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The web around patients with neuroendocrine tumors

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The web around patients with neuroendocrine tumors

Novel ways to inform, support and treat

Grietje Bouma

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Dr. A.M.E. Walenkamp

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Paranimfen

F. (Frederike) Bensch

M. (Marjan) Zwiers

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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.

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Internet-based support programs to alleviate psychosocial and physical symptoms in cancer patients: a literature analysis

Grietje Bouma^{1‡}, Jolien M. Admiraal^{1‡}, Elisabeth G.E. de Vries¹, Carolien P. Schröder¹, Annemiek M.E. Walenkamp¹, Anna K.L. Reyners¹

¹ Department of Medical Oncology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands

[‡] The first two authors contributed equally to the manuscript

Abstract

In this review the effect of internet-based support programs on psychosocial and physical symptoms resulting from cancer diagnosis and treatment is analyzed. Selection of studies was based on the following criteria: (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). Literature search yielded 2032 studies of which 16 fulfilled the eligibility criteria.

Three different internet-based support programs were identified: social support groups, online therapy for psychosocial/physical symptoms and online systems integrating information, support and coaching services. Outcomes improved by these programs in nine studies. Especially fatigue, social support and distress improved, regardless of the program type. All online systems showed positive effects, mainly for social support and quality of life. This analysis indicates that internet-based support programs are effective in improving psychosocial and physical symptoms in cancer patients.

Keywords: oncology, internet, online, support, therapy, effectiveness.

Introduction

A diagnosis of cancer often has a disruptive impact on a patient's life. Cancer patients frequently experience psychosocial and/or physical distressing symptoms [1-3]. The importance of supporting patients adequately regarding symptoms resulting from diagnosis and treatment has been widely recognized [4,5]. However, supportive care needs still go unnoticed frequently [6,7]. To detect and meet the needs of this rapidly expanding patient population, the health care system is urged to develop and employ (cost-)effective programs to educate and support patients.

The internet is a viable medium by which patients can be supported regarding psychosocial and/or physical symptoms. Already in 2007, a Dutch cross-sectional survey on cancer-related internet use demonstrated that 60% of patients frequently used internet by themselves and 9% via others [8], reflecting the high acceptance of internet as a support and information channel. It has important advantages given its wide availability and accessibility, cost-efficiency and ability to provide tailored information and support [8-13]. During the last years, many new eHealth technologies have been introduced in cancer patient care, such as internet-based support programs addressing psychosocial/physical problems, internet-based communication and decision aids to promote shared decision making [14] and mobile applications providing survivorship care plans [15].

Internet-based support programs seem particularly well-suited to fulfill the unmet supportive care needs [4]. These programs have been linked to positive outcomes such as increased knowledge, perceived social support and improved health behaviors for people with chronic diseases [16]. Given the comparable nature of chronic diseases and cancer, these outcomes may also apply to cancer patients [17]. Additionally, several studies showed the feasibility and acceptability of internet-based support programs for both psychosocial and physical symptoms in these patients [4,18,19].

Despite these promising findings, the effects of internet-based support programs specifically designed for cancer patients are less clear. Reviews on the effects of internet-based support programs are scarce in the field of oncology. This paucity is due to the heterogeneous nature of these programs as well as measured study outcomes which renders rigorous evaluation of the effects difficult. The available reviews are either rather broad, for example summarizing all types of internet-based support including non-professional resources [20], or specifically focus on a single type of support program (e.g. online psychological therapy [4]) or tumor type [12]. Also, assessment of study quality has received limited attention. Therefore, the aim of this review was to analyze published clinical trials to assess the effects of internet-based support programs. More specifically, it was examined whether these programs are capable of alleviating psychosocial and/or physical symptoms resulting from cancer diagnosis and treatment. Additionally, the (methodological) quality of the included studies was evaluated.

Methods

Eligibility criteria for article selection

Articles were selected based on the following eligibility criteria.

Study design. Eligible studies were randomized controlled trials (RCT) and non-randomized controlled trials (CT), performed in adult cancer patients (≥ 18 years), 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. Studies in mixed populations were only included if data for cancer patients were reported separately. Studies must have reported original data. Letters to the editor, patient stories, posters, thesis, review studies and non-English records were excluded. Internet-based support program. 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. Programs that were not primarily designed to support/rehabilitate (e.g. treatment decision aids and health behavior change interventions) were beyond the scope of this review and excluded. Programs focusing exclusively on education were only included if the education aimed to support/rehabilitate cancer patients. 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.

Outcomes. Quantitative psychosocial (e.g. distress, anxiety, depression and quality of life (QoL)) and physical variables (e.g. fatigue, insomnia, pain, and sexual problems) were the outcomes of interest.

Search strategy and selection method

The CINAHL, MEDLINE (PubMed) and PsychINFO databases were searched from inception without limitations. For each database, one review author screened the titles and abstract of the retrieved records. Studies that were identified as clearly nonrelevant were excluded at this stage. Studies that were considered as potentially relevant or as ambiguous regarding eligibility were accessed in full-text and evaluated by two authors independently. The last search was performed on 31-01-2014. The following search terms were used alone or in combination: neoplasm, cancer, carcinoma, oncology,

internet, web, online, eHealth, telemedicine, patient education, social support, psycho-education, rehabilitation, support group, support system, therapy, disease management (see Appendix 1 for the full search). The search terms were extensively tested against the output retrieved from initial hand searches. Additionally, reference lists from retrieved articles and relevant systematic reviews were scanned to identify other eligible studies.

Quality assessment

Each included study was assigned a level of evidence according to the Oxford Centre of Evidence Based Medicine [21]. That system distinguishes five levels of evidence ranging from 1 (systematic review of randomized trials; the highest level of evidence) to 5 (mechanism-based reasoning; the lowest level of evidence). Additionally, we assessed the methodological quality of the included studies following a checklist used in a review regarding internet-based interventions in chronic diseases [17], which is an adapted version of the Cochrane Collaboration Back Review Group [22]. We changed the item 'method of randomization explained' into 'randomized groups' as we also included non-randomized CTs. The item on 'assessor blinding' was excluded since it is not feasible to blind the assessor in case of self-report measures. The quality score could range from 0 to 12 points. See Table 3 for the checklist and scoring procedures.

Results

The initial search yielded 2,032 articles and was reduced to 15 original articles (=15 studies) after application of the eligibility criteria. One additional article was identified after examination of the references of included articles and relevant systematic reviews (see Figure 1).

Description of selected included studies

Characteristics of the included studies are summarized in Table 1. All studies were published in 2001 or later, with the majority (N = 10) being published after 2010. Sample sizes ranged from 27 to 450 participants. All studies had a pre- and post-test design to measure outcome differences in the group(s). Twelve studies were RCTs. Three studies used several experimental [23] or control [10,24] groups, all other studies used a single experimental and control group (e.g. wait-list control, control group receiving usual care). One study examined two different types of programs, i.e. an online therapy for psychosocial symptoms with or without additional use of a support group [25].

Table 1. Methodological characteristics of the included studies

Program	Experimental (E) and control groups (C)	Target population and sample size	Disease stage	Treatment phase
Online support groups				
Bosom Buddies [33]	E (N=36): Bosom Buddies C (N=36): wait-list control group	Breast cancer patients (N=72) (≤32 months of diagnosis of primary breast cancer)	Not specified	Not specified
GyneGals [31]	E (N=13): GyneGals C (N=14): wait-list control group	Sexually distressed gynecologic cancer patients (N=27) (<5 years post-diagnosis)	Stage I-III	Follow-up
Online cancer support group [34]	E (N=48): internet cancer support group C (N=20): usual care	Spanish-dominant speaking immigrant breast cancer patients (N=68)	Not specified	During treatment and follow-up
Online support group [35]	E (N=24): moderated online support group C (N=26): peer-led online support group (no use of preselected topics or input from a moderator)	Breast cancer patients (N=50)	Stages I-IV	Follow-up: completed treatment ≤32 months
Online support group [29]	E (N=20): educational and support network program C (N=20): wait-list control group, received resource kit including pamphlets	Prostate cancer patients (N=40) (<5 years post-diagnosis, being married/living with significant other)	Not specified	Not specified
Online therapy for psychosocial/physical symptoms				
CAREss (Counseling about regaining erections and sexual satisfaction) [24]	E1 (N=33): internet-based version of CAREss C1 (N=48): wait-list control group C2 (N=40): face-to-face version of CAREss ^a	Prostate cancer patients (N=121) (heterosexual couples with the male partner having undergone localized prostate cancer treatment)	Stages I-III	Follow-up: definitive surgery or radiotherapy between 3 months and 7 years previously
Internet-based coping program [32]	E (N=32): internet-based coping program C (N=30): waiting-list control group	Early stage breast cancer patients (N=62)	Stage 0-III	Not specified
Onward [25]	E (N=15): Onward (Individual Internet Intervention (III) + internet support group) C (N=16): III only	Various cancer patients: breast, lymphoma, lung, colon, sarcoma and thyroid (N=31)	Stages I-IV	Follow up: after completion radiation or chemotherapy
Sleep Healthy Using The Internet (SHUTti) [26]	E (N=14): SHUTti C (N=14): wait-list control group	Patients with any type of cancer and insomnia (N=28)	Stage I-IV (at inclusion in remission)	Follow up: completed active treatment ≥1 month

Table 1. Methodological characteristics of the included studies (continued)

Program	Experimental (E) and control groups (C)	Target population and sample size	Disease stage	Treatment phase
Online systems				
CHESS (Comprehensive Health Enhancement Support System) [23]	E1 (N=118): CHESS information services	Breast cancer patients (N=450) (≤ 2 months of diagnosis of primary breast cancer or recurrence)	Not specified	Not specified
	E2 (N=109): CHESS information + support services			
	E3 (N=111): CHESS information + support + coaching services C (N=112): internet only			
CHESS [36]	E (N=147): CHESS (full version) C (N=148): received copy of Dr Susan Love's Breast Book	Younger (≤ 60 years) breast cancer patients (N=295) (< 6 months of diagnosis)	Stages I-IV	Not specified
CHESS [37]	E (N=286): CHESS (full version) C (N=51): control group (drawn from a separate RCT)	Low-income breast cancer patients (N=286) (< 1 year of diagnosis or metastatic cancer)	Stages I-IV	Not specified
CHESS [10]	E1 (N=91): CHESS (full version) C1 (N=83): internet access + list of high quality breast cancer websites C2 (N=83): books or audiotapes on breast cancer resources	Breast cancer patients (N=257) (< 61 days of diagnosis)	Stages I-IV	Not specified
Electronic health information support system [30]	E (N=39): electronic health information support system + standard care C (N=145): standard care	Post-surgery head and neck cancer patients (N=184)	Not specified	During treatment and follow-up
Health Navigation [28]	E (N=136): Health Navigation C (N=137): waiting-list control group	Various cancer patients (breast, stomach, colon, uterine, lung, thyroid) with moderate to severe fatigue (N=273)	Stages I-III	Follow up: completed primary treatment ≤ 24 months
WebChoice [27]	E (N=162): WebChoice C (N=163): information sheet with suggestions for publicly available cancer-relevant internet sites	Breast and prostate cancer patients (N=325)	Stages I-IV	During treatment

^a Randomized groups were reported only in the current analysis

Description of participants

The 16 studies comprised 2620 patients. Eight studies focused exclusively on female breast cancer patients. Four studies contained patients with various tumor types [25-28], of which breast cancer patients constituted 39-64%. The remaining studies were performed in patients with prostate [24,29], head and neck [30] and gynecologic cancer [31]. Nine studies included only women and two studies only men [24,29]. The overall median age of the patients was 52 years (range 42-67 years; two studies did not report on age). Seven studies analyzed cancer patients with all disease stages (stage I-IV), whereas four studies only included patients with locally or locally advanced cancer (stage I-III) [24,28,31,32]. Five studies did not specify patients' disease stage [23,29,30,33,34]. Six studies included solely patients who had completed cancer treatment during their follow-up [24-26,28,31,35], one study only included patients during treatment [27] and two studies patients in all treatment phases [30,34]. The remaining studies did not specify patients' treatment phase.

Figure 1. Inclusion process for the literature analysis

Description of internet-based support programs

Table 2 shows the characteristics of the internet-based support programs. Three different types of programs could be distinguished: social support groups [29,31,33-35], online therapy for psychosocial/physical symptoms [24-26,32] and online systems integrating multiple services such as information, support, communication and coaching services [10,23,27,28,30,36,37]. All but one study [34], provided patient education within the program. The majority of the programs provided the opportunity to communicate with peers [10,23,25,27,29-37] and/or professionals [10,23,24,27,28,30,31,34-37]. Exercises such as cognitive-behavioral homework and coping-skills training were part of the program in five studies [23-26,32]. Except for one internet-based support program [26], all programs were facilitated by a moderator. The moderator's role varied and included facilitating a discussion and/or introducing new topics in a support group [33,35], being the expert to ask questions [10,23,27,36,37] or having an active role in the intervention such as chatting, discussing and mailing with participants [24,27,30,31,34]. Two studies [28,29] did not describe the role of the moderator. The duration of the programs ranged from 6 weeks to 1 year.

Outcomes of included studies

The used measurement instruments and corresponding outcomes of the studies are presented in Table 2. Psychosocial outcome measures, such as (health-related) QoL, depression, distress/stress and perceived social support were the most common used outcome measures. Some studies used validated as well as self-constructed or modified questionnaires [10,23,24,26,28,30,31,33,34,36,37].

Positive effects of the internet-based support programs on outcome measures and/or measurement points were reported in nine studies. Of these, seven studies used online systems, one a social support group and one online therapy. Two studies mentioned that the number of included patients was insufficient to detect significant differences [25,31]. Patients in the experimental group experienced a better QoL compared to those in the control group(s) in three studies examining online systems [10,28,30] whereas eight other studies did not report any differences in QoL [23,26,27,29,32,34,36,37]. Two studies found positive effects within the experimental group(s) over time and stable or decreased QoL in the control group, but did not report differences between groups [24,29]. Only one [33] out of seven studies measuring depression found a significant positive effect in favor of the intervention group. A social support group for breast cancer patients resulted in less perceived (post-traumatic) stress [33] and an online system for breast and prostate cancer patients diminished global symptom distress [27]. Other studies using psychological [24,31,32] or sexual distress [31] as outcome measure did not show any effects. Of the six studies having social support as an outcome, three [10,36,37] examining the 'CHESS' program found a positive effect in favor of the intervention group.

Programs focusing on cancer-related fatigue [28] and insomnia [26] showed a positive effect on fatigue.

Only three studies examined long term effects (>3 months post-intervention) [10,23,24] of which one had positive long term effects up till 9 months after the end of the intervention on QoL and social support [10].

Quality assessment of included studies

Using the adapted Cochrane list for internet-based interventions, the median total score for methodological quality was 6 (observed range 1-8). The level of evidence based on the Oxford Centre of Evidence Based Medicine together with the (methodological) quality of the included studies is summarized in Table 3.

Table 2. Characteristics of the internet-based support programs and outcomes of the included studies

Program	Description of program	Duration program and measurement points	Outcome measures and measurement instruments	Positive effect(s) for experimental group(s) compared to control group(s)
Online support groups				
Bosom Buddies [33]	Support group moderated by a mental health professional. Weekly, breast cancer related topics were introduced and discussed.	12 weeks. Measures at baseline and 12 weeks.	<ul style="list-style-type: none"> • Depression: CES-D^e • Posttraumatic stress disorder: PCL-C^f • Anxiety: STAI^g • Stress: PSS^h • Self-efficacy: CBIⁱ • Style of coping with cancer: MINI-MAC^j • Group experience^k 	+ Depression + Posttraumatic stress disorder + Perceived stress
GyneGals [31]	Asynchronous discussion forum moderated by psychologists and provision of psycho-educational materials addressing psychosocial impact of gynaecologic cancer. Weekly, new topics were introduced.	12 weeks. Measures at baseline and post-intervention.	<ul style="list-style-type: none"> • Sexual distress: FSDS-R^k • Anxiety and depression: HADS^l • Illness intrusiveness: IIRS^m 	No significant outcomes (Study not powered to detect significant differences)
Online cancer support group [34]	Support group moderated by a trained bilingual facilitator. Weekly, issues of interest were discussed.	30 weeks. Measures at pre- and post-intervention.	<ul style="list-style-type: none"> • Depression: CES-D^e • Personal growth: PTGI^{n,b} • QoL: FACT-B^{o,b} • Pain^a 	No significant outcomes
Online support group [35]	Support group in a semi-structured (psycho-educational) format using asynchronous communication moderated by a social worker. Weekly, new topics were introduced and discussed.	12 weeks. Measures at baseline, 6, 12 and 16 weeks.	<ul style="list-style-type: none"> • Depression: CES-D^e 	No significant outcomes
Online support group [29]	Educational and support network program for prostate cancer patients.	6 weeks. Measures at baseline, 6 and 8 weeks.	<ul style="list-style-type: none"> • QoL: - SF-12v2^p - EPIC-26^q - Satisfaction with life scale - Relationship satisfaction questionnaire 	No significant outcomes (at 6 weeks: 3 (out of 10) quality of life subscales significantly improved over time)
Online therapy for psychosocial/physical symptoms				
CARESS ^c [24]	Sexual counseling program moderated by therapists. Couples received cognitive-behavioral homework considering sexually-related issues.	12 weeks. Measures at baseline and 12 weeks + 3, 6, 12 months beyond intervention period.	<ul style="list-style-type: none"> • Sexual satisfaction and function for men: IIEF^r • Distress: BSI-18^s • Relationship satisfaction: A-DAS^t 	No formal statistical comparison of E1 with C1/C2 reported (IIEF scores of E1 and C2 improved significantly over time, whereas C1 did not)
Internet-based coping program [32]	Self-guided intervention consisting of coping-skills training exercises, a small discussion board coping group and education on symptom management.	12 weeks. Measures at baseline and 12 weeks.	<ul style="list-style-type: none"> • Health related QoL: FACT-B^q and EuroQoL-5D "feeling thermometer" • Distress: IES^u • Physical well-being: MSAS^v 	No significant outcomes

Table 2. Characteristics of the internet-based support programs and outcomes of the included studies (continued)

Program	Description of program	Duration program and measurement points	Outcomes and measurement instruments	Positive effect(s) for experimental group(s) compared to control group(s)
Online therapy for psychosocial/physical symptoms				
Onward [25]	Program for depression treatment based on cognitive behavioral principles, including an internet support group. Twice a week new lessons and tools were released.	8 weeks. Measures at baseline, 4 and 8 weeks.	<ul style="list-style-type: none"> • Depressive symptoms: HADS¹ 	No significant outcomes (Study not powered to detect significant differences)
SHUTI [26]	Program for improving insomnia symptoms, based on cognitive-behavioral therapy. The program includes 6 interactive cores and a sleep diary.	9 weeks. Measures in 2 weeks before and after intervention.	<ul style="list-style-type: none"> • Insomnia severity: ISI^w • Sleep diary: sleep efficiency (SE), total sleep time (TST), sleep onset latency (SOL) • Fatigue: MFISI-SF^a • Mood: HADS¹ • QoL: SF-12^p 	<ul style="list-style-type: none"> + Insomnia severity + SE (subscale sleep diary) + SOL (subscale sleep diary) + Fatigue
Online systems				
CHES [23]	Home-based system integrating information, support (including discussion groups, 'ask an expert') and coaching services (e.g. for easing distress, healthy relating).	3 months. Measures at baseline, 2 and 6 weeks, 3, 6 and 12 months. (Analysis reported for 6 weeks, 3 and 6 months)	<ul style="list-style-type: none"> • Emotional processing^a • Positive coping: Carver's Brief Cope • Functional well-being: FACT-B^o • Breast cancer concerns: FACT-Bo • Social support: Wisconsin social support scale 	<ul style="list-style-type: none"> 6 weeks + Emotional processing (E1>C) + Positive coping (E2>C) 3 months + Emotional processing (E1>C; E2>C)
CHES [36]	Home-based system integrating information, support and decision services (including health charts, decision aid, action plan).	6 months. Measures at baseline, 2 and 5 months.	<ul style="list-style-type: none"> • Social support^a • QoL: FACT-B^o 	<ul style="list-style-type: none"> 5 months + Social support
CHES [37]	See description above.	4 months. Measures at baseline and 4 months.	<ul style="list-style-type: none"> • Perceived social support^a • QoL: FACT-B^o • Negative emotion^a • Health self-efficacy^a 	<ul style="list-style-type: none"> + Perceived social support + Negative emotion
CHES [10]	See description above.	5 months. Measures at baseline, 2, 4 and 9 months.	<ul style="list-style-type: none"> • QoL: FACT-B^o • Social support^a 	<ul style="list-style-type: none"> 2 months + QoL (E1>C1) + Social support (E1>C1) 4 months + QoL (E1>C1) + Social support (E1>C1; E1>C2) 9 months + QoL (E1>C2) + Social support (E1>C2)
Electronic health information support system [30]	Electronic health information support system, integrating communication (send messages), information, support (peer-to-peer via forum) and health-monitoring.	6 weeks. Measures at baseline, 6 weeks and 3 months.	<ul style="list-style-type: none"> • QoL: QoL questionnaire^d 	<ul style="list-style-type: none"> 6 weeks + 5 (out of 22) subscales 3 months + 1 (out of 22) subscale

Table 2. Characteristics of the internet-based support programs and outcomes of the included studies (continued)

Program	Description of program	Duration program and measurement points	Outcomes and measurement instruments	Positive effect(s) for experimental group(s) compared to control group(s)
Online systems				
Health Navigation [28]	Tailored education program for cancer-related fatigue. Consisting of self-assessment and graphic reports, health advice, online education, enhanced and short message services, caregiver monitoring and support, and health professional monitoring.	12 weeks. Measures at baseline and 12 weeks.	<ul style="list-style-type: none">•Cancer related fatigue: BFI¹ and FSS²•HRQoL: EORTC QLQ-C30^{3a}•Energy conservation: ECS^{4b}•Physical activity: MET^{5a,c}•Nutritional status: MINA^{6d}•Psychological distress: HADSII•Pain: BPI^{7a,e}•Sleep quality/quantity: MOSS-SS^{8f}	+ Cancer related fatigue + Health-related quality of life (only cognitive functional scale)
WebChoice [27]	Interactive health communication application for reducing symptom distress containing an assessment component, tailored symptom self-management support, information section, communication section and a diary.	1 year. Measures at baseline, 3, 6, 9 and 12 months. (analysis for 12 months reported only)	<ul style="list-style-type: none">•Symptom distress: MSAS-SF⁹•Depression: CES-D⁹•Self-efficacy: CBI¹•Health related QoL: 15D-HRQoL instrument•Social support: Medical Outcomes Study Social Survey	+ 1 (out of 3) subscale of MSAS-SF (=global distress index)

^aSelf-constructed questionnaire by the authors, ^bQuestionnaire translated by authors, ^cOnly reporting measurement instruments and outcomes for the male partner, ^d3 out of 22 subscales were self-constructed.

^eCenter for Epidemiological Studies-Depression Scale, ^fPTSD Checklist-Civilian version, ^gState-Trait Anxiety Inventory-state Scale, ^hPerceived Stress Scale, ⁱCancer Behavior Inventory, ^jMINI-Mental Adjustment to Cancer Scale, ^kFemle Sexual Distress Scale-Revised, ^lHospital Anxiety and Depression Scale, ^mIllness Intrusiveness Rating Scale, ⁿPosttraumatic Growth Inventory, ^oFunctional Assessment of Cancer Therapy-Breast, ^pShort Form Health Survey, ^qExtended Prostate Cancer Index Composite, ^rInternational Index of Erectile Function, ^sBrief Symptom Inventory-18, ^tAbbreviated form of the Dyadic Adjustment Scale, ^uImpact of Events Scale, ^vMemorial Symptom Assessment Scale(-short form), ^wInsomnia Severity Index, ^xMultidimensional Fatigue Symptom Inventory-Short Form, ^yBrief Fatigue Inventory, ^zFatigue Severity Scale, ^{aa}European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C 30, ^{ab}Energy-Conservation Strategies Inventory, ^{ac}Metabolic Equivalent of Task, ^{ad}Mini-Nutritional Assessment questionnaire, ^{ae}Brief Pain Inventory, ^{af}Medical Outcome Study-Sleep Scale.

Table 3. Quality assessment of the included studies^{a,b}

Study	Level of evidence ^c	Methodological quality												Total score
		1	2	3	4	5	6	7	8	9	10	11	12	
Online support groups														
Bosom Buddies [33]	2	✓	✓	-	✓	-	✓	✓	-	✓	-	✓	✓	8
GyneGals [31]	2	✓	✓	?	?	-	✓	-	-	✓	-	✓	✓	6
Online cancer support group [34]	3	-	-	-	?	-	-	-	-	?	-	?	✓	1
Online support group [35]	3	✓	-	-	-	✓	✓	-	-	✓	✓	?	✓	6
Online support group [29]	2	✓	✓	?	?	-	-	-	-	✓	-	?	✓	4
Online therapy for psychosocial/physical symptoms														
CAREss [24]	2	✓	✓	?	?	-	✓	✓	✓	✓	-	-	✓	7
Internet-based coping program [32]	2	✓	✓	?	-	-	✓	-	-	✓	-	-	✓	5
Onward [25]	2	✓	✓	?	-	✓	✓	-	-	✓	-	✓	✓	7
SHUTi [26]	2	✓	✓	?	-	-	✓	-	-	✓	-	✓	✓	6
Online systems														
CHESS [23]	2	✓	✓	?	?	-	-	-	✓	✓	✓	?	-	5
CHESS [36]	2	✓	✓	?	?	-	-	-	-	✓	✓	✓	✓	6
CHESS [37]	4	✓	-	-	-	-	✓	-	-	?	-	✓	✓	4
CHESS [10]	2	✓	✓	✓	-	-	✓	-	✓	✓	-	✓	✓	8
Electronic health information support system [30]	3	✓	-	-	-	✓	✓	-	-	✓	-	-	✓	5
Health Navigation [28]	2	✓	✓	✓	✓	-	-	-	-	✓	✓	✓	✓	8
WebChoice [27]	2	✓	✓	?	✓	-	✓	-	-	✓	✓	✓	✓	8

^a1=Specification of eligibility criteria, 2=randomized groups, 3=treatment allocation concealed, 4=groups similar at baseline, 5=explicit description of interventions, 6 = description of compliance, 7 = timing of dropout and comparison with completers, 8 = long-term follow-up (>3 months after post- intervention assessment), 9 = timing of outcome assessment comparable, 10 = sample size described with power calculation, 11 = intention-to-treat analyses, 12 = point estimates and measures of variability.

^b✓ = reported item or yes (1 point), — = unreported item or no (0 points), ? = unclear item or unable to determine (0 points). Total score can be 12.

^c Level of evidence according to the system used by the Oxford Centre for Evidence-Based Medicine.

Discussion

The most apparent result from this review is that the majority of the included studies reported positive effects on patient-reported psychosocial and physical symptoms, regardless of the used program type. This result differs from a similar review conducted in 2010 [20]. That review focused on empirical studies (N = 24 including 37 articles) reporting outcomes of the use of online support/resources by adult cancer survivors. The authors concluded that use of online support/resources showed promising but inconclusive evidence for positive outcomes due to a lack of rigorous evaluations. In the current review rather strict criteria for the final inclusion for analysis of studies were used. For example, only (non-) randomized controlled trials focusing on professionally designed internet-based programs for cancer patients were included. As a result, only five studies included in the previous review met our inclusion criteria. Moreover, our review includes ten studies published since 2010, of which six reported positive outcomes.

Comparable reviews analyzing studies conducted in patients with chronic diseases also showed positive effects of internet-based support programs. A recent systematic review included 17 studies examining online mental health interventions in patients with chronic gastrointestinal conditions. That review showed that these online interventions resulted in less somatic symptoms and an improved quality of life [38]. Another systematic review in patients with various chronic diseases including diabetes, heart failure and COPD (N = 18 RCTs) found beneficial effects of internet-based interventions on patient empowerment [17]. A Cochrane systematic review involving 24 RCTs including in total 3739 patients with chronic diseases found a positive effect of online systems on perceived social support [16]. This finding is in line with our review that showed positive effects for all online systems, mainly for the outcome social support. Given these findings, online systems may well be a generic tool to support patients with various diseases, in different disease stages and treatment phases.

The supportive care needs of cancer patients may differ depending on their socio-demographic and illness-related characteristics. For example, several studies reported that supportive care needs vary by age [39-41]. Therefore, it has been recommended that interventions fit the characteristics and needs of recruited patients [4]. In the current review, patients' median age was relatively young (52 years) compared to the median age of cancer patients at diagnosis which is 66 years [42]. The majority of the studies included in this review focused on breast cancer patients. Whether internet-based support programs should be adapted to age groups and/or tumor types to optimize effectiveness is unclear. Happily, several ongoing trials will shed light on this aspect as studies are ongoing in patients with tumor types such as prostate cancer, lung cancer and neuroendocrine tumors (ClinicalTrials.gov Identifiers NCT01716702, NCT01012401, NCT01849523) [43].

Our methodological quality assessment showed that the included studies could have been improved on several aspects in order to obtain a higher quality level. For example, in 14 of the 16 studies, study completers were not compared with drop-outs. This comparison may provide valuable information regarding which patients benefit from the internet-based support programs. Twelve of the included studies were conducted in the US. Caution is warranted in generalizing these results to patients in other countries because of possible differences in health care systems and expectations of the role of health care professionals as noted by the aforementioned Cochrane review [16].

A few limitations could be noted regarding our review. The included studies made use of many different outcomes. This heterogeneity hampers firm conclusions regarding effects on some less frequently studied outcomes. Also, some included studies had small sample sizes (e.g. [25,31]). The absence of significant effects might be caused by a lack of power instead of true ineffectiveness of the intervention.

Since cancer patients make widespread use of internet-based technologies, the challenge is to provide easy accessible tools that will be of benefit for the individual patient. Internet-based technologies appear at a much greater pace than research can keep up with. A way to resolve this challenge is to examine the efficacy of generic program components and/or underlying principles that are more timeless than the programs themselves as has been proposed previously [44]. Successful implementation into routine cancer care represents another challenge but is crucial to reach the full potential of internet-based support programs. A barrier for patients might be a lack of accessible internet-based support programs that match their supportive care needs and preferences. Patient preferences for internet-based support vary considerably as demonstrated by a recent study on use patterns of the online system 'WebChoice' [45]. It cannot be expected that a few accessible programs will cover the supportive care needs of all patients. We recommend that more effort should be put in the disclosure of available web-based support programs and tools. For example, a portal website could be constructed which contains all available supportive care programs/tools including apps, websites and social media for cancer patients. As such, patients are provided with a choice what type of supportive care programs/tools matches their need and preferences. Ultimately, patients will receive the supportive care they wish for and benefit from the wealth of tools and programs delivered through the internet.

Conflict of interest statement

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All authors drafted, read and approved the final version of the manuscript.

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Appendix 1. Full search databases

MEDLINE (PubMed)

((((Neoplasms[MESH] OR Carcinoma[Mesh]) OR (cancer*[TIAB] OR neoplasm*[TIAB] OR carcinoma*[TIAB] OR oncology[TIAB])) AND ((Internet[Mesh] OR web*[TIAB] OR online*[TIAB] OR internet*[TIAB]) OR (e-health*[TIAB] OR eHealth*[TIAB]) OR (telemedicine[MESH:noexp])) AND ((“Patient Education as Topic”[Mesh]) OR (“Social Support”[Mesh]) OR (psychoeducat*[tiab]) OR (“rehabilitation”[MESH]) OR (support group*[tiab]) OR (support system*[tiab]))))

CINAHL

((((MH “Neoplasms+”) OR (MH “Oncology+”) OR TI (“cancer*” OR “neoplasm*” OR “carcinoma*” OR “oncology”) OR AB (“cancer*” OR “neoplasm*” OR “carcinoma*” OR “oncology”)) AND ((MH Internet+ OR MH telehealth+) OR TI (“internet*” OR “web*” OR “online*” OR “e-health*” OR “eHealth*”) OR AB (“internet*” OR “web*” OR “online*” OR “e-health*” OR “eHealth*”)) AND ((MH “Patient education”) OR (MH “Support, psychosocial”) OR (MH “Psychoeducation”) OR (MH “Rehabilitation, Cancer”) OR (TI “support group*”) OR (TI “support system*”) OR (AB “support group*”) OR (AB “support system*”)))

PsychINFO

((((DE “Neoplasms”) OR (DE “Benign Neoplasms”) OR (DE “Breast Neoplasms”) OR (DE “Endocrine Neoplasms”) OR (DE “Nervous System Neoplasms”) OR (DE “Terminal Cancer”) OR TI (“cancer*” OR “neoplasm*” OR “carcinoma*” OR “oncology”) OR AB (“cancer*” OR “neoplasm*” OR “carcinoma*” OR “oncology”)) AND ((DE “Internet”) OR (DE “Telemedicine”) OR TI (“internet*” OR “web*” OR “online*” OR “e-health*” OR “eHealth*”) OR AB (“internet*” OR “web*” OR “online*” OR “e-health*” OR “eHealth*”)) AND ((DE “Client Education”) OR (DE “Support Groups”) OR (DE “Psychoeducation”) OR (DE “Online Therapy”) OR (DE “Disease Management”) OR (DE “Rehabilitation”) OR (DE “Cognitive Rehabilitation”) OR (DE “Neuropsychological Rehabilitation”) OR (DE “Neurorehabilitation”) OR (DE “Occupational Therapy”) OR (DE “Physical Therapy”) OR (DE “Psychosocial Rehabilitation”) OR TI (“rehab*” OR “support system*” OR “support group*” OR “patient educat*”) OR AB (“rehab*” OR “support system*” OR “support group*” OR “patient educat*”)))

Web-based information and support for patients with a newly diagnosed neuroendocrine tumor: a feasibility study

Grietje Bouma¹, Lotte D. de Hosson¹, Claudia E. van Woerkom¹,
Hennie van Essen¹, Geertruida H. de Bock², Jolien M. Admiraal¹,
Anna K.L. Reyners¹, Annemiek M.E. Walenkamp¹

¹ Department of Medical Oncology, University Medical Center Groningen,
University of Groningen, Groningen, The Netherlands

² Department of Epidemiology, University Medical Center Groningen,
University of Groningen, Groningen, The Netherlands

Abstract

Purpose

Patients with a neuroendocrine tumor (NET) frequently experience physical and psychosocial complaints. Novel strategies to provide information to optimize supportive care in these patients are of interest. The aim of this study was to examine whether the use of a web-based system consisting of self-screening of problems and care needs, patient education and self-referral to professional health care is feasible in NET patients and to evaluate their opinion on this.

Methods

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, quality of life (QoL) and empowerment. The intervention group completed a semi-structured interview to assess patients' opinion on the web-based system.

Results

The participation rate was 77% (20/26 invited patients) with no dropouts. The use of the web-based system had a negative effect on patients' perception and satisfaction of received information (range Cohen's d -0.88 to 0.13). Positive effects were found for distress (Cohen's d 0.75), global QoL (subscale European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30, Cohen's d 0.46), resolving problems with social functioning and finding information (subscales EORTC QLQ-GINET 21, Cohen's d 0.69 respectively 1.04), and feeling informed (subscale empowerment questionnaire, Cohen's d 0.51). The interview indicated that the web-based system was of additional value to standard care.

Conclusions

Use of this web-based system is feasible. Contradictory effects on informing and supporting NET patients were found and should be subject of further research.

Keywords: neuroendocrine tumor, information, support, web-based, internet.

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Introduction

Neuroendocrine tumors (NETs) are rare tumors arising from secretory cells of the neuroendocrine system. Secretion of hormones and/or amines can result in a broad set of symptoms [1,2]. Patients can experience various symptoms as a consequence of the presence of the tumor as well as the release of the hormones secreted by the tumor. Also, side effects of the treatment can bother them. Moreover, diagnosis and treatment of cancer often results in physical, psychological, practical, social and spiritual concerns [3]. Studies in patients with NETs demonstrate that these concerns lead to lower health related quality of life (QoL) compared with the general population [4,5]. In general, when patients with cancer are properly informed, they experience a better health related QoL and less depression and anxiety [6,7]. In addition, providing information also results in an increased participation of patients in decision making, greater satisfaction with care, lower levels of distress and improved sense of control [7-10].

Among patients with cancer, the increasing role of internet as a source of cancer related information is recognized. Web-based patient education and support have become widely accepted [11-13]. We developed a web-based system for NET patients with the aim to examine its feasibility and to evaluate patient's opinion on this. Secondary aims were to explore the effects on patients' perception and satisfaction of received information, distress, health related QoL, and empowerment. The web-based 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.

Methods

Participants

To be eligible for this study, patients had to be newly diagnosed with a NET grade 1 or 2 (according to the World Health Organization 2010 classification) within 3 months before study participation. Any primary site or disease stage was allowed. Patients had to be under surveillance or treatment at the Department of Medical Oncology in the University Medical Center Groningen (UMCG). Additional inclusion criteria were 18 years of age or older and ability to read and write Dutch. Not eligible were patients with an estimated life expectancy of less than 3 months or a second primary tumor with active follow-up or treatment. All eligible patients were invited to participate. Recruitment occurred at the outpatient clinic during October 2013 to January 2014. The study was approved by the medical ethical committee of the UMCG and registered in ClinicalTrials.gov (NCT01849523). All patients gave written informed consent.

Study procedure

For detailed description of study procedures, see Appendix 1. Eligible patients were

informed about the study by their treating medical oncologist during a follow-up visit or by phone if a follow-up visit was not planned at short notice. Patients were asked if they could be approached for study participation by one of the investigators. If this was allowed, the investigator informed the patient orally after the follow-up visit or by phone. Patients were informed about the aims, study procedures, and feasibility design of this study. Following obtained informed consent, patients were randomized in a 1:1 ratio to the standard care group or the intervention group that received standard care with additional access to the web-based system. At baseline, all patients received questionnaires by mail regarding socio-demographic characteristics, health care/internet use, perception and satisfaction of received information (EORTC QLQ-INFO25) and QoL (EORTC QLQ-C30, EORTC QLQ-GINET21). At baseline, the standard care group received the paper-and-pencil version of the Distress Thermometer (DT) and Problem List (PL) by mail. The intervention group had to complete the online version of the DT and PL (content identical to the paper-and-pencil-version). When questionnaires were completed, the intervention group received instructions how to use the web-based system together with log-in information including a personal username and password. At week 12, all patients received questionnaires by mail regarding frequency of visits to psychosocial and/or allied health care professionals, perception and satisfaction of received information, QoL and empowerment (Constructs Empowering Outcomes, CEO questionnaire). The standard care group also received the paper-and-pencil version of the DT and PL by mail. The intervention group was reminded to complete the online version of the DT and PL after 12 weeks. At end of the study, the patients assigned to the intervention group were also invited for a semi-structured interview with the investigator regarding their opinion on the web-based system.

Randomization outcome was not blinded and also notified to the treating medical oncologist. In this manner, all patients could discuss their questions about the retrieved information (e.g. from the web-based system, information leaflets) with their treating medical oncologist, oncology nurse, other health care professionals and/or allied health care workers.

Standard care and study intervention

Standard care for newly diagnosed patients with a NET during the first visit(s) at the Department of Medical Oncology includes verbal information about the diagnosis, evaluating complaints/problems and a physical examination by their treating medical oncologist. Also, newly diagnosed patients visit an oncology nurse with experience in care for NET patients. All patients receive at diagnosis information leaflets of the Dutch Patient Neuroendocrine Tumor Foundation [14]. During follow-up visits, the medical oncologist evaluates and discusses the general well-being, test results, treatment (e.g. options, side effects), answers questions of the patient and performs a physical

examination. If physical and/or psychosocial problems require more in-depth discussion, investigation or treatment, patients can receive a consultation with the oncology nurse or other health care professionals.

In the intervention group, patients received access to the web-based information and support system in addition to standard care during the 12-week study period. The web-based system incorporates elements of self-screening for problems and care needs, tailored support in self-help, patient education and communication with a health care professional. Patients screened themselves for psychosocial/physical problems and care needs by filling out the DT and PL. Immediately after completion of the DT, automated personalized feedback was received upon their reported distress score. For example, feedback emphasizes the possibility for a referral to a health care professional for moderate or severe distress. Thereafter, patients received tailored feedback on physical/psychosocial problems they had reported on the PL. This feedback comprises background information about the problem, advice on how to cope with the problem ('self-help advice') and which health care professional can be consulted when self-help insufficiently alleviates problems. Online completed DT and PL questionnaires with feedback were online saved and coded to ensure that patients could access the feedback and information later.

Also, general information about NETs and diagnostic procedures, treatments, and their side effects is provided by the web-based system. Patients could send an e-mail or request for a telephone call to communicate with the investigator (experienced physician in treating NET patients) in case of questions, problems or a referral wish. A referral wish to a professional or allied health care worker was arranged by the treating medical oncologist.

Measures

Patient characteristics including socio-demographic characteristics, use of previous and current psychosocial and/or allied health care, acquaintance with internet and use of internet to search cancer-related information were assessed by a self-report questionnaire. Information on disease-related characteristics was collected from medical records. Participation and dropout rates and reasons for declining study participation and dropout were tracked.

Patients' perceived amount and satisfaction of received information was measured with the Dutch EORTC QLQ-INFO25 questionnaire, which is a validated questionnaire to evaluate the information received by cancer patients [15]. This questionnaire comprises multi-items grouped into four information provision subscales 'perceived receipt of information about the disease', 'medical tests', 'treatment' and 'other care services' and single-items on 'having received information' in different manners (e.g. written, online, on CD) and on 'satisfaction with, amount of and helpfulness of information'. In addition, two

open questions investigate topics of which patients would like to receive more or less information. All responses are ranged on a four-point Likert scale, except for four single items that have a 'yes/no'-scale. Distress was measured using the validated Dutch DT and PL [3]. The DT consists of a single item asking patients to indicate the amount of overall distress experienced during the past week on an 11-point scale (range '0' no distress – '10' extreme distress). The PL identifies existing practical, family/social, emotional, religious/spiritual and physical problems and was adapted by the investigators according to the issues which are prevalent among and relevant to patients with NETs (in total 31 items). Patients could also add a problem that was not mentioned in the PL. For each reported problem, patients rated the associated experienced amount of distress (range '0' no distress – '10' extreme distress). The PL ends with the question whether the patient has a referral wish to an oncology nurse, peer NET sufferer group, a psychosocial (psychologist, social or pastoral worker) or allied health care professional (e.g. physical therapist, dietician).

QoL was measured with the validated Dutch EORTC QLQ-C30 (version 3) [16] and Dutch EORTC QLQ-GINET21 [17]. The EORTC QLQ-C30 measures cancer-specific QoL comprising five functional scales (physical, role, cognitive, emotional, and social), three symptom scales (fatigue, pain and nausea/vomiting), six single symptoms items (dyspnea, insomnia, loss of appetite, constipation, diarrhea and financial impact) and a global health status/QoL scale. Responses are given on a 4-point Likert scale (range '1' not at all - '4' very much) with higher scores indicating higher QoL at the functional scales and higher symptom burden for the symptom scales. The global health status/QoL scale is scored on a 7-point scale (range '1' very poor - '7' excellent) with higher scores indicating higher QoL. The EORTC QLQ-GINET21 is a disease-specific QoL questionnaire for patients with a gastrointestinal NET to supplement the EORTC QLQ-C30 questionnaire and assesses specific disease symptoms, side effects of treatment, body image, disease related worries, social functioning, communication and sexuality. Responses are given on a 4-point Likert scale (range '1' not at all - '4' very much) with higher scores indicating higher symptom burden for the symptom scales. Empowerment was measured by the Dutch CEO questionnaire, which is developed and tested in different online support groups including breast cancer patients [11,18]. In the questionnaire, 'online support groups' was modified in 'website' for the intervention group and in 'standard care' for the control group. The domains 'being better informed', 'feeling more confident about the relationship with their physician', 'improved acceptance of the illness', 'feeling more confident about the treatment' and 'increased optimism and control over the future' were measured since these domains were expected to be influenced by the web-based system.

Patients' opinion regarding satisfaction with the web-based system was assessed with a semi-structured interview by phone with participants in the intervention group. Ten open-ended, both qualitative and quantitative questions were used and when relevant

the interviewer probed the participant with follow-up questions to include topics not established beforehand. These questions comprised the following issues: contents, lay-out, user-friendliness, perceived usability, usage and future recommendations. The interviews were recorded and afterwards all interviews were transcribed in English. All topics per individual interview related to the purpose of the research were noted and categorized.

Statistical analysis

The purpose of this study was to explore the feasibility and to evaluate patient's opinion on the web-based system on abovementioned endpoints. Twenty NET patients were recruited and randomized. Descriptive statistics (e.g. means, ranges, frequencies) were calculated for all measures. Missing values for the EORTC questionnaires were handled according to the EORTC guidelines [19]. Raw scores of all scales and items of the EORTC questionnaires were linearly transformed to a score ranging from 0 to 100 [19]. Scores of the different problem/empowerment domains of the PL/CEO questionnaire were calculated by taking the mean of the total scores of the items in each domain. Effect sizes for change scores on each endpoint were determined (Cohen's *d*) by using the mean difference between post- and pre-intervention scores of both groups and dividing this difference by the pooled standard deviation. Given the retrospective design of the CEO questionnaire with only a post-intervention measurement, effect sizes of the outcomes of the CEO were calculated by using the mean difference between post-intervention scores of both groups and dividing this difference by the accompanying pooled standard deviation.

All effect sizes are reported so that a positive effect size indicates a desired direction (i.e. improvement of outcome in favor of the intervention group). An effect size (ES) between 0.20-0.50 is defined as small, between 0.50-0.80 as medium and ≥ 0.80 as large. Analyses were performed using the software package SPSS, version 22 for Windows (SPSS, Inc, Chicago, IL, USA).

Results

Participants

Twenty of the 26 invited eligible patients gave informed consent and all patients completed the full study period. Reasons for declining study participation were no access to a computer and internet ($n = 2$), no interest in information and filling out questionnaires ($n = 1$), feeling overburdened ($n = 2$) and not willing to be further confronted with the disease ($n = 1$). Patient and tumor characteristics are summarized in Table 1. There was a minor imbalance between the intervention and control group regarding age, educational level and primary tumor localization. The intervention group consisted of younger, higher educated patients and more patients with a NET of the lung.

During the study, six patients ($n = 1$ in the standard care group) started treatment with a somatostatin analogue and two patients (both in standard care group) with everolimus. Three patients ($n = 1$ in the standard care group) underwent curative surgery and two patients in the intervention group underwent palliative surgery during the study period.

Table 1. Patient and tumor characteristics

	Standard care group ($n = 10$) N ^a	Intervention group ($n = 10$) N ^a
Median age in years (range)	64.0 (45-74)	59.5 (41-74)
Gender M/F	5/5	4/6
Educational level		
Lower vocational education	6	3
Intermediate vocational education	3	5
Higher vocational education/university	1	2
Employment status		
Employed	3	4
Unemployed	7	6
Internet use		
In daily life	8	9
For disease purposes	6	7
Location primary tumor		
Lung	0	3
Pancreas	2	2
Jejunum/ileum	4	4
Unknown	4	1
Disease stage (according to UICC ^b)		
Stage I/II	0	2
Stage III	1	2
Stage IV	9	6
Treatment prior to study participation (%)	80%	50%
Somatostatin analogue	6	4
Curative surgery	0	1
Palliative surgery	4	2
Everolimus	0	1
Radiofrequency ablation	1	0
Other ^c	1	0
Health care use before diagnosis (%)	20%	10%
Physical therapist	1	1
Psychologist	1	0

^aData are expressed as number unless noted otherwise

^bUnion for International Cancer Control

^cProton pump inhibitor

Effect of intervention on outcomes

In the standard care group, one patient was supported by a social worker and another patient by a psychologist during the study period. In the intervention group, two patients received treatment of a physical therapist ($n = 2$) and/or dietician ($n = 1$).

Table 2 presents mean scores of the different subscales of EORTC QLQ-INFO25 at baseline and end of study for the two groups and the accompanying effect sizes. Most outcomes on subscales showed negative effect sizes indicating that the intervention group had less improvement in feeling informed. None of the patients wished to receive less information. At baseline, less patients in the intervention group wished to receive more information (50% vs. 70% in the intervention respectively standard group).

Baseline and end of study mean scores and accompanying effect sizes of the DT and PL are summarized in Table 3. A medium effect size (ES) was observed for distress and social problems in favor of the intervention group. Trivial or small effect sizes were observed for problems in the other domains. Few patients experienced religious/spiritual problems. Outcomes for QoL measured by EORTC QLQ-C30 and EORTC QLQ-GINET21 questionnaires are depicted in Tables 4A and 4B. The intervention group showed a higher increase in QoL (small ES). A moderate ES was observed for cognitive functioning in favor of the standard care group. In contrast, financial difficulties and pain improved more (moderate effect sizes) in the intervention group.

The intervention group showed more improvement on disease-specific problems measured by the EORTC QLQ-GINET21 questionnaire. For example, large effect sizes were observed for disease related worries.

Outcomes of the different domains of empowerment are presented in Table 5. The intervention group felt better informed (moderate ES) and had more confidence in their treatment (small ES). In contrast, the standard care group scored higher for the domain 'acceptance of illness' (small ES) and 'optimism and control over the future' (moderate ES).

Table 2. Perceived information and satisfaction (EORTC QLQ-INFO25)

Pre M: mean score at baseline, Post M: mean score at 12 weeks, SD: standard deviation, ES: Effect Size.

Higher scores means more/better information and satisfaction.

	Standard care group (n = 10)		Intervention group (n = 10)		
Outcome	Pre M (SD)	Post M (SD)	Pre M (SD)	Post M (SD)	ES
Information about..					
Disease	33.33 (21.52)	42.50 (18.19)	35.83 (21.89)	39.17 (19.66)	- 0.30
Medical tests	48.89 (21.72)	56.67 (16.93)	57.78 (15.54)	61.11 (22.38)	- 0.22
Treatments	32.78 (13.21)	44.44 (15.27)	29.44 (17.77)	33.33 (16.56)	- 0.59
Other services	12.50 (14.83)	30.00 (30.73)	10.83 (15.24)	14.17 (16.22)	- 0.74
Different places of care	16.67 (28.32)	23.33 (31.62)	16.67 (28.33)	13.33 (28.11)	- 0.17
How to help yourself	13.33 (23.31)	33.33 (31.43)	20.00 (23.31)	20.00 (28.11)	- 0.88
Received written information	80.00 (42.16)	80.00 (42.16)	100.00 (0.00)	70.00 (48.30)	- 0.52
Received cd/video	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00
Satisfaction with information	46.67 (23.31)	50.00 (23.57)	50.00 (23.57)	56.67 (22.50)	0.13
Wanting to receive more info	30.00 (48.30)	60.00 (51.64)	50.00 (52.70)	60.00 (51.64)	- 0.28
Wanting to receive less info	100.00 (0.00)	100.00 (0.00)	100.00 (0.00)	100.00 (0.00)	0.00
Helpfulness of information	46.67 (17.21)	56.67 (22.50)	46.67 (17.21)	56.67 (27.44)	0.00
Global Score	38.40 (13.30)	48.08 (12.82)	43.10 (10.51)	43.70 (13.66)	- 1.06

Table 3. Distress (Distress thermometer and Problem List)

Pre M: mean score at baseline, Post M: mean score at 12 weeks, SD: standard deviation, ES: effect size.

Higher scores mean more distress/problems.

	Standard care group (n = 10)		Intervention group (n = 10)		
Outcome	Pre M (SD)	Post M (SD)	Pre M (SD)	Post M (SD)	ES
Distress level	4.90 (2.96)	4.60 (3.03)	4.10 (3.32)	2.00 (1.49)	0.75
Problems					
Practical	5.10 (6.42)	5.60 (6.79)	8.20 (13.30)	7.80 (12.75)	0.16
Social	0.20 (0.63)	0.90 (2.03)	2.60 (5.23)	2.00 (3.27)	0.53
Emotional	17.00 (22.40)	12.50 (14.65)	20.10 (19.20)	12.20 (14.40)	0.20
Spiritual	0.00 (0.00)	0.00 (0.00)	0.50 (1.58)	0.40 (0.97)	0.19
Physical	18.10 (11.83)	11.80 (10.62)	16.90 (11.40)	11.70 (11.41)	- 0.10
Global score	40.40 (34.63)	30.80 (27.12)	48.30 (43.33)	34.10 (39.86)	0.18

Table 4A. Quality of life (EORTC QLQ-C30)

Pre M: mean score at baseline, Post M: mean score at 12 weeks, SD: standard deviation, ES: effect size.

Higher scores for quality of life and functioning represents higher quality of life and level of functioning. Higher scores for symptoms represents a higher level of symptomatology.

	Standard care group (n = 10)		Intervention group (n = 10)		
Outcome	Pre M (SD)	Post M (SD)	Pre M (SD)	Post M (SD)	ES
Global quality of life	59.17 (20.95)	58.33 (24.53)	65.83 (26.77)	70.83 (17.67)	0.46
Functioning					
Physical	73.33 (23.09)	76.67 (24.19)	79.33 (27.30)	80.67 (20.23)	- 0.15
Role	61.67 (28.38)	61.67 (32.44)	66.67 (36.00)	70.00 (21.94)	0.15
Emotional	67.50 (36.74)	73.33 (25.99)	70.00 (32.20)	78.33 (20.11)	0.11
Cognitive	78.33 (27.27)	83.33 (24.85)	78.33 (20.86)	70.00 (23.31)	- 0.61
Social	68.33 (14.59)	75.00 (26.35)	73.33 (31.62)	78.33 (20.86)	- 0.08
Symptoms					
Dyspnoea	23.33 (27.44)	20.00 (23.31)	36.67 (33.15)	30.00 (24.60)	0.15
Insomnia	16.67 (23.57)	20.00 (28.11)	23.33 (27.44)	20.00 (28.11)	0.21
Appetite loss	23.33 (35.31)	10.00 (22.50)	20.00 (35.83)	13.33 (23.31)	- 0.30
Constipation	6.67 (14.05)	10.00 (22.50)	16.67 (32.39)	13.33 (23.31)	0.14
Diarrhea	23.33 (22.50)	23.33 (38.65)	16.67 (32.39)	16.67 (32.39)	0.00
Financial difficulties	10.00 (16.10)	23.33 (27.44)	26.67 (43.89)	23.33 (35.31)	0.63
Fatigue	45.56 (31.62)	37.78 (34.03)	33.33 (36.29)	33.33 (28.21)	- 0.40
Nausea and vomiting	13.33 (20.49)	1.67 (5.27)	18.33 (33.75)	10.00 (21.08)	- 0.12
Pain	26.67 (33.52)	25.00 (26.35)	35.00 (38.05)	21.67 (20.86)	0.52

Table 4B. Quality of life (EORTC QLQ-GINET21)

Pre M: mean score at baseline, N: number of patients, Post M: mean score at 12 weeks, SD: standard deviation, ES: effect size.

Higher scores means more or worse symptoms/problems.

	Standard care group (n = 10)				Intervention group (n = 10)				
Outcome	Pre M (SD)	N	Post M (SD)	N	Pre M (SD)	N	Post M (SD)	N	ES
Endocrine symptoms	27.78 (19.07)	10	22.22 (14.81)	10	25.56 (21.63)	10	13.33 (11.48)	10	0.35
Gastrointestinal symptoms	28.00 (22.40)	10	27.33 (14.55)	10	30.67 (29.18)	10	24.00 (21.36)	10	0.34
Treatment related symptoms	14.44 (18.22)	5	15.54 (18.56)	5	14.44 (18.22)	5	23.33 (16.81)	5	- 0.40
Problems social functioning	28.89 (15.89)	10	35.56 (12.62)	10	42.22 (28.11)	10	38.89 (24.15)	10	0.69
Disease related worries	33.95 (26.42)	9	42.59 (31.18)	9	45.00 (28.50)	10	32.22 (22.03)	10	0.92
Pain muscles/bone	16.67 (23.57)	10	16.67 (23.57)	10	37.50 (45.21)	8	37.50 (33.03)	8	0.00
Problems sexual functioning	9.52 (16.27)	7	14.29 (26.23)	7	38.89 (38.97)	6	33.33 (42.16)	6	0.52
Problems receiving information	13.33 (17.21)	10	20.00 (23.31)	10	23.33 (27.44)	10	10.00 (16.10)	10	1.04
Problems body image	20.00 (17.21)	10	13.33 (17.21)	10	3.33 (10.54)	10	6.67 (14.05)	10	- 0.60

Table 5. Empowerment (CEO)

Mean: mean score (at 12 weeks), SD: standard deviation, ES: effect size.

Higher scores represent better empowerment for each outcome.

	Standard care group (n = 10)	Intervention group (n = 10)	
Outcome	Mean (SD)	Mean (SD)	ES
Feeling informed	13.60 (3.86)	15.30 (3.02)	0.51
Confidence in relationship physician	37.06 (6.78)	36.20 (10.17)	- 0.10
Confidence in treatment	16.60 (4.35)	18.60 (4.30)	0.46
Acceptance of illness	17.60 (2.12)	16.40 (5.54)	- 0.29
Optimism and control over future	25.00 (4.69)	22.50 (3.87)	- 0.58

Qualitative and quantitative semi-structured interview

To evaluate patient's opinion on the web-based system all patients in the intervention group were interviewed.

The number of times the web-based system was visited ranged from 2-5 (n = 4 patients), 6-10 (n = 2), 11-15 (n = 3) to 16-20 (n = 1). Frequently visited parts of the web-based system were 'diagnostic procedures' and 'treatments'. The DT, specific information about NET, and the part on 'diagnostic procedures' and 'treatments' were found most useful.

All patients found the web-based system user-friendly.

All but one patient found the information presented by the web-based system understandable. Most patients (n = 6) found the provided information by the web-based system 'pretty complete', 'complete' or 'very complete'. Suggestions for information to add to the web-based system were 'frequently used medications in NET patients other than tumor treatments (e.g. laxatives)', 'advice about healthy life style' and 'life expectancy'. Seven patients preferred information on their type of tumor only. Two patients were also interested in other types of tumors and enjoyed reading about it.

Most patients (n = 8) found the web-based system of additional value. All would recommend this web-based system to peers and believed this should be part of the standard care. Also, several patients considered it of interest for people surrounding the NET patient (e.g. family, friends, general practitioners). All wanted to use the web-based system in the future. Patients would like to use it immediately upon diagnosis.

Discussion

This is the first study examining whether use of a web-based information and support system is feasible in NET patients. The results suggest that use of this web-based system is feasible. The NET patients appreciated the use of the web-based system and found its use of additional value to standard care. This exploratory study was not powered to detect differences between the two groups.

Use of eHealth-tools is increasing and a goal of the European Commission to improve

citizen's health [20]. Given the lack of available eHealth-tools in NET patients, there is an unmet need for a professionally designed web-based information and support system in these patients. Our results provide information to further develop web-based information systems in rare cancer types like NET.

Patients using the web-based information system had less problems with finding adequate information and felt better informed as measured by the EORTC QLQ-GINET21 and CEO. Unexpectedly, the results of the EORTC QLQ-INFO25 demonstrated that use of the web-based system resulted in less improvement of feeling informed and satisfaction of received information. The EORTC QLQ-INFO25 is not specifically developed for patients with an NET, which could potentially explain the observed difference between questionnaires. However, it is possible that a web-based system results in feeling worse informed and more depressed. In contrast to face-to-face contact with health care providers, visiting a web-based system does not offer the possibility to discuss feelings of insecurity in person or to ask questions after having read disturbing information about their disease. Also, the intervention group had less acceptance of illness and less control and optimism regarding the future at the end of the study period. A randomized controlled study examining different types of internet support groups in breast cancer patients, also reported negative effects on depression and anxiety in the internet support patients who received additional information and support of other breast cancer patients [21]. Being provided with more information can possibly be confronting for patients with cancer which may result in an increase of negative thoughts and worse future perspectives.

This study had a small sample size due to the feasibility design. Younger age and higher educational level are associated with more internet use for health care information [22]. Therefore, the intervention group may have had a more critical view on the received information. As a result of these small sample sizes despite randomization, the intervention group was younger, higher educated and comprised three lung NET patients. The DT/PL is an element of the web-based system and therefore the intervention group had to fill out the DT/PL online instead of a paper-and-pencil version. Since the content of the online DT/PL is identical to the paper-and-pencil version, we do not expect that this has affected the outcome.

The results of the current study have given insight into the existing worries and problems of NET patients, but also into the needs and expectations of information and support. This has enabled us to develop a sufficiently powered randomized controlled trial investigating an adapted web-based system for patients with both new and a longer known diagnosis of NET (ClinicalTrials.gov Identifier NCT02472678). Mainly based on the results of the semi-structured interview, adaptations have been made to the web-based system, such as adding new information (e.g. information about commonly used medication by NET patients and average life expectancy), 'truths and hoaxes' about NET

and experiences of patients with different types of NET with their disease. Hopefully, firm conclusions about effects of this web-based system can be drawn after finishing this study. If the web-based system is proven effective after finishing this study, it will become available for all NET patients in the Netherlands.

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Appendix 1. Extensive description study procedures

Eligible patients were informed by their treating medical oncologist about the study during a follow-up visit or by phone if the next follow-up visit was planned beyond 2 months. Patients who were interested in study participation were subsequently approached by one of the investigators and received study information. Following informed consent, patients were randomized in a 1:1 ratio to standard care group or the intervention group that received standard care with additional access to the web-based system. Randomization was performed by e-mail from the investigator to the central data manager of the Department of Medical Oncology (UMCG) who is not involved in the recruitment or treatment of the patients. For allocation to the standard care or intervention group a computer-generated randomization list was used. The allocation sequence was concealed from the investigator. The investigator was informed by e-mail to which group the patient was assigned. The investigator informed the patient by phone about the randomization outcome and further process. Also, the treating medical oncologist was notified about the randomization outcome. After randomization, all patients received questionnaires by mail about socio-demographic characteristics, health care/internet use, perception and satisfaction of received information (EORTC QLQ-INFO25) and quality of life (EORTC QLQ-C30, EORTC QLQ-GINET21) as baseline measurement. The standard care group also received the paper-and-pencil version of the Distress Thermometer (DT) and Problem List (PL). After the investigator had collected these completed questionnaires, the intervention group received via their preferred route an e-mail or letter with a short introduction of the web-based system together with log-in information including a personal username and password. These patients were asked to complete the online DT and PL within one week after having received the log-in information (baseline measure DT and PL). At week 12, all patients received questionnaires by mail about health care use, perception and satisfaction of received information, quality of life and empowerment (Constructs Empowering Outcomes-questionnaire) as end of study measurement. The standard care group also received the paper-and-pencil version of the DT and PL. The intervention group were reminded by e-mail/letter to complete the online version of the DT and PL after 12 weeks. Patients assigned to the intervention group were also requested to complete a semi-structured interview regarding their opinion on the web-based system by phone.

Web-based personalised information and support for patients with a neuroendocrine tumour: randomised controlled trial

L.D. de Hosson^{1‡}, G. Bouma^{1‡}, J. Stelwagen¹, H. van Essen¹,
G.H. de Bock², D.J.A. de Groot¹, E.G.E. de Vries¹, A.M.E. Walenkamp¹

¹ Department of Medical Oncology, University of Groningen,
University Medical Centre Groningen, Groningen, the Netherlands

² Department of Epidemiology, University of Groningen,
University Medical Centre Groningen, Groningen, the Netherlands

[‡]The first two authors contributed equally to the manuscript

Abstract

Background

Patients with a neuroendocrine tumour (NET) frequently have physical and psychosocial complaints. Aim of this study is to determine whether a web-based, personalised information and support system (WINS) reduces distress and/or improves patients' perception of and satisfaction with information received.

Methods

Patients with NET, stratified for those newly diagnosed (<6 months, n = 28) and with a longer history of disease (n = 74), were randomised between standard care (n = 49) and intervention, consisting of access to WINS (n = 53). Primary outcome was change of distress and satisfaction with perceived information measured with the distress thermometer and problem list and the quality of life questionnaire (QLQ)-INFO25. The intervention group also completed a questionnaire based on the technical acceptance model (TAM).

Results

We observed no difference in distress slope and slope of median global score on perceived information and satisfaction between the intervention and control group. Interestingly, 55% of patients wished to receive more information at baseline.

Conclusions

In a population of NET patients, access to WINS did not improve indicators for distress, perception of information and satisfaction with information received, more than standard care only. Despite the need for more information, the WINS does not have added value to the information and care provided by health care professionals.

Background and aims

Neuroendocrine tumours (NETs) are rare tumours with an incidence of 3.5/100,000 per year in the last decade [1,2]. Patients with NET may experience various symptoms from the tumour mass, the output of hormones secreted by the tumour, treatment and accompanying side effects [3]. Patients are frequently metastasized at the time of diagnosis. Patients with metastasized NETs have a relatively long median survival: 100 months for NETs of the small intestine and 60 months for pancreatic NETs [4]. Patients with NET have a lower quality of life (QoL) compared with the general population [5]. For patients with NET it is difficult to find meaningful and understandable information about their diagnosis. Anxiety, higher depression, and stress negatively influenced QoL in patients with NET. Self-efficacy, more social support and optimism are associated with better QoL [6]. Previous research in cancer patients and cancer survivors has consistently shown that high satisfaction with the information received and satisfied information needs were related to better quality of life and lower emotional distress for anxiety and depression [7,8]. Furthermore, internet-based support programs are effective in improving psychosocial and physical symptoms in cancer patients [9]. In addition, in an observational study of NET patients using qualitative interviews, 7 out of 18 patients found the internet to be a useful source of general information [10].

We previously developed a web-based personalised information and support system (WINS), for patients with NETs with the aim of reducing distress and/or improving patients' perception of and satisfaction with information received.

A pilot study demonstrated the feasibility of using WINS in patients with NET [11]. Based on these results and on patients' recommendations, we developed the current version of WINS, which was used in the present study. The aim of this randomised trial is to determine whether WINS reduces distress and/or improves NETs patients' perception of and satisfaction with information received.

Results

Patients

Between May 2015 and October 2016, we included 105 patients in the study (Figure 1). The trial was ended when 91 patients completed the study. Of the 91 patients who completed the study, 46 (12 newly diagnosed) patients were randomised to the intervention group.

Baseline characteristics of included patients are shown in Table 1. At baseline, 78 patients had previously visited the internet for information on NET before randomization. At baseline, 50 patients stated that they wanted to receive more information compared to 31 at end of study. At baseline, 4 patients answered that they would prefer to receive less information. At the end of study no patients gave this answer.

Figure 1. Consort diagram

Table 1. Baseline characteristics

	All patients n=91	Control group n=45	Intervention group n=46
Newly diagnosed patients n (%)	25 (27)	13 (29)	12 (26)
Sex: female n (%)	42 (46)	23 (51)	19 (41)
Age mean in years (SD)	62 (8)	63 (7)	62 (10)
Location of primary tumour n (%)			
Pancreas	21 (23)	9 (20)	12 (26)
Intestine	53 (58)	26 (58)	27 (59)
Stomach/duodenum	3 (3)	2 (4)	1 (2)
Colorectal	2 (3)	2 (4)	1 (2)
Bronchopulmonal	1 (1)	1 (2)	0 (0)
Appendix	1 (1)	1 (2)	0 (0)
Unknown/other	9 (10)	4 (9)	5 (11)
Duration of disease in months mean (SD)	41 (56)	33 (38)	50 (66)
Disease grade n (%)			
1	57 (63)	27 (60)	30 (65)
2	21 (23)	12 (27)	9 (20)
Unknown	13 (14)	6 (13)	7 (15)
Marital state: married n (%)	75 (82)	34 (76)	41 (89)
Education: polytechnic or university n (%)	33 (37)	16 (36)	17 (38)
Internet use n (%)			
Daily	86 (96)	40 (91)	46 (100)
For information about the disease	78 (87)	37 (82)	41 (89)
Treatment during study n (%)			
Surgery	7 (8)	2 (4)	5 (11)
PRRT	2 (2)	1 (2)	1 (2)
SSA	64 (70)	32 (71)	32 (70)
Systemic treatment other than SSA	17 (19)	9 (20)	8 (17)
Treatment before study n (%)			
Surgery	52 (57)	26 (58)	26 (57)
PRRT	2 (2)	0 (0)	2 (4)
Radiotherapy	3 (3)	0 (0)	3 (6)
SSA	65 (71)	32 (71)	33 (72)
Systemic treatment other than SSA	23 (25)	12 (26)	11 (24)
Other (RFA)	1 (1)	0 (0)	1 (2)

n = number, PRRT = peptide receptor radionuclide therapy, RFA = radiofrequency ablation, SSA = somatostatin analogue.

Primary outcomes

The median distress level in both groups was 3 before and after study (Table 2,3). A significant difference in distress was found for only the domain ‘social problems’; at end of study 12 patients in the control group of 45, reported social problems compared to 7 patients at baseline. Four patients at end of study in the intervention group of 46 patients, compared to 10 patients at baseline were found to have social problems ($p<0.01$). The median global score for patients’ perception of and satisfaction with information received, did not improve in the intervention group relative to the control group (Table 2,4). Interestingly, 53 and 57% of patients in the control and intervention group wish to receive more information, respectively. After the intervention less patients in the control group (31%) wished to receive more information versus the patients in the intervention group (38%).

Most patients agreed with the statements mentioned in the additional questionnaire (Table 5). During the study, the median number of visits to the website was 3 (range 2-4), and only 3 patients used the opportunity to ask questions and consult with the researcher for clinical purposes. Other questions were about technical or logistical aspects.

Table 2. Primary outcome, distress and global score of perceived information and satisfaction (EORTC QLQ-INFO25)

Higher scores mean more distress and more/better information and satisfaction. The p-value shows the differences between the pre-post changes of the control group versus the intervention group.

Outcome	Control group (n=45)		Intervention group (n=46)		p-value
	Pre Median (range)	Post Median (range)	Pre Median (range)	Post Median (range)	
Distress level (0-10)	3 (1-5)	3 (1-5)	3 (2-5)	3 (1-5)	NS
Global Score EORTC QLQ-INFO25 (0-100)	49 (37-55)	51 (42-59)	45 (33-56)	38 (47-57)	NS

NS = no significant difference, Pre Median = median score at baseline, Post median = median score a 12 weeks, range = interquartile range.

Table 3. Distress (Distress thermometer and Problem List)

Higher scores mean more distress (from problems). The p-value shows the differences between the pre-post changes of the control group versus the intervention group.

Outcome	Control group (n=45)		Intervention group (n=46)		p-value
	Pre Median (range)	Post Median (range)	Pre Median (range)	Post Median (range)	
Practical problems	0 (0-4)	0 (0-4)	0 (0-4)	0 (0-5)	NS
Social problems	0 (0-0)	0 (0-4)	0 (0-0)	0 (0-0)	0.002
Emotional problems	4 (0-13)	6 (0-12)	7 (1-16)	7 (1-16)	NS
Spiritual problems	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	NS
Physical problems	8 (4-18)	10 (6-19)	13 (7-21)	12 (5-20)	NS
Global score	14 (7-32)	17 (6-44)	21 (12-41)	21 (7-44)	NS

NS = no significant difference, Pre Median = median score at baseline, Post median = median score a 12 weeks, range = interquartile range.

Table 4. Perceived information and satisfaction (EORTC QLQ-INFO25)

Higher scores indicate more/better information and satisfaction. The p-value shows the differences between the pre-post changes of the control group versus the intervention group.

	Control group (n=45)		Intervention group (n=46)		
Outcome	Pre Median (range)	Post Median (range)	Pre Median (range)	Post Median (range)	p-value
Information about					
Disease	50 (33-58)	50 (42-65)	50 (33-60)	50 (33-67)	NS
Medical tests	67 (44-67)	67 (44-67)	67 (56-67)	67 (28-56)	NS
Treatments	44 (25-56)	39 (33-56)	44 (28-56)	8 (0-27)	NS
Other services	17 (0-25)	17 (8-33)	17 (6-23)	8 (0-27)	NS
Different location of care facilities	0 (0-33)	33 (0-33)	0 (0-33)	0 (0-33)	NS
How to help yourself	33 (0-33)	33 (0-33)	17 (0-33)	33 (0-33)	NS
Satisfaction with information	67 (33-67)	67 (33-67)	67 (33-67)	67 (33-67)	NS
Helpfulness of information	67 (50-67)	67 (67-67)	67 (67-67)	67 (33-67)	NS
	Percentage of patients				
Received written information	91	91	78	80	
Received cd/video	2	2	2	0	
Wish to receive more info	53	31	57	38	
Wish to receive less info	2	0	2	0	

cd = compact disk, NS = no significant difference, Pre Median = median score at baseline, Post median = median score a 12 weeks, range = interquartile range.

Table 5. Questionnaire based on patients' opinion and use of the website (based on constructs of the Technology Acceptance Model)

Higher scores indicate more agreement with the statement (except for number of visits).

Intervention group (n=46)	
Outcome	Median (range)
The website is useful to me	4 (4-4)
The information at the website is interesting to me	4 (4-4)
I find this a site that adds value	4 (3-5)
I have a positive attitude towards the website	4 (4-5)
I would recommend the site to peers	4 (3-5)
How often do you visit the website	3 (2-4)

Median: median score (at 12 weeks), range = interquartile range.

Newly diagnosed patients

The planned subgroup analysis for newly diagnosed patients did not detect any difference in this subgroup regarding the global score for distress and the problem domains (Supportive Information (SI), Table S1).

In this subgroup, perceived information and satisfaction did not differ between the control group and intervention group (Table S2). We found a difference for only one item, 'information about the disease in the QLQ-INFO25'; after 12 weeks this score decreased in the intervention group and increased in the control group ($p=0.046$). Most patients agreed with the statements on the self-constructed questionnaire (Table S5).

Discussion

In this randomised trial we found that WINS did not reduce distress nor improved NETs patients' perception of and satisfaction with received information. We found the same results in the pre-planned subgroup analyses with newly diagnosed patients.

Developing a web-based system (WBS) providing patient detailed information corresponding to their individual needs and wishes is difficult [12]. The contact and communication with health care professionals remains a crucial source of information and support for patients with NET. Other web-based studies have shown that web-based technology does not replace patient-provider communication [13]. In one such study, in which 103 cancer patients received questionnaires about the WBS, the highest rated component was receiving an answer from a nurse. In another trial in 766 patients receiving chemotherapy for solid cancers, patients were randomised to either standard care or to standard care plus a web-based self-reporting system. Physicians received symptom printouts at visits and nurses received e-mail alerts when participants of the

intervention group reported severe or worsening symptoms. In this trial, QoL improved (34% vs. 18%; $p < 0.001$) and OS was higher (31 vs. 26 months; $p = 0.03$) in the intervention group compared to the group receiving standard care only [14]. Another example, that web-based technology does not replace patient-provider communication, was presented in a randomised controlled study of a website providing additional information and symptom self-management support in 325 breast and prostate cancer patients. Distress was used as the primary endpoint [15]. Compared to the control group, which was given uniform resource locators (URLs) of publically available cancer information websites, an improvement for patients in the intervention group was found only on the subscale 'global distress index'.

A potential explanation for these findings could be that NET patients obtain sufficient information by usual care that all patients received. In our trial, all patients had easy access to specialists and nurses during standard care, which might have satisfied their need for information. Furthermore, patients were able to get information from the NET patient association [16]. We did not use a control group receiving no information which can be regarded as a limitation of our study.

At baseline half of the patients in both groups indicated that they wanted more information about the disease. During study period, the need for more information decreased in both groups. A decline in the need for information during the course of the disease was observed in other studies analysing patients with other types of cancer [17,18]. Furthermore, patients only visited the WBS sporadically. Patients were not requested to visit the website more frequent, which also could be seen as a limitation. Sporadically visiting a WBS was also reported in other trials using a WBS [15,19]. In a qualitative interview study, one of the three main reasons reported for not using a WBS was that patients had sufficient access to information elsewhere [20]. In two other studies, in patients with cancer and brain tumours, patients reported that they avoided using the WBS because they did not want to be reminded of their suffering or, because they had a preference for other kinds of communication [20,21].

Another limitation is that we could only analyze patients with outcome data on the second assessment, as the primary endpoint was the pre-post change of distress and satisfaction with perceived information. For that, the 14 (13%) of the patients who withdrew early, or who did not complete the end-of-study questionnaires were excluded from the analysis.

Conclusion

In NET patients, WINS did not improve distress scores and patients' perception of or satisfaction with received information, compared to patients receiving standard care only. Despite the need for more information, the WINS does not have added value to the information and care provided by health care professionals.

Methods

Participants

Eligible participants were adult patients treated at the University Medical Centre Groningen Department of Medical Oncology for NET grade 1 or 2 (World Health Organization 2010 classification) with the primary tumour at any site of origin, and who were proficient in Dutch (both reading and writing). Patients with a life expectancy of less than 3 months as evaluated by their doctor were excluded. The study was approved by the medical ethical committee of the UMCG and registered in ClinicalTrials.gov (NCT02472678). All patients gave written informed consent.

Randomisation process and study procedure

For a detailed description of study procedures, see Supportive Information (SI) and Figure 1. The included patients were stratified randomised for those diagnosed within 6 months and those with disease duration ≥ 6 months. Patients were randomised 1:1 to the control group, receiving standard care, or the intervention group, which received standard care with additional access to WINS. At baseline patients' socio-demographic and disease characteristics, internet use and health care use were collected. Patients in both groups received a questionnaire about their perception of and satisfaction with the received information and their QoL. The control group was also given a questionnaire about distress and problems. After returning the questionnaires, patients in the intervention group received log-in information for website access. At the first website visit, the patients were asked to complete a questionnaire about distress and problems at baseline, before they were given access to the other items on the website. At 12 weeks follow-up, all patients were asked to complete the questionnaires again, with an additional questionnaire to assess empowerment. Patients in the intervention group were asked to complete the questionnaire about distress and problems at the WINS instead of completing it with pen and paper. Furthermore, they were requested to complete an additional questionnaire about their use of and opinion about WINS.

Standard care and study intervention

All patients received standard care. At their first visit at the Department of Medical Oncology patients are informed verbally about the disease and they meet the oncology nurse to become acquainted. During follow-up visits, the medical oncologist evaluates the general well-being, discusses possible treatment options and treatment side-effects (if applicable) and answers questions of the patient. Between follow-up visits all patients could consult an oncology nurse 24 hours a day, 7 days a week by telephone. Furthermore, patients were able to get information from the NET patient association [16]. If physical and/or psychosocial problems require more in-depth discussion, investigation or treatment, patients can receive a consultation with the oncology nurse, oncologist or other health care professionals. In the intervention group, the questionnaire about distress and problems served as a self-screening tool for physical and psychosocial problems. By using WINS, patients could obtain personalised information about reported problems. Self-screening was performed by the online version of the Dutch Distress Thermometer (DT) and Problem List (PL). Immediately after completion of the DT and PL. Patients received online information on the physical and psychosocial problems they reported on the digital PL. This information comprises: a) description and background information of their reported problem, b) advice on how to cope with the problem (self-help), c) what health care professional could be consulted when self-help insufficiently alleviates problems. On the WINS, patients could also find general information about the disease, read about the experiences of other NET patients and find links to other relevant websites. Any time, patients could send an e-mail with a question or request a telephone consultation with the investigators (physicians experienced in treating NET patients) in case of questions, problems or request further referral.

Outcome measurements

Illness-related patient characteristics were extracted from the medical records at baseline. All other measurements were performed by self-report questionnaires. Selection of endpoints was based on the results of the pilot study [11]. According to our pre planned protocol our primary endpoint was the combined endpoint of distress the change in distress level combined with change in global score of perception of and satisfaction with information received. Distress was measured using the validated Dutch Distress Thermometer (DT) and Problem list (PL) [22]. This questionnaire consisted of one single item that asks patients to indicate the amount of overall distress experienced during the past week and a PL with several items divided into five domains. Higher scores indicate more distress or more problems. The EORTC QLQ-INFO25 in Dutch was used to evaluate patients' perception of and satisfaction with information received [23]. Higher scores indicate better perceived information provision. The measures of the

validated QLQ-INFO25 are categorized and scored according to the EORTC guidelines. For a more detailed description of the questionnaires, see our pilot study. An additional questionnaire, only given to the intervention group at end of study, was based on the constructs of 'perceived usefulness' and 'attitude and usage' from the revised Technology Acceptance Model and on a self-constructed question on a 5-point Likert scale; if patients recommend WINS to other NET patients [24].

Sample size calculation

Sample size calculation was based on the results of the pilot study, in which only newly diagnosed patients were included. To detect a significant difference in the change of the distress thermometer between the control and intervention group, using an independent t-test with an effect size of 0.6, we calculated that 90 patients had to be included (Supportive Information). Taking into account a dropout of 15 percent, we included 105 patients in this study.

Statistical analysis

For descriptive statistics, mean and standard deviation (SD) for normal distribution and median and interquartile range for other distributions and frequencies were calculated for all measures. The scores of the EORTC questionnaires were calculated according to the EORTC guidelines [23,25,26]. An independent t-test or Mann Whitney U test was performed, depending on the kind of distribution, to detect differences between the pre-post changes of standard care complemented with the WINS versus standard care alone. Given the negative findings of the outcome we did not correct for multiple comparison issues. Subgroup analysis was performed in newly diagnosed patients. Differences were considered significant at $p < 0.05$. Analyses were performed with the software package SPSS, version 23 for Windows (SPSS, Inc, Chicago, IL, USA). Patients who were lost to follow up were excluded from analysis.

List of Abbreviations

CEO	Constructs empowering outcomes
DT	Distress
EORTC	European Organisation for Research and Treatment of Cancer
N	Number
NET	Neuroendocrine tumour
PL	Problem list
QLQ	Quality of life questionnaire
QoL	Quality of life
RCT	Randomised controlled trial
SD	Standard deviation
SI	Supportive information
TAM	Technical Acceptance Model
WBS	Web-based system
WINS	Web-based personalised information and support system

Declarations

Ethics approval and consent to participate

The study was approved by the medical ethical committee of the UMCG. Results were reviewed at regular intervals by an independent data monitoring and ethical committee.

Consent for publication

Not applicable.

Availability of data and material

Patient level data can be made available from the corresponding author after discussion with the trial management committee. Consent from participants for data sharing was not obtained but any shared data will be anonymised.

Competing interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

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Authors' contribution

GB, LDH, DJG, EGV, AMW contributed equally to the development of the protocol. GB, LDH, HE, DJG, EGV and AMW, managed patient enrolment. LDH and GHB analysed the data. GB and LDH drafted the manuscript, and all other members of the writing committee contributed amendments and critical review. All authors had full access to the data and all members of the writing committee approved the final manuscript and the decision to submit for publication. AMW is guarantor.

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Supportive Information

Randomisation process and study procedure

The included patients were stratified randomised for those diagnosed within 6 months and those with disease duration ≥ 6 months. We expected that newly diagnosed patients would have other information needs which could lead to bias if not stratified. Patients were randomised 1:1 to the control group, receiving standard care, or the intervention group, which received standard care with additional access to WINS. Randomisation was performed by the central data manager of the Department of Medical Oncology (UMCG) who was not involved in other aspects of the study. A computer-generated randomisation list was used for allocation to the control or intervention arm. The allocation sequence was concealed from the investigator. The investigator was informed by e-mail to which arm the patient was assigned. The investigator informed the patient by phone about the randomisation outcome and further process. At baseline patients' socio-demographic and disease characteristics, internet use and health care use were collected. Patients in both groups received a questionnaire about their perception of and satisfaction with the received information and their QoL. The control group was also given a questionnaire about distress and problems. After returning the questionnaires, patients in the intervention group received log-in information for website access. At the first website visit, the patients were asked to complete a questionnaire (within 1 week) about distress and problems at baseline, before they were given access to the other items on the website. At 12 weeks follow-up, all patients were asked to complete the questionnaires again, with an additional questionnaire to assess empowerment. Patients in the intervention group were asked to complete the questionnaire about distress and problems at the WINS instead of completing it with pen and paper. Furthermore they were requested to complete an additional questionnaire about their use of and opinion about WINS.

Outcome measurements

QoL was measured by the cancer-specific Dutch EORTC QLQ-C30 (version 3.0) and the NET-specific EORTC QLQ-GINET21 [1,2]. Higher scores indicate higher QoL at the functional and global health/QoL scale and higher symptom burden for the symptom scales of the QLQs [1]. The measures of the validated QLQ-INFO25, QLQ-C30 and QLQ-GINET-21 are categorized and scored according to the EORTC guidelines. The significance of change in QoL is analysed for the QLQ-C30 and for patients who indicated "a little" change either for better or for worse, the mean change in scores was about 5 to 10; for "moderate" change, about 10 to 20; and for "very much" change, greater than 20 [3]. Empowerment was measured with specific domains of the 'Constructs Empowering

Outcomes' (CEO) questionnaire [4]. Higher scores indicate greater empowerment. This questionnaire has a retrospective nature. Furthermore, this questionnaire has not been extensively validated. Consequently, our findings should be interpreted with caution.

Sample size calculation

Sample size calculation was based on the results of the pilot study, in which only newly diagnosed patients were included. The score of distress level had a Cohen's d effect size of 0.75 in favour of the intervention group and an effect size of 1.0 was found in favour of the control group for the global score of the EORTC QLQ-INFO25. Since we expected using a WINS for newly diagnosed patients and for patients diagnosed more than 6 months before inclusion, might have a smaller effect, than for only newly diagnosed patients, we adapted the effect size to 0.6 for the distress thermometer and to 0.8 for the EORTC QLQ-INFO 25. To detect a significant difference in the change of the distress thermometer between the control and intervention group, using an independent t-test with an effect size of 0.6, we calculated that 90 patients had to be included.

Results

No significant differences were found between the control and intervention groups for each symptom, problem, or level of functioning regarding QoL (Table S6). However, power analysis was not performed to detect a difference in empowerment, empowerment was better in the control group, for all constructs, except for 'optimism and control over future' for which no difference was found (Table S7). Most patients agreed with the statements mentioned in the additional questionnaire (Table 5). During the study, the median number of visits to the website was 3 (range 2-4), and only 3 patients used the opportunity to ask questions and consult with the researcher for clinical purposes. Other questions were about technical or logistical aspects.

Newly diagnosed patients

Furthermore, regarding the secondary endpoints, QoL and empowerment, most items did not show significant differences were found between the control and intervention groups (Tables S3-S4). Most patients agreed with the statements on the self-constructed questionnaire (Table S5).

Discussion

In our study, empowerment was better in the control group. In other trials in cancer patients no statistically differences were seen in empowerment between the control group and the intervention group with access to the web-based intervention [5,6].

Due to the indolent natural course of NET, and because NET patients may not have symptoms at study inclusion, it is challenging to demonstrate an improvement in QoL

in this population [7]. In the RADIANT-4, a large randomised controlled trial on the use of everolimus in advanced non-functional, gastrointestinal or lung NET patients, few patients had symptoms at study inclusion [8]. During the study period, global QoL remained stable in both groups, as also seen in our previous study [9].

Despite its well-powered prospective randomised controlled design, our study also has some limitations, in particular the use of the constructs empowering outcome (CEO) questionnaire. Due to the retrospective nature of the CEO questionnaire, no baseline scores could be determined. Furthermore, this questionnaire has not been extensively validated. Consequently, our finding that empowerment at the end of the study was better in the control group should be interpreted with caution.

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Table S1. Distress in newly diagnosed patients (Distress thermometer and Problem List)

Higher scores indicate more distress (from problems). The p-value shows the differences between the pre-post changes of the control group versus the intervention group.

Outcome	Control group (n=13)		Intervention group (n=12)		p-value
	Pre Median (range)	Post Median (range)	Pre Median (range)	Post Median (range)	
Distress level (0-10)	4 (2-6)	5 (2-7)	3 (0-3)	3 (0-3)	NS
Practical problems	0 (0-3)	0 (0-5)	0 (0-0)	0 (0-2)	NS
Social problems	0 (0-0)	0 (0-10)	0 (0-0)	0 (0-0)	NS
Emotional problems	0 (4-12)	0 (0-16)	3 (0-15)	3 (0-8)	NS
Spiritual problems	0 (0-2)	0 (0-0)	0 (0-0)	0 (0-0)	NS
Physical problems	12 (7-18)	14 (5-24)	8 (4-14)	11 (2-15)	NS
Global score	15 (13-33)	35 (9-57)	16 (7-40)	14 (3-27)	NS

NS = no significant difference, Pre Median = median score at baseline, Post median = median score at 12 weeks, range = interquartile range.

Table S2. Perceived information and satisfaction with information in newly diagnosed patients (EORTC QLQ-INFO25)

Higher score indicates more/better information and satisfaction. The p-value shows the differences between the pre-post changes of the control group versus the intervention group.

	Control group (n=13)		Intervention group (n=12)		
	Pre	Post	Pre	Post	
Outcome	Median (range)	Median (range)	Median (range)	Median (range)	p-value
Information about					
Disease	42 (38-63)	58 (46-67)	50 (27-73)	38 (25-67)	0.046
Medical tests	67 (50-67)	67 (56-67)	56 (33-67)	67 (44-67)	NS
Treatments	33 (22-53)	39 (31-61)	42 (24-54)	40 (22-61)	NS
Other services	4 (17-29)	25 (4-50)	13 (0-25)	8 (0-37)	NS
Different location of care facilities	0 (0-33)	25 (4-50)	0 (0-33)	0 (0-58)	NS
How to help yourself	33 (0-33)	33 (0-50)	33 (0-33)	33 (8-58)	NS
Satisfaction with information	67 (33-67)	67 (50-67)	67 (33-67)	67 (33-100)	NS
Helpfulness of information	67 (50-67)	67 (67-67)	67 (67-67)	67 (33-100)	NS
Percentage of patients					
Received written information	100	100	100	82	
Received cd/video	0	8	0	0	
Wish to receive more info	54	15	58	64	
Wish to receive less info	0	0	0	0	
Outcome	Pre M (SD)	Post M (SD)	Pre M (SD)	Post M (SD)	p-value
Global Score	52 (41-57)	55 (52-62)	48 (39-56)	42 (31-63)	NS

cd = compact disk, NS = no significant difference, Pre Median = median score at baseline, Post median = median score a 12 weeks, range = interquartile range.

Table S3A. Quality of life in newly diagnosed patients (EORTC QLQ-C30)

Higher scores for quality of life and functioning indicate higher quality of life and level of functioning. Higher scores for symptoms indicate greater severity. The p-value shows the differences between the pre-post changes of the control group versus the intervention group.

Outcome	Control group (n=13)		Intervention group (n=12)		p-value
	Pre Median (range)	Post Median (range)	Pre Median (range)	Post Median (range)	
Global quality of life	75 (50-83)	75 (54-83)	75 (69-83)	75 (67-83)	NS
Physical	80 (53-100)	80 (53-93)	93 (87-100)	87 (82-98)	NS
Role	67 (42-92)	67 (67-100)	83 (67-100)	83 (53-100)	NS
Emotional	83 (75-100)	83 (63-96)	79 (67-92)	79 (67-100)	NS
Cognitive	67 (67-100)	67 (67-92)	100 (83-100)	75 (67-100)	NS
Social	83 (50-100)	83 (67-100)	100 (83-100)	83 (67-100)	NS
Dyspnea	0 (0-33)	0 (0-50)	0 (0-0)	0 (0-0)	NS
Insomnia	0 (0-33)	33 (17-33)	33 (0-33)	33 (0-33)	NS
Appetite loss	0 (0-33)	0 (0-0)	0 (0-0)	0 (0-0)	NS
Constipation	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	NS
Diarrhea	0 (0-33)	33 (0-67)	0 (0-33)	33 (0-58)	NS
Financial difficulties	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	NS
Fatigue	44 (6-56)	33 (22-44)	17 (3-31)	22 (11-61)	NS
Nausea and vomiting	0 (0-8)	0 (0-17)	0 (0-0)	0 (0-0)	NS
Pain	33 (0-75)	33 (8-42)	8 (0-29)	0 (0-33)	NS

NS = no significant difference, Pre Median = median score at baseline, Post median = median score a 12 weeks, range = interquartile range.

Table S3B. Quality of life in newly diagnosed patients (EORTC QLQ-GINET21)

Higher scores indicate more or worse symptoms/problems. The p-value shows the differences between the pre-post changes of the control group versus the intervention group.

Outcome	Control group (n=13)		Intervention group (n=12)		p-value
	Pre Median (range)	Post Median (range)	Pre Median (range)	Post Median (range)	
Endocrine symptoms	11 (0-33)	0 (0-19)	0 (0-19)	0 (0-8)	NS
Gastrointestinal symptoms	20 (3-40)	27 (9-37)	17 (13-20)	17 (13-32)	NS
Treatment related symptoms	16 (6-28)	22 (6-33)	14 (0-22)	0 (0-22)	NS
Problems social functioning	33 (28-67)	33 (17-61)	33 (25-53)	33 (22-53)	NS
Disease-related worries	33 (19-72)	33 (25-72)	53 (36-67)	33 (17-44)	0.006
Pain muscles/bone	33 (0-50)	33 (8-58)	0 (0-25)	0 (0-33)	NS
Problems sexual functioning	0 (0-58)	17 (0-75)	0 (0-33)	0 (0-42)	NS
Problems receiving information	0 (0-33)	0 (0-0)	0 (0-33)	0 (0-0)	NS
Problems body image	0 (0-33)	0 (0-33)	0 (0-0)	0 (0-0)	NS

NS = no significant difference, Pre Median = median score at baseline, Post median = median score at 12 weeks, range = interquartile range.

Table S4. Empowerment in newly diagnosed patients (CEO)

Higher scores indicate better empowerment for each outcome. The p-value shows the differences between the pre-post changes of the control group versus the intervention group.

	Control group (n=13)	Intervention group (n=12)
Outcome	Median (range)	Median (range)
Feeling informed	16 (14-18)	14 (13-16)
Confidence in relationship physician	34 (33-42)	31 (25-39)
Confidence in treatment	19 (16-20)	16 (10-19)
Acceptance of illness	17 (15-20)	13 (9-20)
Optimism and control over future	24 (23-28)	16 (14-26)

NS = no significant difference, Median = median score (at 12 weeks), range = interquartile range.

Table S5. Questionnaire on patients' opinions and use of the website in newly diagnosed patients (based on constructs of the Technology Acceptance Model)

Higher scores indicate more agreement with the statement except for number of visits.

	Intervention group (n=12)
Outcome	Median (range)
The website is useful to me	4 (4-5)
The information at the website is interesting to me	4 (3-4)
I find this a site that adds value	4 (4-5)
I have a positive attitude towards the website	4 (4-5)
I would recommend the site to peers	4 (3-5)
How often do you visit the website	4 (3-5)

Higher scores indicate more agreement with the statement except for number of visits.

Median = median score (at 12 weeks), range = interquartile range.

Table S6A. Quality of life (EORTC QLQ-C30)

Higher scores for quality of life and functioning indicate higher quality of life and level of functioning. Higher scores for symptoms indicate greater severity. The p-value shows the differences between the pre-post changes of the control group versus the intervention group.

Outcome	Control group (n=45)		Intervention group (n=46)		p-value
	Pre Median (range)	Post Median (range)	Pre Median (range)	Post Median (range)	
Global quality of life	75 (58-83)	75 (62-83)	75 (67-83)	75 (65-83)	NS
Physical	87 (67-100)	87 (67-97)	87 (73-100)	87 (72-100)	NS
Role	83 (50-100)	83 (67-100)	83 (63-100)	83 (67-100)	NS
Emotional	92 (75-100)	83 (67-96)	83 (67-96)	83 (67-94)	NS
Cognitive	100 (67-100)	83 (67-100)	100 (83-100)	100 (67-100)	NS
Social	100 (67-100)	100 (83-100)	100 (67-100)	83 (67-100)	NS
Dyspnea	0 (0-0)	0 (0-33)	0 (0-0)	0 (0-0)	NS
Insomnia	0 (0-33)	33 (0-33)	33 (0-33)	33 (0-33)	NS
Appetite loss	0 (0-33)	0 (0-0)	0 (0-0)	0 (0-0)	NS
Constipation	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	NS
Diarrhea	0 (0-33)	0 (0-50)	0 (0-33)	0 (0-0)	NS
Financial difficulties	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	NS
Fatigue	33 (17-56)	22 (11-44)	22 (11-39)	28 (11-44)	NS
Nausea and vomiting	0 (0-17)	0 (0-8)	0 (0-0)	0 (0-0)	NS
Pain	0 (0-33)	17 (0-33)	17 (0-33)	17 (0-33)	NS

NS = no significant difference, Pre Median = median score at baseline, Post median = median score a 12 weeks, range = interquartile range.

Table S6B. Quality of life (EORTC QLQ-GINET21)

Higher scores indicate more or worse symptoms/problems.

Outcome	Control group (n=45)		Intervention group (n=46)		p-value
	Pre Median (range)	Post Median (range)	Pre Median (range)	Post Median (range)	
Endocrine symptoms	11 (0-33)	11 (0-33)	0 (0-14)	11 (0-33)	NS
Gastrointestinal symptoms	20 (7-27)	20 (12-33)	20 (13-28)	20 (7-33)	NS
Treatment related symptoms	11 (0-22)	17 (0-28)	11 (0-22)	0 (0-22)	NS
Problems social functioning	33 (17-44)	22 (11-33)	33 (22-56)	22 (11-44)	NS
Disease related worries	33 (19-53)	33 (17-50)	44 (22-67)	33 (19-44)	NS
Pain muscles/bone	33 (0-33)	33 (0-33)	33 (0-67)	33 (0-33)	NS
Problems sexual functioning	0 (0-50)	0 (0-33)	17 (0-33)	0 (0-67)	NS
Problems receiving information	0 (0-0)	0 (0-0)	0 (0-33)	0 (0-0)	NS
Problems body image	0 (0-33)	0 (0-33)	0 (0-33)	0 (0-0)	NS

N= no significant difference, Pre Median = median score at baseline, Post median = median score a 12 weeks, range = interquartile range.

Table S7. Empowerment (CEO)

Higher scores represent better empowerment for each outcome.

	Control group (n=45)	Intervention group (n=46)
Outcome	Median (range)	Median (range)
Feeling informed	16 (14-16)	13 (12-14)
Confidence in relationship physician	37 (34-41)	32 (26-37)
Confidence in treatment	19 (16-20)	15 (12-18)
Acceptance of illness	18 (15-20)	15 (11-17)
Optimism and control over future	24 (22-26)	23 (16-25)

NS = no significant difference, Median = median score (at 12 weeks), range = interquartile range.

Use of video-consultation is feasible during follow-up care of patients with a neuroendocrine tumour

Grietje Bouma¹, Lotte D. de Hosson¹, Henny van Essen¹, Elisabeth G.E. de Vries¹,
Derk Jan A. de Groot¹, Annemiek M.E. Walenkamp¹

¹ Department of Medical Oncology, University of Groningen,
University Medical Centre Groningen, Groningen, the Netherlands

Abstract

Purpose

Patients with a neuroendocrine tumour (NET) are increasingly treated in expert centers leading to longer travel times for medical consultations. Video-consultation (VC) potentially allows remote guidance of patients. Studies evaluating VC in NET patients are lacking. Therefore the primary aim of this study was to assess feasibility of VC during follow-up care of NET patients.

Methods

Clinical stable NET patients (N = 20) received two VCs during follow-up care. Feasibility of VC was assessed by calculation of participation/drop-out rate and safety. Satisfaction questionnaires were filled out by patients and physicians. VC time, patient-reported travel time for an outpatient clinic visit and preference for type of consultation were noted.

Results

Participation rate was 84%. Six of the 26 (23%) included patients terminated the study prematurely. No safety concerns were reported. Median score for satisfaction of patients and physicians were 4.6 (range 3.3-4.9, five-point Likert scale) and 4.0 (range 3.5-4.9) respectively, indicating high satisfaction with VC. Technical problems leading to prolonged connection time and impaired audio/video quality were reported by 55% and 40% of the patients and physicians respectively. Median VC time was 13 minutes (range 9-25). Patient-reported duration of a follow-up consultation at the outpatient clinic was 240 minutes (range 100-390). Sixty percent of the patients preferred VC.

Conclusions

Use of VC during follow-up care of patients with clinical stable NET is feasible. Patients' and physicians' acceptability and satisfaction with VC is high, but can be improved by solving technical problems.

Keywords: neuroendocrine tumour, video-consultation, communication, telemedicine.

Introduction

Neuroendocrine tumours (NETs) are rare tumours [1,2]. The 5-year overall survival of NET patients with distant metastases is about 55% [2]. Therefore, NET patients often require for a long time frequent hospital visits. In the Netherlands, most NET patients are treated in 'ENETS (European NeuroEndocrine Tumour Society) centers of excellence' [3]. This coincides with often relatively long distance travel for a follow-up visit. Telemedicine uses information and communication technology to provide health care services to individuals who are at a distance from their health care provider [4]. The use of telemedicine in oncology ('tele-oncology') can be defined as the delivery of oncology services from a distance [5]. Nowadays, tele-oncology is also used for remote consultation, for example by video-consultation (VC). Despite this emerging technology, there is a lack of studies examining the use of VC in the care of cancer patients.

Replacing follow-up consultations at the outpatient clinic by VCs could save time for patients with a NET. Other benefits of using VC can be reduced cost, higher efficiency and increased convenience. Therefore, we aimed to study the feasibility of VC as an alternative for outpatient clinic consultations in NET patients receiving follow-up care.

Methods

Participants

Potential participants were NET patients under surveillance or receiving treatment at the Department of Medical Oncology at the University Medical Center Groningen (UMCG, the Netherlands). Eligible were patients with a medical condition which allowed VC ('clinical stable'), as determined by the treating medical oncologist. Other eligibility criteria were age ≥ 18 years, grade I/II NET (according to the World Health Organization 2010 classification) and having access to required equipment/technology for performing VC.

Newly referred patients, patients in the diagnostic phase of their disease and patients requiring face-to-face consultation and/or physical examination were not eligible. Also, patients with a hearing or visual impairment were excluded.

Eligible patients were recruited until 20 participants had completed the study and accompanying questionnaires. Patients were included between May 2014 to September 2015.

All participants gave written informed consent. The medical ethical committee of the UMCG did not review this study as they declared that this study did not fall under the scope of the Medical Research Involving Human Subjects Act and did not need review. The study was conducted in accordance with the Personal Data Protection Act and the Agreement on Medical Treatment Act. The study was registered in ClinicalTrials.gov (NCT02147106).

Study procedure

In the present study, WebEx® was used for consultation by VC. WebEx® meets the safety requirements and regulations of the UMCG and is supported by the Information and Communication Technology Department of the UMCG. After having obtained written informed consent, participants received by mail baseline questionnaires regarding socio-demographic characteristics, experience with internet/video communication, the total time a conventional follow-up outpatient clinic consultation did take in the past and expectations about VC. Also, participants received a short introduction about installing WebEx® and using VC. Baseline questionnaires had to be returned before the first VC. The investigator contacted each participant to check if installation of WebEx® was successfully or otherwise to help with the installation. The participant received appointment letters for the VC. If indicated, participants received additionally a form for blood analysis which was performed in laboratories near the home of the patient. Results of the blood analysis were collected by the treating medical oncologist before the VC. If possible, VCs were alternately planned with an outpatient clinic consultation. End of study was reached after completion of two VCs, which had to take place within one year, and accompanying questionnaires. At end of study, the patient received by mail questionnaires regarding acceptability and satisfaction with VC, preference for type of consultation and their opinion on using VC. The physician documented after each VC the duration of and reason for VC. Also, after each VC the physician completed a post-intervention questionnaire regarding acceptability and satisfaction with VC. An additional outpatient clinic consultation would be planned within 1 week (e.g. for physical examination or other in-hospital procedures), if this was indicated during VC. Details of the consultation by VC were documented in the medical record according to a standard format developed by the investigator. As in a conventional follow-up outpatient clinic consultation, a letter pertaining to the consultation was sent to the patient's general practitioner and/or referring physician.

Outcome measures

At baseline, socio-demographical characteristics and experience with internet/videocommunication (e.g. Skype, FaceTime) was assessed by a self-report questionnaire. Collection of illness-related characteristics was done by examination of the medical records. The distance of the patients home to the UMCG was calculated in kilometers from the patient's postal code to the postal code of the UMCG using [maps.google.com](https://www.google.com/maps). To evaluate the primary endpoint feasibility the participation and drop-out rates were calculated. Also, reason for declining participation, reason for drop-out and safety concerns (e.g. additional outpatient clinic visits, hospitalization and interventions) were noted.

To explore the by VC saved amount of time for patients, the participants were asked to estimate the total time they spent on a conventional follow up outpatient clinic consultation in the past (leaving home for the consultation till arriving at home, in minutes). The duration of each VC was documented by the physician.

Patients' acceptability and satisfaction with VC was investigated with an in Dutch translated adapted version of the validated Telemedicine Satisfaction Questionnaire (TSQ) [6]. The questionnaire consists of 14 items, representing three aspects of patient satisfaction with telemedicine: 'quality of care provided' (item 5, 7, 8, 10, 11, 13-15), 'similarity to face-to-face encounter' (item 1-4, 9) and 'perception of the interaction' (item 6). Each item is rated using a five-point Likert scale. Higher scores indicate greater satisfaction with telemedicine. At baseline, participants were asked to fill out an adapted version consisting of 12 items instead of 14 (2 post-intervention items were deleted). The items were adapted so they indicate the patients' expectations of VC. At end of study, participants had to fill out the original 14-item TSQ. In both TSQs 'telemedicine' was replaced by 'video-consultation'. Also, participants were asked about their opinion on using VC (e.g. open-ended questions regarding benefits, drawbacks, (technical) problems, necessary improvements) and which follow-up consultation they prefer: 'outpatient clinic consultation', 'video-consultation' or 'no preference'.

Physicians' acceptability and satisfaction with VC was investigated with a self-developed post-intervention questionnaire after each VC. The first part of the questionnaire consists of 6 statements about performing VC. Each item is rated with a five-point Likert scale. Higher scores indicate greater satisfaction with VC. The second part of the questionnaire is composed of open-ended questions regarding (dis-)advantages of using VC for patients and physicians. Also, the physician had the possibility to note improvements regarding VC.

Statistical analysis

Seen the small available group of patients due to the rarity of NET and the primary aim to assess feasibility a sample size was set at 20 patients.

Given the explorative nature of this study descriptive analyses (e.g. means, medians, ranges, frequencies) were calculated for all measures. Analyses were performed using the software package SPSS, version 22 for Windows (SPSS, Inc, Chicago, IL, USA).

Results

Participants and feasibility of video-consultation

Figure 1 summarizes the enrollment and flow of participants. Twenty-six of the 31 (84%) invited patients for study participation were included. Six participants did not

complete the full study (drop-out rate 23%). One participant died due to progressive disease. Patient characteristics are summarized in Table 1. Thirteen of the 20 patients were known with NET for more than three years. The drop-outs had a median age at inclusion of 58 years (range 50-67) and 83% had used videocommunication for personal use or work purposes in the past. No additional visits to the outpatient clinic/hospital or interventions related to VCs were done.

Figure 1. Flow diagram
This flow diagram shows the flow of invited and included patients with reasons for declining study participation and drop-out.

Table 1. Patient characteristics^a (N = 20)

Median age at inclusion in years (range)	64 (47-73)
Median distance to hospital in kilometers (range)	75 (31-218)
Educational level	
Lower vocational level	2 (10)
Intermediate vocational level	5 (25)
Higher vocational level	13 (65)
Employment status	
Employed	7 (35%)
Unemployed	13 (65%)
Marital status	
Married/cohabiting	16 (80)
Living alone	4 (20)
Patients with children	17 (85)
Use of internet in daily life	20 (100)
Use of video-communication in daily life	11 (55)
Median age at diagnosis in years (range)	56 (45-70)
Location primary tumour	
Duodenum	1 (5)
Pancreas	4 (20)
Jejunum/ileum	10 (50)
Colon	1 (5)
Unknown	4 (20)
NET disease stage (according to UICC^b)	
Stage II	1 (5)
Stage IV	19 (95)
Patients receiving treatment at inclusion	20 (100)
Treatment at inclusion study^c	
Somatostatin analogue	16 (80)
Everolimus	3 (15)
Interferon	2 (10)
Other ^d	2 (10)

^a Data are expressed as number (percentage) unless noted otherwise^b Union for International Cancer Control^c Three patients on a somatostatin analogue also used everolimus (N = 1) or interferon (N = 2)^d Proton pump inhibitor

Duration of outpatient clinic consultation and video-consultation

The patient-reported median duration of a conventional follow-up outpatient clinic consultation was 240 minutes (range 100-390). The median duration of a VC was 13 minutes (range 9-25).

Patients' acceptability and satisfaction with video-consultation

At baseline, mean scores on patients' expectations of VC were high (Table 2). Item 4 which is related to the domain 'similarity to face-to-face encounter' and item 8 (related to the domain 'quality of care') were scored lower. At end of study, participants expressed high levels of satisfaction with VC (median 4.6 (range 3.3-4.9), Table 3). The score on item 8 did not improve after having done VC. The scores indicate that participants find VC of good quality and timesaving and are interested to use VC again. At end of study, 12 out of 20 participants preferred VC during follow-up care. Four participants preferred an outpatient clinic consultation and the remaining four participants had no preference. Participants were asked about their opinion about using VC. All participants mentioned the advantage of having no travel and waiting time. Also, having a consultation in their own environment (N = 1) and no travel cost (N = 2) were seen as an advantage. Disadvantages of VC were experiencing technical problems (e.g. with audio, internet connection), which was reported by 55% of the participants. These technical problems resulted in hampered conversation (N = 5), less personal/easy communication (N = 4) and having no to less body language/non-verbal communication (N = 2) than in a face-to-face encounter on the outpatient clinic. One participant missed the ability of a physical exam and another participant mentioned less involvement of his wife during the consultation. Nine patients reported no drawbacks of VC. Half of the patients experienced some degree of technical problems, largely related with audio quality. As a consequence, suggested improvements were better audio quality. Eighteen participants found VC a valuable addition to the care for NET patients. Two participants did not express an opinion. Comments of participants were to alternate follow-up consultations via VC and at the outpatient clinic (N = 4) and preference for an outpatient clinic consultation in case of complaints or discussing results of important investigations such as a CT scan (N = 4).

Table 2. Patients' expectations of video-consultation

Item TSQ	Mean score (SD) (N = 20)
1. I expect to talk easily to my HC provider	4.2 (1.1)
2. I expect to hear my HC provider clearly	4.5 (1.1)
3. I expect that my HC provider is able to understand my HC condition	4.4 (1.0)
4. I expect to see my HC provider as if we met in person	3.7 (1.0)
5. I do not expect to need assistance while using the system	4.1 (0.9)
6. I feel comfortable communicating with my HC provider via VC	4.3 (1.0)
7. I expect the HC provided via VC is consistent	4.1 (0.9)
8. I expect to have better access to HC services by use of VC	3.4 (0.8)
9. VC saves me time travelling to the hospital	4.8 (0.9)
10. I expect to receive adequate attention	4.6 (0.8)
11. I expect that VC provides for my HC need	4.3 (0.9)
12. I expect that VC is an acceptable way to receive HC services	4.4 (0.7)

TSQ: Telemedicine Satisfaction Questionnaire, HC: health-care, VC: video-consultation.

Table 3. Patients' satisfaction with video-consultation

Item TSQ	Mean score (SD) (N = 20)
1. I can easily talk to my HC provider	4.4 (1.1)
2. I can hear my HC provider clearly	4.2 (0.8)
3. My HC provider is able to understand my HC condition	5.0 (0.2)
4. I can see my HC provider as if we met in person	4.0 (1.0)
5. I do not need assistance while using the system	4.0 (1.0)
6. I feel comfortable communicating with my HC provider via VC	4.5 (0.8)
7. I think the HC provided via VC is consistent	4.0 (1.1)
8. I obtain better access to HC services by use of VC	3.4 (1.1)
9. VC saves me time travelling to the hospital	5.0 (0.0)
10. I do receive adequate attention	5.0 (0.2)
11. VC provides for my HC need	4.4 (0.7)
12. I find VC an acceptable way to receive HC services.	4.6 (0.6)
13. I will use VC services again	4.6 (0.7)
14. Overall, I am satisfied with the quality of service being provided via VC	4.7 (0.6)

TSQ: Telemedicine Satisfaction Questionnaire, HC: health-care, VC: video-consultation.

Physicians' acceptability and satisfaction with video-consultation

Three physicians performed VCs with patients during the study period. Median score for satisfaction with VC was 4.0 (range 3.5-4.9) indicating a high level of satisfaction with VC (Table 4). A lower average score was found with regard to the equality for follow-up care of VC to an outpatient clinic consultation. In the second part of the questionnaire, the physicians' opinion regarding VC was evaluated. Mentioned advantages were that VC is sometimes less time consuming in case of patients without problems/complaints, communication with the patient was more efficient, no support of other staff was needed and no cancellation of the appointment if the patient had ailments such as the flu (N = 2). Disadvantages were technical problems, which was reported by the physicians in 40% of the performed VCs. Mentioned technical problems were prolonged connection time and poor quality of the audio and/or internet resulting in difficulty to hear or see the patient. Other drawbacks reported by physicians were having limited information with regard to body language (N = 3) and less easy communication with the person (e.g. caregiver) who accompanied the patient during the VC (N = 2). After one VC, a physician reported less personal communication with the patient. All physicians reported as advantage for the patients that VC is time saving and no need to travel. Mentioned disadvantages for patients are no possibility for a physical exam, less involvement of an accompanying person during a VC and feeling stress/anxiety due to technical/connections problems. All physicians consider VC of additional value in the care of NET patients and would recommend it to colleagues.

Table 4. Physicians' satisfaction with video-consultation

Statements questionnaire	Mean score (SD) (N = 40 questionnaires)
1. I enjoyed the VC with my patient	4.6 (0.5)
2. I felt at ease to talk with the patient via VC	4.1 (0.8)
3. I find that information is adequate provided via VC	4.2 (0.6)
4. I was able to receive a good impression of the overall health condition of the patient during VC	4.1 (0.6)
5. I had no difficulty to discuss emotional/psychological issues	4.1 (0.7)
6. I find VC equal to consultation at the outpatient clinic for follow-up care	3.2 (0.9)

VC: video-consultation.

Discussion

The present study demonstrates that use of VC during follow-up care of NET patients is feasible and well accepted by both patients and physicians.

Recently, a patient-reported survey among NET patients from different countries demonstrated the burden of traveling to a medical appointment and the wish for better access to NET experts/centers [7]. The current study suggests that implementation of VC can lighten this burden and make NET experts/centers better accessible.

Studies examining the use of VC during follow-up care in patients with cancer or orthopedic surgery showed positive outcomes set out hereafter. A randomized trial which compared VC and outpatient clinic visits in men following radical prostatectomy (N= 55) reported equivalent efficiency, similar overall satisfaction with the encounter by the patient and high level of satisfaction for both encounters by the urologist [8]. A single-arm pilot study examining virtual clinical encounters in addition to routine follow-up in 15 patients after pancreatectomy demonstrated that VC was feasible. Also, enhanced communication with health professionals and quality of postoperative care was reported by patients [9]. A study investigating the use of the videochat and voicecall service 'Skype' in addition to conventional follow-up care in patients after having undergone total joint arthroplasty showed less unscheduled clinic visits in the VC group (N = 34) than in patients only receiving conventional follow-up care (N = 44, comprising patients without internet or appropriate electronic devices for using Skype) [10]. Moreover, the patients who had used Skype had a higher level of postoperative satisfaction. Remarkably, the available data on VC during follow-up care is mostly positive. This can be explained by publication bias and/or selection of patients who are familiar with using internet, videocommunication or electronic devices. Noteworthy, all participants in our study had experience with using internet and it is conceivable that patients without internet experience may be reluctant to use VC which warrants adequate patient selection in further studies.

The inability of performing a physical examination may be a concern of patients and physicians conducting VC. However, others demonstrated no changes in the clinical management due to lack of physical examination in patients with several cancer types who had a physical exam within 60 days of their VC [11].

No unforeseen VC related consultations at the outpatient clinic or hospital admissions were necessary during the study period. Probably, this is associated with inclusion of only clinical stable NET patients.

Generalization of our preliminary findings may be hampered by limitations of the study. First, no control group was included and no randomization was performed. Therefore, no comparison can be made with patients' and physicians' satisfaction with follow-up consultation at the outpatient clinic. Second, the sample size was small and consecutively

impossible to perform statistical analysis (e.g. correlation patient characteristics with participation, dropout). Furthermore, by only including clinical stable NET patients there is a selection bias. It is unknown if VC is feasible in clinical unstable NET or neuroendocrine carcinoma (NEC) patients, which both require more frequent encounters with health care professionals.

Lastly, the time patients spent on performing blood analysis in laboratories nearby their home (if applicable) was not measured. However, none of these patients reported this as a disadvantage or drawback of VC.

In conclusion, our findings suggest that VC is of value in the follow-up care of clinical stable NET patients when it is used additional to outpatient clinic consultations. Before implementation of VC in the follow-up care of NET patients, technical problems have to be solved to improve patients' and physician satisfaction.

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Conflict of interest

None to declare.

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Niacin (vitamin B3) supplementation in patients with serotonin-producing neuroendocrine tumor

Grietje Bouma¹, Martijn van Faassen², Gursah Kats-Ugurlu³,
Elisabeth G.E. de Vries¹, Ido P. Kema², Annemiek M.E. Walenkamp¹

¹ Department of Medical Oncology, University Medical Center Groningen,
University of Groningen, Groningen, The Netherlands

² Department of Laboratory Medicine, University Medical Center Groningen,
University of Groningen, Groningen, The Netherlands

³ Department of Pathology, University Medical Center Groningen,
University of Groningen, Groningen, The Netherlands

Abstract

Background/Aims

Tryptophan is the precursor of serotonin and niacin (vitamin B3). The latter is critical for normal cellular metabolism. Tryptophan and niacin can be deficient in patients with serotonin-producing neuroendocrine tumors (NETs). Niacin deficiency may lead to severe symptoms including pellagra. In patients with serotonin-producing NET, data on niacin status are scarce and niacin supplementation hardly receives attention. We aimed to assess the niacin status before and after supplementation in these patients.

Methods

We identified serotonin-producing NET patients who had received oral niacin supplementation (mean dose 144 mg daily) for tryptophan deficiency and/or pellagra-associated symptoms. Presupplementation plasma tryptophan levels and niacin status based on the urinary niacin metabolite N1-methylnicotinamide (N1-MN) before ($n = 42$) and after the start of the supplementation (in 34 paired samples) were assessed. Reference values for urinary N1-MN levels were established in 133 healthy individuals.

Results

The mean presupplementation plasma tryptophan level was $31.8 \pm 9.7 \mu\text{mol/l}$ (reference value 40.0-70.0). Presupplementation urinary N1-MN levels were lower in patients (median $17.9 \mu\text{mol/24 h}$, range 2.6-70.3) compared to healthy controls (median $43.7 \mu\text{mol/24 h}$, range 9.5-169.3, $p < 0.0001$) and below normal in 45% of the patients. Niacin supplementation increased urinary N1-MN levels to high normal levels (median $55.5 \mu\text{mol/24 h}$, range 7.4-489.0) in 86% of the niacin-deficient patients.

Conclusion

In serotonin-producing NET patients, niacin deficiency is prevalent. Therefore, urinary N1-MN deserves to be included in their standard biochemical evaluation. Niacin supplementation normalizes the niacin status in most niacin-deficient serotonin-producing NET patients. A prospective study is warranted.

Keywords: neuroendocrine tumor, serotonin, N1-methylnicotinamide, niacin, vitamin B3.

Introduction

Neuroendocrine tumors (NETs) are rare tumors, with an incidence of 2.4/100,000/year in the Netherlands. NETs derive from enterochromaffin cells and have the ability to produce various biogenic amines and polypeptide hormones of which serotonin is the most prominent [1]. Patients with serotonin-producing NET, in the past referred to as 'carcinoids', can suffer from a carcinoid syndrome characterized by flushing, diarrhea, asthma-like symptoms (e.g. wheezing) and valvular heart disease [1].

Serotonin is derived from the essential amino acid tryptophan, which plays an important role in the regulation of growth, mood, behavior and immune responses [2]. In healthy persons, only 1% of the tryptophan pool is used for serotonin production while the major part is metabolized by the kynurenine pathway to NAD⁺ (metabolically active form of niacin). In patients with a serotonin-producing NET, metabolism of tryptophan is diverted to the serotonin pathway. This can lead to the utilization of 60% of the tryptophan pool for serotonin synthesis in the tumor [3-5]. This derangement may then result in tryptophan and/or niacin (vitamin B3) depletion. A variety of symptoms and complaints related to changes in the skin, gastrointestinal tract and nervous system can be observed with tryptophan and/or niacin deficiency. Best known is pellagra, which is characterized by 'the four Ds': dermatitis, diarrhea, dementia and death [6-8]. The latter may occur in cases of untreated severe niacin and/or tryptophan deficiency. Nowadays, pellagra is rarely seen in the Western world. It is, however, still present in developing countries or individuals at risk as a consequence of malnourishment, such as chronic alcoholics, and patients with gastrointestinal disease or human immunodeficiency virus. Moreover, it can be induced by drugs (e.g. isoniazid, which affects tryptophan metabolism). Administration of niacin rapidly and effectively reduces symptoms and complaints in these persons [6-9].

In patients with serotonin-producing NETs, pellagra and other symptoms suggestive of tryptophan and/or niacin deficiency are reported [3,4,10-12]. Niacin supplementation resulted in a quick and substantial improvement in the symptoms of these patients [4,11]. However, there is scarcely any literature available regarding the systematical assessment of the niacin status in patients with serotonin-producing NET. A study performed in 1957 assessed the niacin metabolite urinary N1-methylnicotinamide (N1-MN) in 4 serotonin-producing NET patients and found that patients with the highest serotonin production had the lowest urinary N1-MN levels [13]. This finding suggests a low niacin status in patients with excessive serotonin-producing NET. More recently, the niacin status in newly diagnosed carcinoid patients, with (n = 36) and without (n = 32) carcinoid syndrome, was analyzed by measuring biologically active forms of niacin, NAD⁺ and NADP⁺ in whole blood [14]. Among the patients with carcinoid syndrome, 28% were biochemically niacin deficient, including 1 patient with signs of pellagra.

Measurement of the 24-hour output of urinary N1-MN is a reliable marker for niacin

deficiency and niacin status after supplementation. In contrast, assessment of the other niacin metabolite, N1-methyl-2-pyridone-5-carboxamide (2-pyr), in 24-hour urine or the ratio of 2-pyr/N1-MN are less accurate measures [15].

The aim of this study was to assess the niacin status by measurement of urinary N1-MN in serotonin-producing NET patients with tryptophan deficiency and/or associated symptoms, who therefore received niacin supplementation. The niacin status was serially assessed before and after supplementation to examine the effectiveness of niacin supplementation.

Materials and methods

Patients

Between January 2006 and February 2014, we identified serotonin-producing NET patients (tumor grades 1 and 2, according to the World Health Organization 2010 classification) under treatment at the Department of Medical Oncology of the University Medical Center Groningen, the Netherlands. Patients who had received niacin supplementation based on low plasma tryptophan levels ($<40 \mu\text{mol/l}$) and/or pellagra-like symptoms, as part of standard care, were included. Assessment of plasma tryptophan levels is part of the standard biochemical evaluation in serotonin-producing NETs in the above-mentioned NET referral center. The diagnosis of serotonin-producing NET was based on increased urinary 5-hydroxyindolacetic acid (5-HIAA; $>3.8 \text{ mmol/mol creatinine}$) [16]) secretion and/or platelet serotonin ($>5.4 \text{ nmol}/10^9 \text{ platelets}$ [16]) level. Histological analysis of the tumor tissue of the patients was centrally reviewed by a dedicated NET pathologist (G.K.-U.).

For the assessment of the 24-hour output of N1-MN in patients, residual archival urine was used. This does not interfere with patient care nor does it involve the physical involvement of the patient. Therefore, no ethical approval is required according to the Dutch legislation (the Medical Research Involving Human Subjects Act) [17].

Healthy individuals ($n = 133$) participating in the LifeLines cohort study [18] served as controls.

The LifeLines cohort study was approved by the Local Medical Ethics Committee of the University Medical Center Groningen, the Netherlands. All participating healthy individuals gave their written informed consent.

Laboratory methods and (pre-)analytical procedures

Presupplementation tryptophan levels in patients were assessed in platelet-rich plasma samples. In case of a missing plasma tryptophan level at the start of niacin supplementation, we used the nearest available plasma tryptophan level before the start

of niacin supplementation. Platelet-rich plasma was collected most often in a nonfasting state during routine outpatient visits. It was obtained by centrifugation at 120 g for 30 min. All platelet-rich plasma was pipetted into a plastic tube and carefully mixed; 0.5 ml served for thrombocyte counting and the remaining plasma was stabilized with a mixture of ethylenediaminetetraacetic acid (EDTA) and ascorbic acid and frozen at -20°C until tryptophan and serotonin analysis by high-performance liquid chromatography fluorometry [19].

Niacin status was evaluated by measuring the 24-hour output of urinary N1-MN.

For the assessment of the niacin status before supplementation, 24-hour urine samples collected before the start of niacin supplementation and the nearest available samples by the assessment of the presupplementation plasma tryptophan level were selected. Patients collected 24-hour urine for 5-HIAA assessment the day before their routine clinic visit. Urine was stabilized with 250 mg EDTA and ascorbic acid mixture (1:1). After mixing, part of the urine was used for routine 5-HIAA analysis [20] and residual material was frozen at -80 °C. N1-MN was analyzed by a newly developed liquid chromatography-tandem mass spectrometry method (LC-MS/MS). In short, 50 µl urine was pipetted into a 96-well plate. Internal standard 1-methylnicotinamide-d3 in acetonitrile was added. Subsequently, the plate was vortexed and calibrators and standards were diluted with acetonitrile. Finally, 5 µl was injected onto an LC-MS/MS system (Spark Holland, the Netherlands) using a Phenomenex Luna HILIC column (2.1 × 150 mm, 3 µm) and a tandem mass spectrometer Xevo TQ-MS (Waters, Milford, Mass., USA) in the selective reaction monitoring mode for mass spectrometric detection. Intra-assay (n = 20) and interassay (n = 12) imprecision was <4% at 3 different N1-MN levels in pooled urine. The quantification limit of N1-MN in urine was 0.170 µmol/l.

Reference ranges for N1-MN in 24-hour urine were established by analyzing 133 urine samples collected from healthy individuals. Reference intervals were calculated using Analyse-it for Excel (Analyse-it Software, Ltd., Leeds, UK).

Statistical analysis

All continuous variables were checked for normality of distribution using Q-Q plots and goodness-of-fit tests. In case of skewed distributions, medians and ranges are presented, and the Mann-Whitney U test was used to compare the significance of the differences in means. Spearman rank correlation analyses were carried out to determine correlations between continuous variables. All tests were performed two-sided, and p values <0.05 were considered significant. Analyses were done using the software package SPSS, version 22 for Windows (SPSS, Inc., Chicago, Ill., USA).

Results

Characteristics of patients and healthy controls

Patient characteristics are summarized in table 1. For this study, we identified 42 patients with a mean age of 64 years (range 41-80) at the start of niacin supplementation. As healthy controls, 52 males (39%) and 81 females (61%) with a median age of 45 years (range 20-79) were used. Most patients received prior treatment including palliative surgical resections and somatostatin analogue and/or interferon. The small intestine was the most frequent site of the primary tumor. All patients had metastatic disease. The mean dose of daily oral niacin supplementation was 144 mg (range 5-300).

Table 1. Patients characteristics (n = 42)

Gender	
Male	20 (48)
Female	22 (52)
Mean age at diagnosis NET, years	60 ± 11
Mean age at start niacin supplementation, years	64 ± 10
Location primary tumor	
Lung	2 (5)
Small intestine	21 (50)
Unknown	18 (43)
Other	1 (2)
Grade NET	
Grade 1	28 (67)
Grade 2	7 (16)
No histological tumor sample available	4 (10)
Insufficient histological tumor sample available for grading	3 (7)
Disease stage	
Stage 4	42 (100)
Antitumor treatment for NET before the start of niacin supplementation	
No	8 (19)
Yes	34 (81)
Type of antitumor treatment before the start of niacin supplementation	
Somatostatin analogue	27 (79)
Palliative surgery	23 (65)
Interferon	11 (32)
Everolimus	4 (12)
Chemotherapy	1 (3)
Peptide receptor radionuclide therapy	3 (9)
Liver embolization	1 (3)
Radiotherapy	4 (12)
Total of different antitumor treatments before the start of niacin supplementation	
1 treatment	12 (35)
2 treatments	12 (35)
3 treatments	3 (9)
≥4 treatments	7 (21)
Type of niacin supplementation	
Nicotinamide	36 (86)
Vitamin B complex	3 (7)
Vitamin B complex forte	2 (5)
Multivitamin	1 (2)

Data are expressed as number with percentages in parentheses or means ± SD.

Tryptophan and niacin status

Prior to the start of niacin supplementation, the mean plasma tryptophan level in patients was 31.8 ± 9.7 $\mu\text{mol/l}$ (range 8.3–51.0). The plasma tryptophan level was below the lower limit of normal (reference value 40–70 $\mu\text{mol/l}$ [19]) in 33 out of 42 (79%) patients. Among patients with normal plasma tryptophan levels, 7 had previous plasma tryptophan levels below the lower limit of normal, 1 had a low normal plasma tryptophan level with complaints of niacin deficiency, and 1 reported niacin deficiency-associated complaints with previous low plasma tryptophan levels. The majority (79%) of plasma tryptophan levels were assessed within 3 months before the start of niacin supplementation (range 0 days to 14 months).

Healthy controls ($n = 133$) were divided into age groups (decades) to examine if urinary N1-MN levels were influenced by age. Mean urinary N1-MN levels did not differ among these age groups ($p < 0.142$). Thereby, the healthy controls could serve as reference for urinary N1-MN levels. Calculated reference ranges for N1-MN in 24-hour urine in healthy controls were 17.3–115.0 $\mu\text{mol}/24$ h.

In 74% of the patients ($n = 31/42$), 24-hour urine for the assessment of presupplementation urinary N1-MN levels was available within 1 week of presupplementation plasma tryptophan level (range 0 days to 4 months). Before supplementation, the median urinary N1-MN level of patients was lower (17.9 $\mu\text{mol}/24$ h, range 2.6–70.3) compared to that of healthy controls (43.7 $\mu\text{mol}/24$ h, range 9.5–169.3, $p < 0.0001$; fig. 1). Based on these reference values, 19 out of 42 (45%) patients had a deficient niacin status at baseline. Among these 19 deficient patients, 15 patients also had a plasma tryptophan level below normal at baseline. The 4 niacin-deficient patients without reduced plasma tryptophan levels had plasma tryptophan levels in the lower range of normal (range 40.5–51 $\mu\text{mol/l}$). Patients with plasma tryptophan levels below normal ($n = 33$) did not have lower N1-MN levels before supplementation (median 17.9 $\mu\text{mol}/24$ h, range 2.6–70.3) compared to patients with sufficient tryptophan levels ($n = 9$; median 25.1 $\mu\text{mol}/24$ h, range 10.1–64.9, $p = 0.483$).

In 34 patients, 24-hour urines were available for niacin status assessment after supplementation. After supplementation, the N1-MN level increased to above normal levels (median 103.3 $\mu\text{mol}/24$ h, range 7.4–545.3) compared to calculated reference values (Fig. 2). In the patients with a deficient niacin status before supplementation ($n = 14$, 5 missing data), the N1-MN level increased to high normal (median 55.5 $\mu\text{mol}/24$ h, range 7.4–489.0) after supplementation. Eventually, 86% of the niacin-deficient patients ($n = 12/14$) had a normal niacin status after supplementation.

Figure 1. Urinary N¹-MN levels in healthy controls (n = 133) and before niacin supplementation in serotonin-producing NET patients (n = 42).

The red lines represent calculated reference ranges for urinary N¹-MN levels (17.3-115.0 $\mu\text{mol}/24\text{ h}$).

Figure 2. Urinary N¹-MN levels before (n = 42) and after niacin supplementation in serotonin-producing NET patients (n = 34).

The red lines represent calculated reference ranges for urinary N¹-MN levels (17.3-115.0 $\mu\text{mol}/24\text{ h}$).

Relationship serotonin production, tryptophan level and niacin status

At baseline, the median serotonin concentration in platelets was 20.0 nmol/10⁹ (range 5.1-44.0), and the median 5-HIAA excretion in urine was 15.0 mmol/mol creatinine (range 2.2-248.9). Urinary 24-hour excretion of 5-HIAA, the metabolite of serotonin, is a measure for serotonin production in NET patients. Niacin-deficient patients (n = 19) did not have a higher urinary 5-HIAA level (median 42.6 mmol/mol creatinine, range 2.2-234.2) compared to patients with a sufficient niacin status (n = 23, median 11.2 mmol/mol creatinine, range 2.2-248.9, p = 0.069). There was no difference in the 5-HIAA level in urine between patients with low plasma tryptophan levels (n = 33, median 17.1 mmol/mol creatinine, range 2.6-248.9) and patients with normal plasma tryptophan levels (n = 9, median 11.4 mmol/mol creatinine, range 2.2-147.4, p = 0.541).

To examine whether increased serotonin production leads to tryptophan and niacin deficiency, we assessed the correlation of urinary 5-HIAA levels with the tryptophan level and niacin status before the start of niacin supplementation (table 2). 5-HIAA levels in 24-hour urine showed a negative correlation with niacin status (p = 0.022, r = -0.352), indicating that before the start of niacin supplementation, NET patients with a higher serotonin production had a lower niacin status. The urinary 5-HIAA level did not correlate with the plasma tryptophan level (p = 0.183).

In the 19 patients with niacin deficiency at baseline, the urinary 5-HIAA level did not correlate with the plasma tryptophan level (p = 0.932) or the niacin status (p = 0.715). In these patients, the plasma tryptophan level correlated with the niacin status (p = 0.022, r = 0.522).

Table 2. Correlations between biochemical parameters (Spearman's rho)

	All patients (n = 42)			Niacin-deficient patients (n = 19)		
	Plasma tryptophan	Urine 5-HIAA	Urine N ¹ -MN	Plasma tryptophan	Urine 5-HIAA	Urine N ¹ -MN
Plasma tryptophan¹	1	-0.209	0.275	1	-0.021	0.522*
Urine 5-HIAA²	-0.209	1	-0.352*	-0.021	1	0.090
Urine N¹-MN³	0.275	-0.352*	1	0.522*	0.090	1

¹ in µmol/l, ² in mmol/mol creatinine, ³ in µmol/24 h

* p < 0.05

Discussion

This is the first study which biochemically evaluated the effectiveness of niacin supplementation in serotonin-producing NET patients with niacin deficiency. Niacin supplementation was effective in normalizing the niacin status in most of these patients. In this study, excessive serotonin production defined by elevated urinary 5-HIAA levels was related to a lower niacin status before the start of niacin supplementation. The difference in urinary 5-HIAA levels between niacin-deficient and niacin-sufficient patients did not reach the significance level, which may be due to the small number of patients. In contrast to earlier findings [19], the plasma tryptophan level was not related to excessive serotonin production. Also, in patients with a too low niacin status, no relation was found for serotonin production and plasma tryptophan level or niacin status. This may be explained by the fact that the plasma tryptophan level and the niacin status are influenced by several factors, such as dietary intake, malabsorption and drug interactions, which may have affected the findings in this study. NAD⁺ is not only de novo synthesized from tryptophan but can also be synthesized via salvage pathways from precursors in the diet, such as nicotinamide and nicotinic acid [21]. Another explanation may be found in the retrospective design of the study. Plasma tryptophan levels were not assessed nearby the 24-hour urine collection for 5-HIAA and N1-MN levels at the start of the niacin supplementation in all patients, which may have interfered in the above-mentioned examined relations.

The plasma tryptophan level is no accurate predictor of niacin status. Eighteen out of 42 patients had low plasma tryptophan levels with adequate niacin status, and 4 niacin-deficient patients had above normal plasma tryptophan levels. Assessment of plasma tryptophan concentrations in 26 healthy individuals showed a significant biological variation during the day with significant increases in plasma tryptophan concentrations after consumptions of meals [22]. Because of the biological variation and the need for drawing blood in a fasting state, it is not accurate and practical to use the plasma tryptophan level for the assessment of the niacin status. Therefore, assessment of the niacin status and the start of niacin supplementation should be based on the resultant of the deficiency, namely the urinary N1-MN level. Fourteen percent of the niacin-deficient patients in our study were still deficient after niacin supplementation. This might be due to the compliance with vitamin supplementation which may not have been accurate at all times. Daily oral administration of niacin is required since it is a water-soluble vitamin and thereby not stored in the body [9]. The prevalence of pellagra in serotonin-producing NET patients is about 5% [12] and especially reveals during the advanced stage of the disease [10]. Niacin deficiency might be underestimated in patients with a serotonin-producing NET. Symptoms of niacin deficiency can resemble and coincide

with symptoms due to serotonin production of NET, such as diarrhea, which impairs the recognition of clinical niacin deficiency. Also, treating physicians may not be aware of niacin deficiency and accompanying pellagra since diagnosing, preventing or treating these conditions have received little attention in earlier literature and current available guidelines for treating NET patients. Given the impact of NET on the patient's quality of life [23,24] and the relatively long-term survival, a valuable additional goal in the care for NET patients should be preventing clinical niacin deficiency such as pellagra.

Regular biochemical evaluation including 24-hour urinary excretion of 5-HIAA is standard practice to evaluate the effect of therapy and tumor progression in serotonin-producing NET patients [25,26]. Given our findings, we consider it of clinical interest to include urinary N1-MN in this biochemical assessment to facilitate early diagnosis and prevention of niacin deficiency. In case of biochemically proven niacin deficiency, supplementation of niacin can easily and effectively treat niacin deficiency and prevent accompanying symptoms.

A prospective study is warranted to assess the prevalence of niacin deficiency and to evaluate the most effective method of niacin supplementation for treating biochemical and clinical niacin deficiency among serotonin-producing NET patients.

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Reasons for the cold immune microenvironment of neuroendocrine tumours

Lotte D. de Hosson^{1‡}, Grietje Bouma^{1‡}, Gursah Kats-Ugurlu²,
Marian Bulthuis², Elisabeth G.E. de Vries¹, Martijn van Faassen³,
Ido P. Kema³, Annemiek. M.E. Walenkamp¹

¹ Department of Medical Oncology, University Medical Center Groningen,
University of Groningen, Groningen, The Netherlands

² Department of Pathology, University of Groningen, University Medical
Centre Groningen, Groningen, The Netherlands

³ Department of Laboratory Medicine, University of Groningen,
University Medical Centre Groningen, Groningen, The Netherlands

Abstract

Tumours can escape the immune system by expressing programmed death-ligand-1 (PD-L1) which allows them to bind to PD-1 on T-cells and avoid recognition by the immune system. In addition, regulatory T-cells (Tregs), indoleamine 2,3-dioxygenase (IDO) and tryptophan 2,3-dioxygenase (TDO) play a role in immune suppression. There is limited knowledge of interaction of neuroendocrine tumours (NETs) with their immune microenvironment and the role of immunotherapy in patients with NET. This study aimed to investigate the immune microenvironment of serotonin-producing (SP) and non-serotonin-producing NETs (NSP-NETs).

Tumours of 33 patients with SP-NET and 18 patients with NSP-NET were studied. Immunohistochemical analyses were performed for PD-L1, T-cells, IDO, TDO, mismatch repair proteins (MMRp) and activated fibroblasts. PD-L1 expression was seen in <1% of the tumour cells and T-cells. T-cells were present in 33% of NETs, varying between 1-10% T-cells per high power field. IDO was expressed in tumour cells in 55% of SP-NETs and 22% of NSP-NETs ($p = 0.039$). TDO was expressed in stromal cells in 64% of SP-NETs and 13% NSP-NETs ($p = 0.001$). None of the tumours had loss of MMRp. TDO-expressing stromal cells also strongly expressed α -smooth muscle antigen (α -SMA) and were identified as cancer associated fibroblasts (CAFs).

In conclusion, NETs lack pre-existing immunity as they do not express PD-L1, contain only few T-cells and were not MMRp deficient. The expression of IDO and TDO in a substantial part of NETs and the presence of CAFs suggest two mechanisms responsible for the cold immune microenvironment. These mechanisms can be further explored to enhance anti-tumour immunity and clinical responses.

Keywords: neuroendocrine tumours, programmed death-ligand-1, indoleamine 2,3-dioxygenase, tryptophan 2,3-dioxygenase, T-cells, immune microenvironment.

Abbreviations

5-HIAA	5-hydroxyindolacetic acid
α -SMA	α -smooth muscle antigen
CAF	cancer associated fibroblast
HE	hematoxylin and eosin
HPLC	high performance liquid chromatography
IDO	indoleamine 2,3-dioxygenase
MMRp	mismatch repair proteins
NEN	neuroendocrine neoplasm
NET	neuroendocrine tumour
NSP-NET	non-serotonin-producing neuroendocrine tumour
PD-L1	programmed death-ligand-1
PD-1	programmed death-1
PFS	progression free survival
PRP	platelet rich plasma
TGF- β	transforming growth factor-beta
TDO	tryptophan 2,3-dioxygenase
Treg	regulatory T-cell
SP-NET	serotonin-producing neuroendocrine tumour
VDS	virtual double staining

Introduction

Neuroendocrine tumours (NETs) comprise a heterogeneous group of tumours, which are predominantly derived from the enterochromaffin cells of the gastro-enteropancreatic tract or bronchopulmonary system [1]. NETs can produce various biogenic amines and polypeptide hormones of which serotonin is the most common [2]. Radical resection of the NET is the only possibility to cure. However, NET patients often present with non-resectable or metastatic disease. Non-curative systemic treatment aimed at controlling symptoms and progression of disease includes somatostatin analogues, interferon, everolimus, sunitinib, peptide receptor radionuclide therapy and chemotherapy [3]. None of the currently used systemic treatments for NET could be graded as substantial clinical beneficial according to the 'European Society of Medical Oncology magnitude of clinical benefit scale' [4]. Therefore, there is an unmet need for new and better systemic treatment modalities.

Over the last years, immunotherapy with immune checkpoint inhibiting antibodies targeting the cell surface proteins programmed death-ligand-1 (PD-L1) on tumour and (non-)immune cells and programmed death-1 (PD-1) on mono-/lymphocytes have shown antitumour activity across numerous tumour types [5]. Targeting of PD-L1 and PD-1 lead to activated T-cells in the tumour microenvironment. There is however limited information as yet with regards to the activity of these drugs in NETs.

There are a number of other factors considered to be associated with a response to checkpoint inhibitor treatment, as shown in clinical studies, such as presence of T-cells, and high mutational tumour load [6,7]. In addition, there is a major interest in the tryptophan-degrading enzymes indoleamine 2,3-dioxygenase (IDO) and tryptophan 2,3-dioxygenase (TDO) along the kynurenine pathway that depletes tryptophan in the tumour microenvironment [8-10]. IDO and TDO are especially of interest in NETs as these tumours often produce serotonin which potentially depletes its precursor, tryptophan (Figure S1) [11].

Overall, strikingly little is known about the complex interactions of NET cells with their surrounding immune microenvironment. Consequently, knowledge about potential targets for immunotherapy in NET patients is limited [12,13]. Therefore, the aim of this study was to investigate the tumour immune microenvironment, i.e. the presence of PD-L1, T-cells, IDO, TDO, MMRp and CAFs in tissue of treatment-naïve SP-NET and NSP-NET patients.

Materials and methods

Participants

Medical records of newly referred NET patients to the Department of Medical Oncology of the University Medical Center Groningen (UMCG) between January 1st, 2008 and

December 31th, 2014 were screened. Patients diagnosed with a NET grade 1 or 2 according to the World Health Organization 2010 classification were selected. A patient was diagnosed with a SP-NET when urinary 24-h excretion of 5-HIAA was >3.8 mmol/mol creatinine and/or platelet serotonin >5.4 nmol/109 platelets [10]. Serotonin production and 5-hydroxyindolacetic acid (5-HIAA) in 24 hour (24-h) urine were measured by high performance liquid chromatography (HPLC) [14].

Included were NET patients with tumour tissue, platelet-rich plasma (PRP) for analysis of serotonin and/or urinary 24-h excretion of 5-hydroxyindolacetic acid (5-HIAA) available before start of systemic antitumour treatment. Somatostatin analogue use was allowed for maximal 14 days before the tumour tissue was collected. Excluded were NET patients with other primary solid/haematological malignancy, auto-immune disease (e.g. colitis) or infectious disease (e.g. hepatitis) as well as patients with concomitant use of treatment interfering with IDO-activity (e.g. interferon).

Patients were clinically staged according to the Union for International Cancer Control guidelines [15]. Histopathological analysis of the formalin-fixed paraffin-embedded tumour tissue of the patients was centrally reviewed by a dedicated NET pathologist (Gursah Kats-Ugurlu).

Tumour histology and immunohistochemistry

In all the tumour samples 3 μ m slides of formalin-fixed paraffin-embedded tumour samples were studied for morphology and mitotic count on standard hematoxylin and eosin (HE) stain and proliferation index was determined using immunohistochemistry based Ki-67 stain (mouse anti-Ki67, MiB-1 clone, dilution 1:100 Dako, Glostrup, Denmark). Two antibodies for PD-L1 staining were used, namely mouse anti-PD-L1 (clone 22C3, 1:50, Dako, Glostrup, Denmark) and rabbit anti-PD-L1 (clone E1L3N, 1:200 Cell Signaling Technology, Danvers, MA, USA). PD-L1 antibodies were applied in the Ventana Ultra staining system. To detect MMR antigens, anti-MLH-1 mouse monoclonal primary antibody (clone M1, Roche Diagnostics, IN, USA), PMS2 rabbit monoclonal antibody (clone EPR3947, Cell Marque, CA, USA), MSH2 mouse monoclonal antibody (clone G219-1129, Cell Marque), CONFIRM anti-MSH6 mouse monoclonal primary antibody (clone 44, Roche Diagnostics) were used. The mouse-anti-CD3 antibody (1:50, Monosan, Sanbio, Uden, the Netherlands) served to recognize T-cells. Antibodies against IDO (mouse anti-IDO, MAB5412, 1:25, Chemicon, Millipore, Amsterdam, the Netherlands), TDO (rabbit anti-TDO2, clone HPA 039611, 1:200, Atlas Antibodies, Bromma, Sweden), desmin (M0760, dilution Dako 1:50, Madrid, Spain), and α -SMA (mouse anti-SMA, clone 1A4, 1:1000, Sigma, MI, USA) were applied. α -SMA and desmin are well-established markers for myofibroblasts and myofibroblast-like cells in the tumour microenvironment, also known as CAFs [16,17].

One pathologist (Gursah Kats-Ugurlu) and two researchers (Grietje Bouma and Lotte D. de Hosson) evaluated the stained slides at a double-head microscope blinded for clinical and histopathological information. To avoid learning effect, every first 10 slides that were scored and slides that were difficult to score, were scored again without knowledge of the first score. Positive external controls were placenta for PD-L1, appendix for the MMR antigens and CD3, lymph node for IDO and prostate for TDO. For α -SMA the pericytes of blood vessels served as internal control.

The tumour and its immediate environment were evaluated. Tumour cells with $\geq 1\%$ positive staining for PD-L1, IDO and TDO were considered as positive. MMRp loss was considered when the tumour cell nucleus showed no staining in comparison to internal inflammatory cells or appendix as external control. T-cells were scored 'present' if $\geq 1\%$ of the cells in a high power field composed of T-cells distributed patchy or diffusely in CD3. PD-L1 showed a membranous staining pattern of the tumour cells. IDO showed a cytoplasmic staining pattern with the presence of acellular small depositions. TDO showed besides a cytoplasmic staining pattern more remarkable expression in the tumour stroma. Finally, a α -SMA staining was performed to further characterise TDO positive stromal cells: on five tumours with TDO expression in stroma, and five without TDO expression in stroma. Furthermore, staining with desmin, another marker for CAFs, was performed. To demonstrate the close vicinity of stroma cells that were identified as CAFs and tumour cells, we used virtual double staining (VDS) (Visiopharm©) with HE and α -SMA. Stained slides were scanned at an objective magnification of x40 using Philips Ultra Fast Scanner 1.6 and saved in their image file format i-Syntax. First, alignment on a large scale was performed at the images of adjacent slides stained for HE and α -SMA. Visiopharm presents the best possible match of the 2 tissue sections on a finer detail level, which is verified by a technician. Thereafter, the cells were identified by shape and size. This was performed by employing a fully automated watershed-based segmentation technique to separate cells positive and negative for α -SMA from the background. To investigate which T-cell subsets were present, VDS was used for 3 tumours stained with CD3 and CD8 antibodies (ready to use antibodies of Ventana BenchMark). The CD3 positive and CD8 positive cells were counted manually by the pathologist and the CD8/CD3 ratio was calculated.

Statistical analysis

For this exploratory study no sample size calculation was performed. Descriptive statistics (e.g. median, ranges, and frequencies) were calculated for all measures. Mann-Whitney U test was used to compare distributions across groups. Associations of categorical variables were tested using the Chi-Square test. Tests were performed two-sided, and P values < 0.05 were considered significant. Analyses were executed using the software package SPSS, version 23 for Windows (SPSS, Inc, Chicago, IL, USA).

Results

Patient characteristics

Clinical and pathological characteristics at the moment of tumour collection of all SP-NET (N = 33) and NSP-NET (N = 18) patients are summarised in Table 1. Thirteen SP-NET patients were shortly treated with somatostatin analogues before the tissue sampling. The short use of somatostatin analogues was unavoidable in 13 out of 51 (25%) patients since this was prescribed to prevent a carcinoid crisis during an invasive procedure.

Expression of PD-L1, MMR, presence of tumour infiltrating T-cells, IDO and TDO expression in NETs.

None of the tumours or T-cells were positive for PD-L1 in anti-22C3 or anti-E1L3N stains. None of the tumours showed loss of the MMRp. T-cells were present in 15 of the 45 samples, varying between 1-10% T-cells per high power field (Table 2). T-cells were most frequently found within the stroma of NETs of the jejunum/ileum which were all SP-NETs (Table 3). Of the 3 tumours which presented T-cells, the CD8/CD3 ratio was 70/120, 6/25 and 3/10 respectively.

IDO expression was restricted to the tumour cells and varied between focal and diffuse presence of intracytoplasmic acellular small depositions. IDO expression in tumour cells was more frequently observed in SP-NETs (55%, 18/33) as compared to NSP-NETs (22%, 4/18) ($p = 0.026$, Table 2).

There were three different patterns of TDO expression in the NETs, namely in tumour cells, in the stroma or in both (Figure 1B and 1C). NETs expressed TDO either in the tumour cells (37%, 17/46) or in the stroma (44%, 18/41) (Table 2). Remarkably, TDO in the stroma was observed in 64% (16/25) evaluable SP-NETs and 13% (2/16) of the NSP-NETs. To investigate the origin of these TDO positive stromal cells, an α -SMA staining was performed on 10 slides. These cells strongly expressed α -SMA and desmin and were spindle-shaped. Furthermore, these cells were located within the vicinity of tumour cells, as shown with VDS (Figure 2). The stromal cells were therefore identified as CAFs [18-20]

Table 1. Clinicopathological characteristics of patients

	NET patients (N=51) ^a	NSP NET (N=18)	SP NET (N=33)
Mean age in years ± SD	62.8 ± 11.0		
Male sex	30 (59)	11 (61)	19 (58)
Primary tumour location			
Lung	2 (4)	2 (11)	0 (0)
Stomach	1 (2)	1 (6)	0 (0)
Duodenum	2 (4)	2 (11)	0 (0)
Pancreas	14 (27)	11 (61)	3 (9)
Jejunum/ileum	22 (43)	0 (0)	22 (67)
Colon/rectum	2 (4)	1 (6)	1 (3)
Unknown	8 (16)	1 (6)	7 (21)
Tumour grade			
Grade 1	34 (67)	8 (44)	25 (76)
Grade 2	16 (31)	10 (56)	6 (18)
Unknown	1 (2)	0 (0)	2 (6)
Disease stage			
Stage 1/2	3 (6)	2 (11)	1 (3)
Stage 3/4	46 (90)	15 (83)	31 (94)
Unknown	2 (4)	1 (6)	1 (3)
Source tissue sample			
Primary tumour	30 (59)	10 (56)	20 (61)
Metastasis	20 (39)	8 (44)	12 (36)
Unknown	1 (2)	0 (0)	1 (3)
Location tissue sample			
Liver	14 (27)	8 (44)	6 (18)
Lymph node	4 (8)	1 (6)	3 (9)
Jejunum/ileum	18 (35)	0 (0)	18 (55)
Pancreas	5 (10)	3 (17)	2 (6)
Duodenum	3 (6)	3 (17)	0 (0)
Lung	2 (4)	1 (6)	1 (3)
Other ^b	5 (10)	2 (6)	3 (9)

^aValues are reported as number (percentage) unless noted otherwise

^bOther sites of the tissue sample collection were mesenterium of the small intestine (N = 2), colon (N = 1), stomach (N = 1), peritoneum (N = 1).

NET = neuroendocrine tumour, NSP-NET = non-serotonin-producing neuroendocrine tumour, SP-NET = serotonin-producing neuroendocrine tumour.

Table 2. Presence of PD-L1 expression, MMRp, T-cells, IDO expression and TDO expression in NETs

	All NET n (%)	NSP-NET n (%)	SP-NET n (%)	p-value
Tissue samples	51 (100)	18 (100)	33 (100)	
PD-L1 expression (22C3 antigen)				
Negative	51 (100)	18 (100)	33 (100)	NS
Positive	0 (0)	0 (0)	0 (0)	
PD-L1 expression (E1L3N antigen)				
Negative	51 (100)	18 (100)	33 (100)	NS
Positive	0 (0)	0 (0)	0 (0)	
MMRp				
Loss of MMRp	0 (0)	0 (0)	0 (0)	NS
No loss of MMRp	51 (100)	18 (100)	33 (100)	
T-cells				
Absent	30 (59)	10 (56)	20 (61)	NS
Present	15 (29)	6 (33)	9 (27)	
Not evaluable	6 (12)	2 (11)	4 (12)	
IDO expression				
Negative	29 (57)	14 (78)	15 (45)	0.039
Positive	22 (43)	4 (22)	18 (55)	
TDO expression in tumour cells				
Negative	29 (63)	11 (65)	18 (62) ^a	NS
Positive	17 (37)	6 (35)	11 (38)	
Not evaluable	5 (10)	1 (6)	4 (12)	
TDO expression in stroma				
Negative	23 (56)	14 (88)	9 (36)	0.001
Positive	18 (44)	2 (13)	16 (64)	
Not evaluable	10 (20)	2 (11)	8 (24)	

^aThree tissue samples of SP-NETs with not evaluable stroma were TDO positive in the tumour.

PD-L1 = programmed death-ligand 1, MMRp = mismatch repair proteins, IDO = indoleamine 2,3-dioxygenase, TDO = tryptophan 2,3-dioxygenase, NET= neuroendocrine tumour, NSP-NET = non-serotonin-producing neuroendocrine tumour, SP-NET = serotonin-producing neuroendocrine tumour.

Table 3. Presence of T-cells and immunohistochemical expression of IDO, TDO and PD-L1 classified by primary origin of the NET

	Jejunum/ileum N	Pancreas N	Lung N	Unknown N	Other N ^a
Tissue samples	22	14	2	8	5
T-cells					
Absent	13	11	0	5	1
Present	7	1	1	3	3
Not evaluable	2	2	1	0	1
IDO expression					
Negative	9	9	2	6	3
Positive	13	5	0	2	2
TDO expression in tumour cells					
Negative	15	6	2	3	3
Positive	4	6	0	5	2
Not evaluable	3	2	0	0	0
TDO expression in stroma					
Negative	2	12	1	5	3
Positive	15	1	0	1	1
Not evaluable	5	1	1	2	1
PD-L1 expression	0	0	0	0	0

^aOther sites of primary origin of the NET are the stomach (N = 1), duodenum (N = 2), colon (N = 1) and the rectum (N = 1).

IDO = indoleamine 2,3-dioxygenase, TDO = tryptophan 2,3-dioxygenase NET; PD-L1 = programmed death-ligand 1, NET = neuroendocrine tumour.

Figure 1. Expression of IDO, TDO and α -SMA and IDO in a serotonin producing NET of the ileum

Illustrative images of indoleamine 2,3-dioxygenase (IDO) and tryptophan 2,3-dioxygenase (TDO) expression in a serotonin producing neuroendocrine tumour (NET) in ileum resection specimen (A, HE, 20x). Magnification of the submucosal NET (B, HE, 200x). In lower magnification IDO is not detectable (C, IDO, 20x). In higher magnification a diffuse, strong brown intracytoplasmic, dot-like IDO expression is seen in tumour cells already in low magnification (D, IDO, 1000x). TDO expression is visible in stromal cells surrounding the tumour cells (E, TDO, 20x and F, TDO, 200x). α -SMA is expressed in stromal cells (grey arrows) between tumour cells (black arrows) and has a stronger expression in areas with more TDO expression (G, α -SMA, 20x and H, α -SMA, 200x).

Figure 2. Expression of α -SMA and desmin in a serotonin-producing NET of the ileum

Illustrative images of α -SMA and desmin expression in a resection specimen of a serotonin-producing NET of the ileum: A (HE, 400x), B (α -SMA, 400x), C (desmin, 400x).

Discussion

We explored the immune microenvironment of NETs. In NETs both tumour and T-cells did not express PD-L1. None of the tumours were MMRp deficient. In addition, only the minority of NETs contained a limited number of T-cells. A substantial part of NETs expressed IDO and TDO. TDO was also expressed by stromal cells. These cells could be identified as CAFs due to the positive staining with α -SMA and desmin. Furthermore, we demonstrated their close vicinity to tumour cells with the aid of VDS.

Our study showed that NETs exhibit a 'cold' tumour microenvironment lacking several characteristics which are currently associated with a response to checkpoint inhibitor treatment [5,21]. The expression of IDO and TDO in a substantial part of NETs and the presence of CAFs suggest two mechanisms responsible for the cold immune microenvironment.

Interestingly, immunohistochemical analysis of lung cancer specimens revealed increased TDO2 expression in CAFs. Furthermore, in a mouse model, administration of a TDO2 inhibitor improved T-cell response, and decreased tumour metastasis in mice with metastatic lung cancer [22]. The enzymes IDO and TDO degrade tryptophan into kynurenines resulting in a tryptophan depleted tumour microenvironment rich of kynurenines. This microenvironment leads to suppression of effector T-cells or the conversion to tumour tolerant regulatory T-cells (Tregs) [8-10]. A number of IDO and TDO inhibitors advanced into clinical trials with or without PD-1 antibody inhibitors in patients with solid tumours. Also, an IDO1/TDO dual inhibitor is currently tested in a phase I study [23-27]. In the ECHO-301/KEYNOTE 252 study, patients with unresectable or metastatic melanoma were randomized to receive pembrolizumab in combination with either epacadostat (an IDO-inhibitor) or placebo. Surprisingly, this phase III study, was recently announced to be terminated early due to failure to improve progression free survival (PFS) [28]. A reason for this failure could be that the IDO inhibitor does not induce novel T-cell responses at the site of the tumour. With the use of vaccination therapy with tumour-associated antigens pro-inflammatory T-cells can be attracted to the tumour microenvironment to induce local inflammation and improve efficacy of checkpoint blockade [29]. In the first clinical trials, treatment with IDO vaccine seems to be well tolerated and without augmented toxicity in patients with metastatic melanoma or lung cancer [30,31]. Recently, a randomized phase I/II trial started for patients with metastatic non-small cell lung cancer analyzing the efficacy of pembrolizumab combined with the IDO vaccine versus pembrolizumab combined with chemotherapy. Furthermore, preclinical studies have suggested that aryl hydrocarbonreceptor could become another possible target of the IDO/TDO kynurenine pathway in the treatment of cancer because of its immunosuppressive role in tumours [32]. Our data show that especially the serotonin-producing NET tumours express IDO and TDO. These patients often have low tryptophan levels as tryptophan is the sole precursor of peripherally and centrally produced serotonin. Potentially, this means that in patients with low tryptophan levels, IDO-mediated immune suppression is most prominent and these patients might therefore be interesting candidates for combination treatment with immune checkpoint inhibitors combined with IDO inhibitors.

In our study we could not find an association between IDO expression and presence of T-cells and this might be an indication of the complex interaction of tumours and their (immune) microenvironment.

Preclinical studies in mouse models of various cancer types showed that CAFs together with other stromal cells are responsible for restricting the accumulation of T-cells in the vicinity of cancer cells [33]. Furthermore, CAFs act by secretion of various growth factors like transforming growth factor-beta (TGF- β) [19,34]. Increased TGF- β in the tumour immune microenvironment is recently recognised to represent a primary mechanism of immune evasion that promotes T-cell exclusion [35]. In patients with metastatic urothelial carcinoma lack of response to immune checkpoint blockade is associated with increased TGF- β signaling in fibroblasts in the tumour microenvironment [35]. Combining TGF- β blockade with immune checkpoint blockade in mouse models increases the antitumour efficacy of the therapy suggesting that identifying and targeting microenvironmental regulators of antitumour immunity may increase the reach of immunotherapeutical approaches [36]. Limited PD-L1 expression in NET cells has also been observed in six studies while in two other studies more than half of the NETs had PD-L1 expression (Table S1) [37-41]. The use of different PD-L1 antibodies across the studies may account for heterogeneous findings. Therefore, we used two validated PD-L1 antibodies, 22C3 and E1L3N, which both showed no expression of PD-L1 in the NET-cells and T-cells.

Grade 3 neuroendocrine neoplasms (NENs) were in contrast to NETs characterized by strong PD-L1 expression [42]. A correlation between the tumour grade and PD-L1 expression was also seen in neuroendocrine neoplasms of pulmonary origin [41,43]. One study investigating 32 patients treated with systemic therapy for gastro-intestinal and pancreatic NENs found that PD-L1 expression was associated with PFS [38]. Furthermore, a multivariate analysis of 80 pulmonary NENs revealed that PD-L1 expression, PD1 expression, and distant metastasis of pulmonary NENs were independently associated with survival time [41].

In the current study, a paucity of T-cells is seen with few CD8 positive cells in accordance with several other studies analysing NET immunohistochemically [44,45]. In one study, samples from 31 midgut NETs (grade 1 and 2) were analysed. Overall, the tumours contained a higher proportion of Tregs compared with matched normal tissue [45]. Other studies examining T-cells in neuroendocrine neoplasms reported more CD3 expressing T-cells. In one of these studies, 68% of pancreatic NETs (N = 87) and 97% of NET liver metastases of patients (N = 39) with various primary tumour sites contained >10 intratumoural T-cells per 10 high power fields. In these two groups, Tregs were found in 34% and 33%, respectively [12]. Others found tumour infiltrating lymphocytes (TILs) in 14 out of 17 samples varying from single positive cells to multiple positive cells [13]. The paucity of T-cells in NETs and the relatively high rate of Tregs might be due to the CAFs and their secreted factors as well as of IDO and TDO expression in the tumour and microenvironmental cells. In other tumour types, such as colorectal, oesophageal and endometrial cancer, an inverse correlation between IDO expression and T-cells has been

observed [46-48]. The PD-1 antibodies pembrolizumab and nivolumab are registered for the treatment of several tumour types. Furthermore, nivolumab is registered for MMRp deficient metastatic colorectal cancer and pembrolizumab for MMRp deficient tumours, irrespective of the primary tumour [6,7,49]. In MMRp-proficient tumours, probable DNA base pairing errors are corrected in newly replicated DNA, leading to microsatellite stable tumours. The equivalence of microsatellite instability testing and MMR immunohistochemistry was shown in endometrium carcinoma. Also, for colorectal cancer the validity of immunohistochemistry for MMRp to identify patients with microsatellite instable cancer was shown [50,51]. In our study, all investigated NETs were MMRp-proficient. This is in line with a study of 35 pancreatic NETs and 34 small intestinal NETs, in which all pNETs and 31 small intestinal NETs were MMRp-proficient [39]. In another study, all of the 70 included pancreatic NETs were microsatellite stable [52].

Scarce data exist about the treatment with immune checkpoint inhibition in NET patients. A small case series describes four NET patients treated with checkpoint inhibitors. All patients showed improved quality of life and a PFS of >3 months, with two out of four still on therapy [53]. In the multicohort phase 1B KEYNOTE-028 study, 41 pretreated patients with pancreas, lung and gut NET were treated with pembrolizumab. Results showed four patients with objective response and 29 patients with stable disease. Eight patients had severe (grade ≥ 3) treatment related adverse events [54]. Multiple phase 1 and 2 trials are currently recruiting NET patients for immune checkpoint inhibitor treatment [53].

Our findings demonstrate that in NET patients tumours express IDO and both tumour and CAFs express TDO. Therefore, we hypothesise that NET patients will potentially benefit from combination immunotherapies to overcome this cold immune microenvironment. Further studies could elucidate the complex immune microenvironment of NETs.

Author contributions

All authors contributed to the study design, data interpretation, and review of the manuscript. Grietje Bouma, Lotte D. de Hosson and Gursah Kats-Ugurlu performed the data collection, and data analysis. Grietje Bouma, Lotte D. de Hosson and Annemiek M.E. Walenkamp performed the literature search, generation of figures, and writing of the manuscript.

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Conflicts of interests

None of the authors declare any conflicts of interests regarding to this study.

Compliance with ethical standards

Since residual archival material was studied which does not interfere with patient care and does not involve the physical involvement of the patient, no ethical approval is required for this study according to Dutch legislation (the Medical Research Involving Human Subjects Act).

Informed consent

Although informed consent was not required, all patients alive (N = 20) were approached. They gave written informed consent to the use of their residual material.

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Figure S1. Overview of tryptophan metabolism: the kynurenine pathway and serotonin pathway

In both pathways, the first enzymatic step is the rate-limiting step.

AADC: aromatic L-amino acid decarboxylase, AANAT: arylalkylamine N-acetyltransferase, AD: aldehyde dehydrogenase, 3HAO: 3-hydroxyanthranilic acid dioxygenase, HIOMT: hydroxyindole-O-methyltransferase, IDO: indoleamine 2,3-dioxygenase, KAT: kynurenine aminotransferase, KYN: kynureninase, MAO: monoamine oxidase, NAD⁺: nicotinamide adenine dinucleotide, QPRT: quinolinic acid phosphoribosyl transferase, TDO: tryptophan 2,3-dioxygenase, TPH: tryptophan hydroxylase, 5-HIAA: 5-hydroxyindoleacetic acid.

Table S1. Overview of studies analysing PD-L1 expression in NET

Used PD-L1 antibody	Type of NET	Method	Percentage of PD-L1 positive cases in tumor; Total of samples	Percentage of PD-L1 positive cases in stroma or immune cells	First author; publication year
E1L3N	GEP-NETs	Tumour cells were positive if $\geq 10\%$ tumour cells were positive, lymphocytes were positive if at least moderately staining was observed.	15%; 48	35% intratumoural/peritumoural cells	Cavalcanti; 2017 [1]
Unknown	Midgut NETs	All cases with moderate or strong staining by Allred score were considered positive.	69%; 32	Not described.	Cives; 2016 [2]
9A11	Small intestine NETs	Based on published criteria.	0%; 64	55% in stroma	Da Silva; 2016 [3]
9A11	Pancreatic NETs	Based on published criteria.	11%; 18	17% in stroma	Da Silva; 2016 [3]
SP-9001	Pulmonary NETs	For each section, the approximate percentage of positive tumour cells and staining intensity determined the PD-L1 staining score.	59%; 80	Not described.	Fan; 2016 [4]
22C3	Carcinoids of the lung	$\geq 1\%$ positive tumour cells was considered as positive.	0%; 57	0% in immune cells	Kasajima; 2018 [5]
SP142	GEP-NETs	$\geq 1\%$ positive tumour cells was considered as positive.	22; 32	Not described.	Kim; 2016 [6]
E1L3N	Small intestine NETs	Specimens with $\geq 5\%$ membranous expression were considered positive.	13%; 70	24% in TILs	Lamarca; 2018 [7]
SP142	Pancreatic NETs	The staining was regarded as positive if its intensity on the membrane of the tumour cells was $\geq 2+$ (on a scale of 0–3) and the percentage of positively stained cells was 5%.	4%; 75	Not described.	Salem; 2018 [8]

PD-L1 = programmed death-ligand-1, NET = neuroendocrine tumour, GEP-NETs = gastroenteropancreatic neuroendocrine tumours, TILs = tumour infiltrating lymphocytes.

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CHAPTER 8

Summary and future perspectives

Summary

Neuroendocrine tumors (NETs) constitute a rare and heterogeneous group of tumors. Most NETs arise in the gastroenteropancreatic tract or bronchopulmonary system, where they are derived from enterochromaffin cells. NETs can produce various biogenic amines and polypeptide hormones which can lead to various symptoms [1,2]. For example, patients with a serotonin producing NET can suffer from the 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 metastatic disease [5]. So, patients can experience various symptoms for a long time due to the localization of the tumor as well as the release of bioactive substances secreted by the tumor. Also, side effects of the treatment itself can bother the patients.

NET patients experience a lower health related quality of life than the general population [6-8]. In general, when patients with cancer are properly informed, they experience a better health related quality of life and less depression and anxiety [9,10]. In addition, providing information also results in an increased participation of patients in decision making, greater satisfaction with care, lower levels of distress and improved sense of control [10-13]. Given these findings better ways of informing and supporting NET patients as well as novel treatments are warranted.

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

Chapter 1 is the general introduction and outlines this thesis.

In **Chapter 2** an extensive literature overview is given of 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 variables such as distress, anxiety, depression, quality of life and physical variables such as 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 (ranging from score 1 (highest level) to score 5 (lowest level)). Our literature search yielded 2032 studies of which 16 fulfilled the eligibility criteria. Three different internet-based support programs were identified: social support groups, online therapy for psychosocial/physical symptoms and online systems integrating information, support and coaching services. Positive effects of the programs on outcomes were reported in nine studies. Especially fatigue, social support and distress improved, regardless of the program type. All online systems showed positive effects, mainly for social support and quality of life. The highest level of evidence of the included studies was score 2, which was the case in 12 studies. These findings indicated that internet-based support programs are effective in improving psychosocial and physical symptoms in cancer patients regardless of the used program type.

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.

In **Chapter 3** we examined the feasibility of our self-developed web-based system in newly diagnosed grade 1 and 2 NET patients and evaluated the patient's opinion on this. 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. Effect sizes for change scores on each endpoint were determined (Cohen's d). A positive effect size indicated a desired direction (i.e. improvement of outcome in favor of the intervention group). The intervention group also completed a semi-structured interview to assess patients' opinion on the web-based system. The participation rate was 77% (20 of 26 invited patients) and all participants completed the study (0% dropout rate). The use of the web-based system had a negative effect on patients' perception and satisfaction of received information (range Cohen's d -0.88 to 0.13). Positive effects were found for distress (Cohen's d 0.75), global quality of life (subscale European Organization for Research and Treatment of Cancer Quality of Life

Questionnaire of cancer patients (EORTC QLQ-C30, Cohen's d 0.46), resolving problems with social functioning and finding information (subscales EORTC QLQ GINET 21 (quality of life questionnaire for neuroendocrine carcinoid patients), Cohen's d 0.69 respectively 1.04), and feeling informed (subscale empowerment questionnaire, Cohen's d 0.51). The semi-structured interview with the intervention group indicated that the web-based system was of additional value to standard care. All interviewed participants would like to use the web-based system in the future. From the results of this study we concluded that use of this web-based system for NET patients was feasible and that patients also appreciate this web-based system. However, we found conflicting effects of the web-based system on informing and supporting NET patients. Therefore, we conducted a randomized controlled follow-up study.

In **Chapter 4** this randomized controlled follow-up study is described. In this study, the effects of the web-based system on perceived distress, patients' perception of and satisfaction with received information, quality of life and empowerment of NET patients were analyzed. The web-based system was adapted based on patients' recommendations and results of the pilot study described in Chapter 3. Eligible participants were adult patients with grade 1 or 2 NET and who were proficient in Dutch, reading and writing. Patients were stratified by 'time since diagnosis', which resulted in 28 patients with newly diagnosed NET within <6 months and 74 patients longer known with NET 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, quality of life 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. No differences between the control and intervention group were found for distress, patients' perception of and satisfaction with received information and quality of life. Empowerment, measured by different domains, was better in the control group, except for the domain 'optimism and control over future' for which no difference was found. The intervention group found the web-based system useful, interesting and of added value, had a positive attitude towards the web-based system and would recommend it to peers. The median score of the questionnaire was 4 on a 5-point Likert scale ranging from 1 to 5. In conclusion, the web-based system did not improve distress, patients' perception and satisfaction of received information, and quality of life more than standard care in NET patients. Empowerment was better in the patients receiving standard care. However, the intervention group had a positive opinion about the use of the web-based system.

In **Chapter 5** we assessed the feasibility of video-consultation in the follow-up care of clinical stable patients with NET. Patients with NETs are increasingly treated in expert centers which leads to longer travel times for medical consultations. Given the

general course of their disease, frequent hospital visits are required for a long time. Video-consultation potentially allows remote guidance of patients and therefore saves time for patients. Calculation of participation and dropout rate, reasons for declining participation, reasons for dropout and safety concerns were used to assess feasibility. In this study, 20 patients received two video-consultations during one year of follow-up. Questionnaires were used to measure satisfaction with video-consultation by patients and physicians. Also, the duration of a video-consultation, the patient-reported travel time for a regular outpatient clinic visit and the patient's preference for type of consultation were recorded. Reasons for no study participation were 'patient's preference for consultation at the outpatient clinic', 'no internet experience by the patient' and 'medical condition does not allow video-consultation'. Twenty-six of the 31 invited patients participated in the study. Six participants did not complete the full study. Reasons for dropout were 'medical condition does not allow video-consultation', 'physicians' preference for outpatient clinic consultation', 'technical problems', 'death of patient' (N = 1, not related to video-consultation) and 'follow-up of patient in another hospital'. No safety concerns were reported. Median score for satisfaction of patients and physicians were 4.6 ranging from 3.3-4.9 on the five-point Likert scale and 4.0 ranging from 3.5-4.9 respectively, indicating high satisfaction with video-consultation. Technical problems leading to prolonged connection time and impaired audio/video quality were reported by 55% of the patients and 40% of the physicians. The median duration of a video-consultation was 13 minutes with a range of 9-25 minutes. The patient-reported duration of a follow-up consultation at the outpatient clinic was 240 minutes ranging from 100-390 minutes. Sixty percent of the patients preferred video-consultation. We demonstrated that use of video-consultation during follow-up care of patients with clinical stable NET is feasible. From these data we concluded that the patients' and physicians' acceptability and satisfaction with video-consultation is high, but can be further improved, particularly by solving technical problems.

Nowadays, there is still an ongoing need and search for new treatment modalities for patients with a NET. The essential amino acid tryptophan is the precursor for serotonin and nicotinamide adenine dinucleotide (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. A variety of symptoms and complaints related to the skin, gastrointestinal tract and nervous system can be seen with tryptophan and/or niacin deficiency. Best known is pellagra, which is characterized by 'the four Ds': dermatitis, diarrhea, dementia and death. In patients with serotonin-producing NETs, pellagra and other symptoms suggestive of tryptophan and/or niacin deficiency are reported. Niacin supplementation resulted in a quick and substantial improvement of symptoms in these patients. **Chapter 6** describes a study in which we examined the niacin status in 42 patients with a serotonin-producing NET

and with tryptophan deficiency and/or associated symptoms, who therefore received oral 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. Reference values for urinary N¹-MN levels were established in 133 healthy individuals. In the 42 patients with NETs the mean plasma tryptophan level was $31.8 \pm 9.7 \mu\text{mol/L}$ (reference value 40.0-70.0 $\mu\text{mol/L}$) before supplementation. Presupplementation urinary N¹-MN levels were lower in patients (median 17.9 $\mu\text{mol}/24\text{-hour}$, range 2.6-70.3) compared to healthy controls (median 43.7 $\mu\text{mol}/24\text{-hour}$, range 9.5 – 169.3, $p < 0.0001$) and below normal in 45% of the patients. With niacin supplementation urinary N¹-MN levels increased to high normal levels (median 55.5 $\mu\text{mol}/24\text{-hour}$, range 7.4 – 489.0). Eventually, 86% of the niacin-deficient patients had a normal niacin status after supplementation. In conclusion, niacin supplementation was effective in normalizing niacin status in previously niacin-deficient patients.

In **Chapter 7** we investigated the tumor microenvironment of NETs to search for potential treatment targets. Tumor tissues of 51 patients with a grade 1 or 2 NET, collected before start of systemic antitumor treatment, were selected. Immunohistochemical analyses of the tumor tissues were performed for programmed death ligand 1 (PD-L1), T-cells (recognized by CD3-staining), indoleamine 2,3-dioxygenase (IDO), tryptophan 2,3-dioxygenase (TDO), mismatch repair proteins and activated myofibroblast and/or myofibroblast-like cells (recognized by alpha-smooth muscle actin and desmin-staining). Before start of systemic antitumor treatment, serotonin was measured by high performance liquid fluorometry of 5-hydroxyindolacetic acid (5-HIAA) in 24-h urine and/or serotonin in platelet rich plasma of the included patients. Tumors of 33 patients with a serotonin-producing NET and 18 patients with a non-serotonin-producing NET were studied. None of the tumor cells and T-cells expressed PD-L1. T-cells were present in 15 out of 45 evaluable NETs, varying between 1-10% T-cells per high power field. T-cells were not infiltrating between tumor cells, but most frequently found within the stroma of NETs of the jejunum/ileum which were all serotonin-producing NETs. IDO was more often expressed in serotonin-producing NETs namely in 18 out of 33 (55%) and 4 out of 18 (22%) of non-serotonin-producing NETs ($p = 0.039$). Unexpectedly, TDO showed prominent staining in stroma in 18 out of 41 (44%) evaluable NETs. TDO was expressed in stromal cells in 16 out of 25 evaluable serotonin-producing NETs and two out of 16 evaluable non-serotonin-producing NETs ($p = 0.001$). Seventeen out of 46 (37%) evaluable NETs had TDO staining in tumor cells. None of the tumors had loss of mismatch repair proteins. Tumors with TDO expressing stromal cells also strongly expressed alpha-smooth muscle actin and desmin, and were therefore identified as cancer associated fibroblasts.

We concluded that NETs have a cold immune microenvironment as they do not express PD-L1, contain only few tumor infiltrating T-cells and have no loss of mismatch repair proteins. We suggest that the cold immune microenvironment of neuroendocrine tumors is at least partly the result of IDO and/or TDO expression and the presence of cancer associated fibroblasts.

Future perspective

In this thesis we have addressed several aspects of informing, supporting and treating patients with a NET. Due to the rarity of NETs, it is difficult for patients to gather information about their disease and to get support. In the Netherlands, NET patients have the possibility to receive information and support via the Dutch Patient Neuroendocrine Tumour Foundation [14]. Also, treating a patient with a NET can be a challenge for health care professionals. Therefore, in the Netherlands most NET patients are treated in the so-called 'ENETS (European NeuroEndocrine Tumor Society) centers of excellence' [15]. This often coincides with relatively long travel distances for patients. It is known, that patients with NETs experience the burden of travelling to a NET center/expert, although travel distances in the Netherlands are limited [8]. Informing and supporting these patients via a web-based system is a novel tool which gives the patient an additional option for gathering information and support 24-hours a day. Internet-based support programs are effective in improving psychosocial and physical symptoms in cancer patients, as we concluded in our review in Chapter 2. In patients with NETs, however, we found conflicting results of our self-developed web-based system on informing and supporting in the pilot study (Chapter 3) and no improvement in distress, perceived information and quality of life in the randomized controlled follow-up study (Chapter 4). Although no positive effects could be found, most patients have the opinion that this web-based system should be part of standard of care and pointed out they would like to use it in the future. In this 'internet era', it is inevitable that these patients demand the ability of receiving online information and support. However, a web-based system will never replace the information and support given face-to-face by their well-known treating health care professional. Further research has to address how the web-based system can be adapted and has to be used to improve perceived information and support. For example, adding more visual illustrations can enhance insight and improve recall of information. This finding has been observed in older colorectal cancer patients who used a website to retrieve cancer information [16]. Also, it is unknown which factors (e.g. psychosocial, clinical, disease-related, internet) are associated with the use and effects of the web-based system in patients with NET. In our study, the web-based system has been used for a short time namely 12 weeks with a short follow-up period. Consequently, effects of long term use during the course of the disease and long term effects of the

web-based system are unknown. In a future study with a larger sample size, it is desirable to investigate which factors are associated with the use and positive effects of the web-based system. Also, the effects of longer use of the web-based system and long term effects deserve further attention. To get a better insight in the effect of the web-based system on patients' empowerment a new validated empowerment questionnaire has to be developed, which can be used for a pre- and post-assessment in future studies.

As described in Chapter 5 video-consultation can be used for easier access to a NET expert and to reduce the burden of travelling for patients with NETs. Video-consultation is a good alternative for an outpatient clinic consultation in clinical stable NET patients having experience with internet/video communication and not requiring physical examination. Since January 2018, a follow-up consultation performed with a video-consultation is in the Netherlands reimbursed as a face-to-face consultation at the outpatient clinic by health care insurances. This can be an extrinsic motivation to conduct (more) video-consultations. However, drawbacks in conducting video-consultations are technical problems as well as concerns about safety (e.g. safe internet connection) and privacy regulations. For good and adequate implementation of video-consultation in standard care, technical problems have to be addressed and a 'patient- and health care professional-friendly' video-consultation application meeting all safety and privacy regulations is required. In our study, we noted that communication with caregivers and/or family of a patient with a NET is less intense and hampered by video-consultation compared to a consultation at the outpatient clinic. For example, caregivers/family joining the patient were sometimes (partly) outside the view of the camera. Also, it can be more difficult for accompanying caregivers/family to participate in the conversation during a video-consultation. Further research is warranted to investigate if caregivers and family members experience a lack of communication or interaction during video-consultation and if this has a negative effect on patients' health (care) and quality of life. Some of the used questionnaires for patients in the study described in Chapter 5 can be adapted to use it for caregivers and family member. Results of these questionnaires can be correlated with patients' reported quality of life.

Treating patients with NETs in referral centers, has raised awareness and recognition of their specific complaints and problems. For example, signs and symptoms of tryptophan and/or niacin depletion due to serotonin-producing NETs are better recognized. As a result, patients with tryptophan and/or niacin deficiency receive earlier treatment with nicotinamide and thereby pellagra or other symptoms can be prevented. As shown in Chapter 6, oral supplementation of nicotinamide in niacin deficiency is easy and effective. Niacin is a water-soluble vitamin and thereby not stored in the body, which requires daily oral administration of niacin supplementation [17]. Further prospectively designed research is required to determine the correct dose of nicotinamide supplementation by assessment of urinary N¹-MN. Here is of interest

to include urinary N¹-MN in the biochemical assessment of serotonin production at diagnosis and during follow-up to establish niacin deficiency on time before symptoms occur. In addition, patients can be informed about the usefulness and correct intake of niacin supplementation and symptoms associated with niacin deficiency.

To search for new treatment modalities in patients with grade 1 and 2 NETs, such as immunotherapy, we established the tumor immune microenvironment as described in Chapter 7. We found a 'cold' tumor immune microenvironment in NETs with absence of PD-L1 expression, limited presence of T-cells, substantial expression of IDO and/or TDO and presence of CAFs. It is expected that use of solely an immune checkpoint inhibitor in patients with NETs is ineffective due to this cold tumor immune microenvironment. Only few data is available on the use of immune checkpoint inhibitors in grade 1 and 2 NETs. The KEYNOTE-028 study was a multicohort phase 1b study including heavily pre-treated grade 1 and 2 PD-L1-positive NETs of the pancreas (N = 16) and carcinoids (N = 25, primary site in the lung, gut or other organ) which were treated with the PD-1 inhibitor pembrolizumab [18]. Four patients experienced a partial response and 13 patients had stable disease for more than 6 months. In the multicohort phase 2 KEYNOTE-158 study, 107 patients with well- and moderately differentiated NETs of several primary sites progressive on or intolerant to more than one line of standard treatment were treated with pembrolizumab [19]. The overall response rate was 3.7%, which was observed as a partial response in 4 patients with a PD-L1 negative tumor. Patients with high grade neuroendocrine tumors demonstrate better responses on immunotherapy. In a phase II trial, 29 patients with metastatic progressive neuroendocrine carcinoma, grade 3 according to WHO 2010, of several sites of origin were treated with the PD-L1 antibody avelumab. After 8 weeks of treatment 32% of the patients had stable disease or partial remission [20]. Dual checkpoint blockade with the PD-1 inhibitor nivolumab and the anti-cytotoxic T-lymphocyte-associated protein 4 (anti-CTLA-4) agent ipilimumab given to 33 patients with low-, intermediate- and high-grade NETs in a phase II trial resulted in an overall response rate of 24%, one complete response and seven partial responses, which were all patients with high-grade NETs [21]. An explanation for the better response in high grade NETs may be the presence of a higher tumor mutational burden.

To enhance the efficacy of immune checkpoint inhibitors in NETs, a transformation into a 'hot' tumor immune microenvironment of NETs might be of interest. Potential opportunities, although still uncertain, are combining immune checkpoint inhibitors with therapies which achieve increase of PD-L1 expression and/or tumor infiltrating T-cells or inhibition of IDO and/or TDO expression. Combination therapy of an IDO and/or TDO-inhibitor with immune checkpoint inhibitors (e.g. PD-1 or PD-L1 inhibitor) is theoretically an interesting strategy for NETs, which has not yet been studied. However, in patients with unresectable or metastasized melanoma, the combination of the IDO-inhibitor epacadostat with the PD-1 inhibitor pembrolizumab versus pembrolizumab

in a phase III-study lacked effect on progression-free or overall survival [22]. Given these and other disappointing results of studies conducted in patients with several tumor types treated with a combination of IDO and PD-1 inhibitor the enthusiasm is currently tempered for this approach.

At this moment, the safety and tolerability of an IDO1/TDO dual inhibitor is evaluated in 30 patients with advanced solid tumors in a phase I study (ClinicalTrials.gov Identifier: NCT03208959). This novel IDO/TDO dual inhibitor might be of interest in the treatment of NET patients given the substantial expression of IDO and/or TDO in neuroendocrine tumors.

Interferon is a standard treatment in patients with a metastasized NET which can relieve the symptoms of a carcinoid syndrome and can have antitumor efficacy [23,24]. In a mice study, interferon led to induction and maintenance of PD-1 on T-cells and PD-1 expression on antigen-specific CD8 positive T-cells was augmented [25]. Combination treatment of interferon with PD-1 inhibitors might deserve a trial in patients with NETs given the results of aforementioned studies.

Another unexplored field in NETs is the role of circulating regulatory T-cells which are associated with suppression of tumor infiltrating T-cells and natural killer (NK) cells. In a currently recruiting study, patients with metastasized or unresectable NETs with a low proliferation rate (tumor proliferation marker Ki67 $\leq 10\%$) are treated with cyclophosphamide and interferon-alpha to evaluate if this treatment regimen decreases the rate of circulatory regulatory T-cells (ClinicalTrials.gov Identifier: NCT02838342).

In conclusion, it is worth to consider and examine new strategies to overcome tumor-induced immune tolerance in NETs as this might allow immune therapy in the future.

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CHAPTER 9

Nederlandse samenvatting (Dutch summary)

Nederlandse samenvatting

Neuro-endocriene tumoren (NET) bestaan uit een zeldzame en heterogene groep tumoren. De meeste NET ontstaan vanuit enterochromafiene cellen in de gastro-entero-pancreatische tractus of in het bronchopulmonaire systeem. NET kunnen verscheidene biogene amines en polypeptide hormonen produceren, die kunnen leiden tot verschillende symptomen. Patiënten met een serotonine producerende NET kunnen last hebben van het carcinoïdsyndroom, dat gekenmerkt wordt door flushes (opvliegers), diarree, astmatische symptomen en carcinoïd hartzieke. Patiënten met een NET kunnen alleen worden genezen als het mogelijk is de tumor geheel te verwijderen. Wanneer er geen genezing mogelijk is, bestaat de behandeling vaak uit langdurige toediening van langwerkende somatostatine-analogen om de ziekteprogressie tegen te gaan en de symptomen te bestrijden. Meestal hebben patiënten met een uitgezaaide laaggradige NET, een graad 1 of 2 volgens de World Health Organisation 2017 classificatie, een relatief indolent beloop met een 5-jaars overleving van ongeveer 55%. Daarom kunnen patiënten langdurig meerdere symptomen hebben. Dit kan komen door de locatie of massa van de tumor, of door het vrijkomen van bioactieve stoffen vanuit de tumor. Daarnaast kunnen patiënten ook last hebben van bijwerkingen van de behandeling.

Patiënten met een NET ervaren een slechtere kwaliteit van leven (KvL) dan gezonde mensen. Als patiënten met kanker goed geïnformeerd worden over hun ziekte zijn ze over het algemeen minder angstig en depressief en ervaren zij een betere KvL. Bovendien nemen goed geïnformeerde patiënten meer deel aan de besluitvorming, hebben ze een grotere tevredenheid over de zorg, ervaren ze minder lasten/problemen (distress) en verbetert hun 'gevoel van controle'. Daarom is het zinvol om de beste methode te ontwikkelen om patiënten met een NET te informeren en ondersteunen. Verder is het belangrijk dat er voor patiënten met een NET nieuwe behandelingen ontwikkeld worden.

Het doel van dit proefschrift was om nieuwe methodes te onderzoeken om patiënten met NET te informeren, ondersteunen en behandelen.

Hoofdstuk 1 is de algemene introductie en geeft een uiteenzetting van dit proefschrift.

In **hoofdstuk 2** wordt een uitgebreid literatuuroverzicht gegeven over de effecten van internet-gebaseerde ondersteuningsprogramma's gericht op psychosociale en fysieke symptomen, die het gevolg zijn van de diagnose en behandeling van kanker. We zochten in de literatuur naar studies die uitgevoerd waren in volwassen patiënten met kanker, waarin kwantitatieve psychosociale en/of fysieke uitkomsten van een internet-gebaseerd ondersteuningsprogramma werd vergeleken met één of meerdere groepen. We selecteerden studies waarin patiënten met solide tumoren in elk ziektestadium, in elke behandelingsfase, met elk type behandeling en ongeacht de tijd sinds diagnose

werden onderzocht. Een internet-gebaseerd ondersteuningsprogramma was gedefinieerd als een programma met als doel om patiënten met psychosociale en/of fysieke symptomen als gevolg van de diagnose en behandeling van kanker te revalideren of te ondersteunen. Het internet-gebaseerd ondersteuningsprogramma moest zijn ontworpen of worden begeleid door één of meerdere gezondheidszorgprofessional(s). Belangrijke uitkomstmaten waren psychosociale variabelen zoals distress, angst, depressie, KvL en fysieke variabelen zoals vermoeidheid, slapeloosheid, pijn en seksuele problemen. De CINAHL, MEDLINE (PubMed) en PsychINFO databasen werden doorzocht vanaf oprichting tot en met januari 2014. Relevante systematische reviews en referenties van de gevonden artikelen werden ook beoordeeld om gemiste studies te identificeren. Alleen Engelstalige studies werden geïnccludeerd. Elke geïnccludeerde studie kreeg een 'level of evidence' volgens de Oxford Centre of Evidence Based Medicine. Deze varieert van score 1 tot score 5 (laagste score). Ons literatuuronderzoek leverde 2032 studies op, waarvan 16 studies in aanmerking kwamen voor inclusie. Drie verschillende typen internet-gebaseerde ondersteuningsprogramma's werden geïdentificeerd: sociale ondersteuningsgroepen, online therapie voor psychosociale/fysieke symptomen en online systemen met gecombineerd aanbod van bijvoorbeeld informatie, ondersteuning en coaching. In negen studies werden positieve effecten van de programma's op de onderzochte uitkomsten gevonden. Onafhankelijk van het type programma verbeterden met name vermoeidheid, sociale ondersteuning en distress. Alle online systemen met gecombineerd aanbod toonden positieve effecten, met name voor sociale ondersteuning en KvL. Twaalf studies scoorden 2 voor 'level of evidence', wat de hoogst behaalde score was van de geïnccludeerde studies. Dit onderzoek toonde dat internet-gebaseerde ondersteuningsprogramma's effectief psychosociale en fysieke symptomen verminderen in patiënten met kanker, ongeacht het type programma dat werd aangeboden.

Aangezien er geen internet-gebaseerd ondersteuningsprogramma voor patiënten met een NET beschikbaar was, ontworpen wij dit zelf. Dit programma geeft patiënten de mogelijkheid om zelf te screenen op fysieke/psychosociale problemen, patiëntinformatie te krijgen over de gerapporteerde problemen en indien nodig, zichzelf door te verwijzen voor aanvullende zorg.

In **hoofdstuk 3** onderzochten we de haalbaarheid van het door ons zelf ontwikkelde internet-gebaseerd programma voor nieuw gediagnosticeerde patiënten met een graad 1 of 2 NET. Tevens evalueerden we de mening van de patiënten over dit programma. Patiënten werden gerandomiseerd tussen de controlegroep die standaardbehandeling kreeg (N = 10) of de interventiegroep waarin patiënten naast de standaardbehandeling 12 weken toegang tot het programma hadden (N = 10). De haalbaarheid van gebruik van het programma werd bepaald door het aantal patiënten wat deelnam aan de studie (participatie ratio) en uitviel tijdens de studie (dropout

ratio). Ook werden de redenen voor het niet deelnemen aan de studie en voor uitval van patiënten tijdens de studie bijgehouden. Patiënten vulden vragenlijsten in over de ontvangen informatie, hun klachten ('distress'), KvL en empowerment. Voor elk eindpunt werd Cohen's d berekend om de effectgroottes voor verschil in scores weer te geven. Een positieve effectgrootte betekende in deze studie een verbetering van de uitkomst in de interventiegroep. Tevens werd er in de interventiegroep een semi-gestructureerd interview door de onderzoeker afgenomen om de mening van de patiënt over het programma te onderzoeken. Twintig van de 26 benaderde patiënten namen deel aan de studie en alle deelnemers voltooiden de studie. Het gebruik van het internet-gebaseerd programma had een negatief effect op de perceptie en tevredenheid van de patiënt over de ontvangen informatie (range Cohen's d -0.88 tot 0.13). Positieve effecten werden gevonden op distress (Cohen's d 0.75), globale KvL (subschaal European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire of cancer patients, EORTC QLQ-C30, Cohen's d 0.46), oplossen van problemen met sociaal functioneren en het vinden van informatie (subschalen EORTC QLQ GINET 21 (questionnaire for neuroendocrine carcinoid patients, Cohen's d 0.69 respectievelijk 1.04), en het gevoel geïnformeerd te zijn (subschaal empowerment vragenlijst, Cohen's d 0.51). Het semi-gestructureerde interview met de interventiegroep liet zien dat patiënten het programma van meerwaarde vonden naast de standaardbehandeling. Alle geïnterviewde participanten wilden het internet-gebaseerd programma in de toekomst blijven gebruiken. Op basis van deze studieresultaten concludeerden wij dat gebruik van het internet-gebaseerd programma door NET patiënten haalbaar is en dat patiënten dit programma waarderen. Daarentegen vonden wij ook tegenstrijdige effecten van het programma op het informeren en ondersteunen van patiënten met een NET. Daarom werd er een vervolgstudie ontworpen, die aan deze bezwaren tegemoet moest komen.

In **hoofdstuk 4** wordt deze studie beschreven. In deze studie werden de effecten van het internet-gebaseerd programma op de klachten (distress), de perceptie en tevredenheid van de patiënt over de ontvangen informatie, KvL en empowerment van patiënten met NET onderzocht. Op basis van aanbevelingen van patiënten en resultaten uit de in hoofdstuk 3 beschreven haalbaarheidsstudie, werd het programma voor start van deze studie iets aangepast. Patiënten kwamen in aanmerking voor de studie indien zij volwassen waren, een graad 1 of 2 NET hadden en in staat waren om Nederlands te lezen en schrijven. Er vond stratificatie van patiënten plaats op basis van 'tijd sinds diagnose'. Er namen 28 patiënten met een nieuw gediagnosticeerd NET en 74 patiënten met een langer gediagnosticeerd (>6 maanden) NET deel aan de studie. Patiënten werden 1:1 gerandomiseerd tussen standaardbehandeling (N = 49) of de interventie bestaande uit standaardbehandeling met tevens toegang tot het programma (N = 53). Patiënten vulden vragenlijsten in betreffende hun klachten (distress), de ontvangen informatie, KvL en empowerment in studieperiode van 12 weken. Aan het eind van

de studie vulden patiënten in de interventiegroep, die daarmee ook toegang tot het programma hadden, een vragenlijst in betreffende hun gebruik en mening over het internet-gebaseerd programma. Er werden geen verschillen gevonden tussen de twee groepen ten aanzien van de klachten, perceptie en tevredenheid van patiënt over de ontvangen informatie en KvL. De groep patiënten zonder toegang tot het programma scoorden beter op verschillende domeinen van empowerment. Voor het empowerment-domein 'optimisme en controle over de toekomst' was er geen verschil tussen de twee groepen. De deelnemers in de interventiegroep vonden het programma bruikbaar, interessant en van additionele waarde naast de standaardbehandeling. Tevens hadden ze een positieve houding ten aanzien van het internet-gebaseerd programma en zouden ze het aanbevelen aan mede-patiënten. De mediane score op de vragenlijst betreffende het gebruik van het internet-gebaseerd programma was 4 op een puntenschaal variërend van 1 (slechtste score) tot en met 5 (beste score). We concludeerden dat het internet-gebaseerd programma niet minder klachten gaf en de perceptie en tevredenheid van patiënten over de ontvangen informatie en de KvL van patiënten met NET niet beter was dan van patiënten die de standaardbehandeling kregen. Daarnaast hadden patiënten die alleen de standaardbehandeling kregen een betere empowerment. De interventiegroep had echter wel een positieve mening over het gebruik van het internet-gebaseerd programma.

In **hoofdstuk 5** onderzochten we de haalbaarheid van videoconsultaties tijdens follow-up van patiënten met een graad 1 of 2 NET, bij wie de behandelend arts een fysiek contact niet absoluut noodzakelijk achtte. Patiënten met een NET worden steeds frequenter behandeld in expertcentra. Dit leidt tot langere reistijden voor hun ziekenhuisbezoeken. Omdat patiënten met een laaggradige NET langdurig met hun ziekte kunnen leven is follow-up middels polikliniekbezoeken vaak langdurig. Via videoconsultatie is het potentieel mogelijk om patiënten op afstand te begeleiden en daardoor ook tijd te besparen voor patiënten. De haalbaarheid van videoconsultatie werd onderzocht door het berekenen van de participatie- en dropout-ratio, het noteren van redenen voor afzien van deelname aan de studie en uitval van participanten tijdens de studie en het bijhouden van mogelijke veiligheidsproblemen betreffende de gezondheid door deelname aan videoconsultatie. In deze studie kregen 20 patiënten twee videoconsultaties binnen 1 jaar. Er werden vragenlijsten gebruikt om de tevredenheid van patiënten en behandelend artsen over de videoconsultaties te onderzoeken. Daarnaast werden de duur van een videoconsultatie, de patiënt-gerapporteerde reistijd voor een regulier follow-up polikliniekbezoek en de voorkeur van patiënt voor het type consult onderzocht. Genoemde redenen voor afzien van studieparticipatie, door zowel de patiënt als de behandelend arts, waren 'voorkeur van patiënt voor follow-up consult op de polikliniek', 'geen ervaring met internet' en 'medische conditie niet geschikt voor videoconsultatie'. Van de 31 uitgenodigde patiënten namen er 26 deel aan de studie. Zes

deelnemers maakten de studie niet af. Redenen voor dropout waren 'medische conditie niet geschikt voor videoconsultatie', 'voorkeur van de arts voor follow-up consult op de polikliniek', 'technische problemen', 'follow-up zorg overgenomen in ander ziekenhuis' en 'overlijden patiënt'. Tijdens de studie overleed er één patiënt, wat niet gerelateerd was aan studiedeelname. Er waren geen problemen met de veiligheid. De mediane score voor tevredenheid van patiënten en artsen was 4.6 (op een 5-punts Likert schaal) respectievelijk 4.0, wat een hoge tevredenheid betreffende videoconsultatie weergeeft. Er werden technische problemen door 55% van de patiënten en 40% van de artsen gerapporteerd. Deze technische problemen leidden tot tijdverlies bij het tot stand te brengen van de verbinding en slechtere/gestoorde audio- en/of beeldkwaliteit. De mediane duur van een videoconsultatie was 13 minuten, variërend van 9 tot 25 minuten. De patiënt-gerapporteerde reisduur voor een regulier follow-up consultatie op de polikliniek was 240 minuten, variërend van 100-390 minuten. Zestig procent van de patiënten gaf de voorkeur aan voor videoconsultatie. Middels deze studie hebben we aangetoond dat videoconsultatie tijdens follow-up van klinisch stabiele NET patiënten haalbaar is. We concluderen op basis van deze studie dat vanuit patiënten en artsen de acceptatie van en tevredenheid over videoconsultatie hoog is. Door het oplossen van technische problemen zou de tevredenheid nog verder kunnen worden verbeterd.

Patiënten met een NET hebben een verhoogd risico op vitaminedeficiënties. Het essentiële aminozuur tryptofaan is de voorloper van serotonine en nicotinamide adenine dinucleotide (NAD⁺), de metabool actieve vorm van niacine (vitamine B3). In patiënten met een serotonine producerende NET wordt tryptofaan gebruikt voor productie van serotonine, waardoor er een tryptofaan- en niacinedeficiëntie kan ontstaan. Dit kan zich uiten in de ziekte pellagra, die gekenmerkt wordt door de 'vier D's': dermatitis, diarree, dementie en dood. Er worden inderdaad zowel pellagra als andere symptomen passende bij tryptofaan- en niacinedeficiëntie beschreven bij patiënten met een serotonine producerende NET. Wanneer deze patiënten worden gesuppleerd met niacine is er snel een aanzienlijke verbetering van de klachten. **Hoofdstuk 6** beschrijft een studie waarin we de niacinestatus van 42 patiënten met een serotonine producerende NET met tryptofaandeficiëntie en/of geassocieerde symptomen onderzochten, waarvoor ze werden behandeld met orale niacinesuppletie. De niacinestatus werd gemeten door bepaling van N¹-methylnicotinamide (N¹-MN) in 24-uurs urine. De excretie van N¹-MN is een betrouwbare maat voor het vaststellen van de niacinestatus. Om de effectiviteit van suppletie met niacine te onderzoeken werd er voor en na suppletie N¹-MN in urine bepaald. In 24-uurs urines van 133 gezonde vrijwilligers werden de referentiewaarden voor N¹-MN vastgesteld. De gemiddelde plasma tryptofaan-waarde voor start van de suppletie in de 42 NET patiënten was $31.8 \pm 9.7 \mu\text{mol/L}$ (referentiewaarde 40.0 - 70 mol/L). Patiënten hadden lagere N¹-MN- waarden in de urine voor start van de niacinesuppletie in vergelijking met de gezonde vrijwilligers (mediaan $17.9 \mu\text{mol/24-uur}$, range 2.6 - 70.3

respectievelijk mediaan 43.7 $\mu\text{mol}/24\text{-uur}$, range 9.5 – 169.3, $p < 0.0001$). Van de patiënten had 45% een te lage niacinestatus. Na suppletie steeg de $\text{N}^1\text{-MN}$ -waarden in urine naar hoog normale waarden (mediaan 55.5 $\mu\text{mol}/24\text{-uur}$, range 7.4 – 489.0). Uiteindelijk had 86% van de niacine-deficiënte patiënten een normale niacinestatus na suppletie. Hiermee toonden we aan dat met suppletie van niacine de niacinestatus in voorheen niacine-deficiënte NET patiënten kan normaliseren.

In **hoofdstuk 7** bestudeerden we de NET tumormicro-omgeving om potentiële doelwitten voor nieuwe behandelingen te identificeren. Hiervoor werd er van 51 patiënten met een graad 1 of 2 NET tumorweefsel geselecteerd, dat verkregen werd voorafgaande aan de start van de systemische anti-tumorbehandeling. Er vond immunohistochemische analyses op dit tumorweefsel plaats, bestaande uit kleuringen van programmed death ligand 1 (PD-L1), T-cellen, indoleamine 2,3-dioxygenase (IDO), tryptofaan 2,3-dioxygenase (TDO), mismatch repair eiwitten en geactiveerde myofibroblasten en/of myofibroblast-gelijkende cellen (middels alfa-smooth muscle actin en desmine-kleuringen). De serotonineproductie van de NET werd vooraf aan start van de systemische anti-tumorbehandeling bepaald door het bepalen van 5-hydroxyindol-azijnzuur (5-HIAA) in 24-uurs urine en/of serotonine in trombocytenrijk plasma door middel van high performance liquid fluorometrie. Er werden gegevens bestudeerd van 33 patiënten met een serotonine producerende NET en van 18 patiënten met een niet-serotonine producerende NET. Er was geen expressie van PD-L1 door de tumor of T-cellen. In 15 van de 45 evalueerbare NET werden 1-10% T-cellen per high powerfield gevonden. T-cellen werden met name gevonden in het stroma van de serotonine producerende dunne darm NET, en niet tussen de tumorcellen. IDO-expressie kwam vaker in serotonine producerende NET voor dan in niet-serotonine producerende NET (55% versus 22%, $p = 0.039$). Er werd duidelijke TDO-expressie in het tumorstroma van 18 van de 41 (44%) evalueerbare NET gevonden. In 16 van de 25 evalueerbare serotonine producerende NET en in twee van de 16 niet-serotonine producerende NET ($p = 0.001$) was er stromale TDO expressie. Van de 46 evalueerbare NET had 17 (37%) TDO-expressie in de tumorcellen. Geen enkele tumor had verlies van mismatch repair eiwitten. Tumoren met TDO-expressie in stromale cellen toonden daar ook sterke expressie van zowel alfa-smooth muscle actin als desmine en werden daarom als kanker geassocieerde fibroblasten geduid.

We concludeerden op basis van deze studie dat NET een koude immunologische micro-omgeving hebben gezien de afwezigheid van PD-L1-expressie, de lage hoeveelheid tumor infiltrerende T-cellen en de aanwezigheid van mismatch repair eiwitten. We suggereren dat de koude immunologische micro-omgeving deels het gevolg kan zijn van de IDO en/of TDO-expressie en de aanwezigheid van kanker geassocieerde fibroblasten.

CHAPTER 10

Dankwoord (Acknowledgments)

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