UNIVERSITY OF COPENHAGEN
FACULTY OF HEALTH AND MEDICAL SCIENCES

Symptomatology of advanced cancer patients admitted to palliative care in Denmark and Chile

PhD Thesis

Leslye Alejandra Rojas Concha

This thesis has been submitted to the Graduate School of Health and Medical Sciences, University of Copenhagen 28 May 2020

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Sources of finance:
'Becas-Chile Scholarship' from the Advanced Human Capital Program of the National Commission for Scientific and Technological Research-CONICYT (study fee and living expenses)

Defence takes place 27 October 2020 in Auditorium CSS 25.01.53, City Campus, University of Copenhagen, Øster Farimagsgade 5, 1353 Copenhagen K

PREFACE

This PhD thesis investigated symptoms and problems reported by advanced cancer patients at admittance to palliative care in Denmark and Chile, using data collected from all specialized palliative care (SPC) units registered in the Danish Palliative Care Database (DPD), and from four SPC services in Chile.

Palliative care has been part of my work as a physical therapist in Chile since 2007, and in recent years, it has been part of my academic development by working on this PhD in Denmark. I will always be grateful for this professional and personal challenge which I will never forget.

Special thanks to my primary supervisor, Professor Mogens Grønvold, who believed in me and gave me this opportunity. Thanks for your committed, generous and positive attitude, as well as constructive and meticulous feedback. A particular thanks to my co-supervisor, Morten Aagaard Petersen, for your great assistance in statistical and methodological aspects during the PhD process. Also, thanks to my co-author Maiken Bang Hansen, for sharing your knowledge and invaluable help to improve the papers.

I would like to thank the rest of my colleagues at The Palliative Care Research Unit of Department of Geriatrics and Palliative Medicine GP, Bispebjerg Hospital; Mathilde Adsersen, Line Lund, Caroline Møller Arnfeldt and Lone Ross, for your wise advice both in academic subjects and in daily life in Denmark.

I thank all the SPC units in Denmark that deliver high-quality data to the DPD making this project possible. I thank the heads of the four palliative care services in Chile for supporting this project, the two psychologists who collaborated in the data collection within their services, and the clinicians and patients who answered the questionnaires.

I wish to thank CONICYT ‘Becas-Chile Scholarship’ for funding my PhD program in Denmark.

Lastly, my deepest gratitude to my beloved siblings, Kathyuska and Christian, and my nieces, Javiera and Camila, for your unconditional love and faith in me when I decided to move abroad. This successful journey would not be possible without your unwavering support and the protection of those loved ones who are no longer here but will always be in my thoughts.

ORIGINAL PAPERS

This thesis is based upon the following papers:

1. Rojas-Concha L, Hansen MB, Petersen MA and Groenvold M. Which symptoms and problems do advanced cancer patients admitted to specialized palliative care report in addition to those included in the EORTC QLQ-C15-PAL? A register-based national study. Support Care Cancer. 2019; 28(4):1725-35.
2. Rojas-Concha L, Petersen MA, Groenvold M. Who report symptoms and problems not covered by the EORTC QLQ-C15-PAL when admitted to specialized palliative care?. *(Draft)*
3. Rojas-Concha L, Hansen MB, Petersen MA, Groenvold M. Content validation of the EORTC QLQ-C15-PAL with advanced cancer patients and health care professionals from palliative care services in Chile. *(Accepted for publication in BMC Palliative Care)*
4. Rojas-Concha L, Hansen MB, Petersen MA, Groenvold M. Symptomatology of advanced cancer patients admitted to palliative care services in Chile: A longitudinal study. *(Draft)*

TABLE OF CONTENTS

ABBREVIATIONS

ALCP: The Latin American Association for Palliative Care (ALCP acronym in Spanish)
ANX: Anxiety
AP: Appetite loss
CI: Confidence interval
CO: Constipation
DEP: Depression
DPD: The Danish Palliative Care Database
DY: Dyspnea
EAPC: The European Association for Palliative Care
EF: Emotional functioning
EORTC QLQ-C15-PAL: The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 15 Palliative Care
EORTC QLQ-C30: The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30
ESAS: The Edmonton Symptom Assessment Scale
FA: Fatigue
FACT-G: Functional Assessment of Cancer Therapy-General survey
FACIT-PAL: The Functional Assessment of Chronic Illness Therapy-Palliative Care
HADS: The Hospital Anxiety and Depression Scale
HCPs: Health care professionals
IAHPC: The International Association for Hospice and Palliative Care
IPOS: The Integrated Palliative care Outcome Scale
KPS: Karnofsky Performance Status
MMSE: Mini-Mental State Examination
MSAS: The Memorial Symptom Assessment Scale
NV: Nausea/vomiting
OR: Odd ratio
PA: Pain
PF: Physical functioning
POS: The Palliative care Outcome Scale
PRO: Patient-reported outcome
QOL: Quality of life

S/Ps: Symptoms and problems

SL: Sleeping difficulties

SPC: Specialized palliative care

USA: The United States of America

WHO: The World Health Organization

WISP: The Write In three Symptoms/Problems instrument

WPCA: The Worldwide Palliative Care Alliance

INTRODUCTION

Background

Palliative care

Palliative care aims to improve the quality of life (QOL) of patients with life-threatening illness through early assessment and treatment of their physical, psychosocial and spiritual problems (1). The World Health Organization (WHO) estimates that 40 million people each year need palliative care, but only 14% of those in need receive it (2). The need for palliative care is increasing worldwide due to aging populations and rising rates of cancer and other non-communicable diseases (3). Cancer is the second leading cause of death in the world and it was responsible for 9.6 million deaths in 2018 (4). In the same year, cancer caused 17,122 deaths in Denmark and 28,443 deaths in Chile (5), which accounts for approximately 29% and 25% of the national mortality in each country, respectively (6, 7). Both the Danish and Chilean health authorities have recommended the provision of palliative for patients with a life-threatening illness such as cancer (8, 9).

Palliative care can be classified in two types; basic palliative care and specialized palliative care (SPC). Basic palliative care is provided by institutions where palliative care is not the primary task for health care professionals (HCPs), e.g., general hospitals, nursing homes, primary care teams, whereas SPC is provided by institutions where palliative care is the main focus for HCPs, e.g., palliative care units in tertiary hospitals and hospices (8, 10). This PhD thesis is based on data collected from all SPC units in Denmark and from four SPC services in Chile.

Palliative care development in Denmark and Chile

Since Dame Cicely Saunders founded the first modern hospice, St. Christopher’s Hospice (11), in London in 1967, there has been extensive development of palliative care services across the world. In 2011, about 58% of the world’s 234 countries had at least one palliative care service, and 20 countries had fully integrated palliative care as part of their healthcare system (12). There is a growing interest in increasing the availability and quality of palliative care services, which has been reflected through the foundation of several international organizations over the past 30 years. Among these organizations that promote the development of hospices and palliative care are the International Association for Hospice and Palliative Care (IAHPC), the Worldwide Palliative Care Alliance (WPCA), the European Association for Palliative Care (EAPC), and the Latin American Association for Palliative Care (ALCP acronym in Spanish) (3).

Denmark has a population of 5.7 million inhabitants. The health care system is publicly funded, and palliative care is free of charge (13). The first SPC service, a hospice, was established in 1992, offering patients symptom relief and other assistance through an exclusive multidisciplinary team (8). By 2016, there were 43 SPC units; 26 hospital-based palliative care teams/units providing outpatient treatment, and 17 hospices providing inpatient treatment. Additionally, 5 of the hospital-based units had mixed functions, and 4 hospices also included home care (14). Between 2010–2015 a total of 49,307 cancer patients over the age of 18 were admitted to SPC in Denmark (15).

By comparison, Chile has over 17.5 million inhabitants and 75% of the population is covered by the public health care system (16). The first palliative care program was promoted by the Ministry of Health in 1995 and aimed to evaluate and relieve pain and other symptoms of patients. This program continues today and guarantees free access to palliative care for all patients with advanced cancer (9). Currently, Chile has 130 public hospital-based palliative care services/units distributed throughout the country (17). Most palliative care services provide outpatient treatment, and a few palliative care services include inpatient treatment and/or home care. Between 2010–2013 a total of 92,601 cancer patients were admitted to palliative care services in Chile, and 99.6% of the patients were over the age of 15 (18). Although Chile was one of the countries with the highest number of palliative care services available in relation to its population in the Americas and Caribbean region in 2011, it had a lower ratio of services per capita (ratio 1:808,000) compared to Denmark (ratio 1:122,000) and other Western European countries (12).

Instruments for symptom assessment in palliative care

To improve the QOL of patients in palliative care, a systematic assessment of their symptoms is needed (19, 20). Symptom assessment can be accomplished through validated patient-reported outcome (PRO) instruments, which measure any aspect of the patient's health condition such as symptomatology and QOL that are reported directly by the patient, i.e., without interpretation by physicians or others (21).

Frequently used validated PRO instruments in palliative care include the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 15 Palliative Care (EORTC QLQ-C15-PAL). This questionnaire is an abbreviated version of the EORTC QLQ-C30, which is one of the most validated and widely used PRO instruments in oncology (22, 23). The EORTC QLQ-C30 was reduced from 30 to 15 items by eliminating items identified as less relevant for palliative care, through interviews with patients and HCPs from six European countries including Denmark (24), and by using statistical methods to shorten some of its scales (25). Since its development in 2006, the EORTC QLQ-C15-PAL has been extensively validated and translated for use in palliative care in different countries (26-35), including Spanish-speaking countries (36, 37). A recent systematic review concluded that among 39 self-administered PRO instruments, the EORTC QLQ-C15-PAL, alongside with the EORTC QLQ-BM22, had the best psychometric properties for the assessment of the health-related quality of life in advanced cancer patients (38). In Chile, the EORTC QLQ-C30 and a few modules have been validated for symptom assessment in cancer patients receiving curative treatment (39, 40), but no instrument had been validated for patients receiving palliative care prior to the current study.

Other PRO instruments commonly used for symptom assessment in palliative care are the 9-item Edmonton Symptom Assessment Scale (ESAS) (41) that measures common physical and psychological symptoms; the 19-item Functional Assessment of Chronic Illness Therapy-Palliative Care (FACIT-PAL) (42) that assesses physical, social, emotional and functional well-being; the Memorial Symptom Assessment Scale (MSAS) (43) that measures the frequency, severity, and distress of 24 physical and psychological symptoms; the 10-item Palliative care Outcome Scale (POS) (44), which identifies the main symptoms and concerns that patients themselves prioritize, and its recent integrated version (IPOS) (45) that incorporates more symptoms and spiritual issues. For the screening of psychological symptoms, one of the most validated and used instruments is the 14-item Hospital Anxiety and Depression Scale (HADS) (46), and for screening for cognitive impairment the Mini-Mental State Examination (MMSE) is commonly used (47).

Some instruments have incorporated an open-ended question in their design to identify symptoms not systematically assessed by PRO questionnaires such as the EORTC QLQ-LC29 (48), ESAS (41), the MSAS (43) the short-form of MSAS-SF (49), and the IPOS scale (45), but to my knowledge, information on which symptoms are reported in these open-ended questions has not been published. Two previous studies examined self-reported symptoms on an open-ended question versus those systematically evaluated using a list of 48–57 symptoms. Both studies concluded that, although the number of self-reported symptoms was lower than those identified under systematic evaluation, none of the instruments covered all symptoms reported by the patients (50, 51).

An open-ended question was also added directly after the EORTC QLQ-C15-PAL to identify symptoms not covered by this questionnaire at admittance to SPC in Denmark. This brief instrument named ‘Write In three Symptoms/Problems’ (WISP) permits patients to report up to three symptoms not included in the EORTC QLQ-C15-PAL and to rate their severity. The EORTC QLQ-C15-PAL and WISP were established as mandatory instruments for symptom assessment of patients admitted to SPC since 2010 in Denmark (8), but no national study has analyzed symptoms and problems (S/Ps) reported on WISP. A single center study has been reported as a congress abstract (52).

Symptomatology at admittance to palliative care

Patients with advanced cancer experience many S/Ps caused by the disease and complications of their treatment. A systematic review from 2007 including 25,074 advanced cancer patients from 44 different studies, concluded that the most prevalent S/Ps systematically assessed by validated questionnaires or standardized interviews were fatigue (74%), pain (71%), lack of energy (69%), weakness (60%) and appetite loss (53%) (53). Two other systematic reviews based on 64 and 57 studies, respectively, compared symptom prevalence between cancer patients and non-cancer patients, and suggested that pain, fatigue, anorexia, dyspnea, and worry were also the most prevalent S/Ps reported by advanced cancer patients (54, 55). Other studies compared self-reported S/Ps versus those systematically evaluated in advanced cancer patients and found that the most prevalent self-reported S/Ps were pain, fatigue, nausea, dyspnea, cough, vomiting, and anorexia (50, 51, 56, 57). Concerning screening for psychological symptoms using HADS (score ≥ 11), studies have reported prevalence of definite anxiety ranging from to 22 to 28%, and definite depression prevalence ranging from 25 to 47% in advanced cancer patients admitted to palliative care (58-61).

Several European studies have explored the level of symptoms at admittance to palliative care using the EORTC QLQ-C30 or the EORTC QLQ-C15-PAL questionnaires. These studies found that the highest mean scores for symptom scales, i.e., high symptomatology, were reported (all on a 0-100 scale) for pain (mean score range: 55–88), fatigue (46–85), appetite loss (59–69) and insomnia (34–57). In addition, patients reported poor QOL (31–55) and impaired physical functioning (20–54). These studies found that the lowest symptomatology scores was seen for nausea/vomiting (mean: 10–31) and constipation (mean: 16–44) (36, 62-65). Similarly, a nationwide study from Denmark found that 31,771 patients admitted to SPC reported severe levels of symptoms and poor physical functioning and QOL, and the highest mean scores were reported for fatigue (mean: 75), appetite loss (mean: 57) and pain (mean: 55) (66). Another study conducted in 397 advanced cancer patients from seven counties, i.e., Taiwan, Canada, Cyprus, Brazil, Egypt, India and France, also found that the highest mean scores were reported for pain (mean: 49), fatigue (mean: 46), and insomnia (mean: 41), whereas appetite loss had the lowest mean score (mean: 29) (67).

Several studies have investigated the symptomatology of patients at admittance to SPC in Denmark, using the EORTC QLQ-C30 or the EORTC QLQ-C15-PAL (61, 66, 68-70) as well as the HADS (61, 62, 69), but little evidence is available on which other symptoms patients may experience that are not covered by these standardized methods, especially considering that no standard instrument is able to collect all symptoms that patients suffer from (50).

Evidence on the symptomatology of patients admitted to palliative care in Chile is sparse. A study from a single palliative care service in Chile found that the most prevalent and severe symptoms reported by 77 patients using the Functional Assessment of Cancer Therapy-General survey (FACT-G) were sleeping difficulties (94.8%; severe 49.4%), fatigue (83.2%; severe 31.2%), sadness (80.5%; severe 26%) and pain 71.5% (19.5% severe) (71). FACT-G scores and EORTC scores are not directly comparable.

Patient characteristics and their association with symptoms and problems

In order to understand the profile of patients reporting S/Ps at admittance to palliative care, it is of interest to identify which demographic and clinical characteristics of patients are associated with each S/P. The literature has shown that sex, age, cancer diagnosis, cohabitation status and inpatient/outpatient status are associated with the levels of many of the S/Ps reported by patients in palliative care, but findings have been inconsistent across studies (65-67, 72-79). Previous studies found that women had more severe anxiety, sleeping difficulties, depression, sweats, nausea/vomiting and reduced physical function than men (65, 73, 75, 77, 78), whereas one study found that men had more severe sleeping difficulties than women (72). Studies exploring the association between age and S/Ps found that younger patients had more severe nausea/vomiting, pain, sleeping difficulties, dyspnea, urinary incontinence, anxiety, and depression than older patients (65, 72, 73, 77). In contrast, other studies found that sleeping difficulties, dyspnea, urinary incontinence, and depression were more severe in older patients compared to younger patients (74, 76, 78).

Concerning cancer diagnosis, some studies found that cancer site was strongly associated with several distressful S/Ps experienced by patients in palliative care (66, 75-79), whereas one study reported no effect of cancer diagnosis (65). In relation to cohabitation status, one study found that patients living with a spouse/cohabiting had poorer social function compared to patients living alone (75). One study reported that inpatients had more reduced physical, role, emotional and social function, poor QOL, and more severe fatigue, pain, nausea, dyspnea, appetite loss and constipation than outpatients (76). Discrepancies between these studies may be explained by several factors; differences in the methodology employed to measure the symptomatology, study sample size, type of analyses performed, or the way some characteristics such as age, cohabitation, and diagnosis were categorized.

Because most of the previous studies on the association between patient characteristics and S/Ps included patients from a single palliative care center, larger studies on these associations are needed to obtain a representative sample. Furthermore, evidence on S/Ps evaluated with open-ended instruments is limited. Therefore, studies to explore patient characteristics associated with S/Ps not systematically assessed by PRO questionnaires would be relevant to expand knowledge on the symptomatology at admittance to palliative care.

Changes in symptomatology over time

Several studies have investigated changes in the symptomatology of patients in palliative care over time using validated questionnaires, but the findings after 2–4 weeks of palliative care varied across studies. Some studies found a significant improvement in emotional function, pain, appetite loss, nausea/vomiting, constipation, physical function, fatigue, sleeping difficulties, QOL and anxiety in patients receiving palliative care for 2–4 weeks (36, 62, 63, 67, 80), whereas other studies reported a significant deterioration of pain, physical function, fatigue, appetite loss and QOL after the same period of time (37, 64, 81). Some studies found pain relief and psychological improvement after one week in palliative care (82-85).

Little is known about patient characteristics associated with the improvement or deterioration of S/Ps in patients receiving palliative care. A study from the United States of America (USA) investigated the predictors of symptom improvement in 406 advanced cancer patients referred to palliative care. That study found that fatigue was more likely to improve in those patients with higher intensity of other symptoms at baseline, such as dyspnea, depression and nausea measured by ESAS. Pain was more likely to improve in patients with intense drowsiness. Old age was associated with improved well-being after 1–4 weeks in palliative care (86). Similarly, a Canadian study examined the predictors of symptom improvement in 150 cancer patients participating in a palliative care team intervention. This study found that female gender was associated with symptom improvement after 1 week of intervention, and the greatest improvement was found in nausea, anxiety, dyspnea, and pain (87). Another study from USA specifically evaluated gastrointestinal symptoms in 202 advanced cancer patients who were referred to palliative surgical consultation. Symptom improvement was seen in patients who received surgical treatment compared to those who did not, and no association was found between symptom improvement and sex, age and current chemo-or biotherapy (88).

While several European countries (29, 35, 36, 63, 64, 80, 82), including Denmark (62, 89), have previously explored changes in the symptomatology of patients with advanced cancer in palliative care, to my knowledge, no study has investigated how the symptomatology of patients admitted to palliative care in Chile changes over time. Better knowledge of patients' symptomatology and how it changes over time may guide clinicians toward more effective interventions for patients receiving palliative care.

Aim and research questions

This PhD thesis aims to investigate symptoms and problems of patients with advanced cancer admitted to palliative care in Denmark and Chile.

Research questions:

- Which symptoms and problems do advanced cancer patients admitted to SPC in Denmark report in addition to those included in the EORTC QLQ-C15-PAL? (Paper I)
- Which subgroups of patients report symptoms and problems not covered by the EORTC QLQ-C15-PAL when admitted to SPC in Denmark? (Paper II)
- Does the EORTC QLQ-C15 PAL questionnaire have appropriate content to assess symptoms and quality of life in patients with advanced cancer receiving palliative care in Chile? (Paper III)
- What is the symptomatology of advanced cancer patients at admittance to palliative care in Chile and how does their symptomatology change during the first month? (Paper IV)

MATERIAL AND METHODS

Study Population

The study population of Papers I and II consisted of patients admitted to SPC between January and December 2016 in Denmark, who were at least 18 years old, had advanced cancer, completed the EORTC QLQ-C15-PAL questionnaire at the first day of contact with SPC or up to three days before, and reported at least one symptom/problem using the WISP instrument.

The study population of Papers III and IV were participants from the palliative care services of four hospitals in Santiago in Chile: Sotero del Rio, San Juan de Dios, Salvador, and Felix Bulnes Cerda. To validate the content of the EORTC QLQ-C15-PAL (Paper III), semi-structured interviews were conducted from October to November 2017. Eligible participants for the interviews were adult outpatients with advanced cancer receiving palliative care, who had knowledge of their diagnosis and had given informed consent, as well as HCPs whose main occupation was in palliative care. The longitudinal study (Paper IV) was conducted from October 2017 to January 2018. This study included adult outpatients with advanced cancer who at admittance to palliative care services had knowledge of their diagnosis, had a Karnofsky Performance Status (KPS) score ≥ 50% (90) and were cognitively able and willing to provide informed consent. Patients who did not speak Spanish and those who were too ill to participate in the interviews or symptom assessments were excluded from the studies (Papers III and IV).

Data collection

This PhD thesis is based on data collected from two data sources: the Danish Palliative Care Database (DPD) and four palliative care services in Chile.

The DPD is a national database that contains clinical and demographic data of all patients referred to SPC in Denmark. It also contains data on the first type of contact (inpatient/outpatient), social variables, and S/Ps reported on the EORTC QLQ-C15-PAL and the WISP instrument by patients admitted to SPC. DPD information is continuously validated against the Danish National Patient Register to increase its completeness (91). Information on sex, age, children, residence, cohabitation status, diagnosis, the first type of contact, and S/Ps reported on WISP was obtained from the DPD for the Papers I and II.

The four Chilean palliative care services involved in this study are among the 130 hospital-based palliative care services/units from the public health care system. In general, most of the palliative care services do not have inpatient units (exclusive beds), and palliative home care is provided by other services/teams (92). In Paper III information on sex, age and hospital was collected from all participants at the beginning of the interviews. Additionally, information on diagnosis was collected for patients, and occupation and years of experience for HCPs. In Paper IV, information on sex, age, civil status, residence, cohabitation status, children, and education was collected at admittance to palliative care services. Clinical information on diagnosis, any prior and current antineoplastic treatment, hospital, and KPS score assessed by the physician was collected from the medical record. S/Ps reported using the EORTC QLQ-C15-PAL, WISP and HADS instruments were collected at admittance to palliative care and one month later.

Instruments

The instruments used in the studies were briefly described in the Introduction. The EORTC QLQ-C30 consists of 30 items covering: five multi-item functional scales (physical, emotional, role, cognitive and social functioning); three multi-item symptom scales (fatigue, pain, nausea/vomiting); one scale measuring global health/QOL status, and six single-item symptoms (sleeping difficulties, dyspnea, constipation, lack of appetite, financial difficulties, and diarrhea). All items are scored from 1 (not at all), 2 (a little), 3 (quite a bit) to 4 (very much), except the two global health/QOL items, which are scored from 1 (very poor) to 7 (excellent) (93). Its abbreviated version for palliative care, the EORTC QLQ-C15-PAL, includes 10 function/symptom scales measuring physical functioning, emotional functioning, pain, fatigue, nausea/vomiting, dyspnea, sleeping difficulties, appetite loss, constipation, and overall QOL. Items of the EORTC QLQ-C30 and EORTC QLQ-C15-PAL questionnaires are scored according to the Scoring Manual (94) and the Addendum from 2006 (95).

WISP is an independent instrument, which consists of an open-ended question allowing patients to report 1–3 S/Ps not covered by EORTC QLQ-C15-PAL questionnaire and score their severity from 1 (not at all) to 4 (very much) (Paper I).

HADS is a 14-item instrument measuring anxiety and depression. The scores for each 7-item subscale of anxiety and depression range from 0 to 21 points. According to the authors, 0–7 points on a subscale indicate a non-case, 8–10 points a possible case, and 11–21 points a definite case of anxiety or depression, respectively (46).

Analyses

Qualitative analyses

Qualitative data obtained from the WISP instrument (Paper I), and the interviews to validate the content of the EORTC QLQ-C15-PAL (Paper III) were codified for further analysis. In paper I, qualitative responses from WISP were grouped into S/P categories, e.g., ‘pain in the neck’ was coded as ‘pain’. If S/Ps categories were not covered by the EORTC QLQ-C15-PAL, new codes were established by using a list of 48 symptoms developed by Homsi et al. (50), and if a S/P was no found in this list, a new category was created.

In the content validation study (Paper III), qualitative and quantitative data were collected simultaneously. The interviews aimed to identify the most relevant EORTC QLQ-C30 dimensions for assessing the outcome of palliative care. The interview process replicates the methods used to abbreviate the EORTC QLQ-C30 (24), and follows the EORTC Quality of Life Group Guidelines for developing questionnaire modules (96). Thus, patients and HCPs were asked to individually evaluate the EORTC QLQ-C30 items according to relevance, appropriateness, relative importance and breadth of coverage. The relevance of each item was scored 1 (not at all), 2 (a little), 3 (quite a bit) or 4 (very much), and if an item was scored 1 or 2, the participant was asked to explain the reasons why the question was scored with no/little relevance. The appropriateness was evaluated asking participants to select ‘inappropriate or upsetting’ items, and the proportions of patients and HCPs who selected these items were estimated. Relative importance was estimated as the proportion of participants who selected each item as one of the 10 most important. For each multi-item scale, the proportion of participants who selected at least one item from the scale was also estimated. In addition, single items and scales were ranked according to the proportion of patients and HCPs who selected the item/scale as one of the 10 most important. This ranking was defined as the ‘importance percentage’ and was calculated as an average across patients and HCPs: (percentage of patients + percentage of HCPs)/2. The breadth of coverage was assessed asking participants to list additional problems that were relevant to assess in palliative care but were not included in the EORTC QLQ-C30. Qualitative data about why some questions were scored with little relevance and the additional problems listed by the participants were classified into categories for further analysis.

Scoring of instruments

All responses from the EORTC QLQ-C15-PAL, the EORTC QLQ-C30 (in terms of relevance), and the WISP instrument were transformed into 0–100 scales with 0 corresponding to ‘not at all’ and 100 to ‘very much’, according to the EORTC Scoring Manuals (94, 95) (Papers II-IV). Higher scores on symptom scales represent worse symptoms for the EORTC QLQ-C15-PAL and WISP, while higher scores on the two functional scales and overall QOL on the EORTC QLQ-C15-PAL represent a better function/QOL. For the ratings of the EORTC QLQ-C30, higher item scores represent a greater item relevance to assess the outcome of palliative care (Paper III).

Statistical analyses

Table 1 summarizes the statistical analyses performed in Papers I–IV, which include descriptive statistics, non-parametric tests, and regression analyses. The prevalence of patients reporting an S/P on the EORTC QLQ-C15-PAL was estimated as those who reported a score of at least ‘a little’ (functioning scores ≤67 or symptom scores ≥33), whereas the prevalence of severe ‘symptom/problem’ was estimated as those who reported a score of at least ‘quite a bit’ (functioning scores ≤34 or symptom scores ≥66), using the cut-points from two previous studies (66, 76) (Paper IV). The prevalence of patients reporting S/Ps on WISP was also estimated as those who reported a score of at least ‘a little’ (Papers I and IV). The prevalences of patients who reported possible anxiety/depression (score ≥8), and definite anxiety/depression (≥11) were estimated using the cut-points defined for HADS (Paper IV). S/P scores of the EORTC QLQ-C15-PAL and WISP were estimated overall and in relation to patient characteristics (Papers II and IV).

In paper II, multiple logistic regressions with backward stepwise selection of explanatory variables were used to investigate the associations between patient characteristics and eleven computed dichotomous outcomes: ‘any additional S/P’ and the ten ‘most prevalent additional S/Ps’, where ‘additional S/P’ was defined as all S/Ps reported on WISP and not covered by the EORTC QLQ-C15-PAL questionnaire. The outcome ‘any additional S/P’ was computed by dividing patients into those who reported at least one additional S/P on WISP and those who did not. For each of the ten most prevalent additional S/Ps reported on WISP, patients were divided into those who had reported the specific symptom and those who had not. Odds ratios (ORs) with 95% confidence intervals (CIs) were used to present these results. In the longitudinal study (Paper IV), multiple linear regressions were used to explore the association between patient characteristics and changes in S/P scores from baseline to follow-up during the first month of palliative care, using a backward stepwise selection. The significance level used across the four papers was 0.05. All analyses were performed using the statistical software Statistical Package for Social Sciences-SPSS versions 22–23.

Table 1. Methodology summary Papers I–IV.

	Paper I *n*=5,447	**Paper II** *n*=5,447	**Paper III** *n*=83	**Paper IV** *n*=201
Study design	Based on a national quality database (DPD)	Based on a national quality database (DPD)	Cross-sectional	Longitudinal
Instruments	WISP	WISP	EORTC QLQ-C30	EORTC QLQ-C15-PAL, HADS and WISP
Outcomes	Prevalence and severity of S/Ps	Patient characteristics associated with ‘any additional S/P’ and ‘each of the ten most prevalent additional S/Ps’ Scores of the ten most prevalent additional S/Ps	Relevance, appropriateness and relative importance of the items Additional issues not covered by the questionnaire	Prevalence, severity and scores of the S/Ps reported at admittance Changes in S/P scores during the first month of palliative care Patient characteristics associated with changes in S/P scores
Descriptive statistics	Proportions, medians and ranges	Proportions, medians, ranges and means	Proportions, medians, ranges and means	Proportions, medians, ranges, means and standard deviations
Non-parametric tests	Chi-square test to compare patients who reported S/Ps on WISP to those who did not (1,788 vs. 3,659)	Chi-square test to compare patients who reported additional S/Ps on WISP* to those who did not (1,295 vs. 4,152)	Mann-Whitney U test to compare item relevance and importance scores between ‘physicians’ and ‘other health care professionals’	Mann-Whitney U and Kruskal-Wallis tests to compare S/P scores according to patient characteristics Wilcoxon signed rank test to compare changes in S/P scores the first month of palliative care
Regression analyses	Not applied	Multiple logistic regressions	Not applied	Multiple linear regressions
Explanatory variables for regression analyses	Not applied	Sex, age, children, cohabitation status, diagnosis, type of first contact	Not applied	Sex, age, civil status, residence, cohabitation status, having children, education, diagnosis, any prior or current antineoplastic treatment and hospital

DPD= Danish Palliative Care Database, WISP= the Write In three Symptoms/Problems instrument, HADS= Hospital Anxiety and Depression Scale, S/Ps= symptoms and problems
*Additional S/Ps: S/Ps reported on WISP and not covered by the EORTC QLQ-C15-PAL questionnaire

RESULTS

Paper I

Research question: Which symptoms and problems do advanced cancer patients admitted to SPC in Denmark report in addition to those included in the EORTC QLQ-C15-PAL?

Study participants: In total, 11,754 patients were referred to SPC in Denmark during 2016. Of whom, 5,447 answered the EORTC QLQ-C15-PAL at admittance to SPC, and 1,788 (32.8%) of these reported at least one S/P on WISP (Fig.1). Most of the patients answering the EORTC QLQ-C15-PAL were over 60 years (81.7%), had older children (79.8%), lived in their private residence (94.6%), and were outpatients (74.6%).

Prevalence and severity of symptoms and problems: A total of 2,796 S/Ps were reported using the WISP instrument, which were classified in four groups: additional S/Ps not included in the EORTC QLQ-C15-PAL (63.6%); S/Ps already included in the EORTC QLQ-C15-PAL (24.8%); diagnoses (10.1%), e.g., neurological diseases, and S/Ps that could not be coded (1.6%). The 2,470 S/Ps already included or not included in the EORTC QLQ-C15-PAL were allocated into 61 S/P categories. Patients who answered the EORTC QLQ-C15-PAL reported on average 0.5 S/Ps on WISP with a median of 0 (range 0–3). The most prevalent S/Ps not included in the EORTC QLQ-C15-PAL were edema (3.4%), dizziness (3.1%), cough (1.6%) and sweats (1.5%), whereas the most prevalent S/Ps already included were aspects of pain (4.2%), impaired physical (2.8%) and emotional function (2.8%) (Table 2). Of the S/Ps, 85% were scored as ‘quite a bit’ or ‘very much’. A more detailed description can be found in Paper I.

Figure 1. Flow-chart of participant inclusion in Denmark for papers I and II.

WISP= Write In three Symptoms/Problems instrument

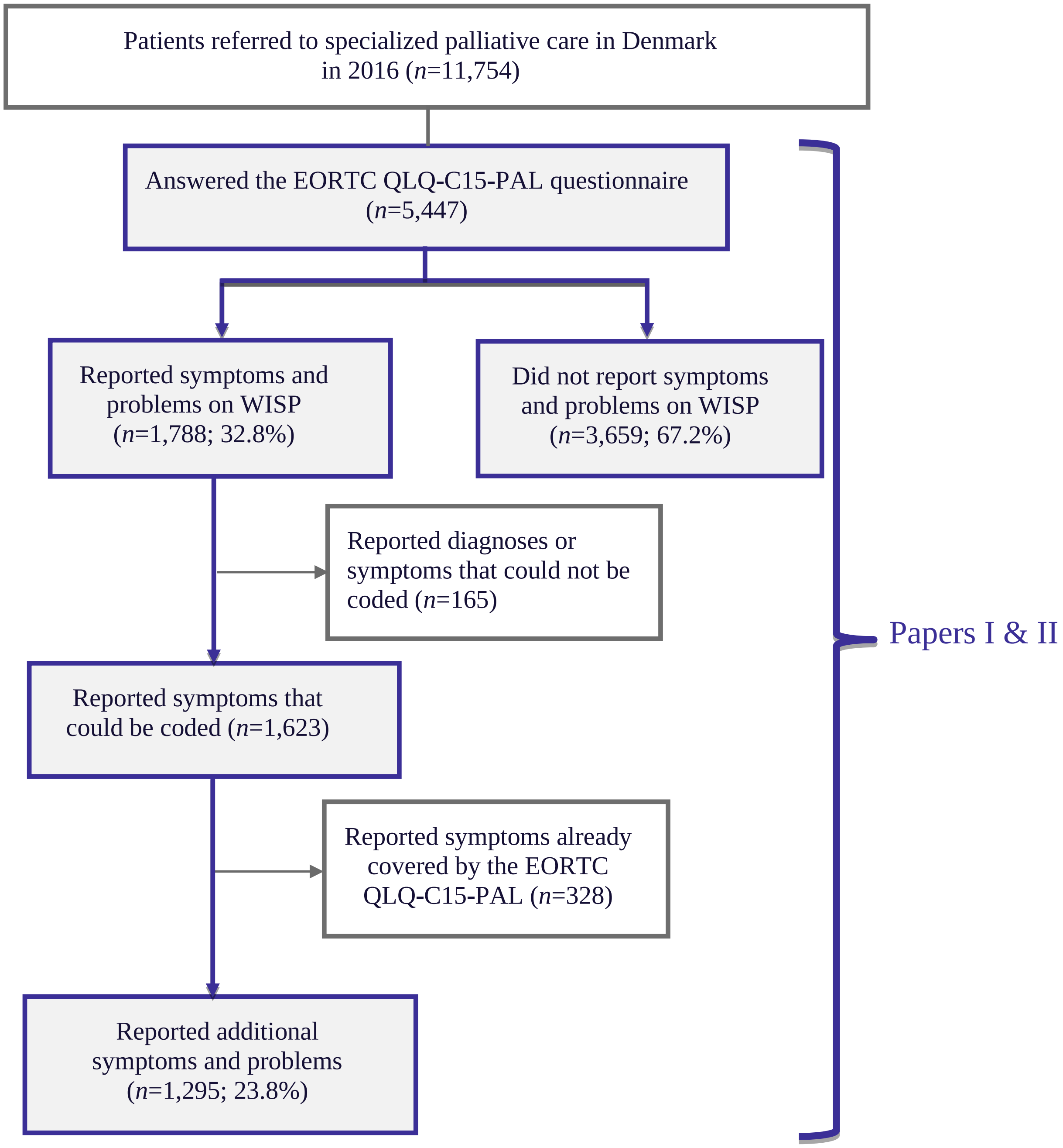


Table 2. Prevalence and severity of the 15 most frequent symptoms and problems reported using the WISP instrument (totally 2,470 symptoms and problems reported by 1,788 patients out of the 5,447 answering the EORTC QLQ-C15-PAL) (*modified from Paper I*).

Symptoms/ problems categories	Prevalence in 5,447 patients answering the EORTC QLQ-C15-PAL		Symptoms/problems reported on WISP N=2,470					
			Severity					
			A little		Quite a bit		Very much	
	N	%	N	%	N	%	N	%
Pain	231	4.2	21	9.1	96	41.6	114	49.4
Edema	183	3.4	32	17.5	60	32.8	91	49.7
Dizziness	169	3.1	56	33.1	71	42.0	42	24.9
Impaired physical functioning	154	2.8	16	10.4	61	39.6	77	50.0
Impaired emotional functioning	152	2.8	9	5.9	61	40.1	82	53.9
Cough	85	1.6	18	21.2	40	47.1	27	31.8
Sweats	80	1.5	10	12.5	38	47.5	32	40.0
Diarrhea	74	1.4	9	12.2	30	40.5	35	47.3
Dry mouth	73	1.3	10	13.7	37	50.7	26	35.6
Incontinence[a]	72	1.3	6	8.3	37	51.4	29	40.3
Sore mouth	69	1.3	18	26.1	22	31.9	29	42.0
Vomiting	66	1.2	9	13.6	30	45.5	27	40.9
Dysphagia	65	1.2	8	12.3	20	30.8	37	56.9
Vision problems	63	1.2	9	14.3	23	36.5	31	49.2
Numbness/tingling	56	1.0	6	10.7	25	44.6	25	44.6

Symptoms and problems already covered by the EORTC QLQ-C15-PAL are in italic

[a] Including urinary, fecal and unspecified incontinence

Paper II

Research question: Which subgroups of patients report symptoms and problems not covered by the EORTC QLQ-C15-PAL when admitted to SPC in Denmark?

Study participants: In 2016, 1,295 (23.8%) patients out of 5,447 who answered the EORTC QLQ-C15-PAL listed additional S/Ps on WISP, i.e., S/Ps not covered by the EORTC QLQ-C15-PAL, at admittance to SPC in Denmark (Fig. 1). The patients reporting additional S/Ps were slightly younger than those not reporting additional S/Ps, and typically had younger children and lived with someone.

Additional symptoms and problems and patient characteristics: In the logistic regression analyses the highest probability of suffering from ‘any additional S/P’ was seen for patients with younger children compared to patients with older children (p=0.008), and for patients living with someone compared to those living alone (p=<0.001). Concerning the most prevalent additional S/Ps, patients with younger children were more likely to report edema (p=0.008) and sore mouth (p=0.038) than patients with older children. Patients living with someone were more likely to report cough (p=0.006) and sweats (p=0.025) than patients living alone. In relation to diagnosis; patients with prostate cancer were more likely to suffer from sweats (p=<0.001); patients with colorectal and prostate cancer more likely to suffer from incontinence (p=0.022), and patients with cancer in female genital organs and the digestive system were more likely to suffer from vomiting (p=<0.001). Outpatients were more likely to report dry mouth than inpatients (p=0.044) (Table 3).

Table 3. Associations between patient characteristics and additional symptoms and problems reported on WISP using stepwise logistic regression *(modified from paper II).*

	Any additional symptom/problem *n*= 1,295[a]	Edema *n*=183[a]	Cough *n*=85[a]	Sweats *n*=80[a]	Dry mouth *n*=73[a]	Incontinence *n*=72[a,b]	Sore mouth *n*=69[a]	Vomiting *n*=66[a]
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Children								
No children	1.26 (1.02-1.54)	1.77 (1.18-2.66)					1.20 (0.57-2.55)	
Children, at least one younger than 18 years	1.34 (1.06-1.71)	2.00 (1.24-3.22)					2.45 (1.23-4.87)	
Children, all at least 18 years old	1.00 (ref. group)	1.00 (ref. group)					1.00 (ref. group)	
Cohabitation								
Living alone	0.76 (0.66-0.86)		0.47 (0.28-0.80)	0.54 (0.31-0.99)				
Living with someone	1.00 (ref. group)		1.00 (ref. group)	1.00 (ref. group)				
Diagnosis (cancer site, ICD-10)								
Digestive system				1.28 (0.62-2.68)		0.95 (0.39-2.34)		6.90 (2.34-20.3)
Colorectal				0.83 (0.32-2.16)		3.07 (1.46-6.47)		6.49 (2.08-20.1)
Lung				1.00 (ref. group)		1.00 (ref. group)		1.00 (ref. group)
Breast				1.07 (0.39-3.00)		1.56 (0.58-4.19)		3.92 (1.05-14.7)
Female genital organs				0.54 (0.12-2.34)		2.04 (0.76-5.46)		14.7 (4.80-44.8)
Prostate				4.10 (2.05-8.25)		2.60 (1.09-6.21)		4.31 (1.15-16.1)
Other cancers				1.48 (0.74-2.94)		1.24 (0.56-2.78)		2.18 (0.64-7.45)
Type of first contact								
Inpatient					0.61 (0.38-0.99)			
Outpatient					1.00 (ref. group)			

An odds ratio above 1 reflects a higher odd of reporting the symptom. Ref.=reference

[a] Number of patients reporting the symptom

[b] including urinary, fecal and unspecified incontinence

Sex and age were not significantly associated with any of the outcomes and no associations were found between any of the patient characteristics and dizziness, diarrhea, dysphagia and therefore, these patient characteristic and outcomes are not shown in the table

Paper III

Research question: Does the EORTC QLQ-C15 PAL questionnaire have appropriate content to assess symptoms and quality of life in patients with advanced cancer receiving palliative care in Chile?

Study participants: A total of 48 patients with advanced cancer and 35 HCPs participated in the interviews to validate the content of the EORTC QLQ-C15-PAL (Fig 2). Patients were on average 59 years of age and the most common diagnoses were prostate cancer (14.6%) and stomach cancer (10.4%). HCPs were on average 41 years of age and the most common profession was physician (34.3%).

Relevance, appropriateness and importance of the EORTC QLQ-C30 items: The 10 most important dimensions selected to assess the outcome of palliative care were pain (96%), physical functioning (89%), sleeping difficulties (80%), emotional functioning (78%), nausea/vomiting (57%), fatigue (56%) and social functioning (49%), lack of appetite (46%), role functioning (43%) and constipation (42%). Pain, sleeping difficulties and nausea/vomiting items were selected as very important and rated with a high relevance, especially by patients. Concerning the physical functioning scale, item 4 ‘stay in bed’ and item 5 ‘need help with self-care’ were rated as the most relevant items of the scale, whereas item 1 ‘strenuous activities’ was rated as the most inappropriate item by 6% of the patients and 9% of the HCPs. The four items on the emotional functioning scale were rated more relevant by patients than HCPs, and item 24 ‘feel depressed’ was selected as the most important item by the participants. Fatigue was selected as one of the most important scales by 77% of patients compared to 34% of HCPs and item 10 ‘need to rest’ was the least important and relevant item of this scale. Social and role functioning scales were considered as very important dimensions by 49% and 43% of the respondents respectively, particularly by patients. Lack of appetite and constipation items were more important for HCPs than patients (Table 4).

Qualitative responses to the questions scored with little relevance showed that item 23 ‘feel irritable’ (emotional functioning scale), item 16 ‘constipation’ and item 8 ‘dyspnea’ were considered as poorly formulated. About 20% and 33% of the respondents suggested linguistic changes for the constipation and dyspnea items respectively, since current questions were difficult to understand by patients (Table 4, Paper III). Further details of the content analyses by each dimension of the EORTC QLQ-C30 can be seen in Paper III.

Breadth of coverage of the EORTC QLQ-C30: Participants reported 91 additional issues that they considered relevant to include when assessing palliative care. These issues were grouped into 10 overall categories and the most frequent were satisfaction with care, emotions and psychological support. Patients reported more issues related to satisfaction with care e.g., satisfaction with HCPs and effectiveness of medication, whereas HCPs reported more issues related to emotions e.g., role loss and mood changes (Table 5, Paper III).

Figure 2. Flow-chart of participant inclusion in Chile for papers III and IV.
PC= palliative care, WISP= Write In three Symptoms/Problems instrument

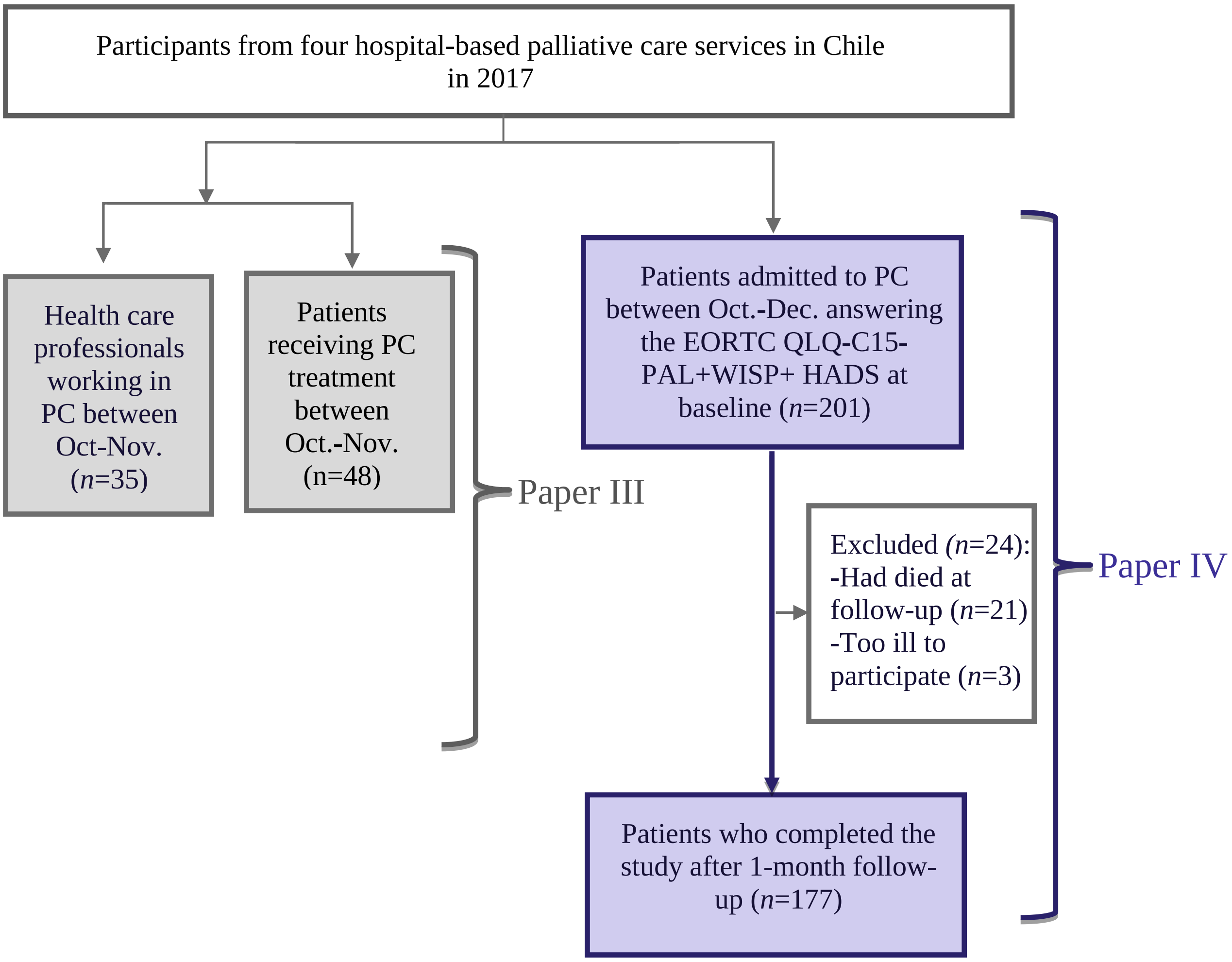


Table 4. Ratings of relevance, inappropriateness and relative importance of the ten most important dimensions of the EORTC QLQ-C30 selected by 48 patients and 35 health care professionals (*modified from Paper III*).

Scale/item	Item	Relevance (mean)		% Inappropriate		% Selected as one of the most important		
		Pts.	HCPs	Pts.	HCPs	Pts.	HCPs	/2[a]
Pain (PA)	**9**	100	97	0	0	96	77	
	19	97	80	2	6	27	54	
Any PA item						98	94	96
Physical functioning (PF)	1	77	64	6	9	40	3	
	2	78	63	2	0	25	3	
	3	76	73	4	3	17	9	
	4	83	85	6	3	23	51	
	5	98	95	0	0	60	71	
Any PF item						98	80	89
Sleeping difficulties (SL)	**11**	97	95	0	0	75	86	80
Emotional functioning (EF)	**21**	95	63	0	3	19	6	
	22	93	68	0	2	21	11	
	23	92	73	0	0	21	17	
	24	98	89	0	0	38	60	
Any EF item						73	83	78
Nausea and vomiting (NV)	**14**	96	88	0	0	25	54	
	15	97	87	0	0	35	46	
Any NV item						46	69	57
Fatigue (FA)	10	97	67	2	3	50	6	
	12	92	73	0	3	31	20	
	18	92	74	2	3	42	14	
Any FA item						77	34	56
Social functioning (SF)	26	93	89	2	3	31	54	
	27	88	83	4	0	8	31	
Any SF item						38	60	49
Lack of appetite (Ap)	**13**	99	86	0	0	35	57	46
Role functioning (RF)	6	95	79	0	0	50	23	
	7	82	57	2	6	31	6	
Any RF item						60	26	43
Constipation (CO)	**16**	92	83	0	0	29	54	42

Items in bold form were extracted from the EORTC QLQ-C30 to form the EORTC QLQ-C15-PAL

[a] The scales/items are ranked according to the ‘importance percentage’

Pts.= Patients, HCPs= health care professionals

Paper IV

Research question: What is the symptomatology of advanced cancer patients at admittance to palliative care in Chile and how does their symptomatology change during the first month?

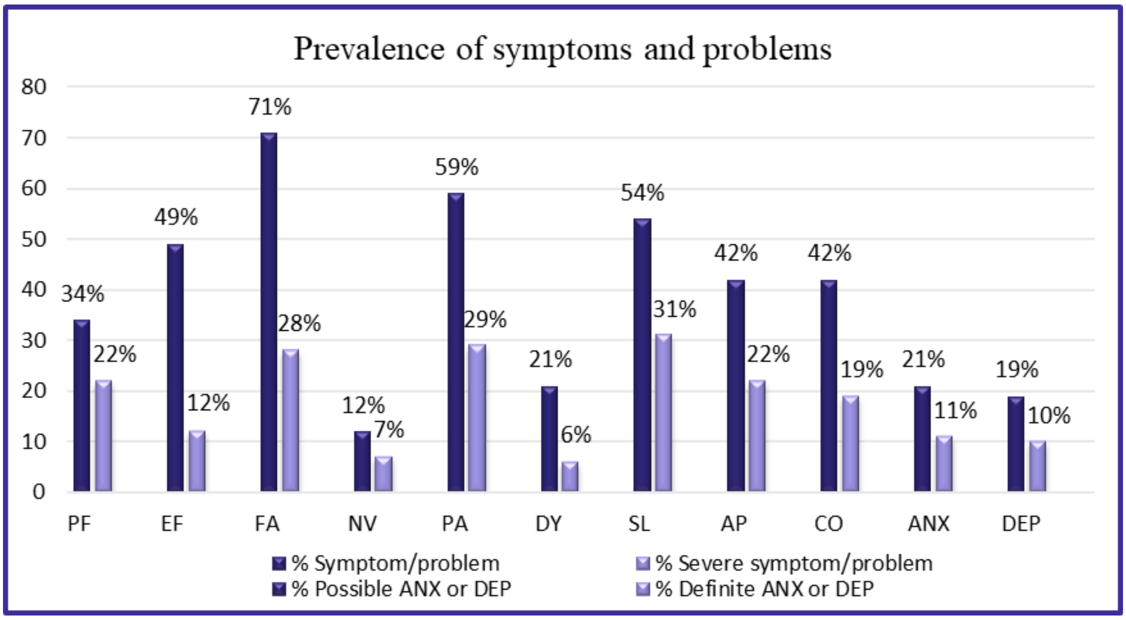
Study participants: From October to December 2017, 394 patients with advanced cancer were admitted to the four palliative care services in Chile. Of these, 201 patients were included in the study answering the EORTC QLQ-C15-PAL, WISP and HADS at baseline, and 177 patients completed the study at 1-month follow-up (Fig. 2). More than half of the patients included in the study were men (51.7%), over 65 years of age (57.2%), married (55.7%), and had not received any prior antineoplastic treatment (51.7%). Most of these patients lived in their private residence (71.1%), had older children (77.1%), and were not receiving any current antineoplastic treatment (94.0%).

Initial symptomatology: Figure 3 shows the prevalence of S/Ps reported on the EORTC QLQ-C15-PAL and HADS at admittance to palliative care. The most prevalent S/Ps reported were fatigue 71% (28% severe), pain 59% (29% severe) and sleeping difficulties 54% (31% severe). These S/Ps also had the highest mean scores on the EORTC QLQ-C15-PAL (41, 39, and 32 respectively). In relation to HADS, 21% of patients reported possible anxiety and 19% possible depression (score ≥ 8), whereas 11% of patients reported definite anxiety and 10% definite depression (score ≥ 11).

S/P scores reported on the EORTC QLQ-C15-PAL and HADS showed statistically significant differences according to sex, age, civil status, residence, children and prior and current antineoplastic treatment (Table 3, Paper IV). Women reported more severe fatigue than men (p=0.022), and younger patients reported more severe nausea/vomiting (p=0.033), dyspnea (p=0.023) and sleeping difficulties (p=0.008) than older patients. Single patients (p=0.003) and patients living in others´ residence (p=0.017) had more reduced physical functioning. Patients with younger children had more severe fatigue (p=0.008) and nausea/vomiting (p=0.039) compared to patients with older children. Patients who did not receive any prior antineoplastic treatment reported more severe appetite loss (p=0.037) than patients who did. Patients in current antineoplastic treatment had more reduced physical and emotional functioning (p=0.010), as well as more severe nausea/vomiting (p=0.039), anxiety (p=0.007) and depression (p=<0.001) than patients who were not in current antineoplastic treatment.

In total, 80 S/Ps were listed on WISP by 72 patients at baseline; 60 corresponded to additional S/Ps, and 20 were S/Ps already included in the EORTC QLQ-C15-PAL. All these S/Ps were grouped into 23 S/P categories, and the most prevalent additional S/Ps listed on WISP were cough (5.5%), bloating (3.5%), and diarrhea (2.5%) (Table 2, Paper IV). Overall, 70% of them were rated as 'quite a bit' or 'very much'.

Fig 3. Prevalence of symptoms and problems in 201 patients who completed the EORTC QLQ-C15-PAL and the Hospital Anxiety and Depression Scale at baseline (*modified from Paper IV*).



EORTC QLQ-C15-PAL: PF=physical functioning, EF=emotional functioning, FA=fatigue, NV=nausea/vomiting, PA=pain, DY=dyspnea, SL=sleeping difficulties, AP= appetite loss, CO=constipation, HADS: ANX=anxiety and DEP=depression

Change in symptomatology: The scores for emotional functioning (p=<0.001), pain (p=<0.001), sleeping difficulties (p=0.005), constipation (p=0.005), and anxiety (p=<0.001) improved significantly during the first month of palliative care. Multivariate analyses showed that emotional functioning and anxiety also had a significant subgroup difference in change over time, where emotional functioning scores worsened for patients living alone with children and anxiety scores had a greater reduction in patients receiving antineoplastic treatment compared to those who did were not as shown in Table 5.

Furthermore, physical functioning, nausea/vomiting, appetite loss, quality of life and depression also presented a significant subgroup difference in change over time. A more positive change in physical functioning and depression scores was observed in patients under current antineoplastic treatment than in patients who were not receiving antineoplastic treatment. A reduction in nausea/vomiting scores was seen for both patients living in a private residence and for patients living with others compared to the remaining residence and cohabitation categories. Similarly, a reduction in appetite loss scores was seen in patients with gallbladder and prostate cancer compared to other diagnoses. A deterioration in QOL scores was seen for patients living in others' residence compared to those who lived in their private residence (Table 5). In contrast, we found no association between patient characteristics and change in S/P scores for pain, fatigue, dyspnea, sleeping difficulties and constipation. Age, sex, civil status, children, education, prior antineoplastic treatment and hospital and were not significantly associated with any of the outcomes, and therefore are not shown in Table 5.

Table 5. Significant associations between patient characteristics and changes in symptom/problem scores from baseline to follow-up obtained from multiple linear regression analyses with backwards stepwise selection. Only the seven scales for which subgroup differences were found are shown.

		EORTC QLQ-C15-PAL					HADS	
	N	Δ PF^a (CI 95%)	Δ EF^a (CI 95%)	Δ NV^b (CI 95%)	Δ AP^b (CI 95%)	Δ QOL^a (CI 95%)	Δ ANX^b (CI 95%)	Δ DEP^b (CI 95%)
Intercept		0.8	-9.0	-1.2	4.5	1.5	-1.3	0.2
Residence								
Others’ residence	47			13.7 (3.2;24.3)		-9.7 (-18.7; -0.7)		
Private residence	130			0.0 (ref. group)		0.0 (ref. group)		
Cohabitation status								
Living alone	10		10.2 (-12.7;33.1)	-1.3 (-19.3;16.7)				
Living with partner	39		9.0 (-5.0;23.0)	-1.8 (-12.8;9.3)				
Living alone with children	34		-17.8 (-32.3; -3.2)	3.4 (-8.1;14.9)				
Living with others	40		2.3 (-11.6; 16.2)	-16.0 (-28.3; -3.7)				
Living with partner and children	54		0.0 (ref. group)	0.0 (ref. group)				
Diagnosis								
Stomach	20				10.9 (-6.6;28.4)			
Colorectal	22				5.5 (-11.5;22.4)			
Breast	16				-9.6 (-27.5;8.3)			
Lung	19				-3.2 (-22.4;16.0)			
Prostate	18				-19.4 (-37.8; -1.1)			
Gallbladder	10				-35.7 (-59.2; -12.2)			
Other cancer	72				0.0 (ref. group)			
Current antineoplastic treatment								
Yes	11	18.6 (0.1; 37.1)					-2.7 (-5.1; -0.3)	-2.9 (-5.4; -0.4)
No	166	0.0 (ref. group)					0.0 (ref. group)	0.0 (ref. group)

PF=physical functioning, EF=emotional functioning, NV=nausea/vomiting, AP= Appetite loss, QOL=Quality of life, ANX=anxiety and DEP=depression
Δ= score at follow-up - score at baseline, CI= confidence intervals
[a] A positive value reflects improvement in the two functioning scales and overall QOL from baseline to follow-up compared to the reference group
[b] A negative value reflects symptom relief in the symptom scales from baseline to follow-up compared to the reference group
Significant association between patient characteristics and outcomes $p<0.05$

DISCUSSION

Main findings

Paper I

The main findings in Paper I were that among the 5,447 patients who completed the EORTC QLQ-C15-PAL at admittance to SPC in Denmark, 32.8% reported a total of 2,796 S/Ps using the WISP instrument. Of these S/Ps 63.6% were additional, i.e., not included in the EORTC QLQ-C15-PAL, 24.8% were S/Ps already included, and 11.7% were diagnoses or responses that could not be coded. Edema, dizziness, cough and sweats were the most prevalent additional S/Ps, while pain, impaired physical and emotional function were the most prevalent S/Ps already included in the questionnaire. Of the S/Ps, 85% were reported as moderate to severe on WISP.

Few studies have investigated self-reported S/Ps using open-ended questions in patients with advanced cancer and thus, the prevalences obtained in WISP can only be compared with these similar studies (50, 51, 56). The prevalence of edema in this study (3.4%) was roughly similar to the prevalence of 4% reported by 200 patients using an open-ended question in the Homsi et al.'s study (50), and similar to the 5% found in two previous studies by Alsirafy et al., where 50 and 89 patients, respectively, also self-reported symptoms (51, 56). The prevalences of dizziness (3.1%) and sweats (1.5%) were similar to Homsi et al. findings, where these symptoms were listed by 3.0% and 2.0% of patients respectively (50). Cough was reported on WISP by 1.6% of patients, which is lower than the findings from two previous studies with a prevalence of cough that ranged from 6-10% (50, 56). Differences in the prevalence of some S/Ps listed on WISP with other studies, which also used an open-ended question to assess the symptomatology of patients, could be explained by the variability of the sample size across studies, as previous studies were relatively small including up to 200 patients.

Concerning S/Ps already measured by the EORTC QLQ-C15-PAL, pain was the most prevalent reported on WISP. This is in line with previous studies indicating that pain is the most frequent self-reported symptom in advanced cancer patients (50, 51, 57, 68). Although pain was already evaluated by two EORTC QLQ-C15-PAL items, item 5 'pain' and item 12 'pain interferes with daily activities', pain was reported by 4.2% of patients mainly reflecting that patients wanted to give more information about the symptom, e.g., the location 'pain in the neck'.

In this study, balance problems and muscular weakness were the most frequent physical problems reported on WISP, which are not measured by the EORTC QLQ-C15-PAL items. Likewise, anxiety was the most frequent emotional problem reported on WISP, which is not specifically measured by this questionnaire, although item 13 'feeling tense', probably reflects anxiety (97). In line with these findings, physical and emotional problems have been reported before as frequent self-reported S/Ps (51, 68).

Patients in this study listed an average of 0.5 S/Ps on WISP, 85% of these S/Ps were reported as moderate to severe. The average confirms that patients self-report S/Ps when these are perceived as very distressing (50, 56) and shows that an open-ended question such as WISP is important to complement validated questionnaires during the symptom assessment of patients.

Paper II

Paper II investigated the results from WISP in more detail and found that the highest probability of reporting 'any additional S/P' on WISP was seen for patients with younger children compared to patients with older children, and for patients living with someone compared to those living alone. It is remarkable that no association was seen between sex, age, cancer diagnosis and type of first contact and 'any additional S/P'.

In the current study, patients with younger children, patients living with someone, outpatients and patients with cancer in the prostate, colorectal, female genital organs and digestive system were more likely to report some of the ten prevalent additional S/Ps. In agreement with this study, earlier studies found that cohabitation status, cancer diagnosis and type of first contact were associated with several S/Ps reported in palliative care (65, 75, 76, 79). However, no associations between sex, age, and each of the ten most prevalent additional S/Ps were found in the present study, contrary to previous findings showing associations between sex, age, and common S/Ps in palliative care (65-67, 72, 73, 75). Additionally, this study found no associations between dizziness, dysphagia, diarrhea, and patient characteristics, differing from two studies indicating that male gender was associated with reporting dysphagia (72), and gynecological and gastrointestinal cancer were associated with reporting diarrhea (76).

To my knowledge, this is the first study to investigate patient characteristics associated with self-reported symptoms in an open-ended question such as WISP. Patients with younger children and patients living with someone had the highest probability of suffering from any additional symptom/problem. This may be explained because parenting younger children increases the probability of experiencing more distressing symptoms (98), and living with someone may help patients to be more aware of their symptoms and reporting them. Similarly, patients with younger children were more likely to suffer from edema and sore mouth than patients with older children, and patients living with someone were more likely to suffer from cough and sweats than patients living alone.

Regarding diagnosis, patients with prostate and colorectal cancer were more likely to suffer from incontinence than other cancer patients. On explanation may be related to the curative treatment these patients received, being that fecal incontinence is a common consequence of radiotherapy (99), and urinary incontinence a consequence of prostatectomy (100) in prostate cancer patients. Likewise, both types of incontinence have been related to the antineoplastic treatment in colorectal cancer patients, as well as the location and progression of their tumor (101). The high probability of reporting sweats among prostate cancer patients may be the result of their androgen deprivation therapy, as it has been shown that more than 60% of patients may experience hot flashes and/or night sweats during this therapy and until a few months later (102-104). In this study, patients with cancer in female genital organs and digestive system were more likely to suffer from vomiting, which is in agreement with other Danish study where any degree of nausea/vomiting was associated with gynecologic and stomach cancer (105). Similarly, the association between nausea/vomiting and cancer in the digestive or gynecological system has been reported by previous studies (77, 79, 106).

Lastly, in this study outpatients were more likely to report dry mouth than inpatients, which differs from earlier literature showing that dry mouth is frequently associated with old age and type of medication (107).

Paper III

The content validation of the EORTC QLQ-C15-PAL performed in Chile, replicating the methods used to abbreviate the EORTC QLQ-C30 across six European countries in Groenvold et al.’s study (24), obtained similar results confirming its content validity for use in palliative care in Chile. Qualitative data identified ten relevant issues not included in the questionnaire and detected linguistic problems in the dyspnea and constipation items.

In the present study, the 48 patients and 35 HCPs interviewed selected pain, physical functioning, sleeping difficulties, emotional functioning, nausea/vomiting, fatigue, social functioning, lack of appetite, role functioning and constipation as the 10 most important dimensions to be used to assess the outcome of palliative care in Chile, of which 8 form the EORTC QLQ-C15-PAL questionnaire (24). These dimensions were prevalent needs in palliative care reported in a previous study, comparing the content of PRO instruments against symptoms reported on medical records (68).

The level of importance given to the five abbreviated scales, i.e., EORTC QLQ-C30 scales that were shortened to fewer items in order to develop the EORTC QLQ-C15-PAL, agreed with the original study (24). Patients mainly selected physical functioning and fatigue as the most important scales, whereas HCPs selected emotional functioning, nausea/vomiting, and global health status/QOL scales. Most of the items of the scales retained in the EORTC QLQ-C15-PAL after abbreviation were also chosen by respondents as relevant topics to measure the outcome of palliative care in Chile.

Regarding the remaining scales, pain was selected as the most important dimension by 96% of respondents, and pain has been widely identified as one of the most frequent and severe symptoms experienced by advanced cancer patients (53-55). Although social and role functioning scales were not maintained in the EORTC QLQ-C15-PAL because the specific items formulations were not appropriate for palliative care, these dimensions were selected as very important by 49% and 43% of the participants in Chile respectively. In a previous qualitative study from a single palliative care service in Chile (108), the main concerns reported by patients were in relation to the need for social support, and their role in the family and society as workers, which may explain why these scales were more relevant for patients than for HCPs.

Qualitative data identified ten relevant additional issues not included in the EORTC QLQ-C15-PAL. The most frequent issues were satisfaction with care, emotions, and psychological support. These issues differ from the study by Groenvold et al. (24), where existential and spiritual problems were the most frequently reported. However, in both studies, HCPs reported twice as many problems as patients, this could be explained by the fact that HCPs have experience from many different patients and because the interview asked for additional problems at the conclusion and, as in the original study, patients may have been too tired or symptomatic to answer.

Furthermore, qualitative data was also helpful in detecting linguistic problems in the dyspnea and constipation items. These items received low relevance scores by 33% and 20% of the respondents respectively, and the main reason was that the translations of these questions were poorly formulated. A complete document with the participants' comments about linguistic problems found in this study was submitted to the Translation Unit of the EORTC Quality of Life Department for possible revision. After their analysis, both items were modified in the Chilean-Spanish version of the EORTC QLQ-C30 and the EORTC QLQ-C15-PAL.

Paper IV

Paper IV showed that patients reported moderate to severe levels of symptoms at admittance to palliative care in Chile. Importantly, after the first month of palliative care, emotional functioning, pain, sleeping difficulties, constipation and anxiety improved significantly. Residence, cohabitation status, diagnosis and current antineoplastic treatment were associated with changes in S/P scores.

At admittance to palliative care, this study had a good consent rate since 80% of the eligible patients gave their written approval to participate. In the present study, fatigue, pain and sleeping difficulties were the most prevalent S/Ps with the highest mean scores. The high prevalences of fatigue and pain are in line with previous studies in which these symptoms were among the most frequently reported by patients in palliative care, except for sleeping difficulties (65, 66, 72, 74, 83, 109-111). Sleeping difficulties was reported by 54% of patients in this study, which is higher than found previously (12–49%) (72, 74, 83, 109-111). However, a preliminary study conducted a single palliative care service in Chile also found a high prevalence of sleeping difficulties

(94.8%) in 77 patients admitted to palliative care (71). The prevalence of definite anxiety (11%) or depression (10%) reported on HADS in the present study (score ≥11) was lower compared to European and American studies, where the prevalence of definite anxiety ranged 22–28% and definite depression ranged 25–47% in patients admitted to palliative care (58-61).

Concerning the WISP instrument, a total of 18 S/Ps not included in the EORTC QLQ-C15-PAL were identified. Almost all these S/Ps have also been self-reported by patients in palliative care in earlier studies (50, 51). The most prevalent additional S/Ps reported in this study were cough (5.5%), bloating (3.5%), and diarrhea (2.5%), which were roughly similar to the prevalences found by Homsi et al.'s study in 200 patients using an open-ended question (50), but higher than the prevalences reported on WISP by 5,447 patients admitted to SPC in Denmark as shown on Paper I. However, 70% of the additional S/Ps in our study were reported as moderate to severe on WISP in line with the symptom severity reported on WISP in Denmark (Paper I), which reaffirms that symptoms are self-reported by patients when they are experienced as severe (50, 56) and highlights the importance of using WISP together with the EORTC QLQ-C15-PAL for an exhaustive symptom assessment.

In the current study, the levels of symptoms found for fatigue, pain and sleeping difficulties were lower compared to earlier European studies using the EORTC QLQ-C15-PAL or the EORTC QLQ-C30 questionnaires (29, 35, 36, 61-66), but similar to one Canadian study (81). This difference may be explained by the fact that Chilean patients included in our study had a better physical function than earlier studies (29, 35, 36, 61-66). Also, these patients had a good performance status (KPS ≥50), excluding the most symptomatic and impaired patients. However, the high performance status observed in the Chilean patients raises the question of whether less of the most severely ill patients were referred to palliative care. In fact, only 62 patients were excluded from this study for having a KPS <50.

In our study, the S/P scores were statistically significantly related to patient characteristics. In line with this study, previous studies also found worse levels of sleeping difficulties (66, 67, 72, 75), and worse levels of nausea/vomiting (66, 70, 72) in younger patients compared to older patients in palliative care; nevertheless, no significant differences were found in fatigue scores by age in two previous studies (67, 70). More sleeping problems presented in younger patients may be explained by the difficulties to face a terminal illness, especially in relation to not being able to fulfill future expectations, plans and worry about their economic future and their families (112).

Moreover, more impaired physical functioning was seen in single patients and patients living in others’ residence, which is similar to a study reporting that single patients had more impaired physical functioning than patients living accompanied (111). This could be explained because patients living alone do not have assistance in their daily activities and thus, may perceive their physical problems as more severe than cohabiting patients. An explanation why patients living in other´s residence experienced more severe physical problems, may be that this category (other´s residence) includes elderly homes where patients frequently have a poor physical function. In this study, patients with younger children reported worse fatigue and worse nausea/vomiting than patients with older children. This may occur because of greater stress involved with parenting younger children increase the chance of distressing symptomatology (98). Finally, patients in current antineoplastic treatment reported worse nausea/vomiting, anxiety, depression and more impaired physical and emotional functioning than patients not in treatment. These symptoms may be related to the side effects of antineoplastic treatment since earlier studies also found high levels of symptoms and more impaired functioning in patients receiving treatment than those who did not (36, 75).

During the first month of palliative care, this study had a very good retention of patients since 80% of the 201 patients who answered the questionnaires at baseline completed the study. In agreement with this study several studies have found that pain, constipation, sleeping difficulties and emotional functioning improved significantly after 2–4 weeks of palliative care (36, 62, 63, 67, 80), whereas other studies found that pain and sleeping difficulties worsened the same period (37, 64). Additionally, two other studies found a significant improvement in anxiety even after one week (62, 82).

Relatively few studies have investigated patient characteristics associated with changes in S/Ps over time, and found that age, sex and the baseline severity of other symptoms were associated with symptom improvement (86, 87), which differs from the findings of this study, since no association was found between age, sex and changes in S/Ps.

In the present study, a more positive change in nausea/vomiting and QOL scores was seen in patients living in their private residence compared to those who did not. One explanation for these positive changes could be that all patients who lived in their private residence lived accompanied, receiving more help from their family caregivers, particularly after being educated about patient care at the start of palliative care. A positive change in emotional functioning scores was seen for patients living alone with children compared to the other categories. This change could reflect that the worry that single parents have regarding the fate of their children when facing a terminal illness can be reduced after the admission to palliative care. Additionally, the worst baseline scores in appetite loss were observed in patients with gallbladder and prostate cancer, which may explain why these patients had a positive change in appetite loss compared to other cancer patients after one month in palliative care. Likewise, worse baseline scores in anxiety, depression and physical functioning were observed in patients receiving current antineoplastic treatment compared to those who were not in treatment, which also could be explained because symptoms with higher baseline scores are more likely to have the greatest improvement (82, 89).

Strengths and limitations

This thesis has several methodological strengths and limitations that should be considered when interpreting the results.

One of the strengths of this thesis is the large dataset available for studying the S/Ps identified using the WISP instrument and associations with patient characteristics; the study provided new insights into the evaluation of symptoms of patients admitted to SPC in Denmark (Papers I–II). The study included a large sample of 5,447 patients admitted to all SPC units in Denmark of whom 1,778 patients reported at least one S/P using the WISP instrument (Paper I), and 1,295 reported S/Ps not included in the EORTC QLQ-C15-PAL (Paper II). Also, the data for these studies were obtained from the high quality database DPD. The DPD comprises the clinical and demographic characteristics of all patients referred to all SPC units in Denmark with high data completeness, close to 100% (91). Complete national data constitute a major advantage compared to single center studies, which are often conducted in university hospitals that are not representative for the entire patient population.

A strength of the longitudinal study (Paper IV) is that it was the first, to my knowledge, in investigating symptoms and quality of life of patients at the start of palliative care and over time, adding new knowledge of the symptomatology of patients in Chilean palliative care services. Additionally, the symptomatology of patients was evaluated trough the EORTC QLQ-C15-PAL and HADS, which are well-known validated instruments for symptom assessment of advanced cancer patients in palliative care (38, 113). Furthermore, the study analysis was carried out without missing data since all patients were able to complete the instruments by themselves or with the assistance of HCPs. Similarly, the content validation of the EORTC QLQ-C15-PAL in Chile was performed without missing data, as during interviews the researcher accompanied both the patients and health professionals during their evaluation of the importance of the EORTC QLQ-C30 items (Paper III).

Finally, the coding of data from open-ended questions such as WISP is time-consuming and requires a carefully constructed coding system. It was a strength that the coding system used to code the Chilean data (Paper IV) could be based on the extensive work carried out in the much larger Danish study (Paper I).

A limitation of this thesis is the inherent disadvantages of using an open-ended question such as the WISP instrument. Firstly, it is known that the number of self-reported symptoms using open-ended questions is lower compared to those reported by standard questionnaires (50). Secondly, patients self-report symptoms which they consider very distressing (56), which means that they may experience other symptoms but not necessarily report them. Thus, the interpretation of the responses from an open-ended question at the group level is very complex, e.g., symptom prevalence will appear low if only a small proportion of the patients having a symptom reports it. In addition, when a low number of patients self-report symptoms the ability to define subgroups of patients and the power to detect differences between them is limited (Paper II). However, when the WISP instrument supplemented the EORTC QLQ-C15-PAL at admittance to palliative care in Denmark and Chile, the recognition of symptoms increased considerably (Paper I and IV).

Other open-ended questions have been added to some PRO instruments such as the EORTC QLQ-LC29 (48), ESAS (41), the MSAS (43) and the short-form of MSAS-SF (49), and the IPOS scale (45), but results on which symptoms are listed in these instruments have to my knowledge not been published. Also, the way these open-ended questions score the intensity of the symptoms varies, e.g., in the ESAS the intensity of the additional symptoms reported in its open-ended question are rated from 0 (no symptom) to 10 (worst possible), and in the IPOS additional symptoms are rated from 0 (not at all) to 4 (overwhelmingly). This means that the results are not directly comparable to each other.

Another limitation of this thesis is that the sample size of the studies conducted in Chile was smaller than planned at the beginning of the studies. In Paper III, for the content validation of the EORTC QLQ-C15-PAL, it was planned to recruit at least 10 patients and 10 HCPs from each palliative care service, but half of the services included in the study had less than 10 professionals in their staff, e.g., the palliative care service of the Hospital San Juan de Dios had two physicians, two nurses and one psychologist when the interviews were conducted. In Paper IV, although we recruited 80% (n=201) of the eligible patients, half of the patients were included from one of the four palliative care services involved in the study, which limited the possibility of comparing the symptomatology of patients between hospitals. Additionally, only outpatients were recruited, because most of the palliative care services did not have an inpatient unit and because palliative home care was provided by other services/teams.

The psychometric properties of the EORTC QLQ-C15-PAL were not statistically tested in Chile and thus, this could be a limitation of this study (Paper III). The construct validity and reliability of this questionnaire for its use in palliative care have been successfully evaluated in several countries worldwide (26-37). Because of the dissimilarities in the organization and availability of palliative care services between Chile and the six European countries where this questionnaire was developed (24), it was decided to conduct a study of content validity in Chile (rather than studying psychometric properties). This led us, for instance, to identify unexpected linguistic problems in two items that were subsequently revised by the EORTC group.

CONCLUSIONS

- Patients with advanced admitted to SPC in Denmark suffered from many symptoms and problems not included in the EORTC QLQ-C15-PAL, and these could be identified by the WISP instrument (Paper I).
- The WISP instrument increases the recognition of symptoms by combining standard methods with individualization. Thus, its use alongside the EORTC QLQ-C15-PAL and the EORTC QLQ-C30 is highly recommended for a comprehensive symptom assessment of patients in palliative care (Paper I).
- Whereas type of first contact, diagnosis, age and sex were not found to be associated, having younger children and living with someone were associated with the highest probability of reporting any additional symptom/problem on WISP at admittance to SPC in Denmark (Paper II).
- The EORTC QLQ-C15-PAL had good content validity for evaluation of symptoms and quality of life of patients receiving palliative care in Chile. The linguistic problems found in the dyspnea and constipation items were revised by the EORTC group. Additional research is needed to address the social dimension in the assessment of patients' quality of life (Paper III).
- Patients with advanced cancer reported moderate to severe levels of S/Ps at admittance to palliative care in Chile, where pain, fatigue and sleeping difficulties had the highest levels of symptom scores (Paper IV).
- Patients reported a significant improvement in emotional functioning, pain, sleeping difficulties, constipation and anxiety during the first month of palliative care in Chile (Paper IV).
- The high performance status observed in patients admitted to palliative care services in Chile raises the question of whether the most severely ill patients were referred to palliative care to a lesser extent (Paper IV).
- Several sociodemographic and clinical patient characteristics were associated with changes in symptom/problem scores in patients from Chilean palliative care services (Paper IV).

PERSPECTIVES

Future research

The WISP instrument showed good qualities to increase the recognition of S/Ps when supplementing the EORTC QLQ-C15-PAL, but future research is needed to determine a clear methodology for the interpretation of its data. For example, WISP results are not comparable with several other PRO instruments that added an open-ended question, mainly because the number of symptoms collected or scoring intensity methods are different from WISP (41, 43, 45). In future research, it would be relevant to explore how to incorporate the most prevalent S/Ps listed on WISP. These should be part of the standardized assessment of symptoms in patients receiving palliative care, especially in those groups of patients where S/Ps were associated to certain patient characteristics, e.g., incontinence (including fecal and urinary incontinence) was significantly associated with colorectal and prostate cancer; therefore, this symptom should be included in the daily symptom assessment of patients with these cancer diagnoses since its presence is a frequent consequence of their antineoplastic treatment.

On the other hand, the EORTC QLQ-C15-PAL had good content validity for the assessment of the outcome of palliative care in Chile. However, it is necessary to investigate which other dimensions may be relevant that are not included in this questionnaire, e.g., the social dimension, since 49% of participants in the interviews selected this scale as very important. Also, a preliminary qualitative study showed that for Chilean patients in palliative care, the most important concerns regarding palliative care needs were related to social support (108). Other aspects not included in this questionnaire that were often mentioned by patients and HCPs were satisfaction with care, psychological issues, and sexuality. These issues may also be considered in future research.

This thesis provides new information on the symptomatology of patients admitted to palliative care in Chile. To expand on this work future studies should incorporate more patients and palliative care services to obtain a broader overview of the current symptomatology of patients receiving palliative care in Chile. It would also be relevant to measure the symptomatology in patients from other types of services than outpatients, e.g., inpatients and patients in home palliative care, considering that previous studies have shown important symptom differences between them (61, 76), and not least to study patients with other life-threatening diagnoses than cancer. Such studies might reveal important differences in relation to referral patterns to palliative care as well as in the provision of palliative care to different groups of patients. Finally, even though some previous studies of palliative care interventions have shown no significant results for symptom control (114), in this thesis several S/Ps improved significantly after the first month in palliative care; therefore, this should be contemplated to promote future longitudinal studies.

Practical implications

International organizations have recommended that the palliative care needs of cancer patients and their families should be assessed through appropriate screening instruments (19, 20). Several studies have demonstrated the relevance of using PRO instruments for the systematic assessment of symptoms in palliative care and thus, to prevent that clinicians may overlook patient symptoms (115, 116). In this context, the Danish Health Authorities have promoted the use of PRO instruments for the evaluation of palliative care needs in patients with a life-threatening illness, such as the EORTC QLQ-C15-PAL questionnaire (8).

Since 2010, when the DPD was launched, the registration of the patient-reported S/Ps on the EORTC QLQ-C15-PAL and WISP for all patients admitted to SPC in Denmark has been established as mandatory (91). Therefore, this information is continuously used by clinicians in the planning of patient care. However, WISP results are still managed at the individual level (patients) and to integrate this information at a group level (SPC units) some steps need to be done, such as developing electronic coding systems, as mentioned below.

In this thesis, it is demonstrated that adding the open-ended WISP instrument to the original EORTC QLQ-C15-PAL questionnaire clearly improves the identification of symptoms that patients experience at admittance to SPC. The WISP study (Paper I) provides a list of 61 symptoms to categorize qualitative responses obtained from WISP into symptoms and problems, but greater efforts are necessary to establish a standard methodology for the comparison of WISP results across all SPC units in Denmark and with other countries, as well as to simplify the analysis of data. Electronic systems for automatic coding may be useful for these procedures based on the (manual) coding systems developed in Paper I, and such automatic coding systems would need translation and repeated validation when used in other countries.

In Chile, the Ministry of Health has recommended through the Clinical Guidelines for the Program "Pain Relief for Advanced Cancer and Palliative Care" the evaluation of patients' symptoms by PRO questionnaires such as ESAS and the EORTC QLQ-C15-PAL (9). However, a decision has not been made for the use of a single symptom assessment instrument that allows comparison of the results between different palliative care services in Chile. These findings in this thesis showed that the EORTC QLQ-C15-PAL is a qualified instrument for this purpose for several reasons. First, it showed good content validity for the assessment of patients' symptomatology in Chile. Second, the linguistic problems found in some items were solved by the EORTC group improving the questionnaire, and to date, it is the only validated instrument for use in Chilean palliative care. Additionally, the WISP instrument also proved to be a good screening of symptoms and problems not covered by the EORTC QLQ-C15-PAL and thus, its use alongside this questionnaire should be considered for a comprehensive symptom assessment of patients in palliative care.

Furthermore, the Clinical Guidelines has also recommended that patients in palliative care and their families should receive social support from palliative care services (9), as well as been emphasized by international organizations (1, 20), but it seems that this recommendation has not been fulfilled by current palliative care services since only one of the four palliative care services involved in this thesis included a social worker as part of their staff. This enhances the importance of including a social dimension in the assessment of the outcome of palliative care that may improve organizational resources of palliative care services.

SUMMARIES

English summary

Introduction: Palliative care aims to improve the quality of life (QOL) of patients with life-threatening illness through early assessment and treatment of their symptoms and problems (S/Ps). Several studies have investigated the symptomatology of patients at admittance to specialized palliative care (SPC) in Denmark through validated questionnaires, but little evidence is available on which other symptoms not covered by standardized methods, patients may experience. In contrast to Denmark, evidence on the symptomatology of patients admitted to palliative care in Chile is sparse, and no instruments have been validated for this purpose.

Aims: This PhD thesis is based on data collected from all SPC units registered in the Danish Palliative care Database (DPD), and from four SPC services in Chile. The aim of Paper I was to investigate the nature, prevalence, and severity of S/Ps reported using the Write In three Symptoms/Problems instrument (WISP) by advanced cancer patients admitted to SPC in Denmark. Paper II aimed to investigate whether sociodemographic variables, diagnosis and type of first contact were associated with S/Ps reported on WISP at admittance to SPC in Denmark. Paper III aimed to investigate the content validity of the EORTC QLQ-C15-PAL as evaluated by patients and health care professionals (HCPs) from palliative care services in Chile, replicating the methods used to abbreviate the EORTC QLQ-C30 among European patients in palliative care. The aim of Paper IV was to examine the symptomatology of advanced cancer patients at admittance to palliative care in Chile and to investigate how this symptomatology changed during the first month and whether these changes were associated with patient characteristics.

Participants: Paper I–II included advanced cancer patients admitted to SPC in Denmark who completed the EORTC QLQ-C15-PAL and reported S/Ps on WISP. Paper III included outpatients receiving palliative care in Chile and HCPs whose main occupation was in palliative care. Paper IV included outpatients with advanced cancer who completed the EORTC QLQ-C15-PAL, WISP and the Hospital Anxiety and Depression Scale (HADS) at admittance to palliative care in Chile.

Methods: In Paper I, S/Ps reported on WISP were categorized qualitatively, and their prevalence and severity were estimated. In Paper II multiple logistic regressions were used to investigate associations between patient characteristics and the most prevalent additional S/Ps reported on WISP. In Paper III, interviews were conducted to evaluate the importance of the EORTC QLQ-C30 items for assessing the outcome of palliative care in terms of their relevance, appropriateness, relative importance and breadth of coverage. In Paper IV, the prevalence and severity of S/Ps reported at admittance were estimated. Changes in S/P scores during the first month were estimated overall and according to patient characteristics. Multiple linear regressions were used to investigate the associations between patient characteristics and changes in S/P scores.

Results: Paper I found that among the 5,447 patients who completed the EORTC QLQ-C15-PAL at admittance to SPC in Denmark, 1,778 reported a total of 2,796 S/Ps on WISP. Of these S/Ps 63.6% were additional, i.e. not included in the EORTC QLQ-C15-PAL, 24.8% were S/Ps already included, and 11.7% were diagnoses or responses that could not be coded. Edema, dizziness, cough and sweats were the most prevalent additional S/Ps. Of the S/Ps, 85% were reported as moderate to severe. Paper II found that the highest probability of reporting any additional symptom/problem was seen for patients with younger children compared to patients with older children, and for patients living with someone compared to those living alone. In addition, patients with younger children, patients living with someone, outpatients and patients with cancer in prostate, colorectal and in female genital organs were more likely to report some of the ten prevalent additional S/Ps. In Paper III, 48 patients and 35 HCPs selected pain, physical functioning, sleeping difficulties, emotional functioning, nausea/vomiting, fatigue, social functioning, lack of appetite, role functioning and constipation as the ten most important dimensions to be used to assess the outcome of palliative care. Qualitative data detected linguistic problems in the dyspnea and constipation items, as well as identified ten relevant issues not included in the questionnaire. Paper IV found moderate to severe levels of S/Ps in 201 patients at admittance to palliative care in Chile. Fatigue, pain and sleeping difficulties were the most prevalent S/Ps and the S/Ps with the highest mean scores. After the first month of palliative care, emotional functioning, pain, sleeping difficulties, constipation and anxiety improved significantly. Residence, cohabitation status, diagnosis and current antineoplastic treatment were associated with changes in S/P scores.

Conclusions: The WISP instrument increases the recognition of symptoms by combining standard methods with individualization. A number of associations were found between the clinical and sociodemographic variables and overall reporting of S/Ps on WISP as well as the occurrence of the specific S/Ps. The EORTC QLQ-C15-PAL had good content validity for evaluation of symptoms and QOL of patients receiving palliative care in Chile. Moderate to severe levels of S/Ps were found in Chilean patients at admittance to palliative care. Several S/Ps improved significantly during the first month of palliative in Chile, and certain patient characteristics were associated with changes in S/P scores.

Danish summary

Introduktion: Formålet med palliativ indsats er at forbedre livskvaliteten hos patienter med livstruende sygdom ved tidligt at vurdere deres symptomer og problemer (S/P'er) og behandle dem. Adskillige studier har anvendt validerede spørgeskemaer til at undersøge patienters symptomatologi ved start af specialiseret palliativ indsats (SPI) i Danmark, men der er begrænset viden om, hvilke andre symptomer, som ikke er dækket af standardiserede metoder, patienter kan opleve. I modsætning til Danmark, mangler der i Chile viden om symptomatologien blandt patienter ved start af SPI og der findes ikke instrumenter valideret til dette formål i Chile.

Formål: Denne ph.d.-afhandling er baseret på data indsamlet fra alle danske SPI enhedergennem Dansk Palliativ Database (DPD) og fra fire Chilenske SPI enheder. Formålet med artikel I var at undersøge type, prævalens og intensitet af S/P'er blandt patienter med fremskreden kræft rapporterede ved start af SPI ved brug af instrumentet 'Write In three Symptoms/Problems instrument (WISP)'. Artikel II undersøgte om der ved start af SPI i Danmark var en sammenhæng mellem henholdsvis sociodemografiske variabler, diagnose og typen af første kontakt og de ti hyppigste S/P'er rapporteret i WISP. I artikel III havde til formål at undersøge indholdsvaliditeten af EORTC QLQ-C15-PAL vurderet af patienter og sundhedsprofessionelle fra palliative enheder i Chile med anvendelse af de metoder, der tidligere var anvendt til at forkorte EORTC QLQ-C30 blandt europæiske patienter. Artikel IV havde til formål at undersøge symptomatologien blandt patienter med fremskreden kræft ved start af SPI i Chile og at undersøge, hvordan symptomatologien ændrede sig den første måned, samt om ændringerne var associerede med patientkarakteristika.

Studiepopulation: Artikel I-II inkluderede danske patienter med fremskreden kræft, der ved start af SPI havde udfyldt EORTC QLQ-C15-PAL og rapporteret S/P'er i WISP. Artikel III inkluderede ambulante patienter fra SPI-enheder i Chile og sundhedsprofessionelle med palliation som hovedbeskæftigelse. Artikel IV inkluderede ambulante patienter med fremskreden kræft, som udfyldte EORTC QLQ-C15-PAL, WISP og 'the Hospital Anxiety and Depression Scale (HADS)' ved start af SPI i Chile.

Metode: I artikel I blev der foretaget en kvalitativ kategorisering af S/P'er rapporteret på WISP og prævalens og intensitet af S/P'erne blev beregnet. I artikel II blev multipel logistisk regression anvendt til at undersøge sammenhængen mellem patientkarakteristika og S/P'er rapporteret på WISP. I artikel III blev der foretaget interviews for at vurdere vigtigheden af EORTC QLQ-C30 spørgsmål, når effekten af palliativ indsats skulle vurderes, herunder spørgsmålenes relevans, om de var passende, relativ vigtighed og hvor vidt de var indholdsmæssigt dækkende. I artikel IV blev prævalensen og intensiteten af S/P'er estimeret ved start af SPI. Ændringer i S/P-scorer efter en måned blev beregnet såvel overordnet som i forhold til patientkarakteristika. Multipel lineær regression blev anvendt til at undersøge sammenhængen mellem patientkarakteristika og ændringer i S/P scorer.

Resultater: I artikel I var der ud af de 5.447 patienter, der besvarede EORTC QLQ-C15-PAL ved start af SPI, 1.778 der rapporterede i alt 2.796 S/P'er i WISP. Af disse var 63,6% af de rapporterede S/P'er 'ekstra', dvs. ikke inkluderet i EORTC QLQ-C15-PAL, 24,8% var allerede inkluderet og 11,7% var enten diagnoser eller svar, der ikke kunne kodes. Ødemer, svimmelhed, hoste og svedtendens var de hyppigste ekstra S/P'er. Af de ekstra S/P'er blev 85% rapporteret på et moderat til højt niveau. Artikel II fandt, at der var større sandsynlighed for at rapportere ekstra S/P'er blandt patienter med yngre børn sammenlignet med patienter med ældre børn, og blandt patienter, der boede sammen med nogen, sammenlignet med dem der boede alene. Derudover havde patienter med yngre børn, patienter, der boede med andre, ambulante patienter, patienter med kræft i prostata, i de kvindelige kønsorganer og patienter med mavetarmkræft den højeste sandsynlighed for at rapportere et af de ti hyppigste ekstra S/P'er. I artikel III udvalgte 48 patienter og 35 sundhedsprofessionelle, smerte, fysisk funktion, søvnbesvær, følelsesmæssig funktion, kvalme/opkast, fatigue, social funktion, manglende appetit, rollefunktion og forstoppelse som de ti vigtigste dimensioner til at vurdere effekten af palliativ indsats. Kvalitative data viste sproglige problemer med spørgsmålene om dyspnø og forstoppelse, og der blev identificeret ti relevante emner, som skemaet ikke inkluderede. Artikel IV fandt moderate til svære niveauer af S/P’er hos 201 patienter ved start af SPI i Chile. Fatigue, smerte og søvnbesvær var de hyppigste S/P’er og samtidig dem med højeste gennemsnitsscorer. Følelsesmæssig funktion, søvnbesvær, forstoppelse og angst blev forbedret signifikant efter en måneds SPI. Ændring i S/P scorer over tid var relateret til boligforhold, samlivsstatus, diagnose og om patienten var i kemobehandling .

Konklusion: WISP-instrumentet forbedrer afdækningen af symptomer ved at kombinere standardmetoder med individualisering. Der blev fundet sammenhænge mellem kliniske og sociodemografiske variabler og rapportering af S/P’er i WISP, både samlet og for de specifikke S/P’er. Indholdsvaliditeten af EORTC QLQ-C15-PAL var god i forhold til at vurdere symptomer og livskvalitet blandt patienter i SPI i Chile. Moderate til svære niveauer af S/P’er blev fundet blandt de chilenske patienter ved start af palliative indsats. En måned efter start af SPI i Chile var der signifikante forbedringer i flere S/P'er, og en række patientkarakteristika var associeret med ændringer i S/P scorer.

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ORIGINAL
PAPERS

PAPER I

Supportive Care in Cancer
https://doi.org/10.1007/s00520-019-04976-x

ORIGINAL ARTICLE

Which symptoms and problems do advanced cancer patients admitted to specialized palliative care report in addition to those included in the EORTC QLQ-C15-PAL? A register-based national study

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Received: 19 March 2019 / Accepted: 28 June 2019

Abstract

Purpose Patients in palliative care are willing to answer short questionnaires, like the EORTC QLQ-C15-PAL; however, patients may suffer from other symptoms and problems (S/Ps) not covered by such questionnaires. Therefore, to identify which other S/Ps patients experience, in addition to those already included in the EORTC QLQ-C15-PAL, we developed a brief instrument to supplement this questionnaire named WISP (Write In three Symptoms/Problems), permitting patients to report 1–3 additional S/Ps and their severity. We aim to investigate the nature, prevalence, and severity of S/Ps reported on WISP.

Methods A register-based study with data obtained from the Danish Palliative Care Database. This study included adults with advanced cancer admitted to specialized palliative care in Denmark, who reported S/Ps on WISP. S/Ps were categorized qualitatively, and their prevalence and severity were calculated.

Results Of the 5447 patients who completed the EORTC QLQ-C15-PAL, 1788 (32.8%) reported at least one symptom/problem using WISP. In total, 2796 S/Ps were reported; 24.8% were already covered by EORTC QLQ-C15-PAL; 63.6% were new, 10.1% were diagnoses and 1.6% could not be coded. S/Ps already covered and new were grouped into 61 categories. The most prevalent S/Ps reported were (in decreasing order) pain, edema, dizziness, impaired physical or emotional function, cough, and sweats. Overall, 85% of the S/Ps were rated as moderate to severe.

Conclusions The WISP instrument strongly improves the recognition of S/Ps by combining standardization with individualization. We recommend its use for comprehensive symptom assessment alongside the EORTC QLQ-C15-PAL, and potentially also alongside the EORTC QLQ-C30.

Keywords EORTC QLQ-C15-PAL · Advanced cancer · Palliative care · Symptom assessment · Prevalence

Introduction

Patients with advanced cancer suffer from many symptoms that arise from their treatment and the disease itself. The most prevalent reported symptoms in advanced cancer patients are fatigue, pain, anorexia, lack of energy, weakness, appetite loss, and worry [1, 2]. Early detection and treatment of symptoms to improve patients' quality of life are the main goals of palliative care [3]. To achieve these goals, systematic assessment of symptoms is needed [4, 5].

Several questionnaires have been validated for assessment of symptoms and/or quality of life in palliative care research such as the Edmonton Symptom Assessment Scale (ESAS) [6], the Functional Assessment of Chronic Illness Therapy-Palliative Care Scale (FACIT-Pal) [7], the McGill Quality of Life questionnaire (MQOL) [8], the Assessment of Quality of life at the End of Life (AQEL) questionnaire [9], and the EORTC QLQ-C30 [10, 11]. There is, however, limited consensus about which instrument should be recommended for use in palliative care considering its length and content for patients at the end-of-life [12].

The European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 15 Palliative (QLQ-C15-PAL) is an abbreviated version of the

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EORTC Quality of Life Questionnaire Core 30 (QLQ-C30), which is one of the most commonly used instruments in cancer research [13]. The advantages of the EORTC QLQ-C30 comprise extensive translations, validations and use in oncology clinical trials, academic studies, and daily clinical practice [14, 15]. However, to reduce the burden on advanced cancer patients, its length was reduced from 30 to 15 items, forming the EORTC QLQ-C15-PAL. This 15-item questionnaire assesses nine symptoms and problems often reported by patients in palliative care such as physical function, emotional function, pain, fatigue, nausea, dyspnea, sleeping difficulties, lack of appetite and constipation, as well as overall quality of life [16].

Although patients in palliative care are willing to answer short questionnaires assessing the most relevant symptoms and problems (S/Ps) [17], they may suffer from other S/Ps not covered by instruments regularly used in palliative care e.g., Homsi et al. study assessed 48 symptoms [18]. Therefore, to identify which other S/Ps patients experience, in addition to those already included in the EORTC QLQ-C15-PAL, we developed a brief instrument to supplement this questionnaire named WISP (Write In three Symptoms/Problems), permitting patients to report voluntarily up to three additional S/Ps experienced in the past week and rate their severity.

The WISP instrument was not included in the original EORTC QLQ-C15-PAL questionnaire, and results have not been published before, except for a preliminary work in 373 patients from a single center, presented as a congress abstract in 2009 [19]. This study aims to investigate the nature, prevalence, and severity of symptoms and problems reported on WISP by advanced cancer patients admitted to specialized palliative care in Denmark.

Methods

Study design and patients

This is a register-based study based on prospectively collected data from the Danish Palliative Care Database (DPD). Patients admitted to specialized palliative care (SPC) between January and December 2016, who were diagnosed with advanced cancer, were at least 18 years old and completed the EORTC QLQ-C15-PAL questionnaire within a time limit (at the first day of contact with SPC or up to 3 days before) were included. If a patient was admitted to more than one SPC unit, only the data from the first admission was used.

Data collection

DPD is a national quality database that contains relevant information of all patients referred to SPC in Denmark (5.7 million inhabitants) since 2010. This database includes information on who referred the patient to SPC, date of SPC referral, diagnosis, demographic factors, and whether the patient was admitted to SPC or not. In addition to this, information on the date of SPC admittance, the type of SPC (inpatient or outpatient), social factors, and the patient-reported S/Ps on EORTC QLQ-C15-PAL and WISP, is registered for patients admitted to SPC [20]. All 43 SPC units, (26 hospital-based palliative care teams/units and 17 hospices), enter the patients' information in a web-based system called "Clinical Measurement System" which deliver data to DPD. According to the Danish Board of Health, it is mandatory for the SPC units to register all patients referred to their SPC in DPD [20]. The information in DPD is constantly validated against the Danish National Patient Register through the unique Danish personal number (CPR), to maximize the completeness of DPD, which is close to 100% [21]. DPD is funded by the Danish Regions and administered by the Danish Clinical Registries (RKKP), which request that all patients are registered, and that individual consent from patients is not applied [22]. In this study, the variables: sex, age, children, residence, cohabitation status, diagnosis, type of first contact, and information on S/Ps reported on WISP were collected from the DPD.

The EORTC QLQ-C15-PAL is an abbreviated version of the EORTC QLQ-30, which is the most widely used instrument in cancer clinical trials [13], and has been extensively validated showing satisfactory validity and reliability [14, 15]. The EORTC QLQ-30 was previously validated in Danish oncology patients [23]. The EORTC QLQ-C15-PAL includes the most important issues for palliative care identified in an international study consisting of interviews with health care professionals and patients [16] and statistical analyses using item response theory [24]. The EORTC QLQ-C15-PAL has been translated and validated in palliative care patients from several countries [25–29]. This questionnaire consists of 15 items measuring nine symptoms/functions and global quality of life (QOL): two multi-item functional scales (physical and emotional function), two multi-item symptom scales (pain and fatigue), a single-item version of the nausea and vomiting scale, four single-item symptom scales (dyspnea, sleeping difficulties, lack of appetite, constipation), and one item referring to overall QOL. Fourteen items are rated from 1 (not at all), 2 (a little), 3 (quite a bit) to 4 (very much), and QOL is rated from 1 (very poor) to 7 (excellent) [30]. In Danish SPC units, the EORTC QLQ-C15-PAL questionnaire is used to screen for the common S/Ps at the admission to SPC in order to inform clinical care.

The WISP instrument is an independent instrument, which was added directly after the EORTC QLQ-C15-PAL (but could be added after any questionnaire). The purpose of adding WISP is to supplement the EORTC QLQ-C15-PAL by measuring any S/Ps experienced by the patients, but not included in the questionnaire. The WISP consists of a single item asking patients to list up to three S/Ps not mentioned in the questionnaire preceding it, in our case the EORTC QLQ-C15-PAL. Responses on WISP were rated similarly to the EORTC QLQ-C15-PAL with four responses options ranging from 1 “not at all” to 4 “very much” (Fig. 1).

The presented paper reports data from the WISP instrument, not the EORTC QLQ-C15-PAL.

Qualitative analysis

The WISP responses were analyzed in two steps. First, all S/Ps reported by the patients using the WISP instrument were codified. S/Ps already covered by the EORTC QLQ-C15-PAL were grouped using categories indicating this (e.g., “pain in the neck” was coded as “pain”). Additionally, responses related to physical functioning were grouped in the category “impaired physical function” and responses about emotional problems were grouped in “impaired emotional function.”

In contrast, if the response concerned S/Ps not included in the EORTC QLQ-C15-PAL, new codes for S/Ps were developed employing the 48 categories of a prior study [18]. When a reported S/Ps did not match any existing categories, a new S/P category was established.

Statistical analyses

Patient characteristics were summarized using proportions for categorical variables and medians with ranges for continuous variables. To compare the patients who reported S/Ps using WISP to those who did not, non-parametric Chi-square test was used because significant p values from Kolmogorov-Smirnov and Shapiro-Wilk tests indicated non-normal distributions. A significance level of 0.05 was applied for these tests. A patient was defined as having S/Ps on WISP if reporting a score of at least 2 (“a little”).

The prevalence of each category was calculated for all patients who completed the EORTC QLQ-C15-PAL. The severity was calculated as the proportion of S/Ps reported as “a little” (mild), “quite a bit” (moderate), and “very much” (severe). Mean and median number of S/Ps was calculated for all patients who answered EORTC QLQ-C15-PAL and for those who reported S/Ps using WISP. All data were analyzed using the statistical software Statistical Package for the Social Sciences (SPSS) version 22.

Results

Patient characteristics

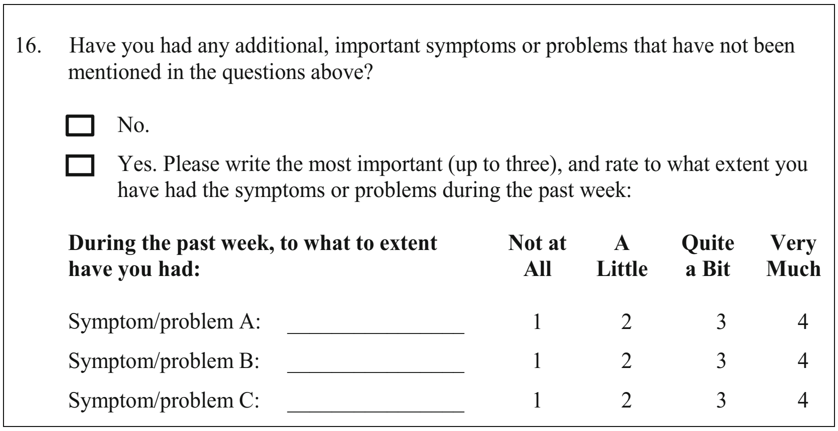
From January to December 2016, 11754 patients were referred to SPC in Denmark. Of these, 5447 had completed the EORTC QLQ-C15-PAL, and 1788 (32.8%) of these reported at least one symptom/problem using WISP. For further details, see Fig. 2.

Demographic and clinical characteristics of eligible patients can be seen in Table 1. Comparison of patients who reported S/Ps using WISP to those who did not showed that the distribution of sex, diagnosis, and type of first contact were not significantly different. Those who reported S/Ps on the WISP were slightly younger and more often lived in their private residence with a spouse or partner. The majority of patients were over 70 years old and were outpatients, and the most common diagnosis was lung cancer.

Prevalence and severity of additional symptoms and problems

A total of 2796 symptoms and problems were listed on WISP (Fig. 3). Of these, 24.8% concerned S/Ps already covered by the EORTC QLQ-C15-PAL and 63.6% were new. About 10.1% of the responses were not really S/Ps, but instead diagnoses such as mucus, neurological diseases, pressure ulcer, ascites, and fungus (Table 2). Finally, 1.6% of the responses could not be coded because the patient only mentioned a part of the body without specifying a symptom or problem ($n = 38$) or were illegible ($n = 7$). Diagnoses and responses that could not be coded were excluded from further analysis.

Fig. 1 The WISP (Write In three Symptoms/Problems) supplementary instrument allowing patients to report up to three symptoms and problems not already covered by the EORTC QLQ-C15-PAL



16. Have you had any additional, important symptoms or problems that have not been mentioned in the questions above?

☐ No.

☐ Yes. Please write the most important (up to three), and rate to what extent you have had the symptoms or problems during the past week:

During the past week, to what to extent have you had:		**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
Symptom/problem A:	_______________	1	2	3	4
Symptom/problem B:	_______________	1	2	3	4
Symptom/problem C:	_______________	1	2	3	4

Fig. 2 Flow-chart of patient inclusion

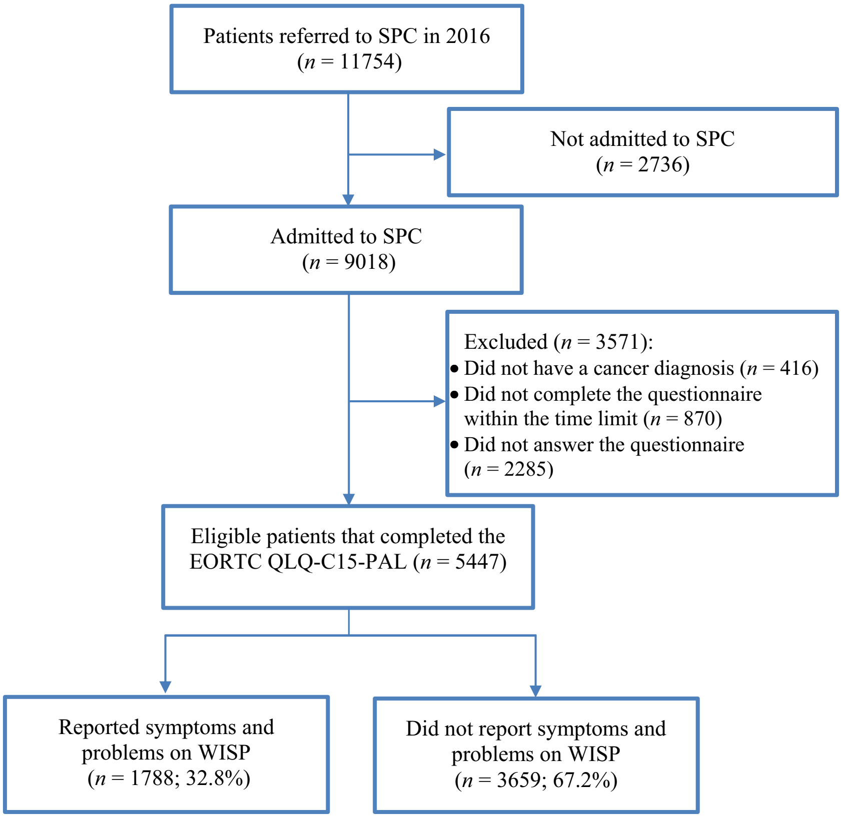


Table 3 illustrates the prevalence, frequency, and severity of S/Ps reported on WISP. In total, 2470 symptoms were grouped into 61 categories. The mean number of S/Ps reported by all patients that completed the EORTC QLQ-C15-PAL was 0.5 with a median of 0 (range 0–3). Patients who reported S/Ps on average reported 1.6 S/Ps with a median of 1 (range 1–3).

The most prevalent S/Ps not covered by the EORTC QLQ-C15-PAL were edema (3.4%), dizziness (3.1%), cough (1.6%), and sweats (1.5%.) The most prevalent S/Ps covered by the EORTC QLQ-C15-PAL were pain (4.2%), impaired physical function (2.8%), and impaired emotional function (2.8%).

The 154 problems categorized under impaired physical function include the following: balance problems (26.0%), muscular weakness (24.0%), paralysis (19.5%), limitations in daily activities (18.2%), and walking problems (12.3%). Problems categorized under impaired emotional function ($N = 152$) include being anxious (54.6%), fearful (22.4%), concerned (11.2%), irritated (8.6%), resigned (2.0%), and sad (1.2%).

Overall, S/Ps listed using WISP were frequently reported as severe (very much) (45%; $n = 1109$) or moderate (quite a bit) (40%; $n = 983$) and in only 15% ($n = 378$) of all cases as mild (a little). The most common S/Ps reported as severe were bloating and constipation (each reported as severe in 75% of cases). Conversely, S/Ps frequently reported as mild were bleeding (43.3%), drowsiness (40.4%), and skin problems (40.0%).

Discussion

The WISP instrument gave patients the possibility to report S/Ps not covered by the widely used EORTC QLQ-C15-PAL questionnaire. In this study, 1788 (32.8%) of the 5447 patients who completed the EORTC QLQ-C15-PAL reported a total of 2796 S/Ps using WISP. These S/Ps were classified in four groups: S/Ps already covered by EORTC QLQ-C15-PAL (24.8%), new S/Ps (63.6%), diagnoses such as mucus (10.1%), and responses that could not be coded (1.6%). The 2470 S/Ps that were either already covered by the EORTC QLQ-C15-PAL or were new were grouped into 61 categories.

The mean number of S/Ps reported using WISP by patients who completed the EORTC QLQ-C15-PAL was 0.5. This is a little lower compared to a mean of 1.3 voluntarily reported symptoms found in a previous study, where 50 advanced cancer patients were asked to list symptoms in an open-ended question before having completed questions about 20 physical symptoms [31]. The study by Homsi et al. conducted in 200 cancer patients found a median of voluntarily reported symptoms of 1 (range, 0–6) [18]; patients in that study were also asked to report symptoms voluntarily before systematic assessment of their symptoms, i.e., in the opposite order than in this study.

The most prevalent S/Ps reported on WISP not covered by EORTC QLQ-C15-PAL were edema, dizziness, cough, and

Table 1 Characteristics of patients that completed the EORTC QLQ-C15-PAL questionnaire who reported or did not report symptoms and problems using the WISP instrument

Characteristics	Reported symptoms and problems on WISP *N* = 1788		Did not report symptoms and problems on WISP *N* = 3659		
	N	%	*N*	%	*p* value
Sex					0.292
Men	918	51.3	1823	49.8	
Women	870	48.7	1836	50.2	
Age (years)					0.001
Median (range)	70	(22–97)	71	(19–99)	
18–39	33	1.8	46	1.3	
40–49	93	5.2	142	3.9	
50–59	248	13.9	430	11.8	
60–69	481	26.9	967	26.4	
70–79	609	34.1	1277	34.9	
80+	324	18.1	797	21.8	
Children					< 0.001
No children	216	12.1	363	9.9	
Children, at least one younger than 18 years	146	8.2	215	5.9	
Children, all at least 18 years old	1391	77.8	2956	80.8	
Unknown	35	2.0	125	3.4	
Residence					0.002
Private (flat, house, etc.)	1713	95.8	3441	94.0	
Nursing home/senior residence	56	3.1	124	3.4	
Other	6	0.3	41	1.1	
Unknown	13	0.7	53	1.4	
Cohabitation status					< 0.001
Living alone	555	31.0	1303	35.6	
Living with spouse/partner	1004	56.2	1956	53.5	
Living with children	40	2.2	42	1.1	
Living with spouse/partner and children	100	5.6	125	3.4	
Living with parents	6	0.3	17	0.5	
Living with others	8	0.4	10	0.3	
Unknown	75	4.2	206	5.6	
Diagnosis (cancer site, ICD-10)					0.524
Head and neck (C00-C14, C32)	51	2.9	104	2.8	
Esophageal (C15)	61	3.4	125	3.4	
Stomach (C16)	45	2.5	105	2.9	
Small intestine (C17)	11	0.6	28	0.8	
Colorectal (C18-C20)	199	11.1	453	12.4	
Liver (C22)	69	3.9	109	3.0	
Pancreatic (C25)	140	7.8	279	7.6	
Lung (C33-C34)	423	23.7	965	26.4	
Melanoma skin cancer (C43)	42	2.3	67	1.8	
Sarcoma (C46-C49)	18	1.0	40	1.1	
Breast (C50)	159	8.9	287	7.8	
Cervical (C53)	17	1.0	34	0.9	
Uterine (C54–55)	32	1.8	59	1.6	
Ovarian (C56, C570-C574)	74	4.1	128	3.5	
Prostate (C61)	133	7.4	273	7.5	

Table 1 (continued)

Characteristics	Reported symptoms and problems on WISP $N = 1788$		Did not report symptoms and problems on WISP $N = 3659$		
	N	%	*N*	%	*p* value
Kidney (etc.) (C64-C66)	63	3.5	116	3.2	
Bladder (C67)	42	2.3	85	2.3	
Brain/CNS (C70-C71, C751-C753)[a]	74	4.1	119	3.3	
Lymphoma (C81-C85)	6	0.3	19	0.5	
Multiple myeloma (C 90)	19	1.1	39	1.1	
Leukemia (C91-C95)	21	1.2	33	0.9	
Other cancer (all other C codes)	45	2.5	115	3.1	
Unknown primary cancer (C76-C80)	44	2.5	77	2.1	
Type of first contact					0.330
Outpatient	1320	73.8	2746	75.0	
Inpatient	468	26.2	913	25.0	

[a] Including the D-codes: D32, D42, D330–332, D352–354, D430–432, D443–445, D333–339, and D433–439. *ICD-10* International Statistical Classification of Diseases and Related Health Problems 10th Revision

sweats. These symptoms were also the most prevalent in a preliminary work carried out in 373 patients in Denmark [19]. In this study, edema was reported by 3.4% of the patients who answered the EORTC QLQ-C15-PAL, which is roughly similar to the 5% edema prevalence reported voluntarily in two studies conducted in Egypt [31, 32]. Dizziness was listed by 3.1% and sweats by 1.5% which is similarly to the findings in Homsi et al.'s study from the USA, where these symptoms were reported by 3.0% and 2.0%, respectively [18]. The prevalence of cough (1.6%) was lower than previously reported voluntarily by cancer patients in the two earlier studies by Homsi et al. (6%) [18] and Alsirafy et al. (10%) [31]. Dizziness and cough are symptoms previously reported not being covered by common instruments using systematic assessment of symptoms [31, 33].

The most prevalent S/Ps already covered by the EORTC QLQ-C15-PAL were pain and impaired physical or emotional function. Although 24.8% of the S/Ps reported using WISP could be categorized as aspects of domains already covered by EORTC QLQ-C15-PAL, it was apparent that patients often wanted to provide additional details, e.g., about the symptom location ("pain in the neck") or intensity. Pain was the most prevalent S/Ps reported using WISP (4.2%) despite that it was already evaluated in two items of the questionnaire (item 5 "pain" and item 12 "pain interfere with daily activities"), and almost all patients in this study described its location. Our finding on the high prevalence of elaborations of the pain experience is in agreement with previous studies indicating that pain is the most common voluntarily reported symptom [18, 31, 32, 34]. Impaired physical or emotional function were also relatively frequent S/Ps. The most frequent physical problems reported were balance problems and muscular weakness, which are not covered by the items asked in the questionnaire (item 1 "short walk," 2 "stay in bed,", and 3 "need help for daily activities"). Anxiety was the most frequent emotional problem not specifically covered by the questionnaire (unless it is understood as covered by "feeling tense"). This is accordance with that anxiety has been found to be one of the most distressing psychological symptoms reported by patients in palliative care settings [35].

In line with other studies, 85% of S/Ps identified in our study were reported as moderate to severe ("quite a bit" or worse), which reaffirms that symptoms are mainly voluntarily reported when they are severe [18, 31]. This also underlines the importance of using open-ended questions in symptom assessment, e.g., the WISP instrument, because even though

Fig. 3 Classification of symptoms and problems reported on the WISP instrument

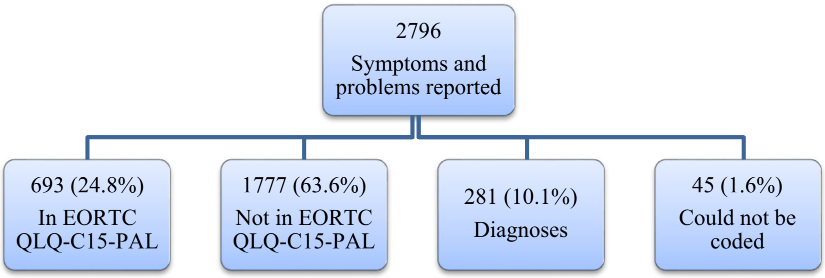


Table 2 Frequency of 281 responses reported on WISP and coded as diagnoses

Diagnoses	*N*	%	Diagnoses	*N*	%
Mucus	48	17.1	Teeth and gums problems	4	1.4
Neurological diseases[a]	15	5.3	Paralytic ileus	4	1.4
Pressure ulcer	14	5.0	Arthritis	3	1.1
Ascites	14	5.0	Poor blood circulation	3	1.1
Fungus	13	4.6	Dehydration	3	1.1
Hemorrhoid	12	4.3	Heart diseases	3	1.1
Catheter problem	11	3.9	Need orthosis or rehabilitation	3	1.1
Surgery	10	3.6	Stiffness	3	1.1
Infection	9	3.2	Herpes zoster	2	0.7
Restless legs disorder	9	3.2	Hypertension	2	0.7
Respiratory diseases[b]	8	2.8	Liver problems	2	0.7
Wound	8	2.8	Pulmonary edema	2	0.7
Inflammation	7	2.5	Facet syndrome	2	0.7
Medication problems	7	2.5	Hand coordination	2	0.7
Peripheral neuropathy	7	2.5	Impotence	2	0.7
Mental disorders[c]	7	2.5	Oxygen problems	2	0.7
Side effects of chemotherapy	7	2.5	Vaginal prolapse	2	0.7
Diabetes	6	2.1	Macular degeneration	1	0.4
Skin nodules	6	2.1	Osteoporosis	1	0.4
Anemia	5	1.8	Photosensitive	1	0.4
Fracture	5	1.8	Renal problem	1	0.4
Hernia	4	1.4	Immune system problem	1	0.4

[a] Including Parkinson, epilepsy, aphasia, dementia, and sclerosis

[b] Including asthma, cold, pneumonia, influenza, and chronic obstructive pulmonary disease

[c] Including obsessive-compulsive, claustrophobia, schizophrenia, and panic

patients in this study only reported on average 0.5 S/Ps, they were often experienced as moderate/severe and thus probably demanding attention.

One strength of this study is that we analyzed a large, prospective, national data set of 1788 advanced cancer patients completing the WISP instrument. In addition, data were collected from the DPD, which registers all cancer patients referred to specialized palliative care in Denmark with a high level of data completeness, permitting analysis without missing data.

Clear limitations of this study are the well-known disadvantages of open-ended questions: even though the WISP instrument increases the number of symptoms identified when supplementing the EORTC QLQ-C15-PAL questionnaire, and can be a useful instrument increasing the comprehensiveness of symptom assessment in palliative care, the interpretation of results on the group level is more complex: the prevalences will be too low, as only a small fraction self-report a given problem [18]. Another measurement system, incorporating an open-ended question is the PRO-CTCAE allowing patients to report symptomatic toxicities not selected for routine assessment [36], and results are not directly comparable, as they will depend not only on the wording of items in the instrument but also on what other symptom questions have already been asked. To our knowledge, open-ended questions to supplement the FACIT-Pal scale or the MQOL questionnaire have not been developed, whereas an open question without the option to rate S/Ps is provided in the AQUEL questionnaire [9]. In addition, an open-ended question is provided in ESAS, but limiting the patient to report up to one additional symptom without the option to identify this symptom [37]. Thus, considering that available instruments do not cover all symptoms experienced by advanced cancer patients [18], the design of WISP may increase the identification of S/Ps improving the comprehensiveness in symptom assessment. Further work is needed to be done to increase the comparability of studies using open-ended questions by establishing standards for data collection, analysis, and the presentation of results.

This study adds important new knowledge about symptom assessment in cancer patients. Our findings demonstrate that adding the open-ended WISP instrument to the original EORTC QLQ-C15-PAL questionnaire strongly improves the recognition of S/Ps that patients experience. Although the available evidence has shown that the number of symptoms reported voluntarily is lower than if systematic assessment

Table 3 Frequency, severity, and prevalence of 61 symptoms and problems reported using the WISP instrument (totally 2470 symptoms and problems reported by 1788 patients out of the 5447 patients completing the EORTC QLQ-C15-PAL). Symptoms and problems already covered by the EORTC QLQ-C15-PAL are in italic

Symptoms/problems categories	Symptoms/problems reported on WISP *N* = 2470								Prevalence in 5447 patients answering the EORTC QLQ-C15-PAL
	Frequency		Severity						
			Mild		Moderate		Severe		
	N	%	*N*	%	*N*	%	*N*	%	%
Pain	231	9.4	21	9.1	96	41.6	114	49.4	4.2
Edema	183	7.4	32	17.5	60	32.8	91	49.7	3.4
Dizziness	169	6.8	56	33.1	71	42.0	42	24.9	3.1
Impaired physical function[a]	154	6.2	16	10.4	61	39.6	77	50.0	2.8
Impaired emotional function[b]	152	6.2	9	5.9	61	40.1	82	53.9	2.8
Cough	85	3.4	18	21.2	40	47.1	27	31.8	1.6
Sweats	80	3.2	10	12.5	38	47.5	32	40.0	1.5
Diarrhea	74	3.0	9	12.2	30	40.5	35	47.3	1.4
Dry mouth	73	3.0	10	13.7	37	50.7	26	35.6	1.3
Incontinence[c]	72	2.9	6	8.3	37	51.4	29	40.3	1.3
Sore mouth	69	2.8	18	26.1	22	31.9	29	42.0	1.3
Vomiting	66	2.7	9	13.6	30	45.5	27	40.9	1.2
Dysphagia	65	2.6	8	12.3	20	30.8	37	56.9	1.2
Vision problems	63	2.6	9	14.3	23	36.5	31	49.2	1.2
Numbness/tingling	56	2.3	6	10.7	25	44.6	25	44.6	1.0
Reduced memory	54	2.2	10	18.5	22	40.7	22	40.7	1.0
Dyspnea	51	2.1	5	9.8	14	27.5	32	62.7	0.9
Existential problems	50	2.0	4	8.0	21	42.0	25	50.0	0.9
Itching	40	1.6	9	22.5	7	17.5	24	60.0	0.7
Urinary problems	38	1.5	8	21.1	11	28.9	19	50.0	0.7
Shakiness	36	1.5	7	19.4	16	44.4	13	36.1	0.7
Confusion	34	1.4	3	8.8	14	41.2	17	50.0	0.6
Myoclonus	32	1.3	8	25.0	15	46.9	9	28.1	0.6
Indigestion	31	1.3	3	9.7	12	38.7	16	51.6	0.6
Fatigue	31	1.3	2	6.5	12	38.7	17	54.8	0.6
Bleeding	30	1.2	13	43.3	10	33.3	7	23.3	0.6
Speaking problems	30	1.2	4	13.3	11	36.7	15	50.0	0.6
Lack of appetite	26	1.1	0	0.0	12	46.2	14	53.8	0.5
Headache	25	1.0	10	40.0	10	40.0	5	20.0	0.5
Social problems	22	0.9	2	9.1	4	18.2	16	72.7	0.4
Sleeping difficulties	21	0.9	2	9.5	6	28.6	13	61.9	0.4
Heaviness	20	0.8	5	25.0	5	25.0	10	50.0	0.4
Hearing problems	20	0.8	0	0.0	6	30.0	14	70.0	0.4
Bloating	20	0.8	0	0.0	5	25.0	15	75.0	0.4
Heartburn	20	0.8	5	25.0	9	45.0	6	30.0	0.4
Fever	19	0.8	2	10.5	12	63.2	5	26.3	0.3
Hallucinations[d]	18	0.7	2	11.1	12	66.7	4	22.2	0.3
Concentration problems	17	0.7	2	11.8	8	47.1	7	41.2	0.3
Nausea	15	0.6	1	6.7	8	53.3	6	40.0	0.3
Skin problems	15	0.6	6	40.0	5	33.3	4	26.7	0.3
Taste change	15	0.6	3	20.0	5	33.3	7	46.7	0.3
Cognitive dysfunction	14	0.6	1	7.1	10	71.4	3	21.4	0.3

Table 3 (continued)

Symptoms/problems categories	Symptoms/problems reported on WISP $N = 2470$								Prevalence in 5447 patients answering the EORTC QLQ-C15-PAL
	Frequency		Severity						
			Mild		Moderate		Severe		
	N	%	*N*	%	*N*	%	*N*	%	%
Hiccup	14	0.6	2	14.3	8	57.1	4	28.6	0.3
Burning sensation	13	0.5	4	30.8	4	30.8	5	38.5	0.2
Hoarseness	13	0.5	2	15.4	5	38.5	6	46.2	0.2
Constipation	12	0.5	2	16.7	1	8.3	9	75.0	0.2
Drowsiness	10	0.4	4	40.0	3	30.0	3	30.0	0.2
Palpitations	9	0.4	3	33.3	2	22.2	4	44.4	0.2
Burping	8	0.3	2	25.0	3	37.5	3	37.5	0.1
Other eye symptoms	7	0.3	1	14.3	4	57.1	2	28.6	0.1
Other ear symptoms	7	0.3	1	14.3	3	42.9	3	42.9	0.1
Bad dreams	6	0.2	1	16.7	2	33.3	3	50.0	0.1
Housing problems	5	0.2	0	0.0	3	60.0	2	40.0	0.1
Hypersalivation	5	0.2	0	0.0	2	40.0	3	60.0	0.1
Disorientation	4	0.2	0	0.0	2	50.0	2	50.0	0.1
Economic problems	4	0.2	1	25.0	1	25.0	2	50.0	0.1
Thirst	4	0.2	0	0.0	2	50.0	2	50.0	0.1
Easy to tears	4	0.2	1	25.0	2	50.0	1	25.0	0.1
Distress in the body	3	0.1	0	0.0	1	33.3	2	66.7	0.1
Weight loss	3	0.1	0	0.0	1	33.3	2	66.7	0.1
Chills	3	0.1	0	0.0	1	33.3	2	66.7	0.1
Total	2470	100	378	15.3	983	39.8	1109	44.9	100

[a] Including the following problems: balance problems, muscular weakness, paralysis, limitations in daily activities, and walking problems

[b] Including the following problems: anxious, fearful, concerned, irritated, resigned, and sad

[c] Including urinary, stool, and unspecified incontinence

[d] Including visual, auditory, and unspecified hallucinations

takes place [18, 34], this study suggests it is relevant to combine systematic assessment with voluntary reporting of symptoms since 64% of the voluntarily reported symptoms on WISP were not covered by EORTC QLQ-C15-PAL. A supplementary, open-ended questionnaire like the WISP instrument may provide a useful solution to this paradox.

How is the information from the EORTC QLQ-C15-PAL and WISP integrated into the clinical workflow in Denmark? Following our previous results demonstrating that clinicians may overlook S/Ps if systematic assessment is not used [38, 39], it was decided at the launch of DPD in 2010 to make the initial symptom assessment using the EORTC QLQ-C15-PAL + WISP a mandatory national quality indicator. Clinicians across the country have adopted this routine. When possible, the questionnaires are completed by the patient before the first encounter with the physician, and if this is not possible, the patient completes it during the consultation (if the patient is capable to do so). In both situations, the clinicians can take the information into account as a supplement to the other information provided in the medical interview, and all knowledge is documented in the medical record. In some of the Danish SPC units, the electronic medical records are structured in a way that allow easy entry of the results from the EORTC QLQ-C15-PAL and WISP.

Conclusions

Patients with advanced cancer admitted to SPC in Denmark experience multiple symptoms and problems not covered by a brief questionnaire such as the EORTC QLQ-C15-PAL. An approach combining standardization with individualization through the WISP instrument may not only increase symptom recognition but may also lead to interventions that may improve patients' quality of life. We therefore recommend the use of the WISP instrument alongside the EORCT QLQ-C15-PAL questionnaire, and potentially also alongside the EORTC QLQ-C30 and modules, when a more comprehensive symptom assessment is needed. More research is needed about the use and interpretation of data from open-ended questions.

The data utilized in this study are available through the Danish Palliative Care Database. Restrictions apply to the availability of these data.

Compliance with ethical standards

Conflict of interest The authors declared that they have no conflict of interest.

Ethical approval This study was based only on registers from the Danish Palliative Care Database requested through the Danish Clinical Registries - RKKP; therefore, it had not impact on any individual's care and not required Scientific Ethics Committee approval according to Danish law. The study was conducted following the approval from the Danish Data Protection Agency (j.nr.: 2012-58-0004/local j.nr. BFH-2017-064 I-Suite no. 05590).

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PAPER II

Who report symptoms and problems not covered by the EORTC QLQ-C15-PAL when admitted to specialized palliative care?

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Abstract

Purpose: Comprehensive assessment of symptoms and problems (S/Ps) may be achieved by combining validated patient-reported outcome (PRO) instruments with open-ended questions. The 'Write In three Symptoms/Problems' (WISP) instrument allows patients to report S/Ps not covered by the EORTC QLQ-C15-PAL. This study investigated whether sociodemographic variables, diagnosis or type of first contact were associated with the reporting of additional symptoms in WISP.

Methods: Data were obtained from the Danish Palliative Care Database for all patients admitted to specialized palliative care (SPC) in Denmark in 2016, who completed the EORTC QLQ-C15-PAL and reported S/Ps on WISP. The associations between patient characteristics and the reporting of (a) any symptom/problem and (b) each of the ten most prevalent S/Ps (edema, dizziness, cough, sweats, diarrhea, dry mouth, incontinence, sore mouth, vomiting and dysphagia), respectively, were investigated using multivariate regression.

Results: In total, 1,295 patients reported additional S/Ps on WISP. Having younger children and living with someone were associated with reporting any additional symptom/problem but not with age, sex, diagnosis or type of first contact. The reporting of the ten most prevalent S/Ps was associated with having cancer diagnosis (prostate, colorectal, female genital organs and digestive system), having younger children, living with someone and being outpatient, whereas no associations were found with sex or age.

Conclusions: The reporting any additional symptom/problem and of some of the additional S/Ps were associated with certain patient characteristics. A better understanding of the profile of patients reporting the diverse range of symptoms not assessed by standard measures may allow clinicians to improve palliative care interventions.

Keywords: Advanced cancer; Palliative care; Symptom assessment; Prevalence, Patient-reported Outcomes

Introduction

Patients with advanced cancer experience a diversity of physical and emotional symptoms that intensify when they approach death (1). Early identification and management of symptoms, as well as maintenance of patients' quality of life (QOL) are important parts of care at the end of life. Patients' symptoms, problems (S/Ps) and QOL can be systematically assessed by validated Patient-Reported Outcome (PRO) instruments such as the EORTC QLQ-C30 questionnaire (2) and its shortened version for palliative care the EORTC QLQ-C15-PAL (3), the Edmonton Symptom Assessment Scale (ESAS) (4), the Memorial Symptom Assessment Scale (MSAS) (5), the McGill Quality of Life questionnaire (MQOL) (6), the Integrated Palliative care Outcome Scale (IPOS) (7), and the Functional Assessment of Chronic Illness Therapy-Palliative Scale (FACIT-PAL) (8).

Systematic assessment of symptoms has been highly recommended to identify symptoms not reported voluntarily by patients (9-12), and to prevent clinicians from underestimating patient symptomatology (13, 14); however, no instruments can measure all symptoms that patients in palliative care may experience, particularly because the instruments have to be brief to limit response burden (11). Therefore, a comprehensive assessment of S/Ps may be achieved by combining PRO instruments with open-ended questions. PRO instruments including an open-ended question are ESAS (4), EORTC QLQ-LC29 (15), IPOS (7), MSAS (5) and its short-form MSAS-SF (16). The way in which information is collected varies, e.g., how many additional symptoms they allow for and how to rate the severity. Frequent symptoms reported by patients with advanced cancer using an open-ended question are pain, fatigue, anorexia, dyspnea, cough, edema, vomiting, and dizziness (9-11).

To increase the recognition of symptoms in patients admitted to specialized palliative care (SPC) in Denmark, a brief instrument named 'Write In three Symptoms/Problems' (WISP) was developed to supplement the EORTC QLQ-C15-PAL (17). WISP is an open-ended question asking patients to report 1–3 S/Ps not covered by this questionnaire and to rate the severity of the S/Ps. The first study using this instrument showed that 2,796 S/Ps were listed on WISP by 5,447 patients admitted to SPC, and 63.6% of the S/Ps were not covered by the EORTC QLQ-C15-PAL, some patients elaborated S/Ps already covered, e.g. the location of pain. The ten most prevalent additional S/Ps reported were edema (3.4%), dizziness (3.1%), cough (1.6%), sweats (1.5%), diarrhea (1.4%), dry mouth (1.3%), incontinence (1.3%), sore mouth (1.3%), vomiting (1.2%), and dysphagia (1.2%) (17).

Several studies suggest that sex, age, cancer diagnosis, performance status and inpatient/outpatient status are associated with symptoms systematically assessed by PRO instruments (18-25). In contrast, the evidence on whether patient characteristics are associated with the diverse range of S/Ps that may be assessed via open-ended questions is very limited. If large differences are found, e.g. between diagnoses, this may improve symptom recognition via diagnosis-adjusted assessment questionnaires. Therefore, in this study we aimed to investigate whether sociodemographic variables, diagnosis (cancer site) and type of first contact (in- or out-patient) were associated with S/Ps reported using the WISP instrument at admittance to SPC in Denmark.

Methods

Patients

This study is based on register data collected from the Danish Palliative Care Database (DPD). Data from all patients admitted to SPC in 2016, who were at least 18 years of age, diagnosed with advanced cancer, completed the EORTC QLQ-C15-PAL at the day of admittance or up to 3 days before, and reported S/Ps using the WISP instrument were included.

Data collection

DPD is a national database administered by the Danish Clinical Registries (RKKP), which comprises relevant clinical and demographic information of all patients referred to SPC in Denmark. Since 2010, it has been mandatory for all 43 SPC units, (26 hospital-based palliative care teams/units and 17 hospices) to report patients’ information to the DPD. This information is continually validated against the Danish National Patient Register, securing DPD patient completeness close to 100% (26). Information on sex, age, children, cohabitation status, diagnosis, type of first contact, and S/Ps reported on WISP was obtained from the DPD.

Questionnaire

The EORTC QLQ-C15-PAL questionnaire is an abbreviated version of the EORTC QLQ-C30 developed for patients in palliative care (3). It contains 15 items to assess the severity of 10 symptoms/functions; physical functioning, emotional functioning, pain, fatigue, nausea, dyspnea, sleeping difficulties, appetite loss, constipation, and overall QOL. Symptoms/functions are scored 1 (not at all), 2 (a little), 3 (quite a bit) or 4 (very much), and overall QOL is scored from 1 (very poor) to 7 (excellent).

WISP is an independent instrument supplementing the EORTC QLQ-C15-PAL. This instrument allows patients to report up to three additional S/Ps (via open-ended responses) and to rate their severity using the response categories (see above) from 1 (not at all) to 4 (very much) (17). The information collected from the EORTC QLQ-C15-PAL and WISP at admission to SPC was available to the clinicians initiating palliative care.

Statistical analyses

We computed the dichotomous outcome ‘any additional symptom/problem’ dividing patients into those who reported at least one additional S/P on WISP, i.e., S/Ps not covered by the EORTC QLQ-C15-PAL, and those who had not reported any additional S/Ps on WISP.

Sociodemographic and clinical patient characteristics were summarized as proportions. Patients who reported additional S/Ps on WISP and those who did not were compared using Chi-square test.

Further, for each of the ten most prevalent S/Ps reported on WISP (see also our previous study (17)), patients were divided into those who had reported the symptom/problem (defined as a score of at least ‘a little’) and those who had not, e.g. reported edema or did not.

We performed logistic regressions to investigate associations between patient characteristics and the computed dichotomous outcomes, ‘any additional symptom/problem’ and ‘each of the ten prevalent symptom/problem’. Stepwise procedure was used until the model only contained covariates significantly associated with the outcomes. The covariates tested were sex, age, having children, cohabitation status, diagnosis and type of first contact, excluding the subgroups ‘unknown’ (see Table 2 for details on these variables). The results from the logistic regressions are reported as odds ratios (ORs) with 95% confidence intervals (CIs).

Finally, for each of the ten most prevalent S/Ps reported on WISP, we converted their scores into 0–100 scales following the scoring manual of the EORTC QLQ-C15-PAL for single items (27), where 0 corresponds to ‘not at all’, 33.3 to ‘a little’, 66.7 to ‘quite a bit’ and 100 to ‘very much’. The mean scores of the S/Ps were calculated according to patient characteristics. Differences in the distribution of S/P scores across patient characteristics were tested using Mann-Whitney U test and Kruskal-Wallis test. A p value <0.05 was considered statistically significant. The analyses were conducted using the statistical software Statistical Package for the Social Sciences (SPSS) version 23.

Results

Characteristics of patients reporting additional symptoms and problems

In 2016, 5,447 patients with advanced cancer were admitted to SPC and completed the EORTC QLQ-C15-PAL, of whom 1,788 patients reported at least one symptom/problem using the WISP instrument (17). Of these, 1,295 patients reported S/Ps not covered by EORTC QLQ-C15-PAL (Fig. 1).

Patient characteristics are presented in Table 1. The distribution of age, children, and cohabitation status was significantly different between patients who reported additional S/Ps to those did not. Patients reporting additional S/Ps on WISP were slightly younger than those who did not. Slightly higher proportions of these patients had younger children and lived with someone. No significant differences were seen according to sex, cancer diagnoses or type of first contact.

Logistic regression analyses showed that the highest probability of experiencing any additional symptom/problem were seen for patients with younger children compared to patients with older children (OR=1.34 ;95% CI:1.06-1.71), and for patients living with someone compared to those living alone (OR=0.76 ;95% CI:0.66-0.86), but not association was found for age.

Figure 1. Patient inclusion.

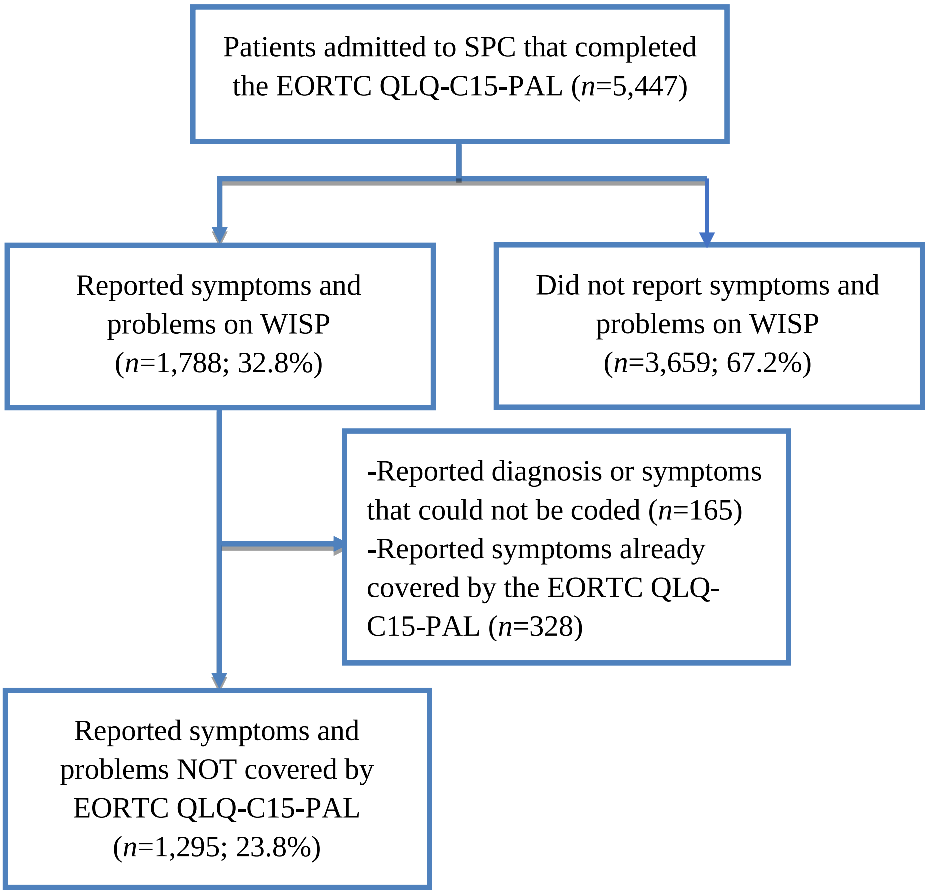

Table 1. Characteristics of patients who reported or did not report additional symptoms and problems using the WISP instrument.

	Reported additional symptoms and problems on WISP *N* = 1,295		Did not report additional symptoms and problems on WISP *N* = 4,152		
	N	%	*N*	%	*p* value
Sex					0.107
Women	618	47.7	2,088	50.3	
Men	677	52.3	2,064	49.7	
Age					0.012
Median (range)	70	(22–96)	71	(19–99)	
18–59	269	20.8	723	17.4	
60–69	349	26.9	1,099	26.5	
70–80+	677	52.3	2,330	56.1	
Children (having)					0.002
No children	155	12.0	424	10.2	
Children, at least one younger than 18 years	106	8.2	255	6.1	
Children, all at least 18 years old	1,008	77.8	3,339	80.4	
Unknown	26	2.0	134	3.2	
Cohabitation status					<0.001
Living alone	386	29.8	1,472	35.5	
Living with someone	854	65.9	2,454	59.1	
Unknown	55	4.2	226	5.4	
Diagnosis (cancer site, ICD-10)					0.424
Digestive system (C15-17 & C22+25)	235	18.1	737	17.8	
Colorectal (C18-C20)	149	11.5	503	12.1	
Lung (C33-34)	299	23.1	1,089	26.2	
Breast (C50)	111	8.6	335	8.1	
Female genital organs (C53-55 & 56, C570-C574)	90	6.9	254	6.1	
Prostate (C61)	99	7.6	307	7.4	
Other cancers (all other C codes)	282	21.8	836	20.1	
Unknown primary cancer (C76-C80)	30	2.3	91	2.2	
Type of first contact					0.845
Inpatient	331	25.6	1,050	25.3	
Outpatient	964	74.4	3,102	74.7	

ICD-10 International Statistical Classification of Diseases and Related Health Problems10th Revision

Associations between patient characteristics and additional symptoms and problems

Results from the logistic regression analyses are presented in Table 2. Patients with younger children had a higher probability of experiencing edema (p=0.008) and sore mouth (p=0.038) than patients with older children. Patients living with someone had a higher probability of experiencing cough (p=0.006) and sweats (p=0.025) than patients living alone. Diagnosis was significantly associated with the probability of reporting additional S/Ps: prostate cancer patients had the highest odds of reporting sweats (p=<0.001); for incontinence this was the case for patients with colorectal and prostate cancer (p=0.022), and the highest odds of reporting vomiting was seen among patients with cancer in female genital organs and in the digestive system (p=<0.001). Outpatients had the highest odds of reporting dry mouth than inpatients (p=0.044).

Sex and age were not significantly associated with any of the outcomes. No associations were found between any of the patient characteristics and dizziness, diarrhea, dysphagia and therefore, these outcomes are not shown in Table 2.

Severity of additional symptoms and problems

Mean scores for the ten most prevalent additional S/Ps reported at admittance to SPC are listed in Table 3 for the whole sample and for subgroups defined by patient characteristics. Note that the scores are estimated among those reporting the S/P and therefore do not reflect whether the S/P was reported frequently or not. The highest mean scores were reported for dysphagia (mean=82), diarrhea (mean=78), edema (mean=77), and incontinence (mean=77).

The distributions of mean scores differed significantly according to sex, diagnosis and type of first contact. Women presented more severe edema and less severe diarrhea than men (p=0.002, and p=0.037 respectively). The largest differences between cancer diagnosis groups were seen for cough, where patients with cancer in the digestive system presented more severe cough than patients with other cancer diagnoses (p=0.043). Inpatients presented more severe cough (p=0.020), diarrhea (p=0.047) and vomiting (p=0.013) than outpatients.

Table 2. Associations between patient characteristics and additional symptoms and problems reported on WISP using stepwise logistic regression.

	Edema *n*=183[a]	Cough *n*=85[a]	Sweats *n*=80[a]	Dry mouth *n*=73[a]	Incontinence *n*=72[a,b]	Sore mouth *n*=69[a]	Vomiting *n*=66[a]
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Children							
No children	1.77 (1.18-2.66)					1.20 (0.57-2.55)	
Children, at least one younger than 18	2.00 (1.24-3.22)					2.45 (1.23-4.87)	
Children, all at least 18 years old	1.00 (ref. group)					1.00 (ref. group)	
Cohabitation status							
Living alone		0.47 (0.28-0.80)	0.54 (0.31-0.99)				
Living with someone		1.00 (ref. group)	1.00 (ref. group)				
Diagnosis (cancer site, ICD-10)							
Digestive system			1.28 (0.62-2.68)		0.95 (0.39-2.34)		6.90 (2.34-20.3)
Colorectal			0.83 (0.32-2.16)		3.07 (1.46-6.47)		6.49 (2.08-20.1)
Lung			1.00 (ref. group)		1.00 (ref. group)		1.00 (ref. group)
Breast			1.07 (0.39-3.00)		1.56 (0.58-4.19)		3.92 (1.05-14.7)
Female genital organs			0.54 (0.12-2.34)		2.04 (0.76-5.46)		14.7 (4.80-44.8)
Prostate			4.10 (2.05-8.25)		2.60 (1.09-6.21)		4.31 (1.15-16.1)
Other cancers			1.48 (0.74-2.94)		1.24 (0.56-2.78)		2.18 (0.64-7.45)
Type of first contact							
Inpatient				0.61 (0.38-0.99)			
Outpatient				1.00 (ref. group)			

An odds ratio above 1 reflects a higher odds of reporting the symptom, Ref.=reference

[a]Number of patients reporting the symptom, [b] including urinary, fecal and unspecified incontinence

Table 3. Mean scores for the ten most prevalent additional symptoms and problems reported on WISP according to patient characteristics.

	Edema N=183^a	Dizziness N=169^a	Cough N=85^a	Sweats N=80^a	Diarrhea N=74^a	Dry mouth n=73^a	Incontinence N=72^{a,b}	Sore mouth N=69^a	Vomiting N=66^a	Dysphagia N=65^a
All	77	64	70	76	78	74	77	72	76	82
Sex										
Women	**83**	66	70	78	**72**	76	78	78	75	85
Men	**72**	62	70	75	**85**	72	77	68	77	79
Age										
18–59	81	69	77	72	63	70	81	82	78	88
60–69	75	63	63	79	79	76	82	60	72	69
70–80+	72	63	70	75	81	74	75	72	77	84
Children										
No children	78	69	77	73	76	76	85	75	67	83
Children, at least one younger than 18	75	58	78	73	80	60	84	63	83	100
Children, all at least 18 years old	77	64	68	76	80	74	75	73	77	80
Cohabitation status										
Living alone	81	65	63	77	83	72	76	74	78	83
Living with someone	76	64	72	77	79	74	79	71	76	82
Diagnosis (cancer site ICD-10)										
Digestive system	80	61	**82**	74	80	73	71	67	77	82
Colorectal	71	63	**75**	73	83	74	73	79	75	93
Lung	77	65	**58**	80	75	75	78	68	67	78
Breast	90	67	**73**	74	73	67	89	93	60	92
Female genital organs	83	71	**78**	84	80	76	84	60	83	84
Prostate	73	64	**-**	72	78	60	78	74	80	72
Other cancers	78	61	**79**	80	79	81	75	79	72	81
Type of first contact										
Inpatient	83	66	**81**	71	**86**	81	71	81	**87**	92
Outpatient	76	63	**67**	77	**75**	70	79	69	**71**	79

Higher mean scores represent worse symptoms. Significant mean score differences across patient characteristics are shown in bold

[a] Number of patients reporting the symptom, [b] including urinary, fecal and unspecified incontinence

Discussion

In this study, 1,295 patients (23.8%) of the patients completing the EORTC QLQ-C15-PAL reported S/Ps not covered by the EORTC QLQ-C15-PAL using the WISP instrument. We found that the probability of reporting any additional symptom/problem was significantly associated with having children and cohabitation status, i.e., patients with younger children and patients living with someone were more likely to report any additional symptom/problem compared with the other categories. One reason why patients with younger children were more likely to report any additional symptom/problem than patients with older children may be related to the stress of parenting younger children, which may increase the risk of distressing symptoms (28). The higher odds of reporting any additional symptom/problem seen in patients living with someone compared to patients living alone, could possibly be explained by the fact that the patient's spouse or relatives can easily identify some symptom, helping patients to recognize and inform their symptoms.

Despite the relatively large sample size we found no association between sex, age and the outcomes any additional symptom/problem or each of the ten prevalent S/Ps, although previous studies indicated that being younger or female were significantly associated with symptoms commonly reported in palliative care (1, 18, 20, 21, 23, 24).

In relation to diagnosis, in our study prostate cancer patients had the highest odds of reporting incontinence and sweats, and patients with colorectal cancer also had the highest odds of reporting incontinence. These associations could be explained by the curative treatment that cancer patients received since it has been shown that radiotherapy increase the risk of fecal incontinence (29), and prostatectomy the risk of urinary incontinence (30) in patients with prostate cancer. The same applies to the high risk of sweats that is probably influenced due to castration/endocrine treatment in prostate cancer, where patients frequently experience hot flushes and/or night sweats during the treatment (31-33). Concerning patients with colorectal cancer, both fecal and urinary incontinence have been associated with their curative treatment and the tumor progression previously (34).

Furthermore, we found that patients with cancer in female genital organs and the digestive system had the highest odds of reporting vomiting, this may be related to the higher risk of intestinal obstruction observed in patients with ovarian and stomach cancer (35). Our findings were similar to those reported by Harder et al.'s study, where Danish patients with gynecological and stomach cancer were significantly associated with having any degree of nausea/vomiting (36). In addition, the association between nausea/vomiting and cancer in the digestive or gynecological system has been reported by previous studies (1, 37, 38). Finally, outpatients had a higher probability of experiencing worse dry mouth than inpatients. Dry mouth is frequently associated with medication and older age, which is different from our findings (39). Finally, we found no association between dizziness, diarrhea, dysphagia and patient characteristics, contrary to two previous studies indicating that gynecological and gastrointestinal cancer diagnoses were associated with more diarrhea (19) and male gender was associated with dysphagia (21).

When interpreting the severity of the ten most prevalent additional S/Ps reported on WISP, we must take into consideration that a symptom gets a high 'severity score' if all patients report a moderate severity. In our study, dysphagia, diarrhea, edema, and incontinence had the highest overall mean scores. Two previous studies using an open-ended question to identify S/Ps not systematically assessed found that diarrhea (11), dysphagia and edema (9) were also reported with moderate to high severity by advanced cancer patients, similarly to our findings.

In the current study, the distribution of S/P scores differed significantly according to sex, diagnosis, and type of first contact. Women presented more severe edema and less severe diarrhea than men. More edema reported by women than men could be related with their cancer diagnosis, since 8.6% and 6.9% of patients in this study suffered from breast cancer and cancer in female genital organs, respectively, and edema is a common consequence of the curative treatment of these cancer diagnoses (40). Patients with cancer in the digestive system suffered from more severe cough than lung cancer patients, which is a surprising finding as cough is one of the most severe symptoms in lung cancer patients (41); however, in our study among those patients who reported cough, patients with lung cancer did it with less severity than patients with other cancer diagnosis. Additionally, we found that inpatients suffered from more severe cough, diarrhea and vomiting than outpatients.

The present study has several strengths. First, it included a large data set of 5,447 patients of whom 1,295 reporting additional S/Ps using the WISP instrument, coming from all SPC units across Denmark. Additionally, the study provides new knowledge about the profile of patients who report S/Ps not systematically covered by common palliative care instruments, e.g., S/Ps not covered by the EORTC QLQ-C15-PAL. As such, to our knowledge, this is the first study of its kind.

In future research, it may be considered to incorporate the most prevalent S/Ps reported on WISP in the daily systematic symptom assessment of patients, particularly in those subgroups where large differences were observed according to patient characteristics, e.g., incontinence should be included in routine symptom assessment for prostate and colorectal cancer patients. Similarly, vomiting should be also included in the symptom assessment of patients with cancer in the gynecological and digestive systems. Furthermore, in future research, it would also be relevant to compare our profile of cancer patients reporting additional S/Ps on WISP with non-cancer patients in palliative care or from other settings.

Conclusions

This large, national study investigated how cancer patients admitted to SPC report symptoms using the open-ended WISP instrument. The probability of experiencing any additional symptom/problem was associated with having younger children and living with someone but apart from this, remarkably no differences were found across sex, age, cancer diagnosis and type of first contact. Seven of the ten most prevalent additional S/Ps were associated with having children, cohabitation, cancer diagnosis and type of first contact. A better understanding of the profile of patients reporting various symptoms not always assessed by standard measures may allow clinicians to improve palliative care interventions.

Acknowledgements

All authors made substantial contributions to the design, analysis of data, critical revision and approved the publication, participating sufficiently to take responsibility for the content of this article.

Conflict of interest

The authors declare that they have no conflict of interest.

Ethical approval

This study was based only on registers from the Danish Palliative Care Database; therefore, it had not impact on any individuals’ care and not required Ethics Committee approval according to Danish law. The study was conducted following the approval from the Danish Data Protection Agency (j.nr.: 2012-58-0004/local j.nr. BFH-2017-064 I-Suite no. 05590).

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Data management and sharing

The data utilized in this study are available through the first author at the Palliative Care Research Unit, Department of Geriatrics and Palliative Medicine GP, Bispebjerg and Frederiksberg Hospital, University of Copenhagen, Denmark. Restrictions apply to the availability of these data.

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PAPER III

Content validation of the EORTC QLQ-C15-PAL with advanced cancer patients and health care professionals from palliative care services in Chile

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Abstract

Background: The assessment of patients' quality of life (QOL) is essential when evaluating the outcome of palliative care; however, no instruments have been validated for measuring symptoms and QOL in patients receiving palliative care in Chile. We aimed to investigate the content validity of the EORTC Quality of Life Questionnaire Core 15 Palliative Care (QLQ-C15-PAL), replicating the methods used previously to shorten the EORTC Quality of Life Questionnaire Core 30 (QLQ-C30) for use among patients in palliative care.

Methods: This cross-sectional study was conducted from October to November 2017 in four palliative care services. Patients with advanced cancer and health care professionals (HCPs) were invited to individual interviews to determine the relevance, appropriateness and relative importance of the 30 items of the QLQ-C30 for evaluating the outcome of palliative care, and whether relevant additional issues should be included.

Results: A total of 48 patients and 35 HCPs participated. The most important dimensions selected were pain, physical functioning, sleeping difficulties, emotional functioning, nausea/vomiting, fatigue, and social functioning. Qualitative data identified important additional issues not covered by the questionnaire such as satisfaction with care, emotions and psychological support, as well as linguistic issues in the dyspnea and constipation items.

Conclusions: The EORTC QLQ-C15-PAL showed good content validity in the assessment of symptoms and QOL of advanced cancer patients; therefore, we recommend the use of this questionnaire in palliative care in Chile. Dyspnea and constipation items were revised by the EORTC group. More research is needed to add a social dimension for a comprehensive assessment of patients' QOL.

Keywords: EORTC QLQ-C15-PAL; Advanced cancer; Palliative care; Symptom Assessment; Quality of life; Patient-reported outcomes

Background

Palliative care aims to improve the quality of life (QOL) of patients through the early detection and treatment of their symptoms [1]. Thus, the assessment of patients' QOL is essential when evaluating the outcome of palliative care. Nevertheless, assessment of QOL may be difficult in patients with advanced cancer due to the number and severity of symptoms they experience. To reduce the burden on patients, patient-reported outcomes (PROs) instruments in palliative care should be brief, cover the main symptoms and problems, and at the same time avoid content of limited relevance.

The European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 15 Palliative Care (QLQ-C15-PAL) is an abbreviated 15-item version of the EORTC Quality of Life Questionnaire Core 30 (QLQ-C30), which is one of the most widely used, validated, translated and published instruments for assessing symptoms and QOL in cancer patients [2]. The QLQ-C15-PAL contains the items of the QLQ-C30 which were identified as the most important for palliative care, based on interviews with health care professionals and patients [3], and on statistical analyses using item response theory [4, 5]. This development process secures that studies may compare their results obtained from the QLQ C15-PAL with studies using the original QLQ-C30 questionnaire [3]. In addition, the QLQ-C15-PAL has been successfully validated and translated in several countries [6-14], including Spanish-speaking countries [15, 16].

The Chilean-Spanish version of the QLQ-C30 and some modules have been validated before [17, 18]. A few studies have used the QLQ-C30 to evaluate patients' QOL in oncology research [19-22], but no instruments have been validated for measuring symptoms and QOL in patients receiving palliative care in Chile. When the QLQ-C15-PAL was developed, its content validity was evaluated by health care professionals and patients from six European countries [3]. However, because of differences between these European countries and Chile in their health care systems, including how palliative care is organized, and the availability of palliative care services, it would be relevant to investigate the content validity of the QLQ-C15-PAL in Chilean population. In Chile most palliative care services are in the public health care system, but some services are fully private. Although Chile has the highest number of palliative care services in Latin America [23], still has a fewer number of palliative services compared to the Western

European countries. In 2013, the ratio of services to the population in Chile was 1: 808,000, which is lower compared to the six European countries with a ratio of services to the population between 1: 48,000 (in the United Kingdom), and 1: 122,000 (in Denmark) [24]. Therefore, we aimed to investigate the content validity of the QLQ-C15-PAL questionnaire with patients and health care professionals from palliative care services in Chile, replicating the methods used previously to shorten the items of the QLQ-C30 among European patients in palliative care [3].

Methods

Patients and health care professionals

This cross-sectional study was conducted from October to November 2017 with participants from the palliative care services of four public hospitals in Santiago in Chile. We planned to recruit at least 10 patients and 10 heath care professionals (HCPs) from each palliative care service.

Outpatients with advanced cancer undergoing palliative care treatment, with knowledge of their diagnosis, and who had given informed consent were eligible. Patients who were too ill to participate in interviews, and non-native Spanish speakers were excluded. HCPs with their main job in palliative care were eligible. For patients, the primary cancer site was registered, occupation and years of experience were registered for HCPs, and demographic characteristics were collected for all participants.

Questionnaires

The Chilean-Spanish version of the QLQ-C30 questionnaire (version 3) was used for this study and was obtained from the EORTC Quality of Life Department in Brussels. The QLQ-C30 consists of 30 items distributed in five functional scales measuring physical, emotional, role, cognitive and social functioning; three symptoms scales measuring fatigue, pain, nausea/vomiting; one scale measuring “global health and quality of life status”, and six single items measuring sleeping difficulties, dyspnea, constipation, lack of appetite, financial difficulties, and diarrhea. All items are rated on 4-points Likert scales that range from 1 (not at all) to 4 (very much), with the exception of the global health/quality of life scale, which is rated from 1 (very poor) to 7 (excellent) [25, 26].

The QLQ-C15-PAL is an abbreviated version of the QLQ-C30, which was developed for patients in palliative care preserving the main advantages of the original questionnaire. The QLQ-C30 was shortened to 15 items by omitting items of the QLQ-C30 that were considered inappropriate or not highly relevant in palliative care by patients and health care professionals in interviews, [3] and by shortening multi-item scales of QLQ-C30 using item response theory [4, 5]. Four scales, i.e., physical functioning, emotional functioning, nausea/vomiting and fatigue, were shortened retaining the items that best predicted scores on the original scales. Due to the low relevance reported in the interviews, the two-item global QOL scale was reduced to one item by omitting overall health, and five scales/items were completely omitted (social, role and cognitive functioning scales, diarrhea and financial difficulties items).

Procedure for interviews

To validate the content of the QLQ-C15-PAL questionnaire, we conducted semi-structured interviews following the procedure originally used to develop a shortened version of the QLQ-C30 for palliative care patients [3], and the EORTC Quality of Life Group Guidelines for developing questionnaire modules [27]. The purpose of these interviews was to identify the most relevant issues for patients in palliative care among those included in the EORTC QLQ-C30 in order to investigate whether the QLQ-C15-PAL also has the appropriate content for use in Chile. Patients were asked to respond to the Chilean-Spanish version of the QLQ-C30 during individual interviews by a trained researcher. The interviewer then invited patients to comment on how well the QLQ-C30 items “evaluated the outcome of the palliative care they received”. Patients were asked to comment on the QLQ-C30 items in terms of relevance, appropriateness, relative importance, and breadth of coverage. The relevance of each item was rated using the response categories 1 “not at all’, 2 “a little”, 3 “quite a bit” and 4 “very much”. If an item was rated 1 or 2, patients were asked to report the reasons, e.g., “Why do you consider this question not or only a little relevant?”. The appropriateness was measured asking patients to identify items they perceived as inappropriate or upsetting. The relative importance was evaluated asking patients to select the 10 most important issues when evaluating the success of palliative care. The breadth of coverage was assessed asking patients to report additional issues that were relevant for them but not covered by the QLQ-C30.

An identical interview was followed for HCPs, but they were required to comment on how well the QLQ-C30 items "evaluated the outcome of palliative care in general", i.e., not for a specific patient, but for patients admitted to palliative care in general. HCPs were asked to comment on relevance, appropriateness, relative importance, and breadth of coverage of the QLQ-C30 items, using the same procedure as described above.

Statistical analysis

Participants' characteristics were expressed as proportions for categorical variables, and as means, standard deviations, medians and ranges for continuous variables. The mean relevance score of each item was calculated after transforming the responses to 0–100 scales with 0 corresponding to "not at all" and 100 to "very much" [26]. The proportion of participants rating each item as "inappropriate or upsetting" and selecting each item as one of the 10 most important were calculated. The proportion of participants who selected at least one of the items from each multi-item scale as one of the 10 most important was also calculated. Single items and multi-item scales were ranked according to the proportion of patients and HCPs selecting them as among the 10 most important. This ranking named 'importance percentage' was calculated as the average: (percentage of patients + percentage of HCPs)/2; although the sample of patients was larger than HCP sample, both received equal weight. Furthermore, this ranking was used to compare the relative importance of the scales and items as perceived by Chilean patients/HCPs with the results of the original study [3]. HCPs were divided in two subgroups, i.e., "physicians" and "other HCPs" to explore differences between the rating of relevance and importance for each dimension of the QLQ-C30, tested by Mann-Whitney U Test. Qualitative data obtained from the interviews were categorized into responses about the lack of relevance in selected items, and the need to include other issues in the questionnaire, respectively. A p value <0.05 was considered statistically significant. Analyses were performed using the statistical software Statistical Package for the Social Sciences (SPSS) version 23.

Results

Participation

A total of 48 patients with advanced cancer and 35 HCPs participated in the interviews. The median age of patients was 60 years, and the most common cancer diagnoses were prostate cancer (14.6%), stomach cancer (10.4%) and multiple myeloma (10.4%). HCPs had a median age of 39 years and the majority were physicians (34.3%), followed by nurses (20.0%), and psychologists (20.0%). For further details see Table 1.

Interviews

Relevance, appropriateness and relative importance of the EORTC QLQ-C30

The quantitative data including ratings of relevance, inappropriateness, and relative importance of items are summarized in Table 2, together with the qualitative data from categorized responses to the question: ‘Why do you consider this question not or only little relevant?’ presented in Table 3, will be discussed simultaneously for each dimension of the QLQ-C30 questionnaire. Scales and items are presented in the order in which they appear in tables 2 and 3, i.e., based on their importance rating, where the 10 most important were pain, physical functioning, sleeping difficulties, emotional functioning, nausea/vomiting, fatigue, social functioning, lack of appetite, role functioning and constipation.

Pain (PA) scale

Pain was selected as the most important dimension of the QLQ-C30 and both items were rated as highly relevant.

Physical functioning (PF) scale

The last item 5 “need help with self-care” was rated as the most important item of the scale, followed by item 4 “stay in bed”. Items 2 “long walk” and 3 “short walk” were rated as less relevant by the respondents, who mentioned that these questions regarding to walking limitations were not appropriate for patients in palliative care. Item 1 “strenuous activities” was the item most often rated as inappropriate by HCPs (26%).

Sleeping difficulties (SL) item

Sleeping difficulties was rated as very relevant and chosen as one of the most important dimensions by 80% of participants.

Emotional functioning (EF) scale

The four items of this scale were rated more relevant by patients than by HCPs; however, 83% of HCPs compared to 73% of patients selected this scale as one of the 10 most important for palliative care. Item 24 “feel depressed” was most often selected as important particularly by HCPs. Nine participants indicated that item 23 “feel irritable” was poorly formulated, e.g., the word “irritable” could be replaced by “angry”.

Nausea and Vomiting (NV) scale

Nausea and vomiting were rated as highly relevant by respondents and selected as two important items by 69% of the HCPs.

Fatigue (FA) scale

More than a half of the patients selected fatigue as an important dimension (77%) in comparison with the HCPs (34%). Item 12 “feel weak” was the least important item selected by patients, mainly because they believed that this symptom was repeatedly measured. HCPs found that item 10 “need to rest” was the least important and less relevant of the scale.

Social functioning (SF) scale

Social functioning scale was selected as an important dimension by 49% of the participants. Both items, item 26 “your physical condition or medical treatment has interfered with your family life” and item 27 “your physical condition or medical treatment has interfered with your social activities” were scored with high relevance, especially item 26.

Lack of appetite (LA) item

Lack of appetite was more selected as an important item by HCPs than by patients (57% vs. 35%).

Role functioning (RF) scale

Role functioning scale was very important for patients (60%), scoring with a high relevance the item 6 “limitations at work or daily activities”.

Constipation (CO) item

Constipation was considered by 42% of the respondents as an important item, and about 20% (*n*=17) of them suggested linguistic changes for this question because it was difficult to understand by patients (See also Table 4).

Financial difficulties (FI) item

This item was chosen as one of the most important by 49% of the HCPs compared to 35% of the patients. Few participants described this item as inappropriate for palliative care setting.

Global health status/ Quality of life (QOL) scale

Participants rate both items as highly relevant. This dimension was selected as one of the most important more often by the HCPs than by patients (54% vs. 23%), although some respondents reported this item as little relevant because they believed the concept “quality of life” is not understood by all patients in palliative care.

Dyspnea (DY) item

Similar numbers of patients and HCPs reported that dyspnea was a not well formulated item making it difficult for patients to comprehend, whereas 33% of participants (*n* = 27) suggested linguistic changes for dyspnea (Table 4).

Cognitive functioning (CF) scale

Cognitive functioning was generally regarded as less important than the other five functioning scales, selected only by 25% of respondents. Item 20 “concentrating problems” was the least relevant item in this scale.

Diarrhea (DI) item

Although rated as relevant, diarrhea was the issue least often selected as important.

The comparison of item relevance and importance scores between physicians (n = 12) and other HCPs (n = 23) showed no significant differences; therefore, they are not shown in Table 2.

Table 1. Characteristics of 48 patients and 35 health care professionals participating in interviews.

Patient characteristics	Patients		Health care professionals	
	N	(%)	*N*	(%)
Sex				
Men	16	(33.3)	9	(25.7)
Women	32	(66.7)	26	(74.3)
Age				
Mean (SD)	59.2	(13.1)	40.9	(12.7)
Median (range)	60	(29–86)	39	(23–70)
Hospitals				
Sotero del Rio	27	(56.3)	12	(34.3)
San Juan de Dios	4	(8.3)	5	(14.3)
Salvador	13	(27.1)	11	(31.4)
Felix Bulnes Cerda	4	(8.3)	7	(20.0)
Diagnosis (cancer site, ICD-10)				
Prostate (C61)	7	(14.6)		
Stomach (C16)	5	(10.4)		
Multiple myeloma (C90)	5	(10.4)		
Breast (C50)	4	(8.3)		
Colorectal (C18-C20)	3	(6.3)		
Melanoma skin cancer (C43)	3	(6.3)		
Uterine (C54-C55)	3	(6.3)		
Ovarian (C56, C570-C574)	3	(6.3)		
Liver (C22)	2	(4.2)		
Sarcoma (C46-C49)	2	(4.2)		
Cervical (C53)	2	(4.2)		
Kidney (C64-C66)	2	(4.2)		
Lymphoma (C81-C85)	2	(4.2)		
Other cancer (all other C codes)	5	(10.4)		
Discipline of HCPs				
Physician			12	(34.3)
Nurse			7	(20.0)
Psychologist			7	(20.0)
Paramedic			6	(17.1)
Physiotherapist			1	(2.9)
Social worker			1	(2.9)
Nutritionist			1	(2.9)
Years of experience of HCPs				
Mean (SD)			13.9	(11.9)
Median (range)			11	(1–42)

SD: standard deviation, ICD-10: International Statistical Classification of Diseases and Related Health Problems 10th Revision

Table 2. Relevance, inappropriateness and importance of items reported by 48 patients and 35 health care professionals.

Scale/item	Item	Relevance (mean)		% Inappropriate		% Selected as one of the most important		
		Pts.	HCPs	Pts.	HCPs	Pts.	HCPs	/2^{a}
Pain (PA)	**9**	100	97	0	0	96	77	
	19	97	80	2	6	27	54	
Any PA item						98	94	96
Physical functioning (PF)	1	77	64	6	9	40	3	
	2	78	63	2	0	25	3	
	3	76	73	4	3	17	9	
	4	83	85	6	3	23	51	
	5	98	95	0	0	60	71	
Any PF item						98	80	89
Sleeping difficulties (SL)	**11**	97	95	0	0	75	86	80
Emotional functioning (EF)	**21**	95	63	0	3	19	6	
	22	93	68	0	2	21	11	
	23	92	73	0	0	21	17	
	24	98	89	0	0	38	60	
Any EF item						73	83	78
Nausea and vomiting (NV)	**14**	96	88	0	0	25	54	
	15	97	87	0	0	35	46	
Any NV item						46	69	57
Fatigue (FA)	10	97	67	2	3	50	6	
	12	92	73	0	3	31	20	
	18	92	74	2	3	42	14	
Any FA item						77	34	56
Social functioning (SF)	26	93	89	2	3	31	54	
	27	88	83	4	0	8	31	
Any SF item						38	60	49
Lack of appetite (AP)	**13**	99	86	0	0	35	57	46
Role functioning (RF)	6	95	79	0	0	50	23	
	7	82	57	2	6	31	6	
Any RF item						60	26	43
Constipation (CO)	**16**	92	83	0	0	29	54	42
Financial difficulties (FI)	28	93	81	4	3	35	49	42
Global health status/	29	97	90	0	0	8	23	
Quality of life (QOL)	**30**	95	89	0	3	15	49	
Any QL item						23	54	39
Dyspnea (DY)	**8**	70	70	2	3	46	17	31
Cognitive functioning (CF)	20	90	54	0	3	21	6	
	25	97	67	0	0	15	14	
Any CF item						33	17	25
Diarrhea (DI)	17	93	79	2	0	17	20	18

The scales/items are ranked according to importance. Items in bold form were extracted from the EORTC QLQ-C30 to form the EORTC QLQ-C15-PAL questionnaire

[a] The mean of the values for patients (Pts.) and health care professionals (HCPs)

Table 3. Categorized reasons why some items were rated as little or not relevant by the participants.

Scale/item	Item	Relevance[a]		Technical issues[b]		Inappropriate[c]		Relative[d]		Not important[e]		Difficult[f]		Total
		Pts.	HCPs	Pts.	HCPs	Pts.	HCPs	Pts.	HCPs	Pts.	HCPs	Pts.	HCPs	
Pain	9				1									1
	19		3		1		2	1						7
Physical functioning	1	5	5			3	3	1						17
	2	4	6	1	1	1		1		1	1			16
	3	4	6	1	2	1	1	1		1				17
	4	3				2	1	1					1	8
	5													-
Emotional functioning	21	1	5	1	2		1		1		1	1		13
	22	1	5	2	1			1		1	1			12
	23		1	4	5			1			1			12
	24		2		3			1						6
Fatigue	10		5		1		1	1		1	1			10
	12		3	2	3		1	2					1	12
	18	1	4	1			1	2			1			10
Nausea and vomiting	14	1	2		2									5
	15		2		1									3
Sleeping difficulties	11				1									1
Social functioning	26	1				1	1	1			1			5
	27		1		2	2		1			2			8
Dyspnea	8	3	5	14	13	1		1		1		1		39
Role functioning	6	2	1		3						1			7
	7	4	11		1	1	2	1						20
Constipation	16		1	10	7									18
Lack of appetite	13		1											1
Financial difficulties	28	1	2		1	2	1					1		8
Global health status/	29		2	1									1	4
Quality of life	30		1	2	3		1	1				1	1	10
Cognitive functioning	20	4	11		1		1				4			21

	25	1	8		1				1					11
Diarrhea	17		3			1			1					5
Total		36	96	39	56	15	17	18	3	5	14	4	4	307

[a] Relevance: statements concerning the degree of relevance, i.e., replicating the quantitative data

[b] Technical issues: statements that the question is not well formulated, reiterative or suggestions to combine items

[c] Inappropriate: statements that the item was inappropriate

[d] Relative: statements that the symptom or problem asked in the item depend of patient's diagnosis

[e] Not important: statements that the item was not important in palliative care

[f] Difficult: the item was seen has difficult to understand

Patients: Pts., health care professionals: HCPs

Table 4. Categorized comments about linguistic issues found in the dyspnea and constipation items of EORTC QLQ-C30.

Scale/item	Item	Participant comments and suggestions for alternative wording (quotation marks)	Pts.	HCPs
Dyspnea	8	Not well formulated	1	2
		"Ran out of air"	1	2
		"Lack of air"	3	4
		"Ran out of breath"	5	2
		"Difficulty breathing"	2	1
		"Maximum tiredness"		2
		Did not understand "short of breath"	2	
		Total	14	13
Constipation	16	"Difficulty defecating"	3	6
		"Troubles defecating"	2	1
		"Bowel movements"	1	2
		Did not understand "constipated"	1	1
		Total	7	10

Patients: Pts., health care professionals: HCPs

Breadth of Coverage of the EORTC QLQ-C30

Patients and HCPs were asked to report additional issues that were not included in the QLQ-C30, which they considered relevant for the outcome of the palliative care. In total, 91 topics were mentioned by the respondents. These were grouped into 10 overalls categories. The three most frequent categories were satisfaction with care, emotions and psychological support. Satisfaction with care included topics about satisfaction of patients with HCPs, and effectiveness of medication, mostly reported by patients. Emotions included topics about role loss and mood changes, and psychological support included phycological needs, and facing life with advanced cancer. For further details see Table 5.

Table 5. Additional issues that would be relevant to include when evaluating the outcome of palliative care.

Additional issues categories	Pts.	HCPs
Satisfaction with care	8	4
Satisfaction with health care professionals, satisfaction with the information received, adherence to treatment, effectiveness of medication and side effects		
Emotions	5	7
Role loss, mood changes, sadness, anhedonia, fear		
Psychological support	6	6
Psychological needs, significant changes to the way of living, facing life with advanced cancer, measure psychological distress, personality disorders		
Sexuality	1	10
Sexual satisfaction, sexual activity		
Social support	4	5
Support from family/relatives, caregivers' distress, cohabitation, e.g., whom do you live with?		
Symptoms and problems	2	7
Visual problems, sleeping tongue, eating/swallowing problems, drowsiness, dementia/delirium, urinary problems		
Existential issues	1	8
Thoughts about death, uncertainty about future, transcendence		
Spiritual issues		6
Spiritual pain, spirituality		
Physical difficulties	3	3
Ability to move around on you own at home, toileting independence		
Economic problems	1	4
Delay in sick leave payment, transportation expenses, e.g., go to hospital		
Total number of issues	31	60

Patients: Pts., health care professionals: HCPs

Discussion

In this study, we performed a content validation of the QLQ-C15-PAL with 48 patients and 35 HCPs from four palliative care services in Chile, replicating the methodology of a previous study conducted in six European countries [3]. In general, our results were similar to that study, confirming the content validity of the QLQ-C15-PAL questionnaire, but we made important observations that will be discussed later.

Of the 10 function/symptom scales included in the EORTC QLQ-C15-PAL questionnaire, eight were selected among the 10 most important dimensions to include in the assessment of palliative care in Chile, i.e., pain, physical functioning, sleeping difficulties, emotional functioning, nausea/vomiting, fatigue, lack of appetite and constipation. Responses about the five shortened scales from the original QLQ-C30 to form the QLQ-C15-PAL were comparable to the Groenvold et al. study [3]. Physical functioning and fatigue scales were particularly important scales by patients, whereas emotional functioning, nausea/vomiting and global health status/QOL scales were essential for HCPs. Most of the items of these scales that were finally retained in the QLQ-C15-PAL, were also selected by our respondents as relevant issues to measure the outcome of palliative care.

The most important dimension selected by the participants was pain (96%), which has been recognized in the literature as one of the most prevalent symptoms reported by advanced cancer patients in palliative care [28, 29]. Other dimensions frequently selected as important were physical functioning (89%), sleeping difficulties (80%), emotional functioning (78%), nausea/vomiting (57%), fatigue (56%) and social functioning (49%). These dimensions were previously identified as prevalent palliative needs in a study investigating the content validity of PROs instruments in palliative care, by comparing patient reported symptoms and problems to what was registered in the medical records [30]. Although social and role functioning were excluded in the development of the QLQ-C15-PAL due to the lack relevance reported in the original study [3], in our study these dimensions were selected as the most important by 49% and 43% of respondents respectively, principally HCPs selected social functioning in relation to family life of patients, and patients selected role functioning in relation to their limitations at work. Patients' concern about their role in the family, the social support they received from family, and personal challenges related to work have been reported before by a palliative care service in a small qualitative study conducted in Chile [31].

Qualitative data corresponding to additional issues not covered by the questionnaire showed that HCPs reported twice as many topics as patients did. A reason may be that HCPs have the perspective of many patients while patients focus on their own situation. Further, the breadth of coverage question was asked at the end of the interview, hence, some patients may have been too fatigued to give comprehensive responses. The main additional issues reported in our study were satisfaction with care, emotions and psychological support. In contrast, additional issues related with existential and spiritual issues were frequently reported by Groenvold et al. [3]. Further research is needed to evaluate which aspects not covered by the QLQ-C15-PAL may be relevant for a comprehensive measurement of the QOL in Chilean palliative care patients, e.g., a social dimension. While social support for patients in palliative care and their families has been recommended by the Chilean Ministry of Health [32], as well as international organizations [1, 33], social needs do not seem to be covered by current palliative care in Chile, as only one of the four palliative care services in this study had a social worker in their teams.

The qualitative data was useful to identify unexpected linguistics issues in the dyspnea and constipation items, since 33% and 20% of the participants reported that these questions were not well formulated or were difficult to understand. A list with the comments about these two items was submitted to the Translation Unit of the EORTC Quality of Life Department for possible revision of the translation of these items. After their analysis, both items were modified in the Chilean versions of the QLQ-C30, and the QLQ-C15-PAL questionnaires.

We recognize some limitations related to this study. First, we did not evaluate statistically the psychometric properties of the QLQ-C15-PAL in Chilean patients; however, it has been extensively validated in previous international studies [6-13]. Second, we planned to recruit at least 10 HCPs from each palliative care service, but half of the services investigated had less than 10 professionals in their teams. Nevertheless, we had no missing data for the study analysis, since the participants were accompanied by the researcher during their self-assessment of the QLQ-C30 or were assisted if necessary.

Conclusions

The EORTC QLQ-C15-PAL showed good content validity in the assessment of symptoms and QOL of advanced cancer patients. Additionally, we identified linguistic issues in the dyspnea and constipation items that were revised by the EORTC group. This questionnaire may help clinicians, and researchers to initiate palliative care interventions that may improve QOL of patients. Therefore, we recommend the use of the EORTC QLQ-C15-PAL in patients receiving palliative care in Chile. More research is needed to add a social dimension for a comprehensive assessment of patients' QOL in Chile.

Declarations

Ethics approval and consent to participate

Study approval was obtained from two Chilean local ethics committees: Comité de Ética Científico Adultos Servicio de Salud Metropolitano Oriente, and Comité Ético Científico Servicio de Salud Metropolitano Sur Oriente (names in Spanish), approval number/ID CECSSMO27122016 and CECSSMSO17082017 respectively. Written informed consent for participation was obtained from all patients involved in this study.

Consent for publication

This manuscript does not contain any specific individual's data.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding

This study was supported by ‘Becas-Chile Scholarship’ from the Advanced Human Capital Program of the National Commission for Scientific and Technological Research-CONICYT. The scholarship was used for salary to the first author of this paper (LRC). Funding sources had no role in the conception of the study, analysis or interpretation of data, in writing the manuscript, or in any other part of the study.

Authors' contributions

LRC and MG conceptualized and designed the study. LRC carried out the interviews and the analyses, drafted the manuscript, and revised the manuscript. MB, MP and MG supervised the study, and critically reviewed the manuscript. All authors read and approved the final manuscript.

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PAPER IV

Symptomatology of advanced cancer patients admitted to palliative care services in Chile: A longitudinal study

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Abstract

Purpose: To examine the symptomatology of advanced cancer patients at admittance to palliative care in Chile and to investigate how the symptomatology changed during the first month, and whether these changes were associated with various patient characteristics.

Methods: A longitudinal study carried out between October 2017 and January 2018 in Chile. Outpatients with advanced cancer completed the EORTC QLQ-C15-PAL and the Hospital Anxiety and Depression Scale at baseline. Prevalence and severity of symptoms and problems (S/Ps) at baseline were calculated. Differences in S/P scores from baseline to follow-up were calculated overall and according to patient characteristics. Multiple linear regression was used to study the associations between patient characteristics and changes in S/P scores.

Results: At baseline 201 patients answered the questionnaires and 177 completed the study. Fatigue, pain, and sleeping difficulties were the most prevalent S/Ps reported, which also had the highest mean scores at baseline. S/P scores varied significantly according to sex, age, civil status, residence, children, prior and current antineoplastic treatment. Emotional functioning, pain, sleeping difficulties, constipation and anxiety improved significantly during the first month of palliative care. Residence, cohabitation status, diagnosis and current antineoplastic treatment were associated with changes in symptom/problem scores.

Conclusions: Chilean patients reported moderate to severe levels of S/Ps at admittance to palliative care. Several S/Ps improved the first month. Certain patient characteristics were associated with changes in symptom/problem scores. This information may guide clinicians to more effective interventions that can improve the quality of life of patients receiving palliative care in Chile.

Keywords: Quality of life; EORTC QLQ-C15-PAL; Advanced cancer; Palliative care; Symptom assessment; patient-reported outcomes

Introduction

Preserving quality of life (QOL) and relieving symptoms in patients with advanced cancer are desired outcomes of palliative care. QOL is a multidimensional construct including important aspects such as disease-related symptoms and problems (S/Ps) (1, 2). Assessment of patients' symptomatology and QOL at the start and during palliative care may help clinicians to improve palliative care interventions. Changes in symptomatology have been investigated previously by using validated QOL questionnaires, but the results were inconsistent across the studies on whether pain, fatigue, appetite loss, QOL, insomnia, constipation, nausea/vomiting and physical or emotional function improved or worsened after 2–4 weeks of palliative care (3-10).

Chile has a population of 17.5 million inhabitants and has 130 hospital-based palliative care services/units in the public healthcare system (11). Despite the large number of palliative services available, it is still a smaller number per capita compared to the rest of the countries of the Americas and the Caribbean (12). Like the rest of the world the burden of cancer is increasing rapidly in Chile (13), and this will increase the future demand for palliative care.

The Ministry of Health in Chile administers the national program "Pain relief for advanced cancer and palliative care", which guarantees free access to palliative care for all patients with advanced cancer and aims at evaluating and controlling symptoms (14). A national report showed that 67% of cancer patients admitted to the program in 2013 self-reported more than nine symptoms. The most prevalent S/Ps listed were pain (90%), digestive symptoms, i.e., anorexia, weight loss, nausea and vomiting (85%), and emotional symptoms, i.e., anxiety, insomnia, and depression (55%) (15). However, to our knowledge no studies have investigated changes in S/Ps and overall QOL of patients receiving palliative care in Chile.

The aims of the current study were 1) to examine the symptomatology of advanced cancer patients at admittance to palliative care services in Chile, 2) to investigate how the symptomatology changed during the first month of palliative care, and 3) to investigate whether these changes were associated with patient characteristics.

Methods

Design

This longitudinal study was carried out between October 2017 and January 2018 in four hospital-based palliative care services in Santiago, Chile. The symptomatology assessments were done at admittance, and one month later. This study was approved by two local ethics committees in Chile. All patients gave written consent.

Patients

This study included outpatients admitted to one of the four palliative care services. All patients had advanced cancer who were ≥ 18 years of age, knowledge of their diagnosis, Karnofsky Performance Status (KPS) score of at least 50% (16), and provided informed, written consent. Patients who declined participation, were non-Spanish speakers, or were considered too ill to participate by the staff were excluded. From all participants, sociodemographic data on sex, age, civil status, residence, cohabitation, children, and education were collected at admittance. Clinical data on diagnosis, any prior and current antineoplastic treatment, hospital, and KPS score assessed by the physician at baseline were collected from the medical record.

Assessments

Patients were invited to participate in the study at their first contact with the palliative care service. Consenting patients received a booklet with the self-assessment questionnaires, i.e., the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 15 Palliative Care (EORTC QLQ-C15-PAL), the Write In three Symptoms/Problems instrument (WISP), and the Hospital Anxiety and Depression Scale (HADS). The first page of the booklet contained questions on sociodemographic information and a question on whether the patient had completed the questionnaires by her-/himself or with the help of a trained clinician. After one month of palliative care, patients who had any appointment or phone calls with the palliative care service were asked again to complete the questionnaires.

The EORTC QLQ-C15-PAL questionnaire consists of 15 items: two functional scales (physical and emotional functioning), seven symptom scales (pain, fatigue, nausea/vomiting, dyspnea, sleeping difficulties, appetite loss, and constipation), and one item referring to overall QOL. Fourteen items employ 4-points scales from 1 (not at all), 2 (a little), 3 (quite a bit) to 4 (very much), and QOL is rated from 1 (very poor) to 7 (excellent) (17). The WISP is an open-ended instrument that permits patients to report up to three S/Ps not covered by the EORTC QLQ-C15-PAL and rate their severity from 1 (not at all) to 4 (very much) (18).

HADS is a self-reporting scale that contains 14 items divided into two subscales, one for anxiety and one for depression. Each subscale comprises 7 items, which are scored through scales ranging from 0 to 3 points, giving a maximum of 21 points per subscale. According to Zigmond and Snaith's criteria, 0–7 points on a subscale represents a 'non-case', 8–10 points a 'doubtful' or possible case, and 11–21 points a 'definite case' of anxiety or depression (19).

For this study, we used the Chilean-Spanish version of the EORTC QLQ-C15-PAL (version 1) obtained from the EORTC Quality of Life Department in Brussels, the WISP instrument (18) translated into Spanish, and the validated Spanish version of HADS (20) .

Statistical analyses

The EORTC QLQ-C15-PAL scores were converted to 0–100 scales according to the Scoring Manual (21). High scores on the two functioning scales and overall QOL represent better function/QOL, while high scores on symptom scales reflect worse symptoms. Mean scores and standard deviations (SD) of the scales in the EORTC QLQ-C15-PAL and HADS were calculated overall and according to patient characteristics at baseline. Differences in the distribution of these S/P scores across patient characteristics were tested with non-parametric analyses using Mann-Whitney U test, and Kruskal-Wallis test because S/P baseline scores were non-normally distributed. Patient characteristic categories with under 5% were grouped into an 'other' category.

At baseline we calculated the prevalence of having a 'symptom/problem' as the proportion of patients who reported EORTC QLQ-C15-PAL scores at least 'a little' (functioning scores ≤67 or symptom scores ≥33). Prevalence of 'severe symptom/problem' was calculated with patients scoring at least 'quite a bit' (functioning scores ≤34 or symptom scores ≥66), using the cut-points described in previous studies (22, 23) for all scales except overall QOL. The prevalence of patients with possible anxiety or depression (score ≥8), and definite anxiety or depression (≥11) were calculated for the HADS (19). Qualitative responses obtained from WISP were grouped into S/P categories using the list of 61 S/P-categories reported previously (18). The prevalence of patients reporting each additional S/P on WISP and the distribution of severity ratings were also calculated.

For patients who completed the study, differences in S/P scores from baseline to follow-up were calculated overall and in relation to patient characteristics; change scores were tested using Wilcoxon signed rank test. In addition, we performed multiple linear regressions with backwards stepwise selection to identify patient characteristics significantly associated with change in S/P scores from baseline to follow-up. The significance level used was 0.05. All analyses were performed using the statistical software Statistical Package for Social Sciences (SPSS) version 23.

Results

Patient characteristics

Figure 1 shows the inclusion of patients. Of the 394 patients admitted to the four palliative care services, 201 (80% of the eligible patients) answered the EORTC QLQ-C15-PAL, WISP and HADS at baseline (Fig. 1). Of these, 21 patients had died at 1-month follow-up, and 3 were too ill to participate, hence, a total of 177 patients completed the study.

Around half of the patients who participated in the study were men (51.7%) and were married (55.7%). The median age was 66 years and the median KPS score was 90. Most patients lived in their private residence with someone, had older children and had a low education level. The most frequent diagnoses were stomach cancer, colorectal cancer and breast cancer. At admittance to palliative care, 51.7% of patients had not received any prior antineoplastic treatment and 94.0% were not in a current antineoplastic treatment. Further details can be seen in Table 1.

Fig. 1. Inclusion of patients.

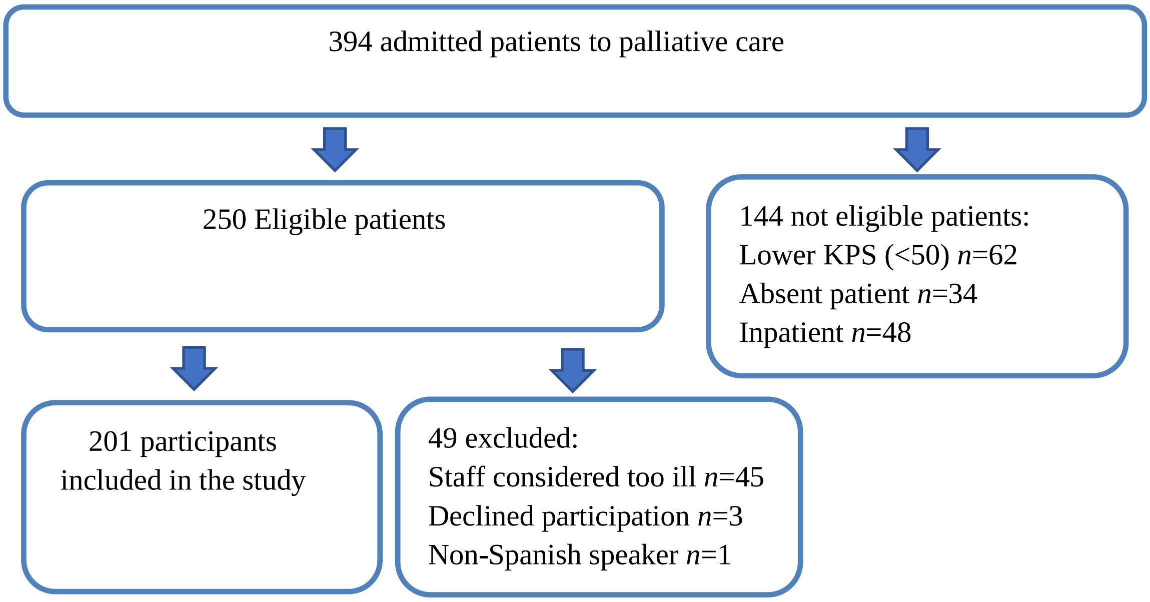


Table 1. Sociodemographic and clinical characteristics at baseline for the 201 patients included in the study.

	N	%
Sex		
Men	104	51.7
Women	97	48.3
Age		
Median (range)	66	(24–90)
<65 years	86	42.8
≥65 years	115	57.2
Civil status		
Single[a]	89	44.3
Married/cohabiting	112	55.7
Residence		
Private residence (house, flat, etc.)	143	71.1
Relatives' residence	49	24.4
Others' residence	9	4.5
Cohabitation		
Living alone	11	5.5
Living with spouse/partner	44	21.9
Living alone with children	39	19.4
Living with others	46	22.9
Living with spouse/partner and children	61	30.3
Children		
No children	22	10.9
Children, at least one younger than 18 years	24	11.9
Children, all at least 18-years-old	155	77.1
Education		
Primary education or lower[b]	94	46.8
Secondary education[c]	74	36.8
Higher education[d]	33	16.4
KPS score		
Median (range)	90	(50–100)
50–60	30	14.9
70–80	36	17.9
90–100	135	67.2
Diagnosis (cancer site, ICD-10)		
Stomach (C16)	26	12.9
Colorectal (C18-C20)	24	11.9
Breast (C50)	21	10.4
Lung (C33-C34)	18	9.0
Prostate (C61)	18	9.0
Gallbladder (C23)	11	5.5
Ovarian (C56,570-C574)	9	4.5
Leukemia (C91-C95)	8	4.0
Liver (C22)	7	3.0
Esophageal (C15)	6	3.0
Pancreatic (C25)	6	3.0
Melanoma skin cancer (C43)	6	3.0
Kidney (C64-C66)	6	3.0
Lymphoma (C81-C85)	5	2.5
Head and neck (C00-C14, C32)	4	2.0

Cervical (C53)	4	2.0
Bladder (C67)	4	2.0
Unknown primary cancer (C76-C80)	4	2.0
Multiple myeloma (C90)	3	1.5
Other cancer (all other C codes)	11	5.5
Any prior antineoplastic treatment		
Yes	97	48.3
No	104	51.7
Current antineoplastic treatment		
Yes	12	6.0
No	189	94.0
Hospital		
Sotero del Rio	99	49.3
San Juan de Dios	46	22.9
Salvador	36	17.9
Felix Bulnes Cerda	20	10.0

[a] Including: divorced, separated and widowed

[b] Compulsory education of 8 years or less

[c] Compulsory education from 9 to 12 years

[d] Education >12years including university, technical or further studies

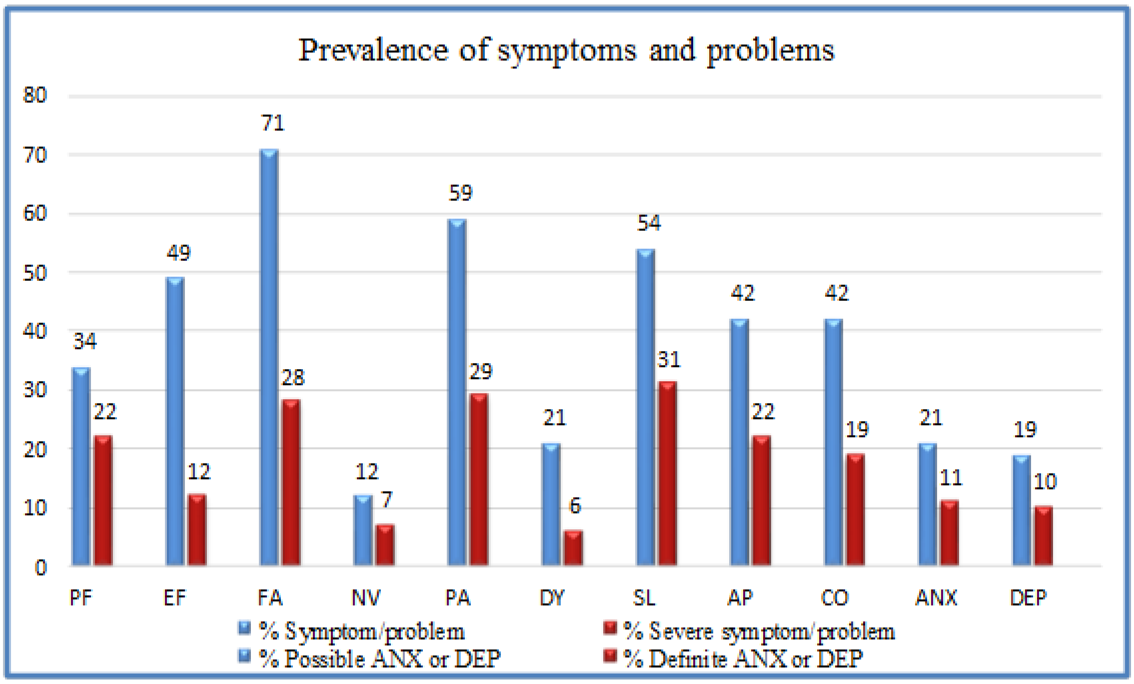
Abbreviations: KPS Karnofsky Performance Status, ICD-10 International Statistical Classification of Diseases and Related Health Problems, 10th Revision

Symptomatology at admittance to palliative care

The prevalences of having a symptom/problem and a severe symptom/problem, respectively, at baseline are presented in Fig 2. The most prevalent S/Ps reported on the EORTC QLQ-C15-PAL were fatigue 71% (28% severely), pain 59% (29% severely) and sleeping difficulties 54% (31% severely). Nausea/vomiting (12%) and dyspnea (21%) were the least prevalent S/Ps. Possible anxiety was reported by 21% of patients on HADS and possible depression by 19%. Definite anxiety and depression were reported by 11% and 10% of patients, respectively.

A total of 72 patients out of 201 (35.8%) reported S/Ps using the WISP instrument at baseline. These patients reported 91 S/Ps in total: 60 were additional S/Ps; 20 were elaborations of S/Ps already covered by the EORTC QLQ-C15-PAL, and 11 were diagnoses or symptoms that could not be coded. In total 80 S/Ps were grouped into 23 S/P categories. The most prevalent additional S/Ps reported on WISP were cough (5.5%), bloating (3.5%), and diarrhea (2.5%). Overall, 70% of the S/Ps were reported as 'quite a bit' to 'very much' (Table 2).

Fig 2. Prevalence of symptoms and problems in 201 patients who completed the EORTC QLQ-C15-PAL and the Hospital Anxiety and Depression Scale (HADS) at baseline



EORTC QLQ-C15-PAL: PF=physical functioning, EF=emotional functioning, FA=fatigue, NV=nausea/vomiting, PA=pain, DY=dyspnea, SL=sleeping difficulties, AP= appetite loss, CO=constipation, HADS: ANX=anxiety and DEP=depression

Table 2. Prevalence and severity of symptoms and problems reported by 201 patients using the WISP instrument at baseline.

Symptoms/problems categories	Prevalence		Symptoms/problems reported on WISP					
			Severity					
			A little		Quite a bit		Very much	
	N	%	*N*	%	*N*	%	*N*	%
Pain[a]	12	6.0	3	25.0	3	25.0	6	50.0
Cough	11	5.5	5	45.5	4	36.4	2	18.2
Bloating	7	3.5	2	28.6	2	28.6	3	42.9
Diarrhea	5	2.5	2	40.0	0	0.0	3	60.0
Hearing problems	4	2.0	1	25.0	1	25.0	2	50.0
Shakiness	4	2.0	2	50.0	2	50.0	0	0.0
Itching	4	2.0	0	0.0	1	25.0	3	75.0
Impaired emotional function[a]	4	2.0	1	25.0	2	50.0	1	25.0
Impaired physical function[a]	3	1.5	0	0.0	2	66.7	1	33.3
Incontinence[b]	3	1.5	1	33.3	1	33.3	1	33.3
Edema	3	1.5	2	66.7	0	0.0	1	33.3
Weight loss	3	1.5	0	0.0	1	33.3	2	66.7
Hiccup	2	1.0	0	0.0	1	50.0	1	50.0
Sore mouth	2	1.0	2	100	0	0.0	0	0.0
Vision problems	2	1.0	1	50.0	1	50.0	0	0.0
Burning sensation	2	1.0	0	0.0	1	50.0	1	50.0
Skin problems	2	1.0	1	50.0	1	50.0	0	0.0
Sweats	2	1.0	0	0.0	0	0.0	2	100
Sleeping difficulties[a]	1	0.5	0	0.0	0	0.0	1	100
Nausea[a]	1	0.5	0	0.0	1	100	0	0.0
Vomiting	1	0.5	0	0.0	1	100	0	0.0
Hypersalivation	1	0.5	1	100	0	0.0	0	0.0
Bleeding	1	0.5	0	0.0	0	0.0	1	100

[a] Symptoms and problems already covered by the EORTC QLQ-C15-PAL, e.g., pain reported in a specific location was classified as ‘pain’, [b] including urinary, fecal and unspecified incontinence

Table 3 shows the EORTC QLQ-C15-PAL and HADS scores overall and according to patient characteristics at baseline. Overall, high symptom levels were found for fatigue, pain, and sleeping difficulties. Women experienced more severe fatigue than men (p = 0.022), and younger patients had more severe nausea/vomiting (p = 0.033), dyspnea (p = 0.023) and sleeping difficulties (p = 0.008) compared to older patients. Single patients (p = 0.003) and patients living in others´ residence (p = 0.017) had more impaired physical functioning. Patients with younger children experienced higher levels of fatigue (p = 0.008) and nausea/vomiting (p = 0.039) than patients with older children. Patients who did not receive any prior antineoplastic treatment experienced more severe appetite loss (p = 0.037) than patients who did. Patients in current antineoplastic treatment experienced more impaired physical and emotional functioning (p = 0.010), as well as more severe nausea/vomiting (p = 0.039), anxiety (p = 0.007) and depression (p = <0.001) compared to those not in treatment.

Table 3. Symptoms, problems and overall quality of life at baseline in relation to sociodemographic and clinical characteristics from 201 patients.

	EORTC QLQ-C15-PAL										HADS	
	PF Mean (SD)	EF Mean (SD)	FA Mean (SD)	NV Mean (SD)	PA Mean (SD)	DY Mean (SD)	SL Mean (SD)	AP Mean (SD)	CO Mean (SD)	QOL Mean (SD)	ANX Mean (SD)	DEP Mean (SD)
All	70 (30)	70 (30)	41 (31)	12 (26)	39 (33)	9 (20)	32 (35)	26 (36)	23 (31)	68 (24)	4.9 (3.9)	4.5 (3.9)
Sex												
Men	73 (29)	71 (31)	36 (31)[a]	10 (25)	37 (32)	7 (17)	30 (35)	23 (34)	21 (29)	69 (23)	4.6 (3.9)	4.3 (3.6)
Women	68 (31)	68 (30)	46 (31)	14 (28)	42 (34)	12 (23)	34 (35)	29 (37)	24 (34)	68 (25)	5.3 (3.9)	4.7 (4.2)
Age												
<65 years	69 (30)	69 (32)	43 (31)	14 (26)[a]	41 (32)	13 (22)[a]	38 (34)[a]	26 (36)	27 (34)	65 (25)	5.0 (3.8)	4.6 (4.1)
≥65years	72 (30)	70 (29)	40 (31)	11 (27)	38 (34)	7 (18)	27 (35)	26 (36)	19 (29)	71 (23)	4.9 (4.0)	4.4 (3.8)
Civil status												
Single	65 (30)[a]	73 (29)	41 (30)	11 (25)	44 (34)	11 (22)	32 (36)	26 (36)	24 (33)	69 (22)	4.7 (3.7)	4.3 (3.8)
Married/cohabiting	75 (29)	67 (32)	41 (33)	13 (28)	36 (31)	8 (19)	32 (35)	25 (36)	22 (30)	68 (25)	5.1 (4.1)	4.6 (4.0)
Residence												
Private residence	73 (29)[a]	69 (32)	41 (32)	12 (26)	38 (34)	8 (20)	33 (36)	27 (36)	22 (31)	68 (25)	5.1 (4.2)	4.5 (4.0)
Others´residence	64 (30)	70 (26)	40 (28)	13 (27)	41 (30)	12 (19)	29 (32)	22 (35)	25 (31)	69 (20)	4.4 (2.8)	4.3 (3.7)
Cohabitation status												
Living alone	74 (29)	63 (42)	40 (33)	6 (8)	32 (40)	9 (22)	30 (43)	27 (33)	9 (22)	71 (21)	4.7 (4.5)	3.7 (2.7)
Living with partner	77 (28)	65 (32)	45 (33)	16 (31)	33 (30)	8 (20)	35 (38)	30 (34)	20 (29)	67 (26)	5.4 (4.4)	4.3 (3.6)
Living alone with children	67 (29)	78 (26)	37 (27)	8 (23)	44 (34)	7 (17)	26 (34)	27 (38)	27 (33)	68 (20)	4.7 (3.7)	4.3 (3.7)
Living with others	66 (29)	70 (29)	37 (32)	15 (30)	41 (32)	13 (24)	33 (35)	20 (34)	25 (35)	71 (24)	4.5 (3.3)	4.0 (3.7)
Living with partner and children	71 (32)	67 (31)	43 (32)	11 (24)	41 (34)	9 (18)	32 (33)	26 (38)	22 (31)	68 (25)	5.0 (4.0)	5.3 (4.6)
Children												
No children	72 (30)	74 (32)	30 (24)[b]	8 (18)[b]	37 (31)	12 (19)	30 (36)	18 (32)	20 (28)	73 (19)	4.0 (3.0)	3.9 (3.2)
Children, at least one younger than 18 years	61 (34)	66 (34)	60 (33)	25 (37)	50 (35)	14 (24)	43 (40)	38 (43)	33 (35)	61 (28)	6.3 (5.4)	4.8 (4.7)
Children, all at least 18	72 (29)	69 (30)	39 (31)	11 (25)	38 (33)	8 (20)	30 (34)	25 (35)	21 (30)	69 (24)	4.8 (3.7)	4.5 (3.9)

Education												
Primary education	73 (29)	66 (30)	40 (30)	13 (28)	39 (32)	10 (23)	36 (37)	27 (38)	19 (32)	71 (24)	5.4 (4.0)	4.7 (4.0)
Secondary education	67 (30)	74 (29)	40 (31)	12 (26)	43 (31)	8 (16)	30 (33)	26 (34)	24 (28)	68 (23)	4.6 (3.8)	4.3 (3.7)
Higher education	74 (30)	70 (33)	43 (35)	10 (22)	33 (37)	13 (20)	25 (33)	22 (35)	30 (36)	61 (25)	4.3 (3.8)	4.4 (4.1)
Diagnosis												
Stomach	75 (28)	73 (30)	41 (28)	14 (33)	38 (34)	9 (26)	35 (38)	31 (34)	35 (36)	59 (27)	4.4 (3.6)	4.6 (3.7)
Colorectal	75 (25)	70 (30)	36 (30)	12 (28)	29 (26)	7 (17)	26 (28)	19 (35)	29 (35)	65 (25)	5.1 (3.6)	4.0 (3.7)
Breast	67 (34)	62 (35)	50 (34)	9 (18)	51 (41)	16 (25)	32 (34)	30 (39)	19 (31)	66 (27)	5.0 (3.9)	4.2 (3.9)
Lung	66 (34)	74 (30)	29 (28)	8 (24)	33 (30)	11 (16)	15 (29)	20 (36)	17 (24)	74 (29)	5.2 (4.2)	5.2 (4.6)
Prostate	73 (31)	65 (31)	30 (36)	6 (13)	32 (36)	2 (8)	26 (41)	28 (43)	15 (29)	74 (21)	5.3 (3.8)	4.1 (3.1)
Gallbladder	82 (22)	68 (36)	43 (33)	11 (30)	32 (31)	12 (22)	33 (30)	42 (45)	18 (23)	77 (17)	3.6 (3.1)	2.6 (2.5)
Other cancer	68 (31)	70 (29)	44 (31)	15 (28)	43 (32)	10 (20)	37 (36)	23 (33)	22 (31)	69 (21)	5.0 (4.2)	4.8 (4.3)
Any prior antineoplastic treatment												
Yes	73 (29)	71 (32)	39 (30)	12 (26)	39 (33)	9 (18)	32 (34)	22 (36)[a]	20 (30)	69 (23)	4.8 (4.0)	3.8 (3.2)
No	68 (30)	68 (29)	42 (33)	13 (27)	40 (32)	10 (22)	31 (36)	29 (36)	25 (33)	68 (25)	5.0 (3.8)	5.1 (4.4)
Current antineoplastic treatment												
Yes	53 (25)[a]	53 (23)[a]	55 (30)	20 (29)[a]	43 (26)	22 (33)	39 (28)	36 (33)	39 (37)	57 (22)	7.2 (2.8)[a]	8.0 (3.1)[a]
No	71 (30)	71 (31)	40 (31)	12 (26)	39 (33)	9 (19)	31 (35)	25 (36)	22 (31)	69 (24)	4.8 (3.9)	4.3 (3.9)
Hospital												
Sotero del Rio	74 (29)	73 (28)	37 (31)	11 (25)	37 (32)	11 (21)	27 (32)	21 (32)	21 (29)	68 (24)	4.1 (3.0)	4.0 (4.0)
San Juan de Dios	69 (29)	71 (29)	42 (30)	42 (30)	15 (30)	7 (21)	34 (39)	30 (41)	21 (32)	70 (22)	5.4 (4.3)	4.9 (3.8)
Salvador	66 (32)	60 (37)	49 (33)	49 (33)	13 (26)	10 (15)	41 (38)	34 (39)	27 (35)	64 (23)	5.9 (4.4)	4.4 (3.6)
Felix Bulnes Cerda	64 (27)	66 (28)	41 (33)	41 (33)	11 (24)	8 (21)	37 (34)	22 (33)	30 (34)	72 (29)	5.9 (4.9)	5.8 (4.2)

PF=physical functioning, EF=emotional functioning, FA=fatigue, NV=nausea/vomiting, PA=pain, DY=dyspnea, SL=sleeping difficulties, AP= appetite loss, CO=constipation, ANX=anxiety and DEP=depression

Mann-Whitney U test[a] and Kruskal-Wallis test[b] $p<0.05$

Change in the symptomatology

Table 4 shows change in the S/P scores of the EORTC QLQ-C15-PAL and HADS after one month of palliative care. Overall, no symptoms significantly worsened. There was significant improvement in the overall mean scores of emotional functioning ($p < 0.001$), pain ($p = < 0.001$), sleeping difficulties ($p = 0.005$), constipation ($p = 0.005$) and anxiety ($p = < 0.001$).

The multivariate analyses are shown in Table 5. For seven of 12 scales a subgroup difference in change over time was found, i.e. for physical functioning, emotional functioning, nausea/vomiting, appetite loss, quality of life, anxiety and depression. Of the seven scales, where subgroup differences in change over time were seen, two scales (emotional functioning and anxiety) also showed an overall significantly change over time (Table 4). Despite the overall improvement in emotional functioning scores, emotional function deteriorated for patients living alone with children (Table 5). A larger reduction in anxiety scores was observed for patients in current antineoplastic treatment compared to those who were not receiving antineoplastic treatment.

For the remaining five scales with significantly different changes over time between subgroups, i.e., physical functioning, nausea/vomiting, appetite loss, quality of life and depression, no significant overall change over time was seen. Diagnosis was associated with change in appetite loss scores: patients with gallbladder and prostate cancer improved compared to other diagnoses (Table 5). A reduction in nausea/vomiting scores was seen for patients living in a private residence compared to those living in others' residence, and for patients living with others compared to the remaining cohabitation categories. A negative change in QOL scores was seen for patients living in others' residence compared to those who lived in their private residence. A more positive change in physical functioning and depression scores was observed for patients in current antineoplastic treatment compared to those not in antineoplastic treatment.

Table 4. Change in symptoms, problems and overall quality of life from baseline to follow-up in relation to sociodemographic and clinical characteristics from 177 patients who completed the study.

		Δ EORTC QLQ-C15-PAL[a]										Δ HADS	
	N	PF	EF	FA	NV	PA	DY	SL	AP	CO	QOL	ANX	DEP
All	177	2	8[b]	-4	-1	-11[b]	-3	-9[b]	-5	-8[b]	-1	-2[b]	0
Sex													
Men	92	2	11	-3	2	-10	0	-9	-2	-6	-3	-1	0
Women	85	2	8	-6	-5	-12	-5	-9	-8	-9	0	-1	0
Age													
<65 years	75	5	10	-5	1	-12	-4	-16	-3	-11	0	-2	0
≥65years	102	0	8	-4	-2	-10	-2	-3	-5	-5	-2	-2	0
Civil status													
Single	75	4	3	-2	1	-15	-6	-5	-4	-8	-2	0	0
Married/cohabiting	102	1	13	-6	-2	-8	0	-12	-5	-8	1	-2	-1
Residence													
Private residence	130	0	11	-6	-3	-9	-2	-10	-7	-7	1	-1	0
Others´ residence	47	6	4	-2	4	-15	-5	-6	4	-10	-8	-1	0
Cohabitation status													
Living alone	10	10	19	-5	1	2	-7	0	6	3	0	-1	0
Living with partner	39	5	18	-15	-2	-10	-2	-23	-11	-10	0	-1	0
Living alone with children	34	-3	-9	5	6	-15	-2	-1	-7	-7	-2	0	0
Living with others	40	5	11	-4	-8	-15	-5	-10	-1	-16	-6	-2	0
Living with partner and Children	54	-2	9	-3	0	-9	0	-5	-2	-3	2	-1	-1
Children													
No children	18	7	6	-2	-1	-13	-9	-8	0	-9	-4	-1	1
Children, at least one younger than 18 years	19	3	9	-15	-7	-15	-2	-12	0	-16	-2	-3	-1
Children, all at least 18	140	1	9	-3	0	-10	-2	-9	-6	-6	-1	-2	0
Education													
Primary education	83	0	12	-5	-6	-12	-5	-17	-7	-4	0	-2	0
Secondary education	65	5	4	-4	5	-19	1	-1	-4	-9	-3	-1	0

Higher education	29	1	11	-5	2	-8	-4	-3	0	-14	4	-1	0
Diagnosis													
Stomach	20	-5	8	5	10	-6	-2	-14	10	-15	7	0	0
Colorectal	22	8	18	-6	1	-8	-2	-11	5	-19	6	-2	-1
Breast	16	2	21	-20	-2	-33	2	-19	-11	0	7	-2	-1
Lung	19	15	9	0	1	-11	-5	0	-4	6	-3	-1	-1
Prostate	18	7	13	2	0	-15	0	-11	-20	0	-2	-2	-1
Gallbladder	10	-9	16	-17	-7	-3	-13	-10	-37	-13	-5	0	0
Other cancer	72	-1	1	-4	-4	-7	-4	-5	-1	-8	-6	-1	1
Any prior antineoplastic treatment													
Yes	90	4	7	-8	-2	-10	-2	-10	-4	-4	-2	-1	-1
No	87	0	11	-2	1	-13	-3	-8	-5	-11	1	-2	-1
Current antineoplastic treatment													
Yes	11	19	23	-12	-3	-10	-15	-27	-15	-18	-1	-4	-3
No	166	1	7	-5	0	-10	-2	-8	-4	-7	-1	-2	0
Hospital													
Sotero del Rio	85	2	5	-3	2	-11	-4	-6	3	-6	-1	-1	-1
San Juan de Dios	44	-2	4	-2	-1	-13	-2	-5	-6	-4	4	-3	0
Salvador	30	6	25	-17	-7	-10	-2	-19	-14	-17	-2	-3	-1
Felix Bulnes Cerda	18	6	5	3	-1	-3	-3	-13	-15	-9	-10	-1	-1

PF=physical functioning, EF=emotional functioning, FA=fatigue, NV=nausea/vomiting, PA=pain, DY=dyspnea, SL=sleeping difficulties, AP= appetite loss, CO=constipation, ANX=anxiety and DEP=depression

Δ = score at follow-up - score at baseline

[a] A positive Δ difference in the two functioning scales and overall QOL reflects improvement and a negative Δ difference reflects relief in symptom scales

[b] Wilcoxon signed rank test $p<0.05$

Table 5. Significant associations between patient characteristics and changes in symptom/problem scores from baseline to follow-up obtained from multiple linear regression analyses with backwards stepwise selection. Only the seven scales for which subgroup differences were found are shown.

		EORTC QLQ-C15-PAL					HADS	
	N	Δ PF^a (CI 95%)	Δ EF^a (CI 95%)	Δ NV^b (CI 95%)	Δ AP^b (CI 95%)	Δ QOL^a (CI 95%)	Δ ANX^b (CI 95%)	Δ DEP^b (CI 95%)
Intercept		0.8	9.0	-1.2	4.5	1.5	-1.3	0.2
Residence								
Private residence	130			0.0 (ref. group)		0.0 (ref. group)		
Others' residence	47			13.7 (3.2;24.3)		-9.7 (-18.7; -0.7)		
Cohabitation status								
Living alone	10		10.2 (-12.7;33.1)	-1.3 (-19.3;16.7)				
Living with partner	39		9.0 (-5.0;23.0)	-1.8 (-12.8;9.3)				
Living alone with children	34		-17.8 (-32.3; -3.2)	3.4 (-8.1;14.9)				
Living with others	40		2.3 (-11.6; 16.2)	-16.0 (-28.3; -3.7)				
Living with partner and children	54		0.0 (ref. group)	0.0 (ref. group)				
Diagnosis								
Stomach	20				10.9 (-6.6;28.4)			
Colorectal	22				5.5 (-11.5;22.4)			
Breast	16				-9.6 (-27.5;8.3)			
Lung	19				-3.2 (-22.4;16.0)			
Prostate	18				-19.4 (-37.8; -1.1)			
Gallbladder	10				-35.7 (-59.2; -12.2)			
Other cancer	72				0.0 (ref. group)			
Current antineoplastic treatment								
Yes	11	18.6 (0.1; 37.1)					-2.7 (-5.1; -0.3)	-2.9 (-5.4; -0.4)
No	166	0.0 (ref. group)					0.0 (ref. group)	0.0 (ref. group)

PF=physical functioning, EF=emotional functioning, NV=nausea/vomiting, AP= Appetite loss, QOL=Quality of life, ANX=anxiety and DEP=depression
Δ= score at follow-up - score at baseline, CI= confidence intervals
Age, sex, civil status, children, education, prior antineoplastic treatment and hospital were not significantly associated with any of the outcomes and therefore not shown. No patient characteristics were significantly associated with pain, fatigue, dyspnea, sleeping difficulties and constipation and thus these outcomes are not shown

[a] A positive value reflects improvement in the two functioning scales and overall QOL from baseline to follow-up compared to the reference group.

[b] A negative value reflects symptom relief in the symptom scales from baseline to follow-up compared to the reference group. Significant association between patient characteristics and outcomes $p<0.05$

Discussion

This Chilean longitudinal study had a high consent rate, since 80% of the patients eligible for this study (n= 250) agreed to participate giving their informed consent. Although the difficulties of conducting a longitudinal study in palliative care are well known and include the mental and physical deterioration of patients with advanced cancer, as well as their proximity to death, we had a good retention of patients, where 88% of 201 patients who answered the questionnaires at baseline completed the study after one month.

Symptomatology at admittance to palliative care

At the start of palliative care, we found that fatigue, pain and sleeping difficulties were the most prevalent S/Ps, and at the same time had the highest mean scores. An earlier study in Chile, also found that sleeping difficulties (94.8%,), fatigue (83.2%), and pain (71.5%) were among the most prevalent symptoms reported by 77 patients admitted to a single palliative care service (24). In previous studies from Europe and Northern America, fatigue and pain have also been reported as some of the most prevalent S/Ps, whereas sleeping difficulties was not among the most prevalent S/Ps (23, 25-31). The prevalence of the different S/Ps were often in the lower end in this study compared to what have been found in previous studies (23, 25-31), except for sleeping difficulties, where the prevalence found in our study (54%) was higher compared to what had been found across previous studies (12–49%) (26-31).

Moreover, in this study the mean scores of pain, fatigue, and sleeping difficulties were lower compared to what was found in previous European studies at admittance to palliative care (5-7, 10, 23, 25, 32-34), except for one Canadian study where similar levels of symptoms were found (3). One explanation of the better S/P mean scores in this study may be that patients had a good performance status (media 90; range 50–100). This may reflect that some of the sickest patients were not included in this study, maybe because they were not referred to palliative care. This is in line with our study having a better mean physical functioning score compared to that of previous studies (4-7, 9, 10, 23, 25, 32-34).

In the current study, the prevalence of possible depression (19%) on HADS (score ≥8) was slightly higher than the prevalence of possible depression (15–16%) in two Chilean preliminary studies, where the emotional symptoms of oncology patients in curative treatment were also measured using HADS; however, the prevalence of possible anxiety in this study (21%) was lower than the prevalence of possible anxiety (range 33–35%) reported in the Chilean studies (35, 36). The lower prevalence of possible anxiety in this study, compared to that of Chilean oncology patients in previous studies, may be explained by the fact that antineoplastic treatment, e.g., chemotherapy and radiotherapy is associated with increased anxiety (37). Similarly, the prevalence of definite depression or anxiety (10–11%) on HADS (score ≥11) in our study, was lower compared to previous European and American studies, where patients in palliative care reported a prevalence of definite depression that ranges from 25 to 47%, and definite anxiety from 22 to 28% (32, 38-40).

Regarding the WISP instrument, patients reported 18 additional S/Ps not covered by the EORTC QLQ-C15-PAL at baseline. Most of these S/Ps were also identified in two previous studies, which compared symptoms voluntarily reported on an open-ended question versus symptoms systematically assessed (41, 42). The most prevalent additional S/Ps reported in this study were cough (reported by 5.5% of the participants), bloating (3.5%), and diarrhea (2.5%); our prevalences were similar to those reported by 200 patients using an open-ended question in Homsi et al.,' study (42), but higher compared to a preliminary study using WISP in 5,447 patients admitted to specialized palliative care in Denmark (18). Differences in the symptom prevalence may be explained because the sample size of this study (n=201) was smaller than the previous study on WISP. Moreover, 70.0% of these additional S/Ps on WISP were reported as moderate to severe, which is in accordance with earlier studies that found patients voluntarily report additional symptoms when they are perceived as severe (42, 43). This is also in line with the study where WISP was developed, where 85% of patients rated S/Ps as moderate to severe (18). The identification of 18 additional S/Ps on WISP, and the fact that they were often reported at a moderate-severe level, stresses the relevance of supplementing the short EORTC QLQ-C15-PAL with the WISP to assure that besides the most common S/Ps, other distressing S/Ps are also possible to report.

In the present study, younger patients experienced more severe sleeping difficulties, dyspnea and nausea/vomiting than older patients. In agreement with our study, earlier studies found higher levels of insomnia in younger patients compared to older patients (9, 23, 28, 44). This may reflect that it is more stressful for young people to cope with a terminal illness due to crushed future dreams, expectations, and economic concerns about the future and their families (45). Similarly, slightly higher levels of nausea /vomiting in younger patients compared to older patients have also been found in previous studies (23, 28, 46). One explanation for this may be that the daily life of younger patients does not allow patients to relax to the same extent as older patients, i.e., older patients are mainly retired versus younger patients who may be parenting children and/or actively working.

In our study, single patients and patients living in ‘others’ residence than private’ had more impaired physical functioning. Similarly, to our results, single patients also reported more impaired physical functioning than cohabiting patients in a previous study (30). This may be explained by patients living alone do not have anyone in their home to help them if they have physical problems and thus, their physical deterioration can occur faster compared to patients who are cohabiting. A reason why patients living in ‘others’ residence’ have more impaired physical function than patients living in their private residence, may be that ‘others’ residence’ also includes elderly homes, where patients often have a very poor physical function. Alternatively, it could reflect that patients move to e.g. their children’s home when the physical functioning deteriorate. Patients with younger children experienced higher levels of fatigue and nausea/vomiting than patients with older children, this may happen because the stress of parenting younger children increases the probability of experience more symptomatology (47).

Furthermore, patients in current antineoplastic treatment reported more severe nausea/vomiting, anxiety, depression, impaired physical and emotional functioning compared to those not receiving antineoplastic treatment. The higher level of symptoms probably may be related to the side effects of the antineoplastic treatment that patients are receiving, as some preliminary studies found that patients in current antineoplastic treatment (chemotherapy and/or radiotherapy) report worse symptomatology and more impaired functioning than those who are not in treatment (5, 44).

Changes in symptomatology after one month of palliative care

We observed significant improvement after one month for emotional functioning, pain, sleeping difficulties, constipation and anxiety. This is encouraging as it shows that, despite the fact that these Chilean patients were in an advanced stage of their disease and thus expected to get worse, it is in fact possible to improve their symptomatology by one month of palliative care. Improvements in the symptomatology after receiving palliative care have also been found in studies from other parts of the world. Some studies showed improvement in pain, appetite loss, constipation, QOL, sleeping difficulties and emotional functioning after 2–4 weeks of palliative care (4-7, 9, 48), and two studies found that pain, constipation and emotional functioning improved already after 1 week (33, 49). In addition, two previous studies, one conducted in Italy using ESAS (50) and the other in Denmark using HADS (6), found that from the start of palliative care anxiety improved significantly after 1 week.

Moreover, in this study, patients living in their private residence had a more positive change in nausea/vomiting and QOL than patients living in other' residence. Perhaps this reflects that these patients received more help from their closest family since all lived accompanied, receiving more support from their family caregivers, especially after being educated on patient care at the start of palliative treatment. While patients overall improved in emotional functioning during the first month of palliative care, patients living alone with children deteriorated. This may indicate that single parents are a particularly vulnerable group whose concerns, e.g., about the future of their children, may increase even if they are admitted to palliative care, especially if they are close to death.

Higher baseline levels of appetite loss for patients with gallbladder cancer may be the explanation to why these patients had the most positive change in appetite loss the first month of palliative care. Also, the worse baseline scores among patients in current antineoplastic treatment compared to those who were not receiving antineoplastic treatment, can probably partly explain why patients in antineoplastic treatment had a more positive change in anxiety, depression and physical functioning scores after a month in palliative.

A few studies have investigated how patient characteristics were associated with changes in S/P scores, and found that age and sex were associated with changes in symptom/problem scores (51, 52), which is different from our study where age and sex were not significantly associated with change in the level of S/Ps.

Strengths and limitations

This longitudinal study has several strengths. First, this study is to our knowledge the first to investigate S/Ps and overall QOL at the start of palliative care in Chile and how the levels of S/Ps change after one month, providing new knowledge of the symptomatology of patients receiving palliative care in Chile. Second, apart from the relatively low attrition for one month, the analysis was performed without missing data because all patients were able to complete the questionnaires by themselves or assisted by a clinician. Finally, patients' symptomatology was measured by the EORTC QLQ-C15-PAL and HADS, which are extensively used and validated instruments for patients in palliative care.

A limitation of the study was the small sample size, which restricted the possibility to perform comparisons of the symptomatology between hospitals. In addition, it was not possible to include patients from other types of services than outpatients, because most of the palliative care services did not have an inpatient unit and because palliative home care is provided by other services/teams.

The current study demonstrated an improvement in S/Ps of patients with advanced cancer after one month of palliative care. Knowledge about symptomatology and QOL of patients at the admittance to palliative care, and over time, is essential for organizational planning of palliative care services. Symptom assessment should be done with the aid of standardized self-reported questionnaires such as the EORTC QLQ-C15-PAL, to contribute to the management of symptoms, and to a assure that clinicians do not overlook symptoms (42, 53). In addition, this study demonstrated the use of WISP increased the identification of symptom not covered by the EORTC QLQ-C15-PAL; therefore, it should also be considered when a more comprehensive assessment of symptoms is required.

In future research, it would be relevant to include more palliative care services to get a broader overview of current symptomatology of advanced cancer patients receiving palliative care in Chile. It would also be relevant to measure S/Ps and overall QOL in hospitalized patients and patients in palliative home care, to understand differences in the symptomatology between types of services at admittance and over time.

Conclusions

In this longitudinal study conducted in four Chilean palliative care services, patients reported moderate to severe levels of S/Ps at admittance to palliative care. The high performance status observed raises the question of whether the most severely ill patients were less likely to be referred to palliative care. Emotional functioning, pain, sleeping difficulties, constipation and anxiety improved significantly during the first month of palliative care. Several sociodemographic and clinical variables were associated with changes in symptom/problem scores. This information on patients' symptomatology may guide clinicians to more effective interventions that may improve the quality of life of patients receiving palliative care in Chile.

Acknowledgements

We are very grateful to all the patients who participated in this study and willingly filled the questionnaires. We would like to thank Dra. María Angélica Becerra, Dr. Daniel Leiva, Dr. Rodrigo Fernández, and Dra. Magaly Sacta for their support to conducting this study in their palliative care services. The invaluable collaboration in the data collection of the psychologists Pedro Rojas and Scarlette Cisternas is highly appreciated.

Conflict of interest

The authors declare that they have no conflict of interest.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of two Chilean research committees: Comité de Ética Científico Adultos Servicio de Salud Metropolitano Oriente ID-CECSSMO27122016, Comité Ético Científico Servicio de Salud Metropolitano Sur Oriente ID-CECSSMSO17082017 (names in Spanish), and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all patients who participated in the study.

Funding

This study was supported by ‘Becas-Chile Scholarship’ from the Advanced Human Capital Program of the National Commission for Scientific and Technological Research-CONICYT.

Data management and sharing

The data utilized in this study are available through the first author at the Palliative Care Research Unit, Department of Geriatrics and Palliative Medicine GP, Bispebjerg and Frederiksberg Hospital, University of Copenhagen, Denmark. Restrictions apply to the availability of these data.

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