



UMC Utrecht

The complex endocrinology of Von Hippel Lindau

Rachel van Leeuwaarde, MD, PhD

Department of Endocrine Oncology, University Medical Center
Utrecht

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Von Hippel Lindau

Endocrine manifestations

Pancreatic neuroendocrine tumors

Pheochromocytomas/ paragangliomas

Adrenal insufficiency after bilateral adrenalectomy

Hemangioblastomas in pituitary region

Somatostatin (growth hormone-inhibiting hormone)

Anterior pituitary gland

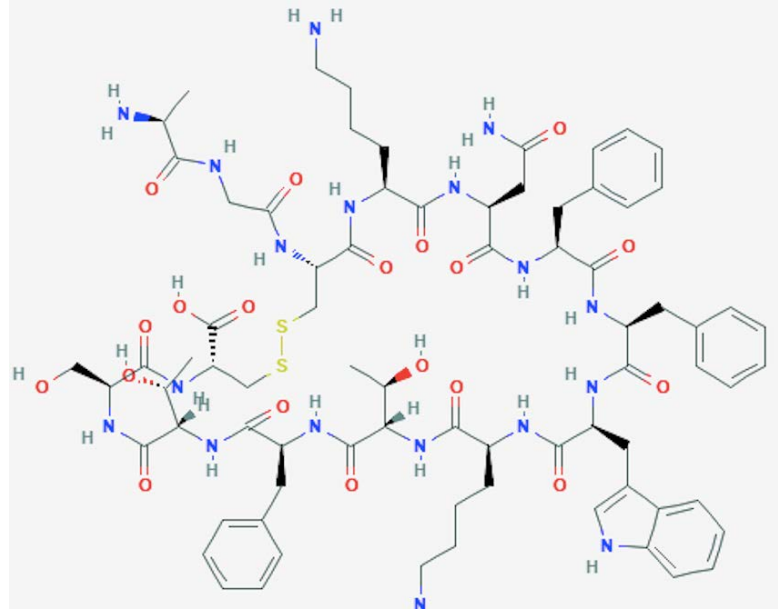
- Inhibition of TSH, GH, prolactine

Gastrointestinal

- Suppresses release of hormones

Carcinogenesis

- Tumorgrowth
- Tumorprogression
- Tumorspread



Patient x

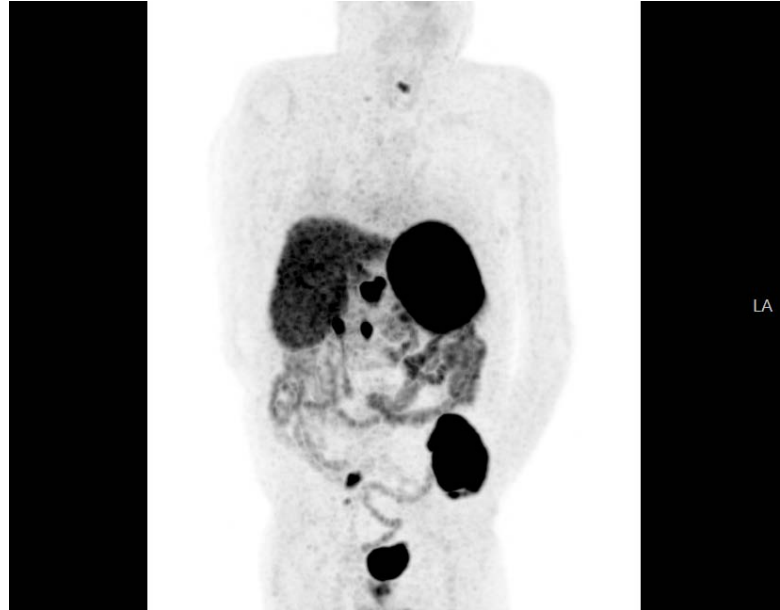
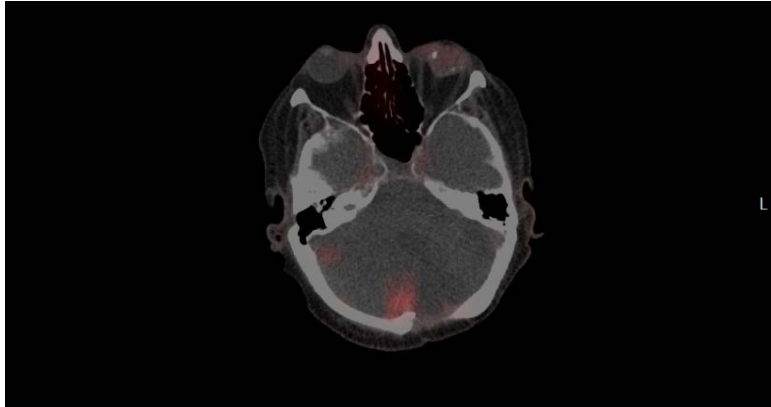
- Multiple surgeries in cerebellum/spinal cord
- Kidney transplantation
- Bilateral adrenalectomy
- WHO performance status 2
- Progressive pancreatic NET in head of pancreas (25 mm)



Q1 – What is the optimal treatment strategy?

1. Surgery
2. Start somatostatin analog
3. Active surveillance
4. Peptide Receptor Radionuclide Therapy (PRRT)

Case: ^{68}Ga -DOTATE imaging



Standardized Uptake Value (SUV)_{max} pNET 43 vs CNS 6

Previous case reports

- 1) ^{68}Ga -Dotanoc PET-CT: visceral and central nervous system uptake (SUV_{max} 18.6 vs 9.9)
- 2) ^{68}Ga -Dotatate PET-CT: high uptake pNET and low uptake in cerebellum and spinal medulla (SUV_{max} 19 vs. 4.1/3.8)

1) Sharma et al. Korean J of Radiology 2014
2) Oh et al. Nucl Med Mol Imaging 2012

Somatostatin expression in VHL related hemangioblastomas

- Strong SSTR receptor expression
- Octreotide induces stromal apoptosis by BAX – caspase-3 pathway unrelated to canonical VHL pathway
- 9 months of treatment with octreotide resulted in central photopenia and volume reduction of suprasellar hemangioblastoma

Tumor	SSTR1	SSTR2a	SSTR3	SSTR4	SSTR5
1	+	+++	++	+	++
2	+++	+++	–	+	+
3	+	++	–	+++	++
4	++	++	–	+/-	–
5	+++	++	–	+	++
6	+++	++	–	+	+/-
7	–	+	–	+	+/-
8	++	+	–	+/-	+
9	++	–	+/-	+/-	++
9 Total	8 Total	8 Total	2 Total	9 Total	8 Total

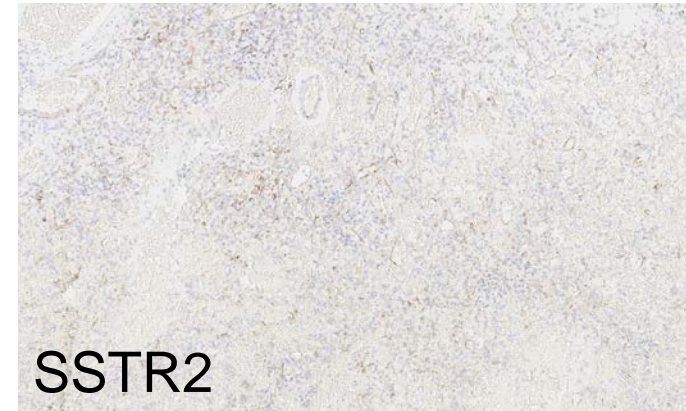
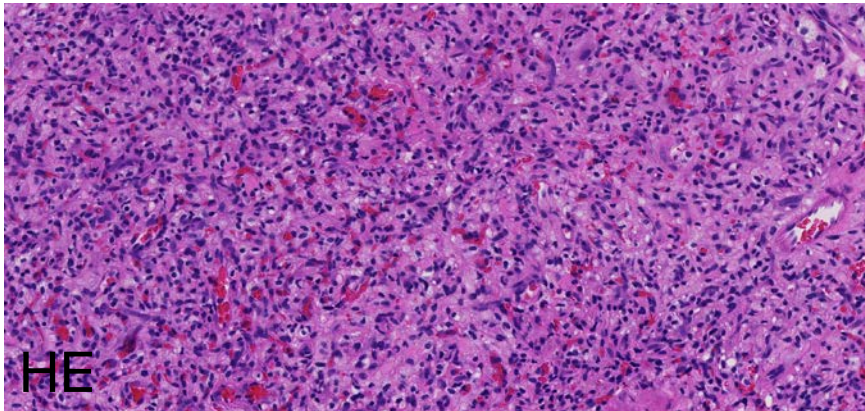
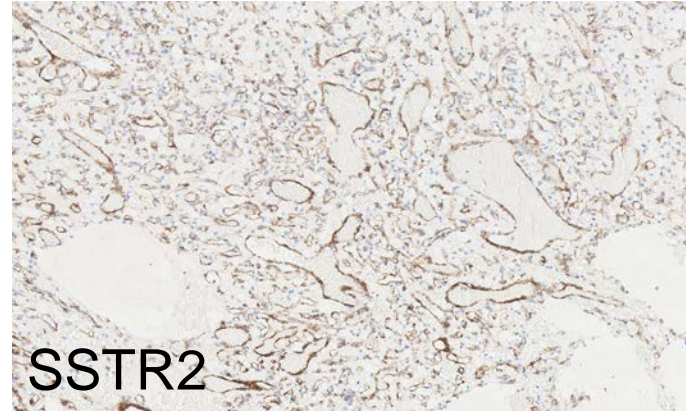
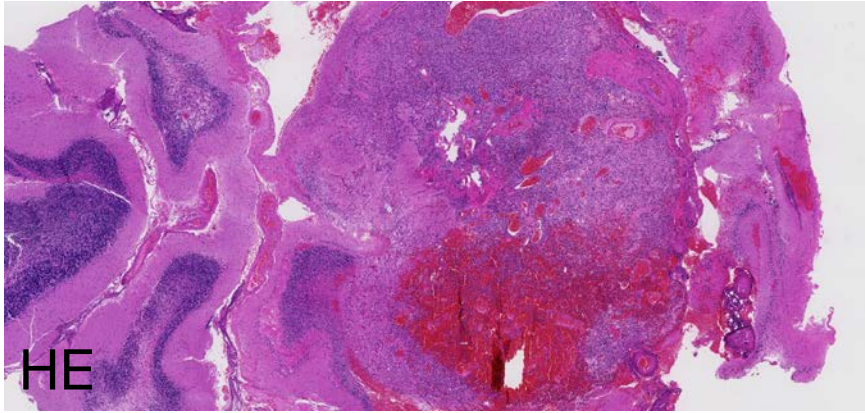
Somatostatin receptor expression

- **Gastro enteropancreatic neuroendocrine tumors**
- Breast tumors
- Renal cell carcinomas
- Lymphomas

SSTR expression in the brain

- Dense network of SSTR receptors in several areas
- Hippocampus and cerebral cortex high affinity
- Spinal cord and cerebellum intermediate affinity
- Meningeomas, astrocytomas, oligodendrogliomas have a high receptor expression

SSTR2 expression in VHL



N	SSTR2
7	-
1	+
4	
6	++
3	+++

Peritumoral vascular system

- Colon carcinomas, renal cell carcinomas, breast cancer
- Independent of receptor in the tumor
- Vasoconstriction → hypoxia and necrosis of tumor;
hypoxia induces angiogenesis

Somatostatin related issues in VHL

Patient x:

- Progressive pNET with relative contraindication for major surgery >> start somatostatin analog
- Hemangioblastomas with high SSTR2 expression, when unresectable or many comorbidities: indication for somatostatin analog?

Q2: when should ^{68}Ga PET CT imaging be performed?

1. Biannually to detect small lesions
2. In prevalent pNETs to detect metastases
3. To evaluate treatment options with Peptide Receptor Radionuclide Therapy (PRRT)
4. 2 & 3

Conclusion

- The role of SSTR receptors in VHL should be further elucidated
- There is a role for SSA and PRRT in patients with VHL
 - Pancreatic NETs
 - In selected hemangioblastomas?

Thank you for your attention!

