

The background of the cover is an abstract, textured composition. It features a deep blue base color, overlaid with irregular, organic shapes in shades of light blue, turquoise, and green. These shapes are separated by thin, dark brown or grey lines, creating a layered, almost topographical effect. The overall texture is grainy and painterly, suggesting a mix of media like paint and paper.

# **Patient-reported symptoms in daily oncology practice**

**Josephine Juliëtte Koldenhof**



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Patiënt-gerapporteerde symptomen in de  
dagelijkse oncologische praktijk

Josephine Juliëtte Koldenhof

## **Patient-reported symptoms in daily oncology practice**

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# **Patient-reported symptoms in daily oncology practice**

Patiënt-gerapporteerde symptomen in  
de dagelijkse oncologische praktijk  
(met een samenvatting in het Nederlands)

Proefschrift

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# CONTENTS

<b>Chapter 1</b>	Introduction Outline of thesis	7
------------------	-----------------------------------	---

## Part 1 Validity of the Utrecht Symptom Diary

<b>Chapter 2</b>	Validation of the Dutch version of the Edmonton Symptom Assessment System.	17
<b>Chapter 3</b>	Validation of a symptom diary for outpatients with cancer receiving intravenous chemotherapy or targeted therapy.	39

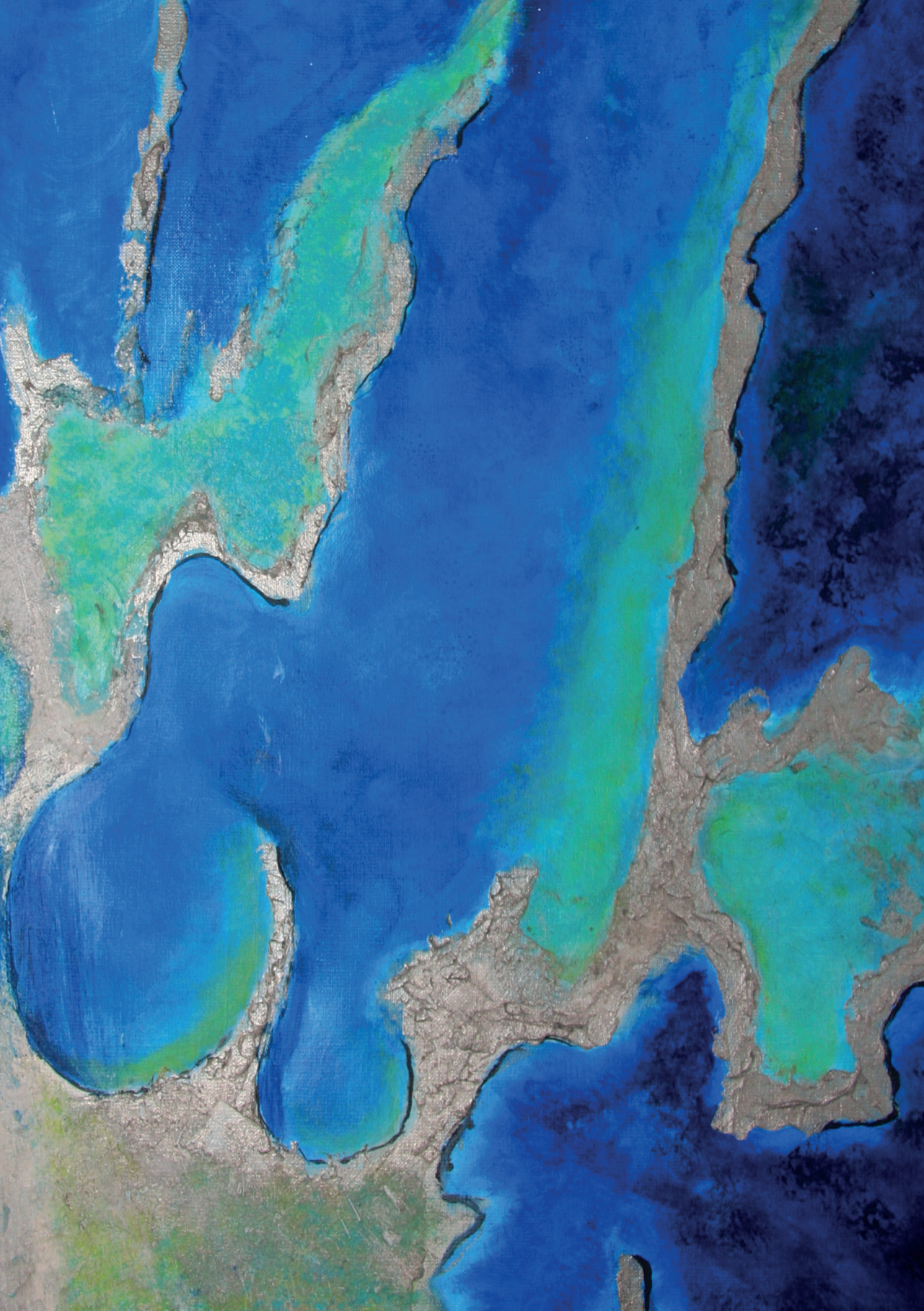
## Part 2 Use of the Utrecht Symptom Diary in different patient groups and settings

<b>Chapter 4</b>	Patient-reported symptoms and stepwise symptom management in patients on epidermal growth factor inhibitors: A retrospective, descriptive cohort study.	59
<b>Chapter 5</b>	Patient-reported outcome measures in a pharmacokinetic study with sunitinib, a prospective cohort study.	77
<b>Chapter 6</b>	Patient-reported outcomes during checkpoint inhibition: insight into symptom burden in daily clinical practice.	97

## Part 3 General discussion

<b>Chapter 7</b>	General Discussion	119
<b>Summaries</b>	Summary Nederlandse samenvatting / Dutch summary	131
<b>Appendices</b>	Dankwoord Curriculum Vitae List of Publications	142 145 146







## Chapter 1

Introduction

Outline of thesis

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The number of patients diagnosed with cancer increases. At the same time cancer patients live longer due to earlier diagnosis and more effective therapies<sup>1,2</sup>. During the course of their disease, patients experience many signs and symptoms – disease and/or treatment-related - that impact health-related quality of life and daily functioning. Clinical signs such as pyrexia and hypertension can be measured. However, symptoms such as pain and fatigue and their impact on daily life, are more difficult to detect. Therefore, for some time, symptoms reported by patients themselves are considered the most reliable indicator of symptom presence and intensity<sup>3-5</sup>. This thesis describes the validation of a Dutch patient-reported outcome measurement tool (PROM) and provides insight into patient-reported symptom prevalence and symptom burden in cancer patients undergoing treatment with targeted therapy and immunotherapy.

## Impact of symptoms

Symptoms impact health-related quality of life during the individual patient journey in the continuum of cancer<sup>6</sup>. Patients undergoing anticancer treatment with curative intent experience lasting symptoms which may negatively affect their quality of life, years after completing treatment<sup>7</sup>. During the palliative phase - when cancer can be treatable but is not curable and which phase can last for many years – persistent symptom burden claims precious time<sup>1,8-10</sup>. If symptoms remain under-recognized, physical, mental, existential and social functioning is affected and opportunities for diagnosis and management of symptoms may be missed<sup>11</sup>.

Although most patients rank survival as their highest priority, they value symptom relief and the ability to continue daily life during and after anticancer treatment<sup>12,13</sup>. Symptom burden can cause uncertainties and physical and mental stress which may influence patients behavior, such as nonadherence to treatment and ineffective use of self-management strategies<sup>14</sup>. During palliative anticancer treatment for example, patients may not report treatment-related symptoms out of fear that the anticancer treatment will be stopped permanently or that worsening of symptoms reflects disease progression<sup>14</sup>.

Since healthcare professionals tend to underestimate symptoms, assessment and monitoring of symptoms reported by patients themselves could very well improve patient care<sup>15-18</sup>. Patient Reported Outcome Measurement tools (PROMs) have shown to be supportive in improvement of patient-professional communication, reduction of symptom severity, reinforcement of patient autonomy and improvement of patient

satisfaction with the care given for patients receiving curative and palliative care<sup>19–21</sup>. This has led to an increase in the use of PROMs in clinical trials, but to a lesser extent in daily clinical practice. In order to provide a tool for assessing symptoms in cancer patients in daily oncology practice, the Utrecht Symptom Diary (USD; Appendix A) was developed.

## The Utrecht Symptom Diary

Worldwide, a frequently used PROM to routinely assess and monitor symptoms in advanced cancer patients is the Edmonton Symptom Assessment System (ESAS)<sup>18,22</sup>. Since its development in 1991, the ESAS has been validated, translated in many languages and adapted with a focus on advanced cancer inpatients<sup>18,19,23</sup>. However, in most oncology in and outpatient wards, patients with all stages of cancer are admitted, patients with or without anticancer treatment. Therefore a Dutch translated and adapted version of the ESAS, the Utrecht Symptom Diary (USD), was developed.

The USD contains a total of 12 items – lack of appetite (anorexia), nausea, abnormal stool, dysphagia, dry mouth, pain, sleeping problems, shortness of breath (dyspnoea), fatigue, anxiety, depressed mood and overall (un)well-being. Symptoms are scored on a zero-to-ten numeric rating scale (NRS), with higher values indicating increasing intensity. Moreover, patients are invited to add symptoms they experience and are not listed on the USD and patients are asked to prioritize symptoms which need attention first from their personal perspective. The USD was developed for daily assessment and monitoring of cancer- and treatment-related multidimensional symptoms, for in- and outpatients, from curative to palliative care.

## Treatment-specific Utrecht Symptom Diary

Over the last decades, anticancer treatment options have increased significantly due to new treatment modalities such as targeted therapy and immunotherapy. With these agents, patients with inoperable or metastatic cancer can obtain very durable responses, lasting for years. In clinical trials adverse events (AEs) are assessed using the Common Terminology Criteria for adverse events (CTCAE)<sup>24</sup>. However, this grading of AEs does not always reflect the impact on patients' daily life. When only using a grading of AEs the impact of symptom burden and the influence of symptom burden on the individual patient's health-related quality of life (HRQL) may be underestimated. As a result patients – although highly motivated for anticancer treatment – may experience difficulty in remaining on treatment.

Insight into symptoms and their burden is essential to provide tailored supportive care such as pro-active symptom management and support of patients in dealing with symptoms and their burden. Consistent and meaningful use of PROMs requires short, to the point, language sensitive and accurate symptom assessment tools and feasibility maximized for clinical use<sup>25</sup>. Therefore, we developed treatment-specific modules of the USD such as the outpatient USD for patients receiving intravenous chemotherapy and/or targeted therapy and the USD immunotherapy. These treatment specific USDs contain most symptoms that - based on the literature - occur in  $\geq 10\%$  of the patients and grade 3/4 AEs.

## **Implementation and use of the Utrecht Symptom Diary**

Since the implementation of the USD in 2003, inpatients at the Medical Oncology department of the UMC Utrecht are invited to complete the USD daily. Patients are asked to score symptom intensity 'at this moment'. USD scores are discussed with the patient by the oncology nurse, and are discussed in grand rounds and multidisciplinary meetings. In this setting, USD scores are used to support individualized treatment decisions and guide supportive care.

Since 2007 treatment and disease specific modules of the USD have been developed. Outpatients are invited to complete the outpatient USD when visiting the hospital for intravenous chemotherapy and/or targeted therapy treatment. They are asked to score symptom burden over the last period of time ('since the last time the USD was offered'). From 2015 the USD became part of the hospital electronic medical files (EMF). This enables patients to complete USD (modules) online in the patient portal of the EMF.

Patients receive written information that the USD scores - besides as part of routine care - are used for research purposes and are offered an opt-out option. For research purposes USD data, patient, disease and treatment-related data are extracted from the medical files and analyzed anonymously.

Over the last years the USD has been implemented in daily practice in other departments of the UMC Utrecht as well as in other (university) hospitals, general practices and hospices in the Netherlands. Moreover, use of the USD is recommended by the Netherlands Quality Framework for Palliative Care<sup>6</sup>. Evaluation of the broad implementation process is not reported in this thesis. This thesis describes the validation of the USD and its use in different oncology patient groups and various settings.



## Outline of this thesis

In the first part of this thesis the validity of the Utrecht Symptom Diary (USD) and outpatient USD is described. In **Chapter 2** the content validity, criterion validity, construct validity and responsiveness of the Utrecht Symptom Diary (USD) as well as the cutoff point per symptom is assessed. **Chapter 3** describes the content validity, criterion validity and construct validity of the added items to the outpatient USD for patients receiving intravenous chemotherapy and/or targeted therapy.

The second part of the thesis focuses on patient-reported symptoms through the use of the USD in different patient groups and various settings. **Chapter 4** describes patient-reported symptoms, dose modifications, and healthcare professional reported adverse events in a cohort of patients treated in daily oncology practice with targeted therapy agents directed against the epidermal growth factor receptor. **Chapter 5** outlines prospectively collected patient-reported symptoms in addition to healthcare professional-reported adverse events in patients participating in a clinical pharmacokinetic study with sunitinib, that also is a form of targeted therapy. **Chapter 6** concerns an observational cohort study analysing patient-reported outcome measures in patients with melanoma or non-small cell lung cancer treated with immunotherapy (i.e. PD(L)1-inhibitors). Patient-reported symptoms, influence of side effects on health-related quality of life were prospectively obtained using the tailored USD immunotherapy.

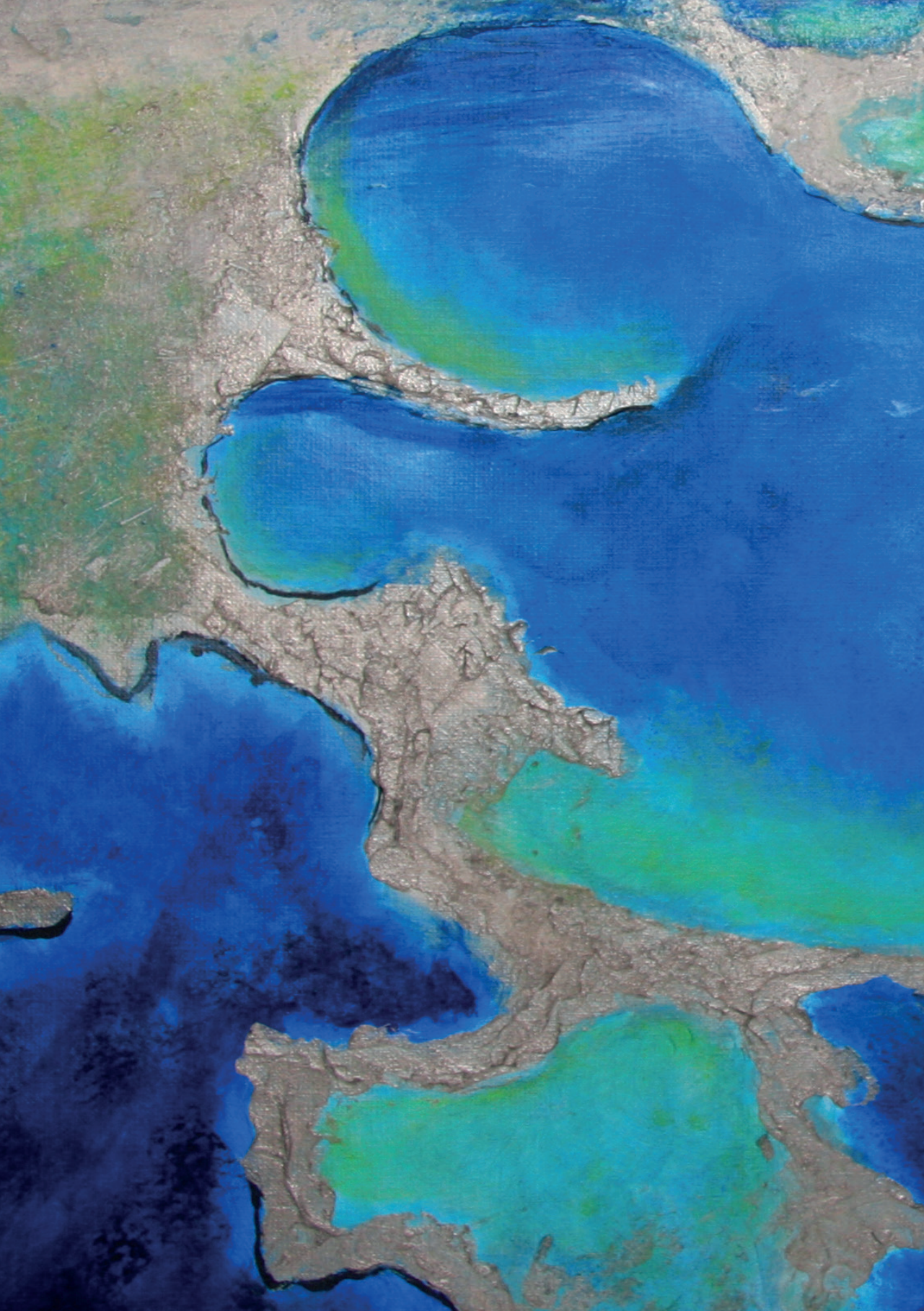
Finally, the general discussion, **Chapter 7** reflects on the main findings and provides perspectives for further development and opportunities of the use of PROMs in in the continuum of patients' individual cancer journey.

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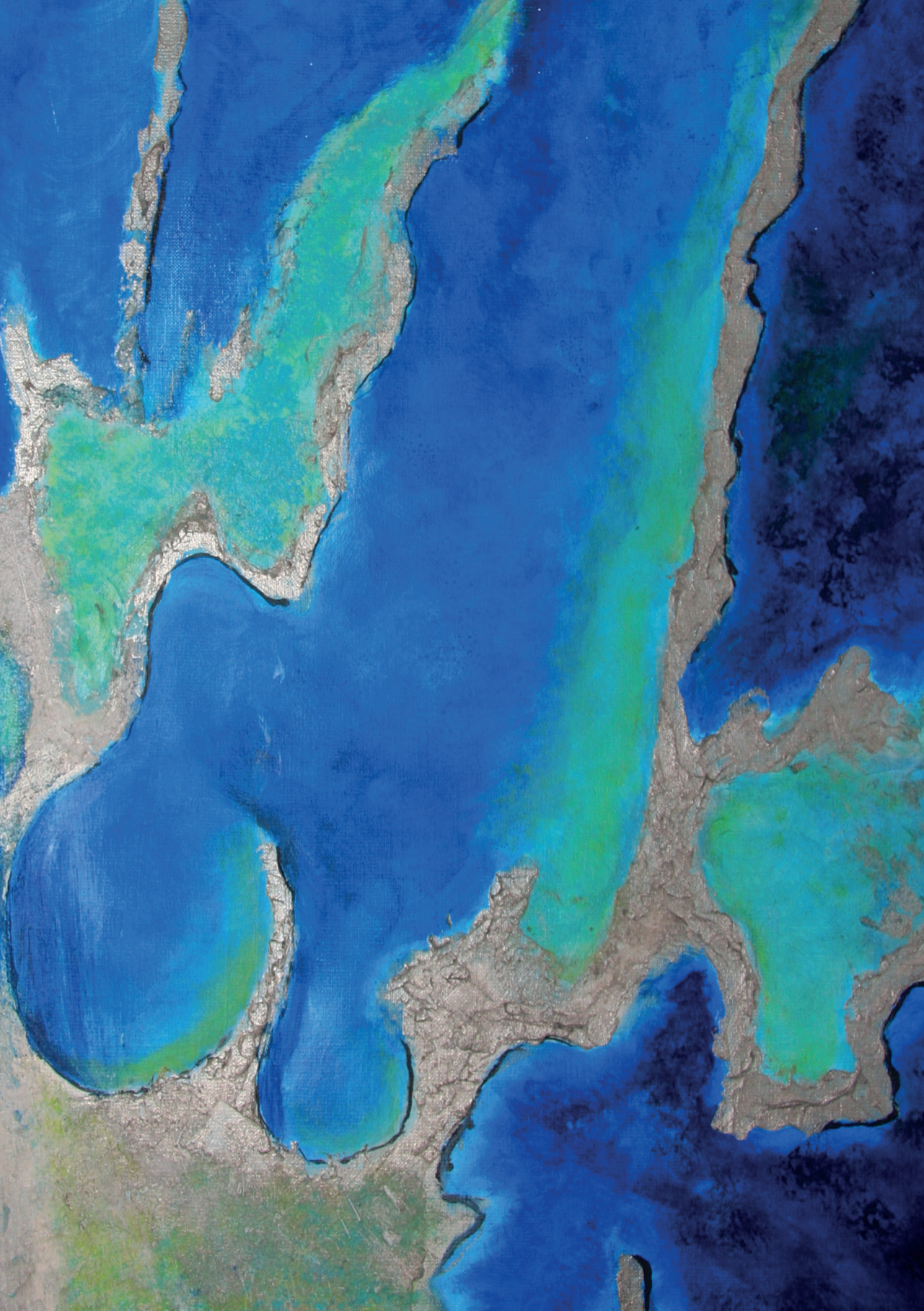


The background is an abstract, textured composition. It features a large, irregular shape in the upper half, filled with a mix of bright green and cyan colors, outlined by a dark, jagged border. The rest of the image is dominated by various shades of blue, ranging from deep navy to a lighter, almost white blue, with some brown and greyish textures interspersed, particularly along the edges of the green shape and in the lower half.

# **PART 1**

## **Validity of the Utrecht Symptom Diary**





## Chapter 2

# Validation of the Dutch version of the Edmonton Symptom Assessment System

---

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## Abstract

**Background.** The Utrecht Symptom Diary (USD) is a Dutch and adapted version of the Edmonton Symptom Assessment System, a patient-reported outcome measurement (PROM) tool to assess and monitor symptoms in cancer patients. This study analyses the validity and responsiveness of the USD and the cutoff points to determine the clinical significance of a symptom score.

**Methods.** Observational longitudinal cohort study including adult in- and outpatients treated in an academic hospital in the Netherlands who completed at least one USD as part of routine care (2012-2019). The distress thermometer and problem checklist (DT&PC) was used as reference PROM.

Content, construct and criterion validity, responsiveness and cutoff points are shown with prevalences, area under receiver operating characteristic (ROC) curve, Chi-squared test, Wilcoxon signed-rank test and, positive and negative predictive values, respectively.

**Results.** A total of 3913 patients completed 22,400 USDs. Content validity was confirmed for all added USD items with prevalences of  $\geq 22\%$ . All USD items also present on the DT&PC demonstrated a good criterion validity (ROC  $> 0.8$ ). Construct validity was confirmed for the USD as a whole and for the items dry mouth, dysphagia and well-being ( $p < 0.0001$ ). USD scores differed significantly for patients when improving or deteriorating on the DT&PC which confirmed responsiveness. Optimal cutoff points (3 or 4) differed per symptom.

**Conclusion.** The USD is a valid 12-item PROM for the most prevalent symptoms in cancer patients, which has content, criterion, and construct validity and detects clinically important changes over time, in both curative and palliative phase.



## Introduction

Cancer patients experience many symptoms caused by their disease and/or its treatment which influence health related quality of life (HRQL). As healthcare professionals tend to underestimate symptoms and family members to over-rate symptoms, symptoms reported by patients themselves are considered to be the most reliable indicators of symptom presence and intensity<sup>1-3</sup>.

Patient-reported outcome measurement tools (PROMs) improve patient-professional communication, reduction of symptom severity, reinforcement of patient autonomy and patients' satisfaction, regardless of the phase of their disease.<sup>4-8</sup> Monitoring symptoms can reduce emergency department visits and improve predictions of life expectancy in terminal ill cancer patients<sup>9,10</sup>.

Worldwide, a frequently used PROM to routinely assess and monitor symptoms in advanced cancer patients without anticancer treatment is the Edmonton Symptom Assessment System (ESAS).<sup>11</sup> Since its development in 1991, the ESAS has been validated, translated and adapted by multiple groups with a focus on advanced cancer inpatients. Reliability (test-retest and inter-rater reliability) and concurrent validity have been studied mostly, using a variety of other instruments to compare the ESAS to. Much less is known about the responsiveness and the cutoff points to distinguish patients with none, mild, moderate and severe symptom burden<sup>4,12,13</sup>.

We developed an adapted Dutch version of the ESAS - the Utrecht Symptom Diary (USD) - which aims to support daily management of symptoms across the entire continuum of cancer care. In the last 20 years, the USD has been implemented in daily practice in several hospitals, general practices and hospices in the Netherlands. Moreover, use of the USD is recommended by the Netherlands Quality Framework for Palliative Care<sup>14</sup>.

This study analyses the validity and responsiveness of the USD as well as the cutoff points per symptom to determine the clinical significance of a symptom score.

## Methods

### Participants

This observational longitudinal cohort comprises all adult cancer patients treated in the University Medical Center (UMC) Utrecht, the Netherlands, who completed at least one USD between August 2012 and July 2019. Within the UMC Utrecht Cancer Center filling out the USD is standard care, which means that each patient during each out-patient treatment and each admission is asked to complete the symptom

diary as a basis for tailoring care. However this does apply to patients with impaired cognitive behavior, not being able to read and understand Dutch language. As a result, no USD is available of these patients. Some participants receive chemotherapy partly in the clinic and partly in the outpatient clinic. This research was not considered subject to the Medical Research Involving Human Subjects Act by the institutional review board of the UMC Utrecht. For each measurement property of the USD we selected a subgroup of patients from this cohort.

### Data collection

For the development of the USD, the ESAS items pain, fatigue, nausea, depression, anxiety, drowsiness, lack of appetite (anorexia), shortness of breath (dyspnoea) and feeling of well-being were translated into Dutch. The items sleeping problems, dry mouth, abnormal stool, and dysphagia were added to the USD, based on their high prevalence in patients with incurable cancer<sup>15,16</sup>. Drowsiness was later excluded because of ambiguity in the Dutch language. The 12 items were clustered in two language specific sections starting with "I have.." and "I feel..". The ESAS item well-being was translated as "I feel good" to "I feel very bad" as the last summarizing question. Moreover, patients were able to add symptoms and to assign priority to symptoms which needed attention first, supporting patients autonomy. Symptoms were scored on a zero-to-ten numeric rating scale (NRS), with higher values indicating increasing symptom intensity.

The USD (Appendix A) was offered daily to all inpatients, to assess and monitor their current symptoms and well-being. Outpatients reported on symptoms and well-being experienced *since the last visit to the outpatient clinic*. In addition, patients were offered the Distress Thermometer and Problem Checklist (DT&PC) at the start of a (new) treatment and when indicated. The Distress Thermometer and Problem Checklist is an internationally accepted and validated PROM recommended for early recognition of symptoms and detection of supportive care needs in cancer patients.<sup>17,18</sup> The Distress Thermometer asks patients to score their distress on a zero-to-ten visual analogue scale (VAS; a higher score indicating more distress).

The Problem Checklist includes 35 items distributed over five domains: practical, family/social, emotional, spiritual, and physical problems. Patients score a symptom dichotomously, experiencing the symptom as a problem or not.

Patient characteristics, disease and treatment-related data and, USD and DT&PC scores, were retrospectively collected from the electronic medical records.

## **Statistical analysis**

Patient characteristics were summarized with descriptive statistics. Definitions, methods and quality criteria for the measurement properties of the USD were based on the COSMIN (Consensus-based Standards for the selection of health Measurement INstruments) initiative<sup>19,20</sup>. Moreover, we analysed cutoff points to determine the clinical significance of a symptom score. Patients with a missing value for the studied USD item were excluded for analysis for that item. R software for statistical computing and graphics v3.5.1 was used for statistical analysis<sup>21</sup>.

### **1. Content validity**

Content validity is defined as the extent to which the concepts of interest are represented by the USD items<sup>20</sup>. To study the patient's perspective on the content, we asked both in- and outpatients in a questionnaire: "were the USD symptoms in line with your symptom burden?". A reported relevance by at least 80% of the patients was considered as a sufficient content validity. In addition, prevalence of the symptoms that were added in the USD to the symptoms of the original ESAS<sup>11</sup> are presented to assess whether these items are relevant for our population.

### **2. Criterion validity**

Criterion validity is defined as the degree to which the USD scores are an adequate reflection of a "gold standard"<sup>19</sup>. In the absence of a gold standard, for this analysis the DT&PC was considered the reference standard.

For each patient, we selected the first DT&PC completed within one day of a USD. The items pain, sleeping problems, nausea, shortness of breath, fatigue, anxiety and depressed mood are identical on both instruments and were used for the criterion validation. The USD item lack of appetite was compared to 'problem with eating' on the DT&PC. The USD item abnormal stool was compared to the DT&PC diarrhoea and constipation.

The area under the curve (AUC) of the receiving–operating curve (ROC) was calculated using the USD scores as predictive values and the DT&PC as the "true"

condition. An AUC of at least 0.70 was considered positive for the criterion validity.<sup>22</sup> The corresponding 95% confidence intervals were computed with 2000 stratified bootstrap replicates<sup>23</sup>.

### **3. Construct validity**

Construct validity is defined as the extent to which USD scores are consistent with theoretically derived hypotheses<sup>19</sup>. Prior to the analyses we formulated one overall hypothesis concerning all USD items and three hypotheses for the items that are not part of the DT&PC, dry mouth, dysphagia and well-being:

- I. "The prevalence and intensity of all symptoms will increase with progression of disease".<sup>15,24</sup> Inpatients were divided into two disease stages: inpatients receiving chemotherapy, either with curative or palliative intent, and inpatients receiving symptom directed palliation only. Outpatients and patients admitted for other reasons than chemotherapy treatment were excluded, as we could not determine their disease stage with certainty. The first completed USD during the first hospital admission was used to compare symptom prevalence and intensity.
- II. "Patients using opioids<sup>25</sup> experience dry mouth more often than patients who do not use opioids". The first USD of each inpatient was selected, due to the availability of a complete medication list. USD scores for dry mouth were compared in patients using and patients not using opioids.
- III. "Patients with head and neck cancer (HNC) experience dysphagia more often than patients with other cancer diagnoses"<sup>26</sup>. The first USD of HNC patients was compared to the first USD of patients with other primary diagnoses.
- IV. "Patients with pain report poorer well-being than patients without pain"<sup>27</sup>. For this purpose we compared well-being on the first USD of all patients reporting a pain score  $\geq 3$  with patients reporting a pain score  $< 3$ .

In the literature, the optimal cutoff point of the ESAS items remains unclear and varies from 2-5 for symptom presence and moderate symptom intensity<sup>28-30</sup>. In previous research we found that HRQL decreased due to the experience of multiple symptoms with scores  $< 3$  at the same time<sup>31-33</sup>. Therefore, we considered a USD score  $\geq 3$  as clinically relevant. For all hypotheses we compared the prevalence of a clinically relevant symptom (USD score  $< 3$  vs  $\geq 3$ ) and intensity (median score) using a Chi-squared test and the nonparametric Mann-Whitney U test, respectively. For the USD item well-being only the intensity was compared, since dichotomization of well-being was not considered to be meaningful.

#### **4. Responsiveness**

Responsiveness is defined as the ability of the USD to detect change over time, a measure of longitudinal validity.<sup>19,22</sup> We selected patients with two subsequent DT&PCs completed within one day of a USD. Per USD item patients were selected who 'improved' (reporting a problem on the first DT&PC and no problem on the second) or 'deteriorated' (no problem on the first DT&PC and a problem on the second). For each USD item we compared the median USD score at both measurement points, using Wilcoxon signed-rank test.

#### **5. Cutoff points**

By using the USD score and the corresponding problem on the DT&PC the cutoff point on the USD that best discriminates between patients with and without a clinically significant symptom score was assessed. We selected the first DT&PC that was completed within one day of a USD of all patients. For each item we explored the performance of cutoff points of 2, 3 and 4 in terms of positive predictive value (PPV) and negative predictive value (NPV), predicting for the presence or absence of the corresponding problem on the DT&PC, respectively.

## **Results**

3913 unique patients with cancer completed over 22,400 USDs. Patient characteristics at the time of the first available USD are presented in table 1, for the whole group, by presence of concurrent DT&PC and by disease stage.

The subgroup of patients with a concurrent DT&PC consisted mainly of outpatients (81%). Sixty percent of the patients received chemotherapy as an outpatient. Nearly all patients receiving symptom directed palliation only were admitted to the hospital, with a median stay of 10 days. Data on Eastern Cooperative Oncology Group (ECOG) performance status (PS) were available for 46% of patients.

#### **Content validity**

A total of 100 patients, 72% inpatients and 28% outpatients, completed the study specific questionnaire. 86% answered that the USD items properly represented their symptom burden. The prevalence of sleeping problems, dry mouth, abnormal stool, and dysphagia are shown in table 2 for the total study population. Prevalence of  $\geq 22\%$  show the importance of these items, confirming content validity of these added USD items.

Table 1. Patient characteristics

	Total		USD and DT&PC within one day		Chemo therapy (curative and palliative)		Symptom directed palliation only	
	N=3913*		N=1353		N=1919		N=224	
Age - mean (SD)	60.6	(13)	59.6	(12)	58.2	(13)	63.4	(12)
Gender male – N (%)	2197	(56)	741	(55)	1027	(54)	125	(56)
Patient – N (%)								
Outpatients	1689	(43)	1101	(81)	1147	(60)	2	(1)
Inpatients	2215	(57)	248	(18)	769	(40)	222	(99)
Missing	9	(<0.1)	4	(<0.1)	3	(<0.1)	NA	NA
Duration admission inpatients (days) - median [IQR]	7	[5-14]	5	[4-7]	6	[4-8]	10	[6-14]
Primary cancer site, N (%)								
Digestive tract	1232	(31)	439	(32)	627	(33)	105	(47)
Bone marrow and lymph nodes	549	(14)	66	(5)	194	(10)	2	(1)
Female genital tract	370	(9)	184	(14)	327	(17)	25	(11)
Head and neck	322	(8)	143	(11)	284	(15)	11	(5)
Central nervous system	255	(7)	39	(3)	60	(3)	1	(0)
Male genital tract	250	(6)	107	(8)	178	(9)	16	(7)
Breast	245	(6)	105	(8)	151	(8)	20	(9)
Skin	244	(6)	143	(11)	24	(1)	24	(11)
Kidney and urinary tract	180	(5)	42	(3)	34	(2)	10	(4)
Lung and mediastinum	168	(4)	65	(5)	11	(1)	1	(0)
Endocrine	43	(1)	5	(0)	9	(0)	4	(2)
Other	55	(1)	15	(1)	20	(1)	5	(2)
ECOG PS, N (%)								
0-1	1430	(37)	595	(44)	1024	(53)	21	(9)
2	236	(6)	60	(4)	128	(7)	24	(11)
3-4	123	(3)	8	(1)	25	(1)	42	(19)
Missing	2124	(54)	690	(51)	742	(39)	137	(61)
Days between ECOG PS and USD - median [IQR]	6	[1-14]	5	[0-13]	6	[1-14]	5	[1-14]

USD=Utrecht Symptom Diary, DT&PC=Distress Thermometer and Problem Checklist, SD=standard deviation, IQR=interquartile range, ECOG PS=Eastern Cooperative Oncology Group performance score, NA=not applicable.



**Table 2.** Content validation

	Prevalence USD score $\geq 3$ N (%)
Sleeping problems (N=3801)	1640 (43)
Dry mouth (N=3497)	1491 (43)
Abnormal stool (N=3698)	1629 (44)
Dysphagia (N=3485)	755 (22)

USD=Utrecht Symptom Diary

### Criterion validity

1353 patients (35%) completed at least once a USD and DT&PC within one day. 82% of the inpatients who filled out a DT&PC completed it on the first admission day. For all items the percentage of missing values was  $\leq 3.5\%$ . See Table 3 for results on criterion validity, comparing the USD scores to the dichotomous outcome of the DT&PC. The lowest AUC is 0.8, demonstrating good criterion validation.

**Table 3.** Criterion validity

	USD and DT&PC (N)	Prevalence on DT&PC (%)	AUC [95% CI]
Pain	1332	35.2	0.91 [0.89-0.93]
Sleeping problems	1329	32.1	0.90 [0.88-0.92]
Anorexia	1323	27.4	0.81 [0.79-0.84]
Abnormal stool	1305	25.4	0.89 [0.87-0.91]
Nausea	1330	13.9	0.91 [0.88-0.94]
Dyspnoea	1325	12.1	0.93 [0.91-0.95]
Fatigue	1332	50.5	0.91 [0.89-0.92]
Anxiety	1326	27.8	0.87 [0.85-0.89]
Depressed mood	1316	22.7	0.87 [0.85-0.90]

USD=Utrecht Symptom Diary, DT&PC=Distress Thermometer and Problem Checklist, AUC=Area under ROC curve, CI=confidence interval

### Construct validity

1919 patients (49%) completed a USD during chemotherapy, and 224 (6%) when receiving symptom directed palliation only. Table 4 summarizes symptom prevalence. During chemotherapy every symptom - except for dyspnoea - occurred in  $>10\%$  of the patients. Highest scores were found for fatigue. During the phase of symptom directed palliation only, every symptom occurred in  $\geq 25\%$ . A median score of  $\geq 3$  was found for 8/12 items. Again, fatigue had the highest intensity. Both the prevalence of USD scores  $\geq 3$  and the median scores were higher for all symptoms in patients receiving

symptom directed palliation only than in patients during chemotherapy. Thus, the first hypothesis, stating that the prevalence and intensity of all symptoms increase with progression of disease, was confirmed, demonstrating the construct validation for all USD symptom items. As shown in table 5, hypotheses 2-4 were confirmed, showing construct validity of the items dry mouth, dysphagia and well-being, respectively.

**Table 4.** Construct validity – Hypothesis 1 “Prevalence and intensity of all symptoms will increase with progression of disease”

	Prevalence – N (%) USD score ≥3		P-value <sup>†</sup>	Intensity – median [IQR]		P-value <sup>‡</sup>
	Chemo therapy	Symptom directed palliation only		Chemo therapy	Symptom directed palliation only	
	N=1919	N=224		N=1919	N=224	
Pain	452 (24)	100 (45)	<0.0001	1 [0-3]	3 [1-6]	<0.0001
Sleeping problems	539 (29)	117 (53)	<0.0001	1 [0-4]	4 [1-7]	<0.0001
Dry mouth	466 (25)	155 (70)	<0.0001	0 [0-3]	5 [2-8]	<0.0001
Dysphagia	318 (17)	62 (28)	<0.0001	0 [0-2]	1 [0-4]	<0.0001
Anorexia	614 (33)	153 (72)	<0.0001	1 [0-5]	6 [3-8]	<0.0001
Abnormal stool	548 (30)	131 (64)	<0.0001	1 [0-5]	5 [2-8]	<0.0001
Nausea	232 (12)	55 (25)	<0.0001	0 [0-1]	0 [0-3]	<0.0001
Dyspnoea	141 (8)	69 (31)	<0.0001	0 [0-1]	1 [0-4]	<0.0001
Fatigue	779 (41)	165 (74)	<0.0001	3 [0-5]	6 [3-8]	<0.0001
Anxiety	356 (19)	77 (36)	<0.0001	0 [0-3]	1 [0-5]	<0.0001
Depressed mood	308 (17)	79 (37)	<0.0001	1 [0-3]	3 [1-6]	<0.0001
Well-being	NA	NA		1 [0-4]	4 [1-7]	<0.0001

USD=Utrecht Symptom Diary, <sup>†</sup> Chi square, <sup>‡</sup> Mann-Whitney U, IQR=inter quartile range, NA=not applicable

### Responsiveness

293 patients (7%) completed >1 DT&PC and USD within one day. The vast majority (>80%) are outpatients as in our clinical setting the DT&PC is mostly offered to outpatients Table 6 shows median scores (IQR) before and after symptom improvement or deterioration. The measurements were on average 42 days apart [IQR 7-122]. For all items the median USD score upon improvement is lower on T2 than on T1 and vice versa upon deterioration. For both improvement and deterioration median change was 3.

**Table 5.** Construct validity – Hypotheses 2 to 4

		N	USD score $\geq 3$ N (%)	P-value <sup>†</sup>	Intensity median [IQR]	P-value <sup>‡</sup>
Dry mouth	Opioid use	537	309 (58)	<0.0001	4 [2-7]	<0.0001
	No opioid use	1678	616 (37)		2 [0-5]	
Dysphagia	Head and neck cancer	322	117 (37)	<0.0001	2 [0-5]	<0.0001
	Other diagnoses	3591	475 (15)		0 [0-2]	
Well-being	Pain score $\geq 3$	1402	NA	NA	5 [3-6]	<0.0001
	Pain score <3	2506	NA		2 [0-4]	

USD=Utrecht Symptom Diary, <sup>†</sup> Chi square, <sup>‡</sup> Mann-Whitney U, IQR=inter quartile range, NA=not applicable

### Cutoff points

Table 7 shows the performance of three different cutoff points (2, 3 and 4) per item on the USD 0-10 NRS. As expected for all items a lower cutoff increases the NPV. For a cutoff point of  $\geq 3$  NPV varied from 0.84 (fatigue) to 0.96 (dyspnoea) and for a cutoff  $\geq 4$  from 0.75 (fatigue) to 0.95 (dyspnoea). For both cutoff scores fatigue, pain and anxiety had the lowest NPV's.

Table 6. Responsiveness

	Improvement				Deterioration			
	N	Median score [IQR]		P-value <sup>‡</sup>	N	Median score [IQR]		P-value <sup>‡</sup>
		T1	T2			T1	T2	
Pain	41	3 [2-5]	2 [0-3]	0.0028	59	0 [0-2]	4 [2-6]	<0.0001
Sleeping problems	51	4 [2-7]	1 [0-2]	<0.0001	53	0 [0-2]	3 [2-5]	<0.0001
Anorexia	45	5 [2-7]	2 [0-5]	0.011	39	1 [0-5]	5 [3-7]	<0.0001
Abnormal stool	23	5 [2-6]	2 [0-3]	0.015	36	1 [0-3]	5 [2-6]	<0.0001
	26	5 [4-6]	2 [1-5]	0.005	46	0 [0-1]	5 [3-7]	<0.0001
Nausea	24	3 [2-5]	1 [0-2]	0.00069	50	0 [0-1]	3 [1-4]	<0.0001
Dyspnoea	13	3 [2-4]	0 [0-2]	0.019	28	0 [0-0]	3 [2-5]	<0.0001
Fatigue	38	4 [3-5]	2 [1-3]	0.00016	70	1 [0-3]	4 [2-5]	<0.0001
Anxiety	31	3 [2-5]	1 [0-2]	<0.0001	35	0 [0-2]	3 [2-5]	<0.0001
Depressed mood	21	4 [3-5]	1 [0-3]	<0.0001	42	0 [0-1]	3 [2-5]	<0.0001

<sup>‡</sup> Wilcoxon test, T1=first concurrent DT&PC and USD, T2=subsequent concurrent DT&PC and USD, IQR= inter quartile range

**Table 7.** Performance of different cutoff points for the USD items

	Cutoff point USD							
	≥2				≥3			
	PPV (95%CI)	NPV (95%CI)	PPV (95%CI)	NPV (95%CI)	PPV (95%CI)	NPV (95%CI)	PPV (95%CI)	NPV (95%CI)
Pain	0.72 [0.68-0.75]	0.94 [0.92-0.96]	0.79 [0.75-0.83]	0.88 [0.86-0.90]	0.85 [0.81-0.89]	0.81 [0.78-0.83]		
Sleeping problems	0.67 [0.63-0.71]	0.95 [0.93-0.96]	0.74 [0.70-0.78]	0.90 [0.87-0.92]	0.83 [0.79-0.87]	0.84 [0.81-0.86]		
Anorexia	0.52 [0.48-0.57]	0.90 [0.88-0.92]	0.59 [0.54-0.63]	0.89 [0.87-0.91]	0.64 [0.59-0.69]	0.87 [0.84-0.89]		
Abnormal stool	0.56 [0.52-0.60]	0.95 [0.93-0.97]	0.65 [0.60-0.70]	0.92 [0.90-0.94]	0.71 [0.66-0.76]	0.89 [0.87-0.91]		
Nausea	0.62 [0.56-0.68]	0.96 [0.95-0.97]	0.77 [0.70-0.83]	0.95 [0.93-0.96]	0.85 [0.77-0.91]	0.93 [0.91-0.94]		
Dyspnoea	0.59 [0.52-0.65]	0.98 [0.97-0.99]	0.69 [0.61-0.76]	0.96 [0.95-0.97]	0.79 [0.71-0.86]	0.95 [0.93-0.96]		
Fatigue	0.77 [0.74-0.80]	0.93 [0.90-0.95]	0.83 [0.80-0.86]	0.84 [0.81-0.87]	0.89 [0.87-0.92]	0.75 [0.71-0.78]		
Anxiety	0.64 [0.60-0.69]	0.92 [0.90-0.93]	0.76 [0.71-0.80]	0.88 [0.86-0.90]	0.80 [0.75-0.85]	0.84 [0.81-0.86]		
Depressed mood	0.55 [0.50-0.60]	0.94 [0.92-0.96]	0.68 [0.62-0.73]	0.90 [0.88-0.92]	0.79 [0.73-0.84]	0.87 [0.85-0.89]		

USD=Utrecht Symptom Diary, PPV=positive predictive value, NPV=negative predictive value, CI=confidence interval

## Discussion

Previous validations of the ESAS have mainly focused on reliability and concurrent validity in advanced cancer inpatients, using a variety of other instruments to compare the ESAS to. Relatively less evidence is available on responsiveness and cutoff points.<sup>4,12,13</sup> Our study fills part of this gap, as we show that the USD, a Dutch and adapted version of the ESAS, is a valid PROM for the most prevalent symptoms in cancer patients within all stages of disease. We also show the content validity of the added items to the USD and the ability to detect clinically important changes over time (responsiveness). Finally, we provide information about the clinical consequences of the generally used cutoff points.

### Content validity

Our results show content validity of all measured items as patients reported them to reflect their symptom burden. The usefulness of our newly added items - sleeping problems, dry mouth, abnormal stool, and dysphagia - is confirmed since they occur in 22-44% of our population. Adding items to the ESAS has occurred before but not specifically in cancer patients.<sup>34,35</sup> Besides synonyms have been used for items such as constipation and sleep-related problems.<sup>36,37</sup> Although dry mouth is not part of the ESAS, it is part of the MD Anderson Symptom Inventory (MDASI), which also is a validated and frequently used PROM in cancer patients.<sup>38</sup> The identification of dysphagia as a symptom to predict life expectancy by Teunissen et al<sup>15</sup> has been endorsed by others<sup>39</sup>, emphasizing the relevance of including this item.

### Criterion validity

We found a good concurrent criterion validation of the USD items pain, sleeping problems, anorexia, abnormal stool, nausea, dyspnoea, fatigue, anxiety and depressed mood, using the dichotomous outcome of the DT&PC. This means the USD is a valid instrument to reflect symptom burden at the time of assessment as well as over a previous period of time. Previous studies have investigated concurrent criterion validity of translated and/or modified versions of the ESAS with other PROMs, as reviewed in detail<sup>4,13</sup>, also concluding that these ESAS versions are valid for symptom assessment in different palliative care settings.<sup>37,40,41</sup> The strength of our study is that the USD uses a NRS and the DT&PC questions whether a symptom was considered a problem, therefore reflecting the patient's perspective on symptom scores. Consequently, insight into patients personal cutoff point can be obtained. In previous studies this was not possible since the PROMs used for comparison both utilized measuring scales. Hui and Bruera<sup>12</sup> reflected on this importance by describing how one patient may consider a score of 6/10 as agonizing while another may find it acceptable.



We used routine clinical data, which may be a limitation of our study. Since we only have information on the DT&PC when it was offered and completed, selection bias may be implied. Secondly, the DT&PC asks patients to report on symptoms over a time window of a week, whereas the USD captures current symptoms for inpatients and symptoms since last visit for outpatients. In our population, 82% of inpatients completed the USD and DT&PC on the first admission day. This makes it very likely that the symptom burden represents the patient's situation of the days before the admission as well.

### **Construct validity**

We found a good construct validity on the USD items dry mouth, dysphagia and well-being. To the best of our knowledge, there is only one other study using hypothesis testing to validate a translated and modified ESAS version in a small convenience sample of 23 cancer patients.<sup>42</sup> Several groups studied construct validity by investigating correlations between clusters of symptoms, hypothesizing a larger underlying construct measured by the ESAS items.<sup>12,43</sup> However, we decided to consider each symptom as an independent 'construct'. A sum score of all items has been studied<sup>41,44</sup>, as suggested by Bruera et al<sup>11</sup> to represent overall symptom distress as a construct. As we question the underlying assumption that low USD scores on multiple symptoms is comparable to a single high symptom score, based on other work of our group<sup>31</sup>, we decided not to summarize scores in this study.

### **Responsiveness**

Our results on responsiveness show that the USD is able to detect clinically significant differences over time for all items, as we show that patients who report improvement or deterioration on items of the DT&PC, have lower and higher USD scores at the second time point, respectively.

Paiva et al<sup>45</sup> studied responsiveness of the Brazilian version of the ESAS using an anchor-based method, asking 80 patients to classify after 21 days whether their symptoms were worse, the same or better than experienced during the first visit. Although they found that the median scores of patients who felt better indeed improved, and those of patients who reported a worsened condition were decreased, they could not show responsiveness for all items. Most probably this was caused by their small sample size and a patient population with a low symptom burden.

The strength of our comparison of the USD to a concurrent DT&PC, is that we compared USD scores to a reflection by the patients of the symptom as a problem

or not, which makes improvement or deterioration of symptoms clinically relevant. We did not find evidence that in- and outpatients score

differently on the USD when a symptom improved or deteriorated according to the DT&PC. Moreover, we performed analyses with multiple measures of one individual patient in order to obtain criterion validity, construct validity and responsiveness data. Patient setting will not likely influence these within-person analyses.

A limitation of our approach is that we do not know which patients remained stable, since reporting a symptom on both T1 and T2 as a problem on the DT&PC does not inform us whether the patient experienced this symptom in the same way at both moments. Consequently, calculating an AUC, which is the measure for responsiveness<sup>22</sup>, as well as the minimal clinically important difference for improvement and deterioration was not possible. The latter was studied by Hui et al for the ESAS<sup>46</sup>, concluding that for all symptoms the optimal cutoff for improvement was  $\geq 1$  point and  $\leq 1$  point for deterioration. Though with sensitivities of only 59-85%, indicating relatively many false negatives, which are patients who actually experienced a symptom change, but are missed with these cutoffs.

### Cutoff points

The symptoms of the ESAS with scores of 0, 1-3, 4-6, and 7-10 are generally considered as absent, mild, moderate, and severe, respectively<sup>29,47,48</sup>. However, we found that, when using NRS  $\geq 4$  as cutoff for moderate symptom burden, except for nausea and dyspnoea, >10% of patients with a score <4 would be misclassified as having 'none' or 'mild' symptoms whereas in fact they reported the symptom as a problem. It is likely that in certain circumstances and for certain items other cutoffs should be used, which also is suggested by Hui et al<sup>49</sup>. Later on in the disease process, patients in our cohort seem to accept a higher symptom burden which endorses the findings of Dalal et al<sup>50</sup> who found that patients with advanced disease reported to pursue a pain score of 3. By using different cutoffs depending on the situation and personal goals of the individual patient a more person centred approach may be achieved, improving shared decision-making<sup>49</sup>.

In conclusion, our results illustrate that the USD is a valid 12-item PROM containing the most prevalent symptoms in cancer patients. The USD has proven content, criterion and construct validity and can detect clinically important symptom changes over time in both in-and outpatients through the whole continuum of cancer care. As a result the USD improves insight into symptom burden in the individual patient which is essential for comprehensive personalized care in daily oncology practice.

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# Appendix A

Utrecht Symptom Diary (USD)  
Core instrument



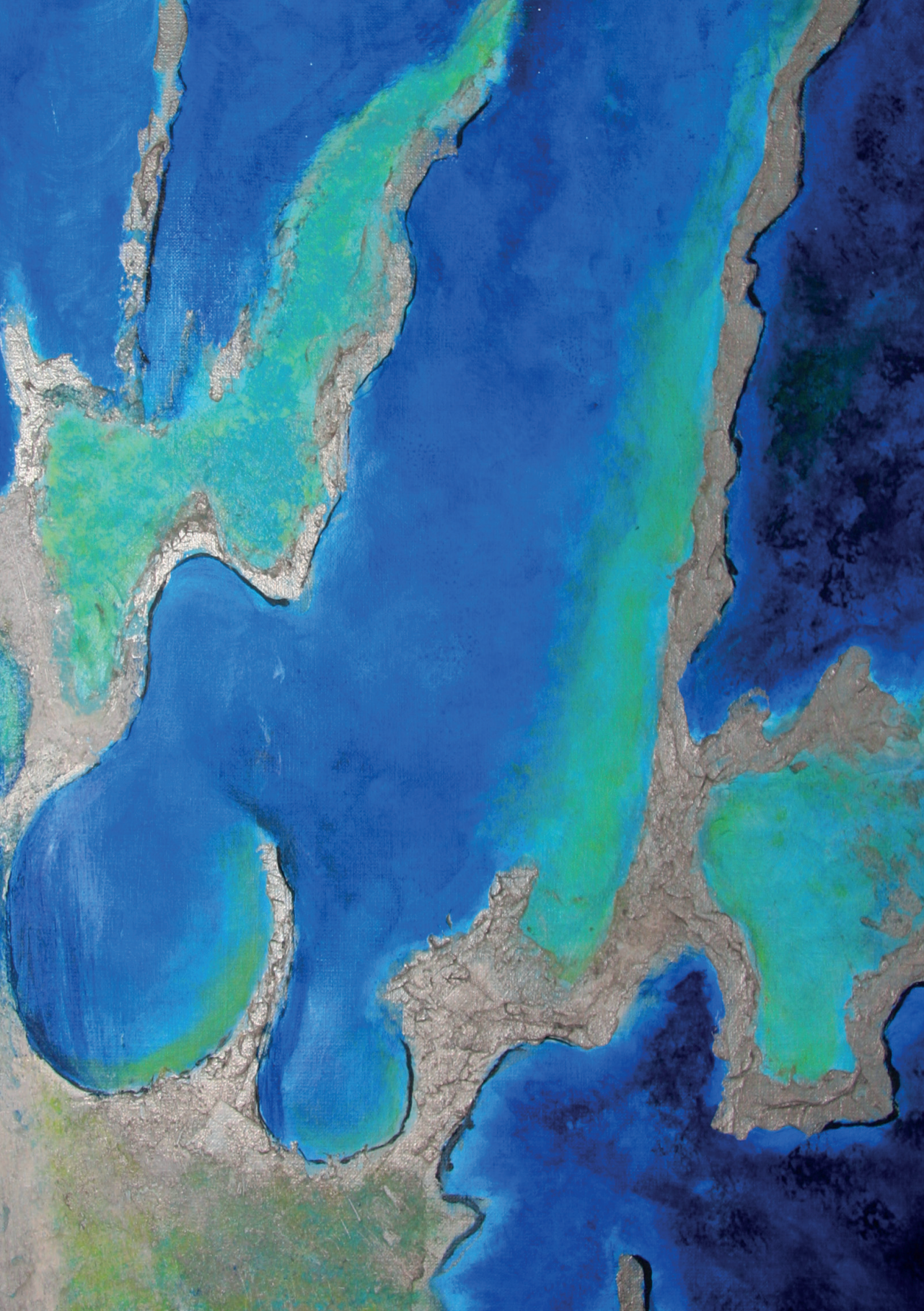
Date    ...../...../.....

**Instruction**

By reporting symptoms on a daily basis together we can plan the appropriate care for you, and evaluate and adjust support when necessary. Could you please circle - per symptom - the number that best describes how much burden you experience at the time of completion? We also ask you 'how you feel' with the item well-being. If you suffer from symptoms and/or feelings that are not listed, please indicate them in the extra lines.

<b>I have/feel</b>		
no pain	0 1 2 3 4 5 6 7 8 9 10	worst possible pain
no sleeping problems	0 1 2 3 4 5 6 7 8 9 10	worst possible sleeping problems
no dry mouth	0 1 2 3 4 5 6 7 8 9 10	worst possible dry mouth
no dysphagia	0 1 2 3 4 5 6 7 8 9 10	worst possible dysphagia
no lack of appetite	0 1 2 3 4 5 6 7 8 9 10	worst possible lack of appetite
no abnormal stool	0 1 2 3 4 5 6 7 8 9 10	worst possible abnormal stool
no nausea	0 1 2 3 4 5 6 7 8 9 10	worst possible nausea
no shortness of breath	0 1 2 3 4 5 6 7 8 9 10	worst possible shortness of breath
no fatigue	0 1 2 3 4 5 6 7 8 9 10	worst possible fatigue
no anxiety	0 1 2 3 4 5 6 7 8 9 10	worst possible anxiety
no depressed mood	0 1 2 3 4 5 6 7 8 9 10	worst possible depressed mood
best feeling of well-being	0 1 2 3 4 5 6 7 8 9 10	worst possible feeling of well-being
<b>Other symptom(s)</b>		
.....	0 1 2 3 4 5 6 7 8 9 10	.....
.....	0 1 2 3 4 5 6 7 8 9 10	.....

Which symptom(s) bother(s) you the most and is your priority for support?



## Chapter 3

# Validation of a symptom diary for outpatients with cancer receiving intravenous chemotherapy or targeted therapy

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Submitted

## Abstract

**Introduction.** The Utrecht Symptom Diary (USD) is a Dutch validated patient-reported outcome measurement (PROM) tool - based on the Edmonton Symptom Assessment System - to assess and monitor symptoms in cancer patients. This study aimed to evaluate the added items on the treatment specific outpatient USD in cancer patients receiving intravenous chemotherapy and/or targeted therapy.

**Methods.** Observational longitudinal retrospective cohort study including all adult outpatients with cancer receiving intravenous chemotherapy and/or targeted therapy in an academic hospital in the Netherlands who completed at least one outpatient USD as part of routine care (2012-2021). Content, criterion and construct validation were assessed.

**Results.** 1733 patients who completed  $\geq 1$  outpatient USD during intravenous chemotherapy and/or targeted therapy were included for analysis. Content validity (relevance, comprehensiveness) was shown. Criterion validation was confirmed for all added items of the outpatient USD – except for the item on oral pain. An additional analysis showed that mouth problems were detected with both outpatient USD items oral pain and dry mouth. Construct validity was confirmed for the items hair changes and skin and nail problems. Construct validity on eye problems was not tested due to the low number of paired outpatient USDs.

**Conclusions.** The outpatient USD is a valid PROM in outpatients with cancer receiving intravenous chemotherapy and/or targeted therapy. Considering its validity in this broad group of patients, we think the outpatient USD is widely applicable. In addition to providing tailored supportive symptom care, the USD-data can be used to increase knowledge about symptom burden in daily practice in this population.



## Introduction

During treatment with chemotherapy and/or targeted therapy cancer patients experience multiple symptoms associated with disease and/or treatment<sup>1,2</sup>. Poorly controlled symptoms can lead to decreased health related quality of life (HRQL), treatment modifications, visits to the emergency department and hospitalization<sup>3</sup>. The use of patient reported outcome measurement (PROMs) tools facilitates identification and management of symptoms<sup>4</sup> and patients' needs<sup>5</sup>. The Edmonton Symptom Assessment System (ESAS) is a valid and frequently used patient-reported outcome measurement tool (PROM) to assess and monitor symptoms in both clinical practice and research<sup>6,7</sup>.

The Utrecht Symptom Diary (USD) is an adapted Dutch translation of the ESAS including 12 items: pain, sleeping problems, dry mouth, dysphagia, lack of appetite, abnormal stool, nausea, shortness of breath, fatigue, anxiety, depressed mood and overall well-being. The USD is used in daily practice in several hospitals, general practices, and hospices in the Netherlands and use of the USD is recommended by the Netherlands Quality Framework for Palliative Care<sup>8</sup>. A recent study has shown the USD to be a valid PROM for cancer patients in both the curative and palliative phase of disease and capable of detecting clinically important changes over time<sup>9</sup>.

A brief, relevant and complete PROM is essential, since patients may become demotivated when PROMs are too long or when symptoms patients find relevant are missing<sup>3,10</sup>. Therefore, different modules of the USD have been developed, targeting specific tumours<sup>11,12</sup> or treatments<sup>13</sup>. Based on the literature and clinical experience the outpatient USD was developed for patients receiving intravenous chemotherapy and/or targeted therapy (Appendix A). Eleven frequently occurring signs and symptoms in patients receiving chemotherapy and/or targeted therapy were added to the USD: taste alteration, oral pain, weight loss, diarrhoea, hair changes, skin problems, nail problems, eye problems, tingling, concentration problems and change in sexuality<sup>1,14,15</sup>.

This study aimed at evaluating the validity of the added items on the outpatient USD in patients receiving intravenous (IV) chemotherapy and/or targeted therapy in the outpatient clinic.

## Methods

### Patient population & setting

In this observational longitudinal cohort study, all adult ( $\geq 18$  years) outpatients with cancer treated with IV chemotherapy and/or targeted therapy and who completed at least one outpatient USD during treatment between June 2012 and January 2021 were included for analysis. Patients were treated with curative or palliative intent at the Department of Medical Oncology, University Medical Center (UMC) Utrecht, the Netherlands. Patients were routinely offered an outpatient USD to assess and monitor symptoms and their burden. They completed the outpatient USD on paper or in the patient portal of the electronic medical files. To tailor care, oncology nurses discussed the clinically relevant USD scores ( $\geq 3$ ) with the patient.

This research was not considered subject to the Medical Research Involving Human Subjects Act by the institutional review board of the UMC Utrecht (METC number 15/087).

### Data collection & analysis

The 23 items of the outpatient USD (Appendix A) were assessed using an 11-point numerical scale (a higher score indicating a higher intensity)<sup>9</sup>. Patients were asked to score each item considering symptoms experienced since the last visit to the outpatient clinic. Alongside the 23 items, patients could add symptoms as an open text and assign priority for supportive care. All outpatient USDs completed during treatment up to three weeks after the last treatment were included, as this is the time frame in which treatment-related symptoms are expected to occur. Data on patient characteristics, disease, treatment, and USD scores were collected retrospectively from the electronic medical files.

We also collected data from the distress thermometer and problem checklist (DT&PC) which was routinely offered to patients at the start of every treatment and when clinically indicated. The DT&PC is a screening tool which is recommended to detect psychosocial care needs<sup>16,17</sup>. The validated distress thermometer (DT) is a self-report measure of distress (Visual Analogue Scale 0-10; a higher score indicating more distress). The problem checklist (PC) identifies problems that cause distress across five domains: physical, practical, family, spiritual, and emotional. Patients are asked to indicate (Yes/No) whether the item has been a problem in the past week including the day it was completed<sup>16,18</sup>. Patients reporting a higher number of problems score higher on the DT<sup>19</sup>.

Descriptive statistics were obtained to summarize the characteristics and symptoms of the patients. R software for statistical computing was used for statistical analysis

(R version 4.0.3 Package epitools). Patients with a missing value for a studied USD item were excluded for the analysis of that item. The percentage of missing items is presented for each item.

Definitions, methods, and quality criteria for the measurement properties of the outpatient USD were based on the Consensus-based Standards for the selection of health Measurement INstruments (COSMIN) initiative<sup>20,21</sup>.

## Validation

### **Content validity**

Content validity is the degree to which the content of an instrument is an adequate reflection of the construct to be measured<sup>20</sup>. In line with COSMIN the items in the outpatient USD were assessed for relevance and comprehensiveness.

To study the relevance of all items in the outpatient USD, we selected the highest score for each patient given to each item during treatment. We considered an item to be relevant when a symptom was scored prevalent (USD score  $\geq 1$ ) by at least 10% of the patients at least once during the treatment trajectory<sup>22</sup>.

To investigate the comprehensiveness and completeness of the outpatient USD, we analyzed the symptoms that were added as open text by the patients during treatment. The open responses were reviewed and categorized in overarching symptoms by clinicians (AG, DZ, JK, SK) who are familiar with the USD. Inclusion of a symptom in the outpatient USD was considered when added by  $\geq 10\%$  of patients.

### **Criterion validity**

Criterion validity is the degree to which the scores of the outpatient USD are an adequate reflection of the gold standard<sup>21</sup>. In the absence of a true gold standard, the DT&PC was used as a reference standard. Criterion validation was analyzed only for the outpatient USD items that were not previously validated<sup>9</sup> and for which a corresponding item was present on the DT&PC. These included: taste alteration, weight loss, diarrhea, oral pain, tingling, concentration problems and change in sexuality.

Per patient we selected the first DT&PC and outpatient USD completed  $\leq 1$  day, during treatment. In line with the previous USD validation study we used the cutoff point  $\geq 3$  as a clinically relevant cutoff score<sup>9,23–25</sup>, resulting in a dichotomous variable which was compared to the DT&PC dichotomized responses (problem Yes/No). For

each item an area under the curve (AUC) of the receiving operating curve (ROC) was calculated and an AUC  $\geq 0.70$  was interpreted as an adequate reflection of the DT&PC<sup>26</sup>. We next performed a subsequent analysis combining the outpatient USD items oral pain and dry mouth, in which we considered the USD positive if at least one of these items scored  $\geq 3$ . This combined variable (1/0) was compared to mouth sores on the DT&PC. Stratified bootstrap replicates of 2000 were used to compute the corresponding 95% confidence interval of the AUC<sup>27</sup>.

**Construct validity**

Construct validity is the degree to which outpatient USD scores are consistent with hypotheses formulated before data analysis<sup>21</sup>. Hypotheses were formulated based on literature and expert opinions of the clinicians for four items on the outpatient USD with no corresponding item on the DT&PC which were: hair changes, and nail, skin and eye problems (Table 1).

Using the McNemars chi-squared test, a paired comparison was done on the outpatient USD completed closest before start treatment against those completed at a the first USD available during treatment, in the time frame the symptom was expected to occur. This time frame was based on the literature and clinical experience and specified in the hypothesis. A hypothesis was only tested if at least 100 paired USDs were available<sup>28</sup>. A level of significance of 5% was used to confirm or reject the test. Again, we used the cutoff  $\geq 3$  to define a clinically relevant USD score.

**Table 1.** Hypotheses

Outpatient USD item	Hypotheses
Hair changes	"Patients using anthracyclines, taxanes (paclitaxel, nab-paclitaxel, docetaxel) and irinotecan for at least six weeks experience hair changes more often than before treatment" <sup>#29,30</sup>
Nail problems	"Patients using panitumumab, cetuximab, docetaxel, paclitaxel, and/or nab-paclitaxel for at least eight weeks experience nail problems more often than before treatment" <sup>#14,31,32</sup>
Skin problems	"Patients using capecitabine for at least six weeks experience skin problems more often than before treatment" <sup>#31,33,34</sup> .
Eye problems	"Patients using trastuzumab, cetuximab and/or panitumumab for at least seven weeks experience eye problems more often than before treatment" <sup>#15,35</sup>

## Results

Between June 2012 and January 2021 2164 patients completed at least once an outpatient USD either before or during treatment at the outpatient clinic.

Table 2 shows the characteristics of the 1733 patients who completed at least one outpatient USD during the selected treatment of IV chemotherapy and/or targeted therapy (up to 3 weeks after the last dose) and were included for analysis: 1147 (66%) received chemotherapy without targeted therapy, 586 (34%) received at least once targeted therapy with or without chemotherapy. Of these patients, 17% completed one outpatient USD, 54% completed 2-5 outpatient USDs and 28%  $\geq 6$  outpatient USDs during this treatment.

In order to estimate the representativity of our study population for all outpatients receiving IV chemotherapy and/or targeted therapy, we analyzed what percentage of patients completed at least one USD. We found that in 2019 95% (575/608) patients treated with chemotherapy and/or targeted therapy completed the outpatient USD at least once.

**Table 2.** Patient characteristics

N=1733		
Age, median [IQR]		61 [52-70]
Gender, N (%)	Female	950 (55)
Treatment, N (%)	Chemotherapy	1147 (66)
	Targeted therapy	225 (13)
	Chemotherapy and targeted therapy	361 (21)
Primary cancer site, N (%)	Digestive tract	829 (48)
	Female genital tract	365 (21)
	Breast	210 (12)
	Head and neck	120 (7)
	Male genital tract	86 (5)
	Central Nervous System	58 (3)
	Other	65 (4)



## Content validity

### Relevance

All items of the outpatient USD that had not been validated previously - were prevalent (USD score  $\geq 1$ ) in  $\geq 10\%$  of the population with prevalence ranging from 42% for nail problems to 76% for taste alteration. Additionally, all items were scored as clinically relevant (score  $\geq 3$ ) at least once during treatment by  $\geq 10\%$  of the patients with percentages ranging from 22% for nail problems to 58% for taste alteration. For all items, the percentage of missings was low; the highest percent missing was found for change in sexuality which was 3% (Table 3).

**Table 3.** Content validity: relevance

	N= 1733		
	Prevalent	Clinically relevant	Missing
Items, N (%)	USD score $\geq 1$	USD score $\geq 3$	
Taste alteration	1324 (76)	1008 (58)	10 (0.6)
Oral pain	897 (52)	514 (30)	3 (0.2)
Weight loss	1227 (71)	842 (49)	7 (0.4)
Diarrhea	1134 (65)	805 (46)	4 (0.2)
Hair changes	1094 (63)	803 (46)	8 (0.5)
Skin problems	1053 (61)	682 (39)	6 (0.3)
Nail problems	729 (42)	376 (22)	4 (0.2)
Eye problems	865 (50)	497 (29)	5 (0.3)
Tingling	1037 (60)	722 (42)	5 (0.3)
Concentration problems	1159 (67)	787 (45)	3 (0.2)
Change in sexuality	739 (43)	489 (28)	58 (3)

USD= Utrecht Symptom Diary

### Completeness

824 unique patients added symptoms as an open text with an average of 2.2 symptoms per patient. The items pain and fatigue were added even though they were already an item on the outpatient USD by 23.3% and 6.9% of the patients, respectively.

**Table 4** shows the symptoms (including specific pain subcategories) identified from the open responses with a prevalence of at least 2%. Since they occurred in  $<10\%$  of the patients, we decided not to add them to the outpatient USD.

**Table 4.** Content validation: completeness

Symptoms	N (%)
Cough	37 (2.0)
Dizziness	59 (3.2)
Itching	39 (2.1)
Pain, subcategories	
Headache	54 (3.0)
Muscle pain	47 (2.6)
Back pain	46 (2.5)
Abdominal pain	36 (2.0)

**Criterion validity**

During treatment until three weeks after treatment completion, 971 patients completed a USD and DT&PC with a  $\leq 1$  day interval.

**Table 5** shows the results on criterion validity. Dichotomous USD scores based on the previously defined cutoff of 3 were compared to the presence of a problem on the DT&PC. Except for oral pain - with an AUC of 0.63 - all the items showed a good criterion validity with an AUC of  $\geq 0.70$ . Reconsidering, we noticed patients who reported mouth problems as a problem on the DT&PC and did not experience oral pain were likely to have experienced dry mouth. The subsequent analysis comparing the USD items dry mouth and/or oral pain with mouth problems on the DT&PC showed a sensitivity of 0.75 and specificity of 0.80. For all items there were  $<10\%$  missing values.

**Construct validity**

The number of patients with USDs corresponding to the hypothesis on the hair changes and the nail, skin and eye problems were 392, 273, 170 and 76 respectively for each of the comparison groups.

**Table 6** shows how the data correlate with the hypothesis generated. Up to 11% of the patients scored an item as present at baseline already. Construct validity was confirmed for the items on hair changes, and nail and skin problems. For the hypothesis on eye problems we had insufficient ( $<100$ ) paired outpatient USDs to test the construct validity.

Table 5. Criterion Validity

Symptoms on USD	N=971				
	DT&PC N (%)		Outpatient USD N (%)		
	Yes	Missing	≥3	Missing	
Taste alteration	146 (15)	10 (1)	181 (19)	22 (2)	0.71
Weight loss	272 (28)	10 (1)	249 (26)	16 (2)	0.70
Diarrhoea	150 (15)	12 (1)	148 (15)	12 (1)	0.75
Oral pain	83 (9)	14 (1)	56 (6)	11 (1)	0.29
Tingling	132 (14)	10 (1)	116 (12)	10 (1)	0.67
Concentration problems	221 (23)	11 (1)	208 (21)	10 (1)	0.61
Changes in sexuality	79 (8)	20 (2)	147 (15)	68 (7)	0.81
					0.89
					0.85 [0.80-0.89]

USD= Utrecht Symptom Diary; DT&PC= Distress Thermometer and Problem Checklist; AUC= Area Under the Curve; CI=confidence interval

**Table 6.** Construct validation

Symptoms		USD score $\geq 3$ N (%)	P-value <sup>a</sup>
Hair changes (N=392)	Before treatment	45 (11)	<.0001
	During anthracyclines, paclitaxel, docetaxel or irinotecan treatment	204 (52)	
Nail problems (N=273)	Before treatment	21 (8)	0.004
	During cetuximab, panitumumab, docetaxel or paclitaxel treatment	41 (15)	
Skin problems (N=170)	Before treatment	19 (11)	0.0004
	During capecitabine	43 (25)	

USD= Utrecht Symptom Diary; <sup>a</sup>McNemars chi-squared test

## Discussion

We developed the outpatient USD in which items were added to the standard USD in order to early recognize and monitor symptoms in outpatients receiving intravenous chemotherapy or targeted therapy. With this large cohort study we assessed the content, criterion and construct validity of all additional items: taste alteration, oral pain, weight loss, diarrhea, hair changes, skin problems, nail problems, eye problems, tingling, concentration problems and change in sexuality. Construct validity of the item on eye problems could not be tested due to a low number of paired USDs.

### Content validation

#### Relevance

Content validity was shown since all additional items on the outpatient USD were prevalent (USD score  $\geq 1$ ) and clinically relevant (USD score  $\geq 3$ ) in  $\geq 10\%$  of the population. These items are in line with the findings by others who also identified these items as frequently occurring and/or being burdensome symptoms in patients treated with chemotherapy and/or targeted therapy<sup>1,2</sup>. In their literature synthesis, Reilly et al<sup>1</sup> found that weight loss, concentration problems and numbness/tingling were reported by  $\geq 40\%$  of the patients, sexual dysfunction and taste alteration by 32%, hair loss/appearance by 21%, diarrhoea by  $\approx 15\%$  and skin changes by  $\approx 13\%$ . Although Reilly et al. did not describe nail and eye problems as frequently reported by patients, healthcare professionals in other studies reported these symptoms as occurring in  $\geq 10\%$  of the patients<sup>15,32</sup>.

### ***Completeness***

The outpatient USD was found to be complete since none of the newly added items in the open responses was reported by  $\geq 10\%$  of the patients.

Reilly et al.<sup>1</sup> reported a high prevalence of nocturia (75%) and cough (52%) in 2/21 studies included in their pooled analysis. Although different cancer types were included in these two studies most included patients were diagnosed with lung cancer. Since these symptoms were mainly reported in patients with lung cancer and they were added by none (nocturia) or few (cough) of the patients in our population, we considered them to be irrelevant to the outpatient USD in our study population. However, it should be taken into account that patients with lung cancer were not present in our cohort.

### ***Criterion validation***

We found a good criterion validation for the items taste alteration, weight loss, diarrhoea, tingling, concentration problems and changes in sexuality, using the DT&PC as reference standard. The criterion validation on the item oral pain – mouth problems on the DT&PC - could initially not be confirmed. In a subsequent analysis validating oral pain and dry mouth together on the DT&PC mouth problems item we found an improved sensitivity and specificity. This implies that patients who report a mouth problem on the DT&PC mainly experience oral pain or dry mouth (or a combination of both) which is thus detected by the outpatient USD.

### ***Construct validation***

The items on nail and skin problems and on hair changes had good construct validity. Skin problems occur in 50-100% of the patients, hair changes in up to 50% of the patients and nail problems in 10-20% of the patients undergoing intravenous chemotherapy and/or targeted therapy<sup>29,31,33,36,37</sup>.

Ali et al.<sup>38</sup> recently described ocular toxicities as commonly occurring in patients in patients receiving cetuximab such as dry eyes (67%), blepharitis (63%), conjunctivitis (10–18%) and eyelid rash (38%) in patients receiving cetuximab and watery eyes (21%) in patients receiving trastuzumab. In our study population we had a low number of paired USDs of patients receiving trastuzumab, cetuximab and/or panitumumab scoring the item eye problems  $\geq 3$ . As a result, we could not assess the hypothesis for the construct validity on the item eye problems. Further research on this item using a higher sample size is needed to test its construct validity<sup>21</sup>.



## Strengths and limitations

A strength of this study is its representation of the population of outpatients with different cancer diagnoses, since all patients receiving intravenous chemotherapy and/or targeted therapy who at least completed one USD were included. We showed that the use of the outpatient USD is feasible since 95% of the patients completed at least one USD during treatment. Moreover we found a low number of missing items.

Furthermore, comparison was made between the outpatient USD and the DT&PC completed within  $\leq 1$  day which enabled the comparison of symptoms that arose within the same period thus reducing the risk of bias. This was also reported by COSMIN as essential for good criterion validation [21]. In line with our previous validation study<sup>9</sup> we consider the comparison of the outpatient USD to a concurrent DT&PC as a strength since patients scored a symptom as present or not on the DT&PC.

A limitation is that we have only data on USDs and DT&PCs when offered and completed since we used routine clinical data. Secondly, despite the fact that we think that our study population is a true representation of the percentage of patients receiving intravenous chemotherapy and patients receiving intravenous targeted therapy it should be noted that the majority of patients in our study were treated with chemotherapy and to a lesser extent with targeted therapy. Lastly, we found that some of the patients scored an item as present at baseline already, most probably due to disease related symptoms, persistent symptoms due to prior treatments, or symptoms related to comorbidity such as an ocular or skin disease. This may have influenced our results.

## Conclusion

Our results show that the outpatient USD is a valid PROM in measuring the most prevalent symptoms that affect outpatients with cancer treated with intravenous chemotherapy and/or targeted therapy. Although further research may clarify our findings on the item eye problems we think that the outpatient USD is widely applicable since it is validated in a broad group of patients with cancer in terms of cancer diagnosis and anticancer treatments. Furthermore, USD data can be used to increase knowledge about symptom burden to optimize supportive symptom care in daily oncology practice in this population.

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## Appendix A: Utrecht Symptom Diary (USD) Outpatient Clinic

### Utrecht Symptom Diary (USD)

Version: Chemotherapy and targeted therapy / outpatient clinic



We would like to know how you feel and which symptoms you experience. We therefore ask you to complete this questionnaire before visiting the outpatient clinic. During your consultation this questionnaire will be discussed.

- Please, circle the number that best describes how much burden you have had: 0 = absence of the symptom or feeling and 10 = the worst possible situation for you either continued presence of the symptom or feeling.
- If you have suffered from symptoms/ feelings that are not listed, please indicate them in the extra lines.

Date: \_\_\_\_\_

I had (since last time requested)												
no pain	0	1	2	3	4	5	6	7	8	9	10	worst possible pain
no lack of appetite	0	1	2	3	4	5	6	7	8	9	10	worst possible lack of appetite
no taste alteration	0	1	2	3	4	5	6	7	8	9	10	worst possible taste alteration
no dry mouth	0	1	2	3	4	5	6	7	8	9	10	worst possible dry mouth
no oral pain	0	1	2	3	4	5	6	7	8	9	10	worst possible oral pain
no dysphagia	0	1	2	3	4	5	6	7	8	9	10	worst possible dysphagia
no weight loss	0	1	2	3	4	5	6	7	8	9	10	worst possible weight loss
no diarrhea	0	1	2	3	4	5	6	7	8	9	10	worst possible diarrhea
no disturbed stool	0	1	2	3	4	5	6	7	8	9	10	worst possible disturbed stool
no hair changes	0	1	2	3	4	5	6	7	8	9	10	worst possible hair changes
no skin problems	0	1	2	3	4	5	6	7	8	9	10	worst possible skin problems
no nail problems	0	1	2	3	4	5	6	7	8	9	10	worst possible nail problems
no eye problems	0	1	2	3	4	5	6	7	8	9	10	worst possible eye problems
no tingling	0	1	2	3	4	5	6	7	8	9	10	worst possible tingling
no concentration problems	0	1	2	3	4	5	6	7	8	9	10	worst possible concentration problems
no sleeping problems	0	1	2	3	4	5	6	7	8	9	10	worst possible sleeping problems
no changes in sexuality	0	1	2	3	4	5	6	7	8	9	10	worst possible change in sexuality
Other symptom:	0	1	2	3	4	5	6	7	8	9	10	

I had (since last time requested)												
no nausea	0	1	2	3	4	5	6	7	8	9	10	worst possible nausea
no shortness of breath	0	1	2	3	4	5	6	7	8	9	10	worst possible shortness of breath
no fatigue	0	1	2	3	4	5	6	7	8	9	10	worst possible fatigue
no anxiety	0	1	2	3	4	5	6	7	8	9	10	worst possible anxiety
no depressed mood	0	1	2	3	4	5	6	7	8	9	10	worst possible depressed mood
Other symptom:	0	1	2	3	4	5	6	7	8	9	10	

I had (since last time requested)												
no unwell-being	0	1	2	3	4	5	6	7	8	9	10	worst possible unwell-being

Which symptom bother(s) you the most and is your priority for support?

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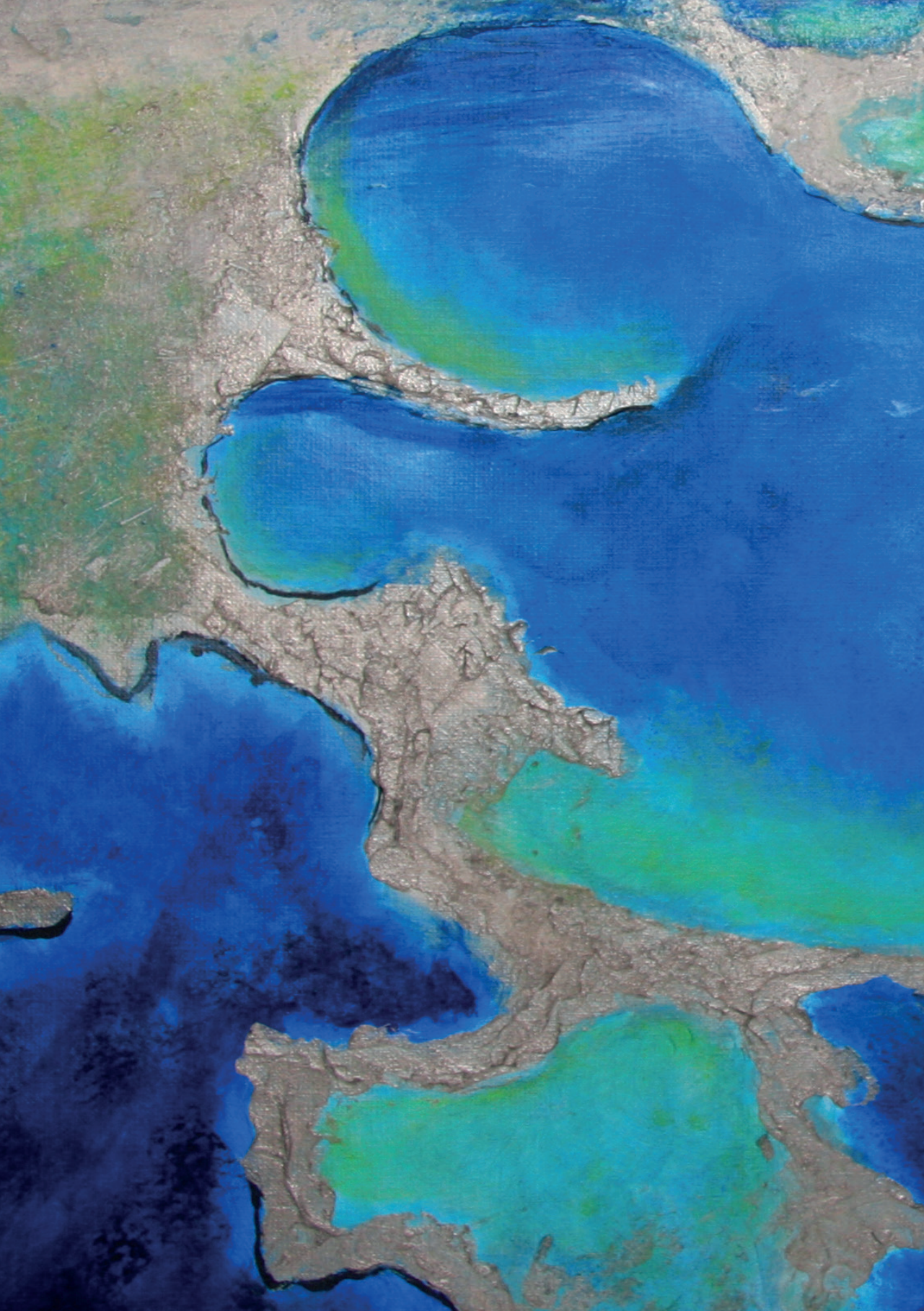


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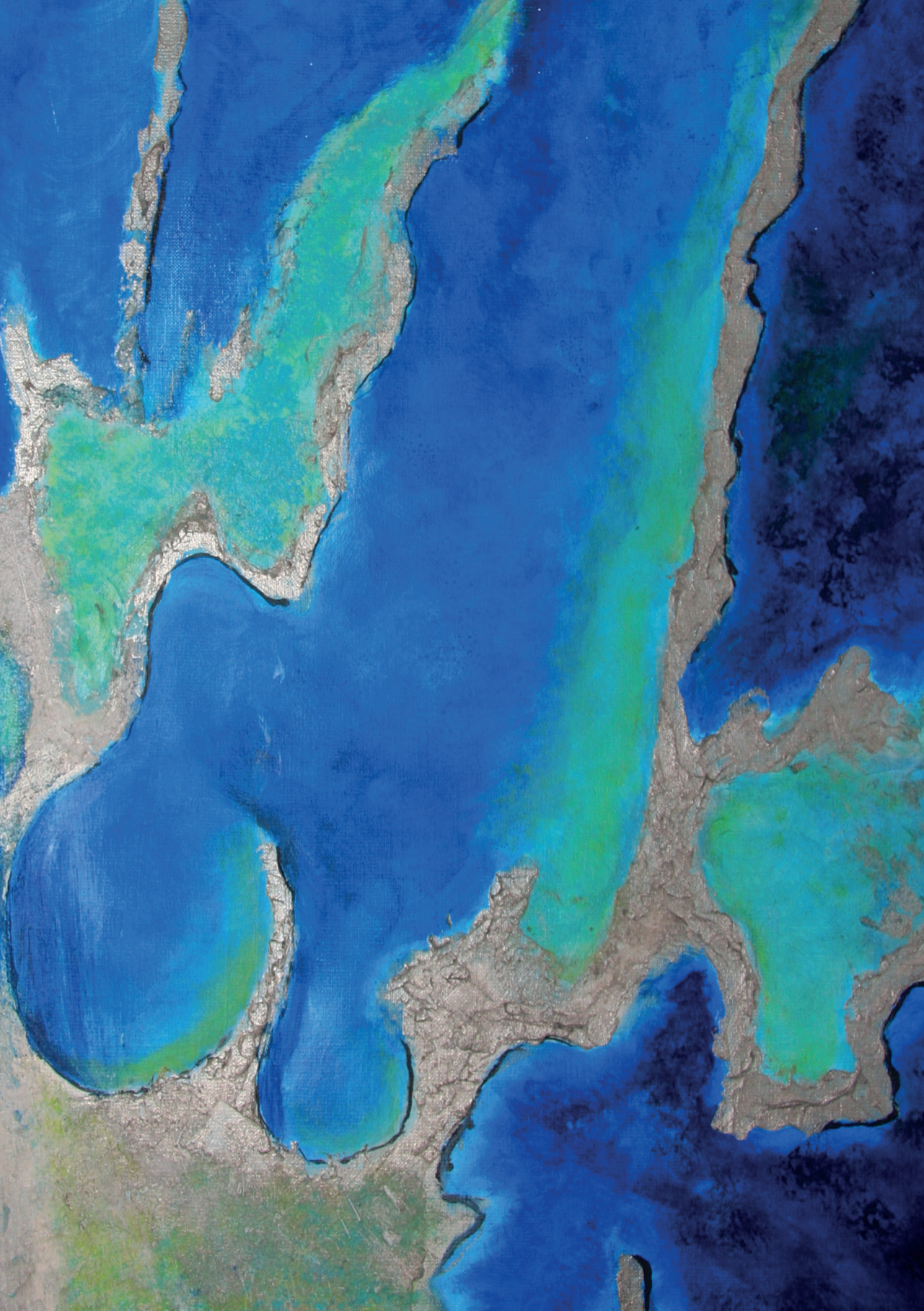


The background is an abstract, textured composition. It features a large, irregular shape in the upper left quadrant, filled with a mix of bright green and cyan colors, resembling a map of a landmass or a satellite image of a coastal area. This shape is surrounded by a deep blue, almost black, background that has a fine, woven texture. The edges of the green/cyan shape are jagged and irregular, with some brownish-grey tones visible along the boundaries. The overall effect is that of a high-contrast, textured print or a digital artwork with a focus on color and form.

## **PART 2**

**Use of the Utrecht Symptom Diary in  
different patient groups and settings**





## Chapter 4

# Patient-reported symptoms and stepwise symptom management in patients on epidermal growth factor inhibitors: a retrospective, descriptive cohort study

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## Abstract

Adverse events (AEs) of epidermal growth factor inhibitors (EGFRi) can influence well-being and lead to dose modifications. This study was set up to gain insight into dose modifications, healthcare professional reported adverse events (AEs) and patient-reported symptoms during EGFRi treatment. In this retrospective, observational cohort study healthcare professional reported AEs and dose modifications were obtained from the medical files and patients reported symptoms by using the Utrecht Symptom Diary (USD). Patients scored each USD item on a 11-point numeric rating scale; a score  $\geq 3$  was considered as clinically relevant.

Eighty-four patients on cetuximab or panitumumab treatment were included for analysis; 71% had squamous cell carcinoma of head and neck and 29% metastatic colorectal carcinoma. Treatment-related dose modifications occurred in 40% of the patients at a median of 5 weeks. The most common healthcare professional reported AEs at week 5 were: rash, dry skin and hypomagnesaemia. The most common clinically relevant (USD score  $\geq 3$ ) patient-reported symptoms were: skin changes, oral pain, lack of appetite, sleeping problems and fatigue. At week 5 clinically relevant fatigue, oral pain and skin changes were reported by  $>70\%$  of the patients and a poor feeling of well-being in more than 60% of the patients. From week 5 well-being decreased.

In conclusion, AEs led to dose modifications in a substantial number of patients. Patients experienced symptoms with moderate to severe intensity and a decreasing well-being during treatment. Early recognition and prompt management of even mild symptoms may assist in maintaining or recovery of well-being.



## Introduction

Monoclonal antibodies against the epidermal growth factor receptor (EGFR) are commonly applied as anti-cancer treatment. The EGFR inhibitors (EGFRi) cetuximab and panitumumab are prescribed with curative and/or palliative intent in patients with squamous cell carcinoma of the head and neck and RAS-wild type metastatic colorectal cancer<sup>1-6</sup>. EGFRi can cause skin toxicities such as maculopapular/papulopustular rash (34-100%), pruritus (8-35%), xerosis/fissures (7-35%) and paronychia (6-12%), as well as hair growth disorders (30%), oral changes (2-36%), eye disorders (3-38%), diarrhoea (29%) and hypomagnesaemia (4%)<sup>5,7-14</sup>.

Skin toxicities may impact patients' emotions, functioning and self-image, leading to anxiety, additional care consumption and a decreased health related quality of life (HRQL).<sup>7,9,15</sup> Adverse events (AEs), can result in dose modifications such as interruptions or reductions in 60% of the patients and treatment discontinuations in 32%<sup>7,15,16</sup>. Dose modifications may affect the overall clinical benefits of treatment. It is a daily clinical challenge to better monitor AEs and manage them promptly to maintain HRQL together with therapy continuation without dose modifications<sup>17</sup>.

The use of patient-reported outcome measures (PROMs) enhances early recognition of symptoms, improves clinician-patient communications and quality of care<sup>18,19</sup>. A meaningful use of PROMs requires a system that provides precise and accurate symptom assessment that is brief and maximizes feasibility for clinical use<sup>20</sup>. The Utrecht Symptom Diary (USD) is a Dutch translation and adapted and validated<sup>21</sup> version of the Edmonton Symptom Assessment System (ESAS), a worldwide frequently used PROM for more than 25 years<sup>22,23</sup>. For this study the USD items associated with EGFR-based treatment and/or impact on emotions and functioning as mentioned above were evaluated<sup>5,7-14</sup>.

Here we describe dose modifications, a selection of healthcare professional reported AEs and patient-reported symptoms, in a cohort of EGFRi treated patients in daily oncology practice.



## Patients and Methods

### Patients

In this retrospective cohort study adult patients with locally advanced and recurrent/metastatic squamous cell carcinoma of the head and neck and patients with metastatic colorectal cancer (or appendix carcinoma) on cetuximab or panitumumab treatment at the department of Medical Oncology of the University Medical Center (UMC) Utrecht in the Netherlands between June 2009 - February 2014, were included. Patients were identified using the computer-aided therapy for oncology system (CATO), which registers all systemic therapy administered.

### Data collection

#### *Dose and dose modifications*

Data regarding dose and dose modifications were obtained from the medical records.

The standard dose of cetuximab is 400 mg/m<sup>2</sup> for the first dose and 250 mg/m<sup>2</sup> for each subsequent administration and of panitumumab 6 mg/kg body weight every two weeks. In patients with locally advanced head and neck cancer, cetuximab is prescribed in combination with radiation therapy for a planned treatment duration of six to seven weeks.

In patients with recurrent and/or metastatic disease, cetuximab is prescribed in combination with platinum-based chemotherapy. EGFRi monotherapy is prescribed in patients with RAS-wild type metastatic colorectal cancer after disease progression on fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens.

### Healthcare professional-reported adverse events

Healthcare professional-reported AE prevalence and severity were obtained from the medical records and graded by the treating physician according to the CTCAE version 4.0<sup>324</sup>. When the grading was missing but the AE was described in such a way grading was possible, the researcher (JK) graded according to the CTCAE. We only present AEs in line with the previously mentioned treatment-related, healthcare professional reported skin toxicities, hair changes, eye disorders, diarrhoea, hypomagnesaemia, infusion-related reactions (IRR), as were radiation dermatitis and radiation mucositis in head and neck cancer patients. AEs were described at week five since median time to dose modification was five weeks. As a result we compared healthcare professional reported AEs and patient-reported symptoms at week five.

## Tool and intervention

### ***Patient-reported outcome measurement (PROM)***

Patient-reported symptoms were assessed using the Utrecht Symptom Diary (USD). The USD encompasses the most prevalent symptoms in advanced cancer patients being pain, sleeping problems, dry mouth, dysphagia, lack of appetite, abnormal stool, nausea, shortness of breath, fatigue, anxiety, depressed mood<sup>25</sup>. The concluding USD item is an overall score of well-being. For the outpatient clinic, the USD was adapted to include the most common adverse events of systemic anticancer treatment, including EGFRi-related adverse events (Appendix A). When visiting the in- or outpatient clinic, patients were asked to complete a USD as standard of care. Patients scored the USD items on paper, on a 0-10 numeric rating scale (0=no burden; 10= worst possible burden) in about five minutes, before each treatment administration. To tailor care, oncology nurses discussed the USD scores with the patients to bring about early recognition of symptoms and symptom burden, and to objectify the effect of interventions performed.

A selection of the previously mentioned EGFR-based treatment-related adverse events and patient-reported symptoms being skin changes, hair changes, eye changes, lack of appetite, oral pain, taste alteration, diarrhoea, sleeping problems, anxiety, depressed mood, fatigue, inactivity and well-being, were entered into a database and evaluated.

### **Symptom management**

For patients included in this study, EGFRi-related AEs were managed according to the Stepwise Intervention management plan EGFRi Utrecht (SIEU) which was developed in collaboration between medical oncologists, dermatologists and oncology. In the SIEU, brief patient education, stepwise symptom management strategies for EGFRi-related skin toxicities and recommended time points for consultation of a dermatologist and/or ophthalmologist were described<sup>26,27</sup>. When symptom management failed dose interruptions for one week were used to avoid dose reductions and discontinuations.

### **Medical Ethics Committee**

The study was conducted in accordance with the Declaration of Helsinki and approved by the UMC Utrecht institutional ethics committee. Since the USD and the SIEU are included in the standard care of the department of Medical Oncology of the UMC Utrecht Cancer Center, the ethics committee determined that informed consent was not required (METC number 15/087).

### Statistical Analysis

Patient and treatment characteristics as well as prevalence and severity of AEs were described. When referring to total treatment duration, time to dose modification, and reasons for and used variants of dose modifications, patients were categorized by treatment (cetuximab/panitumumab) and/or tumour type (head and neck cancer/ colorectal cancer). Patient-reported symptoms were categorized in USD score  $\geq 1$  (prevalent), USD score  $\geq 3$  (clinically relevant) and USD score  $\geq 6$  (severe intensity). All analyses were performed using SPSS 20.0 for Windows software (©2011 SPSS Inc., Armonk, NY: IBM Corp).

## Results

### Patient Characteristics

**Table 1** shows characteristics of all 84 patients included for analysis, of whom 65 (77%) received cetuximab and 19 (23%) panitumumab. Most patients in our cohort were men (68%) and median age was 62 (IQR 56-68). Patients had head and neck cancer (71%) or metastatic colorectal cancer (29%). Of the 60 head and neck cancer patients, 52 (87%) had locally advanced head and neck cancer who were treated with curative intent. Most patients with metastatic colorectal cancer received monotherapy panitumumab or cetuximab with palliative intent; one patient received cetuximab in combination with chemotherapy.

### Total treatment duration

Median total treatment duration was seven weeks (IQR 5-7) in patients with head and neck cancer treated with cetuximab/radiation therapy and six weeks (IQR 2-15) in head and neck cancer patients treated with cetuximab/chemotherapy. In patients with metastatic colorectal cancer on monotherapy EGFRi treatment duration was 14 weeks (IQR 6-24 weeks).

### Dose modifications due to treatment-related adverse events

A dose modification due to treatment-related adverse events occurred in 34/84 patients, mostly due to skin toxicity. A dose discontinuation was used in 19/34 patients. In most of head and neck cancer patients, the last cetuximab administration was cancelled. Furthermore, a dose interruption was used in 12/34 patients, and a dose reduction in 3/84 patients.

**Table 1.** Baseline patient characteristics

Variable, N (%)			All patients 84	Cetuximab 65	Panitumumab 19
Gender	Male		57 (68)	50 (77)	7 (37)
Age	Years, median (IQR)		62 (56-68)	63 (57-68)	62 (49-66)
	≥70		14 (17)	11 (17)	3 (16)
Diagnosis	Head and neck cancer <sup>a</sup>	All	60 (71)	60 (92)	-
		Locally advanced		52 (87)	-
		Recurrent/ metastatic		8 (13)	-
	Colorectal cancer <sup>b</sup>	Metastatic	24 (29)	5 (8)	19 (100)

<sup>a</sup> In patients with locally advanced head and neck cancer, cetuximab is prescribed in combination with radiation therapy for 6 to 7 weeks. In patients with recurrent and/or metastatic disease cetuximab is prescribed in combination with platinum-based chemotherapy.

<sup>b</sup> In patients with colorectal cancer cetuximab and panitumumab are prescribed as monotherapy treatment. One patient is treated with a combination of cetuximab with chemotherapy.

## Healthcare professional-reported adverse events

### *Prevalence and first occurrence of adverse events*

Table 2 shows the prevalence and severity of most common AE's reported by healthcare professionals at week 5, which was median time to dose modification. AEs were mostly grade 1-2. Of the skin toxicities, papulopustular rash (77%), dry skin (50%) and fissures (12%) occurred most. Hypomagnesaemia was reported in 21% of the patients.

Infusion related reactions (IRR) occurred in five patients on cetuximab and during the first administration only when premedication with clemastine and dexamethasone intravenously at first administration was not yet standard of care.

Skin toxicities such as pruritus and maculopapular/papulopustular rash occurred in the first two weeks of treatment, followed by dry skin in week 4.

### **Patient-reported symptoms and well-being**

Figure 1 focuses on 66/84 patients who reported symptom prevalence and intensity by completing the Utrecht Symptom Diary (USD) at least once. A total of 189 USDs were completed, median 3 (IQR 1-4) per patient. Eighteen patients (21%) did not complete a USD for reasons such as unwilling, lack of understanding Dutch language or no USD offered.

**Table 2.** Prevalence and severity of healthcare professional reported adverse events at week 5

All patients N=84		Cetuximab N=65				Panitumumab N=19		
Symptoms, N (%)		CTCAE grade*						
		All grades	1-2	3-4	Unknown <sup>#</sup>	All grades	1-2	3-4
Skin toxicities								
Papulopustular rash	65 (77)	48 (74)	41 (63)	2 (3)	5 (7)	17 (89)	14 (74)	2 (11)
Dry skin	42 (50)	31 (48)	18 (28)	4 (6)	9 (14)	11 (58)	11 (58)	-
Fissures	10 (12)	7 (11)	-	-		3 (16)	-	-
Acneiform rash scalp	9 (11)	6 (9)	-	-		3 (16)	-	-
Maculopapular rash	9 (11)	5 (8)	5 (8)	-		4 (21)	3 (16)	-
Pruritus	5 (6)	3 (5)	2 (3)	-		2 (10)	2 (10)	-
Radiation dermatitis	5 (6)	5 (8)	5 (8)	-		-	-	-
Secondary infection	4 (5)	3 (5)	-	-		1 (5)	-	-
Paronychia	4 (5)	1 (2)	1 (2)	-		3 (16)	3 (16)	-
Skin toxicities, unspecified	3 (4)	2 (3)	-	-		1 (5)	-	-
Eczema	1 (1)	1 (2)	-	-		-	-	-
Edema lips	1 (1)	1 (2)	-	-		-	-	-
Hair changes								
Hypertrichosis	4 (5)	1 (2)	1 (2)	-		3 (16)	3 (16)	-
Facial vellus hair rgroeiveranderingen	2 (2)	1 (2)	1 (2)	-		1 (5)	1 (5)	-
Ocular toxicities								
Dry eyes	3 (4)	1 (2)	-	-		2 (10)	-	-
Blepharitis	3 (4)	-	-	-		3 (16)	-	-
Conjunctivitis/keratitis	1 (1)	-	-	-		1 (5)	-	-
Ocular toxicities, other	1 (1)	1 (2)	-	-		-	-	-
Other toxicities								
Hypomagnesemia	18 (21)	12 (18)	11 (17)	1 (2)		6 (32)	5 (26)	1 (5)
Infusion related reactions	5 (6)	5 (8)	-	-		-	-	-
Mucositis, radiation	4 (5)	4 (6)	-	-		-	-	-
Diarrhoea	3 (4)	1 (2)	-	-		2 (10)	-	-
Candida infection (oral)	1 (1)	1 (2)	-	-		-	-	-

\*Common Terminology of Adverse Events 4.03

\*Grading unspecified in medical files or grading not possible by the researcher

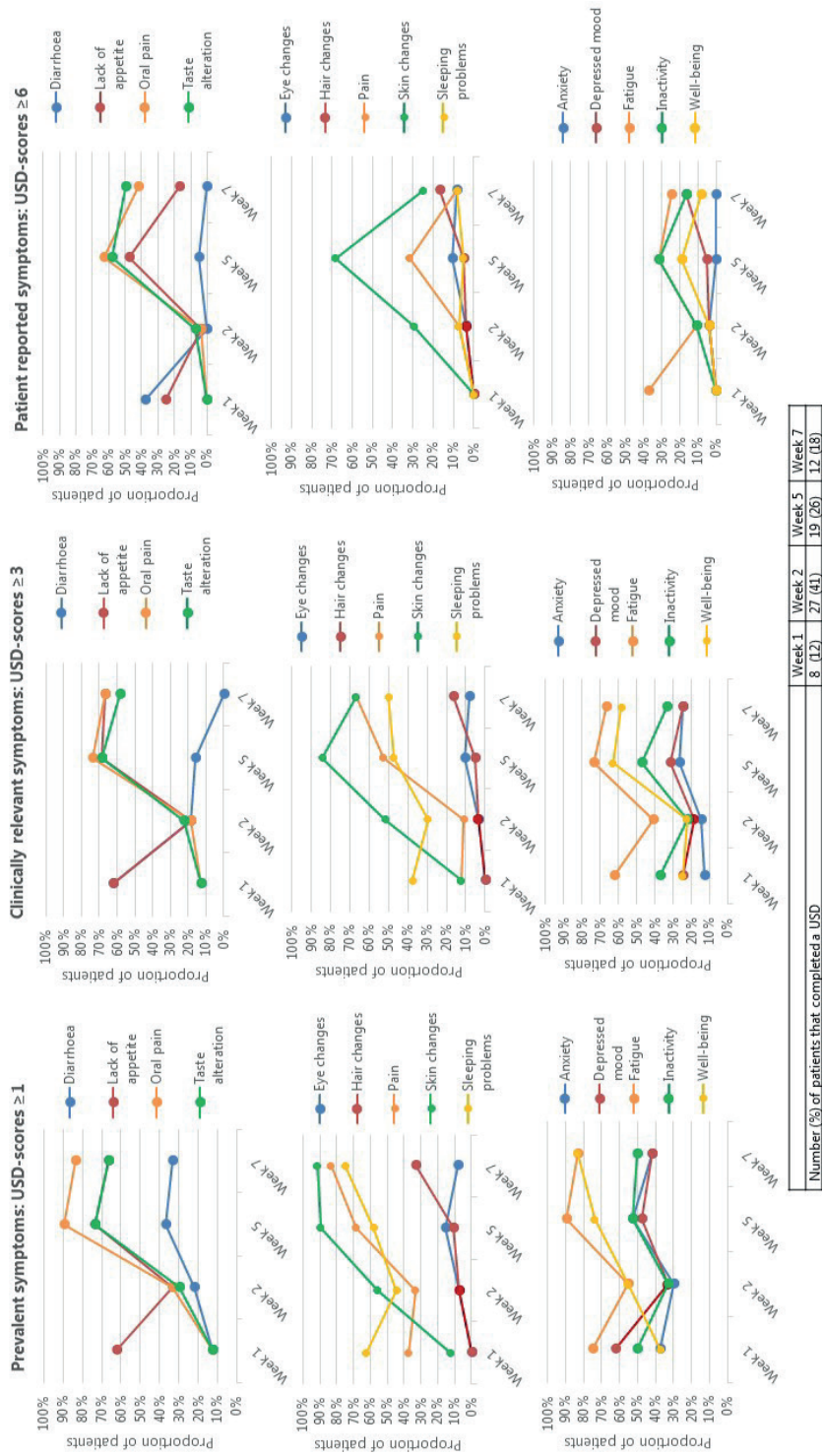


Figure 1. Changes in patient-reported symptoms and well-being during treatment courses (week 1-7)



All measured symptoms were reported as prevalent (USD score  $\geq 1$ ) by at least 10% of the patients at a certain week – except eye changes (0-16%) and hair changes (0-33%).

The top 5 of clinically relevant symptoms (USD score  $\geq 3$ ) at any week were: skin changes (13-84%), oral pain (13-74%), lack of appetite (19-67%), sleeping problems (30-50%) and fatigue (41-74%). Unwell-being (USD score  $\geq 3$ ) was reported by 22-63%.

From week 5 the number of patients reporting severe symptom intensity (USD score  $\geq 6$ ) increased. The top 3 at week 5 were: skin changes (68%), oral pain (63%) and taste alteration (58%). One fifth of patients (19%) reported serious unwell-being (USD score  $\geq 6$ ).

## Discussion

Here we describe the results of a retrospective, observational cohort study on dose modifications, healthcare professional reported adverse events, and patient-reported symptoms and well-being during EGFR-based treatment.

Our study shows a median time to dose modifications due to treatment-related AEs of five weeks, most commonly due to skin toxicity. At week five clinically relevant (USD score  $\geq 3$ ) fatigue, oral pain and skin changes were reported by at least 70% of the patients and poor feeling of wellbeing in about two-thirds of the patients. More than half of the patients experienced severe (USD score  $\geq 6$ ) skin changes, oral pain and taste alteration. The most common healthcare professional at week five reported AEs were: rash, dry skin and hypomagnesaemia. Although healthcare professionals reported mainly low grade AEs at week five, AEs caused dose modifications in a substantial number of patients. The most common clinically relevant patient-reported symptoms at any time point were: skin changes, oral pain, lack of appetite, sleeping problems and fatigue.

In their survey into the impact and symptom management of EGFRi-related skin toxicity in daily clinical setting among healthcare professionals Boone et al.<sup>7</sup> found comparable percentages of dose reductions or discontinuations due to AEs (33% vs 40% in our cohort). In our cohort none of the patients with colorectal cancer discontinued treatment due to AEs. Although most head and neck cancer patients receiving EGFRi in combination with radiation therapy were able to continue treatment for the preferred six to seven weeks, they experienced a variety of treatment-related symptoms. In these patients we found a comparable percentage of

dose modifications due to AEs as Kurakowa et al.<sup>28</sup> who found dose discontinuations in 19% of the patients based upon six planned cycles.

At week 5 skin changes, reported by 90% of our patients, caused a severe symptom burden in 68% of the patients. However healthcare professionals reported papulopustular rash (75%) and dry skin (50%) with fissures (15%) both mainly CTCAE grade 1 or 2 only. The percentage of papulopustular rash is comparable to the findings by Bonner et al.<sup>1</sup>, which again may reflect the underestimation of symptom burden by healthcare professionals. The early onset of skin toxicities in the cetuximab group when compared to panitumumab was most probably caused by the combination of cetuximab with radiation therapy in the head and neck cancer patients whereas patients on panitumumab received mainly monotherapy.

Dry skin and fissures were less often reported in other studies than by patients in our cohort<sup>1,28,29</sup>.

Radiation dermatitis and secondary skin infections reported by healthcare professionals seem to be under-reported in our cohort: 6% in our cohort versus 47-95% of the patients in the study of Bernier et al.<sup>29</sup> and 5% in our cohort versus 50% in the study by Amitay et al.<sup>30</sup>. There might be several explanations for these findings. First, we presented healthcare professional reported AEs at week five while Amitay et al.<sup>30</sup> presented AEs at any time point during treatment. Secondly, early recognition of symptoms and symptom burden by using the USD, followed by prompt (adaption of) and structured symptom management might have prevented secondary infections. Lastly, the different types of skin toxicities caused by EGFRi and/or radiation therapy are hard to distinguish. This may have led to difficulty in using the appropriate terminology and grading of EGFRi and/or radiotherapy-related skin toxicities. This might have hampered uniform communication and subsequent multidisciplinary systematic symptom management. Similar experiences have been described by Duffour et al.<sup>31</sup>. Tools that guide healthcare professionals in grading papulopustular rash as suggested by Wollenberg et al.<sup>32</sup> might be helpful. Since the preferred treatment/symptom management is different for the different skin toxicities, it could also be useful to develop a tool that assists healthcare professionals in distinguishing among various skin toxicities and to define the best method of symptom management in order to further improve these outcomes.

In our cohort oral pain was under-reported by healthcare professionals (10%) in comparison with patients themselves (60%). Insight into symptom burden in the individual patient has been found to be a valuable addition to healthcare

professional-reported, CTCAE-graded AEs, when considering adequate symptom management, influence on HRQL and anti-cancer treatment<sup>17,33</sup>. After visiting their doctor, patients discussed their USD scores with an oncology nurse, which may have led to insight into the degree of symptom burden of oral pain. By combining the objective CTCAE grade with the subjective score of the individual patient, early recognition of symptom burden as well as insight into the effect of interventions performed may be promoted.

The USD-item well-being, in previous studies reported as a valid and reliable single item quality of life measure<sup>34</sup>, showed a severe decrease in well-being during treatment in about 30% of the patients which might be related to the increased symptom intensity of lack of appetite, oral pain, taste alteration and skin changes. In week seven, oral pain and taste alteration still caused a severe symptom burden in about half of the patients and, the proportion of patients with severe burden due to the other measured symptoms was decreased. When symptom burden decreased, well-being recovered.

This study is limited by its retrospective nature, which caused missing data, for example on AE grading, and a relatively low number of completed USDs. Secondly, reported symptoms might differ among tumour types and simultaneously given other anticancer treatments. Due to the low number of patients included in the study comparisons across treatments schedules and/or tumour types were not possible.

Furthermore, the USD was developed, adapted, validated and used to tailor supportive care in daily clinical practice. At the time of the study, the USD validation study was not yet fully completed. At the time of writing this chapter, the validation study has been completed and published.<sup>21</sup> Based on guidelines and expert consensus treatment-specific versions have been developed, such as the USD outpatient clinic (USD OC) have been developed. A validation study on the added items of the USD OC has recently been performed. Nowadays the USD is part of the electronic medical files which have led to an increased number of completed USDs.

The strength of this study is that, by using the USD, insight is given into symptom burden of patients in daily life and practice. Well-being decreased during the first five weeks of treatment, stressing the importance of support and symptom management early in treatment. Our findings suggest that the combination of radiotherapy/EGFRi-related is a toxic treatment heavily impacting well-being.

In conclusion, EGFRi cause AEs that lead to dose modifications in a substantial number of patients. Patients experience symptoms with moderate to severe intensity and a decreasing well-being during treatment. Early recognition and prompt management of even mild symptoms guided by patient-reported symptoms may assist in maintaining and/or improving well-being.

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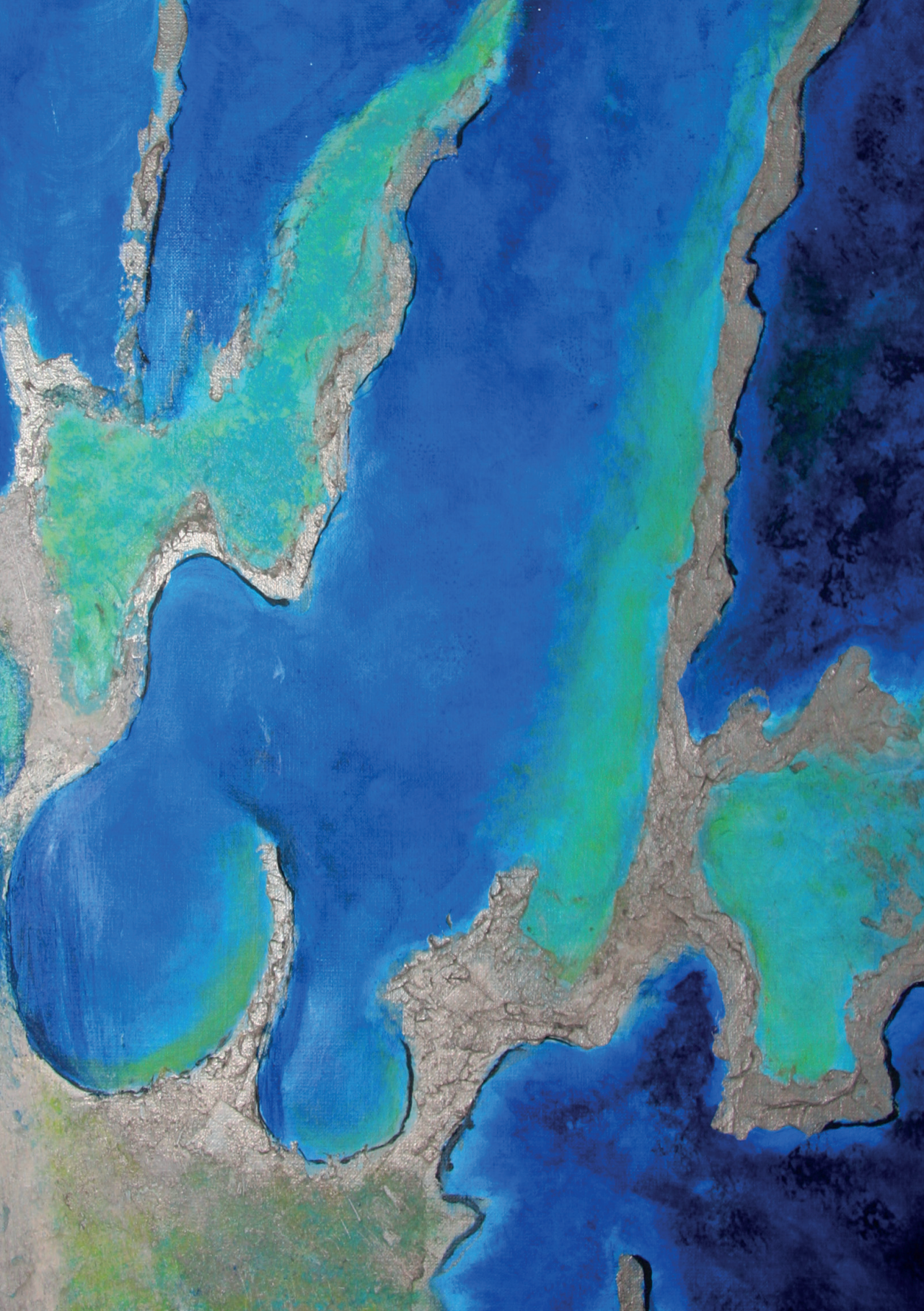
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## Chapter 5

# Patient-reported outcome measures in a pharmacokinetic study with sunitinib, a prospective cohort study

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## Abstract

**Purpose.** During treatment with tyrosine kinase inhibitors, such as sunitinib, patients experience treatment and/or disease-related symptoms. Although application of patient-reported outcome measures (PROMs) enhances early recognition of symptoms, early clinical trials have focused on symptom severity objectified by the Common Terminology Criteria for Adverse Events (CTCAE) in order to evaluate drug safety and to determine a personalized and/or safe dosage range. To gain insight into patient-reported symptoms in addition to healthcare professional-reported adverse events (AEs), a substudy was conducted in an ongoing pharmacokinetic-guided sunitinib dosing study.

**Methods.** Patients participating in a phase 1 clinical trial on pharmacokinetic (PK)-guided dosing of sunitinib in two Cancer Centers were eligible for inclusion/invited for the observational substudy. Patient-reported symptoms and (un)well-being were assessed together with healthcare professional-reported AEs.

**Results.** Twenty-nine patients were included for analysis. Over 50% of them experienced a decreased well-being, caused by symptoms of mild and moderate intensity. Compared to healthcare professionals, all 21 measured symptoms, with the exception of fatigue and vomiting, were reported more often by patients.

**Conclusions.** Application of PROMs in early clinical trials on personalized or individualized oral targeted anticancer agents is feasible and provides additional information to healthcare professional-reported AEs. In depth research is needed to assess the added value of application of PROMs for dose finding in early clinical trials.



## Introduction

Due to advances in preclinical research, perspectives for patients treated in early clinical trials have evolved, with an increasing proportion of patients deriving significant and durable benefit of study treatment<sup>1</sup>. Generally, cancer is more and more considered a chronic disease for which treatments such as targeted therapies are administered continuously until progressive disease and not for a predefined number of cycles<sup>2-4</sup>. Targeted therapy drugs, such as tyrosine kinase inhibitors (TKIs) are prescribed at a fixed dose even though it is known that drug exposure differs among patients due to bioavailability<sup>2</sup>.

During anticancer treatment, patients experience treatment and/or disease-related symptoms. In oncology clinical trials, these symptoms are graded as adverse events (AEs) based on the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE)<sup>5</sup>.

Symptom intensity and burden differ among patients and affect health-related quality of life (HRQL), particularly when patients experience multiple CTC grade 1-2 AEs at the same time and if symptoms are not managed effectively. A decreased HRQL is a serious risk of patient non-adherence and dose modifications, such as early discontinuation<sup>6-9</sup>.

The application of patient-reported outcome measures (PROMs) enhances early recognition of symptoms and improves clinician-patient communications and quality of care<sup>10,11</sup>. A meaningful, and feasible for clinical use of PROMs requires a brief, precise and accurate symptom assessment system<sup>12</sup>. The Utrecht Symptom Diary (USD) is a validated<sup>13</sup> Dutch translation and adapted version of the Edmonton Symptom Assessment System (ESAS), which has been proven to be a strong and highly sensitive tool for symptom experience for more than 25 years<sup>14,15</sup>. In the last decade, the USD has been part of standard care in daily practice of the in- and outpatient clinic and the early clinical trial unit of the department of Medical Oncology (MO) of the University Medical Center (UMC) Utrecht, Cancer Center.

Sunitinib, an anti-angiogenic TKI, is available as standard treatment at a fixed dose for renal cell cancer, pancreatic neuroendocrine tumours and gastrointestinal stromal tumours<sup>16-18</sup>. Especially when patients derive benefit from treatment with TKIs and are being treated for a long period of time, recognition of symptoms and their management becomes more important. We hypothesized that application of



PROMs in an early clinical trial could assist in early recognition of symptoms and assessment of symptom intensity in the individual patient.

Here, we conducted an observational substudy in a phase 1 clinical trial on pharmacokinetic (PK)-guided dosing of sunitinib to gain insight into patient-reported symptoms in addition to healthcare professional-reported AEs<sup>19</sup>.

## Methods

### Patient population and setting

Adult patients for whom sunitinib was considered standard therapy or patients or patients with advanced or metastatic tumours for whom no standard therapy was available were able to participate in the NCT01286896 trial. The trial was performed in three Dutch cancer centres. The main purpose of this trial was to assess whether PK-guided dosing could be performed without causing additional toxicities<sup>19</sup>. Other inclusion criteria were: Eastern Cooperative Oncology Group (ECOG) performance status  $\leq 1$ ; measurable or evaluable disease according to Response Evaluation Criteria Solid Tumours (RECIST) 1.1, estimated life expectancy  $> 12$  weeks, adequate hematologic, hepatic and renal function and no cardiac instability within the previous six months. Patients had to be willing to undergo blood sampling, and had to be able to swallow oral medication. In addition, for this substudy, patients in 2 of the 3 participating centres were asked to complete the USD sunitinib every week during 15 months (2011-2012).

The study protocol was approved by local independent ethics committees, and the study was conducted in accordance with the Declaration of Helsinki. All patients received information regarding the purpose and conduct of this study and provided written informed consent.

### Objectives

In this observational substudy the primary objective of this was to describe patient-reported symptoms and symptom intensity together with healthcare professional reported AEs and severity at different time points.

Primary objectives were to describe (i) prevalence and intensity of symptoms and (un)well-being from the patient's point of view, (ii) prevalence and severity of signs and symptoms from a professional point of view and (iii) differences in proportions of patient-reported symptoms versus healthcare professional-reported AEs.

## Measurements and definitions

### ***Symptom burden and Adverse Events***

Symptom burden was defined as the impact of (multiple) symptoms on physical, emotional and social functioning, reported by patients themselves<sup>9,20</sup>.

AEs were defined as an unfavourable and unintended sign, symptom or disease temporally associated with the use of a medicinal product, whether or not considered to be related to the medicinal product<sup>21</sup>. AEs were graded and reported by the treating<sup>20,22</sup> physician according to CTCAE v4.03<sup>5</sup>.

### ***Intervention and tool.***

Symptom assessment was performed using a treatment-specific module of the USD, the USD sunitinib (Appendix A). This submodule of the USD based on generic disease-related complaints and all AEs with a prevalence  $\geq 10\%$  and all grade 3–4 AEs as mentioned in the investigator's brochure of sunitinib<sup>6</sup> (2007).

Patients scored all 22 items, including an item on (un)well-being, every two weeks, on a 0–10 numeric rating scale (NRS; 0=*no burden*; 10=*worst possible burden*) in about five minutes every week. Missing experienced symptoms could be added by patients themselves and they were invited to prioritize symptoms that need supportive care. To complete the PROM patients are asked to give an overall score of the influence of treatment-related symptoms on HRQL (NRS 0–7, increasing number indicating a higher influence on HRQL). [16]Nurses discussed the USD scores with the patients to bring about early recognition of disease and/or treatment-related symptoms and to evaluate the effect of symptom management strategies performed. USD scores were anonymized entered into a study specific database.

The optimal cutoff point of the ESAS items varies per item and from 2–5 for symptom presence and moderate symptom intensity<sup>20,22</sup>. In a previous study we found that patients on sunitinib experience multiple mild and moderate symptoms in particular<sup>6</sup>. Therefore, the USD scores were categorized in 1–2, 3–5 and  $\geq 6$  in other words a mild, moderate or severe intensity.

### **Dose and dose modifications prospective cohort study**

Sunitinib exposure differs substantially between patients and within patients at different time points due to e.g. patient non-adherence, drug interactions with co-medication, variability in oral drug availability sunitinib<sup>2,19</sup>. In this PK-guided dosing study, patients commenced sunitinib treatment at 37.5 mg once a day continuously.

The sunitinib dose was increased when the target total plasma concentrations of sunitinib  $>50 \text{ ngml}^{-1}$  was not achieved. If the patient suffered from a grade  $\geq 3$  toxicity or intolerable grade 2 toxicity despite supportive care at any moment during the study, the sunitinib treatment was interrupted until adequate recovery (CTCAE grade  $<2$ ). Subsequently, sunitinib treatment was reduced to the next lowest dose level<sup>19</sup>.

### Statistical analysis

Descriptive statistics of patient characteristics, symptoms (severity and intensity) and reasons for and variants of dose modifications and were performed. Statistical analysis was performed using SPSS 20.0 for Windows software (©2011 SPSS Inc.).

## Results

### Patient population

A total of 42 patients participated in the PK guided study. In the substudy the USD was offered to 32 of 42 patients. Twenty nine patients completed at least one USD and were included for analysis (table 1 characteristics). Most patients were men (69%), had an ECOG performance status 1 (72%) and the median age was 61. All patients had metastatic disease. Tumour type was neuro endocrine tumour in 28%, colorectal carcinoma in 21% and other tumour types in 52% of the patients. Most patients received previous treatment, consisting of systemic treatment (72%), surgery (62%) and/or radiation therapy (38%).

### Patient-reported symptoms

A total of 322 USDs was completed by 29 patients (median 16; IQR 13-23). At different time points, USD data were available from 38-83% of the patients on treatment. Frequency and symptom intensity (NRS 0-10) of most relevant disease and/or treatment-related symptoms and (un)well-being at selected time points are shown in figure 1 (for full table: see Appendix B). In general, most patients experienced mild and moderate symptom intensity and did not add individual symptoms.

When looking at baseline scores, all 21 measured symptoms, with the exception of hair changes, itching and nose bleeds, were present in at least 20% of the patients, and pain, lack of appetite, cough, inactivity even caused a severe symptom burden in at least 20% of the patients.

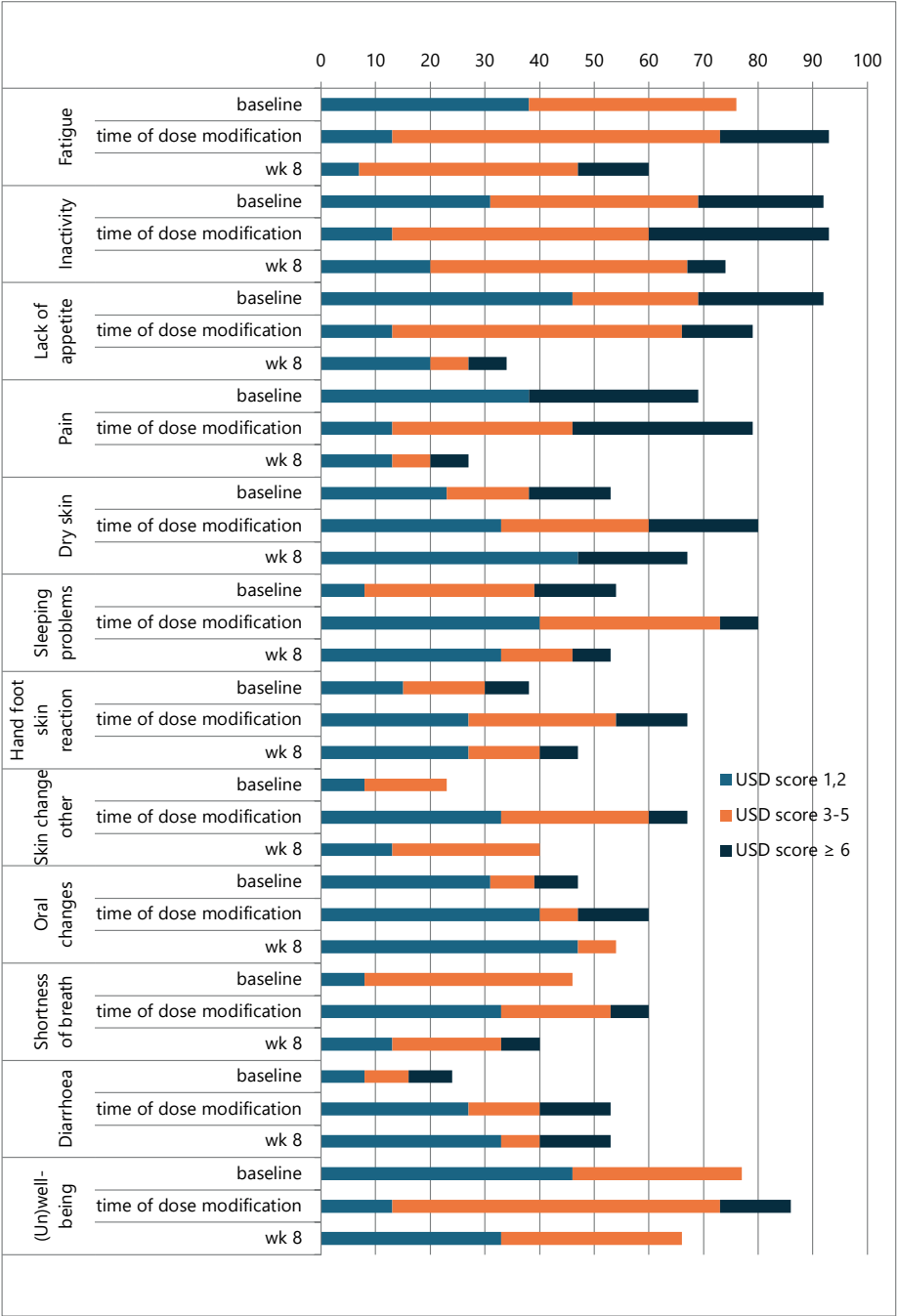
**Table 1.** Baseline characteristics

Characteristics, n (%)		Patients n=29
Gender	male	20 (69)
Age	Median yrs (IQR)	61 (52-65)
	categorized	
	18-35	1 (3)
	36-69	24 (83)
ECOG performance score	≥70	4 (14)
	0	8 (28)
	1	21 (72)
Primary tumor	Neuro endocrine tumor	8 (28)
	Colorectal carcinoma	6 (21)
	Renal cell carcinoma	4 (14)
	Miscellaneous*	11 (38)
Clinical Stage, metastatic		29 (100)
Prior systemic treatment	Systemic therapy	21 (72)
	Surgery	18 (62)
	Radiation therapy	11 (38)
Number of prior systemic treatment regimens	1	9 (31)
	2	2 (7)
	≥3	10 (34)

\*Miscellaneous: uveal melanoma and esophageal carcinoma (both n=2), adeno carcinoma of unknown primary, cervix carcinoma, head and neck carcinoma, mesothelioma, pancreatic carcinoma, solitary fibrous tumor prostate, Ewing sarcoma (all n=1)

When focusing on severe symptom burden reported by at least 20% of the patients, in week two a severe symptom burden was caused due to inactivity (29%), dry skin (21%) and diarrhoea (36%) (Appendix B). At time of dose modification - which was median week five - a severe symptom burden was reported due to fatigue (20%), pain (33%), dry skin (20%) and inactivity (33%) and in week six by fatigue (25%) only. In week eight a severe symptom burden of any symptom was experienced in >20% of the patients.

A severe decrease in well-being was reported most often in week two (21%). Decreased well-being differed in 55-87% of patients between weeks of treatment and was mainly mild to moderate in intensity.



**Figure 1.** Proportions of patients that reported disease and/or treatment-related symptoms and (un) well-being at selected time points

### **Influence of AEs on HRQL**

In line with the validation study<sup>13</sup> a USD score  $\geq 3$  of the item 'influence of AEs on HRQL' (NRS 0-7) was considered to clinically relevant impact HRQL. Because at baseline treatment was not started yet, patients stated not to experience impact on HRQL by side effects of treatment at this point. A clinically relevant impact of side effects on HRQL was experienced by 46% of the patients at time of dose modification and by 20% of the patients at week 8.

### **Healthcare professional-reported adverse events**

In table 2, healthcare professional-reported AEs that occurred in  $\geq 10\%$  of the patients are shown. Severity of AEs was mostly grade 1-2. Healthcare professional-reported pain (76%), fatigue (55%), cough (28%), diarrhoea (24%) and peripheral neuropathy (21%) were present in at least 20% of the patients at baseline already.

### **Patient-reported versus healthcare professional-reported symptoms**

Patient-reported USD scores  $\geq 1$  were compared to healthcare professional-reported any grade symptom prevalence (table 3). All measured symptoms, with the exception of fatigue and vomiting, were more often reported by patients themselves in one or more weeks. Lack of appetite, dry skin, sleeping problems and shortness of breath were reported more often by patients during all measured weeks. Although during treatment, lack of appetite was reported by at least 40% of the patients, healthcare professionals did not. Patients reported sleeping problems about four times as often as healthcare professionals. The same pattern was found for shortness of breath.

**Table 2.** Healthcare professional-reported adverse events

Week (number of patients on treatment)	Baseline (29)	Week 2 (28)	Week 6 (24)	Week 8 (19)	Week 12 (16)
CTCAE* grade, N (%)					
Signs and symptoms occurring in ≥10% of patients and all grade ≥3	All grades ≥3	All grades ≥3	All grades ≥3	All grades ≥3	All grades ≥3
Constipation	3 (10)	6 (21)	1 (4)	0 (0)	0
Cough	8 (28)	4 (14)	2 (8)	2 (10)	3 (19)
Diarrhoea	7 (24)	10 (36)	7 (29)	8 (42)	6 (37)
Dysgeusia	1 (3)	5 (18)	4 (17)	5 (26)	3 (19)
Shortness of breath	4 (14)	4 (14)	1 (4)	0 (0)	1 (6)
Nose bleeds	1 (3)	3 (11)	3 (12)	1 (5)	1 (6)
Fatigue	16 (55)	17 (61)	13 (54)	9 (47)	10 (62)
Hair depigmentation	0	0	1 (4)	3 (16)	2 (12)
Hypertension	0	5 (18)	5 (21)	5 (26)	3 (19)
Infection	1 (3)	4 (14)	1 (4)	2 (10)	2 (12)
Insomnia	0	1 (4)	1 (4)	1 (5)	2 (12)
Nausea	4 (14)	8 (29)	3 (12)	1 (5)	2 (12)
Oral toxicities	1 (3)	7 (25)	9 (37)	4 (21)	4 (25)
Pain	22 (76)	19 (68)	15 (62)	5 (26)	9 (56)
Peripheral sensory neuropathy	6 (21)	4 (14)	4 (17)	1 (5)	1 (6)
Hand-foot skin reaction	0	1 (4)	6 (25)	4 (21)	4 (25)
Skin toxicities, other	3 (10)	8 (29)	14 (58)	8 (42)	5 (31)

\*CTCAE (v4.03)= common terminology criteria for adverse events



**Table 3.** Patient-reported symptoms versus healthcare professional-reported adverse events

Time point (n)	Baseline (13)	Week 2 (14)	Week 6 (20)	Week 8 (15)	Week 12 (6)
Symptom	Difference in proportions <sup>a</sup>				
Fatigue	22%	18%	26%	0%	-13%
Lack of appetite	89%	64%	65%	32%	83%
Diarrhoea	-1%	36%	16%	0%	13%
Constipation	13%	7%	26%	11%	50%
Oral changes*	43%	32%	23%	21%	25%
Pain	28%	21%	23%	0%	52%
Dry skin	47%	36%	63%	42%	60%
Hand foot skin reaction	38%	32%	30%	16%	42%
Skin change, other	23%	29%	18%	5%	65%
Pruritus	15%	32%	41%	26%	50%
Cough	19%	21%	27%	21%	50%
Vomiting	9%	14%	21%	21%	33%
Gastric complaints other <sup>†</sup>	23%	29%	22%	16%	33%
Sleeping problems <sup>‡</sup>	54%	54%	61%	37%	54%
Nose bleeds <sup>®</sup>	12%	11%	3%	37%	27%
Nausea	9%	14%	28%	21%	21%
Shortness of breath	32%	43%	46%	32%	60%
Dizziness	7%	25%	31%	21%	33%

<sup>a</sup>A difference in proportion >0% means that patients reported the symptom more often than healthcare professionals; a difference in proportion <0% means that patients reported the symptom less often than healthcare professionals. \* Healthcare professional-reported oral toxicities \*\* Healthcare professional-reported decubitus, erythema, erythema multiform, hypopigmentation, purpura, rash, rash acneiform, skin disorder, skin hypopigmentation, skin induration <sup>†</sup> Healthcare professional-reported dyspepsia <sup>‡</sup> Healthcare professional-reported insomnia <sup>®</sup> Healthcare professional-reported epistaxis

## Treatment duration and dose modifications

In 2/29 patients, one with renal cell cancer and one pancreatic cancer patient, a dose modification did not occur and they both were still on treatment at time of analysis. Median total treatment duration was 16 weeks (IQR 8-27) and median time until dose modification five weeks (IQR 4-11). Most common reason for dose modification were AEs (17/29 patients; 59%) leading to a dose reduction in 13/29 patients and treatment discontinuation in 4/29 patients. In 3/29 patients the dose was escalated per protocol because the total plasma concentrations of sunitinib >50 ngml<sup>-1</sup> was not achieved.

## Discussion

To our best knowledge, this is the first study that describes patient-reported symptoms parallel to healthcare professional-reported adverse events (AEs) in an early clinical trial with an individualized dosing schedule for the tyrosine kinase inhibitor (TKI) sunitinib.

Patient-reported data showed that symptoms, mainly mild (USD score 1-2) and moderate (USD score 3-5), occurred in various combinations and, intensity differed among patients and time points. Healthcare professionals reported fewer symptoms than patients themselves: depending on the time point, two or three symptoms were registered in  $\geq 50\%$  of the patients.

At time of dose modification, which was median week five, in addition to a decreased well-being, 11 symptoms were reported by more than 50% of the patients: fatigue, inactivity, lack of appetite, pain, dry skin, sleeping problems, hand-foot skin reaction, other skin changes, oral changes, shortness of breath and diarrhoea.

Especially for highly subjective AEs such as fatigue and shortness of breath, it is known that clinicians tend to grade them at a lower severity than patients<sup>24</sup>. In our cohort, however, all measured symptoms were reported more often by patients than by their healthcare professionals. In other words, an experienced symptom intensity may not be the same as severity graded by the CTCAE.

When patient-reported symptoms of this cohort were compared to our previous findings in patients on standard sunitinib treatment at a standard dose of 50 mg, four weeks on two weeks off treatment, we found a comparable prevalence of 9/21 measured symptoms, just as for decreased well-being (difference of  $<10\%$ )<sup>6</sup>. However, fatigue, lack of appetite, pain, dry skin, hand-foot skin reaction, vomiting, hair changes, skin changes, sleeping problems, diarrhoea, gastric complaints and inactivity appeared to be reported more often by patients in this cohort. Probable reasons for these findings may be the more advanced disease stage of patients<sup>9,25</sup> participating in this early clinical trial and/or the escalated sunitinib dose. Patients in our study were treated for a median duration of four months. Only 14% of the patients permanently stopped treatment due to AEs, which is comparable to the percentage of dose discontinuations in patients on standard sunitinib treatment<sup>6,26</sup>. It is suggested that dose individualization for TKIs might help to personalize therapeutics to the individual needs of each patient<sup>2,19</sup>. For individualization of therapy, insight into symptoms and symptom intensity in the individual patient

is important. In this setting, the simultaneous occurrence of multiple mild (i.e. grade 1-2) toxicities could potentially be under-recognized by healthcare professionals, while significantly affecting patients' health related quality of life.

Since patient self-report is considered the most reliable indicator of symptom presence and intensity, the accuracy and efficiency of subjective AE data in early clinical trials and individualized doses of TKIs might be improved by adding standardized and structured collection of patient-reported symptoms to healthcare professional-reported AEs<sup>6,24,27,28</sup>. Additionally, when aiming at individualized dosing, one could use USD scores to formulate target scores for symptom intensity, which has been described as personalized symptom goals by Hui et al.<sup>29</sup>. A maximum tolerance level score, for example, might be useful in making informed therapy decisions regarding dose modifications for the individual patient.

Several limitations of this study should be mentioned. First, this substudy is limited by its sample size and the significant amount of missing data. This hampers reliable comparisons between time points and limits the power for statistical testing. USD data were missing because the USD was offered to and completed by patients when on treatment only. Remarkably, at time of dose modification and week 8 the USD was completed more often. Possibly, patients and nurses may have been more triggered to use the USD after patients experienced an increase in symptoms and/or when a dose modification had been applied (median week 5).

Furthermore, although the sunitinib-specific USD module was developed, based on evidence-based guidelines and experts consensus, this module has not been externally validated. Since patients did not make use of the possibility to add items that they found missing to the USD, the USD module sunitinib could be regarded as to the point for patient self-report level. However, a validation study should be performed in the future to confirm this assumption.

In conclusion, this study observational substudy suggests that assessing patient-reported symptom burden can add information to healthcare professional graded AEs in an early clinical trial and dose individualization study. Better insight into symptom burden caused by multiple grade 1-2 toxicities that might be overlooked by healthcare professionals could be of added value in symptom monitoring in early clinical trials.

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**Appendix A: Utrecht Symptom Diary (USD) Sunitinib**

Date     .... / ..... / .....

In order to treat your symptoms, as prompt as possible we would like to know how you feel and how much symptom burden you experience per symptom. We therefore ask you to complete the checklist below. Could you please indicate how you feel currently or how much symptom burden you experience on a 0-10 scale. During your consultation this checklist will be discussed.

**Explanation**

- Please, circle the number that best describes how much burden you have had: 0 = absence of the symptom or feeling and 10 = the worst possible situation for you either continued presence of the symptom or feeling

If you have suffered from symptoms/ feelings that are not listed, please indicate them in the extra lines.

no oral changes	0	1	2	3	4	5	6	7	8	9	10	worst possible oral changes	
no lack of appetite	0	1	2	3	4	5	6	7	8	9	10	worst possible lack of appetite	
no vomiting	0	1	2	3	4	5	6	7	8	9	10	worst possible vomiting	
no heartburn	0	1	2	3	4	5	6	7	8	9	10	worst possible heartburn	
no other stomach complaints	0	1	2	3	4	5	6	7	8	9	10	worst possible other stomach complaints	
no abnormal stool	0	1	2	3	4	5	6	7	8	9	10	worst possible abnormal stool	
no diarrhoea	0	1	2	3	4	5	6	7	8	9	10	worst possible diarrhoea	
no hair changes	0	1	2	3	4	5	6	7	8	9	10	worst possible hair changes	
no dry skin	0	1	2	3	4	5	6	7	8	9	10	worst possible dry skin	
no hand-foot skin reaction	0	1	2	3	4	5	6	7	8	9	10	worst possible hand-foot skin reaction	
no itching	0	1	2	3	4	5	6	7	8	9	10	worst possible itching	
no other skin changes	0	1	2	3	4	5	6	7	8	9	10	worst possible other skin changes	
no nose bleeds	0	1	2	3	4	5	6	7	8	9	10	worst possible nose bleeds	
no cough	0	1	2	3	4	5	6	7	8	9	10	worst possible coughing	
no pain	0	1	2	3	4	5	6	7	8	9	10	worst possible pain	
no dizziness	0	1	2	3	4	5	6	7	8	9	10	worst possible dizziness	
no sleeping problems	0	1	2	3	4	5	6	7	8	9	10	worst possible sleeping problems	
no nausea	0	1	2	3	4	5	6	7	8	9	10	worst possible nausea	
no shortness of breath	0	1	2	3	4	5	6	7	8	9	10	worst possible shortness of breath	
no fatigue	0	1	2	3	4	5	6	7	8	9	10	worst possible fatigue	
.....	0	1	2	3	4	5	6	7	8	9	10	.....	
.....	0	1	2	3	4	5	6	7	8	9	10	.....	
not inactive	0	1	2	3	4	5	6	7	8	9	10	worst possible inactive	
no unwell-being	0	1	2	3	4	5	6	7	8	9	10	worst possible unwell-being	
<b>To what extent is your quality of life affected by the side effects?</b>													
not affected at all	0	1	2	3	4	5	6	7	worst possible affected				
<b>Which symptom bothers you the most and is your priority for support?</b>													

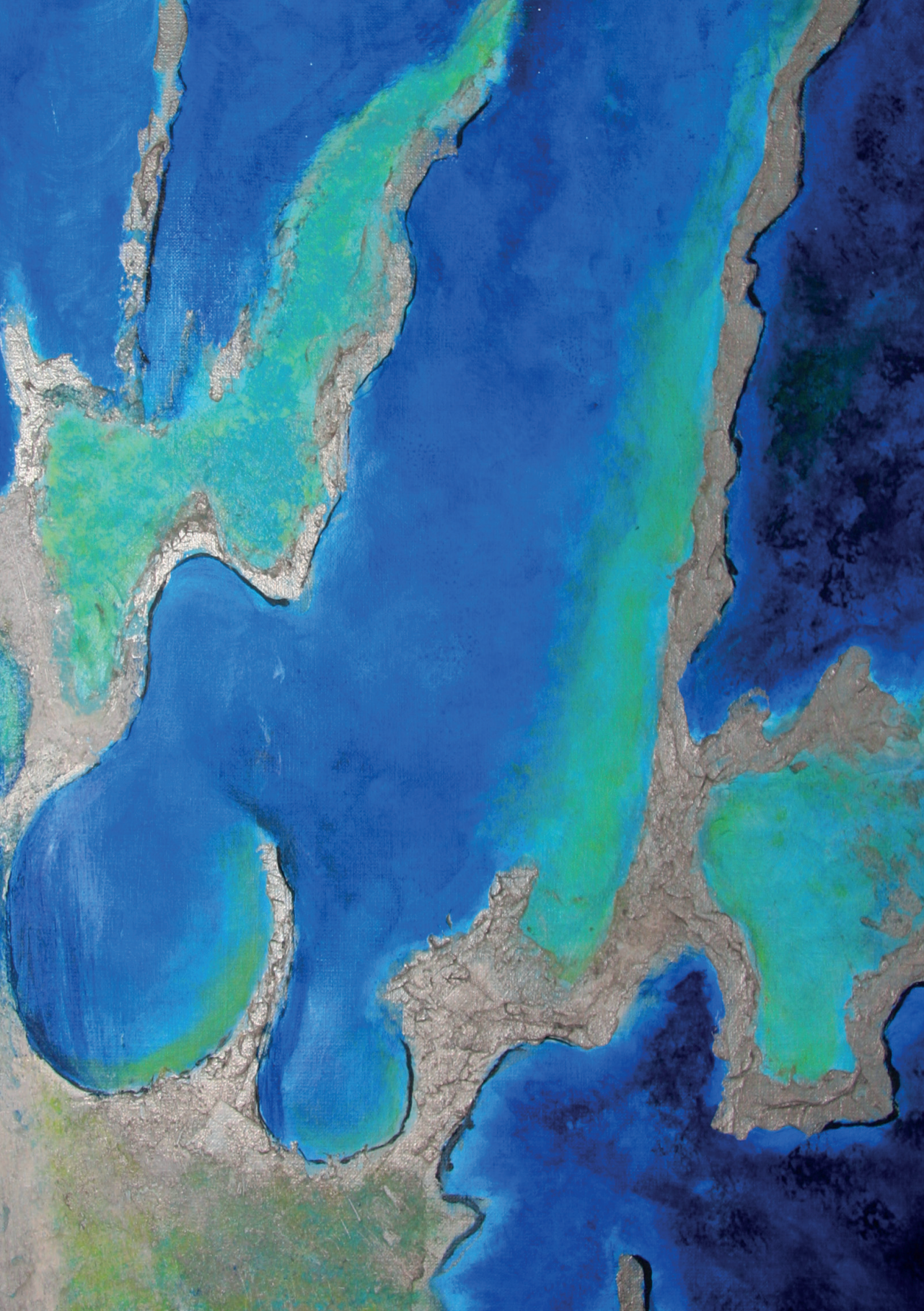


# Appendix B: full table patient-reported symptoms: prevalence and intensity

Time point	At time of dose modification				Baseline				Week 2			
Patients on treatment, N (%)	24 (83)				29 (100)				28 (97)			
Patients on treatment that completed a USD, N (%)	15 (62.5)				13 (45)				14 (50)			
USD score (scale 0-10)* of patients on treatment that completed a USD												
Symptom, %	≥1	1,2	3-5	≥6	≥1	1,2	3-5	≥6	≥1	1,2	3-5	≥6
Fatigue	93	13	60	20	77	38	38	0	79	7	57	14
Inactivity	93	13	47	33	92	31	38	23	64	7	29	29
Lack of appetite	80	13	53	13	92	46	23	23	71	14	43	14
Pain	80	13	33	33	69	38	0	31	64	7	43	14
Dry skin	80	33	27	20	54	23	15	15	50	21	7	21
Sleeping problems	80	40	33	7	54	8	31	15	57	14	36	7
Hand-foot skin reaction	67	27	27	13	38	15	15	8	36	36	0	0
Skin change other	67	33	27	7	23	8	15	0	36	29	7	0
Oral changes	60	40	7	13	46	31	8	8	57	21	36	0
Shortness of breath	60	33	20	7	46	8	38	0	57	29	21	7
Diarrhoea	53	27	13	13	23	8	8	8	71	14	21	36
Cough	47	33	13	0	46	23	0	23	36	29	7	0
Nausea	47	20	13	13	23	8	8	8	43	14	21	7
Heartburn	47	33	7	7	31	23	8	0	43	21	14	7
Gastric complaints other	40	20	13	7	23	15	8	0	29	14	14	0
Hair changes	40	27	7	7	8	8	0	0	14	7	7	0
Abnormal stool	33	20	13	0	23	0	8	15	29	14	7	7
Vomiting	33	13	13	7	23	8	8	8	29	14	14	0
Dizziness	33	33	0	0	23	8	8	8	29	7	14	7
Itching	27	13	13	0	15	0	15	0	36	21	7	7
Nose bleeds	27	20	7	0	15	8	8	0	21	14	7	0
(Un)wellbeing	87	13	60	13	77	46	31	0	71	7	43	21

\*0 = no burden; 10 = worst possible burden

	Week 6				Week 8				Week 12			
	24 (83)				19 (66)				16 (55)			
	20 (83)				15 (79)				6 (37.5)			
USD score (scale 0-10)* of patients on treatment that completed a USD												
	≥1	1,2	3-5	≥6	≥1	1,2	3-5	≥6	≥1	1,2	3-5	≥6
80	20	35	25	60	7	40	13	50	17	33	0	
85	20	50	15	73	20	47	7	100	33	50	17	
65	30	30	5	40	20	7	7	83	33	50	0	
60	15	30	15	27	13	7	7	83	33	33	17	
75	45	15	15	67	47	0	20	67	33	33	0	
65	40	20	5	53	33	13	7	67	50	17	0	
55	30	25	0	47	27	13	7	67	17	50	0	
55	25	25	5	40	13	27	0	83	50	33	0	
60	40	20	0	53	47	7	0	50	33	0	17	
50	30	15	5	40	13	20	7	67	33	33	0	
45	20	10	15	53	33	7	13	50	0	33	17	
35	25	10	0	40	20	20	0	50	33	17	0	
40	20	15	5	33	13	20	0	33	17	17	0	
40	40	0	0	7	7	0	0	33	33	0	0	
30	25	5	0	20	20	0	0	33	17	17	0	
30	20	5	5	27	13	7	7	50	33	0	17	
25	20	5	0	13	7	7	0	50	17	33	0	
25	15	10	0	27	13	13	0	33	17	17	0	
35	25	10	0	27	20	7	0	33	33)	0	0	
45	40	5	0	33	20	13	0	50	33	17	0	
15	5	10	0	27	20	7	0	33	33	0	0	
75	20	45	10	67	33	33	0	50	17	33	0	



## Chapter 6

# Patient-reported outcomes during checkpoint inhibition: insight into symptom burden in daily clinical practice

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## Abstract

**Introduction.** While praised for inducing durable anti-tumour responses, immune checkpoint inhibitors (ICI) also cause immune-related adverse events (irAEs) that can vary in severity and affect health-related quality of life (HRQL). This study was performed to provide insight into the course of symptoms and the influence of irAEs on HRQL measured with the treatment-specific Utrecht Symptom Diary Immunotherapy (USD-I).

**Methods.** In this observational cohort study, melanoma or non-small lung cancer (NSCLC) patients treated with PD(L)1-inhibitors between February 2016 and December 2018 were included. Data on symptoms, wellbeing and influence of side effects on HRQL were obtained using the patient-scored, treatment-specific USD-I, which was completed as part of routine care. Patients scored symptom intensity on a 0-10 numeric rating scale (NRS);  $NRS \geq 3$  considered clinically relevant.

**Results.** A total of 162 melanoma (55%) or NSCLC (45%) patients completed 1493 USDs (median seven per patient). Most common patient-reported clinically relevant symptoms were: inactivity, fatigue, pain, cough and sleeping problems. Symptom prevalence decreased during treatment. Patients generally reported a low influence of side effects on HRQL. A higher number of clinically relevant symptoms at a certain time point correlated with poorer wellbeing.

**Conclusions.** These data illustrate that ICI-treatment is generally well tolerated. However, especially the number of clinically relevant symptoms can impact patients wellbeing. Systematic use of an ICI-tailored PROM could create a window to discuss symptoms in a structured way which may promote personalized care during treatment.

## Introduction

Immunotherapy with immune checkpoint inhibitors (ICI) has radically changed perspectives for many cancer patients, such as patients with advanced melanoma or non-small cell lung cancer (NSCLC). Antibodies against the immune checkpoint programmed cell death protein-1 (anti-PD1), like pembrolizumab and nivolumab, and its ligand (anti-PD-L1) such as durvalumab and atezolizumab, reinvigorate effective anti-tumour immune responses.

Unfortunately, ICI can cause immune-related adverse events (irAEs), ranging from mild to life-threatening. IrAEs may start subclinically, can affect multiple organs simultaneously, and may occur at any moment during treatment up to several weeks after stopping treatment<sup>1,2</sup>. Most common irAEs are dermatitis, myalgia, arthralgia, and fatigue. Other irAEs, such as colitis, pneumonitis, hypophysitis and myocarditis are generally more severe and potentially life-threatening<sup>3</sup>. IrAEs often require active immunosuppressive treatment to prevent serious complications<sup>1,2</sup>. Early recognition of irAEs is considered essential to adequately treat symptoms and to maintain health-related quality of life (HRQL)<sup>4</sup>.

Although patients with cancer rank survival as their highest priority, they also value symptom control and the ability to continue daily life during and after treatment<sup>5</sup>. Little is known about patient-reported symptom prevalence, symptom intensity and HRQL during ICI in daily clinical practice. Insight into HRQL over time is especially relevant for ICI treated patients, because of the durable responses and longer treatment duration<sup>6</sup>. Since it is known that healthcare professionals tend to underestimate symptoms and family members ratings of symptoms are often higher than patient ratings, symptom reporting by patients themselves is considered the most reliable indicator of symptom presence and intensity<sup>7,8</sup>. Use of patient-reported outcome measurements (PROMs) enhances early recognition of symptoms and, improves clinician–patient communications, quality of care and overall survival<sup>9,10</sup>. This has led to an increase in the use of PROMs in clinical trials and to a lesser extent in daily clinical practice. Unfortunately, most PROMs were developed for use in the clinical trial setting, before the introduction of ICI and focus on other symptoms than usually encountered during ICI<sup>11–13</sup>.

Consistent and meaningful use of PROMs requires an easy-to-use and to the point symptom assessment system maximised for clinical use<sup>14</sup>. Worldwide, the most frequently used brief PROM to routinely assess and monitor symptoms in advanced cancer patients is the Edmonton Symptom Assessment System (ESAS), which has



been proven to be a strong and highly sensitive tool for assessing/monitoring symptom experience<sup>7,15</sup>. We developed and validated an adapted version of the ESAS, named the Utrecht Symptom Diary (USD)<sup>16,17</sup>. In 2016 we implemented the treatment-specific USD-module immunotherapy (USD-I) for cancer patients in our tertiary referral centre for melanoma and immunotherapy.

Here, we describe the results of an observational cohort study on patient-reported symptoms measured by USD-I in 162 patients treated with PD(L)1-inhibitors for advanced melanoma or NSCLC. We aim to provide insight into the course of symptoms and wellbeing as well as the influence of side effects on HRQL from a patient perspective.

## Patients and Methods

### Patients

Patients treated with monotherapy nivolumab, pembrolizumab, durvalumab or atezolizumab with curative or palliative intent for melanoma or NSCLC in the University Medical Centre (UMC) Utrecht between February 2016 and December 2018 and who completed at least two USD-I's were included. As part of standard care, each patient visiting the outpatient clinic for ICI administration was asked to complete the USD-I to tailor supportive care. In compliance with Dutch regulations, the use of these data for research purposes was approved by the medical ethical committee and was not considered subject to the Medical Research Involving Human Subjects Act (METC number 16-755/C).

### Definitions & Measurements

The USD-I (Appendix A) - a treatment specific and adapted version of the validated USD<sup>17</sup> - consists of 22 items: lack of appetite, abnormal stool, diarrhoea, blood/mucus in stool, abdominal pain, cough, eye complaints, skin rash, itching, headache, muscle pain, joint pain, numbness or tingling in arms/feet, pain, sleeping problems, nausea, shortness of breath, anxiety, fatigue, depressed mood, inactivity and wellbeing. The items sleeping problems, lack of appetite, abnormal stool, nausea, shortness of breath, fatigue, anxiety, depressed mood and wellbeing have been validated<sup>17</sup>. The other items were added based on generic irAEs with a prevalence of  $\geq 10\%$  and less common but potentially serious irAEs described in clinical trials<sup>18,19</sup>.

Before each treatment episode, patients scored the USD-I items on paper or within the patient environment of the electronic medical files, on a 0-10 numeric rating scale (NRS), with higher values indicating increasing symptom intensity/poorer

wellbeing. Patients generally complete the USD-I in less than five minutes, and have the opportunity to add missing items and to assign priority to symptoms which need support first. Influence of AEs on HRQL was measured by a single-item<sup>20</sup>, answering the question: "To what extent do the side effects of treatment influence your quality of life?" on a 0-7 NRS, with higher values indicating decreased HRQL. Patients are asked to score the intensity of their symptoms over the last period of time (since the last time they visited the outpatient clinic). Nurses reported symptoms with USD-I score  $\geq 3$  in the electronic medical files and discussed them with the patients to bring about early recognition of symptoms and symptom intensity, and to objectify the effect of symptom management interventions deployed. Symptom severity from healthcare professional perspective was graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03<sup>21</sup>.

### Data collection and analysis

Patient characteristics, disease and treatment-related data and USD-I scores were extracted from the electronic medical files. Disease stage of melanoma was classified according to the American Joint Commission on Cancer (AJCC) staging system 7<sup>th</sup> edition and NSCLC to the TNM, both seventh edition<sup>22,23</sup>. Response Evaluation Criteria in Solid Tumours (RECIST 1.1) were used to define response to treatment<sup>24</sup>.

USD-I scores were analysed per time point: baseline (range -2 to 2 weeks), week 4 (2-6), week 8 (6-10), week 12 (10-14), week 16 (14-18), week 20 (18-22), week 24 (22-26), third quarter (week 26-40) and fourth quarter (week 40-53). Per time point one USD-I per patient (the one closest to that time point) was selected for analysis.

USD-I symptom scores were categorized to describe symptom prevalence and intensity at baseline and during treatment, absent (0), prevalent ( $\geq 1$ ), clinically relevant ( $\geq 3$ ), severe ( $\geq 6$ )<sup>17</sup>. For the items wellbeing (NRS 0-10) and influence of side effects on HRQL (NRS 0-7) only the intensity was compared in line with the original USD validation study<sup>17</sup>. Patients with a missing value for the studied USD-I item were excluded for analysis for that item.

All item scores (except influence of side effects on HRQL) were summed to calculate a total symptom distress score, as previously done with the ESAS by Hui et al<sup>25</sup>; total score 0-220, higher scores indicate higher total symptom burden. In this score, when a patient did not score an item, we assumed that that specific item was not prevalent (NRS 0).

Differences in symptom prevalence between time points and tumour types were analysed by using the  $\chi^2$  (or Fisher exact test in case of cell frequencies  $\leq 1$  or  $\geq 20\%$

or expected cell frequencies between 1 and 5). Differences in medians were analysed by using the Mann-Whitney U test.

To test whether a high number of clinically relevant symptoms (NRS  $\geq 3$ ) was correlated with experiencing a poorer wellbeing, a higher influence of side effects on HRQL, and a higher total symptom distress score we used the Spearman's rho coefficient ( $\rho$ ).

Due to the group size in relation to the number of statistical tests, the differences found will be considered as hypothesis generating. Statistical analysis were performed using SPSS 25.0 for Windows software (©2018 IBM SPSS Inc.).

Results

Demographics/patient characteristics

During the selected period 203 patients with melanoma or NSCLC started treatment with anti-PD(L)1 monotherapy and could have had completed at least two USD-Is. A total of 162 out of 203 (80%) patients with melanoma (55%) or NSCLC (45%) completed at least two USD-Is and were included for analysis. Patient characteristics are depicted in table 1. Median age was 66, 59% of the patients were men, and 90% patients had a baseline Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0 or 1. Most (90%) patients were treated with nivolumab or pembrolizumab.

Table 1. Demographics and patient characteristics

Variable (n, %)		n= 162 (100)	
Age (yrs), median (range)	Categorized	<50	66 (33-90)
		50 - 69	21 (13)
		70 - 79	75 (46)
		≥80	66 (41)
Gender, male			95 (59)
ECOG <sup>a</sup> performance status	0		51 (31)
	1		95 (59)
	2		15 (9)
	3		1 (1)
Tumour type	Melanoma, all stages <sup>b</sup>		89 (55)
	Melanoma, per stage <sup>b</sup>	III	3 (3)

**Table 1.** Continued

Variable (n, %)		n= 162 (100)
Tumour type	IV	86 (53)
	Non-small cell lung carcinoma, all stages	73 (45)
	NSCLC, per stage	10 (14)
	IV	63 (39)
Brain metastasis present		40 (25)
		Symptomatic
		25 (15)
Comorbidity present <sup>c</sup>		102 (63)
Cardiovascular		57 (35)
COPD		16 (10)
Diabetes mellitus		11 (7)
Auto-immune disease		6 (4)
Other		63 (39)
Type of immunotherapy	Anti-PD1 <sup>d</sup>	145 (90)
	Nivolumab	45 (28)
	Pembrolizumab	100 (62)
	Anti-PD-L1 <sup>d</sup>	17 (10)
	Durvalumab	8 (5)
	Atezolizumab	9 (6)
Any previous treatment		82 (51)
Any previous immunotherapy		17 (10)
		Ipilimumab
		11 (65)
		Pembrolizumab
		1 (6)
		Ipilimumab/ nivolumab
		5 (29)

<sup>a</sup> ECOG = Eastern Cooperative Oncology Group<sup>b</sup> American Joint Committee on Cancer (AJCC) 7th edition

<sup>c</sup> Comorbidities: Patients could have been diagnosed with multiple comorbidities. Other comorbidities such as other malignancies, obesity, impaired renal function, Of seven patients the comorbidity was unknown<sup>d</sup> PD(L)1 = programmed cell death protein-(ligand)1

## Treatment duration and healthcare professional-reported AEs

At time of analysis, which was May 2021, all patients had stopped treatment. Median follow up from start of treatment was 116 weeks (interquartile range (IQR) 31-171 weeks). Overall median treatment duration was 30 weeks (IQR 10-61), which was 33 weeks for melanoma patients and 18 weeks for NSCLC patients. Most common reasons for treatment discontinuation were: progressive disease (49%), completed

treatment or confirmed response to treatment (26%) and irAEs (19%). Six percent of the patients stopped treatment for other reasons such as bleeding or infection.

CTCAE grade  $\geq 3$  (severe) irAEs occurred in 14% of the patients, and more often in patients previously treated with ICI (53%) versus 10% in patients receiving ICI for the first time;  $p < 0.001$ ). Most reported grade  $\geq 3$  irAEs were: pneumonitis (4%) and hepatitis (3%) (table 2). Twelve percent of the patients were admitted to the hospital for irAEs and systemic steroids were required for irAE management in 17% of the patients.

**Table 2.** Most common and grade 3/4 reported adverse events

Adverse event		Any grade <sup>a</sup>	Grade 3/4 <sup>a</sup>
		n (%)	
Endocrinopathies	Hypophysitis	4 (2)	
	Hypothyroidism	9 (6)	
	Hyperthyroidism	7 (4)	
	Diabetes Mellitus	2 (1)	2 (1)
Gastro-intestinal	Diarrhoea and/or colitis/ duodenitis	16 (10)	3 (2)
	Hepatitis	7 (4)	5 (3)
	Pancreatitis	2 (1)	1 (< 0.5)
	Pancreatic insufficiency	1 (< 0.5)	1 (< 0.5)
Skin	Dermatitis /rash	37 (23)	3 (2)
	Vitiligo	11 (7)	
Other	Pneumonitis	18 (11)	6 (4)
	Arthralgia/bursitis/ arthritis	16 (10)	
	Myalgia	10 (6)	
	Nasal or mucosal dryness/ dry eyes	7 (4)	
	Infusion related reaction	4 (2)	
	Nephritis	3 (2)	
	Vasculitis/arteritis	2 (1)	2 (1)

*Common Terminology Criteria of Adverse events v4.03*

## Patient-reported symptoms

Patients completed a total of 1493 USD-Is, with a median of seven (IQR 4-13) per patient. At baseline, 116 out of 162 patients (72%) completed a USD-I versus 54/64 (84%) patients on treatment in quarter 4 (figure 1).

Every USD-I item was scored present (NRS  $\geq 1$ ) at a certain time point by  $\geq 20\%$  of the patients, except for blood/mucus in stool (5-13% of patients at different time points) (figure 1).

Figure 2 shows the proportions of patients with clinically relevant USD-I scores (NRS  $\geq 3$ ) at the different time points. The top 5 clinically relevant symptoms at any time point were: inactivity (38-56%), fatigue (26-57%), pain (13-23%), cough (11-39%) and sleeping problems (11-29%).

When the different time points were compared to baseline, the prevalence of clinically relevant symptoms decreased for 13 out of 22 USD-I items. The largest decrease was found for cough (from week 12 to quarter 4, compared to baseline differences in proportions were between -18% to -28%; p-value between  $<0.001$  and 0.006) and fatigue (from week 16 to quarter 4, compared to baseline differences in proportions were between -16% and -27%; p-value between 0.003 to 0.030). Contrarily, the prevalence (NRS  $\geq 1$ ) of skin rash and itching increased during treatment. When looking at symptoms with severe intensity (NRS  $\geq 6$ ), only fatigue and inactivity were reported by  $\geq 10\%$  of the patients at least at six out of nine time points; with highest prevalence at week 4 (21% and 24% respectively).

When looking at clinically significant symptoms (NRS  $\geq 3$ ) at baseline per tumour type (Appendix B), NSCLC patients more often reported cough (63% vs 11%;  $p=<0.001$ ), shortness of breath (37% vs 4% vs;  $p=<0.001$ ) and fatigue (67% vs 38%;  $p=0.002$ ) than melanoma patients.

## Total symptom distress score and number of clinically relevant symptoms

The median total symptom distress score at baseline was 26 (IQR 10-43), which at week 12 decreased to 18 (IQR 6-32);  $p=0.007$ . At time of grade  $\geq 3$  irAE occurrence, the median total symptom distress score in the 13/23 patients (57%) who completed a USD-I (range -2 to 3 weeks) was 31 (IQR 16-58). At baseline, patients with NSCLC had a higher score than patients with melanoma; 36 (IQR 22-52) vs 17 (IQR 6-28);  $p<0.001$ .



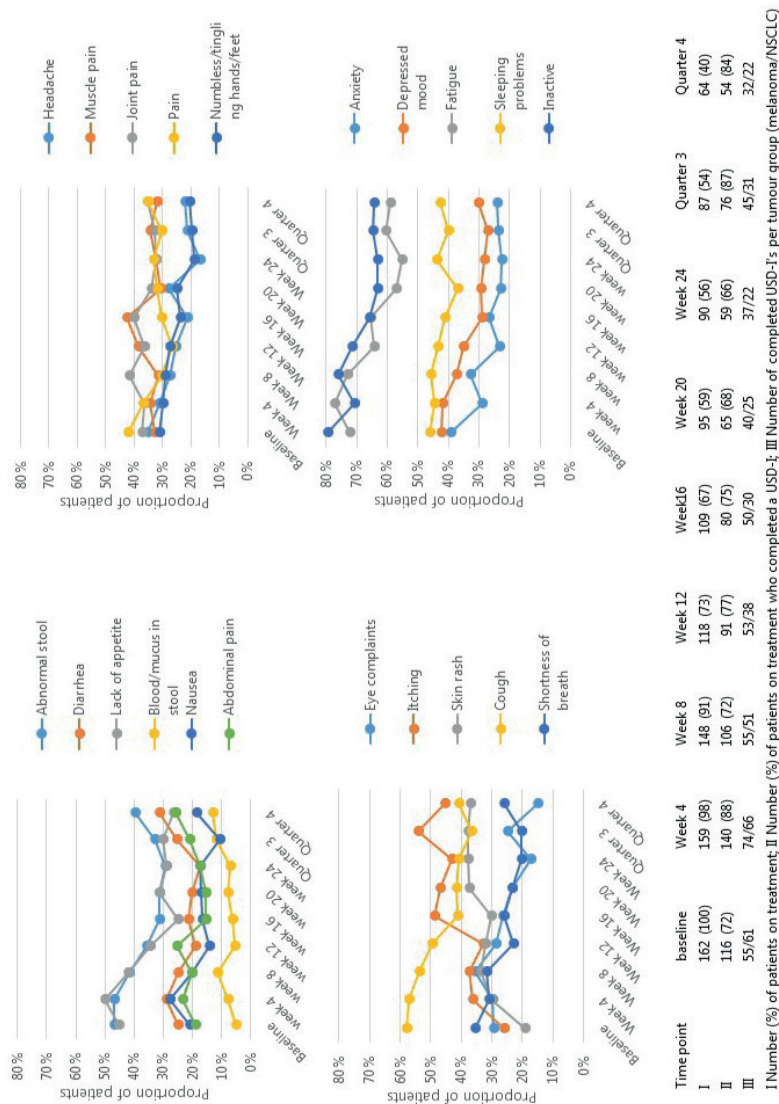


Figure 1. USD scores  $\geq 1$

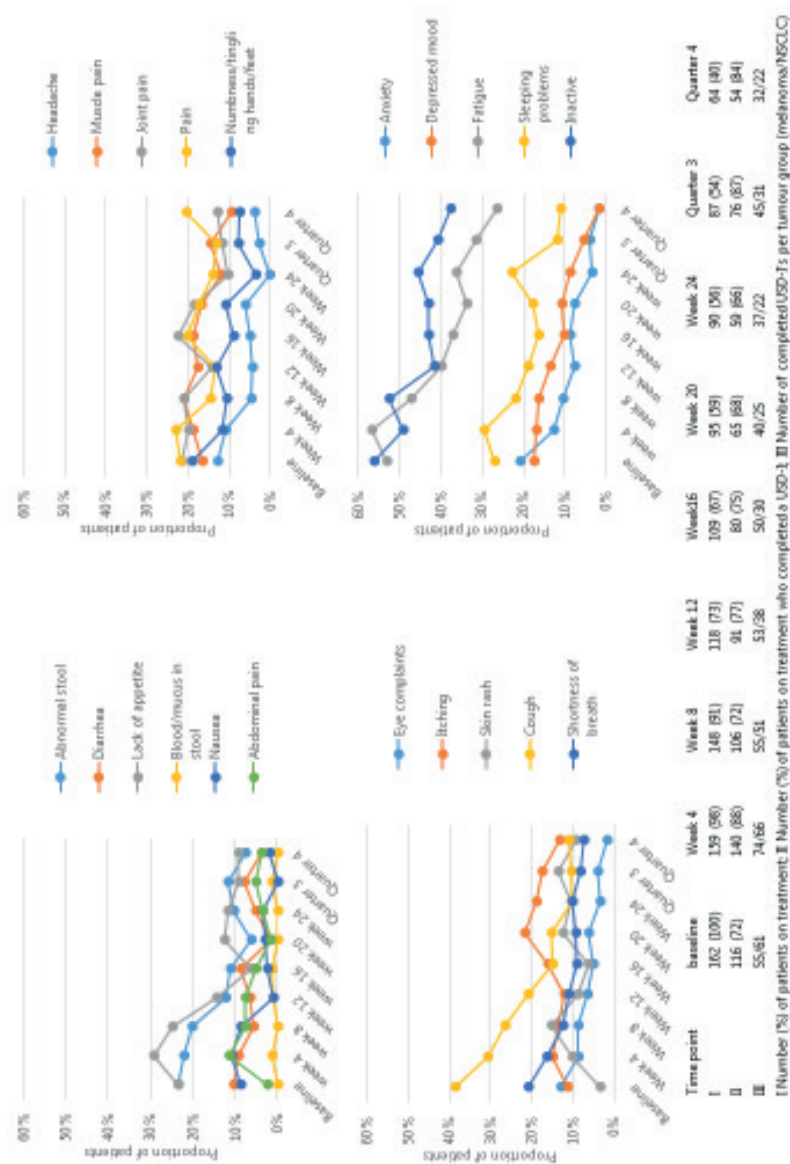


Figure 2. Clinically relevant symptoms (USD scores ≥3)

At baseline, patients reported a median of four (IQR 1-7) clinically relevant symptoms (NRS  $\geq 3$ ), which decreased to one (IQR 0-4) at quarter 3 ( $p=0.011$ ) (figure 3). At time of grade  $\geq 3$  irAE occurrence, the 13/23 patients (57%) who completed a USD-I (range -2 to 3 weeks) reported a median of five (IQR 2-9) clinically relevant symptoms. At baseline patients with NSCLC had a higher number of clinically relevant symptoms than patients with melanoma; median 5 (IQR 3-8) vs median 2 (IQR 1-4);  $p<0.001$ ).

### **Wellbeing and influence of side effects on HRQL**

At baseline, patients reported a relatively good wellbeing; NRS 2; IQR 1-4). During treatment wellbeing scores decreased to 1 or lower after 12 weeks (IQR 0-2 to 0-4), suggesting a slight improvement in wellbeing. Over time, there was a moderate to strong correlation between the number of symptoms NRS  $\geq 3$  and a poor wellbeing with correlation coefficients ( $\rho$ ) ranging from 0.622 to 0.835.

The item influence of side effects on HRQL was the only USD-I item which was missing in  $\geq 10\%$  of cases from week 20 through quarter 3. During treatment patients consistently reported a low influence of side effects on HRQL, median 0 or 1 (IQR 0-1 or 0-2) (figure 3). During treatment, we found moderate positive correlations of influence of side effects on HRQL and total symptom distress score ( $\rho$  varying from 0.713 at week 4 to 0.559 at quarter 4).

### **Added USD-I items and symptoms given priority for support**

From week 4 to quarter 4 oral complaints such as taste alteration, dry mouth, painful tongue, increased dental plaques were added by one to three patients per time point. Patients most often assigned priority to pain (baseline:  $n=5$ ); fatigue (week 4:  $n=5$ ) and muscle pain and/or joint pain (week 16:  $n=4$ ).

## **Discussion**

Our study is one of the first describing patient-reported symptoms during treatment with PD(L)1-inhibitors by using a brief, ICI-tailored PROM in daily clinical oncology practice. The top 5 clinically relevant symptoms reported by patients were: inactivity, fatigue, pain, cough and sleeping problems. When compared to baseline the prevalence and number of clinically significant symptoms decreased, wellbeing slightly increased and patients generally reported a low influence of side effects on HRQL.

Although at baseline most patients had an ECOG PS 0-1, they reported a median of four symptoms that caused relevant symptom burden. The number of symptoms with a NRS  $\geq 3$  correlated with a decreased wellbeing and relevant influence of side effects on HRQL. During the first three months of treatment, the prevalence of clinically relevant abnormal stool, cough, shortness of breath, anxiety, inactivity and fatigue decreased with at least 10%. From week 20 the prevalence of itching and skin rash increased with at least 10%. These data suggest that during ICI treatment patient experienced symptom burden changes from more cancer-related to treatment-related. Although this change could be explained by response to treatment, it is likely also partially explained by the gradual selection of patients with a favourable disease course<sup>6,26</sup>. Since a USD-I is offered before treatment administration, only symptom burden in patients remaining on treatment is shown, excluding patients with progressive disease or treatment discontinuation due to severe irAEs. The decrease of symptom prevalence and symptom intensity as well as increase of wellbeing within three months of treatment are in contrast with findings in our previous studies on patient-reported symptoms during targeted therapy. In these studies, symptom prevalence increased and wellbeing decreased during treatment<sup>27,28</sup>. The increase in wellbeing during treatment in our current study might be explained by the less frequent and relatively late occurrence of irAEs as a result of immunotherapy compared to targeted therapy as well as by more durable responses. Our data endorse the findings of Tykodi et al. and Nishijima et. al who showed that ICI treated patients across tumour types maintained HRQL or even experienced HRQL-improvement, which is in contrast with the HRQL deterioration observed in other anticancer therapies<sup>6,26</sup>.

In this analysis we focused on anti-PD(L)1 monotherapy treated patients. In the last few years combination treatments of anti-PD1 plus anti-CTLA4 and anti-PD1 plus chemotherapy have progressively been applied in melanoma and NSCLC<sup>29-31</sup>. Since treatment-related symptoms more often occur during these combinational treatments, separate analysis in patients receiving these treatments are of interest.

This study shows the potential value of a tailored PROM during ICI treatment. Since the ICI-specific items - except blood/mucus in stool - occur in a relevant number of patients, we consider the addition of these items as relevant, making the USD-I a tailored PROM for assessing and monitoring treatment and cancer-related symptoms during ICI. Since oral complaints (e.g. dry mouth) were spontaneously reported by patients and dry mouth has shown very good validity in the USD validation study<sup>17</sup> we will add this item to the USD-I.

The use of the brief USD-I in clinical practice can contribute to shared decision making by early detection and monitoring of symptoms and their impact over time. As shown by others, the standard use of patient-reported outcomes in clinical practice increases the frequency and depth of discussion of symptoms and is associated with improved symptom control as well as increased patient satisfaction<sup>32</sup>. Discussing the USD-I scores with the patient may have increased insight into the subjective intensity from the patients' perspective, adding valuable information to healthcare professional-assessed AE grading only<sup>26</sup>.

One of the strengths of our study is the good completion rate of 66% to 88% USD-Is per time point in this real world study. The incompleteness of PROM data has been identified as a challenge by others.<sup>6,26</sup> In comparison, questionnaire completion rates in controlled clinical trials with ICI, ranged from 50% to 87%.<sup>6</sup> Compliance could potentially be further increased by an improved electronic data collection instead of using paper questionnaires as suggested by Tykodi et al.<sup>6</sup>. Moreover, training patients and healthcare professionals about the (e)PROM could optimize usage<sup>33,34</sup>.

Our study has some limitations. First of all, we are aware that the differences we observe should be interpreted with some caution because of the number of statistical tests in relation to our group size. Little is known about patient-reported symptoms and their burden during treatment with ICI in daily clinical practice. Therefore we chose a hypothesis-generating approach and to not correct for multiple testing. Secondly, USD-I outcomes were only collected from patients who were on treatment and may primarily be a representation of a 'middle' group of patients, because most common reasons not to complete a USD-I, were no or unchanged symptom burden and clinical deterioration. Furthermore, although the USD is a validated PROM<sup>17</sup>, a validation study for the extra items related to immunotherapy on the USD-I still needs to be performed. The same accounts for the time frame since the USD asks about symptom intensity at that moment ('now') whilst the treatment specific USD-I interrogates symptom burden over the last (treatment) period of time (since the last time the patient visited the outpatient clinic).

In conclusion, these data illustrate that immunotherapy is generally well tolerated. Although patients consistently report a low influence of side effects on HRQL, healthcare professionals should be aware that the number of symptoms with a NRS  $\geq 3$  experienced at the same time can decrease patients wellbeing. Using an ICI-tailored PROM in daily clinical practice could create a window to discuss symptoms and their impact in a structured way and improve personalized care during treatment.

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## Appendix A: Utrecht Symptom Diary (USD)

### **IMMUNOTHERAPY**

Date     .... / ..... / .....

#### **Instruction**

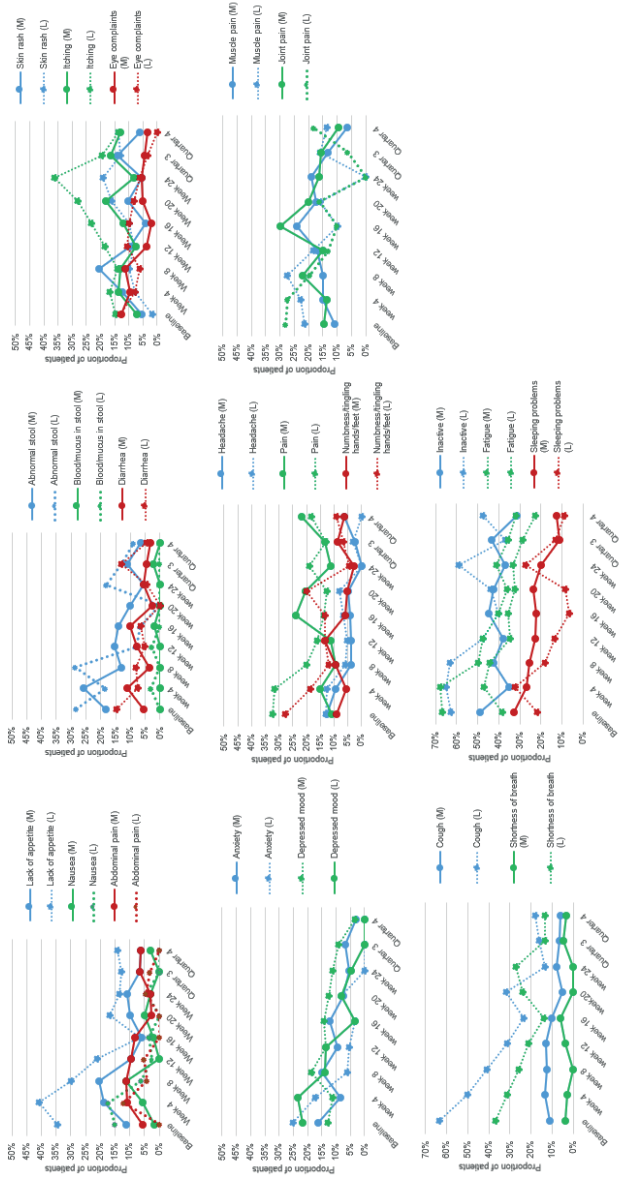
We would like to know how you feel and which symptoms you experience. We therefore ask you to complete this questionnaire before visiting the outpatient clinic. During your consultation this questionnaire will be discussed.

Please, circle the number that best describes how much burden you have had: 0 = absence of the symptom or feeling and 10 = the worst possible situation for you either continued presence of the symptom or feeling

If you have suffered from symptoms/ feelings that are not listed, please indicate them in the extra lines.

I have/felt/been (since last time requested)												
no nausea	0	1	2	3	4	5	6	7	8	9	10	worst possible nausea
no lack of appetite	0	1	2	3	4	5	6	7	8	9	10	worst possible lack of appetite
no abnormal stool	0	1	2	3	4	5	6	7	8	9	10	worst possible abnormal stool
no diarrhoea	0	1	2	3	4	5	6	7	8	9	10	worst possible diarrhoea
no blood/mucus in stool	0	1	2	3	4	5	6	7	8	9	10	worst possible blood/ mucus in stool
no abdominal pain	0	1	2	3	4	5	6	7	8	9	10	worst possible abdominal pain
no cough	0	1	2	3	4	5	6	7	8	9	10	worst possible cough
no shortness of breath	0	1	2	3	4	5	6	7	8	9	10	worst possible shortness of breath
no eye complaints	0	1	2	3	4	5	6	7	8	9	10	worst possible eye complaints
no skin rash	0	1	2	3	4	5	6	7	8	9	10	worst possible skin rash
no itching	0	1	2	3	4	5	6	7	8	9	10	worst possible itching
no headache	0	1	2	3	4	5	6	7	8	9	10	worst possible headache
no muscle pain	0	1	2	3	4	5	6	7	8	9	10	worst possible muscle pain
no joint pain	0	1	2	3	4	5	6	7	8	9	10	worst possible joint pain
no numbness/tingling in arms/legs	0	1	2	3	4	5	6	7	8	9	10	worst possible numbness/ tingling in arms/legs
no pain	0	1	2	3	4	5	6	7	8	9	10	worst possible pain
no sleeping problems	0	1	2	3	4	5	6	7	8	9	10	worst possible sleeping problems
no depressed mood	0	1	2	3	4	5	6	7	8	9	10	worst possible depressed mood
no anxiety	0	1	2	3	4	5	6	7	8	9	10	worst possible anxiety
no fatigue	0	1	2	3	4	5	6	7	8	9	10	worst possible fatigue
not inactive	0	1	2	3	4	5	6	7	8	9	10	worst possible inactive
no unwell-being	0	1	2	3	4	5	6	7	8	9	10	worst possible unwell-being
<b>Other symptom(s)</b>												
.....	0	1	2	3	4	5	6	7	8	9	10	.....
.....	0	1	2	3	4	5	6	7	8	9	10	.....
<b>To what extent your health related quality of life is affected by side effects?</b>												
not affected at all	0	1	2	3	4	5	6	7	8	9	10	worst possible affected
<b>Which symptom bothers you the most and is your priority for support?</b>												

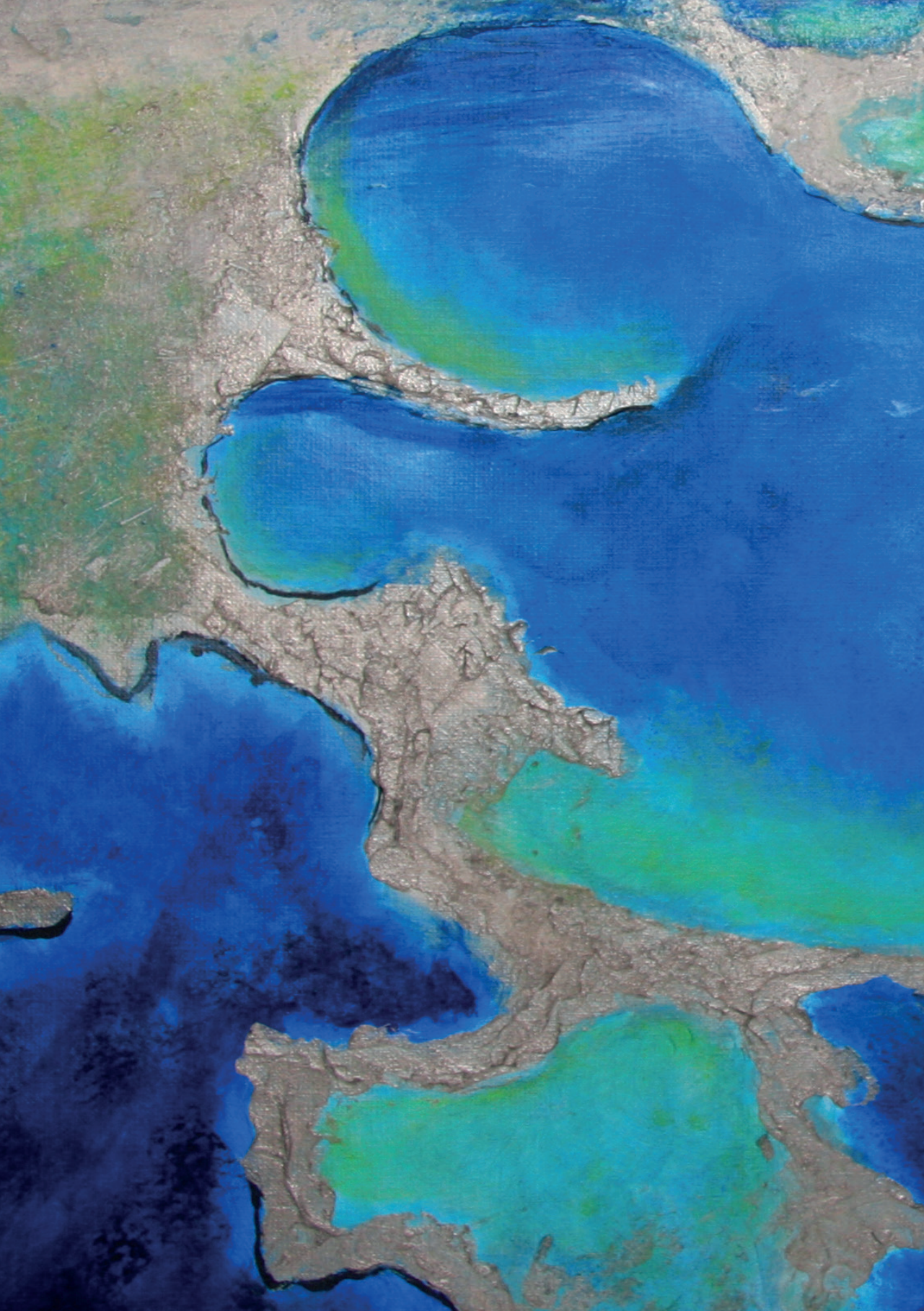
Supplement B: USD scores per tumour type



Time point	baseline	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Quarter 3	Quarter 4
I	162 (100)	159 (98)	148 (91)	118 (73)	109 (67)	95 (59)	90 (56)	87 (54)	64 (40)
II	116 (72)	140 (88)	106 (72)	91 (77)	80 (75)	65 (68)	59 (66)	76 (87)	54 (84)
III	55/61	74/66	55/51	53/38	50/30	40/25	37/22	45/31	32/22

I Number (%) of patients on treatment; II Number (%) of patients on treatment who completed a USD-I; III Number of completed USD-I's per tumour group (melanoma/NSCLC)





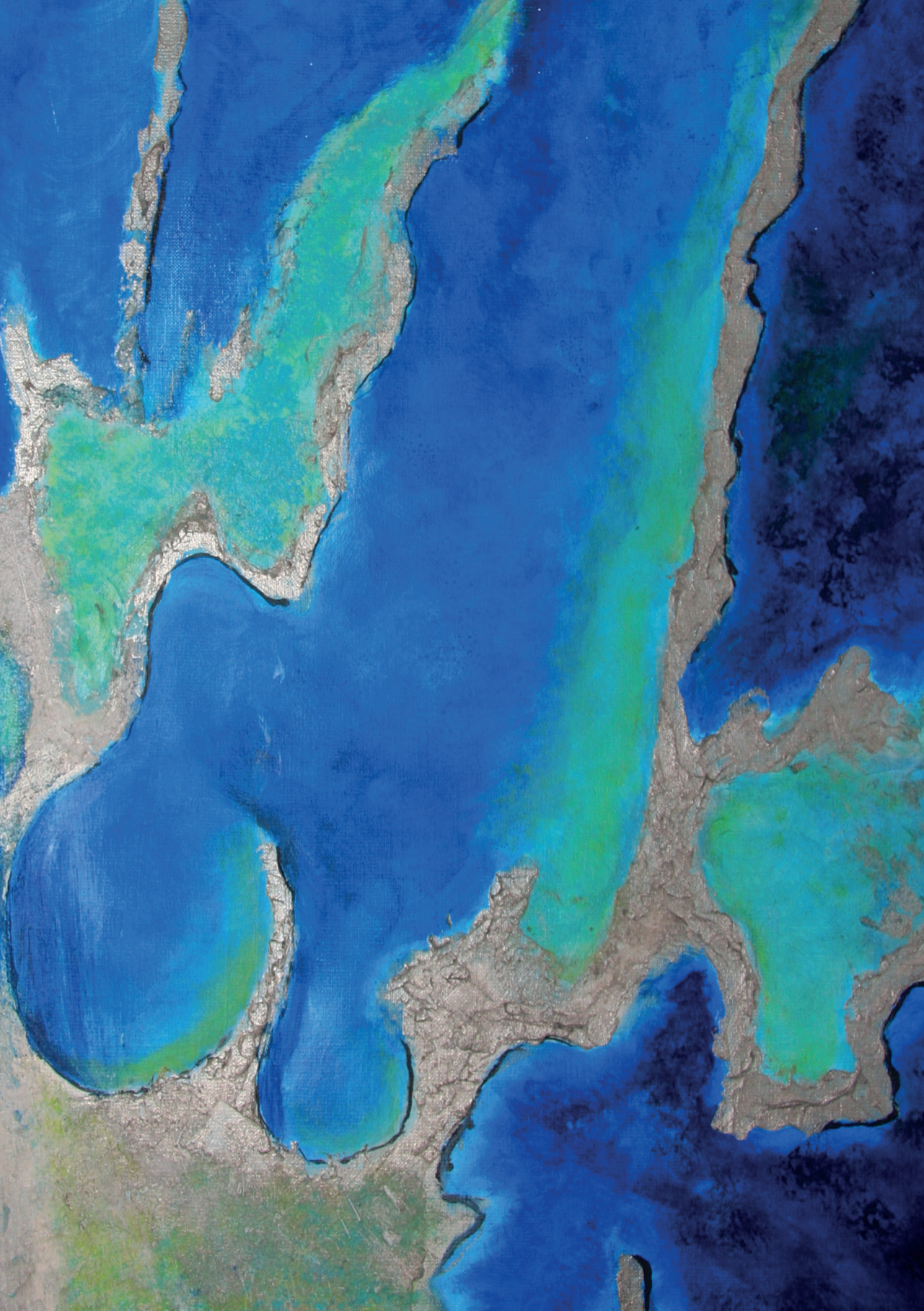


An aerial photograph of a coral reef system. A large, irregularly shaped lagoon with turquoise and light green water is the central feature. It is surrounded by a dark, textured reef edge. Beyond the reef, the water transitions into a deep, dark blue color. The overall shape of the reef and lagoon is somewhat elongated and jagged.

# **PART 3**

## **General discussion**





## Chapter 7

### General Discussion

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Patients with cancer experience disease and/or treatment related signs and symptoms that impact health related quality of life and daily functioning. To tailor supportive care, assessment and monitoring of symptoms through the use of patient-reported outcome measurement (PROM) tools is recommended<sup>1</sup>.

In the first part of this thesis we assessed the validity of the PROM the Utrecht Symptom Diary (USD) in a broad group of patients with cancer and the validity of an expanded USD in the specific setting of outpatient treatment. The second part of the thesis describes patient-reported symptoms, measured with the USD, in different patient groups and various settings with a focus on patients with cancer undergoing treatment with targeted therapy or immunotherapy.

## **Part 1: Validation of the Utrecht Symptom Diary**

The Utrecht Symptom Diary (USD) is a Dutch translated and adapted version of the Edmonton Symptom Assessment System (ESAS)<sup>2,3</sup>. It was developed in our research group in 2003 to assess and monitor symptoms and overall well-being from patients' perspectives in order to tailor supportive care and for daily management of multidimensional symptoms across the entire continuum of cancer<sup>4,5</sup>.

To enhance personalized cancer care, we additionally developed treatment specific USD modules: such as the Outpatient USD and the USD-Immunotherapy. Initially, a pragmatic approach was used. Items were included when - based on clinical studies - they occurred in  $\geq 10\%$  of the patients or were reported as grade  $\geq 3$  adverse events (AEs) with the Common Terminology Criteria for AEs (CTCAE)<sup>6</sup>. Additionally, items were judged by experts. Subsequently developed USD modules - such as the tumor specific USD glioma module developed by IJzerman et al.<sup>7,8</sup> - also included patient participation and structured (pre)testing and evaluation.

Since 2015, the USD modules have been part of the hospital electronic medical files (EMF) and the patient portal of the EMF. This enabled extracting USD data from the electronic medical files together with patient, disease and treatment specific data for research purposes.

We showed that the USD is a valid 12-item PROM for the most prevalent physical and mental symptoms in a broad group of cancer patients. We demonstrated its content, criterion, and construct validity and ability to detect clinically important changes over time, in both curative and palliative phase.



An additional modified USD module was developed for outpatients receiving intravenous chemotherapy with curative or palliative intent. In 2015 frequently occurring symptoms in patients on intravenous targeted therapy were added, leading to the Outpatient USD for patients receiving intravenous chemotherapy and/or targeted therapy. This Outpatient USD also showed to be a comprehensive, relevant, and valid PROM that measures the most prevalent symptoms that affect cancer patients treated with intravenous chemotherapy and/or targeted therapy - with curative and palliative intent - in an outpatient setting. Content validity was shown for all added items on the outpatient USD. Criterion validation was confirmed with the Distress Thermometer & Problem Checklist (DT&PC) as reference standard for all added items of the outpatient USD – except for oral pain. However, with an additional analysis we found that the item oral pain in combination with the item dry mouth (both on the outpatient USD) are able to detect the mouth problems on the reference standard. Although we confirmed content validity on the item on ‘eye changes’ we could not test the hypothesis for the construct validity due to the low number of paired outpatient USDs of patients using trastuzumab, cetuximab and/or panitumumab.

## Part 2: Use of the Utrecht Symptom Diary

We showed that the use of treatment specific symptom diary modules, can add insight into prevalence and severity of symptoms as graded by healthcare professional reported AEs. Especially in patients on targeted therapy, AEs caused dose modifications in a substantial number of patients and patients experienced a decreased well-being during treatment. Symptom severity as graded with the CTCAE does not reflect symptom intensity experienced by patients, as measured with the USD.

This difference is best explained using an example of patients experiencing diarrhoea in our daily practice. In the CTCAE an increase of <4 stools per day over baseline is objectified as a grade 1 diarrhoea<sup>6</sup>. Patients treated with an angiogenic inhibitor regularly reported diarrhoea two times a day. Although according to the CTCAE this is considered a grade 1 AE, some patients scored that item with a USD score  $\geq 6$ , particularly due to the unpredictability of the occurrence of diarrhoea. As a result, a patient was limited in his work as a salesman and another patient no longer dared to go to the theatre, indicating a significant interference with daily life (social dimension). Especially when treatment is successful and will potentially be continued for years, insight into experienced symptom burden of continued

unpredictable 'mild' AEs is warranted since also mild AEs can heavily impact daily functioning and health related quality of life (HRQL).

When analyzing symptom burden during immunotherapy using the USD Immunotherapy we found that patients with melanoma and non-small cell lung cancer undergoing treatment with immune checkpoint inhibition (ICI) with PD(L)-1 inhibitors tolerated treatment generally well. When compared to baseline, well-being increased in patients remaining on ICI-treatment. However, we also showed that an increase of symptoms with a USD score  $\geq 3$  was associated with poor well-being.

So, using the USD in daily clinical practice could create a window to discuss symptoms and their impact on HRQL in a structured way and consequently improve personalized care during treatment. Since patients score the USD items on a NRS from zero-to-ten, monitoring of symptoms and their fluctuations over time is possible. Discussing symptom scores can give insight into a personal symptom goal which can differ per symptom and per patient<sup>9</sup> and per stage of disease<sup>10</sup> and consequently helps in providing personalized supportive care<sup>10,11</sup>. To determine a patient's personalized symptom goal healthcare professionals could ask patients "At what level would you feel comfortable with this symptom?" as suggested by Hui et al.<sup>11</sup>. We therefore ask "what symptom should be prioritized for you?". With this approach, proactive patient involvement in decision making regarding symptom management may also be promoted. Additionally, in collaboration with the patient, symptom scores can give insight into the effect of symptom management strategies employed<sup>11</sup>.

## Opportunities and obstacles

Our data collected in daily practice add to available literature, since most clinical trials have narrow eligibility criteria<sup>12</sup>. As a result, patients with comorbidity, a decreased performance status and older age are less well represented in trials, leading to reduced generalizability of outcomes such as symptom prevalence<sup>13,14</sup>. Insight into symptom prevalence and symptom intensity directly derived from patients in daily oncology practice can contribute to fill this gap since - although no primary endpoint of our studies - we observed that various symptoms were more often reported by patients than by healthcare professionals.

Historically, PROMs are not part of the EMF such as laboratory values<sup>15</sup>. Preferably they should be integrated in the EMF as these are the only data collected directly from the patient<sup>15</sup>. Use of PROMs in daily clinical practice has shown to be feasible<sup>15</sup>, also in older patients and patients with low levels of health literacy<sup>16,17</sup>, and may

advance research that directly benefits the patient. Although we were able to extract data from the EMF we also recognized limitations of the current EMF system available. To promote the role of electronic (e)PROMs in shared decision making, an integrated, dynamic EMF system is required in which the patient portal is equipped and tailored to patient preferences<sup>16</sup> and enables completing PROMs linked to hospital appointments or in between hospital visits. An EMF that generates alerts to nurses or doctors for follow up in case of high symptoms scores<sup>18</sup> and makes PRO-data real-time available to clinicians could directly improve patient care<sup>16,19</sup>.

Another obstacle might be the attitudes of healthcare professionals towards the standardized symptom assessment by using PROMs<sup>20–22</sup>. In the described studies in this thesis the USD most commonly was offered by nurses and symptom scores were discussed with the patient by oncology nurses. The same pattern was found through the use of the ESAS<sup>20</sup>. Although nurses and doctors both considered the use of the ESAS as best practice, doctors reported lower use of the ESAS, looked less often at patients' symptom scores and reported less frequently that use of the ESAS improved the efficiency of the meeting with the patient. As reasons for not offering the ESAS, the researchers speculated that doctors do not experience symptom screening and assessment as part of their roles, and believe that reviewing the ESAS scores is time-consuming<sup>22</sup>. However, although symptoms are more frequently discussed when using PROMs, the duration of the consultation does not increase<sup>23</sup>. Structured use of PROMs is recommended in the professional profile of nurse practitioners<sup>24</sup> as well as by the European Society for Medical Oncology (ESMO)<sup>25</sup>. The ESMO suggests a training program for doctors on this topic, since they consider symptom care an integral and essential part of personalized supportive cancer care.

Sztankay et al<sup>26</sup> studied the educational needs of healthcare professionals concerning use of PROMs in clinical practice. The researchers recommend an e-learning containing basic information, implementation of PROMs in clinical routine, interpretation of PROMs and integration of PROMs into the communication with patients. Based on this paper we developed a USD e-learning which will be launched shortly.

## Limitations

A few limitations of the studies in this thesis are worth mentioning. First, we used routine clinical data which resulted in available data of the USD treatment specific modules only when offered and completed. This may have induced selection bias for several clinical and practical reasons.



Before 2015 USD data were particularly used to tailor supportive care and not added into a database systematically, which may have led to lower completion rates of the USD (Chapter 3). The completion rate of USDs increased when the USD became part of the EMF, since 80% of the patients treated with ICI completed at least two USDs (chapter 5). For the Outpatient USD we showed that 95% of the patients completed at least once a USD and 77% of the patients completed at least two USDs during treatment with intravenous chemotherapy and/or targeted therapy.

From daily practice we know that patients feeling too sick less frequently complete a USD. The same accounts for patients on long-term treatment and patients without (change of) symptom burden. Although nurses noted their stable symptom scores as reason for not completing the USD in the EMF, we decided not to impute the USD scores by 'last observation carried forward', because we could not assume with certainty, that patients would have scored the USD items exactly the same as the last time. Since apart from educating healthcare professionals, training of patients could also increase use of PROMS<sup>16</sup>, a short animated patient video about the USD has being developed.

In this thesis we focused on the validation of the USD and described patient-reported symptoms measured using of the USD in different patients groups. The added value of the use of PROMs has been investigated by others. Graupner et al<sup>27</sup> conducted a systematic review to assess the effectiveness of routine use of PROMs in daily oncology practice. The authors mainly found positive (or no effect) of the use of PROMs in terms of patient outcomes (such as survival, HRQL), patient satisfaction and process indicators (such as patient-doctor communication and fewer emergency visits and hospital admissions). In terms of symptom control they found more positive effects when feedback about symptom scores and/or treatment advice based on the results was provided to patients and/or healthcare professionals.

Basch et al<sup>28</sup> performed a randomized clinical trial in 1191 patients with metastatic cancer to assess whether electronic symptom monitoring during anticancer treatment would improve quality of life outcomes. Patients were randomized into two groups: usual care versus weekly assessment of symptoms electronically using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30). After completion alerts were send to nurses. Responses to the alerts by nurses or oncologists were not dictated by the study. When compared to baseline at three months, physical function, symptom control and HRQL significantly improved in patients in the symptom monitoring arm. Better symptom control was also found in the randomized control trial by Dai et al.<sup>29</sup>.

They concluded that in the first four weeks after lung cancer surgery patients who received PROM-based symptom management reported lower symptom burden than patients receiving usual care.

Since some patients hesitate to contact healthcare professionals for symptoms outside their planned hospital visits Mooney et al.<sup>18</sup> performed a randomized controlled trial in 358 outpatients receiving chemotherapy. Patients were randomized between a usual care arm and a study arm in which patients reported presence and severity of 11 symptoms on a daily basis. The system provided self-care management messages based on evidence-based guidelines to patients and generated alerts to a nurse for follow up when indicated. They found a significant decrease in symptom burden in the intervention group. Considering the fact that they did not find a decreased symptom burden in their previous comparable study<sup>18</sup> without alerts, the authors suggest that besides symptom monitoring, structural interventions based on reported symptoms are needed to decrease symptom burden.

Nipp et al<sup>30</sup> investigated the effect of systemic symptom monitoring on symptom burden and health care use among hospitalized patients with advanced cancer. In their study, 390 inpatients were randomized into an intervention group and usual care group. Both groups reported their symptoms using the ESAS on a daily basis. Patients assigned to the intervention arm had their symptom reports displayed to their healthcare professionals during daily oncology rounds, with alerts for moderate, severe, or worsening symptoms. Patients assigned to usual care did not have their symptom reports displayed to the clinicians. Symptom monitoring with or without alerts did not have a significant effect on patients' symptom burden or length of hospitalization. The authors conclude that these findings do not support routine symptom monitoring in hospitalized patients on a daily basis possibly because hospitalized patients more likely receive more symptom-directed interventions than outpatients. However, the authors also conclude that since patients in the usual care group also scored their symptoms each day, they may have reported their symptoms more often to their healthcare professionals than they would have done without the ESAS and secondly it remained unclear how often clinicians developed a plan to address patients' symptoms<sup>30</sup>.

### **Future perspectives and research**

A USD database of symptom prevalence and symptom burden enables developing a dashboard that displays a symptom top 5 per department and/or per tumour type. Based on these real world patient experiences an ongoing learning system for oncology professionals can be developed to further improve symptom care and cancer care<sup>15</sup>.

On a patient level a personalized dashboard – developed in collaboration with patients - could help patients to adapt and self-manage symptoms and their impact on the several dimensions of life. This collaboration may also lead to the development of specific USD modules initiated by patients and thereby to a next step in shared decision making in symptom management. Insights gained through the USD and its dashboard could also be used in patient information about the disease, its treatment and disease and/or treatment related symptoms.

If the USD would be included in the EMF of all hospitals, standard use is made possible for many patients and their healthcare teams. This would enable building a nationwide symptom database, contributing to further improvement of personalized supportive care of patients with cancer.

Currently, a USD to measure late effects in adolescent and young adult (AYA) patients with testicular germ cell tumour who are in follow up after chemotherapy is being developed. Items are not only generated on the basis of trials but also on the basis of input from patients. Data from this tailored USD could improve supportive care in this specific group in the future<sup>31</sup>.

Moreover patients with melanoma can experience persistent symptoms long after discontinuation of successful ICI-treatment<sup>32,33</sup>. The USD Immunotherapy is offered to these patients as per standard of care to get insight into the prevalence and intensity of symptoms in this setting.

## **Final conclusions**

The studies described in this thesis show the validity of the Utrecht Symptom Diary (USD) and patients' physical and mental symptoms reported through the use of the USD as part of personalized, supportive care in daily oncology practice. Use of the USD gives insight into symptoms and their burden from patients' perspectives and can contribute in the challenge of optimizing health related quality of life by providing tailored symptom care.

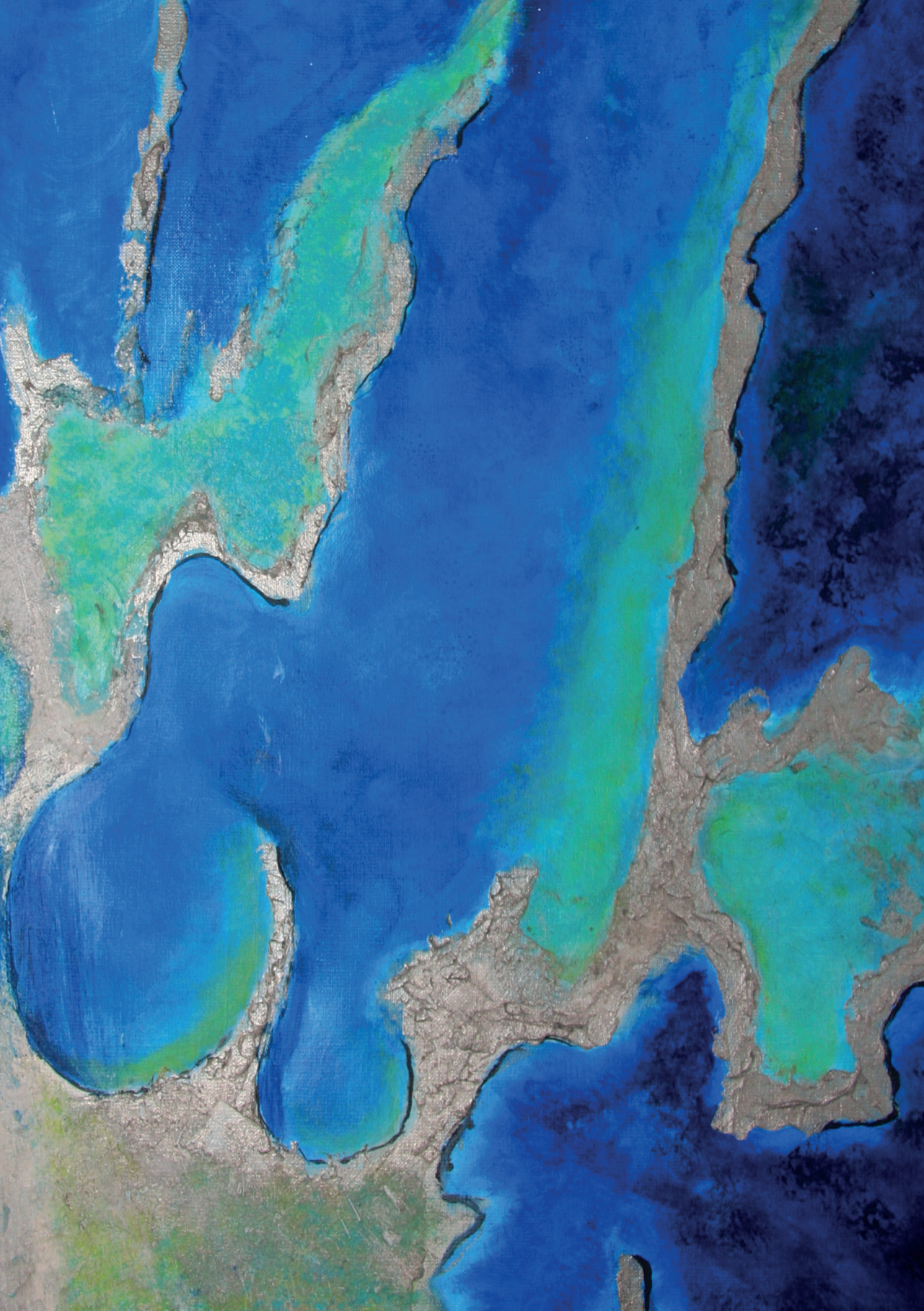
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Summaries

Summary

Samenvatting

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## Summary

The number of patients diagnosed with cancer increases. At the same time cancer patients live longer due to earlier diagnosis and more effective therapies. During the course of their disease, patients experience many disease and/or treatment-related symptoms that impact health-related quality of life and daily functioning. Symptoms and their impact can be overlooked and/or underestimated by healthcare professionals. If symptoms remain under-recognized, physical, mental, existential and social functioning is affected and opportunities for diagnosis and management of symptoms may be missed. Patient-reported outcome measurement tools (PROMs) can be used to assess and monitor symptoms and symptom burden.

### The Utrecht Symptom Diary

The Utrecht Symptom Diary is a Dutch translation and modified version of the Edmonton Symptom Assessment System (ESAS) which is a worldwide frequently used and validated PROM in cancer patients. In 2003, the USD was developed for daily assessment and monitoring of symptoms of cancer and/or treatment-related physical and mental symptoms. It contains a total of 12 items – lack of appetite, nausea, abnormal stool, dysphagia, dry mouth, pain, sleeping problems, shortness of breath, fatigue, anxiety, depressed mood and overall well-being. Symptoms are scored on a zero-to-ten numeric rating scale (NRS), with higher values indicating increasing intensity. Moreover, patients are invited to add symptoms they experience and are not listed on the USD and are asked to prioritize symptoms which need attention in the patient-doctor-nurse conversation first from their personal perspective. Since 2007 treatment and disease specific modules of the USD have been developed. From 2015 the USD became part of the hospital electronic medical files.

Over the last years the USD has been implemented in daily practice in other departments of the UMC Utrecht as well as in other (university)hospitals, general practices and hospices in the Netherlands. Moreover, use of the USD is recommended by the Netherlands Quality Framework for Palliative Care.

This thesis describes the validation of the USD and patient-reported symptoms through the use of the USD in different patient groups and settings.

### Validation of the Utrecht Symptom Diary

In **Chapter 2** the validity and responsiveness of the USD as well as the cut-off points to determine the clinical significance of a symptom score are described. Patients who completed at least one USD as part of routine care were included in this observational



longitudinal cohort study. A total of 3913 unique patients with (advanced) cancer completed over 22.400 USDs. Content, criterion and construct validity of all measured items was found, including the four USD items that were added to the items of the original ESAS. The USD was found to be able to detect clinically important changes over time and suitable for in-and outpatients, patients with curable disease as well as patients through the whole continuum of palliative care.

**Chapter 3** describes an observational longitudinal cohort study which assessed the validity of the Outpatient USD module developed for intravenous chemotherapy and/or targeted therapy. 1733 patients were included for analysis. Content validity was shown in terms of relevance, since all items were positive scored in  $\geq 10\%$  of the patients, and in terms of comprehensiveness, as no additional symptoms were identified from the open responses. Criterion validation was confirmed with the DT&PC as reference standard for all added items of the outpatient USD – except for oral pain. However, with an additional analysis we found that the item oral pain in combination with the item dry mouth (both on the outpatient USD) are able to detect the mouth problems on the reference standard. Construct validity was confirmed for the items skin problems, hair changes and nail problems. For eye problems we had insufficient numbers of paired USDs to assess construct validity.

In conclusion, we showed that the USD OC is a comprehensive, relevant, and valid PROM for outpatients treated with intravenous chemotherapy and/or targeted therapy. Further research is needed to investigate the construct validity of the item eye problems in this population.

### Use of the Utrecht Symptom Diary

**Chapter 4** describes healthcare professional reported adverse events (AEs) and patient-reported symptoms in patients treated with intravenous epidermal growth factor inhibitors (EGFRi). In this retrospective, observational cohort study 87 patients with squamous cell carcinoma of head and neck or metastatic colorectal carcinoma were included. Patients with head and neck cancer received cetuximab in combination with radiation therapy. Patients reported symptom prevalence and intensity by completing a treatment specific USD module developed for outpatients receiving intravenous chemotherapy and/or targeted therapy. A dose modification due to treatment-related AEs occurred in 40% of the patients, mostly due to skin toxicity. The top 5 of clinically relevant symptoms (USD score  $\geq 3$ ) during treatment were: skin changes, oral pain, lack of appetite, sleeping problems and fatigue. Unwell-being (USD score  $\geq 3$ ) was reported by 22-63% at any time during treatment.

We concluded that EGFRi cause AEs that lead to dose modifications in a substantial number of patients. Patients experienced symptoms with moderate to severe intensity and a decreasing well-being during treatment.

**Chapter 5** outlines a substudy conducted within a multicentre pharmacokinetic (PK)-guided clinical trial with the angiogenic inhibitor sunitinib. In this trial patients for whom sunitinib was considered standard therapy or patients with advanced/metastatic tumours for whom no standard therapy was available were included. Healthcare professional reported adverse events (AEs) were described. Patients reported symptoms and unwell-being using the treatment specific USD module sunitinib.

A total of 29 patients were included. Over 50% of the patients experienced a decreased well-being, associated with symptoms of mild (USD score 1-2) and moderate (USD score 3-5) intensity. Compared to healthcare professionals, lack of appetite, oral changes, dry skin, sleeping problems and shortness of breath were reported consequently more often (difference in proportion  $\geq 20\%$ ) by patients. We concluded that in a clinical trial assessing patient-reported symptom burden can add information to healthcare professional graded AEs.

**Chapter 6** reports on patient-reported outcomes during immune checkpoint inhibition (ICI).

162 patients with melanoma or non-small cell lung carcinoma were included in this observational study. The most patient-reported, clinically relevant (NRS $\geq 3$ ) symptoms during treatment were lack of appetite, arthralgia, cough, fatigue, inactivity, myalgia and sleeping problems. Symptom prevalence decreased during treatment. A higher number of clinically relevant symptoms (USD  $\geq 3$ ) correlated with poorer wellbeing. Our data illustrated that ICI-treatment is generally well tolerated. However, especially the number of clinically relevant symptoms can impact patients wellbeing.

## Final conclusions

The studies described in this thesis show the validity of the USD on content, criterion and construct level. In collaboration with the patient, the use of the USD gave insight into symptoms and their impact on quality of life. This insight is essential to provide personalized, supportive care during treatment with targeted therapies and immunotherapy in daily oncology practice.

## Samenvatting

Het aantal patiënten met de diagnose kanker neemt toe. Tegelijkertijd leven patiënten langer doordat de diagnose in een vroeg stadium wordt gesteld en door effectievere behandelingen. In de loop van hun ziekte ervaren patiënten symptomen - ziekte- en/of behandelinggerelateerd - die van invloed zijn op de kwaliteit van leven en het dagelijks functioneren. Symptomen en hun invloed op kwaliteit van leven verschillen van patiënt tot patiënt. Veel onderzoek gaat over symptomen zoals ze door zorgverleners zijn vastgelegd. Symptomen en (on)welbevinden direct gerapporteerd door patiënten zelf wordt beschouwd als de meest betrouwbare indicator van de aanwezigheid en intensiteit van symptomen. Meetinstrumenten waarmee symptomen door patiënten zelf worden gerapporteerd worden ook wel *patient-reported outcome measurement (PROM)* instrumenten genoemd. Dit proefschrift beschrijft de validatie van het Utrecht Symptoom Dagboek (USD), een Nederlandse *PROM*, en geeft inzicht in symptomen en de ervaren last daarvan bij patiënten die behandeld worden met doelgerichte therapie en immunotherapie.

### Impact van symptomen

Patiënten die behandeld worden met medicijnen tegen kanker en hierdoor genezen (curatie), ervaren symptomen die hun kwaliteit van leven negatief kunnen beïnvloeden jaren na het voltooien van de behandeling. Tijdens de palliatieve fase - een fase is die maanden tot jaren kan duren waarbij genezing niet langer mogelijk is - vragen aanhoudende klachten kostbare tijd. Hoewel de meeste patiënten overleving het belangrijkste vinden, vinden ze symptoomverlichting en de mogelijkheid om het eigen dagelijks leven voort te zetten tijdens en na de behandeling ook belangrijk. Als symptomen over het hoofd worden gezien, wordt het fysieke, mentale, existentiële en sociale functioneren beïnvloed en kunnen kansen voor diagnose en behandeling van symptomen worden gemist. Symptoomlast kan onzekerheden en fysieke en mentale stress veroorzaken die het gedrag van patiënten kan beïnvloeden, zoals vermindering van therapietrouw en ineffectief gebruik van zelfmanagementstrategieën.

Zorgverleners kunnen symptomen over het hoofd zien of symptoomlast onderschatten. Het is aangetoond dat PROMs ondersteunend zijn bij het verbeteren van de communicatie tussen patiënten en zorgverleners, het verminderen van de ernst van de symptomen, het versterken van de autonomie en het verbeteren van de tevredenheid over de geleverde zorg. Het USD is ontwikkeld ter ondersteuning in het herkennen en het vervolgen van symptomen over de tijd bij patiënten in de dagelijkse oncologische praktijk.



## Het Utrecht Symptoom Dagboek

Het USD is een Nederlandse aangepaste versie van de Edmonton Symptom Assessment System (ESAS), een wereldwijd veel gebruikte PROM. Het USD is ontwikkeld voor het herkennen en monitoren van ziekte- en/of behandeling-gerelateerde multidimensionele symptomen, en kan gebruikt worden in het hele ziekte-en behandeltraject van patiënten met kanker op alle locaties van zorg.

Het USD bevat 12 items - gebrek aan eetlust, misselijkheid, verstoord ontlastingspatroon, slikklachten, droge mond, pijn, slaapproblemen, benauwdheid, vermoeidheid, angst, somberheid en (on)welbevinden. Items worden gescoord op een nul-tot-tien numerieke rating schaal (NRS), een hogere score betekent een hogere symptoomlast. Patiënten kunnen - indien gewenst - symptomen toevoegen die niet op het USD staan. Ook nodigt het USD de patient uit om prioriteit aan te geven voor symptomen die vanuit hun perspectief als eerste aandacht behoeven. Die uitnodiging ondersteunt de eigen regie in het gesprek met de zorgverlener.

Om ondersteunende zorg op maat te bieden werden tumorspecifieke USD modules zoals het USD gliomen ontwikkeld. Ook werden behandelingsspecifieke USD modules ontwikkeld zoals bijvoorbeeld het USD chemo- en doelgerichte therapie (USD dagbehandeling) en het USD immunotherapie. Op deze manier ontvangt een patiënt een PROM op maat, waarbij de lijst met symptomen zo goed mogelijk aansluit op zijn/haar situatie. Sinds 2015 is het USD beschikbaar in het elektronisch patient dossier (EPD).

Het USD is inmiddels geïmplementeerd in andere (universitaire) ziekenhuizen, in huisartspraktijken, in de thuiszorg en in hospices in Nederland. Daarnaast wordt het gebruik van het USD aanbevolen in het 'Kwaliteitskader voor palliatieve zorg'.

Dit proefschrift beschrijft de validatie van het USD en het gebruik ervan in verschillende patiëntengroepen en settings.

## Deel 1: Validatie van het Utrecht Symptoom Dagboek

In hoofdstuk 2 en hoofdstuk 3 onderzochten we de validiteit van het USD, respectievelijk de USD module chemo-en doelgerichte therapie (USD dagbehandeling).

In **hoofdstuk 2** laten we zien dat het USD een valide 12-item PROM is waarmee de meest voorkomende symptomen worden gemeten bij een brede groep patiënten met kanker. Voor alle 12 items werd inhouds, criterium en construct validiteit

gevonden. Ook detecteert het USD klinisch belangrijke veranderingen gedurende de tijd, zowel in de curatieve als in de palliatieve fase van de ziekte.

In **hoofdstuk 3** tonen we de validiteit van een uitgebreide USD module die in 2015 werd ontwikkeld voor patiënten die op de dagbehandeling intraveneuze – curatieve of palliatieve - chemotherapie en/of doelgerichte therapie krijgen. Inhoudsvaliditeit werd bevestigd van alle toegevoegde items smaakveranderingen, pijnlijke mond, gewichtsverlies, diarree, haarveranderingen, huidproblemen, nagelproblemen, oogproblemen, tintelingen, concentratieproblemen, verandering in seksualiteit. Alle items werden positief gescoord door minimaal 10% van de patiënten en er werden geen aanvullende symptomen geïdentificeerd vanuit de 'vrij in te vullen' symptomen. Criteriumvaliditeit werd bevestigd voor alle toegevoegde items van de USD dagbehandeling - behalve voor het item pijnlijke mond. Constructvaliditeit werd bevestigd voor de items huidproblemen, haarveranderingen en nagelproblemen. Het item oogproblemen konden we niet testen vanwege een te laag aantal gepaarde USDs.

Concluderend zijn zowel de USD 'basis' als de behandelingsspecifieke USD module chemotherapie en/of doelgerichte therapie valide en bruikbare PROMs voor de dagelijkse oncologische praktijk.

## Deel 2: Gebruik van het Utrecht Symptoom Dagboek

In hoofdstuk 4, 5 en 6 beschrijven we het gebruik van het USD in verschillende patiëntengroepen en settings.

**Hoofdstuk 4** beschrijft bijwerkingen gerapporteerd door zorgverleners en patiënt-gerapporteerde symptomen bij 87 patiënten die behandeld werden met intraveneuze epidermale groeifactorremmers (EGFRI). In deze retrospectieve, observationele cohortstudie werden patiënten met een plaveiselcelcarcinoom van het hoofd-hals gebied of met uitgezaaid dikkedarmkanker geïnccludeerd. Patiënten met hoofd-halskanker werden behandeld met cetuximab in combinatie met radiotherapie. Patiënten scoorden symptomen met het USD chemo/doelgerichte therapie (USD dagbehandeling). Bijwerkingen werden door zorgverleners gegradeerd conform de *Common Terminology Criteria for adverse events (CTCAE)*. Een dosisaanpassing als gevolg van bijwerkingen trad op bij 40% van de patiënten, meestal als gevolg van huidtoxiciteit. De top 5 van klinisch relevante patient-gerapporteerde symptomen (USD score  $\geq 3$ ) tijdens de behandeling waren: huidveranderingen, pijnlijke mond, gebrek aan eetlust, slaapproblemen en vermoeidheid. Onwelbevinden (USD-score  $\geq 3$ ) werd gemeld door 22-63% van de patienten op verschillende tijdpunten.

We concludeerden dat EGFRi bijwerkingen veroorzaken die bij een aanzienlijk aantal patiënten tot dosisaanpassingen leiden. Patiënten ervaren symptomen met matige tot ernstige intensiteit en een verminderd welbevinden tijdens de behandeling. Vroege herkenning en snelle aanpak van zelfs milde symptomen kunnen helpen bij het behoud en/of verbeteren van het welbevinden.

**Hoofdstuk 5** beschrijft een substudie uitgevoerd binnen een multicenter farmacokinetiek studie met sunitinib (doelgerichte therapie). In deze prospectieve cohortstudie werden patiënten geïncludeerd die sunitinib als standaardtherapie kregen en met gevorderde/uitgezaaide tumoren die sunitinib als experimentele behandeling kregen. 29 patiënten rapporteerden symptomen en (on)welbevinden met behulp van een behandelingsspecifieke USD-module.

Meer dan 50% van de patiënten ervaarde een verminderd welbevinden als gevolg van symptomen van milde en matige intensiteit. Alle gemeten symptomen, met uitzondering van vermoeidheid en braken, werden vaker gemeld door patiënten dan door zorgverleners.

We concludeerden dat enerzijds een beter inzicht in symptomen die door zorgverleners over het hoofd kunnen worden gezien en anderzijds symptoomlast veroorzaakt door meerdere milde bijwerkingen tegelijkertijd van toegevoegde waarde kan zijn bij door zorgverleners gerapporteerde symptomen in vroeg-klinische onderzoek.

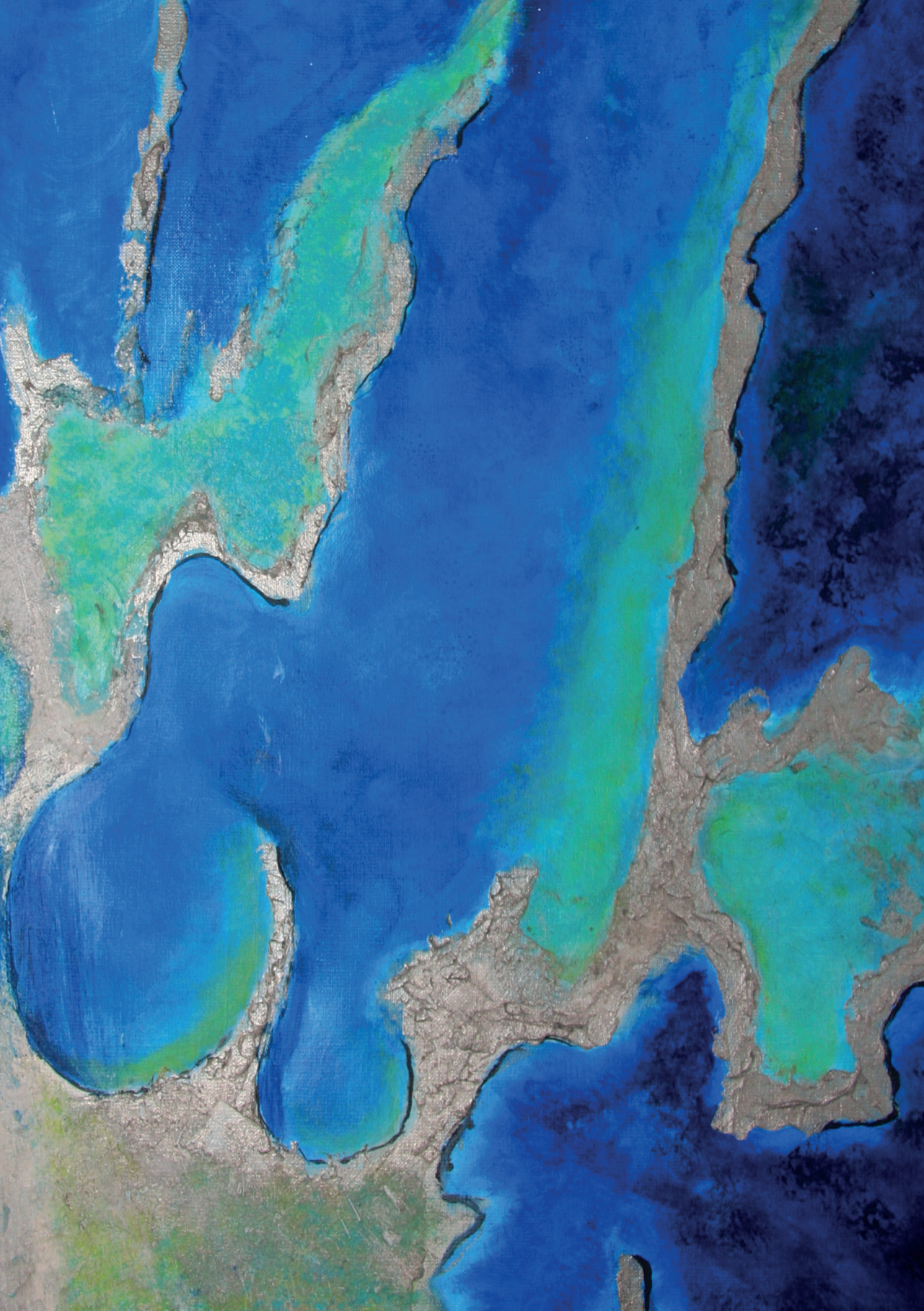
**Hoofdstuk 6** gaat over patiënt-gerapporteerde symptomen van 162 patiënten met melanoom of niet-kleincellig longcarcinoom tijdens immuun checkpoint remming, een vorm van immuuntherapie. De meeste door de patiënt gerapporteerde, klinisch relevante ( $\text{NRS} \geq 3$ ) symptomen tijdens de behandeling waren gebrek aan eetlust, gewrichtspijn, hoest, vermoeidheid, inactiviteit, spierpijn en slaapproblemen. Het aantal positief gescoorde symptomen op een bepaald moment was geassocieerd met een lager welbevinden. In de loop van de behandeling namen klachten af. Dit onderzoek laat zien dat deze vorm van immuuntherapie door veel patiënten goed wordt verdragen. Maar het laat ook zien dat als patiënten tijdens immuuntherapie tegelijkertijd meerdere klinisch relevante symptomen ( $\text{USD score} \geq 3$ ) ervaren, dit van invloed kan zijn op hun welbevinden.

## Conclusie

De in dit proefschrift beschreven studies tonen de validiteit van het Utrecht Symptoom Dagboek (USD) en beschrijven het gebruik van het USD als onderdeel van gepersonaliseerde, ondersteunende zorg tijdens de behandeling met doelgerichte therapie en immunotherapie in de dagelijkse oncologische praktijk.

Inzicht in symptoomlast gerapporteerd door patiënten zelf kan informatie toevoegen aan de door de zorgverlener gegradeerde ernst van bijwerkingen. Vooral bij patiënten met doelgerichte therapie veroorzaakten bijwerkingen een verminderd welbevinden en leidden bijwerkingen tot dosisaanpassingen bij een aanzienlijk aantal patiënten. Het gebruik van het USD kan helpen om symptomen en hun impact op kwaliteit van leven op een gestructureerde manier door de patient zelf te meten en te bespreken, daarmee is de kans op het bieden van gepersonaliseerde zorg en ondersteuning van de eigen regie tijdens de behandeling optimaal.





Appendices

Dankwoord

Curriculum Vitae

List of Publications

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## Dankwoord

*"It always seems impossible until it's done."* – Nelson Mandela

Onderzoek is leren vooruit kijken, (diep) vallen en weer opstaan, mogelijkheden leren zien en zelfvertrouwen krijgen. In de loop van de tijd kreeg ik er steeds meer plezier in, mede door de praktische en mentale hulp en ondersteuning van anderen. Onderzoek doen kun je niet alleen. Graag wil ik daarom iedereen bedanken die een bijdrage heeft geleverd aan dit proefschrift.

Allereerst wil ik alle patiënten bedanken die hun ervaringen met ons deelden. Mensen met kanker in verschillende leeftijdsgroepen en verschillende stadia van de ziekte, mensen die zichzelf liever omschreven als 'partner in onderzoek' in plaats van als patiënt. Zij hebben ons geïnspireerd om kennis te genereren over symptomen en symptoomlast vooral tijdens verschillende behandelingen met doelgerichte- of immuuntherapie. Patiënten zijn zich veelal heel erg bewust van het nieuwe van deze behandelmogelijkheden tegen kanker en blijken enorm gemotiveerd om mee te helpen kennis te ontwikkelen. Ook zij willen meedenken en bijdragen aan het verbeteren van de kwaliteit van zorg, is het niet voor zichzelf dan voor patiënten in de toekomst.

Prof. dr. P. Witteveen, lieve Els, mede door jouw inzet, jouw betrokkenheid en je kritische vragen is verpleegkundig onderzoek tot de mogelijkheden gaan behoren op de afdeling Medische Oncologie. Je onvoorwaardelijke vertrouwen in mij en je enthousiasme hebben me geholpen steeds een volgende stap te zetten. Wat was het ook leuk om samen met Danielle te brainstormen over de rol van de verpleegkundig specialist in patiëntenzorg, onderzoek en onderwijs op onze afdeling. Tijdens ons overleg zat je erbij alsof je zeeën van tijd had. We weten allemaal dat dat niet zo was. Bedankt voor je mentale en praktische ondersteuning!

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Prof. dr. K. Suijkerbuijk, lieve Karijn, wat ben ik blij dat je na je opleiding tot internist-oncoloog in het UMC Utrecht bent gebleven! Bedankt dat je bereid was in te stappen in mijn al lopend promotietraject. Zonder jou was het me niet gelukt! Dank voor je onuitputtelijke geduld, voor het meedenken, je kritische vragen en de ruimte die je hebt gegeven om mijn rol als verpleegkundig specialist in patiëntenzorg, onderwijs en vooral ook onderzoek neer te zetten. Je bent een topper! De dynamiek tussen ons valt ook patiënten op. Zij beschrijven ons als een 'setje' en vragen zich af of we ook samen op vakantie gaan.

Dr. F. van der Baan, lieve Frederieke, wat zijn er door jouw specifieke talenten veel mogelijkheden ontstaan om de USD data te extraheren uit HIX, te analyseren en als gevolg daarvan kennis te vergroten waarmee we de zorg aan onze patiënten verder kunnen verbeteren. Dank dat je mij hebt meegenomen in de methodologische benadering die nodig was bij het valideren van de USD. Wat heb ik veel van je geleerd. Je hebt een belangrijke bijdrage geleverd aan mijn zelfvertrouwen. Ik heb genoten van onze intensieve samenwerking!

Leden van de leescommissie, prof. dr. M. van Dijk, prof. dr. H. Bloemendal, prof. dr. C. van Gils, dr. W. Oldenmenger en prof. dr. L. Schoonhoven. Hartelijk dank voor het lezen en kritisch beoordelen van mijn proefschrift. Prof. dr. R. Zweemer, erg bedankt voor uw deelname aan de oppositie.

Graag wil ik alle coauteurs bedanken voor hun bijdrage aan dit proefschrift. Ook wil ik alle medepromovendi van de 'Melanoom/Immuuntherapie groep' bedanken voor het kritisch doornemen van de hoofdstukken evenals voor de mentale ondersteuning tijdens de Melanoma Research Meetings.

Lieve Sonja, wat jammer dat je dit dat je dit eindproduct niet hebt kunnen zien. Wat zou je trots zijn geweest en wat had ik graag gewild dat je erbij was. Jij hebt je altijd hard gemaakt voor verpleegkundig onderzoek waardoor je voor mij veel mogelijkheden hebt gecreëerd. Dit proefschrift is ook een beetje van jou!

De beste kamergenoten die ik mij kan wensen. Onderzoeksmaatje en collega verpleegkundig specialist Daniëlle Zweers, *partners in crime* op meerdere gebieden. Bedankt voor je adviezen en je peptalks! Ginette Hesselmann, aanwezig bij veel belangrijke momenten in mijn volwassen leven. Daar zitten we dan, samen op een kamer, 38 jaar na het afronden van de inservice opleiding tot verpleegkundige en 13 jaar na het behalen van onze master EBP. 'Vaste' kamergenoten Roel de Weijer, Karin Aarsman, Christien Oudbier en Joanneke Bleichrodt, de kruisbestuiving

op onze kamer is stimulerend en onontbeerlijk voor het bieden van optimale verpleegkundige zorg, ieder op ons eigen aandachtsgebied en op onze eigen wijze.

Oud-kamergenote Paofi Tjia, wat heb je veel betekend voor de ontwikkeling van de verpleegkundig oncologische zorg op onze afdeling en vooral ook landelijk. Ook voor mijn verpleegkundige ontwikkeling was jij enorm van belang.

Collega's van de dagbehandeling, de kliniek en het studieteam van de afdeling Medische Oncologie. Wat fijn dat we elkaar nog steeds kunnen vinden op het gebied van patiëntenzorg en scholing. Marja, Heleen en Irene, dank voor de jarenlange samenwerking en support. Collega's van het poli-secretariaat en het trialbureau. Dank voor de samenwerking.

Collega's en fellows van de medische staf van de afdeling Medische Oncologie, dank voor de fijne samenwerking. Karijn, Annemarleen, Sonja en Marijke van het 'melanoomteam'. Ik had me geen betere collega's kunnen wensen.

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Mijn beste vriendin, wandelmaatje, Ingrid, bedankt voor het meedenken en meelijden én voor je support tijdens de wekelijkse wandelingen waarbij we de week van voor tot achter doornemen. Ik weet serieus niet of ik zonder jou dit promotietraject had kunnen volhouden.

Lieve mams, bedankt voor je onvoorwaardelijke liefde en steun. Wat ben ik toch blij met je. Ik gun iedereen zo'n moeder als jij.

Lieve Iris en Marije. Wat een mooie 1 april mop was dat, niet 1 maar 2 baby's onderweg. Ik ben supertrots op wat voor mooie, slimme, sociale vrouwen jullie zijn geworden. Ik hou van jullie! Wat geweldig dat jullie mijn paranimfen willen zijn.

Lieve Sara, wat een groot geluk dat jij er bent. Ik vind het geweldig om jouw oma te zijn!

## Curriculum Vitae



Josephine Juliëtte (José) Koldenhof werd geboren op 8 juli 1963 in Apeldoorn. In 1981 behaalde zij haar HAVO diploma aan de Rijksscholengemeenschap Schoonoord in Zeist. In 1986 voltooide zij de inservice opleiding tot A-verpleegkundige in het Academisch Ziekenhuis Utrecht. Sinds 1999 werkt zij op de dagbehandeling en de Unit voor Vroeg-klinisch Onderzoek van de afdeling Medische Oncologie van het Universitair Medisch Centrum Utrecht.

In 2011 behaalde ze de *Master Evidence Based Practice in Health Care* aan de Universiteit van Amsterdam op het onderwerp 'Patiënt-gerapporteerde symptomen bij patiënten die werden behandeld met angiogeneseremmers'. In 2015 startte ze haar promotietraject, resulterend in dit proefschrift. Het promotieonderzoek combineerde zij met patiëntenzorg en de Master Advanced Nursing Practice aan de Hogeschool Utrecht. Deze opleiding to verpleegkundig specialist voltooide zij in 2018 met als afstudeeronderzoek 'BRAF/MEK-remming bij patiënten met een inoperabel of gemetastaseerd melanoom: op weg naar passende zorg'.

In 2013 ontving zij de *V&VN Award of Excellence Oncology Nursing*. In 2019, was zij 1 van de 3 genominderen voor de Arendje Jansenprijs, een prijs voor verpleegkundigen die zich hebben weten te onderscheiden op het gebied van een Leven Lang Leren.

Momenteel werkt zij als verpleegkundig specialist met aandachtsgebied melanoom en immuun-en doelgerichte therapie. In de toekomst wil zij zich voor verbetering van kwaliteit van zorg blijven inzetten door de inspirerende combinatie van zorg en onderzoek.

José is trotse moeder van Iris en Marije (1993) en oma van Sara (2023).

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\* Authors contributed equally



