Review Article

Somatostatin receptor imaging in nasopharyngeal cancer

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Abstract: Somatostatin is a neuropeptide better known for its role in inhibiting the secretion of growth hormone, insulin and glucagon. There are five subtypes of somatostatin receptors (SSTRs) with varying tissue distribution and function. They have been reported to be expressed in the brain, pituitary gland, pancreas, gastrointestinal tract, adrenal glands, immune cells and several human tumors. Recently there have been several reports of the presence of somatostatin receptor type 2 in nasopharyngeal cancer (NPC). Somatostatin receptor imaging sheds new insight into the biology of NPC and opens up exciting and novel diagnostic and therapeutic opportunities in the management of NPC.

Keywords: Nasopharyngeal cancer (NPC); somatostatin receptor; 177Lu-Dotatate

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Introduction

Somatostatin is a neuropeptide better known for its role in inhibiting the secretion of growth hormone, insulin and glucagon. Somatostatin analogues, octreotide, lanreotide and pasireotide are currently being used in the management of acromegaly and neuroendocrine tumors. Somatostatin exerts its function by binding to its receptors. There are five subtypes of somatostatin receptors (SSTRs, sstr1–5) with varying tissue distribution and function. They have been reported to be expressed in the brain, pituitary gland, pancreas, gastrointestinal tract, adrenal glands, immune cells and several human tumors (1-3).

Somatostatin receptors in NPC

Neuroendocrine tumors in particular express high levels of somatostatin receptor subtype 2. Radiolabeled octreotide scans (Octreoscan) identify sites of neuroendocrine tumor involvement and select for patients who may be suitable for peptide receptor radionuclide therapy (PRRT).

It is thus very exciting that somatostatin receptors have been reported in nasopharyngeal cancer (NPC). The first report of somatostatin receptors in NPC was by Loh in 2002. Using receptor autoradiography, Loh *et al.* found nine out of 12 NPC histology specimens expressed moderate to high levels of somatostatin receptor subtype 2. None of the non-tumoral nasopharyngeal tissue expressed somatostatin receptors (4).

The first reported imaging only happened 6 years later in 2008 by Bennink *et al.* It occurred rather serendipitously when a 60-year-old North African lady presented with headaches and diplopia. Initial computed tomography (CT) and magnetic resonance imaging (MRI) scans that were performed suggested differentials of a meningioma or a chordoma hence an Indium-111 octreotide scan was performed to help differentiate the two as meningiomas are known to express somatostatin receptors. Octreoscan showed uptake in the primary base of skull lesion and an avid cervical lymph node. Biopsies of the primary tumour

and the lymph node revealed an unsuspected diagnosis of nasopharyngeal carcinoma with a cervical lymph node metastasis (5).

Schartinger *et al.* subsequently reported in 2015, five patients with NPC that had undergone Gallium-68-DOTA-Octreotide positron emission tomography (PET) scan. They had found in an earlier study of head and neck squamous cancers that NPC showed much higher somatostatin receptor avidity compared to the other head and neck squamous cancers. Four out of five of their NPC patients showed high tracer uptake (SUV_{max}: 9.2–17.1) with one showing low uptake (SUV_{max}: 3.6) (6).

Khor *et al.* reported a comparative study between fluorodeoxyglucose (FDG)-PET and DOTA-NOC [DOTA0-(1NAI3) Octreotide] PET in four NPC patients. There was generally good concordance between the two tracers. There was however discordance in the case of recurrent NPC with the recurrent tumor showing greater FDG uptake but low DOTA-NOC uptake. The authors also noted that DOTA-NOC PET/CT may be useful for assessing intracranial involvement as there is less background physiological brain parenchymal uptake. It may also be better at differentiating reactive lymph nodes (7).

The presence of somatostatin receptors in NPC opens up exciting opportunities for the use of PRRT. These patients have few treatment options available and peptide receptor radiotherapy is an attractive option being able to selectively target tissues overexpressing the somatostatin receptor. Further clinical trials are needed to evaluate the effectiveness of this novel treatment which has become standard in gastroenteropancreatic neuroendocrine tumors.

Activation of SSTR activates several downstream pathways

Somatostatin receptors are G-protein coupled receptors. Signaling through somatostatin receptors involves binding of somatostatin or cortistatin to its various receptor subtypes (sstr1–5) in the context of auto-, para- or endocrine stimulation. Binding of these ligands to somatostatin receptors induces G-protein activation and downstream activation of various pathways. The activities of several key enzymes, including adenylyl cyclase, phosphotyrosine phosphatases (PTPases) and mitogen activated protein kinase (MAPK) are modulated by somatostatin receptor G-protein activation. In addition, calcium and potassium channels and the sodium-proton antiporter respond to somatostatin receptor activation and cause changes in the intracellular levels of calcium and potassium ions. In most cells, Ca^{2+} signaling is downregulated by somatostatin receptor activation owing to the inhibition of calcium channels and intracellular Ca^{2+} release or the activation of K^{+} channels, which results in membrane hyperpolarization. The resultant effect of these is a decrease in hormone secretion. The downstream activation of PTPases can result in inhibition of cell growth and increase apoptosis.

All known human somatostatin receptors can inhibit adenylyl cyclase and decrease cyclic adenosine monophosphate (cAMP) levels. This affects various downstream elements, in particular protein kinase A. This in turn acts as an activator of cAMP response-element-binding protein. Somatostatin receptor subtypes can be coupled to various phospholipase C (PLC) isoforms. In certain systems, somatostatin receptor activation increases the enzymatic activity of PLCβ2 and PLCβ3, and hence the intracellular levels of inositol trisphosphate (IP3) and Ca^{2+} (3,8).

From imaging to therapy

The concept of "theranostics" (combination of therapeutics and diagnostics) was coined by the US consultant John Funkhouser, to describe a material that allows the combined diagnosis, treatment and follow up of a disease. This approach allows the selection of a sub-population of patients most likely to benefit from a targeted therapy in accordance with their "molecular profile" at a given time-point, or, conversely, those patients for whom the risk of adverse effects is higher (9). This has been applied successfully for neuroendocrine tumors and has the potential in metastatic NPC, to select patients which may benefit from PRRT (*Figure 1*).

Treatment with radionuclide labeled peptides has shown promising results in neuroendocrine tumors. In the recently reported NETTER-1 trial, it was shown that PRRT with Lu-177 showed significant improvement in progression-free survival (PFS) and overall survival (OS). The estimated rate of PFS at month 20 was 65.2% [95% confidence interval (CI): 50.0–76.8] in the 177Lu-Dotatate group and 10.8% (95% CI: 3.5–23.0) in the control group. The median PFS had not yet been reached in the 177Lu-Dotatate group and was 8.4 months (95% CI: 5.8–9.1) in the control group (hazard ratio for disease progression or death with 177Lu-Dotatate *vs.* control group, 0.21; 95% CI: 0.13–0.33; P<0.001), which represented a 79% lower risk of disease progression or death in the 177Lu-Dotatate group than in the control group. Consistent treatment

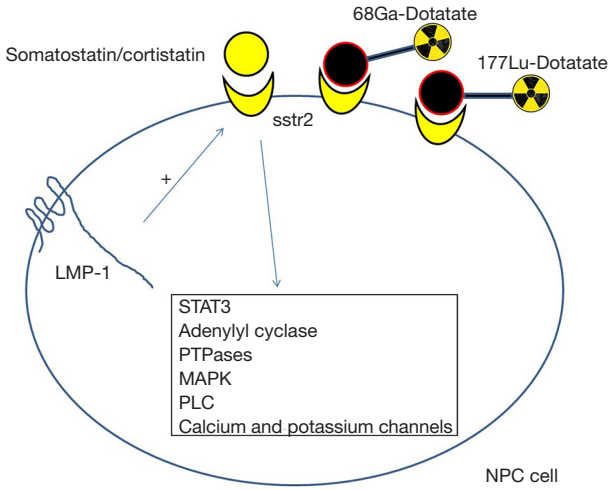

Figure 1 Model of EBV LMP-1 increasing sstr2 expression and its potential theranostic applications. EBV, Epstein-Barr virus; LMP-1, latent membrane protein 1; STAT, signal transducers and activators of transcription; PTPases, phosphotyrosine phosphatases; MAPK, mitogen activated protein kinase; PLC, phospholipase C; NPC, nasopharyngeal cancer.

benefits associated with 177Lu-Dotatate were observed irrespective of stratification factors and prognostic factors, which included levels of radiotracer uptake on somatostatin receptor scintigraphy, tumor grade, age, sex, and tumor marker levels. In a planned interim analysis of OS, a total of 14 deaths in the 177Lu-Dotatate group and 26 deaths in the control group were observed. This represented an estimated risk of death that was 60% lower in the 177Lu-Dotatate group than in the control group (hazard ratio for death with 177Lu-Dotatate group *vs.* control group, 0.40; P=0.004) (10). The possibility of PRRT in NPC is promising and requires further investigation.

In localized and recurrent NPC, somatostatin receptor imaging may assist in radiotherapy target delineation and planning. In particular, in regions around the brain where there is high physiological FDG uptake, somatostatin receptor imaging may help improve the delineation of at risk areas and also allow for a higher radiation boost to be given to these areas.

Conclusions

Somatostatin receptor imaging sheds new insight into the biology of NPC and opens up exciting and novel diagnostic and therapeutic opportunities in the management of NPC.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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