

# Everolimus-induced somatostatin receptor overexpression in a rectal neuroendocrine tumor patient may promote somatostatin receptor-guided radionuclide therapy (peptide receptor radiotherapy) as an additional treatment option

### ABSTRACT

We present a case of Grade II, well-differentiated rectal neuroendocrine tumor in a 39-year-old patient. Following different sequential treatment modalities, the disease progressed both on metabolic (18F-fluorodeoxyglucose positron emission tomography-computed tomography [<sup>18</sup>F-FDG PET/CT]) and somatostatin receptor (SSTR)-imaging (<sup>68</sup>Ga-DOTA-Tyr3-octreotate [<sup>68</sup>Ga-DOTATATE] PET/CT), and the patient received three cycles of peptide receptor radiotherapy (PRRT). Two years later, upon new progression due to the appearance of metabolically active, <sup>68</sup>Ga-DOTATATE PET/CT-negative liver lesions, targeted treatment with everolimus was introduced. Further morphologic and metabolic progression occurred 4 months after everolimus initiation, however, this time liver lesions demonstrated increased SSTR-expression on <sup>68</sup>Ga-DOTATATE PET/CT. Thus, the patient became eligible for a second PRRT course.

**Keywords:** Everolimus, peptide receptor radiotherapy, somatostatin receptor, up-regulation

### INTRODUCTION

Neuroendocrine neoplasms (NENs) most commonly originate from the gastrointestinal tract and pancreas. Although they make up only about 2% of all gastroenteropancreatic (GEP) tumors, their incidence has increased over the past two decades.<sup>[1]</sup> Most GEP-NENs are well-differentiated neuroendocrine tumors (NETs). Peptide receptor radiotherapy (PRRT) is an established effective therapeutic option in progressive somatostatin receptor (SSTR)-positive NETs.<sup>[2]</sup> Since one of the main determinants for using PRRT is the presence of high SSTR-expression in tumors, a variety of drugs as well as radiation have been shown to upregulate SSTRs expression of NETs in an attempt to improve PRRT efficacy.<sup>[3]</sup> Through its inhibition of the mammalian target of rapamycin, everolimus not only regulates cell growth and proliferation in NETs but has also a direct radiosensitization and antiangiogenic effect.<sup>[3]</sup> However, a

SSTR-upregulation following everolimus has not yet been well established in NENs. Here, we present a case of a Grade II, well-differentiated rectal NET, in which following everolimus, we observed reappearance of high uptake on <sup>68</sup>Ga-DOTA-Tyr3-octreotate (<sup>68</sup>Ga-DOTATATE) positron

**MAGDALENA MILEVA, ZÉNA WIMANA, PATRICK FLAMEN, IOANNIS KARFIS**

Department of Nuclear Medicine, Jules Bordet Institute, Université Libre de Bruxelles, Brussels, Belgium


**Address for correspondence:** Dr. Magdalena Mileva, Department of Nuclear Medicine, Jules Bordet Institute - Université Libre de Bruxelles, Rue Héger-Bordet 1, B-1000, Brussels, Belgium.  
E-mail: magdalena.mileva@bordet.be

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emission tomography (PET)/computed tomography (CT) imaging of previously SSTR-negative liver metastases.

### CASE REPORT

A 39-year-old male patient was diagnosed with well-differentiated rectal NET (Grade II, Ki67: 10%) and synchronous hepatic, bone, and pulmonary metastases. After unsuccessful treatment with three cycles of cisplatin/irinotecan, the patient underwent pelvic external beam radiotherapy with subsequent surgical resection of the primary tumor and whole liver selective internal radiotherapy (SIRT) with  $^{90}\text{Y}$ -microspheres. Post-SIRT  $^{68}\text{Ga}$ -DOTATATE PET/CT exhibited disease progression, thus  $^{177}\text{Lu}$ -DOTATATE PRRT was initiated (the total administered activity of 22.5GBq, divided into three cycles), achieving near-complete response. The disease progressed 2 years after the last PRRT with the appearance of new, metabolically active liver lesions, successfully treated by three cycles of capecitabine/temozolomide (CAPTEM) chemotherapy achieving a complete metabolic response with no signs of disease on abdominal magnetic resonance imaging (MRI). Complete response was sustained for 4 months when new liver lesions appeared on the  $^{18}\text{F}$ -fluorodeoxyglucose ( $^{18}\text{F}$ -FDG) PET/CT [Figure 1a and c].  $^{68}\text{Ga}$ -DOTATATE PET/CT confirmed the extrahepatic progression of the disease, however, no SSTR over-expression was observed in the metabolically active new liver lesions [Figure 1b and d]. Contrast-enhanced abdominal MRI confirmed the morphological progression in the liver [Figure 1e] and due to the absence of metabolic

response after one cycle of reintroduced CAPTEM, targeted treatment with everolimus was initiated.

After 4 months under everolimus, further progression of the preexisting liver lesions was observed on  $^{18}\text{F}$ -FDG PET/CT [Figure 2a and c] as well on the abdominal MRI [Figure 2e], but interestingly, they presented with increased radiotracer uptake on the  $^{68}\text{Ga}$ -DOTATATE PET/CT [Figure 2b and d]. This phenomenon suggests that during treatment with everolimus an over-expression of SSTRs in the liver lesions has occurred, making the patient eligible for a second course of PRRT.

### DISCUSSION

Recently published *in vitro* data have demonstrated that certain drugs can up-regulate SSTRs in different NET cell lines through alterations in the epigenetic regulatory mechanisms.<sup>[4]</sup> Nölting *et al.*, showed the upregulation of SSTR-subtype 2 expression in pancreatic and pulmonary NET cell lines under everolimus alone or synergistically combined with a selective PI3K inhibitor.<sup>[5]</sup> In a clinical setting, everolimus has been shown to significantly decrease Ki67 in NETs on repeated biopsies after treatment initiation<sup>[6]</sup> (raising the hypothesis of a possible not only decrease of the rate of proliferation but also, promotion of the cellular differentiation). These results provide a plausible explanation for the disease evolution that we observed in our patient, which cannot solely be attributed to the morphological progression of the lesions. To the best of

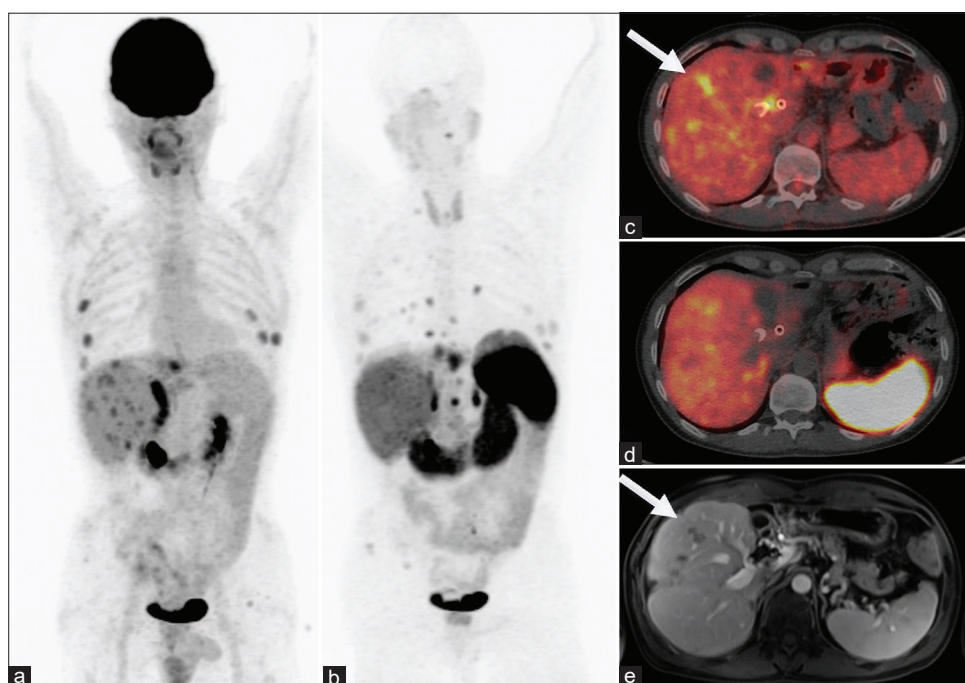
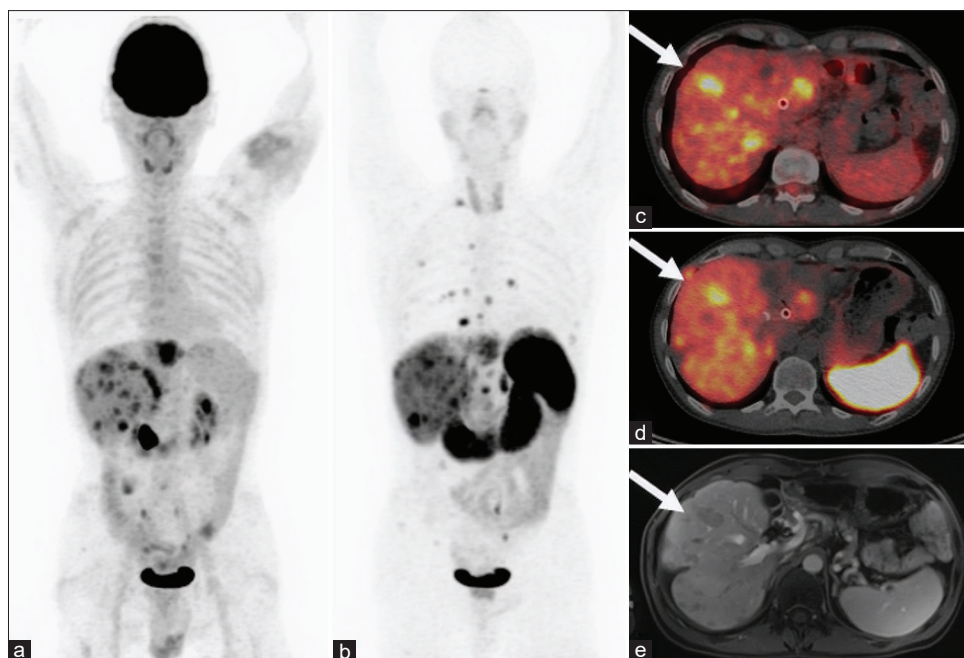


Figure 1: Metabolically active liver metastases of a rectal neuroendocrine tumor (a, c, e), showing no  $^{68}\text{Ga}$ -DOTA-Tyr3-octreotate uptake (b and d)



**Figure 2: Disease progression with increased number and size of metabolically active liver lesions after 4 months of treatment with everolimus (a, c, e); however, appearing of increased uptake on  $^{68}\text{Ga}$ -DOTA-Tyr3-octreotate positron emission tomography-computed tomography imaging (b and d)**

our knowledge, only two similar clinical cases have been published so far, where everolimus or CAPTEM chemotherapy resulted in markedly increased  $^{68}\text{Ga}$ -DOTATATE uptake in the tumor lesions.<sup>[7,8]</sup>

Several reports about targeted agents, immune checkpoint inhibitors, and combination of agents (e.g., RAF and MEK inhibitors) already show promises in re-differentiation of radioiodine-resistant thyroid cancers, where they could improve the efficacy of radioiodine therapy.<sup>[9]</sup> In NET patients, further *in vivo* research is necessary to investigate on SSTRs up-regulation under everolimus, with the purpose of improving and optimizing therapeutic management, especially PRRT.

#### Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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#### Conflicts of interest

There are no conflicts of interest.

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