# Neuroendocrine tumors; measures to improve treatment and supportive care

de Hosson, Lotte Doortje

# 1

# General introduction and outline of the thesis

## Background

Neuroendocrine tumors (NETs) are rare tumors with an incidence 3.5/100,000 per year and a prevalence of 35/100,000 (1-3). The tumor arises from secretory cells of the neuroendocrine system. Patients with NET may experience various symptoms from the tumor mass, the output of hormones secreted by the tumor, and treatment accompanying side effects (4). Median survival in patients with regional and distant metastatic NET is 105 and 56 months respectively, illustrating the indolent nature of most NETs. Patients with localized and metastatic gastro-intestinal NET who have lived with NET for 5 years have a probability of surviving an additional 5 years of 98.2% and 73.5% respectively (3,5). This underscores the fact that most patients live relatively long. Patients with NET have a lower quality of life (QoL) compared with the general population (6-8). Patients are frequently metastasized at the time of diagnosis. Radical surgery is the only curative treatment for patients presenting with local or regional disease, solitary metastases or resectable liver metastases. Non-curative systemic treatment options have variable, limited success (9-20).

Ideally, in trials investigating novel drugs, the primary aim should be to study clinical relevant endpoints such as overall survival (OS) and QoL (21). However, in gastrointestinal and pancreatic NET (GEP-NET) patients, survival analysis can be challenging as the prolonged (natural) course of the disease often results in trials that allow crossover towards the experimental arm, or that allow second line therapies which could influence OS (22-24). Therefore, use of OS as primary endpoint is challenging, and QoL becomes more important to determine meaningful clinical benefit in the treatment of GEP-NET.

In cancer survivors adequate information provision is associated with health related QoL and is an essential aspect of supportive care (25,26). For patients with NET it is difficult to find meaningful and understandable information about their diagnosis. Other important factors influencing QoL in patients with NET are gastro-intestinal problems and increased frequency of bowel movements (27). Furthermore somatostatin analogues (SSA) decrease their pancreatic exocrine function and can result in fat-soluble vitamin deficiencies (28-30). In case of high serotonin production, tryptophan deficiency, could also lead to niacin (vitamin $B_3$) deficiency and lead to symptoms (29,31). Currently, strikingly little is known about how SSA using patients with NET should be best supported and if dietary support and supplementation of vitamins is feasible (32,33).

Clinical symptoms are, among others, associated with reduction in QoL. Symptoms in patients with NET can be caused by the high secretion of neuroendocrine amines. Therefore, local treatment of an active amine producing tumor lesion would be potentially meaningful to improve QoL (34). Previously it was demonstrated that tumor burden measured with total [$^{18}$F]FDOPA uptake correlates with catecholamine pathway activity (35). If lesions with high [$^{18}$F]FDOPA uptake could be identified with a non-invasive

method in patients with small intestinal NET, this might be of added value in the selection of lesions for local treatment.
Over the last years, immunotherapy with immune checkpoint inhibitors like the programmed death-1 and programmed death ligand-1 (PD1 and PD-L1) antibodies have shown antitumor activity across numerous tumor types by activation of T-cells in the tumor microenvironment (36). Interestingly for NETs, there is also a major interest in the tryptophan-degrading enzymes indoleamine 2,3-dioxygenase (IDO) and tryptophan 2,3-dioxygenase (TDO) which are involved in the immune response and are expressed in several tumor types. In serotonin producing NETs IDO and TDO play a special important role since tryptophan is the precursor of the serotonin pathway (37,38). There is, however limited information with regards to the complex interactions of NET tumour cells with their surrounding immune microenvironment. Consequently knowledge about potential targets for immunotherapy in patients with NET is limited.

## Aim of the thesis

The aim of this thesis is to measure and improve the clinical benefit of treatment and supportive care provided to patients with NET. We investigated tailored supportive measures for these patients as well as novel treatment approaches.

## Outline of the thesis

In **chapter 2** an overview of existing literature about trials comparing systemic antitumor treatment for GEP-NET versus a control is presented and their clinical benefit is interpreted. The electronic databases (PubMed, Embase) were searched for papers reporting comparative trials, conducted in adult patients with GEP-NET. The clinical benefit of the investigated therapies reported in the selected trials was determined according to the European Society of Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) and the net health benefit score according to the American Society of Clinical Oncology (ASCO) revised framework by four independent assessors.
QoL is an important factor that contributes to clinical benefit. Factors associated with enhanced QoL include; less clinical symptoms, and adequate information provision (39,40). The internet was found to be a useful source of general information for some patients with NET (41). In **chapter 3A** the feasibility of a web based system consisting of self-screening of problems and care needs in patients with NET was analyzed. Newly diagnosed NET patients were randomized between standard care (n=10) or intervention with additional access to the web-based system (n=10) during 12 weeks.

Patients completed questionnaires regarding received information, distress, QoL, and empowerment. The intervention group completed a semi-structured interview to assess patients' opinion on the web-based system.
Subsequently, in a randomized controlled trial 90 patients with NET were stratified between those newly diagnosed (< 6 months, n=28) or with a longer duration of the disease (n=74) and randomized between standard care (n=49) or intervention with additional access to the web-based system (n=53) during 12 weeks. Patients completed questionnaires about distress, perception and satisfaction of received information, QoL, and empowerment. The intervention group also completed a questionnaire based on the technical acceptance model regarding their use of and opinion on the web-based system (**chapter 3B**).
In **chapter 4** we described a feasibility study**,** in which 15 patients with NET using a SSA for over 6 months were counseled by a dietician for a personalized dietary advice and received supplementation of deficient vitamins A, D, E, K, B12 and vitamin B3 (niacin). Feasibility was assessed by calculation of participation/dropout rate and number of (severe) adverse events related to the intervention. At baseline, after 4 and 18 weeks, vitamins were measured, and QoL, distress, empowerment and nutrition state were assessed.
Part of symptoms in patients with NET are caused by the secretion of neuroendocrine amines and local treatment of a high metabolic active lesion would be another potential method to improve QoL meaningful in patients with NET (34). Therefore, in **chapter 5** we analyzed intertumoral heterogeneity with $^{18}$F-dihydroxyphenylalanine (DOPA) Positron Emission Tomography (PET) scans in patients with small intestinal (SI-) NET and investigated if tumor lesions with substantially higher [$^{18}$F]FDOPA uptake than the majority of the other lesions within a patient could be identified within a patient. [$^{18}$F]FDOPA PET scans of 38 patients, of which 35 serotonin producing, were analyzed. For all tumor lesions the [$^{18}$F]FDOPA uptake was calculated by dividing the standard uptake value (SUV) peak of the tumor lesion by the SUV mean of the background organ. The magnitude of heterogeneity between lesions within a patient was calculated by dividing the lesion with highest [$^{18}$F]FDOPA uptake by the one with lowest [$^{18}$F]FDOPA uptake. In patients (n=20) with more than 10 metastases the lesions with a higher tracer uptake than the upper inner or outer fence (more than 1.5 or 3 times the interquartile range above the third quartile) were defined as lesions with mild or extreme high [$^{18}$F]FDOPA uptake respectively.
In **chapter 6** we investigated the immune microenvironment of neuroendocrine tumors, by pathologic analysis of tumor tissue of 51 patients with serotonin or non-serotonin producing NET grade 1 or 2. Immunohistochemically analyses were performed for PD-L1, T-cells, IDO, TDO, mismatch repair proteins and activated fibroblasts. Serotonin

production was measured by high performance liquid chromatography fluorometry of 5-hydroxyindolacetic acid (5-HIAA) in 24-h urine and/or serotonin in platelet rich plasma. Finally the findings of this thesis are summarized in **chapter 7** followed by a discussion on the scientific and clinical implications and direction for future research.
**Chapter 8** comprises the summary of this thesis in Dutch.

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