17 Intra-arterial ^{111}In-Octreotide Infusions for the Treatment of Meningioma

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17.1 Introduction

Neuroendocrine tumors (NETs) comprise a heterogeneous group of malignancies that arise from neuroendocrine cells throughout the body, most commonly originating from the lung and the gastrointestinal tract.

In the case of brain tumors (Fig. 17.1) a high incidence of sst receptors has been reported in meningiomas, gliomas, and well-differentiated astrocytomas and neuroendocrine secondaries [1–5]. These tumors express a high density of somatostatin receptors compared to the surrounding tissue that allow them to be readily visualized by in vivo receptor imaging methods using labelled somatostatin analogs such as octreotide [4, 6].

NETs were called "carcinoid" 100 years ago and considered as benign neoplasms. Currently, WHO characterized them as malignant, eliminated in 2000, the "carcinoid" label, whereas in 2010 classified them [7–10], including both Ki-67 index and mitotic count, as the following: Low Grade (G1) =<2 mitoses/10 high power fields (HPFs) and ≤2% Ki-67 index; Intermediate Grade (G2) = 2–20 mitoses/10 HPFs or 3–20% Ki-67 index; and High Grade (G3) =>20 mitoses/10 HPFs or >20% Ki-67 index [11, 12] (Table 17.1).

The incidence of NETs is increasing, and it is therefore attracting interest and attention. Generally, the majority of metastases occur in the liver (Fig. 17.2), lungs, and bone. Other sites are rarer, and brain metastases are very rare, so an

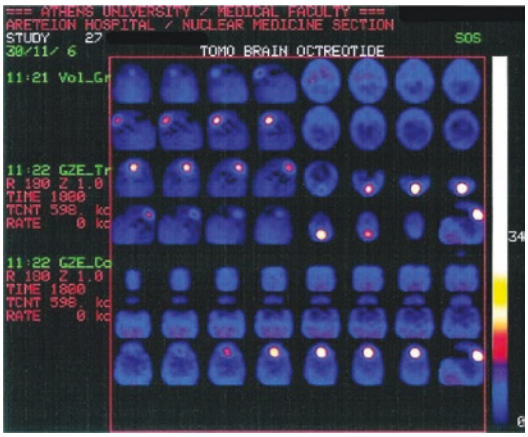

Fig. 17.1 OctreoScan® brain tomo-scintigraphy of a radiologically confirmed meningioma after 111 MBq ^{111}In-Octreotide i.v. 7 h post-injection. Intense radiotracer uptake to the right of the mid-line of the parietooccipital area (visual score IV)

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accurate and timely diagnosis can ensure the implementation of appropriate treatment and have a substantial impact on prognosis.

With a worldwide incidence of 45,000 cases [13], meningiomas are the most common non-glial primary intracranial tumors where surgery consists a promising curative option; however, after complete tumor resection Galldiks et al. [14] and Goldbrunner et al. [15] reported that a 5-year recurrence rate is estimated to 5%, 40%, and 80% in grades I (benign), II (atypical), and III (anaplastic) of the tumor, respectively. At this step very few treatment options are available. According to Kaley et al. [16] and Guedj et al. [13], the progression-free survival of aggressive recurrent meningiomas decreases below 30% at 6 months, while the median overall survival accounts to 3 years for patients with grade III. Surgery remains the only curative option for treatment of meningioma, whereas external beam radiotherapy offers another curative option in meningioma manipulation [15, 17, 18]. Accordingly, a multidisciplinary approach to the management of brain tumors, positive for somatostatin receptors, is required to ensure a consistent and optimal level of care (Table 17.2) [19].

Even after complete surgical removal, meningiomas recur in about 10–32% of the cases within 10 years. As a sequence, among the tumor histotype treated, we evaluated the effectiveness of high doses of ^{111}In-Octreotide infusions following selective catheterization of the internal

Table 17.1 NETs 2010—WHO classification for rectal NETs

Grade	Mitoses per 10 HPFs	Ki-67 index
G1	<2	≤2%
G2	2–10	3–20%
G3	>10	>20%

HPFs high power fields

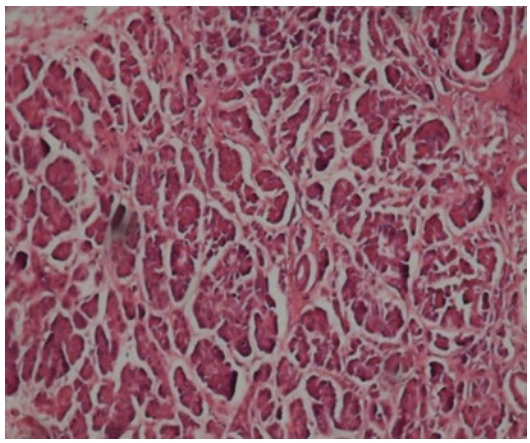

Fig. 17.2 Histological section of a low-grade pancreatic NET metastasized to the liver (Hematoxylin Eosin ×10)

Table 17.2 Multidisciplinary team approach to reviewing lung and liver metastasized patients

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

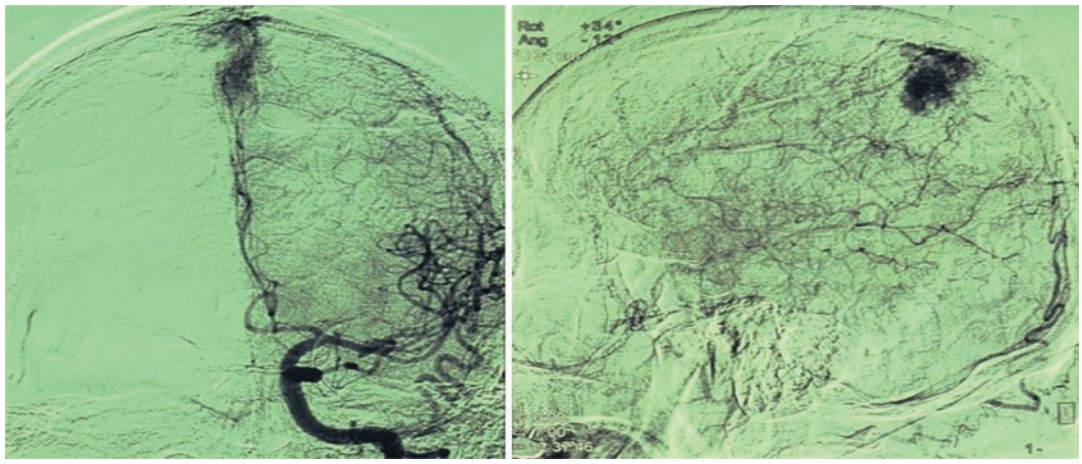

Fig. 17.3 Selective catheterization of the right carotid artery and followed angiography of the meningioma remnant

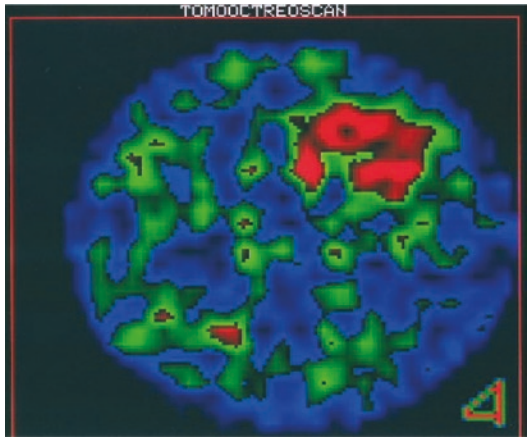

Fig. 17.4 Diagnostic OctreoScan® brain tomoscintigraphy of a radiologically confirmed meningioma after 111 MBq ^{111}In-Octreotide i.v. 7 h post-injection. Intense radiotracer uptake to the right of the midline of the parieto-occipital area (visual score IV) at the level of the tumor remnant

carotid artery (Fig. 17.3), in a recurrent WHO grade II brain meningioma residuals and sst receptor (OctreoScan)-positive, due to the effect of ^{111}In Auger electron emission (Fig. 17.4).

17.2 ^{111}In-Octreotide Treatment Results

A 76-year-old male patient (Table 17.3) had a median Karnofsky performance status 90 at inclusion; the high diagnostic probability of meningioma was based on typical radiologic patterns in CT/MR imaging and positive ^{111}In-Octreotide uptake. The patient had been treated by surgery and radiotherapy.

The average dose per session administered was 5.4 ± 1.7 GBq GBq. Repetitions did not exceed threefold. Response assessment was classified according to the modified Response Evaluating Criteria in Solid Tumors (RECIST). CT/MRI scans were performed as baseline before, during, and after the end of treatment. Toxicity (WHO criteria) was measured using blood and urine tests of renal and bone marrow function.

Brain meningioma load (Table 17.3): A complete and partial response could be not achieved to the treated patient, whereas disease stabilization was observed.

Table 17.3 Patient response to therapy with ^{111}In-Octreotide

Patients	Response evolution	PFS	O S
Meningioma	SD ≫ PD ≫ D	29	43

Table 17.4 Tumor-absorbed dose comparison between i.v. and i.a. administration of ^{111}In-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 g was estimated to be 10.8 mGy/MBq, depending on the histotype of the tumor

A 43-month overall survival time was estimated with a 29-month PFS. Grade 1 erythro-, leuko-, and thrombo-cytopenia was noticed.

On CT the brain tumor mass progressed dramatically. Dosimetric calculations for the intra-arterial infusions are tabulated in Table 17.4 and compared with intra-venous data obtained from cases, rarely intravenously treated.

17.3 Discussion

With a PFS of 29 and 43 months OS in our study (Table 17.5), ^{111}In-Octreotide may represent a promising PRRT option for meningioma cases, antra-arterially treated. PRRT, intravenously performed not with ^{111}In-Octreotide but with β-emitters, i.e., ^{90}Y-DOTATOC or ^{177}Lu-DOTATATE, consists a promising tool for the confrontation not only for low-grade meningiomas but also for high-grade tumors. In a study of Bartolomei et al. [20] on 29 meningioma patients intravenously infused with ^{90}Y-DOTATOC, a SD was observed in 19/29 and a PD in 10/29 cases, accordingly. The authors report a median PFS (from beginning of PRRT)

Table 17.5 Experts on PRRT in brain NETs

Author	Year	Radiopeptide	Origin	ptsno	orr (%)	PFS (months)	OS (months)	CR, PR%	SD%	PD%
van Essen et al.	2006	^{177}Lu-DOTATATE	Meningioma	5	0	nr	nr	0	2 (40)	3 (60)
Bartolomei et al.	2009	^{90}Y-DOTATOC	Meningioma	29	0	13–61	nr	0	19 (65.5)	10 (34.5)
Kreissl et al.	2012	^{177}Lu-DOTATATE and E B R T	Meningioma	10	20	nr	18	1.1	8	0
Minutoli et al.	2014	^{111}In-Octreotide ^{90}Y-DOTATOC ^{177}Lu-DOTATATE	Meningioma	8	25	nr	nr	0.2	5	1
Gerster-Gilliéron et al.	2015	^{90}Y-DOTATOC	Meningioma	15	nr	24	49.7	0.0	13 (86.7)	2 (13.3)
Marincek et al.	2015	^{90}Y-DOTATOC ^{177}Lu-DOTATATE	Meningioma	34	nr	(8/11) 34 (3/11) 12	50 (8/11), 12 (3/11)	0	23	11
Limouris et al.	This study	^{111}In-Octreotide		1	nr	29	43	0	1 (100)	0

rv review study, *rs* retrospective study, *ps* prospective study, *orr* objective response rate, *dcr* disease control rate, *PFS* progression-free survival, *os* overall survival, *nr* non-referred, *E B R T* external beam radiotherapy, *pts no* patients' number

of 61 months for the low-grade group and 13 months for the high-grade cases. According to the results of Kreissel et al. [21], a combination of PRRT using ^{177}Lu-labeled somatostatin analogs with fractionated external-beam radiotherapy is feasible and well tolerated. The authors had an orr of 20% a SD in 80% and an OS of 18 months. Minutoli et al. [22] reported that ^{111}In-labeled somatostatin analogs might be used instead of β-emitting radionuclides in cases with a higher risk of renal toxicity. The authors report a PR for two patients, a SD for five, and a PD for one. According to Guedj and Graillon [13] with a worldwide incidence of 45,000 cases, meningioma is the most common non-glial primary intracranial tumor where many of them present with aggressive features and poor outcomes. In a study of Kaley et al. [16], the PFS of recurrent cases decreases below 30% at 6 months, whereas the median OS is 3 years for grade III.

Peptide receptor radionuclide therapy (PRRT) has gained popularity and an increasing role in positive for somatostatin receptor (SSTR) tumors, confirmed after scintigraphy with ^{111}In-Octreotide or preferably with Gallium-68 DOTATOC. Besides NETs that are the leading example of tumors with SSTR overexpression, meningiomas belong to non-neuroendocrine malignancies overexpressing SSTR too and might serve as a potent option in the meningioma-therapy armamentariums. According to Graillon T et al. [23], meningiomas overexpress SSTR2 in a 67% of cases, confirmed scintigraphically with 68Ga-DOTA-peptides that showed highly elevated uptake [24, 25].

Based on a plethora of studies [26–30], over a hundred meningioma patients were treated with PRRT. Although half of them were pre-treated with external radiotherapy, patients showed safe as well an excellent clinical tolerance. In their report Guedj and Graillon [13] notice that these studies are limited by mixing various types of meningiomas, different PRRT schedules, and follow-up imaging studies. In addition, the growth rate before treatment is not always documented, limiting the interpretation of the PFS, particularly in grade I and "low" grade II meningioma patients. Regarding oncologic endpoints, these promising studies have described disease stabilization for grades I and less aggressive grades II meningiomas in most cases, with a 6-month PFS ranging from 57 to 100%. By contrast, no clear benefit can be seen for more aggressive grade II and III meningiomas, so far. Van Essen et al. [26] report that in a small cohort of four patients treated with [^{177}Lu-DOTA0, Tyr3] octreotate, one of four patients with progressive meningioma had SD and three had PD. One patient with stable meningioma at the beginning of therapy had SD. The authors emphasized that PRRT can be effective only if uptake in tumor deposits on somatostatin receptor scintigraphy with ^{111}In-Octreotide (OctreoScan; Mallinckrodt) is equal to or higher than liver uptake. In a study by Backhaus et al. [27], in a case of a 54-year-old male patient with atypical (WHO grade II) meningioma who underwent one cycle of peptide receptor radionuclide therapy, the post-therapeutic whole-body ^{177}Lu-DOTATATE scintigraphy revealed thoracic uptake arising from previously undetected pulmonic meningioma metastases. The case highlights the importance of consideration of rare/untypical metastatic sides and the value of radiotracer whole-body imaging in identifying these. According to Sabet et al. [28] a patient with anaplastic meningioma and lung metastases resistant to conventional treatment underwent radiopeptide therapy with ^{177}Lu-DOTA-octreotate. The treatment resulted in significant improvement in patient's quality of life and inhibition of tumor progression. The authors noticed that this case may eventually help to establish the value of radiopeptide therapy in patients with this rare condition. In a study of Gerster-Gilliéron et al. [29] reporting on a cohort of 15 recurrent and progressive meningiomas treated with ^{90}Y-DOTATOC in two sessions of 7.4 GBq/m^2 each, a median PFS of 24 months and a mean OS of at least 49.7 months were achieved. Marincek et al. [30], in 34 patients with progressive meningiomas treated with ^{90}Y-DOTATOC and ^{177}Lu-DOTATOC, achieved a SD in 23 patients who showed a mean PFS ranging from 12 months (in 3/11 patients) to 34 months (in 8/11 patients) from the initializa-

tion of the PRRT treatment; the mean OS was 12 months in 3/11 patients and 50 months in 8/11 patients.

As regards dosimetry, according to Cremonesi et al. [31], two main options can be proposed in order to increase the absorbed dose while preserving at risk organs: either to treat with standard activity, i.e., 7.4 GBq/cycle but with variable number of cycles until the biological effective dose limits of the kidney and bone marrow are reached [32] or to treat with four fixed cycles with variable activity per cycle to reach the dose limits [33]. The authors underline the need for the PRRT schedule to be tailored to each situation taking into account the extent of disease, the growth rate, the grade, and SST expression and receptor affinity.

17.4 Conclusions

Prospective randomized trials, with a longer follow-up and a larger number of patients, are required to confirm the efficiency of PRRT in meningiomas. In recurrent WHO grade II tumor residuals, positive for somatostatin receptors, repeated, high doses of ^{111}In-Octreotide fallowing selective catheterization of the internal carotid artery showed an effective therapeutic outcome, i.e., a promising disease control. Given the locoregional modality character of the administration technique plus the extremely short range of ^{111}In Auger and internal conversion electron emission, no nephro-, liver, or myelo-toxicity has so far been observed. This approach in intra-arterially treating meningiomas and generally brain tumors, i.e., oligodendrogliomas positive for sstr2, represents an attractive strategy for the treatment of recurring or progressive symptomatic meningioma, which should be further evaluated.

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