Peptide receptor radionuclide therapy for aggressive pituitary tumors: a monocentric experience

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Short Title: PRRT for giant aggressive pituitary tumors

Key Words: pituitary tumors – aggressive pituitary adenomas – peptide receptor radionuclide therapy – PRRT

Word Count: 2340 words
Abstract

In aggressive pituitary tumours (PT) showing local invasion or growth/recurrence despite multimodal conventional treatment, temozolomide (TMZ) is considered a further therapeutic option, while little data is available on peptide receptor radionuclide therapy (PRRT). We analysed PRRT effectiveness, safety and long-term outcome in three patients with aggressive PT, also reviewing the current literature.

Patient #1 (F, giant prolactinoma) received 5 cycles (total dose 37 GBq) of $^{111}$In-DTPA-octreotide over 23 months, after unsuccessful surgery and long-term dopamine-agonist treatment. Patient #2 (M, giant prolactinoma) underwent 2 cycles (12.6 GBq) of $^{177}$Lu-DOTATOC after multiple surgeries, radiosurgery and TMZ. In Patient #3 (F, non-functioning PT), five cycles (29.8 GBq) of $^{177}$Lu-DOTATOC followed five surgeries, radiotherapy and TMZ. Eleven more cases of PRRT-treated aggressive PT emerged from literature.

Patient #1 showed tumor shrinkage and visual/neurological amelioration over eight-year follow-up, while the other PTs continued to grow causing blindness and neuro-cognitive disorders (patient #2) or monolateral amaurosis (patient #3). No adverse effects were reported.

Including the patients from literature, 4/13 presented tumor shrinkage and clinical/biochemical improvement after PRRT. Response did not correlate with patients’ gender or age, neither with used radionuclide/peptide, but PRRT failure was significantly associated with previous TMZ treatment. Overall, adverse effects occurred only in 2 patients.

PRRT was successful in 1/3 of patients with aggressive PT, and in 4/5 of those not previously treated with TMZ, representing a safe option after unsuccessful multimodal treatment. However, at present, considering the few data, PRRT should be considered only in an experimental setting.
Introduction

Pituitary tumours (PT) are generally benign and slow growing, but in some cases, they can present with the invasion of dura, bone or surrounding structures in the absence of malignant features. In these cases, they are defined as ‘invasive’ or ‘aggressive’ [1]. Moreover, the term “giant” adenoma is usually applied to those tumors exceeding 40 mm in maximum diameter [2].

In PT patients, multimodal treatment, including neurosurgery, drugs and radiotherapy, is generally effective in reducing tumor volume and controlling hormonal hypersecretion, if present [3]. Nevertheless, aggressive PT can be characterized by rapid growth, resistance and/or recurrence despite conventional treatments, making their management extremely challenging [4-7]. According to the latest guidelines, temozolomide (TMZ) can be an option after failure of standard therapies in patients with aggressive PT, while very little data are available on alternative approaches such as peptide receptor radionuclide therapy (PRRT) [7]. The expression of different subtypes of somatostatin receptors (SSTR, mainly 1, 2 and 5 subtype) on PT cells constitute the pathophysiological basis of their treatment with first generation (octreotide, lanreotide) and second generation (pasireotide) somatostatin analogs (SSa), and the rationale of the use of radiolabeled-SSa for diagnostic imaging and PRRT ($^{111}$In-pentetreotide, $^{177}$Lu-DOTA, $^{90}$Y-DOTA, $^{68}$Ga-DOTA) [8, 9].

Herein we report on the effectiveness, safety and long-term outcome of PRRT in three patients (2 F, 1 M) with aggressive giant PT treated by our group, also reviewing the little data available in literature about this therapeutic option.

Patients and methods

Between 2009 and 2015, three patients with giant aggressive PT have been treated with PRRT in our University Hospital, with an interval of 6-9 weeks between each administration, according to a well-established clinical protocol [10]. The study has been approved by the local ethical committee of Messina. The first patient (female, 58-yr old), with giant prolactin (PRL)-secreting pituitary adenoma (prolactinoma), received 5 cycles of $^{111}$In-DTPA-octreotide (total activity 37 GBq) from July 2009 to June 2011. Short-term effectiveness, assessed after the first 4 cycles of this treatment, has been previously reported [11]. Here, we show long-term efficacy and safety during the following 7 years. The second patient (male, 54-yr old),
affected by a giant prolactinoma too, underwent 2 cycles of PRRT with $^{177}$Lu-DOTATOC (total activity 12.6 GBq) in 2015. In the same year, a third case (woman, 53-yr old) with a giant non-functioning PT (NFPT) was treated with $^{177}$Lu-DOTATOC (5 cycles, total activity 29.8 GBq). Some data of these two patients were summarily presented in a previous study [6]. In all cases, tumor expression of somatostatin receptors type 2 (SSTR-2) was preliminarily demonstrated by SSTR-scintigraphic imaging with $^{111}$In-pentetreotide (Octreoscan) and the treatment options were discussed at our institution’s tumor board and approved by the local ethical committee. Each patient (or the daughter, for the first patient who was unconscious at entry) gave written informed consent for treatment. Laboratory investigations were performed before PRRT, to confirm that hematologic, renal and hepatic function were adequate for this treatment. Patients were admitted into a dedicated in-patient radioisotope treatment room. Radionuclides were obtained commercially ($^{111}$In-DTPA-octreotide was provided by Mallinckrodt Medical of Petten, The Netherlands; Perkin Elmer, USA, provided $^{117}$Lu-DOTATOC) and re-constituted in-house. PRRT was performed as previously described for gastro-entero-pancreatic (GEP)NETs [12]. The intention of treatment was to administer a total activity of 37 GBq of $^{111}$In-DTPA-octreotide, or of 30 GBq of $^{177}$Lu-DOTATOC. Intravenous infusion of aminoacids in 1 L of saline solution 0.9% in 4 hours was performed at any cycle of PRRT in order to reduce tubular peptide uptake and minimize renal damage. Intravenous dexamethasone (8mg/2ml for 2 days) was previously administered to reduce/contrast nausea or axial oedema. Planned treatment was based on 5 cycles separated by 8-10 weeks. Full blood count was monitored once every 2 weeks up to two months later after each PRRT cycle thus excluding any eventual myelosuppressive events. All patients underwent a brain magnetic resonance imaging (MRI) scan before PRRT and after 2, 6, 12, 18 and 24 months from PRRT, and every year thereafter.

In addition, we systematically searched for prospective or retrospective studies or case reports of patients affected by pituitary masses and treated with PRRT, cited in PubMed until 2018. The descriptors pituitary tumor, PRRT, peptide receptor radionuclide therapy were combined with the Boolean operators AND and OR, to build the search strategies. By this approach, we found twelve more cases presented in seven scientific papers.
Results

Patient #1

In this patient, macroprolactinoma was diagnosed when she was 42-yr old and trans-sphenoidal surgery was performed after few months of ineffective high-dose cabergoline treatment. At the age of 55-yr, serum PRL concentrations remarkably increased and tumor remnant dramatically grew, despite cabergoline administration. Radiotherapy was started and early interrupted due to a rapid worsening of clinical conditions. After the demonstration of SSTR-2 expression in the tumor by Octreoscan, a single i.m. injection of octreotide LAR 30 mg had been administered, but PT size and PRL levels continued to grow up. When referred to our University hospital, the patient showed critical neurological impairment and was not collaborative. Incomplete ptosis of left eyelid and left oculomotor nerve palsy with mydriasis were evident. PRRT was followed by progressive shrinkage of the pituitary mass, from 63 cc (before treatment) to 3.1 cc at last MRI scan (Figure 1). The biochemical evaluation showed a dramatic decrease of serum PRL values (350.000 U/L before PRRT vs 30.310 U/L at the last evaluation; n.v. 102-496 U/L). Treatment with cabergoline, administered at the dose of 0.5 mg daily before PRRT, was continued at the same dose until the last follow-up visit. Central hypothyroidism and hypogonadism were present before PRRT, and the residual pituitary function did not change over the following years. Computed perimetry, not assessable at admission, showed temporal anopsy in the right eye and nasal anopsy in the left one at last evaluation. Consciousness status and general clinical conditions improved progressively during the first months of treatment, and she regained full autonomy thereafter. PRRT was well tolerated in the absence of any treatment-related adverse events during follow-up.

Patient #2

In the second case, a giant prolactinoma was diagnosed in 2008. Treatment with cabergoline, 3 trans-sphenoidal approaches and hypo-fractionated radiosurgery were not able to control tumor progression. Panhypopituitarism had occurred after radiosurgery. In 2015, he began PRRT but a dramatic increase in tumor size (from 20.2 to 83.6 cc), impairment of visual acuity and worsening of clinical conditions occurred after the second cycle of treatment. For this reason, this therapy was withdrawn and the patient was treated with TMZ and cyclophosphamide, but without any benefit. At present, the patient is still alive but blind, and
he complains of gait difficulties and temporo-spatial disorientation. Moreover, his relatives report that the patient developed behaviour disturbances.

Patient #3

In the third case, a giant NFPT was diagnosed in 2006. The patient underwent 5 trans-sphenoidal approaches, fractionated radiotherapy and TMZ treatment before 2015, when she was referred to the multidisciplinary team of our University Hospital for PRRT. At admission, panhypopituitarism was present. Neuro-ophthalmological examination demonstrated near complete blindness in the right eye and hemianopsia in the left one. Pituitary MRI performed 6 and 12 months after PRRT showed a significant increase in tumor size (from 7.7 cc to 14.1 cc). Further visual field examinations demonstrated a progressive loss of vision in the left eye. PRRT-related adverse events were not reported during the following 3 years.

Review of literature

Until now, extensive data about effectiveness and safety of PRRT are reported in literature for other nine patients with pituitary carcinomas or aggressive adenomas [13-17]. Three patients affected by pituitary carcinoma were treated with $^{90}$Y-DOTATOC (2 cycles), $^{90}$Y-DOTATATE or $^{177}$Lu-DOTATATE (4 cycles), respectively [13, 16, 14]. The first one was affected by Nelson syndrome, the second by acromegaly and the third by NFPT. Tumor progression was stopped only in the NFPT patient, who was followed-up over 40 months [14]. Out of six patients with aggressive pituitary adenomas, two were treated with $^{177}$Lu-DOTATATE (1 and 2 cycles, respectively), one with $^{90}$Y-DOTATATE (4 cycles), one with $^{177}$Lu-DOTATOC (3 cycles), one with $^{177}$Lu-OCTREOTATE and one with $^{68}$Ga-DOTATATE [14, 17, 15, 16]. Out of them, two were affected by acromegaly, two by NFPTs, one by a prolactinoma and one by a silent ACTH-secreting tumor. Tumor shrinkage and biochemical or clinical improvement were reported in an acromegalic and in a NFPT patient, followed-up over 1 and 8 years post-PRRT, respectively [17, 15]. In addition, Lasolle et al. reported very few data about completed or ongoing $^{177}$Lu-DOTATOC treatment in other two patients with aggressive pituitary tumors previously treated with TMZ; nevertheless, tumor progression occurred after PRRT in the first case [18]. Finally, a patient with a pituitary metastasis of ileal primary neuroendocrine tumor was effectively treated with $^{90}$Y-DOTATOC and $^{177}$Lu-DOTATATE by Goglia et al. [19]. Data of all patients are shown in Table 1 and Figure 2.
Overall evaluation

On the basis of our experience and of data from literature, PRRT determined the growth arrest/shrinkage of tumor and clinical/biochemical improvement in four out of 13 patients with aggressive PT and in the patient with pituitary metastasis (Figure 2). Response to PRRT was related nor to gender or age of patients, neither to radionuclide or peptide used for treatment, but resistance was significantly associated with previous TMZ treatment ($\chi^2$: 9.24; p<0.002). Indeed, PRRT was unsuccessful in all the patients previously treated with TMZ, while it was effective in four out of the other five ones (Figure 2). Accordingly, mean overall survival, after PRRT, in the whole cohort of patients was 50.6 ± 13.0 months, while it was 15.0 ± 5.1 months in patients previously treated with TMZ versus 79.2 ± 15.0 months in those who did not undergo TMZ (Figure 3).

Overall, PRRT was generally well tolerated and transient anemia and leucopenia occurred only in a responder acromegalic patient [17]. Severe adverse events-imposed treatment interruption only in a patient with silent ACTH-secreting PT, for the early occurrence of facial pain [14].

Discussion

In this study, we reported about the effects of PRRT in 3 patients with aggressive PT and reviewed the cases described by other Authors. According to the latest guidelines, PRRT can be considered among the therapeutical options of aggressive PT patients when other approaches (surgical reintervention, medical therapies, fractionated or stereotactic radiotherapies, TMZ or other systemic chemotherapies) are not feasible or fail into controlling disease progression [7, 20]. Indeed, although “cold” SSa are sometimes ineffective because of post-receptor resistance, the expression of SSRTs (mainly SSTR-2 and SSTR-5) on PT, demonstrated by functional imaging with Octreoscan or $^{68}$Ga-DOTA Positron emitting tomography (PET), can allow to introduce beta minus-emitters radiopharmaceuticals conjugated to SSa for target therapy [14, 21]. PRRT has been introduced in the 1990s for metastatic or inoperable GEP-NETs and bronchial carcinoids. First, $^{111}$In-pentetreotide was preferred for its clinical efficacy, related to both the therapeutic Auger-emission and the internal conversion electrons after cellular internalization. Then, more efficient compounds have been introduced, like the high energy beta-emitter $^{90}$Y (longer range in soft tissues) and the
beta and gamma emitter $^{177}$Lu [22]. Moreover, the more recent chelated analog [DOTA$^{0}$,Tyr$^{3}$]-octreotate (DOTATATE) has improved the overall effects of PRRT, being characterized by high affinity with SSTR-2 [22-24]. However, in our study responsiveness to PRRT is not associated with the use of a specific radionuclide or peptide. PRRT-related organs radiation exposure is variable, being higher in kidneys and bone marrow. In this context, $^{111}$In-DTPA-octreotide demonstrated a shorter tissue penetration of Auger electrons, avoiding damage to surrounding tissues, and therefore could be more suitable for SNC neoplasms such as aggressive PT. In addition, $^{111}$In-DTPA-octreotide is generally well tolerated, with a lower risk of developing severe side effects [25, 26]. However, to date, patient #1 is the only published case of PT treated with $^{111}$In-DTPA-octreotide. In our case series, one out of three patients experienced a progressive significant PT shrinkage after PRRT with $^{111}$In-DTPA-octreotide, over an 8-year follow-up. In the other two patients, tumor progression was documented at the first MRI control. Our data are in accordance with those of literature [6-7, 14]. Overall, PRRT is effective in about one-third of patients affected by aggressive PT, irrespective if they are aggressive adenomas or carcinomas. This rate of responsiveness is not very different from other approaches such as TMZ or other chemotherapies, largely used in patients with these aggressive tumors [16, 27, 28]. On this regard, it is noteworthy that previous TMZ treatment is significantly associated with PRRT resistance. Indeed, PRRT determined tumor shrinkage or arrest of progression in four out of five patients not previously treated with TMZ. At present, the biological mechanism underlying this resistance is unknown and other studies will be useful to confirm this finding and to explain the molecular causes. Conversely, age or gender of patients, as well as radionuclide or peptide used for treatment, are not predictors of PRRT response. In addition, none of our patients experienced PRRT-related side effects, but transient myelosuppression or facial pain occurred in two cases described in the literature [17, 14].

Our study presents some criticisms. It is retrospective, the patients’ group is small and treatment protocols are inhomogeneous. In addition, dosimetric evaluation was performed in none of our patients. Only in the study by Maclean et al. an inhomogeneous uptake across the tumor was demonstrated in one out of three patients [14]. Nevertheless, there are few studies on PRRT in patients with aggressive PT and this approach could be a very useful option when all the other treatments failed to stop tumor progression and clinical impairment.
In conclusion, our study shows that PRRT can induce PT shrinkage and clinical and/or biochemical improvement in one-third of patients with aggressive PT overall, and in 4/5 of those not previously treated with TMZ. At the same time, PRRT is a safe therapeutic option when surgery and radiosurgery have failed to control tumor progression. Nevertheless, the overall efficacy cannot be established on the basis of the few available studies, and the currently available evidences are biased by the inhomogeneous treatment modalities. For this reason, at present, PRRT can be proposed for aggressive PT only in an experimental setting, after all conventional options have been performed.

Declaration of Interest: The Authors declare they have no conflict of interest that could prejudice the impartiality of the research reported.

Funding: This study is supported by the grant PRIN 2015 N. 2015ZHKFTA of the Department of Instruction, University and Research of the Italian Government.
References


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Figure Legends

Figure 1. Coronal T1-weighted magnetic resonance imaging (MRI) images showing tumor shrinkage in patient #1: before (A; in 2009), during (B; in 2010), one year after (C; in 2012) and 7 years after PRRT (D; in 2016; white arrow: tumor remnant).

Figure 2. Outcome of PRRT in PT patients according to different treatment strategies.

Figure 3. Overall survival in the entire cohort of patients treated with PRRT (A; data available for 12 cases), and in patients treated (B; n=7) or not (C; n=5) with temozolomide before PRRT.
Table 1. Clinical characteristics, treatment modalities and response to peptide receptor radionuclide therapy (PRRT) in the cases reported in literature, and data from our three cases.

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<th>Cycles</th>
<th>Total activity (GBq)</th>
<th>Volume response</th>
<th>Biochemical response</th>
<th>Clinical response</th>
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*: these three patients were affected by pituitary carcinomas. **: the pituitary mass was a metastasis from a primary unknown neuroendocrine tumor (NET), so it is reported at the bottom of the main list above.
†: data about the short-term effectiveness of PRRT treatment in this case have been reported in a previous study by our group (see ref. n. 11).
‡: data concerning these two patients have been summarily presented in the study by Priola et al (see ref. n. 6).
NA: Not Available.; TMZ = Temozolomide; RT = Radiotherapy; GBq = Giga Becquerel; PFS = Progression Free Survival (from PRRT).
Figure 1. Coronal T1-weighed magnetic resonance imaging (MRI) images showing tumor shrinkage in patient #1: before (A; in 2009), during (B; in 2010), one year after (C; in 2012) and 7 years after PRRT (D; in 2016; white arrow: tumor remnant).
Figure 2. Outcome of PRRT in PT patients according to different treatment strategies.

314x185mm (150 x 150 DPI)
Figure 3. Overall survival in the entire cohort of patients treated with PRRT (A; data available for 12 cases), and in patients treated (B; n=7) or not (C; n=5) with temozolomide before PRRT.