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# **Treatment of aggressive recurrent meningiomas: spinning towards peptide receptor radionuclide therapy**

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With a worldwide incidence of 45,000 cases, meningioma is the most common nonglial primary intracranial tumour. Although often associated with indolent behaviour, many patients present tumours with aggressive features and poor outcomes. After complete resection, the 5-year recurrence rate is estimated to 5%, 40% and 80% in grades I (benign), II (atypical) and III (anaplastic), respectively [1,2]. Very few treatment options are available at this step. The progression-free survival of aggressive recurrent meningiomas decreases below 30% at 6 months, while the median overall survival is of 3 years for patients with grade III [3]. It is therefore of main importance to develop new treatment options.

In recent years, Peptide Receptor Radionuclide Therapy (PRRT) with Somatostatin Analogues (SSAs) has gained an increasing role in patients with somatostatin receptor (SST)-expressing tumours, identified and selected in a theranostic view by the use of a companion diagnostic agent corresponding to the same SSA labelled with Indium-111 or preferably Gallium-68 for molecular imaging. In this line, the PRRT results obtained from the NETTER-1 trial in patients with advanced midgut neuroendocrine tumours (NETs) have given a new impetus towards the use of therapeutic nuclear medicine in oncology [4]. Although NETs are the prime example of positive SST tumours, meningiomas express comparable amounts of SST and, unlike NET, also express this profile in aggressive forms [5]. This could potentially open the therapeutic window for PRRT in meningiomas. From a biological standpoint, a recent study confirmed that meningiomas overexpress SST2, with a high expression pattern in 67% of cases, comparable to gastroenteropancreatic NET [5]. These findings agree with imaging studies with  $^{68}\text{Ga}$ -DOTA-SSAs that showed highly elevated tumour uptake [6,7].  $^{68}\text{Ga}$ -DOTA-SSAs PET/CT is currently recommended in meningioma patients by the international recommendation of the RANO group for differential diagnosis, grading, delineation, radiation planning, follow-up, evaluation of response and progression [1]. To

date, the application of PRRT for meningiomas has been mainly used on a compassionate basis. Approximately 120 meningioma patients treated with PRRT have been reported [8-15]. 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 was not always documented, limiting the interpretation of the PFS, particularly in grade I and “low” grade II meningioma patients. Although half of these patients were treated by external radiotherapy prior to PRRT, safety and clinical tolerance were excellent. Moreover, a study has even shown that concomitant treatment by PRRT and external radiotherapy was also well tolerated [14]. Regarding oncologic endpoints, these promising studies have described disease stabilization for grades I and less aggressive grades II meningioma in most cases, with a 6-month PFS ranging from 57 to 100%. By contrast, no clear benefit has been reported for more aggressive grade II and III meningiomas thus far. Beyond the expression of the molecular target, the overview of these studies underlines the need for the PRRT schedule to be tailored to each situation with the integration of several factors in the decision-making process, such as the extent of disease, growth rate, grade, molecular genetics and SST expression. Regarding dosimetry, the relationships between the absorbed dose and the response rate are not well established. To increase the absorbed dose while preserving at risk organs, two main options have been proposed [16]: the standard 7.4 GBq/cycle with a variation in the number of cycles until the Biological Effective Dose limits of kidney and bone marrow are reached [17, 18] or 4 fixed cycles with variable activity per cycle to reach the dose limits [19].

A prospective evaluation of PRRT in meningioma patients with an integration of a dosimetry-based approach, especially in at-risk organs, would be an important step towards a new spin on treating meningioma patients. Improvement roadmaps include the use of various therapeutic isotopes depending on situations, radiosensitizers, intelligence computations, and

potential meningioma-directed applications. Further development also may include the evaluation of early postoperative PPRT in grade II meningiomas as an alternative or in combination with classical radiotherapy.

**Compliance with Ethical Standards:**

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