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LUND
UNIVERSITY

DOCTORAL DISSERTATION

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Abstract
Background and Aims: Radionuclide therapy is systemic, targeted radiotherapy. As such, we can apply the basic principles of radiobiology used in everyday practice in radiation oncology, as a means of tailoring the treatment to each patient and optimizing the balance between efficacy and toxicity. The most common type of radionuclide therapy used for the treatment of neuroendocrine tumors, is ^{177}Lu-DOTATATE. It has proven to be safe and effective, even without any tailoring. The aim of the work presented in this thesis is to systematically explore how we can further improve results for patients by tailoring the treatment.

Methods and Results: The thesis is based on two clinical trials – Iluminet and Gapetto – which were both designed to address different aspects of the overall aim. The Iluminet trial is a phase II trial in which patients, instead of receiving the standard four cycles of 7.4 GBq of ^{177}Lu-DOTATATE, are treated to the maximum number of cycles within the predefined limits for radiation dose to the kidneys. Safety and efficacy data are collected during treatment and follow-up. The Gapetto trial was a prospective observational study looking at the effect of somatostatin analog treatment on the uptake of ^{68}Ga-DOTATATE in PET/CT.

Papers I and II are based on the first 51 patients included in the Iluminet trial. Paper I presents data from an interim analysis of renal function, and also describes the effects that tailoring has on treatment planning. The mean number of treatment cycles the patients received was 5, but there were large interindividual variations. No serious renal toxicity was detected during the 24-month median follow-up. Paper II describes the consequences of simplifying the dosimetric protocol in order to make dosimetry more feasible in clinical practice. The results show that basing dosimetry on just one SPECT-image taken att 96h is as accurate as doing full hybrid dosimetry, which is the reference in the trial protocol.

Paper III describes the pituitary function in 68 evaluable patients during long-term follow-up in the Iluminet trial. A significant decrease in IGF1 was detected, which could be secondary to the radiation received by the pituitary gland during treatment with ^{177}Lu-DOTATATE, but other possible explanations are also discussed.

Paper IV is based on the Gapetto trial. The SUV values in ^{68}Ga-DOTATATE PET/CT were compared before and after initiating treatment with long-acting somatostatin analogs. The effect of the time from the last injection to the PET/CT was also analyzed. Results showed that the use of somatostatin analogs decreased the SUV in normal tissues, but not in tumor. The time since last injection did not affect the SUV-values.

Conclusions: Tailoring radionuclide treatment based on individual dosimetry is feasible and safe, and leads to considerable interindividual variations in the number of treament cycles received. No signs of serious renal or pituitary toxicity have been detected. Dosimetry can be substantially simplified without compromising accuracy. Treatment with long-acting somatostatin analogs improves the tumor-to-normal ratio in ^{68}Ga-DOTATATE PET/CT, and possibly also in the therapeutic setting, i.e. when using ^{177}Lu-DOTATATE to treat neuroendocrine tumors.

Key words ^{177}Lu-DOTATATE, ^{68}Ga-DOTATATE, individualized treatment, neuroendocrine tumors, dosimetry, renal function, pituitary function, somatostatin analogs, PRRT

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Dedicated to my past, present and future patients

Table of Contents

Thesis at a glance

Paper	Aims	Patients	Methods	Findings
I	To analyze the impact of dosimetry on treatment planning, and look for signs of possible renal toxicity.	Interim analysis of the first 51 patients included in the Iluminet trial.	Prospective phase II trial. Descriptive statistics of mean annual change of GFR, number of cycles/patient, renal BED/cycle.	Large inter- and intrapatient variability in BED/cycle, and number of cycles. The majority of patients received > 4 cycles. No signs of significant renal toxicity.
II	To investigate how much the dosimetric protocol can be simplified without compromising accuracy in the dosimetric estimates.	The 22 patients whom, at the time of the interim analysis of the Iluminet trial, had completed treatment as planned.	Prospective phase II trial. Bland-Altman plots comparing the difference between the alternative methods and the protocol dosimetry vs the mean of the two.	SPECT-based dosimetry with 1 imaging timepoint at 96h yields similar results as full dosimetry. SPECT-based is better than planar which is better than no dosimetry (i.e. standard treatment).
III	To analyze pituitary function after dosimetry-based PRRT and long-term follow-up.	The 68 patients, of a total of 103 included in the Iluminet trial, who were evaluable for changes in pituitary function.	Prospective phase II trial. Linear mixed model to analyze the significance of the changes over time. Boxplots to illustrate the changes graphically.	No signs of serious endocrine toxicity was seen. A significant reduction in IGF1 was seen, although it may be explained by other causes than radiation-induced toxicity.
IV	To analyze the effect of treatment with long-acting somatostatin analogs on the uptake of ^{68}Ga-DOTATATE on PET-images.	A total of 262 patients with 495 PET studies contributed with data to the different subgroup analyses.	Prospective observational study. Changes in SUVmax in tumor and normal tissue were compared 1) before and after intitation of SSA, and 2) by time interval from last injection	SSA-treatment did not affect tracer uptake in tumor tissue, but decreased uptake in normal tissue. The interval from last injection did not affect tracer uptake.

Populärvetenskaplig sammanfattning (lay summary in Swedish)

Radionuklidterapi – användandet av radioaktiva, målsökande läkemedel – är än så länge ett litet område inom cancerbehandling, men ett område under snabb tillväxt. Genom kopplingen av en radioaktiv isotop till en tumörsökande molekyl uppnås en selektiv, intern strålbehandling av tumörcellerna, dvs normal vävnad besparas till stor del från de toxiska effekterna av strålningen då läkemedlet framför allt binder sig till tumörceller. Vid ”vanlig” strålbehandling är det en maskin utanför patienten som skickar strålningen in i patients kropp från olika riktningar för att uppnå en hög stråldos i tumören, samtidigt som bestrålningen av de friska organ som ligger i vägen för strålarnas bana genom kroppen minimeras. Vid radionuklidterapi söker läkemedlet själv upp tumörcellerna oavsett var i kroppen de sitter och utan att vi måste peka det i rätt riktning. Det är en behandling som överlag är förenad med betydligt färre biverkningar än klassisk kemoterapi eller strålbehandling, och därtill ofta effektiv i situationer där andra behandlingsmöjligheter uttömts. Denna kombination av egenskaper är så klart tilltalande för både patienten och den behandlande läkaren.

Inom modern cancerbehandling är den nu rådande paradigmen att individualisera behandlingen så att varje patient får maximal chans till god behandlingseffekt med så låg risk som möjligt för biverkningar. Inom kemoterapi och immunoterapi görs det vanligtvis genom att identifiera olika molekylära egenskaper hos en patients tumör som gör den extra mottaglig för den tumörhämmande effekten hos ett specifikt cancerläkemedel.

Inom radionuklidterapi finns ytterligare ett sätt att individualisera behandlingen som bygger på att man kan ta bilder av strålningen som läkemedlet avger. I dessa bilder kan vi se hur läkemedlet fördelat sig i kroppen vid en viss tidpunkt. Utifrån bilderna kan vi beräkna vilken stråldos som uppnås i tumören och i normala organ. Med denna kunskap kan man sedan justera behandlingen på ett individualiserat vis. Detta angreppssätt är fortfarande i sin linda, och behöver förfinas ytterligare för att kunna inkorporeras i klinisk rutin. Denna avhandling beskriver några pusselbitar som vi bidragit med för att närma oss målet med en individanpassad behandling för alla patienter som får radionuklidterapi.

Bridging the Gaps

"Doctors are men who prescribe medicines of which they know little,
to cure diseases of which they know less,
in human beings of whom they know nothing"

Voltaire (1694-1778)

The research process, seen from a birds-eye view, is the process of constantly striving to bridge the gaps of knowledge and understanding. The gaps lie between those islands of knowledge that have emerged as the seas of ignorance have retroceded. What grows on each island is serendipitous – when the right combination of people, circumstances and possibilities meet, something begins to grow – much like the seeds spread by the wind find the right soil. If the climate changes, what once grew may wither and the sea begin to rise again.

The islands of knowledge of radiation began to rise in 1895 with the discovery of x-rays by Wilhelm Conrad Roentgen. In the years between the two world wars, the use of radionuclides in medicine began to develop, for both diagnostic and therapeutic use. In the early 20th century radioactivity was considered a panacea for healthy and ill alike, with spas of radioactive springs, inhalation of radioactive air and a daily dose of radioactive water being advertised in the press. With this came an increase in the incidence of thyroid cancer and leukemia, which in turn was the basis for the development of the fields of radiation protection and radiobiology, and further down the road to the use radiation to treat cancer.

Radionuclide therapy – the use of radioactive drugs to treat disease – is nothing new. What makes it a hot topic today is the simultaneous surge in molecular pathology, imaging technology and personalized medicine. We can now choose our tumor target, design a radioactive missile and image the destruction it wreaks with great detail. This has brought radionuclide therapy to a point where new targets, indications and radioactive drugs are continuously identified.

So the islands may be growing, but the gaps are still wide. We need to widen the bridges between radiobiology, molecular pathology, internal dosimetry, imaging technology and oncology to get the most out of radionuclide therapy. In the following pages, I will map the islands for you and describe our own humble contributions to bridging some of the gaps.

List of papers

This thesis is based on the following original publications, referred to in the text by their Roman numerals:

I. **Sundlöv A,** Sjögreen-Gleisner K, Svensson J, Ljungberg M, Olsson T, Bernhardt P, Tennvall J.
Individualised ^{177}Lu-DOTATATE treatment of neuroendocrine tumours based on kidney dosimetry.
Eur J Nucl Med Mol Imaging. 2017;44:1480-9.

II. **Sundlöv A**, Gustafsson J, Brolin G, Mortensen N, Hermann R, Bernhardt P, Svensson J, Ljungberg M, Tennvall J, Sjögreen-Gleisner K
Feasibility of simplifying renal dosimetry in 177Lu peptide receptor radionuclide therapy.
Eur J Nucl Med Mol Imaging Physics. 2018; 5:12.

III. **Sundlöv A**, Sjögreen-Gleisner K, Tennvall J, Dahl L, Svensson J, Åkesson A, Bernhardt P, Lindgren O
Pituitary function after high-dose 177Lu-DOTATATE therapy and long-term follow-up.
Manuscript

IV. Gålne A, Almquist H, Almquist M, Hindorf C, Ohlsson T, Nordenström E, **Sundlöv A***, Trägårdh E*
A prospective observational study to evaluate the effects of long-acting somatostatin analogs on ^{68}Ga-DOTATATE uptake in patients with neuroendocrine tumors. (* Shared senior authorship)
J Nucl Med. Published on-line on April 18, 2019 as doi:10.2967/jnumed.119.226332

Note: Publication II was awarded the "EJNMMI Physics Best Article Award, 2019"

Related papers

Hagmarker, L., Svensson, J., Ryden, T., van Essen, M., **Sundlöv, A**., Sjögreen Gleisner, K., Gjertsson, P. & Bernhardt, P.
Bone marrow absorbed doses and correlations with hematological response during 177Lu-DOTATATE treatments are influenced by image-based dosimetry method and presence of skeletal metastases
Journal of Nuclear Medicine, Mar 22, 2019 (e-pub ahead of print)

Sjögreen Gleisner, K., Brolin, G., **Sundlöv, A**., Mjekiqi, E., Östlund, K., Tennvall, J., & Larsson, E.
Long-Term Retention of 177Lu/177mLu-DOTATATE in Patients Investigated by γ-Spectrometry and γ-Camera Imaging
J Nucl Med July 1, 2015 vol. 56 no. 7 976-984

Roth, D., Gustafsson, J., **Sundlöv, A**. & Sjögreen Gleisner, K.
A method for tumor dosimetry based on hybrid planar-SPECT/CT images and semiautomatic segmentation
Medical Physics. 45, 11, p. 5004-5018, Nov 2018

Milanetto, A. C., Nordenström, E., **Sundlöv**, **A**. & Almquist, M.
Health-Related Quality of Life After Surgery for Small Intestinal Neuroendocrine Tumours
World Journal of Surgery. 42, 10, p. 3231-3239, 2018

Gustafsson, J., **Sundlöv, A**. & Sjögreen Gleisner, K.,
SPECT image segmentation for estimation of tumour volume and activity concentration in 177Lu-DOTATATE radionuclide therapy
EJNMMI Research. 7, 1, 18. Dec 1, 2017

Abbreviations and Glossary

^{68}Ga	a radioactive isotope of Gallium, a post-transition metal with atomic number 31. It was discovered by a French chemist, who named it after the Latin name for his country – Gallia.
^{166}Ho	a radioactive isotope of Holmium, a rare-earth metal with atomic number 67, discovered by a Swedish chemist and named after the city of Stockholm (Holmia in Latin)
^{177}Lu	a radioactive isotope of Lutetium, also a rare-earth metal with atomic number 71, named after the city of Paris (Lutetia in Latin). Who discovered lutetium is disputed.
^{90}Y	a radioactive isotope of Yttrium, a transition metal with atomic number 39. It was discovered by a Swedish chemist from the town of Ytterby, in the archipelago of Stockholm, from where it also got its name
ACTH	adrenocorticotropic hormone
AD	absorbed dose; the energy deposited in a tissue or organ per unit mass
Angiogenesis	is the process by which new blood vessels are formed, fundamental for the continuous growth of tumors
Auger e^-	are electrons emitted during radioactive decay, but come from the electron shells surrounding the atom's nucleus. Auger electrons have a very short range in tissue (μm).
BED	Biologically effective dose; a means to compare different absorbed doses, required to achieve the same biological effect, when delivered with different fractionation and dose rate.
DCR	Disease control rate = objective response + stable disease in radiological evaluations of therapy response
DNES	the diffuse neuroendocrine system; the origin of NENs

DOTA-X	DOTA is a linker molecule (chelator) that permits radioisotope labeling of SSAs for theranostic use. Depending on the SSA the "X" will be either TOC (OCtreotide with Tyrosine), TATE (octreoTATE) or NOC (octreotide with NaI)
EGFR	Epidermal growth factor receptor
ENETS	European Neuroendocrine Tumour Society
EQD_2	The equivalent dose if given in 2-Gy fractions
^{18}F-FDG	Fluorodeoxyglucose labeled with a radioisotope of fluor (^{18}F) used for PET-imaging
FSH	Follicle-stimulating hormone
fT4	Free thyroxine
G1, G2, G3	Grading system for neuroendocrine tumors based on proliferation rate of the tumor cells
GEP-NET	Gastroentero-pancreatic neuroendocrine tumor
GFR	Glomerular filtration rate; a commonly used measure of renal function. Can be either measured (golden standard) or estimated from plasma levels of creatinine and/or cystatine C
GH	Growth hormone
GI-NEN	Gastrointestinal neuroendocrine neoplasm; i.e. GEP-NEN minus pancreatic NEN
IGF1	Insulin-like growth factor 1
LH	Luteinizing hormone
LQ model	The linear-quadratic model; a radiobiological theory that describes the effects of different ADs/cycle and fractionation schemes on the total BED, for a tissue with a given α/β and repair half-life
MDRD	Abbreviation of Modification of Diet in Renal Disease; a formula commonly used to estimate the GFR based on plasma creatinine, age, sex and race.
MMR	Mismatch repair; an intracellular mechanism to repair mismatch defects in the DNA. Deficiency of MMR confers genetic instability to the cell/tumor, especially in the microsatellite regions of the DNA.
MSI	Microsatellite instability – a predisposition to mutation caused by a deficiency in the mismatch repair system.

NEC	Neuroendocrine carcinoma; poorly differentiated G3 NEN
NEN	Neuroendocrine neoplasm = NET + NEC
NET	Neuroendocrine tumor, i.e. well differentiated NEN G1-G3
NTCP	Normal tissue complication probability
OAR	Organ at risk
PET	Positron emission tomography, a diagnostic imaging method
PFS	Progression-free survival; a term used to evaluate the efficacy of oncological therapies by measuring the time elapsed from the start of treatment to objective and significant tumor growth
pNET	Pancreatic NET
PRRT	Peptide receptor radionuclide therapy
RNT	Radionuclide therapy
ROI	Region-of-interest
SHBG	Steroid-hormone binding globulin
SI-NET	Small intestinal NET
SPECT	Single-photon emission computed tomography; a type of imaging using gamma-emitting radiopharmaceuticals
SSA	Somatostatin analog
SSTR	Somatostatin receptor
SUV	Standardized uptake value; a term used in nuclear medicine imaging to describe the degree of uptake of a radiotracer in a ROI. The activity concentration in the ROI is normalized to the the injected activity and total body weight
TSH	Thyroid stimulating hormone
VEGF	Vascular endothelial growth factor
VOI	Volume-of-interest

Background

"Now, here, you see, it takes all the running you can do, to keep in the same place. If you want to get somewhere else, you must run at least twice as fast as that!"

Lewis Carroll, Alice Through the Looking Glass

Neuroendocrine tumors

History, histology and embryology

Neuroendocrine tumors (NETs) are malignancies that stem from the diffuse neuroendocrine system (DNES) – our internal communication system that pervades all the epithelialized organs of the body connecting the nervous system with the endocrine cells and the gastrointestinal tract – or from endocrine organs such as the thyroid, pancreas or adrenal glands. Although they are, just like other tumors, in part defined by their organ of origin, they have more in common with other NETs than with other malignant tumors of the same organ. Treating patients with NETs means dealing with a spectrum of malignancy ranging from the most indolent to the most aggressive cancers known to man, and incorporating surgery, oncology, endocrinology and nuclear medicine during the disease continuum.

The origins of the story of the neuroendocrine tumors are usually ascribed to the German pathologist Siegfried Oberndorfer who coined the term "karzinoide tumoren" (carcinoid tumors) in 1907 in his publication "Karzinoide Tumoren des Dünndarms". Several decades earlier, however, Paul Langerhans had identified the pancreatic islets, although without understanding their function. In 1897, Nikolai Kulchitsky published his observations that there were "clear cells" interspersed in the intestinal epithelium, which seemed to have a different polarity than the rest. He

suggested that their secretory product was not emptied into the intestinal lumen, but rather to the basal layers of the mucosa. (1, 2) These cells had been characterized by their tendency to stain with silver and chrome, thereby being named argentaffin and enterochromaffin (EC) cells, but their function was still unknown.

In the following decades, further pieces of the puzzle were laid down by the above-mentioned Oberndorfer, who identified the seemingly benign carcinoid tumors of the small bowel, and by Gosset and Masson who found that these carcinoids were made up of EC-cells (1914). Friedrich Feyrter put the puzzle together in 1938 by his proposal of the existence of a "diffuse endocrine system" after finding that the EC-cells were present throughout the gut and pancreas, that this system was the origin of the carcinoid tumors and that these tumors were actually malignant. Later in his career he also studied the interactions between the nervous system and the diffuse endocrine system leading to the concept of the still valid "**diffuse neuroendocrine system**" (DNES)(3).

Further advances were made possible with the advent of immunohistochemistry and electron microscopy. The Swedish pathologist Lars Grimelius developed a new silver staining method which enabled the visualization of the secretory granules in the EC-cells by electron microscopy (4, 5). It was soon clear that these endocrine cells were present in all mucosa-lined organs although with differences in appearance and secretory activity depending on the organ. These observations lead to the concepts of carcinoid tumors of the foregut, midgut and hindgut based on the embryological origins (6). Ingenious embryological experiments carried out during the latter half of the past century studied whether the DNES is of neural crest or endodermal origin, and it seems most believe in the latter (1).

Being tumors of the neuro*endocrine* system, NETs often secrete one or more hormones. The most typical of the hormonal syndromes in NET disease, **the carcinoid syndrome**, was actually first described in 1890 (Ransom, The Lancet) before the "discovery" of this

Nicolai Kulchitsky (1856-1925)

Kulchitsky was a prominent professor of histology at Kharkov University during the reign of the last Russian Czar, Nicolai II. A few years after publishing his findings on the "clear cells" of the intestinal tract, which were later to be named "Kulchitsky cells", he resigned from the University to embark on a career within the Russian administration. Only months before the Bolshevik revolution, he was named Minister of Education for all of Russia, by the Czar himself.

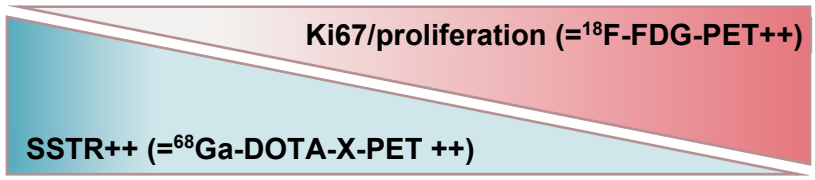
After years of hardship under Bolshevik rule, the Kulchitsky family managed to flee to England on a British battleship, together with the remnants of the imperial family. Once there, Kulchitsky achieved a humble position as research assistant at the University College of London. Things seemed to be looking better again, until, on his 69th birthday, he fell to his death in an elevator shaft.

tumor entity by Oberndorfer. It would take another half-century before the relationship between serotonin and the carcinoid syndrome was confirmed by the Swedish physicians Pernow and Waldenström in 1957 (7). At about the same time another Swedish group had described the **carcinoid heart disease**, i.e fibrosis of the right heart valves leading to severe stenosis, regurgitation and congestive heart failure (8). The hormonal syndromes related to NET are secondary to the type of hormone the particular tumor in question secretes. The carcinoid syndrome is typical for the serotonin-secreting tumors of the small intestine, while pancreatic NET may secrete insulin, glucagon, or gastrin among others. Bronchial NETs are less frequently hormonally active but may, for example, secrete ACTH thereby giving rise to an ectopic Cushing syndrome by stimulating the production of cortisol by the adrenal glands.

When Oberndorfer first presented his findings on carcinoid tumors to the German Pathology Society he was still of the opinion that it was a benign tumor. With hindsight, this is understandable although incorrect. NET of the small intestine are often very slow-growing, and their invasive nature not always evident until they metastasize. With the current WHO classification system (9) NET of the gastrointestinal tract (including pancreas) are divided into three main groups, based on their **proliferative activity – grade 1-3**. The grade 1 (G1) tumors are the most indolent; patients can live for 10 years or more despite metastatic disease. Among the grade 3 (G3) tumors, we find the most aggressive cancers imaginable, where metastatic disease is usually synonymous with death within a year. The grade 2 (G2) tumors are somewhere in between on the prognostic scale.

To define the proliferation rate, immunohistochemical staining is performed on tumor tissue to quantify the protein **Ki67**, which is a marker of cell proliferation. If <3% of the tumor cells are positive for Ki67 the tumor is classified as G1. If the Ki67-index is >20% it is a G3 tumor. The G2 tumors have a Ki67-index between 3 and 20%. Among the G3 tumors there are two subcategories: NET (NE *tumor*) G3 for the well-differentiated tumors, and NEC (NE *carcinoma*) G3 for the poorly differentiated ones. The correct overall term for both NET and NEC is NEN – neuroendocrine neoplasia – a term that is, however, having some difficulties in pervading the jargon of the NET specialists around the world.

The hormonal secretion and the proliferative activity of NENs are often inversely related, i.e. the G3 tumors are rarely hormonally active, while most of the G1 tumors are. This is also true for the relationship between the somatostatin receptor (SSTR) expression and tumor grade. It is as if receptor expression and hormonal production are lost in dedifferentiation. These varying tumor characteristics affect diagnosis, prognosis and therapy of the patients with NENs (see Fig 1).



	G1	G2	G3
SSA	+++	++	(+)
Lutetium	+++	+++	(+)
Afinitor/Sutent	+++	+++	+
Temodal-Xeloda	++	+++	++
Karbo-Etoposid	-	-	+++

Fig 1. There is an inverse relationship between somatostatin receptor expression (as evidenced by SSTR-PET imaging) and the tumors´proliferation rate (as evidenced by ^{18}F-FDG-PET) for NENs. This affects the choice of imaging modality, the prognosis and the treatment as discussed in the text. The number of "+" indicates the relative usefulness of each treatment according to tumor grade, with a "-" indicating lack of usefulness.

Theranostics in NET

Theranostics is a term created by the fusion of the words "therapy" and "diagnostics". It denominates a relatively new area of medicine, closely related to nuclear medicine, where the same cellular target molecule is used to produce both a diagnostic and a therapeutic drug. In the realm of NETs the obvious target is the SSTR.

The somatostatin receptor is a transmembrane receptor ubiquitously expressed in tissues and organs throughout the body, with an especially high receptor density in NETs. There are five subtypes of the SSTR with receptor type and density varying in different types of tissue. Its natural ligand, somatostatin, is an endogenous hormone secreted by the hypothalamus which inhibits hormonal secretion from neuroendocrine cells in endocrine organs and the gastrointestinal tract (10). A synthetic analog of somatostatin (SSA), octreotide, has been in clinical use since the 1980s for the treatment of acromegaly (hypersecretion of growth hormone) and NET.

It is estimated that at least 80% of well-differentiated NETs express the SSTR, with SSTR2 being the most common receptor subtype followed by SSTR1 and 5 (10). Both octreotide and the newer analog lanreotide have a high binding affinity to SSTR2 and 5, and have proven their efficacy in reducing hormonal secretion and tumor growth of NETs (11-14). Further biochemical modification of octreotide has made it possible to bind radioactive isotopes to the SSA (Fig 2), opening the door to the theranostic approach. By choosing a radioisotope with gamma- or positron

emission, we can image SSTR-expression and tumor distribution using SPECT or PET, respectively. If instead we choose a beta-emitting isotope such as ^{177}Lu or ^{90}Y we have the basis for targeted internal radiotherapy, also known as peptide receptor radionuclide therapy (PRRT).

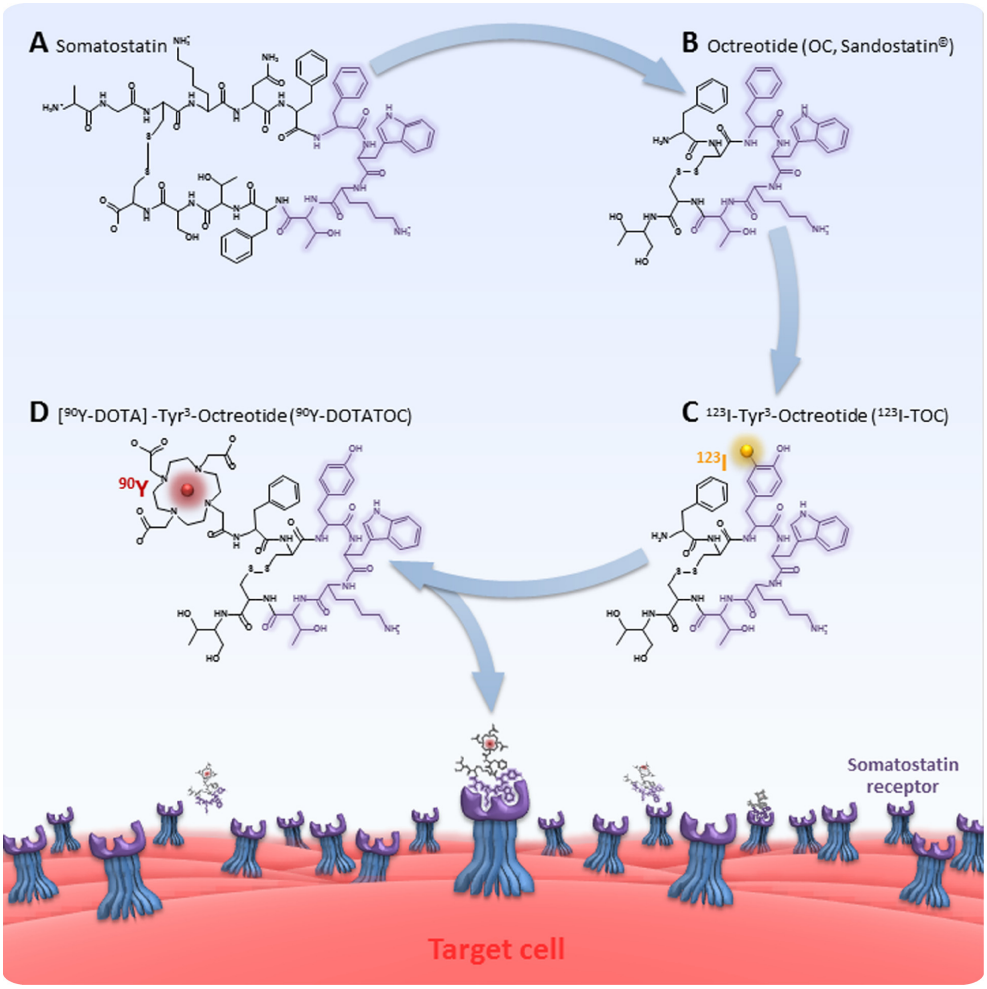


Fig 2. From natural ligand to radiolabeled synthetic analog. (A) shows the biochemical structure of the endogenous hormone somatostatin. Its synthetic analog octreotide (OC, **B)** includes the receptor-binding portion of somatostatin but is a smaller molecule. Tyr3-Octreotide (TOC) is octretide with a tyrosine (in yellow, **C)** in position 3 of the octreotide sequence. TOC can be labeled with radioactive iodine isotopes for imaging or therapy. In this example iodination has been performed using 123I, a γ-emitter that permits scintigraphic imaging of SSTR-expression. **(D)** To be able to lable the abridged octretide molecule TOC with 68Ga for PET-imaging, or 177Lu or 90Y for therapy, it has to be chelated to the radioisotope with a DOTA-molecule. Since all of these analogs of the natural ligand include the receptor-binding portion of somatostatin, they all have the capacity to bind to the SSTR on the target cell.

The most widespread tracers for SSTR PET-imaging are ^{68}Ga-labeled DOTATATE and -TOC. SSTR-PET is primarily used for its high sensitivity and specificity in identifying NET lesions, the so-called **staging** process, which is the basis for choosing the appropriate therapeutic modality. The number, distribution, size and relationship to adjacent structures of the NET lesions is what decides whether the patient is best helped by surgery, oncological treatment or a watch-and-wait strategy. It is also a useful tool in the follow-up of the patients for the evaluation of treatment outcomes (15). In clinical practice, however, the application of theranostics in NET goes beyond mere staging to include diagnosis, prediction of therapeutic outcome, prognostication, and tailoring of therapy.

It is sometimes difficult to obtain sufficient histological material to be able to ascertain a **diagnosis** of NET, either because of the size or location of the tumor lesions, or due to patient comorbidities making surgery or biopsy unnecessarily risky. In such cases, the high sensitivity and specificity of SSTR-PET in identifying NET lesions can serve as a surrogate diagnostic tool. This is one of few tumor types where this is possible, since most other PET tracers lack specificity for a certain tumor type.

As mentioned above, approximately 80% of NETs have a high expression of the SSTR as visualized by SSTR imaging. This is the basis for the theranostic concept in NET, i.e. selection of patients for SSTR-based therapy is done using SSTR-imaging. In the initial years of PRRT, selection was done using ^{111}In-pentetreotide imaging, a.k.a. octreotide scintigraphy (Octreoscan®), using the so-called Krenning scale, which is a qualitative evaluation of tumor uptake compared to normal organ uptake[1]. This is actually the only clinically validated selection method where a high tracer uptake in tumors as compared to uptake in normal organs has shown to be **predictive** of tumor remission after PRRT with ^{177}Lu-DOTATATE (16). The multiple advantages of PET vs SPECT have made SSTR-PET the dominating method for patient selection in recent years, however. Some authors have attempted to define a quantifiable measure from PET that can serve as a selection parameter for PRRT with some success (17-21), but no firm consensus regarding this has been reached. Most centers still seem to use a qualitative evaluation, similar to the Krenning scale, for patient selection (18). A recent direct comparison of ^{111}In-pentetreotide planar scintigraphy vs SSTR-PET showed that the latter gave significantly higher Krenning scores than the former, potentially leading to selection of more patients for PRRT than would have been the case if based on octreotide scintigraphy (22). Whether or not the same level of efficacy is achieved using this new selection method is yet to be determined.

[1] Grade 1: tumor uptake < liver; grade 2: tumor uptake = liver; grade 3: tumor uptake > liver; grade 4: tumor uptake > spleen/kidney.

Tumors that do not have a visible SSTR-expression on imaging, are usually positive on ^{18}F-FDG-PET instead – a type of PET that uses radiolabeled glucose to identify tissues with a high proliferation rate. Several authors have confirmed the negative **prognostic** impact of a positive ^{18}F-FDG-PET in NET patients (23, 24), and the positive prognostic impact of a high uptake on SSTR-PET (25, 26). This has led to the logical proposal to use dual imaging to improve prognostication beyond the current histological grading system. The theoretical advantage of grading by imaging rather than by histology is that with the former you get a picture of the whole tumor load, while the latter only gives information from a microscopically small part. Chan et al have proposed a "NETPET grade" were the degree of uptake of ^{18}F-FDG and ^{68}Ga-DOTATATE in tumors is used to create a multi-tiered grading system ranging from no uptake of ^{18}F-FDG and a high uptake of ^{68}Ga-DOTATATE in one end, to high uptake of ^{18}F-FDG and none of ^{68}Ga-DOTATATE in the other end. According to the authors, the NETPET grade has a significantly stronger correlation to overall survival than does histologic grade, age or the presence of extrahepatic disease (27). Furthermore, recent publications suggest a prognostic value of the total SSTR-expressing tumor volume, with a high tumor volume corresponding to a shorter progression-free survival (PFS) (28).

First author (ref nr)	Number of patients	Variable(s) studied	Results/conclusions
Ezzidin (29)	21	SUV_{mean} and SUV_{max} vs AD/IA	There was a moderate correlation between SUVs and AD/IA
Kratochwil (19)	30	SUV_{max}, T/S and T/L vs responding/non-responding metastases	A SUV_{max}>16.4 predicted lesion response with a sensitivity of 95% and a specificity of 60%
Sharma (20)	55	SUV_{max}, T/S, T/L and $SUV_{max\text{-}av}$ vs objective response and PFS	SUV_{max}>13 at baseline predicts likelihood of objective response
Werner (21)	31	Intratumoral textural features vs PFS	Intratumoral heterogeneity was a positive predictive factor

Table 1. Results of retrospective analyses to find objective, quantifiable PET-measures to predict the effect of PRRT. SUV: standardized uptake value; SUVmax-av: mean SUVmax of the five hottest lesions AD: absorbed dose; IA: injected activity; T/S: tumor-to-spleen ratio of uptake; T/L: tumor-to liver ratio; PFS: progression-free survival

Dual imaging using ^{18}F-FDG- and SSTR-PET can also be useful when choosing the right treatment for the right patient, i.e. **tailoring** therapy. It is not uncommon to see that some tumor lesions are positive on SSTR-PET, others on ^{18}F-FDG-PET and yet others on both. In fact, in one study dual imaging was shown to result in discordance between the two PET tracers in 62.5% of the patients with NEN G1-G3, and to change clinical management in 80% of the patients as compared to radiological imaging and clinical data only (30). If some lesions are ^{18}F-FDG-positive but ^{68}Ga-DOTA-negative, it would hardly be advisable to choose PRRT since the ^{18}F-FDG-positive lesions are more aggressive and will not respond to PRRT since they lack the target

for the treatment, i.e. the SSTR. On the other hand, ^{18}F-FDG-positive tumors that are also ^{68}Ga-DOTA-positive, including G3 tumors, may respond well to PRRT (31).

In summary, although theranostics and functional imaging are already an intregral part of the management of NET, there is still a need to objectively and prospectively evaluate the role of the new players in terms of impact on therapeutic outcomes.

Systemic treatment of advanced NET

The number of treatment options for advanced NET have increased considerably over the past decade, which has probably been a major contributor to the overall survival rates seen in recent epidemiologic reports (32), together with the increasing awareness about NET in general and its disease management in particular. We now have several therapeutic alternatives to offer our patients, but very little evidence to guide sequencing and/or combinations of treatment. Successful management of patients with advanced NET is therefore a multidimensional challenge, which is not easily described by any treatment algorithm. Which of the many therapeutic options available to any given patient at any given point in their disease, depends on several co-existing factors such as the primary tumor origin, the location of the tumor lesions, the proliferation rate and hormonal secretion as well as, of course, the expression or not of the SSTR. The two strongest predictors of treatment efficacy of all these are proliferation rate and SSTR-expression, making classical chemotherapy useless in low-grade tumors and SSTR-based treatments of little use in high-grade tumors, as illustrated in Fig 1.

The first NET-specific systemic treatment to reach the market was the synthetic analog of the endogenous hormone somatostatin – octreotide. Somatostatin itself was first identified in 1973, together with several other peptide hormones, which awarded its "discoverers", Roger Guillemin and Andrew Schally, the Nobel Prize in 1977 (33). Somatostatin has a half-life of only 2-3 minutes, however, so even though its inhibitory effects were understood it lacked therapeutic potential. **Octreotide** was the solution – it has an inhibitory effect on hormonal secretion and a circulating half-life that is 40 times that of the endogenous hormone (34). The long-acting release formula of octreotide was approved by the regulatory authorities in 1997 and was a game-changer for patients in that they could now control their carcinoid syndrome with just one injection a month, instead of multiple daily injections. Shortly thereafter, another SSA reached the market – **lanreotide** (13). Both SSAs were at first used only for hormonal control of the carcinoid syndrome and hormone-secreting pituitary adenomas, but further studies also confirmed their inhibitory effect on tumor growth (12, 14). Both of these drugs are now first-line treatment of low-grade (G1-G2) NET of gastroentero-pancreatic origin (GEP-NET).

For patients suffering from severe carcinoid syndrome, the recent addition of **telotristate** – an inhibitor of the conversion of tryptophane to serotonin – has been a welcome addition to the therapeutic alternatives.

GEP-NETs that either do not express the SSTR, or have progressed on SSA, may be treated with the mTOR-inhibitor **everolimus**. Its mechanism of action – the inhibition of the intracellular enzyme mTOR – leads to reduced cell metabolism, angiogenesis and cell proliferation (35). These are so-called cytostatic effects, rather than cytotoxic, meaning that tumor growth is inhibited but it is rare to see significant tumor shrinkage with this treatment. The same is true for **sunitinib**, a tyrosine-kinase inhibitor approved for the treatment of pancreatic NETs only (36). Sunitinib's main effect is on angiogenesis through its effect on the VEGF receptor. Both of these drugs improve the progression-free survival for NET patients with several months compared to placebo, but are also associated with significant side effects. Most of the side effects are not serious from a medical point of view, but can negatively affect the quality of life for the patients while on treatment. It may therefore be difficult to justify these treatments for patients that are asymptomatic from their slowly progressing metastatic NET, which is not an unusual situation. Recent data also suggest interesting response rates for the newer tyrosine kinase inhibitors **lenvatinib** and **cabozantinib**, which may in future offer further therapeutic options to NET patients (37, 38).

Another treatment option, which is often associated with significant tumor shrinkage, is the combination of **capecitabine** and **temozolomide** (CAPTEM). These two oral chemotherapeutic drugs are used in clinical practice to a far wider extent than the level of evidence would lead to believe, as almost all evidence comes from retrospective analyses. This is most probably due to the very direct clinical experience of a treatment that is both effective and well tolerated, as well as independent of SSTR-expression. The first published evidence of this being an effective treatment came in 2011 and was a retrospective analysis of 30 patients with pancreatic NET, of which 24 experienced some degree of tumor shrinkage (39). Since then a large number of retrospective analyses looking at the efficacy and toxicity of this regimen in other types of NEN, including non-pancreatic primaries and high-grade tumors, have been published. They all confirm that the high disease-control rate (DCR) and low toxicity is not limited to pancreatic NETs (40-45). One of the larger retrospective analyses indicates a DCR of 53% in non-pancreatic GI-NEN, and 33-43% in G3 NEN, although the longest progression-free and overall survival is seen in patients with pancreatic or thoracic primaries, and in G2 tumors (40), which are also the indications in which CAPTEM is primarily used.

For the most highly proliferative tumors, the neuroendocrine carcinomas with a Ki67 of >60%, classical **platinum-based chemotherapy** is the treatment of choice. The response is often dramatic, but unfortunately rarely durable. According to

published retrospective data, the response rate to first-line, platinum-based chemotherapy is 30-50%, but the PFS only 4-6 months. Overall survival is about one year (46). NEC are generally also very sensitive to radiotherapy, which can be used as a complementary treatment for local symptom control or as part of a combined regimen with curative intent for loco-regional disease.

Peptide Receptor Radionuclide Therapy

The first trials with PRRT were done in the 1990s using **^{111}In-pentetreotide**, i.e. the same radiopharmaceutical that was used for diagnostic octreotide scintigraphy, but with an administered activity that was 30 times as high. The therapeutic effect was achieved by the emission of Auger electrons, which have a very short tissue penetration range, making it suboptimal for this clinical application. Even so, according to the results from a phase II trial this treatment led to improved symptoms and reduced hormonal levels in 62% and 81% of the participating patients, respectively. It was also from these early PRRT trials that the first signals of hematologic and renal toxicity came (47).

The next generation of radiopharmaceuticals for PRRT used **^{90}Y-DOTATOC**, which is a pure β-emitter that has both a higher energy and tissue penetration range than its predecessor. The first reports of clinical trials came just around the turn of the century, with very encouraging efficacy results even in the phase I trials (48-52). Toxicity seemed manageable initially, but after some time the number of reports of renal failure began to increase (53-55). At this point, a more systematic approach was taken to the co-infusion of amino acids to reduce the tubular re-absorption of radiolabeled peptide, thereby reducing the absorbed dose to the kidneys with up to 53% (56).

^{177}Lu-DOTATATE entered the therapeutic arena in the early years of this century, based on pre-clinical data indicating a higher affinity for SSTR2 of DOTATATE than of DOTATOC (57). ^{177}Lu is a combined β- and γ-emitter, making it optimal for post-therapeutic imaging. For several years, there was a parallel use of ^{90}Y-DOTATOC and ^{177}Lu-DOTATATE. Some sites combined the two (58-61), while others used ^{90}Y for patients with large tumors and ^{177}Lu for patients with small tumors (62), given the differences in energy and range of the two isotopes (63). The two radiopharmaceuticals were never compared head-to-head in a randomized trial, but accumulating evidence indicated that there was a higher risk of renal toxicity with ^{90}Y-DOTATOC (64), and that ^{177}Lu-DOTATATE was clearly as effective as expected (62, 65-68). During the past decade, PRRT-trials have been dominated by ^{177}Lu-DOTATATE, thereby producing a large body of non-randomized evidence in favor of its safety and efficacy in different types of NET. A recent meta-analysis demonstrated an average disease control rate of 81%, with an objective responses rate of 29% (69).

A randomized **phase III trial** – NETTER-1 – was finally conducted, comparing ^{177}Lu-DOTATATE therapy to high-dose SSA in patients with small intestinal NETs. The trial showed a very convincing result in favor of PRRT (70), with a 20-month improvement in PFS for the experimental arm vs control. This led to regulatory approval in 2018, almost two decades after it was initially used in patients. Based on the phase III results, and additional data from a retrospective review of patients with pancreatic NET (71), the approved standard therapy is now to give patients with SSTR-positive GEP-NET four cycles of 7.4 GBq of ^{177}Lu-DOTATATE.

Description	Trial phase	Status	Number of sites/subjects
^{177}Lu-DOTATATE 7.4 GBq x 5 with 5-week intervals vs 8-10-week intervals	II	Recruiting	1/618
^{177}Lu-DOTATATE vs high-dose octreotide in patients with G2 and G3 advanced GEP-NET	III	Not yet recruiting	?/222
^{177}Lu-DOTATATE vs sunitinib in metastatic pancreatic NET	II	Recruiting	1/80
^{177}Lu-DOTATATE vs SSA in patients with carcinoid heart disease	II	Not yet recruiting	1/20
^{177}Lu-edotreotide vs everolimus in GEP-NET	III	Recruiting	38/300
^{177}Lu-DOTATATE vs CAPTEM vs the combination of both	II	Recruiting	4/72

Table 2. Summary of currently registered, randomized phase II and III trials with ^{177}Lu-PRRT in neuroendocrine tumors. Source: www.clinicaltrials.gov, accessed on October 2, 2019.

Although the approved use of ^{177}Lu-DOTATATE is currently limited to 4 cycles á 7.4 GBq, other treatment protocols have been implemented and studied at different PRRT centers. For example, image-based dosimetry-guided treatment has been extensively studied in Sweden and Canada (72-74). Combined chemo-PRRT for selected patients has been used in Australia (75-77). Salvage treatment, i.e. re-treatment at progression after previous PRRT, has also been reported as effective and safe by several authors (78-81).The results reported from these alternative treatment strategies all seem to indicate that there is room for further improvement of the treatment outcomes, beyond the current standard therapy. However, as long as there is a continued paucity of randomized, prospective trials in the realm of radionuclide therapy (RNT) in general and PRRT in particular, conclusive advances will be difficult to achieve. Table 2 summarizes currently registered randomized trials with ^{177}Lu-PRRT.

Tailoring cancer treatment

The history of modern cancer treatment has been masterly described by oncologist and writer Siddhartha Mukherjee in "The Emperor of All Maladies: A Biography of Cancer" (82). It describes the incessant quest for the cure for cancer. In the early phases, it was all about being surgically more aggressive. With the advent of chemotherapy, the limits for what was possible to achieve pharmacologically were explored by combining different agents and giving ever-higher doses to beat the cancer once and for all. We are now in the molecular era, with targeted therapies and the –omics, overlapping with the era of immunotherapy.

The ruling paradigm in oncology at present is **Personalized Medicine** – selecting the right patient for the right treatment – thereby avoiding treating many for the benefit of just a few. Although conceptually this can be achieved in a variety of ways, the prevailing trend is that of molecular characterization of tumors to define the most effective treatment – a.k.a. **precision medicine**. A growing body of knowledge about the molecular drivers of cancer gave us the first targeted therapies, although still based on primary tumor origin. The process was to identify a molecular driver with a high prevalence in a certain tumor type, and develop a drug specific for that target. This was highly successful for imatinib in chronic myeloid leukemia, where the molecular target is the sine qua non for tumor survival. Less glamourous was the story of the EGFR-inhibitor gefitinib in non-small cell lung cancer that failed in two consecutive phase III trials (83, 84), until it was noted that it worked very well in a small subgroup of patients who had a specific mutation in the EGF-receptor (85, 86). From there, non-small cell lung cancer has become a diagnosis where treatment is more and more defined by which molecular target the patient´s tumor has (or not). This approach is changing oncological drug development from being based on organ-of-origin (breast cancer, lung cancer, etc) through identifying molecular subgroups within each primary tumor group to the more recent trend towards tumor-agnostic clinical trials based solely on the presence of a particular molecular target, independently of the primary tumor origin. Just the last two years, three drugs have received FDA approval based on this principle (e.g. larotrectinib and entrectenib in NTRK-positive cancers, and pembrolizumab in MSI-high/MMR-deficient solid tumors).

Precision medicine in NET

The field of NETs started out well with the identification of somatostatin and its receptor, the SSAs and theranostics, as well as molecularly targeted therapies such as sunitinib, everolimus, cabozantinib and lenvatinib. The process of identifying "druggable" molecular targets in specific patients has proven more challenging, especially in the well-differentiated tumors of the small intestine were the

mutational burden is very low compared to other forms of cancer (87). For the pancreatic NETs the genomic landscape is more variable, and several mutational patterns have been described (88), although so far without immediate clinical implications. One type of molecular aberration that is of importance to a subgroup of NETs are those of the RET-receptor, present in a majority of medullary thyroid cancers. Two non-selective RET-inhibitors, cabozantinib and vandetanib, result in clinically relevant overall response rates although they are also associated with significant toxicity (89, 90). Just recently, very promising early results from two selective RET-inhibitors that are being tested in clinical trials have been presented (91, 92). Immunotherapy, which has entered the oncological treatment arsenal in a large number of different indications, has been tested in NET but with little success, apart for the small but significant exception of merkel cell carcinoma – a NEC of the skin – where immunotherapy is now first-line treatment. This efficacy has, as of yet, not been reproduced in NECs of other origins.

The most well documented method for precision medicine so far in NETs is the **NETest®**. This is a blood-based analysis of 51 gene transcripts (mRNA) representing different "-omes" (SSTRome, proliferome, metabolome, secretome, epigenome and plurome) that has been tested in multiple settings in NETs. According to a recent review (93) it can be used to:

- Diagnose NETs of the small intestine, pancreas, lungs, adrenal glands and paraganglia
- Distinguish stable disease from progressive disease, and metastatic from non-metastatic
- Predict treatment response/failure with SSA and PRRT
- Identify residual disease after surgery of GEP-NETs and broncho-pulmonary NETs

In all of these settings it has been determined to have a sensitivity and specificity >90% and to be superior to other circulating biomarkers and radiological tests.

Despite these results, clinical use has so far been limited. This may be related to the fact that there have been few large, independent validations performed. The largest one to date confirmed a high sensitivity for detection of NET (93%) but a lower specificity than had previously been reported (56%). It could not confirm a correlation between NETest® levels and tumor grade, stage or primary tumor origin. Compared to the currently used biomarker chromogranin A (CgA) NETest® was superior in sensitivity, but CgA superior in specificity. CgA also correlated better with tumor load than did NETest®. (94)

Regarding the use of the NETest® in the PRRT-setting, the possible predictive value was retrospectively studied in a series of 72 NET-patients who had received

PRRT and had stored pre-treatment blood samples. A correlation was found between pre-test levels of a subset of the transciptomes analyzed by the NETest®, and response to treatment. The strength of this correlation was further improved by combining the selected transcriptomes with tumor grade resulting in a positive predictive value of 100% (95). This "PRRT Predictive Quotient" has then been validated in another 86 patients. Both response and non-response could be correctly predicted in >93% of the patients (96).

In summary, the NETest® shows great promise as a useful biomarker in different settings. It could potentially reduce the number of radiological evaluations needed, avoid ineffective treatments and reduce the number of patients in active follow-up after radical surgery. To determine its exact place in NET management, the NETest® will have to be clinically validated in a prospective, randomized and independent fashion to quantify its effect on PFS and OS in comparison to current practices. This has previously been successfully done with similar tests in breast cancer (97, 98).

Tailoring radionuclide therapy

^{177}Lu-DOTATATE is a molecularly targeted therapy whose distribution and pharmacokinetics are possible to image in each patient, opening the door to personalized treatment planning. Despite this, according to the approved dosing the same amount (i.e. activity) of ^{177}Lu-DOTATATE is given to all patients receiving PRRT independently of the size of the patient, the size of the tumor burden, the proliferation rate of the tumor, renal function and any other patient-specific factors. This is especially odd considering that PRRT is systemic *radiotherapy,* i.e. the anti-tumor effect of the treatment will depend on the absorbed (radiation) dose delivered to the tumor, and the toxicity on the absorbed dose (AD) delivered to the normal organs. Add to that the fact that it is possible to image the distribution of the drug in the body, and from those images calculate the AD achieved both in tumors and in the organs at risk. Every single oncology patient´s external beam radiotherapy (EBRT) is individually and painstakingly planned, why not do the same for the patients receiving RNT? For one simple reason: we do not know how best to go about it.

More specifically, the influence of **patient-specific factors** like body size, renal function or tumor burden on the distribution and kinetics of the radiopharmaceutical is not well defined. The AD needed to elicit a tumor response, and the AD limits for the organs at risk, are not either, nor the best way to calculate the AD from the post-therapeutic images. However, there are a lot of islands in the sea of radionuclide therapy research, each one trying to elucidate some little part of the puzzle, bridging some of the many gaps.

One of the early attempts to address the first question was Beauregard et al (99), based on the clinical observation that patients with a low tumor burden tended to have a higher activity uptake in liver, kidney and spleen than those with a high tumor burden, where a greater proportion of the radiopharmaceutical was bound to the tumor. This is known as the **tumor sink effect**, and has also been observed with other radiopharmaceuticals. With only ten patients, chosen for their very varying tumor burden, they found a correlation between urinary excretion, lean body weight and tumor burden on the renal uptake of ^{68}Ga-DOTATATE in PET-images. This Canadian group later applied their observations in a clinical trial aimed to personalize PRRT adjusting the **injected activity** based on renal function and lean body weight (74), targeting a renal AD of 23 Gy. This approach was compared to a simulated standard treatment of 4 x 7.4 GBq and was found to lead to a significant increase in both injected activity and tumor AD, albeit to the price of a high rate of hematological toxicity. The toxicity was not significant enough to cause any treatment interruptions, though. More recently, Werner et al have tried the tumor sink hypothesis in a larger patient sample, confirming a significant negative correlation between body size and normal organ uptake, but no correlation between tumor burden and normal organ uptake (100). They argue, however, that what is seen (or not) in a ^{68}Ga-SSTR-PET may not adequately reflect what happens in therapy with ^{177}Lu-PRRT.

Further data to support the interdependence of the patient-specific factors came from two Swedish groups. Svensson et al (101) saw a significant correlation between (low) **GFR** (i.e. renal function), hematological toxicity and an increased renal AD. This may be explained by a longer circulation time in patients with renal dysfunction leading to a higher radiation exposure to the bone marrow and kidneys. They did not, however, see an inverse correlation between tumor burden and renal AD but recognize that a possible relationship may have been obscured by the fact that the group with a high **tumor burden** also had a significantly lower mean GFR than those with a small tumor burden. Whole-body residence time was positively correlated to tumor burden and hematological toxicity. Garske et al presented data on the effect of changes in tumor burden during treatment from a case report of a patient with a G3 tumor who had a remarkable tumor shrinkage during the treatment period of 7 cycles of 7.4 GBq of ^{177}Lu-DOTATATE (102). Dosimetry based on post-therapeutic images showed how the tumor AD increased, and the bone marrow AD decreased, as the tumor shrank.

Sabet et al (Germany) have studied the question of whether or not **SSTR saturation** (i.e. maximum AD) is achieved with the fixed activity regime of 7.4 GBq. They did so by performing an SSTR-PET a few days before, and 30 minutes after, infusion of ^{177}Lu-DOTATATE. They then compared normalized SUV-values for tumor and normal tissues pre- and post-PRRT and found no significant differences in tumor-

SUV but a significant reduction in normal tissue SUV. The authors concluded that there is room for activity escalation as a means to optimize therapy.

Based on the results presented by Beauregard et al, the Australian co-authors applied the whole concept, including other ways of personalizing PRRT, in their clinical routine (103). Apart from adopting the tumor sink concept to adjust the injected activity and using dual imaging, the same group has also presented results of combining chemotherapy with PRRT (**PRCRT**). They have used this for patients with bulky or aggressive disease (i.e. lesion size > 4cm and/or ^{18}F-FDG+ and/or G3) with high response rates and longer PFS than what would be expected given the negative prognostic factors (Table 3) (61, 77, 104, 105).

Author	Population	N	Therapy	CBR	mPFS (months)	OS
Barber (105)	Locoregionally advanced pNET/dNET	4	IA-adjusted PRRT + 5FU inf	100%	N/A	N/A
Kashyap (77)	^{18}F-FDG+ mNET	52	IA-adjusted PRRT + 5FU inf	N/A	48	NR
Kong (61)	GEP-NET with bulky disease	26	90Y- +/- 177Lu-PRRT + chemo[1]	N/A	33	NR
Thang (104)	mNET G3	28	90Y- +/- 177Lu-PRRT + chemo[1]	74%	All: 9 G3a: 12 G3b: 4	All:19 G3a: 46 G3b: 7

Table 3. Summary of retrospective series of PRRT combined with concomitant chemotherapy.
[1]Different regimens were used: 5FU-infusion, capecitabine or temozolomide+capecitabine.
pNET: pancreatic NET; dNET: duodenal NET; mNET: metastatic NET; IA: injected activity; N/A: not available; NR: not reached; G3a: Ki67<55%; G3b: Ki67>55%; CBR: clinical benefit rate (=stable disease + objective responses)

In summary, most data seem to indicate that patient-specific factors play a role, as is logical, but the weight of each one in the total dosimetric picture is still unclear making solid recommendations hard to put forth. In our islands-gaps-and-bridges metaphor, we see that there are clinical research groups in Australia, Canada, Sweden, Germany and others, trying to apply the logic behind personalizing PRRT each in their own way. Despite not being a coordinated effort, each one sheds a little more light on the subject from different angles. Each one contributes a little to bridging the gaps.

Internal dosimetry

Before looking at the existing data on AD constraints to organs at risk and target AD to tumor tissue, it is necessary to understand the basics of internal dosimetry in order to understand the chain of events that lead to the dose delivery, factors that affect it, and how that dose can be quantified.

A radionuclide is an atom with an excess of energy in its nucleus. To become stable it must emit that extra energy. Three kinds of radiation are particularly relevant for radionuclide therapy:

1. Alpha radiation (α) consisting of a helium atom nucleus (2 protons+2 neutrons) and emitted as part of α decay. Alpha-emitting radionuclides used for therapy typically have an energy in the order of a few MeV, with a very short range.
2. Beta radiation (β) consisting of an electron or a positron emitted as part of beta-decay. Beta-emitting radionuclides used for therapy typically have a maximum β energy between 0.2 MeV and 2 MeV, with a relatively short range.
3. Non-particle radiation in the form of photons, or gamma radiation (γ), which is suitable for gamma-camera imaging. Some of the β-emitting radionuclides used for therapy simultaneously emit γ-radiation (Table 4), making post-therapeutic γ–camera imaging possible, which is the basis for image-based dosimetry.

Radionuclide	Type of emitted radiation	Physical half-life (days)	Max energy / decay (MeV)	Range in tissue (X90, mm)
^{223}Ra	α	11.4	7.5	< 0.1 mm
^{177}Lu	β^- and γ	6.7	0.5	0.4 mm
^{166}Ho	β^- and γ	1.1	1.8	2.8 mm
^{90}Y	β^-	2.7	2.3	4.6 mm
^{131}I	β^- and γ	8.0	0.6	0.6 mm

Table 4. Some commonly used radionuclides in therapy and their main physical properties. X90: the radius within which 90% of the emitted energy is absorbed. Data from http://www.nndc.bnl.gov/ accessed on Oct 28, 2019.

Each radionuclide has a predetermined decay chain, which brings it from an excited state to a stable one. While decaying, it can emit several different types of radiation. This is called "ionizing radiation" because it has the capacity of ionizing atoms, thereby depositing all or part of its energy in that ionization event. The ionized atoms in turn cause different biological effects, which is the mechanism through which the antitumor, and toxic, effects are generated. The most common examples of ionization effects are the production of free radicals and strand-breaks in the DNA.

We have already touched on the subject of absorbed dose, which is obviously a central term in dosimetry – the measurement of dose. In RNT, the absorbed dose (D) is the amount of energy (ε) deposited by radioactive decay, in a volume/organ of a certain mass (m).

$$D = \frac{\varepsilon}{m}$$

The energy is measured in Joule (J) and the mass in kilograms (kg). The unit for the AD will then be J/kg, which is the same as a Gray (Gy).

The amount of energy that is deposited in an organ or other tissue will be determined by

1. the radionuclide used, since this will let us know
    a. the type of emitted radiation (α, β, γ)
    b. the range and energy in each decay and
    c. the physical half-life, i.e. how fast the radionuclide decays
2. how long the radionuclide is retained within the organ/tissue

For example, when ^{177}Lu decays, it emits both β^-- and γ-radiation. The electrons, which are the major contributors to the biological effect of ^{177}Lu, have a mean energy of 0.5 MeV and a range in the order of a millimetre (106). With such a short range, it is reasonable to assume that virtually all the energy from the electrons is deposited within the organ/tissue. The number of decays per second is calculated from the post-therapeutic images – the counts registered by the gamma-camera can be converted to the number of decays that occur within the imaged region of the body. With serial images over several days, we also get information on how long the radionuclide is retained in the organ. By delineating the organs whose AD we want to calculate in the images (Fig 3), and from the images extract how many decays per second (i.e. activity) have occurred in each region at each time-point, we can plot a **time-activity curve** for each of the **regions-of-interest (ROI)**. The area under that curve represents the number of decays that took place in that organ/tissue. The AD for that treatment cycle and organ is obtained by multiplying the number of decays with the energy/decay and divide by the mass of the organ.

A more precise way of estimating the AD than the planar imaging just described, is achieved by including one or more SPECT-images in the post-therapeutic imaging. The advantage of **SPECT**/CT over planar images is that SPECT/CT gives us a 3-dimensional image of the uptake, and we therefore do not risk including over- or underlying activity outside the organ/tissue as we may in planar images. The estimation of activity within the organ/tissue is therefore more precise and can be used to calibrate the amplitude of the time-activity curve prior to calculating the AD.

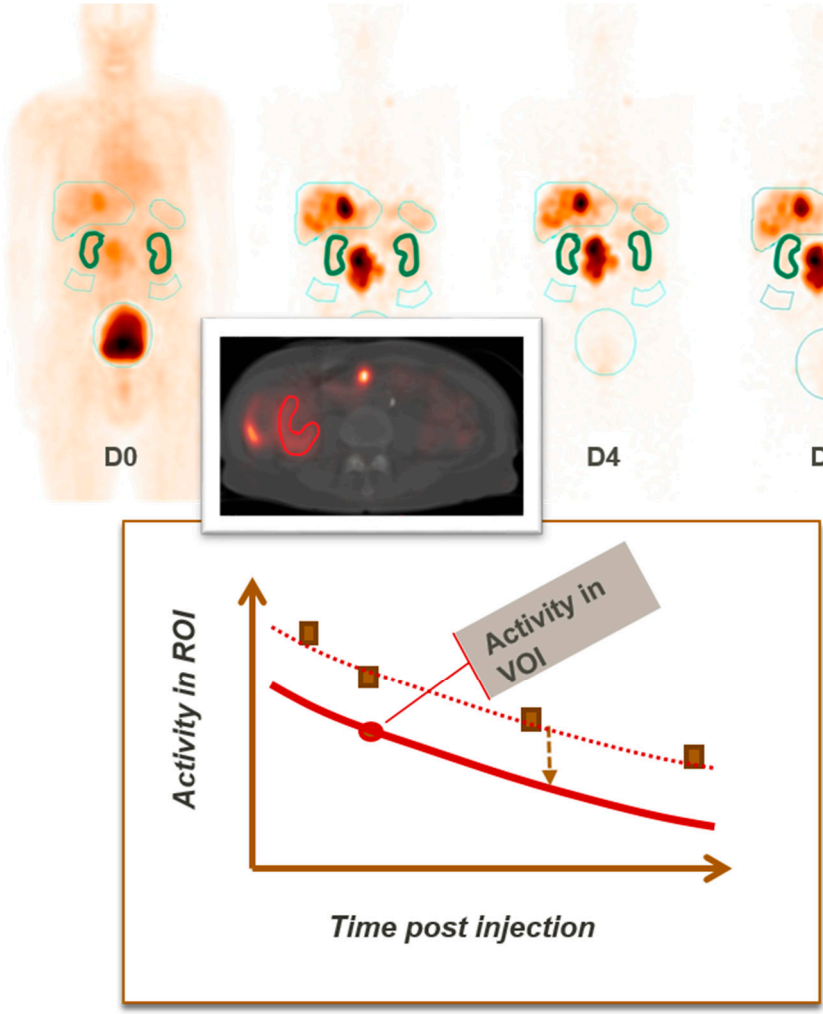


Fig 3. Illustration of planar gamma camera images of a patient (top) from four time-points after treatment with 177Lu-DOTATATE. The kidneys are delineated with a bold, green line and the activity within the region-of-interest plotted on a time-activity curve (dotted red line). The area under the curve (AUC) is the time-integrated activity which, when multiplied by the emitted energy in each decay and divided by the kidney mass, will give the AD to the kidneys. By using a SPECT-image we can get a more precise idea of the activity within the organ and use it to correct the level of the time activity curve (solid red line) before calculating the AUC. Serial imaging with SPECT, instead of the hybrid form represented here, is also an option.

Now that we have come to grips with the AD, a few more terms need to be explained before we look at the biological effects. We mentioned above the physical half-life of a radionuclide as important to calculating the AD, but since RNT involves a systemic drug with its own pharmacokinetics, it is not only the *physical* half-life of the radionuclide that we need to take into account, but also the *biological* half-life. The combined effect of the two is called the ***effective*** **half-life**.

The effective half-life is the major determinant of the **dose rate,** which describes how fast an AD is deposited in an organ (Gy/unit of time). Dose rate, in turn, is an important aspect when it comes to understanding and comparing the biological effect of different types of radiotherapy, different fractionation schemes, etc. For example, EBRT is administered at a dose rate in the order of Gy/min, while RNT delivers its Gy over days or weeks. EBRT also administers the whole AD with the same dose rate, while in RNT the dose rate progressively declines as the radionuclide decays. These differences affect the radiobiological processes underlying the antitumor effect and toxicity of the radiotherapy, to an extent that is so far incompletely understood.

We sometimes need to compare different radiotherapy regimes regarding the AD delivered to both target and risk organs. Since differences in dose rate and fractionation translate into differences in the biological effect, direct comparisons of AD values may be misleading. This relationship between AD, dose rate and fractionation has been extensively studied in EBRT, where it is described through the linear-quadratic (LQ) model. From this model comes the concept of **BED** – biologically effective dose, widely used in EBRT to compare different fractionation schemes. The formula for calculating the BED takes into account the α/β-ratio of the tissue (a measure of how sensitive the tissue is for changes in fractionation and dose rate), the AD/fraction and the total AD (107). To adapt it to the special circumstances relevant for RNT – a low dose rate over a long period of time – the tissue repair capacity and the effective half-life of the radionuclide need to be included in the formula as well (108). From the image-based AD estimate for an organ, we can calculate the BED using the BED-formula for RNT. Doing the same with the EBRT values lets us compare for example 6 Gy delivered to the kidney in 2-Gy fractions through EBRT, with 6 Gy that were delivered to the kidneys over weeks after one cycle of ^{177}Lu-PRRT:

- An AD of 6 Gy given to the kidney in 2-Gy fractions = 10.6 Gy BED[2]
- An AD of 6 Gy given to the kidney during ^{177}Lu-PRRT = 6.7 Gy BED[3]

In this case, the same AD gives a lower BED in RNT (1 cycle) than in EBRT (3 fractions), which interpreted within the LQ-model means a milder biological effect. This is due to the differences in how the energy is deposited in the tissues and organs.

[2] Calculated using an α/β of 2.6 Gy with on-line calculator at https://www.mdcalc.com/radiation-biologically-effective-dose-bed-calculator. Accessed on October 10, 2019.

[3] Calculated using an α/β of 2.6 Gy, T_{rep} 2.8h and T_{eff} of 51.6h, G=0.0515 as in paper I.

Another way to be able to compare different types of radiotherapy is to convert the total BED to the equivalent dose in 2-Gy fractions (EQD_2). For this, too, there are established formulas[2, 3] which give us the following results:

- 23 Gy to the kidney in 2-Gy fractions = 23 Gy EQD_2 (per definition)
- 23 Gy to the kidney from 6 cycles of ^{177}Lu-PRRT = 14.0 Gy EQD_2

So, the custom that has taken form in PRRT to let 23 Gy in AD serve as the limit for the kidney based on data from EBRT (72, 74, 109), is probably not very relevant, which may explain the almost complete lack of nephrotoxicity seen in patients treated to this limit. In fact:

- 23 Gy to the kidney in 2-Gy fractions = 41.0 Gy BED

which, by the way, is conspicuously near the empiric dose-response data from ^{90}Y-PRRT (108, 110), which we will now take a closer look at.

Dose-response in normal organs

There are a couple of basic **conditions that need to be met** to be able to evaluate whether or not there is a relationship between the administered AD (or BED) and toxicity. First of all, the estimation of the AD must 1) have been done, and 2) be accurate enough to not risk possible dose-response relationships to be lost in wide confidence intervals. The most accurate methods of dosimetry are SPECT-based rather than planar (111). The same holds true for the estimation of the toxicity – the method must be accurate enough to detect the type of toxicity that we are looking for. Renal function is preferably measured rather than estimated based on plasma creatinine, since there are other factors affecting creatinine-levels apart from changes in renal function. Last but not least, we must reach AD-levels that are high enough to cause toxicity. By now, given the many years PRRT has been in use and the thousands of patients that have been treated and re-treated, the last condition should not be a problem. Unfortunately, there are few sites that systematically perform dosimetry making it difficult to get dose-response data.

The first attempt to look at a **dose-response relationship for the kidneys** was based on 18 patients who had participated in a phase I trial with **^{90}Y-DOTATOC** (108). Renal dosimetry was based on pre-therapeutic ^{86}Y-DOTATOC PET (since ^{90}Y does not emit γ-radiation to permit post-therapeutic imaging), and renal function on yearly change in creatinine clearance estimates. To detect a dose-response relationship it became clear that it was essential to base the dosimetry on actual patient organ volumes (from CT), instead of standard volumes, and to use BED instead of AD. With these two conditions met, there was a strong ($r=0.93$) and significant ($p<0.0001$) correlation between renal toxicity and dose. Five patients

showed a >20% yearly reduction in renal function, all of which had received >50 Gy BED to the kidneys in 1-4 cycles.

This was followed by Bodei et al (110), who looked at dose-response for kidney and bone marrow, and included an analysis of the effect of **clinical risk factors** for nephropathy. Dosimetry was done using patient-specific organ masses and BED, as proposed by the previous study. From here, some interesting observations were made:

- Renal toxicity became evident 1-5 years after PRRT
- 8/9 patients who experienced renal toxicity had one or more clinical risk factors
- There was no correlation between AD and renal toxicity
- There was a significant correlation between BED and renal toxicity
- The threshold for toxicity was 28 Gy BED for patients without clinical risk factors and 40 Gy for those with
- Patients without risk factors tended to recover a normal renal function despite an initial reduction in creatinine clearance
- Fractionation, i.e. giving more cycles with a lower activity/cycle, seemed to reduce the frequency and degree of renal toxicity.

The patient data from these two publications were later combined to create an **NTCP** (normal tissue complication probability) curve for ^{90}Y-PRRT, which was co-plotted with the corresponding curve for NTCP with EBRT. When BED (but not AD) was used, the two curves were virtually superimposed, supporting the idea that the use of BED in internal dosimetry permits us to extrapolate the much larger experience from normal tissue complications from EBRT to RNT (112). At least this seems to be true for ^{90}Y-PRRT.

There are still no comparable data on **dose-response for ^{177}Lu-DOTATATE** where the basic conditions stated above are met. Specifically, there have not been enough documented cases of high-grade renal toxicity in dosimetry studies of ^{177}Lu-PRRT to be able to identify the BED limit. In one, large, uni-center retrospective study by Bergsma et al, 228 patients that had received up to eight cycles of 7.4 GBq were followed up for three years. Dosimetry was performed with a planar method using standard kidney volumes. Toxicity was evaluated by estimating the creatinine clearance. Despite having reached renal ADs of up to 28 Gy, no grade 3-4 toxicity was observed. This led the authors to conclude that the dose constraints extrapolated from EBRT and ^{90}Y-PRRT are not applicable to ^{177}Lu-PRRT, and that the kidney is not dose-limiting for the latter (113). In the largest SPECT-based dosimetry study of ^{177}Lu-PRRT published so far, 200 patients were treated with the intention of reaching a renal AD of 23 Gy. This was achieved in 123 of them, in 3-9 cycles of 7.4 GBq, but there was only one case of grade 3-4 renal toxicity (72).

Finding a dose-response relationship for the **bone marrow** has also proven challenging, but for different reasons. First of all, bone marrow toxicity may very well be treatment limiting, without the patient having received a high AD (72, 109). This is probably due to the co-existence of other, incompletely understood factors affecting the susceptibility of the bone marrow to cytopenias. Additionally, in dosimetry-based studies, the dose-limit for the kidneys is usually reached before the postulated 2-Gy limit to the bone marrow (109). The possible co-existence of micro- or macroscopic skeletal metastases, which would alter the radiopharmaceutical uptake and thereby the AD, is another complicating factor. This latter phenomenon has recently been systematically studied and the effect of skeletal metastases on bone marrow AD quantified by our group, based on the Iluminet trial (114). A moderate but highly significant relationship between AD and platelet toxicity was found, when using a novel planar and a hybrid planar-SPECT/CT dosimetry method in patients with and without skeletal metastases alike. The AD to the bone marrow was up to 69% higher for patients with metastases.

Another organ which could potentially suffer toxicity after PRRT is the **pituitary** gland. It has, however, received very little attention during the PRRT era of the past two decades. The reason for the pituitary gland being a potential risk organ, is that the endocrine cells located there show a high expression of SSTRs. This is evident on ^{68}Ga-DOTATATE-PET where the pituitary normally has a distinct, high tracer uptake (Fig 4). From EBRT we learn that pituitary radiation effects depend on two factors: the cumulative AD and the follow-up time. Both correlate directly with the likelihood of pituitary insufficiency (115). The only previously published data on pituitary function after PRRT comes from a group of 79 patients that had received 3-4 cycles of 7.4 GBq of ^{177}Lu-DOTATATE and been followed for 12-24 months (116). In these patients, a transient decrease in gonadotropins was found in men, while it was persistent in post-menopausal women. No dosimetry data were reported. Data on pituitary function from the Iluminet trial are presented in paper III.

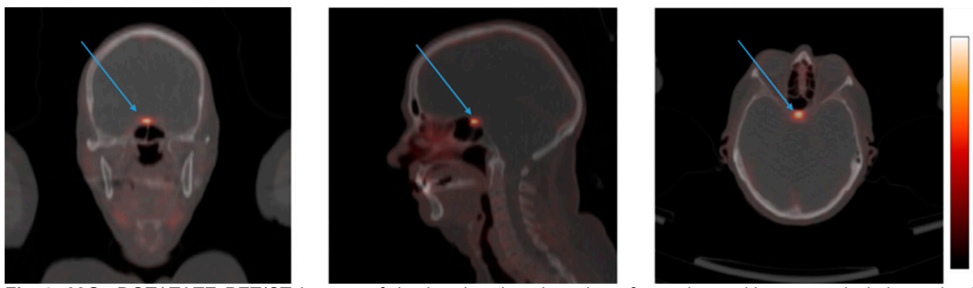


Fig 4. 68Ga-DOTATATE PET/CT images of the head-and-neck region of a patient, with a normal pituitary gland, illustrating the distinct tracer uptake (arrows) indicating a high expression of somatostatin receptors in this endocrine organ. From Paper III.

Dose-response in tumor tissue

If we consider the incomplete data to define the *normal* tissue complication probability in ^{177}Lu-PRRT, the lack of data regarding dose-response in *tumor* tissue is even more striking. Despite there being a well-established relationship between tumor control probability (TCP) and AD to tumor in EBRT, very little data exist on EBRT in NET since it has been considered a "radiation-resistant" tumor. Some data on tumor dose-response with ^{90}Y-PRRT can be found in the early trials. There was a clear dose-response relationship, with the median AD to tumor being six times as high in responding tumors (232 Gy) as in the non-responding ones (37 Gy). There were no non-responding tumors among those that had received >100 Gy (117).

For ^{177}Lu-PRRT, tumor dose-response has only recently been quantitatively explored. Clinical data come from two publications from the Uppsala group who have looked at this in both pancreatic and small intestinal NETs (118, 119). For the analysis in pNET, 24 patients and 42 tumor lesions were included. The median estimated AD in the first cycle was 50 Gy. A strong and significant correlation between AD and % reduction in tumor lesion diameter, for lesions > 4 cm in diameter, was observed. The correlation was still significant, although less pronounced, in lesions 2.2-4 cm in diameter. Despite this clear correlation, the authors did not make a recommendation regarding the target tumor dose to use in treatment planning (118). In the analysis of SI-NETs, 25 patients and tumor lesions were included. Here, the authors chose to look at % reduction in tumor volume in response to AD but found no correlation at all despite seeing a mean reduction in tumor volume of 30% and reaching a mean cumulative AD of >150 Gy (119). An interesting observation in this analysis was the time to best response, which was more than one year for 60% of the patients.

Background summary

So, after this introduction into the challenges of tailoring ^{177}Lu-PRRT of NETs, and before we look at the contents of the papers included in this thesis, what are we left with? What is the state of the art at this point in time? It can be summarized in the following bullet points:

- We have the possibility of being able to image and quantify the distribution of the drug in the patient, but have so far not been able to translate this into a clear clinical benefit for the patients
    - We do not know what tumor AD we should target
    - We do not know the BED limit for toxicity for the kidneys, which is *presumably* the dose-limiting organ
    - An accurate, standardizable dosimetric method has not been established
    - Dosimetry-based therapy has not proven, nor quantified, its worth vs standard therapy
- The use of molecular diagnostics in improving treatment outcomes has not reached regulatory or wide, clinical approval
- The possibility of personalizing therapy further by combination treatments, dual imaging, etc. also needs to prove, and quantify, its worth vs standard therapy.

Aims

"The goal in life is not to be perfect, but to become progressively less stupid"

Marshall B. Rosenberg (1934-2015)

The overall aim of this thesis is to contribute to bridging some of the many gaps that exist on the PRRT map that impede a truly tailored treatment. To this end, we designed two clinical trials – Gapetto and Iluminet – that have now been finalized in terms of inclusion of patients and follow-up. The primary objective of the Gapetto trial has been analysed already, and results published in paper IV, while the secondary and explorative objectives are still under study. The Iluminet trial just terminated follow-up in November 2019 and is pending final analysis. Results of the interim analysis and two exploratory analyses are described in papers I-III. The synopses for both trials can be found in Appendix 1 and 2.

Iluminet

At the time of designing the Iluminet trial, it was already considered standard treatment in ^{177}Lu-PRRT to give 4 cycles á 7.4 GBq. A large cohort from Rotterdam had recently been published documenting its safety and efficacy in a non-randomized setting (16). The publication by Bodei et al was also quite recent, were the BED-limits to the kidneys were estimated to be 28 Gy and 40 Gy, depending on the co-existence or not of risk factors for nephropathy (110). Our own group had already been doing post-therapeutic imaging and dosimetry for some years and realized that most patients do not reach these limits with 4 cycles of treatment (120).

The primary objective of the Iluminet trial was therefore to prospectively study the safety and efficacy of a fully dosimetry-based treatment with ^{177}Lu-DOTATATE. As part of this effort, we would also explore the limits proposed by Bodei et al from ^{90}Y-PRRT and their relevance for ^{177}Lu-DOTATATE. **Secondary objectives** included analysing differences in outcome between patients receiving treatment in Step 1 vs Step 2 (see below in "Methods"), as well as quality of life. We included **exploratory objectives** to investigate the possibility of simplifying the dosimetric method without

compromising accuracy, of developing a novel bone marrow dosimetry method and of specifically studying the dosimetric impact of metastable lutetium. Some of these results are the subject of this thesis, while others have been published separately and are included in the list of "Related Papers" on p.15.

Specifically,

- In Paper I the aim was to study the impact of dosimetry on treatment planning, and to analyse whether there were any signs of kidney toxicity in the first 51 included patients. The background to this, initially unplanned, interim analysis was that the trial was originally designed to include 60 patients. In 2015, however, it was amended to include 100 patients. As we did so, we also decided to perform an interim safety analysis to ensure that there were no unexpectedly high levels of renal toxicity.
- Paper II addresses the exploratory objective of developing a simplified dosimetry method. For dosimetry to be become common practice it needs to not only prove its worth, but also be feasible in a clinical setting, i.e. with less resources on a daily basis than what is the case in a research setting.
- Paper III aims to provide an in-depth analysis on one of the safety aspects, namely the pituitary function when giving dosimetry-based ^{177}Lu-DOTATATE-therapy to the patients, and consequently higher ADs to this gland than is the case in standard therapy.

Gapetto

Based on the assumption that long-acting SSAs can competitively inhibit the binding of ^{68}Ga- and ^{177}Lu-DOTATATE to the SSTR, it is recommended in most PRRT guidelines that SSA treatment be withheld at least 4 weeks prior to ^{177}Lu-DOTATATE treatment. This recommendation seems logical enough, but is not evidence-based. In fact, the little evidence there was at the time of designing the trial seemed to indicate the contrary (121). As we set up the new SSTR-PET method with ^{68}Ga-DOTATATE at our hospital, we therefore decided to prospectively study this phenomenon in a real-world context.

The primary objective of the Gapetto trial, the results of which were published in paper IV, was to describe how the use of SSA affects the uptake of ^{68}Ga-DOTATATE in PET/CT in patients with NET in two specific situations:

- In patients who were *not* on SSA when the first PET was performed, who then initiate SSA-treatment and have another PET performed after that.
- In patients who are on a stable dose of long-acting SSA, study if the uptake is affected by the interval between last SSA-dose and PET-imaging.

Secondary objectives were included to incorporate information from the PET-studies to inform patient selection and treatment planning with ^{177}Lu-DOTATATE, thereby connecting data from Gapetto with data from Iluminet. The **exploratory objectives** were included to systematically optimize imaging parameters.

Patients and Methods

Both the Iluminet and the Gapetto trial were prospective clinical trials that included patients with NETs. Iluminet was a phase II, non-randomized, multicenter trial while Gapetto was a single-center, single-arm, observational study. In this chapter an overview of the methodology used in the two trials is presented, with further details to be found in the corresponding papers.

Iluminet

Patients

The main **inclusion criteria** were:

- Histologically confirmed, advanced or metastatic G1-G2 NET with a high SSTR-expression as evaluated by octreotide scintigraphy (Krenning scale grade 3-4)
- Radiological progression in the last 14 months, and measurable disease according to RECIST 1.1
- Normal bone marrow and liver function, and a renal function with a measured GFR > 50 ml/min
- In patients in treatment with long-acting SSA, the dose must have been stable for at least 3 months prior to inclusion

The main **exclusion criteria** were:

- Performance status ECOG 3-4
- Extensive liver metastases
- Concomitant antitumor treatment other than SSA
- Synchronous metastatic non-NET cancer
- Pregnancy or lactation

Methods

Trial design

Eligible patients were offered dosimetry-based treatment with ^{177}Lu-DOTATATE, meaning that they received 7.4 GBq in each cycle, but the number of cycles was adjusted to a **target renal BED** of 27±2 Gy (step 1) or 40±2 Gy (step 2). Treatment cycles were given at intervals of 8±2 weeks. Patients with risk factors for nephropathy or hematological toxicity were not permitted to continue treatment in step 2, nor were patients who had experienced significant toxicity or progressive disease during step 1. **Risk factors** were defined as: age > 70 years, previous chemotherapy and/or liver embolization, longstanding diabetes or uncontrolled hypertension. Treatment continued until reaching the BED-limits, or interrupted prematurely in case of disease progression, treatment-limiting toxicity, deterioration of clinical status or patient/investigator decision.

The trial design is depicted in Fig 5. Patient inclusion was performed at two Swedish university hospitals. During the course of the trial, two minor amendments and one major amendment were implemented. The latter was the increase in number of patients from 60 to 100, and the minor amendments added the exploratory objectives to the trial and introduced clarifications in study procedures.

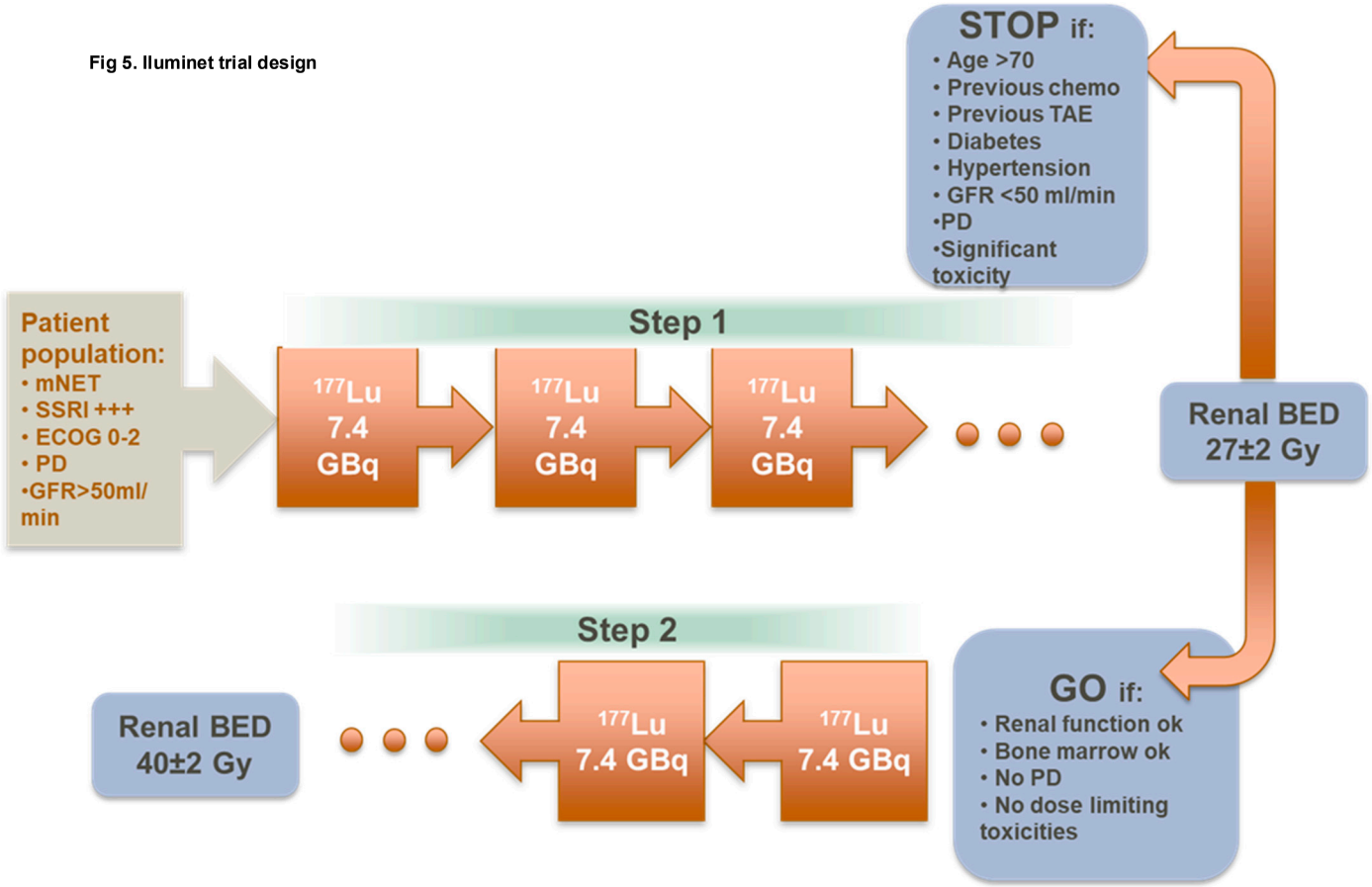
Dosimetric evaluations

Post-therapeutic imaging was the basis for the dosimetric calculations, as described in the section “Internal Dosimetry”. Four whole-body planar images were taken of the patient on day 0 (treatment day), day 1, day 2 *or* 4, and day 7. The second time point varied depending on the weekday on which treatment was given, which differed between the two participating sites. Additionally, a SPECT/CT was performed on day 1, as well as a whole-body X-ray scout image used for attenuation correction. Full dosimetry was performed in all patients and in every treatment cycle. Further details on the dosimetry method can be found in paper II

Efficacy evaluations

Anti-tumor effect was evaluated radiologically according to RECIST 1.1 criteria. CT-scans were performed every three months during treatment and the first year of follow-up, and every six months thereafter. Follow-up continued until progression or death. Tumor markers specific to each tumor subtype were followed with the same intervals as the radiologic evaluations.

Fig 5. Iluminet trial design



Safety/Toxicity evaluations

Toxicity was graded according to CTCAE criteria. Analysis of hematologic, renal and hepatic laboratory parameters were performed at baseline, before each new cycle of treatment, every three months during the first year of follow-up and every six months thereafter. A complete blood count was also performed at least twice between cycles to detect possible treatment-emergent toxicity. Pituitary function was evaluated at baseline and on a yearly basis thereafter for as long as the patient was in active follow-up. Each patient´s **GFR** was measured (mGFR) at baseline and annually thereafter during treatment and follow-up, and additionally according to investigator criteria. It was determined using iohexol or ^{51}Cr-EDTA clearance. In parallel, an estimated value (eGFR, based on plasma creatinine and the MDRD formula) was calculated from the plasma-creatinine values. Any unexpected, clinically significant changes in eGFR prompted a confirmation by mGFR.

Safety analysis (Papers I and III)

In the interim analysis presented in Paper I, changes in renal function were analyzed as the development of the median mGFR over time and as the mean annual change in GFR (ΔGFR). This latter value was estimated for each patient using linear regression of eGFR versus time and dividing the obtained slope by the initial mGFR value. By so doing, we combined the strength of frequent eGFR values, and their information regarding change over time, with the superior accuracy of mGFR in determining the value of the GFR. The annual change in GFR was then used to try to identify a subpopulation of patients that may be at greater risk for renal function loss by pair-wise comparisons between initial mGFR/risk factors/renal BED with the ΔGFR.

Paper III presents the results of the analysis of changes in pituitary function during treatment and follow-up. This was analyzed using a linear mixed model, which allowed for analysis of the complete data set despite variations in number of follow-up values in different patients. This model also takes into account the dependency of repeated measurements in the same patient. Results were also presented graphically using boxplots.

Simplified dosimetry (Paper II)

The patient base for this analysis was the same as for paper I. Using the complete image data set for the EOT_{dose} group (see Fig 6) as a starting point, we defined 9 different alternative dosimetry schemes by eliminating one or several imaging time points from the complete set. The AD was then calculated using the data available from the reduced data set of each alternative scheme and the result compared with the full dosimetry scheme used in the clinical trial. The results were analysed using Bland-Altman plots, which plots the difference between the alternative method and the reference method vs the mean of the two methods.

Bland-Altman plots are commonly used to analyse the agreement between two different methods of measurement. Its advantage vs a correlation analysis is that it will inform of the existence (or not) of a consistent bias between the two methods in a way that is not possible to detect by correlation. Said more plainly, if one method consistently gives values that are 20% lower than the other, the correlation between the two will be high, but the agreement between the two will be low. In a Bland-Altman plot this will show by the line of mean difference not being equal to zero. The limits of agreement in the plot will also inform of how widely the differences of the two measurement methods are spread. Although this information is merely descriptive and says nothing of statistical significance, we can interpret the limits of agreement in relation to what would be an acceptable difference/error in a clinical setting. For the purposes of the present analysis, we decided that an acceptable difference between the simplified dosimetry vs full dosimetry, is one that does not lead to a different number of treatment cycles, despite there being numerical differences in the dosimetric values.

Gapetto

Patients

As the intention was to include "real-world" patients, inclusion and exclusion criteria were wide. Patients came from the departments of oncology and surgery at Skåne University Hospital.

The **inclusion criteria** were:

- Age ≥ 18 years
- Fulfills at least one of the following criteria for imaging with ^{68}Ga-DOTATATE PET/CT:
    - Follow-up of a previously diagnosed, histologically verified, NET with ongoing SSA treatment
    - Under diagnostic work-up for suspected NET and expected to initiate SSA-treatment within the coming year.

The only **exclusion criterium** was pregnancy or lactation.

Methods

After inclusion, patients were programmed for their first ^{68}Ga-DOTATATE PET/CT. On the day of imaging they were asked if they were on SSA treatment, and if so, for the date of the last injection. This was repeated before each of the subsequent ^{68}Ga-DOTATATE PET/CTs as well. There was no stipulated interval between PETs in the protocol, as this was an observational study.

Images were analysed by nuclear medicine physicians specialized in PET-imaging. SUVmax values for normal liver and the five hottest tumor lesions were collected. As the CT was done with diagnostic quality, including intravenous and oral contrast, the clinical report from each PET/CT study was informed both regarding PET-results and radiological (CT) results. When the patient was seen by the referring physician again, after the PET/CT, the disease status of the patient was reported as either stable, progressive or regressive based only on clinical, biochemical and morphological data.

For analysis of the primary endpoint the SUVmax and T/N ratios (ratio of uptake between tumor and normal liver) were compared,

1. before and after initiation of SSA
2. according to the time interval from last injection to PET

An ad hoc analysis was added to look at possible changes in the SUVmax in patients with progressive/stable/regressive disease. Median changes in SUVmax were compared for each of the three groups.

Results

"In God we trust, all others must have data."

Bernhard Fisher (1918-2019)

This is an overview of the key results from the four papers included in this thesis. For a more detailed presentation, please refer to the respective paper.

Iluminet

103 patients were included in the trial between 2011 and 2018. At the time of the interim analysis, on which papers I and II are based, 51 patients had been included, of which 41 had completed treatment or terminated for other reasons. Figure 6 shows patient disposition at the time of the interim analysis.

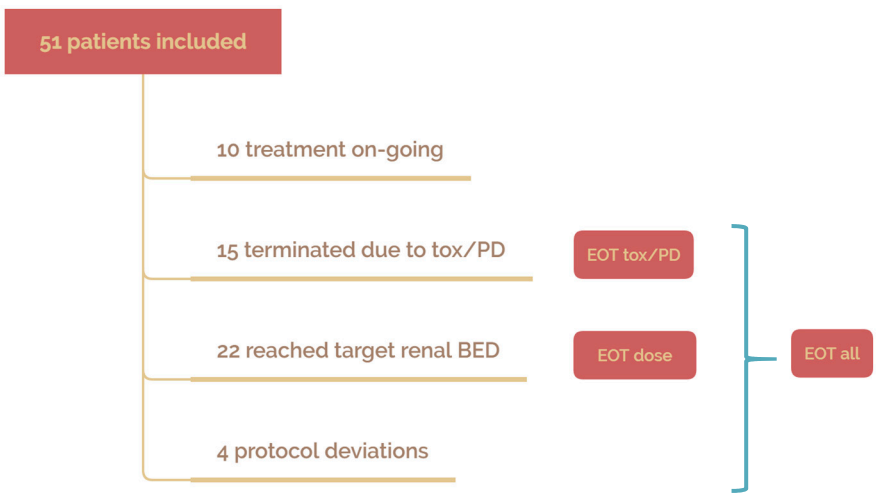


Fig 6. Patient disposition at interim analysis, including the subgroup terminology used in Paper I. EOT: end of treatment.

The following are the key results from **Paper I**:

- There was a large variability in the number of treatment cycles that could be given within the protocol-specified BED limits: 3-7 cycles in Step 1, and 5-8 cycles in Step 2 (see Fig 7).
- There was also a large variability in the renal BED/cycle within each patient (see Fig 7).
- More than two-thirds of the patients could receive more than the standard four cycles.
- No cases of grade 3-4 renal toxicity had occurred among the 41 patients who had terminated treatment at the time of analysis, after a median follow-up of 24 months.
- There was a mean annual GFR-loss of 4.3 mL/min/1.73m^2, with no difference observed when grouped according to initial mGFR, risk factors or cumulative renal BED.

Paper II is based on the same patient material as paper I, but investigates a completely different aspect, namely how we may best simplify the dosimetry protocol (i.e. number of imaging time-points and type of imaging – planar, SPECT or both) in order to make it more doable in everyday clinical practice. The results speak clearly:

- Standard, one-size-fits-all, treatment leads to the greatest variations in cumulative renal BED
- SPECT-based dosimetry is more accurate than planar dosimetry
- Doing dosimetry in the first cycle only, be it planar or SPECT-based, and assuming that the BED will remain constant in the following cycles does not give reliable results
- SPECT-imaging at one time-point in each cycle, preferably at 96 hours post-treatment, yields results that are very close to the full hybrid dosimetry used in the trial.

The first two points really just confirm what we already knew, the third confirms what we already suspected, but the fourth point is the key to being able to make dosimetry more widely available. More about this in the discussion further on.

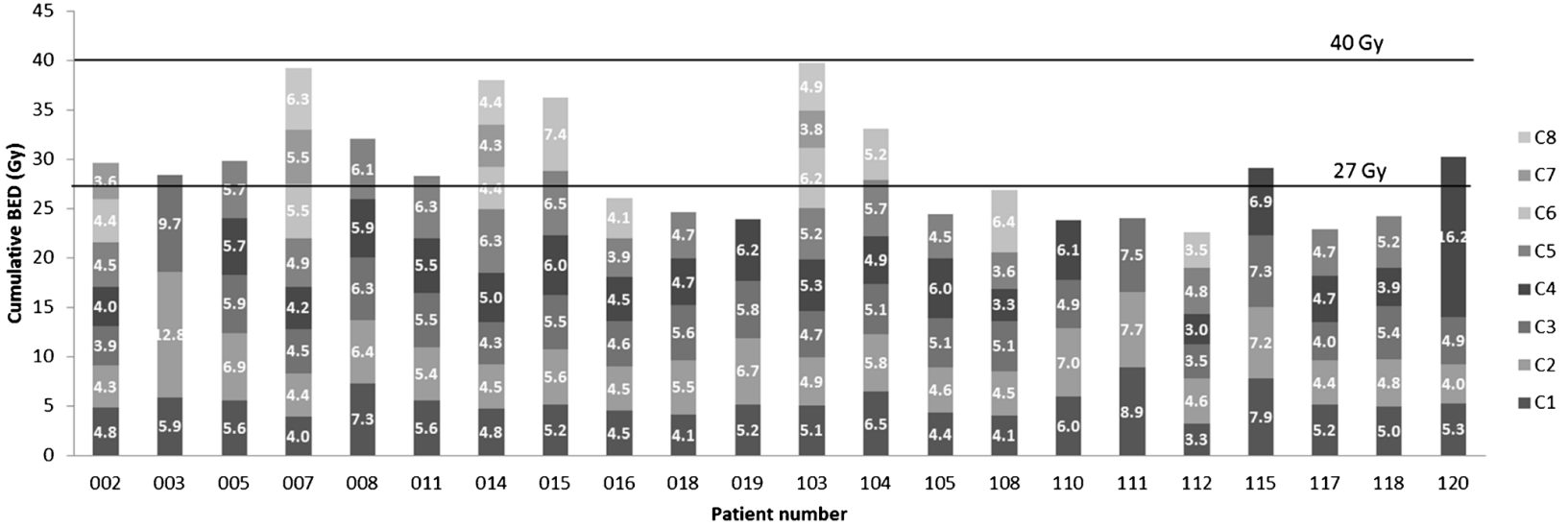


Fig 7. Graphical illustration of the patient-specific dosimetric results of the EOT_{dose} population illustrating the large inter- and intraindividual variations in renal BED. From paper I.

In **Paper III** the results from an analysis of changes in pituitary function are presented. At the time of this analysis, all 103 patients had been included in the trial, however only 68 were evaluable for analysis of pituitary function, as described in Figure 8.

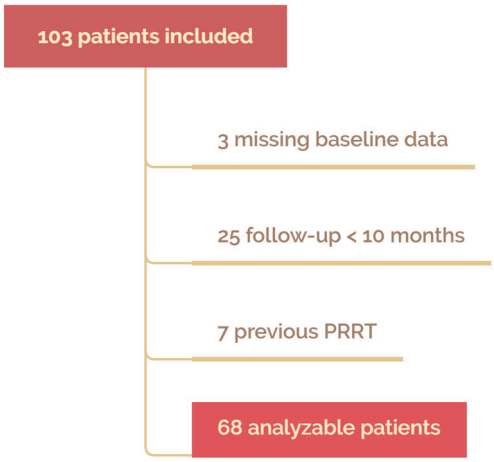


Fig 8. Patient disposition in Paper III

Median follow-up for the 68 patients was 30 months, with a range of 11-89 months. Similar to the interim analysis, the median number of treatment cycles was 5 (3-9) and 69% of the patients had received more than four treatment cycles.

Since the included patients came from all parts of south-western Sweden, laboratory values came from different laboratories with different methods of analysis and thereby different reference intervals. The numerical results of the hormonal levels were therefore not always directly comparable. By normalizing them to the baseline value, we could analyze the % change from baseline.

The key results from paper III were:

- There was a statistically significant and progressive decrease in IGF1-levels (N=65) reflected both in mixed model analysis and boxplot.
- There was a decrease in the median values in the boxplots of LH and FSH in post-menopausal women (N=20) and testosterone/SHBG-ratio (but not testosterone) for men. These changes were, however, non-significant in the mixed model analysis.
- There were no significant changes in thyroid nor adrenal functions in either of the analyses.

Gapetto

296 patients were enrolled between 2013-2016, and 530 ^{68}Ga-DOTATATE PET/CTs performed. Of these, 262 patients had 495 PETs performed with complete data. Due to a large amount of missing or incomplete clinical data, and the specific requirements for each analysis, the evaluable populations for each analysis were, however, much smaller.

The key results from the analyses were as follows:

- Initiation of SSA-treatment did not change the uptake of ^{68}Ga-DOTATATE in tumor tissue, but it reduced uptake in normal liver, the result being an increase in tumor-to-liver ratio. (N=19)
- The length of the interval since last SSA injection was not found to affect the degree of ^{68}Ga-DOTATATE uptake neither in tumors nor in normal liver. (N=37)
- The ad hoc analysis of how disease progression or regression affects the degree of ^{68}Ga-DOTATATE uptake suggests that progression leads to an increased uptake while regression reduces uptake. (N=41)

Discussion

"Better a diamond with a flaw than a pebble without."

Confucius (551-479 BC)

Iluminet

In times of limited resources in patient care, it is understandable that the need for dosimetry is questioned, given the many and fundamental missing data that we struggle with at this point (see "Background Summary"). Nevertheless, it does not seem scientifically reasonable to doubt that a dose-response relationship exists for tumors and normal organs in ^{177}Lu-PRRT, as there is in EBRT and ^{90}Y-PRRT, although we haven´t been able to define it quantitatively yet. If we accept the probability of the existence of a dose-response relationship, we should also accept the need for dosimetry in order to optimize treatment for each patient. It is not the only way, but it is one way. For this to become an acceptable and common practice, we need to define a minimum standard for how it is best done.

So how should dosimetry be performed? Paper I and II both illustrate one important point in answering this question, although from different angles. From paper I we learn that there is great inter- and intra-patient variability in the BED/cycle and thereby in the number of cycles each patient may receive. This leads to the conclusion that if dosimetry is performed, it needs to be done in every cycle. This is further strengthened by the results from paper II where all the alternative treatment strategies that omitted dosimetry in each cycle (methods A, B, D and H in Fig 3 and Table 3 of the article) suffer from a significant degree of inaccuracy in the dosimetric estimations. The same holds true for the planar methods, even when applied in each cycle.

If dosimetry needs to be SPECT-based and be done in every cycle, how many imaging time points do we need per cycle? In 2018, as paper II was being prepared for submission, Hänscheid et al published a very elegant answer to this question (122). Based on mathematical deduction they postulated that if imaging is done at just one time-point post-therapy, and that time-point falls between 75% and 250% of the effective half-life for the radiopharmaceutical, the AD can be estimated with

good accuracy. The optimal time-point was proposed to be 96 hours after treatment. They tested this in a sample of 29 patients, with planar dosimetry, and found high correlations between deduced and actual activity uptake just as postulated.

With these results at hand, we tried Hänscheid´s approach in our own patient material and found a near perfect agreement between single time-point SPECT at 96 hours and the full dosimetry performed in the trial. From a logistical point of view, it would have been desirable to be able to perform a single SPECT at 24 hours (before the patient is released from hospital after treatment), but this did not give as high a level of agreement as the 96 hour time-point. We are not the only ones looking to simplify dosimetry – Del Prete (123) et al and Willowson et al (124) have used similar approaches to ours, to test the validity of single time-point imaging as a basis for dosimetry, with similar results: Single time-point imaging gave acceptable results even at 24 or 72 hours according to these authors. Multiple time-point imaging gave slightly better results, while eliminating dosimetry in subsequent cycles led to the greatest errors.

If that has taken us a step further towards finding a standardized way of doing dosimetry, we are still at a loss regarding what the limits in terms of BED to organs at risk (OARs) should be. At the first analysis of renal function in the Iluminet trial, presented in paper I, we could not contribute further to answering this question for the simple reason that we have "failed" to cause sufficient toxicity to be able to analyze a dose-response relationship. It may be that in the final analysis, with more patients and longer follow-up, such a relationship can be discerned. It seems more likely, however, that we are still not going high enough in renal BED to cause significant toxicity.

Could it be that the pituitary gland, not the kidneys, is actually the dose-limiting organ? The results from paper III gives some support for this idea, although the answer is far from definitive. Ongoing dosimetric analyses may bring further light to the question. Even if the indications of a possible radiation-induced pituitary dysfunction were true, the clinical consequences of a relative GH- or gonadotropin-deficiency are probably negligible in patients that in the vast majority of cases are above 65 years of age and have a limited life expectancy due to the tumor. A detectable radiation-induced toxicity would therefore not necessarily be treatment limiting. It is likely, though, that the indications for PRRT develop in the coming years and that we will see more of re-treatment and perhaps also neoadjuvant or adjuvant treatment. In such situations, pituitary toxicity may be more relevant, given the higher cumulative AD and/or longer life expectancy of the patients. There have also been attempts at using α-emitters for PRRT (125). In such a situation, the distinct pituitary uptake may also be reason for special consideration.

Despite the intrinsic differences between RNT and EBRT – dose rate, fractionation and dose distribution – it cannot be denied that RNT is a type of radiotherapy. The question is to what extent we can extrapolate learnings from EBRT to RNT when looking for ways to individualize treatment planning for the latter in a manner similar to what has been done for decades with the former. Through the LQ model we understand that different ADs/cycle and fractionation schemes affect the total BED, for a tissue with a given α/β and repair half-life, as exemplified in the chapter on Internal Dosimetry. The BED formula for RNT also takes into account the effective half-life of the radiopharmaceutical and the tissue repair capacity, which in the case of RNT occurs simultaneously with radiation delivery (126).

Fractionation is seldom discussed in PRRT and when it is, it usually refers to dividing the injected activity (IA) in multiple fractions without directly considering the AD. Although there will of course be a relationship between IA and AD, it is not linear since the AD will be affected by the pharmacokinetics and biodistribution as well. So far, focus has been on the total AD or BED when analyzing the risk for toxicity in PRRT, e.g. renal dysfunction. The AD/cycle and its effect on toxicity was briefly touched upon by Bodei and Barone (108, 110) who both observed that the patients who had received the highest AD/cycle were those who also suffered from more pronounced renal toxicity. On the other hand, it may be beneficial from a tumor control perspective to be able to increase the IA in order to increase the AD to tumor. To find the right balance, it would be of interest to determine the IA that gives the optimum ratio between tumor AD and AD to OARs. It may also be necessary to determine whether there is a limit in AD/cycle for the OARs (kidneys and bone marrow) that needs to be respected.

By increasing the IA, we can increase the AD/fraction (i.e. AD/cycle) to both tumor and normal organs. For this to have a differential effect between tumor and normal tissue, the α/β and/or the AD/cycle must differ between the two. Is that the case for NET and PRRT? The AD/cycle is usually considerably higher in tumor than kidney, which in itself leads to a higher BED due to the quadratic component of the BED formula. When it comes to the α/β for NET tissue, we do not know its value. Since NETs are only “cancer-like”, i.e. also “normal-tissue-like”, it is possible that the α/β is closer to 3 than to 10 (the typical values used for normal and tumor tissue in EBRT), as seems to be the case for melanoma, sarcoma and prostate cancer (127).

In EBRT, treatment planning focuses on the tumor AD necessary to achieve a high probability of tumor control, within the limits mandated by the dose constraints of the OARs, rather than going to the maximum tolerated dose to the OARs as has been the approach in dosimetry-based PRRT so far. Optimal dosimetry-based treatment planning of PRRT would require determining what the target AD to the tumor should be, how to estimate the IA which that corresponds to, and what renal

and bone marrow BED it would result in. The conditions that need to be met in order to define the tumor AD that corresponds to a high likelihood of response should be similar to the ones that we defined for dose-response in toxicity:

1. an accurate and relevant measure of response, and
2. an accurate and relevant measure of the AD

Which then, is the relevant measure of response? Is tumor shrinkage the best way to define the desired treatment effect? Or is it time to progression? Or duration of response? It may differ between different types of NET. Once we have been able to define the target AD to tumor, and we know the maximum total BED to risk organs, we can adjust the injected activities accordingly, patient-by-patient, treatment-by-treatment. Planning treatment this way would spare potential toxicity in patients in whom the tumor AD can be achieved without going all the way to the maximum BED to the OARs. It would also enable us to identify patients in whom we will not be able to reach the target AD to tumor within the OAR dose constraints, thereby avoiding suboptimal treatment.

The second point, an accurate and relevant measure of the AD, refers to whether or not we need to use BED for tumor tissue as well as for OARs. Normally, tumors are considered not to have the same repair capacity as normal organs and therefore are less sensitive to fractionation effects. This makes BED to tumor a less relevant measure, unless the idea about NETs being "normal-like", as discussed in the introduction, includes a capacity for repair in which case we may need to use BED when analyzing dose-response.

So rather than just pushing the toxicity limits, I believe our efforts may be better spent trying to identify the optimum AD to tumor to be able to produce as high a response-rate as reasonably achievable. We just created the concept of AHARA – as high as reasonably achievable – which is what should guide us when it comes to cancer treatment. The reigning principle in nuclear medicine otherwise – ALARA, as low as reasonably achievable – may have mislead us so far. We should not keep the administered activity as low as reasonably achievable, if by doing so we undertreat the patient. We talk about a 5% chance of renal dysfunction in 5 years' time while forgetting that our patients' primary concern is that they have at least a 50% chance of dying from their tumor in 5 years' time (32). As high a dose (AD) as reasonably achievable, is the dose that gives a sufficiently high likelihood of tumor response to outweigh the potential toxicity within a relevant time frame.

Gapetto

While we were designing, setting up and carrying out the Gapetto trial, there were several others testing the same idea in different ways (128-130). Unfortunately, all of the trials that have studied the effect of SSA-treatment on radiotracer uptake suffer from the same weakness – small sample size and/or being retrospective. Despite this, the combined strength of these studies, including Gapetto and two previously published ones (121, 131), lies in the complete agreement in the results. In all six, the conclusion is the same: treatment with "cold" SSA prior to injection of the radiolabeled SSA increases the tumor-to-normal ratio in the images (Table 5). For diagnostic imaging, this is relevant because it increases detectability of tumor deposits. Whether or not the increased tumor-to-normal ratio is also relevant in the therapeutic setting has not yet been tested but is likely similar. In consequence, the recommendation of suspending SSA 3-4 weeks prior to PRRT or PET should probably be reconsidered.

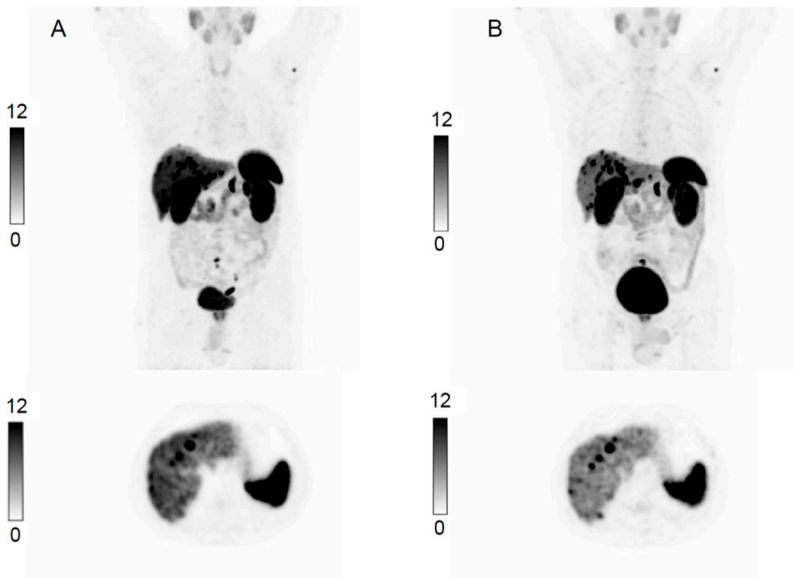


Fig 9. PET-images of a patient from the Gapetto trial before (A) and after (B) initiation of SSA-treatment, illustrating the change in tumor-to-normal ratio in the uptake of the radiotracer. From Paper IV.

The results from these studies seem to indicate that the SSTRs in normal tissues are saturated earlier than those of the tumor tissue. This phenomenon is well known in radioimmunotherapy (RIT), where radiolabeled, tumor-specific antibodies are used to achieve targeted, systemic radiotherapy. An injection of "cold" antibody before the therapeutic dose improves biodistribution and increases tumor uptake of the latter (132).

First author	# of patients	Retro- or Prospective	Variable(s) studied	Results/conclusions
Haug (121)	105	Retrospective	Compares median SUV_{max} and SUV_{mean} in tumors and normal organs, between a group of patients w/ SSA vs a group w/o SSA	Decreased uptake in liver and spleen, unchanged uptake in tumors, leading to an increased tumor-to-normal ratio
Velikyan (131)	6	Prospective	Intra-patient comparison of SUV in tumor and normal organs at 3 time points: w/o prior cold SSA, w/ low-dose SSA and with high-dose SSA	The highest tumor-to-normal ratio was achieved with pre-medication with a low dose (50µg octreotide)
Cherk (128)	21	Retrospective	Intra-patient comparison of SUV_{max} in tumor and normal organs before and after initiation of long-acting SSA therapy	Significant decrease of SUV_{max} in normal organs and increase in tumor, leading to an increased tumor-to-normal ratio after SSA initiation
Ayati (129)	30	Retrospective	Intra-patient comparison of SUV_{max} and SUV_{mean} in tumor and normal organs before and after initiation of long-acting SSA therapy	Significant decrease of SUV_{max} in normal organs and not in tumors, leading to an increased tumor-to-normal ratio after SSA initiation
Aalbersberg (130)	31	Prospective	Intra-patient comparison of SUV_{max} and SUV_{mean} in tumor and normal organs 1 day before and 1 day after injection of long-acting SSA	Significant decrease of SUV_{max} and SUV_{mean} in normal organs but not in tumors, leading to an increased tumor-to-normal ratio after SSA injection

Table 5. Summary of other clinical studies looking at the effect of cold SSA on the uptake of 68Ga-DOTATATE in tumor and normal tissues.

Strengths and limitations

The two clinical trials on which this thesis is based have one basic strength in common and that is that they were carried out. Although small, retrospective series are excellent as an approximation to a clinical query and to better define hypotheses for prospective trials, they are not high-level evidence to guide clinical decision-making. As an oncologist working in the field of therapeutic nuclear medicine, the difference between the two fields in this respect is striking. There seem to be few centers that are willing and able to carry out prospective, academic clinical trials in nuclear medicine, and even fewer that are able to do it as a collaborative effort with two or more centers. Nevertheless, it is necessary in order to systematically and definitively move the field forward in ways that do not necessarily follow the strategies of the involved pharmaceutical companies.

It is understandable, however, that a nuclear medicine unit which primarily deals with diagnostics will not have the type of Clinical Research Unit common to virtually all university hospital oncology departments. This was, in fact, the problem we found when first setting up the Gapetto trial. The solution was found in collaboration – from oncology we were eager to get access to ^{68}Ga-DOTATATE PET and able to run a clinical trial, and from our nuclear medicine department they were willing to set the method up but were not able to run a prospective clinical trial. Through collaboration we could meet our common goals. The same holds true for the Iluminet trial – the collaboration between two medium-sized university hospitals made it possible to carry out the trial in a reasonable amount of time. The differences in opinions, routines, dosimetry protocols, cameras, etc were challenging to bridge, but well worth it in the end.

That said, both trials suffer from limitations as well. The most obvious one regarding the Gapetto trial is probably the choice of design. If our sole purpose had been to systematically look at how initiation of SSA affected radiotracer uptake, we would have chosen a design similar to what was done by Aalbersberg et al (130). They performed a ^{68}Ga-DOTATATE PET/CT 1 day prior to, and 1 day after, the planned injection of the long-acting SSA. It is a well-designed, prospective clinical trial that answers one specific question. In our case, however, we also wanted to look at some other aspects such as how the interval from SSA-injection affects radiotracer uptake and factors relating to ^{177}Lu-PRRT. Since we were also using the trial to set up a new PET-method, we needed to perform image optimization studies as well. Instead of running separate small trials for all of these, or not running a trial at all, we decided to try the observational approach. As an unplanned spin-off effect, we also created a useful database for a sizeable cohort of NET-patients at our site under a three-year period. What we did not foresee when choosing this design, however, was the risk of incomplete data due to the uncontrolled conditions in which a real-world observational trial, per definition, is carried out. When you don't control

treatments, PET-intervals, etc and then want to analyze a specific effect in a specific group of patients, numbers are quickly reduced. The academic context adds to that in the sense that we are sometimes expected to do research with our left hand while taking care of the patients with our right hand, and not everybody is ambidextrous. This increases the risk of missing data, further hampering the scientific value.

At the level of the different substudies of Iluminet, a similar problem is found. The size of any trial population is dictated by the primary objective. When we start looking at secondary and exploratory objectives, or subpopulations within the trial, the numbers rarely permit anything other than generation of hypotheses or finding trends. That does not mean that these analyses are useless – they may be the only evidence there is on the subject – but it is important to understand the limitations of the data and not draw conclusions that go beyond them.

Conclusions

The aims of this thesis were stated as "…to contribute to bridging some of the many gaps that exist on the PRRT map that impede a truly tailored treatment." How far have we really come in bridging the gaps, and which gaps have been bridged? From the analyses conducted so far on the Iluminet and Gapetto trials, we can conclude the following:

- Dosimetry-based PRRT is feasible, and individualizing treatment based on just one factor, namely the renal BED, leads to large variations in the number of treatments each patient can receive.
- Giving four cycles of 7.4 GBq 177Lu-DOTATATE to all patients is rarely optimal from a dosimetric point of view. Most patients can receive more than four cycles.
- We saw no signs of clinically significant renal toxicity at short-term follow-up despite the relatively high renal BED-limits used in the trial.
- The imaging protocol on which post-therapeutic dosimetry is based, can be drastically simplified without sacrificing accuracy. This increases the feasibility of offering dosimetry-based PRRT in more NET-centers around the world.
- The pituitary gland is a potential risk-organ in PRRT, and one that has received little attention so far. Our analysis points to a possible radiation-induced toxicity, but even if confirmed it would be of little clinical consequence and would therefore not be considered treatment-limiting.
- Concomitant use of "cold" somatostatin analogs decreased the uptake of the radiolabeled analog in normal organs in SSTR-PET, but does not affect the uptake in tumor tissue. This increase in tumor-to-normal ratio may also have implications in the therapeutic setting, and puts into question the recommendation of withdrawing long-acting SSA 3-4 weeks prior to PRRT.

Summary and Future Perspectives

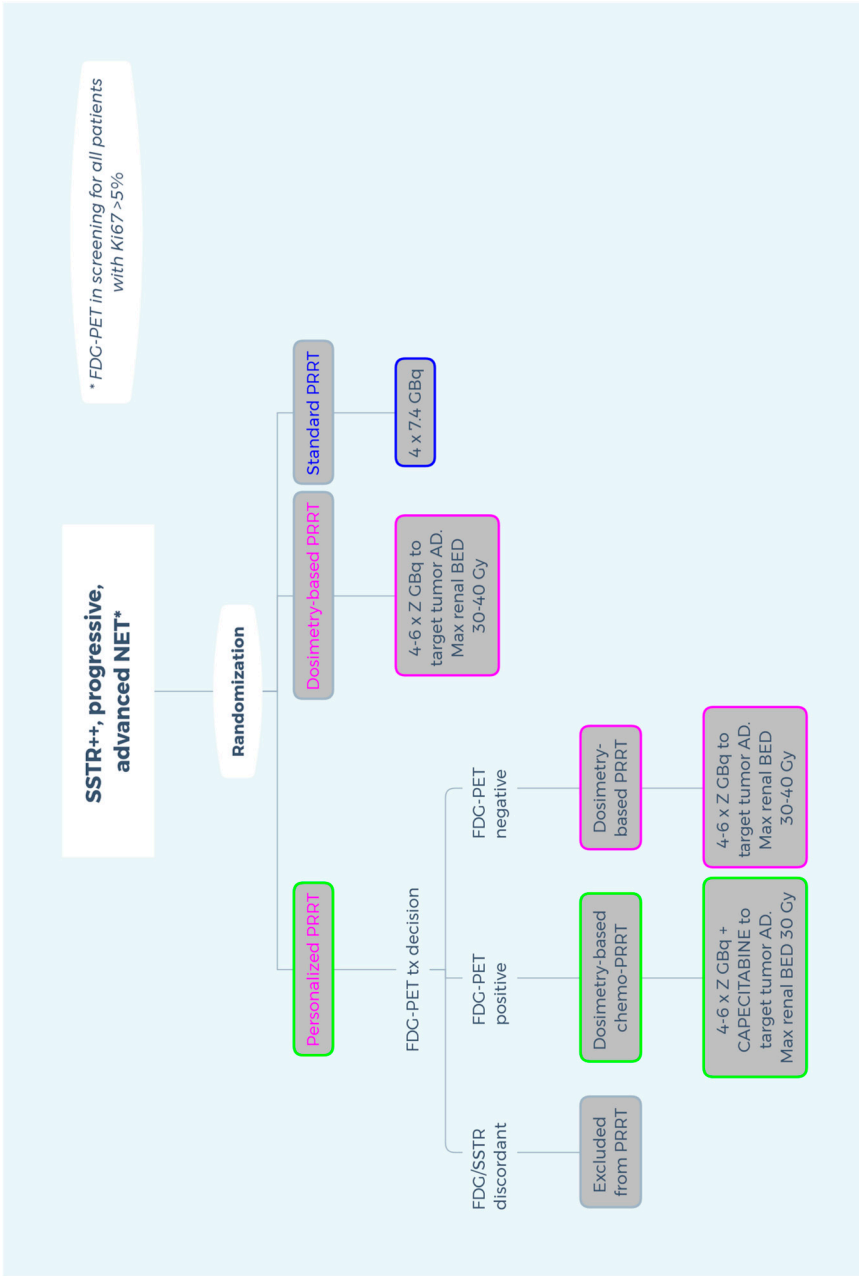
"Perplexity is the beginning of knowledge."

Kahlil Gibran (1883-1931)

Are we then still confused, just on a higher level? In a sense, yes. However, if we put together the different pieces of the puzzle contributed by different research groups in the field of RNT these past decades, it is fair to say that we have come a little further. In brief, the past seventy pages could be summarized as follows:

- Tailoring of radionuclide therapy can be done in several ways, or in a combination of ways, such as
    - Patient selection using dual imaging with FDG- and SSTR-PET
    - Molecular characterization with NETest®
    - Combination treatments
    - Image-based dosimetry
- Image-based dosimetry has several challenges that need to be addressed in order to be feasible in clinical practice
    - A standardized dosimetric method that is sufficiently simple yet reliable to be adopted on a wider scale
    - Defining the target dose to tumor
    - Defining the dose constraints to normal organs
    - Defining the best way to escalate the tumor dose without surpassing the dose restriction for normal organs
- Dosimetry-based PRRT needs to prove itself vs standard therapy
    - Is it better than standard therapy in terms of treatment efficacy and toxicity?
    - How much better?
    - Is the extra effort that it requires justified by its benefits?

As for future perspectives, further analyses of the Iluminet trial, together with the unconcerted but excellent efforts of many other research groups, will take us forward in the first two bullet points. To address the last one, I propose a randomized, international, multicenter trial with the following design:



Such a trial, if well designed and thought through, would give some clear answers to the questions under the last bullet point plus another few. Most of those questions were already posed by Pauwels et al in their review from 2005, based on the phase I trials with ^{90}Y-PRRT. We have not been able to answer the questions because we have not designed the right trials for it. Many have been working in their corner of the world, like ourselves, to solve some little part of the puzzle. Now we need to get together in a concerted effort. Such a trial would require collaboration across several sites and between nuclear medicine, oncology and physics among others. It would be challenging in many ways, but without it we may very well still be asking the same questions another 15 years from now.

Acknowledgements

There are so many people without whom neither this doctoral thesis in itself, nor the clinical trials on which it is based, would have seen the light of day. It is hard to know where to begin when acknowledging the contributions of so many.

As in any clinical research project, the first and foremost gratification goes to the **patients**, who with their trust, patience, time and willingness to participate are the sine qua non of the research.

The unrelenting support of my two supervisors on this journey – **Katarina Sjögreen-Gleisner** and **Jan Tennvall** – has been as fundamental for its completion as for its quality. Katarina's exemplary attention to detail, her self-critical and methodological way of working and her grit has been the perfect counterweight to my own not so well developed skills in those very areas. Jan, on the other hand, has been source of honest and constructive criticism in the realm of clinical research and management of NETs.

The Iluminet trial was a collaboration with the Sahlgrenska University Hospital, from where **Johanna Svensson** and **Peter Bernhardt** have been the perfect partners from the inception, through the design, implementation and still ongoing data collection and analysis.

Research nurses **Kajsa Holgersson** and **Charlotte Fogelström** have been with us from the start – seeing the patients, collecting the data – and continue to be instrumental in ensuring that the Iluminet data base is complete and correct, to the very end. **Anna Weddig** took on the challenge of the Gapetto trial, and ensured that data entry was as complete as could be. **Irene Schönström and Jan Sundberg**, research nurse colleagues at the Clinical Research Unit of Oncology (OKFE), have definitely gained their fair share of gratitude for all the help and support in clinical trial management and GCP over the years.

Anna Åkesson, my statistical lamppost that gives me both support and enlightenment. I was lost before I found you!

Both trials were carried out in the midst of the daily clinical routine, and with the help of the hospitals' resources and personnel. The whole incredible team at the unit for Endocrine Tumors and Radionuclide Therapy took care of the patients and the

imaging. They also make going to work every day not just worth the while, but a true pleasure. **Pernilla & Carl-Fredrik,** you have a *very* special place in my heart. **Nadja –** dosimetry would not have been the same without you! **Jennie, Sara, Sofia, Görel och Lovisa** – you keep me coming back for more!

Physicists from both the Hospital and the University have worked together in the different parts of the whole process from radiopharmaceutical preparation, administration, imaging and dosimetry. Without their professionalism, neither trial would have been possible. We have also worked side by side in data analysis, critical review and translation of research findings to clinical routine. I am truly grateful for the collaboration with **Cecilia Hindorf, Tomas Ohlson, Erik Larsson, Johan Gustafsson and Michael Ljungberg**, just to mention those who have been a part of this from start to finish.

The fantastic collaboration within the multidisciplinary endocrine tumor team in Lund, brings together the best of our different worlds. From the surgical department – **Erik Nordenström, Martin Almquist, Pall Hallgrimsson, Lo Hallin Thompson, Farhad Salem and Mark Their** – always as open to a friendly fight as to a cold beer or a new common research project. From Pathology – **Aleksandar Prazic** – unswerving in his detail and accuracy in the diagnostic process. The endocrinologists with whom an unusually tight and productive collaboration has grown over the years – especially **Stig Valdermarsson, Ola Lindgren and Mikael Lantz** – and from whom I have learned, and continue to learn, so much.

In the same context, my gratitude goes out to other infallible partners at other Departments of the hospital. **Elin Trägårdh, Helen Almquist, Eva Persson and Fredrik Hedeer** at Nuclear Medicine were active in all parts of the Gapetto trial and are always open to discussing my more or less well-developed ideas for new projects. **Anni Gålne**, radiology resident and PhD student who worked with great efficiency and dedication with the data analysis of the Gapetto trial. I look forward to future collaborations with all of you.

The role of the several Heads of Department of Oncology over the years, today represented by **Silke Engelholm** and Head of Radiotherapy **Kirsten Björnlinger**, in enabling this research has been fundamental.

Lastly, but at the same time first and foremost – my Ikigai, the ones that give my life meaning – **Juan, Paula and Oscar**. Juan, who stands steady through all my ups and downs and never hesitates to put the interests of his loved ones before his own. Generous, loyal, loving, strong and intelligent. Paula and Oscar, the most beautiful in the world! Always there for each other. Smart and wise. Words cannot express how much I love you. Around this nucleus in my existence, more love and support comes from my brother, **Peter**, and our parents **Gunnel** and **Björn**. Needless to say, without you I would not be who I am today. I love you all.

Appendix 1 - Synopsis Iluminet trial

Title	A multi-center phase II study evaluating the safety and efficacy of 177Lu-DOTATATE treatment based on kidney dosimetry in patients with disseminated neuroendocrine tumors
Hypothesis	By improved kidney dosimetry, including BED and taking into account potential risk factors (especially for kidney toxicity), it might be possible to give an optimal and personalized treatment with 177Lu-DOTATATE to the patient with metastatic neuroendocrine tumor.
Objectives	Primary objective • To study efficacy and safety of an optimally administered treatment with 177Lu-DOTATATE to a cumulative BED to the kidneys of 27 +/- 2 Gy. Secondary objectives • To study safety and efficacy of an optimally administered treatment with 177Lu-DOTATATE to a cumulative BED to the kidneys of 40 +/- 2 Gy in a selected group of patients without potential risk factors, and compare the results with those achieved after 27 +/- 2 Gy. • To make intra-individual comparisons of tumor response after 27 and 40 (+/- 2) Gy, respectively, in the group of patients who have received the higher dose. • To evaluate how the study treatment affects quality of life Exploratory objectives • To use the protocol-specific detailed dosimetric measurements to develop a model for simplified and individualized dosimetric calculations in order to be able to simplify treatment procedures in the future without compromising patient safety.

	• To investigate to what extent metastabile 177mLu contributes to the absorbed dose. • To study whether the uptake of 68Ga-DOTATATE in pre- and early post-therapeutic PET/CT is predictive of treatment response • To develop an image-based method of bone marrow dosimetry for the whole study population, based on a substudy of blood- and urinebased dosimetry in a limited number of patients
Endpoints	Primary endpoint • Objective tumor response 3 months after receiving a cumulative BED of 27 +/- 2 Gy (step 1) as defined by RECIST v1.1 Secondary endpoints • Objective tumor response 3 months after receiveing a cumulative BED of 40 +/- 2 Gy (step 2) as defined by RECIST v 1.1 • Tumor response after step 1, measured in millimeters • Tumor response after step 2, measured in millimeters • Progression-free survival for patients who have only participated in step 1 • Progression-free survival for patients who have participated in step 2 • Variations in chromogranin A levels during step 1 and step 2 • Toxicity (CTC v 4.0) during and after step 1 • Toxicity (CTC v 4.0) during and after step 2 • Evaluation of quality of life in terms of ECOG performance status • Overall survival for all patients, and for patients in step 1 and step 2, respectively • Changes in self-evaluated QoL from baseline to after step 1 using EORTC QLQ-C30 och EORTC QLQ-GI NET21.

	• Changes in self-evaluated QoL from step 1 to step 2 according to the same questionnaires. Exploratory endpoints • A mathematical dosimetric model, to predict absorbed kidney dose and BED, will be developed based on extra detailed post-therapeutic imaging in a subset of patients and on only one of their respective treatments. The endpoint is the validation of this model in the same patients' later treatments, and also other patients' treatments. • Evaluate an image-based bonemarrow dosimetry after performing a bloodsample-based dosimetry in a few patients • Measurements of wholebody radioactivity at specific timepoints before and after each treatment with 177-Lu-DOTATATE • Measurement of SUV and tumor:normal tissue uptake ratio in a pre- and post-treatment 68Ga-PET/CT during treatment cycle 1. • Determination of the activity concentration in blood and urine at several timepoints post-therapy, and comparing it to imagebased dosimetry of whole body scintigraphy
Inclusion criteria	Step 1 • ECOG 0-2 • Histologically verified neuroendocrine tumor with a Ki67 of ≤ 20% or ≤ 20 mitoses/10 high power fields. If the tissue on which this determination is based is several years old, the investigator should consider the option of acquiring a new determination, especially if the behaviour of the tumor has changed since diagnosis. • Metastatic disease where complete resection is not considered possible or feasible. • Measurable disease • Radiological disease progression during the last 14 months • The largest metastases should have an uptake of 111In-Octreotid that is greater than the uptake in the liver (Krenning grade 3) by planar scintigraphy. Metastases that

	are small, or located centrally, can be evaluated by SPECT to enable a correct estimation of the relative uptake. The majority of the tumor burden must demonstrate an increased uptake for lutetium-treatment to be considered. • Stable dose of somatostatin analogue for the past 3 months. • Estimated survival > 6 months • Neutrophil count >1,5 x 109/L • Platelet count >100 x 109/L • Normal liver function regarding transaminases, PK and albumin. A raised bilirubin which can be considered an isolated effect of liver metastases is not a contraindication as long as the levels remain <2.5 x ULN. • GFR > 50 ml/min • Signed written informed consent Step 2 • Continues to fulfill all of the inclusion criteria, and none of the exclusion criteria, from step 1 (with the exception of the inclusion criterion regarding progressive disease) • A maintained GFR (<40% decrease compared to baseline AND GFR>50 ml/min) • The treatments in step 1 have been administered with a maximal interval of 12 weeks • Age under 70 years • Patients who have received treatment with 177Lu-DOTA-TATE previously, outside the current study, may be considered for Step 2 as long as there are correct dosimetric data from the previous treatment and all inclusion and no exclusion criteria for Step 2 are fulfilled.
Exclusion criteria	Step 1 • Performance Status ECOG 3 & 4. • Proliferation index (Ki67) >20% or > 20 mitoses/hpf • Loco-regional treatment during the last 3 months involving all of the measurable lesions.

	• Chemotherapy during the last 3 months, or longer if persisting toxicity exists. Earlier treatment with mTORi or TKI is permitted. • Other concommittant nephrotoxic treatment • Modifications of the somatostatin analogue dose in the last 3 months • Serious heart disease • Previous radiotherapy including >25% of active bone marrow volume • Preganancy and lactation • Extensive liver metastases (>50% of liver volume) • Symptomatic CNS metastases requiring corticosteroid treatment • Ongoing treatment with interferon. This treatment should be suspended a minimum of 4 weeks before treatment with 177Lu-DOTATATE, or longer if there is persisting signs of toxicity • Patients who have a another metastatic tumor diagnosis Step 2 • Progressive disease since start of study treatment • Organ toxicity grade 3-4 during step 1 • Serious hematological toxicity during previous treatment cycles (ANC<0.5x109 or platelets <50.0) • Longstanding diabetes (>8 years). Patients with a well-controlled diabetes with a history of <8 years and a blood pressure <130/80 and no albuminuria (albumin/creatinine index) can be included. • Hypertension, i e >160/90 (for diabetics >130/80). Antihypertensive pharmacological treatment is permitted as long as there is no manifest albuminuria. • Previous liver embolization • Previous chemotherapy

Calculation of sample size	Supposing that, in accordance to previously published studies, one can expect an objective response rate between 20%-40%. Then the inclusion of 100 patients yields a 95% CI equal to the point estimate +/- 10%, which is considered as an acceptable uncertainty.
Study treatment and procedures	The patients included will receive 7.4 GBq 177Lu-DOTATATE as an intravenous infusion in 30 minutes, with each treatment cycle. This infusion is preceded by the administration of antiemetic drugs and kidney-sparing treatment with intravenous administration of amino acids, the latter of which continues during and after the administration of 177Lu-DOTATATE. This is a dose-escalation study, where the higher treatment dose (40 +/- 2Gy) is only offered to the patients who do not have any risk factors for significant kidney toxicity (ie hypertension, diabetes, kidney disease and old age). As further safety measures we will perform a very detailed kidney dosimetry and base the number of cycles on BED rather than on plain absorbed dose. The detailed kidney dosimetry is as follows: After each treatment cycle a careful calculation of absorbed dose is done, based on 4 whole-body scintigraphies under the first 7 days post-treatment, one whole-body scanogram and a combined CT/SPECT. From these examinations the absorbed kidney dose, and the BED, are calculated. The total number of treatment cycles that will be given to each patient will be based on BED-calculations, as recent publications indicate that this more accurately predicts kidney toxicity (Bodei, 2010). The treatment phase is divided in two steps. In step 1 all patients are offered treatment up to a BED of 27+/- 2 Gy. The treatment cycles are given at 8-12 week intervals. In step 2 those patients are selected that have received treatment in step 1 with no serious complications, and do not have any of the above mentioned risk factors for hematological or nephrological toxicity. This select group of patients will receive a BED och 40 +/- 2 Gy.

Appendix 2 - Synopsis Gapetto trial

Title	A prospective study of the use of ^{68}Ga-DOTATATE PET/CT in patients with neuroendocrine tumors
Hypothesis	^{68}Ga-DOTATATE PET/CT has a high sensitivity and specificity for imaging of somatostatin-receptor positive cells in neuronendocrine tumors (NET). Most NET-patients are treated with somatostatin analogs (SSA), which could potentially affect the outcome of the PET/CT image since both SSA and radiotracer bind to the same receptors.
Objectives	Primary objective • To describe how the use of SSA affects the uptake of ^{68}Ga-DOTATATE in PET/CT in patients with NET in the following situations: a) In patients during diagnostic work-up of suspected NET, who have not yet started treatment with SSA, but do so once the diagnosis is confirmed. b) In patients with ongoing SSA-treatment, study how the length of the interval between last dose of SSA and PET-scan affects uptake. Secondary objectives • To compare the uptake of 68Ga-DOTATATE in tumor vs normal liver (T/N) with the scintigraphic "Krenning index" and uptake of 177Lu-DOTATATE in post-therapeutic images to identify a PET-based predictive index. • In patients with metastatic NET receiving 177Lu-DOTATATE treatment, perform a ^{68}Ga-DOTATATE PET 4-6 weeks after first treatment to study the possibility of early prediction of treatment outcome. Exploratory objectives • Optimize imaging parameters and time from injection of ^{68}Ga-DOTATATE to PET-scan

	● To study the value of prolonged imaging time over the liver for patients with tumor lesions located close to the diaphragm ● To study the value of respiratory gating for patients with tumor lesions located close to the diaphragm
Endpoints	Primary endpoints Variation in uptake intensity of ^{68}Ga-DOTATATE, measured as SUV max and T/N index, in 1-5 target lesions a) For the patients who had not initiated SSA treatment at baseline PET-scan, but have had SSA-treatment for at least 3 months before the next PET-scan b) For the patients who had ongoing SSA at baseline the analysis will be done as a function of the number of days from last injection of SSA to PET-scan. Secondary endpoints ● Correlation between ^{68}Ga-DOTATATE T/N index and treatment outcomes after PRRT, compared to Krenning index. ● Correlation between change in uptake (SUV max and T/N index) of ^{68}Ga-DOTATATE in tumor lesions before and after PRRT treatment, and treatment outcomes. Exploratory endpoints ● Correlation between imaging parameters, incl time from injection to PET-scan, and subjective image quality for clinical diagnostic use ● Correlation between duration of PET-scan and the number of detected liver lesions and their size ● Compare the possibility of detecting and localizing tumor lesions located close to the diaphragm, with and without respiratory gating.

Inclusion criteria	● Age ≥ 18 years
	● The patients informed consent
	● Fulfills at least one of the following criteria for imaging with ^{68}Ga-DOTATATE PET/CT:
	  ● Follow-up of a previously diagnosed, histologically verified, NET with ongoing SSA treatment
	  ● Under diagnostic work-up for suspected NET and expected to initiate SSA-treatment within the coming year.

Exclusion criteria	• Pregnancy or breast feeding
Study procedures	^{68}Ga-DOTATATE is supplied by the department of Radiation Physics, Skånes Universitetssjukhus in Lund. The radiopharmaceutical is administered as a bolus injection in a peripheral vein. After 45-60 minutes a PET/CT scan is performed. The images are evaluated by a nuclear medicine specialist, and relevant data entered into the case report forms. Information regarding last date of SSA injection is collected from the patient through a questionnaire prior to performing the PET-scan. The surgeon or oncologist receiving the results of the scan, and following up on the patient, will judge whether the patient is in remission, progression or stable disease based on available radiology (not taking PET into account), biochemistry and clinical data. The patients deemed to be stable in their disease will be the population for the primary analysis.
Sample size	No formal sample size calculation has been performed. All patients eligible for the trial during the next three years will be offered inclusion after given their written informed consent. We estimate to perform approximately 120 scans/year.

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