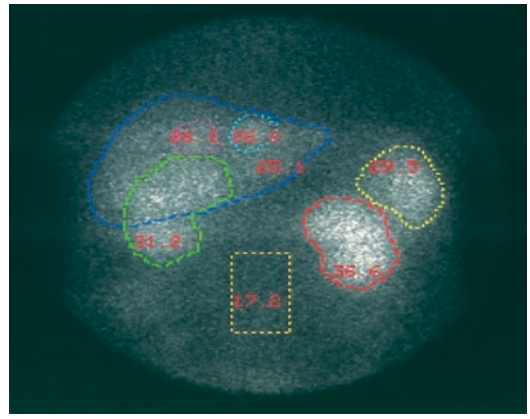

Fig. 6.3 Delineation of organs and creation of Region of Interest (ROIs) on planar Octreoscan for quantitative dosimetry

6.1.3 Equipment and Procedure

The infusions were conducted at the Nuclear Medicine Department of the "Aretaieion" University Hospital. The size and location of the neuroendocrine nodules were assessed using the Couinaud nomenclature [26, 27] based on consensus between the two observers who compared the images obtained with each of the radiologic techniques.

6.1.4 Intravenous Infusion

^{111}In-Octreotide solution was administered via a three-cock catheter; the radionuclide infusion lasted for 20–30 min to avoid side effects, i.e. hypotony, nausea or vomiting. The time interval between consecutive sessions was 7–8 weeks. However, in cases with long-lasting post-treatment, subacute, haematologic toxicity, the intended interval was postponed to 9–10 weeks. The radioactive material was injected by the nuclear physician, covered by a 0.787-inch-thick lead shield (barrel). At the end of the procedure, a 10 mL saline flush was given to deplete any radioactivity that remained in the three-cock catheter wall. Just after the end of the infusion, a stop-cock heparinised catheter was ante-cubitally inserted to drain blood samples 2 h, 4 h, 8 h and 24 h post-catheterisation for dosimetric calculations. For the same reasons, 24 h urine was collected. No pain, except some discomfort during or after the infusion, headache and nausea was noticed. Patients remained obligatory for 24 h in a single bedroom with its own toilet dedicated for hot (radionuclide treated) patients. At the time of the patient discharge behaviour, instructions were given to constrain the doses received by the members of the public and the close family taking into account the dose rate (mSv/h) at 1 m distance from the patient's body.

Planar and SPECT scans were performed for all therapy cycles to calculate tumor and critical organ doses, followed by quantitative dosimetry (Fig. 6.3). Accordingly, absorbed doses delivered to liver metastases, kidneys and red marrow were calculated using OLINDA 1.1 program, and the response assessment was classified, based on RECIST criteria. Response to salvage PRRT was assessed by CT/MRI scans performed before, during and after the end of the treatment, and monthly ultrasound images were studied for liver follow-up measurements. Toxicity (WHO criteria) was measured using blood and urine tests of renal, hepatic and bone marrow functions. PFS analysis was performed with the help of the Kaplan-Meier survival plot.

6.1.5 Blood Sampling

Blood sampling was performed 24 h after the administration. The absorbed dose to the blood was mainly caused by beta radiation originating from activity in the blood. The activity in the blood is determined in a well counter from aliquots of non-heparinised blood samples. Whole blood samples (about 2 mL) were collected at 2, 4, 8 and 24 h post-infusion. The first sample was drawn from the contra-lateral arm within 10 min.

6.2 ^{111}In-Octreotide Treatment Results

6.2.1 Liver Metastatic Load

None of the 10 treated patients resulted in either CR or PR. (Table 6.3): Three out of the ten cases resulted in disease stabilisation, whereas the other seven did not respond at all and died within approximately one and a half years after the end of the therapeutic scheme due to disease aggravation (Table 6.3). The 12-month PFS and OS ratio was 3/10 (30.0%) and 6/10 (60.0%), respectively; the median PFS in months was 8.5 and for OS 17.5 (Fig. 6.4).

A Grade II to III erythro-, leuko- and thrombocytopenia occurred in all PD cases. Dosimetric calculations (Table 6.4) were found as follows: (a) Liver Tumor 11.2 mGy/MBq, (b) Liver 0.40 mGy/MBq, (c) Kidneys 0.51 mGy/MBq, (d) Spleen 1.56 mGy/MBq, (e) bone marrow 0.022 mGy/MBq.

6.2.2 Follow-Up

Patients were in close contact with our institution as it was recommended to them that they perform bi- to tri-monthly ultrasonography of the upper and lower abdomen and undergo specific laboratory examinations that were performed for WBC

Table 6.4 Tumor-absorbed dose comparison between i.v. and i.a. administration of ^{111}In-DTPA^{0}-Octreotide

	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 gr was estimated to be 10.8 mGy/MBq, depending on the tumor's histotype

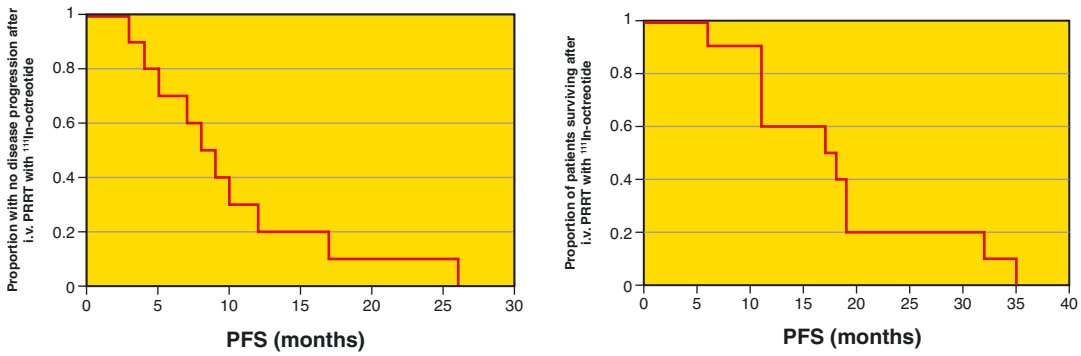

Fig. 6.4 Kaplan-Meier curves for progression-free (left) and overall survival (OS) (right) of ten NETs, intravenously treated with ^{111}In-Octreotide

and RBC counts, platelet counts, haemoglobin, creatinine and Cr-A levels. CT and/or MRI scans were also performed before the initialisation of the therapy and every 6 months thereafter. All laboratory values were compared with the previous ones as well as with ultrasonography, CT and MRI scan images that were obtained before the initialisation of the treatment to assess any changes in tumor consistency and size. As detailed archives are kept for every case, patients were requested to present at the nuclear medicine division at least thrice every year for the evaluation of the response to the procedures that were done based on RECIST guidelines, whereby the disease was classified into two categories, i.e. (a) measurable and (b) non-measurable. In the first category, the nodules had to be distinguished in terms of their diameters that are easily measurable, whereas the second category was that of diffused malignancy. Diameter measurements were performed by using the longest cross-sectional diameter on U/S scans and finally confirmed by CT and/or MRI scan images.

6.3 Discussion

Combating the liver metastatic disease continues to be a major dilemma for the scientists concerned (oncologists, nuclear physicians, gastroenterologists and surgeons) including invasive, minimally invasive and non-invasive therapeutic schemes. A combination of the aforementioned techniques might be the treatment of choice after a thorough evaluation of the malignancy as a whole (generally) and in appropriate hierarchy of the treating methodologies in particular after taking into account the multidisciplinarity of the specialities involved. From the non-invasive therapeutic schemes, Everolimus or Sunitinib and chemotherapeutics aimed to improve possible liver nodule receptibility by trying to ablate, as efficiently as possible, the aggressiveness of the cancerous cell(s). Even though chemotherapy is used and continues to be the treatment of choice to confront the progression of the malignancy, its toxicity limits its application. Surgical liver nodule excision, on the other hand, is regarded as the treatment of preference despite the fear of a further metastatic spread post-surgery. In cases that are eligible for surgery, a 5-year survival rate of 21–44% has been achieved [28]. Given that the neuroendocrine disease spread is highly variable, depending on a plethora of factors, such as the site of the tumor, its origin, tumor functionality or non-functionality, differentiation, receptor homogeneity, mitotic indexes and size that tremendously impact therapy response, an in tandem treatment of PRRT with Octreotide or Lanreotide, Everolimus, and less often with Sunitinib and Streptozotocin, prolongs progression-free survival, overall survival and quality of life among the patients. PRRT combined with other anticancer therapies have appeared to be safe, but, to date, only phase-II clinical trials have been reported in this regard, leaving numerous possible options for further research [28, 29]. Based on worldwide reports, infusing radiopeptide therapies in combination with different therapeutic modalities have proved to be more effective in the manipulation of the neuroendocrine character of these tumors [30]. Tandem schemes with ^{111}In-Octreotide are not recommended as ^{111}Indium's Auger and Internal Conversion Electron emission is not considered as an appropriate candidate for PRRT armamentarium due to electrons' extremely short path length of 2–500 nm.

As it can be derived, in the therapeutic cycle for each patient the response is strongly dependent on the classification category of the neuroendocrine disease. A diffused, non-measurable disease consists of the first main factor of resistance to an efficient response. Practically, the disease has no hope for improvement unless a tiny tumor degeneration degree, whereas the tumor size is, surprisingly, a secondary factor of resistance to an objective response. It should not be ignored that the main drawback of ^{111}In emission is its extremely short range, incapable to destroy a larger cell number than as might be achieved by the use of ^{90}Y or ^{177}Lu, both being addressed approximately to a 250 and 50 cell population, respectively [31]. On the other hand, this short emission does not aggravate the disease apart from some side effects such as transient diarrhoea.

As the majority of the patients do not favour systemic schemes or surgery as well, the PRRT population with the final therapeutic results 'partial response' is not permitted to be abandoned without any further care and treatment. The best solution could be to convince them to shift towards a surgical excision in case the eligibility criteria allow it or to a radiofrequency ablation procedure. Additionally, the simplicity of the radionuclide intra-hepatic infusion allows it to be considered as a preparative procedure for a furthermore potent therapeutic solution. U/S is requested as a follow-up obligatory exam every quarter to evaluate the disease's behaviour and to permit shifting to a more invasive therapeutic modality.

To our knowledge, the advantages of this methodology are that it is: (a) minimally invasive, performed after centesis of the femoral artery and insertion of an appropriate endovascular catheter up to proper hepatic, right or left hepatic artery depending on the vaso-anatomical status of the patient; (b) a super-selective methodology that is systematic and has a targeted character. As it is obvious that much closer to the lesion the radioactivity is delivered such that its uptake by the cellular receptors is higher and hence it has a more destructive effect on the tumor; (c) a simple infusion and not an embolisation. Practically, there are no side effects either during or after the procedure; (d) independent of using a specific tracer to transport the radioactive material to the target as radiolabelled Octreotide is by its nature receptor-trapped and specific.

A drawback of this study however was that it lacked a control group. So, a comparison in terms of the survival advantage with the radionuclide perfusion managed group was not possible.

On the other hand, as the majority of the treated patients had discontinued or finished with chemotherapeutic schemes, the results of the radioactive infusions (tumor shrinkage or consistency changes) could be attributed to the contribution of the radioactive effect (Auger and Internal Conversion electron emission).

We studied the PRRT outcome with ^{111}In-Octreotide, intravenously administrated, in 10 patients suffering from NETs with primaries of different origin. Comparing the international references as a whole, of several expert reports on PRRT (Table 6.5) using ^{111}In-Octreotide an objective response (CR + PR) was observed in 20/139 (14.4%) of the treated cases, whereas the outcome of our tiny cohort is higher, giving an objective response rate of 30%. In 1994, in his first ^{111}In-Octreotide study Eric Krenning [9], including only one patient, reported an ORR of 100.0%, after a cumulative activity of 20.3 GBq.

Table 6.5 Experts working with ^{111}In-Octreotide

Author	No of pts	Cumul. activ. (GBq)	CR	PR	SD	PD
Krenning et al. (1994), *ref. no 19, 20*	1	20.30	–	1 (100%)	–	–
Tiensuu Janson et al. (1999) ref. no 21	5	18.00	–	2 (40%)	3 (60%)	–
Caplin et al. (2000) *ref. no 22*	8	3.10–15.20	–	–	7 (87.5%)	1 (12.5%)[a]
Valkema *et al*. (2002)	26	4.7–160.00	–	2 (8%)	15 (58%)	9 (35%)
Anthony et al. (2002)	26	6.7–46.60	–	2 (8%)	21 (81%)	3 (11%)
Buscombe *et al*. (2003)	12	3.1–36.60	–	2 (17%)	7 (58%)	3 (25%)
Nguyen et al. (2004) *ref. no 23*	15	21.00	–	–	13 (87%)	2 (13%)
Delpassand *et al*. (2008)	29	35.3–37.30	–	2 (7%)	16 (55%)	11 (38%)
Limouris et al. (2008)[b]	17	13.0–77.00	1 (6%)	8 (47%)	3 (18%)	5 (29%)
Limouris GS (this study)	10	5.92–53.28	–	–	3 (30%)	7 (70%)

[a]Unrelated to the tumor cause
[b]Exclusively intra-arterially

In a ^{111}In-Octreotide study by Tiensuu Janson et al. [32] in a cohort of 5 NETs a 100% control disease (CR, PR or SD) was also reported after a cumulative activity of 18 GBq. In 2000, Caplin et al. [33] in a cohort of 8 NETs, treated with ^{111}In-Octreotide of a dosage ranging from 3.10 to 15.20 GBq achieved an SD in 7 (87.5%) patients whereas the remaining one died due to reasons unrelated to the disease. In 2002, Valkema et al. [34] in a study of 26 NETs treated with ^{111}In-Octreotide 2 (8%) patients had PR, 15 (58%) SD and 9 (35%) PD, after a cumulative activity ranging from 4.7 to 160 GBq. The same year, Anthony et al. [35] in 26 NET patients reported a PR in 2 (8%), a SD in 21 (81%) and PD in 3 (11%) after a cumulative activity of ^{111}In-Octreotide ranging from 6.7 to 46.6 GBq. Buscombe et al. in 2003 [36], in a study of 12 NET patients treated cases implementing ^{111}In-Octreotide reported a PR in 2 (17%), an SD in 7 (58%) and a PD in 3 (25%) after a cumulative activity ranging from 3.1 to 36.6 GBq. In a study by Nguyen et al. in 2004 [37] on 15 NETs, treated with ^{111}In-Octreotide after a cumulative activity of 21 GBq, an SD was reached in 13 (87%), whereas the rest 2(13%) patients showed PD. In a study of 29 NET patients, Delpassand et al. [38] reported PR in 2 (7%), SD in 16 (55%) and PD in 11 (38%) patients after a cumulative activity ranging from 35.3 to 37.30 GBq. Finally, in preliminary data of a prospective study of 17 NET patients from our Institution, in 2008, treated with ^{111}In-Octreotide intra-arterially, after catheterisation of the hepatic artery we achieved a CR IN 1 (6%), a PR in 8 (47%), an SD in 3 (18%) and a PD in 5 (29%), after a cumulative activity ranging from 13 to 77 GBq.

6.4 Conclusion

^{111}In-Octreotide was infused in repeated high doses ranging from 4.070 GBq (110 mCi) to 5.920GBq (160 mCi) with a time interval of 6–8 weeks between sessions. This treatment was well-tolerated in all the patients without any marked side effects or complications being observed subsequently. According to the RECIST criteria, a disease control could be achieved in only 3 out of 10 patients. In the other 7 patients, disease progression was recorded, and all of them died approximately 4–7 months after the end of the therapeutic scheme. Radiopeptide intravenous infusions with high activity of ^{111}In-Octreotide even well-tolerated in all patients were disappointing and are not suggested as a therapeutic treatment option in patients with neuroendocrine disease.

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