CHAPTER 1
General introduction
Background
Neuroendocrine tumors (NETs) are a rare and heterogeneous group of tumors. Most NETs occur in the gastroenteropancreatic tract or bronchopulmonary system, where they are derived from enterochromaffin cells. NETs have the ability to produce various biogenic amines and polypeptide hormones which can result in a clinical syndrome [1,2]. For example, patients with a serotonin producing NET can suffer from a carcinoid syndrome characterized by flushing, diarrhea, asthma-like symptoms (e.g. wheezing) and valvular heart disease [3]. Cure of patients with NETs can only be achieved by complete resection of the tumor. In case of non-curable disease, therapy often includes systemic treatment like long-term somatostatin analogues for control of disease progression and symptoms [4]. Most often, low grade (grade 1 and 2, according to World Health Organisation 2017 classification) NETs have a relative indolent nature with a 5-year overall survival of 55% in patients with a metastasized NET [5]. So, patients can experience various symptoms for a long time as a consequence of the presence of the tumor as well as the release of bioactive substances secreted by the tumor. Also, side effects of the treatment itself can bother them. Studies in NET patients addressing the impact of having a NET do indeed demonstrate lower health related quality of life (QoL) in these patients compared with the general population [6-8]. Given these findings better ways of informing and supporting NET patients as well as novel treatments are warranted.

Aim of this thesis
The aim of this thesis is to determine novel ways of informing, supporting and treating patients with a NET.

Outline of this thesis
In Chapter 2 we extensively reviewed the literature to evaluate the effects of internet-based support programs on psychosocial and physical symptoms resulting from cancer diagnosis and treatment. We searched the literature for (non-)randomized controlled trials performed in adult cancer patients comparing quantitative psychosocial and/or physical outcomes of an internet-based support program with (a) comparison group(s). ‘Cancer patients’ were defined as individuals diagnosed with any solid cancer type, irrespective of disease stage, treatment phase, type of treatment and time since diagnosis.
An internet-based support program was defined as any program that aimed to rehabilitate or support cancer patients regarding psychosocial and/or physical symptoms resulting from diagnosis and treatment. The internet-based support program should have been designed by (a) health care professional(s). Studies regarding social support groups were eligible if the groups were moderated by a health care professional. Studies that described programs without access to the internet (e.g. CD-rom or DVD) or to a website (e.g. therapy via e-mail) were excluded. Quantitative psychosocial (e.g. distress, anxiety,
depression, quality of life (QoL)) and physical variables (e.g. fatigue, insomnia, pain and sexual problems) were the outcomes of interest. The CINAHL, MEDLINE (PubMed) and PsychINFO data bases were searched from inception till the last search on 31th January 2014 without limitations. Relevant references from retrieved articles and relevant systematic reviews were also reviewed to identify other eligible studies. Only articles in English were included. Each included study was assigned a level of evidence according to the Oxford Centre of Evidence Based Medicine.

No internet-based support program was available for patients with a NET and therefore we developed a web-based system. This system allows patients to self-screen for physical and psychosocial problems, to get tailored patient education on reported problems and if necessary, to refer themselves to care. The aim of the pilot study described in Chapter 3 was to examine the feasibility of this web-based system and to evaluate patient’s opinion on this. Eligible were newly diagnosed patients with a NET grade 1 or 2, according to the World Health Organization 2010 classification, within 3 months before study participation, with an age of 18 years or older and to be under surveillance or treatment at the Department of Medical Oncology in the University Medical Center Groningen (UMCG). Any primary site of NET and/or disease stage was allowed. Patients were randomized between standard care (N = 10) or intervention with additional access to the web-based system (N = 10) during 12 weeks. The participation and dropout rate were calculated and reasons for declining participation or dropout were noted. Patients completed questionnaires regarding received information, distress, quality of life and empowerment. The intervention group also completed a semi-structured interview to assess patients' opinion on the web-based system.

Based on patients’ recommendations and the results of the pilot study described in Chapter 3, we conducted a randomized controlled study with an adapted web-based system in NET patients with newly diagnosed disease (<6 months) and patients with a longer history of disease. The aim of the study described in Chapter 4 was to determine the effects of this adapted web-based system on perceived distress, patients' perception of and satisfaction with received information, QoL and empowerment. Eligible participants were adult patients with NET grade 1 or 2 (World Health Organization 2010 classification) and who were proficient in Dutch (both reading and writing). Patients were stratified by ‘time since diagnosis’, which resulted in 28 patients with newly diagnosed NET (<6 months) and 74 patients with longer diagnosed disease. Patients were in a 1:1 ratio randomized between standard care (N = 49) or intervention consisting of standard care with additional access to the web-based system (N = 53). Patients completed questionnaires regarding distress, received information, QoL and empowerment during the 12-week study period. At the end of the study period, the patients with access to the web-based system also completed a questionnaire about their use of and opinion about the web-based system.
Chapter 5 describes the study which was performed to assess the feasibility of video-consultation in the follow-up care of clinical stable NET patients. Twenty patients received two video-consultations during one year of follow-up. Feasibility of video-consultation was assessed by calculation of participation/dropout rate and report of reasons for declining participation and dropout. Also, safety concerns were assessed. Satisfaction with video-consultations was measured with questionnaires filled out by patients and physicians. Duration of video-consultation, patient-reported travel time for an regular outpatient clinic visit and patient's preference for type of consultation were recorded.

Nowadays, there is still an ongoing need and search for new treatment modalities to support patients with a NET and to control disease progression. The essential amino acid tryptophan is the precursor for serotonin and NAD+, the metabolically active form of niacin (vitamin B3). In serotonin producing NET patients, the tryptophan is consumed for serotonin production which can result in deficiency of tryptophan and niacin. The aim of Chapter 6 was to assess niacin status in 42 patients with a serotonin producing NET and with tryptophan deficiency and/or associated symptoms, who therefore received niacin supplementation. Niacin status was measured by 24-hour output of urinary N1-methylnicotinamide (N1-MN), which is a reliable marker for assessing niacin status. N1-MN was serially assessed before and after supplementation to examine the effectiveness of niacin supplementation.

In Chapter 7 we investigated the immune microenvironment of NETs. Treatment with immune checkpoint inhibitors (ICIs) has been proven effective in other cancer types. These tumors often express the transmembrane protein programmed death-ligand 1 (PD-L1). Also, presence of T-cells is associated with response to ICIs. In addition to ICIs, there is a major interest in the tryptophan-degrading enzymes indoleamine 2,3-dioxygenase (IDO) and tryptophan 2,3-dioxygenase (TDO). These enzymes deplete tryptophan in the tumor microenvironment along the kynurenine pathway. Tryptophan depletion in tumor microenvironment and increased production of kynurenines lead either to suppression of effector T-cells or conversion of effector T-cells to tumor tolerant regulatory T-cells. IDO and TDO are especially of interest in serotonin producing NETs since tryptophan is also the precursor of serotonin. Little is known about the complex interactions between NETs and their tumor microenvironment. In the search for new drug targets such as immunotherapy, we aimed with this study to get insight in the interaction of NETs with their immune microenvironment.

Tumor biopsies or surgical specimen taken before start of systemic antitumor treatment in 51 patients with a serotonin or non-serotonin producing NET grade 1 or 2, according to the World Health Organisation 2010 classification, were selected. Immunohistochemically analyses were performed for PD-L1, T-cells, IDO, TDO, mismatch repair proteins (MMR) and activated myofibroblasts and/or myofibroblast-like cells (alpha-smooth muscle
actin, desmin). Before start of systemic antitumor treatment, serotonin was measured by high performance liquid chromatography (HPLC) fluorometry of 5-hydroxyindolacetic acid (5-HIAA) in 24-h urine and/or serotonin in platelet rich plasma of the included patients. Before start of systemic antitumor treatment, serotonin was measured by high performance liquid chromatography (HPLC) fluorometry of 5-hydroxyindolacetic acid (5-HIAA) in 24-h urine and/or serotonin in platelet rich plasma of the included patients.

In Chapter 8 a summary of the presented data in this thesis and a general discussion with future perspectives is provided.

Finally, in Chapter 9 the thesis is summarized in Dutch.
References


