177Lu-DOTA-octreotate Radionuclide Therapy of Neuroendocrine Tumours

Dosimetry-Based Therapy Planning and Outcome

ULRIKE GARSKE-ROMÁN
Peptide receptor radionuclide therapy for the internal radiation of neuroendocrine tumours expressing somatostatin receptors has made great advances and offers promising results. $^{177}$Lu-DOTA-octreotate is one of the most widely used radiopptides, but kidneys and bone marrow are organs at risk. Methods of measuring radiation doses to at-risk organs and tumours (dosimetry) on an individual patient basis have been regarded as impracticable and a maximum of 4 treatment cycles has widely been accepted as the treatment standard instead.

The first aim of this thesis was to establish a clinically feasible protocol to calculate absorbed doses to bone marrow and the kidneys during therapy with $^{177}$Lu-DOTA-octreotate. A new dosimetry protocol for the bone marrow was described. Dosimetry for solid organs had previously been described based on 3-dimensional imaging by the research group. In the current thesis it was demonstrated that in most patients only minor changes of the effective half-life occurred in the kidneys. By performing complete dosimetry during the first cycle and comparing it with the uptake in later cycles, it was shown that the absorbed dose can be calculated based on the activity concentration at 24 hours after therapy. The study concluded that 50% of all patients could receive more than the standard 4 treatment cycles with 7.4 GBq $^{177}$Lu-DOTA-octreotate without passing the limit of 23 Gray to the kidneys or 2 Gray to the bone marrow, whereas 20% would tolerate fewer than 4 cycles.

The second aim was to describe treatment outcomes of dosimetry-guided therapy with $^{177}$Lu-DOTA-octreotate. Patients with metastasized colorectal neuroendocrine tumours and bronchial carcinoids were shown to have longer survival with this method than previously reported. Morphological tumour response could be correlated to time to progression. Furthermore, in a case of low-differentiated neuroendocrine cancer it was shown that large tumours with high proliferation can also be treated with this method and that tumour-to-risk organ ratios can improve in later cycles, resulting in a more effective treatment.

Dosimetry-guided, fractionated radionuclide therapy with $^{177}$Lu-DOTA-octreotate is a valuable treatment option for patients with advanced neuroendocrine tumours expressing somatostatin receptors.

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List of Papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.


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<tr>
<td>AC</td>
<td>Atypical carcinoid</td>
</tr>
<tr>
<td>ACTH</td>
<td>Adrenocorticotropic hormone</td>
</tr>
<tr>
<td>ANOVA</td>
<td>Analysis of variance</td>
</tr>
<tr>
<td>APUD</td>
<td>Amine precursor uptake and decarboxylation</td>
</tr>
<tr>
<td>$^{11}$C</td>
<td>Carbon-11</td>
</tr>
<tr>
<td>CgA</td>
<td>Chromogranin A</td>
</tr>
<tr>
<td>Ci</td>
<td>Curie (0.1 Ci=3.7 GBq)</td>
</tr>
<tr>
<td>CT</td>
<td>Computed tomography</td>
</tr>
<tr>
<td>CR</td>
<td>Complete remission</td>
</tr>
<tr>
<td>g</td>
<td>Gramme</td>
</tr>
<tr>
<td>$^{68}$Ga</td>
<td>Gallium-68</td>
</tr>
<tr>
<td>GBq</td>
<td>Giga-Becquerel</td>
</tr>
<tr>
<td>GEP-NET</td>
<td>Gastroenteropancreatic neuroendocrine tumour</td>
</tr>
<tr>
<td>G 1-3</td>
<td>Grade 1-3</td>
</tr>
<tr>
<td>Gy</td>
<td>Gray</td>
</tr>
<tr>
<td>h</td>
<td>Hour(s)</td>
</tr>
<tr>
<td>HED</td>
<td>Hydroxyephrine</td>
</tr>
<tr>
<td>5-HIAA</td>
<td>5-hydroxyindolacetic acid</td>
</tr>
<tr>
<td>5-HTP</td>
<td>5-hydroxytryptophan</td>
</tr>
<tr>
<td>$^{111}$In</td>
<td>Indium-111</td>
</tr>
<tr>
<td>keV</td>
<td>kilo-electron-Volt</td>
</tr>
<tr>
<td>Ki-67</td>
<td>Marker for cell proliferation</td>
</tr>
<tr>
<td>L-DOPA</td>
<td>L-hydroxypenylalanine</td>
</tr>
<tr>
<td>$^{177}$Lu</td>
<td>Lutetium-177</td>
</tr>
<tr>
<td>mCi</td>
<td>milli-Curie</td>
</tr>
<tr>
<td>MEGP</td>
<td>Medium energy general purpose (collimator)</td>
</tr>
<tr>
<td>MIBG</td>
<td>Meta-iodobenzylguanidine</td>
</tr>
<tr>
<td>MIRD</td>
<td>Committee on medical internal radiation dose</td>
</tr>
<tr>
<td>MTO</td>
<td>Metomidate</td>
</tr>
<tr>
<td>m-TOR</td>
<td>Mammalian target for rapamycin</td>
</tr>
<tr>
<td>MR</td>
<td>Minor response</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
</tr>
<tr>
<td>NET</td>
<td>Neuroendocrine tumour</td>
</tr>
<tr>
<td>PD</td>
<td>Progressive disease</td>
</tr>
<tr>
<td>PET</td>
<td>Positron emission tomography</td>
</tr>
<tr>
<td>Acronym</td>
<td>Definition</td>
</tr>
<tr>
<td>---------</td>
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<tr>
<td>p.i.</td>
<td>Post injection</td>
</tr>
<tr>
<td>PR</td>
<td>Partial response</td>
</tr>
<tr>
<td>PRRT</td>
<td>Peptide receptor radionuclide therapy</td>
</tr>
<tr>
<td>RECIST</td>
<td>Response evaluation system in solid tumours</td>
</tr>
<tr>
<td>SD</td>
<td>Stable disease</td>
</tr>
<tr>
<td>SPECT</td>
<td>Single photon emission computed tomography</td>
</tr>
<tr>
<td>ssr2</td>
<td>Somatostatin subtype receptor 2</td>
</tr>
<tr>
<td>TACE</td>
<td>Transarterial liver chemoembolisation</td>
</tr>
<tr>
<td>TC</td>
<td>Typical carcinoid</td>
</tr>
<tr>
<td>$^{99m}$Tc</td>
<td>Technetium-99m</td>
</tr>
<tr>
<td>$t_{eff}$</td>
<td>Effective half-life</td>
</tr>
<tr>
<td>VIP</td>
<td>Vasoactive intestinal peptide</td>
</tr>
<tr>
<td>VOI</td>
<td>Volume of interest</td>
</tr>
<tr>
<td>$^{90}$Y</td>
<td>Yttrium-90</td>
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</tbody>
</table>
Introduction

Worldwide, an increasing incidence of neuroendocrine tumours (NETs) has been observed[1-6]. Their clinical appearance varies greatly depending on the site of origin, the stage (localized disease or metastases present at diagnosis), tumour growth (proliferation) and the presence or absence of hormonal symptoms[7, 8]. Advances of histopathology have provided a deeper understanding of their origin and explanations for their clinical diversity.

Historical background- the concept of neuroendocrine tumours

Neuroendocrine tumours (NETs) are derived from a disseminated system of endocrine cells. The first reports in the literature that may be attributed to the modern concept of NETs were made by Merling when he in 1838 reported on a tumour in the appendix [9, 10]. Oberndorfer is recognized for coining the term “carcinoids” (carcinoma-like) in 1907 for a new type of tumours, which he originally considered to be benign [11, 12], an opinion he changed in a later publication [13].

Expanding knowledge on structural similarities of neural and endocrine cells evolved. Silver staining techniques for different subsets of cells were developed and became a tool to diagnose tumours derived from what became known as the neuroendocrine system. A method originally used for staining nervous cells was modified by Hellman and Hellerström [14] to stain cells in the pancreas (A1 cells), which later on were identified as somatostatin producing cells [15, 16]. Masson developed a stain that reacted with endocrine cells in the gastrointestinal wall and bronchi (“Kultschitzky cells”) as well as with carcinoid tumour cells [17]. Depending on whether an oxidation step was required or not in order to stain the cells, staining techniques were referred to as “argentaffin” or “argyrophilic”. The Masson stain represents an argentaffin method, whereas the Grimelius stain was an argyrophilic technique, originally described to react with pancreatic A2 cells [18], which later were found to produce pancreatic polypeptide (PP) and glucagon [19]. This method proved to be valuable not only for the identification of tumours of the pancreas, but also of other neuroendocrine tumours derived from the embryonal fore-, mid- and hindgut [20].
These staining methods were used for decades for the classification of the tumours of the neuroendocrine system [21]. All silver techniques reacted with so-called dense core granules, later visualised by electron microscopy. These granules stored hormones and were in more recent research found in turn to correlate to Chromogranin A (CgA) expression, a marker widely used for screening and follow-up of NETs [22, 23]. The findings of dense core granules indicated hormonal activity and these storage vesicles of hormones in cells derived from the neuroendocrine system became targets for diagnosis and therapy [22, 24].

The work of Friedrich Feyrter (1895-1973) revolutionized the knowledge on endocrine tumours by introducing a new way of pathophysiological thinking into the contemporary organ-defined pathology. He described disseminated cells in the pancreas and gut (“Helle Zellen”), and realized that there were similarities and interactions between the neuronal and endocrine system, forming a network of neuroendocrine cells with local and distant signalling pathways [25-28]. His work made him the father of the concept of “neuroendocrine tumours”. Pearse worked further on Feyrter’s concept of the diffuse neuroendocrine system and described cells characterized by “amine precursor uptake and decarboxylation” mechanisms (APUD cells)[29].

Based on their embryological origin, NETs can be subdivided into tumours of the embryonal gut (entoderm) and the neural crest. The latter group comprises a relatively small fraction of tumours with more or less pronounced characteristics linking them to the neural system such as pheochromocytomas and paragangliomas. Tumours derived from the embryonal entoderm represent the majority of NETs and present with a large diversity in clinical appearance. They all share common properties that link them to the neuroendocrine system, such as the expression of somatostatin receptors and the uptake of amine precursors, characteristics that are used by modern molecular imaging and therapy methods.

Clinical symptoms

Depending on their origin, proliferation and hormone production, NETs present with a wide range of clinical appearances. On one end of the spectrum there are slow-growing tumours that may produce little symptoms over many years, and are sometimes only diagnosed at late stages due to mechanical symptoms caused by a large tumour burden. On the other end of the spectrum highly aggressive tumours are found, that lead to severe symptoms and can cause death within a short period of time if not adequately treated. The other distinctive feature amongst NETs is the production of hormones, found in about 10-15% of all patients diagnosed with these tumours.
By differentiating the tumours by their embryological origin, different groups of hormonal symptoms are found to be associated.

**Tumours of the embryonal entoderm**

Historically, these tumours have been subdivided into endocrine pancreatic tumours and carcinoids, which are further subdivided into carcinoids of the fore-, mid- and hindgut [32].

The largest group of hormonally active tumours occur in the small intestine or midgut, with a hormonal syndrome consisting of flushes, diarrhoea, bronchial constriction and at times right heart failure due to thickening of the tricuspid valve [33-35]. This syndrome has become known as “classic carcinoid syndrome” and besides tumours of the small intestine, bronchial and thymic carcinoids as well as tumours of the pancreas are at times associated with these symptoms. In 1953, serotonin was mentioned for the first time as causative agent [36]. In 20-30% of the patients with NETs of the small intestine, the classic carcinoid syndrome is present at diagnosis [37], and 85% of the patient will show liver metastases during follow-up [38]. The development of the carcinoid syndrome is positively correlated to a larger tumour burden in the liver, both situations representing negative prognostic factors for survival [39]. Occasionally, the carcinoid syndrome can become life threatening with symptoms of diarrhoea and severe hypotension. The serotonin metabolite 5-hydroxyindolacetic acid (5-HIAA) is a diagnostic marker measured in the urine [40].

NETs of the pancreas and duodenum are referred to as “functioning” when associated with clinical symptoms of hormone production, or “non-functioning” in those cases not associated with clinical symptoms. Unlike the carcinoid syndrome of the small intestinal tumours, hormonal active tumours of the pancreas are often small and less often metastasized [7]. Nonetheless, they can give rise to severe symptoms due to a multitude of hormones produced by them, such as insulin, gastrin and vasoactive intestinal peptide (VIP), giving rise to hypoglycaemic fits, gastric ulcers or severe diarrhoea and hypovolemia.

The patient’s outcome is dependent on the control of the hormonal symptoms as well as the degree of tumour malignancy, defined by proliferation and ability to metastasize [8]. Insulinoma are the most common group of hormonal active gastroenteropancreatic NETs, only 5% of them are metastasized at diagnosis. In contrast, 40% of gastrinoma are metastasized at diagnosis, whereas 70-80% of the rare tumours such as glucagonomas and somatostatinomas are disseminated at diagnosis [7].

Colorectal NETs are usually not associated with hormonal symptoms and show no elevation of CgA. The majority of them are diagnosed at an early stage and have an excellent prognosis if operable. On the other hand have
patients with distant metastases a less favourable prognosis, with only every third surviving 5 years [1].

Bronchopulmonary NETs show a broad range of clinical appearances mostly based on their aggressiveness. They are subdivided into typical (TC) and atypical carcinoid (AC) tumours, large-cell neuroendocrine carcinomas (LCNEC) and the highly malignant small-cell lung carcinomas (SCLC). A minority of less than 5% of bronchopulmonary NETs show hormonal symptoms, amongst them Cushing’s syndrome related to ACTH production, carcinoid syndrome and acromegaly [4]. TCs have the best survival prognosis, whereas less than 5% of patients with SCLC survive 5 years.

Tumours derived from the neural crest

Tissues and tumours of the neural crest have been shown to express receptors for and to produce and to accumulate precursors of catecholamines such as L-DOPA and norepinephrine [41, 42].

Tumours of neural crest origin arise from chromaffin cells, named in analogy with the argentaffin reaction in carcinoids for changing their colour to brown when exposed to chromic salts by complexing catecholamines. These cells share common features with neurons, and hormonal symptoms of the most common of these tumours, the pheochromocytomas are characterized by a hyperactivity of the sympathetic nervous system, causing palpitations, elevated blood pressure, anxiety and weight loss.

The historical findings of “dense core granules”, the targets of the silver and chromic stains of the pathologists have translated in modern days into findings of hormonal activity and storage vesicles for hormones in cells derived from the neuroendocrine system, and have became targets for diagnosis and therapy[22, 24].

The role of nuclear medicine in the management of NETs

Nuclear medicine is a medical speciality providing methods for functional imaging and the treatment of diseases characterized by deranged or impaired cellular function. Especially in the management of neuroendocrine tumours, with a wide range of well-documented and specific targets related to their origin in the endocrine network, nuclear medicine has become a keystone for both diagnosis and therapy. By either labelling hormones themselves or their analogues with detectable radionuclides and/or targeting hormone receptors, neuroendocrine tumours can be imaged, staged and characterized with a specificity that surpasses that for most other tumour groups. By choosing
appropriate radionuclides for treatment, the same mechanisms can also be used for radionuclide therapy.

Nuclear medicine in the diagnosis of NETs

For imaging, tracing agents can be labelled with either gamma emitting radionuclides for conventional gamma camera examinations, or positron emitting radionuclides for PET (positron emission tomography). Imaging on gamma cameras can either be performed in two dimensions (static images or whole body scans), or in three dimensions with single photon emission computed tomography (SPECT). PET radionuclides often have half-lives within minutes or hours. In tissue the emitted positron and an electron annihilates, sending out two opposite directed annihilation photons with an energy of 511 keV each. In a PET camera these photons can be detected simultaneously by a large number of detectors placed in several rings, providing images of high resolution.

Whereas the high image resolution is a great advantage of PET tracers, their short half-life of the tracers and limited availability is a restricting factor. Conventional gamma emitting radionuclides can be chosen for their imaging and labelling properties, with different physical half-lives adjusted to the processes to be studied. Also, gamma decay can be found in a range of radionuclides with good properties for therapy, making them ideal for imaging during therapy for dosimetry and response monitoring. In modern applications, both SPECT and PET cameras are usually combined with a computer tomograph (CT), for both attenuation correction and improved anatomic information.

Tracers targeting hormone synthesis and amine precursor uptake mechanisms

Meta-iodobenzylguanidine (MIBG) is a norepinephrine analogue that uses the amine precursor uptake mechanism and may be incorporated in vesicles or neurosecretory granules of cells derived from the neural crest. It was developed for visualizing the adrenal medulla [41]. Later on, it became widely used for the staging of tumours derived from the neural crest, especially neuroblastoma in children [43, 44] and pheochromocytomas and paragangliomas in adults [44, 45]. Even medullary thyroid tumours, carcinoids of different origin and pancreatic NETs were shown to take up MIBG, but was found to be less sensitive for the detection of these tumours than somatostatin analogues [46, 47]. For PET imaging, hydroxyephedrine (HED) labelled with $^{11}$C was introduced [48-52], rendering excellent information on the stage of patients with neural crest tumours. The complexity of $^{11}$C chemistry
and the short half-life of the isotope of about 20 minutes restrict the application of $^{11}$C–labelled tracers to specialized centres.

Another enzyme involved in the synthesis of corticoid hormones in the cortex of the adrenal gland, metomidate, has been shown to be a sensitive and specific PET tracer for adrenocortical tumours when linked to Carbon-11 ($^{11}$C-MTO) [53-55].

Knowledge of the decarboxylation mechanisms that convert amine precursors into active peptide hormones became important to develop PET tracers for the detection of neuroendocrine tumours. PET with $^{11}$C- and $^{18}$F-labelled L-hydroxyxypenylalanine (L-DOPA) and $^{11}$C-labelled hydroxytryptophan (5-HTP) increased the sensitivity and specificity for detection of NETs and became an important contribution to the correct staging of these patients [56-60].

**Tracers directed towards somatostatin receptors**

Somatostatin receptors are widely expressed in neuroendocrine tumours. In 1989 Krenning et al reported on the scintigraphic visualisation of several neuroendocrine tumours by using a synthetical somatostatin analogue, $^{123}$I-labelled Tyr-3-octreotide [61]. This was the start of a development that should produce several somatostatin analogues binding to the somatostatin receptors.

$^{111}$In-labelled DTPA-octreotide, with high affinity especially to somatostatin receptor type 2 became the gold standard for the diagnostic of neuroendocrine tumours [62-66] and became commercially available. It serves for staging the tumour extent and is a predictor of responsiveness to treatment with somatostatin analogues, unlabelled or, in recent years for the therapy with radiolabeled somatostatin analogues. $^{111}$In has a relatively long half-life of 2.81 days that suited the purpose of imaging after 24 hrs, where best tumour identification was found for this tracer. In recent years, new tracers for both gamma camera imaging and PET imaging have been developed. $^{99m}$Tc labelled EDDA/ HYNIC-TOC is available for gamma camera imaging using a one-day protocol [67, 68].

Several reports on $^{68}$Ga-labelled somatostatin analogues have been published during the last few years. Because of the better sensitivity and image quality combined with shorter imaging protocols PET with $^{68}$Ga-labelled somatostatin analogues will most probably replace $^{111}$In-DTPA-octreotide scintigraphy in the near future [69-72].

**Treatment**

Treatment of NETs is, as for any tumour, largely dependent on the stage of the disease. Different strategies are necessary in the case of localized com-
pared to disseminated disease. Management of hormonal symptoms is often a challenging task and closely interconnected with the response to given therapy.

Surgery

For localized NETs, surgery is the treatment of choice. If the tumour is detected at an early stage, surgery is for many patients curative. When metastases have occurred, surgery has its place as a component in a multidisciplinary approach with the goal to ameliorate symptoms, prevent complications and prolong life [73, 74]. Early surgery in the course of disease may also decrease the risk for development of metastases and consecutively, improve survival [73, 75, 76]. Stenting procedures can alleviate symptoms of vessel obstruction in the mesenteric root [77]. After resection of pancreatic NETs, progression occurs predominantly in distant sites, resulting in the need for systemic treatment [78, 79].

Medical treatment

Biological treatment

Somatostatin analogues

Many neuroendocrine tumours express receptors for somatostatin, a regulatory peptide hormone involved in growth control and neurotransmission. In its endogenous form, it exists in two active forms consisting of 14 and 28 amino acids, respectively. Their physiological half-life is short, in the range of minutes. In humans, 5 different receptor subtypes for somatostatin are known, of which receptor type 2 (ssr2) is most often overexpressed in neuroendocrine tumours [80, 81]. Therapy with somatostatin analogues have been proven to result in increased symptom control by decreasing the hormone production in neuroendocrine tumours, especially in patients with classic carcinoid syndrome, but the effect on survival has still to be proven in randomised studies. Decrease of tumour burden is rarely noticed during treatment with somatostatin analogues [37, 82, 83].

Alpha interferon

Alpha Interferon in combination with somatostatin analogues is the standard regime in modern treatment of midgut carcinoids, and can also be used in patients with GEP-NETs of the pancreas and duodenum. It reduces hormone levels in 50% of the patients and reduces tumour size in 15% [79]. It has been proven to ameliorate the carcinoid syndrome, reduces tumour growth and prolongs survival.
Chemotherapy

Treatment with cytostatic agents has no place in the management of carcinoids of the small intestine.

For patients with well-differentiated metastasised endocrine pancreatic tumours, chemotherapy with a combination of streptozotocin with 5-fluorouracil or doxorubicin is first-line therapy [84]. In this group of patients, the median survival is reported to be in the range of 2 years, with a response rate of 35 to 60% [85, 86]. Also temozolomide has shown some efficacy in patients with well or intermediate differentiated endocrine pancreatic and duodenal tumours [87].

For patients with advanced disseminated tumours of the hindgut (colorectal NETs) as well as the stomach, there is no established first-line treatment [88, 89].

Few chemotherapy regimens have proven effective in treating metastatic bronchial carcinoids, with overall discouraging results [90]. Cisplatinum + etoposide as well as paclitaxel have demonstrated some efficacy [91, 92], and studies of a limited number of patients indicated that temozolomide may be effective as monotherapy [87, 93] (Table 1).

For patients with low differentiated neuroendocrine tumours, disregarding origin, platinum-based chemotherapy in combination with etoposide is first-line treatment [88, 94], but also temozolomide has been applied [95]. Especially cisplatinum is a cytostatic drug with severe potential side effects such as nausea as well as oto- and nephrotoxicity, with consecutive impairment of the quality of life [96]. Newer drugs such as tyrosinkinase inhibitors, mTOR-antagonists and neoangiogenesis inhibitors are still under clinical evaluation [97].

Radionuclide therapy

Besides MIBG, the radionuclide therapy of neuroendocrine tumours has been dominated by the targeted therapies directed towards somatostatin receptors mainly of subtype 2.

After successfully visualizing somatostatin receptors with $^{111}$In-DTPA-octreotide, the next step was to its application for therapy [98]. $^{111}$In decays by electron capture and is mainly a gamma-emitter suitable for diagnostics, but some low energy conversion and Auger electrons in its decay encouraged clinical trials to use it for therapy as well [98-100]. Therapy with $^{111}$In-DTPA-octreotide was found clinically promising with symptomatic relief, but only rarely resulting in a morphologic tumour response [101]. The beta-emitting radionuclides $^{90}$Y and $^{177}$Lu were found more interesting, due to the more favourable ratio between gamma radiation and charged particles having a longer range in tissue that made them more suitable for macroscopic
tumours [102, 103]. Changes in the peptide structure and chelator improved the binding capacities of the radiopharmaceutical and the stability of the complex. Several studies with $^{90}$Y-DOTA-octreotide ($^{90}$Y-DOTATOC) were performed in order to find optimal activities [104-109] with objective responses found in between 9-34% of the patients [109, 110]. Large variations in the patient populations and the therapy protocol make comparisons between studies difficult.

One side effect of the treatment turned out to be kidney failure, especially when re-absorption of the excreted radiopharmaceutical was not blocked by concomitant amino acid infusions [104, 111-114]. A large series of 1109 patients treated in Basel between 1997 and February 2010 was reported on recently, with a morphological response rate of 34.1% (any degree). The treatment was given as single infusions of 3.7 GBq $^{90}$Y-DOTATOC/m$^2$ bodysurface, median number of cycles were 2. For kidney protection, a concomitant infusion of a mixture of arginine and lysine was given during 4 hours, commencing 30 min before the radionuclide therapy. In this group, 103 (9.2%) patients developed permanent kidney toxicity (grade 4 and 5). Reversible haematological toxicity grade 3 and 4 was seen in 12.8% of the patients. Morphological response was seen to correlate with longer survival, and the outcome of patients with high tumour uptake was better.

Therapy with $^{177}$Lu-DOTA-octreotate has been developed in parallel. DTPA-octreotate was shown in a preclinical evaluation found to have better binding capacities as compared to DTPA-octreotide [115]. Two years later, DOTA-octreotate was shown in vitro to have a higher affinity for somatostatin receptors type 2 as compared to DOTA-octreotide [116], the predominant receptor type in NETs.

In comparison to $^{90}$Y, $^{177}$Lu has a longer physical half-life and a shorter beta particle range in tissue. With a half-life of 6.68 days $^{177}$Lu has a lower dose-rate than $^{90}$Y with 64 hours. The longer range in tissue of $^{90}$Y implies a more homogeneous absorbed dose distribution in tumours, but also in the kidney as compared to $^{177}$Lu and $^{111}$In as shown by Konijnenberg et al [117]. The authors concluded that existing models for predicting kidney damage based on average dose to the kidney or cortex from external beam therapy experience are most probably not applicable for those radionuclides. Results from therapy with $^{177}$Lu-DOTA-octreotate have in fact shown that the kidney toxicity in patients treated with this radiopeptide is much lower than with $^{90}$Y-DOTATOC [118, 119]. Results from both $^{90}$Y-DOTATOC and $^{177}$Lu-DOTA-octreotate have shown results that compare favourably to results from other systemic treatment for different types of NETs [99, 118-121].

Dosimetry is a tool to measure absorbed doses in tissue and to predict and control effect and side effects. The absorbed dose is defined by the amount of energy deposited by ionizing radiation by unit mass. It is measured in Gray (Gy; Joule/kg). The use of dosimetry is well established for external
beam radiation, and dosimetry during radionuclide therapy often relates to the experiences from this treatment form [122]. The experience from external beam radiation is not easily transferred to the special conditions of radionuclide therapy. Doses in radionuclide therapy will vary due to changes in uptake, and it is a low-dose-rate radiation to which the body is exposed under a longer time. If dose calculations have been applied, they were often based on 2D imaging[123-125]. This method has major drawbacks, since overlap of tumour uptake can prevent the exact measurement of uptake in risk organs. Furthermore, it is difficult to estimate organ sizes with any precision, and organ sizes can vary substantially, as previously shown [126]. A new way of calculating absorbed doses based on SPECT-CT was developed at the University Hospital of Uppsala. This method uses small volumes of interest (VOI) in order to measure activity concentration at 24 hours, 4 and 7 days in solid organs following therapy with $^{177}$Lu-DOTA-octreotate in order to calculate absorbed doses to kidneys, spleen and tumour-free liver parenchyma[126]. After a study with increasing amounts of activity per cycle up to an accumulated activity of 600-800 mCi [118] most therapy reports for $^{177}$Lu-DOTA-octreotate are based on a protocol of up to 4 cycles with 200 mCi corresponding to 7.4 GBq up to a maximum of 800 mCi (29.6 GBq) [119, 123]. Calculations made by the group in Rotterdam, the leader in the development of therapy with $^{177}$Lu-DOTA-octreotae, indicated that a substantial amount of their patients might not reach an accumulated dose of 23 Gy to the kidneys by an accumulated activity of 800 mCi [110]. This upper limit of activity was accepted in the first place, since bone marrow dosimetry in a group of six patients with limited disease showed an absorbed dose of 260mGy/100 mCi, reaching in the accepted accumulated dose of 2 Gy to the bone marrow with 800 mCi [127]. However, later results by the same group contested this result, showing that bone marrow doses in different patients varied more than previously assumed, and doses to the bone marrow found in this study were lower than previous data indicated[128]. This opened for the thought that a subset of patients may be undertreated with a fixed treatment schedule of 4 cycles with 200mCi (7.4 GBq) of $^{177}$Lu-DOTA-octreotate [110]. Later results indicated also that patients with progressive disease after successful initial therapy with $^{177}$Lu-DOTA-octreotate could safely be retreated with further cycles [129].

With the aim to further increase the efficacy of therapy with radiolabelled somatostatin analogues, combinations of different radionuclides have been suggested [130, 131], as well as the combination with radiosensitizers [132-134].
Aims of the Thesis

Peptide receptor radionuclide therapy has increased in importance for the management of patients with generalized neuroendocrine tumours (NETs). The first part of the thesis aimed to develop an individual dosimetry protocol for patients undergoing therapy with $^{177}$Lu-DOTA-octreotate that could work in the clinic, as a tool for measuring absorbed doses to risk organs and tumours for an optimized treatment (Papers I and II). The aim of the second part was to describe the outcome of fractionated, dosimetry-guided therapy in patients with advanced stages of neuroendocrine tumours (Papers III-V). Specific aims were

- To investigate the effective half-life of $^{177}$Lu in solid organs during therapy and the possibility to customize measurements in subsequent treatment cycles (Paper I)
- To develop a protocol for bone marrow dosimetry and to estimate the possible number of treatment cycles for individual patients before reaching an accumulated absorbed dose of 23 Gray (Gy) to the kidneys or 2 Gy to the bone marrow (Paper II)
- To investigate the outcome of dosimetry-guided therapy with $^{177}$Lu-DOTA-octreotate in patients with metastasized colorectal NETs (Paper III) and bronchial carcinoids (Paper IV) regarding morphological tumour response, time-to-progression and survival
- To describe the changes in uptake and absorbed doses in tumours, kidneys and bone marrow in a patient with a poorly differentiated neuroendocrine carcinoma (Paper V)
Materials and Methods

Patients

All patients described in this thesis suffered from metastasized NETs with high somatostatin receptor expression (grade 3 or 4).

Since September 2010, all patients have been included into a prospective study (EudraCT nr 2009-012260-14), approved by the Regional Ethical Review Board in Uppsala, after signing a written informed consent. Before this time, patients were admitted on a single patient basis for compassionate use with individual permission of the Swedish Medical Products Agency.

For paper I, 30 patients with different tumours diagnoses were analysed. At least two complete dosimetry calculations during their therapy with $^{177}$Lu-DOTA-octreotate were performed.

In paper II, 200 consecutive patients with NETs of different origin undergoing therapy with $^{177}$Lu-DOTA-octreotate were included.

Paper III reports the outcome of 16 patients with advanced colorectal NETs in stage IV, 8 men and 8 women. Ki-67 was available for 15 patients, 13 patients had G2 tumours, one patient each a G1 and G3 tumour. In 12 patients, the primary tumour had been operated; one patient had received external beam radiation for the primary. Six patients had been treated with chemotherapy, one had had a liver transplant, one patient each had been treated with transarterial liver chemoembolization (TACE) and bland liver embolization. Four patients had been treated with somatostatin analogs, two of them in combination with alpha-interferon. Nine patients were in progression at the start of therapy, four received $^{177}$Lu-DOTA-octreotate as a first line therapy. Liver metastases were seen in 14 patients (87.5%), bone and bone marrow metastases in 10 (62.5%).

Paper IV reports on thirteen patients with metastatic bronchial carcinoids treated with $^{177}$Lu-DOTA-octreotate between 2006 and 2011. Five were classified as atypical and four as typical carcinoids. Histological classification was unavailable for four tumours. All patients had advanced metastatic disease (stage IV). Eight patients had previously received chemotherapy, six were receiving treatment with somatostatin analogues, and one patient had had a liver transplant.

Paper V is a case report on a 42-year-old woman with a poorly differentiated neurendocrine carcinoma of unknown origin previously unresponsive to two different chemotherapy protocols. She had a large tumour burden in the liver.
as well as enlarged abdominal, thoracic and pelvic lymph nodes. Small bone metastases were suspected in the sacrum and the thoracic spine. Liver biopsies at two different time points from several liver metastases revealed a Ki-67 rate between 10 and 50%. Somatostatin receptor scintigraphy showed very high uptake (grade 4) in all known tumour lesions. She received 7 cycles of 7.4 GBq $^{177}\text{Lu}$-DOTA-octreotide guided by dosimetry, aiming at an interval of 6 to 8 weeks. Two (first 5 cycles) to four litres (cycle 6 and 7) of a mixed amino acid solution were co-infused at an infusion speed of 250mL/min commencing 30 min before the radionuclide infusion.

**Therapy and Dosimetry**

DOTA-Tyr-3-octreotide was a generous gift from Prof. Eric Krenning (Erasmus Medical Centre, Rotterdam). $^{177}\text{LuCl}_3$ was purchased from IDB (Petten, The Netherlands). The labelling procedure was performed in-house prior to the infusion. For kidney protection, a mixed amino acid solution (Vamin 14gN/L electrolyte-free, Kabi Fresenius ®) was administered. Until Autumn 2008, all patients received 1 liter, which after results from the dosimetric studies was increased to 2 liters.

**Paper I**

Calculation of absorbed doses to kidneys, spleen and liver at their first and 4th cycle performed on 3-D data was based on SPECT/CT images acquired at 24 hours, 4 and 7 days after infusion of the radiopeptide. A previously described measurement of activity concentration in small volumes of interest in kidneys, spleen and liver was applied [126] and the effective half-life ($t_{\text{eff}}$) as well as the absorbed doses in the organs were calculated. Ratios of the results obtained at the fourth and the first cycle results were formed.

**Paper II**

All patients underwent whole-body gamma scintigraphy (anterior and posterior planar acquisitions) and SPECT/CT of the abdomen at 24, 96 and 168 hours after administration of the first therapeutic dose of 7.4 GBq $^{177}\text{Lu}$-DOTA-octreotide. For the first 69 patients, imaging was performed on a Hawkeye Millennium VG (International General Electric, General Electric Medical Systems, Haifa, Israel) dual-headed gamma camera equipped with 5/8” NaI(Tl)-crystals with VPC-5 (MEGP) collimators. For those patients, a 20% energy window around the two dominant gamma ray energies of $^{177}\text{Lu}$, 113.0 and 208.4 keV, was used. For the other 131 patients, imaging was performed on an Infinia (International General Electric, General Electric Medical Systems, Haifa, Israel) dual-headed gamma camera.
Medical Systems, Haifa, Israel) dual-headed gamma camera equipped with 3/8” NaI(Tl)-crystals with VPC-5 (MEGP) collimators. A 20% energy window was placed around the dominant 208.4 keV gamma ray energy of $^{177}$Lu to make the measurements. Imaging with whole body scintigraphy and SPECT/CT was performed as described earlier [126] with the exception that SPECT/CT images were collected with 120 angles with 30 s per frame for the Infinia. Calibration of whole body and SPECT images was based on a 100 ml sphere containing a known amount of activity placed inside a thorax phantom, which was scanned repeatedly. Phantom measurements confirmed that there were no dead time issues in the patient measurements.

Blood samples were drawn from the venous catheter in which the amino acid solution was infused, after rinsing with 10 ml of 0.9% saline. Blood samples (~3 g) were drawn at 0.5, 1.0, 2.5, 4, 8 and 24 h after start of $^{177}$Lu-DOTA-Tyr-3-octreotate administration. In the first 50 patients, additional samples were collected at 96 and 168 h post injection (p.i). Time In 50 patients, additional blood samples were obtained at 96 and 168 h. Moreover, urine was collected from 30 patients during the first 24 h. The absorbed radiation dose to the bone marrow was calculated based on blood and urinary activity curves over time combined with organ-based analysis of the whole body images. The absorbed dose to the kidney was calculated from the pharmacokinetic data obtained from SPECT/CT.

Blood kinetics was analyzed using a bi-exponential model. In 5% of the patients, this model could not explain the blood kinetics, which was the main reason why trapezoidal integration was used to estimate the time-integrated activity concentration for the first 24 hours. For the second phase (after 24h) a single exponential function was assumed with a half-life of 72h that was integrated between 24 h and infinity. The value 72h was taken as an upper value derived from patients in whom late blood samples were taken and that all showed a half-life in blood for the second phase shorter than 72 hours. The late blood phase in all patients was therefore assumed to follow a single exponential curve and was integrated between 24 h and infinity using an effective half-life of 72 h. Assuming that the activity concentration in bone marrow was the same as in blood [128] the time integrated activity concentration obtained for blood was also applied for the calculation of the bone marrow self-dose.

Urine was collected from 30 male patients from the start of infusion and during approximately 24 hours. The first eight urinations were collected in separate vessels while further urinations were pooled in a ninth container. Samples of about 0.1g each were taken. From these samples, the total amount of excreted activity from the body during the first 24 hours was calculated and added to the measured total body activity as calculated from the whole-body scintigraphy after 24 hours. The value obtained was compared
to the administered activity to ensure that the two measurements yielded an activity recovery close to 100%.

The kinetic of the urine excretion was then used to calculate the whole body excretion kinetics and the related activity kinetics in large organs during the first 24 hours. Single measurements were made at 24, 96 and 168 hours. The cumulative activities in large organs were then used as input into a MIRD phantom model to calculate the cross-fire dose to the bone marrow.

The results of the bone marrow dosimetry were combined with those from 3D based kidney dosimetry in order to estimate the maximum tolerated number of cycles with $^{177}$Lu-DOTA-octreotate before reaching an accumulated dose of 2 Gy to the bone marrow or 23 Gy to the kidneys.

**Paper III to V**

The patients were treated with between two to eight cycles of 7.4 GBq $^{177}$Lu-DOTA-octreotate guided by dosimetry as described in [126], Paper I and II, aiming at an accumulated dose of 23 Gray (Gy) to the kidneys or 2 Gy to the bone marrow.

Within kidneys, liver spleen and representative tumours, small volumes of interests (VOIs) of 4 ml were drawn in areas with homogeneous activity distribution on SPECT-CT images performed at 24 hours, 4 and 7 days after the first cycle. During following cycles, the uptake intensity in tumours and kidneys was calculated based on 24 hrs post therapy imaging with SPECT-CT and whole body scan, assuming the same effective half-life as calculated from the previous complete dosimetry. When larger changes in the uptake pattern and tumour burden occurred or anticipated by the clinical aspect, complete dosimetry was repeated.

Bone marrow dosimetry was based on a) calculation of the self-dose derived from the blood and b) calculation of the dose contribution from the rest of the body including tumours, based on whole body scans according to Paper II.

**Paper V**

Full dosimetry for solid organs and tumours was performed during cycles 1, 3 and 6, based on SPECT with low-dose CT at 24 hrs, 4 and 7 days after therapy. For bone marrow dosimetry, whole body scans acquired at the same time points were combined with blood activity curves over time calculated from six venous blood samples taken during the first 24 hours after the infusion, starting directly after the rinsing was finished. For dosimetry during cycle 1, the reported tumour-VOIs were drawn in areas representing the highest uptake within the respective metastasis. For the subsequent calculations the same areas within the tumours were identified.
Response evaluation

Paper III-V: Morphologic response evaluation was performed according to RECIST 1.1 criteria [135] by contrast-enhanced computed tomography (CT) after every second cycle, three months after finished therapy and then every 6th month.

Complete response (CR) is defined as total disappearance of a tumour lesion on (CT), partial response (PR) is equivalent to a decrease of the sum of evaluable tumour diameters by 30% or more, progressive disease (PD) to an increase of 20% or more and/or the appearance of new tumour lesions. Stable disease (SD) is stated if neither criteria for PR nor PD are fulfilled.

When bone metastases (not evaluable according to RECIST criteria) dominated the tumour burden, magnetic resonance imaging (MRI) in combination with positron emission tomography (PET-CT) was applied using $^{11}$C-5-hydroxytryptophan ($^{11}$C-5-HTP)[60, 136, 137] in order to detect new lesions.

Definition of tumour response, survival and time to progression

For statistical analysis, the best morphological response according to RECIST 1.1 was considered. Progression was defined as morphological tumour growth after the start of therapy with $^{177}$Lu-DOTA-octreotate, development of new metastases or a decrease of peripheral blood counts that were ascribed to bone marrow metastases. Survival was calculated from start of therapy and month of diagnosis.

For the nine Swedish patients, survival data were obtained from the civil registration register. For the remaining seven patients, survival data were calculated from the date of last contact. Time to progression was defined from the start of therapy to morphologically confirmed progression based on CT or functional imaging when CT or MRI was inconclusive.

Statistics

Paper I and II

Data were analyzed with an Anderson-Darling test in order to check for normal distribution. Since only half of the data sets passed the test, all data were analyzed as being non-normally distributed. Blood and organ activity concentration data were fitted to exponential functions using the least square
method and the coefficient of multiple determination ($R^2$) was calculated. A non-parametric Wilcoxon paired test was applied to a) test differences between the measured total body activity at 24 h p.i and injected activity minus all activity collected in urine during 24 h, b) the absorbed dose to the bone marrow at a later cycle compared to that of the first cycle and c) the data for the dose limiting organ. The median, 1$^{\text{st}}$ quartile and the 3$^{\text{rd}}$ quartile was calculated for the two phases of the effective half-life of the fit to the bi-exponential function of the blood concentration and the remainder of the body. For the $R^2$-calculations, the total body recovery and the ratio between the absorbed dose to the bone marrow at a late therapy cycle divided by that of the first cycle the following, data are in the following presented as median (1$^{\text{st}}$ quartile - 3$^{\text{rd}}$ quartile). Statistical significance was assumed at $p < 0.05$.

**Paper III and IV**

Statistical analysis using the JMP 10 software package (SAS Institute Inc., SAS Campus Drive, Cary, North Carolina 27513, USA) included distribution analysis, survival analysis (Kaplan-Meier) and bivariate linear regression analysis. Analysis of variance (ANOVA) was performed for the regression analysis. Statistical significance was assumed at a $p$-value of <0.05.
Results

Paper I
The effective half-life ($t_{\text{eff}}$) in kidneys and liver decreased in most of the patients during therapy, resulting in mean ratios slightly lower than one. The variation in the data was small for the kidney and the spleen. Some of them, however, showed a marked decrease in both kidneys. All patients with a substantial decrease of tumour burden during therapy were found in the latter group. By contrast, two patients showed a striking increase of $t_{\text{eff}}$. The first patient who had more than 20% increase received 2 L of amino acid infusion during the first cycle of therapy, but only 1 L during the latter cycle.

Paper II
For a single cycle of 7.4 GBq, the absorbed dose to the bone marrow and the kidney ranged 0.05 to 0.4 Gy and 2 to 10 Gy, respectively. In 197 of 200 patients, the kidneys accumulated an absorbed dose of 23 Gy before the bone marrow reached 2 Gy. Between 2 and 10 cycles of $^{177}$Lu-DOTA-octreotate could be administered until the upper dose limit for the individual patient was reached (Figure 1).

![Figure 1 Maximum number of cycles with 7.4 GBq of $^{177}$Lu-DOTA-octreotate per patient before reaching 2 Gy to the bone marrow or 23 Gy to the kidney](image)
Paper III

Twelve of the 16 patients with the advanced colorectal NETs (75%) reached an accumulated absorbed dose to the kidneys of 23 Gy, ten during the initial therapy and two after progression. None reached an accumulated dose to the bone marrow of 2 Gy. Median follow-up time was 42 months from start of therapy (range 13-80). No major toxicity was observed. No complete remissions were observed. Thirteen patients (81.3%) showed a morphological response with a decrease of the tumour burden of between 14 and 94%. Of these, nine patients (9/16; 56%) obtained partial remission (PR). One patient progressed (PD). The median overall survival was 58 months (Figure 2).

![Graph showing survival of 16 patients with advanced colorectal NETs from start of dosimetry-guided, fractionated therapy with $^{177}$Lu-DOTA-octreotate (Kaplan-Meier).](image)

Six patients (37.5%) died of progressive disease. In six patients who did not receive 23 Gy to the kidneys during the initial treatment, the median time to progression was 24.5 months and for those who reached 23 Gy at the initial therapy, it was 37 months (Figure 3).

![Graph showing time to progression of patients with advanced colorectal NETs after start of fractionated, dosimetry-guided therapy with $^{177}$Lu-DOTA-octreotate subdivided into patients that received an accumulated absorbed dose of 23 Gy to the kidneys at initial therapy (blue line) and those that did not (red line).](image)
A correlation with $R^2$ of 0.53 was demonstrated between morphological response and time to progression (Figure 4).

![Graph showing correlation between morphological response and time to progression.](image)

*Figure 4 Correlation between morphological response assessed according to RECIST 1.1 criteria and time to progression in 16 patients with advanced colorectal NETs after fractionated, dosimetry-guided therapy with $^{177}$Lu-DOTA-octreotate*

**Paper IV**

Median follow-up was 35 months from treatment start (range 11-54) and 118 months from initial diagnosis (range 24-278). Partial response according to RECIST 1.1 was seen in 5/13 patients (PR 38.5%), stable disease in 6/13 (SD 46.2%) and 2/13 patients progressed (PD 15.4%). Ten patients experienced some degree of morphological tumour decrease (76.9%). From therapy start, the median overall survival was 44 months (Figure 5) and the median progression-free survival was 37 months.

![Graph showing survival of patients after start of 177Lu-DOTA-octreotate therapy.](image)

*Figure 5 Survival of 13 patients with advanced bronchial NETs after start of fractionated, dosimetry-guided therapy with $^{177}$Lu-DOTA-octreotate; Blue dots: progression-free patients at time of analysis*
At the time of analysis, seven patients are alive, six of them progression-free with a median follow-up of 41 months (range 16 to 54). From initial diagnosis, overall survival was 138 months. A correlation with $R^2 = 0.63$ was seen between degree of morphological response and progression-free survival.

Immediate bone marrow toxicity was mild, but one patient with previous temozolomide therapy developed acute leukemia 16 months after the start of therapy. No kidney toxicity occurred. An overview of therapy protocols for advanced bronchial carcinoids with reported morphological outcome, mean or median survival data, time to progression and progression-free survival is shown in table 1.
Paper V

Tumour response

Combined chemotherapy managed to decrease only slightly the diameter of a pelvic tumour, while all other metastases continued to grow in size.

After the initiation of $^{177}$Lu-DOTA-octreotate, all metastases decreased and continued to do so at subsequent times of evaluation (Figure 7 and 8). Three months after cycle 7, all liver metastases showed radiological signs of necrosis. At this time, the sum of the tumour diameters had decreased by 44% according to RECIST 1.1 since start of therapy, corresponding to a partial remission (PR). Also according to the scintigraphy acquired during each cycle, the total tumour burden continued to decrease throughout the whole therapy.
Table 1 continued

<table>
<thead>
<tr>
<th>Tumour stage (patients)</th>
<th>Morphologic Response</th>
<th>TTP or PFS</th>
<th>Median Survival</th>
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<tr>
<td>T III (2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T IV (29)</td>
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<td>T IB (2)</td>
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</tr>
<tr>
<td>T III (5)</td>
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<td></td>
</tr>
<tr>
<td>T IV (11)</td>
<td></td>
<td></td>
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<tr>
<td>Advanced disease;</td>
<td>PR 4/13 (31%)</td>
<td>Overall TTP</td>
<td>16 months (short follow-up)</td>
</tr>
<tr>
<td>previous therapy failed</td>
<td>SD 4/13 (31%)</td>
<td>7 months</td>
<td></td>
</tr>
<tr>
<td>Metastatic; 50%</td>
<td>PR 4/23 (17%)</td>
<td>PFS 5.5 /23 patients</td>
<td>All patients: 34.2 months</td>
</tr>
<tr>
<td>progressed on previous</td>
<td>PD 8/23 (35%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>therapy</td>
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<tr>
<td>Metastatic, progression</td>
<td>Any type 24/84 (28.6%)</td>
<td>Mean survival 40 months (31-50 95% CI)</td>
<td></td>
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<tr>
<td>inclusion criteria</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>T III 2/9 (22.2%)</td>
<td>PR 5/9 (56%)</td>
<td>TTP 31 months</td>
<td></td>
</tr>
<tr>
<td>T IV 7/9 (77.8%)</td>
<td>PR/MR 6/9 (67%)</td>
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<tr>
<td>T IV 13/13</td>
<td>5/13 PR (38.9), any</td>
<td>TTP 44 months PFS 37 months</td>
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<tr>
<td></td>
<td>type 9/13 (69.2%)</td>
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</tr>
</tbody>
</table>

Figure 7 Whole body scan (cropped) at 24 hours after each cycle with 7.4 GBq \(^{177}\)Lu-DOTA-octreotate in patient with advanced, poorly differentiated neuroendocrine carcinoma. Upper row: anterior view, lower row: posterior view. Note the decrease of tumour uptake and the change of uptake pattern.
Figure 8 Diameters of the 5 largest metastases in the liver of a patient with poorly differentiated NET of unknown origin. Increase of tumour burden under therapy with cisplatinum and etoposide followed by temozolomide in combination with capecitabine. After start of therapy with 7 cycles of fractionated, dosimetry-guided $^{177}$Lu-DOTA-octreotate, subsequent tumour decrease occurred.

After seven cycles of $^{177}$Lu-DOTA-octreotate with 7.4 GBq each, dosimetry indicated an accumulated absorbed dose to the right kidney of 25.4 Gy and 24.4 Gy to the left kidney. The absorbed doses to the kidneys remained essentially on the same level during the first 4 cycles, but increased slightly towards the end of the treatment (Figure 9).

Figure 9 Absorbed doses to kidneys, liver, spleen, bone marrow and representative tumours in a patient with poorly differentiated neuroendocrine carcinoma undergoing fractionated, dosimetry-guided therapy with $^{177}$Lu-DOTA-octreotate.
The dose to the spleen decreased slightly over time. The absorbed dose to the bone marrow decreased throughout the treatment, both the self-dose calculated from the blood activity (89, 75, and 60 mGy at cycle 1, 3 and 6), as well as the photon contribution from solid organs, tumours and the remainder of the body (121, 106 and 78 mGy, respectively) (Figure 9).

Tumour dosimetry
Applying the same method for dosimetry as described for solid organs also to the tumours, all measured tumours increased their activity concentration and, as a consequence, the absorbed dose throughout the course of therapy. The activity distribution grew more homogeneous during the treatment, while the tumour appeared to shrink concentrically according to the fused SPECT-CT images (Figures 10 and 11). The more homogeneous activity distribution in the remainder of the large liver metastases is obvious in Figure 10.

![Figure 10](image)

*Figure 10* Sagittal view of SPECT-CT over the abdomen at the level of the right kidney, 24 hours after infusion of 7.4 GBq of $^{177}$Lu-DOTA-octreotate. Left: Cycle 1, May 2010. Right: Cycle 7, August 2011. Left upper corner in each image: attenuation correction CT, right upper corner attenuation corrected SPECT, left lower corner fused SPECT-CT, right lower corner maximum intensity projection (MIP). Note the position of the right kidney (arrow) and tracer distribution within the tumours.
Figure 11 SPECT CT images (left) and corresponding diagnostic CT (right) of largest liver metastasis in the left liver lobe at time of dosimetry at cycle 1, 3 and 6 (top to bottom). SPECT-CT images: left upper corner attenuation correction CT, right upper corner attenuation corrected SPECT, left lower corner fused SPECT-CT (all transversal views), right lower corner maximum intensity projection (MIP). Note the concentric shrinkage of the tumour and the increasing homogeneity of the uptake distribution.
Discussion

Malignant tumours, though not curable, can be controlled for an extended period of time [40]. In the special case of neuroendocrine tumours both symptoms caused by tumour growth as well as hormone production need to be treated. Thus, it is of great importance to choose the treatment with best efficacy and lowest degree of side effects.

In this thesis a clinically feasible approach on dosimetry is described, to optimise internal radiation with $^{177}$Lu-DOTA-octreotate. This method also presents an opportunity to monitor and understand in greater detail the dynamic changes of uptake during therapy and the radiobiological implications of it.

Paper I reports on the fact that the effective half-life especially in the kidneys changes only to a minor extent, opening for the possibility to reduce imaging during subsequent cycles, without compromising the prerequisites to calculate absorbed doses in solid organs.

Paper II focuses on the main organs at risk during radionuclide therapy, bone marrow and kidneys. A method of calculating the absorbed bone marrow dose is described. In combination with the results of kidney dosimetry it is shown that 50% of the patients can tolerate more than 4 cycles of $^{177}$Lu-DOTA-octreotate without passing the so far accepted tolerance doses of 23 Gy to the kidneys and 2 Gy to the bone marrow. This implies that these patients may achieve higher tumour doses when treated up to that limit.

The treatment of patients with advanced cases of colorectal NETs and bronchial carcinoids has been a clinical challenge, with very limited treatment options and low efficacy of available systemic treatment options. Paper III and IV present results after application of the novel methods for dosimetry in radionuclide therapy. The results compare favourably to previously reported results of therapy in these patient groups, and the observed side effects were few. Aiming at an absorbed dose to the kidneys of 23 Gy, achieved with up to 8 cycles of 7.4 GBq of $^{177}$Lu-DOTA-octreotate at initial treatment of colorectal NETs, was associated with a longer time to progression than in those that did not reach that dose at initial treatment. The limitations of these studies are that the some of the patients were analysed retrospectively and not in a randomised fashion, and that more patients need to be treated to be able to draw firmer conclusions. Still, the tumour response and survival data are promising.
Imaging during therapy, the concept of theranostics, by using the treatment radionuclide as it is possible with $^{177}$Lu gives a unique insight of dynamic changes that is impossible to achieve with any other therapy. It has been assumed in the literature that the distribution of uptake inside the tumour can change as an effect of previous treatment cycles resulting in a more optimal treatment situation [139] This assumption has now been supported, as seen in Paper V. Increased tumour uptake and absorbed doses are shown to occur at the same time as the uptake in the spleen and bone marrow decreases and the doses to the kidneys only increase slightly.

The results of this thesis concur in many aspects with previously published results, but there are also differences and new observations that can be highlighted.

Peptide receptor radionuclide therapy (PRRT) directed towards somatostatin receptors has become a milestone in the treatment of NETs. It was developed in a succession of clinical achievements in the treatment of this group of tumours, leading to improved symptom control and prolonged survival [83, 140-143]. It has been shown to result in morphologic response in the range of 25 to over 40% of the patients [104, 108, 109, 119, 144], with a dose dependent tumour response [145]. The reported results in this thesis are in agreement with the findings in the literature that objective responses can be achieved and that time endpoints such as overall survival and time to progression are superior in patients that reach a morphological response. On the other hand, also patients with stabilisation of a progressive disease and improved hormonal control can be considered as treatment response, as observed by several authors. Quality of life is an important aspect, and has been reported to improve under radionuclide therapy [120, 146]. It has not been a focus of this work, but the clinical observations in our patients are in good agreement with these findings.

Two radiopeptides have been used predominantly, $^{90}$Y-DOTATOC and $^{177}$Lu-DOTA-octreotate. Due to the different beta particle range of the radionuclides, it has been claimed that $^{90}$Y is a better radionuclide for larger tumours as opposed to $^{177}$Lu, which should be better suited for the treatment smaller lesions [102, 103, 130, 147, 148]. Tumour dosimetry in the current studies showed that $^{177}$Lu-DOTA-octreotate may be the radiopharmaceutical of choice even in large tumours. Kwekkeboom et al. report three- to fourfold higher uptake in 4 out of 5 tumours with basically unchanged uptake in kidneys and spleen, when comparing patients treated with $[^{177}\text{LuDOTA0Tyr3]}$ octreotate and $[^{111}\text{In-DTPA0]}$ octreotide [127]. Optimal tumour-over-kidney uptake is crucial for an optimal treatment result. Taking into account the shorter tissue penetration range of $^{177}$Lu as compared to $^{90}$Y, the same group draws the conclusion that $^{177}$Lu-DOTA-octreotate is the radiolabeled soma-
tostatin analogue of choice for peptide receptor radiotherapy [72], which is in agreement with the discussed findings in this thesis.

Barone et al observed [149] that kidney toxicity during treatment with $^{90}$Y-DOTATOC was increased in patients with low fractionation. Their conclusion was that kidney volumes, dose rate and fractionation play important roles for kidney dosimetry and the prediction of nephrotoxicity. The observation in our present patient of an improved tumour-to-organ dose ratio as a function of previous cycles of therapy adds a new aspect to the discussion. $^{177}$Lu has in comparison to $^{90}$Y a shorter range in tissue, a lower dose rate and offers the advantage of lower irradiation of structures adjacent to the tumours. Repeated cycles of $^{177}$Lu-DOTA-octreotate may lead to improved tumour dose absorption with still acceptable kidney toxicity, if scanning and dosimetry under therapy show a more homogeneous uptake pattern in the tumour. Under these circumstances, the longer half-life of $^{177}$Lu is an advantage, since the ratio of tumour-to non-tumour irradiation improves over time (Figure 12). Thus, very high, and potentially tumoricidal accumulated absorbed doses can be achieved. This pattern is frequent in colorectal NETs with a large tumour burden as they were described in Paper III. A possible contributing factor to an improved tumour uptake may be the receptor-upregulation in cells escaping from low dose radiation as observed in a rodent model [150, 151].

The potential for fractionated therapy with $^{177}$Lu-DOTA-octreotate in patients with high tumour burden, using surveillance dosimetry should be the subject of further evaluation. A recent report comparing therapy with $^{90}$Y-DOTATATE and a combination of $^{90}$Y and $^{177}$Lu-DOTATE indicates a survival advantage for the combination therapy [131]. Our reported findings suggest that a dosimetry-based approach with $^{177}$Lu-DOTA-octreotate might be advantageous over $^{90}$Y-labeled somatostatin analogues and possibly even combination therapy, and should be regarded as a veritable contestant for a randomized study, as suggested by Brans et al. in a reply to this article [152].

Figure 12

Cartoon illustrating the effect on tumour and surrounding tissues in therapy with $^{177}$Lu and $^{90}$Y. The blue ring represents the tumour uptake. The shorter range of $^{177}$Lu renders lower irradiation to adjacent tissue resulting in lower toxicity leaving the option for more treatment cycles.

The beta particle energy deposit of $^{90}$Y has a longer range outside the tumour, resulting in higher toxicity for adjacent tissues and suboptimal dose distribution in smaller tumours.
The clinical guidelines for the treatment of poorly differentiated neuroendocrine tumours with high proliferation rate recommend cisplatinum-based chemotherapy as first line treatment, yielding an objective response rate of 40 to 70%, with a duration of 8 to 11 months and a median survival of 15-19 months [79, 86, 153, 154]. High proliferation is generally regarded as an indicator of low somatostatin receptor expression, and somatostatin scintigraphy is not regularly performed for this reason [154], though this recommendation has been changed in recent years [90]. Cisplatinum-based chemotherapy has recently been shown to have a higher response rate in tumours with a Ki-67 rate of over 55%, nevertheless, these tumours are associated with shorter survival. A study on palliative chemotherapy in poorly differentiated neuroendocrine carcinomas reports a median survival of 11 months for patients that received chemotherapy, compared to 1 months in patients with best supportive care [155]. Only recently, a report focusing on the results of treatment with $^{177}$Lu-octreotide in 81 patients with respect to proliferation rate found comparable outcome in patients with proliferation rates up to 20%, with partial responses in 40%, minor responses in 15% and stable disease in another 34%, with 11% in progressive disease [156]. Only 2 out of 7 patients with a proliferation rate over 20% responded to the treatment that had been given in four cycles with a mean activity of 7.9 GBq at standard intervals of 3 months (10-14 weeks).

The patient reported on in Paper V, with focal Ki-67 values up to 50%, had very high somatostatin receptor expression and is at the time of the report 30 months progression-free after start of therapy. This underlines, that it is worthwhile to investigate somatostatin receptor expression in patients with poorly differentiated neuroendocrine carcinomas. In the small group of bronchial carcinoids reported in Paper IV, no difference in tumour response was seen in correlation to Ki-67 values. The interval between cycles ought to be of significance in highly proliferative tumours, and a shorter interval should be preferred in patients with aggressive tumour biology.

Besides kidney failure that has been predominantly seen as a side effect of $^{90}$Y-DOTATOC, bone marrow toxicity has been the other common side effect reported in association with radionuclide therapy. In Paper IV, we report on one patient that developed acute lymphatic leukemia after therapy with $^{177}$Lu-DOTA-octreotate. This is the second case of acute leukemia that occurred in patients treated with $^{177}$Lu-DOTA-octreotate at the University Hospital of Uppsala, overlooking over 340 patients treated since 2005. The here reported patient had had chemotherapy with temozolomide that had to be stopped due to bone marrow toxicity and fatigue. For the patients groups reported in this thesis, temozolomide and cisplatinum-based protocols have been the predominant first choice for systemic tumour therapy. Both the alkylator temozolomide and cisplatinum are associated with an increased risk for acute leukemia [157-159], and cisplatinum also with kidney toxicity.
Historical observations on women with ovarian cancers treated with alkylating agents either alone or in combination with cisplatinum showed a clearly increased risk for bone marrow malignancy, that seemed to increase further if the patient also had received radiation therapy [158]. This is a fact that cannot be ignored when discussing the succession of different treatment modalities. A better understanding of the effect of low dose rate radiation may be possible when dosimetry of the bone marrow is consequently applied. The suggested method renders a tool for that. The finding that bone marrow doses tend to decrease during therapy, unlike those for the kidneys, was unexpected.

The result of the bone marrow dose calculation gave at hand that in the majority of patients the kidneys were the dose-limiting organs, even if a higher dose limit of 29 Gy to the kidneys was assumed, as proposed by Konijnenberg et al [117]. This is in disagreement with the statement of Esser et al, that 70% of the patients will reach an accumulated dose of 2 Gy before the dose-limit for the kidneys is reached [160]. One explanation may be the way of calculating the cross-doses from adjacent organs and the remainder of the body. Bone marrow is highly vascularised, whereas the surrounding cortical bone contains vessels to a much smaller extent. Commonly used software programs for MIRD calculations assume that the remainder of the body includes solid bone, which means that the S-value for the calculation of cross-fire contains a beta component that is 88.7% of the total S-factor. This will most probably overestimate the bone marrow dose, which is why in the calculations presented in Paper II an S-factor without beta component is chosen. Previously, the calculation of bone marrow doses under therapy with $^{177}$Lu-DOTA-octreotate did not translate particularly well into the decrease of platelets observed [128]. A future study is planned to investigate the correlation between the data in the 200 patients described here and their clinical outcome.

The results reported in this thesis on colorectal NETs and bronchial carcinoids and a case of poorly differentiated neuroendocrine cancer are promising and support the view that treatment with $^{177}$Lu-DOTA-octreotate may be considered earlier in the treatment plan of the individual patient with advanced disease [123].

It has been increasingly acknowledged that dosimetry is an adjunct for optimizing the treatment protocol, to avoid side effects and increase absorbed doses to tumours [161-164].

Combinations with concomitant radiosensitizing drugs have been proposed in order to improve the therapeutic efficacy [132-134]. Individual dosimetry can be of help in the future to tailor therapy protocols, with the goal to find the ideal time point for such combinations, with lowest risk for side effects in relation to expected tumour efficacy. The amount of unlabelled peptide has been shown influential on the tumour uptake [165]. Com-
binations with unlabelled peptides in optimal doses as found by pre-therapeutic examinations may in the future be used in order to optimize the outcome of radionuclide therapy with lowest possible risk for side effects [166].

The thesis concludes that dosimetry is feasible on an individual basis for patients undergoing therapy with $^{177}$Lu-DOTA-octreotate. It is a tool that can be used to improve the understanding of the effects of radionuclide therapy and to improve the therapy outcome.
Conclusions

Paper I

For most patients it is safe to estimate the absorbed dose to the kidneys from the radionuclide uptake at 24 hours assuming an unchanged effective half-life at consecutive therapy cycles. Simplified dosimetry using this approach can serve as a tool to assess the number of treatment cycles for the individual patient. Patients with risk factors for kidney dysfunction and with large changes in tumour volume should be monitored more carefully. Simplified dosimetry according to this approach can serve as guidance for how many cycles of treatment a patient can tolerate.

Paper II

Bone marrow dosimetry based on blood activity curves and whole body imaging is feasible. Applied together with absorbed dose calculations based on a previously published small volume-of interest method for solid organs, 197/200 patients reached accumulated doses of 23 Gy to the kidneys before the dose to the bone marrow reached 2 Gy. The described dosimetry approach enabled an individually adapted therapy, in which 50 % of the patients could receive more than 4 cycles of $^{177}$Lu-DOTA-octreotate with 7.4 GBq before reaching these dose limits. Dosimetry helped to avoid the undertreatment that would have resulted by using a fixed treatment schedule. Twenty percent of the patients qualified for less than 4 cycles.

Paper III and IV

Dosimetry-guided, fractionated therapy with $^{177}$Lu-DOTA-octreotate aiming at an accumulated absorbed dose of 23 Gy to the kidneys is feasible, well tolerated and a favourable treatment option for patients with advanced stages of colorectal NETs as well as for patients with advanced bronchial carcinoids. Morphological tumour response correlated positively with time to progression and overall survival.
Paper V

The reported patient gives evidence that dosimetry-based fractionated therapy with $^{177}$Lu-DOTA-octreotate has the potential to improve the tumour-to-tissue dose as a result of previous treatment cycles. Tumoricidal absorbed radiation doses can be achieved despite a large tumour burden and high proliferation rates. Imaging and dosimetry during therapy is a valuable tool for treatment planning and for the evaluation of outcome.
Future Perspectives

Individual dosimetry for patients undergoing peptide receptor radionuclide therapy is still in the beginning of its clinical application. A multitude of questions need to be addressed in greater detail. Amongst them are:

- The maximal tolerated absorbed dose to the kidneys in the setting of fractionated therapy with $^{177}$Lu-DOTA-octreotate is still not established and further investigations on the effect of different fractioning models are warranted.
- The relationship of absorbed dose to the bone marrow and the future risk for bone marrow malignancy, including the effect of different models of fractioning needs to be explored on an individual basis.
- Pre-therapeutic imaging to quantify the amount of somatostatin receptors expressed by the tumour tissue may in the future serve as a prerequisite to tailor the amount of administered activity in order to achieve optimal receptor saturation.
- The amount of unlabelled peptide is of importance regarding the activity uptake during therapy. Also in this case, pre-therapeutic imaging can have an important role in order to tailor the tumour-to-background ratio.
- Different types of tumours show different response patterns. Dosimetry-based protocols for slow- and fast proliferating tumours need to be developed in order to optimize the risk-benefit ratio.
- Little is known about the level of absorbed tumour doses that can be reached under optimal treatment conditions. The demonstrated improved uptake pattern in later cycles of therapy with increased absorbed tumour doses in a subset of patients needs to be studied further.
- Radiosensitising agents may increase the tumour efficacy, but also the side effects of therapy with $^{177}$Lu-DOTA-octreotate. Individually performed dosimetry may give valuable information on achievable absorbed doses to tumours and risk organs.
- Chemotherapy as well as radionuclide therapy can induce bone marrow malignancy. More data needs to be collected with respect to different tumour types in order to decide on the optimal succession of different treatments.
- Tracers for targeting of tumours other than NETs and with the same efficacy as somatostatin receptor radionuclide therapy need to be developed.
Lovande resultat har erhållits i behandlingen av neuroendokrina tumörer med uttryck av somatostatinreceptorer med en peptidreceptormedierat radionuklidtherapi. 177Lu-DOTA-octreotat är en av de mest använda radiopeptiderna och standardmässigt rekommenderas maximalt fyra behandlingscykler. Mätningar av stråldosen (dosimetri) i de strålkänsligaste organen, njurar och benmärg, och själva tumören för att i stället på individnivå kunna bestämma maximala antalet behandlingar har hittills bedömts som svårt att genomföra regelmässigt.

Det första målet med denna avhandling var att utveckla ett kliniskt tillämpningsbart protokoll för beräkningen av den absorberade stråldosen i benmärg och njurar under behandling med 177Lu-DOTA-octreotat. Dosimetri för organ baserat på tre-dimensionell avbildning har tidigare beskrivits av forskargruppen, och ett nytt protokoll för benmärgs-dosimetri utvecklades. Hos de flesta patienter hittades bara små förändringar av den effektiva halveringstiden i njurarna under loppet av behandlingarna. Komplett dosimetri under första cykeln jämfört med mätningar under senare cyklar visade att den absorberade dosen kan beräknas baserat på aktivitetskonzentrationen ett dygn efter start av varje behandlingscykel. Studiens slutsats var att den rådande behandlingsstandarden leder till suboptimal behandling av en majoritet av patienterna: 50% av alla patienter kunde få fler än fyra behandlingscykler med 7,4 GBq 177Lu-DOTA-octreotat utan att överskrida gränsvärdet av 23 Gray till njurarna eller 2 Gray till benmärgen, och för 20% av patienterna var fyra behandlingscyklar för mycket.

Avhandlingens andra mål var att utvärdera resultatet av en dosimetristyrad behandling med 177Lu-DOTA-octreotat. i patientgrupper med olika typer av neuroendokrina tumörer. Patienter med utspridda tumörer från änd-och tjocktarm respektive från luftvägar och lunga visade sig ha längre överlevnad med denna metod jämfört med tidigare studier och med andra behandlingar. Vidare fanns ett samband mellan minskningen av tumörstorleken och tid fram till tumörprogress. Dessutom visades i ett fall av neuroendokrin cancer att även stora och snabbväxande tumörer kan behandlas med denna metod. I detta fall ökade dosen i tumörerna vid senare behandlingar men inte i friska organ, vilket ledde till en ännu bättre terapeutisk effekt under senare cykler.
Dosimetri-ledd, fraktionerad radionuklidbehandling med $^{177}$Lu-DOTA-octreotat är en värdefull behandlingsmöjlighet för patienter med avancerade neuroendokrina tumörer som uttrycker somatostatinreceptorer.
Zusammenfassung auf Deutsch

Die Peptidrezeptor vermittelte Radionuklidbehandlung zur inneren Strahlentherapie von neuroendokrinen Tumoren hat große Fortschritte gemacht und weist vielversprechende Ergebnisse auf. $^{177}\text{Lu-DOTA-octreotat}$ ist eines der meist verwendeten Radiopeptide. Bisher war man der Ansicht, dass Methoden zur Messung der Strahlendosis (Dosimetrie) für sowohl die Risikorgan Nieren und Knochenmark, als auch für Tumoren in einzelnen Patienten praktisch nicht durchführbar waren. Stattdessen wurde in den meisten Fällen eine Standardbehandlung mit vier Behandlungszyklen à 7,4 GBq durchgeführt.


Das zweite Ziel der Arbeit war die Beschreibung von Ergebnissen einer dosimetrie-gesteuerten Behandlung mit $^{177}\text{Lu-DOTA-octreotat}$. Man konnte zeigen, dass Patienten mit metastasierten colorektalen neuroendokrinen Tumoren und Bronchialkarzinoiden mit dieser Methode längere Überlebenszeiten hatten als mit anderen Behandlungsmethoden. Je besser der Behandlungseffekt auf die Tumoren war, desto längere Zeit verging bis die Tumo-
ren wieder anfingen zu wachsen. Darüber hinaus konnte an einem Patientfall mit einem niedrig differenzierten neuroendokrinen Tumor gezeigt werden, dass auch große Tumoren mit hoher Zuwachsrate erfolgreich mit dieser Methode behandelt werden können und dass sich im Laufe der Behandlung das Verhältnis zwischen Bestrahlung von Tumoren und Risikoorganen verbessern kann, was zu einer effektiveren Behandlung führte.

Dosimetrie-geleitete, fraktionierte Radionuklidbehandlung mit $^{177}$Lu-DOTA-octreotid ist eine wertvolle Behandlungsoption für Patienten mit fortgeschrittener Erkrankung an neuroendokrinen Tumoren, die Somatostatinrezeptoren ausdrücken.
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References


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